HHS Public Access

Author manuscript

ChemMedChem. Author manuscript; available in PMC 2017 March 17.

Published in final edited form as:

ChemMedChem. 2016 March 17; 11(6): 556–561. doi:10.1002/cmdc.201500551.

Norbenzomorphan Framework as a Novel Scaffold for Generating Sigma 2 Receptor/PGRMC1 Subtype Selective Ligands

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Abstract

A novel structural class with high affinity and subtype selectivity for the sigma 2 receptor has been discovered. Preliminary structure affinity relationship data are presented showing that 8-substituted 2,3,4,5-tetrahydro-1,5-methanobenzazepine (norbenzomorphan) derivatives elicit modest to high selectivity for the sigma 2 receptor over the sigma 1 receptor. Indeed, piperazine analog 8-(4-(3-ethoxy-3-oxopropyl)piperazin-1-yl)-1,3,4,5-tetrahydro-1,5-methanobenzazepine-2-carboxylate (SAS-1121) is 574-fold selective for the sigma 2 receptor over the sigma 1 receptor, thereby establishing it as one of the more subtype selective sigma 2 binding ligands reported to date. Emerging evidence has implicated the sigma 2 receptor in multiple health disorders, so the drug-like characteristics of many of the selective sigma 2 receptor ligands disclosed herein, coupled with their structural similarity to frameworks found in known drugs, suggest that norbenzomorphan analogs may be promising candidates for further development into drug leads.

Graphical Abstract

Keywords

Sigma 2 receptor; norbenzomorphan; 1,5-methanobenzazepine; Sig2R/PGRMC1

1. Introduction

In a series of investigations directed toward discovering biologically active small molecules, we developed a general platform for the rapid synthesis of small collections of functionalized heterocyclic scaffolds that can be further diversified by cross-coupling reactions and refunctionalizations [1,2]. One class of heterocycles that piqued our interest is

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Associated Content

General experimental procedures and full characterization is provided for all new, representative compounds. ^{1}H NMR and MS data are provided for all other new compounds.

the substituted norbenzomorphan ring system (Fig. 1, red highlight in **1**–**4**) [2], which has drug-like features, including low molecular weight and conformational rigidity [3,4]. Investigational compounds embodying this framework include **1**, which induces antinociception in an animal pain model [5] and **2**, which inhibits acetylcholinesterase *in vivo* [6]. Screening novel norbenzomorphans prepared in our lab led to the discovery of hit compounds with potentially useful medicinal properties. For example, amide **3** is an inhibitor of striatal-enriched protein tyrosine phosphatase (STEP) [2b], an enzyme that is overactive in Alzheimer's disease (AD) [7], whereas benzylamine **4** is an antagonist of dopamine-3 [8], a target currently being evaluated for treating addiction [9].

The structural resemblance of the norbenzomorphan framework to the closely related scaffolds in psychoactive drugs, including Talwin® (**5**) and Chantix® (**6**), suggests that norbenzomorphan derivatives may possess the favorable pharmacokinetic attributes required of leads for treating neurological disorders. Accordingly, a small set of norbenzomorphans were screened against a comprehensive panel of CNS-based proteins at the Psychoactive Drug Screening Program (PDSP; UNC-Chapel Hill) [10]. Although a number of compounds were identified that exhibit selective binding profiles, we were particularly intrigued by those with high affinity and subtype selectivity for sigma receptors [11], which had not been associated with this class of compounds.

Sigma receptors are a distinct class of non-GPCR receptors that are involved in a variety of critical cellular processes, including regulation of ion concentration, stabilization of cell surface receptors, and induction of apoptosis [12]. Two receptor subtypes, sigma 1 receptor (Sig1R) and sigma 2 receptor (Sig1R), have been identified, and whereas the former has been cloned and sequenced, the latter is not well characterized. Sig2R was reported to reside in the progesterone receptor membrane component 1 (PGRMC1) [13,14], and although this finding has not been universally accepted [15,16], the term Sig2R/PGRMC1 is commonly used to refer to this receptor, thus this convention will be adopted in this report.

This controversy notwithstanding, there is accumulating evidence that Sig2R/PGRMC1is involved in a number of disease states [17,18]. For example, Sig2R/PGRMC1is highly overexpressed in proliferating tumor cells and has been identified as an attractive target for cancer diagnostics. Because agonists of Sig2R/PGRMC1induce cell death in a variety of cancer cell lines, they are also garnering increasing interest as potential chemotherapeutics. Moreover, in several preliminary experiments, we have discovered that ligands that bind to Sig2R/PGRMC1 can exhibit CNS effects and traverse the blood brain barrier (BBB). For example, we discovered that several antagonists of σ2R are neuroprotective in a *C. elegans* model of neurodegeneration [19,20]. In a preliminary pharmacokinetic assessment, we also found that SAS-0132 (**32**) achieves a brain concentration of 3.8 μM within 3 h after a single subcutaneous injection (10 mg/kg) [11,21]. Sig2R/PGRMC1 was recently implicated in AD because it appears to mediate amyloid-β induced-synaptotoxicity [22,23]. Toward discovering brain penetrant Sig2R/PGRMC1 binding ligands that may hold promise for treating a spectrum of CNS disorders, we now describe a set of substituted norbenzomorphans that exhibit high selectivity for Sig2R/PGRMC1over Sig1R.

2. Chemistry

As a point of embarkation, we prepared the key intermediate **12** via a Mannich-type multicomponent assembly process (MCAP) followed by sequential ring closing metathesis, Heck cyclization, and olefin reduction as previously described (Scheme 1) [2b]. Scaffold **12** proved to be well-suited for generating a variety of analogs, including those represented by general structure **13** (Fig. 2). The aryl chloride functional handle present in **12** enabled derivatization via palladium catalyzed cross-coupling reactions to deliver analogs having a range of electrostatic properties and varying degrees of lipophilicity, such as the anilines **14**–**16** and the biaryls **21**–**23** (Scheme 2). The cyclic secondary amines piperidine, piperazine, and morpholine were selected as coupling partners in Buchwald-Hartwig reactions to provide analogs having amino groups at C(8) (Fig. 2) of the norbenzomorphan nucleus. Six-membered, cyclic amines were used in these studies to minimize conformational variables amongst the different aryl amino analogs, which vary primarily in the Lewis basic nature of the C(8) substituent. Boronic acid coupling partners for the Suzuki reactions were chosen to provide both electron-rich and electron-deficient biaryl products (Scheme 2). The Cbz group on N(2) (Fig. 2) of **14**, **16** and **21–23** was then removed using iodotrimethylsilane (TMSI) followed by either acidic or basic workup as previously described [2] to give the corresponding tertiary *N*-benzyl compounds **19**, **20**, **26**, and **27** and the secondary amines **17, 18, 24**, and **25.**

The substituents on the two nitrogen atoms of **15** were then diversified. In the event, the secondary amino group on the piperazine ring of **15** was first *N*-alkylated using standard procedures to give tertiary amines **28–30**, SAS-1121 (**31**), and SAS-0132 (**32**) (Fig. 3A). Substitution at the carbamoyl nitrogen atom of **32** was then varied by removing the Cbz group using TMSI followed by an acidic workup to give **33** (Fig. 3C). Subsequent *N*-sulfonylation or *N*-acylation of **33** under standard conditions delivered **34–37**. Reductive amination of **17** and **18** using several aryl aldehydes and sodium triacetoxyborohydride [$Na(OAc)_3BH$] provided **38–40** (Fig. 3B). Similarly, reductive aminations of **21** and **22** led to analogs **41–44** (Fig. 3D).

3. Pharmacology and Drug-like Attributes

These novel norbenzomorphans were then screened against a comprehensive panel of CNS-based proteins at the PDSP (Table 1) [10]. A cursory examination of the results in Table 1 reveals a number of compounds that exhibit high affinity and subtype selectivity for Sig2R/PGRMC1versus Sig1R. Indeed, Sig2R/PGRMC1 affinity and subtype selectivity is maintained over a considerable range of substituents on the aromatic ring and the nitrogen atom of the norbenzomorphan nucleus (*vide infra*). Although prevailing models of the putative pharmacophore for Sig2R/PGRMC1 binding are generally restricted to a specific ligand class [24], the features that are common to structurally diverse Sig2R/PGRMC1 ligands (*e.g.*, an ionizable nitrogen atom, a hydrogen bond acceptor, and hydrophobic aromatic residues) are present in the vast majority of these norbenzomorphans [25].

A brief summary of the results presented in Table 1 is instructive. Within the morpholine series comprising compounds **16**, **20**, **39**, and **40**, there appears to be a requirement for a

second basic nitrogen atom in the molecule. This tentative assessment is based upon the observation that **16** does not bind to the receptor, whereas the two *N*-benzyl derivatives **20** and **40** exhibit modest Sig2R/PGRMC1 affinity (1,034 nM and 1,258 nM) and a 4-fold preference for σ2R relative to σ1R. The 3,5-dichlorobenzyl analog **39** benefits from a large increase in Sig2R/PGRMC1 binding affinity (92 nM) coupled with a 32-fold increase in selectivity for Sig2R/PGRMC1 over Sig1R. The aryl piperidine derivative **19** displays moderate σ2R affinity (318 nM) and about 8-fold subtype selectivity favoring Sig2R/PGRMC1, and replacing the benzyl group of **19** with a 3-chlorobenzyl substituent (*e.g.*, **38**) affects a marginal decrease in both Sig2R/PGRMC1 affinity and selectivity. For the series of biaryl compounds **27** and **41–44**, SigR affinity appears to be markedly dependent upon the size of the alkyl group at N(2). For example, the *N*-methyl derivatives **41** and **43** exhibit significantly enhanced binding affinity at both Sig1R and Sig2R/PGRMC1 relative to **42** and **44**.

When the C(8) position of the norbenzomorphan ring is substituted with a piperazino moiety, Sig2R/PGRMC1 binding affinity is typically high, and the subtype selectivity can be tuned by altering either R^2 or the alkyl group on the aliphatic nitrogen atom of the piperazine ring. Changing the nature of the alkyl group leads to only modest variations in Sig2R/PGRMC1 affinities, whereas the effects on Sig1R affinity are more pronounced. This is dramatically illustrated by comparing SAS-1121 (**31**), which exhibits 574-fold selectivity for Sig2R/PGRMC1, with other members of this series. To our knowledge, this represents one of the most selective Sig2R/PGRMC1 ligands reported to date [26]. Whereas replacing the Cbz group of SAS-0132 (**32**) with a hydrocinnamoyl (*e.g.*, **36**) or an allyloxycarbonyl (*e.g.*, **37**) moiety leads to a loss in σ2R binding affinity and selectivity, substituting a 3,5-dichlorobenzenesulfonamide group for Cbz affords a 2- to 3-fold increase in Sig2R/PGRMC1 binding affinity and selectivity. Notably, the corresponding *nor*-chloro analog **35** displays much lower affinity for both SigR subtypes, and the presence of a secondary amino group (*e.g.*, **33**) completely abolished binding at Sig1R and Sig2R/PGRMC1.

The binding affinities for the compounds in Table 1 reveal that an array of different substituents at R^1 and R^2 are tolerated in ligands having modest to excellent preference for Sig2R/PGRMC1 over Sig1R, and a number of compounds exhibit < 50 nM affinity for Sig2R/PGRMC1. Notably, many compounds display low affinity relative to Sig2R/PGRMC1 at a broad range of other CNS proteins, including serotonin, adrenergic, dopamine, opioid, and neurotransmitter transporters (See Table S1, Supplementary Information). Some compounds, however, display significant affinity for non-sigma binding sites. For example, **34** exhibits high affinity for $5HT_{1D}$ (K_i = 195 nM), $5HT_6$ (K_i = 82 nM), and α_{2a} (K_i = 162 nM), and **41** binds with sub-micromolar affinity to α_{2c} (K_i = 755 nM) and NET (K_i = 524 nM). As might be expected, the more promiscuous ligands are typically highly lipophilic (*i.e.*, ClogP > 5) [27].

A majority of the sigma ligands described herein have properties suggestive of moderate solubility and good membrane- and BBB permeability [28]. For example, the ClogD (pH 7.4) values range from 2.9–4.5 for the bulk of the compound set, so a high degree of CNS exposure may be anticipated (See Table S2, Supplementary Information). This prediction is supported by the observation that SAS-0132 (**32**) is highly brain penetrant. Moreover,

ligands in this collection lack a highly basic amine function (*e.g.*, $pK_a > 9$), which can be predictive of low hERG channel inhibition [29]. These data collectively suggest that R^1 and R^2 on the norbenzomorphan scaffold can be tuned for Sig2R/PGRMC1 binding to generate promising leads for drug discovery.

4. Conclusion

In summary, a modular synthetic platform was used to rapidly access a variety of substituted norbenzomorphans that exhibit high potency and selectivity for Sig2R/PGRMC1 relative to Sig1R. Notably, it appears to be possible to modulate SigR subtype selectivity by varying the groups at C(8) and N(2) of the norbenzomorphan scaffold. SAS-1121 displays a 574-fold preference for Sig2R/PGRMC1 over Sig1R, suggesting that exceptional Sig2R/PGRMC1 subtype selectivity can be achieved. A representative ligand, SAS-0132, is highly brain penetrant [11] and, like many of the Sig2R/PGRMC1 subtype selective ligands disclosed herein, it has molecular attributes likely to impart desirable absorption, distribution, metabolism, and excretion (ADME) properties [3,4]. Although the important question of whether Sig2R/PGRMC1 can be safely targeted in man remains unanswered, it is significant that the EU approved anxiolytic/antidepressant opipramol has appreciable affinity for Sig2R/PGRMC1 and has been safely used for decades [30]. Previous clinical trials with investigational compounds that bind to Sig2R/PGRMC1, such as siramesine and rimcazole, suggest that pharmacological modulation of Sig2R/PGRMC1 may be safe in man [31]. Ongoing clinical trials with drug candidates that bind to Sig2R/PGRMC1 will further determine if the receptor is drug-gable. For instance, Minerva Neuroscience® has advanced MIN-101 to phase IIb trials for schizophrenia [32], and Cognition Therapeutics® recently launched a phase I study with their AD drug lead, Cog1812 [33]. The discovery of novel Sig2R/PGRMC1 ligands with drug-like features is thus an important component to validating the clinical significance of this receptor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (GM 86192 and GM 24539) and the Robert A. Welch Foundation (F-0652) for their generous support of this work. We are also grateful to Dr. Richard Pederson (Materia, Inc.) for catalyst support and to Dr. Mehrdad Shamloo (Stanford Behavioral and Functional Neuroscience Lab) for conducting pharmacokinetic studies of **32**. Determination of receptor binding profiles was generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2013-00017-C (NIMH PDSP). The NIMH PDSP is Directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA.

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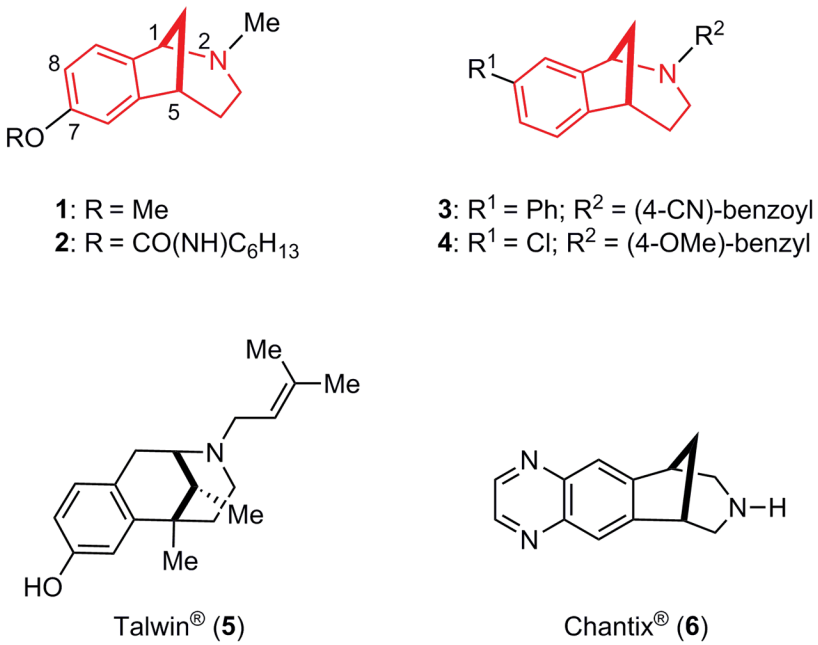
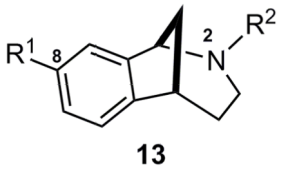


Figure 1.

Norbenzomorphans **1**-**4** and structurally-related psychoactive drugs **5** and **6**.



13

R^1 = piperazinyl; morpholinyl; aryl

R^2 = acyl; sulfonyl; alkyl

Figure 2.

A variety of norbenzomorphan analogs prepared via cross-coupling and *N*-derivatization reactions.

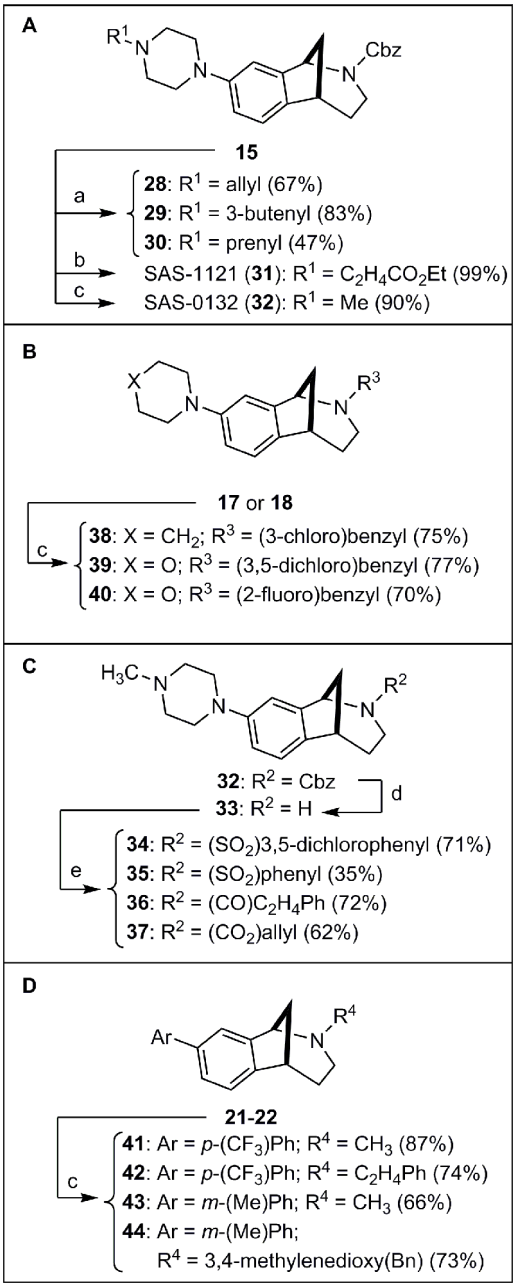
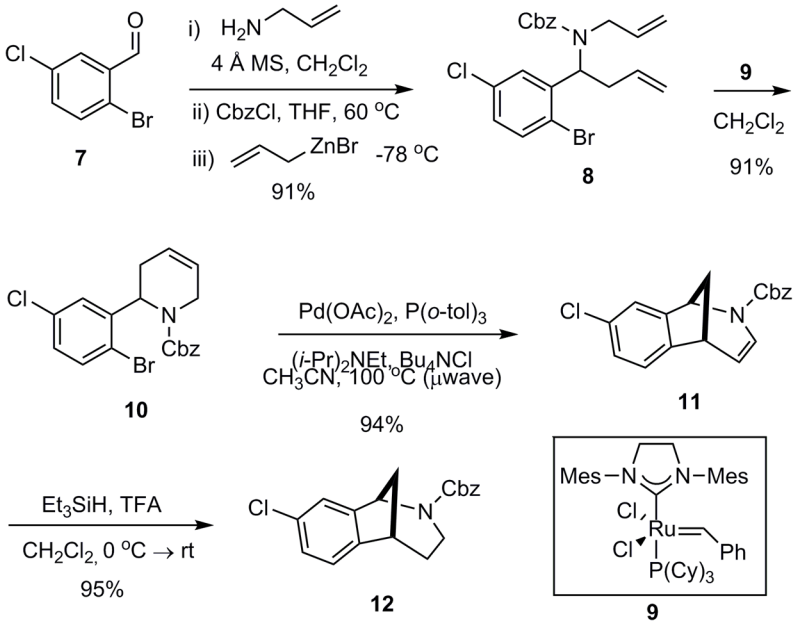


Figure 3.

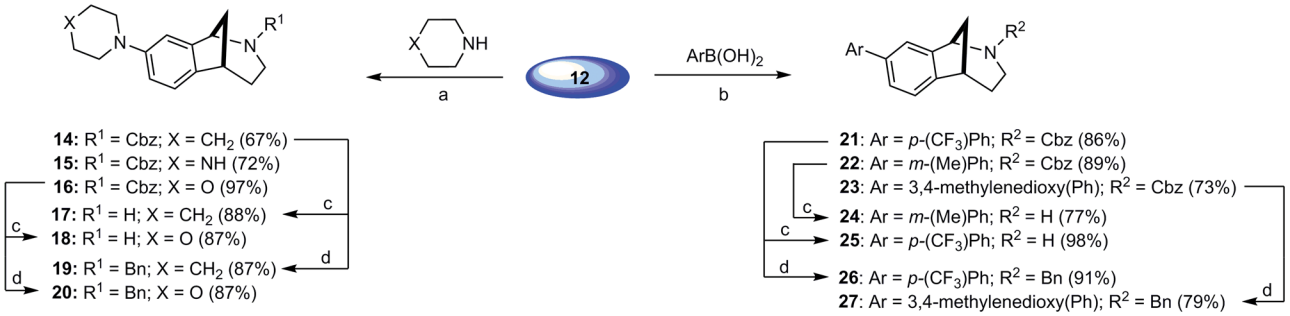
N-Functionalization Reactions.

Nitrogen functionalization reactions. *Reagents and Conditions:* (a) alkyl bromide, CH_3CN, K_2CO_3; (b) ethyl acrylate, EtOH; (c) aldehyde, $Na(OAc)_3BH$, CH_3COOH, CH_2Cl_2; (d) TMSI, CH_2Cl_2, 0 °C → rt, then HCl; (e) acyl or sulfonyl chloride, CH_2Cl_2, Et_3N. **A.** Alkylation and reductive amination of piperazine **15. B.** Reductive amination of 2° amines **17** or **18. C.** Acylation and sulfonylation of 2° amine **33. D.** Reductive amination of biaryls **21** or **22**.



Scheme 1.

Synthesis of chloro norbenzomorphan **12**.



Scheme 2.

Cross-coupling reactions of aryl chloride **12** to generate aniline and biaryl analogs.[a]

[a]Reagents and Conditions: a) $Pd(OAc)_2$, JohnPhos®, NaO*t*-Bu, toluene, 100 °C. b) $Pd[P(t\text{-}Bu)_3]_2$, Cs_2CO_3, 1,4-dioxane, 100 °C. c) TMSI, CH_2Cl_2, 0o C → rt, then HCl. d) TMSI, CH_2Cl_2, 0o C → rt, then $NaHCO_3$ (aq).

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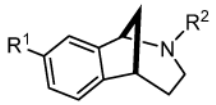
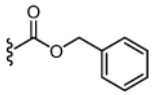
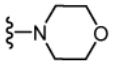
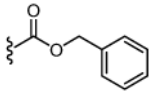
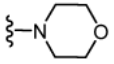
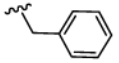
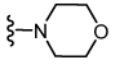
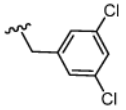
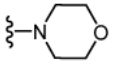
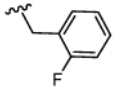
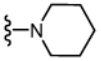
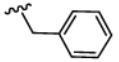
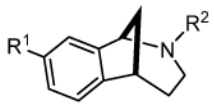
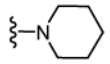
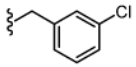
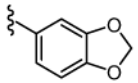
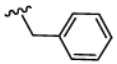
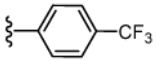
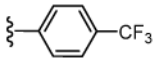
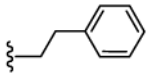
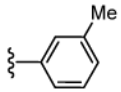
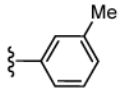
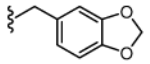
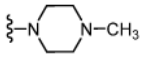
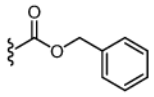
Table 1

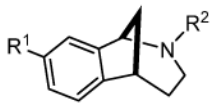
Sigma receptor affinity of norbenzomorphan analogs.

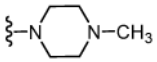
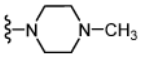
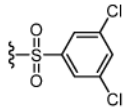
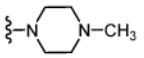
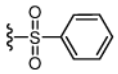
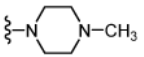
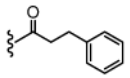
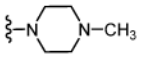
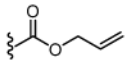
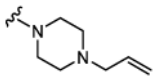
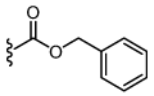
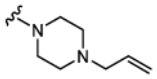
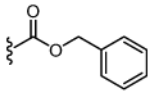


Cmpd	R^1	R^2	Sig1R K_i(nM)[a] pK_i ± SEM[b]	Sig2R K_i(nM) pK_i ± SEM	K_i(Sig1R)/K_i(Sig2R)
12	Cl		* [c]	*	-
16			*	*	-
20			3,777 5.42 ± 0.09	1,034 5.99 ± 0.07	4
39			2,975 5.53 ± 0.09	92 7 ± 0.1	32
40			4,544 5.34 ± 0.09	1,258 5.9 ± 0.1	4
19			2,429 5.61 ± 0.06	318 6.5 ± 0.1	8



Cmpd	R^1	R^2	Sig1R K_i(nM)[a] pK_i ± SEM[b]	Sig2R K_i(nM) pK_i ± SEM	K_i(Sig1R)/K_i(Sig2R)
38			3,519 5.5 ± 0.1	746 6.1 ± 0.1	5
27			3,039 5.5 ± 0.1	723 6.14 ± 0.09	4
41		CH_3	156 6.81 ± 0.09	43 7.36 ± 0.08	4
42			1,058 6.0 ± 0.1	166 6.8 ± 0.1	6
43		CH_3	391 6.41 ± 0.08	133 6.88 ± 0.07	3
44			4,612 5.34 ± 0.08	828 6.08 ± 0.08	6
SAS-0132 (**32**)			497 6.31 ± 0.06	71 7.1 ± 0.1	7



Cmpd	R^1	R^2	Sig1R K_i(nM)[a] pK_i ± SEM[b]	Sig2R K_i(nM) pK_i ± SEM	K_i(Sig1R)/K_i(Sig2R)
33		H	*	*	-
34			442 6.36 ± 0.06	27 7.58 ± 0.08	16
35			*	764 6.12 ± 0.07	-
36			294 6.53 ± 0.08	357 6.45 ± 0.06	1
37			2105 5.68 ± 0.07	442 6.37 ± 0.07	5
28			589 6.23 ± 0.06	34 7.47 ± 0.08	17
29			172 6.76 ± 0.05	16 7.79 ± 0.05	11

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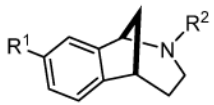
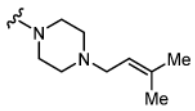
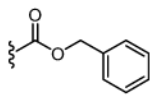
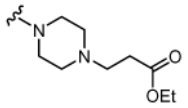
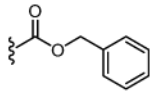


Cmpd	R[1]	R[2]	Sig1R K_i(nM)[a] pK_i ± SEM[b]	Sig2R K_i(nM) pK_i ± SEM	K_i(Sig1R)/K_i(Sig2R)
30			62 7.21 ± 0.05	23 7.64 ± 0.07	3
SAS-1121 (**31**)			9294[d] 5.1 ± 0.1	16.2[e] 7.8 ± 0.16	574

[a] K_i values obtained from non-linear regression of radioligand competition binding isotherms;

[b] SEM calculated for pK_i;

[c] Less than 50% inhibition of radioligand binding with 10 μM test ligand;

[d] average of two IC_{50} determinations;

[e] average of three IC_{50} determinations.