Synthesis and Reactions of 3-Methylthiazolo[3,2-a]benzimidazole-2-carboxylic Acid Hydrazide: Synthesis of Some New Pyrazole, 1,3-Thiazoline, 1,2,4-Triazole and 1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazine Derivatives Pendant to Thiazolo[3,2-a]benzimidazole Moiety

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The reaction of 3-methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid ethyl ester (**1**) with hydrazine hydrate gives the hydrazide **2** which reacts with CS_2/KOH to afford the potassium salt **3**. Treatment of **3** with l-aryl-2-bromoethanones **4a,b** afforded the 1,3-thiazoline derivatives **6a,b**, respectively, while the reaction of **3** with hydrazine hydrate afforded 1,2,4-triazole-3-thione derivative **9**. The reaction of **9** with l-aryl-2-bromoethanones **4a,b** and with hydrazonyl chlorides **11a,b** gave the 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivatives **10a,b** and **12a,b**, respectively. Treatment of hydrazide **2** with phenyl isothiocyanate in refluxing benzene gave the thiosemicarbazide derivative **16**. The latter reaction gave 1,3,4-oxadiazole derivative **17** when benzene was replaced by DMF. Cyclization of the thiosemicarbazide derivative **16** with NaOH resulted in the formation of the 1,2,4-triazole-3-thione derivative **18**.

Keywords: Thiazolo[3,2-a]benzimidazole; Pyrazoles; 1,3,4-Oxadiazoles; 1,3-Thiazolidines; 1,2,4-Triazoles; 1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazines; Hydrazonyl chlorides.

INTRODUCTION

The utility of hydrazides as key intermediates for the synthesis of several series of heterocyclic compounds and the broad spectrum of biological activities of their cyclized products have been reported[1-4] and aroused our interest in exploring the utility of hydrazides as versatile precursors for the synthesis of a variety of substituted heterocycles,[5-9] in addition to the interesting biological activities of thiazolo[3,2-a]benzimidazole derivatives such as antibacterial,[10,11] anti-inflammatory,[12] antiulcer,[13,14] antiviral[15,16] and immunomodulatory[17,18] activities. Also, some thiazolo[3,2-a]benzimidazole derivatives are used for treatment of cancer,[19] neurogenic pain[20] and bone diseases.[21] The above observations prompted us to prepare a new series of heterocycles incorporating thiazolo[3,2-a]benzimidazole moiety starting from the unreported 3-methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid hydrazide (**2**) for biological screening.

RESULTS AND DISCUSSION

The reaction of 3-methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid ethyl ester (**1**) with hydrazine hydrate in refluxing ethanol gave the hydrazide **2**. Its IR spectrum showed the appearance of three absorption bands due to NH_2 and NH functions in addition to the carbonyl absorption band. Its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 246 (M^+) (Scheme I). The hydrazide **2** reacts with carbon disulfide in ethanol in the presence of potassium hydroxide to give the potassium salt **3**, which reacts with l-aryl-2-bromoethanones **4a** and **4b** to give the 1,3-thiazolidine derivatives **6a** and **6b**, respectively. Their structures were confirmed by IR, ^{1}H NMR and mass spectra. For example, The ^{1}H NMR spectrum of **6a** showed a singlet signal (D_2O-exchangeable) at δ 10.97 due to NH function, in addition to a singlet signal of thiazoline moiety at δ 5.08, whereas its mass spectrum showed a peak corresponding to its molecular ion at *m/z*

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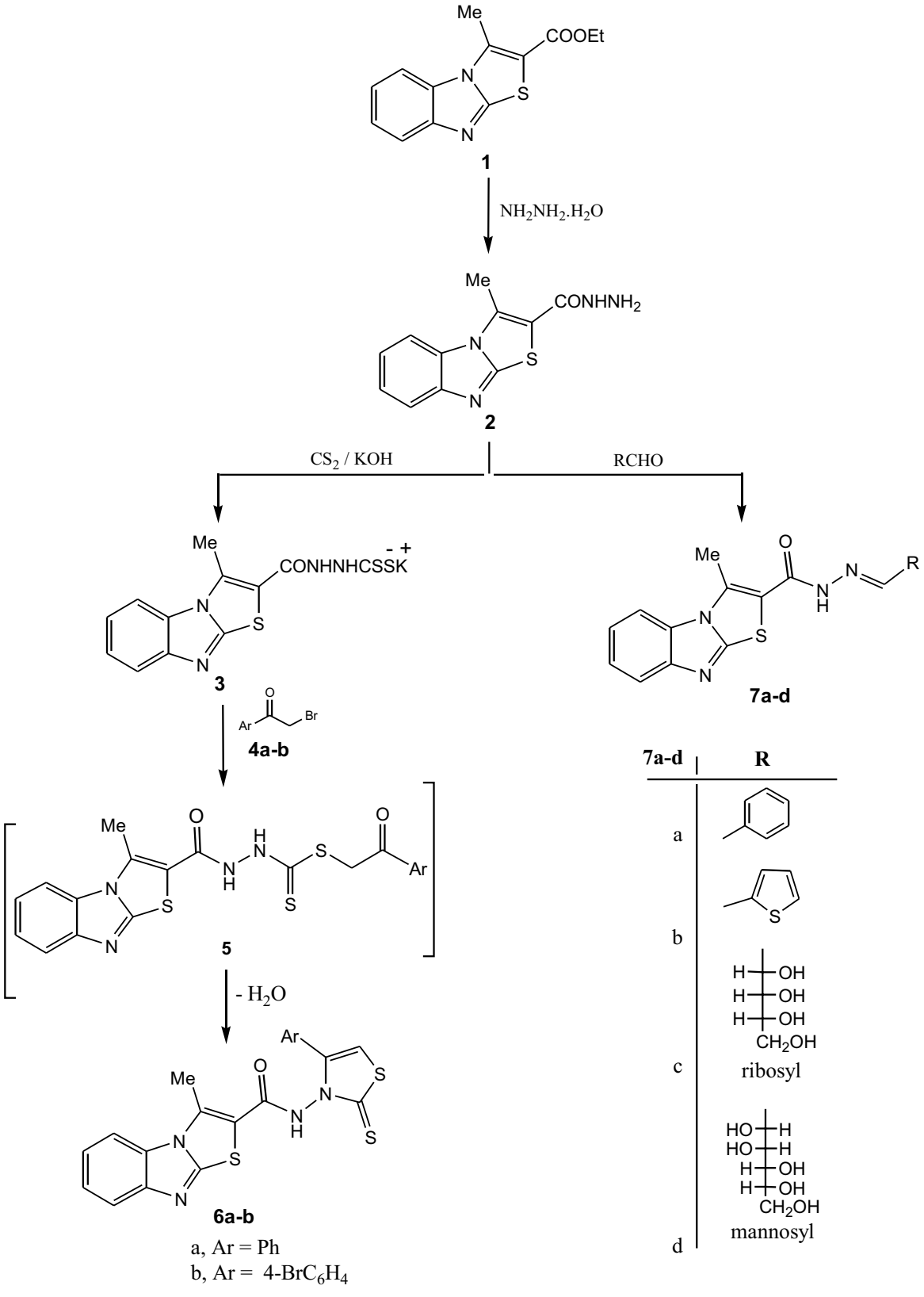
Scheme I


Me
COOEt
N
S
N
1
$NH_2NH_2.H_2O$
Me
$CONHNH_2$
2
CS_2 / KOH
RCHO
Me
CONHNHCSSK
- +
3
Ar
O
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4a-b
Me
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- H_2O
Ar
Me
O
N
S
6a-b
a, Ar = Ph
b, Ar = 4-BrC_6H_4
Me
O
N
H
N
R
7a-d
7a-d
R
a
b
S
c
H—OH
H—OH
H—OH
CH_2OH
ribosyl
d
HO—H
HO—H
H—OH
H—OH
CH_2OH
mannosyl

422 (M^+).

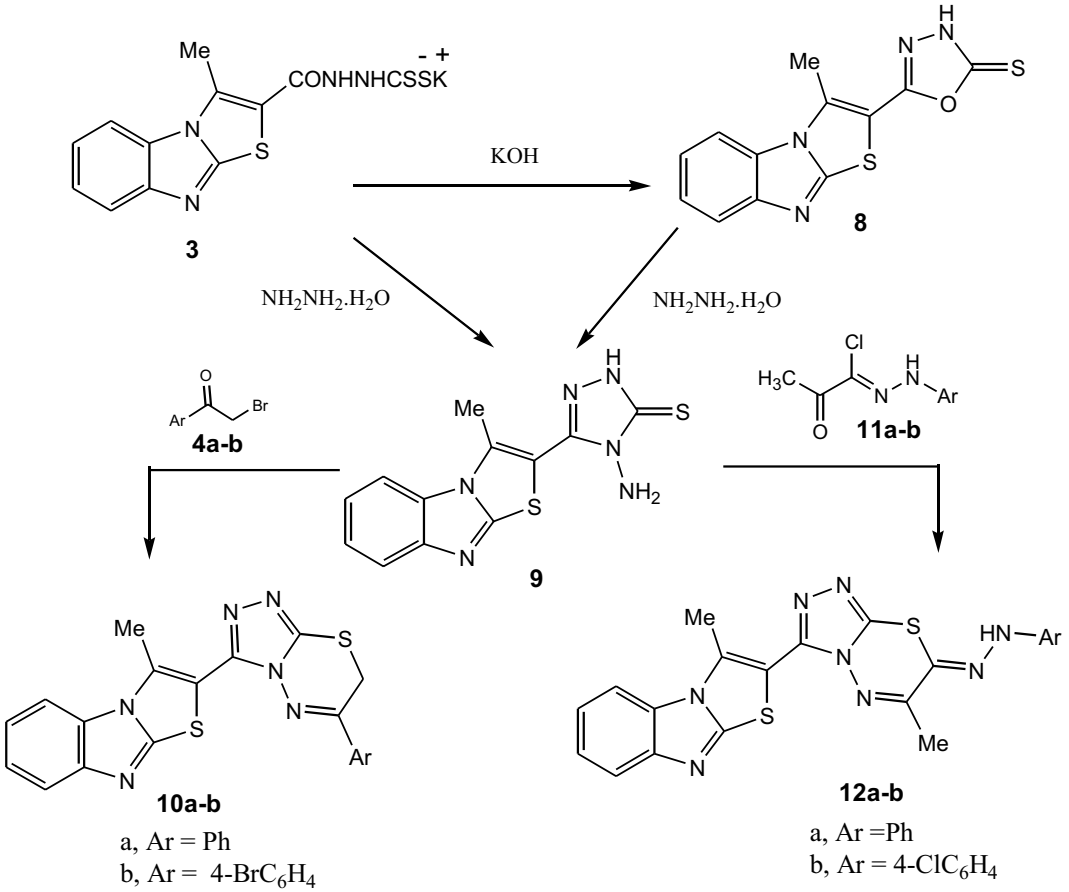
On the other hand, treatment of compound **2** with the appropriate aldehydes in refluxing ethanol yielded the corresponding hydrazones **7a-d** (Scheme I). The structures of the latter products were established on the basis of the appearance of an NH absorption band in the region of 3236-3138 cm^{-1} and a band of carbonyl function in the region of 1660-1639 cm^{-1} in their IR spectra, whereas their ^1H NMR spectra revealed the appearance of a signal due to the -CH=N- proton in the region of 8.05-8.32 ppm and a D_2O-exchangeable signal (NH) in the region of 11.65-11.96 ppm [*cf.* Experimental part].

Heating of the potassium salt **3** in an aqueous solution of potassium hydroxide afforded a product identified as 5-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)-1,3,4-oxadiazole-2-thione (**8**) on the basis of its spectral data (Scheme II). Its IR spectrum revealed an absorption band at 3218 cm^{-1} due to NH function. Its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 288 (M^+) [*cf.* Experimental part].

Moreover, treatment of the potassium salt **3** with hydrazine hydrate in a mixture of ethanol and water afforded 4-amino-5-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)-4H-1,2,4-triazole-3-thione (**9**). Its ^1H NMR spectrum revealed two signals (D_2O-exchangeable) at δ 5.85 (NH_2) and δ 8.75 (NH), whereas its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 302 (M^+) (Scheme II). The structure of compound **9** was further confirmed by an independent synthesis outlined in Scheme II. Thus, treatment of 1,3,4-oxadiazole-2-thione derivative **8** with hydrazine hydrate in refluxing ethanol resulted in the formation of a product identical to compound **9** that was obtained above.

On the other hand, treatment of compound **9** with l-aryl-2-bromoethanone **4a** and **4b** in refluxing ethanol yielded the 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivatives **10a-b** and **12a-b**.

Scheme II

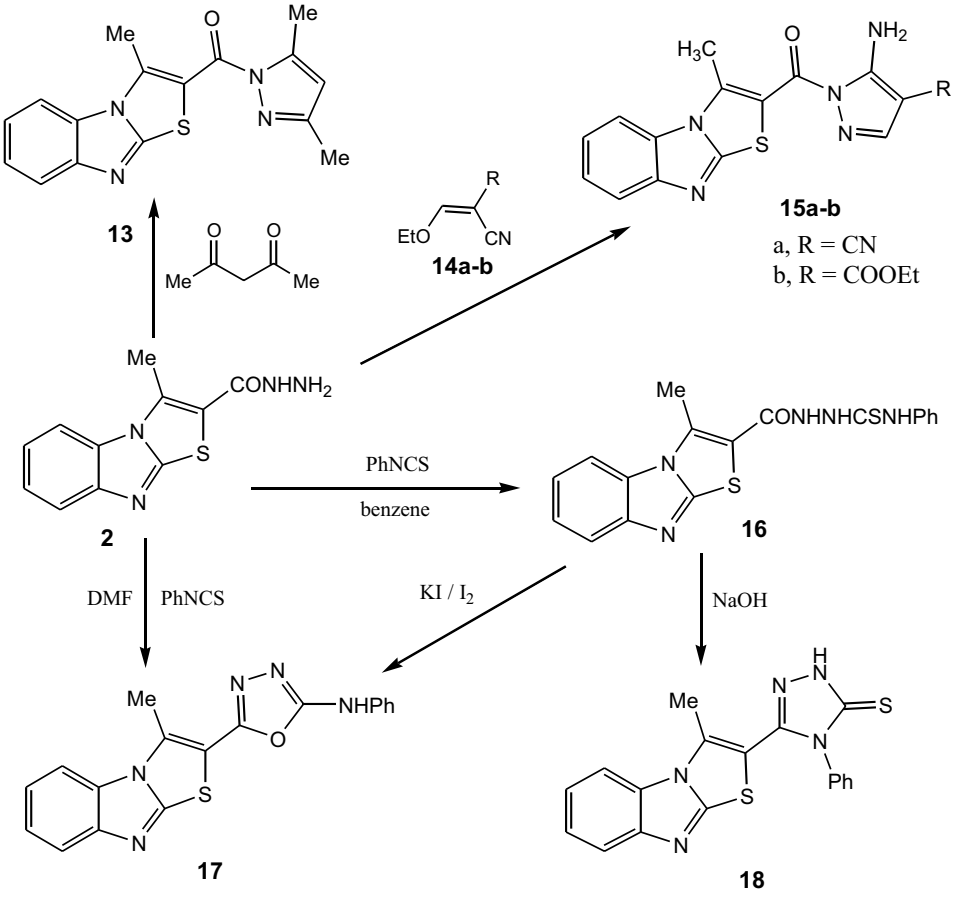


tives **10a** and **10b**, respectively (Scheme II). The latter products were established on the basis of their spectral data: For example, the lack of amino bands in their IR spectra and the appearance of the characteristic signals due to methylene protons of thiadiazine moiety in the region of 4.54-4.57 ppm in their ^{1}H NMR spectra [*cf.* Experimental part].

Similarly, the treatment of **9** with hydrazonyl halides **11a** and **11b** in ethanol afforded the 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivatives **12a** and **12b**, respectively, on the basis of their spectral data. Their ^{1}H NMR spectra showed the D_2O-exchangeable signal corresponding to the NH of hydrazone function in the region of 11.68-11.85 ppm and their mass spectra showed, in each case, a peak corresponding to the molecular ion (Scheme II).

Next, the reaction of hydrazide **2** with pentan-2,4-dione in refluxing ethanol afforded 2-(3,5-dimethyl-pyrazol-1-oyl)-3-methylthiazolo[3,2-a]benzimidazole (**13**) (Scheme III), while the reaction of the hydrazide **2** with ethoxymethylene-malononitrile (**14a**) or with ethoxymethylene-ethyl cyanoacetate (**14b**) in ethanol afforded, in each case, a single product. The reaction products were identified as 5-amino-1-(3-methylthiazolo[3,2-a]benzimidazol-2-oyl)-1H-pyrazole-4-carbonitrile (**15a**) and 5-amino-1-(3-methylthiazolo[3,2-a]benzimidazol-2-oyl)-1H-pyrazole-4-carboxylic acid ethyl ester (**15b**), respectively (Scheme III). The structures of **15a,b** were established on the basis of their spectral data. For example, the IR spectrum of **15a** revealed a band of the amino group at 3425, 3283 cm^{-1} in addition to absorption bands at 2226 and 1675 cm^{-1} corresponding to nitrile and carbonyl functions, respectively, while its ^{1}H NMR showed a broad singlet signal (D_2O-exchangeable) at δ 8.16 due to the amino group in addition to a multiplet at δ 7.31-8.16 due to aromatic protons. Its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 322 [*cf.* Experimental part].

Scheme III



Treatment of the hydrazide **2** with phenyl isothiocyanate in refluxing benzene gave the thiosemicarbazide derivative **16** (Scheme III). The IR spectrum of compound **16** showed three bands due to three NH functions in addition to a carbonyl absorption band at 1650 cm^{-1}. Its ^1H NMR spectrum revealed three signals (D_2O-exchangeable) at δ 8.86, 9.98 and 10.43 assigned to three NH protons. In addition, its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 381 (M^+).

Interestingly, when the latter reaction of the hydrazide **2** with phenyl isothiocyanate was carried out in refluxing DMF instead of benzene, the reaction gave 2-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)-5-phenylamino-1,3,4-oxadiazole (**17**) (Scheme III). The structure of compound **17** was confirmed on the basis of its elemental analysis and spectral data; its IR spectrum revealed the presence of one absorption band due to NH function and the lack of carbonyl absorptions. Its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 347 (M^+). On the other hand, the structure of compound **17** was further confirmed by an independent synthesis by treatment of the thiosemicarbazide derivative **16** with potassium iodide and iodine in the presence of sodium hydroxide (Scheme III).

Furthermore, the intramolecular cyclization of thiosemicarbazide derivative **16** takes place upon heating with sodium hydroxide to produce the 1,2,4-triazole derivative **18** (Scheme III). Its mass spectrum revealed a peak corresponding to the molecular ion at *m/z* 363 (M^+) and its IR was free of NH and carbonyl functions (Scheme III).

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^1H 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 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 3-Methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid ethyl ester (**1**)[22] and hydrazonyl chlorides **11a,b**,[23] were prepared according to reported methods.

3-Methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid hydrazide (2)

A mixture of the ester **1** (2.6 g, 10 mmol) and hydrazine hydrate (0.6 mL, 99%) in 50 mL of absolute ethanol was refluxed for 5 h. The separated white solid was filtered off and recrystallized from EtOH/DMF to give the title compound **2** as white powder in 76% yield, mp. 235-237 °C; IR (KBr) ν_{max}/cm^{-1} 3310, 3222, 3145 (NH, NH_2), 1631 (C=O), 1588 (C=N); ^1H NMR (DMSO-d_6) δ 2.99 (s, 3H, CH_3), 7.26-8.04 (m, 4H, ArH), 9.02 (br. s, 2H, NH_2, D_2O-exchangeable), 9.85 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 247 (M^++1, 99%), 246 (M^+, 100%), 187 (64.6%), 115 (82.0%), 51 (91.4%). For $C_{11}H_{10}N_4OS$ (246.29). Calcd.: C, 53.64; H, 4.09; N, 22.75; S, 13.02%. Found: C, 53.96; H, 4.22; N, 22.40; S, 13.15%.

Potassium 3-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)dithiocarbazate (3)

To a solution of hydrazide **2** (2.5 g, 10 mmol) in ethanol (100 mL), a solution of potassium hydroxide [0.84 g, 15 mmol; in water (10 mL)] and carbon disulfide (3 mL) were added. The reaction mixture was heated under reflux for 3 h, then left to cool. The resulting solid was collected by filtration, washed with ether and dried to give the potassium salt **3** as a pale brown solid in 63% yield which was used directly in the next reactions without further purification, mp. >300 °C; IR (KBr) ν_{max}/cm^{-1} 3340, 3202 (2 NH), 1658 (C=O), 1624 (C=N).

Reaction of potassium salt (3) with α-haloketones 4a,b General procedure

To a solution of the potassium salt **3** (1.8 g, 5 mmol) in ethanol (20 mL), the appropriate l-phenyl-2-bromoethanone (**4a**) or l-(4-bromophenyl)-2-bromoethanone (**4b**) (5 mmol) was added. The reaction mixture was heated under reflux for 2 h. The precipitated solid was collected by filtration, washed with ethanol and dried. Crystallization from EtOH/DMF afforded compounds **6a,b**, respectively.

3-Methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid (4-phenyl-2-thioxo-thiazol-3-yl)amide (6a)

White crystals, Yield 76%, mp. 185-187 °C; IR (KBr)

ν_{max}/cm^{-1} 3414 (NH), 1678 (C=O), 1616 (C=N); ^1H NMR (DMSO-d_6) δ 3.02 (s, 3H, CH_3), 5.08 (s, 1H, thiazoline), 7.28 -8.06 (m, 9H, ArH), 10.97 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 423 (M^++1, 36.9%), 422 (M^+, 54.2%), 239 (47.3%), 296 (35.8%), 185 (31.7%), 156 (100%), 77 (45.1%). For $C_{20}H_{14}N_4OS_3$ (422.55). Calcd.: C, 56.85; H, 3.34; N, 13.26; S, 22.76%. Found: C, 56.56; H, 3.12; N, 12.88; S, 22.94%.

3-Methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid [4-(4-bromophenyl)-2-thioxothiazol-3-yl]amide (6b)

White crystals, Yield (78%), mp. 231-233 °C; IR (KBr) ν_{max}/cm^{-1} 3406 (NH), 1670 (C=O), 1616 (C=N); ^1H NMR (DMSO-d_6) δ 3.07 (s, 3H, CH_3), 5.14 (s, 1H, thiazolidine), 7.34-8.09 (m, 8H, ArH), 10.55 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 505 (M^++4, 6.4%), 503 (M^++2, 3.3%), 501 (M^+, 6.7%), 240 (31.6%), 167 (19.6%), 166 (22.0%), 156 (100%), 81 (82.5%). For $C_{20}H_{13}BrN_4OS_3$ (501.45). Calcd.: C, 47.91; H, 2.61; N, 11.17; S, 19.18%. Found: C, 47.72; H, 2.46; N, 10.88; S, 19.34%.

Reaction of 3-methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid hydrazide (2) with aldehydes General procedure

A mixture of the hydrazide **2** (2.5 g, 10 mmol) and the appropriate aldehyde namely (Benzaldehyde, 2-Thiophenaldehyde, D-(+)-Ribose, D-(+)-Mannose) (10 mmol) in ethanol (30 mL) was refluxed for 3 h (refluxing for 8 h in case of **7c,d**). The solid formed product was collected by filtration, washed with ethanol (with H_2O in case of **7c,d**) and dried. Recrystallization from the proper solvent to afford the corresponding hydrazones **7a-d**.

3-Methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid (1-phenylmethylidene) hydrazide (7a)

White solid, Yield 68%, mp. 270-272 °C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 3155 (NH), 1651 (C=O), 1616 (C=N); ^1H NMR (DMSO-d_6) δ 3.11 (s, 3H, CH_3), 7.22-8.04 (m, 9H, ArH), 8.32 (s, 1H, -CH=N-), 11.85 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 335 (M^++1, 88.6%), 334 (M^+, 100%), 241 (76.3%), 188 (61.8%), 125 (53.0%), 77 (39.5%). For $C_{18}H_{14}N_4OS$ (334.40). Calcd.: C, 64.65; H, 4.22; N, 16.75; S, 9.59%. Found: C, 64.76; H, 4.04; N, 16.98; S, 9.24%.

3-Methylthiazolo[3,2-a]benzimidazole-2-carboxylic acid [1-(thien-1-yl)methylidene] hydrazide (7b)

White solid, Yield 83%, mp. 279-81 °C (EtOH/DMF), IR (KBr) ν_{max}/cm^{-1} 3181 (NH), 1660 (C=O), 1586 (C=N); ^1H NMR (DMSO-d_6) δ 3.22 (s, 3H, CH_3), 7.14-8.10 (m, 7H, 4 ArH and 3H, thiophene), 8.30 (s, 1H, -CH=N-), 11.96 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 341 (M^++1, 16.0%), 340 (M^+, 43.5%), 261 (7.3%), 242 (74.1%), 162 (100%), 111 (82.3%), 65 (64.8%). For $C_{16}H_{12}N_4OS_2$ (340.43). Calcd.: C, 56.45; H, 3.55; N, 16.46; S, 18.84%. Found: C, 56.74; H, 3.68; N, 16.31; S, 18.82%.

***N′*-D-Aldehydoribosyl-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)carbohydrazide (7c)**

White solid, Yield 56%, mp. 158-160 °C (H_2O); IR (KBr) ν_{max}/cm^{-1} 3530-3085 (4OH, NH), 1639 (C=O), 1616 (C=N); ^1H NMR (DMSO-d_6) δ 2.89 (s, 3H, CH_3), 2.99-3.27 (m, 3H, ribose), 3.40-3.58 (m, 2H, ribose), 4.35-5.29 (m, 4H, 4OH, D_2O-exchangeable), 7.26-8.01 (m, 5H, ArH), 8.08 (s, 1H, -CH=N-), 11.65 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 364 (M^++2, 5.9%), 363 (M^++1, 13.6%), 362 (M^+, 8.5%), 189 (100%), 64 (19.4%). For $C_{16}H_{18}N_4O_4S$ (362.41). Calcd.: C, 53.03; H, 5.01; N, 15.46; S, 8.85%. Found: C, 52.76; H, 5.25; N, 15.42; S, 8.64%.

***N′*-D-Aldehydomannosyl-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)carbohydrazide (7d)**

White solid, Yield 49%, mp. 200-203 °C (H_2O); IR (KBr) ν_{max}/cm^{-1} 3520-3060 (5OH, NH), 1656 (C=O), 1546 (C=N); ^1H NMR (DMSO-d_6) δ 3.01 (s, 3H, CH_3), 2.75-3.22 (m, 3H, mannose), 3.34-3.60 (m, 3H, mannose), 4.09-5.32 (m, 5H, 5OH, D_2O-exchangeable), 7.18-8.00 (m, 5H, ArH), 8.05 (s, 1H, -CH=N-), 11.88 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 395 (M^++3, 16.4%), 394 (M^++2, 23.5%), 393 (M^++1, 26.0%), 392 (M^+, 100%), 116 (8.8%), 84 (9.2%). For $C_{17}H_{20}N_4O_5S$ (392.44). Calcd.: C, 52.03; H, 5.14; N, 14.28; S, 8.17%. Found: C, 51.81; H, 5.42; N, 14.03; S, 8.05%.

5-(3-Methylthiazolo[3,2-a]benzimidazol-2-yl)-1,3,4-oxadiazole-2-thione (8)

To the potassium salt **3** (3.6 g, 10 mmol), a solution of potassium hydroxide (1.14 g, 20 mmol) in 30 mL water was added. The reaction mixture was heated under reflux for 2 h, then left to cool and poured into crushed ice and acidified

with dilute hydrochloric acid. The resulting solid was collected by filtration, washed with water and crystallized from EtOH/DMF to give compound **8** as a pale brown solid in 66% yield, mp. 240-242 °C; IR (KBr) ν_{max}/cm^{-1} 3218 (NH), 1616 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.07 (s, 3H, CH_3), 7.31-8.07 (m, 4H, ArH), 11.09 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 289 (M^++1, 98.4%), 288 (M^+, 100%), 242 (75.3%), 187 (49.1%), 151 (44.7%), 118 (62.4%). For $C_{12}H_8N_4OS_2$ (288.35). Calcd.: C, 49.99; H, 2.80; N, 19.43; S, 22.24%. Found: C, 50.23; H, 2.97; N, 19.68; S, 22.51%.

4-Amino-5-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)-4H-1,2,4-triazole-3-thione (9)

Method A

To the potassium salt **3** (3.6 g, 10 mmol) in ethanol-water mixture (1:1, 30 mL) hydrazine hydrate (12 mmol) was added. The reaction mixture was heated under reflux for 2 h, then left to cool and poured into crushed ice. The reaction mixture was acidified with dilute hydrochloric acid. The resulting solid was collected by filtration, washed with water and recrystallized from EtOH/DMF to give compound **9**.

Method B

To a solution of 1,3,4-oxadiazole **8** (2.9 g, 10 mmol) in ethanol (20 mL) hydrazine hydrate (12 mmole) was added. The reaction mixture was heated under reflux for 2 h, then left to cool and poured into crushed ice. The resulting solid was collected by filtration, washed with water and crystallized from EtOH/DMF to give compound **9** as a white solid in 62% yield, mp. 291-293 °C; IR (KBr) ν_{max}/cm^{-1} 3309, 3230, 3129 (NH_2, NH), 1613 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.07 (s, 3H, CH_3), 5.85 (br. s, 2H, NH_2, D_2O-exchangeable), 7.27-8.10 (m, 4H, ArH), 8.75 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 303 (M^++1, 34.7%), 302 (M^+, 48.0%), 264 (35.3%), 203 (100%), 188 (64.6%), 58 (18.8%). For $C_{12}H_{10}N_6S_2$ (302.38). Calcd.: C, 47.67; H, 3.33; N, 27.79; S, 21.21%. Found: C, 47.93; H, 3.64; N, 27.50; S, 20.86%.

Reaction of 4-amino-5-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)-4H-[1,2,4]-triazole-3-thione (9) with α-haloketones 1a,b

General procedure

A mixture of compound **9** (0.60 g, 2 mmol) and the appropriate α-haloketones **4a,b** (2 mmol) in ethanol (30 mL) was refluxed for 8 h. The formed precipitate was filtered off, washed with ethanol and dried. Recrystallization from EtOH/DMF gave compounds **10a,b**, respectively.

3-Methyl-2-(6-phenyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-3-yl)thiazolo[3,2-a]benzimidazole (10a)

White solid, Yield 57%, mp. >300 °C; IR (KBr) ν_{max}/cm^{-1} 1582 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.20 (s, 3H, CH_3), 4.54 (s, 2H, thiadiazine), 7.30-8.14 (m, 9H, ArH); MS *m/z* (%) 405 (M^++3, 28.3%), 404 (M^++2, 33.0%), 403 (M^++1, 26.4%), 402 (M^+, 19.7%), 354 (72.5%), 303 (45.2%), 254 (66.4%), 189 (100%), 122 (84.6%), 77 (61.4%). For $C_{20}H_{14}N_6S_2$ (402.50). Calcd.: C, 59.68; H, 3.51; N, 20.88; S, 15.93%. Found.: C, 59.64; H, 3.34; N, 20.67; S, 15.56%.

3-Methyl-2-[6-(4-bromophenyl)-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-3-yl]thiazolo[3,2-a]benzimidazole (10b)

White solid, Yield 52%, mp. >300 °C; IR (KBr) ν_{max}/cm^{-1} 1603 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.08 (s, 3H, CH_3), 4.57 (s, 2H, thiadiazine), 7.29-8.02 (m, 8H, ArH); MS *m/z* (%) 485 (M^++4, 8.3%), 483 (M^++2, 4.0%), 481 (M^+, 8.6%), 318 (21.6%), 189 (100%), 77 (43.0%). For $C_{20}H_{13}BrN_6S_2$ (481.40). Calcd.: C, 49.90; H, 2.72; N, 17.46; S, 13.32%. Found: C, 49.68; H, 2.46; N, 17.19; S, 13.29%.

Reaction of 4-amino-5-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)-4H-[1,2,4]-triazole-3-thione (9) with hydrazonyl chlorides 11a,b

General procedure

To a solution of compound **9** (0.60 g, 2 mmol) in ethanol (30 mL), the appropriate hydrazonyl chloride **11a,b** (2 mmol) was added. The reaction mixture was heated under reflux for 10 h, then left to cool. The precipitated solid was filtered, washed with ethanol and dried. Crystallization from DMF/H_2O yielded corresponding compounds **12a,b**, respectively.

3-Methyl-2-(7-phenylhydrazono-6-methyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-3-yl)thiazolo[3,2-a]benzimidazole (12a)

Yellow crystals, Yield 58%, mp. >300 °C (DMF/H_2O);

IR (KBr) ν_{max}/cm^{-1} 3414 (NH), 1616 (C=N); ^1H NMR (DMSO-d_6) δ 2.56 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 7.23-8.08 (m, 9H, ArH), 11.85 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 446 (M^++2, 8.4%), 445 (M^++1, 14.1%), 444 (M^+, 12.5%), 390 (9.7%), 375 (18.0%), 347 (22.2%), 299 (100%), 189 (15.8%), 106 (19.3%), 77 (42.6%). For $C_{21}H_{16}N_8S_2$ (444.54). Calcd.: C, 56.74; H, 3.63; N, 25.21; S, 14.43%. Found: C, 56.42; H, 3.29; N, 25.60; S, 14.43%.

3-Methyl-2-[7-(4-chlorophenylhydrazono)-6-methyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-3-yl]thiazolo-[3,2-a]benzimidazole (12b)

Yellow crystals, Yield 62%, mp. >300 °C; IR (KBr) ν_{max}/cm^{-1} 3179 (NH), 1585 (C=N); ^1H NMR (DMSO-d_6) δ 2.56 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 7.23-8.05 (m, 8H, ArH), 11.68 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 480 (M^++2, 11.5%), 479 (M^++1, 24.4%), 478 (M^+, 12.0%), 347 (36.2%), 262 (100%), 77 (34.3%). For $C_{21}H_{15}ClN_8S_2$ (478.99). Calcd.: C, 52.66; H, 3.16; N, 23.39; S, 13.39%. Found: C, 52.34; H, 2.87; N, 23.05; S, 13.64%.

Reaction of hydrazide 2 with acetylacetone, ethoxymethylene-malononitrile (14a) and ethoxymethylene-ethyl cyanoacetate (14b)

General Procedure

To a solution of hydrazide **2** (0.23 g, 1 mmol) in ethanol (20 mL) was added acetylacetone, ethoxymethylene-malononitrile (**14a**) or ethoxymethylene-ethyl cyanoacetate (**14b**) (1 mmol). The mixture was refluxed for 4 h, then allowed to cool. The formed solid was filtered off, washed with ethanol and recrystallized from EtOH/DMF to afford the corresponding pyrazole derivatives **13**, **15a** and **15b**, respectively.

2-(3,5-Dimethyl-pyrazol-1-oyl)-3-methylthiazolo[3,2-a]-benzimidazole (13)

White solid, Yield 88%, mp. 215-217 °C; IR (KBr) ν_{max}/cm^{-1} 1683 (C=O), 1541 (C=N); ^1H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.24 (s, 3H, CH_3), 6.31 (s, 1H, pyrazole), 7.30-8.12 (m, 4H, ArH); MS *m/z* (%) 311 (M^++1, 6.2%), 310 (M^+, 11.5%), 265 (100%), 208 (14.0%), 173 (12.1%), 103 (6.4%), 81 (7.2%). For $C_{16}H_{14}N_4OS$ (310.38). Calcd.: C, 61.92; H, 4.55; N, 18.05; S, 10.33%. Found: C, 62.23; H, 4.29; N, 18.00; S, 10.54%.

5-Amino-1-(3-methylthiazolo[3,2-a]benzimidazol-2-oyl)-1H-pyrazole-4-carbonitrile (15a)

White solid, Yield 72%, mp. 262-264 °C; IR (KBr) ν_{max}/cm^{-1} 3425, 3283 (NH_2), 2226 (C≡N), 1675 (C=O), 16248 (C=N); ^1H NMR (DMSO-d_6) δ 2.25 (s, 3H, CH_3), 7.31-8.16 (m, 5H, 4ArH and 1H, pyrazole), 8.16 (br. s, 2H, NH_2, D_2O-exchangeable); MS *m/z* (%) 323 (M^++1, 16.4%), 322 (M^+, 35.0%), 188 (100%), 131 (67.1%), 118 (48.5%), 80 (72.7%). For $C_{15}H_{10}N_6OS$ (322.35). Calcd.: C, 55.89; H, 3.13; N, 26.07; S, 9.95%. Found: C, 55.85; H, 3.35; N, 25.86; S, 9.81%.

5-Amino-1-(3-methylthiazolo[3,2-a]benzimidazol-2-oyl)-1H-pyrazole-4-carboxylic acid ethyl ester (15b)

White solid, Yield 74%, mp. 255-257 °C; IR (KBr) ν_{max}/cm^{-1} 3412, 3246 (NH_2), 1692, 1664 (2C=O), 1608 (C=N); MS *m/z* (%) 370 (M^++1, 37.5%), 369 (M^+, 25.1%), 315 (84.4%), 240 (55.5%), 188 (100%), 162 (63.4%), 135 (82.6%), 116 (46.0%). For $C_{17}H_{15}N_5O_3S$ (369.40). Calcd.: C, 55.28; H, 4.09; N, 18.96; S, 8.68%. Found: C, 55.53; H, 3.88; N, 18.70; S, 8.75%.

1-(3-Methylthiazolo[3,2-a]benzimidazol-2-oyl)-4-phenylthiosemicarbazide (16)

To a mixture of the hydrazide **2** (2.5 g, 10 mmol) in dry benzene (25 mL), phenyl isothiocyanate (1.35g, 10 mmol) was added, and the reaction mixture was heated under reflux for 5 h, then left to cool. The separated solid was collected by filtration, washed with ethanol and finally crystallized from EtOH/DMF to afford thiosemicarbazide derivative **16** as white crystals in 84% yield, mp. 205-207 °C; IR (KBr) ν_{max}/cm^{-1} 3313, 3224, 3155 (3NH), 1650 (C=O), 1597 (C=N); ^1H NMR (DMSO-d_6) δ 3.11 (s, 3H, CH_3), 7.17-8.09 (m, 9H, ArH), 8.86 (br. s, 1H, NH, D_2O-exchangeable), 9.98 (br. s, 1H, NH, D_2O-exchangeable), 10.43 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 382 (M^++1, 65.9%), 381 (M^+, 37.0%), 201 (100%), 189 (34.6%), 142 (27.5%), 64 (55.3%). For $C_{18}H_{15}N_5OS_2$ (381.48). Calcd.: C, 56.67; H, 3.96; N, 18.36; S, 16.81%. Found.: C, 56.66; H, 4.23; N, 18.23; S, 16.96%.

2-(3-Methylthiazolo[3,2-a]benzimidazol-2-yl)-5-phenylamino-1,3,4-oxadiazole (17)

Method A

To a mixture of hydrazide **2** (2.5 g, 10 mmol) in DMF

(20 mL), phenyl isothiocyanate (1.35 g, 10 mmol) was added, and the reaction mixture was heated under reflux for 8 h, then left to cool, then pour into crushed ice. The separated solid was collected by filtration, washed with ethanol and finally crystallized from EtOH/DMF to give compound **17**.

Method B

To a suspension of the thiosemicarbazide **16** (1.9 g, 5 mmol) in ethanol (4N, 50 mL), sodium hydroxide solution (5 mL) was added with shaking. A solution of iodine and potassium iodide was added dropwise with stirring till the color of iodine persisted. The mixture was refluxed on a water bath for 5 h, then left to cool. The separated solid was filtered off, washed with water and recrystallized from EtOH/DMF to give compound **17** as a white solid, in 78% yield;, mp. 297-299 °C; IR (KBr) ν_{max}/cm^{-1} 3209 (NH), 1589 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.12 (s, 3H, CH_3), 7.03-8.09 (m, 9H, ArH), 10.76 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 349 (M^++2, 73.2%), 348 (M^++1, 60.0%), 347 (M^+, 100%), 308 (18.1%), 240 (55.7%), 222 (19.0%), 123 (35.4%), 82 (64.8%). For $C_{18}H_{13}N_5OS$ (347.40). Calcd.: C, 62.23; H, 3.77; N, 20.16; S, 9.23%. Found: C, 61.86; H, 3.50; N, 20.42; S, 9.15%.

5-(3-Methylthiazolo[3,2-a]benzimidazol-2-yl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (18)

To a suspension of the thiosemicarbazide **16** (1.9 g, 5 mmol) in ethanol, sodium hydroxide solution (1.0 g in 5 mL H_2O) was added. The mixture was refluxed for 4 h, then left to cool. The reaction mixture was acidified with concentrated hydrochloric acid until it becomes neutral (pH 7). The separated solid was filtered off, washed with water and recrystallized from EtOH/DMF to give compound **18** as a white solid in 76% yield, mp. 308-310 °C; IR (KBr) ν_{max}/cm^{-1} 1616 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.89 (s, 3H, CH_3), 7.24-8.03 (m, 9H, ArH), 8.97 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 364 (M^++1, 87.1%), 363 (M^+, 100%), 174 (64.7%), 101 (31.4%), 77 (65.5%). For $C_{18}H_{13}N_5S_2$ (363.47). Calcd.: C, 59.48; H, 3.61; N, 19.27; S, 17.64%. Found: C, 59.65; H, 3.34; N, 19.43; S, 17.56%.

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