2(*3H*)-Benzoxazolone and Bioisosters as "Privileged Scaffold" in the Design of Pharmacological Probes

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Abstract: The 2(*3H*)-benzoxazolone heterocycle and its bioisosteric surrogates (such as 2(*3H*)-benzothiazolinone, benzoxazinone, etc.) have received considerable attention from the medicinal chemists owing to their capacity to mimic a phenol or a catechol moiety in a metabolically stable template. These heterocycles and pyrocatechol have indeed similar pKa's, electronic charge distribution, and chemical reactivity. Therapeutic applications of this template are very broad, and range from analgesic anti-inflammatory compounds (including PPAR-gamma antagonists) to antipsychotic and neuroprotective anticonvulsant compounds. High affinity ligands have been obtained also for dopaminergic (D2 and D4), serotoninergic (5-HT1A and 5-HT-2A), sigma-1 and sigma-2 receptors. Owing to the high number of positive hits encountered with this heterocycle and its congeners, 2(*3H*)-benzoxazolone template certainly deserves the title of "privileged scaffold" in medicinal chemistry.

Keywords: Bioisosterism, privileged scaffolds, 2(*3H*)-benzoxazolone, 2(*3H*)-benzothiazolinone, mixed affinity ligands.

INTRODUCTION

This review highlights two classical concepts in medicinal chemistry, sometimes nowadays considered as old-fashioned, *i.e.* privileged scaffold and bioisosterism within the context of their application to the 2(*3H*)-benzoxazolone heterocycle and its surrogates. We will first briefly define what we mean by "privileged scaffold" and "bioisosterism".

By the term "privileged scaffold" [1], we intend a substructure or template (sometimes also referred to as "motifs" or fingerprints) that when incorporated in a pharmacophore has a high degree of drug likeliness due to the presence of atom or functional group properties that are relevant in ligand binding such as volume, hybridization, partial atomic charge, electronegativity, polarizability, hydrophobicity, hydrogen-bonding potential, local properties that are often parameterized *via* the use of global physicochemical properties, such as molecular weight, log P, molar refractivity, and so on. Viable "privileged scaffolds" often consist of a relatively rigid ring system, which is able to present multiple hydrophobic residues in predictable orientations of space and consequently, without undergoing hydrophobic collapse. Such privileged platforms have been extensively studied for their therapeutic potential and bioavailability. The benzodiazepines, so-called "tricyclics" (such as the benzothiazines), steroids, *N*-arylpiperazines, cyclic hexapeptides and monosaccharides demonstrate that semi-planar scaffolds bind various hormone receptors. The benzodiazepine scaffold which is probably the best known privileged platform, in addition to a considerable number of applications in the generation of ligands for G-protein associated receptors and ion channels has in fact, produced more recently, farnesyl transferase inhibitors, reverse transcriptase inhibitors and ligands for the HIV-1 Tat protein.

Bioisosterism [2] is based on the assumption that "similar" molecules tend to exert "similar" biological activities and since long, medicinal chemists have used this concept to modify the structures of biologically active compounds. While similarity of chemical structures cannot be defined in an objective manner, bioisosteric replacements of atoms or functional groups have paved the way from lead structures to therapeutically useful molecules [3]. More recently, combinatorial chemistry techniques and high throughput screening offer new opportunities in lead discovery and optimization. The discovery of lead demands large, chemically diverse libraries. On the other hand, lead optimization needs similar analogs that cover the chemical space around the leads. In this new context, the principle of bioisosteric replacement of functional groups serves as a successful optimization strategy. Its systematic application has resulted in a broad variety of therapeutically used drugs, many of them finally having the desired combination of favorable properties.

The 2(*3H*)-Benzoxazolone (**1**) heterocycle (henceforward abbreviated BOA) is a bicyclic ring system composed of a phenyl ring fused to a carbamate [4-6] (Fig. **1**). This particular structural feature has several important consequences for the medicinal chemist:

(i) one edge is lipophilic, while the other one is hydrophilic with two hydrogen bonding accepting sites and a single hydrogen bonding donating site;

(ii) this dichotomy is reflected by a rather high dipole moment (4.47 Debye) and a discrete partition coefficient (log P = 0.97);

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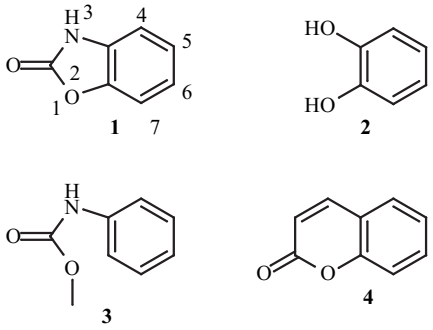


Fig. (1). 2(*3H*)-Benzoxazolone and other heterocycles with structural resemblance.

(iii) BOA is a weak acid in aqueous solution ($pK_a = 8.7$), somewhat comparable to pyrocatechol (**2**) ($pK_a = 9.2$), reason for which BOA is often referred to as a pyrocatechol bioisoster (Fig. **1**);

(iv) BOA constitutes a scaffold of high versatility in organic synthesis, allowing for a wide variety of chemical modifications implying a good directionality in the implementation of the side-chains on a rigid platform;

(v) BOA shares structural resemblance with phenylurethane (**3**) and coumarin (**4**) and *per se* is endowed with hypnotic, analgesic, and antipyretic properties of the former and bactericide properties of the latter [7-9] (Fig. **1**).

BOA (**1**) in many designs also serves as a phenol substitute. To some extent, the sulfur bioisoster, *i.e.* 2(*3H*)-benzothiazolone (**5**), the methylene bioisoster, *i.e.* 2-oxindole (**6**), and the nitrogen bioisoster, *i.e.* benzimidazol-2-one (**7**) have been employed with great success in situations where either a phenol or catechol had to be replaced by a more adequate residue (Fig. **2**).

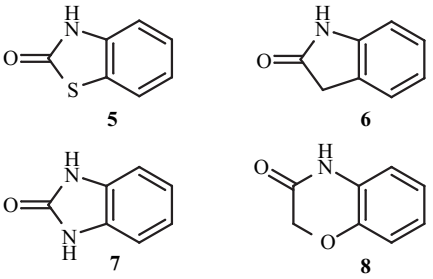


Fig. (2). Some bioisosters of 2(*3H*)-Benzoxazolone (**1**).

The methylene ring expansion of BOA, *i.e.* benzoxazinone (**8**) (Fig. **2**), follows the same strategy of bioisosterism. Theoretical calculations of the charge provide support for this hypothesis (Table **1**).

Hydrophilic phenol and catechol moieties are indeed the subject of fast *in vivo* metabolic processes (liver first-pass effect), leading to even more hydrophilic entities such as glucurono- and sulfoconjugates. Catechols, in addition to their susceptibility to catechol-O-methyl transferase (COMT), are also highly sensitive to oxidative conditions leading to highly toxic ortho-quinone derivatives. The substitution of these unfavorable building blocks by BOA or one of its bioisosteric replacements provides a tool to overcome poor pharmacokinetic characteristics or stability problems for a lead compound containing either a phenol or a catechol in its structure. As bioisosterism introduces local steric and electronic modifications compared to the original model, substitution of either a phenol or a catechol by BOA or one of its aforementioned bioisosters in a lead compound may result in a dramatic change in receptor affinity and selectivity, and/or agonist – antagonist character. This review will highlight this point mainly in the section with the design of pharmacological probes.

Table 1. Charge Located on Phenolic Oxygen or Carbonyl Oxygen (for 5-8) as Calculated Using Mulliken's Method

Compound	Charge
Phenol	-0.31906
Catechol	-0.32642
BOA (**1**)	-0.32988
2(3H)-Benzothiazolone (**5**)	-0.32404
2-Oxindole (**6**)	-0.31919
Benzimidazol-2-one (**7**)	-0.34461
Benzoxazinone (**8**)	-0.34799

CHEMICAL REACTIVITY

The reactivity of BOA permits to define three major types of reactions: *N*-substitution (either alkylation or acylation), aromatic ring electrophilic substitution, and ring opening or expansion reactions.

The enolizable character of the amide moiety allows for several useful transformations at the level of the N(3) position of the heterocycle. *N*-alkylation of **1** proceeds under base-catalyzed conditions to give derivatives of type **9** [10-13], while *N*-acylation is submitted to generalized acid-base catalysis to give derivatives of type **10** (Fig. **3**). Mannich condensation provides ready access to *N*-aminomethyl derivatives **11** [14]. Base-catalyzed Michael addition of acrylonitrile leads to a *N*-cyanoethyl derivative **12** [15]. Reaction of BOA with hydroxaminosulfuric acid is another example of *N*-substitution which gives the cyclic hydrazide structure **13** [16] (Fig. **3**).

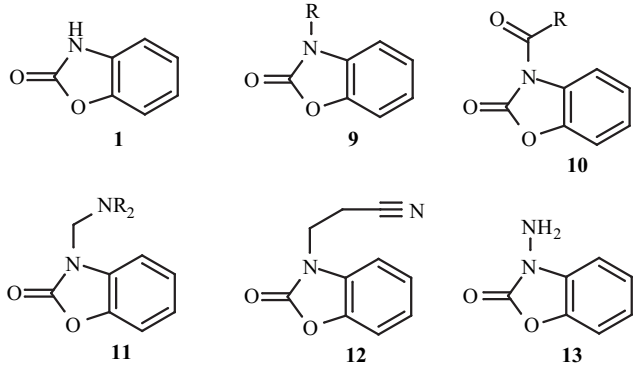
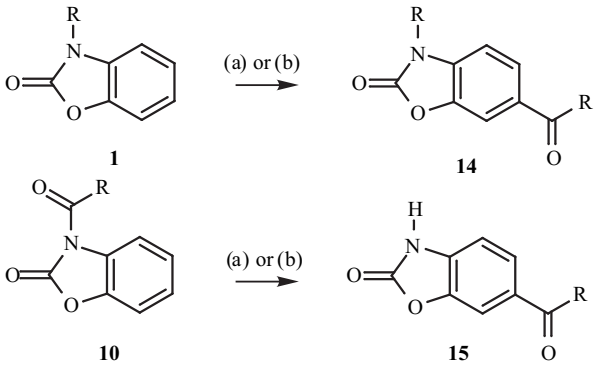


Fig. (3). Possible transformation on the N(3) position of 2(*3H*)-Benzoxazolone (**1**).

Aromatic electrophilic substitution is governed by the overwhelming preference for the 6-position which is



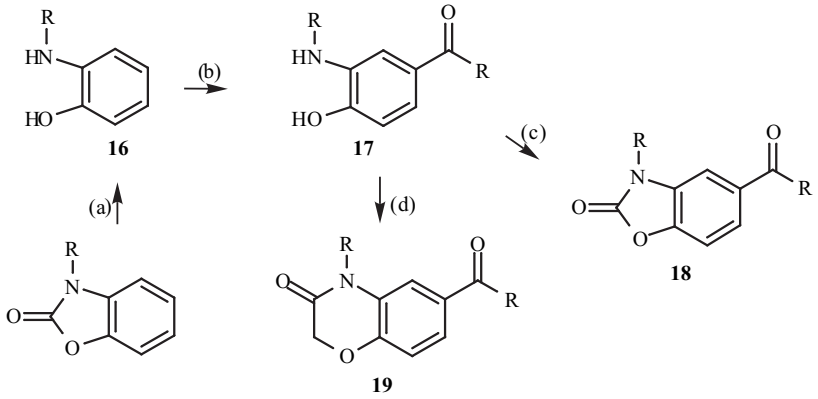
Scheme 1. Access to 6-acyl-BOA derivatives. Methods: (a) RCOOH, PPA, Δ; (b) RCOCl, $AlCl_3$·DMF.

observed not only for the straightforward halogenation, nitration, sulfonation, and chlorosulfonation reactions, but also for the more troublesome Friedel-Crafts acylation (Scheme **1**) [17]. Indeed, in the particular case of the Friedel-Crafts reaction, due to the electron-rich character of BOA, the heterocycle is extensively complexed (or protonated) by the Lewis acid present in the reaction medium, which acts as electrophilic attack of acylium ions. To overcome this problem, the reaction can be run using either a less reactive electrophilic species (polyphosphoric acid, PPA, for example) [18-20] or preferably the $AlCl_3$·DMF complex [21-29], to give 6-acyl derivatives of type **14** (Scheme **1**). As a most fruitful alternative, *N*-acyl derivatives of type **10** can be rearranged at high temperature (160°C) in a Fries-like reaction promoted by $AlCl_3$, to 6-acyl derivatives of type **15** [27] (Scheme **1**).

While BOA derivatives are fairly stable in acid medium, they are quickly hydrolyzed in basic medium, leading to ring opening products such as 2-aminophenols (**16**) [30,31] (Scheme **2**). These 2-aminophenols can be acylated in position 4 (**17**). Subsequent ring closure leads to the otherwise inaccessible 5-acyl-BOA derivatives (**18**). Ring expansion of BOA derivatives to benzoxazinones (such as **19**) can be effected *via* the same 2-aminophenols (Scheme **2**).

THERAPEUTIC APPLICATIONS

Various, rather simple derivatives of BOA have been marketed, *e.g.* Benzolone (**20**, myorelaxant) [32-34],



Scheme 2. Access to 5-acyl-BOA and benzoxazinone derivatives. Methods: (a) aq. NaOH, Δ; (b) RCOCl, $AlCl_3$.DMF; (c) ClCOOEt, TEA; (d) $BrCH_2COOEt$, TEA.

an absolutely mandatory catalyst. As a paradoxical consequence, while BOA behaves as a strongly activated substrate in normal electrophilic substitution conditions (such as bromination, for example), the extensive complexation encountered in the Friedel-Crafts reaction strongly deactivates this type of substrate towards the Paraflex (**21**, sedative analgesic) [35], and Vinizene (**22**, topical antiseptic) (Fig. **4**). 6-Methoxy-BOA (**23**) [36,37] is a product of natural origin found in corn and endowed with insecticide, antimicrobial, and antifungal properties. 6-Benzoyl-BOA (**24a**, X = O, 10194 CERM) and its sulfur bioisoster (**24b**, X = S, S-14080) underwent clinical trials

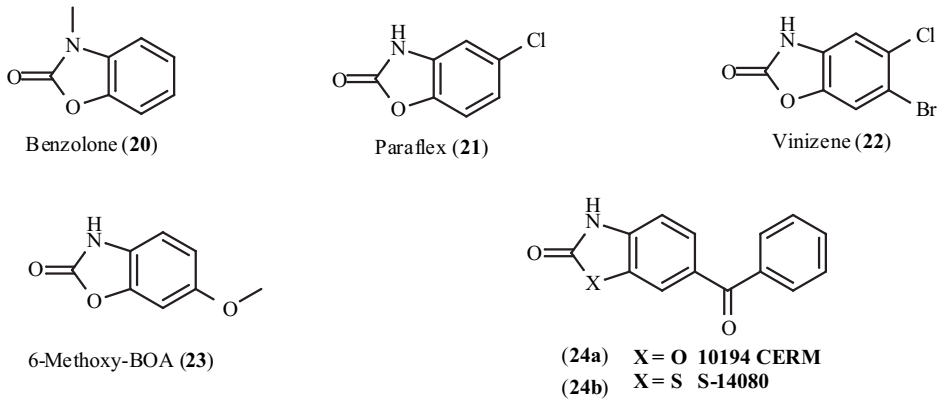


Fig. (4)

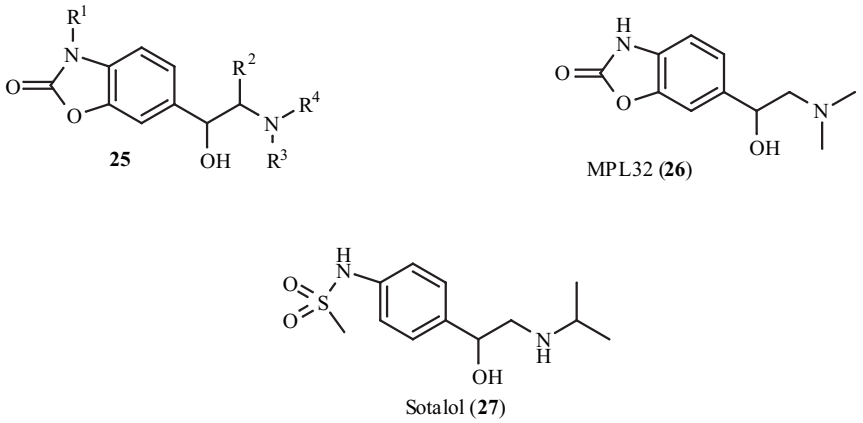


Fig. (5).

until phase II as analgesic [38-41]. S-14080 (**24b**, Fig. **4**) was found to inhibit not only the arachidonic acid inflammatory cascade. In addition to this, **24b** also induces the release of a (however so far unidentified) opioid peptide in periphery (possibly endomorphin, nociceptin) [42-45]. A more recent work was published, expanding the structure-activity relationship of S-14080 as an analgesic compound [46]. 6-Benzoyl-benzoxazolin-2-one (**24a**) and 6-benzoyl-benzothiazolin-2-one (**24b**) also served as lead structures in the design of antiviral compounds, particularly targeted against HIV and CMV species [47].

DESIGN OF PHARMACOLOGICAL PROBES

As BOA can be viewed as a bioisoster of pyrocatechol, it was rather obvious that this scaffold would be employed with success in the design of ligands of the dopamine (mainly D2 and D4) and noradrenaline receptors. The BOA template has also been used with even greater success in the design of mixed affinity ligands of the dopamine and serotonine (5-HT) receptor subtypes.

Compounds with adrenergic activity of general structure **25** were discovered in the 80's [48,49] (Fig. **5**). Among these, the most interesting one, *i.e.* MPL32 (**26**) [50,51], which has a structure very similar to sotalol (**27**) was developed as an antihypertensive agent [52] and went up to phase II clinical trials (Fig. **5**). It is worth noting that, while general structure **25** contains two chiral centers, the less complex – stereochemically speaking – MPL32 has got only one chiral center, and the pharmacological studies were performed on the racemic mixture (Fig. **5**).

More recently, a great deal of efforts were devoted to the design of mixed affinity ligands for the dopamine [53,54] and serotonin receptor subtypes [55]. Among D2 antagonists, haloperidol (**28**) [56], which has also high affinity for the sigma-1 receptor, is known as the prototype of the so-called "typical" antipsychotic drugs [57,58] (Fig. **6**). Its chronic administration gives rise to extrapyramidal [59] side-effects. In this context, it has been observed that the co-administration of haloperidol (**28**) with a 5-HT2A antagonist, such as ritanserine or ketanserine tends to decrease these extrapyramidal effects [60-62]. Atypical antipsychotic drugs such as clozapine (**29**) (Fig. **6**) [63-65] are devoid of undesired effects such as tardive dyskinesia [66] and parkinsonian syndrome [67], which are commonly observed with typical antipsychotic drugs. Empirically, this behavior has been associated to a blend of activities and receptor affinities composed of antagonism at D2 [68] and 5-HT2A and agonism at 5-HT1A.

In view of the potential therapeutic interest for this class of compounds, compounds of general structure **30** were synthesized [69-75] (Fig. **7**). From this pharmacomodulation emerged the benzoxazinone derivative **31,** with a 2-methoxyphenyl and a four methylene linker as the ligand having the most appropriate receptor profile (K_I(5-HT1A) = 0.8 nM, K_I(D2) = 5 nM) [76] (Fig. **7**). In a further effort to improve the profile of this class of structures, a 4-fluorophenylpiperidine moiety (as found in ketanserine) was implemented *via* a two carbon linker to produce additional 5-HT2A antagonism. The most interesting compound in this series OD36 (**32**), a benzothiazolinone derivative showed noteworthy anti-panic activity in animal models and entered preclinical studies [76-78] (Fig. **7**).

The design of OD36 (**32**) can be interpreted in terms of the "message-address" theory in which the message is delivered by the central BOA scaffold on which two address

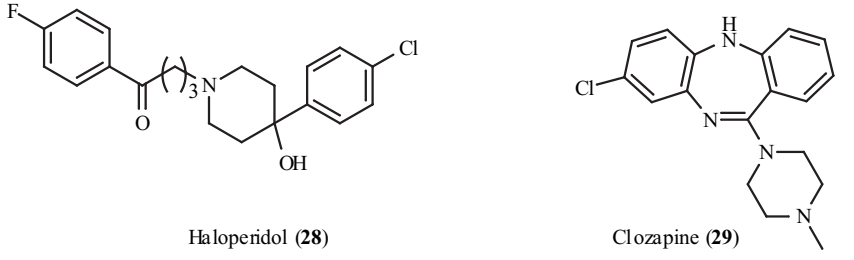


Fig. (6). Structures of Haloperidol (**28**) and Clozapine (**29**).

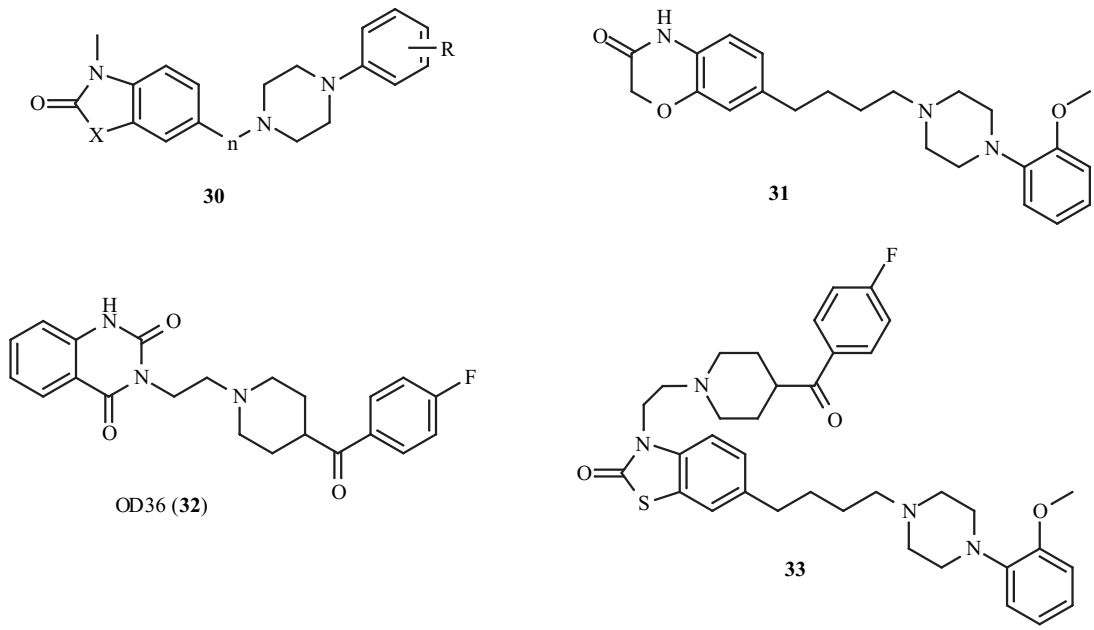


Fig. (7).

systems are attached to provide affinity, both 5-HT1A and 5-HT2A receptors [79] (Fig. **8**). When the benzothiazolinone heterocycle was substituted by a benzoxazinone ring, the affinity for the 5-HT1A and 5-HT2A receptors dropped [80], but the affinity for the D2 receptor was reinforced [K_i(D2) = 0.06 nM]. To our knowledge, this compound is among the best D2 ligands ever synthesized.

Based on a strategy relatively similar to our design of mixed affinity ligands for the dopamine/serotonine receptors (*cfr* general structure **30,** Fig. **7**), we set up a design, based on a central piperazine ring flanked on both nitrogens by arylalkyl side-chains in which one aryl group is electron-rich (BOA or bioisosters), while the other one is electron-deficient to obtain mixed affinity ligands for the 5-HT1A/sigma receptors (*cfr* general structure **34**) (Fig. **9**). Incidentally, along this line, we obtained a high affinity and selectivity sigma-2 ligand [**35**, $K_I(\sigma 2)$ = 2 nM, $K_I(\sigma 1)$ = 140 nM]. Previous works using BOA and benzothiazolinone derivatives gave highly potent sigma-1 ligands. The best ligand (**36**), [$K_I(\sigma 1)$ = 0.6 nM] showed remarkable anticonvulsant properties having a profile and a level of activity similar to phenytoin and carbamazepine [81]. Compound **36** was indeed found very active in the maximal electroshock seizure test and inactive in the subcutaneous pentylenetetrazole test (Fig. **9**).

In the late 80's, normolipemic agents were developed, based on the structure of clofibrate and using the benzoxazinone platform. More recently, the 2(*3H*)-benzothiazolone platform has been used to generate PPARγ (Peroxisome Proliferator-Activated Receptor of the gamma

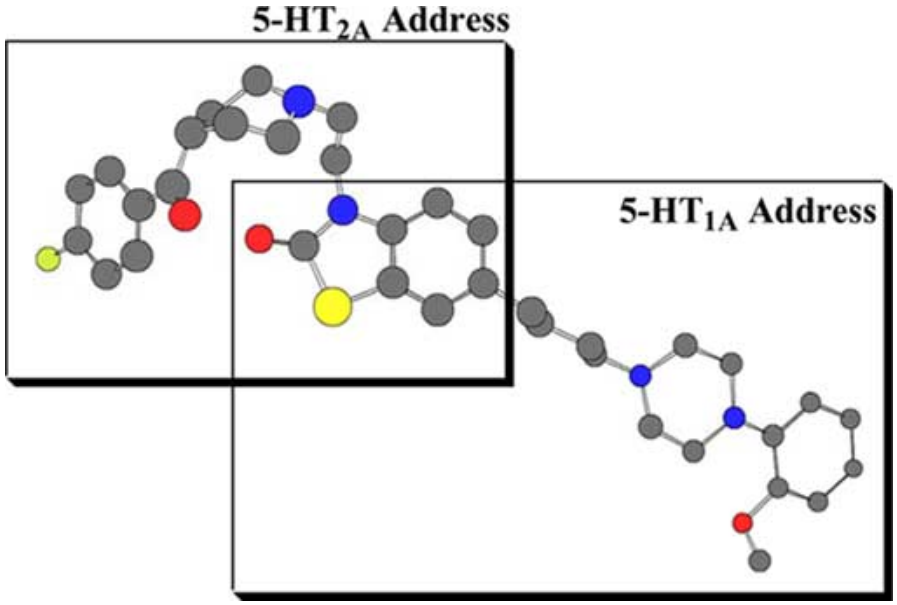


Fig. (8). Application of the message-address theory to the design of a BOA-based 5-HT1A/5-HT2A mixed affinity ligand.

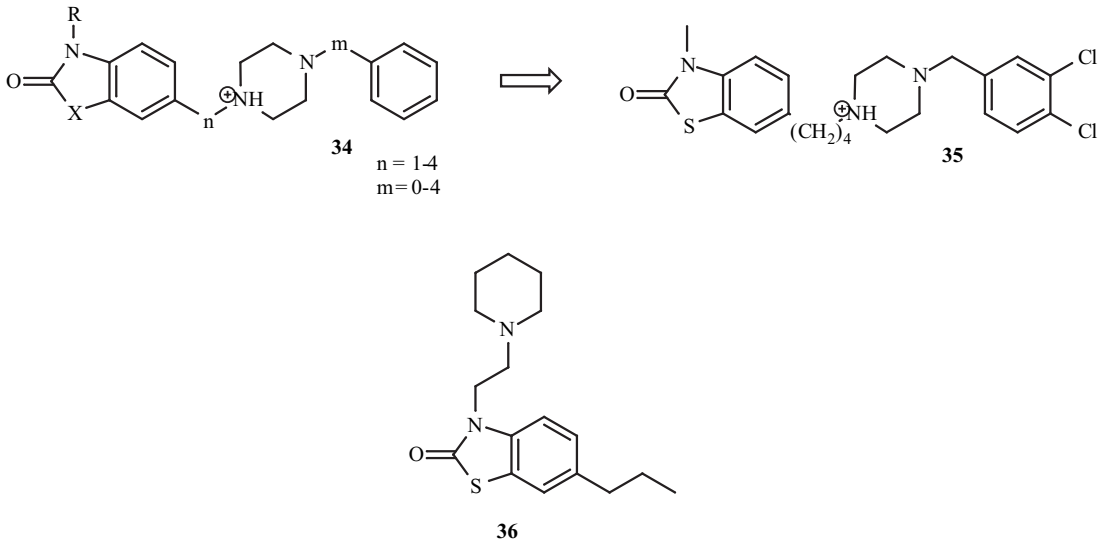


Fig. (9). Mixed affinity ligands for the 5-HT1A/sigma receptors.

subtype) ligands [82-86]. Among the various compounds engendered, compound **37**, a full agonist showed remarkable affinity [K_I(PPARγ) = 1.5 nM) and efficacy (EC_{50} = 32 nM) [87] (Fig. **10**).

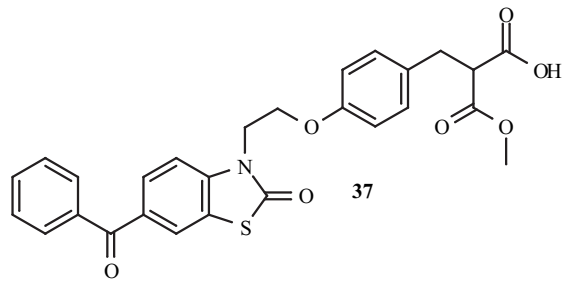


Fig. (10). Full antagonist of PPARγ (Peroxisome Proliferator-Activated Receptor of the γ subtype).

MISCELLANEOUS APPLICATIONS

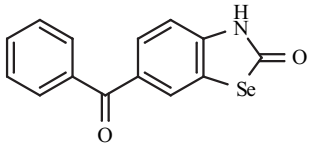
The 6-benzoylbenzoselenozolinone (**38**) (Fig. **11**) initially designed as glutathione peroxidase mimetic was found to be a potent inhibitor of the cyclooxygenase and lipoxygenase pathways *in vitro* [88]. When tested *in vivo* on the rat foot edema induced by various phlogistic agents, it demonstrated interesting anti-inflammatory properties. The 5-benzoylindolin-2-one (**39**), which is structurally related to 10194 CERM (**24a,** Fig. **4**) and S-14080 (**24b,** Fig. **4**) and 6-benzoylbenzoselenozolinone (**38**) also showed anti-inflammatory properties in the Evans-Blue – Carrageenan Pleural Effusion of Sancilio [89] (Fig. **11**). This convergence of anti-nociceptive/anti-inflammatory properties for compounds **24a**, **24b**, **38** and **39** clearly illustrate the validity of the bioisosterism concept in which O, S, Se and methylene are interchangeable. Interestingly enough, compound **39** (Fig. **11**) has demonstrated antiepileptic properties in Maximal Electroshock Seizure (MES) test with a level of activity roughly similar to that of phenytoin and carbamazepine and superior to phenobarbital.

As 10194 CERM (**24a**) and S-14080 (**24b**) were endowed with low oral bioavailability due to intense and rapid liver metabolism, it was anticipated that this oxidative process could be impeded by implementing an electron-withdrawing substituent, which would reduce the overall electronic density of the heterocycle. This was achieved using a benzoxazolinone system in which the benzo moiety was replaced by pyridino system. Pyridine can be considered indeed as a bioisoster of nitrobenzene.

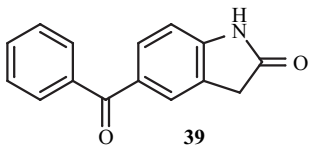
Thus, 1-[(4-aryl-1-piperazinyl)alkyl]oxazolo[5,4-b]pyridin-2(*1H*)-one derivatives and the corresponding structures with a [4,5-b] fusion were synthesized and tested for analgesic activity in mice and rats. The compound with the maximal combination of safety and analgesic efficacy was 1-[[4-(4-fluorophenyl)-1-piperazinyl]propyl]oxazolo[5,4-b]pyridin-2(*1H*)-one (**40**) (Fig. **11**). The mechanism of action of this compound remains unclear, as it was devoid of affinity at opioid and neurokinin receptors [90,91]. In the field of antinociceptive/anti-inflammatory compounds, it is also worth mentioning tiaramide (**41**), which features a 5-chlorobenzothiazolinone in its structure [92]. Tiaramide was also shown to have anti-histaminic activity [93]. Analogs of **41** have been synthesized recently and showed equally antinociceptive/anti-inflammatory properties. Phosalone (**42**, Fig. **11**), a phosphorodithioate-based insecticide and acaracide [94-96] containing a 6-chlorobenzoxazolinone moiety in its structure is a cholinesterase-inhibitor [97]. Phosalone is structurally related to malathion (**43** Fig. **11**), the well known prototypic organothiophosphate insecticide and is used in agriculture to control a variety of insects and mite pests [98].

CONCLUSION

The principle of bioisosterism *i.e.* – similarly shaped molecules are more likely to share biological properties than are other molecules – has long helped to guide drug discovery. In their attempts to optimize lead structures, medicinal chemists intuitively followed the principles of Darwinist evolution. The biological activity and, in later stages, the target selectivity, toxicology or pharmacokinetic behavior serve as the "fitness function" for the "survival" of certain structural entities. Privileged scaffolds contain



6-Benzoylbenzoselenozolinone (**38**)



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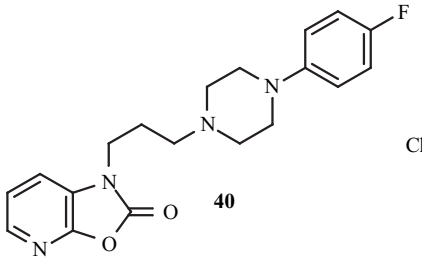

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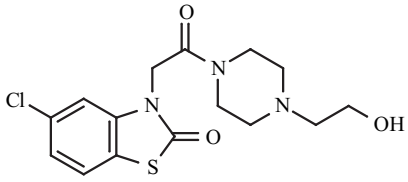
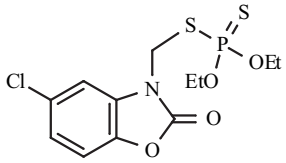
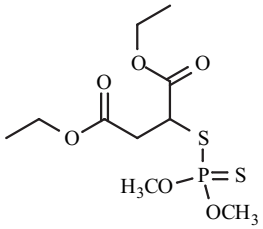


Tiaramide (**41**)



Phosalone (**42**)



Malathion (**43**)

Fig. (11).

structures, features giving better chances of survival. In this context, among these "heroic" substructures, the BOA template and its congeners occupy a place of choice. This review therefore, did not intend to be a compilation of all the published applications of the BOA template in medicinal chemistry, but rather an invitation for the drug designer to think (again?) in terms of bioisosteric replacement, when dealing with the transformation of a lead into a drug. In many peptides, the tyrosine aminoacid appears as a strong signal in the structure (*e.g.* opioid peptides such as the enkephalins, dynorphin, endomorphins, etc.). BOA and its bioisosteric congeners therefore have still a lot of work to accomplish in the context of the design of peptidomimetics. In view of the high number of hits using either BOA or its congeners, the 2(*3H*)-benzoxazolone heterocycle certainly deserves the title of 'privileged scaffold' in medicinal chemistry.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

BOA = 2(3H)-Benzoxazolone

CMV = Citomegalovirus

DMF = *N,N*-dimethylformamide

PPA = Polyphosphoric acic

TEA = Triethylamine

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