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### Benzomorphan Skeleton as Scaffold for Analgesic, Antiviral and Antitumoral drugs

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#### Abstract

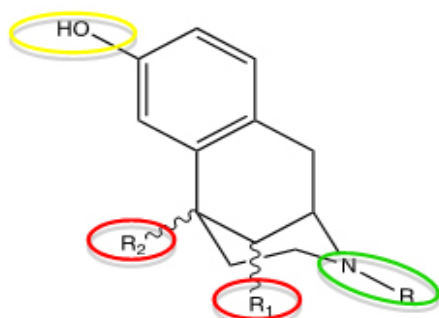
Benzomorphan core is a versatile structure. In fact, it represented the skeleton of drugs with different mechanism of action, from opioid to  $\sigma_1$  receptor, from antiviral to antiproliferative.

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  $\text{Na}^+$  channels and as antiviral.

For instance, Zenazocine[3] (WIN-42,964, Figure 2a) is an opioid



**Figure 1:** Possible structural modifications in the benzomorphan skeleton

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 ( $\sigma_1$ ) receptor. Crobenetine[6] (Figure 2d) is a potent, selective and highly use-dependent  $\text{Na}^+$  channel blocker. Moreover, NITD-2636 [7] is a benzomorphan based compound that displayed a broad spectrum of antiviral activity.

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  $\sigma_1$  receptor.  $\sigma_1$  receptor is highly expressed in various tumor cell types, including breast and prostate tumor cell lines [8,9]. Although the role of  $\sigma_1$  receptor in tumor cell biology remains unclear, it was demonstrated that some  $\sigma_1$  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  $\sigma_1$  antagonist treatment could lead to apoptotic cell death [10,11]. Deactivation of signalling pathways downstream  $\sigma_1$  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  $\sigma_1$  receptor, depending on the efficacy profile, could be a useful strategy either to address the antitumor therapy or to label  $\sigma_1$  receptor that in tumor cell lines are over expressed and to obtain suitable tools to investigate the pharmacology of  $\sigma_1$  receptor.

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

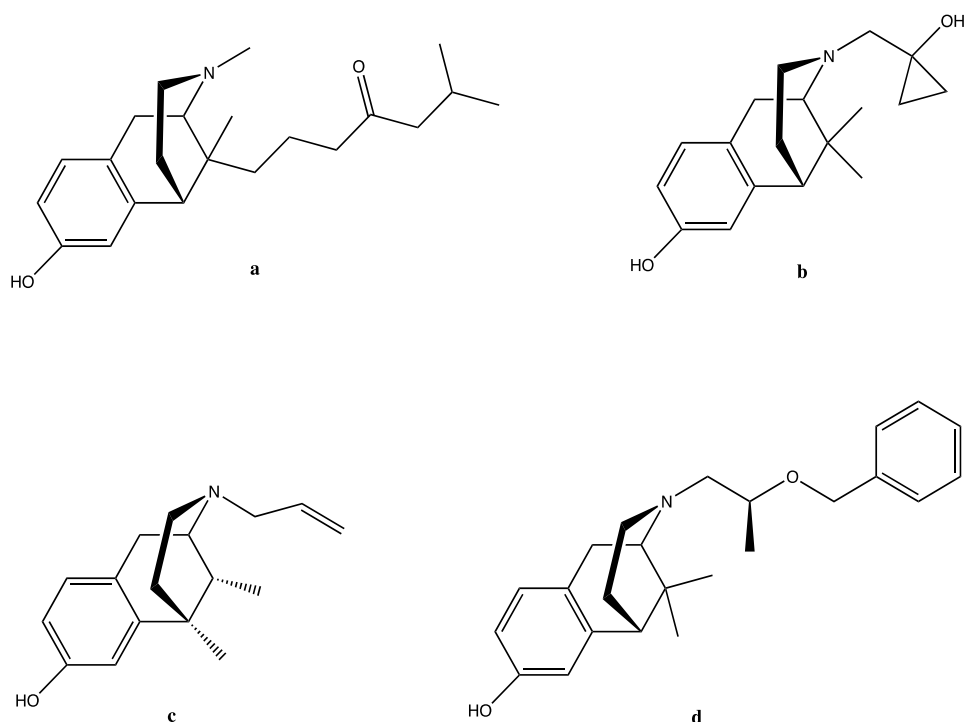


Figure 2: Zenazocine, Bremazocine, Alazocine and Crobenetine structures

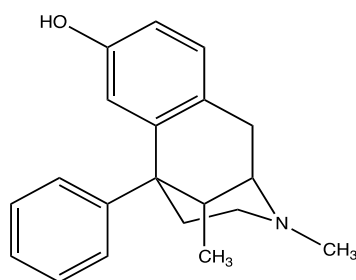


Figure 3: NITD-2636 structure

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