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RESEARCH ARTICLE

Study on Synthesis of Some Novel Thiazepine Derivatives their Antimicrobial Activity

Dave H.*[1], Vyas K.B.[2]

[1]*Research Scholar of JJT University, Jhunjhunu, Rajasthan – 333001, India.*

[2]*Department of Chemistry, Sheth. L.H. Science College, Mansa-382 845, Gujarat, India.*

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ABSTRACT

1-chloro-4-(p-tolyolxy)benzene react with 1-(4-hydrogy phenyl)-ethanone in presence of copper metal as a catalyst gives 1-(4-(4(p-tolyolxy) phenoxy)phenyl) ethanone, this derivatives react with various substituted aldehyde to give corresponding substituted chalcone derivatives. Now these derivatives on condensation with 2-aminobenzenethiol gives the vast range of thiazepine derivatives. Structure elucidation of synthesized compound has been made on the basis of element analysis, 1H NMR Spectra studies. The microbial activity of the synthesized compounds has been studied against the species bacillus subtillis, staphylococcus aureus, Escherichia coli, and salmonella typhi.

KEYWORDS

Synthesis, Heterocyclic substituted chalcone derivatives, Pyrimidine derivatives, Chalcones

INTRODUCTION

Chalcone[1] are the compounds were aromatic substitutes are introduced in to the terminal position of system C═C-C═, So chalcone are characterized by their position of a Ar(A)-CO-CH ═ CH-Ar(B) Structure in which two aromatic ring are linked by an aliphatic three carbon chain, thus chalcones are phenyl-styryl ketones containing reactive ketoethylenic group –C-CO═CH-.

Thiazepine derivatives like Diltiazem[2], clentiaziem[3], have synthesized and reported for anticoagulant[4], antiarterisoclerotic[4], antihypertensive[5], antidepressant etc. activities were comparative study with diazepams[6], clobazam[7] etc. we have synthesized a series of new 1, 4- Thiazepines.

***Address for Correspondence:**
Hitesh Dave
Research Scholar of JJT University,
Jhunjhunu, Rajasthan – 333001, India.
E-Mail Id: hiteshdave1972@gmail.com

Thiazepine derivatives are a non dihydropyridine. (non-DHP) one of the class of drugs so called as calcium channel blockers, therapeutically applicable in the treatment of hypertension, angina pectoris, and in the treatment of many types of arrhythmia. Thiazepine is effective in preventive medication for migraine.

They are of class III antianginal drug and class IV antiarrhythmic[8-10].

Thiazepine derivatives are rapidly metabolized and act as an inhibitor of the enzyme. All effort are done in the research is to synthesized a novel compound that can be used for formulation of anticancer drugs.

EXPERIMENTAL

Preparation of 1-(3-(p-tolyloxy) phenyl) ethanone

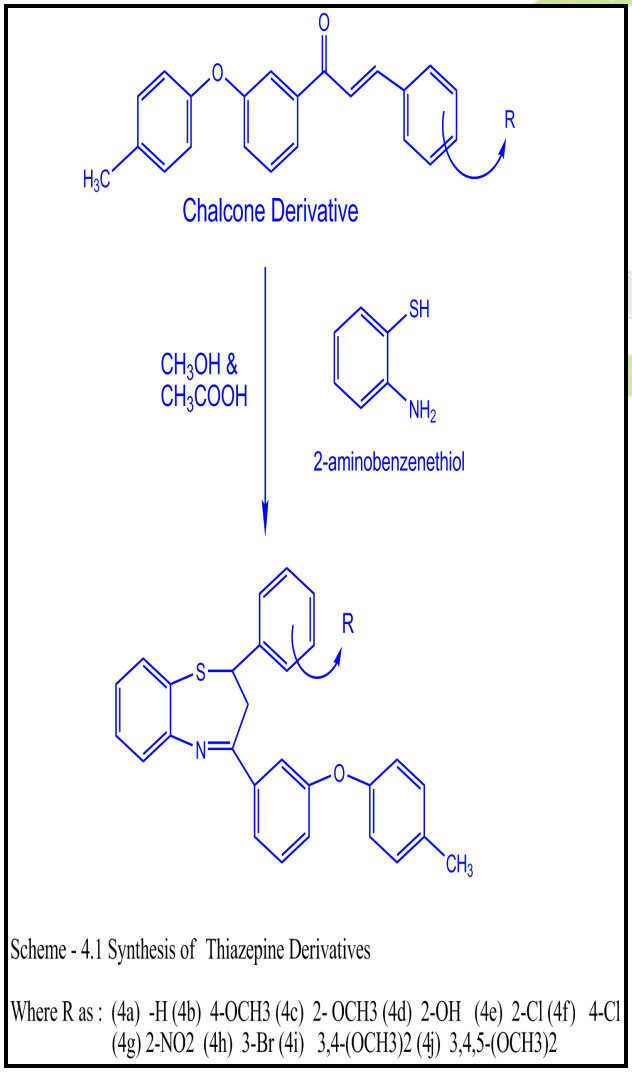
In 250 round bottom flask 1-(3-hydroxy phenyl)ethanone (13.5g,0.1 mole) was dissolved

in pyridine (75 ml) and 1-chloro-4-methylbenzene (23.6 g, 0.01 mole) was added to it with constant stirring by maintaining temperature 25^{0}C. After completion of addition, the mixture was refluxed for 2 hrs. The solid was separated by filtration and crystallized from ethanol.

Preparation of 2-phenyl-4-(3-(p-tolyloxy) phenyl)-2, 3-dihydrobenzo[b][1,4] thiazepine

To well stirred solution of (E)-3-phenyl-1-(3-(p-tolyloxy) phenyl) prop-2-en-1-one (4.2 g, 0.01 mol) with Ortho-aminobenzenethiol (1.4 g, 0.011 mol), moisture free MeOH (100 ml) and ice chilled acetic acid (10.00 ml) was heated to reflux for two hours at 60 to 70^{0}C. Cool the crude product followed by filtration and crystallized by using ethanol (90%).

REACTION SCHEME



Scheme - 4.1 Synthesis of Thiazepine Derivatives

Where R as : (4a) -H (4b) 4-OCH3 (4c) 2- OCH3 (4d) 2-OH (4e) 2-Cl (4f) 4-Cl (4g) 2-NO2 (4h) 3-Br (4i) 3,4-(OCH3)2 (4j) 3,4,5-(OCH3)2

RESULTS AND DISCUSSIONS

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 $CDCl_3$ / 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 synthesized 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 50mg.mL^{-1} in solvent D.M.F. The zone of inhibition was measured in mm. The antimicrobial activity of the synthesized compounds was compared with standard drugs Ampicillin, Penicillin and Tetracycline at the same concentration.

Antibacterial Activity

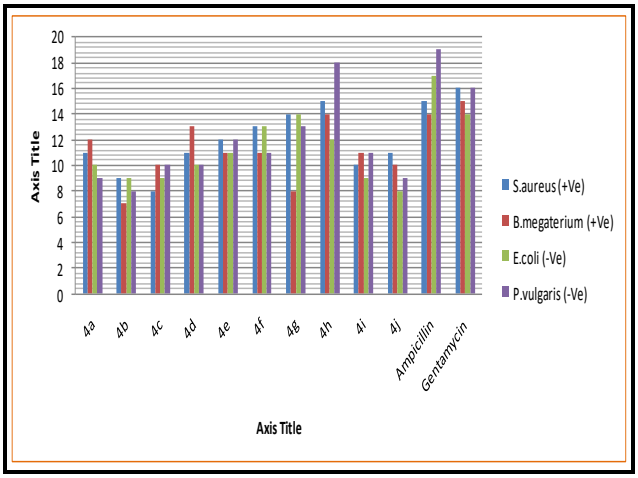


Table 1: Analysis Data

No.	Code No.	R	Molecular Formula	Molecular Weight (g/m)	Yield (%)	M.P. ^{0}C	C %	H %	N %
							Found		
1	4a	-H	$C_{28}H_{23}NOS$	421.55	63	143	79.78	5.53	3.36
2	4b	4-OCH_3	$C_{29}H_{25}NO_2S$	451.751	72	236	77.14	5.60	3.12
3	4c	2-OCH_3	$C_{29}H_{25}NO_2S$	451.751	63	179	77.16	5.62	3.15
4	4d	2-OH	$C_{28}H_{23}NO_2S$	437.725	64	164	76.89	5.70	3.32
5	4e	2-Cl	$C_{28}H_{22}ClNOS$	456.170	75	154	73.74	4.89	3.16
6	4f	4-Cl	$C_{28}H_{22}ClNOS$	456.170	67	136	73.71	4.80	3.11
7	4g	2-NO_2	$C_{28}H_{22}N_2O_3S$	466.723	75	154	72.12	4.76	6.05
8	4h	3-Br	$C_{28}H_{22}BrNOS$	500.621	66	132	67.27	4.54	2.82
9	4i	3,4-$(OCH_3)_2$	$C_{30}H_{27}NO_3S$	481.777	61	157	74.85	5.66	2.97
10	4j	3,4,5-$(OCH_3)_2$	$C_{31}H_{29}NO_4S$	5711.803	69	154	72.80	5.85	2.72

Table 2: Comparison of Thiazepine Derivatives against Standard Drugs

Organism	Compound	Ampicillin	Gentamycin
S.aureus	3-Br	✓	-
B. megaterium	3-Br	✓	✓
E.coli	2-NO_2	-	✓
P. vulgaris	3-Br	✓	✓

IR Spectral Studies

Table 3: I.R. (cm^{-1}) (KBr) spectral data of compound

No.	Code	R	Ar-NO_2	Ar-O-Ar	C=N	-C-R
1	4a	H	1357	1267	1625	-
2	4b	4-OCH_3	1355	1264	1623	2834
3	4c	2-OCH_3	1353	1268	1626	2835
4	4d	2-OH	1356	1262	1612	3442
5	4e	2-Cl	1358	1223	1615	676
6	4f	4-Cl	1344	1266	1623	677
7	4g	2-NO_2	1367	1267	1616	1321
8	4h	3-Br	1358	1254	1612	618
9	4i	3,4-$(OCH_3)_2$	1344	1267	1627	2829
10	4j	3,4,5-$(OCH_3)_2$	1360	1254	1622	2833

1H N.M.R. Spectral Studies

Table 4: 1H N.M.R. ($CDCl_3$) spectral data of compound

No.	Code	R	Chemical Shift (δ ppm)		
			Ar-R	-CH_3	-CH (methylene of Thiazepine)
1	4a	H	6.7-8.7	2.61	2.31
2	4b	4-OCH_3	3.85	2.60	2.29
3	4c	2-OCH_3	3.87	2.62	2.24
4	4d	2-OH	5.30	2.63	2.34
5	4e	2-Cl	-	2.57	2.36
6	4f	4-Cl		2.55	2.25
7	4g	2-NO_2	-	2.64	2.31
8	4h	3-Br	-	2.61	2.4

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) Comparable to that of standard drugs Ampicillin and Gentamycin.

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REFERENCES

1. Prasad, Y. R., Rao, A. L., & Rambabu, R. (2008). Synthesis and antimicrobial activity of some chalcone derivatives. Journal of Chemistry, 5(3), 461-466.
2. Won, S. J., Liu, C. T., Tsao, L. T., Weng, J. R., Ko, H. H., Wang, J. P., & Lin, C. N. (2005). Synthetic chalcones as potential anti-inflammatory and cancer chemopreventive agents. European journal of medicinal chemistry, 40(1), 103-112.
3. Yu, D.C., Panfilova, L.V., & Boreko, E.I. (1982). Synthesis and antiviral activity of unsaturated ketones of thiopene series. *Pharm. Chem*, 16, 103-105.
4. Liu, X. L., Xu, Y. J., & Go, M. L. (2008). Functionalized chalcones with basic functionalities have antibacterial activity against drug sensitive Staphylococcus aureus. European journal of medicinal chemistry, 43(8), 1681-1687.
5. Ares, J. J., Outt, P. E., Randall, J. L., Johnston, J. N., Murray, P. D., O'Brien, L. M., & Ems, B. L. (1996). Synthesis and biological evaluation of flavonoids and related compounds as gastroprotective agents. Bioorganic & Medicinal Chemistry Letters, 6(8), 995-998.
6. Lahtchev, K. L., Batovska, D. I., Parushev, S. P., Ubiyvovk, V. M., & Sibirny, A. A. (2008). Antifungal activity of chalcones: a mechanistic study using various yeast strains. European journal of medicinal chemistry, 43(10), 2220-2228.
7. Rao, Y. K., Fang, S. H., & Tzeng, Y. M. (2009). Synthesis and biological evaluation of 3′, 4′, 5′-trimethoxychalcone analogues as inhibitors of nitric oxide production and tumor cell proliferation. Bioorganic & medicinal chemistry, 17(23), 7909-7914.
8. Ram, V. J., Saxena, A. S., Srivastava, S., & Chandra, S. (2000). Oxygenated chalcones and bischalcones as potential antimalarial agents. Bioorganic & medicinal chemistry letters, 10(19), 2159-2161.
9. Patel, R.N., Patel, P.V., Desai, K.R., Purohit, P.Y., Nimavat K.S., & Vyas, K.B. (2012). Synthesis of new heterocyclic Schiff base, thiazolidinone and azetidinone compounds and their antibacterial activity and anti –hiv activities, *Heteroletters*, 2(1), 99-105.
10. Papo, N., Shai, Y. (2003). A novel lytic peptide composed of dl-amino acids selectively kills cancer cells. *Peptides*, 24, 1693 -1703.

