Available online at www.elixirpublishers.com (Elixir International Journal)

Organic Chemistry

Elixir Org. Chem. 53 (2012) 11718-11721

ISSN: 2229-712X

Synthesis on study of 2-methyl-5-nitro-n-(4-(3-(2-oxo-6-phenyl-1,2,5,6-tetrahydropyrimidin-4-yl)phenoxy)phenyl)benzenesulfonamide and their antimicobial activity

Rajarshi N. Patel[1,*], K.S. Nimavat[2], K.B. Vyas[3] and Piyush V. Patel[4]

[1]JJT University, Rajasthan, India.

[2]Department of Chemistry, Government Science College,Gandhinagar-382 015,Gujarat, India.

[3]Department of Chemistry, Sheth .L.H. Science Collage– Mansa-382 845, Gujarat, India.

[4]Department of Chemistry, Veer Narmad South Gujarat University- 395007, Gujarat, India.

ARTICLE INFO

Article history:

Received: 2 April 2012;

Received in revised form:

19 November 2012;

Accepted: 28 November 2012;

Keywords

Chalcone derivates,
Antimicrobial agents,
Synthesis,
Heterocyclic substituted chalcone derivative,
Sulphonamide derivatives,
Pyrimidin derivatives,
Antimicrobial activity.

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 NH_2CONH_2 in presence of dilute HCl gives2-methyl-5-nitro-N-(4-(3-(2-oxo-6-phenyl-1,2,5,6-tetrahydropyrimidin-4yl) phenoxy)phenyl)benzenesulfonamide (N-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.

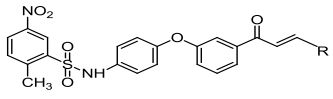
Introduction

There is growing interest in the pharmacological potential of natural products is 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 chemoprevenive and mutagenic as well as antiviral, insecticidal and enzyme inhibitory properties2,3. A number of chalcones having hydroxy, alkoxy groups in different position have been reported to possess anti- bacterial4, antiulcer5, antifungal6, antioxidant7, vasodilatory8, antimitotic9, antimalarial 10, antileshmanial11 and inhibition of chemical mediators release, inhibition of leukotriene B412, inhibition of tyrosinase13,14 and inhibition of aldose reductase15 activities. Appreciation of these findings motivated us to synthesize chalcones as a potential template for antimicrobial agents.

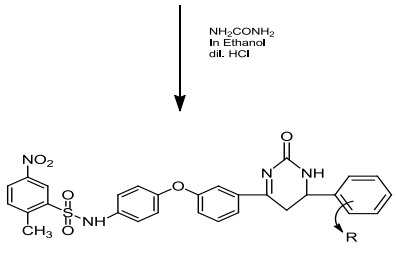
Materials And Methods

2-methyl-5-nitro-N-(4-(3-(2-oxo-6-aryl-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



Chalcone Derivative



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

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-4yl) phenoxy) phenyl) benzenesulfonamide

A mixture of (E)-N-(4-(3-cinnamoylphenoxy)phenyl)-2-

Tele:
E-mail addresses: Dadaji.raja@gmail.com

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%,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.

(b)N-(4-(3-(6-(4-methoxyphenyl)-2-oxo-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 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.

(c)N-(4-(3-(6-(2-methoxyphenyl)-2-oxo-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 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.

(**d)N-(4-(3-(6-(2-hydroxyphenyl)-2-oxo-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 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-(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-(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-(6-(2-nitrophenyl)-2-oxo-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 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-(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-(3,4-dimethoxyphenyl)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-(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 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.

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	$C_{29}H_{24}N_4O_6S$ (556.589)	152	65	63.82	63.50	4.29	4.38	7.96	7.99
b	4-OCH_3	$C_{30}H_{26}N_40_7S$ (586.615)	208	63	62.79	62.24	4.32	4.32	7.54	7.58
c	2-OCH_3	$C_{30}H_{26}N_40_7S$ (586.615)	206	68	60.79	60.26	4.30	4.32	7.54	7.60
d	2-OH	$C_{29}H_{24}N_4O_7S$ (572.588)	158	68	59.70	59.40	4.61	4.60	7.73	7.77
e	2-Cl	$C_{29}H_{23}ClN_4O_6S$ (591.034)	150	70	60.37	60.69	3.60	3.22	7.48	7.51
f	4-Cl	$C_{29}H_{23}ClN_4O_6S$ (591.034)	152	60	56.07	56.10	3.21	3.29	7.48	7.53
g	2-NO_2	$C_{29}H_{23}N_5O_8S$ (601.587)	190	70	52.85	52.90	3.80	3.78	9.79	9.82
h	3-Br	$C_{29}H_{23}BrN_4O_6S$ (635.485)	198	60	56.26	56.22	3.66	3.60	6.93	6.96
i	3,4$(OCH_3)_2$	$C_{31}H_{28}N_4O_8S$ (616.641)	206	65	54.20	54.24	4.42	4.42	7.16	7.20
j	3,4,5$(OCH_3)_3$	$C_{32}H_{30}N_4O_9S$ (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.)	
		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

Results And Discussion

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

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=Ostretching, 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 dppm (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 _g/mL (0.1ml dose level) and are comparable to that of standard drugs Chloramphenicol and Fluconazole respectively.

Acknowledgements:

The authors are thankful to Suleshvari pharma ltd for providing research facilities. They are also grateful to and the Department of Biosciences, Sardar Patel University, Vallabh Vidyanagar, for screening the newly synthesised compounds for their antimicrobial activities; Suleshvari Pharma ltd, for scanning the IR spectra and ^{1}H NMR spectra of newly synthesised compounds.

References

1. Prasad YR, Rao AL and Rambabu R. Synthesis and Antimicrobial Activity of some Chalcone Derivatives. E-Journal of Chemistry, 2008;5(3):461-466.
2. Won SJ, Liu CT, Tsao LT, Ko HH, Wang JP, Lin CN. Synthetic chalcones as potential anti-inflammatory and cancer chemo protective agents. European Journal of Medicinal Chemistry,2005;40: 103-112
3. Yu DC, Panfilova LV, Boreko EI. Synthesis and antiviral activity of unsaturated ketones of thiopene series. Pharm. Chem, 1982;16: 103-105.
4. Liu XL,. Xu YJ, Go ML. Functionalized chalcones with basic functionalities have antibacterial activity against drug sensitive Staphylococcus aureus. European Journal of Medicinal Chemistry, 2008; 43 :681-1687
5. Jeffrey JA, Pamela EO, Jared LR, Jeffrey NJ, Peter DM, Linda MO Pamela SW, and Beth LE. Synthesis and biological evaluation of flavonoids and related compounds as gastro-protective agents. Bioorganic & Medicinal Chemistry Letters, 1996; 6 (8): 995-998.
6. Lahtchev KL, Batovska DI, Parushev SP,. Ubiyvovk VM, Sibirny A. Antifungal activity of chalcones: A mechanistic study using various yeast strains. European Journal of Medicinal Chemistry, 2008; 43: 2220-2228.
7. Rao YK, Fang SH, Tzeng YM. Synthesis and biological evaluation of 3, 4,5-trimethoxychalcone analogues as inhibitors of nitric oxide production and tumor cell proliferation. Bioorganic & Medicinal Chemistry, 2009; 17:7909–7914.
8. Ram VJ, Saxena A, Srivastava S and Chandra S . Oxygenated chalcones and bischalcones as potential antimalarial agents. Bioorganic & Medicinal Chemistry Letters 2000;10: 2159-2161.
9. Khatib S, Nerya O, Musa R, Shmuel M, Tamir S, Vaya J. Chalcones as potent tyrosinase inhibitors: the importance of a 2,4-substituted resorcinol moiety. Bioorganic & Medicinal Chemistry, 2005; 13: 433-441.
10. Papo N, Shai Y. A novel lytic peptide composed of dl-amino acids selectively kills cancer cells. Peptides 2003; 24: 1693 -1703.