# Synthesis and Evaluation as NOP Ligands of Some Spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones and Spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazolines]

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**Some spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones 3 and spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo-[1,5-*c*]quinazolines] 4 were synthesized and evaluated as ligands of the nociceptin receptor. The examined compounds showed partial agonistic activity, except compounds 3, 4n that proved to be pure antagonists.**

**Key words** spiropiperidine; spiropiperidine triazoloquinazoline; nociceptin receptor ligand; opioid

The nociceptin (NOP) receptor is the latest identified member of the transmembrane G-protein coupled receptors family comprising $\delta$, $\kappa$ and $\mu$ opioid receptors.[1)]

Its original homology cloning and the isolation from brain extracts of the endogenous ligand, the heptadecapeptide nociceptin (NC),[2,3)] gave rise to a great interest in clarifying its physiological functions. The receptor, distributed in both central and peripheral nervous systems and in non-neuronal tissues, revealed to be involved in several processes including modulation of nociception,[2,3)] locomotor activity,[3)] reversal of stress-induced analgesia,[4)] modulation of learning and memory,[5—7)] regulation of neurotransmitter and hormone release,[8,9)] neuronal differentiation.[10,11)]

In the last years NOP receptor has become an important biological target for a number of potential therapeutic applications associated with pain, stress and anxiety, cognitive deficiency, eating and other disorders.[12)] At the same time, consistent advances have been attained in the design and discovery of new ligands, and many nonpeptide small molecules were developed as agonists or antagonists.[13—17)]

Among several scaffolds, spiropiperidines showed to be an interesting and promising class of NOP ligands. They are structurally related to lofentanyl (Fig. 1), a $\mu$-selective opiate ligand having also affinity for the NOP receptor.

The NOP active site[18,19)] was first investigated by computational studies on its complex with nociceptin[20,21)] and lofentanyl.[21)] Anyway spiropiperidines[22)] were useful tools for the elucidation of the mechanism of interaction of small non peptidic molecules. These studies indicated the electrostatic interaction of protonated piperidinic nitrogen with Asp130 and a hydrogen bond between the small molecule and Thr305 as determinant features for affinity.

Most of the spiropiperidines have been reported to possess high agonistic activity and selectivity as Ro 64-6198[14)] (Fig. 1) which also exhibited anxiolytic properties.

The interest in this scaffold of compounds also relies in their capability of reversing their biological effect after small structural modifications. Some antagonists developed by Banyu[15)] (Fig. 1) that differ from their "isomer" Ro 64-6198 in the imidazolinone amidic sequence, can be mentioned as an example.

The intriguing and often complex structure–activity relationships of spiropiperidinic NOP ligands led us to synthesize a series of new spiropiperidine-quinazolinones **3** and spiropiperidine-triazoloquinazolines **4** whose structure partly recalled some very potent agonists by Roche[16)] (Fig. 1). Our aim was to explore the influence of the following structural features on affinity and selectivity:

- the presence of a fused benzene ring instead of the typical *N*-phenyl substituent
- the inversion of the NH–CO sequence respect to the lead molecules
- the different length and branching of the alkylsubstituent on the cyclohexane ring
- the substitution of the amidic moiety by a fused triazole ring.

## Results and Discussion

**Chemistry** The synthetical pathway to the target compounds is outlined in Fig. 2.

The 1-substituted piperidones **2** were obtained by reaction

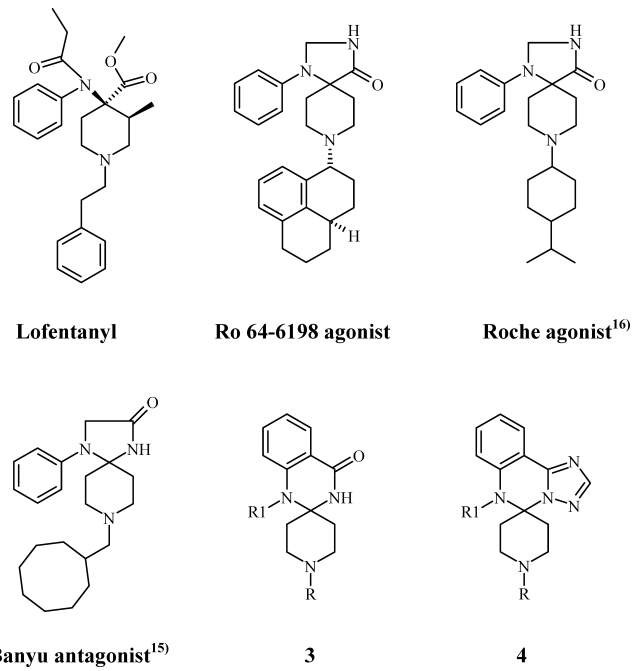


Fig. 1. Structures of NOP Receptor Ligands and of the Synthesized Compounds

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of the 1-ethyl-1-methyl-4-oxopiperidinium iodide **1**[23] with the corresponding amines in a hydroalcoholic medium in the presence of sodium carbonate at reflux. The reaction of **1** with 4-alkylcyclohexylamines used as isomeric mixtures,[24] gave the expected *cis* and *trans* isomers which were separated by column chromatography on aluminium oxide or silica gel by eluting with ethyl acetate/hexane mixtures. The assignment of their configuration was performed by $^1$H-NMR in pyridine-$d_5$ solution. The *cis* isomer always eluted first.

Compounds **2** were allowed to react with anthranylamides in an acetic acid–sulfuric acid mixture to give spiro compounds **3**. Reaction of **2** with 2-([1,2,4]triazol-3-yl)aniline[25] in the same acidic medium gave the [1,5-*c*] fused compounds **4**.

*N*6′-Methylation of compounds **4d *cis*** and **4e *cis*** was achieved by reaction with formic acid and sodium borohydride to give **4m *cis*** and **4n *cis*** respectively.

In order to obtain an experimental evidence that we had [1,5-*c*] and not [4,3-*c*] ring fusion, we synthesized the 5,6-dihydro-[1,2,4]triazolo[1,5-*c*]quinazoline by reduction of the [1,2,4]triazolo[1,5-*c*]quinazoline[25] with sodium borohydride and observed that its H-2 signal in the $^1$H-NMR spectrum in DMSO-$d_6$ had the same position ($\delta$=8.04 ppm) of the corresponding H-2′ protons in compounds **4**.

**Pharmacology** The binding affinities of the synthesized compounds were measured by employing [$^{125}$I]-nociceptin as radiotracer. The most active compounds were also tested on $\delta$, $\kappa$ and $\mu$ receptors to estimate their selectivity towards all the opioid receptor subtypes. In such experiments we used [$^3$H]-naltrindole for $\delta$, and [$^3$H]-diprenorphine for $\kappa$ and $\mu$ as radioligands. The results are shown in Tables 1 and 2.

The biological efficacy of the compounds was evaluated as their ability to enhance the binding of [$^{35}$S]GTP$\gamma$S in the presence of GDP, using membranes isolated from cells transfected with NOP receptors. This assay, based on GTP/GDP exchange on the G protein $\alpha$ subunit, is a direct measure of receptor-mediated G protein activation (Fig. 3). The membranes were prepared from a cell line expressing a tandem fusion protein between the NOP receptor and the $\alpha$ subunit of $G_o$. As previously reported[26] the forced 1 : 1 stoichiometry of expression of receptor and G$\alpha$ subunit in such system greatly enhances the GTP$\gamma$S response and allows to detect even small levels of ligand efficacy.

Moreover, for the *cis* compounds **3d**, **e**, **m**, **n**, **s**, **t** and **4d**, **e**, **m**, **n** we scanned the [$^{35}$S]GTP$\gamma$S binding response at a wide range of GDP concentrations in order to reveal the full or partial agonism and the antagonism, of these compounds (Fig. 4).

The *cis* compounds **3m**, **3n**, **4m** and **4n** were also tested for their potency to affect nociceptin-stimulated GTP$\gamma$S binding. The dose-response curves are reported in Fig. 5.

**Binding Affinity for NOP Receptor** The most active compounds ($IC_{50}$ values $<10\,\mu$M) are reported in Table 1. The compounds **3f**, **g**, **i** and their $N^1$-methylated analogues **3o**, **p**, **r**, bearing the aromatic substituent benzyl, phenethyl and dibenzosuberyl on the piperidine nitrogen atom, showed low affinity and have not been taken into account in the selectivity and intrinsic activity experiments.

The binding data of 4-alkylcyclohexyl derivatives indicated that branched alkyl groups, *iso*-propyl for **3d**, **m**, **s** and **4d**, **m** and *tert*-butyl for **3e**, **n**, **t** and **4e**, **n**, enhanced potency

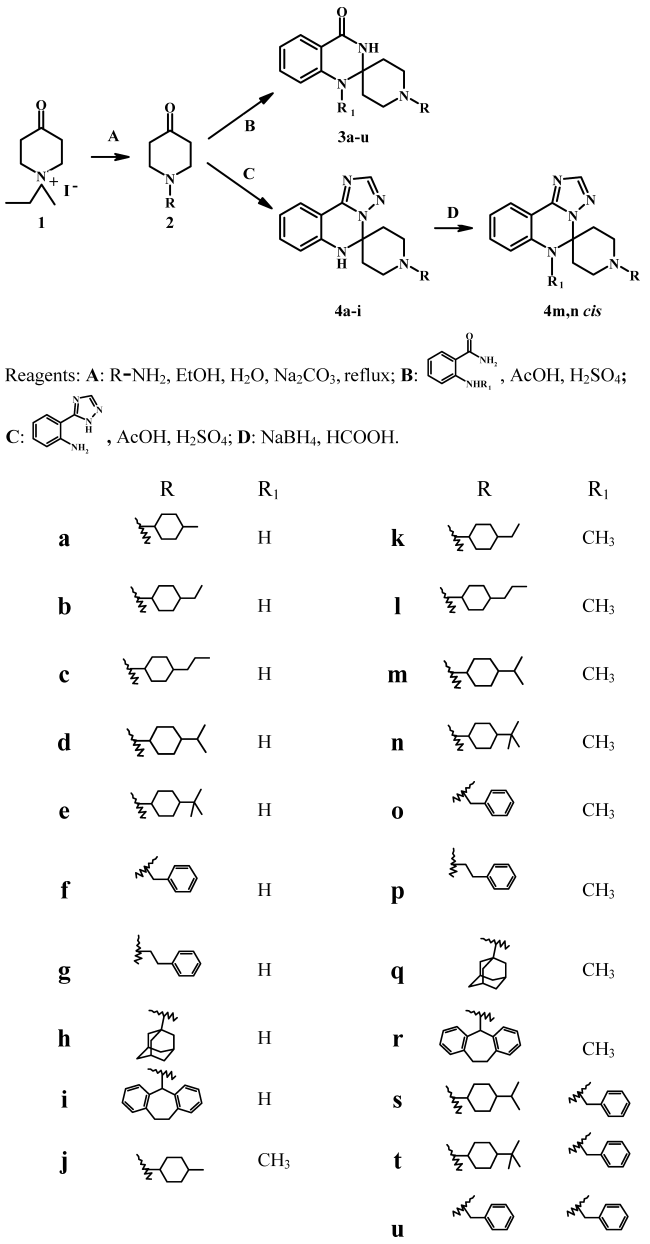



Fig. 2. Synthetical Route to Compounds **3** and **4**

compared to linear methyl, ethyl and propyl substituents (**3a**—**c**, **4a**—**c**).

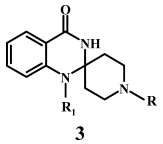
In both series **3** and **4** the *cis* conformers showed a higher affinity than their *trans* isomers. This configurational effect resulted more evident in the *iso*-propyl derivatives **3d**, **m**, whose *cis* isomers were about 20 folds more active than their corresponding *trans*.

Methylation or benzylation on the quinazolinone $N^1$ tended not to affect the affinity of the ligands while $N^1$-benzylation of the less active compounds **3d *trans*** and **3f**, led to a 10-fold increased affinity (**3f** $IC_{50}$=50.8 $\mu$M, **3u** $IC_{50}$= 5.1 $\mu$M).

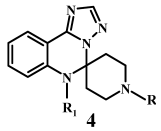
The substitution of the amide function $HN_3$–$C_4$=O with the isosteric triazole ring, to give compounds **4**, resulted in a general increase of potency mainly for the *N*-methyl and *N*-ethylcyclohexyl compounds **3a**, **b**.

In conclusion, the binding studies suggest two essential structural requirements for the affinity: a bent molecular

Table 1. *In Vitro* Affinity of Compounds **3** and **4**



**3**



**4**

| R | $R_1$ | Compound | $IC_{50}$ ($\mu$M) | | | |
|---|---|---|---|---|---|---|
| | | | NOP | $\mu$ | $\delta$ | $\kappa$ |
| 4-Ethylcyclohexyl | H | **3b** ***cis*** | 4.2±0.5 | — | — | — |
| 4-Propylcyclohexyl | H | **3c** ***cis*** | 4.9±0.8 | — | — | — |
| 4-*i*-Propylcyclohexyl | H | **3d** ***cis*** | 0.6±0.2 | 118±6 | >1000 | 49.2±1.9 |
| 4-*i*-Propylcyclohexyl | H | **3d** ***trans*** | 10.7±2.2 | — | — | — |
| 4-*t*-Butylcyclohexyl | H | **3e** ***cis*** | 0.9±0.1 | 36.7±4.9 | >1000 | 10.3±1.2 |
| 4-*t*-Butylcyclohexyl | H | **3e** ***trans*** | 4.9±1.4 | — | — | — |
| Adamantyl | H | **3h** | 1.7±0.3 | >1000 | >1000 | >1000 |
| 4-Ethylcyclohexyl | Methyl | **3k** ***cis*** | 4.8±0.9 | — | — | — |
| 4-Propylcyclohexyl | Methyl | **3l** ***cis*** | 4.8±1.2 | — | — | — |
| 4-*i*-Propylcyclohexyl | Methyl | **3m** ***cis*** | 0.6±0.3 | 8.0±0.6 | >1000 | 35.8±1.5 |
| 4-*i*-Propylcyclohexyl | Methyl | **3m** ***trans*** | 13.5±3.5 | — | — | — |
| 4-*t*-Butylcyclohexyl | Methyl | **3n** ***cis*** | 0.50±0.02 | 43.6±3.0 | >1000 | 12.1±1.1 |
| 4-*t*-Butylcyclohexyl | Methyl | **3n** ***trans*** | 3.9±0.6 | — | — | — |
| Adamantyl | Methyl | **3q** | 7.3±1.4 | 105±9 | >1000 | 21.6±2.6 |
| 4-*i*-Propylcyclohexyl | Benzyl | **3s** ***cis*** | 0.5±0.2 | 3.6±0.2 | >1000 | 3.1±0.2 |
| 4-*i*-Propylcyclohexyl | Benzyl | **3s** ***trans*** | 1.8±0.2 | — | — | — |
| 4-*t*-Butylcyclohexyl | Benzyl | **3t** ***cis*** | 1.1±0.5 | 1.0±0.5 | >1000 | 2.9±0.2 |
| 4-*t*-Butylcyclohexyl | Benzyl | **3t** ***trans*** | 3.2±0.5 | — | — | — |
| Benzyl | Benzyl | **3u** | 5.1±0.9 | — | — | — |
| 4-Methylcyclohexyl | H | **4a** ***cis*** | 4.0±0.5 | >100 | >1000 | 46±4.9 |
| 4-Methylcyclohexyl | H | **4a** ***trans*** | 10.0±0.6 | — | — | — |
| 4-Ethylcyclohexyl | H | **4b** ***cis*** | 1.6±0.7 | >100 | >1000 | 41±4.5 |
| 4-Ethylcyclohexyl | H | **4b** ***trans*** | 3.8±1.2 | — | — | — |
| 4-Propylcyclohexyl | H | **4c** ***cis*** | 5.2±0.1 | — | — | — |
| 4-*i*-Propylcyclohexyl | H | **4d** ***cis*** | 0.5±0.1 | 18.6±1.5 | >1000 | 12.1±1.9 |
| 4-*i*-Propylcyclohexyl | H | **4d** ***trans*** | 2.5±0.6 | — | — | — |
| 4-*t*-Butylcyclohexyl | H | **4e** ***cis*** | 0.50±0.06 | 7.8±1.4 | >1000 | 5.1±0.9 |
| 4-*t*-Butylcyclohexyl | H | **4e** ***trans*** | 3.9±0.1 | — | — | — |
| Adamantyl | H | **4h** | 1.2±0.1 | 45.6±3.5 | >1000 | 14.4±2.3 |
| 4-*i*-Propylcyclohexyl | Methyl | **4m** ***cis*** | 4.1±0.9 | 82.8±3.0 | >1000 | 16.7±2.4 |
| 4-*t*-Butylcyclohexyl | Methyl | **4n** ***cis*** | 1.3±0.3 | 12.5±1.9 | >1000 | 3.6±1.1 |

Radioligands: [$^{125}$I]-nociceptin for NOP, [$^3$H]-naltrindole for $\delta$ and [$^3$H]-diprenorphine for $\kappa$ and $\mu$ receptors. Data are given as mean±S.D. ($n$=3).

Table 2. Selectivity towards $\delta$, $\kappa$ and $\mu$ Receptors of *cis iso*-Propyl-, *tert*-Butylcyclohexyl and Adamantyl Derivatives **3** and **4**

| Compound | $\delta^{a)}$ | $\kappa^{b)}$ | $\mu^{c)}$ |
|---|---|---|---|
| **3d** ***cis*** | >100 | 82 | >100 |
| **3e** ***cis*** | >100 | 11 | 40 |
| **3h** | >100 | >100 | >100 |
| **3m** ***cis*** | >100 | 57 | 14 |
| **3n** ***cis*** | >100 | 23 | >100 |
| **3q** | >100 | 3 | 16 |
| **3s** ***cis*** | >100 | 7 | 7 |
| **3t** ***cis*** | >100 | 3 | 1 |
| **4d** ***cis*** | >100 | 46 | 37 |
| **4e** ***cis*** | >100 | 11 | 17 |
| **4h** | >100 | 12 | 39 |
| **4m** ***cis*** | >100 | 2.5 | 19 |
| **4n** ***cis*** | >100 | 3 | 10 |

*a*) Selectivity expressed as $\delta$ $IC_{50}$/NOP $IC_{50}$ ratio. *b*) Selectivity expressed as $\kappa$ $IC_{50}$/NOP $IC_{50}$ ratio. *c*) Selectivity expressed as $\mu$ $IC_{50}$/NOP $IC_{50}$ ratio.

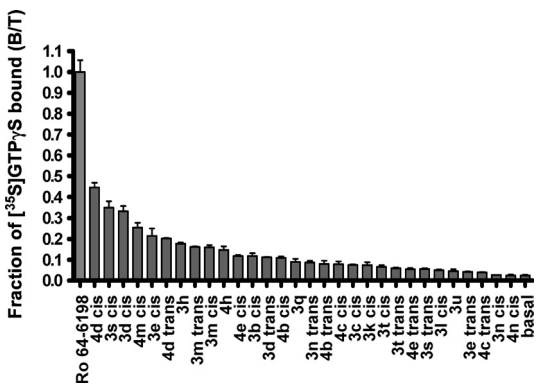



Fig. 3. Effect of Compounds **3** and **4** on G Protein $\alpha$-Subunit Activation

The binding of [$^{35}$S]GTP$\gamma$S was measured in the presence of 300 nM GDP as described in Experimental using membranes prepared from cells transfected with NOP receptors. All compounds were present at a concentration of 100 $\mu$M. Data are expressed as Bound/Total ratio of the radioligand (0.1 nM) and values are the mean± S.D. ($n$=3).

shape, derived from the *cis* 1,4-disubstitution of cyclohexane ring (Fig. 6) and a branched hydrophobic tail as *iso*-propyl or *tert*-butyl group. A lipophilic probe in the quinazolinone portion represented by $N^1$-methyl or benzyl substituents did not appear a strict requirement for affinity.

**Selectivity towards $\delta$, $\kappa$ and $\mu$ Receptors** The most ac-

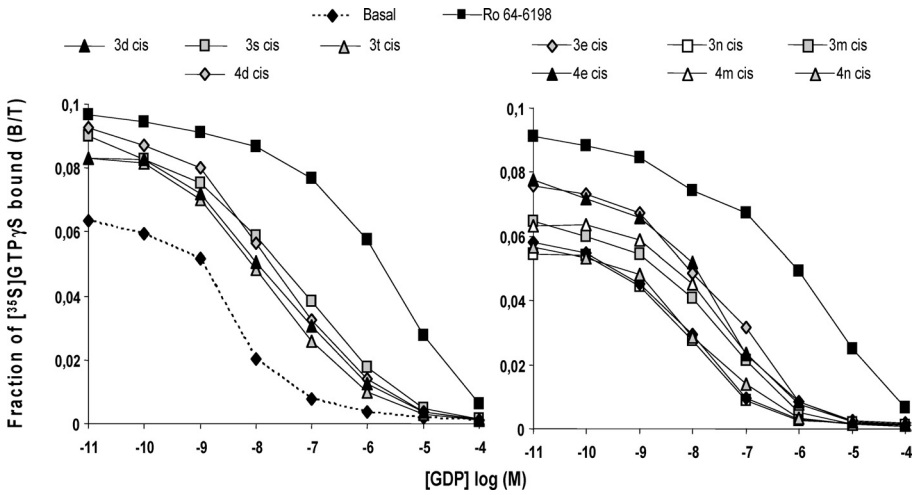



Fig. 4. Effects of the *cis* Compounds **3d**, **e**, **m**, **n**, **s**, **t** and **4d**, **e**, **m**, **n** on GPTγS Binding in Comparison with the Agonist Ro 64-6198

The binding of [$^{35}$S]GTPγS was measured at increasing GDP concentrations as indicated on *x*-axis, in the absence (BAS) or in the presence of the ligands. Compounds **3n *cis*** and **4n *cis*** exhibit lack of stimulation at all concentrations of GDP.

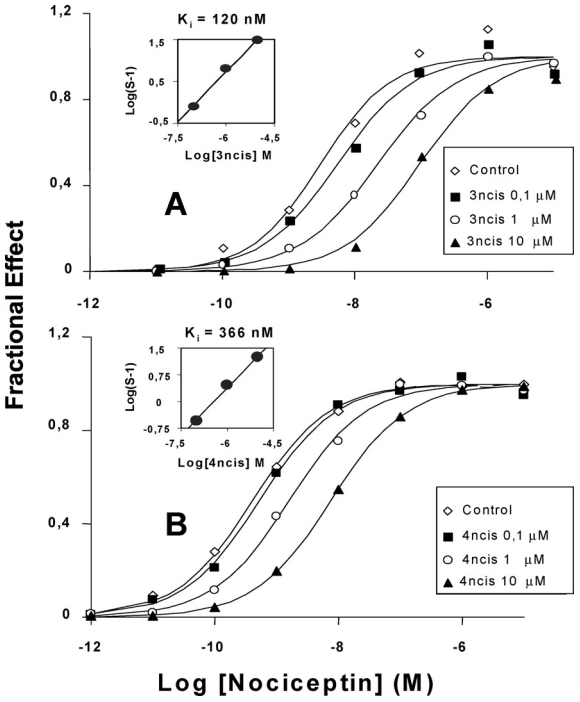



Fig. 5. Antagonism of Nociceptin-Mediated Activation of $Ga_o$ Induced by Compounds **3n *cis*** and **4n *cis***

Concentration–response curves for nociceptin-mediated stimulation of [$^{35}$S]GTPγS in the presence of 300 nM GDP were performed in membranes expressing the $ORL_1$-$Ga_o$ fusion protein as described in Experimental. Curves were generated in the absence and presence of increasing concentrations of either **3n *cis*** (A) or **4n *cis*** (B), as indicated. Data points, after subtraction of basal activity (specific binding measured in the absence of nociceptin) were plotted as fractional effect by dividing all values for the net cpm stimulated by 10 mM nociceptin in the control curve of each experiment. Data were analysed using ALLFIT (see Experimental), to compute the $EC_{50}$ in the absence and presence of the various concentrations of antagonist. Insets: Schild analysis of the data. The log of the shift induced by each agonist (*i.e.* ratio of $EC_{50}$ in the presence *vs.* absence of antagonist minus one, S-1) is plotted as a function of the log of the antagonist concentration. Linear regression analysis of the data gave the following results (±standard error): (A) slope 0.82±0.06, *x* value at *y*=0 ($pA_2$), 5.71±0.38; (B) slope 0.89±0.06, *x* value at *y*=0 ($pA_2$), 5.71±0.38.

tive compounds **3** and **4** were tested for selectivity on the opioid δ, κ and μ receptors (Tables 1, 2). In general compounds **3** tended to be more selective than triazoles **4**. They all showed no affinity for the δ and a moderate to good selectivity towards the μ subtype, whereas the κ subtype selectivity ratio resulted lower. Adamantyl substituted **3h** was the most selective compound showing a selectivity ratio higher than 100 for δ, κ and μ receptors.

These quinazolinone and triazoloquinazoline spiroderivatives tended to possess higher κ *vs.* μ affinity compared to analogue spiropiperidines bearing a *N*-phenylimidazolinone ring.[16] These results confirm the hypothesis that the heterocyclic portion may be mainly responsible for selectivity in these structures.[27] The tetrahydroquinazoline moiety featuring compounds **3** and **4**, seems to be more suitable for interaction with the κ receptor.

**Biological Efficacy** The biological efficacy of compounds **3** and **4** expressed as ability to enhance the binding of [$^{35}$S]GTPγS in the presence of GDP, in membranes from cells transfected with NOP receptors, is reported in Fig. 3. This assay is a direct measure of the receptor-mediated G-protein activation.

The examined compounds showed a variable partial agonistic activity that gradually decreased to pure antagonism in *tert*-butyl $N^1$-methyl derivatives **3n *cis*** and **4n *cis***. The results reported in the histogram (Fig. 3) evidenced that the higher efficacy was related to the presence of the *iso*-propyl substituent. Other structural features, as *cis* or *trans* configuration, seemed not to be directly related to the biological effect, although the highest activities both as regards partial agonism and antagonism were associated to compounds in the *cis* configuration (**3d *cis***, **3e *cis***, **3s *cis***, **4d *cis***, **4m *cis***, **3n *cis*** and **4n *cis***).

A study at several GDP concentrations confirmed the partially agonistic character of all compounds and the antagonism of **3n *cis*** and **4n *cis***.

In Fig. 4 the dose–response curves for the ***cis*** compounds **3d**, **3e**, **3m**, **3n**, **3s**, **3t**, **4d**, **4e**, **4m** and **4n** are reported as an example.

To analyze the mechanism of antagonism exerted by compounds **3n *cis*** and **4n *cis*** we performed a classical Schild analysis.[28] We measured the effects of increasing concentrations of the antagonist on the concentration–response curves

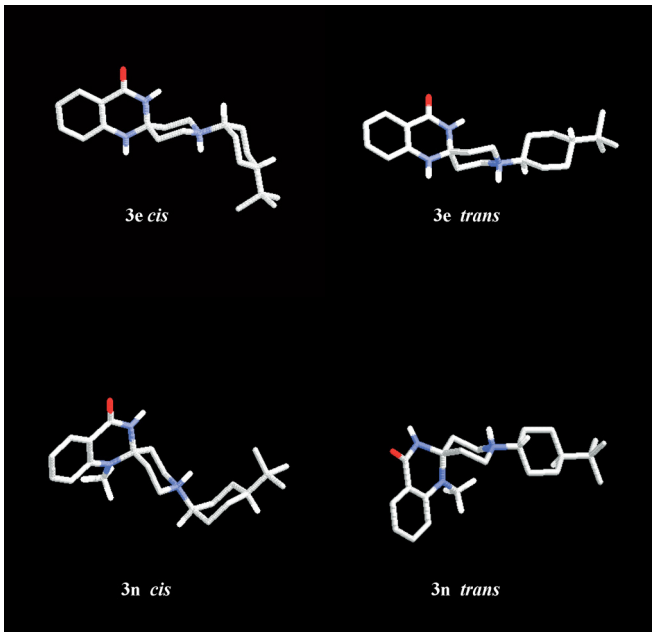



Fig. 6. Configurations *cis* and *trans* of the Compounds **3e** and **3n** Depicted in Their Lowest Energy Conformation

The structures were generated assuming the molecules to be mono-protonated under physiological conditions.

of nociceptin. Both compounds induced a rightward shift of the nociceptin-stimulated binding of [$^{35}$S]GTP$\gamma$S without changing the maximum agonist stimulation (Fig. 5). The corresponding $K_i$ determined by the Schild plots, was $1.2\times10^{-7}$ M (**3n *cis***) and $3.7\times10^{-7}$ M (**4n *cis***), in good agreement with binding results. The slope of the Schild plot ($0.82\pm0.06$, $0.89\pm0.06$ respectively) indicated both compounds as competitive antagonists.

**Molecular Modeling Studies** To get a deeper insight into the molecular bases of the interaction between NOP receptor and the synthesized compounds, molecular modeling techniques were employed.

All the calculations were conducted on a Silicon Graphic Octane R10000 workstation, within the Sybyl 6.91 software package (Tripos, Inc. St. Louis, MO, U.S.A.).

The partial agonists $N^1$-H **3d *cis***, **3e *cis***, **4d *cis*** and **4e *cis*** and their $N^1$-methyl derivatives **3m *cis***, **3n *cis***, **4m *cis*** and **4n *cis*** were taken into account. The pure agonist Ro 64-6198[14] and the pure antagonist Banyu[15] were also investigated as a comparison.

The most stable molecular conformation was determined by a simulated annealing protocol (10 cycles, heating the system up to 2000 K in 1000 fs, annealing subsequently to 0 K in 2000 fs) followed by a geometrical optimization (through the semi-empirical molecular orbital approach provided by the MOPAC 2000[29] program package) and a systematic search on the single bond between the piperidine and

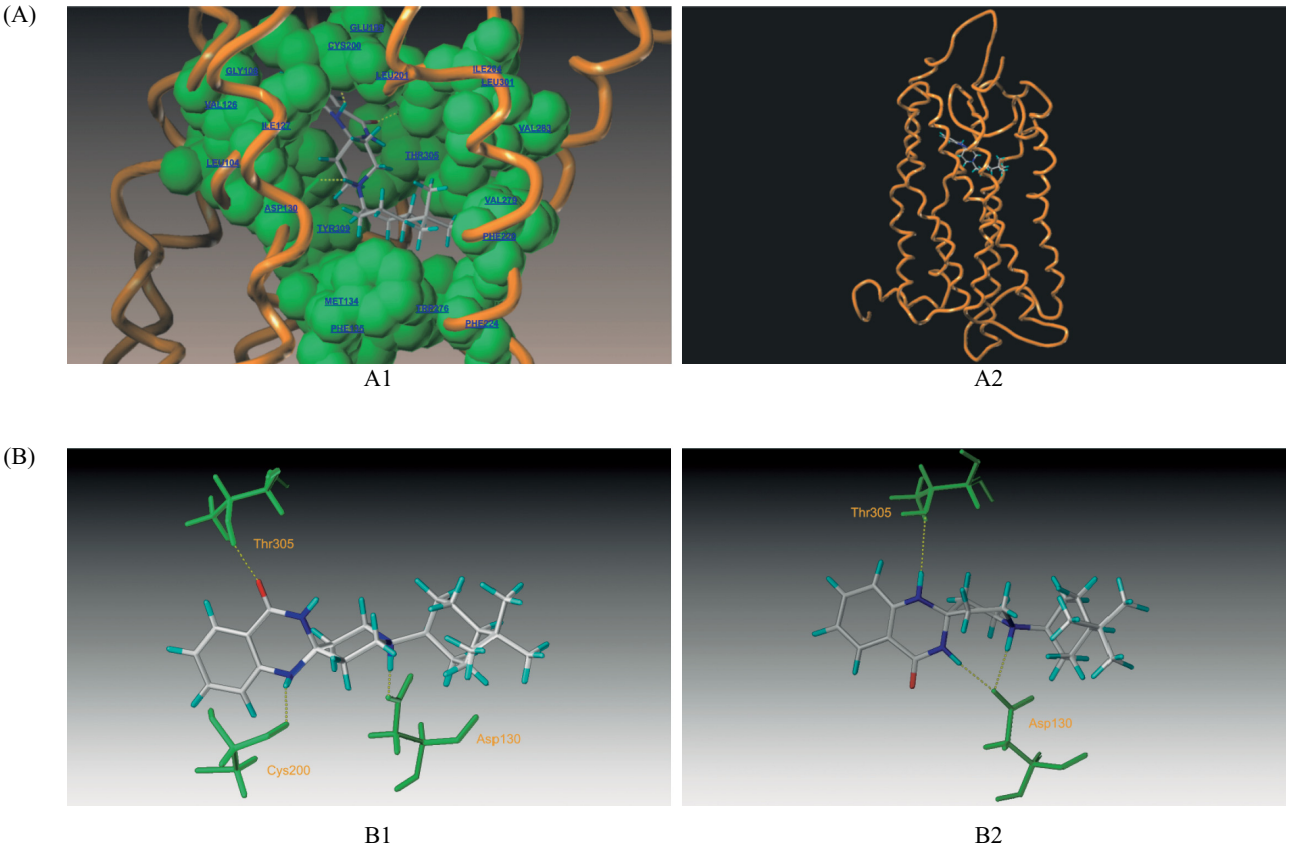



Fig. 7. (A) The Ligand-NOP Receptor Complex is Depicted

A1: Compound **3e *cis*** inserted in the binding pocket. A2: A side view of the NOP receptor, the bottom of the figure represents the intracellular side.

(B) The Final Results of the Two Docking Attempts are Depicted

Intermolecular interactions are represented by dashed lines. B1: In the first docking attempt ligand **3e *cis*** points the carbonyl function toward Thr305. B2: In the second docking attempt ligand **3e *cis*** points the $N_1$–H group toward Thr305.

the R substituent (30° steps). The structures were generated assuming that the molecules were protonated on the piperidine nitrogen.

Subsequently each ligand was manually docked into the binding site of the NOP receptor[22] in the middle of the transmembranes (TM) 3, 5, 6 and 7 at the head of the receptor (Fig. 7A) and between two pockets: the first one formed by Leu104, Gly108, Val126, Ile127, Ile198, Glu199, Cys200, Leu201, Leu301, Tyr309 and the second one formed by Tyr131, Met134, Phe135, Ile204, Phe215, Phe220, Phe224, Trp276, Val279, Val283. The Asp130 was chosen as an anchoring residue, as suggested by Tophan *et al.*[30]

Energy minimisation followed the docking, therefore the lower energy structure of the protein–ligand complex was predicted together with the biologically active conformation of each ligand.

This procedure highlighted the possibility that each *cis* $N^1$-H compound **3d**, **3e**, **4d** and **4e** could form two isoenergetic complexes with the NOP receptor, while $N^1$-methylated **3m**, **3n**, **4m** and **4n** presented only one way of docking to the receptor. All the generated protein-ligand complexes shared the following interactions:

a) a salt-bridge between Asp130 and the protonated piperidine nitrogen. This interaction has been established to be fundamental amongst many NOP ligands[21,22] and it is of utter importance in the binding of nociceptin itself to its receptor.[18,21]

b) various dispersive interactions between the aromatic moiety and the lipophilic residues in the first pocket and other dispersive interactions between the alkylcyclohexyl substituent of the ligands and the lipophilic residues in the second pocket.

Moreover the first complex of *cis* compounds **3d**, **3e**, **4d** and **4e** with NOP receptor showed a hydrogen bond (2.5—2.7 Å) between the carbonyl oxygen of the quinazolinone ring or triazoloquinazoline $N^1$-nitrogen and the hydroxyl group of Thr305, and a quite strong hydrogen bond (1.5 Å) between the hydrogen at the $N^1$-position of the quinazolinone ring and the carbonyl oxygen of Cys200 (Fig. 7B1).

In the second complex the same compounds pointed the $N^1$-H group to Thr305 forming a hydrogen bond acting as donors (Fig. 7B2).

These results agreed with the models proposed for the complexes between NOP receptor and nociceptin[18] and NOP receptor with other potent agonists.[22]

$N^1$-Methylated *cis* **3m**, **3n**, **4m** and **4n** bound the receptor by a moderate interaction of the quinazolinone carbonyl (**3m**, **n**) or triazoloquinazoline $C^{10b}=N^1$ (**4m**, **n**) groups with Thr305 hydroxyl group.

These results highlighted the ligand molecular groups involved in the binding affinities but did not provide any information about structural requirements responsible for intrinsic activity. In fact on the basis of molecular modeling studies we could not explain why only the methylated *cis tert*-butylderivatives **3n** and **4n** showed antagonist activity. In this series of compounds we can only hypothize that the simultaneous presence of chemical groups as methyl and *tert*-butyl conferred to the ligands an optimally sized and directed conformation able to inactivate the receptor.

## Conclusions

We have synthesized a series of new spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones and of spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazolines] that displayed moderate to good affinity for the NOP receptors and behaved as partial agonists.

The peculiarity of this scaffold of ligands is that the substituent on the $N^1$-position of the piperidine ring affected the affinity and modulated the efficacy. Moreover the presence of a methyl substituent on the quinazoline $N^1$ joined to the presence of a *tert*-butylcyclohexyl tail led to a loss of the intrinsic activity.

Molecular modeling on the complexes with the NOP receptor suggested that the non-conservative aminoacid Thr305 together with Asp130 can be considered of critical importance in the interaction of spiropiperidines with NOP receptor. The recent hypothesis that efficacy of spiropiperidines is also related to a lipophilic interaction between the cycloalkyl substituent and the receptorial hydrophobic second pocket neighbouring the Asp130,[27] has also been confirmed.

In summary, our series of compounds could be further exploited as tools for studying receptor interactions as related to biological efficacy.

### Experimental

Melting points were determined on a Köfler hot stage apparatus, unless otherwise stated, and are uncorrected. Column chromatographic separations were accomplished on Merck silica gel (70—230 mesh) or on Merck aluminium oxide 90. The purity of each compound was checked on silica gel C. Erba 60 $F_{254}$ or Merck aluminium oxide 60 $F_{254}$ (type E) plates and spots were located by UV light. Sodium sulfate was used to dry organic solutions. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values.

The $^1$H-NMR spectra and COSY experiments were performed on Bruker Avance 700 and 400 instruments in pyridine-$d_5$, in order to improve the spectral resolution of the aliphatic region, or in $CDCl_3$ or DMSO-$d_6$ solution; all values are reported in ppm ($\delta$) and standard abbreviations were used (a=apparent; b=broad; d=doublet; dd=doublet of doublets; dt=doublet of triplets; m=multiplet; q=quadruplet; qt=quintet, s=singlet; sh=sharp, t=triplet; tt=triplet of triplets, u=unresolved).

Electron Ionisation Mass spectra were recorded on a HP 59980 B spectrometer operating at 70 eV.

Amantadine was obtained from its commercial hydrochloride by displacement with aqueous sodium hydroxide. The 5*H*-10,11-dihydrodibenzo-[*a*,*d*]cyclohepten-5-amine was prepared according to the literature.[31] The 4-substituted cyclohexylamines were obtained, in the form of *cis–trans* isomeric mixture,[24] by reduction with lithium aluminium hydride of the corresponding oximes, which was performed in refluxing tetrahydrofuran according to a conventional procedure[32]; 1-benzyl-4-piperidone **2e** and 1-phenethyl-4-piperidone **2f** were purchased by Fluka.

**General Procedure for the Preparation of the 1-Substituted 4-Piperidones 2** To a suspension of the appropriate amine (0.02 mol) and sodium carbonate (1.4 g, 0.013 mol) in refluxing ethanol (60 ml) under stirring, was dropwise added a solution of **1**[23] (8.1 g, 0.03 mol) in water (20 ml), and the mixture refluxed for 2 h. The resulting solution was evaporated *in vacuo* to remove ethanol, then strongly alkalinized with 20% aqueous sodium hydroxide and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel by eluting with a 1 : 1 ethyl acetate–hexane mixture in the case of **2e** or on aluminium oxide by eluting with a 1 : 3 ethyl acetate–hexane mixture for the other compounds.

***cis*-1-(4-Methylcyclohexyl)-4-piperidone (2a *cis*)** Compound **2a** *cis* was obtained from 4-methylcyclohexylamine (isomeric mixture) in 20% yield, pale yellow oil. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.87 (3H, d, 4′-$CH_3$), 1.38 (6H, m, H-2′$_{ax}$, H-6′$_{ax}$, H-3′, H-5′), 1.56 (3H, m, H-2′$_{eq}$, H-6′$_{eq}$, H-4′$_{eq}$), 2.26 (1H, t, H-1′$_{ax}$, $J$=8.2 Hz), 2.40 (4H, t, H-3, H-5), 2.65 (4H, t, H-2, H-6). MS *m*/*z*: 195 ($M^=$), 170, 138. *Anal.* Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17.

Found: C, 74.02; H, 10.49; N, 7.04.

***trans*-1-(4-Methylcyclohexyl)-4-piperidone (2a *trans*)** Compound **2a *trans*** was obtained from 4-methylcyclohexylamine (isomeric mixture) in 21% yield, pale yellow oil. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.81 (3H, d, 4′-$CH_3$), 0.85 (2H, m, H-3′$_{ax}$, H-5′$_{ax}$, $J$=12.9 Hz), 1.15 (3H, overlapped q and m, H-2′$_{ax}$, H-6′$_{ax}$, H-4′$_{ax}$, $J$=12.4 Hz, $J$=2.3 Hz,), 1.61 (2H, d, H-3′$_{eq}$, H-5′$_{eq}$, $J$=13.1 Hz), 1.73 (2H, d, H-2′$_{eq}$, H-6′$_{eq}$, $J$=11.6 Hz), 2.33 (1H, t, H-1′$_{ax}$, $J_{diax}$=11.7 Hz, $J_{ax\text{-}eq}$=3.0 Hz), 2.40 (4H, t, H-3, H-5), 2.67 (4H, t, H-2, H-6). MS *m/z*: 195 ($M^+$), 170, 138. *Anal.* Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.98; H, 11.00; N, 7.49.

***cis*-1-(4-Ethylcyclohexyl)-4-piperidone (2b *cis*)** Compound **2b *cis*** was obtained from 4-ethylcyclohexylamine (isomeric mixture) in 30%, yield, pale yellow oil. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.83 (3H, t, ethyl $CH_3$), 1.23 (2H, qt, 4′-ethyl $CH_2$), 1.27 (1H, m, H-4′$_{eq}$, $J$=5.0 Hz), 1.37 (4H, m, H-2′$_{ax}$, H-3′$_{ax}$, H-5′$_{ax}$, H-6′$_{ax}$), 1.47 (2H, bm, H-3′$_{eq}$, H-5′$_{eq}$), 1.52 (2H, bd, H-2′$_{eq}$, H-6′$_{eq}$), 2.29 (1H, t, H-1′$_{ax}$, $J_{diax}$=8.0 Hz, $J_{ax\text{-}eq}$=5.3 Hz), 2.41 (4H, t, H-3, H-5), 2.66 (4H, t, H-2, H-6). MS *m/z*: 209 ($M^+$), 170, 138. *Anal.* Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.48; H, 11.42; N, 6.56.

***trans*-1-(4-Ethylcyclohexyl)-4-piperidone (2b *trans*)** Compound **2b *trans*** was obtained from 4-ethylcyclohexylamine (isomeric mixture) in 11% yield, pale yellow oil. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.81 (5H, overlapped m and t, H-3′$_{ax}$, H-5′$_{ax}$, ethyl $CH_3$), 0.92 (1H, um, H-4′$_{ax}$), 1.14 (4H, m, H-2′$_{ax}$, H-6′$_{ax}$, 4′-ethyl $CH_2$), 1.69 (2H, d, H-3′$_{eq}$, H-5′$_{eq}$, $J_{gem}$=12.4 Hz), 1.78 (2H, d, H-2′$_{eq}$, H-6′$_{eq}$, $J_{gem}$=11.9 Hz), 2.34 (1H, t, H-1′$_{ax}$, $J_{diax}$=11.7 Hz, $J_{ax\text{-}eq}$=3.1 Hz), 2.41 (4H, t, H-3, H-5), 2.68 (4H, t, H-2, H-6). MS *m/z*: 209 ($M^+$), 170, 138. *Anal.* Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.98; H, 10.91; N, 6.43.

***cis*-1-(4-*n*-Propylcyclohexyl)-4-piperidone (2c *cis*)** Compound **2c *cis*** was obtained from 4-*n*-propylcyclohexylamine (isomeric mixture) in 11% yield, pale yellow oil. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.87 (3H, t, *n*-propyl $CH_3$), 1.24 (4H, bm, *n*-propyl $CH_2$–$CH_2$), 1.32—1.60 (9H, m, H-2′, H-3′, H-5′, H-6′, H-4′), 2.30 (1H, t, H-1′, $J$=7.6 Hz), 2.42 (4H, t, H-3, H-5), 2.67 (4H, t, H-2, H-6). MS *m/z*: 223 ($M^+$), 170, 138. *Anal.* Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.59; H, 11.40; N, 6.52.

***trans*-1-(4-*n*-Propylcyclohexyl)-4-piperidone (2c *trans*)** Compound **2c *trans*** was obtained from 4-*n*-propylcyclohexylamine (isomeric mixture) in 11% yield, pale yellow oil. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.86 (5H, overlapped m and t, H-3′$_{ax}$, H-5′$_{ax}$, *n*-propyl $CH_3$), 1.08 (3H, m, H-4′, *n*-propyl $CH_2$), 1.17 (2H, q, H-2′$_{ax}$, H-6′$_{ax}$, $J$=12.4 Hz, $J$=3.2 Hz), 1.25 (2H, qt, 4′-*n*-propyl $CH_2$), 1.72 (2H, d, H-3′$_{eq}$, H-5′$_{eq}$, $J_{gem}$=12.7 Hz), 1.77 (2H, d, H-2′$_{eq}$, H-6′$_{eq}$, $J_{gem}$=13.5 Hz), 2.37 (1H, t, H-1′$_{ax}$, $J_{diax}$=11.9 Hz, $J_{ax\text{-}eq}$=3.4 Hz), 2.41 (4H, t, H-3, H-5), 2.69 (4H, t, H-2, H-6). MS *m/z*: 223 ($M^+$), 170, 138. *Anal.* Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.07; H, 11.18; N, 6.41.

***cis*-1-(4-*iso*-Propylcyclohexyl)-4-piperidone (2d *cis*)** Compound **2d *cis*** was obtained from 4-*iso*-propylcyclohexylamine (isomeric mixture) in 11% yield, pale yellow oil. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.80 (6H, d, *iso*-propyl $CH_3$), 1.02 (1H, m, H-4′$_{ax}$), 1.32 (4H, m, H-2′$_{ax}$, H-6′$_{ax}$, H-3′$_{eq}$, H-5′$_{eq}$), 1.48 (1H, m, *iso*-propyl CH), 1.57 (2H, m, H-3′$_{ax}$, H-5′$_{ax}$), 1.63 (2H, m, H-2′$_{eq}$, H-6′$_{eq}$), 2.28 (1H, as, H-1′$_{eq}$), 2.42 (4H, t, H-3, H-5), 2.66 (4H, t, H-2, H-6). MS *m/z*: 223 ($M^+$), 170, 138. *Anal.* Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.36; H, 11.39; N, 5.97.

***trans*-1-(4-*iso*-Propylcyclohexyl)-4-piperidone (2d *trans*)** Compound **2d *trans*** was obtained from 4-*iso*-propylcyclohexylamine (isomeric mixture) in 10% yield, pale yellow oil. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.81 (6H, d, *iso*-propyl $CH_3$), 0.88 (3H, m, H-3′$_{eq}$, H-5′$_{eq}$, H-4′$_{ax}$), 1.15 (2H, q, H-2′$_{ax}$, H-6′$_{ax}$, $J$=10.4 Hz, $J$=3.2 Hz), 1.32 (1H, m, *iso*-propyl CH), 1.65 (2H, ut, H-3′$_{ax}$, H-5′$_{ax}$), 1.79 (2H, d, H-2′$_{eq}$, H-6′$_{eq}$, $J_{gem}$=12.0 Hz), 2.33 (1H, t, H-1′$_{ax}$, $J_{diax}$=11.6 Hz, $J_{ax\text{-}eq}$=3.6 Hz), 2.41 (4H, t, H-3, H-5), 2.71 (4H, t, H-2, H-6). MS *m/z*: 223 ($M^+$), 170, 138. *Anal.* Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 74.95; H, 10.91; N, 6.08.

***cis*-1-(4-*tert*-Butylcyclohexyl)-4-piperidone (2e *cis*)** Compound **2e *cis*** was obtained from 4-*tert*-butylcyclohexylamine (isomeric mixture) in 14% yield, white solids from hexane, mp 57—59 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.85 (9H, s, *tert*-butyl), 1.02 (1H, m, H-4′$_{ax}$), 1.25 (2H, t, H-3′$_{ax}$, H-5′$_{ax}$, $J_{gem}$=13.4 Hz, $J_{vic\ diax}$=12.9 Hz, $J_{vic\ ax\ eq}$=2.8 Hz), 1.37 (2H, sh m, H-3′$_{eq}$, H-5′$_{eq}$), 1.39 (2H, t, H-2′$_{ax}$, H-6′$_{ax}$), 1.92 (2H, dd, H-2′$_{eq}$, H-6′$_{eq}$, $J_{gem}$=14.7 Hz, $J$=2.1 Hz), 2.21 (1H, sh m, H-1′$_{eq}$, $J$=2.8 Hz), 2.38 (4H, sh m, H-3, H-5), 2.64 (4H, sh m, H-2, H-6). MS *m/z*: 237 ($M^+$), 222, 180, 170, 166, 138. *Anal.* Calcd for $C_{15}H_{27}NO$: C, 75.89; H, 11.47; N, 5.90. Found: C, 75.50; H, 11.36; N, 6.12.

***trans*-1-(4-*tert*-Butylcyclohexyl)-4-piperidone (2e *trans*)** Compound **2e *trans*** was obtained from 4-*tert*-butylcyclohexylamine (isomeric mixture) in 15% yield, white solids from hexane, mp 66—67 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.80 (9H, s, *tert*-butyl), 0.84 (1H, t, H-4′$_{ax}$, $J$=12.0 Hz), 0.88 (2H, q, H-3′$_{ax}$, H-5′$_{ax}$, $J$=11.9 Hz), 1.13 (2H, q, H-2′$_{ax}$, H-6′$_{ax}$, $J$=12.3 Hz), 1.69 (2H, d, H-3′$_{eq}$, H-5′$_{eq}$, $J$=11.7 Hz), 1.80 (2H, d, H-2′$_{eq}$, H-6′$_{eq}$, $J$=11.5 Hz), 2.31 (1H, tt, H-1′$_{ax}$, $J_{vic\ diax}$=11.7 Hz, $J_{vic\ ax\ eq}$=3.1 Hz), 2.42 (4H, t, H-3, H-5), 2.72 (4H, t, H-2, H-6). MS *m/z*: 237 ($M^+$), 222, 180, 166, 138. *Anal.* Calcd for $C_{15}H_{27}NO$: C, 75.89; H, 11.47; N, 5.90. Found: C, 76.03; H, 11.70; N, 5.77.

**1-(1-Adamantyl)-4-piperidone (2h)** Compound **2h** was obtained from amantadine in 39% yield, white solids from hexane, mp 85—86 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 1.13 (3H, d, H-2′$_{ax}$, H-8′$_{ax}$, H-9′$_{ax}$, $J_{gem}$=12.1 Hz), 1.19 (3H, d, H-2′$_{eq}$, H-8′$_{eq}$, H-9′$_{eq}$, $J_{gem}$=12.1 Hz), 1.22 (6H, bs, H-4′, H-6′, H-10′), 1.60 (3H, bs, H-3′$_{eq}$, H-5′$_{eq}$, H-7′$_{eq}$), 2.02 (4H, t, H-3, H-5), 2.36 (4H, t, H-2, H-6). MS *m/z*: 233 ($M^+$), 190, 176, 164, 135, 106. *Anal.* Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 76.96; H, 10.27; N, 5.91.

**(5*H*-10,11-Dihydrodibenzo[*a*,*d*]cyclohepten-5-yl)-4-piperidone (2i)** Compound **2i** was obtained from 5*H*-10,11-dihydrodibenzo[*a*,*d*]cyclohepten-5-amine in 50% yield, white solid from ethanol, mp 116—118 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 2.40 (4H, t, H-3, H-5), 2.65 (4H, t, H-2, H-6), 2.87 (2H, m, H-10′, H-11′), 4.10 (2H, m, H-10′, H-11′), 4.12 (1H, s, H-5′), 7.18 (8H, m, aromatics). MS *m/z*: 291 ($M^+$), 192, 178, 165, 115. *Anal.* Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.27; N, 4.81. Found: C, 82.39; H, 7.49; N, 5.05.

**General Procedure for the Preparation of the Spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones 3a—i and of the Spiro[piperidine-4,5′-[1,2,4]triazolo[1,5-*c*]quinazolines] 4a—i** A solution of the appropriate piperidone **2** (0.01 mol) and anthranylamide (1.4 g, 0.01 mol) for compounds **3a**—**i** or 3-(2-aminophenyl)-[1,2,4]triazole[25] (1.6 g, 0.01 mol) for compounds **4a**—**i** in acetic acid (14 ml) with two drops of sulfuric acid, was kept under stirring at room temperature for 2—4 h; then the mixture was diluted with water and alkalinized with 8% aqueous sodium hydroxide; the resulting precipitate was collected by filtration, washed with water, then with diethyl ether and dried *in vacuo*.

***cis*-1-(4-Methylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3a *cis*)** Compound **3a *cis*** was obtained from **2a *cis*** in 47% yield, white solids from ethyl acetate, mp 210—212 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.88 (3H, d, 4″-$CH_3$), 1.39 (7H, m, H-3″, H-5″, H-2″$_{ax}$, H-6″$_{ax}$, H-4″$_{eq}$), 1.63 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$), 1.76 (4H, m, H-3, H-5), 2.22 (1H, t, H-1″$_{ax}$, $J$=7.4 Hz), 2.58 (4H, m, partially under solvent signal, H-2, H-6), 6.62 (1H, t, H-6′, $J_{ortho}$=7.1 Hz), 6.63 (1H, s, 1′-NH), 6.80 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 7.20 (1H, t, H-7′, $J_{ortho}$=7.9 Hz), 7.56 (1H, d, H-5′, $J_{ortho}$=7.6 Hz), 7.93 (1H, s, 3′-NH). MS *m/z*: 313 ($M^+$), 296, 256, 228, 217, 200, 189, 173, 160, 152, 141, 126, 120, 98. *Anal.* Calcd for $C_{19}H_{27}N_3O$: C, 72.80; H, 8.68; N, 13.41. Found: C, 73.03; H, 8.34; N, 13.29.

***trans*-1-(4-Methylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3a *trans*)** Compound **3a *trans*** was obtained from **2a *trans*** in 47% yield, white solids from ethyl acetate, mp 215—218 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.86 (5H, overlapped m and d, H-3″$_{eq}$, H-5″$_{eq}$, 4″-$CH_3$), 1.24 (2H, m, H-2″$_{ax}$, H-6″$_{ax}$), 1.39 (1H, at, H-4″$_{ax}$, $J$=10.1 Hz), 1.74 (8H, m, H-3, H-5, H-2″$_{eq}$, H-6″$_{eq}$, H-3″$_{ax}$, H-5″$_{ax}$), 2.24 (1H, t, H-1″$_{ax}$, $J$=11.8 Hz), 2.54 (4H, m, H-2, H-6), 6.62 (1H, t, H-6′, $J_{ortho}$=7.5 Hz), 6.63 (1H, s, 1′-NH), 6.80 (1H, d, H-8′, $J_{ortho}$=8.2 Hz), 7.22 (1H, t, H-7′, $J_{ortho}$=7.3 Hz), 7.56 (1H, d, H-5′, $J_{ortho}$=7.8 Hz), 7.95 (1H, s, 3′-NH). MS *m/z*: 313 ($M^+$), 296, 256, 228, 217, 189, 173, 160, 141, 126, 120, 112, 98. *Anal.* Calcd for $C_{19}H_{27}N_3O$: C, 72.80; H, 8.68; N, 13.41. Found: C, 72.49; H, 9.00; N, 13.78.

***cis*-1-(4-Ethylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3b *cis*)** Compound **3b *cis*** was obtained from **2b *cis*** in 48% yield, white solids from ethyl acetate, mp 210—212 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.82 (3H, t, ethyl $CH_3$), 1.27 (2H, qt, ethyl 4″-$CH_2$), 1.39 (7H, m, H-3″, H-5″, H-2″$_{ax}$, H-6″$_{ax}$, H-4″$_{eq}$), 1.58 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$), 7.91 (1H, s, 3′-NH), 1.75 (4H, m, H-3, H-5), 2.24 (1H, t, H-1″$_{ax}$, $J$=7.4 Hz), 2.49 (4H, m under solvent signal, H-2, H-6), 6.61 (1H, s, 1′-NH), 6.62 (1H, t, H-6′, $J_{ortho}$=7.7 Hz), 6.79 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 7.21 (1H, t, H-7′, $J_{ortho}$=7.9 Hz), 7.55 (1H, d, H-5′, $J_{ortho}$=7.7 Hz). MS *m/z*: 327 ($M^+$), 310, 256, 228, 217, 189, 173, 160, 155, 140, 126, 120, 110. *Anal.* Calcd for $C_{20}H_{29}N_3O$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.45; H, 8.59; N, 12.52.

***trans*-1-(4-Ethylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3b *trans*)** Compound **3b *trans*** was obtained from **2b *trans*** in 48% yield, white solids from ethyl acetate, mp 216—218 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.83 (5H, overlapped m and t, H-3″$_{eq}$, H-5″$_{eq}$, ethyl $CH_3$), 1.14 (4H, m, H-2″$_{ax}$, H-6″$_{ax}$, ethyl 4″-$CH_2$), 1.40 (1H, at, H-4″$_{ax}$, $J$=7.9 Hz), 1.74 (8H, sh m, H-3, H-5, H-2″$_{eq}$, H-6″$_{eq}$, H-3″$_{ax}$, H-5″$_{ax}$), 2.23 (1H, t, H-1″$_{ax}$, $J$=10.7 Hz), 2.54 (4H, m, H-2, H-6), 6.61 (1H, s, 1′-NH), 6.62 (1H, t, H-6′,

$J_{ortho}$=7.5 Hz), 6.80 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 7.21 (1H, t, H-7′, $J_{ortho}$=7.5 Hz), 7.55 (1H, d, H-5′, $J_{ortho}$=7.7 Hz), 7.92 (1H, s, 3′-NH). MS *m/z*: 327 ($M^+$), 310, 256, 228, 217, 189, 173, 160, 155, 140, 126, 120, 110. *Anal.* Calcd for $C_{20}H_{29}N_3O$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.53; H, 9.15; N, 13.04.

***cis*-1-(4-*n*-Propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3c *cis*)** Compound **3c** *cis* was obtained from **2c** *cis* in 49% yield, white solids from ethyl acetate, mp 208—210 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.81 (3H, t, *n*-propyl $CH_3$), 1.22 (4H, m, H-2″$_{ax}$, H-6″$_{ax}$, *n*-propyl $CH_2$), 1.42 (7H, m, H-3″, H-5″, H-4″, 4″-*n*-propyl $CH_2$), 1.52 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$), 1.84 (4H, m, H-3, H-5), 2.23 (1H, sh m, H-1″$_{eq}$, $J$=2.7 Hz), 2.60 (4H, m, H-2, H-6), 6.62 (1H, t, H-6′, $J_{ortho}$=7.2 Hz), 6.67 (1H, s, 1′-NH), 6.80 (1H, d, H-8′, $J_{ortho}$=8.2 Hz), 7.20 (1H, t, H-7′, $J_{ortho}$=8.0 Hz), 7.57 (1H, d, H-5′, $J_{ortho}$=7.8 Hz), 7.94 (1H, s, 3′-NH). MS *m/z*: 341 ($M^+$), 324, 256, 228, 217, 189, 173, 160, 154, 140, 124, 120. *Anal.* Calcd for $C_{21}H_{31}N_3O$: C, 73.86; H, 9.15; N, 12.31. Found: C, 74.02; H, 8.88; N, 11.99.

***trans*-1-(4-*n*-Propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3c *trans*)** Compound **3c** *trans* was obtained from **2c** *trans* in 49% yield, white solids from ethyl acetate, mp 224—226 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.83 (5H, bt, *n*-propyl $CH_3$, H-3″$_{eq}$, H-5″$_{eq}$), 1.14 (3H, m, *n*-propyl $CH_2$, H-4″$_{ax}$), 1.25 (4H, m, *n*-propyl 4″-$CH_2$, H-2″$_{ax}$, H-6″$_{ax}$), 1.73 (8H, m, H-3, H-5, H-2″$_{eq}$, H-6″$_{eq}$, H-3″$_{ax}$, H-5″$_{ax}$), 2.22 (1H, t, H-1″$_{ax}$, $J_{diax}$=10.6 Hz), 2.51 (4H, m, H-2, H-6), 6.62 (1H, t, H-6′, $J_{ortho}$=7.6 Hz), 6.65 (1H, s, 1′-NH), 6.79 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 7.22 (1H, t, H-7′, $J_{ortho}$=7.3 Hz), 7.55 (1H, d, H-5′, $J_{ortho}$=7.6 Hz), 7.95 (1H, s, 3′-NH). MS *m/z*: 341 ($M^+$), 324, 256, 228, 217, 189, 173, 169, 160, 154, 140, 124, 120. *Anal.* Calcd for $C_{21}H_{31}N_3O$: C, 73.86; H, 9.15; N, 12.31. Found: C, 73.49; H, 8.93; N, 12.04.

***cis*-1-(4-*iso*-Propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3d *cis*)** Compound **3d** *cis* was obtained from **2d** *cis* in 64% yield, white solids from ethyl acetate, mp 232—234 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.83 (6H, d, *iso*-propyl $CH_3$), 1.07 (1H, bm, H-4″), 1.31 (2H, m, H-3″$_{eq}$, H-5″$_{eq}$,), 1.37 (2H, d, H-2″$_{ax}$, H-6″$_{ax}$), 1.47 (3H, m, H-3″$_{ax}$, H-5″$_{ax}$, *iso*-propyl CH), 1.69 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$), 1.76 (4H, m, H-3, H-5), 2.24 (1H, sh m, H-1″$_{eq}$, $J$=2.8 Hz), 2.44 (2H, m, H-2$_{ax}$, H-6$_{ax}$), 2.58 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.61 (1H, s, 1′-NH), 6.64 (1H, t, H-6′, $J_{ortho}$=7.3 Hz), 6.79 (1H, d, H-8′, $J_{ortho}$=7.9 Hz), 7.21 (1H, t, H-7′, $J_{ortho}$=7.5 Hz), 7.55 (1H, d, H-5′, $J_{ortho}$=7.6 Hz), 7.89 (1H, s, 3′-NH). MS *m/z*: 341 ($M^-$), 324, 256, 228, 217, 189, 173, 160, 154, 140, 120, 110. *Anal.* Calcd for $C_{21}H_{31}N_3O$: C, 73.86; H, 9.15; N, 12.31. Found: C, 74.08; H, 9.37; N, 12.53.

***trans*-1-(4-*iso*-Propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3d *trans*)** Compound **3d** *trans* was obtained from **2d** *trans* in 75% yield, white solids from ethyl acetate, mp 242—244 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.82 (6H, d, *iso*-propyl $CH_3$), 0.95 (3H, m, H-3″$_{eq}$, H-4″$_{ax}$, H-5″$_{eq}$), 1.17 (2H, dd, H-2″$_{ax}$, H-6″$_{ax}$), 1.38 (1H, m, *iso*-propyl CH), 1.73—1.82 (8H, m, H-3, H-5, H-2″$_{eq}$, H-6″$_{eq}$, H-3″$_{ax}$, H-5″$_{ax}$), 2.20 (1H, t, H-1″$_{ax}$, $J_{diax}$=12.0 Hz), 2.56 (4H, m, H-2, H-6), 6.63 (2H, m, H-6′, 1′-NH), 6.79 (1H, d, H-8′, $J_{ortho}$=8.0 Hz), 7.21 (1H, t, H-7′, $J_{ortho}$=7.1 Hz), 7.55 (1H, d, H-5′, $J_{ortho}$=7.5 Hz), 7.90 (1H, s, 3′-NH). MS *m/z*: 341 ($M^+$), 324, 256, 228, 217, 189, 173, 169, 160, 154, 140, 138, 120, 110. *Anal.* Calcd for $C_{21}H_{31}N_3O$: C, 73.86; H, 9.15; N, 12.31. Found: C, 73.63; H, 8.79; N, 12.66.

***cis*-1-(4-*tert*-Butylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3e *cis*)** Compound **3e** *cis* was obtained from **2e** *cis* in 40% yield, white solids from ethyl acetate, mp 258—260 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.82 (9H, s, *tert*-butyl), 1.05 (1H, m, H-4″$_{ax}$), 1.19 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$), 1.30 (2H, t, H-2″$_{ax}$, H-6″$_{ax}$), 1.33 (4H, m, H-3″, H-5″), 1.77 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 1.99 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.22 (1H, sh m, H-1″$_{eq}$, $J$=2.7 Hz ), 2.44 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.58 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.63 (1H, t, H-6′, $J_{ortho}$=7.3 Hz), 6.67 (1H, s, 1′-NH), 6.81 (1H, d, H-8′, $J_{ortho}$=7.9 Hz), 7.23 (1H, t, H-7′, $J_{ortho}$=7.4 Hz), 7.57 (1H, d, H-5′, $J_{ortho}$=7.6 Hz), 7.94 (1H, s, 3′-NH). MS *m/z*: 355 ($M^+$), 338, 254, 236, 228, 199, 173, 160, 154, 138, 120. *Anal.* Calcd for $C_{22}H_{33}N_3O$: C, 74.32; H, 9.36; N, 11.82. Found: C, 74.02; H, 9.71; N, 11.49.

***trans*-1-(4-*tert*-Butylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3e *trans*)** Compound **3e** *trans* was obtained from **2e** *trans* in 40% yield, white solids from ethyl acetate, mp 262—263 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.82 (9H, s, *tert*-butyl), 0.93 (3H, m, H-3″$_{eq}$, H-4″$_{ax}$, H-5″$_{eq}$), 1.19 (2H, t, H-2″$_{ax}$, H-6″$_{ax}$), 1.74—1.86 (8H, m, H-3, H-5, H-2″$_{eq}$, H-6″$_{eq}$, H-3″$_{ax}$, H-5″$_{ax}$), 2.20 (1H, t, H-1″$_{ax}$, $J_{diax}$=10.2 Hz), 2.57 (4H, m, H-2, H-6), 6.63 (1H, t, H-6′, $J_{ortho}$=7.3 Hz), 6.65 (1H, s, 1′-NH), 6.81 (1H, d, H-8′, $J_{ortho}$=8.0 Hz), 7.22 (1H, t, H-7′, $J_{ortho}$=7.1 Hz), 7.57 (1H, d, H-5′, $J_{ortho}$=7.5 Hz), 7.96 (1H, s, 3′-NH). MS *m/z*: 355 ($M^+$), 338, 254, 236, 228, 168, 160, 154, 138, 120. *Anal.* Calcd for $C_{22}H_{33}N_3O$: C, 74.32; H, 9.36; N, 11.82. Found: C, 74.58; H, 9.68; N, 12.00.

**1-Benzylspiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3f)** Compound **3f** was obtained from **2f** in 49% yield, off-white solids from dimethylformamide, mp 255—257 °C (lit.[33] 262.0—262.5 °C from methanol). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.84 (4H, bm, H-3, H-5), 2.76 (4H, bm, H-2, H-6), 3.49 (2H, s, benzyl $CH_2$), 6.65 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 6.74 (1H, s, 1′-NH), 6.80 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 7.24 (6H, m, H-7′, benzyl aromatics), 7.58 (1H, d, H-5′, $J_{ortho}$=7.7 Hz), 8.04 (1H, s, 3′-NH). MS *m/z*: 307 ($M^+$), 290, 216, 189, 173, 161, 146, 134, 120, 106, 91. *Anal.* Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.55; H, 6.53; N, 13.44.

**1-Phenethylspiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3g)** Compound **3g** was obtained from **2g** in 51% yield, white solids from methanol, mp 170—173 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.77 (4H, m, H-3, H-5), 2.49 (6H, m under solvent signal, H-2, H-6, phenethyl N–$CH_2$), 3.47 (2H, t, phenethyl $CH_2$), 6.62 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 6.68 (1H, s, 1′-NH), 6.80 (1H, d, H-8′, $J_{ortho}$=8.0 Hz), 7.28 (6H, m, H-7′, phenethyl aromatics), 7.58 (1H, d, H-5′, $J_{ortho}$=7.5 Hz), 7.97 (1H, s, 3′-NH). MS *m/z*: 321 ($M^+$), 304, 230, 217, 202, 189, 173, 160, 134, 120, 91. *Anal.* Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.08. Found: C, 74.83; H, 6.82; N, 13.36.

**1-(1-Adamantyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3h)** Compound **3h** was obtained from **2h** in 44% yield, white solids from ethyl acetate, mp 277—280 °C (dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.58, 1.65, 1.74, (16H, three as, H-3, H-5, H-4″, H-6″, H-10″, H-2″, H-8″, H-9″), 2.04 (3H, bs, H-3″, H-5″, H-7″), 2.59 (2H, m, H-2$_{ax}$, H-6$_{ax}$,), 2.71 (2H, m, H-2$_{eq}$, H-6$_{eq}$), 6.63 (2H, overlapped s and t, 1′-NH, H-6′, $J_{ortho}$=7.6 Hz), 6.80 (1H, d, H-8′, $J_{ortho}$=7.7 Hz), 7.22 (1H, dt, H-7′, $J_{ortho}$=7.3 Hz, $J_{meta}$=1.6 Hz), 7.95 (1H, s, NH), 7.56 (1H, dd, H-5′, $J_{ortho}$=7.7 Hz, $J_{meta}$=1.5 Hz). MS *m/z*: 351 ($M^+$), 334, 217, 194, 179, 135, 122. *Anal.* Calcd for $C_{22}H_{29}N_3O$: C, 75.17; H, 8.32; N, 11.96. Found: C, 74.92; H, 7.96; N, 12.08.

**1-(5*H*-10,11-Dihydrodibenzo[*a*,*d*]cyclohepten-5-yl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3i)** Compound **3i** was obtained from **2i** in 51% yield, white solids from ethyl acetate, mp 280—282 °C; $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.72 (4H, m, H-3, H-5), 2.40 (4H, m, H-2, H-6), 2.73 (2H, m, H-10″, H-11″), 3.90 (2H, m, H-10″, H-11″), 4.10 (1H, s, H-5″), 6.65 (1H, t, H-6′, $J_{ortho}$=7.7 Hz), 6.66 (1H, s, 1′-NH), 6.80 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 7.13 (9H, m, H-7′, dibenzosuberyl aromatics), 7.54 (1H, dd, H-5′, $J_{ortho}$=7.7 Hz, $J_{meta}$=1.5 Hz), 7.88 (1H, s, 3′-NH). MS *m/z*: 409 ($M^+$), 218, 193, 178, 160, 115. *Anal.* Calcd for $C_{27}H_{27}N_3O$: C, 79.18; H, 6.65; N, 10.26. Found: C, 78.85; H, 6.94; N, 10.39.

***cis*-1-(4-Methylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4a *cis*)** Compound **4a** *cis* was obtained from **2a** *cis* in 31% yield, white solids from ethyl acetate, mp 205—207 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.33 (3H, d, $CH_3$), 0.80—0.85 (6H, m, H-2″$_{eq}$, H-3″, H-5″, H-6″$_{eq}$), 1.04—1.08 (3H, m, H-2″$_{ax}$, H-4″, H-6″$_{ax}$), 1.65 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 1.68 (1H, t, H-1″$_{ax}$ $J$=7.8 Hz), 2.05 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.38 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.38 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.94 (1H, t, H-9′), 7.15 (1H, d, H-7′), 7.28 (1H, t, H-8′), 7.49 (1H, bs, NH), 8.21 (1H, d, H-10′), 8.34 (1H, s, H-2′). MS *m/z*: 337 ($M^+$), 280, 225, 213, 192, 178, 126. *Anal.* Calcd for $C_{20}H_{27}N_5$: C, 71.18; H, 8.07; N, 20.76. Found: C, 71.02; H, 7.84; N, 20.86.

***trans*-1-(4-Methylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4a *trans*)** Compound **4a** *trans* was obtained from **2a** *trans* in 38% yield, white solids from ethyl acetate, mp 220—225 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.77 (3H, d, $CH_3$), 0.81 (2H, sh m, H-3″$_{eq}$, H-5″$_{eq}$), 1.12—1.16 (3H, m, H-2″$_{ax}$, H-4″, H-6″$_{ax}$), 1.57 (2H, bd, H-3″$_{ax}$, H-5″$_{ax}$), 1.71 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$), 2.17 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.24 (1H, t, H-1″$_{ax}$, $J$=11.2 Hz), 2.64 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.74 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.83 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.93 (1H, t, H-9′), 7.18 (1H, d, H-7′), 7.27 (1H, t, H-8′), 7.59 (1H, bs, NH), 8.22 (1H, d, H-10′), 8.34 (1H, s, H-2′). MS *m/z*: 337 ($M^+$), 280, 225, 213, 192, 178, 126. *Anal.* Calcd for $C_{20}H_{27}N_5$: C, 71.18; H, 8.07; N, 20.76. Found: C, 71.41; H, 8.42; N, 20.48.

***cis*-1-(4-Ethylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4b *cis*)** Compound **4b** *cis* was obtained from **2b** *cis* in 37% yield, white solids from ethyl acetate, mp 154—156 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.81 (3H, t, $CH_2$–$\underline{CH_3}$), 1.20—1.77 (3H, m, H-4″$_{eq}$, $\underline{CH_2}$–$CH_3$), 1.29—1.39 (4H, m, H-2″$_{ax}$, H-3″$_{ax}$, H-5″$_{ax}$, H-6″$_{ax}$), 1.39—1.41 (2H, m, H-3″$_{eq}$, H-5″$_{eq}$), 1.53—1.55 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$), 2.17 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.23 (1H, t, H-1″$_{ax}$, $J$=8.4 Hz), 2.57 (2H, t, H-3$_{ax}$, H-5$_{ax}$,), 2.63—2.66 (2H, m, H-2$_{ax}$, H-6$_{ax}$), 2.89 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.94 (1H, t, H-9′), 7.18 (1H, d, H-7′), 7.28 (1H, t, H-8′), 7.49 (1H, bs, NH), 8.21 (1H, d, H-10′), 8.34 (1H, s, H-2′). MS *m/z*: 351 ($M^+$), 280, 225, 213, 192, 155, 140. *Anal.* Calcd for $C_{21}H_{29}N_5$: C, 71.76; H, 8.32; N, 19.93. Found: C, 71.53; H, 8.64; N, 19.58.

***trans*-1-(4-Ethylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]tria-**

**zolo[1,5-*c*]quinazoline] (4b *trans*)** Compound **4b** *trans* was obtained from **2b** *trans* in 41% yield, white solids from ethyl acetate, mp 199—201 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.75 (2H, m, H-3″$_{eq}$, H-5″$_{eq}$), 0.79 (3H, t, $CH_2$–$\underline{CH_3}$), 0.87 (1H, m, H-4″$_{ax}$), 1.07—1.12 (2H, q, $\underline{CH_2}$–$CH_3$), 1.13—1.15 (2H, d, H-2″$_{ax}$, H-6″$_{ax}$), 1.66 (2H, d, H-3″$_{ax}$, H-5″$_{ax}$,), 1.73 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$), 2.17 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.26 (1H, t, H-1″$_{ax}$, $J$=11.6 Hz), 2.65 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.74 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.85 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.94 (1H, t, H-9′), 7.15 (1H, d, H-7′), 7.27 (1H, t, H-8′), 7.59 (1H, bs, NH), 8.21 (1H, d, H-10′), 8.34 (1H, s, H-2′). MS *m*/*z*: 351 ($M^+$), 280, 225, 213, 192, 155, 140. *Anal.* Calcd for $C_{21}H_{29}N_5$: C, 71.76; H, 8.32; N, 19.93. Found: C, 71.88; H, 7.95; N, 20.01.

***cis*-1-(4-*n*-Propylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4c *cis*)** Compound **4c** *cis* was obtained from **2c** *cis* in 38% yield, white solids from ethyl acetate, mp 130—131 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.85 (3H, t, $CH_2$–$CH_2$–$\underline{CH_3}$), 1.14—1.17 (2H, m, $CH_2$–$\underline{CH_2}$–$CH_3$), 1.19–1.22 (2H, m, $\underline{CH_2}$–$CH_2$–$CH_3$), 1.29—1.33 (2H, m, H-3″$_{ax}$, H-5″$_{ax}$), 1.35—1.39 (3H, m, H-2″$_{ax}$, H-4″, H-6″$_{ax}$), 1.39—1.41 (2H, m, H-3″$_{eq}$, H-5″$_{eq}$), 1.53—1.57 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$), 2.17 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.23 (1H, t, H-1″$_{ax}$ $J$=8.4 Hz), 2.59 (2H, t, H-3$_{ax}$, H-5$_{ax}$,), 2.65 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.90 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.94 (1H, t, H-9′), 7.18 (1H, d, H-7′), 7.28 (1H, t, H-8′), 7.52 (1H, bs, NH), 8.21 (1H, d, H-10′), 8.34 (1H, s, H-2′). MS *m*/*z*: 365 ($M^+$), 225, 213, 206, 197, 187, 154. *Anal.* Calcd for $C_{22}H_{31}N_5$: C, 72.29; H, 8.55; N, 19.16. Found: C, 72.51; H, 8.27; N, 19.31.

***trans*-1-(4-*n*-Propylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4c *trans*)** Compound **4c** *trans* was obtained from **2c** *trans* in 37% yield, white solids from ethyl acetate, mp 172—174 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.77 (2H, d, H-3″$_{eq}$, H-5″$_{eq}$), 0.81 (3H, t, $CH_2$–$CH_2$–$\underline{CH_3}$), 1.00—1.10 (3H, m, H-4″$_{ax}$, $CH_2$–$\underline{CH_2}$–$CH_3$), 1.12—1.15 (2H, m, H-2″$_{ax}$, H-6″$_{ax}$), 1.16—1.21 (2H, m, $\underline{CH_2}$–$CH_2$–$CH_3$), 1.66 (2H, m, H-3″$_{ax}$, H-5″$_{ax}$,), 1.74 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$), 2.17 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.27 (1H, t, H-1″$_{ax}$, $J$=11.2 Hz), 2.65 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.75 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.85 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.94 (1H, t, H-9′), 7.18 (1H, d, H-7′), 7.28 (1H, t, H-8′), 7.59 (1H, bs, NH), 8.22 (1H, d, H-10′), 8.35 (1H, s, H-2′). MS *m*/*z*: 365 ($M^+$), 225, 213, 206, 197, 187, 154. *Anal.* Calcd for $C_{22}H_{31}N_5$: C, 72.29; H, 8.55; N, 19.16. Found: C, 72.38; H, 8.36; N, 19.38.

***cis*-1-(4-*iso*-Propylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4d *cis*)** Compound **4d** *cis* was obtained from **2d** *cis* in 70% yield, white solids from ethyl acetate, mp 180—182 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.84 (6H, d, *iso*-propyl $CH_3$), 0.98 (1H, m, H-4″), 1.24—1.34 (4H, m, H-2″$_{ax}$, H-6″$_{ax}$, H-3″$_{eq}$, H-5″$_{eq}$), 1.44 (1H, m, *iso*-propyl CH). 1.50 (2H, m, H-3″$_{ax}$, H-5″$_{ax}$), 1.64 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$), 2.17 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.24 (1H, t, H-1″$_{eq}$ $J$=4.8 Hz), 2.54 (2H, t, H-3$_{ax}$, H-5$_{ax}$,), 2.65 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.92 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.95 (1H, t, H-9′), 7.16 (1H, d, H-7′), 7.29 (1H, t, H-8′), 7.49 (1H, s, NH), 8.21 (1H, d, H-10′), 8.34 (1H, s, H-2′). MS *m*/*z*: 365 ($M^+$), 280, 252, 225, 213, 206, 197, 184, 169, 154. *Anal.* Calcd for $C_{22}H_{31}N_5$: C, 72.29; H, 8.55; N, 19.16. Found: C, 71.98; H, 8.79; N, 19.04.

***trans*-1-(4-*iso*-Propylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4d *trans*)** Compound **4d** *trans* was obtained from **2d** *trans* in 68% yield, white solids from ethyl acetate, mp 200—202 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.78 (6H, d, *iso*-propyl $CH_3$), 0.84 (3H, m, H-3″$_{eq}$, H-4″$_{ax}$, H-5″$_{eq}$), 1.13 (2H, q, H-2″$_{ax}$, H-6″$_{ax}$), 1.28 (1H, m, *iso*-propyl CH), 1.61 (2H, d, H-3″$_{ax}$, H-5″$_{ax}$), 1.77 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$), 2.17 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.24 (1H, t, H-1″$_{ax}$, $J$=12.0 Hz), 2.66 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.76 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.87 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.94 (1H, t, H-9′), 7.14 (1H, d, H-7′), 7.28 (1H, t, H-8′), 7.59 (1H, bs, NH), 8.21 (1H, d, H-10′), 8.34 (1H, s, H-2′). MS *m*/*z*: 365 ($M^+$), 280, 252, 225, 213, 206, 197, 184, 154, 138. *Anal.* Calcd for $C_{22}H_{31}N_5$: C, 72.29; H, 8.55; N, 19.16. Found: C, 72.12; H, 8.23; N, 18.95.

***cis*-1-(4-*tert*-Butylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4e *cis*)** Compound **4e** *cis* was obtained from **2e** *cis* in 40% yield, white solids from ethyl acetate, mp 150—152 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.80 (9H, s, *tert*-butyl), 0.97 (1H, t, H-4″$_{ax}$, $J$=8.4 Hz), 1.21 (2H, t, H-3″$_{ax}$, H-5″$_{ax}$), 1.25—1.39 (4H, m, H-2″$_{ax}$, H-3″$_{eq}$, H-5″$_{eq}$, H-6″$_{ax}$), 1.94 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$), 2.16—2.18 (3H, m, H-3$_{eq}$, H-5$_{eq}$, H-1″$_{eq}$), 2.46 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.62 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.98 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.94 (1H, t, H-9′), 7.16 (1H, d, H-7′), 7.28 (1H, t, H-8′), 7.50 (1H, bs, NH), 8.21 (1H, d, H-10′), 8.33 (1H, s, H-2′). MS *m*/*z*: 379 ($M^+$), 328, 297, 220, 213, 197, 184. *Anal.* Calcd for $C_{23}H_{33}N_5$: C, 72.78; H, 8.77; N, 18.45. Found: C, 72.56; H, 8.93; N, 18.19.

***trans*-1-(4-*tert*-Butylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4e *trans*)** Compound **4e** *trans* was obtained from **2e** *trans* in 40% yield, white solids from ethyl acetate, mp 208—210 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.78 (9H, s, *tert*-butyl), 0.80—0.89 (3H, m, H-3″$_{eq}$, H-4″$_{ax}$, H-5″$_{eq}$), 1.38 (2H, dd, H-2″$_{ax}$, H-6″$_{ax}$), 1.67 (2H, m, H-3″$_{ax}$, H-5″$_{ax}$), 1.80 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$), 2.18 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.23 (1H, t, H-1″$_{ax}$, $J$=11.2 Hz), 2.65 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.77 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.90 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.94 (1H, t, H-9′), 7.14 (1H, d, H-7′), 7.28 (1H, t, H-8′), 7.59 (1H, bs, NH), 8.21 (1H, d, H-10′), 8.35 (1H, s, H-2′). MS *m*/*z*: 379 ($M^+$), 220, 213, 197, 168, 138, 184. *Anal.* Calcd for $C_{23}H_{33}N_5$: C, 72.78; H, 8.77; N, 18.45. Found: C, 72.54; H, 8.40; N, 18.17.

**1-Benzylspiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4f)** Compound **4f** was obtained from **2f** in 43% yield, white solids from ethyl acetate, mp 158—160 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 2.00 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.35 (2H, t, H-3$_{ax}$, H-5$_{ax}$), 2.55 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.97 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 3.63 (2H, s, benzyl $CH_2$), 4.61 (1H, bs, NH), 6.86 (1H, d, H-7′), 6.94 (1H, t, H-9′), 7.28—7.36 (6H, m, H-8′, benzyl protons), 7.90 (1H, d, H-10′), 7.97 (1H, s, H-2′). MS *m*/*z*: 331 ($M^+$), 240, 213, 197, 185, 172. *Anal.* Calcd for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13. Found: C, 72.68; H, 6.23; N, 21.42.

**1-Phenethylspiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4g)** Compound **4g** was obtained from **2g** in 42% yield, white solids from ethyl acetate, mp 134—136 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 2.07 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 2.38—2.55 (4H, m, H-2$_{ax}$, H-3$_{ax}$, H-5$_{ax}$ H-6$_{ax}$), 2.70—2.88 (4H, m, phenethyl $CH_2$–$CH_2$), 3.07 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 4.64 (1H, bs, NH), 6.86 (1H, d, H-7′), 6.99 (1H, t, H-9′), 7.26—7.35 (6H, m, H-8′, phenyl protons), 7.90 (1H, d, H-10′), 7.97 (1H, s, H-2′). MS *m*/*z*: 345 ($M^+$), 254, 225, 213, 197, 186. *Anal.* Calcd for $C_{21}H_{23}N_5$: C, 73.01; H, 6.71; N, 20.28. Found: C, 73.28; H, 6.50; N, 20.08.

**1-(1-Adamantyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4h)** Compound **4h** was obtained from **2h** in 39% yield, white solids from ethyl acetate, mp 260—264 °C (dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.55—1.63 (6H, dd, H-2″, H-8″, H-9″), 1.68 (6H, bs, H-4″, H-6″, H-10″), 1.92 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J$=12.8 Hz), 2.05 (3H, bs, H-3″$_{eq}$, H-5″$_{eq}$, H-7″$_{eq}$), 2.17 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J$=10.8 Hz), 2.62 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J$=10.8 Hz), 2.96 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 6.82 (1H, t, H-9′), 7.00 (1H, bs, NH), 7.05 (1H, d, H-7′), 7.24 (1H, t, H-8′), 7.65 (1H, d, H-10′), 7.99 (1H, s, H-2′). MS *m*/*z*: 375 ($M^+$), 240, 216, 164, 135. *Anal.* Calcd for $C_{23}H_{29}N_5$: C, 73.56; H, 7.79; N, 18.65. Found: C, 73.23; H, 8.07; N, 18.44.

**1-(5*H*-10,11-Dihydrodibenzo[*a*,*d*]cyclohepten-5-yl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4i)** Compound **4i** was obtained from **2i** in 37% yield, white solids from ethyl acetate, mp 129—131 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.89 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J$=12.4 Hz), 2.18 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J$=13.2 Hz), 2.44 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J$=12.5 Hz), 2.56 (2H, d, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=12.0 Hz), 2.75—2.80 (2H, dd, H-10″, H-11″), 3.92—3.98 (2H, dd, H-10″, H-11″), 4.18 (1H, s, H-5″), 6.82 (1H, t, H-9′), 7.03—7.23 (10H, m, dibenzosuberyl aromatics, H-7′ and NH), 7.24 (1H, t, H-8′), 7.64 (1H, d, H-10′), 8.00 (1H, s, H-2′). MS *m*/*z*: 433 ($M^+$), 242, 193, 115. *Anal.* Calcd for $C_{28}H_{27}N_5$: C, 77.57; H, 6.28; N, 16.16. Found: C, 77.46; H, 5.92; N, 16.03.

**General Procedure for the Preparation of the 1′-Methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones 3j—r** A solution of the appropriate piperidone **2** (0.01 mol) and 2-methylaminobenzamide[34] (1.5 g, 0.01 mol) in acetic acid (14 ml) with two drops of sulfuric acid, was refluxed for 30 min; then the mixture was cooled, diluted with water, alkalinized with 8% aqueous sodium hydroxide and repeatedly extracted with ethyl acetate. The organic phase was then dried over sodium sulfate, evaporated *in vacuo* and crystallized from the appropriate solvent.

***cis*-1′-Methyl-1-(4-methylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3j *cis*)** Compound **3j** *cis* was obtained from **2a** *cis* in 29% yield, white solids from ethyl acetate, mp 183—186 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.86 (3H, d, 4″-$CH_3$), 8.49 (1H, s, NH), 1.39 (7H, m, H-3″, H-5″, H-2″$_{ax}$, H-6″$_{ax}$, H-4″), 1.60 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$, $J$=8.1 Hz), 1.90 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.8 Hz), 2.03 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J$=12.8 Hz), 2.17 (1H, t, H-1″$_{ax}$, $J$=6.9 Hz), 2.53 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J$=11.4 Hz), 2.74 (3H, s, N–$CH_3$), 2.80 (2H, d, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=11.6 Hz), 6.85 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 6.95 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.43 (1H, t, H-7′, $J_{ortho}$=7.4 Hz), 8.39 (1H, d, H-5′, $J_{ortho}$=7.6 Hz). MS *m*/*z*: 327 ($M^+$), 310, 270, 242, 231, 203, 187, 175, 161, 153, 140, 134, 125. *Anal.* Calcd for $C_{20}H_{29}N_3O$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.04; H, 9.18; N, 12.65.

***trans*-1′-Methyl-1-(4-methylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3j *trans*)** Compound **3j** *trans* was obtained from **2a** *trans* in 29% yield, white solids from ethyl acetate, mp 219—221 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.78 (3H, d, 4″-$CH_3$), 0.83 (2H, d, H-3″$_{eq}$, H-5″$_{eq}$, $J_{gem}$=12.1 Hz), 1.12 (1H, um, H-4″$_{ax}$), 1.19 (2H, q, H-2″$_{ax}$, H-6″$_{ax}$, $J$=12.3 Hz), 1.60 (2H, d, H-3″$_{ax}$, H-5″$_{ax}$, $J_{gem}$=11.9 Hz), 1.73 (2H, d, H-2″$_{eq}$, H-

6″$_{eq}$, $J_{gem}$=11.4 Hz), 1.91 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.0 Hz), 2.02 (2H, dt, H-3$_{ax}$, H-5$_{ax}$, $J$=12.5 Hz, $J$=5.1 Hz), 2.23 (1H, t, H-1″$_{ax}$, $J_{diax}$=11.5 Hz), 2.72 (4H, m, H-2, H-6), 2.75 (3H, s, N–CH$_3$), 6.85 (1H, d, H-8′, $J_{ortho}$= 8.2 Hz), 6.96 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.43 (1H, t, H-7′, $J_{ortho}$=7.5 Hz), 8.39 (1H, d, H-5′, $J_{ortho}$=7.5 Hz), 8.49 (1H, s, NH). MS *m*/*z*: 327 (M$^+$), 270, 242, 231, 203, 187, 175, 161, 153, 140, 134, 125. *Anal.* Calcd for $C_{20}H_{29}N_3O$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.27; H, 9.15; N, 13.09.

***cis*-1-(4-Ethylcyclohexyl)-1′-methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3k *cis*)** Compound **3k** *cis* was obtained from **2b** *cis* in 31% yield, white solids from ethyl acetate, mp 173—174 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.85 (3H, t, ethyl CH$_3$), 1.21 (2H, qt, ethyl CH$_2$), 1.40 (7H, m, H-3″, H-5″, H-2″$_{ax}$, H-6″$_{ax}$, H-4″), 1.56 (2H, m, H-2″$_{eq}$, H-6″$_{eq}$, $J$=8.7 Hz), 1.89 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.5 Hz), 2.02 (2H, dt, H-3$_{ax}$, H-5$_{ax}$, $J$=12.8 Hz, $J$=4.1 Hz), 2.22 (1H, t, H-1″$_{ax}$, $J$=7.8 Hz), 2.60 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J$= 11.6 Hz), 2.74 (3H, s, N–CH$_3$), 2.79 (2H, d, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=11.8 Hz), 6.84 (1H, d, H-8′, $J_{ortho}$=8.2 Hz), 6.95 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.43 (1H, t, H-7′, $J_{ortho}$=7.3 Hz), 8.37 (1H, d, H-5′, $J_{ortho}$=7.6 Hz), 8.65 (1H, s, NH). MS *m*/*z*: 341 (M$^+$), 270, 242, 231, 203, 192, 187, 175, 167, 161, 154, 140, 134, 120, 110. *Anal.* Calcd for $C_{21}H_{31}N_3O$: C, 73.86; H, 9.15; N, 12.31. Found: C, 74.02; H, 8.82; N, 12.45.

***trans*-1-(4-Ethylcyclohexyl)-1′-methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3k *trans*)** Compound **3k** *trans* was obtained from **2b** *trans* in 31% yield, white solids from ethyl acetate, mp 200—202 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.77 (2H, d, H-3″$_{eq}$, H-5″$_{eq}$, $J_{gem}$= 11.6 Hz), 0.81 (3H, t, ethyl CH$_3$), 0.89 (1H, bm, H-4″$_{ax}$), 1.10 (2H, qt, ethyl CH$_2$), 1.18 (2H, q, H-2″$_{ax}$, H-6″$_{ax}$, $J$=11.7 Hz), 1.67 (2H, d, H-3″$_{ax}$, H-5″$_{ax}$, $J_{gem}$=11.9 Hz), 1.77 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$, $J_{gem}$=11.3 Hz), 1.91 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=11.9 Hz), 2.03 (2H, bt, H-3$_{ax}$, H-5$_{ax}$, $J_{gem}$, $J_{diax}$=11.8 Hz, $J_{ax-eq}$=5.2 Hz), 2.24 (1H, t, H-1″$_{ax}$, $J_{diax}$=11.6 Hz), 2.76 (7H, overlapped s and m, H-2, H-6, N–CH$_3$), 6.85 (1H, d, H-8′, $J_{ortho}$=8.3 Hz), 6.96 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.43 (1H, t, H-7′, $J_{ortho}$=8.0 Hz), 8.38 (1H, d, H-5′, $J_{ortho}$= 7.5 Hz), 8.52 (1H, s, NH). MS *m*/*z*: 341 (M$^+$), 270, 242, 230, 203, 192, 187, 175, 167, 160, 154, 140, 134, 110. *Anal.* Calcd for $C_{21}H_{31}N_3O$: C, 73.86; H, 9.15; N, 12.31. Found: C, 74.16; H, 9.31; N, 12.56.

***cis*-1′-Methyl-1-(4-*n*-propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3l *cis*)** Compound **3l** *cis* was obtained from **2c** *cis* in 31% yield, white solids from ethyl acetate, mp 140—141 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.85 (3H, t, *n*-propyl CH$_3$), 1.19 (4H, m, H-2″$_{ax}$, H-6″$_{ax}$, *n*-propyl CH$_2$), 1.40 (7H, m, H-3″, H-4″, H-5″, *n*-propyl 4″-CH$_2$), 1.57 (2H, at, H-2″$_{eq}$, H-6″$_{eq}$, $J$=8.6 Hz), 1.91 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.3 Hz), 2.04 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J_{gem}$=12.7 Hz, $J_{diax}$=11.4 Hz, $J_{ax-eq}$=3.4 Hz), 2.20 (1H, t, H-1″$_{ax}$, $J$=6.7 Hz), 2.54 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J_{gem}$=11.2 Hz), 2.75 (3H, s, N–CH$_3$), 2.81 (2H, bd, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=11.8 Hz), 6.86 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 6.96 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.43 (1H, t, H-7′, $J_{ortho}$=7.8 Hz), 8.39 (1H, d, H-5′, $J_{ortho}$=7.6 Hz), 8.45 (1H, s, NH). MS *m*/*z*: 355 (M$^+$), 270, 242, 231, 221, 206, 203, 187, 181, 175, 168, 161, 153, 134, 124, 110. *Anal.* Calcd for $C_{22}H_{33}N_3O$: C, 74.32; H, 9.36; N, 11.82. Found: C, 74.55; H, 9.19; N, 12.13.

***trans*-1′-Methyl-1-(4-*n*-propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3l *trans*)** Compound **3l** *trans* was obtained from **2c** *trans* in 31% yield, white solids from ethyl acetate, mp 206—208 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.78 (2H, d, H-3″$_{eq}$, H-5″$_{eq}$, $J_{gem}$=11.7 Hz), 0.84 (3H, t, *n*-propyl CH$_3$), 1.05 (3H, m, H-4″, *n*-propyl CH$_2$), 1.17 (2H, t, H-2″$_{ax}$, H-6″$_{ax}$, $J_{gem}$=11.4 Hz), 1.22 (2H, qt, *n*-propyl 4″-CH$_2$), 1.68 (2H, m, H-3″$_{ax}$, H-5″$_{ax}$, $J_{gem}$=12.0 Hz), 1.78 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$, $J_{gem}$=11.3 Hz), 1.91 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.1 Hz), 2.03 (2H, dt, H-3$_{ax}$, H-5$_{ax}$, $J_{gem}$=12.8 Hz, $J_{diax}$= 10.6 Hz, $J_{ax-eq}$=5.5 Hz), 2.25 (1H, t, H-1″$_{ax}$, $J_{diax}$=11.6 Hz, $J_{ax-eq}$=3.0 Hz), 2.75 (7H, overlapped s and m, H-2, H-6, N–CH$_3$), 6.85 (1H, d, H-8′, $J_{ortho}$= 8.3 Hz), 6.96 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.44 (1H, t, H-7′, $J_{ortho}$=7.2 Hz), 8.39 (1H, d, H-5′, $J_{ortho}$=7.5 Hz), 8.51 (1H, s, NH). MS *m*/*z*: 355 (M$^+$), 340, 270, 242, 231, 221, 206, 203, 187, 181, 175, 168, 161, 153, 134, 124, 110. *Anal.* Calcd for $C_{22}H_{33}N_3O$: C, 74.32; H, 9.36; N, 11.82. Found: C, 74.21; H, 8.99; N, 12.07.

***cis*-1′-Methyl-1-(4-*iso*-propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3m *cis*)** Compound **3m** *cis* was obtained from **2d** *cis* in 50% yield, white solids from ethyl acetate, mp 142—144 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.83 (6H, d, *iso*-propyl CH$_3$), 1.00 (1H, bm, H-4″), 1.27 (2H, d. H-3″$_{eq}$, H-5″$_{eq}$), 1.35 (1H, t, H-2″$_{ax}$, H-6″$_{ax}$,), 1.44 (1H, m, *iso*-propyl CH), 1.51 (2H, t, H-3″$_{ax}$, H-5″$_{ax}$), 1.66 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$), 1.92 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.4 Hz), 2.03 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J_{gem}$=12.7 Hz, $J_{diax}$=11.4 Hz, $J_{ax-eq}$=3.4 Hz), 2.19 (1H, sh m, H-1″$_{eq}$, $J$=2.7 Hz), 2.52 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J_{gem}$=11.2 Hz), 2.74 (3H, s, N–CH$_3$), 2.83 (2H, d, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=11.8 Hz), 6.86 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 6.96 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.43 (1H, t, H-7′, $J_{ortho}$=7.8 Hz), 8.39 (1H, d, H-5′, $J_{ortho}$= 7.6 Hz), 8.50 (1H, s, NH). MS *m*/*z*: 355 (M$^+$), 270, 242, 231, 221, 206, 203, 187, 181, 175, 168, 161, 153, 138, 134, 124, 110. *Anal.* Calcd for $C_{22}H_{33}N_3O$: C, 74.32; H, 9.36; N, 11.82. Found: C, 74.13; H, 9.70; N, 11.98.

***trans*-1′-Methyl-1-(4-*iso*-propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3m *trans*)** Compound **3m** *trans* was obtained from **2d** *trans* in 70% yield, white solids from ethyl acetate, mp 199—201 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.78 (6H, d, *iso*-propyl CH$_3$), 0.85 (3H, m, H-3″$_{eq}$, H-4″$_{ax}$, H-5″$_{eq}$), 1.16 (2H, dd, H-2″$_{ax}$, H-6″$_{ax}$, $J_{gem}$=11.4 Hz), 1.29 (1H, m, *iso*-propyl CH), 1.61 (2H, d, H-3″$_{ax}$, H-5″$_{ax}$, $J_{gem}$=12.0 Hz), 1.80 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$, $J_{gem}$=11.3 Hz), 1.91 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$= 11.6 Hz), 2.02 (2H, dt, H-3$_{ax}$, H-5$_{ax}$, $J_{gem}$=11.8 Hz, $J_{diax}$=10.6 Hz, $J_{ax-eq}$= 5.5 Hz), 2.22 (1H, t, H-1″$_{ax}$, $J_{diax}$=11.6 Hz, $J_{ax-eq}$=3.0 Hz), 2.75 (7H, overlapped s and m, H-2, H-6, N–CH$_3$), 6.85 (1H, d, H-8′, $J_{ortho}$=8.3 Hz), 6.96 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.44 (1H, t, H-7′, $J_{ortho}$=7.2 Hz), 8.38 (1H, d, H-5′, $J_{ortho}$=7.5 Hz), 8.54 (1H, s, NH). MS *m*/*z*: 355 (M$^+$), 342, 270, 242, 231, 221, 206, 203, 187, 181, 175, 168, 161, 153, 138, 134, 124, 110. *Anal.* Calcd for $C_{22}H_{33}N_3O$: C, 74.32; H, 9.36; N, 11.82. Found: C, 74.49; H, 9.27; N, 11.59.

***cis*-1-(4-*tert*-Butylcyclohexyl)-1′-methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3n *cis*)** Compound **3n** *cis* was obtained from **2e** *cis* in 32% yield, white solids from methanol, mp 190—192 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.83 (9H, s, *tert*-butyl), 0.99 (1H, m, H-4″$_{ax}$, $J_{diax}$=13.4 Hz, $J_{diax}$=11.3 Hz, $J_{ax-eq}$=4.1 Hz), 1.24 (2H, t, H-2″$_{ax}$, H-6″$_{ax}$, $J_{gem}$=13.8 Hz, $J_{diax}$=13.3 Hz, $J_{ax-eq}$=2.5 Hz), 1.35 (4H, m, H-3″, H-5″), 1.92 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.3 Hz), 1.97 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$, $J_{gem}$=14.0 Hz, $J_{eq-ax}$= 2.2 Hz), 2.02 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J_{gem}$=12.2 Hz, $J_{diax}$=12.2 Hz, $J_{ax-eq}$= 3.8 Hz), 2.13 (1H, sh m, H-1″$_{eq}$, $J$=2.7 Hz), 2.38 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J_{gem}$= 11.5 Hz, $J_{diax}$=11.4 Hz), 2.71 (3H, s, N–CH$_3$), 2.88 (2H, d, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=11.5 Hz), 6.86 (1H, d, H-8′, $J_{ortho}$=7.4 Hz), 6.96 (1H, t, H-6′, $J_{ortho}$= 7.4 Hz), 7.43 (1H, t, H-7′, $J_{ortho}$=7.2 Hz, $J_{meta}$=1.7 Hz), 8.39 (1H, d, H-5′, $J_{ortho}$=7.6 Hz, $J_{meta}$=1.6 Hz), 8.48 (1H, s, NH). MS *m*/*z*: 369 (M$^+$), 354, 270, 242, 231, 220, 202, 188, 175, 167, 161, 152, 138, 134, 120, 110. *Anal.* Calcd for $C_{23}H_{35}N_3O$: C, 74.75; H, 9.55; N, 11.37. Found: C, 74.99; H, 9.24; N, 11.23.

***trans*-1-(4-*tert*-Butylcyclohexyl)-1′-methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3n *trans*)** Compound **3n** *trans* was obtained from **2e** *trans* in 32% yield, white solids from ethyl acetate, mp 253—255 °C. $^1$H-NMR (Pyridine-$d_5$) $\delta$: 0.78 (9H, s, *tert*-butyl), 0.83 (1H, t, H-4″$_{ax}$, $J_{diax}$=11.9 Hz, $J_{ax-eq}$=2.6, 2.2 Hz), 0.86 (2H, q, H-3″$_{eq}$, H-5″$_{eq}$, $J_{gem}$= 12.0 Hz), 1.15 (2H, q, H-2″$_{ax}$, H-6″$_{ax}$, $J_{gem}$=12.1 Hz, $J_{diax}$=11.9 Hz, $J_{ax-eq}$= 2.1 Hz), 1.67 (2H, d, H-3″$_{ax}$, H-5″$_{ax}$, $J_{gem}$=11.5 Hz), 1.83 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$, $J_{gem}$=12.1 Hz), 1.93 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.0 Hz), 2.04 (2H, bt, H-3$_{ax}$, H-5$_{ax}$, $J_{gem}$=2.0 Hz, $J_{diax}$=9.9 Hz), 2.21 (1H, t, H-1″$_{ax}$, $J_{diax}$=11.5 Hz), 2.76 (3H, s, N–CH$_3$), 2.73—2.80 (4H, m, H-2, H-6), 6.85 (1H, d, H-8′, $J_{ortho}$=7.7 Hz), 6.96 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.43 (1H, t, H-7′, $J_{ortho}$=7.4 Hz, $J_{meta}$=1.6 Hz), 8.39 (1H, d, H-5′, $J_{ortho}$=7.6 Hz, $J_{meta}$=1.6 Hz). MS *m*/*z*: 369 (M$^+$), 354, 270, 242, 231, 220, 202, 187, 175, 167, 161, 152, 138, 134, 119, 110. *Anal.* Calcd for $C_{23}H_{35}N_3O$: C, 74.75; H, 9.55; N, 11.37. Found: C, 74.40; H, 9.25; N, 11.18.

**1-Benzyl-1′-methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3o)** Compound **3o** was obtained from **2f** in 24% yield, white solids from ethyl acetate, mp 158—160 °C (lit.[35] 158—159 °C from methanol). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.67 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.5 Hz), 1.92 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J$=12.4 Hz), 2.39 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J$=11.2 Hz), 2.59 (2H, d, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=11.8 Hz), 2.79 (3H, s, N–CH$_3$), 3.47 (2H, s, benzyl CH$_2$), 6.82 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 6.87 (1H, d, H-8′, $J_{ortho}$=8.1 Hz), 7.28 (5H, sh m, benzyl aromatics), 7.39 (1H, dt, H-7′, $J_{ortho}$=7.3 Hz, $J_{meta}$= 1.6 Hz), 7.69 (1H, dd, H-5′, $J_{ortho}$=7.6 Hz, $J_{meta}$=1.6 Hz), 8.02 (1H, s, NH). MS *m*/*z*: 321 (M$^+$), 308, 230, 203, 187, 175, 161, 146, 134, 118, 91. *Anal.* Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.08. Found: C, 74.48; H, 7.50; N, 13.41.

**1′-Methyl-1-phenethyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3p)** Compound **3p** was obtained from **2g** in 30% yield, white solids from ethanol, mp 163—165 °C.$^1$H-NMR (DMSO-$d_6$) $\delta$: 1.69 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.3 Hz), 1.91 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J$=10.5 Hz), 2.43 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J$=11.0 Hz), 2.55 (2H, d partially under solvent signal, H-2$_{eq}$, H-6$_{eq}$), 2.67 (4H, m, phenethyl CH$_2$–CH$_2$), 2.79 (3H, s, NCH$_3$), 6.83 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 6.88 (1H, d, H-8′, $J_{ortho}$=7.8 Hz), 7.22 (5H, m, phenethyl aromatics), 7.36 (1H, t, H-7′, $J_{ortho}$=7.3 Hz), 7.70 (1H, d, H-5′, $J_{ortho}$=7.4 Hz), 8.03 (1H, s, NH). MS *m*/*z*: 335 (M$^+$), 244, 231, 216, 203, 187, 174, 160, 134, 91. *Anal.* Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.40; H, 7.16; N, 12.21.

**1-(1-Adamantyl)-1′-methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3q)** Compound **3q** was obtained from **2h** in 38% yield, white solids from ethyl acetate, mp 255—257 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.56 (3H, d, H-2″$_{ax}$, H-8″$_{ax}$, H-9″$_{ax}$, $J_{gem}$=12.1 Hz), 1.60 (3H, d, H-2″$_{eq}$, H-8″$_{eq}$, H-9″$_{eq}$, $J_{gem}$=12.1 Hz), 1.64 (6H, bs, H-4″, H-6″, H-10″), 1.68 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J$=12.0 Hz), 1.80 (2H, t, H-3$_{ax}$, H-5$_{ax}$, $J$=11.7 Hz), 2.03 (3H, bs, H-3″$_{eq}$, H-5″$_{eq}$, H-7″$_{eq}$), 2.45 (2H, t, H-2$_{ax}$, H-6$_{ax}$, $J$=11.0 Hz), 2.54 (2H, d partially under solvent signal, H-2$_{eq}$, H-6$_{eq}$), 2.79 (3H, s, $NCH_3$), 6.81 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 6.86 (1H, d, H-8′, $J_{ortho}$=7.8 Hz), 7.39 (1H, t, H-7′, $J_{ortho}$=7.4 Hz), 7.68 (1H, s, H-5′, $J_{ortho}$=7.5 Hz), 7.98 (1H, s, NH). MS *m/z*: 365 ($M^+$), 337, 230, 216, 202, 187, 178, 164, 135. *Anal.* Calcd for $C_{23}H_{31}N_3O$: C, 75.58; H, 8.55; N, 11.50. Found: C, 75.48; H, 8.32; N, 11.72.

**1-(5*H*-10,11-Dihydrodibenzo[*a*,*d*]cyclohepten-5-yl)-1′-methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3r)** Compound **3r** was obtained from **2i** in 34% yield, white solids from ethyl acetate, mp 261—263 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.62 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=12.6 Hz), 1.84 (2H, m, H-3$_{ax}$, H-5$_{ax}$), 2.36 (4H, m, H-2, H-6), 2.77 (5H, overlapped s and m, N–$CH_3$, H-10″, H-11″), 3.93 (2H, m, H-10″, H-11″), 4.10 (1H, s, H-5″), 6.82 (1H, t, H-6′, $J_{ortho}$=7.3 Hz), 6.87 (1H, d, H-8′, $J_{ortho}$=7.9 Hz), 7.13 (8H, m, dibenzosuberyl aromatics), 7.38 (1H, t, H-7′, $J_{ortho}$=7.4 Hz, $J_{meta}$=1.7 Hz), 7.68 (1H, dd, H-5′, $J_{ortho}$=7.6 Hz, $J_{meta}$=1.6 Hz), 7.94 (1H, s, NH). MS *m/z*: 423 ($M^+$), 232, 203, 193, 187, 178, 165, 134, 115. *Anal.* Calcd for $C_{28}H_{29}N_3O$: C, 79.40; H, 6.90; N, 9.92. Found: C, 79.12; H, 7.16; N, 9.73.

**General Procedure for the Preparation of the 1′-Benzylspiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones 3s—u** A solution of the appropriate piperidone (0.01 mol) and 2-benzylaminobenzamide[36] (2.3 g, 0.01 mol) in acetic acid (20 ml) with two drops of sulfuric acid, was refluxed for 3 h; then the mixture was cooled, diluted with water, made alkaline with 8% aqueous sodium hydroxide and repeatedly extracted with ethyl acetate. The organic phase was dried over sodium sulfate, evaporated *in vacuo* and the residue crystallized from the appropriate solvent.

***cis*-1′-Benzyl-1-(4-*iso*-propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3s *cis*)** Compound **3s *cis*** was obtained from **2d *cis*** in 68% yield, white solids from ethyl acetate, mp 162—164 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.81 (6H, d, *iso*-propyl $CH_3$), 1.04 (1H, m, H-4″), 1.28 (2H, m, H-3″$_{eq}$, H-5″$_{eq}$), 1.36 (2H, t, H-2″$_{ax}$, H-6″$_{ax}$,), 1.49 (3H, m, H-3″$_{ax}$, H-5″$_{ax}$, *iso*-propyl CH), 1.61 (2H, m, H-2$_{eq}$, H-6$_{eq}$), 1.85 (4H, bs, H-3, H-5), 2.22 (1H, sh m, H-1″$_{eq}$), 2.44 (2H, m, H-2$_{ax}$, H-6$_{ax}$), 2.71 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 4.59 (2H, s, 1′-benzyl $CH_2$) 6.66 (1H, t, H-8′, $J_{ortho}$=8.4 Hz), 6.75 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.27 (6H, m, overlapped benzyl group aromatics and H-7′), 7.71 (1H, d, H-5′, $J_{ortho}$=7.6 Hz), 8.03 (1H, s, NH). MS *m/z*: 431 ($M^+$), 346, 312, 307, 285, 279, 263, 250, 221, 206, 180, 161, 132, 110. *Anal.* Calcd for $C_{28}H_{37}N_3O$: C, 77.91; H, 8.64; N, 9.74. Found: C, 78.03; H, 8.35; N, 9.91.

***trans*-1′-Benzyl-1-(4-*iso*-propylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3s *trans*)** Compound **3s *trans*** was obtained from **2d *trans*** in 70% yield, white solids from ethyl acetate, mp 232—234 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.81 (6H, d, *iso*-propyl $CH_3$), 0.93 (3H, m, H-3″$_{eq}$, H-4″$_{ax}$, H-5″$_{eq}$), 1.15 (2H, dd, H-2″$_{ax}$, H-6″$_{ax}$, $J_{gem}$=11.4 Hz), 1.38 (1H, m, *iso*-propyl CH), 1.55 (2H, m, H-3″$_{ax}$, H-5″$_{ax}$, $J_{gem}$=12.0 Hz), 1.78 (2H, d, H-2″$_{eq}$, H-6″$_{eq}$, $J_{gem}$=11.3 Hz), 1.84 (4H, bs, H-3, H-5), 2.20 (1H, t, H-1″$_{ax}$, $J_{diax}$=11.6 Hz, $J_{ax\text{-}eq}$=3.0 Hz), 2.60 (4H, m, H-2, H-6), 4.61 (2H, s, 1′-benzyl $CH_2$), 6.66 (1H, d, H-8′, $J_{ortho}$=8.2 Hz), 6.76 (1H, t, H-6′, $J_{ortho}$=7.3 Hz), 7.27 (1H, t, H-7′, $J_{ortho}$=7.4 Hz), 7.32 (5H, m, benzyl group aromatics), 7.71 (1H, d, H-5′, $J_{ortho}$=7.5 Hz), 8.04 (1H, s, NH). MS *m/z*: 431 ($M^+$), 340, 312, 307, 285, 279, 263, 250, 221, 206, 180, 168, 138, 110. *Anal.* Calcd for $C_{28}H_{37}N_3O$: C, 77.91; H, 8.64; N, 9.74. Found: C, 77.72; H, 8.98; N, 9.85.

***cis*-1′-Benzyl-1-(4-*tert*-butylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3t *cis*)** Compound **3t *cis*** was obtained from **2e *cis*** in 21% yield, white solids from ethyl acetate, mp 200—202 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.77 (9H, s, *tert*-butyl), 1.01 (1H, m, H-4″), 1.27 (6H, m, H-2″$_{ax}$, H-6″$_{ax}$, H-3″, H-5″), 1.86 (6H, m, H-2$_{ax}$, H-6$_{ax}$, H-3$_{ax}$, H-5$_{ax}$, H-2″$_{eq}$, H-6″$_{eq}$) 2.20 (2H, d, H-3$_{eq}$, H-5$_{eq}$, $J_{gem}$=10.2 Hz), 2.29 (1H, t, H-1″$_{eq}$, $J$=6.4 Hz), 2.76 (2H, d, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=11.7 Hz), 4.59 (2H, s, 1′-benzyl $CH_2$) 6.69 (1H, t, H-8′, $J_{ortho}$=8.4 Hz), 6.76 (1H, t, H-6′, $J_{ortho}$=7.4 Hz), 7.27 (6H, m, overlapped benzyl group aromatics and H-7′), 7.71 (1H, d, H-5′, $J_{ortho}$=7.6 Hz), 8.03 (1H, s, NH). MS *m/z*: 445 ($M^+$), 354, 326, 307, 299, 263, 250, 235, 220, 182, 161, 132, 91. *Anal.* Calcd for $C_{29}H_{39}N_3O$: C, 78.16; H, 8.82; N, 9.43. Found: C, 78.03; H, 8.53; N, 9.71.

***trans*-1′-Benzyl-1-(4-*tert*-butylcyclohexyl)-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3t *trans*)** Compound **3t *trans*** was obtained from **2e *trans*** in 21% yield, white solids from ethyl acetate, mp 254—256 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.82 (9H, s, *tert*-butyl), 0.93 (3H, m, H-3″$_{ax}$, H-4″$_{ax}$, H-5″$_{ax}$), 1.18 (2H, m, H-2″$_{ax}$, H-6″$_{ax}$), 1.86 (8H, m, H-3, H-5, H-2″$_{eq}$, H-3″$_{eq}$, H-5″$_{eq}$, H-6″$_{eq}$), 2.24 (1H, t, H-1″$_{ax}$), 2.65 (4H, m, H-2, H-6), 4.61 (2H, s, 1′-benzyl $CH_2$), 6.68 (1H, d, H-8′, $J_{ortho}$=8.2 Hz), 6.77 (1H, t, H-6′, $J_{ortho}$=7.3 Hz), 7.29 (1H, t, H-7′, $J_{ortho}$=7.4 Hz), 7.32 (5H, m, benzyl group aromatics), 7.73 (1H, d, H-5′, $J_{ortho}$=7.5 Hz), 8.12 (1H, s, NH). MS *m/z*: 445 ($M^+$), 354, 326, 299, 279, 263, 250, 235, 220, 182, 161, 132, 91. *Anal.* Calcd for $C_{29}H_{39}N_3O$: C, 78.16; H, 8.82; N, 9.43. Found: C, 77.95; H, 8.93; N, 9.34.

**1,1′-Dibenzylspiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3u)** Compound **3u** was obtained from **2f** in 12% yield, white solids from ethyl acetate, mp 233—235 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.98 (4H, sh m, H-3, H-5), 2.26 (2H, m, H-2$_{ax}$, H-6$_{ax}$), 2.77 (2H, bd, H-2$_{eq}$, H-6$_{eq}$, $J_{gem}$=11.7 Hz), 3.46 (2H, s, 1-benzyl $CH_2$), 4.52 (2H, s, 1′-benzyl $CH_2$), 6.53 (1H, d, H-8′, $J_{ortho}$=8.4 Hz), 6.62 (1H, bs, NH), 6.73 (1H, t, H-6′, $J_{ortho}$=7.3 Hz), 7.24 (11H, m, overlapped benzyl group aromatics and H-7′), 7.90 (1H, d, H-5′, $J_{ortho}$=7.6 Hz). MS *m/z*: 397 ($M^+$), 306, 279, 263, 251, 210, 187, 172, 160, 146, 134, 118, 91. *Anal.* Calcd for $C_{26}H_{27}N_3O$: C, 78.56; H, 6.85; N, 10.57. Found: C, 78.69; H, 6.48; N, 10.36.

**General Procedure for the Preparation of the 1′-Methyl-spiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones 4m, n** To a stirred and ice-cooled solution of the appropriate compound **4** (0.0013 mol) in formic acid (15 ml), sodium borohydride (13.2 mmol) was very slowly and carefully added in small portions; cooling and stirring were continued until compound **4** disappeared as revealed by TLC. The mixture was poured in ice, made alkaline by aqueous sodium hydroxide and extracted with ethyl acetate. The organic phase dried on sodium sulfate was evaporated and the obtained residue was chromatographed on aluminium oxide eluting by an ethyl acetate/hexane 2 : 1 (v/v) mixture.

***cis*-1′-Methyl-1-(4-*iso*-propylcyclohexyl)-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4m *cis*)** Compound **4m *cis*** was obtained from **4d *cis*** in 25% yield as pale yellow solids, mp 110—112 °C (from ethyl ether). $^1$H-NMR ($CDCl_3$) $\delta$: 0.83 (6H, d, *iso*-propyl $CH_3$), 1.07 (1H, m, H-4″$_{ax}$ $J$=9.8 Hz), 1.31 (2H, dt, H-3″$_{eq}$, H-5″$_{eq}$), 1.40—1.70 (7H, m, H-2″, H-3″$_{ax}$, H-5″$_{ax}$, H-6″, *iso*-propyl CH), 1.83 (2H, d, H-3$_{eq}$, H-5$_{eq}$), 1.99 (2H, t, H-3$_{ax}$, H-5$_{ax}$,), 2.20 (1H, t, H-1″$_{eq}$ $J$=4.8 Hz), 2.72 (3H, s, $NCH_3$), 2.79 (2H, t, H-2$_{ax}$, H-6$_{ax}$), 2.98 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 7.25—7.41 (3H, m, H-7′, H-8′, H-9′), 7.98 (1H, s, H-2′), 8.31 (1H, d, H-10′). MS *m/z*: *Anal.* Calcd for $C_{23}H_{33}N_5$: C, 72.78; H, 8.77; N, 18.45. Found: C, 72.98; H, 8.54; N, 18.37.

***cis*-1-(4-*tert*-Butylcyclohexyl)-6′-methyl-spiro[piperidine-4,5′(6′*H*)-[1,2,4]triazolo[1,5-*c*]quinazoline] (4n *cis*)** Compound **4n *cis*** was obtained from **4e *cis*** in 30% yield as white solids, mp 143—145 °C (from ethyl acetate). $^1$H-NMR ($CDCl_3$) $\delta$: 0.79 (9H, s, *tert*-butyl), 1.00 (1H, bt, H-4″$_{ax}$), 1.22—2.06 (14H, m, H-6$_{ax}$, H-3, H-5, H-1″$_{eq}$, H-2″, H-3″, H-5″, H-6″), 2.70 (3H, s, $NCH_3$), 2.77 (1H, t, H-2$_{ax}$), 3.00 (2H, d, H-2$_{eq}$, H-6$_{eq}$), 7.24—7.44 (3H, m, H-7′, H-8′, H-9′), 7.99 (1H, s, H-2′), 8.32 (1H, d, H-10′). MS *m/z*: 393 ($M^+$), 223, 220, 208, 180, 171, 166, 124. *Anal.* Calcd for $C_{24}H_{35}N_5$: C, 73.24; H, 8.97; N, 17.80. Found: C, 73.29; H, 8.65; N, 17.59.

**5,6-Dihydro-[1,2,4]triazolo[1,5-*c*]quinazoline** Sodium borohydride (1.0 g, 0.026 mol) was portionwise added to a suspension of [1,2,4]triazolo[1,5-*c*]quinazoline[25] (0.5 g, 0.003 mol) in methanol (25 ml) and the mixture left at room temperature under stirring for 2 h; then the solvent was removed *in vacuo* and the residue suspended in water and extracted with chloroform; the organic layer was then dried with sodium sulfate and the solvent evaporated *in vacuo* giving the product in 75% yield, colorless solid from benzene, mp 200—201 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 5.54 (2H, d, H-5), 6.81 (1H, dd, H-7), 6.86 (1H, t, H-9), 6.97 (1H, bs, $N_6$–H), 7.27 (1H, dt, H-8), 7.65 (1H, dd, H-10), 8.05 (1H, s, H-2). MS *m/z*: 172 ($M^+$), 145. *Anal.* Calcd for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.93; H, 4.43; N, 32.25.

**NOP Receptor Binding Assay in Membrane Preparations** Enriched plasma membranes from transfected cells were prepared by differential centrifugations[37] and stored at −80 °C (protein concentration 2—4 mg/ml) until used. The binding of $^{125}$I-Tyr$_{14}$-nociceptin (Perkin Elmer Life Sciences) was measured in 1 ml reaction mixture containing 50 mM Hepes–Tris pH 7.4, 10 mM $MgSO_4$, 10 $\mu$M leupeptin, 10 $\mu$M bestatin, 0.1 mg/ml bacitracin, 0.1% (w/v) bovine serum albumin (BSA), and 3 $\mu$g of membrane proteins from HEK-293 cells transfected with the NOP receptor as previously described.[26] The concentration of radiotracer was maintained constant at 50000—100000 cpm in the presence of increasing concentrations of compounds to be tested. Reactions lasted 90 min at room temperature and were terminated by rapid filtration onto GF/B glass fiber filtering microplates pretreated with 0.1% Ethylene Imine Polymer (PEI) (Filtermate 196; Packard Instruments, Meriden, CT). Filters were washed three times with 1 ml of ice-cold 50 mM

Tris–HCl pH 7.4 and allowed to dry for 30 min at 37 °C. The plates were counted in a Top Count (Packard Instruments) after the addition (50 $\mu$l) of Microscint 20 (Packard) to each well.

$IC_{50}$ values were obtained by fitting the competition curves according to a 4-parameter logistic model (ALLFIT program).[38]

**$\delta$, $\kappa$, $\mu$ Receptors Binding Assay** The binding affinities for human $\delta$, $\kappa$ and $\mu$ receptors were determined with [$^3$H]-naltrindole for $\delta$ receptor and with [$^3$H]-diprenorphine for $\kappa$ and $\mu$ receptors.[39,40]

A suspension of membranes (5—15 $\mu$g) of HEK-293 cells expressing $\delta$ receptors[26] and $\kappa$ receptors (Perkin Elmer Life Sciences) and of CHO cells expressing $\mu$ receptors (Perkin Elmer Life Sciences) was incubated with the radioligand (30000—50000 cpm) at room temperature for 2 h in a total volume of 1 ml containing 50 mM Hepes–Tris pH 7.4, 100 mM NaCl, 0.1 mg/ml bacitracin, 0.1% (w/v) BSA and increasing concentrations of compounds to be tested. Samples were incubated for 90 min at room temperature, filtered onto GF/B glass fiber filtering microplates (Filtermate 196; Packard Instruments, Meriden, CT, U.S.A.) and washed three times with 1 ml of ice cold 50 mM Tris–HCl pH 7.4 prior to scintillation counting on a Packard Top Count.

$IC_{50}$ values were obtained by fitting the competition curves according to a 4-parameter logistic model (ALLFIT program).[38]

**GTP$\gamma$S Binding** The $^{35}$S GTP$\gamma$S binding was determined in a 1 ml reaction mixture containing 50 mM Hepes–Tris pH 7.4, 1 mM dithiothreitol (DTT), 100 mM NaCl, 10 mM $MgSO_4$, 0.1 nM $^{35}$S GTP$\gamma$S (Perkin Elmer Life Sciences), 300 nM GDP (or concentrations varying between 0.1 nM and 100 $\mu$M) and 1—2 $\mu$g of membrane proteins, with or without compounds to be tested.[26] The dose–response curves of nociceptin were determined in absence and in presence of fixed concentrations of the tested compounds (0.1, 1, 100 $\mu$M).[41] Samples were incubated for 90 min at room temperature, filtered onto GF/B glass fiber filtering microplates (Filtermate 196; Packard Instruments, Meriden, CT. U.S.A.) and washed three times with 1 ml of ice cold 50 mM Tris–HCl pH 7.4 prior to scintillation counting on a Packard Top Count. Non specific binding was determined in the presence of 10 $\mu$M GTP$\gamma$S.

The data of dose–response experiments were analyzed using program ALLFIT, to compute the $EC_{50}$ in the absence and presence of the various concentrations of antagonist.[38]

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