An Efficient Multicomponent and Stereoselective Synthesis of New Spiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine] Derivatives

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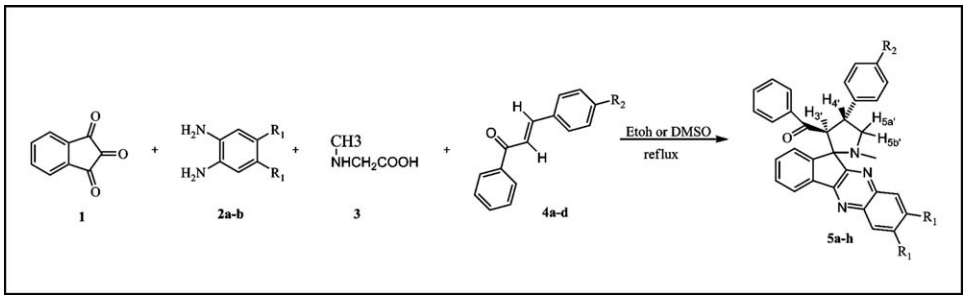

New spiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine] derivatives were prepared in high yield stereoselectively from an efficient multicomponent 1,3-dipolar cycloaddition reaction between ninhydrin, phenylenediamine, sarcosine, and chalcones. The regiochemistry and stereochemistry of resultant cycloadducts have been determined by several 2D NMR spectroscopic techniques and X-ray single crystal diffraction.

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INTRODUCTION

The pyrrolidine ring is an important part of many natural products [1]. Highly substituted pyrrolidine have been extremely attended, because those are the structural units in many of pharmacologically active compounds and alkaloids like hygrine, nicotine, tropine, and cocaine [2]. Recently, some new pyrrolidine based compounds have also been introduced as novel drugs with promising anti-HIV and antibacterial activities [3].

Systematic investigation also shows that quinoxalines are one of the important classes of benzo fused heterocycles used as intermediate in organic synthesis, the other applications of this important motif includes dying, synthesis of pharmaceuticals and organic semiconductors [4,5]. It is expected that generating a quinoxaline moiety at C-2′ position of the pyrrolidine ring as a spiro linkage might result in significant enhancement in the biological and pharmacological activities of the obtained product.

In recent years, there has been increasing interest in multicomponent intermolecular 1,3-dipolar cycloaddition reactions, because of their ability to generate different molecular structures with a minimum number of states [6–8]. One of the most important target molecules are pyrrolidine based structures, which are produced by the reaction of azomethine ylides with olefins [9,10].

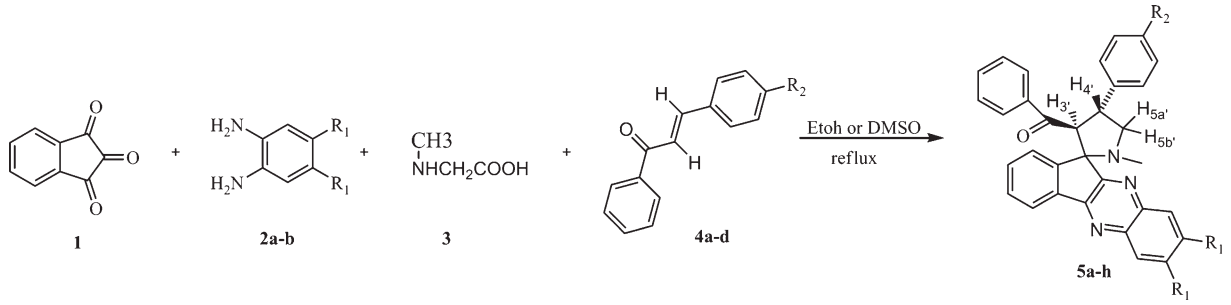
Since little attention has been given to the preparation of spiro pyrrolidine of Quinoxaline and due to the above reasons and as a part of our ongoing research program on the synthesis of various spiro heterocycles [11–15], we herein report, a facile method for the synthesis of a novel class of spiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine] (**5a-h**) via a one pot four component 1,3-dipolar cycloadition reaction (scheme 1).

RESULT AND DISCUSSION

The multicomponent reaction was carried out between ninhydrin **1**, phenylenediamine **2**, sarcosine **3,** and chalcone **4** under reflux condition in DMSO and EtOH as solvent. As indicated in Table 1, all the reactions were completed in about 2 h in DMSO and about 5 h in EtOH. Although the reactions in DMSO are faster, ethanol gives them the remarkable advantage of the products precipitation in which the products simply can be separated by filtration from the reaction mixture. Using some other solvents or carrying out the reaction under microwave irradiation conditions did not improve the yield and no product formation was observed under ultrasonic condition.

As can be seen on Scheme 2, compound **6** was generated initially by reaction of ninhydrin **1** with 1,2-

Scheme 1



phenylenediamine **2** and then the intermediate **7** was obtained as a result of the reaction between sarcosine **3** and indenoquinoxaline-11-one **6**. Compound **7** underwent decarboxylation to afford azomethine ylide **8**. The alkyl spiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine] **5** derived in high yield from addition of chalcone dipolarophile **4** to azomethine ylide **8** through a [3 + 2] cycloaddition reaction.

Interestingly, the cycloaddition reaction of the The Alkyl spiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine] **5** with different substituted chalcones yields only one isomer that their exact region and stereochemistry were assigned herein using ^{1}H and ^{13}C and several 2D NMR spectroscopic techniques. For example, the ^{1}H NMR spectrum of **5a** exhibits two triplet signal at δ 3.71 and δ 3.99 ppm, a multiplet at δ 4.78 and a doublet at δ 4.96 ppm, which are related to $H_{5'a}$, $H_{5'b}$, $H_{4'}$, and $H_{3'}$ protons, respectively. The ^{13}C NMR spectrum displays 27 signals, which are classified into 1 methyl, 1 methylene, 16 methines, and 9 quaternary carbons including to a spiro carbon by DEPT 135 experiments. Also on the basis of HMQC spectrum, correlations between aliphatic carbons and corresponding hydrogens were determined.

The proton spectrum displays two signals at δ 4.78 and δ 4.96 ppm ($H_{4'}$, $H_{3'}$, respectively) and the absence of any correlation between them in the ROESY spectrum shows that the $H_{4'}$ hydrogen could be trans to $H_{3'}$. This is also confirmed from the weak NOE between them. To determine the exact regioselectivity, the connectivity of the carbons in the molecular structure was elucidated by analysis of the HMBC spectra. Based on the HMBC spectrum, there is no correlation between H_5, $H_{5'}$ protons and the signal of carbonyl group, which confirms presence of the carbonyl group at C-3′ position (instead of C-4′ in **9a**). The stereochemical structure of **5a** is shown in Scheme 2. Using the above mentioned 2D NMR spectroscopic techniques for the other products **5b-5h** showed the same regioselectivity and stereoselectivity around pyrrolidine ring as in case of **5a**.

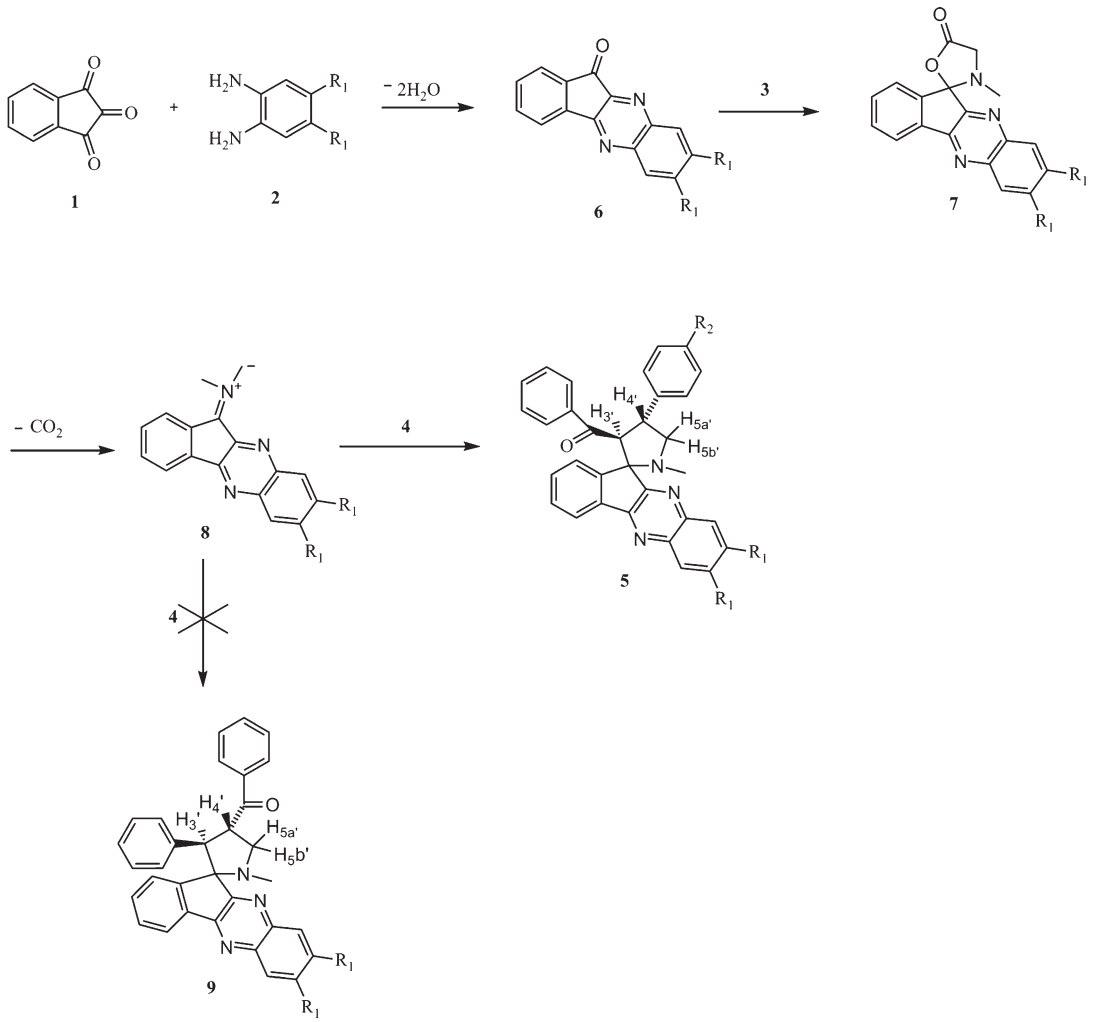
We also were able to obtain suitable crystals of the **5e** for crystallography to confirm the assigned stereochemistry of products **5**. The ORTEP view of single crystal X-ray analysis of **5e** with atomic numbering is shown in Figure 1. Regioisomer **5** (No. **9** in Scheme 2) with a trans stereochemistry between $H_{4'}$ and $H_{3'}$ protons, as suggested by NMR spectroscopy, has been confirmed by the X-ray structure. In addition, X-ray diffraction measurements showed that the configuration of the five-membered ring is envelope with the nitrogen atom being out of plane from the rest of the ring atoms and the *N*-methyl occupying the axial position. Also, the X-ray structure of the molecule reveals that $H_{3'}$ proton and the pyrazine ring of quinoxaline moiety at spiro carbon are cis to each other in pyrrolidine ring.

Table 1

Synthesis of spiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine] **5a–h**.

			EtOH (solvent)		DMSO(solvent)	
Product **5**	R_1	R_2	Time(h)	Yield(%)	Time(h)	Yield(%)
a	H	H	5	89	2	86
b	H	Me	5	93	2	90
c	H	Cl	5	87	2	86
d	H	OMe	5	84	2	85
e	Me	H	5	88	2	83
f	Me	Me	5	91	2	90
g	Me	Cl	5	86	2	84
h	Me	OMe	5	84	2	82

Scheme 2



EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on FT-IR 102MB BOMEM apparatus. ^{1}H and ^{13}C, DEPT 135, ROSEY, HMQC, and HMBC spectra were determined on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of (1′-methyl-4′-phenylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)(phenyl)-methanone under refluxing of ethanol (5a). A mixture of ninhydrin **1a** (0.178 g, 1 mmol) and 1,2-phenylenediamine **2a** (0.108 g, 1 mmol) was stirred for 10 min in ethanol (10 mL). To this solution was added sarcosine **3** (0.089 g, 1 mmol) and chalcone **4a** (0.208 g, 1 mmol) and was heated under reflux for about 5 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate was washed with 3 mL cold ethanol (70%) to afford pure **5a** in 89% yield.

Typical procedure for the preparation of (1′-methyl-4′-phenylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)(phenyl)methanone under refluxing of DMSO (5a). A mixture of ninhydrin **1a** (0.178 g, 1 mmol) and 1,2-phenylenediamine **2a** (0.108 g, 1 mmol) was stirred for 10 min in DMSO (10 mL). To this solution was added sarcosine **3** (0.089 g, 1 mmol) and chalcone **4a** (0.208 g, 1 mmol) and was heated under reflux for about 2 h (the progress of the reaction was monitored by TLC). After completion, the solution was cooled, then water was added to the mixture and the separated solid was filtered off and recrystallized in methanol to give pure **5a** in 86% yield.

(1′-Methyl-4′-phenylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)(phenyl)methanone (5a) Yellow crystals; m.p. 207–209°C; ir (KBr) (ν_{max}/cm^{-1}): CO 1690. ^{1}H NMR (CDCl3) δ_H: 1.98 (s, 3H, N—CH3), 3.71 (t, 1H, J = 8.5, H-5′$_a$), 3.99 (t, 1H, J = 9.0, H-5′$_b$), 4.73–4.82 (m, 1H, H-4′), 4.96 (d, 1H, J = 9.4, H-3′), 6.71–8.34 (m, 18H, ArH); ^{13}C NMR (CDCl3) δ_C: 34.9 (N—CH3), 44.2 (C-4′), 61.7 (C-5′), 63.9 (C-3′), 74.8 (spiro carbon), 121.5–163.6 (21 signals arom), 197.9 (CO); m/z: 467. Anal. Calcd for C32H25N3O: C, 82.20; H, 5.39; N, 8.99. Found: C, 82.1; H, 5.3; N, 8.9.

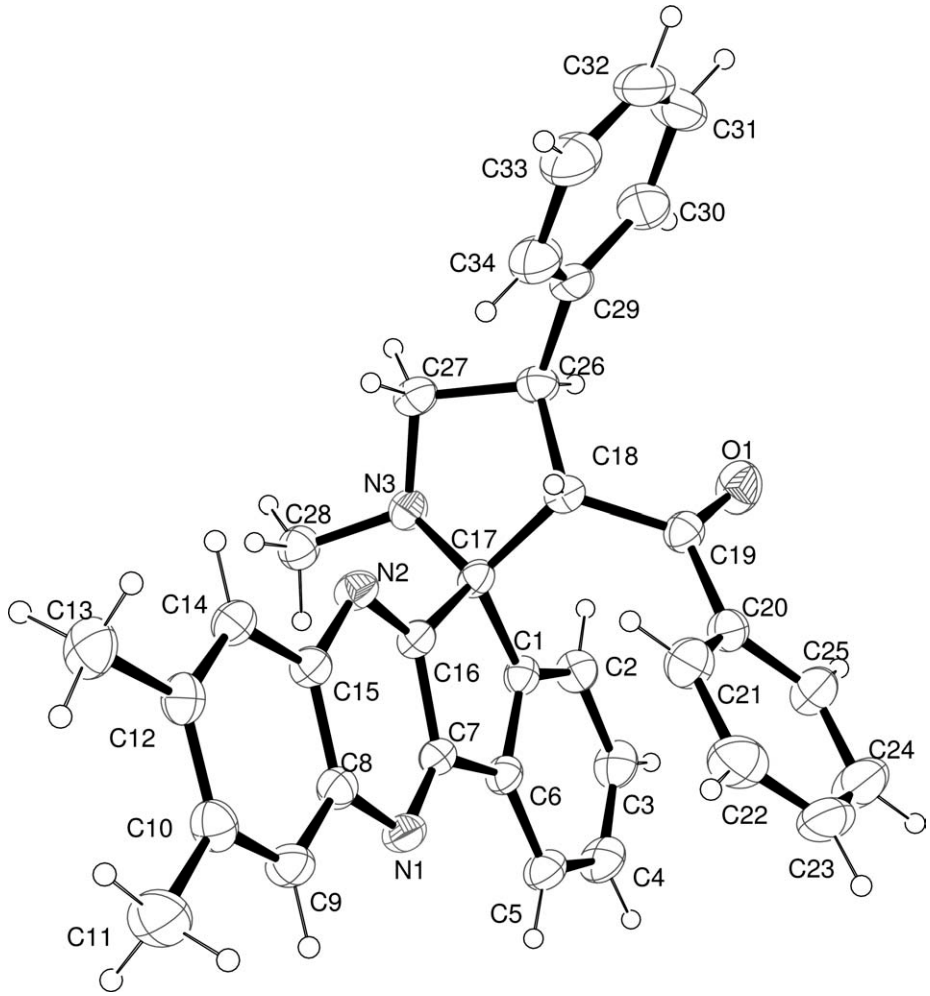


Figure 1. Crystal structure and atom numbering of **5e**.

(1′-Methyl-4′-p-tolylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)(phenyl)methanone (5b) Yellow crystals; m.p. 167–169°C; ir (KBr) (ν_{max}/cm^{-1}):CO 1691. ^{1}H NMR (CDCl3) δ_H: 1.98 (s, 3H, N—CH3), 2.35 (s, 3H, CH3), 3.70 (t, 1H, J = 8.2, H-5′$_a$), 3.98 (t, 1H, J = 8.9, H-5′$_b$), 4.72–4.80 (m, 1H, H-4′), 4.95 (d, 1H, J = 9.4, H-3′), 6.68–8.36 (m, 17H,ArH); ^{13}C NMR (CDCl3) δ_C: 21.1 (CH3), 34.9 (N—CH3), 43.8 (C-4′), 61.7 (C-5′), 64.0 (C-3′), 74.8 (spiro carbon), 121.4–163.5 (21 signals arom), 198.0 (CO); m/z: 481. Anal. Calcd for C33H27N3O; C, 82.30; H, 5.65; N, 8.73; O, 3.32. Found: C, 82.3; H, 5.6; N, 8.7.

(4′-(4-Chlorophenyl)-1′-methylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)(phenyl)methanone (5c) Yellow crystals; m.p. 179–181°C; ir (KBr) (ν_{max}/cm^{-1}):CO 1698. ^{1}H NMR (CDCl3) δ_H: 1.97 (s, 3H, N—CH3), 3.66 (t, 1H, J = 8, H-5′$_a$), 3.94 (t, 1H, J = 9, H-5′$_b$), 4.71–4.79 (m, 1H, H-4′), 4.88 (d, 1H, J = 9.3, H-3′), 6.72–8.32 (m, 17H, Ar—H); ^{13}C NMR (CDCl3) δ_C: 34.8 (N—CH3), 43.5 (C-4′), 61.5 (C-5′), 64.0 (C-3′), 74.7 (spiro carbon), 121.5–163.4 (21 signals arom), 197.8 (CO); m/z: 501. Anal. Calcd for C32H24ClN3O; C, 76.56; H, 4.82; N, 8.37. Found: C, 76.6; H, 4.8; N, 8.4.

(4′-(4-Methoxyphenyl)-1′-methylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)(phenyl)methanone (5d) Yellow crystals; m.p. 153–155°C; ir (KBr) (ν_{max}/cm^{-1}):CO 1696. ^{1}H NMR (CDCl3) δ_H: 1.97 (s, 3H, N—CH3), 3.68 (t, 1H, J = 8.1, H-5′$_a$), 3.81 (s, 3H, O—CH3), 3.96 (t, 1H, J = 9, H-5′$_b$), 4.69–4.78 (m, 1H, H-4′), 4.92 (d, 1H, J = 9.5, H-3′), 6.69–8.34 (m, 17H, Ar—H); ^{13}C NMR (CDCl3) δ_C: 34.9 (N—CH3), 43.5 (C-4′), 55.3 (O-CH3), 61.7 (C-5′), 64.1 (C-3′), 74.8 (spiro carbon), 114.1–163.6 (21 signals arom), 198.1 (CO); m/z: 497. Anal. Calcd for C33H27N3O2; C, 79.66; H, 5.47; N, 8.44; O, 6.43. Found: C, 79.6; H, 5.5; N, 8.4.

Phenyl(1′,7,8-trimethyl-4′-phenylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)methanone (5e) Light yellow crystals; m.p. 244–246°C; ir (KBr) (ν_{max}/cm^{-1}): CO 1688. ^{1}H NMR (CDCl3) δ_H: 1.98 (s, 3H, N—CH3), 2.55 (s, 3H, CH3), 2.60 (s, 3H, CH3), 3.66 (t, 1H, J = 8.4, H-5′$_a$), 3.95 (t, 1H, J = 8.8, H-5′$_b$), 4.73–4.81 (m, 1H, H-4′), 4.96 (d, 1H, J = 9.4, H-3′), 6.73–8.31 (m, 16H, Ar—H); ^{13}C NMR (CDCl3) δ_C: 20.3 (CH3), 20.4 (CH3), 34.8 (N—CH3), 43.9 (C-4′), 61.6 (C-5′), 63.9 (C-3′), 74.7 (spiro carbon), 121.3–153.1 (18 signals arom), 198.0 (CO); m/z: 495. Anal. Calcd for C34H29N3O; C, 82.40; H, 5.90; N, 8.48. Found: C, 82.5; H, 5.9; N, 8.5.

Phenyl(1′,7,8-trimethyl-4′-p-tolylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)methanone (5f) Light yellow crystals; m.p. 136–138°C; ir (KBr) (ν_{max}/cm^{-1}): CO 1694. ^{1}H NMR (CDCl3) δ_H: 1.97 (s, 3H, N—CH3), 2.36 (s, 3H, CH3),

2.56 (s, 3H,CH3), 2.60 (s, 3H, CH3), 3.69 (t, 1H, J = 8.1, H-5′$_a$), 3.96 (t, 1H, J = 8.2, H-5′$_b$), 4.70–4.78 (m, 1H, H-4′), 4.93 (d, 1H, J = 9.4, H-3′), 6.70–8.11 (m, 15H, Ar—H); ^{13}C NMR (CDCl3) δ_C: 20.3 (CH3), 20.4 (CH3), 21.1 (CH3) 34.9 (N—CH3), 43.8 (C-4′), 61.7 (C-5′), 63.9 (C-3′), 74.7 (spiro carbon), 121.1–152.9 (18 signals arom), 198.1 (CO); m/z: 509. Anal. Calcd for C35H31N3O; C, 82.48; H, 6.13; N, 8.25. Found: C, 82.5; H, 6.2; N, 8.3.

(4′-(4-Chlorophenyl)-1′,7,8-trimethylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)(phenyl)methanone (5g) Light yellow crystals; m.p. 208–210°C; ir (KBr) (ν_{max}/cm^{-1}): CO 1708. ^{1}H NMR (CDCl3) δ_H: 1.96 (s, 3H, N—CH3), 2.56 (s, 3H, CH3), 2.60 (s, 3H, CH3), 3.68 (t, 1H, J = 8.3, H-5′$_a$), 3.93 (t, 1H, J = 8.7, H-5′$_b$), 4.69–4.76 (m, 1H, H-4′), 4.86 (d, 1H, J = 9.3, H-3′), 6.71–8.09 (m, 15H, Ar—H); ^{13}C NMR (CDCl3) δ_C: 20.3 (CH3), 20.4 (CH3), 34.8 (N—CH3), 43.6 (C-4′), 61.4 (C-5′), 63.9 (C-3′), 74.6 (spiro carbon), 121.1–152.9 (18 signals arom), 198.0 (CO); m/z: 529. Anal. Calcd for C34H28ClN3O; C, 77.04; H, 5.32; N, 7.93. Found: C, 76.9; H, 5.3; N, 7.9.

(4′-(4-Methoxyphenyl)-1′,7,8-trimethylspiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidine]-3′-yl)(phenyl)methanone (5h) Light yellow crystals; m.p. 194–196°C; ir (KBr) (ν_{max}/cm^{-1}): CO 1699. ^{1}H NMR (CDCl3) δ_H: 1.94 (s, 3H, N—CH3), 2.54 (s, 3H, CH3), 2.58 (s, 3H, CH3), 3.66 (t, 1H, J = 8, H-5′$_a$), 3.78 (s, 1H, O—CH3), 3.92 (t, 1H, J = 8.6, H-5′$_b$), 4.67–4.75 (m, 1H, H-4′), 4.87 (d, 1H, J = 9.1, H-3′), 6.71–8.10 (m, 15H, Ar—H); ^{13}C NMR (CDCl3) δ_C: 20.3 (CH3), 20.3 (CH3), 34.8 (N—CH3), 43.5 (C-4′), 55.3 (O-CH3), 61.7 (C-5′), 63.9 (C-3′), 74.6 (spiro carbon), 114.0–162.6 (19 signals arom), 198.1 (CO); m/z: 525. Anal. Calcd for C, 79.97; H, 5.94; N, 7.99. Found: C, 80.1; H, 6.1; N, 8.1.

The X-ray data of compound 5e Light yellow crystals of compound **5e** were obtained by slow evaporation from *n* hexane: ethanol (1:4). $C_{34}H_{29}N_3O_1$, M = 495.60 g/mol, Triclinic system, space group Pi, a = 9.208(2), b = 11.279(3), c = 14.161(4) Å, α = 108.043(19)°, β = 101.497(19)°, γ = 101.685(18)°, V = 1314.0 (5) Å^3, Z = 2, Dc = 1.253 g cm^{-3}, μ(Mo-Kα) = 0.076 mm^{-1}, crystal dimention of 0.23 × 0.18 × 0.10 mm.The structure was solved by using SHELXS [16]. The structure refinement and data reduction was carried out with SHELXL of the X-Step32 suite of programs [17]. The nonhydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1 = 0.0988, wR_2 = 0.2210, and S = 1.244 with 344 parameters using 7058 independent reflection (θ range = 1.98 – 29.24°). Hydrogen atoms were located from expected geometry and were not refined.

Crystallographic data for **5e** has been deposited with the Cambridge Crystallographic Data Center. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 789415, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or deposit@ccdc.cam.ac.uk.

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REFERENCES AND NOTES

[1] Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. Tetrahedron 1997, 53, 12789.

[2] O'Hagan, D. Nat Prod Rep 2000, 17, 435, and previous annual reports in this series.

[3] Suresh Babu, A. R.; Dhamodharan, V.; Raghunathan, R. Synth Commun 2009, 39, 2889.

[4] Gazit, A.; App, H.; McMohan, G.; Chen, J.; Levitzki, A.; Bohmer, E. D. J Med Chem 1996, 39, 2170.

[5] Sehlstedt, U.; Aich, P.; Bergman, J.; Vallberg, H.; Nordon, B.; Graslund, A. J Mol Biol 1998, 278, 31.

[6] Ramon, D. J.; Yus, M. Angew Chem Int Ed 2005, 44, 1602.

[7] Strubing, D.; Neumann, H.; Hubner, S.; Klaus, S.; Beller, M. Tetrahedron Lett 2005, 61, 11345.

[8] Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. Org Lett 2005, 7, 2297.

[9] Tsuge, O.; Kanemasa, S. Advances in Heterocyclic Chemistry; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 45, pp 232.

[10] Lown, J. W. 1,3-Dipolar Cycloaddition Chemistry; Padwa, A., Ed.; Wiley: New York, 1984; Vol.1, pp 653.

[11] Jadidi, K.; Ghahremanzadeh, R.; Mehrdad, M.; Ghanbari, M.; Arvinnezhad, H. Monatsh Chem 2008, 139, 277.

[12] Jadidi, K.; Ghahremanzadeh, R.; Mehrdad, M.; Darabi, H. R.; Khavasi, H. R.; Asgari, D.; Eslami, P.; Arvinnezhad, H. Ultrason Sonochem 2008, 15, 124.

[13] Jadidi, K.; Moghaddam, M. M.; Aghapoor, K.; Ghahremanzadeh, R. J Chem Res (S) 2007, 79.

[14] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. Tetrahedron 2009, 65, 2005.

[15] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. J Comb Chem 2009, 11, 341.

[16] Sheldrick, G. M. SHELXS97. University of Gottingen, Germany, 1997.

[17] Stoe and Cie, X-STEP32. Version 1.07e. Stoe and Cie, Darmstadt, Germany, 2000.