Synthesis and antimicrobial activity of certain benzimidazole and fused benzimidazole derivatives

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Novel benzimidazole and fused benzimidazole derivatives such as triazinobenzimidazoles 3a-f, oxadia-zylthio-methyl-1H-benzimidazoles 5a-e, triazollythiomethyl-1H-benzimidazoles 7a,b, thiazolidinyl-methyl-1H-benzimidazoles 9a-e and pyrimidopyrrolobenzimidazoles 12a,b have been synthesized via several reactions of the key intermediate 2-chloromethyl-1H-benzimidazole with various reagents. Moreover, triazinobenzimidazoles 15a-e have been prepared starting with 2-cyanomethyl-1H-benzimidazole. Finally, another series of oxadiazoles 21a,b and triazoles 23a,b linked to benzimidazole moiety at one position have been synthesized starting with 2-mercapto-1H-benzimidazole. The structures of the newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral studies. Some of the newly synthesized compounds exhibit significant antimicrobial activity, the most active compound is 21a.

Keywords: Benzimidazole, fused benzimidazole, antimicrobial activity

Literature survey has revealed the importance of benzimidazoles as antimicrobial agents9. It has also been reported that certain triazinobenzimidazoles have a broad antimicrobial spectrum3. In addition, certain 1,2,4-triazoles and 1,3,4-oxadiazoles exhibit good antimicrobial activity1,10. Moreover, incorporation of barbituric acid with benzimidazole nucleus has produced new antimicrobial agents4. Motivated by the above mentioned facts herein is reported the synthesis and antimicrobial evaluation of new benzimidazole series conjugated with 1,3,4-oxadiazole, 1,2,4-triazole, 1,3-thiazole rings 5a,b, 21a,b, 7a,b, 23a,b and 9a-e respectively and new fused benzimidazoles as triazinobenzimidazoles, pyrimidopyrrolobenzimidazoles 3a-f, 15a-c and 12a,b respectively.

Chemistry

The target compounds were synthesized as depicted in Schemes I, II and III. The key intermediates, 2-chloromethyl-, 2-cyanomethyl- and 2-mercapto-1H-benzimidazole 1, 13, and 16, were prepared according to reported procedures11-13. Treating the key intermediate 1 with different aromatic acid hydrazides using n-butanol as solvent gave 2-[(N-acylhydrazino)methyl]-1H-benzimidazoles 2a-f which on heating with polyphosphoric acid underwent cyclodehydration to afford 1-aryl-3,4-dihydro-[1,2,4]triazino[4,5-a]benzimidazoles 3a-f. The 5-mercapto-oxadiazole and 5-mercaptotriazole intermediates 4 and 6 respectively were prepared according to literature procedures14-16. On reacting them with 1, it was found advantageous to use anhydrous sodium acetate with ethanol as solvent in order to get high yield of the required 2-[(5-aryl-1,3,4-oxadiazol-2-yl)thiomethyl]-1H-benzimidazoles 5a-e and 2-[(5-aryl-4-phenyl-4-H-1,2,4-triazol-3-yl)-thiomethyl]-1H-benzimidazoles 7a,b. Also, the 5-arylidenethiazolidine-2,4-diones 8a-e were prepared by refluxing the aromatic aldehydes with thiazolidine-2,4-dione according to the reported procedures17,18. Reaction of 1 with the NH function of 8a-e succeeded only when the reaction was carried out in acetone:water (3:1) in the presence of potassium carbonate to afford 2-[(5-arylidenec-2,4-dioxothiazolidin-3-yl)methyl]-1H-benzimidazoles 9a-e. The barbituric acid derivative 10a was prepared following the procedure reported by Biltz and Witte19, while the thiobarbituric acid derivative 10b was commercially available. These barbituric acid derivatives were converted in situ to their potassium salts and then allowed to react with the key intermediate 1 to afford the required 2-[(1,3-dimethyl-2,4,6-trioxopyrimidin-5-yl)methyl]-1H-benzimidaz-
ole 11a and 2-[(1,3-diethyl-4,6-dioxo-2-thioxopyrimidin-5-yl)methyl]-1H-benimidazole 11b. Heating compounds 11a,b with phosphorous oxychloride in the presence of N,N-dimethylaniline afforded the cyclized 1,3-dimethyl-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrimido[5,4:4,5]pyrrolo[1,2-a]benzimidazole 12a and 1,3-diethyl-1,2,3,4-tetrahydro-4-oxo-2-thioxo-5H-pyrimido[5,4:4,5]pyrrolo[1,2-a]benzimidazole 12b respectively. Chlorination of the 6-position in the barbituric acid moiety of 11a,b probably occurs prior to an in situ cyclization as indicated by the absence of NH bands (3400-3200 cm\(^{-1}\)) in IR of 12a,b and the absence of the singlet proton of NH at \(\delta\) 13-14 in their \(^1\)H NMR spectra (Scheme I).

Treating the key intermediate 13 with ethyl chloroformate in the presence of pyridine afforded the ester 14 in excellent yield as reported by Slouka\(^{20}\). Coupling this ester with certain heterocyclic diazonium salts in pyridine also gave the cyclized triazino[4,5-a] benzimidazole derivatives 15a-c and no hydrazones could be separated in accordance with Slouka’s report on aromatic diazonium salts\(^{20}\). Proof

\begin{align*}
\text{Scheme I} & \quad \text{Synthesis of compounds 3a-f, 5a-e, 7a,b, 9a-e, 12a,b. Reagents and conditions:} \\
(i) & \quad n-C_4H_9OH; (ii) PPA; (iii) & (iv) C_2H_5OH/CH_3COONa; (v) & (vi) acetone/water/K_2CO_3; (vii) POCl}_3
\end{align*}
EISA et al.: SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF BENZIMIDAZOLE DERIVATIVES

The newly synthesized compounds have been subjected to preliminary screening (qualitative screening) of their in vitro antimicrobial activity against Gram-positive (Bacillus subtilis and Staphylococcus aureus) and Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa) using disc diffusion assay\textsuperscript{22,23}. Gentamycin (30 µg/mL) was used as a reference standard. Compounds which exhibited moderate activity (inhibition zone > 15 mm) were subjected to a quantitative assay in order to determine their minimum inhibitory concentrations (MICs) using the two-fold serial broth dilution assay\textsuperscript{24,25} (Table I).

Results and Discussion

From the microbiological data it was observed that compounds 21\textsubscript{a} and 23\textsubscript{a} have the maximum activity.
against *Bacillus subtilis* comparable to that of Gentamicin. While compounds 21b, 23b, 5e, 7a and 15c showed from high to moderate activity. Compound 3e showed maximum activity while compounds 9a and 23a exhibited only a moderate activity against *Staphylococcus aureus*. On the other hand, all compounds exhibited good activity against *Escherichia coli*, whereby compounds 5d,e, 7a,b, 12a,b, 15b,c, 21a,b and 23a,b showed activity superior to that of the standard. Only compound 3a showed moderate activity against *Pseudomonas aeruginosa*. The other compounds were found inactive or having only weak activity against the four tested microorganisms.

The structure-activity relationship study among the newly synthesized compounds revealed that: incorporation of 1,3,4-oxadiazole ring or 1,2,4-triazole ring into the benzimidazole moiety at 1-position via methylene bridge developed significantly potent antimicrobial analogues (21a and 23a) against *Bacillus subtilis* and providing higher potencies analogues (21a,b and 23a,b) than the compared standard (gentamycin) against *Escherichia coli*. Moreover, incorporation of 1,3,4-oxadiazole ring (substituted at 3-position by 2- or 4-hydroxyphenyl moiety) or 1,2,4-triazole ring (substituted at 3-position by a pyridyl or thiényl moiety) into the benzimidazole moiety at 2-position through thiomethylene bridge (5d,e and 7a,b) developed more effective antimicrobial agents than the compared standard drug against *Escherichia coli*. In addition benzimidazole moiety in the fused heterocyclic systems such as triazinobezimidazoles developed potent antimicrobial agent 3e against *Staphylococcus aureus* and higher potent agent 15b,c superior to that of the standard compound against *Escherichia coli*. Likewise incorporation of benzimidazole moiety in the fused tetracyclic system pyrimidopyrrolo-
benzimidazoles 12a,b improved the potency against *Escherichia coli* superior to that of the standard Gentamycin. Finally, it could be pointed out that generally high and wide spectrum of antibacterial activity was exhibited by compound 21a of the chemical skeleton 1-[(5-methylthio)-[1,3,4]oxadiazol-2-yl)methyl]-2-benzylthiobenzimidazole comparable to other tested compounds.

### Experimental Section

#### Chemistry

Melting points (°C) were determined using a Fischer-Jones melting point apparatus and are uncorrected. Microanalyses (CHN) were performed at the microanalytical center, Cairo University. Infrared spectra (KBr), were run on Mattson 5000 FT-IR Spectrometer (υ in cm⁻¹). ¹H NMR spectra were recorded on a FT-NMR Spectrometer (300 MHz) Demini Varian and a Varian unity plus 300 spectrometer using TMS as an internal standard (chemical shifts in δ, ppm) at Cairo University (Egypt) and Georgia State University (USA) respectively. Mass spectra were recorded on Jeol JMS-600Hz spectrometer at Cairo University. TLC analysis was carried out on silica gel-protected aluminum sheets (Type 60 F 254, Merck) and the spots were detected under UV-Lamp at λ 254 nm.

2-[(N-Acylhydrazino)methyl]-1H-benzimidazoles, 2a-f

To a solution of 1 (1.66 g, 0.01 mole) in n-butanol (20 mL), the appropriate acid hydrazide (0.02 mole) was added and the reaction-mixture was heated under reflux for 30 hr. The precipitated solid was filtered, washed with hot n-butanol and dried.

2-[(N-Benzoylhydrazino)methyl]-1H-benzimidazole, 2a

Crystallized from dimethylformamide/water, yield 75%, m.p. 280-82°C. IR (KBr): 3330, 3320, 3100 (3NH), 1691 cm⁻¹ (C=O); MS: m/z (%) 266 (5, M⁺), 159 (77), 131 (62), 105(79), 77(100). Anal. Calcd for C_{15}H_{14}N_{4}O (266.30): C, 67.65; H, 5.30; N, 21.04. Found: C, 67.55; H, 5.33; N, 21.12%.

2-[(N-(4-Methylbenzoyl)hydrazino)methyl]-1H-benzimidazole, 2b

Crystallized from methanol, yield 78%, m.p. 290-92°C. IR (KBr): 3310, 3200, 3120 (3NH), 1690 cm⁻¹ (C=O). Anal. Calcd for C_{16}H_{16}N_{4}O (280.32): C, 68.55; H, 5.75; N, 19.95. Found: C, 68.64; H, 5.71; N, 20.01%.

2-[(N-(4-Bromobenzoyl)hydrazino)methyl]-1H-benzimidazole, 2c

Crystallized from dimethylformamide, yield 65%, m.p. >300°C. IR (KBr): 3320, 3220, 3150 (3NH), 1685 cm⁻¹ (C=O). Anal. Calcd for C_{15}H_{13}BrN_{4}O (345.19): C, 52.19; H, 3.80; N, 16.23. Found: C, 52.34; H, 3.76; N, 16.17%.

2-[(N-(4-Nitrobenzoyl)hydrazino)methyl]-1H-benzimidazole, 2d

Crystallized from dimethylformamide/water, yield 72%, m.p. 226-28°C. IR (KBr): 3350, 3240, 3150

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(3NH), 1690 cm\(^{-1}\) (C=O). Anal. Calcd for C\(_{15}\)H\(_{13}\)N\(_2\)O\(_3\) (311.30): C, 57.87; H, 4.21; N, 22.50. Found: C, 58.12; H, 4.17; N, 22.58%.

2-\{[N-(2-Hydroxybenzoyl)hydrazino]methyl\}-1H-benzimidazole, 2e

Crystallized from dimethylformamide, yield 61%, m.p. >300°C. IR (KBr): 3500 (OH), 3340, 3230, 3120 (3NH), 1670 cm\(^{-1}\) (C=O). Anal. Calcd for C\(_{15}\)H\(_{13}\)N\(_2\)O\(_2\) (282.30): C, 63.82; H, 5.00; N, 19.85. Found: C, 63.96; H, 4.96; N, 19.97%.

2-\{[N-(4-Hydroxybenzoyl)hydrazino]methyl\}-1H-benzimidazole, 2f

Crystallized from dimethylformamide, yield 63%, m.p. >300°C. IR (KBr): 3450 (OH), 3340, 3330, 3150 (3NH), 1685 cm\(^{-1}\) (C=O). Anal. Calcd for C\(_{15}\)H\(_{13}\)N\(_2\)O\(_2\) (282.30): C, 63.82; H, 5.00; N, 19.85. Found: C, 63.98; H, 5.12; N, 19.52%.

1-Aryl-3,4-dihydro-[1,2,4]triazino[4,5-a]benzimidazoles, 3a-f

A solution of compound 2a-f (0.01 mole) in polyphosphoric acid (20 mL) was heated in an oil bath at 120°C for 6 hr and then cooled. The reaction-mixture was poured on crushed ice, neutralized by ammonia solution, filtered, washed with water and dried.

1-Phenyl-3,4-dihydro-[1,2,4]triazino[4,5-a]benzimidazole, 3a

Crystallized from dimethylformamide, yield 65%, m.p. >300°C. IR (KBr): 3210 (NH), 1641 cm\(^{-1}\) (C=N); \(^1\)H NMR (DMF-\(d_7\)): \(\delta\) 7.40 (s, 2H, CH\(_2\)), 7.12-7.35 (m, 3H), 7.50 (d, \(J = 8.4\) Hz, 2H), 7.61 (d, \(J = 7.8\) Hz, 2H), 8.60 (d, \(J = 8.4\) Hz, 2H), 13.30 (s,1H, NH, D\(_2\)O exchangeable). Anal. Calcd for C\(_{15}\)H\(_{13}\)N\(_4\) (248.28): C, 72.56; H, 4.87; N, 22.57. Found: C, 72.82; H, 4.81; N, 22.19%.

1-(4-Methylphenyl)-3,4-dihydro-[1,2,4]triazino[4,5-a]benzimidazole, 3b

Crystallized from ethanol, yield 68%, m.p. >300°C. IR (KBr): 3190 (NH), 1615 cm\(^{-1}\) (C=N); \(^1\)H NMR (DMF-\(d_7\)): \(\delta\) 2.51 (s, 3H, CH\(_3\)), 4.05 (s, 2H, CH\(_2\)), 7.20 (d, \(J = 7.5\) Hz, 2H), 7.48 (d, \(J = 8.4\) Hz, 2H), 7.64 (d, \(J = 7.5\) Hz, 2H), 8.51 (d, \(J = 8.4\) Hz, 2H), 12.10 (s,1H, NH, D\(_2\)O exchangeable). Anal. Calcd for C\(_{16}\)H\(_{14}\)N\(_4\) (262.31): C, 73.26; H, 5.38; N, 21.36. Found: C, 73.54; H, 5.54; N, 21.20%.

1-(4-Bromophenyl)-3,4-dihydro-[1,2,4]triazino[4,5-a]benzimidazole, 3c

Crystallized from dimethylformamide, yield 75%, m.p. 275-77°C. IR (KBr): 3120 cm\(^{-1}\) (NH); \(^1\)H NMR (DMF-\(d_6\)): \(\delta\) 3.73 (s, 2H, CH\(_2\)), 7.11 (d, \(J = 7.6\) Hz, 2H), 7.33 (d, \(J = 8.4\) Hz, 2H), 7.42 (d, \(J = 7.6\) Hz, 2H), 7.61 (d, \(J = 8.4\) Hz, 2H), 11.46 (s,1H, NH, D\(_2\)O exchangeable). Anal. Calcd for C\(_{15}\)H\(_{13}\)Br\(_2\)N\(_2\) (327.18): C, 55.06; H, 3.39; N, 17.12. Found: C, 55.38; H, 3.24; N, 17.33%.

1-(4-Nitrophenyl)-3,4-dihydro-[1,2,4]triazino[4,5-a]benzimidazole, 3d

Crystallized from dimethylformamide, yield 70%, m.p. 296-98°C. IR (KBr): 3300 cm\(^{-1}\) (NH); \(^1\)H NMR (DMF-\(d_6\)): \(\delta\) 4.08 (s, 2H, CH\(_2\)), 7.16 (d, \(J = 8.4\) Hz, 2H), 7.48 (d, \(J = 7.5\) Hz, 2H), 7.62 (d, \(J = 8.4\) Hz, 2H), 7.86 (d, \(J = 7.5\) Hz, 2H), 12.53 (s,1H, NH, D\(_2\)O exchangeable). Anal. Calcd for C\(_{15}\)H\(_{13}\)Br\(_2\)N\(_2\) (293.28): C, 61.43; H, 3.78; N, 23.88. Found: C, 61.70; H, 3.62; N, 24.12%.

1-(2-Hydroxyphenyl)-3,4-dihydro-[1,2,4]triazino[4,5-a]benzimidazole, 3e

Crystallized from dimethylformamide/water, yield 65%, m.p. 270-72°C. IR (KBr): 3350 (OH), 3260 cm\(^{-1}\) (NH); \(^1\)H NMR (DMF-\(d_6\)): \(\delta\) 4.20 (s, 2H, CH\(_2\)), 6.20-7.38 (m, 4H), 7.60 (d, \(J = 8.4\) Hz, 2H), 7.93 (d, \(J = 8.4\) Hz, 2H), 10.18 (s,1H, OH, D\(_2\)O exchangeable), 12.40 (s,1H, NH, D\(_2\)O exchangeable). Anal. Calcd for C\(_{15}\)H\(_{13}\)O\(_2\) (264.28): C, 68.17; H, 4.58; N, 21.20. Found: C, 68.29; H, 4.82; N, 21.51%.

1-(4-Hydroxyphenyl)-3,4-dihydro-[1,2,4]triazino[4,5-a]benzimidazole, 3f

Crystallized from dimethylformamide/water, yield 68%, m.p. 248-50°C. IR (KBr): 3390 (OH), 3215 cm\(^{-1}\) (NH); \(^1\)H NMR (DMF-\(d_6\)): \(\delta\) 4.45 (s, 2H, CH\(_2\)), 6.95 (d, \(J = 7.5\) Hz, 2H), 7.48 (d, \(J = 8.4\) Hz, 2H), 7.61 (d, \(J = 7.5\) Hz, 2H), 7.81 (d, \(J = 8.4\) Hz, 2H), 10.20 (s,1H, OH, D\(_2\)O exchangeable), 12.50 (s,1H, NH, D\(_2\)O exchangeable). Anal. Calcd for C\(_{15}\)H\(_{13}\)O\(_2\) (264.28): C, 68.17; H, 4.58; N, 21.20. Found: C, 68.41; H, 4.69; N, 21.47%.

2-[(5-Aryl-1,3,4-oxadiazol-2-yl)thiomethyl]-1H-benzimidazoles, 5a-e and 2-[(5-aryl-4-phenyl-4H-1,2,4-triazol-3-yl)thiomethyl]-1H-benzimidazoles, 7a,b

To a solution of 1 (1.66 g, 0.01 mole) in absolute ethanol (30 mL), the proper oxadiazole derivative 4 or
phenyltriazole derivative 6 (0.01 mole) and fused sodium acetate (0.83 g, 0.01 mole) were added and the mixture was heated under reflux for 12 hr, after cooling, the product was collected by filtration and dried.

2-[(5-(4-Methylphenyl)-1,3,4-oxadiazol-2-yl)thiomethyl]-1H-benzimidazole, 5a

Crystallized from ethanol, yield 82%, m.p. 218-20°C. IR (KBr): 3250 (NH), 1635 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆): δ 2.30 (s, 3H, CH₃), 4.80 (s, 2H, CH₂), 7.17 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 7.5 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 12.42 (s,1H, NH, D₂O exchangeable). Anal. Calcd for C₁₉H₁₉N₅O₄S (366.42): C, 63.33; H, 3.68; N, 14.47%. Found: C, 63.54; H, 4.34; N, 17.52%.

2-[(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)thiomethyl]-1H-benzimidazole, 5b

Crystallized from ethanol, yield 85%, m.p. 174-76°C. IR (KBr): 3330 (NH), 1622 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆): δ 2.30 (s, 3H, CH₃), 7.09 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 7.5 Hz, 2H), 7.95 (d, J = 8.7 Hz, 2H), 12.60 (s,1H, NH, D₂O exchangeable). Anal. Calcd for C₁₉H₁₁BrN₅O₄S (387.25): C, 49.62; H, 2.86; N, 14.47. Found: C, 49.83; H, 2.83; N, 14.64%.

2-[(5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl)thiomethyl]-1H-benzimidazole, 5c

Crystallized from ethanol, yield 79%, m.p. 206-08°C. IR (KBr): 3260 (NH), 1570 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆): δ 4.83 (s, 2H, CH₂), 7.14 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H), 8.38 (d, J = 7.5 Hz, 2H), 12.53 (s,1H, NH, D₂O exchangeable); MS: m/z (%) 355 (1.33, M⁺+2), 353 (15.48, M⁺), 223 (7.3), 131 (100), 104 (86.4), 76 (90.4). Anal. Calcd for C₁₆H₁₁N₅O₃S (353.36): C, 54.38; H, 3.14; N, 19.82. Found: C, 54.72; H, 3.16; N, 19.79%.

2-[(5-(2-Hydroxyphenyl)-1,3,4-oxadiazol-2-yl)thiomethyl]-1H-benzimidazole, 5d

Crystallized from ethanol, yield 72%, m.p. 196-98°C. IR (KBr): 3400 (OH), 3100 (NH), 1590 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆): δ 4.65 (s, 2H, CH₂), 7.32-7.51 (m, 4H), 7.63 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.7 Hz, 2H), 10.24 (s,1H, OH, D₂O exchangeable), 12.54 (s,1H, NH, D₂O exchangeable). Anal. Calcd for C₁₆H₁₂N₅O₄S (324.36): C, 59.25; H, 3.73; N, 17.27. Found: C, 59.52; H, 3.69; N, 17.21%.

2-[(5-(4-Hydroxyphenyl)-1,3,4-oxadiazol-2-yl)thiomethyl]-1H-benzimidazole, 5e

Crystallized from ethanol, yield 75%, m.p. 256-58°C. IR (KBr): 3430 (OH), 3150 (NH), 1585 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆): δ 4.60 (s, 2H, CH₂), 7.01 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 7.6 Hz, 2H), 8.20 (d, J = 8.4 Hz, 2H), 9.95 (s, 1H, OH, D₂O exchangeable), 12.48 (s,1H, NH, D₂O exchangeable). Anal. Calcd for C₁₆H₁₂N₅O₄S (324.36): C, 59.25; H, 3.73; N, 17.27. Found: C, 59.48; H, 3.72; N, 17.18%.

2-[(4-Phenyl-5-(3-pyridyl)-4H-1,2,4-triazol-3-yl)thiomethyl]-1H-benzimidazole, 7a

Crystallized from dimethylformamide/ethanol, yield 87%, m.p. 246-48°C. IR (KBr): 3325 (NH), 1585 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆): δ 4.66 (s, 2H, CH₂), 7.12-7.48 (m, 5H), 7.61-8.47 (m, 8H), 12.45 (s,1H, NH, D₂O exchangeable). Anal. Calcd for C₁₉H₁₆N₆S (384.46): C, 65.61; H, 4.19; N, 21.86. Found: C, 65.92; H, 4.24; N, 21.92%.

2-[(4-Phenyl-5-(thien-2-yl)-4H-1,2,4-triazol-3-yl)thiomethyl]-1H-benzimidazole, 7b

Crystallized from dimethylformamide/ethanol, yield 85%, m.p. 258-60°C. IR (KBr): 3280 cm⁻¹ (NH); ¹H NMR (DMSO-d₆): δ 4.57 (s, 2H, CH₂), 6.77-7.61 (m, 12H), 12.31 (s,1H, NH, D₂O exchangeable); MS: m/z (%) 391 (12.84, M⁺+2), 389 (100, M⁺), 258 (32.9), 185 (42.3), 131 (91.8), 77 (89). Anal. Calcd for C₂₉H₁₈N₈S (389.50): C, 61.67; H, 3.88; N, 17.98. Found: C, 61.93; H, 3.91; N, 17.92%.

2-[(5-Arylidene-2,4-dioxothiazolidin-3-yl)methyl]-1H-benzimidazoles, 9a-e

To a solution of 1 (1.66 g, 0.01 mole) and potassium carbonate (1.51 g, 0. 11 mole) in acetone:water mixture (30 mL:10 mL), the appropriate 5-arylidene-thiazolidine-2,4-dione (0.01 mole) was added. The reaction-mixture was heated under reflux for 24 hr, then cooled and refrigerated overnight. The separated solid was filtered and dried.

2-[(5-(4-Bromobenzylidene)-2,4-dioxothiazolidin-3-yl)methyl]-1H-benzimidazole, 9a

Crystallized from ethanol/water, yield 82%, m.p. 160-62°C. IR (KBr): 3324 (NH), 1744, 1720 cm⁻¹ (C=O); MS: m/z (%) 416 (18.79, M⁺+2), 414 (18.44, M⁺), 335 (13.9), 214 (7.4), 173 (100), 131 (22.45), 89 (19.6); ¹H NMR (DMSO-d₆): δ 5.08 (s, 2H, CH₂), 7.13 (d, J = 7.5 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H),
2-[[5-(4-Methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]methyl]-1H-benimidazole, 9b

Crystallized from methanol, yield 89%, m.p. 142-44°C. IR (KBr): 3335 (NH), 1735, 1725 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ 3.80 (s, 3H, CH₃), 3.18 (s, 3H, CH₃), 5.08 (s, 2H, CH₂), 7.14-7.49 (m, 7H, Ar-H), 7.93 (s, 1H, olefinic CH=), 12.50 (s, 1H, NH, D₂O exchangeable). Anal. Calcd for C₁₉H₁₄N₂O₃S (395.43): C, 60.75; H, 4.47; N, 13.51%; Found: C, 60.94; H, 4.71; N, 13.74%.

2-[[5-(3,4-Dimethoxybenzylidene)-2,4-dioxothiazolidin-3-yl]methyl]-1H-benimidazole, 9d

Crystallized from ethanol, yield 79%, m.p. 172-74°C. IR (KBr): 3290 (NH), 1712, 1706 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ 3.02 (s, 3H, CH₃), 5.04 (s, 2H, CH₂), 7.11 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 7.83 (s, 1H, olefinic CH=), 12.30 (s, 1H, NH, D₂O exchangeable). Anal. Calcd for C₂₀H₁₇N₂O₃S (378.45): C, 63.47; H, 4.79; N, 14.80. Found: C, 63.81; H, 4.71; N, 14.97%.

2-[[5-(4-N,N-Dimethylaminobenzylidene)-2,4-dioxothiazolidin-3-yl]methyl]-1H-benimidazole, 9e

Crystallized from ethanol/water, yield 73%, m.p. 126-28°C. IR (KBr): 3325 (NH), 1721, 1716, 1600 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ 3.02 (s, 3H, CH₃), 3.18 (s, 3H, CH₃), 5.04 (s, 2H, CH₂), 7.51 (d, J = 3.9 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.82 (d, J = 3.9 Hz, 1H), 8.09 (s, 1H, olefinic CH=), 12.25 (s, 1H, NH, D₂O exchangeable). Anal. Calcd for C₁₉H₁₂N₂O₃S (352.34): C, 59.07; H, 3.41; N, 12.92. Found: C, 59.34; H, 3.33; N, 13.13%.

2-[[1,3-Dimethyl-2,4,6-trioxopyrimidin-5-yl]methyl]-1H-benimidazole, 11a and 2-[[1,3-diethyl-4,6-dioxo-2-thioxopyrimidin-5-yl]methyl]-1H-benimidazole, 11b

To a solution of 1 (1.66 g, 0.01 mole) and potassium carbonate (1.51 g, 0.11 mole) in acetone:water mixture (60 mL:20 mL), 1,3-dimethylbarbituric acid (1.56 g, 0.01 mole) or 1,3-diethylthiobarbituric acid (2 g, 0.01 mole) was added. The reaction-mixture was heated under reflux for 2 hr, then cooled and neutralized with concentrated hydrochloric acid. The separated solid was filtered, washed with water and dried. The crude product was purified by dissolving in potassium carbonate solution and reprecipitation with concentrated hydrochloric acid.

2-[[1,3-Dimethyl-2,4,6-trioxopyrimidin-5-yl]methyl]-1H-benimidazole, 11a

Yield 84%, m.p. >300°C. IR (KBr): 3410 (NH), 1725, 1705, 1680 cm⁻¹ (C=O); MS: m/z (%) 286 (100, M⁺), 239 (45.3), 144 (47.4), 57 (60.7). Anal. Calcd for C₁₉H₁₄N₂O₃S (286.29): C, 58.73; H, 4.93; N, 19.57. Found: C, 58.97; H, 4.71; N, 19.74%.

2-[[1,3-Diethyl-4,6-dioxo-2-thioxopyrimidin-5-yl]methyl]-1H-benimidazole, 11b

Yield 90%, m.p. >300°C. IR (KBr): 3410 (NH), 1743, 1712 (C=S); MS: m/z (%) 332 (5.15, M⁺), 300 (67.4, M⁺), 297 (45.6), 199 (100), 131 (58.9), 69 (27.5). Anal. Calcd for C₁₉H₁₂N₂O₃S (330.40): C, 58.16; H, 5.49; N, 16.96. Found: C, 58.52; H, 5.58; N, 17.22%.

1,3-Dimethyl-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrimido[5:4:5]pyrrolo[1,2-a]benzimidazole, 12a

A solution of 11a (2.86 g, 0.01 mole) or 11b (3.3 g, 0.01 mole) and N,N-dimethylaniline (1.21 g, 0.01 mole) in phosphorous oxychloride (20 mL) was heated under reflux for 6 hr. The reaction-mixture was then poured on crushed ice and the separated solid was filtered, dried and purified by recrystallization from dimethylformamide.

1,3-Dimethyl-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrimido[5:4:5]pyrrolo[1,2-a]benzimidazole, 12b

Yield 77%, m.p. 210-12°C. IR (KBr): 1723, 1707 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ 2.85 (s, 3H, CH₃), 3.20 (s, 3H, CH₃), 4.10 (s, 2H, CH₂), 7.28 (d, J
1,3-Diethyl-1,2,3,4-tetrahydro-4-oxo-2-thioxo-5H-pyrimido[5,4:4,5]pyrrolo[1,2-α]benzimidazole, 12b

Yield 81%, m.p. 240-42°C. IR (KBr): 1711 (C=O), 1238 cm⁻¹ (C=S); MS: m/z (%): 314 (23.24, M⁺ +2), 312 (16.06, M⁺), 283 (100), 239 (11.9), 177 (21.9), 133 (50.08), 89 (50.04); ¹H NMR (DMSO-d₆): δ 1.15-1.21 (t, J = 4 Hz, 6H), 4.02 (s, 2H, CH₂), 4.45-4.52 (q, J = 4 Hz, 4H), 7.43 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H). Anal. Calcd for C₁₆H₁₄N₄O (312.39): C, 61.52; H, 5.16; N, 17.93. Found: C, 61.81; H, 5.21; N, 17.77%.

4-Cyano-2-heteraryl-1,2-dihydro-1-oxo-[1,2,4]triazino[4,5-α]benzimidazoles, 15a-c

To a solution of 14 (2.29 g, 0.01 mole) in pyridine (20 mL) in ice bath, a solution of the appropriate diazonium hydrochloride [amine (0.01 mole), 36% HCl (3 mL), ice water (10 mL) and NaNO₂ (0.7 g, 0.01 mole)] was added with continuous stirring 24 hr. Then the reaction mixture was diluted with ice-cooled water (200 mL) and the formed precipitate was collected by filtration and dried.

4-Cyano-2-(1,2-dihydro-1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl)-1,2-dihydro-1-oxo-[1,2,4]triazino[4,5-α]benzimidazole, 15a

Crystallized from ethanol, yield 85%, m.p. 290-292°C. IR (KBr): 2220 (CN), 1720, 1680 cm⁻¹ (C=O); MS: m/z (%): 397 (36.4, M⁺), 305 (2.6), 235 (1.2), 144 (6.7), 90 (11.3), 56 (100); ¹H NMR (DMSO-d₆): δ 2.30 (s, 3H, C-CH₃), 3.25 (s, 3H, N-CH₃), 7.41-7.60 (m, 5H), 7.78 (d, J = 8.4 Hz, 2H), 8.30 (d, J = 8.4 Hz, 2H). Anal. Calcd for C₁₈H₁₈N₂O₂ (397.39): C, 63.47; H, 3.80; N, 24.67. Found: C, 63.78; H, 3.85; N, 24.61%.

4-Cyano-2-[1-(4-6-dimethylpyrazol-3,4-b)pyridine]-3-yl]-1,2-dihydro-1-oxo-[1,2,4]triazino[4,5-α]-benzimidazole, 15b

Crystallized from dimethylformamide/ethanol, yield 78%, m.p. 300-02°C. IR (KBr): 3450 (NH), 2210 (CN), 1735 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ 2.38 (s, 3H, CH₃), 2.58 (s, 3H, CH₃), 7.12 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 8.4 Hz, 2H), 13.95 (s, 1H, NH, D₂O exchangeable). Anal. Calcd for C₁₈H₁₃N₃O (356.34): C, 60.67; H, 3.39; N, 31.45. Found: C, 61.02; H, 3.31; N, 31.51%.

4-Cyano-2-(2-methyl-1H-benzimidazol-5-yl)-1,2-dihydro-1-oxo-[1,2,4]triazino[4,5-α]benzimidazole, 15c

Crystallized from ethanol, yield 80%, m.p. 261-63°C. IR (KBr): 3390 (NH), 2225 (CN), 1762 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ 2.70 (s, 3H, CH₃), 7.20 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 8.12 (s, 1H), 13.80 (s, 1H, NH, D₂O exchangeable). Anal. Calcd for C₁₈H₁₄N₂O (341.33): C, 63.34; H, 3.25; N, 28.73. Found: C, 63.49; H, 3.22; N, 28.65%.

Ethyl 2-benzylthiobenzimidazol-1-yl-acetate, 18

To a solution of 17 (2.4 g, 0.01 mole) and dry potassium carbonate (1.51 g, 0.01 mole) in dimethylformamide (20 mL), ethyl chloroacetate (1.83 g, 0.015 mole) was added. The reaction-mixture was heated at 100°C for 18 hr, then filtered off to remove the inorganic materials, diluted with ice-cooled water (100 mL) and then extracted with ethyl acetate (3×50 mL). The organic extract was dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure and the residue was purified by recrystallization from methanol.

Yield 61%, m.p. 48-50°C. IR (KBr): 1744 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ 1.20 (t, J = 7 Hz, 3H), 4.12 (q, J = 7 Hz, 2H), 4.58 (s, 2H, S-CH₂), 5.01 (s, 2H, N-CH₂), 7.20-7.60 (m, 9H, Ar-H). Anal. Calcd for C₁₈H₁₅N₂O₂S (326.46): C, 66.23; H, 5.56; N, 8.58. Found: C, 66.45; H, 5.61; N, 8.51%.

2-Benzylthiobenzimidazol-1-yl-acetic acid hydrazide, 19

To a solution of the ester 18 (3.26 g, 0.01 mole) in absolute ethanol (40 mL), hydrazine hydrate (98%) (1 g, 0.02 mole) was added. The reaction-mixture was heated under reflux for 2 hr and then cooled. The separated solid was filtered, dried and purified by recrystallization from ethanol.

Yield 96%, m.p. 196-98°C. IR (KBr): 3320 (NH₂), 3295 (NH), 1685 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ 4.56 (s, 2H, S-CH₂), 4.72 (s, 2H, N-CH₂), 7.16-7.41 (m, 11H, Ar-H and CONHNH₂, D₂O exchangeable), 9.38 (s, 1H, CONHNH₂, D₂O exchangeable). Anal. Calcd for C₁₈H₁₆N₄O₂ (312.39): C, 61.52; H, 5.16; N, 17.93. Found: C, 61.77; H, 5.14; N, 17.71%.
2-Benzylthio-1-[(5-mercapto-1,3,4-oxadiazol-2-yl)-methyl]-1H-benzimidazole 20 and 2-benzylthio-1-[(5-mercapto-4-phenyl-4H,1,2,4-triazol-3-yl) methyl]-1H-benzimidazole, 22

To a solution of the acid hydrazide 19 (3.12 g, 0.01 mole) and potassium hydroxide (0.56 g, 0.01 mole) in 95% ethanol (50 mL), carbon disulfide (0.83 g, 0.011 mole) or phenylisothiocyanate (1.35 g, 0.01 mole) was added. The reaction-mixture was heated under reflux for 12 hr and then concentrated under reduced pressure. The residue was dissolved in water and neutralized with concentrated hydrochloric acid. The separated solid was filtered and dried.

2-Benzylthio-1-[(5-mercapto-1,3,4-oxadiazol-2-yl)-methyl]-1H-benzimidazole, 20

Crystallized from ethanol/water, yield 64%, m.p. 155-57°C. ¹H NMR (DMSO-d₆): δ 4.58 (s, 2H, S-CH₂), 5.02 (s, 2H, N-CH₂), 7.04-7.62 (m, 9H), 10.47 (s, 1H, SH). Anal. Calcd for C₁₅H₁₄N₂O₂S: C, 64.31; H, 4.46; N, 16.30. Found: C, 65.22; H, 4.79; N, 15.88%.

2-Benzylthio-1-[(5-mercapto-4-phenyl-4H,1,2,4-triazol-3-yl) methyl]-1H-benzimidazole, 22

Crystallized from ethanol/water, yield 70%, m.p. 212-14°C. ¹H NMR (DMSO-d₆): δ 4.55 (s, 2H, S-CH₂), 4.92 (s, 2H, N-CH₂), 7.11-7.75 (m, 14H), 7.42 (d, J = 8.4 Hz, 2H), 10.25 (s, 1H, SH). Anal. Calcd for C₂₅H₂₃N₅S₂: C, 64.98; H, 4.77; N, 15.79. Found: C, 65.22; H, 4.81; N, 15.88%.

1-[(5-Alkylthio-1,3,4-oxadiazol-2-yl)methyl]-2-benzylthio-1H-benzimidazoles, 21a,b and 1-[(5-alkylthio-4-phenyl-4H,1,2,4-triazol-3-yl)methyl]-2-benzylthio-1H-benzimidazoles, 23a,b

To a solution of compound 20 or 22 (0.01 mole) and potassium carbonate (1.38 g, 0.01 mole) in dimethylformamide (20 mL), the appropriate alkyl iodide (0.015 mole) was added. The reaction-mixture was stirred at RT for 12 hr; then poured on crushed ice (100 mL). The formed solid was filtered, dried and purified by recrystallization from ethanol.

1-[(5-Methylthio-1,3,4-oxadiazol-2-yl)methyl]-2-benzylthio-1H-benzimidazole, 21a

Yield 75%, m.p. 152-54°C. MS: m/z (%) 368 (4.9, M⁺), 338 (6.92), 281 (5.47), 239 (12.06), 207 (13.63), 119 (8.67), 91 (100); ¹H NMR (DMSO-d₆): δ 2.66 (s, 3H, CH₃), 5.58 (s, 2H, S-CH₂), 5.87 (s, 2H, N-CH₂), 7.21-7.52 (m, 9H, Ar-H). Anal. Calcd for C₁₀H₁₆N₄O₂S: C, 58.67; H, 4.38; N, 15.21. Found: C, 58.91; H, 4.42; N, 15.16%.

1-[(5-Ethylthio-1,3,4-oxadiazol-2-yl)methyl]-2-benzylthio-1H-benzimidazole, 21b

Yield 82%, m.p. 188-90°C. ¹H NMR (DMSO-d₆): δ 1.26 (t, J = 6 Hz, 3H), 3.94 (q, J = 6 Hz, 2H), 4.57 (s, 2H, S-CH₂), 4.96 (s, 2H, N-CH₂), 6.84-7.15 (m, 5H), 7.24 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H). Anal. Calcd for C₁₉H₁₄N₅O₂S: C, 59.66; H, 4.74; N, 14.65. Found: C, 59.83; H, 4.79; N, 14.71%.

1-[(5-Methylthio-4-phenyl-4H,1,2,4-triazol-3-yl)-methyl]-2-benzylthio-1H-benzimidazole, 23a

Yield 80%, m.p. 202-04°C. ¹H NMR (DMSO-d₆): δ 2.49 (s, 3H, CH₃), 3.35 (s, 2H, S-CH₂), 3.52 (s, 2H, N-CH₂), 7.03-7.47 (m, 14H). Anal. Calcd for C₅₂H₃₃N₅S₂: C, 64.98; H, 4.77; N, 15.79. Found: C, 65.22; H, 4.81; N, 15.88%.

1-[(5-Ethylthio-4-phenyl-4H,1,2,4-triazol-3-yl)-methyl]-2-benzylthio-1H-benzimidazole, 23b

Yield 86%, m.p. 212-14°C. ¹H NMR (DMSO-d₆): δ 1.21 (t, J = 6 Hz, 3H), 3.01 (q, J = 6Hz, 2H), 3.96 (s, 2H, S-CH₂), 4.39 (s, 2H, N-CH₂), 5.37 (s, 2H, N-CH₂), 7.07-7.52 (m, 14H). Anal. Calcd for C₅₂H₃₃N₅S₂: C, 65.62; H, 5.07; N, 15.30. Found: C, 65.79; H, 5.01; N, 15.39%.

Microbiology

*In vitro* antimicrobial activity was carried out using disc diffusion assay. Whatman No. 1 filter paper discs of 5 mm diameter were sterilized by autoclaving for 15 min at 121°C. The sterile discs were impregnated with the test compounds (500 µg/disc). The agar plates were inoculated with standard inoculum (10⁵ cells/mL broth) of the test organism (local strains) namely, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. The impregnated discs were placed on the agar plate medium, and the plates were incubated at 5°C for 1 hr to permit good diffusion and then transferred to an incubator at 37°C for 24 hr. The diameter of inhibition zone was measured using a caliber, to the nearest mm. Gentamycin (30 µg/mL) was used as standard. Among the tested compounds, those exhibiting moderate activity (inhibition zone > 15 mm) were subjected to a quantitative assay in order to determine their minimum inhibitory concentrations (MICs).
using the two-fold serial broth dilution assay. Standardized bacterial inocula were prepared by touching the top of four or five colonies of single type and inoculating them into a tube containing 5 mL of Mueller-Hinton broth (Difco) at pH 7.3. Incubations of these microorganism suspensions were carried out at 35°C until a visible turbidity was obtained. Finally, the culture was diluted so that, after inoculation, each microplate well had an inoculum size of 5×10^5 colony forming units/mL. Antibacterial assays were performed in Mueller-Hinton broth (Difco) at pH 7.3. Gentamycin was used as standard drug. All the tested compounds were dissolved in dimethylsulfoxide.

**Conclusion**

A series of benzimidazole conjugated with 1,3,4-oxadiazole or 1,2,4-triazole or 1,3-thiazole rings and benzimidazole in the fused heterocyclic system such as triazinobenzimidazoles or tetracyclic pyrimidopyrrolobenzimidazoles were synthesized and tested for their antibacterial activity. Some of the investigated derivatives presented interesting antibacterial activity. Some of the investigated derivatives presented interesting antibacterial activity. Some of the investigated derivatives presented interesting antibacterial activity.

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**References**