Research Article

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Study on synthesis of Chalcone & Pyrimidine Heterocyclic compound & their Antimicobial Activity

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Abstract: 4-chloroaniline reacts with 1-(4-hydroxyphenyl)-ethanone in presence of 1-napthonicacid & copper metal as a catalyst gives 1-(4-(4-aminophenoxy)phenyl)ethanone, which on further condensation with 4-nitrotoluene-2-sulfonyl chloride gives N-(4-(4-acetylphenoxy)phenyl)-2-methyl-5-nitrobenzenesulphonamide. This derivative react wit various substituted aldehydes to give corresponding substituted chalcone derivatives (H-1). Now these derivative (H-1) on condensation with thiourea gives 2-methyl-5-nitro-N-(4-(3-(6-aryl-phenyl-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)benzenesulphoneamide derivatives (H-2). Structure elucidation of synthesized compounds has been made on the basis of the elemental analysis, ^{1}H NMR spectral studies. The antimicrobial activity of the synthesized compound has been studied against the species “Bacillus Subtillis”, “Staphylococcus aureus”, “Escherichia Coli” and “salmonella typhi”.

Key words: Synthesis, Heterocyclic substituted chalcone derivatives, Sulphonamide derivatives, Pyrimidin derivatives , antimicrobial activity.

INTRODUCTION:

Chalcones are 1,3 -diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β- unsaturated carbonyl system. α, β- unsaturated containing the reactive ketoethylenic group –CO-CH=CH- ,presence of α, β- unsaturated carbonyl system in chalcone makes it biologically active.Some substituted chalcones and their derivatives have been reported to possess some interesting biological properties such as antibacterial [1], antifungal, insecticidal [2], anesthetic [3],analgesic, ulcerogenic [4] etc.

The replacement of two –CH units in benzene by nitrogen atoms gives pyrimidines. Some substituted pyrimidines and there derivatives have been reported to possess antimicrobial, antitumour and antifungal [5] activities. All these observations and the essential role of heterocyclic chalcone derivatives, pyrazoline derivatives and pyrimidine derivatives in certain biological reactions encourage us to synthesis all these heterocyclic derivatives.

EXPERIMENTAL:

Preparation of N-(4-(4-acetylphenoxy)phenyl)-2-methyl-5nitrobenzenesulfonamide: In a 250 ml round bottom flask , 1-(4-(4-aminophenoxy)phenyl)ethanone (13.5 g, 0.1mol) was dissolved in pyridine (75 ml) and 4-nitrotoluene-2-sulfonyl chloride (23.6 g , 0.1 mol) was added to it with constant

stirring maintaining the temperature below 25°c. After the completion of the addition the mixture was refluxed for 2 hours, and then it was cooled and poured into crushed ice. Solid was separated by filtration and crystalline from ethanol. Yield 86% , M.P. 192°c.

(a) Preparation of 2-methyl-5-nitro-N-(4-(3-(6-phenyl-2-thioxo-1,2,5,6- tetrahydropyrimidin-4-yl)phenoxy)phenyl)benzenesulfonamide: A mixture of (E)-N-(4-(3-cinnamoylphenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.42 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 63% , M.P. 195°c.

(b) N-(4-(3-(6-(4-methoxyphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide:A mixture of (E)-N-(4-(3-(3-(4-methoxyphenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.44 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 59% , M.P. 198°c.

(C) N-(4-(3-(6-(2-methoxyphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide:A mixture of (E)-N-(4-(3-(3-(2-methoxyphenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.45 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 66% , M.P. 187°c.

(D) N-(4-(3-(6-(2-hydroxyphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide:A mixture of (E)-N-(4-(3-(3-(2-hydroxyphenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.47 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 75% , M.P. 194°c.

(E) N-(4-(3-(6-(2-chlorophenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide:A mixture of (E)-N-(4-(3-(3-(2-chlorophenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.44 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 61% , M.P. 190°c.

(F) N-(4-(3-(6-(4-chlorophenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide:A mixture of (E)-N-(4-(3-(3-(4-chlorophenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.45 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 60% , M.P. 190°c.

(G) 2-methyl-5-nitro-N-(4-(3-(6-(2-nitrophenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)benzenesulfonamide:A mixture of (E)-2-methyl-5-nitro-N-(4-(3-(3-(2-nitrophenyl)acryloyl)phenoxy)phenyl)benzenesulfonamide (0.46 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 76% , M.P. 182°c.

(H) N-(4-(3-(6-(3-bromophenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide:A mixture of (E)-N-(4-(3-(3-(3-bromophenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.44 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 69% , M.P. 190°c.

(I) N-(4-(3-(6-(3,4-dimethoxyphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy) phenyl)-2-methyl-5-nitrobenzenesulfonamide:A mixture of ((E)-N-(4-(3-(3-(3,4-dimethoxyphenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.44 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 66% , M.P. 193°c.

(J) 2-methyl-5-nitro-N-(4-(3-(2-thioxo-6-(3,4,5-trimethoxyphenyl)-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)benzenesulfonamide:A mixture of (E)-2-methyl-5-nitro-N-(4-(3-(3-(3,4,5-trimethoxyphenyl)acryloyl)phenoxy)phenyl)benzenesulfonamide (0.44 g, 0.001 mol) and thiourea (0.08gm, 0.001 mol) in ethanol (30 ml) and con.HCl (20 ml) was refluxed for 12 hours. The reaction mixture was than filtered while hot, allow to cool and neutralized with NaOH. The resulting solid was washed several times with water, dried and crystalised from ethanol. Yield 72% , M.P. 191°c.

A short review of results of antibacterial screening of the compounds of this section is mentioned here

(I) Against staphylococcus aureus:

Maximum activity were found in compound (h) zone of inhibition -14.0 m.m and minimum activity were found in compounds (a) , (b) and (i) zone of inhibition -7.0 m.m

(II) Against Escherichia Coli :

Maximum activity were found in compound (g) zone of inhibition -14.0 m.m and minimum activity were found in compounds (d) zone of inhibition -6.0 m.m

MATERIALS AND METHOD:

All melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected.The I. R. spectra were recorded with KBr pellets on Perkin - Elmer - 783 spectrophotometer and 1HN.M.R. spectra were recorded on a Varian Geminy 200 MHz spectrophotometer with CDCl3 / DMSOd6 as a solvent using tetramethylsilane (T.M.S.) as an internal standard; the chemical shift values are in d ppm. The purity of the compounds was checked by thin layer chromatography (T.L.C.) on silica gel coated glass plates. The elemental analysis (i.e. C, H and N analysis) has been done on Carlo - Erba - 1108 analyzer and the values are within the permissible limits (i.e. + 0.5) of their calculated values.Antimicrobial activity of newly synthesised compounds was studied against gram-positive bacteria"Staphylococcus aureus" and gram-negative bacteria "Escherichia coli" (for antibacterial activity) and against the culture "Candela albicans" (for antifungal activity). The antimicrobial screening was carried out by cup - plate method10 at a concentration of 50 mg/mL in solvent D.M.F. The zone of inhibition was measured in mm. The antimicrobial activity of the synthesised compounds was compared with standard drugs Ampicillin, Penicillin and Tetracycline at the same concentration.

RESULTS AND DISCUSSIONS:

The antimicrobial activities of newly synthesised compounds were compared with known antibiotics like Ampicillin, Penicillin and Tetracycline and all the compounds show moderate to good activity. Structure elucidation of synthesised compounds has been made on the basis of elemental analysis, I.R. spectral studies and 1H N.M.R. spectral studies and all the compounds gave satisfactory elemental analysis, I.R. and 1H N.M.R. spectral measurements.

I.R. Spectral Studies:

I.R. (cm-1) (KBr) spectral data of compound :-

A) 1662 n (C=O stretching, chalcone moiety); 1604 n (C=N stretching, pyrimidine moiety);1585 (C=C stretching, chalcone moiety); 1526 n (N=O stretching, Ar-NO2 at phenyl ring of chalcone moiety);1348 n (S=O stretching, Ar-SO2NH-Ar); 735 n(C-Cl stretching, Ar-Cl at phenyl ring).

B) 3400 n (N-H stretching, pyrimidine moiety); 1658 n (C=O stretching, pyrimidine moiety); 1465 n (C-H bending, -CH2- of pyrimidine ring); 1340 n (S=O stretching, Ar-SO2NH-Ar); 745 n (C-Cl stretching, Ar-Cl at phenyl ring).

C) 3367 n (N-H stretching, pyrimidine moiety); 2833 n (C-H stretching, Ar-OCH3 at phenyl ring); 1352 n (S=Ostretching, Ar-SO2NH-Ar); 1198 n (C=S stretching, pyrimidine moiety); 736 n (C-Cl stretching, Ar-Cl at phenyl ring).

1H N.M.R. Spectral Studies:

1H N.M.R. (CDCl3) spectral data of compound

A) 3.30 d ppm (s, 2H, -CH2- of pyrimidine ring); 3.38 d ppm (s, 1H, Ar-CH); 7.03 to 7.75 d ppm (m,14H, Ar-H); 7.79 d ppm (d, 1H, -CH=CH-Ar); 8.14 d ppm (d, 1H, -CO-CH=CH-); 8.22 d

ppm (s, 1H, Ar-SO2NH-Ar).

B) 3.35 d ppm (s, 2H, -CH2- of pyrimidine ring); 3.41 d ppm (s, 1H, Ar-CH); 3.78 d ppm (s, 3H, Ar-OCH3 at phenyl ring); 7.01 to 7.71 d ppm (m, 14H,Ar-H); 7.84 d ppm (s, 1H, -NH- of - pyrimidine ring); 8.24 d ppm (s, 1H, Ar-SO2NH-Ar).

C) 3.33 d ppm (s, 2H, -CH2- of pyrimidine ring); 3.40 d ppm (s, 1H, Ar-CH); 3.80 d ppm (s, 3H, Ar-OCH3 at phenyl ring); 6.99 to 7.68 d ppm (m,14H, Ar-H); 7.83 d ppm (s, 1H, -NH- of pyrimidine ring); 8.20 d ppm (s, 1H, Ar-SO2NH-Ar).

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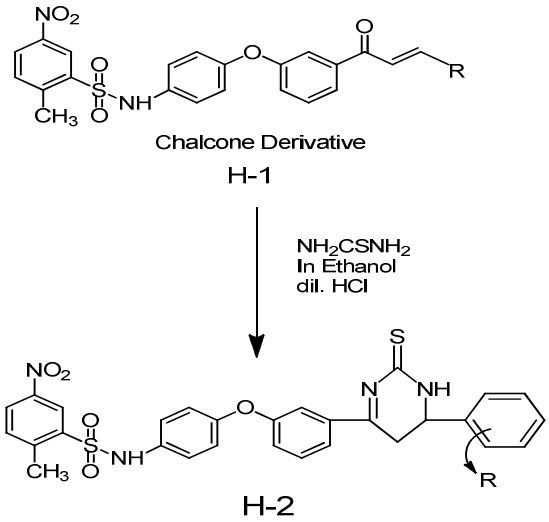

2-methyl-5-nitro-N-(4-(3-(6-aryl- phenyl-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)benzenesulphoneamide derivatives (H-2).

Where R = (a) Benzaldehyde
(b) 4-anisaldehyde
(c) 2-anisaldehyde
(d) Salicyaldehyde
(e) 2-chlorobenzaldehyde
(f) 4-chlorobenzaldehyde
(g) 2-nitrobenzaldehyde
(h) 3-bromobenzaldehyde
(I) 3,4-dimethoxybenzaldehyde

(j) 3,4,5-trimethoxybenzaldehyde

PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS

Compd. No.	R	M.F [M.W. g/m]	M.P (°C)	YIELD (%)	% Analysis (calcd.) Found (F) and Required (R)					
					% C		% H		% N	
					(F)	(R)	(F)	(R)	(F)	(R)
a	H	$C_{29}H_{24}N_4O_5S_2$ (572.655)	195	63	60.82	63.21	4.22	4.29	9.78	9.82
b	4-OCH_3	$C_{30}H_{26}N_40_6S_2$ (602.681)	198	59	59.79	60.12	4.35	4.35	9.30	9.32
c	2-OCH_3	$C_{30}H_{26}N_40_6S_2$ (602.681)	187	66	59.79	60.12	4.35	4.35	9.30	9.30
d	2-OH	$C_{29}H_{24}N_4O_5S_2$ (588.654)	194	75	59.17	59.63	4.11	4.65	9.52	9.56
e	2-Cl	$C_{29}H_{23}ClN_4O_5S_2$ (606.080)	190	61	57.37	56.19	3.82	3.26	9.23	9.33
f	4-Cl	$C_{29}H_{23}ClN_4O_5S_2$ (607.100)	190	60	57.37	56.19	3.82	3.26	9.23	9.33
g	2-NO_2	$C_{29}H_{23}N_5O_7S_2$ (617.652)	182	76	56.39	54.70	3.75	3.85	11.34	11.35
h	3-Br	$C_{29}H_{23}BrN_4O_5S_2$ (651.551)	190	69	53.46	53.40	3.56	3.66	8.60	8.39
i	3,4(OCH_3)$_2$	$C_{30}H_{28}N_4O_7S_2$ (632.707)	193	66	58.85	55.60	4.46	4.40	8.86	8.67
j	3,4,5(OCH_3)$_3$	$C_{32}H_{30}N_4O_8S_2$ (662.733)	191	72	57.99	57.83	4.56	4.02	8.45	8.45

ANTIBACTERIAL ACTIVITY:

Compound No.	R	Zone of inhibition (m.m.)	
		Staphylococcus aureus	Escherichia coli
A	H	7	9
B	4-OCH_3	7	8
c	2-OCH_3	8	10
D	2-OH	9	6
e	2-Cl	10	12
f	4-Cl	12	10
g	2-NO_2	13	14
h	3-Br	14	12
i	3,4$(OCH_3)_2$	7	8
j	3,4,5$(OCH_3)_3$	9	9

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