SYNTHESIS AND REACTIONS OF SOME NEW BENZIMIDAZOLE DERIVATIVES

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4-Amino-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)pyridine-3-carbonitrile (**3**) was obtained from reaction of 2-cyanomethyl-1*H*-benzimidazole **1** with chlorobenzaldehyde followed by reaction with malononitrile. Reaction of (**3**) with cyclohexanone, formic acid and hydrazine hydrate afforded tetrahydrobenzonaphthyridine amine, pyrido[4,3-*d*]pyrimidin-4(3*H*)one and pyrazolo[4,3-*c*]pyridine-3-amine, respectively. Heterocyclization of (**3**) with carbon disulfide and benzoyl isothiocyante gave the corresponding pyrido[3,4-*d*]pyrimidindithione and thioxopyrido[4,3-*d*]pyrimidine methanone. While, the reaction of (**3**) with ethyl cyanoacetate, diethyl malonate and nitrous acid afforded oxo-1,6-naphthyridin-3-carbonitrile, carboxylate and pyrido[4,3-*d*][1,2,3]triazine, respectively. Dihydroimidazol pyridin-4-amine was obtained from reaction of (**3**) with ethylendiamine and carbon disulfide. Finally, cyclization of (**3**) with triethyl orthoformate, in the presence of hydrazine hydrate, afforded pyrido[4,3-*d*]pyrimidin-3-ylamine.

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Introduction

Benzimidazole and its condensed system compounds serve as important ligands e.g. with cobalt as in vitamine B_{12} and with many other transition metal.[1,2,3] Benzimidazole and its derivatives have important pharmacological activities as antifungals, antitumorals and antivirals[4]. Most common antifungal agents containing imidazole nucleus are Clotriamazole, Miconazole and Ketoconazole [5,6].

Experimental

Melting points were recorded using SMP30 Melting Point Apparatus (Stuart) and are uncorrected. The IR spectra were record on KBr discs using a FTIR 600 Series spectrophotometer (JASCO) and ^{1}H NMR spectra (δ ppm) were recorded on a Varian 300 MHz spectrometer using $CDCl_3$ as solvent. Elemental analyses were carried out on Micro Analytical Center at Cairo University.

2-(1*H*-Benzimidazol-2-yl)-3-(4-chlorophenyl) acrylonitrile (2)

To a solution of 2-cyanomethyl-1*H*-benzimidazole (**1**) (0.1 mol) in 30 mL ethanol, 4-chlorobenzaldehyde (0.1 mol) was added with few drops of pyridine then refluxed for 2 h. The solution was poured on crush ice and stirred until solid products appeared. The solid products was filtrated off, washed with water several times, dried and recrystallized from ethanol, yield 90 %. m.p. 235-237 °C. IR (KBr): 1640 (C=C), 2240 (C-N), 3260 cm^{-1} (N-H) cm^{-1}. ^{1}HNMR ($CDCl_3$): 3.6 (s, 1H, C=CH-Ar), 7.0-7.8 (m, 8H, Ar-H) 8.6 (s, 1H, NH). Anal Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02 %; Found: C, 68.79; H, 3.61; N, 14.99 %.

4-Amino-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)pyridine-3-carbonitrile (3)

To a solution of (**2**) (0.1 mol) in ethanol (40 mL), malononitrile (0.1 mol) was added with few drop of pyridine and refluxed for 5 h. The solution was poured on crush ice and stirred until solid products appeared. It was filtrated off and recrystallized from ethanol, yield 88 %. m.p 308-310 °C. IR (KBr): 2240 (CN) and 3260, 3390 (NH_2) cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.3 (s, 2H, NH_2), 7, 7.8 (m, 9H, Ar-H and pyridine protons), 8.2 (s, 1H, NH). Anal Calcd. for $C_{19}H_{12}ClN_5$: C, 66.00; H, 3.50; N, 20.25 %; Found: C, 65.98; H, 3.52; N, 20.22 %.

4-(1*H*-Benzimidazol-2-yl)-3-(4-chlorophenyl)-6,7,8,9-tetrahydrobenzo[*b*][1,6]naphthyridin-10-amine (4)

Compound (**3**) (0.01 mol) was added to cyclohexanone (15 mL) containing anhydrous zinc chloride (0.01 mol) and the reaction mixture was refluxed for 30 min. The complex with zinc chloride was separated from solution and dissolved in 40% sodium hydroxide (10 mL), and extracted with benzene. The benzene layer was evaporated to give solid product (**4**), which was dried and recrystallized from benzene, yield 73 %. m.p 328-330 °C. IR (KBr): 3000 (C-H aliphatic), 3320, 3220 (NH_2), 1560 (C=N) cm^{-1}. ^{1}HNMR ($CDCl_3$): 1.5 (s, br, 4H, C-7 and C-8), δ 2.2 (s, br, 2H, C-9), 6.0 (s, 2H, NH_2), 7.4-7.8 (m, 9H, Ar-H and pyridine protons), 8.6 (s, 1H, NH). Anal Cacld. For $C_{25}H_{20}ClN_5$: C, 70.50; H, 4.73; N, 16.44 %; Found: C, 70.53, H, 4.72; N, 16.42 %.

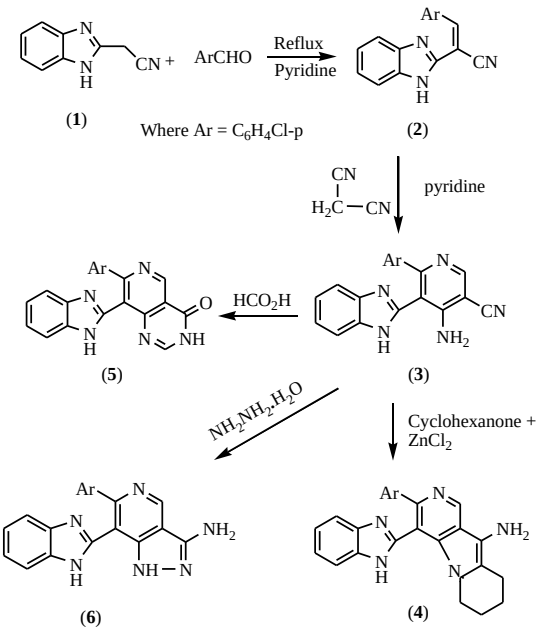
8-(1*H*-Benzimidazol-2-yl)-7-(4-chlorophenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (5)

A solution of compound (**3**) (0.01 mol) in formic acid (15 mL) was refluxed for 6 h. The excess of formic acid was removed by vacuum evaporator. The residue was dried and recrystallized from ethanol, yield 54 %. m.p. 324-327 °C. IR

(KBr): 3430 (OH), 3130 (NH group), 1740 (C=O) cm^{-1}. ^{1}HNMR ($CDCl_3$): 6.8, 8.2 (m, 9H, Ar-H and pyridine protons), 12 (s, br, 1H, OH). Anal Cacld. For $C_{20}H_{12}ClN_5O$: C, 64.26; H, 3.24; N, 18.74 %; Found: C, 64.24; H, 3.23; N, 18.75 %.

7-(1*H*-Benzimidazol-2-yl)-6-(4-chlorophenyl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (6)

To a solution of compound (**3**) (0.01 mol) in ethanol (30 mL) hydrazine hydrate (0.03 mol) was added. Then the reaction mixture refluxed for 3 h. After cooling mixture, the solid precipitate was filtered off, dried and crystallized from ethanol, yield 61%. m.p 225-227 ºC. IR (KBr): 3260, 3330 (NH_2), 1540 (C=N) cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.1 (s, br, 2H, NH_2), 6.9-8.4 (m, 9H, Ar-H and pyridine protons), 12.1 (s, br, 1H, NH). Anal Calcd. For $C_{19}H_{13}ClN_6$: C, 63.25; H, 3.63; N, 23.29 %; Found: C, 63.18; H, 3.69; N, 23.27 %.



Scheme 1. Synthesis of compounds (**2**) – (**6**).

8-(1*H*-Benzimidazol-2-yl)-7-(4-chlorophenyl)pyrido[4,3-*d*]pyrimidin-2,4-(1*H*,3*H*)-dithione (7)

To a solution of compound (**3**) (0.01 mol) in DMF (30 mL) carbon disulfide (20 mL) was added. Then reaction mixture heated on a water bath for 10 h. After cooling mixture, the solid precipitate was collected by vacuum filtration, dried and crystallized from ethanol, yield 61 %. m.p 321-324 ºC. IR (KBr): 3200 (NH), 2550 (SH), 1340 (C=S) cm^{-1}. ^{1}HNMR ($CDCl_3$): 8.3 (s, 1H, NH), 7.4-7.8 (m, 9H, Ar-H and pyridine protons). Anal Calcd. For $C_{20}H_{12}ClN_5S_2$: C, 56.93; H, 2.87; N, 16.60; S, 15.20 %; Found: C, 56.97; H, 2.79; N, 16.68; S, 15.18 %.

(8-(1*H*-Benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-4-imino-2-thioxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)(phenyl)methanone (8)

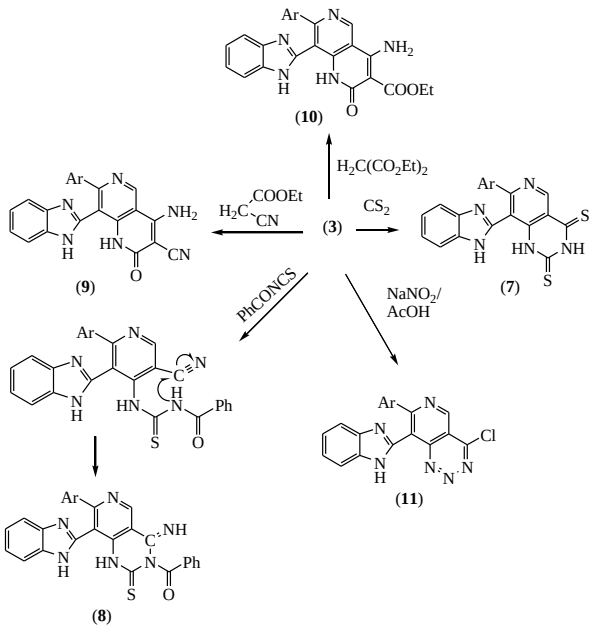
A mixture of benzoyl isothiocyanate [prepared by refluxing a mixture of ammonium thiocynate (0.012 mol) and benzoyl chloride (0.01 mol) in dioxane (20 mL) for 20 min] and (**3**) (0.01mol) in dioxane (20 mL) refluxed for 5 h. After cooling, the solid precipitate was filtrated off, dried and crystallized from ethanol, yield 55%. m.p 318-320 ºC. IR (KBr): 3200 (NH), 1760 (C=O), 1340 (C=S) cm^{-1}. ^{1}HNMR ($CDCl_3$) 3.3 (s, 1H, NH), 7.1, 7.8 (m, 14H, Ar-H and pyridine protons). Anla. Calcd. For $C_{27}H_{17}ClN_6OS$: C, 63.71; H, 3.37; N, 16.51; S, 6.30 %; Found: C, 63.78; H, 3.37; N, 16.57; S, 6.28 %.

4-Amino-8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-2-oxo-1,6-naphthyridin-3-carbonitrile (9)

To a solution of compound (**3**) (0.01 mol) in acetic acid (20 mL) ethyl cyanoacetate and ammonium acetate (6 g) were added, The reaction mixture was heated with stirring for 3 h. After cooling, the mixture was diluted with ethanol, the solid precipitate filtered off, dried and crystallized from ethanol, yield 70%. m.p 286-287 ºC. IR (KBr): 2220 (CN), 3230, 3320 (NH_2), 1630 (C=O) cm^{-1}. Anal. Calcd. For $C_{22}H_{13}ClN_6O$: C, 64.01; H, 3.17; N, 20.36 %; Found: C, 64.06; H, 3.22; N, 20.33 %.

Ethyl 4-amino-8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-2-oxo-1,6-naphthyridine-3-carboxylate (10)

To a solution of compound (**3**) (0.01 mol) in acetic acid (20 mL) diethyl malonate and ammonium acetate (6 g) were added and heated with stirring for 3 h.



Scheme 2. Synthesis of compounds (7) – (**11**).

After cooling, the mixture diluted with ethanol, the solid precipitate was collected by vacuum filtration, dried and crystallized from ethanol, yield 73%. m.p 270-271ºC. IR (KBr): 1670 (C=O), 3230, 3330 (NH_2) cm^{-1}. ^{1}HNMR ($CDCl_3$): 3.8 (t, 3H, CH_3), δ 7.4-7.8 (m, 9H, Ar-H and pyridine protons), 12.0 (s, br, 1H, OH).

8-(1*H*-Benzimidazol-2-yl)-4-chloro-7-(4-chlorophenyl)pyrido[4,3-*d*][1,2,3] triazine (11)

A solution of sodium nitrite (0.01 mol) in water (10 mL) was added to cold solution of (**3**) (0.005 mol) in acetic acid (30 mL). Then concentrated hydrochloric acid (15 mL) added. After completing of addition, the ice path removed and the mixture stirred for 2 h. Solid product collected by filtration, crystallized from ethanol, yield 70%. m.p 257-259 ºC. IR (KBr): 1530 (C=N), 3060 (Ar-H) cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.8 (s, br, 1H, NH), 7.1-7.8 (m, 9H, Ar-H and pyridine protons). Anal. Calcd. For $C_{19}H_{10}Cl_2N_6$: C, 58.03; H, 2.56; N, 21.37 %; Found: C, 58.06; H, 2.57; N, 21.36 %.

3-(1*H*-Benzimidazol-2-yl)-2-(4-chlorophenyl)-5-(4,5-dihydro-1*H*-imidazol-2-yl)pyridin-4-amine (12)

To a suspension of compound (**3**) (0.02 mol) in benzene (20 mL) ethylenediamine (3 mL) and carbon disulfide (1 mL) were added drop wise. Then reaction mixture heated on a water bath for 3 h. Then the solution was diluted with ethanol (30 mL), the solid precipitate was collected by filtration, dried and crystallized from ethanol, yield 61%. m.p 276-277 ºC. IR (KBr): 1560 (C=N), 3220, 3360 (NH_2) cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.1 (s, 2H, NH_2), 8.8 (s, br, 1H, NH), 7.1-7.8 (m, 9H, Ar-H and pyridine protons). Anal. Cacld. For $C_{21}H_{17}ClN_6$: C, 64.86; H, 4.41; N, 21.61 %; Found: C, 64.88; H, 4.44; N, 21.66 %.

Ethyl-*N*-(3-cyano-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)-pyridin-4-yl) formimidate (13)

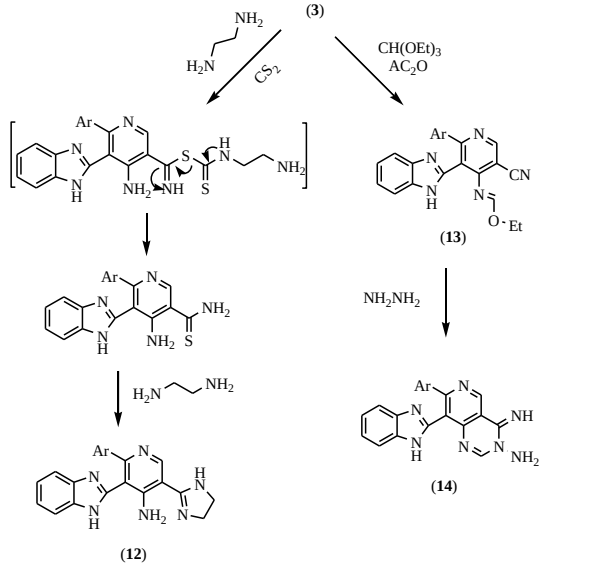
To a solution of compound (**3**) (0.02 mol) in acetic anhydrous (20 mL), triethyl orthoformate (3 mL) was added and reaction mixture refluxed for 5 h. Solid precipitate was collected, dried and crystallized from ethanol, yield 83%,. m.p 258-259 ºC. IR (KBr): 1540 (C=N), 3240 (NH), 1120 (C-O-C) 2220 (CN) cm^{-1}. Anal Calcd. for $C_{22}H_{16}ClN_5O$: C, 65.76; H, 4.01; N, 17.43 %; Found: C, 65.78; H, 4.06; N, 17.42 %.

8-(1*H*-benzo[*d*]imidazol-2-yl)-7-(4-chlorophenyl)-4-iminopyrido[4,3-*d*]pyrimidin-3(4*H*)-amine (14)

To a suspension of compound (**13**) in benzene (20 mL), hydrazine hydrate (4 mL) was added and stirred for 2 h. The solid precipitate was collected by filtration, dried and crystallized from ethanol, yield 59%. m.p 281-282 ºC. IR (KBr) 1540 (C=N), 3250, 3340 (NH_2) cm^{-1}. ^{1}HNMR ($CDCl_3$) 3.4 (s, 1H, NH), 7.3-8.0 (m, 9H, Ar-H and pyridine protons), 8.9 (s, 2H, NH_2). Anal. Calcd. For $C_{20}H_{14}ClN_7$: C, 61.94; H, 3.64; N, 25.28 %; Found: C, 61.98; H, 3.64; N, 25.25 %.

Results and discussion

2-(1*H*-Benzimidazol-2-yl)-3-(4-chlorophenyl)acrylonitrile (**2**) has been prepared by reaction of 2-(cyanomethyl)benzimidazole (**1**) and 4-chlorobenzaldehyde and then allowed to react with malononitrile to give 4-amino-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)pyridine-3-carbonitrile (**3**) The structure of compound (**3**) was confirmed by spectral and analytical data as given above in the experimental section.



Scheme 3. Synthesis of compounds (**12**) – (**14**).

As a continuation of our program for the synthesis of new condensed heterocyclic rings,[7,8] herein we wish to report the condensation of compound (**3**) with cyclohexanone in presence of anhydrous zinc chloride yielded 4-(1*H*-benzimidazol-2-yl)-3-(4-chlorophenyl)-6,7,8,9-tetrahydro-benzo[*b*][1,6] naphthyridin-10-amine (**4**). While the reaction of compound (**3**) with formic acid yielded 8-(*1H*-benzimidazol-2-yl)-7-(4-chlorophenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**5**). Cyclization of compound (**3**) was achieved by treatment with hydrazine hydrate to give 7-(*1H*-benzimidazol-2-yl)-6-(4-chlorophenyl)-1*H*-pyrazolo[4,3-*c*]-pyridin-3-amine (**6**) (Scheme 1). The structure of all these compounds has been assigned on basis of spectroscopic and analytical data.

Condensation of compound (**3**) with carbon disulfide to yielded 8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)pyrido[4,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dithione (**7**). Reaction of compound (**3**) with benzoyl isothiocyanate gives (8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-4-imino-2-thioxopyrido[4,3-d]pyrimidin-3(4H)-yl)(phenyl)methanone (**8**). Treatment of compound (**3**) with ethyl cyanoacetate in ethanol in presence of ammonium acetate[9] resulted in the formation of 4-amino-8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-2-oxo-1,6-naphthyridin-3-carbonitrile (**9**). Similarly, treatment of compound (**3**) with diethyl malonate give ethyl 4-amino-8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-2-oxo-1,6-naphthyridine-3-carboxylate (**10**). Diazotization of compound (**3**) using nitrous lead to formation of 8-(1*H*-benzimidazol-2-yl)-4-chloro-7-(4-chlorophenyl)pyrido[4,3-*d*][1,2,3]triazine (**11**) (Scheme 2).

Compound (**3**) was reacted with excess of ethylenediamine in presence of carbon disulfide[10] to afford 3-(*1H*-benzimidazol-2-yl)-2-(4-chlorophenyl)-5-(4,5-dihydro-*1H*-imidazol-2-yl)pyridin-4-amine (**12**). The structure of compound (**12**) has assigned on basis of its spectroscopic data. The IR spectra revealed the presence of (NH_2) at 3220, 3360 cm^{-1}, there is no absorption band for (CN) and (C=S). Compound (**3**) react with triethyl orthoformate yielded ethyl-N-(3-cyano-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)pyridin-4-yl)formimidate (**13**) which underwent further cyclization in presence of hydrazine hydrate at room temperature affording to produce 8-(1*H*-benzo[*d*]imidazol-2-yl)-7-(4-chlorophenyl)-4-iminopyrido[4,3-*d*]pyrimidin-3(4*H*)-amine(**14**) (Scheme 3). The structures of all these compounds were elucidated from its spectral and elemental analysis data.

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