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1,3-Dihydro-2,1,3-benzothiadiazol-2,2-diones and 3,4-dihydro-1*H*-2,1,3-benzothidiazin-2,2-diones as ligands for the NOP receptor

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Abstract—A series of 1,3-dihydro-2,1,3-benzothiadiazol-2,2-diones (**I**) and 3,4-dihydro-1*H*-2,1,3-benzothidiazin-2,2-diones (**II**) were prepared. While the five-member ring series (**I**) did not show good affinity for opioid receptors, the six-member ring series (**II**) exhibited extremely high affinity and selectivity for the NOP receptor and showed full agonist activity, as determined by stimulation of GTPγ[^{35}S] binding.

1. Introduction

In 1994, several research groups identified a new opioid receptor to join the three already well-known MOP, KOP and DOP (formerly mu, kappa and delta) receptors.[1,2] The following year the endogenous, peptide ligand N/OFQ (nociceptin/orphanin FQ) was paired with it.[3] Although this new NOP receptor (previously named ORL-1) is a member of the G-protein coupled receptor superfamily with ca. 47% identity to the classical opioid receptors, typical opioid ligands (small molecule or peptide) do not bind to the NOP receptor with appreciable affinity. In addition, N/OFQ itself has little affinity for the other opioid receptors.

NOP receptors have been identified both centrally and peripherally in several mammalian species, including humans.[4] They have been implicated in a number of biological processes including pain and analgesia, learning and memory, motor performance, feeding, cough, cardiovascular function and anxiety.[5] In rodents N/OFQ has been shown to block conditioned place preference to morphine, while not producing any place preference on its own. Moreover, in microdialysis experiments performed in rats, icv administration of N/OFQ partially inhibits serotonin and dopamine release in the nucleus accumbens, suggesting an involvement in reward/abuse behavior.[6]

Given the potential usefulness of the NOP receptor and the inherent problems in working with peptide ligands (e.g. lack of permeability, metabolic instability), it is not surprising that reports of small molecule NOP receptor ligands have appeared in the literature (Fig. 1). Structural types showing either agonist (**1**,[7] **2**,[8] and **5**[9]) or antagonist (**3**,[10] **4**,[11] **6**,[12] and **7**[13]) activity at the NOP receptor, or both (**8**[14] and **9**[15]), have been reported. Recently, several structural requirements associated with agonist and/or antagonist function have been proposed.[15]

As part of a program targeting small molecules as potential new therapeutic agents for the treatment of pain, we have identified several structures showing activity at the NOP receptor. In this paper we wish to report the synthesis and biological activity for two of these structural types.

2. Design of NOP receptor ligands

In planning potential ligands for the NOP receptor, examination of known ligands led us to a working

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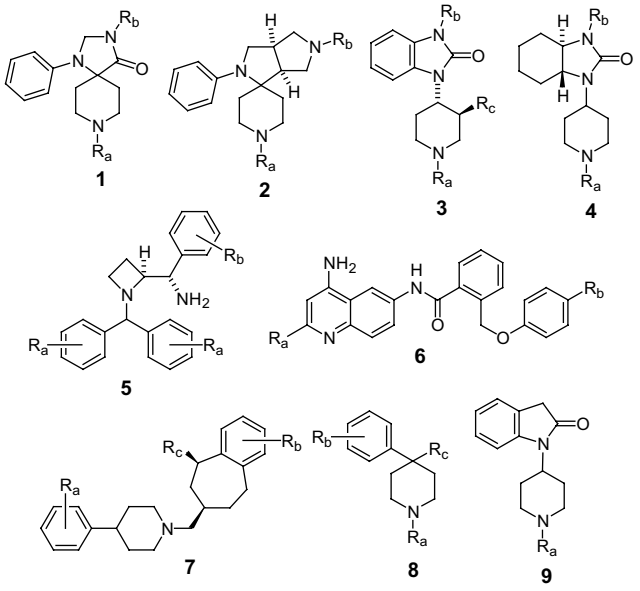


Figure 1. Structures of representative NOP receptor ligands.

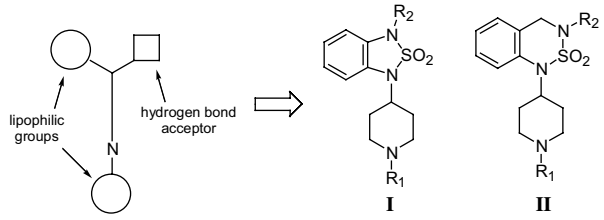


Figure 2. Working model leading to 1,3-dihydro-2,1,3-benzothiadiazol-2,2-diones (**I**) and 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-diones (**II**).

model consisting of a basic nitrogen at one end of the molecule, to which is attached a lipophilic tail group (Fig. 2). At the other end of the molecule there appears to be the requirement for a second lipophilic portion (not necessarily aromatic, e.g. **4**). In addition, at this end of the molecule there also appears to be the preference for a hydrogen bond acceptor.[16–18] We chose to investigate the use of an SO_2 group as a hydrogen bond acceptor. The incorporation of an SO_2 group has the potential to influence metabolic stability, bioavailability and permeability, as well as binding and functional activity.[19] Based upon this, a series of 1,3-dihydro-2,1,3-benzothiadiazol-2,2-diones (**I**) and 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-diones (**II**) were prepared.

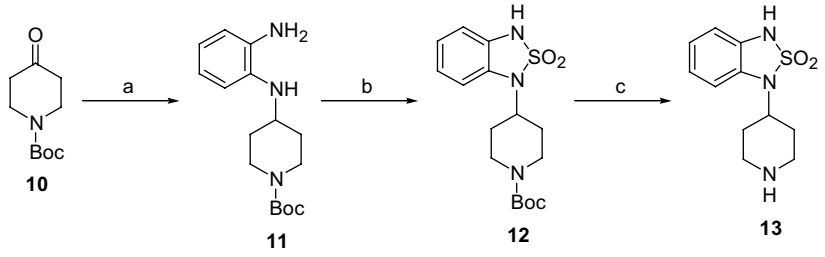
3. Synthesis and screening of NOP receptor ligands

Our approach to the synthesis of 1,3-dihydro-2,1,3-benzothiadiazol-2,2-diones and 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-diones as ligands for the NOP receptor involved synthesis of the two head groups **13** and **18** (Schemes 1 and 2, respectively),[20] followed by attachment of a series of lipophilic tail groups (Scheme 3).

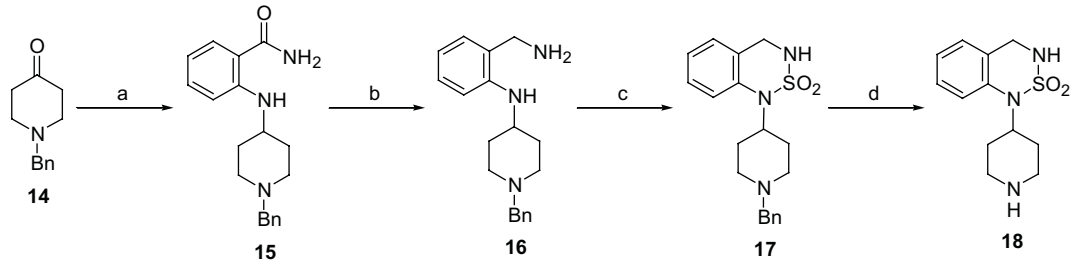
Reductive amination of ketone **10** with 1,2-phenylenediamine gave **11** in 53% yield. As in our previous work,[11] we attribute the relatively low yield of the desired product to further reaction of **11** with a second equivalent of ketone **10** to give a dialkylated product. Cyclization of **11** to the 1,3-dihydro-2,1,3-benzothiadiazol-2,2-dione ring system, **12**, was effected in good yield by refluxing with sulfamide in pyridine. Cleavage of the Boc protecting group under acidic conditions furnished the head group **13**. The synthesis of the 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-dione head group **18** followed a similar approach. Reductive amination of ketone **14** with anthranilamide gave the diamine **15**. Reduction of the amide functionality in **15** to the primary amine with lithium aluminum hydride, followed by cyclization with sulfamide as in the five-member ring series gave the 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-dione **17**. Removal of the benzyl protecting group via standard hydrogenolysis conditions gave the head group **18**.

With the two head groups in hand, attachment of tail groups was accomplished by either alkylation with an alkyl halide (R_1 = **a**–**d**) or reductive amination with an appropriate ketone (R_1 = **e**–**k**).[21] The choice of tail groups was based on previous work by ourselves and others.[7–15] In the case of tail groups **g**–**j**, the products obtained were diastereomeric mixtures and were screened as such. In only one case (**20h**) were the diastereomers separated and screened independently (vide infra).

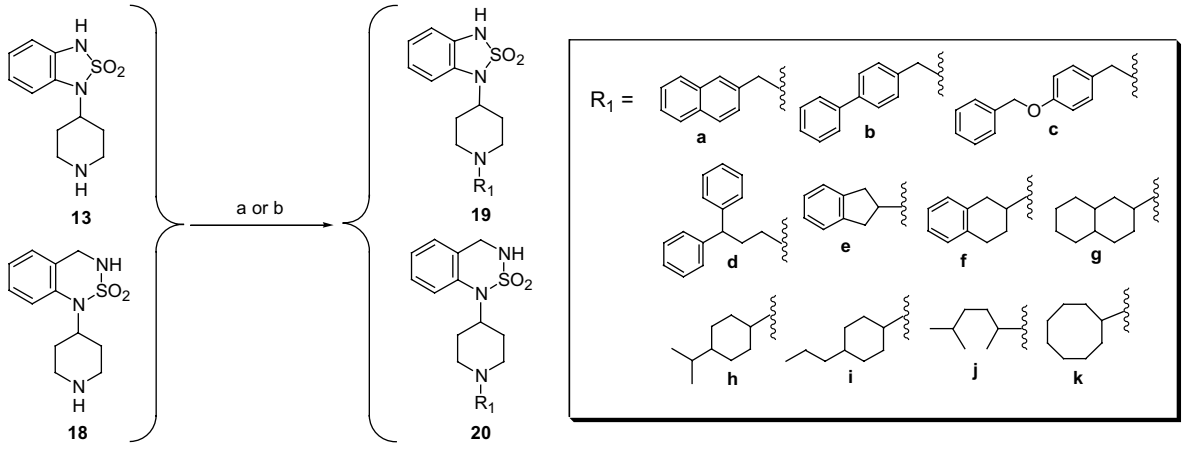
Compounds were screened for binding affinity at the human NOP receptor using [^{3}H]-nociceptin concentration–inhibition binding assays. In addition, compounds were screened for binding affinity at the human MOP, KOP



Scheme 1. Synthesis of head group **13**. Reagents and conditions: (a) 1,2-phenylenediamine, $NaBH(OAc)_3$, HOAc, DCE (53%); (b) $NH_2SO_2NH_2$, pyridine, reflux (79%); (c) HCl, EtOAc (91%).



Scheme 2. Synthesis of head group **18**. Reagents and conditions: (a) anthranilamide, $NaBH(OAc)_3$, HOAc, DCE (58%); (b) $LiAlH_4$, dioxane, reflux (71%); (c) $NH_2SO_2NH_2$, pyridine, reflux (67%); (d) H_2, 10% Pd/C, MeOH, H_2O (89%).



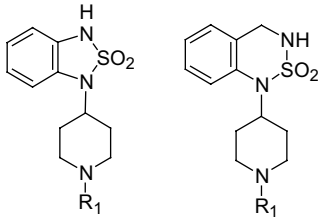
Scheme 3. Attachment of R_1 tail groups to head groups **13** and **18**. Reagents and conditions: (a) alkyl halide, Et_3N, DMF, 80 °C; (b) ketone, $NaBH_3CN$, HOAc, MeOH.

and DOP receptors in similar radioligand binding assays that utilized [^{3}H]-diprenorphine, [^{3}H]-U69,593 and [^{3}H]-naltrindole, respectively. Functional activities at both the NOP and MOP receptors were determined using GTPγ[^{35}S] binding assays. The activities of N/OFQ and DAMGO were used for normalization of functional GTPγ[^{35}S] binding data generated for the NOP and MOP receptors, respectively (maximal effect (E_{max}) elicited by 60 nM N/OFQ or 10 μM DAMGO = 100%; background binding in the absence of agonist = 0%). Because of our interest in identifying NOP receptor ligands, only those compounds that showed binding affinities (K_i values) at the NOP receptor of $\leqslant$1 μM were evaluated at the other three receptors. All compounds that were screened at the KOP and DOP receptors showed poor binding affinity ($K_i > 2$ μM). Additional details of the in vitro assays employed have been described in previous papers from our labs.[11,22]

In the case of the 1,3-dihydro-2,1,3-benzothiadiazol-2,2-dione series (**19**), despite the variety of lipophilic tail groups only two compounds showed sub-micromolar activity at the NOP receptor (Table 1). Compound **19g** contains a decalin ring system as a tail group, whereas **19h** contains a 4-isopropylcyclohexyl tail group. Both of these tail groups have been shown in previous studies to impart good NOP receptor potency and selectivity. Compound **19g** shows 24-fold selectivity for the NOP receptor over the MOP receptor, whereas **19h** showed only 2-fold selectivity. This class of compounds as a whole, however, did not show enough activity to warrant further investigation.

The 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-dione series (**20**) showed greater promise. While some compounds containing aromatic tail groups showed poor affinity for the NOP receptor (**20b**,**c** and **20f**), others were much better, with **20d** and **20e** showing excellent potency and agonist activity. As we have noted in other series, the 3,3-diphenylpropyl tail group as in **20d** imparts greater selectivity for the MOP receptor (6-fold). It is interesting that **20e** with its 2-indanyl tail group is 57-fold more potent than the related 2-tetralin analog **20f**. Introduction of aliphatic tail groups provided us with compounds that demonstrated some interesting SAR. Compound **20g** with its fully reduced decalin tail group is 91-fold more potent at the NOP receptor than **20f**. The highly flexible tail group in **20j** shows excellent potency, although the selectivity over the MOP receptor is somewhat reduced compared to other tail groups in this series. Finally, relocating a single methyl group in going from **20i** to **20h** improves potency 38-fold. In addition, **20h** is 34-fold selective for the NOP receptor, whereas **20i** is essentially equipotent at NOP and MOP

Table 1. Binding and functional data for **19** and **20** at NOP and MOP receptors



19 **20**

Compds	NOP			MOP		
	K_i (nM)[a]	GTPγ[^{35}S] EC_{50} (nM)	GTPγ[^{35}S] E_{max} (%)	K_i (nM)[a]	GTPγ[^{35}S] EC_{50} (nM)	GTPγ[^{35}S] E_{max}(%)
N/OFQ	0.18 ± 0.04	0.09 ± 0.06	98 ± 0.6	Nd[b]	Nd	Nd
DAMGO	Nd	Nd	Nd	36.7 ± 18.6	202 ± 52	95 ± 0.4
19a	>10,000	Nd	Nd	Nd	Nd	Nd
19b	>10,000	Nd	Nd	Nd	Nd	Nd
19c	7114 ± 913	Nd	Nd	Nd	Nd	Nd
19d	4461 ± 1722	Nd	Nd	Nd	Nd	Nd
19e	5670 ± 1294	Nd	Nd	Nd	Nd	Nd
19f	3454 ± 441	Nd	Nd	Nd	Nd	Nd
19g	225 ± 117	3363 ± 551	66 ± 11	5545 ± 1414	Pa[c]	Pa
19h	357 ± 58	3067 ± 838	78 ± 9	748 ± 122	Pa	Pa
19i	5102 ± 1065	Nd	Nd	Nd	Nd	Nd
19j	3592 ± 686	Nd	Nd	Nd	Nd	Nd
19k	2297 ± 567	Nd	Nd	Nd	Nd	Nd
20a	609 ± 81	5589 ± 2116	83 ± 12	294 ± 39	> 10,000	66 ± 6
20b	9535 ± 2699	Nd	Nd	Nd	Nd	Nd
20c	1878 ± 638	Nd	Nd	Nd	Nd	Nd
20d	83 ± 6	1651 ± 459	99 ± 1	13 ± 3	801 ± 116	81 ± 5
20e	46 ± 13	496 ± 71	98 ± 2	660 ± 110	ANT[d]	ANT
20f	2614 ± 586	Nd	Nd	Nd	Nd	Nd
20g	28.7 ± 8.3	160 ± 44.6	94 ± 7.8	91.7 ± 17.2	1475 ± 178	14 ± 3.4
20h	6.1 ± 1.7	38 ± 11	92 ± 7	207 ± 36	Pa	Pa
20i	231 ± 33	1609 ± 1102	96 ± 5.3	188 ± 20	3138 ± 406	26 ± 2
20j	40 ± 8	1581 ± 228	84 ± 2	73 ± 20	3162 ± 292	59 ± 1
20k	187 ± 14	2009 ± 310	79 ± 5	1376 ± 543	ANT	ANT
20h *cis*	2.6 ± 0.2	12 ± 2	99 ± 1	89 ± 28	620 ± 115	16 ± 4
20h *trans*	3.7 ± 0.6	14 ± 1	93 ± 7	112 ± 37	799 ± 122	16 ± 3

[a] Values are the mean of at least three experiments.
[b] Nd = not determined.
[c] Pa = partial agonist.[23]
[d] ANT = antagonist.[24]

receptors. Chromatographic separation of **20h** into its *cis*- and *trans*-isomers did not show any significant difference in potency or selectivity between the two isomers. This is in contrast to the results seen for this tail group in other NOP small molecule series (e.g. **1**, **2** and **9**).

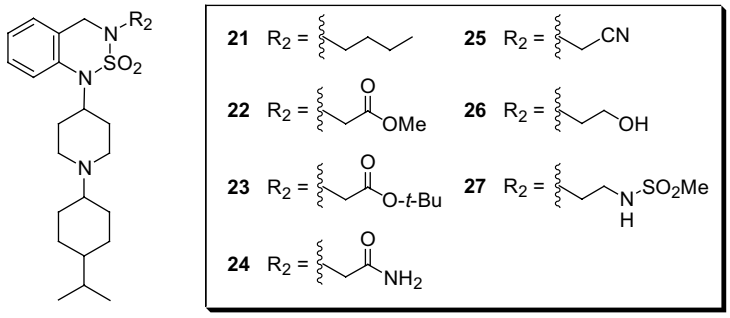
With compound **20h** showing good affinity and agonist potency for the NOP receptor, as well as good selectivity over the MOP receptor, we wished to determine what would be the effect of introduction of an additional substituent (R_2) on the six-member ring head group. Such compounds were prepared in a straightforward manner by simple alkylation of **20h** (Scheme 4). Screening of these compounds showed good affinity for the NOP receptor (Table 2). However, most of the R_2 substituents lowered the selectivity of the compounds for the NOP receptor versus the MOP receptor. Compounds **24** and **27**, however, still showed respectable selectivity (23- and 21-fold, respectively). In the case of **25**, the compound is essentially equipotent at both NOP and MOP receptors.

Finally, as a measure of metabolic stability, compounds were incubated with rat liver microsomes for 30 min followed by HPLC analysis to determine the percentage of compound remaining. Compounds in the five-member ring series showed good metabolic stability (50–90%) while compounds in the six-member ring series surprisingly showed very poor metabolic stability (0–23%), with **20h** having 0% remaining after 30 min.

4. Conclusion

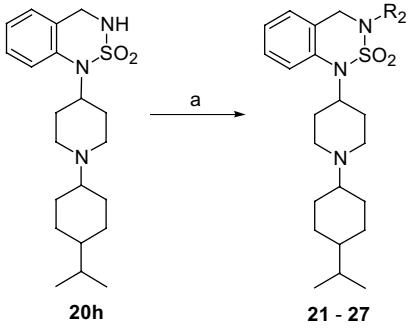
In summary, based on a working model we have prepared a series of 1,3-dihydro-2,1,3-benzothiadiazol-2,2-

Table 2. Binding and functional data for **21**–**27** at NOP and MOP receptors



Compds	NOP			MOP		
	K_i (nM)[a]	GTPγ[^{35}S] EC_{50} (nM)	GTPγ[^{35}S]E_{max} (%)	K_i (nM)[a]	GTPγ[^{35}S] EC_{50} (nM)	GTPγ[^{35}S]E_{max} (%)
N/OFQ	0.18 ± 0.04	0.09 ± 0.06	98 ± 0.6	Nd[b]	Nd	Nd
DAMGO	Nd	Nd	Nd	36.7 ± 18.6	202 ± 52	95 ± 0.4
21	18 ± 7	78 ± 12	94 ± 1	38 ± 9	>10,000	14 ± 4
22	41 ± 21	166 ± 30	92 ± 3	182 ± 24	Pa[c]	Pa
23	63 ± 1	484 ± 125	61 ± 4	289 ± 95	Pa	Pa
24	3.9 ± 1.7	22 ± 5	97 ± 4	92 ± 15	555 ± 141	14 ± 4
25	33 ± 11	227 ± 19	98 ± 1	25 ± 4	344 ± 95	19 ± 0.1
26	7.4 ± 2.1	33 ± 6	95 ± 3	86 ± 23	Pa	Pa
27	5 ± 2	34 ± 19	98 ± 1	106 ± 26	Pa	Pa

[a] Values are the mean of at least three experiments.
[b] Nd = not determined.
[c] Pa = partial agonist.[23]



Scheme 4. Attachment of R_2 groups to **20h**. Reagents and conditions: (a) NaH, alkyl halide, DMF.

diones and 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-diones as small molecule ligands for the NOP receptor. In vitro screening has shown that while the former five-member ring series was not especially active, the latter six-member ring series showed excellent affinity and potent agonist activity at the NOP receptor. Introduction of additional substituents onto the head group of compound **20h** provided a series of compounds that were of comparable potency but with a tendency towards reduced selectivity versus the MOP receptor. Unfortunately, compounds in the six-member ring series showed poor metabolic stability in the rat liver microsome assay. Thus, it would appear that the use of an SO_2 group as a hydrogen bond acceptor in these two series of NOP receptor ligands has met with mixed success. The information gained in this study should prove valuable in the further design of NOP receptor ligands.

Acknowledgements

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16. Recently, Bröer, et al.[17] reported the results of their molecular modeling studies on the NOP receptor and NOP receptor agonists (e.g. **1** and **2**) in which they arrived at a pharmacophore model similar to the model we describe in Figure 2. While their model includes a basic nitrogen and two lipophilic residues, it favors a hydrogen bond donor rather than a hydrogen bond acceptor based on their observed interaction between an amide NH (e.g. **1**, R_b = H) and the oxygen of Thr-305 in their model of the NOP receptor. While we certainly do not dispute their receptor modeling data, we still favor the hydrogen bond acceptor view, given the fact that our compounds **21**–**27** retain NOP receptor binding and agonist activity despite not having a hydrogen bond donor.
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