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SYNTHESIS AND PHYSICO-CHEMICAL CHARACTERIZATION OF SOME NOVEL OXAZINE DERIVATIVES

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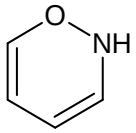
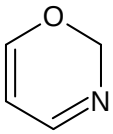
ABSTRACT
Series of oxazepine derivatives were synthesized from Schiff's base as aldehyde derivatives by using semicarbazide as starting material. Then equimolar quantities of prepared Schiff's base reacts with pthallic anhydride or succinic anhydride undergo cycloaddition reaction in the presence of organic solvent benzene give an oxazepine ring system. Chemical structures of the synthesized compounds were confirmed on the basis of their spectral data.[1] Oxazine derivatives are an important class of heterocyclic, which has attracted much synthetic interest due to their wide range of biological activities. Oxazine is a heterocyclic compounds can be formally derived from benzene and its reduction products, by suitable substitution of carbon (and hydrogen) atom by nitrogen and possess important biological activities like sedative, analgesic, antipyretic, anticonvulsant, anti tubercular, antitumor, antimalarial, and anti microbial.[2] Oxazines are heterocyclic compounds containing one nitrogen and one oxygen .There are three isomers exist depending on the relative position of the hetero atoms and relative position of the double bonds.1,2-,1,3-, and 1,4- are the o- analogue of the three isomeric diazines.When the oxygen and nitrogen atoms are present the name oxazine is used and the position of the atoms are indicated by numbers.[3]

KEYWORD: semicarbazide, equimolar, cycloaddition.

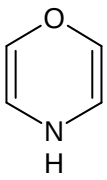
INTRODUCTION



2*H*-1,2-oxazine



2*H*-1,3-oxazine



4*H*-1,4-oxazine

Aromatic oxazines are first synthesized in 1944 by Holly and Cope through Mannich reactions. Comparatively little work has been done on simple derivative of these ring system and most of these concerns the reduced 1, 3 and 1, 4 compounds. The most important simple 1, 4-oxazine is morpholine or tetrahydro-1, 4-oxazine, which is a colorless liquid, which is miscible with water. Oxazine heterocyclics have special interest because they constitute an important class of natural and non natural products and show useful biological activities,and its increasing importance in pharmaceutical and biological field.[4]

SYNTHETIC METHODOLOGY

Preparation of chalcones

Take 0.01mol benzaldehyde & 0.01 mol acetophenone in 10 ml 95% ethanol in a flask .3.5 ml 6M NaOH solution was added to the reaction mixture stirr well for 10 minutes. Cool in ice bath until crystal formation.Recrystallise from ethanol.[5]

Cyclization step

The formed unstable chalcones were further cyclised with 0.015 mol of urea and sodium acetate 0.015mol in 25 ml ethanol was refluxed for 6 hrs.The mixture was concentrated and poured in to ice. The precipitate obtained was filtered washed and recrystallised from ethanol.

SCHEME

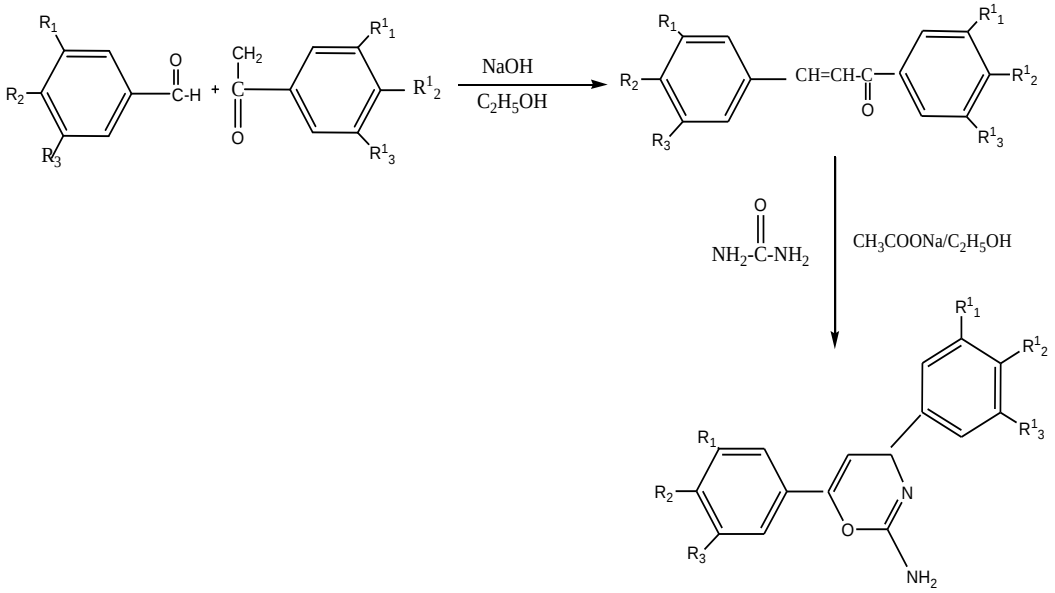


Fig. 1

MATERIALS USED

Aldehyde and acetophenone derivatives,ethanol,ureaFTIR spectrophotometer, digital melting point apparatus.

DERIVATIVES PREPARTION

With the use of different aldehydes and acetophenone 25 oxazine derivatives were prepared. All of its physico chemical properties were determined by both manually and with the help of a software chemsketch and Molinspiration online service.

DERIVATIVES PREPARED

SAMPLE	R_1	R_2	R_3	R_4	R'_1	R'_2	R'_3	R'_4
LM1	H	H	Cl	H	H	H	OH	H
LM2	H	NO_2	H	H	H	H	OH	H
LM3	H	H	NO_2	H	H	H	OH	H
LM4	Cl	H	Cl	H	H	H	OH	H
LM5	H	H	CH_3	H	H	H	Br	H
LM6	H	H	Cl	H	H	H	Br	H
LM7	Cl	H	H	H	H	H	Br	H
LM8	H	Cl	H	H	H	H	Br	H
LM9	H	NO_2	OCH_3	H	H	H	Br	H
LM10	NO_2	H	H	H	H	H	Br	H
LM11	H	H	NO_2	H	H	H	Br	H
LM12	OCH_3	H	OCH_3	H	H	H	Br	H
LM13	H	H	$NH(CH_3)_2$	H	H	H	Br	H
LM14	CH_3	H	H	H	H	H	Br	H
LM15	H	H	CH_3	H	H	H	Br	H
LM16	H	H	Cl	H	H	H	NH_2	H
LM17	H	Cl	H	H	H	H	NH_2	H
LM18	Cl	H	Cl	H	H	H	NH_2	H
LM19	H	NO_2	H	H	H	H	NH_2	H
LM20	H	H	NO_2	H	H	H	NH_2	H
LM21	H	Br	H	H	H	H	NH_2	H
LM22	OCH_3	H	OCH_3	H	H	H	NH_2	H
LM23	CH_3	H	H	H	H	H	NH_2	H
LM24	H	H	CH_3	H	H	H	NH_2	H
LM25	CH_3	H	H	H	H	H	CH_3	H

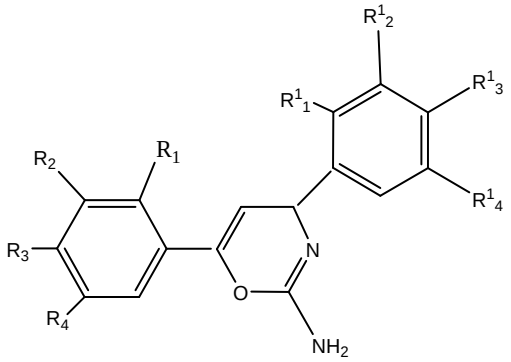


Fig. 2

TABLE 1: DERIVATIVES PREPARED

Physico chemical analysis of all compounds were detected .Thin layer chromatography was performed.	
Solubility	ethanol, acetone, ethyl acetate (soluble) Chloroform. Water (sparingly soluble)
Solvent system used is	ethyl acetate: ethanol: water = 3: 2: 2 proportions.[6]
Detection medium;	UV chamber
Rf value is calculated by	distance travelled by the solute /distance travelled Solvent

Table 2: PHYSICO CHEMICAL PROPERTIES

sample	Molecular formula	Molecular weight	Melting point	Yield	R_f value	NATURE	COLOUR	Refractive Index in Cm^3	Surface Tension in mdyne/cm	Density In g/cm^3
LM1	$C_{16}H_{13}Cl\ N_2O_2$	300.73 g	138^0C	81%	0.69	crystal	Light yellow	1.6	51.8	1.37
LM2	$C_{16}H_{13}N_3O_4$	311.29 g	119^0C	79 %	0.63	crystal	creme	1.6	62.3	1.4
LM3	$C_{16}H_{12}N_3O_4$	311.29 g	123^0C	70%	0.62	crystal	yellow	1.6	62.3	1.4
LM4	$C16H12N2Cl_2O_2$	335.18g	134^0C	80%	0.59	crystal	yellow	1.6	53.1	1.4
LM5	$C_{17}H_{15}BrN_2O$	343.21 g	133^0C	82%	0.63	crystal	brown	1.6	46.6	1.4
LM6	$C_{16}H_{12}N_2OBr\ Cl$	363.63 g	107^0C	80%	0.70	crystal	colorless	1.6	50.8	1.5
LM7	$C_{16}H_{12}N_2OBr\ Cl$	363.63 g	107^0C	80%	0.70	crystal	colorless	1.6	50.8	1.5
LM8	$C_{16}H_{12}N_2OBr\ Cl$	363.63 g	131^0C	78%	0.67	crystal	colorless	1.6	50.8	1.5
LM9	$C_{16}H_{12}Br\ N_3O_3$	374.18 g	133^0C	79%	0.69	crystal	brown	1.6	60.4	1.6
LM10	$C_{16}H_{12}Br\ N_2O_3$	374.18 g	131^0C	81%	0.68	crystal	brown	1.6	60.4	1.6
LM11	$C_{16}H_{12}Br\ N_3O_3$	374.18 g	134^0C	83%	0.68	crystal	brown	1.6	60.4	1.6
LM12	$C_{18}H_{17}Br\ N_2O_3$	389.24 g	128^0C	74%	0.70	crystal	yellow	1.6	45.5	1.4
LM13	$C_{18}\ H_{18}BrN_3O$	372.25 g	121^0C	71%	0.65	crystal	yellow	1.6	45.9	1.4
LM14	$C17H15BrN_2O$	343.21g	133^0C	75%	0.68	crystal	crème	1.6	46.6	1.4
LM15	$C_{17}H_{15}BrN_2O$	343.21 g	126^0C	70%	0.68	crystal	colorless	1.6	46.6	1.4
LM16	$C_{16}H_{14}\ Cl\ N_3O$	299.75 g	133^0C	86%	0.67	crystal	yellow	1.6	52.8	1.37
LM17	$C_{16}H_{14}\ Cl\ N_3O$	299.75 g	136^0C	85%	0.62	crystal	yellow	1.6	52.8	1.37
LM18	$C_{16}H_{13}\ Cl_2N_3O$	334.19 g	138^0C	71%	0.61	crystal	orange	1.6	54.1	1.46
LM19	$C_{16}H_{14}N_4O_3$	310.30 g	135^0C	89%	0.63	crystal	orange	1.6	63.5	1.4
LM20	$C_{16}H_{14}N_4O_3$	310.30 g	135^0C	70%	0.61	crystal	Brick red	1.6	63.5	1.4
LM21	$C_{16}H_{14}BrN_3O$	344.20 g	118^0C	81%	0.68	crystal	yellow	1.6	55	1.5
LM22	$C_{18}H_{19}N_3O_3$	325.36 g	126^0C	76%	0.67	crystal	yellow	1.6	46.8	1.28
LM23	$C_{17}H_{17}N_3O$	279.33 g	131^0C	78%	0.68	crystal	yellow	1.6	48.2	1.24
LM24	$C_{17}H_{17}N_3O$	279.33 g	121^0C	80%	0.70	crystal	colorless	1.6	48.2	1.24
LM25	$C_{18}H_{18}N_2O$	278.34 g	138^0C	76%	0.71	crystal	colorless	1.6	41.2	1.14

Spectral studies

IR spectral studies were perfomed in FTIR Spectrophotometer in Pushpagiri College of Pharmacy. and NMR studies are carried out in STIC INDIA Cochin. Each compounds were checked and confirmed the structure.[6]

Table 3: SPECTRAL DETAILS

Sample.ID	IR peaks(cm^{-1})	NMR peaks (ppm)
LM1	3339(Arom),1628(C=N) 1289(C-O-C)'1543(N-H)	7.366-7.387 (4H ,multiplet of oxazine ring), 4.165(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring)
LM2	3161(Arom),1650(C=N) 1286(C-O-C)'1557(N-H)	7.723-7.8 (4H ,multiplet of oxazine ring), 3.5(2H ,singlet of aldehyde substituted arom - ring),2.5 (2H, doublt of AP substituted Arom-ring),8.1-8.7(4H,m of Ar-H)
LM3	3358(Arom),1655(C=N) 1215(C-O-C)'1534(N-H)	7.6-7.7 (4H ,multiplet of oxazine ring), 5.407(2H ,singlet of aldehyde substituted arom - ring),1.7 (2H, doublt of AP substituted Arom-ring).8-8.2(4H,m of Ar-H)
LM4	3373(Arom),1664(C=N) 1258(C-O-C)'1579(N-H)	7.2 – 7.9 (4H ,multiplet of oxazine ring), 4.8(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring),8-8.1(4H,m of Ar-H)
LM5	3354(Arom),1663(C=N) 1291(C-O-C)'1522(N-H)	7.3-7.8 (4H ,multiplet of oxazine ring), 4.7(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring) ,8.1-8.2 (4H,m of Ar-H)
LM6	3350(Arom),1654(C=N) 1275(C-O-C)'1558(N-H)	7.2-7.8 (4H ,multiplet of oxazine ring), 3.46(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring) , 8.1-8.2 (4H,m of Ar-H)
LM7	3350(Arom),1660(C=N) 1271(C-O-C)'1581(N-H)	7.3-7.8 (4H ,multiplet of oxazine ring) ,1.5 (2H, doublt of AP substituted Arom-ring), 8.1-8.2 (4H,m of Ar-H)
LM8	3351(Arom),1662(C=N) 1262(C-O-C)'1565(N-H)	7.3-7.9 (4H ,multiplet of oxazine ring), 3.9(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring)
LM9	3358(Arom),1663(C=N) 1213(C-O-C)'1582(N-H)	7.2-7.9 (4H ,multiplet of oxazine ring), 3.5 (2H ,singlet of aldehyde substituted arom - ring),1.2 (2H, doublt of AP substituted Arom-ring), 8.1-8.2 (4H,m of Ar-H)
LM10	3261(Arom),1591(C=N) 1296(C-O-C)'1557(N-H)	7.4-7.9 (4H ,multiplet of oxazine ring), 4.7(2H ,singlet of aldehyde substituted arom - ring),1.2 (2H, doublt of AP substituted Arom-ring), 8.-8.8 (4H,m of Ar-H)
LM11	3358(Arom),1658(C=N) 1213(C-O-C)'1582(N-H)	7.5-7.9 (4H ,multiplet of oxazine ring), 4.7(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring), 8-8.2 (4H,m of Ar-H)
LM12	3354(Arom),1655(C=N) 1236(C-O-C)'1580(N-H)	7.1-7.8 (4H ,multiplet of oxazine ring), 4.7(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring)
LM13	3354(Arom),1646(C=N) 1223(C-O-C)'1549(N-H)	7.2-7.8 (4H ,multiplet of oxazine ring), 4.7(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring),
LM14	3029(Arom),1654(C=N) 1251(C-O-C)'1507(N-H)	7-7.8 (4H ,multiplet of oxazine ring), 5.1(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring)
LM15	3350(Arom),1656(C=N) 1222(C-O-C)'1560(N-H)	7.2-7.8 (4H ,multiplet of oxazine ring), 2.39(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring)
LM16	3340(Arom),1590(C=N) 1226(C-O-C)'1488(N-H)	7.1-7.9 (4H ,multiplet of oxazine ring), 4.175(2H ,singlet of aldehyde substituted arom - ring),1.2 (2H, doublt of AP substituted Arom-ring)
LM17	3330(Arom),1621(C=N) 1228(C-O-C)'1552(N-H)	7.3-7.9 (4H ,multiplet of oxazine ring), 4.1(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring)
LM18	3328(Arom),1651(C=N) 1257(C-O-C)'1557(N-H)	7.2-7.9 (4H ,multiplet of oxazine ring), 4.1-4.7(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring), 8.00 (4H,m of Ar-H)
LM19	3420(Arom),1629(C=N) 1231(C-O-C)'1552(N-H)	7.5-7.9 (4H ,multiplet of oxazine ring), 4.2(2H ,singlet of aldehyde substituted arom - ring),1.6 (2H, doublt of AP substituted Arom-ring), 8.2-8.5 (4H,m of Ar-H)
LM20	3484(Arom),1634(C=N) 1230(C-O-C)'1505(N-H)	7.6-7.9 (4H ,multiplet of oxazine ring), 4.2(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring), 8.0-8.2 (4H,m of Ar-H)
LM21	3328(Arom),1651(C=N) 1227(C-O-C)'1577(N-H)	7.2-7.9 (4H ,multiplet of oxazine ring), 4.179(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring)
LM22	3414(Arom),1651(C=N) 1227(C-O-C)'1515(N-H)	7.2-7.9 (4H ,multiplet of oxazine ring), 4.186(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring)
LM23	3339(Arom),1626(C=N) 1240(C-O-C)'1570(N-H)	7.0-7.8 (4H ,multiplet of oxazine ring), 4.1(2H ,singlet of aldehyde substituted arom - ring),1.5 (2H, doublt of AP substituted Arom-ring), 8.0-8.3 (4H,m of Ar-H)
LM24	3458(Arom),1624(C=N) 1284(C-O-C)'1511(N-H)	7.2-7.9 (4H ,multiplet of oxazine ring), 4.140(2H ,singlet of aldehyde substituted arom - ring),2.3 (2H, doublt of AP substituted Arom-ring)
LM 25	3360(Arom),1602(C=N) 1245(C-O-C)'1507(N-H)	7.0-7.9 (4H ,multiplet of oxazine ring), 5.1(2H ,singlet of aldehyde substituted arom-ring,2.4(2H,singlet of AP-sub arom) ring

CHN ANALYSIS

Structure of the compounds were again confirmed by detecting the percentageof carbon, hydrogen and nitrogen prescent in the structure.following table represent the percentage of CHN from calculations with the help of molecular formula and the analysis result.[7]

CALCULATED				ANALYTICAL		
Sample	**N%**	**C%**	**H%**	**N%**	**C%**	**H%**
LM1	9.31	63.9	4.36	8.16	67.17	3.59
LM2	13.5	61.7	4.21	12.9	67.66	4.19
LM3	13.5	61.7	4.21	11.4	65.53	4.77
LM4	8.36	57.3	3.61	8.75	57.79	3.36
LM5	8.16	59.49	3.19	7.98	58.05	3.29
LM6	7.70	52.85	3.33	7.10	52.88	3.39
LM7	7.70	52.85	3.33	7.44	55.40	3.74
LM8	7.70	52.85	3.33	7.66	53.20	3.30
LM9	11.23	51.36	3.23	10.41	54.75	3.12
LM10	11.23	51.36	3.23	10.03	51.84	3.14
LM11	11.23	51.36	3.23	10.68	50.86	3.88
LM12	7.20	55.54	4.40	6.77	50.87	5.30
LM13	11.29	58.08	4.87	10.83	56.02	4.98
LM14	8.16	59.49	4.41	7.28	56.20	4.26
LM15	8.16	59.49	4.41	7.98	58.94	4.38
LM16	14.02	64.16	4.7	13.30	65.21	4.05
LM17	14.02	64.11	4.7	13.64	65.70	4.72
LM18	12.57	57.50	3.92	12.65	56.63	3.79
LM19	18.06	61.93	4.55	17.65	60.66	4.50
LM20	18.06	61.93	4.55	17.57	60.88	3.25
LM21	12.21	55.83	4.10	12.60	55.03	3.81
LM22	12.91	66.45	5.89	12.21	64.34	4.78
LM23	15.04	73.10	6.13	12.44	72.61	5.72
LM24	15.04	73.10	6.13	15.77	76.42	5.11
LM25	10.06	77.67	6.52	10.79	78.25	6.88

LIPINSKY RULE OF FIVE

Lipinsky rule of five is a rule of thumb to evaluate drug likeness or to determine if a chemical compound with acertain pharmacological activity has properties that would make it a likely orally active drug in humans. The rule describes molecular properties important for a drugs pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion (ADME). However, the rule does not predict if a compound is pharmacologically active.[8],[9]

In general an orally active drug has

1. Not more than 5 hydrogen bond donors.
2. Not more than 10 hydrogen bond acceptors.
3. Molecular weight not higher than 500.
4. Calculated octanol /water partition (C log P) not higher than 5.
5. Number of rotatable bonds in a given molecule should be kept below 10.

Molecules violating more than one of these rules may have problem with their bioavailability.

SAMPLE CODE	C log P	MW	nON	nOHNH	n rot b	n- violations
LM1	3.10	300.75	4	3	2	0
LM2	2.36	311.30	7	3	3	0
LM3	2.38	311.30	7	3	3	0
LM4	3.71	335.19	4	3	2	0
LM5	4.16	343.22	3	2	2	0
LM6	4.39	363.64	3	2	2	0
LM7	4.34	363.64	3	2	2	0
LM8	4.37	363.64	3	2	2	0
LM9	3.65	374.19	6	2	3	0
LM10	3.62	374.19	6	2	3	0
LM11	3.67	374.19	6	2	3	0
LM12	3.75	389.25	5	2	4	0
LM13	3.79	372.27	4	2	2	0
LM14	4.11	343.22	3	2	2	0
LM15	4.16	343.22	3	2	2	0

LM16	2.66	299.76	4	4	2	0
LM17	2.63	299.76	4	4	2	0
LM18	3.26	334.21	4	4	2	0
LM19	1.92	310.31	7	4	3	0
LM20	1.94	310.31	7	4	3	0
LM21	2.77	344.21	4	4	2	0
LM22	2.02	325.37	6	4	4	0
LM23	2.38	279.34	4	4	2	0
LM24	2.43	325.37	6	4	4	0
LM25	3.75	278.36	3	2	2	0

CONCLUSION

All the 25 derivatives were synthesized conveniently and they have good oral bioavailability also. The chemicals needed for the synthesize of this compound is relatively cheep and easy to available. The spectral results shows that the compounds are nitrogen and oxygen containing seven membered heterocyclic compound ie, an oxazepine ring.

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