Elemental Fluorine for the Greener Synthesis of Life-Science Building Blocks

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A thesis entitled

Elemental Fluorine for the Greener Synthesis of Life-Science Building Blocks

by

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Abstract

Fluorinated organic compounds are increasingly important in many areas of our modern lives, especially in pharmaceutical and agrochemical applications where the incorporation of this element can have a major influence on biochemical properties. The introduction of the carbon-fluorine bond into such systems is typically carried out using well established multistep, nucleophilic fluorination processes that usually lead to large waste streams. Despite the availability of alternative electrophilic fluorination methods which have found several applications on discovery scale, the direct transformation of C-H to C-F bonds on large scale is scarce. Elemental fluorine is the only electrophilic fluorinating reagent that is viable for manufacturing scale applications, but, in spite of the advances in this field in the past 25 years, there are only a handful of processes where it is used, most notably in the manufacturing of 5-fluorouracil.

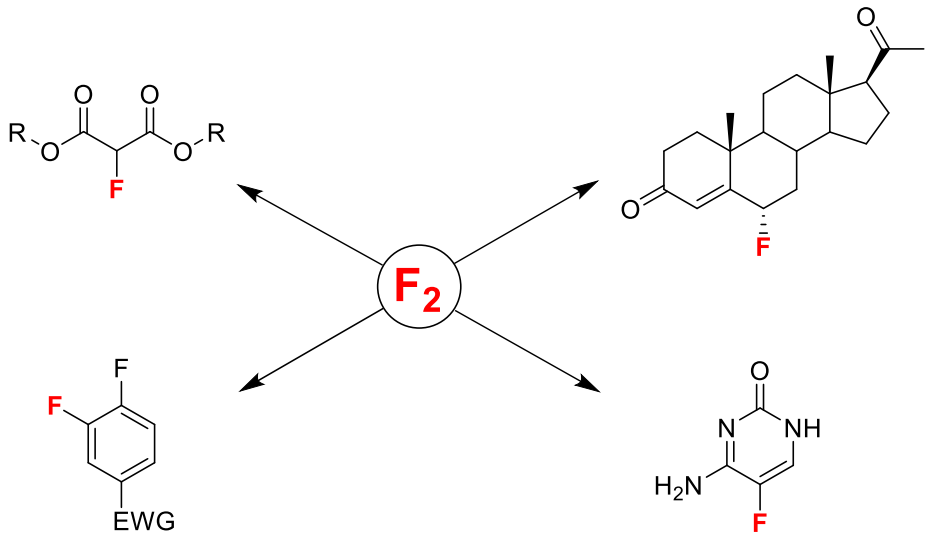

Figure 1: Life-science related systems investigated in this thesis.

In this thesis the direct fluorination of several industrially relevant organic systems was investigated with an aim to provide optimised, high yielding and scalable processes that could be compared with existing manufacturing methods using a green chemistry metrics package developed by the EU IMI Chem21 consortium. First, we found that the copper catalysed direct fluorination of simple malonate esters provided the desired 2-fluoromalonate derivatives in excellent yield and purity and upon comparison with halogen exchange methods from the literature we concluded that the process is comparable in efficiency and environmental impact, however, it achieves these results in a single step. The direct fluorination of a more complex aliphatic system, progesterone, highlighted that even though the desired reaction takes place

to some extent, in such complex systems there are a large number of competing side reactions that prevent good conversion and simple isolation procedures.

The direct fluorination of aromatic systems was one of the most important areas to investigate as fluorobenzene derivatives are the largest sub-group of fluorine containing life-science products. The assessment of this reaction in the case of a range of aromatic derivatives revealed that in order to avoid the formation of large amounts of polyfluorinated side products the reaction should only be progressed to 50-60 % conversion, but the separation of a two component mixture can be difficult using non-chromatographic methods because of the similar physical properties of the product and starting material.

The direct fluorination of cytosine, to afford the WHO Essential Medicine Flucytosine, was successfully carried out under batch fluorination conditions, however, transferring the process to continuous flow showed a distinct improvement of selectivity and higher yields. This process was further evaluated on larger scale, in collaboration with Sanofi and MEPI the continuous fluorination reaction was demonstrated on over 100 g/h scale and following optimisation studies significant quantities of the product were isolated for further assessment. Green metrics analysis of this process demonstrated a large improvement in material usage and overall yield between the current manufacturing method (3 steps from 5-fluorouracil) and our process. Finally, the synthesis and reactions of previously unknown fluorinated acyl Meldrum's acid derivatives are described, highlighting the potential of this system to be used as a polyfunctional intermediate in the synthesis of monofluorinated aliphatic compounds.

Acknowledgement

First of all, I would like to thank Professor Graham Sandford for all his support, encouragement and patience throughout my time in Durham that helped me maintain my enthusiasm even in times when Chemistry was not in my favour.

Working as part of the Chem21 consortium was an amazing experience where I had the opportunity to learn from and work with leading experts from both industry and academia and our collaborations within the project were some of the best experiences of my PhD. A special thank you is due to Catherine Alder (GSK) for green metrics discussions and Annelyse Conté (MEPI) for all her work during the Flucytosine project, and I would also like to thank the work and support of Nicky Willis, Joe Adams, John Hayler, Andy Wells, Alan Rabion, Sandrine Grenier, Kai Rossen, Jean-Paul Seuwin, Laurent Pichon, Rob McElroy and Louise Summerton in various Chem21 projects.

My research in Durham would not have been possible without the excellent work of all the support staff especially the workshops and analytical services. Thank you to Malcolm and Aaron for always helping me out with my glassware requests also to Paul, Neil and Omer in the mechanical and electrical workshops. The work of Alan, Catherine and Juan in NMR, Dave and Pete in MS, Lenny in chromatography and Dima in crystallography is gratefully acknowledged, they were always available for discussions and to give me a helping hand when needed.

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Finally, I would like to thank my family and friends for their continued support and encouragement. I could not list everything I would like to thank my wife Eszter for, so I am not even going to try, but it is much appreciated.

Memorandum

The work described in this thesis was carried out at Durham University between October 2012 and December 2015. This thesis is the work of the author, except where acknowledged by reference, and has not been submitted for any other degree. The copyright of this thesis rests with the author. No quotation from it should be published without the prior written consent and information derived from it should be acknowledged.

Parts of this work have been the subject of the following publications:

1) A. Harsanyi, G. Sandford, *Green Chem.* **2015**, *17*, 2081-2086, *Organofluorine Chemistry: Applications, sources and sustainability.*
2) A. Harsanyi, G. Sandford, *Green Chem.* **2015,** *17,* 3000-3009, *Fluorine gas for Life Science syntheses: Green metrics to assess selective direct fluorination for the synthesis of 2-fluoromalonate esters.*
3) A. Harsanyi, G. Sandford, *Org. Proc. Res. Dev.* **2014,** *18,* 981-992, *2-Fluoromalonate Esters: Fluoroaliphatic Building Blocks for the Life Sciences.*
4) A. Harsanyi, G. Sandford, *WO/2016/030662,* **2016,** *Process for Producing Flucytosine and Flucytosine Derivatives.*

This work has been presented, in part, at:

1) 21st International Symposium on Fluorine Chemistry and 6th International Symposium on Fluorous Technologies, 23-28 August 2015, Como, Italy, *poster presentation, Poster Award of the German Fluorine Chemistry Working Group.*
2) 19th Annual ACS Green Chemistry and Engineering Conference, 13-17 July 2015, North Bethesda, MD, *oral presentation.*
3) RSC Fluorine Subject Group Meeting, 16-17 April 2015, Durham, *poster and oral presentations.*
4) RSC Fluorine and Carbohydrate Subject Group Meeting, 2-3 September 2013, Southampton, *oral presentation, Prize for Oral Presentation.*

Nomenclature and abbreviations

Ac	Acyl
Accufluor™	1-Fluoro-4-hydroxy-diazonia[2.2.2]bicyclooctane bis(tetrafluoroborate)
ACS	American Chemical Society
ACS GCI	American Chemical Society Green Chemistry Institute
AE	Atom economy
aHF	Anhydrous hydrogen fluoride
API	Active Pharmaceutical Ingredient
ASAP	Atmospheric solid analysis probe
BINOL	1,1'-Bi-2-naphtol
b.p.	Boiling point
Bu	Butyl
t-Bu	Tertiary butyl
CDI	Carbonyldiimidazole
CFC	Chlorofluorocarbon
COSY	Correlation spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	Dicyclohexyl carbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
Deoxofluor™	Bis(2-methoxyethyl)aminosulfur trifluoride
DMAc	N,N-Dimethylacetamide
DMAP	4-(N,N-Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidone
DMSO	Dimethyl sulfoxide
DSC	Differential scanning calorimetry
EDG	Electron donating group
E factor	Environmental factor

EI	Electron impact (ionisation)
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
FDA	(United States) Food and Drugs Administration
FEP	Fluorinated ethylene-propylene copolymer
5-FU	5-Fluorouracil
Halex	Halogen exchange
HCFC	Hydrochlorofluorocarbon
HFC	Hydrofluorocarbon
HFP	Hexafluoropropene
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single-quantum correlation spectroscopy
IR	Infra-red
LCA	Life cycle assessment
Me	Methyl
MEK	Methyl-ethyl ketone, 2-butanone
MI	Mass intensity
MIBK	Methyl-isobutyl ketone
m.p.	Melting point
MTBE	Methyl *tert*-butyl ether
M.S.	Molecular sieves
MW.	Molecular weight
NFSI	N-Fluorodibenzenesulfonimide
NME	New molecular entity
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
OD	Outside diameter
Ph	Phenyl
PMI	Process mass intensity
ppm	Part per million
i-Pr	iso-Propyl

PTFE	Poly(tetrafluoroethylene)
RME	Reaction mass efficiency
rt	Room temperature
SDF	Selective direct fluorination
Selectfluor™	1-Chloromethyl-4-fluoro-diazonia[2.2.2]bicyclooctane bis(tetrafluoroborate)
SM	Starting material
SS	Stainless steel
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl-
TLC	Thin layer chromatography
UV	Ultra-violet
XtalFluor™	(Diethylamino)difluorosulfonium tetrafluoroborate
WHO	World Health Organisation

Table of contents

Chapter 1.: Green Chemistry Principles for Fluorination

The research leading to this thesis is part of a large European public-private partnership, the EU IMI CHEM21 project which aims at delivering greener and more sustainable manufacturing methods to the pharmaceutical industry. The project members are six large pharmaceutical companies, five small and medium sized companies and thirteen European universities. The technologies in the project range from synthetic organic chemistry to bio-catalytic transformations and synthetic biology with a focus on the use of green chemistry tools to assess new synthetic methodologies for pharmaceutical manufacture. Our role in this project was to demonstrate whether elemental fluorine is a viable, greener reagent for the formation of C-F bonds in life science related compounds. This chapter will introduce the origin and role of fluorine in life sciences and methods for the use of F_2 in organic synthesis, then will briefly discuss green chemistry principles and methods that were used in this research.

1.1 Organofluorine chemistry

Although fluorine is a very abundant element on our planet, it is much under-appreciated by the general public. Probably the most well-known uses are in toothpaste (usually as SnF_2 or NaF) and in some places drinking water fluorination (in the form of H_2SiF_6), but these are complemented by the other uses of this fascinating element in essentially all areas of our lives.

1.1.1 Origin of fluorine

Even though fluorine is present in many different minerals in the Earth's crust, only three of these are suitable for industrial scale mining. Cryolite (Na_3AlF_6) used to be mined for the manufacture of aluminium, but all large deposits have been depleted over the years.[1]

Figure 2: Fluorine containing minerals: fluorapatite ($Ca_5(PO_4)_3F$), fluorite (CaF_2) and cryolite (Na_3AlF_6).[2–4]

Currently, most of the fluorine atoms that are used in commercial applications originate from fluorspar (CaF_2) which is converted to anhydrous HF, but known reserves of this strategic mineral are estimated to last for only another 100 years.[5] Fluorapatite ($Ca_5(PO_4)_3F$) is a potential alternative fluoride source, because, this mineral is a contaminant in abundant phosphate rock. Therefore, the manufacturing of phosphoric acid for the fertiliser industry produces fluorosilicic acid (H_2SiF_6) as a side product which is not being used to a great extent for any synthetic purpose[6,7] and could, in the future, provide anhydrous HF feedstock.

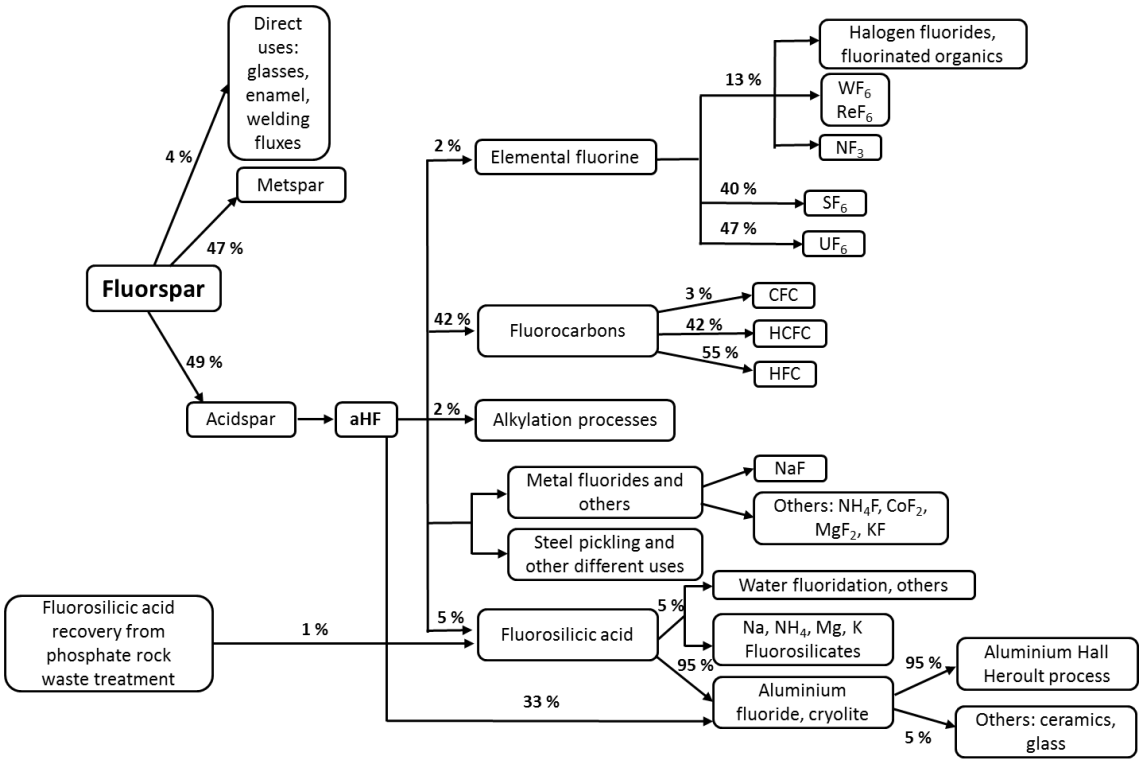


Figure 3: Industrial uses of fluorspar.[6]

Low purity fluorspar, also called metspar, is used as a flux material in iron smelting, while the high purity mineral is almost exclusively converted to anhydrous hydrogen fluoride (aHF), which is the key starting material to all synthetic fluorinated chemicals from inorganic fluorides to the most complex fluorinated organic systems (Figure 3.).

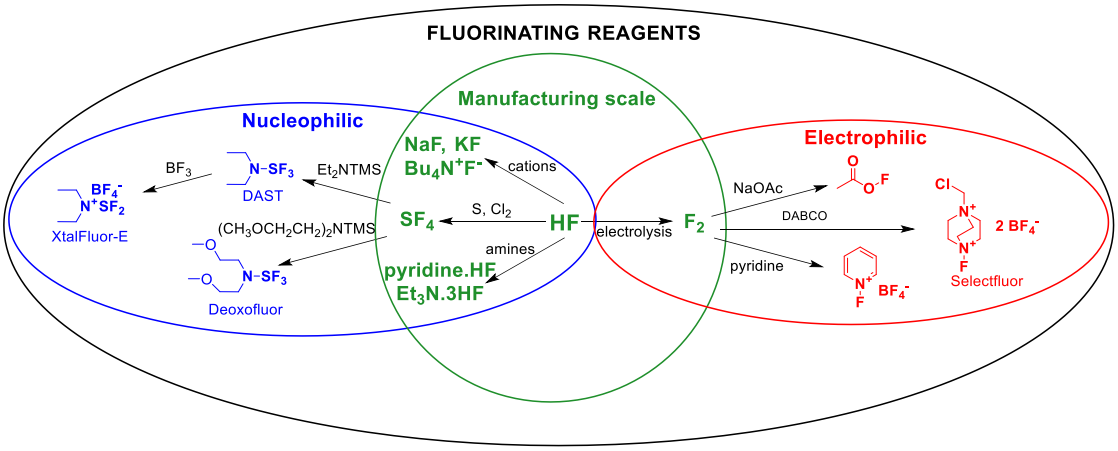


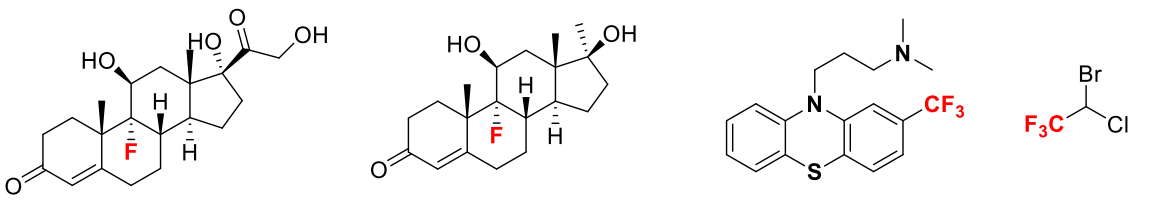
Figure 4: Common fluorinating reagents used in organofluorine chemistry.

In organofluorine chemistry, hydrogen fluoride is by far the most important reagent, as essentially all fluorinating reagents are derived from it in a few steps and, generally, the more steps required to synthesise a reagent the more expensive it becomes. For these reasons, reagents other than HF, its amine complexes, inorganic fluorides and elemental fluorine are in general the only viable reagents for large scale manufacturing of fluorinated organic compounds. Other reagents that were developed to enable a number of useful transformations to be carried out without specialist equipment (for example Selectfluor™ or DAST) are rarely used on the manufacturing scale, mainly for economic reasons (Figure 4.), but have found widespread applications in, for example, drug discovery programmes.[5]

1.1.2 Fluorine in pharmaceuticals

Contemporary medicine benefits from over one hundred years of drug discovery and development and, consequently, today we have access to pharmaceuticals for the treatment of a range of diseases. Despite the advances, there is still extensive investment into new medicines as there are many untreated diseases and there is always need for safer and more effective pharmaceuticals.

Incorporation of fluorine into biologically active organic compounds was first reported in the early 1950's when Fried and Sabo discovered that introduction of a single fluorine atom to a corticosteroid system significantly increased its activity.[8] This discovery was followed by FDA approval of Fludrocortisone in 1955.

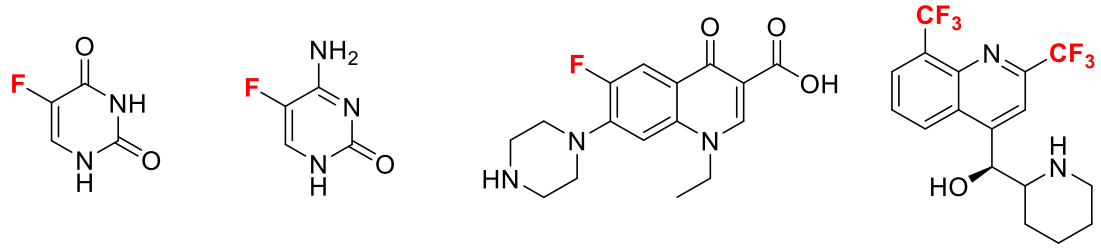


Fludrocortisone, **1** (1955) | Fluoxymesterone, **2** (1956) | Triflupromazine, **3** (1957) | Halothane, **4** (1958)

Figure 5: Fluorine containing drugs from the early years (year of FDA approval).

The early years of fluorinated pharmaceuticals contributed significantly to the understanding of the biological effects of various fluorinated substituents. For example, Triflupromazine (**3**) was the first approved drug that contained a trifluoromethyl group in its structure and, in this case, the introduction of a CF_3 group possibly leads to an increase in the lipophilicity of this antipsychotic compound to enable it to pass the blood-brain barrier more easily.

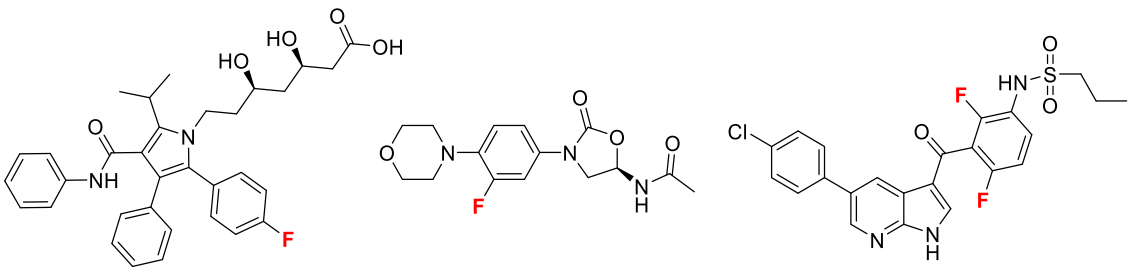
Most fluorine containing drugs introduced during the 1950-1980's were steroid and anti-psychotic compounds structurally similar to the first examples above, however, some very important discoveries were also made in these decades. One drug, 5-fluorouracil (**5**), was found to be an effective treatment for various cancers and has been used extensively since and another, structurally related system, 5-fluorocytosine (**6**), was also introduced in this period for the treatment of fungal infections. The discovery of 6-fluoroquinolones, for example Norfloxacin (**7**), in the 1980's led to a very successful class of compounds that are used for the treatment of bacterial infections. [9]



Fluorouracil, **5** (1961) | Flucytosine, **6** (1971) | Norfloxacin, **7** (1986) | Mefloquine, **8** (1989)

Figure 6: Significant fluorinated drugs form the 1960's - 80's.

It was only in the 1990's when fluorinated aromatic rings started becoming the most prominent fluorinated drug sub-unit, a trend that appears to have increased ever since. Fluorine atoms are frequently introduced to aromatic sub-units to increase metabolic stability as it is well documented that the incorporation of fluorine at metabolically labile positions blocks oxidative pathways, therefore, increasing the half-life of the molecule in an organism.[10,11] Some notable examples of fluorobenzene substituted drugs include Atorvastatin (**9**), Linezolid (**10**) and Vemurafenib (**11**).



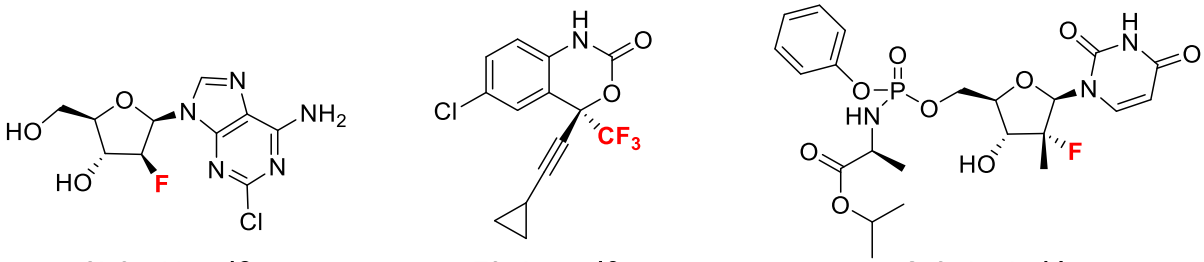
Atorvastatin, **9** (1996)

Linezolid, 1**0** (2000)

Vemurafenib, **11** (2011)

Figure 7: Fluorobenzene structure containing drugs (FDA approval year).

The diversity of fluorinated substituents has been increasing, with new functional groups, for example CF_3CF_2- and -CF_2-, finding more use in commercially valuable drugs recently. Chiral fluorinated systems have also been used since the early days, but most of these compounds were fluorinated steroids, however, in the past 10 - 15 years, fluorine atoms attached to stereogenic centres have started appearing in different systems along with trifluoromethyl substituents at chiral centres (Figure 8).



Clofarabine, **12** (2004)

Efavirenz, **13** (1998)

Sofosbuvir, **14** (2013)

Figure 8: Chiral fluorinated drug structures (FDA approval year).

In September 2015, the FDA of the United States listed over 1600 approved small molecule drugs (www.drugbank.ca) and approximately 10 % of these drugs (155) contain at least one fluorine atom. However, this ratio has been increasing over the years and in the last decade, approximately 25 % of all new small molecule drugs launched to the market contained fluorine.[12–17] Amongst these drugs various fluorine containing functional groups are found, but there are a few types of systems that are dominant, for example, fluoro- and trifluoromethyl-aromatics and alkyl fluorides (Figure 9).

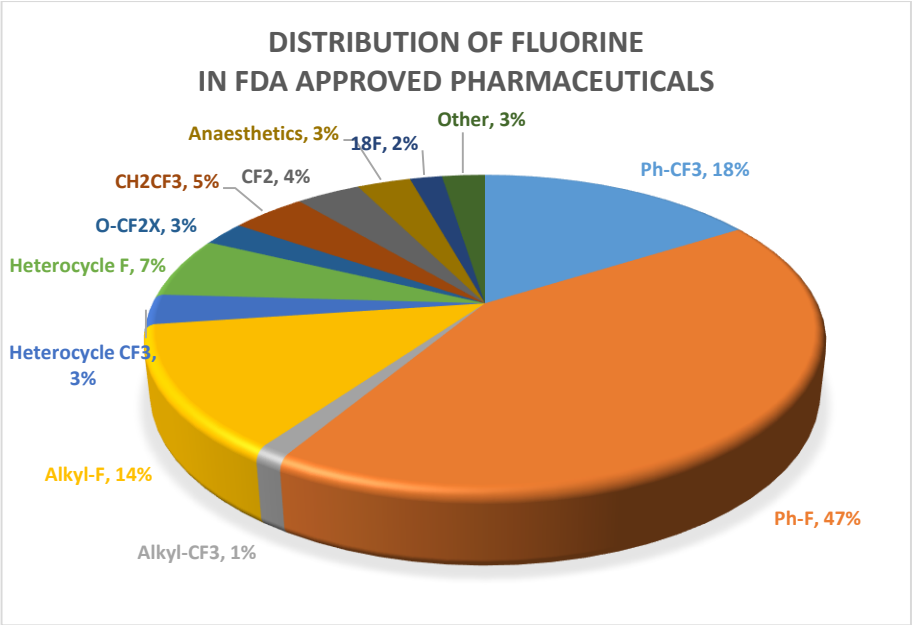
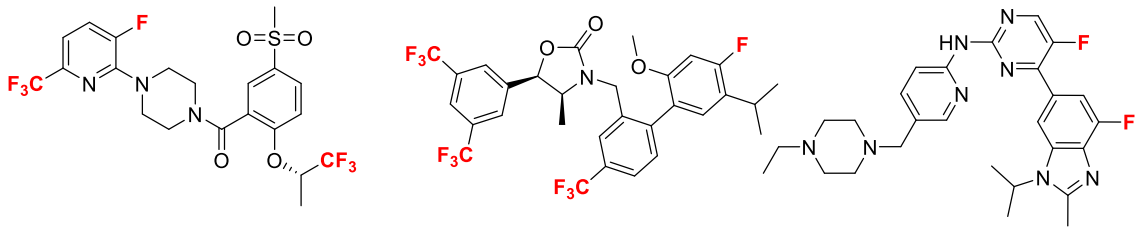


Figure 9: Distribution of fluorinated functional groups in FDA approved APIs.

From a fluorine chemistry point of view, the variety of fluorine containing functionalities in drugs has been growing and this is certain to continue in the future. To attempt to predict the future of fluorinated pharmaceuticals, we assembled a collection of fluorinated drug candidates from Phase 2 and Phase 3 clinical trials, using the publically available pipeline details of the largest pharmaceutical companies (see Appendix III.). This list contains 49 original New Molecular Entities, which all together contain over 60 fluorinated structural elements showing that in the future it is going to be more common to have several different fluorinated functional groups present in the same molecule (Figure 10.).



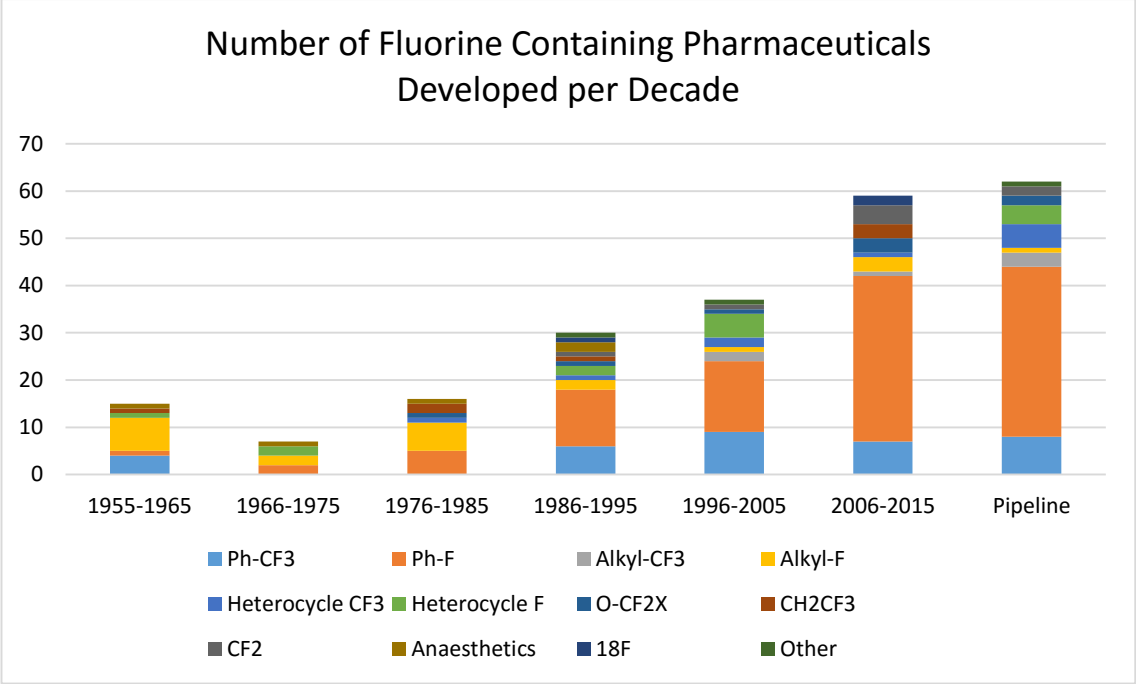
Bitopertin, **15**
Roche Phase II.
neuroscience

Anacetrapib, **16**
Merck Phase III.
cardio-vascular

Abemacyclib, **17**
Eli Lilly Phase II.
breast cancer

Figure 10: Late stage drug candidates containing several different fluorinated functionalities.

Analysis of fluorinated drug systems by decade clearly supports the already described trends in the change in fluorinated structures. In the future, fluoroaromatic compounds are not going to lose their dominance, but most likely there will be more aliphatic and heteroaromatic systems which can sometimes be challenging to synthesise, especially on the manufacturing scale.



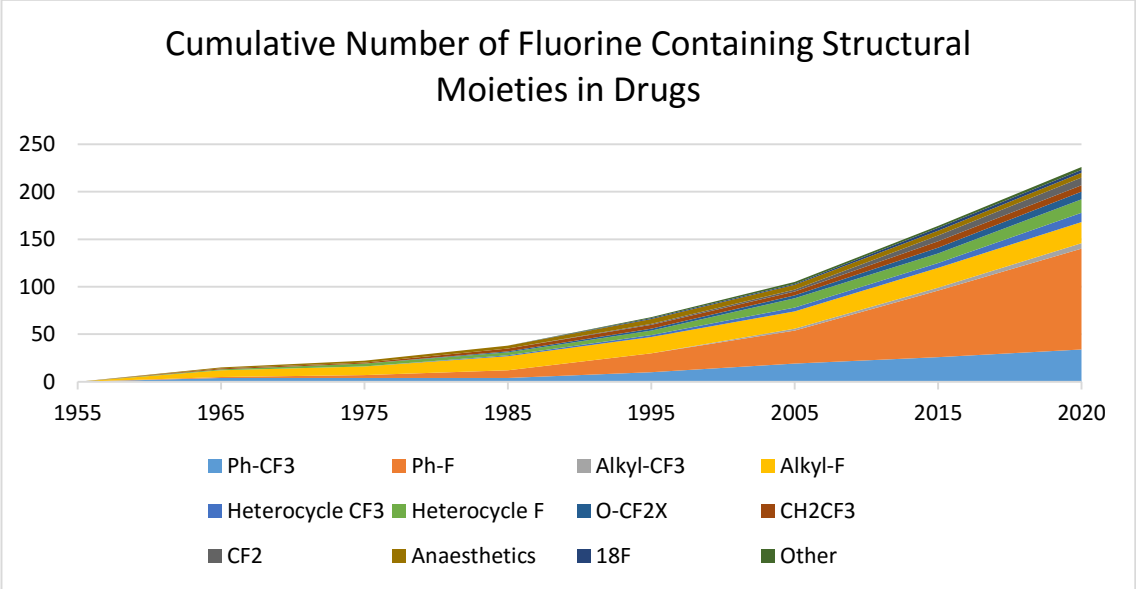


Figure 11: Change of fluorine containing functional groups in FDA approved drugs in the past 60 years.

To enable the emergence of fluorinated systems, synthetic methods for the incorporation of fluorine and fluorinated functional groups have been developed and, with the recent advances in late stage fluorination and fluoroalkylation methods, more complex systems are now accessible on the discovery scale than ever before.[18–20] This advancement will, therefore, increase the need for scalable and economically viable methods for the synthesis of new fluorinated building blocks for API systems on the manufacturing scale beyond drug discovery.

1.1.3 C-F bond formation for the synthesis of life science compounds

Naturally occurring organofluorine compounds are extremely rare, only a handful of them have been isolated[21] and most are derivatives of fluoroacetic acid, which is the metabolite of a fluorinated sugar derivative synthesised by the fluorinase enzyme.[22,23] Therefore, essentially all organofluorine compounds rely on synthetic chemistry to form the carbon-fluorine bond. The formation of C-F bonds has been of interest for over a hundred years and the detailed discussion of existing methodologies is outside of the scope of this review, however, there are excellent books[24–27] and review papers[18,28–34] discussing this topic in detail. In this chapter some fluorination methods will be illustrated using syntheses of life-science products as target molecules to exemplify the use of various fluorinating systems and the types of transformations typically used in life science syntheses.

1.1.3.1 Nucleophilic fluorination methods (C-X → C-F)

One of the most widely used methods for the introduction of a C-F bond into an aliphatic structure is the nucleophilic substitution of a halogen with a fluoride source. Depending on the system this can be very efficient, but when acidic hydrogen atoms are in the α position to the halogen, elimination can lead to significant side product formation. One of the most important applications of this method is the synthesis of trifluoromethyl-aromatic compounds from the corresponding trichloromethyl derivatives using a Lewis acid catalyst to facilitate the transformation (Swarts process). This reaction is still the key step in the synthesis of a large number of trifluoromethylated pharmaceuticals and agrochemicals despite being discovered in the 1920's.

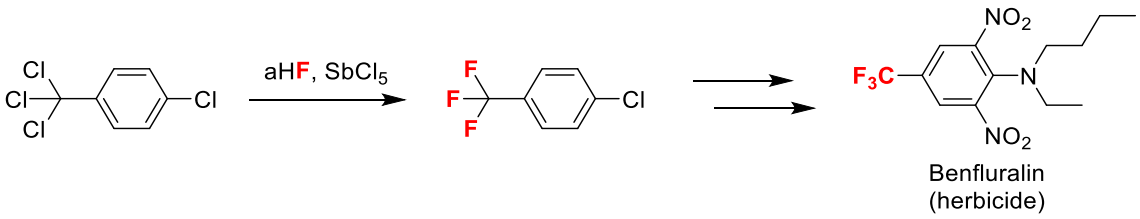
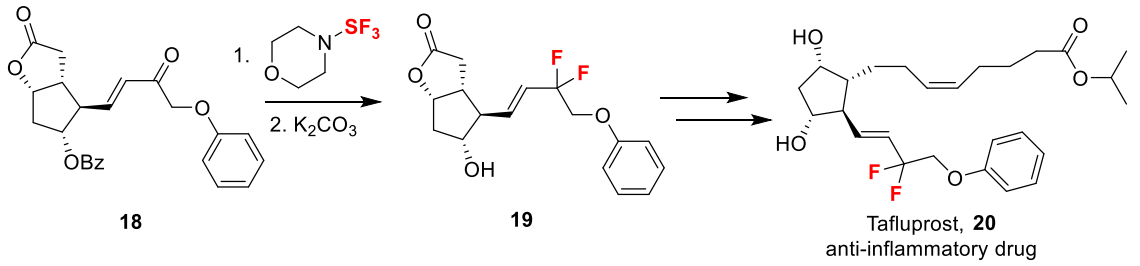


Figure 12: Synthesis of trifluoromethyl-chlorobenzene, a key intermediate in the synthesis of herbicides.[35]

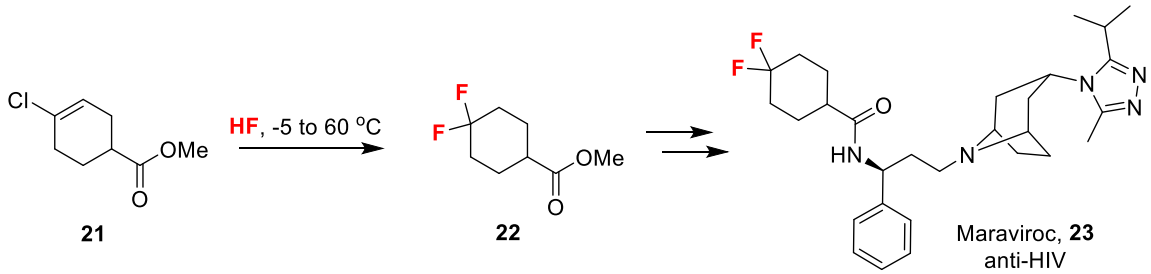
A specific case of nucleophilic fluorination is deoxofluorination. In this case, the fluorinating reagent, most often SF_4 or a formal derivative of this reagent such as DAST, reacts with alcohols, carbonyl compounds and carboxylic acids to afford the corresponding mono-, di- and tri-fluorinated products. The deoxofluorinating reagent not only acts as a fluoride source but, after reacting with the oxygen nucleophile, as a leaving group as well.



18 19

Figure 13: Deoxofluorination of a key intermediate in the synthesis of Tafluprost.[36]

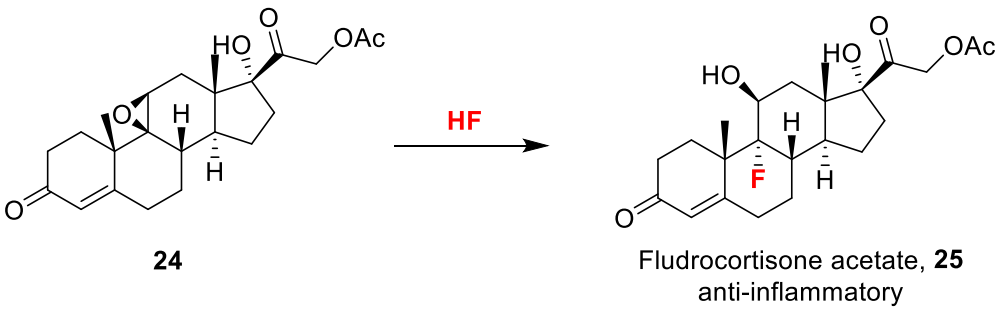
Although direct addition of hydrogen fluoride to olefins looks like an attractive approach to form C-F bonds, this method is not used frequently on hydrocarbon systems, mainly because polymerisation and rearrangements can occur as side reactions. However, this hydrofluorination is used for the fluorination of partially halogenated olefins such as for the synthesis of an intermediate of Maraviroc (**23**), an anti-HIV drug developed by Pfizer.



21 22

Figure 14: HF addition route to Maraviroc intermediate.[37]

The most straightforward synthesis of 2-fluoro alcohols is the reaction of epoxides with a suitable fluoride source. This method has been used for decades for the synthesis of chiral fluorinated systems starting from the chiral epoxide and HF, especially in the case of 9α-fluorocorticosteroids.



24

Figure 15: Synthesis of Fludrocortisone acetate from the corresponding epoxide.[8]

As discussed in Chapter 1.1.2, fluorinated aromatic compounds are the single most frequent sub-units found in fluorinated pharmaceuticals and methods for the incorporation of fluorine into these structures have been subject to research for a long time.[38]

It is without doubt that the most versatile and well known method for aromatic fluorination is the Balz-Schiemann reaction: the transformation of anilines to fluorobenzene derivatives via

diazotisation using either tetrafluoroboric acid (original method), pyridine.HF complex (Olah's reagent) or anhydrous hydrofluoric acid (preferred for industrial scale).[39] The main disadvantage of this reaction is that several synthetic steps are required to convert the aromatic substrate to the fluorinated derivative.

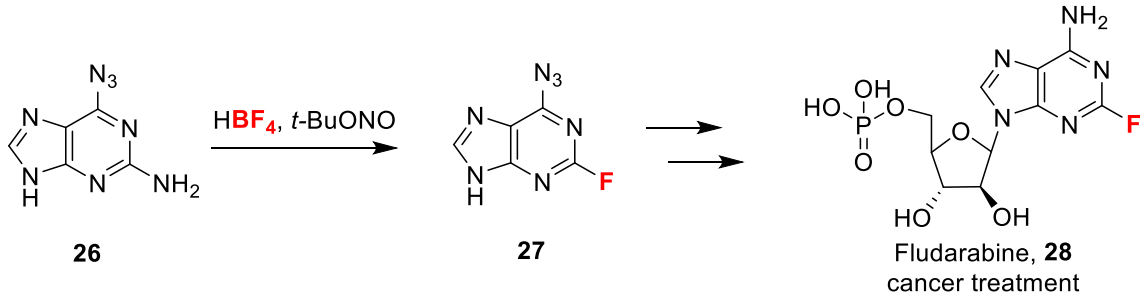


Figure 16: Balz-Schiemann reaction to synthesise 2-fluoropurine intermediate of Fludarabine.[40]

Although the Balz-Schiemann reaction has a broad substrate scope, this method has its limitations as well, for example, in the case of very electron deficient anilines (e.g. polyfluorinated anilines), introducing a fluorine atom using this procedure becomes more difficult and inefficient due to the reduced basicity of the starting anilines.

A commonly used method to synthesise fluoroarenes with multiple electron withdrawing groups is the halogen exchange (Halex) reaction between an activated chlorinated aromatic compound and a nucleophilic fluoride source, most often KF. This method has found applications in the synthesis of poly- and perfluorinated heteroaromatic systems. Recently, several new, late stage aromatic fluorination methods have been developed[41], but these remain in the toolbox of the discovery scientists as they are too expensive for large scale applications and are not discussed here in detail.

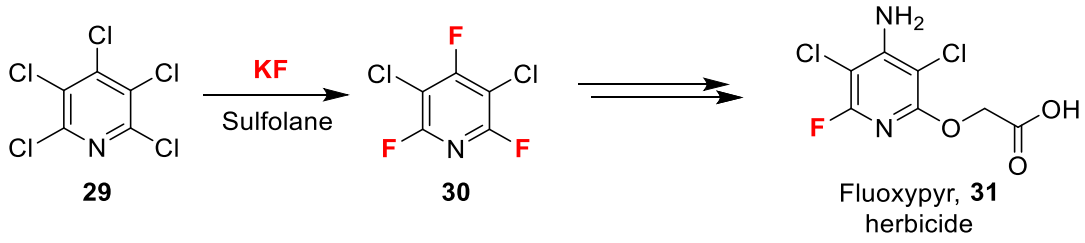


Figure 17: Halex fluorination of pentachloropyridine in the synthesis of Fuoxypyr.[42]

1.1.3.2 Electrophilic fluorination methods (C-H → C-F)

While nucleophilic fluorination methods are well established in the synthesis of life sciences, alternative electrophilic methods are rarely used in manufacturing. The main reason why electrophilic fluorination has not found many large scale applications is the perceived lack of easy to use, inexpensive and safe reagents for this transformation. For decades, the only available electrophilic fluorinating reagents were perchloryl fluoride ($FClO_3$)[43], fluorine gas[29] and O-F reagents, for example, acetyl hypofluorite (CH_3COOF) and trifluoromethyl hypofluorite (CF_3OF)[44]. Although these reagents enabled valuable transformations, they require specialist equipment and precautions for scale up and only fluorine gas is used in the synthesis of a few drug compounds, which is discussed in a later chapter.

In the early 1990's several safe, bench-stable electrophilic reagents were developed belonging to the N-F reagent class. N-Fluoropyridinium salts, Selectfluor™ and NFSI (page 3) were the first commercially available reagents and they have made enormous contributions to synthetic chemistry since their discoveries.[45–47] For example, the introduction of fluorine into electron rich aromatic and heterocyclic compounds is also possible[48,49,50], but because of the high costs associated with these reagents, they are seldom used in large scale processes. Recently, a large scale enantioselective fluorination using NFSI was reported in the synthesis of kilogram quantities of preclinical drug candidate **34** (Figure 18).[51]

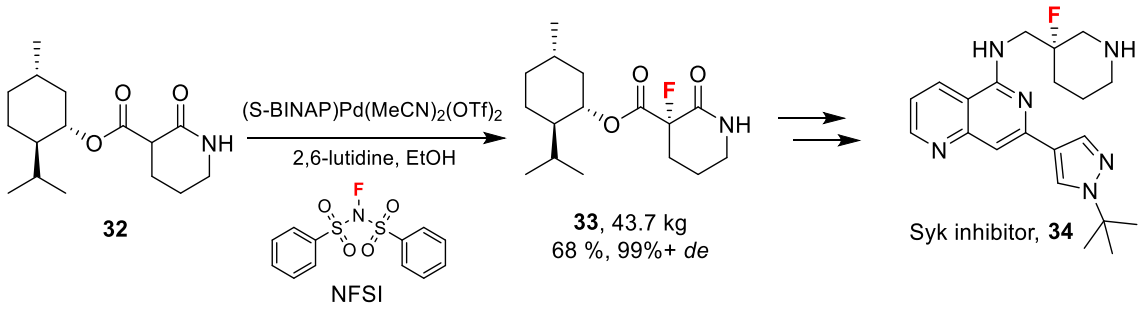


Figure 18: Large scale enantioselective fluorination using NFSI.[51]

In summary, current large-scale fluorination methods described above are typically multistep, nucleophilic fluorine source based reactions involving anhydrous HF, with varying overall yield and selectivity. In contrast, although a large number of electrophilic C-H fluorination processes have been developed for laboratory scale, most of these reactions suffer from expensive reagents with low atom economy, thus, not finding wide spread large scale applications. In theory, the simplest, most inexpensive and convenient C-H to C-F transformation could be achieved using fluorine gas in selective direct fluorination processes, which is the topic of the next section.

1.1.4 Selective direct fluorination

The isolation of elemental fluorine was one of the greatest challenges of 19th century inorganic chemists, and after many failed attempts by the most prominent scientists of the time[52], it was Henri Moissan who succeeded in 1886.[53] Moissan's original method, the electrolysis of HF in the presence of KF, forms the basis of modern, industrial scale F_2 generation, the difference is that the expensive platinum electrodes have been replaced by high surface area carbon and the temperature is increased to 70-130 °C to keep the KF.2HF electrolyte in the molten phase.[54] Today, fluorine gas is commercially available in various forms (pure or diluted with an inert gas) and on different scales, however, large scale users prefer on-site generation.

Figure 19: Solvay Fluor's fluorine gas product range[55] and Linde's on-site fluorine generation system[56].

While the largest scale uses of elemental fluorine are in inorganic chemistry, mainly manufacturing of UF_6 for nuclear energy and SF_6 for the electronics industries, it is also used for the synthesis of organofluorine compounds.[6] The first chemist to react organic compounds with fluorine gas was Moissan, but apart from explosions and the possible isolation of carbon tetrafluoride, not many useful reactions were performed in subsequent decades.[53] The most significant development in perfluorination chemistry using elemental fluorine took place during the Manhattan Project during the Second World War, when the need for chemicals compatible with corrosive UF_6 generated a lot of interest in perfluorocarbons.[57] This application is still a major use of fluorine gas in organic chemistry and advances in this field have been reviewed[29], but the topic is outside the scope of this chapter.

The difficulty of selective direct fluorination reactions is the result of replacing weak fluorine-fluorine (155 kJ/mol)[58] and carbon-hydrogen bonds (440 kJ/mol for CH_3-H) with stronger carbon-fluorine (481 kJ/mol for CH_3-F) and hydrogen-fluorine (569 kJ/mol) bonds.[59] This large amount of reaction heat (ΔH = 445 kJ/mol) needs to be removed from the reaction to minimise undesired side reactions, however, dilution of fluorine with nitrogen, and the use of appropriate, non-reactive solvents is now known to facilitate SDF processes.

The early uses of fluorine gas focused on the direct functionalisation of unactivated C-H bonds in aliphatic systems and it was found that hydrogen atoms in the tertiary position are the most reactive sites.[60–62] The mechanism of this process is described in the literature as an electrophilic aliphatic substitution which is facilitated by the solvent's (for example, chloroform) fluoride acceptor properties.[63]

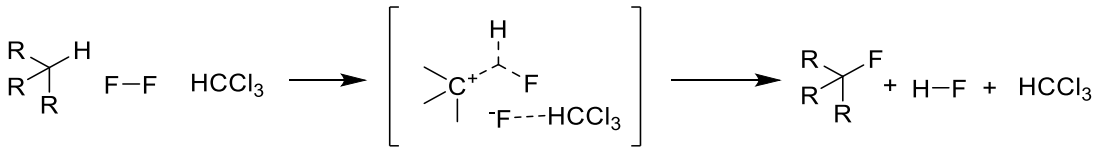


Figure 20: Mechanism of the electrophilic aliphatic fluorination of a tertiary hydrocarbon.[63]

This proposed mechanism is further supported by the fact that this C-H fluorination reaction proceeds with the complete retention of stereochemistry which was observed during the direct fluorination of various steroid derivatives.[64–66] Secondary C-H bonds can also be functionalised, but the lack of selectivity of the reaction does not make this a synthetically useful method.[67]

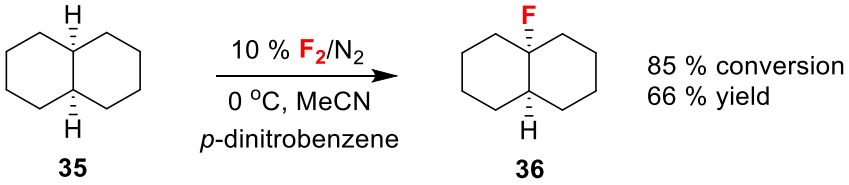


Figure 21: Direct fluorination of *cis*-decalin with the retention of stereochemistry.[68]

An important C-H fluorination reaction is the direct fluorination of ethylene carbonate in the manufacturing of monofluorinated derivative **38** which is used in lithium batteries as an electrolyte solvent.[69]

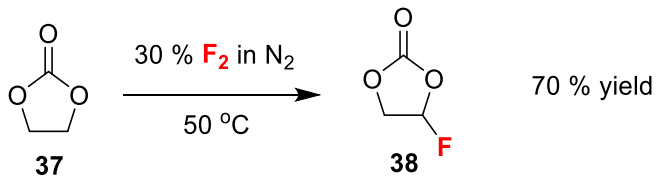


Figure 22: Direct fluorination of ethylene carbonate.[69]

Active methylene compounds, especially 1,3-dicarbonyl derivatives, are some of the most widely used substrates to demonstrate the effectiveness of electrophilic fluorinating reagents, but elemental fluorine was found to be too reactive to be used for this transformation for a long time.[70] One of the early methods, reported by Purrington, used TMS-enolates in $CFCl_3$ at cryogenic temperatures with dilute (5 % in nitrogen) fluorine gas to successfully fluorinate malonate derivatives in good yield (59 – 73 %)[71], however, the Montreal Protocol banned the use of chlorofluorocarbons (CFCs), making this process obsolete.

In the early 1990's Chambers and co-workers discovered that the selective fluorination of 1,3-dicarbonyl compounds can be achieved in formic acid solution using 10 % fluorine in nitrogen via electrophilic fluorination of their respective enolates. They found that the conversion depends on the enol content in equilibrium and kinetics of the enolisation of the carbonyl compound, for example, ethyl acetoacetate (fast enolisation) gives much higher conversion than ethyl 2-methylacetoacetate (slow enolisation).[72] The introduction of a second fluorine atom to the 2-position is much slower than the first fluorination reaction, which makes it possible to isolate the monofluorinated products in good yields.[73] This fluorination methodology was adopted by industry and is currently used in the manufacturing process of Pfizer's antifungal drug Voriconazole (**41**).[74]

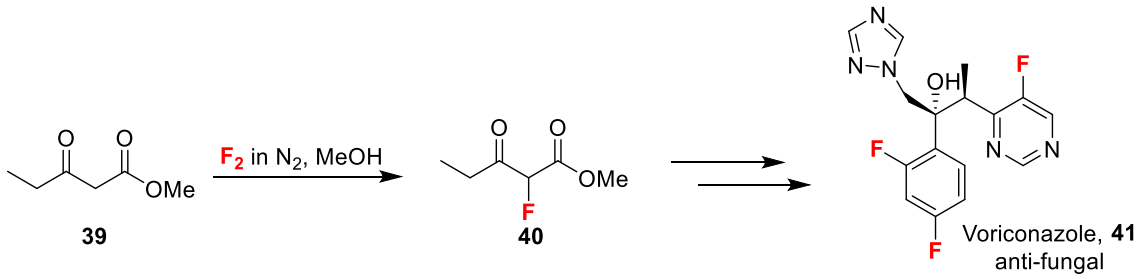


Figure 23: Direct fluorination of methyl 3-oxopentanoate in the synthesis of Voriconazole.[74]

Malonate derivatives do not enolise as easily as ketoesters or diketones, therefore, their fluorination was originally performed in the presence of a strong base in acetonitrile solvent and, depending on the amount of the base used in the reaction, mono- and difluorinated diethyl malonate esters were obtained as the major products.[75] To improve the conversion of these fluorination processes, the Durham group developed a Lewis-acid catalysed method for the fluorination of 1,3-dicarbonyl compounds which also enabled the catalytic fluorination of malonate esters,[76] but the use of chiral BINOL ligands in combination with the metal catalyst did not lead to any enantio-enrichment of the fluorinated product.[77]

To gain better control over the fluorination process and to minimise polyfluorination, continuous flow micro-reactors were developed in Durham[78] that allowed the fluorination of ethyl acetoacetate to progress in higher conversion and selectivity than in typical batch reactions.[79]

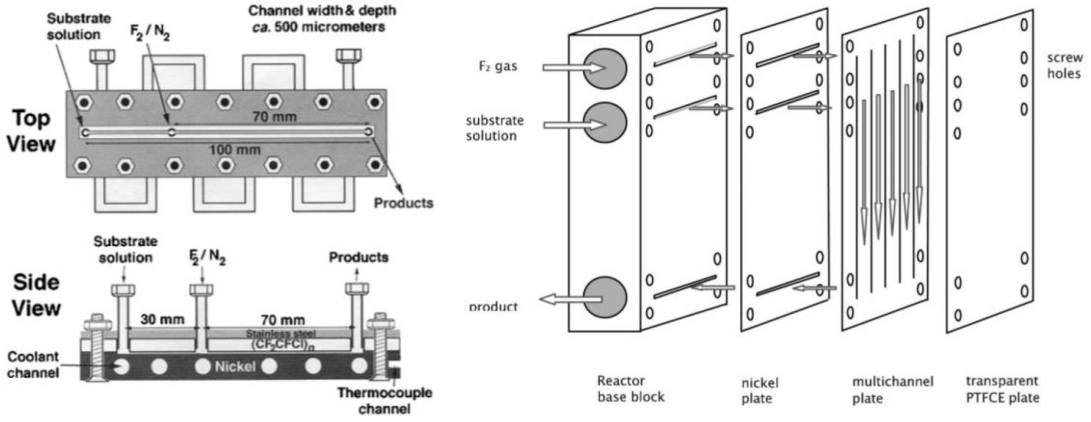


Figure 24: Single- and multi-channel microreactors for continuous flow fluorination.[79,80]

To increase the scale of operation from a single reaction channel, multi-channel reactors were designed (up to 30 channels) which allowed the fluorination of over 100 g of a dicarbonyl compound in 24 hours.[80] Recently, continuous flow fluorination techniques were used in a two-step fluorination-cyclisation process to synthesise 4-fluoropyrazole derivatives.[81]

When the conditions of the dicarbonyl fluorination method were extended to TMS-enolates and enol acetates it was found that the latter are better substrates in this reaction because of their higher stability in acidic solution, but even with these substrates, the main side products were the parent ketones from the hydrolysis of the enolates.[82]

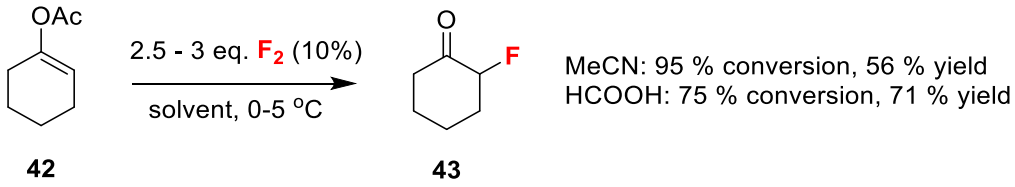


Figure 25: Direct fluorination of cyclohexanone enol acetate.[82]

Direct electrophilic aromatic fluorination has been the subject to research for a long time especially that it is the direct, attractive alternative of the multistep Balz-Schiemann reaction. Following the pioneering work of Grakauskas on the fluorination of benzene and a few derivatives,[83] in the early 1980's Misaki reported the direct fluorination of phenolic compounds and, while most reactions gave the expected mixture of *o*- and *p*-substituted phenols, the fluorination of *p*-cresol (**44**) led to a mixture of 2-fluoro-*p*-cresol (**45**) and de-aromatised product **46**.[84,85] Although electron rich aromatic compounds react very efficiently with fluorine, the formation of large amounts of polymeric tar significantly reduced the isolated yields [86] which is not improved significantly by carrying out the reaction in continuous flow[87].

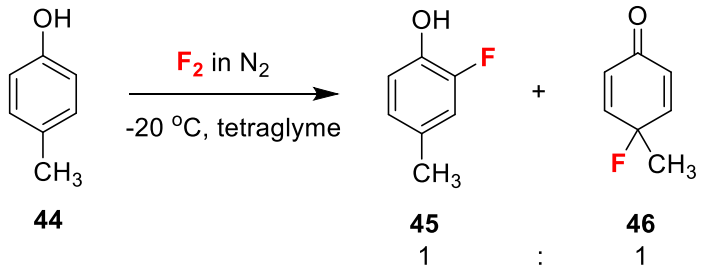
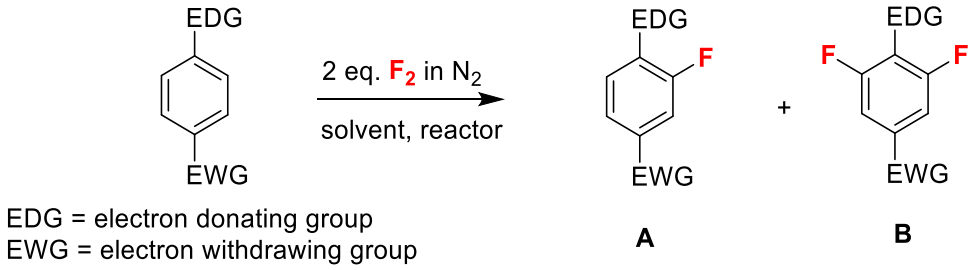
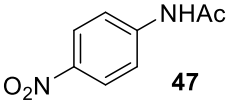
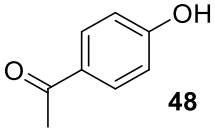
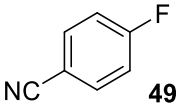
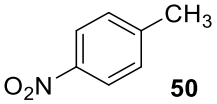
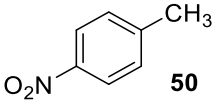
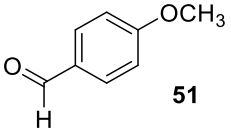


Figure 26: Direct fluorination of *p*-cresol.[84]

When electron deficient benzene derivatives are subjected to direct fluorination, high conversion and good selectivity can be achieved by the use of appropriate, protic solvents, for example, formic and sulfuric acid.[88,89]

Table 1: Direct fluorination of 1,4-disubstituted aromatic systems.



Benzene derivative	Solvent	Reactor	Conversion	A Yield	B Yield
 **47**	HCOOH	Batch	100 %	60 %	8 %
 **48**	HCOOH	Batch	83 %	41 %	7 %
 **49**	HCOOH	Batch	67 %	40 %	Trace
 **50**	HCOOH	Batch	63 %	50 %	Trace
 **50**	H_2SO_4	Batch	75 %	81 %	2 %
 **51**	MeCN	Flow	91 %	82 %	7 %

Chambers and co-workers reported the fluorination of a range of 1,4-disubstituted benzene derivatives both in batch and continuous flow regimes (Table 1.),[90–92] which demonstrated clear

trends for fluorination reactions. For example, under identical conditions, the electron donating group has a large effect on the conversion, giving 100 % conversion for 4-nitroacetanilide (**47**) compared with 63 % for 4-nitrotoluene (**50**), however, the large difference between conversion and yield suggests significant tar formation in the case of the acetanilide. Similar difference can be observed between the solvent that is used for this reaction, in the case of 4-nitrotoluene, sulfuric acid gives significantly higher conversion and yield. Carrying out the reactions has a distinct effect on selectivity, these reactions have noticeably less di-fluorinated side product in the crude reaction product. The low conversion of 1,3-dinitrobenzene suggests a very sluggish reaction between fluorine and very electron deficient aromatic systems. The fluorination of the benzene ring of quinoline systems is also possible, but to achieve good conversion, large excess of fluorine is required together with 30 % oleum as a reaction solvent.[93]

Uracil and related pyrimidines were the first heteroaromatic compounds that were fluorinated using fluorine gas in the early 1970's, and this synthesis of 5-fluorouracil was the first selective direct fluorination process that was operated on the manufacturing scale.[94]

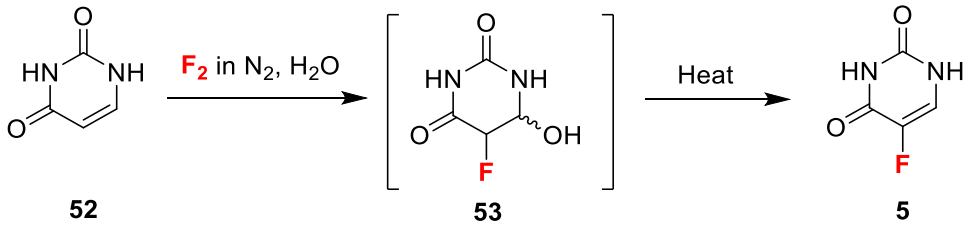


Figure 27: Direct fluorination of uracil.[94]

Pyridines, on the other hand, when reacted with elemental fluorine at low temperatures, form N-fluoropyridinium fluorinating reagents which were described above. Other heteroaromatic systems that were successfully fluorinated using fluorine gas include purine[95], 1,5-naphthydrine[96] (Figure 28) and flavones[97].

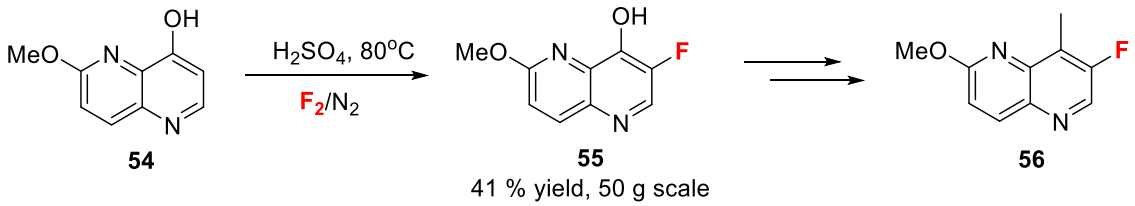


Figure 28: Direct fluorination of a 1,5-naphthydrine.[96]

One of the most characteristic reactions of the halogen elements is their electrophilic addition to olefins and it is not surprising that this was one of the early reactions attempted with fluorine gas, but unlike chlorine or bromine, the direct addition of fluorine proceeds with *syn* stereo-selectivity. This unexpected result was explained by a carbocationic intermediate and a fluoride ion coming from the same F_2 molecule in a "tight ion pair" process.

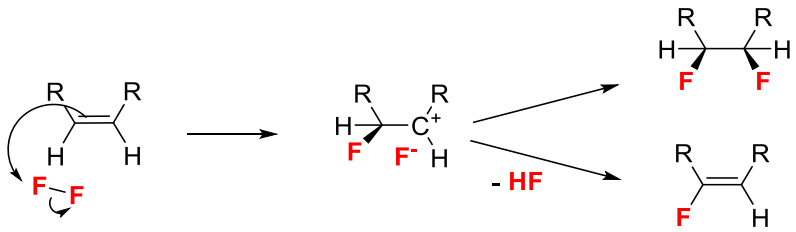


Figure 29: Proposed mechanism for the *syn* addition of fluorine to olefins.[98]

This mechanism also explains the presence of trifluorinated side products, where the first carbocation eliminates a proton to give a fluoroolefin which then reacts with another F_2 molecule.[98] This mechanism was confirmed by a recent mechanistic and computational study using transannular dienes by Fokin and co-workers.[99] Direct addition of fluorine can also be used to synthesise tetrafluoroethyl-benzenes from phenylacetylenes[100] and di- and trifluoronucleosides[101].

In conclusion, over the past 40 years, elemental fluorine has been shown to be a viable reagent for direct fluorination of organic systems and a lot of understanding of the mechanism of SDF processes has been gained. Despite the advances in the safe handling of this reagent, such as the introduction of continuous flow reactors, fluorine is still generally regarded as an unsafe, non-selective reagent by the organic chemistry community and only a handful of processes are operated on the manufacturing scale.

From a green chemistry perspective, to the best of our knowledge there is no literature available on metrics analysis of C-F bond formation, however, there is no significant difference between methods from a safety point of view, as essentially all C-F bonds are derived from anhydrous HF. The selective direct fluorination approach offers the formation of the C-F bond in a single step, therefore should, in theory, be more efficient and less wasteful than the alternative multi-step processes. This thesis aims to assess the use of F_2 as a viable, greener reagent for the construction of C-F bonds in compounds using green chemistry methodologies and also an introduction to the principles of green chemistry and metrics based analysis follows.

1.2 Green Chemistry Toolkit

Green chemistry is concerned with the design of safer, less wasteful and environmentally benign chemical products and processes. As a field of chemistry, it emerged at the end of the 20th century, as a response to deleterious environmental issues caused by the chemical industry during a period of exceptional growth following the Second World War and it has been the focus of intensive research over the past twenty years. It is important to mention that green chemistry not only includes the manufacture and use of chemical products, but involves the whole life-cycle, therefore, several metrics have been developed to numerically assess the impact of chemical manufacturing methods on the environment.

This chapter aims to provide an introduction to this field with a special focus on the synthesis of APIs, solvents and methods to measure and compare different processes from a green chemistry point of view.

1.2.1 Green chemistry principles

In the late 1990's Anastas and Warner were the first to summarise the field of green chemistry in their monograph "Green Chemistry: Theory and Practice" where they introduced their 12 Principles of Green Chemistry that highlight key areas of interest in the development of environmentally benign processes.[102]

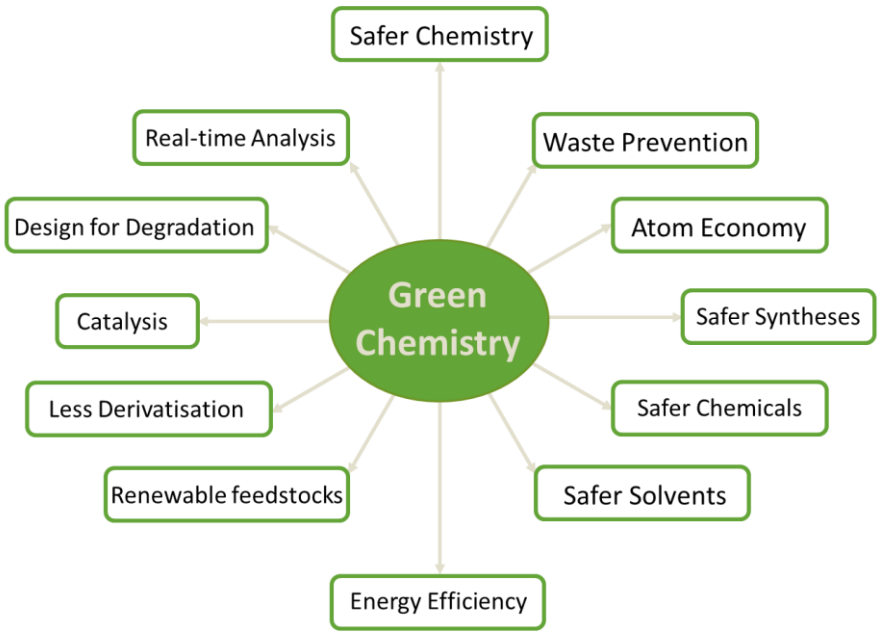


Figure 30: Keywords describing the 12 principles of green chemistry.[102]

These principles are a clear representation of all the issues that lead to the emergence of green chemistry, with safety being the number one area of concern, from safer processes to safer chemical products. The second most important message from these principles is efficiency, where waste prevention, less derivatisation and atom economy clearly emphasise the need for

more efficient synthetic processes that, in turn, will be more profitable. Interestingly, sustainability is not in the centre of these principles, bio-renewable feedstocks being the only reference to this important topic. Although the principles represent a holistic view on how a greener chemical process should be designed, they are often taken out of context and misused by synthetic chemists assuming that focusing on one aspect of green chemistry makes the whole process greener while, in general, this is not the case.[103]

1.2.2 Green chemistry in the pharmaceutical industry

The chemical industry is one of the largest contributors to global environmental pollution and this is in part due to the manufacturing processes that transform simple hydrocarbons to sophisticated organic systems. Depending on the complexity of the target molecule, manufacturing of APIs can involve up to several dozens of synthetic steps which all add up to a large waste to product ratio.[104]

Table 2: Typical E factor values in the chemicals industry.[104]

Industry segment	Volume (t/y)	E factor ($kg_{waste}/kg_{product}$)
Bulk chemicals	10^4 - 10^6	<1 – 5
Fine chemicals	10^2 - 10^4	5 – 50<
Pharmaceuticals	10 - 10^3	25 – 100<

The syntheses of Active Pharmaceutical Ingredients (APIs) are some of the smallest scale manufacturing processes in the chemical industry, often due to the very high bio-activity or the small number of patients in some rare disease areas, but because of the multistep nature of these reactions APIs produce the largest amount of waste per kg of product manufactured (Table 2). To address this issue, in the past 10-15 years pharmaceutical companies have been investing into various green chemistry programs, for example the ACS Green Chemistry Institute's Pharmaceutical Roundtable, where industry-wide benchmarking methods are developed in a non-competitive environment.[105] The main areas where the pharmaceutical industry has contributed significantly to the advancement of green chemistry are green metrics and qualitative guidelines to facilitate the selection of greener solvents, reagents and processes and these issues are discussed next.

1.2.3 Solvents

A recent cradle-to-gate Life Cycle Assessment (LCA) of a typical pharmaceutical product highlighted that solvents alone are the largest contributor to the environmental impact.[106] They are not only responsible for 75 % of the energy use, but contribute over 80 % of life cycle mass

(excluding water), 70 % of Photochemical Ozone Creation Potential and 50 % of Green House gas emissions. When process water is included in the mass input analysis of a manufacturing process, solvents account for over 50 % of the total mass (Figure 31).[107]

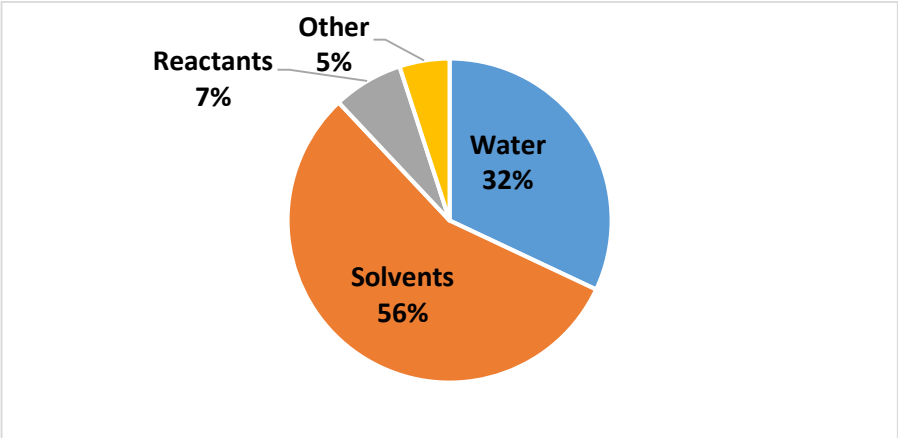


Figure 31: Composition of input materials by mass in the synthesis of an API.[107]

Environmental impact is only one of the areas where solvents have a large contribution with safety and health hazards being other, even more important aspects. These three factors form the basis of several solvent guides that were published by Pfizer[108], GSK[107] and Sanofi[109] and the EU IMI Chem21 network[110]. In a recent review of solvent guides[111] it was highlighted that there is an agreement between the surveyed guides about over 65 % of the commonly used solvents, showing that different methodologies and priorities lead to similar classification of solvents.

In general, alcohols, esters and ketones are the most acceptable 'green' solvents, with only the very volatile systems having some safety issues. On the other hand, hydrocarbons, haloalkanes and ethers are usually in the undesirable category, mostly because of health and safety reasons, for example, peroxide formation in ethers or low ignition point. Dipolar aprotic solvents are very often used in the synthesis of polar APIs, but several of these have acute toxicity that makes them undesirable, therefore, finding safer replacements for such solvents is a key area of green chemistry research.[112] Also, there are solvents that are in the hazardous or highly hazardous categories, for example, benzene, chloroform or carbon tetrachloride for their known carcinogenicity or nitromethane for its potentially explosive property.

Table 3: Overall ranking of solvents based on 5 different guides.[111]

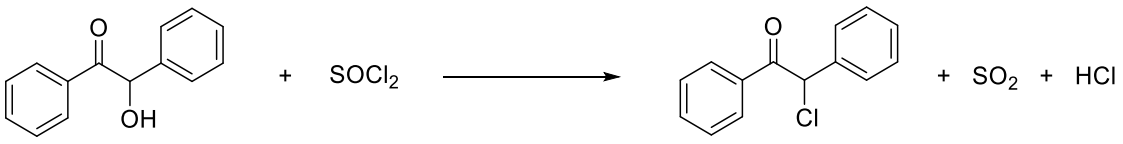
Recommended	Water, EtOH, i-PrOH, *n*-BuOH, EtOAc, i-PrOAc, *n*-BuOAc, anisole, sulfolane
Recommended or Problematic	MeOH, *t*-BuOH, benzyl alcohol, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, MeOAc, AcOH, Ac_2O
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylenes, chlorobenzene, acetonitrile, DMPU, DMSO
Problematic or Hazardous	MTBE, THF, cyclohexane, DCM, formic acid, pyridine
Hazardous	Diisopropyl ether, 1,4-dioxane, DME, pentane, hexane, DMF, DMAc, NMP, methoxy ethanol, TEA
Highly Hazardous	Diethyl ether, benzene, CCl_4, chloroform, DCE, nitromethane

While these guidelines have been developed to help scientists find safer, more acceptable solvents for the reactions they are carrying out, there are no strict rules and every case should be properly assessed to find the most suitable solvent for a given process. Implementing these guides in discovery laboratories can also make a significant difference, for example, replacing DCM - methanol mixtures used for chromatography with ethyl acetate - ethanol at Amgen's Drug Discovery Department lead to a 60 % reduction in the use of DCM between 2010 and 2013.[113]

1.2.4 Assessing and measuring greenness

Yield has been used as a measure of success of chemical reactions for hundreds of years but a detailed comparison of different processes is now required to assess the environmental impact of competing possible manufacturing routes.

Atom Economy (AE) was the first alternative metric that is capable of comparing different transformations. It was introduced in 1991 by Trost to evaluate the efficiency of synthetic transformations based on how many atoms of the starting materials are actually incorporated into the final product. [114] However, as a metric, AE has serious limitations as it only compares the net reactions, does not include solvent usage, stoichiometry, work-up, yield and other very important process parameters. The advantage of this metric is that it allows quick assessment of alternative synthetic routes without conducting any experiments and shows the best possible outcome (100% yield, 1 : 1 stoichiometry) for the reactions.



57
MW = 212.25
m = 21.2 g

MW = 118.96
m = 25.1 g

58
MW = 230.69
m = 19.3 g
84 % yield

$$AE = \frac{Molecular\ Weight\ of\ Product}{Total\ Molecular\ Weight\ of\ Reactants} \times 100$$

$$AE = \frac{230.69}{212.25 + 118.96} \times 100 = \mathbf{70}$$

$$RME = \frac{Mass\ of\ Isolated\ Product}{Total\ Mass\ of\ Reactants} \times 100$$

$$RME = \frac{19.3}{21.2 + 25.1} \times 100 = \mathbf{42}$$

Figure 32: AE and RME calculations of a single step reaction.[115]

Reaction Mass Efficiency (RME) is a variation of atom economy, where yield and reactant stoichiometry are taken into account in the calculations. In the literature there are several ways to calculate RME[116–118] but in this thesis the simplest and generally accepted method is used: dividing the isolated product mass by the sum of the masses of reactants appearing in the reaction equation (Figure 32). Even though RME gives a better indication of the real efficiency of a reaction than AE, it does not account for the work-up chemicals, solvents and other auxiliaries which are the largest contributors to the reaction mass and waste.

The first quantitative metric that took all materials involved in a synthesis into consideration was Sheldon's Environmental Factor ($E = \frac{m\ waste}{m\ product}$) which found wide spread application in process development.[119] The minimum theoretical value for E factor is 0, meaning that no waste is generated in the synthesis of a compound but process water is generally not included because the quantities used would mask the effect of all other factors.

Process Mass Intensity is a very similar metric to the E factor, the only difference is that it includes all input material in the equation ($E = \frac{total\ m\ in\ process}{m\ product}$) meaning it can be expressed easily from the E factor just by adding 1.[120] Members of the ACS GCI Pharmaceutical Roundtable have argued that PMI is a better method to describe processes mostly from a philosophical point of view as it does not focus on waste but on materials used for the production of the high value commercial product. This has also been supported by LCA analysis that shows that the input materials have a much larger contribution to life cycle impacts than waste and waste treatment. Consequently, lowering the amount of all input materials is more important than minimising waste.[120] While E factor and PMI are both useful tools to analyse and improve processes, neither

of these metrics give qualitative information on the chemicals used in the process. The most complete assessment of any chemical product is Life Cycle Assessment (LCA) which includes mass balances, energy usage and CO_2 emission measurements not only for the manufacturing process but also for transport, formulation and waste treatment.

Although there exist some complex metrics packages[121–123], to address the need for a metrics system that provides both qualitative and quantitative data on processes, the Chem21 network developed a new, holistic metrics package.[124] The package consists of four different levels of complexity: 'Zero Pass' evaluates screening level reactions, 'First Pass' is to compare optimised reactions with literature alternatives, 'Second' and 'Third Pass' are for pilot and manufacturing scale operations. The 'First Pass' metrics package is the most appropriate for the assessment of laboratory scale, therefore, in this thesis it is used for the assessment of fluorination reactions. This metrics package was developed as an internal Chem21 website based spreadsheet (Table 4), which is automatically populated and analysed from uploaded experimental and safety data. Yield, Conversion and Selectivity have pre-set values for the colour coding, the solvents are ranked based on the Chem21 selection guide[110] while health and safety ranking is based on the data obtained from material safety data forms of the chemicals used. The colour coding is not intended to make decisions on certain aspects of the reaction, but are to raise attention and highlight areas for improvement or concern. A very useful aspect of the database is the breakdown of the PMI numbers into different sub-values which further helps process improvement by showing areas where the largest contribution to the overall value come from. Even though this package is easy to handle and very informative for the assessment of single step reactions, in this form, it is not easy to use for the assessment of multi-step reactions. The assessment of these reactions can, however, be helped significantly by this toolkit by analysing them in single steps and combining the data.

Table 4: First Pass metrics datasheet for a single step reaction.

Property	Value	Flags
Yield	x %	
Conversion	x %	
Selectivity	x %	
Reaction Mass Efficiency	X	
Atom Economy	X	
Solvents		
Health and Safety		
Mass Intensity: Total		
Mass Intensity: Reaction		
Mass Intensity: Reaction chemicals		
Mass Intensity: Reaction solvents		
Mass Intensity: Workup		
Mass Intensity: Workup chemicals		
Mass Intensity: Workup solvents		
Catalysts used		
Catalysts recovered		
Reactor		
Elements		
Energy		
Work up		

In conclusion, the analysis and comparison of chemical processes from a green chemistry point of view is possible now that there are a number of methods available for the practicing chemists, however, it is very important to use the right tools for a given problem. When comparing in-house reactions with literature data, it is crucial to select the benchmark carefully and to be consistent when making assumptions on material usage in processes when data is not available.

1.3 Conclusion

The growing abundance of fluorinated systems in drug discovery and life science products increases the demand for greener, scalable and economically viable methods for the formation of C-F bonds.[112] Elemental fluorine has the potential to fulfil these requirements as it is a potentially atom economic, inexpensive reagent produced routinely on the manufacturing scale, even though, it's use in organic synthesis has not been widely adopted.

Chapter 2.: Direct Fluorination of Malonate Esters

2.1 Aims

This thesis aims to establish whether elemental fluorine is a viable green fluorinating reagent for the direct transformation of C-H bonds to C-F bonds using a quantitative green metrics approach. To achieve this, selective direct fluorination methods will be developed for a range of model substrates. During the optimisation of these processes special emphasis will be placed on the green chemistry aspects, for example, solvent selection, work-up, process intensification and the potential for catalysis. The optimised processes will be assessed using the green chemistry tools described in Chapter I.: mass based metrics calculations and qualitative comparison of chemicals used in the processes.

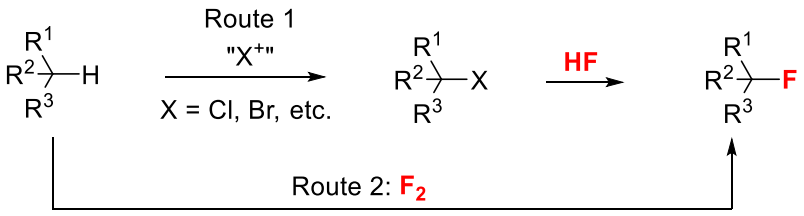


Figure 33: Potential routes to aliphatic fluorinated compounds.

For aliphatic fluorinated compounds direct fluorination reactions (Route 2) will be compared with alternative nucleophilic fluorination methods (Route 1) that have been reported in the literature and are used in large scale manufacturing processes. These typically multistep processes (Figure 33) should, in theory, be less atom economic and potentially more wasteful than direct fluorination reactions. The difference in step-count is even larger for the synthesis of fluorinated aromatic compounds as these are almost exclusively manufactured using the Balz-Schieman reaction which starts with the nitration of the parent compound followed by reduction, diazotation and fluorination using HF.

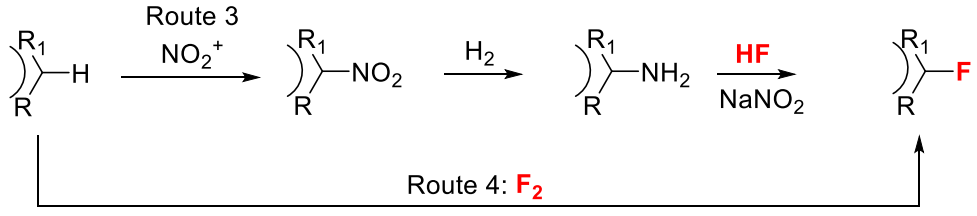


Figure 34: Direct fluorination and Balz-Schiemann approaches to aromatic fluorination.

In principle, selective direct fluorination is the most straightforward and atom-economic approach for the transformation of C-H bonds to C-F bonds, therefore, if a simple isolation and purification method can be developed, SDF processes may be able to compete with the

alternative syntheses. In this thesis, appropriate life-science starting materials will be used in the studies, for example, malonate esters, aromatic and heterocyclic compounds and steroid derivatives. Once optimised, the processes will be compared to existing manufacturing processes using green chemistry metrics, to establish whether direct fluorination could be used as a realistic alternative. To the best of our knowledge, no such comparative study exists in the literature on C-F bond forming reactions and hopefully these analyses will facilitate the acceptance of fluorine as a viable reagent by the wider chemistry community.

2.2 Selective direct fluorination of malonate esters

Malonate esters are very important building blocks in organic synthesis, their chemistry is very well developed[125] and a wide range of alkylation, acylation, Knoevenagel, aldol, reduction, Michael addition, nucleophilic substitution and annelation processes are utilised in many important syntheses. They frequently appear in retrosynthetic planning strategies from University sophomore classes onwards. In comparison, however, corresponding chemistry of dialkyl fluoromalonate esters is not developed to any great extent and only a few examples of various alkylation[126–128], Michael addition[129–132] and heterocycle formation[133–136] processes have been described previously, providing an indication of the potential synthetic utility of this multi-functional, selectively fluorinated system. We reviewed the synthesis and reactions of fluoromalonate esters recently.[137]

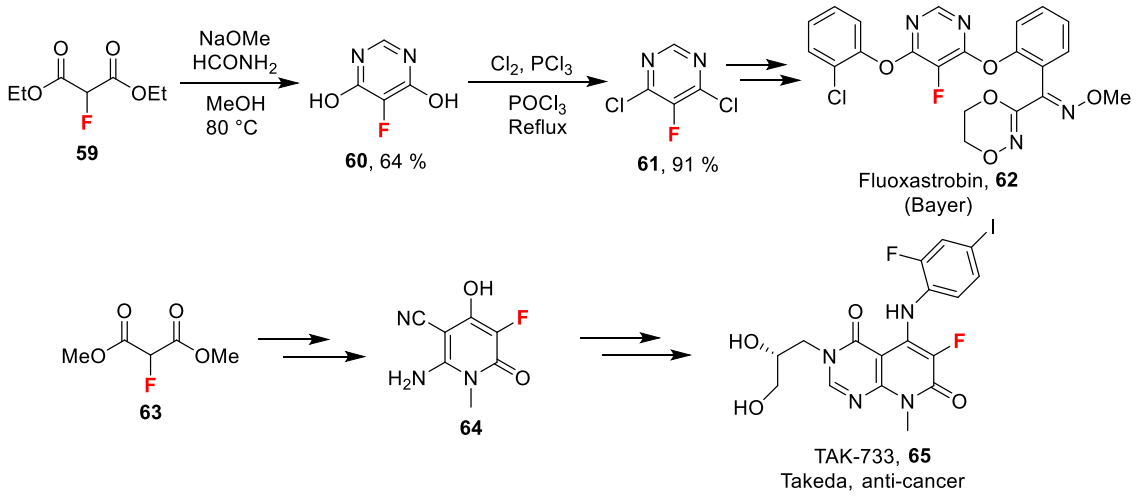


Figure 35: 2-Fluoromalonate esters used in the synthesis of Fluoxastrobin and TAK-733.

A growing number of patents utilising fluoromalonate as a substrate for the synthesis of a range of biologically active systems have been published recently[138–141] and reviewed[137]. For example, Fluoxastrobin (Fandango®), a fungicide marketed by Bayer CropScience that has achieved global annual sales of over €140m since its launch in 2005[142,143], and TAK-733, an anti-cancer drug candidate[144], employ 2-fluoromalonate esters as the key fluorinated starting material (Figure 35).

The relatively recent developments in fluoromalonate chemistry are most probably due to the commercial availability of dimethyl and diethyl fluoromalonate at reasonable prices from speciality chemical suppliers. No special handling procedures are required when using fluoromalonate esters for synthetic processes beyond employing the usual laboratory and industrial safety precautions.

Given the existing use of fluoromalonate esters in commercial manufacturing processes, our initial studies in the use of a green metric approach to fluorination concerned the comparison of current fluorination methodologies for the synthesis of 2-fluoromalonate esters with a direct fluorination approach.

2.3 Synthesis of dialkyl 2-fluoromalonate esters[137]

The synthesis of 2-fluoro-1,3-dicarbonyl systems is possible using electrophilic and nucleophilic fluorination methodologies but not all methods are suitable for the large scale manufacture of these compounds. Below, methods for the preparation of fluoromalonate esters is briefly reviewed with a focus on identifying synthetic routes with a potential for large scale application.

2.3.1 Electrophilic fluorination of malonate enol derivatives

Replacement of methylene hydrogen atoms of malonate esters by fluorine using an electrophilic fluorinating agent offers the most direct method for the synthesis of fluoromalonate esters and, over the last 60 years, several procedures have been developed using the fluorinating reagents available at the time. The first example of fluorination of malonate esters using perchloryl fluoride ($FClO_3$) was published in 1958.[145] When $FClO_3$ was passed through an ethanolic solution of sodium diethyl malonate, a 50 : 50 mixture of diethyl malonate and diethyl 2,2-difluoromalonate was obtained rather than the expected diethyl 2-fluoromalonate while two equivalents of NaOEt and $FClO_3$ gave pure diethyl 2,2-difluoromalonate in high yield. Fluorination of a small range of 2-substituted malonic esters gave the corresponding fluoromalonate product, however, this fluorination methodology was not widely adopted because of the highly oxidising and potentially explosive nature of perchloryl fluoride.

In the 1980's, the development of novel electrophilic fluorinating reagents of the O-F and N-F class allowed the synthesis of a wider range of 2-fluoro-1,3-dicarbonyl systems. Acetyl hypofluorite (CH_3COOF), developed by Rozen, was the first successful reagent to monofluorinate 1,3-dicarbonyl systems in reasonable yield and purity (Figure 36a).[146] *N*-Fluoro-2-pyridone can conveniently be prepared from 2-trimethylsiloxy pyridine with elemental fluorine (5% in N_2)[147] and is capable of fluorinating sodium dialkyl malonates, but yields are poor, reaching only 39% in the case of diethyl 2-phenylmalonate (**69**, Figure 36b). *N*-Fluoro-*N*-alkylsulfonamides, introduced by Barnette[148] in the early 1980s, were prepared by passing dilute (3-5 % in N_2)

fluorine gas through a solution of the corresponding sulfonamide in an inert solvent and their fluorinating power was demonstrated by reaction with a series of carbanion systems, most of which gave the desired monofluorinated product in good yield.[148] Similarly, DesMarteau synthesised a range of *N*-fluoro-perfluoroalkylsulfonimides[149] from elemental fluorine that readily react with carbanionic substrates and essentially give the fluorinated product in quantitative yield (96 % for diethyl 2-methylmalonate) but their hazardous preparation (use of neat fluorine that is liquefied during the reaction) precludes widespread use of these reagents. More recently another class of *N*-fluorosulfonamide was developed that uses oxathiazione dioxides as easily accessible starting materials.[150] The most stable and promising fluorinating reagent is benz-1,2,3-oxathiazin-4-(3-F)-one 2,2-dioxide which fluorinates various carbon nucleophiles (Figure 36c). Similarly, for the fluorination of carbanions, *N*-fluoro-2,4,6-trimethylpyridinium triflate (trifluoromethanesulfonate) was found to react with the diethyl malonate sodium salt to give diethyl 2-fluoromalonate and other, substituted malonates provided access to the corresponding fluorinated products in high yield.[45] Recently a hypervalent iodine reagent based synthesis has also been published (Figure 36d).[151]

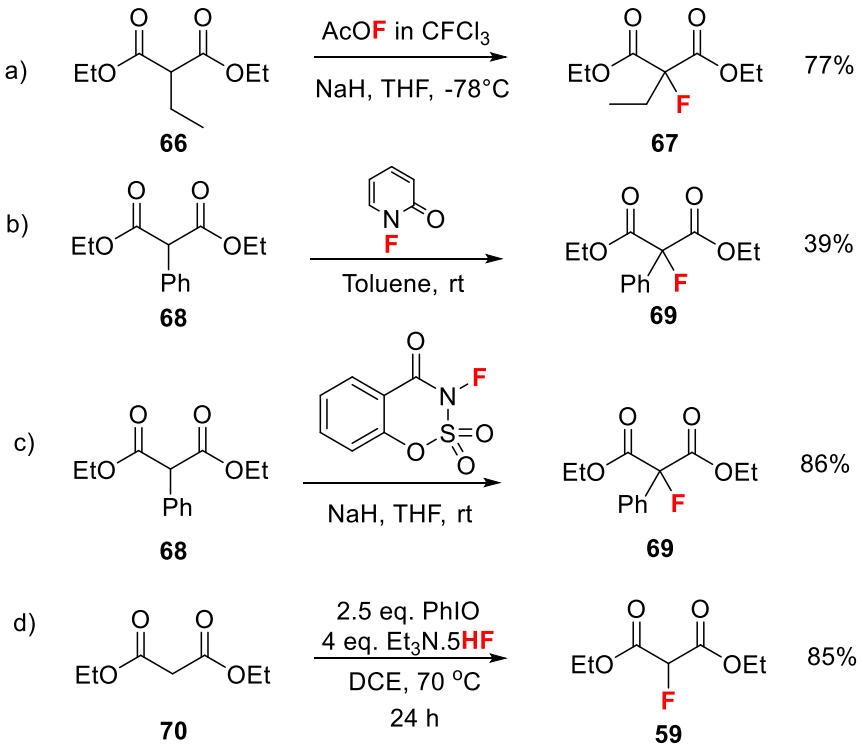


Figure 36: Initial processes for the synthesis of 2-fluoromalonate esters using (a) acetyl hypofluorite; (b) N-fluoropyridone; (c) benz-1,2,3-oxathiazin-4-(3-F)-one 2,2-dioxide, (d) iodosobenzene and $Et_3N.5HF$.

In the past twenty years, *N*-fluorobenzenesulfonimide (NFSI) and Selectfluor™ have emerged as the most popular electrophilic fluorinating reagents of the N-F class because they are shelf stable, solid, commercially available reagents that do not require any additional handling

procedures beyond the usual precautions taken in a research laboratory. NFSI was used, for example, in the asymmetric fluorination of prochiral malonate esters[152] (Figure 37.) and reaction of Selectfluor™ with diethyl 2-phenylmalonate salt afforded the fluorinated product **67** in almost quantitative yield (93 %)[153]. Similarly, several fluoromalonate derivatives have been prepared using Selectfluor™, for use as liquid crystal compounds[154] and potential pharmaceutical targets (Figure 37.).[155]

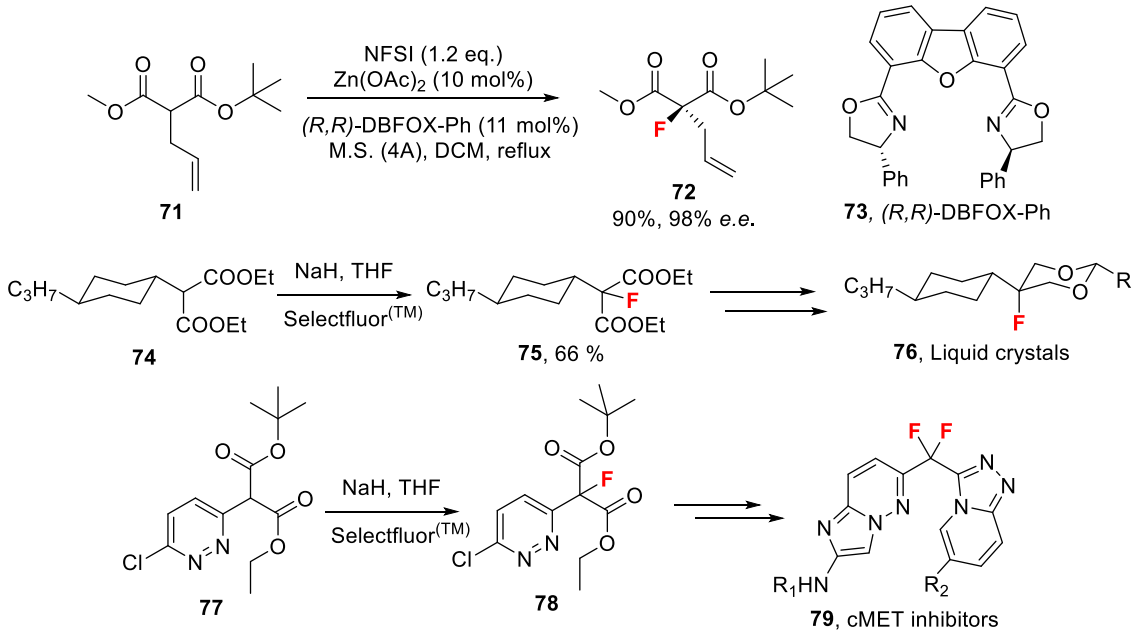


Figure 37: Synthesis of fluoromalonate derivatives using NFSI and Selectfluor™.

The direct fluorination of malonates with elemental fluorine gas was believed to be impractical until it was demonstrated by Purrington that it is possible to selectively fluorinate trimethylsilyl-malonate derivatives.[71] The starting material in this case was the corresponding silyl enol ether that was fluorinated with dilute (5% in N_2) fluorine gas in an inert Freon solvent (Figure 38a). The use of elemental fluorine for the synthesis of fluoromalonate esters was further developed by Chambers.[75] Fluorination of several dialkyl sodio-malonates in acetonitrile solution gave a product mixture that contains mono and difluorinated product and their relative ratio depends on the quantity of base used. With one equivalent of NaH, 37 % mono- and 23 % difluorinated malonate esters were obtained while, when adding 2.25 equivalents of NaH, the difluorinated product was the major product (37 %) along with 14 % monofluoro malonate. Substituted dialkyl malonate salts react with elemental fluorine to provide high yields of the corresponding fluorinated derivatives (Figure 38b).[75]

Fluorination of diethyl malonate in a continuous flow microreactor using acetonitrile as reaction medium gave several mono- and difluorinated products but with low selectivity.[156] The change of substrate to Meldrum's acid followed by treatment of the crude reaction mixture with ethanol

before the work-up stage gave mono- and difluoromalonate derivatives which could be easily separated (Figure 38c). However, the selectivity problem for direct fluorination of malonate substrates was solved when it was discovered that the addition of a catalytic amount of copper nitrate ($Cu(NO_3)_2.2.5\ H_2O$) could activate the malonate substrate towards direct fluorination (Figure 38d) in 78 % yield.[76]

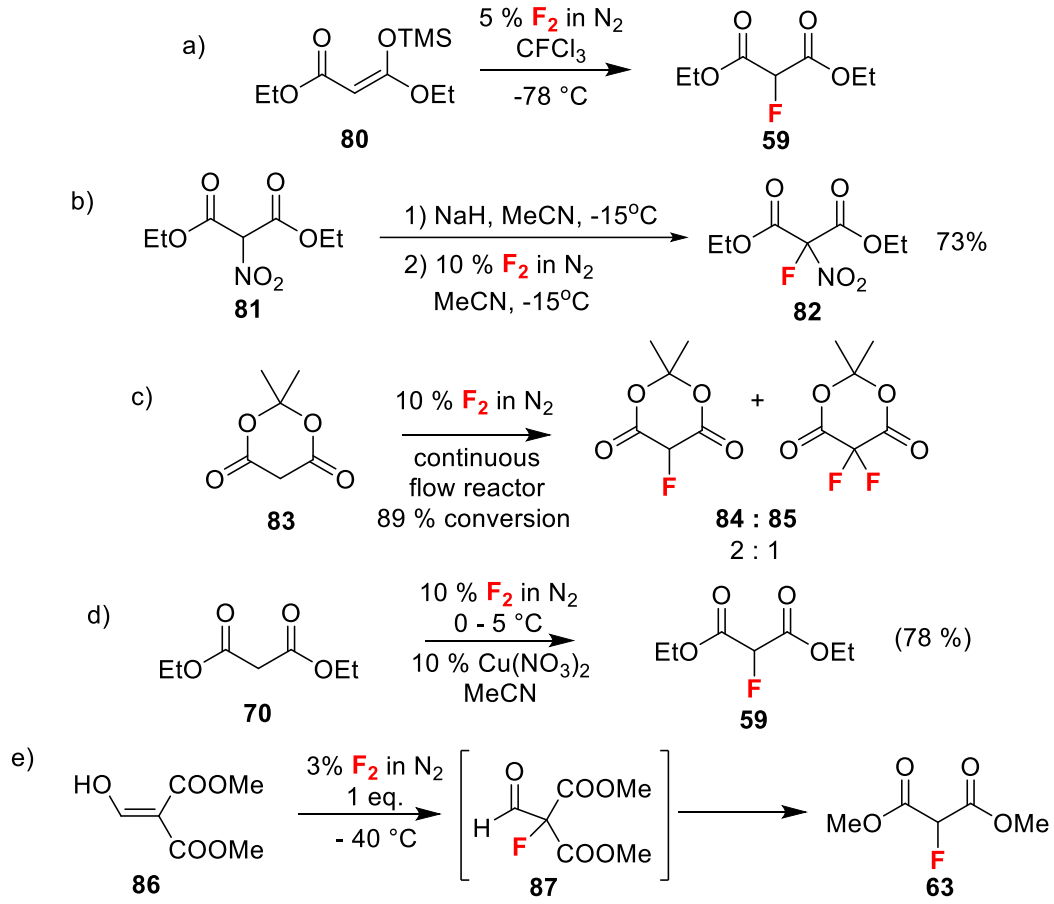


Figure 38: Synthesis of fluoromalonate esters using fluorine gas.

As an alternative approach, dialkyl 2-formyl malonates readily react with elemental fluorine to yield dialkyl 2-fluoro-2-formyl malonates that can easily be deformylated to yield exclusively the monofluorinated product in good yield (Scheme 38e).[157]

2.3.2 Halogen exchange reactions

Halogen exchange of chlorine by fluorine using a suitable source of fluoride ion offers an alternative approach to the synthesis of fluoromalonate derivatives. In the early 2000s' several patents were filed by Bayer[158,159] and Solvay[160] concerning reactions of amine-hydrogen fluoride complexes with diethyl chloromalonate (**88**, Figure 39).

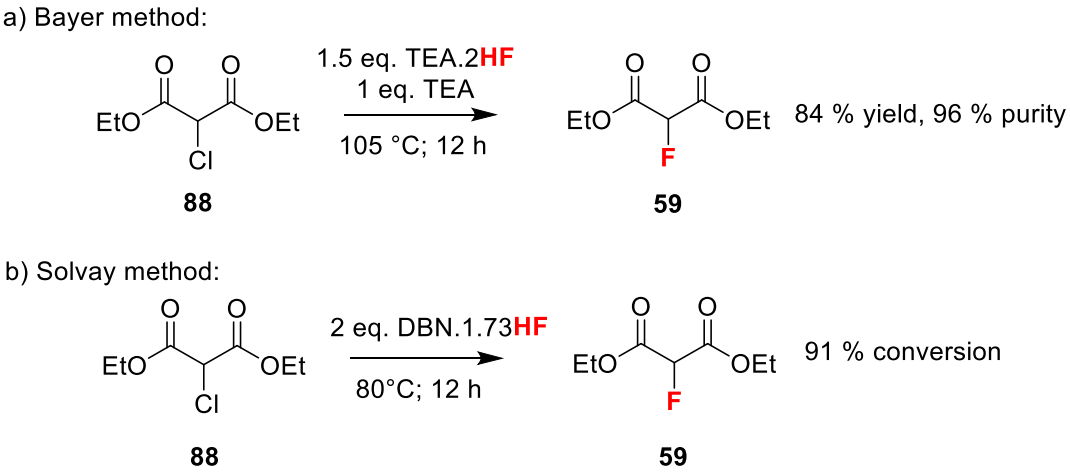


Figure 39: Synthesis of fluoromalonates by Halogen exchange processes.

Bayer's procedure uses trimethylamine tris(hydrofluoride) to give diethyl 2-fluoromalonate in 82 % yield while Solvay's process uses DBN.HF complex as the fluoride ion source to give **59** in 91% conversion on a large scale, as stated in the relevant patent descriptions.

2.3.3 Miscellaneous preparations

The condensation of fluoroacetic acid derivatives with alkyl chloroformate is another possible route for the synthesis of dialkyl fluoromalonate derivatives, but these reactions give diethyl 2-fluoromalonate in low yield (21 %).[133] A similar procedure was developed using less toxic ethyl bromofluoroacetate which was reacted with tributylphosphine to form an ylid that was acylated using ethyl chloroformate, to give diethyl 2-fluoromalonate (Figure 40).[161]

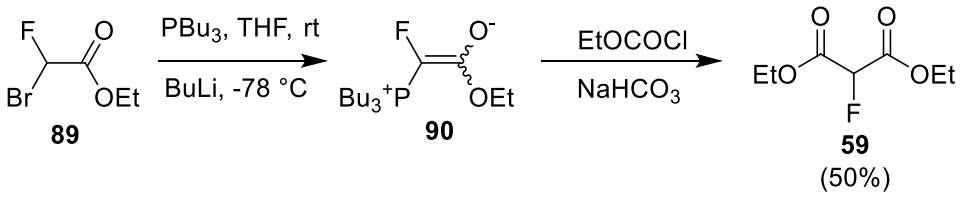


Figure 40: Acylation of ethyl bromofluoroacetate.

A method involving sequential solvolysis of hexafluoropropene to give dialkyl 2-fluoromalonates in good yield was published by Ishikawa and co-workers in the early 1980s (Figure 41).[162,163] Since hexafluoropropene (HFP, **91**) is manufactured on a very large scale for the production of various fluoropolymers, it is a relatively inexpensive starting material. When HFP is reacted with an alcoholic solution of sodium alkoxide, conjugate addition of an alcohol leads to an ether that can be hydrolysed by concentrated sulfuric acid to give alkyl 2,3,3,3-tetrafluoropropanoate. When this ester is reacted with an alcoholic sodium alkoxide solution, elimination of HF gives the corresponding acrylic acid derivative that immediately undergoes further addition followed by acidic hydrolysis to give the desired dialkyl fluoromalonate.

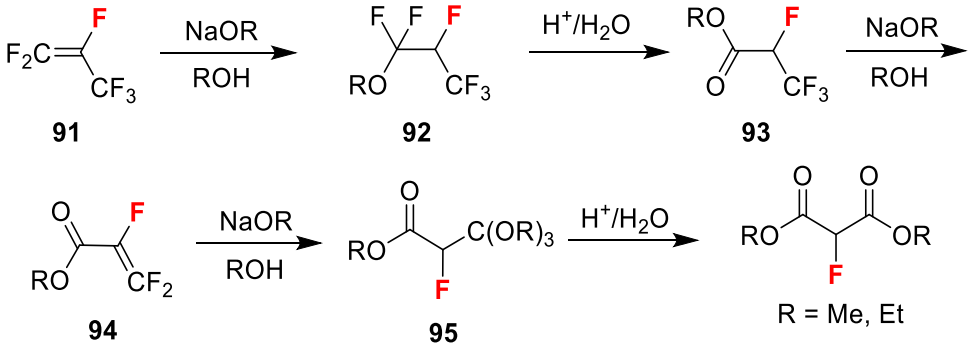


Figure 41: Sequential solvolysis of hexafluoropropene.[163]

In conclusion, there are several methods for the synthesis of fluoromalonate esters and derivatives, but only three methods are viable for large scale preparation. In this chapter, the direct fluorination of diethyl malonate, catalysed by copper nitrate, is reassessed and optimised with a view to intensifying this transformation and reducing its overall environmental impact. Upon optimisation, a comparison of the green metrics of selective direct fluorination with corresponding literature HFP and Halex routes for the synthesis of fluoromalonates to determine the relative merits of the three possible routes (Figure 42).

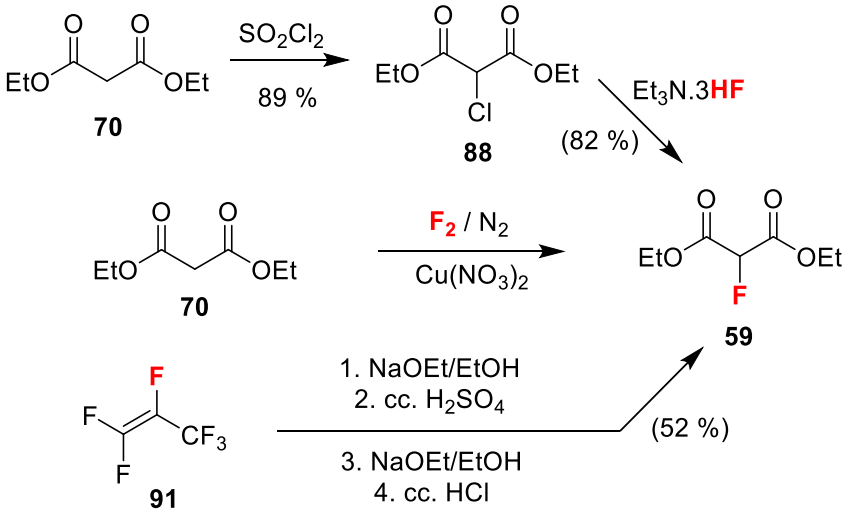


Figure 42. Potentially scalable fluoromalonate syntheses.

2.4 Optimisation of the fluorination of malonate esters

Before a comparison of the green metrics between the three possible large scale processes for the synthesis of fluoromalonate esters (Figure 42) could be carried out, some primary goals for the optimisation of a selective direct fluorination process for the synthesis of dialkyl 2-fluoromalonate esters were targeted following the principles of green chemistry. Complete conversion of the starting material is essential because it can be difficult to separate the starting material from the desired monofluorinated product by simple distillation. Fluorine gas usage should be minimised because neutralisation of excess reagent could potentially generate

significant amounts of hazardous waste. In order to reduce waste streams and intensify the fluorination process, replacement and/or reduction of all environmentally harmful solvents was targeted. The effects of temperature, catalyst and reactant (malonate ester and fluorine gas) concentration were investigated.

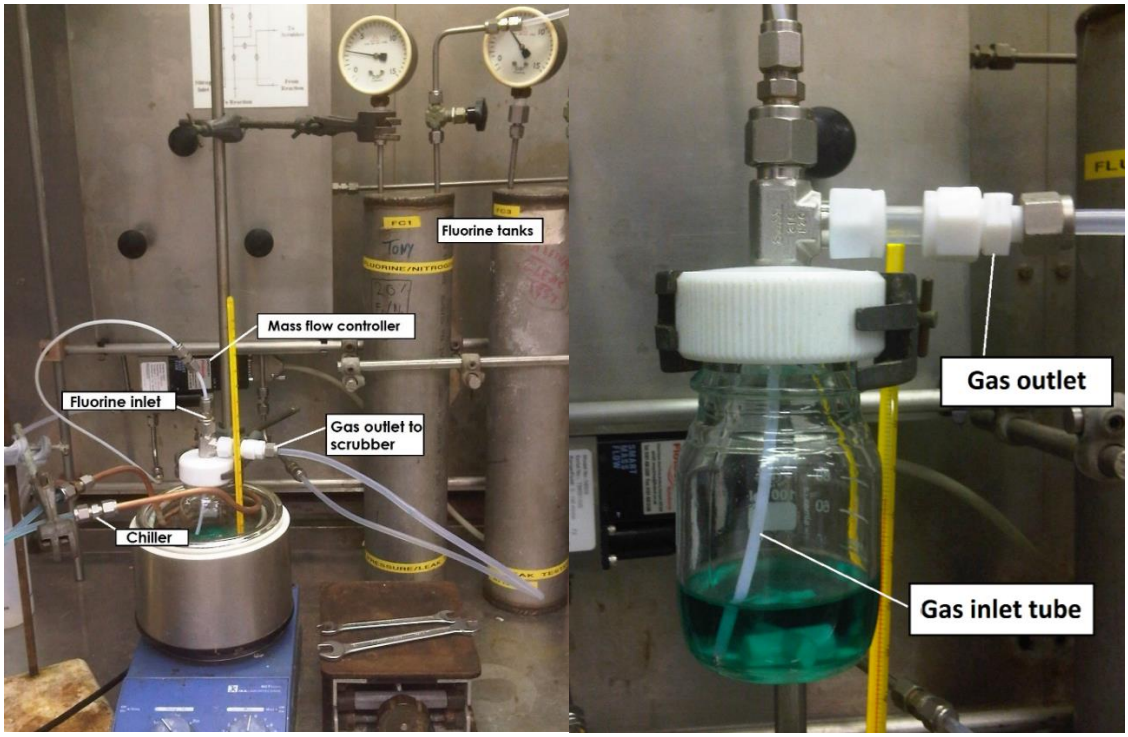


Figure 43: Small scale direct fluorination equipment (left) and 100 mL glass reactor (right).

In our laboratory fluorine is supplied from a commercial cylinder containing 20 % *v/v* F_2 in nitrogen, which is transferred and, if required, diluted with nitrogen in stand-alone cylinders with an overall pressure not exceeding 5 bars. Fluorine is dispensed from these storage cylinders at regulated flow rates using Brooks mass-flow controllers, typically in the range of 20-100 mL/min and introduced under the liquid surface in the reactor through a narrow bore (1/8" OD) FEP tube. The reaction mixture is stirred vigorously using a large, cross shaped magnetic stirrer bar to ensure maximum gas-liquid surface as the reaction takes place at the phase boundary. Exhaust gasses, containing residual fluorine, HF and solvent, are directed to a solid scrubber filled with granular soda lime (mixture of CaO and $CaCO_3$) to neutralise all corrosive and volatile waste.[76]

To better understand the relationship between fluorine gas introduction and rate of conversion, real time IR spectroscopic monitoring of the reaction was chosen as the most suitable technique. The use of ReactIR apparatus[164] was enabled by a sufficient difference in the carbonyl group stretching frequencies (1734 cm^{-1} for diethyl malonate **70** and 1775 cm^{-1} for diethyl 2-fluoromalonate **59**) and provided an *in situ* reaction profile (Figure 44).

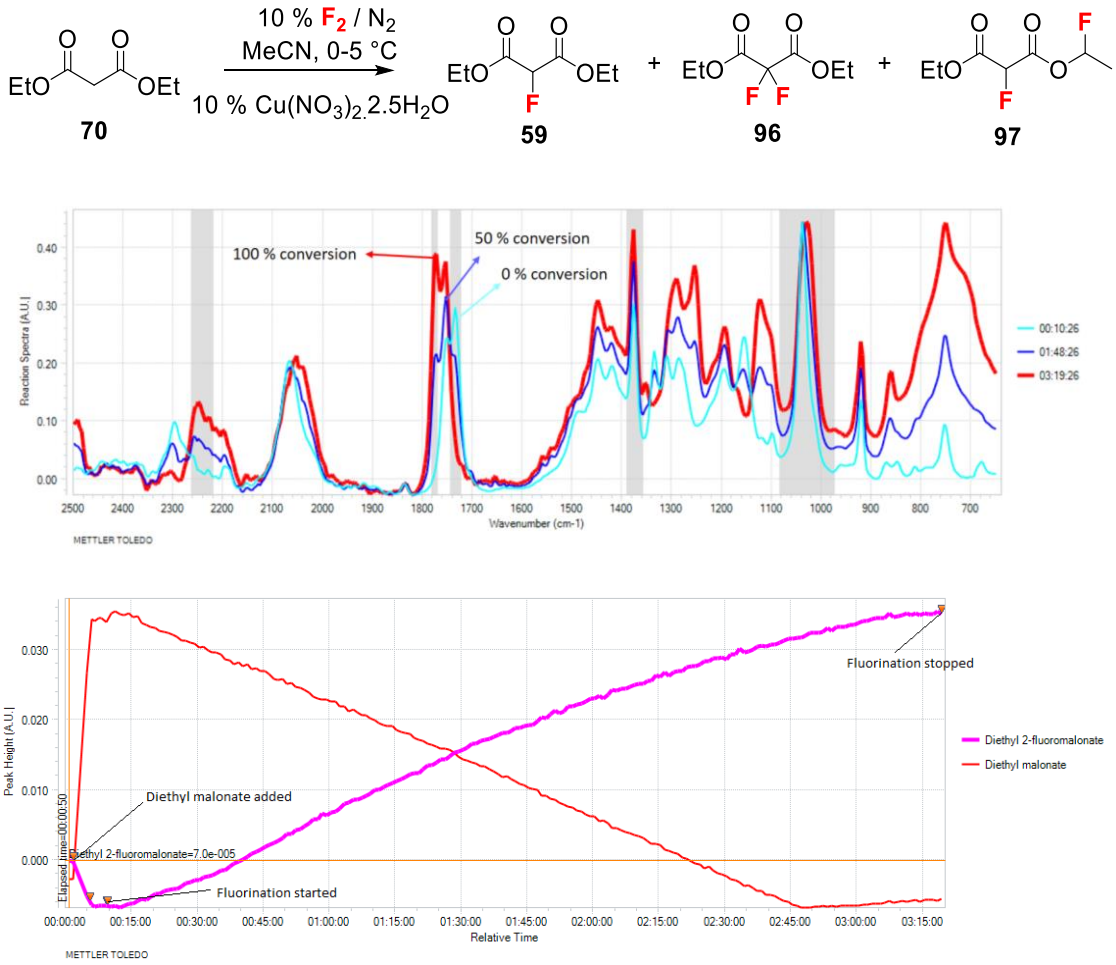


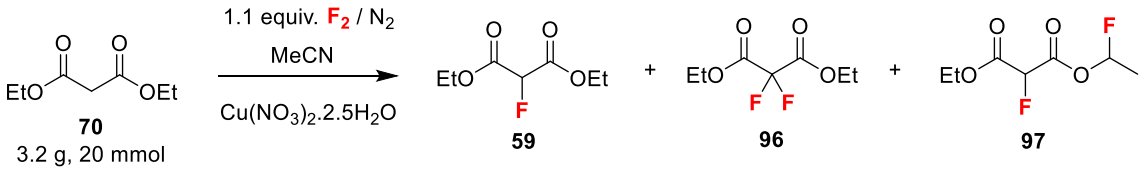
Figure 44: Top: IR spectra of the fluorination reaction at 0 % (light blue), 50 % (dark blue) and 100 % (red) conversions; bottom: *in situ* monitoring of the fluorination of diethyl malonate.

The real time reaction monitoring of the reaction between diethyl malonate and fluorine in acetonitrile solution in the presence of $Cu(NO_3)_2$ catalyst (Figure 44) revealed that the reaction begins instantly upon initiation of fluorine introduction and the reaction conversion is directly proportional to the amount of fluorine gas passed into the reaction vessel. When the intensity of the fluoromalonate carbonyl peak (1775 cm^{-1}) reached a maximum, the introduction of fluorine gas was stopped, the sample was poured into a larger volume of water (150 mL) and extracted three times with ethyl acetate. The organic phase was washed with water, $NaHCO_3$ solution and brine, then dried and evaporated to leave a crude product which was analysed by ^{1}H and ^{19}F NMR spectroscopy.

The effect of concentration of fluorine in nitrogen, reaction temperature, copper nitrate catalyst loading and concentration of malonate substrate in acetonitrile were varied to optimise the fluorination process (Table 5). Additionally, reactions described in Table 5 allowed an assessment of various factors that have a major influence on the environmental impact of the process such as solvent usage, reaction temperature and the amount and composition of waste

generated. In each case 20 mmol (3.20 g) of diethyl malonate was used as substrate in the above described 100 mL fluorination reactor. First, the starting malonate and the catalyst were weighed in the reactor then acetonitrile was added, the reactor lid was closed, the mixture cooled to the desired temperature and nitrogen was introduced to the mixture for 5-10 minutes with stirring. After purging the system with nitrogen, fluorine was introduced at a prescribed rate using the mass-flow controller for the desired length of time, then, the fluorine flow was stopped and the vessel was purged again with nitrogen to remove traces of fluorine. The mixture was worked up as above, in the case of the ReactIR experiment, the isolated mass of crude material was obtained and analysed by ^{1}H and ^{19}F NMR spectroscopy to determine the conversion of starting material and yield of fluorinated products (Table 5).

Table 5: Fluorination of diethyl malonate ester using fluorine gas catalysed by $Cu(NO_3)_2.2.5H_2O$.



Entry no.	T / °C	$C_{malonate}$ (mol/L)	Catalyst (mol%)	F_2 in N_2 (% v/v)	Conversion (^{1}H NMR)	59/96/97 ratio (^{19}F NMR)	Isolated weight
1	0-5	1.0	10	10	100 %	93.5/4.5/2	3.37 g
2	0-5	1.5	10	10	100 %	94/4/2	3.30 g
3	0-5	1.0	5	10	97 %	95/4/1	3.53 g
4	0-5	1.0	2.5	10	82 %	95/4/1	3.51 g
5	RT	1.0	10	10	56 %	97.5/1.5/1	3.33 g
6	0-5	1.0	10	15	85 %	97.5/1.5/1	3.47 g
7	0-5	1.0	10	20	100 %	94/3/3	3.50 g
8	0-5	2.0	5	20	52 %	92/5/3	3.40 g

Complete conversion of the starting material was observed and diethyl fluoromalonate was formed with 93 % selectivity after introducing 1.1 equivalents of fluorine into the reaction mixture. The small excess of fluorine explains the unexpectedly small amount of difluorinated side products **96** (4.5 %) and **97** (2.5 %) which were the major impurities (6.5 and 9.0 % respectively) when a larger excess of fluorine gas (1.8 eq.) was used.

In all cases, small quantities of side products were formed which were identified by ^{19}F NMR and these originate from two different processes: difluoromalonate **96** is produced from the enolisation of diethyl fluoromalonate which is much slower than the enolisation of the diethyl

malonate substrate, while the fluoroethyl derivative **97** is postulated to form via a cyclic electrophilic process.[68]

The data in Table 5 suggest that the concentration of the malonate ester substrate in acetonitrile has no apparent effect on the outcome of the reaction although solvent is required for these reactions because diethyl malonate does not dissolve the catalyst. Additionally, the use of high dielectric constant media, such as acetonitrile, have been found to be beneficial for the control of selectivity of electrophilic direct fluorination processes.[89] For convenience, a 1.5 M concentration of malonate in acetonitrile was chosen for further reactions which is approximately 5 mL solvent per 1 mL of diethyl malonate.

The concentration of fluorine gas, between 10 – 20 % *v/v* in nitrogen, does not affect the selectivity of the reaction and the quality of the product either, as exemplified by the product mixtures obtained from reactions 1, 2 and 7 (Table 5) which have identical compositions. In contrast, carrying out the fluorination reactions at room temperature rather than cooling the reaction mixture to 0-5 °C leads to increased catalyst decomposition which results in an insoluble copper species that on occasion blocked the fluorine gas inlet tube. In addition, without cooling, the exothermic nature of this fluorination reaction led to a slight reaction temperature increase (from 20 to 29 °C in a small scale laboratory experiment) resulting in loss of some solvent and some decomposition of the catalyst and product degradation.

Lowering the concentration of the copper nitrate catalyst led to a significantly slower reaction, as would be expected, and required the use of a larger excess of fluorine gas to enable sufficiently high conversion. For example, the reaction proceeded in the presence of only 2.5 mol % catalyst, but in this case 40 % excess fluorine was required to reach 100 % conversion.

Typical literature work-up procedures for direct fluorination reactions involve pouring the reaction mixture into 3 to 5 volumes of water and extracting the resulting mixture three times with dichloromethane. The combined organic fraction is typically washed with water, saturated sodium bicarbonate solution and dried over sodium sulfate before evaporation of the solvent to give the crude reaction product. We sought to improve the literature work-up to enable recycling of the reaction solvent and substitute the use of environmentally harmful dichloromethane in the reaction work-up stage. Upon completion of fluorine gas addition, acetonitrile was evaporated for reuse and then the residue was partitioned between ethyl acetate and water, the organic phase was washed with water, saturated Na_2CO_3 solution and saturated brine and dried prior to evaporation under reduced pressure. Modification of the workup procedure in this manner enables the recovery of acetonitrile and ethyl acetate and significantly reduces the amount of aqueous waste generated. When direct reuse of the

recovered acetonitrile was attempted without any further purification of the recycled solvent, a copper containing precipitate was formed presumably because of the high HF content of the solvent (0.63 M by titration). Therefore, before reuse of the solvent, HF must be removed. Stirring the recovered reaction solvent with solid Na_2CO_3 lowered the acid content to an acceptable level (0.04 M) and when a second fluorination reaction was carried out in the recovered, neutralised acetonitrile, no change in the fluorination product profile was observed.

Upon completion of these optimisation studies, the reaction was scaled up using the best conditions: 40 g of diethyl malonate and 5.8 g copper nitrate (10 mol %) were dissolved in 200 mL of acetonitrile in a 500 mL fluorination reactor. The mixture was stirred using a mechanical stirrer at 650 rpm to ensure efficient mixing of the phases and 20 % *v/v* fluorine was introduced at 80 mL/min 6.5 hours (1.1 eq.). To reduce the volume of solvent used in the workup, the acetonitrile was first evaporated in vacuum, then ethyl acetate and water were added, the aqueous phase extracted once more with EtOAc then the extracts were washed with saturated $NaHCO_3$ solution and brine. After drying and evaporation of the solvent, 44.4 g of 95 % pure diethyl fluoromalonate was obtained, which was distilled under vacuum (102-103 °C at 18 mbar) to yield 34.7 g of high purity (99 %+) material.

Related malonate esters were also subjected to direct fluorination using the optimised conditions established above. In the case of di-*tert*-butyl malonate (**98**), fluorination was carried out on 12 g scale and 100 % conversion was achieved after the introduction of 1.2 equivalents of fluorine gas affording the desired product **99** in 96 % isolated yield. The purity of the crude product was higher than 97 % by ^1H and ^{19}F NMR spectroscopy without any further purification and as expected, the only side product was the 2,2-difluorinated product.

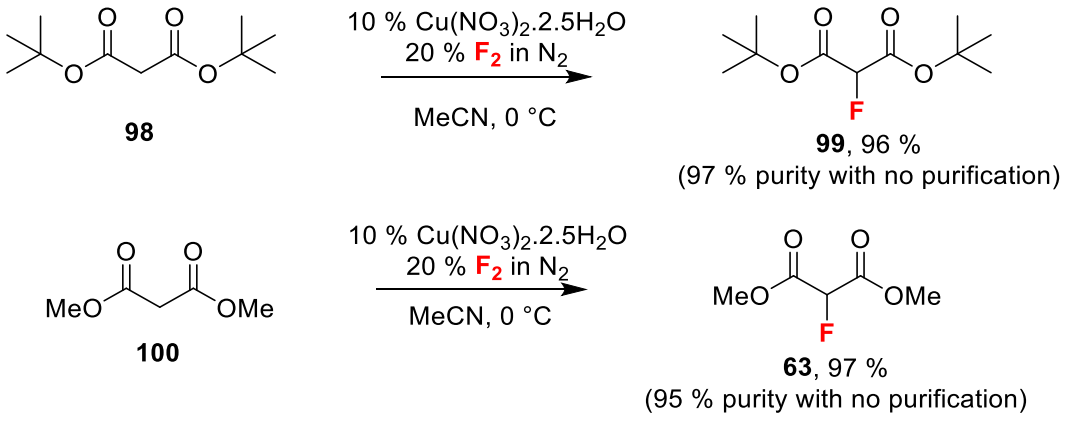


Figure 45: Fluorination of dimethyl and di-*tert*-butyl malonates.

From an atom economy point of view, methyl ester derivatives are preferable substrates compared to ethyl or other higher alkyl esters since they lead to smaller quantities of waste and so the fluorination of dimethyl malonate was investigated. Using 10 % catalyst and 1.1

equivalents of fluorine, 20 g of dimethyl malonate (**100**) was fluorinated to afford dimethyl fluoromalonate in 97 % yield and 95 % purity after isolation by simple work-up and no further purification. In this case, the only side product was dimethyl 2,2-difluoromalonate which was separated from **63** by fractional distillation to afford high purity dimethyl fluoromalonate which crystallises at room temperature (Figure 46).

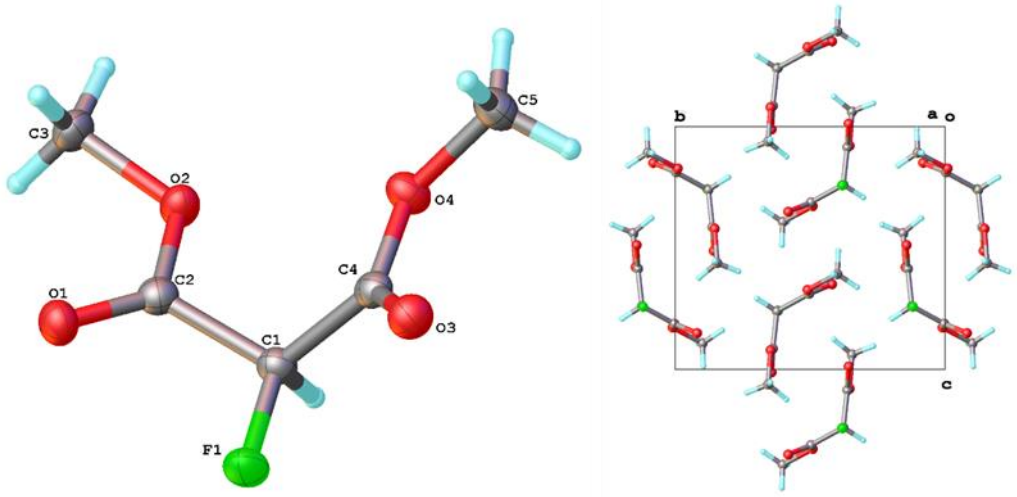
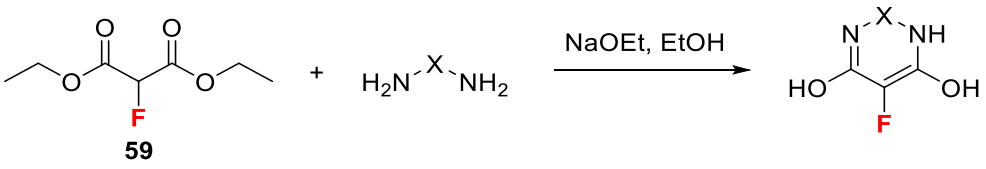


Figure 46: Dimethyl malonate molecular structure and crystal packing.

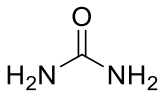
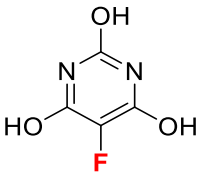
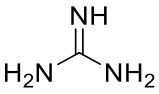
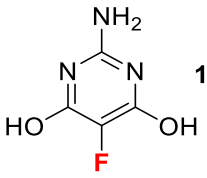
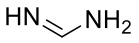
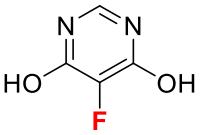
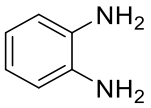
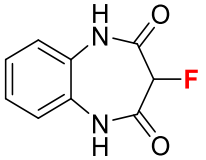
2.5 Synthesis of fluorinated heterocycles from fluoromalonate esters

Condensation of fluoromalonate esters with dinucleophiles is a convenient route to multifunctional fluorinated heterocyclic scaffolds.[137] A number of nitrogen dinucleophiles were reacted with the crude diethyl fluoromalonate product synthesised above (92-95 % purity) to afford pyrimidine and diazepane derivatives which could be purified readily by recrystallization and demonstrates the usefulness of 95 % purity fluoromalonate material for further synthesis.

Table 6: Synthesis of fluorinated heterocycles using crude (95% pure) diethyl fluoromalonate ester.



59

Dinucleophile	Product	Yield / %
 **101**	 **105**	51
 **102**	 **106**	86
 **103**	 **60**	64
 **104**	 **107**	68

In particular, crude diethyl fluoromalonate prepared above reacts efficiently with formamidine to give fluoropyrimidine **60**, a key intermediate in the synthesis of Fluoxastrobin, in good yield (64 %) and purity, which is comparable with previously reported optimised 61-78 % yields.[158]

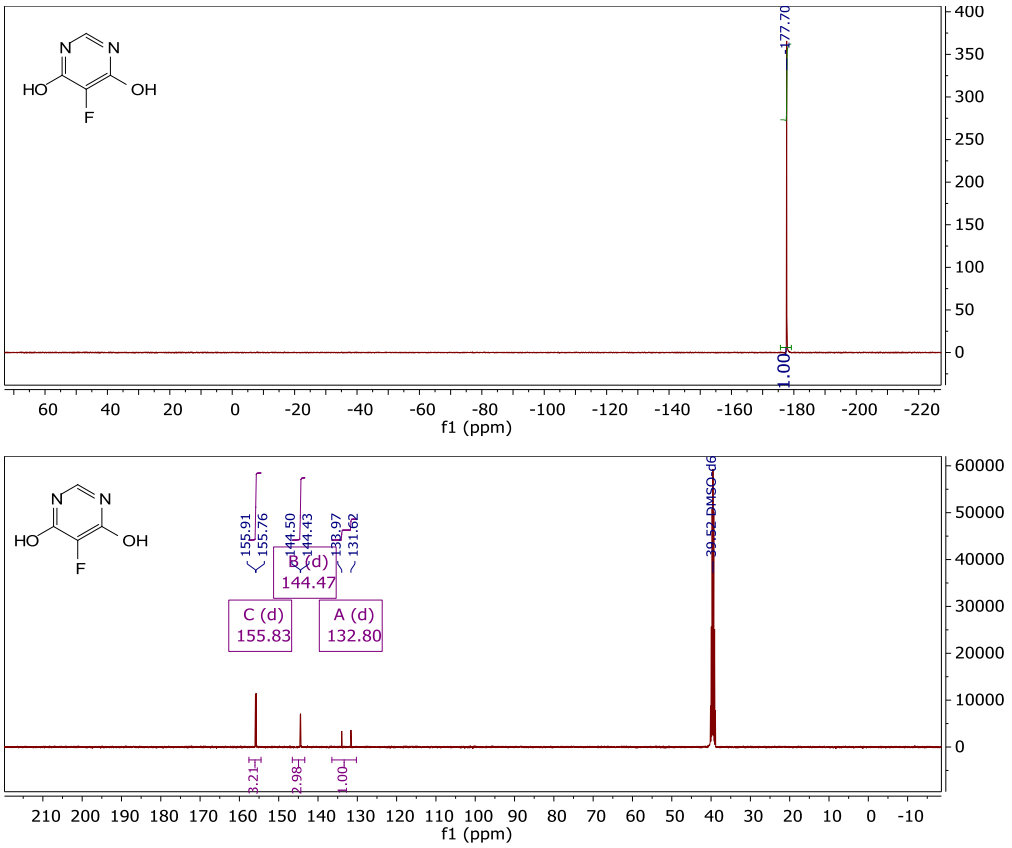
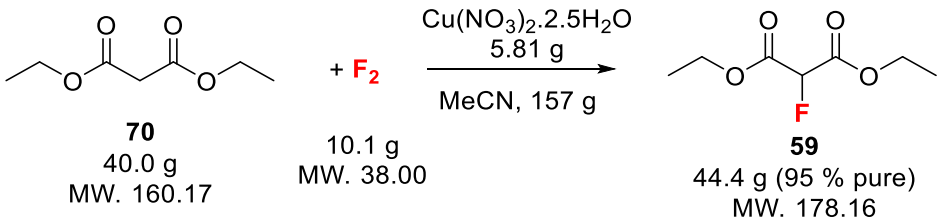


Figure 47: ^{19}F and ^{13}C NMR spectra of 5-fluoro-4,6-dihydroxypyrimidine.

2.6 Green metrics assessment

To compare the metrics of the optimised direct fluorination process with other methods for the synthesis of fluoromalonate esters, the Chem21 "First Pass" metrics package, was implemented as described in Chapter 1.[124]

2.6.1 Direct fluorination metrics



Workup: EtOAc (100 mL,90 g), saturated $NaHCO_3$ solution (25 g), brine (24 g)
Distilled product: 34.7 g, 99 %+ pure

Figure 48: Direct fluorination method for the synthesis of diethyl fluoromalonate.

For the calculation of atom economy, only a balanced reaction equation and the molecular weights of the reactants are necessary, as this metric does not involve catalysts, reagents or solvents. In this case, the calculation is very simple, the molecular weight of diethyl fluoromalonate (178.16 g/mol) is divided by the sum of the molecular weights of diethyl malonate and fluorine (160.17 + 38.00 = 198.17) giving 89.9 % as the atom economy of this

reaction meaning that almost 90 % of the atoms involved in the reaction are incorporated into the desired product and only 10 % is waste.

$$AE(Direct\ Fluorination) = \frac{178.16}{160.17 + 38.00} \times 100 = \mathbf{89.9}$$

Reaction mass efficiency is a more useful tool than atom economy, as it takes yield and stoichiometry into consideration. For the calculation of RME, the product weight is divided by the combined mass of the reactants, which gives 88.6 % for the crude product and 69.3 % for the distilled, high purity material. RME can be used together with AE in a way that AE is the theoretical maximum, as these two metrics will be equal in the case of one to one stoichiometry and 100 % yield, therefore, the closer the RME value is to the AE, the better the reaction is. In this case (RME = 88.6), the crude product is very close to the AE (89.9), meaning that the yield is very high and only a small excess of reactants is used.

$$RME(Direct\ Fluorination) = \frac{44.4}{40.0 + 10.1} \times 100 = \mathbf{88.6}$$

$$RME(Direct\ Fluorination\ Distilled) = \frac{34.7}{40.0 + 10.1} \times 100 = \mathbf{69.3}$$

The most comprehensive metric used in this thesis is mass intensity (MI), which describes how much material is used in the synthesis for every kg of product obtained. To calculate the MI of the direct fluorination step, the weight of diethyl fluoromalonate is divided by the sum of all components from the reaction and the workup: reactants, catalyst, solvents and aqueous washes. The MI calculated for the crude product is 9.0 $kg_{material}/kg_{product}$ which is a relatively low number, and only increases to 11.6 when it is calculated for the distilled, 99%+ pure product. It is often useful to calculate the MI for different stages of a reaction, this way it is easy to highlight the problematic areas of a process, where more improvement is needed. In this reaction, solvents are the largest contributors to MI, but with recycling and reuse of solvents, this number could be lowered further.

$$MI(Direct\ Fluorination) = \frac{40.0 + 5.8 + 157 + 10.1 + 50 + 90 + 25 + 24}{44.4} = \mathbf{9.0}$$

$$MI(Direct\ Fluorination\ Distilled) = \frac{40.0 + 5.8 + 157 + 10.1 + 50 + 90 + 49}{34.7} = \mathbf{11.6}$$

$$MI(Direct\ Fluorination\ Reaction) = \frac{40.0 + 5.8 + 10.1 + 157}{44.4} = \mathbf{4.6}$$

$$MI(Direct\ Fluorination\ Reaction\ Distilled) = \frac{40.0 + 5.8 + 10.1 + 157}{34.7} = \mathbf{5.7}$$

$$MI(Direct\ Fluorination\ Solvents) = \frac{157 + 50 + 90}{44.4} = \mathbf{6.7}$$

$$MI(Direct\ Fluorination\ Solvents\ Distilled) = \frac{157 + 50 + 90}{34.7} = \mathbf{8.6}$$

$$MI(Direct\ Fluorination\ Workup) = \frac{50 + 90 + 24 + 25}{44.4} = \mathbf{4.3}$$

$$MI(Direct\ Fluorination\ Workup\ Distilled) = \frac{50 + 90 + 24 + 25}{34.7} = \mathbf{5.5}$$

2.6.2 Halogen exchange method metrics

The halogen exchange reaction requires the industrial synthesis of high purity chloromalonate ester since the purity of the final fluoromalonate product largely depends on the efficiency and selectivity of this step. The chlorination reaction with sulfuryl chloride is reasonably selective and pure diethyl chloromalonate can be obtained in good yield[165] after vacuum distillation and it is reasonable to assume that this reaction is suitable for large scale synthesis. The halogen exchange reaction is also very efficient since HF.amine systems are convenient, reactive sources of fluoride ion and additionally, they can be handled safely since they are less volatile than aHF and are commercially available on the multi-ton scale.

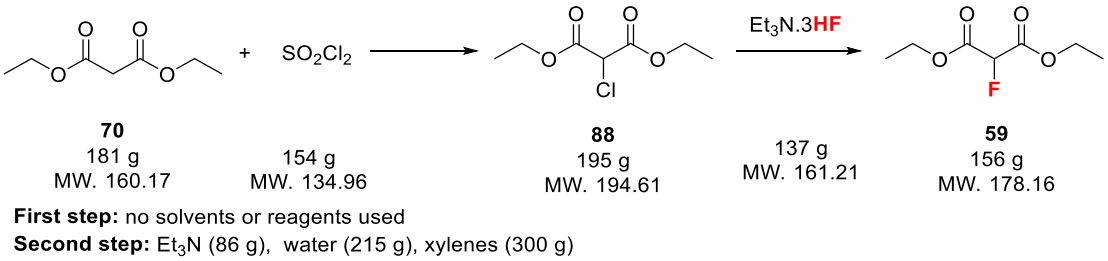


Figure 49: Halogen exchange method for the synthesis of diethyl fluoromalonate.

The assessment of a literature processes requires more attention as not all the necessary data is reported in typical synthetic procedures and in these cases, realistic assumptions about the quantities have to be made. In the case of the halogen exchange method the data was sufficient, but to simplify the calculations the chlorination step was "scaled up" on paper from the reported 100 g scale to give the exact amount of diethyl chloromalonate required in the second steps in the reported yield.

The metrics calculations are very similar to the direct fluorination step, but this is a two-step procedure, therefore, the molecular weight and the mass of the intermediate diethyl chloromalonate is not included. For the two steps, the atom economy of this reaction is only 39.2 %, which is mainly due to the high molecular weight of sulfuryl chloride and $Et_3N.3HF$,

however, the RME value of 33.0 % shows that the reaction is high yielding and is not using large excesses of the reagents.

$$AE(Halex) = \frac{178.16}{160.17 + 134.96 + 161.21} \times 100 = \mathbf{39.2}$$

$$RME(Halex) = \frac{156}{181 + 154 + 137} \times 100 = \mathbf{33.0}$$

In this case, the mass intensity calculation was also relatively straightforward and, again, the intermediate chloromalonate ester has to be left out of the calculations. The PMI of this reaction is very low, only 6.9, which is the result of a solventless first step and a very concentrated halogen exchange reaction. In this reaction the solvents were also important contributors, but with recycling the xylenes used for extraction, this number could be lowered further.

$$PMI(Halex) = \frac{181 + 154 + 137 + 86 + 300 + 215}{156} = \mathbf{6.9}$$

$$PMI(Halex\ Reaction) = \frac{181 + 154 + 137 + 86 + 300}{156} = \mathbf{5.5}$$

$$PMI(Halex\ Solvents) = \frac{300 + 215}{156} = \mathbf{3.3}$$

$$PMI(Halex\ Workup) = \frac{215 + 300}{156} = \mathbf{3.3}$$

2.6.3 HFP method metrics

Hexafluoropropene (HFP) is an important, inexpensive perfluorinated building block used for the synthesis of various well known fluoropolymers and refrigerant gases and is, therefore, available on the industrial scale.[166] In the literature, it was reported that HFP can be reacted with various alcohols to yield the corresponding fluoromalonate ester derivatives in a multistep process and the synthesis of methyl ester **63** was described in detail. Yields for diethyl fluoromalonate and its intermediate precursors were also reported and for the metrics calculations, the same scale was used using ethanol as in the reaction with methanol.[163] From the experimental procedures only the mass balances are needed for metrics calculations, but in some instances data was missing. For example, in the first stage of the reaction, a concentrated sulphuric acid solution (approximately 500 mL total volume) was quenched in ice-water, but the quantity of ice was not reported, thus, we assumed that 3.5 kg was used, which is approximately 500 g of ice for 100 g of the acid. When estimating other unquantified materials, a very conservative approach was applied to avoid artificial inflation of the metrics results.

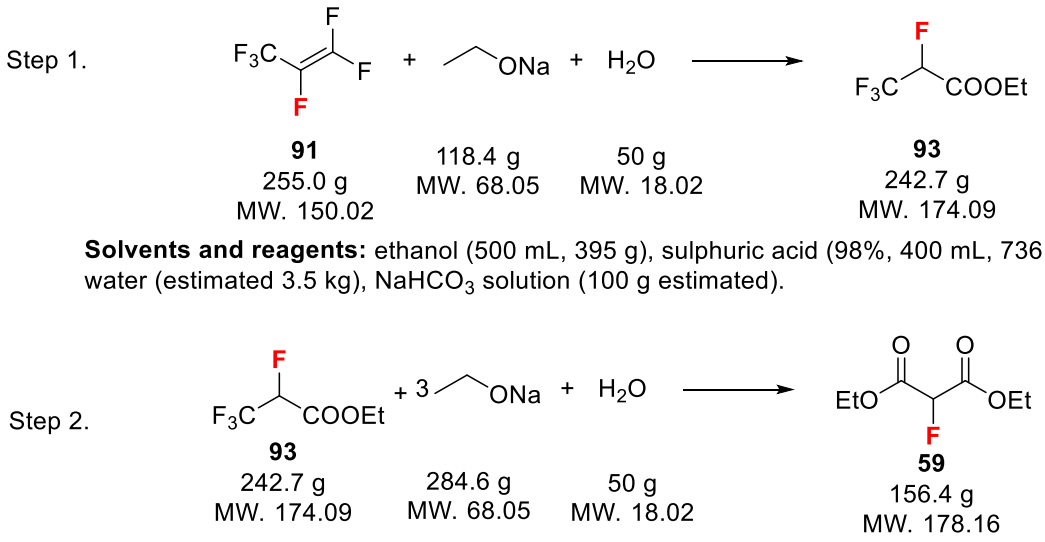


Figure 50: HFP solvolysis method for the synthesis of diethyl fluoromalonate.

The atom economy of this reaction (39.1) is comparable to that of the Halex method (39.2), but in this case a different, more complex starting material was used which would imply that this process is less likely to be greener than the alternative. The comparison of RME values gives the same conclusion, as because of the lower yield of the HFP route it is only 20.6 which means that close to 80 wt% of the reactants is lost in this process.

$$AE(HFP\ method) = \frac{178.16}{150.02 + 4 \times 68.05 + 2 \times 18.02} \times 100 = \mathbf{39.1}$$

$$RME(HFP\ method) = \frac{156.4}{255 + 403 + 100} \times 100 = \mathbf{20.6}$$

The biggest difference between the HFP route and the other alternative syntheses is in the PMI, where the alternative routes are almost an order of magnitude better. The high PMI of this process (62.1) is mostly due to the use of concentrated sulfuric acid solvent and its aqueous quench as shown by the PMI of the workup (44.1).

$$PMI(HFP\ method) = \frac{255 + 403 + 6100 + 1026 + 736 + 300 + 292 + 597}{156.4} = \mathbf{62.1}$$

$$PMI(HFP\ Reaction) = \frac{255 + 403 + 100 + 1026 + 736 + 292}{156.4} = \mathbf{18.0}$$

$$PMI(HFP\ Solvents) = \frac{6000 + 1026 + 357 + 240}{156.4} = \mathbf{48.8}$$

$$PMI(HFP\ Workup) = \frac{6000 + 300 + 240 + 356}{156.4} = \mathbf{44.1}$$

In conclusion, the synthesis of fluoromalonates by reaction of HFP with ethanol and H_2SO_4 affords good purity product in fair yield, but, from an environmental impact point of view, this is a very wasteful and low-atom economy process. Firstly, the synthesis of the starting material requires many steps, ultimately by reaction of low molecular weight hydrocarbons with chlorine gas and subsequent halogen exchange in a very energy intensive process and, secondly, a significant amount of hazardous, strongly acidic waste is generated in the reaction of HFP with ethanol.

Besides quantitative metrics, the Chem21 First Pass metrics package includes qualitative assessment for several factors, for example, solvents, catalysis, energy and safety. When comparing the three processes, only the HFP method uses an undesirable solvent, diethyl ether, for an extraction, however, in a manufacturing environment this could easily be replaced with a safer and environmentally benign alternative. The other solvents in the reactions are acceptable from a green chemistry point of view and most of them have potential for recovery and reuse.

The only catalytic process is the direct fluorination reaction which uses hydrated copper nitrate to catalyse the enolisation of malonate esters. This catalyst is not only inexpensive, but the catalyst metal is easily separated into the aqueous stream and, in theory, could be recovered using conventional inorganic chemistry methods.

The energy requirement for these reactions is very difficult to assess under laboratory conditions and the only guideline in the First Pass metrics package is that between 0 - 70 ^{o}C the reaction is flagged green, anywhere outside this range, but between -20 – 140 ^{o}C is amber and outside that range is red.[124] Considering these guidelines both the HFP and the Halex method are marked amber, while the direct fluorination without distillation is green and when the distillation is included it is amber because of the energy intensity and the relatively high temperatures of the vacuum-distillation process. The qualitative assessment of downstream processing classifies isolation and purification procedures into green, amber and red groups, which usually corresponds to the amount of material and energy required for the given method. Aqueous workup followed by extraction and vacuum distillations are present in all three methods, therefore, in this regard there is no significant difference between these processes. The comparison of the health and safety aspects does not show any difference either, all reactions involve HF either as starting material or byproduct meaning that they are all classified as highly corrosive and very toxic.

Table 7: Comparative green metrics of fluoromalonate syntheses.

Fluoromalonate synthesis	HFP method	Halex cumulative	Cu catalysed direct fluorination (distilled)
Yield [Purity %]	52 % [n/a]	77 [96 %]	99 [95 %] (77 [99%+])
Atom Economy (AE)	39.1	39.2	89.9
Reaction Mass Efficiency (RME)	20.6	33.0	88.6 (69.3)
Step MI/PMI Total	62.1	6.9	9.0 (11.6)
PMI/MI Reaction	18.0	5.5	4.6 (6.1)
PMI/MI Solvents	48.8	3.3	6.7 (8.6)
PMI/MI Workup	44.1	3.3	4.3 (5.5)
Solvents	EtOH Et_2O	Xylenes	Acetonitrile Ethyl-acetate
Catalyst	-	-	$Cu(NO_3)_2.2.5H_2O$
Critical element	-	-	Cu (recoverable)
Energy	High	Medium	Low (Medium)
Workup/purification	Extraction Evaporation Vac.-Distill.	Extraction Multiple Vac. Distill.	Extraction Evaporation (Vac. Distill.)
Health & Safety	Corrosive Toxic Flammable	Corrosive Toxic	Corrosive Toxic Oxidiser
Chemicals of environmental concern	-	-	
Availability	Expensive	Good	Good

In conclusion, the green chemistry assessment of the potential synthetic methods for the production of fluoromalonate esters clearly demonstrates that the direct fluorination and the Halex methods are superior to the HFP based synthesis which is most apparent in the comparison of the industrially most used PMI metric. However, it is not possible to make a decision between the other two methods, as they are both very efficient and produce only a small amount of waste.

2.7 Conclusion

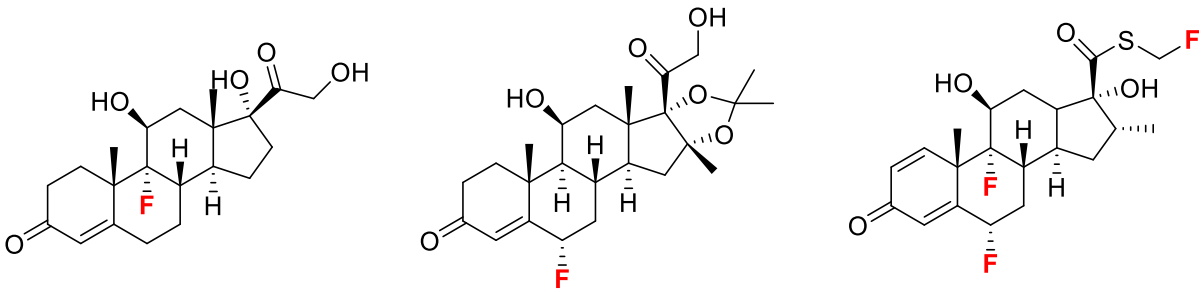
The selective direct fluorination (SDF) process for the synthesis of 2-fluoromalonate esters has been re-evaluated and optimised on a reasonable scale in the laboratory (50 g scale) both in terms of product yield, purity (99 % crude yield, 95 % purity, after distillation 77 % yield and 99% purity) and green reaction metrics. The PMI value of the SDF process is, even at this relatively small scale, under 10, an industry benchmark figure that demonstrates an efficient and effective, environmentally benign chemical syntheses. A comparison of green metrics between the SDF process and established multi-step syntheses derived from hexafluoropropene ethanolysis and halogen exchange chemistry shows that SDF compares very favourably in terms of environmental impact for the synthesis of important fluorinated building blocks on larger scale.

Chapter 3.: Direct Fluorination of Drug-Like Systems

In the previous section it was demonstrated that using elemental fluorine for the selective direct fluorination of malonate esters is a viable and potentially greener synthetic method than the alternative halogen exchange route. However, pharmaceutical compounds are usually structurally more complex and have fluorine substituents in diverse positions, therefore, to establish the viability of selective direct fluorination processes of drug-like systems, in this chapter, the direct fluorination of pharmaceutically relevant steroids and aromatic compounds will be discussed. Similarly to the previously described work, the aim was to identify and optimise processes for comparative green metrics analysis between SDF and alternative routes.

3.1 6-Fluorocorticosteroids

In the history of the development of small molecular drug substances fluorine containing steroids made a big difference. Sabo and co-workers discovered in the early 1950's that the introduction of a single fluorine atom into a corticosteroid increased its potency tenfold[8] and since then several fluorinated steroids have been introduced to the marketplace for the treatment of various conditions.



Fludrocortisone, **1**
Na^+ level regulator

Flurandrenolide, **108**
anti-inflammatory

Fluticasone, **109**
anti-inflammatory

Figure 51: Existing fluorocorticosteroid drugs.

3.1.1 Literature methods for the synthesis of fluorosteroids

The incorporation of fluorine into steroid systems is typically carried out using conventional nucleophilic fluorination strategies, especially at the 9α position where ring opening of the corresponding epoxide with HF gives the desired product.

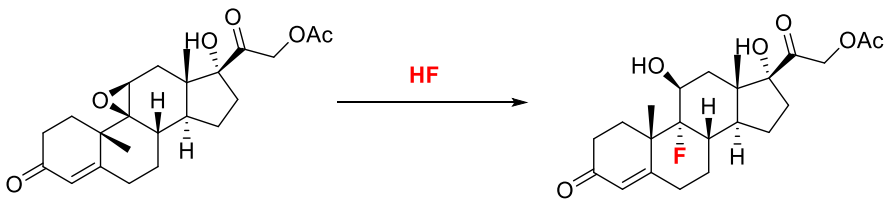


Figure 52: Synthesis of 9α-fluorocortisone acetate.[8]

The early syntheses of 6-fluorosteroids involved a long, multi-step procedure where a double bond at the 5-6 position was oxidised to the corresponding epoxide which was opened with a fluoride source then, subsequently, the 5-hydroxy group was eliminated to give the fluorinated 4,5-unsaturated product (Figure 53).[167,168] While this method enabled the synthesis of 6-fluorocorticosteroids from readily available starting materials, this is a very wasteful and inefficient way to synthesise these compounds.

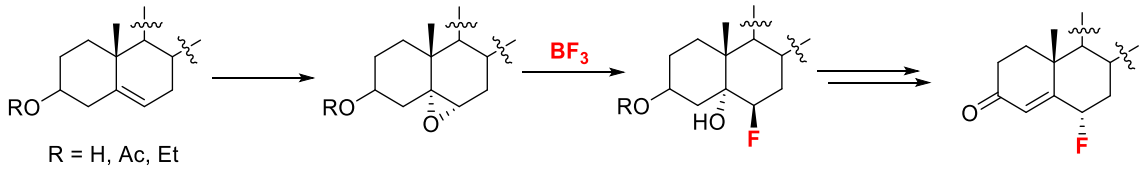
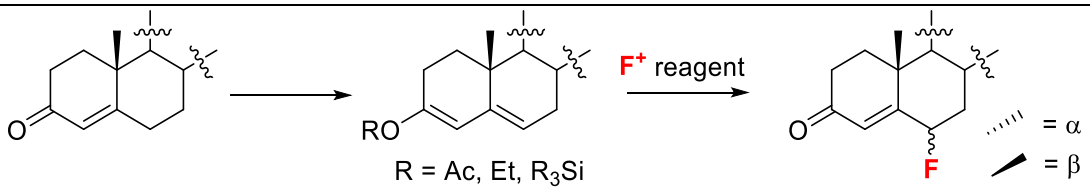
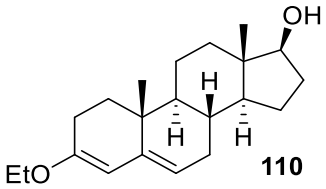
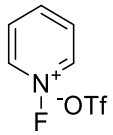
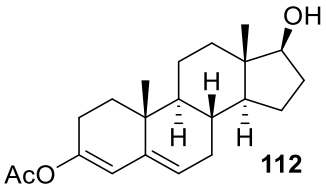
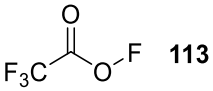
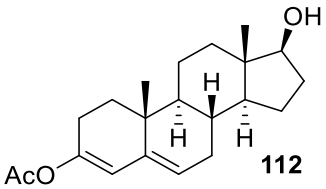
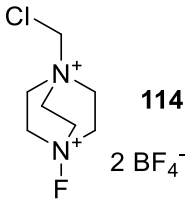
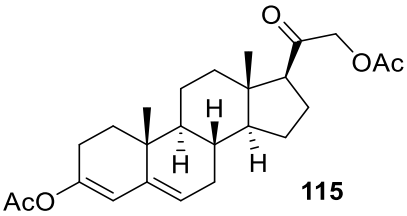
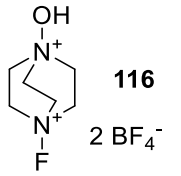


Figure 53: Epoxide ring opening based introduction of the 6-fluoro functionality into steroid systems.

Electrophilic fluorination reactions have been of interest for a long time and over the past 50 years several reagents have been developed which have been shown to be useful for the synthesis of 6-fluorosteroids. Early examples of this transformation included the use of perchloryl fluoride[169] and trifluoroacetyl hypofluorite (CF_3COOF)[170], but these reagents are not suitable for large scale use because of their high reactivity and potential to form explosive mixtures. In more recent years, several N-F reagents, for example N-fluoropyridinium salts[45], Selectfluor[49] or Accufluor[171] have been used for the fluorination of steroid enolate derivatives and because of the high value of fluorosteroids, this is an area where they found larger scale applications (for example in the manufacture of Fluticasone).

Table 8: Electrophilic fluorination of steroid enolate systems.



Enolate	F^+ reagent	Yield / %	α : β selectivity
 **110**	 **111**	72	1 : 2
 **112**	 **113**	70	1 : 1.5
 **112**	 **114** 2 BF_4^-	95	1 : 1.5
 **115**	 **116** 2 BF_4^-	89	1 : 2.2

Even though most electrophilic fluorinating reagents are synthesised using elemental fluorine, there have only been very few examples in the literature where fluorine gas was reacted with steroid substrates and all these examples focused on the fluorination of tertiary C-H positions.[64–66] Rozen and co-workers observed that the regio-selectivity of the fluorination reaction can be influenced by substituents in the vicinity of the tertiary C-H positions as electron withdrawing groups decrease electron density in the C-H bond, lowering their reactivity towards elemental fluorine.

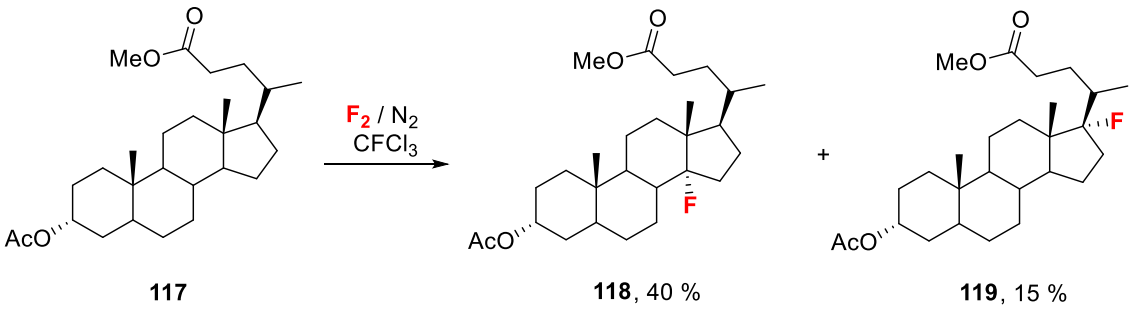


Figure 54: Direct fluorination of 5β-cholanic acid-3α-ol acetate methyl ester.

Given the importance of 6-fluorosteroids in medicinal applications, it is surprising that elemental fluorine has not been investigated as a potential reagent for the synthesis of these systems. In this chapter the selective direct fluorination of progesterone enol acetate is discussed, which was chosen as a relatively simple model substrate that contains the necessary enolisable α–β unsaturated ketone system that directs the fluorination at the 6 position.

3.1.2 Synthesis of progesterone derivatives

It was shown in a previous chapter that fluorine gas can react with enolate systems to form α-fluoroketones in reasonable yield and good selectivity, but only structurally very simple systems have been fluorinated using this methodology. In this study we aimed to investigate whether elemental fluorine is a viable reagent for the synthesis of 6-fluorosteroids via the direct fluorination of their enolate derivatives.

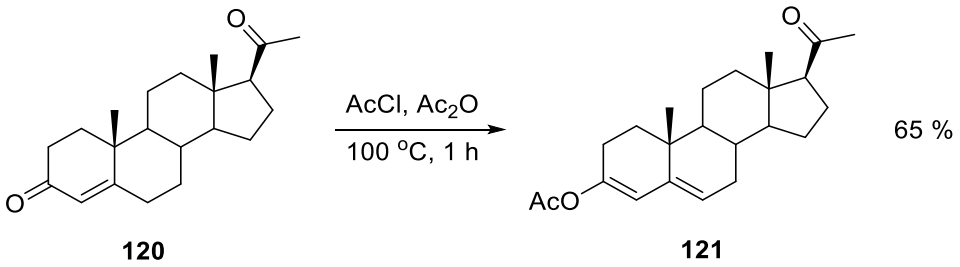


Figure 55: Synthesis of progesterone enol acetate.

The synthesis of the enol acetate of progesterone was performed following a modified literature procedure.[172] Progesterone was dissolved in the mixture of acetyl chloride and acetic anhydride and was heated to 100 °C for 1 h. After confirming full conversion of the starting material with TLC analysis, the mixture was allowed to cool to room temperature and concentrated to one third of the original volume under reduced pressure at 25 °C when a white precipitate formed. The product was filtered, washed with cold acetonitrile and dried under vacuum at 35 °C to afford progesterone enol acetate in 65 % yield and satisfactory purity for further synthesis as shown by ^{1}H and ^{13}C NMR spectroscopic analysis. The structure was confirmed by the assignment of all ^{1}H and ^{13}C peaks using COSY, HSQC and HMBC NMR spectroscopic techniques which were in agreement with previously reported values[173].

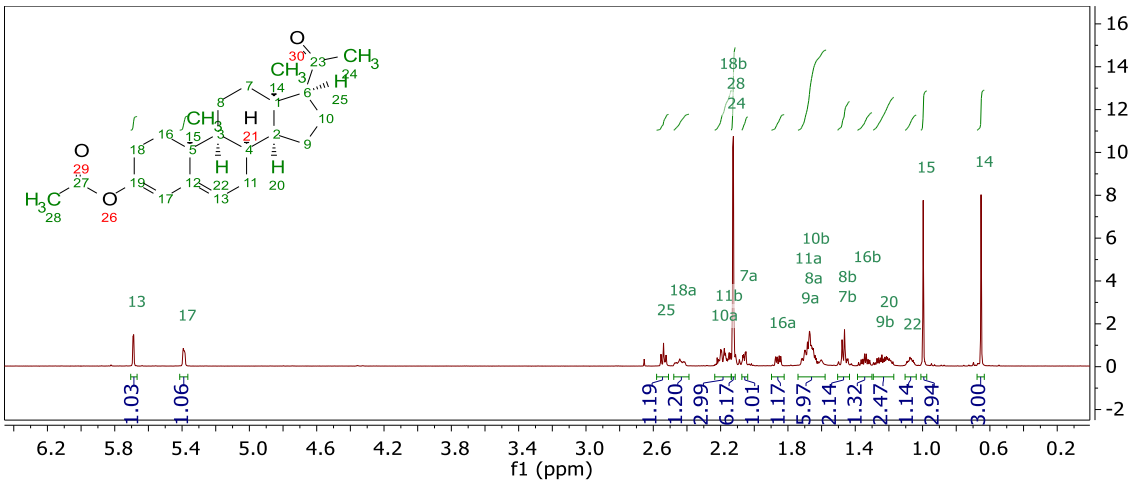


Figure 56: ^{1}H NMR spectrum of progesterone enol acetate.

For the analysis of a product mixture following direct fluorination, ^{1}H NMR spectroscopy was deemed unsuitable because of the complexity of the ^{1}H NMR spectra of steroid compounds (e.g. Figure 56), therefore, a HPLC method was sought. To achieve accurate analysis results, analytical samples of both 6-fluoroprogesterone isomers were synthesised to be used as standards. These compounds were synthesised using Selectfluor™ in a mixture of acetonitrile and acetone adopting a method previously reported in the literature.[49]

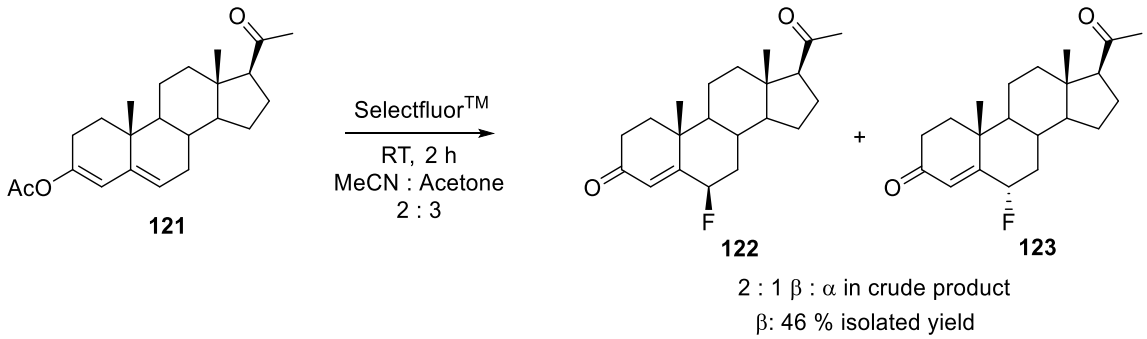


Figure 57: Fluorination of progesterone enol acetate using Selectfluor.

After simple aqueous workup, the crude reaction product was a mixture of two isomers (1 : 2 ratio: -183 and -166 ppm in the ^{19}F NMR spectrum), of which, the major product (-166 ppm) was isolated using column chromatography in good yield and purity. As NMR spectroscopic analysis was not sufficient to establish the stereochemistry of the major isomer, crystals suitable for X-ray crystallography were grown by slowly evaporating a pure sample dissolved in acetone and subsequent analysis (Figure 60) confirmed that this isomer was 6β-fluoroprogesterone (**122**).

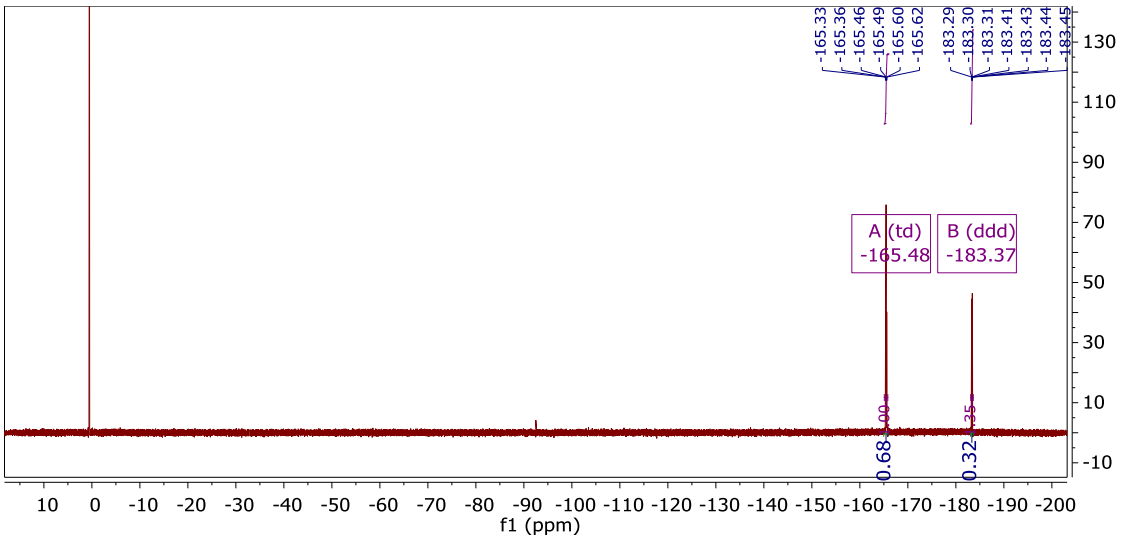


Figure 58: ^{19}F NMR spectrum of the crude fluorinated product.

Even though the α and β isomers were separable by column chromatography, a larger sample of the α isomer was obtained by the enolisation of the crude product mixture with dry HCl in acetic acid to transform the mixture into the thermodynamically more stable α form (**123**).[174]

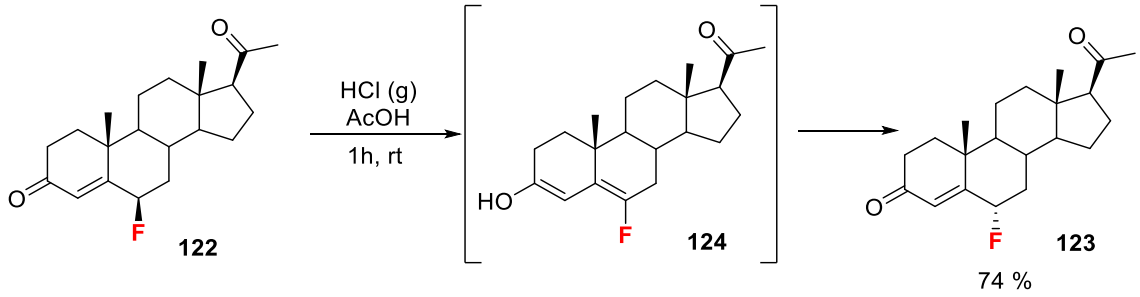


Figure 59: Synthesis of 6α-fluoroproesterone.

The crude product contained a small amount of β isomer, but after recrystallisation from methanol, pure crystals of 6α-fluoroprogesterone were isolated in good yield (74 %) and the structure of the α-isomer was also confirmed using NMR spectroscopy and by X-ray crystallography.

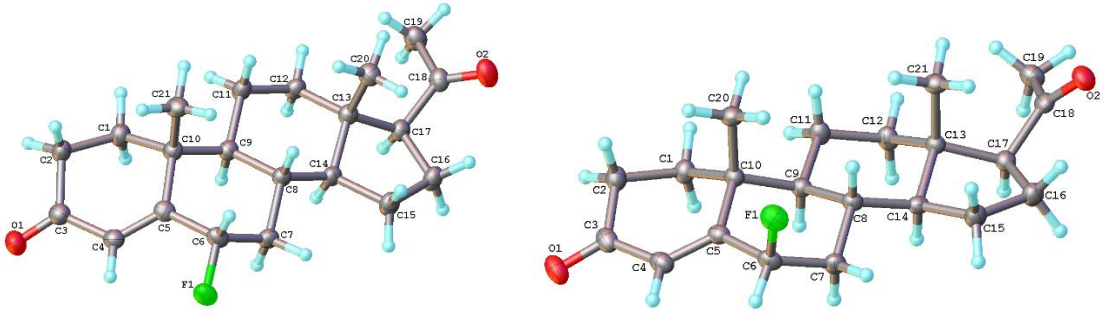


Figure 60: Molecular structure of 6α- and 6β-fluoroprogesterone as determined by X-ray crystallography.

3.1.2 Quantitative analysis method development

With analytical samples of 6α– and 6β-fluoroprogesterone isomers in hand we were able to establish a reliable HPLC method for product analysis. It is described in the literature that the side-product of enol-acetate fluorination is the hydrolysed, non-fluorinated ketone, therefore, the HPLC method was developed to give good separation of three proposed main components of a fluorination crude product: progesterone, 6α- and 6β-fluoroprogesterone. The separation of such non-polar compounds is best carried out using reverse-phase chromatography, thus, the analysis was optimised on a Waters C18 column using water and acetonitrile as mobile phase with 0.1 % formic acid additive. Base-line separation was achieved using the following method: after injection, the sample was eluted at 1.5 ml/min flow rate for 3 minutes with a mixture of 60 % water (0.1 % HCOOH) and 40 % acetonitrile (0.1 % HCOOH) then the acetonitrile was increased to 95 % over 15 minutes and this was maintained for a further 3 minutes. The UV detection was carried out at 237 nm, as all desired compounds have strong absorption at this wavelength.

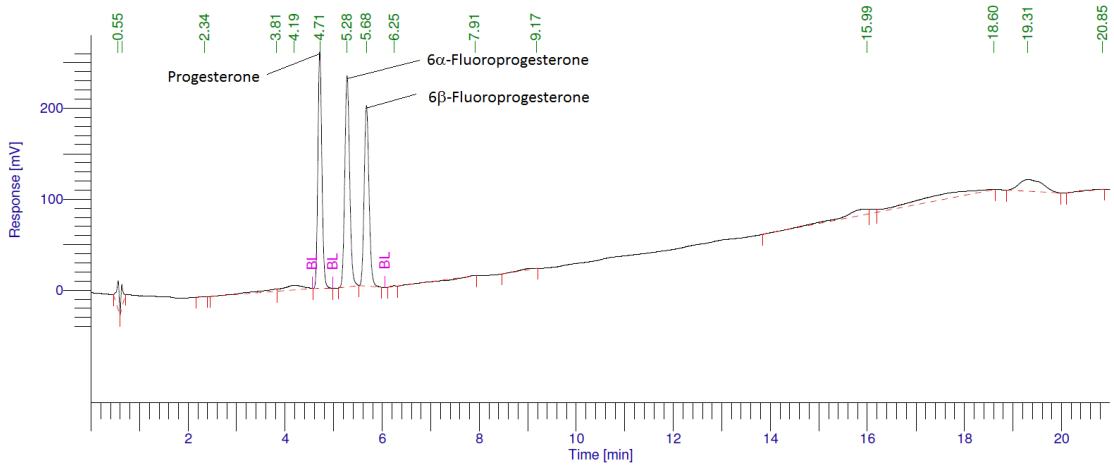
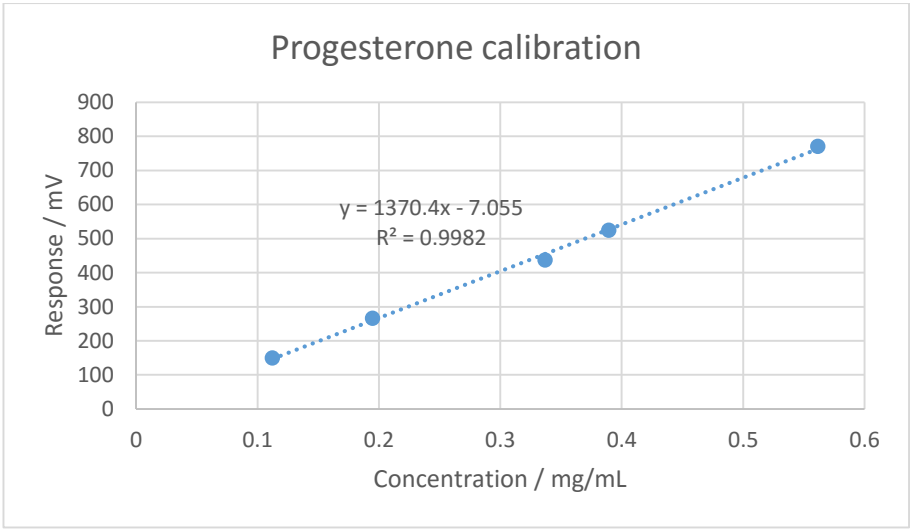
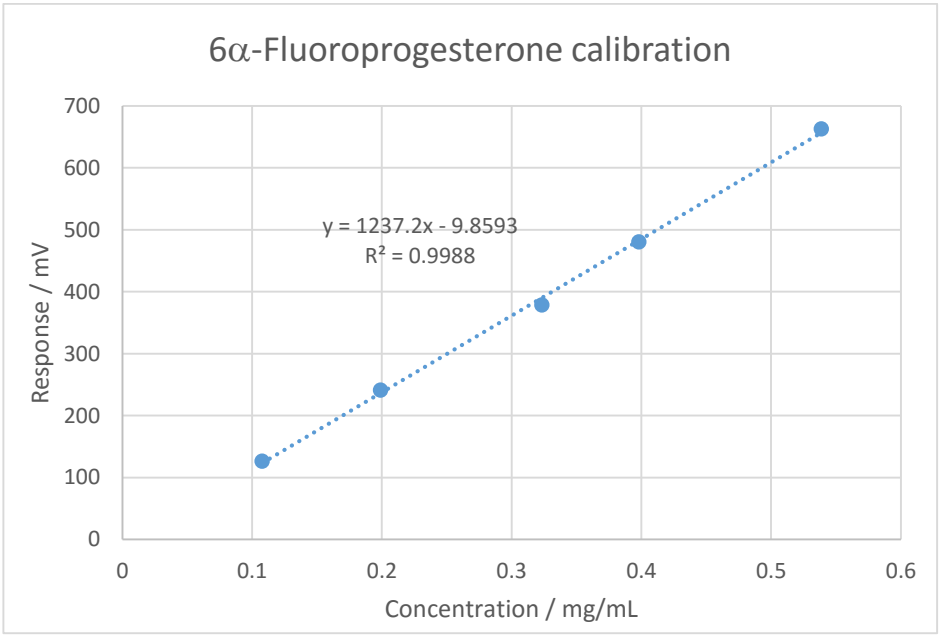


Figure 61: HPLC-UV chromatogram of a mixture of progesterone, 6a- and 6b-fluoroprogesterone.

To accurately determine the amount of the desired products in a crude reaction mixture, calibration curves were measured for the three known components. The concentration range where these compounds can be accurately measured with HPLC was between 0.1 and 0.5 mg/mL and, therefore the calibration was carried out in this range using 5 data points for each component.





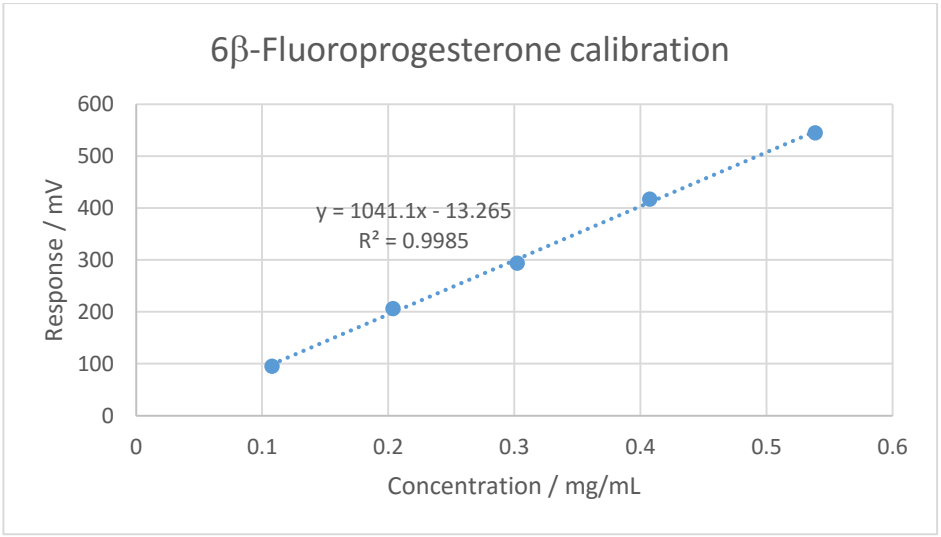


Figure 62: Calibration curves for the determination of progesterone, 6α- and 6β-fluoroprogesterone.

All three calibration curves give excellent linear relation ($R^2 \geq 0.99$) between product concentration and they were validated by analysing an artificial sample of known concentration of each component which confirmed the accuracy of the method (Table 9). The results clearly show that this method is suitable for the determination of the amounts of the three desired components in a reaction product mixture with the relative error of the measurement being less than 5 %.

Table 9: Validation results of the calibration curves.

Compound	Concentration (mg/mL)	Measured concentration (mg/mL) (average of 5 injections)
Progesterone	0.3370	0.3197±0.0090
6α-Fluoroprogesterone	0.3232	0.3059±0.0128
6β-Fluoroprogesterone	0.3021	0.2953±0.0210

3.1.4 Direct fluorination of progesterone enol acetate

Direct fluorination was carried out in formic acid solution as it was shown in the literature to be the preferred solvent for the fluorination of enolate systems.[82] Progesterone enol acetate (1.06 g) was dissolved in formic acid and reacted with a small excess of fluorine gas (1.4 equivalents); after evaporation of the solvent 1.02 g of yellow oily material was obtained which was dissolved in acetonitrile in a volumetric flask (25 mL) and an aliquot was diluted twentyfold for HPLC analysis.

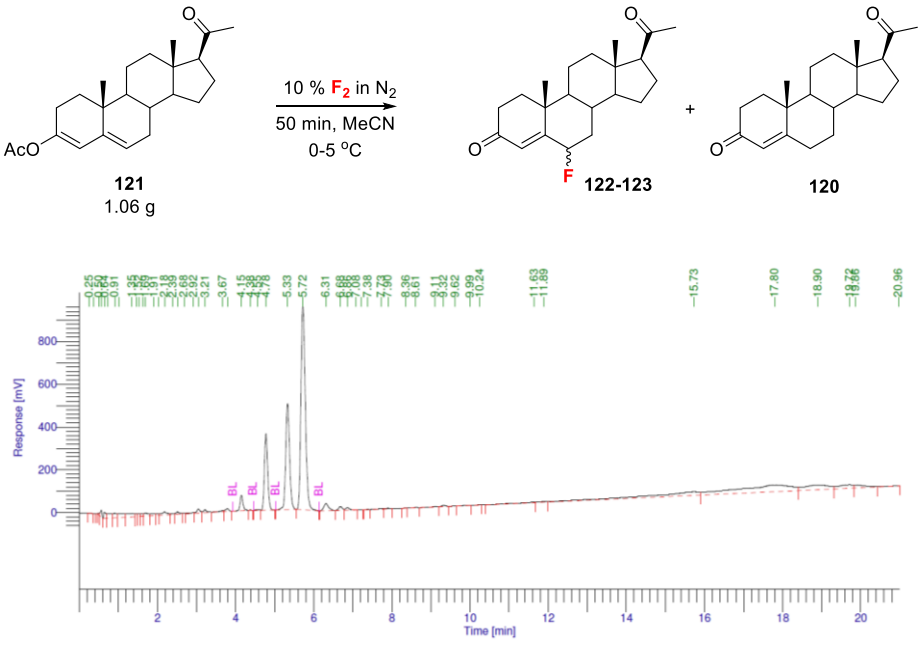


Figure 63: HPLC-UV chromatogram of the crude product from the direct fluorination of progesterone enol acetate.

The chromatogram showed full conversion of the starting material and the presence of the desired products as main components along with some minor impurities, but integration revealed that only half of the product mass could be accounted for by these three compounds. Interestingly, the selectivity of the direct fluorination (α to β, 1 : 2) is similar to that of the Selectfluor™ reaction, but most likely, the conjugated π-bond system responsible for the UV detection is destroyed under these conditions making several side products undetectable. When a larger excess of fluorine gas (2.1 eq.) was used, the amount of product observed by HPLC was even less (400 mg from a 1 g sample).

Table 10: Quantitative analysis of the reaction products by HPLC-UV.

Product	Retention time (min)	Calculated amount (mg)
6α-Fluoroprogesterone	4.78	80.1
6β-Fluoroprogesterone	5.33	158.2
Progesterone	5.72	272.9

After HPLC analysis, 1.02 g of the product was recovered from solution by evaporating the solvent and was subjected to normal phase column chromatography initially using toluene and ethyl acetate then ethyl acetate and methanol to maximise material recovery from the silica phase. Four different fractions were collected and analysed by NMR spectroscopy.

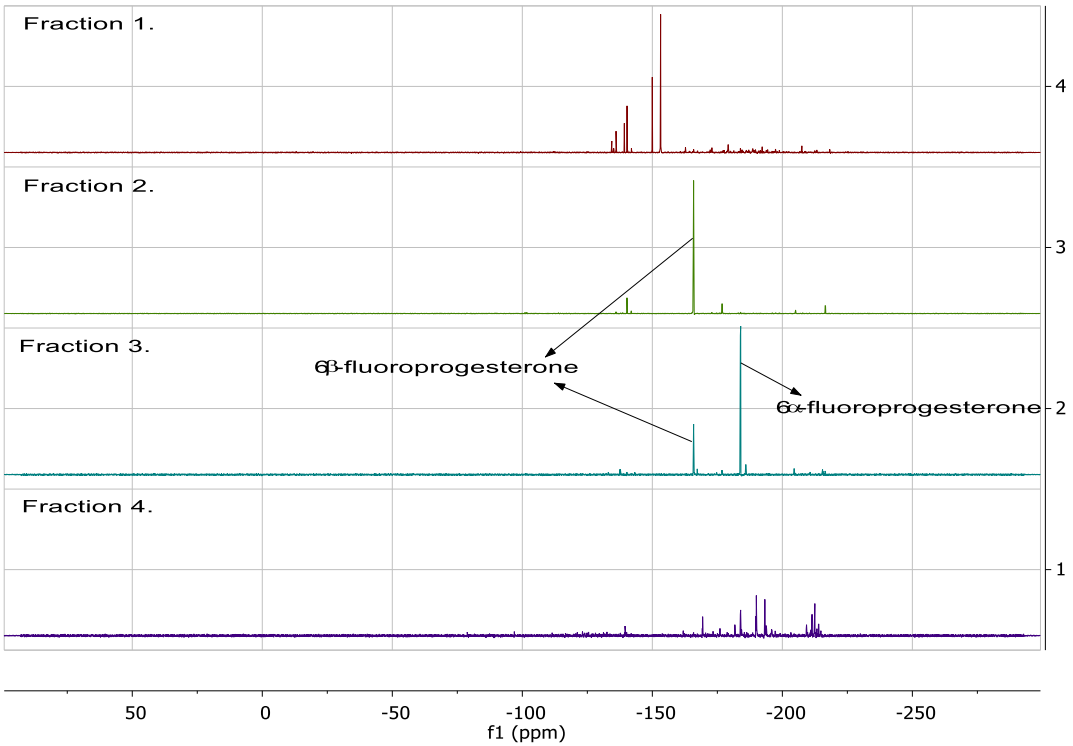


Figure 64: ^{19}F NMR spectra of the various fractions from the purification of a progesterone enol acetate fluorination mixture.

The first fraction (0.10 g) contained several unidentified fluorinated compounds, the second (0.19 g) was mainly a mixture of progesterone and 6β-fluoroprogesterone with only minor fluorinated contaminations. The third and largest fraction (0.47 g) contained a small amount of 6β- and 6α-fluoroprogesterone along with several unidentified non-fluorinated species while the final fraction (0.19 g) only contained unknown partially fluorinated material. Attempts to further purify any of the fractions was unsuccessful. The unidentified material could potentially contain other C-H fluorinated compounds, F_2 addition derivatives or possible carbon skeleton rearrangement products as it is known that HF can facilitate these transformations.

3.1.5 Conclusion

The direct fluorination approach to 6-fluorosteroid systems was investigated in this chapter using progesterone as a model substrate. Pure analytical samples of 6α- and 6β-fluorprogesterone were synthesised using Selectfluor™ and were used to develop a HPLC-UV method for the quantitative analysis of reaction mixtures. Direct fluorination led to full conversion of the starting material, however, HPLC-UV analysis showed that only 50 % of the material was converted to known compounds and the remaining material was as unidentifiable mixture of compounds that were not detected by the detection method used for the HPLC analysis. Efforts to purify and isolate pure products from the mixture were unsuccessful. Consequently, synthesis of 6β-fluorosteroids needs to be carried out using alternative electrophilic reagents, such as Selectfluor™ or NFSI, as fluorine gas leads to large amount of unidentified material that cannot be separated from the desired products using conventional purification methods.

3.2 Fluoroaromatic derivatives

Fluorobenzene derivatives are present in a wide range of life science products with over 35 % of fluorine containing pharmaceuticals contains at least one fluorine atom attached to an aromatic ring (Chapter 1.), however, the synthesis of these systems still heavily relies on wasteful, multi-step processes such as the Balz-Schiemann reaction or nucleophilic halogen exchange methods.

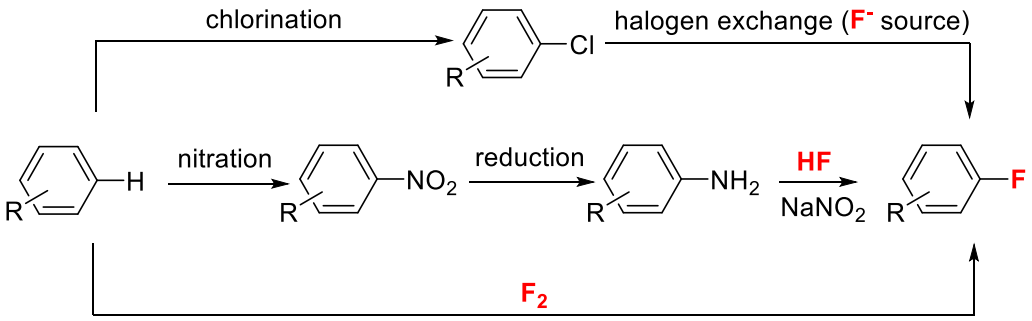


Figure 65: Aromatic fluorination methods.

3.2.1 Aims

Direct fluorination methods have been developed for aromatic fluorination previously at Durham and it was found that 1,4-disubstituted benzene derivatives bearing both an electron withdrawing and an electron donating group are good substrates for this reaction, giving 3-fluoro-1,4-disubstituted benzene derivatives in good yield following chromatographic purification. Such fluorinated aromatic systems, in which the fluorine substituent is in the *meta* position to an electron withdrawing group, appear in the synthesis of various biologically active systems such as Losmapimod or Linezolid (Figure 66).

In this chapter, the direct fluorination of model 1,4-disubstituted benzene systems is reinvestigated with an aim to identify substrates where the isolation and purification can be achieved without the use of chromatography and on a reasonable scale. After finding the optimal reaction conditions, the reactions will be scaled up to synthetically useful scale (10-20 g) and purified to provide data for green metrics analysis and comparison with Balz-Schiemann processes.

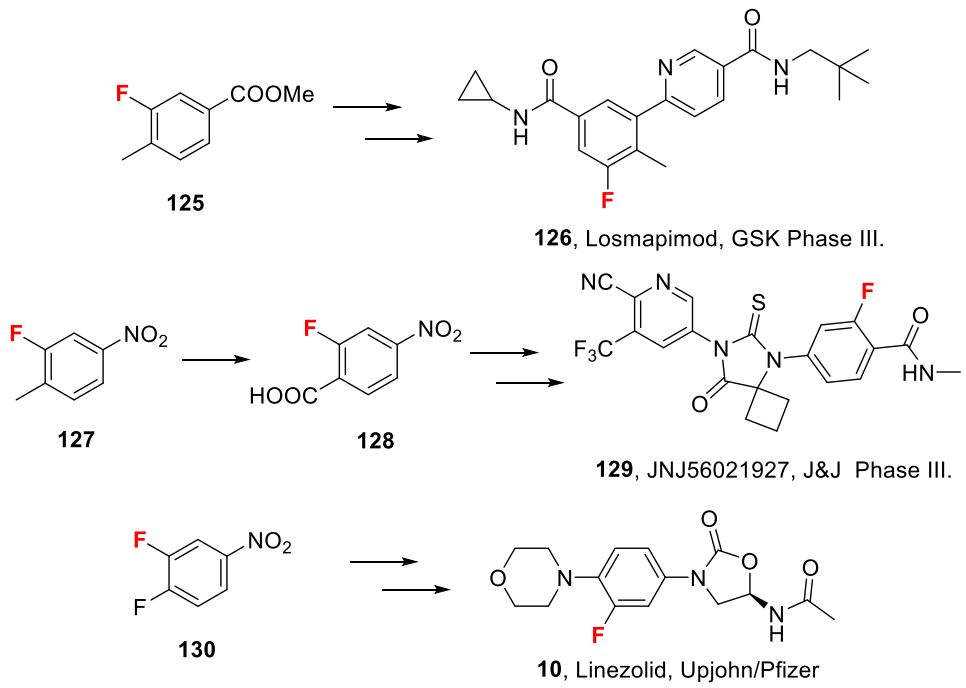


Figure 66: Active pharmaceutical ingredients containing a 3-fluorobenzene structure.

3.2.2 Fluorination of aromatic substrates

For the direct fluorination study a number of compounds were selected based on literature use in pharmaceutical syntheses and consultation with colleagues from pharmaceutical companies participating in the Chem21 project. 3,4-Difluorobenzonitrile and 3,4-difluoronitrobenzene were identified as pharmaceutically relevant systems where the synthesis is potentially possible using fluorine gas and the known synthetic routes are available from the literature. All fluorination reactions were performed in the already described batch fluorination apparatus mainly using mechanically stirred larger (250 mL) reactors.

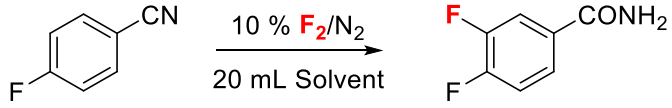
Figure 67: Larger scale baffled batch reactors used for fluorination.

3.2.3 Fluorination of 4-fluorobenzonitrile

Direct fluorination of 4-fluorobenzonitrile has been reported[90] to proceed with good conversion in formic and sulfuric acid solvents, therefore, this reaction was investigated in more detail to meet the aims discussed above.

In a typical reaction, 1.21 g of 4-fluorobenzonitrile was dissolved in the reaction solvent in a fluorination reactor, the mixture was purged with nitrogen for 5-10 minutes then fluorine was introduced at 40 mL/min (10 mmol/h) rate. After the introduction of the desired amount of fluorine, the fluorine flow was stopped, the mixture was purged with nitrogen to remove traces of fluorine and, following an aqueous workup, the crude product was isolated either by filtration (H_2SO_4 reactions) or by extraction with ethyl acetate (formic acid reactions). The crude product was analysed by ^{19}F NMR spectroscopy to determine the composition of the isolated material.

Table 11: Screening of reaction conditions for the fluorination of 4-fluorobenzonitrile.



49
1.21 g (10 mmol)

131

No.	Fluorine equivalent	Solvent	Conversion (^{19}F NMR)	Notes
1	1.5	H_2SO_4	22 %	0.79 g solid, **131** + **49** (hydrolysed)
2	2.5	H_2SO_4	30 %	0.75 g solid, **131** + **49** (hydrolysed)
3	3.5	H_2SO_4	54 %	0.72 solid, **131** + **49** (hydrolysed)+2% trifluoro
4	4.5	H_2SO_4	82 %	0.34 g solid, **131** + **49** (hydrolysed)+10 % trifluoro
5	1.5	HCOOH	37 %	0.80 g oil, **131** + **49** (hydrolysed) + unknown
6	2.5	HCOOH	55 %	0.63 g oil, **131** + **49** (hydrolysed), tri-F, unknown
7	3.5	HCOOH	70 %+	0.88 g oil, **131** + **49** (hydrolysed), lot of small side products
8	4.5	HCOOH	85 %+	0.75 g oil, **131** + **49** (hydrolysed), trifluoro, lot of other imps.

At lower conversions (entries 1-2) the selectivity of the reaction is good and only the hydrolysed starting material and the desired product **131** were observed both in sulphuric and formic acid

solution. However, with increasing the conversion by using a further excess of F_2, other polyfluorinated side products appeared. The recovery of the product was significantly better from formic acid solutions, but the selectivity of the reaction was higher in the case of sulfuric acid, therefore, the latter was chosen as the reaction solvent for subsequent experiments.

To establish purification methods, the reaction was carried out on larger scale (5 g) in sulfuric acid using 20 % fluorine gas in nitrogen (3 equivalents) and after standard workup only a small amount of product was isolated (0.2 g). Neutralisation of the aqueous solution with ammonia precipitated a crystalline material which was recovered (3.9 g) by vacuum filtration. ^{19}F NMR analysis of the product showed that it was a mixture of amide **131** with hydrolysed starting material and some minor impurities.

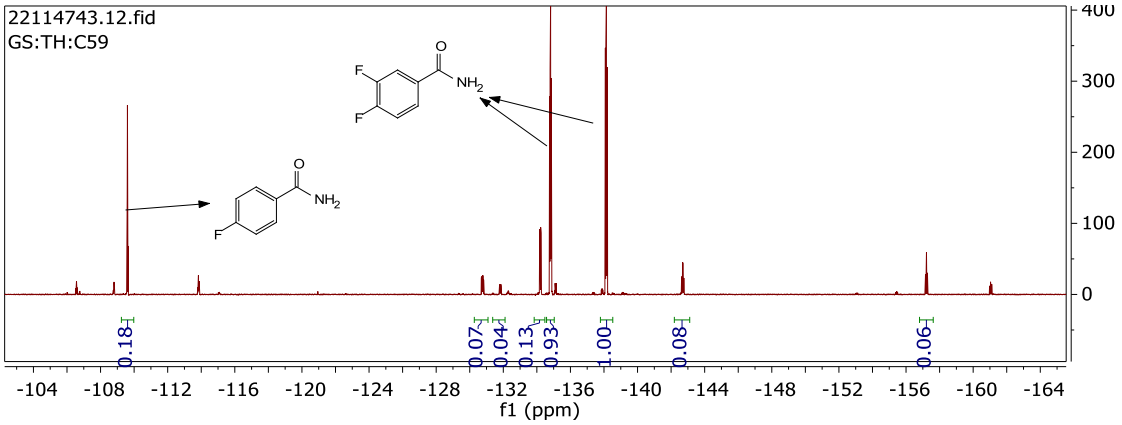


Figure 68: ^{19}F NMR spectrum of the crude product of the larger scale fluorination.

In order to separate the difluorinated product from the mono- and polyfluoro impurities, 1 g samples of the crude product were recrystallized from various solvents, but no improvement in purity was observed in solvents with varying polarity (Figure 69). It is possible that these amides crystallise in a dimeric hydrogen bonded form and the pair formation is not selective.

Given the difficulties in simple purification of this substrate, a different approach was sought and 3,4-difluorobenzoic acid was identified as a target that is the precursor of the desired nitrile.

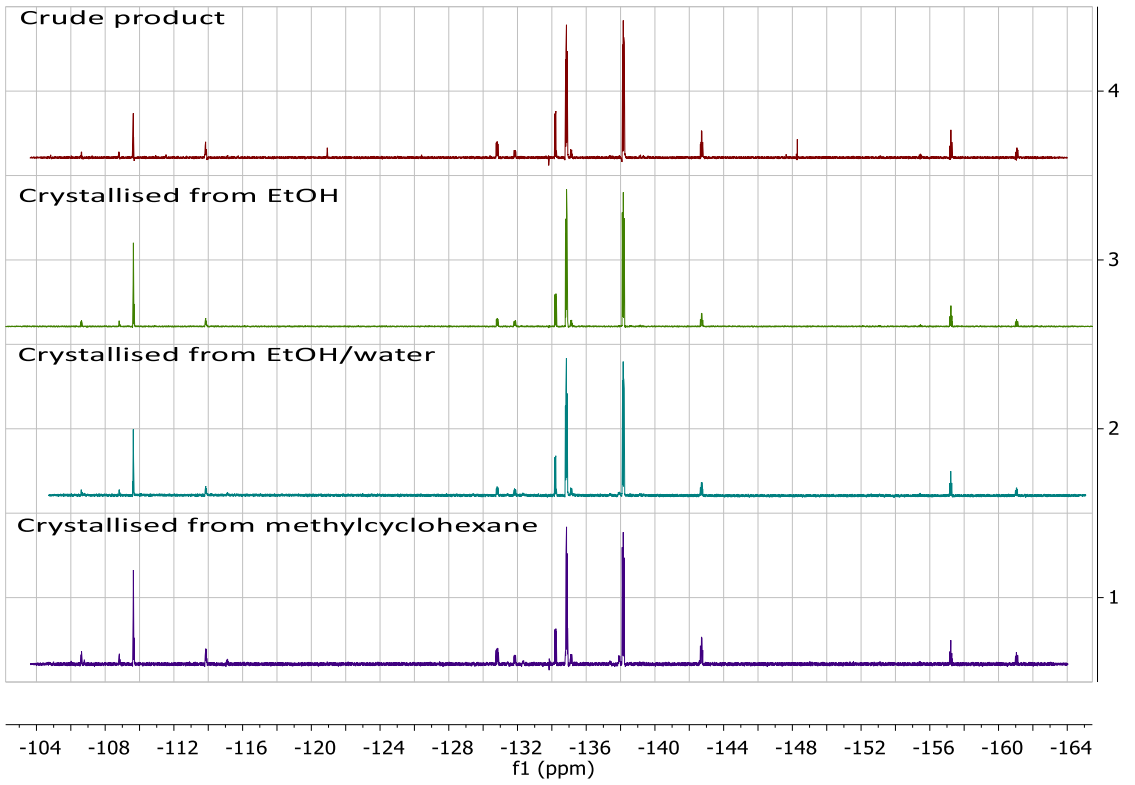


Figure 69: ^{19}F NMR spectra of crude and recrystallized 3,4-difluorobenzamide from ethanol, 50% aqueous ethanol and methylcyclohexane.

3.2.4 Fluorination of 4-fluorobenzoic acid

An alternative approach to 3,4-difluorobenzonitrile is to convert the difluorinated benzoic acid to the benzamide and then dehydrate the amide to the corresponding nitrile. The fluorination of 4-fluorobenzoic acid was one of the early examples of successful aromatic fluorination reactions and it was reported to produce the desired 3,4-difluorobenzoic acid product along with other polyfluorinated products.[89]

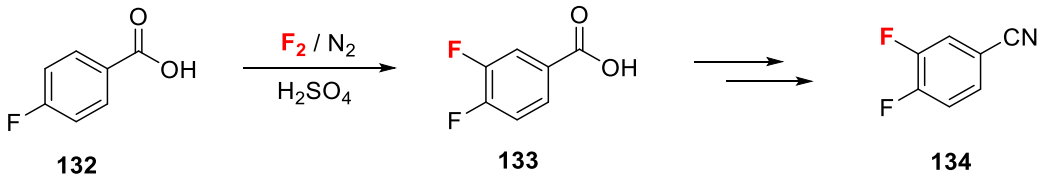


Figure 70: Alternative approach to 3,4-difluorobenzonitrile.

To investigate the viability of this route 4-fluorobenzoic acid (14 g scale) was fluorinated in concentrated sulfuric acid using two equivalents of fluorine (20 %*v/v* in nitrogen) at room temperature to achieve 40 % conversion of the starting material with relatively small amount of side products (<4 %). The crude product (13.8 g) was isolated after quenching the reaction mixture in a large excess of ice and extraction into ethyl acetate.

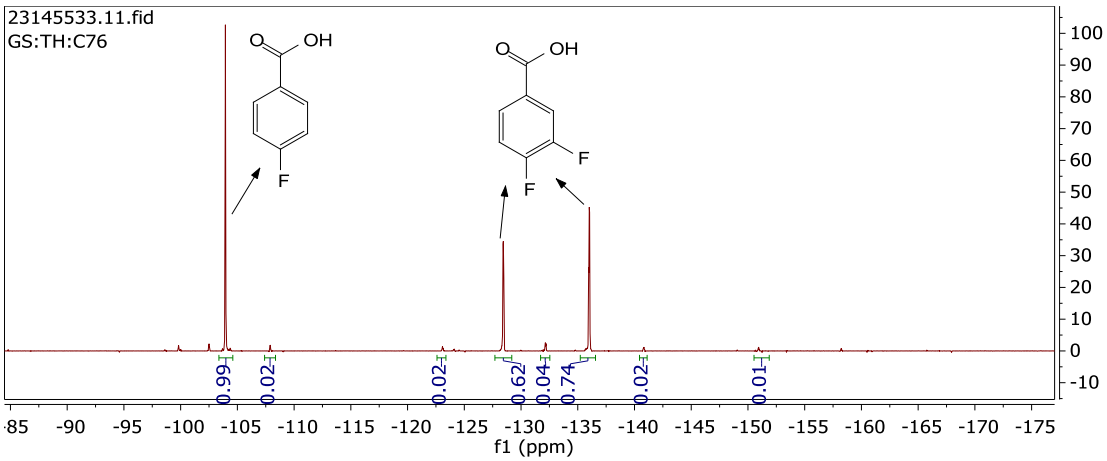
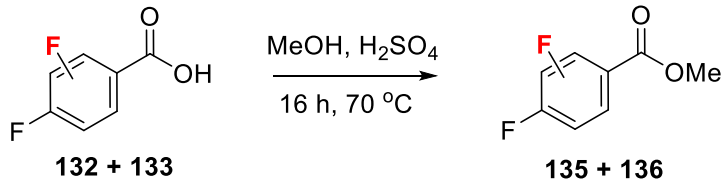


Figure 71: ^{19}F NMR spectrum of the crude product from the direct fluorination of 4-fluorobenzoic acid.

As recrystallization would possibly lead to similar problems as in the case of the benzamide, the crude acid was esterified with methanol to produce the methyl ester derivative of the mixture (11.6 g) and this mixture distilled under vacuum to assess this purification method.



132 + 133 **135 + 136**

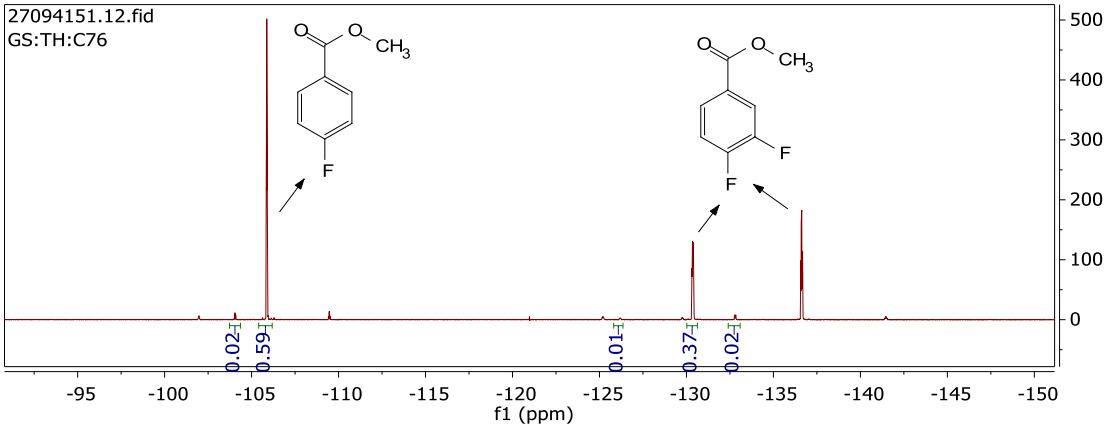


Figure 72: ^{19}F NMR spectrum of crude methyl 3,4-difluorobenzoate.

Vacuum distillation of the mixture of methyl ester derivatives was carried out using a Fischer micro Spaltrohr® MMS 255 distillation apparatus equipped with a valve to control the reflux ratio and a fraction collector for eight separate 1.5 mL fractions (Figure 73).

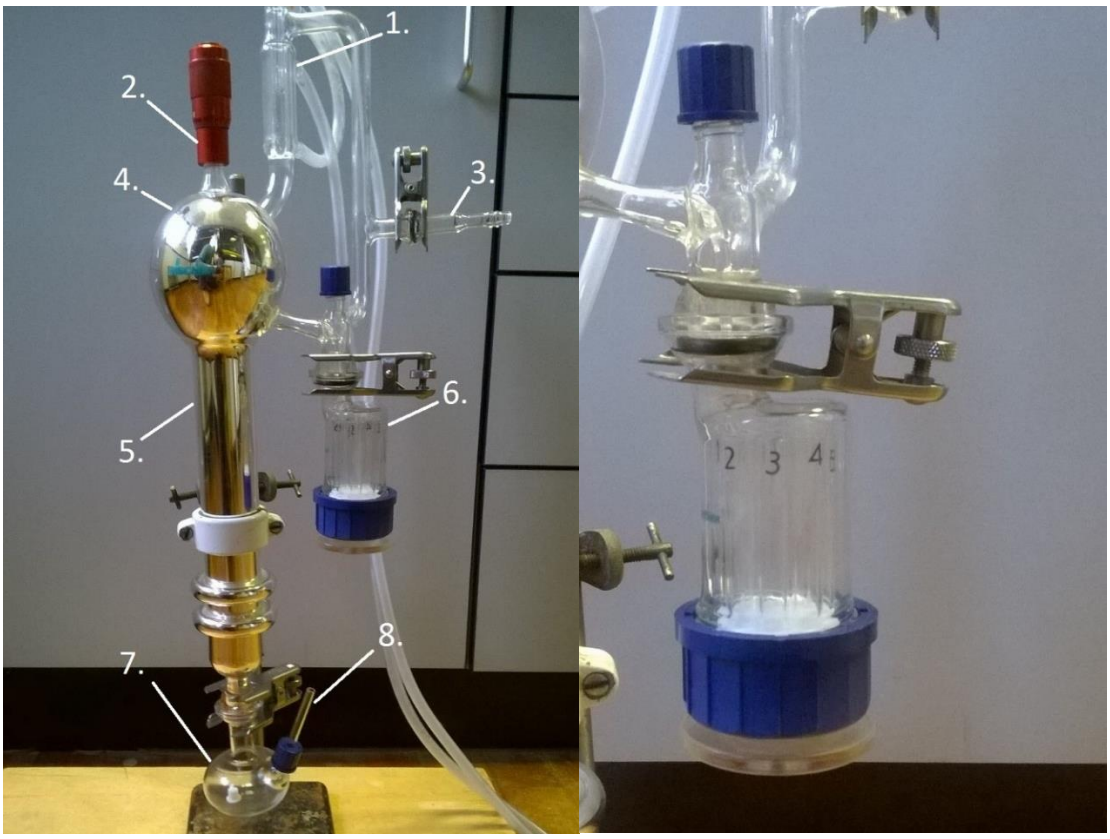


Figure 73: Fischer Spaltrohr® distillation setup (left) with condenser (1), reflux valve (2), vacuum connection (3), thermocouple well (4 and 8), vacuum jacketed column (5), fraction collector (6, also on the right) and distillation flask (7).

The crude mixture of fluorinated methyl benzoates was distilled at 19 mbar pressure and the product boiled at 88-89 °C. After collecting eight, approximately 1 mL samples, the distillation was terminated and all fractions were analysed by ^{19}F NMR spectroscopy to determine their composition.

Table 12: Composition of distillate fractions from the fluorination of 4-fluorobenzoic acid.

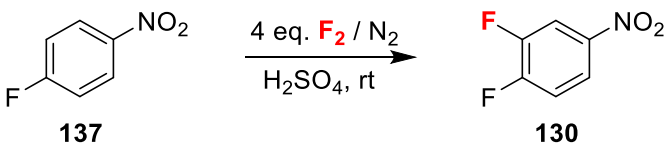
Fraction	Methyl 4-fluorobenzoate %	Methyl 3,4-difluorobenzoate %	Others %	Fraction mass / g
Starting mixture	59	37	4	11.46
Fr. 1	66	33	1	0.95
Fr. 2	66	33	1	1.08
Fr. 3	66	33	1	1.1
Fr. 4	65	33	2	1.03
Fr. 5	65	33	2	1.02
Fr. 6	66	33	1	1.38
Fr. 7	65	34	1	1.16
Fr. 8	64	34	2	1.69
Residue	52	36	12	1.27
Total recovered				10.68

The excellent mass recovery (93 %) shows that the distillation column retains only a small amount of material and fortunately most of the impurities are less volatile than the starting material or the product. However, the two main components, methyl 4-fluorobenzoate and methyl 3,4-difluorobenzoate, possibly form an azeotrope, as their relative ratio in all distillation fractions remains constant within the error of the measurement, therefore, their separation was not possible under these distillation conditions.

In conclusion, although the direct fluorination approach to 3,4-difluorobenzonitrile seems viable, the fluorination reaction is selective only at low conversions (up to 50 %) and the separation of the various products is very difficult using non-chromatographic methods. These results encouraged the assessment of other similar compounds and fluorination of 4-fluoronitrobenzene was selected as another potentially viable substrate.

3.2.5 Fluorination of 4-fluoronitrobenzene

4-Fluoronitrobenzene is less reactive under similar reaction conditions than 4-fluorobenzonitrile or 4-fluorobenzoic acid and since, in formic acid, only 13% conversion was achieved and on small scale (1.4 g, 10 mmol) even in sulphuric acid only 48 % of the starting material was converted when four equivalents of fluorine was used (Figure 74).



137 130

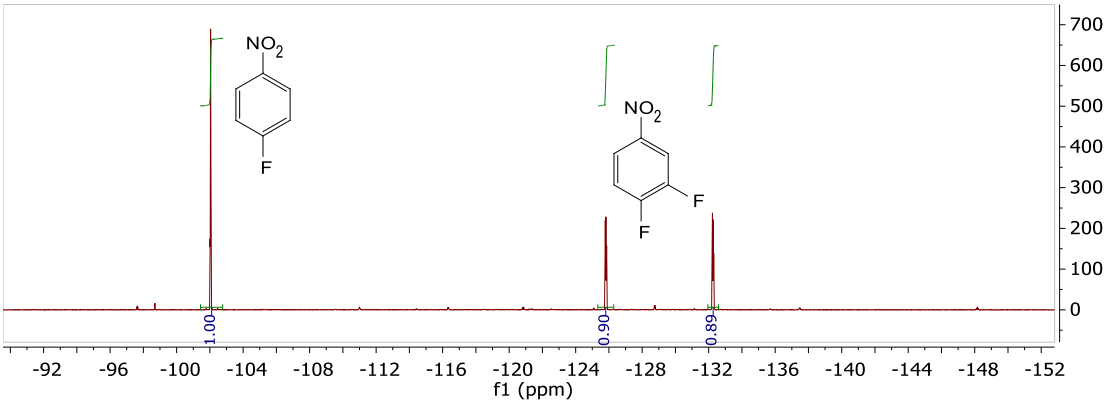
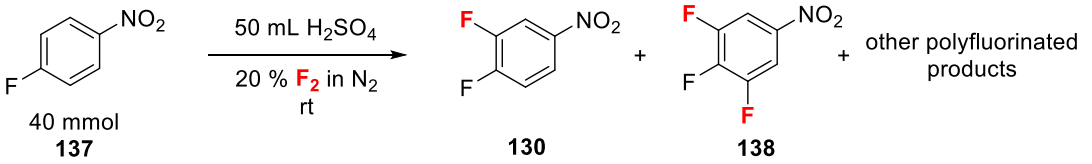


Figure 74: ^{19}F NMR spectrum of the small scale fluorination of 4-fluoronitrobenzene.

The low conversion was mainly attributed to inefficient mixing, as concentrated sulfuric acid has high viscosity and the magnetic stirrer used was not powerful enough. In order to improve mixing, a mechanical stirrer was used in all later experiments instead of magnetic stirring, but to efficiently use this, the reaction had to be scaled to 40 mmol (5.6 g) scale for which 50 mL of solvent was used in a 250 mL glass reactor. To shorten reaction time, concentration of fluorine was also increased to 20 % from the initial 10 % as from previous experience, the concentration of fluorine does not have large effect on the selectivity of these reactions. Under these conditions, multiple batches were fluorinated to obtain sufficient quantity of material for a fractional vacuum distillation. During these reactions, a noticeable exotherm was detected, which may explain the formation of tar.

The results from these separate experiments demonstrate the reproducibility of this fluorination reaction as the quantity and the composition of the obtained product was very consistent throughout the batches. Steam distillation as an alternative isolation methodology was also investigated in one case and although the isolated amount was approximately 20 % less, this product was a transparent yellow oil while the product isolated by solvent extraction was a dark brown viscous oil heavily contaminated with tar.

Table 13: High conversion fluorination of 4-fluoronitrobenzene.



Starting material / F_2 equivalents	Isolation method	Isolated product	Product composition (^{19}F NMR)
5.71 g / 4.5 eq.	EtOAc extraction	5.42 g	74 % **130**, 5 % **137**, 7 % **138**, 14 % other trifluoro isomers, tar
5.75 g / 4.5 eq.	Steam distillation	4.10 g	75 % **130**, 9 % **137**, 5 % **138**, 11 % other trifluoro isomers, **no tar**
5.66 g / 4.5 eq.	EtOAc extraction	5.50 g	75 % **130**, 8 % **137**, 5 % **138**, 12 % other trifluoro isomers, tar
5.74 g / 4.5 eq.	EtOAc extraction	5.46 g	76 % **130**, 6 % **137**, 5 % **138,** 13 % other trifluoro isomers, tar

The four batches were combined and 20.2 g of material was subjected to fractional vacuum distillation using the above described Fischer Spaltrohr® equipment. At 1 mbar pressure seven fractions (11.3 g) were obtained at 65-70 °C and were analysed by ^{19}F NMR spectroscopy. Some volatile material also condensed in the dry-ice trap of the vacuum pump and a significant amount (8.61 g) of non-volatile, viscous tar residue remained.

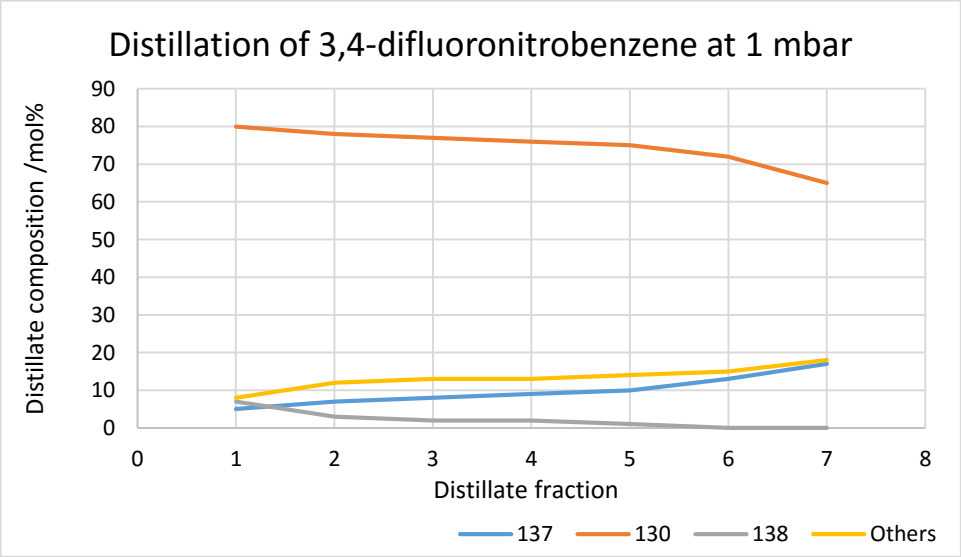


Figure 75: High vacuum distillation of 3,4-difluoronitrobenzene obtained by direct fluorination.

Even though the purification of the product under these conditions was not achieved, the composition chart provided some useful information (Figure 75). The trifluorinated side product

138 (grey line) is slightly more volatile than the desired product **130** (orange line), therefore, even if it is formed in higher quantity, separation should be possible under optimised distillation conditions on an industrial distillation column. The separation of the lower boiling starting material (blue line) from the desired product should also be possible by vacuum distillation. The problem of isolating pure product is the presence of other, unidentified di- and trifluoronitrobenzene isomers which do not separate easily by distillation. Overall, the pressure in the distillation needs to be increased to allow better separation of the components and the composition of the crude product should be limited to a maximum of three major, separable components, also, tar should be separated before distillation to reduce the amount of reactive material in the distillation flask.

Consequently, in the next set of experiments the fluorination was carried out at lower temperature (0 °C) to decrease side product and tar formation and the scale of the reaction was increased to 100 mmol (14.1 g in 70 mL cc H_2SO_4) scale to give distillable quantities of product in shorter time. To improve gas-liquid mixing a new 250 mL reactor was designed with four, larger bafflers and used in the further reactions. Fluorination was carried out as usual, the crude product was isolated by extraction and the material from two batches was combined, dissolved in hexane and filtered to remove a significant amount of tar. This crude product (17.7 g, 53 % 4-F, 43 % 3,4-diF, 4 % others) was distilled (19 mbar, 88 - 92 °C) to obtain 12.6 g of material in a total of 8 fractions.

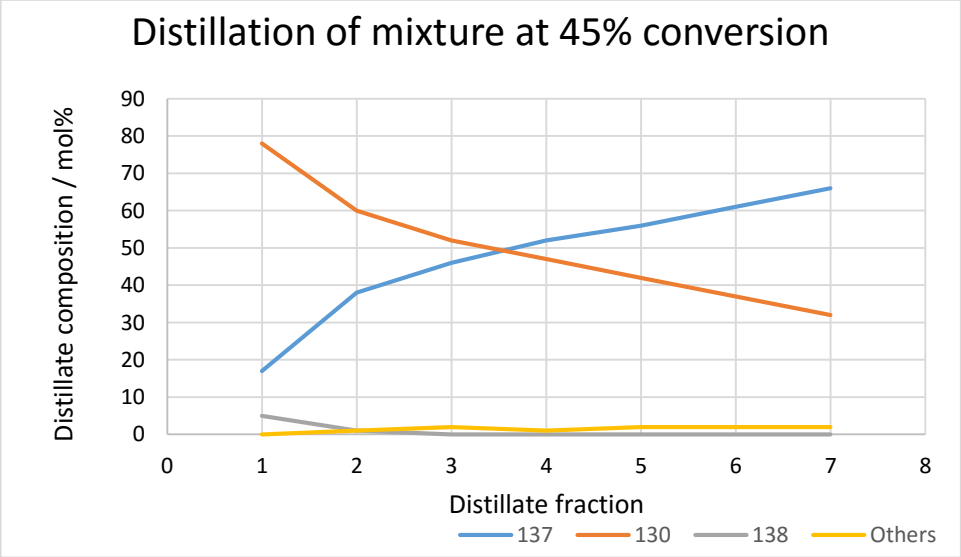


Figure 76: Vacuum distillation of a partially converted fluorination mixture.

Figure 76 shows the composition of the fractions and, although, the 3,4,5-trifluoronitrobenzene side product is present in significant quantity, it can be separated from the rest of the mixture as it is almost exclusively present in the 1st distillation fraction. This chart also shows that the starting material is slightly less volatile than the product, as the first three distillation fractions

are enriched in the difluorinated product. In order to gain further understanding of the optimal distillation conditions, distillations were carried out on artificial mixtures of 4-fluoronitrobenzene and 3,4-difluoronitrobenzene under vacuum using the Fischer MMS 255 fractionating column.

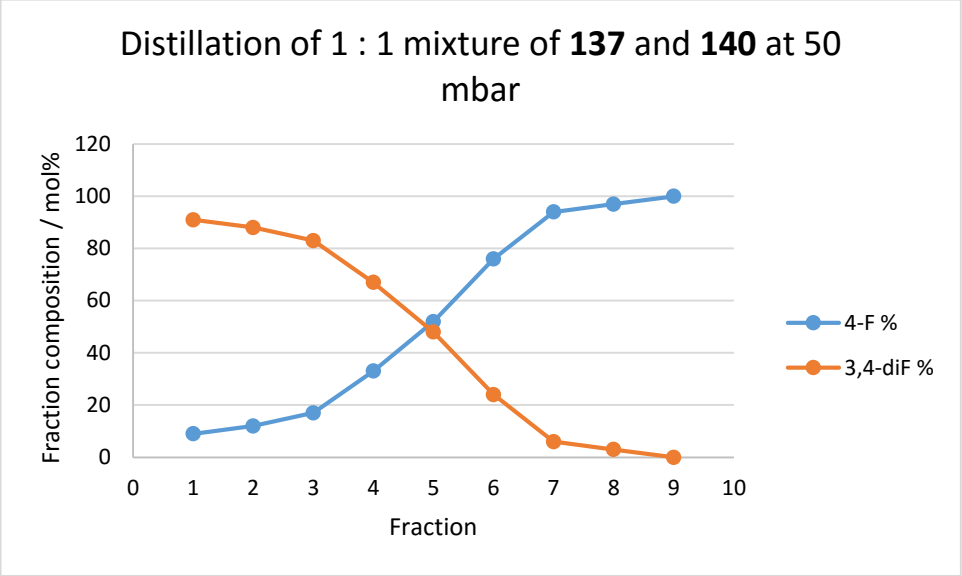


Figure 77: Distillation of an artificial mixture of 4-fluoronitrobenzene and 3,4-difluoronitrobenzene.

Although the distillation was carried out carefully, allowing the best possible separation of components, none of the fractions contained pure difluoronitrobenzene. In this distillation 93 % of the distilled material was recovered in various fractions which shows that the column used retains only a very small amount of material. The highest purity fraction was 92 % pure, which is promising result for a mixture of two compounds that have very similar boiling point (Fraction 1 boiled at 105-107 °C while fraction 8 at 110-112 °C at 50 mbar pressure).

To assess the potential safe temperature range for the distillation step, DSC measurements were conducted on pure samples of 4-fluoronitrobenzene and 3,4-difluoronitrobenzene (Figure 78). These measurements revealed that both compounds begin to decompose above 150 °C with a significant exotherm (392 and 384 J/g respectively). These results clearly limit the possible vacuum/temperature range for a potential distillation.

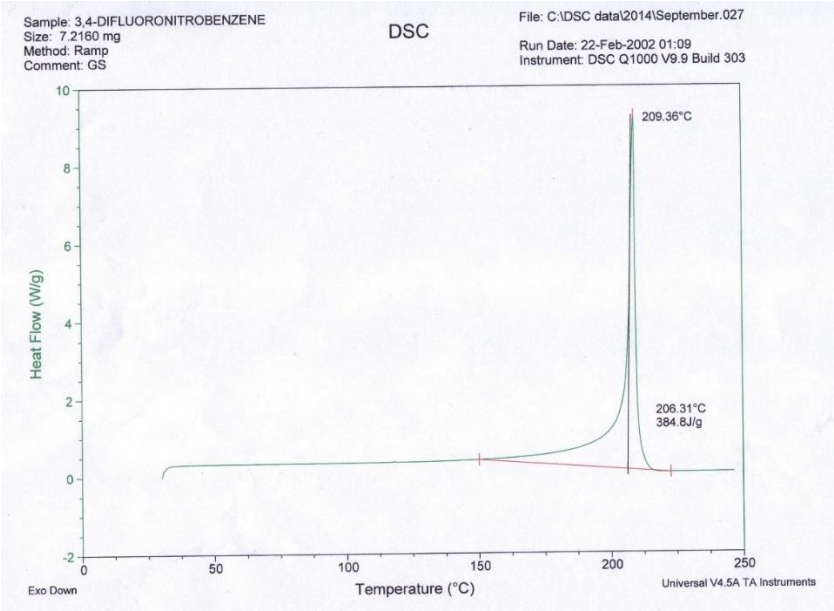
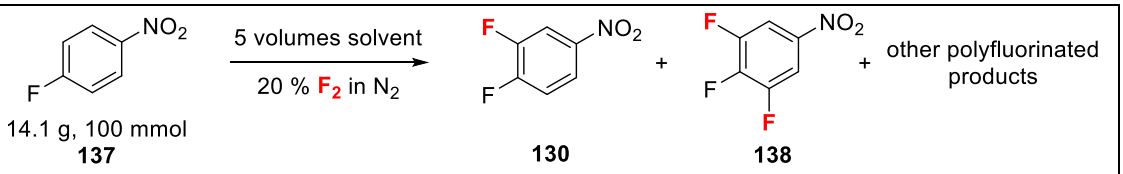


Figure 78: Differential Scanning Calorimetric analysis of 3,4-difluoronitrobenzene.

A major issue of using concentrated sulfuric acid as the only reaction solvent is that it will eventually give a large waste stream after the aqueous workup. In order to control this, other solvent systems were investigated on larger, 100 mmol scale using two equivalents of fluorine. To obtain comparable results, the crude product was subjected to steam or vacuum distillations to remove tar and the volatile fractions were weighed and analysed by ^{19}F NMR spectroscopy.

As the choice of solvents for direct fluorinations is limited, most viable solvents were investigated either in pure form or in combination with sulfuric acid. Sulfuric acid in acetonitrile gave high conversions of the starting material, but unfortunately this reactive mixture lead to a large amount of tar which decreased the mass of the isolated volatile material. The fluorination proceeds to moderate conversion (35-40 %) in acetonitrile without any additive, but tar formation was an issue in this case as well. Other, more unconventional solvents such as methanol or propionic acid did not prove suitable for this reaction probably because of the reaction of fluorine gas with the solvents.

Table 14: Solvent screening for the direct fluorination of 4-fluoronitrobenzene.



Solvent	Temperature	Isolation	Tar removal	Product weight	Composition (^{19}F NMR)
H_2SO_4	0 °C	Extraction	Vac. dist.	11.60 g	56 % **130**, 40 % **137**, 4% others
H_2SO_4	0 °C	Extraction	Vac. dist.	11.56 g	58 % **130**, 37 % **137**, 5 % others
H_2SO_4/MeCN 1/6	-10 °C	Extraction	Kugelrohr	4.57 g	79% **130**, 13 % **137**, 8 % others*
H_2SO_4/MeCN 1/6	-10 °C	Evaporation	Steam dist. (in)**	7.00 g	14 % **137**, 70 % **130**, 4 % **138**, 12 % others
MeCN	-10 °C	Evaporation	Vac. Dist.	3.07 g	63 % **137**, 34 % **130**, 3% others*
MeCN	-10 °C	Evaporation	Steam dist. (ext)**	10.90 g	60 % **137**, 36 % **130**, 3% others
Propionic acid	-10 °C	Evaporation	Steam dist. (in)	8.02 g	95 % **137**, 5 % **130**
H_2SO_4/MeOH 1/9	-10 °C	Evaporation	Steam Dist. (in)	10.26 g	96 % **137**, 4 % **130**

* Significant amount of tarry distillation residue; ** (in): 150 mL water added and product collected in Dean-Stark trap; (ext): external steam generator used with standard distillation setup.

3.2.6 Conclusion

Based on the results discussed in this chapter it is not possible to carry out a detailed green metrics analysis of any of these aromatic direct fluorination processes, moreover, the lack of literature data for the alternative Balz-Schiemann syntheses of such simple fluoroaromatic systems makes benchmarking difficult and highly inaccurate in these cases. The only metric that could be used is Atom Economy, which does not require any experimental data, but this metric alone does not provide a meaningful basis for comparison, therefore, the calculations are not discussed here. In conclusion, direct fluorination of aromatic substrates may be viable in cases where isolation and purification of the desired product is easily achievable and, in such a case, the process should be comparable with the alternative Balz-Schiemann route using green metrics packages.

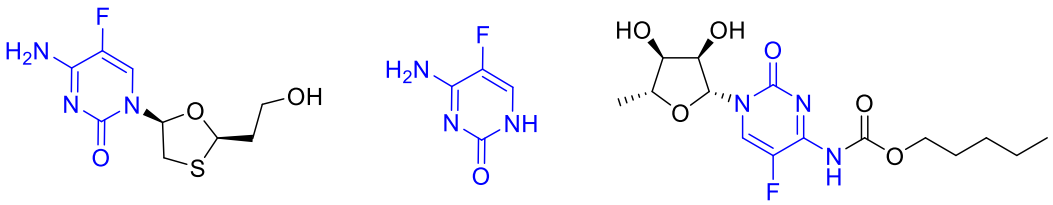
Chapter 4.: Synthesis of Flucytosine

Fluorinated heterocyclic systems are a very important class of compounds that are present in a number of pharmaceutical and agrochemical products and 5-fluoropyrimidines are one of the most frequent member of this class. In this chapter, a direct fluorination approach to the synthesis of 5-fluorocytosine (Flucytosine) will be investigated with the aim of providing a more efficient synthesis than the existing methods to this important API.

4.1 Flucytosine: an essential medicine

Flucytosine is an important medicine for the treatment of various fungal infections which was discovered in the 1960's at Hoffman la Roche and was introduced to the US market in 1971. Flucytosine itself shows no antifungal activity, but in fungal cells it is transformed to 5-fluorouracil (5-FU) by the enzyme cytosine deaminase and it is 5-fluorouracil that inhibits various protein synthesis processes inside these cells.[175] In 2013, Flucytosine was re-included to the core list of WHO Essential Medicines for the treatment of *cryprococcal meningitis* in HIV patients which is the most common cause for the disease and accounts for 20-25 % of AIDS related mortality in sub-Saharan Africa. The combination of high dose (100 mg/kg/day) Flucytosine and Amphotericin B form the initial treatment of *cryptococcal meningitis* recommended by WHO and is considered as the gold standard, achieving significantly higher survival rates then the most widely used fluconazole monotherapy. The main reasons for the low use of Flucytosine in sub-Saharan African countries are the lack of registration with local authorities and the high cost of the medicine[176], therefore, an inexpensive large scale synthesis of this important drug is much needed to facilitate availability in these countries.

The 5-fluorocytosine structure is also found in two other active pharmaceutical ingredients: Capecitabine, an oral chemotherapy drug for the treatment of various cancers and Emtricitabine, a nucleoside reverse transcriptase inhibitor for the treatment of HIV, which is marketed in various combination therapies such as Atripla® and Truvada® by Gilead, with annual sales of over $5 bn.



139, Emtricitabine (Gilead)

6, Flucytosine

140, Capecitabine (Roche)

Figure 79: 5-Fluorocytosine containing drugs.

It is difficult to estimate global production of Flucytosine, but clearly, the use of this fluoropyrimidine derivative as a constituent of several drugs and drug combination therapies presents significant commercial and environmental opportunities, if step-change improvements in the production of Flucytosine can be developed at a competitive price and using sustainable solvents and feedstock. It is estimated that hundreds of thousands of deaths in Sub-Saharan Africa occur on an annual basis from *cryptococcal meningitis,* so given a treatment of approximately 70 g per person, potentially up to 30t of Flucytosine is required every year to treat all patients.

4.1.1 Current synthetic routes to Flucytosine

Although there are several nucleophilic aromatic substitution based synthetic methods for the synthesis of 5-fluorocytosine[177–179], we believe that only the route using 5-fluorouracil (5-FU) as starting material is implemented on the manufacturing scale.[180] This process relies on the large scale availability of 5-FU, which is prepared on the manufacturing scale via direct fluorination of uracil[94,181–185], a process that has been in operation for over 40 years.

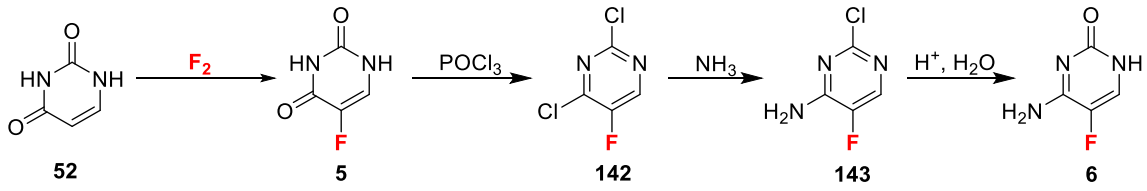


Figure 80: Flucytosine manufacturing route.[186,187]

While it is difficult to assess routes to Flucytosine due to commercial sensitivity, the Hoffmann-la-Roche patent discussing a potential synthetic process shows that 5-FU is treated with $POCl_3$ and *N,N*-dimethylaniline to yield 2,4-dichloro-5-fluoropyrimidine in good yield after distillation. This intermediate was reacted with aqueous ammonia solution and hydrolysed in concentrated hydrochloric acid, to yield 5-fluorocytosine from 5-fluorouracil in an overall 64 % yield (3 steps from 5-FU, Figure 80).

As the direct fluorination of uracil was shown to be a scalable, selective process, it is reasonable to assume that the electrophilic fluorination of cytosine, a more activated system, should proceed just as easily. In the literature, there are a few examples for the fluorination of cytosine and derivatives, for example using CF_3OF, a highly toxic electrophilic fluorinating reagent.[188] The direct fluorination of cytosine with fluorine gas was reported on several occasions, but in most cases incomplete conversion and low yields were observed. [189–191] The only successful direct fluorination reaction was reported in anhydrous HF at -50 °C, but the difficulty of carrying this reaction out on larger scale makes it unlikely to be used in production. [192] In another publications fluorine was used to examine the mechanism of direct fluorination of cytosine in acetic acid with

radiolabelled [^{18}F] fluorine. The formation of Flucytosine was observed in low (20-25 %) radiochemical yield along with various other fluorinated heterocycles. [193,194]

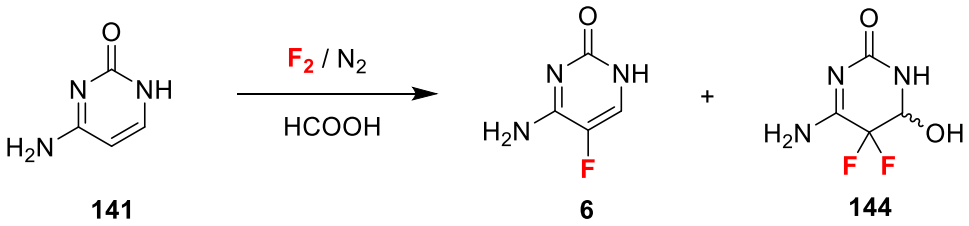
In this chapter, we revisited the direct fluorination of cytosine with an aim to transfer the batch reaction to a continuous flow process suitable for scale-up and to compare the green metrics of the direct fluorination approach with the competing 5-fluorouracil based synthesis.

4.2 Direct fluorination of cytosine: proof of concept study

4.2.1 Laboratory scale studies

Literature reports discussed above suggested that direct fluorination of cytosine in acidic solvents should be feasible and we found that solubility of cytosine in formic acid, a preferred solvent for SDF processes, was relatively high, up to 12 % *w/w*, which enables the reaction to be run at higher than 1 mol/L concentrations. To assess the reaction, 1.1 g of cytosine was dissolved in formic acid and fluorinated in a 100 mL glass fluorination reactor using 10 % fluorine gas in nitrogen.

Table 15: Batch fluorination of cytosine.



F_2 equivalents	Conversion (^{1}H NMR)	6 to 144 ratio in crude product (^{19}F NMR)
1.0	80 %	2.5 : 1
1.5	98 %	1 : 1.1
1.75	99 %+	1 : 1.3

The fluorination reaction progresses easily under the reaction conditions, and high conversion of cytosine was achieved with one equivalent of fluorine, but to reach complete conversion, an excess of fluorine was required leading to a low isolated yield (38 %). However, significant amounts of polyfluorinated products were also observed by ^{19}F NMR spectroscopic analysis of the crude product. The difluorinated product was described in the literature before and is possibly formed in the reaction of fluorine and the desired product 5-fluorocytosine (Figure 81).[193,194]

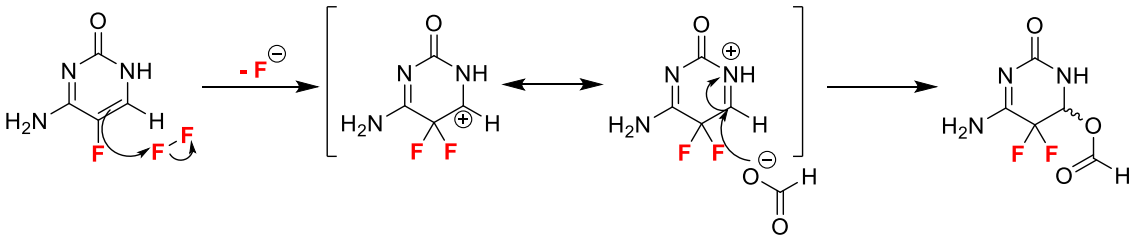


Figure 81: Possible mechanism of the fluorination of fluorocytosine to the difluorinated side product.

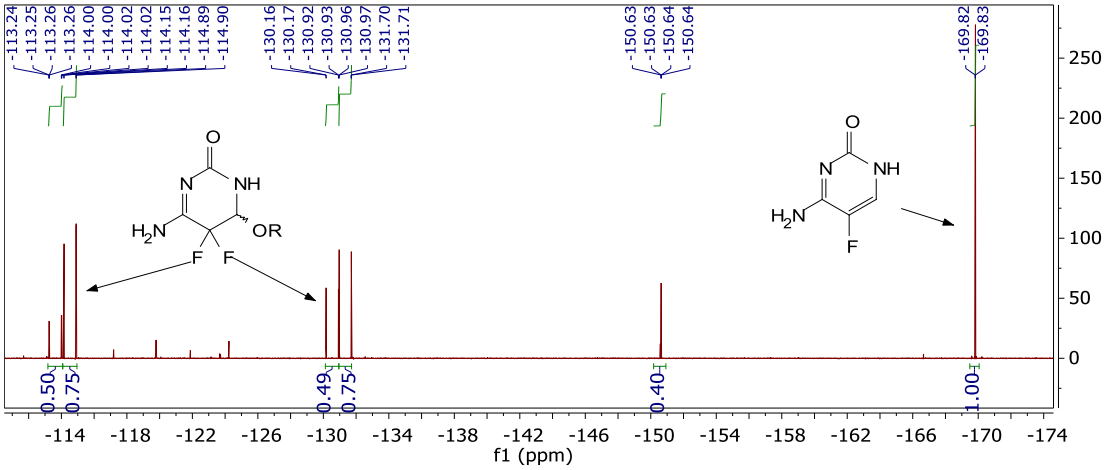


Figure 82: ^{19}F NMR spectrum of the crude product from the direct fluorination of cytosine in batch.

In the ^{19}F NMR spectrum the two fluorine atom chemical shifts show that the aromaticity of the pyrimidine ring is no longer present and the fluorine atoms are in axial and equatorial positions, hence the large geminal F-F coupling. Our attempts to isolate and purify this side product have been unsuccessful, but it was observed that, depending on the work-up solvents, several 5,5-difluoro-4,5-dihydropyrimidine-2-one species were present in solution.

The separation of Flucytosine from all other side-products was easily achieved by recrystallisation of the crude reaction product from water, however, the separation of unreacted starting material from the flucytosine product was not possible. In order to minimise the amount of cytosine in the final product, 100 % conversion is required and in this case (entry 3, Table 15), after recrystallisation, the desired mono-fluorinated product was isolated as the only product in 38 % yield.

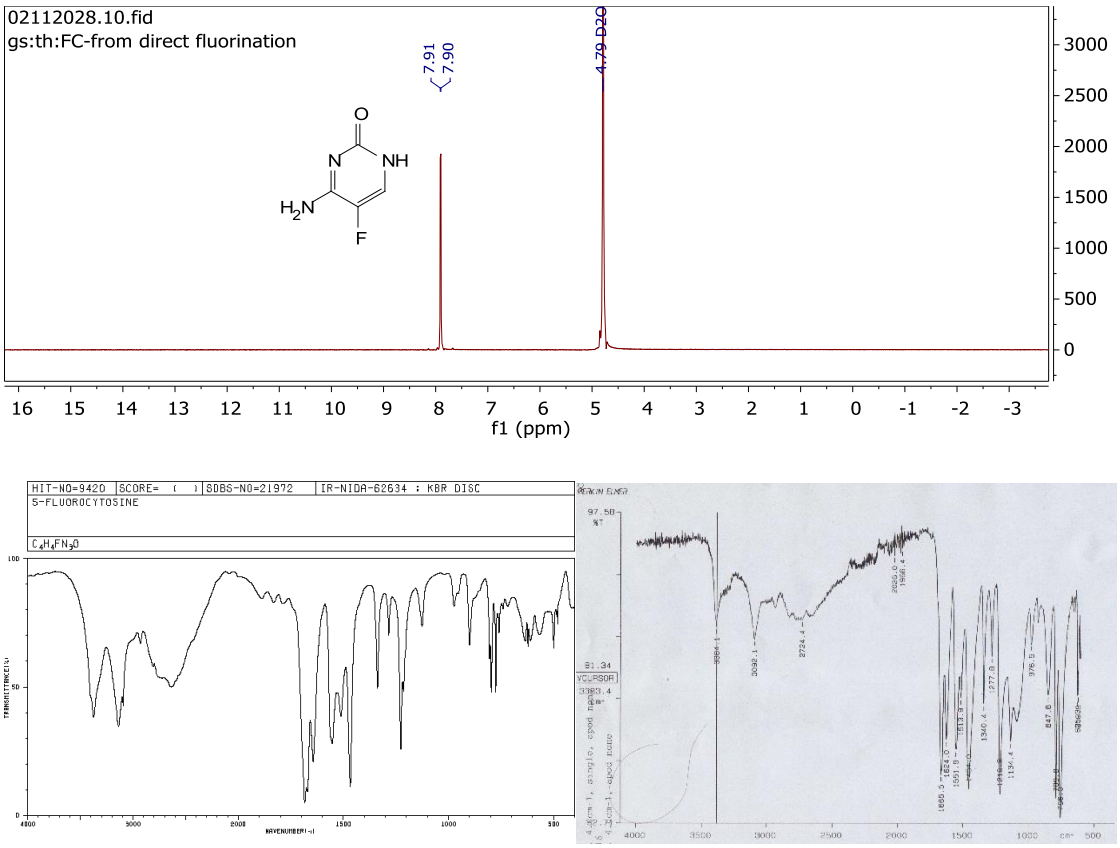


Figure 83: ^{1}H NMR (D_2O+DCl) spectrum of pure Flucytosine synthesised by direct fluorination (top), IR spectra of Flucytosine from literature (bottom left) and from direct fluorination (bottom right).

Based on ^{19}F NMR spectroscopic experiments, the recovery of 5-fluorocytosine from the aqueous recrystallization is excellent, as the liquor only contains trace amounts of the desired product. The purified product was fully characterised using all available analytical methods, for example, the ^{1}H NMR spectrum recorded in D_2O with a drop of DCl in Figure 83 shows that the final product does not contain any significant amount of cytosine or formic acid from the direct fluorination reaction. Also, comparison of a literature IR spectrum (Figure 83 bottom left) obtained from the SDBS database shows excellent correlation with the spectrum of the product obtained by direct fluorination (Figure 83 bottom right).

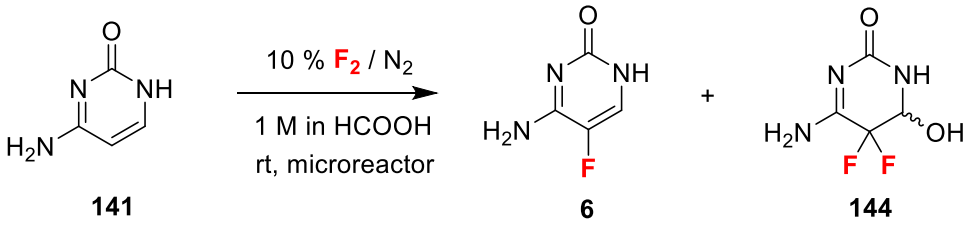
In conclusion, these preliminary findings demonstrated that batch fluorination processes can be used to synthesise Flucytosine in acceptable yield, but the formation of significant quantities of di-fluorinated product leads to lower isolated yields. In order to overcome this limitation, the use of continuous flow processing methods was investigated to improve the selectivity of this reaction.

4.2.2 Laboratory scale continuous flow processes

Reactions between liquid and gas phases often benefit from various continuous processing techniques[195] and in the Durham Fluorine Group continuous flow microreactors have been

developed and used for a considerable time and their usefulness was demonstrated in the fluorination of a wide range of substrates.[78–80,87] The single channel microreactor that was developed in our laboratory for selective fluorination is built from a nickel or stainless steel plate having a 100 mm long 0.5 mm deep and 0.5 mm wide channel which is covered with transparent fluoropolymer (poly(chlorotrifluoroethylene)) and stainless steel plates. The solution of the substrate in an appropriate solvent is introduced via a syringe pump, while fluorine gas is introduced via a mass-flow controller and the mixture from the reactor is collected in a round bottomed flask which is connected to a soda lime scrubber that is used to neutralise excess fluorine and HF in the gas stream. Using this continuous flow system, a 1M solution of cytosine was fluorinated with 10 % fluorine gas in nitrogen. The reactions were run for two hours at 2 mmol/h cytosine flow, the solvent evaporated and the crude product recrystallised from water and the final product composition was determined by ^{1}H and ^{19}F NMR spectroscopy.

Table 16: Continuous flow fluorination of cytosine.



141 **6** **144**

Cytosine flow	Fluorine flow	Crude product	Crystallised product	
(1M in HCOOH)	**(10 % in N_2), eq.**	**141 : 6 : 144 (^{1}H and ^{19}F NMR)**	**141 : 6 (^{1}H NMR)**	**Yield (g, %)**
2 mL / h (2 mmol / h)	8 mL/min (2.0 mmol/h), 1.0	9 : 83 : 8	1 : 9	0.32 g, 62 %
2 mL / h (2 mmol / h)	10 mL/min (2.5 mmol/h) 1.5	5 : 87 : 8	1 : 14	0.31 g, 61 %
2 mL / h (2 mmol / h)	12 mL/min (3.0 mmol/h) 1.75	1 : 89 : 9*	>99 % pure **6**	0.27 g, 52 %

* Some other unidentified fluorinated side products also observed.

Screening of fluorine to cytosine flow ratios showed that 1.5 equivalents of fluorine gas resulted in full conversion of cytosine and pure Flucytosine was obtained in higher yield (52-62 %) than previously in batch reactions. The ^{1}H NMR spectrum of the crude products for all reactions showed that there is a significantly smaller amount of di-fluorinated side product (**144**) in the mixture, which clearly demonstrates the advantage of flow systems over batch reactions due to decreased contact time between F_2 and reaction mixture (Figure 84).

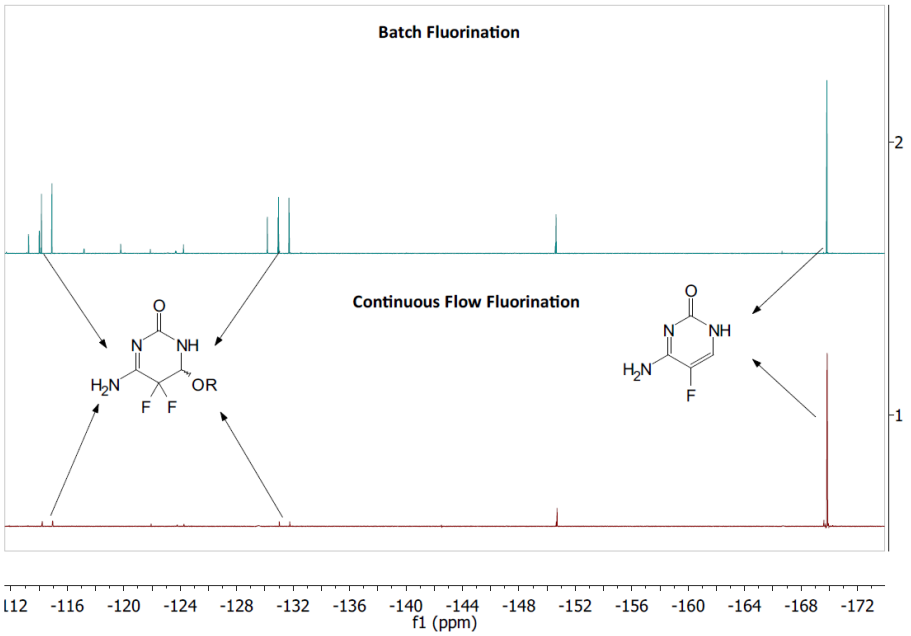


Figure 84: ^{19}F NMR spectra of crude products from batch and continuous flow fluorinations.

Despite having several multi-channel reactors that were developed for fluorinations, scaling up in microreactors can be challenging. Rather than multiplying the number of channels, increasing the diameter and the volume of the reactor could offer another, simpler option for scaling up.

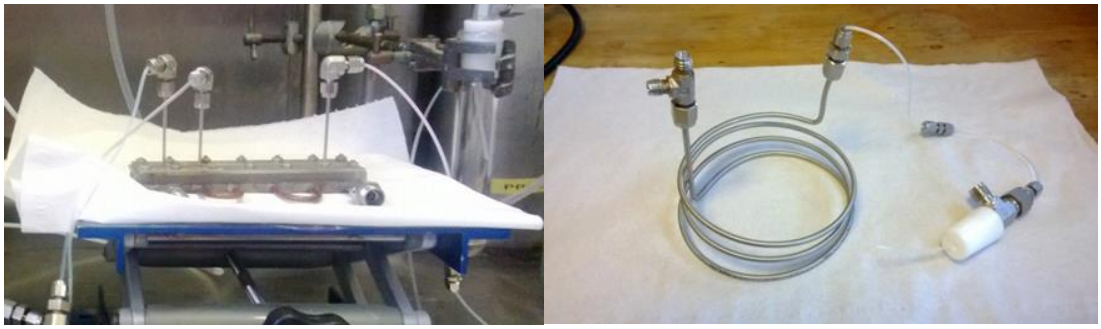
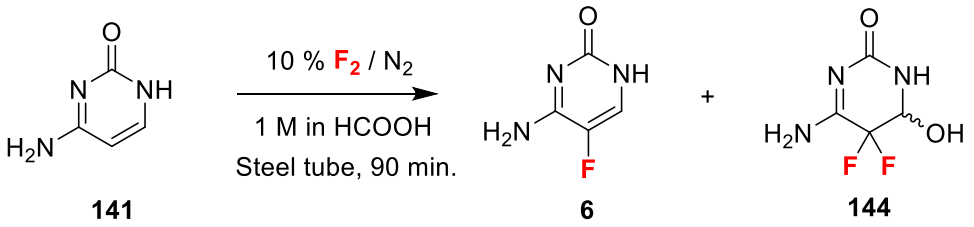


Figure 85: Single channel microreactor (left) and stainless steel coil reactor (right) used for fluorination.

When the reaction was performed in a coiled 1 m long stainless steel tube reactor (1.4 mm ID), similar isolated yield (63 %) and complete conversion of the starting material were observed at 4 mmol/h rate. The better conversion and lower fluorine excess required can be explained by the significantly longer residence time of the two reactors (*approx.* 5 minutes vs. 10-15 seconds) and the good initial mixing of the solutions in a T piece at the beginning of the reactor.

Table 17: Fluorination of cytosine in 1/8" stainless steel reactor.



141 **6** **144**

Cytosine flow	Fluorine flow	Crude product	Crystallised product	
(1M in HCOOH)	**(10 % in N_2), eq.**	**141 : 6 : 144 (^{1}H and ^{19}F NMR)**	**141 : 6 (^{1}H NMR)**	**Yield (g, %)**
4 mL / h (4 mmol / h)	16 mL/min (4.0 mmol/h), 1.0	5 : 88 : 7	1 : 17.5	0.51 g, 66 %
4 mL / h (4 mmol / h)	18 mL/min (4.5 mmol/h) 1.12	1 : 92 : 7	1 : 79	0.50 g, 64 %
4 mL / h (4 mmol / h)	20 mL/min (5.0 mmol/h) 1.25	1 : 96 : 3	>99% pure **6**	0.46 g, 59 %
4 mL / h (4 mmol / h)*	20 mL/min (5.0 mmol/h) 1.25	1 : 94 : 5	>99% pure **6**	0.49 g, 63 %

* HPLC pump used instead of syringe pump.

The above discussed results raised the interest of several industrial members of the Chem21 consortium and Sanofi decided to investigate the scalability of the continuous flow direct fluorination reaction in partnership with Maison Européenne des Procédés Innovants (MEPI), a flow chemistry specialist contract research organisation.

4.2.3 Sanofi-MEPI collaboration

At the beginning of the collaboration with Sanofi and MEPI several objectives were set and the project was divided into four work packages that covered all areas of the project from technology transfer to an extended length continuous pilot scale experiment.

Work package one (WP1) consisted of knowledge transfer from Durham University to Sanofi and MEPI which was completed in the form of a face-to-face meeting and the transfer of various technical reports, as described above, and literature reviews to our partners. The aim of WP2 was to transfer the continuous flow fluorination method to MEPI's meso-scale reactor and to assess process variables and possible downstream processing methods. Process development work and further data collection for safety assessment was scheduled for WP3 and WP4, with the latter including longer reaction times, up to 8 hours continuous processing, and analytical assessment of the isolated product against Flucytosine API requirements. The following chapter

discusses the technology transfer and chemical development aspects of the project with a focus on process understanding and downstream processing. The author spent a three-week placement at MEPI carrying out all the reactions described below in collaboration with scientists from MEPI (Annelyse Conté and Jean-Paul Seuwin) and Sanofi (Alain Rabion and Sandrine Grenier).

4.3 Direct fluorination of cytosine: pilot scale studies

4.3.1 SiC Boostec® reactor setup

The most critical element of scaling up the direct fluorination process is the selection of appropriate equipment that is both resistant to the corrosive reaction medium (fluorine, HF and acidic solvent) and has excellent heat exchange properties to remove the large amount of heat generated in the process. Silicon carbide is one of the materials that meets these criteria and a meso-scale Boostec® reactor was the equipment of choice for this fluorination process as it was used previously at MEPI with fluorine gas on larger scale.[196] Another advantage of this system is that the manufacturing scale analogue, capable of processing up to 300 kg of material per hour, is commercially available from Corning.[197]

Figure 86: SiC reactor plate of the Boostec® reactor.

This reactor is built from alternating process plates, made of silicon carbide (Figure 86), and aluminium heat exchanger plates. For the fluorination of cytosine, a reactor built from six process plates was used with 16 m total channel length and 61 mL reactor volume. The processing plates are connected with SiC channels and the process fluids are only exposed to corrosion resistant materials, for example, hastelloy (pumps and tubing), passivated stainless steel (gas inlet connection) or PTFE/FEP (tubing). The reactor is equipped with twelve temperature probes, most of them located in the first (5 probes) and second (3 probes) reaction plates where most of the reaction takes place.

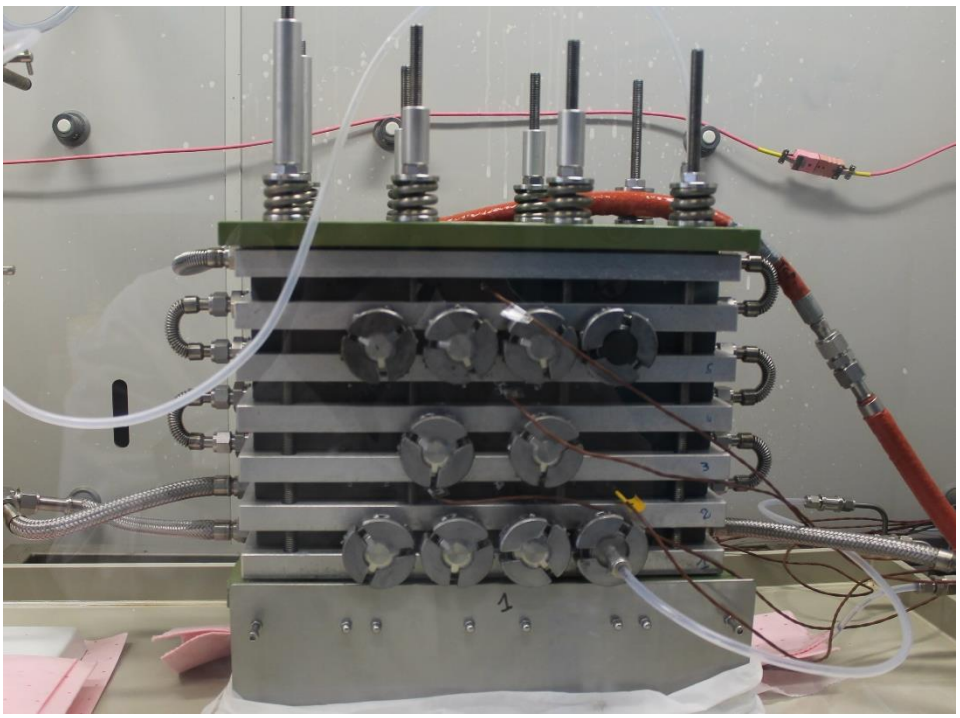


Figure 87: Boostec® reactor used in the cytosine fluorination studies.

Process fluids are introduced at the bottom of the reactor via mass flow controllers and a specialist software was used to monitor reactor temperatures, flow rates and pressures. The reactor temperature is controlled using an external thermostat unit (Julabo) and the reactor is also equipped with a back pressure regulating valve to enable slight pressurisation of the reactor contents.

After passing the reaction mixture and fluorine through the reactor, the product stream could be sampled for analysis and isolation studies through a three-way valve or it is neutralised in a stirred tank reactor and a gas scrubber filled with 10% NaOH solution (Figure 88). This arrangement not only enables the safe handling of fluorine on larger scale but the collection of large amount of experimental data is also possible due to the in-line sampling system.

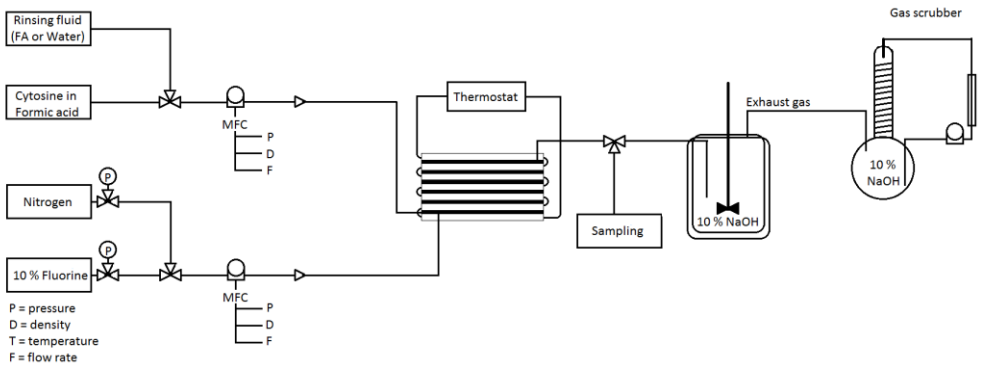


Figure 88: Schematic diagram of the continuous flow equipment used for the fluorination of cytosine.

Before any work was undertaken, the reactor was leak and pressure tested to ensure safe operating conditions and in all experiments the following operating procedure was implemented: first, the thermostat unit was turned on to bring the reactor to the desired temperature then nitrogen flow was initiated at a prescribed flow rate. It is important to always initiate the gas flow first in gas-liquid reactions to avoid any liquid entering the gas flow-controller unit, however, this latter is also protected by a one-way valve. When the temperature of the reactor had stabilised, formic acid was introduced at high flow rate until the liquid was detected at the outlet of the reactor, then the flow rate was adjusted to the liquid flow rate of the fluorination reaction. After the liquid and gas flow rates and pressures stabilised, typically 10-15 minutes, the liquid inlet was changed to cytosine solution in formic acid and the flow rate was allowed to stabilise before switching from nitrogen to 10 % v/v fluorine in nitrogen.

When experiments were finished, a reverse order shutdown procedure was followed: fluorine introduction was stopped by closing the valves between the cylinder and the flow controller and fluorine flow rate was allowed to drop to 0 g/h (10-15 seconds). Then, nitrogen flow was initiated and the cytosine solution was replaced with pure formic acid and after 5 minutes the nitrogen flow was stopped and the reactor was flushed with formic acid for a further 10 minutes. At this point, formic acid was replaced with water and was passed through the reactor for 30-45 minutes until the solution at the outlet was close to neutral pH. After finishing the cleaning procedure, the reactor was kept filled with water until further use.

Residence time is often an important factor in continuous flow reactions, therefore, it was important to experimentally measure this parameter because in the case of gas-liquid reactions it cannot be calculated easily. We determined residence time with a residence time distribution experiment: flow-rates were set at the desired values with formic acid and nitrogen and 2 mL of concentrated methylene blue solution was injected in the liquid flow at the inlet of the reactor. The time difference between injection and detection at the outlet of the reactor gave the residence time values and, as expected, with increasing the flow rates the residence time decreases. The experimental residence time measurements also allowed the calculation of the volume occupied by the liquid phase in the reactor that appears to be 25 % of the total volume (Table 18) irrespective of the operating conditions.

Table 18: Measurement of gas-liquid residence time.

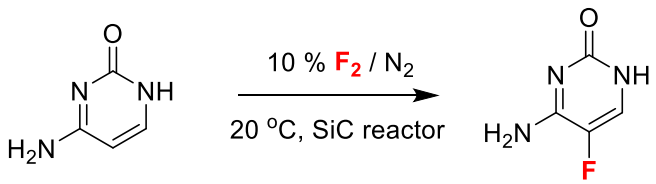
Flow rate (g/h)		Theoretical residence time (100 % liquid) / s	Experimental residence time / s	Experimental Liquid volume ratio
Liquid	Gas			
600	133	447	108	0.24
600	180	447	109	0.24
600	224	447	112	0.25
900	257	298	78	0.26
1200	225	227	55	0.24
600	0	447	445	-

After the safety and operational testing of the reactor, direct fluorination studies were carried out to evaluate the process and identify critical parameters.

4.3.2 Pilot scale fluorination: study of reaction parameters

Initially, the best conditions identified during the development stage in Durham were directly transferred to the Boostec® reactor: 1M (8.9 % w/w) cytosine solution in formic acid was reacted with 1.3 equivalents of 10 % fluorine at 20 °C. This reaction was also used to measure the stabilisation time of the experiment to establish a representative sampling procedure in the steady state. After initiating the fluorine flow, samples were collected every five minutes and analysed by HPLC-UV. As it is shown in Table 19, after ten minutes the reaction profile did not change and the reaction showed excellent conversion and selectivity, therefore, in further experiments, after adjusting the reaction conditions, the mixture was allowed to stabilise for ten minutes before taking a sample for analysis.

Table 19: Stabilisation time measurement of the direct fluorination of cytosine.



141
1 M in HCOOH

6

Time	T / °C	Flow rate / g/h		F_2 molar ratio	Conversion (HPLC % A/A)	Selectivity (HPLC % A/A)
		1M Cytosine	10 % F_2/N_2			
5 min	20	600	181	1.3	97.5	95.1
10 min	20	600	181	1.3	99.1	95.4
15 min	20	600	181	1.3	99.1	97.6
20 min	20	600	181	1.3	99.3	95.7

Although the initial results from the technology transfer were excellent, we set out to explore the reaction parameters to gain a better understanding of the fluorination reaction and to define a parameter space that leads to high conversion and selectivity.

Temperature was expected to be an important factor in this process, therefore, the reaction was carried out at three different temperatures that were selected based on the freezing point of the solvent (8-9 °C) and previous experience with fluorination reactions. Two series of experiments were conducted, one at 8.9 % w/w cytosine concentration with 1.3 equivalents of fluorine and the other at 11 % w/w cytosine concentration using 1.1 equivalents of fluorine gas. In both cases a negative effect of temperature was observed (Figure 89): with increasing temperature, conversion of cytosine decreased noticeably.

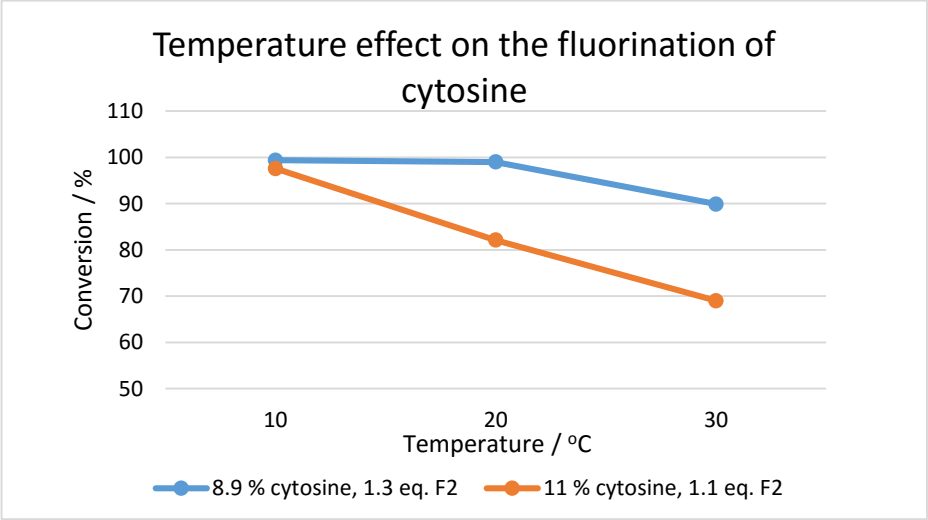


Figure 89: Effect of temperature on the fluorination of cytosine.

There are a number of possible explanations to the observed drop in conversion, for example, the change of viscosity of the cytosine solution with increasing temperature potentially has an impact on mixing, gas inlet pressure and flow characteristics that can all lead to different conversion rates. There may also be a competing reaction of fluorine with formic acid with increasing reaction rates at higher temperatures.

In order to investigate whether the observed effect is due to a distinct temperature effect or to changes in gas inlet pressure, a set of isobar experiments were also performed. In these reactions the drop in inlet pressure, caused by increasing temperature, was counteracted by the application of back pressure to maintain isobar conditions in the reactor and minimise the effects on hydrodynamics. When the results from these experiments were compared with the previously shown temperature effect without back pressure, they suggested that applying back pressure had a larger negative effect than temperature alone (Figure 90). It is possible that the

application of back pressure had more influence on flow dynamics than the change in viscosity and lowering the inlet pressure.

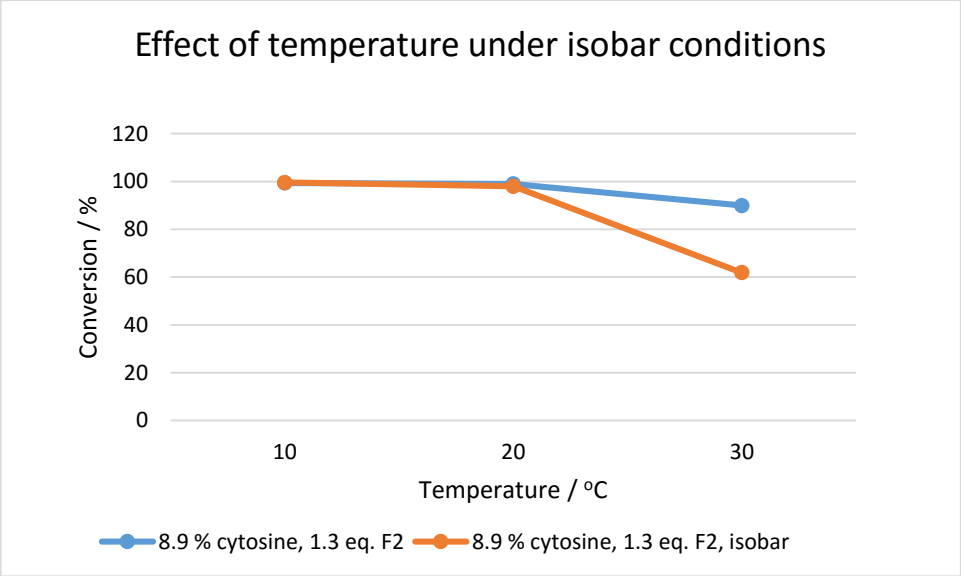


Figure 90: Comparison of the effect of temperature with and without applied back pressure.

To further investigate the effect of back pressure, fluorination reactions were carried out at several temperatures and cytosine concentrations while changing the applied back pressure and, as shown in Figure 91, a significant negative effect was observed in all cases which is further enhanced by increasing the reaction temperature (grey line versus blue line in Figure 91). Such a large drop in conversion can only be explained by a dramatic decrease in mixing and change in flow characteristics. It is also important to highlight that to maintain the same fluorine to cytosine ratio throughout the different concentration reactions, the gas-liquid ratio was changed significantly which had unavoidable influence on the flow regime in the reactor. Thus, it is difficult to confirm whether the observed effects are derived from any single factor or arise from their combination.

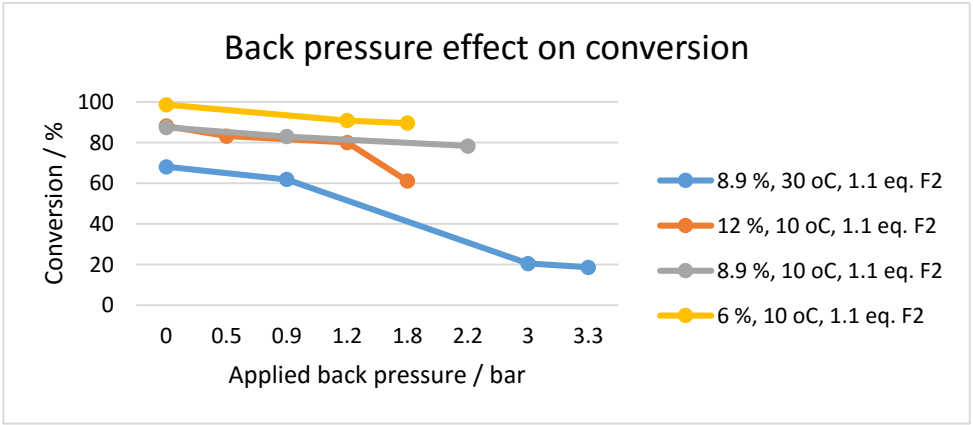


Figure 91: Investigating the effect of artificial back pressure on the fluorination of cytosine.

The above experiments gave a clear indication about the effect of back pressure and temperature, but the effect of inlet gas pressure was not determined. This parameter is also very important from a scalability point of view as larger scale equipment and higher flow rates would lead to higher pressure difference between the inlet and the outlet ends of the reactor. A simple way of increasing the inlet pressure without diluting the gas phase or changing the stoichiometry of the reaction is to increase the overall flow rate. Interestingly, we found that the overall starting pressure does not have any statistically significant effect on either conversion or selectivity (Table 20) which further supports the argument that the negative effects observed above were due to changes in the flow regime caused by the back pressure. During this series of reactions, with the maximum gas flow rate limited to 5 bar, liquid flow rates of over 1.2 kg/h were achieved equalling to over 100 g/h productivity in this large laboratory scale equipment.

Table 20: Investigation of the effect of flow rates.

T / °C	Cytosine concentration (% w/w)	Flow rate / g/h		F_2 molar ratio	Conversion (HPLC % A/A)	Selectivity[a] (HPLC % A/A)	Inlet pressure / bar
		Cytosine solution	10 % F_2/N_2				
10	8.9	600	181	1.3	**99.5**	92.1	2.1 bar inlet pressure
10	8.9	900	272	1.3	**99.1**	91.6	3.3 bar inlet pressure
10	8.9	1000	303	1.3	**99.7**	92.1	3.6 bar inlet pressure
10	8.9	1200	363	1.3	**99.7**	92.3	4.5 bar inlet pressure
10	8.9	600	157	1.1	**90.6**	93.0	1.8 bar inlet pressure
10	8.9	800	209	1.1	**94.7**	93.2	2.6 bar inlet pressure
10	8.9	1000	263	1.1	**91.6**	93.4	3.3 bar inlet pressure
10	8.9	1200	313	1.1	**92.3**	93.2	4.0 bar inlet pressure
10	8.9	1400	367	1.1	**91.5**	92.7	4.8 bar inlet pressure

a; Selectivity was determined by dividing Flucytosine peak area by the sum of all peaks except cytosine.

To investigate the effect of cytosine concentration and keeping scalability, throughput and solvent use in mind, the fluorination of cytosine was carried out at concentrations between 6 and 11 % w/w. 6 % was the lowest practical concentration selected (13 volumes of solvent) and 11 % was the highest concentration where crystallisation of cytosine was not observed after allowing the solution to cool to ambient temperature. All reactions were conducted at 10 °C and 600 g/h liquid flow rates with appropriate gas flow rates to provide 1.3 equivalents of fluorine

for all reactions. Figure 92 shows that it was only at lower concentrations (6-7 %) where a small negative effect (1-2 % lower conversion) was observed but between 8 and 11 % concentration the reaction conversion was consistently above 99.5 % indicating that using higher concentration solutions is viable and has no negative impact on conversion or selectivity. This observed effect also supports the hypothesis that increasing the gas-liquid ratio leads to enhanced mixing and flow properties that further facilitate the reaction.

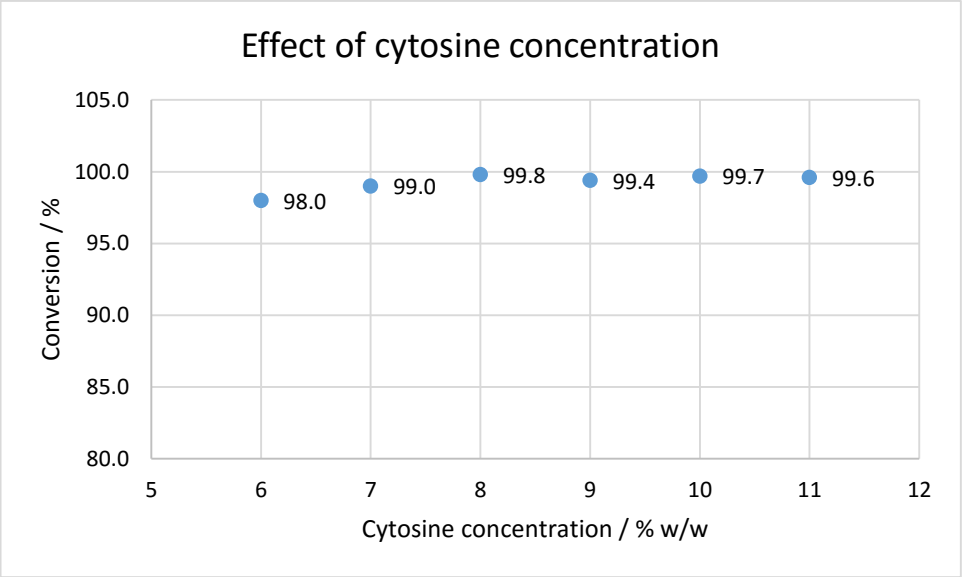


Figure 92: Effect of cytosine concentration on conversion in the direct fluorination of cytosine.

The effect of fluorine stoichiometry was studied on a range between 1.0 to 1.5 equivalents using 10 % v/v fluorine. However, as it was not possible to alter the F_2 concentration, this also led to changes in flow characteristics and gas-liquid ratios. The experiments were carried out at 10 °C and 600 mL/h liquid flow rates at 8.9 and 11 % w/w cytosine concentrations and analysed to determine conversion of the starting material. The results clearly support the previously mentioned influence of gas-liquid ratio, for example, there is approximately 30 % difference in the conversion using 1.0 and 1.1 equivalents of fluorine in the case of the 8.9 % concentration experiment (Figure 93) which cannot be explained simply by the difference in stoichiometry. The higher observed conversions at 11 % cytosine concentration compared to the 8.9 % series also suggests better mixing of fluids due to the improved gas-liquid ratio.

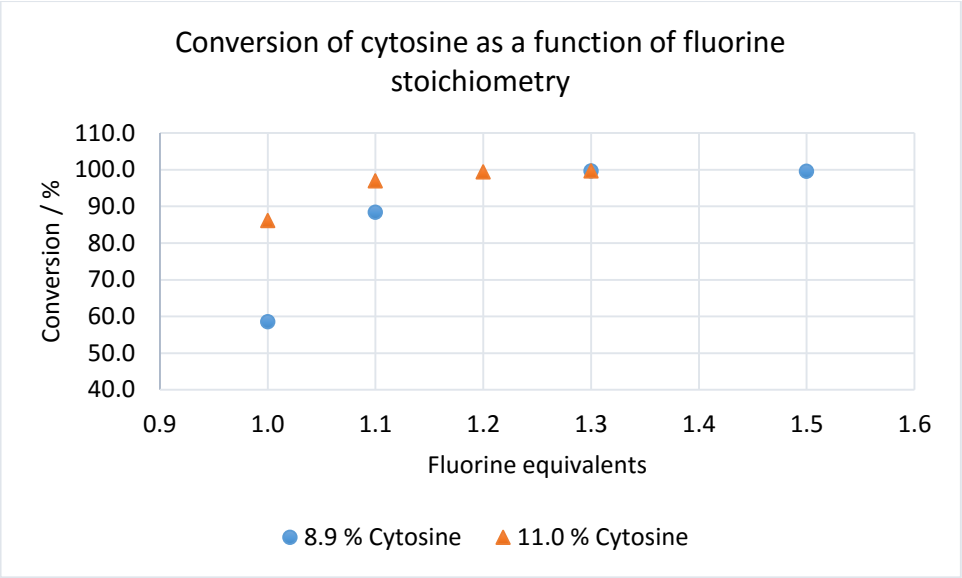


Figure 93: Effect of fluorine stoichiometry on the fluorination of cytosine.

From a manufacturing point of view there was another parameter that needed to be assessed which is more related to process economics than the chemistry itself. All of the above reactions were carried out in anhydrous formic acid, which is more expensive than industrial grade formic acid that has a water content of 5-15 %. To assess the effect of water on this fluorination reaction, 10 % w/w cytosine solutions with increasing water content up to 20 % w/w were reacted with 1.3 equivalents of fluorine at 10 °C and 600 mL/h flow rate. At higher than 20 % water content cytosine precipitated from solution after allowing the solution to cool to ambient temperature. The results obtained in this set of experiments indicate that additional water has a small negative effect on the fluorination of cytosine, however, conversion was high even in the case of 20 % added water (92 %).

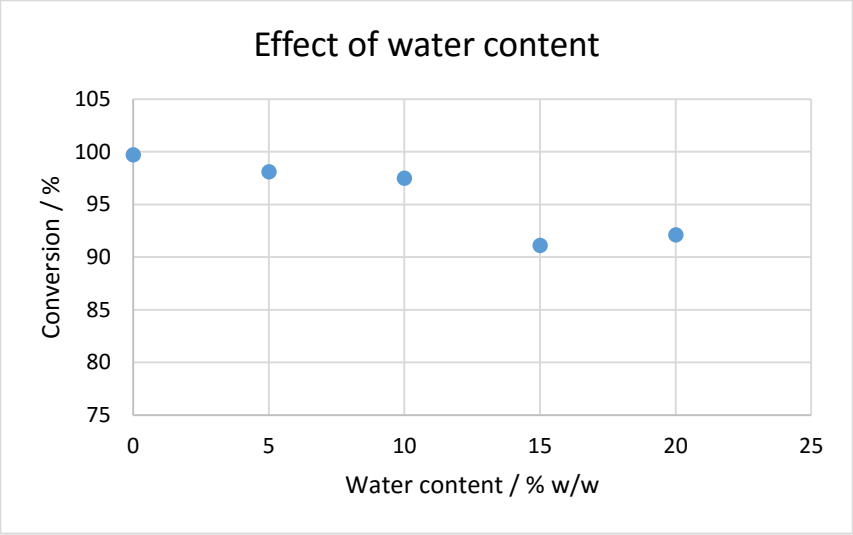


Figure 94: Effect of additional water on the fluorination of cytosine.

In conclusion, this parametric study highlighted the importance of fluid mechanics as the most influential process parameters relating to changes in mixing and flow parameters. We also demonstrated that the fluorination efficiency does not change with increasing flow rate and excellent conversion was achieved over a broad range of operating conditions which all suggest the potential for further scale-up. However, all experiments focused on the conversion of cytosine only and to gain more understanding of this fluorination process, we sought to fully account for the amount of fluorine used, which is discussed in the next section.

4.3.3 Fluorine mass balance

To assess the mass balance of fluorine in the direct fluorination of cytosine, the conversion of fluorine gas needed to be measured. Knowing the amount of residual fluorine in the gas phase is also important for the safety assessment of any further processing of the exhaust gas stream.

Quantitative measurement of elemental fluorine can only be achieved indirectly, using redox titration methods: first, fluorine oxidises iodide ions to elemental iodine which can subsequently be analysed by titration with a standardised thiosulfate solution. One fluorine molecule reacts with two iodide ions to form one molecule of iodine and two fluoride ions. As this reaction takes place in an aqueous solution, it is possible that fluorine first reacts with water to form HOF and HF, but HOF - a very strong oxidising agent - can also oxidise two iodide ions, giving identical net outcome. The liberated iodine is titrated with thiosulfate solution according to the equation in Figure 95.

$$F_2 + 2KI \longrightarrow 2KF + I_2$$
$$F_2 + H_2O \longrightarrow HOF + HF$$
$$HOF + 2\ KI \longrightarrow KF + KOH + I_2$$
$$2\ S_2O_3^{2-} + I_2 \longrightarrow 2I^- + S_4O_6^{2-}$$

Figure 95: Redox processes in the determination of fluorine.

For accurate analysis of the gas exhaust stream, purpose designed equipment was constructed. After the reactor outlet, a three-way valve was used to redirect the product flow into the sampling device where gas-liquid separation was achieved in a 1 L screw cap bottle equipped with a PTFE cap having a ¼" Swagelok inlet form the Boostec reactor and a ¼" Swagelok gas outlet. The gas outlet from the phase separator flask was connected to a custom made three necked 500 mL round bottomed flask (583 mL total volume). This flask was equipped with two PTFE taps to enable gases to pass through the system and a PTFE lined septum for injecting the KI solution into the sealed flask.

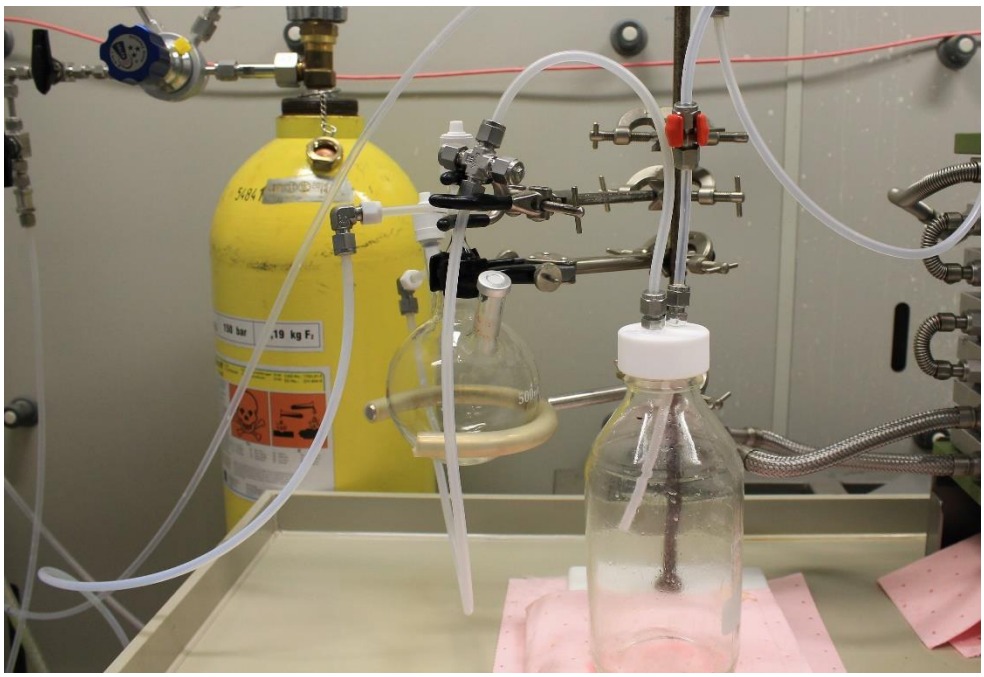


Figure 96: Gas sampling system used for the determination of fluorine in the gas flow.

For representative sampling the exhaust gas stream was allowed to flow through the sampling flask for 10 minutes (more than 25 volumes) to completely replace the starting atmosphere in the flask. After this the flow was stopped by turning the three-way vale to redirect the flow to the neutralising reactor, the flask sealed and 10 mL 1M KI solution injected (large excess of I^-). After shaking the contents for 2 minutes to ensure complete reaction of any oxidant in the gas phase and iodide in the liquid phase, the contents of the flask were washed into a 250 mL conical flask with deionised water and were titrated with 0.1 M $Na_2S_2O_3$ solution to determine the iodine content.

To set a reference point to this study, first, the fluorine content of commercial 10 % *v/v* fluorine was determined using this equipment by passing the gas through the sampling equipment for 15 minutes without any liquid flow. Titration of the liberated iodine showed that the flask contained 2.46 mmol F_2 (average of three measurements) which is in good correlation with the theoretical 2.39 mmol (treating the gas mixture as an ideal gas at 20 ^oC).

To determine whether there is any background reaction between formic acid and fluorine, pure formic acid was subjected to fluorination under optimal reaction conditions (204 g/h of 10% fluorine and 600 g/h formic acid at 10 ^oC), the gas phase was sampled and analysed as before. Titration showed that in this experiment, only 0.02 mmol of fluorine was present in the sampling flask showing that more than 99% of the fluorine had reacted with the solvent. To assess whether fluorine formed any O-F species in this reaction, the liquid phase was also analysed using the same iodometric method. The reaction mixture was collected for 5 minutes (approximately 60 mmol fluorine passed through the reactor), excess KI solution was added,

diluted with water and titrated with thiosulfate solution, which showed the presence of 0.1 mmol of oxidant, probably in the form of HOF from the water content of formic acid.

The reaction of fluorine and formic acid probably leads to the formation of HF and CO_2, but attempts to demonstrate the presence of CO_2 by *in situ* IR spectroscopy failed. The mechanism of the reaction is probably similar to that of chlorine and formic acid which has been described in the literature.[198,199] This mechanism is further supported by the previously observed reaction of fluorine with aromatic aldehydes to produce acid fluorides.[92]

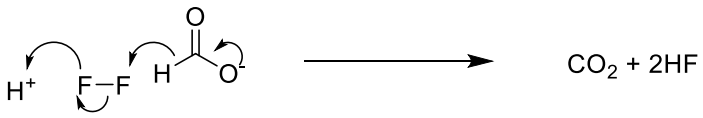


Figure 97: Possible mechanism of the fluorine-formic acid reaction.

To prove that most of the fluorine reacts in the cytosine fluorination reaction under typical operating conditions, the gas phase of a reaction was sampled and analysed using the same method as above. Titration of the released iodine indicated the presence of 0.04 mmol of fluorine, corresponding to higher than 98 % conversion. This measurement was repeated at 30 ^{o}C (0.05 mmol residual fluorine) and at 10 and 30 ^{o}C with 1.5 bar applied back pressure (0.04 and 0.01 mmol F_2 respectively). Under all these reaction conditions over 98 % conversion of fluorine was observed.

In conclusion, fluorine was shown to react not only with cytosine itself, but with neat formic acid as well, even at 10 ^{o}C leaving only a very low concentrations of fluorine (less than 0.1 % by volume) amounts that needs to be neutralised after the reaction. This suggests that a competition reaction between cytosine and formic acid with fluorine can also be a factor in the lower cytosine conversions at higher reaction temperatures.

The analysis of fluoride was also carried out and it was found that the gas phase contains a low concentration of HF (26 - 40 mg/L) and, most of the fluoride remained in the reaction mixture. When formic acid was recovered from a crude fluorination mixture, the distilled formic acid contained only 50 mg/L fluoride, demonstrating the potential for formic acid solvent reuse.

In this chapter we demonstrated that the direct fluorination of cytosine in a large scale continuous flow reactor is feasible and explored a broad range of operating conditions. The most important factors influencing the conversion of cytosine were fluorine stoichiometry, temperature and fluid mechanics. We also demonstrated that the solvent, formic acid, and cytosine are in a competing reaction with fluorine, as even at lower conversions of cytosine, only a trace amount of unreacted fluorine was detected.

After establishing a range of good operating conditions for the fluorination of cytosine, we focused on the development of a simple, scalable isolation procedure to separate Flucytosine from the formed side products.

4.3.4 Isolation studies

The laboratory scale isolation method – evaporation to dryness and recrystallisation from water – was deemed unsuitable for larger scale synthesis, therefore, we aimed to develop a practical, high yielding procedure for the isolation of pure 5-fluorocytosine from the post fluorination reaction mixture.

During initial isolation studies, it was established that dilution of the reaction mixture with methanol, water or acetonitrile does not result in any solid precipitate, but neutralisation of acidic aqueous solution of fluorocytosine with ammonia enables the isolation of a solid product. To limit the number of potential solvents, the main criteria for a desirable anti-solvent were established: miscibility with formic acid, relative low polarity, low cost and relative greenness. For solvent assessment, a comparative solvent guide (Figure 98), based on the individual guides of 5 organisations, developed by the Chem21 consortium was used.[111]

Family	Solvent	AZ	GCI-PR	GSK	Pfizer	Sanofi[a]	Issues	Overall[b]
Water	Water	—	—	24	Preferred	Recommended	—	Recommended
Alcohols	MeOH	19	14	14	Preferred	Recommended	—	TBC
	EtOH	16	13	17	Preferred	Recommended	—	Recommended
	i-PrOH	16	16	17	Preferred	Recommended	—	Recommended
	n-BuOH	17	13	18	Preferred	Recommended	—	Recommended
	t-BuOH	20	15	15	Preferred	Subst. adv.	—	TBC
	Benzyl alcohol	—	11	20	—	Subst. adv.	—	TBC
	Ethylene glycol	—	13	21	Usable	Subst. adv.	—	TBC
Ketones	Acetone	21	15	15	Preferred	Recommended	—	TBC
	MEK	21	16	15	Preferred	Recommended	—	TBC
	MIBK	22	17	15	—	Recommended	—	TBC
	Cyclohexanone	—	14	20	—	Subst. adv.	—	TBC
Esters	Methyl acetate	—	14	14	—	Subst. adv.	—	TBC
	Ethyl acetate	18	15	16	Preferred	Recommended	—	Recommended
	i-PrOAc	18	13	18	Preferred	Recommended	—	Recommended
	n-BuOAc	13	14	21	—	Recommended	—	Recommended
Ethers	Diethyl ether	27	21	3	Undesirable	Banned	H224	HH
	Diisopropyl ether	—	—	4	Undesirable	Subst. adv.	Perox.	Hazardous
	MTBE	24	21	4	Usable	Subst. adv.	—	TBC
	THF	23	16	4	Usable	Subst. adv.	H351	TBC
	Me-THF	24	15	11	Usable	Recommended	—	Problematic
	1,4-Dioxane	28	21	11	Undesirable	Subst. req.	—	Hazardous
	Anisole	18	13	18	—	Recommended	—	Recommended
	DME	21	23	2	Undesirable	Subst. req.	H360	Hazardous

Figure 98: The relevant section of the comparative solvent guide.[111]

Based on the above criteria *n*-butanol, *i*-propanol, acetone and ethyl acetate were selected for the study along with 30% NaOH and 25% NH_3 solutions for the neutralisation approach.

Flucytosine solution was prepared by fluorinating an 8.9 % w/w solution of cytosine in anhydrous formic acid using 1.5 equivalents of 10 % fluorine in nitrogen. Precipitations were performed by adding the 'anti-solvent' to the flucytosine solution drop-wise and stirring the mixture at 10-12°C for an hour. The precipitate was filtered, washed with the precipitation solvent (2x5mL) and the solid and liquid phases analysed by HPLC (Table 21). After drying in air

overnight the samples were weighed to compare yields. The best recoveries were achieved by the neutralisation approaches and when less-polar alcohol solvents were used.

Table 21: Initial 5-fluorocytosine precipitation experiments.

No.	Flucytosine solution	Precipitation conditions	Notes
1	10 mL	7 mL 30% NaOH solution	1.00 g dry solid, white precipitate, pH 3, washed 2x5mL H_2O
2	10 g	10 mL 25% NH_3 solution	1.24 g wet solid, Light brown precipitate, washed with 2x5mL H_2O
3	10 g	10 mL *n*-Butanol	0.65 g dry solid, White precipitate, washed with 2x5mL *n*-Butanol
4	10 g	40 mL *i*-Propanol	0.70 g dry solid, washed with 2x5mL *i*-PrOH
5	10 g	10 mL Acetone	0.54 g dry solid, washed with 2x5 mL acetone
6	10 g	10 mL Ethyl Acetate	0.30 g dry solid, white precipitate, washed with 2x5 mL EtOAc

Figure 99: The isolated solid products from the initial precipitation experiments.

All precipitations yielded high purity (99.5 %+) Flucytosine crude product and, as shown by HPLC-UV analysis and the only detectable impurity in the solid samples was cytosine (Table 22 and Figure 100). Analysis of the liquors showed varying concentrations of residual fluorocytosine and increased ratios of the impurities. From the further optimisation study, ethyl acetate and ammonia were excluded because of poor recovery (EtOAc) and quick formation of a strongly coloured impurity (ammonia).

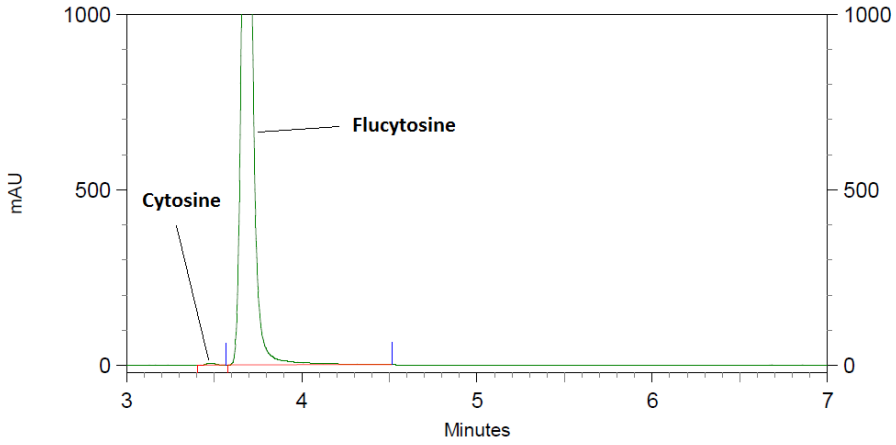


Figure 100: HPLC-UV chromatogram of the solid product precipitated using n-butanol.

Table 22: HPLC analysis results of the liquors and the solid products.

Sample	Cytosine %	Flucytosine %	Difluoro %	Others %	Flucytosine concentration
NaOH liq.	0.22	77.15	21.63	1.00	3 g/L
NaOH solid	0.60	**99.40**	0	0	-
NH_3 liq.	0.28	77.06	20.75	1.91	11 g/L
NH_3 solid	0.50	**99.50**	0	0	-
BuOH liq.	0.12	92.22	2.82	4.78	15 g/L
BuOH solid	0.23	**99.77**	0	0	-
*i*PrOH liq.	0.39	83.32	6.31	9.98	3 g/L
***i*PrOH solid**	0.24	**99.76**	0	0	-
Acetone liq.	0.09	93.67	2.10	4.14	17 g/L
Acetone solid	0.14	**99.86**	0	0	-
EtOAc liq.	0.11	92.98	2.19		15 g/L
EtOAc solid	0.14	**99.86**	0	0	-

During the precipitation optimisation study a stock solution from the fluorination of 10% cytosine in formic acid was used that contained approximately 88% fluorocytosine, 0.5% cytosine, 8% difluorinated impurity and 3.5% other impurities as determined by HPLC analysis of the crude reaction mixture. In this study 500 μL fractions of this stock solution were mixed with varying quantities of the precipitation solvents and were allowed to settle overnight at 4°C. After centrifuging the mixtures for 5 minutes at 10^4 rpm the liquid phases were analysed for flucytosine content and some representative solid products were also analysed for purity after decanting the liquor and washing with some fresh solvent.

As a reference point two samples were diluted with deionised water and, as expected, no precipiate formation was observed. HPLC analysis of these samples showed that they contained approximately 72 mg of fluorocytosine and from the analyses of the supernatant solution of the precipitation samples the amount of product left in solution was determined. Based on these results (Figure 101) acetone was discarded from further experiments as the solution flucytosine content indicated less than 50% recovery in all solvent ratios.

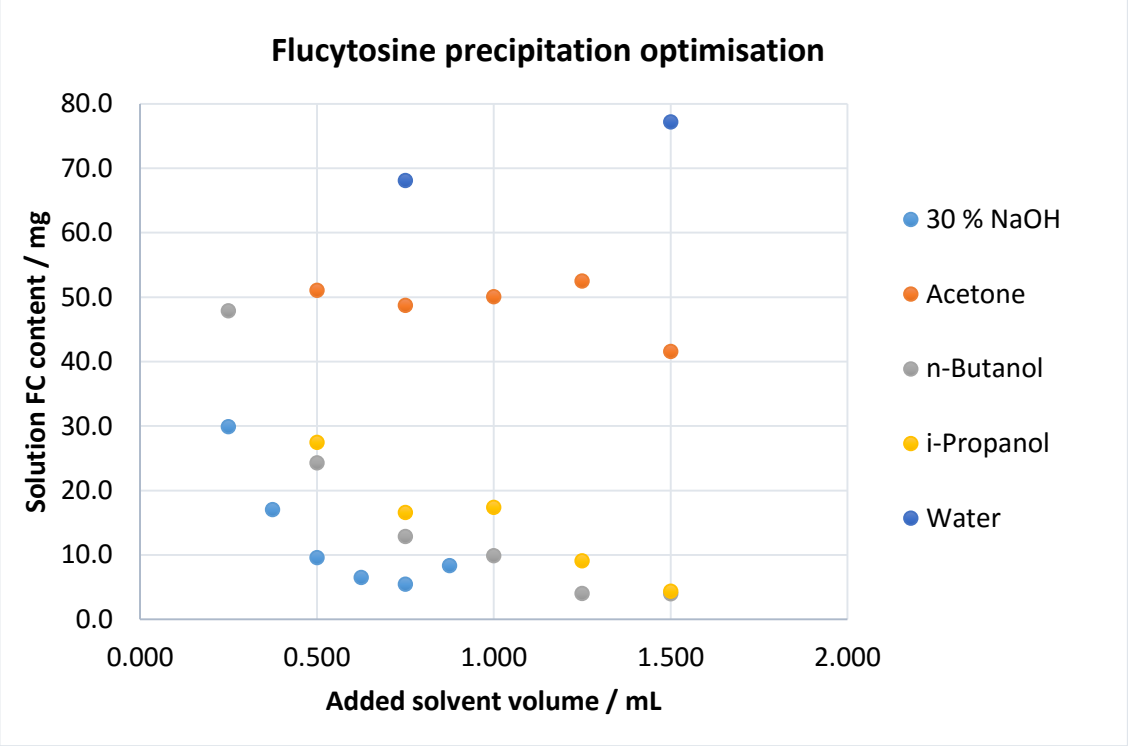


Figure 101: Precipitation optimisation study.

Fluorocytosine solubility in sodium hydroxide/sodium formate solution had a minimum point at pH 4 showing that a larger excess of NaOH also dissolves the amphoteric product, but despite the pH dependence, it is a very cost effective method for the isolation of the crude product. At higher solvent ratios *n*-butanol (2.5 volumes) and *i*-propanol (3 volumes) both gave excellent product recovery and they enable faster filtration and drying than the aqueous workup. In order to validate the optimisation results these three methods were further investigated on larger scale.

50 mL (69.5 g, containing approximately 7 g of Flucytosine) fractions of the crude product solution from a direct fluorination reaction were treated with 30% NaOH solution (75 mL, 100 g), *i*-propanol (150 mL, 117 g) and *n*-butanol (125 mL, 101 g) respectively. While the NaOH solution addition produced a significant exotherm (up to 75°C), which led to some coloured impurities and could be an issue when scaled any further, no exotherm was observed in the case

of the other two solvents. After stirring the mixtures overnight, the solid product was collected by filtration and were washed with 10 mL solvent before being dried in air overnight.

Table 23: 50 mL scale isolation experiments.

Precipitation solvent	Product weight[a] / g	Product purity / %	Positive	Negative
30% NaOH	7.14 (wet)	99.6	cost, close to neutral pH (4)	large exotherm, highest solution FC content
i-PrOH	6.58	99.8	Faster drying	larger volume/mass required
n-BuOH	6.57	99.8	lower volume than IPA	cost (?)

a; Approximately 7.5 g expected weight at 100 % yield and recovery.

These larger scale experiments gave very similar results to the small scale trials and the HPLC purity of all products was above 99.5% A/A by HPLC-UV analysis, cytosine being the main impurity (0.2%), but in the NaOH precipitated product a small amount (0.2%) of the difluorinated impurity was also detected. ^{1}H and ^{19}F NMR spectroscopic analysis of the samples showed that none of the samples contained any solvent residue, but all of them showed varying levels of formic acid (probably as flucytosine formate) and fluoride (as HF). The highest levels of both impurities were found in the sample precipitated with 30% NaOH solution, but 15-20 mol% formic acid/formate was also present in the other samples. The fluoride content analysis is not accurate by NMR spectroscopy as the resonance (aprox. -130 ppm) is a broad singlet and the integration may not be quantitative.

To demonstrate the scalability of this experiment, 10 % cytosine solution in formic acid and fluorine was passed through the reactor for one hour and the produced mixture (620 g) was treated with butanol (1 kg) to yield 62.8 g air dried product that was 99.8 % pure by HPLC.

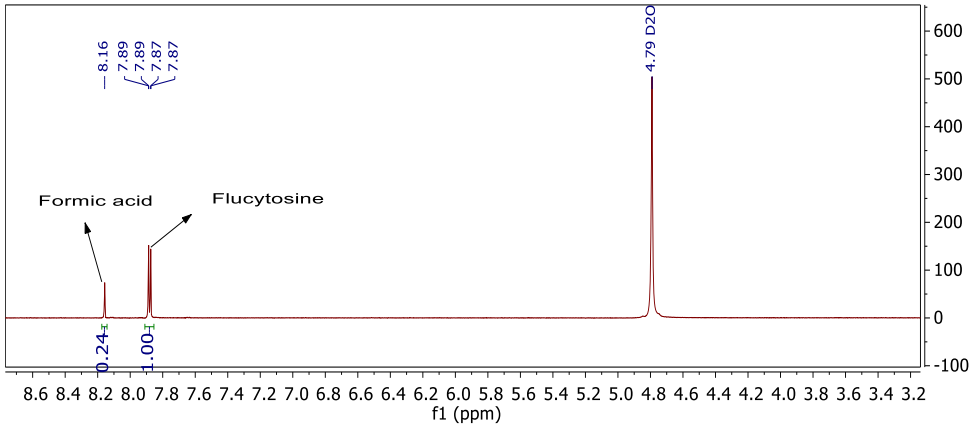


Figure 102: ^{1}H NMR spectrum of isolated Flucytosine with formic acid impurity.

Even though the large scale isolation experiment gave excellent results using *n*-butanol, because of its lower cost, further development was carried out with *i*-propanol. In these experiments the same fluorination conditions were used as before: 600 g/h 10 wt% cytosine in formic acid, 204 g/h 10 % F_2 V/V in N_2, 10 °C, Boostec reactor.

Previous results on small scale indicated that addition of three volumes of IPA is necessary to achieve the best results and to confirm these results, precipitation of Flucytosine using IPA was repeated on larger (50 mL product solution) scale (Table 24).

Table 24: Room temperature precipitation experiments on 50 mL reaction mixture scale.

FC solution[a] / g	IPA / mL	T / °C	$c_{(FC)}$ mg / mL, normalised	Isolated mass[b] / g
-	-	-	130.5	-
63.6	75	20	22.3	6.4
64.7	100	20	13.3	6.7
64.0	125	20	11.4	6.8
63.7	150	20	8.6	6.9

a; 600 g/h 10 % w/w cytosine in formic acid, 204 g/h 10 % F_2 V/V in N_2, 10 °C, b; 7.1 g expected at 100 % yield and recovery.

The mixtures were stirred for three hours at ambient temperature, filtered and the filtrate diluted to 250 mL then analysed by HPLC-UV (sample further diluted 10 times). The results show that the addition of two volumes of IPA is enough to precipitate 90 % of the Flucytosine in solution, but with three volumes even better recovery is possible (93.5 % recovery). To investigate whether precipitation temperature has an effect on product recovery, the same sequence was repeated on 25 mL scale and was allowed to precipitate overnight in the refrigerator (4 °C). Control samples were kept at room temperature (23 °C) and in the freezer (-18 °C) (Table 25).

Table 25: Effect of temperature on precipitation.

FC solution / g	IPA / mL	T / °C	$c_{(FC)}$ g / L	Isolated mass / g
-	-	-	135.6	-
32.0	37	4	33.0	2.7
31.8	50	4	14.3	3.1
31.9	62	4	11.5	3.3
31.7	75	4	9.5	3.4
31.9	50	23	19.3	3.1
32.2	50	-18	14.6	3.1

From the data obtained it appears that the precipitation is not influenced significantly by temperature and allowing the samples to age for longer time has no significant benefit either. Recovering formic acid before precipitation is a desirable option, rather than attempting to recover and purify the solvents after the filtration of Flucytosine. The precipitation mixture is reactive, leading to a three component solvent mixture (formic acid, IPA and iso-propyl formate), making distillation of pure components more difficult. To assess the effect of formic acid removal on product recovery, two larger scale experiments were conducted. 400 mL samples of crude product solutions were distilled to concentrate to approximately half of the original volume. The solutions were analysed by HPLC and Flucytosine was precipitated by adding three volumes of IPA, stirring overnight at room temperature, filtering and washing with a further portion of IPA. After drying in air the solids were analysed by HPLC to confirm purity (Table 26).

Table 26: Effect of solvent recovery on solution composition.

Reaction number	F132	F133
Net weight / g	505.6	508.5
Distillation temperature (external) / °C	130-135	25-28
Atmosphere	Air	Vacuum (20 mbar)
Distillation time	Approx. 3 h	Approx. 3 h
Weight after distillation / g	249.3	275.9
Colour after distillation	Dark brown	Orange
HPLC purity (before dist.)	94.5 %	93.1 %
HPLC purity (after dist.)	93.0 %	95.4 %

Although evaporation at atmospheric pressure left a darker residue, HPLC analysis showed that the colour did not correspond to a significantly lower Flucytosine content, the main difference was in the impurity profile of the mixture, some impurities are no longer observed, while the relative intensity of other impurities was increased (Figure 103).

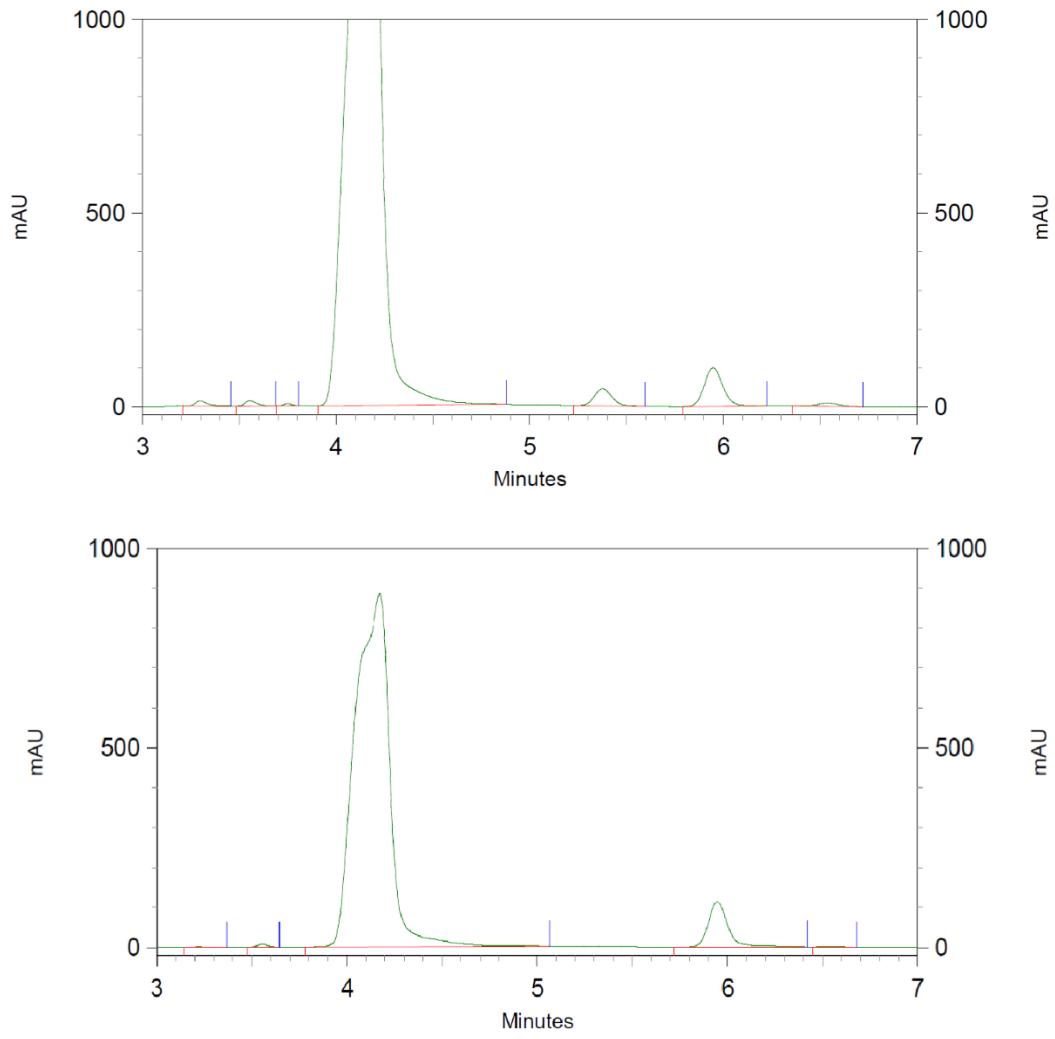


Figure 103: Impurities in crude Flucytosine solution before (top) and after (bottom) distillation of excess formic acid from the product mixture at atmospheric pressure.

When the distillation was carried out under vacuum, the residue did not turn very dark, it had similar colour to the solutions that were left at room temperature for a longer period of time. HPLC analysis of the solution showed no change in impurities, therefore, this method is probably a better way to reduce the amount the amount of solvents used.

NMR analysis of the solid samples obtained from these experiments showed that they are very similar in purity, the sample that was left to dry in air longer did not contain *i*-propanol or formic acid which shows that with adequate drying, all solvents can be removed from the solid sample before final purification. Fluorinated impurities (most likely fluoride) were still present in the samples, but previously it was demonstrated that these can be removed by a further re-precipitation from hydrochloric acid solution.

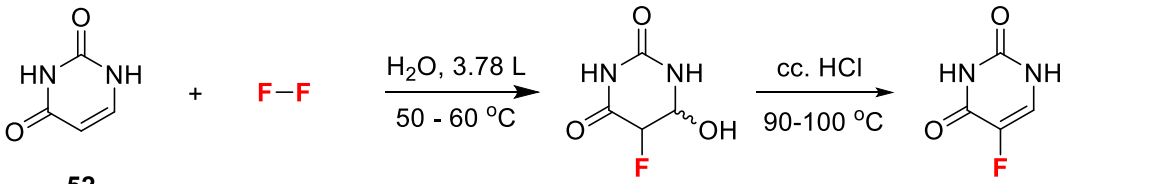
In summary, the large scale isolation studies discussed in this chapter provide several realistic alternative options to the original laboratory scale work-up procedure based on an anti-solvent

precipitation approach using environmentally acceptable solvents. Good product recovery (above 90 %) and excellent crude purity (99.5 % and higher by HPLC) were achieved using these methods and recovery of some of the reaction solvent formic acid was also possible leading to recycling opportunities and a decreased use of the precipitation solvent.

4.3 Green metrics assessment of Flucytosine synthesis methods

To evaluate the continuous flow synthesis of Flucytosine, mass based green metrics were used to compare the commercial process with the new, direct fluorination method. For the assessment of the literature process, some assumptions had to be made, for example, that the most likely used commercial method for the fluorination of uracil is the aqueous system, described in a patent[183] which are mostly low yielding reactions (20-30 %) and the only large scale (100 g+) example available from the literature was used for the calculation of green metrics. The syntheses of uracil and cytosine are not included in this comparison as they are both synthesised from urea and a 1,3-dicarbonyl (or equivalent) acyclic precursor on the industrial scale and are both commercially available, inexpensive compounds.

The direct fluorination of uracil has been described in several patents and this process is known to be used in production processes. The most likely method to be used on manufacturing scale is that of PCR who have been manufacturing this compound for decades, although, real yields are probably significantly higher than the ones reported.[189]



52
MW.: 112.09
454 g

MW.: 38.00
221 g

53
MW.: 148.09
192 g

5
MW.: 130.08
335 g (from three batches)

Work up and purification materials: conc. HCl (assuming 6x100 mL = 600 mL = 720 g), water (300 mL + 500 mL + 3.79 L = 4.59 kg), charcoal (20 g).

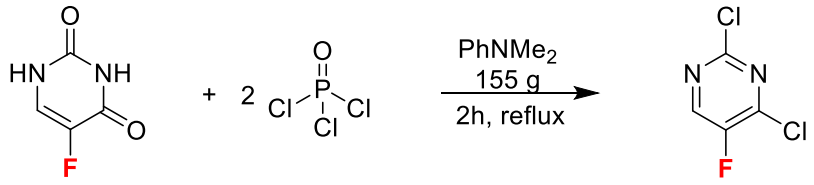
$$AE(Fluorination) = \frac{130.08}{112.09 + 38.00} \times 100 = \mathbf{86.7}$$

$$RME(Fluorination) = \frac{335}{1362 + 663} \times 100 = \mathbf{16.5}$$

$$MI(Fluorination) = \frac{1362 + 663 + 720 + 16020 + 20}{335} = \mathbf{56.1}$$

Figure 104: Material balance and green metrics of the literature synthesis of 5-FU.

Even though the reaction is very atom efficient and relative high concentrations are applied throughout the synthesis, because of the low reported yield of the reaction, mass efficiency is low and the mass intensity value is relatively high (56.1 kg/kg). The next step of the literature process is the chlorination of 5-FU which was carried out using $POCl_3$ according to the original Roche patent.[178]



5
MW.: 130.08
104 g

MW.: 153.32
1472 g

142
MW.: 166.96
112.5 g

Workup and purification materials: diethyl ether (1.2 L, 847 g), ice (500 g).

$$AE(Chlorination) = \frac{166.96}{130.08 + 2 \times 153.32} \times 100 = \mathbf{38.2}$$

$$RME(Chlorination) = \frac{112.5}{104 + 2 \times 123} \times 100 = \mathbf{32.1}$$

$$MI(Chlorination) = \frac{104 + 166 + 1472 + 847 + 500}{112.5} = \mathbf{27.5}$$

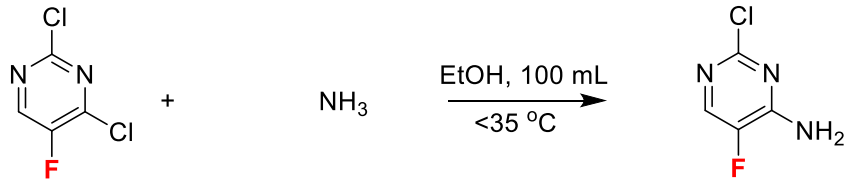
$$AE(Cumulative) = \frac{166.96}{\frac{130.08}{0.867} + 2 \times 153.32} \times 100 = \mathbf{36.6}$$

$$RME(Cumulative) = \frac{112.5}{\frac{104}{0.165} + 2 \times 123} \times 100 = \mathbf{12.8}$$

$$MI(Cumulative) = \frac{104 \times 56.1 + 106 + 1472 + 847 + 500}{112.5} = \mathbf{77.9}$$

Figure 105: Green metrics and materials balance for the chlorination of 5-fluorouracil.

The green metrics show that this reaction does not perform very well in terms of atom efficiency, but most of the Mass Intensity is derived from the large excess of $POCl_3$ which can be recycled for further use in manufacturing processes and as with the previous step, in a real process the reaction would possibly be more concentrated and, a less hazardous solvent would be used. The following step in the synthesis is nucleophilic aromatic substitution of the chlorine atom at the 4-position with ammonia. This reaction proceeds with good regio-selectivity and gives the desired 4-amino-2-chloro-5-fluoropyrimidine in good yield (79 %) after purification.



142
MW.: 166.96
10.0 g

MW.: 17.03
6.3 g (25 mL 28 % solution)

143
MW.: 147.57
6.83 g

Materials used in work-up and purification: water (125 mL, 125 g).

$$AE(Amination) = \frac{147.57}{166.96 + 17.03} \times 100 = \mathbf{80.2}$$

$$RME(Amination) = \frac{6.83}{10 + 6.3} \times 100 = \mathbf{41.9}$$

$$MI(Amination) = \frac{10 + 78.9 + 22.5 + 125}{6.83} = \mathbf{34.6}$$

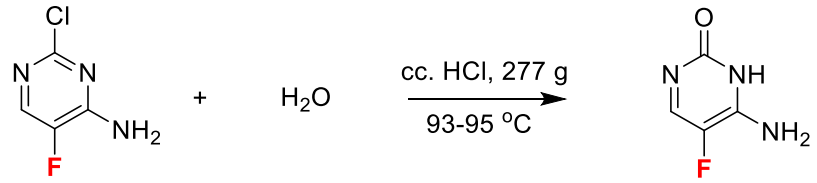
$$AE(Cumulative) = \frac{147.57}{\frac{166.96}{0.366} + 17.03} \times 100 = \mathbf{31.2}$$

$$RME(Cumulative) = \frac{6.83}{\frac{10}{0.128} + 6.3} \times 100 = \mathbf{8.1}$$

$$MI(Cumulative) = \frac{10 \times 77.9 + 78.9 + 22.5 + 125}{6.83} = \mathbf{147.2}$$

Figure 106: Green metrics and material inventory of the S_NAr reaction.

The final step of the literature process is the hydrolysis of the 2-chloropyrimidine derivative which was achieved by heating the intermediate with aqueous hydrochloric acid. 5-Fluorocytosine was isolated in excellent yield by precipitation from the concentrated reaction solution with aqueous ammonia solution.



143
MW.: 147.57
34.0 g

MW.: 18.02
4.2 g (1 eqiv.)

6
MW.: 129.09
28.65 g

Materials used in work-up and purification: 37% HCl (231 mL, 277 g, for RME calculations assume 4.2 g water, 1 equivalent), water (150 mL), 28 % ammonia (29 mL, 20.5 g), ethanol (25 mL, 20 g), diethyl ether (25 mL, 18 g).

$$AE(Hydrolysis) = \frac{129.09}{147.57 + 18.02} \times 100 = \mathbf{78.0}$$

$$RME(Hydrolysis) = \frac{28.65}{34 + 4.2} \times 100 = \mathbf{75.0}$$

$$MI(Hydrolysis) = \frac{34 + 277 + 150 + 20.5 + 20 + 18}{28.65} = \mathbf{16.9}$$

$$\boldsymbol{AE(Cumulative)} = \frac{129.09}{\frac{147.56}{0.312} + 18.02} \times 100 = \mathbf{30.5}$$

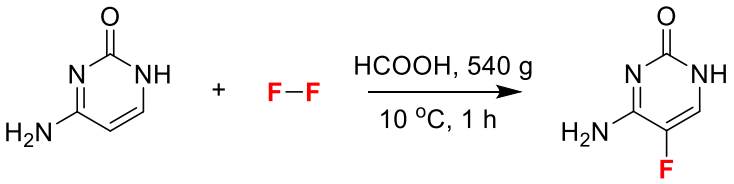
$$\boldsymbol{RME(Cumulative)} = \frac{28.65}{\frac{34}{0.081} + 4.2} \times 100 = \mathbf{6.8}$$

$$\boldsymbol{PMI(Cumulative)} = \frac{34 \times 147.2 + 277 + 150 + 20.5 + 20 + 18}{28.65} = \mathbf{191.6}$$

Figure 107: Material balance and green metrics of the synthesis of 5-fluorocytosine.

The overall green metrics of the literature process (Figure 107) describe a highly inefficient method with four separate synthetic steps and large amounts of materials used to produce the desired product. Even though a large fraction of the material usage originates from the inefficient fluorination of uracil, the remaining three steps still contribute significantly to the results.

In comparison, the continuous flow direct fluorination process described in this thesis is a single step transformation and the crude product can be isolated very easily by a simple precipitation. The green metrics of this process are very favourable, especially when compared with the alternative literature method. The PMI of 28.9 is a relatively low number, but with further optimisation of formic acid removal before precipitation this could potentially be reduced significantly. As elemental fluorine is used in both the literature and our methods, the safety requirements for both processes are similar, but handling hazardous, very exothermic reactions in a continuous process is considered safer than batch techniques.



141
MW.: 111.10
60.0 g

MW.: 38.00
26.7 g

6
MW.: 129.09
58.0 g

Materials used for workup and isolation: n-butanol (1049 g).

$$\boldsymbol{AE(Fluorination)} = \frac{129.09}{111.10 + 38.00} \times 100 = \mathbf{86.6}$$

$$\boldsymbol{RME(Fluorination)} = \frac{58.0}{60 + 26.7} \times 100 = \mathbf{66.9}$$

$$\boldsymbol{MI(Fluorination)} = \frac{60 + 540 + 25.7 + 1049}{58.0} = \mathbf{28.9}$$

Figure 108: Inventory and green metrics of the direct fluorination process.

4.4 Conclusion

In this chapter a new, continuous flow direct fluorination process for the synthesis of Flucytosine was discussed. After initial discovery work on laboratory scale the reaction was transferred to a pilot scale continuous flow reactor setup and optimisation studies were carried out to gain thorough process understanding.

- Excellent conversion using a small excess of fluorine (1.2 – 1.3 equivalents).
- Controlling the reaction temperature is important, highest conversions at 10 °C.
- Reaction throughput is not limiting conversion: up to 1.4 kg solution per hour rate.
- High cytosine concentrations are beneficial: 10 – 11 % solutions in formic acid used.
- Back pressure influences the gas-liquid ratio and has a large negative effect on conversion.
- Mixing of the gas and liquid phases is influenced by several parameters and has a large impact on cytosine conversion.

The downstream processing of the fluorination mixture was also developed with an emphasis of reduced solvent usage and application of green solvent guides for solvent selection.

- Formic acid recovery before isolation enables potential solvent recycling.
- Environmentally friendly solvents *i*-PrOH and *n*-BuOH used for precipitations.
- Excellent recovery (90% +) of high purity (99 % +) crude Flucytosine by precipitation.

Green metrics comparison of the new method with the existing fluorouracil based route highlighted the advantage of this methodology (Table 27). The most important metric, besides overall yield, is Process Mass Intensity which shows the total input material required per kilogram of product and in the case of these two processes the new route requires approximately 85 % less material and, of course, one synthetic step is probably more commercially viable than four.

Table 27: Comparison of key green metrics of the two alternative processes.

	Fluorouracil route	**Cytosine fluorination**
Steps	4	**1**
Yield	13.5 %	**83 %**
Atom Economy	30.5 %	**86.6 %**
Reaction Mass Efficiency	6.8 %	**66.9 %**
Process Mass Intensity	191.6	**28.9**

Since the completion of this study, more scale up work has been carried out by the Sanofi/MEPI team to demonstrate feasibility of producing API grade Flucytosine on the manufacturing scale.

Chapter 5.: Synthesis and Reactivity of α-Fluorotricarbonyl Compounds

As discussed in earlier chapters, fluorinated aliphatic building blocks are very important for the synthesis of a range of fluorinated aliphatic and heterocyclic systems, thus, the development of robust and scalable methods for the synthesis of polyfunctional fluorinated building blocks continues to be of interest. Fluorinated carbonyl compounds bearing functionalities such as esters, amides, ketones and aldehydes may be used in further synthesis and the chemistry of α-fluorocarbonyl compounds, especially 2-fluoro-1,3-dicarbonyl derivatives, is well developed and understood as discussed above. However, despite their potential usefulness in synthesis the corresponding 2-fluorotricarbonyl compounds are very rare in the literature and their reactivity compared to the non-fluorinated analogues has not been described in any detail.

Meldrum's acid (**83**) is a very frequently used building block in organic synthesis as an alternative to dialkyl malonate esters and has been used extensively in the synthesis of complex organic systems and natural products.[200] Acylation of Meldrum's acid gives a particularly important class of compounds as they are versatile intermediates for the synthesis of a large range of β-dicarbonyl derivatives.[201]

Acyl Meldrum's acids are easily synthesised from carboxylic acids by using coupling reagents (DCC, CDI, etc.) or from the corresponding mixed anhydride or acid chloride[202] and the desired product is often used without any purification in subsequent synthetic steps.

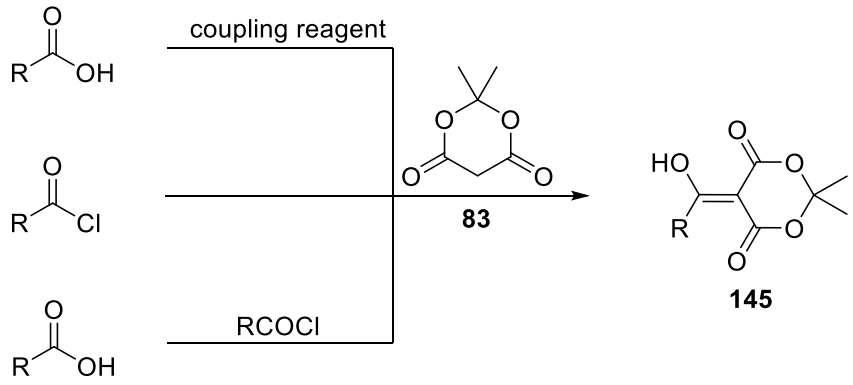


Figure 109: Typical methods for the synthesis of acyl-Meldrum's acid derivatives.

The acylation reaction is typically carried out in halogenated solvents (dichloromethane or chloroform) in the presence of two equivalents of base (usually pyridine or DMAP) and affords the desired product in high yields after removing residues of the coupling reagent and the base from the mixture. In the solid phase acyl Meldrum's acid derivatives (**145**) exist primarily in the enol form which was demonstrated using X-ray crystallographic analysis.[203]

Acyl Meldrum's acid derivatives react with a range of nucleophiles leading to a variety of different carbonyl compounds for example β-keto(thio)esters, β-ketoamides and methyl ketones after loss of acetone and CO_2 (Figure 110). The generally accepted mechanism for these transformations is the thermal elimination of acetone to give the corresponding ketene which further reacts with the nucleophile reagents before or after losing CO_2.[201]

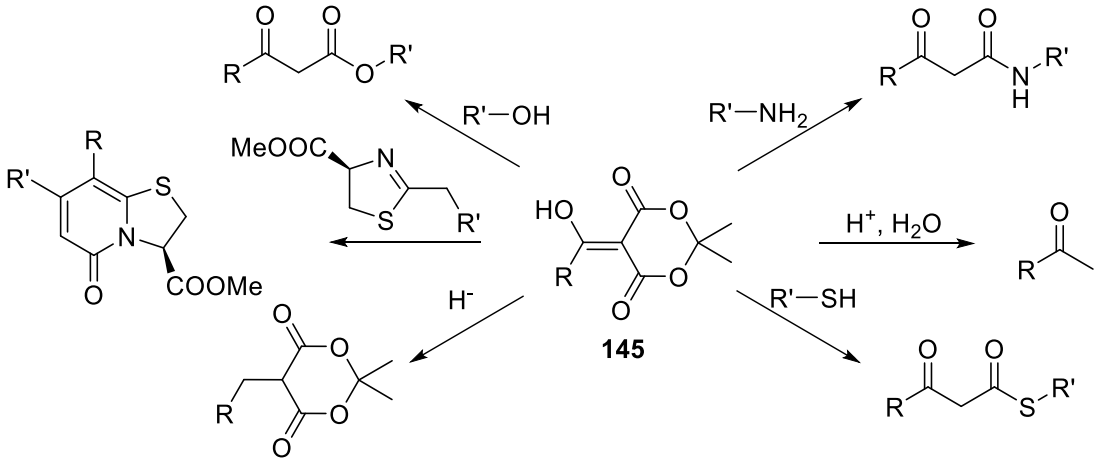


Figure 110: Reaction of acyl Meldrum's acids with various nucleophiles.

Our aim was to prepare corresponding 2-fluorotricarbonyl compounds and use these building blocks to prepare a range of α-fluorocarbonyl derivatives such as ketones, β-keto-esters, amides and thioesters from a common synthetic intermediate.

5.1 Chemistry of 2-fluorotricarbonyl compounds

5.1.1 Aims

In this chapter we aimed to synthesise acyl-Meldrum's acid derivatives and fluorinate them in the α-position using the electrophilic fluorinating reagent Selectfluor™ to gain access to the potentially polyfunctional fluorinated tricarbonyl compounds.

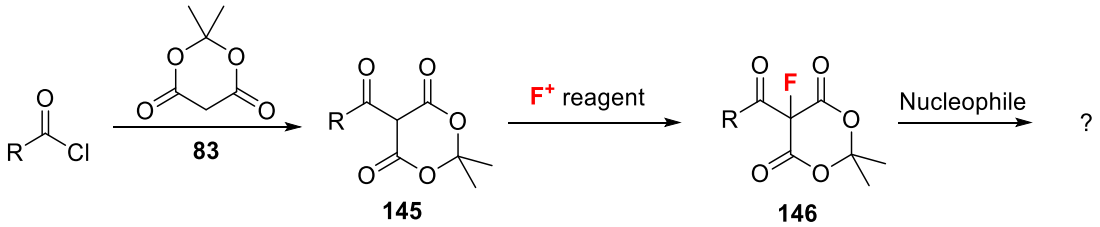


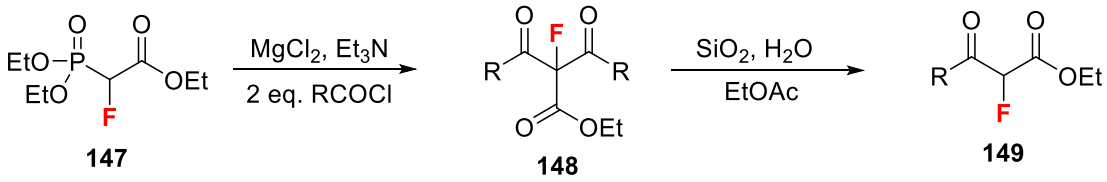
Figure 111: Synthesis and potential use of α-fluorotricarbonyl compounds derived from Meldrum's acid.

Subsequently, the chemistry of 2-acyl-2-fluoro-Meldrum's acid derivatives could be established and reactions with a number of nucleophilic reactants could be explored with a main aim of developing a general procedure for the transformation of aromatic carboxylic acids to fluoromethyl ketones or α-fluoroketoester derivatives.

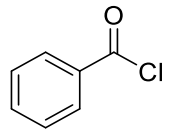
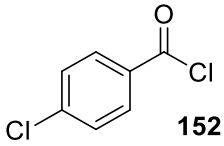
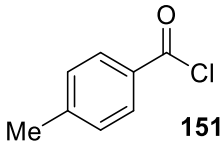
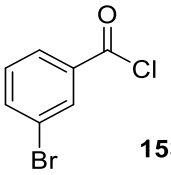
5.1.2 α-Fluorotricarbonyl compounds

Despite the extensive use of tricarbonyl compounds, especially acyl Meldrum's acid derivatives, in organic synthesis there is very little evidence in the literature on the synthesis and use of fluorinated derivatives. A few examples were synthesised by double acylation of ethyl fluoroacetate[204] and by the fluorination of tricarbonyl compounds using perchloryl fluoride[205], but there is only one general method available in the literature. Kim and co-workers reported that triethyl 2-fluorophosphonoacetate can be acylated twice using the $MgCl_2$-Et_3N system to afford the corresponding diketoesters in good yield. It was also reported that these compounds easily undergo de-acylation to the desired 2-fluoro-3-ketoester products in excellent yield (Table 28).[206,207]

Table 28: Synthesis of 2-fluoro-3-ketoesters via a fluorotricarbonyl intermediate.

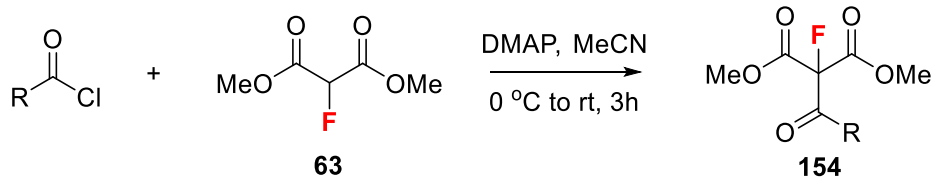


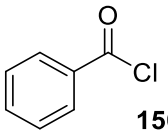
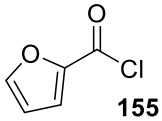
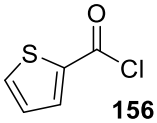
147 148 149

Acid chloride	149 yield / %	Acid chloride	149 yield / %
 **150**	78	 **152**	82
 **151**	88	 **153**	83

More recently, in our laboratory, the acylation of fluoromalonate esters was investigated in detail as part of a final year undergraduate research project.[208] Contrary to non-fluorinated malonate esters, the acylation of fluoromalonate esters does not require addition of a Lewis-acid catalyst and a simple base such as trimethylamine or DMAP is sufficient to generate the enolate system that reacts readily with aromatic acid chlorides (Table 29).

Table 29: Acylation of dimethyl fluoromalonate.



Acid chloride	154 yield / %
 **150**	45
 **155**	67
 **156**	56

Although the desired β-keto-diesters could be isolated and characterised, these compounds were found to be highly moisture sensitive. The hydrolysis product was identified as dimethyl fluoromalonate showing that the cleavage of a C-C bond is the main reaction, however, when tricarbonyl compound derived from benzoyl chloride was heated in acidic solution, the formation of α-fluoroacetophenone was observed in moderate conversion (30 %).

The above results encouraged us to further investigate the synthesis and reactions of fluoro-tricarbonyl compounds. Fluorinated acyl Meldrum's acid derivatives were identified as suitable candidates that can be hydrolysed under acidic conditions, potentially reducing C-C bond cleavage products. This chapter discusses the synthesis and some reactions of these poly-functional fluorinated building blocks.

5.2 Synthesis and reactions of fluorinated acyl Meldrum's acid derivatives

In order to assess the properties and chemical reactivity of fluorinated acyl Meldrum's acid derivatives a method for their synthesis needed to be developed as these compounds have not been described in the literature before. Our synthetic strategy involved acylation of Meldum's acid followed by fluorination of the isolated product using an electrophilic fluorinating reagent to give the desired fluorotricarbonyl compounds that can be used in subsequent reactions.

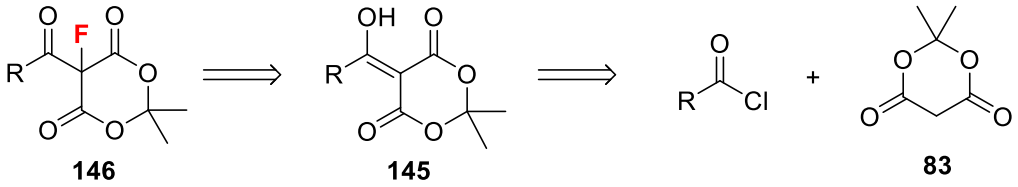
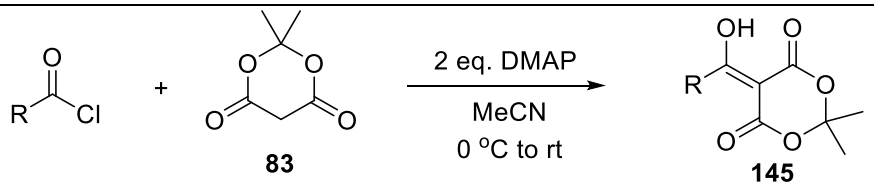


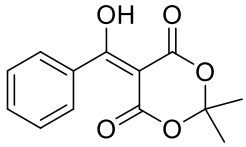
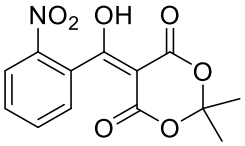
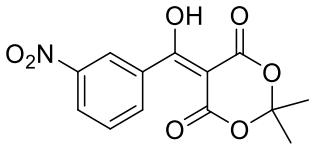
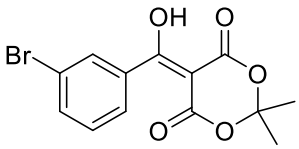
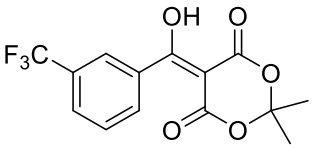
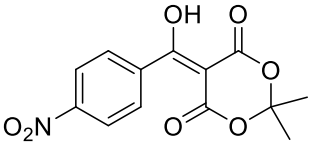
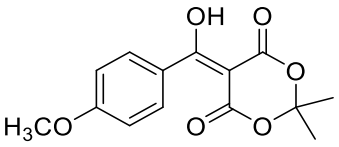
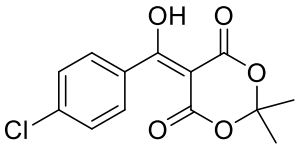
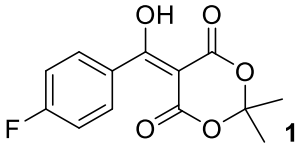
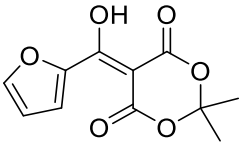
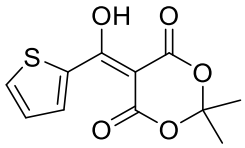
Figure 112: Synthetic strategy for the synthesis of fluorinated acyl Meldrum's acid derivatives.

5.2.1 Acylation of Meldrum's acid

As it was described earlier, the acylation of Meldrum's acid is typically carried out in halogenated hydrocarbon solvents (chloroform, dichloromethane, etc.) in the presence of a pyridine base and the crude product is often used without any further purification.[202] To decrease the environmental impact of this reaction acetonitrile was used to replace chlorinated hydrocarbon solvents. After the reaction reached completion, aqueous hydrochloric acid was added to dissolve the precipitated DMAP hydrochloride and acetonitrile was evaporated from the mixture under reduced pressure to precipitate the desired product. After filtering off the solids and washing with water to remove traces of DMAP.HCl, the product was dried under vacuum (40 °C at 20 mbar) to afford the desired acyl Meldrum's acid derivatives in good yield and purity (Table 30). When the crude product purity was not sufficient, the solid was recrystallized from a minimum amount of acetone to yield high purity crystalline material.

Table 30: Synthesis of acyl Meldrum's acid derivatives.



Product	Yield / %	Product	Yield / %
 **157**	90	 **163**	59
 **158**	85	 **164**	79
 **159**	86	 **165**	91
 **160**	40	 **166**	65
 **161**	60	 **167**	74
 **162**	78		

The pure, solid products were all isolated as the enol form, as shown by ^{13}C NMR spectroscopy (three distinct C=O environments) and X-ray crystallography, however, the equilibrium between the enol and keto tautomers was observed by ^{1}H NMR spectroscopy that was acquired after the solution reached equilibrium (8-10 hours).

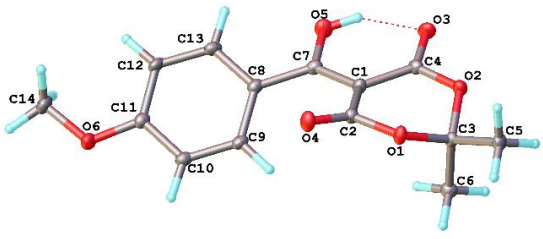


Figure 113: Molecular structure of **160** confirming the enol form of the product.

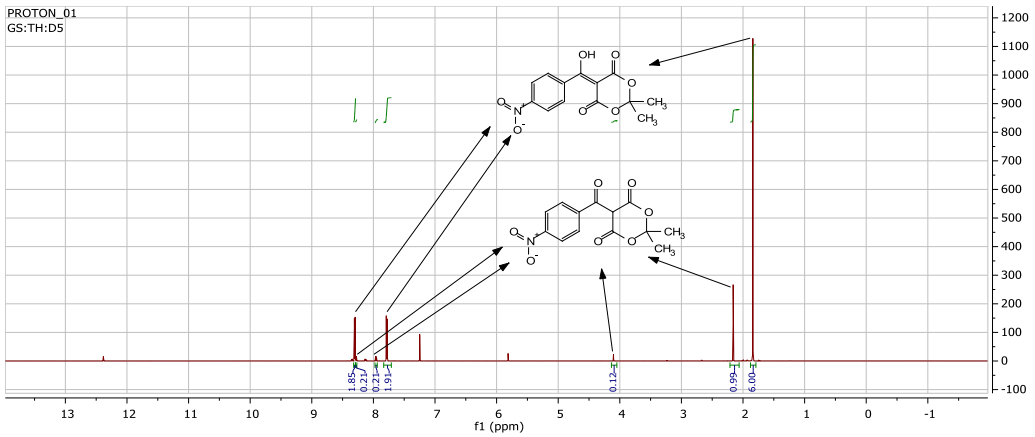


Figure 114: ^{1}H NMR spectrum of **165** showing keto and enol tautomer forms (keto : enol, 1 : 9).

The high enol content of these compounds, typically above 98 % in solid phase, suggests that the electrophilic fluorination should proceed easily, even without the addition of further base or Lewis acid catalyst.

5.3.2 Fluorination of acyl Meldrum's acids

The fluorination of enolate derivatives can be carried out using a wide range of electrophilic fluorinating reagents and Selectfluor™ was chosen as the reagent of choice for its fluorinating power and ease of separation from the desired product. The fluorinations were carried out in acetonitrile, a typical solvent for fluorinations using Selectfluor™, at ambient temperature over 16 hours when ^{19}F NMR spectroscopic analysis of the mixture confirmed full conversion to the desired tricarbonyl product.

Reaction of 2-nitrobenzoyl Meldrum's acid with Selectfluor™ (Figure 115) was worked up in a conventional way: the reaction mixture was quenched into a large excess of water, the product extracted with ethyl acetate, washed with aqueous $NaHCO_3$ solution, dried and evaporated to dryness to afford the crude product. The crude yield of the product was only 70 % and this contained several fluorinated impurities that weren't present before the workup procedure. The purification of the crude product was carried out using column chromatography on silica gel, but instead of the desired product, 2-fluoro-2'-nitroacetophenone was isolated in 38 % yield which inspired the re-evaluation of the post-reaction treatment of the product.

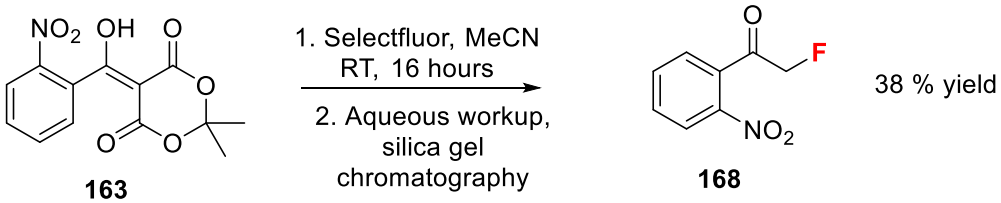
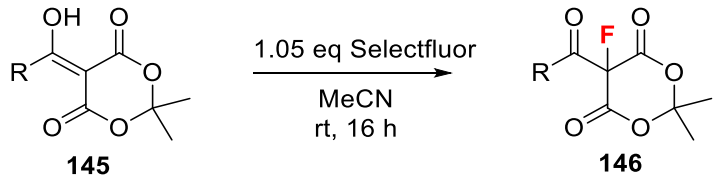
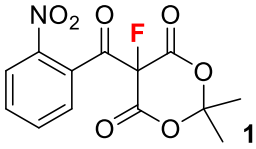
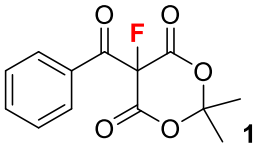
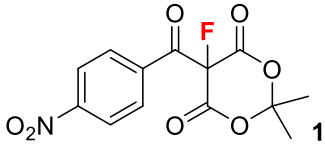
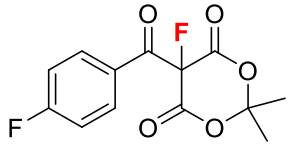
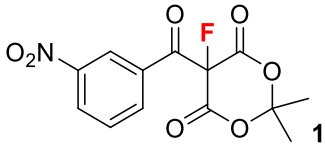
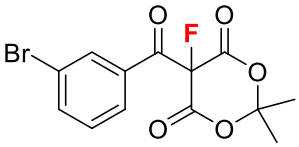
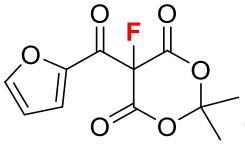
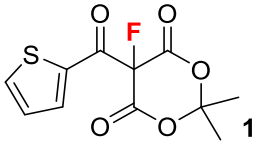


Figure 115: Fluorination of **163** and subsequent decomposition of the product during purification.

As the analysis of the crude product suggested that some of the product decomposition had occurred during the aqueous workup, we sought to eliminate this step from the procedure. After the reaction reached completion acetonitrile was removed under vacuum to leave a solid mixture of the desired product and depleted Selectfluor™. The isolation of the tricarbonyl product was achieved by selective dissolution into ethyl acetate and evaporation of the solvent after filtering off the Selectfluor™ salt residues. In some cases, the crude product was further purified by dissolving in a small volume of dichloromethane followed by the addition of a larger volume of hexane and the removal of dichloromethane by atmospheric pressure distillation. After cooling at 0-5 °C for 12-16 hours, the desired fluorotricarbonyl products were isolated in good yield as fine powders, and in some cases, crystalline products were obtained by further recrystallisation from acetone.

Table 31: Fluorination of acyl Meldrum's acid derivatives.



Product	Yield / %	Product	Yield / %
 169	75	 173	74
 170	75	 174	70
 171	45	 175	64
 172	92	 176	93

Under these reaction conditions both aromatic substrates bearing electron withdrawing and electron donating substituents were successfully fluorinated and competing aromatic fluorination was not observed even in the case of the electron rich thiophene derivative. These compounds were found to be stable for a long time (over a month) as long as moisture was

excluded and the samples were kept in a refrigerator. X-ray crystallographic analysis of two fluorinated acyl Meldrum's acid derivatives showed that the cyclohexane ring of these compounds takes a distorted boat conformation where the torsion angle between the fluorine atom and the C=O oxygen atoms of the ring is only approximately 30° (Figure 116). The difference between the conformations of the two methyl groups was also observed by ^{1}H and ^{13}C NMR spectroscopy where the chemical shifts corresponded to one axial and one equatorial environment.

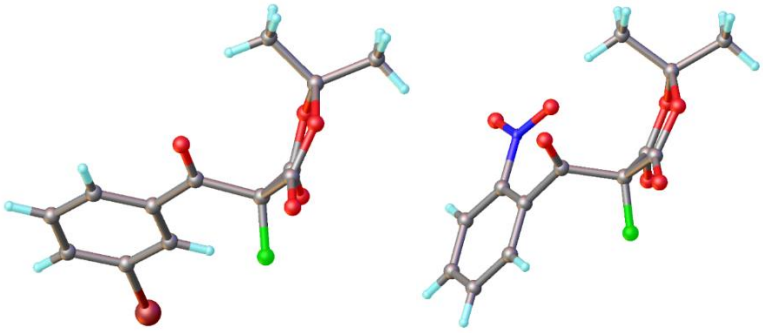
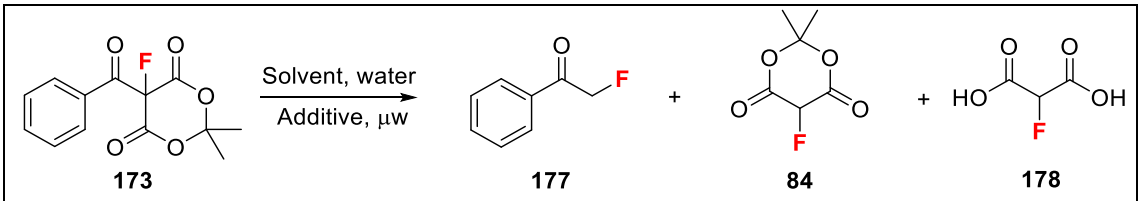


Figure 116: Distorted boat conformation of fluorinated Meldrum's acid derivatives.

5.3.3 Synthesis of 2-fluoroacetophenone derivatives

Our first attempt at isolating a fluorinated acyl Meldrum's acid derivative (Figure 115) indicated that the hydrolysis and decarboxylation of these systems could, in principle, easily be achieved and to develop and understand this reaction a range of conditions were screened on 1 mmol scale (Table 32). From the hydrolysis studies of dimethyl (benzoyl)fluoromalonate[208] it was apparent that basic hydrolysis of this class of compounds would lead the cleavage of the C-C bond as the main reaction, therefore, in this study, acid catalysed hydrolysis conditions were investigated. The requirement for an acid catalyst was further confirmed when in the presence of water without additive (Table 32/1) only low conversion of the starting material was observed and the main fluorinated product from this reaction was fluorinated Meldrum's acid.

Table 32: Screening conditions for the synthesis of 2-fluoroacetophenone.



173 177 84 178

No	Solvent	Additive	Water	T / °C	t / min	Composition
1	Acetone	-	0.1 mL	100	20	91 % **173**, 1 % **177**, 8 % **84**
2	Acetone	0.1 mL 1M HCl	-	90	20	67 % **173**, 23 % **177**, 5 % **84**, 5 % **178**
3	Acetone	1 eq. $TsOH.H_2O$	0.1 mL	90	20	68 % **177**, 7 % **84**, 25 % **178**
4	Acetone	1 eq. $TsOH.H_2O$	-	100	20	11 % **173**, 30 % **177**, 20 % **84**, 38 % **178**
5	Acetone	2 eq. $TsOH.H_2O$	-	100	20	2 % **173**, 36 % **177**, 62 % **178**
6	Acetone	1 eq. $TsOH.H_2O$	0.1 mL	100	20	60 % **177**, 40 % **178**
7	Acetone	1 eq. $TsOH.H_2O$	0.1 mL	110	20	75 % **177**, 25 % **178**
8	Acetone	1 eq. $TsOH.H_2O$	0.2 mL	100	20	73 % **177**, 27 % **178**
9	Acetone	1 eq. K_2CO_3	0.1 mL	100	20	No reaction
10	Acetone	0.1 mL 37 % HCl	-	100	20	34 % **173**, 56 % **177**, 10 % **178**
11	Acetone	0.05 mL 37 % HCl	0.05 mL	100	20	35 % **173**, 48 % **177**, 3 % **84**, 14 % **178**
12	Acetone	0.5 eq. $TsOH.H_2O$	0.1 mL	100	30	76 % **177**, 24 % **178**
13	AcOH	1 eq. $TsOH.H_2O$	-	100	20	36 % **177**, 64 % **178**
14	AcOH	1 eq. $TsOH.H_2O$	0.1 mL	100	20	55 % **177**, 45 % **178**

Screening of reaction conditions revealed that *p*-toluenesulfonic acid monohydrate is a suitable catalyst for the reaction and larger than one equivalent quantity is not required, however, when only 50 mol% was used the reaction required a longer reaction time to reach full conversion. Additional water improved the selectivity and conversion of the reaction, but more than 0.1 mL water per mmol starting material did not have any further benefit. The overall selectivity of the reaction could not be improved further than 75 % in the case of this substrate and, after isolation and column chromatographic purification, this resulted in 56 % isolated yield of 2-

fluoroacetophenone. The selectivity of this reaction can be explained with the difference in mechanism compared with the non-fluorinated analogues as in these compounds there is no acidic hydrogen atom in the α position, therefore, the formation of the ketene intermediate is not possible. However, in these compounds there are two different type of carbonyl centres that could react with a nucleophilic species such as water and the relative reaction rates between these centres determines the selectivity of the reaction.

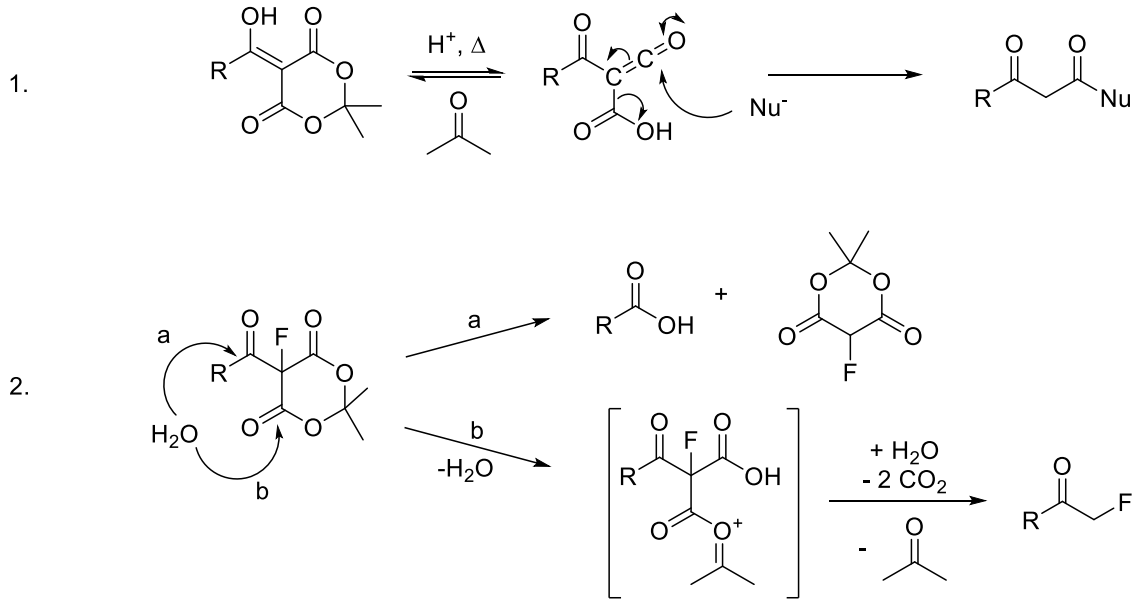


Figure 117: Possible mechanisms of the hydrolysis of fluorinated acyl Meldrum's acid derivatives.

The best reaction conditions were applied to a range of aromatic and heteroaromatic fluorinated Meldrum's acid derivatives to yield aryl-fluoromethyl ketones in good yield after flash column chromatographic purification (Table 33). The higher yields obtained in the synthesis of the **168** and **184** suggest that an *ortho* substituent capable of resonance stabilisation can improve the selectivity of the decarboxylation. The structure of the products was conformed using NMR spectroscopy and mass spectrometry and in the case of some products, such as 2-fluoro-2'-nitroacetophenone, X-ray crystallography (Figure 118).

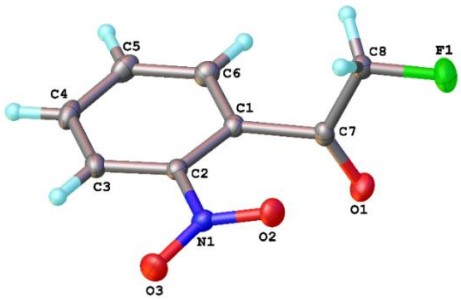
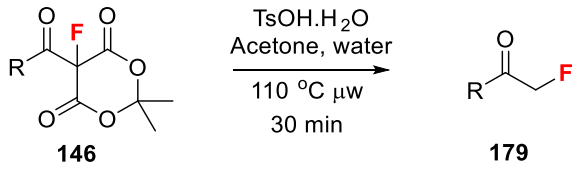
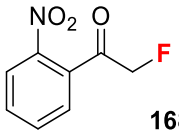
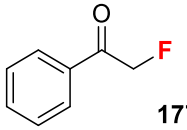
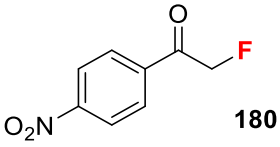
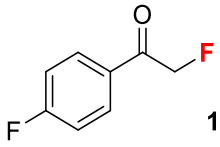
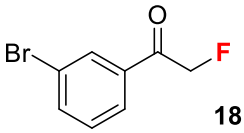
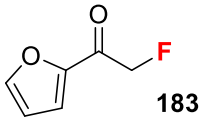
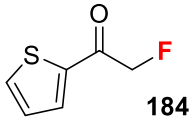


Figure 118: Molecular structure of **168** as determined by X-ray crystallography.

Table 33: Synthesis of α-fluoroacetophenone derivatives.



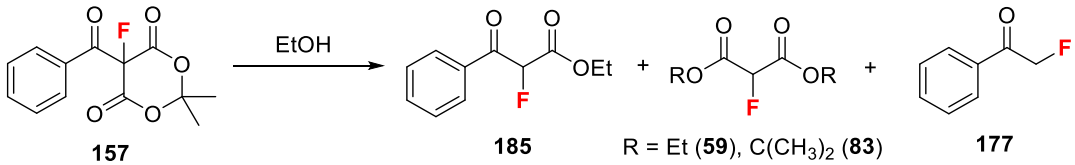
146 → 179

Product	Yield / %	Product	Yield / %
 **168**	89	 **177**	56
 **180**	41	 **182**	62
 **181**	35	 **183**	51
 **184**	73		

5.3.4 Ethanolysis of fluorinated acyl Meldrum's acid derivatives

After the decarboxylation of the fluorinated tricarbonyl compounds was successfully demonstrated, we sought to expand the synthetic utility of this system and an obvious direction was to replace water with another oxygen centered nucleophile such as ethanol.

Table 34: Screening conditions for the ethanolysis of 5-benzoyl-5-fluoro-1,3-dioxane-4,6-dione.



157 → **185** + RO/OR + **177**

T / °C	t / min	Composition
60	30	38 % **157**, 61 % **185**, 1 % **59**
70	30	25 % **157**, 72 % **185**, 3 % **59 + 83**
80	30	12 % **157**, 84 % **185**, 4 % **59 + 83**
90	30	10 % **157**, 84 % **185**, 5% **59 + 83**, 1 % **177**
100	30	3 % **157**, 86 % **185**, 10 % **59 + 83**, 1 % **177**
60	60	97 % **185**, 3 % **59 + 83**
80	60	94 % **185**, 6 % **59 + 83**

Reaction of **157** with ethanol was carried out without the addition of acid catalyst and even at 60 °C, good conversion of the starting material was observed. The results in Table 34 show that the conversion could be increased by either increasing the temperature or the reaction time, but at higher temperatures the selectivity of the reaction decreases, therefore, for best results longer reaction time (60 minutes) and lower reaction temperature (60 °C) are preferred.

The corresponding reaction of the furoyl derivative was carried out on preparative scale and ethyl 2-fluoro-3-(2-furyl)-3-oxopropionate was obtained in good yield (55 %) after column chromatography. Despite the high selectivity (90 %+, Figure 119), the yield of the reaction is relatively low due to the difficult chromatographic separation from the side product 2-(fluoroacetyl)furane.

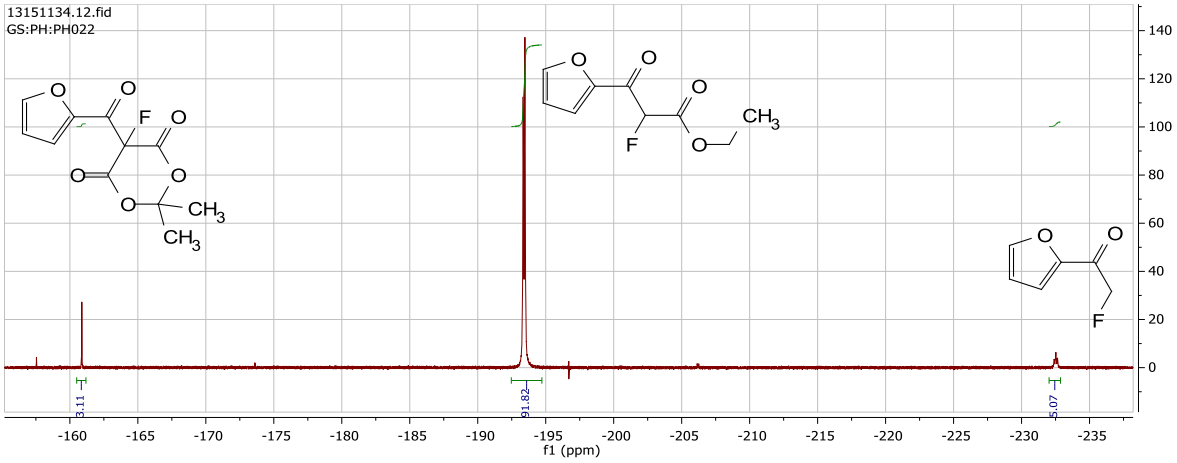


Figure 119 ^{19}F NMR spectrum of a crude ethanolysis product.

5.4 Conclusion

In this chapter the synthesis and reactivity of fluorinated acyl Meldrum's acid derivatives was described. With modification of literature conditions, Meldrum's acid was acylated under more environmentally friendly conditions and the product isolation was significantly simplified. Fluorination was carried out using Selectfluor™ and the desired fluorotricarbonyl compounds were obtained in good yield. Hydrolysis of these intermediates led to fluoroacetophenone derivatives in a simple process, overall providing a multistep approach for the transformation of carboxylic acids to the corresponding fluoromethyl ketones. In initial experiments, it was demonstrated that fluorotricarbonyl compounds can also be transformed into the ketoester analogues by simply heating them in ethanol, showing that they are useful building blocks that are suitable for the rapid generation of a variety of ketoester derivatives.

Chapter 6.: Conclusions and Future Work

In this thesis the selective direct fluorination of a range of life-science building blocks was described with an aim to identify high yielding, selective processes that can be analysed using the green metrics package[124] developed by the Chem21 consortium.

Following optimisation and process intensification, a copper catalysed direct fluorination process for the synthesis of fluoromalonate esters afforded these important, polyfunctional building blocks in excellent yields (95-97 %) on larger laboratory scale. Subsequent green metrics comparison with existing methodologies showed that this method is comparable with the industrially used halogen exchange reaction and is superior to the sequential solvolysis of hexafluoropropene. A potential extension of this research could be to optimise the direct fluorination of other, synthetically important, dicarbonyl compounds and to compare these reactions with alternative synthetic methods, for example, halogen exchange or fluoroacetic acid based processes.

Attempts to fluorinate a structurally more complex system, progesterone, showcased the limitations of elemental fluorine: even though the desired products were identified by HPLC analysis of the crude reaction mixture, isolation of pure product was not possible because of a large number of unidentified sire products. Despite these results, the synthesis of more simple α-fluoroketones from the corresponding enolate compounds using fluorine gas is still an attractive approach and after some optimisation it would be interesting to compare this reaction with the existing alternative methods from a green metrics point of view.

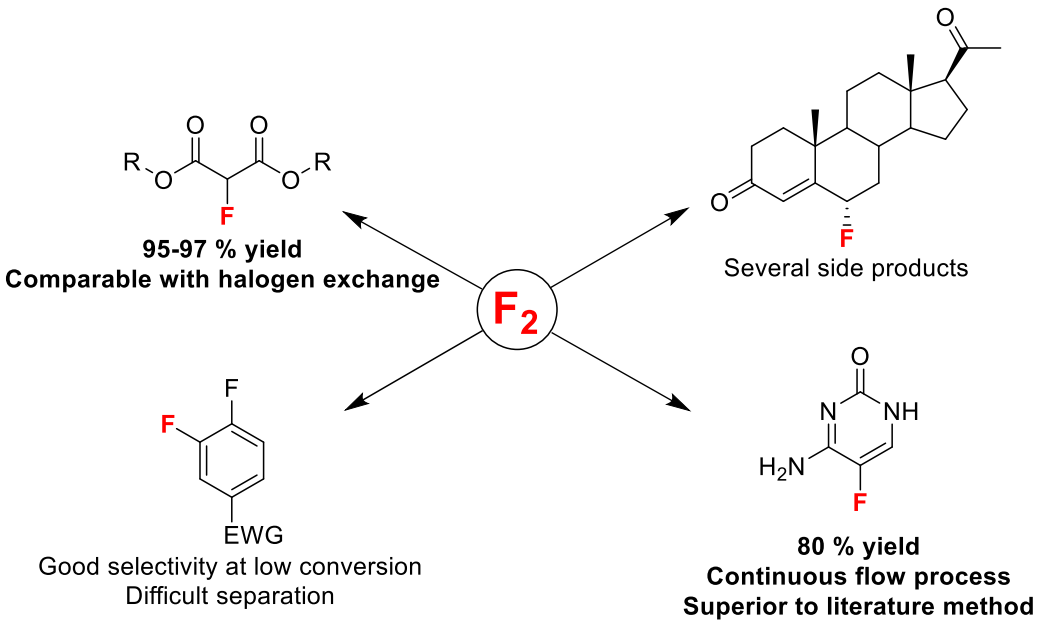


Figure 120: Overview of direct fluorination studies.

The fluorination of aromatic systems was carried out on a range of systems and we found that the reaction outcome needs to be balanced between conversion and selectivity, but despite all efforts to purify the investigated systems, the few reactions that were investigated were developed to a stage where green metrics analysis was possible. Future research in this area could focus on the fluorination of some more activated aromatic systems such as aniline or phenol derivatives which have been shown to give the desired products in higher selectivity and yield both under batch and continuous flow fluorination conditions.[91] Optimising such a reaction would allow the green metrics comparison of a direct fluorination process with the typically used Balz-Schiemann reaction.

In contrast, direct fluorination of cytosine, a highly activated heterocyclic system, was shown to be a viable reaction under batch fluorination conditions and was subsequently transferred to continuous flow which further improved the reaction selectivity. In order to assess the scalability of this reaction, the process was transferred to a meso-scale silicon carbide reactor in a collaboration project with Sanofi and MEPI and was further optimised to yield high purity Flucytosine in higher than 80 % yield. Comparison of green metrics against the industrially used four step process showed that our method is clearly superior not just in overall yield and step count but it's PMI value is significantly lower too. In further work this fluorination reaction is being investigated by our Sanofi/MEPI collaborators to assess the commercial viability of this process.

Overall, using the Chem21 green metrics package we demonstrated that in cases when the direct fluorination process could be optimised it is comparable or better than existing synthetic methods. Although these examples only covered areas where fluorinated bioactive compounds are known, with the ever increasing number and diversity of new fluorinated systems it is important to bear in mind that elemental fluorine is a very economical reagent in synthesis and its use should be investigated whenever a cost effective solution is sought.

Finally, previously unknown fluorinated acyl Meldrum's acid derivatives were synthesised in good yield in two steps from aromatic acid chlorides and were shown to undergo reactions with nucleophiles such as water or ethanol. A distinct advantage of this approach over the fluorination of dicarbonyl systems is the potentially increased selectivity as α-difluorination is not possible.

One of the areas for potential future research is the further exploration of the reactions of these polyfunctional building blocks and to extend the range of substrates to heterocyclic and aliphatic carboxylic acid derivatives.

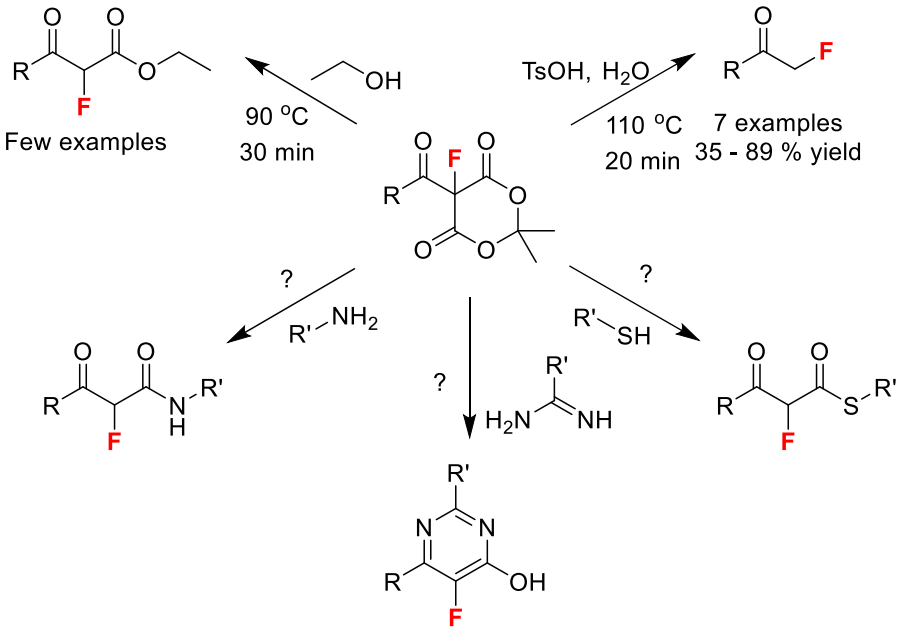


Figure 121: Possible reactions of fluorinated acyl Meldrum's acid systems.

To investigate the scalability of the synthesis of these Meldrum's acid derivatives, their fluorination using elemental fluorine could be of potential interest. As the enol content of acyl Meldrum's acids is very high, the direct fluorination process may even proceed without any added Lewis acid catalyst or base.

Chapter 7.: Experimental

7.1. General

Hydrogen, fluorine and carbon nuclear magnetic resonance spectra (^{1}H, ^{19}F and ^{13}C NMR) were obtained using Bruker 400 Ultrashield spectrometers (^{1}H NMR at 400 MHz, ^{19}F NMR at 376 MHz and ^{13}C NMR at 101 MHz). HSQC, HMBC and NOESY experiments were recorded on Varian VNMRS-600 and VNMRS-700 instruments, using residual solvent peaks as the internal standard (^{1}H NMR; $CHCl_3$ at 7.26 ppm, ^{19}F NMR; $CFCl_3$ at 0.00 ppm and ^{13}C NMR; $CDCl_3$ at 77.16 ppm). NMR spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and assignment.

GC-MS data were obtained using a Trace GC-MS (Thermo-Finnigan) or a QP2010-Ultra (Shimadzu) instrument operating in electron impact ionization (EI) mode. Accurate mass analyses were performed on a Xevo QtoF mass spectrometer (Waters Ltd, UK) with an accurate solids analysis probe (ASAP) or a TQD UPLC (Waters) instrument operating in electrospray ionisation mode.

Melting point data were obtained using a Gallenkamp apparatus at atmospheric pressure and are uncorrected. Infra-red (IR) spectroscopy was performed on a Perkin Elmer 1600 Series FTIR with an ATR probe. *In-situ* IR spectroscopy was performed using a Mettler Toledo React IR instrument equipped with a diamond probe.

HPLC analysis of steroid samples was carried out on a PerkinElmer instrument with UV detection at 237 nm using an XBridge C18, 100x4.6 mm, 3.5μm (Waters) column at 25 ^{o}C with the following method: elution started with 60 % water/40 % acetonitrile with 0.1 % TFA which was increased to 5% water/95 % acetonitrile with 0.1 % TFA over 15 minutes at 1.5 mL/min flow rate.

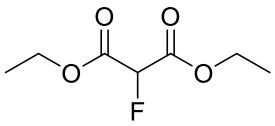
HPLC analysis of Flucytosine samples was carried out on a Thermo ACCELA600 instrument with UV detection at 260 nm using a Phenomenex LUNA® C18(2), 250x4 mm, 5µm (Waters) column at 40 °C with isocratic elution using the following eluent at 0.6 mL/min flow rate: 13.6g KH_2PO_4, 20 mL MeOH, Ultra Pure Water QSP 1L, pH adjusted to 2 with H_3PO_4.

Fluorinations were carried out in a glass fluorination reactor (100 mL, 250 mL or 500 mL) unless otherwise stated. The reactors were built from a standard glass bottle with GL 45 thread joint and a PTFE screw cap or a glass flange head, equipped with a gas inlet/outlet head built of Stainless Steel, PTFE and FEP Swagelok components.

7.2. Experimental to Chapter 2.

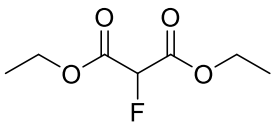
7.2.1 Direct fluorination of malonate esters

Diethyl malonate fluorination: general reaction (59)



Diethyl malonate (3.20 g, 20 mmol) and copper nitrate hydrate ($Cu(NO_3)_2.2.5H_2O$; 0.46 g, 2 mmol) were dissolved in acetonitrile (17 mL) and placed into the fluorination reactor and the mixture was cooled to 0-5 °C. After purging the system with N_2 for 5 minutes, fluorine gas (10 % *v/v* in N_2, 45 mL/min, 22 mmol) was passed into the stirred mixture for 2h. The reactor was purged with nitrogen for 10 minutes, the solvent was removed *in vacuo* and the residue partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL) and the combined organic layers were washed with saturated brine (10 mL). After drying over sodium sulfate, the solvent was evaporated to leave *diethyl 2-fluoromalonate* (3.37 g, 94 % yield, 93.5 % purity) as a colourless liquid. IR (neat, cm^{-1}): 2986, 1747, 1243, 1187, 1097, 1020; δ_H ($CDCl_3$, 400 MHz) 1.31 (6H, t, $^3J_{HH}$ 7.2, CH_3), 4.31 (4H, q, $^3J_{HH}$ 7.2, CH_2), 5.26 (1H, d, $^2J_{HF}$ 48.3, CHF); δ_F ($CDCl_3$, 376 MHz): - 195.58 (d, $^2J_{HF}$ 48.3, CH-F); δ_C ($CDCl_3$, 100 MHz) 14.04 (CH_3), 62.80 (CH_2), 85.39 (d, $^1J_{CF}$ 198.2, C-F), 164.20 (d, $^2J_{CF}$ 24.1, C=O); m/z (EI^+) 179 (5 %, $[M+H]^+$), 133 (44 %, $[M\text{-}OEt]^+$), 105 (49 %, $[M\text{-}COOEt]^+$), 78 (100 %, $[CH_2FCOOH]^+$). Spectroscopic data were identical with those previously reported and side products were identified from their reported ^{19}F NMR shifts.[163]

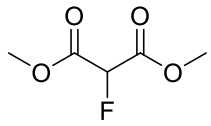
Diethyl fluoromalonate large scale fluorination (59)



Diethyl malonate (40.0 g, 0.25 mol) and copper nitrate hydrate ($Cu(NO_3)_2.2.5H_2O$; 5.81 g, 25 mmol) were dissolved in acetonitrile (200 mL) and placed in 500 mL fluorination vessel, cooled to 0-5 °C and stirred at 650 rpm using an overhead stirrer. After purging the system with N_2 for 5 minutes, fluorine gas (20 % *v/v* in N_2, 80 mL/min, 265 mmol) was introduced into the mixture for 6 hours and 30 minutes. The reactor was purged with nitrogen for 10 minutes, the solvent removed *in vacuo* and the residue partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous phase was extracted once more with ethyl acetate (50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (20 mL). After drying over sodium sulfate, the solvent was evaporated to leave *diethyl 2-fluoromalonate* (44.4

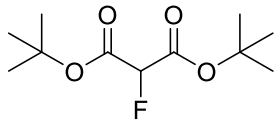
g, 99% yield, 95 % purity) as a light yellow, transparent liquid. This crude product was distilled to afford high purity fluoromalonate (34.7 g, 77 % yield, 99%+ purity) as a colourless liquid, bp. 102-103 °C (18 mbar), (lit.: 110-112 °C, 29 mbar)[163], spectroscopic data as above.

Dimethyl 2-fluoromalonate (63)



Dimethyl malonate (19.8 g, 0.15 mol) and $Cu(NO_3)_2.2.5H_2O$ (3.50 g, 15 mmol) were dissolved in acetonitrile (85 mL), the mixture was cooled to 0-5 °C and stirred at 650 rpm using an overhead stirrer. After purging the system with N_2 for 5 minutes, fluorine gas (20 % *v/v* in N_2, 50 mL/min, 170 mmol) was introduced into the reaction mixture for 7 h. After purging with nitrogen for 20 minutes, the solvent was removed *in vacuo* and the residue was partitioned between water (30 mL) and ethyl acetate (20 mL). The aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic layer was washed with saturated brine (20 mL). After drying over sodium sulphate, the solvent was evaporated under reduced pressure to give *dimethyl 2-fluoromalonate* (21.8 g, 97% yield, 95 % purity) as a colourless oil; IR (neat, cm^{-1}) 2962, 1748, 1438, 1250, 1206, 1112, 1016; δ_H ($CDCl_3$, 400 MHz) 3.85 (6H, s, CH_3), 5.31 (1H, d, $^2J_{HF}$ 48.0, CHF); δ_F ($CDCl_3$, 376 MHz): -195.73 (d, $^2J_{HF}$ 48.0, CH-F); δ_C ($CDCl_3$, 100 MHz) 53.48 (CH_3), 85.19 (d, $^1J_{CF}$ 197.2, C-F), 164.39 (d, $^2J_{CF}$ 24.0, C=O); m/z (EI^+) 150 (3 %, $[M]^+$), 119 (42 %, $[M\text{-}OMe]^+$), 91 (73 %, $[M\text{-}COOMe]^+$), 59 (100 %, $[COOMe]^+$). Spectroscopic data in agreement with previously published data.[163]

Di-*tert*-butyl 2-fluoromalonate (99)



Di-*tert*-butylmalonate (12.0 g, 55 mmol) and copper nitrate catalyst (1.16 g, 5 mmol) were dissolved in acetonitrile (50 mL), placed in a fluorination vessel and the mixture was cooled to 0-5 °C. After purging the system with N_2 for 5 minutes, fluorine gas (20 % *v/v* in N_2, 44 mL/min, 60 mmol) was introduced for 5 h. The reaction was then purged with nitrogen for 10 minutes, the solvent was removed under reduced pressure and the residue was partitioned between water (10 mL) and ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) then the combined organic layer was washed with saturated brine (10 mL). After drying over sodium sulphate, the solvent was evaporated under reduced pressure to leave *di-tert-butyl 2-fluoromalonate* (12.57 g, 96% yield, 97 % purity) as a colourless liquid; IR (neat, cm^{-1}) 2980,

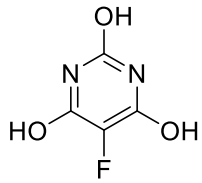
1744, 1369, 1252, 1143; δ_H ($CDCl_3$, 400 MHz) 1.49 (18H, s, CH_3), 5.01 (1H, d, $^2J_{HF}$ 48.9, CHF); δ_F ($CDCl_3$, 376 MHz): -193.79 (d, $^2J_{HF}$ 48.9, CH-F); δ_C ($CDCl_3$, 100 MHz) 27.95 (CH_3), 84.01 (C-CH_3), 85.97 (d, $^1J_{CF}$ 196.5, C-F), 163.32 (d, $^2J_{CF}$ 24.5, C=O); m/z (EI$^+$) 162 (20 %, [M-O*t*Bu+H]$^+$), 57 (100 %, [*t*Bu]$^+$).

7.2.2 Synthesis of 5-fluoropyrimidine derivatives from diethyl fluoromalonate

5-Fluoro-4,6-dihydroxypyrimidine (60)

Formamidine acetate (2.06 g, 20 mmol) was added to the solution of sodium (1.38 g, 60 mmol) in anhydrous ethanol (40 mL) and the mixture was heated to reflux. Diethyl 2-fluoromalonate (3.20 g, 18 mmol) was added dropwise over 20 minutes and the mixture was heated at reflux for 6 h. After cooling to room temperature, the solution was evaporated to dryness, the residue was dissolved in water (20 mL), acidified with HCl (5 mL), the precipitate was filtered, washed with water (5 mL), ethanol (2x5 mL) and diethyl ether (2x5 mL). After drying *in vacuo, 5-fluoro-4,6-dihydroxypyrimidine* (1.50 g, 64 %) was obtained as a brown powder. m.p.: > 300 °C; ([M+H]$^+$, 131.0244, $C_4H_4FN_2O_2$ requires: [M]$^+$, 131.0257); IR (neat, cm^{-1}) 3053, 2639, 1633, 1547, 1388, 1213; δ_H (DMSO *d_6*, 400 MHz) 7.90 (1H, s, C-H), 12.38 (2H, bs, OH); δ_F (DMSO *d_6*, 376 MHz): -178.06 (s); δ_C (DMSO *d_6*, 100 MHz) 132.79 (d, $^1J_{CF}$ 235.6, C-F), 144.46 (d, $^4J_{CF}$ 7.7, C-H), 155.83 (d, $^2J_{CF}$ 15.0, C-OH); m/z (ASAP) 131 (100 %, [M+H]$^+$).

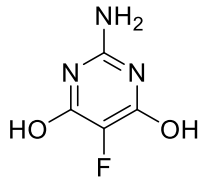
5-Fluorobarbituric acid (105)



Urea (1.50 g, 25 mmol) was added to the solution of sodium (1.2 g, 53 mmol) in anhydrous ethanol (50 mL) and the mixture was heated to reflux. Diethyl 2-fluoromalonate (4.45 g, 25 mmol) was added dropwise over 10 minutes and the mixture was heated at reflux for 1 h. After cooling to room temperature, the solution was filtered, the residue was washed with ethanol (20 mL), dissolved in water (30 mL) and acidified with HCl to pH 1. The precipitated product was recrystallized from the liquor to afford *5-fluorobarbituric acid* (1.87 g, 51 %) as a tan powder. m.p.: >300 °C; ([M+H]$^+$, 147.0206, $C_4H_4FN_2O_3$ requires: [M]$^+$, 147.0204); IR (neat,cm^{-1}) 2926, 2828, 1578, 1383, 1241, 1128; δ_F (D_2O + NaOD, 376 MHz): - 191.95 (s); δ_C (D_2O + NaOD, 100

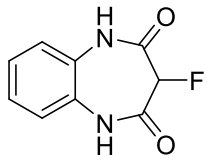
MHz) 131.89 (d, $^{1}J_{CF}$ 214.4, C-F), 157.77 (d, $^{4}J_{CF}$ 6.2, C-NH), 164.59 (d, $^{2}J_{CF}$ 13.4, C=O); m/z (ASAP) 147 (25 %, $[M+H]^{+}$).

2-Amino-5-fluoro-4,6-dihydroxypyrimidine (106)



Guanidine sulfate (5.95 g, 55 mmol) was added to the solution of sodium (2.50 g, 110 mmol) in anhydrous ethanol (100 mL) and the mixture was heated to reflux. Diethyl 2-fluoromalonate (8.90 g, 50 mmol, 93 % pure) was added dropwise over 20 minutes and the mixture was heated at reflux for 6 h. After cooling to room temperature, the solution was evaporated to dryness, the residue was dissolved in water (20 mL), neutralised with HCl to pH 7, the precipitated product was filtered, washed with water (5 mL), ethanol (2x5 mL) and diethyl ether (2x5 mL). After drying *in vacuo, 2-amino-5-fluoro-4,6-dihydroxypyrimidine* (6.21 g, 86 %) was obtained as a pink powder. m.p.: >300 °C ($[M+H]^{+}$, 146.0357, $C_4H_5FN_3O_2$ requires: $[M]^{+}$, 146.0366); IR (neat,cm^{-1}) 3343, 3100, 2916, 2731, 1600, 1557, 1415, 1358, 1204; δ_H (DMSO d_6, 400 MHz) 7.00 (2H, bs, N-H), 11.1 (2H, bs, OH); δ_F (DMSO d_6, 376 MHz): - 197.05 (s); δ_C (DMSO d_6, 100 MHz) 125.13 (d, $^{1}J_{CF}$ 208.6, C-F), 149.26 (d, $^{4}J_{CF}$ 2.3, C-H), 155.12 (d, $^{2}J_{CF}$ 18.0, C-OH); m/z (ASAP) 146 (100 %, $[M+H]^{+}$).

3-Fluoro-1-H-1,5-benzodiazepine-2,4-dione (107)



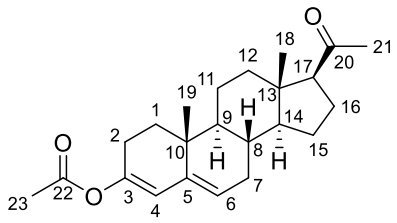
o-Phenylenediamine (2.70 g, 25 mmol) was added to the solution of sodium (1.2 g, 53 mmol) in anhydrous ethanol (50 mL) and the mixture was heated to reflux. Diethyl 2-fluoromalonate (4.45 g, 25 mmol) was added dropwise over 10 minutes and the mixture was heated at reflux for 2 h. After cooling to room temperature, the solution was filtered, the residue was washed with ethanol (20 mL), dissolved in water (30 mL) and acidified with HCl to pH 1. The mixture was cooled in ice, filtered, washed with water (2x10mL) and dried *in vacuo* to afford *3-fluoro-1-H-1,5-benzodiazepine-2,4-dione* (3.23 g, 68 %) as a tan powder. m.p.: >300 °C, ($[M+H]^{+}$, 195.0567, $C_9H_8FN_2O_2$ requires: $[M]^{+}$, 195.0570); IR (neat,cm^{-1}) 3084, 2951, 1727, 1681, 1500, 1159; δ_H (DMSO d_6, 400 MHz): 5.57 (1H, d, $^{2}J_{HF}$ 46.4, CHF), 7.15-7.19 (2H, m, Ar-H), 7.22 (2H, dt, $^{3}J_{HH}$ 6.6, $^{4}J_{HH}$ 3.5, Ar-H), 10.81 (2H, bs N-H); δ_F (DMSO d_6, 376 MHz): - 207.99 (d, $^{2}J_{HF}$ 46.4 C-F); δ_C (DMSO

d$_6$, 100 MHz) 85.12 (d, $^1J_{CF}$ 184.5, C-F), 122.55, 125.52, 128.41, 163.36 (d, $^2J_{CF}$ 23.2, C=O), 164.59 (d, $^2J_{CF}$ 13.4, C=O); m/z (ASAP) 195 (100 %, $[M+H]^+$), 135 (23 %, $[M-COCHF]^+$).

7.3 Experimental to Chapter 3.

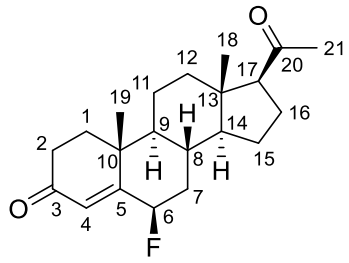
7.3.1 Synthesis of progesterone derivatives

Progesterone enol acetate (121)



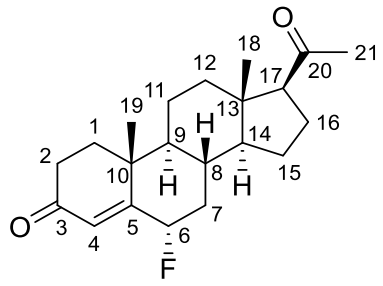
Progesterone (14.65 g, 46.5 mmol) was dissolved in the mixture of acetyl chloride (30 mL, 420 mmol) and acetic anhydride (40 mL, 250 mmol) and was heated to 100 °C for 1 h. After allowing the mixture to cool to room temperature, the mixture was concentrated to one third of the original volume under reduced pressure at 25 °C when a white precipitate formed. The product was filtered and washed with cold acetonitrile (2x10 mL) and dried under vacuum at 35 °C to afford *progesterone enol acetate* (10.74 g, 65 %) as a white solid, mp. 119-123 °C (lit. 130-132 °C, cryst from methanol)[172]; ($[MH]^+$, 357.2452. $C_{23}H_{33}O_3$ requires: $[M]^+$, 357.2430); IR (cm^{-1}): 2939, 1748, 1703, 1365, 1219, 1202, 1188, 1119; ^{1}H NMR ($CDCl_3$, 600 MHz): 0.65 (3H, s, C**18**H$_3$), 1.00 (3H, s, C**19**H$_3$), 1.04-1.10 (1H, m, C**9**-H), 1.18-1.29 (2H, m, C**14**H, C**15**H), 1.30-1.38 (1H, m, C**1**H), 1.43-1.50 (2H, m, C**11**H, C**12**H), 1.58-1.73 (5H, m, C**11**H, C**16**H, C**15**H, C**7**H, C**8**H), 1.85 (1H, dd, $^2J_{HH}$ 12.5, $^3J_{HH}$ 5.5; C**1**H), 2.03-2.06 (1H, m, C**12**H), 2.12 (3H, s, C**23**H$_3$), 2.13 (3H, s, C**21**H$_3$), 2.14-2.22 (3H, m, C**16**H, C**2**H, C**7**H), 2.41-2.47 (1H, m, C**2**H), 2.54 (1H, t, $^3J_{HH}$ 9.0, C**17**H), 5.39 (1H, m, C**4**H), 5.69 (1H, d, $^4J_{HH}$ 1.9, C**6**H); ^{13}C NMR ($CDCl_3$,151 MHz): 13.50 (C**18**), 19.00 (C**19**), 21.24 (C**23**), 21.37 (C**11**), 22.99 (C**16**), 24.55 (C**15**), 24.93 (C**2**), 31.69 (C**2**), 31.87 (C**7**), 31.89 (C**8**), 33.93 (C**1**), 35.04 (C**10**), 38.96 (C**12**), 44.24 (C**13**), 48.02 (C**9**), 57.16 (C**14**), 63.83 (C**17**), 117.08 (C**6**), 123.81 (C**4**), 139.50 (C**5**), 147.18 (C**3**), 169.52 (C**22**), 209.64 (C**20**).; m/z (ASAP): 357 (15 %, $[M+H]^+$), 314 (92 %, $[M+H-CH_3CO]^+$), 297 (56 %, $[M-CH_3COO]^+$).

6β-Fluoroprogesterone (122)



Progesterone enol acetate (1.50 g, 4.2 mmol) was dissolved in the mixture of acetonitrile (20 mL) and acetone (30 mL), Selectfluor (1.56 g, 4.4 mmol) was added and the mixture was stirred at ambient temperature for 2 hours. Water (150 mL) was added, the precipitate was filtered and re-dissolved in ethyl acetate (30 mL). After washing with brine (15 mL) and drying over Na_2SO_4, the solvent was evaporated in vacuum and after column chromatography (silica, hexanes : ethyl acetate, 10:1 to 3:1, Rf.: 0.18 in 3:1 mixture) *6β-fluoroprogesterone* (0.65 g, 46% yield) was isolated as a white solid. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation an acetone solution of 6β-fluoroprogesterone. Mp.: 152-156 °C (lit.: 159-161 ^{o}C, from benzene)[174], ([MH]$^+$, 333.2204. $C_{21}H_{30}FO_2$ requires: [M]$^+$, 333.2230); IR (cm^{-1}): 2932, 1700, 1682, 1386, 1355, 1228, 1193, 1161; ^{1}H NMR ($CDCl_3$, 600 MHz): 0.69 (3H, s, C**18**H_3), 0.99 (1H, td, $^2J_{HH}$ 11.4, $^3J_{HH}$ 3.9, C**9**H), 1.10-1.27 (2H, m, C**7**H, C**14**H), 1.30 (3H, d, $^5J_{FH}$ 1.3, C**19**H_3), 1.30-1.34 (1H, m, C**15**H), 1.44 (1H, td, $^2J_{HH}$ 12.7, $^3J_{HH}$ 3.9 Hz, C**12**H), 1.48-1.54 (1H, m, C**11**H), 1.62-1.77 (4H, m, C**1**H, C**11**H, C**15**H, C**16**H), 1.90-1.94 (1H, m, C**8**H), 2.05-2.11 (2H, m, C**1**H, C**12**H), 2.12 (3H, s, C**21**H_3), 2.17-2.24 (2H, m, C**11**H, C**7**H), 2.43 (1H, dt, $^2J_{HH}$ 16.9, $^3J_{HH}$ 3.3, C**2**H), 2.51-2.58 (2H, m, C**2**H, C**17**H), 4.99 (1H, dt, $^2J_{HF}$ 48.6, $^3J_{HH}$ 2.5, C**6**HF), 5.87 (1H, d, $^4J_{HF}$ 5.0, C**4**H); ^{19}F NMR (376 MHz): -166.0 (td, $^2J_{HF}$ 47.8, $^3J_{HF}$ 12.6); ^{13}C NMR ($CDCl_3$,151 MHz): 13.45 (C**18**), 18.53 (C**19**), 20.98 (C**11**), 22.99 (C**16**), 24.37 (C**15**), 30.09 (C**8**), 31.59 (C**21**), 34.34 (C**2**), 37.04 (C**1**), 37.35 (d, $^2J_{FC}$ 23.5, C**7**), 37.97 (C**10**), 38.65 (C**12**), 44.11 (C**13**), 53.21 (C**9**), 55.99 (C**14**), 63.55 (C**17**), 93.41 (d, $^1J_{FC}$ 166.0, C**6**), 128.57 (C**4**), 161.67 (d, $^2J_{FC}$ 12.6, C**5**), 199.88 (C**3**), 209.19 (C**20**); m/z (ASAP): 333 (100%, [M+H]$^+$), 313 (98%, [M-F]$^+$), .

6α-Fluoroprogesterone (123)



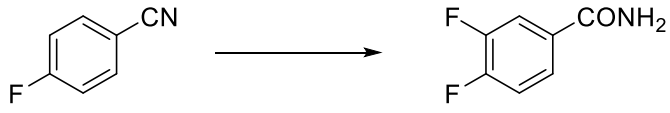
6β-Fluoroprogesterone (0.65 g, 1.9 mmol) was dissolved in glacial acetic acid (25 mL) and dry HCl gas was bubbled into the solution for 1.5 hours (approx. 20 bubbles/min). The solvent was evaporated and the crude product (19:1 α:β) was recrystallized from methanol (5mL) to give 6*α-fluoroprogesterone* (0.48 g, 74% yield) as colourless needles. Mp.: 144-147 °C (lit.: 146-148, from acetone-hexane)[174]; IR (cm^{-1}): 2948, 1700, 1680, 1357, 1269, 1225, 1186, 1059; ^{1}H NMR ($CDCl_3$, 600 MHz): 0.66 (3H, s, C**18**H_3), 0.99 (1H, m, C**9**H), 1.18 (3H, d, C**19**H_3), 1.23-1.33 (3H, m, C**7**H, C**14**H, C**15**H), 1.39-1.46 (2H, m, C**11**H, C**12**H), 1.56-1.62 (1H, m, C**8**H), 1.62-1.67 (1H, m, C**11**H), 1.67-1.76 (2H, m, C**15**H, C**16**H), 1.76-1.82 (1H, m, C**1**H), 2.03-2.10 (2H, m, C**1**H, C**12**H), 2.12 (3H, s, C**21**H_3), 2.16-2.22 (1H, m, C**16**H), 2.26-2.32 (1H, m, C**7**H), 2.35-2.39 (1H, m, C**2**H), 2.44 (1H, td, $^{2}J_{HH}$ 14.5, $^{3}J_{HH}$ 3.4, C**2**H), 2.54 (1H, t, $^{3}J_{HH}$ 8.5, C**17**H), 5.09 (1H, ddd, $^{2}J_{FH}$ 47.9, $^{3}J_{HH}$ 12.3, $^{3}J_{HH}$ 5.6, C**6**HF), 6.09 (1H, s, C**4**H); ^{19}F NMR (376 MHz): - 183.37 (ddd, $^{2}J_{FH}$ 47.9, $^{3}J_{HH}$ 12.3, $^{3}J_{HH}$ 5.6, C**6**HF); ^{13}C NMR ($CDCl_3$,151 MHz): 13.41 (C**18**), 18.20 (C**19**), 21.03 (C**11**), 22.96 (C**16**), 24.47 (C**15**), 31.60 (C**21**), 33.52 (C**8**), 33.83 (C**2**), 36.42 (C**1**), 38.48 (d, $^{2}J_{FC}$ 17.7, C**7**), 38.49 (C**12**), 39.24 (C**10**), 44.00 (C**13**), 53.56 (C**9**), 55.74 (C**14**), 63.41 (C**17**), 88.22 (d, $^{1}J_{FC}$ 183.9, C**6**), 119.88 (d, $^{3}J_{CF}$ 14.8 C**4**), 165.80 (d, $^{2}J_{FC}$ 11.2, C**5**), 198.79 (C**3**), 209.09 (C**20**); m/z (ESI): 333 (100 %, $[M+H]^+$).

Direct fluorination of progesterone enol acetate

Progesterone enol acetate (1.07 g, 3.0 mmol) was dissolved in formic acid (98 %, 30 mL) in a 100 mL glass fluorination reactor and cooled to 0-5 °C in a water bath. The solution was purged with nitrogen for 5 minutes (20 mL/min) then fluorine (10 % *v/v* in nitrogen, 20 mL/min) was introduced for 50 minutes (1.4 equivalents), the initially colourless solution turned yellow. After the fluorination, the vessel was purged with nitrogen, the contents transferred to a round bottomed flask and evaporated to dryness to leave a yellow, viscous oil behind (1.02 g). The product was dissolved in acetonitrile (25 mL) in a volumetric flask, a 1 mL aliquot was diluted twentyfold and analysed by HPLC-UV.

7.3.2 Direct fluorination of aromatic systems

Direct fluorination of 4-fluorobenzonitrile (small scale screening)

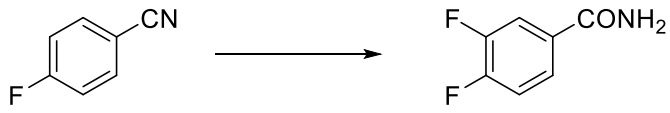


49 **131**

Method A: 4-Fluorobenzonitrile (1.22 g, 10 mmol) was dissolved in sulfuric acid (98 %, 20 mL) in a 100 mL glass fluorination reactor and cooled in a 0 °C water bath. The solution was stirred vigorously and purged with nitrogen for 5 minutes before the fluorine flow (40 mL/min, 10 mmol/h) was initiated. Fluorine was introduced for the desired time (between 1.5 and 4.5 hours) then the mixture was purged with nitrogen and poured in ice (100 g). The precipitated product was filtered, washed with water (10 mL) and dried under vacuum. The dry product was analysed by ^{1}H and ^{19}F NMR spectroscopy. ^{19}F NMR (DMSO *d6*, 376 MHz): - 103.18 (tt, $^{3}J_{HF}$ 8.9, $^{4}J_{HF}$ 5.3 Hz) for 4-fluorobenzamide and - 128.81 (dddd, $^{3}J_{FF}$ 22.6, $^{3}J_{HF}$ 10.5, $^{4}J_{HF}$ 7.6 $^{5}J_{HF}$ 4.3 Hz), - 135.51 (dddd, $^{3}J_{FF}$ 22.6, $^{3}J_{HF}$ 10.6, $^{4}J_{HF}$ 8.0, $^{5}J_{HF}$ 1.4 Hz) for **131**.

Method B: 4-Fluorobenzonitrile (1.22 g, 10 mmol) was dissolved in formic acid (98 %, 20 mL) in a 100 mL glass fluorination reactor and cooled in a 0 °C water bath. The solution was stirred vigorously and purged with nitrogen for 5 minutes before the fluorine flow (40 mL/min, 10 mmol/h) was initiated. Fluorine was introduced for the desired time (between 1.5 and 4.5 hours) then the mixture was purged with nitrogen and poured into water (100 mL) and extracted with ethyl acetate (2x30 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL) and dried over Na_2SO_4. After evaporation of the solvent in vacuum, the product was obtained as a dark oil and was analysed by ^{1}H and ^{19}F NMR spectroscopy.

Direct fluorination of 4-fluorobenzonitrile (larger scale)

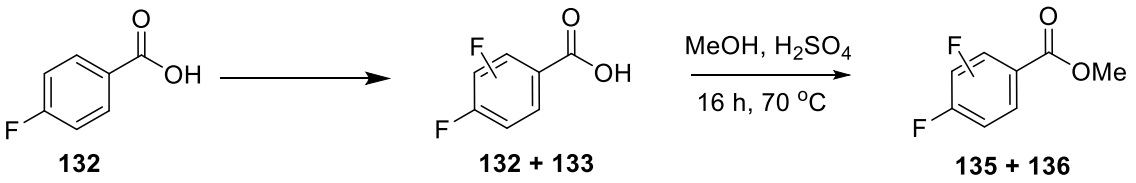


49 **131**

4-Fluorobenzonitrile (4.85 g, 40 mmol) was dissolved in concentrated sulfuric acid (50 mL, 98 %) in a 250 mL fluorination reactor equipped with a mechanical overhead stirrer. The mixture was placed in a room temperature (20 °C) water bath, purged with nitrogen for 5-10 minutes then fluorine (20 %*v/v* in nitrogen) was introduced for 3 hours (80 mL/min, 40 mmol/h, 120 mmol). The reactor was purged free of fluorine with nitrogen (10-15 minutes) and the mixture was poured into ice (350 g). A small amount of precipitate was formed, filtered then concentrated

ammonia solution (28 %, 100 mL) was added in small portions to precipitate the product. After filtration, the solid was washed with water (50 mL) and dried in vacuum to afford a brown powder (3.9 g). The solid was analysed by ^{1}H and ^{19}F NMR spectroscopy then 1 g samples were recrystallized from ethanol (1 mL), aqueous ethanol (5 mL of 1:1 mixture) and methylcyclohexane (5 mL). The crystallised solids were filtered, dried and analysed by ^{1}H and ^{19}F NMR spectroscopy.

Direct fluorination of 4-fluorobenzoic acid

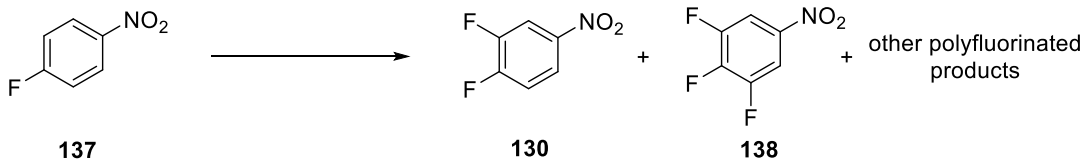


4-Fluorobenzoic acid (14.0 g, 100 mmol) was dissolved in concentrated sulfuric acid (60 mL, 98 %) in a 250 mL fluorination reactor equipped with a mechanical overhead stirrer. The mixture was placed in a cooled (0-5 °C) water bath, purged with nitrogen for 5-10 minutes then fluorine (20 %*v/v* in nitrogen) was introduced for 5 hours (80 mL/min, 40 mmol/h, 0.2 mol). The reactor was purged free of fluorine with nitrogen (10-15 minutes) and the mixture was poured on ice (500 g). The precipitate was filtered, the solid dissolved in ethyl acetate (200 mL), the residual water was separated and the organic phase was dried on Na_2SO_4. The solvent was evaporated under vacuum to leave the crude product (13.8 g) as a tan solid which was analysed by NMR spectroscopy. ^{19}F NMR ($CDCl_3$, 378 MHz): - 103.90 – (- 103.98) (1F, m, 4-fluorobenzoic acid); - 128.37 – (- 128.50) (0.6 F, m, 3,4-difluorobenzoic acid), - 135.94 – (- 136.09) (0.6 F, m, 3,4-difluorobenzoic acid). The solid was suspended in methanol (80 mL), concentrated sulfuric acid was added (2 mL) and the mixture was heated to reflux for 16 hours. After cooling to room temperature, the solvent was removed in vacuum, the residue was dissolved in ethyl acetate (100 mL), washed with saturated $NaHCO_3$ solution (2x30 mL) and water (30 mL) then dried on Na_2SO_4 and evaporation of the solvent gave a crude product (11.6 g) as a brown oil and 11.46 g was transferred to the Fisher Spaltrohr® distillation equipment. After evacuating the equipment to 19 mbar pressure, the reflux valve was closed and the mixture was refluxed in the column for an hour to equilibrate the mixture. The collection of the distillate was started at approximately 10 drops/minute speed with a reflux ratio of 1:5 to 1:10. After collecting eight, approximately 1 mL samples the distillation was terminated and all fractions were analysed by NMR spectroscopy to determine the composition of the fractions. ^{19}F NMR ($CDCl_3$, 378 MHz): - 105.87 (1F, t, $^{3}J_{HF}$ 7.4 Hz, methyl 4-fluorobenzoate), - 130.38 (0.6 H, dd, $^{3}J_{FF}$ 21.0, $^{3}J_{HF}$ 10.5 Hz, methyl 3,4-difluorobenzoate), - 136.62 (dt, $^{3}J_{FF}$ 21.0, $^{3}J_{HF}$ 8.9 Hz, methyl 3,4-difluorobenzoate).

Table 35: Distillation fractions of crude methyl 3,4-difluorobenzoate.

Fraction	Methyl 4-fluorobenzoate %	Methyl 3,4-difluorobenzoate %	Others %	Fraction mass / g
Starting mixture	59	37	4	11.46
Fr. 1	66	33	1	0.95
Fr. 2	66	33	1	1.08
Fr. 3	66	33	1	1.1
Fr. 4	65	33	2	1.03
Fr. 5	65	33	2	1.02
Fr. 6	66	33	1	1.38
Fr. 7	65	34	1	1.16
Fr. 8	64	34	2	1.69
Residue	52	36	12	1.27

Direct fluorination of 4-fluoronitrobenzene (high conversion)



4-Fluoronitrobenzene (5.71 g, 40 mmol) was dissolved in sulfuric acid (50 mL) in a 250 mL batch fluorination reactor, placed in a room temperature water bath and purged with nitrogen for 5 minutes. Fluorine (20 % v/v in nitrogen, 80 mL/min, 40 mmol/h) was introduced to the vigorously stirred mixture (650 rpm) for 4.5 hours then the reactor was purged free from fluorine with nitrogen (15 minutes) and poured in ice water (200 mL).

Workup A: The product was extracted into ethyl acetate (2x50 mL), washed with saturated $NaHCO_3$ solution (50 mL), water (50 mL) and brine (50 mL) then dried over Na_2SO_4. Evaporation of the solvent under vacuum afforded a brown oil (5.42 g, 5.50 g and 5.46 g from three identical batches).

Workup B: The aqueous mixture was further diluted with water and was set up for distillation. Water was distilled out from the mixture until only one phase was observed in the distillate (approximately 150 mL) then extracted with ethyl acetate (40 mL), dried on Na_2SO_4 and evaporated under reduced pressure to afford a clear yellow oil (4.10 g).

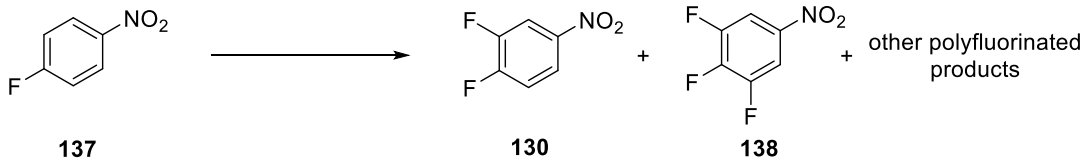
Four separate batches were analysed by ^{19}F NMR and GC-MS then combined and distilled under reduced pressure (65-70 ^{o}C at 1 mbar), 7 fractions were collected. Products were identified by

their ^{19}F NMR shifts: 4-fluoronitrobenzene (- 102.03 ppm)[209], 3,4-difluoronitrobenzene (- 126.6 ppm, - 133.0 ppm)[90], 3,4,5-trifluoronitrobenzene (- 130.66 ppm (2F), - 150.24 ppm (1F))[210].

Table 36: Fraction from the distillation of crude 3,4-difluoronitrobenzene.

Fraction	Mass / g	4-Fluoro-nitrobenzene %	3,4-Difluoro-nitrobenzene %	3,4,5-Trifluoro-nitrobenzene %	Others %
1	1.87	5	80	7	8
2	1.82	7	78	3	12
3	1.76	8	77	2	13
4	1.88	9	76	2	13
5	1.68	10	75	1	14
6	1.54	13	72	0	15
7	0.76	17	65	0	18

Direct fluorination of 4-fluoronitrobenzene (low conversion)

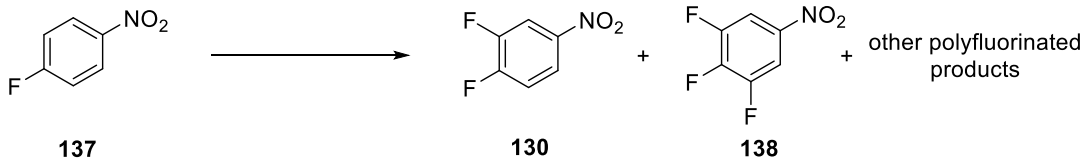


4-Fluoronitrobenzene (14.1 g, 100 mmol) was dissolved in sulfuric acid (70 mL) in a 250 mL batch fluorination reactor, placed in 0 °C water bath and purged with nitrogen for 5 minutes. Fluorine (20 % v/v in nitrogen, 80 mL/min, 40 mmol/h) was introduced to the vigorously stirred mixture (650 rpm) for 5 hours (200 mmol F_2) then the reactor was purged free from fluorine with nitrogen (15 minutes) and poured in ice water (300 mL). Two separate batches were combined, extracted with ethyl acetate (3x100 mL), washed with saturated $NaHCO_3$ solution (100 mL), water (100 mL) and brine (100 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure, the product filtered through a pad of Celite to remove insoluble tarry material to give a dark oil (17.7 g). The product was distilled using the Fischer Spaltrohr® column (20 mbar, 88-90 °C) to afford 7 fractions (12.59 g in total) that were analysed using ^{19}F NMR spectroscopy.

Table 37: Composition of distillate fractions as determined by ^{19}F NMR spectroscopy.

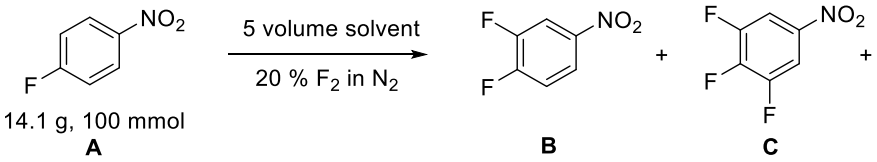
Fraction	Mass / g	4-Fluoro-nitrobenzene %	3,4-Difluoro-nitrobenzene %	3,4,5-Trifluoro-nitrobenzene %	Others %
1	1.75	17	78	5	trace
2	2.11	38	60	1	1
3	1.75	46	52	trace	2
4	2.09	52	47	trace	1
5	1.58	56	42	trace	2
6	1.7	61	37	trace	2
7	1.61	66	32	trace	2

Direct fluorination of 4-fluoronitrobenzene – solvent screen



4 –Fluoronitrobenzene (14.1 g, 100 mmol) was dissolved in the appropriate solvent or solvent mixture (70 mL), cooled to 0-5 ^{o}C and purged with nitrogen or 5 minutes. Fluorine (20 % v/v, 80 mL/min) was introduced into the mixture for 5 hours (2 equivalents), then the mixture was purged with nitrogen to remove traces of fluorine. The mixture was poured into water (250 mL) and extracted with ethyl acetate (3x50 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (2x30 mL) and brine (30 mL) then dried over Na_2SO_4. After evaporation of the solvent in vacuum, the crude product was treated to remove tar and analysed by ^{19}F NMR spectroscopy to determine composition.

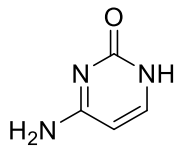
Table 38: Composition of isolated product in the solvent screening experiments.



Solvent	Temperature	Isolation	Tar removal	Product weight	Composition
H_2SO_4	0 °C	Extraction	Vac. dist.	11.60 g	56 % **B**, 40 % **A**, 4% others
H_2SO_4	0 °C	Extraction	Vac. dist.	11.56 g	58 % **B**, 37 % **A**, 5 % others
H_2SO_4/MeCN 1/6	-10 °C	extraction	Kugelrohr	4.57 g	79% **B**, 13 % **A**, 8 % others
H_2SO_4/MeCN 1/6	-10 °C	Evaporation	Steam dist.	7.00 g	14 % **A**, 70 % **B**, 4 % **C**, 9 % other monofluoro(!), 3 % other
MeCN	-10 °C	evaporation	Vac. Dist.	3.07 g	63 % **A**, 34 % **B**, 3% others*
MeCN	-10 °C	evaporation	Steam dist.	10.90 g	60 % **A**, 36 % **B**, 3% others
Propionic acid	-10 °C	evaporation	Steam dist. (in)	8.02 g	95 % **A**, 5 % **B**
H_2SO_4/MeOH 1/9	-10 °C	evaporation	Steam Dist. (in)	10.26 g	96 % **A**, 4 % **B**

7.4 Experimental to Chapter 4.

7.4.1 Synthesis of cytosine (141)



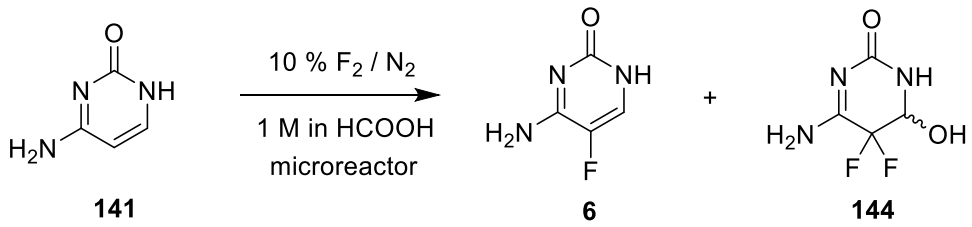
Urea (15.6 g, 0.26 mol) and sodium ethoxide (16.3 g, 0.24 mol) were suspended in m-xylene (60.0 g) in a 250 mL three necked flask equipped with overhead stirrer and the mixture was heated in a 130 °C oil bath (reflux of xylene-ethanol azeotrope). Cyanoacetaldehyde diethyl acetal (28.6 g, 0.20 mol) was added over 1 hour via a syringe pump and the mixture was refluxed (difficult to stir, yellow slurry). After 1.5 hours, the condenser was replaced by a distillation head and ethanol was distilled until the head temperature reached 90 °C. By this point 27.2 g distillate was collected. After the mixture was allowed to cool below 80 °C, water (50 mL) was added to dissolve all solids. The phases were separated and the aqueous phase was cooled in ice while acetic acid (13.7 mL, 14.4 g, 0.24 mol) was added in small portions (yellow precipitate forms). After filtration, the solid was washed with water (2x10 mL) and dried in vacuum at 40 °C to leave *cytosine* (19.8 g, 89 %) as a yellow solid. ^{1}H NMR (400 MHz, D_2O + DCl): 6.02 (1H, d, $^{3}J_{HH}$ 7.5 Hz, C**5**-H);. 7.60 (1H, d, $^{3}J_{HH}$ 7.5 Hz, C**6**-H); ^{13}C NMR (101 MHz, D_2O + DCl): 93.9 (C**5**-H), 146.17 (C**5**-H), 149.29 (C**2**=O), 160.15 (C**4**-NH_2); in agreement with the literature values[211].

7.4.2 Batch fluorination – typical procedure

Cytosine (1.11 g, 10 mmol) was dissolved in formic acid (25 mL) and was kept at 20 °C in a water bath. Fluorine (10 % in N_2) was introduced to the vigorously stirred solution at 25 mL/min (7.5 mmol / h) for 160 minutes (2 equivalents of fluorine). The mixture was purged with nitrogen to remove traces of fluorine, the solvent was removed *in vacuo* and the residue was recrystallized from water (10 mL) to yield *5-fluorocytosine* (0.49 g, 38 % yield) as a tan crystalline solid. M.p.: 295 - 300 °C (decomposes), ($[M]^+$ 129.0337, $[M]^+$ requires: 129.0338); IR (cm^{-1}): 3384, 3092, 2724, 1665, 1624, 1551, 1454, 1216; ^{1}H NMR (400 MHz, D_2O+DCl) 7.83 (1H, d, $^{3}J_{HF}$ 4.8 Hz); ^{19}F NMR (400 MHz, D_2O+DCl) -169.7 (1F, d, $^{3}J_{HF}$ 4.8 Hz); ^{13}C NMR (100 MHz, D_2O+DCl): 130.67 (d, $^{2}J_{CF}$ 29.6 Hz), 135.25 (d, $^{1}J_{CF}$ 232 Hz), 147.88, 153.65 (d, $^{2}J_{CF}$ 23.4 Hz); MS (ASAP): 111 (37 %, $[M+H-F]^+$), 129 (8 %, $[M]^+$), 130 (100 %, $[M+H]^+$); all analytical data identical with that of a commercial sample.

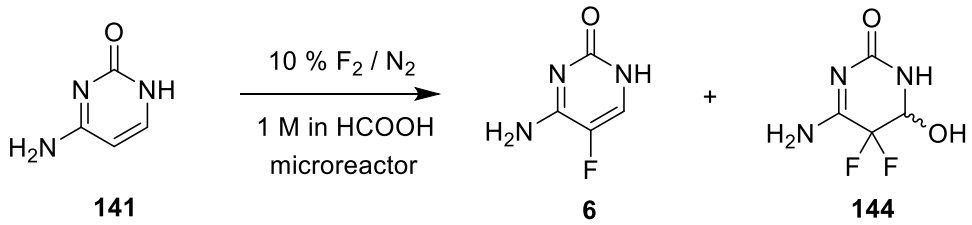
7.4.3 Small scale continuous fluorination

Continuous flow fluorination: ideal conditions for microreactor



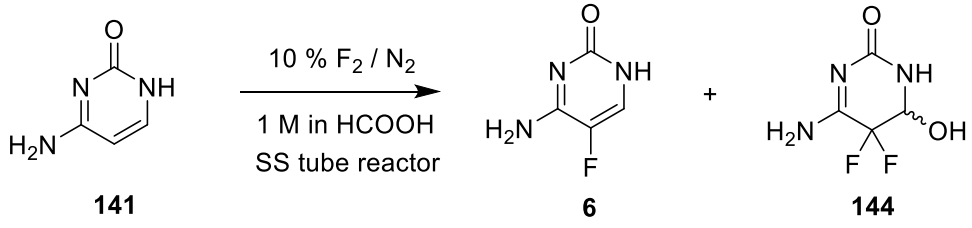
A 1 M stock solution of cytosine in formic acid was prepared and used for fluorinations. The solution was introduced to the microreactor at 2 mL/h (2 mmol/h) while the flow of fluorine was set according to Table 16. Fractions were collected for 120 minutes, the solvent was evaporated and the product was recrystallized from water (5 mL). The product was filtered, dried *in vacuo* and analysed using ^{1}H and ^{19}F NMR spectroscopy.

Synthesis of Flucytosine in the microreactor



1 M cytosine solution was introduced at 2 mL/h while fluorine (10 % in N_2) was introduced at 15 mL/min (3.75 mmol/h). The reaction was conducted for 12 minutes, the collected fraction was evaporated and recrystallised from water (4 mL). The crystallised product was filtered and dried to afford tan crystals of *5-fluorocytosine* (0.27 g, 52 % yield, 99 % purity).

Synthesis of Flucytosine in the stainless steel tube reactor



1.0 M cytosine solution in formic acid was introduced at 4.0 mL/h (4.0 mmol/h) while fluorine (10 % in N_2) was introduced at 20 mL/min (5 mmol/h). The reaction was conducted for 90 minutes, the collected fraction was evaporated and the residue was recrystallized from water (7 mL). After filtration, the product was dried under reduced pressure to afford *5-fluorocytosine* (0.49 g, 63 % yield, 99%+ pure) as a tan powder.

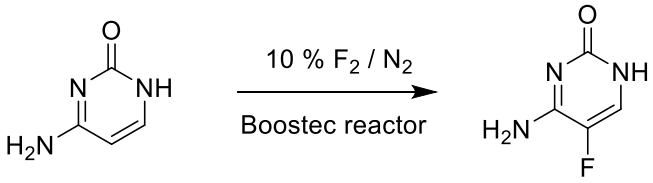
7.4.4 Scale-up of the continuous flow fluorination of cytosine

Fluorination in Boostec SiC reactor: typical procedure

Cytosine solution in formic acid (10 wt%, 600 g/h) and fluorine (10 vol. % in nitrogen, 204 g/h) were passed through the SiC reactor at 10 °C and after reaching steady state (15 minutes) the product liquid phase was collected for 60 minutes to yield a yellow solution (620 g). To this solution *n*-butanol (1000 g, 1.23 L) was added in five portions (no exotherm observed) and the mixture was stirred at room temperature overnight. After filtration, the solid was washed once with *n*-butanol (60 mL) and dried in air to leave Flucytosine (58.0 g, 99.8 % by HPLC, 83 % yield).

Results of direct fluorinations in the Boostec® reactor

After adjusting reaction conditions, the reaction was allowed to stabilise for ten minutes then sampled for HPLC analysis to determine conversion and selectivity.



T / °C	Cytosine concentration (% w/w)	Flow rate / g/h		F_2 molar ratio	Conversion (% A/A)	Selectivity (% A/A)	Inlet pressure
		Cytosine solution	10 % F_2/N_2				
10	8.9	600	181	1.3	99.4	92.0	2.1 bar
20	8.9	600	181	1.3	99.0	92.2	1.9 bar
30	8.9	600	181	1.3	89.9	91.7	1.7 bar
10	11.0	600	194	1.1	97.6	92.6	2.3 bar
20	11.0	600	194	1.1	82.1	92.7	2.2 bar
30	11.0	600	194	1.1	69.0	93.2	2.0 bar
10	8.9	600	181	1.3	99.6	92.2	2.2 bar
20	8.9	600	181	1.3	98.0	92.4	2.3 bar with 0.3 bar back pressure
30	8.9	600	181	1.3	61.9	95.0	2.4 bar with 0.9 bar back pressure
30	8.9	600	153	1.1	68.1	94.6	1.5 bar
30	8.9	600	153	1.1	61.9	95.0	2.4 bar with 0.9 bar back pressure
30	8.9	600	153	1.1	20.5	94.6	4.5 bar with 3.0 bar back pressure
30	8.9	600	153	1.1	18.6		4.8 bar with 3.3 bar back pressure
10	12.0	600	206	1.1	88.2	93.5	2.5 bar
10	12.0	600	206	1.1	83.2	93.1	3.0 bar with 0.5 bar back pressure
10	12.0	600	206	1.1	80.1	93.3	3.7 bar with 1.2 bar back pressure
10	12.0	600	206	1.1	61.1	93.2	4.3 bar with 1.8 bar back pressure

T / °C	Cytosine concentration (% w/w)	Flow rate / g/h		F_2 molar ratio	Conversion (% A/A)	Selectivity (% A/A)	Inlet pressure / bar
		Cytosine solution	10 % F_2/N_2				
10	8.9	600	153	1.1	87.5	94.2	1.8 bar
10	8.9	600	153	1.1	83.0	94.0	2.7 bar with 0.9 bar back pressure
10	8.9	600	153	1.1	78.3	93.9	4.0 bar with 2.2 bar back pressure
10	6.0	600	103	1.1	98.7	94.7	1.3 bar
10	6.0	600	103	1.1	90.9	94.5	2.5 bar with 1.2 bar back pressure
10	6.0	600	103	1.1	89.6	94.6	3.0 bar with 1.8 bar back pressure
10	8.9	600	181	1.3	99.6	92.2	2.2 bar
20	8.9	600	181	1.3	98.0	92.4	2.3 bar with 0.3 bar back pressure
30	8.9	600	181	1.3	61.9	95.0	2.4 bar with 0.9 bar back pressure
10	8.9	600	181	1.3	99.5	92.1	2.1 bar inlet pressure
10	8.9	900	272	1.3	99.1	91.6	3.3 bar inlet pressure
10	8.9	1000	303	1.3	99.7	92.1	3.6 bar inlet pressure
10	8.9	1200	363	1.3	99.7	92.3	4.5 bar inlet pressure
10	8.9	600	157	1.1	90.6	93.0	1.8 bar inlet pressure
10	8.9	800	209	1.1	94.7	93.2	2.6 bar inlet pressure
10	8.9	1000	263	1.1	91.6	93.4	3.3 bar inlet pressure
10	8.9	1200	313	1.1	92.3	93.2	4.0 bar inlet pressure
10	8.9	600	181	1.3	99.5	92.1	2.1 bar inlet pressure
10	8.9	1400	367	1.1	91.5	92.7	4.8 bar inlet pressure

T / °C	Cytosine concentration (% w/w)	Flow rate / g/h		F_2 molar ratio	Conversion (% A/A)	Selectivity (% A/A)	Inlet pressure
		Cytosine solution	10 % F_2/N_2				
10	6.0	600	122	1.3	98.0	92.6	1.4 bar
10	7.0	600	143	1.3	99.0	93.2	1.5 bar
10	8.0	600	163	1.3	99.8	92.5	1.9 bar
10	9.0	600	184	1.3	99.4	92.6	2.0 bar
10	10.0	600	204	1.3	99.7	92.3	2.3 bar
10	11.0	600	224	1.3	99.6	91.4	2.6 bar
10	8.9.	600	133	1.0	58.6	94.0	1.8 bar
10	8.9	600	157	1.1	88.5	93.3	1.9 bar
10	8.9	600	181	1.3	99.7	92.8	2.1 bar
10	8.9	600	206	1.5	99.8	91.4	2.3 bar
10	11.0	600	179	1.0	86.2	93.0	2.1 bar
10	11.0	600	194	1.1	97.0	92.6	2.3 bar
10	11.0	600	209	1.2	99.7	92.1	2.4 bar
10	11.0	600	224	1.3	99.6	91.4	2.6 bar

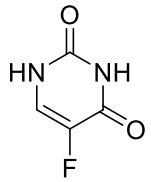
Precipitation optimisation

To a sample (500 μL) of a crude reaction mixture, from the fluorination of an 8.9 % cytosine solution in formic acid with 1.5 equivalents of fluorine, a known volume of the anti-solvent was added in a 2 mL Eppendorf vial, the sample shaken then allowed to stand overnight at 4 °C. The samples then were centrifuged for 5 minutes at 10000 rpm and a 250 μL sample of the supernatant was diluted hundredfold and analysed by HPLC.

Precipitation solvent	Solvent volume/mL	Total volume/mL	Liq. FC concentration (g/L)	FC mass in solution / mg	Solid purity / %
30 % NaOH	0.250	0.750	39.9	29.9	-
30 % NaOH	0.375	0.875	19.5	17.1	-
30 % NaOH	0.500	1.000	9.6	9.6	-
30 % NaOH	0.625	1.125	5.8	6.5	-
30 % NaOH	0.750	1.250	4.4	**5.5**	-
30 % NaOH	0.875	1.375	6.1	8.4	99.0
Acetone	0.500	1.000	51.1	51.1	-
Acetone	0.750	1.250	39.0	48.8	-
Acetone	1.000	1.500	33.4	50.1	-
Acetone	1.250	1.750	30.0	52.5	99.5
Acetone	1.500	2.000	20.8	41.6	99.4
n-Butanol	0.250	0.750	63.9	47.9	-
n-Butanol	0.500	1.000	24.3	24.3	-
n-Butanol	0.750	1.250	10.3	12.9	-
n-Butanol	1.000	1.500	6.6	9.9	-
n-Butanol	1.250	1.750	2.3	**4.0**	99.6
n-Butanol	1.500	2.000	2.0	**4.0**	99.4
i-Propanol	0.500	1.000	27.5	27.5	-
i-Propanol	0.750	1.250	13.3	16.6	-
i-Propanol	1.000	1.500	11.6	17.4	-
i-Propanol	1.250	1.750	5.2	9.1	99.5
i-Propanol	1.500	2.000	2.2	**4.4**	99.5
Water	0.750	1.250	54.5	68.1	-
Water	1.500	2.000	38.6	77.2	-

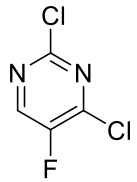
7.4.4 Literature syntheses for metrics calculations

Literature synthesis of 5-Fluorouracil (5)[189]



Experimental procedure (US 3954758): "To a Teflon lined reactor equipped with gas bubblers, demineralised water (3.78 L) and uracil (454 g) were added. While bubbling nitrogen through the system (260 mL/min), the slurry was heated by an internal Teflon coil to 50-60 °C. Fluorine flow was started at 0.354 g/min from each of four bubblers. As the temperature started to rise, water at 0 °C was passed through the internal coil. The temperature was maintained between 60-70 °C throughout the reaction. The addition of fluorine was stopped after 221 g (5.81 mol) were added. The resultant clear solution was removed from the reactor, filtered then cooled to about 0 °C for 18 hours. The white crystalline product was removed by filtration, washed with ice water and dried yielding 192 g of uracil fluorohydrin monohydrate ($C_4H_7FN_2O_4$). The uracil fluorohydrin monohydrate was divided in two parts, placed in a pyrex vessel and conc. HCl (100 mL) was added to each. The slurry was heated between 90-100 °C for about 15 minutes. After cooling to 0 °C, the white solid was removed by filtration and washed with cold water (*assume 50 mL*). Several runs were combined (*assumed 3 identical batches*), 425 g, slurried in demineralised water (*assume 500 mL*), filtered then dissolved in demineralised water (3.79 L) at 95-100 °C. The solution was passed through a column of 20 g of activated carbon. The product was crystallised at 0 °C, removed by filtration and dried at 100 °C yielding 335 g pure (99 %+) 5-fluorouracil."

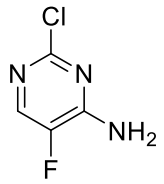
Literature synthesis of 2,4-dichloro-5-fluoropyrimidine (142)[178]



Experimental procedure (US3040026): "A mixture of 5-fluorouracil (104 g, 0.8 mol) and N,N-dimethylaniline (166 g, 1.37 mol) in $POCl_3$ (1472 g, 9.6 mol) was heated to reflux for two hours. After cooling to room temperature, $POCl_3$ was removed under reduced pressure (18-22 mmHg, 22-37 °C). The residue was then poured into a vigorously stirred mixture of diethyl ether (500 mL) and ice (500 g). After separating the ether layer, the aqueous layer was extracted with ether (500 mL then 200 mL). The combined fractions were dried over sodium sulfate, filtered and the

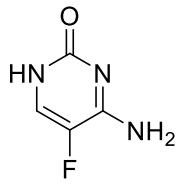
ether removed by vacuum distillation (10-22 ^{0}C). The residue, a yellow solid melting at 37-38 ^{o}C, weighed 120 g, corresponding to 90% yield. Vacuum distillation of 115 g of this material (74-80 ^{0}C, 16 mmHg) gave a white solid (108 g, 84.5 %) melting at 38-39 ^{o}C."

Literature synthesis of 4-amino-2-chloro-5-fluoropyrimidine (143)[178]



Experimental procedure (US3040026): "To a solution of 2,4-dichloro-5-fluoropyrimidine (10.0 g, 0.06 mol) in ethanol (100 mL), concentrated ammonia solution (25 mL) was slowly added. A slightly opalescent solution resulted. The temperature gradually rose to 35 ^{o}C, the solution was then cooled in ice to 18 ^{o}C and thereafter remained below 30 ^{o}C. After three hours, a Volhard titration showed that 0.0545 mol of chlorine was present in ionic form. Storage in a refrigerator overnight resulted in some crystallisation of ammonium chloride. A white sludge, resulting from the evaporation of the reaction mixture at 40 ^{o}C, was slurried with water (75 mL), filtered and washed free of chloride (*assume another 50 mL water*). After drying in vacuo, the product melted at 196.5-197.5 ^{o}C, yield 6.44 g. Evaporation of the mother liquors yielded a second crop of 0.38 g, raising the total yield to 6.82 g (79.3 %)."

Literature synthesis of 5-fluorocytosine (6)[178]



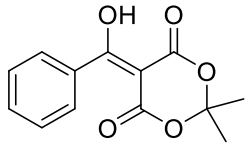
Experimental procedure (US3040026): "A slurry of 2-chloro-4-amino-5-fluoropyrimidine (34.0 g, 0.231 mol) in concentrated hydrochloric acid (231 mL) was heated in a water bath at 93-95 ^{o}C for 125 minutes. The reaction was followed by means of ultraviolet spectrophotometry using the absorption at 245, 285 and 300 μm as a guide. The absorption at 300 μm rose to a maximum after 120 minutes and then dropped slightly. The clear solution was cooled to 25 ^{o}C in an ice bath then evaporated to dryness under vacuum at 40 ^{o}C. After slurrying with water three times (*assume 3x20* mL) and re-evaporating, the residue was dissolved in water (100 mL). To this solution, concentrated ammonia (29 mL) was added dropwise, the resulting precipitate was filtered, washed free of chloride with water (*assume 50 mL*), then with alcohol (*assume ethanol, 25 mL*) and ether (*assume diethyl ether, 25 mL*). After drying in vacuo at 65 ^{o}C, the product

weighed 22.3 g. An additional 6.35 g was obtained by evaporation of the mother liquor, thus yielding a total of 28.65 g (96 %)."

7.5 Experimental to Chapter 5.

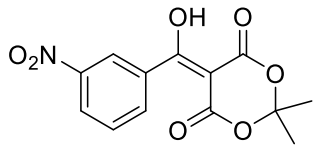
7.5.1 Synthesis of acyl Meldrum's acid derivatives

5-Benzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione (157) - general procedure



Meldrum's acid (14.4 g, 100 mmol) and DMAP (24.4 g, 200 mmol) were dissolved in acetonitrile (250 mL) and cooled in ice-water. Benzoyl chloride (14.1 g, 11.5 mL, 100 mmol) was dissolved in acetonitrile (50 mL) and added dropwise over 40 minutes. The mixture was stirred overnight then 1M HCl (200 mL) was added, the mixture stirred for 5 minutes (clear solution) and was concentrated to approximately 150 mL under vacuum. The precipitated product was filtered, washed with water (15 mL) and dried in vacuum to yield *5-benzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione* (22.5 g, 90 % yield) as a yellow solid. Mp. 95-97 °C (with decomposition) (lit. 103-104 ^{o}C, from acetone)[212], ([M-H]$^{-}$, 247.0605. $C_{13}H_{11}O_5$ requires: [M]$^{+}$, 247.0606); IR (cm^{-1}): 2998, 1736, 1652, 1549, 1379, 1201, 1136; ^{1}H NMR (400 MHz, $CDCl_3$): 1.84 (6H, s, CH3), 7.47 (2H, t, $^{3}J_{HH}$ 7.9, C**3**-H), 7.60 (1H, tm, $^{3}J_{HH}$ 7.5, C**4**-H), 7.66-7.69 (2H, m, C**2**-H), 15.47 (1H, bs, OH); ^{13}C NMR (100 MHz, $CDCl_3$): 26.91 (**C**H_3), 91.06 (**C**$(CH_3)_2$), 106.11 (**C**=COH), 128.17 (C**3**-H), 129.58 (C**2**-H), 132.82 (C**1**-C), 133.44 (C**4**-H), 159.90 (C=**C**OH), 171.09 (**C**=O), 189.37 (**C**=O). m/z (ESI): 247 [M-H]$^{-}$, 207 (100 %, [M-C_3H_5]$^{-}$).

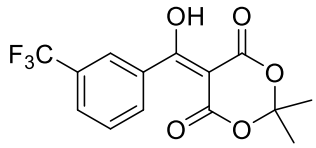
5-(3-Nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (158)



3-Nitrobenzoyl chloride (9.27 g, 50 mmol) was reacted according to the general procedure to afford *5-(3-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (12.46 g, 85 % yield) as a yellow solid. Mp.: 87-89 ^{o}C; ([M-H]$^{-}$, 292.0443. $C_{13}H_{10}NO_7$ requires: [M]$^{+}$, 292.0457); IR (cm^{-1}): 3083, 2951, 1742, 1671, 1526, 1346, 1199; ^{1}H NMR (600 MHz, $CDCl_3$): 1.86 (6H, s, CH_3), 7.67 (1H, t, $^{3}J_{HH}$ 8.0, C**5**-H), 7.96 (1H, dm, $^{3}J_{HH}$ 8.0, C**6**-H), 8.43 (1H, dm, $^{3}J_{HH}$ 8.0, C**4**-H), 8.49 (1H, m, C**2**-H); ^{13}C NMR (151 MHz, $CDCl_3$): 27.12 (**C**H_3), 92.05 (**C**$(CH_3)_2$), 105.82 (**C**=COH), 124.56 (C**2**-H), 127.35 (C**4**-

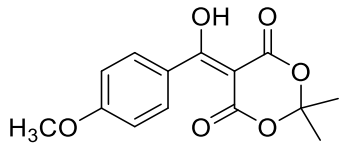
H), 129.35 (C**5**-H), 134.42 (C**6**-H), 135.10 (C**1**-C), 147.88 (C**3**-NO_2), 159.46 (C=**C**OH), 170.91 (**C**=O), 186.51 (**C**=O). m/z (ESI): 292 (100 %, $[M-H]^-$).

5-(3-Trifluoromethylbenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (159)



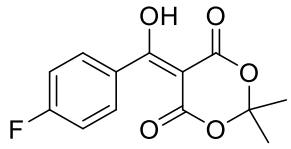
3-Trifluoromethylbenzoyl chloride (6.25 g, 4.52 mL, 30 mmol) was reacted according to the general procedure to afford *5-(3-trifluoromethyl-benzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (8.18 g, 86 % yield) as a yellow solid. Mp. 102-104°C, ($[M-H]^-$, 315.0480 $C_{14}H_{10}F_3O_5$ requires: $[M-H]^-$, 315.0487); IR (cm^{-1}) 3000, 1734, 1560, 1136, 1075; ^{1}H NMR (400 MHz, $CDCl_3$): 1.85 (6H, s, CH_3), 7.60 (1H, t, $^3J_{HH}$ 7.9 Hz, C**5**-H), 7.82-7.84 (1H, m, Ar), 7.84-7.85 (1H, m, Ar-H), 7.91 (1H, s, C**2**-H), 15.62 (1H, bs, OH); ^{19}F NMR (376 MHz, $CDCl_3$): - 62.81 (s, 3F, CF_3); ^{13}C NMR (101 MHz, $CDCl_3$): 26.92 (**C**H_3), 91.56 (**C**$(CH_3)_2$), 106.43 (**C**H=COH), 123.48 (q, $^1J_{CF}$ 273 Hz, **C**F_3), 126.22 (q, $^3J_{CF}$ 3.9 Hz, C**4**-H), 128.60 (C**5**-H), 129.56 (q, $^3J_{CF}$ 3.6 Hz, C**2**-H), 130.79 (q, $^2J_{CF}$ 33.1 Hz, C**3**-CF_3), 132.74 (C**6**-H), 133.51 (**C**1-C), 159.47 (C=**C**OH), 170.91 (**C**=O), 187.54 (**C**=O); m/z (ESI): 315 (100 %, $[M-H]^-$).

5-(4-Methoxybenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (160)



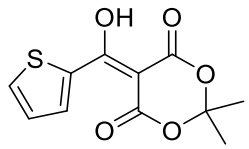
4-Methoxybenzoyl chloride (5.12 g, 30 mmol) was reacted according to the general procedure to afford *5-(4-methoxybenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (3.36 g, 40 % yield) as a yellow solid after recrystallisation from acetone (20 mL). Mp. 99-102 °C (lit. 111-112 °C)[212]; ($[M-H]^-$, 277.0712 $C_{14}H_{13}O_6$ requires: $[M]^+$, 277.0712); IR (cm^{-1}): 3057, 2981, 2847, 1733, 1599, 1505, 1377, 1263, 1133; ^{1}H NMR (400 MHz, $CDCl_3$): 1.84 (6H, s, C**H**$_3$), 3.89 (3H, s, OC**H**$_3$), 6.95 (2H, d, $^3J_{HH}$ 8.8, C**3**-**H**), 7.74 (2H, d, $^3J_{HH}$ 8.8, C**2**-**H**), 15.48 (1H, bs, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$): 26.85 (**C**H_3), 55.69 (O**C**H_3), 89.78 (**C**$(CH_3)_2$), 104.81 (**C**=COH), 113.64 (C**3**-H), 124.64 (C**2**-H), 132.61 (C**1**-C), 160.54 (C**4**-OCH_3), 164.44 (C=**C**OH), 171.30 (**C**=O), 188.33 (**C**=O). m/z (ESI): 277 (100%, $[M-H]^-$) , 175 (89 %, $[M-CH_3COCH_3-CO_2]^-$).

5-(4-Fluorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (161)



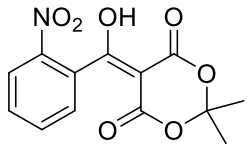
4-Fluorobenzoyl chloride (4.76 g, 30 mmol) was reacted according to the general procedure to afford *5-(4-fluorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (4.83 g, 60 % yield) as a white solid after recrystallization from acetone. Mp. 97-100 °C, ([M-H]$^-$, 265.0526 $C_{13}H_{10}FO_5$ requires: [M-H]$^-$, 265.0512); IR (cm^{-1}): 3003, 1726, 1601, 1387, 1299, 1201, 1135; ^{1}H NMR (400 MHz, $CDCl_3$): 1.84 (6H, s,C**H**$_3$), 7.12-7.17 (2H, m, C**3**-H), 7.71-7.74 (2H, m, C**2**-H), 15.56 (1H, bs,O**H**); ^{19}F NMR (376 MHz, $CDCl_3$): - 103.74 (m); ^{13}C NMR (101 MHz, $CDCl_3$): 26.95 (**C**H$_3$), 90.87 (**C**(CH$_3$)$_2$), 105.18 (**C**=COH), 115.58 (d, $^2J_{CF}$ 22.2 Hz, C**3**-H), 128.80 (C**1**-C), 132.49 (d, $^3J_{CF}$ 9.5 Hz, C**2**-H), 160.00 (C=**C**OH), 165.95 (d, $^1J_{CF}$ 255.9 Hz, C**4**-F), 171.15 (**C**=O), 188.05 (**C**=O); m/z (ESI): 265 (100 %, [M-H]$^-$), 163 (71 %, [M-CH$_3$COCH$_3$-CO$_2$)]$^-$).

5-(2-Thiophenecarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (162)



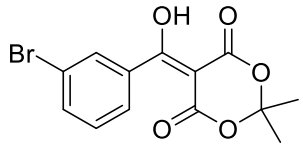
2-Thiophenecarbonyl-chloride (4.40 g, 3.2 mL, 30 mmol) was reacted according to the general procedure to afford *5-(2-thiophenecarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (5.97 g, 78 %) as a brown solid. Mp.: 79-80°C, ([M-H]$^-$, 253.0171 $C_{11}H_9O_5S$ requires: [M-H]$^-$, 253.0171); IR (cm^{-1}) 3099, 1722, 1648, 1476, 1373, 1071; ^{1}H NMR (400 MHz, $CDCl_3$): 1.83 (6H, s, CH$_3$), 7.21 (1H, dd, $^3J_{HH}$ 5.0, $^3J_{HH}$ 4.1 Hz, C**4**-H); 7.84 (1H, dd, $^3J_{HH}$ 5.0, $^4J_{HH}$ 1.2 Hz, C**5**-H), 8.46 (1H, dd, $^3J_{HH}$ 4.1, $^4J_{HH}$ 1.2 Hz, C**3**-H), 15.96 (1H, bs, OH); ^{13}C NMR (101 MHz, $CDCl_3$): 26.64 (**C**H$_3$), 88.69 (**C**(CH$_3$)$_2$), 104.80 (**C**H(C=O)), 128.18 (C**4**-H), 134.74 (C**2**-C), 137.27 (C**5**-H), 138.61 (C**3**-H), 160.33 (C=**C**OH), 171.75 (**C**=O), 179.37 (**C**=O) , m/z (ESI) 253 (100 %, [M-H]$^-$).

5-(2-Nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (163)



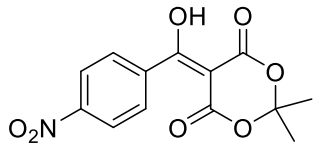
2-Nitrobenzoyl chloride (7.43 g, 40 mmol) was reacted according to the general procedure to afford *5-(2-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (6.95 g, 59 % yield) as a yellow solid. Mp. 105-107 °C (with decomposition), ([M-H]$^-$, 292.0446. $C_{13}H_{10}NO_7$ requires: [M]$^+$, 292.0457); IR (cm^{-1}): 3087, 2970, 1744, 1681, 1537, 1355, 1201, 1137; ^{1}H NMR (400 MHz, $CDCl_3$): 1.77 (6H, s, CH$_3$), 7.46 (1H, dd, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.5, C**4**-H), 7.71 (1H, ddd, $^3J_{HH}$ 8.3, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.5, C**5**-H), 7.79 (1H, td, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.2, C**6**-H), 8.27 (1H, dd, $^3J_{HH}$ 8.3, $^4J_{HH}$ 1.2, C**3**-H), 15.32 (1H, bs, OH); ^{13}C NMR (101 MHz, $CDCl_3$): 27.12 (**C**H$_3$), 99.69 (**C**(CH$_3$)$_2$), 106.20 (**C**=COH), 124.77 (C**6**-H), 128.95 (C**3**-H), 130.04 (C**1**-C), 131.61 (C**4**-H), 134.19 (C**5**-H), 146.25 (C**2**-NO$_2$), 159.48 (C=**C**OH), 170.64 (**C**=O), 187.34 (**C**=O); m/z (ESI): 292 (100 %, [M-H]$^-$).

5- (3-Bromobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (164)



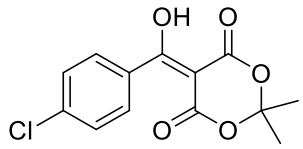
3-Bromobenzoyl chloride (6.58 g, 3.96 mL, 30 mmol) was reacted according to the general procedure to afford *5-(3-bromobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (7.75 g, 79 % yield) as a yellow solid. Mp. 92-93°C, ([M-H]$^-$, 324.9712 $C_{13}H_{10}O_5Br$ requires: [M-H]$^-$, 324,9721;); IR (cm^{-1}): 3062, 2942, 1730, 1650, 1540, 1137, 1031; ^{1}H NMR (400 MHz, $CDCl_3$): 1.84 (6H, s, CH_3), 7.34 (1H, t, $^3J_{HH}$ 7.9 Hz, C**5**-H), 7.58 (1H, dm, $^3J_{HH}$ 7.7 Hz, C**4**-H), 7.71 (1H, dm, $^3J_{HH}$ 8.04 Hz, C**6**-H), 7.78 (1H, s, C**2**-H), 15.49 (1H, bs, OH); ^{13}C NMR (101 MHz, $CDCl_3$): 27.03 (**C**H_3), 91.51 (**C**$(CH_3)_2$), 105.45 (**C**=COH), 122.19 (C**3**-Br), 128.19 (C**6**-H), 129.69 (C**5**-H), 132.06 (C**2**-H), 134.68 (C**1**-C), 136.11 (C**4**-H), 159.59 (C=**C**OH), 170.98 (**C**=O), 187.62 (**C**=O); m/z (ESI): 325 ([M(^{79}Br)-H]$^-$), 327 ([M(^{81}Br)-H]$^-$).

5-(4-Nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (165)



4-Nitrobenzoyl chloride (9.27 g, 50 mmol) was reacted according to the general procedure to afford *5-(4-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (13.43 g, 91 % yield) as a yellow solid. Mp.: 98-101 °C (lit. 113-114 °C)[212] ([M-H]$^-$, 292.0463. $C_{13}H_{10}NO_7$ requires: [M]$^+$, 292.0457); IR (cm^{-1}): 3074, 2999, 2952, 1739, 1662, 1516, 1349, 1195, 1138; ^{1}H NMR (700 MHz, $CDCl_3$): 1.85 (6H, s, CH_3), 7.79 (2H, d, $^3J_{HH}$ 8.8, C**2**-H), 8.31 (2H, d, $^3J_{HH}$ 8.8, C**3**-H); ^{13}C NMR (175 MHz, $CDCl_3$): 27.15 (**C**H_3), 92.36 O(**C**$(CH_3)_2$), 105.86 (**C**=COH), 123.40 (C**3**-H), 130.37 (C**2**-H), 138.70 (C**1**-C), 150.17 (C**4**-NO_2), 159.34 (C=**C**OH), 170.70 (**C**=O), 186.85 (**C**=O). m/z (ESI): 292 (100 %,[M-H]$^-$).

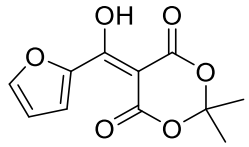
5-(4-Chlorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (166)



4-Chlorobenzoyl chloride (5.25 g, 30 mmol) was reacted according to the general procedure to afford *5-(4-chlorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (5.54 g, 65 % yield) as an off white solid after recrystallization from acetone. Mp. 100-103 °C (lit. 106 °C)[212]; ([M-H]$^-$, 281.0219 $C_{13}H_{10}ClO_5$ requires: [M]$^+$, 281.0217); IR (cm^{-1}): 3001, 1729, 1662, 1582, 1549, 1384, 1284, 1135; ^{1}H NMR (400 MHz, $CDCl_3$): 1.84 (6H, s, CH_3), 7.42-7.46 (2H, m, C**3**-H), 7.61-7.64 (2H, m, C**2**-H),

15.54 (1H, bs, O-H); ^{13}C NMR (101 MHz, $CDCl_3$): 26.99 (CH_3), 91.16 (**C**$(CH_3)_2$), 105.28 (**C**=COH), 128.61 (C**2**-H), 131.10 (C**3**-H), 131.12 (C**1**-C), 139.96 (C**4**-Cl), 159.83 (C=**C**OH), 171.08 (**C**=O), 188.05 (**C**=O); m/z (ESI): 281 (100 %, $[M-H]^-$), 241 (88 %, $[M-CH_3CH=CH]^-$), 179 (82 %, $[M-CH_3COCH_3-CO_2]^-$).

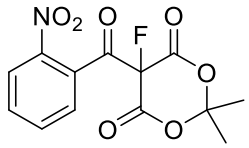
5-(2-Furoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (167)



2-Furoyl-chloride (3.91 g, 2.95 mL, 30 mmol) was reacted according to the general procedure to afford *5-(2-furoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (5.28 g, 74 % yield) as a pale brown solid. Mp.: 79-80°C, ($[M-H]^-$, 237.0399 $C_{11}H_9O_6$ requires: $[M-H]^-$, 237.0405); IR (cm^{-1}) 3127, 2995, 1725, 1646, 1550, 1376; ^{1}H NMR (400 MHz, $CDCl_3$): 1.81 (6H, s, CH_3), 6.66 (1H, dd, $^3J_{HH}$=3.8, $^3J_{HH}$ 1.6 Hz, C**4**-H), 7.77 (1H, dd, $^3J_{HH}$ 1.6, $^4J_{HH}$ 0.8 Hz, C**5**-H), 8.12 (1H, dd, $^3J_{HH}$=3.8, $^4J_{HH}$ 0.8 Hz, C**3**-H), 15.80 (1H, bs, OH); ^{13}C NMR (101 MHz, $CDCl_3$): 26.64 (**C**H_3), 88.44 (**C**$(CH_3)_2$), 104.97 (**C**=(C-OH)), 113.44 (C**4**-H), 126.20 (C**3**-H), 146.05 (C**2**-H), 148.80 (C**5**-C), 159.47 (C=**C**-OH), 171.65 (**C**=O), 173.62 (**C**=O); m/z (ESI): 237 (100 %, $[M-H]^-$).

7.5.2 Fluorination of acyl Meldrum's acid derivatives

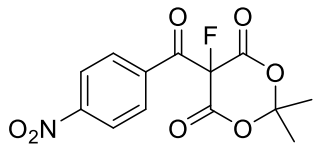
5-Fluoro-5-(2-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (169) - general procedure



5-(2-Nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.40 g, 15.0 mmol) was dissolved in acetonitrile (50 mL), Selectfluor (5.50 g, 15.5 mmol) was added then the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated to dryness under vacuum, the solids suspended in ethyl acetate (50 mL) filtered and washed with ethyl acetate (30 mL). The ethyl acetate solution was evaporated under reduced pressure, the residue dissolved in dichloromethane (20 mL), hexane (60 mL) was added and the solution was concentrated at atmospheric pressure until solids started to appear (approximately 30 mL). After cooling at 4 °C overnight the product was filtered and dried under vacuum to afford *5-fluoro-5-(2-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (3.50 g, 75 % yield) as a tan powder. Mp. 125-127 °C (with decomposition); IR (cm^{-1}): 3009, 1795, 1753, 1729, 1535, 1350, 1316, 1133; ^{1}H NMR (600 MHz, $CDCl_3$): 1.86 (3H, s, C**H$_3$**), 2.04 (3H, s, C**H$_3$**), 7.52 (1H, d, $^3J_{HH}$ 7.6 Hz, C**6**-H), 7.77 (1H, m, C**4**-H), 7.84 (1H, tm, $^3J_{HH}$ 7.6 Hz, C**5**-H), 8.27 (1H, dm, $^3J_{HH}$ 8.2 Hz, C**3**-H); ^{13}C NMR (151 MHz, $CDCl_3$): 27.99 (CH_3 axial), 30.29 (CH_3 equatorial), 90.50 (d, $^1J_{CF}$ 209.0 Hz, C-F), 109.98 (d, $^4J_{CF}$ 2.0 Hz, **C**$(CH_3)_2$),

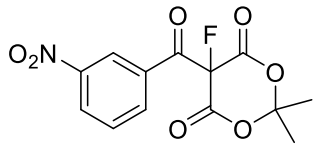
124.69 (C**3**), 129.22 (d, $^{4}J_{CF}$ 3.6 , C**6**), 130.84 (d, $^{3}J_{CF}$ 2.5, C**1**), 132.41 (C**4**), 134.78 (C**5**), 145.80 (C**2**), 157.90 (d, $^{2}J_{CF}$ 23.2 HZ, **C**=O), 189.15 (d, $^{2}J_{CF}$ 32.6, **C**=O); ^{19}F NMR (376 MHz, $CDCl_3$): - 162.56 (1F, d, $^{5}J_{HF}$ 1 Hz); m/z (ASAP): $[M]^+$ not detected, 184 (25 %, $[M\text{-}CH_3COCH_3\text{-}2xCO_2]^+$), 150 (10 %, $[M\text{-}C_6H_6FO_4]^+$).

5-Fluoro-5-(4-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (170)



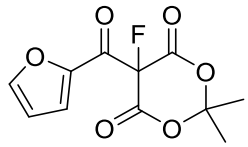
5-Fluoro-5-(4-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.40 g, 15.0 mmol) was reacted according to the general procedure to afford *5-fluoro-5-nitrobenzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione* (3.32 g, 75 % yield) as a tan solid. Mp.: 135-137 ^{o}C (with decomposition); IR (cm^{-1}): 3120, 3056, 1787, 1742, 1699, 1525, 1322, 1157; ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (3H, s, C**H$_3$**), 1.95 (3H, s, C**H$_3$**), 8.42 – 8.33 (4H, m, C**2**-H, C**3**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 158.17 (1F, t, $^{5}J_{HF}$ 1.4 Hz, C-F).; ^{13}C NMR (101 MHz, $CDCl_3$): 27.96 (**C**H_3), 30.28 (**C**H_3), 91.48 (d, $^{1}J_{CF}$ 213 Hz, **C**-F), 109.94 (d, $^{4}J_{CF}$ 1.6 Hz, **C**$(CH_3)_2$), 124.01 (C**3**-H), 132.08 (d, $^{4}J_{CF}$ 6.3 Hz, C**2**-H), 136.69 (d, $^{3}J_{CF}$ 4.1 Hz, C**1**-C), 151.43 (C**4**-NO_2), 158.81 (d, $^{2}J_{CF}$ 23.2, **C**=O), 188.15 (d, $^{2}J_{CF}$ 27.9, **C**=O); m/z (ASAP): $[M]^+$ not detected, 268 (100 %, $[M\text{-}C_3H_7]^+$); 210 (35 %, $[M\text{-}CH_3COCH_3\text{-}CO_2]^+$), 150 (15 %, $[M\text{-}C_6H_6FO_4]^+$).

5-(3-Nitrobenzoyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (171)



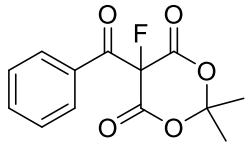
5-(3-Nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.40 g, 15 mmol) was reacted according to the general procedure to afford *5-(3-nitrobenzoyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione* (2.10 g, 45 %) as a tan powder. Mp.: 129-133 °C; IR (cm^{-1}): 3098, 1790, 1756, 1695, 1528, 1314, 1297, 1150; ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (3H, s, C**H$_3$**), 1.95 (3H, s, C**H$_3$**), 7.78 (1H, t, $^{3}J_{HH}$ 8.1 Hz, C**5**-H), 8.54 (1H, ddd, $^{3}J_{HH}$ 8.2, $^{5}J_{FH}$ 2.3, $^{4}J_{HH}$ 1.4 Hz, C**6**-H), 8.58 (1H, dm, $^{3}J_{HH}$ 7.9 Hz, C**4**-H), 9.01 (1H, dd, $^{4}J_{HH}$ 1.4, $^{5}J_{FH}$ 3.0 Hz, C**2**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 157.91 (1F, dd, $^{5}J_{HF}$ 3.0, $^{5}J_{HF}$ 2.3 Hz, C-**F**); ^{13}C NMR (101 MHz, $CDCl_3$): 27.81 (**C**H_3), 30.11 (**C**H_3), 91.31 (d, $^{1}J_{CF}$ 213 Hz, **C**-F), 109.78 (d, $^{4}J_{CF}$ 1.7 Hz, **C**$(CH_3)_2$), 125.63 (d, $^{5}J_{CF}$ 5.9 Hz, C**2**-H), 129.37 (C**4**-H), 130.26 (d, $^{5}J_{CF}$ 1.2 Hz, C**5**-H), 133.21 (d, $^{3}J_{CF}$ 4.1 Hz, C**1**-H), 136.20 (d, $^{4}J_{CF}$ 7.3 Hz, C**6**-H), 148.41 (C**3**-NO_2), 158.68 (d, $^{2}J_{CF}$ 23.2 Hz, **C**=O), 187.19 (d, $^{2}J_{CF}$ 27.3 Hz, **C**=O); m/z (ASAP): $[M]^+$ not detected, 268 (100 %, $[M\text{-}C_3H_7]^+$), 210 (27 %, $[M\text{-}CH_3COCH_3\text{-}CO_2]^+$), 150 (10 %, $[M\text{-}C_6H_6FO_4]^+$).

5-(2-Furoyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (172)



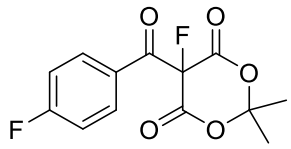
5-(2-furoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.76 g, 20 mmol) was reacted according to the general procedure to afford *5-(2-furoyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione* (4.43 g, 92 %) as a brown solid and was used without any further purification. Mp.: 124-126 °C, IR (cm^{-1}): 3146, 1793, 1751, 1666, 1455, 1288, 1143; ^{1}H NMR (400 MHz, $CDCl_3$): 1.87 (3H, s, C**H$_3$**), 1.93 (3H, s, C**H$_3$**), 6.69 (1H, dd, $^{3}J_{HH}$ 3.7, $^{3}J_{HH}$ 1.7 Hz, C**4**-H), 7.78 (1H, dd, $^{3}J_{HH}$ 1.7, $^{4}J_{HH}$ 0.8 Hz, C**5**-H), 7.83 (1H, td, $^{3}J_{HH}$ 3.7, $^{4}J_{HH}$ 0.8 Hz, C**3**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 160.73 (1F, d, $^{5}J_{HF}$ 3.3 Hz, C-F); ^{13}C NMR (101 MHz, $CDCl_3$): 27.99 (CH_3), 30.11 (CH_3), 89.90 (d, $^{1}J_{CF}$ 209 Hz, C-F), 109.55 (d, $^{4}J_{CF}$ 1.5 Hz, **C**$(CH_3)_2$), 113.695 (d, $^{5}J_{CF}$ 1.9 Hz, C**4**-H), 125.91 (d, $^{4}J_{CF}$ 10.7 Hz, C**3**-H), 147.40 (d, $^{3}J_{CF}$ 3.9 Hz, C**2**-C), 150.17 (C**5**-H), 158.94 (d, $^{2}J_{CF}$ 23.1 Hz, **C**=O), 174.05 (d, $^{2}J_{CF}$ 25.9 Hz, **C**=O); m/z (ASAP): $[M]^+$ not detected, 214.0 (100 %, $[M\text{-}CH_2{=}CH\text{-}CH_3]^+$).

5-Benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (173)



5-Benzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione (2.48 g, 10.0 mmol) was reacted according to the general procedure to afford *5-benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione* (1.98 g, 74 % yield) as a yellow solid. Mp.: 109-112 °C; IR (cm^{-1}): 3071, 3019, 1797, 1756, 1675, 1305, 1202, 1146; ^{1}H NMR (400 MHz, $CDCl_3$): 1.86 (3H, s, C**H$_3$**), 1.92 (3H, s, C**H$_3$**), 7.53 (2H, m, C**3**-H), 7.69 (1H, m, C**4**-H), 8.22 (2H, m, C**2**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 157.97 (t, $^{5}J_{HF}$ 1.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): 27.67 (**C**H_3), 30.19 (**C**H_3), 92.13 (d, $^{1}J_{CF}$ 216 Hz, **C**-F), 109.43 (**C**$(CH_3)_2$), 128.90 (C**3**-H), 130.87 (d, $^{4}J_{CF}$ 6.1 Hz, C**2**-H), 132.06 (d, $^{3}J_{CF}$ 4.1 Hz, C**1**-C), 135.51 (C**4**-H), 159.15 (d, $^{2}J_{CF}$ 23.2, **C**=O), 188.16 (d, $^{2}J_{CF}$ 26.4, **C**=O); m/z (ASAP): $[M]^+$ not detected, 223 (27 %, $[M\text{-}C_3H_7]^+$); 165 (100 %, $[M\text{-}CH_3COCH_3\text{-}CO_2]^+$).

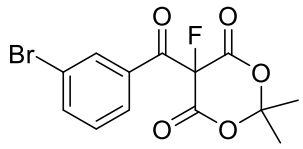
5-Fluoro-5-(4-fluorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (174)



5-(4-Fluorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.00 g, 15.0 mmol) was reacted according to the general procedure to afford *5-fluoro-5-(4-fluorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (3.01 g, 70 % yield) as an off white solid. Mp.: 91-95 °C; IR (cm^{-1}): 3076, 1796,

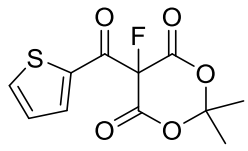
1751, 1684, 1589, 1304, 1238, 1144; ^{1}H NMR (400 MHz, $CDCl_3$): 1.86 (3H, s, C**H$_3$**), 1.91 (3H, s, C**H$_3$**), 7.16 – 7.25 (2H, m, C**3**-H), 8.29 (2H, ddt; $^{2}J_{HH}$ 7.1, $^{3}J_{HF}$ 5.3, $^{3}J_{HH}$ 1.9 Hz, C**2**-H) ^{19}F NMR (376 MHz, $CDCl_3$): - 99.41 (1F, m, Ar-F), -157.36 (1F, m); ^{13}C NMR (101 MHz, $CDCl_3$): 27.81 (**C**H_3), 30.26 (**C**H_3), 92.10 (d, $^{1}J_{CF}$ 213 Hz, **C**-F), 109.66 (d, $^{4}J_{CF}$ 1.9 Hz, **C**$(CH_3)_2$), 116.48 (d, $^{2}J_{CF}$ 22.1 Hz, C**3**-H), 128.52 (dd, $^{3}J_{CF}$ 4.2, $^{4}J_{CF}$ 3.1 Hz, C**1**-C), 134.22 (dd, $^{3}J_{CF}$ 10.0, $^{4}J_{CF}$ 6.4 Hz, C**2**-H), 159.18 (d, $^{2}J_{CF}$ 23.4, **C**=O), 167.27 (d, $^{1}J_{CF}$ 260.1 Hz, C**4**-F), 186.84 (d, $^{2}J_{CF}$ 26.1, **C**=O); m/z (ASAP): $[M]^+$ not detected, 241 (100 %, $[M\text{-}C_3H_7]^+$); 183 (92 %, $[M\text{-}CH_3COCH_3\text{-}CO_2]^+$), 123 (48 %, $[M\text{-}C_6H_6FO_4]^+$).

5-(3-Bromobenzoyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (175)



5-(3-Bromobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (6.53 g, 20 mmol) was reacted according to the general procedure to afford *5-(3-bromobenzoyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione* (4.43 g, 64 %) as a tan powder, crystalline product suitable for X-ray crystallography was obtained by recrystallisation from acetone. Mp. 104-106 °C; IR (cm^{-1}): 3111, 1751, 1685, 1565, 1398, 1308, 1142; ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (3H, s, C**H$_3$**), 1.94 (3H, s, C**H$_3$**), 7.44 (1H, t, $^{3}J_{HH}$ 8.0 Hz, Ar-H), 7.84 (1H, ddd, $^{3}J_{HH}$ 8.0, $^{4}J_{HH}$ 2.0, $^{4}J_{HH}$ 1.0 Hz, C**4**-H), 8.20 (1H, dm, $^{3}J_{HH}$ 7.9 Hz, C**6**-H), 8.28 (1H, q, $^{4}J_{HH}$ 1.7 Hz, C**2**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 158.06 (dd, 1F, $^{5}J_{HF}$ 2.1, $^{5}J_{HF}$ 1.4 Hz, C-**F**); ^{13}C (101 MHz, $CDCl_3$): 27.85 (**C**H_3), 30.28 (**C**H_3), 91.78 (d, $^{1}J_{CF}$ 214 Hz, **C**-F), 109.69 (d, $^{4}J_{CF}$ 1.5 Hz, **C**$(CH_3)_2$), 123.20 (C**3**-Br), 129.59 (d, $^{4}J_{CF}$ 7.4 Hz, C**6**-H), 130.54 (C**5**-H), 133.51 (d, $^{4}J_{CF}$ 5.3 Hz, C**2**-H), 133.78 (d, $^{3}J_{CF}$ 4.1 Hz, C**1**-C), 138.44 (C**4**-H), 159.00 (d, $^{2}J_{CF}$ 23.4 Hz, **C**=O), 187.52 (d, $^{2}J_{CF}$ 26.8 Hz, **C**=O); m/z (ASAP): $[M]^+$ not detected, 183 (96 %, $[M(^{79}Br)\text{-}C_6H_6FO_4]^+$), 185 (100 %, $[M(^{81}Br)\text{-}C_6H_6FO_4]^+$)., 243 (77 %, $[M(^{79}Br)\text{-}CH_3COCH_3\text{-}CO_2]^+$)., 245 (75 %, $[M(^{81}Br)\text{-}CH_3COCH_3\text{-}CO_2]^+$).

5-Fluoro-5-(2-thiophenecaronyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (176)



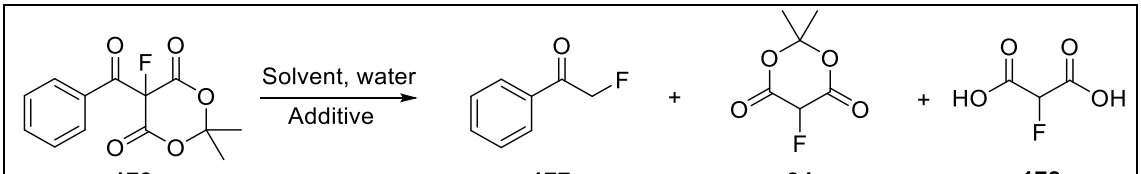
5-(2-Thiophenecarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.08 g, 20 mmol) was reacted according to the general procedure to afford *5-(2-thiophenecarbonyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione* (5.07 g, 93 %) as a light brown solid and was used without any further purification. Mp.:98 – 100 °C; IR (cm^{-1}) 3104, 3005, 1751, 1653, 1407, 1308, 1092; ^{1}H NMR (400MHz, $CDCl_3$): 1.85 (3H, s, CH_3), 1.92 (3H, s, CH_3), 7.25 (1H, dd, $^{3}J_{HH}$ 4.9, $^{3}J_{HH}$ 4.0 Hz, C**4**-H), 7.91

(1H, dd, $^{3}J_{HH}$ 4.9, $^{4}J_{HH}$ 1.1 Hz, C**5**-H), 8.37 (1H, ddd, $^{3}J_{HH}$ 4.0, $^{5}J_{HF}$ 3.0, $^{4}J_{HH}$ 1.1 Hz, C**3**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 157.78 (1F, d, $^{5}J_{HF}$ 3.0 Hz, C-F); ^{13}C NMR (101 MHz, $CDCl_3$): 27.91 (CH_3), 30.22 (CH_3), 91.32 (d, $^{1}J_{CF}$ 213 Hz, C-F), 109.62 (d, $^{5}J_{CF}$ 1.7 Hz, **C**$(CH_3)_2$), 129.51 (d, $^{5}J_{CF}$ 2.0 Hz, C**4**-H), 137.42 (d, $^{3}J_{CF}$ 5.2 Hz, C**2**-C), 138.71 (d, $^{4}J_{CF}$ 11.3 Hz, C**3**-H), 138.81 (d, $^{5}J_{CF}$ 2.2 Hz, C**5**-H), 158.99 (d, $^{2}J_{CF}$ 23.4 Hz, **C**=O), 180.10 (d, $^{2}J_{CF}$ 26.4 Hz, **C**=O); m/z (ASAP): $[M]^+$ was not detected, 111 (100 %, $[M\text{-}C_6H_6FO_4]^+$), 171 (86 %, $[M\text{-}CH_3COCH_3\text{-}CO_2]^+$), 229 (16 %, $[M\text{-}CH_2{=}CH\text{-}CH_3]^+$).

7.5.3 Synthesis of 2-fluoroacetophenone derivatives

Screening of hydrolysis conditions

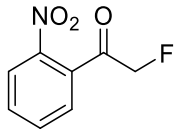
5-Benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (0.27 g, 1 mmol) was weighed in a 5 mL microwave vial, all other additives and solvent (5 mL) were added, the vial sealed with a cap and heated at the desired temperature (T) for the reaction time (t) in a Biotage™ microwave. After cooling to room temperature, a sample (0.1 mL) sample was diluted with deuterochloroform and analysed by ^{19}F NMR spectroscopy.



173 **177** **84** **178**

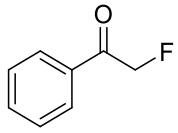
No	Solvent	Additive	Water	T / °C	t / min	Composition
1	Acetone	-	0.1 mL	100	20	91 % **173**, 1 % **177**, 8 % **84**
2	Acetone	0.1 mL 1M HCl	-	90	20	67 % **173**, 23 % **177**, 5 % **84**, 5 % **178**
3	Acetone	1 eq. $TsOH.H_2O$	0.1 mL	90	20	68 % **177**, 7 % **84**, 25 % **178**
4	Acetone	1 eq. $TsOH.H_2O$	-	100	20	11 % **173**, 30 % **177**, 20 % **84**, 38 % **178**
5	Acetone	2 eq. $TsOH.H_2O$	-	100	20	2 % **173**, 36 % **177**, 62 % **178**
6	Acetone	1 eq. $TsOH.H_2O$	0.1 mL	100	20	60 % **177**, 40 % **178**
7	Acetone	1 eq. $TsOH.H_2O$	0.1 mL	110	20	75 % **177**, 25 % **178**
8	Acetone	1 eq. $TsOH.H_2O$	0.2 mL	100	20	73 % **177**, 27 % **178**
9	Acetone	1 eq. K_2CO_3	0.1 mL	100	20	No reaction
10	Acetone	0.1 mL 37 % HCl	-	100	20	34 % **173**, 56 % **177**, 10 % **178**
11	Acetone	0.05 mL 37 % HC	0.05 mL	100	20	35 % **173**, 48 % **177**, 3 % **84**, 14 % **178**
12	Acetone	0.5 eq. $TsOH.H_2O$	0.1 mL	100	30	76 % **177**, 24 % **178**
13	AcOH	1 eq. $TsOH.H_2O$	-	100	20	36 % **177**, 64 % **178**
14	AcOH	1 eq. $TsOH.H_2O$	0.1 mL	100	20	55 % **177**, 45 % **178**

2-Fluoro-2'-nitroacetophenone (168) - general procedure



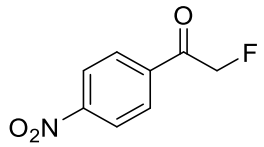
5-Fluoro-5-(2-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.24 g, 4.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.76 g, 4.0 mmol) were dissolved in acetone (20 mL) in a microwave vial (25 mL). Water (0.4 mL) was added, the vial sealed and irradiated at 100 °C for 30 minutes. After the mixture was allowed to cool to ambient temperature, the pressure was carefully released by piercing the rubber septum with a needle. The mixture was evaporated to dryness, the residue dissolved in ethyl acetate (50 mL), washed with saturated $NaHCO_3$ solution (2x20 mL) and brine (20 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure and the product was purified by silica gel column chromatography (hexanes : ethyl acetate, 5 : 1, Rf.: 0.15) to afford *2-fluoro-2'-nitroacetophenone* (0.65 g, 89 % yield) as an off white solid. Mp.: 69-71 °C; ($[M+H]^+$, 184.0407 $C_8H_7FNO_3$ requires: $[M+H]^+$, 184.0410); IR (cm^{-1}): 2945, 1724, 1421, 1517, 1348, 1221, 1094, 1076; ^{1}H NMR (700 MHz, $CDCl_3$): 5.14 (2H, d, $^2J_{HF}$ 47.2 Hz, CH_2F), 7.47 (1H, dd, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.4 Hz, C6-H), 7.69 (1H, ddd, $^3J_{HH}$ 8.2, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.4 Hz, C**4**-H), 7.80 (1H, td, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.2 Hz, C**5**-H), 8.19 (1H, dd, $^3J_{HH}$ 8.2, $^4J_{HH}$ 1.2 Hz, C**3**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 225.74 (1F, t, $^2J_{HF}$ 47.3 Hz, CH_2F); ^{13}C NMR (176 MHz, $CDCl_3$): 84.34 (d, $^1J_{CF}$ 185.4 Hz, **C**H_2F), 124.01 (C**3**-H), 128.50 (d, $^4J_{CF}$ 1.2 Hz, C**6**-H), 131.65 (C**4**-H), 133.63 (d, $^3J_{CF}$ 2.1 Hz, C**1**-C), 134.70 (C**5**-H), 146.77 (C**2**-NO_2), 199.11 (d, $^2J_{CF}$ 25.2 Hz, **C**=O); m/z (ASAP): 184 (100 %, $[M+H]^+$), 164 (15 %, $[M-F]^+$).

2-Fluoroacetophenone (177)



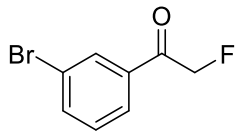
5-Fluoro-5-(benzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.07 g, 4.0 mmol) was reacted according to the general procedure to afford *2-fluoroacetophenone* (0.31 g, 56 % yield) as a yellow oil. Rf.: 0.27 (hexanes : ethyl acetate, 5 : 1); ($[M+H]^+$, 139.0559 C_8H_8FO requires: $[M+H]^+$, 139.0559); IR (cm^{-1}): 3066, 2938, 1703, 1598, 1450, 1231, 1086; ^{1}H NMR (400 MHz, $CDCl_3$): 5.53 (2H, d, $^2J_{HF}$ 46.9 Hz, CH_2F), 7.45 – 7.54 (2H, m, C**3**-H), 7.58 – 7.66 (1H, m, C**4**-H), 7.83-7.92 (2H, m, C**2**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 231.44 (t, $^2J_{HF}$ 47.0 Hz, CH_2F);. ^{13}C NMR (101 MHz, $CDCl_3$): 83.64 (d, $^1J_{CF}$ 182.6 Hz, **C**H_2F), 127.94 (d, $^4J_{CF}$ 2.6 Hz, C**2**-H), 129.03 (C**3**-H), 133.80 (C**1**-C), 134.24 (C**4**-H), 193.52 (d, $^2J_{CF}$ 15.5 Hz, **C**=O); m/z (ASAP): 139 (49 %, $[M+H]^+$).

2-Fluoro-4'-nitroacetophenone (180)

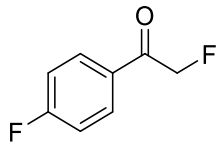


5-Fluoro-5-(4-nitrobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.24 g, 4.0 mmol) was reacted according to the general procedure to afford *2-fluoro-4'-nitroacetophenone* (0.30 g, 41 % yield) as a yellow crystalline solid. Mp.: 90 - 93 °C; ($[M+H]^+$, 184.0412 $C_8H_7FNO_3$ requires: $[M+H]^+$, 184.0410); IR (cm^{-1}): 2945, 1724, 1421, 1517, 1348, 1221, 1094, 1076; ^1H NMR (600 MHz, $CDCl_3$): 5.52 (2H, d, $^2J_{HF}$ 46.8 Hz, CH_2F), 8.05-8.14 (2H, m, C**2**-H), 8.30-8.40 (2H, m, C**3**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 229.21 (t, $^2J_{HF}$ 46.9 Hz, CH_2F); ^{13}C NMR (176 MHz, $CDCl_3$): 84.02 (d, $^1J_{CF}$ 185.1 Hz, **C**H_2F), 124.23 (C**3**-H), 129.47 (d, $^4J_{CF}$ 3.5 Hz, C**2**-H), 138.34 (d, $^3J_{CF}$ 1.2 Hz, C**1**-C), 150.97 (C**4**-NO_2), 192.75 (d, $^2J_{CF}$ 17.0 Hz, **C**=O); m/z (ASAP): 184 (53 %, $[M+H]^+$), 150 (37 %, $[M-CH_2F]^+$).

3'-Bromo-2-fluoroacetophenone (181)



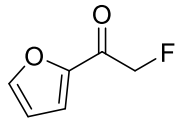
5-(3-Bromobenzoyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (1.04 g, 3 mmol) was reacted according to the general procedure to afford *3'-bromo-2-fluoroacetophenone* (0.23 g, 35 % yield) as a white crystalline solid. Mp. 39-40 °C; Rf.: 0.27 (hexane : ethyl acetate, 5 : 1); ($[M+H]^+$, 216.9664 C_8H_7BrFO requires: $[M]^+$, 216.9661), IR (cm^{-1}): 3068, 2932, 1708, 1590, 1567, 1424, 1223, 1096; ^1H NMR (400 MHz, $CDCl_3$): 5.48 (2H, d, $^2J_{HF}$ 46.8 Hz, CH_2F), 7.37 (1H, t, $^3J_{HH}$ 7.9 Hz, C**5**-H), 7.74 (1H, ddd, $^3J_{HH}$ 8.0, $^4J_{HH}$ 2.0, $^4J_{HH}$ 1.0 Hz, C**4**-H), 7.80 (1H, ddd, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.6, $^4J_{HH}$ 1.0 Hz, C**6**-H), 8.02 (1H, t, $^4J_{HH}$ 2.0 Hz, C**2**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 230.17 (1F, t, $^2J_{HF}$ 47.0 Hz, CH_2F); ^{13}C NMR (101 MHz, $CDCl_3$): 83.62 (d, $^1J_{CF}$ 183.6 Hz, CH_2F), 123.34 (C**3**-Br), 126.55 (d, $^4J_{CF}$ 2.9 Hz, C**6**-H), 130.61 (C**5**-H), 131.09 (d, $^4J_{CF}$=2.9 Hz, C**2**-H), 135.46 (C**1**-C), 137.09 (C**4**-H), 192.43 (d, $^2J_{CF}$ 16 Hz, **C**=O); m/z (ASAP): 216.9 (98%, $[M(^{79}Br)+H]^+$), 218,9 (100%, $[M(^{81}Br)+H]^+$).**2,4'-Difluoroacetophenone (182)**



5-Fluoro-5-(4-fluorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.00 g, 3.5 mmol) was reacted according to the general procedure to afford *2,4'-difluoroacetophenone* (0.34 g, 62 % yield) as a white crystalline solid. Mp.: 52-53 °C; Rf.: 0.26 (hexanes : ethyl aceate, 5 :1) ($[M+H]^+$,

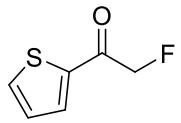
157.0465 $C_8H_7F_2O$ requires: $[M+H]^+$, 157.0464); IR (cm^{-1}): 2951, 1685, 1593, 1508, 1406, 1231, 1159, 1080; ^1H NMR (400 MHz, $CDCl_3$): 5.48 (2H, d, $^2J_{HF}$ 47.0 Hz, CH_2F), 7.08-7.22 (2H, m, C2-H), 7.89-8.02 (2H, m, C**3**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 103.17 (1F, m, Ar-F), - 229.89 (1F, t, $^2J_{HF}$ 46.9 Hz, CH_2F); ^{13}C NMR (101 MHz, $CDCl_3$): 83.55 (d, $^1J_{CF}$ 183.3 Hz, **C**H_2F), 116.16 (d, $^2J_{CF}$ 22.0 Hz, C**3**-H), 130.19-130.26 (m, C**1**-C), 130.76 (dd, $^3J_{CF}$ 9.5, $^3J_{CF}$ 3.2 Hz, C**2**-H), 166.21 (d, $^1J_{CF}$ 256.7 Hz, C**4**-F), 192.03 (d, $^2J_{CF}$ 16.0 Hz, **C**=O); m/z (ASAP): 157 (100 %, $[M+H]^+$), 123 (16 %, $[M-CH_2F]^+$).

2'-(2-Fluoroacetyl)furane (183)



5-(2-Furoyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (1.02 g, 4 mmol) was reacted according to the general procedure to afford *2'-(2-fluoroacetyl)furane* (0.26 g, 51 %) as a pale yellow crystalline solid. Mp.: 28-30°C; Rf.: 0.14 (hexane : ethyl acetate, 5 : 1); ($[M+H]^+$, 129.0352 $C_6H_6O_2F$ requires: $[M]^+$, 129.0345); IR (cm^{-1}): 3126, 1671, 1464, 1293, 1027; ^1H NMR (400 MHz, $CDCl_3$): 5.32 (2H, d, $^2J_{HF}$ 46.9 Hz, CH_2F), 6.60 (1H, dd, $^3J_{HH}$ 3.6, $^4J_{HF}$ 1.8, C**4**-H), 7.38 (1H, ddd, $^3J_{HH}$ 3.6, $^4J_{HF}$ 1.6, $^4J_{HH}$ 0.8 Hz, C**3**-H), 7.64 (1H, dd, $^3J_{HH}$ 1.8, $^4J_{HH}$ 0.7 Hz, C**4**-H); ^{19}F NMR (376 MHz, $CDCl_3$): - 232.32 (1F, t, $^2J_{HF}$ 46.9 Hz, CH_2F); ^{13}C NMR (101 MHz, $CDCl_3$): 83.29 (d, $^1J_{CF}$ 183.4 Hz, CH_2F), 112.70 (d, $^5J_{CF}$ 1.2 Hz, C**4**-H), 119.49 (d, $^4J_{CF}$ 6.4 Hz, C**3**-H), 147.40 (C**5**-H), 150.06 (C**2**-C), 182.82 (d, $^2J_{CF}$ 17.9 Hz, **C**=O) ; m/z (ASAP) 129 (100 %, $[M+H]^+$).

2'-(2-Fluoroacetyl)thiophene (184)



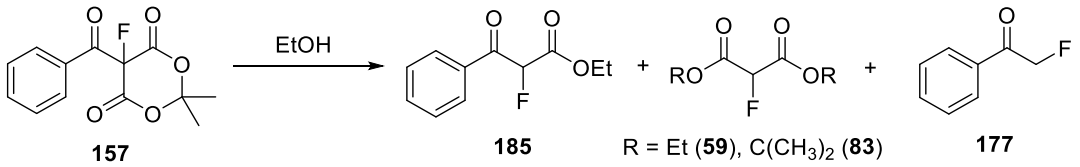
5-(2-Tiophenecarbonyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (1.09 g, 4 mmol) was reacted according to the general procedure to afford *2'-(2-fluoroacetyl)thiophene* (0.42 g, 73 %) as a yellow solid. Mp.: 54-56 °C; Rf.: 0.22 (hexane : ethyl acetate, 5 : 1); ($[M+H]^+$, 145.0123, C_6H_6FOS requires: $[M]^+$, 145.0112); IR (cm^{-1}): 3086, 2940, 1671, 1516, 1414, 1250, 1096; ^1H NMR (400 MHz, $CDCl_3$): 5.33 (2H, d, $^2J_{HF}$ 47.2 Hz, CH_2F), 7.19 (1H, dd, $^3J_{HH}$ 4.9, $^3J_{HH}$ 3.9 Hz, C**4**-H), 7.75 (1H, ddd, $^3J_{HH}$ 4.9, $^4J_{HH}$ 1.1, $^5J_{HF}$ 0.6 Hz Hz, C**3**-H), 7.88 (1H, dt, $^3J_{HH}$ 3.9, $^4J_{HH}$ 1.1 Hz, C**5**-H); ^{19}F NMR (376 MHz, $CDCl_3$): -226.66 (1F, t, $^2J_{HF}$ 47.1 Hz, CH_2F); ^{13}C NMR (101 MHz, $CDCl_3$): 84.09 (d, $^1J_{CF}$ 185.4 Hz, CH_2F), 128.59 (d, $^5J_{CF}$ 1.3 Hz, C**4**-H), 133.37 (d, $^4J_{CF}$ 6.6 Hz, C**3**-H), 135.10 (d, $^5J_{CF}$ 1.7 Hz, C**5**-H), 140.12 (d, $^3J_{CF}$ 2.7 Hz, C**2**-C), 187.32 (d, $^2J_{CF}$ 18.2 Hz, C=O) ; m/z (ASAP): 145 (100 %, $[M+H]^+$).

7.5.4 Synthesis of 2-fluoro-3-ketoesters

Ethanolysis of 5-benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione

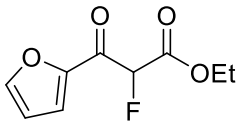
5-Benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (0.26 g, 1.0 mmol) was dissolved in anhydrous ethanol (5 mL) and heated to the prescribed temperature for a pre-determined time. The mixture was allowed to cool to ambient temperature, a 0.1 mL sample was diluted with $CDCl_3$ (0.6 mL) and analysed by ^{19}F NMR spectroscopy.

^{19}F NMR (376 MHz, $CDCl_3$): - 158.8 (**157**), - 191.4 (**185**)[213], - 194.8 (**59**), - 207.3 (**83**), -231.4 (**177**).



T / °C	t / min	Composition
60	30	38 % **157**, 61 % **185**, 1 % **59**
70	30	25 % **157**, 72 % **185**, 3 % **59 + 83**
80	30	12 % **157**, 84 % **185**, 4 % **59 + 83**
90	30	10 % **157**, 84 % **185**, 5% **59 + 83**, 1 % **177**
100	30	3 % **157**, 86 % **185**, 10 % **59 + 83**, 1 % **177**
60	60	97 % **185**, 3 % **59 + 83**
80	60	94 % **185**, 6 % **59 + 83**

Ethyl 2-fluoro-3-(furan-2-yl)-3-oxopropanoate



5-Fluoro-5-(2-Furoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.02 g, 4 mmol) was dissolved in ethanol (20 mL) and heated at 60°C for 60 minutes with microwave irradiation. After cooling to ambient temperature, the solvent was evaporated, the residue dissolved in ethyl-acetate (20 mL) and washed with saturated $NaHCO_3$ solution (10 mL). After evaporation, silica gel column chromatography afforded *ethyl 2-fluoro-3-(furan-2-yl)-3-oxopropanoate* (0.45 g, 55 %) as a yellow oil. Rf.: 0.05 (dichloromethane : hexane, 2 : 3); ($[M+H]^+$, 201.0563 $C_9H_{10}FO_4$ requires: $[M+H]^+$, 201.0569); IR (cm^{-1}): 3137, 2985, 1760, 1678, 1568, 1462, 1258, 1017; ^1H NMR (400 MHz, $CDCl_3$): 1.23 (3H, t, $^3J_{HH}$ 7.1 Hz, CH3), 4.25 (2H, m, CH_2), 5.69 (1H, d, $^1J_{HF}$ 48.3 Hz, CHF), 6.59 (1H, dd, $^3J_{HH}$ 3.7, $^3J_{HH}$ 1.7 Hz, C**4**-H), 7.46 (1H, ddd, $^3J_{HH}$ 3.7, $^5J_{HF}$ 2.0, $^4J_{HH}$ 0.7 Hz, C**3**-H), 7.69 (1H, dd, $^3J_{HH}$ 1.7, $^4J_{HH}$ 0.7 Hz, C**5**-H); ^{19}F NMR (376 MHz, $CDCl_3$): -193.48 (1F, d, $^1J_{HF}$ 48.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): 13.96 (CH_3), 62.79 (CH_2), 89.14 (d, $^1J_{CF}$ 196.9 Hz, CH-F), 112.97 (C**4**-H), 121.99

(d, $^{4}J_{CF}$ 6.1 Hz, C**3**-H), 148.60 (C**5**-H), 149.2d (d, $^{3}J_{CF}$ 1.5 Hz, C**2**-C), 164.46 (d, $^{2}J_{CF}$ 24.5 Hz, **C**=O), 177.56 (d, $^{2}J_{CF}$ 21.3 Hz, C=O); m/z (ESI): 201 (100 %, $[M+H]^{+}$), 173 (61 %, $[M-C_2H_4]^{+}$).

Bibliography

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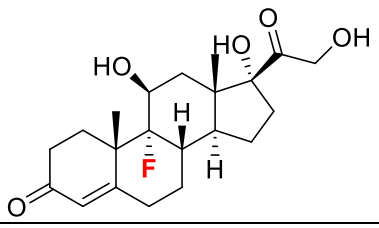
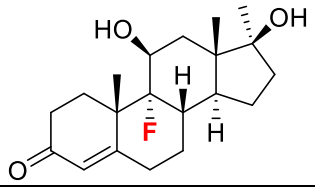
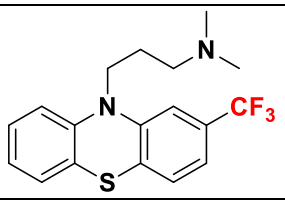
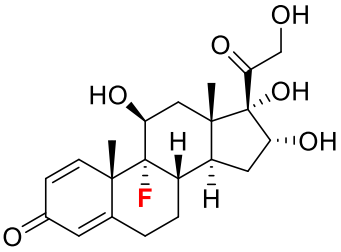
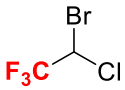
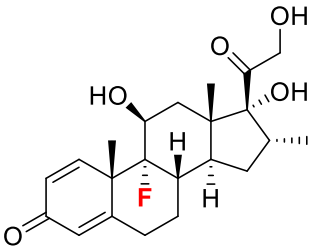
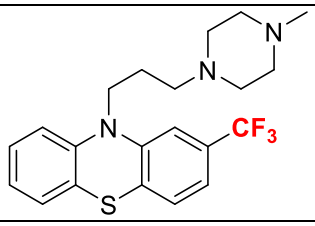
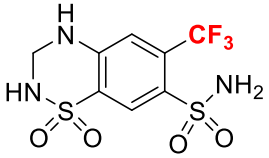
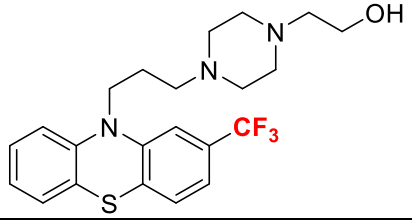
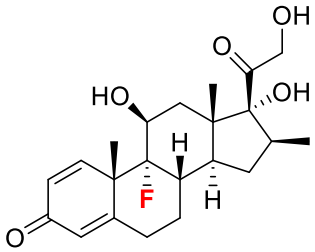
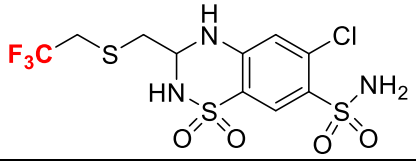
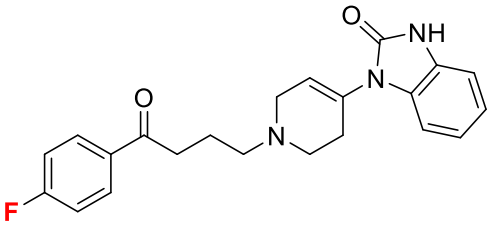
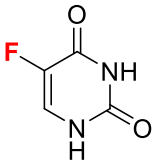
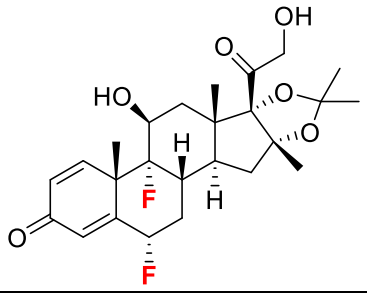
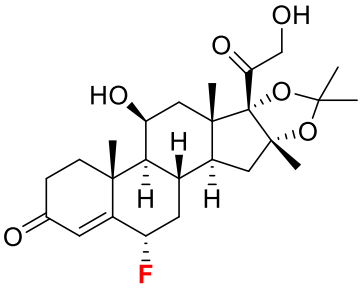
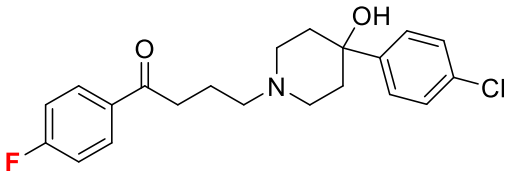
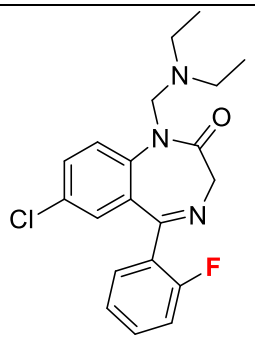
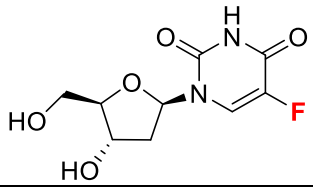
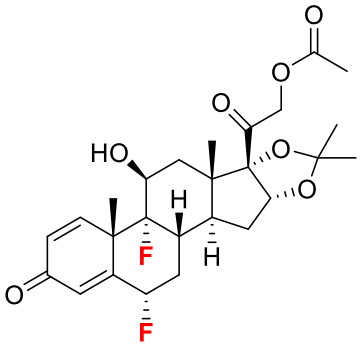
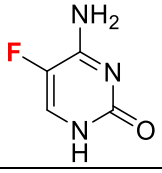
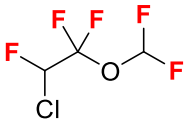
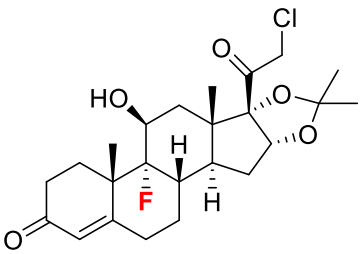
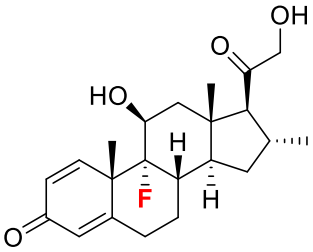
Appendix I.: X-ray Crystallography Data

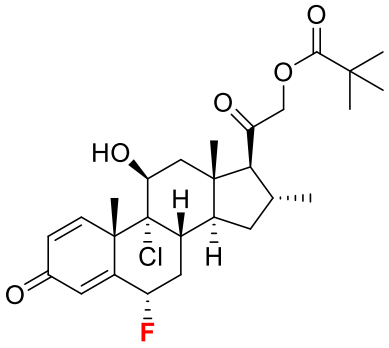
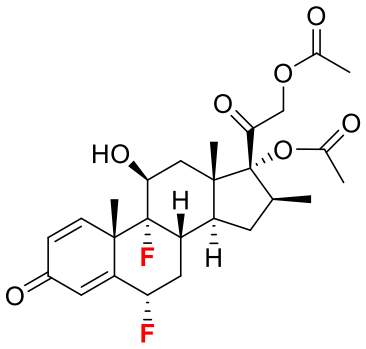
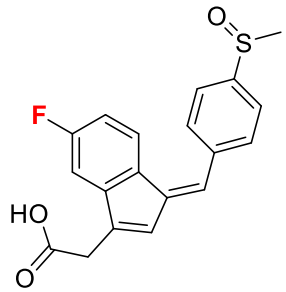
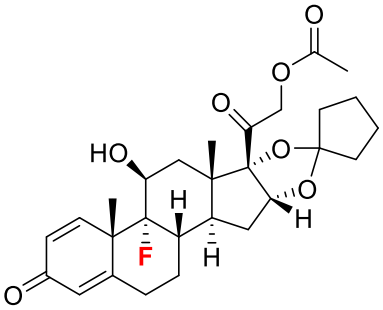
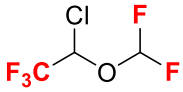
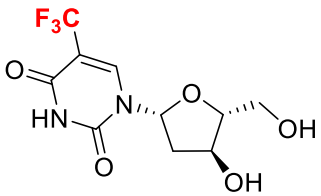
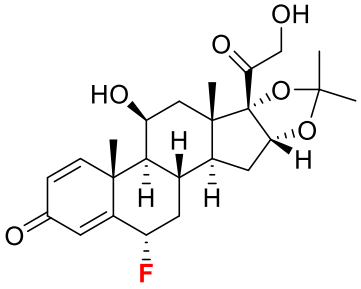
X-ray crystallographic data related to all compounds analysed can be found in the electronic appendix.

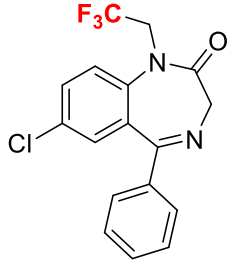
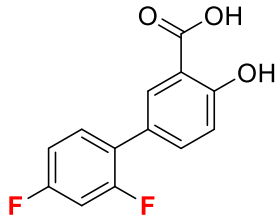
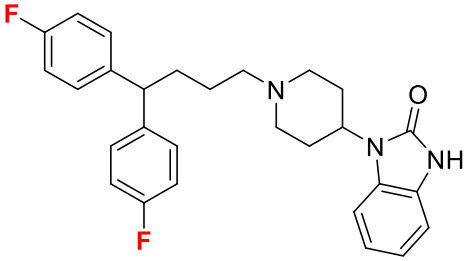
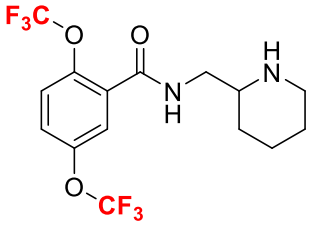
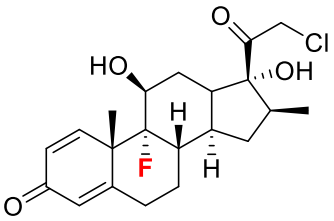
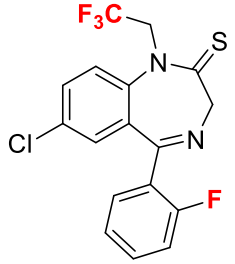
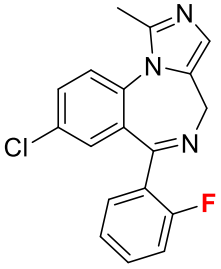
Appendix II. FDA Approved Fluorinated APIs

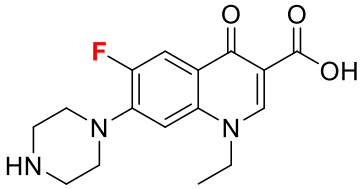
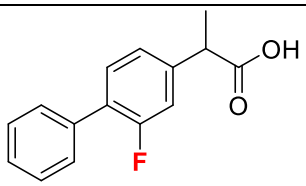
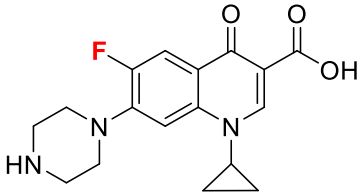
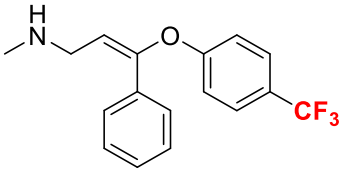
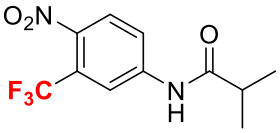
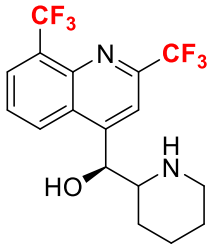
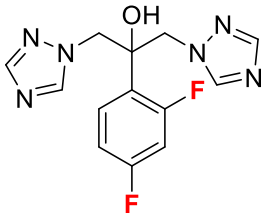
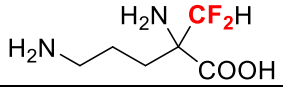
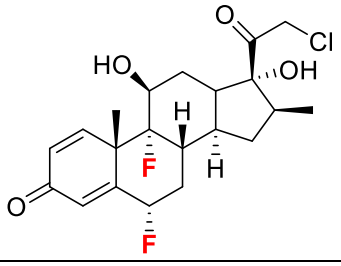
No	API name (use) [other]	Structure	FDA approval year
1	Fludrocortisone acetate		1955
2	Fluoxymesterone		1956
3	Triflupromazine		1957
4	Triamcinolone		1957
5	Halothane		1958
6	Dexamethasone		1958
7	Trifluoperazine		1959
8	Hydroflumethazide		1959

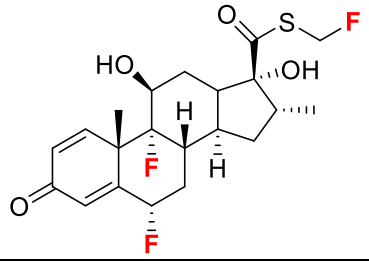
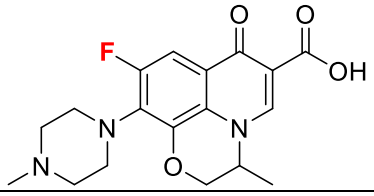
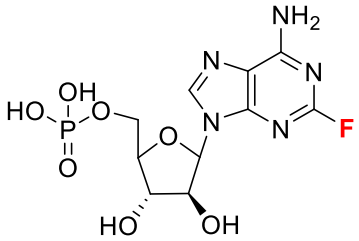
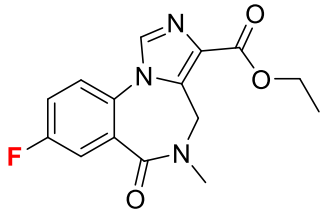
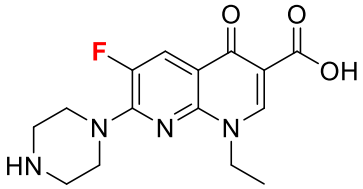
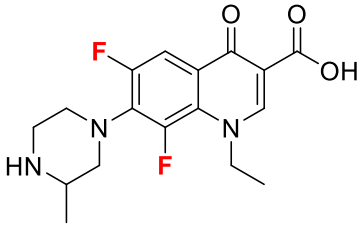
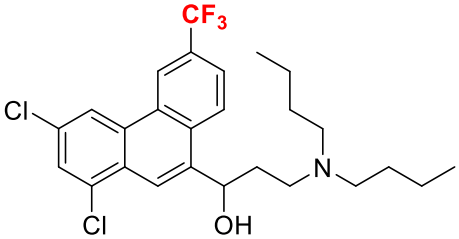
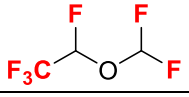
9	Fluphenazine		1959
10	Betamethazone		1961
11	Polythiazide		1961
12	Droperidol		1961
13	Fluorouracil		1962
14	Fluocinolone acetonide		1963
15	Flurandrenolide		1965
16	Haloperidol		1967

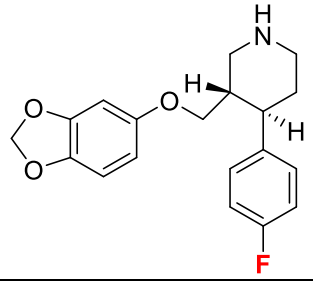
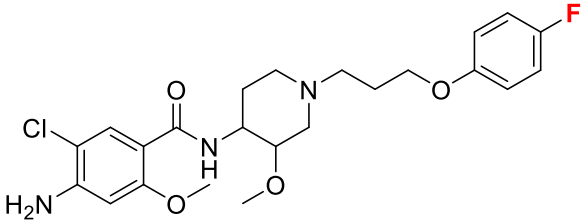
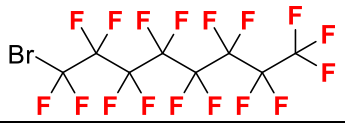
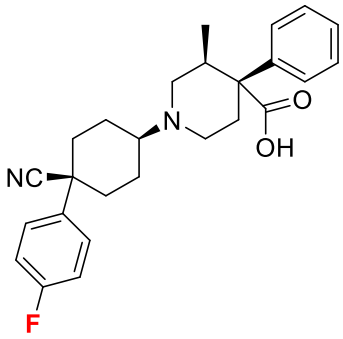
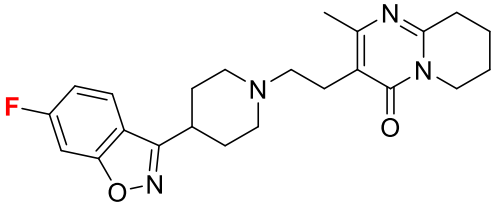
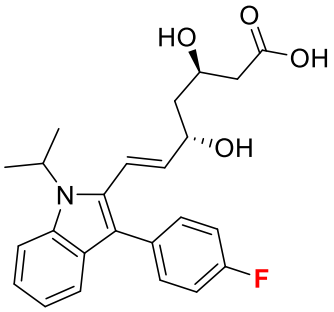
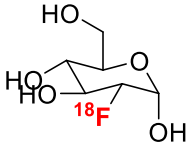
17	Flurazepam		1970
18	Fluoxuridine		1970
19	Fluocinonide		1971
20	Flucytosine		1971
21	Enflurane		1972
22	Halcinonide		1974
23	Desoxymethasone		1977

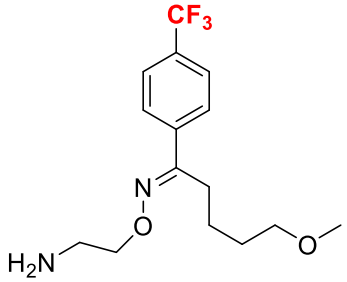
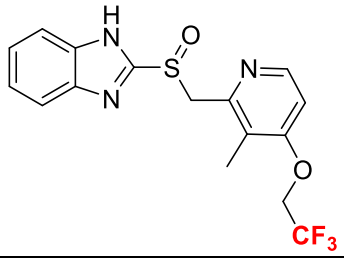
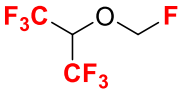
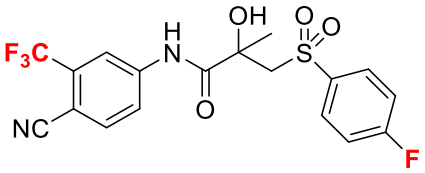
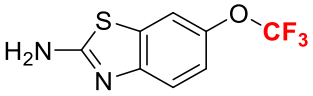
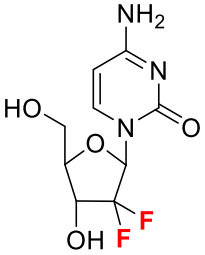
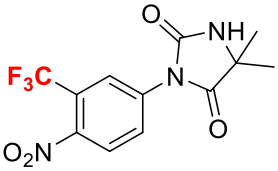
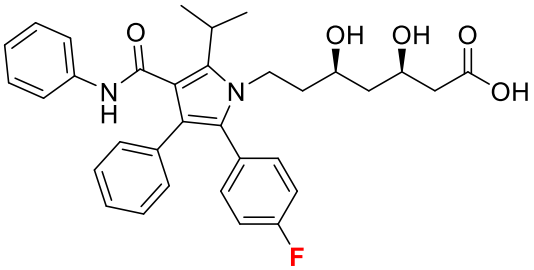
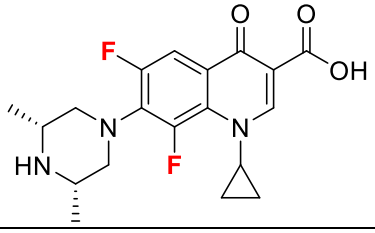
24	Clocortolone		1977
25	Diflorasone		1977
26	Sulindac		1978
27	Amcinonide		1979
28	Isoflurane		1979
29	Trifluridine		1980
30	Flunisolide		1981

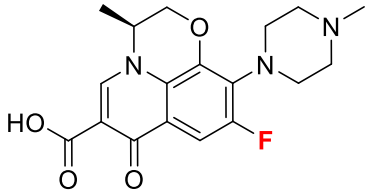
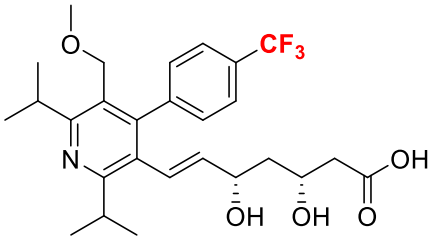
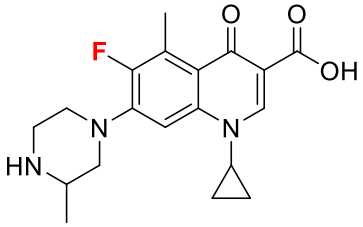
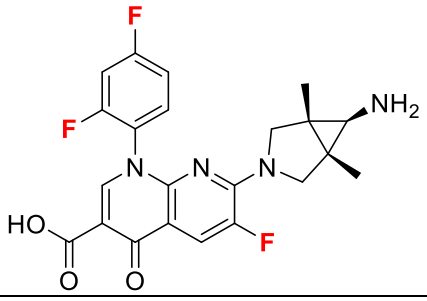
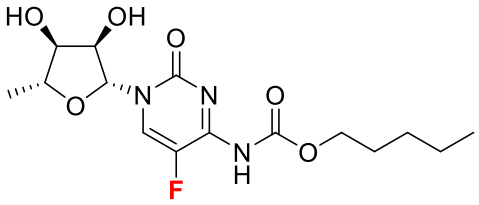
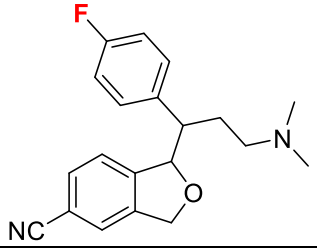
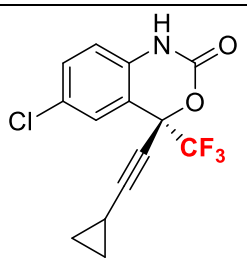
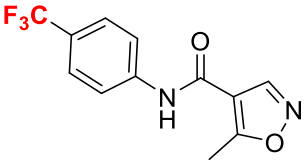
31	Halazepam		1981
32	Diflunisal		1982
33	Pimozide		1984
34	Flecainide		1985
35	Clobetasol		1985
36	Quazepam		1985
37	Midazolam		1985

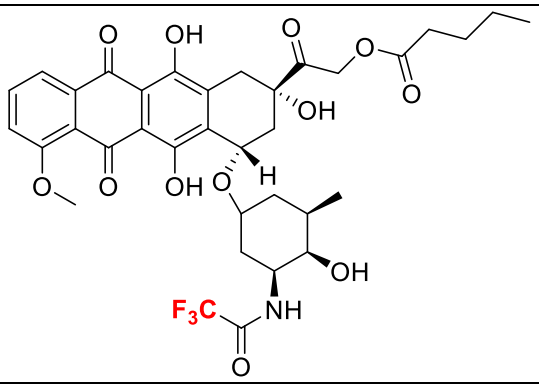
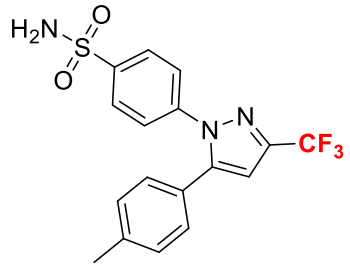
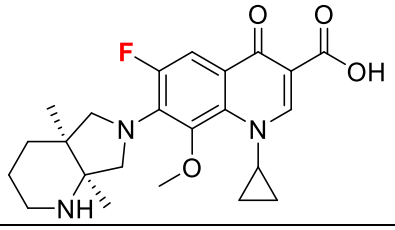
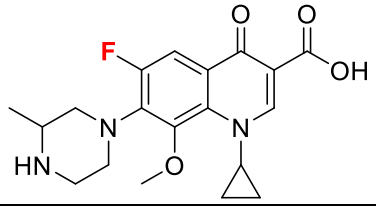
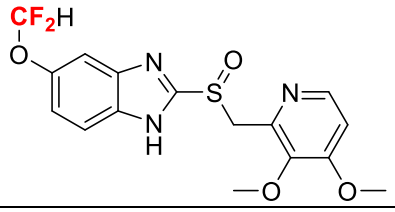
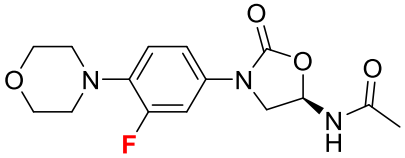
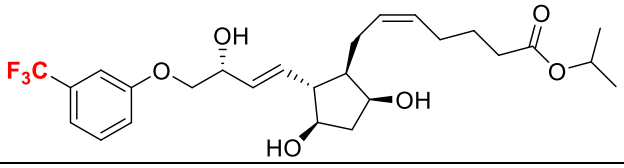
38	Norfloxacin		1986
39	Flurbiprofen		1986
40	Ciprofloxacin		1987
41	Fluoxetine		1987
42	Flutamide		1989
43	Mefloquine		1989
44	Fluconazole		1990
45	Eflornithine		1990
46	Halobetasol		1990

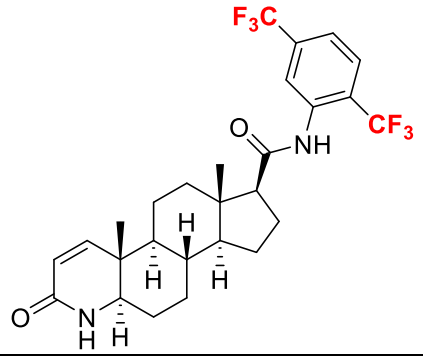
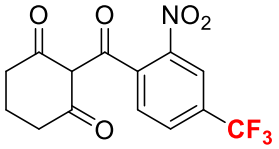
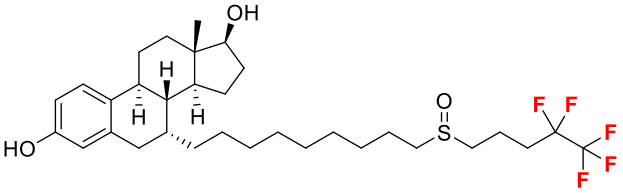
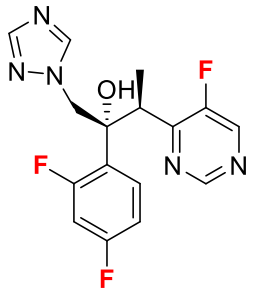
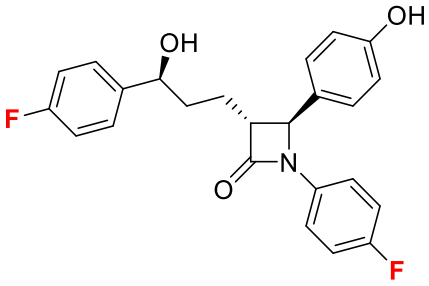
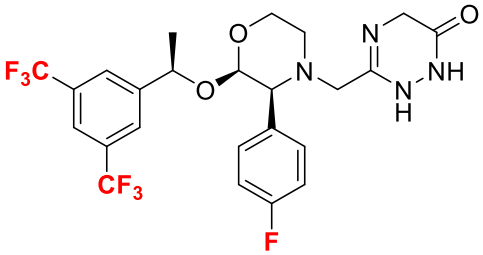
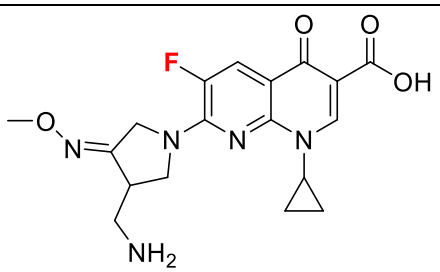
47	Fluticasone		1990
48	Ofloxacine		1990
49	Fludarabine		1991
50	Flumazenil		1991
51	Enoxacin		1991
52	Lomefloxacin		1992
53	Halofantrine		1992
54	Desflurane		1992

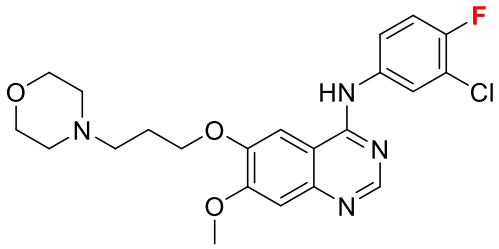
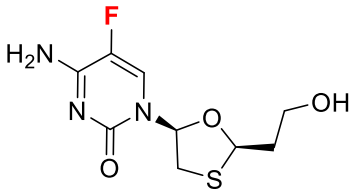
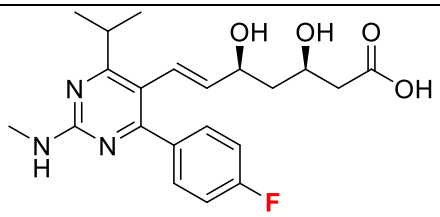
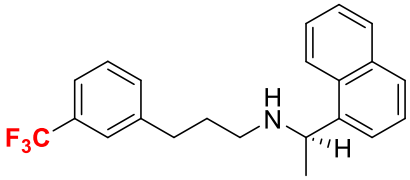
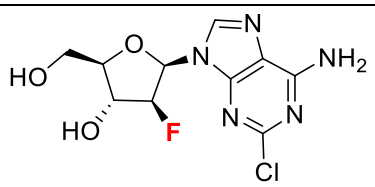
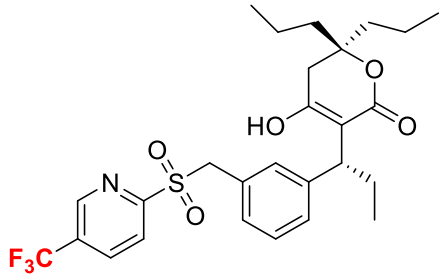
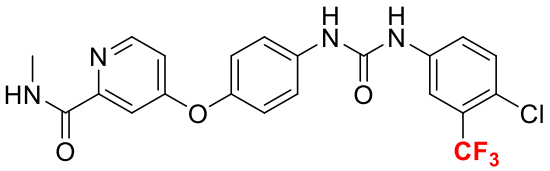
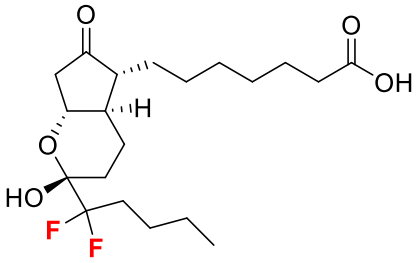
55	Paroxetine		1992
56	Cisapride		1993
57	Perfluobron		1993
58	Levocabastine		1993
59	Risperidone		1993
60	Fluvastatin		1993
61	^{18}F-deoxy glucose		1994

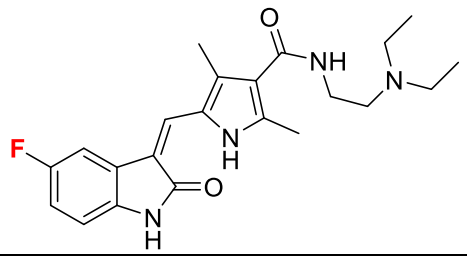
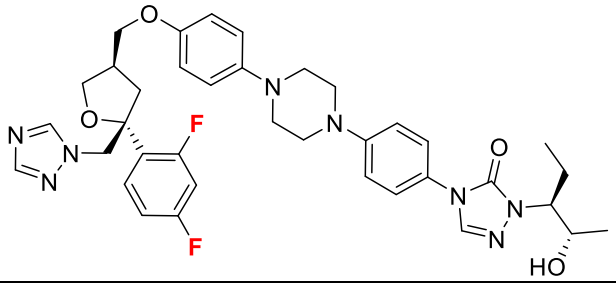
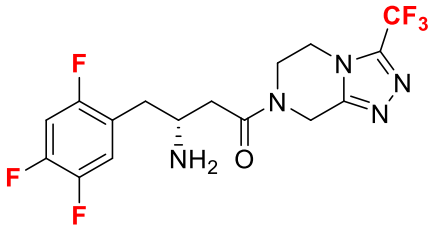
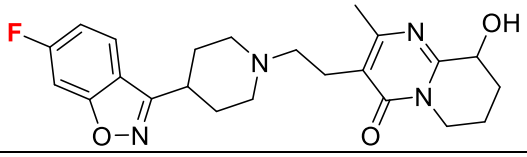
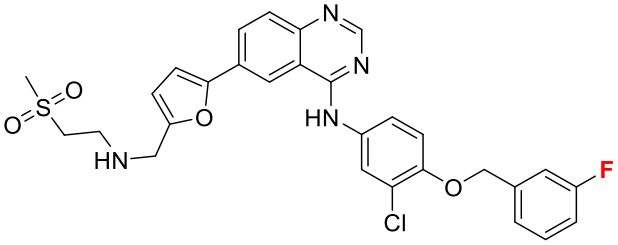
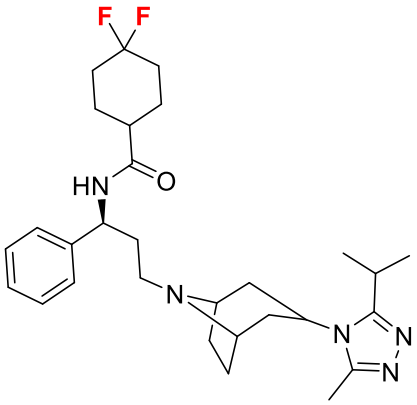
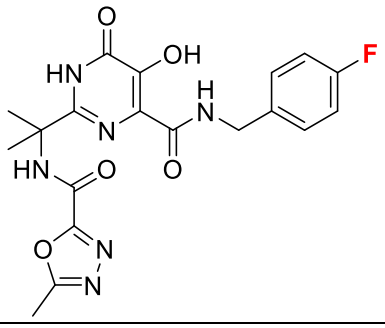
62	Fluvoxamine		1994
63	Lansoprazole		1995
64	Sevoflurane		1995
65	Bicalutamide		1995
66	Riluzole		1995
67	Gemcitabine		1996
68	Nilutamide		1996
69	Atorvastatin		1996
70	Sparfloxacin		1996

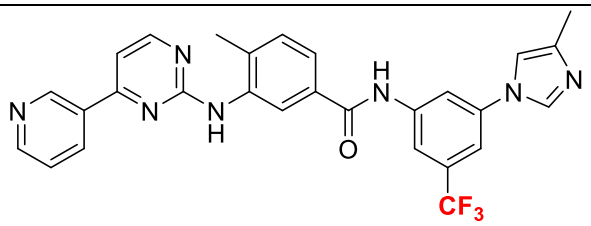
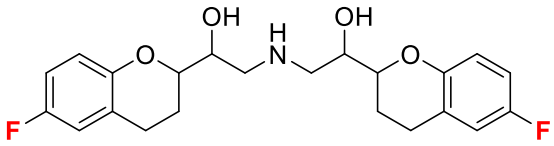
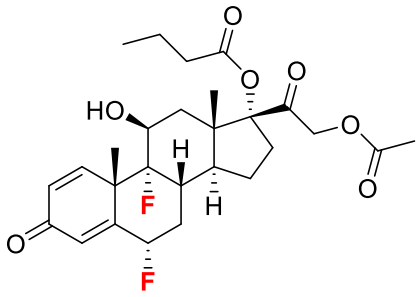
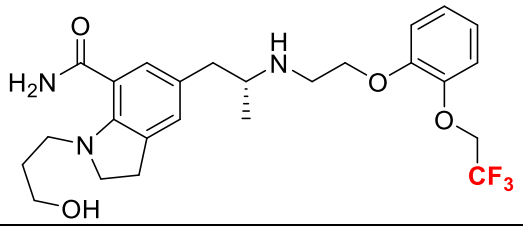
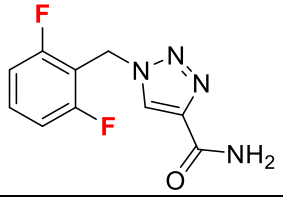
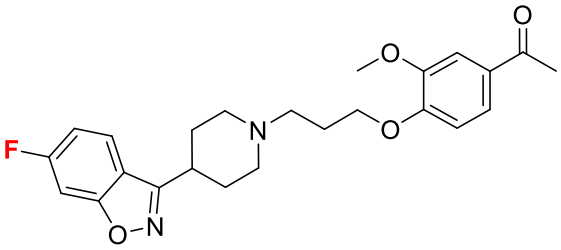
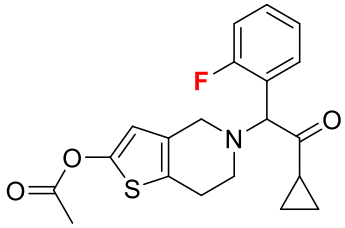
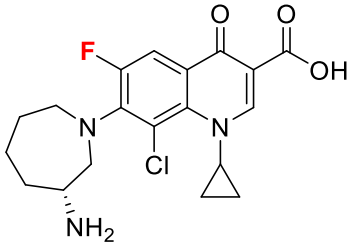
71	Levofloxacin		1996
72	Cerivastatin [Bayer]		1997
73	Grepafloxacin [GSK]		1997
74	Trovafloxacin [Pfizer]		1997
75	Capecitabine [Roche]		1998
76	Citalopram [Forest lab.]		1998
77	Efavirenz [Bristol-Meyers Squibb]		1998
78	Leflunomide [Sanofi]		1998

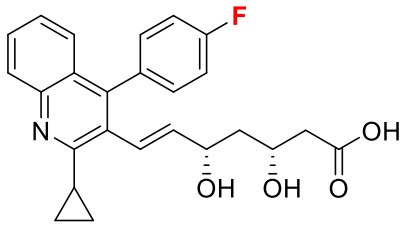
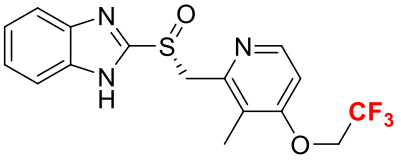
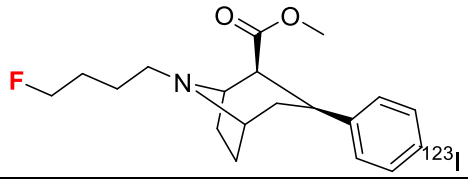
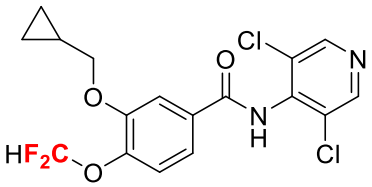
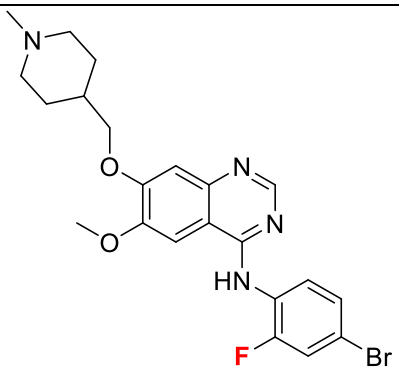
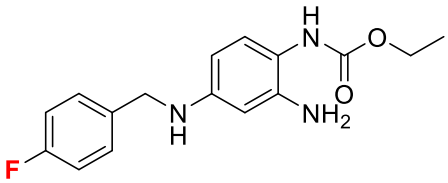
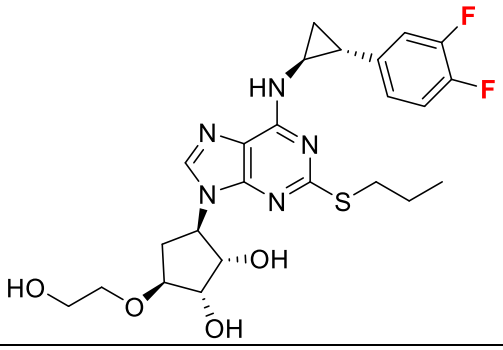
79	Valrubicin [Endo]		1998
80	Celecoxib [Pfizer]		1998
81	Moxifloxacin [Bayer]		1999
82	Gatifloxacin		1999
83	Pantoprazole []		2000
84	Linezolid [Upjohn]		2000
85	Travoprost [Alcon, now part of Novartis]		2001

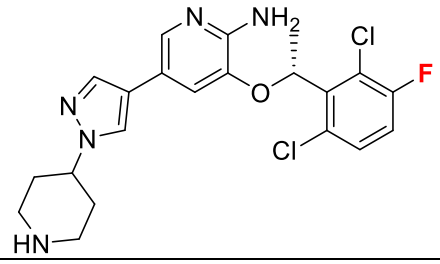
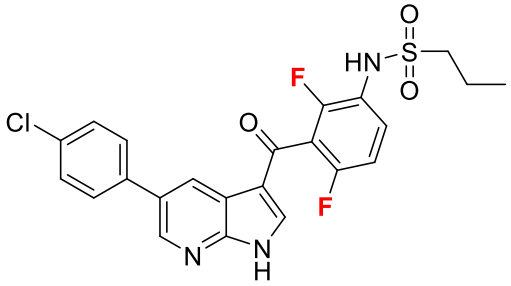
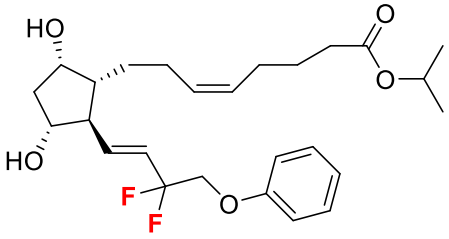
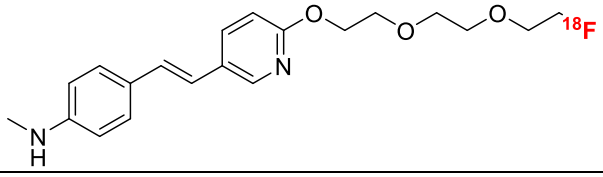
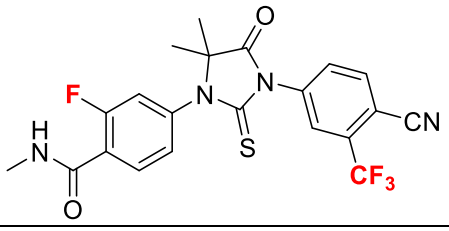
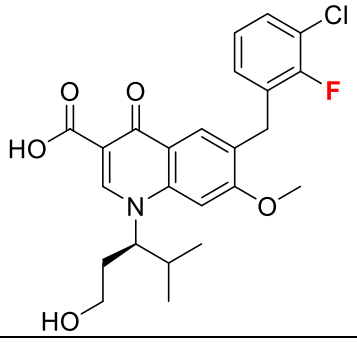
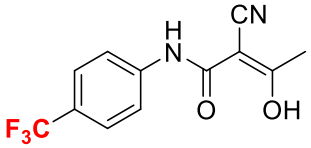
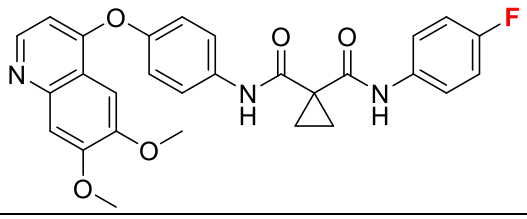
86	Dutasteride [GSK]		2001
87	Nitisinone [Sobi]		2002
88	Fulvestrant [AstraZeneca]		2002
89	Voriconazole [Pfizer]		2002
90	Ezetimbe [Merck & Co.]		2002
91	Aprepitant (antiemetic) [Merck]		2003
92	Gemifloxacin (antibacterial) [LG lifescience]		2003

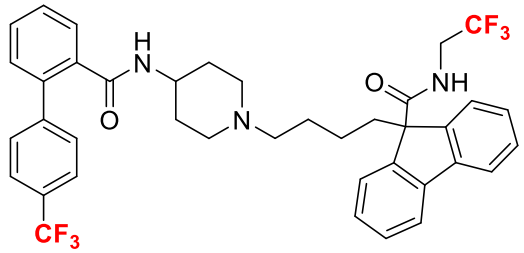
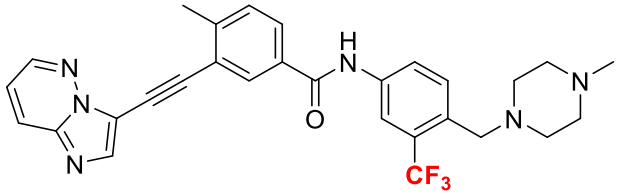
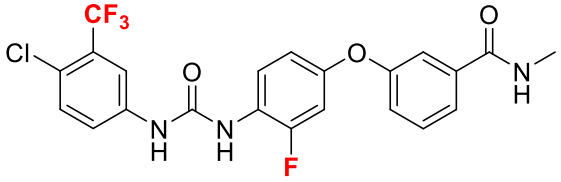
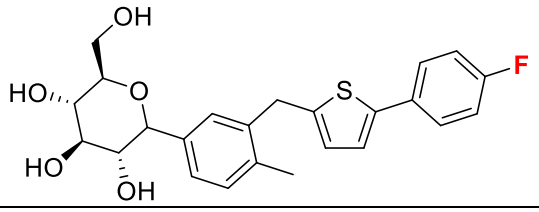
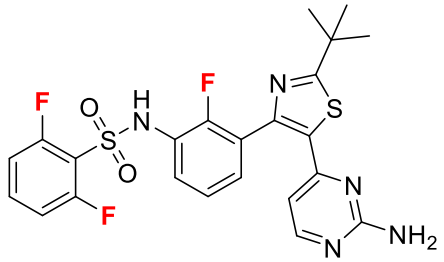
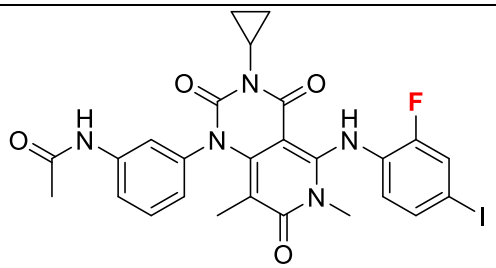
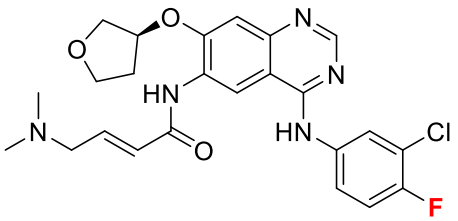
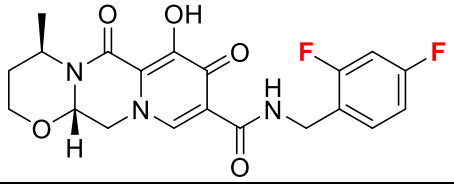
93	Gefitinib (cancer treatment) [AstraZeneca]		2003
94	Emtricitabine (HIV treatment) [Gilead]		2003
95	Rosuvastatin (cholesterol lowering) [AstraZeneca]		2003
96	Cinacalcet (hyperparathyroidism treatment) [Amgen]		2004
97	Clofarabine (leukaemia treatment) [Genzyme]		2004
98	Tipranavir (HIV treatment) [Boehringer-Ingelheim]		2005
99	Sorafenib (cancer treatment) [Bayer]		2005
100	Lubiprostone (constipation treatment) [Sucampo]		2006

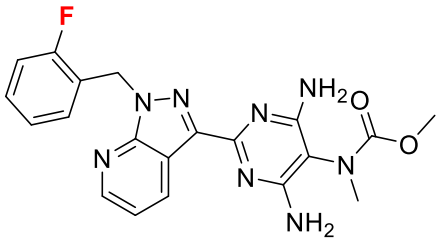
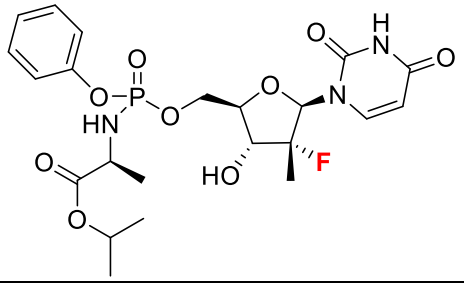
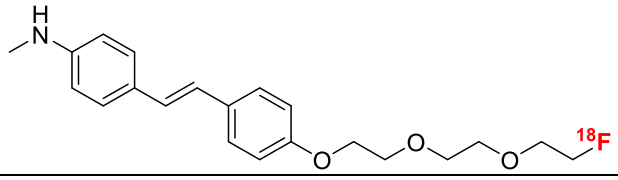
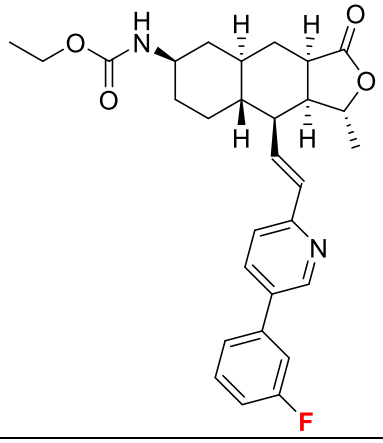
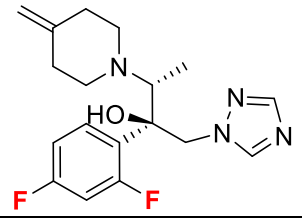
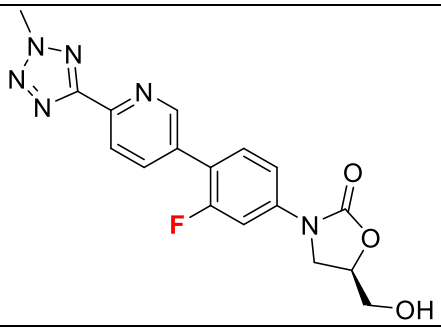
101	Sunitinib (cancer treatment) [Pfizer]		2006
102	Posaconazole (antifungal) [Schering Plough]		2006
103	Sitagliptin (Diabetes) [Merck Sharp Dohme]		2006
104	Paliperidone (Schizophrenia) [Janssen]		2006
105	Lapatinib (Cancer treatment) [GSK]		2007
106	Maraviroc (HIV treatment) [Pfizer]		2007
107	Raltegravir (HIV treatment) [Merck Sharp Dohme]		2007

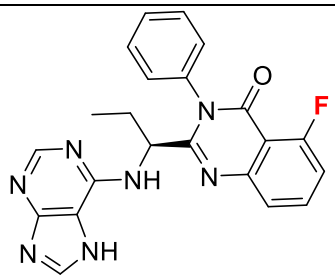
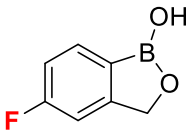
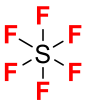
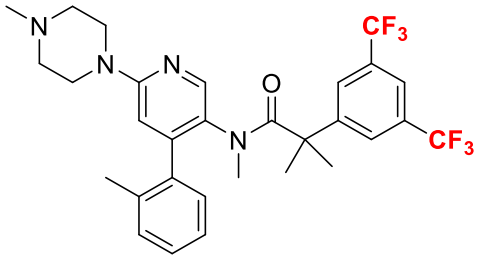
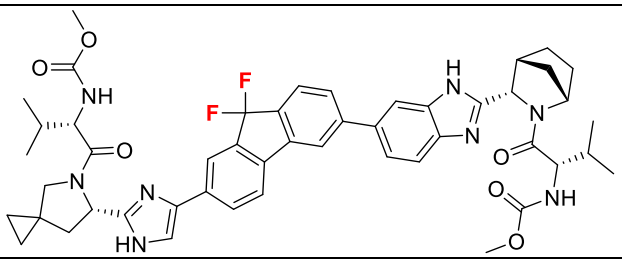
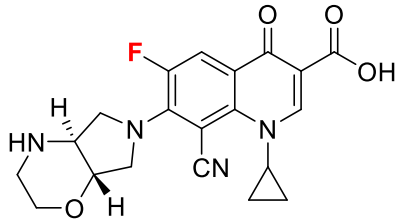
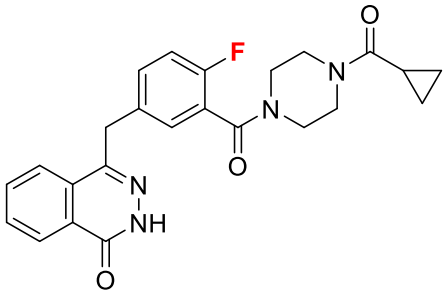
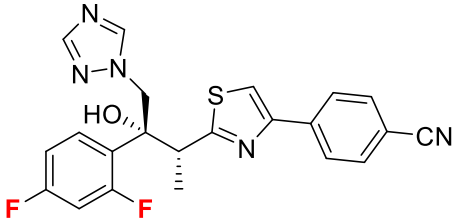
108	Nilotinib (leukaemia treatment) [Novartis]		2007
109	Nebivolol (β blocker) [Forest labs.]		2007
110	Difluprednate (anti-inflammatory, eye drops) [Alcon pharms.]		2008
111	Silodosin (prostate something) [Watson labs.]		2008
112	Rufinamide (epilepsy) [Eisai]		2008
113	Iloperidone (schizophrenia) [Novartis]		2009
114	Prasugrel (heart attack prevention) [Eli Lilly]		2009
115	Besifloxacin		2009

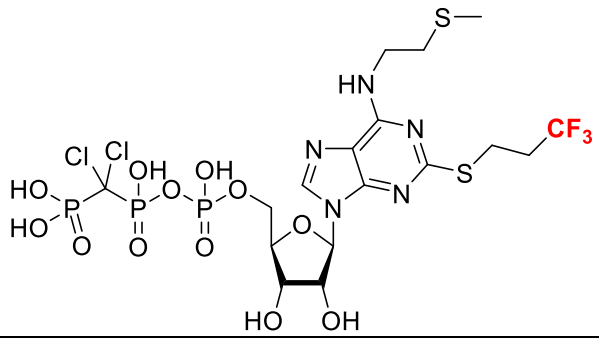
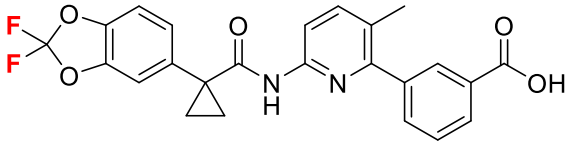
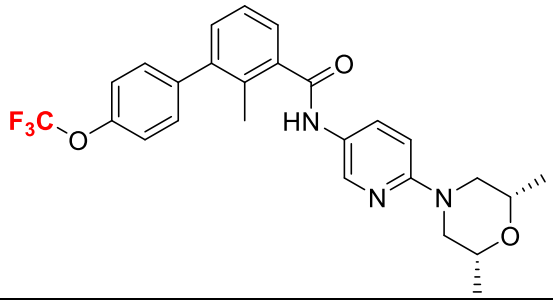
116	Pitavastatin (cholesterol lowering) [Kowa]		2009
117	Dexlansoprazole		2009
118	Ioflupane (Prkinson's disease diagnosis) [GE Healthcare]		2011
119	Roflumilast (COPD treatment) [Forest Res. Inst.]		2011
120	Vandetanib (Cancer treatment) [AstraZeneca]		2011
121	Ezogabine (epilepsy) [GSK]		2011
122	Ticagrelor (heart attack prevention) [AstraZeneca]		2011

123	Crizotinib (cancer treatment) [Pfizer]		2011
124	Vemurafenib (Cancer treatment) [Hoffman La Roche]		2011
125	Tafluprost (anti-inflammatory, eye drops) [Merck Sharp Dohme]		2012
126	Florbetapir (PET-tracer for Alzheimer's) [Avid Radiopharms]		2012
127	Enzalutamide (cancer treatment) [Astellas]		2012
128	Elvitegravir (HIV-1) [Gilead]		2012
129	Teriflunomide (multiple sclerosis) [Sanofi]		2012
130	Cabozantinib (cancer treatment) [Exelixis]		2012

131	Lomitapide (cholesterol lowering) [Aegerion]		2012
132	Ponatinib (leukaemia treatment) [Ariad]		2012
133	Regorafenib (cancer treatment) [Bayer Healthcare]		2012
134	Canagliflozin (Janssen)		2013
135	Dabrafenib (GSK)		2013
136	Trametinib (GSK)		2013
137	Afatinib (Boehringer)		2013
138	Dolutegravir (GSK?)		2013

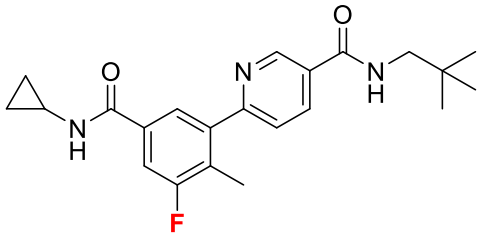
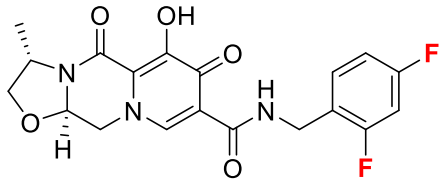
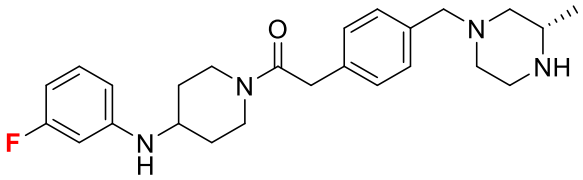
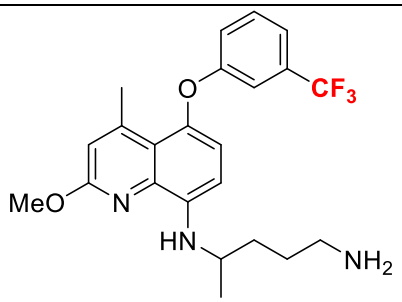
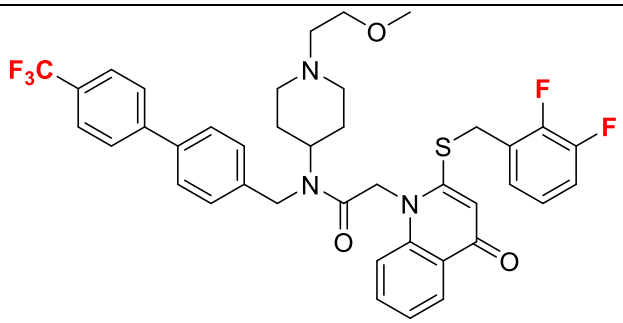
139	Riociguat (Bayer)		2013
140	Sofosbuvir (Gilead)		2013
141	Florbetaben		2014
142	Vorapaxar (Merck)		2014
143	Efinaconazole (Dow)		2014
144	Tedizolid (Cubist) antibacterial		2014

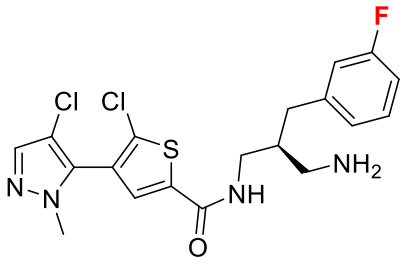
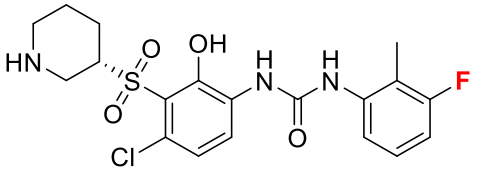
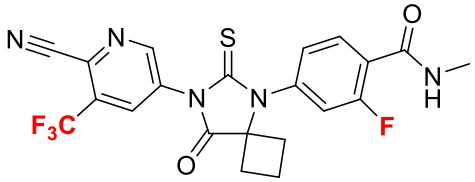
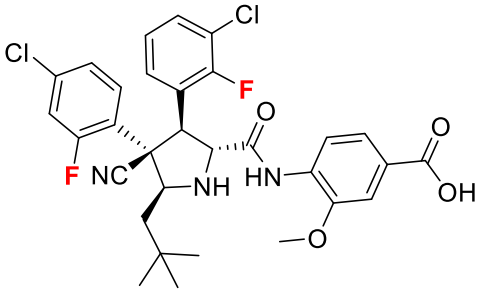
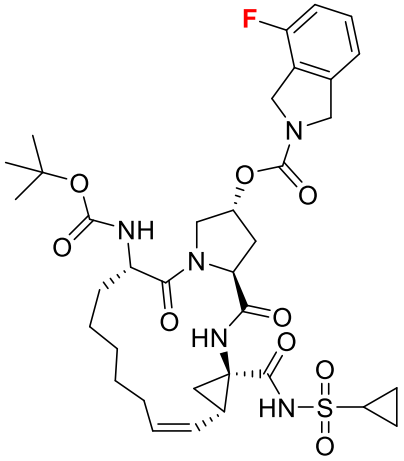
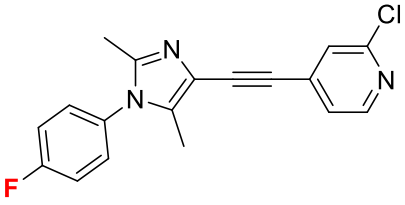
145	Lidelalisib (Gilead) leukaemia		2014
146	Tavaborol (Anachor) anti-fungal		2014
147	Sulfur hexafluoride (Bracco) MRI contrast		2014
148	Netupitant (Helsinn healthcare) oncology		2014
149	Ledipasvir (Gilead) Hep-C		2014
150	Finafloxacin (Alcon) Antibiotic		2014
151	Olaparib (AZ) oncology		2014
152	Isavuconazole (Astellas)		2015

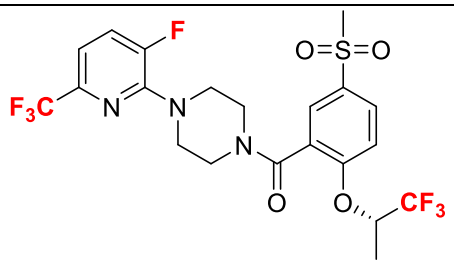
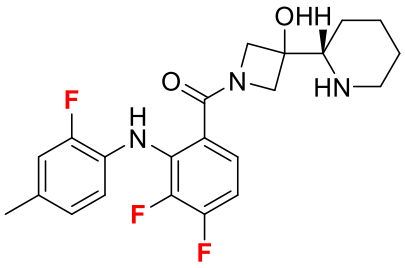
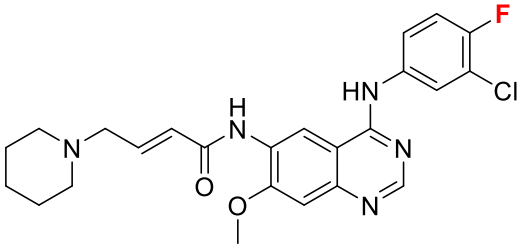
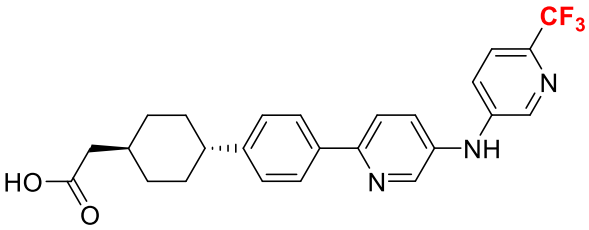
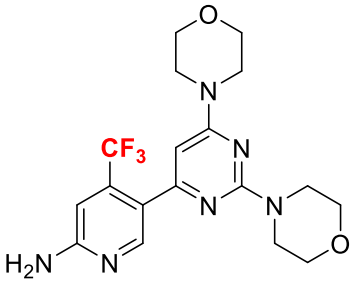
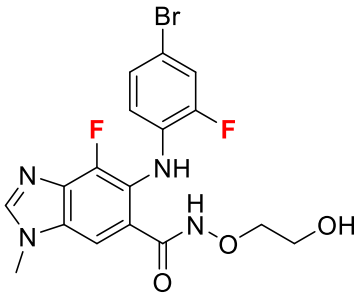
153	Cangrelor (Medicines Co.)		2015
154	Lumacaftor (Vertex, cystic fibriosis)		2015
155	Sonidegib (Novartis, cancer)		2015

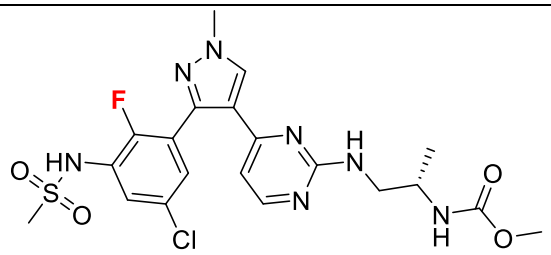
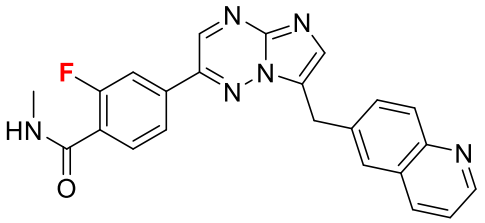
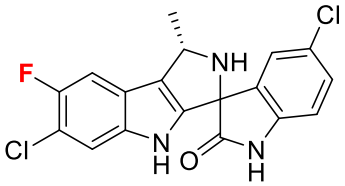
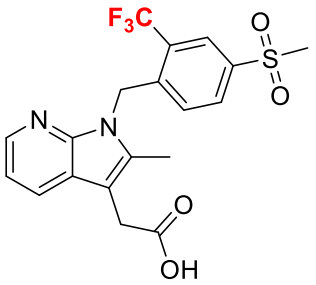
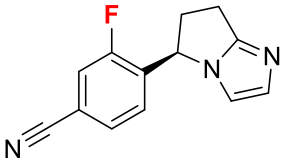
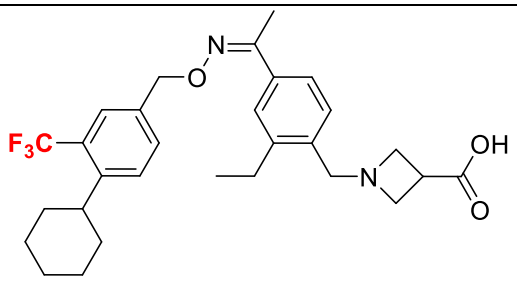
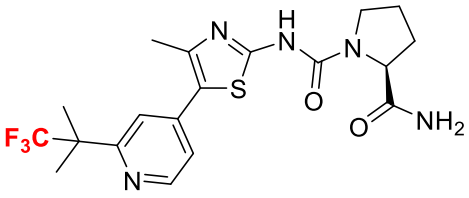
Appendix III. Fluorinated Compounds in Late Stage Clinical Trials

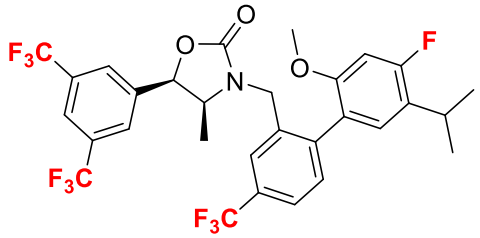
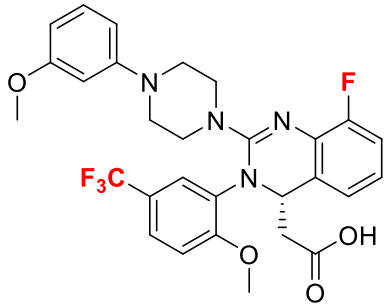
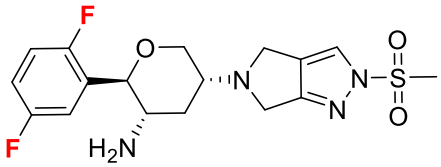
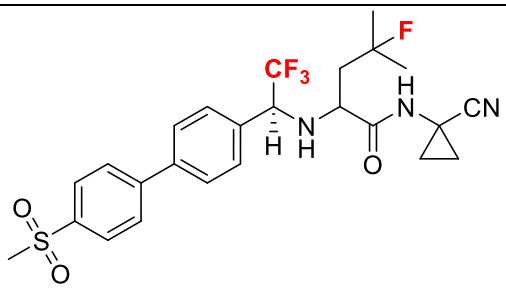
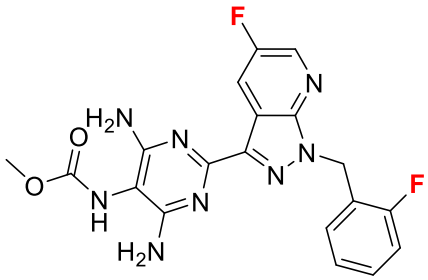
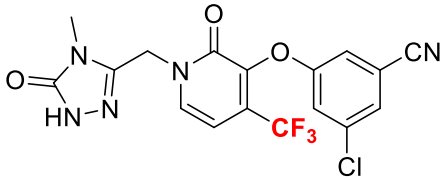
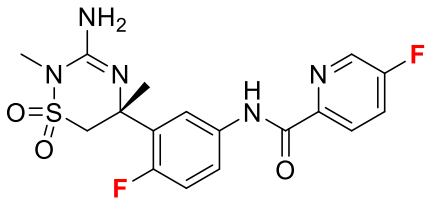
The following list contains the identifiable structures from the following companies' pipeline: J&J, Pfizer, Novartis, Roche, Sanofi, Merck, GSK, Bayer, BMS, AbbVie, Eli Lilly, AZ, Takeda, Astellas, Gilead, Celgene, Vertex. Data is accurate as of 2/9/15.

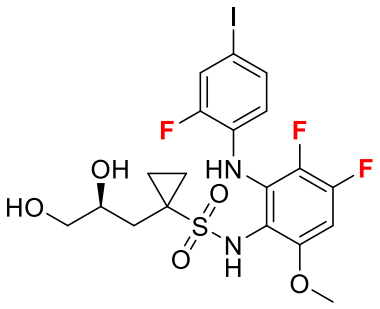
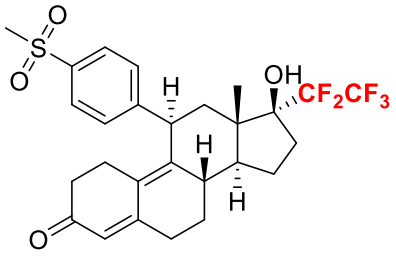
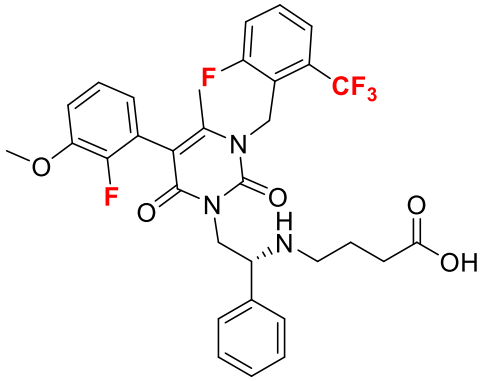
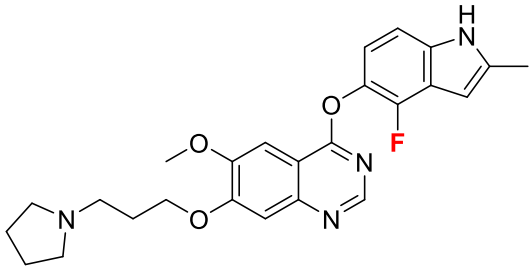
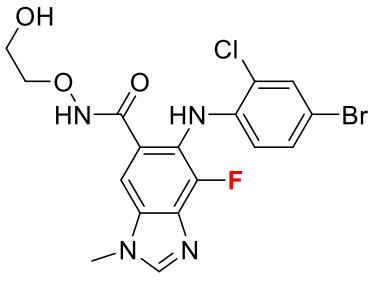
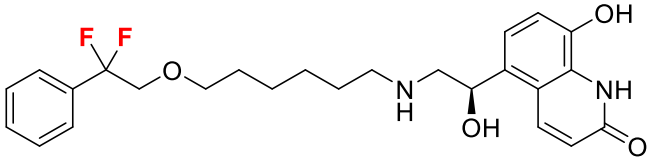
Name	Structure	Other data
Losmapimod		GSK Phase II. for COPD also for Acute Coronary Syndrome
Cabotegravir		GSK Phase II. HIV
Camicinal		GSk Phase II. Gastroparesis
Tafenoquine		GSK Phase III. Anti-malaria
Rilaplidib		GSK Phase II. Alzheimer's

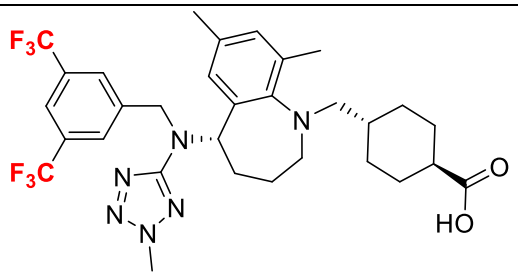
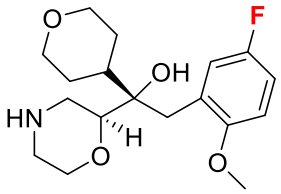
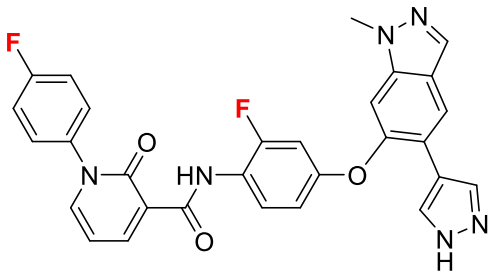
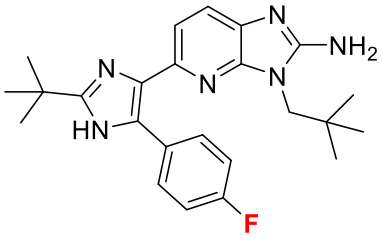
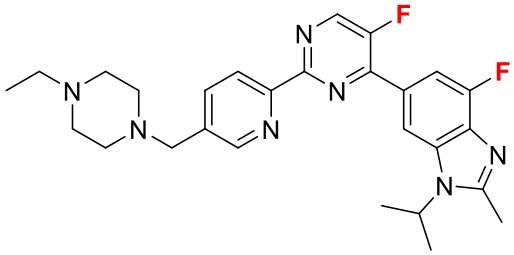
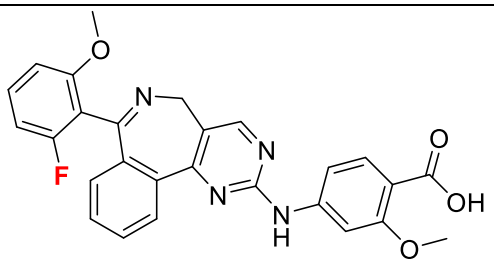
Afuresertib		GSK Phase I. multiple myeloma
Danirixin		GSK Phase II. COPD
JNJ56021927		J&J Phase III. Prostate cancer
Idasanutlin		Roche Phase I. Oncology
Danoprevir		Roche Phase II. Hep. C
Basimglurant		Roche (Phase 2) Anti-depressant

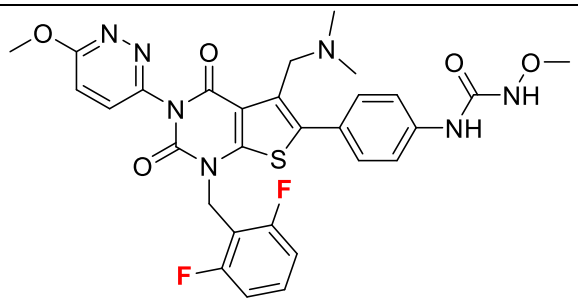
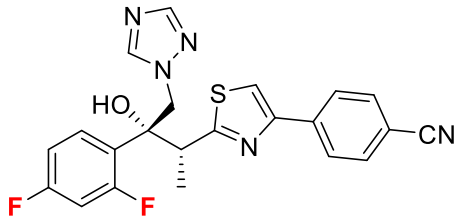
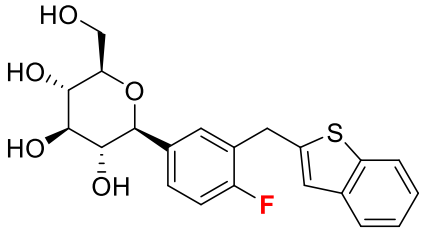
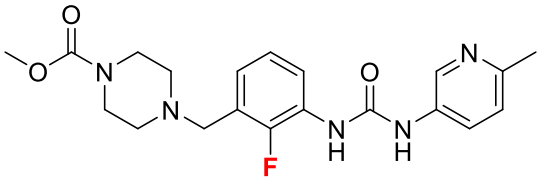
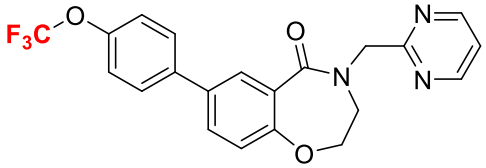
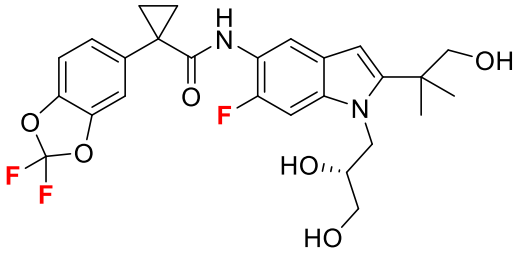
Bitopertin		Roche Phase II. neuroscience
Cobimetinib		Roche Phase II. Oncology
Dacomitinib		Pfizer Phase III. Oncology
Pradigastat		Novartis Phase III. familial chylomicronaemia syndrome (Phase 3)
Buparlisib		Novartis Breast cancer
Binimetinib		Novartis (Phase 3) Melanoma

Encorafenib		Novartis (Phase 3) Melanoma
Capmatinib		Novertis (Phase 2) Oncology
Cipargamin		Novartis anti-malaria (Phase 2)
Fevipiprant		Novartis Respiratory (Phase 2)
Osilodrostat		Novartis (Phase 3) Cushing's
Siponimod		Novartis Phase III. MS
Alpelisib		Novartis (Phase 1) Solid tumors

Anacetrapib		Merck Phase III. cholesterol and cardiovascular disease
Letermovir		Merck (Phase 3) Anti-viral
Omarigliptin		Merck (Phase 3) Diabetes
Odanacatib		Merck Phase III. Osteoporosis
Vericiguat Riociguat		Merck + Bayer (Phase 2) Heart failure
Doravirine		Merck (Phase 3) Antiviral
Verubecestat		Merck (Phase 3) Alzheimers

Refametinib		Bayer Phase II. Cancer
Vilaprisan		Bayer (Phase 2)
Elagolix		AbbVie Phase III. Endometriosis
Cediranib		AZ Phase III. Oncology
Selumetinib		AZ Phase III. various cancers
Abediterol		AZ Phase 2 COPD

Evacetrapib		Ely Lilly Phase III. cardiovascular
Edivoxetine		Eli Lilly Phase II. antidepressant
Merestinib		Eli Lilly (Phase 2) Oncology
Ralimetinib		Eli Lilly (Phase 2) oncology
Abemaciclib		Eli Lilly Phase II. Breast cancer
Alisertib		Takeda Phase II. cancer (T cell lymphoma)

Relugolix		Takeda Phase II. Endometriosis
Isavuconazole		Astellas Phase III. Antifungal
Ipragliflozin		Astellas Phase III. type 2 diabetes
Omecamtiv		Amgen Cardiac
Eleclazine		Gilead (Phase 2)
VX-661		Vertex Phase 3