Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

1-[1-(Decahydronaphthalen-1-yl)piperidin-4-yl]indolin-2-one: one of a novel series of nociceptin receptor ligands:

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.054
wR factor = 0.162
Data-to-parameter ratio = 13.1

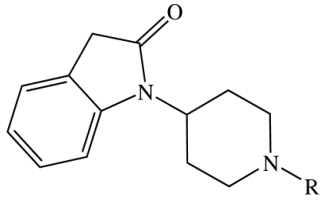
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 13 May 2004
Accepted 2 June 2004
Online 26 June 2004

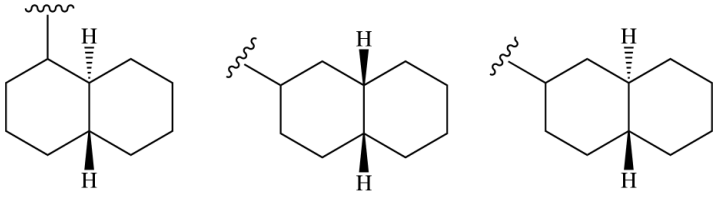
The title compound, $C_{23}H_{32}N_2O$, is a member of the family of nociceptin receptor ligands derived from *N*-(4-piperidinyl)-indolin-2-ones. Modifications of the piperidine *N*-substituent can produce both agonists and antagonists, the title compound being an agonist with moderate affinity.

Comment

The nociceptin receptor (NOP receptor, previously known as the opioid receptor-like receptor, ORL1) was discovered in 1994 (Mollereau *et al.*, 1994). This new member of the family of opioid receptors did not 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.



where R is one of the following side chains



(1) (2) (3)

A series of *N*-(4-piperidinyl)indolin-2-ones were 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. In this paper, we report a member of this new series of NOP ligands. This series is particularly interesting because subtle structural changes in the nature of the piperidine N-1 substituent resulted in conversion of potent antagonists into potent agonists. The title compound, (1), is an agonist with moderate affinity. Interestingly, the spatial posi-

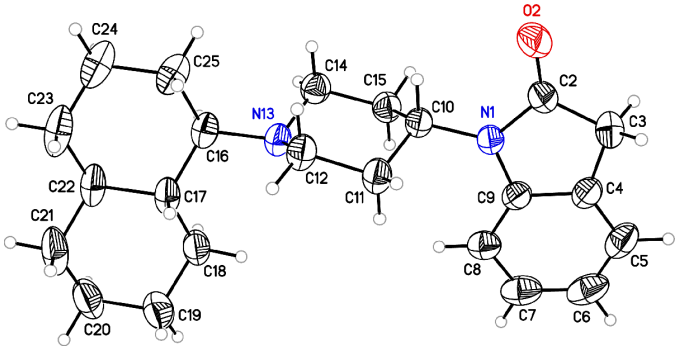


Figure 1
View of the title compound, showing the labeling of the non-H atoms. Displacement ellipsoids are drawn at the 30% probability level.

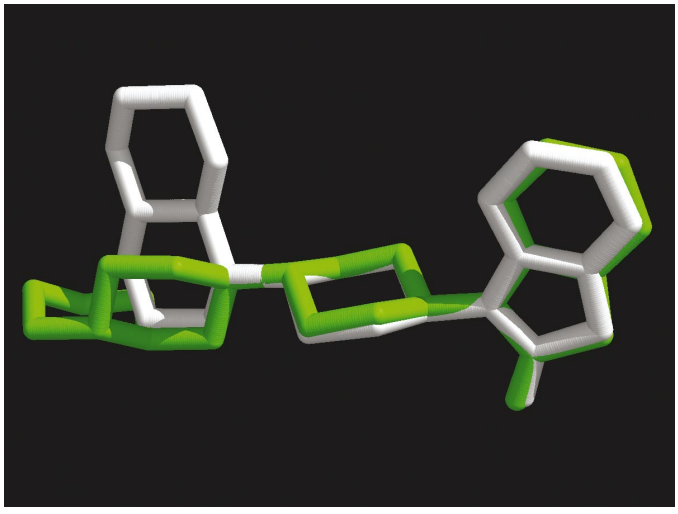


Figure 2
Overlay of 1-[1-(decahydronaphthalen-1-yl)piperidin-4-yl]indolin-2-one (white) and 1-[1-(decahydronaphthalen-3-yl)piperidin-4-yl]indolin-2-one (green), demonstrating the difference in spatial orientations of the substituent groups.

tion of the piperidinyl *N*-substituent with respect to the piperidine ring plays a significant role in determining the affinity of these compounds for the NOP receptor. While the 1-*trans* decalinyl compound (1) is a moderate agonist, the related 2-decalinyl compounds (2) and (3) are potent agonists. An overlay of compounds (1) and (2) (Fig. 2) clearly demonstrates the differences between the spatial orientation of the 1-decalinyl group of (1) and the 2-decalinyl group of (2). Crystals of the 2-*cis* decalinyl compound, (3), have not yet been obtained; however, the *cis* and *trans* configuration of the 2-decalinyl compounds do not appear to affect the affinity, since both compounds (2) and (3) are equipotent at the NOP receptor.

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

$C_{23}H_{32}N_2O$
M_r = 352.51
Monoclinic, $P2_1/c$
a = 8.9714 (2) Å
b = 8.6150 (2) Å
c = 26.4673 (7) Å
β = 99.155 (2)°
V = 2019.56 (8) Å^3
Z = 4
D_x = 1.159 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 3559 reflections
θ = 3.6–28.3°
μ = 0.54 mm^{-1}
T = 293 (2) K
Needle, colorless
0.21 × 0.08 × 0.04 mm

Data collection

Bruker SMART 6000 CCD diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2002)
T_{min} = 0.892, T_{max} = 0.978
10382 measured reflections
3085 independent reflections
2167 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 62.4°
$h = -9 \rightarrow 9$
$k = -8 \rightarrow 9$
$l = -28 \rightarrow 30$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.162
S = 1.03
3085 reflections
236 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0929P)^2 + 0.1732P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0075 (7)

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 the riding-model approximation, with $U_{iso} = 1.2U_{eq}$ of the carrier atom.

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, 2002); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL* and *MidasPlus* (Version 2.1; Ferrin *et al.*, 1988); software used to prepare material for publication: *SHELXTL*.

This work was supported in part by the National Institutes on Drug Abuse (NIDA), the Office of Naval Research (ONR) and the Naval Research Laboratory (NRL).

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