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REACTIVITY OF 2-(1-METHYL-1*H*-BENZO[*d*]IMIDAZOL-2-YL)-2-NITROSOACETONITRILE: A FACILE ONE-POT SYNTHESIS OF BENZIMIDAZO[1,2-*a*]PIPERAZINE DERIVATIVES

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Abstract – Several new heterocyclic compounds such as benzimidazo[1,2-*a*]piperazine derivatives (**5-7;9,10** and **14,15,17**) have been synthesized by the reactions of the versatile 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-nitroso-acetonitrile (**2**) with malononitrile derivatives (**3a-e**) and 2-cyanomethyl-benzimidazole derivatives (**1b,c**). Oxidation of iminopyrazino[1,2-*a*]benzimidazole-3-carbothioamide derivatives **9** via refluxing in aqueous H_2O_2 solution afforded iminopyrazino[1,2-*a*]benzimidazole-3-carboamide derivatives **10**. Also, reaction of **9** with 1-aryl-2-bromoethanone derivatives (**11a,b**) in refluxing DMF, the Hantzsch-type thiazoles (**12a,b**) were obtained. All newly synthesized compounds were elucidated by considering the data of both elemental and spectral analysis.

There is a growing interest over the past years for the synthesis of benzimidazole based heterocycles due to the crucial role of benzimidazole unit in the functions of biologically important molecules.[1] Benzimidazole-based ployhetrocycles has exhibited interesting biological properties. For example, benzimidazoquinazolines,[2] benzimidazoisoquinolines[3] and benzimidazo[2,1-*a*]isoindolones[4] were reported as potent antitumor agents. Benzimidazo[2,1-*b*]quinazolines are potent immunosuppressors[5] and benzimidazo[2,1-*b*]benzo[*f*]isoquinoline ring system[6] is present in pharmacologically active compounds. Isoindolo[2,1-*a*]benzimidazoles are also known to be sedatives and tranquilizers.[7] Benzimidazole fungicides have been shown to be outstanding agents in disease control.[8]

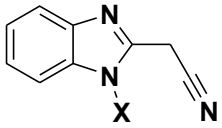
Benzimidazole is a well known famous structure in medicinal chemistry with various biological activities. The properties of benzimidazole and its analogs have been studied since over hundred years. However a special interest of researchers towards benzimidazole derivatives was originated by the fact that 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole is a basic part of the structure of vitamine B_{12}.[9] Moreover

benzimidazole is a structural unit of naturally occurring nucleotide, due to which it easily interacts with the biopolymers of living system. This character is responsible for its numerous biological aspects like antihelminthic,[10] antifungal,[11] antiviral[12] and antineoplastic[13] activities. Since proteases have been linked with several disease states, including thrombosis, inflammation, bronchoconstiction and tumor growth and invasion.[14] In the past few decades, benzimidazole and its derivatives have grasped much attention due to their chemotherapeutic values[17] and pharmacological properties.[16]

On the other hand, piperazine derivatives have shown to posses diverse biological properties including anthelmintic, antihistamine, anti-ketonic, anticonvulsant, anti HIV and as potential cocaineabuse therapeutic agent.[17] Also, the importance of imidazo[1,2-*a*]pyrazines[18] stems especially from their remarkable anticancer[19] and antimicrobial activities[20] along with antihypertensive,[21] antibroncospastic[22] and inotropic activities[23] on the cardiovascular system.

In continuation of our recent interest in the synthesis of heterocycles bearing benzimidazole moiety.[24-31] we report here nitrosation of 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)acetonitrile (**1a**) affording the 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-nitrosoacetonitrile (**2**) and its utility in the synthesis of the benzimidazo[1,2-*a*]piperazine derivatives.

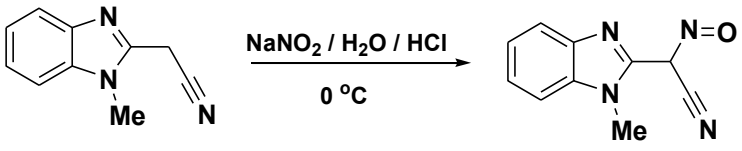
Nitrosation of 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)acetonitrile **1a** by sodium nitrite in ethanolic hydrochloric acid mixture afforded 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-nitrosoacetonitrile **2**. The assignment of structure **2** was supported by elemental analysis and spectral data. The IR spectrum showed the absorption band at 2209 cm^{-1} assignable to nitrile group. Its H^1 NMR spectrum exhibited two singlet signals at δ 3.51 and 3.79 ppm assignable to CH and NCH_3 protons, respectively. Its ^{13}C NMR showed peak at 48.5 assignable to aliphatic carbon. Also, its mass spectrum showed the molecular ion peak at *m/z* 200 (m^+, 89) which is in agreement with the expected to the molecular formula ($C_{10}H_8N_4O$) Scheme 2.



1	a	b	c
X	Me	H	CO_2Et

1a-c

Scheme 1

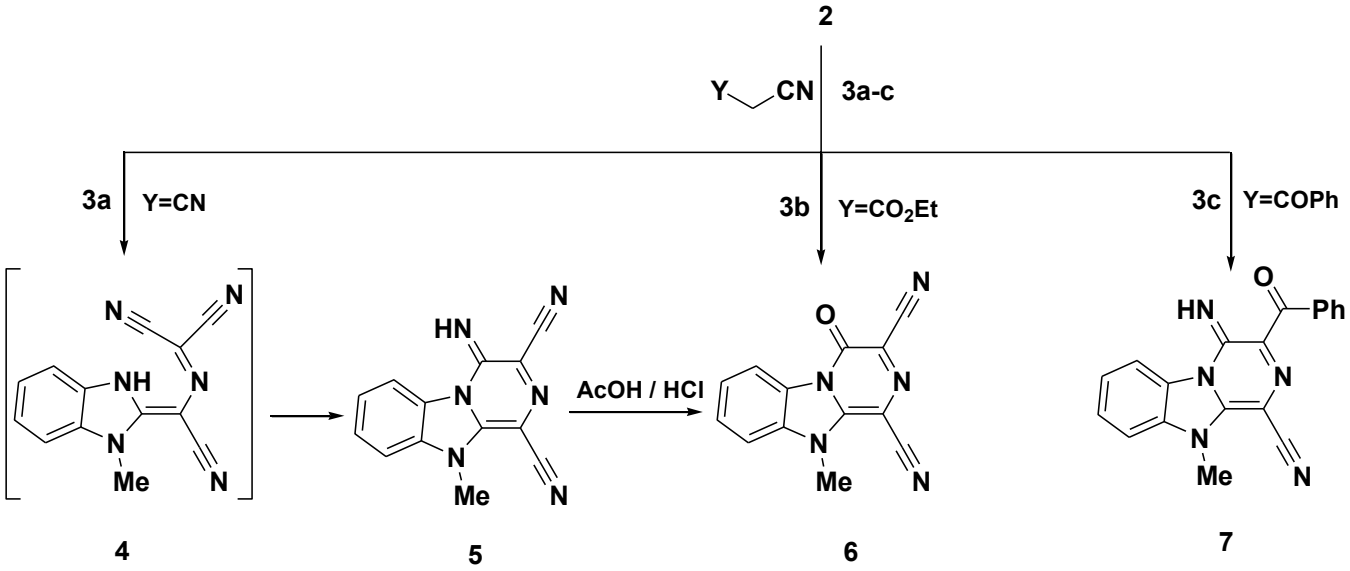


1a **2**

Scheme 2

Reaction of **2** with malononitrile (**3a**), ethyl cyanoacetate (**3b**), benzoylacetonitrile (**3c**), cyanothioacetamide (**3d**), and cyanoacetamide (**3e**) in ethanol containing an equivalent amount of triethylamine as a basic catalyst gave the benzimidazo[1,2-*a*]piperazine derivatives (**5-7** and **9, 10**), respectively.

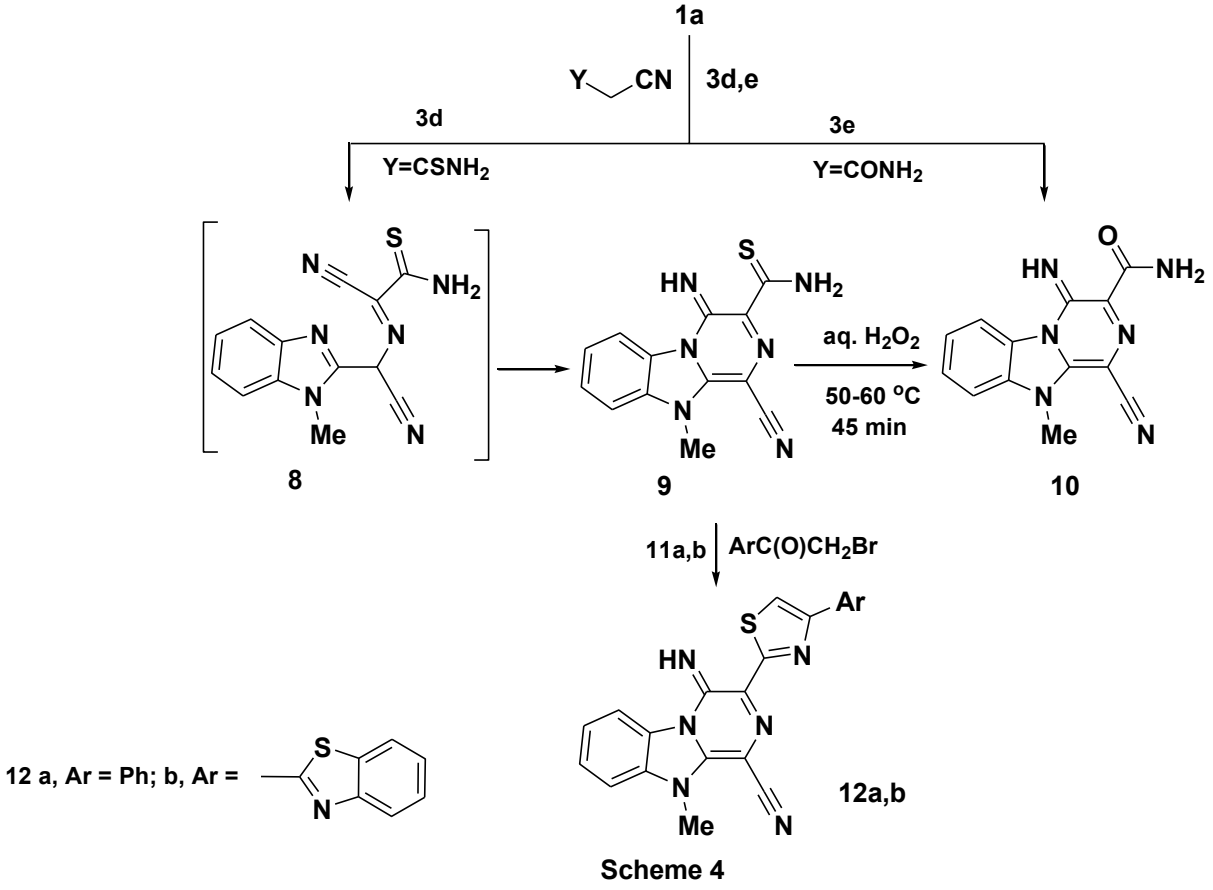
For example, compound **2** reacts with malononitrile **3a** to yield a compound which formulated as 4,10-dihydro-10-methyl-4-iminobenzimidazo[1,2-*a*]piperazine-1,3-dicarbonitrile **5**. The structure of **5** was confirmed on the basis of analytical and spectral data. The IR of **5** showed a NH and two nitrile bands at 3105, 2204 and 2198 cm^{-1}, respectively. Its H^1 NMR spectrum revealed singlet signal at δ 11.08 ppm that was integrated for one proton due to exocyclic NH proton of pyrazine ring. Its mass spectrum showed the molecular ion peak at *m/z* 248 (m^+, 56) which is in agreement with the expected to the molecular formula ($C_{13}H_8N_6$). Compound **5** was assumed to be formed through condensation of **2** with malononitrile via nitroso form to afford the non-isolable acyclic **4** which underwent intramolecular cyclization to give the final isolable product **5** (Scheme 3). Similarly, compound **2** reacts with ethyl cyanoacetate (**3b**) affording 4,10-dihydro-10-methyl-4-oxobenzimidazo[1,2-*a*]piperazine-1,3-dicarbonitrile **(6)** via loss of ethanol. The structure of **6** was confirmed on the basis of analytical and spectral data. The IR of **6** showed a carbonyl and nitrile bands at 1693, 2186 and 2210 cm^{-1}, respectively. Its H^1 NMR spectrum revealed singlet signal at δ 3.68 ppm that was integrated for three protons due to $–NCH_3$ protons, in addition to absence of signals due to ester group. Its mass spectrum showed the molecular ion peak at *m/z* 249 (m^+, 32) which is in agreement with the expected to the molecular formula ($C_{13}H_7N_5O$). Compound **6** could be also obtained by hydrolysis of **5** in AcOH/HCl mixture (Scheme 3).



Scheme 3

Similarly, compound **2** reacted with benzoylacetonitrile (**3c**), cyanothioacetamide (**3d**), and cyanoacetamide (**3e**) in ethanol containing an equivalent amount of triethylamine as a basic catalyst gave the benzimidazo[1,2-*a*]pyrazine derivatives (**7,9** and **10**), respectively (*see experimental section*).

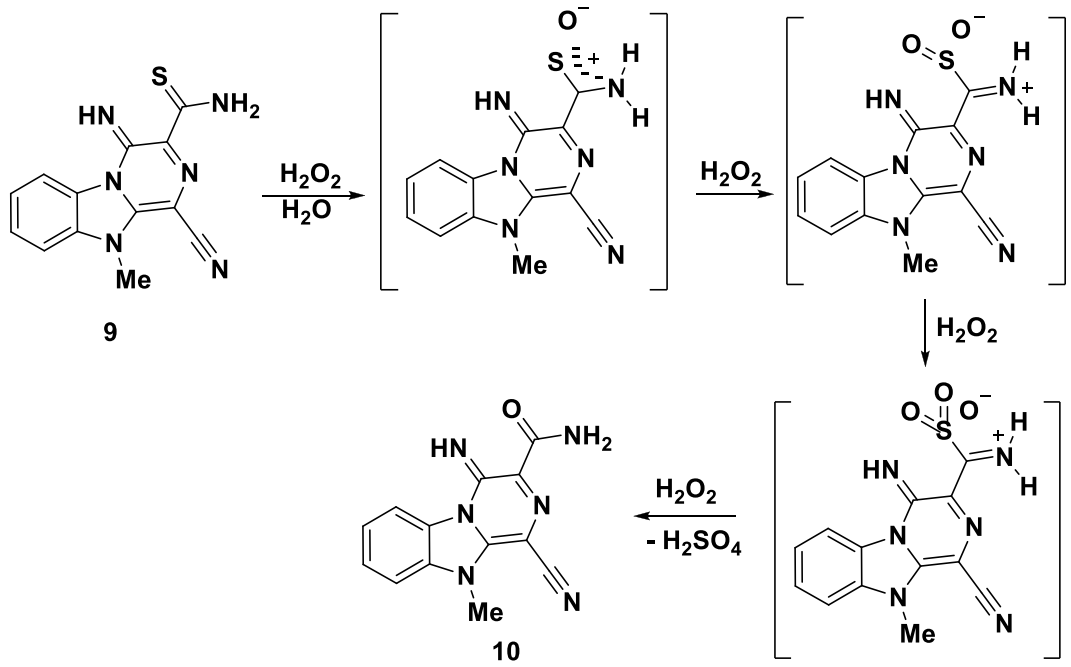
Reaction of **9** with 1-aryl-2-bromoethanone derivatives (**11a,b**) in refluxing DMF, the Hantzsch-type thiazole (**12a,b**) were obtained. The structures of (**12a,b**) were confirmed on the basis of analytical and spectral data. For example, the IR of 4,10-dihydro-10-methyl-3-(4-phenylthiazolyl)-4-iminopyrazino[1,2-*a*]benzimidazole-3-carbonitrile (**12a**) showed a NH and nitrile bands at 3295 and 2196 cm^{-1}, respectively. Its H^1 NMR spectrum revealed signals at δ 10.08, and 7.10-7.87 ppm due to NH and thioazolyl *CH-5*, and phenyl protons, respectively. Its mass spectrum showed a molecular ion peak at m/z 382 (m^+, 38) corresponding to a molecular formula ($C_{21}H_{14}N_6S$) (Scheme 4).



Scheme 4

Also, we carried out the oxidation of thioamide 1-cyano-4,10-dihydro-10-methyl-4-iminopyrazino[1,2-*a*]benzimidazole-3-carbothioamide (**9**). Although the oxidation of the thioamide is very unpredictable and can proceed in several routes,[32-34] depending on the structures of both the substrate and the oxidant, as well as on the reaction conditions. The oxidation process may lead to the formation of amides, thioamide-S-oxides, 1,2,4-thiadiazoles, disulfides, benzothiazoles, α-oxothioamides, 1,2-dithiolium salts, 1,2,4-dithiazoles, 1,2,3-thiadiazolium salts, etc.[34] However, the oxidation of 3-aminoprop-2-enethioamides and related compounds with neighboring NHR and C=S moieties is known to be one of the most convenient

methods for the construction of isothiazole unit.[35] We carried out the oxidation of 1-cyano-4,10-dihydro-10-methyl-4-iminopyrazino[1,2-*a*]benzimidazole-3-carbothioamide **9** and not expected the product because our compound has imino instead of amino group. Surprisingly, 1-cyano-4,10-dihydro-10-methyl-4-iminopyrazino[1,2-*a*]benzimidazole-3-carboamide (**10**) was isolated when thioamide **9** was gently heated to 50-60 °C with aqueous H_2O_2 for 45 min. The plausible mechanism for the formation of amide **10** includes an oxidation of sulfenate fragment followed by hydrolysis[36] (Scheme 5).

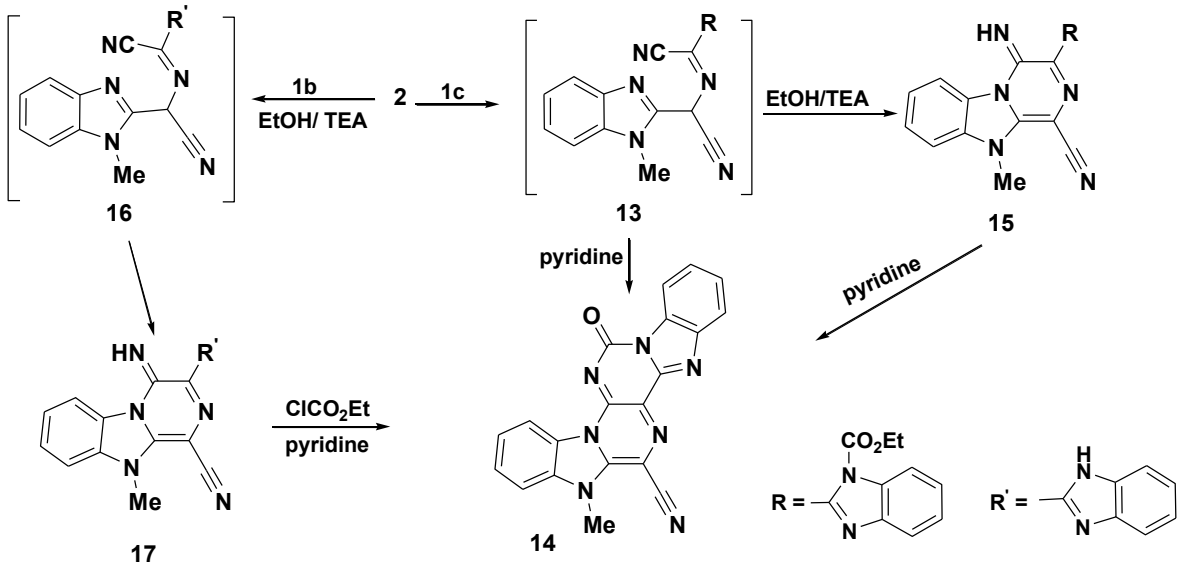


Scheme 5. The plausible mechanism for the formation of amide **10**

In conjunction with this work we report here novel synthesis of benzimidazo[1”,2”:1’,2’]pyrazino[5’,6’:5,4]-pyrimido[1,6-*a*]benzimidazole derivative. It has been found that ethyl 2-cyanobenzimidazole-1-carboxy-late (**1c**) allows a fruitful, one-step synthesis of several polyheterocyclic ring via its reaction with **2**. Thus, reaction of (**1c**) with **2** in refluxing pyridine afforded directly the 16-cyano-1,8-dihydro-1-methyl-8-oxobenzimidazo[1”,2”:1’,2’]pyrazino[5’,6’:5,4]pyrimido-[1,6-*a*]benzimidazole (**14**). The form-ation of **14** as assumed to proceed via non-isolable intermediate (**13**) which undergoes spontaneous intramolecular cyclization under the reaction conditions to give the final product **14** (Scheme 6). The structure of **14** was established on the basis of their elemental analyses and spectral data (*see experimental section*). It is noteworthy that compound **2** reacted with (**1c**) in refluxing ethanol containing triethylamine as basic catalyst furnished 3-(1-(ethoxycarbonyl)-1*H*-benzimidazole-2-yl)-4,10-dihydro-10-methyl-4-iminopyr-azino[1,2-*a*]benzimidazole-1-carbonitrile **(15)** which undergo a ready intramolecular cyclization under refluxing in pyridine affording a product identical (TLC, mp and spectra) with **14**.

The assignment of structure **15** was supported by elemental analysis and spectral data. The IR spectrum showed the absorption bands at 1719, 2198 and 3295 cm^{-1} assignable to ethoxycarbonyl, nitrile and NH group, respectively. Its H^1 NMR spectrum exhibited triplet and quartet signals at δ 1.17 and 4.2 ppm assignable to ester protons, in addition to, singlet signal at δ 11.01 ppm due to NH proton. Its mass spectrum showed the molecular ion peak at *m/z* 411 (m^+, 46) which is in agreement with the expected to the molecular formula ($C_{22}H_{17}N_7O_2$) (Scheme 6).

Moreover, the structure of the product **14** was confirmed by unambiguous synthesis in two steps by the reaction sequence in (Scheme 6). Thus, reaction of (**1b**) with **2** furnished 3-(1-*H*-benzimidazol-2-yl)-4,10-dihydro-10-methyl-4-iminobenzimidazo[1,2-*a*]pyrazine-1-carbonitrile (**17**). The assignment of structure **17** was supported by elemental analysis and spectral data. The IR spectrum showed the absorption bands at 3421, 2310 and ca. 2220 cm^{-1} assignable to NH and nitrile groups, respectively. Its H^1 NMR spectrum exhibited three singlet signals at δ 3.79, 9.98 and 10.83 ppm assignable to NCH_3 and 2NH groups, in addition to, aromatic signals at δ 7.13-7.89 ppm. The absence of CH in the H^1 NMR spectra of compound (**17**) excludes the presence of the intermediate (**16**) and indicates that it exists almost entirely in the 4-iminobenzimidazo[1,2-*a*]pyrazine derivative **17**. Its mass spectrum showed the molecular ion peak at *m/z* 339 (m^+, 33) which is in agreement with the expected to the molecular formula ($C_{19}H_{13}N_7$) (Scheme 6). Treatment of **17** with ethyl chloroformate in pyridine afforded a product identical (all spectra) with compound **14**.



Scheme 6

In the present work we describe the syntheses of several new heterocyclic compounds such as benzimidazo[1,2-*a*]piperazine derivatives (**5-7;9,10** and **14,15,17**) have been synthesized by the reactions of the versatile 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-nitrosoacetonitrile **2** with malononitrile

derivatives **3a-e** and 2-cyanomethylbenzimidazole derivatives **1b,c**. Oxidation of iminopyrazino[1,2-*a*]benzimidazole-3-carbothioamide derivatives **9** via refluxing in aqueous H_2O_2 solution afforded iminopyrazino[1,2-*a*]benzimidazole-3-carboamide derivatives **10**. Also, reaction of **9** with 1-aryl-2-bromoethanone derivatives **11a,b** in refluxing DMF, the Hantzsch-type thiazole **12a,b** were obtained.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in DMSO-d_6 at 300 *MHz* on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70Ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 1-Methylbenzimidazol-2-ylacetonitrile **1a**[37] and 1-(benzothiazol-2-yl)-2-bromoethanone **11b**[38] were prepared according to the reported literature.

2-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-nitrosoacetonitrile (2).

2-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)acetonitrile (**1a**) (10 mmol) was dissolved in a mixture of hydrochloric acid (10 mL) and EtOH (30 mL), then cooled in ice bath at 0 °C. A cold solution of sodium nitrite (20 mmol) was added dropwise throughout a period of 30 min. The reaction mixture was allowed to stand about 24 h, in a refrigerator. The solid product so formed was filtered off, washed with water several times, dried and recrystallized from EtOH to give pale white crystals; yield (86%); mp 173-174 °C. IR (KBr, cm^{-1}): υ 2209 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 3.79 (s, 3H, CH_3), 3.51 (s, 1H, CH), 7.13 (d, *J* = 7.8 *Hz*, 2H, Ar-H), 7.84 (d, *J* = 7.8 *Hz*, 2H, Ar-H); ^{13}C NMR δ (ppm): 142.7, 138.8, 135.5, 124.6 (2C), 121.2 (2C), 115.8, 48.5, 32.1; MS *m/z* (%): 200 (M^+, 89). Anal. Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.96; H, 4.10; N, 28.03%.

Synthesis of benzimidazo[1,2-*a*]pyrazine derivatives (5-7;9,10;15 and 17).

General Procedure: To a solution of nitroso **2** (10 mmol) and the appropriate malononitrile **3a**, ethyl cyanoacetate **3b**, benzoylacetonitrile **3c**, cyanothioacetamide **3d**, cyanoacetamide **3e**, 2-cyano-methylbenzimidazole **1c** and ethyl 2-(cyanomethyl)-1*H*-benzimidazole-1-carboxylate **1b** (10 mmol), in EtOH (30 mL), and triethylamine (10 mmol) was added. The reaction mixture was refluxed for 1-2 h, and then allowed to cool. The formed solid product was filtered off, washed with EtOH and recrystallized from DMF/EtOH to afford the corresponding benzimidazo[1,2-*a*]pyrazine derivatives (**5-7; 9,10; 15** and **17**), respectively.

Synthesis of 4,10-dihydro-10-methyl-4-oxobenzimidazo[1,2-*a*]piperazine-1,3-dicarbonitrile 6.

Refluxing of compound **5** in mixture of HCl/AcOH (30 mL, 1:3) for 6 h. The reaction solution was allowed to cool and then diluted with water. The solid was filtered off, washed with water, dried and recrystallized from DMF/EtOH afforded product identical (mp, mixed mp and spectra) with compound **6**.

Synthesis of 1-cyano-4,10-dihydro-10-methyl-4-iminopyrazino[1,2-*a*]benzimidazole-3-carboamide (10).

A solution of compound **9** (10 mmol) in aqueous hydrogen peroxide (30%, 30 mL) was heated at 60-70 °C for 1 h. Upon cooling to room temperature, the solid was filtered off, washed with water, dried and recrystallized from DMF/EtOH afforded product identical (all spectra) with compound **10**.

4,10-Dihydro-10-methyl-4-iminobenzimidazo[1,2-*a*]pyrazine-1,3-dicarbonitrile 5.

Yield (72%); orange crystals (from DMF/EtOH); mp 226-227 °C. IR (KBr, cm^{-1}): υ 3105 (NH), 2204, 2198 (2CN). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ (ppm): 3.68 (s, 3H, CH_3), 7.10 (d, *J* = 7.6 *Hz*, 2H, Ar-H), 7.79 (d, *J* = 7.8 *Hz*, 2H, Ar-H), 11.08 (s, 1H, NH, *D*$_2$*O*-exchangeable); MS *m/z* (%): 248 (M^+, 56). Anal. Calcd for $C_{13}H_8N_6$: C, 62.90; H, 3.25; N, 33.85. Found: C, 62.84; H, 3.31; N, 33.89%.

4,10-Dihydro-10-methyl-4-oxobenzimidazo[1,2-*a*]piperazine-1,3-dicarbonitrile 6.

Yield (46%); yellow crystals (from DMF/EtOH); mp 210-212 °C. IR (KBr, cm^{-1}): υ 2210, 2186 (2CN), 1693 (CO); ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ (ppm): 3.68 (s, 3H, CH_3), 7.07 (d, *J* = 7.9 *Hz*, 2H, Ar-H), 7.81 (d, *J* = 7.8 *Hz*, 2H, Ar-H); ^{13}C NMR δ (ppm): 166.4, 162.8, 158.6, 139.1, 126.3, 124.2, 121, 119.9, 118, 115.7, 114.8, 63.4, 31.8; MS *m/z* (%): 249 (M^+, 32). Anal. Calcd for $C_{13}H_7N_5O$: C, 62.65; H, 2.83; N, 28.10. Found: C, 62.69; H, 2.86; N, 28.15%.

3-Benzoyl-4,10-dihydro-10-methyl-4-iminobenzimidazo[1,2-*a*]piperazine-1-carbonitrile 7.

Yield (54%); brown powder (from DMF/EtOH); mp 268-269 °C. IR (KBr, cm^{-1}): υ 3235 (NH), 2208 (CN), 1678 (CO); ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ (ppm): 3.73 (s, 3H, CH_3), 7.11-7.83 (m, 9H, Ar-H), 11.24 (s, 1H, NH, *D*$_2$*O*-exchangeable); MS *m/z* (%): 327 (M^+, 20). Anal. Calcd for $C_{19}H_{13}N_5O$: C, 69.71; H, 4.00; N, 21.39. Found: C, 69.69; H, 4.06; N, 21.44%.

1-Cyano-4,10-dihydro-10-methyl-4-iminopyrazino[1,2-*a*]benzimidazole-3-carbothioamide 9.

Yield (45%); brown powder (from DMF/EtOH); mp 281-283 °C. IR (KBr, cm^{-1}): υ 3105 (NH), 2204 (CN). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ (ppm): 3.73 (s, 3H, CH_3), 7.10 (d, *J* = 7.7 *Hz*, 2H, Ar-H), 7.79 (d, *J* = 7.8 *Hz*, 2H, Ar-H), 9.46 (brs, 1H, NH, *D*$_2$*O*-exchangeable), 10.75 (s, 2H, NH_2, *D*$_2$*O*-exchangeable); MS *m/z* (%): 282 (M^+, 25). Anal. Calcd for $C_{13}H_{10}N_6S$: C, 55.30; H, 3.57; N, 29.77. Found: C, 55.26; H, 3.62; N, 29.33%.

1-Cyano-4,10-dihydro-10-methyl-4-iminopyrazino[1,2-*a*]benzimidazole-3-carboamide 10.

Yield (36%); brown powder (from DMF/EtOH); mp 259-260 °C. IR (KBr, cm^{-1}): υ 3105 (NH), 2198 (CN). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ (ppm): 3.73 (s, 3H, CH_3), 7.13 (d, *J* = 7.8 *Hz*, 2H, Ar-H), 7.79 (d, *J* = 7.8 *Hz*, 2H, Ar-H), 8.68 (s, 1H, NH, *D*$_2$*O*-exchangeable), 9.95 (s, 2H, NH_2, *D*$_2$*O*-exchangeable); ^{13}C NMR δ (ppm): 168.6, 162.3, 148.6, 134.5, 129.2, 127.3, 121.5, 119, 118.7, 118.1, 115.4, 62.9, 31.4; MS *m/z* (%): 266 (M^+, 20). Anal. Calcd for $C_{13}H_{10}N_6O$: C, 58.64; H, 3.79; N, 31.56. Found: C, 58.66; H, 3.82;

N, 31.60%.

3-(1-(Ethoxycarbonyl)-1H-benzimidazol-2-yl)-4,10-dihydro-10-methyl-4-iminopyrazino[1,2-*a*]benzimidazole-1-carbonitrile 15.

Yield (56%); pale brown powder (from DMF/EtOH); mp 292-293 °C. IR (KBr, cm^{-1}): υ 3295 (NH), 2198 (CN), 1719 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 1.17 (t, *J* = 7.2 *Hz*, 3H, CH_3), 3.82 (s, 3H, CH_3), 4.2 (q, *J* = 7.2 *Hz*, 2H, CH_2), 7.12-7.94 (m, 8H, Ar-H), 11.01 (s, 1H, 1NH, D_2O-exchangeable); MS *m/z* (%): 411 (M^+, 24). Anal. Calcd for $C_{22}H_{17}N_7O_2$: C, 64.23; H, 4.16; N, 23.83. Found: C, 64.27; H, 4.2; N, 23.86%.

3-(1*H*-Benzimidazol-2-yl)-4,10-dihydro-10-methyl-4-iminobenzimidazo[1,2-*a*]piperazine-1-carbonitrile 17.

Yield (61%); brownish-red powder (from DMF/EtOH); mp 277-278 °C. IR (KBr, cm^{-1}): υ 3421 2310 (2NH), 2220 (CN); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 3.79 (s, 3H, CH_3), 7.13-7.89 (m, 8H, Ar-H), 9.98 (s, 1H, NH, D_2O-exchangeable), 10.83 (s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 339 (M^+, 33). Anal. Calcd for $C_{19}H_{13}N_7$: C, 67.25; H, 3.86; N, 28.89. Found: C, 67.21; H, 3.91 N, 28.95%.

Synthesis of 4,10-dihydro-10-methyl-3-(4-phenylthiazol-2-yl)-4-iminopyrazino[1,2-*a*]benzimidazole-3-carbonitrile 12a and 4,10-dihydro-10-methyl-3-(4-(benzothiazol-2-yl)lthiazol-2-yl)-4-iminopyrazino[1,2-*a*]benzimidazole-3-carbonitrile 12b.

General Procedure: The solution of compound **9** (10 mmol) in DMF (30 mL), the appropriate 1-aryl-2-bromoethanone derivatives (**11a,b**) (10 mmol), was kept under reflux for 1-2 h. Upon cooling to room temperature, the solid deposit was filtered off, washed with EtOHAc and recrystallized from DMF/EtOH to afford the corresponding (**12a,b**), respectively.

4,10-Dihydro-10-methyl-3-(4-phenylthiazol-2-yl)-4-iminopyrazino[1,2-*a*]benzimidazole-3-carbonitrile 12a.

Yield (57%); yellow crystals (from DMF/EtOH); mp > 300 °C. IR (KBr, cm^{-1}): υ 3295 (NH), 2196 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 3.76 (s, 3H, CH_3), 7.10-7.76 (m, 9H, Ar-H, thiazolyl H-5), 10.08 (s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 382 (M^+, 38). Anal. Calcd for $C_{21}H_{14}N_6S$: C, 65.95; H, 3.69; N, 21.97. Found: C, 65.89; H, 3.72; N, 21.99%.

4,10-Dihydro-10-methyl-3-(4-(benzothiazol-2-yl)thiazol-2-yl)-4-iminopyrazino[1,2-*a*]benzimidazole-3-carbonitrile 12b.

Yield (29%); pale brown crystals (from DMF/EtOH); mp > 300 °C. IR (KBr, cm^{-1}): υ 3262 (NH), 2200 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 3.74 (s, 3H, CH_3), 7.10-8.02 (m, 8H, Ar-H, thiazolyl H-5), 10.12 (s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 439 (M^+, 20). Anal. Calcd for $C_{22}H_{13}N_7S_2$: C, 60.12; H, 2.98; N, 22.31. Found: C, 60.07; H, 3.03; N, 22.27%.

16-Cyano-1,8-dihydro-1-methyl-8-oxobenzimidazo[1",2":1',2']pyrazino[5',6':5,4]pyrimido[1,6-*a*]ben-zimidazole 14.

Method A: To a cold solution of compound **17** (10 mmol) in pyridine (30 mL) was added ethyl chloroformate dropwise with stirring over a period of 20 min. The reaction mixture was heated on the water bath for 24 h, left to cool and then diluted with water containing hydrochloric acid. The solid was filtered off, washed with water, dried and recrystallized from DMF to give compound **14**; Yield (54%); brown powder (DMF); mp > 300 °C. IR (KBr, cm^{-1}): υ 2201 (CN), 1668 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 3.75 (s, 3H, CH_3), 7.11-8.1 (m, 8H, Ar-H); MS *m/z* (%): 365 (M^+, 10). Anal. Calcd for $C_{20}H_{11}N_7O$: C, 65.75; H, 3.03; N, 26.84. Found: C, 65.71; H, 3.10; N, 26.88%.

Method B: Refluxing of compound **15** (10 mmol) in pyridine (30 mL) for 2-3 h. The reaction solution was allowed to cool and then diluted with water containing HCl. The solid was filtered off, washed with water, dried and recrystallized from DMF afforded product identical (all spectra) with compound **14**.

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