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Synthesis, Characterization and Evaluation of Pyridobenzimidazole Derivatives as Potential Antimicrobial Agents

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ABSTRACT

Novel pyridobenzimidazole derivatives were synthesized and characterized using spectral techniques like IR, NMR, mass spectroscopy and elemental analysis. For the synthesis pyridobenzimidazole derivatives, 2'-amino-3',5'-dicarbonitrile, 4'-methyl pyrido-[1,7-a]benzimidazole 1(a-b) treated with Carbon Disulphide (CS2) in aq. K2CO3 to afford dithiocarbamate intermediates which were further desulfurylized with 2,4,6-trichloro-1,3,5-triazine (TCT) to provide compounds 2(a-b) which on further condensation with benzoyl hydrazine hydrazide gave compounds 3(a-b) which was treated with both H2SO4 and NaOH to give compounds 4(a-b) and 6(a-b), respectively. 4(a-b) which refluxed with hydrazine hydrate formed 5(a-b) and 6(a-b) were reacted with methyl iodide to give compounds 7 (a-b). All synthesized derivatives screened against a series of reference strains of bacteria and fungi showed significant to moderate activity against tested bacterial strains whereas some compounds exhibited potent fungicidal activity.

Keywords: Pyrido Benzimidazole, Isothiocyanate, Thiadiazole, Aminothiazole, Triazole, Antimicrobial activity, Fungicidal activity

INTRODUCTION

Pyridobenzimidazoles are most biological activity [1,2] The main method for preparation of pyridobenzimidazoles starting from cyanomethylbenzimidazole can occur via Knoevenagel reaction followed by cyclocondensation, Michael addition and reaction with enaminones and cyclocondensation with β-dicarbonyl compounds. Cyclization of 2-(1-cyano-2-(benzylidin)-1*H*-benzimidazole with malononitrile or ethyl cyanoacetate (R=Aromatic subs.; R1=CN, CO2Et) in ethanol in the presence of piperidine produced pyridobenzimidazole [3,4]. Thiosemicarbazides (-N=C=S group) have been known to show pronounced biological activities [5]. 2-Aminothidiazole [6] is great interest as antitumor and 1,3,4-thiadiazole derivatives shows most biological activities [7,8]. The 1, 2, 4–triazole exhibits broad spectrum of biological activities [9-15].

MATERIALS AND METHODS

The reactions were monitored by Thin Layer Chromatography (TLC) using 0.25 mm E-Merck silica gel plates, which were visualized in iodine chamber. Melting points were taken in open capillaries and are uncorrected. ^{1}H spectra in DMSO-d6 on 300 MHz using Tetramethylsilane (TMS) as an internal standard.

Synthesis of compounds

2'-Isothiocyanato-3',5'-dicarbonitrile, 4'-methyl pyrido-[1,7-a]benzimidazole 2(a-b)

To a mixture of 2'-amino-3',5'-dicarbonitrile, 4'-methyl pyrido-[1,7-*a*]benzimidazole 1(a-b) (0. 40 mol) and solution of K2CO3 (0.080 mol) in 50 ml of water and 3.64 g of CS2 (0.048 mol) was added dropwise within 20-30 min at room temperature. After complete addition the mixture was stirred for 24 h. Reaction is monitored by TLC. Then, the reaction mixture was cooled 0-5°C and a solution of 3.7 g of 2,4,6-trichloro-1,3,5-triazine (TCT) (0.010 mol) in 50 ml of Dichloromethane (CH2Cl2) was added dropwise. After the addition was complete, the mixture was stirred for another 2 h to accomplish the reaction. The reaction mixture was then basified to pH > 10 with 5 N NaOH obtained a clear solution. The organic layer was separated and the aqueous phase was extracted with CH2Cl2 (3 × 50 ml). The combined organic layers were dried over anhydrous Na2SO4, filtered and the solvent was removed in vacuum get 2'-isothiocyanato-3',5'-dicarbonitrile, 4'-methyl pyrido-[1,7-a]benzimidazole 2(a-b).

2'-(Carbamothioyl-amino)benzohydrazide-3',5'-dicyano,4'-methylpyrido[1,7-a]benzimidazole 3(a-b)

2'-Isothiocyanato-3', 5'-dicarbonitrile,4'-methyl pyrido-[1,7-a]benzimidazole 2(a-b) (0.004 mol) dissolved in absolute ethanol at room temperature was added into the solution of benzyl hydrazine (0.004 mol) was dissolved in absolute ethanol (80 ml) with continuous stirring. The reaction mixture was refluxed 5-6 h and completion of reaction monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature. The resultant brown solid was filtered and recrystallized from methanol to get pure product 2'-(carbamothioyl-amino)benzohydrazide-3',5'-dicyano,4'-methylpyrido-[1,7-a]benzimidazole 3(a-b).

2'-(2'-Phenyl-1',3',4,'thiodiazol-amino)-3',5'-dicyano, 4'-methyl pyrido [1,7-a]benzimidazole 4(a-b)

2'-(Carbamothioylamino)benzohydrazide-3',5'-dicyano,4-methylpyrido-[1,7-a]benzimidazole 3(a-b) (0.025 mol) was added lot wise to Conc. H2SO4 (25 ml) at 0-5°C with continuous stirring. The reaction mixture was stirred further for 3 h at room temperature. The reaction mass was poured into crushed ice (100 g) and stirred for 30 min. The separated product was filtered and recrystallized from a mixture of ethanol and water (1:1) to get compound 2'-(2'-phenyl 1',3',4,'thiodiazol-amino)-3',5'-dicyano, 4'-methyl pyrido [1,7-a]benzimidazole 4(a-b).

2'-[(1'-Amino-2'-phenyl-1', 2',4'-triazol)-amino]-3',5'-dicarbonitrile 4'-methyl pyrido[1,7-a]benzimidazole 5(a-b)

2'-(2'-Phenyl 1',3',4,'thiodiazol-amino)-3',5'-dicyano, 4'-methyl pyrido-[1,7-a]benzimidazole 4(a-b) (0.01 mol) and hydrazine hydrate (0.015 mol) was refluxed in ethanol for about 4 h. The solvent and the excess hydrazine hydrate were removed under reduced pressure, the residue washed with ether, then recrystallized from methanol to give the product 2'-[(1'-amino-2'-phenyl-1',2',4'-triazol)-amino]-3',5'-dicarbonitrile-4'-methyl pyrido[1,7-*a*]benzimidazole 5(a-b).

2'-(5'-Phenyl-3'-thiol-1',2',4'-triazol-4-yl) 3',5'-dicarbonitrile 4'-methyl pyrido[1,7-a]benzimidazole 6(a-b)

2'-(Carbamothioyl-amino)benzohydrazide-3',5'-dicyano,4'-methylpyrido[1,7-a]benzimidazole 3(a-b) (0.03 mol) was added lot wise to sodium hydroxide solution (2 N, 25 ml). The reaction mixture was refluxed for 2-3 h and completion of the reaction was monitored by TLC. The reaction mass was cooled to room temperature and filtered. The filtrate was acidified with 2N hydrochloric acid to pH=2. The precipitated yellow colored solid was filtered, washed thoroughly with water (20 ml) and dried. The crude compound was recrystallized from ethanol'water (4:1) to get pure compound 2'-(5'-phenyl-3'-thiol-1',2',4'-triazol-4-yl) 3',5'-dicarbonitrile 4'-methyl pyrido[1,7-*a*]benzimidazole-6(a-b).

2'-(5'-Phenyl-3'-mercapto methyl-1',2',4'-triazol-4-yl) 3',5'-dicarbonitrile 4'-methyl pyrido-[1,7-a]benzimidazole-7(a-b)

2'-(5'-Phenyl-3'-thiol-1',2',4'-triazol-4-yl)3',5'-dicarbonitrile4'-methylpyrido[1,7-*a*]benzimidazole 6(a-b) (0.03 mol) in Dimethylformamide (DMF) then added (0.032 mol) triethyl amine stirred for 30 min at room temperature then added methyl iodide (0.03 mol) and the completion of the reaction was monitored by TLC. The reaction was accomplished with in 3 h at room temperature. After accomplished reaction added water buff colored solid obtained was filter off. The compound was recrystallized from ethanol'water (4:1) to get pure compound 2'-(5'-phenyl-3'-mercapto methyl-1',2',4'-triazol-4-yl) 3',5'-dicarbonitrile 4'-methyl pyrido-[1,7-*a*]benzimidazole-7(a-b).

Characterization of synthesized compounds

2'-Isothiocyanato-3', 5'-dicarbonitrile, 4'-methyl pyrido-[1,7-a]benzimidazole (2a)

Molecular formula: C15H7N5S, melting point: 190-194°C, Yield: 72%, elemental analysis % (Calculated) Found: C(62.27)62.58, H(2.44)2.39, N(24.21)24.31, S(11.08)11.17. IR (KBr): 3001(-CH), 2245(CN), 2185 and 2140 (-N=C=S), 1560, 1310, 1188 cm-1. 1H-NMR (DMSO-d6'TMS) δ=2.47 (s, 3H, CH3), δ=7.45.-7.83 (m, 4H, Ar-H). M+1: 289.31.

6-Chloro-2'-isothiocyanato-3', 5'-dicarbonitrile, 4'-methyl pyrido-[1,7-a]benzimidazole (2b)

Molecular formula: C15H6N5ClS, melting point: 181-185°C, Yield: 65%, elemental analysis %(Calculated) Found: C(55.65)55.88, H(1.87)1.90, N(21.63)21.31, Cl(10.95)11.17, S(9.90)9.79. IR (KBr): 2985(-CH), 2255 (CN), 2175 and 2150 (-N=C=S), 1566, 1319, 1178, 1065 cm-1. 1H-NMR (DMSO-d6'TMS) at δ=2.41 (s, 3H, CH3), δ 7.65.-7.93 (m, 3H, Ar-H). M+2: 323.76.

2'-(Carbamothioyl-amino)benzohydrazide-3',5'-dicyano,4'-methylpyrido[1,7-a]benzimidazole (3a)

Molecular formula: C22H15N7OS, melting point: 210-215°C, Yield: 56%, elemental analysis %Calculated) found: C(62.10)59.58, H(3.55)3.39, N(23.04)23.31, S(7.54)7.45.

IR (KBr): 3535 (NH), 2985(-CH), 2249(CN), 1682(-CONH), 1560, 1292 (-C=S), 1310 cm-1. 1H-NMR (DMSO-d6'TMS) at δ=2.24 (s, 3H, CH3), δ=7.45.-7.96 (m, 9H, Ar-H), δ=9.05 (s, 1H, NH, D2O exchangeable), δ=9.30 (s, 1H, NH, D2O exchangeable) and δ 9.51(s, 1H, NH, D2O exchangeable). M+1: 425.47.

2'-(Carbamothioylamino)benzohydrazide-6-chloro-3',5'-dicyano,4-methylpyrido[1,7-a]benzimidazole (3b)

Molecular formula: C22H14ClN7OS, melting point: 194-199°C, Yield: 67%, elemental analysis% (Calculated) found: C(57.45)57.58, H(3.07) 3.18, Cl(7.71) 7.65, N(21.32)21.39, S(6.97) 7.15. IR (KBr): 3435 (NH), 2981(-CH), 2237(CN), 1692(-CONH), 1565, 1298(-C=S), 1310 cm-1. 1H-NMR (DMSO-d6'TMS) at δ=2.39 (s, 3H, CH3), δ=7.35.-7.90 (m, 8H, Ar-H), δ=8.95 (s, 1H, NH, D2O exchangable), δ=9.47 (s, 1H, NH, D2O exchangable) and δ=9.59 (s, 1H, NH, D2O exchangable). M+2: 461.76.

2'-(2'-Phenyl-1',3',4,'thiodiazol-amino)-3',5'-dicyano, 4'-methyl pyrido [1,7-a]benzimidazole (4a)

Molecular formula: C22H13N7S, melting point: 216-221°C, yield: 58%, elemental analysis % (Calculated) found: C(64.85)65.05, H(3.22) 3.39, N(24.09)24.31, S(7.87) 7.65. IR (KBr): 3228 (> NH), 3040 (-CH), 2247 (CN), 1560, 1196, 1069 cm-1. 1H-NMR (DMSO-d6'TMS) at δ=2.41 (s, 3H, CH3), δ=7.54-8.26 (m, 9H, Ar-H) 9.90(s, 1H, NH, D2O exchangable). M+1: 407.45.

6-Chloro-2'-(2'-phenyl 1',3',4,'thiodiazol-amino)-3',5'-dicyano, 4'-methyl pyrido [1,7-a]benzimidazole (4b)

Molecular formula: C22H12N7ClS, melting point: 232-237°C, Yield: 68%, elemental analysis% (Calculated) found: C(59.80)59.75, H(2.74) 2.83, N(22.19)22.31, Cl(8.05)8.15, S(7.27) 7.15. IR (KBr): 3220 (> NH), 2993(-CH), 2257 (CN), 1550, 1206, 1061 cm-1. 1H-NMR (DMSO-d6'TMS) at δ=2.31 (s, 3H, CH3), δ=24.-8.01 (m, 8H, Ar-H) δ 9.14 (s, 1H,-NH, D2O exchangable). M+2: 443.53.

2'-[(1'-Amino-2'-phenyl-1', 2',4'-triazol)-amino]-3',5'-dicarbonitrile 4'-methyl pyrido[1,7-a]benzimidazole (5a)

Molecular formula: C22H15N9, melting point: 201-104°C, yield: 65%, elemental analysis% (Calculated) found: C(65.18)65.28, H(3.73) 3.69, N(31.09)31.31. IR (KBr): 3440(> NH2), 3318 (> NH), 2996(-CH), 2245 (CN), 1559, 1203, 1060 cm-1. 1H-NMR (DMSO-*d*6): δ=2.26 (s, 3H, CH3) δ=7.04.-7.36 (m, 9H, Ar-H), δ=2.82 (s, 2H, NH2, D2O exchangable), δ=9.45(s, 1H, NH, D2O exchangable). M+1: 405.45.

6-Chloro-2'-[(1'-amino-2'-phenyl-1', 2',4'-triazol)-amino]-3',5'-dicarbonitrile 4'-methyl pyrido[1,7-a]benzimidazole 5b

Molecular formula: C22H14ClN9, melting point: 245-249°C, yield: 56%, elemental analysis% (Calculated) found: C(60.08)60.28, H(3.21)3.35, N(28.66)28.46, Cl(8.06)7.95. IR(KBr): 3490(> NH2), 3289(> NH), 2956(-CH), 2219(CN), 1569, 1189, 1065 cm-1. 1H NMR (DMSO-*d*6): δ=2.38 (s, 3H, CH3), δ=7.28.-7.96 (m, 8H, Ar-H), δ=2.58(s, 2H,-NH2 D2O exchangable), δ=4.45(s, 1H, NH, D2O exchangable). M+2: 441.87.

2'-(5'-phenyl-3'-thiol-1',2',4'-triazol-4-yl) 3',5'-dicarbonitrile 4'-methyl pyrido[1,7-a]benzimidazole 6a

Molecular formula: C22H13N7S, melting point: 188-192°C, yield: 55%, elemental analysis% (Calculated) found: C(64.85)65.05, H(3.22)3.39, N(24.09)24.31, S(7.87)7.65. IR (KBr): 3040 (-CH), 2551 (SH), 2257 (CN), 1550, 1185, 1079 cm-1. 1H-NMR (DMSO-d6'TMS) at δ=1.92(s, 1H,-SH), δ=2.56 (s, 3H, CH3), δ=7.36-8.06 (m, 9H, Ar-H). M+1: 407.45.

6-Cholro-2'-(5'-phenyl-3'-thiol-1',2',4'-triazol-4-yl)-3',5'-dicarbonitrile-4'-methyl pyrido[1,7-a]benzimidazole (6b)

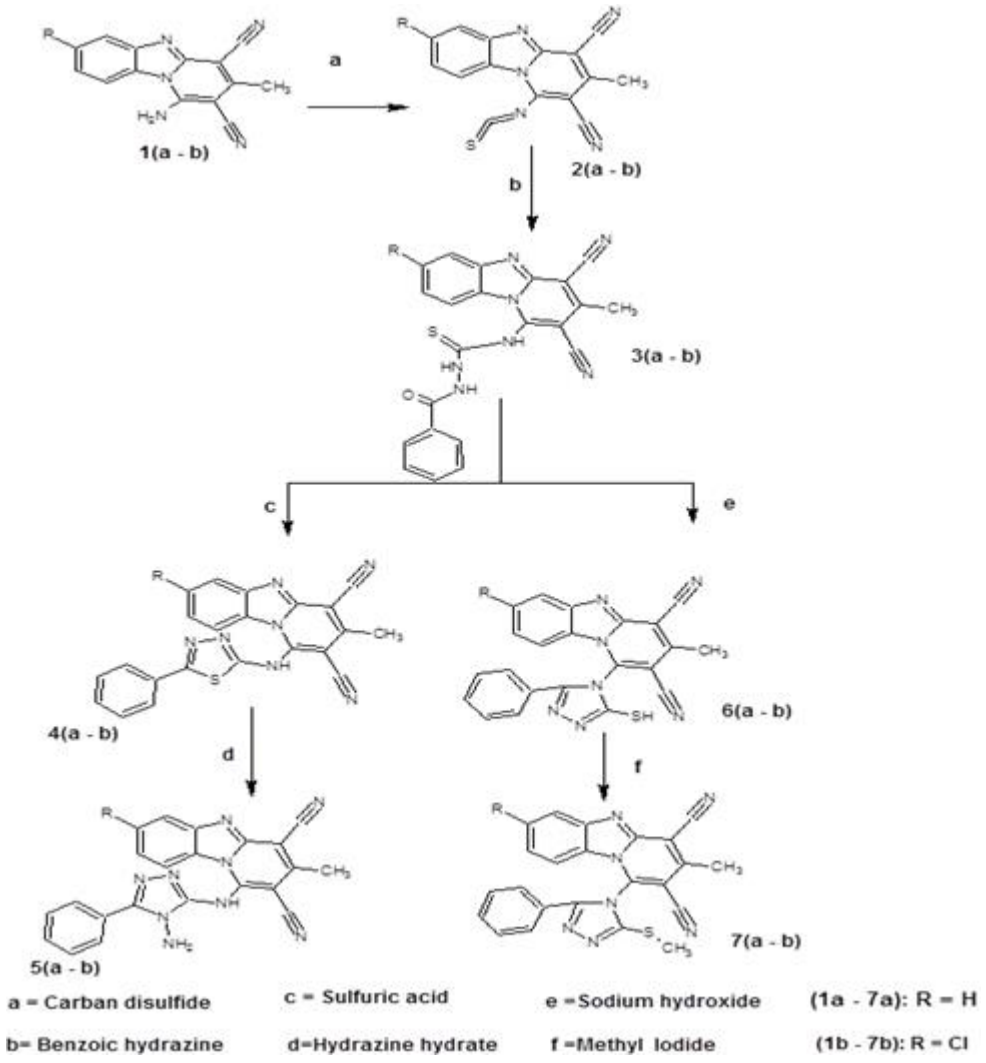
Molecular formula: C22H12N7ClS, melting point: 232-237°C, yield: 68%, elemental analysis% (Calculated) found: C(59.80)59.75, H(2.74) 2.83, N(22.19)22.31, Cl(8.05)8.15, S(7.27) 7.15. IR (KBr):3050 (-CH), 2735 (-SH), 2253 (CN), 1315 and 1132 cm-1.1H NMR (DMSO-d6'TMS) at δ 1.82(s, 1H,-SH), δ 2.46 (s, 3H, CH3), δ 7.49-8.56 (m, 8H, Ar-H). M+2: 441.45.

2'-(5'-Phenyl-3'-mercapto methyl-1',2',4'-triazol-4-yl) 3',5'-dicarbonitrile 4'-methyl pyrido[1,7-a]benzimidazole (7a)

Molecular formula: C23H15N7S, melting point: 237-241°C, yield: 63%, elemental analysis% (Calculated) found: C(65.54)65.58, H(3.59) 3.49, N(23.26)23.31, S(7.61) 7.65. IR (KBr): 3140, 3001(-CH), 2245 (CN), 1560, 1188, 1065 cm-1. 1H-NMR (DMSO-*d*6): at δ=2.63 (s, 3H, CH3), δ=2.92(s, 3H, SCH3), δ=7.53-8.26 (m, 9H, Ar-H). M+1:421.28.

6-Chloro-2'-(5'-phenyl-3'-mercapto methyl-1',2',4'-triazol-4-yl) 3',5'-dicarbonitrile 4'-methyl pyrido[1,7-a]benzimidazole (7b)

Molecular formula: C23H14ClN7S, melting point: 220-225°C, yield: 78%, elemental analysis% (Calculated) found: C(60.59)60.58, H(3.10) 3.39, N(21.51)21.31, Cl (7.78)7.65, S(7.03) 7.15. IR (KBr): 3021(-CH), 2249 (CN), 1560, 1182, 1062 cm-1. 1H-NMR (DMSO-*d*6): δ=2.66 (s, 3H, CH3), δ=2.79(s, 3H, SCH3), δ=7.24-8.30 (m, 8H, Ar-H). M+2: 457.56.



RESULTS AND DISCUSSION

In order to prepare pyridobenzimidazole derivatives previously synthesized 2'-amino-3',5'-dicarbonitrile,4'-methyl pyrido[1,7-*a*]benzimidazole1(a-b) was used as a building block for synthesis of various derivatives. 1(a-b) on treatment with CS2 in aqueous K2CO3 to afford dithiocarbamate intermediates which were further desulfurylized with TCT to provide compound 2'-isothiocyanato-3',5'-dicarbonitrile,4'-methylpyrido-[1,7-a]benzimidazole 2(a-b). Non-presence of strong NH2 band and presence of 2140 cm-1 (-N=C=S) in IR spectra. 1H-NMR spectrum of compound showed absent singlet of 2H confirmed that conversion of NH2 to NCS is achieved. 2(a-b) which on further condensation with benzoyl hydrazine hydrazide gave compound 2'-(carbamothioyl-amino)benzohydrazide-3',5'-dicyano-4'-methylpyrido[1,7-a]benzimidazole 3(a-b). IR spectra 3435 cm-1 (NH), 1692 cm-1 (-CONH), 1298 cm-1 (-C=S) and 1H-NMR shows three singlet for (s, 1H, NH), protons were D2O exchangeable. 3(a-b) which was treated with H2SO4 gave compound 2'-(2'-phenyl 1',3',4,'thiodiazol-amino)-3',5'-dicyano, 4'-methyl pyrido [1,7-a]benzimidazole 4(a-b). Absence of band of 1692 cm-1 (-CONH), 1298 cm-1 (-C=S) in IR spectra and 1H-NMR shows singlet for (s, 1H, NH, D2O exchangeable). 4(a-b) which refluxed with hydrazine hydrate formed 2'-[(1'-amino-2'-phenyl-1', 2',4'-triazol)-amino]-3',5'-dicarbonitrile-4'-methyl pyrido[1,7-*a*]benzimidazole 5(a-b). IR and 1H NMR spectrum of compound showed that a band at 3440 cm-1 (> NH2) and 3318 cm-1 (> NH) and singlet at δ=2.82(s, 2H, NH2, D2O exchangeable) and δ=9.45 (s, 1H, NH, D2O exchangeable). 3(a-b) which was treated with sodium hydroxide formed 2'-(5'-phenyl-3'-thiol-1', 2',4'-triazol-4-yl) 3',5'-dicarbonitrile 4'-methyl pyrido[1,7-*a*]benzimidazole 6(a-b). IR spectrum of compound showed that a band at 2551 cm-1 (SH) and 1H-NMR showed singlet at δ=1.92(s, 1H,-SH). 6(a-b) was reacted with methyl iodide to give compound 7(a-b). IR spectrum of compound showed that absence of a band at 2551 cm-1 (SH) and1H-NMR spectrum showed that absence of singlet at δ=2.92(s, 3H, SCH3).

Table 1: Antibacterial activity

Compounds	Zone of inhibition (mm)							
	Staphylococcus aureus		*Salmonella typhi*		*Escherichia coli*		*Aspergillus niger*	
	50 µg'ml-1	100 µg'ml-1	50 µg'ml-1	100 µg'ml-1	50 µg'ml-1	100 µg'ml-1	50 µg'ml-1	100 µg'ml-1
2a	12	16	10	16	12	18	12	17
2b	13	18	12	16	12	20	13	19
3a	11	17	12	18	13	15	15	20
3b	12	18	11	15	11	16	14	19
4a	14	18	15	20	10	15	15	21
4b	17	19	14	18	12	17	13	18
5a	15	20	15	21	14	19	12	17
5b	18	21	16	20	16	20	11	15
6a	12	18	15	19	15	20	10	16
6b	16	19	14	17	14	18	12	18
7a	14	18	12	18	13	17	11	16
7b	13	16	11	19	16	15	13	19

Antibacterial activity was evaluated by the paper disc method. The Muller-Hinton agar and 5 mm diameter paper discs of Whatman no. 1 were used. The compounds were dissolved in DMSO. The filter paper discs were soaked in different solutions of the compounds, dried and then placed in the petriplates previously seeded with the test organisms *Salmonella typhi*, *Escherichia coli* and *Staphylococcus aureus*. The plates were incubated for 24-30 h at 28 ± 2°C and the inhibition zone around each disc was measured.

Antifungal screening

The antifungal activity of the compounds was evaluated against *Aspergillus niger* by the agar plate technique. The Sabouraud dextrose agar and 5 mm diameter paper discs of Whatman no.1 filter paper were used. The compounds were dissolved in DMSO. The filter paper discs were soaked in different solutions of the compounds, dried and then placed in the petriplates previously seeded with the test organisms *A. niger*. The plates were incubated for 48 h at 25 ± 2°C and the inhibition zone around each disc was measured.

Antimicrobial activity

The Inhibition zone against the bacterium *S. aureus, E. coli* and fungus *A. niger*, due to the different substituted pyridobenzimidazole derivatives is shown in Table 1. Highest antimicrobial potential was observed with compounds 4b, 5a, 5b and 6b against *S. aureus.* Compounds 4a, 5a, 5b, 6a were found to be potent against *S. typhi* whereas compounds 2b, 5b, 6a exhibited inhibitory activity against *E. coli*. On the other hand compounds 3a, 4a, 3b, 7b showed highest antifungal potential against *A. niger*.

CONLCUSIONS

Spectral techniques used in the scheme confirm the formation and synthetic route of novel pyridobenzimidazole derivatives. From the result of antibacterial and antifungal activity it is seen that synthesized derivatives exhibited significant to moderate activity. This confers all the newly synthesized thiosemicarbazide, triazole, thiadiazoles, aminothidiazole derivatives of pyridobenzimidazole are biologically active towards the tested bacterial and fungal strains.

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