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SYNTHESIS AND BIOLOGICAL EVALUATION OF BENZOTHIAZOLE DERIVATIVES OF PYRIMIDINES, ACRYLONITRILES, AND COUMARINS†

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Abstract- A number of benzothiazole derivatives of 2-aminopyrimidines (**3a-b**, **5**, **6a-b**, and **7**), benzothiazole-3-arylacrylonitriles (**10a-c**), and benzothiazol-2-yl-coumarins (**18a c**, and **20**) were synthesized by reacting benzothiazole derivatives with dicarbonyl compounds, and aromatic aldehydes. The unexpected 2-(4-methoxyphenyl)benzo[*d*]thiazole (**14**) was obtained as a unique product *via* the reaction of 2-aminothiophenol with ethyl 3-(4-methoxyphenyl)-2-scyanoacrylate. 2-(Benzo[*d*]thiazol-2-yl)-3-(4-hydroxyphenyl)acrylonitrile (**10a**) exhibited activity against *Staphylococcus aureus***.** 2-(Benzo[*d*]thiazol-2-ylamino)pyrimidine-4,6-(1*H*,5*H*)-dione (**3b**) showed antibacterial activity selectivity against *Corynebacterium xerosis*. 2-(Benzo[*d*]thiazol-2-ylamino)-6-methylpyrimidin-4(3*H*)-one (**5**) showed weak anti-fungal activity against *Candida albicans*.

INTRODUCTION

The benzothiazole nucleus is found in various marine or terrestrial natural compounds, which have interesting biological activities.[1-4] The compounds having benzothiozole moiety are reported to exhibit different bioactivities including antitumor,[5,6] antimicrobial,[7] anti-mycobacterial,[8] and antimalarial[9] activities.

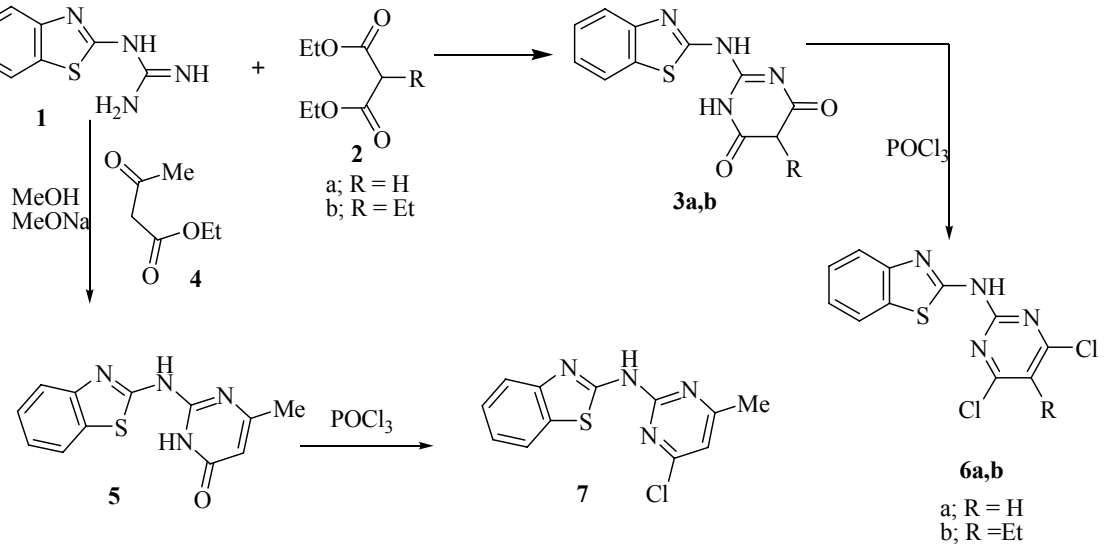
It has also been reported in the literature that 2- and 5-substituted benzothiazoles and its bioisosteres; benzoxazole and benzimidazole derivatives had antimicrobial activities against some Gram-positive, Gram-negative bacteria and the yeast *Candida albicans*, and these compounds provided a wide variety of in vitro antimicrobial effects especially against the enterobacter *Pseudomonas aeruginosa* and the yeast *Candida albicans*.[10-20]

† A part of the work was presented at the Canadian Society of Chemistry Conference, Saskatoon in May 2005.

Pyrimidines,[21] acrylonitriles,[22] and coumarins[23] have also shown potent antimicrobial activities. In our continuing effort to synthesize bioactive compounds,[24] we have synthesized some novel benzothiazole derivatives of pyrimidines, acrylonitriles and coumarins and evaluated their antimicrobial activities.

RESULTS AND DISSCUSSION

Reacting the guanidinobenzothiazole derivative (**1**)[25] with diethyl malonate (**2a**) or diethyl ethylmalonate (**2b**) in bromobenzene yielded the corresponding 2-(benzo[*d*]thiazol-2-ylamino)pyrimidine-4,6-(1*H*,5*H*)-dione (**3a**) and 2-(benzo[*d*]thiazol-2-ylamino)-5-ethylpyrimidine-4,6-(1*H*,5*H*)-dione (**3b**), respectively. Analogously, heating **1** with ethyl acteoacetate (**4**) in methanol in the presence of sodium methoxide resulted in the formation of 2-(benzo[*d*]thiazol-2-ylamino)-6-methylpyrimidin-4(3*H*)-one (**5**) (Scheme 1). Compounds (**3a**, **3b** and **5**) were isolated as stable white solids and spectroscopic methods were used to determine their structures. The ^{1}H NMR spectra of compounds (**3a**, **3b** and **5**) showed characteristic signals for the protons at position 5 as a singlet at δ 5.05, 3.25 and 5.34 respectively. The ^{1}H NMR spectrum of compound (**3b**) showed two signals as a quartet at δ 2.32 and a triplet at δ 1.05 due to the ethyl group. The amide protons resonated at δ 11.62-11.31, while the amine bridge-head protons appeared at δ 7.44-7.32 for these compounds.



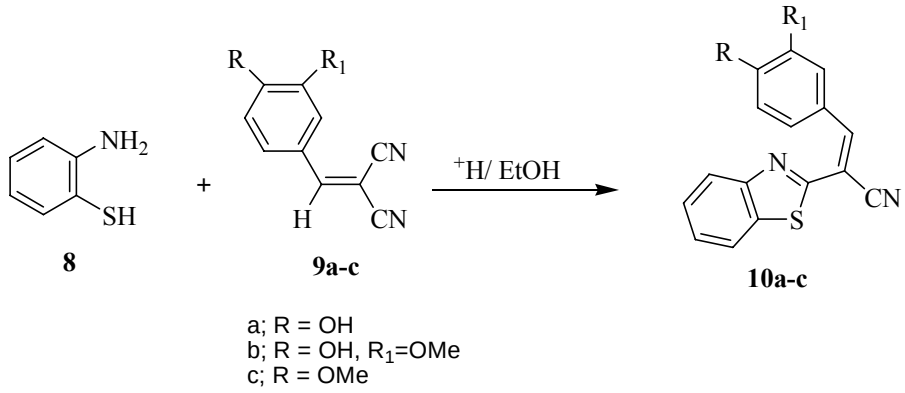
Scheme 1

Reaction of compounds (**3a**, **3b** and **5**) with phosphorous oxychloride resulted in the formation of chloropyrimidine derivatives (**6a,b** and **7**) (Scheme 1). The ^{1}H NMR spectra of **6a**, **6b** and **7** exhibited downfield signals for H-5 and ethyl group in shifted at δ 7.46, 7.45, 2.60 and 1.30, respectively. These observations suggested the aromatization of the pyrimidine ring and the presence of the neighboring chlorine atoms as well.

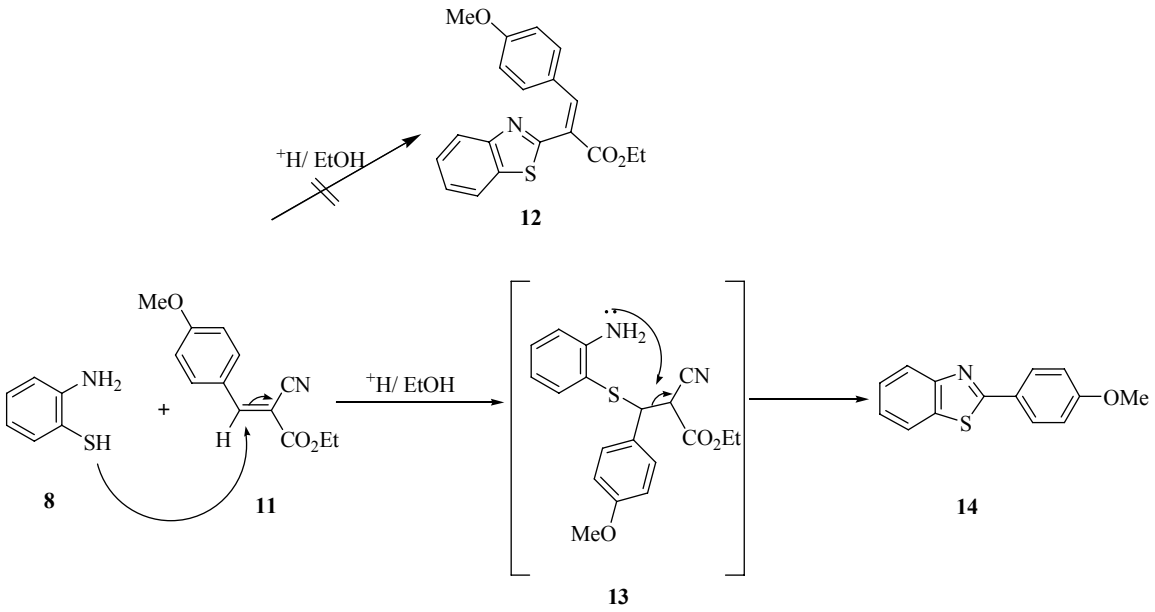
As previously reported,[26] reaction of o-aminothiophenol (**8**) with α-cyanocinnamonitrile (**9a-c**)[27] under acidic conditions was carried out to produce 2-(benzo[*d*]thiazol-2-yl)-3-arylacrylonitriles (**10a,b** and

10c[26]) (Scheme 2). Under these reaction condition, ethyl 3-(4-methoxyphenyl)-2-cyanoacrylate (**11**)[28] afforded 2-(4-methoxyphenyl)benzo[*d*]-thiazole (**14**) as a unique product. This product was unexpectedly formed as we were expecting to get ethyl 2-(benzo[*d*]thiazole-2-yl)-3-(4-methoxyphenyl)acrylate (**12**) as a product in this reaction. The formation of compound (**14**) might be due to the nucleophilic addition of the thiol group to the acrylate β-carbon to give an acyclic intermediate (**13**), which underwent cyclization and elimination of ethyl cyanoacetate[29] (Scheme 3). The role of acetic acid in the formation of compound (**14**) was not clearly understood.

Structures of **10a,b** were confirmed with the aid of spectroscopic data. The ^{1}H NMR spectra showed the characteristic signals for olefinic protons at δ 8.26-8.18 as singlets. The formation of compound (**14**) was evident from the ^{1}H NMR spectrum, which did not show the resonances for olefinic and carboxylic ester protons. The MS of **14** also confirmed its structure, which exhibited molecular ion peak at *m/z* 241 as a base peak.

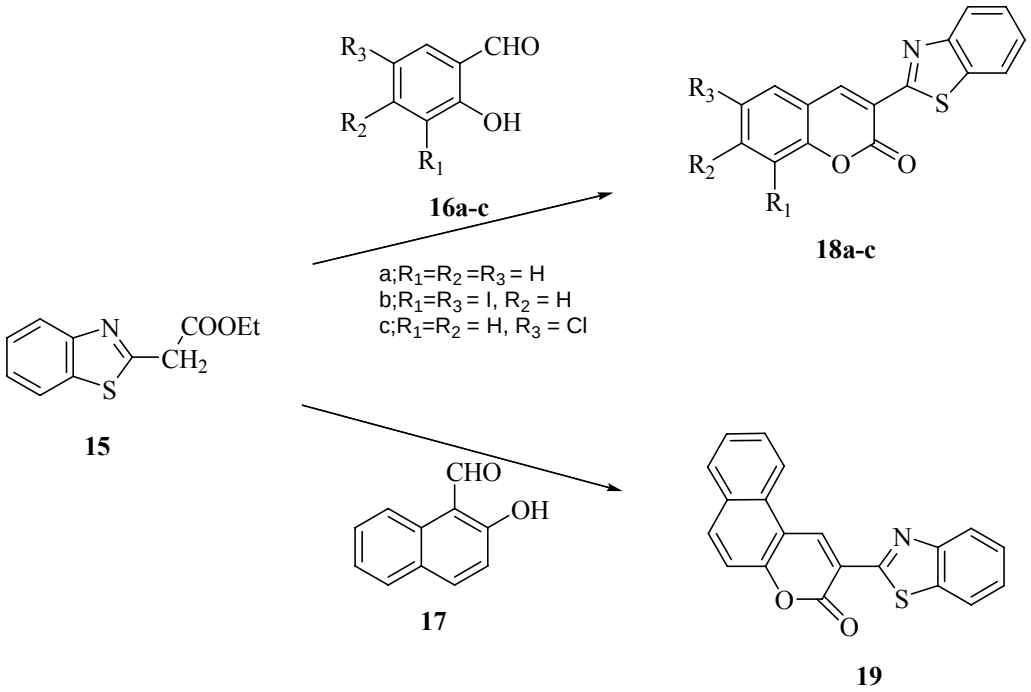


Scheme 2



Scheme 3

Synthesis of 3-(benzo[*d*]thiazol-2-yl)coumarins *via* Knoevenagel condensation of 2-(benzo[*d*]thiazol-2-yl)acetonitrile with 2-hydroxybenzaldehydes and subsequent acid hydrolysis of iminocoumarins has been reported.[30,31] In this study a new procedure was developed one-step reaction for the synthesis of these compounds. This was accomplished by the reaction of ethyl 2-(benzo[*d*]thiazole-2-yl)acetate (**15**)[32] and the appropriate aromatic aldehydes (**16a-c**, or **17**) under the basic condition at room temperature for 1 h to give the corresponding 3-(benzo[*d*]thiazol-2-yl)coumarin derivatives (**18a,**[30] **b, c,**[31] and **19**[33]) (Scheme 4). The ^{1}H NMR data indicated the formation of the coumarin ring hence, the low-field resonances at δ 9.05-9.79 was due to the C-4 proton of the coumarin system along with signals for the protons of the benzthiazole fragment.



Scheme 4

Antimicrobial activity of all synthesized compounds was assayed against various pathogenic bacteria and *Candida albicans* by using disk agar diffusion method. 2-(Benzo[*d*]thiazol-2-ylamino)pyrimidine-4,6-(1*H*,5*H*)-dione (**3b**) and 2-(benzo[*d*]thiazol-2-yl)-3-(4-hydroxyphenyl)acrylonitrile (**10a)** exhibited moderate antibacterial activity against *Staphylococcus aureus* and *Corynebacterium xerosis,* respectively. The minimal inhibitory concentrations of compounds (**3b** and **10**) were found to be 35 and 40 μg/mL, respectively. 2-(Benzo[*d*]thiazol-2-ylamino)-6-methylpyrimidin-4(3*H*)-one (**5**) showed weak anti-fungal activity against *Candida albicans*.

EXPERIMENTAL

Melting points were measured in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker DPX 300 spectrometer, in DMSO-d_6, with chemical shifts being

calculated from the solvent signals. NH, NH_2 and OH groups were confirmed doing D_2O exchange ^1H NMR spectroscopy.13C NMR spectra were also recorded on the same instrument at 75 MHz. MS spectra were reported on Hewlett Packard 5989 B Mass Spectrometer. IR spectra were recorded on Bomem MB-Series FT-IR spectrophotometer by using KBr pellet.

2-(Benzo[*d*]thiazol-2-ylamino)-5-substituted pyrimidine-4,6-(1*H*,5*H*)-diones (3a-b)

A solution of **1** (1.92 g, 10 mmol) and the appropriate substituted diethyl malonate (10 mmol) in bromobenzene (20 mL) was refluxed for 4 h. After cooling it to rt, the separated solid product was filtered, washed with ethanol and dried.

3a was white solid from DMF-ethanol; mp >260 ^oC; yield 80 %; ^1H NMR δ 11.62 (br, NH amide, 1H), 7.82 (d, benzothiazole, J = 8.8 Hz, 1H), 7.40 (d, benzothiazole, J = 7.2 Hz, 1H), 7.32 (s, NH, 1H), 7.22 (t, benzothiazole, J = 8.8 Hz, 1H), 7.12 (t, benzothiazole, J = 7.2 Hz, 1H), 5.05 (s, H-5, 2H); IR cm^{-1} (KBr) 3436 (amide NH) 3026 (bridge-head NH), 1650, 1608 (C=O); Anal. Calcd for $C_{11}H_8N_4O_2S$: C, 50.76; H, 3.10; N, 21.53; S, 12.32. Found: C, 51.16; H, 3.11; N, 21.28.

3b was a white solid from ethanol; mp 258-260 ^oC; yield 83 %; ^1H NMR δ 11.31 (br, NH amide, 1H), 7.78 (d, benzothiazole, J = 8.8 Hz, 1H), 7.66 (d, benzothiazole, J = 7.2 Hz, 1H), 7.44 (br s, NH, 1H), 7.36 (t, benzothiazole, J = 8.8 Hz, 1H), 7.10 (t, benzothiazole, J = 7.2 Hz, 1H), 3.25 (s, H-5, 1H), 2.32 (q, CH_2, J = 3.2 Hz, 2H), 1.05 (t, CH_3, J = 3.2 Hz, 3H); IR cm^{-1} (KBr) 3333 (amide NH) 3063 (bridge-head NH), 1710, 1663 (C=O); Anal. Calcd for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.19; N, 19.43; S, 11.12. Found: C, 54.47; H, 4.30; N, 19.23.

2-(Benzo[*d*]thiazol-2-ylamino)-6-methylpyrimidin-4(3*H*)-one (5)

To a mixture of **1** (1.92 g, 10 mmol) and methanol (5 mL); a solution of ethyl acetoacetate (**4**) (1.30 g, 10 mmol) in sodium methoxide and methanol (10 mL) was added. The reaction mixture was heated while stirring for 1 h until complete precipitation. The white solid product was collected by filtration, dried and recrystallized from DMF-ethanol mp >260 ^oC; yield 85 %; ^1H NMR δ 10.90 (br, NH amide, 1H), 7.70 (d, benzothiazole, J = 8.8 Hz, 1H), 7.40 (d, benzothiazole, J = 7.2 Hz, 1H), 7.23 (t, benzothiazole, J = 8.8 Hz, 1H), 7.11 (t, benzothiazole, J = 7.2 Hz, 1H), 5.34 (s, H-5, 1H); 2.45 (s, CH_3, 3H); IR cm^{-1} (KBr) 3386 (amide NH), 3263 (bridge-head NH), 1686 (C=O); Anal. Calcd for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69; S, 12.41. Found: C, 55.43; H, 3.95; N, 21.72.

General procedure for the synthesis of 6a, b and 7

Compounds (**3a**, **b** and **5**) (10 mmol) were heated under reflux for 4 h with excess of phosphorous oxychloride (20 mL). The reaction mixture was then decanted portion wise on ice. The solid formed was filtered, washed with water and ether and then dried under reduced pressure.

***N*-(4,6-Dichloropyrimidin-2-yl)benzo[*d*]thiazol-2-amine (6a)**

Yellow solid from DMF-ethanol mp >260 ^oC; yield 80 %; ^1H NMR δ 7.99 (d, benzothiazole, J = 8.8 Hz, 1H), 7.70 (d, benzothiazole, J = 7.2 Hz, 1H), 7.45 (s, H-5, 1H), 7.43 (t, benzothiazole, J = 8.8 Hz, 1H),

7.25 (t, benzothiazole, J = 7.2 Hz, 1H); IR cm^{-1} (KBr) 3051 (bridge-head NH); MS m/z (%): 297 (M^+, 66), 296 (M^+-1, 100), 261 (88), 225 (17); Anal. Calcd for $C_{11}H_6N_4Cl_2S$: C, 44.46; H, 2.04; Cl, 23.86; N, 18.85; S, 10.79. Found: C, 44.43; H, 2.19; N, 18.55.

***N*-(4,6-Dichloro-5-ethylpyrimidin-2-yl)benzo[*d*]thiazol-2-amine (6b)**

White solid from DMF-ethanol mp >260 °C; yield 83 %; ^{1}H NMR (300 MHz) δ 8.0 (d, benzothiazole, J = 8.8 Hz, 1H), 7.71 (d, benzothiazole, J = 7.2 Hz, 1H), 7.43 (t, benzothiazole, J = 8.8 Hz, 1H), 7.25 (t, benzothiazole, J = 7.2 Hz, 1H), 2.60 (q, CH_2, J = 3.5 Hz, 2H), 1.30 (t, CH_3, J = 3.5 Hz, 3H); IR cm^{-1} (KBr) 3057 (bridge-head NH); Anal. Calcd for $C_{13}H_{10}N_4Cl_2S$: C, 48.01; H, 3.10; Cl, 21.80; N, 17.23; S, 9.86. Found C, 48.39; H, 3.00; N, 17.48.

***N*-(4-Chloro-6-methylpyrimidin-2-yl)benzo[*d*]thiazol-2-amine (7)**

Off white solid from DMF-ethanol mp >260 °C; yield 85 %; ^{1}H NMR δ 8.00 (d, benzothiazole, J = 8.8 Hz, 1H), 7.71 (d, benzothiazole, J = 7.2 Hz, 1H), 7.46 (s, H-5, 1H), 7.40 (t, benzothiazole, J = 8.8 Hz, 1H), 7.25 (t, benzothiazole, J = 7.2 Hz, 1H), 2.50 (s, CH_3, 3H); IR cm^{-1} (KBr) 3160 (bridge-head NH); Anal. Calcd for $C_{12}H_9N_4ClS$: C, 52.08; H, 3.28; Cl, 12.81; N, 20.24; S, 11.59. Found: C, 51.76; H, 3.40; N, 19.99.

2-(Benzo[*d*]thiazol-2-yl)-3-arylacrylonitrile (10a-c)

To a mixture of α-cyanocinnamonitrile derivatives (**9a-c**) (10 mmol) and 2-aminobenzenethiol (**8**) (1.25 g, 10 mmol) in ethanol (10 mL), acetic acid (0.63 g, 10 mmol) was added. The mixture was refluxed for 3 h, and then allowed to stand overnight. The resultant yellow precipitate is isolated by suction and recrystallized from a suitable solvent. Yield 84-87 %.

10a yellow crystals from ethanol-water; mp 218-220 °C; ^{1}H NMR δ 10.67 (br, OH, 1H), 8.18 (s, =CH, 1H), 8.07 (d, benzothiazole, J = 8.8 Hz, 1H), 7.98 (d, benzothiazole, J = 7.2 Hz, 1H), 7.90 (d, aromatic, J = 8.1 Hz, 1H), 7.51 (t, benzothiazole, J = 8.8 Hz, 1H), 7.43 (t, benzothiazole, J = 7.2 Hz, 1H), 6.94 (d, aromatic, J = 8.1 Hz, 2H); IR cm^{-1} (KBr) 3347 (OH), 2214 (CN); Anal. Calcd for $C_{16}H_{10}N_2OS$: C, 69.04; H, 3.62; N, 10.06; S, 11.52. Found: C, 68.65; H, 3.51; N, 10.36.

10b yellow crystals from chloroform ; mp 175-177 °C; ^{1}H NMR δ 10.38 (br, OH, 1H), 8.26 (s, =CH, 1H), 8.14 (d, benzothiazole, J = 8.8 Hz, 1H), 8.03 (d, benzothiazole, J = 7.2 Hz, 1H), 7.83 (s, aromatic, 1H), 7.65 (d, aromatic, J = 8.1 Hz, 1H), 7.56 (t, benzothiazole, J = 8.8 Hz, 1H), 7.49 (t, benzothiazole, J = 7.2 Hz, 1H), 6.94 (d, aromatic, J = 8.1 Hz, 1H), 3.85 (s, OCH_3, 3H); IR cm^{-1} (KBr) 3067 (OH), 2209 (CN); Anal. Calcd for $C_{17}H_{12}N_2O_2S$: C, 66.22; H, 3.92; N, 9.08; S, 10.40. Found: C, 65.83; H, 3.82; N, 9.29.

2-(4-Methoxyphenyl)benzo[*d*]thiazole (14)

A mixture of ethyl 3-(4-methoxyphenyl)-2-cyanoacrylate (**11**) (2.31 g, 10 mmol), 2-aminothiophenol (**8**) (1.25 g, 10 mmol) and few drops of acetic acid was refluxed in ethanol (10 mL) for 3 h. The solution was cooled to rt and allowed to stand overnight. The solid precipitate was collected by filtration and recrystallized from ethanol; mp 115-117 °C; yield 95 % (2.289 g); ^{1}H NMR δ 8.13 (d, benzothiazole, J =

8.8 Hz, 1H), 8.07 (d, aromatic, J = 8.1 Hz, 2H), 8.02 (d, benzothiazole, J = 7.2 Hz, 1H), 7.56 (t, benzothiazole, J = 8.8 Hz, 1H), 7.43 (t, benzothiazole, J = 7.2 Hz, 1H), 7.11 (d, aromatic, J = 8.1 Hz, 2H), 3.87 (s, OCH_3, 3H); IR cm^{-1} (KBr) 1605 (C=N); MS m/z (%): 241 (M^+, 100), 226 (42), 198 (34), 154 (12), 121 (6), 108 (5), 69 (13), 45 (9); Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: C, 70.02; H, 4.68; N, 6.05.

3-Benzo[*d*]thiazol-2-yl)coumarin derivatives (18a-c and 19)

A mixture of ethyl 2-(benzo[*d*]thiazol-2-yl)acetate (**15)** (1.11 g, 5 mmol), the appropriate aromatic aldehyde (5 mmol) and few drops of piperidine in ethanol (10 mL) was stirred at rt where an immediate precipitation occurs. The stirring was continued for 30 min. until complete precipitation. The solid formed was filtered, dried and recrystallized from the appropriate solvent.

3-(Benzo[*d*]thiazol-2-yl)coumarin (18a)

White crystals from ethanol mp 215 ^oC; yield 98 %; ^1H NMR δ 9.05 (s, H-4, 1H), 8.13 (d, benzothiazole, J= 8.8 Hz, 1H), 8.01 (m, benzothiazole and aromatic, 2H), 7.59 (t, benzothiazole, J = 8.8 Hz, 1H), 7.49 (m, benzothiazole and aromatic, 4H); IR cm^{-1} (KBr) 1717 (C=O).

3-(Benzo[*d*]thiazol-2-yl)-6,8-diiodocoumarin (18b)

White crystals from DMF-ethanol mp >260 ^oC; yield 99 %; ^1H NMR δ 9.05 (s, H-4, 1H), 8.42 (s, aromatic, 1H), 8.36 (s, aromatic ,1H), 8.13 (d, benzothiazole, J= 8.8 Hz, 1H), 8.04 (d, benzothiazole, J= 7.2 Hz, 1H), 7.53 (t, benzothiazole, J = 8.8 Hz, 1H), 7.46 (t, benzothiazole, J = 7.2 Hz, 1H); IR cm^{-1} (KBr) 1726 (C=O); Anal. Calcd for $C_{16}H_7NO_2I_2S$: C, 36.18; H, 1.33; I, 47.79; N, 2.64; S, 6.04. Found: C, 35.79.; H, 1.24; N, 2.87.

3-(Benzo[*d*]thiazol-2-yl)-6-chlorocoumarin (18c)

White crystals from DMF-ethanol mp 239-241 ^oC; yield 97 %; ^1H NMR δ 9.01 (s, H-4, 1H), 8.31 (s, aromatic, 1H), 8.15 (d, benzothiazole, J= 8.8 Hz, 1H), 8.10 (d, aromatic, J = 8.1 Hz, 2H), 8.04 (d, benzothiazole, J= 7.2 Hz, 1H), 7.53 (t, benzothiazole, J = 8.8 Hz, 1H), 7.45 (t, benzothiazole, J = 7.2 Hz, 1H), IR cm^{-1} (KBr) 1728 (C=O).

3-(Benzo[*d*]thiazol-2-yl)- 3*H*-benzo[*f*]coumarin (19)

White crystals from DMF mp >260 ^oC; yield 98 %; ^1H NMR δ 9.79 (s, H-4, 1H), 8.66 (d, aromatic, J = 8.4 Hz, 1H), 8.31 (d, benzothiazole, J= 8.8 Hz, 1H), 8.17(m, benzothiazole and aromatic, 6H), 7.59 (t, benzothiazole, J = 8.8 Hz, 1H), 7.48 (t, benzothiazole, J = 7.2 Hz, 1H), IR cm^{-1} (KBr) 1711 (C=O).

ANTIMICROBIAL EVALUATION

All of the synthesized compounds (**3a**, **b**, **5**, **6a**, **b**, **7**, **10a-c**, **14**, **18a-c** and **19**) were tested for antibacterial activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus agalactiae*, *Staphylococcus typhimu*, *Bacillus cereus*, and *Corynebacterium xerosis* at a dose of 25 μg/mL by using the agar disk diffusion assay.[34]

INHIBITION ZONE MEASURMENT

The method of choice for the antimicrobial assay was the Kirby-Bauer Disc method. The compounds to be tested were dissolved in DMSO and 32-250 μL of each of these solutions was applied on serial paper disks with a diameter of 7 mm. These disks were allowed to dry and then placed on Mueller Hinton II agar inoculated with the test organism. These plates were then incubated at 37 ^{o}C for 24 h and the resulting inhibition zones were measured. A control without the test compound was included for each organism.

MINIMAL INHIBITORY CONCENTRATION (MIC)

The *MIC* values were measured by using the standard broth dilution antimicrobial susceptibility test.[35] The test organism were grown in Mueller Hinton II agar for 24h at 37 ^{o}C. The compounds to be tested were dissolved in DMSO and two-fold serial dilutions were prepared. The tubes were then inoculated with 100 μL of the 24h test organism culture and were incubated at 37 ^{o}C for 24 h.

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