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Benzomorphan Skeleton as Scaffold for Analgesic, Antiviral and Antitumoral drugs

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Abstract

Benzomorphan core is a versatile structure. In fact, it represented the skeleton of drugs with different mechanism of action, from opioid to σ1 receptor, from antiviral to antiproliferative.

Based upon these considerations, the design, synthesis and biological evaluation of benzomorphan-based compounds as putative antiviral and/or antitumoral drug candidates could represent a valid and versatile strategy.

Keywords: Benzomorphan, Antiviral, Antitumoral, Sigma-1, Opioid, Mu opioid receptor, Delta opioid receptor, Kappa opioid receptor.

Benzomorphan has been the subject of exploration in medicinal chemistry. Benzomorphan is a structure derived by structure-activity relationship (SAR) studies based on simplification of morphine skeleton[1]. In fact, benzomorphans are mostly known for their potential analgesic profile via opioid receptor interaction[2]. However, it is possible consider the benzomorphan structure a versatile scaffold. Modification and replacement of the functional group attached to the basic nitrogen and the hydroxyl phenolic group, as well as group change in position 6 or 7 of the benzomorphan skeleton (Figure 1) led to a different class of drugs which variably act on the opioid and sigma receptors, on the Na^+ channels and as antiviral.

For instance, Zenazocine[3] (WIN-42,964, Figure 2a) is an opioid analgesic in phase II clinical trials that acts as a partial agonist of the mu and delta opioid receptors (MOR and DOR). Similarly, Bremazocine[4] (Figure 2b) is a kappa opioid receptor (KOR) agonist related to pentazocine and possesses potent and long-lasting analgesic and diuretic effects. Alazocine ((-)-SKF-10,047, Figure 2c) [5] is the first drug discovered to act at sigma1 (σ1) receptor. Crobenetine[6] (Figure 2d) is a potent, selective and highly use-dependent Na^+ channel blocker. Moreover, NITD-2636 [7] is a benzomorphan based compound that displayed a broad spectrum of antiviral activity.

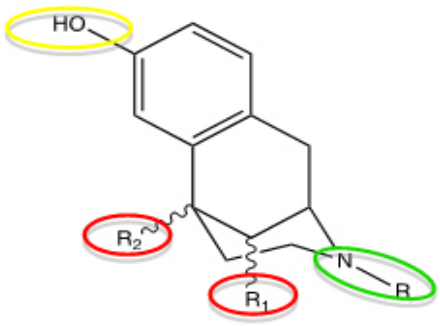

Figure 1: Possible structural modifications in the benzomorphan skeleton

Wang et al., by a systematic study consisting in the screening of libraries with diverse compound structures with antiviral activity, identified NITD-2636 (Figure 3). This last owns a benzomorphan core structure and exerts antiviral activity through suppression of viral RNA translation. Modification on the NITD-2636 structure, led to a series of derivatives that maintained the antiviral profile.

Interestingly, as previously reported the dextrorotatory benzomorphan (+)SKF-10047 binds σ1 receptor. σ1 receptor is highly expressed in various tumor cell types, including breast and prostate tumor cell lines [8,9]. Although the role of σ1 receptor in tumor cell biology remains unclear, it was demonstrated that some σ1 receptor putative antagonists inhibit tumor cell proliferation in vitro and inhibit tumor growth in mouse tumor xenograft experiments. Moreover, it was also proved that the protracted σ1 antagonist treatment could lead to apoptotic cell death [10,11]. Deactivation of signalling pathways downstream σ1 receptor was shown to have an effect on cell proliferation and survival and that cancerous cells are significantly more susceptible than non-cancerous cells to a negative regulation. Thus, synthesis of benzomorphan-based compounds with high affinity and selectivity versus σ1 receptor, depending on the efficacy profile, could be a useful strategy either to address the antitumor therapy or to label σ1 receptor that in tumor cell lines are over expressed and to obtain suitable tools to investigate the pharmacology of σ1 receptor.

Building upon these considerations, the design and synthesis of benzomorphan-based compounds opportunely modified could represent a valid and versatile strategy.

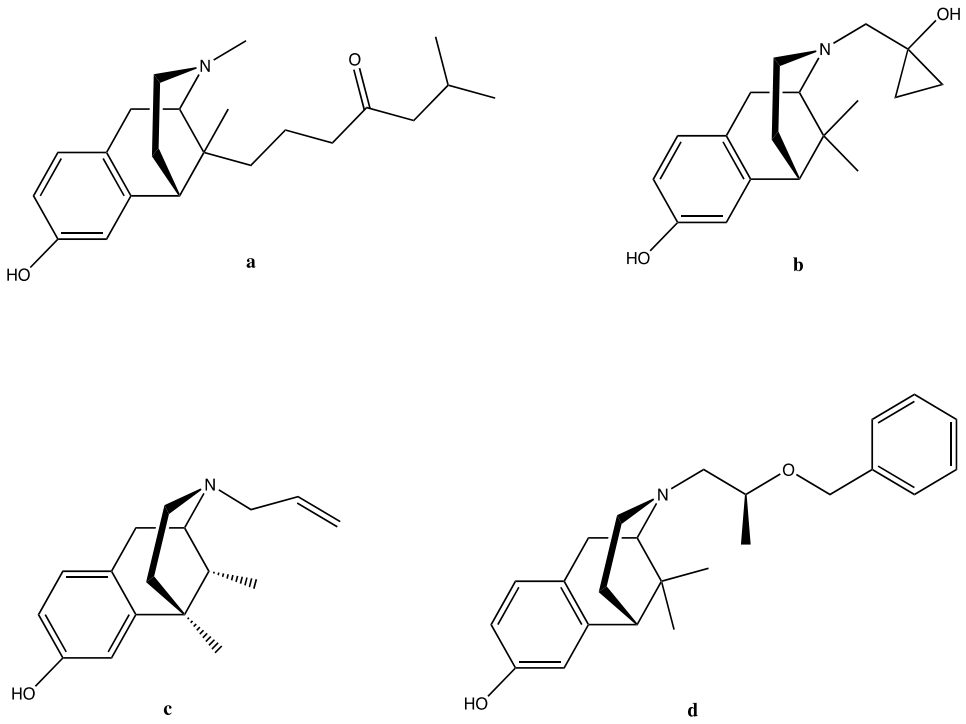

Figure 2: Zenazocine, Bremazocine, Alazocine and Crobenetine structures

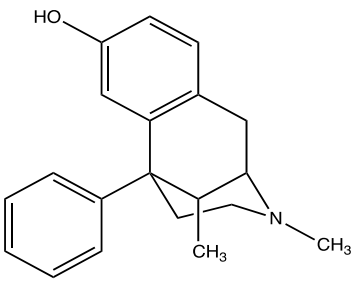

Figure 3: NITD-2636 structure

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