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Review article

Benzomorphan scaffold for opioid analgesics and pharmacological tools development: A comprehensive review

Rita Turnaturi [a, *], Agostino Marrazzo [a], Carmela Parenti [b, 1], Lorella Pasquinucci [a, 1]

[a] Department of Drug Sciences, Medicinal Chemistry Section, University of Catania, Viale A. Doria, 6, 95100, Catania, Italy
[b] Department of Drug Sciences, Pharmacology Section, University of Catania, Viale A. Doria, 6, 95100, Catania, Italy

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ABSTRACT

Benzomorphan, derived by morphine skeleton simplification, has been the subject of exploration in medicinal chemistry for the development of new drugs and pharmacological tools to explore opioid pharmacology *in vitro* and *in vivo*. Building upon these evidences, the design and synthesis of benzomorphan-based compounds, appropriately modified at the basic nitrogen and/or the phenolic hydroxyl (8-OH) group, represent a valid and versatile strategy to obtain analgesics. In this review, to improve the body of information in this field, we report structure activity-relationships (SARs) of benzomorphan-based compounds analysing data literature of last 25 years. Collectively, SARs data highlighted that the benzomorphan nucleus represents a template in the achievement of a specific functional profile, by modifying N-substituent or 8-OH group.

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1. Introduction

Morphine is the gold standard option in pain management although its analgesic properties are often accompanied by several unwanted side effects such as respiratory depression, sedation, constipation, analgesic tolerance and addiction [1,2]. To elicit analgesia without its undesirable side effects, morphine skeleton has been continuously modified and simplified over the years [3–5]. Benzomorphan, derived by structure-activity relationships (SARs) on morphine skeleton simplification, has been the subject of exploration in medicinal chemistry for the development of new drugs and pharmacological tools to explore opioid pharmacology *in vitro* and *in vivo* [6]. Thus, benzomorphan structure could be considered a versatile scaffold and the modifications of the functional groups attached to basic nitrogen and the phenolic hydroxyl group (8-OH), as well as group changes in position 6 or 7 (Fig. 1) led to different class of drugs that variably act as Na^+ channel blockers, antivirals, sigma or opioid receptor ligands [7].

Crobenetine [8] (Fig. 1) is a potent, selective and highly use-dependent Na^+ channel blocker. Moreover, NITD-2636 [9] (Fig. 1) is a benzomorphan-based compound that displayed a broad spectrum of antiviral activity through suppression of viral RNA translation. Diversely, Alazocine [10] ((+)-SKF-10,047, Fig. 1) is the first

* Corresponding author.
E-mail address: rita.turnaturi@tiscali.it (R. Turnaturi).
[1] These authors contributed equally to this review.

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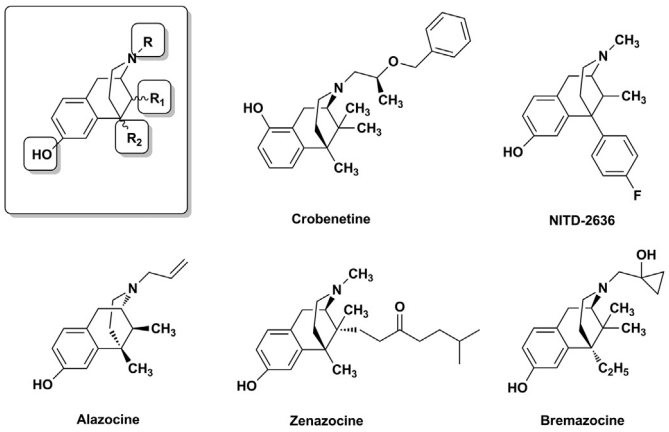

Fig. 1. Structures of benzomorphan derivatives.

drug discovered to act at sigma1 receptor (σ1R). In particular, benzomorphans are mostly known for their potential analgesic profile via opioid receptor interaction. For instance, Zenazocine [11] (WIN-42,964, Fig. 1), an opioid analgesic in phase II clinical trials, acts as a partial agonist of the mu and delta opioid receptors (MOR and DOR). Similarly, Bremazocine [12] (Fig. 1), a kappa opioid receptor (KOR) agonist related to pentazocine, possesses potent and long-lasting analgesic and diuretic effects. Building upon these evidences, the design and synthesis of benzomorphan-based compounds appropriately modified could represent a valid and versatile strategy.

In this review we provide an overview of the synthesized and pharmacological screened benzomorphan-based compounds, highlighting the influence of their structural modifications for interaction with opioid receptors.

2. Structure-activity relationships

On the basis of the resolution of amount of benzomorphan-based compounds into (−)- and (+)-antipode, pioneering investigations established that the (−)-(2*R*,6*R*,11*R*) configuration is preferred for opioid receptors interaction [13]. Indeed, it was demonstrated that the (−)-benzomorphans have identical (−)-morphine configuration. Although analgesic properties reside in (−)-benzomophans and (+)-(2*S*,6*S*,11*S*) antipodes possess different activity, a limited number of (+)- and (−)-*N*-substituted *N*-normetazocine derivatives. such as (+)- and (−)-N-2-phenylethyl *N*-normetazocine [(+)- and (−)-phenazocine] (Fig. 2), in spite of their stereochemistry, exhibited both σ1R and opioid receptors affinity but with marked differences [14].

It was also highlighted the critical importance of a) basic nitrogen and b) 8-OH group that, in the rigid benzomorphan scaffold, are at a distance comparable to that of endogenous opioid peptides [6]. Also, the substituents in the basic nitrogen and the modifications in the 8-OH group are determinant for opioid receptors recognition [3]. Contrarily to the morphine and morphinan series, in which the presence of 8-OH group is critical for opioid activity, the same trend was not found for the benzomorphan series [5]. Acetoxy or amine groups in lieu of the 8-OH afforded to an equivalent or increased analgesia [3–5]. When 8-OH was replaced with methyl group or halogens, an inverted trend was reported [5]. Concerning to *N*-substituent, the alkyl groups (from methyl to hexyl) improve opioid receptors interaction although a slight decrease was reported for the *N*-ethyl derivative. The introduction of *N*-cyclopropylmethyl, -allyl, -dimethyl allyl, -cyclobutylmethyl substituents, switches the functional profile from agonism to antagonism, as reported for morphans and morphinans [3–7].

2.1. Substitution on phenolic hydroxyl

Cyclazocine (±)-**1**, a KOR/MOR ligand, was undergone clinical evaluation and showed a short duration of action in humans. A goal in opioid research was to identify long-acting MOR and KOR compounds. Thus, Wentland et al. [15] synthesized (−)-cyclazocine (−)-**1** derivatives characterized by isosteric replacement of 8-OH with 8-NH_2 and 8-(substituted)-amino groups (Fig. 3) with the aim to retard O-glucuronidation and to increase duration of action.

The SARs on these compounds showed that the primary amino analogue (−)-**2** maintained high affinity for MOR and KOR with an increase of DOR selectivity, while compound (−)-**3**, with a secondary amino substituent containing a phenyl ring, was the most potent and selective KOR ligand of this series (Table 1). In mouse acetic acid writhing test, compounds (−)-**2** and (−)-**3** had a KOR-mediated antinociceptive effect similar to (−)-**1**. Moreover, they antagonized morphine-induced antinociception showing MOR antagonist properties [16]. Thus, 8-NH_2 and 8-(monosubstituted)-amino groups were effective in bioisosteric replacement of 8-OH in cyclazocine derivatives. Instead, the introduction of tertiary amino substituents in position 8 provided ligands with low affinity. These results highlighted the importance of H-bond interaction between the 8-NH, as well as the 8-OH, of the ligand (donor) and the opioid receptor (acceptor). Moreover, the improved MOR and KOR affinity profile of compound (−)-**3** evidentiated that the 8-(phenyl)-amino group, in addition to the H-bond interaction, could favorably interact with a hydrophobic receptor pocket.

Afterwards, Wentland et al. [17] synthesized 8-amino derivatives of cyclazocine (±)-**1**, ethylketocyclazocine (EKC) (±)-**4** and their respective enantiomers, ketocyclazocine and Mr2034 (−)-**5** (Fig. 4).

Their objective was to prepare an expanded series of 8-(substituted)-amino ligands with different benzomorphan core structures. In addition to 8-alkyl- or 8-aryl-amino groups, 8-heteroaryl-amino groups were introduced to probe potential H-bond donor/acceptor sites at MOR and KOR. In competitive binding experiments most of them showed K_i values in nanomolar range but higher than reference compounds. All synthesized compounds displayed a preference for MOR and KOR over DOR with the (−)-(2*R*,6*R*,11*R*)-isomers featured by better K_i values. Only the cyclazocine derivatives bearing NH(4-$CH_3OC_6H_4$), (±)-**6**, and NH(3-pyridinyl), (±)-**7**, groups at position 8 displayed high MOR ($K_i = 0.47$ and 0.6 nM, respectively) and KOR ($K_i = 0.29$ and 0.5 nM, respectively) affinity (Table 1). The significantly enhanced affinity of compounds (±)-**6** and (±)-**7** showed that MOR and KOR hydrophobic pocket could establish another H-bond interaction with the heteroaryl acceptor (e.g., 3-pyridinyl).

On the basis of cyclazocine scaffold, Wentland et al. [18] synthesized the long-acting benzomorphan 8-carboxamidocyclazocine (±)-**8** (8-CAC) and the 8-carboxamido analogue (±)-**9** of EKC (±)-**5** (Fig. 5).

The aim of this study was to identify a bioisoster of 8-OH that retained H-bond donating properties and improved pharmacokinetic properties. Both compounds (±)-**8** (8-CAC) and (±)-**9** showed high MOR and KOR affinity comparable to the lead compounds (Table 1). Moreover, the enantiomer of 8-CAC, active at opioid receptors, was (−)-(2*R*,6*R*,11*R*)-**8**. Compound (±)-**8** (8-CAC) stimulated the [^{35}S]GTPγS binding both at MOR and KOR ($EC_{50} = 4.9$ nM and 8.8 nM, respectively) [19]. In 55 °C warm-water tail-flick test (±)-**8** (8-CAC), i.c.v. injected, produced a significant antinociceptive effect and, administered after the selective opioid antagonists, β-FNA and norBNI, resulted a MOR/KOR agonist confirming the *in vitro* data. Analgesia was more pronounced in mouse writhing test where (±)-**8** (8-CAC), i.p. administered, produced antinociception for up to 15 h resulting a long-lasting analgesic in