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The design and synthesis of a novel quinolizidine template for potent opioid and opioid receptor-like (ORL1, NOP) receptor ligands

Ling Jong, Nurulain Zaveri* and Lawrence Toll

Biosciences Division, SRI International, 333 Ravenswood Ave., Menlo Park, CA 94025, USA

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Abstract—A new class of high affinity opioid and opioid receptor-like receptor (ORL1 receptor, NOP receptor) ligands has been designed by conformational restriction of piperidine-based NOP receptor ligands, resulting in a novel quinolizidine scaffold. Different modifications of the pendant functional groups on the scaffold provide differential activities at the opioid and NOP receptors. While the conformational rigidity will provide an improved understanding of the NOP and opioid receptor binding pockets, these compounds also provide a new template for the design of novel opiate and NOP ligands.

Nociceptin (NC, Orphanin FQ (N/OFQ)) is the endogenous ligand for the opioid receptor-like (ORL1) receptor (now called the NOP receptor).[1,2] Although NOP/ORL1 is a member of the opioid receptor family, and is a G-protein coupled receptor, it does not bind opiates with high affinity. The NOP receptor and nociceptin have been implicated in several physiological pathways including pain, anxiety, and drug addiction.[3,4] A variety of studies have suggested that NOP agonists may be useful clinically for treatment of anxiety,[5] and antagonists may have analgesic activity.[6–8] In addition, various pharmacological and genetic manipulations have indicated that this receptor and N/OFQ may also be involved in morphine tolerance,[9] feeding,[10] learning and memory,[11,12] cardiovascular and renal systems,[13,14] among others. Therefore, development of highly selective and potent NOP ligands could provide new classes of drugs for several human disorders.

Since nociceptin is a 17-amino acid peptide, several earlier studies have resulted in the identification of modified N/OFQ-based peptide ligands for the NOP receptor (reviewed in ref 15). Very selective peptide agonists as well as antagonists have now been identified.[16–18] However, despite this enhanced understanding of the structural requirements of N/OFQ-like peptides, the information is not sufficient to support rational small-molecule NOP ligand design. Furthermore, the use of peptide ligands is plagued with inherent limitations with respect to metabolic stability.

Recently, several small-molecule NOP agonists and antagonists have been reported in the literature[19–25] and patents (reviewed in ref 15). Several of these ligands possess very high selectivity for the NOP receptor versus other opioid receptors. For example, Kolczewski et al. recently reported novel spiropiperidine-based pyrrolopyrroles, of which compound **1** (Fig. 1) was identified as a potent NOP agonist ($K_i = 0.49$ nM) with >1000-fold selectivity over the μ, δ, and κ opioid receptors.[25] Similarly, Kawamoto et al. disclosed a series of benzimidazole-based ligands of which J-113397 (Fig. 1) was reported as a potent, selective NOP antagonist, with >600-fold selectivity over the opioid receptors.[21]

It is interesting to note that all small-molecule NOP ligands disclosed thus far contain a common piperidine core and bear close structural resemblance to lofentanil

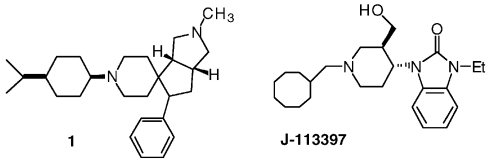

Figure 1. Structures of some known NOP small-molecule ligands.

* Corresponding author. Tel.: +1-650-859-6041; fax: +1-650-859-3153; e-mail: nurulain.zaveri@sri.com

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and the anilidopiperidine class of opioid ligands.[26] Most of these reported ligands were discovered through high throughput screening of large libraries and the resulting hits were optimized for potency and selectivity versus other opioid receptors by modifying the various substituent groups on the central piperidine ring.[20,21] For example, the initial lead compound from which J-113397 was developed, was J-1 (Fig. 2), a non-selective lead with an IC_{50} of 200 nM for displacement of [^{125}I] Tyr^{14} nociceptin and with a 2-fold higher affinity at κ receptors. Introduction of a α-methyl and a 2-chloro group in the *N*-benzyl substituent increased binding affinity to NOP by about 33-fold (IC_{50} = 5.9 nM), and afforded a 8- and 5-fold selectivity versus μ and κ receptors, respectively. Further modifications of the piperidine nitrogen substituent further increased the selectivity and resulted in a potent antagonist, J-113397.[21] Similar approaches have been used to develop other small-molecule NOP agonists and antagonists like Ro 64-6198, NNC 63-0532, and JTC-801.[20,23,24]

At present, high-throughput screening coupled with classical medicinal chemistry is still the most common strategy for identification and development of small molecule NOP agonists or antagonists. The discovery of these selective NOP agonist and antagonists has afforded a considerable opportunity to develop a high affinity binding pharmacophore for the NOP receptor, which can be used to accelerate future drug discovery. Such a pharmacophore can also incorporate features that afford selectivity for NOP versus other opioid receptors. However, most known potent NOP ligands, such as J-113397 and Ro 64-6198, are built around a central piperidine core, and the greater mobility of their piperidine *N*-substituents permits them to assume many different positions in space. Such flexible molecules are unlikely to provide useful information, because their flexibility permits them to assume several possible low energy conformations at the receptor site. We decided to use conformational restriction around the piperidine *N*-substitution to enhance the selectivity of these piperidine-based ligands for the NOP receptor. Such an approach would also result in novel scaffolds that can be a starting point to develop new classes of NOP ligands not based on the piperidine core and give further insight into the pharmacophore for high affinity binding as well as selectivity versus other opioid receptors.

Our rational NOP ligand design was based on an SAR analysis of the two structurally similar NOP ligands, J-1 and J-2 reported by Kawamoto et al. that have significantly different binding affinities (Fig. 2).[21] J-1 exhibited low NOP affinity (IC_{50} = 200 nM) and a 2-fold higher affinity at the κ receptor. Its affinity and selectivity were improved by the addition of an α-methyl and 2-chloro groups to the *N*-benzyl substituent, which led to J-2 (IC_{50} = 5.9 nM and 8- and 5-fold selectivity versus μ and κ receptors). It is likely that the steric interactions of these added substituents restricts the rotation of the *N*-benzyl substituent to a smaller number of allowable conformations, resulting in increased affinity and selectivity. Computer-aided structural analysis of J-1 and J-2 revealed that J-1 has two low energy conformers, J-1A and J-1B, with only 0.38 Kcal/mol of energy difference (Fig. 2). This means the two conformations are almost equally populated, whereas, J-2A is a more favorable conformer, compared with J-2B, whose energy is 1.55 *K*cal/mol higher. Therefore, the potent NOP activity of J-2 may largely be due to the contribution of the global low-energy conformer, J-2A.

We reasoned that conformational restriction of the low-energy conformer of J-2 (viz. J-2A) could provide an enhancement in affinity and perhaps selectivity, by locking the piperidine *N*-substituent in a defined space with respect to the piperidine ring. This would also provide more definitive information about the spatial and steric requirements at the NOP and opioid binding pockets and result in a new scaffold. We designed the rigid molecule, **SR 14136** that mimics the low energy conformers J-1A and J-2A. The *N*-α-methylbenzyl substituent was locked into a quinolizidine ring system, such that the phenyl group of the *N*-substituent now occupies a spatial position resembling that in J-1A and J-2A (Fig. 2). Minor modifications of the functional groups around this novel template (**SR 14135**–**SR 14140**) were also carried out and yielded interesting results.

The target compounds (**SR 14135**–**SR 14140**) were synthesized as shown in Scheme 1. A Robinson-type annulation procedure was chosen for the key step in the synthesis of the quinolizidine skeleton,[27] as shown in Scheme 1. The imino ether **I-2** was obtained from readily available **I-1** in four steps: esterification, oxime transformation, lactam formation, and imino ether conversion. Reaction of **I-2** with ethyl 3-oxo-4-pentenoate (Nazarov reagent)[28] via Robinson-type annulation was followed by stereospecifically reducing the tetrasubstituted double bond to afford the *trans*-fused quinolizidine **I-3** with equatorial phenyl and ethoxycarbonyl substituents

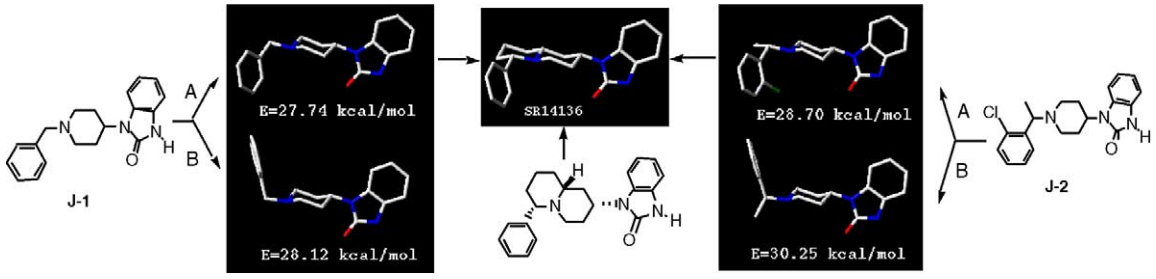
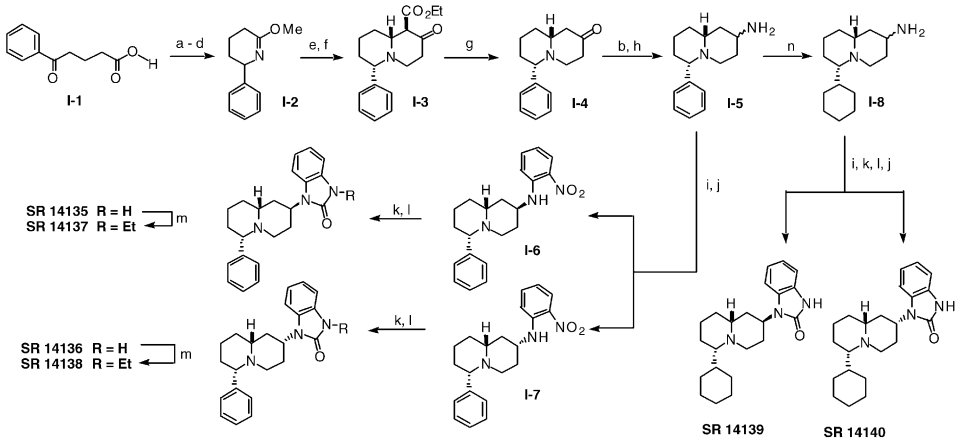


Figure 2. Rational NOP ligand design.



Scheme 1. (a) $SOCl_2$, CH_3OH; (b) $NH_2OH{\cdot}HCl$, NaOAc, CH_3OH; (c) H_2, 5% Pd/C, CH_3CO_2OH; (d) Me_2SO_4; (e) ethyl 3-oxo-4-pentenoate, *p*-TsOH; (f) *i*-Bu_3AlH; (g) HCl (aq); (h) $LiAlH_4$; (i) 2-fluoronitrobenzene; (j) Column separation; (k) H_2, 10% Pd/C; (l) 1,1-carbonyldiimidazole; (m) NaH, CH_3CH_2I; (n) H_2, PtO_2, CH_3CO_2H.

at C-6 and C-1, respectively. The stereochemistry of **I-3** was confirmed by NOE (nuclear Overhauser effect) experiments. Subsequent decarboxylation of **I-3** led to the 2-ketoquinolizidine **I-4**, which was then converted to the amine **I-5** obtained as a C-2 diastereomeric mixture. The coupling of **I-5** and 2-fluoronitrobenzene was followed by chromatographic separation to yield **I-6** and **I-7** with the relative stereochemistry indicated. Hydrogenation of **I-6** and **I-7** followed by cyclization afforded **SR 14135** and **SR 14136**, respectively,[21] which were further converted to **SR 14137** and **SR 14138** by *N*-ethylation. The final target compounds were characterized by NMR and mass spectrometry.[29] NOE confirmed that **SR 14136** possessed equatorial C-2 and C-6 substituents, whereas **SR 14135** has an axial C-2 benzimidazolinyl moiety and an equatorial C-6 phenyl group. **SR 14139** and **SR 14140** were similarly converted from **I-8**, which was produced from **I-5** by platinum-catalyzed hydrogenation,[30] using the same synthetic routes described for **SR 14135** and **SR 14136**.[29]

These new quinolizidine-based ligands were tested for binding affinity at human NOP receptors, and human μ-, δ-, and κ-opioid receptors, all transfected into CHO cells. Binding to NOP was conducted with [^{3}H] N/OFQ, as described previously.[31] Binding to the opioid receptors utilized the selective agonists [^{3}H] DAMGO, [^{3}H] Cl-DPDPE, and [^{3}H] U69593 for the μ, δ, and κ receptors, respectively.[32] Functional activity of these compounds was determined by stimulation of [^{35}S] GTPγS binding to cell membranes, as we have described previously.[16,32] Binding affinities and functional activity are shown in Table 1.

Among the diastereomeric pairs, in each case, the equatorial diastereoisomer (**SR 14136**, **SR 14138**, and **SR 14140**) was found to have higher affinity than the corresponding axial diastereoisomer (**SR 14135**, **SR 14137**, and **SR 14139**) by one to two orders of magnitude at all four receptors. **SR 14136** was found to be the most potent compound in this series, and had NOP binding affinity very comparable to J-2. However, it also has high affinity for μ and κ, indicating that the conformational restriction also provides favorable binding for the μ and κ receptors. None of the compounds synthesized had significant affinity at the δ opioid receptor. Addition of an ethyl group to the *N*-benzimidazolinyl moiety significantly decreases affinity at κ but also at NOP, while maintaining μ affinity. Saturation of the pendant phenyl ring as in **SR 14140** (corresponding to the piperidine *N*-benzyl substituent in J-2) leads to a significant decrease in affinity at μ, with a slight decrease at NOP while maintaining κ affinity. Thus, minor modifications of this template can

Table 1. Structure–activity relationships of the quinolizidine class of ORL ligands[a]

Compd	Receptor binding				[^{35}S]GTPγS binding					
	K_i (nM)				NOP		μ		κ	
	NOP	μ	κ	δ	EC_{50}	% Stim.	EC_{50}	% Stim.	EC_{50}	%Stim.
SR 14135	786±302	47.7±0.5	271±16	>10,000	>10,000		>10,000		>10,000	
SR 14136	5.7±0.1	5.24±0.52	1.1±0.35	1720±670	65±30	89±4	198±22	55±13	4.7±1.4	100±11
SR 14137	535±332	17.6±1.0	987±300	1838±709	>10,000		>10,000		>10,000	
SR 14138	19.6±3.8	2.54±0.2	22.7±3.6	1492±746	165±66	87±7	105±23	83±2	210±1	79±8
SR 14139	189±20	119±11	227±99	>10,000	>10,000		>10,000		>10,000	
SR 14140	28.7±5.9	46.8±2.6	2.3±0.1	2075±1037	678±206	51±13	>10,000		20.9±1.8	43±5
N/OFQ	0.06±0.01				4.0±0.1	100				

[a] Receptor binding and [^{35}S]GTPγS binding were conducted as described previously.[16,31] K_i values were derived from the equation $K_i = IC_{50}/(1 + [L]/K_d)$, where [L] (the concentration of the radioligand) is approximately 0.2, 1.9, 1.1, and 1.2 nM for NOP, μ, κ, and δ binding, respectively. Each experiment was conducted a minimum of twice in triplicate. An EC_{50} value of >10,000 for [^{35}S]GTPγS binding could indicate either low affinity or lack of agonist activity.

modulate the binding affinity and selectivity for NOP versus opioid receptors.

Functional activity studies suggest that compounds **SR 14136** and **SR 14138** are full agonists at the NOP receptor. Intriguingly, **SR 14136** is a very potent κ agonist (Table 1), being nearly 10 times more potent than the standard κ agonist U69593 (data not shown). Saturation of the pendant phenyl ring as in **SR 14140** lowers efficacy at both NOP and κ, and completely abolishes efficacy at μ receptors. This trend toward decreased agonist efficacy with saturated *N*-substituents is similar to the results of Kawamoto et al.[21] where they observe agonist activity for compounds J-1 and J-2, which contain the aromatic *N*-benzyl substituent, but find antagonist activity with compounds bearing cycloalkyl substituents at the piperidine nitrogen as in J-113397.

Although our novel quinolizidine template does not provide a selective NOP ligand, our results clearly indicate that appropriate structural modifications of this new template can yield selective ligands. This conformationally rigid template will give further insight into the binding pockets of the NOP and opioid receptors.

It is noteworthy that **SR 14136** is a high affinity, potent κ agonist. It has been generally assumed that a selective κ agonist would be a powerful analgesic agent without the respiratory, gastrointestinal and addictive side effects of μ-based opioids. Most synthetic κ agonists fall into two main structural classes: the benzomorphans (bremazocine, ethylketocyclazocine) and the arylacetamides (U-50488). On the other hand, it has been suggested that κ-selective antagonists could provide a long-lasting drug abuse treatment strategy.[33] We have shown that modifications of the pendant groups of our novel template can modulate agonist efficacy (compare **SR 14136** and **SR 14140**). Thus, this quinolizidine template now offers a new scaffold to develop selective κ receptor-based agonists and antagonists. Work is currently underway in our laboratory to explore the potential of this novel series of opioid ligands.

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29. Overall yields of the final compounds were between 5 and 10%. All final compounds were isolated as free bases and were characterized by NMR and mass spectrometry. NMR was carried out on a Varian 300 MHz NMR and mass spectrometry on a Finnigan LCQ DUO LC/MS/MS

system with an electrospray ionization (ESI) probe. **SR 14135**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.95 (m, 9H), 2.15–2.45 (m, 3H), 2.85 (m, 1H), 3.00 (dd, 1H), 4.42 (m, 1H), 7.00–7.15 (m, 3H), 7.20–7.45 (m, 6H), 9.5 (br.s, 1H, NH). ES–MS for $C_{22}H_{25}N_3O$: 348.2 ($M^+ + H$). **SR 14136**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45–1.95 (m, 8H), 2.20–2.40 (m, 2H), 2.55 (m, 1H), 2.70 (m, 1H), 3.00 (m, 1H), 3.43 (dd, 1H), 4.52 (m, 1H), 7.00–7.15 (m, 4H), 7.20–7.45 (m, 5H), 9.30 (br.s, 1H, NH). ES–MS for $C_{22}H_{25}N_3O$: 348.2 ($M^+ + H$). **SR 14137**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H), 1.40–1.95 (m, 9H), 2.20–2.40 (m, 3H), 2.85 (m, 1H), 2.98 (dd, 1H), 3.95 (q, 2H), 4.45 (m, 1H), 6.95–7.10 (m, 3H), 7.20–7.45 (m, 6H). ES–MS for $C_{24}H_{29}N_3O$: 376.2 ($M^+ + H$). **SR 14138**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H), 1.40–1.95 (m, 8H), 2.20 (m, 1H), 2.30 (m, 1H), 2.50 (m, 1H), 2.65 (m, 1H), 3.00 (m, 1H), 3.40 (m, 1H), 3.95 (q, 2H), 4.50 (m, 1H), 6.95–7.15 (m, 4H), 7.20–7.41 (m, 5H). ES–MS for $C_{24}H_{29}N_3O$: 376.2 ($M^+ + H$). **SR 14139**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00–2.00 (m, 21H), 2.05 (m, 1H), 2.20 (m, 1H), 2.41 (m, 1H), 3.35 (m, 1H), 4.40 (m, 1H), 7.00–7.15 (m, 3H), 7.30 (m, 1H), 9.65 (br.s, 1H, NH). ES–MS for $C_{22}H_{31}N_3O$: 354.3 ($M^+ + H$). **SR 14140**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00–2.20 (m, 19H), 2.35 (m, 2H), 2.65 (m, 2H), 2.85 (m, 1H), 3.12 (m, 1H), 4.61 (m, 1H), 7.05 (m, 3H), 7.30 (m, 1H), 9.05 (br.s, 1H, NH). ES–MS for $C_{22}H_{31}N_3O$: 354.2 ($M^+ + H$).

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