Asian Journal of Chemistry; Vol. 28, No. 1 (2016), 95-98

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19241

Microwave-Assisted Synthesis of New 6-Ureido-4-anilinoquinazoline Derivatives

YOUGUANG ZHENG, CAIYUN GAO, RONGRONG HUANG, YI LIU*, YUNSHENG XUE and LIN AN

College of Pharmacy, Xuzhou Medical College, Xuzhou 221004, P.R. China

*Corresponding author: E-mail: zhengyouguang@yahoo.com.cn; njuliuyi2003@yahoo.com.cn

Received: 8 April 2015; *Accepted*: 28 May 2015; *Published online*: 5 October 2015; AJC-17553

An efficient rapid method for the synthesis of new 6-ureido-4-anilinoquinazoline derivatives derived from 2-amino-5-nitrobenzoic acid under microwave irradiation has been developed. All of the new compounds were identified by ^{1}H NMR, ^{13}C NMR, IR, MS and elemental analyses.

Keywords: Quinazolinone derivatives, 4-Anilinoquinazoline, 2-Amino-5-nitrobenzoic acid, Microwave irradiation, Efficient rapid method.

INTRODUCTION

Quinazoline and quinazolinone derivatives have continued to attract a widespread interest for a long time due to their diverse pharmacological activities, among which, 4-aminoquinazolines are useful as fungicides, anti-inflammatory, anticancer, antimicrobial, antimalarial and antihypertensive agents [1-5]. Microwave assisted organic synthesis (MAOS) continues to affect synthetic chemistry significantly by enabling rapid, reproducible and scaleable chemistry development [5-10]. In this paper, the new 6-ureido-4-anilinoquinazoline derivatives were synthesized under microwave irradiation.

EXPERIMENTAL

All the reagents were purchased from commercial sources and used without further purification. Melting points were measured in open capillaries and are uncorrected. IR spectra were determined as KBr pellets on a Thermo Nicolet 6700 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO on a Bruker Avance 500 spectrometer; chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethyl silane (TMS), used as an internal standard. Mass spectra (MS) were obtained from Agilent 1100LC/MS Spectrometry Services. All compounds were routinely checked by TLC with silica gel GF-254 glass plates and viewed under UV light at 254 nm. The microwave reactions were performed in a Shanghai SINEO's MAS-II microwave reactor.

Synthesis of compound 2: A mixture of 2-amino-5-nitrobenzoic acid (36.9 g, 0.203 mol) and formamidine acrtate (42.5 g, 0.360 mol) in ethylene glycol monomethyl ether (150 mL) was heated under reflux for 30 h, or the reaction vessel was open and heated under microwave irradiation for 1 h at 124 °C. After completion of the reaction, the excess ethylene glycol monomethyl ether was removed by *vacuo*. The residue was washed by 0.01 M ammonia water to give compound (**2**) [78 % thermal, 92 % microwave], m.p.: 283 °C [Lit. m.p.: 283-285 °C] [11].

Synthesis of compounds 3 to 5: Compounds **3** to **5** were prepared according to the work of Shaul *et al.* [12].

General procedure for the synthesis of compound 6a-j: Compound **5** (2 mmol) and toluene (50 mL) were placed in a flask and then isocyanate was added. The mixture was refluxed for 3 h, yielding floccose precipitate. The resulting solid was collected by filtration and washed with toluene to obtain crude product, which was purified by chromatographic column to yield compound **6a-j**.

General microwave procedure for the synthesis of compound 6a-j: Compound **5** (2 mmol) and toluene (50 mL) were placed in open reaction vessel. The reaction vessel was positioned in the centre of the microwave cavity and irradiated (500 W) for 15-25 min at 65 °C. After completion of the reaction, the filtrate was evaporated to dryness *in vacuo*. The residue was purified by column chromatography using CH_2Cl_2/MeOH (100:2 v/v) as an eluent.

Compound 6a: m.p.: 256-259 °C. IR (KBr, ν_{max}, cm^{-1}): 1656 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.26 (s, 3H, CH_3), 7.11 (d, 2H, J = 8.2 Hz, Ar-H), 7.43 (dd, 3H, J_1 = 8.1 Hz, J_2 = 9.5 Hz, Ar-H), 7.81(m, 3H, Ar-H), 8.16 (d, 1H, J = 4.6 Hz, Ar-H), 8.49 (s, 1H, Ar-H), 8.54 (s, 1H, Ar-H), 8.77, 8.92, 9.86 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 20.3, 109.9, 115.6, 116.3, 116.6, 118.5, 122.5, 122.6, 123.7, 126.6, 128.3, 129.2, 130.9, 136.9, 137.9, 145.6, 151.7, 152.3, 152.6, 154.9, 157.1.

MS: $[M+H]^+$ = 422.0; Elemental analysis: Calcd. (%): C 62.29, H 4.09, N 16.27; Found (%): C 62.64, H 4.06, N 16.60.

Compound 6b: m.p.: 259-263 °C; IR (KBr, ν_{max}, cm^{-1}): 1697 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.17 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 7.05 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.21 (s, 1H, Ar-H), 7.30 (d, 1H, *J* = 1.9 Hz, Ar-H), 7.43 (t, 1H, Ar-H), 7.76 (d, 1H, *J* = 8.9 Hz, Ar-H), 7.82 (m, 1H, Ar-H), 7.86(t, 1H, Ar-H), 8.16 (dd, 1H, J_1 = 2.6 Hz, J_2 = 2.6 Hz, Ar-H), 8.49 (d, 1H, *J* = 2.2 Hz, Ar-H), 8.53, 8.68, 8.89 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 18.6, 19.5, 109.6, 115.4, 115.8, 116.3, 116.4, 119.6, 122.5, 122.5, 123.6, 126.4, 128.4, 129.6, 129.6, 136.3, 136.7, 137.1, 137.8, 145.7, 152.3, 152.5, 156.9. MS: $[M+H]^+$ = 436.0; Elemental analysis: Calcd. (%): C 62.91, H 4.45, N 15.97; Found (%): C 63.38, H 4.39, N 16.07.

Compound 6c: m.p.: 226-230 °C; IR (KBr, ν_{max}, cm^{-1}): 1697 (C=O); ^{1}H NMR (DMSO-d_6) δ: 7.41 (t, 1H, Ar-H), 7.63 (d, 1H, *J* = 8.8 Hz, Ar-H), 7.71 (dd, 2H, J_1 = 2.2 Hz, J_2 = 2.1 Hz, Ar-H), 7.82-7.85 (m, 1H, Ar-H), 7.94 (d, 1H, *J* = 2.0 Hz, Ar-H), 8.12 (d, 1H, *J* = 2.4 Hz, Ar-H), 8.20 (dd, 1H, J_1 = 2.6 Hz, J_2 = 2.6 Hz, Ar-H), 8.44 (d, 1H, *J* = 9.1 Hz, Ar-H), 8.57 (s, 1H, Ar-H), 9.17, 9.34, 9.76 (s, each 1H, 3 × NH). ^{13}C NMR (DMSO-d_6) δ: 110.7, 115.4, 116.2, 116.5, 116.8, 116.9, 116.9, 122.6, 122.7, 123.2, 123.7, 124.6, 126.9, 128.5, 131.99, 136.6, 136.7, 137.1, 139.2, 146.1, 152.4, 152.6, 157.0. MS: $[M+H]^+$ = 510.0; Elemental analysis: Calcd. (%): C 51.95, H 3.84, N 14.18; Found (%): C 51.78, H 3.57, N 13.73.

Compound 6d: m.p.: 260-264 °C; IR (KBr, ν_{max}, cm^{-1}): 1657(C=O); ^{1}H NMR (DMSO-d_6) δ: 7.33-7.38 (m, 2H, Ar-H), 7.44 (t, 1H, Ar-H), 7.52-7.56 (m, 2H, Ar-H), 7.79 (t, 1H, Ar-H), 7.80-7.88 (m, 2H, Ar-H), 8.15-8.19 (m, 1H, Ar-H), 8.50 (d, 1H, *J* = 2.1 Hz, Ar-H), 8.55, 9.01, 9.86 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 110.2, 115.4, 116.1, 116.4, 119.7, 119.8, 122.4, 122.5, 123.4, 123.6, 125.5, 126.5, 126.6, 128.4, 128.5, 136.7, 137.4, 138.4, 145.8, 152.4, 156.9. MS: $[M+H]^+$ = 442.0; Elemental analysis: Calcd. (%): C 56.66, H 3.10, N 15.57; Found (%): C 57.03, H 3.19, N 15.83.

Compound 6e: m.p.: >250 °C; IR (KBr, ν_{max}, cm^{-1}): 1634 (C=O); ^{1}H NMR (DMSO-d_6) δ: 7.28-7.30 (m, 1H, Ar-H), 7.35 (t, 1H, Ar-H), 7.76 (t, 1H, Ar-H), 7.78 (d, 1H, *J* = 8.9 Hz, Ar-H), 7.84-7.89 (m, 3H, Ar-H), 8.19 (t, 1H, Ar-H), 8.56 (t, 2H, Ar-H), 8.65 (t, 1H, Ar-H), 9.14, 9.43, 9.85 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 110.7, 112.2, 115.5, 116.5, 120.9, 121.1, 124.3, 124.4, 125.8, 126.8, 128.5, 130.1, 130.2, 137.1, 140.9, 141.1, 146.1, 148.1, 152.5, 152.6, 157.0. MS: $[M+H]^+$ = 510.0; Elemental analysis: Calcd. (%): C 52.41, H 3.07, N 17.19; Found (%): C 52.63, H 3.15, N 17.53.

Compound 6f: m.p.: 248-250 °C; IR (KBr, ν_{max}, cm^{-1}): 1697(C=O); ^{1}H NMR (DMSO-d_6) δ: 2.17 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 7.05 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.21 (dd, 1H, J_1 = 2.1 Hz, J_2 = 2.0 Hz, Ar-H), 7.27-7.30 (m, 2H, Ar-H), 7.36 (t, 1H, Ar-H), 7.77 (d, 1H, *J* = 8.9 Hz, Ar-H), 7.88 (dd, 2H, J_1 = 1.7 Hz, J_2 = 1.6 Hz, Ar-H), 8.19 (s, 1H, Ar-H), 8.49 (d, 1H, *J* = 2.1 Hz, Ar-H), 8.56 (s, 1H, Ar-H), 8.69, 8.89, 9.83 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 18.6, 19.5, 109.8, 115.6, 115.9, 119.6, 120.7, 121.0, 124.1, 125.7, 126.5, 128.4, 129.6, 129.6, 130.2, 136.3, 137.1, 137.8, 141.0, 145.8, 152.3, 152.5, 156.9. MS: $[M+H]^+$ = 462.0; Elemental analysis: Calcd. (%): C 59.34, H 4.26, N 14.89; Found (%): C 59.75, H 4.36, N 115.15.

Compound 6g: m.p.: 265-268 °C; IR (KBr, ν_{max}, cm^{-1}): 1706 (C=O); ^{1}H NMR (DMSO-d_6) δ: 7.27-7.37 (m, 2H, Ar-H), 7.62-7.71 (m, 2H, Ar-H), 7.78 (d, 1H, *J* = 8.9 Hz, Ar-H), 7.88 (t, 2H, Ar-H), 8.19 (d, 2H, *J* = 2.0 Hz, Ar-H), 8.54 (d, 1H, *J* = 1.6 Hz, Ar-H), 8.57 (s, 1H, Ar-H), 9.16, 9.38, 9.86 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 110.8, 115.5, 116.8, 116.9, 120.8, 120.9, 122.5, 123.0, 123.1, 124.2, 125.7, 126.8, 128.4, 130.1, 131.9, 137.0, 139.1, 141.1, 146.1, 152.4, 152.6, 157.0. MS: $[M+H]^+$ = 536.1; Elemental analysis: Calcd. (%): C 49.11, H 2.61, N 12.58; Found (%): C 49.23, H 2.63, N 113.05.

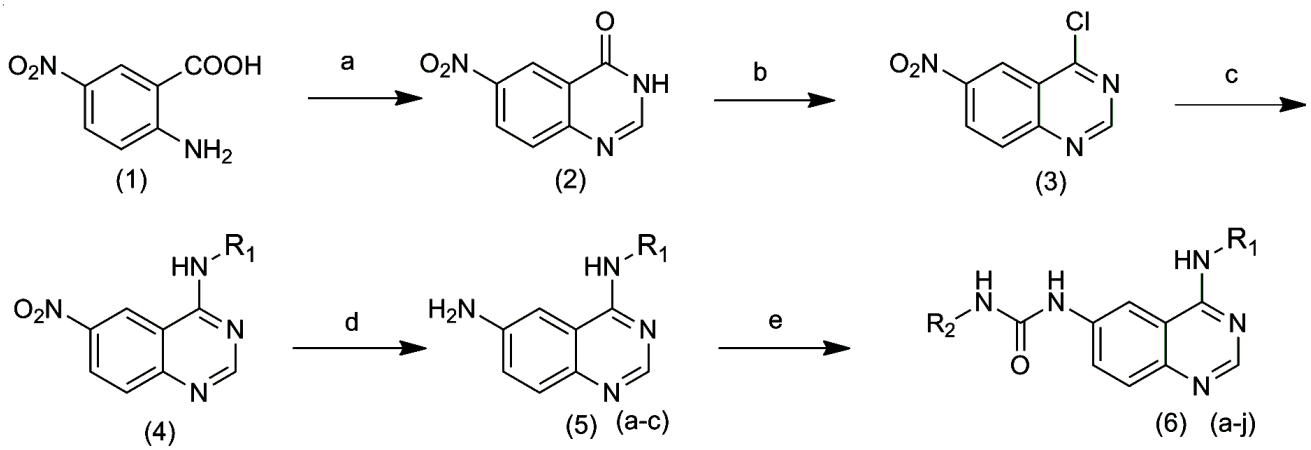
Compound 6h: m.p.: 214-220 °C; IR (KBr, ν_{max}, cm^{-1}): 1686 (C=O); ^{1}H NMR (DMSO-d_6) δ: 7.40 (dd,4H, J_1 = 8.8 Hz, J_2 = 5.0 Hz), 7.55 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.78-7.85 (m, 2H, Ar-H)), 7.97 (t, 2H, Ar-H), 8.09(s, 1H, Ar-H), 8.70 (d, 2H, Ar-H), 9.44, 9.47, 10.72 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 110.4, 114.9, 119.8, 121.0, 122.2, 124.5, 125.6, 125.7, 127.3, 127.6, 128.5, 130.3, 138.4, 138.7, 139.8, 150.6, 152.4, 158.1. MS: $[M+H]^+$ = 468.0; Elemental analysis: Calcd. (%): C 53.72, H 3.59, N 14.82; Found (%): C 53.81, H 3.23, N 14.94.

Compound 6i: m.p.: 249-252 °C; IR (KBr, ν_{max}, cm^{-1}): 1655 (C=O); ^{1}H NMR (DMSO-d_6) δ: 5.25 (s, 2H, -CH_2-), 7.15-7.21 (m, 1H, Ar-H), 7.27 (t, 2H, Ar-H), 7.33 (t, 3H, Ar-H), 7.46 (dd, 1H, J_1 = 6.0 Hz, J_2 = 6.1 Hz, Ar-H), 7.53 (t, 2H, Ar-H), 7.70 (dd, 2H, J_1 = 2.4 Hz, J_2 = 8.9 Hz, Ar-H), 7.84 (dd, 1H, J_1 = 1.6 Hz, J_2 = 1.7 Hz, Ar-H), 8.00 (t, 1H, Ar-H), 8.47 (t, 2H, Ar-H), 8.97, 9.02, 9.73 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 69.4, 110.3, 113.7, 114.0, 114.3, 114.6, 115.3, 119.8, 121.0, 122.2, 123.1, 124.0, 125.5, 126.4, 128.3, 128.5, 130.3, 130.4, 133.5, 137.2, 138.4, 145.7, 149.4, 152.4, 152.6, 157.0, 160.5, 163.7. MS: $[M+H]^+$ = 548.0; Elemental analysis: Calcd. (%): C 60.89, H 3.73, N 12.52; Found (%): C 61.32, H 3.68, N 12.77.

Compound 6j: m.p.: 240-242 °C; IR (KBr, ν_{max}, cm^{-1}): 1707 (C=O); ^{1}H NMR (DMSO-d_6) δ: 5.26 (s, 2H, -CH_2-), 7.15-7.34 (m, 4H, Ar-H), 7.44-7.51 (m, 1H, Ar-H), 7.62-7.85 (m, 5H, Ar-H), 7.99 (d, 1H, *J* = 2.5Hz, Ar-H), 8.20 (d, 1H, *J* = 2.2Hz, Ar-H), 8.50 (s, 2H, Ar-H), 9.13, 9.38, 9.77 (s, each 1H, 3 × NH); ^{13}C NMR (DMSO-d_6) δ: 69.4, 110.8, 113.7, 114.0, 114.3, 114.6, 115.3, 116.8, 116.9, 122.3, 123.1, 123.2, 124.1, 126.6, 128.3, 130.3, 130.4, 131.9, 133.4, 136.8, 139.1, 145.9, 149.5, 152.4, 152.8, 157.1, 160.5, 163.7. MS: $[M+H]^+$ = 616.0; Elemental analysis: Calcd. (%): C 56.07, H 3.00, N 11.05; Found (%): C 56.51, H 3.11, N 11.36.

RESULTS AND DISCUSSION

The synthesis of 4-anilinoquinazoline derivates (**6a-j**) is outlined in **Scheme-I**, which started with 2-amino-5-nitrobenzoic acid. We investigated the reaction between 2-amino-5-nitrobenzoic acid (**1**) and formamidine acetate in ethylene glycol monomethyl ether [under reflux for 30 h or pressurized microwave irradiation for 1 h. Compound (**2**) was chloridated by thionyl chloride to give compound (**3**), which was astable due to theelectro attracting group nitro in the C6. Compound **4** was obtained after a reaction of amination between compound **3** and aniline in 75-88 % yields. Reduction of compound **4** used Rany Ni/H_2 in alcohol to achieve compound **5**, which

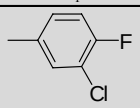
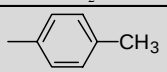
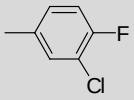
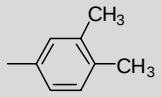
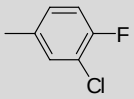
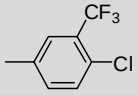
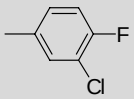
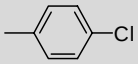
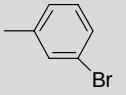
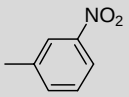
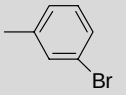
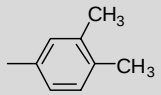
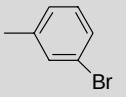
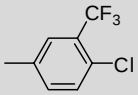
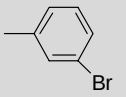
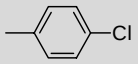
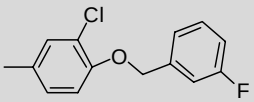
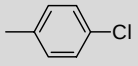
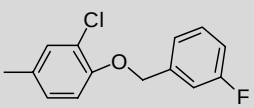
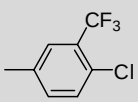


Reagents and conditions: a) formamidine acrtate, microwave, 120-125 °C, 1 h; b) thionyl chloride, DMF, reflux; c) aniline, isopropanol, reflux; d) rany Ni/H_2, alcohol; e) isocyanate, toluene, reflux, or isocyanate, toluene microwave, 105-110 °C, 10 min

Scheme-I: Synthesis of the 4-anilinoquinazoline derivates (**6a-j**)

was treated with isocyanate to afford compound (**6a-j**). All the target compounds were purified by chromatographic column and identified by ^{1}H NMR, ^{13}C NMR, IR, MS and elemental analyses (**Scheme-I**, Fig. 1, Table-1).

TABLE-1
STRUCTURE OF COMPOUNDS **6a-j**

Entry	R_1	R_2
6a		
6b		
6c		
6d		
6e		
6f		
6g		
6h		
6i		
6j		

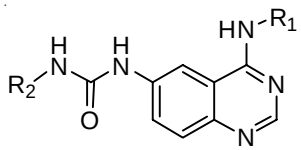
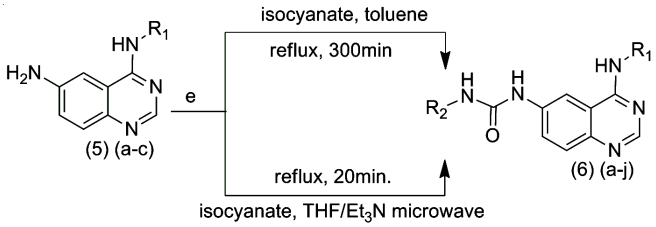


Fig. 1. Structure of compound **6a-j**

The synthesis of the 6-ureido-4-anilinoquinazoline derivatives (**6a-j**) were carried out under both microwave irradiation and normal reflux conditions (**Scheme-II**). First, the target compounds were obtained in conventional toluene reflux condition and unfortunately the yields were not so high. In order to obtain these 6-ureido-4-anilinoquinazoline derivatives (**6a-j**) in higher yields with shorter reaction times under mild reaction conditions, we turned our attention to microwave irradiation. Comparisons of the step by conventional and microwave methods are depicted in Table-2. Formation of the desired

TABLE-2
SYNTHESIS OF 6-UREIDO-4-ANILINOQUINAZOLINE DERIVATIVES (**6a-j**)

Entry	Microwave method			Conventional method		
	Temp. (°C)	Time (min)	Yield (%)	Temp. (°C)	Time (min)	Yield (%)
6a	63-66	20	58	108-110	300	46
6b	63-66	20	67	108-110	300	53
6c	63-66	15	75	108-110	300	62
6d	63-66	15	71	108-110	240	59
6e	63-66	25	38	108-110	600	20
6f	63-66	20	70	108-110	300	55
6g	63-66	20	62	108-110	300	53
6h	63-66	20	65	108-110	300	48
6i	63-66	25	63	108-110	360	56
6j	63-66	25	54	108-110	360	38



Scheme-II: Synthesis of 6-ureido-4-anilinoquinazoline derivatives (**6a-j**)

compounds was accelerated by microwave irradiation with remarkable decreases in reaction times and significant enhancements of yields as compared with the conventional method.

ACKNOWLEDGEMENTS

The authors are grateful for the financial support by the National Basic Research Program of China (No. 2011CB933503); National Natural Science Foundation of China (No.812024-90); Natural Science Foundation of Jiangsu Province (BK20130216); Jiangsu Key Laborotary of Brain Disease Bioinformation in Xuzhou Medical College (Jsbl11103).

REFERENCES

1. D.J. Connolly, D. Cusack, T.P. O'Sullivan and P.J. Guiry, *Tetrahedron*, **61**, 10153 (2005).
2. A. Witt and J. Bergman, *Curr. Org. Chem.*, **7**, 659 (2003).
3. W.L.F. Armarego, *Adv. Heterocycl. Chem.*, **1**, 253 (1963).
4. S. Madapa, Z. Tusi, A. Mishra, K. Srivastava, S.K. Pandey, R.S. Tripathi, K. Puri and S. Batra, *Bioorg. Med. Chem.*, **17**, 222 (2009).
5. B. Marvania, P.C. Lee, R. Chaniyara, H.J. Dong, S. Suman, R. Kakadiya, T. Chou, T.C. Lee, A. Shah and T.L. Su, *Bioorg. Med. Chem.*, **19**, 1987 (2011).
6. W.S. Chow and T.H. Chan, *Tetrahedron Lett.*, **50**, 1286 (2009).
7. A. Rauf, S. Sharma and S. Gangal, *ARKIVOC*, 137 (2007).
8. C.O. Kappe and D. Dallinger, *Nat. Rev. Drug Discov.*, **5**, 51 (2006).
9. W.D. Shipe, S.E. Wolkenberg and C.W. Lindsley, *Drug Discov. Today. Technol.*, **2**, 155 (2005).
10. H.A. Saad, M.M. Youssef and M.A. Mosselhi, *Molecules*, **16**, 4937 (2011).
11. J. Domarkas, F. Dudouit, C. Williams, Q. Qiyu, R. Banerjee, F. Brahimi and B.J. Jean-Claude, *J. Med. Chem.*, **49**, 3544 (2006).
12. M. Shaul, G. Abourbeh, O. Jacobson, Y. Rozen, D. Laky, A. Levitzki and E. Mishani, *Bioorg. Med. Chem.*, **12**, 3421 (2004).