HETEROCYCLES, Vol. 81, No. 10, 2010, pp. 2369 - 2376. © The Japan Institute of Heterocyclic Chemistry
Received, 1st August, 2010, Accepted, 18th August, 2010, Published online, 18th August, 2010
DOI: 10.3987/COM-10-12032

AN EFFICIENT SYNTHESIS OF NEW THIAZOLE BASED HETEROCYCLES

Yahia N. Mabkhot,[1] Nabila A. Kheder,[2,3] and Ahmad M. Farag[2,*]

[1]Department of Chemistry, Faculty of Science, King Saud University, 2455, Riyadh 11751, Saudi Arabia

[2]Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt; [3]On leave to Department of Pharmaceutical Chemistry, Faculty of Pharmacy, King Khalid University, Abha, Saudi Arabia

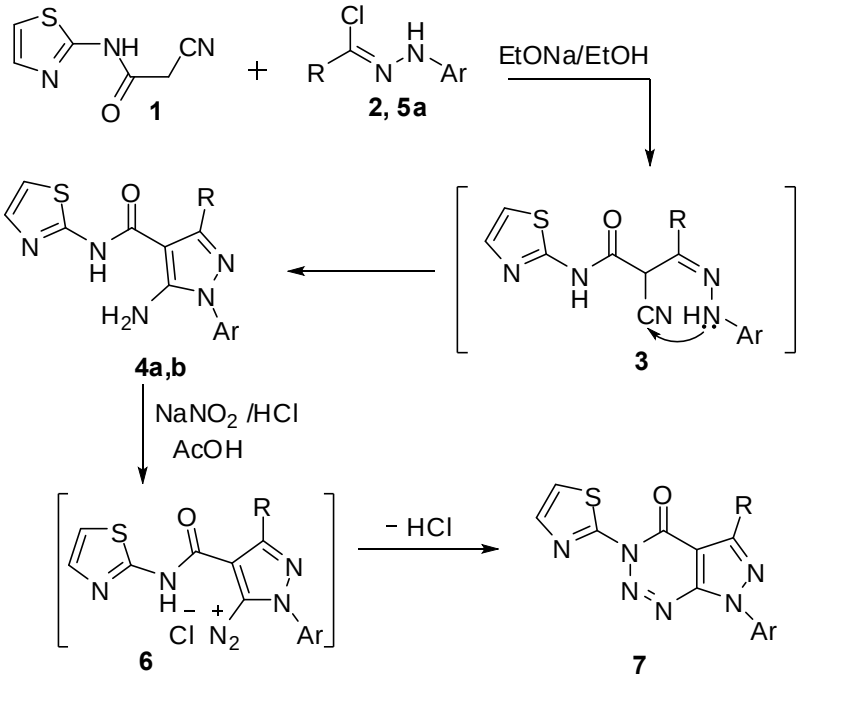
E-mail: afarag49@yahoo.com

Abstract – Synthesis of new aminopyrazole, pyrazolo[3,4-*d*]-1,2,3-triazine, 1,3,4-thiadiazole, thiophene and 1,2-dihydropyridine derivatives containing thiazole template has been carried out by simple, efficient and good yielding routes starting from the versatile and readily accessible 2-cyano-*N*-(thiazol-2-yl)acetamide.

Thiazoles and their derivatives have attracted continuing interest over the years because of their diverse biological activities.[1,2] They found application in drug development for the treatment of allergies,[3] hypertension,[4] inflammation,[5] schizophrenia,[6] bacterial[7] and HIV infections.[8] They are also used as hypnotics,[9] for the treatment of pain,[10] and as inhibitors of LFA-1/ICAM-1 mediated cell adhesion.[11] In addition, thiazole derivatives show strong FabI and FabK inhibitory effects with potent antibacterial activity.[12] In view of the above mentioned findings, and as a continuation of our interest in the synthesis of a variety of heterocyclic ring systems for biological evaluation,[13-28] we report in the present work the synthesis of some heterocycles containing thiazole template. During our search, we have found that 2-cyano-*N*-(thiazol-2-yl)acetamide (**1**) [29] is a versatile, readily accessible building block for synthesis of the target compounds.

Treatment of the acetamide **1** with 2-oxo-*N'*-phenylpropanehydrazonoyl chloride (**2**)[30] in ethanolic sodium ethoxide, at room temperature, furnished a single product identified as the aminopyrazole derivative **4a**. The IR spectrum of the reaction product exhibited absorption bands at 3443, 3331, 3191, 1692 and 1638 cm^{-1} due to amino, amide-NH and two carbonyl groups, respectively. Prompted by the foregoing results and to generalize this reaction, we have also studied the behaviour of the acetamide **1** towards the 2-oxo-2-(phenylamino)-*N'*-p-tolylacetohydrazonoyl chloride (**5a**),[31] under the same experimental

conditions, which led to the respective aminopyrazole derivative **4b**. When the aminopyrazole **4a** was treated with nitrous acid, it furnished one isolable product which was analysed correctly for $C_{15}H_{10}N_6O_2S$. The structure of the isolated product was assigned as 5-acetyl-7-phenyl-3-(thiazol-2-yl)-3*H*- pyrazolo[3,4-*d*]-1,2,3-triazin-4(7*H*)one (**7**), based on its elemental analyses and spectral data. For example, the IR spectrum of the reaction product revealed the disappearance of the amino and amide-NH absorption bands in the region 3450-3000 cm^{-1} and showed two strong carbonyl bands at 1729 and 1680 cm^{-1}.



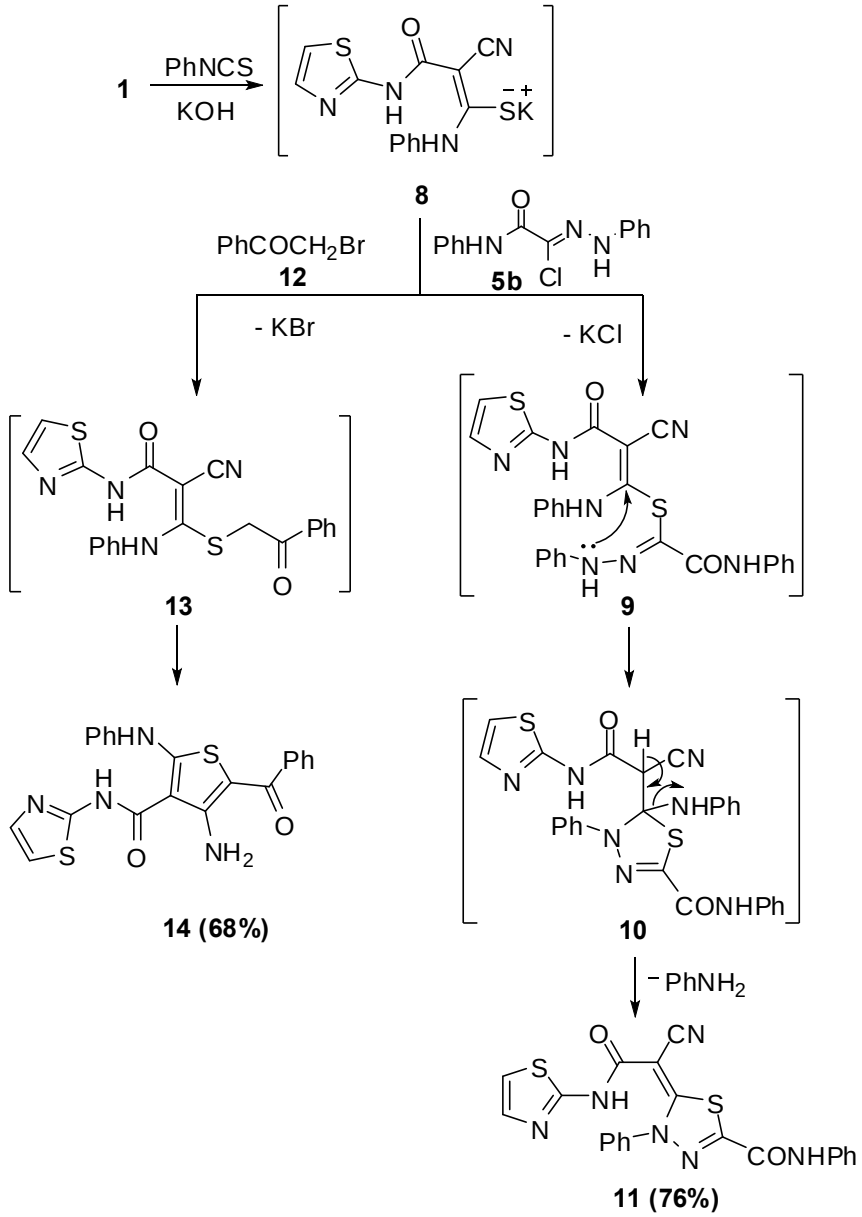
	2,4a,7	4b,5a
R	MeCO	PhNHCO
Ar	Ph	4-MePh

4a (63%), **4b** (68%), **7**(61%)

Scheme 1

The nucleophilic addition of the acetamide **1** to an equimolar amount of phenyl isothiocyanate in DMF, in the presence of potassium hydroxide, afforded the corresponding potassium salt intermediate **8**. Cyclization of the intermediate **8**, *in situ*, with the hydrazonyl chloride **5b** gave 5-(1-cyano-2-oxo-2-(thiazol-2-ylamino)ethylidene)-*N*,4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (**11**) as depicted in Scheme 2. The IR spectrum of the product **11** revealed, absorption bands at 3385, 3065, 2193 1682 and 1647 cm^{-1} corresponding to two NH, nitrile and two carbonyl groups, respectively. Its ^1H NMR spectrum displayed two D_2O-exchangeable signals at δ 10.85 and 11.68 due to two NH protons, in addition to an aromatic multiplet in the region δ 7.05-7.77. The aforementioned results indicate that the reaction of the intermediate potassium salt **8** with the hydrazonayl chloride **5b** proceeds, *via* elimination of potassium chloride and aniline, respectively.

Similarly 1-phenyl-2-bromoethanone (**12**)[32] reacted with the intermediate potassium salt **8**, formed *in situ* under the same experimental conditions, and afforded the corresponding aminothiophene derivative **14** (Scheme 2). The IR spectrum of compound **14** revealed absence of nitrile absorption band while, its ^{1}H NMR spectrum showed three D_2O-exchangeable signals at δ 8.80, 11.98 and 13.19 due to NH_2 and two amide proton, respectively in addition to an aromatic multipelt in the region δ 7.05-8.04.

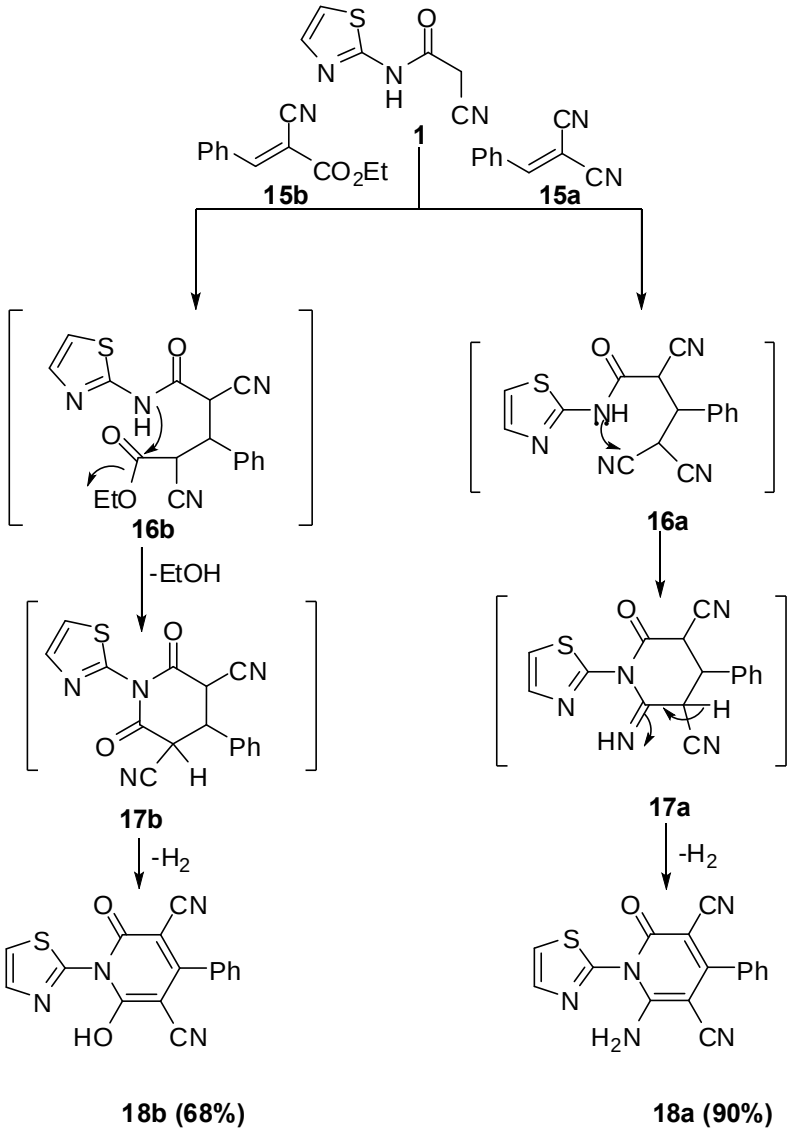


Scheme 2

Refluxing of equimolar amounts of the acetamide **1** and 2-benzylidenemalononitrile (**15a**),[33] in the presence of a catalytic amount of piperidine afforded 1 : 1 cycloadduct (Scheme 3). The structure of the isolated cycloadduct was identified as 6-amino-2-oxo-4-phenyl-1-(thiazol-2-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (**18a**) on the basis of its elemental analyses and spectral data. Compound **18a** is assumed to be

formed *via* an initial Michael type adduct **16a** followed by an intramolecular cyclization and subsequent oxidation to the final product (Scheme 3).

When compound **1** was treated with 2-cyano-3-phenyl-2-propenoic acid ethyl ester (**15b**),[33] in ethanol and in the presence of a catalytic amount of piperidine, it gave the corresponding pyridine-3,5-dicarbonitrile **18b** (Scheme 3).



Scheme 3

Compound **18b** was formed initially *via* Michael type addition followed by elimination of ethanol molecule and subsequent dehydrogenation. The IR spectrum of the reaction product revealed the absence of amino absorption bands and exhibited absorption bands at 1715 and 2222 cm^{-1} due to amid carbonyl and two nitrile groups, respectively. Moreover, its ^1H NMR spectrum showed a broad D_2O-exchangable signal at δ 12.6 due to OH proton in addition to aromatic multiplet in the region δ 7.24-8.74.

In conclusion, the reactivity of 2-cyano-*N*-(thiazol-2-yl)acetamide (**1**) was investigated, as a versatile and readily accessible building block, for the synthesis of new heterocycles incorporating thiazole ring of biological and pharmaceutical importance.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus (Weiss-Gallenkamp, London, UK). The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (Pye Unicam Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian, Palo Alto, CA, USA). ^{1}H spectra were run at 300 MHz in deuterated dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer (Shimadzu) at 70 eV. Elemental analyses were carried out at the Micro-analytical Center of Cairo University, Giza, Egypt. 2-Cyano-*N*-(thiazol-2-yl)acetamide (**1**)[29] is commercially available. Hydrazonoyl chlorides **2**[30] **5a, 5b**[31] 1-phenyl-2-bromoethanone (**12**),[32] 2-benzylidenemalononitrile (**15a**)[33] and 2-cyano-3-phenyl-2-propenoic acid ethyl ester (**15b**)[33] were prepared according to the literature procedures.

Reaction of acetamide 1 with hydrazonoyl halides 2 and 5a.

General procedure

2-Cyano-*N*-(thiazol-2-yl)acetamide (**1**) (0.33 g, 2 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (46 mg, 2 mmol) and absolute EtOH (20 mL)] with stirring. After stirring the resulting solution for 15 min., compound **2** or **5a** (2 mmol) was added portionwise and the reaction mixture was stirred further for 12 h at room temperature. The resulted solid product was filtered off, washed with water and dried. Recrystallization from the DMF/EtOH afforded the corresponding pyrazole derivatives **4a** and **4b**, respectively.

3-Acetyl-5-amino-1-phenyl-N-(thiazol-2-yl)-1H-pyrazole-4-carboxamide (4a).

Yield (63%), mp 246-247 ^{o}C; IR (KBr) v 3443-3331 (NH_2), 3191 (NH), 1692 (C=O), 1638 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.43 (s, 3H, CH_3), 4.01 (s, 2H, D_2O-exchangeable, NH_2), 7.08-7.86 (m, 7H, ArH), 12.2 (s, 1H, D_2O-exchangeable NH). Anal. Calcd for $C_{15}H_{13}N_5O_2S$: C, 55.03; H, 4.00; N, 21.39. Found: C, 55.13; H, 4.05; N, 21.35%.

5-Amino-N^3-phenyl-N^4-(thiazol-2-yl)-1-(p-tolyl)-1H-pyrazole-3,4-dicarboxamide (4b).

Yield (68%), mp 279-280 ^{o}C; IR (KBr) v 3314-3356 (NH_2), 3200 (NH), 3036 (NH), 1692 (C=O), 1672 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H, CH_3), 7.12-7.56 (m, 13H, ArH+ NH_2), 11.25 (s, 1H, D_2O-exchangeable, NH), 14.0 (s, 1H, D_2O-exchangeable NH); MS *m/z* (%) 418 (M^+, 32.78), 99 (7.78), 84 (23.89). Anal. Calcd for $C_{21}H_{18}N_6O_2S$: C, 60.27; H, 4.34; N, 20.08. Found: C, 60.21; H, 4.24; N, 20.18%.

5-Acetyl-7-phenyl-3-(thiazol-2- yl)-3H-pyrazolo[3,4-d]-1,2,3-triazin-4(7H)-one (7).

To a solution of 5-aminopyrazole **4a** (0.33 g, 1 mmol) in acetic acid (5 mL) was added HCl (6 M, 1 mL). The mixture was then cooled to 0-5 ^{o}C and sodium nitrite (69 mg) was added portionwise while stirring. The reaction mixture was left to stand in an ice bath for 1 h and was then diluted with water, filtered off, washed with water and finally recrystallized from DMF/EtOH to afford compound **7**: Yield (61%), mp 265-266 ^{o}C; IR (KBr) v 1729 (C=O), 1680 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.53 (s, 3H, CH_3), 7.10-7.87 (m, 7H, ArH). Anal. Calcd for $C_{15}H_{10}N_6O_2S$: C, 53.25; H, 2.98; N, 24.84. Found: C, 53.15; H, 2.92; N, 24.86%.

5-(1-Cyano-2-oxo-2-(thiazol-2-ylamino)ethylidene)-N,4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carb-oxamide (11) and 4-amino-5-benzoyl-2-(phenylamino)-N-(thiazol-2-yl)thiophene-3- carboxamide (14).

General Procedure

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in DMF (20 mL) was added the acetamide **1** (0.33 g, 2 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then 2-oxo-*N'*-phenyl-2-(phenylamino)-acetohydrazonoyl chloride (**5b**) (0.55 g, 2 mmol) or 2-bromo-1-phenylethanone (**12**) (0.40 g, 2 mmol) was added portionwise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for additional 12 h, during which the reactant went into solution and a yellow product precipitated. The solid product was filtered off, washed with EtOH and dried. Recrystallization from DMF/EtOH afforded compounds **11** and **14**, respectively.

11: Yield (76%), mp 293-295 ^{o}C; IR (KBr) v 3385 (NH), 3065 (NH), 2193 (C≡N), 1682, 1647 (2C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.05-7.77 (m, 12H, ArH), 10.85 (s, 1H, D_2O-exchangeable, NH), 11.68 (s, 1H, D_2O-exchangeable NH); MS *m/z* (%) 448 (M^++1, 2.88), 446 (25.21), 127 (5.47). Anal. Calcd for $C_{21}H_{14}N_6O_2S_2$: C, 56.49; H, 3.16; N, 18.82. Found: C, 56.42; H, 3.25; N, 18.77%.

14: Yield (68%), mp 232-233 ^{o}C; IR (KBr) v 3625 (NH), 3550-3600 (NH_2), 1663, 1645 (2C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.05-8.04 (m, 12H, ArH), 8.80 (s, 2H, D_2O-exchangeable NH_2), 11.98 (s, 1H, D_2O-exchangeable, NH), 13.19 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%) 421 (2.89), 420 (M^+, 11.04), 127 (33.5), 84 (6.84). Anal. Calcd for $C_{21}H_{16}N_4O_2S_2$: C, 59.98; H, 3.84; N, 13.32. Found: C, 59.88; H, 3.80; N, 13.38%.

6-Amino-2-oxo-4-phenyl-1-(thiazol-2-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (18a).

To a solution of 2-benzylidenemalononitrile (**15a**) (0.77 g, 5 mmol) in EtOH (20 mL) was added an equimolar amount of acetamide **1** (0.84 g, 5 mmol), and few drops of piperidine and the reaction mixture was heated under reflux for 2 h. The solid product was collected by filtration, washed with EtOH and then crystallized from DMF to afford compound **18a** in 90% yield, mp > 300 ^{o}C (DMF); IR (KBr) v 3312 and

3350 (NH_2), 2216 (C≡N), 2208 (C≡N), 1666 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.57-7.60 (m, 5 H, ArH), 7.94-7.93 (d, 1H, *J* = 3.0 Hz), 8.00-7.99 (d, 1H, *J* = 3.0 Hz), 8.77 (s, 2H, D_2O-exchangeable NH_2). Anal. Calcd for $C_{16}H_9N_5OS$: C, 60.18; H, 2.84; N, 21.93. Found: C, 60.25; H, 2.92; N, 21.85%.

6-Hydroxy-2-oxo-4-phenyl-1-(thiazol-2-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (18b).

To a solution of 2-cyano-3-phenyl-2-propenoic acid ethyl ester (**15b**) (1.0 g, 5 mmol) in EtOH (20 mL) was added an eqimolar amount of the acetamide **1** (0.84 g, 5 mmol), and few drops of piperidine and the reaction mixture was heated under reflux for 2 h. The solid product that obtained was collected by filtration, washed with EtOH and then crystallized from DMF to afford **18b** in 68% yield, mp > 300 ^oC; IR (KBr) v 2226 (2C≡N), 1693 (C=O), 1641 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.53-9.34 (m, 7H, ArH), 14.24 (s, 1H, D_2O-exchangeable OH); MS *m/z* (%) 321 (18.1), 320 (M^+, 100.0), 127(11.6). Anal. Calcd for $C_{16}H_8N_4O_2S$: C, 59.99; H, 2.52; N, 17.49. Found: C, 60.08; H, 2.48; N, 17.39%.

REFERENCES

1. J. Quiroga, P. Hernandez, B. Insuasty, R. Abonia, J. Cobo, A. Sanchez, M. Nogueras, and J. N. Low, *J. Chem. Soc., Perkin Trans. 1*, 2002, 555.
2. I. Hutchinson, S. A. Jennings, B. R. Vishnuvajjala, A. D. Westwell, and M. F. G. Stevens, *J. Med. Chem.*, 2002, 45, 744.
3. K. D. Hargrave, F. K. Hess, and J. T. Oliver, *J. Med. Chem.*, 1983, **26**, 1158.
4. W. C. Patt, H. W. Hamilton, M. D. Taylor, M. J. Ryan, D. G. Taylor Jr., C. J. C. Connolly, A. M. Doherty, S. R. Klutchko, I. Sircar, B. A. Steinbaugh, B. L. Batley, C. A. Painchaud, S. T. Rapundalo, B. M. Michniewicz, and S. C. J. Olson, *J. Med. Chem.*, 1992, **35**, 2562.
5. P. K. Sharma, S. N. Sawnhney, A. Gupta, G. B. Singh, and S. Bani, *Indian J. Chem.*, 1998, **37B**, 376.
6. J. C. Jean, L. D. Wise, B. W. Caprathe, H. Tecle, S. Bergmeier, C. C. Humblet, T. G. Heffner, L. T. Meltzner, and T. A. Pugsley, *J. Med. Chem.*, 1990, **33**, 311.
7. K. Tsuji and H. Ishikawa, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1601.
8. F. W. Bell, A. S. Cantrell, M. Hogberg, S. R. Jaskunas, N. G. Johansson, C. L. Jordon, M. D. Kinnick, P. Lind, J. M. Morin Jr., R. Noreen, B. Oberg, J. A. Palkowitz, C. A. Parrish, P. Pranc, C. Sahlberg, R. J. Ternansky, R. T. Vasileff, L. Vrang, S. J. West, H. Zhang, and X. X. Zhou, *J. Med. Chem.*, 1995, **38**, 4929.
9. N. Ergenc, G. Capan, N. S. Günay, S. Özkirimli, M. Güngor, S. Özbey, and E. Kendi, *Arch. Pharm. Pharm. Med. Chem.*, 1999, **332**, 343.
10. J. S. Carter, S. Kramer, J. J. Talley, T. Penning, P. Collins, M. J. Graneto, K. Seibert, C. Koboldt, J. Masferrer, and B. Zweifel, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1171.
11. P. J. Sanfilippo, M. C. Jetter, R. Cordova, R. A. Noe, E. Chourmouzis, C. Y. Lau, and E. Wang, *J. Med.*

Chem., 1995, **38**, 1057.

12. H. Kitagawa, T. Ozawa, S. Takahata, M. Iida, J. Saito, and M. Yamada, *J. Med. Chem.*, 2007, **50**, 4710.
13. K. M. Dawood, N. A. Kheder, E. A. Ragab, and S. N. Mohamed, *Phosphorus, Sulfur, Silicon and the Related Elements*, 2010, **185**, 330.
14. M. R. Shaaban, T. M. A. Eldebss, A. F. Darweesh, and A. M. Farag, *J. Chem. Res.*, 2010, 8.
15. A. M. Farag, A. S. Mayhoub, T. M. A. Eldebss, A. E. Amr, K. A. K. Ali, N. A. Abdel-Hafez, and M. M. Abdulla, *Arch. Pharm. Chem Life Sci*, 2010, **343**, 384.
16. N. A. Kheder, E. S. Darwish, and K. M. Dawood, *Heterocycles*, 2009, **78**, 177.
17. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Heterocycles*, 2009, **78**, 937.
18. N. A. Kheder, *Heterocycles*, 2009, **78**, 1281.
19. A. M. Farag, N. A. Kheder, and Y. N. Mabkhot, *Heterocycles*, 2009, **78**, 1787.
20. N. A. Kheder, *Heterocycles*, 2009, **78**, 1815.
21. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Heterocycles*, 2008, **75**, 887.
22. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Heterocycles*, 2008, **75**, 2937.
23. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *ARKIVOC*, 2008, (***xvii***), 107.
24. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Synth. Commun.*, 2008, **38**, 3170.
25. A. M. Farag, A. S. Mayhoub, S. E. Barakat, and A. H. Bayomi, *Bioorg. Med. Chem.*, 2008, **16**, 4569.
26. A. M. Farag, A. S. Mayhoub, S. E. Barakat, and A. H. Bayomi, *Bioorg. Med. Chem.*, 2008, **16**, 881.
27. M. R. Shaaban, T. S. Saleh, A. S. Mayhoub, A. Mansour, and A. M. Farag, *Bioorg. Med. Chem.*, 2008, **16**, 6344.
28. A. S. Girgis, N. Mishriky, A. M. Farag, W. I. El-Eraky, and H. Farag, *Eur. J. Med. Chem.*, 2008, **43**, 1818.
29. G. N. Walker, US pat. 4435407, 1984.
30. W. Dieckmann and O. Platz, *Chem. Ber.*, 1905, **38**, 2986.
31. A. S. Shawali and A. O. Abdelahmid, *Tetrahedron*, 1971, **27**, 2517.
32. R. M. Cowper and L. H. Davidson, *Org. Synth. Coll. Vol., II*, 1943, 840.
33. P. Shanthan Rao and R. V. Venkataratnam, *Tetrahedron Lett.*, 1991, **32**, 5821.