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Synthesis and SAR studies of 3-phenoxypropyl piperidine analogues as ORL1 (NOP) receptor agonists

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Abstract—A series of 3-phenoxypropyl piperidine analogues have been discovered as novel ORL1 receptor agonists. Structure–activity relationships have been explored around the 3-phenoxypropyl region with several potent and selective analogues identified.

The G-protein-coupled receptor opioid receptor-like-1 (ORL1, known as NOP)[1] is the fourth member of the opioid receptor family. It shares a high degree of sequence homology with classical opioid receptors mu, delta and kappa (MOP, DOP, KOP, respectively). However, typical opioid ligands (such as dynorphin A) do not bind to the ORL1 receptor with appreciable affinity.[2] The endogenous agonist for the ORL1 receptor is nociceptin (NC, also known as orphanin FQ), a 17-amino acid neuropeptide. The ORL1 receptor and NC have been implicated in several physiological pathways including cognition, pain, locomotion, anxiety, neuroendocrine control and modulation of cardiovascular and respiratory function.[3] Both analgesia and hyperalgesia have been observed after administration of NC in rodents; the effect appears to be dependent on the dose of NC and route of administration. In addition to these complex biological data there are limitations in using NC because of the inherent poor metabolic stability. Therefore, the development of highly selective and potent ORL1 ligands could help elucidate the role of the ORL1 receptor in pain. Recently, several research groups have disclosed their efforts in the search for small molecule ORL1 agonists and antagonists.[4] In this communication we would like to report our discovery and preliminary SAR investigations of a novel series of selective ORL1 agonists for treatment of peri-operative pain.

The affinities (K_i values) of compounds at the opioid receptor family of receptors were determined by radioligand binding experiments performed in triplicate. Competition binding was performed in membranes prepared from Chinese hamster ovary (CHO) cells expressing hORL1, hMOP and hDOP receptors using leucyl-[^{3}H]nociceptin, [^{3}H]diprenorphine and [^{3}H]naltrindole, respectively.[5] Affinity at KOP was determined by [^{3}H]U69593 binding in a native guinea pig brain preparation. The functionality of compounds at ORL1 were determined using Flashplate™ (Perkin Elmer, UK) technology by measuring cellular decreases in forskolin-stimulated cAMP in CHO cells stably transfected with hORL1 receptor. The potency and efficacy of compounds were determined in duplicate and compared to the reference ORL1 agonist nociceptin. Additionally a mouse vas deferens (MVD) preparation was used to determine whether compounds have ORL1 and/or hMOP agonist activity in a native system.

Keywords: ORL1; Nociception; Opioid; Analgesia.
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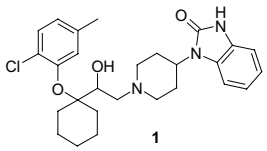

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Figure 1. Lead compound generated from screening.

Our screening hit **1** (Fig. 1) showed high affinity for ORL1 with a K_i of 12 nM, and modest selectivity over MOP (K_i = 58 nM). The compound behaved as an agonist with modest potency (IC_{50} = 957 nM) and good efficacy (82% of NC response) in the cAMP flashplate assay. The focus of this study was on the development of a water soluble ORL1 ligand for use in an intravenous formulation. The hydrochloride salt of racemic **1** had a satisfactory solubility in water, which combined with the ORL1 activity made this an ideal starting point for optimisation.

During initial hit validation, deletion studies of **1** (Table 1), showed that removal of the phenol ether moiety resulted in a 50-fold reduction in affinity for the ORL1 receptor (**2**). A further reduction in affinity for ORL1 was seen with the removal of the hydroxy moiety (**3**). The need for both the hydroxy and spirocyclohexyl were emphasised by analogues **4**, **5** and **6**, as the absence of either group dramatically reduced affinity for the ORL1 receptor.

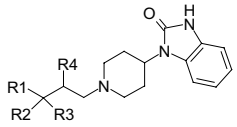
In order to further explore the preliminary structure–activity relationships (SAR) developed through deletion studies we decided to maintain the phenol ether unit and change the lipophilic spirocyclohexyl region and hydroxy H-bond acceptor/donor region.

The synthesis of novel racemic 3-phenoxypropyl piperidine analogues with various 3-alkyl groups is outlined in Scheme 1. Thus Grignard addition to commercially available aldehydes (**7**) with vinylmagnesium bromide afforded the corresponding alkyl vinyl alcohols (**8**). Mitsunobu reaction using 2-chloro-5-methylphenol gave the desired aryl ethers (**9**). Subsequent epoxidation with *m*CPBA afforded the key intermediate epoxides (**10**). When the alkyl vinyl alcohol features an aryl group (R = Ph) the synthesis proceeded via epoxidation of the alkene, using *m*CPBA, followed by Mitsunobu coupling (**8** → **11** → **10**).[6] This procedure avoided the complications of the S_N2' type side reactions seen with the aryl vinyl alcohols.[7] In the case of **1**, the key intermediate epoxide (**10**) is prepared from α-bromination of cyclohexylaldehyde (**12**).[8] Disappointingly this reaction could not be achieved for the 4-, 5- and 7-membered carbocycles. Nucleophilic displacement with 2-chloro-5-methyl phenol gave the spirocyclohexylphenoxy aldehyde (**14**), which was easily transformed to the epoxide using trimethylsulfoxonium iodide in the presence of sodium hydride and DMSO. The epoxides (**10**) were then reacted with 4-(2-keto-1-benzimidazolinyl) piperidine to give the desired aminoalcohols (**15**–**23**). Transformation of the hydroxyl to amine was executed via mesylation using methylsulfonyl chloride; subsequent displacement with the amine in DMF resulted in the desired diamines (**24** and **25**). For those compounds (**15**–**23**) which contain a mixture of diastereomers the ratios were determined using ^{1}H NMR spectroscopy. The single diastereomers (**22** and **23**) were isolated using a combination of crystallisation from methanol followed by silica gel chromatography. All compounds were isolated in racemic form as the hydrochloride salts.

It was found that separation of the diastereoisomeric mixture was nontrivial and simplification of the lead structure, by deletion of the hydroxy moiety, was explored to obtain SAR on the optimal alkyl group (Scheme 2). Utilising the Friedel–Crafts procedure developed by Donnelly and co-workers[9] acid chlorides (**28**) were transformed to the corresponding 3-chloro-1-alkyl-1-propanones (**29**) (R = Ph, commercially available) with aluminium chloride and excess ethene. Subsequent reduction to the secondary alcohol with $LiAlH_4$ and coupling using Mitsunobu conditions[10] accessed the phenoxyalkylpropyl chloride (**31**). Displacement reaction using 4-(2-keto-1-benzimidazolinyl) piperidine and potassium carbonate in DMF resulted in the desired phenoxypropylamines (**26**–**46**).[11]

With the SAR established for the alkyl linker we then rapidly explored the SAR in the phenolic region retaining the ^{i}propyl group for optimisation. Compounds were prepared as described earlier (Scheme 2).

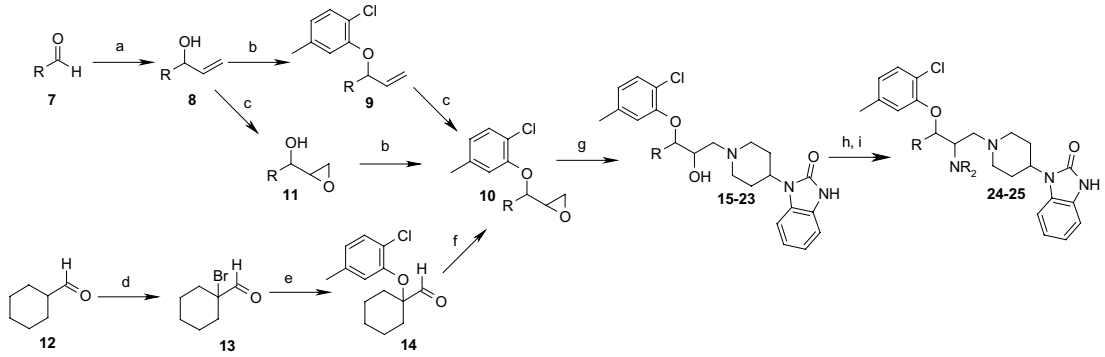
Table 1. Receptor binding of deletion analogues of screening hit **1**



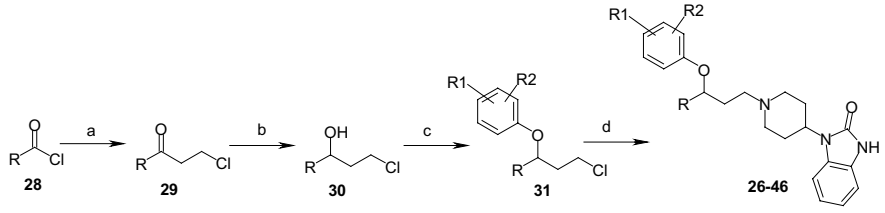
Compd	R1	R2	R3	R4	ORL1 K_i (nM)	MOP K_i (nM)
1	2-Chloro-5-methylphenoxy	–$(CH_2)_5$–		OH	12	58
2	H	–$(CH_2)_5$–		OH	620	—
3	2-Chloro-5-methylphenoxy	–$(CH_2)_5$–		H	1115	—
4	2-Chloro-5-methylphenoxy	H	H	H	282	410
5[a]	2-Chloro-5-methylphenoxy	H	H	OH(*S*)	905	—
6[a]	2-Chloro-5-methylphenoxy	H	H	OH(*R*)	1920	—

— = Not tested.

[a] Compounds prepared from homochiral starting materials.



Scheme 1. Reagents and conditions: (a) 1.0 M vinyl magnesium bromide in THF; (b) 2-chloro-5-methyl phenol, DIAD, PPh_3, THF; (c) *m*CPBA, DCM; (d) bromine, DCM; (e) 2-chloro-5-methyl phenol, NaH, toluene; (f) trimethylsulfoxonium iodide, NaH, DMSO; (g) 4-(2-keto-1-benzimidazolinyl) piperidine, MeOH; (h) methanesulfonyl chloride, DiPEA, DCM; (i) imidazole or dimethylamine, DMF.

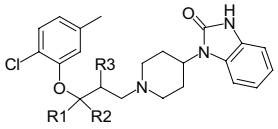


Scheme 2. Reagents and conditions: (a) ethene, $AlCl_3$, DCM; (b) $LiAlH_4$, THF; (c) phenol, DIAD, PPh_3, THF; (d) 4-(2-keto-1-benzimidazolinyl) piperidine, K_2CO_3, NaI (cat.), DMF.

The SAR of the 3-phenoxy region is shown in Tables 2 and 3. While ^{n}propyl (**17**), ^{i}butyl (**20**) and phenyl (**22**) groups show comparable affinity to the lead (**1**) there was no improvement in functional activity over the original hit (Table 2). Other alkyl groups (**15**–**16**) show a decrease in affinity for ORL1 and tend to be more selective for the MOP. Furthermore replacement of the hydroxy unit with either an imidazole moiety (**24**) or dimethylamine group (**25**) was detrimental to ORL1 affinity.

Surprisingly, compounds **26** and **27** (Table 2) showed comparable affinity for ORL1 as the lead **1** with similar selectivity over MOP. More encouraging was the

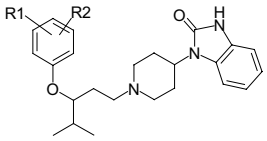
Table 2. SAR of the propyl linker



Compd	R1	R2	R3	Diast. ratio	ORL1 K_i (nM)	MOP K_i (nM)	cAMP	
							IC_{50} (nM)	% NC response
1	–$(CH_2)_5$–		OH	—	12	58	957	82
15	Me	H	OH	53:47	838	118	—	—
16	Et	H	OH	3:1	60	45	—	—
17	^{n}Pr	H	OH	84:16	20	27	1058	97
18	^{i}Pr	H	OH	2:1	108	88	—	—
19	^{c}Hex	H	OH	55:45	462	103	—	—
20	^{i}Bu	H	OH	1:1.8	28	166	1081	88
21	Benzyl	H	OH	1:1.6	768	355	—	—
22	Ph	H	OH	96:4	38.2	114	797	93
23	Ph	H	OH	6:94	125	144	—	—
24	–$(CH_2)_5$–		Imidazole	—	509	477	—	—
25	–$(CH_2)_5$–		NMe_2	—	815	102	—	—
26	Ph	H	H	—	8.3	16.7	240	81
27	^{i}Pr	H	H	—	10.8	65.2	140	101

— = Not tested.

Table 3. SAR of the phenol region



Compd	R1	R2	ORL1 K_i (nM)	MOP K_i (nM)	cAMP	
					IC_{50} (nM)	% NC response
32	2-Me	H	42	21	—	—
33	2-Et	H	37	23	—	—
34	2-CF_3	H	24	24	1730	79
35	2-^{i}Pr	H	113	20	—	—
36	2-F	5-Me	25	67	244	70
37	2-NO_2	5-Me	39	62	165	58
38	2-Me	5-NO_2	218	196	—	—
39	2-Me	5-NH_2	14	47	128	104
40	2-Me	5-Me	11	65	131	89
41	2-Me	5-OMe	4	59	38	100
42	2-Cl	5-Me	11	65	141	101
43	2-Cl	5-OMe	3	58	80	101
44	2-Cl	5-F	126	56	5179	51
45	2-Me	4-F	32	38	9837	67
46	3-Me	4-F	52	103	1532	78

— = Not tested.

dramatic improvement (7-fold) in functional activity for compound **27**. This suggests the hypothesis that the H-bond properties of the hydroxy group is required is misguided and conformational constraints may play a bigger role in this region.

Earlier deletion studies confirmed the need for an aryl-ether group (compound **2**, Table 1). It appears from the results shown in Table 3 that 2,5-disubstitution of the phenol is preferred. Bulky alkyl groups in the 2-position show a lower affinity for ORL1 (**35**) but retain MOP affinity. However, small alkyl or halogen groups are well tolerated, suggesting that the 2-position is involved in orientating the molecule into a particular conformation. It appears that electronic effects in the 2-position have little bearing on affinity with the electron withdrawing nitro group (**37**) showing only a slight decrease in affinity compared to the corresponding methyl group in this position (**40**). Electron withdrawing groups in the 5-position reduce affinity for ORL1, whereas 5-amino (**39**), 5-methyl (**40**) and 5-methoxy (**41**) are all well tolerated. The highest potency compound is the 2-methyl-5-methoxyphenol analogue (**41**) with improved affinity for ORL1 and a ~20-fold improvement in functional activity compared to the original hit **1**.

In summary we have developed a simplified synthetic route to 3-phenoxypropyl piperidine analogues to explore ORL1 SAR around the original hit compound **1**. These compounds all show agonist activity with high to moderate affinity towards ORL1. In particular **41** displayed high affinity with good functional potency and efficacy and modest selectivity (MOP/ORL1 = 15, KOP/ORL1 = 25 and DOP/ORL1 = 191). Furthermore, the activity of **41** in the MVD assay (IC_{50} = 977 nM) was attenuated by a selective ORL1 antagonist, but not by naloxone, demonstrating that although the compound has affinity for the MOP receptor it is not a functional MOP agonist. Solubility is compatible with an intravenous formulation and preliminary in vivo experiments have shown **41**, to have an ED_{50} = 1.07 μmol/kg (intravenous administration) in the second phase of the mouse formalin paw test,[12] thus suggesting this compound has antinociceptive properties. Further work with **41** should aid in the elucidation of the role of the ORL1 receptor in the processing of nociceptive information and determine the therapeutic potential of ORL1 agonists as analgesics. Further in vivo studies will be the subject of future publications for this series of compounds.

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