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PC-Model Studies of 7 methoxy- 2H-3-Aryl-3, 4-dihydro-1,3 benzoxazine-Aryl-3, 4-dihydro-4-methyl 7 methoxy -1, 3 benzoxazine Biological activity

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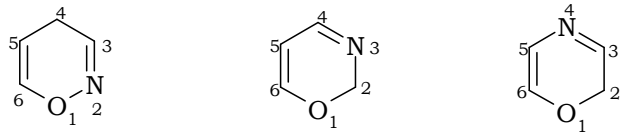
Abstract

An optimization of the reaction conditions in solvent free and solution phase microwave assisted synthesis of (7 Methoxy) 2H-3-Aryl-3, 4-dihydro-1,3 benzoxazine derivatives.The reported methods for the synthesis of substituted benzoxazine derivatives. 2-Hydroxy3-methoxy benzaldehyde and 1-(2-Hydroxyphenyl) ethanol on the reaction with different primary aromatic amines gave methoxy 2-(arylimino) methylphenols and 2-[1-arylimino) ethyl] phenols respectively Synthesized Compound (1). on reduction with sodium borohydride gave 2- methoxy (arylamino) methylphenols and 2- [1-(aryl amino) ethyl] phenols, Synthesized Compound (2). Which further cyclised with formaldehyde to form the final synthetic derivatives as methoxy 2H-3-aryl-3, 4-dihydro-1, 3-benzoxazines and 2H-3-aryl-3, 4-dihydro-4 methyl- 1,3-methoxy benzoxazines. PC-model values, antimicrobial and antifungal activity studies.

Keywords: Azoles, oxazoles, isoxazole, benzoxazines, heterocyclic.

Introduction

One of the most important features in methoxy 1,3 benzoxazines chemistry is that they used as may be starting materials for further transformations. With the aim of extending information on the reactivity of methoxy 1,3 benzoxazine and also synthesizing from them the bioactive new heterocyclic[1-3] derivatives. The methoxy 1, 3-benzoxazine structure has fascinated due to its wide range of biological and chemical properties[3-5]. Methoxy 1, 3-benzoxazine nucleus is present in a large number of pharmacologically active molecules[6]. Calcium channel antagonists, central nervous system drugs, analgesics and others. Moreover, disubstituted-methoxy1, 3-benzoxazines constitute an interesting group[7], which could find important application as intermediates in several synthetic pathways directed towards the preparation of bioactive polycyclic hetero systems. Unfortunately, these applications have not been rigorously studied[8-9], and only a few synthetic methods are available for their preparations. In the course of research directed towards the synthesis of new therapeutic related to natural products, several polycyclic compounds containing the methoxy1,3-benzodioxine derivatives have been prepared, but the analogous 2,3-disubstituted-1,3-benzoxazine has not yet been described[10-11]. As part of this we investigated the synthesis[12-14] 2, 3-disubstituted-1,3-benzoxazines which could be used as key intermediate in the synthesis of other polycyclic heterocyclic compounds[15]. According to position of oxygen and nitrogen atoms in the ring[16], three kinds of oxazines [I-III] are possible which are 1,2-oxazine, 1,3-oxazine and 1,4-oxazine.

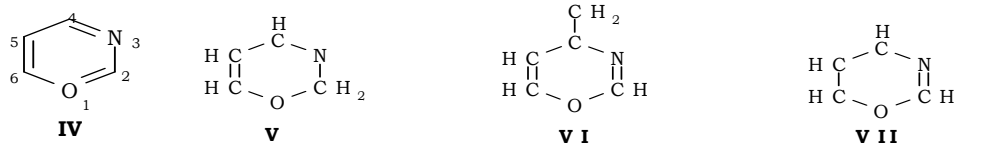


I **II** **III**

1,2-oxazine 1,3-oxazine 1,4-oxazine

Scheme-1

Due to the divalency of oxygen, only two double, bonds are present in the. oxazines and an extra hydrogen atom to be disposed of[17], which may be attached to carbon in a methylene group or to nitrogen in an amino group consequently isomeric form of each kind of oxazine are possible. In 1, 3-oxazines [IV] two hetero atoms one oxygen and one nitrogen atoms lie in 1,3-position in the six membered ring of 4 carbon atoms[18]. 1,3-oxazine derivatives with two double bonds can exist in three isomeric forms [V-VII].

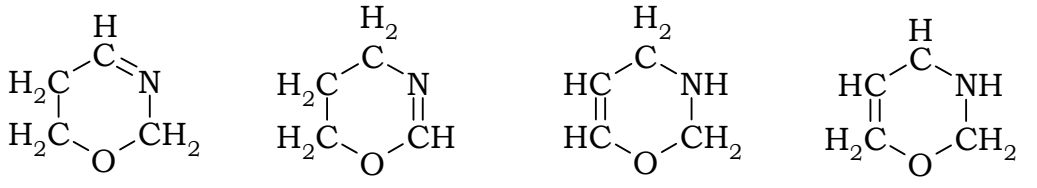


IV **V** **V I** **V II**

1,3-oxazine 1,3-2H-oxazine 1,3-4H-oxazine 1,3-6H-oxazine

Scheme-2

Of these isomes only 1, 3-4H oxazine are well known which were first obtained by Wohl in 1901. General method for the preparation of 1,3-4H-oxazines was given by Gabriel Karrer and Miyamichi . The compounds having one double bend are known as dihydro compounds of 1,3-oxazines[19]. The structures (VIII-XI) of the possible are give in shceme-3.

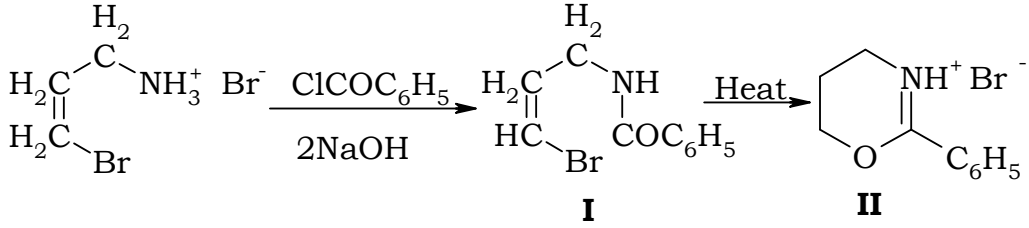


VIII **IX** **X** **XI**

5,6-dihydro-1,3-2H-oxazine | 5,6-dihydro-1,3-4H-oxazine | 3,4-dihydro-1,3-2H-oxazine | 2,3-dihydro-1,3-6H-oxazine

Scheme-3

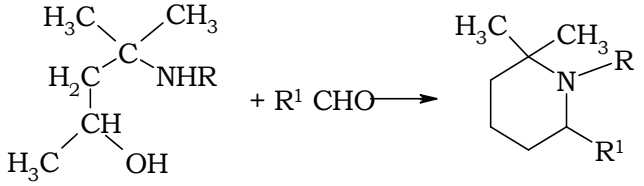
Among the 5, 6-dihydro-1,3-4H-oxazines are well known 1,3-oxazines, first it was obtained by Gabrial and Elfeldt . In 1891 by benzoylation of y-bromopropul amine forms as an intermediate product (I), which on heating gives 5,6-dihydro-1,3-4H-oxazines hydro-bromide scheme-4.



I **II**

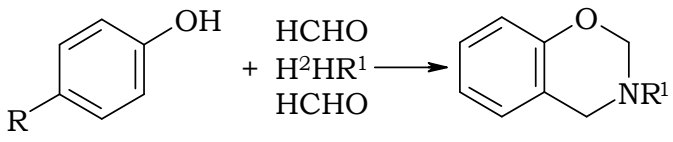
Scheme-4

The fully saturated ring is tetra hydro 1,3-oxazine. This method for their preparation was described by Kohn . It can be obtained by cyclizing 3-amino propan-1-ol derivatives with aldehyde[20] Scheme-5.



Scheme-5

Later number of authors obtained these derivatives in similar way wing both aldehyde and ketone as cyclizing agents .Earlier Kohler, Bruee Hicks and Fischer. Reported the method for preparation of benzo derivative of 1, 3-oxazine. Dihydro derivatives of 1, 3-benzoxazine can be prepared .By the reaction of p-sub situated phenols with formaldehyde (2 moles) and primary aliphatic amines (1 mole) scheme-6.

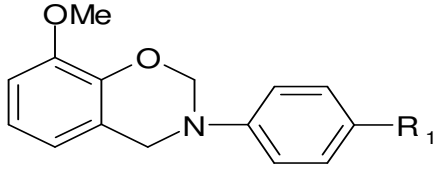


Scheme-6

The dihydro derivatives are more stable then the 1,3-benzoxazines themselves towards hydrolyzing agents.The 1,3-oxazines lack. The stability of the oxazoles and are readily hydrolyzed by dilute acid in the presence of dilute acid (preferably methanolic or ethanolic). The tetra hydro derivatives of 1,3-oxazines can readily by hydrolyzed with ring opening . Stability of 1,3-oxazine varies oxazines prepared by cyclization using aliphatic aldehydes are more stable then those formed from aromatic aldehydes. Besides some other method. These compounds can also be prepared by mannich reaction of a primary amine with the appropriate phenol (i.e. salicylaldehyde and (2-hydroxy-3-methoxy benzaldehyde) in presence of an excess of formaldehyde

Materials and Methods

Molecular structures of 7 Methoxy-1,3-benzoxazine derivatives.



Scheme-7

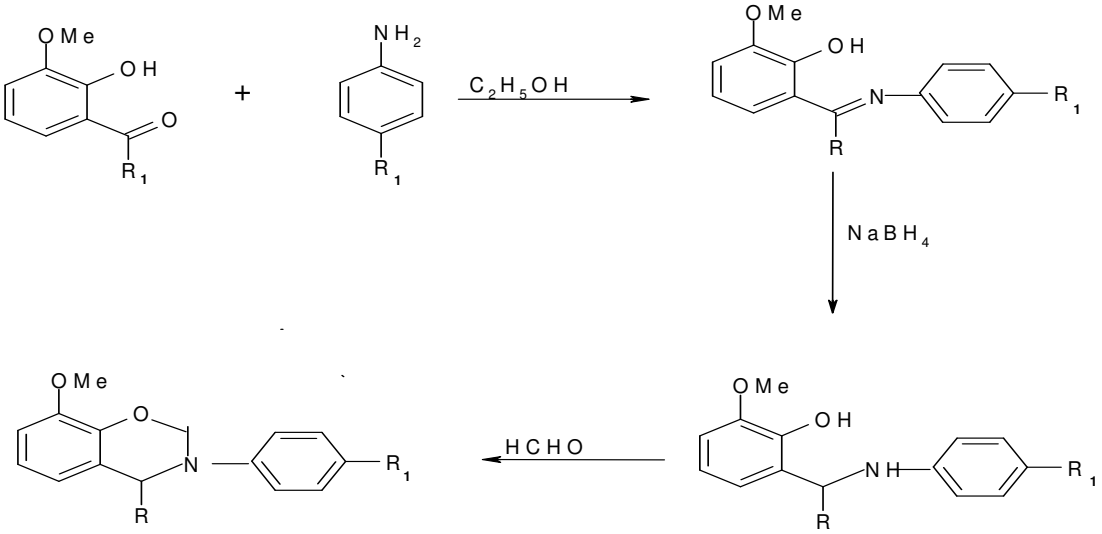
Step-1. Synthesis of 2- (Arylimino-methoxy)-Methyl Phenol. A mixture of 2-Hydroxy 7-methoxy benzaldehyde 2.67 gm (0.03mole) and appropriate aromatic amine (0.05 mole) in

ethanol (30ml) was refluxed on water bath for 30 min. crystalline residue was obtained on cooling the reaction mixture. The product was dried and crystallized from chloroform-petrol (1:4v/v] to furnish 2-(arylimino) methyl phenol. The amines taken are 1 = o-chloro-aniline, 2 = m-chloro-aniline, 3 = p-chloro-aniline, 4 = o-nitro aniline, 5= m-nitro-aniline, 6 = p-nitro-aniline, 7 = o,m-di-nitro-aniline, 8 = p-bromo- aniline. Studies.

Step - 2.Synthesis of 2-(Arylimino-methoxy)-Methyl Phenol: Sodium borohydride (0.5gm) was added to a solution of 2-(aryl aminomethoxy) methyl phenol (0.05mole) in methanol and the mixture was stirred for 30 minute at room temperature. The mixture was then poured in to ice cold water. The compound separated, was filtered off and crystallized from ethanol to yield (2-arylamino-methoxy)-methyl phenol.

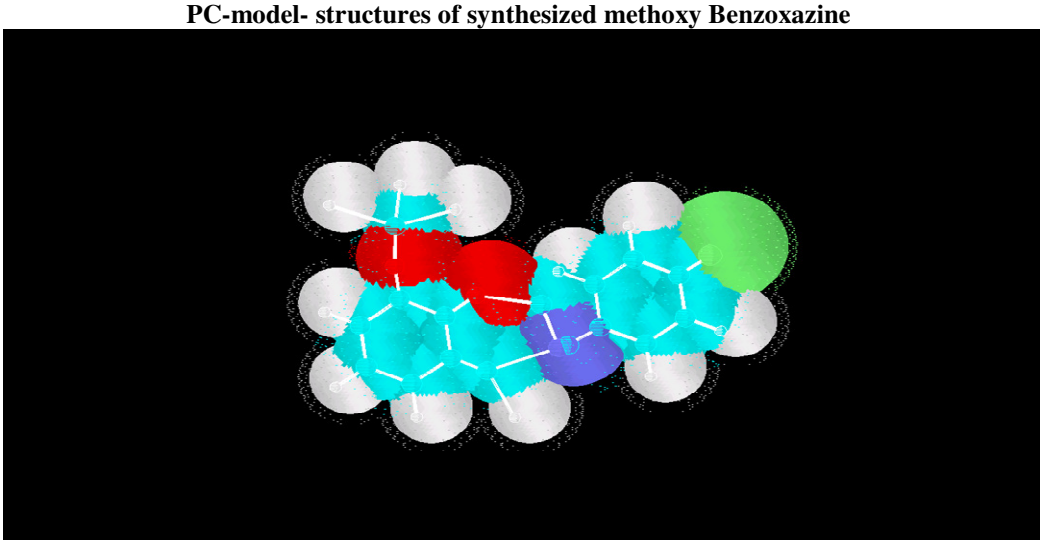
Step-3.Synthesis of 7 methoxy 2H-3-(aryl)-3,4-Dihydro1, 3benzoxazine. The reaction mixture 2-(aryl amino) methyl phenol (0.05mole) and formalin 37 % (1ml) were refluxed in ethanol (20ml) for 6 hrs. The product separated out after pouring the reaction mixture in to ice cold water and then filtered and crystallized from ethanol to yield methoxy 2H -3 –(aryl) -3, 4 –dihydro -1, 3 –benzoxazines.

Reaction III



Scheme-8

PC-model- structures of synthesized methoxy Benzoxazine



METHOXY BENZOXAZINE

Figure-1

Methodology

Melting points were determined in open capillaries on a Campbell apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer and ^{1}HNMR spectra on a Bruker 80 MHz instrument (CDRI, Lucknow). The Biological activity were recorded on Department of Botany Dr.H.S.Gour University sagar m.p.India Elemental analysis was found satisfactory for the synthesized heterocyclic derivatives Physical data of the compounds are given in Table.

Table-1
Physical data of the Compounds Methoxy Benzoxazine

Compd. No.	R	R_1	Mol. For.	M.P. (°C)	Yield %
Mebenzx.-1	H	*o*- Chloro phenyl	$C_{14}H_{12}NOCl$	135	84
Mebenzx.-2	H	m-Chloro phenyl	$C_{14}H_{12}NOCl$	125	62
Mebenzx.-3	H	*p*-chloro phenyl	$C_{14}H_{12}NOCl$	119	78
Mebenzx.-4	H	*o*- nitro phenyl	$C_{14}H_{12}N_2O_3$	101	96
Mebenzx.-5	H	m-nitro phenyl	$C_{14}H_{12}N_2O_3$	114	95
Mebenzx.-6	H	*P -nitro* phenyl	$C_{14}H_{12}N_2O_3$	145	82
Mebenzx.-7	H	*o,p-dinitro*phenyl	$C_{14}H_{12}N_2O_3$	131	73
Mebenzx.-8	H	p-BromoPhenyl	$C_{14}H_{12}N_2O_3$	132	87

Table-2
Characterization of IR data:

Group type	Vibration mode	Frequency (cm^{-1})
Oxazine ring	-CH (str.) in–OCH_2	2916.51
	-CH (str.) in –NCH_2	2840.14
	-C-N (str.) in –NCH_2	1268.54
	C-O(str.) in –OCH_2	1048.85
	-CH (bend.) in–OCH_2	1511.26
	-CH (bend.) in –NCH_2	1459.42
Aromatic ring	-CH (str.)	3038.55,3008.19
	C=C (str.)	1612.75
	-CH (bend.)	1014.45
Ar-OCH_3	C-H(str.) in-OCH_3	2878.46
	C-O (str.) in Ar-OCH_3	1160.57
Ar-Cl	C-Cl(str.) in Ar-Cl	764.98

Table-3
Characterization of H^1 NMR data

Signal No.	Chemical shift (in δ ppm)	Multiplicity	Relative no. of protons	Inference
1.	7.18-7.84	Multiplet	7	Ar-H
2.	4.65	Singlet	2	-OCH_2 of Benzoxazine ring
3.	3.62	Singlet	2	-NCH_2 of Benzoxazine ring
4.	3.91	Singlet	3	-OCH_3 of Ar-OCH_3

Table-4
PC-model Methoxy benzoxazine derivatives Computational studies

Compound Code	Position	Substituent	B.L. C-N	B.A N-C.	Dihedral Angle C-N-C	Mol. Volu.	VDW	Dip.Mom
Mebenzx.-1	12	2 – Cl	1.460	120.67	162.37	276	8.03	4.197
Mebenzx.-2	13	3 – Cl	1.463	121.02	165.39	276	2.11	26.18
Mebenzx.-3	14	4 – Cl	1.463	121.02	166.70	276	10.30	2.479
Mebenzx.-4	12	2-NO_2	1.462	120.13	178.47	286	517.4	2.312
Mebenzx.-5	13	3-NO_2	1.463	121.05	173.00	286	11.36	1.895
Mebenzx.-6	14	4-NO_2	1.463	120.85	165.95	286	29.96	1.736
Mebenzx.-7	12,14	2,4-diNO_2	1.458	120.63	167.10	331	10.51	1.512
Mebenzx.-8	14	4 – Br	1.461	121.16	167.76	323	10.74	1.089

2H-3-(4'-Chlorophenyl)-3,4-dihydro-7-methoxy 1,3- Benzoxazine

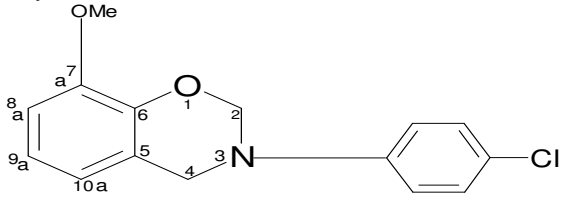


Table-5
Z-Matrix Parameters for Methoxy benzoxazine as Otained from PC Model

1	C	0.000000	0	0.000000	0	0.000000	0	0
2	C	1.400824	1	0.000000	0	0.000000	0	100
3	C	1.399224	1	120.00851	1	0.000000	0	210
4	C	1.400651	1	119.98815	1	0.000000	1	321
5	C	1.399190	1	120.02097	1	0.000000	1	432
6	C	1.400846	1	119.98487	1	0.000000	1	543
7	C	1.103117	1	120.01196	1	-180.000000	1	543
8	O	1.103109	1	119.99234	1	-180.000000	1	654
9	N	1.256615	1	117.43054	1	180.000000	1	754
10	C	1.315405	1	123.19303	1	0.000000	1	865
11	C	2.958650	1	178.23798	1	180.000000	1	975
12	C	1.400825	1	179.19838	1	0.000000	1	1197
13	C	1.399224	1	59.189850	0	1.000000	1	1197
14	C	1.400648	1	119.988388	1	180.000000	1	13119
15	C	1.399191	1	120.02084	1	0.000000	1	141311
1	C	1.400847	1	119.98483	1	.000000	1	151413
17	O	1.103109	1	119.99925	1	180.000000	1	123
18	C	1.154033	1	174.93384	1	-180.000000	1	1712
19	H	1.099999	1	119.93913	1	-180.000000	1	231
20	H	1.100001	1	119.95537	1	-180.000000	1	321
21	H	1.099999	1	120.04121	1	180.000000	1	432
22	H	1.110107	1	105.0081	1	55.221573	1	754
23	H	1.110107	1	105.0081	1	-55.221626	1	754
24	H	1.110107	1	111.36355	1	-121.58308	1	1086
25	H	1.110108	1	111.36356	1	121.58315	1	1086
25	H	1.109929	1	109.99899	1	180.000000	1	18171
26	H	1.109878	1	110.00001	1	59.998241	1	18171
27	H	1.109878	1	109.99994	1	-59.998177	1	18171
28	H	2.578174	1	95.96003	1	160.07054	1	12119
29	H	1.100000	1	119.955322	1	0.000000	1	13119
30	H	1.100000	1	120.041214	1	-180.000000	1	141311
31	H	1.100001	1	119.948929	1	180.000000	1	151413
32	Cl	1.100000	1	120.052704	1	-180.000000	1	161514

precisegnorm=0.01 Mebenz.2

Table-6
Antibacterial activityof Methoxy Benzoxazine-derivatives antibacterial activity zones of inhibition (mm)

Compound code	*E. coli*		*Bacillus subtalis*		*Pseudomonas alcaligens*		*Salmonella* sp.	
	2%	4%	2%	4%	2%	4%	2%	4%
Mebenz.1	10	11	11	14	8	10	12	13
Mebenz.2	8	10	12	15	10	13	9	11
Mebenz.3	9	12	8	10	11	12	10	12
Mebenz.4	12	12	15	18	12	15	14	16
Mebenz.5	12	13	10	11	13	15	12	14
Mebenz.6	10	12	13	12	11	14	8	10
Mebenz.7	11	12	13	14	13	14	9	10
Mebenz.8	12	16	16	19	10	13	13	11
Standard drug	15	18	16	19	14	16	14	13

Table-7
Antifungal activity of Methoxy Benzoxazine Antifungal activity zones of inhibition (mm)

Compound code	*Penicillium citrinum*		*Aspergillus flavus*		*Rhizoctonia bataticola*		*Aspergillus niger*	
	2%	4%	2%	4%	2%	4%	2%	4%
Mebenz.1	11	13	13	15	9	11	12	15
Mebenz.2	12	11	10	15	12	16	10	13
Mebenz.3	17	20	15	18	17	20	14	17
Mebenz.4	10	12	19	13	12	15	12	14
Mebenz.5	19	15	14	19	13	12	18	12
Mebenz.6	10	11	12	14	10	13	12	15
Mebenz.7	9	14	10	10	13	17	10	14
Mebenz.8	10	12	10	15	13	14	12	13
Standard drug	15	20	16	19	17	22	18	21

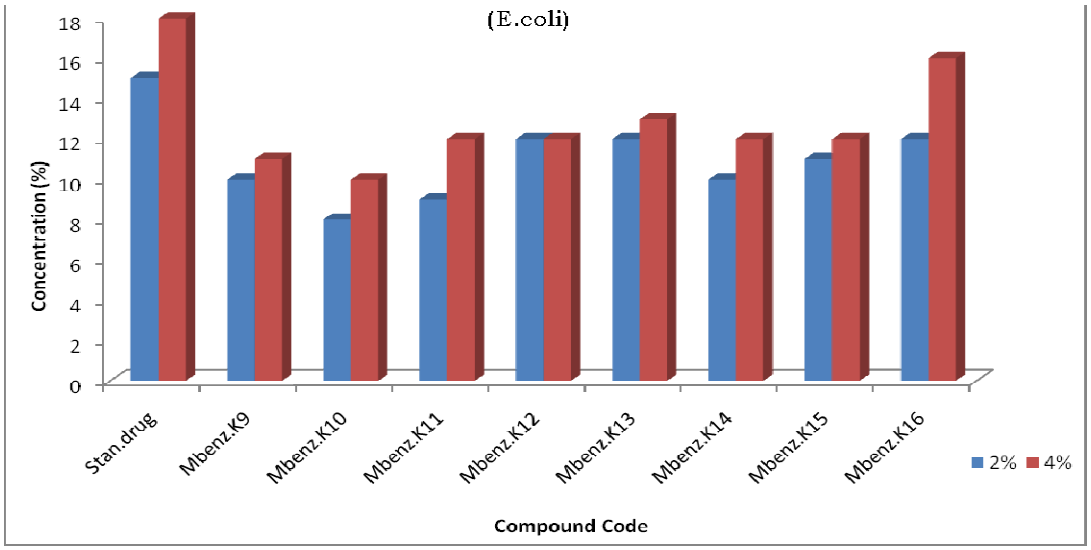


Figure-2
Antibacterial activity of methoxy benzoxazine derivatives

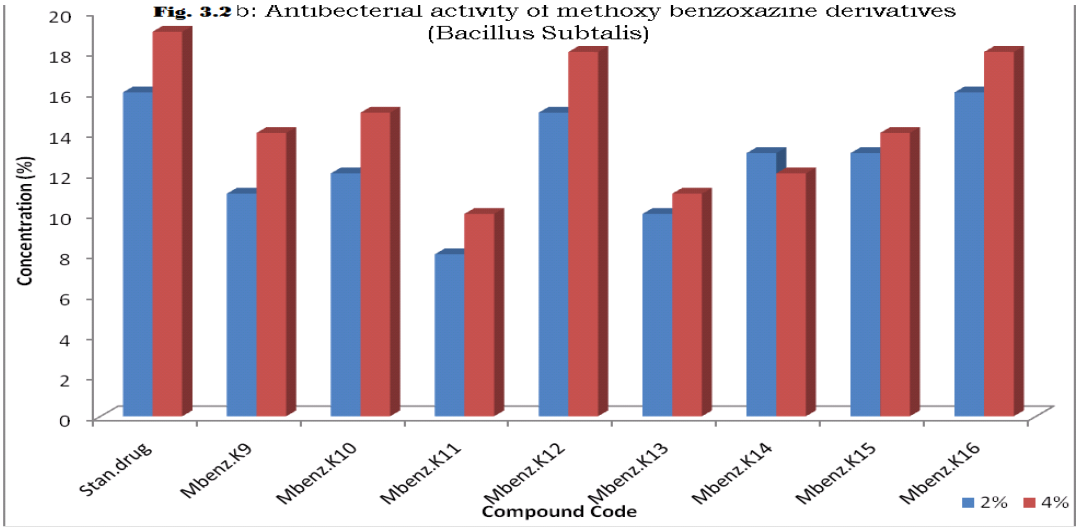


Figure-3
Antibacterial activity of methoxy benzoxazine derivatives

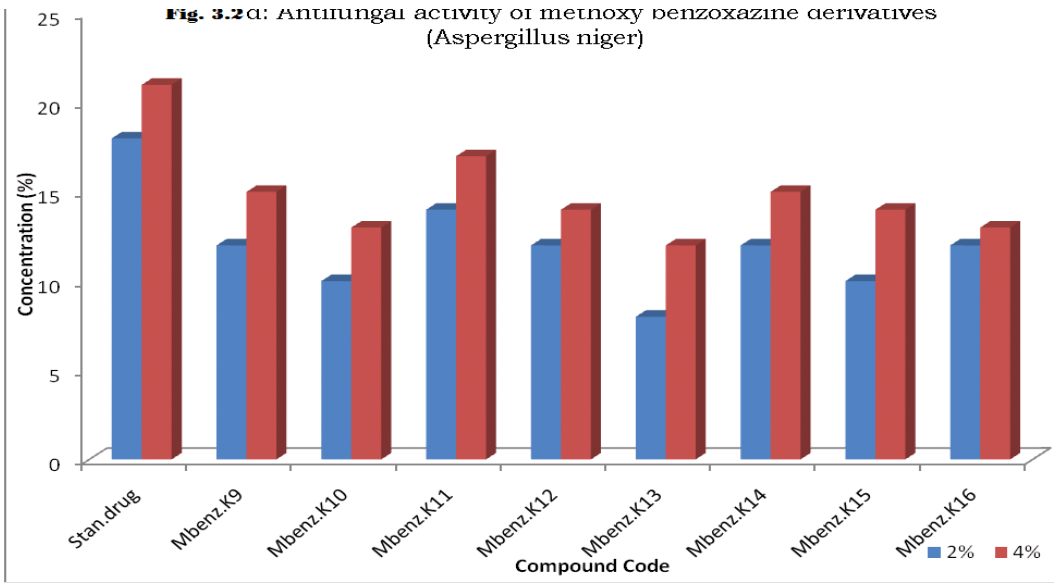


Figure-4
Antibacterial activity of methoxy benzoxazine derivatives

Table-8
Antibacterial activity of methoxy benzoxazine variation with Dipole moment values

Comp. code	Dip. Mom	*E. coli*		*Klebsiella pneumo-niae*		*Pseudo-monas alcaligens*		*Salmonella* sp.	
		2%	4%	2%	4%	2%	4%	2%	4%
Mebenzx.1	1.089	10	12	13	16	11	14	8	10
Mebenzx.2	1.512	11	12	13	14	13	14	9	10
Mebenzx.3	1.735	8	10	12	15	10	13	9	11
Mebenzx.4	1.895	10	11	11	14	8	10	12	13
Mebenzx.5	2.312	12	13	10	11	13	15	12	14
Mebenzx.6	2.479	14	17	15	18	12	15	14	16
Mebenzx.7	2.618	9	12	8	10	11	12	10	12
Mebenzx.8	4.197	12	16	16	19	10	13	13	16

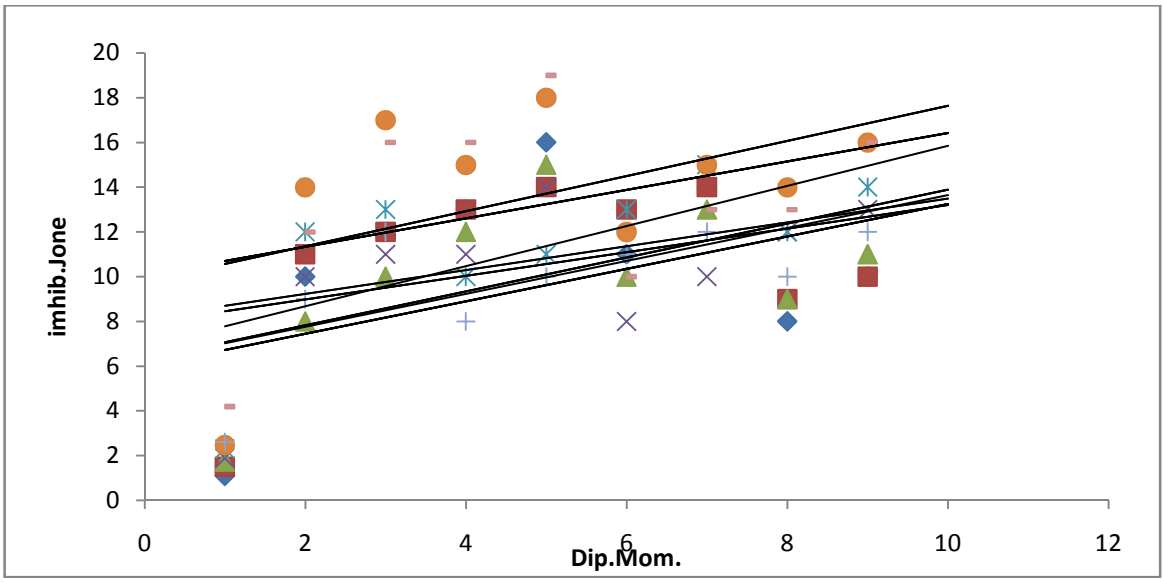


Figure-5

Table-9
Antifungal activity of methoxy benzoxazine variation withDipole moment values

Compound code	Dip. Mom	*Penicillium citrinum*		*Aspergillus flavus*		*Rhizoctonia bataticola*		*Aspergillus niger*	
		2%	4%	2%	4%	2%	4%	2%	4%
Mebenz.1	1.089	11	13	13	15	11	13	13	15
Mebenz.2	1.512	9	11	10	15	9	11	10	15
Mebenz.3	1.735	17	20	15	18	17	20	15	18
Mebenz.4	1.895	10	12	9	13	10	12	9	13
Mebenz.5	2.312	9	10	14	10	9	10	14	10
Mebenz.6	2.479	10	11	12	14	10	11	12	14
Mebenz.7	2.618	9	14	10	10	9	14	10	10
Mebenz.8	4.197	10	12	10	15	10	12	10	15

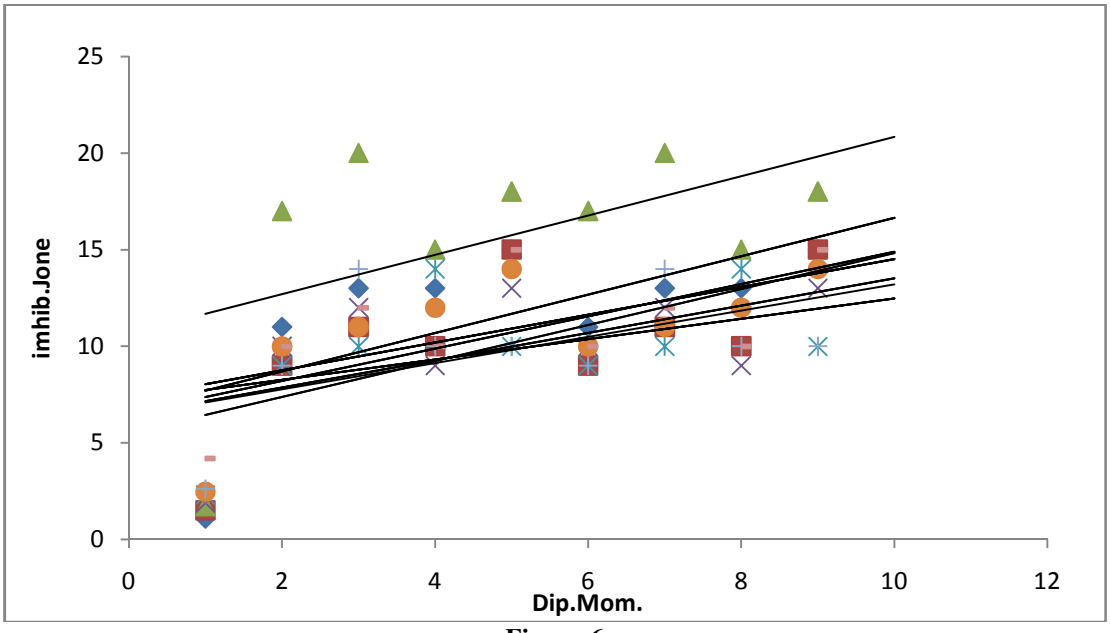


Figure-6

Results and Discussion

We report the formation of methoxy 1, 3-benzoxazine derivatives which indicate that the new approach enables the synthesis of 2, 3-disubstituted-1,-3 benzoxazines as the lactone 10, considered on useful intermediate preparation of new polycyclic systems. Directed *ortho*-lithiation of protected benzoxazines allows facile go for 2, 3-disubstituted methoxy 1, 3-benzoxazines. Moreover, the removal of the *N*-protecting group in the alkylation provides the unprotected methoxy 1, 3-benzoxazines as central scaffolds for designed pharmaceutical compounds.

Conclusion

The dihydro derivatives are more stable then the 1,3-benzoxazines themselves towards hydrolyzing agents. The 1,3-oxazines lack. The stability of the oxazoles and are readily hydrolyzed by dilute acid in the presence of dilute acid (preferably methanolic or ethanolic). The tetra hydro derivatives of 1,3-oxazines can readily by hydrolyzed with ring opening .Stability of 1,3-oxazine varies oxazines prepared by cyclization using aliphatic aldehydes are more stable then those formed from aromatic aldehydes.The compounds of 7 methoxy 1,3-benzoxazine pharmaceutical compounds which indicate that the new approach enables the synthesis of 2, 3-disubstituted-1,-3 benzoxazines as the lactone 10, considered on useful intermediate preparation of new polycyclic systems.

Acknowledgement

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References

1. Shakya S., Verma N. and Gupta A., *J. Med. Chem.* **52,** 5793 **(2009)**

2. Ashok S., Holla B.S. and Kumari N.S., *Eur. J. Med. Chem.* **42,** 380 **(2007)**

3. Harikrishna S. and Limaye S.N, *J. Inst. Chemist* India, **78,** 81**(2006)**

4. Katrizky A.R., Singh S.K, Cai C. and Bobrov S, *J. Org. Chem.* **71,** 3364 **(2006)**

5. Hansen B. S., Begtrup M. and Ankersen M., *Bioorg. Med. Chem. Lett* ., **14**, 17 **(2004)**

6. Achatzb S. and Domling A., *Bioorg. Med. Chem. Lett,* **16,** 6360 **(2006)**

7. Fadda A., Bondock A., Rabie R. and Etman H.A. *Turk. J. Chem*. **32,** 259 **(2008)**

8. Kazemizadeh R. and Ramazani N., *AARKIVOC,* **22,** 360 **(2002)**

9. Ferenczi R., and Dinya Z. Antus, *Heterocyclic Comp.,* **11,** 491 **(2005)**

10. Maiti B., Chanda K. and Sun C., *M. Org. Lett*., **11,** 4826 **(2009)**

11. Tuccinardi T., Calderone V., *Curr. Med.* **14,** 3105 **(2007)**

12. Kadi A. and Al-Deeb O.A., *Eur.J.Med.* **42,** 235 **(2007)**

13. Ates-Alagoz Z., Yildiz S. and.Buyukbingol E., *Chemotherapy,* **53,** 110 **(2007)**

14. Dyachenko V., Dyachenko V.D. and Rusanov B.E., *Russ. J. Org. Chem*., **43**, 83 **(2007)**

15. Shakya S., Verma N. and Gupta A., *J. Med. Chem.* **52**, 5793 **(2009)**

16. Mistry R.N. and Desai K.R., *Eur J Chem,* **2(6),** 30 **(2005)**

17. Indorkar D., Limaye N. and Chourasia O.P., *Asian J.of Res.chem*., **5(9),** 1059 **(2012)**

18. Tawab S., Mustafa A. and Kira M., *Nature,* **186**, 165 **(1960)**

19. Tuchilus A., Florescu C. and Mangalagiu M.I., *J. Heterocycl. Chem.,* **44,** 1149 **(2007)**

20. Moisan A., Rebek L., J. Jr. *Org. Lett.*, ***9*,** 3733 **(2007)**

21. Rimaz M., Khalafy J. and Noroozi Pesyan N., *Aust. J. Chem.,* **63**, 507 **(2010)**