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Fungicidal Efficacy of Some New Azoles Towards *F. oxysporum, R. solani and S. rolfsii*

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Abstract: A series of substituted pyrimidine derivatives **3**, dihydropyrimidine **4**, dihydropyridine-3-crabonitrile **6**, pyridine derivatives **7,8** and tetrahydropyrdine-3-carbonitrile derivatives **9** were synthesized by reaction of 1*H*-benzimidazole-2-acetonitile **1** with a series of nitrogen bearing reagents. Most of the synthesized azoles were screened for their fungicidal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Sclortium rolfsii* fungi, Some of the tested azoles exhibited high potency against the tested fungi at ranges 250- 1500 ppm.

Key words: 1*H*-benzimidazole-2-acetonitile · Fungicidal efficacy · *F. oxysproum* · *R. solani* · *S. rolfsii*

INTRODUCTION

In continuation of our studies on the chemistry of benzimidazole ring system and as a part of our ongoing program directed towards developing new approaches to a variety of heterocycles incorporating a benzimidzole moiety for biological screening, we report here on the synthesis of 2-cyanomethylbenzimidazole as building block of the title compounds [1-10].

Benzimidazole ring system and its related compounds attract wide interest on account of their fungicidal [11-15], herbicidal [16], pesticidal [17], antimicrobial [18-22], anthelmentic [23-26] and plant growth regulating properties [23]. On the other hand several benzimidazole derivatives have been found to possess antiviral [27-30], antiparasitic [24], also they have found wide medicinal applications as pharmaceutical potent [23, 31] antihypertensive [32], antihistaminic [33, 34], anticancer [35-37], anti-inflammatory agents [25, 35, 39] and for treatment of cardiovascular disease [40]. Prompted by the aforesaid numerous biological activities we disclose the details of successful synthetic approaches to some new fused heterocycles derived from benzimidazole nucleus. A conceptually attractive entry to these compounds lies in the reactivity of the readily accessible benzimidazole -2-ylacetonitrile [1].

Chemistry: The limited substitution pattern motivated the search for an alternative efficient route to the adopted system which would permit the preparation of wider range of substitution for biological screening.

In our present study 1*H*-benzimidazole-2-acetonitrile [1] was allowed to react with aromatic aldehyde in boiling ethanol in the presence of few drops of piperidene as a basic catalyst to afford acrylonitrile derivatives **(2)a-e** which were identified as 2-(1*H*-benzo[d]imidazol-2-yl)-3-(substituted phenyl)acrylonitrile. (*cf.* Scheme 1).

Treatment of arylidene **2a-c** with thiourea and /or urea at refluxing temperature in ethanolic sodium ethoxide furnish the corresponding pyrimidene derivatives 4-amino-5-(1*H*-benzo[d]imidazol-2-yl)-6-(substituted phenyl)pyrimidine-2(1*H*)-thione **3a-d**. The IR spectrum of compound **3a** revealed the appearance of stretching vibration of NH_2 group at range of 3422cm^{-1} and stretching vibration of C=S at 2363 cm^{-1}. Assignment of structure **3** was substantiated on the basis of their correct elemental aynalysis as well as compatible spectral data. It is evident from IR and ^{1}H NMR spectra of compound **3a**, as an example, that it could be present in the lactam - lactim dynamic equilibrium where as the lactam or oxo form is thermodynamically more stable due to the fact that oxo form is more stabilized by 54.4 kj.mol^{-1} than the enol form [41, 42], while the reaction of acrylonitriles **2c-e**

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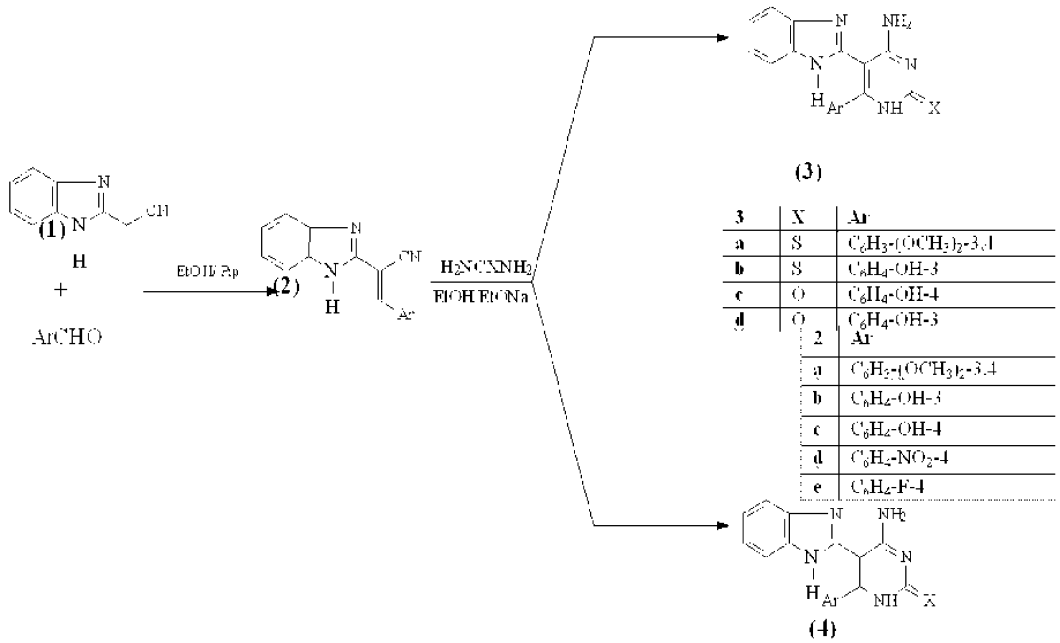


3	X	Ar
a	S	C_6H_3-(OCH$_3$)$_2$-3,4
b	S	C_6H_4-OH-3
c	O	C_6H_4-OH-4
d	O	C_6H_4-OH-3

2	Ar
a	C_6H_3-(OCH$_3$)$_2$-3,4
b	C_6H_4-OH-3
c	C_6H_4-OH-4
d	C_6H_4-NO$_2$-4
e	C_6H_4-F-4

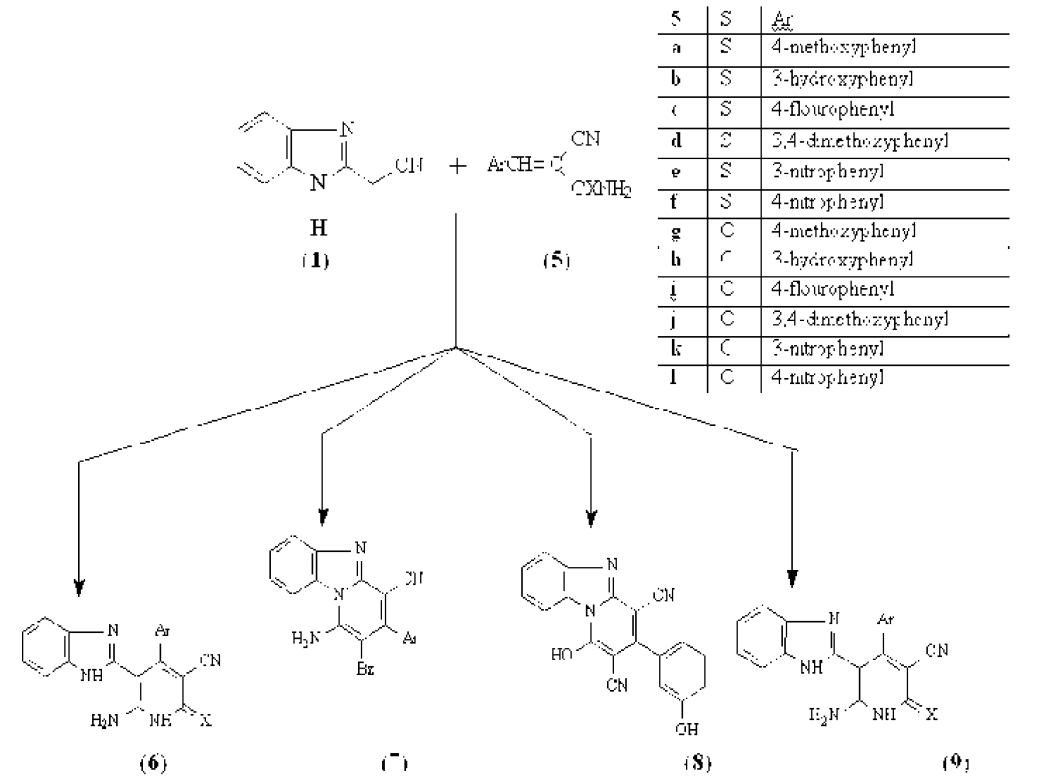
4	X	Ar
a	S	C_6H_4-F-4
b	S	C_6H_4-OH-4
c	O	C_6H_4-NO$_2$-4
d	O	C_6H_4-F-4

Scheme (1)

with thiourea and /or urea under the same reaction conditions revealed the formation of 4-amino-5-(1H-benzo[d]imidaol-2-yl)-6-(4-substituted phenyl)-5,6-dihydropyrimidine-2(1H)-thione (oxone) **4a-d**. Both elemental analysis and spectral data of such compounds provide satisfying evidences of the proposed structure.

When 1*H*-benzimidazole-2-acetoniteile **1** was refluxed with acrylonitriles **5a, b, g, k and i** in ethanol in the presence of few drops of piperidene for 3-4 hrs, the corresponding pyridine derivatives 6-amino-5-(1H-benzo[d]imidaol-2-yl)-4-(substituted phenyl)-2-thioxo (oxo)-1,2-dihydropyridine-3-carbonitrile **6a-e** were obtained. The structure of the obtained compounds were established on the basis of their elemental analysis together with their compatible spectral data. On the other hand treatment of compound **1** with acrylonitrile **5h-j** under the same reaction conditions afforded the pyridine derivatives **7a,b** and **8**. In this case the reaction proceeds with dearylation of acrylonitrile **5h-j** and formation of an arylidene between benzimidazole-2-acetonitrile and aromatic aldehyde moiety then attack of the newly synthesized arylidene with benzimidazole-2-actonitrile and cyanoacetamide moiety to afford the derivative **7a,b** and **8** respectively and this according to the stability of the tetrahedral cabonium ion, the nucleophlicity of β-carbon atom and the inductive effect of the substituted phenyl group. By the same way and under the same reaction conditions, when acrylonitrile **5c-f** was treated with 1*H*-benzimidazole-2-acetonitrile **1**, a new product was obtained in each case which assigned as 6-amino-5-(1*H*-benzo[d]imidazol-2-yl) - 4 - (substituted phenyl) - 2 - thioxo - 1, 2, 5, 6-tetrahydropyridine-3-carbonitrile **9a-d**. The structures of the isolated compounds were established from their elemental analysis and spectral data.

Antifungal Activity Assays: Antifungal activity was studied using *in vitro* contact assay which producing hyphal growth inhibition [43]. Briefly potato dextrose agar (PDA) was used to evaluate the effect of some selected compounds. Fifty milliliters of the aforementioned medium were poured into 150 ml conical flask and autoclaved at 121°C for 20 min. Three drops of 25% lactic acid were added to prevent bacterial contamination. The calculated amount of each tested compound were carried out (v/v) by dissolving certain weight of tested compound in 10 ml of DMSO. 0.5 % of Teween 80 emulsifier was added to the medium. Exact volumes (1000, 500, 250, 125 and 62.5 µl)



5	S	Ar
a	S	4-methoxyphenyl
b	S	3-hydroxyphenyl
c	S	4-flourophenyl
d	S	3,4-dimethoxyphenyl
e	S	3-nitrophenyl
f	S	4-nitrophenyl
g	C	4-methoxyphenyl
h	C	3-hydroxyphenyl
i	C	4-flourophenyl
j	C	3,4-dimethoxyphenyl
k	C	3-nitrophenyl
l	C	4-nitrophenyl

6	X	Ar
a	S	4-methoxyphenyl
b	S	3-hydroxyphenyl
c	O	4-methoxyphenyl
d	O	3-nitrophenyl
e	O	4-nitrophenyl

7	Ar
a	4-flourophenyl
b	3, 4-dimethoxyphenyl

9	X	Ar
a	S	4-flourophenyl
b	S	3, 4-dimethoxyphenyl
c	S	3-nitrophenyl
d	S	4-nitrophenyl

Scheme (2)

of each antifungal compound were added to the media after sterilization (at 45-50°C) to obtain series of concentrations 250, 500, 750, 1000 and 1500 ppm. Plates containing media mixed with DMSO were included as a solvent control. Also, DMSO and Tween 80 (4/1 v/v) were added to PDA medium as a solvent/emulsifier control. Finally, PDA plates treated with distilled water only were served as a negative control. PDA media flasks were distributed aseptically into 9 cm diameter petri dishes.

Discs (5mm diameter) of the tested species were cut from newly prepared cultures of *S. rolfsii, R. solani and F. oxysporum* on PDA and place the mycelial surface down on opposite surface of the test plates on the center of dishes. The plates were then incubated at 28±2°C. The extension diameter (mm) of hyphae from the center of the dishes sides was measured by caliper after 4 days for both *R. solani, S. rolfsii* and after 6 days of *F. oxysporum* fungi. Mean of fungal growth measurement were calculated from 3 replicates of each tested compounds. The percentage of growth inhibition was calculated for each compound. The estimated effective concentration (LC_{50}) which gives 50 % inhibition of fungi radial growth, toxicity index and slopes of toxicity lines for each compound under investigation were determined and presented in (Table 1).

The data represented in table (1) showed the effect of selected synthesized azoles on fungus *Rhizoctonia solani* after 4 days of incubation on PDA at 28°C. These data revealed that the dihydropyridine derivative **9d** was the most effective compounds followed by 9a and 6a, where LC_{50}'s were (336.67, 417.67 and 477.83 ppm) respectively. On the other hand the pyremidine derivative 3c (LC_{50} 1103.17 ppm) was the compound with the lowest efficacy on the tested fungus.

Table 1: Fungicidal activity of some selected new synthesized azoles on *R. solani*, *F. oxysporum* and *S. rolfsii* fungi

	Rhizoctonia solani				*Fusarium oxysporum*				*Sclortium rolfsii*			
Comp.	LC_{50}	LC_{90}	Toxicity Index	Slope	LC_{50}	LC_{90}	Toxicity Index	Slope	LC_{50}	LC_{90}	Toxicity Index	Slope
3a	1046.96	2813.87	32.157	2.985	902.19	2696.31	50.503	2.695	730.01	196.26	70.30	3.277
3c	1103.17	2483.91	30.519	3.636	2082.76	8064.82	21.876	2.18	959.12	1633.83	53.51	5.54
4b	618.71	1603.47	54.415	3.099	1227.3	5590.8	37.125	1.946	987.53	1798.82	51.97	4.921
4c	764.54	1687.39	44.036	3.728	2723.93	19700.7	16.727	1.491	700.72	1459.18	73.24	4.023
6a	477.83	1485.42	70.46	2.60	1077.09	4346.98	42.30	2.12	728.12	1448.50	70.48	4.29
6c	686.87	1216.96	49.016	5.159	704.69	1555.03	64.656	3.728	1060.86	208.82	48.38	3.28
7a	826.45	2296.2	40.737	2.888	512.87	1406.38	88.839	2.925	1207.99	2249.34	42.48	4.747
8	991.96	1901.96	33.94	4.533	1002.73	2653.96	45.439	3.032	920.18	2629.3	55.77	2.811
9a	417.67	984.41	80.61	3.44	1047.87	2184.06	43.48	4.02	904.92	2056.77	56.71	3.59
9d	336.67	694.86	100.00	4.08	455.63	1258.35	100.00	2.91	513.21	1385.99	100	2.97

Also, the data exhibited in table (1) showed the effect of selected azoles on fungus *Fusarium oxysporum* after 6days of incubation on PDA at 28°C. The data revealed that also the dihydropyridine derivative **9d** was the most active compound followed by pyrimidine derivative **7a** and **6a** there LC_{50} (455.63, 512.87 and 704.69 ppm), respectively. While pyrimidine derivative **4c** was the least efficient compound, where its LC_{50} was 2723.93 ppm.

The data represented in table (1) showed the effect of selected synthesized azoles on fungus *Sclortium rolfsii* after 4 days of incubation on PDA at 28°C. These data revealed that, also the dihydropyridine derivative **9d** (LC_{50} 513.21 ppm) was the most active compound followed by **4c, 6a, 3a** and **9a** (LC_{50} 700.72, 728.12, 730.01 and 904.93 ppm) respectively. On contrast compound **7a** (LC_{50} 1207.99 ppm) was the least effective derivative.

General Conclusion:

- Compound **9d** has been found to be the most potent compound, while compounds **3c** and **7a** were less effective azoles on *R. solani*, *F. oxysporum* and *S. rolfsii* respectively.
- The fungus *R. solani* was more sensitive to the tested azoles then *S. rolfsii* and finally *F. oxysporum* fungus.
- *S. rolfsii* fungus exhibited great sensitivity to the tested azoled although benzimidazole fungicide not reported for controlling this fungus.
- The tested azoles could be used in a proper formulation form against these fungi.

Experimental: All melting points are uncorrected and were determined on an electric melting point (electrothermal 9200A) apparatus. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 1H-Gemini 200 MHz and /or Jeol JNM-EX using TMS as internal reference. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer operating at 70 ev. Microanalytical data were performed in the Microanalytical Data Center at Cairo University.

4-amino-5-(1H-benzo[d]imidazolyl)-6-(substituted phenyl)pyrimidine-2(1H)-thione (oxone) 3a-d: Thiourea (0.66 g, 10 mmol) or urea (0.5 g, 10 mmol) was added to a solution of acrylonitrile **2a-c** in ethanolic sodethoxide, the reaction mixture was then refluxed for 3-4 h. The reaction mixture was cooled at room temperature and poured portion wise with stirring onto crushed ice containing few drops of HCl and left to stand in refrigerator for 1hr. The solid product was filtered off, dried and recrystalized from the proper solvent to give the pyrimidenes **3a-d**.

3a)- Yield 65%, (ethanol), mp = 196 - 98°C., IR spectrum ν (cm^{-1}): 3422and 3250 (NH, NH_2), 3060 (CH-aromatic), 2926 (CH-aliphatic),) and 1636 (C=N). ^{1}H NMR spectrum (DMSO) δ (ppm) = 11.2 (s, 1*H*, NH benzimidazole proton), 8.2-7.2 (m, 7H, aromatic protons), 5.1 (s, 2H, NH2), 3.4 (s, 6H, 2O-CH_3) and 2.5 (s, 1*H*, NH pyrimidene proton). Found C 59.97, H 4.62, N 18.42 and S 8.32. Calculated for $C_{19}H_{17}N_5O_2S$ (379.421), C 60.13, H 4.51, N 18.46 and S 8.44. Ms, m/z =379.15, 5.15%.

3b)- Yield 68 %, (benzene), mp = 205 - 07°C. IR spectrum ν (cm^{-1}): 3387 and 3190 (NH_2, NH, OH), 3070 (CH-aromatic), 2984 (CH-aliphatic) and 1658 (C=N). Found C 60.61, H 3.96, N 20.01 and S 9.65. Calculated for $C_{17}H_{13}N_5OS$ (335.384), C 60.87, H 3.91, N 20.88 and S 9.55.MS, m/z = 335.15, 6.74 %.

3c)- Yield 72%, (acetonitrile), mp = 221 -23°C. IR spectrum ν (cm^{-1}): 3387, 3190 (NH, OH and NH2), 3070 (CH-aromatic), 2984 (CH-aliphatic) and 1685 (C=O). ^{1}H NMR (CDCl3) δ (ppm) = 11.8 (s, 1*H*, NH benzimidazole proton), 9.01 (s, 1*H*, NH pyrimidine proton), 7.6-7.1 (m, 8H, aromatic protons) and 5.2 (s, 3H, NH2 and OH). Found C 63.57, H 4.21 and N 21.97. Calculated for $C_{17}H_{13}N_5O_2$ (319.324), C 63.93, H 4.10 and N 21.93. MS, m/z = 320.15, 4.83 %.

3d)- Yield 78%, (ethyl acetate), mp = 214 -16°C. IR spectrum ν (cm^{-1}): 3388, 3269 (NH, OH and NH_2), 3068 (CH-aromatic) and 1699(C=O). Found C 63.97, H 3.99 and N 22.21. Calculated for $C_{17}H_{13}N_5O_2$ (319.324), C 63.93, H 4.10 and N 21.93. Ms, m/z = 319.15, 4.83%.

4-amino-5-(1H-benzo[d]imidaol-2-yl)-6-(4-substituted phenyl)-5,6-dihydro-pyrimidine-2(1H)-thione (oxone) 4a-d: Equimolar amount of acrylonitrile **2c-e** and thiourea and / or urea were heated under reflux for 3 - 4 h in ethanolic sodium ethoxide. The reaction was then left to cool, poured into cold water containing few drops of HCl and left to stand in refrigerator for 1hr. The solid products that separated out were filtered off, washed with cold water, dried and then recrystalized from suitable solvent to yield the pyrimidenes **4a-d.**

4a)- Yield 78%, (DMF/water), mp = 261-63°C. IR spectrum ν (cm^{-1}): 3420, 3177 (NH,OH and NH_2), 3067 (CH-aromatic) and 2924(CH-aliphatic). ^{1}H NMR (DMSO) δ (ppm) = 12.1 (s, 1H, NH benzimidazole proton), 9.5 (s, 1*H*, NH pyrimidine proton), 7.8-7.0 (m, 8H, aromatic protons), 5.2 (s, 2H, NH_2) and 3.5 (2s, 2H, methylene protons) Found C 59.51, H 4.51, F, 5.37, N 21.00 and S 9.32.Calculated for $C_{17}H_{14}FN_5S$. (339.382), C 60.15, H 4.15, F 5.59, N 20.64 and S 9.44.. Ms. m/z = 342.0, 2.35%.

4b)-Yield 61 %, (benzene), mp= 226°C. IR spectrum ν(cm^{-1}): 3422 (NH and OH), 3065 (CH-aromatic) and 2981 (CH-aliphatic). Found C 59.82, H 5.18, N 19.95 and S 9.51. Calculated for $C_{17}H_{15}N_5OS$ (337.4), C 60.51, H 4.48, N 20.76 and S 9.50. Ms. m/z = 337.15, 0.28 %.

4c)-Yield 56%, (ethanol), mp= 196-98°C. IR spectrum ν (cm^{-1}): 3422, 3177 (NH, OH), 3065 (CH-aromatic) 2980(CH-aliphatic) and 1648 (C=O). ^{1}H NMR (DMSO) δ (ppm) = 12.0 (s, 1*H*, NH benzimidazole proton), 9.1 (s, 1*H*, NH pyrimidine proton), 8.0-7.0 (m, 8H, aromatic protons), 6.6 (s, 2H, NH_2), 5.0 (d, 1*H*, CH pyrimidine) and 4.0 (d, 1*H*, pyrimidine). Found C 57.8, H 4.15 and N 24.21. Calculated for $C_{17}H_{14}N_6O$. (350.342), C 58.22, H 4.02 and N 23.99. Ms. m/z = 350.0, 53.3 %.

4d)-Yield 59 %, (ethyl acetate), mp= 218 -20°C. IR spectrum ν(cm^{-1}): 3450- 3168 (NH_2 and NH), 3070 (CH-aromatic), 2897 (CH-aliphatic) and 1695 (C=O). Found C 63.22, H 3.98, F 5.95 and N 21.24. Calculated for $C_{17}H_{14}FN_5O$ (323.322), C 63.14, H 4.36, F 5.87 and N 21.66. Ms. m/z = 323.322, 0.10 %.

6-amino-5-(1H-benzo[d]imidazol-2-yl)-4-(substituted phenyl)-2-thioxo/[oxo]-1,2-dihydropyridine-3-carbonitrile 6a-e: A suspension of **5a, b, g, k and I** (10 mmol) and 1*H*-benzimidazole-2-acetonitrile 1 (1.57 gm, 10 mmol) in ethanol 30 ml containing a catalytic amount of piperdine as a basic medium was refluxed for 4 - 6 h. (TLC control), left to cool and then poured drop wise on water / crushed ice mixture containing few drops of HCl. The formed solid product was filtered off, washed with water. Dried and crystallized from suitable solvent to give the aforementioned pyridine derivatives **6a-e**.

6a)-Yield 72%, (DMF / water), mp =281-83°C.IR spectrum ν (cm^{-1}): 3369, 3287 and 3169 (NH, NH_2)3070 (CH-aromatic), 2962 (CH-aliphatic) and 2215(CN). ^{1}H NMR (DMSO) δ (ppm) = 12.4 (s, 1H, NH benzimidazole proton), 9.1 (s, 1H, pyridine proton), 7.9-7.1 (m, 8H, aromatic protons), 4.5 (s, 2H, NH_2) and 3.4 (s, 3H, O- CH_3). Found C 64.22, H 4.25, N 18.63 and S 8.69. Calculated for $C_{20}H_{15}N_5$ OS (373.415), C 64.32, H 4.05 N 18.76 and S 8.58. Ms. m/z =374, 0.31%.

6b)-Yield 77%, (ethanol / DMF (1:1)), mp= 275-77°C IR spectrum ν (cm^{-1}): 3375 broad (NH, OH, NH_2) 3080 (CH-aromatic) and 1848 (CN). Found C 63.42, H 3.42 N 19.95 and S 8.85. Calculated for $C_{19}H_{13}N_5$ OS (359.289), C 63.49, H 3.64, N 19.48 and S 8.92.

6c)-Yield 68 %, (acetonitrile), mp= 251-53°C IR spectrum ν (cm^{-1}): 3561, 3377 (NH, NH_2) 3065 (CH-aromatic), 2935 (CH-aliphatic) and 2208 (CN). Found C 67.06, H 4.35 and N 19.81. Calculated for $C_{20}H_{15}N_5O_2$ (357.355), C 67.21, H 4.23and N 19.59. Ms, m/z = 357.15, 3.68 %.

6d)-Yield 78%, (DMF), mp= 262-64°C.IR spectrum ν (cm^{-1}): 3298, 3188 (NH, OH, NH_2), 3111 (CH-aromatic), 2214(CN) 1625 (C=N) and 1551, 1517 (NO_2). ^{1}H NMR (DMSO) δ (ppm) = 12.0 (s, 1H, NH benzimidazole proton), 10.0 (s, 1H, pyridine proton), 8.3-6.8 (m, 8H, aromatic protons) and 5.01 (s, 2H, NH_2). Found C 61.51, H 3.05 and N 22.81. Calculated for $C_{19}H_{12}N_6O_3$ (372.328), C 61.28, H 3.24 and N 22.57. Ms. m/z = 372.15, 1.09%.

6e)-Yield 75 %, (DMF), mp= 272°C.-73°C IR spectrum ν (cm^{-1}): 3561, 3422 broad, 3325 (NH, OH, NH_2) 3060 (CH-aromatic), 2221 (CN), 1636 (C=N) and 1589, 1524 (NO_2). Found C 60.99, H 3.45 and N 22.75. Calculated for $C_{19}H_{12}N_6O_3$ (372.328), C 61.28, H 3.24 and N 22.57. Ms, m/z = 372.15, 6.14 %.

6-amino-5-(1H-benzo[d]imidazol-2-yl)-4-(substituted phenyl)pyrido[1,2-a]benzimidazole-3-carbonitrile 7a,b. 2-hydroxy-4-(3-hydroxy phenyl)pyrido[1,6-a]benzimidazole -3,5-dicarbonitrile 8: A suspension of **5h-j** (10 mmol) and 1H-benzimidazole-2-acetonitrile 1 (1.25 g, 10mmol) in 30 ml ethanol containing few drops of piperidene as a basic medium was boiled under reflux for 4 - 6 h. (TLC control), the reaction mixture was cooled and then

diluted with water/ice mixture containing drops of HCl. The precipitated solid was filtered off, washed with water, dried in air and crystallized from the proper solvent to afford **7a,b** and **8.**

7a)- Yield 85%, (DMF), mp= 271°C-73°C. IR spectrum ν (cm^{-1}):3390, 3181 (NH, NH_2), 3070 (CH-aromatic), 2213 (CN) and 1647 (C=N). Found C 71.89, H 3.49, F 4.31and N 20.31. Calculated for $C_{25}H_{15}FN_6$ (418.412), C 71.75, H 3.61, F 4.54 and N 20.08. Ms. m/z = 418.412,19.39s %.

7b)- Yield 88%, (DMF), mp =281°C-82°C. IR spectrum ν (cm^{-1}): 3294, 3185 (NH, NH_2), 3108 (CH-aromatic), 2926 (CH-aliphatic), 2213 (CN) and 1624 (C=N). 1H NMR DMSO) δ (ppm) = 12.2 (s, 1H, NH benzimidazole proton),, 8.2-7.2 (m, 11H, aromatic protons), 5.1 (s,2H, NH_2) and 4.1 (s, 6H, 2O-CH_3). Found C 70.03, H 4.56 and N 18.48. Calculated for $C_{27}H_{20}N_6O_2$ (460.202), C 70.46, H 4.38 and N 18.26. MS, m/z = 460.0, 13.17 %.

8)- Yield 88%, (acetonitrile), mp =241-43°C. IR spectrum ν (cm^{-1}): broad 3195 (OH), 3090 (CH-aromatic), 2212 (CN) and 1627(C=N). ^{1}H NMR (DMSO) δ (ppm) = 8.6 (s, 1H, OH pyridine proton), 8.0-7.0 (m, 8H, aromatic protons) and 5.1 (s, 1H, OH phenyl proton)). Found C 69.66, H 3.51 and N 17.51. Calculated for $C_{19}H_{10}N_4O_2$ (326.29), C 69.93, H 3.09 and N 17.17. MS, m/z = 327.0, 36.2 %.

6-amino-5-(1H-benzo[d]imidazol-2-yl)-4-(substituted phenyl)-2-thioxo-1, 2, 5, 6-tetrahydropyridine-3-carbonitrile 9a-d.

A suspension of **5c-f** (10 mmol) and 1H-benzimidazole-2-acetonitrile 1 (1.57 g, 10 mmol) in ethanol 30 ml containing a catalytic amount of piperdine as a basic medium was refluxed for 4-6 h. (TLC control), left to cool and then poured drop wise on water/crushed ice mixture containing few drops of HCl. The formed solid product was filtered off, washed with water. Dried and crystallized from suitable solvent to give the aforementioned tetrahydropyridine derivatives 9a-d.

9a)-Yield 80 %, (DMF/water), mp= 195 dec IR spectrum ν (cm^{-1}): 3294, 3184 (NH, NH_2) 3080 (CH-aromatic), 2214 (CN) and 1626 (C=N).Found C 62.53, H 4.01, F 5.41, N 19.08 and S 8.97. Calculated for $C_{19}H_{14}FN_6S$ (363.397), C 62.79, H 3.88, F 5.22, N 19.27 and S 8.82. Ms, m/z = 363.65,65.0 %.

9b)-Yield 82 %, (DMF/ethanol), mp= 291-93°C IR spectrum ν (cm^{-1}): 3319, 3247, 3206 (NH, NH_2) 3009 (CH-aromatic), 2926(CH- aliphatic), 2215 (CN) and 1645 (C=N).1H NMR DMSO) δ (ppm) = 12.6 (s,1H, NH benzimidazole proton), 8.2 (s, 1H, NH pyridine proton), 7.8-7.0 (m, 7H, aromatic protons) 4.2 (s, 2H, NH_2), 3.7 and 3.5 (2s, 6H, 2O-CH3) and 2.5 (s, 2H, 2CH pyridine protons). Found C 61.87, H 4.85, N 17.41 and S 7.99. Calculated for $C_{21}H_{19}N_5O_2S$ (405.457), C 62.20, H 4.72 N 17.27 and S 7.90. Ms, m/z = 405, 1.24%.

9c)-Yield 77 %, (DMF), mp < 300 °C IR spectrum ν (cm^{-1}): 3366, 3206 (NH, NH_2) 3063 (CH-aromatic), 2213 (CN),1626 (C=N) and 1524, 1346 (NO_2).Found C 57.99, H 3.52, N 21.81 and S 8.45. Calculated for $C_{19}H_{14}N_6O_2S$ (390.404), C 58.45, H 3.61, N 21.52 and S 8.21. Ms, m/z = 393.0, 0.47%.

9d)-Yield 85 %, (DMF), mp < 300 °C IR spectrum ν (cm^{-1}): 3366 broad (NH, NH_2) 3010 (CH-aromatic), 2213 (CN),1666 (C=N) and 1576, 1515 (NO_2).Found C 58.61, H 3.59, N 21.35 and S 8.02. Calculated for $C_{19}H_{14}N_6O_2S$ (390.404), C 58.45, H 3.61, N 21.52 and S 8.21. Ms, m/z = 390.25, 1.96%.

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