Synthesis and Pharmacological Evaluation of 1,2-Dihydrospiro[isoquinoline-4(3*H*),4′-piperidin]-3-ones as Nociceptin Receptor Agonists

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Some synthesized 1,2-dihydrospiro[isoquinoline-4(3*H*),4′-piperidin]-3-ones were evaluated as ligands for nociceptin receptor (NOP receptor). Their affinity was established by binding studies, and efficacy was investigated by GTP binding experiments. Selectivity toward DOP, KOP, and MOP receptors was assessed, and structural requirements affecting affinity and selectivity were remarked. Most notably, compound **6d** displayed nanomolar NOP receptor affinity and showed more than 800-fold selectivity. The new structures exerted full or partial agonistic activity.

Introduction

In 1994, a receptor clearly related to the opioid receptors was discovered. It was named ORL1 receptor[1] (NOP, according to the current nomenclature[2]), and one year later its endogenous ligand the heptadecapeptide nociceptin or orphanin N/OFQ[3] was identified. The NOP-N/OFQ system is widely distributed in both central and peripheral nervous system and is also present in some non-neural tissues.[4] This complex system is involved in many physiological processes including pain, anxiety, learning and memory, blood pressure regulation, and others,[5] but until now, the diverse biological actions of nociceptin have not been fully clarified. Efforts in drug discovery led to the identification of small molecules active on NOP receptor. Agonists are potential therapeutic agents for anxiety, neuropatic pain, cough, drug abuse, and urinary incontinence, and antagonists could find application as analgesics and memory enhancers and in the treatment of Parkinson's disease, depression and obesity. Among NOP receptor–ligands, piperidine derivatives bearing in the 4-position either a spiro junction with systems as 4-imidazolidinone,[6,7] 2-indolinone,[8] isobenzofuran[9] and hexahydropyrrole[3,4-*c*]pyrrole[10] or cyclic substituents such as phenyl,[6a] benzimidazolinone,[11] and dihydroindolinone[12] received the most attention. These derivatives bear a lipophilic moiety on the piperidine nitrogen atom. Zaveri et al. hypothesized that the heterocyclic moiety of the 4-spiropiperidine was a determinant of affinity and selectivity and that the lipophilic N-substituent was responsible for intrinsic activity.[12] A valuable representative of this class of compounds is the potent agonist Ro 64-6198,[6a] whose pharmacology and potential therapeutic applications were recently reviewed.[13] In a previous work,[14] we reported a series of spiropiperidinequinazolinones that resembled the Ro 64-6198 structure and that displayed moderate affinity but high selectivity. Because selectivity more than affinity represents the problem with the development of NOP ligands, these results encouraged us to further exploit the spiropiperidine scaffold. Now, to better understand the structural requirements for receptor interaction, we report an investigation on a new series of 1,2-dihydrospiro[isoquinoline-4(3*H*),4′-piperidin]-3-ones (Figure 1, compounds **5** and **6**) that differ from Ro 64-6198 analogues in having a fused benzene ring instead of a phenyl substituent and in having a dihydroisoquinolinone ring instead of an imidazolinone. We also inserted a fluorine atom in the aromatic ring as fluorine

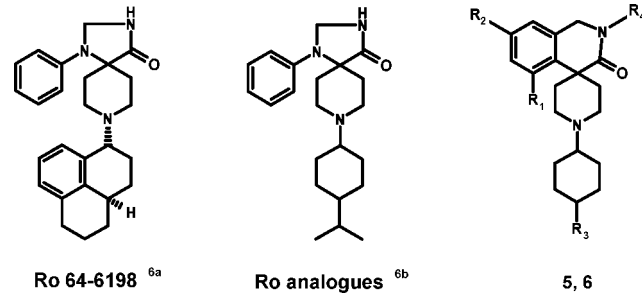

Figure 1. Structures of Roche NOP agonists and 1,2-dihydrospiro[isoquinoline-4(3*H*),4′-piperidin]-3-ones **5** and **6**.

proved to enhance NOP affinity in analogous structures.[8] Molecular modeling methods were employed to gather information on the structural requirements for affinity and selectivity of the studied ligands.

Chemistry. The synthetic pathway to the compounds **5** and **6** is outlined in Scheme 1.

Reductive amination of 4-alkylcyclohexanones with 4-cyano-4-arylpiperidines **1**[15] and sodium triacetoxyborohydride[16] afforded the *cis*- and *trans*-1-(4-alkylcyclohexyl)-4-aryl-4-cyanopiperidines **2**. They were separated by chromatography and unambiguously characterized by 1D and 2D ^{1}H and ^{13}C NMR, by measurement of the coupling constants of axial and equatorial protons in cyclohexane, and by comparison with literature reports on analogous structures.[14] Literature on NOP ligands bearing a 4-alkylcyclohexyl substituent reported that cis isomers are always more potent than the corresponding trans.[6b] In this paper, the trans isomers were not taken into account, and the following synthetical steps were carried on the cis isomers. Hydrolysis of nitriles **2** in an acetic acid/sulfuric acid/water 2:1:1 mixture gave carboxylic acids **3**. These were treated with $SOCl_2$ to obtain the acyl chlorides and subsequently reacted with benzylamine or methylamine to obtain the *N*-substituted amides **4**. The Pictet−Spengler reaction of compounds **4** with paraformaldehyde[17] gave the 1,2-dihydrospiro[isoquinoline-4(3*H*),4′-piperidin]-3-ones **5**. Debenzylation of compounds **5p**−**u** by reaction with phenol, and 85% phosphoric acid[18] afforded compounds **6d**,**f**,**g**,**i**. This reaction when applied to compounds **5q** and **5t** led to the isoquinolinone ring opening and afforded the unsubstituted carboxamides **7e** and **7h** instead of the expected **6e** and **6h**. Attempts to synthesize **6** by direct cyclization of the corresponding unsubstituted 1-(4-alkylcyclo-

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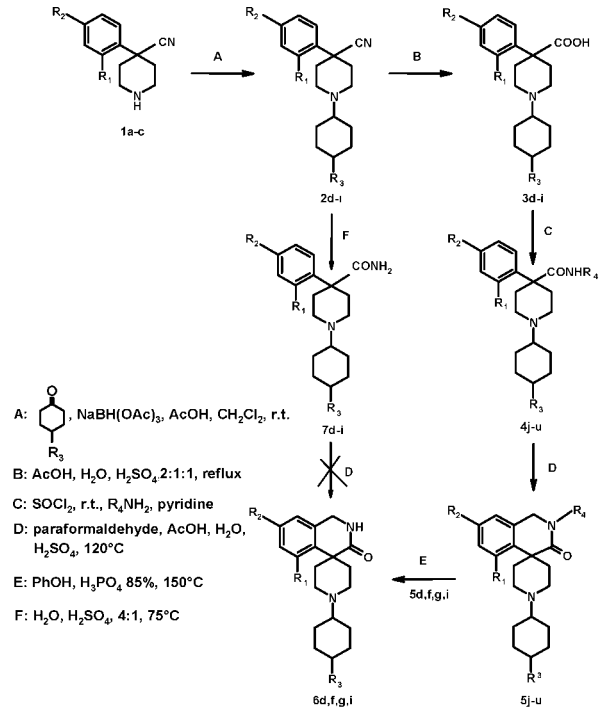
Scheme 1. Synthetic Route to Compounds **5** and **6**



Index	R_1	R_2	R_3	R_4
a	H	H	-	-
b	F	H	-	-
c	H	F	-	-
d	H	H	isopropyl	-
e	F	H	isopropyl	-
f	H	F	isopropyl	-
g	H	H	*tert*-butyl	-
h	F	H	*tert*-butyl	-
i	H	F	*tert*-butyl	-
j	H	H	isopropyl	methyl
k	F	H	isopropyl	methyl
l	H	F	isopropyl	methyl
m	H	H	*tert*-butyl	methyl
n	F	H	*tert*-butyl	methyl
o	H	F	*tert*-butyl	methyl
p	H	H	isopropyl	benzyl
q	F	H	isopropyl	benzyl
r	H	F	isopropyl	benzyl
s	H	H	*tert*-butyl	benzyl
t	F	H	*tert*-butyl	benzyl
u	H	F	*tert*-butyl	benzyl

hexyl)-4-aryl-4-piperidinecarboxamides **7** only afforded the methylated compounds **5j**−**o** in very low yield (5–8%) (Supporting Information).

Pharmacology. Binding affinities for NOP, KOP, MOP, and DOP receptors were measured.[14,19] The ligand efficacy was evaluated as the ability to enhance the binding of [^{35}S]GTPγS at fixed and increasing ligand concentration[14,19] (Figures 2 and 3).

Results and Discussion

Binding experiments results (Table 1) evidenced that the isoquinolinonespiropiperidine moiety was suitable for NOP receptor interaction. Molecular modeling investigations on the ligand−NOP receptor complex (Figure 4) showed that our compounds were anchored by a salt bridge between the basic nitrogen and Asp130 residue as reported for structurally similar opioid ligands.[20] The lactamic sequence that characterized our molecules as well as several NOP ligands[6,8] assured their affinity. Compounds **6** interacted with Thr305 using the amide portion as hydrogen bond donor (Figure 4, top) in agreement with what Bröer et al. described for Ro 64-6198.[20] The introduction of a methyl group on the 2-nitrogen atom (compounds **5j**,**m**) was not detrimental for affinity as the amide maintained interaction with Thr305 by acting as a H-bond acceptor (Figure 4, bottom). Changing the methyl group to a benzyl group influenced the binding affinity only slightly. A fluorine atom at the isoquinolinone moiety of 2-methyl compounds **5j**,**m** strongly affected affinity (up to 50-fold decrease) especially when it was in the 5-position (**5k**,**n**). Although fluorine and hydrogen atoms have similar steric features, the former possesses a negative inductive effect. Thus, when the

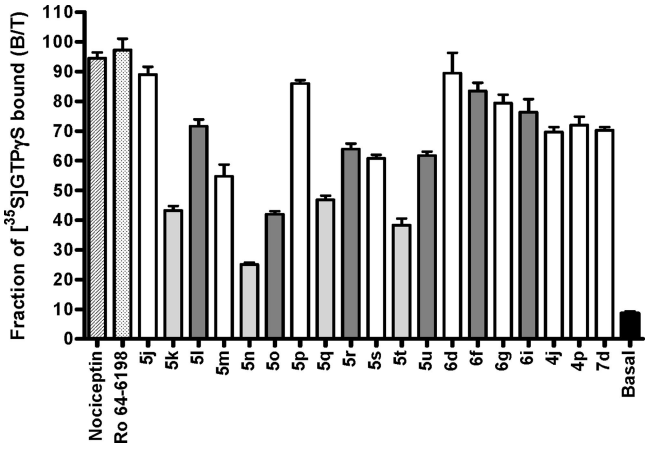


Figure 2. Effect of the new piperidine derivatives on G protein α-subunit activation. The binding of [^{35}S]GTPγS was measured in the presence of 300 nM GDP using membranes prepared from HEK-293 cells stable transfected with human NOP receptors. All compounds were present at a concentration of 10 μM. Data are expressed as bound/total ratio of the radioligand (0.1 nM) and values are the mean ± SEM (n = 3).

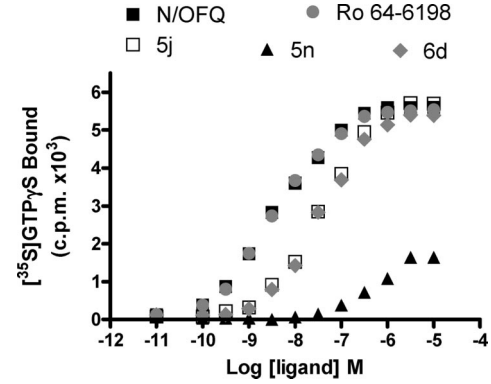


Figure 3. Concentration–response curves for stimulation of GTPγS binding by the compounds **5j**, **5n**, and **6d** in comparison with the curves of N/OFQ and Ro 64-6198. The binding of [^{35}S]GTPγS was measured in triplicate at increasing ligand concentrations and in the presence of 300 nM GDP. All data were computed by subtracting the binding in the absence of ligand.

Table 1. Opioid Receptors Binding Affinity of the New Piperidine Derivatives

	K_i (nM) ± SD[a]				selectivity	
compd	NOP	DOP	KOP	MOP	KOP/NOP	MOP/NOP
N/OFQ[5b]	0.13 ± 0.01	>10^4	>10^4	3030 ± 371	>77000	23307
Ro 64–6198[20]	0.39	1380	89	47	228	121
5j	3.1 ± 1.2	>10^4	557 ± 40	476 ± 43	180	154
5k	186 ± 74	>10^4	412 ± 12	2075 ± 63	2	11
5l	8.9 ± 0.2	>10^4	103 ± 18	540 ± 48	12	61
5m	21 ± 2	>10^4	178 ± 44	1005 ± 77	9	48
5n	395 ± 33	>10^4	3600 ± 1630	7800 ± 4150	9	20
5o	147 ± 45	>10^4	1150 ± 157	3503 ± 480	8	24
5p	6.6 ± 1.3	>10^4	928 ± 17	1340 ± 91	140	203
5q	12 ± 2	>10^4	123 ± 9	6500 ± 3050	10	542
5r	26 ± 9	>10^4	1920 ± 110	1875 ± 119	74	72
5s	51 ± 16	>10^4	97 ± 6	215 ± 20	2	4
5t	81 ± 4	>10^4	190 ± 12	247 ± 43	2	3
5u	136 ± 38	>10^4	1104 ± 255	1582 ± 183	8	12
6d	4.7 ± 1.4	>10^4	3827 ± 650	5406 ± 1605	814	1150
6f	23 ± 1	>10^4	3977 ± 1025	6755 ± 1325	173	294
6g	42 ± 6	>10^4	3844 ± 910	6139 ± 916	92	146
6i	90 ± 16	>10^4	3641 ± 875	5155 ± 1105	40	57
4j	130 ± 45	>10^4	>10^4	>10^4	>70	>70
4p	65 ± 23	>10^4	>10^4	2600 ± 96	>150	40
7d	92 ± 29	>10^4	>10^4	>10^4	>100	>100

[a] Membrane proteins from HEK-293 cells stable transfected with the human NOP[19] or DOP or KOP receptors (Perkin-Elmer Life Sciences) (3–5 μg) and membrane proteins from CHO cells expressing human MOP receptors (Perkin-Elmer Life Sciences) (5–15 μg) were incubated with the specific receptor radioligand (30000–50000 cpm) in a total volume of 1 mL.[14,19] Increasing concentrations of compounds to be tested were added and samples were incubated for 90 min at room temperature. Radioligands: [^{125}I]-nociceptin for NOP, [^{3}H]-naltrindole for DOP, and [^{3}H]-diprenorphine for KOP and MOP receptors. Data are given as mean ± SD (n = 3).

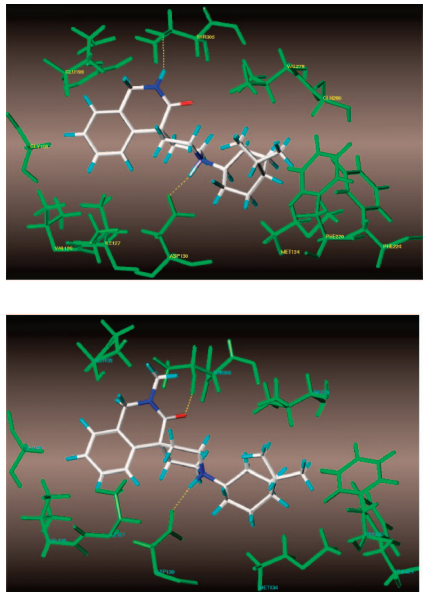


Figure 4. Stereoview of compounds **6d** (top) and **5j** (bottom) inserted in the binding pocket of a NOP receptor 3D model.[20] Intermolecular interactions are represented by dashed lines.

halogen was in the 5-position, its negative partial charge generated a repulsive interaction with the negatively charged Asp130, whose oxygen was only 2 Å far. Asp130 had to move away to minimize repulsion, and the salt bridge with the piperidine nitrogen was consequently weakened. When fluorination occurred at the 7-position, only a moderate decrease in activity was observed (**5l**,**o**). This is because no interaction between fluorine and Asp130 was present in this case. The slight reduction in affinity might be due to repulsive effects exerted toward Tyr309 phenolic oxygen and toward the Cys200 sulfur. Insertion of fluorine in the 2-benzyl derivatives **5p**,**s** was not excessively harmful to affinity. The detrimental effect was expressed mainly when the substituent was inserted in 7-position (**5r**,**u**). Furthermore, small variations in the size of alkylcyclohexyl tail appeared critical for affinity. As already observed,[6b] 4-isopropyl seemed more suitable than *tert*-butyl for receptor binding. Affinity decrease observed, for instance, in compounds **5m**, **5s**, and **6g**, compared with the analogues **5j**, **5p**, and **6d**, could be explained by modeling observations: receptor−**5j** complex showed a bad steric contact between one methyl group of the isopropyl substituent, Val279, and Val283 (the two residues had to shift slightly to make room for the methyl group). Also, Met134 was slightly displaced to accommodate the 3-methylene of the cyclohexyl ring. However, the lipophilic pocket residues revealed a certain degree of mobility, and these shifts did not imply a significant energy increase of the receptor–ligand complex when compared to the complex with Ro 64-6198. On the contrary, the presence of the more cumbersome *tert*-butyl group at the cyclohexyl 4-position led to a substantial energy increase of the receptor–ligand complex. This behavior was caused by a bad steric contact that *tert*-butyl had with Val202, a residue not reported as part of the lipophilic pocket by Bröer.[20] All of the compounds lack affinity for DOP receptor. Their NOP vs MOP selectivity was generally greater than that for NOP vs KOP. Multiple sequence alignment of NOP, KOP, and MOP receptor transmembrane domains[21] evidenced that threonine at the NOP 305-position is replaced by isoleucine in the KOP and MOP receptor transmembrane helix TM7 at the 316- and 324-positions, respectively. The presence of an isoleucine makes impossible the hydrogen bond formation and determines the poor **6d** affinity for KOP and MOP receptors. This can explain compound **6d** excellent selectivity profile. In 2-substituted compounds **5j** and **5p**, the hydrogen bond interaction is replaced by hydrophobic interactions between isoquinolinone 2-methyl or 2-benzyl groups and isoleucine. This explains the higher affinity for KOP and MOP receptors of the 2-substituted compounds compared to **6d**. Moreover loss in selectivity for NOP receptor seemed to be generally related to the molecular hydrophobicity increase caused by introduction of lipophilic groups as *tert*-butyl and/or fluorine atom. GTPγS binding experiments at NOP receptor in the presence of

compounds **5** and **6** were performed to test efficacy of our compounds. The results are reported in Figure 2. As illustrated by the histogram, the isopropyl derivatives **5j**, **5p** showed agonism and their intrinsic activity was variously influenced by the introduction of fluorine in the heterocyclic portion. Efficacy decreased in the *tert*-butyl-substituted **5m**, **5s** whereas compounds **6** were less affected by both the presence of the halogen and the nature of the alkyl group in the lipophilic portion. To ascertain if compounds **5j** and **6d** were full or partial agonists and to exclude antagonism for the less potent **5n**, stimulation of [^{35}S]GTPγS was measured in concentration–response curves in comparison with N/OFQ and Ro 64-6198 (Figure 3). Compounds **5j** and **6d** behaved as full agonists, whereas **5n** exhibited partial agonist activity. Through a ligand-based analysis, Zaveri et al.[12] showed that the ligand lipophilic moiety is supposedly responsible for intrinsic activity. It was observed that when the lipophilic moiety of agonists is subject to 1-carbon homologation at the piperidine side, antagonists are generated. Thus, she theorized the presence of a trigger site in the receptor lipophilic pocket that induced major conformational changes in the receptor when activated by agonists. Antagonists instead accommodated their lipophilic moiety in the same receptor pocket but did not activate that trigger. To corroborate such a theory and to find out which residue in particular may constitute the trigger point, further docking investigations were carried out. Upon inserting an agonist such as **5j** in the 3D NOP-receptor model, Trp276 shifted to make room for the methylene in the 2-position at the R-cyclohexyl ring. This in turn caused a displacement of Asn311, resulting in the disruption of the hydrogen bonds that Asn311 forms with Cys275 and Gly308. When analogous structures bearing a methylene bridge between piperidine ring and the R-cyclohexyl group were docked instead, these major conformational changes did not manifest. Therefore, it may be reasonably assumed that those changes were linked to the receptor activation, with Trp276 being the trigger site envisaged by Zaveri.[12] Preliminary investigation on the pharmacological characteristics of the amides **4** and **7** showed an affinity decrease in comparison with their cyclized analogues. In Table 1, data regarding affinity and selectivity of **4j**, **4p**, and the 2-unsubstituted derivative **7d** have been reported. These compounds, investigated for potency at the NOP receptor, showed a non-negligible effect on G protein α-subunit activation (Figure 2). A thorough evaluation of the biological activity of the open amides will be conducted later and reported elsewhere.

Experimental Section

General Procedures. Compounds were purified by column chromatography on Merck aluminum oxide 90 and their purity checked on Merck aluminum oxide 60 F254 (type E) plates. Sodium sulfate was used to dry organic solutions. Melting points were determined on a Köfler apparatus. Elemental analyses were within ±0.4% of the theoretical values. The ^{1}H and ^{13}C NMR spectra were performed on a Bruker Avance 400 instrument, and chemical shifts were expressed in ppm (δ). Mass spectra were recorded on a HP 59980 B spectrometer operating at 70 eV. GDP and GTPγS were purchased by Sigma, N/OFQ was from Bachem, and Ro 64-6198 was kindly provided by Roche. Receptor radioligands, [^{125}I-Tyr^{14}]nociceptin, [^{3}H]naltrindole and [^{3}H]diprenorphine, and labeled nucleotide [^{35}S]GTPγS were purchased by Perkin-Elmer Life Sciences. Molecular modeling calculations were performed using the Sybyl 7.1 software package (Tripos, Inc., St. Louis, MO) running under the Linux operating system.

General Procedure for the Synthesis of the *cis*-1-(4-Alkylcyclohexyl-4-aryl-4-piperidinecarbonitriles 2d−i. Compound **1** (16 mmol) and 4-isopropylcyclohexanone (16 mmol) were dissolved in 1,2-dichloroethane (46 mL). NaBH(OAc)$_3$ (4.6 g, 22 mmol) and AcOH (0.9 mL, 16 mmol) were sequentially added to the solution, which was stirred overnight at room temperature. Aqueous NaOH (10%) was added, and the layers were separated. The organic phase was evaporated under reduced pressure. Purification by chromatography on Al_2O_3 eluting with ethyl acetate/*n*-hexane (15:85) afforded cis and trans isomers **2** in an approximately 7:3 ratio.

General Procedure for the Synthesis of the *cis*-1-(4-Alkylcyclohexyl)-4-aryl-4-piperidinecarboxylic acids 3d−i. A solution of **2** (10 mmol) in a AcOH/H_2O/H_2SO_4 (2:1:1) mixture (120 mL) was refluxed for 3 h. Most of the acetic acid was evaporated under reduced pressure, and the residue was diluted with H_2O and alkalinized to pH 9 with aqueous NaOH (10%). The pH of the cloudy solution was adjusted to 4–5 with acqueous HCl (15%). Compounds **3** separated as white precipitates and were collected by filtration, washed with H_2O and diethyl ether, and dried under vacuum.

General Procedure for the Synthesis of the *cis*-1-(4-Alkylcyclohexyl)-4-aryl-*N*-methyl-4-piperidinecarboxamides 4j−o. A suspension of **3** (3.0 mmol) in $SOCl_2$ (15 mL) was stirred overnight at room temperature. $SOCl_2$ was removed under reduced pressure, and $MeNH_2 \cdot HCl$ (0.24 g, 3.6 mmol) was added to the solid residue. The mixture was cooled to 0 °C, and pyridine (30 mL) and *N,N*-ethyldiisopropylamine (2.1 mL, 12 mmol) were added dropwise. The mixture was stirred overnight at room temperature. The volatiles were evaporated, and the residue was suspended in H_2O and extracted three times with ethyl acetate. The solvent was removed to afford the compounds **4j−o**, which were purified by crystallization from ethyl acetate/hexane.

General Procedure for the Synthesis of the *cis*-1-(4-Alkylcyclohexyl)-4-aryl-*N*-benzyl-4-piperidinecarboxamides 4p−u. A suspension of **3** (3.0 mmol) in $SOCl_2$ (15 mL) was stirred overnight at room temperature. $SOCl_2$ was removed under reduced pressure. The solid residue was cooled to 5 °C, and pyridine (30 mL) and benzylamine (6.0 mmol) were carefully added. The mixture was stirred overnight at room temperature. The volatiles were evaporated, and the residue was suspended in H_2O and extracted three times with ethyl acetate. The solvent was removed to afford the compounds **4p−u**, which were purified by crystallization from ethyl acetate.

General Procedure for the Synthesis of the *cis*-2-Substituted 1,2-Dihydrospiro[isoquinoline-4(3*H*),4′-piperidin]-3-ones 5j−u. A mixture of compound **4j** (1.4 mmol) and paraformaldehyde (3 mmol) in AcOH (3.0 mL), Ac_2O (1.5 mL), and H_2SO_4 (0.2 mL) was heated at 140 °C for 3 h. An additional amount of paraformaldehyde (3 mmol) was added, and the solution was maintained at 140 °C for 6 h. The mixture was allowed to cool to room temperature, diluted with H_2O (15 mL), alkalinized with aqueous NaOH (10%), and extracted three times with ethyl acetate. The combined organic extracts were evaporated. Crude **5j** was purified by chromatography on Al_2O_3 eluting with ethyl acetate/*n*-hexane (20:80) and crystallized from ethyl acetate (19% yield): mp 96–97 °C; ^{1}H NMR (pyridine-d_5) δ 7.54 (d, 1H), 7.35 (t, 1H), 7.27 (t, 1H), 7.20 (d, 1H), 4.45 (s, 2H, 1-CH_2) 3.07 (s, 3H, NCH_3), 2.95 (t, 2H, H-2_{ax},H-6_{ax} d), 2.80 (d, 2H, H-2_{eq},H-6_{eq}), 2.36 (d, 2H, H-3_{eq},H-5_{eq}), 2.30 (m, 1H, H-1′$_{eq}$, $J_{eq\text{-}ax} = 6.2$ Hz, $J_{eq\text{-}eq} = 3.1$ Hz), 2.05 (t, 2H, H-3_{ax}, H-5_{ax}), 1.79 (m, H-2′$_{eq}$, H-6′$_{eq}$), 1.60 (m, 2H, H-3′$_{ax}$, H-5′$_{ax}$), 1.49 (m, 1H, isopropyl CH), 1.42 (m, 2H, H-2′$_{ax}$, H-6′$_{ax}$), 1.33 (m, 2H, H-3′$_{eq}$, H-5′$_{eq}$), 1.03 (m, 1H, H-4′$_{ax}$, $J_{ax\text{-}ax} = 11.7$ Hz, $J_{ax\text{-}isopropylCH} = 7.9$ Hz, $J_{ax\text{-}eq} = 3.8$ Hz), 0.89 (d, 6H, isopropyl CH_3); ^{13}C NMR (pyridine-d_5) δ 173.9, 142.8, 134.0, 128.4, 127.1, 126.8, 125.6, 61.3, 52.7, 47.9, 44.8, 43.5, 35.5, 33.5, 30.7, 27.6, 26.4, 21.2; MS (EI) *m*/*z* 354 (M^+). Anal. ($C_{23}H_{34}N_2O$) C, H, N.

General Procedure for the Synthesis of the *cis*-1,2-Dihydrospiro[isoquinoline-4(3*H*),4′-piperidin]-3-ones 6d,f,g,i. Compound **5p** (1.0 mmol) was added to a solution of PhOH (3.2 mmol) in 85% H_3PO_4 (7.0 mL). The mixture was kept at 150 °C, and the progress of the reaction was monitored by TLC (Al_2O_3 ethyl acetate/hexane 20:80) for about 3 h. The solution was poured on crushed ice, acidified with aqueous HCl (5%), and washed with ethyl acetate. The aqueous phase was alkalized with aqueous NaOH (20%) and extracted with ethyl acetate (3 × 15 mL). The solvent was

evaporated under vacuum. Crude **6d** was crystallized from ethyl acetate (32% yield): mp 172–174 °C; ^{1}H NMR (pyridine-d_5) δ 8.90 (bs, 1H, NH), 7.58 (d, 1H), 7.36 (t, 1H), 7.24 (t, 1H), 7.20 (d, 1H), 4.61 (s, 2H, 1-CH_2), 3.05 (t, 2H, H-2_{ax}, H-6_{ax}), 2.88 (m, 2H, H-2_{eq}, H-6_{eq},), 2.48 (d, 2H, H-3_{eq}, H-5_{eq}), 2.31 (m, 1H, H-$1'_{eq}$, $J_{eq\text{-}ax}$ = 5.9 Hz, $J_{eq\text{-}eq}$ = 3.0 Hz), 2.15 (t, 2H, H-3_{ax}, H-5_{ax}), 1.78 (m, H-$2'_{eq}$, H-$6'_{eq}$), 1.60 (m, 2H, H-$3'_{ax}$, H-$5'_{ax}$), 1.52 (m, 1H, isopropyl CH), 1.45 (m, 2H, H-$2'_{ax}$, H-$6'_{ax}$), 1.34 (m, 2H, H-$3'_{eq}$, H-$5'_{eq}$), 1.04 (m, 1H, H-$4'_{ax}$, $J_{ax\text{-}ax}$ = 11.6 Hz, $J_{ax\text{-}isopropylCH}$ = 7.7 Hz, $J_{ax\text{-}eq}$ = 3.9 Hz), 0.86 (d, 6H, isopropyl CH_3); ^{13}C NMR (pyridine-d_5) δ 176.7, 143.3, 135.3, 128.2, 127.1, 126.8, 125.6, 61.3, 48.1, 45.5, 45.0, 43.5, 33.1, 30.8, 27.6, 26.4, 21.2; MS (EI) *m*/*z* 340 (M^+). Anal. ($C_{22}H_{32}N_2O$) C, H, N.

General Procedure for the Synthesis of *cis*-1-(4-Alkylcyclohexyl)-4-aryl-4-piperidinecarboxamides 7d−i. Compound **2** (2.5 mmol) was added to a mixture of sulfuric acid (5.6 mL) and water (1.3 mL). The solution, kept at 75 °C for 2 h, was cooled to room temperature, poured on crushed ice, alkalinized with aqueous sodium hydroxide (10%), and extracted with ethyl acetate three times. The volatiles were evaporated and the compounds **7** were crystallized from ethyl acetate.

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Supporting Information Available: Pharmacological data of some amides **4** and **7**. Molecular modeling methods. Procedure for preparation of compounds **5j−o** from **7d−i**. Spectral data and microanalyses of compounds **2−7**. Procedures for pharmacological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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