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A novel receptor ligand: 1-(1-cyclooctyl-piperidin-4-yl)indolin-2-one

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.005 Å
Disorder in main residue
R factor = 0.048
wR factor = 0.135
Data-to-parameter ratio = 8.3

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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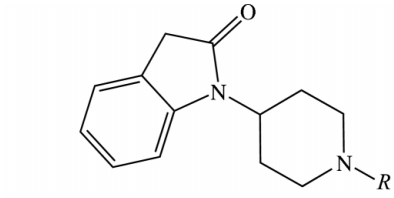
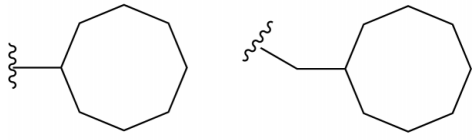
The title compound, $C_{21}H_{30}N_2O$, is a member of the family of nociceptin receptor ligands derived from *N*-(4-piperidinyl)-2-indolinones. Modifications of the piperidine *N*-substituent can produce both agonists and antagonists, with the title compound being a partial agonist with high affinity. The cyclooctyl ring is disordered over two positions.

Comment

In this paper, we report on a member of a new series of ligands for the nociceptin receptor (NOP receptor, previously known as the opioid receptor-like receptor, ORL1). This series of *N*-(4-piperidinyl)-2-indolinones was discovered as a new structural class of NOP receptor ligands (Zaveri *et al.*, 2004). Modifications of the piperidine *N*-substituent produced both potent agonists and antagonists, with modest selectivities over other opioid receptors.



Where *R* is one of the following side chains:



(1) (2)

The NOP receptor is a new member of the family of opioid receptors that were discovered in 1994 (Mollereau *et al.*, 1994), and were found not to bind classical opioids with appreciable affinity. The natural ligand for this new receptor, orphanin FQ (frequently called nociceptin), was later independently identified by two groups as a heptadecapeptide (Reinscheid *et al.*, 1995; Meunier *et al.*, 1995). The physiological role of the NOP receptor and its ligand has been the focus of intense research. Both the NOP receptor and its ligand share significant homology with the classical opioid receptors and their endogenous ligands, although none of the known opioid ligands or synthetic opiates bind appreciably to the NOP receptor.

This series of ligands is particularly interesting because subtle structural changes in the nature of the piperidine N-1 substituent result in conversion of potent antagonists into

potent agonists. The title compound, (1), is a partial agonist with high affinity. The steric characteristics of the substituent greatly affect the activity. By simply linking the cyclooctyl group *via* a methylene, one creates a compound, (2), which is an NOP antagonist (Zaveri *et al.*, 2004). Along with the change in activity, there is an increase in the selectivity between the various opioid receptors.

The title compound crystallizes in the monoclinic space group *Pn*. The cyclooctyl ring is disordered over two positions with the relative populations of 70:30. The populations were initially refined, then set at 70:30 for the final refinements. The bond lengths, angles, and anisotropic displacement parameters of the atoms of the cyclooctyl ring were restrained to help stabilize the refinement of the disordered group.

Experimental

Ligands in this series were synthesized by reductive amination of the appropriate aldehyde or ketone with the common intermediate *N*-1-(4-piperidinyl)-1,3-dihydroindol-2-one (Zaveri *et al.*, 2004).

Crystal data

$C_{21}H_{30}N_2O$
$M_r = 326.47$
Monoclinic, *Pn*
$a = 5.9170\ (2)$ Å
$b = 16.5865\ (6)$ Å
$c = 9.9576\ (4)$ Å
$\beta = 104.128\ (2)^\circ$
$V = 947.70\ (6)$ Å^3
$Z = 2$
$D_x = 1.144$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 1838 reflections
$\theta = 2.7$–53.4°
$\mu = 0.54$ mm^{-1}
$T = 293\ (2)$ K
Plate, colorless
0.54 × 0.16 × 0.02 mm

Data collection

Bruker SMART 6000 CCD diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)
$T_{min} = 0.747$, $T_{max} = 0.989$
4915 measured reflections
2411 independent reflections
1979 reflections with $I > 2\sigma(I)$
$R_{int} = 0.026$
$\theta_{max} = 62.5^\circ$
$h = -6 \rightarrow 5$
$k = -18 \rightarrow 18$
$l = -10 \rightarrow 11$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.048$
$wR(F^2) = 0.135$
$S = 1.03$
2411 reflections
290 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0913P)^2 + 0.0168P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.025$
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.14$ e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.0028 (10)

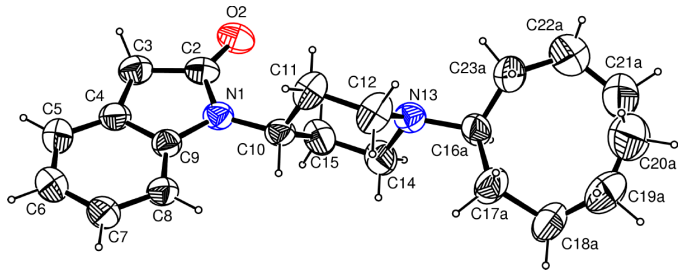


Figure 1
View of the title compound, showing the labeling of the non-H atoms. Only the major component of the disorder is shown for clarity. Displacement ellipsoids are drawn at the 30% probability level.

All H atoms were placed in calculated positions, with C—H distances ranging from 0.93 to 0.98 Å and included in the refinement in riding-model approximation, with $U_{iso}(H) = 1.2U_{eq}$ of the carrier atom. In the absence of significant anomalous dispersion effects Friedel pairs were merged and the Flack (1983) parameter removed from the CIF.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2002); data reduction: *SAINT* and *XPREP* (Bruker, 2001); program(s) used to solve structure: *SHELXTL* (Bruker, 2000); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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