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Discovery and optimization of a novel Neuromedin B receptor antagonist

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ABSTRACT

The discovery and parallel synthesis of potent, small molecule antagonists of Neuromedin B receptor based on the ary-hexahydro-dibenzodiazepin-1-one core is described.

In mammals, the bombesin family of G protein-coupled receptors consists of three subtypes:[1] Neuromedin B receptor (NMBR, BB_1),[2] Gastrin-releasing peptide receptor (GRPR, BB_2),[3] and BRS-3.[4] While high affinity endogenous ligands for BRS-3 are unknown, Neuromedin B (NMB) and Gastrin-releasing peptide (GRP) were discovered in the early 1980s.[5,6] NMB and GRP share sequence homology in the C-terminal region and mediate a range of biological mechanisms via action at their receptors. These include CNS-related responses such as thermoregulation,[7] satiety,[8] control of circadian rhythm,[9] and modulation of fear and anxiety responses,[10,11] as well as peripheral functions including macrophage activation[12] and gastrointestinal hormone release.[13] In addition, there is considerable literature suggesting a role in control of cellular proliferation.[14]

Previously, we and others described the discovery of small molecule ligands for NMBR.[15] In an effort to develop tool compounds to define how these receptors influence pathological processes, we report here the identification and optimization of potent and selective NMBR antagonists. The initial lead in this series, benzodiazepine **1** (Fig. 1), was identified as an NMBR antagonist from a high-throughput screen (HTS). Compound **1** displayed encouraging potency in a NMB displacement assay (IC_{50} = 300 nM)[16] and was selective (10 μM or greater) against a panel of other GPCR targets, including GRPR and other neuropeptide receptors. The benzodiazepine scaffold is highly amenable to diversification using parallel synthesis, and we were able to rapidly prepare and evaluate over 200 compounds as part of a series of small libraries to facilitate the discovery of a novel, potent spirocyclic derivative. Data on the most representative compounds are presented herein.

The synthesis of benzodiazepines is well documented.[17] **A** series of libraries based on **1** was prepared as described in Scheme 1 using the modified method reported by Blache et al.[17b] The synthesis began with a condensation between a 2-nitroaniline (**A**) and a 1,3-cycloalkane dione. The resulting enamine (**B**) was either methylated or left unchanged before reduction to the diamine (**C**).[18] Formation of the seven-member ring was accomplished via a Mannich-type cyclization between the diamine and an aryl aldehyde, this cyclization was carried out at room temperature in ethanol containing a catalytic amount of acetic acid.[19] Alkylation of the resulting secondary amine (D) was easily effected by treatment with an aldehyde and $Na(AcO)_3BH$.[20] All of the final products were purified by preparative HPLC.[21]

An analysis of the preliminary SAR derived from the HTS data suggested that the methyl substituent on the fused aryl of **1** is re-

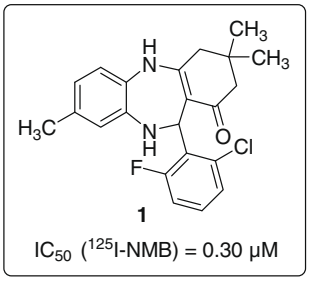

Figure 1.

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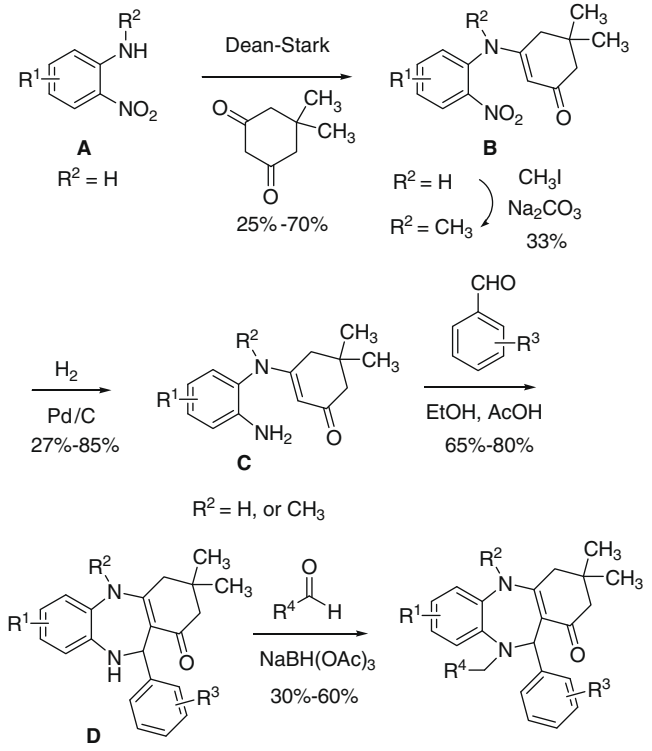
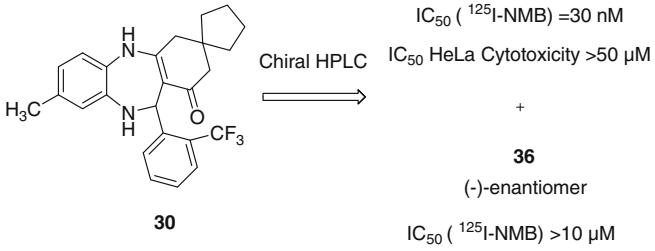


Scheme 1.

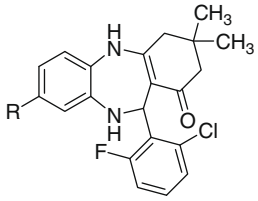


Scheme 2.

quired for binding affinity. Therefore, in the first library alternatives to the methyl group were examined. As the data in Table 1 show, efforts to replace the methyl group with polar functions yielded ligands with diminished binding affinity. However electron-deficient functions were tolerated, as exemplified by the CF_3 and Cl analogs **2** and **3**. For subsequent libraries, we elected to maintain CH_3 substitution as R.

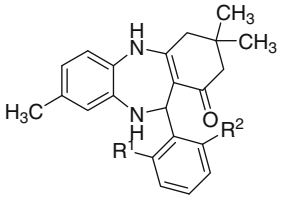
A second library focused on variants of the exocyclic phenyl motif. The data in Table 2 summarize the results of this study. Compounds **12**, **15** and **17** nicely illustrate the impact on binding affinity of the exocyclic aryl substituents of **1**. Compound **12**, for instance, shows that removal of the fluorine atom has a minimal effect on binding. However when the chlorine atom is removed, as in compound **15**, binding affinity is diminished fourfold. The reduced binding affinity of the difluoro compound **16** shows that the electron withdrawing nature of the substituents is not a key factor influencing binding. This point is further supported by compound **10**, which bears a space-filling substituent on a relatively electron rich aryl.

Table 1



ID #	R	IC $_{50}$ (^{125}I-NMB) (μM)
1	CH_3	0.30
2	CF_3	0.37
3	Cl	0.86
4	CF_3O	1.3
5	CN	1.3
6	CH_3O	2.2
7	COOH	10
8	OH	10
9	$CONH_2$	10

Table 2

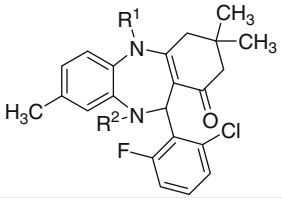


ID #	R^1	R^2	IC_{50} (^{125}I-NMB) (μM)
1	F	Cl	0.30
10	H	CH_3S	0.20
11	H	CF_3	0.25
12	H	Cl	0.28
13	H	NO_2	0.55
14	H	CH_3O	1.1
15	H	F	1.3
16	F	F	2.5
17	H	H	6.9

The next series of compounds was prepared to examine the effects of alkylating the benzodiazepine nitrogen atoms. The data, summarized in Table 3, show that methylation at R^1 resulted in a dramatic loss of affinity (**18**), while alkylation at R^2 conferred a marginal increase in potency (**19**, **20** and **21**).

We next turned our attention to the alicyclic portion of the molecule (Table 4). Significant loss of affinity was observed for the unsubstituted (**25**) and ring contracted (**29**) analogs, indicating that the cyclohexyl ring and the geminal dimethyl are important contributors to binding. Moreover, no improvements were ob-

Table 3



ID #	R^1	R^2	IC_{50} (^{125}I-NMB) (μM)
1	H	H	0.30
18	CH_3	H	10
19	H	CH_3	0.17
20	H	C_2H_5	0.18
21	H	*i*-C_4H_9	0.15