Short communication

Preparation of Spiropiperidines in Water

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th 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.[1–3] Spirocyclic carbamate **A** (Figure 1) has been tested as a novel, highly selective[4] nitric oxide synthase inhibitor. Spiropiperidine-quinazoline **B** and its derivatives are used to treat inflammatory disease and pain.[5] As a ligand of the nociceptin receptor, *cis*-spiropiperidine **C** exhibits a 20-fold higher affinity than that of its *trans* stereoisomer.[6] 4-Oxaimidazolidine heterocycle **D** has been used as an antagonist against addiction to narcotic analgesics,[7] while

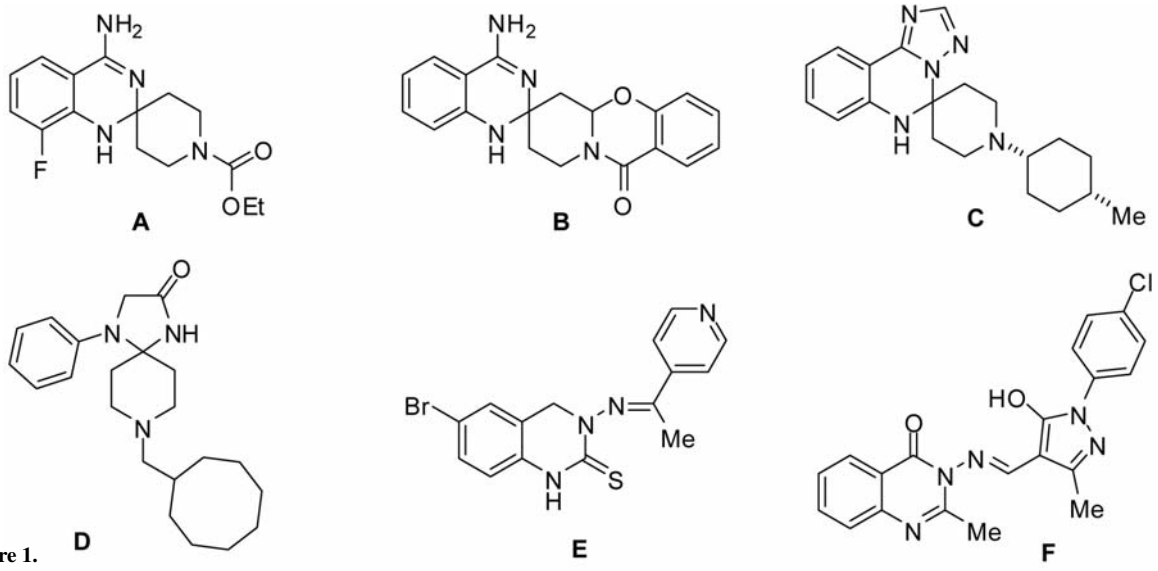


Figure 1.

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

Kouznetsov et al. reported[16,17] 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].[16,17] Spiro-[1,2,4-benzotriazine-3(4*H*),4'-(1'-substituted)-piperidines] were obtained through the air oxidation of 2-aminophenylhydrazones of *N*-benzylpiperidones.[18] The effect of microwave irradiation on the formation of the spiroimidazolidinone was investigated by *Feliu et al.*[19] 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 α-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.[20,21]

2. Results and Discussion

We turned our attention to a greener and sustainable[22,23] approach for the preparation of an *N*-benzylpiperidine derivative of 2',2"-disubstituted spiroquinazolinones. 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,[24–28] for the preparation of 2-pyrrolecarbaldimines,[29] octahydroquinazolinones,[30] 3,4-dihydropyrimidinones,[31] pyrazoles and diazepines.[32]

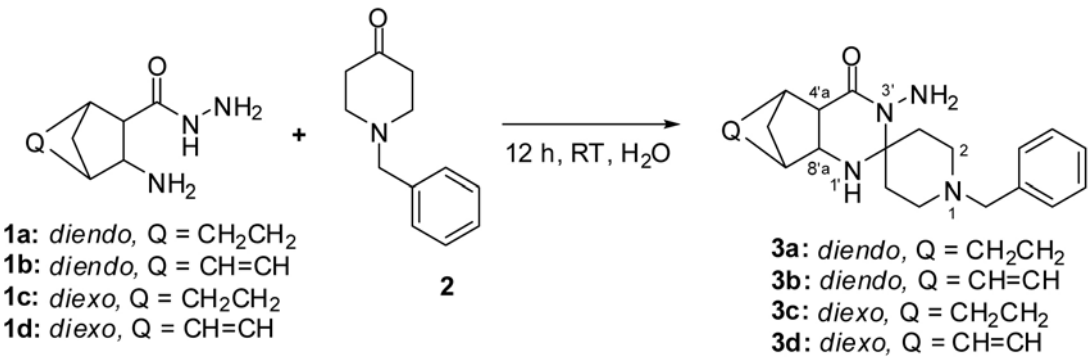
We already developed a method by which *diendo*- and *diexo*-3-aminonorbornane(ene)-2-carbohydrazides (**1a-1d**) were applied to form heterocycles. Refluxing of the above hydrazides with γ-oxoacid or γ-ketoester in toluene yielded methylene-bridged phthalazino[1,2-*b*]quinazolinones[33] or cyclopenta[5,6]pyridazino[6,1-*b*]quinazolinones.[34]

Our present aim was to expand the possibilities through the condensation of **1a-1d**[33] with 1-benzylpiperidin-4-one (**2**). The target of this project was to prepare methylene-bridged spiropiperidines. 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 spiropiperidine 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 quinazolinones **3a** and **3b**, and their *diexo* analogues **3c** and **3d** were isolated by simple filtration. Under neutral conditions, the corresponding spiropiperidones were obtained in 92–97% yields.

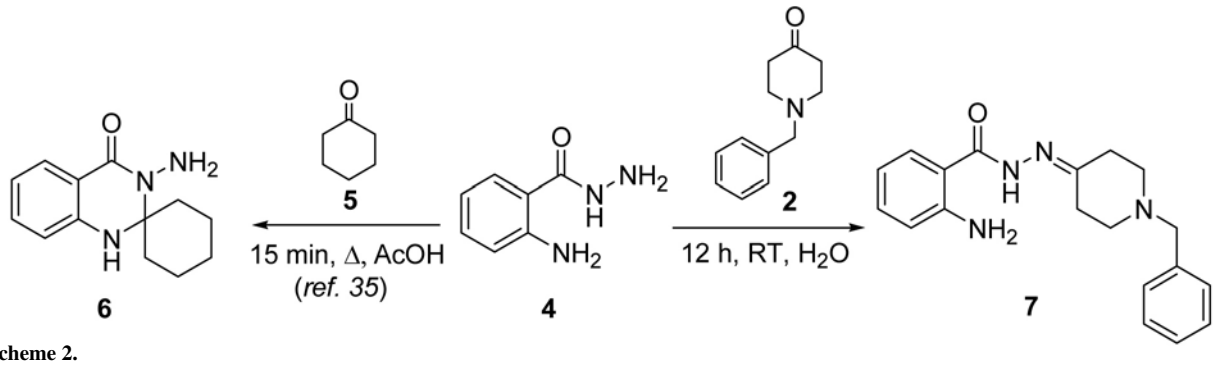
Only a few reports describe the spirocyclization of anthranylhydrazide **4** with cycloalkanones. 3'-Amino-1', 2'-dihydrospiro[cyclohexane-1,2'-quinazolin]-4'(3'*H*)-one **6** was formed when **4** was refluxed with cyclohexanone **5** in acetic acid[35] (Scheme 2) or in ethanol.[36] It is important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

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

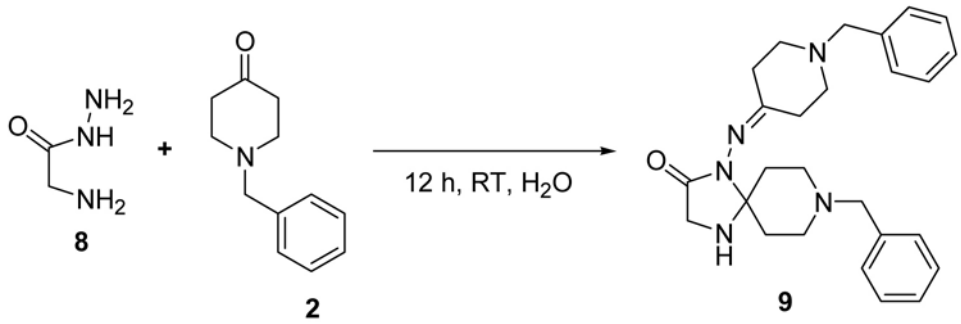


Scheme 1.



Scheme 2.

the reaction of glycine hydrazide[40] **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 spirocylization 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.[41–44]

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}).[45] The presumed *diendo* and *diexo* configurations of the spirotricyclic compounds **3a**, **3b** and **3c**, **3d** were proved by ^{1}H-NMR spectroscopy. For **3a** and **3b,** the *diendo* annelation of the norbornene moiety is revealed by the splittings.[46] On *diendo* annelation, 4'a-H exhibits a *dd* split, proved by the value of ~ 4 Hz[47] 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 ~ 7.5 Hz). Each of the spiro compounds **3a**–**3d** and **9** gave a ^{13}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.[48] The formation of 3'-amino-substituted compounds was confirmed by the appearances of NH_2 signals in the ^{1}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 spiropiperidines. The condensations of 3-aminonorborane(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}H-NMR (400 Hz) and ^{13}C-NMR (100 MHz) 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 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 (H_2O); IR (KBr, cm^{-1}): 3437 (NH), 3334, 3311 (NH_2), 1623 (C=O), 1587 (C=O); ^{1}H-NMR ($CDCl_3$): δ 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 CH_2), 4.17 (2H, s, NH_2), 7.18–7.37 (5H, m, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 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 $C_{20}H_{28}N_4O$ (%): C, 70.56; H, 8.29; N, 16.46. Found: C, 70.25; H, 8.48; N, 16.30; *m/z* $[M+H]^+$\'e341.2.

***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 (H_2O); IR (KBr, cm^{-1}): 3419 (NH), 3317, 3301 (NH_2), 3056 ($\nu_{=CH}$), 1601 (C=O), 1572 (C=O), 733 ($\delta_{=CH}$); ^{1}H-NMR ($CDCl_3$): δ 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 CH_2), 3.80 (1H, br s, 8'a-H), 4.06 (2H, s, 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}C-NMR (DMSO-d_6): δ 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 (2x-C), 128.6 (2xC) 133.9, 138.4, 138.5, 168.6; Anal. calcd. for $C_{20}H_{26}N_4O$ (%): C, 70.98; H, 7.74; N, 16.55. Found: C, 71.05; H, 7.48; N, 16.30; *m/z* $[M+H]^+$\'e339.1.

***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 (H_2O); IR (KBr, cm^{-1}): 3414 (NH), 3320, 3312 (NH_2), 1623 (C=O), 1588 (C=O); ^{1}H-NMR (DMSO-d_6): δ 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 CH_2), 4.51 (2H, s, NH_2), 7.19–7.36 (5H, m, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 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 $C_{20}H_{28}N_4O$ (%): C, 70.56; H, 8.29; N, 16.46. Found: C, 70.32; H, 8.35; N, 16.22; *m/z* $[M+H]^+$\'e341.2.

***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 (H_2O); IR (KBr, cm^{-1}): 3426 (NH), 3319, 3311 (NH_2), 3062 ($\nu_{=CH}$), 1622 (C=O), 1586 (C=O), 702 ($\delta_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 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, 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}C-NMR (DMSO-d_6): δ 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 $C_{20}H_{26}N_4O$ (%): C, 70.98; H, 7.74; N, 16.55. Found: C, 70.75; H, 7.96; N, 16.21; *m/z* $[M+H]^+$\'e339.2.

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 (H_2O); IR (KBr, cm^{-1}): 3458, 3296 (NH_2), 3229 (NHCO), 1622 (C=O), 1586 (C=O), 756 (Ar $\gamma_{=CH}$); ^{1}H-NMR (DMSO-d_6): δ 2.35–2.49 (6H, m, cycloalkyl CH_2), 2.52–2.58 (2H, m, cycloalkyl CH_2), 3.54 (2H, s, benzyl CH_2), 6.15 (2H, br s, NH_2), 6.48–7.48 (9H, m, Ar-H), 10.41 (1H, s, NHCO); ^{13}C-NMR (DMSO-d_6): δ 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 $C_{19}H_{22}N_4O$ (%): 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_2O); IR (KBr, cm^{-1}): 3285 (NH), 1685 (C=O), 1637 (C=N); ^{1}H-NMR (DMSO-d_6): 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); ^{13}C-NMR (DMSO-d_6): 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 $C_{26}H_{33}N_5O$ (%): C, 72.36; H, 7.71; N, 16.23. Found: C, 72.55; H, 7.98; N, 16.01; *m/z* $[M+H]^+$ 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*-benzilpiperidinonom 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*-benzilpiperidinona do ustreznega -benzilpiperidin-4-ilidenamino-1,4,8-triazaspiro[4,5]dekana. Vsi produkti so bili enostavno izolirani s filtracijo z odličnimi izkoristki in čistočo.