



Synthesis on study of novel chalcone derivatives and their antimicrobial activity

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ABSTRACT

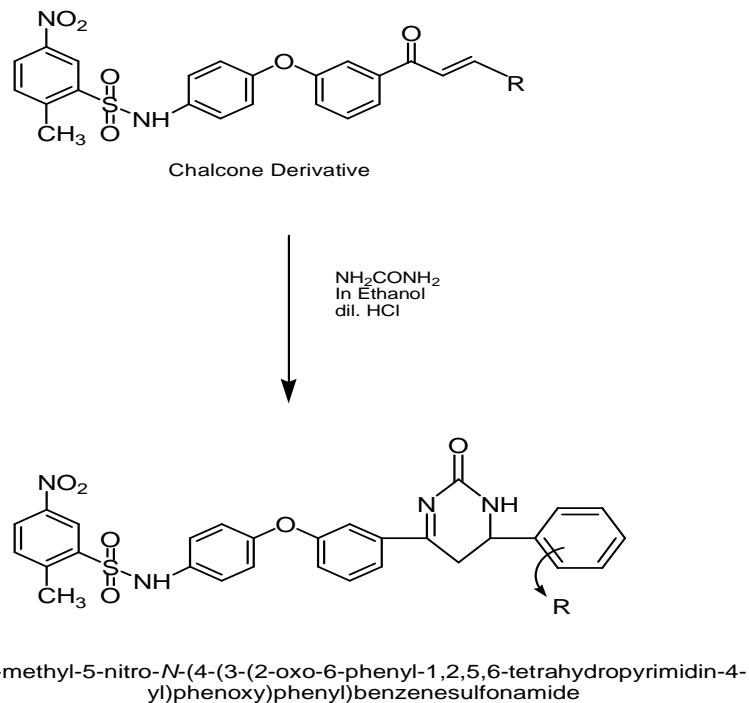
4-chloroaniline reacts with 1-(4-hydroxyphenyl)-ethanone in presence of 1-naphthonic acid and copper metal as a catalyst gives 1-(4-(4-aminophenoxy) phenyl)ethanone, which on further condensation with 4-nitrotoluene-2-sulfonyl chloride gives N-(4-(4-acetylphenoxy)phenyl)-2-methyl-5-nitrobenzenesulphonamide. This derivative reacts with various substituted aldehydes to give corresponding substituted chalcone derivatives (N-1). Now these derivatives (N-1) on condensation with NH_2CONH_2 in presence of dilute HCl gives 2-methyl-5-nitro-N-(4-(3-(2-oxo-6-phenyl-1,2,5,6-tetrahydropyrimidin-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 subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi*.

Keywords: Chalcone derivatives, Antimicrobial agents, Synthesis, heterocyclic substituted chalcone derivative, sulphonamide derivatives, pyrimidin derivatives, antimicrobial activity.

INTRODUCTION

There is growing interest in the pharmacological potential of natural products as chalcones constitute an important group of natural products. Chemically, they consist of open chain flavanoids in which the two aromatic rings are joined by a three carbon α . β unsaturated carbonyl system. The presence of a reactive α , β unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity¹. In recent years a variety of chalcones have been reviewed for their cytotoxic, anticancer chemopreventive and mutagenic as well as antiviral, insecticidal and enzyme inhibitory properties^{2,3}. A number of chalcones having hydroxy, alkoxy groups in different position have been reported to possess anti-bacterial⁴, antiulcer⁵, antifungal⁶, antioxidant⁷, vasodilatory⁸, antimitotic⁹, antimalarial¹⁰, antileishmanial¹¹ and inhibition of chemical mediators release, inhibition of leukotriene B¹², inhibition of tyrosinase^{13,14} and inhibition of aldose reductase¹⁵ activities. Appreciation of these findings motivated us to synthesize chalcones as a potential template for antimicrobial agents.

MATERIALS AND METHODS



(figure - 1)

2-methyl-5-nitro-N-(4-(3-(2-oxo-6-phenyl-1,2,5,6-tetrahydropyrimidin-4-yl)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-oxo-6-phenyl-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)benzenesulfonamide

A mixture of (E)-N-(4-(3-cinnamoylphenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (4.2 g, 0.01 mol), urea (0.60 g, 0.01 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%, 20 ml), was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was then filtered while hot, allow to cool. The resulting solid was crystallized from ethanol.

(b) N-(4-(3-(4-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide

A mixture of (E)-N-(4-(3-(4-methoxyphenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.44 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%, 20 ml), was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was then filtered while hot, allow to cool. The resulting solid was crystallized from ethanol.

(c) N-(4-(3-(2-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide

A mixture of (E)-N-(4-(3-(2-methoxyphenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.45 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%, 20 ml), was refluxed

on water-bath at 60-70 for 2 hours. The reaction mixture was than filtered while hot, allow to cool .The resulting solid was crystallized from ethanol.

(d)N-(4-(3-(2-hydroxyphenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide

A mixture of (E)-N-(4-(3-(2-hydroxyphenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.47 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%,20ml),was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was than filtered while hot, allow to cool .The resulting solid was crystallized from ethanol.

(e)N-(4-(3-(6-(2-chlorophenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide

A mixture of (E)-N-(4-(3-(2-chlorophenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.44 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%,20ml),was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was than filtered while hot, allow to cool .The resulting solid was crystallized from ethanol.

(f)N-(4-(3-(6-(4-chlorophenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide

A mixture of (E)-N-(4-(3-(4-chlorophenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.45 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%,20ml),was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was than filtered while hot, allow to cool .The resulting solid was crystallized from ethanol.

(g) 2-methyl-5-nitro-N-(4-(3-(2-nitrophenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy) phenyl benz-enesulfonamide

A mixture of (E)-2-methyl-5-nitro-N-(4-(3-(2-nitrophenyl)acryloyl)phenoxy)phenyl) benzenesulfonamide (0.46 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%,20ml),was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was than filtered while hot, allow to cool .The resulting solid was crystallized from ethanol.

(h)N-(4-(3-(6-(3-bromophenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide

A mixture of (E)-N-(4-(3-(3-bromophenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.44 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%,20ml),was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was than filtered while hot, allow to cool .The resulting solid was crystallized from ethanol.

(i)N-(4-(3-(6-(3,4-dimethoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide

A mixture of (E)-N-(4-(3-(3,4-dimethoxy phenyl)acryloyl)phenoxy)phenyl)-2-methyl-5-nitrobenzenesulfonamide (0.44 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%,20ml),was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was than filtered while hot, allow to cool .The resulting solid was crystallized from ethanol.

(j)2-methyl-5-nitro-N-(4-(3-(2-oxo-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-(3,4,5-trimethoxyphenyl)acryloyl) phenoxy) phenyl benzenesulfonamide (0.44 g, 0.001 mol) and urea (0.60 g, 0.01 mol) and hydrochloric acid (20 ml) in ethanol (95%,20ml),was refluxed on water-bath at 60-70 for 2 hours. The reaction mixture was than filtered while hot, allow to cool .The resulting solid was crystallized from ethanol.

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 Gemini 200 MHz spectrophotometer with CDCl₃ / DMSO_{d6} as a solvent using tetramethylsilane (T.M.S.) as an internal standard; the chemical shift values are in δ 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			
					(F)	(R)	(F)	(R)	(F)	
a	H	C ₂₉ H ₂₄ N ₄ O ₆ S (556.589)	152	65	63.82	63.50	4.29	4.38	7.96	7.99
b	4-OCH ₃	C ₃₀ H ₂₆ N ₄ O ₇ S (586.615)	208	63	62.79	62.24	4.32	4.32	7.54	7.58
c	2-OCH ₃	C ₃₀ H ₂₆ N ₄ O ₇ S (586.615)	206	68	60.79	60.26	4.30	4.32	7.54	7.60
d	2-OH	C ₂₉ H ₂₄ N ₄ O ₇ S (572.588)	158	68	59.70	59.40	4.61	4.60	7.73	7.77
e	2-Cl	C ₂₉ H ₂₃ ClN ₄ O ₆ S (591.034)	150	70	60.37	60.69	3.60	3.22	7.48	7.51
f	4-Cl	C ₂₉ H ₂₃ ClN ₄ O ₆ S (591.034)	152	60	56.07	56.10	3.21	3.29	7.48	7.53
g	2-NO ₂	C ₂₉ H ₂₃ N ₅ O ₈ S (601.587)	190	70	52.85	52.90	3.80	3.78	9.79	9.82
h	3-Br	C ₂₉ H ₂₃ BrN ₄ O ₆ S (635.485)	198	60	56.26	56.22	3.66	3.60	6.93	6.96
i	3,4(OCH ₃) ₂	C ₃₁ H ₂₈ N ₄ O ₈ S (616.641)	206	65	54.20	54.24	4.42	4.42	7.16	7.20
j	3,4,5(OCH ₃) ₃	C ₃₂ H ₃₀ N ₄ O ₉ S (646.667)	215	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.)	
		<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
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 ¹H NMR spectral studies and all the compounds gave satisfactory elemental analysis, IR and ¹H NMR spectral measurements.

IR Spectral Studies**I.R. (cm⁻¹) (KBr) spectral data of compound :-**

A) 1662 n (C=O stretching, chalcone moiety); 1604 n (C=N stretching, tetrahydropyrimidin moiety); 1585 n (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, tetrahydropyrimidin moiety); 1658 n (C=O stretching, tetrahydropyrimidin 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, tetrahydropyrimidin moiety); 2833 n (C-H stretching, Ar-OCH₃ at phenyl ring); 1352 n (S=O stretching, Ar-SO₂NH-Ar); 1198 n (C=S stretching, tetrahydropyrimidin 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 tetrahydropyrimidin 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 tetrahydropyrimidin 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 tetrahydropyrimidin ring); 8.24 d ppm (s, 1H, Ar-SO₂NH-Ar).
 C) 3.33 d ppm (s, 2H, -CH₂- of tetrahydropyrimidin 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 tetrahydropyrimidin 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 μ g/mL (0.1ml dose level) and are comparable to that of standard drugs Chloramphenicol and Fluconazole respectively.

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