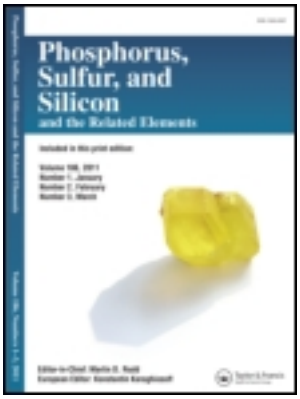

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Synthesis and Fungicidal Activity of New Imidazoles from 2-(Chloromethyl)-1H-benzimidazole

H. M. F. Madkour [a] , A. A. Farag [b] , S. Sh. Ramses [b] & N. A. A. Ibrahiem [b]

[a] Chemistry Department, Ain Shams University, Cairo, Egypt

[b] Central Agricultural Pesticides Laboratory, Agriculture Research Center, Dokki, Giza, Egypt

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Synthesis and Fungicidal Activity of New Imidazoles from 2-(Chloromethyl)-1*H*-benzimidazole

H. M. F. Madkour
Chemistry Department, Ain Shams University, Cairo, Egypt

A. A. Farag
S. Sh. Ramses
N. A. A. Ibrahiem
Central Agricultural Pesticides Laboratory, Agriculture Research Center, Dokki, Giza, Egypt

*A series of substituted 2-thiomethylbenzimidazoles **2–4**, 2-phenoxy-methylbenzimidazoles **5** and 2-aminomethylbenzimidazoles **6** and **7** were synthesized by reactions of 2-chloromethylbenzimidazole **1** with dithiocarbamate, pyrimidine-2-thiones, phenol derivatives, as well as primary aromatic and heterocyclic amines, respectively. Most of the synthesized compounds were screened for their antifungal activity against B. sinerea, F. solani, R. solani, and fungi. Some of the tested compounds showed 100% inhibition for the fungal growth at concentration ranges of 200–1000 ppm.*

INTRODUCTION

Our present work is a continuation of our ongoing program in utilizing readily obtainable materials in the synthesis of different biologically active heterocycles.[1–3] The benzimidazole ring system and its related compounds play an important role in pharmaceutical and agricultural fields due to their broad spectrum of biological activities. Such a ring system has been reported to be a characteristic part of antifungal,[4–8] antibacterial,[9–15] and antiviral agents.[16–19] Benzimidazoles also are useful as insecticides,[20–22] acaricides,[22,23] nematocides,[24] herbicides, and other plant-protective agents in the field of pest control.[25–28] The aforesaid numerous biological activities of benzimidazoles prompted us to study the antifungal activity of some new benzimidazole derivatives, which easily can be synthesized from the highly reactive

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Address correspondence to H. M. F. Madkour, Ain Shams University, Chemistry Department, Faculty of Science, Cairo, Egypt. E-mail: nfmakour@yahoo.com

2-(chloromethyl)-1*H*-benzimidazole. We hope that these new compounds can be useful agents in the field of pest control.

RESULTS AND DISCUSSION

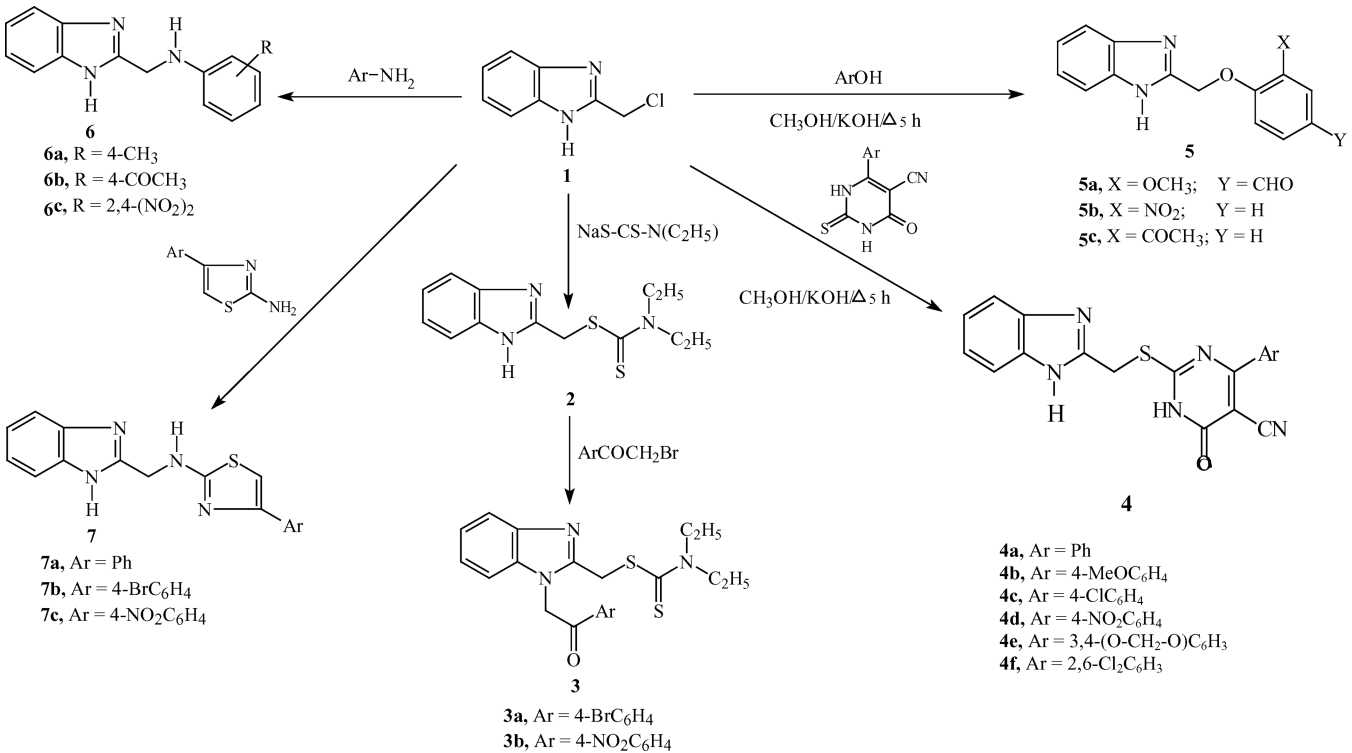
Chemistry

The key starting material 2-(chloromethyl)-1*H*-benzimidazole (**1**) is considered a bifunctional compound, which is prepared by the standard methods.[29] The treatment of compound **1** with sodium N,N-diethyldithiocarbamate in dry methanol under reflux afforded S-(1*H*-benzimidazol-2-yl)methyl diethyldithiocarbamate (**2**) (cf. Scheme 1). Both elemental and spectral data of compound **2** are consistent with the assigned structure (cf. Experimental).

Compound **2** is considered a typical heterocyclic imine, which can be alkylated with different alkylating agents. Thus, treatment of **2** with substituted phenacyl bromides in dry dioxane in the presence of 2,4-dimethylpyridine as a basic catalyst led to a substitution on position 1 of the benzimidazole ring under the formation of compounds **3a**, **b**, which were formulated as [1-(2-aryl-2-oxoethyl)-1*H*-benzimidazol-2-yl]methyl diethyl dithiocarbamates (**3**). The structure of **3** is confirmed by the disappearance of the NH-stretching vibration at 3423 cm^{-1} in compound **2**, the disappearance of the NH signal in the ^{1}H-NMR spectrum which appeared at 12 ppm in compound **2**, and the mass spectra which showed the expected molecular ion peaks corresponding to the molecular weights of derivatives **3a**, **b**.

When solutions of 6-aryl-5-cyano-4-oxo-1,2,3,4-tetrahydropyrimidin-2-thiones in ethanol in the presence of catalytic amounts of potassium hydroxide were heated under reflux for 5 h with imidazole **1**, the corresponding S-alkylated products **4a–f** were formed. The structural assignment of these 6-aryl-2-(1*H*-benzimidazol-2-ylmethylthio)-3,4-dihydro-4-oxopyrimidine-5-carbonitriles (**4**) was substantiated on the basis of their correct elemental analyses and spectroscopic data.

By the same way, compound **1** reacted with substituted phenols to give the products **5a**, **b**. On the other hand, treatment of imidazole **1** with different primary aromatic as well as heterocyclic amines in refluxing ethanol in the presence of potassium iodide and potassium hydroxide for 6 h afforded the corresponding N-alkylated products **6** and **7** (cf. Scheme 1). The products obtained were identified to be 2-arylaminobenzimidazoles and 4-aryl-2-(1*H*-benzimidazol-2-ylmethylamino)-1,3-thiazoles (**6**) and (**7**) respectively. Both elemental analyses



SCHEME 1

and spectroscopic data of these compounds provided satisfying evidence for the proposed structures (cf. Experimental).

BIOLOGICAL STUDY

Fungicidal Activity of Some Selected Newly Synthesized Imidazoles on the Linear Growth of *B. cinerea, F. solani,* and *R. solani* Fungi

Materials and Method

Potato-Dextrose Agar (PDA) was used to evaluate the effect of some selected compounds under investigation on the mycelial linear growth of three fungi. Fifty mL of the aforementioned medium were poured into 150-mL conical flasks and autoclaved at 121°C for 20 min. Three drops of 25% lactic acid were added to prevent bacterial contamination.

Dilutions for each of the tested compounds were carried out (v/v) by dissolving appropriate amounts of each compound in 10 mL of 95% acetone. Equal volumes of the solutions were added to sterile molten (40°C) PDA to get a series of concentrations of 250, 500, 750, 1000, and 1500 ppm for each compound in PDA. A zero (o) concentration treatment was prepared for each fungus, which contained 1% (v/v) of 95% acetone to ensure equivalent acetone concentration in all treatments. Compounds-amended PDA were dispensed aseptically into 9-cm diameter petridishes.

Plugs of mycelium (4 mm diameter) were cut from the margins of actively growing cultures of the *B. cinerea, F. Solani*, and *R. Solani* fungi and placed in the center of compound-amended and unamended PDA plates with 4 replicate plates for each fungus-compound combination. All plates were incubated at 25 ± 1°C. Colony diameter (in mL) was measured after 3 days for *R. Solani* and 7 days for *B. Cinerea* and *F. Solani* fungi, and the percentage of growth inhibition was calculated for each compound. The estimated effective concentration (EC_{50}) which gives 50% inhibition of fungi radial growth, toxicity index, and slopes of toxicity lines for each compound under investigation were determined and tabulated in Table I.

Results and Discussion

The data in Table I indicate that compound **6c** is the most potent compound. Its EC_{50} values are 26.0, 40.3, and 80.2 ppm as compared with the known fungicide **Tecto** or (1,3-thiazol-4-yl)-benzimidazole (EC_{50} values are 38.2, 105.0, and 37.3 ppm) for *R. solani*, *B. cinerea*, and *F. solani* fungi, respectively. This means that compound **6c** exhibits a higher fungicidal activity than **Tecto** on *R. solani* and *B. cinerea* fungi but a lower activity than the standard fungicide on *F. solani* fungus.

TABLE I Fungicidal Activity of Some Selected Newly Synthesized Compounds on *B. cinerea*, *F. solani*, and *R. solani* Fungi

	B. cinerea			*F. solani*			*R. solani*		
Comp. No.	Estimated EC_{50} (ppm)	Toxicity Index***	Slope*	Estimated EC_{50} (ppm)	Toxicity Index	Slope	Estimated EC_{50} (ppm)	Toxicity Index	Slope
2	164.4	15.8	1.29	400.4	6.5	1.26	427.4	6.1	1.85
3b	1619.3	1.6	3.4	1370.9	1.9	7.12	1386.7	1.9	3.27
4b	1316.4	2.0	1.94	1832.6	1.4	1.54	**	**	**
4e	768.5	3.4	2.55	845.7	3.1	1.36	401.1	6.5	2.6
4f	475.7	5.5	1.9	46.8	55.6	0.73	1276.9	2.0	4.58
5a	665.2	3.9	2.9	1340.5	1.9	3.96	942.41	2.8	2.9
6a	485.9	5.4	1.67	773.7	3.4	2.13	492.5	5.3	1.9
6c	40.3	64.5	2.58	80.2	32.4	4.94	26.0	100	2.07
7a	181.0	14.4	2.81	130.2	20	3.69	364.9	7.1	3.29
7bS	457.6	5.7	2.15	600.9	4.3	1.95	358.7	7.2	1.34
Tecto	105.0	24.8	0.71	38.2	68.1	0.9	37.6	61.2	1.1

* The slope of toxicity line that represents the relation between the logarthmic concentration and % of growth inhibition.

** No growth inhibition.

** Toxicity index is the percentage of estimated EC_{50} with respect to the most potent one that has 100% toxicity index.

Also *F. solani*, fungus is sensitive to compound **4f** as compared with the other two fungi where its EC_{50} is 46.8 ppm. The response of the *F. solani* fungus to compound **4f** differed from its response to the other tested compounds. It is more sensitive to compound **4f** than to the other compounds. On the other hand, compounds **3b** and **4b** have the highest EC_{50} values for the tested fungi. They are 1619.3, 1370.9, and 1386.7 ppm for compound **3b** and 1316.4 and 1832.6 for compound **4b** for *B. cinerea*, *F. solani*, and *R. solani* fungi, respectively. *R. solani* fungus was found to be more resistant to compound **4b** where its EC_{50} could not be calculated. The data also revealed that the response of tested fungi to compound **7a** was approximately the same and the response to compound **6a** also was approximately the same, whereas the sensitivity to compound **7a** was higher than that to compound **6a**.

Generally, substitution of the chlorine atom of compound **1** with different groups caused dramatic changes in its effectiveness. Substitution of the chlorine atom with different primary amines caused an increase in its activity (compounds **6** and **7**). Also, substitution with a thiocarbamate group causes moderate changes in benzamidazole activity (compound **2**). On the other hand, substitution with pyrimidinthione diminished the benzimidazole activity (compounds **4b**, **e**).

CONCLUSION

- Compound **6c** was found to be the most potent one followed by compounds **2** and **7a** on 3 tested fungi, but compound **4b** had no effect on *R. solani* fungus and only a weak effect on the other two fungi.
- *F. solani* fungus was found to be sensitive to compounds **6c** and **4f** but *B. cinerea* and *R. solani* fungi were sensitive only to **6c**.
- *B. cinerea* fungus had the higher sensitivity to the tested compounds but *R. solani* fungus had the higher resistant.

EXPERIMENTAL

All melting points are uncorrected and were determined on an electric melting point (Gallenkamp) apparatus. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer (ν_{max} in cm^{-1}). ^{1}H-NMR spectra were recorded on Jeol JNM-EX 200 MHz spectrometers and chemical shifts are expressed in δ (ppm) using TMS as an internal reference. Mass spectra were recorded on GCMS-QP 1000 EX mass spectrometer opening at 70 eV. Microanalytical data were obtained from the Microanalytical data center at Cairo University. The spectroscopic data confirmed the proposed structures of the new imidazoles **2**–**7**.

S-(1*H*-benzimidazol-2-yl)methyl N, N-diethyldithiocarbamate 2

2-chloromethylbenzimidazole **1** (1.67 gm, 10 mmol) was added to a solution of sodium N,N-diethyldithiocarbamate (2.25 gm, 10 mmol) in 50 mL of dry methanol and the reaction mixture was refluxed for 3 h. The reaction mixture was cooled at room temperature and poured portionwise with stirring onto crushed ice containing drops of ammonia solution and left overnight in a refrigerator. The solid product was filtered off, dried, and recrystallized from benzene to give the dithiocarbamate **2**.

(**2**) Yield 85%; m.p. 153–155°C. Found: C, 55.80; H, 6.17; N, 15.20; and S, 22.91. Calculated for $C_{13}H_{17}N_3S_2$ (279.44): C, 55.88; H, 6.13; N, 15.04; and S 22.93; IR: 3423 (NH), 3056 (CH-arom.), 2975 (CH-aliph.), 1638 (C=N) and 1271(C=S); ^{1}HNMR ($CDCl_3$): 1.22 (q, 6H, $2CH_2 - \underline{CH_3}$, J = 7.02), 3.76, 3.98 (2q, 4H, $\underline{2\ CH_2}$-CH_3, J = 7.02), 4.78 (s, 2H, CH_2-S), 7.18–7.55 (m, 4H, Ar-H) and 12.45 (br. S, 1H, NH); MS [m/z (r.%)]: 279 (M^+, 24.8), 163 (100), 131 (45), 117 (12.5), 116 (64), 88 (59.3), and 77 (34).

[1-(2-Aryl-2-oxoethyl)-1*H*-benzimidazol-2-yl]methyl N,N-diethyl Dithiocarbamates 3a,b

A solution of compound **2** (10 mmol) and a catalytic amount of 2,4-dimethylpyridine in 40 mL of dry dioxane was stirred at r.t. for 1 h.

The phenacyl bromide derivative (10 mmol) was added with continuous stirring and heating under reflux for 10 h. The reaction mixture then was concentrated, left to cool, and poured onto iced water with stirring. The solid product that deposited was filtered off and recrystallized from benzene/dioxane to give compounds **3a**, **b**.

(**3a**) Yield 50%; m.p. 178–180°C. Found: C, 52.80; H, 4.65; Br, 16.80; N, 8.9; and S, 13.40. Calculated for $C_{21}H_{22}BrN_3OS_2$ (276.44): C, 52.94; H, 4.65; Br, 16.77; N, 8.82; and S, 13.46; IR: 3051 (CH-arom.), 2977 (CH-aliph.), 1690 (C=O, aroyl ketone), 1678 (C=N) and 1264 (C=S); MS [m/z (r.%)]: 476 (M^+, 13.4), 444 (9.4), 364 (17.6), 183 (100), 157 (78.1), and 76 (30).

(**3b**) Yield 60%; m.p. 198–200°C. Found: C, 56.60; H, 4.90; N 12.70; and S, 14.55. Calculated for $C_{21}H_{22}N_4O_3S_2$ (442.55): C, 56.99; H, 5.01; N, 12.66; and S, 14.49; IR: 3050 (CH-arom.), 2979 (CH-aliph.), 1739 (aroyl ketone), 1624 (C=N), 1530, 1442 (NO_2) and 1272 (C=S); ^{1}HNMR (DMSO-d_6): 1.27 (q, 6H, $2CH_2$-$\underline{CH}_3$, J = 7.32), 3.70, 4.05 (2q, 4H, $2CH_2$-CH_3, J = 7.32), 4.88 (s, 2H, CH_2-S), 5.84 (s, 2H, CH_2CO), 7.19–7.83 (m, 8H, Ar-H); MS [m/z (r.%)]: 444 (m^++2, 5.4), 442 (M^+, 0.4), 364 (10.4), 259 (33.9), 145 (63.3), and 76 (100).

6-Aryl-2-(1*H*-benzimidazol-2-ylmethylthio)-4-oxo-3,4-dihydro-pyrimidine-5-carbonitriles 4a–f

A solution of the 6-aryl-5-cyano-4-oxo-1,2,3,4-tetrahydro-pyrimidin-2-thione (10 mmol) in 50 mL of ethanol containing (10 mmol) of KOH was stirred for 1 h. Compound **1** (10 mmol) then was added portionwise and the solution was stirred under reflux for 3 h. The reaction mixture was left aside at r.t. and then was poured with stirring into crushed ice. The solid products that separated out were filtered off and recrystallized from the appropriate solvents to give the carbonitriles derivatives **4a–f**.

(**4a**) Yield 75%; (dil. ethanol); m.p. 153–155°C. Found: C, 64.40; H, 3.70; N, 19.50; and S, 8.85. Calculated for $C_{19}H_{13}N_5OS$ (359.41): C, 64.49; H, 3.64; N, 19.49; and S, 8.92; IR: 3320, 3185 (NH), 3063 (CH-arom.), 2952 (CH-aliph.), 2213 (CN), 1736 (C=O) and 1620 (C=N); ^{1}HNMR (DMSO-d_3): 4.49 (s, 2H, CH_2-S), 7.01–7.83 (m, 9H, Ar-H), 8.45 (s, 1H, pyrimidine-NH) and 12.39 (br. s, 1H, NH); MS [m/z (r.%)]: 360 (M^+ +1, 53), (M^+, not observed), 261 (21), 173 (50), 131 (100) and 104 (46).

(**4b**) Yield 78%; (dil. ethanol); m.p. 162–164°C. Found: C, 61.50; H, 3.84; N, 18.10; and S, 8.30. Calculated for $C_{20}H_{15}N_5O_2S$ (389.43): C, 61.68; H, 3.88; N, 17.99; and S, 8.23; IR: 3200 (NH), 3010 (CH-arom.), 2937 (CH-aliph.), 2220 (CN), 1678 (C=O) and 1591(C=N); ^{1}HNMR (DMSO-d_3): 3.86 (s, 3H, OCH_3), 4.88 (s, 2H, CH_2-S), 7.14–7.77 (m,

8H, Ar-H), 8.27 (s, 1H, pyrimidine-NH) and 11.23 (br. s, 1H, NH); MS [m/z (r.%)]: 389 (M^+, 1.3), 203 (12), 144 (10), 114 (13), and 59 (100).

(**4c**) Yield 70%; (ethanol); m.p. 180–182°C. Found: C, 58.22; H, 3.13; Cl, 9.10; N, 17.75; and S, 8.10. Calculated for $C_{19}H_{12}ClN_5OS$ (393.91): C, 57.94; H, 3.07; Cl, 9.00; N, 17.78; and S, 8.14; IR: 3380, 3200 (NH), 3080 (CH-arom.), 2952 (CH-aliph.), 2214 (CN), 1738 (C=O) and 1625 (C=N); MS [m/z (r.%)]: 393 (M^+, 12), 341 (4.2), 275 (8), 256 (21), 132 (45), 97 (52), 82 (58), and 69 (100).

(**4d**) Yield 75%; (ethanol); m.p. 218–220°C. Found: C, 56.50; H, 2.83; N, 20.80; and S, 7.90. Calculated for $C_{19}H_{12}N_6O_3S$ (404.41): C, 56.43; H, 2.99; N, 20.78; and S, 7.93; IR: 3385 (NH), 3070 (CH-arom.), 2923 (CH-aliph.), 2209 (CN) 1654 (C=O), 1624 (C=N), 1521 and 1346 (NO_2); MS [m/z (r.%)]: 405 (M^+ +1, 1.2), 404 (M^+, 1.5), 377 (2.6), 325 (9.8), 264 (87), 218 (65), 131 (100), and 91 (39).

(**4e**) Yield 87%; (dil. ethanol); m.p. 147–150°C; Found: C. 59.30; H, 3.40; N, 17.25; and S, 7.85. Calculated for $C_{20}H_{13}N_5O_3S$ (403.42): C, 59.54; H, 3.25; N, 17.36; and S, 7.95; IR: 3320, 3182 (NH), 3060 (CH-arom.), 2905 (CH-aliph.), 2215 (CN) 1728(C=O) and 1610 (C=N); ^{1}HNMR (DMSO-d_3): 4.60 (s, 2H, CH_2-S), 5.8 (s, 2H, OCH_2O), 7.09–8.37 (m, 7H, Ar-H), 8.78 (s, 1H, pyrimidine-NH) and 12.20 (br. s, 1H, NH); MS [m/z (r.%)]: 405 (M^+ +2, 8.14), 403 (M^+, not observed), 231 (30), 198 (9.3), 142 (14), 77 (33), and 59 (100).

(**4f**) Yield 72%; (dil. ethanol); m.p. 157–160°C. Found: C, 53.40; H, 2.60; Cl, 16.58; N, 16.50; and S, 7.31; Calculated for $C_{19}H_{11}Cl_2N_5OS$ (428.39): C, 53.28; H, 2.58; Cl, 16.55; N, 16.55; and S, 7.48; IR: 3314 (NH), 3064 (CH-arom.), 2951 (CH-aliph.), 2225 (CN) 1728 (C=O) and 1638 (C=N); MS [m/z (r.%)]: 429 (M^+ +1, 2.42), 428 (M^+, not observed), 82 (100), and 73 (4.5).

2-Aryloxymethylbenzimidazoles 5a–f

The substituted phenol (10 mmol) was dissolved in 40 mL of ethanol containing (10 mmol) of KOH and the solution was stirred for 1 h. Imidazole **1** (10 mmol) was added with continuous stirring and heating under reflux for 5 h. The reaction mixture was cooled at r.t., poured into crushed ice, and kept in a refrigerator for 2 h. The solid products that separated out were filtered off and recrystallized in a proper solvent after drying to give compounds **5a–c**.

(**5a**) Yield 50%; (benzene); m.p. 145–148°C. Found: C, 68.17; H, 5.04; and N, 9.90. Calculated for $C_{16}H_{14}N_2O_3$ (282.29): C, 68.07; H, 5.00; and N, 9.92; IR: 3386 (NH), 3054 (CH-arom.), 2911 (CH-aliph.), 1675 (C=O) and 1603 (C=N); ^{1}HNMR (DMSO-d_3): 3.71 (s, 3H, OCH_3), 5.42 (s, 2H, CH_2-O), 7.21–7.57 (m, 7H, Ar-H), 9.82 (s, 1H, CHO) and 12.82 (br. s,

1H, NH); MS [m/z (r.%)]: 282 (M^+, 1.22), 251 (11.3), 152 (3.5), 131 (100), 104 (8.2), and 67 (12).

(**5b**) Yield 55%; (benzene/dioxane); m.p. 188–190°C. Found: C, 62.50; H, 4.27; and N, 15.60. Calculated for $C_{14}H_{11}N_3O_3$ (269.23): C, 62.44; H, 4.11; and N, 15.60; IR: 3227 (NH), 3060 (CH-arom.), 2966 (CH-aliph.), 1679 (C=N) and 1512, 1345 (NO_2); MS [m/z (r.%)]: 269 (M^+, 6.3), 223 (11.4), 193 (1.4), 147 (3), 138 (1.6), 131 (100), 104 (10.4), and 77 (15.4).[30]

(**5c**) Yield 40%; (benzene/dioxane); m.p. 82–84°C. Found: C, 72.20; H, 5.35; and N, 10.57. Calculated for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.29; and N, 10.52; IR: 3200 (NH), 3035 (CH-arom.), 2966 (CH-aliph.), 1671 (C=O) and 1639 (C=N); MS [m/z (r.%)]: 266 (M^+, 6.24), 251 (2.3), 223 (2.57) 136 (2.86), 131 (20.9), 78 (100), and 77 (29.84).

2-Arylaminomethylbenzimidazoles 6a–c

A mixture of benzimidazole **1** (10 mmol), substituted aniline (10 mmol) and KI (10 mmol) in 50 mL of ethanol was heated under reflux. After 6 h, KOH (10 mmol in 5 mL of water) was added with continuous stirring and heating for 2 h. The reaction mixture was left aside at r.t. and poured into crushed ice water. The solid products that precipitated were filtered off and recrystallized from a suitable solvent to afford the substituted anilines **6a–c**.

(**6a**) Yield 75%; (benzene); m.p. 175–177°C. Found: C, 76.16; H, 6.21; and N, 17.50. Calculated for $C_{15}H_{15}N_3$ (237.30): C, 75.92; H, 6.36; and N, 17.71; IR: 3449, 3337 (NH), 3109 (CH-arom.), 2928 (CH-aliph.), and 1630 (C=N); MS [m/z (r.%)]: 237 (M^+, 32), 146 (3.9), 131 (88), 107 (100), 77 (46), and 65 (25).

(**6b**) Yield 78%; (benzene); m.p. 96–98°C. Found: C, 72.50; H, 5.65; and N, 15.77. Calculated for $C_{16}H_{15}N_3O$ (265.33): C, 72.43; H, 5.69, and N, 15.84; IR: 3402, 3328 (NH), 3052 (CH-arom.), 2920 (CH-aliph.), 1688 (C=O) and 1579 (C=N); MS [m/z (r.%)]: 266 (M^++1, 11.9), 265 (M^+, 82), 222 (9.9), 131 (100), 91 (66), and 77 (88).

(**6c**) Yield 70%; (acetonitrile); m.p. 178–180°C. Found: C, 53.80; H, 3.50; and N, 22.52. Calculated for $C_{14}H_{11}N_5O_4$ (313.28): C, 53.67; H, 3.54; and N, 22.36; IR: 3428 (NH), 3049 (CH-arom.), 2911 (CH-aliph.), 1615 (C=N), 1520 and 1421 (NO_2); ^{1}HNMR (DMSO-d_3): 4.47 (d, 2H, $\underline{CH_2}$NH, J = 5.7 Hz), 6.17 (t, 1H, CH_2 $\underline{NH}$, J = 5.7 Hz), 6.80–7.48 (m, 7H, Ar-H) and 12.34 (br. s, 1H, NH); MS [m/z (r.%)]: 313 (M^+, 15.3), 259 (78), 166 (11), 131 (69), 99 (31), and 57 (100).

4-Aryl-2-(1*H*-benzimidazol-2-ylmethylamino)-1,3-thiazoles 7a–c

Equimolar amounts of imidazole **1**, 4-aryl-1,3-thiazol-2-amine derivatives, and KI in ethanol were heated under reflux for 7 h. An equimolar

amount of KOH then was added with continuous stirring and refluxed for 3 h. The reaction mixture was left to cool and poured into cold water. The solid products that separated out were filtered off, washed with cold water, dried, and then recrystallized from a suitable solvent to yield the thiazoles **7a–c**.

(**7a**) Yield 80%; (ethanol); m.p. 108–110°C. Found: C, 66.41; H, 4.40; N, 18.35; and S, 10.50. Calculated for $C_{17}H_{14}N_4S$ (306.38): C, 66.64; H, 4.61; N, 18.29; and S, 10.46; IR: 3435, 3256 (NH), 3114 (CH-arom.), 2980 (CH-aliph.), and 1599 (C=N); ^{1}HNMR ($CDCl_3$): 4.28 (d, 2H, $\underline{CH_2}NH$, J = 6.9 Hz), 5.27 (t, 1H, CH_2 NH, J = 6.9 Hz), 6.69 (s, 1H, thiazole H-5), 7.18–7.77 (m, 9H, Ar-H) and 11.80 (br. s, 1H, NH); MS [m/z (r.%)]: 306 (M^+, not observed), 304 (M^+-2H, 28), 200 (25), 175 (13), 132 (100), 102 (28), and 77 (39).

(**7b**) Yield 70%; (ethanol); m.p. 138–140°C. Found: C, 52.58; H, 3.49; Br, 20.90; N, 14.60; and S, 8.50. Calculated for $C_{17}H_{13}BrN_4S$ (385.28): C, 52.98; H, 3.40; Br, 20.74; N, 14.54; and S, 8.32; IR: 3438, 3288 (NH), 3118 (CH-arom.), 2925 (CH-aliph.), and 1622 (C=N); MS [m/z (r.%)]: 386 ($M^+ + 1$, 12.4) 385 (M^+, 11.4), 256 (94), 212 (25), 131 (100), 105 (22.2), 77 (40), and 65 (21).

(**7c**) Yield 60%; (acetonitrile); m.p. 198–200°C. Found: C, 58.11; H, 3.82; N, 19.90; and S, 9.10. Calculated for $C_{17}H_{13}N_5O_2S$ (351.39): C, 58.10; H, 3.73; N, 19.93; and S, 9.12; IR: 3399 (NH), 3113 (CH-arom.), 2925 (CH-aliph.), 1596 (C=N) and 1511, 1430 (NO_2); MS [m/z (r.%)]: 351 (M^+, 8.91) 262 (10.5), 221 (100), 132 (48), and 89 (21).

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