J. Chem. Sci. Vol. 124, No. 3, May 2012, pp. 647–655.

Activated anilide in heterocyclic synthesis: Synthesis of new hydrazo, dihydropyridazine, tetrahydropyridine, dihydropyridine and pyranopyridine derivatives

IBRAHIM SAAD ABDEL HAFIZ[a,*], MAHMOUD MOHAMED MAHFOUZ RAMIZ[b] and MOHAMED AHMED ELIAN[a]

[a]Department of Chemistry, Faculty of Education, Suez Canal University, Arish 45511, Egypt
[b]Department of Physics and Mathematical Engineering, Faculty of Electronic Engineering, Minoufyia University, Menouf 32952, Egypt
e-mail: dr_ibrahim.saad@yahoo.com

MS received 16 September 2011; revised 26 December 2011; accepted 11 January 2012

Abstract. A series of new hydrazo, dihydropyridazine, tetrahydropyridine, dihydropyridine and pyranopyridine derivatives with known biological activity have been prepared through the reactions of 3-oxo-3-phenyl-N-(pyridine-3-yl) propanamide **3** and enaminonitrile **17** with some electrophilic reagents, nucleophilic reagents, and aryl diazonium salts. The newly synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral studies.

Keywords. Hydrazo; dihydropyridazine; tetrahydropyridine; dihydropyridine; pyranopyridine.

1. Introduction

The pyridine nucleus is one of the most important heterocycles found in many natural products, pharmaceuticals and functional materials.[1] Several substituted pyridines and their derivatives were reported to exhibit significant antimicrobial,[2] antiinflammatory[3] and anticancer activities.[4] Other evidence for the potent activity of pyridine in biological systems is its presence in the important vitamins niacin and pyridoxine (vitamin B6) and also in highly toxic alkaloids such as nicotine.[5–7] The wide-ranging biological activity associated with many substituted pyridine derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest.

During the past decades increasing interest in the synthesis and biological activities of pyridazine derivatives has been observed.[8–10] Pyridazine compounds have been reported to possess varied biological activities such as anticonvulsant,[9] antibacterial,[11] antiinflammatory[12] anticancer[13] and antiplatelet[14] activities. These facts have prompted us to synthesize some novel pyridazine derivatives. Recently, pyridazinone nucleus has been extensively studied in the search for new and selective medicinal agents as drugs acting on the cardiovascular system.[15,16]

There has been considerable interest in the development of novel compounds with anticonvulsant, antidepressant, analgesic, antiinflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, antitumoral, vasodilator, antiviral and antischistosomiasis activities. Hydrazones possessing an azometine -NHN=CH- proton constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities.[17–25] These observations have been guiding factors for the development of new hydrazones that possess expected biological activities, because we have been involved in a program aimed at developing new rout for the synthesis of heterocyclic compounds of biological interest.[26,27] In previous studies, we reported the utility of polyfunctionally substituted heterocycles in heterocyclic synthesis.[28,29] In continuation of this work and as apart of our biological chemistry programme we report here the utility of 3-oxo-3-phenyl-N-(pyridine-3-yl) propanamide **3** and enaminonitrile **17** in the synthesis of a wide variety of unique heterocyclic systems with expected biological activities.

2. Experimental

Melting points were determined using a Büchi apparatus and are uncorrected. The purity of compound was

*For correspondence

confirmed by TLC using Merck silica gel $60F_{254}$ plates using toluene, ethyl acetate and methanol as a mobile phase and spots were visualized under UV radiation. IR spectra (KBr) were recorded on a Bruker-Vector 22 instrument (Bruker) and frequencies are expressed in cm^{-1}. NMR spectra were recorded with a Varian Gemini spectrometer (300 MHz and 200 MHz) with TMS as the internal reference. Chemical shifts were reported on a ppm scale (δ) relative to TMS as a standard. EI-mass spectra were recorded with a Shimadzu Qp–2010 plus. Elemental analyses were performed at the Microanalytical Centre at the Faculty of Science, Cairo University, Egypt.

2.1 *Preparation of 3-oxo-3-phenyl-N-(pyridin-3-yl)propanamide (**3**)*

A mixture of 3-aminopyridine (10 mmol) and ethyl benzoylacetate (10 mmol) was refluxed in xylene (30 mL) for 5 h. The reaction mixture was allowed to cool and the separated solid product was collected by filtration and crystallized from ethanol to give compound **3** as white crystals, 85% Yield; mp 100–102°C; IR (KBr) 3424 (NH), 3050 (CH-arom), 2923 (CH-aliph), 1685 and 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.16 (s, 2H, CH_2), 7.24–8.70 (m, 9H, aromatic H), 9.67 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 45.10, 123.25, 124.60, 127.8, 127.8, 128.2, 128.2, 132.2, 135.25, 135.90, 137.3, 153.20,172.5, 191.70. MS (*m/z*) 240 (M^+), Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66; Found: C, 69.94; H, 5.01; N, 11.61.

2.2 *General procedure for the synthesis of hydrazo derivatives **5a–d***

A cold suspension of aryl diazonium salts **4a–d** (10 mmol) (prepared from 10 mmol of aryl aromatic amine with the appropriate quantities of sodium nitrite and hydrochloric acid) was gradually added to a cold solution (0–5°C) of **3** (10 mmol) in ethanol (50 mL) containing sodium acetate (2 g) with continuous stirring for 1 h. The resulting reaction product was filtered off, washed with water and crystallized from the proper solvent to give compounds **5a–d**.

2.2a *3-Oxo-3-phenyl-2-(2-phenylhydrazono)-N-(pyridin-3-yl)propanamide (**5a**)*: Formed as yellow crystals (ethanol); 85% Yield; mp 150–152°C; IR (KBr) 3363 and 3128 (NH), 3050 (CH-arom), 1716 and 1655 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.14–8.90 (m, 14H, aromatic H), 11.77 (s, 1H, NH), 14.72 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 116.00, 116.00, 125.00, 125.55, 126.70, 126.70, 129.40, 129.40,131.40, 131.40, 132.95, 134.20,135.40,135.90, 137.60, 146.5, 149.20, 154.50, 160.00, 192.90. MS (*m/z*) 344 (M^+), Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27; Found: C, 69.71; H, 4.63; N, 16.23.

2.2b *2-(2-(4-Chlorophenyl)hydrazono)-3-oxo-3-phenyl-N-(pyridin-3-yl)propanamide (**5b**)*: Formed as pale yellow crystals (ethanol); 88% Yield, mp 178–180°C; IR (KBr) 3311 and 3142 (NH), 3070 (CH-arom), 1608 and 1658 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.13–8.44 (m, 13H, aromatic H), 8.88 (s, 1H, NH), 11.70 (s, 1H, NH); MS (*m/z*) 378 (M^+), Anal. Calcd. for $C_{20}H_{15}ClN_4O_2$: C, 63.41; H, 3.99; Cl, 9.36; N, 14. 79; Found: C, 63.38; H, 3.94; Cl, 9.31; N, 14.74.

2.2c *3-Oxo-3-phenyl-N-(pyridin-3-yl)-2-(2-p-tolylhydrazono)propanamide (**5c**)*: Formed as dark yellow crystals (ethanol); 82% Yield; mp 175–177°C; IR (KBr) 3337 and 3116 (NH), 3050 (CH-arom), 2921 (CH-aliph), 1617 and 1649 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H, Me), 7.10–8.43 (m, 13H, aromatic H), 8.91 (s, 1H, NH), 11.82 (s, 1H, NH); MS (*m/z*) 358 (M^+), Anal. Calcd. for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15. 63; Found: C, 70.33; H, 5.01; N, 15.58.

2.2d *2-(2-(4-Methoxyphenyl)hydrazono)-3-oxo-3-phenyl-N-(pyridin-3-yl)propanamide (**5d**)*: Formed as dark yellow crystals (ethanol/DMF); 90% Yield; mp 210–212°C; IR (KBr) 3285 and 3150 (NH), 3090 (CH-arom), 2934 (CH-aliph), 1634 and 1668 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H, MeO), 6.89–9.10 (m, 13H, aromatic H), 12.02 (s, 1H, NH), 14.81 (s, 1H, NH); MS (*m/z*) 374 (M^+), Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14. 96; Found: C, 67.32; H, 4.80; N, 14.91.

2.3 *General procedure for the synthesis of dihydropyridazine derivatives **7a–d***

A mixture of compounds **5a–d** (10 mmol), ammonium acetate (10 mmol) and malononitrile (10 mmol) was fused in domestic microwave oven for 3 min. The solid precipitate so formed was treated with ethanol and filtered out and crystallized from the proper solvent.

2.3a *5-Cyano-6-imino-1,4-diphenyl-N-(pyridin-3-yl)-1,6-dihydropyridazine-3-carboxamide (**7a**)*: Formed as red-brown crystals (ethanol); 52% Yield; mp 160–162°C; IR (KBr) 3441 and 3298 (NH), 3100 (CH-arom), 2196 (CN), 1625 (C=O) cm^{-1}, ^{1}H NMR

($CDCl_3$) δ 7.26–8.01 (m, 15H, arom-H and NH group), 10.00 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 107.75, 123.00, 124.70, 124.70, 124.95 125.25, 127.30, 128.90, 128.90, 129.90, 129.90, 131.00, 131.00, 132.30, 133.90, 135.2, 137.50, 141.00, 144.45, 149.50, 152.00, 158.50, 164.80. MS (*m/z*) 392 (M^+), Anal. Calcd. for $C_{23}H_{16}N_6O$: C, 70.04; H, 4.11; N, 21.42; Found: C, 69.97; H, 4.09; N, 21.27.

2.3b *1-(4-Chlorophenyl)-5-cyano-6-imino-4-phenyl-N-(pyridin-3-yl)-1,6-dihydropyridazine-3-carboxamide (**7b**)*: Formed as pale yellow crystals (ethanol); 57% Yield; mp 188–190°C; IR (KBr) 3315 and 3207 (NH), 3049 (CH-arom), 2206 (CN), 1648 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90–7.88 (m, 14H, arom-H and NH group), 10.12 (s, 1H, NH); MS (*m/z*) 426 (M^+); Anal. Calcd. for $C_{23}H_{15}ClN_6O$: C, 64.72; H, 3.54; Cl, 8.31; N, 19.60; Found: C, 64.38; H, 3.50; Cl; 8.24; N, 19.55.

2.3c *5-Cyano-6-imino-4-phenyl-N-(pyridin-3-yl)-1-p-tolyl-1,6-dihydropyridazine-3-carboxamide (**7c**)*: Formed as red-brown crystals (ethanol); 54% Yield; mp 170–172°C; IR (KBr) 3272 and 3128 (NH), 2921(CH-aliph), 2197 (CN), 1626 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H, Me); 7.10–7.92 (m, 14H, arom-H and NH group), 9.87 (s, 1H, NH); Anal. Calcd. for $C_{24}H_{18}N_6O$: C, 70.92; H, 4.46; N, 20.68; Found: C, 70.89; H, 4.41; N, 20.61.

2.3d *5-Cyano-6-imino-1-(4-methoxyphenyl)-4-phenyl-N-(pyridin-3-yl)-1,6-dihydro-pyridazine-3-carboxamide (**7d**)*: Formed as red-brown crystals (dioxane); 58% Yield; mp 178–180°C; IR (KBr) 3300 and 3285 (NH), 3064 (CH-arom), 2921(CH-aliph), 2201 (CN), 1647 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, MeO); 7.30–8.12 (m, 14H, arom-H and NH group), 10.22 (s, 1H, NH); MS (*m/z*) 424 (M^++2); Anal. Calcd. for $C_{24}H_{18}N_6O_2$: C, 68.24; H, 4.29; N, 19.89; Found: C, 68.11; H, 4.15; N, 19.70.

2.4 *General procedure for the synthesis of tetrahydropyridine derivatives **10a–d***

A mixture of propanamide derivatives **3** (10 mmol) and arylidenemalononitriles **10a–d** (10 mmol) in ethanol (100 mL) containing catalytic amount of piperidine was heated under reflux for 5 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give the tetrahydropyridine derivative **10a–d**.

2.4a *2-Amino-5-benzoyl-6-oxo-4-phenyl-1-(pyridin-3-yl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**10a**)*: Formed as white crystals (dioxane); 85% Yield; mp 243–245°C; IR (KBr) 3250, 3194 (NH_2), 3064 (CH-arom), 2934 (CH-aliph), 2187 (CN), 1699 and 1654 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (d, 1H, J = 6.6 Hz, H-4), 4.92 (d, 1H, J = 6.6 Hz, H-5), 7.26–8.14 (m, 14H, aromatic H), 8.78 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 37.95, 68.60, 83.80, 115.40, 122.50, 126.80, 127.40, 127.40, 128.35, 129.2, 129.2, 129.60, 129.60, 131.70, 131.70, 135.30, 138.50, 140.00, 140.90, 141.35, 148.70, 157.40, 169.10, 194.70. Anal. Calcd. for $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20; Found: C, 73.02; H, 4.52; N, 14.16.

2.4b *2-Amino-5-benzoyl-4-(4-chlorophenyl)-6-oxo-1-(pyridin-3-yl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**10b**)*: Formed as white crystals (dioxane); 60% Yield; mp 238–240°C; IR (KBr) 3250, 3165 (NH_2), 3050 (CH-arom), 2923 (CH-aliph), 2178 (CN), 1702 and 1685 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.32 (d, 1H, J = 8.1 Hz, H-4), 5.35 (d, 1H, J = 8.1 Hz, H-5), 7.42–8.61 (m, 13H, aromatic H), 8.62 (s, 2H, NH_2); MS (*m/z*) 428 (M^+), Anal. Calcd. for $C_{24}H_{17}ClN_4O_2$: C, 67.21; H, 4.00; Cl, 8.27; N, 13.06; Found: C, 67.17; H, 3.95; Cl, 8.22; N, 13.01.

2.4c *2-Amino-5-benzoyl-4-(2-chlorophenyl)-6-oxo-1-(pyridin-3-yl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**10c**)*: Formed as white crystals (dioxane); 78% Yield; mp 214–216°C; IR (KBr) 3343, 3250 (NH_2), 3073 (CH-arom), 2954 (CH-aliph), 2194 (CN), 1690 and 1655 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.62 (d, 1H, J = 6.6 Hz, H-4), 4.87 (d, 1H, J = 6.6 Hz, H-5), 7.27–8.68 (m, 13H, aromatic H), 8.75 (s, 2H, NH_2); Anal. Calcd. for $C_{24}H_{17}ClN_4O_2$: C, 67.21; H, 4.00; Cl, 8.27; N, 13.06; Found: C, 67.18; H, 3.95; Cl, 8.23; N, 13.02.

2.4d *2-Amino-5-benzoyl-4-(2,4-dichlorophenyl)-6-oxo-1-(pyridin-3-yl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**10d**)*: Formed as brown crystals (ethanol); 70% Yield; mp 140–142°C; IR (KBr) 3349, 3337 (NH_2), 3086 (CH-arom), 2960 (CH-aliph), 2210 (CN), 1680 and 1635 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.55 (d, 1H, J = 6.6 Hz, H-4), 4.79 (d, 1H, J = 6.6 Hz, H-5), 7.18–8.54 (m, 12H, aromatic H), 8.98 (s, 2H, NH_2); MS (*m/z*) 465 (M^++2), Anal. Calcd. for $C_{24}H_{16}Cl_2N_4O_2$: C, 62.22; H, 3.48; Cl, 15.30; N, 12.09; Found: C, 62.18; H, 3.43; Cl, 15.25; N, 12.04.

2.5 *General procedure for the synthesis of tetrahydropyridine derivative **16a,b***

A mixture of propanamide **3** (10 mmol) and 2-(ethoxymethylene) malononitrile **13a** (10 mmol) or ethyl 2-cyano-3-ethoxyacrylate **13b** (10 mmol) in ethanol (100 mL) containing catalytic amount of piperidine was refluxed for 7 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl, the solid product so formed was collected by filtration and crystallized from the proper solvent.

2.5a *2-Amino-5-benzoyl-4-ethoxy-6-oxo-1-(pyridin-3-yl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**16a**)*: Formed as brown crystals (dioxane); 65% Yield; mp 232–234°C; IR (KBr) 3348, 3182 (NH_2), 2948 (CH-aliph), 2213 (CN), 1620 and 1641 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.55 (t, 3H, J = 8.5 Hz, Me), 2.88 (q, 2H, CH_2), 4.20 (d, 1H, J = 5.2 Hz, H-4), 5.19 (d, 1H, J = 5.2 Hz, H-5), 7.35–8.51 (m, 9H, aromatic H), 8.61 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 18.70, 58.20, 66.30, 66.40, 83.60, 108.30, 122.60,128.30, 129.50, 129.50, 131.60, 131.60, 134.90, 137.00, 138.00, 138.50, 145.70, 156.00, 167.90, 195.90, MS (m/z) 362 (M^+), Anal. Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46; Found: C, 66.25; H, 4.98; N, 15.41.

2.5b *Ethyl-2-amino-5-benzoyl-4-ethoxy-6-oxo-1-(pyridin-3-yl)-1,4,5,6-tetrahydropyridine-3-carboxylate (**16b**)*: Formed as pale brown crystals (ethanol/dioxane); 70% Yield; mp 176–178°C; IR (KBr) 3425, 3148 (NH_2), 3029 (CH-arom), 2973 (CH-aliph), 1611 and 1710 and 1740 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.20 (t, 3H, J = 5.8 Hz, Me), 1.60 (t, 3H, J = 6.1 Hz, Me), 3.00 (q, 2H, CH_2), 3.84 (q, 2H, CH_2), 4.19 (d, 1H, J = 5.2 Hz, H-4), 5.33 (d, 1H, J = 5.2 Hz, H-5), 7.04–8.77 (m, 9H, aromatic H), 8.78 (s, 2H, NH_2); MS (m/z) 409 (M^+), Anal. Calcd. for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26; Found: C, 64.49; H, 5.61; N, 10.21.

2.6 *Preparation of 2-ethyl-4-methyl-6-oxo-1, 6-dihydropyridine-3-carbonitrile (**21**)*

A mixture of β-enaminonitrile **17** (10 mmol) and ethyl acetoacetate (10 mmol) was refluxed in xylene (30 mL) for 7 h. The reaction mixture was allowed to cool and the separated solid product was collected by filtration and crystallized from ethanol to give compound **21** as pale yellow crystals (ethanol/dioxane); 70% Yield; mp 136–138°C; IR (KBr) 3330 (NH), 2973 (CH-aliph), 2220 (CN), 1661 (C=O); ^1H NMR ($CDCl_3$) δ 1.19 (s, 3H, Me), 1.29 (t, 3H, J = 4.5 Hz, Me), 2.66 (q, 2H, CH_2), 4.99 (br, 1H, NH), 6.10 (s, 1H, H-pyridine); MS (m/z) 164 (M^++2), Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27; Found: C, 66.60; H, 6.18; N, 17.22.

2.7 *General procedure for the synthesis of dihydropyridine derivatives **22a,b***

A cold suspension of aryl diazonium salts **4b,c** (10 mmol) was gradually added to a cold solution (0–5°C) of **21** (10 mmol) in ethanol (50 mL) containing anhydrous sodium acetate (2 g) with continuous stirring for 1 h. The resulting reaction product was filtered off, washed with water and crystallized from the proper solvent to give compounds **22a,b**

2.7a *5-((4-Chlorophenyl)diazenyl)-2-ethyl-4-methyl-6-oxo-1,6-dihydropyridine-3 carbonitrile (**22a**)*: Formed as red brown crystals (ethanol); 78% Yield; mp 100–102°C; IR (KBr) 3435 (NH), 2921 (CH-aliph), 2200 (CN), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 4.7 Hz, Me), 2.15 (s, 3H, Me), 2.81 (q, 2H,CH_2), 7.22–7.88 (m, 4H, arom-H), 8.01 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) 12.30, 18.00, 23.5, 83.20, 110.10, 112.80, 123.70, 123.70, 124.00, 130.90, 130.90, 144.60, 153.40, 155.20, 185.60. MS (m/z) 301 (M^++1), Anal. Calcd. for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; Cl, 11.79; N, 18.63; Found: C, 59.88; H, 4.32; Cl, 11.74; N, 18.58.

2.7b *2-Ethyl-4-methyl-6-oxo-5-(p-tolyldiazenyl)-1,6-dihydropyridine-3-carbonitrile (**22b**)*: Formed as brown crystals (ethanol); 87% Yield; mp 101–103°C; IR (KBr) 3342 (NH), 2921 (CH-aliph), 2196 (CN), 1627 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H, Me), 2.42 (s, 3H, Me), 1.22 (t, 3H, J = 4.5 Hz, Me), 2.78 (q, 2H, CH_2), 7.15–7.90 (m, 4H, arom-H), 8.00 (s, 1H, NH); MS (m/z) 282 (M^++2), Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99; Found: C, 68.50; H, 5.72; N, 19.94.

2.8 *General procedure for preparation of pyranopyridine derivatives **27a,b***

A mixture of 2-ethyl-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile **21** (10 mmol) and arylidenemalononitriles **8b,c** (10 mmol) in ethanol (50 mL) containing catalytic amount of piperidine was heated under reflux for 4 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with

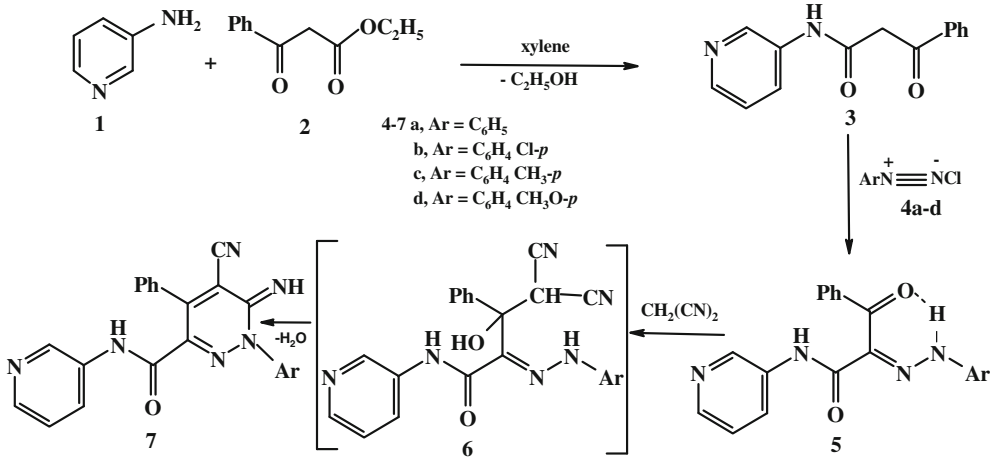
HCl, The solid product so formed was collected by filtration and crystallized from the proper solvent.

2.8a *2-Amino-4-(4-chlorophenyl)-7-ethyl-5-methyl-4H-pyrano[2,3-b]pyridine-3,6-dicarbonitrile (**27a**)*: Formed as pale yellow crystals (ethanol); 73%. Yield; mp 100–102°C; IR (KBr) 3428, 3300 (NH_2), 2934 (CH-aliph), 2206 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3H, Me), 1.72 (t, 3H, J = 5.5 Hz, Me), 3.95 (q, J = 5.5 Hz 2H, CH_2), 5.69 (s, 1H, 4H-pyrane), 7.05–7.54 (m, 6H, aromatic and NH_2); ^{13}C NMR ($CDCl_3$) δ 14.60, 21.30, 31.00, 33.90 77.80, 103.00, 113.90, 117.50 119.20, 131.70, 131.70, 132.40, 134.40, 134.40, 137.00, 148.45, 168.00, 173.20, 178.20. MS (m/z) 350 (M^+), Anal. Calcd. for $C_{19}H_{15}ClN_4O$: C, 65.05; H, 4.31; Cl. 10.11; N, 15.97; Found: C, 65.01; H, 4.28; Cl. 10.08; N, 15.92.

2.8b *2-Amino-4-(2-chlorophenyl)-7-ethyl-5-methyl-4H-pyrano [2,3-b]pyridine-3,6-dicarbonitrile (**27b**)*: Formed as pale yellow crystals (ethanol); 89% Yield; mp 106–108°C; IR (KBr) 3343, 3300 (NH_2), 2934 (CH-aliph), 2196 (2CN) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 5.5 Hz, Me), 1.12 (s, 3H, Me), 3.47 (q, J = 5.5 Hz 2H, CH_2), 5.00 (s, 1H, 4H- pyrane), 7.11–8.27 (m, 6H, aromatic and NH_2); MS (m/z) 350 (M^+), Anal. Calcd. for $C_{19}H_{15}ClN_4O$: C, 65.05; H, 4.31; Cl, 10.11; N, 15.97; Found: C, 65.12; H, 4.25; Cl. 10.00; N, 15.85.

3. Results and discussions

It has been found that 3-aminopyridine **1** reacted readily with ethyl benzoylacetate **2** to give 3-oxo-3-phenyl-N-(pyridine-3-yl) propanamide **3**. Establishing structure **3** was based on its elemental analysis and spectral data. Thus, ^1H-NMR spectrum of compound **3** revealed the presence of a singlet signals at δ = 4.14 ppm corresponding to methylene group, a multiplet signal at δ = 7.24 – 8.70 ppm corresponding to aromatic protons and singlet signal at 9.67 ppm corresponding to NH group. The mass spectrum of **3** showed a molecular ion peak at m/z 240 (M^+) in agreement with its molecular formula $C_{14}H_{12}N_2O_2$ and a number of fragments agree with the proposed structure. The IR spectrum of the same compound is in accordance with the proposed structure. Compound **3** underwent several chemical transformations via its reaction with a variety of electrophilic and nucleophilic reagents. Thus, when compound **3** is allowed to couple with aryl diazonium salts **4a–d** affords the corresponding aryl hydrazones **5a–d** based on their spectral data. For example, the ^1H NMR spectrum of **5a** showed the presence of a multiple signal at δ = 7.14 – 8.90 ppm corresponding to aromatic protons and two signals at δ = 11.77 and 14.72 ppm corresponding to two NH groups, It should be emphasized here that the signal corresponding to amino function of hydrazo group appears at downfield at δ = 14.72 ppm due to the intramolecular hydrogen bonding with carbonyl group.[30] The IR spectrum of the same product further supports the hydrozo structure. Fusion of aryl hydrazones **5a–d** with malononitrile in domestic microwave oven for 3 min afforded the dihydropyridazines **7a–d** via intermediacy of **6a–d** (scheme 1). Formation of **7a** is formed via losing H_2O and subsequent cyclization of the intermediate **6a**. Establishing structure **7** for the reaction of malononitrile with **5** was based on its elemental analysis and spectral data. For example, the ^1H NMR of **7a** revealed the presence of a multiplet

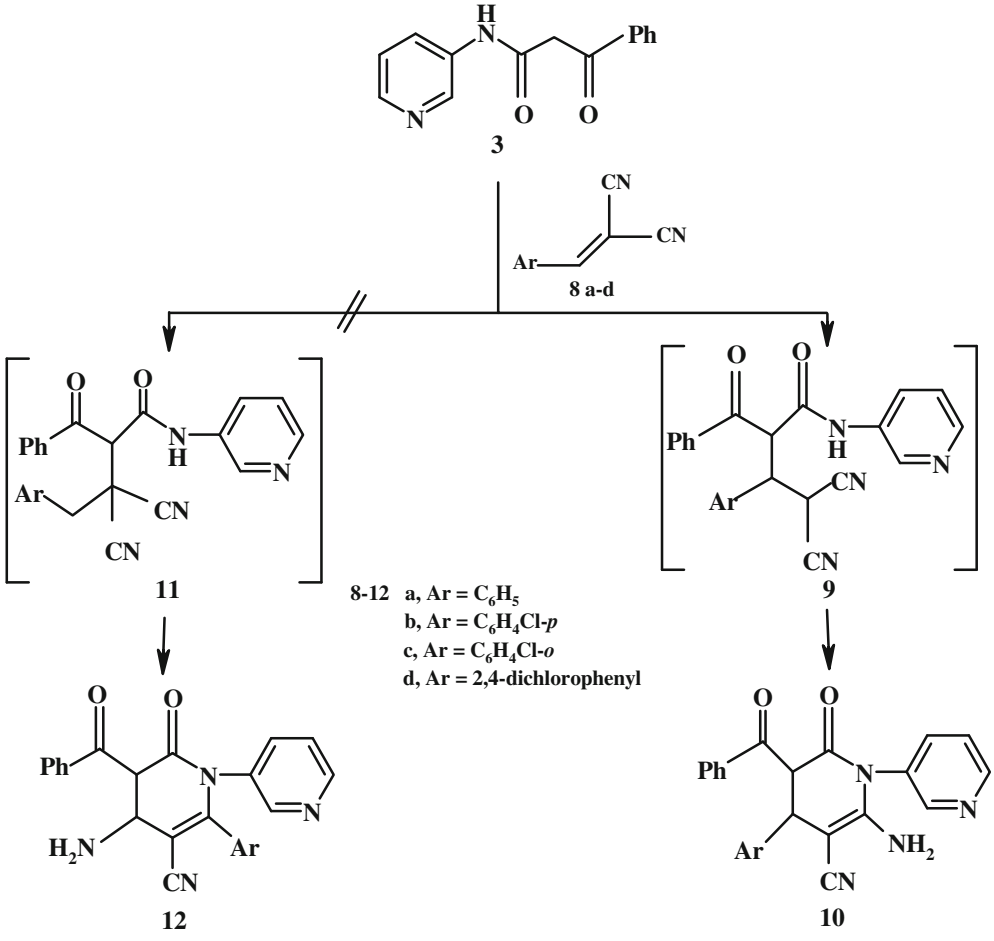


Scheme 1. Synthesis of dihydropyridazine derivatives **7a–d**.

signal at δ = 7.26 − 8.01 ppm corresponding to aromatic protons and NH group. The second NH group appeared as a singlet signal at δ = 10.00 ppm. The mass spectrum of the same product is in accordance with the proposed structure. Thus, it showed a very intense molecular ion peak at 394 (M^++2) and a number of fragments agree with the proposed structure.

Furthermore, the behaviour of **3** toward arylidenemalononitriles was also investigated. Thus, when 3-oxo-3-phenyl-N-(pyridine-3-yl)propanamide **3** refluxed with arylidenemalononitrile **8a** in ethanol containing catalytic amount of piperidine afforded the tetrahydropyridine **10a** rather than its isomeric structure **12a** based on its spectral data. For example, the 1H-NMR of compound **10a** revealed the presence of two doublet signals at δ = 4.25 and δ = 4.92 ppm corresponding to methine protons at C-4 and C-5, a multiplet signal at δ = 7.26 − 8.14 ppm corresponding to aromatic protons and singlet signal at δ = 8.78 ppm corresponding to amino group. Compound **10a** is believed to be formed via Michael type addition on the double bond system of **8a** to give the non isolable intermediate **9a** that cyclizes in the same reaction condition to give **10a** (scheme 2). Similarly, compound **3** reacted with arylidenemalononitriles **8b–d** in refluxing ethanol to give tetrahydropyridine **10b–d** via intermediacy of **9b–d** (scheme 2).

The foregoing results prompted us to investigate the behaviour of **3** towards some activated double bond such as 2-(ethoxymethylene)malononitrile **13a** and ethyl 2-cyano-3-ethoxyacrylate **13b**. Thus, when **3** is refluxed with **13a** in ethanol containing a catalytic amount of piperidine, tetrahydropyridine **16a** was obtained via intermediacy of the non isolable intermediates **14a** and **15a** (scheme 3). The structure of **16a** was established on the basis of its elemental analysis and spectral data. For example, the ^{1}H-NMR of **16a** displayed a triplet and quartet signals at δ = 1.55 and 2.88 ppm corresponding to methyl and methylene groups, respectively, two doublet signals at δ = 4.20 ppm and δ = 5.19 ppm for the methine protons at C-4 and C-5 of the pyridine moiety, a multiplet signal of aromatic protons at δ = 7.35 − 8.51 ppm and a singlet signal at δ = 8.61 ppm characteristic



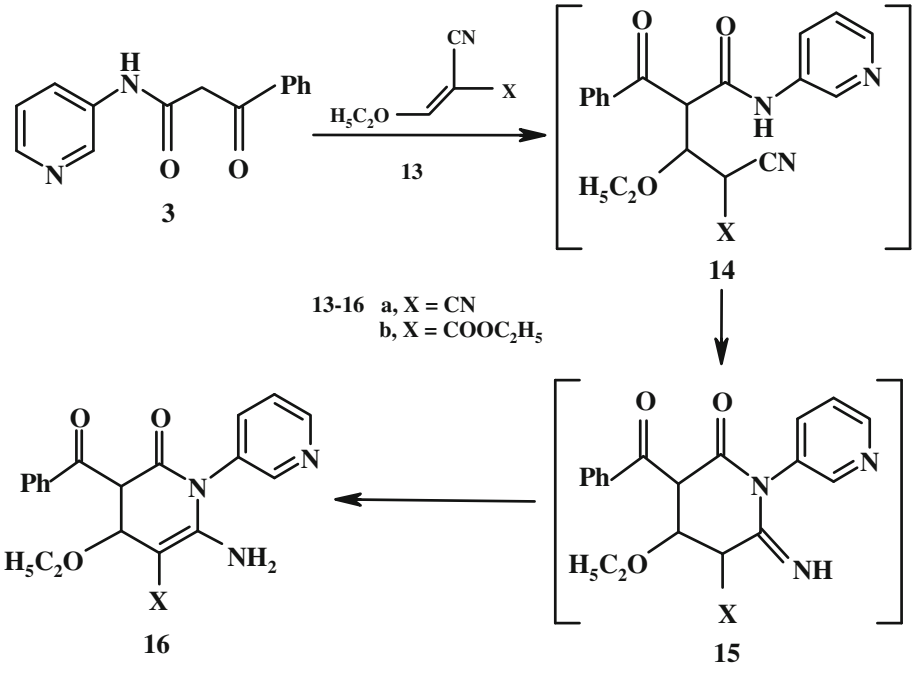
Scheme 2. Sythesis of tetrahydropyridine derivatives **10a–d**.

to amino group. The mass spectrum of compound **16a** showed a molecular ion peak at m/z 362 (M^+) corresponding to a molecular formula $C_{20}H_{18}N_4O_3$. In the same manner, anilide **3** reacted with ethyl 2-cyano-3-ethoxyacrylate **13b** in refluxing ethanol piperidine solution to give tetrahydropyridine **16b** via intermediacy of **14b** and **15b** (scheme 3). The identity of structure **16b** was confirmed by its elemental analysis and spectral data.

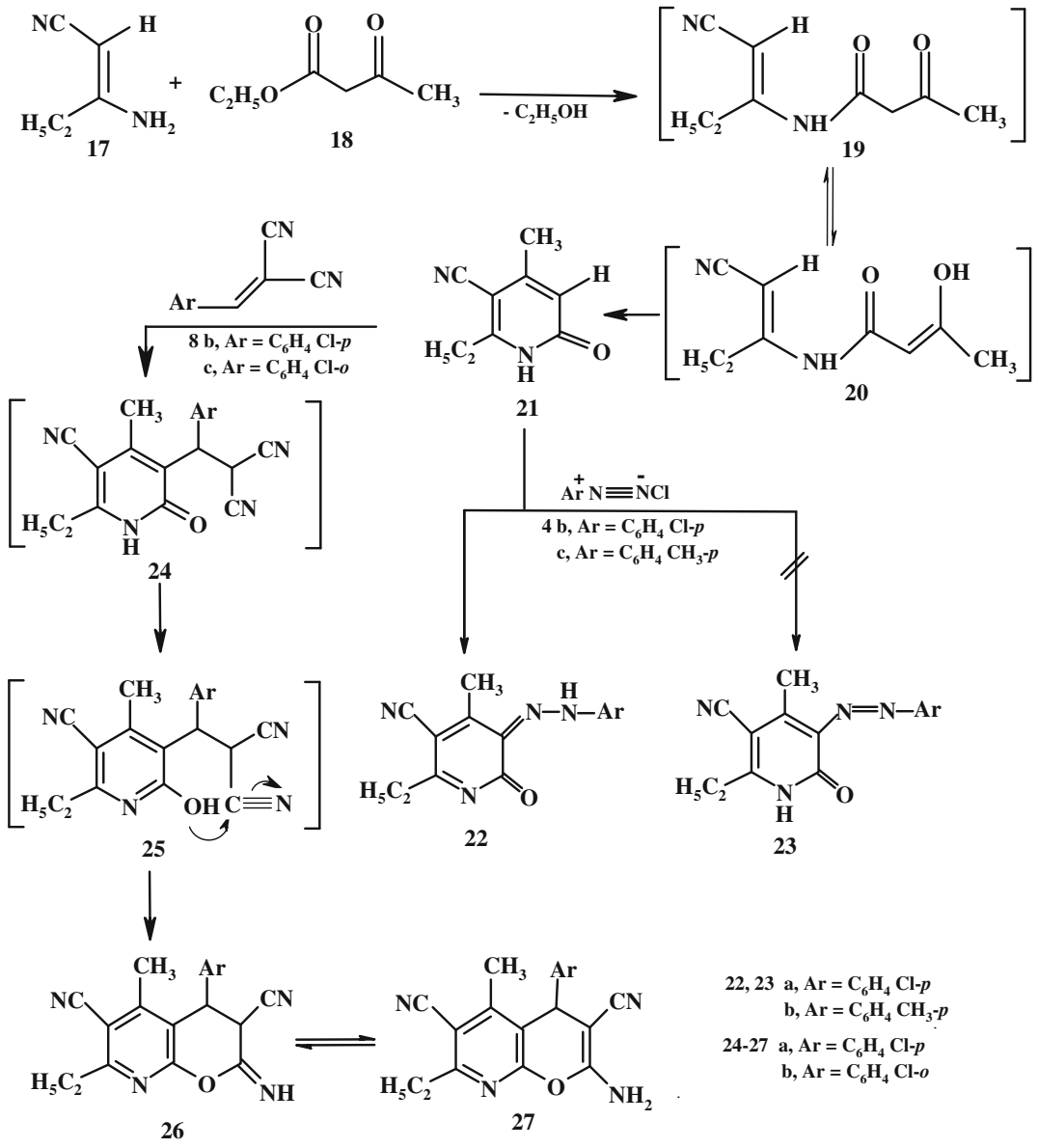
The behaviour of enaminonitrile **17** with ethyl acetoacetate **18** in refluxing xylene afforded the dihydropyridine **21** via intermediacy of acyclic intermediates **19** and **20** that readily tautomerize and cyclized into **21** via losing water molecule (scheme 4). The structure of the latter product was established on the basis of its elemental analysis and spectral data. Thus, the ^{1}H NMR of **21** showed a singlet signal at $\delta = 1.19$ ppm for the methyl group, a triplet signal at $\delta = 1.29$ ppm corresponding to methyl group, a quartet signal at $\delta = 2.66$ ppm characteristic to methylene group, and a broad signal at $\delta = 4.99$ ppm due to NH function and a singlet signal at $\delta = 6.10$ ppm corresponding to aromatic proton at C-3. The mass spectrum of the same product is in accordance with the proposed structure. Thus, it showed molecular ion peak at 164 (M^++2) and a number of fragments agrees with the proposed structure.

The synthetic potentiality of compound **21** towards a variety of electrophilic reagents and aryl diazonium salts was also investigated. Thus, when **21** is allowed to couple with aryl diazonium salts **4b** a compound with molecular formula $C_{15}H_{13}ClN_4O = 300$ was obtained. This was considered to be the hydrazo compound **22** or its tautomeric structure **23**. Structure **23** was ruled out and structure **22** was established for this reaction product based on its elemental analysis and spectral data. For example, the proton ^{1}H NMR revealed the presence of a signal corresponding to amino function at higher field $\delta = 8.01$ ppm. On the other hand, if the reaction product is **23** one would expect that amino function to appear at much lower field (scheme 4). Similarly, compound **21** coupled with aryl diazonium salt **4c** to give **22b** based on its spectral analyses. The behaviour of **21** toward arylidenemalononitrile reagents was also investigated. Thus, treatment of **21** with arylidenemalononitrile **8b** in ethanol piperidine solution afforded a product identified as 2-amino-4-(4-chlorophenyl)-7-ethyl-5-methyl-4H-pyrano[2,3-b]pyridine-3,6-dicarbonitrile (**27a**).

Formation of **27a** from **21** and arylidenemalononitrile **8b** is believed to be formed via Michael type addition of compound **21** on the double bond system of **8b** to give the acyclic intermediate **24a** which is then underwent cyclization and subsequent tautomerism to give **27a** as demonstrated in scheme 4. The structure of the latter product was established on the basis of its elemental analysis and spectral data. Similarly, **21** reacted with arylidenemalononitrile **8c** in the same reaction condition to afford pyranopyridine **26b** (scheme 4). The



Scheme 3. Synthesis of tetrahydropyridine derivative **16a,b**.



Scheme 4. Synthesis of pyranopyridine derivatives **27a,b**.

identity of the product **27b** was established on the basis of elemental analyses and spectral data.

4. Conclusion

The synthesis of a number of new hydrazo, dihydropyridazine, tetrahydropyridine, dihydropyridine and pyranopyridine derivatives with expected biological activities was achieved by utilizing the chemistry of propanamide **3** and enaminonitrile **17**.

Acknowledgement

The authors are grateful to Prof. A E Khodair, Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia, Egypt, for valuable support and improving this manuscript.

References

1. (a) Teague S J 2008 *J. Org. Chem.* **73** 9765; (b) Movassaghi M, Hill M D and Ahmad O K J 2007 *Am. Chem. Soc.* **129** 10096
2. Amr A E, Abo-Ghalia M and Abdalah M M 2006 *Z. Naturforsch.* **61b** 1335
3. Amr A E, Mohamed A M and Ibrahim A A 2003 *Z. Naturforsch.* **58b** 861
4. Amr A E, Mohamed A M, Mohamed S F, Abdel-Hafez N A and Hammam A G 2006 *Bioorg. Med. Chem.* **14** 5481
5. Zhou Y, Kijima T, Kuwahara S, Watanabe M and Izumi T 2008 *Tetrahedron Lett.* **49** 3757

6. Franco L H, Joffe E B K, Puricelly L, Tatian M, Seldes A M and Palermo J A 1998 *J. Nat. Prod.* 611130
7. (a) Farhanullah A N, Goel A and Ram V J 2003 *J. Org. Chem.* **68** 2983; (b) Joule J A, Smith G and Mills K 1995 *Heterocyclic chemistry* (London: Chapman and Hall) 3rd edn., pp. 72
8. Oka Y, Omura K, Miyake A, Itoh K, Tomimoto M, Tada N and Yurugi S 1975 *Chem. Pharm. Bull.* **23** 2239
9. Matsuura I, Yoneda F and Nitta Y 1966 *Chem. Pharm. Bull.* **14** 1010
10. Kricka L 1996 *Pure Appl. Chem.* **68** (I0), 1825
11. Sivakumar R, Anbalagan N, Vedachalam G and Joseph T L 2003 *Biol. Pharm. Bull.* **26(10)** 1407
12. Nagwade R R, Khanna V V, Bhagwat S S and Shinde D B 2005 *Eur. J. Med. Chem.* **40** 1325
13. Sacchi A, Laneri S, Arena F, Abigente E, Gallitelli M, D'amico M, Filippelli W and Rossi F 1999 *Eur. J. Med. Chem.* **34** 1003
14. Park E H and Park M S vatives 2007 *J. Kor. Chem. Soc.* **51(3)** 244
15. Frank H and Heinisch G 1990 Pharmacologically active Pyridazines Part I; In *Progress in medicinal chemistry*, G P Ellis, G B West (eds) Amsterdam: Elsevier **27**, 1
16. Frank H and Heinisch G 1992 Pharmacologically active Pyridazines Part II; In *Progress in medicinal chemistry*, G P Ellis, D K Luscombe (eds) Amsterdam: Elsevier **29**, 141
17. Rollas S, Gülerman N and Erdeniz H 2002 *Farmaco* **57** 171
18. Küçükgüzel Ş G, Rollas S, Küçükgüzel İ and Kiraz M 1999 *Eur. J. Med. Chem.* **34** 1093
19. Küçükgüzel Ş G, Oruç E E, Rollas S, Şahin F and Özbek A 2002 *Eur. J. Med. Chem.* **37** 197
20. Kaymakçıoğlu K B, Oruç E E, Unsalan S, Kandemirli F, Shvets N, Rollas S and Anatholy D 2006 *Eur. J. Med. Chem.* **41** 1253
21. Todeschini A R, Miranda A L, Silva C M, Parrini S C and Barreiro E 1998 *J. Eur. J. Med. Chem.* **33** 189
22. Fraga A G M, Rodrigues C R, Miranda A L P, Barreiro E J and Fraga C A M 2000 *Eur. J. Pharm. Sci.* **11** 285
23. Walcourt A, Loyevsky M, Lovejoy D B, Gordeuk V R and Richardson D R 2004 *Int. J. Biochem. Cell Biol.* **36** 401
24. Gemma S, Kukreja G, Fattorusso C, Persico M, Romano M, Altarelli M, Savini L, Campiani G, Fattorusso E and Basilico N 2006 *Bioorg. Med. Chem. Lett.* **16** 5384
25. Küçükgüzel Ş G, Rollas S, Erdeniz H and Kiraz M 1999 *Eur. J. Med. Chem.* **34** 153
26. Abdel Hafiz I S 2000 *Z. Naturforsch.* **55b** 321
27. Abdel Hafiz I S, Darwish E S and Mahmoud F F 1999 *J. Chem. Res.* (M). 3254
28. Gaber H M, Abdel Hafiz I S, ElSawy K M and Sherif M S 2010 *Acta Chim. Slov.* 57
29. Hussein A M, Ishak E A, Abdel Hafiz I S and Elnagdi M H 2007 *Phosphorus, Sulfur, Silicon.* **182** 2897
30. Hafiz A, Ibrahim S, Ramiz M M M and Sarhan A A M 2011 *Chin. J. Chem.* **29** 1154