Synthesis of methylene- and epoxy-bridged spiroquinazolinones

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Dedicated to Professor Harri Lönnberg on the occasion of his 60th birthday

Abstract

Boiling *diendo*-2-aminobicyclo[2.2.1]hept-5-ene-3-carboxamide **6a** or *diexo*-2-amino-7-oxabicyclo[2.2.1]hept-5-ene-3-carboxamide **6b** with cycloalkanones **7** in ethanol yielded methylene- and epoxy-bridged 2-spiroquinazolinones **9**–**18**.

Keywords: Spirocyclization, cyclocondensation, 2-spiroquinazolinones, *diendo*-, *diexo*-(oxa)-norbornene derivatives, methylene-, epoxy-bridged quinazolinones

Introduction

A number of 2-spiroquinazolinones have been reported to possess biological and pharmaceutical activities. Tranquilizing activity has been observed in 1'*N*-substituted spiro[cyclohexane-1,2'(1*H*)-quinazolin]-4'(3'*H*)-one[1] **1** (Figure 1). Compound **2** was found to be a potent inhibitor of inosine 5'-monophosphate dehydrogenase type II.[2] As a ligand of the nociceptin receptor, *cis*-spiropiperidine **3** exhibited a 20-fold higher affinity than that of its *trans* stereoisomer.[3] Spirocyclic carbamate **4** has been tested as a novel, highly selective[4] nitric oxide synthase inhibitor. Some spiro[heterocycloalkyl-2'(1'*H*)quinazolin]-4'(3'*H*)-ones demonstrate antiamebic activity *in vitro*[5] and had been investigated as central nervous system depressants.

The plant-growth regulator agent octahydroquinazoline-2-spirocyclohexane **5**[6] increases the height and green mass of barley and wheat.[7] 2-Spiroquinazolinones are also key intermediates for the synthesis of cycloalkanone-2-carboxamides,[8] acridin-9-ones[9] and *cis*-3-azacepham analogs.[10]

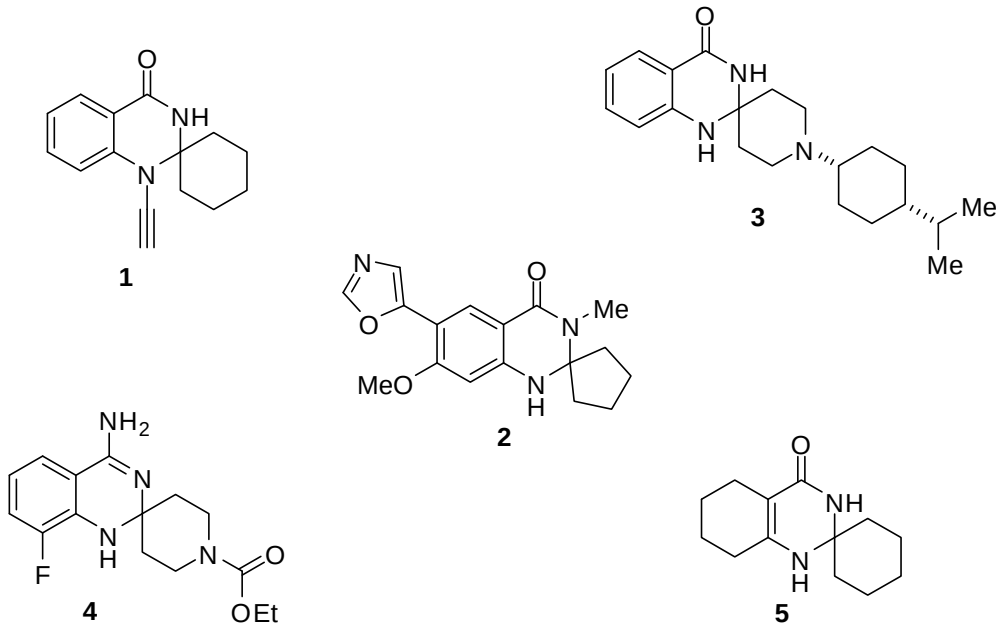


Figure 1

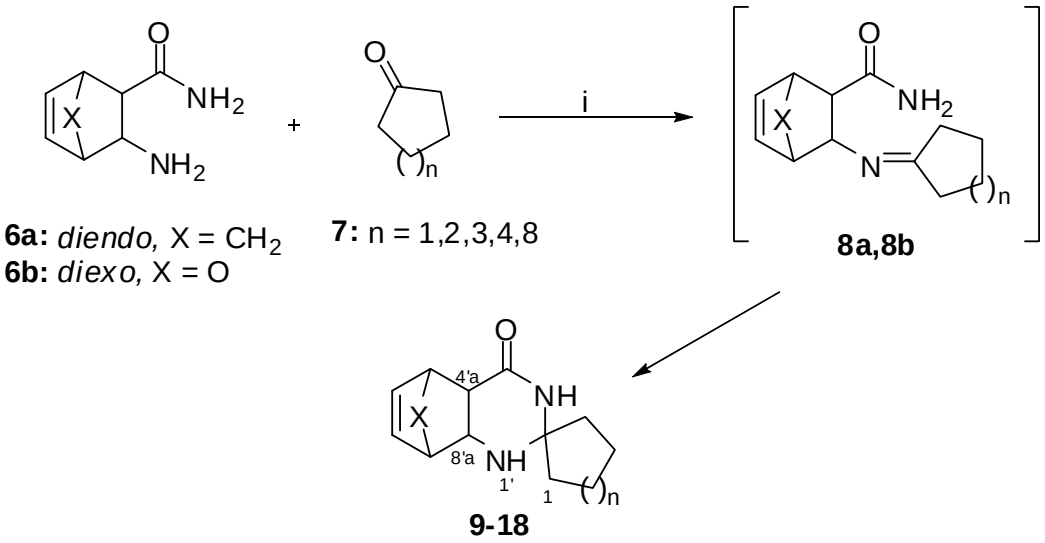
Böhme and *Böing* reported[11] that the room-temperature treatment of anthranilamide with cyclohexanone or cyclopentanone in ethanol saturated with hydrogen chloride provided a facile synthesis of spiro[cycloalkane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-ones. Heating of monosubstituted anthranilamides with cyclic ketones without solvents[12] was an effective method for the preparation of spiroquinazolinones. The cyclization of anthranilamide with ketones in absolute ethanol,[13] in refluxing trifluoroethanol[14] or under microwave irradiation[15] is also known. Other methodologies too have been employed, for example with isatoic anhydride[16,17] or anthranylhydrazide[18] as starting compound. For the preparation of spiro-1,2-dihydroquinazolin-4(3*H*)ones, a new method, the reductive cyclization of 2-nitrobenzamides with carbonyl compounds, was introduced by *Shi et al.*[19,20]

Results and Discussion

Only a few reports describe the spirocyclization of saturated anthranilamides with cycloalkanones. Hexahydrospiro[cyclohexane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one was formed when hexahydroanthranilamide was refluxed with cyclohexanone in the presence of a catalytic amount of *p*-toluenesulfonic acid in ethanol.[21] It is important to stress that the stereochemistry of this saturated analog has not been reported. Nevertheless, considering the different melting points of *cis*- and *trans*-perhydrospiro[cyclohexane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one,[22] it is presumed that the *cis* diastereoisomer was synthetized.

Our present aim was to expand the possibilities with the cyclocondensation of *diendo*-2-aminonorbornene-3-carboxamide **6a** and *diexo*-2-amino-7-oxanorbornene-3-carboxamide **6b** with cycloalkanones. The target of this project was to prepare methylene- and epoxy-bridged spiroquinazolinones. Moreover, the chemical and stereochemical features of these partially saturated heterocycles, like their aromatic analogs, should be of importance from pharmacological aspects.

The Diels-Alder reaction of cyclopentadiene with maleic anhydride, subsequent opening with NH_4OH, decomposition of the amide with hypochlorite, esterification and ammonolysis yielded the *diendo*-3-aminonorbornene-2-carboxamide **6a**.[23] 5,6-Dehydrocantharidine (*diexo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride) was transformed to the aminocarboxamide **6b** by ammonolysis, followed by Hoffmann degradation to the racemic β-amino acid, esterification and ammonolysis.[24] On refluxing with cycloalkanones **2** in ethanol, *diendo*-aminonorbornenecarboxamide **6a** was cyclized to 5',8'-methylene-spiro[cycloalkane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-ones **9**–**13**. *diexo*-Aminooxanorbornenecarboxamide **6b** was used to prepare the corresponding epoxy-bridged 2-spiroquinazolines **14**–**18**. The two-step reaction via the formation of Schiff bases **8a** and **8b** to produce spiroheterocycles **14**–**18** took place consecutively. Under neutral conditions, the corresponding 2',2''-disubstituted quinazolinones were obtained in 65–88% yields (Scheme 1).



6a: *diendo,* X = CH_2
6b: *diexo,* X = O

7: n = 1,2,3,4,8

9: *diendo,* X = CH_2; n = 1
10: *diendo,* X = CH_2; n = 2
11: *diendo,* X = CH_2; n = 3
12: *diendo,* X = CH_2; n = 4
13: *diendo,* X = CH_2; n = 8

14: *diexo,* X = O; n = 1
15: *diexo,* X = O; n = 2
16: *diexo,* X = O; n = 3
17: *diexo,* X = O; n = 4
18: *diexo,* X = O; n = 8

Scheme 1. (i) EtOH, reflux, 2 h, 65–88%.

During the cyclization, aminobicycloalkenecarboxamides **6a** and **6b** always retain their configurations. The constitutions of the compounds were proved via their IR and NMR spectra. The IR spectra of **9**–**18**, with an (oxa)norbornene skeleton, contain a characteristic absorption in the regions 3081-3060 cm^{-1} ($\nu_{=CH}$) and 745-697 cm^{-1} ($\delta_{=CH}$). The position of the latter band is governed by the stereochemical features of the spiroquinazolinones: in the IR spectra of the *exo* isomers, these bands are in a lower interval (713–697 cm^{-1}) than in the case of the *endo* stereoisomers (745–733 cm^{-1}).[25] The presumed *diendo* and *diexo* configurations of the spirotricyclic compounds **9**–**13** and **14**–**18** were proved by ^{1}H-NMR spectroscopy. For **9**–**13,** the *diendo* annelation of the norbornene moiety is revealed by the splittings.[26] 4'a-H for *diendo* annelation exhibits a dd split, proved by the value of ~ 4 Hz[27] for the 4'a, 5' H-H coupling. The NOE interaction between the annelational 4'a and 8'a-H and the *endo*(*anti*) H in the bridging CH_2 is an unequivocal confirmation of the *diendo* annelation of the norbornene moiety. The *diexo* annelation of the oxanorbornene to perhydropyrimidinone[28] in **14**–**18** follows from the d split of the 4'a-H, which is a doublet due to the coupling with 8'a-H (split by 6.8–6.9 Hz). In the HETCOR experiments on **9**–**13,** a broad singlet or broad doublet appeared at 0.55–0.90 ppm, which did not correlate with any carbon signal. This proton is that of the 1'NH secondary amine group.

Each of the spiro compounds **9**–**18** gave a ^{13}C signal at 67–78 ppm for a quaternary C-2. This chemical shift appears reasonable for an –$NHCR_2NH$– system, where R is an alkyl group.[13]

In experiments to gain retro Diels-Alder products,[29] **9**–**13** were heated under different conditions, such as by refluxing in chlorobenzene or by heating to the melting point, but no characteristic cycloreversion products were detected.

Experimental Section

General Procedures. Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H-NMR(400 Hz), ^{13}C-NMR (100 MHz) and 2D (NOESY, HSQC, HMBC) spectra were recorded on a Bruker Avance DRX 400 spectrometer, with TMS as internal reference and DMSO-d_6 or $CDCl_3$ as solvent. FT-IR spectra recordings were performed on a Perkin-Elmer 100 FT-IR spectrometer. Elemental analysis was carried out on a Perkin-Elmer 2400 elemental analyzer.

General procedure for the preparation of *diendo*- and *diexo*-5',8'-(epoxy)methylene-4'a,5',8',8'a-tetrahydrospiro[cycloalkane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-ones 9-18

A mixture of aminocarboxamides **6a** or **6b** (0.05 mmol) and cycloalkanones **7** (0.075 mmol) in EtOH (10 mL) was refluxed for 2 h. After evaporation to half volume, 15 mL of Et_2O was added to the solution and the mixture was left to stand for 1 h. The precipitates of **9–18** were filtered off, washed with Et_2O and crystallized with the solvents reported in association with the melting point.

***diendo*-5',8'-Methylene-4'a,5',8',8'a-tetrahydrospiro[cyclopentane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (9).** Yield: 83%; colorless needles; m.p.: 219–221 °C (EtOAc); IR (KBr, cm^{-1}): 3292 (NH), 3164 (NHCO), 3075 ($\nu_{=CH}$), 1639 (C=O), 1572 (C=C), 742 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 0.90 (1H, br s, 1'-NH), 1.34-1.98 (10H, m, 1-4-H and 9'-H), 2.42 (1H, dd, *J* = 3.8 Hz, *J* = 8.8 Hz, 4'a-H), 2.94 (1H, s, 8'-H), 3.14 (1H, s, 5'-H), 3.79 (1H, m, 8'a-H), 6.13 (1H, dd, *J* = 3.0 Hz, *J* = 5.1 Hz, 7'-H), 6.21 (1H, dd, = 2.8 Hz, *J* = 5.2 Hz, 6'-H), 7.98 (1H, s, 3'-NH); ^{13}C-NMR (DMSO-d_6): δ 22.05, 23.32, 38.07, 38.80, 42.19, 45.33, 45.79, 46.49, 55.04, 77.64, 133.33, 138.74, 171.14; Anal. calcd. for $C_{13}H_{18}N_2O$ (%): C, 71.53; H, 8.31; N, 12.83. Found: C, 71.35; H, 8.48; N, 12.50.

***diendo*-5',8'-Methylene-4'a,5',8',8'a-tetrahydrospiro[cyclohexane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (10).** Yield: 76%; colorless crystals; m.p.: 243–244 °C (EtOAc); IR (KBr, cm^{-1}): 3301 (NH), 3163 (NHCO), 3074 ($\nu_{=CH}$), 1644 (C=O), 1573 (C=C), 744 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 0.59 (1H, d, *J* = 11.8 Hz, 1'-NH), 1.08-1.88 (12H, m, 1-5-H and 9'-H), 2.46 (1H, dd, *J* = 4.0, *J* = 8.8 Hz, 4'a-H), 2.96 (1H, s, 8'-H), 3.14 (1H, s, 5'-H), 3.72 (1H, m, 8'a-H), 6.14 (1H, dd, *J* = 2.9 Hz, *J* = 5.7 Hz, 7'-H), 6.21 (1H, dd, = 2.8 Hz, *J* = 5.6 Hz, 6'-H), 7.75 (1H, s, 3'-NH); ^{13}C-NMR ($CDCl_3$): δ 22.47, 22.75, 25.88, 37.72, 39.52, 43.96, 46.71, 47.03, 48.15, 55.56, 70.52, 133.41, 140.96, 170.58; Anal. calcd. for $C_{14}H_{20}N_2O$ (%): C, 72.38; H, 8.68; N, 12.06. Found: C, 72.09; H, 8.52; N, 12.00.

***diendo*-5',8'-Methylene-4'a,5',8',8'a-tetrahydrospiro[cycloheptane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (11).** Yield: 79%; colorless crystals; m.p.: 228–230 °C (EtoAc); IR (KBr, cm^{-1}): 3301 (NH), 3159 (NHCO), 3076 ($\nu_{=CH}$), 1639 (C=O), 1572 (C=C), 742 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 0.58 (1H, d, *J* = 11.5 Hz, 1'-NH), 1.22-1.82 (14H, m, 1-6-H and 9'-H), 2.44 (1H, dd, *J* = 4.0, *J* = 8.8 Hz, 4'a-H), 2.94 (1H, s, 8'-H), 3.14 (1H, s, 5'-H), 3.72 (1H, m, 8'a-H), 6.14 (1H, dd, *J* = 2.8 Hz, *J* = 5.7 Hz, 7'-H), 6.21 (1H, dd, = 2.9 Hz, *J* = 5.6 Hz, 6'-H), 7.89 (1H, s, 3'-NH); ^{13}C-NMR ($CDCl_3$): δ 22.13, 22.23, 29.41, 29.51, 40.16, 43.49, 44.04, 46.46, 46.77, 47.90, 55.71, 74.31, 133.14, 140.64, 172.77; Anal. Calcd. for $C_{15}H_{22}N_2O$ (%): C, 73.31; H, 9.00; N, 11.37. Found: C, 73.13; H, 8.81; N, 11.31.

***diendo*-5',8'-Methylene-4'a,5',8',8'a-tetrahydrospiro[cyclooctane-1,2'(1'*H*)-quinazolin]-4'(3*H*')-one (12).** Yield: 71%; colorless powder; m.p.: 208–210 °C (EtOAc); IR (KBr, cm^{-1}): 3301 (NH), 3169 (NHCO), 3070 ($\nu_{=CH}$), 1641 (C=O), 1572 (C=C), 745 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 0.55 (1H, br s, 1'-NH), 1.16-1.82 (16H, m, 1-7-H, 9'-H), 2.45 (1H, dd, *J* = 4.0, *J* = 8.6 Hz, 4'a-H) 2.95 (1H, s, 8'-H), 3.14 (1H, s, 5'-H), 3.74 (1H, m, 8'a-H), 6.14 (1H, dd, *J* = 2.8 Hz, *J* = 5.6 Hz, 7'-H), 6.21 (1H, dd, = 2.9 Hz, *J* = 5.7 Hz, 6'-H), 7.83 (1H, s, 3'-NH); ^{13}C-NMR ($CDCl_3$): δ 21.96, 22.71, 25.28, 28.14, 29.18, 35.00, 39.10, 43.82, 46.79, 47.12, 48.17, 56.08, 74.12, 133.48, 140.98, 172.90; Anal. calcd. for $C_{16}H_{24}N_2O$ (%): C, 73.81; H, 9.29; N, 10.76. Found: C, 73.51; H, 8.09; N, 10.42.

***diendo*-5',8'-Methylene-4'a,5',8',8'a-tetrahydrospiro[cyclododecane-1,2'(1'*H*)-quinazolin]-4'(3*H*')-one (13).** Yield: 75%; colorless powder; m.p.: 180–182 °C (EtOAc); IR (KBr, cm^{-1}): 3291 (NH), 3211 (NHCO), 3060 ($\nu_{=CH}$), 1650 (C=O), 1573 (C=C), 733 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 0.69 (1H, br s, 1'-NH), 1.08-1.68 (24H, m, 1-11-H, 9'-H), 2.47 (1H, dd, *J* =

4.0 Hz, *J* = 8.7 Hz 4'a-H), 2.93 (1H, s, 8'-H) , 3.15 (1H, s, 5'-H) 3.78 (1H, br m, 8'a-H), 6.13 (1H, dd, *J* = 2.8 Hz, *J* = 5.6 Hz, 7'-H), 6.21 (1H, dd, = 2.9 Hz, *J* = 5.6 Hz, 6'-H), 7.58 (1H, s, 3'-NH); ^{13}C-NMR (DMSO-d_6): δ 18.25, 19.67, 21.65, 21.90, 22.11, 22.17, 25.49, 25.83, 25.90, 32.84, 35.10, 42.28, 45.50, 45.95, 46.47, 54.39, 72.26, 133.30, 138.87, 170.70; Anal. calcd. for $C_{20}H_{32}N_2O$ (%): C, 75.90; H, 10.19; N, 8.85. Found: C, 75.76; H, 9.82; N, 8.72.

***diexo*-5',8'-Epoxy-4'a,5',8',8'a-tetrahydrospiro[cyclopentane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one** (**14**). Yield: 78%; colorless crystals; m.p.: 176–177 °C (EtOAc); IR (KBr, cm^{-1}): 3268 (NH), 3182 (NHCO), 3081 ($\nu_{=CH}$), 1656 (C=O), 1572 (C=C), 712 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 1.32-1.85 (9H, m, 1-4-H and 1'-NH), 1.96 (1H, d, *J* = 6.9 Hz, 4'a-H), 3.23 (1H, m, 8'a-H), 4.69 (1H, s, 8'-H), 5.14 (1H, s, 5'-H), 6.40 (1H, dd, *J* = 1.4 Hz, *J* = 5.8 Hz, 7'-H), 6.54 (1H, dd, = 1.4 Hz, *J* = 5.8 Hz, 6'-H), 8.30 (1H, s, 3'-NH); ^{13}C-NMR (DMSO-d_6): δ 22.05, 23.26, 37.31, 38.73, 41.30, 53.06, 77.06, 80.78, 82.51, 134.03, 137.44, 169.60; Anal. calcd. for $C_{12}H_{16}N_2O_2$ (%): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.25; H, 7.45; N, 12.51.

***diexo*-5',8'-Epoxy-4'a,5',8',8'a-tetrahydrospiro[cyclohexane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (15).** Yield: 73%; colorless crystals; m.p.: 158–160 °C (EtOAc); IR (KBr, cm^{-1}): 3288 (NH), 3172 (NHCO), 3078 ($\nu_{=CH}$), 1646 (C=O), 1575 (C=C), 713 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 1.05-1.70 (10H, m, 1-5-H), 1.77 (1H, d, *J* = 13.3 Hz, 1'-NH) 2.00 (1H, d, *J* = 6.8 Hz, 4'a-H), 3.16 (1H, m, 8'a-H), 4.70 (1H, s, 8'-H), 5.13 (1H, s, 5'-H), 6.39 (1H, dd, *J* = 1.6 Hz, *J* = 5.8 Hz, 7'-H), 6.54 (1H, dd, *J* = 1.5 Hz, *J* = 5.8 Hz, 6'-H), 8.09 (1H, s, 3'-NH); ^{13}C-NMR (DMSO-d_6): δ 22.11, 22.90, 25.89, 36.71, 38.37, 42.39, 52.93, 69.11, 81.75, 83.40, 134.87, 138.41, 170.29; Anal. calcd. for $C_{13}H_{18}N_2O_2$ (%): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.35; H, 7.41; N, 11.81.

***diexo*-5',8'-Epoxy-4'a,5',8',8'a-tetrahydrospiro[cycloheptane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (16).** Yield: 68%; colorless crystals; m.p.: 166–168 °C (EtOH/EtOAc), IR (KBr, cm^{-1}): 3301 (NH), 3159 (NHCO), 3071 ($\nu_{=CH}$), 1653 (C=O), 1573 (C=C), 698 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 1.25-1.81 (13H, m, 1-6-H and 1'-NH), 2.00 (1H, d, *J* = 6.8 Hz, 4'a-H), 3.20 (1H, d, *J* = 6.5, 8'a-H), 4.71 (1H, s, 8'-H), 5.15 (1H, s, 5'-H), 6.41 (1H, dd, *J* = 1.6 Hz, *J* = 5.8 Hz, 7'-H), 6.57 (1H, dd, *J* = 1.5 Hz, *J* = 5.8 Hz, 6'-H), 8.24 (1H, s, 3'-NH); ^{13}C-NMR (DMSO-d_6): δ 22.13, 21.38, 28.95 (2x), 38.76, 41.47, 41.75, 52.42, 72.27, 80.82, 82.53, 133.90, 137.57, 169.33; Anal. calcd. for $C_{14}H_{20}N_2O_2$ (%): C, 67.71; H, 8.12; N, 11.28. Found: C, 67.39; H, 7.91; N, 11.01.

***diexo*-5',8'-Epoxy-4'a,5',8',8'a-tetrahydrospiro[cyclooctane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (17).** Yield: 65%; colorless crystals; m.p.: 170–172 °C (EtOAc); IR (KBr, cm^{-1}): 3302 (NH), 3162 (NHCO), 3075 ($\nu_{=CH}$), 1652 (C=O), 1574 (C=C), 697 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 1.30-1.83 (15H, m, 1-7-H and 1'-NH), 1.95 (1H, d, *J* = 6.8 Hz, 4'a-H), 3.14 (1H, m, 8'a-H), 4.65 (1H, s, 8'-H), 5.09 (1H, s, 5'-H), 6.35 (1H, dd, *J* = 1.5 Hz , *J* = 5.8 Hz, 7'-H), 6.51 (1H, dd, *J* = 1.4 Hz, *J* = 5.8 Hz, 6'-H), 8.16 (1H, s, 3'-NH); ^{13}C-NMR (DMSO-d_6): δ 20.79, 21.40, 24.13, 27.10, 28.16, 33.29, 36.88, 41.46, 52.47, 71.76, 80.88, 82.51, 133.89, 137.57, 169.26; Anal. calcd. for $C_{15}H_{22}N_2O_2$ (%): C, 68.67; H, 8.45; N, 10.68. Found: C, 68.49; H, 8.49; N, 10.41.

***diexo*-5',8'-Epoxy-4'a,5',8',8'a-tetrahydrospiro[cyclododecane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (18).** Yield: 88%; colorless powder; m.p.: 200–202 °C (EtOH); IR (KBr, cm^{-1}): 3271 (NH), 3200 (NHCO), 3077 ($\nu_{=CH}$), 1642 (C=O), 1572 (C=C), 704 ($\delta_{=CH}$); ^{1}H-

NMR (DMSO-d_6): δ 1.06-1.65 (23H, m, 1-11-H and 1'-NH), 1.97 (1H, d, *J* = 6.8 Hz, 4'a-H), 3.18 (1H, d, *J* = 6.8, 8'a-H), 4.64 (1H, s, 8'-H), 5.10 (1H, s, 5'-H), 6.35 (1H, dd, *J* = 1.3 Hz , *J* = 5.6 Hz, 6'-H), 6.51 (1H, dd, *J* = 1.3 Hz, *J* = 5.6 Hz, 7'-H), 7.91 (1H, s, 3'-NH); ^{13}C-NMR (DMSO-d_6): δ 18.26, 19.64, 21.69, 21.87, 22.13, 22.18, 25.49, 25.87 (2x), 32.06, 34.87, 41.43, 52.37, 71.72, 80.92, 82.50, 133.95, 137.46, 169.21; Anal. calcd. for $C_{19}H_{30}N_2O_2$ (%): C, 71.66; H, 9.50; N, 8.80. Found: C, 71.57; H, 9.61; N, 8.71.

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