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RESEARCH ARTICLE

Synthesis and Antimicrobial Activity of 2-(substituted)-4-[2-(10-p-chlorobenzyl) phenothiazinyl]-6-(substituted aryl)pyrimidines

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ABSTRACT

A series of novel 2-(substituted)-4-[2-(10-pchlorobenzyl)phenothiazinyl]-6-(substituted aryl)pyrimidines have been synthesized by cyclocondensation of chalcones, obtained by the interaction of 2-acetyl phenothiazine with substituted aromatic aldehydes, with urea, thiourea, and guanidine. Structures of title compounds were elucidated by their IR, ^{1}H NMR spectral data, molecular weight determination, and microanalyses. Antimicrobial activities against gram-positive and gram-negative bacteria were evaluated by the Filter Paper Disc Method.

Keywords: Antimicrobial activity, Phenothiazine, Pyrimidines.

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1. Introduction

Pyrimidines have been identified as better ones among various types of heterocycles owing to their manifold high efficacy of actions. The importance of pyrimidine derivatives is well manifested by the presence of pyrimidine nucleus in vitamin B2 and folic acid, DNA, and RNA [1]. Synthesis of substituted pyrimidine has been reported in several reviews [2]. Moreover, pyrimidine derivatives also exhibit several biological properties viz. antitumor [3], [4], antiviral [5], antifungal [6], anticancer [7], antibacterial [8], anti-inflammator [9], analgesic [10], antagonist [11], [12], antifolate [13], anrimicrobial [14], anti-HIV [15], antiplatelet [16], antifilarial [17], activities etc. In the textile industry, they are promising dyes [18]; in agriculture, derivatives of pyrimidines play vital roles as pesticides and insecticides. In coordination chemistry, pyrimidine compounds have been reported as very effective ligands [19], owing to several donor sites, with transition metals to form complexes.

The high versatility of pyrimidine derivatives in general and those pyrimidinyl heterocyclics containing nitrogen and sulphur hetero atoms, exhibiting a wide range of biological properties, in particular, encouraged us to synthesize new pyrimidine derivatives by the interaction of chalcones [20] with guanidine, urea, and thiourea via condensation route. Structures of new molecules have been assigned on the basis of their microanalyses, molecular weight determination, IR, and ^{1}H NMR. Some of the new compounds have been assayed for their antibacterial properties against some gram-positive and gram-negative bacteria.

2. Experiment

Melting points of all pyrimidine products were determined by the melting point apparatus with open glass capillaries. Microanalysis of compounds was done at the chemistry department, I.I.T, Roorkee, on Vario-el III, Element-R. Infrared spectra of pyrimidines were recorded in KBr medium in 500 cm^{-1}–4000 cm^{-1} range on Thermo Nicolet Nexus FT-IR spectrometer at chemistry department, I.I.T, Roorkee whereas ^{1}H NMR spectra of samples were recorded in $CDCl_3$medium at Jamia Hamdard University, Delhi.

TABLE I: Physical Properties and Analyses Data of Compounds

Compound	Color	Melting point (C)	Yield (%)	Molecular weight		Elemental analyses %					
						C		H		N		S	
				Found	Calcd.	Found	Calcd.	Found	Calcd	Found	Calcd	Found	Calcd
1a	Light brown	168	56	512.8	511.8	68.2	68	4.09	3.71	8.57	8.21	6.56	6.25
1b	Yellow brown	155	64	525.3	527.5	65.67	65.97	3.94	3.6	8	7.96	12.29	12.1
1c	Yellow brown	155	58	512.8	510.5	68.36	68.16	4.34	3.91	10.59	10.96	6.76	6.26
3a	Brown	163	68	571.4	572.5	60.34	60.79	3.48	3.31	7.62	7.33	5.44	5.59
3b	Yellow orange	155	64	588.2	588.5	59.35	59.13	3.56	3.22	7.6	7.13	10.71	10.9
3c	Yellow brown	156	65	571.4	571.5	60.86	60.89	3.65	3.49	10.19	9.79	5.88	5.59
4a	Brown	167	74	540.5	538.5	64.77	64.62	3.74	3.52	10.8	10.39	6	5.94
4b	Dark brown	160	56	555.5	554.5	62.97	62.75	2.99	3.42	10.22	10.02	11.67	11.5
4c	Brown	164	51	533.3	536.5	64.41	64.74	3.87	3.72	13.28	13	6.03	5.95
5c	Dark brown	170	54	540.5	537.5	64.42	64.74	3.86	3.72	13.09	13	6.15	5.95
6a	Light Brown	165	65	533.3	536.5	69.56	69.33	4.38	4.65	10.89	10.43	5.96	5.63
6b	Brown	163	68	547.9	552.5	67.32	67.33	4.36	4.52	10.17	10.13	11.36	11.6
6c	Brown	163	45	533.5	535.5	69.18	69.46	4.42	4.85	12.93	13.07	6.22	5.97
8b	Brown	173	63	571.4	569.5	65.5	65.32	4.26	4.21	7	7.37	11.04	11.2
8c	Yellow brown	150	56	547.9	552..5	66.98	67.33	4.58	4.52	10.6	10.13	5.37	5.79
9c	Brown	158	67	579.7	582.5	64.3	65.92	6.2	6.35	9.4	9.61	5.61	5.49

2.1. *General Procedure for Synthesis of Substituted Phenothiazinyl Pyrimidines*

Chalcones synthesized earlier from this laboratory [20] have been used as starting materials for the synthesis of substituted phenothiazinyl pyrimidines.

An equimolar (0.01 mol) mixture of chalcone and each of guanidine, thiourea, and urea in dry ethanol (50 ml) was refluxed for 10 h–12 h. During refluxing, aqueous NaOH solution (40%, 5 ml) was added dropwise slowly in 2 h–3 h Scheme 1. The reaction mixture was allowed to stand till acquired at room temperature. The solid product separated was filtered, washed with cold ethanol and water successively, and dried in air.

2.2. *Antimicrobial Activity of Phenothiozinyl Pyrimidines*

Antimicrobial studies on newly synthesized phenothiazinyl pyrimidines were performed using filter paper disc Diffusion method against Enterococus foecium, Enterorcus faecalis, Escherichia coli, and Bacillus subtitles bacteria, and Candida albicans and Axpergillous niger fungi. Whatman filter paper-1 discs (6.5 mm) sterilized by dry heat at 140°C were saturated with test solution placed on surface of sterilized nutrient agar medium for bactericidal study and sabouraud dextrose agar and potato dextrose agar medium for candida albicans and Aspergillus niger respectively for fungicidal study in petri dishes which were preinoculated with test organisms. All these petri dishes were incubated for 48 h, and inhibition zones were measured. Control solvent (tween-80-water,1:9,v/v) was used as blank. The maximum inhibition zone noted is shown in Table III.

3. Results and Discussion

Molecular weights and microanalysis data are consistent with the deduced molecular formulae of compounds. IR spectra of cyclocondensation products of chalcones with urea, thiour, and guanidine reveal the occurrence of ν C=N band [21] in the range 1625–1674 cm^{-1} which could be attributed to pyrimidine ring formation. One or two bands in 3384–3445 cm^{-1}, 1178–1209, and 1308–1414 cm^{-1}.

And 3349–3477 cm^{-1}& 1568–1675 cm^{-1} and 1225–1325 cm^{-1} and 2562–2594 cm^{-1} ranges assigned only to νOH, δOH & νC-O, and νN-H & δNH and νC-N (primary amine) and νS-H vibrations respectively obviously indicate the presence of phenolic OH, amino and -SH groups in the products. Besides characteristic bands of pyrimidine ring and its substituents (-OH,-NH_2-SH), except ketonic (C=O) and (C=C) chain groups have been found intact in the products (Tables I and II). Aryl para-substituent compounds exhibit their characteristic stretching vibrations in 809 cm^{-1}–848 cm^{-1}range, whereas meta aryl substituents depicted vibrations at ~750 cm^{-1}; νC-Cl observed in the 746 cm^{-1}–776 cm^{-1} range. In ^{1}H NMR spectra, the disappearance of bands corresponding to >C=CHR and -C-COH=C< of chalcones and peaks of OH, NH, and SH 7.18–7.39 δ, 5.05–5.15 δ and 3.75–3.96 δ regions, respectively observed, confirm the formation of pyrimidine ring.

From Table III, it is evident that compound 4b is highly active against E. faecalis and 8c against E. coli, whereas 4c, 6b, and 6c exhibit excellent results against B. subtilis. Compounds 3b against

TABLE II: Spectral Data of Compounds

Compoud	IR (KBR, CM-1)	HNMR ($CDCl_3$, ppm)
1a	1668(C=N), 3428(O-H), 1413(OH,CO), 819(p), 747(C-Cl)	6.98 (Ar-H), 7.38(OH)
1b	1669(C=N), 1359(C-N), 821(P), 748(C-Cl), 2589(S-H)	6.97(Ar-H), 3.79(SH)
1c	1668(C=N), 1357(C-N), 3407, 3473 (N-H), 1225, 1292(C-N,PRI.NH_2), 818(P), 747 (C-Cl)	6.95(Ar-H), 5.06(N-H)
3a	1668(C=N), 3440(Br,OH), 1414(OH,CO), 1312(C-N), 816(p), 746(C-Cl)	6.97(Ar-H), 7.39(O-H)
3b	1671(C=N), 1344(C-N), 814(p), 747(C-Cl), 2570(S-H)	7.00(Ar-H), 3.80(S-H)
3c	1625(C=N), 3402(N-H), 1625(N-H), 1250(C-N), 819(p), 753(C-Cl)	7.03(Ar-H), 5.13(N-H)
4a	1626(C=N), 3384(O-H), 1209, 1308(OH,C-O), 808(m), 746(C-Cl)	6.51 (Ar-H), 7.18(N-H)
4b	1625(C=N), 746(m), 746(C-Cl)	7.21(Ar-H), 3.78(S-H)
4c	1671(C=N), 3396(N-H), 1579(N-H), 1263(C=N), 755(ml), 755(C-Cl)	7.26 (Ar-H), 5.10(N-H)
5c	1642(C=N), 3463(N-H), 1578(N-H), 1325(C-N), 848(pl), 776(C-Cl)	7.23 (Ar-H), 5.12(N-H)
6a	1672(C=N), 3422(Br), (O-H), 1235, 1403(OH,CO), 813(P), 748(C-Cl)	6.68(Ar-H), 7.32(O-H)
6b	1663(C=N), 815(P), 745(C-Cl), 2562(S-H)	6.76(Ar-H), 3.82(S-H)
6c	1650(C=N),3447(N-H), 1650, 1580(N-H), 1299(C-N,PRI.NH_2), 813(P),747 (C-Cl)	6.68 (Ar-H), 5.05(N-H)
8b	1671(C=N), 748,810(m,p) 748(C-Cl), 2594(S-H)	6.93(Ar-H), 3.96(S-H)
8c	1675(C=N), 3349(N-H), 1570,1675(N-H), 1261, (C-N,PRI.NH_2), 751(m), 811 (p), 751(C-Cl)	6.96 (Ar-H), 5.15(N-H)
9c	1672(C=N), 1312(C-N), 3374, 3377(N-H), 1568, 1672(N-H), 1312(C-N), 1749(m), 815(p), 698(C-Cl)	6.99 (Ar-H), 5.15(N-H)

TABLE III: Antibacterial Activity Of Substituted Pyrimidines

Compound	Zone of inhibition (mm)			
	E Coli	B.Subtilis	E.Faecium	E.Faecalis
1a	10 (0.05)	21 (0.51)	11 (0.05)	10 (0.05)
1c	25 (5.10)	24 (0.51)	29 (0.51)	10 (5.10)
3b	29 (0.06)	27 (0.06)	15 (0.06)	11 (0.06)
4b	10 (0.05)	20 (0.05)	28 (5.50)	34 (0.06)
4c	10 (0.52)	35 (5.37)	11 (0.05)	12 (0.05)
6b	29 (0.52)	34 (0.06)	21 (0.06)	11 (5.52)
6c	10 (0.05)	36 (0.54)	13 (0.05)	11 (0.05)
8b	10 (0.06)	19 (0.06)	27 (0.57)	10 (0.06)
8c	31 (0.55)	20 (0.05)	15 (0.55)	12 (0.55)
9c	10 (0.58)	20 (5.82)	28 (0.58)	13 (0.58)
Control	10	10	10	10
Benzylpenicillin	20 (0.20)	18 (0.20)	–	20 (0.20)
Chloramphenicol	14 (0.20)	16 (0.20)	–	14 (0.20)

Note: Values in Parenyhesis are Concentration $\mu g \mu L^{-1}$.

E. coli and B. subtilis, 4b, 8b, and 9c against E. faecium, 4b against E. coli, and 8c against E. faecium, E. coli, and B. subtilis showed moderate activity. Some compounds showed either mild or no activity. In p-substituted mercapto products inhibition zone order $Br<N(CH_3)<NO_2$ against E. faecium and E. faecalis, and $NO_2<N(CH_3)<Br$ against E. coli and B. subtilis similar and opposite to electronegativity sequence of substituted groups respectively indicated positive effects of electronegativities of substituents of E. faecium and E. faecalis bacteria. P-substituted fluoro compounds 1a and 1c showed good activity against B. subtilis and E. faecium and dimethyl amino compounds against E. faecium, E. coli, and B. subtilis bacteria. The number of methoxy groups corresponded to inhibition in all three bacteria except E. coli. Both p-substituted fluoro compounds showed enhanced activity of the amino group than hydroxy, $OH \leq NH_2$, against all four bacteria.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

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