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Synthesis and characterization of novel 5, 6 – benz 1,3 – oxazepine 4,7 – dione derivatives from semicarbazone

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ABSTRACT

Drugs used for pharmacotherapy of psychopharmacological disorders have more importance now days. Among them the most important are oxazepine derivatives. Oxazepine are seven membered heterocyclic compounds which contribute various important activities. The present study involves the synthesis of series of eight number of 5,6 – Benz 1,3 – Oxazepine 4, 7 – Dione(AO.I-AOII) derivatives by cyclo addition reaction between schiff base (semicarbazone) and phthalic anhydride with dry benzene as the solvent. Schiff base is synthesized by the condensation reaction of semicarbazide hydrochloride with various aromatic aldehydes in the presence of sodium acetate. All the prepared compounds were characterized by its melting point, TLC, solubility in various solvents, and various physicochemical parameters are predicted using ACD/Chemsketch software. Chemical structure of all the synthesized were confirmed by spectrum obtained by FTIRand[1]HNMR spectroscopy and elementary (CHN) analysis.

Keywords: Semicarbazide Hydrochloride, Aromatic aldehydes, Schiff bases, Cycloaddition, Phthalic anhydride, Oxazepinediones.

1. INTRODUCTION

Most of the potent and biologically active medicinal agents contain heterocyclic ring with nitrogen and oxygen as the special element. The present work involves the synthesis of eight semicarbazones and eight 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dione from the above semicarbazone. The chemical structures of the oxazepinedione derivatives were studied. Thenewly synthesized compounds 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dione contains oxazepine as the core nucleus, which is a seven membered heterocyclic compound which contain oxygen and nitrogen as the hetero atom in 1st and 3rd position, were two ketone moietyattached to the 4th and 7th position of the ring and a benzene ring is fused with 6th and 7thposition. Compare to the other oxazepine derivatives (e.g. dibenzoxazepines, benzoxazepines etc.). The method for the synthesis of 1.3 - Oxazepine 4, 7 - Dione is limited. One of the recently used methods is cyclo addition reaction[1, 2]. It is a type of pericyclic reaction. The method [1] used for the synthesis in this work is pericyclic cyclo addition, which is classified as a 5+2 = 7, which implying five-atom component plus two-atom component leading to seven-membered heterocyclic ring. Here the five atom involved in the synthesis of oxazepinedione derivativecomponent is the anhydride nucleus of phthalic anhydride and the two atom component is C=N of schiff base or imine.The mechanism involves the addition of one σ- carbonyl to π-bond (N=C) to give 4- membered cyclic and 5-membered cyclic ring of anhydride in the same transition state ,which opens into various anhydride (E.g.: phthalic anhydride) to a give 7-membered cyclic ring 1, 3-oxazepine 4, 7 dione.

The intermediate (schiff base) used in this reaction issemicarbazone which is synthesized by the usual condensation reaction in which an aromaticaldehydes with a primary amine (semicarbazide) forms an imine in the presence of mild acid. Mechanism involve nucleophilic Addition to the carbonyl group and elimination of a water molecule so, too, reaction of an aldehyde or ketone with a reagent having the general structureNH_2 – Z (where Z contains an O or N atom bonded to the –NH_2 group) forms an imine derivative. The overall reaction results in

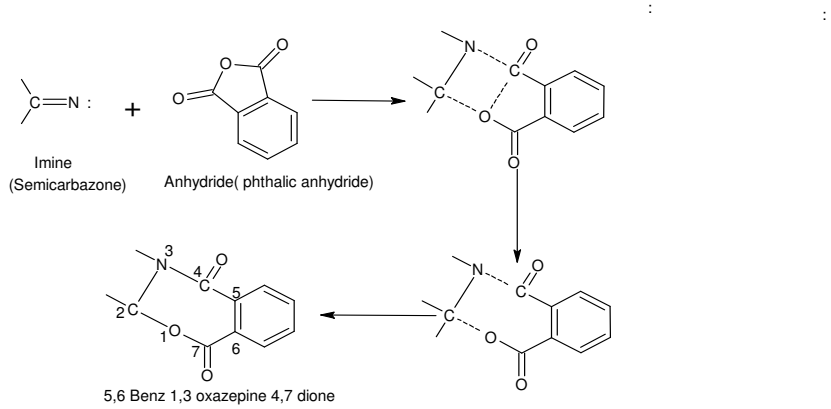
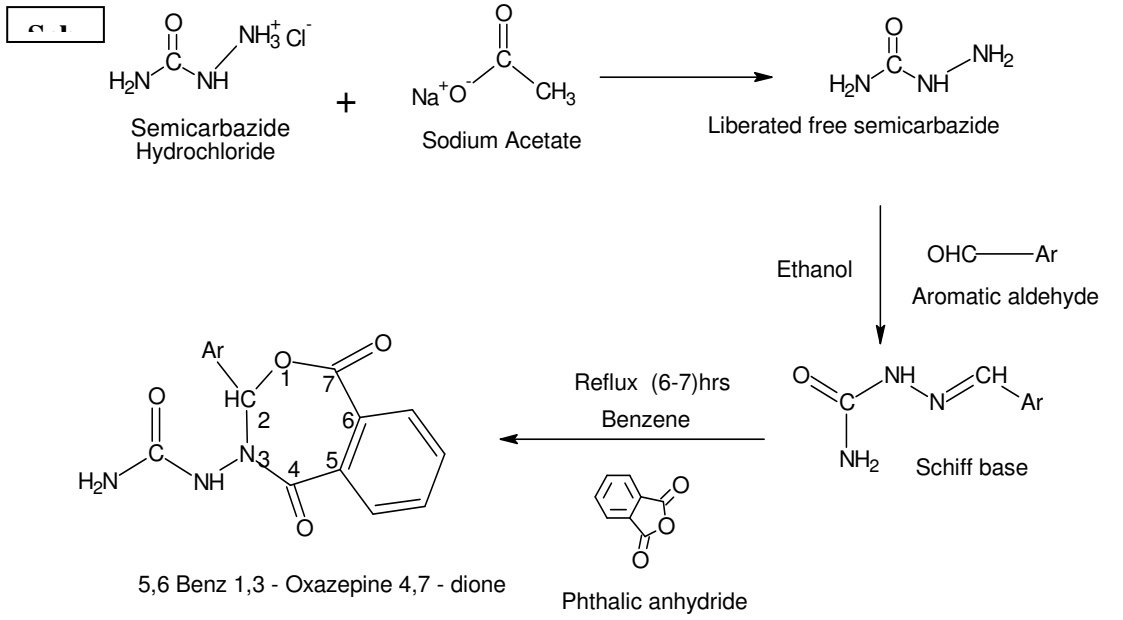
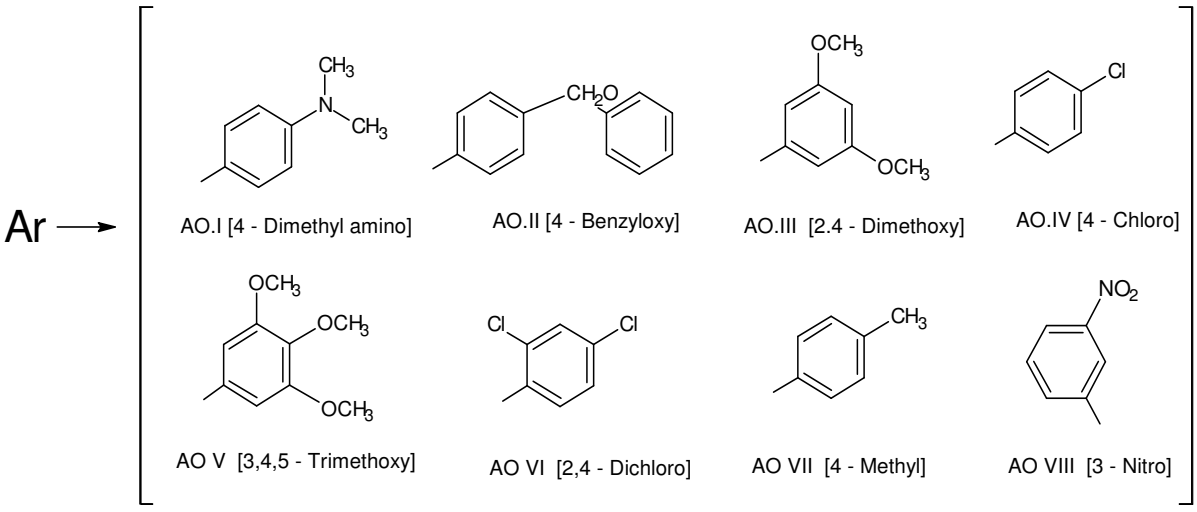


Figure - 1: Mechanism





Aldehydes used [Ar - CHO]

Scheme -1: Synthesis of Oxazepinedione from semicarbazide hydrochloride is as follows.

replacement of C = O by C = N. Schiff-basecompounds have been used as fine chemicals and medical substrates. Compared to otherderivatives of oxazepine much less studiesare so far conducted for oxazepinediones. Itincludes antimicrobial studies [3], antitumor activity [4], anticorrosive studies [5] and anticonvulsant studies [6].

2. MATERIALS AND METHODS

- The reagents that were used for the synthesis of oxazepinedione derivatives were laboratory grade and those were obtained from Spectrum, Otto and Chemco.
- Characterization of prepared compounds by molecular formula, molecular weight, colour, physical state, percentage yield and solubility profiles with certain solvents like alcohol, acetone, ethyl acetate, $CHCl_3$, 0.1N NaOH, and 0.1N HCl.
- Analytical chromatography was performed by TLC plate with Silica Gel 60 F254 as stationary phase which is a product of Merck KGaA, Germany and mobile phase used was Ethyl acetate: Methanol : Strong Ammonia (85:10:5) and detection is done withUV- detector.
- Melting point was recorded by using melting point apparatus (Veego, model no: VMP –D).
- Prediction of physicochemical properties like surface tension, density, index of refraction, molar volume, polarizability using ACD/Chemsketch Software
- Spectral characterizations were done using IR spectra, obtained from Shimadzhu FT-IR Affinity, using KBr discs. ^{1}HNMR spectra with $CDCl_3$ as solvent and TMS as standard and elementary analysis were done at SAIF, STIC, Cochin

2.1. General synthesis

2.1.1. General procedure for synthesis of schiff base {Semicarbazone}

Dissolve 0.02M of semicarbazide hydrochloride and 2g of crystallized sodium acetate in 5ml ofwater in a conical flask, then add 0.02M of aromatic aldehyde (Ar– CHO) and shake well toobtain a turbid mixture. Add alcohol (acetone free) until a clear solution is obtained; shake themixture for a few minutes and allow to stand. The semicarbazone crystallizes from the coldsolution on stand. Filter off the crystals, wash with a little cold water and recrystallized fromethanol.[7,8,14]

2.1.2. General procedure for synthesis of 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dione

Accurately weighed about an equimolar quantity, i.e. 0.01M of synthesized semicarbazone (schiffbase) in the above step and 0.01M of phthalic anhydride into a round bottom flask. Add 25ml ofbenzene as solvent and then reflux the reaction mixture for 6 – 7hrs in a water bath. Cool thereaction mixture in an ice bath for several hours. Filter off the precipitated product and therecrystallized it from ethanol. [11-13]

3. RESULTS

Eight number of 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dione were synthesized by cyclo addition by refluxing semicarbazones and phthalic anhydride for 7hrs. The imine group converted to oxazepine ring. Physico chemical properties like molecular formula, molecular weight, physical state, colour, melting point,percentage yield and $R_f$value of the synthesized compounds are given in the table 1. ACD/Chemsketch Software is used for drawing the chemical structures also used for the prediction of various physicochemical properties like surface tension, density, index of refraction, molar volume, Polarizability, which are given in the table no 2. FT–IR spectrum helps to confirm the presence of various functional group, which are given the below as figure no 2, 4,6,8,12,14,16,18. ^{1}H–NMR help to identify the oxazepine ring with the presence of various protons and the spectrum is given the figure no: 2,4,6,8,10,12,14,16elemental analysis data were also used to confirm the chemical structure of synthesized 5,6 – Benz 1,3 – Oxazepine 4, 7 – Dione.

3.1. Spectral data

3.1.1. 2-p (-N-dimethyl phenyl)-3-(semicarbazone)-2, 3-dihydro-5, 6 Benz [1, 3]-oxazepine -4,7 dione (AO.I)

IR (KBr, cm-1) 1574.91, 1544.08 {Ar C=C}, 3030{Ar C-H}, 1748.55 {C=O}, 3477.80{N-H of amide}, 1410.99{C-N of amide}, 1680{C=O of amide}, 1206.53 {C–N Ar-NH 2}, 1374.34{Sym C–H bending of CH3}. ^{1}HNMR (δ, ppm) 2.981 {s, 6H, (N $(CH_3)_2$}, 10 {s, 1H, NH}, 7.752 {s, 1H, of Oxazepine ring, O-CH-N}, 7.575 – 7.678{m, 8H, Ar H}, 2.5 {s, 2H ofamide}. CHN ANALYSIS (Cal/Ana %) C{61.01/50.78}, H{5.12/4.5}, N {15.81/8.44}.[15]

3.1.2. 2-p (-Benzyloxy phenyl)-3-(semicarbazone)-2, 3-dihydro-5, 6 Benz [1,3]-oxazepine -4, 7 dione (AO.II)

IR (KBr, cm-1) 1598.09 {Ar C=C}, 3064.06{Ar C-H},2910.11{Aliphatic C-H},1670.43{C=O}, 1248.96 {C-O }3472.02 {N-H of amide}, 1451.50 {C-N of amide}, 1649.21{C=O ofamide}, 1173.73 {C–O-C of ether}.^{1}HNMR (δ,ppm) 10.095 {s,1H, NH} 7.788 {s,1H ,ofOxazepine ring, O-CH-N}, 6.416 – 7.662 {13H,

Ar-H}, 2.5 {s, 2H of amide}, 5.135{s, 2H ofCH_2}.**CHN ANALYSIS(Cal/Ana%)** C{66.18/63.33}, H{4.59/5.77}, N {10.07/15.79}.

3.1.3. 2- (2, 4- Dimethoxy phenyl)-3-(semicarbazone)-2, 3-dihydro-5, 6 Benz [1,3]-oxazepine -4, 7 dione (AO.III)

IR (KBr, cm-1) 1604.84 {Ar C=C}, 3027.12{Ar C-H}, 2834.52{Aliphatic CH},1695.50{C=O}, 1265.36{C-O}3468.16{N-H of amide}, 1421.60{C-N of amide},1695.50C=O of amide}, 1133.23, 1026.17{C–O-C of ether}, :: ^{1}HNMR (δ,ppm) 10.096 {s,1H,NH} 7.764 {s,1H ,of Oxazepine ring, O-CH-N}, 6.491 – 7.428 {7H, Ar-H}, 2.5 {s, 2H ofamide}, 3.812{s, 3H of OCH_3},3.775{s, 3H of OCH_3}. CHN ANALYSIS (Cal/Ana %)C{58.22/55.48}, H{4.61/6.84}, N {11.32/17.48}.

3.1.4. 2-p (-Chloro phenyl)-3-(semicarbazone)-2, 3-dihydro-5, 6 Benz [1, 3] -oxazepine -4, 7 Dione (AO.IV)

IR (KBr, cm-1) 1597.13{Ar C=C}, 3087.20{Ar C-H}, 2996.54{Aliphatic C-H}, 1669.46{C=O}, 1300.08 {C-O} 3464.30{N-H of amide}, 1404.24{C-N of amide}, 1693.157{C=O of amide}, 1090.79{Ar-Cl}. ^{1}HNMR (δ,ppm) 10.302{s,1H, NH} 7.826 {s,1H,of Oxazepine ring, O-CH-N}, 6.524 – 7.767 {8H, Ar-H}, 2.5 {s, 2H of amide}.CHNANALYSIS(Cal/Ana%)C{58.43/50.37}, H{3.47/4.7},N{14.61/20.18}.

3.1.5. 2- (3, 4, 5 Trimethoxy phenyl)-3-(semicarbazone)-2, 3-dihydro-5, 6 Benz [1,3]-oxazepine -4, 7 dione (AO.V)

IR (KBr, cm-1) 1576.87{Ar C=C}, 3020{Ar C-H}, 2980.15{Aliphatic CH}, 1682.96{C=O}, 1236.42{C-O }3510.13{N-H of amide}, 1413.38 {C-N of amide}, 1680.07{C=O of amide}, 1124.55{C–O-C of ether}.^{1}HNMR (δ,ppm) 10.224 {s,1H, NH}, 2.5{s, 2H of amide}, 7.750 {s,1H ,of Oxazepine ring, O-CH-N}, 6.541, 7.014{6H, Aromatic Hydrogen}, 3.818{s, 6H of OCH_3}, 3.674{s, 3H of OCH_3}.CHNANALYSIS (Cal/Ana %) C{61.34/52.71}, H{4.79/6.49}, N {13.42/15.17}.

3.1.6. 2- (2, 4- Dichloro phenyl)-3-(semicarbazone)-2, 3-dihydro-5, 6 Benz [1,3]-oxazepine -4, 7 dione (AO.VI).

IR (KBr, cm-1) 1595.20{Ar C=C}, 3074.66{Ar C-H}, 2923.25{Aliphatic C-H}, 1728.29{C=O}, 1218.10{C-O} 3470.09{N-H of amide}, 1417.74{C-N of amide}, 1658.85{C=O of amide}, 1051.25{Ar-Cl}. ^{1}HNMR (δ,ppm) 10.535 {s,1H, NH}, 2.5 {s, 2H of amide}, 8.182 {s,1H ,of Oxazepine ring, O-CH-N}, 6.625-8.248{7H,Ar-H}.CHNANALYSIS(Cal/Ana%)C{50.55/47.00},H{2.92/4.85},N{11.05/15.17}.

3.1.7. 2-p (Toluyl)-3-(semicarbazone)-2, 3-dihydro-5, 6 Benz [1,3]- oxazepine -4, 7 dione (AO.VII)

IR (KBr, cm-1) 1588{Ar C=C}, 3151.82{Ar C-H}, 3040 Aliphatic C-H}, 1670{C=O},1228.71{C-O} 3466.23{N-H of amide}, 1431.24{C-N of amide}, 1649.21{C=O of amide},2986.12{C-H stretch of CH3}, 1355{C-H bend of CH3}. ^{1}HNMR (δ, ppm) 10.150 {s, 1H, NH},2.5 {s, 2H of amide}, 7.805 {s, 1H, of Oxazepine ring, O-CH-N}, 6.430-7.605{8H, Ar - H}, 2.314{s, 3H of CH_3}. CHN ANALYSIS (Cal/Ana %) C{56.86/60.51}, H{4.77/7.10}, N{10.47/23.66}.

3.1.2. 2- (3- Nitro phenyl)-3-(semicarbazone)-2, 3-dihydro-5, 6 Benz [1,3]- oxazepine -4, 7 dione (AO.VIII)

IR (KBr, cm-1) 1556.62{Ar C=C}, 3033.19{Ar C-H}, 2821.01{Aliphatic C-H}, 1672.36, 1682.00{C=O}, 1250.59{C-O} 3458.16{N-H of amide}, 1400.13{C-N of amide}, 1667.53C=O of amide}, 1506.47{N=O stretch of NO2}851.61{C-N Ar stretch of NO_2}. ^{1}HNMR(δ, ppm) 10.601 {s, 1H, NH}, 2.5 {s, 2H of amide}, 7.936 {s, 1H, of Oxazepine ring, O-CH-N},6.680-8.229{8H, Ar H}.CHN ANALYSIS (Cal/Ana %) C{53.94/48.99}, H{3.39/3.87}, N{15.72/19.36}.

4. DISCUSSIONS

All the synthesized 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dionederivatives are solid in nature Out of the eight derivative AO I have dark brown colour due to dimethyl amino group, AO.III(2,4–Dimethoxy) and AO VIII(3 – nitro)derivatives having yellow color and all other having off white to pure white color. In case of physical state, AO IV, AO V, AOVII contains 4 – chloro, 3,4,5 – Trimethoxy and 4 – Methyl groups respectively have crystalline nature while others AO I (dimethyl amino), AO II(4 – Benzyloxy),AO.III (2,4–Dimethoxy) AO VI(2,4 – Dichloro), AO VIII (3 – nitro) derivatives are amorphous in nature. While evaluating the solubility profile all the synthesized compounds are soluble in ethanol and acetone. Among the compounds 2-(2, 4-Dimethoxy phenyl)-3-(Semicarbazone)-2, 3-dihyro-5, 6 Benz [1, 3]-Oxazepine-4, 7-Dione.(AO III) having highest percentage yield and lowest percentage yield was given by 2-(p-nitro phenyl)-3-(Semicarbazone)-2, 3-dihyro-5, 6 Benz [1, 3]-Oxazepine-4, 7-Dione. (AO VIII). Product formed was confirmed by variation in the R_f value given by the intermediate imine and product 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dione.

IR spectra [2,12] gives valuable information regarding the presence of oxazepine ring. FT-IR spectrum of compound schiff base showedappearance of a strong absorption bands

Table - 1: Physicochemical properties of synthesized 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dione derivatives (AO.1-VII)

Sample code	Molecular Formula	Mole weight	Physical state	Color	Melting point	Yield (% w/w)
AO.I	$C_{18}H_{18}N_4O_4$	354.35	Amorphous	Reddish Brown	187^{0}C	76.6
AO.II	$C_{23}H_{19}N_3O_5$	417.41	Amorphous	Off White	196^{0}C	79.3
AO.III	$C_{18}H_{17}N_3O_6$	371.34	Amorphous	Yellow	161^{0}C	90.2
AO.IV	$C_{16}H_{12}N_3O_4Cl$	345.73	Crystalline	Pure White	165^{0}C	81.6
AO.V	$C_{19}H_{19}N_3O_7$	401.37	Crystalline	Off White	191^{0}C	77.7
AO.VI	$C_{16}H_{11}N_3O_4Cl_2$	380.18	Amorphous	White	234^{0}C	83.3
AO.VII	$C_{17}H_{15}N_3O_4$	325.31	Crystalline	Pure White	175^{0}C	77.01
AO.VIII	$C_{16}H_{12}N_4O_6$	356.28	Amorphous	Light Yellow	185^{0}C	63.4

Table - 2: Chromatographic analysis by TLC and R_f value determination

Sample Code	R_f Value (retention factor)
AO.I	0.46
AO.II	0.42
AO.III	0.69
AO.IV	0.80
AO.V	0.83
AO.VI	0.77
AO.VII	0.83
AO.VIII	0.94

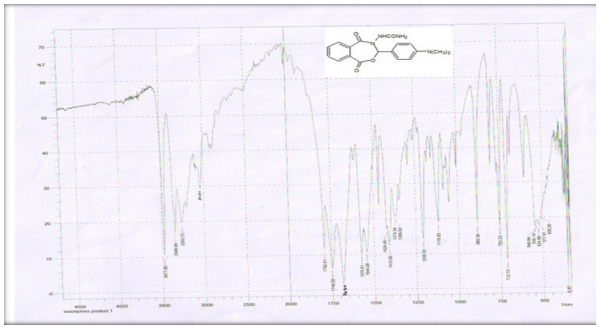


Figure - 2: IR spectrum of AO I.

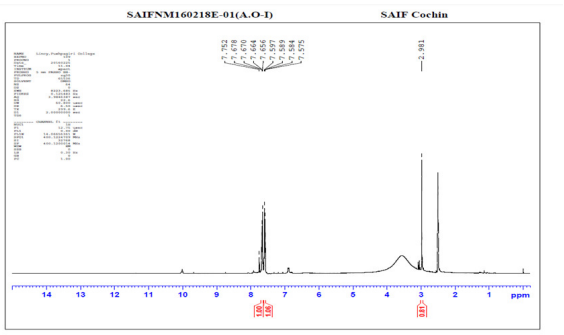


Figure - 3: ^{1}HNMRspectrum of AO I.

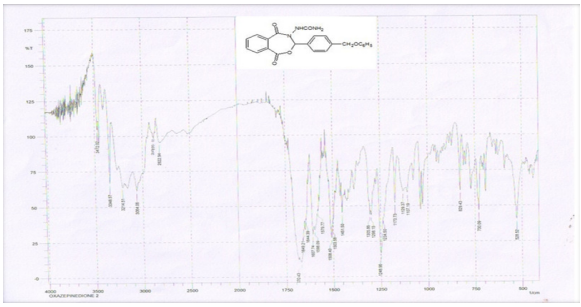


Figure - 4: IR spectrum of AO II.

Table - 3: Physico chemical properties predicted using ACD/Chemsketch software

Sample Code	Density [g/cm^3]	Surface Tension [$dyne/cm$]	Index of Refraction	Parachor[cm^3]	Molar Volume[cm^3]	Polarizability[cm^3]
AO.I	1.41 ± 0.1	71.9 ± 5.0	1.676 ± 0.03	729.2 ± 6.0	250.4 ± 5.0	37.38 ± 0.5 10^{-24}
AO.II	1.42 ± 0.1	73.5 ± 5.0	1.692 ± 0.03	857.0 ± 6.0	292.6 ± 5.0	44.49 ± 0.5 10^{-24}
AO.III	1.45 ± 0.1	70.8 ± 5.0	1.655 ± 0.03	741.8 ± 6.0	255.7 ± 5.0	37.22 ± 0.5 10^{-24}
AO.IV	1.55 ± 0.1	77.5 ± 5.0	1.697 ± 0.03	661.7 ± 6.0	223.0 ± 5.0	34.08 ± 0.5 10^{-24}
AO.V	1.44 ± 0.1	69.3 ± 5.0	1.642 ± 0.03	800.4 ± 6.0	277.4 ± 5.0	39.74 ± 0.5 10^{-24}
AO.VI	1.62 ± 0.1	79.7 ± 5.0	1.704 ± 0.03	698.8 ± 6.0	233.8 ± 5.0	36.00 ± 0.5 10^{-24}
AO.VII	1.42 ± 0.1	71.5 ± 5.0	1.676 ± 0.03	662.8 ± 6.0	227.8 ± 5.0	34.00 ± 0.5 10^{-24}
AO.VIII	1.59 ± 0.1	86.8 ± 5.0	1.709 ± 0.03	681.6 ± 6.0	223.3 ± 5.0	34.56 ± 0.5 10^{-24}

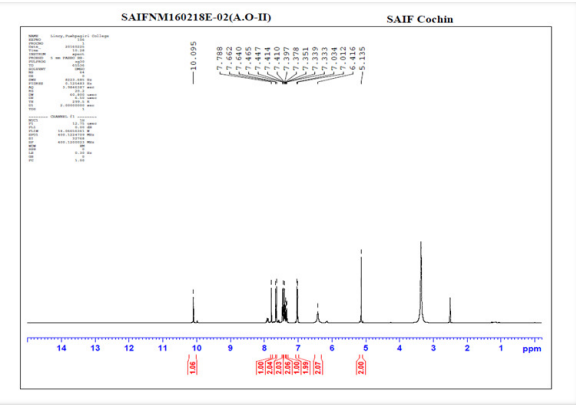


Figure - 5: ^{1}HNMRspectrum of AO II

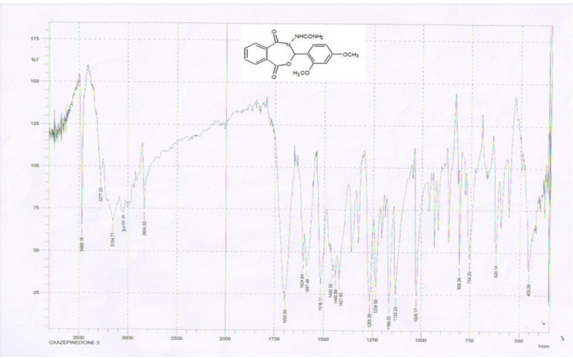


Figure - 6: IR spectrum of AO III.

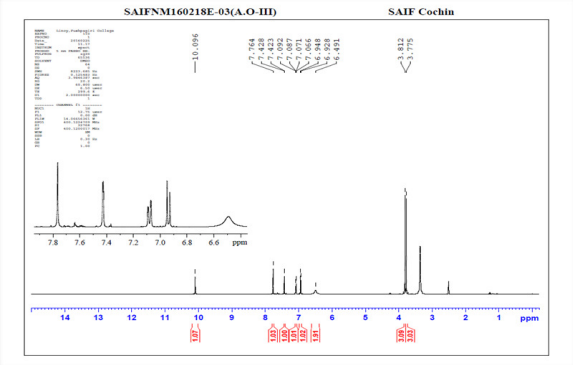


Figure - 7: ^{1}HNMR spectrum of AO III.

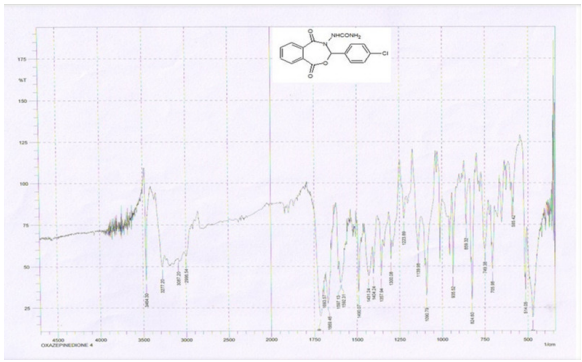


Figure - 8: IR spectrum of AO IV

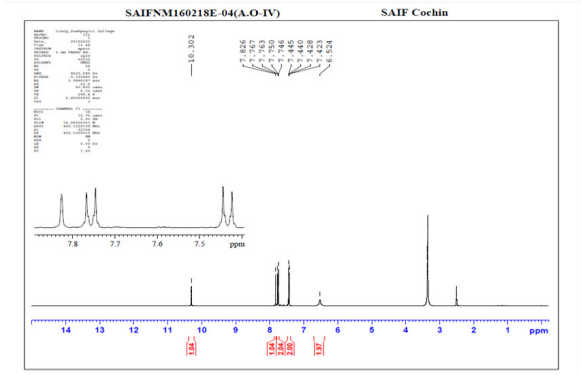


Figure - 9: ^{1}HNMRspectrum of AO IV.

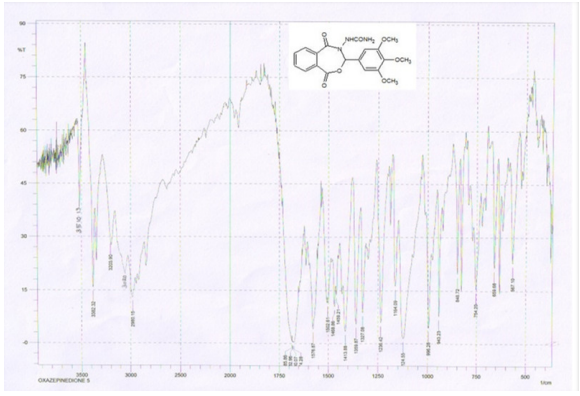


Figure - 10: IR spectrum of AO V.

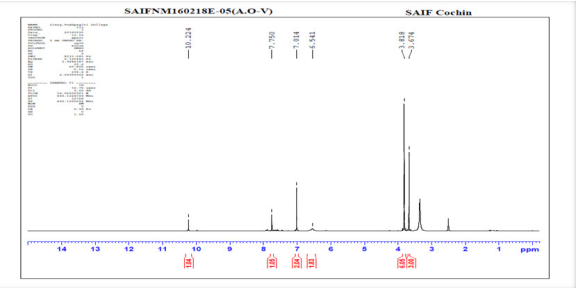


Figure - 11: [1]HNMRspectrum of AO V.

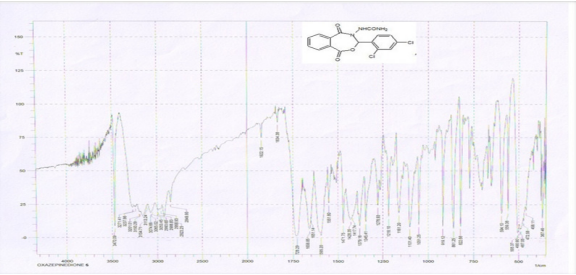


Figure - 12: IR spectrum of AO VI.

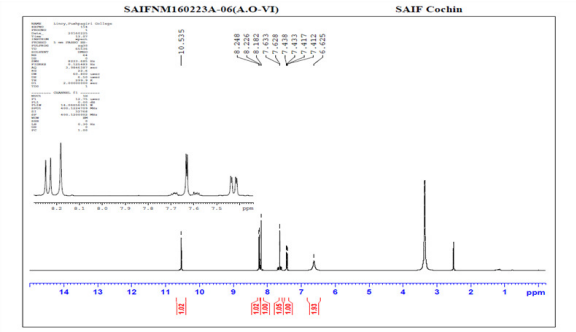


Figure - 13: [1]HNMRspectrum of AO VI.

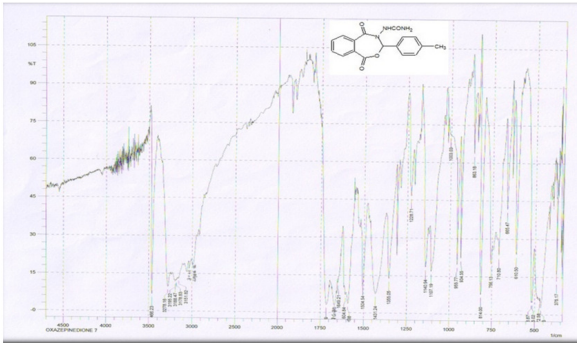


Figure - 14: IR spectrum of AO VII.

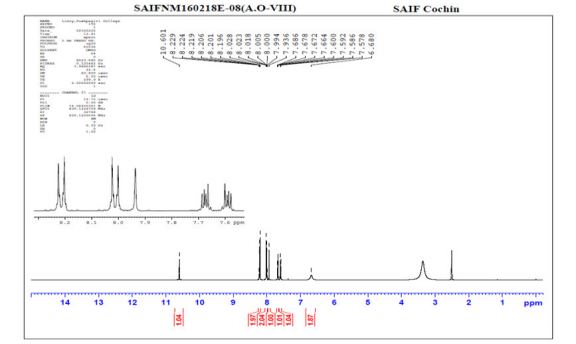


Figure - 15: [1]HNMR spectrum of AO VII.

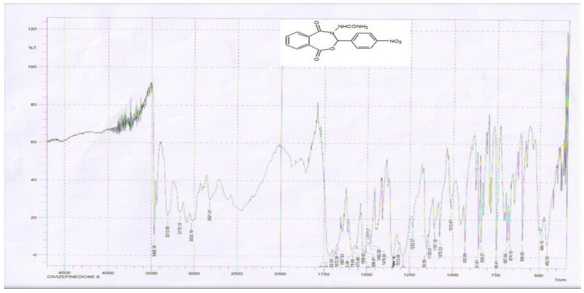


Figure - 17: IR spectrum of AO VIII.

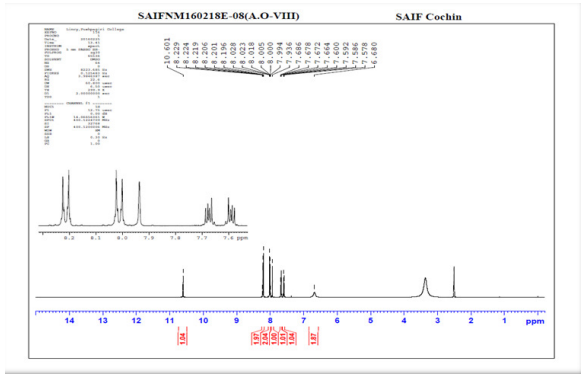


Figure - 18: [1]HNMRspectrum of AO VIII.

at range of 1660 - 1650cm^{-1}due to the presence of (C=N)and appearance strong bands in the region of 3464cm^{-1}due to asymmetric and symmetric stretching vibration of (-NH_2) group. While these strong bands were disappear and strong bands were appeared in the region of 1760cm^{-1} due to (lactones) groups of 1, 3-oxazepine compounds. Also, the absorption band at the range near to1400cm-1 is due the presence of C–N stretching of amide. Other data of functional groups are written in the results.

In proton NMR spectra [2,12], the core oxazepine ring can be identified by two peaks. Singlet peak in the range of 10 δ, ppm indicate the presence of one hydrogen due to NH in the ring and singlet peak in the region of 7-8δ, ppm indicate the presence of one hydrogen due to O-CH-N of Oxazepine ring, The presence of 2 amide hydrogen can detect by the presence of singlet peak at 2.5 δ,ppm. Finally the aromatic hydrogen can be identified by the presence multiplet at the range 7.575 – 7.678δ, ppm which depends upon the substitution on the aromatic ring. Other data for the peak for hydrogen in the functional group are given in the results. Along with the elementary analysis data the structure of the synthesized compounds can be confirmed.

5. CONCLUSION

The objective of the study was to synthesize 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dione (AO.1-VII). All the synthesized compounds were characterized by their physicochemical properties like melting point, colour, physical

state etc. Chromatographical analysis, TLC was performed and R_f value was determined. Solubility profile with various solvent was also determined. Chemical structure of 5, 6 – Benz 1, 3 – Oxazepine 4, 7 – Dione was determined by IR and ^{1}HNMRspectral data and CHNS analysis. All these confirmed the structure of the synthesized compounds.

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