A Remarkable One-Pot Sequential Four-Component Synthesis of Tetrahydroquinazolines via an Isocyanide-Based Multicomponent Reaction

Ahmad Shaabani,*[a] Mojtaba Mahyari,[a] Morteza Aghaei,[a] Sajjad Keshipour,[a] Seik Weng Ng[b]

[a] Faculty of Chemistry, Shahid Beheshti University, G. C., P. O. Box 19396-4716, Tehran, Iran
Fax +98(21)29903247 ; E-mail: a-shaabani@sbu.ac.ir

[b] Department of Chemistry, University of Malaya, 50603, Kuala Lumpur, Malaysia

Received: 16.04.2013; Accepted after revision: 21.06.2013

Abstract: A novel one-pot sequential four-component strategy has been developed for the synthesis of tetrahydroquinazolines using either an aliphatic or an acyl halide, an isocyanide, and a 1,3-diamine, in methanol at 60 °C, in good to moderate yields without using a catalyst.

Key words: quinazoline, multicomponent, isocyanide

Quinazolines with regard to their pharmacophore properties have attracted great attention in medicinal chemistry.[1–4] These compounds possess diverse biological activities including anticancer and antihyperglycaemic, anticonvulsant, antibacterial, and antidiabetic activity.[5–11] In particular, quinazolines with the structure **A** are privileged scaffolds.[12–14] 2-Styrylquinazolin-4-one (SQZ),[1,15] 2,3-dihydro-2-aryl-4-quinazolinones (DHPQZ), 2,3- and 6-chloro-2-(3-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one[16] B demonstrate potent inhibition of tubulin polymerization and antitumor activities, respectively (Figure 1). Thus, the development of efficient protocols to prepare quinazoline derivatives continues to be of importance.[17–19]

Multicomponent reactions (MCR) offer the advantage of atom-economy by gathering different parts of the starting materials into the final product.[20] MCR are effective tools in the modern drug-discovery processes and are amenable to fast, automated, and high-throughput preparation of organic compounds.[21] The pharmaceutical industry has increasingly focused on diversity-oriented and biased combinatorial libraries.[22] Finally, the development of novel MCR can be considered as an interesting topic for academic research that also satisfies a practical interest of applied science.[23–26]

As part of our current studies on the synthesis of benzodiazepines[27–29] and the chemistry of isocyanides,[30–32] a novel approach to the synthesis of benzodiazepine derivatives **5** via a one-pot sequential isocyanide-based multicomponent condensation reaction of an acyl chloride **1**, an isocyanide **2**, and a 1,3-diamine **3** was designed. However, analysis of the spectroscopic data led us to conclude that the desired products **5a** or **5b** were not obtained; instead the reaction proceeded via an unexpected route yielding a new class of tetrahydroquinazoline-2-carboxamide derivatives **4** (Scheme 1).

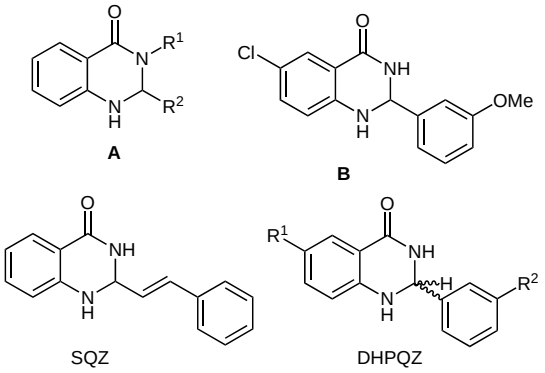


Figure 1 Some biologically active quinazoline derivatives

In a trial experiment, cyclohexyl isocyanide and benzoyl chloride were heated under solvent-free conditions at 60 °C for two hours, followed by addition of 2-aminobenzamide or 2-aminobenzylamine in MeOH as a solvent at 60 °C for 24 hours led to the formation of the tetrahydroquinazoline-2-carboxamide derivatives **4a** or **4g** in good yields, respectively.

In light of this success, we explored the reaction scope by varying the structure of acyl halides **1**, isocyanides **2**, and 1,3-diamines **3**. As indicated in Figure 2, the reactions proceed efficiently and produced compounds **4a**–**i** in fairly good yields. Owing to the great diversity of substitution patterns, this reaction may be used for the production of combinatorial libraries.

The structures of compounds **4a**–**i**[41] were deduced from their elemental analysis, mass, IR, ^{1}H NMR, and ^{13}C NMR spectral data. For example, the ^{1}H NMR spectrum of **4b** exhibited a multiplet for the cyclohexyl ring at δ = 1.14–1.60 ppm, a broad singlet at δ = 3.50 ppm for the cyclohexyl CHNH, two broad singlets for the NH protons at δ = 6.70 and 6.93 ppm, a multiplet at δ = 7.28–7.79 ppm for H aromatic and a singlet at δ = 8.53 ppm for the CONH proton. The ^{1}H-decoupled ^{13}C NMR spectrum of **4b** showed 21 distinct resonances in agreement with the proposed structure.

Finally, the structure of **4b** was confirmed unambiguously by single-crystal X-ray analysis (Figure 3).

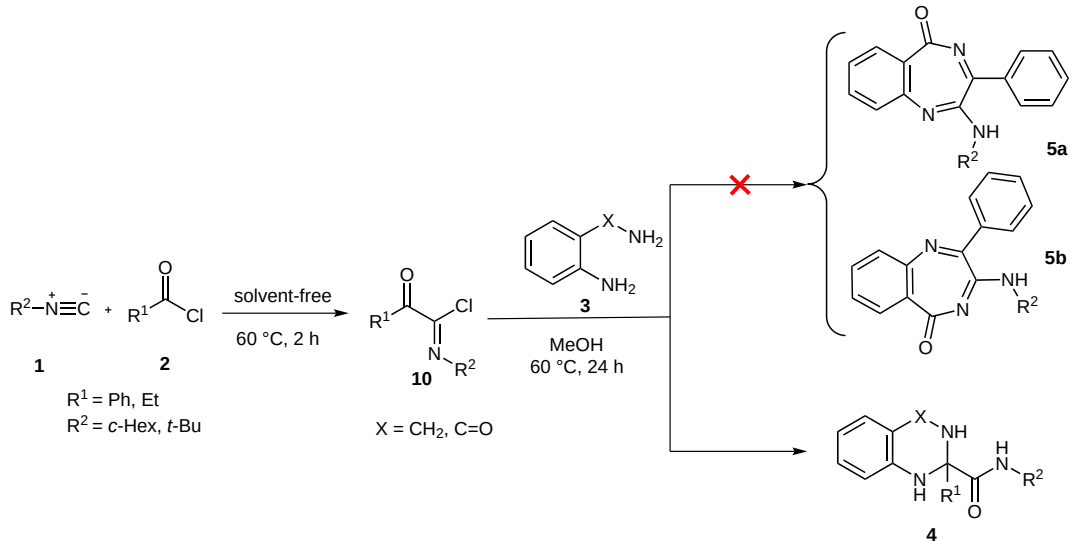
SYNLETT 2013, 24, 1968–1972
Advanced online publication: 07.08.2013
DOI: 10.1055/s-0033-1339465; Art ID: ST-2013-D0346-L

In all cases, although the reaction gave the desired product in 54–70% yields, cyclohexylammonium chloride was also obtained in about 10% yield.

The versatility of this reaction with respect to the linear ethylenediamine (**6**) and *o*-phenylenediamine (**7**) was also studied. As indicated in Scheme 2, a one-pot condensation reaction of 4-bromobenzoyl chloride, or cyclohexyl isocyanide with ethylenediamine (**6**), or *o*-phenylenediamine (**7**), did not give the expected multicomponent condensation product **10**; instead the reactions afforded the corresponding (2*E*,2′*E*)-2,2′-[ethane-1,2-diylbis(azan-1-yl-1-ylidene)]bis[2-(4-bromophenyl)-*N*-cyclohexylacetamide] (**8**) and (2*E*,2′*E*)-2,2′-]1,2-phenylenebis(azan-1-yl-1-ylidene)]bis[2-(4-bromophenyl)-*N*-cyclohexylacetamide] (**9**), respectively.

It is worth noting that these products are similar to Schiff base[17] and bridging ligands.[18] These bridging ligands could complex with metals and encourage the formation of dendritic structures or linear arrays. Recently, due to the interesting bulk properties of these compounds such as electrical conductivity and light harvesting, synthesis of these compounds are of interest.[19]

Although no detailed mechanistic studies have been carried out at this point, it is conceivable that the initial event is the formation of *N*-cyclohexyl-2-oxo-2-phenylacetimidoyl chloride (**11**) from Nef reaction between acyl chloride **1** and isocyanide **2**.[33–37]As with previous reports,[35,38] we wished to obtain benzodiazepine derivatives **5** from reaction between intermediate **11** and diamine **3** through pathway A. However, the experimental results show that



Scheme 1 Designed reaction for the synthesis of benzodiazepine derivatives vs. the unexpected pathway toward the quinazoline compounds

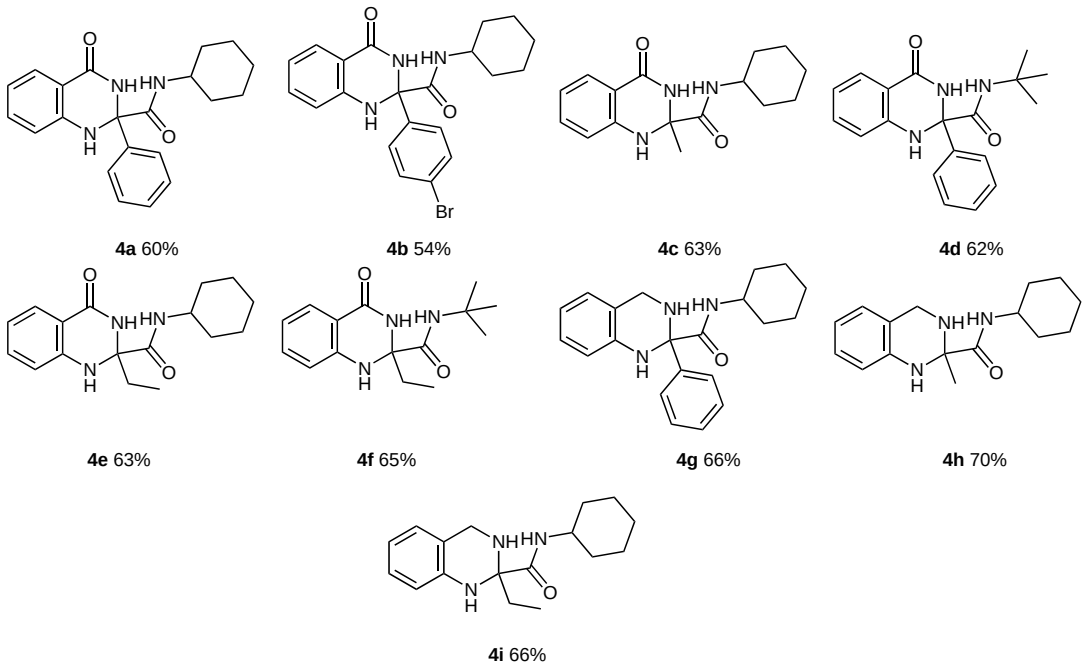
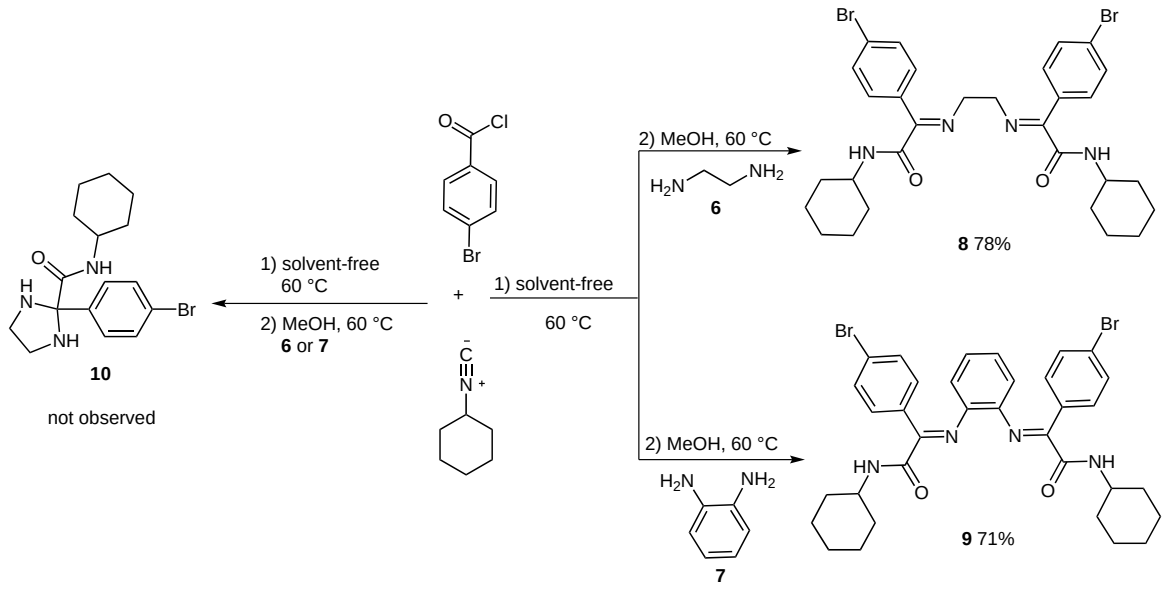


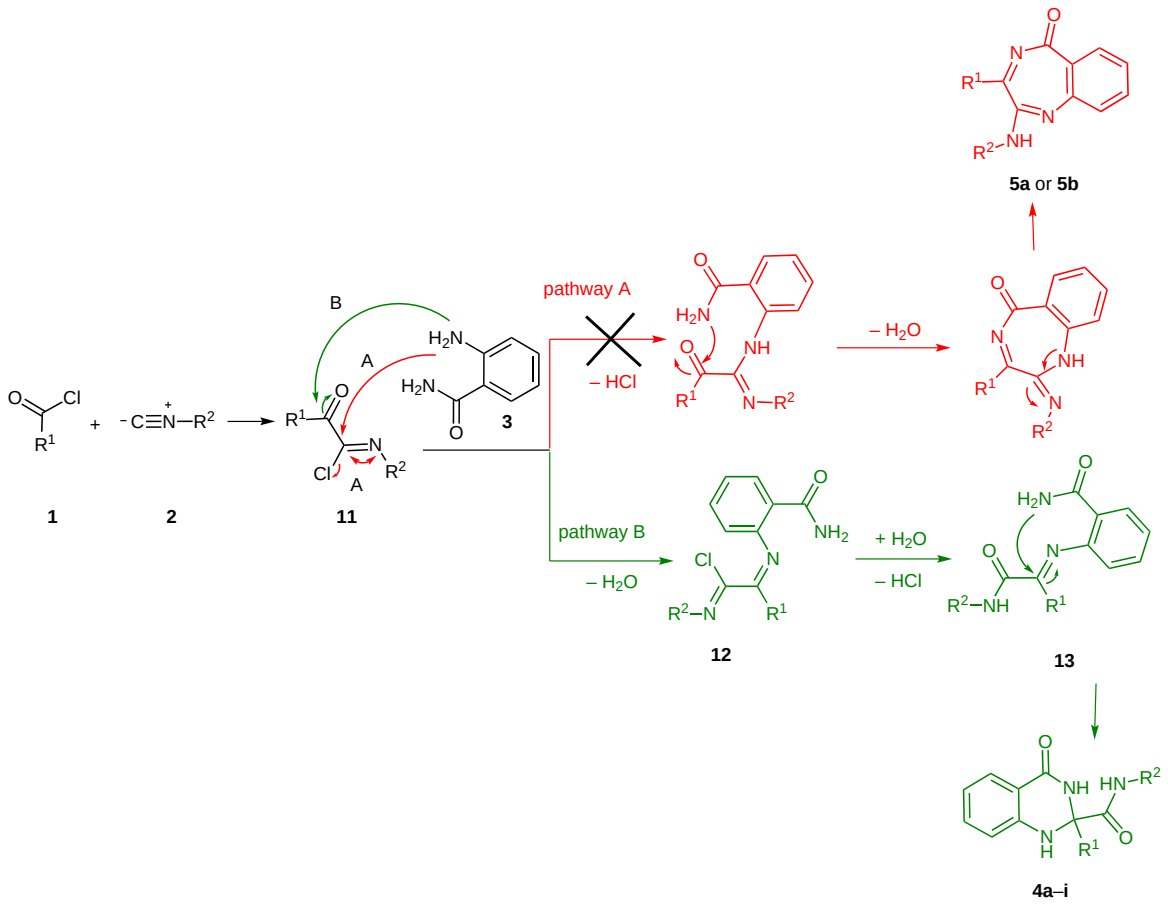
Figure 2 The structures of products **4a–i**



Scheme 2 Use of ethylenediamine and *o*-phenylenediamine instead of 1,3-diamines

the reaction proceeds via an unexpected pathway B yielding tetrahydroquinazoline-2-carboxamide derivatives **4** (Scheme 3).

Cyclohexyl ammonium chloride as a byproduct is probably obtained from acidic hydrolysis of the isocyanide with HCl generated in the reaction[39,40] and cyclization of the diamine on the imidoyl moiety or on the carboxamide (after hydrolysis of the imidoyl chloride). It is important to note that gas chromatographic analysis of the crude reaction mixture identified the formation of formic acid as a by-product, which supports the former proposed mechanism.



Scheme 3

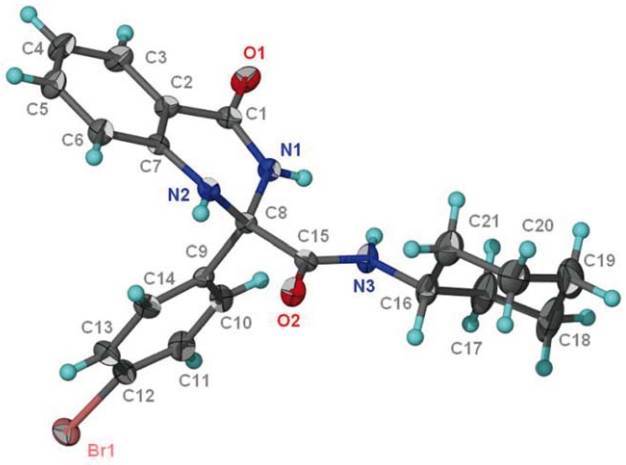


Figure 3 ORTEP diagram of product **4b**

In summary, we have developed a novel one-pot sequential four-component condensation reaction leading to a new class of tetrahydroquinazoline-2-carboxamide and 2-oxo-acetimidamide compounds starting from simple and readily available materials under mild reaction conditions without using any catalyst. The reactions show functional-group tolerance and relatively good yields, and product isolation is straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

Acknowledgment

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University.

References and Notes

(1) Jiang, J. B.; Hesson, D.; Dusak, B.; Dexter, D.; Kang, G.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721.
(2) Yale, H. J.; Kalkstein, M. *J. Med. Chem.* **1967**, *10*, 334.
(3) Neil, G. L.; Li, L. H.; Buskirk, H. H. *Cancer Chemother. Pharmacol.* **1972**, *56*, 163.
(4) Hamel, E.; Lin, C. M.; Plowman, J.; Wang, H. K.; Lee, K. H.; Paull, K. D. *Biochem. Pharmacol.* **1996**, *51*, 53.
(5) Tiwari, A. K.; Mishra, A. K.; Bajpai, A.; Mishra, P.; Sharma, R. K.; Pandey, V. K.; Singh, V. K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4581.
(6) Ram, V. J.; Tripathi, B. K.; Srivastava, A. K. *Bioorg. Med. Chem.* **2003**, *11*, 2439.
(7) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659.
(8) Touroutoglou, N.; Pazdur, R. *Clin. Cancer Res.* **1996**, *2*, 227.
(9) Jackman, A. L.; Harrap, K. R.; Boyle, F. T. *Invest. New Drugs* **1996**, *14*, 305.
(10) Sielecki, T. M.; Johnson, T. L.; Liu, J.; Muckelbauer, J. K.; Grafstrom, R. H.; Cox, S.; Boylan, J.; Burton, C. R.; Chen, H.; Smallwood, A.; Chang, C.-H.; Boisclair, M.; Benfield, P. A.; Trainor, G. L.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1157.
(11) Bonomi, P. E. *Expert Opin. Invest. Drugs* **2003**, 1395.
(12) Alaimo, R. J.; Russell, H. E. *J. Med. Chem.* **1972**, *15*, 335.
(13) Cooper, E. R. A.; Jackson, H. *J. Reprod. Fertil.* **1973**, *34*, 445.
(14) Kuo, S. C.; Lee, H. Z.; Juang, J. P.; Lin, Y. T.; Wu, T. S.; Chang, J. J.; Lednicer, D.; Paull, K. D.; Lin, C. M. *J. Med. Chem.* **1993**, *36*, 1146.
(15) Lin, C. M.; Kang, G.; Roach, M.; Jiang, J.; Hesson, D.; Luduena, R.; Hamel, E. *Mol. Pharmacol.* **1991**, *40*, 827.
(16) Hour, M. J.; Huang, L. J.; Kuo, S. C.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K. H. *J. Med. Chem.* **2000**, *43*, 4479.
(17) Coskun, N. *Tetrahedron Lett.* **2004**, *45*, 8973.
(18) Csütörtöki, R.; Szatmári, I.; Koch, A.; Heydenreich, M.; Kleinpeter, E.; Fülöp, F. *Tetrahedron* **2011**, *67*, 8564.
(19) Balakumar, C.; Lamba, P.; Pran Kishore, D.; Lakshmi Narayana, B.; Venkat Rao, K.; Rajwinder, K.; Raghuram Rao, A.; Shireesha, B.; Narsaiah, B. *Eur. J. Med. Chem.* **2010**, 4904.
(20) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
(21) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 1241.
(22) Schreiber, S. L. *Science* **2000**, *287*, 1964.
(23) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(24) Orru, R. V.; De Greef, M. *Synthesis* **2003**, 1471.
(25) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
(26) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, **2005**.
(27) Shaabani, A.; Maleki, A.; Mofakham, H.; Moghimi-Rad, J. *J. Org. Chem.* **2008**, *73*, 3925.
(28) Shaabani, A.; Rezayan, A. H.; Keshipour, S.; Sarvary, A.; Ng, S. W. *Org. Lett.* **2009**, *11*, 3342.
(29) Shaabani, A.; Maleki, A.; Hajishaabanha, F.; Mofakham, H.; Seyyedhamzeh, M.; Mahyari, M.; Ng, S. W. *J. Comb. Chem.* **2009**, *12*, 186.
(30) Keshipour, S.; Shojaei, S.; Shaabani, A. *Tetrahedron* **2012**, *68*, 6141.
(31) Ghadari, R.; Hajishaabanha, F.; Mahyari, M.; Shaabani, A.; Khavasi, H. R. *Tetrahedron Lett.* **2012**, *53*, 4018.
(32) Shaabani, A.; Keshipour, S.; Shaabani, S.; Mahyari, M. *Tetrahedron Lett.* **2012**, *53*, 1641.
(33) Nef, J. U. *Justus Liebigs Ann. Chem.* **1892**, *270*, 267.
(34) Coffinier, D.; El Kaim, L.; Grimaud, L. *Org. Lett.* **2009**, *11*, 1825.
(35) El Kaim, E.; Grimaud, L.; Wagschal, S. *Synlett* **2009**, 1315.
(36) Mossetti, R.; Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2010**, *12*, 820.
(37) Coffinier, D.; El Kaim, L.; Grimaud, L. *Synlett* **2010**, 2474.
(38) El Kaim, L.; Grimaud, L.; Patil, P. *Org. Lett.* **2011**, *13*, 1261.
(39) Walborsky, H.; Niznik, G. *J. Org. Chem.* **1972**, *37*, 187.
(40) (a) Azuaje, J.; Coelho, A.; Maatougui, A. E.; Blanco, J. M.; Sotelo, E. *ACS Comb. Sci.* **2011**, *13*, 89. (b) Lim, Y. Y.; Stei, A. R. *Can. J. Chem.* **1971**, *49*, 2455. (c) Gassman, P. G.; Haberman, L. M. *Tetrahedron Lett.* **1985**, *26*, 4971. (d) Priestley, E. S.; Decicco, C. P. *Org. Lett.* **2000**, *2*, 3095.
(41) ***N*-Cyclohexyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4a) – Typical Procedure**
To magnetically stirred benzoyl chloride (0.14 g, 1.00 mmol) was added cyclohexyl isocyanide (0.11 g, 1.00 mmol), and the reaction mixture was heated for 2 h at 60 °C. After cooling, MeOH (5 mL) and 2-aminobenzamide were added, and the reaction mixture was stirred for 24 h at 60 °C. After completion of the reaction (TLC), the solvent was removed under vacuum, the residue was crystallized from CH_2Cl_2–*n*-hexane (3:1), and the product **4a** was obtained as a white solid (0.21 g, 60%); yield 0.21 g (60%); mp 222–225 °C. IR (KBr): 3381, 3324, 2932, 2844, 1649, 1612, 1492, 1461 cm^{-1}. ^1H NMR (300.13 MHz, DMSO-d_6): δ = 1.08–1.59 (10 H, m, 5 CH_2 of *c*-Hex), 3.52 (1 H, br s, CH of *c*-Hex), 6.69 (1 H, br s, NH), 6.93 (1 H, br s, NH), 7.25–7.70

(9 H, m, CHAr), 8.41 (1 H, br s, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 24.6, 25.5, 32.4, 48.8, 75.5, 114.7, 115.5, 118.2, 126.8, 127.6, 128.7, 129.0, 134.0, 141.4, 147.2, 163.9, 170.3. MS: *m/z* (%) = 350 (90) [M$^+$ + 1], 223 (100), 297 (25), 145 (15), 119 (30), 92 (60), 55 (65). Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.10; H, 6.58; N, 12.17.

2-(4-Bromophenyl)-*N*-cyclohexyl-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4b)

Yellow powder; yield 0.23 g (54%); mp 242–245 °C. IR (KBr): 3371, 3326, 2922, 2830, 1659, 1622, 1483, 1454 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.14–1.60 (10 H, m, 5 CH_2 of *c*-Hex), 3.50 (1 H, br s, CH of *c*-Hex), 6.69 (1 H, br s, NH), 6.92 (1 H, br s, NH), 7.28–7.79 (8 H, m, CHAr), 8.53 (1 H, br, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 24.7, 24.8, 32.3, 48.9, 75.1, 114.7, 115.6, 118.3, 122.4, 127.6, 129.1, 129.3, 131.6, 131.8, 134.1, 140.9, 147.0, 163.8, 169.8. Anal. Calcd for $C_{21}H_{22}BrN_3O_2$: C, 58.89; H, 5.18; Br, 18.66; N, 9.81. Found: C, 58.75; H, 5.24; N, 9.96.

***N*-Cyclohexyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4c)**

White powder; yield 0.18 g (63%); mp 232–235 °C. IR (KBr): 3413, 3321, 3002, 2923, 2852, 1624, 1580, 1525, 1455 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.07–1.70 (10 H, m, 5 CH_2 of *c*-Hex), 1.88 (3 H, s, CH_3), 2.89 (1 H, br s, CH of *c*-Hex), 7.21 (1 H, br s, NH), 7.38 (1 H, br s, NH), 7.55–7.90 (4 H, m, CHAr), 8.60 (1 H, br, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 24.2, 25.0, 25.2, 30.7, 49.7, 78.1, 115.1, 122.3, 124.8, 126.3, 126.8, 128.1, 135.1, 147.4, 155.4, 164.3. Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.80; H, 7.43; N, 14.69.

***N*-*tert*-Butyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4d)**

White powder; yield 0.20 g (62%); mp 182–184 °C. IR (KBr): 3260, 3191, 2964, 2926, 2837, 1635, 1612, 1511 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.57 (9 H, s, 3 CH_3), 6.62 (1 H, br s, NH), 6.65 (1 H, br s, NH), 6.74–7.33 (9 H, m, Ar), 7.89 (1 H, br, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 29.7, 45.7, 80.1, 114.7, 116.2, 118.7, 126.4, 127.3 128.3, 129.1, 133.9, 134.0, 141.0, 154.0, 164.5. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.64; H, 6.61; N, 12.90.

***N*-Cyclohexyl-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4e)**

White powder; yield 0.19 g (63%); mp 176–179 °C. IR (KBr): 2983, 2940, 2862, 2825, 1701, 1644, 1618, 1498, 1455 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.08–1.88 (13 H, m, 5 CH_2 of *c*-Hex and CH_3), 2.28 (2 H, br, CH_2CH$_3$), 2.90 (1 H, br s, CH of *c*-Hex), 7.11 (1 H, br s, NH), 7.19 (1 H, br s, NH), 7.36–7.91 (4 H, m, CHAr), 8.55 (1 H, br, CONH). ^{13}C NMR (62.83 MHz, DMSO-d_6): δ = 23.2, 24.7, 25.4, 32.9, 35.2, 48.4, 76.4, 113.9, 114.1, 117.3, 126.9, 131.8, 148.5, 159.2, 167.1. Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.69; H, 7.62; N, 14.09.

***N*-*tert*-Butyl-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4f)**

Brown powder; yield 0.18 g (65%); mp 157–159 °C. IR (KBr): 3259, 2968, 2895, 1634, 1613, 1515, 1492, 1385 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.22–1.33 (14 H, br s, 3 CH_3 of *t*-Bu, CH_2CH_3 and CH_2CH$_3$), 6.59 (1 H, br s, NH), 6.67 (1 H, br s, NH), 7.17–7.91 (4 H, m, CHAr), 8.10 (1 H, br, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 27.5, 29.4, 51.4, 67.3, 78.4, 114.2, 114.7, 116.8, 127.6, 133.6, 147.6, 158.4, 168.4. MS: *m/z* (%) = 276 (25) [M$^+$ + 1], 223 (80), 200 (15), 177 (15), 161 (100), 120 (25), 92 (25), 58 (75). Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.49; H, 7.74; N, 15.18.

***N*-Cyclohexyl-2-phenyl-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4g)**

White powder; yield 0.22 g (66%); mp 153–159 °C. IR (KBr): 2940, 2862, 2730, 1675, 1606, 1511, 1442 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.07–1.89 (10 H, m, 5 CH_2 of *c*-Hex), 2.88 (2 H, br, CH_2, ArCH_2), 3.40 (1 H, br s, CH of *c*-Hex), 6.63 (1 H, br s, NH), 6.72 (1 H, br s, NH), 7.14–7.24 (9 H, m, Ar), 8.35 (1 H, br, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 24.2, 25.0, 30.6, 41.1, 49.7, 76.6, 117.2, 118.4, 127.4, 126.2, 127.5, 127.6, 128.5, 129.2, 131.3, 150.1, 151.2, 167.9. Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.12; H, 7.44; N, 12.62.

***N*-Cyclohexyl-2-methyl-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4h)**

White powder; yield 0.19 g (70%); mp 145–148 °C. IR (KBr): 3425, 3336, 3021, 2936, 1637, 1587, 1500, 1461 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.07–1.70 (10 H, m, 5 CH_2 of *c*-Hex), 1.89 (3 H, s, CH_3), 2.89 (1 H, br s, CH of *c*-Hex), 3.86 (2 H, br, CH_2, ArCH_2), 6.56 (1 H, br s, NH), 6.69 (1 H, br s, NH), 7.01–7.15 (4 H, m, CHAr), 8.26 (1 H, br, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 24.2, 25.0, 30.7, 38.9, 40.9, 49.7, 82.2, 116.0, 116.6, 117.7, 129.8, 130.9, 147.5, 159.1, 165.2. Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.48; N, 15.37. Found: C, 70.39; H, 8.57; N, 15.24.

***N*-Cyclohexyl-2-ethyl-1,2,3,4-tetrahydroquinazoline-2-carboxamide (4i)**

White powder; yield 0.19 g (66%); mp 149–151 °C. IR (KBr): 3381, 3325, 3014, 2932, 2869, 1648, 1612, 1503 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.84–1.67 (13 H, m, 5 CH_2 of *c*-Hex and CH_3), 1.89 (2 H, br s, CH_2CH$_3$), 2.88 (1 H, br s, CH of *c*-Hex), 3.39 (2 H, br, ArCH_2), 6.56 (1 H, br s, NH), 6.70 (1 H, br s, NH), 7.13–7.28 (4 H, m, CHAr), 8.20 (1 H, br, $CONH_2$). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 15.6, 24.2, 25.0, 30.6, 40.7, 41.1, 49.7, 77.3, 117.2, 118.4, 127.4, 127.6, 129.3, 131.3, 150.1, 157.3, 164.5. Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 71.21; H, 8.64; N, 14.70.

(2*E*,2′*E*)-2,2′-[Ethane-1,2-diylbis(azan-1-yl-1-ylidene)]bis[2-(4-bromophenyl)-*N*-cyclohexylacetamide] (8)

White powder; yield 0.50 g (78%); mp 202–204 °C. IR (KBr): 3244, 3071, 2093, 2853, 1623, 1553, 1448 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.22–1.84 (20 H, m, 10 CH_2 of *c*-Hex), 2.15–2.21 (4 H, m, 2 CH_2), 3.10 (2 H, br s, 2 NH), 3.64–3.75 (2 H, m, 2 CH of *c*-Hex), 7.16–7.60 (10 H, m, CHAr), 7.74 (2 H, br, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 24.8, 25.5, 32.8, 46.1, 84.6, 125.6, 128.2, 128.4, 141.8, 172.9. MS: *m/z* = 646 (10) [M$^+$ + 2], 644 (20) [M$^+$], 642 (10) [M$^+$ – 2], 604 (15), 518 (50), 478 (25), 392 (15), 351 (20), 335 (30), 321 (10), 266 (20), 210 (25), 184 (60), 102 (15), 83 (70), 55 (100). Anal. Calcd for $C_{28}H_{38}N_4$, C, 78.10; H, 8.89; N, 13.01. Found: C, 78.01; H, 8.95; N, 13.05.

(2*E*,2′*E*)-2,2′-[1,2-Phenylenebis(azan-1-yl-1-ylidene)]bis[2-(4-bromophenyl)-*N*-cyclohexylacetamide] (9)

White powder; yield 0.49 g (71%); mp 162–163 °C. IR (KBr): 3338, 3297, 2933, 2878, 2854, 1644, 1514, 1485, 1455 cm^{-1}. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.24–1.83 (20 H, m, 10 CH_2 of *c*-Hex), 2.82 (4 H, br, 2 CH_2), 3.64 (2 H, br s, 2 CH of *c*-Hex), 7.49–7.66 (8 H, m, CHAr), 7.72 (2 H, br, CONH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 25.0, 25.5, 32.7, 46.6, 48.0, 84.5, 123.0, 128.8, 129.9, 131.0, 175.2. Anal. Calcd for $C_{28}H_{36}Br_2N_4$, C, 57.15; H, 6.17; Br, 27.16; N, 9.52. Found: C, 57.10; H, 6.09; N, 9.61.

