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"Dry" and "Wet" Green Synthesis of 2,2′-Disubstituted Quinazolinones

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An extremely convenient, environmentally benign spirocyclization under either aqueous or solventless conditions, developed for the preparation of spiro[cyclohexane-1,2′-(1′*H*)-quinazolin]-4′(3′*H*)-one (**3**), has been utilized to convert α- and β-aminocarboxamides **5a**, **5b**, **6a–c** and **9** and cycloalkanones **2**–**2b** and alkanones **2c–e** into 1,4-diazaspiro-[4.5]decan-2-one (**10**) and *cis*-, *diexo*- or *diendo*-2,2′-disubstituted quinazolinones **5a**, **5b**, **7a–f** and **8**. *diexo*-Methylene-bridged carboxamides **6a** and **6b** were treated "on water" with *N*-benzylpiperidinone (**11**) to afford spiropiperidine–quinazolinones **12a** and **12b**. All these reactions were performed at room temperature, without any catalyst or co-solvent, and gave yields of up to 99 %.

Introduction

The development of cleaner, safer and eco-friendly chemical processes is an important goal for chemists in both academia[1] and industry.[2] A number of strategies have been produced for the synthesis of heterocyclic compounds, such as reactions performed in aqueous[3] or solvent-free[4] media, mechanochemical mixing (grindstone and ball-mill chemistry)[5] or the use of ionic liquids[6] or microwave[7] or ultrasonic[8] irradiation. The best solvent is "no solvent".[9] The Kaupp group pointed to the sustainable character of gas–solid reactions in the absence of solvents and stressed that they must be performed to completion with 100 % yield of a single product. They demonstrated such favourable behaviour in more than 1000 gas–solid and stoichiometric solid–solid synthetic reactions.[10] The solid-state mechanism, which involves phase rebuilding (anisotropic molecular migrations within crystals), phase transformation and crystal disintegration, is the basis for the technical design.[11] 2-Spiroquinazolinones are an important class of fused heterocycles that have attracted significant interest in medicinal chemistry, in view of their great variety of biological and pharmaceutical activities.[12] Moreover, they are key intermediates for the synthesis of cycloalkanone-2-carboxamides,[13] acridin-9-ones,[14] *cis*-3-azacepham analogues[15] and 1β-methylcarbapenem derivatives.[16] It has been reported[17] that the room-temperature treatment of anthranilamide with cyclohexanone or cyclopentanone in ethanol saturated with hydrogen chloride allows facile synthesis of spiro[cycloalkane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones. The heating of monosubstituted anthranilamides with cyclic ketones without solvent[18] proved to be an effective method for the preparation of spiroquinazolinones. The cyclization of anthranilamide with ketones in absolute ethanol[19] or in refluxing trifluoroethanol[20] is also known. For the preparation of spiro-1,2-dihydroquinazolin-4(3*H*)-ones, a new method has been introduced: the reductive cyclization of 2-nitrobenzamides with carbonyl compounds.[21] Modification of the Friedländler reaction of 2-aminobenzonitriles with cyclohexanone in the prenes.[22]

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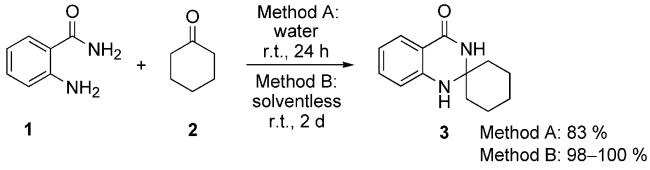
Results and Discussion

We have developed efficient and environmentally benign methodology for the preparation of spiropiperidines.[23] The spirocyclization of carbocyclic 2-aminocarbohydrazides with *N*-benzylpiperidinone in water at room temperature in the absence of any additive led to 3′-aminospiropiperidine–quinazolinones. All products precipitated from the reaction mixture and were obtained in excellent yields. Simplifying that system in the present work, we investigated the cyclocondensation of anthranilamide (**1**) and cyclohexanone (**2**) at room temperature in aqueous medium (Method A). It was somewhat surprising that spiroquinazoline **3** started to precipitate from a stirred, stoichiometric mixture of **1** and **2** in water at room temperature after about 15 min (Scheme 1). Compound **3** was isolated in high yield the next day by simple filtration.

We next investigated this cyclization under solventless conditions. After equivalent amounts of **1** and **2** had stirred for 15 min, the initially heterogeneous reaction changed into a honey-like paste;[24] when left to stand for 2 d, this resulted in crystalline **3** in 98–100 % purity (Method B). Numerous ways have been described in the literature to synthesize **3** from **1** and **2**. A survey of some of the most useful classical and modern methods for the preparation of



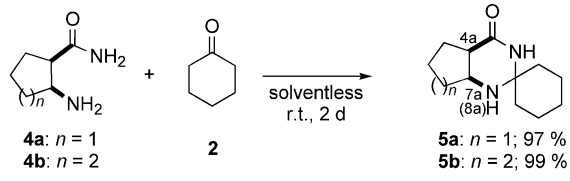
Scheme 1.

heterocycle **3** is presented in Table 1. Additionally, a comparison is made between the reaction conditions of known procedures and our current synthetic approach.

Table 1. Synthesis of spiro[cyclohexane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (**3**) from cyclohexanone (**2**) and anthranilamide (**1**) (Scheme 1).

Entry	Solvent	Temp. [°C]	Time [d]	Catalyst/ Reagent	[equiv.]	Yield [%]	Ref.
1	ethanol	78	0.007	HCl	1	88	[17]
2	ethanol	78	0.25	*p*-TSA	2.0	–	[19b]
3	–	155	0.002	$SOCl_2$	10.7	97	[18b]
4	–	100	0.01	–	2.2	97	[18a]
5	benzene	80	0.17	*p*-TSA	1	70	[15]
6	trifluoro-ethanol	79	0.29	–	3	88	[20]
7	ethanol	25	0.17	HCl	1.6	60	[19a]
8	(MW)	(300 W)	0.007	–	5	91	[18c]
9	ethanol	25	0.024	NH_4Cl	1	97	[19c]
10	water	25	1	–	1	83	present work
11	_	25	2	–	1	98–100	present work

In view of these interesting results and the relatively small numbers of reports describing the spirocyclization[25] of saturated or partially saturated anthranilamides[26–28] with (cyclo)alkanones, we studied the condensation of *cis*-hexahydroanthranilamide (**4b**)[29] and its cyclopentane homologue **4a**[30] with **2** (Scheme 2).



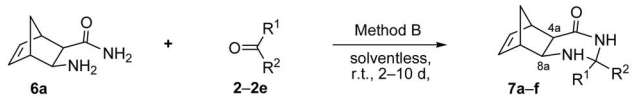
Scheme 2.

Under solventless conditions, **5a**, the *cis*-hexahydro derivative of 3′,5′,6′,7′-tetrahydro[cyclohexane-1,2′-cyclopenta[*d*]pyrimidin]-4′(1′*H*)-one,[31] and **5b**[25] were obtained quantitatively.

It was recently reported that *diendo*-methylene- and *diexo*-epoxy-bridged tetrahydrospiroquinazolinones were prepared from the corresponding 2-aminocarboxamides with cycloalkanones in boiling ethanol without the use of any catalyst.[32]

To extend those results, *diexo*-3-aminonorbornene-2-carboxamide (**6a**) and ketones **2**–**2e** were reacted under the "dry" conditions to give 2,2′-disubstituted quinazolinones **7a**–**f** (Table 2).

Table 2. Solventless synthesis of *diexo*-2,2′-disubstituted quinazolinones **7a**–**f** from 3-aminocarboxamide **6a** with ketones **2**–**2e**.

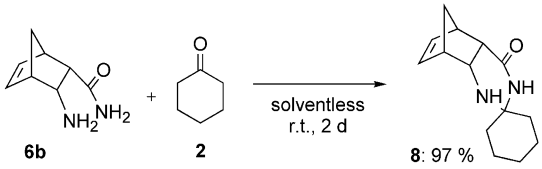


Entry	R^1	R^2		Time [d]	Ketone [equiv.]	Product	Yield [%]
1	$R^1 + R^2 = (CH_2)_5$		**2**	2	1	**7a**	99
2	$R^1 + R^2 = (CH_2)_4$		**2a**	2	1	**7b**	99
3	$R^1 + R^2 = (CH_2)_6$		**2b**	2	1	**7c**	98
4	CH_3	CH_3	**2c**	2	2	**7d**	99
5	CH_3	C_2H_5	**2d**	2	2	**7e**	94
6	C_2H_5	C_2H_5	**2e**	10	2		98

In all cases, during conventional magnetic stirring, condensation was carried out in a closed system to avoid the escape of **2**–**2e**. For the preparation of quinazolinones **7d**–**f**, alkanones **2c**–**e** were applied in 100% excess, while cycloalkanones **2**–**2b** were used in equimolar amounts. The excess amounts of volatile reagents **2c**–**e** were removed by evaporation. Reactions were complete in 2 d at room temperature, except for **7f**, which was formed in a yield of 98% in 10 d. It is noteworthy that when the same reaction conditions were applied to the cyclization of the solid starting compounds, that is, **6a** and cyclooctanone or cyclododeca-

none, no product was obtained. In the solid–solid system, the condensations proceeded much more slowly than in the liquid–solid system.[5f]

On the other hand, it was observed that the solventless spirocyclization of cyclohexanone (**2**) with *diendo* stereoisomer **6b** proceeded to afford methylene-bridged spiro compound **8** in high yield after 2 d, as shown in Scheme 3.



Scheme 3.

It is presumed that the cyclizations of α- and β-aminoamides with ketones under either aqueous or solventless conditions take place without the formation of a Schiff base; the intermediate carbinolamines (hemiaminals)[33] are transformed into the 2,2′-disubstituted quinazolinones directly by the elimination of water. Under virtually dry conditions, the presence of moisture and other impurities in the starting reagents,[24] and the continuously increasing amount of water formed as a byproduct, appear likely to promote the formation of the tetrahedral carbinolamine intermediate.[34] In many reactions, significant rate enhancements were observed in water as compared with organic solvents. This acceleration has been attributed to many factors, including the hydrophobic effect, enhanced hydrogen bonding in the transition state and the cohesive energy density of water.[35]

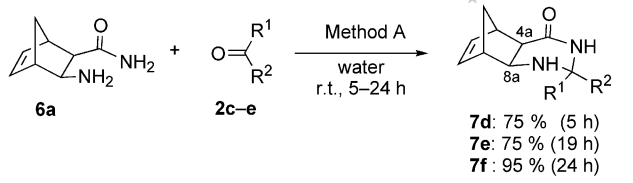
Following the above studies, we investigated the additive effect of water in the slower condensation of **6a** and **2e**, where steric resistance to formation of the carbinolamine probably occurs. In the presence of a stoichiometric amount of water, cyclization of amide **6a** with diethyl ketone (**2e**) at room temperature was complete in 6 d, giving rise to **7f** in a yield of 96%. It is important that the addition of either substoichiometric (0.5 equiv.) or superstoichiometric (3 or 10 equiv.) amounts of water to the reaction mixture of **6a** and **2e** did not lead to a beneficial effect on the reaction rate.

In marked contrast with the latter observations, the formation of tricyclic compounds **7d**–**f** was accelerated in the presence of a large excess of water. The reactions of 2.5 mmol of **6a** with 5 mmol of **2c**, **2d** (solubility in water at 20 °C 292 g/1000 mL) or **2e** (solubility in water 50 g/1000 mL) "in" or "on" 5 mL of water gave quinazolinones **7d**–**f** in excellent yields and purities (Scheme 4).

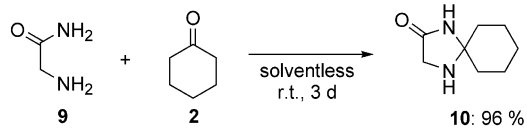
To investigate the limit of the solventless condensation/cyclization, we explored the above-mentioned strategies in the reaction of **2** with glycinamide (**7**)[36] (Scheme 5).

From the "dry" reaction mixture of commercially available **2** and **9**, a solid product, 1,4-diazaspiro[4.5]decan-2-one (**10**),[37] was obtained in high yield in 3 days.

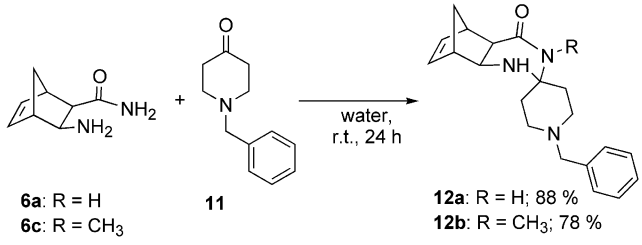
Accordingly, the generality of the solvent-free reactions was investigated for the synthesis of spiropiperidine–quinazolinones **12a** and **12c**. After several days, the NMR spectroscopic data indicated that the unsolidified mixture of **6a** or **6c**[38] with *N*-benzylpiperidin-4-one (**11**) contained *diexo*-methylene-bridged spiropiperidines in yields of not more than ca. 50%. As the reactions of water-insoluble organic compounds in aqueous suspensions have recently received a great deal of attention,[39] and because of the special properties[40] of water as compared with those of commonly employed organic solvents, we decided to attempt to prepare **12a** and **12b** in aqueous medium (Scheme 6).



Scheme 4.



Scheme 5.



Scheme 6.

diexo-3-Aminobicyclo[2.2.1]hept-5-ene-2-carboxamide (**6a**) or *diexo*-3-amino-*N*-methylbicyclo[2.2.1]hept-5-ene-2-carboxamide (**6c**) was dissolved in water and *N*-benzylpiperidin-4-one (**11**) was added dropwise. During stirring at room temperature, spiropiperidine derivative **12a** or **12b** started to precipitate in about 30 min. After stirring for 24 h at ambient temperature, the precipitated *diexo*-methylene-bridged tetrahydro-2′,2′′-disubstituted quinazolinones were isolated by simple filtration. Under neutral conditions, the corresponding spiropiperidones were obtained in yields of 78–88%.

All of the 2,2′-disubstituted quinazolinones, 1,4-diazaspiro[4.5]decane-2-one were characterized by IR,[23,41] ^{1}H NMR[23,42–46] and ^{13}C NMR spectroscopy and elemental analyses. ^{13}C NMR spectroscopic data were in agreement with literature data; compounds gave a ^{13}C signal at 66–78 ppm for a quaternary C-2. This shift appears reasonable for a –NHCR$_2$NH– system, where R is an alkyl group.[19a]

Conclusions

In conclusion, green approaches have been devised for the preparation of synthetically and pharmaceutically relevant 2,2′-disubstitutedquinazolinones and spiropiperidines. In the presence of moisture and impurities in the starting compounds, the solventless condensations of carboxamides **4a**, **4b**, **6a**, **6b** and **9** with (partially) water-soluble alkanones **2c**–**e** or slightly water-soluble (i.e. cyclohexanone: 87 g/1000 mL at 20 °C) cycloalkanones **2**, **2a** and **2b** gave 1,4-diazaspiro[4.5]decan-2-one **10** and quinazolinones **5a**, **5b** and **7a**–**f**. At ambient temperature, all of these reactions, except that of **6a** with **2**, were complete in 48–72 h without the need for any catalyst. On application of the aqueous protocol (Method A) for the preparation of **7d**–**f**, significantly enhanced reaction rates were observed. From the less water-soluble (12 g/1000 mL at 20 °C) *N*-benzylpiperidin-4-one (**11**) and bridged carboxamides **6a** and **6b**, spiropiperidines **12a** and **12c** were formed in "on water" reactions. These methods include some important features, such as the solvent-free medium, the use of water as a green solvent and mild reaction conditions. Moreover, the experimental procedures are very easy to carry out.

Experimental Section

General: Melting points were determined with a Kofler apparatus and are uncorrected. ^{1}H NMR (400 Hz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker Avance DRX 400 spectrometer, with TMS as internal reference and [D$_6$]DMSO as solvent. FTIR spectra recordings were performed with a Perkin–Elmer 100 FTIR spectrometer. Elemental analyses were carried out with a Perkin–Elmer 2400 elemental analyzer.

Spiro[cyclohexane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3)

Method A: To a stirred mixture of **1** (1.36 g, 10.0 mmol) in water (10 mL) was added cyclohexanone (**2**; 0.98 g, 10.0 mmol) in portions. After vigorous stirring at room temperature for 24 h in a round-bottomed flask (25 mL) sealed with a teflon cap, spiro compound **3** precipitated. It was filtered off, washed with water (5 mL) and dried upon a porous plate at 100 °C. Yield: 1.79 g (83%). M.p. 228–230 °C (H_2O) (ref.[17] 225 °C).

Method B: Stoichiometric amounts of **1** (1.36 g, 10.0 mmol) and **2** (0.98 g, 10.0 mmol) were stirred for 15 min in a round-bottomed flask (10 mL) sealed with a teflon cap. After standing at room temperature for 2 d, the ^{1}H NMR spectroscopic data on the solidified product proved the presence of **3** in 98–100% purity. Colourless powder. M.p. 225–228 °C. IR (KBr): $\tilde{\nu}$ = 3367 (ν_{NH}), 3173 (ν_{HNCO}), 1647 (ν_{CONH}), 1610 ($\nu_{C=C,Ar}$), 761 ($\nu_{C=H,Ar}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.06–1.88 (m, 10 H, 2–6-H), 6.55 (s, 1 H, 1′-NH), 6.56–7.62 (m, 4 H, ArH), 7.84 (s, 1 H, 3′-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 20.9 (2×C), 24.5, 37.2 (2×C), 67.9, 114.5, 114.6, 116.5, 127.2, 133.2, 146.8, 163.4 ppm. $C_{13}H_{16}N_2O$ (216.29): calcd. C 72.19; H 7.46; N 12.95; found C 72.25, H 7.62, N 12.81.

***diexo*-2-Ethyl(methyl)-2′-ethyl(methyl)-5,8-methano-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-ones (7d–7f)**

Method A: To a stirred solution of **6a** (0.38 g, 2.5 mmol) in water (5 mL) was added alkanone **2c**, **2d** or **2e** (5.0 mmol) in portions at room temperature. After vigorous stirring for 5 h (**7d**), 19 h (**7e**) or 24 h (**7f**) in a round-bottomed flask (25 mL) sealed with a teflon cap, quinazolinones **7d**–**f** precipitated. These were filtered off, washed with water (5 mL) and dried upon a porous plate at 100 °C.

***diexo*-2,2′-Dimethyl-5,8-methano-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-one (7d):** Yield: 0.36 g (75%). Colourless powder. M.p. 229–233 °C (H_2O).

***diexo*-2-Ethyl-5,8-methano-2′-methyl-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-one/*diexo*-2′-ethyl-5,8-methano-2-methyl-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-one (1:1; 7e):** Yield: 0.38 g (75%). Colourless powder. M.p. 189–192 °C (H_2O).

***diexo*-2,2′-Diethyl-5,8-methano-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-one (7f):** Yield: 0.38 g (95%). Colourless powder. M.p. 181–183 °C (H_2O).

Method B: A mixture of **6a** (0.76 g, 5.0 mmol) and ketone **2c**, **2d** or **2e** (10.0 mmol) was stirred for 15 min in a round-bottomed flask (10 mL) sealed with a teflon cap. After standing at room temperature for 2 d, the excess amount of **2c** or **2d** was removed by evaporation under reduced pressure, whereas the excess amount of **2e** was evaporated off after 10 d. The purities of 2,2′-disubstituted quinazolinones **7d**–**f** were established by ^{1}H NMR measurements.

***diexo*-2,2′-Dimethyl-5,8-methano-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-one (7d):** Yield: 99%. Colourless powder. M.p. 244–246 °C. IR (KBr): $\tilde{\nu}$ = 3287 (ν_{NH}), 3159 (ν_{HNCO}), 3062 ($\nu_{=CH}$), 1645 (ν_{CONH}), 1573 ($\nu_{C=C}$), 710 ($\nu_{=CH}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 1.14–1.30 (m, 7 H, 2×CH$_3$ and 9-H) 1.56 (d, *J* = 8.9 Hz, 1 H, 9-H), 1.78 (d, *J* = 7.4 Hz, 1 H, 4a-H), 2.02 (d, *J* = 7.9 Hz, 1 H, 1-NH), 2.61 (s, 8-H), 1 H, 3.08 (t, *J* = 7.4 Hz, 1 H, 8a-H), 3.19 (s, 1 H, 5-H), 6.13 (dd, *J* = 2.8 Hz, *J* = 5.5 Hz, 1 H, 7-H), 6.24 (dd, *J* = 2.8 Hz, *J* = 5.5 Hz, 1 H, 6-H), 7.99 (s, 1 H, 3-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 27.5, 29.3, 41.5, 43.8, 44.3, 47.2, 53.4, 66.5, 135.4, 138.1, 170.7 ppm. $C_{11}H_{16}N_2O$ (192.26): calcd. C 68.72, H 8.39, N 14.57; found C 68.43, H 8.61, N 14.68.

***diexo*-2-Ethyl-5,8-methano-2′-methyl-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-one/*diexo*-2′-ethyl-5,8-methano-2-methyl-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-one (1:1; 7e):** Yield: 94%. Colourless powder. M.p. 190–193 °C. IR (KBr): $\tilde{\nu}$ = 3294 (ν_{NH}), 3166 (ν_{HNCO}), 3058 ($\nu_{=CH}$), 1643 (ν_{CONH}), 1573 ($\nu_{C=C}$), 708 ($\delta_{=CH}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.80 and 0.85 (t, *J* = 7.5 Hz, 3 H, 2-CH$_2$*CH*$_3$), 1.14 and 1.19 (s, 1 H, 2-CH$_3$), 1.22 (d, *J* = 8.7 Hz, 2 H, 9-H), 1.40–1.61 (m, 6 H, 2-*CH*$_2$CH$_3$ and 9-H), 1.75 and 1.82 (d, *J* = 7.3 Hz, 1 H, 4a-H), 2.04 (br. s, 2 H,1-NH) 2.63 (s, 2 H, 8-H), 2.98 and 3.08 (d, *J* = 7.4 Hz, 1 H, 8a-H), 3.18 (s, 2 H, 5-H), 6.13 (m, 2 H, 7-H), 6.24 (m, 2 H, 6-H), 7.85 and 8.04 (s, 1 H, 3-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 7.8 and 9.5, 25.7 and 26.1, 32.8 and 34.4, 39.6 and 39.9, 42.0 and 42.4, 44.9 (2×C), 47.8 and 47.9, 53.4 (2×C), 69.1 and 69.5, 135.9 (2×C), 138.6 and 138.7, 171.2 and 171.5 ppm. $C_{12}H_{18}N_2O$ (206.29): calcd. C 69.87, H 8.80, N 13.58; found C 69.63, H 8.61, N 14.38.

***diexo*-2,2′-Diethyl-5,8-methano-2,3,4a,5,8,8a-hexahydroquinazolin-4(1*H*)-one (7f):** Yield: 98%. Colourless powder. M.p. 186–188 °C. IR (KBr): $\tilde{\nu}$ = 3293 (ν_{NH}), 3196 (ν_{HNCO}), 3061 ($\nu_{=CH}$), 1635 (ν_{CONH}), 1572 ($\nu_{C=C}$), 708 ($\delta_{=CH}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 0.77 (t, *J* = 7.4 Hz, 3 H, 2-CH$_2$*CH*$_3$), 0.82 (t, *J* = 7.4 Hz, 3 H, 2-CH$_2$*CH*$_3$), 1.22 (d, *J* = 8.6 Hz, 1 H, 9-H) 1.37–1.59 (m, 5 H, 2-*CH*$_2$CH$_3$ and 9-H), 1.78 (d, *J* = 7.2 Hz, 1 H, 4a-H), 1.97 (br. s, 1 H, 1-NH), 2.64 (s, 1 H, 8-H), 3.02 (d, *J* = 7.2 Hz, 1 H, 8a-H), 3.17 (s, 1 H, 5-H), 6.11 (dd, *J* = 2.9 Hz, *J* = 5.3 Hz, 1 H, 7-H), 6.24 (dd, *J* = 3.0 Hz, *J* = 5.2 Hz, 1 H, 6-H), 7.90 (s, 1 H, 3-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 7.7, 9.3, 30.2, 31.3, 42.8, 44.6, 45.4, 48.5, 53.3, 71.6, 136.2, 139.1, 171.9 ppm.

$C_{13}H_{20}N_2O$ (220.32): calcd. C 70.87, H 9.15, N 12.72; found C 70.63, H 9.01, N 12.68.

***diendo*- and *diexo*-5′,8′-Methano-4′a,5′,8′,8′a-tetra-hydrospiro-[cycloalkane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones (7a–c and 8)**

Method B: Stoichiometric amounts of **6a** or **6b** (5.0 mmol) and cycloalkanone **2**, **2a** or **2b** (5.0 mmol) were stirred for 15 min in a round-bottomed flask (10 mL) sealed with a teflon cap. After standing at room temperature for 2 d, the purities of solidified 2-spiroquinazolinones **7a**–**c** and **8** were determined by ^{1}H NMR measurements.

***diexo*-5′,8′-Methano-4′a,5′,8′,8′a-tetrahydrospiro[cyclohexane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (7a):** Yield: 99%. Colourless powder. M.p. 232–234 °C. IR (KBr): $\tilde{\nu}$ = 3298 (ν_{NH}), 3164 (ν_{HNCO}), 3058 ($\nu_{=CH}$), 1668 (ν_{CONH}), 1572 ($\nu_{C=C}$), 701 ($\delta_{=CH}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.23 (d, J = 9.0 Hz, 1 H, 9′-H), 1.10–1.82 (m, 11 H, 2–6-H and 9′-H), 1.79 (d, J = 6.8 Hz, 1 H, 4a′-H), 1.87 (br. s, 1 H, 1-NH), 2.66 (s, 1 H, 8′-H), 2.99 (d, J = 6.8 Hz, 1 H, 8′a-H), 3.19 (s, 1 H, 5′-H), 6.13 (dd, J = 2.8 Hz, J = 5.4 Hz, 1 H, 7′-H), 6.23 (dd, J = 2.7 Hz, J = 5.4 Hz, 1 H, 6′-H), 7.89 (s, 1 H, 3′-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.2, 22.1, 25.0, 35.7, 37.3, 42.0, 43.8, 44.4, 47.2, 52.6, 68.0, 135.6, 138.0, 170.9 ppm. $C_{14}H_{20}N_2O$ (232.33): calcd. C 72.38, H 8.68, N 12.06; found C 72.60, H 8.91, N 12.15.

***diexo*-5′,8′-Methano-4′a,5′,8′,8′a-tetrahydrospiro[cyclopentane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (7b):** Yield: 99%. Colourless powder. M.p. 239–241 °C. IR (KBr): $\tilde{\nu}$ = 3282 (ν_{NH}), 3155 (ν_{HNCO}), 3058 ($\nu_{=CH}$), 1641 (ν_{CONH}), 1572 ($\nu_{C=C}$), 708 ($\delta_{=CH}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.23 (d, J = 8.6 Hz, 1 H, 9′-H), 1.38–1.69 (m, 7 H, 2–5-H and 9′-H), 1.69–1.92 (m, 2 H, 2–5-H), 1.76 (d, J = 7.4 Hz, 1 H, 4a′-H), 2.10 (br. s, 1 H, 1-NH), 2.63 (s, 1 H, 8′-H), 3.05 (d, J = 7.4 Hz, 1 H, 8′a-H), 3.20 (s, 1 H, 5′-H), 6.14 (dd, J = 2.7 Hz, J = 5.6 Hz, 1 H, 7′-H), 6.24 (dd, J = 2.7 Hz, J = 5.6 Hz, 1 H, 6′-H), 8.12 (s, 1 H, 3′-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.9, 23.3, 37.3, 38.5, 41.9, 43.8, 44.3, 47.1, 53.8, 77.0, 135.6, 137.9, 171.1 ppm. $C_{13}H_{18}N_2O$ (218.30): calcd. C 71.53, H 8.31, N 12.83; found C 71.60, H 8.11, N 12.75.

***diexo*-5′,8′-Methano-4′a,5′,8′,8′a-tetrahydrospiro[cycloheptane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (7c):** Yield: 98%. Colourless powder. M.p. 212–214 °C. IR (KBr): $\tilde{\nu}$ = 3303 (ν_{NH}), 3158 (ν_{HNCO}), 3061 ($\nu_{=CH}$), 1634 (ν_{CONH}), 1569 ($\nu_{C=C}$), 695 ($\delta_{=CH}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.22 (d, J = 8.9 Hz, 1 H, 9′-H), 1.38–1.75 (m, 13 H, 2–7-H and 9′-H), 1.76 (d, J = 6.8 Hz, 1 H, 4a′-H), 1.83 (br. s, 1 H, 1-NH), 2.64 (s, 1 H, 8′-H), 3.00 (d, J = 7.0 Hz, 1 H, 8′a-H), 3.19 (s, 1 H, 5′-H), 6.13 (dd, J = 2.6 Hz, J = 5.6 Hz, 1 H, 7′-H), 6.23 (dd, J = 2.6 Hz, J = 5.6 Hz, 1 H, 6′-H), 7.99 (s, 1 H, 3′-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.2, 21.4, 28.9, 29.0, 38.6, 41.7, 42.0, 43.8, 44.4, 47.3, 53.1, 72.1, 135.6, 138.1, 171.0 ppm. $C_{15}H_{22}N_2O$ (246.36): calcd. C 73.13; H 9.00; N 11.37; found C 72.90, H 8.81, N 11.55.

***diendo*-5′,8′-Methano-4′a,5′,8′,8′a-tetrahydrospiro[cyclohexane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (8):** Yield: 97%. Colourless powder. M.p. 240–243 °C (ref.[32] 243–244 °C). The analytical and spectroscopic data on **8** were identical to those in the literature.[32]

1,4-Diazaspiro[4.5]decan-2-one (9) and *cis*-Hexahydrospiro[cyclohexane-1,2′-cycloalka[*d*]pyrimidin]-4′(1′*H*)-ones (5a and 5b): Stoichiometric amounts of **4a**, **4b** or glycinamide **9**[36] (5.0 mmol) and cyclohexanone (**2**; 0.49 g, 5.0 mmol) were stirred for 15 min in a round-bottomed flask (10 mL) sealed with a teflon cap. The reaction mixture of **4a** or **4b** and **2** was left to stand at room temperature for 2 d, and that of **9** and **2** for 3 d. The purities of solidified spiro compounds **10**, **5a** and **5b** were determined by ^{1}H NMR measurements.

1,4-Diazaspiro[4.5]decan-2-one (10): Yield: 96%. Colourless powder. M.p. 115–118 °C (ref.[37a] 118–119 °C). IR (KBr): $\tilde{\nu}$ = 3279 (ν_{NH}), 3186 (ν_{HNCO}), 1690 (ν_{CONH}) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 1.19–1.59 (m, 10 H, 5–9-H), 2.81 (br. s, 1 H, 3-NH), 3.14 (s, 2 H, 3-H), 8.33 (s, 1 H, 1-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 22.3 (2 × C), 24.7, 37.6 (2 × C), 48.2, 75.1, 175.3 ppm. $C_8H_{14}N_2O$ (154.21): calcd. C 62.31, H 9.15, N 18.17; found C 62.01, H 9.02, N 18.45.

***cis*-Hexahydrospiro[cyclohexane-1,2′-cyclopenta[*d*]pyrimidin]-4′(1′*H*)-one (5a):** Yield: 97%. Colourless powder. M.p. 195–197 °C. IR (KBr): $\tilde{\nu}$ = 3263 (ν_{NH}), 3166 (ν_{HNCO}), 1651 (ν_{CONH}) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.04–1.74 (m, 13 H, 2–6-H and 5′-7′-H), 1.74 (d, J = 9.6 Hz, 1 H, 1′-NH), 1.80–2.02 (m, 3 H, 5′ and 7′-H), 2.22 (m, 1 H, 4′a-H), 3.44 (m, 1 H, 7′a-H), 7.58 (s, 1 H, 4′-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 22.3, 22.9, 24.0, 26.0, 30.1, 34.2, 36.4, 39.3, 44.8, 52.0, 69.5, 172.7 ppm. $C_{12}H_{20}N_2O$ (208.31): calcd. C 69.19, H 9.68, N 13.45; found C 69.18, H 9.48, N 13.55.

***cis*-Hexahydrospiro[cyclohexane-1,2′(1′*H*)-quinazolin]-4′(1′*H*)-one (5b):** Yield: 99%. Colourless powder. M.p. 150–152 °C (ref.[25b] 148–149 °C). IR (KBr): $\tilde{\nu}$ = 3254 (ν_{NH}), 3168 (ν_{HNCO}), 1646 (ν_{CONH}) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.02–1.71 (m, 17 H, 2–6-H and 5′-8′-H), 1.79 (d, J = 12.9 Hz, 1 H, 1′-NH), 1.91 (dt, J = 4.2 Hz, J = 11.8 Hz, 1 H, 4′a-H), 2.01 (m, 1 H, 5′-H), 3.13 (m, 1 H, 8′a-H), 7.40 (s, 1 H, 4′-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 20.6, 22.6, 23.1, 25.6, 25.9, 26.0, 30.6, 37.0, 40.6, 43.3, 45.3, 69.2, 173.5 ppm. $C_{13}H_{22}N_2O$ (222.33): calcd. C 70.23, H 9.97, N 12.60; found C 69.98, H 9.68, N 12.55.

***diexo*-1-Benzyl-(3′-methyl)-5′,8′-methano-4′a,5′,8′,8′a-tetrahydrospiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-ones (12a and 12b):** To a stirred solution of β-aminocarboxamide **6a** or **6c** (5.0 mmol) in water (10 mL) was added 1-benzyl-4-piperidinone (**11**; 0.95 g, 5.0 mmol) in portions at room temperature. After vigorous stirring for 24 h in a round-bottomed flask (25 mL) sealed with a teflon cap, product **12a** or **12b** precipitated. It was filtered off, washed with water (10 mL) and dried upon a porous plate at 100 °C.

***diexo*-1-Benzyl-5′,8′-methano-4′a,5′,8′,8′a-tetrahydrospiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (12a):** Yield: 1.42 g (88%). Colourless powder. M.p. 225–228 °C (H_2O). IR (KBr): $\tilde{\nu}$ = 3301 (ν_{NH}), 3172 (ν_{HNCO}), 3059 ($\nu_{=CH}$), 1635 (ν_{CONH}), 1573 ($\nu_{C=C}$), 734 ($\gamma_{=CH,Ar}$), 701 ($\delta_{=CH}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.23 (d, J = 8.9 Hz, 1 H, 9′-H), 1.43–1.54 (m, 2 H, 3-H and 5-H), 1.56 (d, J = 8.7 Hz, 1 H, 9′-H), 1.68–1.94 (m, 2 H, 3-H and 5-H), 1.78 (d, J = 7.6 Hz, 1 H, 4a′-H), 1.87 (d, J = 9.9 Hz, 1 H, 1′-NH), 2.22–2.57 (m, 4 H, 2-H and 6-H), 2.66 (s, 1 H, 8′-H), 2.99 (t, J = 8.3 Hz, 1 H, 8′a-H), 3.20 (s, 1 H, 5′-H), 3.44 (s, 2 H, benzyl-H), 6.13 (dd, J = 2.9 Hz, J = 5.6 Hz, 1 H, 7′-H), 6.23 (dd, J = 2.9 Hz, J = 5.6 Hz, 1 H, 6′-H), 7.19–7.33 (m, 5 H, Ar-H), 7.93 (s, 1 H, 3′-NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 35.1, 36.7, 42.0, 43.8, 44.4, 47.1, 48.5, 49.3, 52.5, 61.9, 66.6, 126.7, 128.1 (2 × C), 128.7 (2 × C), 135.6, 138.0, 138.7, 171.0 ppm. $C_{20}H_{25}N_3O$ (323.44): calcd. C 74.27, H 7.79, N 12.99; found C 74.38, H 7.58, N 12.65.

***diexo*-1-Benzyl-3′-methyl-5′,8′-methano-4′a,5′,8′,8′a-tetrahydrospiro[piperidine-4,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (12b):** Yield: 1.31 g (78%). Colourless powder. M.p. 162–164 °C (H_2O). IR (KBr): $\tilde{\nu}$ = 3316 (ν_{NH}), 3061 ($\nu_{=CH}$), 1617 ($\nu_{C=O}$), 1572 ($\nu_{C=C}$), 746 ($\gamma_{=CH,Ar}$), 701 ($\delta_{=CH}$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.22 (d, J = 8.8 Hz, 1 H, 9′-H), 1.54–1.78 (m, 4 H, 3-H, 5-H and 9′-H), 1.81 (d, J = 7.2 Hz, 1 H, 4a′-H), 1.96 (d, J = 10.2 Hz, 1 H,

1′-NH), 2.05–2.65 (m, 5 H, 2-H, 6-H and 3-H), 2.71 (s, 1 H, 8′-H), 2.82 (s, 3 H, CH_3), 2.95 (t, J = 8.7 Hz, 1 H, 8′a-H), 3.24 (s, 1 H, 5′-H), 3.46 (s, 2 H, benzyl-H), 6.14 (dd, J = 2.4 Hz, J = 5.2 Hz, 1 H, 7′-H), 6.24 (dd, J = 2.5 Hz, J = 5.3 Hz, 1 H, 6′-H), 7.18–7.38 (m, 5 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 26.6, 30.3, 34.6, 42.5, 43.8, 45.3, 47.2, 49.1, 49.3, 51.1, 61.9, 71.3, 126.8, 128.1 (2×C), 128.8 (2×C), 135.7, 138.0, 138.7, 170.0 ppm. $C_{21}H_{27}N_3O$ (337.47): calcd. C 74.74, H 8.06, N 12.45; found C 74.39, H 7.78, N 12.65.

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