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1-Naphthyl-2-cyanoacetamide in heterocyclic synthesis: synthesis and evaluation of the antimicrobial activity of some new pyridine, pyrimidine, and naphtho[2,1-*b*] oxazine derivatives

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Abstract 1-Naphthyl-2-cyanoacetamide **1** reacts with arylidene malononitrile to afford a novel 2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile derivative **6**. Heating of **1** under reflux with the 1,3-diketones acetylacetone and benzoylacetone furnished the corresponding 3-cyano-2-pyridones derivatives **7** and **8**, respectively. Fusion of **1** with 2 mol malononitrile afforded pyridinylacetamide **9**. Condensation of **1** with nitrosonaphthols or salicylaldehyde afforded naphthoxazines **11** and **13**, or chromene **17**, respectively. Coupling of **1** with 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-diazonium chloride gave the hydrazone **15**, which cyclized with acetic acid to afford the corresponding pentaaza derivative **16**. Treatment of **1** with DMF–DMA gave acrylamide **19**, which when reacted with hydrazine hydrate, *o*-phenylenediamine, thiourea, or guanidine hydrochloride to afford the corresponding 3-aminopyrazole, diazepine, and pyrimidine derivatives **20**, **21**, **22**, and **23** respectively. The newly synthesized compounds were characterized by elemental analysis and use of spectral data (IR, ^{1}H NMR, ^{13}C NMR, and MS).The newly synthesized compounds were tested for their in-vitro antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) bacteria. The results clearly showed that most of the synthesized compounds had mild to moderate activity against the bacteria.

Dedicated to the author's father Mr Rabie Shafek who died in the third day of Eid Al-Adha, 6 October 2014

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Introduction

Nitrogen derivatives of 2-cyanoacetamide are extremely important precursors in heterocyclic synthesis [1–6]. The simplest and most convergent preparation of this class of compounds has been described elsewhere [7]. They are used as reactants because the carbonyl group, the active hydrogen on C-2, and the cyano function of these compounds are suitably positioned to enable reactions with common reagents to form a variety of heterocyclic compounds with pharmacological applications, for example anti-inflammatory [8, 9], antitumor [10, 11], and antibacterial and antifungal [12–15] activity, use as analgesic agents [16] and AKT inhibitors [17], and other medicinal properties [18, 19]. Because of this biological importance and as a part of our program of development of new approaches to synthesis of heterocyclic compounds expected to have biological activity [20–23] we report herein of the utility of 1-naphthyl-2-cyanoacetamide, **1**, as a building block for synthesis of several new thiazolidine, pyrazole, pyridine, oxazine, and chromene derivatives.

Experimental

All melting points were measured on a Gallenkamp melting point apparatus. IR spectra (KBr) were acquired with a Perkin–Elmer model 157 infrared spectrophotometer. NMR spectra were acquired, at Stockholm University, with a Bruker spectrometer at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR) in DMSO-d_6 as solvent and with TMS as internal standard; and chemical shifts are expressed as δ/ppm. Mass spectra were acquired with GCMS-QP1000 EX and Jeol JMS600 spectrometers at 70 eV. Elemental analysis was performed by the microanalytical unit of the Faculty of Science, Cairo University.

Reaction of cyanoacetamide, **1**, with aromatic aldehydes, general procedure

Equimolar amounts of **1** (0.21 g, 1 mmol) and the aldehydes 4-hydroxybenzaldehyde (0.122 g,1 mmol) or piperonal (0.15 g, 1 mmol) in ethanol (15 mL) containing few drops of piperidine were heated under reflux for 30 min. The solid product which precipitated was isolated by filtration, dried, and recrystallized from 2:1 EtOH–DMF to afford compounds **2a** and **2b**, respectively.

(E)-2-Cyano-3-(4-hydroxyphenyl)-N-(naphthalen-1-yl) acrylamide ***(2a)***

Yellow crystals; yield 97 %; mp 170–172 °C; IR (KBr): υ/cm^{-1} = 2,214 (CN), 1,662 (C=O), MS *m/z* (%): 314 (M^+, 13.5), 212.0 (M^+, 58.3), 172.8 (25), 169.8 (93.7), 142.0 (39.9), 128.0 (2.6) Anal. Calcd. for $C_{20}H_{14}N_2O_2$ (314.3): C, 76.42; H, 4.49; N, 8.91 % Found: C, 76.56; H, 4.57; N, 8.69 %.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-cyano-N-(naphthalen-1-yl) acrylamide ***(2b)***

Yellow crystals; yield 95 %; mp 170–172 °C; IR (KBr): υ/cm^{-1} = 2,213 (CN), 1,650 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 6.21 (s, 2H, CH_2), 7.17–8.01 (m, 10H, Ar–H), 8.32 (s, 1H, CH), 10.41 (s, H, NH).^{13}C-NMR (100 MHz, DMSO-d_6): δ/ppm = 161.61, 151.2, 150.75,148.13, 133.74, 133.08, 128.81, 128.2, 128.13, 126.67, 126.21, 126.17, 126.06, 125.55, 123.56, 123.11, 116.91, 109.11, 108.09, 103.65, 102.41; MS *m/z* (%): 343 (M^++1, 13.5), 342.0 (M^+, 58.3), 199.8 (100), 169.8 (93.7), 142.0 (39.9), 128.0 (2.6) Anal. Calcd. for $C_{21}H_{14}N_2O_3$ (342.3): C, 73.68; H, 4.12; N, 8.18 % Found: C, 73.60; H, 4.17; N, 8.12 %.

Synthesis of 6-amino-4-(aryl)-1-(naphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **(6a**, **b)**

An equimolar amount of 2-cyano-*N*-(naphthalen-1-yl)acetamide **1** (0.21 g, 1 mmol) and few drops of triethylamine were added to a solution of the appropriate arylidene malononitrile (1 mmol) in ethanol (20 mL). The mixture was heated under reflux for 2 h, then left to cool to room temperature. The solid product that formed was collected by filtration, washed with ethanol, then recrystallized from EtOH–DMF to give the corresponding pyridin-2-one derivatives **6a**, **b**.

6-Amino-4-(4-hydroxyphenyl)-1-(naphthalen-1-yl)-2-oxo-1,2 dihydropyridine-3,5-dicarbonitrile ***(6a)***

White crystals; yield 85 %; mp > 300 °C; IR (KBr): υ/cm^{-1} = 2,218 (CN), 1,682 (C=O), 3,424 (NH_2), ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 6.8–8.01 (m, 11H, Ar–H), 8.10 (s, 2H, NH_2). 10.10 (s, 1H, OH), MS *m/z* (%): 378 (M^+, 100), 361.0 (21.0), 349 (10.9), 225 (8.5), 169 (12.3), 127 (67.8). Anal. Calcd. for $C_{23}H_{14}N_4O_2$ (378.4): C, 73.01; H, 3.73; N, 14.81, Found: C, 73.15; H, 3.58; N, 14.69 %.

6-Amino-4-(benzo[d][1,3]dioxol-5-yl)-1-(naphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile ***(6b)***

White crystals; yield 80 %; mp > 300 °C; IR (KBr): υ/cm^{-1} = 2,214 (CN), 1,667 (C=O), 3,425 (NH_2), MS *m/z* (%): 406 (M^+, 100), 378 (17.6), 203 (15.1), 169 (16.7), 127 (84.7). Anal. Calcd. for $C_{24}H_{14}N_4O_3$ (406.4): C, 70.93; H, 3.47; N, 13.79, Found: C, 70.85; H, 3.58; N, 13.69 %.

Reaction of cyanoacetamide derivative **1** with 1,3-dicarbonyl compounds, general procedure

A mixture of compound **1** (0.21 g, 1 mmol) and an equimolar amount of the appropriate 1,3-dicarbonyl compound (acetylacetone 0.1 g, benzoylacetone 0.16 g, or dimedone 0.14 g) (1 mmol) in ethanol (15 mL) containing few drops of piperidine was heated under reflux for 2 h. The reaction mixture was cooled and the

solid obtained was isolated by filtration and recrystallized from ethanol to give compounds **7**, **8**, or **18**, respectively.

*4,6-Dimethyl-1-(naphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile **(7)***

Colorless crystals; yield 95 %; mp 243 °C; IR (KBr): υ/cm^{-1} = 2,220 (CN), 1,730 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 1.87 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.57 (s, 1H, CH of pyridine ring), 7.3–8.12 (m, 7H, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm = 20.66, 20.78, 100.27, 109.3, 115.82, 121.24, 125.94, 126.29, 126.83, 127.92, 128.62, 128.70, 129.63, 133.74, 133.92, 152.43, 160.21, 160.50. MS *m/z* (%): 274 (M^+, 100), 258.8 (51.31), 244.9 (24.4), 217.3 (11.1), Anal. for $C_{18}H_{14}N_2O$ Calcd.: C, 78.81; H, 5.14; N, 10.21 % Found: C, 78.79; H, 5.17; N, 10.23 %.

*6-Methyl-1-(naphthalen-1-yl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile **(8)***

Colorless crystals; yield 90 %; mp 235 °C; IR (KBr): υ/cm^{-1} = 2,217 (CN), 1,728 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 1.96 (s, 3H, CH_3), 6.62 (s, 1H, CH of pyridine ring), 7.11–7.66 (m, 12H, Ar–H). MS *m/z* (%): 336.05 (M^+, 100), 337.05 (M^++1, 25.95), 338.1 (M^++2, 5.75), 320.05 (42.19), 259.05 (21.52), 236.1 (10.34), 219.01 (4.49), 206.1 (4.20), Anal. for $C_{23}H_{16}N_2O$ (336.13) Calcd.: C, 82.12; H, 4.79; N, 8.33 %. Found: C, 82.18; H, 4.73; N, 8.37 %.

*(E)-2-Cyano-2-(3, 3-dimethyl-5-oxocyclohexylidene)-N-(naphthalen-1-yl) acetamide **(18)***

White crystals; yield 90 %; mp 204–205 °C; IR (KBr): υ/cm^{-1} = 2,213 (CN), 1,715, 1,650 (2C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 0.8 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 1.98 (s, 2H, CH_2), 2.50 (s, 2H, CH_2), 3.21 (s, 2H, CH_2), 7.53–8.18 (m, 7H, Ar–H), 8.65 (s, 1H, NH), MS *m/z* (%): 331.1 (M^+, 1.0), 249.1 (2.12), 207.0 (9), 170.1 (7), 143.1 (55), Anal. for $C_{21}H_{20}N_2O_2$ (332.15) Calcd.: C, 75.88; H, 6.06; N, 8.43 % Found: C, 75.81; H, 6.16; N, 8.51 %.

*Synthesis of 2-(4,6-diamino-3,5-dicyanopyridin-2-yl)-N-(naphthalen-1-yl) acetamide **(9)***

Method A A mixture of compound **1** (0.21 g, 1 mmol) and malononitrile (0.132 g, 2 mmol) in a round-bottomed flask containing piperidine (four drops) was fused in an oil bath at 140 °C for 0.5 h, then left to cool. The solid product was washed with ethanol.

Method B A mixture of 3-amino-2,4-dicyanocrotononitrile (0.13 g, 1 mmol) and 1-naphthyl-2-cyanoacetamide **1** (0.21 g, 1 mmol) was fused in an oil bath at 140 °C for 0.5 h, and then left to cool. The solid product was washed with ethanol.

Yellow powder; Yield 65 %; mp 215 °C; IR (KBr): υ/cm^{-1} = 3,423 (NH), 2,218, 2,214 (2CN), 3,450, 3,455 ($2NH_2$) 1,628 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 3.82 (s, 2H, CH_2), 7.12–7.8 (m, 7H, Ar–H), 9.88 (s, 2H, NH_2), 10.23 (s, 1H, NH). MS *m/z* (%): 342.0 (M^+, 42.1), 201 (31.6), 187.2 (26.3), 169.6 (84.2), 142.4

(78.9). Anal. for $C_{19}H_{14}N_6O$ (342.35) Calcd.: C, 66.66; H, 4.12; N, 24.55 %. Found: C, 66.60; H, 4.18; N, 24.59 %.

*Synthesis of naphthoxazine derivatives **11** and **13** and chromene derivative **17***

1-Nitroso-2-naphthol (0.17 g, 1 mmol), 2-nitroso-1-naphthol (0.17 g, 1 mmol), or salicylaldehyde (0.12 g, 1 mmol), was added to a solution of compound **1** (0.21 g, 1 mmol) in ethanol (25 mL) containing few drops of piperidine and the mixture was heated under reflux for 4 h. The solid products formed on pouring into an ice–water mixture containing few drops of hydrochloric acid was collected by filtration, dried, and recrystallized from ethanol to afford compounds **11**, **13**, or **17**, respectively.

*N-(Naphthalen-1-yl)-3-oxo-3H-naphtho[2,1-b][1,4]oxazine-2-carboxamide **(11)***

Violet crystals; yield 70 %; mp 236–238 °C; IR (KBr): υ/cm^{-1}=3,336 (NH), 1,695, 1,655 (2CO), 1,583 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.25–7.99 (m, 13H, Ar–H), 10.25 (s, H, *N*H-amidic). MS *m*/*z* (%): 366 (M^+, 53.3), 350.1 (18.2), 269. 338.1 (4.82), 316.2 (18.), 237.1 (6.4), 224 (100) Anal. Calcd. for $C_{23}H_{14}N_2O_3$ (336): C, 75.40; H, 3.85; N, 7.65 %. Found: C, 75.45; H, 3.76; N, 7.48 %.

*N-(Naphthalen-1-yl)-2-oxo-2H-naphtho [1,2-b][1,4]oxazine-3 carboxamide **(13)***

Violet crystals; yield 75 %; mp 230–232 °C; IR (KBr): υ/cm^{-1} = 3,340 (NH), 1,703, 1,659 (2CO), 1,580 (C=N), ^{1}H-NMR (400 MHz, DMSO-d_6): δ/ppm = 7.49–8.10 (m, 13H, Ar–H), 10.40 (s, H, NH amidic). Anal. Calcd. for $C_{23}H_{14}N_2O_3$ (336.1): C, 75.40; H, 3.85; N, 7.65 %. Found: C, 75.58; H, 3.80; N, 7.61 %.

*2-Imino-N-(naphthalen-1-yl)-2H-chromene-3-carboxamide **(17)***

Orange crystal; yield 95 %; mp 241 °C; IR (KBr): υ/cm^{-1} = 3,450, 3,300 (2NH), 1,680 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.31–8.68 (m, 11H, Ar–H), 8.68 (s, 1H, chromene-CH), 9.49 (s, 1H, NH), 13.38 (s, 1H, NH); MS *m*/*z* (%): 314 (M^+, 6.8), 314 (72.6), 285 (8.2), 171 (21.9), 144 (17.8); Anal. Calcd. for $C_{20}H_{12}NO_2$ (314.3): C, 76.47; H, 4.49; N, 8.91 %. Found: C, 76.55; H, 4.43; N, 8.85 %.

Coupling reaction of **1** with aromatic amine diazonium salts compounds, general procedure

A cold solution of the appropriate diazonium chloride (2 mmol; prepared by adding cold sodium nitrite solution (0.14 g, 2 mmol) to a cold suspension of the appropriate aromatic amine (2 mmol) in conc. HCl (1.5 mL) with stirring) was added, with continuous stirring, to a cold solution of **1** (0.42 g, 2 mmol) at 0–5 °C in pyridine (20 mL). The mixture was left to stand for 2 h, diluted with water, then filtered. The

arylazo derivatives **14a–c** thus obtained was dried and recrystallized from 2:1 EtOH–DMF.

*(E)-2-(Naphthalen-1-ylamino)-2-oxo-N-(p-tolyl)-acetohydrazonoyl cyanide **(14a)***

Reddish brown powder; yield 85 %; mp 215 °C; IR (KBr): υ/cm^{-1} = 3,415, 3,460 (2NH), 2,215 (CN), 1,655 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 2.29 (s, 3H, CH_3), 7.18–7.99 (m, 11H, Ar–H), 10.19 (s, 1H, NH), 11.91 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm = 160.65, 139.91, 133.73, 133.46, 132.72, 129.58, 129.39, 128.19, 128.08, 126.2, 126.12, 126.1, 124.05, 123.21, 121.8, 116.21, 111.57, 106.85, 26.29, 20.45, MS *m/z* (%): 327.8 (M^+, 31.8), 327.5 (M^+, 36.4), 170 (86.4), 142 (68.2). Anal. Calcd. for $C_{20}H_{16}N_4O$ (328.37) C, 73.15; H, 4.91; N, 17.06 %, Found: C, 73.20; H, 4.87; N, 17.11 %.

*(E)-N-(4-Methoxyphenyl)-2-(naphthalen-1-ylamino)-2-oxoacetohydrazonoyl cyanide **(14b)***

Reddish brown; yield 90 %; mp 205 °C; IR (KBr): υ/cm^{-1} = 3,420, 3,450 (2NH), 2,218 (CN), 1,648 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 3.76 (s, 3H, OCH_3), 6.95–7.99 (m, 11H, Ar–H), 10.17 (s, 1H, NH), 11.92 (s, 1H, NH). MS *m/z* (%): 344.7 (M^+, 5.7), 313 (9.2), 222 (16.2) 208 (12.1), 143.0 (100), 142 (23.9). Anal. Calcd. for $C_{20}H_{16}N_4O_2$ (344.37): C, 69.76; H, 4.68; N, 16.27 %, Found: C, 69.70; H, 4.61; N, 16.37 %.

*(E)-N-(4-Chlorophenyl)-2-(naphthalen-1-ylamino)-2-oxoacetohydrazonoyl cyanide **(14c)***

Yellow powder; yield 65 %; mp 205 °C; IR (KBr): υ/cm^{-1} = 3,456, 3,425 (2NH), 2,215 (CN), 1,635 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.42 -8.0 (m, 11H, Ar–H), 10.29 (s, 1H, NH), 12.02 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ/ppm = 161.25, 142.08, 134.64, 133.93, 130.51, 130.38, 129.93, 128.97, 128.91, 127.54, 127.07, 126.44, 125.18, 124.21, 118.73, 112.21, 109.29, MS *m/z* (%): 348 (M^+, 7.0), 316 (3.3), 208 (12.19), 169.6 (3.3), 142.4 (11.1). Anal. Calcd. for $C_{19}H_{13}ClN_4O$ (348.79): C, 65.43; H, 10.16; N, 16.06 %, Found: C, 65.49; H, 10.3; N, 16.12 %.

*Synthesis of 2-cyano-N-(naphthalen-1-yl)-2-[(4,6-dimethyl-1H-pyrazolo[3,4-b] pyridin-3-yl) hydrazono] acetamide **(15)***

4,6-Dimethyl-2*H*-pyrazolo[3,4-*b*]pyridine-3-yl diazonium salt (prepared by dissolving sodium nitrite (0.14 g, 2 mmol) in water (2 mL) and adding to a cold solution of 3-amino-4,6-dimethyl-2*H*-pyrazolo[3,4-*b*]pyridine (0.32 g, 2 mmol) containing the appropriate amount of hydrochloric acid, with continuous stirring) was added, in portions, over a period of 30 min, to a cold (0–5 °C) solution of **1** (0.42 g, 2 mmol) in pyridine (20 mL). The reaction mixture was kept in an icebox overnight and then diluted with water. The solid that precipitated was isolated by

filtration, washed with water, dried, and recrystallized from 2:1 EtOH–DMF to give compound **15**.

Brown powder; yield 60 %; mp 204–205 °C; IR (KBr): υ/cm^{-1} = 3,490 (NH), 2,215 (CN), 1,639 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 2.56 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 4.08 (s, 1H, CH), 7.49–8.09 (m, 8H, Ar–H), 10.27 (s, 1H, NH); MS *m*/*z* (%): 384 (M^+, 0.9), 383 (0.2), 341.7 (58.9), 278 (3.8), 236 (3.8) 208 (3.1), 143.0 (100), 127 (4.0). Anal. Calcd. for $C_{21}H_{17}N_7O$ (383.42): C, 65.79; H, 4.47; N, 25.57 % Found: C, 65.85; H, 4.56; N, 25.49 %.

Synthesis of 4-imino-8,10-dimethyl-N-(naphthalen-1-yl)-4,6-dihydropyrido [2′,3′:3,4] pyrazolo[5,1-c][1,2,4]triazine-3-carboxamide ***(16)***

A solution of **15** (0.383 g, 1 mmol) in glacial acetic acid (20 mL) was heated under reflux for 3 h, then left to cool. The precipitate that formed was isolated by filtration, washed with ethanol, and recrystallized from 1:1 EtOH–DMF to give compound **16**.

Brown powder; yield 75 %; mp > 300 °C; IR (KBr): υ/cm^{-1} = 3,424, 3,460, 3,485 (3NH), 1,639 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 2.53 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 7.29–7.95 (m, 8H, Ar–H), 9.20, (s, 1H, NH) 10.41 (s, 1H, NH). MS *m*/*z* (%): 383 (1.2), 278 (4.1), 236 (2.5) 213 (3.1), 170 (2.3) 143.0 (100). Anal. Calcd. for $C_{21}H_{17}N_7O$ (383.4) C, 65.79; H, 4.47; N, 25.57 %, Found: C, 65.86; H, 4.51; N, 25.66 %.

Synthesis of (E)-2-cyano-3-(dimethylamino)-N-(naphthalen-1-yl) acrylamide ***(19)***

Dimethylformamide dimethylacetal (DMF-DMA) (0.24 g, 2 mmol) was added to a solution of **1** (0.42 g, 2 mmol) in xylene (20 mL). The reaction mixture was heated under reflux for 3 h, then poured into ice-cold water. The resulting precipitate was isolated by filtration, dried, and recrystallized from 1:2 EtOH–DMF to give compound **19**.

Brown glassy crystals; yield 85 %; mp 145 °C; IR (KBr): υ/cm^{-1} = 3,450 (NH), 1,695 (C=O), 2,180 (CN), ^{1}H NMR (400 MHz, DMSO-d_6): δppm = 3.32 (s, 3H, NCH_3), 3.33 (s, 3H, NCH_3), 7.47–7.95 (m, 7H, Ar–H), 9.19 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm = 165.36, 157.44, 134.6, 134.2, 129.67, 128.98, 126.8, 126.69, 126.44, 126.35, 123.75, 123.47, 120.56, 71.43, 47.83, 39.05, MS *m*/*z* (%): 265 (M^+, 3.1), 264.9 (18.5) 123 (100), 169.2 (2.7), 142 (4.4), 80.0 (12.8). Anal. Calcd. for $C_{16}H_{15}N_3O$ (265.31) C, 72.43; H, 5.70; N, 15.84 % Found: C, 72.54; H, 5.61; N, 15.78 %.

Synthesis of 3-amino-N-(naphthalen-1-yl)-1H-pyrazole-4-carboxamide ***(20)***

A mixture of **19** (0.53 g, 2 mmol) and hydrazine hydrate 98 % (0.5 mL, 5 mmol) was heated in ethanol (10 mL) on water bath for 1 h. The separated product was isolated by filtration and recrystallized from DMF–EtOH to give compound **20**.

Yellow powder; yield 65 %; mp 208 °C; IR (KBr): υ/cm^{-1} = 3,455, 3,460 (2NH), 1,635 (C=O), 3,420 (NH_2), ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.50–8.18 (m, 7H, Ar–H), 9.0 (s, 1H, NH), 9.70 (s, 1H, NH), 10.27 (s,

2H, NH_2), ^{13}C-NMR (100 MHz, DMSO-d_6): δ/ppm = 165.89, 157.59, 134.54, 133.4, 129.49, 128.04, 127.73, 126.09, 125.92, 123.48, 121.32, 117.83, 93.19, 85.13, Anal. Calcd. for $C_{14}H_{12}N_4O$ (252.27): C, 66.65; H, 4.79; N, 22.21 % Found: C, 66.54; H, 4.65; N, 22.27 %.

Reaction of **19** with some nitrogen nucleophiles, general procedure

o-Phenylenediamine (0.22 g, 2 mmol), guanidine hydrochloride (0.19 g, 2 mmol), or thiourea (0.15 g, 2 mmol) was added to a solution of compound **19** (0.53 g, 2 mmol) in 1:1 DMF–EtOH (10 mL). The reaction mixture was heated under reflux for 6 h, the solvent was evaporated under reduced pressure, and the residue was treated with ethanol, isolated by filtration, dried, and recrystallized from DMF–EtOH to afford compounds **21**, **22**, and **23**, respectively.

*4-Amino-N-(naphthalen-1-yl)-1H-benzo[b][1,4] diazepine-3-carboxamide (**21**)*

Deep yellow powder; yield 75 %; mp 242–243 °C; IR (KBr): υ/cm^{-1} = 3,460 (NH), 3,440 (NH_2), 1,645 (C=O). ^{1}H NMR (DMSO-d_6): δ/ppm = 5.22 (s, 1H, CH), 7.52 – 7.87 (m, 11H, Ar–H), 9.00 (s, 1H, NH), 9.25 (s, 2H, NH_2), MS *m*/*z* (%): 328.1 (M^+, 0.7), 264 (8.8) 123 (100), 169.8 (1.0), 142 (2.4), 76.9 (3.1). Anal. Calcd. for $C_{20}H_{16}N_4O$ (328.13): C, 73.15; H, 4.91; N, 17.06 %, Found: C, 73.26; H, 5.01; N, 17.0 %.

*2,4-Diamino-N-(naphthalen-1-yl)pyrimidine-5-carboxamide (**22**)*

Pale yellow powder; yield 70 %; mp > 300 °C; IR (KBr): υ/cm^{-1} = 3,458 (NH), 3,440, 3,445 ($2NH_2$), 1,653 (C=O). ^{1}H NMR (DMSO-d_6): δ/ppm = 7.40–8.43 (m, 8H, Ar–H), 8.75 (s, 2H, NH_2), 10.38 (s, 2H, NH_2), 12.18 (s, 1H, NH), Anal. Calcd. for $C_{15}H_{13}N_5O$ (279.11): C, 64.51; H, 4.69; N, 25.07 %, Found: C, 64.61; H, 4.62; N, 25.01 %.

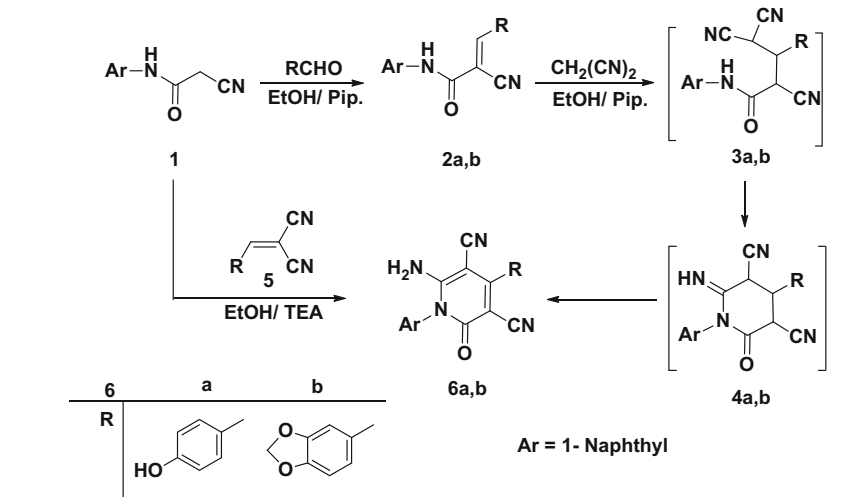
*4-Amino-N-(naphthalen-1-yl)-2-thioxo-1,2-dihydropyrimidine-5-carboxamide **(23)***

Deep yellow crystals; yield 90 %; mp 254–256 °C; IR (KBr): υ/cm^{-1} = 3,423 (NH), 3,356 (NH_2), 1,651 (C=O), 1,155 (C=S). MS *m*/*z* (%): 297.1 (M^++1, 55.1), 296.1 (M^+, 55.1), 226 (53), 169 (54.0), 127 (68). Anal. Calcd. For $C_{15}H_{12}N_4OS$ (296.35): C, 60.80; H, 4.08; N, 18.91 % Found: (296.35): C, 60.70; H, 4.12; N, 18.78 %.

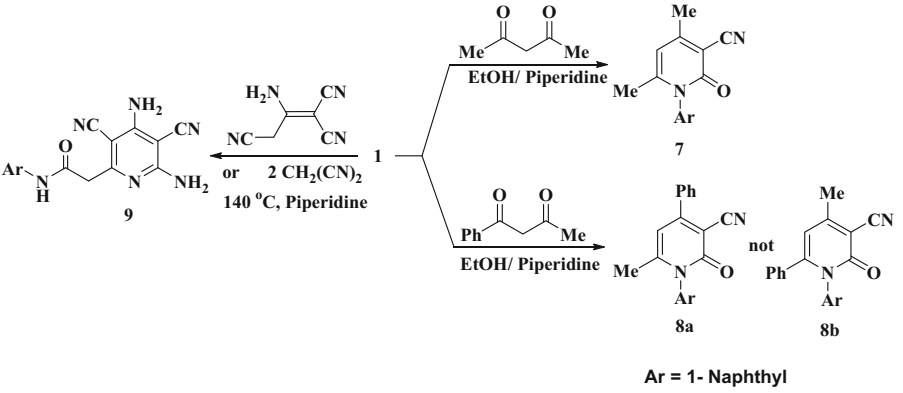
Results and discussion

Chemistry

The reaction sequences used for synthesis of the title compounds are depicted in Schemes 1, 2, 3, 4, 5 and 6. The starting compound, 1-naphthyl-2-cyanoacetamide **1**

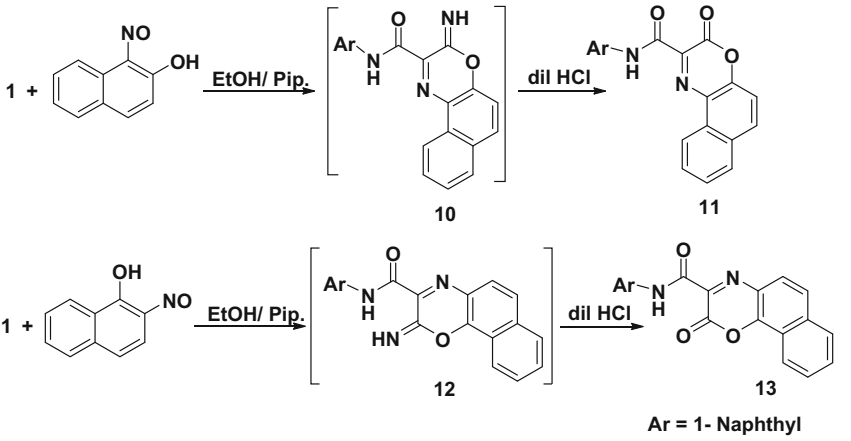


Scheme 1 Synthetic route to pyridine derivatives

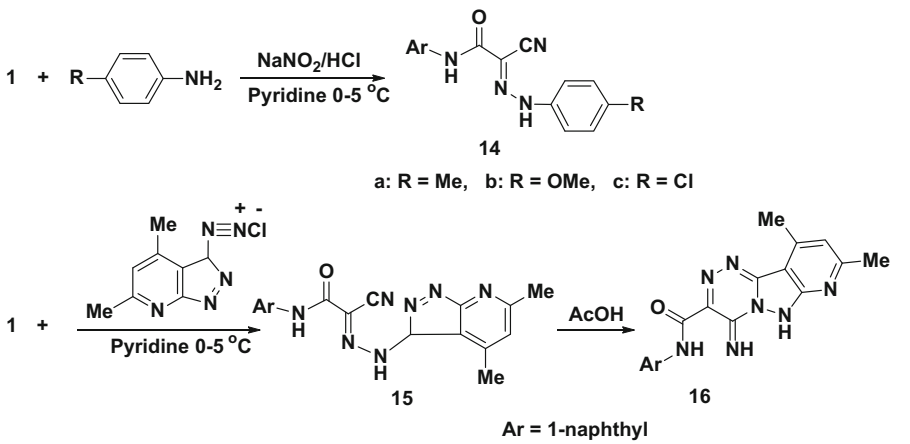


Scheme 2 Reaction of **1** with common bidentate reagents

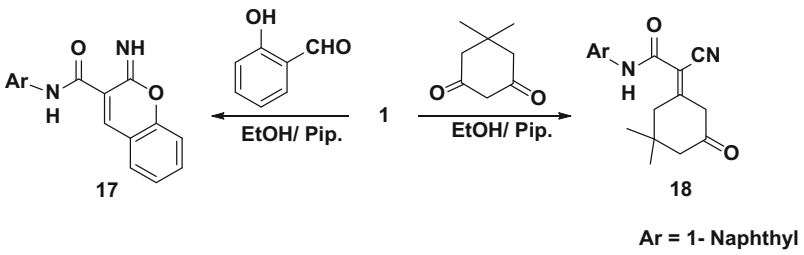
[24], as versatile precursor, was reacted with common reagents to obtain a variety of heterocyclic compounds. Thus, compound **1** reacted with some aromatic aldehydes to afford the corresponding benzylidene derivatives **2a**, **b**. Treatment of the latter compounds with malononitrile furnished the aminopyridone derivatives **6a**, **b**. The IR spectrum of compound **6a** contained absorption bands at 3,424, 2,218, and 1,682 cm^{-1} ascribed to amino, nitrile, and carbonyl, respectively. Formation of **6** may be proceeded via Michael type addition followed by auto-oxidation of the intermediates **4a**, **b**. The structures of **6a**, **b** were confirmed chemically by alternative synthesis, by reaction of **1** with the benzylidenemalononitriles **5** under a similar reaction conditions to give products identical in all respects (mp, mixed mp, and spectral analysis) with **6a**, **b** (Scheme 1).



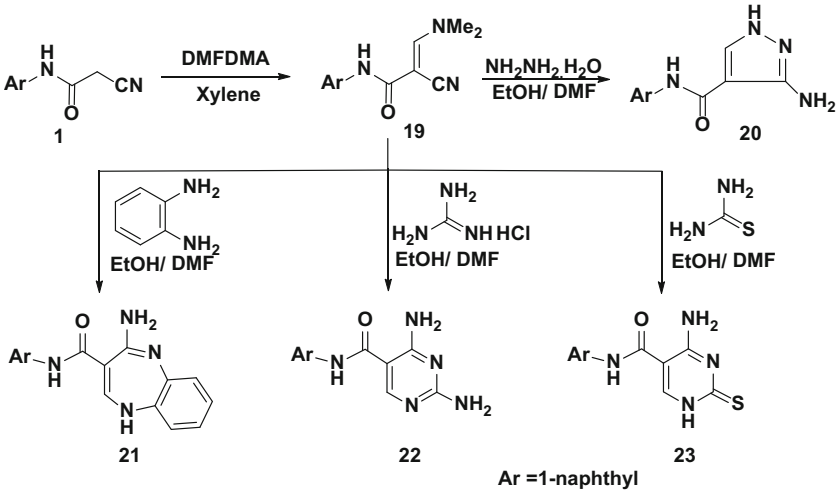
Scheme 3 Formation of naphthoxazine derivatives



Scheme 4 Coupling reaction of **1** with different aromatic amines



Scheme 5 Reaction of **1** with aldehyde and ketone



Scheme 6 Preparation of pyrazole, diazepine, and pyrimidine derivatives

It is well known that many 2-pyridone derivatives have diverse biological activity, e.g. as cardiotonic agents and potential HIV-1 specific reverse transcriptase inhibitors [25, 26]. This study was performed to determine the reactivity of cyanoacetamide derivative **1** toward C-nucleophilic reagents. Thus, reaction of 1-naphthyl-2-cyanoacetamide **1** with acetylacetone, a *β*-diketone, in boiling ethanol containing a catalytic amount of piperidine yielded the pyridine-2-one **7** derivative, and reaction of **1** with benzoylacetone afforded a product with the chemical formula $C_{23}H_{16}N_2O$. It seems two isomers could be formed, **8a** and **8b**, but TLC monitoring indicated formation of one product, **8**. The ^{1}H NMR spectrum contained a methyl proton at δ 1.96 ppm and a methine proton at δ 6.70 ppm, indicative of the more stable and less sterically hindered structure **8a**.

The biological activity of pyridine derivatives is well established and attempts have been made to obtain more active and less toxic pyridine derivatives [27]. In continuation of our medicinal projects with the purpose of developing new procedures for synthesis of pyridines [20] we report here reaction of **1** with malononitrile in the molar ratio 1:2 to give pyridinylacetamide **9** (Scheme 2). The structure of **9** was established on the basis of its IR and ^{1}H NMR spectra. The IR spectrum contains bands at 2,218 and 2,214 cm^{-1} ascribed to two CN groups. The ^{1}H NMR spectrum contained CH_2 as singlet signal at δ 3.82 ppm. A logical mechanism for this reaction was based on dimerization of malononitrile in basic medium to give the malononitrile dimer followed by its reaction with **1** to give **9**. This sequence was confirmed by its alternative synthesis—fusion of **1** with the malononitrile dimer in the molar ratio 1:1 in the presence of a catalytic amount of piperidine gave a single product identical in all respects to **9** (mp, mixed mp, and spectra).

Cyclocondensation of compound **1** with equimolar amounts of 1-nitroso-2-naphthol or 2-nitroso-1-naphthol in boiling ethanol containing a catalytic amount of

piperidine afforded naphthoxazines **11** and **13**, respectively (Scheme 3). The structure **11** was established on the basis of the IR spectrum, which contained an absorption band at 3,336 cm^{-1} (NH). Its ^1H NMR spectrum contained a multiplet at δ 7.25–7.99 ppm, ascribed to aromatic protons, and a D_2O-exchangeable singlet at δ 10.25 ppm for the NH proton. The mass spectrum of **11** contained the molecular ion peak at *m/z* 336.1 (M^+), which is in agreement with the molecular formula $C_{23}H_{14}N_2O_3$.

The reactivity of the methylene group of compound **1** was tested in an electrophilic azo-coupling reaction with aromatic diazonium salts, to yield the corresponding coupling products **14a–c**. Formation of **14a–c** was established on the basis of the presence of a peak at 2,220 cm^{-1} from the CN group in the IR spectra of the products. The ^1H NMR spectrum of **14a** contained a singlet signal at δ 2.29 ppm, corresponding to methyl protons, and a D_2O-exchangeable singlet signal at δ 11.91 ppm from the hydrazo proton. Moreover, its ^{13}C NMR spectrum contained a signal at 20.45 ppm corresponding to the carbon of a methyl group. Coupling of cyanoacetamide **1** with diazotized 3-amino-4,6-dimethyl-2*H*-pyrazolo[3,4-*b*]pyridine in pyridine at 0–5 °C gave hydrazone derivative **15**. Formation of triazine derivative **16** was achieved in excellent yield by heating compound **15** in glacial acetic acid. There was no evidence of a nitrile functional group in the IR spectrum of **16** (Scheme 4).

Chromene derivatives are important compounds with a wide range of pharmacological properties [28, 29]. We report herein reaction of 1-naphthyl-2-cyanoacetamide **1** with salicylaldehyde to form a single product in excellent yield; this was identified as 2-imino-*N*-(naphthalen-1-yl)-2*H*-chromene-3-carboxamide **17**. The ^1H NMR spectrum of compound **17** contained a singlet signal at δ 8.68 ppm attributable to C_4–H proton of the chromene moiety, and a D_2O-exchangeable signal at δ 13.83 ppm characteristic to the imino proton. Condensation of **1** with dimedone in boiling ethanol furnished chalcone **18** in excellent yield (Scheme 5).

Heating of **1** with dimethylformamide dimethylacetal (DMF-DMA) in dry xylene furnished clear brown glassy crystals of **19** in reasonable yield. Elemental analysis and spectral data were in agreement with formation of the enaminonitrile product **19**. Its ^1H NMR spectrum contained singlet signals at δ 3.32 and 3.33 ppm corresponding to the protons of the two methyl groups. The mass spectrum contained a molecular ion peak at *m/z* 265 corresponding to the molecular formula $C_{16}H_{15}N_3O$. The reactivity of enaminonitrile **19** toward some nitrogen nucleophiles was investigated. Thus, **19** reacted with hydrazine hydrate, *o*-phenylenediamine, guanidine hydrochloride, and thiourea to give the corresponding pyrazole, diazepine, and pyrimidine derivatives **20–23**, respectively. The latter compounds are believed to be formed by addition of the amino group to the ethylenic double bond followed by loss of dimethylamine. Intramolecular cyclization gave the final isolated products **20–23**. The structure of **21** was established on the basis of its IR spectrum which contained bands related to NH_2 and NH. The mass spectrum contained a molecular ion peak at *m/z* 328.13 corresponding to a molecular formula $C_{20}H_{16}N_4O$ (Scheme 6).

Table 1 Inhibition zone (mean diameter of inhibition in mm) as a criterion of antibacterial activities of the newly synthesized compound

Compound no.	Inhibition zone (mm)			
	Gram-positive bacteria		Gram-negative bacteria	
	Staph. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*
2a	20 (±0.03)	17 (±0.08)	15 (±0.05)	12 (±0.02)
2b	21 (±0.08)	15 (±0.02)	14 (±0.08)	11 (±0.03)
7	18 (±0.02)	18 (±0.05)	12 (±0.08)	14 (±0.08)
9	17 (±0.04)	11 (±0.09)	10 (±0.08)	11 (±0.04)
14a	15 (±0.08)	18 (±0.08)	19 (±0.08)	13 (±0.02)
14c	13 (±0.01)	20 (±0.04)	13 (±0.02)	14 (±0.07)
15	20 (±0.05)	14 (±0.02)	14 (±0.01)	11 (±0.04)
16	12 (±0.08)	12 (±0.01)	15 (±0.07)	16 (±0.06)
17	19 (±0.09)	19 (±0.03)	14 (±0.09)	13 (±0.02)
18	17 (±0.05)	16 (±0.06)	14 (±0.06)	14 (±0.07)
20	15 (±0.02)	11 (±0.04)	10 (±0.08)	19 (±0.1)
21	13 (±0.07)	10 (±0.03)	10 (±0.08)	10 (±0.02)
23	22 (±0.05)	15 (±0.01)	21 (±0.09)	19 (±0.08)
Blank (DMSO)	0	0	0	0
Reference drug				
β-Lactam (penicillin) Augmentin	21 (±0.05)	21 (±0.07)	21 (±0.04)	21 (±0.05)
β-Lactam (Cephalosporins) Fortum	22 (±0.04)	22 (±0.05)	22 (±0.06)	22 (±0.05)

Sensitive (mm) or more = 22–21, intermediate (mm) = 19–20, resistant (mm) or less = 18

Biological activity

Thirteen of the newly synthesized compounds were evaluated for in-vitro antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) bacteria. The disc diffusion method was used for determination of antibacterial activity. A 10 mg/mL solution in dimethyl sulfoxide was used. Beta-lactam antibiotics were used as reference drugs. To study the effects of discs saturated with the chemicals, nutrient agar was inoculated with the bacteria then incubated at 37 °C for 24 h. The diameter of the inhibition zone (IZ; mm, along two axes, in accordance with WHO recommendations) for each compound was then recorded. No inhibition zones were observed for DMSO. The results are listed in Table 1.

Some of the compounds were active against the Gram-positive and Gram-*negative* bacteria. It should be also noticed that:

- Chalcones **2a** and **2b** had high antibacterial activity, possibly because of the presence of *p*-hydroxyaryl and piperonyl moieties.

- Introduction of a coumarinyl moiety at position 3 of the carboxamide linkage resulted in biologically active compound **17**, especially against Gram-positive bacteria.
- Pyrazole **20** and thioxo-pyrimidine **23** (Scheme 6) compounds had the greater antibacterial potential that the pyridinones (Scheme 2).
- The presence of a diazepine moiety at position 3 of the carboxamide linkage reduced the antibacterial activity of the compounds.

Conclusion

Novel pyrazolotriazine, pyridone, diazepine, and pyrimidine derivatives incorporating the naphthyl moiety have been synthesized and their antibacterial activity evaluated. The results clearly showed that most of the compounds had mild to moderate activity against Gram-positive and Gram-negative bacteria, and that coupling of a naphthyl moiety to thioxo-pyrimidine through a carboxamide linkage improves the antibacterial activity.

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