HETEROCYCLES, Vol. 75, No. 11, 2008, pp. 2791 – 2802. © The Japan Institute of Heterocyclic Chemistry
Received, 3rd May, 2008, Accepted, 3rd July, 2008, Published online, 7th July, 2008. COM-08-11427

A FACILE SYNTHESIS OF SOME NEW 7,8-DIHYDROSPIRO-{IMIDAZO[1,2-*a*]PYRIDINE-7,3'-INDOLINE}-2'-ONE DERIVATIVES

Maher F. El-Zohry,* Thanaa A. Mohamed, and Essam M. Hussein

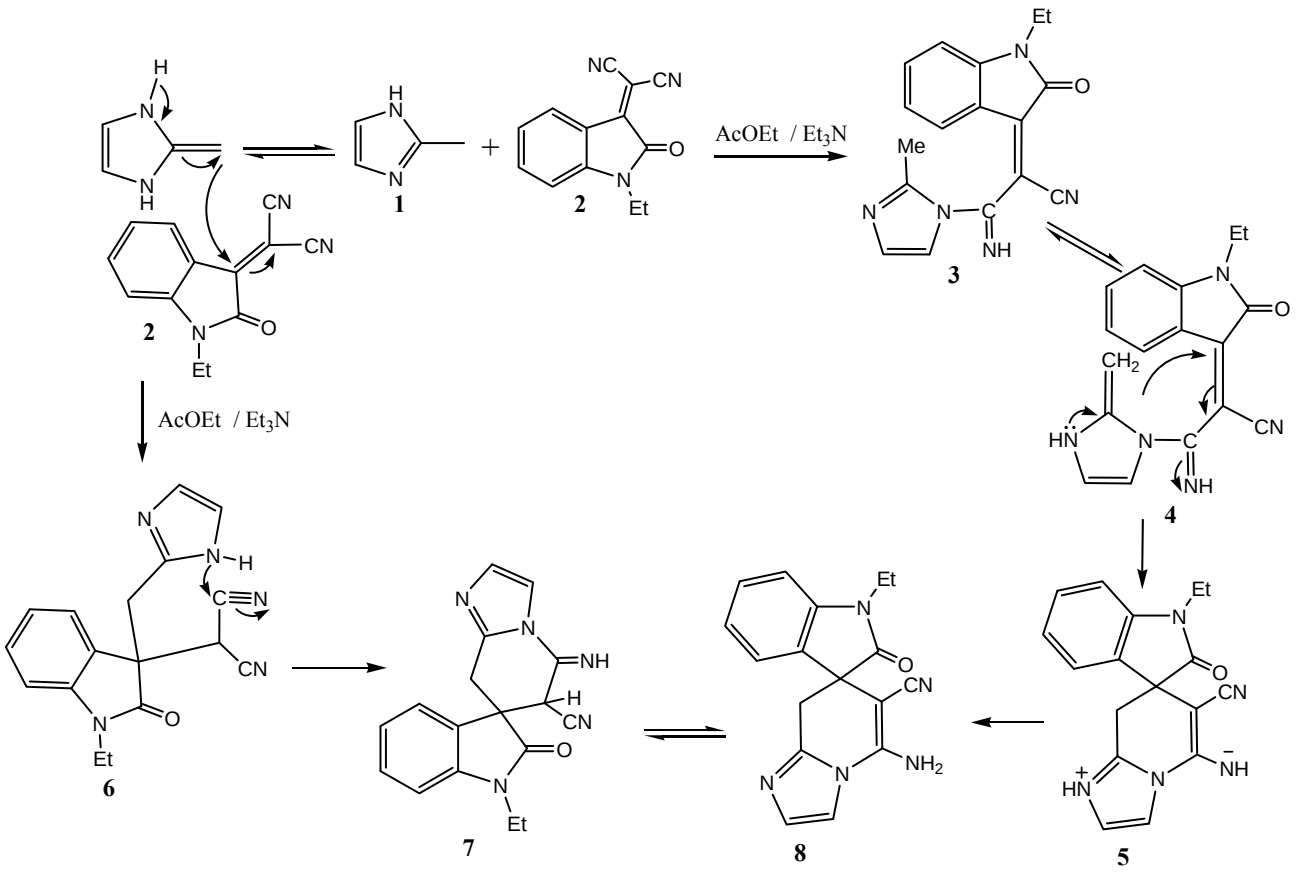
Department of Chemistry, Faculty of Science, Assiut University, Assiut 71516, Egypt
*Corresponding author: e-mail: mfzohry@yahoo.com

Abstract — 2-Methylimidazole (**1**) reacted with 3-dicyanomethylidine-1-ethyl-2-oxoindoline (**2**) in ethyl acetate to afford 5-amino-6-cyano-7,8-dihydro-1'-ethylspiro{imidazo[1,2-*a*]pyridine-7,3'-indolin}-2'-one (**8**), which used as a key intermediate for the synthesis of fused spiroheterocyclic derivatives of imidazo-pyridopyrimidine and/or imidazonaphthyridine nucleus incorporated indoline moiety. The chemical structures of all synthesized compounds were elucidated by the elemental and spectroscopic analyses.

Imidazole derivatives showed diverse biological activities e.g. they are used as factors Xa inhibitors,[1] alpha-2-adrenoceptor agonists,[2] and antithrombotics.[3] Several annulated pyridines isolated from natural sources possess broad spectrum of therapeutic activity. Members of this class were found to be protectors against gastric erosion,[4] coronary vasodilator, and blood-pressure-heightening agents.[5] They also proved to be tuberculostatic, antiviral, fungicidal, insecticidal, and pesticidal,[6,7] and pyrimidine derivatives have been used as adenosine kinase inhibitors.[8]

From this point of view and in continuation to our previous work[9-16] we report herein the synthesis of some new spiroheterocycles of imidazopyridines and imidazopyridopyrimidine and/or imidazo-naphthyridine containing indoline moiety. Our syntheses started with the reaction of 2-methylimidazole (**1**) with 3-dicyanomethylidine-1-ethyl-2-oxoindoline (**2**) in ethyl acetate in the presence of catalytic amount of triethylamine to afford 5-amino-6-cyano-7,8-dihydro-1'-ethylspiro{imidazo[1,2-*a*]pyridine-7,3'-indolin}-2'-one (**8**).

The formation of compound (**8**) could be explained by the following tow possible mechanisms, which could be illustrated in (**Schemes 1**). The first mechanism is supposed that compound (**8**) is obtained by the following[17,18]: initial nucleophilic attack by the *NH* of compound (**1**) on one nitrile carbon of (**2**) gives rise to intermediate (**3**) which are in equilibrium with the tautomer (**4**).



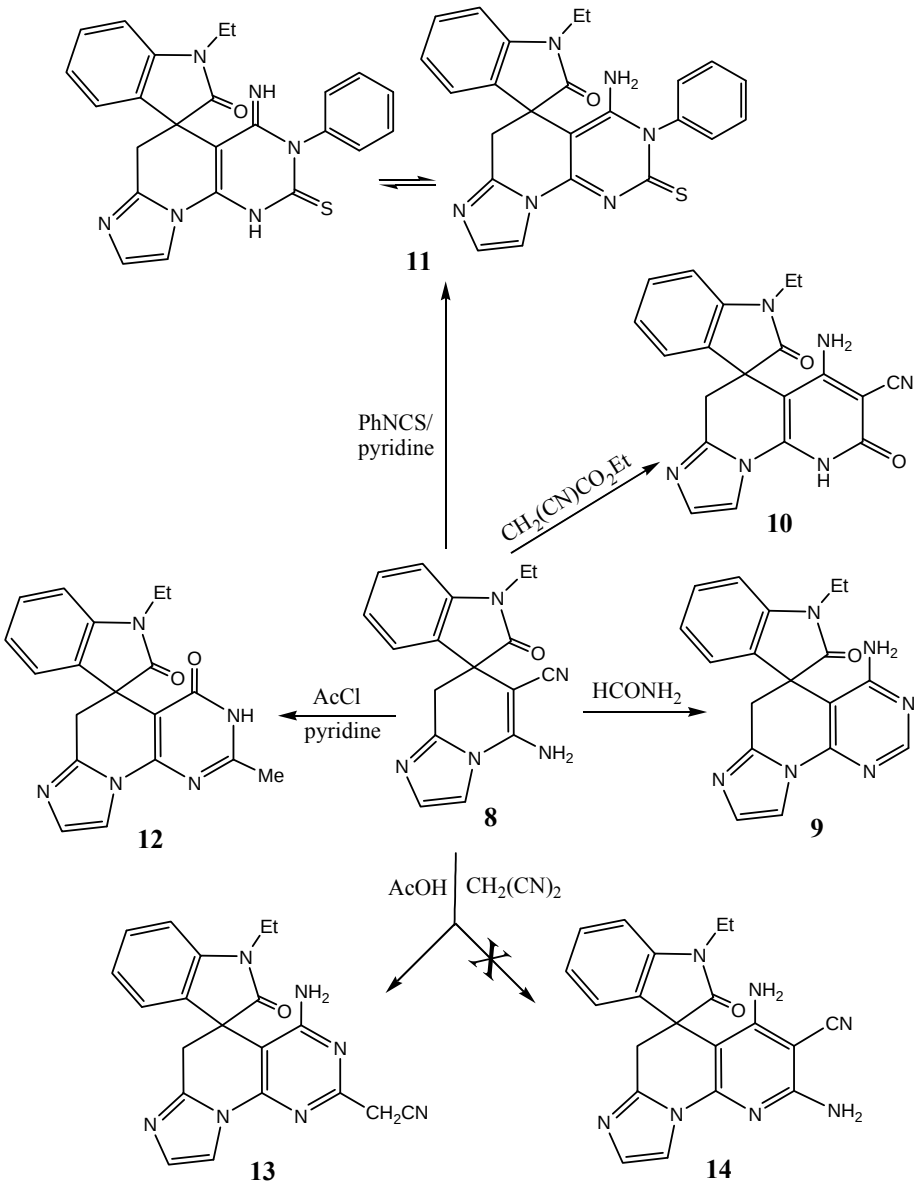
Scheme 1

The latter, exhibit nucleophilic character at the terminal methylene carbon atom which attacks C3 of (**2**) giving (**5**) which is ultimately isolated as (**8**). The second alternative mechanism is supposed that compound (**8**) is obtained by Michael addition reaction and cyclization.

Compound (**8**) was subjected to further reactions to give fused spiroheterocyclic systems incorporate pyrimidine nucleus in addition to imidazo[1,2-*a*]pyridine and indoline moieties.

Compound (**8**) was used as a key intermediate for the synthesis of fused spiroheterocyclic derivatives of imidazopyridopyrimidine and/or imidazonaphthyridine nucleus incorporated indoline moiety.

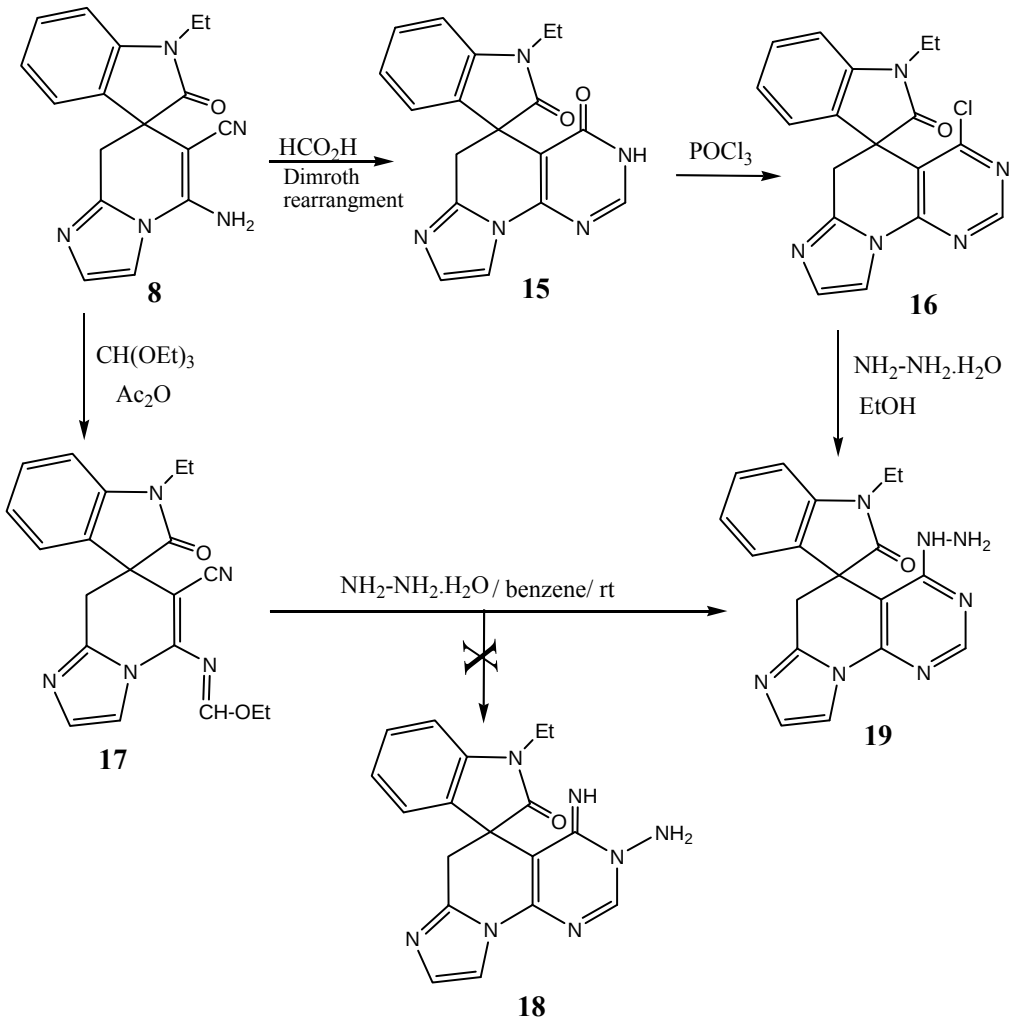
Thus, the reaction of (**8**) with formamide afforded 4-amino-5,6-dihydro-1'-ethylspiro{imidazo-[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indolin}-2'-one (**9**), while the reaction with ethyl cyanoacetate in acetic acid gave 4-amino-3-cyano-1,5,6-trihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-*b*]pyridine-5,3'-indoline}-2,2'-dione (**10**). Reaction of (**8**) with phenyl isothiocyanate in pyridine gave 4-amino-3,5,6-trihydro-1'-ethyl-2'-oxo-3-phenylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indolin}-2-thione (**11**), while the reaction with acetyl chloride afforded 3,5,6-trihydro-1'-ethyl-2-methylspiro-{imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indoline}-2',4-dione (**12**). Reaction of (**8**) with malononitrile in acetic acid yielded 4-amino-2-cyanomethyl-5,6-dihydro-1'-ethylspiro{imidazo[1',2':1,6]-pyrido[2,3-*d*]pyrimidine-5,3'-indoline}-2'-one (**13**) rather than the expected 2,4-diamino-3-cyano-5,6-dihydro-1'-ethylspiro{imidazo[1,2-*a*]naphyridine-5,3'-indolin}-2' -one (**14**) (**Scheme 2**).



Scheme 2

The synthesis of 3,5,6-trihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indoline}-2',4-dione (**15**) was achieved by refluxing compound (**8**) with formic acid, which was converted to its corresponding 4-chloro derivative (**16**) by refluxing with phosphorus oxychloride. The latter compound was readily reacted with hydrazine hydrate in absolute ethanol to afford the corresponding hydrazino derivative (**19**). However, 6-cyano-5-ethoxymethinimino-7,8-dihydro-1'-ethylspiro{imidazo[1,2-*a*]-pyridine-7,3'-indolin}-2'-one (**17**) was obtained by refluxing compound (**8**) with triethyl orthoformate.

Many reports stated that hydrazinolysis of compounds analogous to (**17**) in polar[19,20] and/or nonpolar[21] solvents, gave the respective imino derivatives that could be isolated and identified. Surprising, using a nonpolar solvent (benzene), compound (**19**) was obtained directly without isolation of the imino derivative (**18**)[22] (**Scheme 3**). This could be explained by a nucleophilic attack by the hydrazine molecule on the nitrile carbon of compound (**17**) followed by cyclization via elimination of ethanol molecule to give the thermodynamically more stable derivative (**19**).

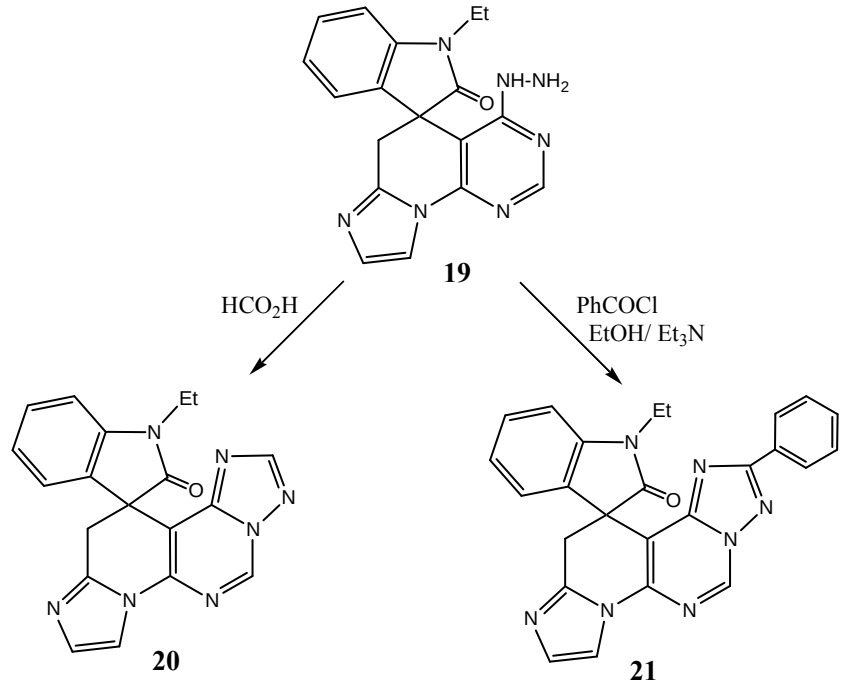


Scheme 3

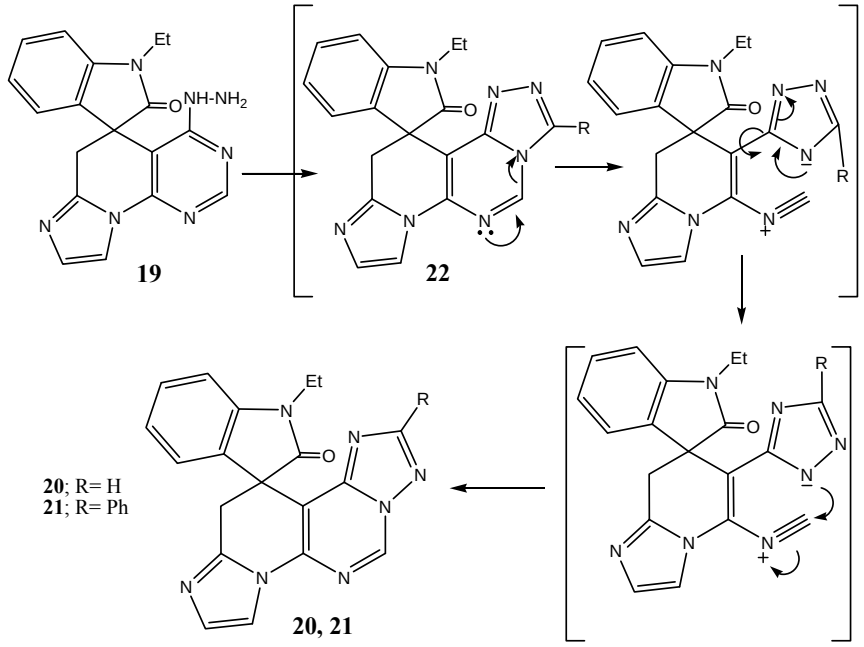
Compound (**19**) was used for the synthesis of some new spirotriazoloimidazopyridopyrimidine derivatives. Previous observations revealed that [1,2,4]triazolo[4,3-*c*]pyrimidines can isomerize under different suitable reaction conditions to the thermodynamically more stable [1,2,4]triazolo[1,5-*c*]-pyrimidines.[22-25] This isomerization was reported early by Miller *et al.*[26,27] when they treated [1,2,4]triazolo[4,3-*c*]pyrimidine derivatives with an acid, base, or thermally.

Thus, refluxing of (**19**) with formic acid afforded 11,12-dihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido-[2,3-*d*]triazolo[5",1"-*f*]pyrimidine-12,3'-indolin}-2'-one (**20**), while the reaction with benzoyl chloride in refluxed ethanol[22] and catalytic amount of triethyl amine gave 11,12-dihydro-1'-ethyl-2-phenylspiro-{imidazo[1',2':1,6]pyrido[2,3-*d*][1,2,4]triazolo[5",1"-*f*]pyrimidine-12,3'-indolin}-2'-one (**21**) (**Scheme 4**).

This could be explained by the formation of the 11,12-dihydrospiro{imidazo[1',2':1,6]pyrido[2,3-*d*]-[1,2,4]triazolo[3",4"-*f*]pyrimidine-12,3'-indoline}derivative (**22**) first, which on heating or in the presence of an acid[24,25] or base[24,26] rearranged to the thermodynamically stable form of 11,12-dihydrospiro-{imidazo[1',2':1,6]pyrido[2,3-*d*][1,2,4]triazolo[5",1"-*f*]pyrimidine-12,3'-indolin}derivatives (**20,21**) (**Scheme 5**).

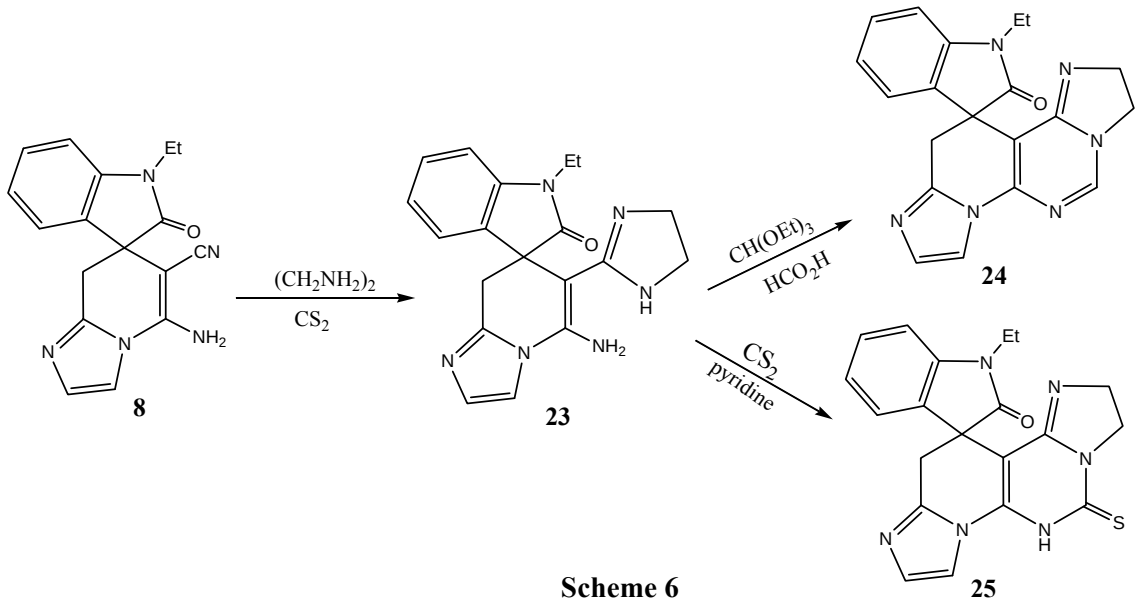


Scheme 4



Scheme 5

5-Amino-7,8-dihydro-1'-ethyl-6-(4,5-dihydro-1*H*-imidazol-2-yl)spiro{imidazo[1,2-*a*]pyridine-7,3'-indolin}-2'-one (**23**) was obtained from (**8**) by reaction with ethylenediamine. Compound (**23**) when refluxed with triethyl orthoformate in acetic acid afforded 11,12-dihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido-[2,3-*d*]imidazolino[2",1"-*f*]pyrimidine-12,3'-indolin}-2'-one (**24**), while, reaction with carbon disulfide in pyridine gave 6,11,12-trihydro-1'-ethyl-2'-oxospiro{imidazo[1',2':1,6]pyrido[2,3-*d*]imidazolino[2",1"-*f*]-pyrimidine-12,3'-indolin}-5-thione (**25**) (**Scheme 6**).



Scheme 6

EXPERIMENTAL

The time required for completion of each reaction was monitored by TLC. All melting points are uncorrected and were measured on a Gallen Kamp apparatus. The IR spectra were recorded on a Shimadzu 470 IR spectrometer (KBr) ν_{max} cm^{-1}. The ^{1}H and ^{13}C-NMR spectra were measured on Varian EM-200 MHz Spectrometer with TMS as internal standard. Mass spectra were determined on a Jeol-600 spectrometer. Elemental analyses were performed on an elemental analysis system GmbH varioel $V_{2.3}$. Column chromatography was performed with silica-gel (230-400 mesh).

Synthesis of 5-amino-6-cyano-7,8-dihydro-1'-ethylspiro{imidazo[1,2-*a*]pyridine-7,3'-indolin}-2'-one (8):

A suspension of 2-methylimidazole (**1**) (0.01 mol) and 3-dicyanomethylidine-1-ethyl-2-oxoindoline (**2**) (0.01 mol) in AcOEt (20 mL) and Et_3N (1 mL) was heated under reflux on water bath for 3 h. Then the reaction mixture was cooled, the solvent was evaporated under vacuum. The crude solid product was subjected to column chromatography using silica-gel as stationary phase and AcOEt-acetone (3:1) as eluent, dried and recrystallized from ethyl acetate to give pale green crystals (76%), mp 200-202 ºC. IR: ν_{max} cm^{-1} 3300, 3200 (NH_2), 2200 (CN), 1705 (C=O), 1625 (C=N); ^{1}H-NMR (DMSO-d_6): δ 7.80-6.65 (m, 6H, Ar-H); 6.60 (s, 2H, NH_2); 3.34 (q, 2H, CH_2); 1.95 (s, 2H, CH_2 *pyridine*); 1.13 (t, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 12.8 (CH_3), 32.5 (CH_2), 43.8 (CH_2), 54.4 (quaternary C), 69.7 (C), 117.5 (CN), 117.7 (CH), 122.3 (CH), 125.1 (CH), 127.7 (2CH), 127.8 (C), 130.0 (CH), 144.9 (C), 148.7 (C=N), 156.5 (C), 170.9 (C=O); MS m/z (rel.int. %): 305.12 (M^+, 1%); 240.10 (23%); 135.04 (100%); 77.04 (11%). Anal. Calcd for $C_{17}H_{15}N_5O$ (305.33): C, 66.87; H, 4.95; N, 22.94. Found: C, 66.79; H, 4.86; N, 22.88.

Synthesis of 4-amino-5,6-dihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indolin}-2'-one (9):

A mixture of compound (**8**) (0.01 mol) and formamide (15 mL) was heated under reflux for 3 h, the reaction mixture was allowed to cool, the formed product was collected, and it was purified by silica-gel column chromatography using AcOEt-toluene (3:1) as eluent. Dried and recrystallized from EtOH to give brown crystals (61%), mp 210-212 °C. IR: ν_{max} cm^{-1} 3300, 3200 (NH_2), 1700 (C=O), 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 8.76 (s, 2H, NH_2); 8.05 (s, 1H, CH *pyrimidine*); 7.80-6.65 (m, 6H, Ar-H); 3.34 (q, 2H, CH_2); 1.85 (s, 2H, CH_2 *pyridine*); 1.12 (t, 3H, CH_3). Anal. Calcd for $C_{18}H_{16}N_6O$ (332.36): C, 65.05; H, 4.85; N, 25.29. Found: C, 65.01; H, 4.77; N, 25.20.

Synthesis of 4-amino-3-cyano-1,5,6-trihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-*b*]pyridine-5,3'-indoline}-2,2'-dione (10):

A solution of compound (**8**) (0.01 mol), and ethyl cyanoacetate (0.01 mol) in AcOH (15 mL) was refluxed for 3 h. The solid product formed during the reflux was collected by filtration, washed well with EtOH (5 mL), dried, and recrystallized from AcOH to give red crystals (65%), mp 243-245 °C. IR: ν_{max} cm^{-1} 3300, 3200 (NH_2), 3100 (NH), 2200 (CN), 1700 (C=O), 1680 (C=O), 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 9.90 (s, 1H, NH); 8.82 (s, 2H, NH_2); 7.81-6.67 (m, 6H, Ar-H); 3.34 (q, 2H, CH_2); 1.83 (s, 2H, CH_2 *pyridine*); 1.13 (t, 3H, CH_3). Anal. Calcd for $C_{20}H_{16}N_6O_2$ (372.38): C, 64.51; H, 4.33; N, 22.57. Found: C, 64.45; H, 4.26; N, 22.45.

Synthesis of 4-amino-3,5,6-trihydro-1'-ethyl-2'-oxo-3-phenylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*]-pyrimidine-5,3'-indolin}-2-thione (11):

A solution of phenyl isothiocyanate (0.015 mol) in dry pyridine (5 mL) was added dropwise with stirring, at rt within 15 min, to a solution of compound (**8**) (0.01 mol) in dry pyridine (15 mL). The reaction mixture was heated under reflux with stirring for 8 h, cooled and poured into ice/water mixture containing a few drops of acetic acid. The solid product thus formed was collected and purified by silica-gel column chromatography using AcOEt-benzene (5:1) as eluent. Dried and recrystallized from dioxane to give bright yellow crystals (54%), mp 267-269 °C. IR: ν_{max} cm^{-1} 3300, 3200 (NH_2), 1705 (C=O), 1640 (C=N), 1450 (C=S); ^{1}H-NMR (DMSO-d_6): δ 8.30-6.34 (m, 11H, Ar-H); 5.91 (s, 2H, NH_2); 3.32 (q, 2H, CH_2); 1.95 (s, 2H, CH_2 *pyridine*); 1.16 (t, 3H, CH_3); Anal. Calcd for $C_{24}H_{20}N_6OS$ (440.52): C, 65.44; H, 4.58; N, 19.09; S, 7.28. Found: C, 65.39; H, 4.50; N, 18.99; S, 7.24.

Synthesis of 3,5,6-trihydro-1'-ethyl-2-methylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indoline}-2',4-dione (12):

A mixture of compound (**8**) (0.01 mol) and acetyl chloride (0.01 mol) in pyridine (15 mL) was heated under reflux for 4 h. Then the reaction mixture was allowed to cool and poured into an ice/water mixture. The formed solid product was collected by filtration, washed with cold water several times, dried and recrystallized from EtOH to give orange crystals (61%), mp 233-235 °C. IR: ν_{max} cm^{-1} 3250 (NH), 1705 (C=O), 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 11.40 (s, 1H, NH); 7.95-6.46 (m, 6H, Ar-H); 3.39 (q, 2H,

CH_2); 2.95 (s, 3H, CH_3); 1.96 (s, 2H, CH_2 *pyridine*); 1.15 (t, 3H, CH_3). Anal. Calcd for $C_{19}H_{17}N_5O_2$ (347.37): C, 65.69; H, 4.93; N, 20.16. Found: C, 65.65; H, 4.89; N, 20.15.

Synthesis of 4-amino-2-cyanomethyl-5,6-dihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*]-pyrimidine-5,3'-indolin}-2'-one (13):

A solution of compound (**8**) (0.01 mol), and malononitrile (0.01 mol) in AcOH (15 mL) was refluxed for 2 h. The solid product formed during reflux was collected by filtration, washed well with EtOH (5 mL), dried, and recrystallized from AcOH to give brown crystals (67%), mp 252-255 °C. IR: ν_{max} cm^{-1} 3200, 3100 (NH_2), 2200 (CN), 1700 (C=O), 1645 (C=N); ^{1}H-NMR (DMSO-d_6): δ 8.30 (s, 2H, NH_2); 7.94-6.50 (m, 6H, Ar-H); 4.06 (s, 2H, CH_2); 3.31 (q, 2H, CH_2); 1.94 (s, 2H, CH_2 *pyridine*); 1.13 (t, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 12.5 (CH_3), 23.8 (CH_2), 38.7 (CH_2), 43.6 (CH_2), 58.4 (quaternary C), 112.3 (C), 114.2 (CH), 117.9 (CN), 122.5 (CH), 124.9 (CH), 127.7 (2CH), 129.7 (CH), 137.8 (2C), 144.8 (CH), 161.6 (C=N), 164.5 (C=N), 166.5 (C), 170.9 (C=O). Anal. Calcd for $C_{20}H_{17}N_7O$ (371.40): C, 64.68; H, 4.61; N, 26.40. Found: C, 64.60; H, 4.58; N, 26.30.

Synthesis of 3,5,6-trihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indoline}-2',4-dione (15):

A mixture of compound (**8**) (0.01 mol) and formic acid (15 mL) was heated under reflux for 3 h, the reaction mixture was cooled, poured into an ice/water mixture and the formed solid product was filtered off, dried and recrystallized from EtOH to give orange crystals (70%), mp 228-230 °C. IR: ν_{max} cm^{-1} 3300 (NH), 1705 (C=O), 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 11.62 (s, 1H, NH); 8.19 (s, 1H, CH *pyrimidine*); 7.95-6.50 (m, 6H, Ar-OH); 3.36 (q, 2H, CH_2); 1.96 (s, 2H, CH_2 *pyridine*); 1.13 (t, 3H, CH_3); Anal. Calcd for $C_{18}H_{15}N_5O_2$ (333.34): C, 64.86; H, 4.54; N, 21.01. Found: C, 64.78; H, 4.46; N, 20.95.

Synthesis of 4-chloro-5,6-dihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indolin}-2'-one (16):

Compound (**15**) (0.01 mol) was refluxed in phosphorus oxychloride (20 mL) for 3 h. The reaction mixture was cooled and poured into ice/water (containing a few drops of pyridine) to give a precipitate, which was collected by filtration, dried, and recrystallized from EtOH to give dense yellow crystals (65%), mp 197-199 °C. IR: ν_{max} cm^{-1} 1705 (C=O), 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 8.21 (s, 1H, CH *pyrimidine*); 7.95-6.55 (m, 6H, Ar-H); 3.35 (q, 2H, CH_2); 1.96 (s, 2H, CH_2 *pyridine*); 1.13 (t, 3H, CH_3). Anal. Calcd for $C_{18}H_{14}ClN_5O$ (351.79): C, 61.46; H, 4.01; N, 19.91; Cl, 10.08. Found: C, 61.38; H, 3.95; N, 19.83; Cl, 10.00.

Synthesis of 6-cyano-5-ethoxymethinimino-7,8-dihydro-1'-ethylspiro{imidazo[1,2-*a*]pyridine-7,3'-indolin}-2'-one (17):

Compound (**8**) (0.01 mol) was refluxed in triethyl orthoformate (15 mL) for 4 h. The solvent was removed under reduced pressure; the formed solid product was collected by filtration, dried, and

recrystallized from EtOH to give yellow crystals (69%), mp 210-212 °C. IR: ν_{max} cm^{-1} 2200 (CN), 1705 (C=O), 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 7.80-6.75 (m, 6H, Ar-H); 5.71 (s, 1H, CH); 4.10 (q, 2H, CH_2O); 3.34 (q, 2H, CH_2N); 1.95 (s, 2H, CH_2 *pyridine*); 1.33 (t, 3H, CH_3); 1.12 (t, 3H, CH_3). Anal. Calcd for $C_{20}H_{19}N_5O_2$ (361.40): C, 66.47; H, 5.30; N, 19.38. Found: C, 66.40; H, 5.18; N, 19.25.

Synthesis of 5,6-dihydro-1'-ethyl-4-hydrazinospiro{imidazo[1',2':1,6]pyrido[2,3-*d*]pyrimidine-5,3'-indolin}-2'-one (19):

Method A: A mixture of compound (**16**) (0.01 mol) and hydrazine hydrate (10 mL) was refluxed in absolute EtOH (15 mL) for 5 h. The solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give bright yellow crystals (67%), mp 218-220 °C.

Method B: To a mixture of compound (**17**) (0.01 mol), hydrazine hydrate (10 mL) in dry benzene (15 mL) was stirred at rt for 6 h. The solvent was removed under reduced pressure, and the residue was recrystallized from EtOH to give bright yellow crystals (70%). Compound (**19**) prepared by this method is identical in all respects (physical and spectral data) to these prepared by *method A*.

IR: ν_{max} cm^{-1} 3300, 3200 (NH_2), 3100 (NH), 1705 (C=O), 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 8.08 (s, 1H, CH *pyrimidine*); 7.92-6.45 (m, 6H, Ar-H); 5.78 (s, 1H, NH); 4.82 (s, 2H, NH_2); 3.34 (q, 2H, CH_2); 1.98 (s, 2H, CH_2 *pyridine*); 1.12 (t, 3H, CH_3). Anal. Calcd for $C_{18}H_{17}N_7O$ (347.37): C, 62.24; H, 4.93; N, 28.23. Found: C, 62.10; H, 4.84; N, 28.16.

Synthesis of 11,12-dihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*][1,2,4]triazolo[5",1"-*f*]-pyrimidine-12, 3'-indoline}-2'-one (20):

Compound **(19)** (0.01 mol) was refluxed in formic acid (20 mL) for 6 h. The reaction mixture was cooled and poured into ice/water. The formed solid product was collected by filtration, dried and then recrystallized from AcOH to give yellow crystals (60%), mp 227-229 °C. IR: ν_{max} cm^{-1} 1705 (C=O), 1640 (C=N), 1625 (C=N); ^{1}H-NMR (DMSO-d_6): δ 8.12-6.40 (m, 8H, Ar-H); 3.35 (q, 2H, CH_2); 1.97 (s, 2H, CH_2 *pyridine*); 1.12 (t, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 12.4 (CH_3), 38.7 (CH_2), 43.6 (CH_2), 58.7 (quaternary C), 114.3 (CH), 123.2 (2CH), 127.8 (2CH), 129.2 (C), 129.9 (CH), 137.9 (2C), 139.5 (CH=N), 144.8 (C), 148.9 (C), 151.0 (CH=N), 164.2 (C), 170.9 (C=O); MS m/z (rel.int. %): 357 (M^+, 30%); 301 (55%); 284 (100%); 267 (20%); 256 (25%); 227 (20%); Anal. Calcd for $C_{19}H_{15}N_7O$ (357.37): C, 63.86; H, 4.23; N, 27.44. Found: C, 63.73; H, 4.16; N, 27.38.

Synthesis of 11,12-dihydro-1'-ethyl-2-phenylspiro{imidazo[1',2':1,6]pyrido[2,3-*d*][1,2,4]triazolo-[5",1"-*f*]pyrimidine-12,3'-indolin}-2'-one (21):

A mixture of compound (**19**) (0.01 mol), benzoyl chloride (5 mL), and Et_3N (0.5 mL) was refluxed in absolute EtOH (15 mL) for 7 h. The solvent was removed under reduced pressure and the residue was subjected to column chromatography using silica-gel as stationary phase and AcOEt as eluent. The product was collected and recrystallized from AcOH to give orange crystals (52%), mp 237-239 °C. IR:

ν_{max} cm^{-1} 1700 (C=O), 1645 (C=N), 1625 (C=N); ^{1}H-NMR (DMSO-d_6): δ 8.35-6.46 (m, 12H, Ar-H); 3.35 (q, 2H, CH_2); 2.00 (s, 2H, CH_2 *pyridine*); 1.12 (t, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 12.4 (CH_3), 38.5 (CH_2), 43.6 (CH_2), 58.7 (quaternary C), 114.3 (CH), 123.0 (2CH), 127.5 (2CH), 127.8 (2CH), 128.8 (CH), 129.3 (2CH), 129.4 (C), 129.7 (CH), 130.4 (C), 137.7 (2C), 139.5 (CH=N), 144.9 (C), 148.4 (C), 160.0 (C=N), 164.3 (C), 170.9 (C=O). Anal. Calcd for $C_{25}H_{19}N_7O$ (433.46): C, 69.27; H, 4.42; N, 22.62. Found: C, 69.21; H, 4.36; N, 22.55.

Synthesis of 5-amino-7,8-dihydro-1'-ethyl-6-(4,5-dihydro-1*H*-imidazol-2-yl)spiro{imidazo[1,2-*a*]-pyridine-7,3'-indolin}-2'-one (23):

To a mixture of compound (**8**) (0.01 mol), and ethylenediamine (0.011 mol), carbon disulfide (1 mL) was added dropwise. The resulting reaction mixture was heated on a water bath for 10 h. After cooling, the reaction mixture was diluted with water and the solid product was collected by filtration, washed with water, dried, and recrystallized from EtOH to give yellow crystals (50%), mp 219-221 °C. IR: ν_{max} cm^{-1} 3310, 3200 (NH_2), 3190 (NH), 1700 (C=O), 1645 (C=N); ^{1}H-NMR (DMSO-d_6): δ 10.13 (s, 1H, NH); 8.02-6.66 (m, 6H, Ar-H); 6.02 (s, 2H, NH_2); 4.09 (t, 2H, CH_2); 3.92 (t, 2H, CH_2); 3.32 (q, 2H, CH_2); 2.01 (s, 2H, CH_2 *pyridine*); 1.11 (t, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 12.6 (CH_3), 33.5 (CH_2), 43.6 (CH_2), 50.4 (quaternary C), 51.9 ($2CH_2$), 72.7 (C), 117.8 (CH), 122.1 (CH), 124.8 (CH), 127.7 (2CH), 127.8 (C), 129.2 (CH), 140.2 (C-NH_2), 144.8 (C), 147.2 (C), 160.0 (C=N), 170.9 (C=O). Anal. Calcd for $C_{19}H_{20}N_6O$ (348.40): C, 65.50; H, 5.76; N, 24.12. Found: C, 65.44; H, 5.68; N, 24.01.

Synthesis of 11,12-dihydro-1'-ethylspiro{imidazo[1',2':1,6]pyrido[2,3-d]imidazolino[2",1"-*f*]-pyrimidine-12,3'-indolin} -2'-one (24):

A mixture of compound (**23**) (0.01 mol), triethyl orthoformate (10 mL) and glacial AcOH (1 mL) was heated under reflux for 6 h. After cooling, the formed solid product was collected by filtration, dried, and recrystallized from EtOH to give yellow crystals (52%), mp 231-233 °C. IR: ν_{max} cm^{-1} 1700 (C=O), 1645 (C=N), 1625 (C=N); ^{1}H-NMR (DMSO-d_6): δ 8.15 (s, 1H, CH*pyrimidine*); 8.02-6.66 (m, 6H, Ar-H); 4.12 (t, 2H, CH_2); 3.94 (t, 2H, CH_2); 3.33 (q, 2H, CH_2); 2.00 (s, 2H, CH_2 *pyridine*); 1.12 (t, 3H, CH_3); Anal. Calcd for $C_{20}H_{18}N_6O$ (358.40): C, 67.02; H, 5.06; N, 23.45. Found: C, 66.86; H, 4.96; N, 23.32.

Synthesis of 6,11,12-trihydro-1'-ethyl-2'-oxospiro{imidazo[1',2':1,6]pyrido[2,3-*d*]imidazolino-[2",1"-*f*]pyrimidine-12, 3'-indolin}-5-thione (25):

A mixture of compound (**23**) (0.01 mol) and carbon disulfide (10 mL) in dry pyridine (20 mL) was heated on a water bath for 20 h, then the reaction mixture was left to cool. The formed solid product was collected by filtration, washed with water, dried and recrystallized from MeOH to give yellow crystals (45%), mp 276-278°C. IR: ν_{max} cm^{-1} 3200 (NH), 1700 (C=O), 1640 (C=N), 1455 (C=S); ^{1}H-NMR (DMSO-d_6): δ 10.02 (s, 1H, NH); 8.01-6.58 (m, 6H, Ar-H); 4.10-3.89 (m, 4H, $2CH_2$ *imidazoline*); 3.33 (q, 2H, CH_2); 2.01 (s, 2H, CH_2 *pyridine*); 1.12 (t, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 12.5 (CH_3), 33.5 (CH_2),

43.8 (CH_2), 49.2 (CH_2), 50.6 (quaternary C), 50.8 (CH_2), 79.9 (C), 117.6 (CH), 122.1 (CH), 124.9 (CH), 127.8 (2CH), 127.8 (C), 129.7 (CH), 142.8 (C-NH), 144.9 (C), 147.5 (C), 163.1 (C=N), 170.9 (C=O), 178.4 (C=S). Anal. Calcd for $C_{20}H_{18}N_6OS$ (390.46): C, 61.52; H, 4.65; N, 21.52; S, 8.21. Found: C, 61.48; H, 4.60; N, 21.40; S, 8.17.

REFERENCES

1. D. J. P. Pinto, J. R. Pruitt, J. Cacciola, J. M. Favig, Q. Han, M. J. Orwat, M. L. Quan, and K. A. Rossi, PCT Int. Appl. WO 98 28,269 (Cl. C07D207/34), 2 jul 1998, US Appl. 879,944 20 jun 1997, 438 pp (*Chem. Abstr.,* 1998, **129**, 109090n).
2. T. L. Cupps, S. E. Bogdan, R. T. Henry, R. J. Sheldon, W. L. Seibel, and J. J. Ares, PCT Int. Appl. WO 98 23,609 (Cl. C07D403/12), 4 jun 1998, US Appl. 31,740 25 Nov 1996, 53 pp (*Chem. Abstr.,* 1998, **129**, 41131u).
3. J. Altenburger, G. Lassalle, V. Martin, and D. Galtier, PCT Int. Appl. WO 98 22,443 (Cl. C07D233/54), 28 May 1998, FR Appl. 96/14, 309, 22 Nov 1996, 101 pp (*Chem. Abstr.,* 1998, **129**, 41129z).
4. D. E. Beattie, R. Crossley, A. C. W. Curran, G. T. Dixon, D. G. Hill, A. E. Lawrence, and R. G. Sheperd, *J. Med. Chem.,* 1977, **20**, 714.
5. S. Masahiko, K. Eiji, and K. Mitsutaka, Japan Patent No. 7200,811 (Cl. C07D, A61k) 15 March 1969 (*Chem. Abstr.,* 1972, **76**, 140574j).
6. A. Studeneer, G. Salbeck, L. Emmel, and W. Knauf, Ger. Offen. 2,361,438 (Cl. C07D) 26 jun 1975 (*Chem. Abstr.,* 1975, **83**, 114227y).
7. M. S. Al-Thebeiti, *Il Farmaco,* 2000, **55**, 109.
8. S. S. Bhagwat, C. Lee, M. D. Cowart, J. McKie, and A. L. Grillot, PCT Int. Appl. WO 98 46, 605 (Cl. CO7D471/04) 22 Oct. 1998, US Appl. 838, 216, 16 Apr. 1997; 172 pp (*Chem. Abstr.,*1998, **129**, 316240b).
9. A. A. Al-Ahmadi and M. F. El-Zohry, *J. Chem. Tech. Biotechnol.,* 1995, **62**, 366.
10. M. S. Al-Thebeiti and M. F. El-Zohry, *Heteroatom Chemistry,* 1995, **6**, 567.
11. A. A. Al-Ahmadi and M. F. El-Zohry, *Heteroatom Chemistry,* 1996, **7**, 171.
12. M. S. Al-Thebeiti, M. F. El-Zohry, S. S. Al-Lihaibi, and F. A. A. Tirkistani, *Bull. Polish Acad. Sci. Chem.,* 1998, **46**, 351.
13. M. F. El-Zohry, A. A. Al-Ahmadi, and F. A. Aquily, *Phosphorus, Sulfur and Silicon,* 2001, **175**, 1.
14. A. A. Abdel-Hafez and M. F. El-Zohry, *Heterocyclic Commun.*, 2001, **7**, 583.
15. M. F. El-Zohry, A. A. Al-Ahmadi, and F. A. Aquily, *Heterocyclic Commun.,* 2002, **8**, 187.
16. M. F. El-Zohry, Y. A. Elossaily, Th. A. Mohamed, and E. M. Hussein, *Heterocycles,* 2008, **75**, 955.

17. D. Döpp, M. A. Gomaa, G. Henkel, and A. M. Nour El-Din, *J. Chem. Soc., Perkin Trans. 2*, 1996, 573.
18. M. A. Gomaa, Sh. K. Mohamed, and A. M. Nour El-Din, *J. Chem. Res. (S),* 1997, 284.
19. A. H. Bedair, H. A. Emam, N. A. El-Hady, K. A. R. Ahmed, and A. M. El-Agrody, *Il Farmaco,* 2001, **56**, 965.
20. E. A. El-Rady, *Phosphorus, Sulfur and Silicon,* 2006, **181**, 2213.
21. M. S. Al-Thebeiti, *Heterocycles,* 1999, **51**, 1311.
22. M. S. Mohamed, A. E. Rashad, M. E. A. Zaki, and S. S. Fatahala, *Acta Pharm.*, 2005, **55**, 237.
23. C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananthan, and V. S. Bhadti, *J. Heterocycl. Chem.,* 1981, **18**, 43.
24. A. E. Rashad, O. A. Heikal, A. O. H. El-Nezhawy, and F. M. E. Abdel-Megeid, *Heteroatom Chem.,* 2005, **16**, 226.
25. C. G. Dave and R. D. Shah, *J. Heterocycl. Chem.,* 2000, **37**, 757.
26. G. W. Miller and F. L. Rose, *J. Chem. Soc.,* 1964, 5642.
27. G. W. Miller and F. L. Rose, *J. Chem. Soc.,* 1965, 3396.