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Review

Fluorine in medicinal chemistry: A review of anti-cancer agents☆

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Abstract

In this review those fluorinated compounds which have found a role as anti-cancer agents are summarized. The emphasis is to highlight the important drugs but also to highlight the latest developments on emerging compounds. This has been done as comprehensively as possible with the objective of informing readers of some of the latest developments in this area.

Keywords: Pharmaceutical; Fluoro-substituent; Drug; Prodrug; Anti-cancer agent

Contents

1. Introduction

The occurrence of a fluorine substituent in commercial pharmaceutical compounds continues to increase by 2% in 1970 to estimates of more that 18% at present. The figures are higher (currently above 28%) in agrochemicals [1]. In the US in 2002, 9 in 31 new drugs licensed in 2002 contained a fluo-rine [2]. Thus, it can be conservatively estimated that globally about 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom. This is a high frequency considering organo-fluorine compounds are virtually absent as natural products, the traditional source of bioactives [3]. The very special effects of fluorine have proven difficult to divine in detail and the high frequency of the element in small molecule bioactives has generally arisen from intense structure–activity relationship (SAR) studies, rather than rational predictive outcomes [4]. Of course some of the effects

☆ This is the first of three invited reviews dealing with different aspects of the use of compounds containing the C–F bond in medicinal chemistry. The other reviews will appear in subsequent issues during 2006.

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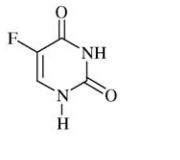
of fluorine substitution are relatively straightforward to interpret in that the fluorine substituent, when strategically positioned, can suppress adventitious metabolism, relative to the hydrocarbon analogue. However, it is never easy to predict the influence of fluorine substitution on the overall pharmacokinetic in a given situation. This remains a trial and error process. The importance of organo-fluorine compounds in medicinal chemistry continues to stimulate interest in the origins of the more cryptic effects of fluorine introduction. For example now the availability of extensive X-ray data of small molecule interactions with proteins, has begun to reveal generic stabilizing interactions between the C–F bond and the protein, which improve our understanding of the predictable influence of fluorine incorporation [5].

In this review, which is part of a series of three from different laboratories, we summarise those fluorinated compounds which have found a role as anti-cancer agents. The emphasis is not only to highlight the important drugs in each case but also to highlight the latest developments on emerging compounds. We have tried to do this as comprehensively as possible but as always it is difficult to mine into the pharmaceutical patent and licensing literature, and consequently the review will fall short as a comprehensive account. It is hoped that readers interested in this topic will become informed of some of the latest developments in this area.

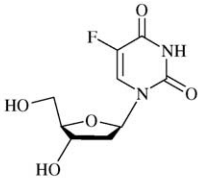
2. Anti-cancer

2.1. Thymidylate synthase inhibitors

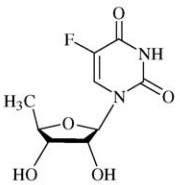
The development of pharmacological agents able to counteract the mechanisms of drug resistance in oncology has remained a major goal for the past two decades. Fluorinated organic molecules are known to perform a wide range of biological functions and fluorinated anti-cancer agents have become a focus in the development of new therapies for cancer. An increasing number of fluorinated antimitotic/antitumour agents have now becoming available for cancer treatment [6]. The most widely used are the 5-fluoropyrimidines such as 5-fluorouracil (5-FU) **1**, 5-fluoro-2′-deoxyuridine (FdUrd) **2**, and their prodrug derivatives **3–8** [7]. Such prodrugs are converted to the bioactive in vivo.



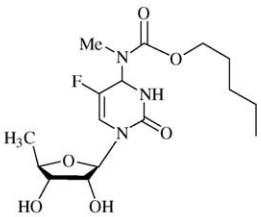
5-fluorouracil (FU) **1**



floxuridine (FdUrd) **2**



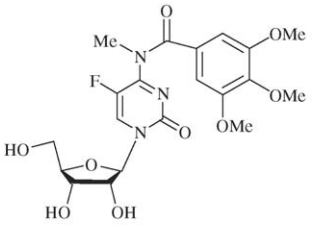
furtulon (5'dFUrd) **3**



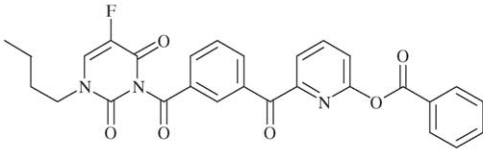
capecitabine (CAP) **4**, xeleoda

Heidelberger et al. [8] synthesized 5-FU in 1957, as an antimetabolite. The active form of these drugs is the uridine 5′-phosphate, which is generated in vivo. 5-FU and its derivatives are potent mechanism based inhibitors of thymidylate synthase (TS), an enzyme which converts 2′-deoxyuridine-5′-monophosphate (dUMP) to 2′-deoxythymidine-5′-monophosphate (dTMP) utilizing 5,10-methylenetetrahydrofolate as the source of the methyl group as well as the reductant [9]. This transformation represents the sole de novo source of dTMP, a building block for DNA-synthesis and repair [10]. A number of detailed reviews on the mechanism of TS inhibition by 5-FU and derivatives have been published [11] and an understanding of 5-FU mechanism of action has resulted in major therapeutic advances in the past 15 years. Thus, inhibition of TS by antimetabolites remains a classic approach and a key strategy for suppressing cell division in cancerous tissue [12].

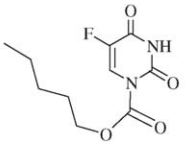
5-FU has been used extensively in the treatment of skin cancers and a variety of solid tumours, such as breast, colorectal and gastric cancers. It is usually administered by intravenous bolus or by continuous infusion. Although the latter route is generally the more efficient and less toxic, it is costly and inconvenient [13]. Unfortunately, treatment of cancer with 5-FU has been found to cause neurotoxic and cardiotoxic side effects. Toxicity also derives from the lack of selectivity of the drug towards tumours and resistance can occur if the cell produces excess quantities of dUMP to compete with the drug for the active site [14].



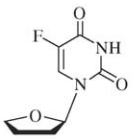
galocitabine **5**



emitefur (BOF-A2) **6**



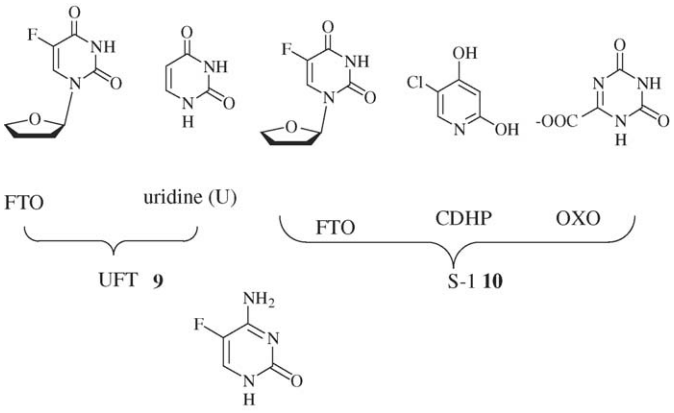
camofur **7**



ftorafur (FTO) **8**

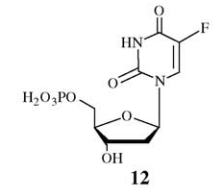
Pharmacological strategies developed to enhance the therapeutic index of 5-FU have included the addition of non-

fluorinated biochemical modulators such methotrexate, cisplatin, oxiplatin, levamisole, leucovorin and irinotecan (CPT-11) [15]. Such combination therapies have resulted in improved efficacy in the treatment of gastrointestinal cancers, breast cancers and head and neck cancers. Unfortunately, the strategies have not been effective in the management of metastic colorectal cancer where studies have shown an increase in response rates without significantly impacting survival [16]. Several oral 5-FU prodrugs such as furtulon **3**, capecitabine **4**, galocitabine **5**, emitefur **6**, camofur **7** and ftorafur (tegafur **8**) have also been developed to improve such side effects and are being used clinically, either alone or in combination therapy with other anti-cancer agents, in several countries [17]. Several combinations with 5-FU and its derivatives display promising anti-cancer activity and low toxicity. For example tegafur plus uracil **9** (UFT) [18] and S-1 **10** [19] plus fluorocytosine **11** [20] have been developed in the past 20 years.



5-fluorocytosine (FC) **11**

The ethynyl analogue of 5-fluoro-2′-deoxyuridine-5′-phosphate **12**, 5-ethynyl-2′-deoxyuridine-5′-phosphate **13**, also known as eniluracil (GW 776) is another potent inhibitor of dihydropyridine dehydrogenase [21]. This has the potential to become involved in an irreversible interaction *via* enzyme-mediated conversion of the acetylenic side-chain to a chemically reactive allene [22]. However, inhibition of dTMP synthase by **13** was found also to require the presence of 5,10-methylenetetrahydrofolate; in addition the activity of the enzyme recovered very rapidly [23], so this mechanism is not substantiated. 5-Fluoropropynyl-dUMP **14**, an improved derivative of **13**, has been designed, based on a mechanistic rationale, as a prototype of a new generation of dTMP synthase inhibitors [24]. Novel radiation-activated prodrugs of the antitumour agent 5-FdUrd, possessing an indolequinone structure (IQ-FdUrd) **15**, have been designed [25]. IQ-FdUrd has been shown to be a potential prototype compound for radiation-activated antitumour prodrugs that are useful for radiation treatment of tumours [25]. Historically, methotrexate **16** has been an extremely useful and widely prescribed TS inhibitor but it is limited by its toxicity and appears to cause more damage to the cell genome than it gains from inhibition [26]. Gallagher and co-worker [27] and Jackson et al. [28] have recently reported phase II/III results indicating that the fluorinated analogue of methotrexate, ZD9331, **17** is active against ovarian cancer cell lines that are resistant to classical TS inhibitors and comparable to gemcitabine in the treatment of pancreatic cancer.



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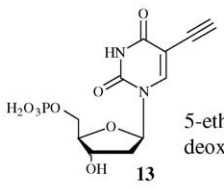
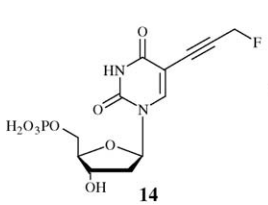


13 5-ethynyl-2'-deoxyuridine 5'-phosphate



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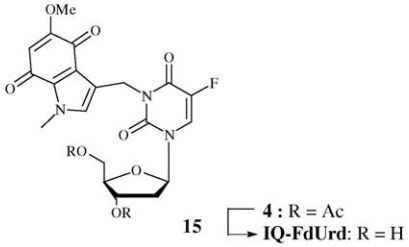

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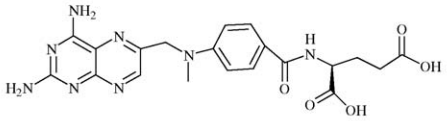
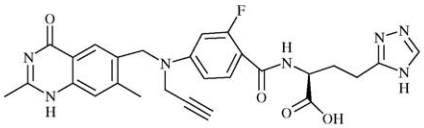


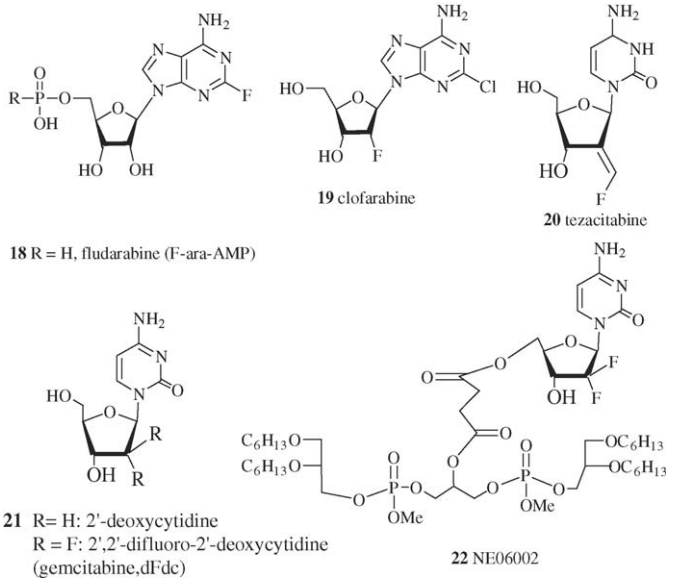
16
methotrexate



17
ZD9331

2.2. Topoisomerase inhibitors

Fluorinated adenosine antimetabolites, such as fludarabine **18** (F-ara-A), clofarabine **19** and tezacitabine **20** are DNA polymerase inhibitors, which are useful chemotherapeutic agents against a variety of cancers [29]. Fludarabine was approved in Europe for clinical treatment of chronic lyphocytic leukemia (CCL) in 1994 and during its preclinical phase it was also shown to display antitumour activity against acute myelogenous leukemia (AML) [30]. Combination therapies with cytosine-arabinoside (ara-C) are currently being developed for the treatment of AML [30]. More recently novel *o*-alkyglycerophospholipid derivatives of fludarabine (Fludara®) **18** have also been developed [31]. Clinical trials for clofarabine **19** and tezacitabine **20** against a variety of liquid and solid tumour indications are ongoing [29,32].

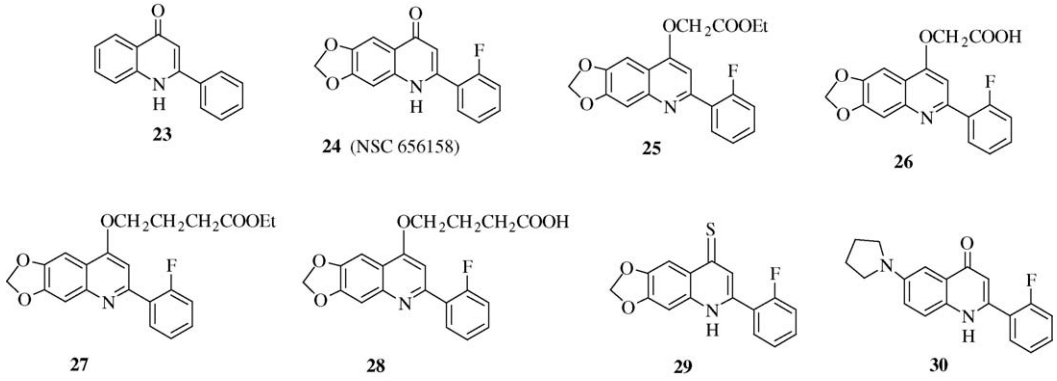


Gemcitabine (2,2-difluorodeoxyribofuranosylcytosine) **21b**, dFdC is a difluorinated analogue of deoxycytidine **21a,** currently marketed as Gemzar® for the treatment of non-small cell lung and pancreatic cancers. The drug acts as an antimetabolite, inhibiting ribonucleotide reductase and DNA-synthesis. Phase II clinical studies will explore gemcitabine as an agent against a large panel of solid tumours [33]. Structurally, gemcitabine differs from ara-C by its substituent on the 2′ position of the sugar ring. Gemcitabine is also a more potent DNA-synthesis inhibitor and more cytotoxic than ara-C [34]. However, the compound has a narrow therapeutic index due to rapid deamination by an endogenous enzyme, deoxycytidine deaminase, to its corresponding inactive uracil derivative (dFDU). Recent efforts aimed at improving the half-life and reducing the toxicity of gemcitabine, lead to the conjugation of gemcitabine with the ether analogue of cardiolipin *via* a succinate ester as prodrug [35]. Preclinical studies on this novel gemcitabine–lipid conjugate **22** showed promising anti-cancer properties [35b]. Improved DNA topoisomerase inhibitors are currently attracting interest among researchers in academia and pharmaceutical companies [36]. Recently, novel oncogene inhibitors including CX-3543, have advanced to phase II clinical trials for the treatment of pancreatic cancer [37].

2.3. Microtubule-stabilizing agents

Paclitaxel (Taxol®) and docetaxel (Taxotere®) are two of the most important anti-cancer drugs, approved for clinical use in chemotherapy against various human cancers and tumours [38]. Since the discovery of these microtubule-stabilizing agents [38a], other drugs have been found to exert analogous effects. This is the case for the natural products such as vinca [39], epithiolones [40], sarcodictyins [41], discodermolide [42], laulimalide [43], peloruside [44], combretastatin [45], campthothecin [46] and the anthracyclines [47]. Many synthetic fluorinated analogues of these natural products are now available for use in cancer/tumour chemotherapy. These will he discussed in a forthcoming review in this series.

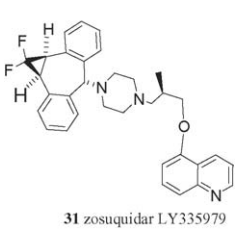
Lee et al. have reported the synthesis and biological evaluation of a series of 2-phenyl-4-quinolones (**23**, **24**) as a new class of antimitotic/antitumour agents [48]. SAR studies of this series of compounds led to the discovery of NSC 656158 **23** which showed potent cytoxicity and inhibition of tubulin polymerisation. Most importantly, **24** demonstrated good in vivo activity against the OVCAR-3 ovarian cancer cell line, prolonging the life span of mice bearing the tumour by 130%. The exceptional in vivo activity of **24** has stimulated the synthesis and further characterization [49] of pharmacophores of additional fluorinated quinolones (**25–30**).



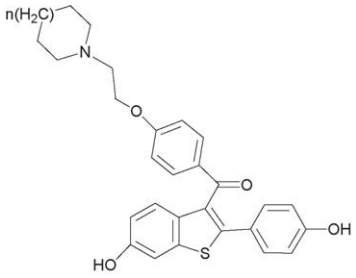
2.4. Multidrug efflux protein resistance

The appearance of multidrug resistance (MDR) tumour cells caused by members of the ATP-binding cassette (ABC) family of transport proteins is a serious problem in cancer chemotherapy [50]. In humans, two ABC transporters have been identified that cause resistance in tumour cells. These are P-glycoprotein (Pgp) (MDR1) and the multidrug resistance associated protein (MRP1). Zosuquidar (LY 335979) **31**, a difluorocyclopropyldibenzosuberane derivative, has been developed specifically as a selective Pgp inhibitor and appeared devoid of other pharmacological properties on MRP1- or BCRP-mediated drug resistance [51]. Phase I clinical trial results were reported in 2002 showing good anti-cancer potency but some risk of neurotoxicity at high dosage [52]. Zosuquidar is currently in phase III clinical trials in acute myelogenous leukemia

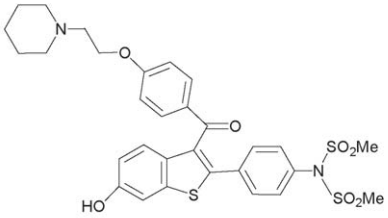
as a first-line therapy and in combination with daunorobicin and cytarabine.



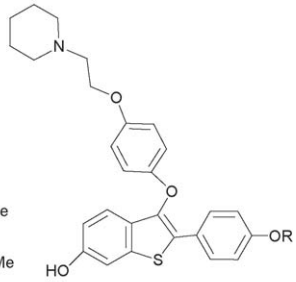
31 zosuquidar LY335979



32 raloxifene: n = 1
33 LY117018, n = 0

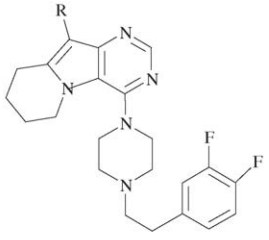


34 LY329146 raloxifene analogue

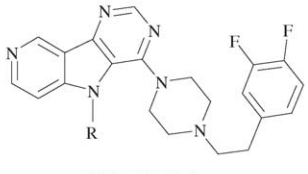


35 arzoxifene R = CH_3
36 desmethylated arzoxifene (DMA) R = H

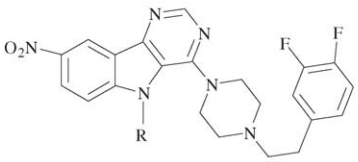
There have been several recent reports dealing with the synthesis and SAR of indolopyrimidines and pyrrolimidines as selective modulators of MRP1-mediated MDR [53]. A report from Eli Lilly [54] indicates that raloxifene **32**, and its analogue **33–36** act as selective modulators of MRP1-mediated MDR. Three novel templates [53], **37–39** have been developed as MRP1 modulators through rational design by identifying the key pharmacophore interaction at the 7-position of the pyrrolopyridine template. Studies [55] on these templates gave a number of potent MRP1 modulators with greater selectivity against Pgp. Their in vivo efficacies were also demonstrated in xenograft models, exemplified by compound XR12890, **40**.



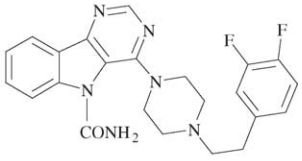
37 R = -CN, -COPh, heterocycles



38 R = H, alkyl,



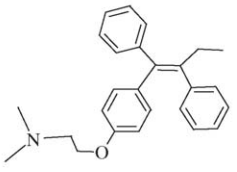
39 R = H, alkyl,



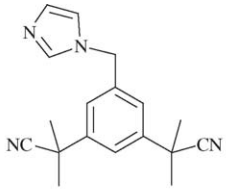
40 XR12890

2.5. Anti-estrogens

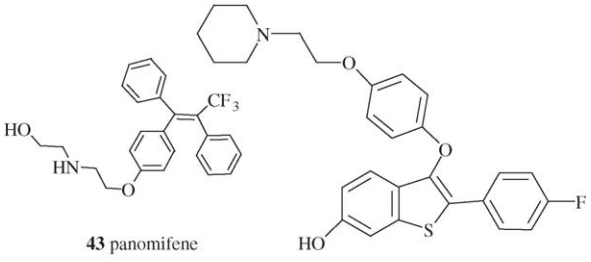
Anti-estrogens are well established in the treatment of hormone-dependent breast cancer [56]. Tamoxifen (nolvadex) **41**, a non-steroidal triphenylethylene derivative is long known [57] to exhibit anti-estrogenic properties in vivo. Although, tamoxifen has been very successful in the treatment of breast cancer, it is associated with an increased risk of endometrial hyperplasia and cancer [58]. In addition, the use of tamoxifen and a 4-hydroxy-derivative, is limited by the development of drug resistance [58]. Selective aromatase inhibitors (AIs), anastrozole **42** and derivatives have demonstrated advantages over tamoxifen as first-line treatments for advanced cancers [59]. Anastrozole, is also more effective as an adjuvant treatment in early, operable breast cancer and is being increasingly used in the adjuvant setting. Generally, the selective oestrogen receptor modulators (SERMs), such as raloxifene, arzoxifene and derivatives **32–36** show minimal activity in tamoxifen-resistant disease and show no superiority over tamoxifen as a first-line treatment [60]. Panomifene **43** (EGIS-5656, GYKI-13504), a trifluoromethyl tetra-substituted alkene, is a follow-up molecule to tamoxifen and is reported to exhibit anti-estrogenic activity superior to that of tamoxifen in the treatment of breast cancer [61]. Recent effort [62] in the development of endocrine treatment options for advanced cancers has established that 4′-F-DMA **44** showed anti-estrogenic activity comparable to raloxifene and 4′-fluoro-substitution in DMA prevents quinoid formation responsible for raloxifene toxicity. These studies suggest that 4′-F-DMA might be a promising SERM with similar activity to DMA and raloxifene and with less toxicity.



41 tamoxifen



42 anastrozole

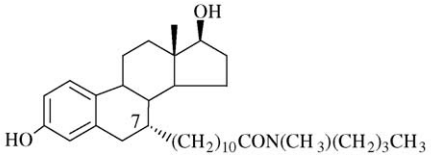


43 panomifene

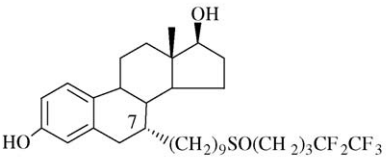
44 4-F'-DMA

The latest additions to the armamentarium for treating advanced endocrine-responsive breast cancer are the 'pure' steroidal anti-estrogens [63,64] ICI 164,384, **45** and ICI 182,780 (fulvestrant) **46**, which are characterized by an alkylamine side-chain at the 7α-position of the B ring in the steroid oestradiol **47**. In fulvestrant (Faslodex®; AstraZeneca), the amide moiety of ICI 164,384 was replaced by a sulfinyl

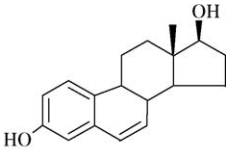
group, and the terminal alkyl function was fluorinated to reduce potential metabolic attack [65]. Fulvestrant, which unlike tamoxifen, is a new type of oestrogen receptor antagonist with no agonist effects and it is now licensed in the EU and USA for the treatment of postmenopausal women with hormone-sensitive advanced breast cancer following progression on prior anti-estrogen therapy [66]. Approval was based on data from two multicentre phase III trials that demonstrated fulvestrant was at least as effective as the third-generation aromatase inhibitor (AI), anastrozole **42** as a second-line treatment of advanced breast cancer [67].



45 ICI164,384

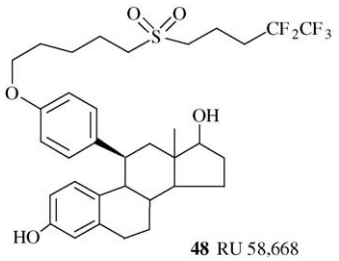


46 fulvestrant ICI182,780

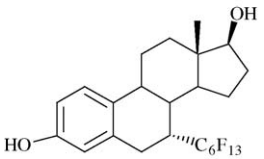


47 oestradiol

The pure anti-estrogen RU 58668 **48** has been reported to cause a protein synthesis dependent paralysis of ER in the particulate fractions of the cytoplasm that depend entirely on an intact ligand-binding domain [68]. The therapeutic potential of **48** in breast cancer treatment has also been reported [68]. These studies suggest that **48** may be used for the treatment of ER+ patients, which are primarily resistant to tamoxifen treatment and as an adjuvant to prevent the development of metastases. Blazejewski et al. [69], have also reported the synthesis, characterization and the strong anti-estrogenicity of the 7α-perfluoroalkylestradiol derivatives **49** and **50**.



48 RU 58,668



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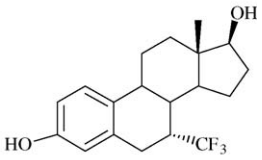
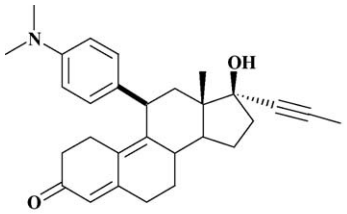
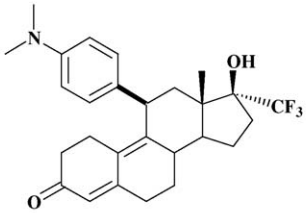


50

In oncology, prevention and treatment of hormone-dependent breast cancer by anti-progestins continues to offer promising prospects [70]. Mifepristone (RU 38486) **51**, has been registered as an anti-progestin but it is now known that it exhibits potent anti-glucorticoid side effects [70]. A recent report by Cleve et al. [71] on the effect of fluorine containing substituents in mifeprestone identified the highly potent progesterone receptor antagonists **52–55**, ZK 230211 which proved to be an extraordinary potent anti-progestin with the best receptor selectivity reported so far [71].



51 mifespristone
RU 38 486



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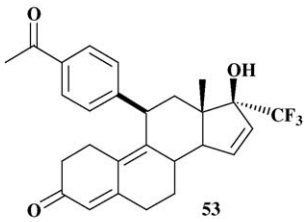
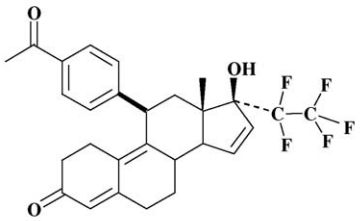
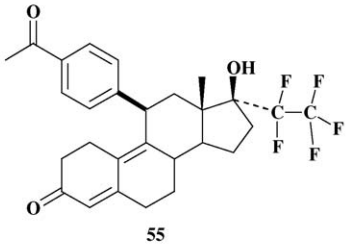


53



54 ZK 230211



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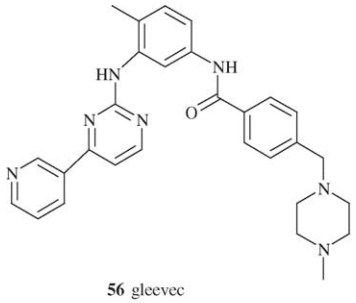
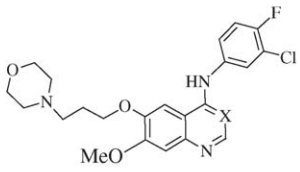
2.6. Protein kinase inhibitors

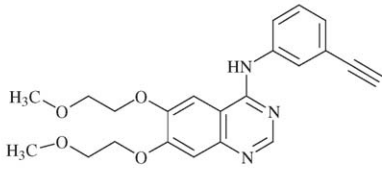
Most signal transduction pathways are mediated by protein kinases regulating every aspect of cell function. It is now well established that cancer is caused by the mutation and aberrant expression of critical genes [72] and protein kinase inhibitors have become the focus of development of new therapies for cancer [73]. The success of this therapeutic method is exemplified by the efficacy and regulatory approval [74] of small molecule catalytic inhibitors such as imatinib mesylate (gleevec) **56**. The success of imatinib has also led to the investigation of a growing number of compounds that interfere with the development of more common tumours in the lung, colon, breast and prostrate [75]. Among the recently approved [76] drugs are gefitinib (iressa) **57** and erlotinib (tarceva) **58**, as well as therapeutic antibodies to the ERBB2 receptor (trastuzumab, hepceptin) and epidermal growth factor receptor (EGFR) (cetuximab, erbitux) and the angiogenic vascular endothelial growth factor isoform VEGF-A ligand (bevacizumab, avastin).



56 gleevec

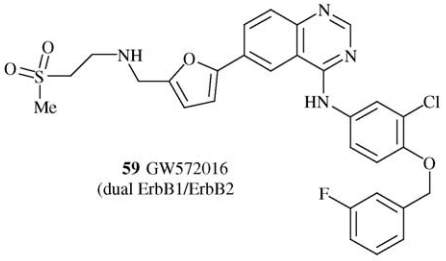


57 gefitinib ZD 1839 (iressa) X = N
X = C-CN

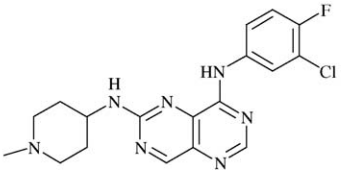


58 tarceva

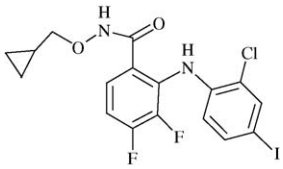
The clinical and commercial successes emerging from these approved kinase-directed drugs, have led to remarkable discoveries in the past decade, of newer kinase-directed drug templates [77]. A significant number of these compounds, targeted to cancer kinases, are in preclinical studies and development [78]. Many, if not all, of those containing fluorinated groups have been found to have a significant therapeutic impact [79]. For example, GW572016 **59** and BX-1382BS **60**, continue to show promising results in clinical trials on cancer patients [80].



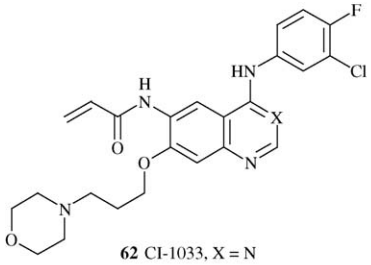
59 GW572016
(dual ErbB1/ErbB2



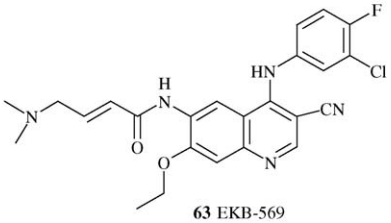
60 BX-1382BS



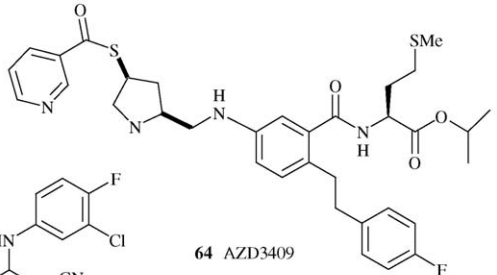
61 CI-1040



62 CI-1033, X = N
X = C-CN

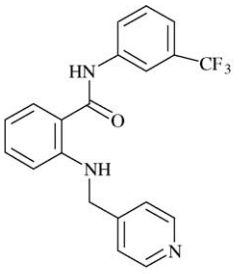


63 EKB-569

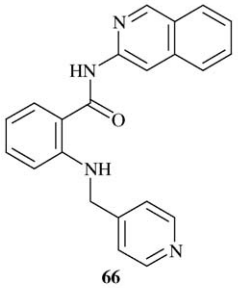


64 AZD3409

The discovery of C1-1040 (PD184352) **61** as a highly potent and selective inhibitor of MEK, the kinase that connects RAF kinases to the ERK1/2, provided a promising, non-cytotoxic approach to the clinical management of colon cancer [81]. EKB-569 **63**, from this series has been initiated [85]. The AstraZeneca compound AZD 3409 **64**, which has both the key thiol and carboxylate groups blocked in a double prodrug strategy, has recently advanced to the clinical stage [86].



65 2-[(4-pyridyl)methyl]amino- *N*-[3-trifluoromethyl)phenyl]benzamide



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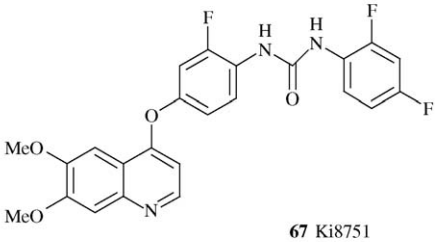
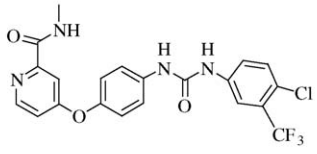


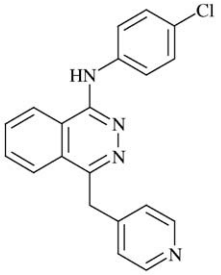
67 Ki8751

While **56** and **57** function as conventional reversible binding inhibitors of the target enzymes, researchers at Wyeth Research and Pfizer have been working on irreversible binding inhibitors [82]. Among the compounds developed, CI-1033 **62** (Pfizer Inc.), a low-molecular-weight inhibitor of tyrosine kinase activity, differs from **56** and **57** because it is not specific for EGFR and can thus bind irreversibly with other members of the erbB family of receptor tyrosine kinases to cause inhibition. CI-1033 is now in early phase clinical trials [83]. The EGFR and HER-2 kinase inhibitory activities and the cell growth inhibition of a series of 4-anilinoquinoline-3-carbonitrile analogues (**57b, 61b**) of ZD1839, and CI-1033 have also been reported [84]. A phase I clinical trial of the lead compound

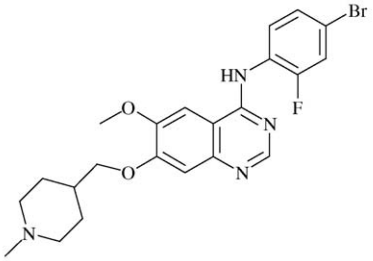
Researchers at Novartis and Schering [87] have synthesized and evaluated two novel anthranilamides **65** and **66** as potent and selective VEGF receptor kinase inhibitors. Kubo et al. [88] have also reported the synthesis, SAR and biological activities for *N*-phenyl-*N*′-{4-(4-quinolyloxy)phenyl}urea derivatives. In this report the representative clinical candidate **67** (Ki8751), showed a potent inhibitory activity for VEGF-2 with an IC_{50} of 0.9 nM and a high selectivity for many other kinases of over 1000-fold. It was noted that **67** showed excellent antitumour activity against some human tumour xenografts in nude mice and rats following oral administration once a day for 14 days at 5 mg/kg without significant toxicity [88].



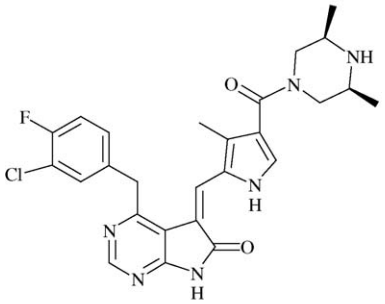
68 sorefenib BAY 43-9006



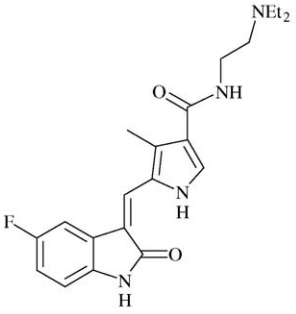
69 vatalanib PTK 787



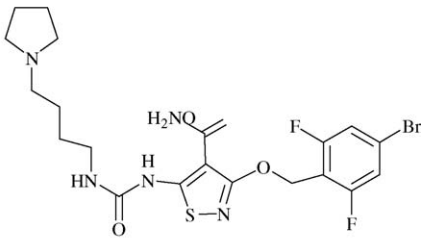
70 vandetanib ZD 6474



71a indolinone SU-11955

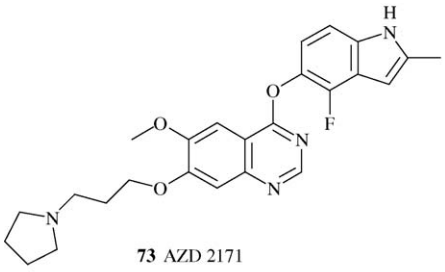


71b indolinone SU-11248

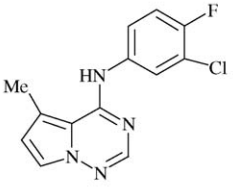


72 isothiazole CP-547632

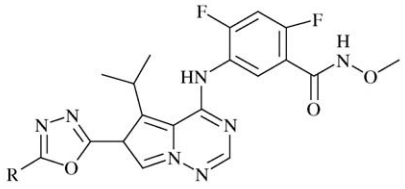
The biaryl urea inhibitor BAY 43-9006 (sorafenib) **68**, is now in phase II clinical trials and known to inhibit a broad range of kinases including the vascular endothelial growth factor receptor tyrosine kinases (VEGFR-1 and VEGFR-2) pyrrolopyrimidines (cmk and fmk) have been tested in vitro against ribosomal protein S6 kinases (RSK) and were found to inhibit RSK activity with similar potencies, however, fmk showed the greater chemical stability.



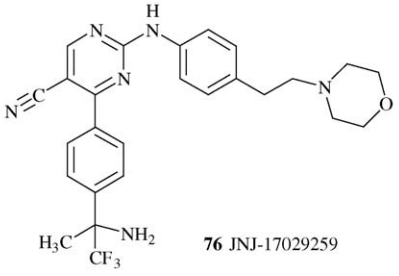
73 AZD 2171



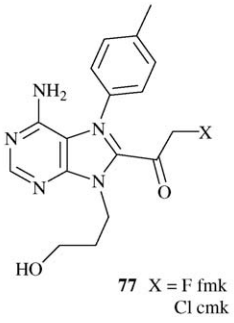
74 dual EGFR and HER2 protein tyrosine kinase



75 R = CHF_2, $CH_2SO_2CH_3$, $CF_2SO_2CH_3$



76 JNJ-17029259

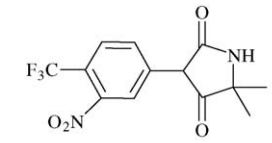


77 X = F fmk
Cl cmk

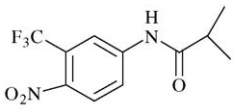
[89]. A number of orally active small-molecule inhibitors of VEGFR-2 are currently undergoing clinical evaluation, including the anilinophthalazine (PTK787/ventalanib **69**, Schering/Novartis, phase III), the anilinoquinazoline (ZD6474, vandetanib **70**, AstraZeneca, phase II), the indolinones **71** (SU11925 **71a**, SU11248 **71b**/sutent, Pfizer, phase III), the isothiazole **72** (CP-547632, Pfizer, phase I/II) and a second-generation quinazoline **73** (AZD-2171, AstraZeneca, phase 1) [90]. Recently, Hunt et al. at Bristol-Myers Squibb [91,92], have developed a novel series of halogenated pyrrolo[2,1-*f*][1,2,4]triazines such as **74** as dual EGFR and HER2 inhibitors. A further search by the same group for novel analogues of the quinazoline template led to the synthesis and significant antitumour efficacy of the orally active pyrrolo[2,1-*f*][1,2,4]triazines **75** as a dual VEGFR-2 and fibroblast growth factor receptor-1 inhibitors [92]. Emanuel et al. [93] have reported that the Celltech compound JNJ-17029259 **76**, which has a 5-cyanopyridine scaffold, is an orally bioavailable inhibitor of VEGF-mediated signal transduction. It prevents angiogenesis, and inhibits solid-tumour growth in human tumour xenograft models. Cohen et al. [94], have recently described a structural bioinformatics approach in the design of halomethylketone pyrrolopyrimidines **77** (cmk and fmk) as selective, irreversible kinase inhibitors. Both electrophilic

2.7. Anti-androgens

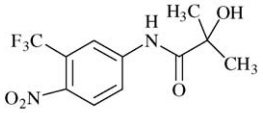
The search for non-steroidal anti-androgens that will block the pharmacological effects of testosterone, led to the development of fluorinated compounds such as nilutamide **78**, flutamide **79**, and hydroxyflutamide **80**, drugs which are widely used for the treatment of mestastic prostrate cancer [95]. Subsequently, (*R*,*S*)-bicalutamide **81** (casodex), now the leading anti-androgen used in the treatment of prostate cancer [96] was developed after consideration of the hydroxyflutamide (HF) structure and this drug has a longer half-life (6 days) and a higher binding affinity to the androgen receptor (AR) than HF [96]. Although its anti-androgenic activity is almost exclusively exhibited by the (*R*)-enantiomer, casodex is sold as a racemate. Zanda and co-workers [97] have recently described the synthesis of the trifluoromethyl analogue of casodex **81** in racemic form and this compound **82** showed significant in vitro anti-proliferative activity against the human prostate cancer cell line LNCaP comparable to casodex. This group is currently developing the synthesis of single enantiomers of **82**, in order to compare their anti-proliferative activity to that of racemic casodex and to investigate the effect of the incorporation of fluorine in connection with the stereochemistry.



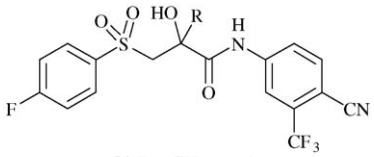
78 nilitamide



79 flutamide



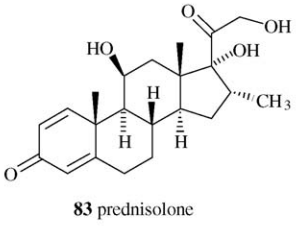
80 hydroyflutamide



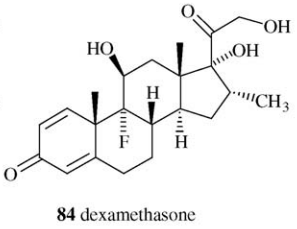
81 R = CH_3 casodex
82 R = CF_3 **1**

2.8. Anti-inflammatory/analgesia in cancer treatment

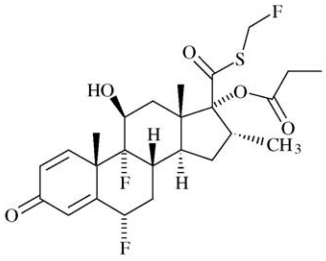
The anti-inflammatory effects of endogenous steroids have stimulated the development of glucocorticoid (GC) derivatives, such as prednisolone **83**, dexamethasone **84**, and fluticasone propionate **85**, which are widely used against a broad spectrum of inflammatory diseases and to alleviate pains associated with certain cancers [98]. However, the use of GCs is associated with a number of side effects that include oedema, weight gain, muscle weakness, diabetes mellitus and osteoporosis [99]. The anti-inflammatory and immune suppressive properties of GCs have been attributed to transrepression (TR), whereas some of the side effects (e.g. diabetes, glaucoma) have been ascribed to transactivation (TA). There has been considerable interest in the development of selective GCs agonists showing dissociation between TA and TR activities that could provide therapeutic agents with reduced side effects [99]. Several SARs in the design of new classes of ligands for the glucocorticoid receptor (GR) have recently been described in the scientific and patent literature [100]. For example, the effect of the trifluoromethyl group as a pharmacophore on the binding and agonist activity of a GR ligand has been described [101]. A lead compound **86** and the more recent analogue ZK 216348 **87** have been reported as selective GR agonists demonstrating dissociation between TA and TR activities [100]. The design and synthesis of a series of new non-steroidal glucocorticoid modulators **88–93** through application of an 'agreement docking' method have also been described [101]. The observation of TR/TA selectivity due to small changes in structure made these compounds attractive for a full lead optimization program for potent and selective fluorinated drugs [100,101].



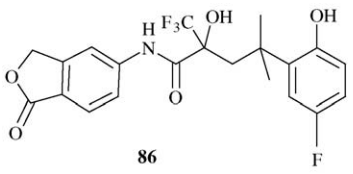
83 prednisolone



84 dexamethasone



85 fluticasone propionate



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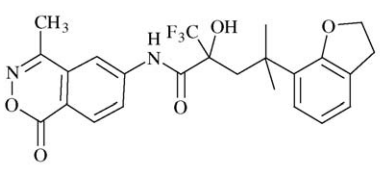
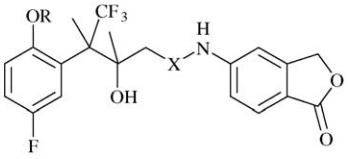
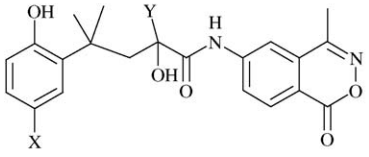


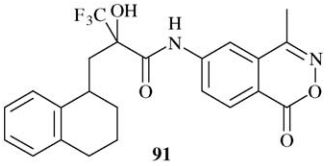
87 ZK 216348, (+)-enantiomer



88 R = H, X = CO (rac)
89 R = Me, X = CH_2 (rac)



90 a X = Br, Y = CF_3 (rac)
b, X = F, Y = CF_3 (+ent)
c X = F, Y = CH_3 (rac)



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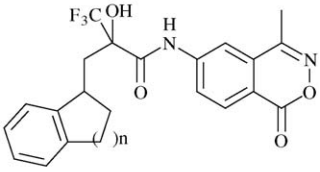
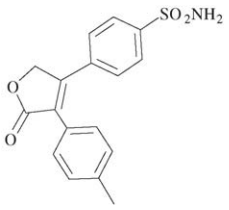


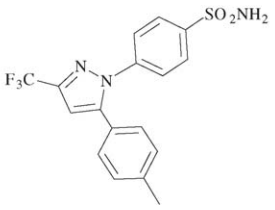
92 n = 1
93, n = 3

2.9. Non-steroidal anti-inflammatory drugs

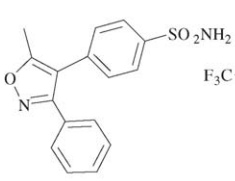
A remarkable number of fluorinated non-steroidal anti-inflammatory drugs (NSAID), which are classified depending on their inhibitory properties, have been reported. Among these compounds are the inhibitors of transthyretin amyloid formation [102], the fenamates (flufenamic acid **94** and niflumic acid **95**) and diflunisal **96**. A novel series of the potent NSAIDs, the fluoroindolecarboxylic acids (sulindac sulfide **97**, L-88, 607 **98**) and fluoroindole-*N*-sulfonyl acids **99,** has also been reported [103]. These are compounds that are analogues of indomethacin **100** and achieve analgesic and antipyretic activity through the inhibition of cyclo-oxygenases [103].



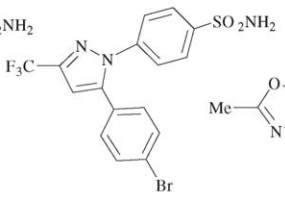
101 rofecoxib
vioxx



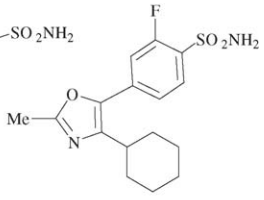
102 colecoxib



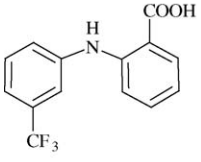
103 valdecoxib



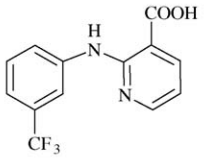
104 SC-558



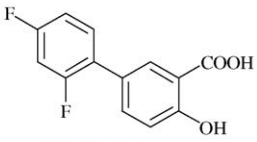
105 JTE-522



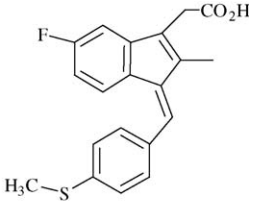
94 flufenamic acid



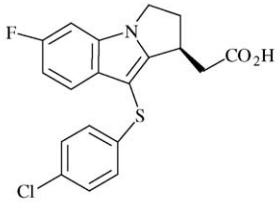
95 niflumic acid



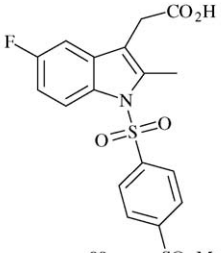
96 diflunisal



97 sulindac sulfide



98 L-888,607



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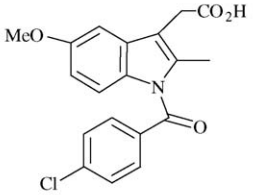


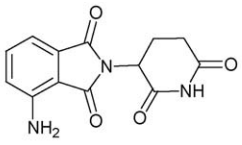
100 indomethacin

The discovery of the two isoforms of the cyclo-oxygenases, COX-1 and COX-2 in the early 1990s [104], offered opportunities to develop a new generation of fluorinated NSAIDs with reduced side effects such as gastrointestinal damage attributed to inhibition of COX-1. Traditional non-fluorinated NSAIDs such as indomethacin and aspirin inhibit both COX-1 and COX-2. Research efforts aimed at identifying selective COX-2 inhibitors have led to the discovery of rofecoxib **101** (vioxx, Merck) and colecoxib **102** (celebrex, Pfizer), approved by the FDA in 1999 and valdecoxib **103** (bextra, Pfizer) approved in 2001 [105]. More recently [106], it has been discovered that vioxx and bextra are associated with increased cases of stroke and heart diseases, and in 2004 they were withdrawn from the market. However, the fluorinated derivatives SC-558 **104**, and JTE-552 **105**, of valdecoxib and rofecoxib have been developed and are in clinical trials [107]. The therapeutic applications of selective COX-2 inhibitors in the treatment of cancers and Alzheimer disease are under investigation [108].

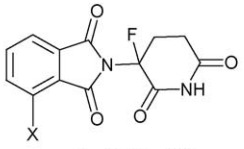
2.10. Thalidomide and novel analogues

Thalidomide **106** was originally marketed as a sedative during the 1950s but its teratogenic effects led to its withdrawal from the world market in 1962 [109]. There has, however, been a renewed interest in thalidomide following reports that it has an ability to inhibit angiogenesis and act as a selective inhibitor of tumour necrosis factor-α (TNF-α) in the lipopolysaccharide (LPS) stimulated human monocytes, which provides a rational for its anti-inflammatory effects [110]. There is a current effort to develop analogues of thalidomide that might have beneficial effects without the teratogenic side effects. Recent reports by Takeuchi et al. [110a] and Man et al. [110b] have described the development of a series of more potent non-cytotoxic α-fluoro-substituted thalidomide analogues **107** and these are currently in preclinical trials. Independent discoveries by researchers at Smithkline Beecham (now GSK), followed by Merck, RWJ and more recently Eli Lilly have led to some fluorinated

pyridinylimidazole p38 MAB kinase pharmacophores [111]. The prototypical inhibitors, SB203580 **108**, SB242235 **109**, L-790070 **110**, RWJ67657 **111** and **112** have been advanced to preclinical or clinical studies for therapeutic intervention of acute and chronic inflammatory diseases.

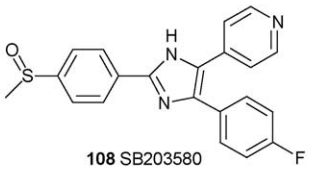


106 [3(R,S)-thalidomide]

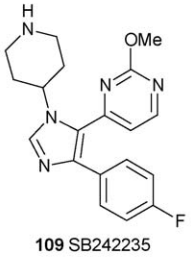


X - H, NO_2, NH_2

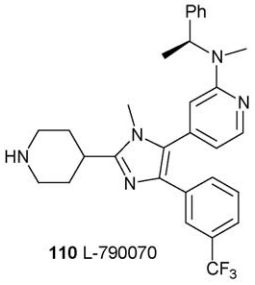
107 fluorothalidomide



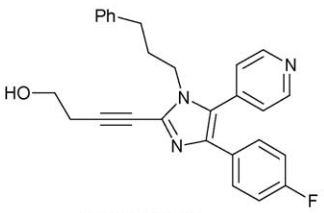
108 SB203580



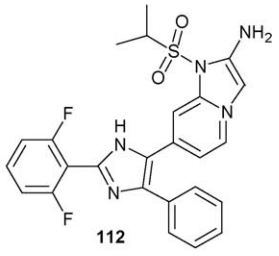
109 SB242235



110 L-790070



111 RWJ67675

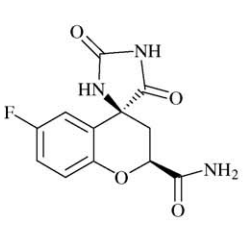


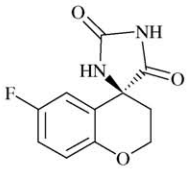
112

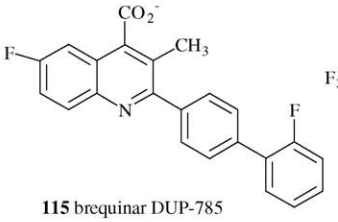
chronic obstructive pulmonary diseases) [115], leflunomide **117** and VML-295 (LY293111) **118** (anti-cancer/psoriasis) [116], T0901317 **119** and 2,4,6-trisubstituted pyridines **120** have been reported as potent farnesoid X receptor (FXR) modulators and they have emerged as target drugs for inflammation and cancers

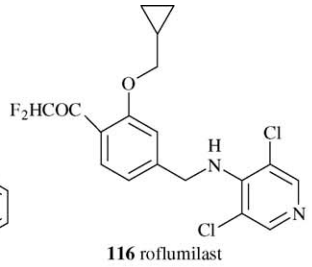
2.11. Miscellaneous cancer drugs

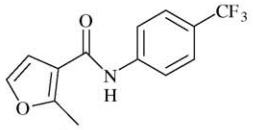
In the last decade there has been a growing number of promising fluorinated drugs and drug candidates with multiple bioactivities [112]. For example, fidarestat **113** and sorbinil **114** (anti-cancer/anti-diabetic) [113], brequinar **115** (antitumour/immunosuppressive) [114], roflumilast **116** (anti-inflammatory/ [117]. Fluorinated gonadotropin-releasing hormone (hGnRH) receptor antagonists **121** and **122** are in clinical development for the treatment of human reproductive diseases and gynecological cancer [118] and the steroid sulfatase inhibitors **123, 124** have recently been reported as more potent compounds than their non-fluorinated analogues **125**, **126** as inhibitors of steroid dependent cancers [119].

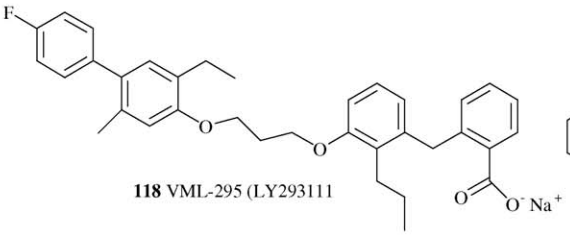

113 fidarestat (2S4S)
SNK-860

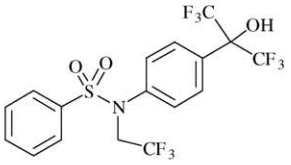

114 sorbinil


115 brequinar DUP-785


116 roflumilast


117 leflunomide


118 VML-295 (LY293111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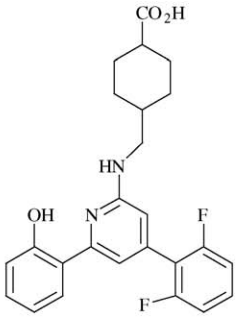
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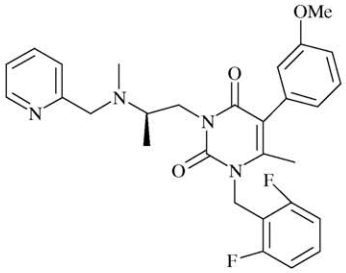
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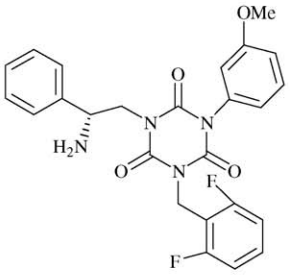
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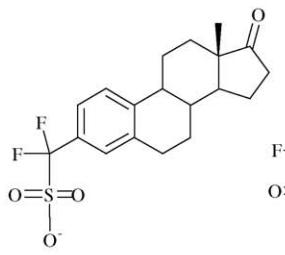
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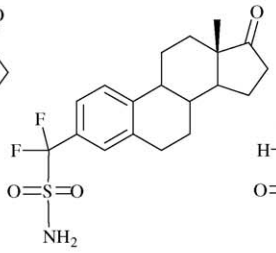
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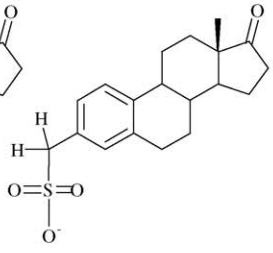
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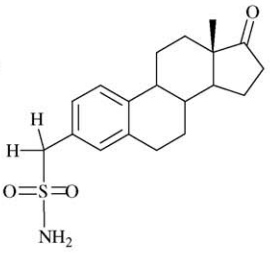
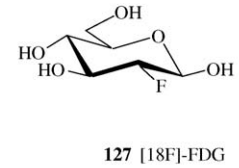

126

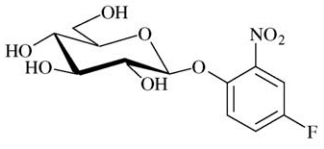
2.12. Some recent developments in positron emission tomography (PET) and ^{19}F NMR imaging in cancer

The application of positron emission tomograpy as a diagnostic tool for a range of cancers [120,121] is increasing and the international commitment to delivering PET services to major cancer centres and specialist hospitals is growing rapidly in all developed countries. Fluorinated molecules and fluorine technologies are central to this development due to the relatively long half-life of the positron emitting isotope fluorine-18 ($t_{1/2}$ = 110 min). [^{18}F]-2-Fluoro-2-deoxyglucose (FDG) **127** is the most widely used PET probe for cancer diagnosis. PET imaging using (FDG) **127** is significantly more effective in detecting many types of tumours than CT or MRI imaging procedures and FDG dominates this sector [122]. Fluoroalkyl **131** and fluoroaryl **132** radiolabeled (^{18}F) analogues of valdecoxib **133–134** were recently reported as potential radiotracers for imaging COX-2 drugs with PET and as EGFR bioprobes [123]. There have also been recent reports of the synthesis of [^{18}F] SU11248 [124], [^{18}F] analogues of ICI 182,780 (faslodex) [125] and hydroflutamide derivatives [126] as potential PET tracer for imaging cancer tyrosine kinase, and androgen receptor image-guided treatment of prostate cancer. A novel enzymatic method for C–^{18}F bond formation and the synthesis of 5′-[^{18}F]-fluoro-5′-deoxyadenosine **130** ([^{18}F]-5′-FDA) for imaging with PET has recently been described [127,128]. This utilizes the fluorinase enzyme which has been isolated and over-expressed from *Streptomyces*

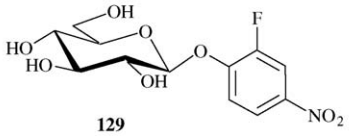
cattleya and the enzyme is the first biotechnological method for incorporating the fluorine-18 isotope [129]. In terms of more recent [^{19}F]-developments in imaging technology 4-fluoro-2-nitrophenyl-β-D-galactopyranoside (PFONPG) **128** and its isomer **129** have been presented as novel prototype NMR-sensitive reporter molecules, for the treatment of prostrate cancer [130,131].



127 [18F]-FDG



128 PFONPG



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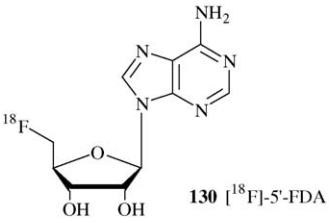
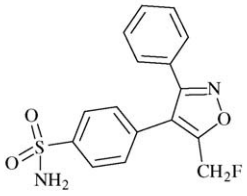


130 [^{18}F]-5'-FDA



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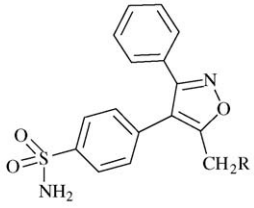
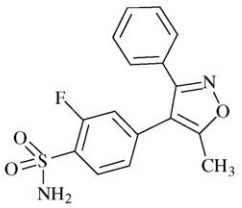
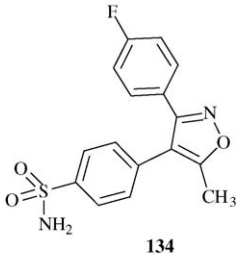


132 valdecoxib R = H,
R = ^{19}F
R = ^{18}F



133



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3. Final comments

Many of the drugs highlighted here and currently used in chemotherapy have developed from the early era of toxic drugs which arrest DNA replication in a rather direct manner. These are typified by the thymidylate synthase and DNA polymerase inhibitors. The search for novel cancer treatments has however entered a new postgenome era and the emphasis now is on influencing cell signalling mechanisms such as those triggered by kinases [77]. Selective inhibition of the kinome constituents and related signalling proteins has opened up a diversity of new drug targets and we can expect a continued proliferation of structurally diverse small molecule bioactives emerging from such research programmes. This review highlights the situation that fluorine will continue to play an important role in these developing areas of medicinal chemistry due to its attractive properties for inclusion in structure–activity relationship screens.

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