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1-[1-(*trans*-4-Isopropylcyclohexyl)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 = 103 K
Mean σ(C–C) = 0.003 Å
R factor = 0.034
wR factor = 0.093
Data-to-parameter ratio = 9.0

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

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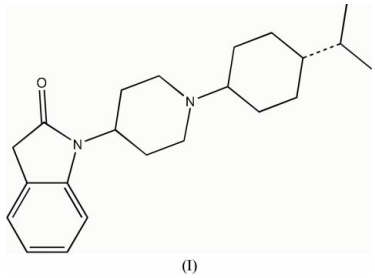
The title compound, $C_{22}H_{32}N_2O$, is a member of the family of nociceptin receptor ligands derived from *N*-(4-piperidinyl)-2-indolinones. Modifications of the piperidine *N*-substituent can produce both agonists and antagonists, with the title compound being a weak agonist. The molecule lies on a crystallographic mirror plane.

Comment

A series of *N*-(4-piperidinyl)-2-indolinones have been discovered as a new structural class of nociceptin 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.

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 to 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. Although both the NOP receptor and its ligand share significant homology with the classical opioid receptors and their endogenous ligands, none of the known opioid ligands or synthetic opiates bind appreciably to the NOP receptor.



(I)

In this paper, we report a member of a new series of NOP ligands based on the 1,3-dihydroindolin-2-one heterocyclic scaffold. 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, (I), is a weak agonist. Changing only the configuration of the cyclohexyl–isopropyl group from *trans* to *cis* produces a strong agonist (Zaveri *et al.*, 2004).

The title compound crystallizes in the monoclinic space group *Cm*. The molecule is bisected by a mirror plane with the indolinone group in this plane and the remainder of the

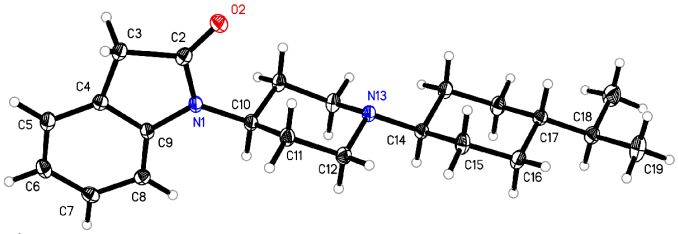


Figure 1
View of the title compound, showing the labeling of the non-H atoms. Displacement ellipsoids are drawn at the 50% probability level.

molecule (including the piperidinyl and cyclohexyl rings) perpendicular to this plane. All bond lengths and angles are within the expected range of values.

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). Suitable crystals were grown by evaporation of a solution in a mixture of dichloromethane and hexane (approximately 1:1).

Crystal data

$C_{22}H_{32}N_2O$
M_r = 340.50
Monoclinic, *Cm*
a = 7.9959 (7) Å
b = 6.8268 (7) Å
c = 17.2125 (17) Å
β = 92.670 (2)°
V = 938.55 (16) Å^3
Z = 2
D_x = 1.205 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3559 reflections
θ = 3.6–28.3°
μ = 0.07 mm^{-1}
T = 103 (1) K
Plate, colorless
0.42 × 0.26 × 0.09 mm

Data collection

Bruker SMART 1000 CCD diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)
T_{min} = 0.891, T_{max} = 0.993
3852 measured reflections
1224 independent reflections
1189 reflections with $I > 2\sigma(I)$
R_{int} = 0.025
θ_{max} = 28.3°
$h = -10 \rightarrow 10$
$k = -8 \rightarrow 9$
$l = -22 \rightarrow 21$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.093
S = 1.11
1224 reflections
136 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0566P)^2 + 0.1948P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

All H atoms were placed in calculated positions, with C—H distances ranging from 0.95 to 0.99 Å, and included in the refinement in the riding-model approximation, with $U_{iso} = 1.2U_{eq}$(carrier atom) ($1.5U_{eq}$ for methyl). In the absence of significant anomalous dispersion effects, Friedel pairs were merged.

Data collection: *SMART* (Bruker, 1999); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2000) and *XPREP* (Bruker, 1997); 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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