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Research Article

Synthesis and physico-chemical characterization of some novel oxazepine 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.

Keywords: Oxazepine, Semicarbazide, Schiff base

1. Introduction

Azo compounds constitute one of the largest classes of industrially synthesized organic compounds. Aliphatic azo compounds like azobisisobutylonitrile (AIBN), can be used as radical initiators in polymerization of alkenes to make plastics. Aromatic azo compounds' are used as acid-base indicators such as methyl red, methyl orange and Congo red. Schiff bases are important intermediate for synthesis of some bioactive compounds. Furthermore they are reported to show a variety of interesting biological actions, including antibacterial, antifungal, anticonvulsant, anti-inflammatory, and antitubercular[1].

The development of simple synthetic route to widely used organic compounds ring, using readily available reagents is one of the main objectives of the organic synthesis. Nitrogen heterocycles are of a special interest because they constitute an important class of natural and non natural products, Many of which exhibit useful biological activities, One –pot efficient synthesis of heterocyclic derivatives, may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegenerative disorders.

These rings also possess anticancer, muscle relaxant, hypnotic, diuretic, antihypertensive and are widely used in pharmaceuticals promoted the synthesis of oxazepine rings.

2. Synthetic Methodology

1, 3 - Oxazepine 4, 7 - dione was synthesized from imine (schiff base) which is obtain by the reaction of a primary amine with aromatic aldehyde with simultaneous removal of water molecule. Here the primary amine used is a semicarbazide. Then equimolar quantities of prepared schiff base and phthalic anhydride and succinic anhydride, which undergo cycloaddition reaction in the presence of organic solvent benzene. General scheme for the reaction is as given below.[2]

2. Materials Used

Semicarbazide hydrochloride, Succinicanhydride, Phthallic anhydride, Benzene, 2,4 dimethoxy benzaldehyde, 2-methyl benzaldehyde, 2-nitro benzaldehyde, 3-bromo benzaldehyde, 4-chloro benzaldehyde, 3-nitro benzaldehyde,4-bromo benzaldehyde,4-nitro benzaldehyde-dimethyl amino benzaldehyde,2,4- dichloro benzaldehyde, 3,4,5-trimethoxy benzaldehyde, 4-ethoxy benzaldehyde, 5-chloro salsilaldehyde, 3,4-dihydroxy benzaldehyde.

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Scheme 1

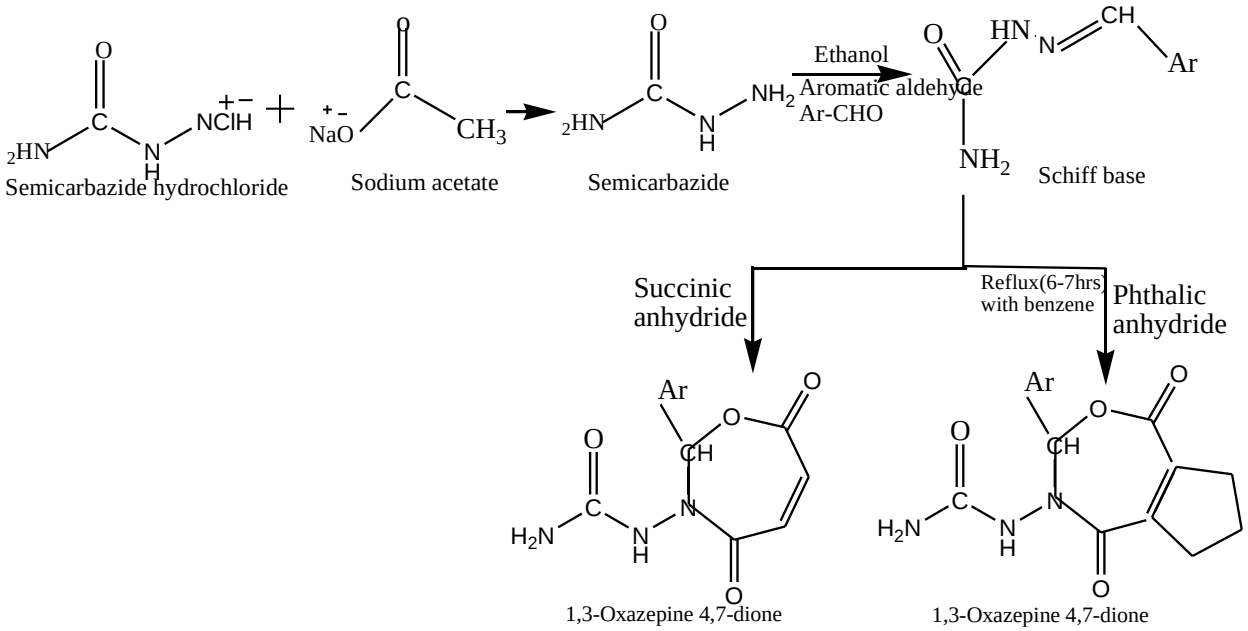

Figure 1: Scheme 1

3. Results and Discussion

3.1 Derivatives prepared with succinic anhydride

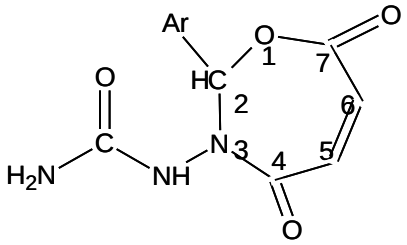

Figure 2: Derivatives prepared with succinic anhydride

Table 1: Derivatives prepared with succinic anhydride

Sample	Ar
M1	4-Chloro BA
M2	3-Nitro BA
M3	4-Bromo BA
M4	2,4-DIMETHOXY BA
M10	2-Nitro BA
M11	3,4-Dimethoxy BA
M21	2-Methyl BA
M22	4-Nitro BA
M23	3-Bromo BA
M24	P-Dimethyl amino BA
M25	3-Chloro BA

3.2 Derivatives prepared with phthalic anhydride

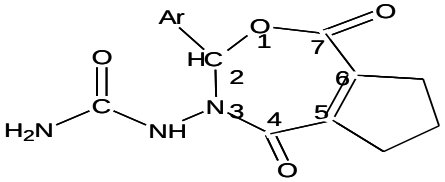

Figure 3: Derivatives prepared with phthalic anhydride

Table 2: Derivatives prepared with phthalic anhydride

Sample	Ar
M5	4-Chloro BA
M6	3-Nitro BA
M7	4-Bromo BA
M8	2,4-DIMETHOXY BA
M9	2-Nitro BA
M12	3,4-Dimethoxy BA
M13	2-Methyl BA
M14	4-Nitro BA
M15	3-Bromo BA
M16	P-Dimethyl amino BA
M17	3-Chloro BA
M18	2-Chloro BA
M19	4-Methyl BA
M20	2,4- Dichloro BA

3.3 Physico chemical properties

Physico chemical analysis of all compounds were detected .Thin layer chromatography was performed.[3]
Solubility:ethanol, acetone, ethyl acetate (soluble), Chloroform. Water (sparingly soluble)
Solvent system used: ethyl acetate: ethanol: water = 3: 2: 2 proportions.[4]
Detection medium: UV chamber
Rf value is calculated by: distance travelled by the solute /distance travelled Solvent.

Table 3: Physico chemical properties

Serial no	sample	Molecular formula	Molecular weight	Melting point	Yield	R_f value	Nature	Colour
1	M1	$C_{18}H_{17}N_3O_7$	387 g	153^0C	72%	0.61	crystal	Light yellow
2	M2	$C_{16}H_{15}N_3O_4$	313 g	163^0C	80%	0.68	crystal	white
3	M3	$C_{15}H_{12}N_4O_6$	344 g	150^0C	75%	0.61	crystal	Light yellow
4	M4	$C_{15}H_{12}BrN_3O_4$	378 g	158^0C	71%	0.71	crystal	white
5	M5	$C_{13}H_{10}ClN_3O_5$	323 g	170^0C	70%	0.61	crystal	white
6	M6	$C_{13}H_{10}N_4O_7$	334 g	161^0C	81%	0.68	crystal	Light yellow
7	M7	$C_{13}H_{10}BrN_3O_4$	368 g	158^0C	60%	0.70	crystal	White
8	M8	$C_{15}H_{15}N_3O_7$	349 g	161^0C	72%	0.72	crystal	Light yellow
9	M9	$C_{13}H_{10}N_4O_7$	334 g	163^0C	68%	0.69	crystal	Yellow
10	M10	$C_{15}H_{12}ClN_3O_4$	333 g	167^0C	60%	0.61	crystal	white
11	M11	$C_{15}H_{12}BrN_3O_4$	378 g	160^0C	71%	0.72	crystal	white
12	M12	$C_{15}H_{15}N_3O_7$	349 g	170^0C	68%	0.72	crystal	Light yellow
13	M13	$C_{14}H_{13}N_3O_5$	303 g	168^0C	62%	0.69	crystal	yellow
14	M14	$C_{13}H_{10}N_4O_7$	334 g	163^0C	62%	0.71	crystal	crème
15	M15	$C_{13}H_{10}BrN_3O_5$	368 g	171^0C	72%	0.62	crystal	white
16	M16	$C_{15}H_{16}N_4O_5$	332 g	165^0C	60%	0.70	crystal	brown
17	M17	$C_{13}H_{10}N_3O_5Cl$	323 g	166^0C	78%	0.69	crystal	white
18	M18	$C_{13}H_{10}ClN_3O_5$	323 g	168^0C	61%	0.63	crystal	white
19	M19	$C_{14}H_{13}N_3O_5$	303 g	165^0C	70%	0.70	crystal	white
20	M20	$C_{14}H_{13}N_3O_5$	358 g	168^0C	68%	0.69	crystal	white
21	M21	$C_{15}H_{12}ClN_3O_4$	333 g	165^0C	68%	0.70	crystal	white
22	M22	$C_{18}H_{19}N_3O_5$	389 g	168^0C	71%	0.73	crystal	white
23	M23	$C_{17}H_{17}N_3O_5$	343 g	171^0C	78%	0.67	crystal	crème
24	M24	$C_{16}H_{12}ClN_3O_6$	377 g	150^0C	70%	0.68	crystal	white
25	M25	$C_{15}H_{15}N_3O_4$	301 g	161^0C	73%	0.61	crystal	brown

3.4 Spectral studies

IR and NMR Peaks of synthesized compounds were listed in the table.

Table 4: IR and NMR Peaks of synthesized compounds

Sample ID	IR peaks(cm^{-1})	NMR peaks (ppm)
M1	1584(c=o lactone),2980(N-H),1667(CHN),1069(aromatic)	7.5-7.7 (4H, multiplet of heterocyclic ring), 4.2(2H, singlet of aldehyde substituted arom - ring),
M2	1573(c=o lactone),3033(N-H), 1670 (CH-N),1070(aromatic)	7.5-7.9 (4H, multiplet of heterocyclic ring), 2.5(2H, singlet of aldehyde substituted arom - ring),
M3	1599(c=o lactone),3168(N-H), 1599(CH-N),1071(aromatic)	7.5-7.9 (4H, multiplet of heterocyclic ring), 4.7(2H, singlet of aldehyde substituted arom - ring),
M4	1584(c=o lactone),2849(N-H), 1667(CH-N),1069(aromatic)	7.5-7.6 (4H, multiplet of heterocyclic ring), 4.5(2H, singlet of aldehyde substituted arom - ring),
M5	1587(c=o lactone),3138(N-H), 1666(CH-N),1011(aromatic)	7.4-7.8(4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M6	1581(c=o lactone),2932(N-H), 1698(CH-N),1079(aromatic)	7.6-7.9 (4H, multiplet of heterocyclic ring), 2.41(2H, singlet of aldehyde substituted arom - ring),
M7	1586(c=o lactone),3060(N-H), 1666(CH-N),1098(aromatic)	7.5-7.8 (4H, multiplet of heterocyclic ring), 2.42(2H, singlet of aldehyde substituted arom - ring),
M8	1574(c=o lactone),3039(N-H), 1671(CH-N),1069(aromatic)	7.5-7.9(4H, multiplet of heterocyclic ring), 2.5 (2H, singlet of aldehyde substituted arom - ring),
M9	1598(c=o lactone),2925(N-H), 1688(CH-N),1137(aromatic)	7.5-7.9 (4H, multiplet of heterocyclic ring), 2.42(2H, singlet of aldehyde substituted arom - ring),
M10	1574(c=o lactone),2646(N-H), 1668(CH-N),1070(aromatic)	7.4-7.8 (4H, multiplet of heterocyclic ring), 2.5(2H, singlet of aldehyde substituted arom - ring),
M11	1584(c=o lactone),2867(N-H), 1663(CH-N),1069(aromatic)	7.5-7.6 (4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M12	1597(c=o lactone),2928(N-H), 1621(CH-N),1014(aromatic)	7-7.7 (4H, multiplet of heterocyclic ring), 2.3(2H, singlet of aldehyde substituted arom - ring),
M13	1591(c=o lactone),2921(N-H), 1655(CH-N),1092(aromatic)	7.9 (4H, multiplet of heterocyclic ring), 2.47(2H, singlet of aldehyde substituted arom - ring),
M14	1577(c=o lactone),2945(N-H), 1653(CH-N),1020(aromatic)	7.7 (4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M15	1597(c=o lactone),3062(N-H), 1689(CH-N),1068(aromatic)	7.3-7.6 (4H, multiplet of heterocyclic ring), 2.42(2H, singlet of aldehyde substituted arom - ring),
M16	1577(c=o lactone),2914(N-H), 1651(CH-N),1175(aromatic)	7.4-7.7 (4H, multiplet of heterocyclic ring),2.99(2H, singlet of aldehyde substituted arom - ring),
M17	1409(c=o lactone),2930(N-H), 1683(CH-N),1197aromatic)	7.3-7.9 (4H, multiplet of heterocyclic ring), 2.42(2H, singlet of aldehyde substituted arom - ring),
M18	1412(c=o lactone),2920(N-H), 1685(CH-N),1033(aromatic)	7.3-7.4(4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M19	1505(c=o lactone),2919(N-H), 1660(CH-N),1016(aromatic)	7.1-7.8 (4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M20	1592(c=o lactone),2918(N-H), 1682(CH-N),1098(aromatic)	7.4-7.6(4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M21	1586(c=o lactone),2921(N-H), 1693(CH-N),1071(aromatic)	7.3-7.9 (4H, multiplet of heterocyclic ring), 2.5(2H, singlet of aldehyde substituted arom - ring),
M22	1581(c=o lactone),2941(N-H), 1679(CH-N),1123(aromatic)	7.7 (4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M23	1596(c=o lactone),2984(N-H), 1698(CH-N),1043(aromatic)	7.6-7.7 (4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M24	1532(c=o lactone),3040(N-H), 1652(CH-N),1094(aromatic)	7.1-7.9 (4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),
M 25	1584(c=o lactone),2931(N-H), 1655(CH-N),1082(aromatic)	7.1-7.6 (4H, multiplet of heterocyclic ring), 2.4(2H, singlet of aldehyde substituted arom - ring),

3.5 CHN Analysis

Structures of the compounds were again confirmed by detecting the percentage of carbon, hydrogen and nitrogen present in the structure. Following table represent the percentage of CHN from calculations with the help of molecular formula and the analysis result.

Table 5: CHN Results

	Calculated			Analytical		
Sample	**N%**	**C%**	**H%**	**N%**	**C%**	**H%**
M1	10.85	55.81	4.42	10,21	54.91	3.71
M2	13.41	61.34	4.83	12.52	54.90	3.42
M3	16.27	52.33	3.51	16.88	51.15	2.84
M4	11.11	47.64	3.20	10.52	52.77	3.15
M5	12.98	48.24	3.11	11.97	46.86	3.56
M6	16.76	46.71	3.02	16.04	45.15	3.82
M7	11.41	42.41	2.74	10.13	40.61	2.69
M8	12.03	51.5	4.3	10.51	50.86	3.75
M9	16.76	46.7	3.03	15.53	42.36	4.79
M10	12.03	53.98	3.62	10.72	52.44	2.70
M11	11.11	47.64	3.20	10.55	49.23	3.10
M12	12.03	51.58	4.33	11.41	50.19	4.32
M13	13.8	55.4	4.3	13.83	53.62	4.10
M14	16.76	46.71	3.02	15.06	49.08	3.40
M15	11.41	42.41	2.74	10.74	38.94	2.49
M16	16.86	54.21	4.85	16.82	53.05	5.07
M17	12.98	48.24	3.11	12.21	47.30	4.02
M18	12.98	48.24	3.11	11.07	46.37	3.94
M19	13.86	55.45	4.32	12.10	38.79	4.20
M20	11.73	43.60	2.53	10.36	40.14	2.84
M21	12.59	53.98	3.62	11.93	50.04	3.02
M22	10.79	55.53	4.92	9.55	54.49	5.30
M23	12.24	59.47	4.99	11.49	57.66	4.30
M24	11.12	50.87	3.20	12.10	48.89	3.91
M25	13.95	59.79	5.02	12.69	53.64	5.26

3.6 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 a certain 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.[5]

In general an orally active drug has [6]

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.

Table 6: Lipinsky Rule analysis of the synthesized compounds

Sample Code	C log P	MW	nON	nOHNH	n rot b	n- violations
M1	1.39	399.36	10	3	5	0
M2	1.79	353.33	8	3	3	0
M3	1.30	384.30	11	3	4	0
M4	2.15	418.20	8	3	3	0
M5	0.62	325.71	8	3	3	0
M6	0.10	336.26	8	3	4	0
M7	0.75	370.16	8	3	3	0
M8	0.02	351.31	10	3	5	0
M9	0.10	336.26	9	3	4	0
M10	2.02	373.75	8	3	3	0
M11	2.15	418.20	8	3	3	0
M12	0.21	351.31	10	3	5	0
M13	0.39	305.29	8	3	3	0
M14	0.10	336.26	9	3	4	0
M15	0.75	370.16	8	3	3	0
M16	0.04	334.33	9	3	4	0
M17	0.62	325.71	8	3	3	0
M18	0.62	325.71	8	3	3	0
M19	0.39	305.29	8	3	3	0
M20	1.23	360.15	8	3	3	0
M21	2.02	373.75	8	3	3	0
M22	1.37	429.38	9	3	6	0
M23	1.78	383.36	9	3	5	0
M24	1.73	389.75	9	4	3	0
M25	1.39	339.31	8	3	3	0

4. Conclusion

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

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