

Short Communication

Synthesis of Isoxazoles and Cyanopyridines
Bearing Benzo(b)thiophene Nucleus as
Potential Antitubercular and
Antimicrobial Agents

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Abstract

Isoxazole (2a-1) and cyanopyridine (3a-1) derivatives have been prepared by condensing chalcones (1a-1) with hydroxylamine hydrochloride and malononitrile respectively. While compounds 1a-1 have been synthesized by the reaction of p-(3'-chloro-2'-benzo(b)thiophenylamino)-acetophenone with different aldehydes. All the compounds were screened for their antitubercular and antimicrobial activities. The structures of newly synthesized compounds were established on the basis of elemental analyses, IR, ¹H NMR and Mass spectral data.

Keywords: Isoxazole; Cyanopyridine; Chalcone; Antitubercular activity; Antimicrobial activity

Introduction

Isoxazole derivatives constitute a unique class of nitrogen and oxygen containing five member heterocycles while cyanopyridine constitutes a six member heterocycles. During the past years considerable evidence has accumulated to demonstrate the importance of isoxazole and cyanopyridine derivatives. They are associated with wide spectrum of biological activities such as antiviral [1], anthelmintics [2], anti-inflammatory [3], anticonvulsant [4] and insecticidal [5] activity *etc.* Hence, it appeared of interest to prepare some new isoxazole and cyanopyridine derivatives.

The starting compounds 1-[p-(3'-chloro-2'-benzo(b)thiophenylamino)-phenyl]-3-aryl-2-propen-1-ones (**1a-1**) were synthesized [6] by the reaction of p-(3'-chloro-2'-benzo(b)thiophenylamino)-acetophenone

with different aldehydes. Compounds **1a-1** on cyclization [7] with hydroxylamine hydrochloride in presence of sodium acetate furnished 1-[p-(3'-chloro-2'-benzo(b)thiophenylamino)-phenyl]-5-aryl-isoxazoles (**2a-1**) while cyclo condensation [8] of compounds 1a-1 with malononitrile in presence of ammonium acetate furnished 2-amino-3-cyano-4-p-methoxyphenyl-6-[benzo(b)thiophenyl amino)-phenyl]-pyridine.

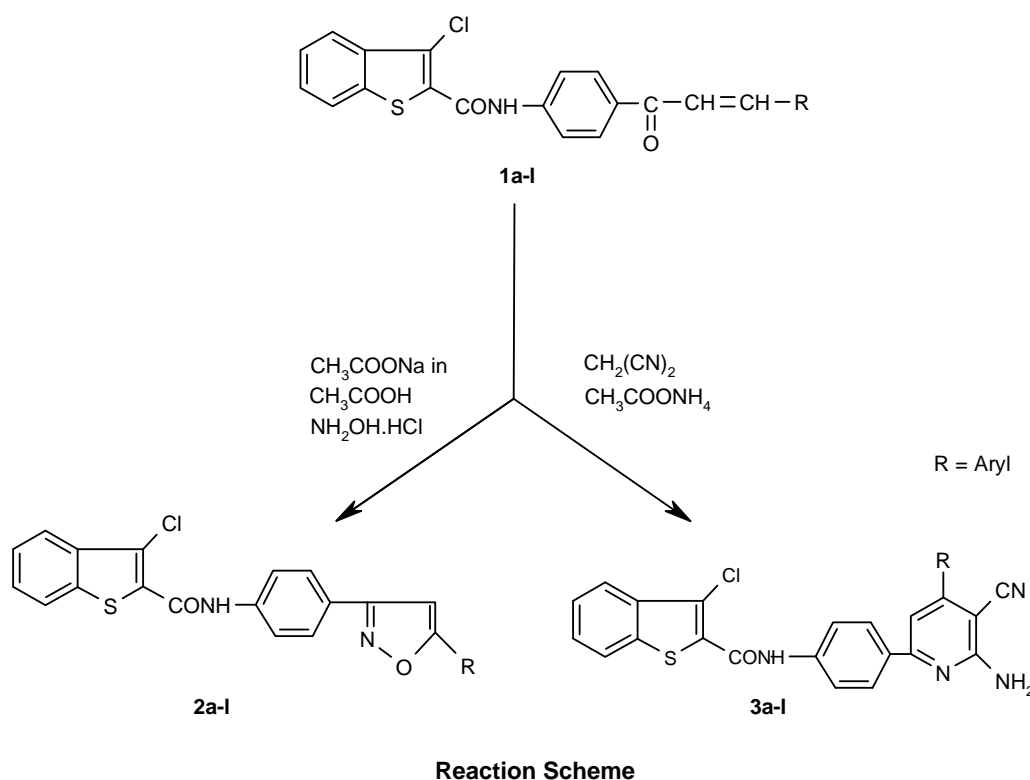
Elemental and spectral analyses supported the constitution of all products. The product was screened for their antitubercular and antimicrobial activities.

Results and Discussion

Antitubercular Activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis and Antimicrobial

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Acquisition Co-ordinating Facility (TAACF) USA. Antitubercular activity was evaluated at 6.25 $\mu\text{g/ml}$ concentration against *Mycobacterium tuberculosis H₃₇Rv* in BACTEC 12B medium using the ALAMAR radiometric system. The antimycobacterial activity data were compared with standard drug Rifampin at 0.25 $\mu\text{g/ml}$ concentration which showed 98% inhibition.

From the result it has been found that 1g, 1i, 2d, 2g, 2i, 3c, 3d, and 3i compounds showed activity against *Mycobacterium tuberculosis H₃₇Rv* (Table 1).

Antimicrobial Activity

Antimicrobial activity was assayed by using the cup-plate agar diffusion method against bacteria *Escherichia coli*, *Proteus vulgaris*, *Bacillus megaterium*, *Staphylococcus aureus* and fungus *Aspergillus niger* at 40 $\mu\text{g/ml}$ concentration using amoxicillin, ampicillin, ciprofloxacin, erythromycin and griseofulvin as standards.

From the result it is found that the compounds 1d, 1f, 2e, 3c, 3e were highly active against *E. coli*, compounds 1a, 1d, 2d, 2j, 3k were highly active against *P. vulgaris*, and compounds 3d, 3j were highly active against *B. mega* in addition all the compounds showed activity against *S. aureus* and *A. niger* (Table 1).

Experimental

Thin layer chromatography was used for reaction follow up and purity of the synthesized compounds. The melting points were determined in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on a Shimadzu FTIR-8400 instrument, ¹H NMR spectra on a Bruker AC-300 MHz FT NMR spectrometer using TMS as an internal standard and mass spectra on a Jeol D-300 spectrometer. All the compounds gave satisfactory elemental analyses.

Synthesis of 1[p-(3'-chloro-2'-benzo(b)thiophenoylamino)-phenyl]-3-(p-methoxyphenyl)-2-propen-1-ones (1f)

An ethanolic solution of p-(3'-chloro-2'-benzo(b)thiophenoylamino)-acetophenone (3.30 g, 0.01 mol) and p-methoxy benzaldehydes (1.35 g, 0.01 mol) in presence of catalytic amount of 40% KOH was stirred for 24 h at room temperature. It was then poured over crushed ice and the product formed was crystallized from ethanol. **1f** (78%), m.p. 158°C, C₂₅H₁₈ClNO₃S Found: C, 67.11, H, 3.57, N, 3.12; requires: C, 67.09, H, 3.54, N, 3.13%. ν_{max} 3055(CH=CH, aromatic), 2958 (CH₃ asym.), 1659 (C=O), 730 (C-S-C), 545 (C-Cl)

Table 1. Antitubercular and antimicrobial screening results of compounds **1a-l**, **2a-l**, and **3a-l**

Compound	% Inhibition antitubercular activity	Zones of inhibition in mm				
		Antibacterial activity			Antifungal activity	
		<i>E. coli</i>	<i>P. vulgaris</i>	<i>B. mega</i>	<i>S. aureus</i>	<i>A. niger</i>
1a	00	16	21	15	23	18
1b	19	14	15	19	17	17
1c	00	17	19	18	28	14
1d	00	22	20	16	23	21
1e	23	20	10	06	21	18
1f	47	21	18	12	27	15
1g	74	11	16	13	19	09
1h	56	13	14	15	19	22
1i	97	14	15	18	18	14
1j	51	08	12	13	28	16
1k	39	14	19	14	19	14
1l	23	17	16	18	24	23
2a	08	15	17	16	28	14
2b	20	14	14	25	26	26
2c	23	17	13	13	27	21
2d	69	19	23	14	22	18
2e	05	21	20	15	24	08
2f	10	11	19	16	26	12
2g	70	16	18	19	24	18
2h	55	08	24	18	21	16
2i	69	21	20	23	20	24
2j	43	07	22	15	19	14
2k	11	12	13	19	23	18
2l	43	06	17	18	25	20
3a	-	16	12	21	20	23
3b	-	13	19	18	23	15
3c	87	21	16	17	23	17
3d	75	10	18	22	27	21
3e	-	21	14	13	17	15
3f	54	19	12	17	17	18
3g	-	16	13	21	20	14
3h	-	18	15	17	20	21
3i	61	03	19	13	31	20
3j	-	09	18	22	24	16
3k	-	15	21	16	25	13
3l	-	03	14	19	30	18
Ampicillin	-	16	15	15	18	00
Amoxycillin	-	17	25	16	22	00
Ciprofloxacin	-	20	28	15	28	00
Erythromycin	-	25	26	20	18	00
Griseofulvin	-	00	00	00	00	22

Table 2. Physical and analytical data of compounds **1a-l**, **2a-l**, and **3a-l**

Compound	R	M.F.	m.p. (°C)	Yield%	% of Nitrogen	
					Calculated	Found
1a	C ₆ H ₅ -	C ₂₄ H ₁₆ ClNO ₂ S	224	65	3.35	3.32
1b	3-Br-C ₆ H ₄ -	C ₂₄ H ₁₅ BrClNO ₂ S	152	63	2.82	2.79
1c	2-Cl-C ₆ H ₄ -	C ₂₄ H ₁₅ Cl ₂ NO ₂ S	149	70	3.09	3.07
1d	3-Cl-C ₆ H ₄ -	C ₂₄ H ₁₅ Cl ₂ NO ₂ S	158	68	3.09	3.06
1e	4-N(CH ₃) ₂ -C ₆ H ₄ -	C ₂₆ H ₂₁ ClN ₂ O ₂ S	182	67	6.08	6.05
1f	4-OCH ₃ -C ₆ H ₄ -	C ₂₅ H ₁₈ ClNO ₃ S	158	68	3.12	3.13
1g	3,4-(OCH ₃) ₂ -C ₆ H ₃ -	C ₂₆ H ₂₀ ClNO ₄ S	169	72	2.93	2.94
1h	3,4,5-(OCH ₃) ₃ -C ₆ H ₂ -	C ₂₇ H ₂₂ ClNO ₅ S	174	58	2.75	2.73
1i	4-SCH ₃ -C ₆ H ₄ -	C ₂₅ H ₁₈ ClNO ₂ S ₂	128	61	3.02	3.01
1j	2-NO ₂ -C ₆ H ₄ -	C ₂₄ H ₁₅ ClN ₂ O ₄ S	176	64	6.05	6.02
1k	4-NO ₂ -C ₆ H ₄ -	C ₂₄ H ₁₅ ClN ₂ O ₄ S	171	72	6.05	6.03
1l	4-OC ₆ H ₅ -C ₆ H ₄ -	C ₃₀ H ₂₀ ClNO ₃ S	178	71	2.74	2.71
2a	C ₆ H ₅ -	C ₂₄ H ₁₅ ClN ₂ O ₂ S	228	65	6.51	6.48
2b	3-Br-C ₆ H ₄ -	C ₂₄ H ₁₄ BrClN ₂ O ₂ S	160	63	5.51	5.48
2c	2-Cl-C ₆ H ₄ -	C ₂₄ H ₁₄ Cl ₂ N ₂ O ₂ S	108	70	6.03	6.01
2d	3-Cl-C ₆ H ₄ -	C ₂₄ H ₁₄ Cl ₂ N ₂ O ₂ S	126	68	6.03	6.02
2e	4-N(CH ₃) ₂ -C ₆ H ₄ -	C ₂₆ H ₂₀ ClN ₃ O ₂ S	193	67	8.88	8.85
2f	4-OCH ₃ -C ₆ H ₄ -	C ₂₅ H ₁₇ ClN ₂ O ₃ S	180	68	6.09	6.05
2g	3,4-(OCH ₃) ₂ -C ₆ H ₃ -	C ₂₆ H ₁₉ ClN ₂ O ₄ S	171	72	5.71	5.68
2h	3,4,5-(OCH ₃) ₃ -C ₆ H ₂ -	C ₂₇ H ₂₁ ClN ₂ O ₅ S	179	58	5.38	5.38
2i	4-SCH ₃ -C ₆ H ₄ -	C ₂₅ H ₁₇ ClN ₂ O ₂ S ₂	122	61	5.88	5.85
2j	2-NO ₂ -C ₆ H ₄ -	C ₂₄ H ₁₄ ClN ₃ O ₄ S	156d	64	8.84	8.81
2k	4-NO ₂ -C ₆ H ₄ -	C ₂₄ H ₁₄ ClN ₃ O ₄ S	220	72	8.84	8.82
2l	4-OC ₆ H ₅ -C ₆ H ₄ -	C ₃₀ H ₁₉ ClN ₂ O ₃ S	116d	71	5.36	5.38
3a	C ₆ H ₅ -	C ₂₇ H ₁₇ ClN ₄ OS	168	68	11.65	11.61
3b	3-Br-C ₆ H ₄ -	C ₂₇ H ₁₆ BrClN ₄ OS	126	73	11.46	11.45
3c	2-Cl-C ₆ H ₄ -	C ₂₇ H ₁₆ Cl ₂ N ₄ OS	108	61	10.85	10.81
3d	3-Cl-C ₆ H ₄ -	C ₂₇ H ₁₆ Cl ₂ N ₄ OS	150	65	10.85	10.79
3e	4-N(CH ₃) ₂ -C ₆ H ₄ -	C ₂₉ H ₂₂ ClN ₅ OS	180	70	13.37	13.31
3f	4-OCH ₃ -C ₆ H ₄ -	C ₂₈ H ₁₉ ClN ₄ O ₂ S	160	72	10.96	10.92
3g	3,4-(OCH ₃) ₂ -C ₆ H ₃ -	C ₂₉ H ₂₁ ClN ₄ O ₃ S	92	63	10.36	10.28
3h	3,4,5-(OCH ₃) ₃ -C ₆ H ₂ -	C ₃₀ H ₂₃ ClN ₄ O ₄ S	96	61	9.81	9.75
3i	4-SCH ₃ -C ₆ H ₄ -	C ₂₈ H ₁₉ ClN ₄ OS ₂	124	68	10.63	10.61
3j	2-NO ₂ -C ₆ H ₄ -	C ₂₇ H ₁₆ ClN ₅ O ₃ S	144	71	13.32	13.29
3k	4-NO ₂ -C ₆ H ₄ -	C ₂₇ H ₁₆ ClN ₅ O ₃ S	160	69	13.32	13.26
3l	4-OC ₆ H ₅ -C ₆ H ₄ -	C ₃₃ H ₂₁ ClN ₄ O ₂ S	91	64	9.77	9.77

cm^{-1} . δ 3.83(3H, s, OCH_3), 7.04(1H, dd, $\text{CH}=\text{CH}$), 8.19(1H, dd, $\text{CH}=\text{CH}$), 7.02-8.04 (12H, m, ArH); MS=m/z (448, M^+)

Similarly, other compounds were prepared. The physical data are recorded in Table 2.

Synthesis of 1-[p-(3'-chloro-2'-benzo(b)thiophenoyl amino)-phenyl]-5-aryl-isoxazoles (2f)

Compound **1f** (4.47 g, 0.01 mol) in ethanol and anhydrous sodium acetate (0.81 g, 0.01 mol) dissolved in minimum amount of acetic acid was added to a solution of hydroxylamine hydrochloride. Then the reaction mixture was refluxed on oil-bath for 7-8 h. The product was isolated and crystallized from ethanol. **2f** (69%), m.p. 180°C , Anal. Calcd for $\text{C}_{25}\text{H}_{17}\text{ClN}_2\text{O}_3\text{S}$ Found: C, 65.21, H, 3.69, N, 6.09 %. requires: C, 65.19, H, 3.64, N, 6.05 %. ν_{max} 1461 (C=N, isoxazole ring), 837 (N-O, isoxazole ring), 755 (C-Cl) cm^{-1} . δ 3.84 (3H, s, OCH_3), 7.58-8.11 (12H, m, ArH); MS=m/z (460, M^+);

Similarly, other compounds were prepared. The physical data are recorded in Table 2.

Synthesis of 2-amino-3-cyano-4-p-methoxyphenyl-6-[benzo(b)thiophenoyl amino)-phenyl]-pyridine (3f)

A mixture of 1-[p-(3-Chlorobenzo(b)thiophenoyl amino)-phenyl]-3-p-methoxy phenyl-2-propen-1-one (4.48 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) in presence of ammonium acetate (6.61 g, 0.08 mol) dissolved in ethanol (20 ml), was heated under reflux for 12 h. The products was isolated and recrystallized from ethanol. **3f** (72%), m.p. 160 Anal. Calcd. for $\text{C}_{28}\text{H}_{19}\text{ClN}_4\text{O}_2\text{S}$; Requires:C, 67.42; H, 3.53; N, 11.55%;

Found: C, 67.37; H, 3.51; N, 11.51%. ν_{max} 2204 (CN), 1578 (C=N, pyridine ring), 754 (C-Cl) cm^{-1} . δ 3.84(3H, s, OCH_3), 7.56-8.06 (13H, m, ArH); MS=m/z (510, M^+);

Similarly, other compounds were prepared. The physical data are recorded in Table 2.

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