Tricyclic Structures in Medicinal Chemistry: An Overview of their Recent Uses in Non-CNS Pathologies

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Abstract: Tricyclic compounds are sometimes considered as synonima of drugs healing central nervous system pathologies, although there are some well known examples of tricyclic derivatives marketed for different indications, such as antihistamines, antivirals and antiulceratives. Following the insertion of tricyclic structures in the "privileged structures" pool, several compounds bearing a central 7-membered ring and two aryl rings at its sides have been reported, and some of them have been progressed to advanced clinical trials.

An overview of tricyclic derivatives reported in the literature since 1995, that are investigated for indications not directly related to central nervous system affections, shows the potential of these structures in a broad range of therapeutical indications, going from antiviral and anticancer compounds to the therapy of cardiovascular diseases. Very recent examples confirm the usefulness of tricyclic structures for the modern medicinal chemists.

Key Words: Tricycles, privileged structures.

INTRODUCTION

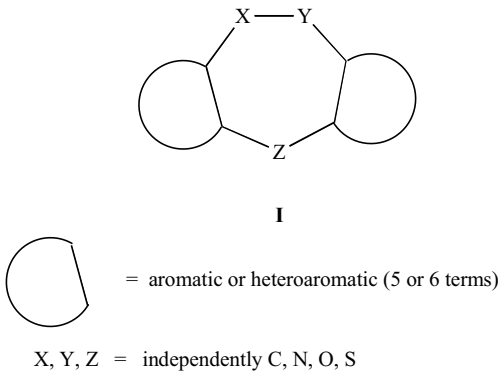
In 1988 Evans and co-workers [1] defined the concept of privileged structure [2]. As an example of structure “able to provide high affinity ligands for more than one type of receptor” they cited the case of cyproheptadine, a tricyclic molecule previously studied at Merck Sharp and Dohme.

Tricyclic compounds are sometimes considered as synonima of drugs healing central nervous system pathologies although there are some well known examples of tricyclic derivatives marketed for different indications. Some of these are Loratadine (Schering-Plough), as antihistamine, Nevirapine (Boehringer Ingelheim) as a non-competitive HIV-1 reverse transcriptase (RT) inhibitor and Pirenzepine (Thomae, Boehringer Ingelheim) as antiulcerative, gastric acid inhibitor.

This review deals with tricyclic derivatives of general formula **I** (Scheme (**1**)) recently reported (since 1995) in the literature, that are investigated for indications not directly related to central nervous system affections. Both binders at membrane receptors and enzyme inhibitors are taken into consideration. Many potential therapeutical applications are presented, depending on the various mechanism of action: amongst the other antiviral, anticancer and antiinflammatory agents. Very recent examples confirm the broad usefulness of tricyclic structures in different therapeutical fields.

ANTIVIRAL AGENTS: NON-NUCLEOSIDE INHIBITORS OF HIV-1 REVERSE TRANSCRIPTASE

The dipyridodiazepinone nevirapine (Viramune, Fig. (**1**)) [3] is one of the most effective non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs), used for the treatment of the acquired immune deficiency syndrome (AIDS) in combination with nucleoside inhibitors in cocktail-based therapies.



Scheme (1). General formula of tricyclics.

At the beginning of the nineties, the first two articles were published describing, respectively the structure activity relationship (SAR) of the pyridodiazepinones culminating in the selection of nevirapine itself [4] and the discovery of pyridobenzooxazepinones and dibenzoazepinones as potent HIV-1 RT inhibitors [5]. Later on Boehringer Ingelheim showed the rest of their study conducted onto tricyclic structures. Although a certain tolerance for structural variations onto the tricyclic core was observed, so that the introduction of thioamide [2] and olefin [6] in place of the lactam bridge gave rise to good inhibitors, the work was almost focused on nevirapine close analogs.

As previously demonstrated, the dipyridodiazepinone nucleus is essential to maximize the activity in respect to the benzopyridodiazepinones and dibenzodiazepinones, and it was also shown that nevirapine actually corresponds to the best isomeric form [7]. Taking the easily accessible 5-methyl-11-ethyl analog of nevirapine (**1** (Fig. (**1**)) as the ref-

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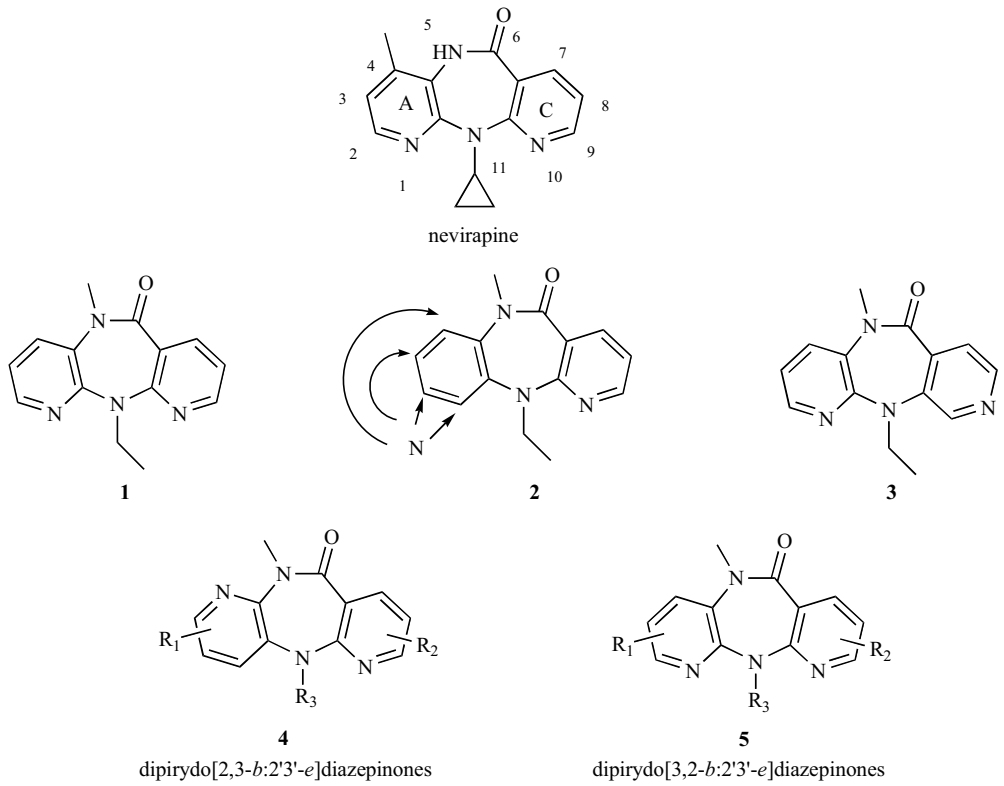


Fig. (1). HIV-1 RT inhibitors from Boehringer-Ingelheim: nevirapine and isomeric analogues.

erence, four known isomers on the A ring (see **2**) and one isomer in the C ring (**3**) were reported as less active compounds. The in vitro RT inhibitory activity of **1** was only marginally lower than that of nevirapine (IC_{50} (μM) 0.125 and 0.084 respectively) while that of the isomers **2-3** was only in one case submicromolar ($0.35 < IC_{50}$ (μM) < 6.4). During a SAR study onto the dipyrido[2,3-*b*:2',3'-*e*]diazepinones (**4**), where the critical methyl substituent at position 4 of nevirapine was replaced once again by a methyl group onto the nitrogen of the central amide, Proudfoot *et al.* [8] compared IC_{50} (μM) values of the new compounds with that of the already investigated dipyrido[3,2-*b*:2',3'-*e*]diazepinones series (**5** (Fig. (**1**)). The choice of the nature and the position of substituents employed in the SAR study was dictated by the results on the previous dipyrido[3,2-*b*:2',3'-*e*]diazepinones series. The introduction of lipophilic substituents on the A ring alone (for example R_1 = 2,3-dimethyl, R_2 = H, R_3 = ethyl, IC_{50}, (μM) = 0.19) or its combination with the introduction of an amino group at position 8 (R_1 = 2,3-dimethyl, R_2 = 8-NH_2, R_3 = ethyl, IC_{50}, (μM) = 0.15) were confirmed to enhance enzyme inhibition. Despite these improvements, the new isomers remained generally weaker inhibitors than nevirapine and its close analogs and were thus abandoned.

During the development of nevirapine, it was found that the major cause of the viral resistance, was the mutation of the native RT, which substitutes cysteine for tyrosine-181 (Y181C RT). Taking advantage from the great number of compounds obtained during the previous screening, Proudfoot and collegues [9] found that the insertion of proper aryl substituents in position 2 on the A ring provided new 5-methyl-11-ethyl and 5-methyl-11-cyclopropyl derivatives endowed with good combined activity against the two forms of the enzyme. Starting from the observation that the 2-chloro derivative shows improved activity in respect to nevirapine both for the native and the mutated form of RT, they presented the activity of about fifty 2-(hetero)aryl-substituted products (**6** (Fig. (**2**)). Amongst all the substitutions, 3-furanyl, 2-and 3-pyrrolyl, 4-pyrazolyl, 4-hydroxy- and 4-amino-phenyl and 3-(6-amino-pyridyl)-dipyridodiazepinones, showed IC_{50} (μM) values < 0.08 (obtained for nevirapine) against the wild-type RT (WT-RT) and interesting values ($0.04 < IC_{50}$ (μM) < 0.27) against the Y181C RT. Furthermore, four of them (**7-10**) showed a good activity profile even when tested against other clinically significant mutated enzymes (L100I, K103N, P236L, E138K), that are known to be related to the insurgence of resistance during the treatment with other structurally unrelated NNRTIs.

Further improvements in terms of potency against an expanded panel of RT mutants were done by changing the 2-pyrrol-3-yl substituent of **7** with a larger indole-based ring [10]. The activity of 2-indol-3-yl-dipyridodiazepinone **11** was extremely interesting, showing IC_{50} values < 100 nM for the wild tipe and for all the mutants (Y181C, Y188L, K103N, V106A, G190A, P236L). In order to reduce the solubility concerns ascribed to these compounds, some attempts were done to introduce an aza-indole structure in place of indole but it generally lowered the inhibitory potency.

In the same period, many attempts were undertaken [11] in order to optimize the activity of nevirapine-like inhibitors by the introduction of a lipophilic pendant in position 4 of the tricyclic core (**12**). A few good WT-RT inhibitors were

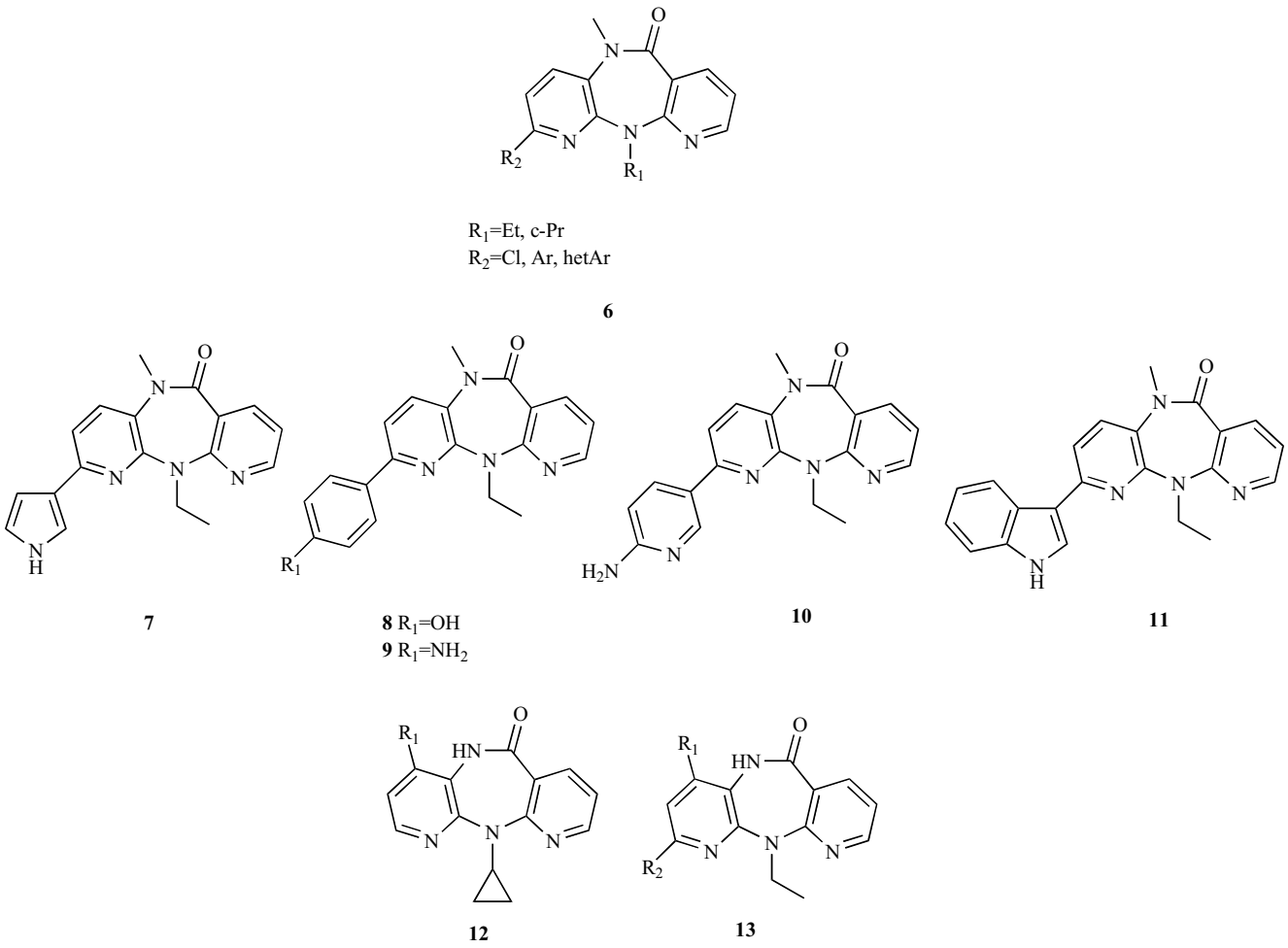


Fig. (2). Broad spectrum HIV-1 RT inhibitors: A-ring functionalization.

obtained from this approach, but the attempt to exalt their activity against the Y181C RT by re-introducing a substituent in position 2 (**13**), completely failed, indicating a non-additive behavior of the two substitutions.

For many years all the efforts were focused on the functionalization of the A ring because of some previous indications that the modification of C ring was irrelevant if not detrimental. At the end of the nineties new results emerged [12] indicating that arylethyl substitution on position 8 of C ring can confer enhanced potency against Y181C RT. In fact, 2-halo-8-arylethyl-dipyridodiazepinones (**14-17** (Fig. (**3**)) showed additivity contributes by the double substitution giving a good potency profile against both Y181C RT and Y188L RT. On the basis of structural considerations, researchers hypothesized that this pattern of substitution should maximize interactions with conserved aromatic residues on the enzyme at the expense of interactions with more frequently mutated residues. On the other hand, these structures suffered of a fast and extensive metabolism in respect to nevirapine, especially directed to the benzylic position of the arylethyl pendant, together with poor bioavailability.

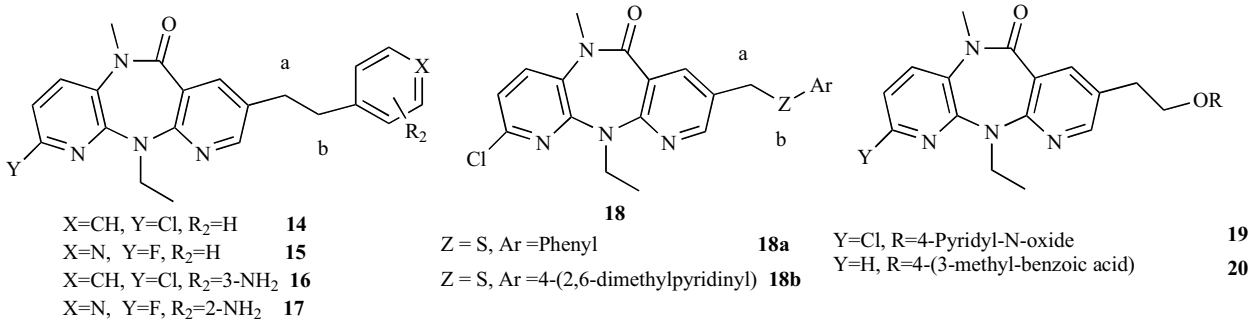


Fig. (3). Broad spectrum HIV-1 RT inhibitors: modifications on 8 position of C ring.

Improved pharmacological profiles for WT and mutate forms of RT were reported [13, 14] together with pharmacokinetic ameliorations, for analogs containing a heteroatom on the ethylene linker in position 8. The introduction of oxygen or sulphur atom alternatively on β position and of different substituents on the distal aromatic ring gave more potent products (**18**). In particular **18a** and its pyridine analog **18b** were reported as the most active compounds ever synthesized with IC_{50} values < 50 nM for all the enzyme forms tested. Secondary tests for *in vitro* metabolic stability in human liver microsome (where nevirapine was extremely stable) and cytotoxicity (MTT assay for nevirapine was > 500 μM) showed that small variations in the 8-substituent structure gave quite diverse results in terms of ADME profile. These compounds were finally abandoned in favour of 8-(2-aryloxyethyl)dipyridodiazepinones **19** and **20** [15] which displayed excellent and broad antiviral activity against a panel of clinically relevant RT double mutants (e.g. K103N/Y181C, K103N/P225H) and, according to the authors, good biopharmaceutical properties.

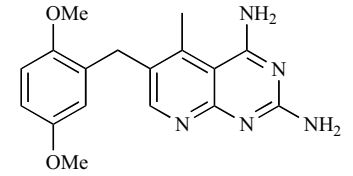
Despite these features, after more than ten years, no clinical development is reported for nevirapine analogs.

During the years following the discovery of nevirapine, other companies investigated the possibility to build other tricyclic NNRTIs with original structures. Menarini researchers [16, 17] obtained active compounds introducing a sulphur in the central seven-membered ring. Amongst the pyridobenzo and dipyrido-thiadiazepindioxides, the 8,9-dimethylderivative (**21** (Fig. (**4**)) showed the same cellular antiviral activity of nevirapine (measured by the inhibition of HIV-1 replication in a CD4+ lymphoblastoid cell line, infected with HIV/IIIB strain) together with an adequate low cytotoxicity. The attempt to shift the alkyl pendant from the central cycle to the adjacent nitrogen as in **22** gave rise to less potent compounds.

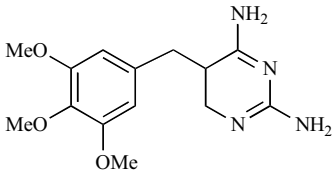
Artico and others described the discovery of a new series, obtained by changing the phenyl C ring of nevirapine with a pyrrole and introducing a sulphone into the short bridge of the central seven membered ring (**23**) [18]. Both enzymatic and cellular tests indicated that 8-chloro 5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines are slightly less potent compounds in respect to nevirapine, maintaining a good selectivity index in terms of cellular cytotoxicity.

ANTIPARASITIC AGENTS: DIHYDROFOLATE REDUCTASE INHIBITORS

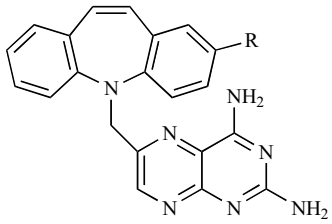
Amongst the opportunistic organisms causing significant morbidity and mortality in patients with AIDS and other immune system disorders, there are *Pneumocystis carinii* (Pc), *Toxoplasma gondii* (Tg) and *Mycobacterium avium* (Ma). These infective deseases are usually treated with common antibacterials such as piritrexim, a dihydrofolate reductase (DHFR) inhibitor endowed with high potency but low selectivity between the microorganism and the human form of the enzyme, or trimethoprim (low potency, high selectivity) (Fig. (**5**)). The need for a potent and selective lipophilic DHFR inhibitor emerged to overcome the drawbacks of the



piritrexim



trimethoprim



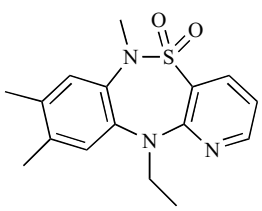
R=H **24**

R=O(CH$_2$)$_n$COOH **25**

R=C≡C(CH$_2$)$_n$COOH **26**

Fig. (5). Hetero-dimeric anti-parasitic compounds.

available drugs. Starting from some structural informations about the shape and dimensions of the liphophilic pocket of the microorganisms active site, Rosowsky at the Dana-Faber Cancer Institute [19], identified a class of very potent DHFR inhibitors which contain a tricyclic moiety. During the optimization process [20, 21] the early unsubstituted lead **24** was functionalized with ethereal or alkyne junctions and a carboxylic acid end, giving rise to potentiated inhibitors **25-26**



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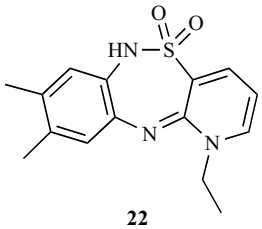

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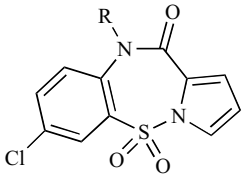


23

R=H

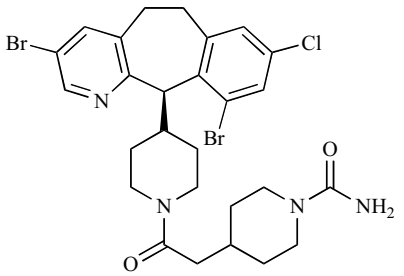
R=Me

Fig. (4). Tricyclic sulfur containing HIV-1 RT inhibitors.

able to exert a very selective activity against Pc, Tg and Ma DHFR ($1 < IC_{50}$ (nM) < 80, $10 < IC_{50}$ (nM) < 40 and $0.7 < IC_{50}$ (nM) < 12, respectively). Such compounds are only weak inhibitors of the rat liver DHFR ($41 < IC_{50}$ (nM) < 3000) which is considered a portrayal of the human DHFR, giving an indication of good selectivity.

ANTICANCER AGENTS: FARNESYL PROTEIN TRANSFERASE INHIBITORS

Lonafarnib (Sarasar, Sch-66336) (Fig. (**6**)) [22], is the tricyclic Farnesyl Protein Transferase (FPT) inhibitor at the highest level of clinical development for the treatment of Ras proteins dependent tumors with an oral administration regimen. Schering-Plough has started Phase III studies in 2003.



Lonafarnib

Fig. (6). Lonafarnib.

Ras proteins exert an important role in cellular replications, playing their action only after some post-translational modifications, such as farnesylation by FPT. Ras genes are often mutated in tumors (especially in pancreas and colon), hence the blockage of FTP activity has been considered useful to inhibit the tumor growth although it is already not completely elucidated if these potential drugs should be considered as single agents or coadjuvants in chemotherapy. In the past decades many efforts were spent to identify substrate-like peptidic inhibitors which were useful to give the proof of concept on the usage of FTPi. Unfortunately they suffered of unacceptable metabolic instability and consequently poor or none *in vivo* activity. Since the breakthrough of the discovery of the first non-peptidic, non sulfydryl, tricyclic inhibitor series (**27**, Fig. (**7**) [23, 24], obtained by simple modifications of loratadine structure (see below, Fig. **9**), many SAR studies were conducted to optimize *in vivo* activity of these molecules. The first lead compound **27a**, containing the 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b] pyridine moiety, demonstrated to be able to inhibit the transfer of tritiated-farnesyl from farnesyl pyrophosphate to Ha-Ras containing its native C-terminal sequence (Ha-Ras-CVLS) with FPT IC_{50} of 0.25 μM. Interestingly, it is only weakly active (IC_{50} (μM) > 46) in the inhibition of geranyl-geranyl protein transferase (GGPT), which is considered as an indication of selectivity, being GGPT involved in membrane association of other proteins. Otherwise, sulphonamidic derivatives of structure **27b** showed dual FTP/GGPT inhibitory activity [25].

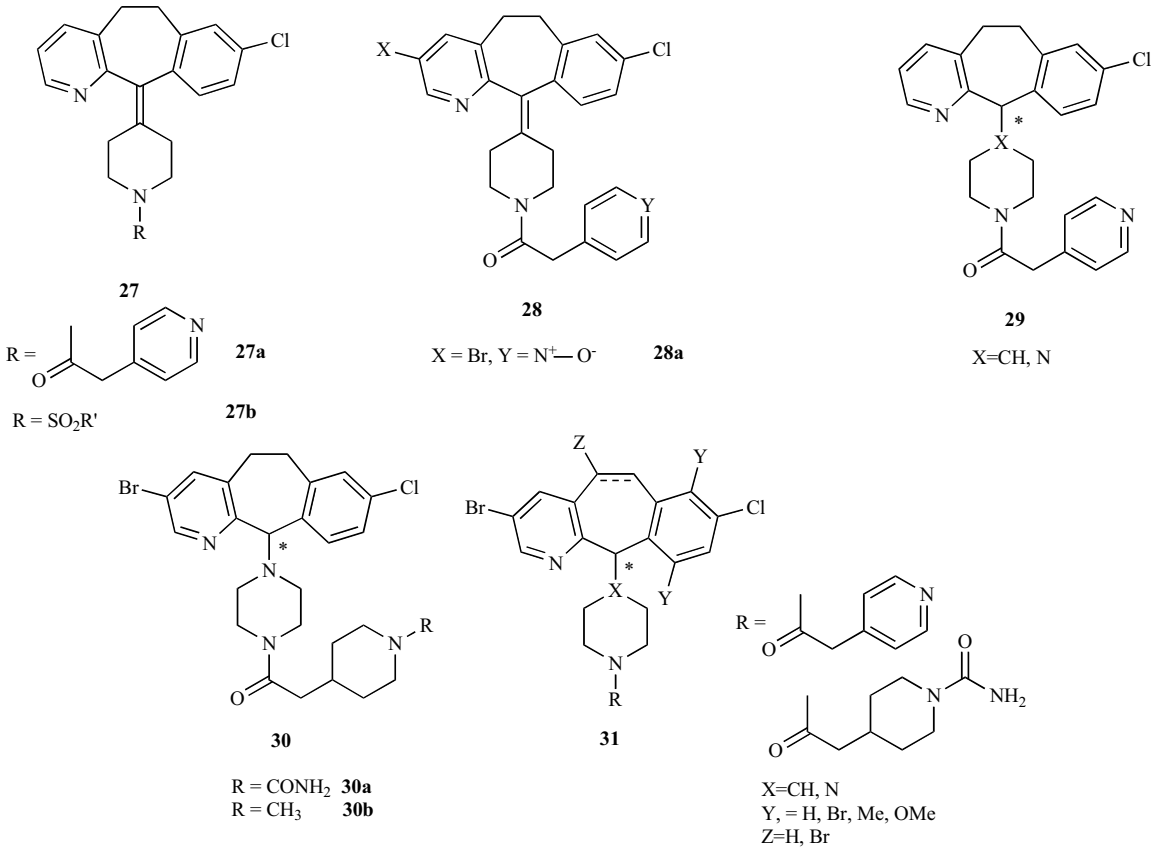


Fig. (7). Loratadine derived FTP inhibitors.

The effect of introducing a substituent in 3-position of tricyclic core has been largely studied [26] and it was found that the enzyme is able to host a medium-size, non-hydrophilic group as a methyl or a halogen (**28**). Pharmacokinetic properties and *in vivo* efficacy of these compounds were further improved by oxidizing the nitrogen of the distal pyridine moiety (**28a**). It has been demonstrated [27] that enhancement of activity is achievable by reducing the exocyclic double bond and also introducing a piperazine moiety in place of piperidine such as in **29**, maintaining a good selectivity. These inhibitors suffer of fast clearance rates; despite this, they exert a certain *in vivo* antitumor activity in animal models after oral administration. The introduction of a piperidine in place of the distal pyridine (**30**) gave rise to potent compounds, especially when the terminal nitrogen was ureidic as in **30a**. Surprisingly, the methyl analog **30b** showed muscarinic activity [28]. The insertion of a third non-polar substituent onto the tricycles (**31**) [17, 29], chosen amongst Br, Me and OMe, preferentially in position 10, gave rise to a series of nanomolar inhibitors from which lonafarnib emerged for its favorable pharmacokinetic and pharmacodynamic profile [17], being its bioavailability of about 75% after oral administration. The explanation of the drastic improvements of such compound seems to lie in the capability of the 10-substituent to force the butterfly-like conformation of the tricyclic moiety in a pseudo-axial disposition of the 11-piperidine group [30]. More recently, thanks to X-ray structural information about the lonafarnib binding mode to the active site of FTP, many efforts were focused on the introduction of a properly spaced substituent able to strongly interact with a proximal zinc atom on the enzyme. Two new classes of nanomolar inhibitors were reported, where selected nitrogen-containing pendants are linked to the piperidine (**32** (Fig. (**8**)) [31, 32] or to the bridge-head of the seven-membered ring (**33**) [33], respectively.

Independently, a research group of the Université de Lille 2 reported [34] to have developed a new series of tricyclic FPT inhibitors characterized by the presence of a sulphonamide bridge-head and a 4-cyanobenzylimidazole tail able to act as a zinc-chelator (**34**).

MDR REVERSAL AGENTS AND MODULATORS

Multidrug resistance (MDR), the acquired drug resistance of cancer cells and microorganisms to a variety of chemotherapeutic drugs, can affect several classes of cytotoxic drugs causing a major problem in cancer and antiinfective chemotherapy. An altered membrane transport, associated with the membrane P-glycoprotein overexpression and resulting in lower intracellular concentrations of cytotoxic drugs, is considered as a major event of MDR [35].

Starting from the previously reported MDR reversal agent MS-073 (Fig. (**9**), [36]), Syntex researchers described in 1995 a series of derivatives bearing a cyclopropane condensed on the central seven-membered ring [37]. The derivatives improved or maintained the potency of MS-073 in reversing resistance to doxorubicin in an *in vitro* cell assay. Interestingly, dichloro- and difluoro-cyclopropane fused compounds also showed excellent acid stability, while the low oral bioavailability of the starting lead MS-073 was ascribed to its acid lability (as the Authors noted, the dibenzosuberyl moiety present in MS-073 was used as an amine protecting group removable under mild acid conditions).

In fact, the oral bioavailability of the difluoro compound RS-33295-198, later LY-335979 or zosuquidar (Fig. (**9**)) was confirmed by its activity after oral administration in several MDR *in vivo* models [38, 39]. Zosuquidar was later progressed to clinical studies. Phase I/II trials in several different tumor types and in combination with many different chemotherapy agents were performed; a phase II study

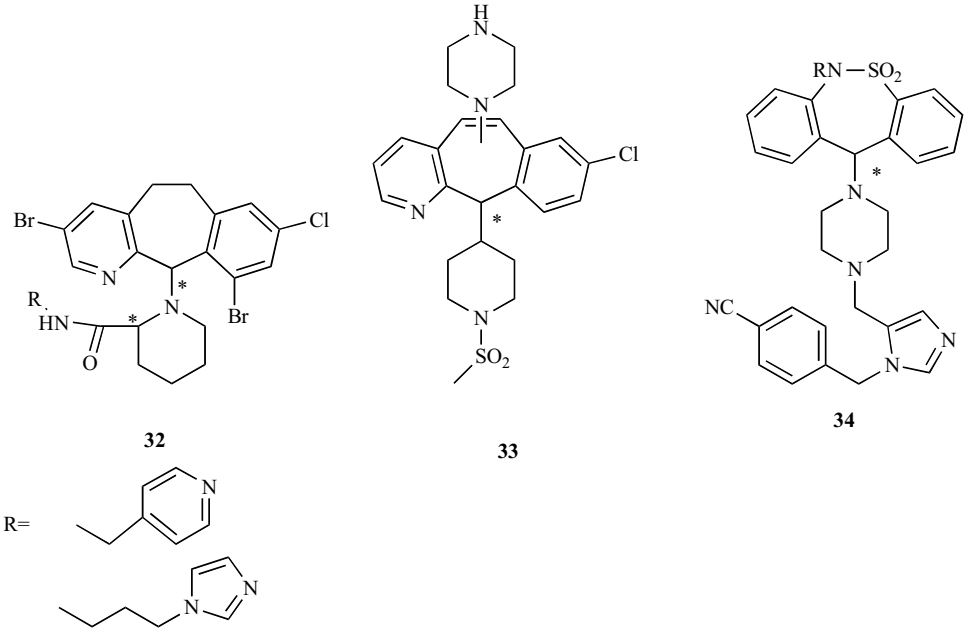


Fig. (8). Second generation FTP inhibitors: Zn-chelators.

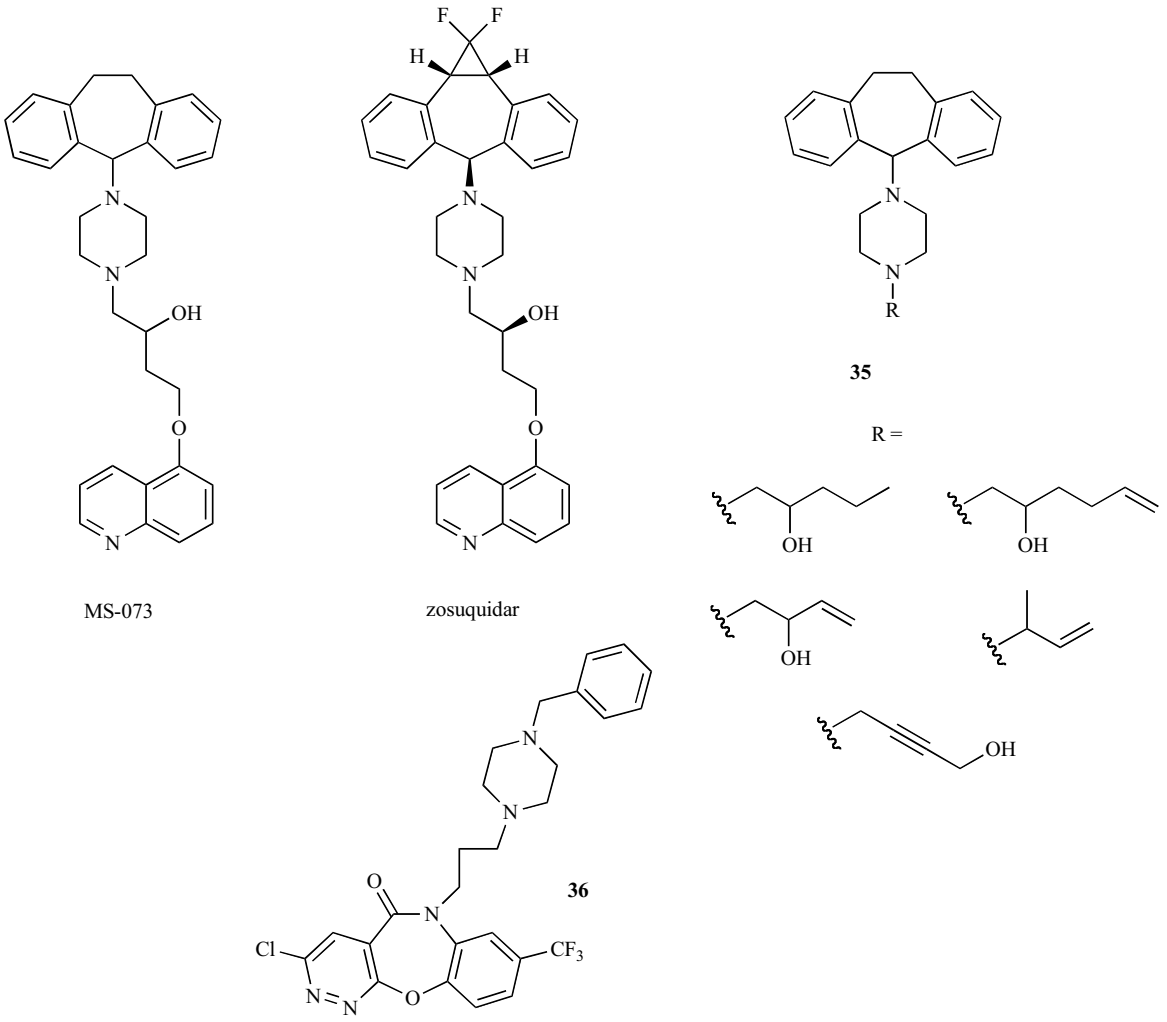


Fig. (9). Tricyclic piperazines as MDR reversal agents.

evaluating zosuquidar in combination with daunorubicin and cytarabine in older patients with newly diagnosed acute myeloid leukemia (AML) is presently ongoing in the US [40].

Later, dibenzosuberylpiperazines of similar structure to MS-073 were proposed by Osa *et al.* [41] to revert resistance to antimalarial drugs in *Plasmodium falciparum*. In particular, several compounds were tested for their ability to reverse chloroquine (CQ) resistance in an *in vivo* model of rodent malaria by *Plasmodium chabaudi*. The compounds were not effective *per se* as antimalarial agents; on the other hand, administration of the seven test compounds (50 mg/kg dose) combined with CQ (3-4 mg/kg) gave high reversal activities. Best compounds (**35**) share, as a common feature, short alkenyl or alkynyl side-chains. Longer chains or additional aromatic groups seem to lower the activity; although quite all the derivatives bear an hydroxy group in the side chain (as it was in MS-073), this does not appear to guarantee high MDR reversal activity.

Keeping in mind the structure of zosuquidar and those of tricyclic MDR reversal agents reported in the patent literature [42], Matuszczak at al. described in 2004 [43] a series of pyridazino[3,4-b][1,5]benzoxazepin-5(6H)ones substituted with propylene-linked basic side chains such as **36**. The idea was to maintain the tricyclic core and the basic side chain with at least one tertiary nitrogen that characterized previous structures. New compounds were investigated for the ability to reverse MDR at vincristine-pretreated HeLa-MDR1 cells, and were found to be effective chemosensitizers with activity comparable to that of the known MDR modulator verapamil at 1-5 μM concentration. The observed effects were not caused by direct drug cytotoxicity, as it was shown through comparative studies of incubation of compounds in the same cell line in the absence of vincristine, where no significant antiproliferative effect was noticed.

In a different approach, Servier researchers [44] modified the structure of their previously reported triazine compound S-9788, a MDR modulator that had showed some interesting properties in phase I clinical studies but whose development was hampered by cardiovascular side effects. Several tricyclic moieties, described in Fig. (**10**), were inserted that constrain the diphenylmethylene group of S-9788. The majority of the compounds, all bearing a purine group linked to the tricycle through a 4-aminopiperidine, were at least as active as S-9788 and markedly more active than verapamil in the *in vitro* MDR reversal tests. Simple dibenzocyclohepta-

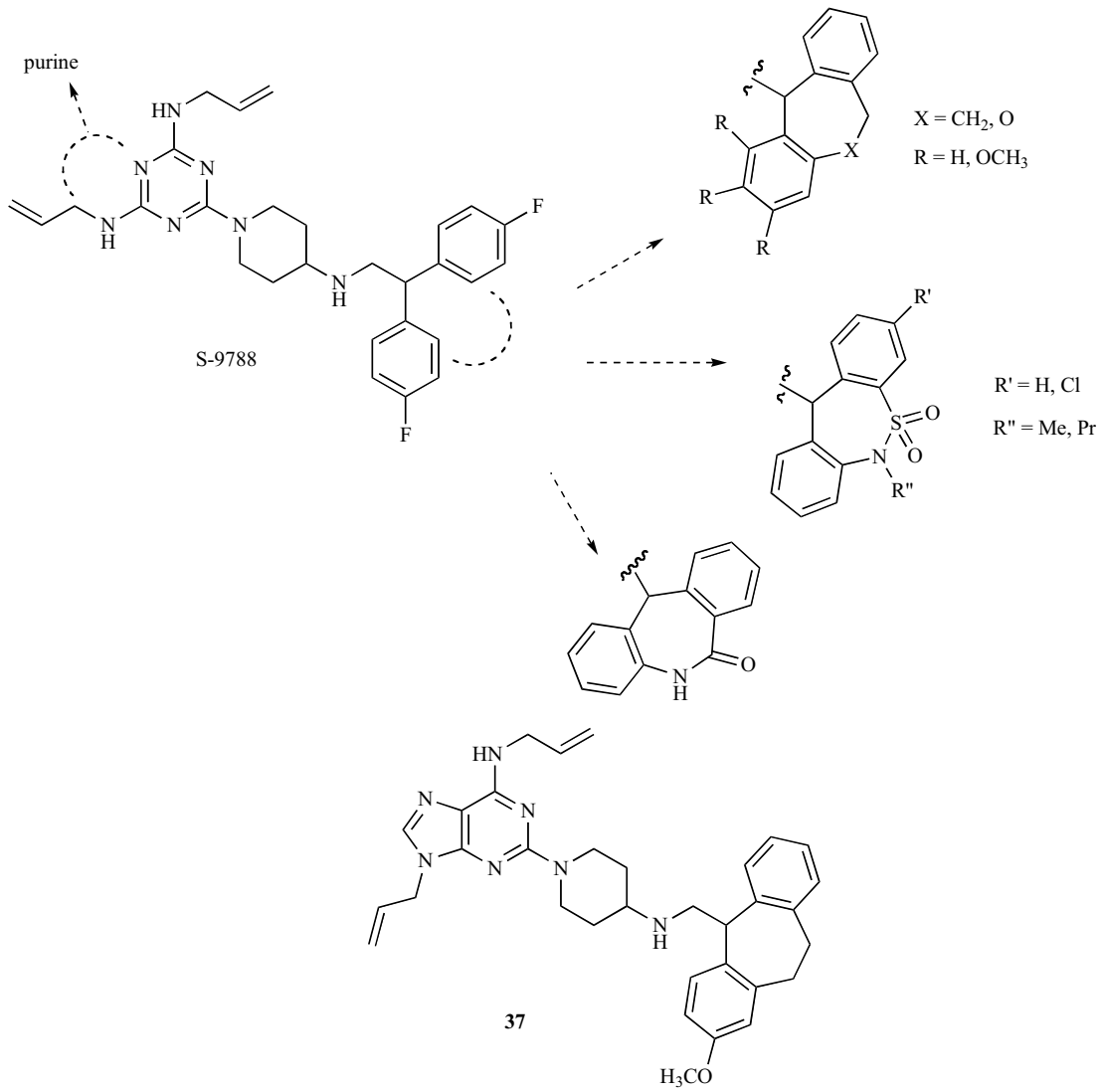
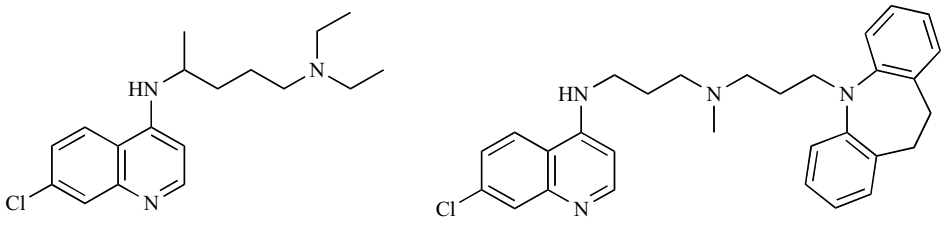


Fig. (10). Tricycle-substituted purines as MDR reversal agents.

dienes such as **37** showed the most interesting *in vivo* activity, fully restoring the sensitivity of P388/VCR murine leukemia to vincristine (VCR) when administered orally in association with VCR.

The modification of chloroquine (CQ) side-chain through the insertion of a dibenzoazepine moiety was recently reported by Peyton *et al.* [45] as an approach to reverse resistance to chloroquine itself. The new hybrid molecules, such as **38** (Fig. (**11**)) were termed as "reversed chloroquines" and are considered to be both antimalarial and reversal agents. An *in vitro* assay against both CQ-sensitive and CQ-resistant strains of *Plasmodium falciparum* indicated that **38** was effective at low-nM concentrations against both strains. A preliminary study in mice demonstrated oral efficacy against *P. chabaudi* at the dose of 64 mg/kg/day for 4 days. However **38** is considered too hydrophobic to have sufficient oral bioavailability in humans.

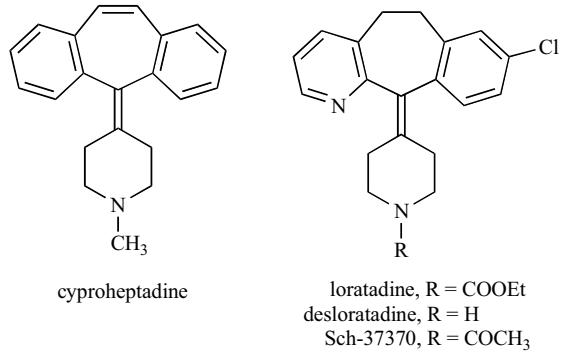


chloroquine **38**

Fig. (11). Reversed chloroquines.

ANTIHISTAMINIC AGENTS

A number of well known antihistaminic drugs share a tricyclic structure, such as cyproheptadine [46] (Fig. (**12**)), loratadine ad desloratadine [47].

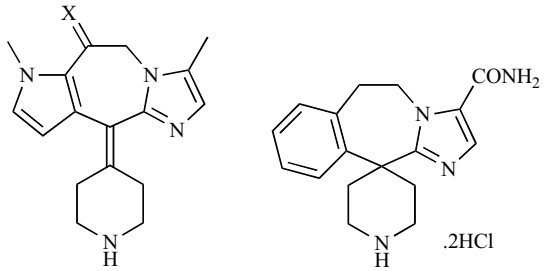


cyproheptadine

loratadine, R = COOEt
desloratadine, R = H
Sch-37370, R = $COCH_3$

Fig. (12). Tricyclic antihistamine drugs.

In the search of novel H_1 antihistamines, loratadine was taken by Johnson & Johnson researchers as a reference for a series of norpiperidine imidazoazepines (**39-41** (Fig. (**13**)) targeted to the therapy of dermatological disorders [48]. The



X = H_2 **39**
X = O, fumarate **40**

41

Fig. (13). Norpiperidine imidazoazepines by Johnson & Johnson.

objective was to identify potent and selective H_1 antihistamines, while reducing the sedative side effects. Thus, in addition to *in vitro* and *in vivo* activity, main physicochemical properties and the potential to cross the blood-brain barrier of the new compounds were evaluated and compared with reference antihistamines. *In vitro* activity of compound **41**, evaluated in a binding test with the human cloned H_1 histamine receptor expressed in CHO cells, was at least equal (Ki = 19 nM) to that of loratadine (Ki = 37 nM). *In vivo* activity was also evaluated in different animal species in a series of experiments, aimed at assessing the ability to protect against lethal anaphylactic shock and the effect on inhibiting and blocking cutaneous reactions. After oral or subcutaneous administration, **41** and some of its analogues showed a potency comparable to reference antihistamines. Compound **41** also showed good solubility in water (around 10 mg/mL in buffered solutions at pH 6-8). Its low $logD_{7.4}$ value ($logD_{7.4}$ = -1.3 for **41** *vs*. 4.58 for loratadine), suggests a negligible brain penetration, thus a low potential for sedative side effects. This was confirmed by quantitative autoradiography in guinea-pigs 3 h after oral administration of **41**. In addition, as some of the antihistamine drugs were related to potential cardiac side effects, *in vitro* and *in vivo* cardiovascular safety was also evaluated, showing no potential for **41** to prolong the QT interval, an effect that has been related to serious cardiac arrhythmias. Thus **41** has been proposed for further development in the dermatology field, as a safe antihistamine compound without the contamination of sedative activity.

Different attempts were made over the years, to modify tricyclic antihistamines in order to achieve combined activity on H_1 histamine and other targets involved in the asthma process. In fact, although the involvement of histamine in various allergic and inflammatory diseases is well known, the use of classical antihistamine agents for the treatment of other diseases, such as asthma, has not been successful.

Looking to more effective antiasthmatic agents, Zhang *et al.* [49] chose as a target dual antagonists of histamine H_1- and leukotriene D_4 (LTD_4) receptors, as actions of LTD_4 and histamine were considered complementary during inflammation and allergic responses. The starting point was an *in vitro* anti-LTD_4 screening of 22 known H_1-antihistamines, from which cyproheptadine was selected. In order to increase the weak potency of cyproheptadine at the LTD_4 receptor and its selectivity, some structural characteristics of LTD_4 itself, namely aminoacid or dipeptide moieties, were inserted on the piperidine nitrogen of cyproheptadine. This reduced by 100-1000 fold the cyproheptadine activity at the H_1 receptor but elevated by 10-100 fold its anti-LTD_4 activity. Further modifications led to compound **42** (Fig. (**14**)), that showed well balanced affinity at the H_1 (K_D = 0.41 μM) and LTD_4 (K_D = 1.55 μM) receptors. It also exhibited higher *in vivo* potency, in inhibiting antigen induced contraction of guinea-pig trachea, than selective H_1 or LTD_4 antagonists.

A similar approach led UCB researchers to link the loratadine scaffold to an N-hydroxyurea, the 5-lipoxygenase (5-LO) inhibiting moiety of zileuton [50]. A linker containing a phenyl ring was chosen for metabolic purposes. Compound **43** showed balanced *in vitro* activity *vs.* the H_1 receptor (binding, Ki = 19 nM) and *vs.* 5-LO (inhibition of calcium ionophore-induced leukotriene B_4 (LTB_4) formation in a human whole blood (HWB) assay, IC_{50} = 185 nM). Interestingly, both standard compounds loratadine (Ki = 414 nM) and zileuton (IC_{50} = 873 nM) were less active in the assay at the H_1 receptor or in inhibiting 5-LO, respectively. In guinea-pigs, **43** significantly inhibited histamine-induced bronchoconstriction and *ex vivo* LTB_4 production. However, its oral bioavailability was only 8% in rats.

Antagonists of platelet activating factor (PAF) and histamine were described by Schering, in analogy to their previously reported dual antagonist Sch-37370 (Fig. (**12**)) that reached phase II trials in asthma. A first series of compounds contained piperazine in place of the piperidinylidene ring, to increase conformational mobility [51] (Fig. (**14**)). Similar structural requirements for PAF activity were found in the two piperidinylidene and piperazine series, with the acetamides Sch-37370 (IC_{50} = 0.61 μM in inhibiting PAF-induced platelet aggregation of human platelet rich plasma) and **44** (IC_{50} = 0.40 μM in the same assay) being the most potent. On the other side, compound of the new series were somewhat weaker as antihistamines, with **44** showing Ki =

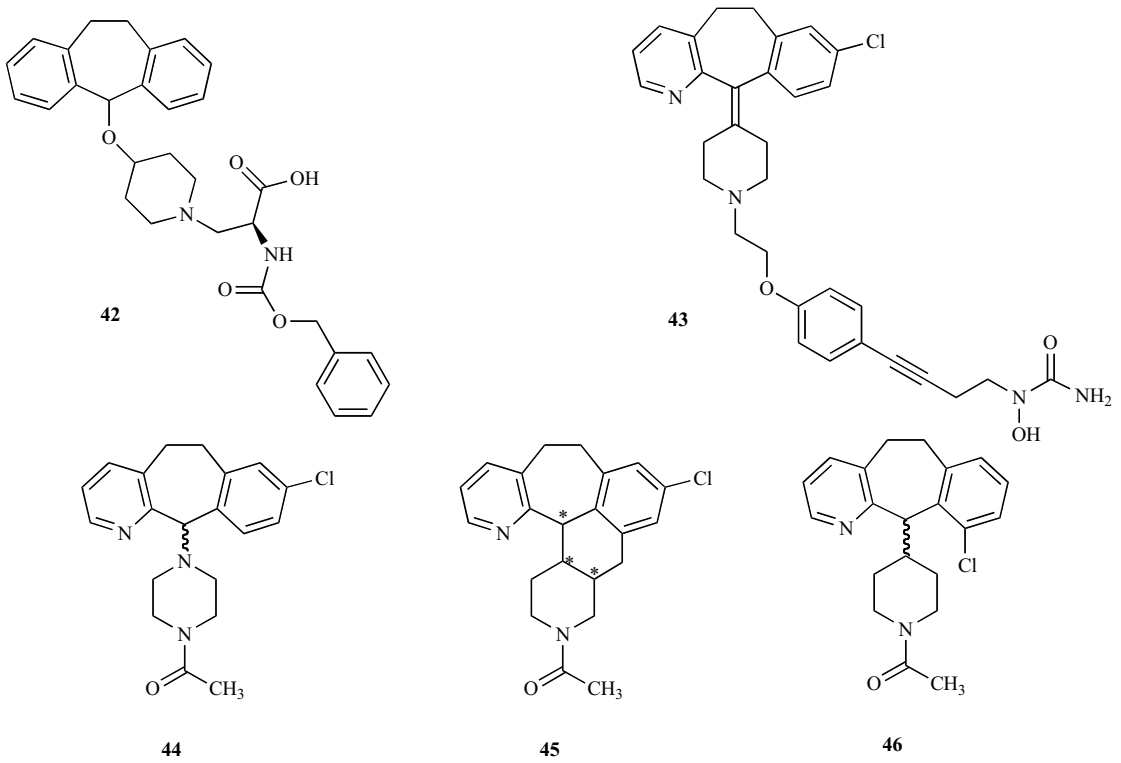


Fig. (14). Dual ligands of H_1 histamine and LTD_4, 5-lipoxygenase or PAF as potential antiasthma agents.

5.4 μM in the H_1-binding assay, and its piperidinylidene counterpart Sch-37370 about one order of magnitude more potent (Ki = 0.32 μM). As most of the piperazine derivatives including **44**, contain an asymmetric centre, the compound was resolved into its two enantiomers: the S-enantiomer showed about tenfold higher PAF activity than the R-enantiomer, while the latter was found to have higher affinity at the H_1 receptor, indicating that the individual activities predominate in separate enantiomers.

Considering the parallel structure-activity relationships (SARs) in the piperidinylidene and piperazine series, a common bioactive conformation at the PAF receptor was postulated. Constrained analogues that might mimic this conformation were synthesized [52], such as the pentacyclic piperidine analogue **45** that contains three asymmetric centers and can potentially exist as four possible diastereomeric pairs. Two diastereoisomers were synthesized in racemic form: in either case, they were inactive as PAF agents. Further conformational studies and molecular dynamics calculations led to the hypothesis that, although the conformational constraint of the pentacyclic system in **45** may offer an entropic advantage contributing to anti-PAF potency, the same constraint increases the steric bulk in an area of the PAF receptor where large substituents are not tolerated. In fact also the C-10 substituted tricyclic analog **46**, where the chlorine atom occupies a zone in the space similar to that occupied by the additional cycle in **45**, gave poor anti-PAF activity ((IC_{50} = 14.3 μM).

Recently, a role for histamine antagonists at the newly discovered H_4 receptor (H_4R) was proposed in the therapy of asthma, inflammatory bowel disease, and several dermatological disorders [53]. Leurs *et al.* [54] took as a reference the widely used tricyclic antipsychotic drug clozapine (Fig. (**15**)), that was shown to act as an antagonist on several G-protein coupled receptors (GPCRs) and as a full agonist at

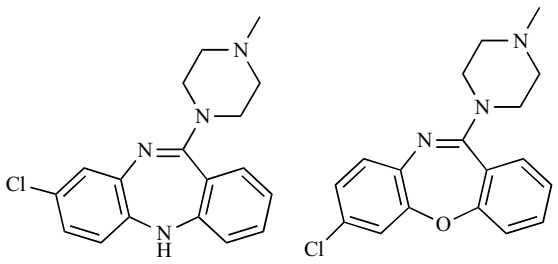


Fig. (15). Clozapine and the novel H_4 histamine receptor agonists.

the human H_4R. Clozapine was considered a good starting point also for its relatively small and rigid tricyclic scaffold. A series of dibenzodiazepine analogues were synthesized to explore the SAR of this class of compounds at the human H_4R. Replacement of the NH bridge between the two benzene rings in clozapine with NMe, CH_2 or S slightly reduced receptor affinity in the binding test (displacement of [^{3}H]-histamine from human H_4R expressed in SK-N-MC cells), while substitution with oxygen increased H_4R affinity of about 4-fold. These differences were likely ascribed to the changes in the dihedral angle between the planes of both aromatic rings in the presence of different bridge atoms, although electronic or steric effects might also give a contribution. Apart from the methyl group, any other substituent at

the piperazine nitrogen was detrimental for receptor affinity, due presumably to steric effects for larger alkyl groups, and to decreased basicity for hydrogen and for morpholine and piperidine analogs lacking the "external" nitrogen. Shifting the chlorine substituent to different positions on benzene rings or replacing it with fluorine gave a series of derivatives, from which compound **47** (pKi = 7.55 in the binding assay) was selected for further studies. Interestingly, most of the cited compounds, including **47,** were full or partial agonist at the H_4R. Binding assays at the other histamine receptors showed for **47** a 5-fold higher affinity for the H_1R (pKi = 8.11) than that for the H_4R and a much lower affinity for H_2R (pKi = 5.06) and H_3R (pKi = 5.04). These data suggest that a compound can be designed that is relatively inactive at the H_2R and the H_3R, while binding in the lipophilic domains of the H_1R and H_4R active sites. These dual action ligands have been suggested to be a potential new way to treat inflammatory diseases.

ARGININE-VASOPRESSIN ANTAGONISTS AND AGONISTS

The nonapeptide arginine vasopressin (AVP), also known as anti-diuretic hormone, is responsible for numerous biological actions. It directly and indirectly influences water balance, osmotic salt balance, and blood pressure acting though three different GPCRs, namely the V_{1a}, V_{1b}, and V_2 receptors. In particular V_2 receptors, are involved in balancing the re-absorption and elimination of the body's free-water content [55]. Thus, the blockade of these receptors by V_2 antagonists may be useful in the treatment of excess renal absorption of free water, correcting the fluid retention in diseases such as congestive heart failure or liver cyrrosis [56]. On the other hand, V_2 agonists have been proposed in the treatment of nocturnal enuresis [57].

Since 1998, Wyeth-Ayerst researchers have published a series of papers describing tricyclic V_2 receptor antagonists and agonists. Keeping as an initial reference the structure of the previously reported selective V_2 antagonist OPC-31260 (later launched by Otsuka in Japan as mozavaptan for hyponatremia [58]), they synthesized a series of pyrrole fused benzodiazepines (Fig. (**16**)) [59]. With the objective to enhance selectivity for binding to V_2 receptors over V_{1a} receptors, they introduced chloro, fluoro, methoxy, and methyl substituents in the two phenyl rings of the 4-(benzoylamino)benzoyl side chain. Introduction of a chloro or a

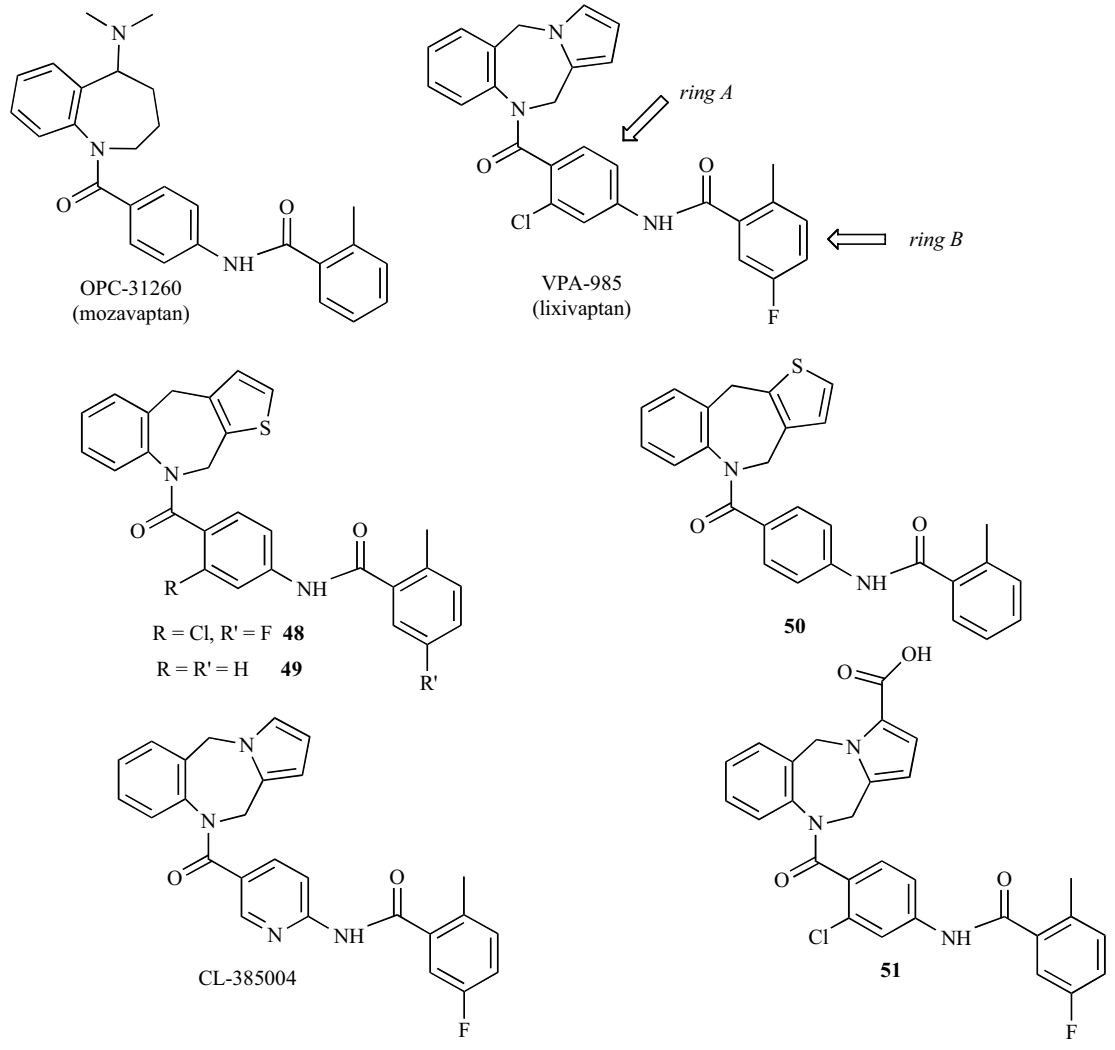


Fig. (16). Lixivaptan and analogues as V_2 receptor AVP antagonists.

methyl group at the C-3 position of phenyl ring A enhanced the selectivity for binding to human AVP V_2 receptors while substituents as chlorine or methoxy at the C-2 position had little effect on potency and selectivity. Interestingly, the trend on the human receptors was not reflected in binding affinities for rat receptors, where none of the compounds, with the only exception of VPA-985 (V_{1a}/V_2 affinity >100), showed V_2 *vs.* V_{1a} selectivity.

Compound VPA-985 (lixivaptan) showed high affinity at the human V_2 receptor (IC_{50} = 1.2 nM), with high selectivity (V_{1a}/V_2 affinity = 192) over the V_{1a} human receptor. The compound was also active after oral administration in *in vivo* animal models and in clinical studies. Lixivaptan is presently undergoing phase III clinical trials (by Biogen Idec and Cardiokine) in congestive heart failure patients with hyponatremia [60].

The Wyeth group also described a small set of derivatives such as **48-50** where a thiophene ring is fused to the benzazepine instead of pyrrole [61]. Compound **48** with the same substitution pattern as lixivaptan was five-fold less active in binding to human receptors than lixivaptan itself, but the *in vivo* activity (urine output increase in conscious AVP-treated and water loaded rats *vs.* control) was almost identical for both the pyrrole and the thiophene compounds. Removal of the chlorine and fluorine substituent as in **49** increased the affinity for the human V_2 receptor when compared to **48**, while decreasing *in vivo* activity. Finally, the differently fused thiophene derivative **50** exhibited lower *in vitro* and very poor *in vivo* activity.

A series of compound where the phenyl ring A is replaced with a 3-pyridinyl moiety and the phenyl ring B bears different substituents were also prepared, with the objective of increasing the polarity and thus the water solubility of lixivaptan through the insertion of a basic aromatic ring [62]. The compound (CL-385004) with the same substitution pattern as lixivaptan in the B ring gave best results, with good oral activity in rats also at low dose levels. *In vitro* affinity for other compounds was reported, although on the rat receptor only. When the methyl group on the B ring was replaced by small size (H or F) or polar (NO_2 or NH_2) substituents, a sharp decrease in the affinity for both V_2 and V_{1a} receptors was noticed. Attempts to insert additional basic groups, such as alkyldimethylamines, on the pyrrole ring or into the spacer between A and B rings were also unsuccessful, leading to a decrease of *in vitro* affinity.

Further modifications aimed at an increase of water solubility were realized through the insertion of ionizable acid or basic groups on the pyrrole ring [63]. Carboxy acid derivatives, such as **51** maintaining the same substitution pattern as in lixivaptan or the 2-phenyl analogue on the B phenyl ring, showed nanomolar affinity for the V_2 receptor (IC_{50} = 14 and 4 nM, respectively) and *in vivo* activity after i.v. administration, but lacked oral activity. Acylamines (Fig. (**17**)) also gave good affinity for the V_2 receptor (IC_{50} = 11.5 nM for **52**); and potent oral *in vivo* activity; the target solubility was achieved through the selection of a suitable salt (citrate for **52**). A number of amines were also synthesized with the general structure **53**. Compound WAY-140288 (R = $N(CH_3)_2$, R' = H, R" = OCH_3) was obtained as a crystalline molecule, soluble in water (2.2 mg/mL in water + 30% PEG-200) also as the free base. It bound to the human V_2 receptor with an IC_{50} value of 5.2 nM, and, at 10 mg/kg os, gave a five-fold

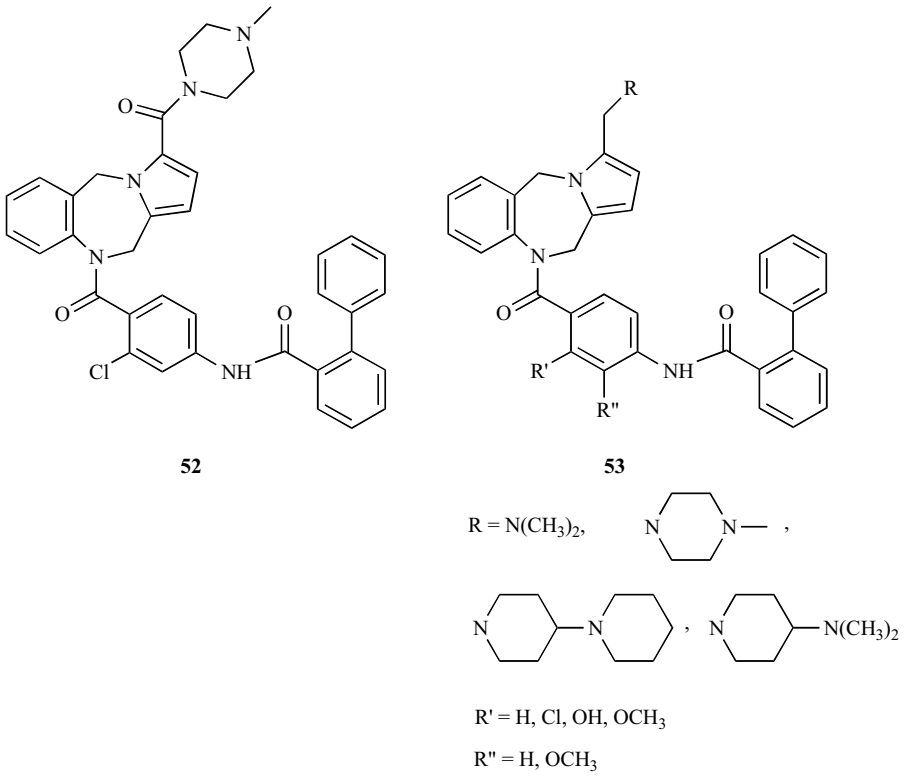


Fig. (17). Amine substituted pyrrolebenzodiazepines as water soluble V_2 antagonists.

increase of urine volume in water-loaded conscious rats when compared to controls.

An extensive evaluation of different tricyclic scaffolds was then performed by Wyeth researchers [64], using as a starting point structure **54** (Fig. (**18**)), that shows a simplified substitution pattern on the A and B phenyl rings when compared to lixivaptan. Results are summarized in Table **1**. None of the tricyclic scaffolds (including some whose structure is out of the limits set for the present review) showed superior properties when compared to the pyrrolebenzodiazepine typical of lixivaptan and of **54**. The 10,11-dihydro-5H-dibenzo[*b,f*]azepine skeleton, as in **55**, lowered the affinity to the V_2 receptor of at least 200 times. The isomeric 5,6-dihydro-11H-dibenzo[*b,e*]azepine, as in **56**, was comparable to **54** as for *in vivo* activity but showed lower V_2 affinity and V_{1a}/V_2 selectivity. Insertion in the central seven membered ring of an additional heteroatom (O, S, NH) led to a loss (**57**) or an inversion (**58-59**) of the V_{1a}/V_2 selectivity, and to compounds not active in the reported *in vivo* test.

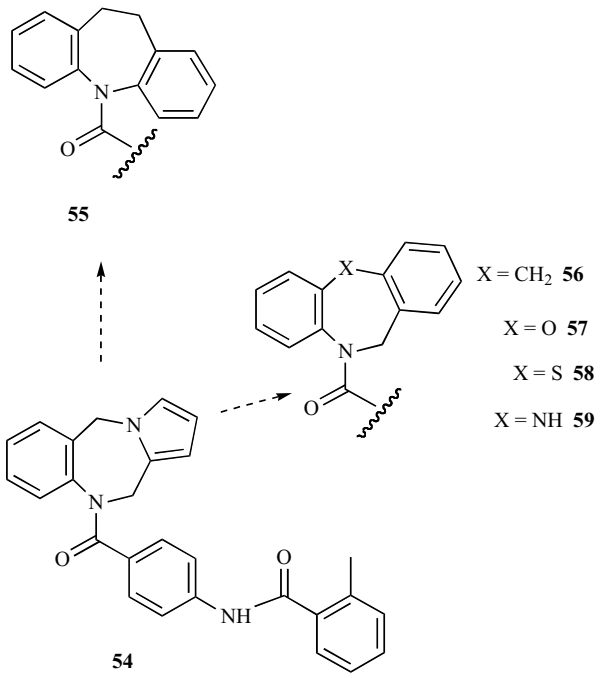


Fig. (18). Screening of different tricyclic scaffolds as V_2 antagonists.

Further work [65], aimed at evaluating different linkers connecting A and B phenyl rings, confirmed the superiority of the amide bond as for *in vitro* and *in vivo* V_2 antagonist activity. However when the B (outer) ring was replaced by a pyrazole ring directly connected to the A ring, compound WAY-VNA-932 (Fig. (**19**)), with agonist properties at the V_2 receptor, selectivity *vs.* the V_{1a} receptor and antidiuretic *in vivo* activity, was obtained [66].

WAY-VNA-932 competitively binds to the human V_2 and V_{1a} receptors in stably transfected CHO cells, with Ki = 39.9 nM and 465 nM, respectively. It showed full agonist behaviour *in vitro*, in the assay of stimulation of the formation of cAMP in LV2 cells, with EC_{50} = 0.73 nM. Oral efficacy as antidiuretic was observed in male and female rats (ED_{50} = 0.4 and 0.2 mg/kg, respectively), conscious dogs (ED_{50} = 0.1 mg/kg), conscious monkeys (ED_{50} = 0.28 mg/kg), and in naturally AVP deficient Brattleboro rats (a model of diabetes insipidus; ED_{50} = 0.1 mg/kg) [67].

A new class of orally active, vasopressin V_2 receptor selective agonists was then obtained by replacing with a pyridine the pyrrole ring fused to the benzodiazepine in previous compounds [68]. Evaluation of *in vivo* antidiuretic activity in rats was selected as the primary screening, to facilitate the rapid identification and ranking of potent orally active agonists. At the dose of 10 mg/kg po, most compounds showed good activity, with greater agonist potency for 3-alkyl pyrazoles **60** *vs.* 5-alkyl pyrazoles **61**. Halogen containing substituents on the phenyl ring were well tolerated, with activity maintained also at 1 mg/kg oral dose for X = Cl, Br, CF_3, while a methyl group, and, in a lesser extent, a trifluoro-

Table 1. ***In Vitro*** **Activity at the Rat V_2 Receptor,** ***In Vitro*** **Selectivity** ***vs.*** **the Rat V_{1a} Receptor and** ***In Vivo*** **Activity of Compounds 54-59**

Compound	V_2 IC_{50}, nM [a]	V_{1a}/V_2 [b]	Urine Volume (mL/4 h) [c]
lixivaptan	2.3	178	22
54	4	9.5	15.8
55	860	2.9	*n.t.*
56	68	2.2	15.2
57	1.7	0.88	*n.t.*
58	860	0.46	7.7
59	42	0.45	7.4

n.t. = not tested

([a]) *In vitro* activity: inhibition of ^{3}H-AVP binding to rat kidney medullary V_2 receptors. ([b]) *In vitro* selectivity: IC_{50} ratio in the binding assays (inhibition of ^{3}H-AVP binding to rat hepatic V_{1a} receptors or rat kidney medullary V_2 receptors). ([c]) *In vivo* activity: volume of urine collected in 4 h in water loaded (30 mL/kg) Sprague–Dawley rats treated (ip) with AVP (0.4 mg/kg), as compared with the urine volume (12.1 mL) in control rats.

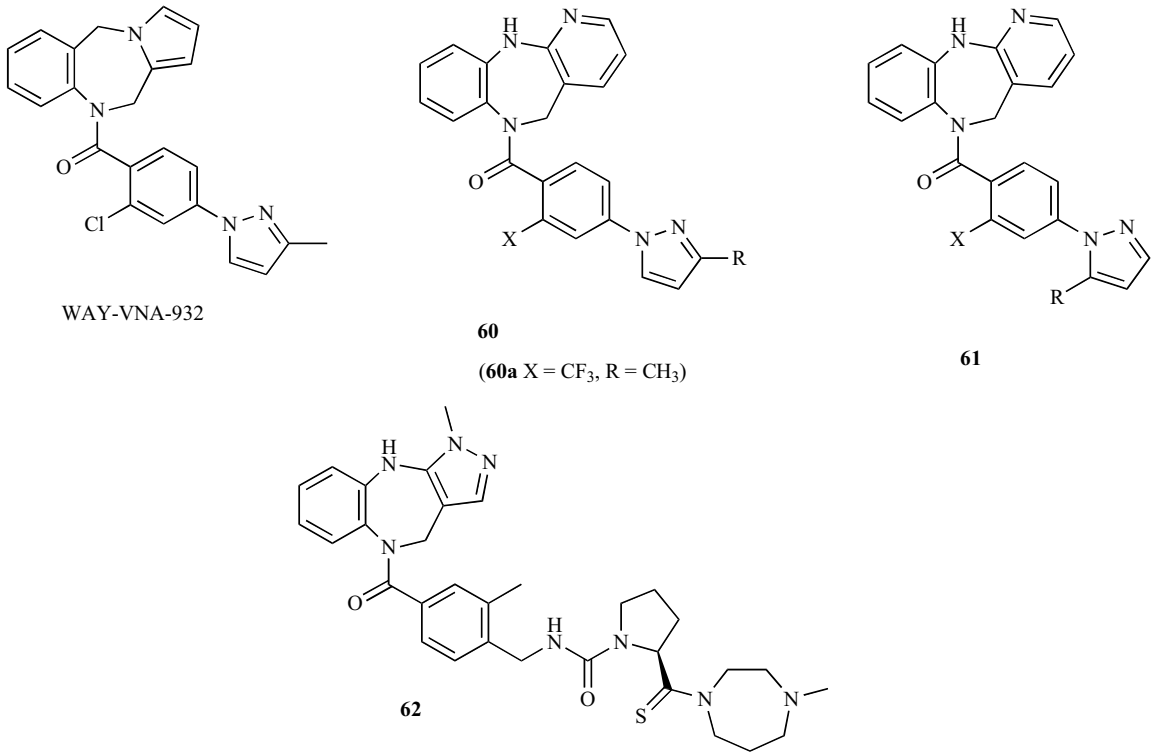


Fig. (19). Diaryldiazepines as V_2 receptor or OT receptor agonists.

methyl, were the best on the pyrazole ring. Compound **60a** showed a similar *in vivo* profile as WAY-VNA-932 (see above), with ED_{50} = 0.1 mg/kg in conscious rats, ED_{50} = 3 mg/kg in conscious dogs and monkeys, and ED_{50} < 0.1 mg/kg in naturally AVP deficient Brattleboro rats. The *in vitro* functional test confirmed its agonist activity with EC_{50} = 1.67 nM; however **60a** the compound showed weaker binding affinity for the cloned human V_2 receptor than WAY-VNA-932 (IC_{50} = 493 nM *vs.* 80 nM).

A 2004 paper [69] from Ferring Research and the University of Lille confirms the role of tricyclic diaryldiazepines as privileged structures in this field. Looking for non peptide agonists of oxytocin (OT), a cyclic nonapeptide hormone with a number of physiological roles (*e.g.* in the onset and progress of labour and in the regulation of male and female sexual response), and considering the close relation between OT and AVP, the authors screened a library of 50,000 comp onds designed as V_2 agonists for their OT agonist activity in a functional report gene assay. Interestingly, while most of the hits were bicyclic thienylazepines, a significant increase in potency at the human OT receptor was attained by restoring the tricyclic skeleton as in **62**. The compound gave EC_{50} = 33 nM at the human OT receptor, with a maximal effect of the same degree as OT, and at least 25-fold selectivity over the V_2 receptor.

RETINOIDS AND RETINOID ANTAGONISTS

A number of dibenzodiazepine derivatives are known to interfere with retinoidal actions [70]. The isomeric dibenzodiazepines **63** and **64** (Fig (**20**)) were found to exert opposite regulatory activities when combined with with retinoic acid, or *N*-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid (Am80). Compound **63** inhibited either agonist induced differentiation of HL-60 cells, whereas **64** enhanced the same differentiation inducing activities. The synthesis of various analogs led to increase potency in either antagonist (**65** (Fig. **20**)) or synergist (**66** (Fig. **20**)) activities. During this study, **67** was also described to be an antagonist with slightly lower activity than **63**. Interestingly, the structural isomer **68** was later object of broad investigation as an antagonist rather than a synergist. Actually, slight modifications on the scaffold of the series derived from **64** allowed to obtain either synergists or antagonists, among which compound **68** emerged as one of the more potent antagonist [71]. Although the role of the nitro group was initially obscure since it could be replaced by a methoxy group or a phenyl group without significant loss of activity, compound **68** was shown to possess a promising pharmacological profile for the development of structurally congener new drugs against diseases such as type 2 diabetes [72, 73].

VITRONECTIN RECEPTOR ANTAGONISTS

Two industrial groups described RGD peptidomimetics featuring a tricyclic moiety in their structures and showing nanomolar potency as selective antagonists at the integrin $\alpha_v\beta_3$, the so-called vitronectin receptor. Fig. (**21**) exemplifies the results obtained by the two groups in term of molecular structure. The research leading to SB 265123 [74] was in fact a succesful follow-up study stemming from a previous equipotent antagonist featuring a 1,4-benzodiazepine system in the place of the tricyclic group, and possessing a poor pharmacokinetic profile [75]. The eudismic ratio of SB 265123 versus the distomer was found to be ca 140 and, more importantly, it showed prominent pharmacokinetic properties in

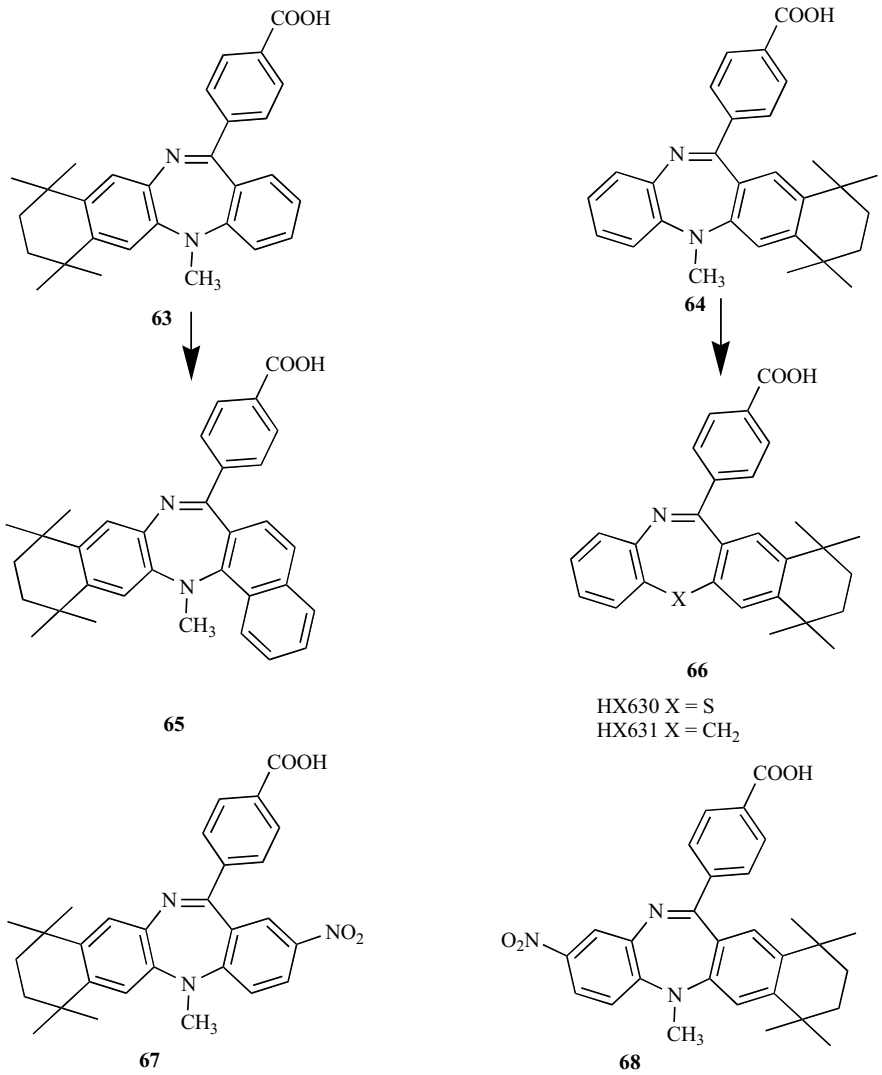


Fig. (20). Retinoid related tricycles.

rats (oral bioavailability: ≈100%). The antagonist **69** was derived by researchers at Knoll/BASF Pharma, after the disclosure of SB 265123 structure, and by taking advantage of corporate previous experience in the field of tricyclic compounds. Differently from SB 265123, the Knoll/BASF antagonists were studied as the racemates. Moreover, this kind of tricyclic framework is featured by intrinsic planar chirality. Thence, the introduction of a stereogenic center at the central position of the internal ring, gives rise to a couple of racemic diasteroisomers, the interconversion of which was found by the authors to be slow (24-48 h) at room temperature, not enough, however, to allow them to study the isomers separately [76]. Interesting, in a subsequent paper by the same group [77], the above observation was reported to be one of the reasons determining the removal of one of the two aromatic rings from the tricyclic core, which did not cost in term of affinity.

MISCELLANEOUS

Many other potential applications are described for tricycles in recent years. Structurally diverse tricyclic skeletons are contained in many enzyme inhibitors as well as in receptor agonists and antagonists and deeper investigations are ongoing for many of them. Some of the most innovative and representative ones are here summarized in a very brief and not exaustive manner.

Starting from the observation that tricyclic psychotropic drugs can induce defibrillation and reduce the ischemic area in the heart following coronary occlusion, compounds of structure **70** (Fig. (**22**)) were built as the first ventricular defibrillating drugs. [78]

In the attempt to obtain an *in vivo*, blood-brain barrier penetrating, effective antiprion compound, a chimeric heterodimeric molecule (**71**) was built by assembling an acridine nucleus, present in other antiprion molecules such as quinacrine, with the ethylene bridge-head tricycle derived by imipramine, obtaining an unprecedented activity in cellular tests. [79]

Tricyclic compound **72** was chosen as a hit during the research of new non-aminoglycoside antibiotics. The observation of its binding to the A-site RNA, conducted through MS and NMR methodologies, was confirmed by a competi-

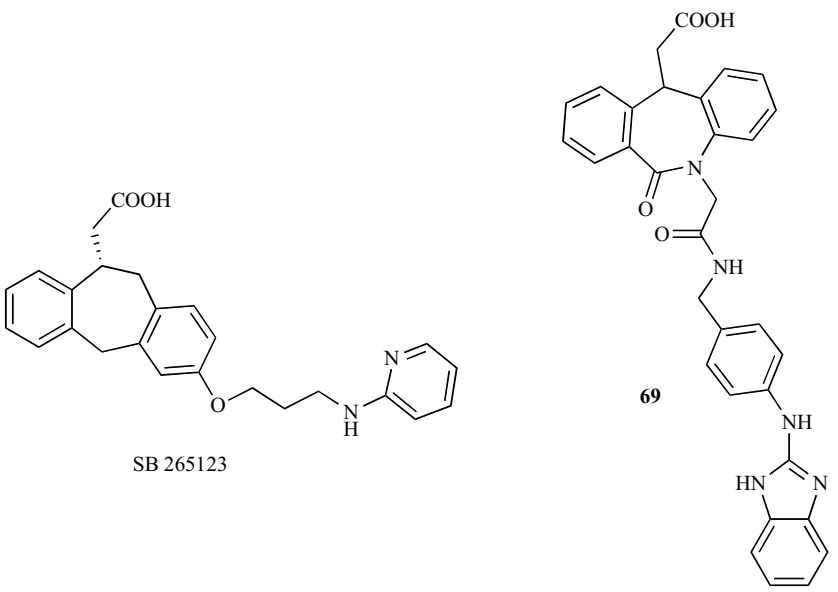


Fig. (21). Vitronectin receptor antagonists.

tive binding experiment between **72** and paromomycin from which it was clear that the two molecules compete for the same binding site [80].

Two recently isolated natural dibenzooxazepinones (**73**) were reported to be active in radical scavenging, exerting a good antioxidant behaviour when tested *in vitro* versus known natural antioxidant molecules as ascorbic acid and α-tocoferol [81].

Pyrrolobenzodiazepine (PBD) derivatives such as **74** have been extensively described as pro-apoptotic molecules

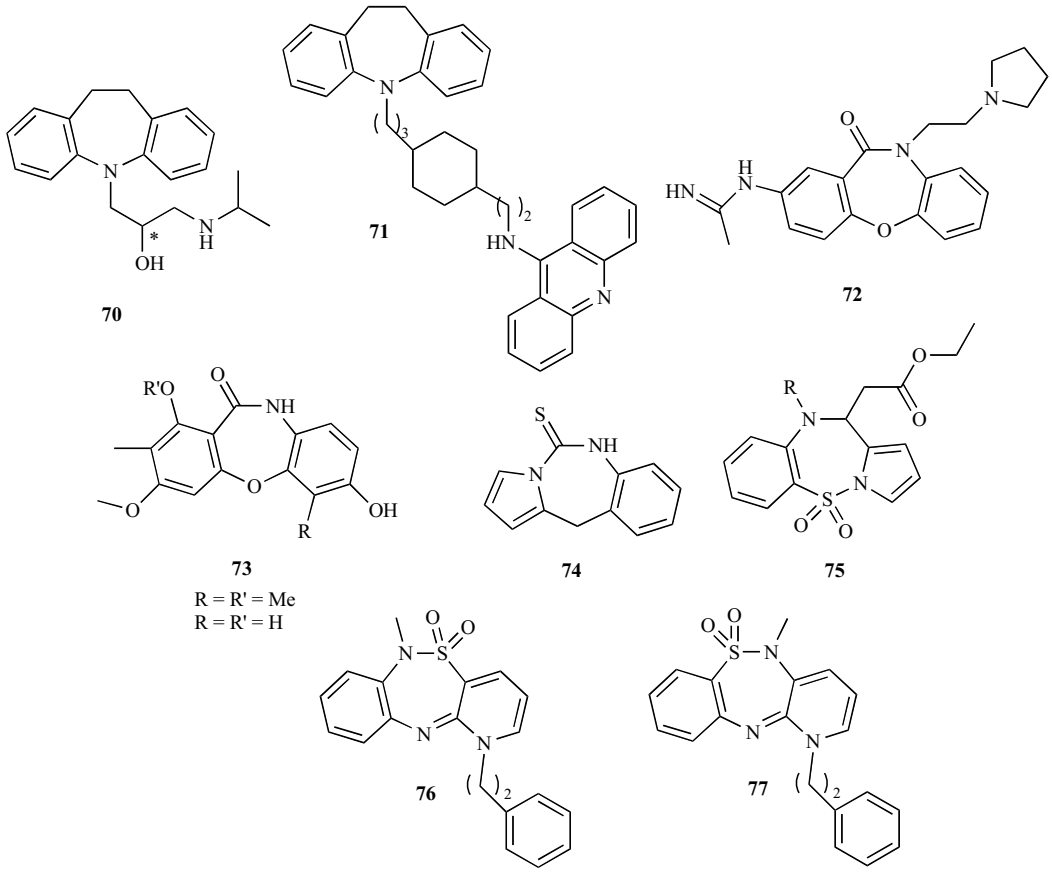
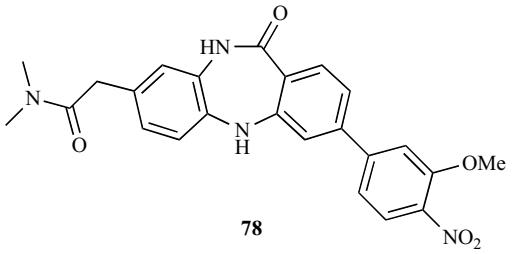


Fig. (22). Overview on recent innovative applications for tricycles.

exerting their action via a non-covalent DNA interaction and have been considered a proper platform for the construction of non-toxic anticancer drugs. [82, 83]. More recently Italian academic researchers have reconsidered their NNRTI of structure **23**, thanks to their similarity to the PBDs, to build new pro-apoptotic and potentially anti-leukaemic tricycles of structure **75** [84].

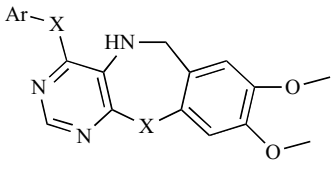
Benzopyridothiadiazepine dioxide derivatives (**76, 77**), whose skeleton was already present in low potency anti-AIDS compounds (**22** (Fig. (**4**)), were recently reported as antimitotic compounds. They exert a potent inhibition of tubulin polymerization and are under SAR study in order to optimize cytotoxicity and bioavailability [85].

Finally, various reports appeared in the literature during 2006-2007 regarding the identification of hit or lead tricyclic compounds showing inhibitory activity against diverse kinases: structures (**78-80**) and corresponding target enzyme sub-types are summarized in Fig. (**23**) [86-89].



78

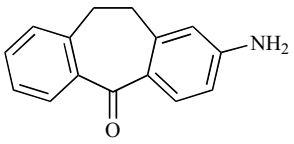
checkpoint kinase 1 (Chk1)



79

X=NH, O, S

epidermal growth factor receptor tyrosine kinase



80

p38 MAP kinase

Fig. (23). Inhibitors of kinases.

CONCLUSIONS

Although tricyclic structures are sometimes considered as synonima of drugs healing central nervous system pathologies, a large number of them have been considered and developed for different therapeutical indications, going from antiinfective and anticancer agents to cardiovascular or anti-inflammatory drugs.

It is noteworthy that extensive modulations of pharmacokinetic parameters together with modulations of selectivity against biological targets was obtained by simply varying the lateral chains of many of these tricycles, indicating that the tricyclic moiety has not intrinsic preferencial pharmacological interactions nor unavoidable physicochemical drawbacks, and can constitute a precious pharmacologically validated platform to build new drugs.

Very recent examples demonstrate the usefulness of tricyclic structures in a broad range of therapeutical fields, confirming that these compounds can still have a place in the tool-kit of the modern medicinal chemist.

ABBREVIATIONS

AIDS	=	Acquired immune deficiency syndrome
AML	=	Acute myeloid leukemia
AVP	=	Arginine vasopressin
CQ	=	Chloroquine
DHFR	=	Dihydrofolate reductase
FPT	=	Farnesyl Protein Transferase
GGPT	=	Geranylgeranyl protein transferase
GPCRs	=	G-protein coupled receptors
HWB	=	Human whole blood
H_4R	=	H_4 receptor
Ha-Ras-CVLS	=	Ha-Ras containing its native C-terminal sequence
LTD_4	=	Leukotriene D_4
LTB_4	=	Leukotriene B_4
Ma	=	*Mycobacterium avium*
MDR	=	Multidrug resistance
NNRTIs	=	Non-nucleoside HIV-1 reverse transcriptase inhibitors
OT	=	Oxytocin
PAF	=	Platelet activating factor
PBD	=	Pyrrolobenzodiazepine
Pc	=	*Pneumocystis carinii*
RT	=	Reverse transcriptase
SAR	=	Structure activity relationship
Tg	=	*Toxoplasma gondii*
VCR	=	Vincristine
WT-RT	=	Wild-type reverse transcriptase
5-LO	=	5-lipoxygenase

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