Fluorine-Containing Diazines in Medicinal Chemistry and Agrochemistry

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Abstract  The combination of a fluorine atom and a diazine ring, which both possess unique structural and chemical features, can generate new relevant building blocks for the discovery of efficient fluorinated biologically active agents. Herein we give a comprehensive review on the biological activity and synthesis of fluorine containing, pyrimidine, pyrazine and pyridazine derivatives with relevance to medicinal and agrochemistry.

Keywords  Pyrimidine • Pyrazine • Pyridazine • Fluorine • Bioactive compounds • Medicinal chemistry • Agrochemistry

Abbreviations

AHAS  acetohydroxy acid synthase
ATP  adenosine triphosphate
B₂(Pin)₂  Bis(pinacolato)diboron
BCR  B-cell receptor
Boc  tert-butoxycarbonyl
BOP  benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
Bu  Butyl
CDK  cyclin-dependent kinase
CDMT  2-chloro-4,6-dimethoxy-1,3,5-triazine
CLL  chronic lymphocytic leukemia
CNS  central nervous system
CSA  camphorsulfonic acid
CyJohnPhos  2-(dicyclohexyl-phosphino)biphenyl
DAST  diethylaminosulfur trifluoride
Dbap  Dibenzylideneacetone
DHFU  Dihydrofluourouracil
DIC  diisopropyl carbodiimide
DIBAL  diisobutylaluminium hydride
DIPEA  ethyl diisopropyl amine
DMF  Dimethylformamide
DMSO  dimethyl sulfoxide
DNA  deoxyribonucleic acid
dppe  bis(diphenylphosphino)ethane
Dppf  1,1'-bis(diphenylphosphino)ferocene
DPP-4  dipeptidyl peptidase
dTMP  deoxythymidine monophosphate
dUMP  deoxyuridine monophosphate
EPA  environmental protection agency
FDA  Food and Drug Administration
FdUDP  fluorodeoxyuridine diphosphate
1 Introduction

Diazenes are aromatic six-membered heterocycles that contain two sp²-hybridized nitrogen atoms in the ring. The three diazene isomers are pyridazine (1,2-diazine), pyrimidine (1,3-diazine) and pyrazine (1,4-diazine). The most important naturally occurring diazenes are the pyrimidine bases uracil, thymine, and cytosine, which comprise the fundamental nucleoside building blocks in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Pyrazines occur frequently as
constituents in foodstuffs and are responsible for their flavor and strong aroma. Although being present in very small amounts, they are highly odiferous and can be detected at extremely low concentrations. Unlike other heterocycles found in many important natural products, pyridazines were discovered only after 1970, and relatively few pyridazines have thus far been isolated from natural sources. As synthetic compounds, all diazines constitute an important pharmacophoric moiety present in many drugs acting on various pharmacological targets as well as agrochemicals.

Inspite of organofluorine compounds are almost absent as natural products, ~25 % of drugs in the pharmaceutical pipeline and ~15 % of agrochemicals contain at least one fluorine atom. One of the earliest synthetic fluorinated drugs is the antineoplastic agent 5-fluorouracil, derivative of pyrimidine, an antimetabolite first synthesised in 1957. Since the advent of 5-fluorouracil, fluorine substitution is commonly used in contemporary medicinal and agrochemistry to improve metabolic stability, bioavailability and protein–ligand interactions. In this review only compound bearing fluoro or fluoroalkyl substituent in diazine ring are discussed. Among fluorine-containing diazines now 12 drugs and 10 agrochemicals are presented on the market. This review provides an information about fluorinated diazines as drugs or agrochemicals and their mode of action as well as synthesis. The review is divided in two parts. First part dedicated to the medicinal and synthetic chemistry of fluorinated diazines that have reached at least clinical development phase. The second one dedicated to the biological role and the chemistry of the marketed agrochemicals based on fluorinated diazines.

## 2 Fluorine-Containing Diazines in Medicinal Chemistry

It is widely accepted that compounds containing fluorine atoms have a remarkable record in medicinal chemistry and play a continuing role in providing lead compounds for potential therapeutic applications. The reasons for that have been discussed extensively in a number of books and reviews [1, 2]. In this view, fluorine-containing diazines are not the exception; they have attracted attention of medicinal chemists since 1950s when Fluorouracil (1) was introduces as anti-cancer drug. Analysis of MDDR (MDL Drug Data Report) data retrieved 1,150 hits derived from fluorine-containing diazines [3]. Nearly a third part of them is represented by anti-cancer agents (Fig. 1); other important classes (more than 100 examples) include compounds with antiviral (mainly anti-HIV) and antiarthritic activity.

According to MDDR, 106 compounds containing a fluorinated diazine moiety have entered pre-clinical studies, 40 of them have reached clinical phase, and 12 of these have become drug substances (Fig. 2). In the following sections, fluorine-containing diazine derivatives that have reached at least clinical development phase will be discussed, focusing on their aspects related to medicinal and synthetic organic chemistry.
3 Anti-cancer Agents

3.1 Fluorouracil and Floxuridine

The use of fluorinated diazines as anti-cancer agents is the major field of their application in medicinal chemistry. The first representative of this class, Fluorouracil (1) was developed by Charles Heidelberger and co-workers in 1957 [4]. It was approved by U.S. FDA [5] in 1962 as antineoplastic agent in the treatment of advanced colorectal cancer. Fluorouracil represents a class of rationally designed anticancer agents which act as antimetabolites. The observation that rat hepatomas utilized radiolabeled uracil more avidly than normal tissues [6] implied that the enzymatic pathways for utilization of uracil or its close analogs differed between malignant and normal cells – a feature which might provide a target for antimetabolite chemotherapy. A minimal modification of uracil by introducing a single fluorine atom allowed for implementation of cellular uptake and metabolic activation of 1 via the same transport processes and enzymes involved in the case of uracil. However, in the case of essential biological targets, remarkable differences are observed due to unique properties of the fluorine atoms, which result in inhibition of the metabolic and signal pathways involved. Although all the details of the mechanism by which Fluorouracil gives its biological effect are not elucidated, a remarkable progress has been made over the past half a century in elucidating its cellular and clinical pharmacology [7, 8].
The key steps in Fluorouracil metabolism are shown in Scheme 1. Up to 80% of 1 administered as injection is transformed to dihydrofluorouracil (DHFU, 13) by dihydropyrimidine dihydrogenase (mostly in liver tissues). However, this metabolite is not involved into antineoplastic activity; instead, 13 itself and its further metabolites are responsible for most of the toxic effects of 1. The main mechanism of activation of Fluorouracil is conversion to fluorouridine monophosphate (FUMP, 14), either directly by orotate phosphoribosyltransferase, or via fluorouridine (FUR, 15) through the sequential action of uridine phosphorylase and uridine kinase. 14 is then phosphorylated to give fluorouridine diphosphate (FUDP, 16), which can be either phosphorylated again to the active metabolite fluorouridine triphosphate (FUTP, 19), or reduced to fluorodeoxuryridine diphosphate (FdUDP, 18) by ribonucleotide reductase. In turn, 18 can either be dephosphorylated or phosphorylated to generate
the active metabolites fluorodeoxyuridine monophosphate (FdUMP, 19) and fluorodeoxyuridine triphosphate (FdUTP, 19), respectively.

An alternative activation pathway involves the thymidine phosphorylase catalysed conversion of 1 to Floxuridine (FUDR, 4), which is then phosphorylated by thymidine kinase to give 19. The metabolite of 1 – Floxuridine – is itself used as an anti-cancer agent [9]. It was launched in 1970 by Hospira Inc [5]. Upon rapid injection, most of Floxuridine is catabolized to Fluorouracil; hence similar effects on the organism are obtained in this case. On the contrary, when 4 is slowly administered into the arterial blood, it is mostly transformed to 19; thus toxic effects are diminished comparing to 1 [10].

It has long been recognized that one of the main mechanisms underlying Fluorouracil action is inhibition of thymidylate synthase by fluorodeoxyuridine monophosphate

**Scheme 1** Metabolism of Fluorouracil (active metabolites are shown in bold)
Thymidylate synthase belongs to a class of enzymes required for DNA replication, and its activity is higher in rapidly proliferating cells. In particular, thymidylate synthase is responsible for methylation of deoxyuridine monophosphate (dUMP, 21) to deoxythymidine monophosphate (dTMP, 22) with the use of 5,10-methylenetetrahydrofolate (23) as a cofactor (Scheme 2) [12]. With fluorodeoxyuridine monophosphate, a slowly-reversible ternary complex 24 is formed instead. Inhibition of thymidylate synthase leads to deoxyribonucleotide imbalance, and hence to interference with DNA synthesis and repair. Alternative mechanism of DNA-directed Fluorouracil effect is misincorporation of fluorodeoxyuridine triphosphate (20) into DNA. Analogously, fluorouridine triphosphate (17) is extensively incorporated into different RNA species, disrupting their normal processing and function [7, 8, 11].

Scheme 2  Thymidylate synthase inhibition by fluorodeoxyuridine monophosphate (19)

Two principal approaches were used for the preparation of Fluorouracil (Scheme 3). One of the first methods [13, 14] commenced from ethyl fluoroacetate which was subjected to Claisen condensation with ethyl formate to give 25. The salt 25 was
introduced into reaction with S-alkylisothiourea to give fluoropyrimidines 26, which were hydrolysed to give 1. Several variations of this method were also described; their common drawback was the use of highly toxic fluoroacetic acid derivatives.

Scheme 3 Syntheses of Fluorouracil (1)

In an alternative approach, Fluorouracil was prepared by direct fluorination of different pyrimidine derivatives, including uracil [15], cytosine [16], and orotic acid [17]. In the latter method, the initially obtained fluoroorotic acid 27 was subjected to decarboxylation. The use of two-step reaction sequence was claimed to be advantageous due to simplified product isolation and purification.

Early synthesis of Floxuridine commenced from Fluorouracil (1) which was transformed into its mercury salt 28 and then allowed to react with 2-deoxy-D-ribofuranosyl chloride derivative 29 (Scheme 4) [18]. The product 30 was subjected to alkaline hydrolysis to give Floxuridine (4).

Scheme 4 Syntheses of Floxuridine (4)
As in the case of Fluorouracil, newer syntheses of Floxuridine relied on direct fluorination of uracil derivatives. Fluorination of uridine $^{31}$ was done using fluorine $^{[19]}$, acetyl fluoride $^{[20]}$, and CF$_3$OF $^{[21]}$. The latter reagent gave good but still moderate yield of the product $^4$ (47 %). The use of a two-step reaction sequence, i.e. fluorination of diacetoxy derivative $^{32}$ and hydrolysis, improved the yield of $^4$ to 82 % over two steps $^{[21, 22]}$.

### 3.2 Prodrugs of Fluorouracil

Despite Fluorouracil remains the main agent for the treatment of certain cancer types (i.e. colorectal) $^{[23]}$, it displays various side effects due to its nonspecific cytotoxicity, poor distribution to tumor sites, and serious limitations in effectiveness due to drug resistance. Apart from modulation of Fluorouracil biological action through combination therapies $^{[7, 24]}$, a number of drugs and clinical candidates acting as prodrugs of $^1$ and/or $^4$ were developed (Table 1).

| Structure | INN or ID, development phase | Company |
|-----------|-----------------------------|---------|
| $^3$      | Tegafur Launched (1979)     | Latvian institute of organic synthesis |
| $^5$      | Doxifluridine Launched (1987) | Hoffmann –La Roche, Chugai Pharmaceutical |
| $^{33}$   | OGT 719 Phase I             | Oxford GlycoSciences |
| $^{34}$, R = n-C$_{14}$H$_{29}$ | TT-62 Phase II | Teijin Pharma |

(continued)
### Table 1 (continued)

| Structure | INN or ID, development phase | Company |
|-----------|------------------------------|---------|
| ![Structure 35](image) 35, R = (2)-pentadec-7-en-1-yl | T-506 Phase II | Toyama Chemical |
| ![Structure 2](image) 2 | Carmofur Launched (1981) | Yamanouchi Pharmaceutical, Mitsui Chemicals |
| ![Structure 36](image) 36 | Atofluding Phase III | Xian Lijun Pharmaceutical |
| ![Structure 37](image) 37 | Emitefur, BOF-2A Phase III | Otsuka Pharmaceutical |
| ![Structure 38](image) 38 | 5-FP Phase I | Astex Pharmaceuticals, Yale University |
| ![Structure 6](image) 6 | Capecitabine Launched (1998) | Hoffman La Roche |
| ![Structure 39](image) 39 | Galocitabine Phase II | Hoffman La Roche |
The first example of Fluorouracil prodrug is Tegafur (3) developed in 1960s in Latvia [25, 26]. Tegafur is an oral slow-release prodrug formulation of Fluorouracil which is readily absorbed through the gastrointestinal tract. The major pathway of metabolic activation of 3 includes hydroxylation by hepatic cytochrome P450 enzymes, mostly CYP2A6 (Scheme 5) [27].

![Scheme 5 Metabolic activation of Tegafur (3)](image)

Apart from Fluorouracil, 4-hydroxybutyraldehyde and succinic dialdehyde are also formed, which are further transformed into γ-butyrolactone and 4-hydroxybutyric acid [28]. Tegafur was shown to be 2–5 times more potent and less toxic than 1; hence lower doses of 3 can be utilized, resulting in decreased neurotoxicity without compromising the antitumor effects.

Another prodrug of Fluorouracil – Doxifluridine (5), which also implies the idea of attachment of sugar-like moiety to the molecule of 1, was launched in Japan in 1987 [29]. The mechanism of metabolic activation of 5 is rather simple and includes hydrolysis to Fluorouracil by thymidine phosphorylase [299]. Since the level of thymidine phosphorylase is significantly higher in several types of solid tumours (in particular, colorectal, breast, and kidney cancers) as compared with normal tissues, Doxifluridine possesses a higher therapeutic index for these types of cancers. The use of 5 is somewhat limited by gastrointestinal toxicity after oral administration due to release of 1 by intestinal pyrimidine nucleoside phosphorylase [30].

Yet another sugar-modified Fluorouracil derivative – OGT 719 (33), in which galactose is incorporated onto the fluoropyrimidine moiety, was developed by Oxford GlycoSciences and had reached Phase I clinical study [31]. In 1999, the company decided to discontinue development of 33 as the results of Phase I/II clinical study were not sufficiently strong to justify large scale Phase II studies. OGT 719 was rationally designed to reduce the systemic toxicity normally associated with Fluorouracil while retaining activity against tumors localized in the liver, in which it may be preferentially localized through the asialoglycoprotein receptors [32]. These receptors are present on the surface of hepatocytes and recognise various sugar-containing biomolecules through terminal galactose and N-acetylgalactosamine residues. The metabolic activation of OGT 719 occurs once the compound enters hepatocytes, where the galactose molecule is cleaved from the Fluorouracil residue.
Two derivatives of Floxuridine – TT-62 (34) and T-506 (35) have reached Phase II clinical trials in Japan [3]. The compounds showed significant antitumor activity by oral administration; moreover, they slowly released Floxuridine, and the effective level of 4 was prolonged [33, 34]. The gastro-intestinal disturbances and loss of body weight were serious side effects of 34 and 35.

Several prodrugs of Fluorouracil were obtained by acylation or carbamoylation of N-1 and/or N-3 atoms of the pyrimidine ring of 1. In particular, an oral drug Carmofur (2) which is 1-hexylcarbamoyl derivative of 1 was launched in Japan in 1981 and later – in other countries [35]. The carbamate moiety in 2 decomposes gradually in neutral water or in basic conditions, but it is strongly resistant to acidic hydrolysis and hence can survive acid in the stomach. The 1-hexylcarbamoyl moiety also facilitates the rapid uptake of 2 through the cell membrane [36]. The metabolic activation of Carmofur involves oxidation and scission of the side-chain with slow release of 1 [37]. Two main routes of the side chain transformation are \( \omega \)-oxidation and \( \omega-1 \)-oxidation: metabolites 40–43 were detected after administration of Carmofur (Fig. 3) [38]. Non-enzymatic hydrolytic decomposition of 2 and its metabolites also contributes to release of 1.

Another oral prodrug of Fluorouracil, Atofluding (36) is a diacyl derivative of 1. Atofluding has reached Phase III clinical trials in China [39]. The activation of 36 includes its fast non-enzymatic hydrolysis to 3-o-toluyl-5-Fluorouracil (44) following oral administration; 44 is then slowly metabolized to 1 (Scheme 6) [40]. Since the acetyl group of Atofluding is not stable and prone to decompose, impairing quality control for the preparation, a possibility of direct application of 44 was also considered [41].

![Chemical structures of prodrugs](image)

**Fig. 3** Metabolites of Carmofur (2)

**Scheme 6** Metabolic activation of Atofluding (36)
An interesting idea was behind design of Emitefur (37), a prodrug of Fluorouracil which was developed by Otsuka Pharmaceutical and has reached Phase III clinical trials in Japan [3, 42, 43]. The structure of 37 contains the fragments of two biologically active components: Fluorouracil (1) and 3-cyano-2,6-dihydroxypyridine (45), which is a potent inhibitor of dihydropyrimidine dehydrogenase. Therefore, 37 is a double prodrug which not only delivers Flouorouracil but also prevents its enzymatic biotransformation to the dihydropyrimidine derivative 12. Metabolic activation of 37 occurs via rapid cleavage of the ester bonds by esterase to give 45 and 1-ethoxymethyl-5-fluorouracil (46) (Scheme 7). The intermediate 46 is further metabolized to 1 by microsomal enzymes in the liver [44].

![Scheme 7 Metabolic activation of Emitefur (37)](image)

All the prodrugs of Fluorouracil discussed above contained the fragment of 1 in their structure; their transformation to 1 included hydrolysis reaction as the key step. On the contrary, 5-fluoro-2-pyrimidinone (5-FP, 38) which has been studied in Phase I clinical trials [45] is activated through oxidative process. In particular, pyrimidine 38 is transformed to 1 by aldehyde oxidase, which is present in high concentrations in the human livers but not in the gastrointestinal tract [46].

Two prodrugs of 1, Capecitabine (6) and Galocitabine (39), are 5-fluorocytidine derivatives. Both the compounds were developed by Hoffman La Roche; whereas Capecitabine was launched in 1998, Galocitabine was terminated at Phase II clinical trials [47]. Both the compounds are close analogues as well as prodrugs of Doxifluridine (5), which was used as the lead compound in their design. The main goals of such design were to minimize the mielotoxicity and to increase the tumor selectivity of 5. In fact, Capecitabine (6) indeed demonstrated minimal mielotoxicity in clinical studies. Although the therapeutic indices of 39 were much higher in mice tumor models than in the case of 5, it was not efficiently metabolised to the active species in humans. The metabolic activation of 6 and 39 includes their hydrolysis by carboxylesterase or acylamidase in liver to give 5′-deoxy-5-fluorocytidine (47), which is then transformed to 5 by cytidine deaminase (Scheme 8) [48].
Syntheses of Fluorouracil prodrugs relied on either chemical modification of 1 or direct fluorination of the corresponding pyrimidine derivatives. In particular, Tegafur (3) was obtained from 1 by reaction with 2,3-dihydrofuran [49–54], 2-chloro- [55, 56], 2-alkoxy- [57], 2-acetoxytetrahydrofuran [58, 59, 300], and 4-trimethylsilyloxybutyaldehyde dimethyl acetal (48) (Scheme 9) [60]. Alternatively, 3 was prepared via fluorination of compound 49 [61] or ester 50 [62].

One of the early syntheses of Doxifluridine (5) [63, 64] commenced from Floxuridine (4) which reacted with thionyl chloride to give cyclic sulphite 51 (Scheme 10). Methanolysis of 51 upon treatment with sodium methylate gave 52, which was reduced with tributyltin to give 5. In an analogous approach, the compound 5 was prepared via iodide 53, in turn obtained from 4 in two steps (Scheme 11) [65]. It should be noted that direct transformation of 4 into the corresponding iodide was done with low yield of the product, hence the protection strategy was necessary to use. Bromide 54 was a key intermediate in one more analogous scheme [66].

**Scheme 8** Metabolic activation of Capecitabine (6) and Galocitabine (39)

**Scheme 9** Syntheses of Tegafur (3)
Scheme 10  Syntheses of Doxifluridine (5) from Floxuridine (4)

Scheme 11  Syntheses of Doxifluridine (5) from Fluorouracil (1)
Several syntheses of Doxifururidine relied on glycosylation of Fluorouracil derivative 55. In particular, 5′-deoxyrybose derivatives 56, 57, and 58 were used for that purpose (Scheme 11) [67, 68]. Finally, direct fluorination of 5′-deoxyuridine derivatives with F₂/N₂ [69] or AcOF [70] was also described.

Syntheses of OGT 719 (33) relied on glycosylation of the compound 55 (Scheme 12). Reaction of 55 with bromide 59 [71, 72] or acetate 60 [73] gave tetraacetyl derivative 61, which was transformed to 33 upon deprotection. With 60 as the glycosylating reagent, in situ generation of 55 from Fluorouracil was also described [74].

![Scheme 12](image)

Scheme 12  Synthesis of OGT 719 (33)

TT-62 (34) was prepared as a free acid (62) from 63 which reacted with tosylchloride and tetradecylphosphate to give the corresponding phosphodiester, which upon deprotection gave 34 (Scheme 13) [75].

![Scheme 13](image)

Scheme 13  Synthesis of TT-62 (34) as a free acid 62

Synthesis of T-506 (35) commenced from Fluorouracil derivative 64 (Scheme 14) [76]. Compound 64 reacted with 2-bromoethyl phosphorodichloridate to give bromide 65. Compound 65 was transformed to 35 upon reaction with trimethylamine.

![Scheme 14](image)
Synthesis of Carmofur (2) and Atofluding (36) was performed in obvious and straightforward manner. Carmofur (2) was prepared by reaction of Fluorouracil (1) and \( n \)-hexylisocyanate (Scheme 15) [77, 78]. Alternative approach included reaction of 1 with phosgene and then – with \( n \)-hexylamine.

Synthesis of Atofluding (36) relied on a stepwise double acylation of Fluorouracil with acetic anhydride and then – with \( \alpha \)-toluoyl chloride (Scheme 16) [79].
Emitefur (37) was obtained by stepwise reaction of building blocks 46, 67, and 66 in the presence of triethylamine (Scheme 17) [80–82]. Compound 66 was prepared by benzylation of 3-cyano-2,6-dihydroxypyridine (45), whereas 46 – by ethoxymethylation of the silyl derivative 55.

Scheme 17  Synthesis of Emitefur (37)

Early syntheses of 5-fluoro-2-pyrimidinone (38) relied on desulfurization of Fluorouracil thio-derivatives. In particular, reaction of pyrimidine derivatives 68 with P<sub>2</sub>S<sub>5</sub> followed by treatment with Raney nickel and gave alkoxy derivative 69, which was transformed to 38 upon acidic hydrolysis (Scheme 18) [83]. A more straightforward transformation sequence was also described; including reaction of Fluorouracil (1) with P<sub>2</sub>S<sub>5</sub> and reduction of thione 70 with Raney nickel [84, 85]. Alternatively, the thione 70 was alkylated to give derivative 71, which was either oxidated and then hydrolyzed [86] or subjected to reaction with hydrazine and then – silver oxide [301]; in both cases, 38 was obtained. A completely different synthetic scheme commenced from fluoroacetic acid which was subjected to Vilsmeier-type formylation to give 2-fluoro-3-dimethylamino-acrolein (72) [87]. Reaction of 72 with triethyloxonium tetrafluoroborate and dimethylamine gave the salt 73, which led to 38 upon reaction with urea. Finally, 38 was also obtained by direct fluorination of 2-pyrimidinone [88, 89].

Syntheses of Capecitabine (6) started from 5-fluorocytosine (9) (see further sections for the preparation of 9, which is used as antifungal drug). In particular, compound 70 reacted with 1,2,3-tri-O-acetyl-5-deoxy-β-D-ribofuranose (58) to give diacetyl derivative 72, which was acylated with n-pentylchloroformate and then
hydrolyzed, resulting in the formation of 6 (Scheme 19) [90–95]. Variations of this method using a silyl derivative of 70 instead of 70 itself [68, 96], as well as 1-\(O\)-acetyl-2,3-O-isopropylidene-5-deoxy-\(D\)-ribofuranose (73) (Scheme 20) [96] or 1,2,3-tri-\(O\)-methoxycarbonyl-5-deoxy-\(D\)-ribofuranose [97] as the sugar sources were also reported. Syntheses of Galocitabine (39) were performed analogously to that of Capecitabine, 3,4,5-trimethoxybenzoyl chloride being used instead of \(n\)-pentylichloroformate at the corresponding steps [68, 89, 90, 98].
Apart from Floxuridine, Fluorouracil and its pro-drugs, there are two additional examples of anti-cancer agents which also act as antimetabolites and have reached clinical development phase, \textit{i.e.} both Trifluridine (7) (as a component of TAS-102) and FTC-092 (74) (Fig. 4) were developed by Taiho Pharmaceutical. These...
compounds are derivatives of \( \alpha,\alpha,\alpha \)-trifluorothymine and are thus structurally related to Fluorouracil. Trifluridine was approved by FDA as an ophthalmic drug against herpes virus in 1995 (see also further sections) \[5\]; it is now being investigated in Phase III clinical trials as a component of anti-cancer drug TAS-102 (which is a combination of 7 and Tipiracil (75)) \[99\] FTC-092 was evaluated for antitumor activity in Phase I clinical trials \[3\].

The active principle of both TAS-102 and FTC-092 with anti-cancer effect is Trifluridine (7). As in the case of Fluorouracil, one of the mechanisms by which compound 7 exhibits its antitumor activity is inhibition of thymidylate synthase \[100\]. More precisely, Trifluridine is transformed into \( \alpha,\alpha,\alpha \)-trifluorothymidine monophosphate (76) by thymidine kinase (Scheme 21); similarly to the Fluorouracil derivatives discussed in the previous sections, compound 76 is true inhibitor of thymidylate synthase. However, compound 7 exhibits an anticancer effect on colorectal cancer cells that have acquired Fluorouracil resistance as a result of the overexpression of thymidylate synthase.

![Scheme 21](image-url)
Therefore, an alternative mechanism of action is also in operation, namely, incorporation of α,α,α-trifluorothymidine triphosphate (77) into DNA, which results in single-strand breaks, followed by double-strand breaks when the cells progress to a subsequent DNA replication phase [101]. The major drawback of Trifluridine (7) is its high susceptibility to biodegradation, which is catalysed by thymidine phosphorylase and gives α,α,α-trifluorothymine (78) and 2-deoxy-α-D-ribose 1-phosphate (79) [102]. In the case of TAS-102, this issue is overcome by co-administration of thymidine phosphorylase inhibitor Tipiracil (75) [103], whereas improved biological effect of FTC-092 upon oral administration is achieved by its gradual biotransformation, mainly through the action of liver microsomes, releasing 7 over a long period [104].

The first synthesis of Trifluridine commenced from trifluoromethylacrylonitrile (80) which reacted with HBr and then with urea to give amide 81 in moderate yield. Hydrolysis of 81 was accompanied by cyclization and led to dihydropyrimidine 82 (Scheme 22). Two-step aromatization of 81 gave α,α,α-trifluorothymine (78). Compound 78 was transformed to 7 in low yield (8%) by enzymatic glycosylation [105]. The yield of the last step in this sequence was significantly improved when 78 was preliminarily transformed to bis-silyl derivative 83, and chloride 84 was used for glycosylation [106, 107].

Scheme 22 Syntheses of Trifluridine (7) via α,α,α-trifluorothymine (78)
An alternative approach to 7 was based on direct trifluoromethylation of the corresponding deoxyuridine derivatives 32 or 84, using CF₃COOH–XeF₂ [108] and CF₃I–Cu–HMPA [109] as the reagents, respectively (Scheme 23).

![Scheme 23 Syntheses of Trifluridine (7) via trifluoromethylation of deoxyuridines](image)

FTC-092 (74) was prepared by regioselective benzylation of Trifluridine (7) (Scheme 24) [110]. As in the case of 7, direct trifluoromethylation was also used for synthesis of 74. The following sequence was established as the most practical: tritylation of 2′-deoxy-5-iodouridine (85), 3′-O-benzylation, N³-benzoylation, cross-coupling reaction with CF₃Cu reagent, and acidic deprotection (Scheme 25) [111]. Alternatively, 74 was prepared in low yield by glycosylation of α,α,α-trifluorothymine using the bis-silyl derivative 83 (Scheme 26) [112].

![Scheme 24 Synthesis of FTC-092 (74) from Trifluridine (7)](image)
An approach to cancer treatment which relies on using fluorinated uracil analogues as antimetabolites is the most recognised in the field of fluorinated diazines relevant to medicinal chemistry. However, other strategies are also gaining momentum; in particular, several compounds which act as kinase inhibitors (i.e. 87–92) have reached clinical development phase (Table 2).

Compound LY-2835219 (87) is currently being developed by Eli Lilly and Co.; monomesylate salt of 87 has entered Phase I clinical trials in patients with advanced cancer in 2011 [113]. It acts as a potent oral inhibitor of the cyclin-dependent kinases 4 and 6 (CDK4/6), playing a key role in regulating cellular proliferation [114]. In particular, these cyclin D-dependent kinases facilitate progression of gap 1 cell cycle phase (G1) by phosphorylating retinoblastoma susceptibility protein (Rb), which prevents association of Rb with E2F transcription factor, and thus relieves transcriptional repression by the Rb-E2F complex. In addition, these
kinases also sequester CDK interacting and kinase inhibitory proteins (Cip/Kip) from their complexes with cyclin-dependent kinase 2 (CDK2), facilitating activation of CDK2 with cyclin E [115]. Monomesylate salt of 87 inhibits CDK4 and CDK6 with IC50 values of 2 and 10 nM, respectively; moreover, it is able to cross blood-brain barrier and therefore has the potential for the treatment of brain tumors and metastases [114].

Fostamatinib disodium (Tamatinib fosdium, 88), which is prodrug of Tamatinib (92) (Scheme 27), was discovered by Rigel; it is currently studied in Phase II clinical trials by Rigel and AstraZeneca Plc. for treatment of B-cell lymphoma [113]. Apart from that, compound 88 is also investigated as agent for treatment of autoimmune thrombocytopenia and rheumatoid arthritis. Because of its poor pharmaceutical properties, Tamatinib (92) is orally administered as the methylene phosphate

| Structure | INN or ID, development phase, company | Target |
|-----------|---------------------------------------|--------|
| 87        | LY-2835219, Phase I, Eli Lilly         | CDK4/6 |
| 88        | Fostamatinib disodium, Phase II, Rigel, AstraZeneca | Syk |
| 89        | R-763, AS-703569, Phase I, Rigel, Merck Serono | Aurora kinases |
| 90        | PF-03814735, Phase I, Pfizer           | Aurora kinases |
| 91        | AZD-1480, Phase I, AstraZeneca         | JAK2   |

tableskinases also sequester CDK interacting and kinase inhibitory proteins (Cip/Kip) from their complexes with cyclin-dependent kinase 2 (CDK2), facilitating activation of CDK2 with cyclin E [115]. Monomesylate salt of 87 inhibits CDK4 and CDK6 with IC50 values of 2 and 10 nM, respectively; moreover, it is able to cross blood-brain barrier and therefore has the potential for the treatment of brain tumors and metastases [114].

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prodrug 88. Fostamatinib disodium (88) is quickly cleaved to 92 by alkaline phosphatases that are present on the apical brush-border membranes of the intestinal enterocytes, after which the more hydrophobic 92 can be readily absorbed [116].

Tamatinib (92) acts as an ATP-competitive inhibitor of Spleen tyrosine kinase (Syk) – a non-receptor tyrosine kinase which is a key component of the B-cell receptor (BCR) signaling pathway [117]. It is shown that BCR-mediated signaling through Syk occurs to a greater degree and for a longer duration in neoplastic cells than in nonmalignant B-cells. Inhibition of the Syk pathway prevents chronic lymphocytic leukemia (CLL) cells from interacting with the microenvironment, and promotes proapoptotic signals.

R-763 (89), also known as AS-703569, is another kinase inhibitor discovered by Rigel. It was investigated in Phase I clinical trials for several types of tumors by Rigel and Merck Serono; the latest study was terminated in 2012, concerning a review of the available clinical data and low probability of completing the trial based on the observed recruitment rate [113]. Compound 89 inhibits Aurora kinases – serine/threonine kinases which are essential for cell proliferation, mainly due to regulation of gap 2 and mitotic cell cycle phases (G2/M). Over-expression of Aurora kinases is found in several human cancers and correlated with histological malignancy and clinical outcomes. Although the biological functions of two types of Aurora kinases (A and B) are different, in both cases their inhibition induces apoptosis of the cell, leading to similar phenotypes. Some other kinases are also inhibited by 89, in particular Fms-like tyrosine kinase 3 (FLT3) [118].

One more Aurora kinase inhibitor – PF-03814735 (90) – was developed by Pfizer; it has been investigated in Phase I clinical trials for treatment of solid tumors (the study completed in 2012) [113]. PF-03814735 was generally well tolerated with manageable toxicities, and a recommended phase II dose could be established; however, clinical or metabolic antitumour activity was limited [119]. Similarly to R-763 (89), compound 90 inhibits both Aurora A and B kinases; other kinases are affected to a lesser extent [120]. Therefore, PF-03814735 (90) produces a block in cytokinesis, resulting in inhibition of cell proliferation and the formation of polyploid multinucleated cells.

AZD-1480 (91) was developed by AstraZeneca and studied in Phase I clinical trials for treatment of advanced solid malignancies (the study terminated in 2012) [113]. AZD-1480 is an ATP-competitive inhibitor of Janus kinase 2 (JAK2) – an
intracellular non-receptor tyrosine kinase that transduce cytokine-mediated signals via the Janus kinase – signal transducer and activator of transcription (JAK–STAT) signaling pathway. In particular, inhibition of JAK2 blocks Stat3 signaling, associated with chronic cytokine stimulation in some tumors [121]. X-Ray diffraction study of complex formed by 91 and JAK2 shows that the donor-acceptor-donor hydrogen-bonding motif provided by aminopyrazole fragment forms three hydrogen bonds with an adenine binding pocket, whereas the fluoropyrimidine ring occupies a nearby hydrophobic pocket [122].

Synthesis of LY-2835219 (87) relied on selective functionalization of 2,4-dichloro-5-fluoropyrimidine (93), which can be easily obtained from Fluorouracil (1) (Scheme 28) [123]. First, boronic ester 94 was prepared from aniline 95 in three steps, including benzimidazole ring construction and palladium-catalyzed coupling with pinacol diborane. Suzuki-type reaction of 93 and 94 resulted in selective functionalization at C-4 of the pyrimidine ring and gave chloride 96. Buchwald-Hartwig coupling of 96 with amine 97 (prepared in two steps from 1-ethylpiperazine (98) and (99)) gave the final product 87.

Scheme 28  Synthesis of LY-2835219 (87)
Analogously, selective functionalization of \( \text{93} \) was used for the preparation of Fostamatinib disodium (\( \text{88} \)) (Scheme 29). In particular, reaction of \( \text{93} \) with equimolar amount of amine \( \text{100} \) and then – with 3,4,5-trimethoxyaniline (\( \text{101} \)) gave Tamatinib (\( \text{92} \)) [124]. It should be noted that no detailed procedures of performing these transformations were given in the initial patent; moreover, synthesis of the starting compound (amine \( \text{100} \)) is not documented to date. To obtain Fostamatinib disodium (\( \text{88} \)), compound \( \text{92} \) was treated with chloride \( \text{102} \) and \( \text{Cs}_2\text{CO}_3 \); further deprotection subsequent and salt formation gave the target product \( \text{88} \) [125].

![Scheme 29 Synthesis of Fostamatinib disodium (88)](image)

Similar approach was used for the synthesis of R-763 (\( \text{89} \)) (Scheme 30) [126]. In this case, lactam \( \text{102} \), which was obtained from norbornadiene (\( \text{103} \)) and Graf isocyanate (\( \text{ClISO}_2\text{NCO} \)), was protected with Boc\(_2\)O and then subjected to ring-opening with aqueous ammonia to give amide \( \text{104} \). Deprotection of \( \text{104} \) followed by arylation with \( \text{93} \) gave an intermediate \( \text{105} \), which was then treated with \( \text{N}-\text{arylpiperazine derivative} \quad \text{106} \) (prepared in two steps from 4-fluoro-3-methylnitrobenzene (\( \text{107} \))) to give racemic \( \text{89} \). Optically pure \( \text{89} \) was obtained either by chiral stationary phase HPLC applied at different steps of the synthesis, or \textit{via} enzymatic resolution of Boc-protected lactam \( \text{102} \).
It is not surprising that synthesis of PF-03814735 (90) also followed analogous strategy, 2,4-dichloro-5-trifluoromethylpyrimidine (111) being used as a key fluorinated diazine building block instead of 93 (Scheme 31) [302]. The synthetic scheme commenced from amine 108 which was N-trifluoroacetylated, then nitrated, and subjected to a change of the protecting group to give Boc derivative 109. Two alternative pathways were developed for further transformations. In the first one, compound 109 was reduced into fused aniline derivative 110 which reacted with 111 to give compound 112. Deprotection of 112 followed by coupling with N-acetylglycine led to the formation of chloride 113.

Alternatively, compound 109 was deprotected, coupled with N-acetylglycine, reduced catalytically and then arylated with 111 to give 113. Finally, compound 113 reacted with cyclobutyl amine to give the final product 90 as racemate. Both enantiomers of 90 were also obtained using this scheme if Boc derivative 109 was subjected to chiral stationary phase HPLC prior further transformations.

Although a similar strategy was used for the preparation AZD-1480 (91), in this case the fluorinated diazine moiety is not in a central part of the molecule; hence a different approach was used for the construction of the fluorinated...
Scheme 31  Synthesis of racemic PF-03814735 (rac-90)
pyrimidine fragment. As in the previous syntheses discussed in this section, 91 was obtained by selective functionalization of 5-substituted 2,4-dichloropyrimidine derivative (i.e. 114), first by reaction with aminopyrazole 115 and then – with chiral amine 116 (Scheme 32) [122, 127]. For the preparation of enantiopure 116, two approaches were developed, both starting from nitrile 117, in turn prepared from 2-chloro-5-fluoropyrimidine (118) [127]. In the first method, compound 117 was reduced with DIBAL into aldehyde 119, which reacted with Ellman’s sulfide-amide 120 to give imine 121. Reaction of 121 with MeMgBr and subsequent deprotection led to the formation of 116. Alternatively, 117 was treated with MeMgBr and then – Ac₂O to give enamine derivative 122, which was subjected to enantioselective rhodium-catalyzed hydrogenation with (S,S)-Et-DuPhos as a chiral ligand. The resulting chiral amide 123 was obtained with more than 99 % ee. After a change of the protecting group, Boc derivative 124 was deprotected to give the target amine hydrochloride 116.

Scheme 32  Synthesis of AZD-1480 (91)
4 Antiviral, Antibacterial and Antifungal Agents

4.1 Anti-HIV Agents

The fight against HIV infection is another important field where fluorinated diazines have remarkable record, including approved drug Emricitabine (8) and 7 compounds that have reached clinical development phase (compounds 125–131) (Table 3). All these compounds act as HIV reverse transcriptase inhibitors and fall into two categories: fluorocytidine analogues (8 and 125–127) and trifluoromethyl-substituted quinazolone derivatives (128–131).

Table 3 Anti-HIV drugs – derivatives of fluorinated diazines [5, 113]

| Structure | INN or ID, development phase | Company                        |
|-----------|------------------------------|--------------------------------|
| ![Emtricitabine](image) | Emtricitabine | Emory University, Gilead Sciences |
| ![Emtricitabine](image) | Launched (2003) | Emory University, Gilead Sciences |
| ![Racivir](image) | Racivir | Pharmasset |
| ![Racivir](image) | Phase II | Pharmasset |
| ![Elvucitabine](image) | Elvucitabine | Yale University, Achillion Pharmaceuticals |
| ![Elvucitabine](image) | Phase II | Yale University, Achillion Pharmaceuticals |
| ![Dexelvucitabine](image) | Dexelvucitabine | Emory University, Incyte Co. |
| ![Dexelvucitabine](image) | Phase II | Emory University, Incyte Co. |

(continued)
**Table 3** (continued)

| Structure | INN or ID, development phase | Company                  |
|-----------|------------------------------|--------------------------|
| ![image](image1) | DPC-961  Phase I            | DuPont Pharmaceuticals  |
| ![image](image2) | DPC-963  Phase I            | DuPont Pharmaceuticals  |
| ![image](image3) | BMS-561390, DPC-083 Phase II | DuPont Pharmaceuticals,  |
|           |                              | Bristol-Myers Squibb    |
| ![image](image4) | DPC-082  Phase I            | DuPont Pharmaceuticals  |

Emtricitabine (8) was discovered in Emory University (Atlanta, USA); development of the drug was completed by Gilead Sciences, and the compound was approved by FDA under trade name Emtriva® in 2003. It is also marketed in combinations with other anti-HIV agents, *i.e.* Tenofovir (132, used as a prodrug) (Truvada®), Efavirenz (133) and Tenofovir (Atripla®), Rilpivirine (134) and Tenofovir (Complera®), and Elvitegravir (135), Cobicistat (136), and Tenofovir (Stribild®) [5] Emtricitabine is a close analogue of Lamivudine (137), which is an example of nucleoside analogs – an important class of reverse transcriptase inhibitors, which has gained much attention since the initial success of the first representative, Zidovudine (138) [128] (Fig. 5).  

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combinations with other anti-HIV agents, *i.e.* Tenofovir (132, used as a prodrug) (Truvada®), Efavirenz (133) and Tenofovir (Atripla®), Rilpivirine (134) and Tenofovir (Complera®), and Elvitegravir (135), Cobicistat (136), and Tenofovir (Stribild®) [5] Emricitabine is a close analogue of Lamivudine (137), which is an example of nucleoside analogs – an important class of reverse transcriptase inhibitors, which has gained much attention since the initial success of the first representative, Zidovudine (138) [128].

Emtricitabine (8) is very similar to Lamivudine (137) with respect to its activity, convenience, safety and resistance profile; the only remarkable difference is longer intracellular half-life of 8. Analogously to 137, the biologically active form of 8 is triphosphate 139, which is formed by a stepwise phosphorylation of 8 (Scheme 33). Compound 139 can be considered as 2,3-dideoxycytidine trifosphate analogue and acts as a competitive inhibitor and alternate substrate of the normal deoxycytidine triphosphate (140). As a competitive inhibitor of the normal substrate, 139 inhibits incorporation of 140 into the growing DNA chain by viral reverse transcriptase; as an alternate substrate, it is incorporated into this chain (as 141) and acts as a chain terminator (since 141 is missing the 3’-hydroxyl group required for further chain elongation) [128, 129].

Fig. 5 Some active ingredients of anti-HIV drugs
Although Emtricitabine might have the potential for toxicity caused by interaction with human mitochondrial DNA enzymes, both in vitro and in vivo testing results show that this is not a serious issue. Low toxicity of 8 as compared to other nucleoside reverse transcriptase inhibitors is a remarkable advantage of this drug. As with all representatives of this class, the major drawback of 8 is rapid development of drug resistance by a single point mutation of viral reverse transcriptase [129]. The main route of elimination of 8 is renal excretion, mostly unchanged (86 % of the dose). The metabolic transformations of Emtricitabine include oxidation of the sulphur atom to form the 3′-sulfoxide diastereomers (9 %) and conjugation with glucuronic acid to give 2′-O-glucuronide (4 %) [130].

A racemic form of Emtricitabine, Racivir, was also studied in clinics by Pharmasset and has reached Phase II trials [113], designed to measure its efficacy in patients harbouring virus resistant to Lamivudine. It was shown that D(+)-enantiomer 125 is less potent and more toxic than Emtricitabine itself. One of the reasons behind lower potency of 125 is that 8 is phosphorylated by deoxycytidine kinase to a greater extent; therefore, the active form (139) is formed more readily for (-)-enantiomer [131, 132].

Elvucitabine (126) and its enantiomer Dexelvucitabine (127) were discovered in Yale University (New Haven, USA) and Emory University (Atlanta, USA), respectively. Both compounds were further developed by commercial companies (Achillion Pharmaceuticals and Incyte Co., respectively), and have reached Phase II clinical trials [113]. Development of 127 was terminated due to inability to pair with other cytidine analogues and higher risk of hyperlipasemia. Phase II studies of 126 were suspended because of bone marrow suppression in several patients [133].
mode of action of Elvucitabine is quite similar to that of Emtricitabine; the major advantages of 126 include long plasma half-life (up to ten times greater than that of 8) and superior potency against common resistance mutations [134].

Four compounds DPC-961 (128), DPC-961 (129), DPC-083 (130), and DPC-082 (131) were developed by DuPont Pharmaceuticals as non-nucleoside reverse transcriptase inhibitors. All the compounds have reached Phase I clinical trials; DPC-083 (130) was further progressed into Phase II trials by Bristol-Myers Squibb after the company had acquired DuPont Pharmaceuticals; however, the development was stopped in 2003 due to poor pharmacokinetics [135]. The compounds are close analogues of Efavirenz (133) – a non-nucleoside reverse transcriptase inhibitor approved by FDA in 1998 [5]. All the compounds 128–131 showed similar to Efavirenz activity towards wild-type virus in vitro; however, they were more effective towards single-mutation variants and showed lower plasma serum protein binding [136, 137].

It might be assumed that mechanism of action of 128–131 is similar to that of Efavirenz, which is known to bind within the non-nucleoside inhibitor binding pocket of reverse transcriptase [138], both spatially and also functionally associated with the substrate-binding site.

Metabolism of DPC-961 (128) was studied in rats. Analogously to Efavirenz, the main metabolite is glucuronide conjugate 142 (more than 90% of excreted dose in the bile) (Scheme 34). However, a glutathione conjugate 143 was also isolated, which is presumably formed via oxirene intermediate 144; in this view, metabolism of 128 was different from that of 133 [139].

Scheme 34  Main metabolites of DPC-961 (128) in rats
Early synthesis of Emtricitabine (8) commenced from L-gulose (145) (Scheme 35) [140]. Selective tosylation of 145 followed by acetylation gave 146. Treatment of 146 with HBr in AcOH yielded the bromo derivative 147, which was refluxed with O-ethylxanthate and then deacetylated using NH₄OH in MeOH to obtain the 1,6-thioanhydro-L-gulopyranose (148). Selective oxidative cleavage of vicinal cis diol in 148 by NaIO₄ and reduction with NaBH₄, followed by protection of the resulting diol as the acetone yielded the 1,3-oxathiolane derivative 149. Silyl protection of the hydroxyl group followed by deprotection of the isopropylidene moiety afforded derivative 150. Oxidative cleavage of vicinal diol 150 by Pb(OAc)₄ followed by pyridinium dichromate (PDC) oxidation gave the acid 151. Treatment of 151 with Pb(OAc)₄ – pyridine in anhydrous THF afforded acetate 152. Reaction of 152 with fluorocytosine derivative 153, separation of anomers and subsequent deprotection gave 8. The same
approach starting from D-mannose or D-galactose was used for the preparation of D-enantiomer 125 [141].

Most of the methods describing the preparation of Emtricitabine (and Racivir) rely on the construction of 1,3-oxathiolane ring by reaction of glycolaldehyde or glyoxalic acid derivatives with mercaptoacetic acid or mercaptoacetic aldehyde (which exists as 1,4-ditiane 154). For example, one of the first of syntheses of this type commenced from allyl alcohol which was silylated and then subjected to ozonolysis to give glycolaldehyde derivative 155 (Scheme 36) [142]. Reaction of 155 with mercaptoacetic acid afforded 1,3-oxathiolane 156, which was reduced with LiAlH(O\textsubscript{t}Bu)\textsubscript{3} or DIBAL and then acetylated to form 157. Finally, reaction of 157 with silylated fluorocytosine derivative 158 followed by deprotection led to the formation of racemic 8 (Racivir).

More than 15 preparations described in patents are variations of the above synthetic scheme. In particular, to obtain optically pure Emtricitabine, lipase-catalyzed enzymatic resolution, as well as chiral stationary phase HPLC was used [143]. However, the most effective procedure included separation of menthyl derivatives. This method evolved significantly since the first publication (which in fact relied on separation of all the 4 possible diastereomers) [144]; one of the recent multigram preparations is shown in the Scheme 37 [145]. The first step of the synthesis included formation of methyl ester 159 from glyoxalic acid and L-menthol. Reaction of 159 with 1,4-ditiane 154 gave 1,3-oxathiolane 160 as a mixture of cis diastereomers.
Compound 160 was transformed to chloride 161 by treatment with thionyl chloride and methanesulfonic acid. Reaction of 161 and 158 led to the formation of 162, which was separated as a single diastereomer by transformation to oxalate and subsequent crystallization. Finally, reduction of 162 with NaBH₄ gave Emtricitabine (8) which was isolated as hydrochloride.

An interesting variation of the method was patented by Glaxo Wellcome Inc [146]. Their synthesis was started from 2,4-dichloro-5-fluoropyrimidine (93) (Scheme 38). Reaction of 93 with NaOEt and then – with anion of 2,2-dimethoxyethanol gave pyrimidine derivative 163, which upon detection formed aldehyde 164. Reaction of 164 and 154 led to the formation of 1,3-oxathiolane 165, which was acetylated to give 166. Treatment of 166 with TMSOTf resulted in rearrangement leading to 167, which was transformed to racemic 8 (Racivir) by reaction with ammonia.

A number of methods for the preparation of Elvucitabine (126) were reported in the literature. In the first synthetic scheme developed in Yale University [147], 2′-deoxy-5-fluoro-β-L-uridine (168), which is enantiomer of Flouxuridine (4), was used as the key intermediate (Scheme 39). Compound 168 can be prepared in
Scheme 38  Synthesis of racemic 8 (Racivir) patented by Glaxo Wellcome Inc. (Relative configurations are shown)

several steps from L-arabinose. Mesylation of 168 followed by alkaline cyclization led to the formation of oxetane 169, which was transformed to cytidine derivative 170. Compound 170 was rearranged to 126 by treatment with t-BuOK in DMSO.

Synthesis of Elvucitabine (126) developed by chemists from Vion Pharmaceuticals commenced from lactone 171 (Scheme 40), which can be obtained in 4 steps from

Scheme 39  Synthesis of Elvucitabine (126) developed in Yale University
D-glutamic acid [148]. Phenylselenation of enolate generated from 171 proceeded highly diastereoselectively and led to 172.

Phenylselenide 172 was reduced with DIBAL and then acetylated to give acetate 173 as a mixture of anomers. Reaction of 173 with 158 was also diastereoselective due to the steric effect of bulky phenylselenyl substituent and gave β anomer 174 in almost quantitative yield. Oxidative elimination of the selenide substituent from 174 and subsequent deprotection gave Elvucitabine (126) as a single enantiomer. An analogous synthesis was described by chemists from Emory University [149].

Syntheses of Dexelvucitabine (127) [150] and later – Elvucitabine (126) [151] were described, starting from D- and L-xylose, respectively, both using almost the same methodology. In particular, D-xylose was transformed into the dibenzoyl derivative 181 using standard manipulations (Scheme 41). Under modified Appel conditions (I₂/PPh₃/imidazole), 181 gave unstable glycal 182, which reacted with fluorocytosine derivative 158 and N-iodosuccinimide to yield 183. Compound 183 was subjected to reductive elimination and deprotection to give 127.

Preparation of Dexelvucitabine (127) on a kilogram scale starting from 5-fluorocytidine (184) was developed by chemists from Pharmasset (Scheme 42).

Scheme 40  Synthesis of Elvucitabine (126) by Vion Pharmaceuticals

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Compound 184 was subjected to bromoacylation with excess of 2-acetoxy-2-methylpropionyl bromide (185) to give a mixture of esters 186 and 187. This mixture was subjected to reductive elimination to give 188, which was transformed to 127 upon alcoholysis.

Another synthesis of 127 relied on palladium mediated Ferrier rearrangement-type glycosidation of a furanoid glycal (Scheme 43) [153]. The initial steps of

**Scheme 41** Synthesis of Dexelvucitabine (127)

[152]. Compound 184 was subjected to bromoacylation with excess of 2-acetoxy-2-methylpropionyl bromide (185) to give a mixture of esters 186 and 187. This mixture was subjected to reductive elimination to give 188, which was transformed to 127 upon alcoholysis.

Another synthesis of 127 relied on palladium mediated Ferrier rearrangement-type glycosidation of a furanoid glycal (Scheme 43) [153]. The initial steps of

**Scheme 42** Synthesis of Dexelvucitabine (127) by Pharmasset
the synthesis were quite similar to those shown in Scheme 41. The major difference was the use of polymer-supported PPh₃ at the glycal generation step, which allowed for isolation of unstable glycal 189 with more than 90% purity. Palladium-catalyzed reaction of 189 with 5-fluorocytosine (9) was accompanied by Ferrier-type rearrangement and led to derivative 190, which was transformed to 127 upon deprotection.

All the reported syntheses of DPC-961 (128) and DPC-963 (129) commenced from the corresponding o-amino-α,α,α-trifluoroacetophenones 191 (Scheme 44).

![Scheme 43: Synthesis of Dexelvucitabine (127)](image)

In the first preparations of 128 and 129, 191 reacted with TMSNCO to give adducts 192, which were transformed to cyclic imines 193 upon dehydration. Reaction of 193 with lithium cyclopropylacetylenide gave racemic 128 and 129, which were subjected to chiral stationary phase HPLC to isolate 128 and 129 as pure enantiomers [136, 137]. Several improvements were reported for this synthetic scheme. In particular, diastereoselective additions of lithium cyclopropylacetylenide to the derivatives of 193 containing residues of α-phenylethyl amine or camphic acid were developed [154, 155]. Moreover, an enantioselective modification of this method employing amino alcohol 194 as an asymmetric catalyst was discovered [156, 157]. Another enantioselective method involved reaction of the derivatives of 193 and cyclopropyl acetylene itself, catalysed by amino alcohol derivatives (e.g. 195) and Zn(OTf)₂ [158].

DPC-083 (130) and DPC-082 (131) were obtained by reduction of 128 and 129, respectively, with LiAlH₄ [136, 137]. Recently, an alternative approach to the synthesis
of 130 was reported, which relied on enantioselective organocatalytic Mannich-type reaction of imine derivative 196 and cyclopropyl methyl ketone (Scheme 45) [159]. Although enantioselectivity of the key step was moderate (ee 75 %), it could be easily enhanced to >99 % by a single recrystallization of intermediate 197.

Scheme 44  Synthesis of DPC-961 (128) and DPC-963 (129)

Scheme 45  Synthesis of DPC-083 (130) using organocatalytic Mannich-type reaction
4.2 Other Antiviral Agents

Apart from anti-HIV drugs discussed in the previous section, two additional antiviral agents can be mentioned: Trifluridine (7) and Favipiravir (198). Trifluridine (7) was mentioned above as a component of Phase III investigational drug TAS-102. It is however more known as an ophthalmic anti-herpes agent launched by Glaxo Wellcome (now merged into GlaxoSmithKline) in 1980 [5]. It is effective against herpetic keratitis, and seems to be especially useful in ‘difficult’ cases [160]. High susceptibility to biodegradation of Trifluridine is advantageous for its use as ophthalmic drug, as its action in other tissues is thus prevented. As in the case of anti-tumor activity, the mechanism of antiviral action of 7 involves the inhibition of viral replication. Trifluridine does this by incorporating into viral DNA during replication, which leads to the formation of defective proteins and an increased mutation rate [161]. Inhibition of thymidylate synthetase also seems to contribute into antiviral effect of 7. The details of these processes, as well as synthesis of 7 were discussed in the above sections.

Favipiravir (198) has been discovered by Toyama Chemicals; it is currently in Phase III (Japan) and Phase II (USA) clinical trials [113, 162]. Favipiravir is under development as an agent against influenza virus, however, it was also tested against other RNA viruses, including arenaviruses, bunyaviruses, West Nile virus (WNV), yellow fever virus (YFV), and foot-and-mouth disease virus (FMDV) [163]. A proposed mechanism of action of 198 includes its biotransformation into ribofuranosyltriphosphate derivative 199 (Scheme 46), which inhibits influenza virus RNA polymerase in the host cells [164].

![Scheme 46](image)

Scheme 46  A proposed pathway of Favipiravir (198) bioactivation

One of the syntheses of 198 is based on pyrazine 200 (Scheme 47) [165, 166]. Compound 200 was transformed to methoxy derivative 201 via diazotization step; 201 was then subjected to Buchwald – Hartwig amination to give 202. Ester 202 was transformed to amide 203; diazotization of 203 in the presence of pyridine hydrofluoride led to the formation of fluoro derivative 204. The last step of the synthesis included deprotection of the methyl ether to give 198.
Scheme 47  Synthesis of Favipiravir (198) reported in 2002

Several syntheses of 198 involved difluoro derivative 205 as a key intermediate which was prepared in 4 steps from readily available materials (Scheme 48) [166, 167]. Acidic hydrolysis of 205 gave amide 206, which upon mild alkaline hydrolysis led to 198. Alternatively, compound 198 was obtained by mild alkaline hydrolysis of 205 followed by reaction with H$_2$O$_2$–NaOH, or by reaction of 205 with allyl or benzyl alcohol, removal of the protection, and hydrolysis. Recently, an improved version of this method was patented, which allowed authors to claim its industrial applicability [168].

Scheme 48  Synthesis of Favipiravir (198) via the key intermediate 205
One more method for the preparation of 198 commenced from pyrazine derivative 207, which was transformed to dichloride 208 using Sandmeyer reaction (Scheme 49) [166]. Hydrolysis of the ester moiety in 208 followed by one-pot chloroanhydride formation, introduction of fluorine atom and amination gave derivative 209, which was transformed into 198 by diazotization and subsequent hydrolysis.

Several other approaches to the synthesis of Favipiravir (198) were also described, most of them relying on direct fluorination of pyrazine derivatives with molecular fluorine [166]. All they were low-yielding and allowed for the preparation of milligram quantities of the final product.

### 4.3 Antibacterial Agents

A single compound is discussed in this category, namely GSK-1322322 (210), which was developed by GlaxoSmithKline and has reached Phase II clinical trials in bacterial skin infections [113] and Phase III – in community-acquired bacterial pneumonia [169]. Compound 210 acts as an inhibitor of peptide deformylase – an enzyme that removes the formyl group during eubacterial peptide elongation. Bacterial protein synthesis initiates with formyl-methionyl-tRNA and, consequently, all polypeptides newly synthesized in bacteria contain an N-formyl-methionine terminus. This residue is further removed in two steps catalyzed by peptide deformylase and methionine aminopeptidase, respectively. Inhibition of peptide deformylase increase production of bacterial N-formylated polypeptide, which prevents bacteria growth and possibly triggers an enhanced immune response [170]. Peptide deformylase is a metalloprotease, which mostly utilizes Fe$^{3+}$ in its active site. It was shown for analogs of 210 that N-formyl-N-hydroxylamine function coordinated to metal ion when the inhibitor was bound to the enzyme [171].
Synthesis of 210 was started from preparation of chiral diamine 211 (Scheme 50) [172]. In particular, D-serine methyl ester was converted to N-benzyl derivative 212, which was transformed into carboxylic acid 212 using reaction with chloroacetyl chloride and subsequent hydrolysis. Carboxylic acid 212 was subjected to coupling with benzyl amine, reduction, reaction with ethyl oxalyl chloride and reductive cyclization to give bicyclic compound 213. Finally, 211 Two-step reduction of 213 led to the formation of diamine 211, which was isolated as dihydrochloride. Reaction of 211 with dichloro derivative 215 and then – hydrazine hydrate gave the product 216, which was coupled with carboxylic acid 217 and subjected to catalytic hydrogenation to give 210.

Scheme 50  Synthesis of GSK-1322322 (210)
4.4 Antifungal Agents

Two drugs were launched as anti-fungal agents to date: Flucytosine (9) (Valeant, 1971) and Voriconazole (10) (Pfizer, 2002) (Fig. 6) [5]. Flucytosine itself has no antifungal activity; its activity results from the rapid conversion into Fluorouracil (1) within susceptible fungal cells [173]. The mechanism of cytotoxic effect of Fluorouracil has been discussed in the previous sections. Flucytosine is taken up by fungal cells by cytosine permease, which is the transport system for cytosine and adenine. Inside the fungal cells, 9 is deaminated to 1 by cytosine deaminase. The specificity of this step is crucial for the narrow antifungal spectrum of 9: mammalian cells as well as fungi lacking cytosine deaminase are not sensitive to 9. On the other hand, Fluorouracil itself cannot be used as an antifungal drug, since it is only poorly taken up by fungal cells and is too toxic to human cells.

The major drawback of Flucytosine is rapid development of resistance in fungi, either by mutations or by increased synthesis of pyrimidines; this limits the use of 9 as a single antifungal agent. Monotherapy with Flucytosine is currently only used in some cases of chromoblastomycosis and in uncomplicated candidosis; in all other cases, 9 is used together with other agents, usually Amphotericin B [173].

The effect of Voriconazole (10) is exerted within the fungal cell membrane. In particular, cytochrome P450-dependent 14-α-lanosterol demethylase is inhibited, which prevents the conversion of lanosterol (217) to ergosterol (218) – an important component of yeast and fungal cell membranes which does not occur in mammals (Scheme 51). This mechanism results in the accumulation of toxic methylsterols and inhibition of fungal cell growth and replication [174].
Voriconazole is active against many fungal infections, including invasive aspergillosis, *Pseudallescheria, Scedosporium, Fusarium* infections [175]. It is also proposed for empirical antifungal therapy [176]. An important advantage of Voriconazole is high oral bioavailability (96 %). The most common side effect, which is unique for Voriconazole among other azole antifungals, is a reversible disturbance of vision (photopsia): it occurs in nearly a third of patients but rarely leads to discontinuation of the drug [174]. Resistance to Voriconazole still remains uncommon, although an increase of resistance and continued surveillance with greater use of the drug has been reported [177].

The first synthesis of Flucytosine (9) has been reported in 1957 [13, 14]. The synthetic scheme is quite similar to that for Fluorouracil (1); in the case of 9, compound 27 was subjected to reaction with PCl₅ and then – liquid ammonia to give 219, which was transformed to 9 upon hydrolysis (Scheme 52). In an alternative method, compound 70 (prepared from Fluorouracil) reacted with SOCl₂ to give 220, which was transformed to 9 upon reaction with ammonia in methanol [84]. Another synthesis commenced from 2,5-difluoro-4-chloropyrimidine, which, however, is not readily accessible [178]. Flucytosine was also obtained by direct fluorination of cytosine using CF₃OF (85 % yield) [179, 180], fluorine [181, 182], and AcOF [20].

![Scheme 52 Syntheses of Flucytosine (9)](image)

Despite numerous syntheses of Voriconazole (10) were documented, they all followed the same synthetic strategy, namely, addition of anion 221 to ketone 222, followed by isolation of necessary diastereomeric pair and its resolution with 10-camphorsulphonic acid (Scheme 53). Three different approaches were used for the generation of anion 221 or the corresponding organometallic species. First of them relied on deprotonation of the pyrimidine derivative 222 (prepared from the fluorinated keto ester 223 or dichloro derivative 93) by strong bases such as LDA (Scheme 54) [183–189].
The main drawback of this method was low diastereoselectivity of the key step; therefore tedious separation of diastereomers was necessary. Another approach to generation of 221 relied on ZnCl$_2$-catalyzed decarboxylation of salts 224, prepared from 225 (Scheme 55) [190]. In this case, the desired diastereomeric pair was obtained with much better selectivity (6.5:1). The last approach relied on Reformatsky-type reaction involving 222 and bromides 226 (prepared from 223 [191, 192] or its thio analogues [193–195]) or sulfonates 227 (prepared from 93) (Scheme 56) [196, 197]. In this case, good diastereoselectivities were obtained.
Seven compounds designed as agents acting at central and/or peripheral nervous system have reached at least Phase II clinical trials, and only one of them was launched (Table 4) [3, 113]. These compounds address different biological targets and act as skeletal muscle relaxants (Afloqualone (11)), antipsychotics (BMY-14802 (228), A-437203 (229), and JNJ-37822681 (230)), nootropic agents (BMY-21502 (231)) or analgesics (BW-BW-4030W92 (232) and GW-842166X (233)).

5 Agents Acting at Nervous System

Seven compounds designed as agents acting at central and/or peripheral nervous system have reached at least Phase II clinical trials, and only one of them was launched (Table 4) [3, 113]. These compounds address different biological targets and act as skeletal muscle relaxants (Afloqualone (11)), antipsychotics (BMY-14802 (228), A-437203 (229), and JNJ-37822681 (230)), nootropic agents (BMY-21502 (231)) or analgesics (BW-BW-4030W92 (232) and GW-842166X (233)).
### Table 4  Derivatives of fluorinated diazines – nervous system modulators [3, 5, 115]

| Structure | INN or ID, development phase, company | Action |
|-----------|--------------------------------------|--------|
| ![Structure](image) | Afloqualone, launched (1983), Mitsubishi Tanabe Pharma | Skeletal muscle relaxant |
| ![Structure](image) | BMY-14802, BMS-181100, Phase II, Bristol-Myers Squibb | Antipsychotic |
| ![Structure](image) | ABT-925, A-437203, Phase II, Abbott | Antipsychotic |
| ![Structure](image) | JNJ-37822681, Phase II, Johnson & Johnson | Antipsychotic |
| ![Structure](image) | BMY-21502, BMS-181168, Phase II, Bristol-Myers Squibb | Nootropic |
| ![Structure](image) | BW-4030W92, Phase II, GlaxoSmithKline | Analgesic |
| ![Structure](image) | GW-842166X, Phase II, GlaxoSmithKline | Analgesic |
5.1 Skeletal Muscle Relaxants

A representative of fluorinated diazines, Afloqualone (11), was launched in 1983 in Japan as a central acting muscle relaxant [198]. It is an analogue of Methaqualone (234) (Fig. 7) – a drug widely used as a hypnotic, for the treatment of insomnia, and as a sedative and muscle relaxant in 1970s, but reclassified as a Schedule I controlled substance in USA in 1984 [199].

The mechanism of action of Afloqualone is not well studied. It was shown that its site of action is different from that of other central acting muscle relaxants, i.e. Mephenesin, Chlormesazone or Diazepam [200]. GABA-enhancing effect was also demonstrated [303]. The main routes of metabolism of 11 in human include N-acetylation, followed by hydroxylation at the 2′-methyl and acetyl methyl carbons, as well as glucuronidation of the aromatic amino group. This pattern of metabolism is similar to that observed in monkeys and rats, but drastically different from that in dogs [304].

Synthesis of Afloqualone commenced from 5-nitroanthranilic acid (235) which was transformed to amide 236 via the corresponding chloroanhydride (Scheme 57) [201]. Catalytic reduction of 236 followed by acetylation gave 237, which reacted with chloroacetyl chloride to form quinazoline 238. Nucleophilic substitution of chlorine atom in 238 with fluorine led to the formation of 239, which upon deprotection gave Afloqualone (11). Alternatively, compound 236 was subjected to acylation with fluoroacetyl chloride or anhydride to give amide 240 [202]. Refluxing of 240 with acetic anhydride gave quinazoline 241, which was reduced to Afloqualone either by catalytic hydrogenation or using SnCl2.

5.2 Antipsychotics

All three compounds discussed in this section (i.e. 228–230) have reached Phase II clinical trials as agents for treatment Schizophrenia. Development of BMY-14802 (228) was discontinued more than 10 years ago. For ABT-925 (229), Phase II trials were terminated in 2011; for JNJ-37822681 (230), the latest clinical study was completed in February 2012 [113]. Despite the disease addressed by 228–230 is common, the compounds express their effect through interactions with different biological targets. In particular, BMY-14802 (228) developed by Bristol-Myers Squibb acts as a dual antagonist of σ1 and 5-HT1A receptors. However, it should be
noted that relative role of these two targets in biological effect of 228 was debated in the literature. Whereas in pigeons, the effect was serotonergically mediated primarily through 5-HT$_{1A}$ receptors [203], in other model systems, these interactions did not seem to contribute significantly to the potential antipsychotic action of the compound [204]. Although studies in animal models supported for the suggestion that BMY-14802 (228) may possess antipsychotic properties [205], clinical trials showed lack of efficacy in Schizophrenia treatment [206].
Recently, BMY-14802 was proposed as a promising candidate for clinical trials of L-DOPA-induced dyskinesia – a common side effect observed during prolonged use of L-DOPA in Parkinson disease patients [207]. It was shown that the compound suppresses abnormal involuntary movements related to L-DOPA-induced dyskinesia via its 5-HT$_{1A}$ agonistic effect.

ABT-925 (229) developed by Abbott is a selective D3 receptor antagonist [208]. It was suggested that selective antagonists of D3 receptor might be promising antipsychotic agents lacking the presumed D2 receptor-mediated side effects, although D3 antagonists may express their effect via mechanisms that cannot be reflected by the commonly used animal models [209]. It was shown that ABT-925 produced cognitive signals but did not achieve sufficient D3 receptor occupancy at the doses used in clinical studies [210]. Nevertheless, these studies allowed for the assumption that the development and clinical testing of newer D3 receptor antagonists with higher potency at D3 receptors, enabling sufficient receptor occupancy, is highly warranted [211].

On the contrary, JNJ-37822681 (230) is a D2 highly selective receptor antagonist and hence acts in a mode analogous to that of most marketed antipsychotics [212]. JNJ-37822681 is characterized by a rapid dissociation rate from the dopamine D2 receptor, which was hypothesized to confer antipsychotic efficacy and improved tolerability [213]. Clinical studies in patients with an acute exacerbation of schizophrenia showed that JNJ-37822681 had similar biological activity but lesser tendency to induce weight gain compared to a known antipsychotic drug, Olanzapine (242) [214] (Fig. 8).

Synthesis of BMY-14802 (228) commenced from pyrimidine derivative 243 which reacted with piperazine 244 to give derivative 245 (Scheme 58) [215, 216]. Reduction of the compound 245 followed by deprotection gave amine 246, which was alkylated with chloride 247 and then subjected to acidic hydrolysis to form ketone 248. Reduction of 248 allowed BMY-14802 (228) to be obtained. Pure enantiomers of 228 were also obtained. To achieve this, the following methods were used: resolution of 228 with using reaction with α-phenylethyl isocyanate [217] or lipase-catalyzed acetylation or hydrolysis [218], alkylation of 245 with enantiopure alcohols 249 [219]; and microbial reduction [305] or Ru-catalyzed enantioselective hydrogenation [220] of 248.
ABT-925 (229) was obtained starting from amidine 250 and ethyl trifluoroacetacetate to give pyrimidine 251 (Scheme 59) [221]. Reaction of 251 with SOCl₂ and then – piperazine led to the formation of amine 252. Selective alkylation of 252 with 1-bromo-3-chloropropane gave chloride 253, which reacted with thiouracil anion to form ABT-925 (229).

Scheme 58  Synthesis of racemic BMY-14802 (228)

Scheme 59  Synthesis of ABT-925 (229)
Synthesis of JNJ-37822681 (230) was quite trivial and relied on selective functionalization of 4-aminopiperidine core, first with 3-chloro-6-trifluoromethylpyridazine (254) and then – with 3,4-difluorobenzaldehyde (Scheme 60) [222].

Scheme 60 Synthesis of JNJ-37822681 (230)

5.3 Nootropic Agents

BMY-21502 (231) was developed by Bristol-Myers Squibb as nootropic agent (i.e. for cognition disorders) and has reached Phase II clinical studies. The compound was effective in vitro [223] as well as in animal models [223–227, 306] that may predict cognitive enhancement. The mode of action of BMY-21502 is poorly understood. It was shown that the compound has an anti-anoxic action, and activation of the CNS cholinergic system is involved as one of the causative mechanisms for this effect [228]. Clinical trials showed that BMY-21502 was not significantly superior to placebo in Alzheimer’s disease; moreover, although generally well tolerated, 231 also had a higher rate of discontinuations [229, 230].

Synthesis of BMY-21502 (231) optimized for large scale preparations commenced from malonodiamide and ethyl trifluoroacetate, which reacted to give pyrimidine 255 (Scheme 61) [231]. Compound 255 was transformed into dichloro derivative 256 upon treatment with POCl3. Reaction of 256 with piperidine 257 (prepared from 4-pyridinylmethyl chloride in two steps) gave 258, which was reduced catalytically to form BMY-21502 (231). Alternatively, BMY-21502 was obtained by arylation of 257 with 4-chloro-2-trifluoromethylpyrimidine (259) [232].
5.4 Analgesics

Both the compounds discussed in this section, i.e. BW-4030W92 (232) and GW 842166X (233), were developed by GlaxoSmithKline. Development of BW-4030W92 was discontinued in 2002; the latest Phase II clinical studies of GW-842166X were completed in 2009 [113]. BW-4030W92 (232) was developed as a CNS-acting antihyperalgesic agent (i.e. for treatment of increased sensitivity to pain). It is an analogue of anticonvulsant drug Lamotrigine (260) (Fig. 9), used in the treatment of epilepsy and bipolar disorder [233]. Like Lamotrigine, BW-4030W92 binds to the transmembrane segment S6 in domain IV of α subunit of voltage-gated sodium channels (Na\textsubscript{v}), thus acting as a pore blocker [234]. It is assumed that neuropathic pain is partially mediated by an increase in the density of Na\textsubscript{v} channels in injured axons and their dorsal root ganglions. Clinical studies in patients with chronic neuropathic pain showed that although BW-4030W92 significantly lowered allodynia severity at the first day, the effect did not maintain in further treatment [235].

GW-842166X (233) is a selective CB2 receptor full antagonist which has potent analgesic, anti-inflammatory and anti-hyperalgesic actions. It was selected as a clinical candidate after lead optimization of a pyrimidine ester 261 (GK02076, Fig. 9), identified in a focused screen as a partial agonist at the CB2 receptor with
micromolar potency [236]. The compound was evaluated as an analgesic for treatment of inflammatory pain (Phase I trials) and dental pain (Phase II trials) [113]. In the latter study, single doses of GW842166 failed to demonstrate clinically meaningful analgesia in the setting of acute dental pain [237].

Synthesis of BW-4030W92 (232) started from 2,3-dichlorobenzaldehyde (262) which was transformed into nitrile 263 (Scheme 62) [238]. Compound 263 which reacted with ethyl diethoxyacetate – t-BuOK and then – ethyl iodide to give enol ether 264. Reaction of 264 with guanidine afforded pyrimidine derivative 265, which upon deprotection gave aldehyde 266. Compound 266 was reduced with sodium borohydride and then subjected to reaction with diethylaminosulphur

![Scheme 62 Synthesis of racemic BW-4030W92 (rac-232)](image-url)
trifluoride (DAST) to give racemic 232. Alternatively, nitrile 263 reacted with ethyl fluoroacetate – t-BuOK and then – ethyl iodide to give enol ether 267, which was transformed to racemic 232 by reaction with guanidine. Resolution of enantiomers of 232 was achieved by crystallization of dibenzoyl-L-tartaric acid salt; the more active R-enantiomer was isolated.

In the synthesis of GW-842166X (233), commercially available pyrimidine 268 reacted with 2,4-dichloroaniline to give ester 269, which was subjected to hydrolysis followed by amide coupling with 4-aminomethyltetrahydropyran (270) to afford 233 (Scheme 63) [236, 239, 240].

Scheme 63  Synthesis of GW-842166X (233)

6  Other Classes

In the previous sections, compounds targeting cancer cells or nervous system, as well as those fighting foreign organisms were discussed.

Three compounds do not fall into any of these categories. Fostamatinib disodium (88) was mentioned above as an anti-cancer investigational drug, but it was also studied as agent for autoimmune diseases, i.e. rheumatoid arthritis (currently in Phase III) and autoimmune thrombocytopenia (in Phase II). Gemigliptin (12) was approved as an anti-diabetic drug in South Korea in 2012. PF-04634817 (271) was discontinued after Phase I studies as an agent for liver fibrosis; nevertheless, it is currently investigated in diabetic nephropathy (Fig. 10) (Phase II, October 2012) [113].
As it was mentioned in the previous sections, the active principle of Fostamatinib disodium (88) is Tamatinib (92), which is formed by enzymatic hydrolysis of 88 in the intestine. As in the case of lymphoma, the effect of 88 in autoimmune diseases is related to inhibition of Spleen tyrosine kinase (Syk) by 92 [241, 242]. As Syk has the central role in transmission of activating signals within B cells, inhibition of this enzyme lowers expression of a number of pro-inflammatory cytokines and hence leads to immunosuppression [243]. Fostamatinib has shown significant efficacy in the treatment of patients with rheumatoid arthritis not responding to Methotrexate (272) (a drug which is used conventionally in therapy), although a number of adverse events were observed [244]. If these results are confirmed once Phase III studies are completed, it may find a place in the treatment of patients with rheumatoid arthritis with poor response to conventional therapy (Fig. 11).
Gemigliptin (12) was developed by LG Life Sciences as an inhibitor of dipeptidyl peptidase 4 (DPP-4) – a target of oral drugs used to treat type 2 diabetes (characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency) [245]. The first representative of this class, Sitagliptin (273) was launched in 2006. In human body, Gemigliptin is metabolized to LC15-0636, which is a major active metabolite, by cytochrome P450 3A4 isozyme [246]. Inhibition of DPP-4 results in increase of incretin levels (which is normally inactivated by DPP-4), in particular glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) [247]. Incretins inhibit glucagons release and stimulate insulin secretion, which leads to decrease in glucose blood levels. Clinical trials showed efficacy and safety of Gemigliptin administered once daily as a monotherapy, [248] as well as in addition to Metformin (274) [249] for type 2 diabetes patients.

PF-04634817 (271) is a Pfizer’s investigational drug, initially developed as agent for liver fibrosis – formation of excess fibrous connective tissue in liver [250]. The development of the compound was discontinued since February 2012 after Phase I trials. Recently, a Phase II study of PF-04634817 in diabetic nephropathy – a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli [251] – was registered [113]. PF-04634817 is an antagonist of chemokine receptors (i.e. CCR2 and CCR5) [252]. These chemokine receptors are important players in the trafficking of monocytes/macrophages and in the functions of other cell types relevant to pathogenesis of many diseases [253], including liver fibrosis [307] and diabetic nephropathy [254].

Gemigliptin (12) was prepared by a convergent synthesis involving key intermediates 275, 276 and 277 (Scheme 64) [255]. Compound 275 was obtained by Swern oxidation of β-amino acid derivative 278. Both 276 and 277 were prepared starting from N-Boc-3-piperidone 279. In particular, 279 reacted with diethylaminosulfur trifluoride (DAST) to give difluoro derivative 280. Ru-catalyzed oxidation of 280 led to the formation of amide 281, which was subjected to ring-opening with NaOMe and then acidic deprotection to give hydrochloride 276. To obtain 277, N-Boc-3-piperidone was deprotonated and then acylated with ethyl trifluoroacetate to give β-diketone 282. Reaction of 282 with trifluoroacetamidine followed by deprotection afforded 277. Further step of the synthesis included reductive amination of aldehyde 275 with amine 276, which was accompanied with piperidone ring formation to give 283. Full deprotection of 283 followed by selective protection of the amino group gave carboxylic acid 284, which was coupled with amine 277 to afford Boc derivative 285. Finally, deprotection of 285 led to the formation of Gemigliptin (12).

Synthesis of optically active PF-04634817 (271) based on commercially available (-)-Vince Lactam as chirality source. Starting from (-)-Vince Lactam the chiral key 4-amino-2-cyclopentene-1-carboxylic acid derivative 286 was synthesized. The compound 286 is dimethyl pyrrole protected form of corresponding aminoacid, which was subjected to amide coupling with Boc-protected diamine 287 to give
Fluorine-Containing Diazines in Agrochemistry

Agrochemistry is one of more important field of application of the fluorinated compounds which is widely recognized [256, 257]. Eleven derivatives of fluorine-containing diazines are agrochemicals: 8 compounds (292–299) are herbicides;
Fluoxastrobin (300) is a fungicide, Fluacrypyrim (301) – an acaricide, and Flufenerim (302) is currently under development as an insecticide (Fig. 12).

8 Herbicides

8.1 Protoporphyrinogen Oxidase Inhibitors

Uracil derivatives Butafenacil (292, Inspire®, Rebin®) and Benzfendizone (293) were introduced as herbicides in 1998, whereas their pyridazine-derived analogue Flufenpyr-ethyl (295) – in 2000 [258]. Butafenacil (developed by Syngenta
AG) is used for weed control in grapes, nut crops, pome and stone fruits and also as a cotton defoliant [259]. It was registered in Australia and approved by U. S. environmental protection agency. Benzfendizone (developed by FMC Corporation) is a post-emergence herbicide that provides good control of grass and broadleaf weeds in tree fruits and vines, as a cotton defoliant, and in total vegetation control [256]. Flufenpyr-ethyl (developed by Sumitomo Chemical

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**Fig. 12** Agrochemicals derived from fluorine-containing diazines

AG) is used for weed control in grapes, nut crops, pome and stone fruits and also as a cotton defoliant [259]. It was registered in Australia and approved by U. S. environmental protection agency. Benzfendizone (developed by FMC Corporation) is a post-emergence herbicide that provides good control of grass and broadleaf weeds in tree fruits and vines, as a cotton defoliant, and in total vegetation control [256]. Flufenpyr-ethyl (developed by Sumitomo Chemical
Company) was registered in USA for use on corn, soybeans and sugarcane [259].

The most recent example is Saflufenacil (294, Kixor®), introduced by BASF in 2009 for preplant burndown and selective PRE dicot weed control in multiple crops, including corn. [260].

Compounds 292–295 act as inhibitors of protoporphyrinogen oxidase (Protox) – an enzyme in the chloroplasts of the plant cells that oxidizes protoporphyrinogen IX (303) to produce protoporphyrin IX (304) (Scheme 66) [261]. In turn, 304 is a precursor molecule for both chlorophyll and heme. When protoporphyrinogen oxidase is inhibited, protoporphyrinogen IX is accumulated and transferred from chloroplasts into the cytoplasm, where non-enzymatic conversion of 303 to 304 occurs. When present in cytoplasm, 304 is cytotoxic due to interaction with oxygen upon action of light, which results in formation of singlet O₂ molecules. ¹O₂ causes lipid peroxidation, membrane disruption and plant cell death.

Butafenacil is known to be eye, skin and respiratory tract irritant in humans [262]. It also demonstrated very high toxic effect to algae, and moderate toxicity to fish, aquatic invertebrates and honeybees. For Benzfendizone and Flufenpyr-ethyl, no reports on toxic effects are available. Acute mammalian toxicology studies of Saflufenacil indicate that herbicide has low toxicity for mammals after ingestion, dermal exposure or inhalation. It is not an irritant for eyes and skin and does not act as a sensitizer.

Studies of the structure–activity relationship (SAR) of uracile derivatives as protox inhibitor showed that presence of a polyfluorinated alkyl group at position 6 of the uracil ring critical. Alkyl groups such as methyl at position 6 of the uracil ring resulted in compounds with low or no biological activity [263].

Limited data are available on the synthesis of Butafenacil (292). In particular, it was prepared by esterification of carboxylic acid 305, [264] as well as by reaction of isocyanate 306 with ester 307 (Scheme 67) [265]. Preparation of neither 305 nor 306 was disclosed in the corresponding patents, although synthesis of carboxylic acid 305 was partially described elsewhere [266].

![Scheme 66](image-url) Biological role of protoporphyrinogen oxidase
Benzfendizone (293) was obtained from ethyl trifluoromethylaminocrotonate (308) which reacted with isocyanate 309 in the presence of NaH and then directly methylated to give 310 (Scheme 68) [267]. Demethylation of phenol moiety in 310 followed by alkylation with benzyl chloride 311 gave Benzfendizone.

The synthesis of Saflufenacil (294) is similar to Benzfendizone synthesis, but on the key step of uracile formation instead of isocyanate corresponding urethane 316 was used in basic conditions. Starting amine 315 was obtained in 3 steps from acid...
The final step of Saflufenacil formation is alkylation by Me$_2$SO$_4$ in phase transfer conditions (Scheme 69) [268].

Scheme 69  Synthesis of Saflufenacil (294)

In the preparation of Flufenpyr-ethyl (295), hydrazones 318 or 319 were the key synthetic intermediates (Scheme 70) [269–271]. Both compounds 318 and 319 were prepared by reaction of dibromoketone 320 and the corresponding hydrazines 321 and 322, in turn obtained by reduction of diazonium salts 323 and 324. Alternatively, hydrazone 319 was prepared by reaction of 324 and ethyl trifluoroacetooacetate, followed by hydrolysis and decarboxylation.

Further transformations of 319 included reaction with (carbethoxylidene)triphenylphosphorane resulting in the formation of pyridazine derivative 327. Acidic hydrolysis of 327 led to 328, which was alkylated with ethyl bromoacetate to give 295 (Scheme 71).
Scheme 70  Syntheses of key intermediates for Flufenpyr-ethyl (295)

Scheme 71  Synthesis of Saflufenacil via Wittig approach (295)

Alternatively, either 318 or 319 reacted with methylmalonic acid to give adducts 329 or 330, which underwent cyclization upon heating with carboxylic acid and a base to give 331 and 327, respectively. Both 331 and 327 were transformed to Flufenpyr-ethyl (295) as described above (Scheme 72).
8.2 Acetohydroxy Acid Synthase Inhibitors

Compounds discussed in this section are derivatives or analogues of sulfonylurea herbicides – agrochemicals which began the present low-dose era of herbicide chemistry in 1970s [257]. Primisulfuron-methyl (299) (from Ciba-Geigy Corporation and Syngenta AG) is a sulfonylurea derivative introduced in 1990 [262]. It is used for post-emergence control of actively growing weeds in corn and in non-cropland areas [272]. Cloransulam-methyl (296), Florasulam (298), and Diclosulam (297), all developed by Dow AgroSciences, are examples of the triazolopyrimidine sulfonanilide herbicides; they were introduced in 1998, 1999, and 2000, respectively. Cloransulam-methyl is used for soil-applied and post-emergence control of broadleaf weeds in soybeans [273]. Florasulam is a highly-selective broadleaf herbicide which is registered for use in cereals in many countries around the world. Diclosulam-based products are registered for use to control annual and certain perennial broadleaf weeds; they can be applied as soil, foliar, or burndown treatments in crops such as sugar cane, peanuts and soybeans and in forestry applications.

Compounds 296–299 inhibit acetohydroxy acid synthase (AHAS), formerly known as acetolactate synthase. Its activity is not present in animals, but it has been found in all plants where measurements have been attempted. Acetohydroxy acid synthase catalyses the first step in production of branched amino acids (leucine, valine and isoleucine) (Scheme 73), which are obviously needed for the protein synthesis and cell growth. The compounds 296–299 seem to bind within the substrate-access channel of the enzyme, thus blocking α-ketocarboxylate access to the active site. While these herbicides are undoubtedly highly successful, resistance developed due to mutations within AHAS is becoming a serious problem [274, 275].
Primisulfuron-methyl is a slightly toxic for skin, inhalation and eye exposure, with little metabolic activity in mammalian. It is slightly toxic to freshwater fish, aquatic organisms and to marine shrimp and has no toxic effect on birds and honey-bees [276]. Cloransulam-methyl can be highly toxic to certain aquatic plants and algae on an acute basis; it is practically nontoxic to other non-plant organisms. Florasulam is highly toxic to aquatic organisms and slightly toxic to birds, and Diclosulam is very highly toxic to aquatic organisms [272].

In contrast to uracile herbicides in which CF\textsubscript{3}-group is critical for activity in fluorinated triazolopyrimidine series fluorine atom responsible for the metabolic transformation of the herbicides. The different metabolic pathway of the triazolopyrimidine herbicide diclosulam and Cloransulam-methyl are guided by the fluorine atom at the 7-position on the triazolopyrimidine ring system (Scheme 74). The predominance of one pathway is very crop specific. In cotton, 296 and 297 are metabolized by the displacement of the 7-fluoro substituent on the triazolopyrimidine ring by a hydroxy group, forming 332. Its soybean selectivity is attributed to facile conjugation with homo-glutathion (homoGSH), which displaces the 7-fluoro substituent (333). This mechanism was found to only occur in soybeans for these herbicides. In maize and wheat, 296 and 297 are detoxified by hydroxylation at the 4-th position on the aniline moiety (334) followed by subsequent glycosidation [277].
Cloransulam-methyl (296) and Diclosulam (297) were obtained by reaction of sulfonyl chloride 340 with the corresponding aniline derivatives (Scheme 75). Synthesis of 340 commenced from dichloropyrimidine 335 [278], which reacted with KF and then – hydrazine hydrate to give 337. Reaction of 337 with CS₂/Et₃N and then – benzyl chloride was accompanied by Dimroth rearrangement and gave

Scheme 74  Metabolism of Cloransulam-methyl (296) and Diclosulam (297) in crops

Cloransulam-methyl (296) and Diclosulam (297) were obtained by reaction of sulfonyl chloride 340 with the corresponding aniline derivatives (Scheme 75). Synthesis of 340 commenced from dichloropyrimidine 335 [278], which reacted with KF and then – hydrazine hydrate to give 337. Reaction of 337 with CS₂/Et₃N and then – benzyl chloride was accompanied by Dimroth rearrangement and gave

Scheme 75  Synthesis of Cloransulam-methyl (296) and Diclosulam (297)
[1,2,4]triazolo[1,5-c]pyrimidine derivative 338, which was transformed to 339 by treatment with EtONa. Finally, chlorination of 339 in H$_2$O–CHCl$_3$ led to the formation of 340. Reaction of 340 with the corresponding aniline derivatives was performed in the presence of Me$_3$SiCl–NaI [278], as well as of N-arylsulfilimine compounds 341 [279] or 1,2-diols (e.g. 1,2-propanediol) [280].

Florasulam (298) was synthesised starting from dichloropyrimidine 93, which was converted to dimethoxy derivative 342. The reaction of 342 with hydrazine hydrate in MeOH regioselectively leads to hydrazine 343, which was cyclized with CS$_2$ into [1,2,4]triazolo[4,3-c]pyrimidine-3-thion 344. The based catalysed Dimroth rearrangement of 344 gave [1,2,4]triazolo[1,5-c]pyrimidine-2-thione 345. Oxidation of 345 followed by chlorination and sulfamide coupling afforded target Florasulam (298) in high preparative yield (Scheme 76) [281–283].

![Scheme 76 Synthesis of Florasulam (298)](image)

The synthesis of Primisulfuron-methyl (299) started from reaction of diethyl malonate and thiourea (Scheme 77) [284]. The resulting pyrimidine derivative 348 was methylated, difluoromethylated and then oxidized to give sulfone 351. Reaction of 351 with aqueous ammonia gave heteroaromatic amine 352, which was transformed to Primisulfuron-methyl (299) upon treatment with isocyanate 353.
Mitochondrial Respiratory Chain Inhibitors

Fluoxastrobin (300) is a pesticide from Bayer CropScience for the control of fungal diseases, which was registered by U. S. environmental protection agency (EPA) in 2005 [276]. Fluoxastrobin is used on peanuts, tuberous and corm vegetables, leaf petiole vegetables, fruiting vegetables and turf. Fluacrypyrim (301) was discovered by BASF AG and introduced in 2002 by Nippon Soda Co., shows acaricidal effect against all stages of tetranychid [285]. Both 299 and 300 are representative of strobilurin family with parent compound Strobilurin A (354) (Fig. 13), discovered in late 1970s [286]. Interestingly, Fluacrypyrim (301) is the first representative of strobilurin family which is not used as a fungicide.

Strobilurins are the part of the larger group of the so-called quinone outside inhibitors (QoI) – compounds which act at the quinol outer binding site of the cytochrome bc1 complex. This enzyme, also referred to as ubiquinol: ferricytochrome c reductase, or complex III, is the third complex in the electron transport chain – a cascade of enzymes which couples electron transfer between NADH and O2 with the transfer of H+ ions across a membrane to generate chemical energy in the form of adenosine triphosphate (ATP) [287]. The overall result of the reaction catalyzed by cytochrome bc1 complex is reduction of ferricytochrome c by oxidation of ubiquinol (355) and the concomitant pumping of 4 protons from the mitochondrial matrix to the intermembrane space. The mechanism of this process is too sophisticated to be discussed herein. It is important that the enzyme has two binding sites for the substrate 355 or its oxidized form 356 (Fig. 14), i.e. outer (Qo) and inner (Qi), and the quinone outside inhibitors bind to the outer site. This leads to inhibition of mitochondrial respiration – a process which is essential to all living organisms. The selective biological effect of quinone outside inhibitors on certain organisms (i.e. fungi or mites) is achieved by differential penetration and
degradation between various species, leading to a combination of high fungicidal (or acaricidal, in the case of \(301\)) potency and good crop safety [288]. Unfortunately, resistance has already evolved to this class of pesticides in some plant pathogens in certain geographical areas [289].

Although the *in vitro* fungicidal activity of the natural strobilurin A was discovered soon, its agrobiological testing *in vivo* was difficult because of its volatility and the inherent lability of the \((E,Z,E)\)-triene system, which resulted in rapid photolytic or metabolic degradation. The unusual structural simplicity of this natural product soon made it a target for chemical derivatization. Below a set of isosterical replacement in a course of lead optimization of natural strobirulin A leading to commercial synthetic products shown on the Fig. 15.

The first sequence leads to first commercialized strobilurin azoxystrobin (1996, Amistar®, Syngenta) and to fluoxastrobin (\(300\)), which structure combines a methoximino 5,6-dihydro-1,4,2-dioxazin-2-yl toxophore (Bayer toxofore) with an optimally adjusted side-chain bearing a 6-(2-chlorophenoxy)-5-fluoro-pyrimidin-4-yl-oxy moiety as an essential element. Fluoxastrobin (\(300\)) has an advantage as no reorientation of the toxophore is necessary for binding to the target. The SARs studies indicate that the fluorine atom has a beneficial effect on the phytotoxicity and leaf systemicity. Another sequence leads to Picoxystrobin (2002, Acanto®, Syngenta), which has a 6-CF\(_3\)-pyridin-2-yl moiety in its arylalkyl ether side-chain. An indication switch from the fungicidally to acaricidally active strobilurin type with \(\beta\)-methoxyacrylate pharmacophore is achieved by exchange of the 6-CF\(_3\)-pyridin-2-yl moiety in the arylalkyl ether side-chain of Picoxystrobin with a 2-iPrO-6-CF\(_3\)-pyrimidin-4-yl moiety to give fluacrypyrim (\(301\)).

Fluoxastrobin (\(300\)) was obtained by reaction of compounds 359 and 360 in the presence of K\(_2\)CO\(_3\) (Scheme 78) [290]. Compound 359 was prepared by reaction of 4,5,6-trifluoropyrimidine (\(358\)) with potassium \(\alpha\)-chlorophenolate. In turn, 358 was obtained from 5-chloro-4,6-difluoropyrimidine (\(357\)) by reaction with KF.
Fig. 15  Map of isosterical replacement for lead optimization of natural strobirulin A

Scheme 78  Synthesis of Fluoxastrobin (300)

The synthesis of key intermediate 360 bearing unusual fragment of 5,6-dihydro-1,4,2-dioxazin was developed by Bayer in 2002. Synthesis started from
benzofuran-3-one which was converted to oxime 362. Nitrozation of 363 with followed alkylation with bromoethanol leads to bisoxime 364, with under acidic treatment gave target dioxazin 360 (Scheme 79) [291].

Scheme 79  Synthesis of key intermediate 360

Preparation of Fluacrypyrim (301) started with reaction of O-isopropylisourea hydrochloride and ethyl trifluoroacetooacetate to give pyrimidine 361 (Scheme 80) [292]. Alkylation of 361 with bromide 362 (or the corresponding chloride 363 [293].
in the presence of alkali or K₂CO₃ gave Fluacrypyrim. Cu₂O-catalyzed alkylation of 361 was also developed for the synthesis of 300 [295]. Compounds 362 and 363 were obtained using several closely related methods. In particular, TiCl₄-mediated reaction of chloride 366 and methyl orthoformate was used to obtain 363 (Scheme 81) [293, 294]. Alternatively, 366 reacted with methyl formate in the presence of TiCl₄–Et₃N to give 367, which was treated with p-toluenesulfonic acid in methanol to give 363. Yet another method included reaction of 367 with methyl orthoformate to give 368, which was transformed to 363 upon treatment with methanesulfonic acid.

Another approach to Fluacrypyrim (301) commenced from pyrimidine derivative 364, which reacted with methyl formate in the presence of TiCl₄–Et₃N to give 365 (Scheme 81) Synthesis of key intermediate 363

Methylation of 365 using methyl orthoformate or dimethyl sulphate and alkali led to the formation of 301.

The last pesticide from this section is Flufenerim (Flumfen® 302), which is under development by Ube Industries as an insecticide. It is reported to control aphids, whiteflies, and cotton leafworm, but has no activity against thrips [296]. Since Flufenerim is chemically related to Pyrimidifen (Miteclean® 369) (Fig. 16), it was initially believed to have similar mechanism of action, i.e. inhibition of the mitochondrial electron transport of NADH dehydrogenase (NADH: ubiquinone oxidoreductase, complex I) – an enzyme which transfers electrons from NADH to ubiquinone and hence opens the electron transport chain cascade. Nevertheless, it was shown that 302 reduced activity of acetylcholinesterase – an effect which possibly can be addressed to interaction with other systems [297].

Flufenerim (302) was prepared from 4,5-dichloro-6-ethylpyrimidine (347) (Scheme 82) [298]. Compound 370 was chlorinated with chlorine gas; the product 371 thus obtained was subjected to nucleophilic substitution with AcOK to give acetate 372, which upon hydrolysis and subsequent reaction with diethylaminosulphur trifluoride (DAST) gave fluoride 374. Finally, reaction of 374 with amine 375 led to the formation of Flufenerim (302).
Conclusions and Outlook

Since discovery of the first fluorinated diazine – antineoplastic agent 5-fluorouracil more than 20 compounds from the class were introduced into the market. Undoubtedly the success was achieved due to joint progress of medicinal chemistry, agrochemistry as well as synthetic methods of heterocyclic and fluoroorganic chemistry. The continued progresses in these fields of science allow us to predict that the number of fluorine containing diazines as drugs or agrochemicals on the market will be increased. Recent trends in using of perfluorinated diazines as core scaffold for the synthesis of a diverse array of polysubstituted fluorinated diazines for HTS increases probability of these compounds as potential hits and leads. Also the new methodologies of direct introduction of fluorinated substituent, like Baran approach, continue to appear facilitating further investigation. Moreover in the chemical space covered by fluorinated diazines remains “white spots”. Thus diazine scaffold decorated by important in med and agrochem fluorinated fragments such as -CHF₂, -CH₂CF₃, -OCF₃, -SCF₃, -SF₅ not investigated because the synthetic chemistry of these compounds on development phase or not developed at all. Therefore the comprehensive investigations in the field of fluorinated diazines still are interesting both for academic and industrial scientists.
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