α-Fluorinated Ethers as "Exotic" Entity in Medicinal Chemistry

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Abstract: After nitrogen, fluorine occupies the position of second favorite heteroelement in life science-oriented research. In contrast, the trifluoromethoxy group is still perhaps the least well understood fluorine substituent, although its occurrence has significantly increased in the recent years.

Today, significant application areas for trifluoromethoxy substituted pharmaceuticals are in the field of analgesics, anesthetics, cardiovascular drugs, respiratory drugs, psychopharmacologic drugs, neurological drugs, gastrointestinal drugs and anti-infective therapeutics.

The present review will give an overlook of its use in medicinal chemistry.

Key Words: Fluorine, trifluoromethoxy group, anesthetics, cardiovascular drugs, respiratory drugs, neurological drugs, gastrointestinal drugs, anti-infective therapeutics.

INTRODUCTION

Nowadays, fluorine containing compounds are synthesized in pharmaceutical research on a routine basis and about 10% of all marketed pharmaceuticals contain fluorine. There has been an enormous increase in the use of fluorine containing compounds for medicinal applications. For example, nine of the 31 new chemical entities approved in 2002 contain one or several fluorine atoms. According to the World Drug Index (WDI), there are 128 fluorinated compounds with US trade names [1].

In fact, the incorporation of fluorine into a drug allows a simultaneous change of the electronic, lipophilic and steric parameters, all of which can influence both the pharmacodynamic and pharmacokinetic properties of drugs [2]. What is so particular about fluorine? Due to its comparable size, the fluorine atom (1.47 Å) can mimic a hydrogen atom (1.20 Å) or a hydroxy group (1.40 Å) in a bioactive compound with respect to steric requirements at receptor sites. Its high electronegativity (4.0 according to the Pauling scale) can have a pronounced influence on the reactivity pattern of a molecule. The high C–F bond energy of 116 kcalmol^{-1} compared to the C–H (98 kcalmol^{-1}), C–N (73 kcalmol^{-1}) and C–halogen bond (C–Cl = 81 kcalmol^{-1}, C–Br = 68 kcalmol^{-1} and C–I = 57 kcalmol^{-1}) leads to an increased metabolic, oxidative and thermal stability. Moreover, the presence of fluorine atoms in biologically active molecules can enhance their lipophilicity and thus their *in vivo* uptake and transport.

Another fluorinated substituent, the trifluoromethoxy group, is becoming more and more important in agrochemical research but also in pharmaceutical chemistry. However, the trifluoromethoxy group is perhaps the least well understood fluorine substituent. When asked to draw up a list of textbook substituents, hardly anyone would consider associating such an "exotic entity" like trifluoromethoxy to the lastingly popular carboxy, acetyl, formyl, nitro, amino, hydroxy and sulfo groups. Nevertheless, the occurrence of OCF_3-substituted, mainly aromatic compounds, has significantly increased in the recent years. The basic raw material for such products, trifluoromethoxybenzene, is produced today on an industrial scale [3]. Some 30 000 OCF_3-containing structures are presently compiled in chemical data bases. They are documented in more than 7 000 literature references. Although most of these are patent applications, there are also close to 500 pertinent research articles published in scientific journals.

What makes the introduction of OCF_3 into pharmaceutically relevant compounds particularly intriguing is their unique electron distribution. The geminal combination of an alkoxy or aryloxy group with a fluorine atom offers the possibility of bonding/non-bonding resonance which can be formally expressed by the superposition of a covalent and an ionic limiting structure.

On the basis of its electronic properties, which are close to those of chlorine or a fluorine atom [4], the trifluoromethoxy group has been referred to as a super- [5] or a pseudo-halogen [6]. In addition, the fluorinated carbon adjacent to an oxygen atom increases lipophilicity as shown by the high value of the OCF_3 hydrophobic substituent parameter [7].

While both trifluoromethyl and trifluoromethoxy substituents invariably boost the lipophilicity (Table **1**), single fluorine atoms may alter this parameter in either direction. If the halogen occupies a vicinal or homovicinal position with respect to a hydroxy, alkoxy or carbonyl oxygen atom, it enhances the solvation energy in water more than in organic

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Table 1. Lipophilicity Increments π as Assessed for Mono-Substituted Benzenes H_5C_6-X. [9,10]

Substituent	π	Substituent	π
X = H	0.00	X = CH_3	0.56
X = F	0.14	X = CF_3	0.88
X = Cl	0.71	X = OCF_3	1.04
X = Br	0.86	X = SCF_3	1.44
X = I	1.12	X = SF_5	1.23
X = OCH_3	-0.02		

solvents (such as 1-octanol or chloroform) and hence lowers the lipophilicity [8]. Conversely, a fluorine atom placed in the vicinity of a basic nitrogen center will diminish the donor capacity of the latter and, as a corollary, cause a strong lg*D* (lg*P*) increase.

It appears that the OCF_3 substituent is far more lipophilic (π = +1.04) than the halogens and lies between a CF_3 (π = +0.88) and a SCF_3 (π = +1.44) group. It may thus replace advantageously a fluorine atom (π = +0.14) in most molecules with the benefit of increased lipid solubility.

2. α-FLUORINATED ETHERS IN PHARMACEUTICAL CHEMISTRY

In the 1950s and 1960s the successful development of α-fluorinated ethers as volatile, non-toxic, non-explosive and fast-acting inhalation anesthetics was quickly followed by applications of anti-inflammatory agents. Numerous new α-fluorine containing compounds have been prepared, clinically evaluated and in many cases, marketed as drugs with enhanced effectiveness, often coupled with diminished side-effects. Today, significant application areas for α-fluorinated ether are analgesics, anesthetics, cardiovascular drugs, respiratory drugs, psychopharmacologic drugs, neurological drugs, gastrointestinal drugs and anti-infective therapeutics.

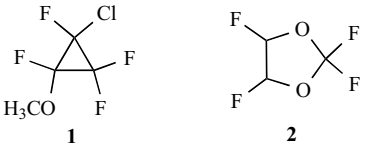
2.1. Anesthetic Drugs

Investigations of the anesthetic properties of α-fluorinated ethers were undertaken on the rational basis that replacement of the hydrogen atom in already known "anesthetic molecules" by fluorine should result in derivatives having improved thermal stabilities relative to the inhalation anesthetics in common use at that time (cyclopropane and ether), like the halo ether anesthetic Fluoroxene (Fluoromar®, F_3C-H_2C-O-CH=CH_2; boiling point: 43.0 ± 25.0 °C). Metabolic stability is a desirable feature as *in vivo* decomposition may produce toxic metabolites. Therefore, numerous analogues [11] were prepared and evaluated (Table **2**).

Meanwhile, cyclic analogues bearing the fluorinated 1,3-dioxolanes moiety [12] have largely replaced Fluoroxene in its clinical use. Although almost structurally identical, the replacement of chlorine (Isoflurane, entry 2) by fluorine (Desflurane, entry 1) gives an improved pharmacokinetic profile. The fluorinated derivative is less soluble in blood and tissue and produces a fast onset action and a more rapid recovery from anesthesia. Because six of the seven fluorine atoms in Sevoflurane (entry 3) are magnetically identical, this drug is a good candidate for *in vivo* magnetic resonance imaging [13]. The basic concept that anesthetic activity is related to the colligative properties of compounds rather than to any specific structural features suggested that anesthetic potency might be encountered in α-fluorinated compounds of widely different structures. Therefore cyclic α-fluorinated ether structures, like the cyclopropane Aliflurane [14] (**1**) (26-P) and the dioxolane Dioxychlorane [15] (**2**) are also described as useful anesthetics (Fig. **1**). Many anesthetics currently used are powerful positive allosteric modulators of $GABA_A$ [16].

Table 2. α-Fluorinated Ethers Used as Anesthetics

Entry	α-Fluorinated Ethers	b.p. [°C]	Common Names	Brand Names
1	F_2HC-O-$CHFCF_3$	12.4 ± 25.0	Desflurane	Suprane®
2	F_2HC-O-$CHClCF_3$	48.5 ± 0.0	Isoflurane	Forane®
3	FH_2C-O-$CH(CF_3)_2$	49.5 ± 25.0	Sevoflurane	Sevofrane®
4	F_2HC-O-CF_2-CHFCl	59.9 ± 25.0	Enflurane	Ethrane®
5	F_2HC-O-CHF-CF_2-CHF_2	60.9 ± 25.0	BAX 3224	Synthane®
6	H_3C-O-CF_2-CHFBr	87.0 ± 25.0	Roflurane	DA 893
7	H_3C-O-CF_2-$CHCl_2$	105.0 ± 0.0	Methoxy-flurane	Pentrane®



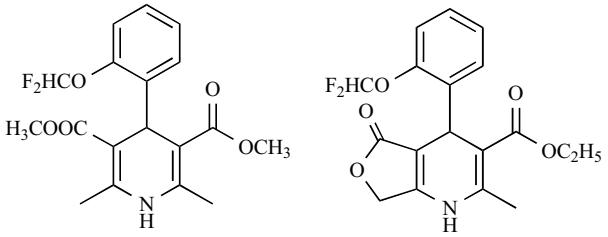
1 **2**

Fig. (1). Cyclic α-fluorinated ether structures used as anesthetics.

2.2. Cardiovascular Drugs

Antihypertensive Drugs

1,4-Dihydropyridines containing a $OCHF_2$ group like Riodipine (**3:** Foridon®, Phoridone®, Riosedyl®), are known as $Ca^{2\oplus}$ antagonists. They show antihypertensive and anti-anginal effects [17]. On the other hand, the analogue **4** (CGP 28392) is described as a $Ca^{2\oplus}$ channel agonist and induces long-term opening of $Ca^{2\oplus}$ channels from purified rat muscle transverse tubules (*t*-tubules) incorporated into planar phospholipid bilayers (Fig. **2**) [18].



3: Riodipine **4**: CGP 28392

Fig. (2). 1,4-Dihydropyridines containing a $OCHF_2$ group as $Ca^{2\oplus}$ (ant)agonists.

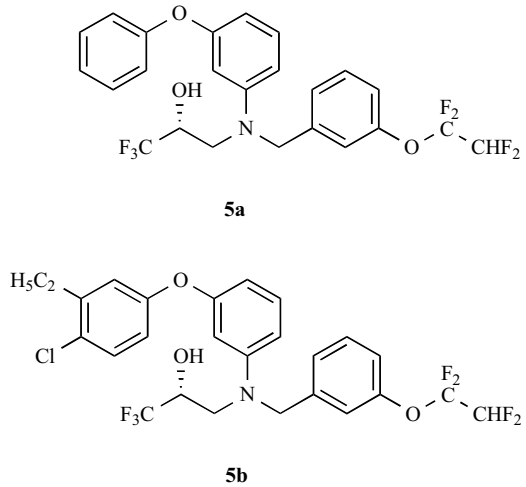
Atherosclerosis Agents

Coronary heart disease has been for some time the leading cause of death in the Western world. Thickening of the artery wall in this condition leads to both myocardial infarcts and stroke. Several compounds have been reported to be potent **c**holesterol **e**ster **t**ransfer **p**rotein (CETP) inhibitors and thus to effect cellular lipids. The OCF_2CHF_2-compound **5a** (SC-795) is a potent CETP inhibitor with an IC_{50} of 20 nM in buffer and 600 nM in the presence of human serum [19]. Recently, the asymmetric synthesis of the *R*-(+)-enantiomeric 4-chloro-ethylphenoxy analogue **5b** was described (Fig. **3**) [20]. The latter compound shows strong increased inhibitory activity of CETP in buffer (IC_{50} = 0.77 nM, 59 nM in human serum).

Potassium Channel Activator

A potassium channel opener has been considered as a vasorelaxing agent working through hyperpolarization of vascular smooth muscle cells. The cardio protective Celikalim (**6**: WAY-120491) [21] is a putative $K^{\oplus}$ channel activator that has been shown to lower blood pressure in animal models and humans (Fig. **4**) [22]. More recently derivatives **7** of Tamoxifene were developed as calcium activated $K^{\oplus}$ channel openers (BK channels) [23].

Furthermore, Celikalim is a potent $K^{\oplus}$ channel opener in dog and human airway smooth muscles [24]. It elicits renal effects through ATP-sensitive $K^{\oplus}$ channel in the renal vascu-

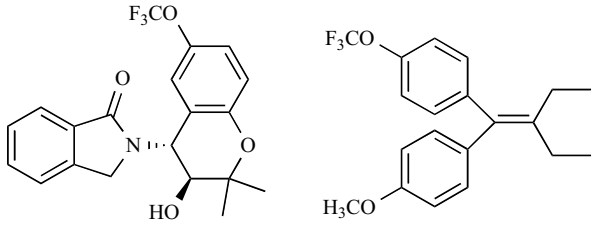


5a

5b

Fig. (3). OCF_2CHF_2-containing CETP inhibitors.

latures and renal tubules and the renal effect of **6** may not be altered in hyperconjugation [25].



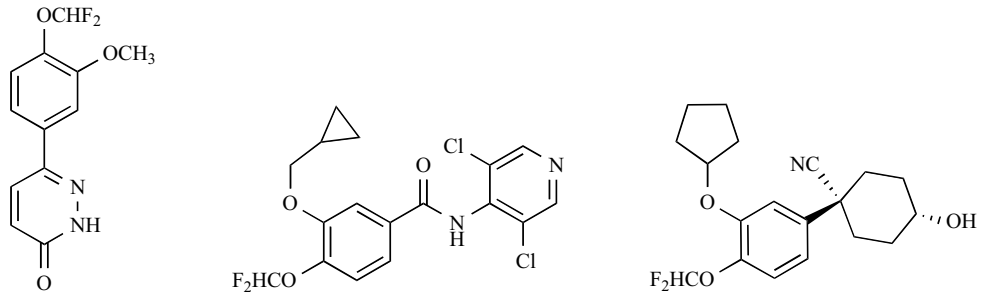
6: Celikalim **7**

Fig. (4). The cardio protective Celikalim (**6**).

2.3. Respiratory Drugs (Asthma Therapy)

Cyclic nucleotide phosphodiesterase (PDEs) constitute a broad family of enzymes responsible for the hydrolysis and subsequent deactivation of the second messenger's cAMP and cGMP [26]. The cAMP specific PDE4 isoenzymes [27], encoded by four genes (A-D), are particularly abundant in inflammatory and immune cells and in airway smooth muscle [28]. The first crystal structure of the PDE4D catalytic domain and the bronchospasmolytic Zardaverine (**8:** BY 290) as inhibitor, has recently been published (Fig. **5**) [29].

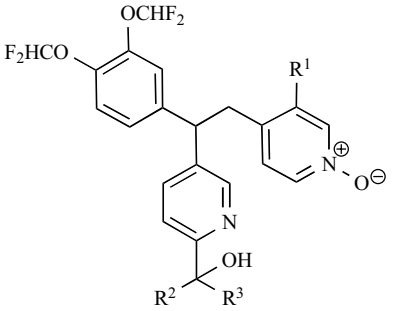
Zardaverine (**8**; Fig. **5**) [30], a mixed PDE3/4 inhibitor, binds in a highly conserved pocket that includes the catalytic metal binding site and fills only a portion of the active site pocket. It was found that more selective PDE4 inhibitors like Roflumilast (**9:** BY 217) [31] have additional functional groups that can utilize the remaining empty space for increased binding energy and selectivity. Roflumilast (**9**; Fig. **5**) is a specific PDE4 inhibitor being developed for the potential treatment of asthma and chronic obstructive pulmonary disease (COPD) [32-34]. Selective PDE4 inhibitors were compared for their abilities to suppress superoxide anion production from guinea pig eosinophils, to inhibit the catalytic activity of human $PDE4_A$, and to bind to the high-affinity rolipram-binding site (HARBS) [35,36]. The novel cyanocyclohexane **10** (Fig. **5**) was the most potent compound in these three assays measuring IC_{50} of 0.045, 0.02, and 0.025 μM, respectively.



8: Zardaverine **9**: Roflumilast **10**

Fig. (5). Structures of PDE4 inhibitors.

Stabilisation of Roflumilast (**9**) towards metabolism through replacing the alkoxy groups by $OCHF_2$, and oxidation of the pyridine to the *N*-oxide led to a novel series of triarylethane derivatives of general structure **11** (Fig. **6**), bearing a 3,4-bis(difluoromethoxy)phenyl unit and a 2-pyridine-methanol residue **11a** (L-791,943) [37]. The evaluation of the SAR in this series led to the identification of the diastereomeric **11c** which gives highly selective inhibition of phosphodiesterase type 4A (PDE4A) (IC_{50} = 2.0 nM) but without inhibition of other PDE isoforms at up to 5.0 μM [38,39]. In monkeys, **11c** displayed good bioavailability (73%), a shorter half-life than **11a** and a low liability for emesis (10 mg/kg p.o.).



11a: $R^1 = H$; $R^2 = R^3 = CF_3$ L-791,943

11b: $R^1 = CH_3$; $R^2 = R^3 = CF_3$

11c: $R^1 = H$; $R^2 = CH_3$, $R^3 = C_6H_5$

Fig. (6). Novel series of triarylethane derivatives of Roflumilast.

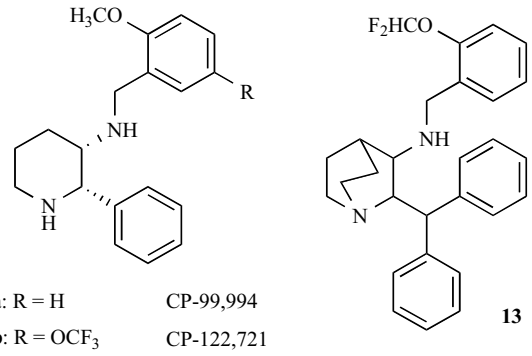
11c exhibits excellent *in vitro* activity (HWB IC_{50} = 0.16 μM), desirable pharmacokinetic parameters and good efficacy in guinea pig models of ovalbumin-induced bronchoconstriction (0.3 mg/kg i.p.) and in the sheep model of ascaris-induced bronchoconstriction (0.5 mg/kg i.v.) for 4 days.

The potencies of Roflumilast (**9**) and its derivative **11b** were determined in human and guinea pig whole blood by qPCR. Roflumilast (**9**) was more potent than **11b** [40].

2.4. Psychopharmacologic Drugs

Anxiolytics

During the last decade, the search and development of small molecules as antagonists at the neurokinin-1 (NK_1) receptor represent an important opportunity to further explore novel therapeutic agents. The OCF_3-containing piperidine **12b** (Fig. **7**; CP-122,721) was designed to improve the oral activity of the parent compound **12a** (Fig. **7**; CP-99,994). It proved to be 400-fold more potent orally than **12a** in a study monitoring inhibition of aerosolized capsaicin-induced lung plasma extravasation in the guinea pig [41]. Recently, compound **13**, which is the $OCHF_2$ derivative (Fig. **7**) of the NK_1 receptor antagonist Ezlopitant [42], was specifically claimed for treatment of a large number of therapeutic indications like pain, anxiety and HIV infection.



12a: R = H CP-99,994

12b: R = OCF_3 CP-122,721

13

Fig. (7). OCF_3-containing NK_1 receptor antagonists.

Antipsychotics

Subtype selective antagonism of the 5-HT_{2A} receptor (5-hydroxy-tryptamine, 5-HT) is considered to represent a useful strategy in the treatment of psychosis and potentially in the improvement of sleep quality. Recent studies with the lead structure ML-100907 resulted in structures with a high affinity for this receptor subtype (**14**, Fig. **8**) [43].

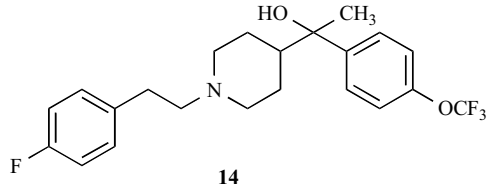


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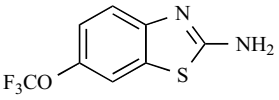
Fig. (8). OCF_3 bearing 5-HT_{2A} receptor antagonists.

Neurologic Drugs

Riluzole (**15:** Rilutek®, Fig. **9**) [44-46], a OCF_3-substituted 2-amino-benzothiazole, is known to affect motor neu-



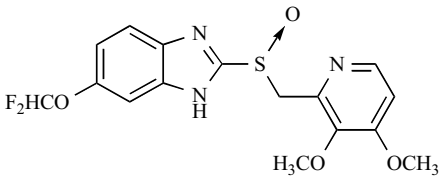
15: Riluzole (Rhone-Poulenc Rorer)

Fig. (9). Riluzole (**15**) for various neurological diseases.

rons by at least three mechanisms, including inhibition of glutamate release, inhibition of post-synaptic events following glutamate receptor stimulation, and stabilization of the voltage gated sodium channels (*vgSChs*). It is the first drug approved for treatment of Amyotropic Lateral Sclerosis [47], to treat schizophrenia [48] and other neurological diseases [49].

2.5. Gastrointestinal Drugs (Antiulcer Drugs)

Substituted benzimidazoles like Omeprazole, Lansoprasole, Rabeprazole (all non α-fluorinated ethers) and the pH-selective (-)-Pantoprazole (**16:** pantoprazole sodium, Rifun®, Pantozol®, Pantec®, see Fig. **10**) [50] are known as gastric proton pump inhibitors (PPIs) [51]. All PPIs accumulate in the acidic space of the secreting parietal cell, where their active forms create disulfide bonds with key cysteines of the $H^{\oplus}$, $K^{\oplus}$-ATPase. (-)-Pantoprazole **(16)**, an irreversible proton pump inhibitor, reached its first market worldwide for acute treatment of gastric and duodenal ulcers and gastroesophageal reflux disease. This profile is different to other PPIs and is likely related to the unique binding of **16** to cysteine 822, a binding site which is buried deep within the membrane domain of the pump and may therefore be inaccessible to reducing agents. The binding stoichiometry assay of *in vivo* labeled enzyme showed about 2 moles of both Omeprazole and Pantoprazole were bound per mole phosphoenzyme of the $H^{\oplus}$, $K^{\oplus}$-ATPase, as has been found for isolated enzyme under acid transporting conditions. This finding would be consistent with binding to two cysteines per mole active enzyme, cycsteine 813 and 892 for Omeprazole and cysteine 813 and 822 for Pantoprazole on each molecule of inhibited pump [52].

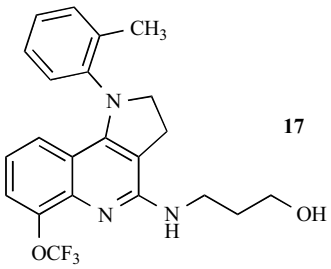


16:(-)-Pantoprazole

Fig. (10). Pantoprazole (**16)** as gastric proton pump inhibitors (PPIs).

Thus, **16** is a valuable alternative to other PPIs in the treatment of acid-related disorders. Furthermore, the PPIs were found to have *in vitro* activity against three different isolates of *Plasmodium falciparum* [53].

Recently, the effects of novel quinoline derivatives of type **17** (AU-006) were described [54]. The quinoline **17** prevented gastric lesions induced by 95 % ethanol when given orally (30-300 mg/kg). Its protective effect against gastric lesions was not affected by an NO synthase inhibitor (Fig. **11**).

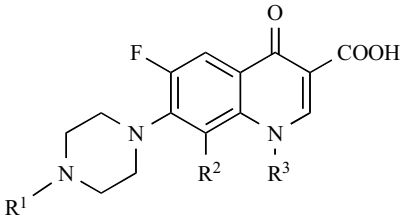


17

Fig. (11). Compound **17** preventing gastric lesions.

2.6. Antiviral Drugs

Recent studies in *anti*-HIV chemotherapy have produced stunning progress in a relatively short period of time [55]. The *anti*-HIV-1 activities and pharmacokinetics of a series of aryl-piperazinyl fluoroquinolones **18** are reported [56]. The SAR study revealed that the substituent at the C-8 position of **18** plays an important role in *anti*-HIV-1 activities. Hydrophobicity of the substituent at this position seems to be one of the key factors for antiviral activity. Thus, the inhibitory effect can be further enhanced by substitution of the methoxy group hydrogens in compound **18a** (IC_{50} = 1.8±0.6 μM; CC_{50} = 26±2 μM) with fluorine atoms. Finally, the $OCHF_2$ analogue **18b** (IC_{50} = 0.25±0.04 μM; CC_{50} = 15±2 μM) was found to be the most active in this series of congeners [57]. Compound **18c** has been shown to inhibit replication of herpes viruses, including human cytomegalovirus, varicella-zoster virus and herpes simplex virus types 1 and 2, which are important opportunistic pathogens in AIDS patients [58]. However, in this case the introduction of a OCF_3 group at the C-8 position proved to be superior (**18d:** IC_{50} = 0.11 μM; CC_{50} = 0.75 μM) to that of a $OCHF_2$ group (**18c:** IC_{50} = 0.22 μM; CC_{50} = 8.3 μM) to achieve higher *anti*-HIV-activity (Fig. **12**) [59].



18a: R^1 = pyrid-2-yl; R^2 = OCH_3; R^3 = cyclopropyl

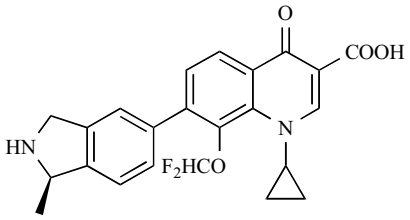
18b: R^1 = pyrid-2-yl; R^2 = $OCHF_2$; R^3 = cyclopropyl

18c: R^1 = 2-H_3CO-C_6H_4; R^2 = OHF_2; R^3 = C_2H_5

18d: R^1 = 2-H_3CO-C_6H_4; R^2 = CF_3; R^3 = C_2H_5

Fig. (12). Anti-HIV active compounds.

Garenoxacin (**19:** T-3811, Fig. **13**), a DNA topoisomerase ATP hydrolysing inhibitor, has recently completed phase III clinical tests. Garenoxacin (**19**) is a quinolone that demonstrates activity against a wide range of Gram-positive and Gram-negative bacterial pathogens like *E. coli* (MIC_{50} = 0.03 μg/ml), *Enterococcus* spp. (MIC_{50} = 0.25 μg/ml) and *Pseudomonas aeruginosa* (MIC_{50} = 1 μg/ml) [60]. The *in vivo* data obtained with humans reveal that Garenoxacin (**19**)



19: Garenoxacin

Fig. (13). Garenoxacin (**19**) as DNA topoisomerase ATP hydrolysing inhibitor.

is likely to be effective for the treatment of respiratory tract infections caused by *S. pneumoniae* [61].

Dimeric trifluoromethoxyacridine (**20**) derivatives were prepared as pathogen-inactivating nucleic acid intercalators. It was found that a spacer length of six carbon atoms results in the best virus inactivation, when tested at the relatively high dose of 100 μM (Fig. **14**) [62].

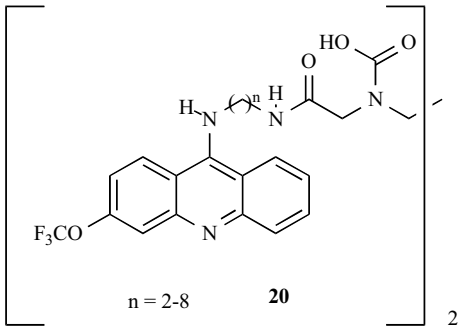


Fig. (14). Anti-pathogenic acridines.

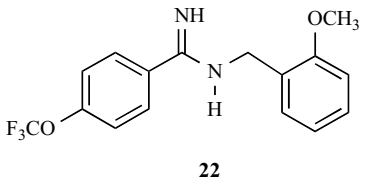
2.7. Antifungal Agents

Systemic fungal infections of immunocompromized hosts continue to be a major problem in infectious disease chemotherapy. Several reports appeared on the synthesis and evaluation of novel azoles with activity against Fluconazole resistant *C. albicans* and *Aspergillus*. Thus the tetrazolone [63] **21a** was reported to have efficacies in animal models comparable or superior to fluconazole. The novel broad spectrum agent **21b** contains the 4-piperazinyl-phenyl-triazolone side chain common to Itraconazole and Posaconazole, and displays similar potency and spectrum as the latter (Fig. **15**) [64]. Furthermore, it could be shown on the basis of *in vitro* data obtained with *C. albicans*, that the use of a thio-1,3-dioxane-diene spacer (**21c**) results in antifungal properties as well [65].

The *in vitro* activity of Syn2869 (**21b**) showed good activity against different dematiaceous molds with MIC_{50} ranging from 0.06 to 0.25 μg/mL. No activity against the hyaline molds was observed. The results suggest that Syn2869 (**21b**) could be effective against a range of mold infections in humans [66].

2.8. Diagnostic agents

N-methyl-D-aspartate (NMDA) receptors are expressed in the human CNS and exist as assemblies made from both NR1 and NR2 receptor subunits. Positron emission tomography (PET) tracers which target the NR2B receptor could allow a non-invasive imaging in the living brain under various disease states. The amidine derivative **22** bearing a trifluoromethoxy-phenyl group was shown to have a specific binding *in vitro* for the NR2B containing NMDA receptors. This selectivity is of high importance because of the regional distribution of NR2B and its involvement in diseases like schizophrenia or chronic pain (Fig. **16**) [67].



22

Fig. (16). NR2B selective amidine **22**.

CONCLUDING REMARKS

"Fluorine leaves nobody indifferent … . As a substituent it is rarely boring, but always good for a surprise … . Apparently the smallest halogen emits several kinds of electronic effects which …… may counterbalance or amplify each other" [68]. An in-depth analysis of why organic fluorine is so special and often behaves as the "odd man out" has recently traced back some of its most characteristic features to

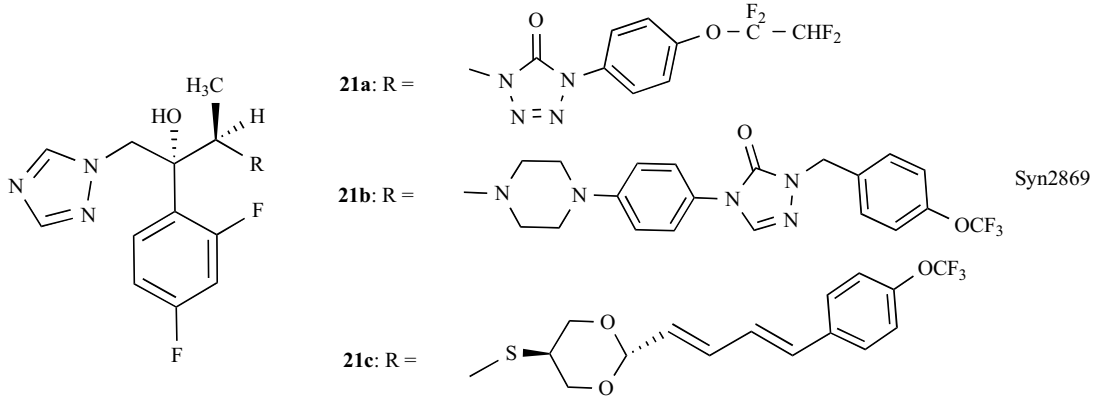


Fig. (15). Novel antifungal broad spectrum agents **21**.

the poor molecular polarizability of organofluorine compounds, the lowest relative to the molecular volume among all standard element derivatives [69].

In the life science field one employs single fluorine atoms, difluoromethylene units and trifluoromethyl or trifluoromethoxy groups to tailor pK_a values [68], to foster cell penetration by improving the passive permeation through the blood/brain barrier and all kinds of biological membranes, [66] to help accumulate substances in tissues and to enhance the substrate binding to protein-type receptors by making use of the "polar hydrophobic effect" [70]. All this contributes to the critical "bioavailability" of therapeutically active compounds.

A particularly intriguing subject is the role of fluorine as a mimic. The isosteric relationship between fluorine and oxygen (Van der Waals radii of 1.47 and 1.52 Å, respectively) is often emphasized. However, unlike the hydroxy group, organic fluorine is a very poor hydrogen bond acceptor and no hydrogen bond donor *et al*. [66]. Thus, the replacement of a hydroxy group by a fluorine atom may totally perturb the interaction pattern. On the other hand, fluorine and hydrogen, are sufficiently similar in size (Van der Waals radii of 1.47 and 1.20 Å, respectively) to be able to imitate each other (except in rare cases such as the deplanarization of biphenyls by introduction of halogen atoms in the *ortho* positions of biphenyls [71,72]). In general, fluorine should prove practically isosteric with hydrogen as far as substrate-enzyme and agonist-receptor recognition is concerned.

Fluorine will remain an important tool to modulate the properties of biologically active substances and α-fluorinated ethers will without doubt claim a major role in the future evolution of the field [73].

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