

Short communication

# Preparation of Spiropiperidines in Water

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Dedicated to Professor Branko Stanovnik on the occasion of his 70<sup>th</sup> birthday

## Abstract

An environmentally benign spirocyclization is described for the synthesis of 4-spiropiperidines from 2-aminocarbohydrazides in water at room temperature without any catalyst. The condensation of carbocyclic 2-aminocarbohydrazides with *N*-benzylpiperidinone (**2**) led to 3'-aminospiropiperidine-quinazolinones (**3a-3d**). Anthranilic hydrazide **4** gave 2-amino-*N'*-(1-benzylpiperidin-4-ylidene)benzohydrazide (**7**), while glycine hydrazide (**8**) reacted with 2 moles of **2** to afford 1-benzylpiperidin-4-ylidenamino-1,4,8-triazaspiro[4.5]decane (**9**). All products precipitated from the reaction mixture and were obtained in excellent yields. No further work-up or purification was necessary.

**Keywords:** Spirocyclization, spiropiperidines, spiroquinazolines, green synthesis, aqueous media, methylene-bridged quinazolines

## 1. Introduction

The piperidine ring is a common heterocyclic unit in many alkaloids, and is a key moiety in numerous drug candidates. A number of 4-spiropiperidines have been reported to possess biological and pharmaceutical activities.<sup>1-3</sup> Spirocyclic carbamate **A** (Figure 1) has been tested

as a novel, highly selective<sup>4</sup> nitric oxide synthase inhibitor. Spiropiperidine-quinazoline **B** and its derivatives are used to treat inflammatory disease and pain.<sup>5</sup> As a ligand of the nociceptin receptor, *cis*-spiropiperidine **C** exhibits a 20-fold higher affinity than that of its *trans* stereoisomer.<sup>6</sup> 4-Oxaimidazolidine heterocycle **D** has been used as an antagonist against addiction to narcotic analgesics,<sup>7</sup> while

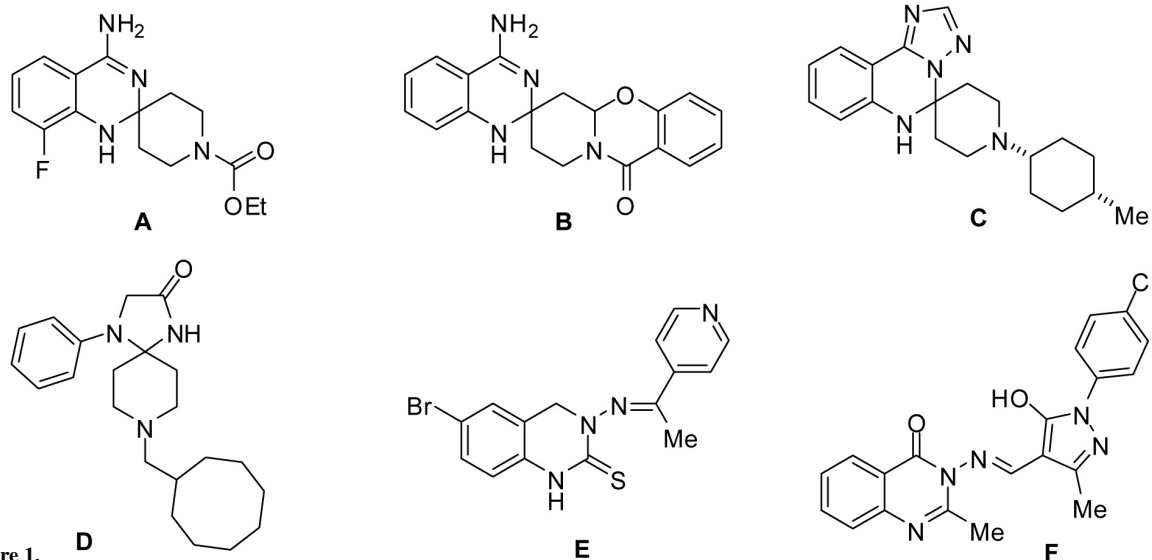


Figure 1.

some 1,4,8-triazaspiro[4.5]decan-2-ones display a high inhibitory index against the B-16 melanoma cell line.<sup>8</sup> Moreover, compounds with a 3*N*-aminoquinazoline motif demonstrate interesting activities. Substituted aminoquinazolinethione **E**, for instance, exerts excellent insecticidal activity against greenhouse whitefly,<sup>9</sup> and quinazolin-4-one **F** exhibits inhibitory activity against haematopoietic prostaglandin D2 synthase.<sup>10</sup> 3*N*-Aminoquinazolines are key intermediates for the synthesis of naphtho-fused 1,4,5-oxadiazepinoquinazolines,<sup>11</sup> biologically active Schiff bases,<sup>12,13</sup> triazocinoquinazolines<sup>14</sup> and 2-alkyl/aryl quinazolines.<sup>15</sup>

Kouznetsov *et al.* reported<sup>16,17</sup> that a four-step synthetic route from commercially available 1-benzyl-4-piperidinone and anilines provided an efficient preparation of spiro[piperidine-4,2'-(1'*H*)quinolines].<sup>16,17</sup> Spiro[1,2,4-benzotriazine-3(4*H*),4'-(1'-substituted)-piperidines] were obtained through the air oxidation of 2-aminophenylhydrazones of *N*-benzylpiperidones.<sup>18</sup> The effect of microwave irradiation on the formation of the spiroimidazolidinone was investigated by Feliu *et al.*<sup>19</sup> As compared with conventional heating, the microwave-assisted solid-phase synthesis of 1,4,8-triazaspiro[4.5]decan-2-one derivatives from 1-benzyl-piperidin-4-one (**2**) and an  $\alpha$ -amino acid amide was significantly improved. Spirocyclization of 1-acetyl-4-piperidone with 1,2-diamino-2-methylpropane in refluxing benzene gave 8-acetyl-2,2-dimethyl-1,4,8-triazaspiro[4.5]decane.<sup>20,21</sup>

## 2. Results and Discussion

We turned our attention to a greener and sustainable<sup>22,23</sup> approach for the preparation of an *N*-benzylpiperidine derivative of 2',2''-disubstituted spiroquinazolines. The use of water as a solvent for organic transformations offers numerous environmental benefits. In many reactions, a significant rate enhancement is observed in water relative to organic solvents. Water was found to be an ideal solvent for the multicomponent synthesis of heterocycles,<sup>24–28</sup> for the preparation of 2-pyrrolicarbaldimines,<sup>29</sup> octahydroquinazolines,<sup>30</sup> 3,4-dihydropyrimidinones,<sup>31</sup> pyrazoles and diazepines.<sup>32</sup>

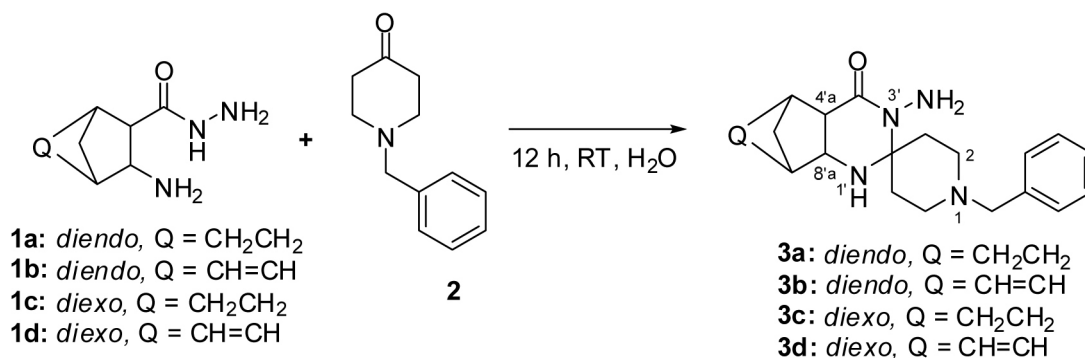
We already developed a method by which *diendo*- and *diexo*-3-aminonorbornane(ene)-2-carbohydrazides (**1a–1d**) were applied to form heterocycles. Refluxing of the above hydrazides with  $\gamma$ -oxoacid or  $\gamma$ -ketoester in toluene yielded methylene-bridged phthalazino[1,2-*b*]quinazolines<sup>33</sup> or cyclopenta[5,6]pyridazino[6,1-*b*]quinazolines.<sup>34</sup>

Our present aim was to expand the possibilities through the condensation of **1a–1d**<sup>33</sup> with 1-benzylpiperidin-4-one (**2**). The target of this project was to prepare methylene-bridged spiro-piperidines. Moreover, the chemical and stereochemical features of these saturated and partially saturated heterocycles, like those of their aromatic analogues, should be of importance from pharmacological aspects. To *diendo*-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide **1a**, or *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide **1b**, or *diexo*-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide **1c**, or *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide **1d** dissolved in water, *N*-benzylpiperidin-4-one was added dropwise. During stirring at room temperature, in about 10 min spiro-piperidine derivatives **3a–3d** started to precipitate (Scheme 1). After stirring for 12 h at ambient temperature, the precipitated *diendo*-methylene-bridged hexahydro- and tetrahydro-2',2''-disubstituted quinazolines **3a** and **3b**, and their *diexo* analogues **3c** and **3d** were isolated by simple filtration. Under neutral conditions, the corresponding spiro-piperidones were obtained in 92–97% yields.

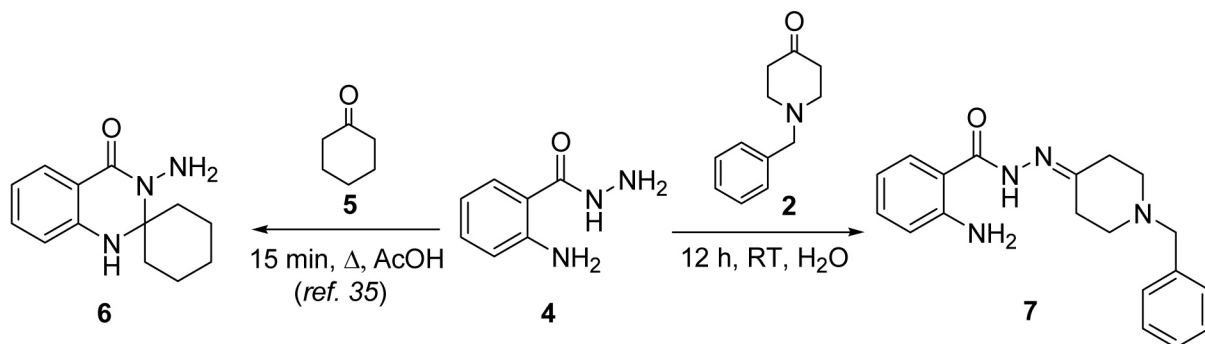
Only a few reports describe the spirocyclization of anthranilhydrazide **4** with cycloalkanones. 3'-Amino-1',2'-dihydrospiro[cyclohexane-1,2'-quinazolin]-4'(3'*H*)-one **6** was formed when **4** was refluxed with cyclohexanone **5** in acetic acid<sup>35</sup> (Scheme 2) or in ethanol.<sup>36</sup> It is important to note that a 3-cyclohexylidenamino derivative was obtained on the condensation of **4** and 2 or more equivalents of cyclohexanone.<sup>37–39</sup>

On analogy with the synthesis of **3a–3d**, we attempted to prepare their aromatic derivatives. The condensation of anthranilic hydrazide **4** with **2** gave only the hydrazone **7** in high yield. This can be explained by the less nucleophilic character of the aromatic amine.

To investigate the limit of spirocyclization in water, we decided to explore the above-mentioned strategies in

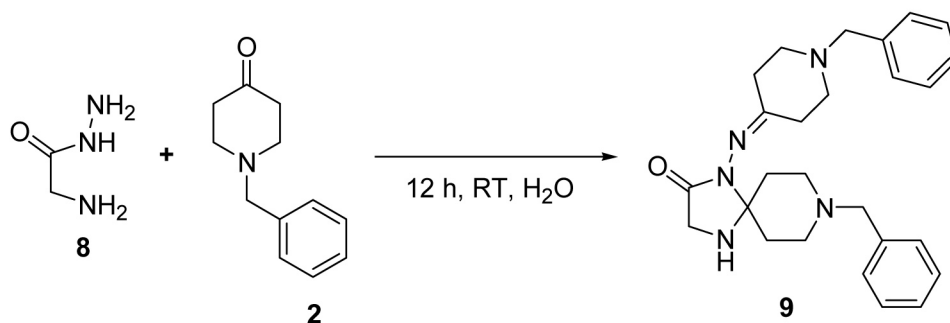


Scheme 1.



Scheme 2.

the reaction of glycine hydrazide<sup>40</sup> **8** and **2**; again, a crystalline product was precipitated in moderate yield (Scheme 3). The product was not an 1-amino-8-benzyl-2-oxo-1,4,8-triazaspiro[4.5]decane, but its benzylpiperidin-4-ylidenamino analogue **9**, which was formed by the condensation of **8** with 2 moles of **2**. When the reaction was repeated with 2 moles of **2** the yield of **9** increased to 87%.



Scheme 3.

It is presumed that the spirocyclization of aminohydrazides with benzylpiperidinone in aqueous media takes place without the formation of a Schiff base; the intermediate carbinolamines (hemiaminals) are transformed into the spiro compounds directly, by the elimination of water.<sup>41–44</sup>

During the cyclization, aminobicycloalkane(ene) carbohydrazide **1a–1d** retained their configurations in all cases. The constitutions of the compounds were proved via their IR and NMR spectra. The IR spectra of **3b** and **3d**, with a norbornene skeleton, exhibit a characteristic absorption bands in the regions 3080–3050  $cm^{-1}$  ( $\nu_{=CH}$ ) 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* isomer, this band is in a lower interval (702  $cm^{-1}$ ) than for the *endo* stereoisomer (734  $cm^{-1}$ ).<sup>45</sup> The presumed *diendo* and *diexo* configurations of the spirotricyclic compounds **3a**, **3b** and **3c**, **3d** were proved by <sup>1</sup>H-NMR spectroscopy. For **3a** and **3b**, the *diendo* annelation of the norbornene moiety is revealed by the splittings.<sup>46</sup> On *diendo* annelation, 4'-a-H exhi-

bits a *dd* split, proved by the value of  $\sim 4$  Hz<sup>47</sup> for the 4'-a-5' H-H coupling. The *diexo* annelation of the norbornane(ene) to the perhydropyrimidinone in **3c** and **3d** follows from the *d* split of 4'-a-H, which is a doublet due to the coupling with 8'-a-H (split by  $\sim 7.5$  Hz). Each of the spiro compounds **3a–3d** and **9** gave a <sup>13</sup>C signal for a quaternary C-2' at 73–79 ppm. This chemical shift appears reasonable for an  $-NHCR_2NH-$  system, where R is an alkyl

group.<sup>48</sup> The formation of 3'-amino-substituted compounds was confirmed by the appearances of  $NH_2$  signals in the <sup>1</sup>H-NMR spectra (4.06–4.51 ppm) and the lack of two NH groups in IR.

### 3. Conclusion

In conclusion, a green approach has been demonstrated for the preparation of synthetically and pharmaceutically relevant spiro-piperidines. The condensations of 3-amino-norborane(ene)-2-hydrazides (**1a–1d**) with 1-benzylpiperidin-4-one (**2**) gave 3'-amino-substituted spiro[piperidine-4,2'-quinazolin]ones **3a–3d**, while from less nucleophilic anthranilic hydrazide (**4**) a hydrazone **7** was formed. It was somewhat surprising that in the reaction of glycine hydrazide with 1-benzylpiperidin-4-one only a double condensed 1,4,8-triazaspiro[4.5]decane derivative **9** was obtained. At ambient temperature, all these reactions were complete in 12 h in water without the need for any catalyst. This method includes some important as-

pects, such as the use of water as a green solvent and mild reaction conditions.

## 4. Experimental

Melting points were determined on a Kofler apparatus and are uncorrected.  $^1\text{H-NMR}$  (400 Hz) and  $^{13}\text{C-NMR}$  (100 MHz) spectra were recorded on a Bruker Avance DRX 400 spectrometer, with TMS as internal reference and DMSO- $d_6$  or  $\text{CDCl}_3$  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 analyser.

**Preparation of diendo- and diexo-3'-amino-1-benzyl-5',8'-methano-4'a,5',(6',7')8',8'a-(hexa)tetrahydrospiro[piperidine-4,2'(1'H)-quinazolin]-4'(3'H)-ones (3a–3d).** To a stirred solution of hydrazides **1a–1d** (5.0 mmol) in 10 mL of water, 0.95 g (5.0 mmol) of 1-benzyl-4-piperidinone (**2**) was added in portions at room temperature. After vigorous stirring for 12 h, products **3a–3d** precipitated. The precipitates of **3a–3d** were filtered off, washed with water (15 mL), and dried upon a porous plate at 100 °C.

**diendo-3'-Amino-1-benzyl-5',8'-methano-4'a,5',6',7',8',8'a-hexahydrospiro[piperidine-4,2'(1'H)-quinazolin]-4'(3'H)-one (3a).** Yield: 97%; colourless powder; m.p.: 202–204 °C ( $\text{H}_2\text{O}$ ); IR (KBr,  $\text{cm}^{-1}$ ): 3437 (NH), 3334, 3311 ( $\text{NH}_2$ ), 1623 (C=O), 1587 (C=O);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.20–1.61 (8H, m, 2-6-H, 1'-NH, 6'-H, 7'-H 9'-H) 1.72 (1H, dd,  $J = 3.0$ ,  $J = 13.5$  Hz, 9'-H), 2.05 (1H, dd,  $J = 4.1$  Hz,  $J = 8.8$  Hz, 4'a-H), 2.24–2.46 (3H, m, 2-6-H), 2.50 (1H, s, 8'-H), 2.65–2.88 (4H, m, 2-6-H, 5'-H), 3.47 (1H, br s, 8'a-H), 3.54 (2H, s, benzyl  $\text{CH}_2$ ), 4.17 (2H, s,  $\text{NH}_2$ ), 7.18–7.37 (5H, m, Ar-H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  21.4, 23.4, 30.3, 35.0, 37.2, 40.0, 40.8, 45.2, 49.1, 49.5, 50.0, 62.3, 74.2, 126.6, 127.8 (2xC), 128.6 (2xC) 138.5, 170.5; Anal. calcd. for  $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}$  (%): C, 70.56; H, 8.29; N, 16.46. Found: C, 70.25; H, 8.48; N, 16.30;  $m/z$   $[\text{M}+\text{H}]^+\text{e}341.2$ .

**diendo-3'-Amino-1-benzyl-5',8'-methano-4'a,5',8',8'a-tetrahydrospiro[piperidine-4,2'(1'H)-quinazolin]-4'(3'H)-one (3b).** Yield: 94%; colourless powder; m.p.: 186–188 °C ( $\text{H}_2\text{O}$ ); IR (KBr,  $\text{cm}^{-1}$ ): 3419 (NH), 3317, 3301 ( $\text{NH}_2$ ), 3056 ( $\nu_{\text{CH}}$ ), 1601 (C=O), 1572 (C=O), 733 ( $\delta_{\text{CH}}$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  0.63 (1H, br s, 1'-NH), 1.17 (1H, d,  $J = 13.0$  Hz, 2-6-H) 1.48 (1H, d,  $J = 8.7$  Hz, 9'-H), 1.64 (1H, d,  $J = 8.8$  Hz, 9'-H), 1.78–2.49 (4H, m, 2-6-H), 2.64 (1H, dd,  $J = 4.0$  Hz,  $J = 8.5$  Hz, 4'a-H), 2.69–2.81 (3H, m, 2-6-H), 3.15 (1H, s, 8'-H), 3.47 (1H, s, 5'-H), 3.56 (2H, s, benzyl  $\text{CH}_2$ ), 3.80 (1H, br s, 8'a-H), 4.06 (2H, s,  $\text{NH}_2$ ), 6.18 (1H, dd,  $J = 2.9$  Hz,  $J = 5.3$  Hz, 7'-H), 6.44 (1H, dd,  $J = 2.9$  Hz,  $J = 5.0$  Hz, 6'-H), 7.22–7.39 (5H, m,

Ar-H);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  31.0, 34.3, 43.4, 46.1 (2xC), 47.0, 49.0, 49.3, 52.3, 61.8, 73.7, 126.7, 128.1 (2xC), 128.6 (2xC) 133.9, 138.4, 138.5, 168.6; Anal. calcd. for  $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}$  (%): C, 70.98; H, 7.74; N, 16.55. Found: C, 71.05; H, 7.48; N, 16.30;  $m/z$   $[\text{M}+\text{H}]^+\text{e}339.1$ .

**diexo-3'-Amino-1-benzyl-5',8'-methano-4'a,5',6',7',8',8'a-hexahydrospiro[piperidine-4,2'(1'H)-quinazolin]-4'(3'H)-one (3c).** Yield: 93%; colourless powder; m.p.: 183–185 °C ( $\text{H}_2\text{O}$ ); IR (KBr,  $\text{cm}^{-1}$ ): 3414 (NH), 3320, 3312 ( $\text{NH}_2$ ), 1623 (C=O), 1588 (C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  0.99 (1H, d,  $J = 10.2$  Hz, 9'-H) 1.12–2.01 (9H, m, 2-6-H, 1'-NH, 6'-H, 7'-H and 9'-H), 2.05 (1H, d,  $J = 7.5$  Hz, 4'a-H ), 2.09 (1H, s, 8'-H), 2.22–2.60 (5H, m, 2-6-H), 2.62 (1H, s, 5'-H) 3.04 (1H, t,  $J = 8.4$  Hz, 8'a-H) 3.45 (2H, s, benzyl  $\text{CH}_2$ ), 4.51 (2H, s,  $\text{NH}_2$ ), 7.19–7.36 (5H, m, Ar-H);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  26.1, 28.5, 29.9, 33.5, 33.8, 40.1, 42.0, 49.0, 49.1, 49.4, 54.7, 61.9, 72.4, 126.7, 128.1 (2xC), 128.7 (2xC) 138.9, 168.3; Anal. calcd. for  $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}$  (%): C, 70.56; H, 8.29; N, 16.46. Found: C, 70.32; H, 8.35; N, 16.22;  $m/z$   $[\text{M}+\text{H}]^+\text{e}341.2$ .

**diexo-3'-Amino-1-benzyl-5',8'-methano-4'a,5',8',8'a-tetrahydrospiro[piperidine-4,2'(1'H)-quinazolin]-4'(3'H)-one (3d).** Yield: 92%; colourless powder; m.p.: 162–164 °C ( $\text{H}_2\text{O}$ ); IR (KBr,  $\text{cm}^{-1}$ ): 3426 (NH), 3319, 3311 ( $\text{NH}_2$ ), 3062 ( $\nu_{\text{CH}}$ ), 1622 (C=O), 1586 (C=O), 702 ( $\delta_{\text{CH}}$ );  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  1.22 (1H, d,  $J = 9.6$  Hz, 9'-H), 1.38–1.81 (4H, m, 9'-H, 2-6-H and 1'-NH), 1.86 (1H, d,  $J = 7.5$  Hz, 4'a-H), 1.96–2.61 (6H, m, 2-6-H), 2.68 (1H, s, 8'-H), 2.92 (1H, t,  $J = 8.2$  Hz, 8'a-H), 3.16 (1H, s, 5'-H), 3.43 (2H, s, benzyl-H) 4.51 (2H, s,  $\text{NH}_2$ ), 6.11 (1H, dd,  $J = 2.9$  Hz,  $J = 5.7$  Hz, 7'-H), 6.22 (1H, dd,  $J = 2.8$  Hz,  $J = 5.6$  Hz, 6'-H), 7.16–7.33 (5H, m, Ar-H);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  30.0, 33.8, 43.4, 43.8, 45.4, 47.4, 49.0, 49.3, 50.8, 61.9, 73.1, 126.7, 128.1 (2xC), 128.6 (2xC) 135.5, 138.3, 138.8, 168.6; Anal. calcd. for  $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}$  (%): C, 70.98; H, 7.74; N, 16.55. Found: C, 70.75; H, 7.96; N, 16.21;  $m/z$   $[\text{M}+\text{H}]^+\text{e}339.2$ .

**Preparation of 2-amino-N'-(1-benzylpiperidin-4-ylidene)benzohydrazide (7).** To a stirred solution of anthranilic hydrazide (**4**) (0.76 g, 5.0 mmol) in 15 mL of water, 0.95 g (5.0 mmol) of 1-benzyl-4-piperidinone (**2**) was added in portions at room temperature. After vigorous stirring for 12 h, product **7** precipitated. The precipitate of **7** was filtered off, washed with water (15 mL), and dried upon a porous plate at 100 °C.

Yield: 91%; colourless needles; m.p.: 165–167 °C ( $\text{H}_2\text{O}$ ); IR (KBr,  $\text{cm}^{-1}$ ): 3458, 3296 ( $\text{NH}_2$ ), 3229 (NHCO), 1622 (C=O), 1586 (C=O), 756 (Ar  $\gamma_{\text{CH}}$ );  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  2.35–2.49 (6H, m, cycloalkyl  $\text{CH}_2$ ), 2.52–2.58 (2H, m, cycloalkyl  $\text{CH}_2$ ), 3.54 (2H, s, benzyl  $\text{CH}_2$ ), 6.15 (2H, br s,  $\text{NH}_2$ ), 6.48–7.48 (9H, m, Ar-H), 10.41 (1H, s, NHCO);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  28.9, 35.3, 52.9, 54.0,

62.2, 115.5, 117.0, 127.8 (2xC), 129.1 (2xC), 129.6 (4x C), 139.2, 150.3, 162.1, 166.1; Anal. calcd. for C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>O (%): C, 70.78; H, 6.88; N, 17.38. Found: C, 70.59; H, 6.91; N, 17.21.

**1-(Benzylpiperidin-4-ylidenamino)-8-benzyl-2-oxo-1,4,8-triazaspiro[4.5]decane (9).** To a stirred solution of glycine hydrazide (**8**) (0.45 g, 5.0 mmol) in 10 mL of water, 0.95 g (5.0 mmol) or 1.89 g (10.0 mmol) of 1-benzyl-4-piperidinone (**2**) was added in portions at room temperature. After vigorous stirring for 12 h, product **9** precipitated. The precipitate **9** was filtered off, washed with water (10 mL), and dried upon a porous plate at 100 °C.

Yield: 45% or 87% (based on hydrazide **8**); colourless powder; m.p.: 141–143 °C (H<sub>2</sub>O); IR (KBr, cm<sup>-1</sup>): 3285 (NH), 1685 (C=O), 1637 (C=N); <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 1.43–2.76 (16H, m 2-6-H), 3.02 (1H, t, *J* = 9.3 Hz, 4-NH), 3.25 (2H, d, *J* = 9.2 Hz 3-H), 3.47 (2H, s, benzyl-H), 3.55 (2H, s, benzyl-H), 7.20–7.37 (10H, m, Ar-H); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 31.4, 33.4 (2xC), 35.4, 47.5, 50.2 (2xC), 53.3, 54.1, 61.9, 62.8, 78.4, 127.7, 127.8, 129.0 (2xC), 129.1 (2xC), 129.5 (2xC), 129.6 (2xC) 139.2, 139.5, 167.9, 174.6; Anal. calcd. for C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O (%): C, 72.36; H, 7.71; N, 16.23. Found: C, 72.55; H, 7.98; N, 16.01; *m/z* [M+H]<sup>+</sup> 432.2.

## 5. Acknowledgements

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## Povzetek

Opisana je okolju prijazna nekatalizirana spirociklizacija za pripravo 4-spiropiperidinov iz 2-aminokarbohidrazidov v vodi kot topilu. Kondenzacije karbocikličnih 2-aminokarbohidrazidov z *N*-benzilpiperidinom so vodile do 3'-aminospiropiperidine-kinazolinonov, antranilhidrazid je dal 2-amino-*N'*-(1-benzilpiperidin-4-iliden)benzohidrazid, medtem ko je glicinhidrazid regiral z dvema ekvivalentoma *N*-benzilpiperidina do ustreznega -benzilpiperidin-4-ilidena-1,4,8-triazaspiro[4,5]dekana. Vsi produkti so bili enostavno izolirani s filtracijo z odličnimi izkoristki in čistočo.