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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Asunto : Solicitud de patente para: **DIHIDRO Y TETRAHIDRO
OXAZOLOPIRIMIDINONAS SUSTITUIDAS,
PREPARACIÓN Y USO DE LAS MISMAS**
Solicitante : SANOFI-AVENTIS
Fecha solicitud : 09 de septiembre de 2009

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. 14129 notificado por fijación en lista del 14 de agosto de 2012.

2. Mediante oficio No. 14129 el Examinador a cargo del estudio de patentabilidad de la presente solicitud, en virtud del artículo 46 de la Decisión 486, solicitó la presentación de los siguientes documentos:

2.1 E. M. SASBATINI ET AL: "Metabotropic glutamate receptors: potential therapeutic applications of recently disclosed new chemical entities" EXPERT OPIN. THER. PATENTS, vol. 14, no. 11, 2004, pages 1593-1604, XP002504928.

2.2 FORFAR ET AL: "Synthesis, Structure, and Preliminary Evaluation of Cycloaddition Compounds with Unsaturated Carboxylic Esters" ARCHIV DERPHARMAZIE, vol. 323, no. 11, 1990, pages 905-909, XP002504929 Weinheim, DE.

2.3 FORFAR ET AL: "An easy Route to 2-Substituted-2,3-dihydro-5(7)H-oxazolo(3, 2-a)pyrimidin-5-ones and 7-ones Starting from the Corresponding 2-Amino-2-oxazolines" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 38, no. 4, 2001, pages 823-827, XP002504930.

3. Respuesta al requerimiento

Con el ánimo de dar respuesta al requerimiento formulado por el Examinador, se presenta junto con el presente memorial, copia de los tres documentos arriba mencionados.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

5. Anexos

- E. M. SASBATINI ET AL: "Metabotropic glutamate receptors: potential therapeutic applications of recently disclosed new chemical entities" EXPERT OPIN. THER. PATENTS, vol. 14, no. 11, 2004, pages 1593-1604, XP002504928.
- FORFAR ET AL: "Synthesis, Structure, and Preliminary Evaluation of Cycloaddition Compounds with Unsaturated Carboxylic Esters" ARCHIV DERPHARMAZIE, vol. 323, no. 11, 1990, pages 905-909, XP002504929 Weinheim, DE.
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Señor Director,


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Expert Opinion

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Metabotropic glutamate receptors: potential therapeutic applications of recently disclosed new chemical entities

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Glutamate is the main excitatory neurotransmitter in the mammalian CNS and it exerts its action through ionotropic and metabotropic receptors. Whereas ion channels have been heavily exploited in the recent past, metabotropic glutamate receptor (mGlu) research has been hampered by the lack of potent and selective molecules with 'drug-like' structures. A new wave of ligands has recently been disclosed by a number of pharmaceutical companies highlighting the great interest around these potential therapeutic targets. This review endeavours to provide the reader with an updated and detailed panorama of the patent literature of this exciting field, also tackling non-competitive and allosteric modulators. Those skilled in the art know that it is quite difficult to extract structure-activity relationship (SAR) information from a patent or to draw 'definitive' conclusions on a compound if biological data are not specifically provided. Accordingly, the main aim of this review will be to provide the reader with the most relevant information available and to report the structures of the newly unveiled chemical entities. Other very interesting compounds recently disclosed in the primary literature will not be exhaustively covered here, but they are surely worth a further check in the available literature databases, a few examples will be mentioned only where a novel therapeutic area is disclosed or if major insights are provided.

Keywords: agonist, allosteric modulator, antagonist, anxiety, cognitive disorders, depression, metabotropic glutamate receptor (mGlu), pain, schizophrenia

Expert Opin. Ther. Patents (2004) 14(11):1593-1604

1. Introduction

Metabotropic glutamate receptors (mGlu) belong to family C of the seven transmembrane (7-TM) receptors; they couple to G proteins (G-protein-coupled receptors [GPCRs]) and control the activity of membrane enzymes and ion channels [1-3]. A distinctive feature of the mGlu is the large N-terminal domain which contains the glutamate binding site [4,5] and, together with the parathyroid calcium sensing receptor, the GABA_B receptor and the vomeronasal receptor, they form a separate family of GPCRs showing very little homology with other cloned receptors [6-8].

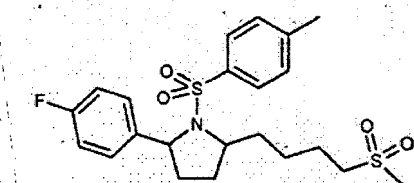
To date, the mGlu family consists of eight subtypes that have been cloned and named mGlu₁ – mGlu₈ according to the succession of their molecular cloning. These eight receptors are divided into three classes on the basis of sequence similarity, pharmacology and transduction mechanisms: Group I (mGlu₁ and mGlu₃), Group II (mGlu₂ and mGlu₇) and Group III (mGlu₄, mGlu₆, mGlu₇ and mGlu₈).

Based on the models currently available in the literature, these receptors seem to behave in a very dynamic fashion: the transmembrane region is both able to interact with the N-terminal domain or to directly interact with the G protein

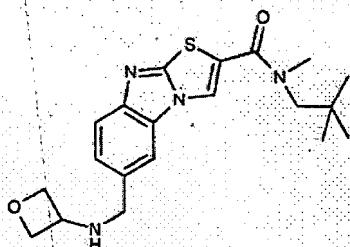
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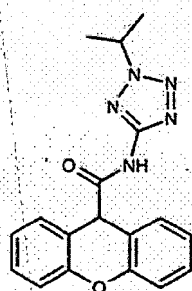


1 Hoffmann-La Roche

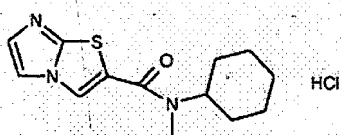


2 Yamanouchi

Figure 1. mGlu₁ modulators.



3 Hoffmann-La Roche



4 Yamanouchi

Figure 2. mGlu₁ agonists.

to vehiculate a signal after appropriate activation through allosteric/modulatory sites.

Moreover, and very interestingly, both positive and negative modulation is possible with appropriate new chemical entities.

This fascinating and unique feature amongst GPCRs has been recently postulated and modelled [9,10].

The selective distribution of the metabotropic receptors [11] should guarantee therapeutic effect with very few side effects. Nonetheless, despite all the interesting results achieved so far in preclinical models, no definitive study in humans can yet confirm this hypothesis.

2. mGlu₁ ligands

2.1 Modulators

As reported in the introduction, in the last few years an increasing number of molecules able to interact in a non-competitive manner with the glutamate binding site has been reported. Moreover, beyond the classical non-competitive antagonists, a number of modulators have also been reported as well.

In this interesting field, Hoffmann-La Roche reported the activity of novel sulfonylpyrrolidine derivatives (1, Figure 1) claiming their use for the treatment of a variety of acute and chronic neurological disorders [101].

Interestingly enough, these compounds are stated to have affinity for metabotropic glutamate Type 1 receptors (mGlu₁) with both inhibitory and/or activating activity. The effective concentration for half maximum response (EC₅₀) values for 13 compounds, reported in a table within the patent, were in the range of 0.16 – 4.40 μM, with compound 1 having an EC₅₀ value of 0.16 μM.

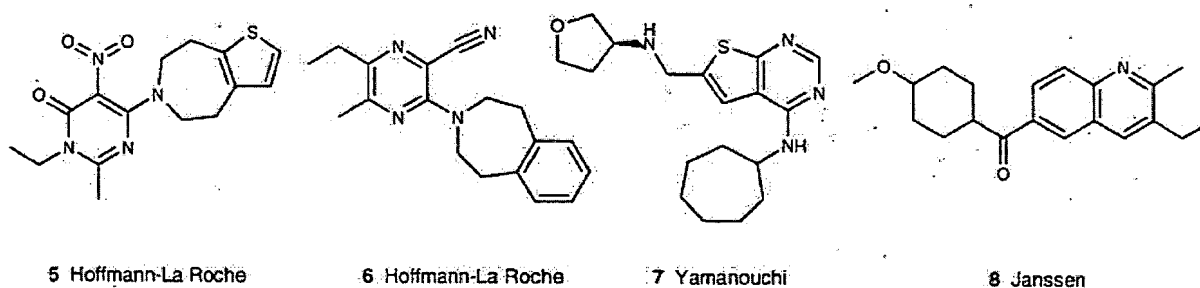
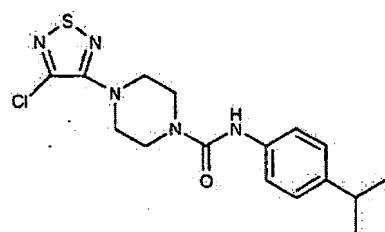
In the same field, Yamanouchi (2, Figure 1) reported some aminomethyl-substituted thiazolobenzimidazole derivatives [102] exemplified by compound 2, which showed a 50% inhibition concentration (IC₅₀) value of 2 nM. These compounds are stated to be metabotropic glutamate receptor modulators and their application is foreseen in the prevention and treatment of Parkinson's disease, anxiety and pain.

2.2 Agonists

Another important area is represented by the synthesis of mGlu agonists. Until recently, many mGlu agonists contained carboxylic acids (or their isosteres) in their structures, making the crossing of the blood-brain barrier rather difficult if an active-transport mechanism was not involved.

In the mGlu₁ field, agonist molecules are usually claimed to be active in a number of CNS diseases. Hoffmann-La Roche disclosed novel tetrazole derivatives (3, Figure 2) as group 1 metabotropic glutamate receptor agonists [103]. These compounds are claimed to be beneficial for the treatment of cognitive disorders, schizophrenia, hypoxia and hypoglycaemia. The compounds were found to have EC₅₀ values ranging from 0.045 (3) to 2 μM.

Prevention and treatment of cerebral infarction, on the other hand, are claimed by Yamanouchi [104] for their imidazothiazole derivatives (4, Figure 2). These compounds are claimed to be agonists of the mGlu₁ subtype and compound 4 is endowed with an EC₅₀ value of 20 nM.

Figure 3. mGlu₁ antagonists.Figure 4. Mixed mGlu_{1/5}.

2.3 Antagonists

In the mGlu₁ antagonist field, Hoffmann-La Roche recently disclosed two patents: in the first [105] they claimed a new class of tetrahydro-heterocycloazepinyl pyrimidine derivatives (5, Figure 3), and in the second [106], novel 1,2,4,5-tetrahydro-benzo (or thieno)[d]azepine-pyrazine or -triazine derivatives are reported (6, Figure 3).

The therapeutic areas of possible intervention for compound 5 are related to epilepsy, pain, psychosis, schizophrenia and cognitive disorder. The mGlu₁ antagonistic activity was reported for nine compounds with affinity values ranging from 0.069 (for compound 5) to 49 μ M.

For analogues of exemplified derivative 6, claimed activity relates to the treatment of acute or chronic neurological disorders and, among the different data presented, the specified compound had an IC₅₀ value of 0.006 μ M.

Yamanouchi also became active in this area with the patenting of novel thienopyrimidine derivatives (7, Figure 3) [107]. They claim a derivative as active as 5 nM. Also in this case, the claimed activities relate to pain, migraine, various neurodegenerative diseases and also cerebrovascular disease and diabetic nephropathy.

Finally, as far as mGlu₁ antagonists are concerned, Janssen reported novel quinoline derivatives (8, Figure 3) [108] that could be able to prevent a number of glutamate-induced diseases of the CNS. The *in vitro* inhibitory activity in transfected Chinese hamster ovary (CHO) cells of one of the best compounds reported, gave a pIC₅₀ value of 8.58.

Very recently, new non-competitive pyrrole antagonists were described in the primary literature and a report of anti-nociceptive activity was presented [12].

3. Mixed mGlu_{1/5} antagonists

Spanning the Group I metabotropic receptors, Euroceltique recently claimed the use of thiadiazolypiperazines (9, Figure 4) as mixed mGlu_{1/5} antagonists for the treatment of pain, depression or anxiety [109]. Compound 9, which is the best example reported in the patent and which should act as a non-competitive antagonist, is endowed with an IC₅₀ value of 374.4 nM.

4. mGlu₅ ligands

4.1 Antagonists

In the mGlu₅ antagonist field (Figure 5), a new application for a previously reported compound was filed by Novartis [110] who claimed the use of 2-methyl-6-(phenylethynyl)pyridine (also known as MPEP; 10, Figure 5) for treating pruritic conditions.

Similar acetylenic structures were disclosed by Hoffmann-La Roche [111]. Novel phenylethenyl or phenylethynyl derivatives (11), with a range of activities from 0.011 (for the specified compound) to < 10 μ M, were reported. Their field of application varies from treating a number of CNS disorders, including Parkinson's disease, schizophrenia, anxiety and depression, to diseases such as pain, migraine and nicotine addiction.

Additional phenylacetylene derivatives (12) were reported by Novartis Pharma as mGlu₅ antagonists [112] (or possibly mGlu₅ modulators) useful for the treatment of a long list of CNS related disorders, including schizophrenia, anxiety, depression, itching and drug abuse. The best example is reported to inhibit quisqualate-induced inositol phosphate turnover in human mGlu₅-expressing cells with an IC₅₀ value of 30 nM.

In this field, Euroceltique filed a patent where 1-(pyridin-2-yl)piperazine derivatives (13) are claimed as potential treatment for major depressive disorders [113]. An example compound reported in the patent had an IC₅₀ value of 8.9 nM.

Metabotropic glutamate receptors: potential therapeutic applications of recently disclosed new chemical entities

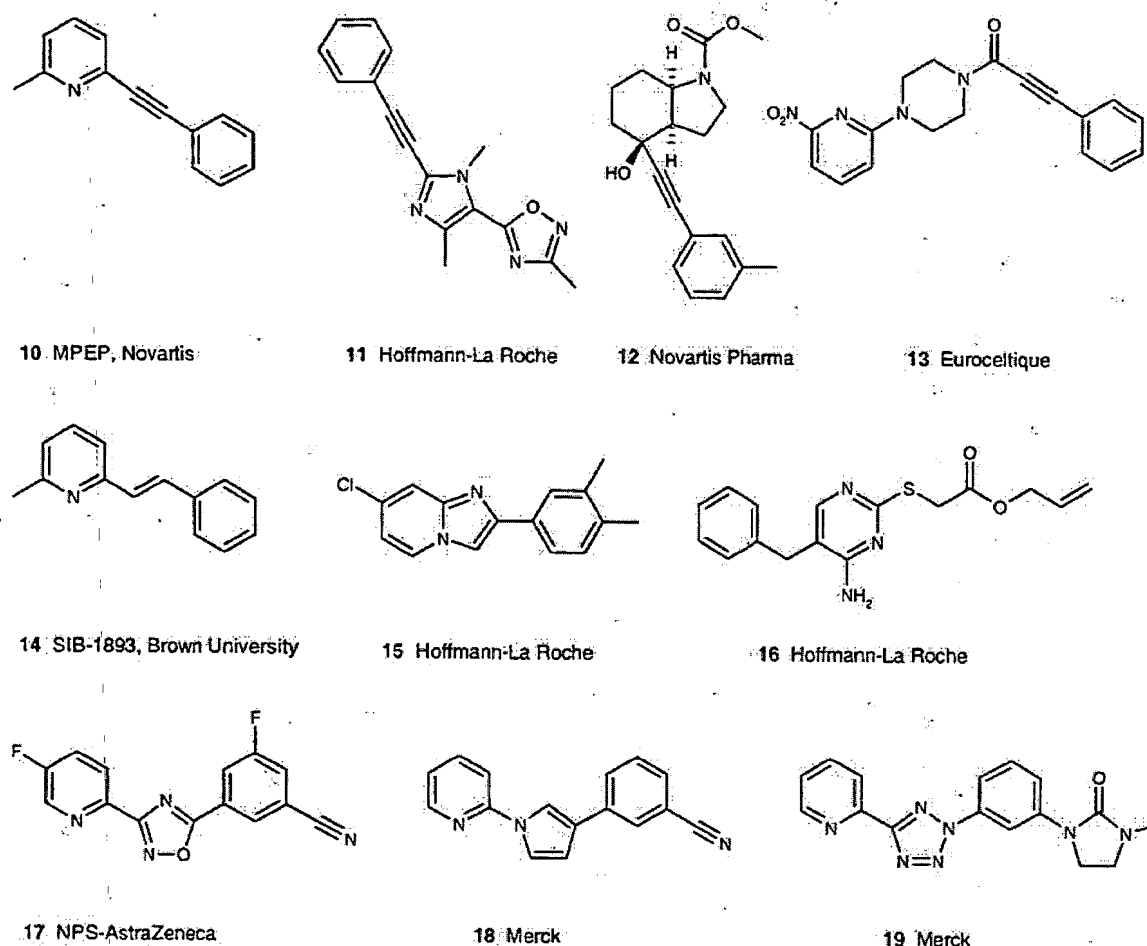


Figure 5. mGlu5 antagonists.

Other interesting claims for the application of mGlu₅ antagonists, such as Fragile-X syndrome, autism, mental retardation, schizophrenia or Down's syndrome, are presented in a patent from Brown university (known as SIB-1893, 14) [114].

Hoffmann-La Roche [115,116] also identified imidazo[1,2-a]pyridine derivatives and 4-amino-2-thioalkylpyrimidine derivatives (15 and 16, respectively). In the former case, compounds showed *in vitro* IC₅₀ values ranging 0.037 – 10 µM, whereas in the latter the compounds had IC₅₀ values ranging 0.12 – 3.85 µM. As for their activity, the compounds are claimed to be useful for treating AIDS dementia, substance dependence, brain injuries and hypoxia.

Other interesting non-CNS related and potentially new therapeutic areas are claimed by NPS and AstraZeneca (17) [117] for their mGlu₅ antagonists. They foresee use for the inhibition of transient lower oesophageal sphincter relaxations (TLESRs), the treatment of gastro-oesophageal reflux disease (GERD), the prevention of reflux, and the treatment or prevention of regurgitation, asthma, chronic laryngitis, lung disease and failure to thrive. These

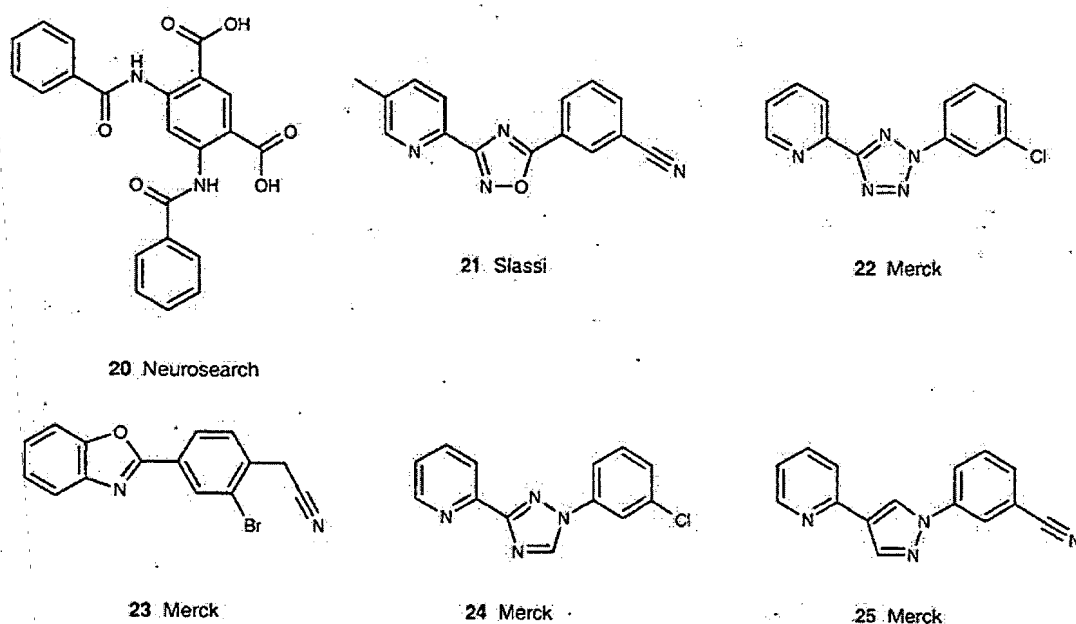
compounds were tested for their activity against TLESRs (defined as a decrease in lower oesophageal sphincter pressure in relation to intragastric pressure) *in vivo*. It was shown that the inhibition of TLESRs was 70% for the specified compound at 1 µmol/kg/h given as an infusion for 60 min, compared with 32 and 43% for the positive control MPEP at 4 and 6 µmol/kg/h, respectively.

Finally, novel heteroaryl substituted pyrroles (18, Figure 5) were disclosed by Merck to be mGlu₅ inhibitors [118]. The compounds are claimed to have IC₅₀ values of ≤ 10 µM. Moreover, they also filed a patent in which 1,3-bisaryltetrazole derivatives (19) [119], endowed with IC₅₀ values of ≤ 10 µM were disclosed.

Very recently, anxiolytic properties of heteroaryl mGlu₅ antagonists have been published in the primary literature [13].

4.2 Modulators/ligands

Neurosearch disclosed the use of non-competitive selective mGlu₅ antagonists (20, Figure 6) or partial agonists to treat diseases responsive to modulation of an aspartate or a

Figure 6. mGlu₅ modulators/ligands.

glutamate receptor, and the specified compound had an IC₅₀ value of 1.9 μ M [120].

Slassi *et al.* [121] disclosed novel 3-(pyridin-2-yl)-5-(substituted phenyl)-1,2,4-oxadiazoles (21, Figure 6) and related heterocyclic analogues as ligands/antagonists at mGlu receptors, particularly mGlu₅ receptors. The compounds have shown IC₅₀ values ranging 11–9140 nM in a fluorometric imaging plate reader (FLIPR) assay using cultured primary astrocytes, but no specific biological data associated with individual compounds were presented.

Merck recently [122] reported novel heteroaryl substituted tetrazole derivatives (22) as mGlu₅ modulators, but no specific biological data are reported.

In another patent they reported fused heterobicyclo-substituted phenyl derivatives (23) as mGlu₅ modulators [123]. There are numerous therapeutic applications listed for their use, which include pain, anxiety, depression, bipolar disorder, drug or tobacco withdrawal, dementia, Alzheimer's and Parkinson's diseases.

Moreover, Merck [124] presented novel triazole derivatives (24) and their ability to modulate mGlu₅ responses with IC₅₀ values of ≤ 10 μ M. Finally, they also reported heteroaryl substituted pyrazoles (25) stated to have IC₅₀ values of < 10 μ M [125].

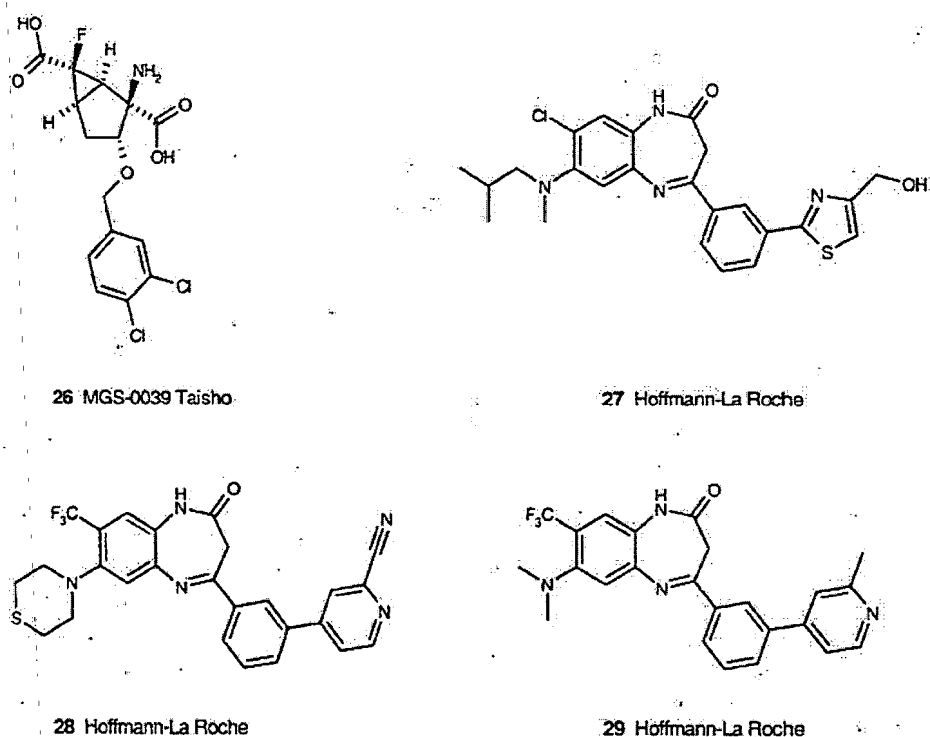
Two very recent articles from primary sources [14,15] also respectively pointed out the possible role of mGlu₅ agonists in neuroprotection and disclosed allosteric modulators for this receptor.

5. mGlu₂ and mGlu₃ ligands

5.1 Antagonists

In the field of mGlu_{2/3} antagonists, Taisho [126] disclosed a novel template belonging to the series of the modified 2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acids (WO2003061698; 26, Figure 7), for the treatment of depression. This novel series of mGlu_{2/3} antagonists has been discovered by incorporating a hydroxy or alkoxy group at the C-3-position of the corresponding 2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, which is a known potent group II mGlu agonist. Compound 26 (also known as MGS-0039) showed high affinity for both mGlu₂ ($K_i = 2.38$ nM) and mGlu₃ ($K_i = 4.46$ nM), and it has been demonstrated to behave as a competitive antagonist. No significant activity at other mGlu receptors or a series of other receptors and transporters, has been detected. Furthermore, compound 26 exhibited dose-dependent oral absorption (plasma C_{max}: 214 $\pm$ 56.7, 932 $\pm$ 235 and 2960 $\pm$ 1150 ng/ml for 3 mg/kg, 10 mg/kg and 30 mg/kg, p.o., respectively) and even a modest brain penetration (brain C_{max}: 13.2 ng/ml for 10 mg/kg, p.o., 6 h). Very importantly, compound 26 (at 0.3–3 mg/kg, i.p.) demonstrated a dose-dependent antidepressant-like effect in the rat forced swimming test and in the mouse tail suspension test, whereas it had no apparent effect in the rat social interaction or in the rat elevated plusmaze models [16,17].

Metabotropic glutamate receptors: potential therapeutic applications of recently disclosed new chemical entities

Figure 7. mGlu_{2/3} antagonists.

Hoffmann-La Roche claimed new dihydrobenzo[b][1,4]diazepin-2-one derivatives (27, Figure 7) as metabotropic glutamate receptor-2 antagonists for the treatment of acute and/or chronic neurological disorders [127]. The compounds were tested *in vitro* for their antagonistic activity at mGlu₂. The K_i values for 29 compounds ranged 3 – 125 nM. They also disclosed alternatively substituted dihydrobenzo[b][1,4]diazepin-2-one derivatives (WO02083665; 28) for the treatment of acute and/or chronic neurological disorders [128]. The K_i values for 24 compounds ranged 0.9 – 91 nM. Finally, as a further exploration around the same dihydrobenzodiazepin-2-one scaffold, they also claimed further derivatives (WO03066623; 29) for the treatment or prevention of acute and/or chronic neurological disorders [129]. These compounds gave K_i values of ≤ 0.06 μ M for mGlu₂.

5.2 Agonists

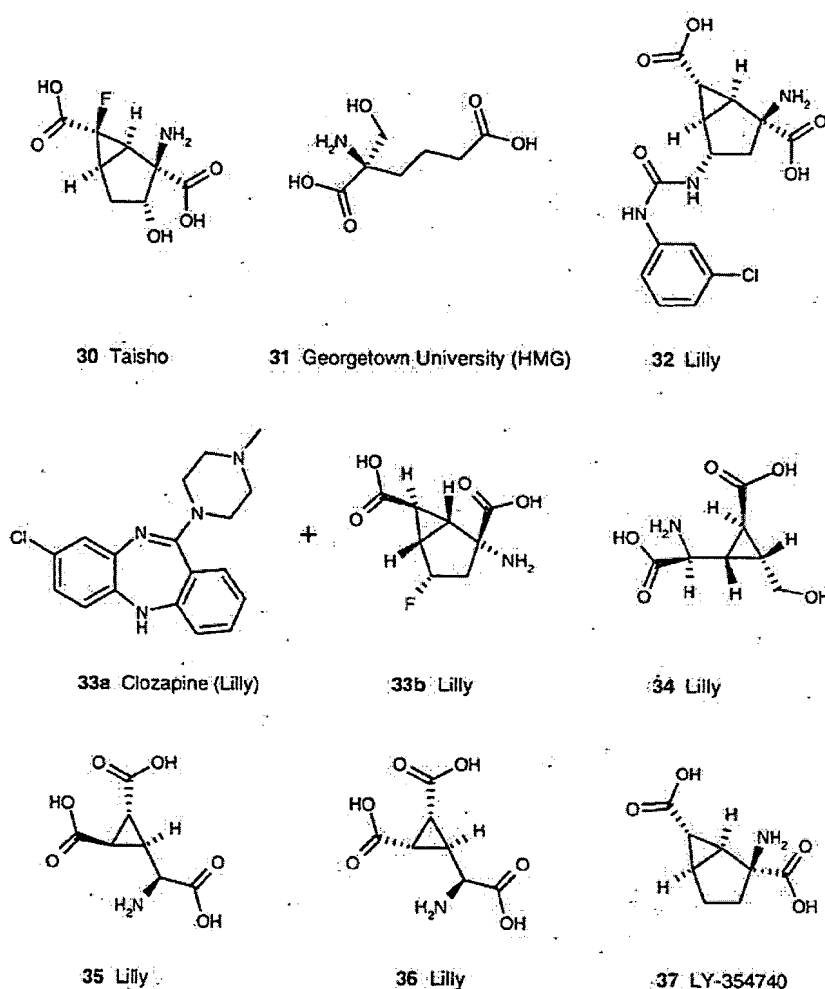
A great deal of work has been performed in the field of mGlu_{2/3} agonists, especially in the search for novel prodrugs which, in the past three years, have represented a fertile ground for the improvement of the pharmacokinetic profile of existing ligands.

As far as novel ligands are concerned, Taisho reported 2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (30, Figure 8) as an mGlu₂ agonist [130]. This compound showed an IC_{50} value of 476 nM.

Researchers from Georgetown University [131] published a 2-substituted L-glutamate analogue, namely (2S)-hydroxymethylglutamic acid (also known as HMG, 31, Figure 8). HMG is claimed to act as a relatively potent agonist of the Group II receptor mGlu₃ whilst also functioning as a weak antagonist at mGlu₂. Moreover, this compound has little or no activity on the Group I or Group III mGlu receptors. No specific data are reported.

Lilly disclosed novel 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives (32) [132]. These compounds are derivatives of the well-established bicyclo[3.1.0]hexane-2,6-dicarboxylic acid series (see [134]). The most active compound had K_i values of 511.5 and 9.54 nM at mGlu₂ and mGlu₃ receptors, respectively, and behaved as an agonist in a functional assay, with EC_{50} values of 60.68 and 18.15 nM at mGlu₂ and mGlu₃ receptors, respectively.

In another patent, Lilly disclosed a method for treating a psychiatric disorder using a combination of an atypical antipsychotic (clozapine) with an mGlu₂ and/or mGlu₃ receptor agonist as the second component (33a and b) [133]. The method is stated to have decreased drug-related side effects typically observed with such treatments, conferring an unexpected benefit for the patient whilst potentiating the efficacy of the atypical antipsychotic itself. The *in vivo* efficacy of the combination was assessed in an animal model of schizophrenia. The results showed that the combination produced a synergistic interaction, reducing PCP-induced

Figure 8. mGlu_{2/3} agonists.

ambulations to a level less than that of the atypical antipsychotic clozapine alone, at 10 mg/kg.

An important biological result was reported for (+)-(2*S*,1'*S*,2'*R*,3'*R*)-2-(2'-carboxy-3'-hydroxymethylcyclopropyl)glycine (34), a potent mGlu₂ and mGlu₃ agonist that proved to be orally active in both fear-potentiated startle (animal model for anxiety) and PCP-induced motor activation (animal model for psychosis) assays in rats [18].

In another report [19], the biological activities of both (2*S*,1'*S*,2'*S*,3'*R*)-2-(2'-carboxy-3'-methylcyclopropyl)glycine (35), a highly potent and selective agonist for Group II metabotropic glutamate receptors, and its epimer (at the C3' center), compound 36, have been investigated. In particular, compound 35 resulted in systemically four orders of magnitude more active in the fear-potentiated startle model of anxiety in rats, than the rigid constrained bicyclic system LY-354740 ((+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 37, Figure 8), which was the first known, highly-selective and

potent agonist for Group II metabotropic glutamate receptors [134]. This result suggests that a conformationally-constrained bicyclic system is not a requirement to achieve highly-selective and potent Group II mGlu agonists.

As previously stated, many efforts are being carried out in order to optimise the overall profile of mGlu_{2/3} agonists through an extensive exploration of prodrug compounds. Successful drug development requires not only a suitable pharmacological activity, but also efficient drug delivery to the target site. In particular, orally administered drugs must first cross the intestinal epithelial cells to get into the systemic circulation. LY-354740 (37), has a very low oral bioavailability (3 – 5%) in humans that is believed to arise from poor absorption through the gastrointestinal tract. A great deal of work has been carried out at Lilly with the aim of identifying specific prodrugs that deliver a sufficiently high plasma concentration of the parent compound, LY-354740.

Lilly has thus filed several patents in this field. They disclosed a novel alanyl amide derivative of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (38, Figure 9) for the treatment of neurological disorders or psychiatric disorders such as schizophrenia, depression, bipolar disorder and anxiety [135]. The compound is a prodrug of LY-354740 with improved oral efficacy. In binding experiments, LY-354740 binds with high affinity (K_i values ranging 80 – 125.6 nM) to human and rat metabotropic glutamate receptors, whereas the corresponding prodrug had no significant activity. In a rat fear potentiated startle model, compound 38 had an MED value of 0.01 mg/kg p.o. compared to 3 mg/kg p.o. for LY-354740, and the plasma exposure levels, following oral administration at the same dose, were ~ 15-fold higher in the prodrug-treated animals than in those receiving the parent LY-354740 alone.

Similarly, Lilly communicated different amide derivatives (39, Figure 9) as prodrugs of LY-354740 with improved oral potency [136]. At doses of 5 mg/kg p.o., the compounds achieved plasma levels ranging 2180 – 8812 ng/ml (8812 ng/ml for compound 39, sum of concentrations at 0.5 and 1 h) compared to a plasma level of 466 ng/ml following administration of the parent compound.

Other prodrugs [137] of LY-354740 (WO03006489; 40, Figure 9) for treating neurological and psychiatric disorders have been identified and again, the *in vivo* exposure of LY-354740 following oral administration of the prodrug compound was compared with that for parent compound LY-354740 alone. The compounds were administered in rats at a single dose of 5 mg/Kg p.o. The results showed that the plasma concentration of LY-354740 alone (466 ng/ml) was significantly lower than that measured following administration of the prodrug compound 40 (1248 ng/ml, concentrations at 0.5h and 1h).

Alternative prodrugs of LY-354740 [138] are exemplified by compound 41 (WO03045898). Rat plasma concentrations of the parent LY-354740 (as a sum of those at 0.5 h and 1h) following oral dosing of eleven prodrugs at 5 mg/kg, are reported and compared with the same value for LY-354740. In particular, compound 41 gave a value of 4786 ng/ml, again considerably higher than the 466 ng/ml obtained for the parent compound.

As a further example of an improved approach for maintaining LY-354740-like safety and efficacy with increased oral bioavailability, they also claimed derivatives such as compound 42 (WO03057661). In this case, the plasma concentration values (sum of concentrations at 0.5h and 1 h) ranged 1459 – 4945 [139]. In particular, the plasma concentration for compound 42 was 4887 ng/ml.

A novel synthetic excitatory amino acid prodrug (43; R = L-alanyl), has been claimed by Lilly for the treatment of neurological and psychiatric disorders [140].

Lastly, sulfonylbicyclo[3.1.0]hexane-4,6 dicarboxylic acid derivatives (44) have also been identified at Lilly as prodrugs of mGlu₂ receptor agonists [141]. The parent compound, (+)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic

acid was discovered some years ago as an active mGlu₂ agonist (US5688826 [142]). Compound 44 gave combined plasma concentrations for the parent drug of 225 ng/ml after administration at 10 mg/kg p.o., which were comparable to the plasma concentrations of the parent drug administered at the same dose.

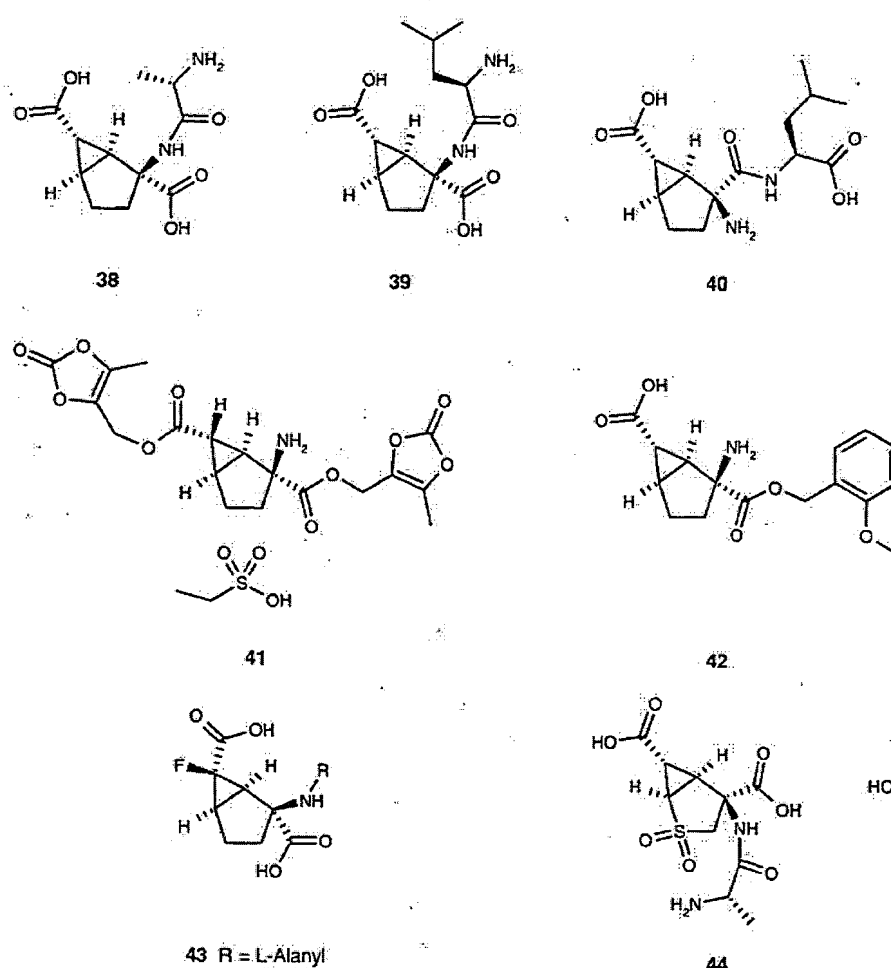
Recently, a number of interesting studies have been published in the primary literature to demonstrate the potential of mGlu_{2/3} agonists for the treatment of anxiety related disorders.

For example, it has been demonstrated that LY-354740 (37), exhibits anxiolytic-like properties in various rodent models [20]. *In vivo* microdialysis has been used to examine the effects of LY-354740 on extracellular monoamine levels in the medial prefrontal cortex (mPFC) of rats previously subjected to immobilisation stress, which significantly elevates extracellular levels of noradrenaline (NA) and dopamine (DA) in the mPFC. Systemic administration of LY-354740 (30 mg/kg, s.c.) significantly attenuated the immobilisation-induced increases in both NA and DA. This evidence suggests that LY-354740 may exert anti-stress effect by blocking stress-related increases in catecholamines in the mPFC via mGlu_{2/3} receptor activation.

In another report, the effect of LY-354740 in a pre- versus post-fear conditioning paradigm was investigated and compared with diazepam [21]. Diazepam (0.3, 0.6 and 1.0 mg/kg i.p.) attenuated both pre- and post-fear conditioning startle responses in a dose-related manner in rats, while LY-354740 (0.03, 0.3 and 3.0 mg/kg i.p.) did not disrupt pre-conditioning startle responses at doses that attenuated post-fear conditioning responses. The benzodiazepine antagonist, flumazenil, selectively reversed suppression of fear responses to diazepam (0.6 mg/kg i.p.) whilst not affecting fear suppression induced by LY-354740 (0.3 mg/kg ip). Furthermore, the mGlu_{2/3} receptor antagonist LY-341495 did not disrupt fear-enhanced startle per se, but completely reversed the postconditioning anxiolytic effects of LY-354740 in this model, and had no effect on fear suppression by diazepam. These results demonstrate that fear suppression by diazepam and LY-354740 involves different neuronal mechanisms. Interestingly, in contrast to disruption of fear conditioning as well as fear suppression by diazepam, LY-354740 had selective effects on fear expression, suggesting anxiolytic actions without the associated memory impairment.

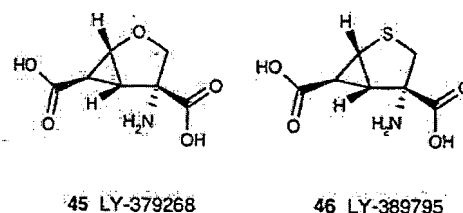
Another interesting feature of mGlu_{2/3} agonists is their ability to decrease the evoked release of glutamate at certain (fore-brain, limbic) glutamatergic synapses, indicating that the functional role of mGlu₂ and/or mGlu₃ receptors is to suppress glutamate excitations. This suggests a mechanism for dampening glutamate excitation under pathological states resulting from excessive glutamate release.

Based, in part, on the psychotomimetic actions of phencyclidine (PCP)-like drugs, excessive or pathologic glutamate release has been implicated in a number of clinical conditions, including psychosis. Thus, the pharmacology of multiple mGlu_{2/3} receptor agonists have

Figure 9. mGlu_{2/3} agonists: Lilly prodrugs.

been investigated in PCP treated rats [22]. Agonists for mGlu_{2/3} receptors, such as LY-354740, have been shown to block certain behavioural responses to PCP in rats. In addition, LY-354740 potently suppress glutamate release in rat prefrontal cortex and these actions are blocked by a selective mGlu_{2/3} antagonist. As glutamatergic dysfunction seems to be implicated in psychotic states, such as schizophrenia, clinical studies with mGlu_{2/3} agonists may be warranted to further explore the validity of the glutamatergic hypothesis of schizophrenia.

Another promising therapeutic area for Group II ligands is pain. Recently, the involvement of Group II metabotropic receptors in acute and persistent pain states was evaluated in several *in vivo* models with selective and potent Group II agonists. LY-354740, LY-379268 (45, Figure 10) and LY-389795 (46, Figure 10) attenuated late-phase paw-licking pain behavior in a dose-dependent manner in the formalin model of persistent pain [23]. The order of potency of the agonists was LY-389795 > LY-379268 > LY-354740. Also, in

Figure 10. mGlu_{2/3} agonists for pain.

the L5/L6 spinal nerve ligation model of neuropathic pain in rats, LY-379268 significantly reversed mechanical allodynia behavior in a dose-related manner.

5.3 mGlu₂ positive allosteric modulators

Very recently, Merck reported the discovery of positive allosteric potentiators for the mGlu₂ receptor in the primary literature [24], in addition to those previously disclosed by Lilly [25]. The

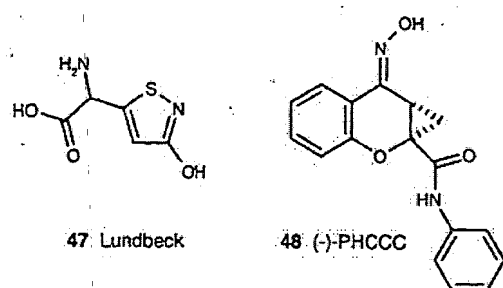


Figure 11. mGlu₄ ligands.

Merck compounds belong to the class of phenyl-tetrazolyl acetophenones and were shown to be active in two rodent models with potential relevance for schizophrenia: the inhibition of ketamine-induced noradrenaline release and ketamine-induced hyperactivity.

6. mGlu₄ ligands

Lundbeck disclosed new isothiazol-5-ylacetic acid derivatives (WO03070712; 47, Figure 11) for the treatment of numerous CNS diseases, pain and neurodegeneration resulting from stroke or brain injury [143]. Interestingly, the compounds are thioderivatives of the natural product ibotenic acid, which is found in the fly agaric mushroom, *Amanita muscaria*. Compound 47 showed agonist activity in the micromolar range at mGlu₄ receptors. No specific data were reported.

Also, in the field of mGlu₄, it is worth noting that recently, [26] two compounds, 2-methyl-6-(2-phenylethenyl)pyridine (SIB-1893; 14, Figure 5), a non-competitive antagonist of metabotropic glutamate receptor Type-5, and the well-known mGlu₃ antagonist MPEP (10, Figure 5), have been shown to act also as positive allosteric modulators for the hGlu₄ receptor.

As further evidence of the fact that Group III receptors can also be positively modulated is the finding that (-)-PHCCC ((-)-*N*-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide, 48) also acts as a positive allosteric modulator for mGlu₄ [27].

7. Expert opinion

The search for novel and selective mGlu receptor ligands continues to attract interest both in the industry and in the academia. Considerable efforts are currently being made towards the identification of ligands with more favourable drug-like properties; therefore endowed with an improved pharmacological and safety profile with respect to the first aminoacidic-like series identified more than a decade ago.

In addition, a quite different trend can be observed in these last few years. There is a strong move towards the identification of structures endowed with modulatory properties or able to interact with specific receptors through allosteric sites. Yet, in the mGlu_{2/3} field, the quest for specific agonists/modulators remains very active.

In the latest patents (and also in the primary literature) a number of novel chemical templates have been recently identified by both universities and pharmaceutical companies. The great majority of these new chemical entities can be considered as attractive leads for a chemical optimisation programme, particularly in the case of the receptors belonging to Groups I and II, which continue to represent the most productive fields of research. Many of these structures allowed further insight into the different therapeutic areas of interest (i.e., the vast majority of CNS diseases, which are often associated with a high unmet medical need) proving their pharmacological effect in different preclinical models or in culture tissue.

At the same time, although the search for novel and more diverse chemical entities remains an important task, scientists are also working on the optimisation of known series with the aim to further expand from the original amino acid structures or, in other cases when this is not feasible, to extensively investigate prodrug compounds, which should hopefully lead to molecules with better physicochemical and pharmacokinetic properties, thus improving bioavailability as well as the crucial capacity to cross the blood-brain barrier for CNS-related disorders.

Whereas reliable models for psychiatric diseases are still debatable, a number of preclinical models for other CNS illnesses have been developed. Many of the compounds described in the patents and in the primary literature reported here, clearly showed efficacy in the animal counterpart. Some of them might have the potential to further progress to human volunteer studies and definitively shed light on their potential value. Unfortunately, so far none of these molecules (and of the efforts associated with them) have been rewarded with the fundamental achievement of reaching the marketplace. Therefore, the potential innovative therapeutic applications already envisaged by the scientific community have not yet been confirmed.

Nonetheless, despite the fact that this promise has not yet been fulfilled, it is highly probable that, given the scenario described above, the active search for drug-like compounds, especially in the field of allosteric modulators, will continue to represent an intense and fruitful area of research for both academia and pharmaceutical companies in the upcoming years.

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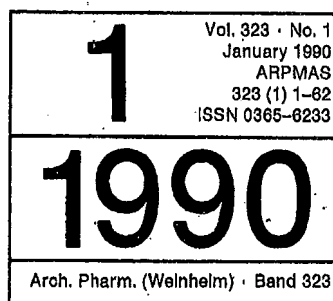
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2-Amino-2-oxazolines, III:

Synthesis, Structure, and Preliminary Pharmacological Evaluation of Cycloaddition Compounds with Unsaturated Carboxylic Esters

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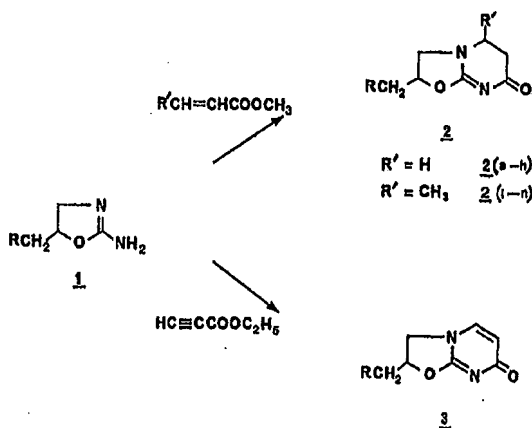
The reaction of 5-substituted 2-amino-2-oxazolines with unsaturated carboxylic esters yielded 2,3,5,6-tetrahydro- and 2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones. The structure of these compounds was established by IR- and NMR-spectra and by X-ray crystallography. They were tested for anti-arrhythmic and hypocholesterolemic activities.

2-Amino-2-oxazoline, 3. Mitt.: Synthese, Struktur und vorläufige pharmakologische Bewertung von Cycloadditionsverbindungen mit ungesättigten Estern

Aus 5-substituierten 2-Amino-2-oxazolinen entstehen mit ungesättigten Carbonsäureestern 2,3,5,6-Tetrahydro- und 2,3-Dihydro-7H-oxazolo[3,2-a]pyrimidin-7-one. Die Struktur dieser Verbindungen wurde durch IR- und NMR-Spektren sowie durch Röntgenstrukturanalyse geklärt. Die Substanzen wurden auf antiarrhythmische und lipidsenkende Wirkung geprüft.

2,3-dihydrooxazolo[3,2-a]pyrimidines are substantially useful as intermediates for the synthesis of pyrimidines derivatives¹. They were reported as cyclic derivatives of the pyrimidine bases and were related to the structure of potent carcinostatic cyclonucleosides^{2,3}.

In order to extend our research on 2-amino-2-oxazolines we synthesized derivatives of 2,3,5,6-tetrahydro- and 2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones corresponding to the general formulae 2 and 3 (Scheme 1), from the reaction of various 5-substituted 2-amino-2-oxazolines with unsaturated carboxylic esters. 2-Amino-2-oxazoline can react under this form or under its imino-2-oxazolidine tautomeric form⁴. In the first case we have shown that the endo nitrogen is more reactive than the exo one whereas in the second case the contrary occurs. Consequently two different series of cycloaddition compounds could a priori be expected. In our experimental conditions a single series of compounds was isolated and the structure was established by X-ray crystallography.



Scheme 1.

Synthesis

2-substituted-2,3,5,6-tetrahydro-7H-oxazolo[3,2-a]pyrimidin-7-ones 2

Various 2-amino-2-oxazolines 1 were prepared according to ^{5,6}. Treatment of 1 with a slight excess of methyl acrylate or methyl crotonate in boiling dry toluene gave compounds 2 in good yields (Scheme 1). As early noticed^{7,8} the two nitrogen atoms of 2-amino-2-oxazolines are potent nucleophilic centers. The cycloaddition of unsaturated esters might occur on these centers leading to both pyrimidin-7-one and/or 5-one^{9,10}. In our case the reaction led to a single derivative. Structure 2j was established by X-ray crystallography.

The spectral data of 2,3,5,6-tetrahydro-7H-[3,2-a] pyrimidin-7-ones 2 are reported in Table 1. The IR spectra of 2 in the solid state show CO and CN absorptions at 1600 and 1670 cm⁻¹^{1,8}. In the ¹H-NMR spectra the protons at the C-2 and C-3 form an ABX system, the C-2 methine H is found at about 5 ppm. In compounds 2i-2n the methyl protons appear as a doublet near 1.3 ppm. The ¹³C-NMR spectra of 2b and 2j are identical except for the C-6 and 5-CH₃ atoms. The ¹³C-NMR spectrum of compound 2j showed the presence of two diastereoisomers. Two peaks appeared for C-2, C-5, CH₂ of the lateral chain and CH₃ (Δδ=0.55 ppm). HPLC analysis on a C-18 reversed phase column (mobile phase methanol/phosphate buffer pH 6.6, 45/55) was performed with the compound 2j. Two peaks appeared at retention times 5.06 and 5.6 min with a ratio of about 1:1.

17

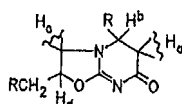


Table 1: Analytical and spectroscopic data of 2

Cpd.	R	R'	Formula Mol.W.	F(°C)*	H _a	H _b	H _c	H _d	Yield %
2a	CH ₃ O	H	C ₁₈ H ₁₂ N ₂ O ₃ 184	136 ^b	2.64 t, 2H	3.55 t, 2H	3.88-3.37 m, 2H	5.1-4.8 m, 1H	69
2b		H	C ₁₃ H ₁₄ N ₂ O ₃ 246	95 ^b	2.67 t, 2H	4-3.5 m, 4H		5.2-4.9 m, 1H	74
2c	(C ₂ H ₅) ₂ N	H	C ₁₁ H ₁₉ N ₃ O ₂ 225	111 ^a	2.70 t, 2H	4.1-3.4 m, 4H		5.2-4.8 m, 1H	63
2d		H	C ₁₂ H ₁₉ N ₃ O ₂ 237	147 ^a	*2.73 t, 2H	4-3.5 m, 4H		5.3-4.8 m, 1H	66
2e		H	C ₁₁ H ₁₇ N ₃ O ₃ 239	132 ^c	2.69 t, 2H	4.2-3.3 m, 4H		5.3-4.7 m, 1H	58
2f	C ₆ H ₅ CH ₂ NCH ₃	H	C ₁₅ H ₁₉ N ₃ O ₂ 273	123 ^a	2.66 t, 2H	3.8-3.3 m, 4H		5.1-4.7 m, 1H	52
2g		H	C ₁₇ H ₂₂ N ₄ O ₂ 314	163 ^b		4.1-2.4 m, 6H		5.3-4.7 m, 1H	61
2h	CH ₃ -N	H	C ₁₂ H ₂₀ N ₄ O ₂ 252	124 ^b	2.9-2.4 m	4.1-3.3 m, 4H		5.3-4.7 m, 1H	53
2i	CH ₃ O	CH ₃	C ₁₉ H ₁₄ N ₂ O ₃ 198	Oil	3.1-2.1 m, 2H	4.2-3.2 m, 3H		5.2-4.6 m, 1H	39
2j		CH ₃	C ₁₄ H ₁₆ N ₂ O ₃ 260	150 ^a	2.9-2.2 m, 2H	4.3-3.6 m, 3H		5.6-5.2 m, 1H	76
2k	(C ₂ H ₅) ₂ N	CH ₃	C ₁₂ H ₂₁ N ₃ O ₂ 239	107 ^a	3-2.3 m, 2H	4.2-3.2 m, 3H		5.2-4.6 m, 1H	62
2l		CH ₃	C ₁₃ H ₂₁ N ₃ O ₂ 251	134 ^a	3-2.2 m, 2H	4.2-3.2 m, 3H		5.2-4.6 m, 1H	71
2m		CH ₃	C ₁₂ H ₁₉ N ₃ O ₃ 253	120 ^c	** 2.9-1.9 m, 2H	4.2-3.1 m, 3H		5.3-4.7 m, 1H	65
2n	C ₆ H ₅ CH ₂ NCH ₃	CH ₃	C ₁₆ H ₂₁ N ₃ O ₂ 287	108 ^a	3-2.3 m, 2H	4.1-3.5 m, 3H		5.4-4.9 m, 1H	56

* Recryst. Solvent: a: CCl₄ - b: CHCl₃/CCl₄ - c: Toluene - d: J between 7 and 8 Hz

** DMSO [D₆]

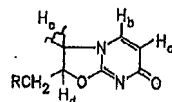


Table 2: Analytical and spectroscopic data of 3

Cpd.	R	Formula Mol.W.	F(°C)*	H _a	H _b	H _c	H _d	Yield %
3a	Cl	C ₇ H ₇ ClN ₂ O ₂ 186.5	189 ^a	5.8** d, 1H	7.7 d, 1H	5.6-5.1 1H	4.6-3.9	76
3b	CH ₃ O	C ₈ H ₁₀ N ₂ O ₃ 182	124 ^b	6.05 d, 1H	7.35 d, 1H	5.2-4.9 1H	4.6-3.95 2H	59
3c	(CH ₃) ₃ C-O	C ₁₁ H ₁₆ N ₂ O ₃ 224	173 ^b	6 d, 1H	7.4 d, 1H	5.3-4.9 1H	4.6-4.1 2H	51
3d		C ₁₃ H ₁₂ N ₂ O ₃ 244	174 ^a	**5.8 d, 1H	7.8 d, 1H	5.7-5.1 1H	4.7-3.9	70
3e	(C ₂ H ₅) ₂ N	C ₁₁ H ₁₇ N ₃ O ₂ 223	190 ^c	5.9 d, 1H	7.5 d, 1H	5.3-4.8 1H	4.6-3.9 2H	63
3f		C ₁₂ H ₁₇ N ₃ O ₂ 235	177 ^c	6 d, 1H	7.4 d, 1H	5.4-4.8 1H	4.7-3.9 2H	67
3g		C ₁₇ H ₂₀ N ₄ O ₂ 312	175 ^c	6 d, 1H	7.3 d, 1H	5.30-4.9 1H	4.6-3.95 2H	58

* Recryst. Solvent: a: EtOH - b: CCl₂CHCl - c: Toluene - d: In all cases H_a and H_b appear as doublets with J_{ortho} = 8 Hz - e: H_c and H_d always appear as unresolved multiplets

** DMSO [D₆]

2-substituted-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones 3

The reaction of heterocyclic nitrogen compounds carrying an α -amino group with acetylene carboxylates has been widely investigated. According to the heterocyclic nucleus it can generate both the isomeric pyrimidin-7-ones or 5-ones¹⁰⁻¹⁴. The treatment of various 5-substituted 2-amino-2-oxazolines with ethyl propiolate in boiling ethanol gave the corresponding 2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones 3.

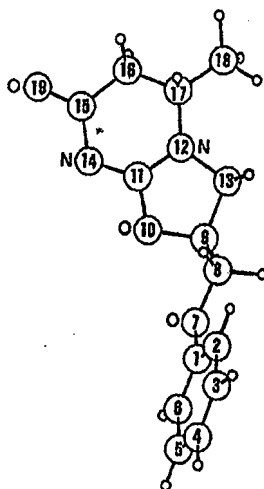
The structure of 3c was identified by spectral data (Table 2). As already noticed^{12,15} the IR-spectra of pyrimidin-7-ones and 5-ones are quite different. The amide bond of 7-ones appears below 1650 cm^{-1} while the same absorption for 5-ones is above 1680 cm^{-1} . The $^1\text{H-NMR}$ spectra of 3c display two multiplets for the C-2 and C-3 protons at 5.3-4.9 and 4.6-4.1 ppm (ABX system). All components 3 show the olefinic C-5 and C-6 protons at 7.4 and 6 ppm. These data are similar to the findings of Inaki for cyclic compounds of uracil and thymine¹³ and to those of Kinoshita for thiazolo[3,2-a]pyrimidin-7-ones¹⁴. The $^{13}\text{C-NMR}$ spectra of 3a can be used for the establishment of the proposed structure. The most deshielded signal (171.3 ppm) is assigned to C-7 and is consistent with a pyrimidin-7-one structure. In the thiazolo[3,2-a]pyrimidin-5-ones the C=O-carbon is found at 161 ppm¹⁶. Similar values are reported for some tautomeric pyrimidines: 169.8 ppm for 1-methyl-4-oxo- and 161.4 ppm for 3-methyl-4-oxo-pyrimidines¹⁷.

X-Ray Crystallography

Crystal data are presented in Table 3. The cell-dimensions and orientation matrix were calculated by least-squares method from the angular values of 25 reflections collected with an Enraf-Nonius CAD-4 diffractometer. The intensities were collected with ω / θ scan mode and graphite monochromated $\text{CuK}\alpha$ radiation ($\lambda = 1.54178\text{ \AA}$). No appreciable drop in intensity of two standard reflections checked every 90 min was noticed. The data were corrected for Lorentz- and polarization effects but not for absorption.

The structure was solved by direct methods using the MULTAN 80 Program System and the statistically weighted tangent formula¹⁸. All remaining calculations based on the programs CRISTA, CRISAF, CRISEC, and UTIL from the Laboratory of Crystallography (Univ. of Bordeaux I, Talence) were carried out on a Mini 6-92 CII-Honeywell-Bull computer. Block-diagonal matrix least-squares refinements were performed for a scale factor, and positional, and anisotropic thermal parameters of the non-hydrogen atoms. The hydrogen atoms, located from difference Fourier maps, were included in the calculations and refined with isotropic thermal parameters. The function minimized was $\sum w ||F_o| - |F_c||^2$ where $w = 1$ if $|F_o| < P$, $P = [F_o^2(\text{max})/10]^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$. The scattering factors for non-hydrogen atoms were those proposed by Cromer and Waber¹⁹ and those for H atoms were from Stewart, Davidson, and Simpson²⁰.

The fractional atomic coordinates and Beq values of non-hydrogen atoms are presented in Table 4. Bond lengths and angles are presented in Tables 5 and 6. The conformation is shown in Fig. 1*.



Projection of the molecule showing the numbering scheme

Examination of the bond lengths and angles (Tables 5 and 6) shows a delocalization of the π electrons around C(11). The shortening of the C(11)-N(14) bond ($1.299(7)\text{ \AA}$) vs C(11)-N(12) ($1.311(7)\text{ \AA}$) would indicate that the double bond is better localized between the former. However the bond angles around N(12) would indicate that the hybridization state is close to sp^2 . The observed bond lengths are comparable to those found in opened related imino-2-oxazolidines⁴. The oxazoline ring is almost flat with C(9) and C(13) slightly below the plane defined by O(10), C(11), N(12) and N(14) ($-0.029(6)$ and $-0.015(6)\text{ \AA}$, respectively). The dihydropyrimidine ring is twisted with C(15), C(16) and C(17) at $0.076(6)$, $0.145(9)$ and $-0.116(9)\text{ \AA}$ from the same plane.

The conformation of the chain is extended as indicated by the torsion angles C(6)-C(1)-O(7)-C(8) = $-176(1)^\circ$, C(1)-O(7)-C(8)-C(9) = -174° and O(7)-C(8)-C(9)-C(13) = -178° .

Pharmacology

All new compounds were screened for anti-arrhythmic and hypocholesterolemic activities.

Anti-arrhythmic activity

Only compounds 2c and 3c show slight activity in this test. The percentages of mice which did not display cardiac arrhythmia 30 min after administration of the test compounds were 33% for 2c (60 mg/kg i.p.) and 66% - 33% for 3c (100, 50 mg/kg i.p.). In the same conditions the ED 100 for quinidine was found at 100 mg/kg.

Hypocholesterolemic activity

Reductions in serum cholesterol and heparin precipitating betalipoproteins concentrations were observed for some

* Weitere Einzelheiten zur Kristallstrukturuntersuchung können beim Fachinformationszentrum Energie, Physik, Mathematik D-7514 Eggenstein - Leopoldshafen 2, unter Angabe der Hinterlegungsnummer..., des Autors und des Zeitschriftenzitantes angefordert werden.

Tab. 3: Crystal Data

Molecular formula	C ₁₄ H ₁₆ N ₂ O ₃
Molecular weight	260.3
Symmetry	Monoclinic
Space group; Z	P2 ₁ /a; 4
Unit-cell parameters	a = 12.698(1) Å b = 9.428(1) c = 12.113(1) β = 111.83(1)°
Volume (Å ³)	1335.3(1)
Number of reflections used for the determination of unit-cell parameters; 2θ range (deg)	25; 14-32
Density (calcd)	1.295
Number of measured reflections	2378
Number of observed reflections	1082
I ≥ 3σ(I)	
Number of refined parameters	235
2θ range scanned (deg)	1-130
μ(CuKα) (cm ⁻¹)	7.7
Crystal dimensions (mm)	0.67 x 0.30 x 0.10
Solvent of recrystallization	Ethanol
Final R	0.062

Table 4: Atomic coordinates (x 104) and equivalent isotropic temperature factors

$$B_{eq} = \frac{4}{3} \sum_i \sum_j h_{ij}^2 a_i^2 a_j^2$$

	x	y	z	Beq(Å ²)
O(1)	2193(6)	3805(8)	4787(6)	6.1(3)
O(2)	2812(5)	3059(8)	4088(5)	6.0(3)
O(3)	1858(6)	2367(8)	3068(6)	7.2(3)
O(4)	690(7)	2468(10)	2815(8)	9.4(5)
O(5)	287(6)	3225(12)	3538(7)	10.1(6)
O(6)	1052(6)	3884(11)	4543(6)	9.2(4)
O(7)	2869(3)	4525(6)	5907(4)	7.2(2)
O(8)	4073(5)	4571(7)	6088(5)	5.6(3)
O(9)	4580(5)	5267(7)	7285(5)	5.5(3)
O(10)	4408(3)	4322(5)	6155(3)	5.9(2)
C(11)	5424(5)	3867(6)	8980(5)	4.7(2)
N(12)	6263(4)	4881(6)	8769(4)	5.2(2)
O(13)	5873(5)	5484(7)	7707(6)	5.7(3)
N(14)	5442(4)	3110(6)	9827(4)	5.7(2)
O(15)	6498(6)	2858(7)	10880(6)	6.0(3)
O(16)	7504(6)	3542(11)	10547(7)	10.8(6)
O(17)	7418(6)	4242(12)	9477(7)	10.8(6)
O(18)	8308(7)	4788(14)	9190(8)	11.7(6)
O(19)	6622(4)	2110(6)	11515(4)	6.6(3)

2,3,5,6-tetrahydro- and 2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones. For 2g with a dose level of 400 and 200 mg

Table 5: Bond lengths (Å)

O(1)-O(2)	1.368(8)	O(10)-O(11)	1.337(6)
O(1)-O(6)	1.367(9)	O(11)-N(12)	1.311(7)
O(1)-O(7)	1.389(7)	O(11)-N(14)	1.289(7)
O(2)-O(3)	1.393(9)	N(12)-O(13)	1.456(7)
O(3)-O(4)	1.390(10)	N(12)-O(17)	1.423(9)
O(4)-O(5)	1.387(11)	N(14)-O(15)	1.359(7)
O(5)-O(6)	1.387(11)	O(15)-O(16)	1.473(10)
O(7)-O(8)	1.426(7)	O(16)-O(19)	1.214(7)
O(8)-O(9)	1.503(8)	O(16)-O(17)	1.422(11)
O(9)-O(10)	1.468(6)	O(17)-O(18)	1.398(12)
O(9)-O(13)	1.526(8)		

p.o. the reductions in these two tests were 20% - 24% and 11% - 13% respectively. For bezafibrate the results were 33% - 38% at the dose level 200 mg p.o.. The activity of 2g was not accompanied by a significant decrease in the HPL/cholesterol ratio. Following a dose of 100 mg/kg, no estrogenic activity was noted in conjunction with this hypocholesterolemic effect.

Conclusion

The pharmacological screening showed only little activity for these series of 2-substituted-2,3,5,6-tetrahydro- and 2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones. In particular the activity on the CNS which characterizes related opened series⁶ (one molecule in clinical trials) disappeared. As we have shown non-substituted nitrogen atoms are certainly involved in the antidepressant activity, binding to the corresponding receptor. In the present case the loss of activity could be attributed to the enclosing of the two nitrogen atoms in the pyrimidine ring. The oxazolo[3,2-a]pyrimidin-7-ones being structurally close to some potent carcinostatic cyclonucleosides will be tested for such activity.

Experimental Part

Chemistry

Satisfactory elemental analysis with deviations of ± 0.4% of the calculated values were obtained for all new compounds. - Uncorrected melting points: KOFLER hot-stage. - IR-spectra: Acoulab, Beckman KBr discs. - ¹H- and ¹³C-NMR spectra: Bruker WH 90 and Bruker WP 60, tetramethylsilane as int. standard. - Purity of synthesized compounds was checked by thin-layer chromatography, Kieselgel 60 F 254 (Merck). - HPLC analysis: Waters μBondapak C18 column (30 cm x 3.9 mm i.d. 10μ particle size), Waters chromatograph equipped with a LC Spectrophotometer.

General procedure for the synthesis of 2-substituted-2,3,5,6-tetrahydro-7H-oxazolo[3,2-a]pyrimidin-7-ones

30 mmol of 1 and 40 mmol of methyl acrylate or methyl crotonate were refluxed in 50 ml of dry toluene for 3 h. The mixture was concentrated under reduced pressure and the residue crystallized after trituration with ether. The solid was recrystallized from appropriate solvent. The NMR spectrometric data for 2b and 2j which are representative of the title compounds are listed below.

2-Phenoxymethyl-2,3,5,6-tetrahydro-7H-oxazolo[3,2-a]pyrimidin-7-one (2b)

¹H-NMR (90 MHz, CDCl₃): δ (ppm) = 2.67 (2H, C-6); 4-3.5 (m, 4H, C-5 and C-3); 4.2 (2H, OCH₂); 5.2-4.9 (m, 1H, C-2); 7.4-6.7 (m, 5H, phenyl). - ¹³C-NMR (DMSO D₆): δ ppm = CO 178; C=N 167.5; phenyl

Table 6: Bond angles (°)

C(2)-C(1)-C(8)	121.2(6)	O(10)-C(11)-N(14)	117.9(6)
C(2)-C(1)-O(7)	124.3(6)	N(12)-C(11)-N(14)	130.5(6)
C(8)-C(1)-O(7)	114.6(5)	C(11)-N(12)-C(13)	113.2(4)
C(1)-C(2)-C(3)	119.7(5)	C(11)-N(12)-C(17)	120.1(6)
C(2)-C(3)-C(4)	118.9(8)	C(13)-N(12)-C(17)	126.5(6)
C(3)-C(4)-C(6)	120.6(7)	C(9)-C(13)-N(12)	101.2(4)
C(4)-C(5)-C(8)	119.8(7)	C(11)-N(14)-O(15)	114.8(6)
C(1)-C(8)-C(5)	120.0(7)	N(14)-C(15)-C(16)	119.6(6)
C(1)-O(7)-C(8)	118.1(4)	N(14)-C(15)-O(19)	121.0(6)
O(7)-C(8)-C(5)	105.9(4)	C(16)-O(15)-O(19)	119.4(6)
C(8)-C(9)-C(10)	108.2(4)	C(16)-C(18)-C(17)	120.7(7)
C(8)-C(9)-C(13)	113.2(4)	N(12)-C(17)-C(18)	111.6(6)
C(10)-C(9)-C(13)	105.0(4)	N(12)-C(17)-C(18)	120.3(7)
C(9)-C(10)-C(11)	109.1(4)	C(16)-C(17)-C(18)	127.2(8)
O(10)-C(11)-N(12)	111.5(4)		

158, 129.7, 121.3, 114.7; C-2 76.4; OCH₂ 67.8; C-3 48.4; C-5 40.2; C-6 29.4.

2-Phenoxymethyl-5-methyl-2,3,5,6-tetrahydro-7H-oxazolo[3,2-a]pyrimidin-7-one (2j)

¹H-NMR (90 MHz, DMSO D₆): δ (ppm) = 1.4 (3H, CH₃); 2.9-2.2 (m, 2H, C-6); 4.3-3.6 (m, 3H, C-5 and C-3); 4.5 (m, 2H, OCH₂); 5.6-5.2 (m, 1H, C-2); 7.7-7 (m, 5H, phenyl). ¹³C-NMR (DMSO D₆): δ (ppm) = CO 177.9; C=N 167.1; phenyl 158.2, 129.7, 121.3, 114.7; C-2 76; OCH₂ 67.8; C-5 47; C-3 45.9; C-6 37.5; CH₃ 18.

General procedure for the synthesis of 2-substituted-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones

10 mmol of 1 and 10 mmol of ethyl propiolate were refluxed in 80 ml of ethanol for 6 h. The mixture was concentrated under reduced pressure and the residue crystallized after trituration with ether. The final solids were recrystallized from appropriate solvents. The NMR spectrometric data for 3a, representative of the title compounds, are listed below.

2-Chloromethyl-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-one (3a)

¹H-NMR (90 MHz, DMSO D₆): δ (ppm) = 4.6-3.9 (m, 4H, C-3 and CH₂Cl); 5.6-5.1 (m, 1H, C-2); 5.8 (1H, C-6); 7.7 (1H, C-5). ¹³C-NMR (DMSO D₆): δ (ppm) = CO 171.3; C=N 160.3; C-5 138.3; C-6 107.9; C-2 77.3; CH₂Cl 48.6; C-3 45.5.

Pharmacology

Anti-arrhythmic activity

Male Swiss mice were intraperitoneally dosed with the test compounds. Thirty min later they were submitted to deep chloroform anaesthesia which prolongs the refractory period and depresses the myocardial excitability. A compound is assessed as anti-arrhythmic if more than 66% of mice by group do not display cardiac arrhythmia and heart rate above 200 beats/min (BKG). Test compounds were prepared as aqueous solutions. Small amounts of DMSO were used to increase the solubility. At the concentration employed, DMSO did not produce any arrhythmic or anti-arrhythmic effect.

Hypocholesterolemic activity

Male Swiss mice, made hypercholesterolemic by being fed a high cholesterol-cholic acid diet for seven days, were dosed on the sixth and seventh

days p.o. (one half the total recorded dose was given on day 6 followed by the other half on day 7). After fasting overnight the reduction in serum cholesterol concentration was determined. The reduction of the serum heparin precipitating lipoprotein concentrations (corresponding to LDL and VLDL fractions) was assessed in the same hypercholesterolemic mice.

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An easy Route to 2-Substituted-2,3-dihydro-
5(7)*H*-oxazolo[3,2-*a*]pyrimidin-5-ones and 7-ones
Starting from the Corresponding 2-Amino-2-oxazolines

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The isomeric 2-substituted-7(5)-methyl-2,3-dihydro-5(7)*H*-oxazolo[3,2-*a*]pyrimidin-5-ones **3a-b** and 7-ones **2a-b,7a** were synthesized by cyclocondensation from the 5-substituted-2-amino-2-oxazolines **1a-b** with biselectrophiles. In boiling ethanol, the reaction of **1a-b** with acetylenic esters led to a mixture of **2a-b,7a** with a small amount of (*E*)-2-*N*-(2-ethoxycarbonyl-ethylen)-5-substituted-2-imino-oxazolines **5a-b**. The ring annulation between **1a-b** and diketens gave the 2-substituted-7-hydroxy-7-methyl-2,3,6,7-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrimidin-5-ones **4a-b** which can be easily dehydrated to provide the 2-substituted-7-methyl-2,3-dihydro-5*H*-oxazolo[3,2-*a*]pyrimidin-5-ones **3a-b**.

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Interest in the synthesis of nucleoside analogues stems from their antiviral and antitumoral activities [1-4]. Much effort has been devoted to simplify the structures leading to the synthesis of various acyclonucleosides. New pyrimidinones have been defined as synthons to produce new classes of acynucleosides by reaction with the appropriate nucleophiles [5-7]. We have recently developed the preparation of related bicyclopymidinones based on the reactivity of the amidine moiety of 2-amino-2-oxazolines [8-9].

In this work we report the one-step ring-annulation of 5-[(2-methylphenoxy)methyl]- **1a** and 5-[(1-phenyl-4-piperazinyl)methyl]-2-amino-2-oxazoline **1b** with

potent biselectrophiles, acetylenic esters or diketene, leading to the isomeric 2-substituted-5-methyl-2,3-dihydro-7(5)*H*-oxazolo[3,2-*a*]pyrimidin-7-ones **2a-b,7a** and 5-ones **3a-b**. The raw materials **1a-b** were prepared according to the method previously described by the authors [10-11].

In refluxing ethanol, the condensation of **1a-b** with ethyl 2-butyrate afforded the corresponding 2-substituted-5-methyl-2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidin-7-ones **2a-b** in 48% and 57% yield respectively, and to the (*E*)-2-*N*-(1-methyl-2-ethoxycarbonyl-ethylen)-5-substituted-2-imino-oxazolines **5a-b** in lower yields (10-11%). The corresponding pyrimidin-5-ones **3a-b** were easily obtained

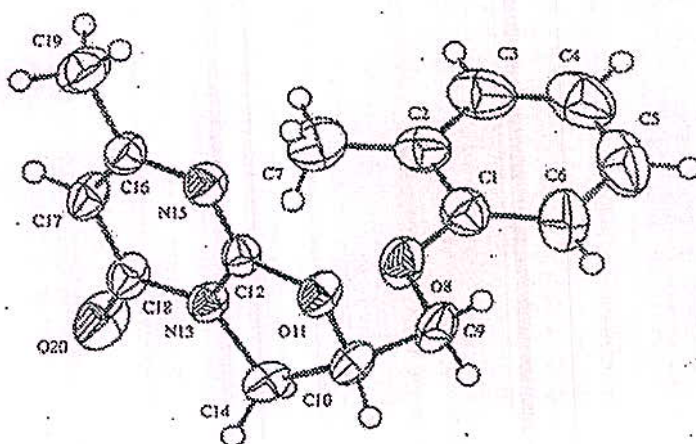


Figure 1. Side view of the crystal structure of **3a** with our numbering scheme. displacement ellipsoids are drawn at the 30% probability level.

Scheme 1

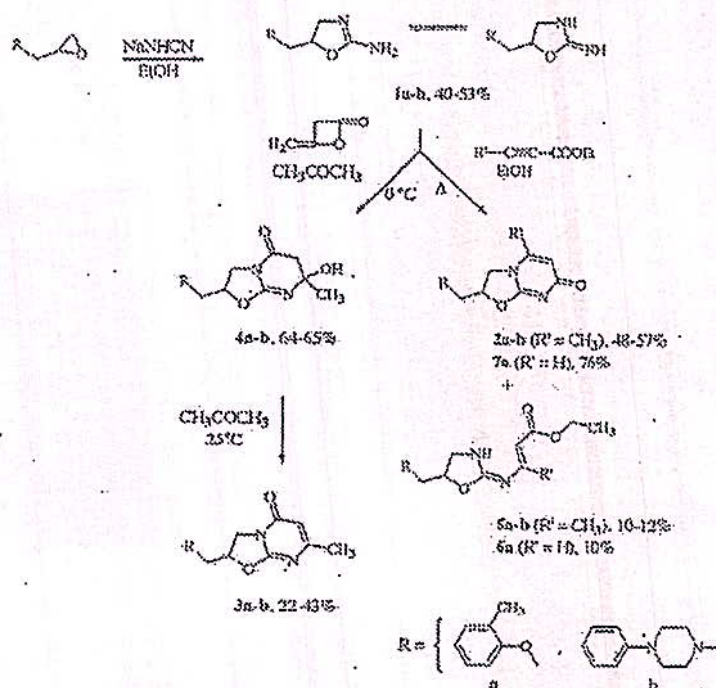


Table 1

Crystal Data and Structure Refinement for Compound 3a

Formula	C ₁₅ H ₁₆ N ₂ O ₃
Molecular weight	272.30
Crystal size (mm)	0.40 × 0.15 × 0.10
Lattice	monoclinic
Sp. Gr.	P2 ₁ /c
a (Å)	12.817(2)
b (Å)	14.5120(10)
c (Å)	7.487(2)
β (°)	99.86(2)
D (mg/m ³)	1.318
F(000)	576
Z	4
Temperature	296(2) K
μ (mm ⁻¹)	0.763
h, k, l	0 15, 0 17, -8 +8
h (Å)	1.54178
No. of reflections	2330
No. of observed reflections	2330
Volume (Å ³)	1372.0(4)
No. of variables	182
R (F)	0.0457
Rw (F)	0.1329

by reaction of 1a-b with diketene via the intermediates 2-substituted-7-hydroxy-7-methyl-2,3,6,7-tetrahydro-5H-oxazolo[3,2-a]pyrimidin-5-ones 4a-b. By performing the reaction at 0 °C in acetone, we succeeded in isolating these unstable cyclic hemiaminals 4a-b, which result from a concerted addition [12-13].

Structural elucidation of 2a-b was achieved by ¹H and ¹³C nmr on the basis of previous results for the 2-aryl-2,3-dihydrooxazole[3,2-a]pyrimidin-7-one series published by Agami *et al.* [5-7]. The ¹H nmr spectrum of 2a showed, at 5.75 ppm, the characteristic singlet for the proton at position 6, whereas it was found at 5.89 ppm for 3a. In the ¹³C nmr spectrum, the signals at 107.0 ppm (C-6), 160.8 ppm (C-N) and 172.5 ppm (C=O) confirmed the structure of 2a. Different values of the C=O were also noticed in the ¹³C nmr spectra of both compounds 2a and 3a, at 172.5 ppm for the first one and at 166.1 ppm for the second one.

Some differences were observed in the ¹H nmr spectra of the two regioisomers 2b and 3b, i.e., the H-6 signal was observed at 5.72 ppm for 2b and at 5.64 ppm for 3b. The pyrimidin-5-one structure of 3a has been confirmed by

Table 2
Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic
Displacement Parameters ($\text{\AA}^2 \times 10^3$) for Compound 3a

atom	x	y	z	U(eq)
C(1)	4767(2)	1253(1)	10503(3)	50(1)
C(2)	4777(2)	1092(2)	12267(3)	55(1)
C(3)	5872(2)	1109(2)	12596(4)	73(1)
C(4)	6448(2)	1263(2)	11226(5)	79(1)
C(5)	5938(2)	1449(2)	9519(5)	80(1)
C(6)	4829(2)	1444(2)	9134(4)	70(1)
C(7)	4140(2)	924(2)	13749(3)	81(1)
O(8)	3179(1)	1214(1)	10281(2)	57(1)
C(9)	2572(2)	1360(2)	8539(2)	51(1)
C(10)	1444(2)	1156(1)	8695(2)	43(1)
O(11)	1331(1)	158(1)	8899(2)	43(1)
C(12)	1310(1)	-24(1)	10657(2)	33(1)
N(13)	1181(1)	756(1)	11565(2)	35(1)
C(14)	1093(2)	1561(2)	10380(2)	41(1)
N(15)	1383(1)	-848(1)	11284(2)	40(1)
C(16)	1336(1)	-901(1)	13121(2)	40(1)
C(17)	1222(2)	-157(1)	14154(2)	45(1)
C(18)	1131(2)	752(1)	13413(2)	43(1)
C(19)	1432(2)	-1833(2)	13885(3)	68(1)
O(20)	1014(2)	1481(1)	14186(2)	66(1)

Table 3
Bond lengths ($\text{\AA}$) and Angles ($^\circ$) for Compound 3a

C(1)-C(6)	1.379(3)	C(10)-C(14)	1.378(3)
C(1)-O(8)	1.378(2)	O(11)-C(12)	1.347(2)
C(1)-C(2)	1.394(3)	C(12)-N(13)	1.383(2)
C(2)-C(3)	1.383(3)	C(12)-N(15)	1.345(2)
C(2)-C(7)	1.505(4)	N(13)-C(18)	1.396(2)
C(3)-C(4)	1.383(4)	N(13)-C(14)	1.460(2)
C(4)-C(5)	1.366(4)	N(15)-C(16)	1.389(2)
C(5)-C(6)	1.391(4)	C(16)-C(17)	1.352(3)
O(8)-C(9)	1.415(2)	C(16)-C(19)	1.492(3)
O(9)-C(10)	1.499(3)	C(17)-C(18)	1.428(3)
C(10)-O(11)	1.467(2)	C(18)-C(20)	1.226(2)
C(6)-C(1)-O(8)	124.4(2)	N(13)-C(12)-N(15)	127.4(2)
C(6)-C(1)-C(2)	121.4(2)	N(15)-C(12)-O(11)	121.8(2)
O(8)-C(1)-C(2)	114.2(2)	N(13)-C(12)-O(11)	110.79(14)
C(1)-C(2)-C(3)	117.7(3)	C(12)-N(13)-C(18)	121.9(2)
C(1)-C(2)-C(7)	120.1(2)	C(12)-N(13)-C(14)	111.67(14)
C(3)-C(2)-C(7)	122.1(2)	C(18)-N(13)-C(14)	126.43(14)
C(4)-C(3)-C(2)	121.6(3)	N(13)-C(14)-C(10)	101.03(14)
C(4)-C(3)-C(7)	119.5(2)	C(12)-N(15)-C(16)	113.72(14)
C(4)-C(3)-C(7)	120.7(3)	C(17)-C(16)-N(15)	123.3(2)
C(1)-C(6)-C(5)	119.1(3)	C(17)-C(16)-C(19)	122.1(2)
C(1)-O(8)-C(9)	119.4(2)	N(15)-C(16)-C(19)	114.6(2)
O(8)-C(9)-C(10)	106.5(2)	C(16)-C(17)-C(18)	121.8(2)
O(11)-C(10)-C(9)	108.5(3)	O(20)-C(18)-N(13)	119.6(2)
O(11)-C(10)-C(14)	104.20(14)	O(20)-C(18)-C(17)	128.4(2)
C(9)-C(10)-C(14)	114.4(2)	N(13)-C(18)-C(17)	112.0(2)
C(12)-O(11)-C(10)	108.26(13)		

X-ray crystallography (Figure 1). Bond lengths and angles (Table 3) do not show surprising features. The 2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidin-5-one moiety is

almost planar, the maximum deviation from planarity is found for C(12) lying 0.007(2) $\text{\AA}$ from the plane C(12), N(13), N(15), C(16), C(17) and C(18).

During the addition of ethyl butynoate, we obtained a slight part of the non-cyclized esters 5a-b isolated as the (*E*) conformers. This structural result was established by analyzing the spectrum of the corresponding compound 6a obtained from 1a with ethyl propiolate. This reaction led to the major pyrimidin-7-one 7a (76%) with 6a in poor yield (10%). The ^1H nmr spectrum of 6a exhibited the presence of two typical *trans* olefinic protons at 8.13 and 5.03 ppm with a coupling constant *J* of 14 Hz. This conformation could explain the relative stability of 5a-b, 6a towards an ulterior intramolecular cyclization involving the second nucleophilic nitrogen atom [14]. A comparable behavior of related amidines towards other bis/electrophiles was previously described [15-17].

In conclusion, we studied the reactivity of 5-substituted-2-amino-2-oxazolines 1a-b as synthons to provide new pyrimidinones 2a-b, 3a-b, 7a. The 2-substituted-7-methyl-2,3-dihydro-5*H*-oxazolo[3,2-*a*]pyrimidin-5-ones 3a-b were easily obtained from diketene after dehydration of the intermediates 4a-b. On the other hand, the second regioisomers 2-substituted-5-methyl-2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidin-7-ones 2a-b, 7a were generated from acetylenic esters by a ring-annulation involving the endocyclic nitrogen atom of the 2-amino-2-oxazolines 1a-b. During this reaction, the non-cyclized (*E*)-2-*N*-(2-ethoxycarbonyl-ethylenyl)-5-substituted-2-imino-oxazolines 5a-b, 6a were isolated in slight yields. These methodologies are particularly adapted to the synthesis of such heterocycles which may find applications either as bioactive compounds or as useful intermediates for further transformations.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained with a Bruker IFS 25 spectrophotometer. The nmr data were recorded with a Bruker AC-200 spectrometer. Chemical shifts (δ in ppm) and coupling constants (*J* in Hz) were measured using TMS as the internal standard. Silica gel SDS-60 (70-230 mesh) was used for column chromatography. Microanalyses were carried out at the Service central d'analyse CNRS, Vernaison, France.

Crystal Structure Determinations

Colourless single crystal of 3a was obtained by slow evaporation from methanol solution. The crystallographic data are presented in Table 1. In both cases, the unit cell dimensions were determined using the least-squares fit from 25 reflections ($q < 25^\circ$). Intensities were collected with an Enraf-Nonius CAD-4 diffractometer using monochromated $\text{CuK}\alpha$ radiation by the $\omega/2\theta$ scan technique to a limit of 65° . The intensities were corrected for Lorentz and polarization effects, and empirical (ψ scans) absorption correction was applied. Both structures were determined by direct methods using MULTAN 80 [18]. The

scattering factors were taken from [19]. C, N and O atoms were refined anisotropically. The H-atoms were placed in theoretical positions or were located from difference Fourier maps were refined isotropically. The convergence largest D/s, were <1 (on Ds), the highest peaks in final difference maps were 0.318 and -0.309 e.Å⁻³. The atomic coordinates presented in Table 2 have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, U.K.

General Procedure for Preparation of 2-Substituted-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-one 2a-b/7a and (E)-2-N-(2-Ethoxycarbonyl-ethyl)-5-substituted-2-iminooxazolines 5a-b/6a.

To a solution of 2-aminio-2-oxazoline (1a-b) (30 mmol) in ethanol (50 mL) was added ethyl 2-butyrate or ethyl propionate (40 mmol). The reaction mixture was heated at reflux for 6 hours. The ethanol was evaporated *in vacuo* and the residue was separated by column chromatography on silica gel (chloroform/methanol: 90/10 v/v) to give 2a-b/7a and 5a-b/6a.

2-[(2-Methylphenoxy)methyl]-5-methyl-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-one (2a).

Compound 2a was obtained as colourless crystals (Toluene), yield 48%; mp 148–149 °C; ir (potassium bromide): ν 1660 (CO). ¹H nmr (deuteriochloroform): δ 7.10 (t, 1H, J = 7.90 Hz, H-5'), 7.08 (d, 1H, J = 7.90 Hz, H-6'), 6.86 (t, 1H, J = 7.90 Hz, H-4'), 6.75 (d, 1H, J = 7.90 Hz, H-3'), 5.75 (s, 1H, H-6), 5.28 (m, 1H, H-2), 4.43 (m, 1H, H-3), 4.26 (m, 2H, H-3 and OCH₂), 4.17 (m, 1H, OCH₂), 2.19 (s, 3H, CH₃); ¹³C nmr: δ 172.5 (CO), 160.8 (C=N), 155.6 (C-5), 146.7 (C-1'), 130.9 (C-3'), 126.9 (C-5'), 126.5 (C-2'), 121.5 (C-4'), 110.8 (C-6'), 107.0 (C-6), 75.4 (C-2), 67.6 (OCH₂), 46.2 (C-3), 17.6 (CH₃); 15.7 (CH₃). *Anal.* Calcd. for C₁₅H₁₆N₂O₃: C, 66.18; H, 5.95; N, 10.29. Found: C, 66.40; H, 5.95; N, 10.15.

2-(1-Phenyl-4-piperazinylmethyl)-5-methyl-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-one (2b).

Compound 2b was obtained as colourless crystals, yield 36%; mp 93–95 °C; ir (potassium bromide): ν 1660 (CO). ¹H nmr (deuteriochloroform): δ 7.23 (t, 2H, J = 7.60 Hz, H-3' and H-5'), 6.87 (d, 2H, J = 7.60 Hz, H-2' and H-6'), 6.83 (t, 1H, J = 7.60 Hz, H-4'), 5.72 (s, 1H, H-6), 5.07 (m, 1H, H-2), 4.30 (dd, 1H, J = 11.55 and 8.90 Hz, H-3a), 4.02 (dd, 1H, J = 11.55 and 7.10 Hz, H-3b), 3.13 (t, 4H, J = 4.85 Hz, CH₂ pip.), 2.84 (d, 2H, J = 5.25 Hz, NCH₂), 2.73 (m, 4H, CH₂ pip.), 2.18 (s, 3H, CH₃); ¹³C nmr: δ 166.2 (CO), 161.2 (C=N), 152.0 (C-7), 143.5 (C-1'), 129.1 (C-3' and C-5'), 128.0 (C-4'), 116.2 (C-2' and C-6'), 105.7 (C-6), 77.5 (C-2), 60.3 (NCH₂), 54.2 (CH₂ pip.), 49.2 (CH₂ pip.), 45.8 (C-3), 24.0 (CH₃). *Anal.* Calcd. for C₁₉H₂₂N₄O₃: C, 66.18; H, 6.74; N, 17.16. Found: C, 66.50; H, 6.73; N, 17.28.

2-[(2-Methylphenoxy)methyl]-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-one (7a).

Compound 7a was obtained as colourless crystals (Toluene), yield 76%; mp 51–52 °C; ir (potassium bromide): ν 1650 (CO). ¹H nmr (deuteriochloroform): δ 7.31 (d, 1H, J = 7.40 Hz, H-5'), 7.05 (m, 2H, H-3' and H-4'), 6.87 (t, 1H, J = 7.50 Hz, H-6'), 6.71 (d, 1H, J = 7.50 Hz, H-6'), 5.93 (d, 1H, J = 7.40 Hz, H-6), 5.30 (m, 1H, H-2), 4.50–4.11 (m, 4H, 2CH₂), 1.94 (s, 3H, CH₃).

Anal. Calcd. for C₁₄H₁₄N₂O₃: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.18; H, 5.51; N, 10.78.

(E)-2-N-(1-Methyl-2-ethoxycarbonyl-ethyl)-5-[(2-methylphenoxy)methyl]-2-iminooxazolines (5a).

Compound 5a was obtained as pale yellow oil, yield 10%; ir (potassium bromide): ν 3320 (NH), 1765 (CO). ¹H nmr (deuteriochloroform): δ 7.13 (m, 2H, H-3' and H-6'), 6.90 (m, 1H, H-4'), 6.75 (m, 1H, H-3'), 5.61 (s, 1H, CH=), 4.79 (m, 1H, CH), 4.20–3.81 (m, 6H, 3CH₂), 2.77 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 1.25 (t, 3H, J = 7.0 Hz, CH₃).

Anal. Calcd. for C₁₇H₂₂N₂O₄: C, 64.13; H, 6.96; N, 8.80. Found: C, 64.27; H, 7.05; N, 8.92.

(E)-2-N-(1-Methyl-2-ethoxycarbonyl-ethyl)-5-(1-phenyl-4-piperazinylmethyl)-2-iminooxazolines (5b).

Compound 5b was obtained as a yellow oil, yield 11%; ir (potassium bromide): ν 3325 (NH), 1720 (CO). ¹H nmr (deuteriochloroform): δ 7.24 (t, 2H, J = 7.50 Hz, H-3' and H-5'), 6.89 (d, 2H, J = 7.50 Hz, H-2' and H-6'), 6.84 (t, 1H, J = 7.50 Hz, H-4'), 5.59 (s, 1H, CH=), 4.60 (m, 1H, CH), 4.25–4.07 (m, 4H, 2CH₂), 3.85 (m, 1H, CH₂), 3.59 (dd, 1H, J = 9.30 and 7.25 Hz, CH₂), 3.16 (m, 4H, CH₂ pip.), 2.71 (s, 3H, CH₃), 2.65 (m, 4H, CH₂ pip.), 1.29 (t, 3H, J = 7.10 Hz, CH₃).

Anal. Calcd. for C₂₃H₂₈N₄O₄: C, 64.49; H, 7.58; N, 15.04. Found: C, 64.57; H, 7.63; N, 14.91.

(E)-2-N-(2-Ethoxycarbonyl-ethyl)-5-[(2-methylphenoxy)methyl]-2-iminooxazolines (6a).

Compound 6a was obtained as a pale yellow oil, yield 10%; ir (potassium bromide): ν 3340 (NH), 1770 (CO). ¹H nmr (deuteriochloroform): δ 8.14 (d, 1H, J = 14.0 Hz, CH=), 7.20 (m, 2H, H-3' and H-4'), 6.88 (t, 1H, J = 7.70 Hz, H-5'), 6.75 (d, 1H, J = 7.70 Hz, H-6'), 5.54 (bs, 1H, NH), 5.03 (d, 1H, J = 14.0 Hz, CH=), 4.93 (m, 4H, 2CH₂), 3.75 (m, 2H, CH₂), 2.14 (s, 3H, CH₃), 1.27 (t, 3H, J = 7.10 Hz, CH₃).

Anal. Calcd. for C₁₆H₂₀N₂O₄: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.27; H, 6.81; N, 8.97.

General Procedure for Preparation of 2-Substituted-7-methyl-2,3-dihydro-5H-oxazolo[3,2-a]pyrimidin-5-one (3a-b).

A solution of 2-substituted-7-hydroxy-7-methyl-2,3,6,7-tetrahydro-5H-oxazolo[3,2-a]pyrimidin-5-one (4a-b) (30 mmol) in 50 mL of acetone was stirred at 25 °C during 24 hours. The solvent was removed and the oily residue was triturated in diethyl ether to provide 3a and 3b.

2-[(2-Methylphenoxy)methyl]-7-methyl-2,3-dihydro-5H-oxazolo[3,2-a]pyrimidin-5-one (3a).

Compound 3a was obtained as colourless crystals (Toluene), yield 43%; mp 125–127 °C; ir (potassium bromide): ν 1685 (CO). ¹H nmr (deuteriochloroform): δ 7.09 (t, 1H, J = 7.50 Hz, H-5'), 7.07 (d, 1H, J = 7.50 Hz, H-6'), 6.85 (t, 1H, J = 7.50 Hz, H-4'), 6.72 (d, 1H, J = 7.50 Hz, H-3'), 5.89 (s, 1H, H-6), 5.24 (m, 1H, H-2), 4.31 (m, 3H, H-3 and OCH₂), 4.13 (dd, 1H, J = 10.70 and 3.05 Hz, OCH₂), 2.19 (s, 3H, CH₃), 1.97 (s, 3H, CH₃); ¹³C nmr: δ 166.1 (CO), 160.9 (C=N), 138.9 (C-7), 153.6 (C-1'), 130.9 (C-3'), 126.8 (C-2' and C-5'), 121.5 (C-4'), 110.7 (C-6'), 105.5 (C-6), 76.2 (C-2), 67.8 (OCH₂), 44.1 (C-3), 23.9 (CH₃), 15.6 (CH₃).

Anal. Calcd. for C₁₃H₁₆N₂O₃: C, 66.18; H, 5.88; N, 10.29. Found: C, 66.39; H, 6.13; N, 10.42.

2-[(1-phenyl-4-piperazinyl)methyl]-7-methyl-2,3-dihydro-5H-imidazo[3,2-a]pyrimidin-5-one (3b).

Compound 3b was obtained as colourless crystals, yield 57%; mp 130–131 °C; η (potassium bromide): ν 1695 (CO). ^1H nmr (deuteriochloroform): δ 7.25 (t, 2H, $J = 7.65$ Hz, H-3' and H-5'), 6.92 (d, 2H, $J = 7.65$ Hz, H-2' and H-6'), 6.86 (t, 1H, $J = 7.65$ Hz, H-4'), 5.64 (s, 1H, H-6), 4.58 (m, 1H, H-2), 3.87 (dd, 1H, $J = 11.60$ and 9.00 Hz, H-3a), 3.62 (dd, 1H, $J = 11.60$ and 7.20 Hz, H-3b), 3.20 (t, 4H, $J = 4.95$ Hz, CH_2 pip.), 2.76 (s, 3H, CH_3), 2.70 (m, 4H, CH_2 pip.), 2.65 (d, 2H, $J = 5.20$ Hz, NCH_2); ^{13}C nmr: δ 168.1 (CO), 155.9 (C=N), 154.1 (C-3), 151.1 (C-1'), 139.2 (C-3') and 50.9 (C-4'), 119.9 (C-4'), 116.2 (C-2' and C-6'), 99.6 (C-6), 72.3 (C-2), 55.0 (NCH_2), 54.0 (CH_2 pip.), 39.9 (C-3), 49.1 (CH_2 pip.), 16.5 (CH_3).

Anal. Calcd. for $C_{15}H_{22}N_4O_2$: C, 66.18; H, 6.74; N, 17.16.
Found: C, 66.32; H, 6.76; N, 17.25.

General Procedure for the Preparation of 2-Substituted-7-hydroxy-7-methyl-2,3,6,7-tetrahydro-5H-oxazolo[3,2-c]pyrimidin-5-one (4a-h).

A solution of the required 2-amino-2-oxazoline Ia-b (36 mmoles) in 50 ml of acetone was cooled to 0 °C. Then, dithiurea (40 mmoles) was slowly added. After the addition was complete, the mixture was stirred at 0 °C. A precipitate was observed after 30 minutes. It was isolated by filtration and dried in yield Ia-b.

2-[2-(Methoxyphenoxy)methyl]-7-hydroxy-7-methyl-2,3,6,7-tetrahydro-5H-oxazolo[3,2-a]pyrimidin-5-one (4a) (racemic form).

Compound 4a was obtained as colourless crystals, yield 64%; mp 139–141 °C (it spouts into bromide); ν 3185 (OH), 1710 (C=O), 1411 cm⁻¹ (deuterochloroform); δ 7.11 (m, 2H, H-5' and H-6'), 6.91 (m, 1H, H-4'), 6.75 (m, 1H, H-3'), 5.18 and 5.01 (2m, 1H, H-2), 4.35–4.01 (m, 4H, CH₂), 2.83–2.56 (m, 2H, CH₂), 2.13 (m, 4H, CH₂) and 0H₁, 1.52 (2s, 3H, CH₃).

Anal. Calcd. for $C_{15}H_{15}N_2O_2$: C, 62.07; H, 6.21; N, 9.65. Found: C, 62.15; H, 6.15; N, 9.73.

2-(1-Phenyl-4-piperazinyl)methyl-7-hydroxy-7-methyl-2,3,6,7-tetrahydro-5H-oxazolo[3,2-c]pyrimidin-5-one (4b) (racemic form).

Compound 4b was obtained as colourless crystals, yield 65%; mp 133–134 °C; η (potassium bromide): ν 3200 (OH), 1700 (C=O). ^1H nmr (deuteriochloroform): δ 7.40 (m, 2H, H-3' and H-5'), 7.05 (m, 2H, H-2' and H-6'), 7.01 (m, 1H, H-4'), 4.83 (m, 1H, H-2), 3.73 (m, 1H, H-3a), 3.47 (m, 1H, H-3b), 3.17 (m, 4H, NCH₂), 2.65 (th, 6H, NCH₃), 1.80 (th, 3H, OH). 166

and 1.65 (2s, 3H, CH₃); ¹³C nmr: δ 167.3 and 167.2 (CO), 153.6 and 153.5 (C=N), 150.9 and 150.8 (C-1'), 128.9 (C-3' and C-5'), 119.6 (C-4'), 115.9 and 115.8 (C-2' and C-6'), 83.5 and 83.4 (C-7), 75.9 and 75.7 (C-2), 69.1 and 69.0 (NCH₃), 53.9 and 53.8 (CH₃ pip), 49.0 and 48.9 (CH₃ pip), 44.5 and 44.4 (C-3), 42.2 and 42.1 (C-6), 30.4 (CH₃).

Anal. Calcd. for $C_{19}H_{28}N_8O_3$: C, 62.71; H, 6.97; N, 16.26.
Found: C, 62.95; H, 7.13; N, 16.34.

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