Original Article

SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF NEW PYROLLIDONE DERIVATIVES

Dipti Ganesh Phadtare[1*], Laxanikant A Kawale[1], Vandana S Nade[2]

[1] Department of Pharmaceutical Chemistry, M. V. P. Samaj's College of Pharmacy, Gangapur Road, Nashik- 422 002, India.
[2] Department of Pharmacology, M. V. P. Samaj's College of Pharmacy, Gangapur Road, Nashik- 422 002, India.
Email: aditi24aug@gmail.com

DOI: 10.47750/pnr.2022.13.S09.1251

Abstract

Anticonvulsants are diverse group of medicinal agents which is used in the treatment of epileptic seizures. These are also one of the increasingly being used medicines in the treatment of bipolar disorders as well as some of the borderline disorders which are associated with the personality such as mood stabilizers and neuropathic pain.

Introduction

Anticonvulsant drugs are also called as anti-seizure drugs and the stabilize the cell membranes and suppress the abnormal electric impulses in the cerebral cortex. These drugs are used to prevent seizures but do not provide a cure. They are also known as antiepileptic drugs (AEDs). Anti-seizure drugs are classified as CNS depressants. There are three main pharmacological effects of anti-seizure medications including;

1) They increase the threshold of activity in the motor cortex to make it more difficult for a nerve to become excited.

2) They prevent the spread of seizure discharge from its origin by suppressing the transmission of impulses from one nerve to next.

3) The decrease the speed of the nerve impulse conduction within a given neuron.

Cllasification:

I.Barbiturates

Most of the barbiturate are sedative and hypnotics.

e. g. Phenobarbitone, Metharbital, Mephobarbiton

II.Hydantoins

These are close structural relatives of barbituric acid, differing due to the lack of C-6 ozo group. The lack of this carbonyl group decreases the acidity. Du to this is a weaker acid than that of barbiturates.

e. g. Phenytoin, Phenyl ethyl hydantoin, ethotoin, Mephenytoin.

III.Oxazolidinedione

Replacement of the –NH group at position 1 of the Hydantoin systems with oxygen atom yields the ocazolidine-2,4- dione system, trimethadione is only clinically used.

e. g. Trimethadione, Paramethadione, Malidione.

IV.Succinimides

They inhibit T-type calcium channels and inhibit the three cycle per second thalamic 'spike and wave' discharge in absence seizures.

e. g. Phensuximide, Methsuximide, Ethosuximide.

V.Acetyl urea derivatives or phenyl acetyl urea

It is a congener and ring opened analogue of phenytoin and is structurally related to the barbiturates and to other hydantoins.

e.g. Phenytoin, Phenyl ethyl acetyl urea

VI. Benzodiazepines

They are used to induce feeliings of calm, drowsiness and sleep. They act by facilitating the binding of the inhibitory neurotransmitter GABA at various GABA receptors throughout the CNS.

e.g. Nitrazepam, Clonazepam.

VII. Carbonic anhydrase inhibitors

These are used for inhibition of the resorption of bicarbonate by the tubular cells, leafing to retention of bicarbonate in the tubular lumen.

e.g. Acetazolaminde, Ethoxazolamide, Sulthiame.

VIII. Gamma amino butyric acid (GABA) analogues

These are used as primary inhibitory neurotransmitter for the central nervous system (CNS). It is used to reduce neuronal excitability by inhibiting nerve transmission.

e.g. Progabide, Vigabatrin, Gabapentin, Tiagabin.

IX. Iminostilbenes

It inihibits activity of voltage-gated sodium channels and as a result stabilizes hyperexcited neurons, suppressing propagation of excitatory impulses.

e.g. Carbamazepine

X. Newer anticonvulsants

These are modified and newer antiepileptic drugs used to reduce neuronal excitability by promoting sodium channel inactivation, inhibiting T-type calcium channels, or enhancing gamma- aminobutyric acid type A receptor mediated inhibition.

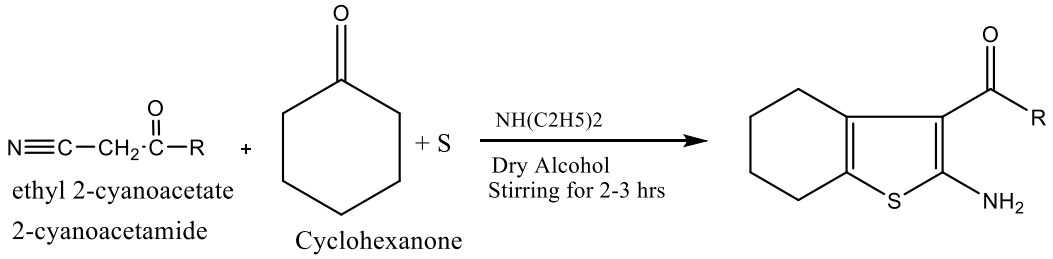
e.g. Denzimol, Denzinamide, Zonisamide, Lamotrigine, Fosphenytoin, Nafimidone, Topiramate.

XI. Miscellaneous

e. g. Sodium valproate, Primidone.

The synthesis of the target compound has been achieved by adopting following synthetic procedure;

STEP 1



ethyl 2-cyanoacetate

2-cyanoacetamide

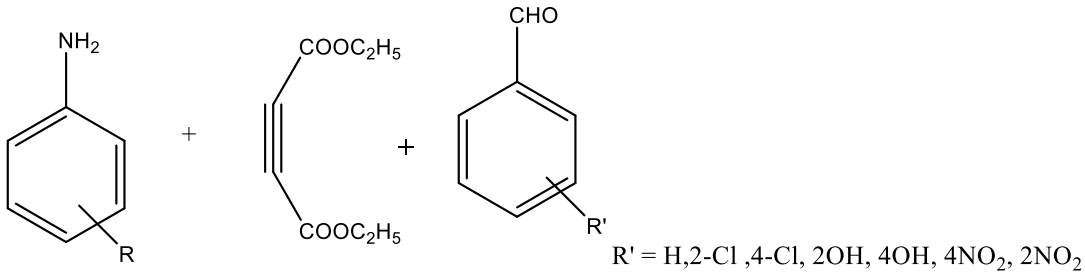
R= OC_2H_5, NH_2

Cyclohexanone

i) 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide

ii) ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

STEP 2



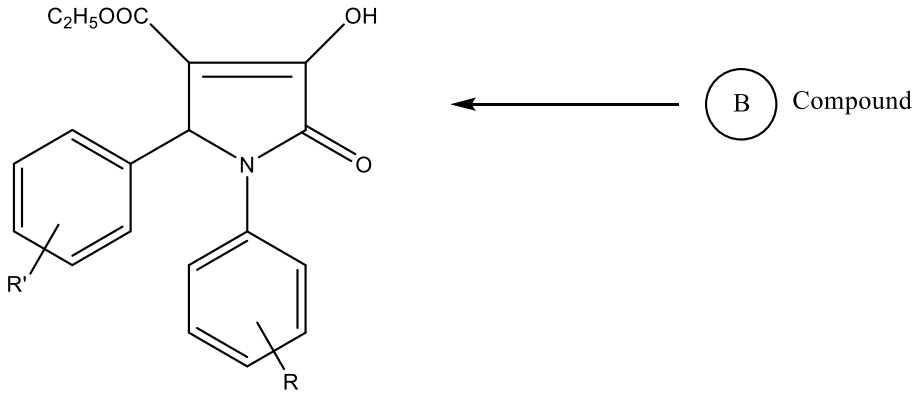
R' = H,2-Cl ,4-Cl, 2OH, 4OH, $4NO_2$, $2NO_2$

Aniline

R= H,2Cl ,4Cl

diethyl acetylene dicarboxylate

Ultrasound Irradiation or Reflux for 10-15 hrs



ethyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate

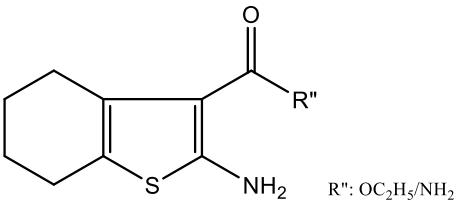
Preparation of Ethyl 2-Amino -4,5,6,7 Tetrahydro Benzothiopene 3 -Carboxylate

Step-1: A equimolar mixture of cyclohexanone (10 ml ,0.1mol), Sulphur (3.2 gm,0.1mol), Ethyl cyano acetate (10 ml,0.1 mol) and diethyl amine (15 ml,0.1 mol) in dry ethanol (20 ml) were placed in 500 ml round bottomed

flask and stirred for 90 minutes. The reaction mixture was poured into mixture of ice-cold water with constant stirring and then was left a side for 3 hours. The separated solid was collected by filtration and dried.

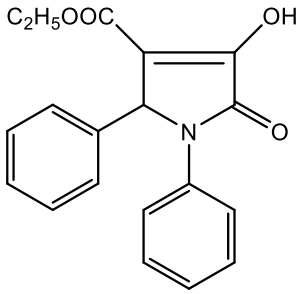
Step 2: A solution of aniline (0.091 ml, 1 mmol) and diethyl acetylenedicarboxylate (0.160 ml, 1 mmol) in ethanol (4 ml) was magnetically stirred at room temperature. To the mixture, 4-chlorobenzaldehyde (0.141 g, 1 mmol) and citric acid monohydrate (0.42 g, 2 mmol) were added and the content was sonicated under ultrasound irradiation. The same reaction was also conducted without sonication at room temperature. The progress of the reactions was checked by TLC (n-hexane : EtOAc, 10 : 7). After completion of the reactions, the solid product was filtered and the pure product was obtained by recrystallization from hot ethanol.

Step 3



2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3 carboxamide

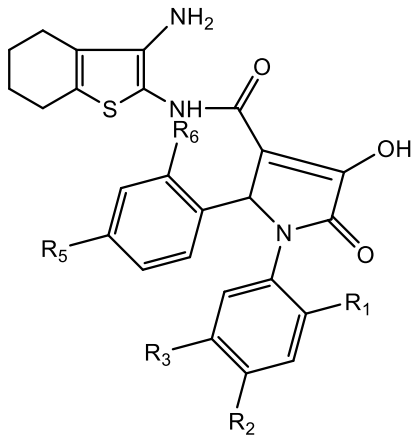
ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate



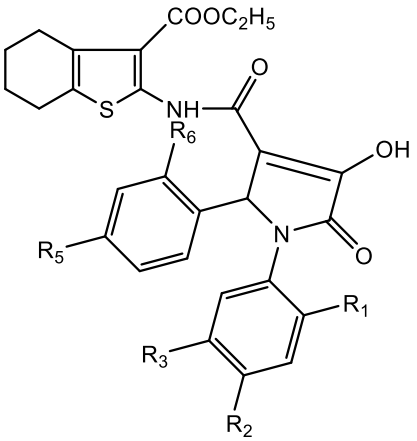
ethyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate

Glacial acetic acid

Reflux at 60C for 4 to 5 hrs



N-(3-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide

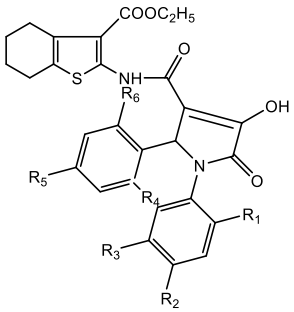


ethyl 2-(4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate

Step 3: In Step 3 : 50 ml Glacial Acetic Acid, A compound (0.01mol) and B compound (0.01 mol) refluxed at 60C for 4 to 5 hrs. The reaction mixture was distilled at low pressure to remove excess acetic acid through evaporation. The yellow residue was filtered, dried and recrystallised from ethanol to gives crystalline products.

Compound / Product code	R	R1	R2	R3	R4	R5	R6	Mol. Formula (mol.wt)	Solvent to Recrystallization	M.p°c (yield%)	Rf. value
1	-OC_2H_5	H	H	H	H	H	H	$C_{28}H_{26}N_2O_5S$ (502.0)	Ethanol	241-242 (60%)	0.69
2	”	H	H	H	H	H	2-Cl	$C_{28}H_{25}ClN_2O_5S$ (537.027)	Ethanol	250-252 (61%)	0.58
3	”	H	H	H	H	4-Cl	H	$C_{28}H_{25}ClN_2O_5S$ (537.027)	Ethanol	254-256 (50%)	0.59
4	”	H	H	H	H	H	2-NO_2	$C_{28}H_{25}N_3O_7S$ (547.141)	Ethanol	249-251 (51%)	0.60
5	”	H	H	H	H	4-NO_2	H	$C_{28}H_{25}N_3O_7S$ (547.141)	Ethanol	230-231 (52%)	0.61
6	”	H	H	H	H	H	2-OH	$C_{28}H_{28}N_2O_6S$ (518.581)	Ethanol	257-259 (49%)	0.58
7	”	H	H	H	H	4-OH	H	$C_{28}H_{28}N_2O_6S$ (518.581)	Ethanol	233-234 (53%)	0.59
8	”	2-Cl	4-Cl	5-Cl	-F	-Cl	-F	$C_{28}H_{20}Cl_4F_2N_2O_5S$ (676.94)	Ethanol	257-258 (62%)	0.64
9	-NH_2	H	H	H	H	H	2-Cl	$C_{26}H_{22}ClN_3O_4S$ (507.102)	Ethanol	261-262 (61%)	0.40
10	”	H	H	H	H	4-Cl	H	$C_{26}H_{22}ClN_3O_4S$ (507.102)	Ethanol	235-237 (62%)	0.41
11	”	H	H	H	H	4-NO_2	H	$C_{26}H_{22}N_4O_6S$ (510.541)	Ethanol	240-242 (70%)	0.44
12	”	H	H	H	H	H	2-NO_2	$C_{26}H_{22}N_4O_6S$ (510.541)	Ethanol	263-265 (71%)	0.47
13	”	H	H	H	H	4-OH	H	$C_{26}H_{23}N_3O_5S$ (489.543)	Ethanol	259-261 (59%)	0.51
14	”	H	H	H	H	H	2-OH	$C_{26}H_{23}N_3O_5S$ (489.543)	Ethanol	248-250 (62%)	0.52
15	”	2-Cl	4-Cl	5-Cl	H	4-NO_2	2-NO_2	$C_{26}H_{18}Cl_3N_5O_8S$ (666.878)	Ethanol	265-267 (60%)	0.67

Evaluation of General Structure Of Pyrrolidone Derivatives



Compound / Product code	IUPAC name	R	R1	R2	R3	R4	R5	R6	Mol. Formula (mol.wt)
P1	ethyl 2-(4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$-OC_2H_5$	H	H	H	H	H	H	$C_{28}H_{26}N_2O_5S$ (502.0)
P2	ethyl 2-(4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	H	2-Cl	$C_{28}H_{25}ClN_2O_5S$ (537.027)
P3	ethyl 2-(2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	4-Cl	H	$C_{28}H_{25}ClN_2O_5S$ (537.027)
P4	ethyl 2-(4-hydroxy-2-(2-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	H	2-NO_2	$C_{28}H_{25}N_3O_7S$ (547.141)
P5	ethyl 2-(4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	4-NO_2	H	$C_{28}H_{25}N_3O_7S$ (547.141)
P6	ethyl 2-(2-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	H	2-OH	$C_{28}H_{26}N_2O_6S$ (518.581)

P7	ethyl 2-(4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	4-OH	H	$C_{28}H_{26}N_2O_6S$ (518.581)
P8	ethyl 2-(2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-(2,4,5-trichlorophenyl)-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	2-Cl	4-Cl	5-Cl	H	-Cl	H	$C_{28}H_{22}Cl_4N_2O_5S$ (640.94)

Compound / Product code	IUPAC name	Mol. Formula (mol.wt)	Solvent to Recrystallization	M.p°c (yield%)	Rf. value
P1	ethyl 2-(4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$C_{28}H_{26}N_2O_5S$ (502.0)	Ethanol	241-242 (60%)	0.69
P2	ethyl 2-(4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$C_{28}H_{25}ClN_2O_5S$ (537.027)	Ethanol	250-252 (61%)	0.58
P3	ethyl 2-(2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$C_{28}H_{25}ClN_2O_5S$ (537.027)	Ethanol	254-256 (50%)	0.59
P4	ethyl 2-(4-hydroxy-2-(2-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$C_{28}H_{25}N_3O_7S$ (547.141)	Ethanol	249-251 (51%)	0.60
P5	ethyl 2-(4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$C_{28}H_{25}N_3O_7S$ (547.141)	Ethanol	230-231 (52%)	0.61
P6	ethyl 2-(2-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$C_{28}H_{26}N_2O_6S$ (518.581)	Ethanol	257-259 (49%)	0.58
P7	ethyl 2-(4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$C_{28}H_{26}N_2O_6S$ (518.581)	Ethanol	233-234 (53%)	0.59
P8	ethyl 2-(2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-(2,4,5-trichlorophenyl)-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	$C_{28}H_{22}Cl_4N_2O_5S$ (640.94)	Ethanol	257-258 (62%)	0.64

SPECTRAL DATA

P1: m/e: 502 **; FTIR(cm-1):** 3040 (Ar-CH str.); 3380 (N-H str),2853-2925 (-NH-CO str.); 1670(-CONH str.); 1640 (N-H bending) 1612 (-C=N str.); 1580 ,1527 ,1480 (Aromatic Ring Stretching) **;1H NMR (DMSO-d6) δ ppm:** 11.05(s, 1H, OH), 8.15 (s,1H,NH-CO) ,5.6 (s, 1H, Pyrrolidinone), 6.9-8.1 (m, 10H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.36 (m,3H,CH3 of COOC2H5) 2.5-2.6 (d,4H,Tetra Hydro Benzo thiophene),1.2-1.6 (d,4H,Tetra Hydro Benzo thiophene)

P2: m/e: 537.027 ; **FTIR(cm-1):** 3098 (Ar-CH str.); 3310 (N-H str), 2870 (-NH-CO str.); 1670(-CONH str.); 1580 (-C=N str.); 680 (C-S str), 650.85 (-C-Cl str.) **1H NMR (DMSO-d6) δ ppm):** 12.1(s, 1H, OH), 7.96 (s,1H,NH-CO) ,5.52 (s, 1H, Pyrrolidinone), 7.1-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.26 (m,3H,CH3 of COOC2H5) 2.1-2.3 (d,4H,Tetra Hydro Benzo thiophene),1.2-1.7 (d,4H,Tetra Hydro Benzo thiophene)

P3: m/e: 537.027 ; **FTIR(cm-1):** 3153 (Ar-CH str.); 3430 (N-H str), 2930 (-NH-CO str.); 1689(-CONH str.); 1591 (-C=N str.); 691 (C-S str), 679.21 (-C-Cl str.) **1H NMR (DMSO-d6) δ ppm** 12.1(s, 1H, OH), 7.96 (s,1H,NH-CO) ,5.52 (s, 1H, Pyrrolidinone), 7.1-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.26 (m,3H,CH3 of COOC2H5) 2.1-2.3 (d,4H,Tetra Hydro Benzo thiophene),1.2-1.7 (d,4H,Tetra Hydro Benzo thiophene)

P4: m/e: 547.141 ; **FTIR(cm-1):** 3145 (Ar-CH str.); 3397 (N-H str), 2880 (-NH-CO str.); 1673(-CONH str.); 1560.10 (N-O str),1575.7 (-C=N str.); 685 (C-S str).**1H NMR (DMSO-d6) δ ppm**: 11.15(s, 1H, OH), 8.2 (s,1H,NH-CO) ,5.7 (s, 1H, Pyrrolidinone), 6.7-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.256 (m,3H,CH3 of COOC2H5) 2.5-2.6 (d,4H,Tetra Hydro Benzo thiophene),1.2-1.7 (d,4H,Tetra Hydro Benzo thiophene)

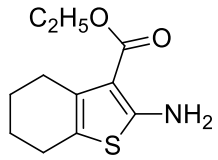
P5: m/e: 547.141; **FTIR(cm-1):** 3155 (Ar-CH str.); 3320 (N-H str), 2778 (-NH-CO str.); 1643(-CONH str.); 1580 (N-O str),1597.7 (-C=N str.); 675 (C-S str).**1H NMR (DMSO-d6) δ ppm:** 11.15(s, 1H, OH), 8.2 (s,1H,NH-CO) ,5.7 (s, 1H, Pyrrolidinone), 6.7-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.256 (m,3H,CH3 of COOC2H5) 2.5-2.6 (d,4H,Tetra Hydro Benzo thiophene),1.2-1.7 (d,4H,Tetra Hydro Benzo thiophene)

P6: m/e: 518.58 ; **FTIR(cm-1)**: 3124.44 (Ar-CH str.); 3610.24 (-OH str.),3410 (N-H str),2865.87 (-NH-CO str.); 1685.43(-CONH str.);1586.7(-C=N str.); 723(C-S str).**1H NMR (DMSO-d6) δ ppm**: 10.65(s, 1H, OH), 8.63 (s,1H,NH-CO) ,8.82 (s,1H, Phenyl-OH),5.4 (s, 1H, Pyrrolidinone),6.9-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.26 (m,3H,CH3 of COOC2H5) 2.1-2.3 (d,4H,Tetra Hydro Benzo thiophene),1.29-1.5 (d,4H,Tetra Hydro Benzo thiophene)

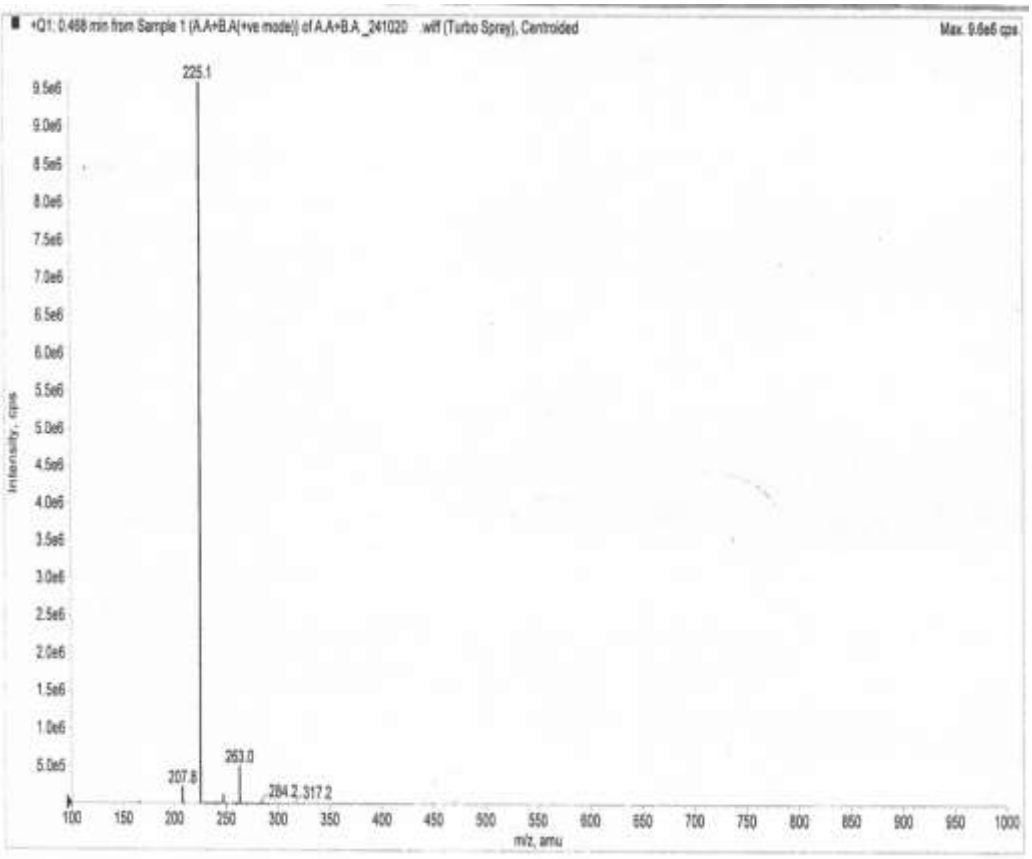
P7: m/e: 518.18; **FTIR(cm-1)**: 3310.32 (Ar-CH str.); 3720.20 (-OH str.),3376 (N-H str),2740 (-NH-CO str.); 1670.38(-CONH str.);1554.8(-C=N str.); 705(C-S str)**1H NMR (DMSO-d6) δ ppm**: 10.65(s, 1H, OH), 8.63 (s,1H,NH-CO) ,8.82 (s,1H, Phenyl-OH),5.4 (s, 1H, Pyrrolidinone),6.9-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.26 (m,3H,CH3 of COOC2H5) 2.1-2.3 (d,4H,Tetra Hydro Benzo thiophene),1.29-1.5 (d,4H,Tetra Hydro Benzo thiophene)

P8: m/e: 640.94; **FTIR(cm-1)**: 3183.74 (Ar-CH str.); 3384 (N-H str), 2930 (-NH-CO str.); 1640(-CONH str.); 1627 (-C=N str.);689 (C-S str), 608.85 (-C-Cl str.) ;**1H NMR (DMSO-d6) δ ppm**: 11.8(s, 1H, OH), 8.4 (s,1H,NH-CO) ,5.32 (s, 1H, Pyrrolidinone),6.9-8.5 (m, 6H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.34(m,3H,CH3 of COOC2H5) 2.4-2.6 (d,4H,Tetra Hydro Benzo thiophene),1.7-1.76 (d,4H,Tetra Hydro Benzo thiophene)

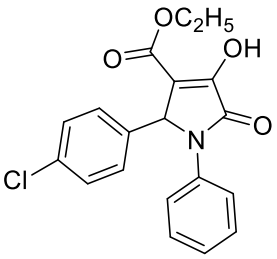
SPECTRAL STUDY OF INTERMEDIATES:



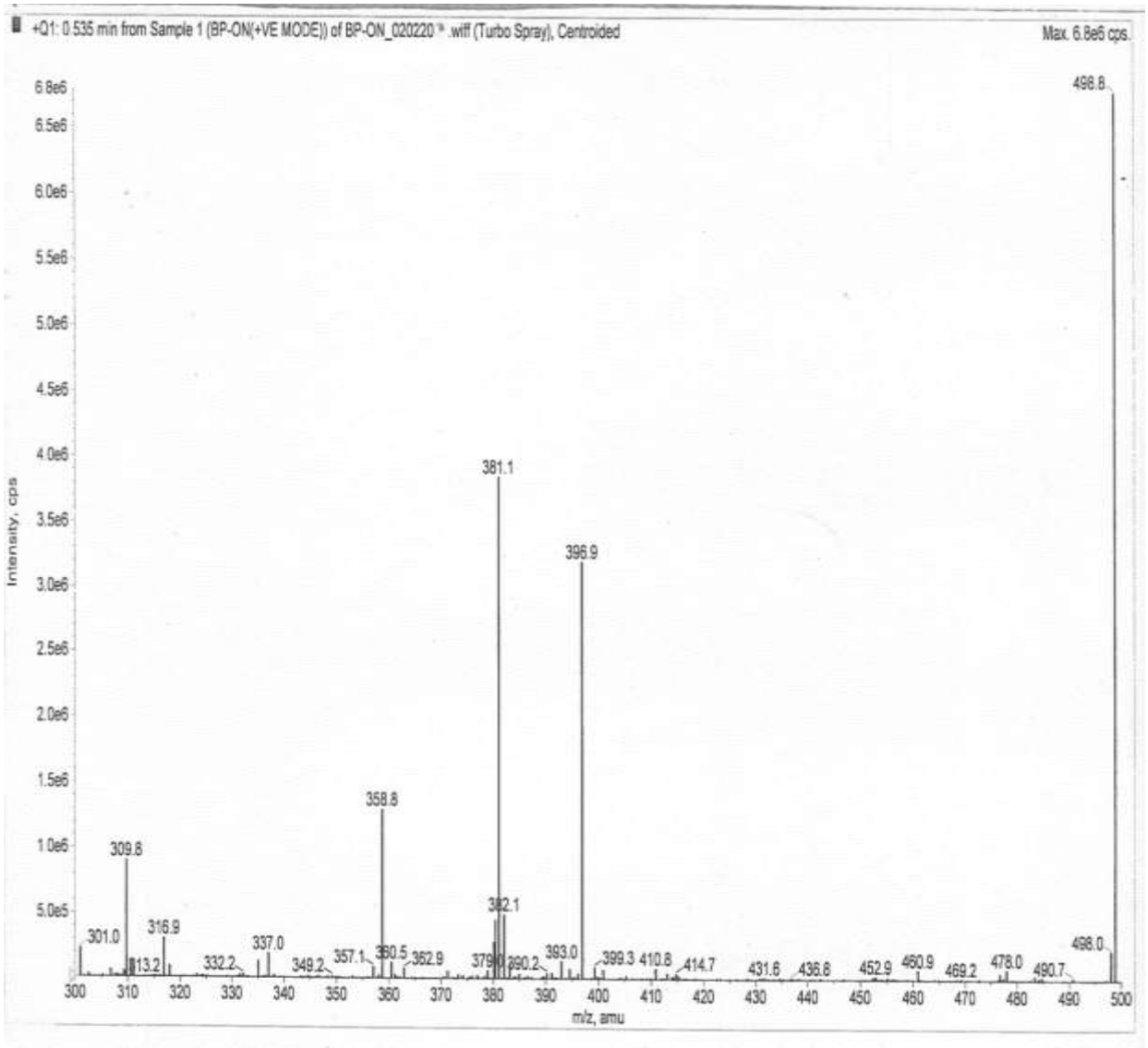
ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate



Calculated Mol.Wt:225 Observed Mol.Wt:225.1(Peak M^+)



ethyl 2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate



Calculated Mol.Wt: 357.8 Observed Mol.Wt: 358 .8(Peak :M^+)

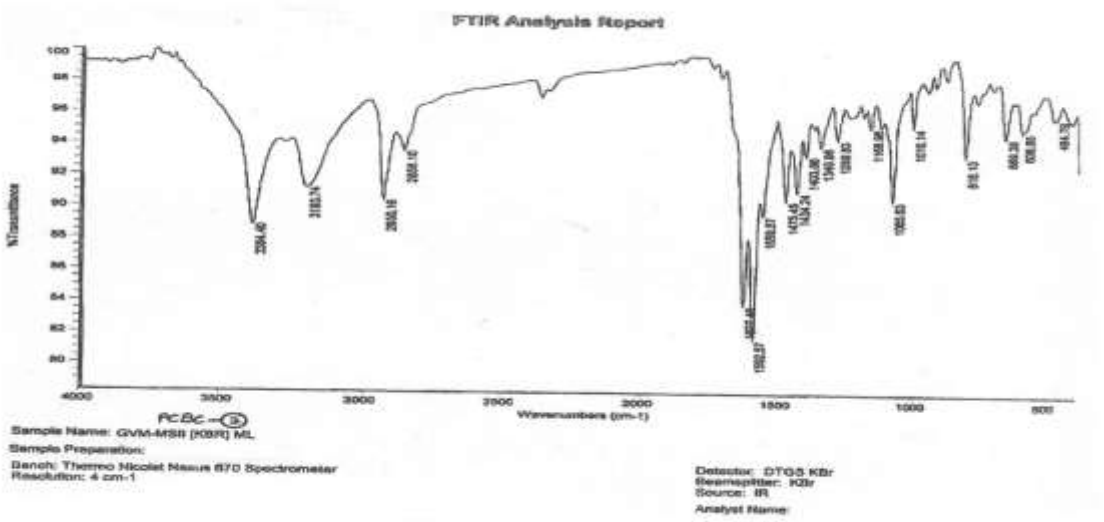
SPECTRAL DATA:

Spectral investigations were used to determine the structure of some final purified substances. At acceptable ranges, FT-IR spectra revealed typical absorption bands for specific functional groups. Chemical shift values are likewise found to be within the predicted range. Compound HRMS revealed molecular ion peaks that corresponded to the molecular formula.

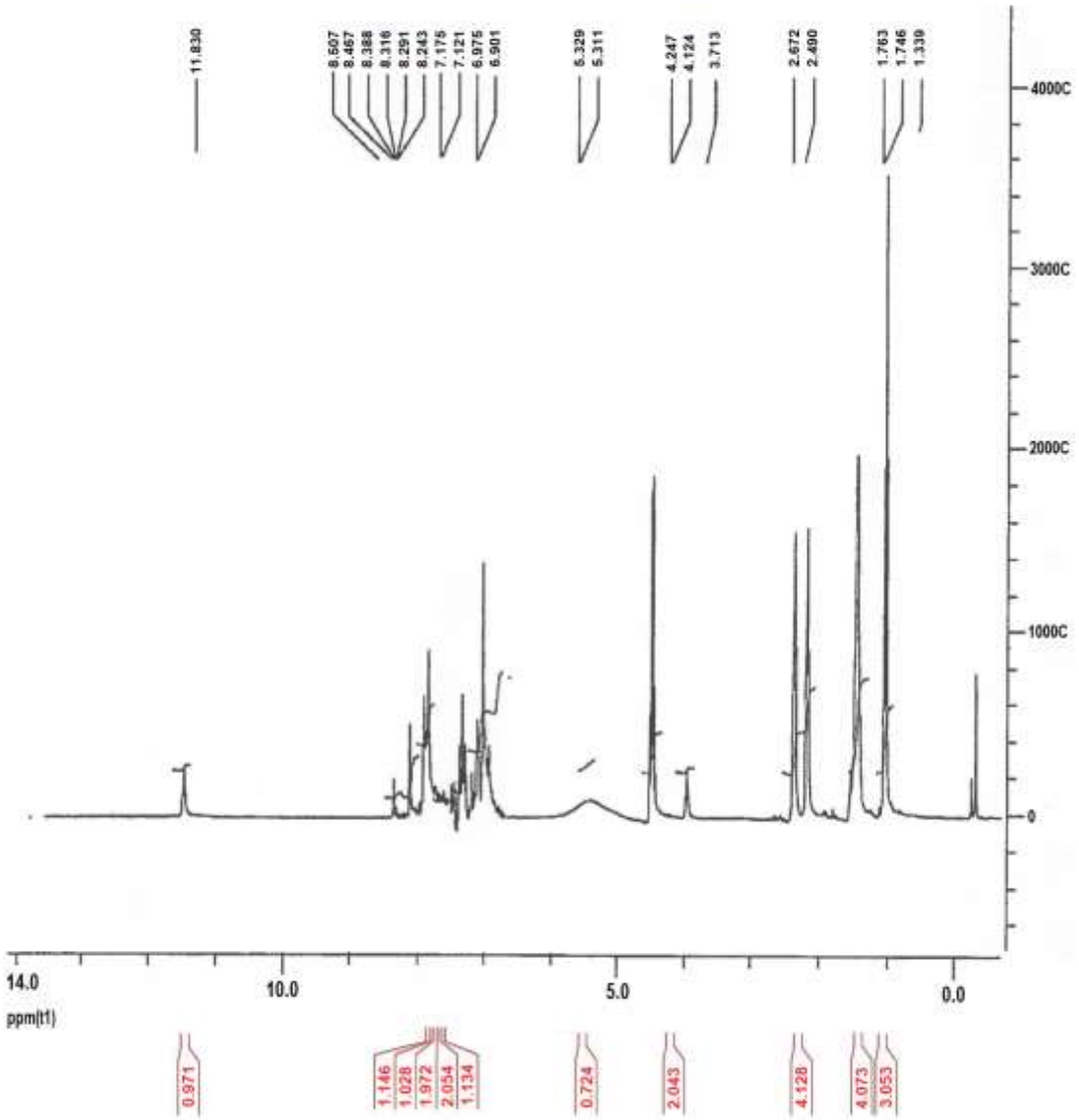
The synthesis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate from Ethyl 2 Cyano Acetate was confirmed with Mass Spectrometry at 225.1

Synthesis of ethyl 2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate was confirmed with Mass at (M+1 Peak)

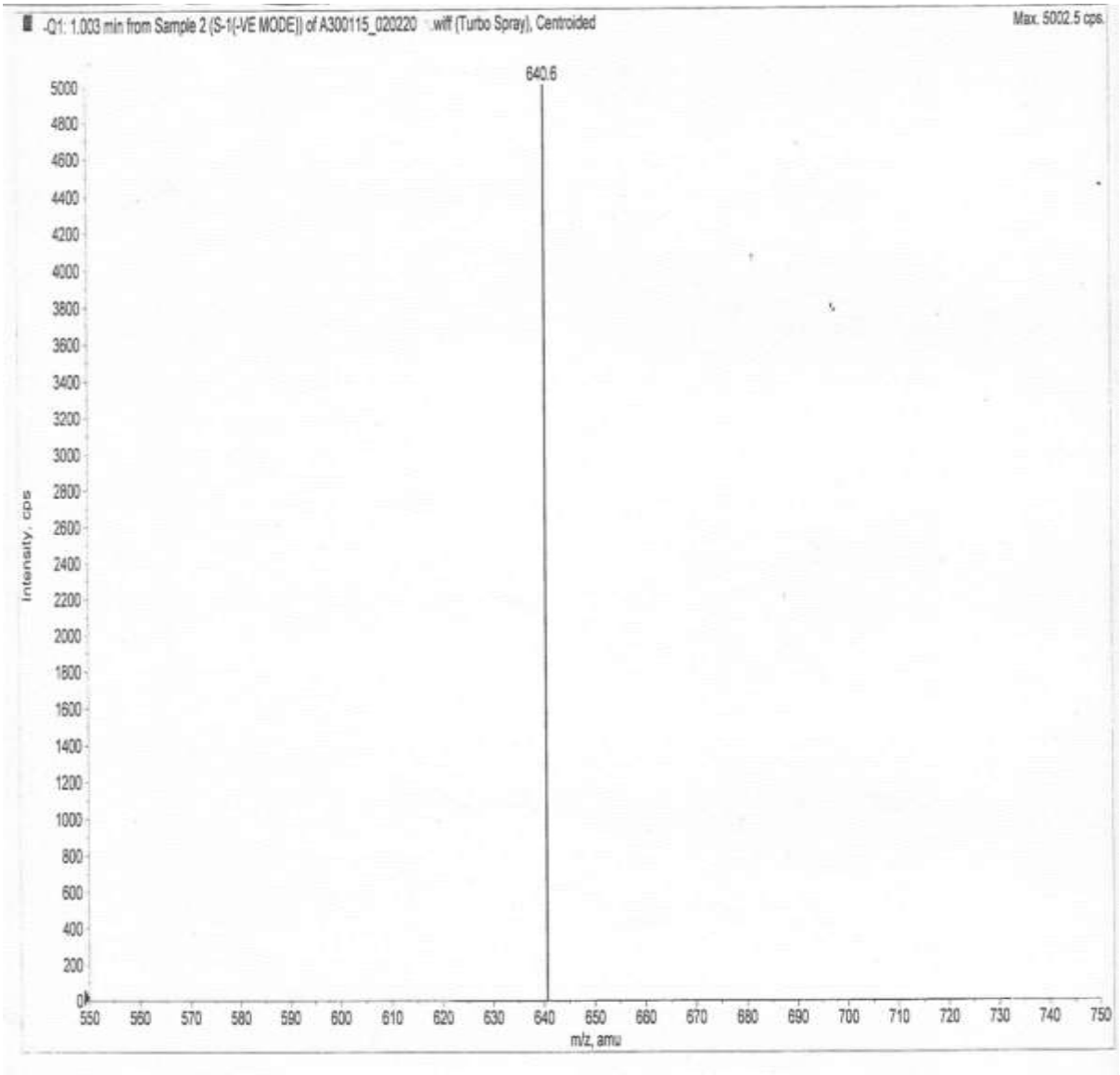
Compound / Product code	IUPAC name	R	R1	R2	R3	R4	R5	R6	Mol. Formula (mol.wt)
P8	ethyl 2-(2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-(2,4,5-trichlorophenyl)-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	2-Cl	4-Cl	5-Cl	H	-Cl	H	$C_{28}H_{22}Cl_4N_2O_5S$ (640.94)



IR Spectral Data : 3183.74 (Ar-CH str.); 3384 (N-H str), 2930 (-NH-CO str.); 1640(-CONH str.); 1627 (-C=N str.); 1475 ,1559 ,1592 (Aromatic Ring Stretching),689 (C-S str), 608.85 (-C-Cl str.)



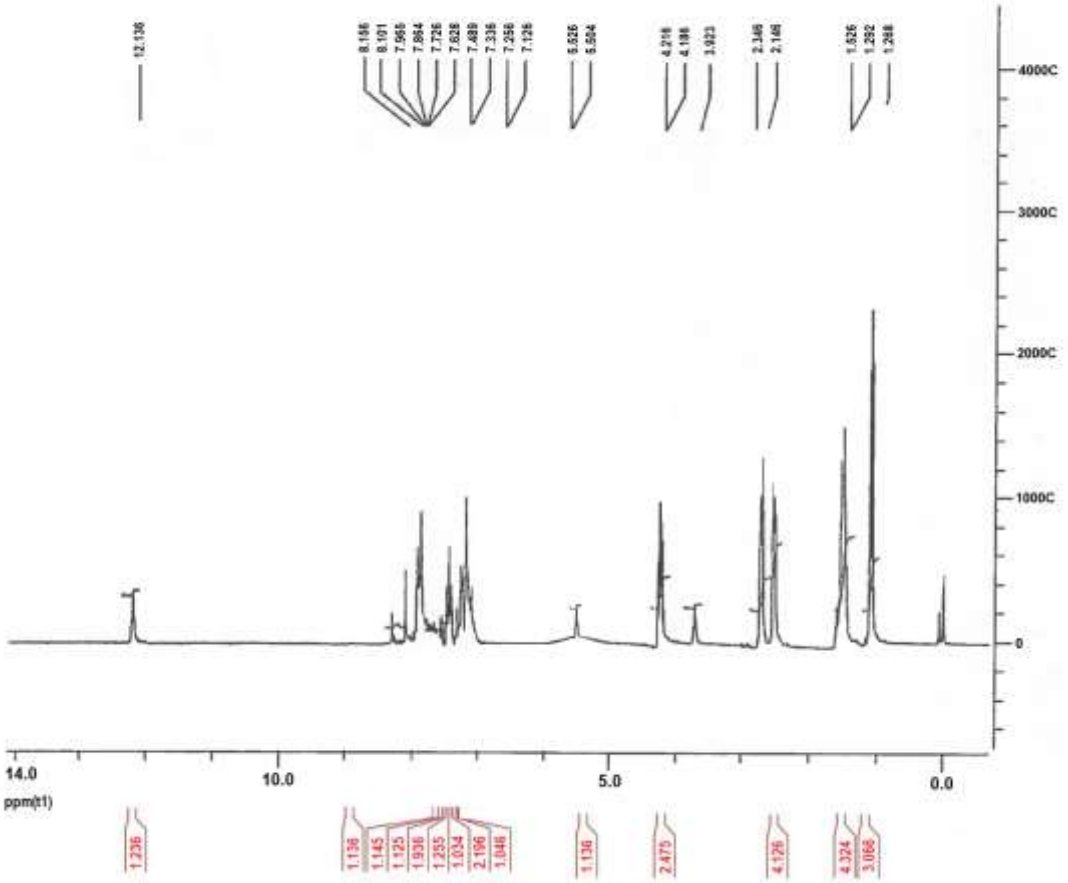
1H NMR (DMSO-d6) δ ppm: 11.8(s, 1H, OH), 8.4 (s,1H,NH-CO) ,5.32 (s, 1H, Pyrrolidinone),6.9-8.5 (m, 6H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.34(m,3H,CH3 of COOC2H5) 2.4-2.6 (d,4H,Tetra Hydro Benzo thiophene),1.7-1.76 (d,4H,Tetra Hydro Benzo thiophene)



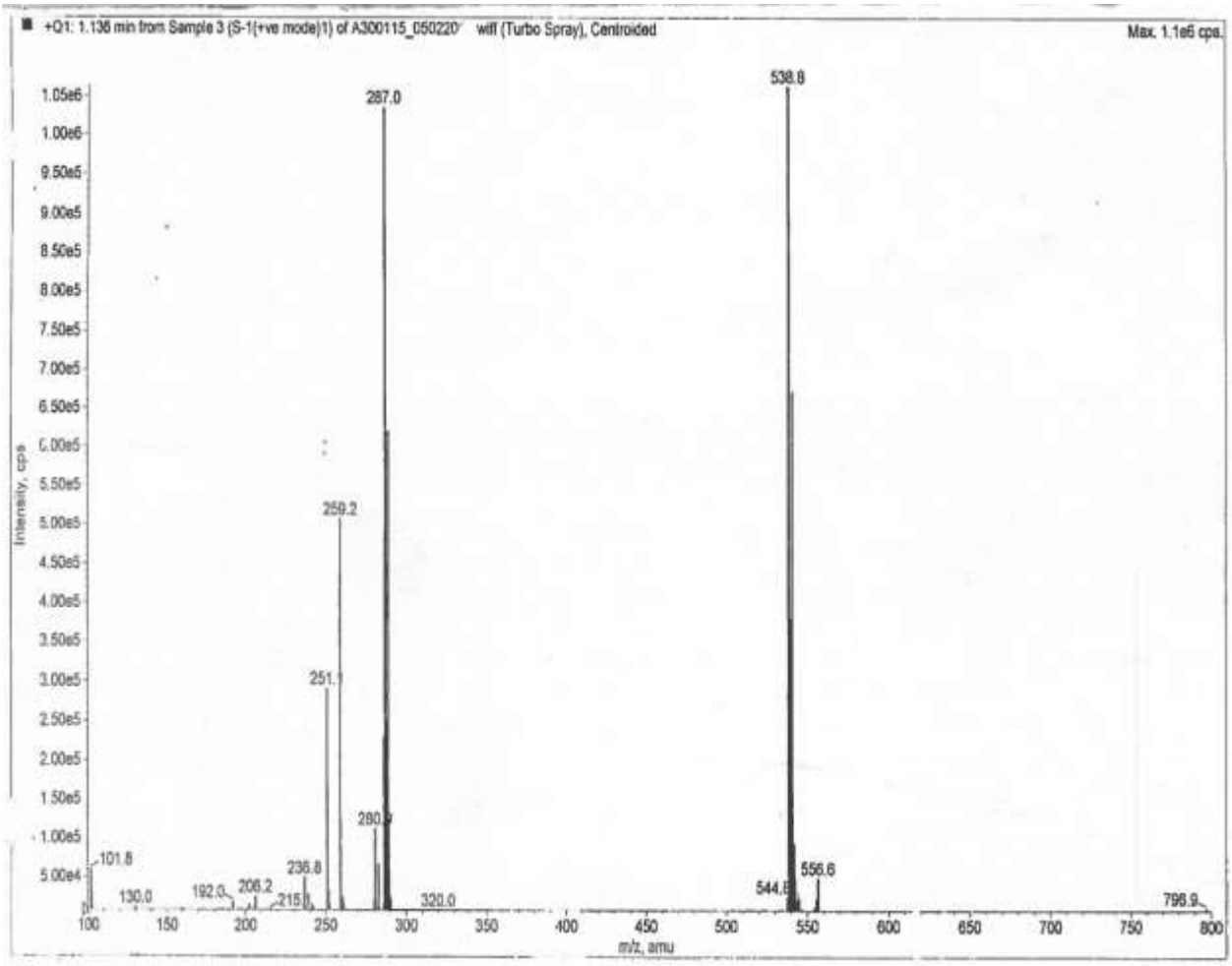
Calculated Mol.Wt:640 Observed Mol.Wt:640.9(Peak: M+1)

Compound / Product code	IUPAC name	R	R1	R2	R3	R4	R5	R6	Mol. Formula (mol.wt)
P2	ethyl 2-(4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	H	2-Cl	$C_{28}H_{25}ClN_2O_5S$ (537.027)
P3	ethyl 2-(2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	4-Cl	H	$C_{28}H_{25}ClN_2O_5S$ (537.027)

NMR SPECTRUM:

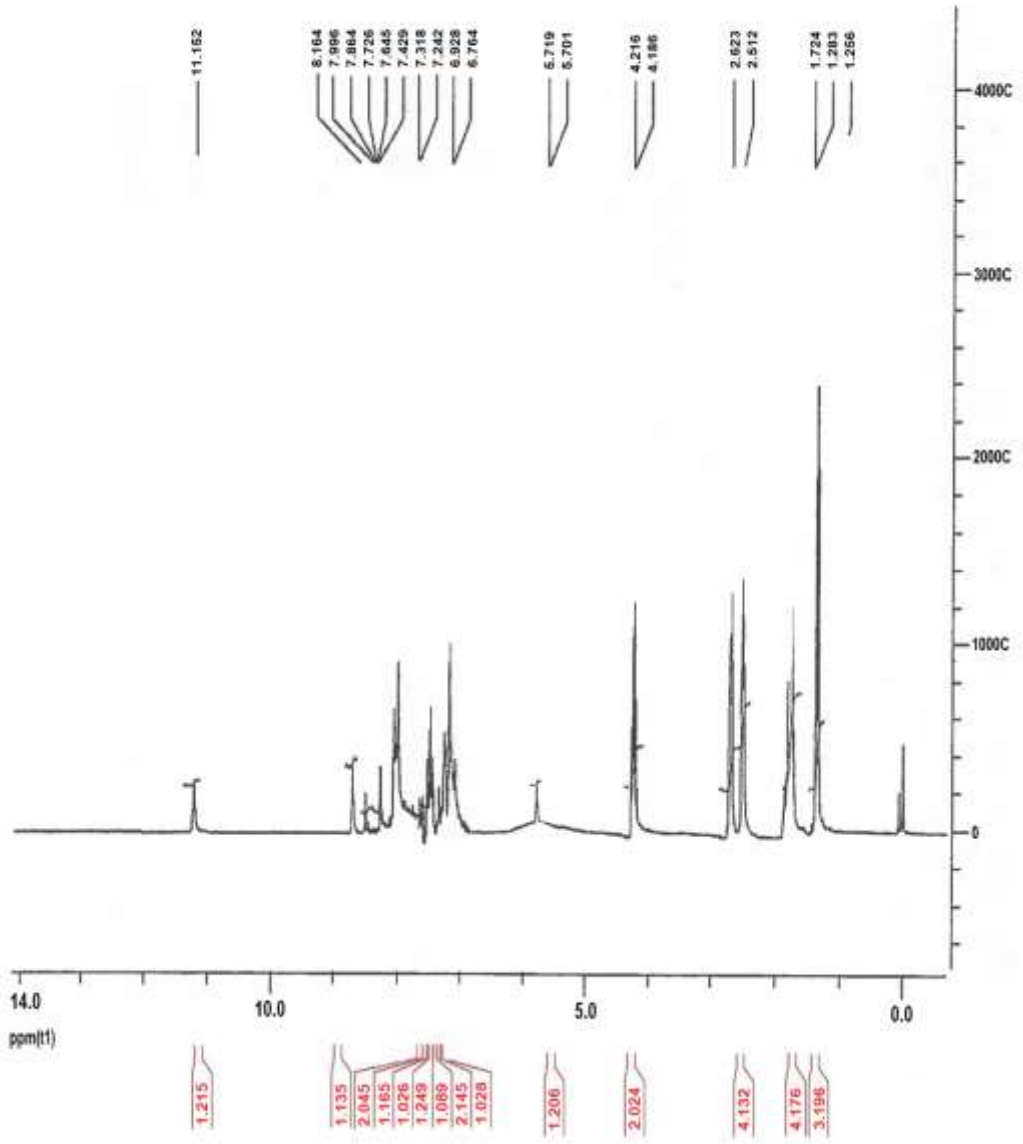


1H NMR (DMSO-d6) δ ppm: 1H NMR (DMSO-d6) δ ppm): 12.1(s, 1H, OH), 7.96 (s,1H,NH-CO) ,5.52 (s, 1H, Pyrrolidinone), 7.1-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.26 (m,3H,CH3 of COOC2H5) 2.1-2.3 (d,4H,Tetra Hydro Benzo thiophene),1.2-1.7 (d,4H,Tetra Hydro Benzo thiophene)



Calculated Mol Wt: 537.027 Observed Mol.Wt:538.8(Peak : 538.8)

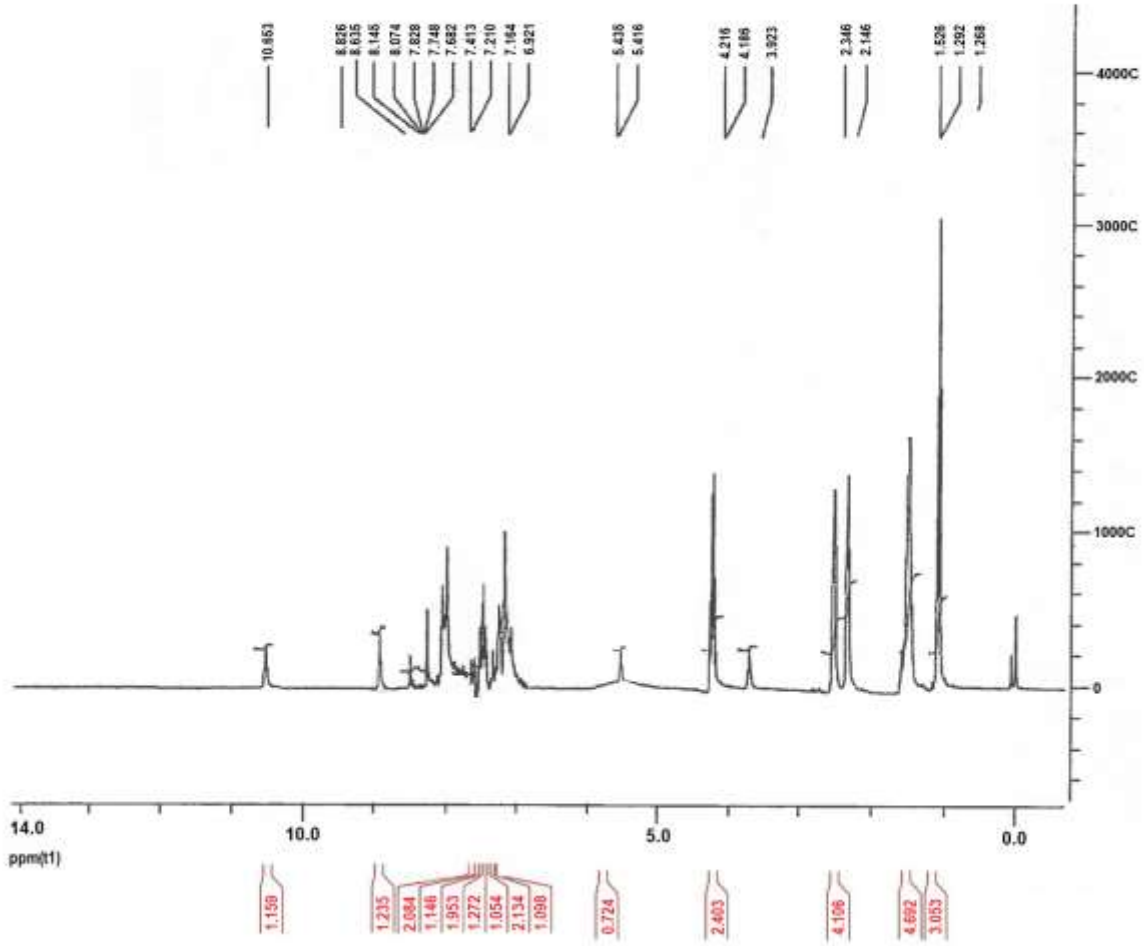
Compound / Product code	IUPAC name	R	R1	R2	R3	R4	R5	R6	Mol. Formula (mol.wt)
P4	ethyl 2-(4-hydroxy-2-(2-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	H	2-NO_2	$C_{28}H_{25}N_3O_7S$ (547.141)
P5	ethyl 2-(4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	4-NO_2	H	$C_{28}H_{25}N_3O_7S$ (547.141)



1H NMR (DMSO-d6) δ ppm: 1H NMR (DMSO-d6) δ ppm : 11.15(s, 1H, OH), 8.2 (s,1H,NH-CO) ,5.7 (s, 1H, Pyrrolidinone), 6.7-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.256 (m,3H,CH3 of COOC2H5) 2.5-2.6 (d,4H,Tetra Hydro Benzo thiophene),1.2-1.7 (d,4H,Tetra Hydro Benzo thiophene)

Compound / Product code	IUPAC name	R	R1	R2	R3	R4	R5	R6	Mol. Formula (mol.wt)
P6	ethyl 2-(2-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-	”	H	H	H	H	H	2-OH	$C_{28}H_{26}N_2O_6S$

	carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate								(518.581)
P7	ethyl 2-(4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate	”	H	H	H	H	4-OH	H	$C_{28}H_{26}N_2O_6S$ (518.581)



1H NMR (DMSO-d6) δ ppm: 1H NMR (DMSO-d6) δ ppm): 10.65(s, 1H, OH), 8.63 (s,1H,NH-CO) ,8.82 (s,1H, Phenyl-OH),5.4 (s, 1H, Pyrrolidinone),6.9-8.1 (m, 9H, Ar-H), 4.1-4.2 (d,2H,CH2 of COOC2H5) 1.26 (m,3H,CH3 of COOC2H5) 2.1-2.3 (d,4H,Tetra Hydro Benzo thiophene),1.29-1.5 (d,4H,Tetra Hydro Benzo thiophene)

SCREENING OF PYROLLIDONE DERIVATIVES FOR ASSESSING

A) Anticonvulsant activity by using – Subcutaneous Pentylenetetrazol (PTZ) seizure model

B) Behavioural Testing i) Rotarod Test ii) Anxiolytic Activity

MATERIALS:

Experimental Animals:

Wistar strain rats (200-220 g) of either sex was used for the study. Animals were procured for seven days and housed in polypropylene cages and maintained under the standard laboratory environmental conditions; temperature 25 ± 2ºC, 12: 12 h L: D cycle and 50 ± 5% RH with free access to food and water ad libitum. Animals were acclimatized to laboratory conditions before the test. All the experimental work carried out during the light period (08:00-16:00 h). The study carried out in harmony with the guidelines given by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi (India). The Institutional Animal Ethical Committee of M.V.P.S College of Pharmacy, Nashik approved the protocol of the study (IAEC/Dec 2021).

Toxicity Studies:

Female albino mice weighing 25-20 g were used for study. Pyrrolidone Derivatives (3000 mg/ml) were dissolved in water. Three Mice were given Perorally with the pyrollidone derivatives at doses of 1000 mg/kg, 1500 mg/kg and 2000 mg/kg. The mice were observed and those that dies during this period were recorded.

Compound	Toxicity (deadmice / total mice)		
Dose (mg/kg)	1000	1500	2000
P1	0/3	2/3	3/3
P3	0/3	2/3	3/3
P8	0/3	2/3	3/3
P9	0/3	3/3	3/3
P12	0/3	2/3	3/3
P15	0/3	3/3	3/3

The Table 1 shows the acute toxicity of Pyrrolidone derivatives . The mice administered with P1 , P3 P8,P9,P12 and P15 survived at the dose of 1000 mg/kg but died at 1500 mg/kg and 3000 mg/kg .

METHODS:

A. Anticonvulsant Activity:

All the solutions of standard drugs were prepared in water. The test compounds (50 mg/kg), Diazepam (4mg/kg) were administered orally. Pentylenetetrazole (80 mg/kg) dissolved in 0.9% sodium chloride solution was administered in the posterior midline of the mice and the onset and severity of convulsions was noted for the

control group. The test group was administered with the selected compounds 30 min prior to the subcutaneous administration of PTZ. The absence or presence of an episode of clonic convulsions was taken as the end point. The data were analysed by one-way ANOVA followed by Dunnett's test using Graph Pad Prism software.

PROCEDURE:

a. Mice were divided into twelve groups as given above. Each group having 5 animals weighing about 200-220 g and the animals were allowed free access to standard laboratory diet and drinking water.

b. Drug treatment in different animal group will be as mentioned in methods

c. Pentylenetetrazol (dose 80 mg/kg, ip; Prepared Stock solution containing 8mg/ml, Injected 1ml/100 g of body weight of mouse).

d. Weigh and number the animals. Divided the animals as per the group. Injected Pentylenetetrazol to control group and noted the onset of action (indicated by Straub's tail, Jerky movement of whole body and convulsions) and severity of convulsions due to drug. Administered the drug samples (proposed anticonvulsant drug) to the animal perorally.

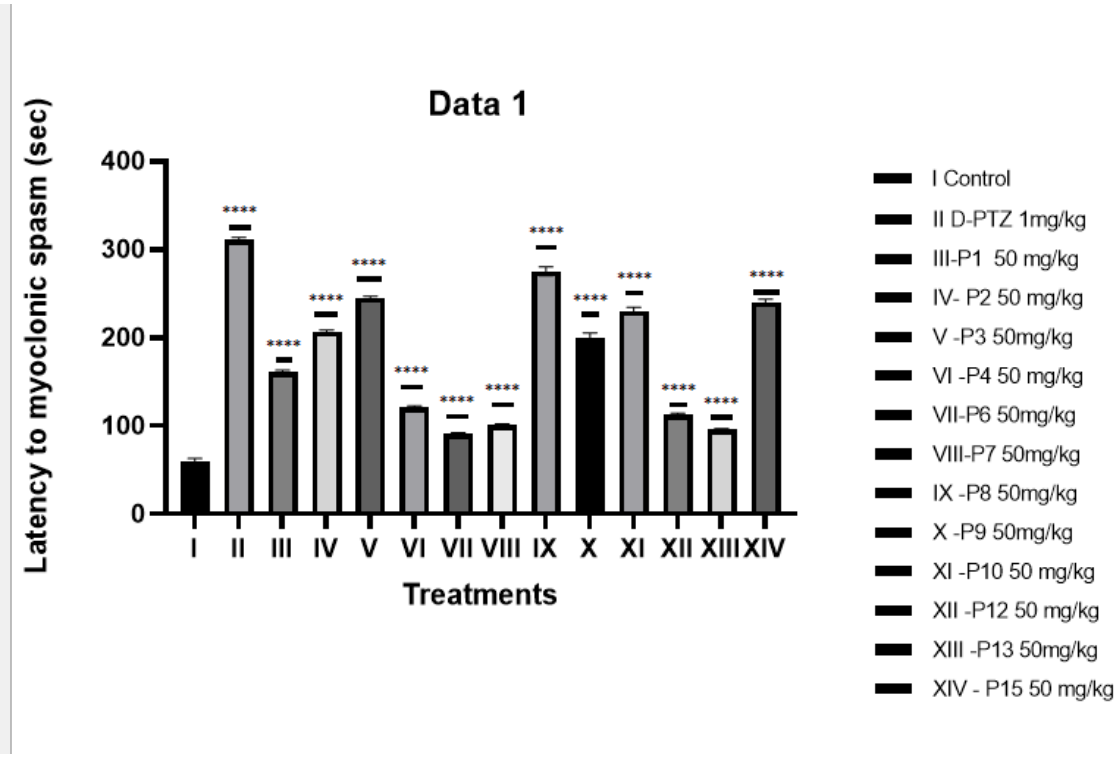
e. After 30 min injected pentylenetetrazol to these animals. Noted onset and severity of convulsions. Noted either delay or complete abolition of convulsions in mice treated with proposed anticonvulsant.

Treatment (Dose , mg/kg ,Orally)	*Latency to Myoclonic Spasm +/- SEM(s)*	*Latency to Clonic Spasm +/- SEM(s)*	*No of Animals Recovered*	*Protection against Mortality (%)*
Control	*60.06 ± 3.2*	*83.38 ± 4.03*	*5/5*	*0*
Diazepam 1 mg/kg	*310.74 ± 2.82*	*50.80 ± 1.07*	*0/5*	*100 %*
P1- 50 mg/kg	*160.80 ± 2.20*	*184.78 ± 4.90*	*2/5*	*40 %*
P2- 50 mg/kg	*207.06 ± 1.80*	*390.21 ± 1.23*	*5/5*	*100 %*
P3- 50 mg/kg	*245.21 ± 1.80*	*430.64 ± 2.02*	*5/5*	*100 %*
P4- 50 mg/kg	*120.71 ± 2.08*	*270.20 ± 5.07*	*3/5*	*60 %*
P6-50 mg/kg	*90.53 ± 2.01*	*203.65 ± 4.12*	*3/5*	*60 %*
P7- 50 mg/kg	*101.20 ± 1.08*	*230.03 ± 1.64*	*3/5*	*100 %*
P8- 50 mg/kg	*275.35 ± 4.70*	*470.61 ± 2.10*	*5/5*	*100 %*
P9- 50 mg/kg	*200.3 ± 5.27*	*384.20 ± 3.20*	*5/5*	*100 %*
P10-50 mg/kg	*230.44±4.05*	*401.26± 1.01*	*5/5*	*00 %*
P12- 50 mg/kg	*112.07 ± 2.43*	*251.54 ± 1.40*	*3/5*	*100 %*
P13-50mg/kg	*95.87± 1.10*	*240.62 ± 2.24*	*3/5*	*60 %*
P15- 50 mg/kg	*240.11 ± 3.28*	*410.62 ± 3.20*	*4/5*	*80 %*

RESULT:

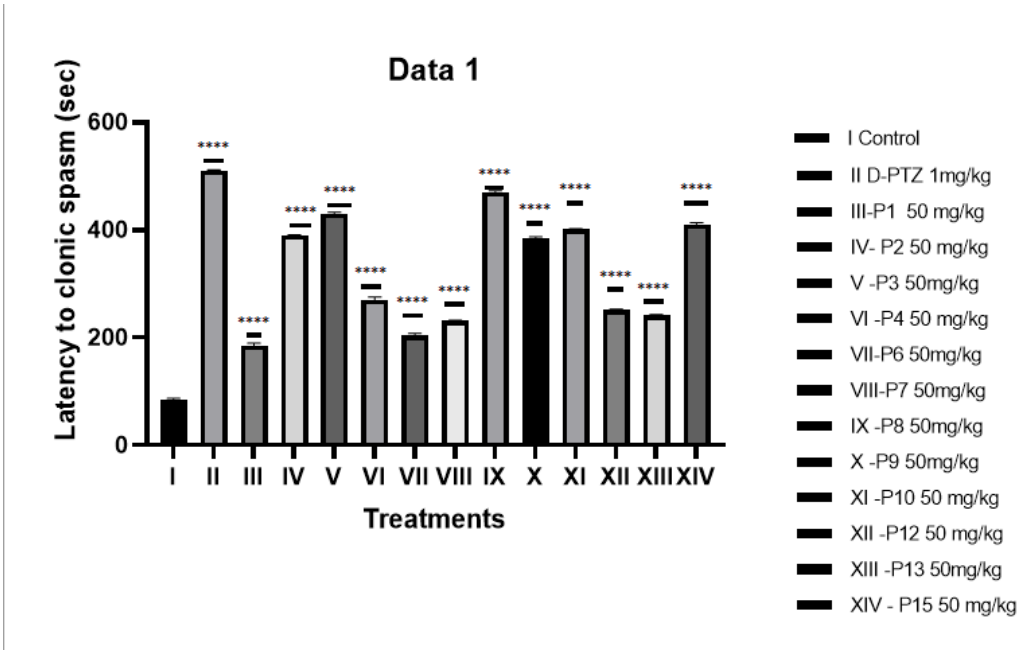
a) Treatments Vs Latency to myoclonic spasm

Group II to XIV showed significant ($p<0.0001$) increase in latency in myoclonic spasm as compared to Group I



All values expressed as mean ± S.E.M. All Groups Viz II,to XIII are compared with group I One-Way ANOVA followed by Dunnett's test. $p < 0.0001$

b) Treatments Vs Latency to clonic spasm(sec)



Group II,to XIII showed significant ($p<0.0001$) increase in Latency in clonic convulsions as compared to Group I. All values expressed as mean ± S.E.M. All Groups Viz II,to XIII are compared with group I One-Way ANOVA followed by Dunnett's test. $p < 0.0001$

B. Behavioural testing:

i) Rotarod test

The test is used to evaluate the activity of drugs interfering with motor coordination.

PROCEDURE:

1. The apparatus consists of a horizontal wooden rod or metal rod coated with rubber with 3cm diameter attached to a motor with the speed adjusted to 2 rotations per minute.

2. The rod was 75 cm in length and was divided into 6 sections by plastic discs, thereby allowing the simultaneous testing of 6 mice or rats.

3. The rod was in a height of about 50 cm above the tabletop in order to discourage the animals from jumping off the roller.

4. Cages below the sections serve to restrict the movements of the animals when they fall from the roller.

5. Wistar rats of either sex weighing in range 200-220g undergo a pretest on the apparatus. Only those animals which have demonstrated their ability to remain on the revolving rod for at least 1 minute was used for the test.

6. The test compounds were administered orally. Sixty min after oral administration the rats were placed for 1 min on the rotating rod. The number of animals falling from the roller during this time was counted.

7. The rotarod test was used to assess motor coordination and balance. Rats must maintain their balance on a rotating rod.

8. The rod was rotated at 4 rpm and gradually increased to 20 rpm. The latency time required for the rat to fall off the rod rotating at different speeds or under continuous acceleration (e.g., from 4 to 20 rpm) was recorded

Treatment (Dose, mg/kg, Orally)	*Latency to fall off +/- SEM(s)*
Control	*47.23 ± 1.32*
Diazepam 1 mg/kg	*14.24 ± 0.50*
P1- 50 mg/kg	*17.17 ± 1.25*
P2- 50 mg/kg	*41.78 ± 1.29*
P3- 50 mg/kg	*32.40 ± 3.10*
P4- 50 mg/kg	*24.08 ± 1.25*
P6-50 mg/kg	*34.53 ± 0.65*
P7- 50 mg/kg	*27.12 ± 1.20*
P8- 50 mg/kg	*09.36 ± 3.25*

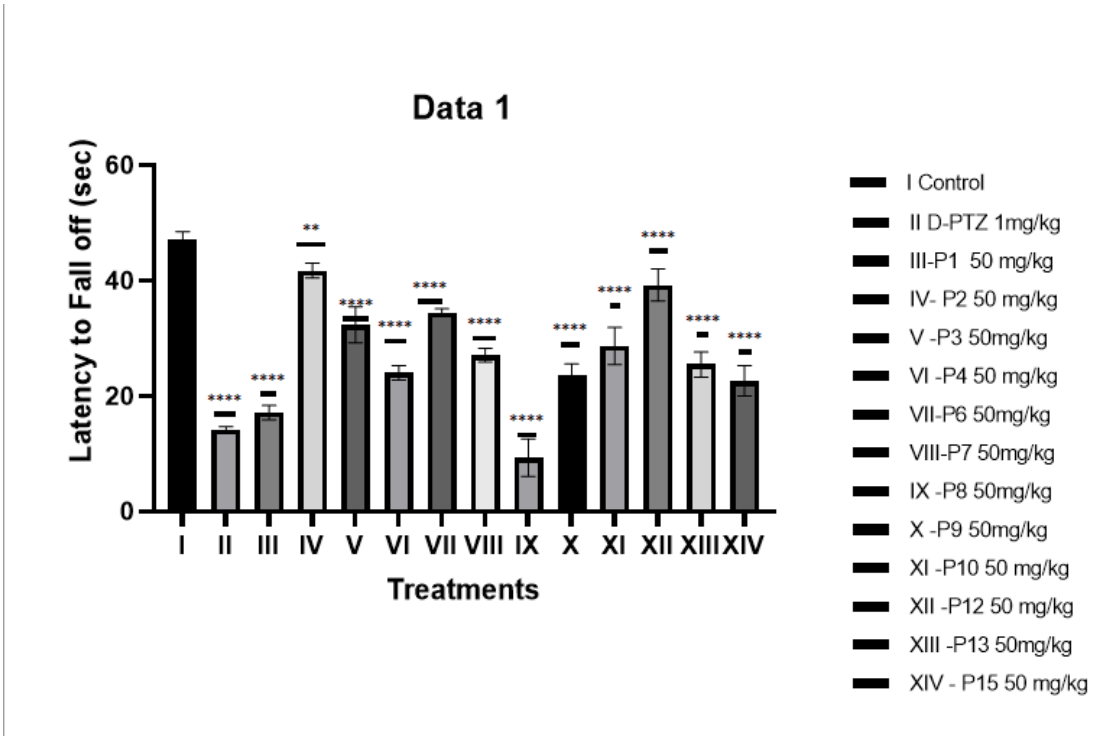
P9- 50 mg/kg	*23.64 ± 1.97*
P10-50 mg/kg	*28.70 ± 3.21*
P12- 50 mg/kg	*39.30 ± 2.78*
P13-50mg/kg	*25.50 ± 2.19*
P15- 50 mg/kg	*22.65 ± 2.63*

STATISTICAL ANALYSIS:

All results were expressed as mean ± SEM. All the data of groups were analysed by applying one-way analysis of variance followed by Dunnett's test using Graph Pad Prism 9.4.1 software (GraphPad®, San Diego, CA, USA).

Effect of Pyrrolidone Derivatives (Dose 100mg/ml) on motor activity:

Group II,To XIV showed significant ($p<0.0001$) decrease in latency to fall off from rotarod as compared to Group I except Group IV ($p<0.005$) showed significant decrease in latency to fall off from rotarod as compared to Group I Group IV,V,VI,VII,VIII,X,XI, XII XIII and XIV showed significant ($p<0.0001$) increase in latency to fall off from rotarod as compared to Group II. Group III showed not significant ($p<0.5$) decrease in latency to fall off from rotarod as compared to Group II while Group IX showed significant ($p<0.005$) decrease in latency to fall off from rotarod as compared to Group II



All Groups Viz II, III,IV,V,VI,VII,VIII,IX,X,XI,XII,XIII are compared with group I. One-Way ANOVA followed by Dunnett's test. Group II to XIV $p < 0.0001$ for Group IV: $p<0.005$

ii) Anxiolytic Activity:

Hole Board test

Purpose and Rationale:

Certain aspects of animal behaviour, such as curiosity and exploration, have been tested. They used an open field with holes in the ground into which the animals could poke their noses.

PROCEDURE:

1. Rats of either sex (Wistar rats) with a weight between 200-220 g were used.

2. The hole-board consist of wooden box (40 × 40 cm) with 16 holes (diameter of 3 cm) distributed evenly on the floor.

3. The animal's tendency to insert its head into the holes was observed and quantified.

4. The board was elevated so that the rats poking its nose into the hole, does not see the bottom.

5. Vehicle-treated control and drug-treated animals could explore the holes in the board every day for 5 min, and the total number of pokes per 5 min was recorded for each rat.

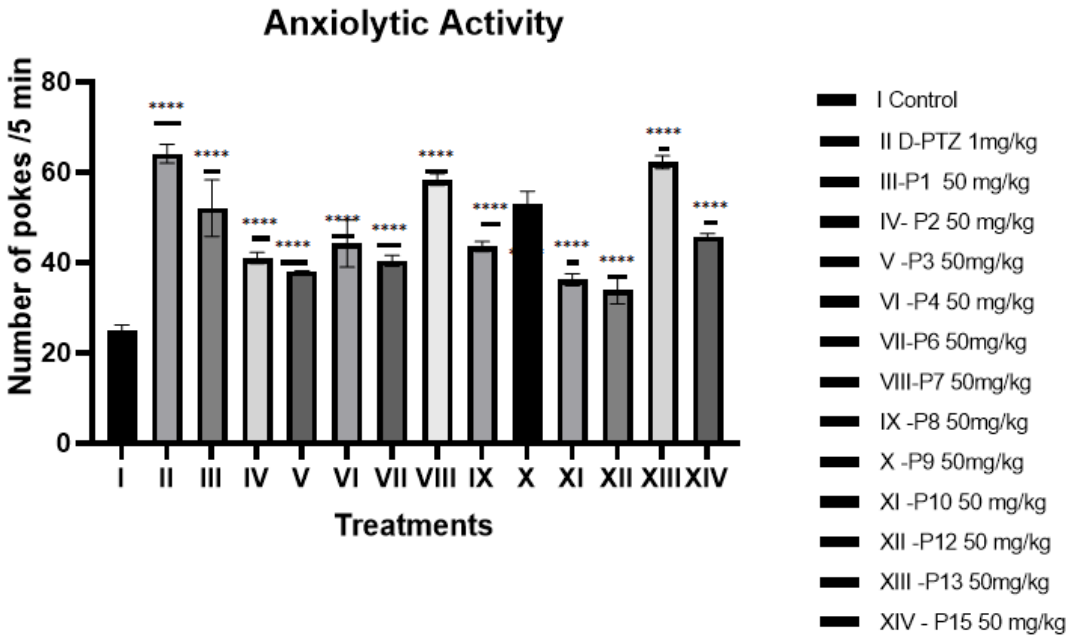
6. Nose-poking was thought to indicate curiosity and was measured by visual observation in the earliest description and counted by electronic devices in more recent modifications.

7.

Treatment (Dose, mg/kg, Orally)	*Number of Nose Poking +/- SEM(s)*
Control	*25.10 ± 1.15*
Diazepam 1 mg/kg	*64.12± 2.10*
P1- 50 mg/kg	*52.10 ± 6.29*
P2- 50 mg/kg	*41.05 ± 1.22*
P3- 50 mg/kg	*38.04 ± 0.10*
P4- 50 mg/kg	*44.27 ± 5.21*
P6-50 mg/kg	*40.41 ± 1.21*
P7- 50 mg/kg	*58.38 ± 1.31*
P8- 50 mg/kg	*43.61 ±1.08*
P9- 50 mg/kg	*53.10 ± 2.76*
P10-50 mg/kg	*36.20 ± 1.37*
P12- 50 mg/kg	*33.89 ± 3.03*
P13-50mg/kg	*62.29 ± 1.43*
P15- 50 mg/kg	*45.76 ± 0.70*

Effect of Pyrrolidone Derivatives (With dose: 50 mg/kg) on number of poking's in Hole Board test:

Group II to XIV showed significant ($p<0.0001$) increase in nose poking's as compared to Group I.



All values expressed as mean ± S.E.M. All Groups Viz II,III,IV,V,VI,VII,VIII,IX,X,XI,XII,XIII,XIV are compared with group I .One-Way ANOVA followed by Dunnett's test. $p < 0.0001$

Discussion:

The newly suggested pharmacophore model in the current series fulfills all pharmacophoric necessary criteria for anticonvulsant activity. Understanding the relationship between these compounds structure and activity was facilitated to increase by the findings of the biological evaluation. According to SAR studies, several substitutions on the aromatic ring exerted the anticonvulsant action in distinct ways. Introduction of N phenyl contributes to increase in anticonvulsant activity.The para substituted phenyl at 2 position of 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxamido has increased the effectuality against seizures induced by PTZ, that might be due to inhibition at GABA receptor. Replacement of chloro moiety in P2 ,P3 and P9 with NO2 group in P4,P5 has reduced the activity. Interestingly compound P8 and P15 with more than one chlorine substituents showed the promising activity and did not exhibited any significant effect on motor coordination at the dose administered. These observations accentuate that the hydrophobic and lipophilic domains in the molecule are responsible for the potent anticonvulsant activity. The above results suggest that the nature and position of functional groups are always related to the favourable biological activities.

Novelty

The ligand-based pharmacophore approach is an important strategy for designing novel anticonvulsant agent new drugs, and some other anticonvulsant active components. The structural characteristics of typical anticonvulsant agents, such as ethosuximide, levetiracetam, brivaracetam and seletracetam showed that these drugs shared a common pyrrolidinone moiety in their molecules. we assumed that the compound containing pyrrolidinone moiety in a single molecule could be favourable to anticonvulsant activity. The pyrrolidone (2-oxopyrrolidine) family of chemicals has been the subject of research for more than three decades. Experimental and clinical work first focused on their so-called nootropic effects; later came the possibilities for neuroprotection after stroke and use as antiepileptic agents.

References

1. Tiantian Wang.;Shiyang Dong.;Xiaodong Chen.; Kun Qian.;Huayu Wang A Design, synthesis, biological evaluation, homology modeling and docking studies of (E)-3-(benzo[d][1,3]dioxol-5-ylmethylene)pyrrolidin-2-one derivatives as potent anticonvulsant agents. Bioorganic & Medicinal Chemistry Letters Volume 28, Issue 8, 2018,Pages 1324-1329

2. Chahrazed Benhaoua.One-Pot Synthesis of Pyrrolidine-2-ones from Erythruronolactone and Amine.Organic Chemistry International Volume 2012, Article ID 482952, 6 pages

3. George Brine et al., Synthesis and Anticonvulsant Screening of 3,3-Diphenyl-2-pyrrolidone Derivatives. Journal of pharmaceutical Sciences, Vol. 72. No. 6, June 1983

4. Nader Ghaffari Khaligh.;Taraneh Mihankhah.;Mohd Rafie Johan.; Salam J.J. Titinchi Microwave-assisted synthesis of pyrrolidinone derivatives using 1,1'-butylenebis(3-sulfo-3Himidazol-1-ium) chloride in ethylene glycol .Green Process Synth 2019; 8: 373–381

5. Hamideh Ahankar.;Ali Ramazani.;,Katarzyna Ślepokura.;Tadeusz Lisb .;Sang Woo Joo. Synthesis of pyrrolidinone derivatives from aniline, an aldehyde and diethyl acetylenedicarboxylate in an ethanolic citric acid solution under ultrasound irradiation. Green Chem., 2016, 18, 3582–3593.

6. L. A. Zhmurenko.;S. A. Litvinova.; G. V. Mokrov.;I. G. Kovale.; T. A. Voronina,L. N. Nerobkova.; T. A. Gudasheva. Synthesis Of 4-Phenylpyrrolidone Derivatives With Anticonvulsant And Nootropic Activity. Pharmaceutical Chemistry Journal, Vol. 53, No. 5, August, 2019

7. Hitoshi Sasaki.;Yoshiyuki Mori.; Junzo Nakamura.;Juichiro Shibasaki.Synthesis and Anticonvulsant Activity of 1-Acyl-2-pyrrolidinone Derivatives J. Med. Chem. 1991,34,628-633

8. Benoit M. Kenda.; Alain C. Matagne.; Patrice E. Talaga.;Patrick M. Pasau.;Edmond Differding. Discovery of 4-Substituted Pyrrolidone Butanamides as New Agents with Significant Antiepileptic Activity. J. Med. Chem. 2004, 47, 530-549

9. Simon Shorvon, Pyrrolidone derivatives THE LANCET ,Vol 358 , December 1, 2001

10. Tae-Woo Kwon.;Pan-Suk Kwon.;Suk-Jin Song.;Min-Soo ParN .;Jong-Won Choi . Synthesis and Anticonvulsant Evaluation of 5-Vinyl-pyrrolidin-2-ones: A Potential GABA-AT Inhibitor. Bull. Korean Chem. Soc. 2002, Vol. 23, No. 6 917

11. Bjorn Ringdahl, 5-Methyl-2-pyrrolidone Analogues of Oxotremorine as Selective Muscarinic Agonists, J. Med. Chem. 1988,31,683-688

12. Małgorzata Góra .; Anna Czopek .;Anna Rapacz.; Anna Dziubin.; Monika Głuch-Lutwin.; Barbara Mordyl.; Jolanta Obniska . Synthesis, Anticonvulsant and Antinociceptive Activity of New Hybrid Compounds: Derivatives of 3-(3-Methylthiophen-2-yl)-pyrrolidine-2,5-dione. Int. J. Mol. Sci. 2020, 21, 5750

13. Anna Rapacz .; Sabina Rybka .; Jolanta Obniska.; Kinga Sałat .; Beata Powroźnik.;Elżbieta Pękala.; Barbara Filipek. Evaluation of anticonvulsant and antinociceptive properties of new N-Mannich bases derived from pyrrolidine-2,5-dione and 3-methylpyrrolidine-2,5-dione. Naunyn-Schmiedeberg's Arch Pharmacol (2016) 389:339–348

14. Cerine C. Hansen.;Hanna Ljung.; Eylert Brodtkorb.;Arne Reimers. Mechanisms Underlying Aggressive Behavior Induced by Antiepileptic Drugs: Focus on Topiramate, Levetiracetam, and Perampanel. Behavioural Neurology Volume 2018, Article ID 2064027, 18 pages

15. Giovanna Li Petri.; Maria Valeria Raimondi.;· Virginia Spanò.; Ralph Holl.; Paola Barraja.; Alessandra Montalbano. Pyrrolidine in Drug Discovery: A Versatile Scafold for Novel Biologically Active Compounds. Topics in Current Chemistry (2021) 379:34

16. Priyanka Kumari Choubey.; Avanish Tripathi .; Piyoosh Sharma.; Sushant Kumar Shrivastava Design, synthesis, and multitargeted profiling of N-benzylpyrrolidine derivatives for the treatment of Alzheimer's disease .Bioorg Med Chem. 2020 Nov 15;28(22):115721.

17. I. L. Bonta.; C. J. De Vos H. Grijsen.; F. C. Hillen.; E. L. Noach.;A. W. Sim. 1-Hydroxy-3-amino-pyrrolidone-2 (HA-966): a new GABA-like compound, with potential use in extrapyramidal diseases. Br. J. Pharmac. (1971), 43, 514-535.

18. Shao-Hua Xiang.;Hong-Qiu Yuan.; Pei-Qiang Huang. A versatile approach to cis-5-substituted 4-hydroxy-2-pyrrolidinones: asymmetric synthesis of angiogenesis inhibitor streptopyrrolidine. Tetrahedron: Asymmetry 20 (2009) 2021–2026

19. Annapurna Pendri.; Timothy L. Troyer.;Michael J. Sofia.;Michael A. Walker.; B. Narasimhulu Naidu.;Jacques Banville.; Nicholas A. Meanwell. Solid Phase Synthesis of Novel Pyrrolidinedione Analogs as Potent HIV-1 Integrase Inhibitors. J. Comb. Chem. 2010, 12, 84–90

20. S V. L. Gein.; V. N. Vychegzhanina.; E. B. Levandovskaya..;B. Ya. Syropyatov.; M. I. Vakhrin.; V. Voronina.;N. V. Synthesis And Antibacterial And Analgesic Activity Of 5-Aryl-4-Acyl-3-Hydroxy-1- (2,2-Dimethoxyethyl)-3-Pyrrolin-2-Ones

21. Vijay Singh.; Rashmi Saxena.; Sanjay Batra. Simple and Efficient Synthesis of Substituted 2-Pyrrolidinones, 2-Pyrrolones, and Pyrrolidines from Enaminones of Baylis-Hillman Derivatives of 3-Isoxazolecarbaldehydes. J. Org. Chem. 2005, 70, 353-356

22. Sabina Rybka, Jolanta Obniska, Anna Rapacz, Barbara Filipek & Paweł Żmudzk. Synthesis and anticonvulsant activity of new N mannich bases derived from benzhydryl- and isopropyl-pyrrolidine-2,5-dione J Enzyme Inhib Med Chem, Early Online: 1–10

23. Krzysztof Kamina.;Sabina Rzepka.;Jolanta Obniska.Synthesis and anticonvulsant activity of new 1-[2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]pyrrolidine-2,5-diones. Bioorg. Med. Chem. Lett. 21 (2011) 5800–5803.

24. Adeleh Moshtaghi Zonouz.; Issa Eskandari.; Behrooz Notash.;Efficient Synthesis Of 3-Pyrrolin-2-One Derivatives In Aqueous Media. Synthetic Communications1, 0: 1–7, 2015.

25. Rajib Sarkar, Chhanda Mukhopadhyay. Admicellar catalysis in multicomponent synthesis of polysubstituted pyrrolidinones Tetrahedron Letters,Volume 54, Issue 28, 10 July 2013, Pages 3706-3711