Synthesis, Structure and Some Reactions of 4a',5',6',7',8',8a'-Hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]-quinazolines]

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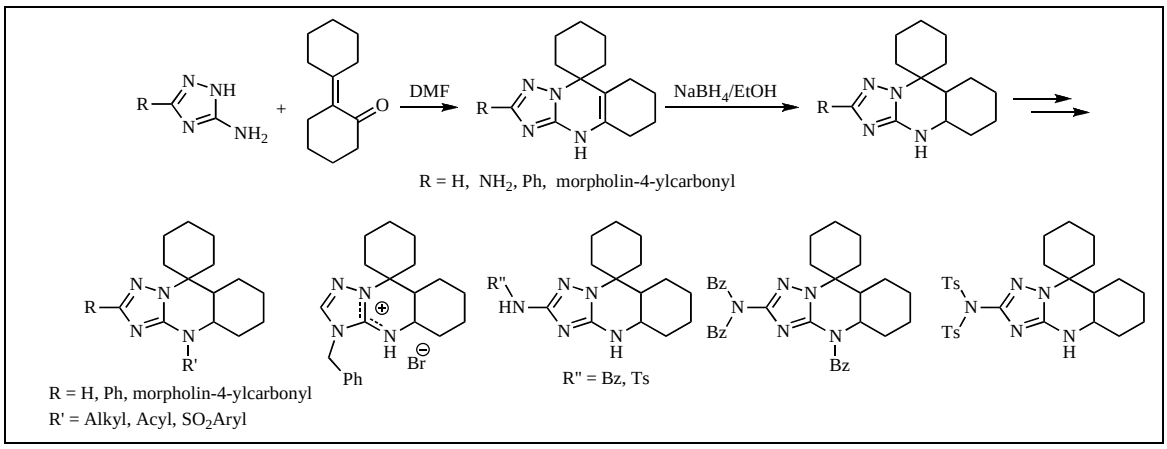

2'-Substituted 5',6',7',8'-tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] **3a-d** were synthesized by condensation of 3-substituted 5-amino-1,2,4-triazoles **1a-d** with 2-cyclohexylidene cyclohexanone **2** in DMF. The compounds **3** were hydrogenated with sodium borohydride in ethanol to give 2'-substituted *cis*-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] **4a-d** in high yields. The reactions of alkylation, acylation and sulfonylation of the compounds **4** were studied. The structure of the synthesized compounds was determined on the basis of NMR measurements including HSQC, HMBC, NOESY techniques and confirmed by the X-ray analysis of **6** and **11b**. The described synthetic protocols provide rapid access to novel and diversely substituted hydrogenated [1,2,4]triazolo[5,1-*b*]quinazolines.

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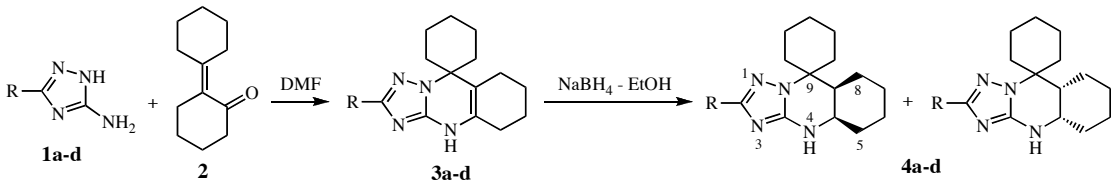
INTRODUCTION

Fused [1,2,4]triazoloazines containing partially hydrogenated pyrimidine ring attract attention as pharmacologically active compounds and models for studying the structural properties and synthetic possibilities of partially hydrogenated heterocycles [1-6]. During recent years, great interest was focused on [1,2,4]triazolo[5,1-*b*]-quinazolines with different degrees of hydrogenation of the quinazoline moiety [7-16]. In many respects it is caused by the fact that the compounds containing annelated 1,2,4-triazole and quinazoline rings exhibit antihypertensive activity [14,15] and act as antagonists of adenosine [17,18] and nociceptin receptors [2].

From a variety of synthetic methods [7-16,19-21] the condensation of 3-substituted 5-amino-1,2,4-triazoles with aldehydes and 1,3-cyclohexandione or alkylidene- and arylidenecyclohexanones [8,9,12,13,20] is the most appropriate way to synthesize partially hydrogenated [1,2,4]triazolo[5,1-*b*]quinazolines. These reactions allow to modify substituents at the positions 2 and 9 of the triazolo[5,1-*b*]quinazoline system.

The susceptibility of the dihydropyrimidine moiety of fused heterocycles to oxidative aromatization as well as to hydrogenation allows to enlarge remarkably the structural diversity of those compounds [1]. For [1,2,4]triazolo[5,1-*b*]quinazolines, oxidative aromatization of 9-(aryl)-6,6-dimethyl-5,6,7,9-tetrahydro-4*H*-[1,2,4]triazolo[5,1-*b*]-quinazolin-8-ones [13] and of 6,8,9-triphenyl-4,7,8,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazoline [10] was realized. However, hydrogenation of 6,8,9-triphenyl-4,7,8,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazoline by sodium borohydride was unsuccessful due to impossibility of rearrangement of this substance into imine tautomer necessary for reduction [10]. Therefore, it is of interest to investigate the possibility of hydrogenation of other triazolo[5,1-*b*]quinazolines containing dihydropyrimidine moiety. The present article

Scheme 1



a: R = H; **b**: R = NH_2; **c**: R = C_6H_5; **d**: R = morpholin-4-ylcarbonyl

is devoted to the synthesis of 4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] **4** by hydrogenation of 5',6',7',8'-tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] **3**. Special consideration is given to the structure analysis of the compounds **4** and their reactions with electrophilic reagents.

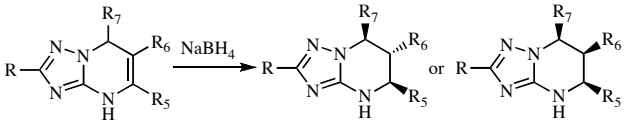
RESULTS AND DISCUSSION

5',6',7',8'-Tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]-triazolo[5,1-*b*]quinazolines] **3a-d** were obtained by condensation of 3-substituted 5-amino-1,2,4-triazoles **1a-d** with 2-cyclohexylidene cyclohexanone **2** (Scheme 1). Compounds **3a,b** have been described earlier [20]. The ^{1}H NMR spectra of the heterocycles **3c,d** exhibit the following signals: characteristic resonances for the CH_2-groups at 1.1-2.3 ppm, singlet for NH at 9.2 ppm and signals of the substituent at the position 2.

The application of sodium borohydride is one of the most useful methods for hydrogenation of the heterocycles containing azolopyrimidine fragment [6,22-25]. As established in our study, the substances **3a-d** can be easily hydrogenated with sodium borohydride in ethanol to give 4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro-[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] **4a-d** as only one diastereoisomer with 84-90% yields (Scheme 1). This fact was confirmed by the absence of signals of some extra diastereoisomers in the ^{1}H NMR spectra of crude products. In comparison with the starting materials **3a-d**, in the ^{1}H NMR spectra of the substances **4a-d** the integral intensity of aliphatic protons at 1.3-2.2 ppm is larger on 1H and the signal of NH is shifted to 6.4-7.1 ppm. In addition, a broad singlet for H-4a appears at 3.6-3.8 ppm. It is of interest to note that hydrogenation of 5,6,7-trisubstituted 4,7-dihydro[1,2,4]triazolo[1,5-*a*]-pyrimidines can lead to the products with either *trans* [6] or *cis* orientation [24] of the substituents at the positions 6 and 7 of the triazolopyrimidine system (Scheme 2).

In accordance with a very low value of the constant $J_{H\text{-}4a,H\text{-}8a}$ (therefore, H-4a is observed as a broad singlet in the ^{1}H NMR spectra), hydrogenation of the compounds **3a-d** leads to *cis*-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro-[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] **4a-d** as a mixture of (4a*R*,8a*S*) and (4a*S*,8a*R*) enantiomers (Scheme 1). The configuration of the compounds **4a-d** was confirmed unambiguously by X-ray diffraction study of their transformation products – benzyl **6** and furoyl **11b** derivatives (Figures 1 and 2).

Scheme 2

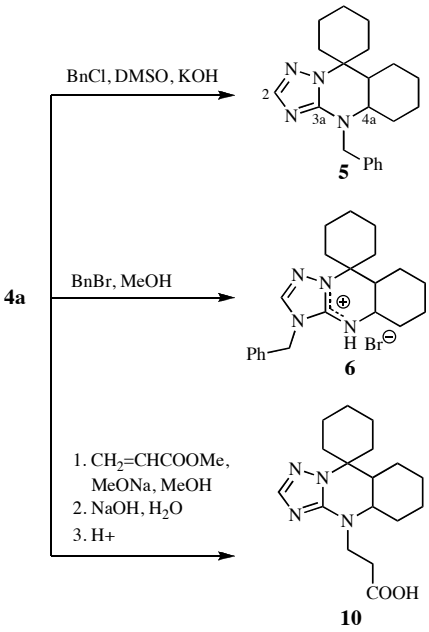


The molecules of triazoloquinazolines **4a-d** contain at least three nucleophilic centers N-1, N-3 and N-4, at which electrophilic reactions may take place. Modification of the compounds **4** by means of alkylation, acylation and sulfonylation reactions would allow to increase remarkably the structural diversity of these compounds and modify their biological activity. From this point of view, we can assume that in these reactions the compounds **4** will behave similarly to 4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidines [24]. However, until recently only alkylation of 5,7-diphenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine by dimethyl sulfate in the presence of KOH to give 4-methyl derivative [24] was described. Other reactions with electrophiles were not studied. Therefore, in this paper we investigated the alkylation, acylation and sulfonylation of compounds **4**.

Alkylation was studied on examples of the reaction of compound **4a** with benzylhalogenides and methylacrylate (Scheme 3). The reaction with benzyl chloride in DMSO in the presence of KOH led to the formation of 4-benzyl derivative **5**, whereas refluxing of **4a** with benzyl bromide in methanol in the absence of base gave a bromide of the 3-benzyl derivative **6**. The position of benzyl group in the compounds **5** and **6** was established on the basis of heteronuclear correlation NMR measurements (HMBC and HSQC). The HMBC spectrum of the compound **5** contains the geminal correlation peaks of the benzyl CH_2 protons (4.23 ppm and 5.14 ppm) with C-3a (155 ppm) and C-4a (48 ppm), while the correlation peak with C-2 (149 ppm) is not observed. However, in the HMBC

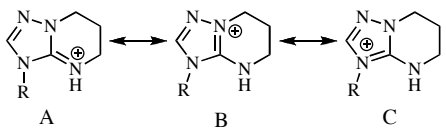
spectrum of the compound **6** the methylene protons of the benzyl group (5.23 ppm) correlate with the carbon atoms C-2 (140 ppm) and C-3a (146 ppm), whereas the correlation peak with C-4a is absent. The structure of compound **6** was additionally confirmed by X-ray diffraction study. In the ensuing discussion of the structure, the crystallographic numbering system will be used (Figure 1).

Scheme 3



In accordance with the X-ray diffraction data compound **6** exists as a salt formed by bromide anion and organic cation (Figure 1). The position of the hydrogen atom at the N(1) atom is established unambiguously from the electron density difference map. This allows one to assume that the structure of the organic cation may be described as a superposition of three resonance structures (Scheme 4).

Scheme 4



It should be noted that the C(1)-N(2) bond (1.356(3) Å) in the compound **6** is longer as compared with the C(1)-N(4) and C(1)-N(1) bonds which are equalized (1.331(3) Å and 1.326(3) Å, respectively). Such a redistribution of the electron density was observed in the similar fragments with the positively charged N(1) atom in the structures **7** [26] and **8** [27] (Scheme 5). In the case

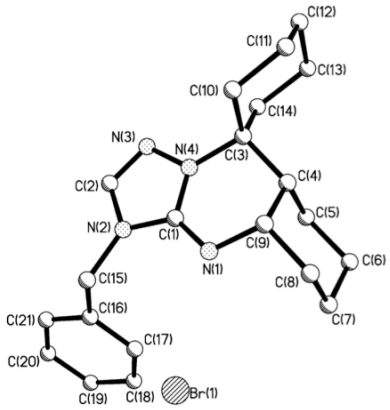
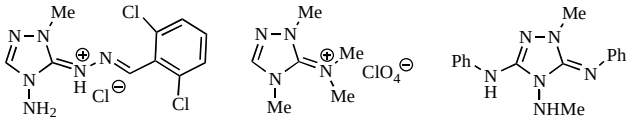


Figure 1. The molecular structure of compound **6**.

of uncharged fragment in structure **9** [28] corresponding to the C(1)-N(1) bond in **6** is shortened and corresponding to the C(1)-N(2) and C(1)-N(4) bonds are equalized. This allows one to suggest that the A and B resonance structures introduce the main contribution in the structure of the compound **6**.

Scheme 5



The bromide anion and the organic cation are bonded by the N(1)-H(1N)…Br(1) intermolecular hydrogen bond (H…Br 2.40 Å, N-H…Br 170°). The tetrahydropyrimidine ring of organic cation adopts the asymmetric half-chair conformation. Deviations of the C(4) and C(9) atoms from the mean plane of the remaining atoms of the ring are 0.55 Å and -0.17 Å, respectively. The fused cyclohexane and tetrahydropyrimidine rings have *cis*-junction (the H(4)-C(4)-C(9)-H(9) torsion angle is 55º). Both cyclohexane rings adopt the chair conformation.

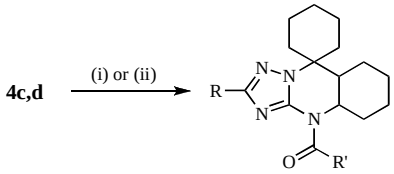
The interaction of **4a** with methylacrylate in the absence of strong base was unsuccessful under various experimental conditions. However, refluxing of **4a** with excess of methylacrylate in methanol in the presence of MeONa and subsequent one-pot hydrolysis of the resultant ester allowed to obtain acid **10** in 77% yield. The position of the carboxyethyl group was established by HMBC and HSQC experiments. The HMBC spectrum of compound **10** contains correlation peaks of NCH_2 protons (3.32 ppm and 3.96 ppm) with C-3a (153.4 ppm) and C-4a (47.4 ppm), whereas the correlation peaks of these protons with C-2 (148.1 ppm) are not observed.

The obtained results show that compounds **4** bear resemblance to 1-substituted 5-amino-1,2,4-triazoles in

alkylation. In the presence of strong bases, 1-substituted 5-amino-1,2,4-triazoles are alkylated at the exocyclic amino group (position 4 of the triazoloquinazoline system **4**). In this case, the deprotonation of amino group precedes the attack of electrophile [29]. Alkylation of 1-substituted 5-amino-1,2,4-triazoles in neutral media occurs at the atom with the highest electronic density, *e.g.* N-4 of the triazole ring (the position 3 of the system **4**) [30,31].

Acylation of compounds **4c** and **4d** resulted in the formation of 4-acyl derivatives **11a,b** (Scheme 6). The ^{1}H NMR spectra of compounds **11a,b** show no signals for H-4, and the signal of H-4a is shifted downfield by 0.64 ppm in comparison with the starting material **4c,d**. This fact indicates that the acyl group is bonded to the N-4 atom rather than to the N-1 or N-3. The position of the acyl group in the substance **11a** was also confirmed by ^{13}C NMR. The chemical shift of C-2 (157.9 ppm) in the ^{13}C NMR spectrum was almost the same in comparison with that in the spectrum of the starting substance **4c** (157.4 ppm), whereas the signal of C-3a was shifted upfield by 4 ppm apparently owing to the effect of magnetic anisotropy of the acetyl group.

Scheme 6



11a,b

11a: R = C_6H_5, R' = Me;
11b: R = morpholin-4-ylcarbonyl, R' = 2-furyl

Reagents and conditions: (i) Ac_2O, refluxing for 2.5 h; (ii) furoyl chloride / Py, refluxing for 15 min

The direction of the acylation was unequivocally confirmed by X-ray diffraction study of the compound **11b** (Figure 2).

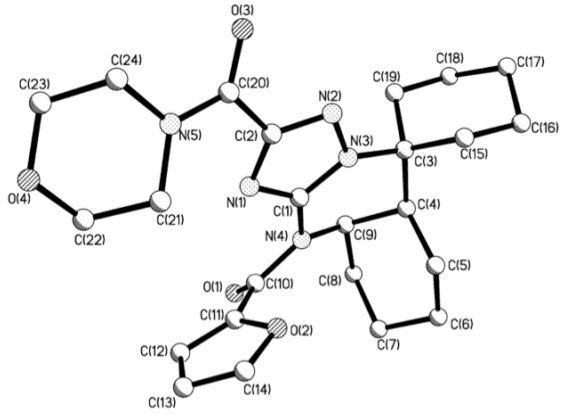
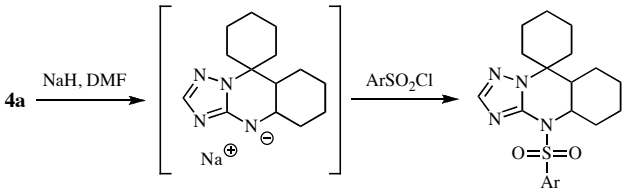


Figure 2. The molecular structure of compound **11b**.

The tetrahydropyrimidine ring of the compound **11b** adopts the half-chair conformation. The tetrahydropyrimidine and C(4)…C(9) cyclohexane ring have *cis*-junction (the H(4)-C(4)-C(9)-H(9) torsion angles is –61°). Morpholine and both cyclohexane rings of the compound **11b** adopt the chair conformation. The carbonyl group of the substituent at the N(4) atom is turned noticeably relatively the C(1)-N(4) bond (the C(1)-N(4)-C(10)-O(1) torsion angle is 137.2(2)°) and is non-coplanar to the plane of the furane ring (the O(1)-C(10)-C(11)-C(12) torsion angle is –22.6(3)°). The carbonyl group of the substituent at the C(2) atom is non-coplanar to the triazole ring (the N(2)-C(2)-C(20)-O(3) torsion angle is 22.1(2)°). The nitrogen atom of the morpholine ring has a slightly pyramidal configuration (the sum of the bond angles centered on the N(5) atom is 357.7°).

All attempts of sulfonylation of **4a** with sulfonyl-chlorides in boiling pyridine were unsuccessful, only the starting compounds were isolated from the reaction mixtures. The sulfonyl derivatives **12a,b** were synthesized in 40% yield trough sulfonylation of the sodium salt of the compound **4a** obtained *in situ* by the action of NaH (Scheme 7). The direction of sulfonylation was determined by the ^{1}H and ^{13}C NMR spectra. Similarly to the acyl derivatives **11a,b**, in the ^{1}H NMR spectra of **12a,b** the signal of H-4 is absent, and moreover, the signal of H-4a is shifted downfield by about 0.8 ppm in comparison with the starting substance **4a**. In the ^{13}C NMR spectrum of **12b** the signal of C-2 is almost invariable, whereas the signal of C-3a is shifted upfield 6.3 ppm in comparison with the spectrum of starting compound **4a** due to magnetic anisotropy of the sulfonyl group. Furthermore, the signal of the *o*-protons of the tosyl group (7.93 ppm) gives the cross-peaks with the signals of H-4a (4.50 ppm) and CH_2 protons (0.74 ppm and 2.46 ppm) in the NOESY spectrum of **12b**. This finding unambiguously confirmed the fact that the N-4 sulfonyl derivative was obtained.

Scheme 7



a: Ar = C_6H_5; **b**: R = *p*-$CH_3C_6H_4$ **12a,b**

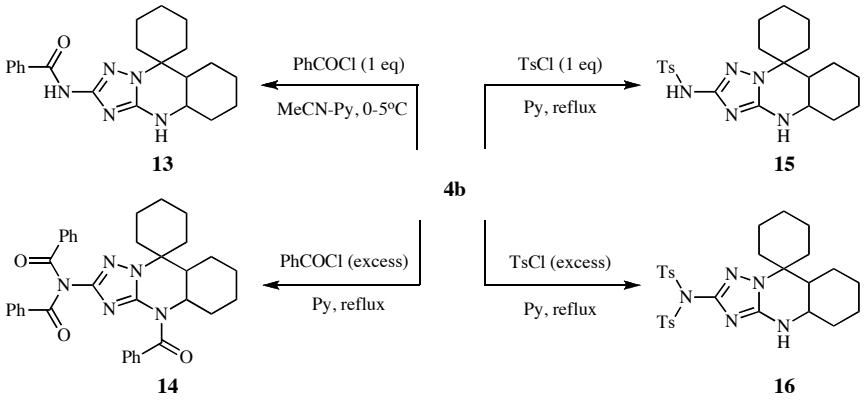
Compound **4b** contains reactive amino group at position 2, therefore its behavior in the acylation reactions is very special. The benzoylation of **4b** with equimolar amount of benzoyl chloride under mild conditions led to the formation of monobenzoyl derivative **13**, whereas

refluxing in pyridine with excess of benzoyl chloride gave the tribenzoyl derivative **14** (Scheme 8). In the ^{1}H NMR spectrum of **13** the signal of the amino group disappears, and a broad singlet of amide proton at 10.27 ppm appears. The singlet of H-4 is conserved and shifted downfield of about 0.5 ppm, the position of the H-4a signal is almost invariable (in comparison with **4b**). In the spectrum of the tribenzoyl derivative **14** the signals of NH are absent; the chemical shift of H-4a (4.45 ppm) is characteristic of the 4-acyl derivatives. In comparison with the starting compound **4b**, in the ^{13}C NMR spectrum of **14**, the carbon signals of the triazole ring are shifted upfield due to magnetic anisotropy of the carbonyl groups. Complete similarity of the signals of two benzoyl groups in the ^{1}H and ^{13}C NMR spectra confirms the structure of **14** and excludes alternative structures of N-1 and N-3 isomers.

Short-time refluxing of **4b** with an equimolar amount or a small excess of tosyl chloride in pyridine led to the formation of sulfamide **15**, whereas long-time refluxing with an excess of tosyl chloride gave the disulfonyl derivative **16** (Scheme 8). The ^{1}H NMR spectrum of the substance **15** contains a broad singlet of sulfamide proton at 10.45 ppm, the singlet of H-4 is shifted downfield of about 0.5 ppm, and the chemical shift of H-4a is not changed (in comparison with **4b**). In the ^{1}H NMR spectrum of **16** the NH signals of amino and sulfamide groups are absent, the singlet of H-4 (7.31 ppm) is downfield shifted in comparison with the starting compound **4b** (6.37 ppm), whereas the position of H-4a signal is almost unchanged. The signal of C-2 (148.5 ppm) in the ^{13}C NMR spectrum is shifted upfield by 11.7 ppm in comparison with **4b** (160.2 ppm), whereas the signal of C-3a is shifted downfield only by 1.4 ppm. Complete similarity of the signals of both tosyl groups in the ^{1}H and ^{13}C NMR spectra confirms unambiguously the structure of the compound **16**.

On the whole, the obtained results show, that in the acylation reactions the compounds **4c,d** are similar to 1-substitured 5-amino-1,2,4-triazoles [32], whereas the compound **4b** is analogous to 1-substitured 3,5-diamino-1,2,4-triazoles [33-35].

Scheme 8



CONCLUSION

Hydrogenation of 5',6',7',8'-tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] **3a-d** in ethanol leads to the formation of *cis*-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] **4a-d** in a good yield. The structure of *cis*-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolines] can be easily modified by alkylation, acylation and sulfonylation reactions in which the compounds **4a,c,d** behave analogously to 1-substituted 5-amino-1,2,4-triazoles, and compound **4b** is similar to 1-substituted 3,5-diamino-1,2,4-triazoles. The high susceptibility of the compounds **4** to functionalization opens up the possibility for their use in combinatorial synthesis.

EXPERIMENTAL

Melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker DRX500 instrument at 500 MHz and 125 MHz respectively and Bruker AM300 instrument at 300 MHz (75 MHz for ^{13}C) in DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were recorded in the form of m/z (intensity relative to base 100) on a Finnigan MAT Incos 50 at 70 eV. Elemental analyses were determined using a Perkin-Elmer 2400 instrument.

2-Cyclohexylidene cyclohexanone **2** [36] and 5-amino-3-(morpholin-4-ylcarbonyl)-1,2,4-triazole **1d** [37] were obtained by known methods. All other chemicals are commercially available.

General Procedure for the preparation of 5',6',7',8'-tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]-quinazolines] 3a-d. A mixture of triazole **1a-d** (5 mmol) and the compound **2** (5 mmol) was refluxed in DMF (0.8 mL) for 2 hours, diluted with ethanol (4 mL) and cooled to room

temperature. The precipitate that formed was collected by filtration and recrystallized.

5',6',7',8'-Tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]-triazolo[5,1-*b*]quinazoline] (**3a**). This compound was obtained in 56% yield as white crystals (ethanol), mp 234-235°, lit [20] mp 233-234°. Spectral data for compound **3a** were in agreement with those, reported in the literature [20].

2'-Amino-5',6',7',8'-tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (**3b**). This compound was obtained in 82% yield as white crystals (DMF-ethanol), mp 264-265°, lit [20] mp 251°. Spectral data for compound **3b** were in agreement with those, reported in the literature [20].

2'-Phenyl-5',6',7',8'-tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (**3c**). This compound was obtained in 60% yield as white crystals (DMF-ethanol), mp 194-196°; ^{1}H NMR: δ 1.21-1.30 (m, 1H), 1.58-1.89 (m, 11H), 2.05-2.30 (m, 6H), 7.32-7.51 (m, 3H, phenyl), 7.88-8.02 (m, 2H, phenyl), 9.20 (s, 1H, NH); ^{13}C NMR: δ 22.09, 22.82, 23.47, 23.88, 25.19, 26.55, 34.76, 61.46, 106.85, 125.77, 128.72, 128.95, 132.35, 150.12 (C-3a), 157.23 (C-2) ; MS: m/z 320 (M^+, 56), 291 (21), 277 (100), 264 (23), 217 (23), 174 (42), 160 (13). *Anal*. Calcd. for $C_{20}H_{24}N_4$: C, 74.97; H, 7.55; N, 17.48. Found: C, 75.14; H, 7.61; N, 17.26.

2'-(Morpholin-4-ylcarbonyl)-5',6',7',8'-tetrahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (**3d**). This compound was obtained in 58% yield as white crystals (ethanol), mp 186-188°; ^{1}H NMR: δ 1.13-1.29 (m, 1H), 1.49-1.88 (m, 11H), 1.95-2.08 (m, 6H), 3.56-3.69 (m, 8H, morpholine), 9.25 (s, 1H, NH); MS: m/z 357 (M^+, 16), 314 (21), 243 (100), 217 (92), 201 (43), 187 (41). *Anal*. Calcd. for $C_{19}H_{27}N_5O_2$: C, 63.84; H, 7.61; N, 19.59. Found: C, 63.79; H, 7.64; N, 19.72.

General Procedure for the preparation of 4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo-[5,1-*b*]quinazolines] 4a-d. To a stirred suspension of compound **3a-d** (4 mmol) in ethanol (10 mL) sodium borohydride (0.23 g, 6 mmol) was subsequently added in small portions at 50-60° within 20 minutes. After the addition was complete, the reaction mixture was evaporated to small volume and diluted with water (10 mL). The formed precipitate was collected by filtration, washed with water and recrystallized.

4a',5',6',7',8',8a'-Hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (**4a**)**.** This compound was obtained in 85% yield as white crystals (ethanol), mp 220-222°; ^{1}H NMR: δ 0.88 (m, 1H), 1.18-1.88 (m, 16H), 2.00-2.15 (m, 2H), 3.73 (br s, 1H, H-4a), 6.81 (br s, 1H, NH), 7.29 (s, 1H, H-2); ^{13}C NMR: δ 19.58, 20.70, 22.00, 22.21, 25.34, 25.60, 30.22, 32.05, 36.07, 37.63, 45.45 (C-4a), 59.86 (C-9), 148.41 (C-2), 153.15 (C-3a); MS: m/z 246 (M^+, 16), 217 (13), 203 (20), 191 (22), 162 (23), 137 (28), 123 (22), 97 (18), 85 (36), 41 (100). *Anal*. Calcd. for $C_{14}H_{22}N_4$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.21; H, 9.12; N, 22.49.

2'-Amino-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (**4b**)**.** This compound was obtained in 87% yield as white crystals (DMF-ethanol), mp 291-293°; ^{1}H NMR: δ 0.93-2.01 (m, 19H), 3.64 (br s, 1H, H-4a), 4.68 (br s, 2H, NH_2), 6.37 (br s, 1H, NH); ^{13}C NMR: δ 19.22, 20.36, 21.65, 21.95, 25.04, 25.33, 29.97, 31.64, 35.64, 36.67, 44.95 (C-4a), 58.33 (C-9), 151.84 (C-3a), 160.20 (C-2); MS: m/z 261 (M^+, 100), 232 (26), 218 (40), 206 (15), 190 (21), 176 (17), 162 (42), 99 (99). *Anal*. Calcd. for $C_{14}H_{23}N_5$: C, 64.34; H, 8.87; N, 26.79. Found: C, 64.00; H, 9.00; N, 27.01.

2'-Phenyl-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (**4c**)**.** This compound was obtained in 90% yield as white crystals (ethanol), mp 176-177°; ^{1}H NMR: δ 0.97-2.23 (m, 19H), 3.80 (br s, 1H, H-4a), 7.01 (br s, 1H, NH), 7.25-7.37 (m, 3H, phenyl), 7.87 (m, 2H, phenyl); ^{13}C NMR: δ 19.60, 20.75, 22.03, 22.24, 25.35, 25.60, 30.26, 32.08, 36.03, 37.58, 45.39 (C-4a), 60.18 (C-9), 125.69, 128.61, 128.80, 132.74, 154.02 (C-3a), 157.35 (C-2); MS: m/z 322 (M^+, 29), 161 (28), 146 (100), 104 (57), 91 (19), 81 (38), 77 (47), 41 (92). *Anal*. Calcd. for $C_{20}H_{26}N_4$: C, 74.50; H, 8.13; N, 17.37. Found: C, 74.69; H, 8.17; N, 17.14.

2'-(Morpholin-4-ylcarbonyl)-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (**4d**)**.** This compound was obtained in 84% yield as white crystals (ethanol), mp 198-199°; ^{1}H NMR: δ 0.89 (m, 1H), 1.29-2.11 (m, 18H), 3.57-3.78 (m, 9H, H-4a and morpholine), 7.09 (br s, 1H, NH); ^{13}C NMR: δ 19.54, 20.71, 21.92, 22.12, 25.25, 25.48, 30.06, 31.96, 35.87, 37.61, 42.50 (NCH_2), 45.39 (C-4a), 47.38 (NCH_2), 60.57 (C-9), 66.58 (OCH_2), 66.94 (OCH_2), 153.13 (C-3a), 161.49 (C-2), 174.04 (C=O); MS: m/z 359 (M^+, 14), 246 (28), 203 (18), 191 (10), 81 (42), 41 (100). *Anal*. Calcd. for $C_{19}H_{29}N_5O_2$: C, 63.48; H, 8.13; N, 19.48. Found: C, 63.56; H, 8.18; N, 19.27.

4'-Benzyl-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (**5**)**.** Finely ground KOH (0.77 g, 13.75 mmol) was added to a solution of compound **4a** (1.70 g, 6.91 mmol) in DMSO (8.5 mL) and the resultant mixture was stirred at room temperature within 10 minutes. Then benzylchloride (1.14 g, 9.0 mmol) was added slowly and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then poured onto 40 mL of water. The formed precipitate was collected by filtration and recrystallized from ethanol to give 1.64 g (72%) of **5**, mp 155-157°; ^{1}H NMR: δ 0.90 (m, 1H), 1.21-1.79 (m, 15H), 2.08-2.23 (m, 3H), 3.47 (br s, 1H, H-4a), 4.23, 5.14 (2d, each 1H, CH_2 of benzyl, J = 15.8 Hz) 7.17-7.32 (m, 5H, phenyl), 7.45 (s, 1H, H-2); ^{13}C NMR: δ 19.65, 21.16, 21.62, 21.96, 25.26, 25.41, 27.43, 31.79, 37.11, 37.97, 47.98 (C-4a), 48.65 (CH_2 of benzyl), 59.49 (C-9), 127.62, 127.88, 128.90, 138.01, 148.52 (C-2), 154.98 (C-3a); *Anal*. Calcd. for $C_{21}H_{28}N_4$: C, 74.96; H, 8.39; N, 16.65. Found: C, 74.74; H, 8.42; N, 16.84.

3'-Benzyl-4a',5',6',7',8',8a'-hexahydro-3'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolinium] bromide (**6**)**.** A mixture of compound **4a** (0.5 g, 2.03 mmol), benzyl bromide (0.45 g, 2.64 mmol) and methanol (3 mL) was refluxed for 4 h and cooled to ambient temperature. After standing overnight the crystals that precipitated were collected by filtration and recrystallized from ethanol to give 0.7 g (82%) of **6**, mp 230-232; ^{1}H NMR: δ 0.69 (m, 1H), 1.21-1.79 (m, 14H), 1.93-2.11 (m, 3H), 2.33 (d, 1H, J = 12.9), 4.00 (br, 1H, H-4a), 5.20, 5.28 (2d, each 1H, CH_2 of benzyl, J = 15.8 Hz), 7.13-7.46 (m, 5H, phenyl), 8.60 (s, 1H, H-2), 9.07 (br s, 1H, NH); ^{13}C NMR: δ 19.41, 20.57, 21.56, 21.67, 24.86, 24.91, 28.88, 30.87, 34.77, 36.83, 46.60 (C-4a), 47.43 (CH_2 of benzyl), 62.94 (C-9), 128.16, 128.97, 129.45, 134.69, 140.01 (C-2), 146.26 (C-3a); *Anal*. Calcd. for $C_{21}H_{29}N_4Br$: C, 60.43; H, 7.00; N, 19.14. Found: C, 60.14; H, 7.22; N, 18.89.

3-(4a',5',6',7',8',8a'-Hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazolin]-4'-yl)propanoic acid (**10**)**.** Compound **4a** (0.5 g, 2.03 mmol) and methylacrylate (0.96 g, 11.03 mmol) were added to a solution of sodium (0.09 g, 3.91 mmol) in methanol (3 mL). The resulted mixture was refluxed

for 8 hours, then diluted with solution of NaOH (0.44 g, 11 mmol) in water (2 mL) and additionally refluxed for 30 minutes. The solution was cooled, diluted with water (30 mL) and extracted with chloroform (10 mL). The water layer was acidified by acetic acid. The resultant solid was collected by filtration, washed with water and crystallized from ethanol to give 0.5 g (77%) of **10**, mp 228-229°; ^{1}H NMR: δ 0.81-1.80 (m, 16H), 2.06-2.36 (m, 4H), 2.55 (m, 1H), 3.32 (m, 1H), 3.71 (br s, 1H, H-4a), 3.96 (m, 1H,) 7.39 (s, 1H, H-2), 12.25 (br s, 1H, OH); ^{13}C NMR: δ 19.17, 20.54, 21.31, 21.68, 24.87, 25.08, 27.16, 30.79 (C-2 of propanoic acid), 31.46, 36.94, 37.21, 40.14 (C-3 of propanoic acid), 47.38 (C-4a), 59.05 (C-9), 148.06 (C-2), 153.41 (C-3a), 173.16 (C=O); MS: m/z 318 (M^+, 40), 273 (12), 259 (18), 245 (22), 41 (100). *Anal*. Calcd. for $C_{17}H_{26}N_4O_2$: C, 64.13; H, 8.23; N, 17.60. Found: C, 64.22; H, 8.28; N, 17.77.

4'-Acetyl-2'-phenyl-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro-[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (11a). A mixture of compound **4c** (1 g, 3.10 mmol) and acetic anhydride (4 mL) was refluxed for 2 hours, diluted with 10 mL of water and cooled to room temperature. The precipitate that formed was collected by filtration and recrystallized from ethanol to give 1.02 g (90%) of **11a**, mp 143-144°; ^{1}H NMR: δ –0.11 (m, 1H), 0.85-0.96 (m, 1H), 1.13-1.24 (m, 1H), 1.38-1.83 (m, 12H), 2.00 (br, 1H), 2.20-2.29 (m, 1H), 2.48 (m, 4H, CH_3 and CH), 3.31 (br, 1H), 4.44 (br s, 1H, H-4a), 7.40-7.47 (m, 3H, phenyl), 7.96-7.98 (m, 2H, phenyl); ^{13}C NMR: δ 20.39, 21.86, 22.03, 22.08, 24.56, 24.90, 25.24, 28.49, 31.24, 34.00, 41.27, 51.22 (C-4a), 62.29 (C-9), 125.95, 129.14, 129.52, 131.42, 149.97 (C-3a), 157.87 (C-2), 170.30 (C=O); MS: m/z 364 (M^+, 1), 43 (100), 41 (19). *Anal*. Calcd. for $C_{22}H_{28}N_4O$: C, 72.50; H, 7.74; N, 15.37. Found: C, 72.71; H, 7.69; N, 15.21.

4'-(2-Furoyl)-2'-(morpholin-4-ylcarbonyl)-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]-quinazoline] (11b). A mixture of compound **4d** (1 g, 2.78 mmol), pyridine (2 mL) and furoyl chloride (0.55 g, 4.18 mmol) was refluxed for 15 minutes, diluted with 3 mL of ethanol and cooled to room temperature. The precipitate that formed was collected by filtration and recrystallized from ethanol to give 0.81 g (64%) of **11b**, mp 180-183°; ^{1}H NMR: δ 0.98-1.97 (m, 16H), 2.17 (m, 1H), 2.69 (m, 1H), 3.31 (br, 1H), 3.41-3.55 (m, 8H, morpholine), 4.39 (br s, 1H, H-4a), 6.68 (br, 1H, furan), 7.26 (m, 1H, furan), 7.87 (br, 1H, furan); *Anal*. Calcd. for $C_{24}H_{31}N_5O_4$: C, 63.56; H, 6.89; N, 15.44. Found: C, 63.51; H, 6.94; N, 15.19.

4'-(Phenylsulfonyl)-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro-[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (12a). Sodium hydride (0.2 g, 5 mmol, 60% dispersion in mineral oil) was added carefully to a solution of compound **4a** (0.5 g, 2.03 mmol) in dry dimethylformamide (3 mL). The mixture was magnetically stirred at 50-60 °C for 30 minutes and cooled to -5 °C. The solution of benzenesulfonyl chloride (0.708 g, 4.0 mmol) in dry dimethylformamide (2 mL) was added drop by drop within 5 minutes and resulted mixture was additionally stirred for 20 minutes then poured onto water (20 mL). The precipitate was collected by filtration, washed thoroughly with water, cold (0°) ethanol and crystallized from chloroform-ethanol (1:3) mixture to give 0.31 g (40%) of **12a**, mp 173-175°; ^{1}H NMR: δ –0.18 (m, 1H), 0.83-1.68 (m, 15H), 1.88 (br, 1H), 2.04 (m, 1H), 1.20 (m, 1H), 4.49 (br s, 1H, H-4a), 7.58-7.77 (m, 4H, 3H of phenyl and H-2), 8.06 (m, 2H, phenyl); MS: m/z 386 (M^+, 12), 322 (68), 295 (15), 279 (20), 245 (84), 240 (30), 225 (10), 141 (18), 77 (100), 41 (59). *Anal*. Calcd. for $C_{20}H_{26}N_4O_2S$: C, 62.15; H, 6.78; N, 14.50. Found: C, 62.21; H, 6.78; N, 14.73.

4'-[(4-Methylphenyl)sulfonyl]-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (12b). This compound was prepared analogously to compound **12a.** Yield 0.32 g (40%), mp 188-189°; ^{1}H NMR: δ –0.17 (m, 1H), 0.74 (q, 1H, J = 13.0), 1.09-1.69 (m, 13H), 1.90 (br, 1H), 2.05 (m, 1H), 2.38 (s, 3H, CH_3), 2.46 (m, 2H), 4.50 (br s, 1H, H-4a), 7.43 (d, 2H, J = 8.2, aromat.), 7.74 (s, 1H, H-2), 7.93 (d, 2H, J = 8.2, aromat.); ^{13}C NMR: δ 19.00, 20.82, 21.10, 21.27, 21.33, 23.92, 24.68, 29.23, 30.92, 34.09, 42.02, 53.66, 60.75 (C-9), 127.46, 129.70, 136.68, 144.41, 146.88 (C-3a), 148.61 (C-2); MS: m/z 400 (M^+, 2), 336 (57), 293 (15), 254 (22), 245 (35), 175 (19), 155 (38), 91 (100). *Anal*. Calcd. for $C_{21}H_{28}N_4O_2S$: C, 62.97; H, 7.05; N, 13.99. Found: C, 62.69; H, 6.98; N, 14.16.

2'-(Benzoylamino)-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro-[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]quinazoline] (13). A cold (0°) solution of benzoyl chloride (0.27 g, 1.9 mmol) dissolved in 1 mL of dry acetonitrile was added drop by drop to a magnetically stirred mixture of compound **4b** (0.5 g, 1.9 mmol), dry acetonitrile (2 mL) and pyridine (0.5 g, 6 mmol) at 0-5 °C. After the addition was complete, the solution was stirred for 30 minutes and then diluted with water (10 mL). The resultant solid was collected by filtration, washed with water and crystallized from ethanol to give 0.42 g (61%) of **13**, mp 142-144°; ^{1}H NMR: δ 1.00 (m, 1H), 1.27-2.07 (m, 18H), 3.78 (br s, 1H, H-4a), 6.90 (br s, 1H, NH), 7.44-7.55 (m, 3H, phenyl), 7.90 (m, 2H, phenyl), 10.27 (br s, 1H, CONH); MS: m/z 365 (M^+, 31), 322 (16), 310 (10), 204 (31), 189 (34), 105 (100), 77 (85). *Anal*. Calcd. for $C_{21}H_{27}N_5O$: C, 69.01; H, 7.45; N, 19.16. Found: C, 69.20; H, 7.58; N, 18.90.

4'-Benzoyl-2'-(*N*-benzoylbenzamido)-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]-quinazoline] (14). A mixture of compound **4b** (0.5 g, 1.9 mmol), pyridine (3 mL) and benzoyl chloride (0.93 g, 6.6 mmol) was refluxed for 1 hour then water (10 mL) was added. The resultant solid was collected by filtration and recrystallized from ethanol to give white crystals (0.71 g, 65%) of **14**, mp 189-190°; ^{1}H NMR: δ 0.16 (m, 1H), 0.88 (m, 1H), 1.23-1.94 (m, 14H), 2.42 (m, 2H), 2.62 (m, 1H), 4.45 (d, 1H, H-4a, J = 2.9 Hz), 7.33-7.57 (m, 15H, phenyl protons); ^{13}C NMR: δ 19.65, 21.01, 21.16, 21.50, 24.30, 24.55, 27.67, 30.90, 34.39, 39.09, 51.48 (C-4a), 62.11 (C-9), 128.1, 128.37, 128.64, 128.69, 131.60, 132.84, 133.33, 135.13, 149.50, 153.30 (C-2, C-3a), 169.58 (C=O), 171.06 (2C=O); MS: m/z 400 (M^+, 2), 336 (57), 293 (15), 254 (22), 245 (35), 175 (19), 155 (38), 91 (100). *Anal*. Calcd. for $C_{35}H_{35}N_5O_3$: C, 73.28; H, 6.15; N, 12.21. Found: C, 73.22; H, 6.08; N, 12.46.

2'-([(4-Methylphenyl)sulfonyl]amino)-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]-quinazoline] (15). A mixture of compound **4b** (0.5 g, 1.9 mmol), pyridine (3mL) and tosyl chloride (0.43 g, 2.28 mmol) was refluxed for 10 minutes, then water (10 mL) was added. The resultant solid was collected by filtration and recrystallized from DMF-ethanol mixture (1:3) to give white crystals (0.55 g, 70%) of **15**, mp 232-234°; ^{1}H NMR: δ 0.83 (m, 1H), 1.23-1.98 (m, 18H), 2.35 (s, 3H, CH_3), 3.66 (br s, 1H, H-4a), 6.86 (br s, 1H, NH), 7.33 (d, 2H, J = 8.2, aromat.), 7.74 (d, 2H, J = 8.2, aromat.), 10.45 (br s, 1H, SO_2NH); m/z 415 (M^+, 36), 306 (11), 260 (46), 254 (21), 245 (28), 239 (25), 218 (16), 107 (38), 91 (100). *Anal*. Calcd. for $C_{21}H_{29}N_5O_2S$: C, 60.70; H, 7.03; N, 16.85. Found: C, 60.95; H, 7.18; N, 16.53.

2'-(bis[(4-Methylphenyl)sulfonyl]amino)-4a',5',6',7',8',8a'-hexahydro-4'*H*-spiro[cyclohexane-1,9'-[1,2,4]triazolo[5,1-*b*]-quinazoline] (16). A mixture of compound **4b** (0.5 g, 1.9

mmol), pyridine (3mL) and tosyl chloride (0.9 g, 4.8 mmol) was refluxed for 1 hour, then water (10 mL) was added. The resultant solid was collected by filtration and recrystallized from DMF-ethanol mixture (1:3) to give white crystals (0.76 g, 70%) of **16**, mp 246-248°; ^{1}H NMR: δ 0.83 (m, 1H), 1.25-2.05 (m, 18H), 2.43 (s, 6H, 2CH_3), 3.80 (br s, 1H, H-4a), 7.31 (br s, 1H, NH), 7.44 (d, 4H, J = 8.2, aromat.), 7.84 (d, 4H, J = 8.2, aromat.); ^{13}C NMR: δ 19.09, 20.25, 21.20 (2CH_3), 21.46, 21.54, 24.83, 24.89, 29.56, 31.51, 36.15, 37.26, 44.73 (C-4a), 60.08 (C-9), 128.26, 129.53, 136.44, 145.15, 148.51 (C-2), 153.27 (C-3a); MS: m/z 569 (M^+, 2), 414 (20), 155 (25), 91 (100). *Anal.* Calcd. for $C_{28}H_{35}N_5O_4S_2$: C, 59.03; H, 6.19; N, 12.29. Found: C, 58.96; H, 6.08; N, 12.47.

X-ray diffraction study. The colorless crystals of **6** ($C_{21}H_{29}N_4Br$) are monoclinic. At 293 K a = 9.628(4), b = 9.605(2), c = 11.077(2) Å, β = 100.19(2)°, V = 1008.2(5) Å^3, M_r = 417.39, Z = 2, space group $P2_1$, d_{calc}= 1.375 g/cm^3, μ(MoK_α) = 2.051 mm^{-1}, F(000) = 436. Intensities of 8472 reflections (4611 independent, R_{int} = 0.021) were measured on the «Xcalibur-3» diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 60°). The structure was solved by direct method using SHELXTL package [38]. The absorption correction was carried out using multi-scan method (T_{min}=0.685, T_{max}=0.821). Position of the hydrogen atoms were located from electron density difference maps and refined in isotropic approximation. Absolute configuration of chiral centres was established based on Flack parameter 0.009(7). Full-matrix least-squares refinement against F^2 in anisotropic approximation using 4594 reflections was converged to wR_2 = 0.067 (R_1 = 0.031 for 3144 reflections with F>4σ(F), S = 0.860. The final atomic coordinates, and crystallographic data for molecule **6** have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC).

The colorless crystals of **11b** ($C_{24}H_{31}N_5O_4$) are monoclinic. At 293 K a = 7.585(1), b = 31.462(1), c = 9.803(2) Å, β = 91.98(1)°, V = 2338(1) Å^3, M_r = 453.57, Z = 4, space group $P2_1/n$, d_{calc}= 1.289 g/cm^3, μ(MoK_α) = 0.090 mm^{-1}, F(000) = 968. Intensities of 13830 reflections (5317 independent, R_{int} =0.039) were measured on the «Xcalibur-3» diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, 2Θmax = 55°). The structure was solved by direct method using SHELXTL package [38]. Position of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with U_{iso} = 1.2U_{eq} of carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation using 5278 reflections was converged to wR_2 = 0.097 (R_1 = 0.042 for 2420 reflections with F>4σ(F), S = 0.785. The final atomic coordinates, and crystallographic data for molecule **11b** have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC).

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