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3-(4-Piperidinyl)indoles and 3-(4-piperidinyl)pyrrolo-[2,3-*b*]pyridines as ligands for the ORL-1 receptor

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Abstract—A novel series of indoles and 1*H*-pyrrolo[2,3-*b*]pyridines having a piperidine ring at the 3-position were synthesized and found to bind with high affinity to the ORL-1 receptor. Structure–activity relationships at the piperidine nitrogen were investigated in each series. Substitution on the phenyl ring and nitrogen atom of the indole and 1*H*-pyrrolo[2,3-*b*]pyridine cores generated several selective high-affinity ligands that were agonists of the ORL-1 receptor.

In 1994, the opioid receptor-like 1 (ORL-1) was identified as the fourth opioid receptor. ORL-1 is a G-protein coupled receptor having close sequence homology to the μ, κ, and δ-opioid receptors. However, none of the classical opioid ligands show significant affinity to the ORL-1 receptor. In 1995, a 17-amino acid peptide named nociceptin (or orphanin FQ) was identified as an endogenous ligand for the ORL-1 receptor.[1,2] Since that time, many significant reports have appeared that describe the biology of the receptor and ligand. Numerous pharmacological studies have suggested that ORL-1 agonists may be clinically useful for the treatment of stress and anxiety, opioid dependence, and withdrawal.[3,4] Other accounts suggested that ORL-1 antagonists may be useful as analgesics and might enhance learning ability and memory.[5,6] Attracted by these potential therapeutic properties, many research groups were drawn to the area, resulting in numerous publications and patent applications describing non-peptidic small molecule agonists and antagonists of the ORL-1 receptor.[7–9]

Despite the sequence homology between nociceptin and the opioates, opioids do not bind the ORL-1 receptor with high affinity. Traditional nonpeptidic opioid ligands such as morphine (μ-opioid agonist), U50, 488 (κ-opioid agonist), and SNC80 (δ-opioid agonist) have been extensively used in several species to establish and characterize the opioids associated with their pharmacological properties.[10]

It is not surprising that some of the first non-peptide molecules having affinity for ORL-1 were based on traditional opioid ligands. In particular the morphinan analogues have been a resourceful class having both ORL-1 and μ-opioid affinity. It is the case of buprenorphine, a μ-opioid partial agonist marketed for pain but with a significant activity for the ORL-1 receptor and whose efficacy is thought to be mediated via the ORL-1 receptor.[9,11] Similarities between non-peptide derivatives of the ORL-1 receptor and the opioids might be found but will translate in different pharmacological actions when tested in vivo.[12–14] Traditional opioates have been used as a platform and modification of their structure generated simpler piperidine frameworks.[9] Further structure–activity relationship (SAR) around these frameworks produced new scaffolds with enhanced potency for ORL-1 and more important improved selectivity over the opioid receptors. Once developed, any new small ligand series targeting ORL-1 will be compared to the classic opioids in order to differentiate their potential therapeutic values. Such analyses will be important if we want to develop any ORL-1 agonist/antagonist drugs (still no ORL-1 drugs have reached the market yet) toward a better

Keywords: ORL-1; Nociceptin; Opioid receptor-like (ORL); Orphanin FQ (OFQ); N/OFQ peptide (NOP); Agonist; Indole; Piperidine; Pyridine; Anxiety; Stress; Learning; Memory.
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understanding of the CNS pathways and its associated mechanisms.

It is interesting to note that many reported small-molecule ORL-1 ligands incorporate a piperidine framework found in spiropiperidine, spirofused benzofuran, spiroindane/indene, benzimidazole/benzimidazolinone, and aryl piperidine structures.[15] Through extensive SAR work focused on piperidine nitrogen substitution in each of the scaffolds, cyclooctylmethyl, naphthylmethyl, and acenaphthenyl groups have been found to confer high affinity for ORL-1 (Fig. 1).

We considered that 3-(4-piperidinyl)- and 3-(3-pyrrolidinyl)indoles[16–22] and 3-(4-piperidinyl)pyrrolo-[2,3-*b*]-pyridines [23–27] would be valuable scaffolds for incorporating substitution to obtain ORL-1 receptor activity. Our synthetic route started by reacting commercially available or readily prepared substituted indoles or pyrrolo[2,3-*b*]pyridines with a protected piperidin-4-one under basic or acidic conditions (Scheme 1).[25,28–30] The resulting protected tetrahydropyridines were reduced to the piperidine or directly deprotected. Substituents on the piperidine nitrogen were introduced through reductive amination, nucleophilic substitution, or amide coupling reactions. In a few examples, the final analogues were alkylated at the 1-position of the indole under basic conditions (NaH).

Compounds were evaluated for ORL-1 and opioid receptor binding affinities in radioligand binding assays (Tables 1–3). K_i values for binding to human recombinant ORL-1 were determined by measuring the ability to compete with ^{125}I-Tyr^{14}-nociceptin for binding to membranes prepared from HEK-293 cells expressing ORL-1. K_i values for binding to human recombinant opioid receptors were determined using membranes isolated from HEK-293 cells expressing the μ-, κ-, or δ-opioid receptors. Labeled agonists specific for each opioid receptor were used as competitors in the selectivity binding assays: ^{3}H-DAMGO for μ, ^{3}H-U69,593 for κ, and ^{3}H-DDPDE for δ. Functional (agonist) activity was assayed using a HEK-293 cell line that overexpresses the ORL-1 receptor together with the Gqi5 G protein (Molecular Devices) to detect signaling by a calcium flux assay.

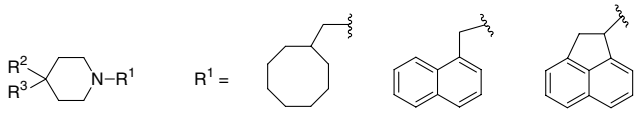
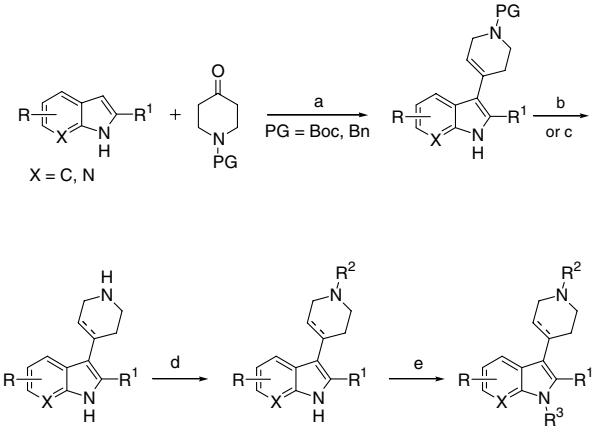


Figure 1. Piperidine-containing substituents that have been shown to exhibit ORL-1 receptor affinity.

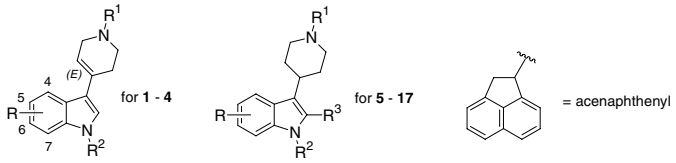


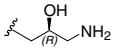
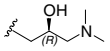
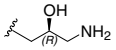
Scheme 1. Reagents and conditions: (a) KOH or NaOH, MeOH reflux 60–95%; (b) piperidine series: H_2, Pd/C (PG = Bn) or H_2, PtO_2 then TFA, or 6 N HCl (if PG = Boc), 70–90%; (c) tetrahydropyridine series: TFA or 6 N HCl (if PG = Boc), 60–90%; (d) reductive amination [R^2–CHO, $NaBH(OAc)_3$], nucleophilic substitution (base, R^2–Br or R^2–I) or peptide coupling (HO_2C–R^4, EDCI or HATU, DIPEA, DMF); (e) NaH, DMF or THF then R^3–X [X = Br, I, Cl], 55–90%.

Tables 1–3 detail the SAR studies that were conducted. Acenaphthenyl, cyclooctylmethyl, and naphthylmethyl groups were introduced because they are known to confer high affinity for the ORL-1 receptor. In addition, amino and hydroxyl substituted alkyl chains were incorporated in order to improve water solubility. In the tetrahydropyridine series (Table 1), ORL-1 activity was not observed at the screening concentration (5 μM) with N-benzyl substitution (**1**) or when there was the racemic acenaphthenyl substituent used in conjunction with an electron-withdrawing cyano group in the 5-position (**2**). Introduction of a chiral propanolamine on the indole nitrogen provided increased affinity for ORL-1 (**3**, ORL-1 K_i = 1.6 μM) with modest selectivity over μ-opioid receptor. Improved affinity and selectivity for ORL-1 were obtained with the acenaphthenyl substituent and a fluorine in the 6-position (**4**, ORL-1 K_i = 0.16 μM, >30× selectivity over μ, κ, and δ).

The 3-(4-piperidinyl)indoles **5**–**17** generally had good affinity for the ORL-1 receptor, with the most potent analogues bearing acenaphthenyl substitution. For example, with the 5-chloroindole core the NH indole with piperidine N-benzyl substitution (**5**) had modest ORL-1 activity (ORL-1 K_i = 1.14 μM), and the 2-methyl-5-chloroindoles **6**–**8** revealed a progression in increasing activity when going from naphthalene-1-ylmethyl **6** to cyclooctylmethyl **7** to acenaphthenyl **8** (ORL-1 K_i = 0.010 μM, ratio μ/ORL-1 = 25 and κ/ORL-1 = 65). In the functional assay, **8** acted as a partial agonist with modest potency (**8**, ORL-1 EC_{50} = 54.6 μM). In a similar manner, 5-fluoroindoles displayed increasing ORL-1 activity from naphthalene-1-ylmethyl **9** to cyclooctylmethyl **10** to acenaphthenyl **11** (ORL-1 K_i = 0.018 μM, ratio μ/ORL-1 = 27 and κ/ORL-1 = 100). Compound **11** was a partial ORL-1 agonist (**11**, ORL-1 EC_{50} = 27.2 μM). It is interesting to note that cyclooctylmethyl analogue **10** had the greatest potency for the κ-opioid receptor among those we examined (κK_i = 0.18 μM), and no appreciable δ-opioid activity was observed. Introduction of a propanolamine onto the indole nitrogen (**12**) produced modest affinity for ORL-1 (ORL-1 K_i = 0.97 μM) but did increase solubility at low pH (4-fold compared to parent compound **10**). Benzyl substitution on the indole nitrogen was not tolerated (**13**). The 6-fluoroindole core with the acenaphthenyl group on the piperidine had good affinity for ORL-1 and moderate selectivity for the μ-opioid receptor (**14**, ORL-1 K_i = 0.052 μM, ratio μ/ORL-1 = 17 and

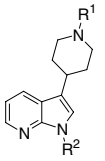
Table 1. Receptor binding data for 3-(4-piperidinyl)indoles

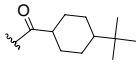


Compound	R	R^1	R^2	R^3	ORL-1 K_i[a] (μM)	μK_i (μM)	κK_i (μM)	δK_i (μM)	ORL-1 EC_{50} (μM)
1	5-Cl	Benzyl	H		>5	0.50	1.01	>5	—[b]
2	5-CN	Acenaphthenyl	H		>5	>5	>5	>5	—
3	5-CN	Acenaphthenyl			1.65	4.14	>5	>5	—
4	6-F	Acenaphthenyl	H		0.16	>5	>5	>5	—
5	5-Cl	Benzyl	H	H	1.14	0.23	0.33	>5	—
6	5-Cl	Naphthalene-1-ylmethyl	H	Methyl	>5	0.88	0.75	>5	—
7	5-Cl	CH_2-cyclooctyl	H	Methyl	0.71	1.36	0.33	4.18	—
8	5-Cl	Acenaphthenyl	H	Methyl	0.010	0.26	0.68	2.75	54.6
9	5-F	Naphthalene-1-ylmethyl	H	H	0.80	0.50	0.82	>5	—
10	5-F	CH_2-cyclooctyl	H	H	0.29	1.08	0.18	>5	—
11	5-F	Acenaphthenyl	H	H	0.018	0.50	1.89	>5	27.2
12	5-F	CH_2-cyclooctyl		H	0.97	2.7	1.9	>5	—
13	6-Cl	Acenaphthenyl	Benzyl	H	>5	>5	>5	>5	—
14	6-F	Acenaphthenyl	H	H	0.052	0.90	>5	>5	—
15	6-F	Acenaphthenyl		H	0.062	0.76	>5	>5	—
16	7-Cl	CH_2-cyclooctyl	H	H	0.66	0.43	1.17	>5	—
17	7-Cl	Acenaphthenyl	H	H	0.057	0.26	2.6	>5	> 80

[a] Receptor K_i values are means of three values.
[b] Dash, not determined.

Table 2. Receptor binding data for 3-(4-piperidinyl)pyrrolo[2,3-*b*]pyridines



Compound	R^1	R^2	ORL-1 K_i[a] (μM)	μK_i (μM)	κK_i (μM)	δK_i (μM)	ORL-1 EC_{50} (μM)
18	CH_2-cyclohexyl	H	3.5	>5	>5	>5	—[b]
19	*n*-Hexyl	H	>5	>5	>5	>5	—
20	1-(4-Phenoxy-benzyl)	H	>5	0.33	>5	>5	—
21	Naphthalene-1-ylmethyl	H	0.82	0.34	0.71	>5	—
22	CH_2-cyclooctyl	H	0.55	2.0	3.89	>5	—
23	Acenaphthenyl	H	0.004	0.39	2.78	>5	4.2
24	Acenaphthenyl	Methyl	0.081	0.90	>5	>5	—
25	Acenaphthenyl	$–CH_2CH_2OH$	0.094	0.53	>5	>5	—
26		H	>5	>5	>5	>5	—

[a] Receptor K_i values are means of three values.
[b] Dash, not determined.

κ/ORL-1 = 100). Introduction of a propanolamine on the indole nitrogen (**15**) did not appreciably change binding for ORL-1 and selectivity. In addition, the aminoalcohol side chain enhanced solubility of **15** at pH 2 (6-fold increase) compared to parent compound **14**. Finally, using the 7-chloroindole core, acenaphthe-

Table 3. Receptor binding of substituted 3-piperidinyl-1*H*-pyrrolo[2,3-*b*]pyridines analogues

Compound	ORL-1 K_i (μM)	μK_i (μM)	κK_i (μM)	δK_i (μM)
31	>5	>5	>5	>5
32	0.002	0.17	4.3	>5

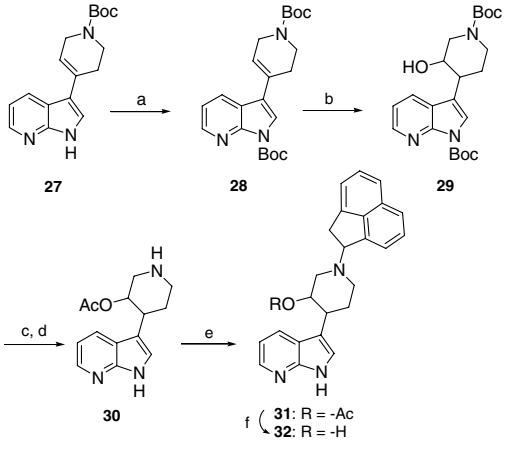
Receptor K_i values are means of three values.

nyl substitution (**17**, ORL-1 $K_i = 0.057$ μM) was again more potent than cyclooctylmethyl (**16**, ORL-1 $K_i = 0.66$ μM).

In the 3-(4-piperidinyl)pyrrolo[2,3-*b*]pyridine series, cyclohexylmethyl **18**, hexyl **19**, and 4-phenoxybenzyl **20** had weak affinity for ORL-1 (ORL-1 $K_i > 3$ μM), whereas napthhalene-1-ylmethyl **21** and cyclooctylmethyl **22** had modest affinity for ORL-1 (ORL-1 $K_i = 0.5$–1.0 μM) (Table 2). The 4-phenoxybenzyl **20** and naphthalene-1-ylmethyl **21** actually proved to be more potent for μ than ORL-1 (μ$K_i = 0.33$ and 0.34 μM, ratio ORL-1/μ = 15 and 2.4, respectively). Introduction of an acenaphthenyl on the piperidine (**23**) generated the most potent analogue for ORL-1 with a $K_i = 0.004$ μM and at least 100× selectivity toward the opioid receptors (ratio μ/ORL-1 = 98, κ/ORL-1 = 690, and δ/ORL-1 > 1000).

Compound **23** (racemic mixture) was a full ORL-1 agonist in the functional assay with an EC_{50} of 4.2 μM. Further substitution of the indole nitrogen with either methyl (**24**) or hydroxyethyl (**25**) groups resulted in a ca. 20× loss of affinity for ORL-1 and a slight decrease of affinity for the μ-opioid receptor. Finally, an amide attachment to the piperidine (**26**) resulted in a strong reduction of binding affinity for the ORL-1 and opioid receptors.

Next we investigated hydroxylation of the intermediate **28**, obtained after Boc protection of **27** (Scheme 2).[29] Hydroboration with borane-dimethyl sulfide followed by oxidative workup afforded *trans* alcohol **29** as a mixture of diastereoisomers. After acetylation and deprotection to afford **30**, the acenaphthenyl group was incorporated to give **31** (Table 3). To our surprise, compound **31** showed poor affinity for ORL-1 and the opioid receptors, probably due to unfavorable steric interactions. After hydrolysis of the acetate to alcohol **32**, binding for ORL-1 and selectivity toward the opioid receptors were entirely recovered (ORL-1 $K_i = 0.002$ μM, ratio μ/ORL-1 = 67, κ/ORL-1 > 1000 and δ/ORL-1 > 1000).



Scheme 2. Reagents and conditions: (a) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 80%; (b) BH_3SMe_2, THF, 0 °C to rt, then NaOH, H_2O_2, 30–50%; (c) Ac_2O, Py, DMAP, CH_2Cl_2, 74%; (d) TFA or 6 N HCl, 100%; (e) 1-bromoacenaphthene, K_2CO_3, KI, DMF, 62%; (f) 0.5 M MeONa in MeOH, rt, 92%.

Acenaphthenyl analogue **23** was also selected for ADME screening. Compound **23** had a short half-life ($t_{1/2} \sim 15$ min) and only 14% of the parent compound remained after incubating with human liver microsomes (HLM) for 60 min. Metabolite identification studies in HLM demonstrated that the major metabolite resulted primarily from loss of the acenaphthenyl moiety, while the 3-(4-piperidinyl)pyrrolo[2,3-*b*]pyridine ring system remained intact.

In summary, we have examined the 3-(4-piperidinyl)-indole and 3-(4-piperidinyl)pyrrolo[2,3-*b*]pyridine scaffolds and identified compounds that have nanomolar affinity for ORL-1 and good selectivity versus the opioid receptors. We explored structure–activity relationships at three different positions on the various cores. As demonstrated in other series,[15,31] incorporation of the acenaphthenyl group on the piperidine conferred potent ORL-1 affinity. In particular, compounds **8**, **11**, **23**,[32] and **32**[32] displayed high affinity for ORL-1 (K_i = 0.010, 0.018, 0.004, and 0.002 μM, respectively) and modest to good selectivity over μ- and κ-opioid receptors (∼25× to 100× versus μ and ∼65× to >1000× versus κ). The 3-(4-piperidinyl)pyrrolo[2,3-*b*]pyridine series proved to be most potent and selective for ORL-1. Functional testing indicated that **8**, **11**, and **23** are agonists or partial agonists at the ORL-1 receptor and may therefore be active in biological models of stress and anxiety.

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32. Analytical data for compounds **23** and **32**. Compounds were characterized by ^{1}H NMR and MS. Compound **23**: ^{1}H NMR (400 MHz, DMSO) δ 11.38 (1H, br s), 8.15 (1H, dd, J = 1.40 Hz and 4.65 Hz), 7.95–7.93 (1H, m), 7.73 (1H, d, J = 8.20 Hz), 7.66 (1H, d, J = 8.15 Hz), 7.57–7.50 (1H, m), 7.48–7.46 (2H, m), 7.34–7.32 (1H, m), 7.20–7.19 (1H, m), 7.00–6.97 (1H, m), 4.94 (1H, br s), 3.39–3.36 (2H, m), 2.96–2.88 (2H, m), 2.76–2.65 (2H, m), 2.38–2.31 (2H, m), 1.96–1.82 (2H, m), 1.78–1.65 (2H, m); MS (ES$^+$) *m*/*z* 354.3 (MH)$^+$. Compound **32**: (diastereoisomeric mixture) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (2H, br s), 8.28 (2H, br s), 8.00 (2H, d, J = 7.91 Hz), 7.22–7.69 (2H, m), 7.63 (2H, d, J = 8.2 Hz), 7.55–7.51 (4H, m), 7.49–7.43 (2H, m), 7.30 (2H, d, J = 6.77 Hz), 7.14 (2H, br s), 7.05 7.08 (2H, dd, J = 4.70 Hz and 7.80 Hz), 5.16–5.06 (2H, m), 5.01–4.98 (2H, m), 3.46–3.43 (2H, m), 3.19–3.15 (1H, m), 3.01–2.98 (1H, m), 2.95–2.88 (2H, m), 2.76–2.73 (1H, m), 2.59–2.53 (1H, m), 2.43 (1H, t, J = 9.90 Hz), 2.36–2.30 (1H, m), 2.24 (1H, t, J = 10.10 Hz), 2.09–1.96 (4H, m), 1.72 (3H, s), 1.38 (3H, s); MS (ES$^+$) *m*/*z* 412.1 (MH)$^+$.