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Synthesis and Biological Evaluation of N-(Substituted Cinnamoyl)-Piperazine Derivatives

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Abstract:

Cinnamamides and their derivatives have verities of applications in medicinal as well as pharmaceutical fields. Large numbers of Cinnamamides derivatives were extracted from plants and many of them are prepared in laboratory by different routes. In the content different piperazine derivatives of cinnamamides were synthesized by convenient Wittig reaction pathway by using Wittig reagent with piperazine heterocyclic moiety and different aromatic aldehydes. All the synthesized compounds were characterized by using IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral analysis. All synthesized Cinnamoyl piperazine derivatives undergoes biological evaluation shows remarkable result.

Keywords:- Biological evaluation, Piperazine, aromatic aldehydes, Cinnamamides.

Introduction:

Cinnamamides and its derivatives were reported to shows variety of applications in different fields, such as medicinal, pharmaceuticals[1], agricultural and many other fields. Cinnamamides and derivatives possess broad spectrum of physiological function and biological activities[2] and reported as Sedatives, nervous central system depressant[3], anticonvulsant, antiallergic, muscle relaxant, antioxidant[4], local anesthetic[5], Antimycobacterial[6], Cytotoxicity[7] and Antioxidant[8]. The N-Feruloyl piperazine derivatives showed cytotoxic activity towards cancer cells and they have significant DNA binding activity[9]. It also shows different activities in agricultural field such as their avian repellent[10], Anti-fungicidal, insecticidal and herbicidal activities[11]. Such vast and important literature survey encourages the author to undertake the present research work and the Wittig reaction is an important method for the synthesis of cimamamides. So by taking this fact in consideration, the aim of this research article was to synthesize some novel the series of (2E)-1-(peperazin-1-yl)-3-substituted phenylprop-2-en-1-one Cinnamamides derivatives from Wittig reagent with piperazine moiety and to carry out their biological evaluation towards antibacterial and antifungal activities. Synthesized compounds were characterized by elemental analysis and spectral studies.

Material And Method:

Synthesis of Wittig reagent containing piperazine moiety-

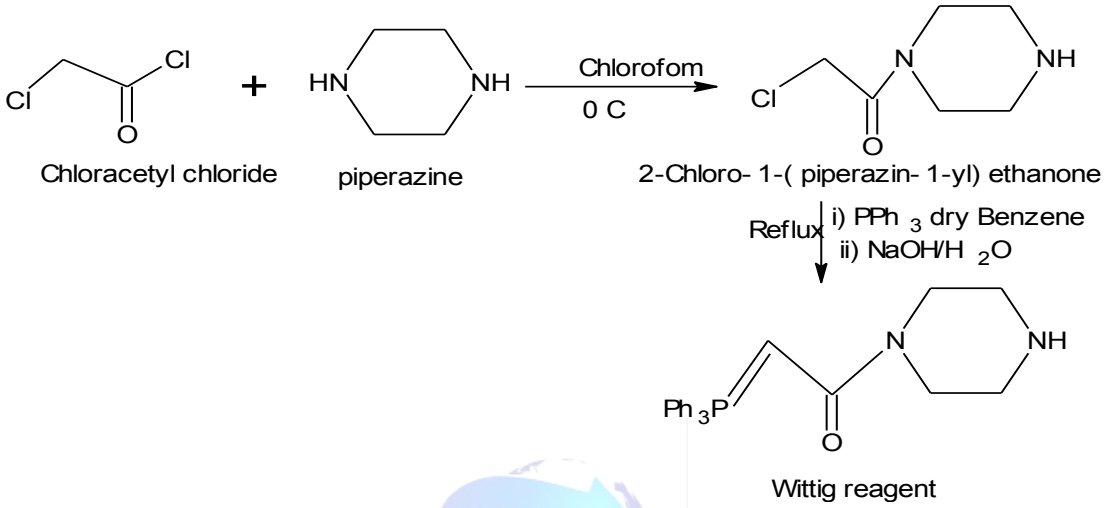
The equal molar concentration of solution of chloro-acetylchloride and piperazine in chloroform at 0^{o}C with continuous stirring in fuming chamber gives Piperazine chloracetamide. When this reaction mixture gives the salt by adding its solution in benzene to the stirred solution of triphenylphosphine and reaction mixture was refluxed for 4-6 hrs. The solid products obtained were filtered and air dried. Thus for purification obtained salt was dissolved in 100 ml water then 90 ml of dry benzene, add 1-2 drops of phenolphthalein indicator and add NaOH solution in it till pink colour persist this was indicates that the neutralization of present acid from reagent. Then

benzene layer was separated and washed with water and concentrated to one third volume. Finally the product scratched with n-hexane to obtain solid Wittig reagent.

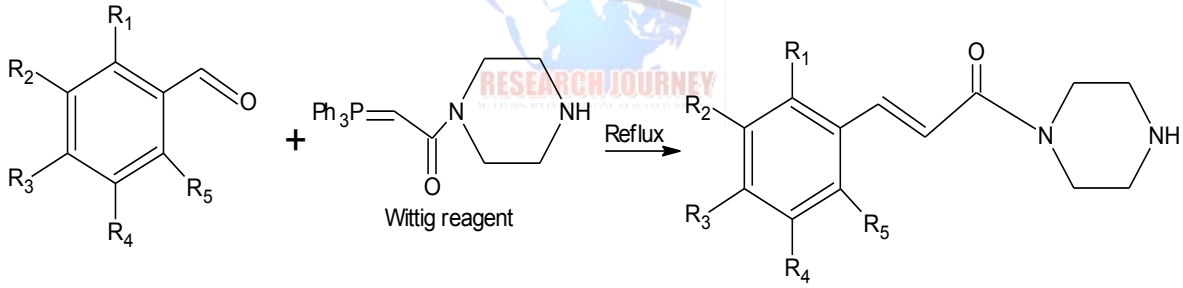
Synthesis of N-(substituted cinnamoyl)-Piperazine OR (2E)-1-(peperazin-1-yl)-3-Substituted phenylprop-2-en-1-one Cinnamamides –

Equimolar solution of Wittig reagent and different aromatic aldehydes were taken in dry benzene and refluxed for 4 to 6 hrs. The progress of reaction was monitored by thin layer chromatography. Melting points were taken by open capillary method. All Synthesized compounds were purified by column chromatography. Obtained compounds were characterized by elemental analysis and spectral studies. All chemicals used were of analytical grade.

Scheme-1



Scheme-2



(2E)- 1-(piperazine- 1-yl)-3-subtituted phenylprop- 2-en-1-one cinnamamides (Ia-Ij)

Table-1:-Substituted aromatic aldehydes used in the synthesis of Cinnamamides

Compounds	R1	R2	R3	R4	R5
Ia	H	H	H	H	H
Ib	H	H	OMe	H	H
Ic	H	OMe	OMe	H	H
Id	H	OMe	OMe	OMe	H
Ie	H	-O-CH_2-O-		H	H
If	NO_2	H	H	H	H
Ig	H	H	Cl	H	H
Ih	H	H	NO_2	H	H
Ii	H	H	$N(Me)_2$	H	H
Ij	H	H	OH	H	H

Table-2:- Characteristics data for synthesized Cinnamamides

Compounds	Molecular Formula	Mol. Weight	Yield %	M.P. ^{0}C
Ia	$C_{13}H_{16}N_2O$	216	72	90
Ib	$C_{14}H_{18}N_2O_2$	246	84	136
Ic	$C_{15}H_{20}N_2O_3$	276	82	181
Id	$C_{16}H_{22}N_2O_4$	306	74	229
Ie	$C_{14}H_{16}N_2O_3$	260	70	201
If	$C_{13}H_{15}N_3O_3$	261	68	248
Ig	$C_{13}H15ClN_2O$	251	62	132
Ih	$C_{13}H_{15}N_3O_3$	261	71	226
Ii	$C_{15}H_{21}N_3O$	259	74	158
Ij	$C_{13}H_{16}N_2O_2$	232	80	274

Spectral Data Studies- Spectral data information of representative synthesized compounds are as follows

Ia=(2E)-1-(peperazin-1-yl)-3- phenylprop-2-en-1-one Cinnamamides

^{1}H NMR (300 MHz, CDCl3) δ: 3.62-3.84 m 8H, 6.68 d (J= 15.2 Hz) 1H, 6.92d (J= 15.2 Hz) 1H, 7.36-7.56m 6H.

^{13}C NMR (75 MHz, CDCl3) δ: 175, 136, 139, 130, 129, 128, 126, 122, 52, 48;

IR (KBr, cm-1) :-3040, 1690, 1610; **MS** (ESI): 216.13(M^+).

Ib=(E)-3-(p-Methoxyphenyl)-1-(1-piperazinyl)-2-propen-1-one Cinnamamide

^{1}H NMR-(δ):-3.81(s), (3H); 6.9d, (2H); 7.4d, (2H); 6.7(d), (1H), (CH=CHCO), J=15.8HZ; 7.6d, (1H), (CH=CHC$_6$H$_5$) J=15.8HZ; 7.2(d), (2H); 7.4(d), (2H).

^{13}C NMR (δ ppm):166, 159, 136, 128, 114, 114, 55, 45.

IR (cm^{-1}): 3070, 2925, 1475; **MS** (ESI): 246.14 (M^+).

Biological Evalution:

Antimicrobial Screening-

Antibacterial and antifungal activities of newly synthesized compounds (Ia-Ij) were carried out by using discs diffusion method. The solution of compounds was prepared in DMF solvent. Plates were incubated 18- 24hrs at 37^{0}C and zone of inhibition were measured in mm. Result have been incorporated in table, all synthesized compound were found to be moderately active against bacteria and fungi.

Table No. 3- Antibacterial activities of the compounds (in mm)

Compounds →	**Ia**	**Ib**	**Ic**	**Id**	**Ie**	**If**	**Ig**	**Ih**	**Ii**	**Ij**
Bacterial strain ↓	Zone of Inhibition in mm ← →									
E. coli	08	08	10	12	NI	11	10	11	10	11
S. aureus	12	NI	08	08	08	09	NI	10	NI	12
S. typi	13	08	08	16	10	10	NI	12	07	10
B. pumilis	09	06	07	NI	08	12	09	10	NI	12
P. vulgaris	13	10	09	08	07	08	11	08	10	NI

NI-Inactive (No Zone of Inhibition)

Table No. 4 Antifungal activities of the compounds (in mm)

Compounds →	**Ia**	**Ib**	**Ic**	**Id**	**Ie**	**If**	**Ig**	**Ih**	**Ii**	**Ij**
Bacterial strain ↓	Zone of Inhibition in mm ← →									
Apergilius	10	08	09	08	NI	10	06	08	09	07

niger										
Apergilius fumigate	NI	10	12	08	11	08	NI	06	07	14
Rhizopus	08	NI	08	10	12	08	09	06	NI	06
Cadida albicans	26	14	12	26	18	16	10	NI	10	NI
Neurospora crassa	10	08	06	NI	07	NI	08	10	06	10

NI-Inactive (No Zone of Inhibition)

Result And Discussion:

All synthesized novel cinnamamides compounds contained heterocyclic moiety in the form of Piperazine. The Wittig reaction is an important method for the synthesis of alkenes. By using this method novel cinnamamides containing heterocyclic moiety entitled (2E)-1-(Piperazin-1-yl)-3-substituted phenylprop-2-en-1-one Cinnamamides are synthesized from different aromatic aldehydes and Wittig reagents having good yields. The yields of synthesized compounds were ranging from 62 to 84%. Biological screening of synthesized compounds shows remarkable result. In antibacterial screening compounds Ia, Id, If, Ih, Ij shows high activity while other moderately active. In antifungal screening Ia, Ib, Id, If, Ij shows high activity while other moderately active. All synthesized compounds were characterized on the basis of melting point, elemental analysis, IR spectra, ^{1}HNMR, ^{13}CNMR and mass spectral analysis.

Conclusion:

The objective of the present study was to synthesize and Biological Evaluation of N-(substituted cinnamoyl)-Piperazine derivatives containing heterocyclic moiety piperazine by using Wittig reagent and different aromatic aldehydes in dry benzene viz. Wittig reaction. The results of synthesized compounds were ranging from 62 to 84%. On the basis of melting point, elemental analysis, IR spectra, ^{1}HNMR, ^{13}CNMR and mass spectral analysis the characterization and yield of synthesized compounds, it was proved that given method is very useful for synthesis of N-(substituted cinnamoyl)-piperazine derivatives. In the biological evaluation under the antibacterial and antifungal activity of synthesized compounds gave very good result, thus synthesized compounds have variety of application in different field.

References:

1. Gregory N. Beatch Cindy J. Longley, Michael J. Walker Richard A. Wall (2010).Patent No US7, 687, 536 B2, 1-36.
2. Han X. B., Feng H. J., Chen G. R., Li Y. C. (2003).Chin. J. Med. Chem.13, 334-355.
3. Fatima Velez-Gonzalez, David Ortegon-Reyna, Angel A Ramos (2008). ARKIVOC (v), 55-64.
4. Pathan R.U. and Patil S. L. (2008). Oriental Journal of Chemistry, Vol. 24(2), 709-712.
5. Yumei Xiao Yang, BoLi Huizhu, Yuan Shuqing Wan, Yanjun Xu and Zhaohai Qin (2008). Molecules,16, 8945-8957.
6. Hsieh T. J, Chang F. R, Chia Y. C, Chen C. Y, Chiu H. F, Wu Y. C, J. (2001). Nat. Prod., 64, 616-619.
7. Simonyan A. V, (1999). Synthesis of cinnamic acid derivatives, Pharmaceutical Chem. J., 33, 158.
8. Brackman Gilles Celen, Shari Hillaert Ulrik, Calenbergh Serge Van, Paul Cos Maes,
9. Louis Nelis Hans, J Coenye Tom (2011). PlosOne, 6, 1,16084.
10. Kakwani Manoj D, Desai Palsule, Lele Arundhati C, Ray Muktikant, Rajan M G, (2011). Bioorganic & Medicinal Chemistry Letters, Vol. 21, 6523–6526.
11. Dhavale D D, Sindkhedkar M D, Mali R S (1995). J. Chem. Res., 414-415.

12. Simon Koma Okwute & Henry Omoregie Egharevba (2013). International Journal of Chemistry, Vol. 5, No. 3, 99-122.
13. Sharma, R. S., Rajalakshmi, M., Sharma, R. S., & Jeyaraj, D. A. (2001). Current Status of Fertility Control Methods in India. J. Biosc., 26, 4, 391-405.
14. Negoro, K., Yonetoku, Y., Maruyama, T., Yoshida, S., Takeuchi, M., Ohta, M. (2012). Bioorg. & Med. Chem., 20, 2369.
15. Ramirez, E.; Sánchez, M.; Rosa L.; Leon, M.; Quintero, L.; Sartillo-Piscil, F.; (2010).Tetrahedron Letters, 51, 2178.
16. Bryzgalov, A. O.; Dolgikh, M. P.; Sorokina, I. V.; Tolstikova, T. G.; Sedova, V. F.; Shkurko, O. P. (2006). Bioorg. Med. Chem. Lett., 16, 1418.
17. De, P.; Koumba, Yoya; G., Constant P.; Bedos-Belval, F.; Duran, H.; et al. Design, synthesis, and biological evaluation of new cinnamic derivatives as antituberculosis agents. J Med Chem. 54 (2011): 1449-1461.
18. Narasimhan, B.; Belsare, D.; Pharande, D.; Mourya, V.; Dhake, A. Esters, amides and substituted derivatives of cinnamic acid: synthesis, antimicrobial activity and QSAR investigations. Eur J Med Chem. 39 (2004): 827-834.