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Synthesis on study of 2-methyl-5-nitro-n-(4-(3-(2-aryl-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenoxy)phenyl) benzenesulfonamide and their antimicobial activity

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ABSTRACT

4-chloroaniline reacts with 1-(4-hydroxyphenyl)-ethanone in presence of 1-napthonicacid and 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 (N-1). Now these derivative (N-1) on condensation with 2-aminobenzenethiol gives 2-methyl-5-nitro-N-(4-(3-(2-phenyl-2,3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenoxy)phenyl)benzenesulfonamide (N-2). Structure elucidation of synthesized compounds has been made on the basis of the elemental analysis, ^1H 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.

Keywords: Synthesis, heterocyclic substituted chalcone derivatives, sulphonamide derivatives, pyrimidin derivatives, antimicrobial activity.

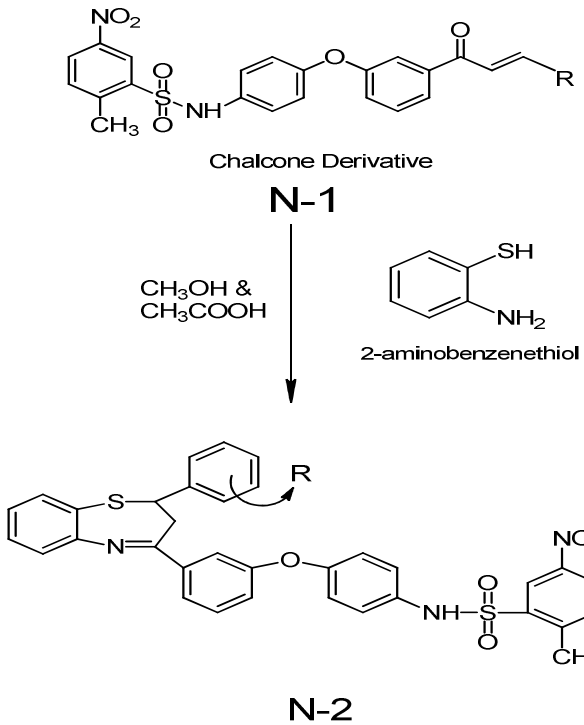
INTRODUCTION

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[6-10].All efforts are done in this research is to synthesized a novel compound that can be used for formulation of anticancer drugs.

EXPERIMENTAL SECTION



2-methyl-5-nitro-N-(4-(3-(2-aryl-2,3-dihydrobenzo[b][1,4]thiazepin-4-l)phenoxy)phenyl)benzenesulfonamide (N-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

Preparation of N-(4-(4-acetylphenoxy)phenyl)-2-methyl 5-nitrobenzenesulfonamide

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-(2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl) phenoxy)phenyl) benzenesulfonamide

A mixture of (E)-N-(4-(3-cinnamoylphenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (4.2 g, 0.01 mol) and 2-aminobenzenethiol (1.4 gm, 0.011 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 65%, M.P. 145°C.

(b)N-(4-(3-(2-(4-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 63%, M.P. 238°C.

(c)N-(4-(3-(2-(2-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 68% , M.P. 170°C.

(d)N-(4-(3-(2-(2-hydroxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 68% , M.P. 168°C.

(e)N-(4-(3-(2-(2-chlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 70% , M.P. 150°C.

(f)N-(4-(3-(2-(4-chlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 60% , M.P. 136°C.

(g)2-methyl-5-nitro-N-(4-(3-(2-(2-nitrophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 70% , M.P. 150°C.

(h)N-(4-(3-(2-(3-bromophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 60% , M.P. 136°C.

(i)N-(4-(3-(2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 65% , M.P. 155°C.

(j)2-methyl-5-nitro-N-(4-(3-(2-(3,4,5-trimethoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-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 2-aminobenzenethiol (0.08gm, 0.001 mol) in anhydrous methanol (100 mL) and glacial acetic acid (10 mL) was refluxed on water-bath at 60-70 for 2 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 crystallized from ethanol. Yield 67% , M.P. 153°C.

Melting points

All melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected. The IR spectra were recorded with KBr pellets on Perkin - Elmer - 783 spectrophotometer and 1H NMR 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

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 $mg.mL^{-1}$ 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 DISCUSSION

Table 1: Physical and analytical data of compounds

Compound 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	$C_{34}H_{27}N_3O_5S_2$ (621.725)	145	65	63.82	63.50	4.29	4.38	7.96	7.99
b	4-OCH_3	$C_{35}H_{29}N_30_6S_2$ (651.751)	238	63	62.79	62.24	4.32	4.32	7.54	7.58
c	2-OCH_3	$C_{35}H_{29}N_30_6S_2$ (651.751)	170	68	60.79	60.26	4.30	4.32	7.54	7.60
d	2-OH	$C_{34}H_{27}N_3O_6S_2$ (637.725)	168	68	59.70	59.40	4.61	4.60	7.73	7.77
e	2-Cl	$C_{34}H_{26}ClN_3O_5S_2$ (656.170)	150	70	60.37	60.69	3.60	3.22	7.48	7.51
f	4-Cl	$C_{34}H_{26}ClN_3O_5S_2$ (656.170)	136	60	56.07	56.10	3.21	3.29	7.48	7.53
g	2-NO_2	$C_{34}H_{26}N_4O_7S_2$ (666.723)	150	70	52.85	52.90	3.80	3.78	9.79	9.82
h	3-Br	$C_{34}H_{26}BrN_3O_5S_2$ (700.621)	136	60	56.26	56.22	3.66	3.60	6.93	6.96
i	3,4(OCH_3)$_2$	$C_{36}H_{31}N_3O_7S_2$ (681.777)	155	65	54.20	54.24	4.42	4.42	7.16	7.20
j	3,4,5(OCH_3)$_3$	$C_{37}H_{33}N_3O_8S_2$ (711.803)	153	67	60.00	59.83	4.50	4.22	6.81	6.85

Table 2: Antibacterial activity

Compound No.	R	Zone of inhibition (m.m.)	
		Staphylococcus aureus	*Escherichia coli*
A	H	10	9
B	4-OCH_3	8	8
C	2-OCH_3	7	8
D	2-OH	10	9
E	2-Cl	11	10
F	4-Cl	12	12
G	2-NO_2	13	14
H	3-Br	15	12
I	3,4(OCH_3)$_2$	9	8
J	3,4,5(OCH_3)$_3$	10	7

A short review of results of antibacterial screening of the compounds of this section is mentioned as follows:

- Against *Staphylococcus aureus*:

Maximum activity were found in compound (h) zone of inhibition -15.0 m.m and minimum activity were found in compound (c) zone of inhibition -7.0 m.m.

- Against *Escherichia coli*:

Maximum activity were found in compound (g) zone of inhibition -14.0 m.m and minimum activity were found in compounds (j) zone of inhibition -7.0 m.m.

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, IR spectral studies and ^{1}H NMR spectral studies and all the compounds gave satisfactory elemental analysis, IR and 1H NMR spectral measurements.

IR Spectral Studies

IR (cm-1) (KBr) spectral data of compound:

A) 1662 n (C=O stretching, chalcone moiety); 699 n (C-S-C stretching, thiazepin moiety); 1636 (C=N 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) 699 n (C-S-C stretching, thiazepin moiety); 1638 n (C=N stretching, thiazepin moiety); 1340 n (S=O stretching, Ar-SO2NH-Ar); 745 n (C-Cl stretching, Ar-Cl at phenyl ring).

C) 2833 n (C-H stretching, Ar-OCH3 at phenyl ring); 1352 n (S=O stretching, Ar-SO2NH-Ar); 1636 n (C=N stretching, thiazepin moiety); 736 n (C-Cl stretching, Ar-Cl at phenyl ring).

^{1}H NMR Spectral Studies

^{1}H NMR (CDCl3) spectral data of compound

A) 3.30 d ppm (s, 2H, -CH2- of thiazepin 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 thiazepin 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 -thiazepin ring); 8.24 d ppm (s, 1H, Ar-SO2NH-Ar).

C) 3.33 d ppm (s, 2H, -CH2- of thiazepin 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 thiazepin ring); 8.20 d ppm (s, 1H, Ar-SO2NH-Ar).

CONCLUSION

The screening results revealed that the compounds (h) showed significant antimicrobial activity. In particular compounds (d) and (j) showed moderate to considerable antibacterial and antifungal activities against all the organisms employed at a conc. of 1000 _g/mL (0.1ml dose level) and are comparable to that of standard drugs Chloramphenicol and Fluconazole respectively.

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