Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 17–18

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# A Sigma-1 Receptor Selective Analogue of BD1008. A Potential Substitute for (+)-Opioids in Sigma Receptor Binding Assays

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Received 3 September 1999; accepted 4 October 1999

**Abstract**—A simple, achiral monoamine sigma-1 ($\sigma_1$) receptor selective ligand ($\sigma_2 K_i/\sigma_1 K_i$ >2000) is described, which could replace the chiral (+)-pentazocine or dextrallorphan as a $\sigma_1$ masking agent in $\sigma_2$ binding assays. 

The sigma ($\sigma$) receptor was first described by Martin as a subtype of opioid receptors, based on the actions of racemic benzomorphans such as (±)SKF10,047.[1] However, the fact that (±)SKF10,047 is a nonspecific ligand led to confusing pharmacological interpretations, where the effects due to interaction with opioid and phencyclidine sites were viewed as $\sigma$ mediated effects.[2] It is now accepted that the $\sigma$ receptor system consists of at least two subtypes, namely $\sigma_1$ and $\sigma_2$, with pharmacological profiles distinct from any known receptor class.[3] The $\sigma_1$ receptor was recently cloned, and represents a novel protein.[4] The $\sigma_2$ receptor has yet to be cloned, and work is limited due to the paucity of selective ligands and the lack of a radiolabeled selective ligand for binding assays.[3] At present, $\sigma_1$ binding affinity is assessed by displacement of the $\sigma_1$ selective [$^3$H]-(+)-pentazocine,[3] and $\sigma_2$ affinity is assessed through the displacement of non-selective [$^3$H]-ditolylguanidine ([$^3$H]-DTG) in the presence of cold (+)-pentazocine or dextrallorphan to mask $\sigma_1$ sites.[3,5] Obviously, the use of a chiral material simply to block $\sigma_1$ sites is not ideal. Although the development of a $\sigma_2$ selective radiolabel is a major goal in this area, the current $\sigma_2$ procedure could be improved by the development of an inexpensive achiral ligand with high $\sigma_2/\sigma_1$ selectivity to block $\sigma_1$ sites. Herein, we report the initial preparation and evaluation of a novel monoamine (AC915) with the above characteristics and a $\sigma_2/\sigma_1$ selectivity of >2000-fold.

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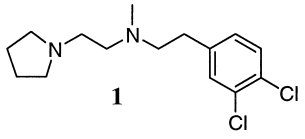
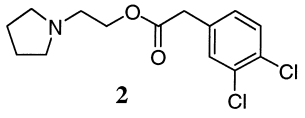
BD1008 (**1**) is a high affinity $\sigma_1$ and $\sigma_2$ ligand with great selectivity over other receptor systems (Table 1).[6] The fact that similar phenylpentylamines prepared by Glennon[7] displayed excellent $\sigma_1$ affinity, led to the conclusion that the central basic nitrogen is not essential for $\sigma_1$ affinity.[8] However, masking the central basic nitrogen as an amide, led to ligands of reduced $\sigma_1$ and $\sigma_2$ affinity,[9] showing that an amide is detrimental to $\sigma_1$ affinity in this series. Thus, considering that a simple and economical synthesis was required, it was decided to investigate the removal of the nitrogen completely and introduce an ester.



**1**



**2**

## Chemistry and Pharmacology

1-(2-Hydroxyethyl)pyrrolidine was coupled with 3,4-dichlorophenylacetic acid by the use of DCC and DMAP in $CHCl_3$ at ambient temperature overnight to give **2**, which was isolated by HCl extraction (1 M) and oxalic acid salt formation from acetone (mp 164–165 °C).[10]

0960-894X/00/$ - see front matter 
PII: S0960-894X(99)00590-9

**Table 1.** Binding affinities of 1, 2 and (+)-pentazocine at sigma receptors

| Compound | $K_i$ (nM) ± SEM | | |
|---|---|---|---|
| | $\sigma_1$[a] | $\sigma_2$[b] | $\sigma_2/\sigma_1$ |
| **2** (AC915) | 4.89 ± 0.29 | > 10,000 | 2040 |
| **1** BD1008 | 2.2 ± 0.65 | 8.10 ± 2.2 | 4 |
| (+)-Pentazocine | 3.1 ± 0.3 | 1542 ± 313 | 500 |

[a]Displacement of $^3$[H]-(+)-pentazocine.
[b]Displacement of $^3$[H]-DTG in the presence of dextrallorphan.

**2** was evaluated in competition assays at $\sigma_1$ and $\sigma_2$ sites (Table 1) using methods reported previously.[3,5]

These data show that **2** has only a 2-fold lower $\sigma_1$ affinity than BD1008, but the introduction of the ester has abolished $\sigma_2$ affinity, to give a compound of >2000-fold selectivity for $\sigma_1$ receptors. Thus, it appears that the central nitrogen of **1** is not essential for recognition at $\sigma_1$, a finding in agreement with Glennon,[7] but is essential for recognition at $\sigma_2$.

The removal of the central amine of BD1008, and replacement with an ester has yielded a highly-selective achiral $\sigma_1$ ligand, which can be easily and economically prepared without the need for chromatography. Thus, **2** (AC915) has the required properties to replace the expensive (+)-opioids as a masking agent in $\sigma_2$ binding assays.

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