Synthesis, Conformational Analysis and Free Radical Scavenging Activity of Some New Spiropyranoquinolinones

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A series of novel spiroadamantyl- and spirocyclical substituted pyranoquinolin-2-ones were synthesized and the conformation of the pyran ring was investigated. The free radical scavenging activity of the synthesized compounds was determined by their interaction with the stable free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH). All compounds tested scavenged the DPPH radical and among them derivatives possessing extended conjugation showed the highest activity.

Key words pyranoquinolinone; conformation; radical scavenging effect; 1,1-diphenyl-2-picrylhydrazyl (DPPH)

The cellular damage caused by the reactions of oxygen centered free radicals and reactive oxygen species (ROS) with DNA, structural or enzymatic proteins, polyunsaturated fatty acids and other macromolecules has been implicated in a variety of pathological events underlying age-related and post ischemic neurodegeneration[1] and other biological disorders such as heart disease, atherosclerosis, stroke, inflammation and cancer.[2—4] Mammalian cells have evolved an array of biochemical defense systems, including enzymes (superoxide dismutase, catalase and peroxidase) and low molecular weight compounds (ascorbic acid, vitamin E and glutathione) for protecting their components against the ROS that arise from endogenous metabolic processes or from various exogenous sources. However, the overproduction of these species and/or the decreased production of cellular antioxidants are responsible for the oxidative stress state, in which oxidant production surpasses the endogenous antioxidant capacities. Some tissues and the brain in particular are easily susceptible to oxidative damage under conditions of oxidative stress, due to their high levels of oxygen consumption and the elevated unsaturated fatty acids and iron stores.[5]

Consequently, elucidation of the mechanism of action and research on more active antioxidants of natural or synthetic origin continue to receive a great deal of attention for use in the development of potential chemoprotective therapeutics able to prevent or reduce oxidative stress-induced damage.

A number of quinolinones, including the novel antiulcer agent rebamipide (2-(4-chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid, Fig. 1) have been shown to scavenge hydroxyl radicals and inhibit superoxide production from polymorphonuclear leukocytes.[6,7] On the other hand, ethoquin (1,2-dihydro-6-ethoxy-2,2,4-trimethylquinoline, Fig. 1) and several 1,2-dihydro and 1,2,3,4-tetrahydroquinoline derivatives have been described as powerful antioxidants for the potential treatment of pathologies implicating central oxidative stress.[8—10] With these in mind, we have synthesized a number of structurally related derivatives in an effort to investigate their potential to act as radical scavengers and to exhibit antioxidant activity thereof. The new compounds possess the quinolin-2-one ring system fused to a pyrane or dihydropyrane ring, which bears spiro- substituents of various sizes. We investigated the importance of the extended conjugation, which is due to the presence of the pyrane ring, towards the flexibility adopted by the corresponding dihydropyrane analogues.

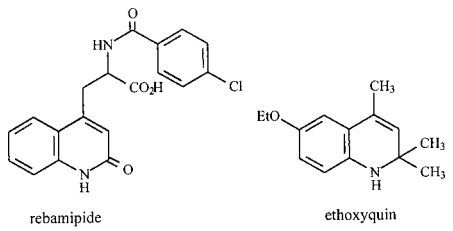

Fig. 1. Structures of Rebamipide and Ethoxyquin

Results and Discussion

Chemistry For the synthesis of the target derivatives we used the 2-spirocyclical substituted 4-chromanones **3a**,[11] **3b**[11] and **3c** (Chart 1), which were prepared through nitration of the commercial 2-hydroxyacetophenone (**1**)[12] and subsequent treatment with the appropriate carbocyclic ketone in the presence of pyrrolidine.[13] The nitro group of the chromanones **3a**—**c** was then reduced with tin(II) chloride in refluxing acetone to result in the corresponding anilines **4a**—**c**, which upon treatment with acetic anhydride gave the acetamides **5a**—**c**. Nitration of these acetamides with fuming nitric acid in acetic acid[14] provided the 2-spirocyclical substituted 5-nitro-6-acetamido-4-chromanones **6a**—**c**, which were subjected to borohydride reduction, followed by dehydration of the resulting 2-spiro-4-chromanols **7a**—**c**, in the presence of an acidic catalyst, to furnish the 2-spirochromenes **8a**—**c**.

For the preparation of the corresponding spiroadamantylchromene **14**, we used 3-nitro-4-acetamidophenol (**12**)[15] as starting material, obtained from commercial 4-acetamidophenol (**9**), as depicted in Chart 2. Reaction of **12** with 2-chloro-2-ethynyladamantane[16] provided the acetylenic ether **13** which upon thermal cyclization in refluxing *N*,*N*-diethylaniline provided the isomeric chromenes **14** and **15**. Both isomers were easily separated by flash chromatography on silica gel and fully characterized on the basis of NMR data.

Acid hydrolysis of the acetamides **8a**—**c** and **14** with a 5 N HCl solution resulted in the corresponding 6-aminoderivatives **16a**—**d** (Chart 3), which *via* diazotization and reaction with potassium iodide were converted to the corresponding

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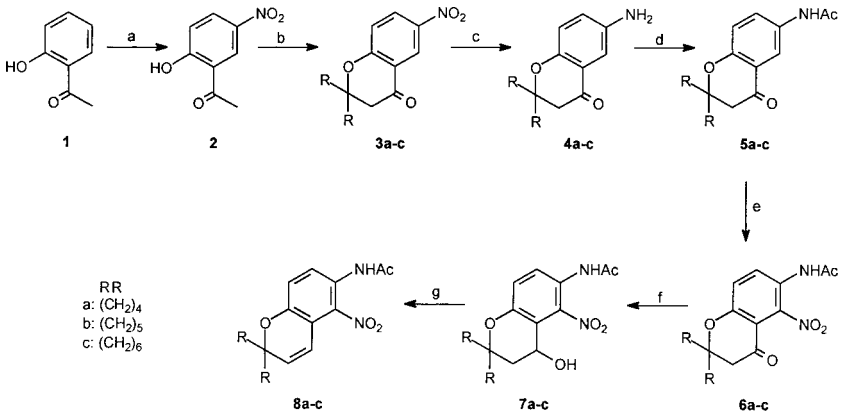
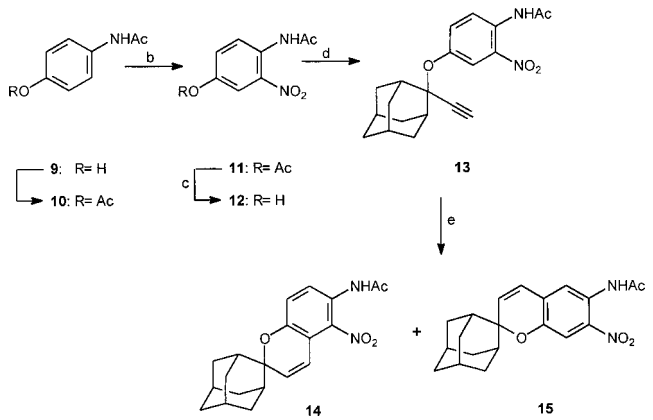


a: conc. HNO_3, AcOH, 30 °C, 56%, b: carbocyclic ketone, pyrrolidine, toluene, reflux, 70—90%, c: $SnCl_2 \cdot 2H_2O$, acetone, reflux, 80—85%, d: Ac_2O, r.t., 90—95%, e: fuming HNO_3, AcOH, r.t., 80—87%, f: $NaBH_4$, MeOH, r.t., 95%, g: *p*-TsOH, toluene, reflux, 90—95%.

Chart 1



a: Ac_2O, reflux, 96%, b: fuming HNO_3, AcOH, reflux, 40%, c: 40% NaOH, r.t., 85%, d: 2-chloro-2-ethynyladamantane, K_2CO_3, KI, CuI, acetone, reflux, 82%, e: *N*,*N*-diethylaniline, reflux, 64% of **14**, 4% of **15**.

Chart 2

iodides **17a**—**d**. The palladium-mediated coupling of these halides with acrylic acid in aqueous *N*,*N*-dimethylformamide (DMF) in the presence of potassium carbonate[17] resulted in the nitrocinnamic acids **18a**—**d**.

Reduction of the nitro group of compounds **18a**—**d** with tin(II) chloride in refluxing acetone gave the amino acids **19a**—**d**, which were subsequently ring-closed under reflux conditions in 4% HCl solution, to afford the corresponding pyranoquinolin-2-ones **20a**—**d**. Catalytic *syn*-hydroxylation of compounds **20a**—**d** with osmium tetroxide and *N*-methylmorpholine-*N*-oxide as oxidizing reagent[18] yielded the corresponding *cis*-diols **21a**—**d**.

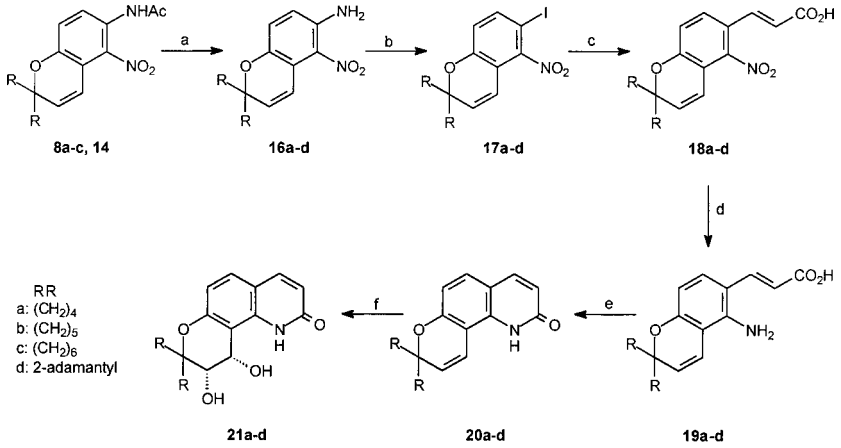
Conformational Analysis To our knowledge the conformation adopted by the pyran ring of dihydropyranoquinolinones has not been extensively studied. On the contrary, there are a number of reports on structurally analogous compounds bearing a dihydropyran ring, with hydroxyl substitutions. The crystal structure of pyranocoumarin derivatives reveals that the pyran ring conformation depends on the presence or absence of substituent on the hydroxyl group adjacent to the benzylic position.[19] The pyran ring of some derivatives of 1,2-dihydro-1,2-dihydroxyacronycine proved to be more rigid and to adopt only one conformation, orienting the benzylic OH group in pseudoequatorial position.[20] On the other hand the biological activity of some pyranothioxanthenone derivatives has been related to the possibility of dimmer formation *via* hydrogen bonds through the suitably oriented hydroxyl groups of the pyran ring.[21] Therefore, it was of interest to investigate the pyran ring conformation of the synthesized spiroquinolinones reported herein.

The pyran ring is expected to adopt two half-chair conformations, with 8′-C and 9′-C on opposite sides of the ring plane. Those conformations were constructed using Macromodel software,[22] geometry was optimized using MM2* force field and the resulting structures, represented by **21c**, are shown in Fig. 2 along with their relative energies. Calculated energy differences between conformers I and II for derivatives **21a**—**d** were found to vary from 2.2 kcal/mol for **21c** up to 5.7 kcal/mol for **21d**.

Protons at 9′-C and 10′-C are *gauche* in both conformers, thus the corresponding coupling constant is not useful for conformational analysis since it is expected to be similar for both conformers. Consequently, nuclear Overhauser effects (NOE's) were used in order to fully characterize the compound's structure and are exemplified here for the cycloheptyl-substituted derivative **21c**. Correlation detected in the nuclear Overhauser effect spectroscopy (NOESY) spectrum between the 10′-H with protons of the cycloheptyl ring resonating at 1.58 and 1.70 ppm, suggests that 10′-H adopts a pseudoaxial orientation (conformer I), and thus these cycloheptyl protons were assigned as 7″-H. If conformer II exists in solution one should expect to observe NOE's between 10′-OH and the cycloheptyl ring protons at 2″-C, but these were not detected.

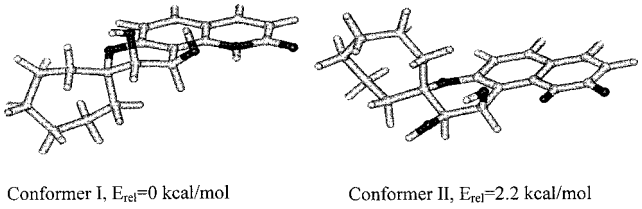
The above observations suggest that conformer I is predominant in solution, probably due to stabilization through the formation of a hydrogen bond between NH and 10′-O, in agreement with the MM2 calculated energy difference.

It should be noted here that the energy values resulting from the calculations showed that the spirocyclohexyl derivative is, as expected, the most stable (values expressed in kcal/mol: **21a**: −11.8, **21b**: −14.4, **21c**: −5.2, **21d**: −1.5). The same is also true for compounds **20a**—**d** (values expressed in kcal/mol: **20a**: 10.1, **20b**: 5.6, **20c**: 14.0, **20d**: 18.6).



a: 5 N HCl, reflux, 86—96%, b: i) $NaNO_2$, H_2SO_4, H_2O, ii) KI, r.t., 53—71%, c: $Pd(OAc)_2$, PPh_3, K_2CO_3, acrylic acid, DMF, H_2O, 100 °C, 45—60%, d: $SnCl_2 \cdot 2H_2O$, acetone, reflux, 49—60%, e: 4% HCl, reflux, 75—88%, f: OsO_4, 4-methylmorpholine-*N*-oxide, *t*-BuOH/THF/H_2O, r.t., 59—84%.

Chart 3



Conformer I, E_{rel}=0 kcal/mol Conformer II, E_{rel}=2.2 kcal/mol

Fig. 2. Representation of the Low Energy Conformations for Derivative **21c** Derived from Molecular Mechanics Calculations

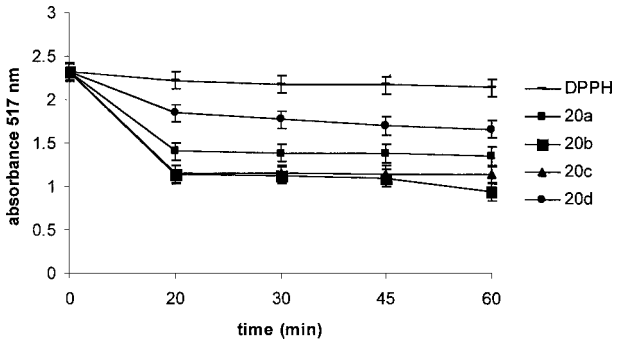


Fig. 3. DPPH Reduction, as Evaluated by the Decrease in Absorbance, at 517 nm, as a Function of Time at 200 μM Concentration of Compounds **20a**—**d**

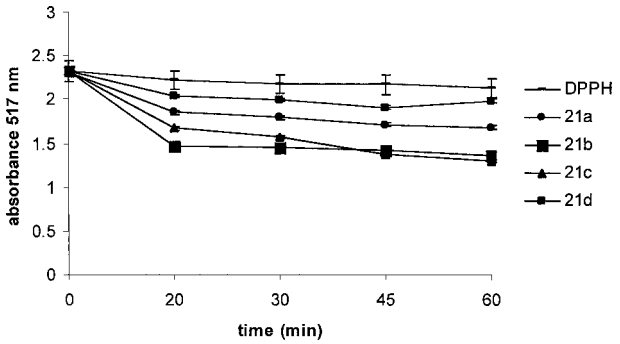


Fig. 4. DPPH Reduction, as Evaluated by the Decrease in Absorbance, at 517 nm, as a Function of Time at 200 μM Concentration of Compounds **21a**—**d**

Table 1. Effect of the Examined Compounds on Their Interaction with DPPH (200 μM)

Comp.	Percentage of interaction with DPPH					
	[DPPH] μM[a)]					
	5	10	50	100	200	400
20a	1	5	7	11	36	45
20b	11	14	20	42	48	66
20c	14	18	21	38	48	50
20d	2	3	6	10	16	19
21a	0	1	4	7	16	20
21b	8	13	20	25	35	36
21c	14	19	20	20	21	32
21d	2	3	4	4	5	8
Ascorbic acid	1	14	73	97	98	98

a) Based on absorbance values of samples with the tested compounds, against controls containing equal volume of the solvent. Standard deviation of absorbance values was less than ±10%, n=3—5.

Antioxidant Activity In the last years considerable research interest has focused on investigating the antioxidant properties of pharmacologically active compounds and several experimental protocols have been developed for this purpose.[23] The antioxidant action is considered to be a complex process which may include prevention of formation or scavenging of free radicals, consequently, it was of interest to investigate the interaction of the synthesized compounds **20a**—**d** and **21a**—**d** with the stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. In this assay antioxidants react with DPPH (which gives a strong absorption at 517 nm) and produce a colorless 2, 2-diphenyl-1-picrylhydrazine.[24] The change of absorbance produced in this reaction has been widely used to test the ability of several molecules to act as free radical scavengers.[25] Figures 3 and 4 show the time course dependent DPPH radical scavenging activity of compounds **20a**—**d** and **21a**—**d**, respectively, at a concentration of 200 μM. The percentage of interaction of the examined compounds with DPPH was measured in six different sample concentrations and is presented in Table 1.

All the tested compounds were found to interact with DPPH (Figs. 3, 4). Nevertheless, compounds **20a**—**d** were

more potent than compounds **21a**—**d**. It seems that the extended conjugation of **20a**—**d** against **21a**—**d** is a favorable characteristic for the increased free radical scavenging activity. The order of interaction with DPPH at 400 μM was found to be: **20b**≈**20c**>**20a**>**21b**≈**21c**>**21a**>**20d**>**21d**. It can be assumed that concerning the size of the spiro group, the cyclohexyl substituted derivative possesses the highest scavenging activity in both series of compounds. This is in agreement with the relative stability resulting from the theoretical calculations. On the other hand, the presence of the adamantane moiety (**20d** and **21d**) results in a considerable decrease of activity against DPPH. This could be correlated to a negative contribution of steric parameters to the reducing ability of DPPH.[26)]

Experimental

General Remarks Melting points were determined on a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra and two dimensional (2D) spectra were recorded on a Bruker Avanche 400 instrument, whereas ^{13}C-NMR spectra were recorded on a Bruker AC 200 spectrometer in deuterated solvents and were referenced to TMS (δ scale). The signals of ^{1}H and ^{13}C spectra were unambiguously assigned by using 2D NMR techniques: correlation spectroscopy (COSY), NOESY ^{1}H-detected heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond connectivity (HMBC). Flash chromatography was performed on Merck silica gel 60 (0.040—0.063 mm). Analytical thin layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates. Elemental analyses were within ±0.4% of the theoretical values.

3′,4′-Dihydro-6′-nitrospiro[cycloheptane-1,2′(2′*H*)[1]benzopyran]-4′-one (3c) A solution of 2-hydroxy-5-nitroacetophenone[12)] (**2**) (4.0 g, 0.022 mol), cycloheptanone (3.39 ml, 0.029 mol) and pyrrolidine (0.46 ml, 5.52 mmol) in anhydrous toluene was refluxed for 4 h in a Dean–Stark apparatus. The reaction mixture was then extracted with a 9% HCl solution and the organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 10/1 to 6/1 as the eluent to provide **3c** (4.3 g, 71%). mp: 96 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.3—2.2 (12H, m, cycloheptane H), 2.79 (2H, s, H-3′), 7.04 (1H, d, J=9.1 Hz, H-8′), 8.29 (1H, dd, J=9.1, 2.9 Hz, H-7′), 8.70 (1H, d, J=2.9 Hz, H-5′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.87, 29.26, 38.26 (cycloheptane C), 48.33 (C-3′), 86.56 (C-2′), 119.62 (C-8′), 120.06 (C-4′a), 123.16 (C-5′), 130.48 (C-7′), 141.48 (C-6′), 164.00 (C-8′a), 190.60 (C-4′). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.80; H, 6.13; N, 4.81.

3′,4′-Dihydro-4′-oxospiro[cyclopentane-1,2′(2′*H*)[1]benzopyran]-6′-amine (4a) To a solution of **3a** (1 g, 4.05 mmol) in acetone (50 ml) was added $SnCl_2 \cdot 2H_2O$ (3.66 g, 16.20 mmol) and the mixture was heated at reflux for 6 h. The reaction mixture was filtered through a celite pad, the filtrate was made alkaline with aqueous ammonia and extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated to dryness to give pure **4a** (720 mg, 82%). mp: 128 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.1 (8H, m, cyclopentane H), 2.75 (2H, s, H-3′), 3.49 (2H, br s, NH_2, D_2O exchangeable), 6.73 (1H, d, J=8.8 Hz, H-8′), 6.85 (1H, dd, J=8.8, 2.6 Hz, H-7′), 7.12 (1H, d, J=2.6 Hz, H-5′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.78, 37.25 (cyclopentane C), 47.17 (C-3′), 89.50 (C-2′), 110.85 (C-5′), 119.19 (C-8′), 121.01 (C-4′a), 124.39 (C-7′), 139.85 (C-6′), 153.67 (C-8′a), 193.07 (C-4′). *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.93; H, 6.66; N, 6.70.

The following compounds were prepared according to the procedure described for **4a**.

3′,4′-Dihydro-4′-oxospiro[cyclohexane-1,2′(2′*H*)[1]benzopyran]-6′-amine (**4b**): Yield: 85%. mp: 162 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.2—2.0 (10H, m, cyclohexane H), 2.60 (2H, s, H-3′), 3.53 (2H, br s, NH_2, D_2O exchangeable), 6.74 (1H, d, J=8.8 Hz, H-8′), 6.83 (1H, dd, J=8.8, 2.9 Hz, H-7′), 7.08 (1H, d, J=2.9 Hz, H-5′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.32, 25.10, 34.51 (cyclohexane C), 48.22 (C-3′), 79.28 (C-2′), 110.52 (C-5′), 118.94 (C-8′), 120.81 (C-4′a), 124.48 (C-7′), 139.88 (C-6′), 152.68 (C-8′a), 192.96 (C-4′). *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.52; N: 5.90.

3′,4′-Dihydro-4′-oxospiro[cycloheptane-1,2′(2′*H*)[1]benzopyran]-6′-amine (**4c**): Yield: 83%. mp: 184 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.3—2.2 (12H, m, cycloheptane H), 2.65 (2H, s, H-3′), 3.48 (2H, br s, NH_2, D_2O exchangeable), 6.75 (1H, d, J=8.8 Hz, H-8′), 6.84 (1H, dd, J=8.8, 2.9 Hz, H-7′), 7.08 (1H, d, J=2.9 Hz, H-5′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.77, 29.11, 37.89 (cycloheptane C), 48.88 (C-3′), 83.43 (C-2′), 110.37 (C-5′), 118.94 (C-8′), 120.66 (C-4′a), 124.42 (C-7′), 139.76 (C-6′), 152.82 (C-8′a), 192.98 (C-4′). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.32; H, 7.84; N, 5.95.

3′,4′-Dihydro-4′-oxospiro[cyclopentane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (5a) A solution of the amine **4a** (4.1 g, 0.019 mol) in acetic anhydride (50 ml) was stirred for 12 h at room temperature. The bulk of acetic anhydride was removed *in vacuo*, water was added to the residue and it was extracted with dichloromethane. The product was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 2/1 as the eluent to give **5a** (4.45 g, 91%). mp: 160 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.1 (8H, m, cyclopentane H), 2.15 (3H, s, CH_3), 2.78 (2H, s, H-39), 6.88 (1H, d, J=8.8 Hz, H-89), 7.32 (1H, br s, NH, D_2O exchangeable), 7.65 (1H, d, J=2.6 Hz, H-59), 7.91 (1H, dd, J=8.8, 2.6 Hz, H-79). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.84 (cyclopentane C), 24.30 (CH_3), 37.42 (cyclopentane C), 47.01 (C-39), 90.08 (C-29), 117.50 (C-59), 119.16 (C-89), 120.59 (C-49a), 129.50 (C-79), 131.41 (C-69), 157.20 (C-89a), 168.64 (NHCO), 192.66 (C-49). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.20; H, 6.44; N, 5.78.

The following compounds were prepared according to the procedure described for **5a**.

3′,4′-Dihydro-4′-oxospiro[cyclohexane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (**5b**): Yield: 95%. mp: 179 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.2—2.0 (10H, m, cyclohexane H), 2.15 (3H, s, CH_3), 2.66 (2H, s, H-3′), 6.93 (1H, d, J=8.8 Hz, H-8′), 7.56 (1H, br s, NH, D_2O exchangeable), 7.62 (1H, d, J=2.6 Hz, H-5′), 7.88 (1H, dd, J=8.8, 2.6 Hz, H-7′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.35 (cyclohexane C), 24.26 (CH_3), 25.14, 34.66 (cyclohexane C), 48.18 (C-3′), 80.08 (C-2′), 117.32 (C-5′), 119.01 (C-8′), 120.44 (C-4′a), 129.66 (C-7′), 131.25 (C-6′), 156.42 (C-8′a), 168.55 (NHCO), 192.55 (C-4′). *Anal.* Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.65; H, 6.84; N, 5.01.

3′,4′-Dihydro-4′-oxospiro[cycloheptane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (**5c**): Yield: 93%. mp: 137 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.1 (12H, m, cycloheptane H), 2.14 (3H, s, CH_3), 2.69 (2H, s, H-3′), 6.90 (1H, d, J=8.9 Hz, H-8′), 7.64 (1H, d, J=2.5 Hz, H-5′), 7.76 (1H, br s, NH, D_2O exchangeable), 7.90 (1H, dd, J=8.9, 2.5 Hz, H-7′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.89, 29.24 (cycloheptane C), 24.20 (CH_3), 38.13 (cycloheptane C), 48.88 (C-3′), 84.28 (C-2′), 117.23 (C-5′), 118.95 (C-8′), 120.30 (C-4′a), 129.67 (C-7′), 131.39 (C-6′), 156.53 (C-8′a), 168.81 (NHCO), 192.83 (C-4′). *Anal.* Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.40; H, 7.47; N, 4.62.

3′,4′-Dihydro-5′-nitro-4′-oxospiro[cyclopentane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (6a) To a stirred solution of **5a** (4.4 g, 0.017 mol) in glacial acetic acid (10 ml) at 5 °C was added dropwise fuming nitric acid (2 ml) and the resulting mixture was refluxed for 4 h. The solution was then poured onto ice and the precipitate was filtered, washed with water and air-dried to give pure **6a** (4.5 g, 87%). mp: 195 °C (EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.1 (8H, m, cyclopentane H), 2.14 (3H, s, CH_3), 2.84 (2H, s, H-3′), 7.06 (1H, d, J=9.1 Hz, H-8′), 7.44 (1H, br s, NH, D_2O exchangeable), 8.04 (1H, d, J=9.1 Hz, H-7′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.68 (cyclopentane C), 24.03 (CH_3), 37.32 (cyclopentane C), 46.69 (C-3′), 91.19 (C-2′), 112.20 (C-4′a), 121.68 (C-8′), 122.71 (C-6′), 132.60 (C-7′), 140.33 (C-5′), 157.52 (C-8′a), 169.04 (NHCO), 188.60 (C-4′). *Anal.* Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.46; H, 5.08; N, 8.91.

The following compounds were prepared according to the procedure described for **6a**.

3′,4′-Dihydro-5′-nitro-4′-oxospiro[cyclohexane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (**6b**): Yield: 79%. mp: 202 °C (EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.2—2.0 (10H, m, cyclohexane H), 2.16 (3H, s, CH_3), 2.72 (2H, s, H-3′), 7.12 (1H, d, J=9.2 Hz, H-8′), 7.39 (1H, br s, NH, D_2O exchangeable), 8.07 (1H, d, J=9.2 Hz, H-7′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.31 (cyclohexane C), 24.14 (CH_3), 24.92, 34.51 (cyclohexane C), 47.99 (C-3′), 81.51 (C-2′), 112.07 (C-4′a), 121.60 (C-8′), 122.67 (C-6′), 132.66 (C-7′), 140.14 (C-5′), 156.81 (C-8′a), 168.93 (NHCO), 188.63 (C-4′). *Anal.* Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.29; H, 5.74; N, 8.92.

3′,4′-Dihydro-5′-nitro-4′-oxospiro[cycloheptane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (**6c**): Yield: 85%. mp: 210—211 °C (dec) (EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.1 (12H, m, cycloheptane H), 2.14 (3H, s, CH_3), 2.75 (2H, s, H-3′), 7.09 (1H, d, J=9.3 Hz, H-8′), 7.45 (1H, br s, NH, D_2O exchangeable), 8.05 (1H, d, J=9.3 Hz, H-7′). ^{13}C-NMR ($CDCl_3$,

50 MHz) δ: 21.76, 29.15 (cycloheptane C), 24.00 (CH_3), 37.97 (cycloheptane C), 48.63 (C-3′), 85.75 (C-2′), 111.92 (C-4′a), 121.58 (C-8′), 122.50 (C-6′), 132.72 (C-7′), 140.19 (C-5′), 156.94 (C-8′a), 169.03 (NHCO), 188.69 (C-4′). *Anal.* Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.18; H, 6.03; N, 8.38.

(±)-3′,4′-Dihydro-4′-hydroxy-5′-nitrospiro[cyclopentane-1,2′(2′*H*)-[1]benzopyran]-6′-acetamide (7a) $NaBH_4$ (567 mg, 15 mmol) was added to a solution of **6a** (4 g, 13.2 mmol) in methanol (25 ml) at 0 °C. The reaction mixture was stirred at room temperature for 24 h, the solvent was then vacuum-evaporated, 2 M HCl was added and the product was extracted into dichloromethane, the solvent was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 6/1 as the eluent to give **7a** (3.9 g, 96%). mp: 145 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.1 (10H, m, 8×cyclopentane H, H-3′), 2.01 (3H, s, CH_3), 3.85 (1H, br s, OH, D_2O exchangeable), 4.99 (1H, dd, J=6.1, 6.7 Hz, H-4′), 6.80 (1H, d, J=9.1 Hz, H-8′), 7.48 (1H, d, J=9.1 Hz, H-7′), 8.20 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.36 (cyclopentane C), 23.47 (CH_3), 36.27 (C-3′), 38.05, 39.00 (cyclopentane C), 60.94 (C-4′), 86.63 (C-2′), 117.90 (C-4′a), 120.88 (C-8′), 122.20 (C-6′), 126.27 (C-7′), 143.25 (C-5′), 151.18 (C-8′a), 169.49 (C=O). *Anal.* Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.74; H, 5.69; N, 8.93.

The following compounds were prepared according to the procedure described for **7a**.

(±)-3′,4′-Dihydro-4′-hydroxy-5′-nitrospiro[cyclohexane-1,2′(2′*H*)[1]-benzopyran]-6′-acetamide (**7b**): Yield: 96%. mp: 152 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.3—2.1 (10H, m, cyclohexane H), 2.00 (2H, m, H-3), 2.09 (3H, s, CH_3), 3.76 (1H, br s, OH, D_2O exchangeable), 5.02 (1H, dd, J=5.9, 6.5 Hz, H-4′), 6.86 (1H, d, J=9.2 Hz, H-8′), 7.52 (1H, d, J=9.2 Hz, H-7′), 8.02 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.26 (cyclohexane C), 23.57 (CH_3), 25.19 (cyclohexane C), 32.88 (C-3), 36.35 (cyclohexane C), 60.10 (C-4′), 76.82 (C-2′), 117.91 (C-4′a), 120.83 (C-8′), 122.33 (C-6′), 126.28 (C-7′), 143.05 (C-5′), 150.74 (C-8′a), 169.52 (C=O). *Anal.* Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 60.30; H, 6.11; N, 8.40.

(±)-3′,4′-Dihydro-4′-hydroxy-5′-nitrospiro[cycloheptane-1,2′(2′*H*)[1]-benzopyran]-6′-acetamide (**7c**): Yield: 94%. mp: 142—143 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.1 (12H, m, cycloheptane H), 2.14 (3H, s, CH_3), 2.26 (2H, m, H-3′), 3.79 (1H, br s, OH, D_2O exchangeable), 5.13 (1H, dd, J=6.2, 6.6 Hz, H-4′), 6.96 (1H, d, J=9.2 Hz, H-8′), 7.78 (1H, d, J=9.2 Hz, H-7′), 8.02 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.80, (cycloheptane C), 24.37 (CH_3), 29.57, 40.04 (cycloheptane C), 41.53 (C-3′), 60.92 (C-4′), 81.36 (C-2′), 117.98 (C-4′a), 121.97 (C-8′), 123.18 (C-6′), 126.06 (C-7′), 142.29 (C-5′), 150.80 (C-8′a), 168.74 (C=O). *Anal.* Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 60.88; H, 6.80; N, 8.37.

5′-Nitrospiro[cyclopentane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (8a) A solution of **7a** (4.6 g, 0.015 mol) and *p*-toluenesulfonic acid (279 mg, 1.47 mmol) was refluxed in anhydrous toluene for 4 h in a Dean–Stark apparatus. The reaction mixture was washed with water and the organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 8/1 to 4/1 as the eluent to give **8a** (4 g, 93%). mp: 117 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.1 (8H, m, cyclopentane H), 2.15 (3H, s, CH_3), 5.87 (1H, d, J=10.2 Hz, H-3′), 6.42 (1H, d, J=10.2 Hz, H-4′), 6.94 (1H, d, J=8.8 Hz, H-8′), 7.81 (1H, d, J=8.8 Hz, H-7′), 8.27 (1H, brs, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.56 (cyclopentane C), 24.63 (CH_3), 39.07 (cyclopentane C), 87.14 (C-2′), 116.10 (C-4′a), 117.70 (C-4′), 121.10 (C-8′), 124.10 (C-6′), 124.58 (C-7′), 133.45 (C-3′), 138.98 (C-5′), 150.23 (C-8′a), 168.63 (C=O). *Anal.* Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.70; H, 5.36; N, 9.54.

The following compounds were prepared according to the procedure described for **8a**.

5′-Nitrospiro[cyclohexane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (**8b**): Yield: 91%. mp: 132—133 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.3—2.0 (10H, m, cyclohexane H), 2.14 (3H, s, CH_3), 5.82 (1H, d, J=10.2 Hz, H-3′), 6.38 (1H, d, J=10.2 Hz, H-4′), 7.00 (1H, d, J=8.8 Hz, H-8′), 7.80 (1H, d, J=8.8 Hz, H-7′), 8.32 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.24 (cyclohexane C), 24.55 (CH_3), 25.06, 35.47 (cyclohexane C), 76.45 (C-2′), 116.21 (C-4′a), 117.39 (C-4′), 121.14 (C-8′), 124.08 (C-6′), 124.81 (C-7′), 134.11 (C-3′), 139.15 (C-5′), 150.17 (C-8′a), 168.70 (C=O). *Anal.* Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.63; H, 5.77; N, 9.01.

5′-Nitrospiro[cycloheptane-1,2′(2′*H*)[1]benzopyran]-6′-acetamide (**8c**): Yield: 95%. mp: 124 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.3—2.1 (12H, m, cycloheptane H), 2.14 (3H, s, CH_3), 5.84 (1H, d, J=10.2 Hz, H-3′), 6.34 (1H, d, J=10.2 Hz, H-4′), 6.98 (1H, d, J=8.8 Hz, H-8′), 7.80 (1H, d, J=8.8 Hz, H-7′), 8.29 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.50, 29.40 (cycloheptane C), 24.58 (CH_3), 38.81 (cycloheptane C), 80.97 (C-2′), 115.88 (C-4′, C-4′a), 121.25 (C-8′), 123.93 (C-6′), 124.61 (C-7′), 134.98 (C-3′), 139.00 (C-5′), 150.06 (C-8′a), 168.59 (C=O). *Anal.* Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.19; H, 6.50; N, 8.81.

4-[(2-Ethynyltricyclo[3,3,1,1^{3,7}]decan-2-yl)oxy]-2-nitro-acetamide (13) 2-Chloro-2-ethynyladamantane[16] (486 mg, 2.50 mmol) was added to a mixture of 3-nitro-4-acetamidophenol[15] (**12**) (330 mg, 1.68 mmol), anhydrous K_2CO_3 (465 mg, 3.37 mmol), KI (475 mg, 2.86 mmol) and CuI (6.5 mg, 0.034 mmol) in acetone (50 ml) under argon and the reaction mixture was stirred at 70 °C for 12 h. The solvent was removed under vacuum, water was added to the residue and the product was extracted into dichloromethane, the organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude material was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 10/1 as the eluent to give **13** as an oil (489 mg, 82%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.4 (14H, m, adamantane H), 2.24 (3H, s, CH_3), 2.76 (1H, s, C≡CH), 7.53 (1H, dd, J=9.1, 2.2 Hz, H-5), 8.10 (1H, d, J=2.2 Hz, H-3), 8.58 (1H, d, J=9.1 Hz, H-6), 10.07 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 25.44 (CH_3), 26.32, 26.65, 31.46, 34.77, 36.09, 37.34 (adamantane C), 78.25 (C≡C–H), 80.60 (C≡C–H), 84.06 (C-2′), 115.48 (C-3), 122.98 (C-6), 127.98 (C-5), 129.04 (C-1), 136.61 (C-2), 150.62 (C-4), 168.81 (C=O). *Anal.* Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found C, 68.01; H, 6.13; N, 7.79.

5′-Nitrospiro[tricyclo[3,3,1,1^{3,7}]decane-2,2′(2′*H*)[1]benzopyran]-6′-acetamide (14) A mixture of **13** (550 mg, 1.55 mmol) in *N*,*N*-diethylaniline was heated at 180 °C for 90 min. After cooling, a 9% HCl solution was added to the reaction mixture and the product was extracted into dichloromethane. The organic phase was then washed twice with a 9% HCl solution, dried (Na_2SO_4) and evaporated to dryness. The crude material was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 8/1 as the eluent and the isomer **15** (7′-nitrospiro[tricyclo[3,3,1,1^{3,7}]-decane-2,2′-(2′*H*)[1]benzopyran]-6′-acetamide) was eluted first (22 mg, 4%). Data for **15**: mp: 202 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.4 (14H, m, adamantane H), 2.24 (3H, s, CH_3), 6.47 (2H, m, H-3′, H-4′), 7.68 (1H, s, H-8′), 8.38 (1H, s, H-5′), 10.21 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 25.56 (CH_3), 26.59, 27.07, 32.40, 33.46, 35.96, 37.69 (adamantane C), 81.02 (C-2′), 112.70 (C-8′), 119.36 (C-5′), 122.26, 135.09 (C-3′, C-4′), 129.17 (C-6′), 130.53 (C-4′a), 135.82 (C-7′), 147.88 (C-8′a), 168.86 (C=O). *Anal.* Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.88; H, 6.09; N, 7.92. The next fraction was eluted using cyclohexane/EtOAc 6/1 and contained **14**, (350 mg, 64%). Data for **14**: mp: 182 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.3—2.4 (14H, m, adamantane H), 2.16 (3H, s, CH_3), 6.32 (1H, d, J=10.2 Hz, H-3′), 6.47 (1H, d, J=10.2 Hz, H-4′), 7.09 (1H, d, J=9.1 Hz, H-8′), 7.87 (1H, d, J=9.1 Hz, H-7′), 8.44 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ (ppm): 26.56, 26.87, 26.96, 32.29, 32.43, 35.36, 37.53 (adamantane C and CH_3), 80.12 (C-2′), 117.12 (C-4′a), 117.96 (C-4′), 121.49 (C-8′), 124.36 (C-6′), 124.56 (C-7′), 132.53 (C-3′), 138.65 (C-5′), 149.79 (C-8′a), 168.61 (C=O). *Anal.* Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.42; H, 6.24; N, 7.74.

5′-Nitrospiro[cyclopentane-1,2′(2′*H*)[1]benzopyran]-6′-amine (16a) A solution of **8a** (438 mg, 1.52 mmol) in EtOH (50 ml) was refluxed with HCl 5 N (25 ml) for 2 h. The organic phase was vacuum-evaporated, the resulting solution was made alkaline and extracted with dichloromethane. The solvent was dried (Na_2SO_4) and evaporated to dryness to yield **16a** (322 mg, 86%). mp: 118—119 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.1 (8H, m, cyclopentane H), 5.05 (2H, br s, NH_2, D_2O exchangeable), 5.81 (1H, d, J=10.2 Hz, H-3′), 6.56 (1H, d, J=8.8 Hz, H-7′), 6.74 (1H, d, J=10.2 Hz, H-4′), 6.84 (1H, d, J=8.8 Hz, H-8′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.48, 38.29 (cyclopentane C), 85.97 (C-2′), 117.05 (C-4′a), 117.82 (C-7′), 119.64 (C-4′), 123.98 (C-8′), 131.71 (C-3′, C-5′), 137.72 (C-6′), 145.22 (C-8′a). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.71; H, 5.38; N, 11.22.

The following compounds were prepared according to the procedure described for **16a**.

5′-Nitrospiro[cyclohexane-1,2′(2′*H*)[1]benzopyran]-6′-amine (**16b**): Yield: 92%. mp: 116—117 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.3—1.9 (10H, m, cyclohexane H), 5.13 (2H, br s, NH_2, D_2O exchangeable), 5.75 (1H, d, J=10.2 Hz, H-3′), 6.57 (1H, d, J=8.8 Hz, H-7′), 6.70 (1H, d, J=10.2 Hz, H-4′), 6.89 (1H, d, J=8.8 Hz, H-8′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ:

21.34, 25.15, 34.94 (cyclohexane C), 75.61 (C-2′), 116.95 (C-4′a), 117.99 (C-7′), 119.14 (C-4′), 124.01 (C-8′), 131.69 (C-5′), 132.11 (C-3′), 137.87 (C-6′), 144.85 (C-8′a). *Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.54; H, 6.28; N, 10.63.

5′-Nitrospiro[cycloheptane-1,2′(2′*H*)[1]benzopyran]-6′-amine (**16c**): Yield: 88%. mp: 89 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.1 (12H, m, cycloheptane H), 5.07 (2H, br s, NH_2, D_2O exchangeable), 5.71 (1H, d, J=10.2 Hz, H-3′), 6.56 (1H, d, J=8.8 Hz, H-7′), 6.65 (1H, d, J=10.2 Hz, H-4′), 6.84 (1H, d, J=8.8 Hz, H-8′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.51, 29.29, 38.18 (cycloheptane C), 79.56 (C-2′), 116.62 (C-4′a), 117.73 (C-4′), 117.92 (C-7′), 124.14 (C-8′), 131.61 (C-5′),133.16 (C-3′), 137.76 (C-6′), 144.80 (C-8′a). *Anal.* Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.81; H, 6.76; N, 10.50.

5′-Nitrospiro[tricyclo[3,3,1,1^{3,7}]decane-2,2′(2′*H*)[1]benzopyran]-6′-amine (**16d**): Yield: 96%. mp: 196 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.3 (14H, m, adamantane H), 5.19 (2H, br s, NH_2, D_2O exchangeable), 6.22 (1H, d, J=10.2 Hz, H-3′), 6.61 (1H, d, J=9.1 Hz, H-7′), 6.79 (1H, d, J=10.2 Hz, H-4′), 6.98 (1H, d, J=9.1 Hz, H-8′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 26.74, 27.14, 32.47, 33.54, 34.86, 37.62 (adamantane C), 78.86 (C-2′), 118.07 (C-4′a, C-7′), 119.87 (C-4′), 124.43 (C-8′), 130.68 (C-3′), 131.50 (C-5′), 138.21 (C-6′), 144.64 (C-8′a). *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.00; H, 6.41; N, 9.06.

6′-Iodo-5′-nitrospiro[cyclopentane-1,2′(2′*H*)[1]benzopyrane] (17a) The nitroderivative **16a** (370 mg, 1.5 mmol) was dissolved in a mixture of concentrated H_2SO_4 (4.5 ml) and water (11 ml) with warming and then was cooled to 0 °C. A solution of $NaNO_2$ (116 mg, 1.68 mmol) in water (2 ml) was added dropwise and the mixture was stirred at room temperature for 4 h, followed by dropwise addition of a solution of KI (349 mg, 2.1 mmol) in water (3 ml). The resulting mixture was stirred at room temperature for 12 h, the product was extracted into dichloromethane, the organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 12/1 as the eluent to give pure **17a** as an oil (300 mg, 56%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.6—2.2 (8H, m, cyclopentane H), 5.80 (1H, d, J=10.2 Hz, H-3′), 6.17 (1H, d, J=10.2 Hz, H-4′), 6.62 (1H, d, J=8.4 Hz, H-8′), 7.49 (1H, d, J=8.4 Hz, H-7′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.55, 39.56 (cyclopentane C), 72.99 (C-6′), 87.99 (C-2′), 116.09 (C-4′a), 116.37 (C-4′), 120.12 (C-8′), 133.79 (C-3′), 138.97 (C-7′), 151.54 (C-5′), 153.73 (C-8′a). *Anal.* Calcd for $C_{13}H_{12}INO_3$: C, 43.72; H, 3.39; N, 3.92. Found: C, 43.33; H, 3.48; N, 4.16.

The following compounds were prepared according to the procedure described for **17a**.

6′-Iodo-5′-nitrospiro[cyclohexane-1,2′(2′*H*)[1]benzopyrane] (**17b**): Yield: 53%. Oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.1—2.0 (10H, m, cyclohexane H), 5.78 (1H, d, J=10.2 Hz, H-3′), 6.14 (1H, d, J=10.2 Hz, H-4′), 6.68 (1H, d, J=8.8 Hz, H-8′), 7.49 (1H, d, J=8.8 Hz, H-7′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 20.93, 24.81, 35.60 (cyclohexane C), 72.94 (C-6′), 77.84 (C-2′), 115.92 (C-4′), 116.11 (C-4′a), 120.15 (C-8′), 134.48 (C-3′), 138.98 (C-7′), 151.42 (C-5′), 153.56 (C-8′a). *Anal.* Calcd for $C_{14}H_{14}INO_3$: C, 45.30; H, 3.80; N, 3.77. Found: C, 45.54; H, 3.67; N, 3.79.

6′-Iodo-5′-nitrospiro[cycloheptane-1,2′(2′*H*)[1]benzopyrane] (**17c**): Yield: 71%. Oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.1 (12H, m, cycloheptane H), 5.81 (1H, d, J=10.2 Hz, H-3′), 6.12 (1H, d, J=10.2 Hz, H-4′), 6.66 (1H, d, J=8.8 Hz, H-8′), 7.50 (1H, d, J=8.8 Hz, H-7′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.50, 29.46, 39.25 (cycloheptane C), 72.92 (C-6′), 82.02 (C-2′), 114.69 (C-4′), 116.01 (C-4′a), 120.35 (C-8′), 135.33 (C-3′), 139.04 (C-7′), 151.55 (C-5′), 153.70 (C-8′a). *Anal.* Calcd for $C_{15}H_{16}INO_3$: C, 46.77; H, 4.19; N, 3.64. Found: C, 46.72; H, 4.09; N, 3.81.

6′-Iodo-5′-nitrospiro[tricyclo[3,3,1,1^{3,7}]decane-2,2′(2′*H*)[1]benzopyrane] (**17d**): Yield: 68%. mp: 217—219 °C (Et_2O). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.3 (14H, m, adamantane H), 6.25 (1H, d, J=10.2 Hz, H-3′), 6.32 (1H, d, J=10.2 Hz, H-4′), 6.77 (1H, d, J=8.8 Hz, H-8′), 7.55 (1H, d, J=8.8 Hz, H-7′). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 26.56, 26.92, 32.27, 32.39, 35.69, 37.58 (adamantane C), 73.32 (C-6′), 81.15 (C-2′), 116.71 (C-4′), 117.19 (C-4′a), 120.48 (C-8′), 133.08 (C-3′), 139.20 (C-7′), 151.57 (C-5′), 153.54 (C-8′a). *Anal.* Calcd for $C_{18}H_{18}INO_3$: C, 51.08; H, 4.29; N, 3.31. Found: C, 51.10; H, 4.18; N, 3.43.

3-{5″-Nitrospiro[cyclopentane-1′,2″(2″*H*)[1]benzopyran-6″-yl]}propen-2-oic Acid (18a) A mixture of **17a** (236 mg, 0.66 mmol), $Pd(OAc)_2$ (4.3 mg, 0.02 mmol), PPh_3 (10.1 mg, 0.039 mmol), K_2CO_3 (457 mg, 3.30 mmol) and acrylic acid (0.08 ml, 1.20 mmol) in DMF (5 ml) and water (1 ml) was stirred at 100 °C for 12 h, then cooled, diluted with water and extracted with diethyl ether. The aqueous layer was acidified under cooling and the resulting precipitate was filtered. The product was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 8/2 as the eluent, to provide **18a** (119 mg, 60%). mp: 226 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.6—2.2 (8H, m, cyclopentane H), 5.85 (1H, d, J=10.2 Hz, H-3″), 6.26 (1H, d, J=10.2 Hz, H-4″), 6.32 (1H, d, J=15.7 Hz, H-2), 6.89 (1H, d, J=8.8 Hz, H-8″), 7.44 (1H, d, J=8.8 Hz, H-7″), 7.58 (1H, d, J=15.7 Hz, H-3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.64, 39.92 (cyclopentane C), 88.52 (C-2″), 114.48 (C-4″a), 116.26 (C-4″), 118.87 (C-6″), 119.18 (C-2), 119.38 (C-8″), 127.55 (C-7″), 133.54 (C-3″), 139.30 (C-3), 147.54 (C-5″), 155.56 (C-8″a), 171.29 (C-1). *Anal.* Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.92; H, 5.33; N, 4.46.

The following compounds were prepared according to the procedure described for **18a**.

3-{5″-Nitrospiro[cyclohexane-1′,2″(2″*H*)[1]benzopyran-6″-yl]}propen-2-oic Acid (**18b**): Yield: 63%. mp: 223 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.2—2.0 (10H, m, cyclohexane H), 5.85 (1H, d, J=10.2 Hz, H-3″), 6.25 (1H, d, J=10.2 Hz, H-4″), 6.33 (1H, d, J=15.7 Hz, H-2), 6.97 (1H, d, J=8.8 Hz, H-8″), 7.46 (1H, d, J=8.8 Hz, H-7″), 7.58 (1H, d, J=15.7 Hz, H-3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.11, 24.95, 36.05 (cyclohexane C), 78.58 (C-2″), 114.70 (C-4″a), 116.07 (C-4″), 118.94 (C-6″), 119.34 (C-8″, C-2), 127.67 (C-7″), 134.29 (C-3″), 139.30 (C-3), 147.59 (C-5″), 155.59 (C-8″a), 170.77 (C-1). *Anal.* Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.63; H, 5.38; N, 4.31.

3-{5″-Nitrospiro[cycloheptane-1′,2″(2″*H*)[1]benzopyran-6″-yl]}propen-2-oic Acid (**18c**): Yield: 55%. mp: 215 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.1 (12H, m, cycloheptane H), 5.86 (1H, d, J=10.2 Hz, H-3″), 6.20 (1H, d, J=10.2 Hz, H-4″), 6.32 (1H, d, J=15.7 Hz, H-2), 6.93 (1H, d, J=8.8 Hz, H-8″), 7.44 (1H, d, J=8.8 Hz, H-7″), 7.63 (1H, d, J=15.7 Hz, H-3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.52, 29.48, 39.53 (cycloheptane C), 82.55 (C-2″), 114.36 (C-4″a), 114.56 (C-4″), 118.82 (C-6″), 119.41 (C-8″, C-2), 127.54 (C-7″), 135.05 (C-3″), 139.09 (C-3), 147.49 (C-5″), 155.49 (C-8″a), 171.05 (C-1). *Anal.* Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.87; H, 5.99; N, 3.95.

3-{5″-Nitrospiro[tricyclo[3,3,1,1^{3,7}]decane-2′,2″(2″*H*)[1]benzopyran-6″-yl]}propen-2-oic Acid (**18d**): Yield: 45%. mp: >250 °C (EtOAc). ^{1}H-NMR ($CDCl_3$–CD_3OD, 400 MHz) δ: 1.2—2.1 (14H, m, adamantane H), 6.00 (1H, d, J=10.5 Hz, H-3″), 6.03 (1H, d, J=15.8 Hz, H-2), 6.11 (1H, d, J=10.5 Hz, H-4″), 6.76 (1H, d, J=8.8 Hz, H-8″), 7.16 (1H, d, J=15.8 Hz, H-3), 7.23 (1H, d, J=8.8 Hz, H-7″). ^{13}C-NMR ($CDCl_3$–CD_3OD, 50 MHz) δ: 26.09, 26.46, 31.68, 32.78, 35.43, 37.01 (adamantane C), 81.08 (C-2″), 114.93 (C-4″a), 115.96 (C-4″), 118.87 (C-6″), 119.05, 120.23 (C-2, C-8″), 127.10 (C-7″), 132.39 (C-3″), 136.84 (C-3), 146.84 (C-5″), 154.48 (C-8″a), 167.83 (C-1). *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.38; H, 5.82; N, 3.60.

3-{5″-Aminospiro[cyclopentane-1′,2″(2″*H*)[1]benzopyran-6″-yl]} propen-2-oic Acid (19a) To a solution of **18a** (813 mg, 2.7 mmol) in acetone (30 ml) was added $SnCl_2 \cdot 2H_2O$ (3 g, 13.5 mmol) and the mixture was stirred at 70 °C for 24 h. The solvent was vacuum-evaporated, water was added to the residue and it was made alkaline with a 28% ammonia solution. The precipitate was filtered off through a layer of celite, washed with water and the combined filtrate was acidified to pH 5 with concentrated HCl to give a solid. The product was purified by reprecipitation from aqueous ammonia to give pure **19a** (417 mg, 57%). mp: >250 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.6—2.0 (8H, m, cyclopentane H), 5.86 (1H, d, J=9.9 Hz, H-3″), 6.31 (1H, d, J=14.1 Hz, H-2), 6.63 (1H, d, J=8.1 Hz, H-8″), 7.19 (1H, d, J=9.9 Hz, H-4″), 7.42 (1H, d, J=8.1 Hz, H-7″), 7.78 (1H, d, J=14.1 Hz, H-3). ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 23.27, 38.74 (cyclopentane C), 87.19 (C-2″), 107.28 (C-4″a), 108.36 (C-2), 112.20 (C-8″), 114.25 (C-6″), 116.71 (C-4″), 129.15 (C-3″), 129.22 (C-7″), 135.11 (C-5″), 141.21 (C-3), 154.51 (C-8″a), 163.07 (C-1). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.05; H, 6.44; N, 5.22.

The following compounds were prepared according to the procedure described for **19a**.

3-{5″-Aminospiro[cyclohexane-1′,2″(2″*H*)[1]benzopyran-6″-yl]}propen-2-oic Acid (**19b**): Yield: 60%. mp: >250 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.2—1.9 (10H, m, cyclohexane H), 5.65 (1H, d, J=10.0 Hz, H-3″), 6.08 (2H, m, H-2, H-8″), 6.73 (1H, d, J=10.0 Hz, H-4″), 7.27 (1H, d, J=8.6 Hz, H-7″), 7.81 (1H, d, J=15.6 Hz, H-3). ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 20.33, 24.18, 35.67 (cyclohexane C), 76.18 (C-2″), 106.50 (C-2), 107.00 (C-4″a), 112.06 (C-6″), 115.12 (C-8″), 117.82 (C-4″), 128.51 (C-7″), 129.08 (C-3″), 140.40 (C-3), 144.14 (C-5″), 153.69 (C-8″a), 168.16 (C-1). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.61; H, 6.59; N, 4.85.

3-{5″-Aminospiro[cycloheptane-1′,2″(2″*H*)[1]benzopyran-6″-yl]}propen-2-oic Acid (**19c**): Yield: 52%. mp: >250 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.3—2.0 (12H, m, cycloheptane H), 5.65 (1H, d, J=9.9 Hz, H-3″), 6.05

(1H, d, J=8.4 Hz, H-8″), 6.10 (1H, d, J=15.4 Hz, H-2), 6.68 (1H, d, J=9.9 Hz, H-4″), 7.26 (1H, d, J=8.4 Hz, H-7″), 7.80 (1H, d, J=15.4 Hz, H-3). ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 20.97, 28.75, 38.54 (cycloheptane C), 79.56 (C-2″), 106.08 (C-2), 107.10 (C-4″a), 111.93 (C-6″), 113.97 (C-4″), 116.75 (C-8″), 128.11 (C-3″), 128.23 (C-7″), 140.26 (C-3), 144.09 (C-5″), 155.06 (C-8″a), 168.21 (C-1). *Anal.* Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.56; H, 6.82; N, 4.50.

3-{5″-Aminospiro[tricyclo[3,3,1,1^{3,7}]decane-2′,2″(2″*H*)[1]benzopyran-6″-yl]}propen-2-oic Acid (**19d**): Yield: 49%. mp: >250 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.45—2.30 (14H, m, adamantane H), 6.31 (1H, d, J=9.7 Hz, H-3″), 6.58 (1H, d, J=15 Hz, H-2), 6.60 (1H, d, J=8.3 Hz, H-8″), 7.21 (1H, d, J=9.7 Hz, H-4″), 7.28 (1H, d, J=8.3 Hz, H-7″), 7.84 (1H, d, J=15 Hz, H-3). ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 26.01, 26.38, 31.70, 32.62, 35.34, 37.00 (adamantane C), 81.15 (C-2″), 107.32 (C-4″a), 112.82 (C-6″), 114.81 (C-2), 116.06 (C-4″), 119.88 (C-8″), 128.56 (C-3″), 128.67 (C-7″), 133.71 (C-3), 146.65 (C-5″), 154.07 (C-8″a), 167.20 (C-1). *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.67; H, 6.81; N, 3.94.

Spiro[cyclopentane-1,8′(8′*H*)-pyran[2,3-*h*]quinolin]-2′(1′*H*)-one (20a) A mixture of **19a** (35.2 mg, 0.13 mmol) and 4% HCl solution was heated at reflux for 2 h, After cooling the precipitate was filtered and the crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 3/1 as the eluent to give **20a** (26.3 mg, 80%). mp: 200—202 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.3 (8H, m, cyclopentane H), 5.82 (1H, d, J=10.2 Hz, H-9′), 6.50 (1H, d, J=9.5 Hz, H-4′), 6.68 (1H, d, J=8.4 Hz, H-6′), 7.21 (1H, d, J=10.2 Hz, H-10′), 7.26 (1H, d, J=8.4 Hz, H-5′), 7.64 (1H, d, J=9.5 Hz, H-3′), 11.54 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.52, 39.32 (cyclopentane C), 87.48 (C-8′), 107.99 (C-10′a), 113.02 (C-6′), 114.60 (C-4′a), 116.33 (C-10′), 117.91 (C-3′), 128.39 (C-5′), 129.45 (C-9′), 134.86 (C-10′b), 141.36 (C-4′), 155.22 (C-6′a), 164.67 (C-2′). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.99; H, 5.70; N, 5.18.

The following compounds were prepared according to the procedure described for **20a**.

Spiro[cyclohexane-1,8′(8′*H*)-pyran[2,3-*h*]quinolin]-2′(1′*H*)-one (**20b**): Yield: 75%. mp: 218 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.2—2.1 (10H, m, cyclohexane H), 5.80 (1H, d, J=10.1 Hz, H-9′), 6.50 (1H, d, J=9.2 Hz, H-4′), 6.73 (1H, d, J=8.5 Hz, H-6′), 7.18 (1H, d, J=10.1 Hz, H-10′), 7.28 (1H, d, J=8.5 Hz, H-5′), 7.65 (1H, d, J=9.2 Hz, H-3′), 11.14 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.16, 25.22, 35.76 (cyclohexane C), 77.37 (C-2′), 108.06 (C-10′a), 113.07 (C-6′), 114.64 (C-4′a), 115.90 (C-10′), 117.87 (C-3′), 128.51 (C-5′), 130.18 (C-9′), 134.89 (C-10′b), 141.41 (C-4′), 155.16 (C-6′a), 164.64 (C-2′). *Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.40; H, 6.20; N, 5.41.

Spiro[cycloheptane-1,8′(8′*H*)-pyran[2,3-*h*]quinolin]-2′(1′*H*)-one (**20c**): Yield: 83%. mp: >250 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.4—2.1 (12H, m, cycloheptane H), 5.80 (1H, d, J=10.2 Hz, H-9′), 6.48 (1H, d, J=9.2 Hz, H-4′), 6.70 (1H, d, J=8.4 Hz, H-6′), 7.02 (1H, d, J=10.2 Hz, H-10′), 7.33 (1H, d, J=8.4 Hz, H-5′), 7.63 (1H, d, J=9.2 Hz, H-3′), 11.16 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.54, 29.50, 39.20 (cycloheptane C), 81.39 (C-8′), 107.63 (C-10′a), 113.26 (C-6′), 114.25 (C-4′a), 114.52 (C-10′), 117.76 (C-3′), 128.47 (C-5′), 131.27 (C-9′), 134.67 (C-10′b), 141.46 (C-4′), 155.14 (C-6′a), 164.46 (C-2′). *Anal.* Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.98; H, 6.53; N, 5.22.

Spiro[tricyclo[3,3,1,1^{3,7}]decane-2,8′(8′*H*)-pyran[2,3-*h*]quinolin]-2′(1′*H*)-one (**20d**): Yield: 88%. mp: >250 °C (EtOAc). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.5—2.4 (14H, m, adamantane H), 6.29 (1H, d, J=10.2 Hz, H-9′), 6.48 (1H, d, J=9.1 Hz, H-4′), 6.81 (1H, d, J=8.8 Hz, H-6′), 6.92 (1H, d, J=10.2 Hz, H-10′), 7.32 (1H, d, J=8.8 Hz, H-5′), 7.65 (1H, d, J=9.1 Hz, H-3′), 10.22 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 26.74, 27.07, 32.31, 33.54, 35.42, 37.71 (adamantane C), 80.68 (C-8′), 108.52 (C-10′a), 113.07 (C-6′), 114.51 (C-4′a), 115.79 (C-10′), 118.05 (C-3′), 128.66 (C-5′), 129.08 (C-9′), 134.63 (C-10′b), 141.37 (C-4′), 154.50 (C-6′a), 163.83 (C-2′). *Anal.* Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.80; H, 6.61; N, 4.27.

(±)-*cis*-9′,10′-Dihydro-9′,10′-dihydroxyspiro[cyclopentane-1,8′(8′*H*)-pyran[2,3-*h*]quinolin]-2′(1′*H*)-one (21a) Compound **20a** (300 mg, 1.18 mmol) was added to a solution of OsO_4 (1.3 ml, 0.012 mmol, 2.5% in *tert*-butanol) and *N*-methylmorpholine-*N*-oxide (192 mg, 1.64 mmol) in a 10 : 3 : 1 mixture of *tert*-BuOH : THF : H_2O (15 ml) and the reaction mixture was stirred at room temperature for 3 d. A saturated $NaHSO_3$ solution (3 ml) was then added and the mixture was stirred at room temperature for 2 h. The solvents vacuum-evaporated and the residue was purified by column chromatography (silica gel) using a mixture of CH_2Cl_2/MeOH 95/5 as the eluent to give **21a** (221 mg, 65%). mp: 229—230 °C (EtOH). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.5—2.0 (8H, m, cyclopentane H), 3.71 (1H, dd, J=4.7, 5.1 Hz, H-9′), 5.03 (1H, dd, J=4.7, 7.8 Hz, H-10′), 5.34 (1H, d, J=5.1 Hz, 9′-OH, D_2O exchangeable), 5.74 (1H, d, J=7.8 Hz, 10′-OH, D_2O exchangeable), 6.30 (1H, d, J=9.4 Hz, H-4′), 6.60 (1H, d, J=8.6 Hz, H-6′), 7.44 (1H, d, J=8.6 Hz, H-5′), 7.81 (1H, d, J=9.4 Hz, H-3′), 10.63 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 23.64, 23.86, 34.59, 34.85 (cyclopentane C), 63.89 (C-10′), 69.47 (C-9′), 89.94 (C-8′), 107.48 (C-10′a), 112.44 (C-6′), 113.21 (C-4′a), 117.44 (C-3′), 128.42 (C-5′), 139.78 (C-10′b), 140.92 (C-4′), 154.89 (C-6′a), 161.50 (C-2′). *Anal.* Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.84; H, 6.08; N, 4.93.

The following compounds were prepared according to the procedure described for **21a**.

(±)-*cis*-9′,10′-Dihydro-9′,10′-dihydroxyspiro[cyclohexane-1,8′(8′*H*)-pyran[2,3-*h*]quinolin]-2′(1′*H*)-one (**21b**): Yield: 84%. mp: 230 °C (EtOH). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.2—1.7 (9H, m, cyclohexane H), 2.04 (1H, m, cyclohexane H), 3.67 (1H, t, J=5.0 Hz, H-9′), 5.06 (1H, d, J=5.0 Hz, H-10′), 5.26 (1H, d, J=5.0 Hz, 9′-OH, D_2O exchangeable), 5.70 (1H, brs, 10′-OH, D_2O exchangeable), 6.30 (1H, d, J=9.5 Hz, H-4′), 6.65 (1H, d, J=8.8 Hz, H-6′), 7.46 (1H, d, J=8.8 Hz, H-5′), 7.81 (1H, d, J=9.5 Hz, H-3′), 10.59 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 20.76, 20.88, 24.97, 31.04, 31.14 (cyclohexane C), 63.08 (C-10′), 69.24 (C-9′), 79.16 (C-8′), 107.15 (C-10′a), 112.32 (C-6′), 113.21 (C-4′a), 117.33 (C-3′), 128.48 (C-5′), 139.84 (C-10′b), 140.89 (C-4′), 154.56 (C-6′a), 161.48 (C-2′). *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.99; H, 6.20; N, 4.57.

(±)-*cis*-9′,10′-Dihydro-9′,10′-dihydroxyspiro[cycloheptane-1,8′(8′*H*)-pyran[2,3-*h*]quinolin]-2′(1′*H*)-one (**21c**): Yield: 59%. mp: >250 °C (EtOH). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.3—1.8 (11H, m, cycloheptane H), 2.26 (1H, m, cycloheptane H), 3.70 (1H, d, J=4.0 Hz, H-9′), 5.04 (1H, d, J=4.0 Hz, H-10′), 5.45 (2H, br s 2×OH, D_2O exchangeable), 6.30 (1H, d, J=9.5 Hz, H-4′), 6.61 (1H, d, J=8.8 Hz, H-6′), 7.44 (1H, d, J=8.8 Hz, H-5′), 7.81 (1H, d, J=9.5 Hz, H-3′), 10.37 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 21.74, 21.88, 30.05, 35.27 (cycloheptane C), 63.69 (C-10′), 69.18 (C-9′), 84.20 (C-8′), 107.38 (C-10′a), 112.84 (C-6′), 113.51 (C-4′a), 117.66 (C-3′), 128.74 (C-5′), 140.24 (C-10′b), 141.21 (C-4′), 155.05 (C-6′a), 161.77 (C-2′). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.81; H, 6.59; N, 4.48.

(±)-*cis*-9′,10′-Dihydro-9′,10′-dihydroxyspiro[tricyclo[3,3,1,1^{3,7}]decane-2,8′(8′*H*)-pyran[2,3-*h*]quinolin]-2′(1′*H*)-one (**21d**): Yield: 72%. mp: >250 °C (EtOH). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.5—2.3 (14H, m, adamantane H), 3.74 (1H, m, H-9′), 4.93 (1H, m, H-10′), 5.55 (1H, d, J=5.1 Hz, 9′-OH, D_2O exchangeable), 5.68 (1H, br s, 10′-OH, D_2O exchangeable), 6.26 (1H, d, J=9.5 Hz, H-4′), 6.72 (1H, d, J=8.8 Hz, H-6′), 7.39 (1H, d, J=8.8 Hz, H-5′), 7.73 (1H, d, J=9.5 Hz, H-3′), 10.43 (1H, br s, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 26.31, 27.10, 32.28, 33.62, 35.21, 37.90 (adamantane C), 63.20 (C-10′), 69.33 (C-9′), 80.05 (C-8′), 108.05 (C-10′a), 112.83 (C-6′), 114.11 (C-4′a), 117.56 (C-3′), 128.96 (C-5′), 137.34 (C-10′b), 141.12 (C-4′), 154.23 (C-6′a), 162.63 (C-2′). *Anal.* Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.46; H, 6.51; N, 4.19.

NMR Spectra and Molecular Calculations COSY and NOESY spectra were acquired with 1024 complex points for 256 experiments with 2 s recycling delay, TPPI phase cycle and 1 s mixing time for NOESY. The heteronuclear single quantum coherence (HSQC) spectrum was obtained using B_0 gradient pulses, 128 FIDs in the t_1 domain and 1 K in the t_2 domain, 8 transients for each t_1 experiment and recycling delay of 1.5 s. Molecular simulations were performed with Macromodel 6.5[22] using MM2* as force field implemented in Macromodel.

Measurement of DPPH Radical Scavenging The method has been previously described in detail.[27] Briefly, to a solution of DPPH (final concentration 200 μM) in absolute ethanol, an equal volume of the compound dissolved in ethanol was added at various concentrations (5—400 μM). Ethanol was added to the control solution. Absorbance was recorded at 517 nm after 20, 30, 45 and 60 min of incubation at room temperature.[28] Each experiment was performed at least in triplicate and the standard deviation in absorbance values was less than ±10%.

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