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STRUCTURE ACTIVITY RELATIONSHIP STUDIES OF SYNTHESIZED UREA DIAMIDES ON CNS DEPRESSION AND SLEEPING TIME POTENTIATION EFFECT

Ravikumar V. Modi* and Prof Dr Dhrubo Jyoti Sen
Department of Quality Assurance and Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Hemchandracharya North Gujarat University, Arvind Baug, Mehsana-384001, Gujarat, India
Phone: 00-91-2762-247711, Fax: 00-91-2762-247712, Email: dhrubosen69@yahoo.com

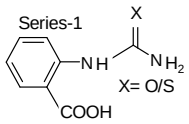
ABSTRACT

Two different series of urea diamides have been synthesised by keeping X=O/S to form urea/thiourea derivatives in 2 and 4 substitutions in the phenyl rings by carboxylic acid and carboxamide to form diamides for screening of CNS depression and sleeping time synergistic activity on mice with reference standard drugs benzodiazepine and barbiturate. It has been found that all the test compounds have sleep inducing property due to the presence of open chain urea/thiourea linkage and the urea/thiourea diamide derivatives were found longer duration of sleep inducing property due to the presence of two amide linkages and out of which the thiourea derivative and thiourea diamide derivatives showed lesser duration than urea and urea diamide linkage. Sleeping time potentiation effect was studied for the test compounds by using pentobarbitone as barbiturates and diazepam as benzodiazepines on male albino mice. The 2-substituted derivatives were found less active than 4-substituted derivatives due to the steric hindrance and ortho effect. All the observations were noted for four groups of mice and the bioassay result was tabulated after statistical parameters for significance of pharmacological screening: Student's-t-test and P-value. The CNS depression occurs due to the action on GABA receptor having free NH_2 and COOH groups: H_2N-CH_2-CH_2-CH_2-CH_2-COOH (γ-amino butyric acid). The synthesized compounds which have free –C(O/S)-NH_2 (urea/thiourea) groups and –COOH groups shows the CNS depression effect and the maximum activity has been shown by the compound-6 in which amido as well as urea linkages are in para position to each other which blocks the GABA receptor and results CNS depression. The same attachment shows lesser action in case of ortho substitution due to ortho effect and steric hindrance. All the test results were found significant to a high extent for the structure activity relationship studies of the synthesized molecules and the maximum activity has been shown by the COMPOUND-6 (4-Amido phenyl urea) having two amide groups.

INTRODUCTION

The structure activity relationship study for the synthesised eight compounds has been divided into two series: 2-substituted and 4-substituted phenyl ureas having variable atoms in (X). X=O (urea) and X=S (thiourea) for carboxylic acid and carboxamide substitutions in phenyl ring produces open chain ureas which have been screened for CNS depression study by using closed chain ureas (barbiturate=pentobarbitone) and bioisosteric closed chain ureas (benzodiazepines=diazepam) to identify the correlation analogy between closed chain and open chain ureas on CNS depression and sleeping time potentiation[1-3].

Series of Synthesized Molecules:-

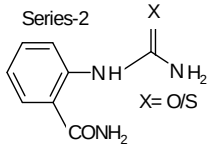


*Corresponding author's Email:

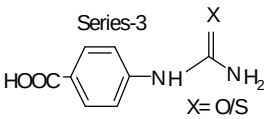
dhrubosen69@yahoo.com

Telephone: **00-91-2762-247711**

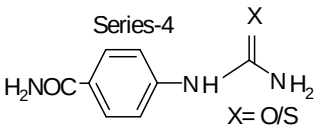
Compound-1: 2-carboxy-phenyl urea
Compound-3: 2-carboxy-phenyl thiourea



Compound-2: 2-carboxamido-phenyl urea
Compound-4: 2-carboxamido-phenyl thiourea

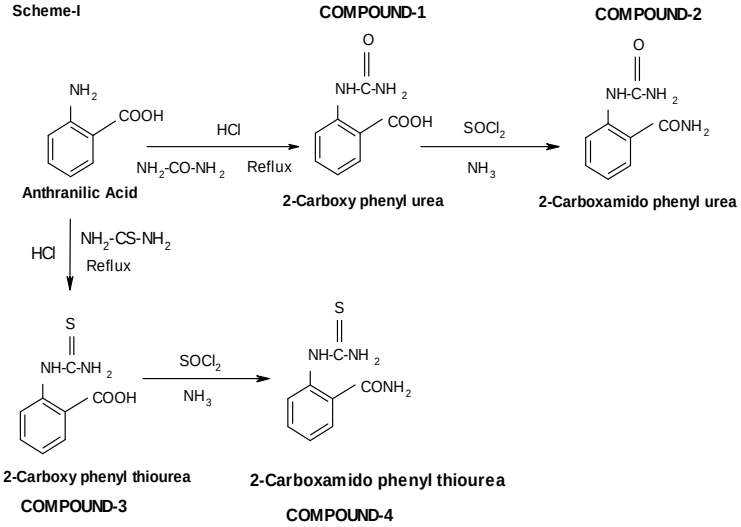


Compound-5: 4-carboxy phenyl urea
Compound-7: 4-carboxy phenyl thiourea



Compound-6: 4-amido phenyl urea
Compound-8: 4-amido phenyl thiourea

Scheme for Synthesis of Compounds (1-4):-



Synthesis[4-8]**:**

Synthesis of 2-carboxy phenyl urea:

Compound-1:

Anthranilic acid (mol) was first treated with hydrochloric acid to make its hydrochloride salt. Then it was refluxed with urea (mol) for one hour until all the solids has been solubilised. The solubilised mass was cooled in ice to get the solid. It was filtered and recrystallized from benzene-ethanol mixture to get pure product: **Compound-1**.

Synthesis of 2-carboxamido phenyl urea:

Compound-2:

2-carboxy phenyl urea (mol) was refluxed with thionyl chloride (mol) for one hour until the entire solid has been dissolved. It was cooled and treated with strong ammonium hydroxide to get the solid[7]. It was then recrystallized with aqueous ethanol to get the pure product: **Compound-2**.

Synthesis of 2-carboxy phenyl thiourea:

Compound-3:

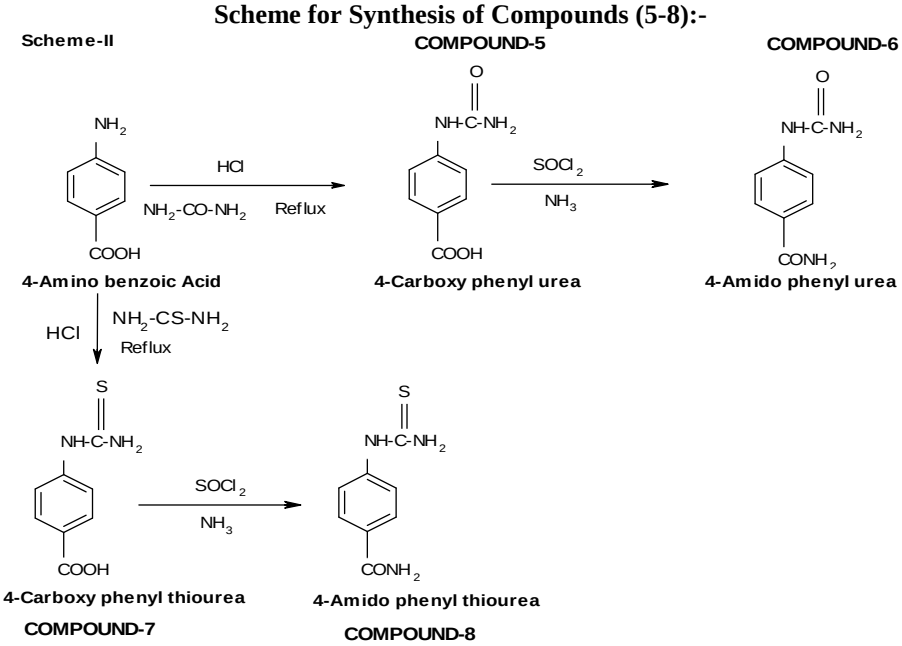
Anthranilic acid (mol) was first treated with hydrochloric acid to make its hydrochloride salt. Then it was refluxed with thiourea (mol) for one hour until all the solids has been solubilised. The solubilised mass was cooled in ice to get the solid. It was filtered and recrystallized from benzene-ethanol mixture to get pure product: **Compound-3**.

Synthesis of 2-carboxamido phenyl thiourea:

Compound-4:

2-carboxy phenyl thiourea (mol) was refluxed with thionyl chloride (mol) for one hour until the entire solid has been dissolved. It was cooled and treated with strong ammonium hydroxide to get the solid. It was then recrystallized with aqueous ethanol to get the pure product: **Compound-4**.

Scheme for Synthesis of Compounds (5-8):-



Synthesis[9-12]**:**

Synthesis of 4-carboxy phenyl urea:

Compound-5:

4-amino benzoic acid (mol) was first treated with hydrochloric acid to make its hydrochloride salt. Then it was refluxed with urea (mol) for one hour until all the solids has been solubilised. The solubilised mass was cooled in ice to get the solid. It was filtered and recrystallized from benzene-ethanol mixture to get pure product: **Compound-5**.

Synthesis of 4-amido phenyl urea:

Compound-6:

4-carboxy phenyl urea (mol) was refluxed with thionyl chloride (mol) for one hour until the entire solid has been dissolved. It was cooled and treated with strong ammonium hydroxide to get the solid. It was then recrystallized with aqueous ethanol to get the pure product: **Compound-6**.

Synthesis of 4-carboxy phenyl thiourea:

Compound-7:

Anthranilic acid (mol) was first treated with hydrochloric acid to make its hydrochloride salt. Then it was refluxed with thiourea (mol) for one hour until all the solids has been solubilised. The solubilised mass was cooled in ice to get the solid. It was filtered and recrystallized from benzene-ethanol mixture to get pure product: **Compound-7**.

Synthesis of 4-amido phenyl thiourea:

Compound-8:

4-carboxy phenyl thiourea (mol) was refluxed with thionyl chloride (mol) for one hour until the entire solid has been dissolved. It was cooled and treated with strong ammonium hydroxide to get the solid. It was then recrystallized with aqueous ethanol to get the pure product: **Compound-8**.

Solubility Parameters:-

Table-1

Compounds	Solubility	Polarity
2-CARBOXY PHENYL UREA	Hot Water (1mg/ml), Methanol (2mg/ml)	Semi polar
2-CARBOXAMIDO PHENYL UREA	Hot Water (1mg/ml)	Semi polar
2-CARBOXY PHENYL THIOUREA	Water (1mg/ml), Methanol (1mg/ml)	Polar
2-CARBOXAMIDO PHENYL THIOUREA	Hot Water (1mg/ml)	Semi polar
4-CARBOXY PHENYL UREA	Water (1mg/ml), Methanol (2mg/ml)	Polar
4-AMIDO PHENYL UREA	Hot Water (1mg/ml)	Semi polar
4-CARBOXY PHENYL THIOUREA	Water (1mg/ml), Methanol	Polar
4-AMIDO PHENYL THIOUREA	Hot Water (1mg/ml)	Semi polar

Physicochemical Parameters:-

Table-2

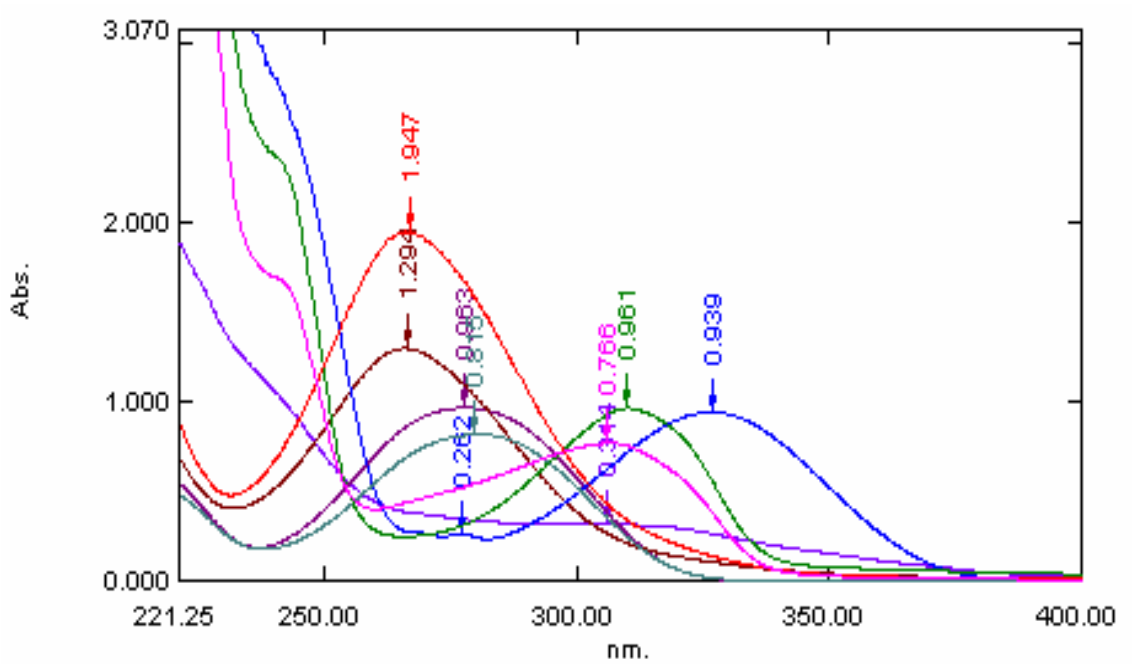
Compounds	% Yield	M.P. °C	Polarity	Molecular Formula	N% Calculated	N% Found
2-CARBOXY PHENYL UREA	77.37%	158-162	Semi Polar	$C_8H_8N_2O_3$	15.555	15.983
2-CARBOXAMIDO PHENYL UREA	68.33%	101-103	Semi Polar	$C_8H_9N_2O_2$	16.969	17.218
2-CARBOXY PHENYL THIOUREA	82.48%	176-178	Polar	$C_8H_8N_2O_2S$	14.285	14.574
2-CARBOXAMIDO PHENYL THIOUREA	56.66%	120-122	Semi Polar	$C_8H_9N_2OS$	15.469	15.872
4-CARBOXY PHENYL UREA	80.29%	260-262	Polar	$C_8H_8N_2O_3$	15.555	15.886
4-AMIDO PHENYL UREA	48.33%	304-306	Semi Polar	$C_8H_9N_2O_2$	16.969	17.438
4-CARBOXY PHENYL THIOUREA	76.64%	252-254	Polar	$C_8H_8N_2O_2S$	14.285	14.674
4-AMIDO PHENYL THIOUREA	71.66%	295-297	Semi Polar	$C_8H_9N_2OS$	15.469	15.787

Spectral Datas:-

U.V. Spectras

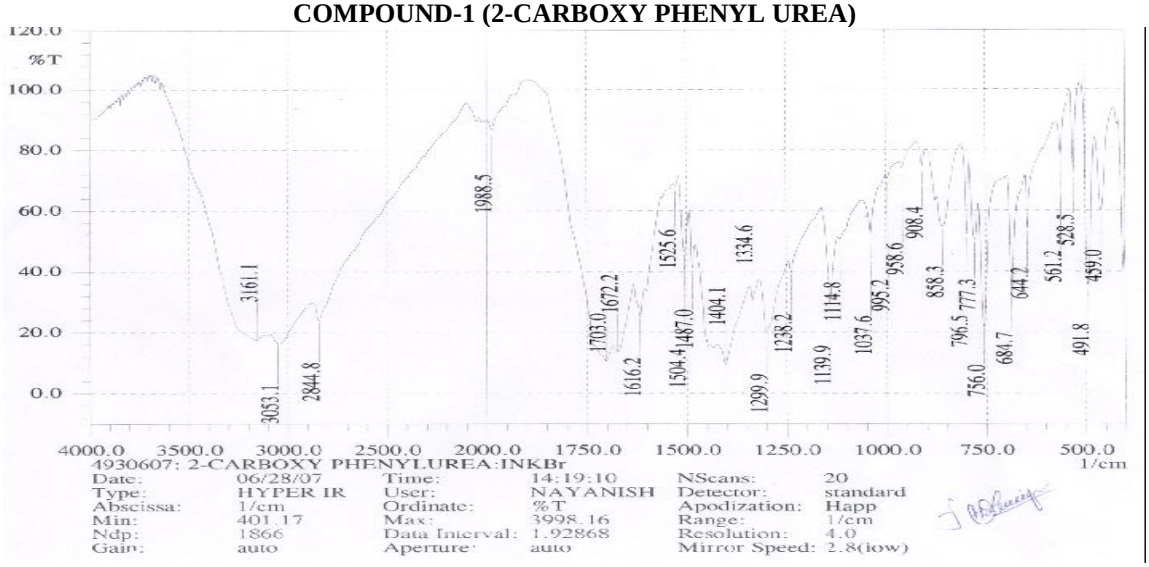
Table-3

Compounds	λ_{max}	Absorbance
2-CARBOXY PHENYL UREA	306.2	0.766
2-CARBOXAMIDO PHENYL UREA	310.4	0.960
2-CARBOXY PHENYL THIOUREA	326.8	0.939
2-CARBOXAMIDO PHENYL THIOUREA	306.6	0.314
4-CARBOXY PHENYL UREA	277.6	0.963
4-AMIDO PHENYL UREA	266.6	1.940
4-CARBOXY PHENYL THIOUREA	279.6	0.815
4-AMIDO PHENYL THIOUREA	266.4	1.294



Infra-red (I.R.) Spectras

COMPOUND-1 (2-CARBOXY PHENYL UREA)



Aromatic

- ✓ 3053 cm^{-1} - Aromatic C-H Stretching.
- ✓ 1404.1, 1487 cm^{-1} - C=C ring Stretching.
- ✓ 684.7, 756, 773.3, 769.5, 858.3 cm^{-1} – Out of Plane C-H Bending.
- ✓ 756 (Strong Band) cm^{-1} - Ortho Substituted Benzene.
- ✓ 684.7 (One Band) and 756, 773.3, 796.5 (One Strong Band) cm^{-1} – Meta Substituted Benzene.
- ✓ 796.5 (Strong Band) cm^{-1} - Para Substituted Benzene.

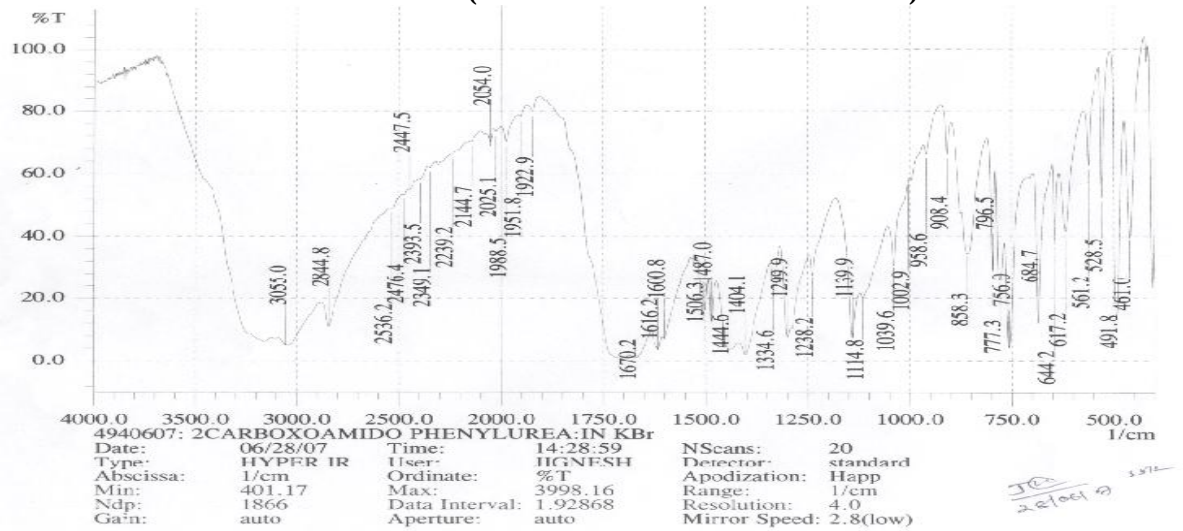
Amines and Amides

- ✓ 1616.2 cm^{-1} – N-H Bending at Primary Amine or Amide.
- ✓ 1037.6 1114.8 1139.9 1238.2 cm^{-1} – C-N Stretching Aliphatic Amine.

Carboxylic Acid

- ✓ 1404 cm^{-1} – C-O-H In-Plane bending.
- ✓ 1703 cm^{-1} – C=O Stretching.

COMPOUND-2 (2-CARBOXAMIDO PHENYL UREA)



Aromatic

- ✓ 3055 cm^{-1} - Aromatic C-H Stretching.
- ✓ 1404.1, 1444.6 cm^{-1} - C=C ring Stretching.
- ✓ 684.7, 756, 777.3, 796.5, 858.3 cm^{-1} – Out of Plane C-H Bending (Aromatic).
- ✓ 756 (Strong Band) cm^{-1} - Ortho Substituted Benzene.
- ✓ 684.7 (One Band) and 756, 777.3, 796.5 (One Strong Band) cm^{-1} – Meta Substituted Benzene.
- ✓ 796.5 (Strong Band) cm^{-1} - Para Substituted Benzene.

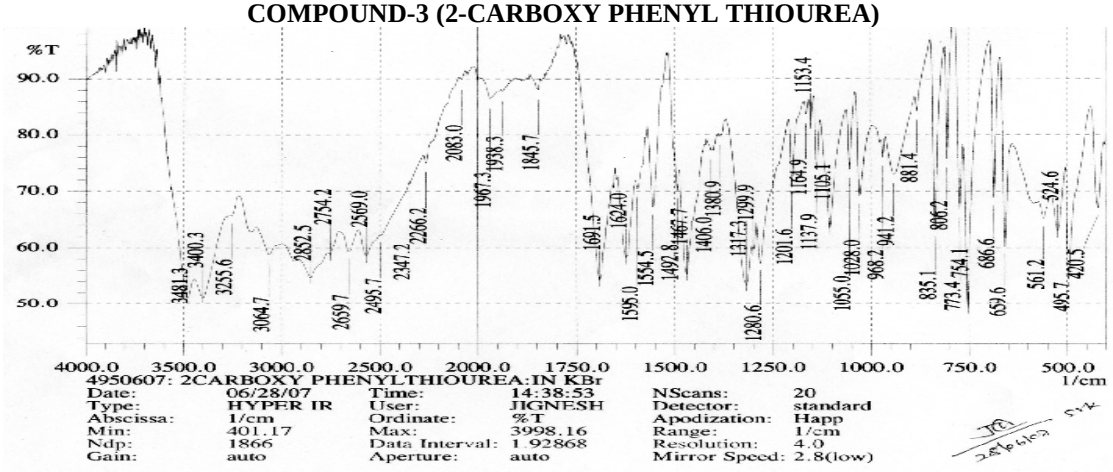
Amines and Amides

- ✓ 2239.2 cm^{-1} – C≡N Stretching.
- ✓ 1600.8, 1616.3 cm^{-1} – N-H Bending Primary Amine or Amide.
- ✓ 1039.6, 1114.8, 1139.9, 1238.2 cm^{-1} – C-N Stretching Aliphatic Amine.

Carboxylic Acid

- ✓ 1404.1 cm^{-1} – C-O-H In-Plane bending.

COMPOUND-3 (2-CARBOXY PHENYL THIOUREA)



Aromatic

- ✓ 3064.7 cm^{-1} - Aromatic C-H Stretching.
- ✓ 1406, 1467.7, 1492.8 cm^{-1} - C=C ring Stretching.
- ✓ 656.6, 754.1, 773.4, 806.2, 835.1, 881.4 cm^{-1} – Out of Plane C-H Bending (Aromatic).
- ✓ 754.1 (Strong Band) cm^{-1} - Ortho Substituted Benzene.
- ✓ 686.6 (One Band) and 754.1, 773.4, 806.2 (One Strong Band) cm^{-1} – Meta Substituted Benzene.
- ✓ 806.2, 835.1 (Strong Band) cm^{-1} - Para Substituted Benzene.

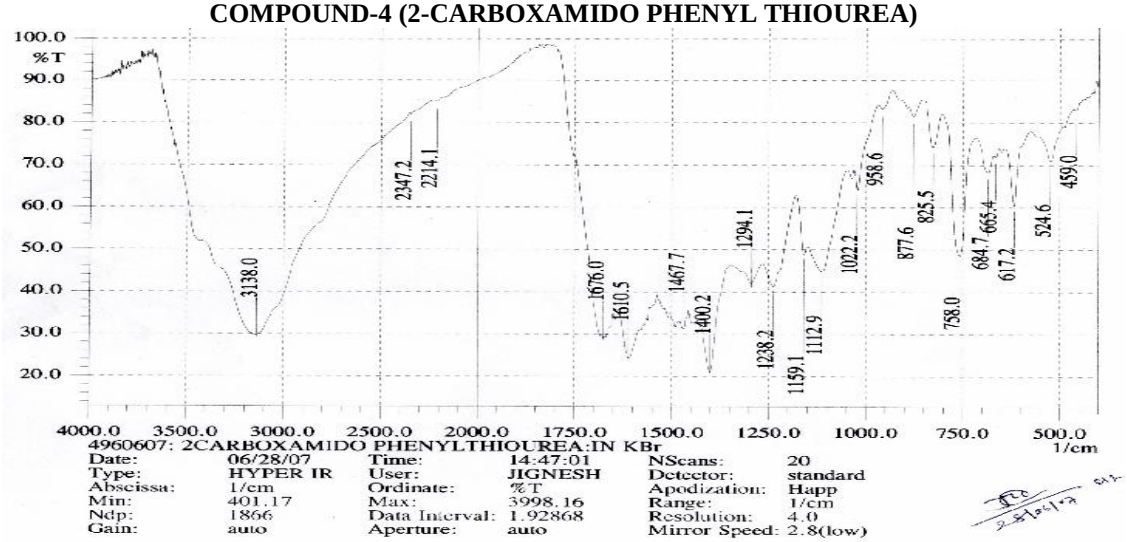
Amines and Amides

- ✓ 2239.2 cm^{-1} – C≡N Stretching.
- ✓ 3255.6, 3400.3, 3481.3 cm^{-1} – O-H Stretching.
- ✓ 3400.3, 3481.3 cm^{-1} – N-H Stretching.
- ✓ 1595, 1624 cm^{-1} – N-H Bending Primary Amine or Amide.
- ✓ 1028, 1055, 1105.1, 1153.4, 1164.9, 1201.6 cm^{-1} – C-N Stretching Aliphatic Amine.

Carboxylic Acid

- ✓ 1406 cm^{-1} – C-O-H In-Plane bending.

COMPOUND-4 (2-CARBOXAMIDO PHENYL THIOUREA)



Aromatic

- ✓ 1400.2, 1467.7 cm^{-1} - C=C ring Stretching.
- ✓ 684.7, 758, 825.5, 877.6 cm^{-1} – Out of Plane C-H Bending (Aromatic).
- ✓ 758 (Strong Band) cm^{-1} - Ortho Substituted Benzene.
- ✓ 684.7 (One Band) and 758 (One Strong Band) cm^{-1} – Meta Substituted Benzene.
- ✓ 825.5 (Strong Band) cm^{-1} - Para Substituted Benzene.

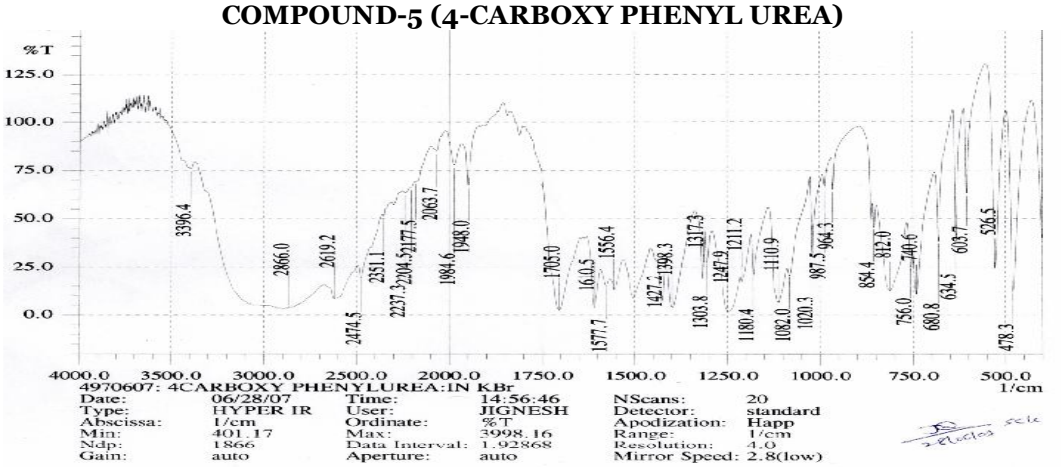
Amines and Amides

- ✓ 2214.1 cm^{-1} – C≡N Stretching
- ✓ 1610.5 cm^{-1} – N-H Bending Primary Amine or Amide.
- ✓ 1022.2, 1112.9, 1159.1, 1238.2, 1249.1 cm^{-1} – C-N Stretching Aliphatic Amine.

Carboxylic Acid

- ✓ 1400.2 cm^{-1} – C-O-H In-Plane bending.

COMPOUND-5 (4-CARBOXY PHENYL UREA)

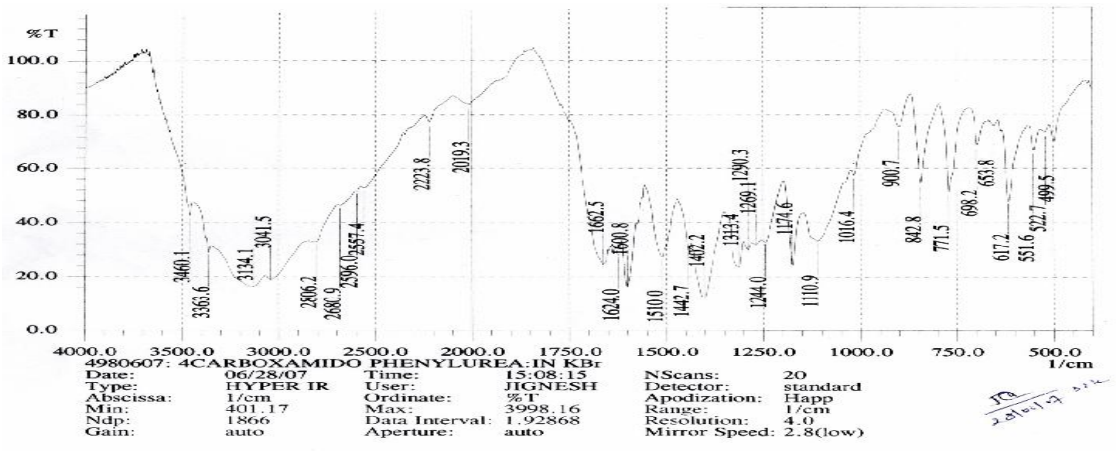


Aromatic
- ✓ 1427.2 cm^{-1} - C=C ring Stretching.
- ✓ 680.8, 740.6, 756, 812, 854.4 cm^{-1} – Out of Plane C-H Bending (Aromatic).
- ✓ 740.6, 756 (Strong Band) cm^{-1} - Ortho Substituted Benzene.
- ✓ 680.8 (One Band) and 756 (One Strong Band) cm^{-1} – Meta Substituted Benzene.
- ✓ 812 (Strong Band) cm^{-1} - Para Substituted Benzene.

Amines and Amides
- ✓ 2237.3 cm^{-1} – C≡N Stretching.
- ✓ 3396.4 cm^{-1} – O-H Stretching.
- ✓ 3396.4 cm^{-1} – N-H Stretching.
- ✓ 1610.5 cm^{-1} – N-H Bending Primary Amine or Amide.
- ✓ 1020.3, 1082, 1110.9, 1180.4, 1211.2, 1247.9 cm^{-1} – C-N Stretching Aliphatic Amine.

Carboxylic Acid
- ✓ 1398.3, 1427.2 cm^{-1} – C-O-H In-Plane bending.

COMPOUND-6 (4-AMIDO PHENYL UREA)

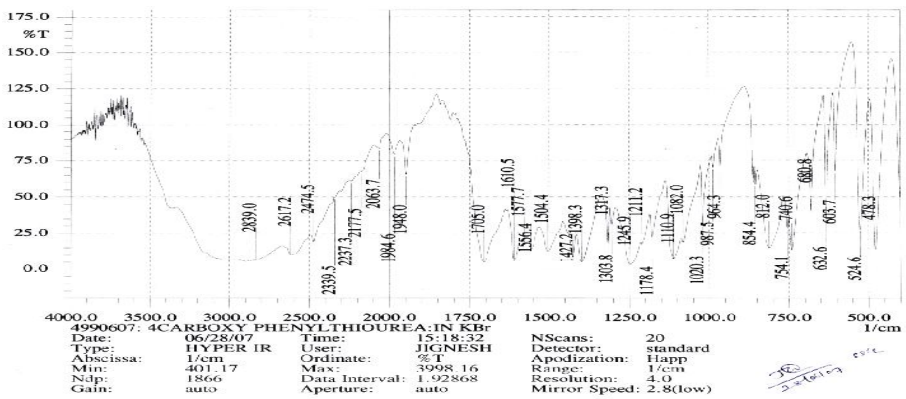


Aromatic
- ✓ 3041.5 cm^{-1} - Aromatic C-H Stretching.
- ✓ 1402.2, 1442.7, 1600.8 cm^{-1} - C=C ring Stretching.
- ✓ 698.2, 771.5, 842.8, 900.7 cm^{-1} – Out of Plane C-H Bending (Aromatic).
- ✓ 770 (Strong Band) cm^{-1} - Ortho Substituted Benzene.
- ✓ 698.2 (One Band) and 771.5 (One Strong Band) cm^{-1} – Meta Substituted Benzene.
- ✓ 806.2, 835.1 (Strong Band) cm^{-1} - Para Substituted Benzene.

Amines and Amides
- ✓ 2223.8 cm^{-1} – C≡N Stretching.
- ✓ 3363.6, 3460.1 cm^{-1} – O-H Stretching.
- ✓ 3363.6, 3460.1 cm^{-1} – N-H Stretching.
- ✓ 1600.8, 1624 cm^{-1} – N-H Bending Primary Amine or Amide.
- ✓ 1110.9, 1174.6, 1244 cm^{-1} – C-N Stretching Aliphatic Amine.

Carboxylic Acid
- ✓ 1402.2, 1440 cm^{-1} – C-O-H In-Plane bending.

COMPOUND-7 (4-CARBOXY PHENYL THIOUREA)



Aromatic
- ✓ 1427.2, 1504.4 cm^{-1} - C=C ring Stretching.
- ✓ 680.8, 740.6, 754.1, 812, 854.4 cm^{-1} – Out of Plane C-H Bending (Aromatic).
- ✓ 740.6, 754.1 (Strong Band) cm^{-1} - Ortho Substituted Benzene.
- ✓ 680.8 (One Band) and 754.1 (One Strong Band) cm^{-1} – Meta Substituted Benzene.
- ✓ 812, 854.4 (Strong Band) cm^{-1} - Para Substituted Benzene.

Amines and Amides
- ✓ 2237.3 cm^{-1} – C≡N Stretching.
- ✓ 3400.3, 3481.3 cm^{-1} – N-H Stretching.
- ✓ 1578.8, 1610.5 cm^{-1} – N-H Bending Primary Amine or Amide.
- ✓ 1020.3, 1082, 1110.9, 1178.4, 1211.2, 1245.9 cm^{-1} – C-N Stretching Aliphatic Amine.

Carboxylic Acid
- ✓ 1398.3, 1427.2 cm^{-1} – C-O-H In-Plane bending.

COMPOUND-8 (4-AMIDO PHENYL THIOUREA)

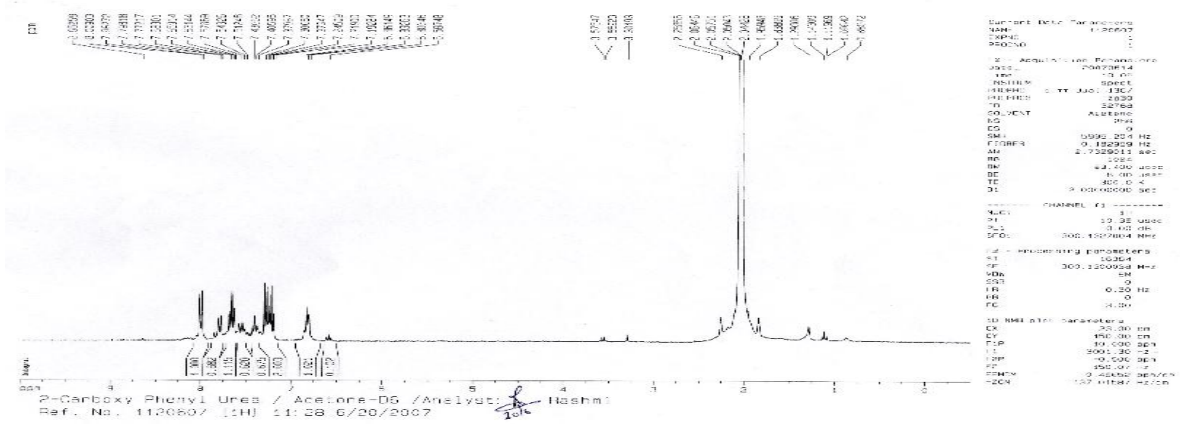
Aromatic
- ✓ 3043.5 cm^{-1} - Aromatic C-H Stretching.
- ✓ 1402.2, 1602.7 cm^{-1} - C=C ring Stretching.
- ✓ 698.2, 771.5, 813.9, 844.8, 898.8 cm^{-1} – Out of Plane C-H Bending (Aromatic).
- ✓ 771.5 (Strong Band) cm^{-1} - Ortho Substituted Benzene.
- ✓ 698.2 (One Band) and 771.5 (One Strong Band) cm^{-1} – Meta Substituted Benzene.
- ✓ 813.9, 844.8 (Strong Band) cm^{-1} - Para Substituted Benzene.

Amines and Amides
- ✓ 2229.6 cm^{-1} – C≡N Stretching.
- ✓ 1602.7, 1625.9 cm^{-1} – N-H Bending Primary Amine or Amide.
- ✓ 1512.1 cm^{-1} - N-H Bending Secondary Amine or Amide.
- ✓ 1037.6, 1112.9, 1174.6, 1244 cm^{-1} – C-N Stretching Aliphatic Amine.

Carboxylic Acid
- ✓ 1402.2 cm^{-1} – C-O-H In-Plane bending.

NMR Spectras (Proton NMR)

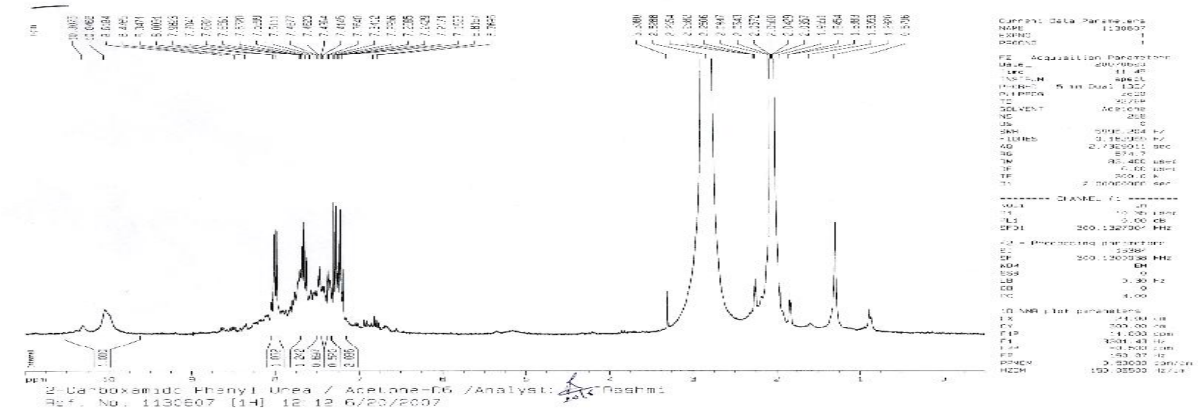
COMPOUND-1 (2-CARBOXY PHENYL UREA)



Interpretation:

- ✓ ^{1}H NMR: δ, 6.58-8.65 (4H, Aryl), 1.000 (H_1A of Benzene-NH-CO-NH_2), 1.115 (H_2A), 2.003 (H_2B), 2.003 (H_2B- Four Peaks), 1.021 (-NH-NH_2).
- ✓ Downfield occurs due to –COO group.

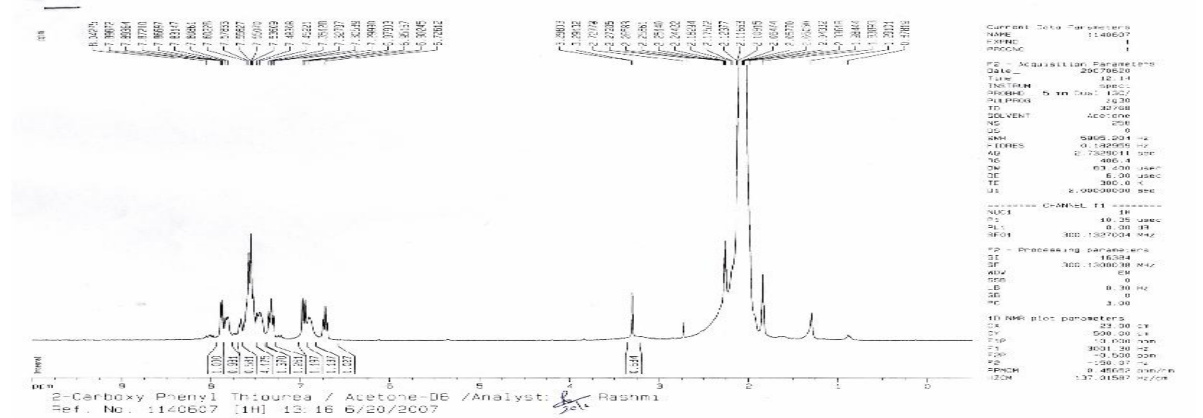
COMPOUND-2 (2-CARBOXAMIDO PHENYL UREA)



Interpretation:

- ✓ ^{1}H NMR: δ, 6.58-10 (4H, Aryl), 1.000 (H_1A of Benzene-NH-CO-NH_2), 1.032 (Aromatic Doublet), 1.242 (H_2A), 2.096 (Aromatic Triplet).

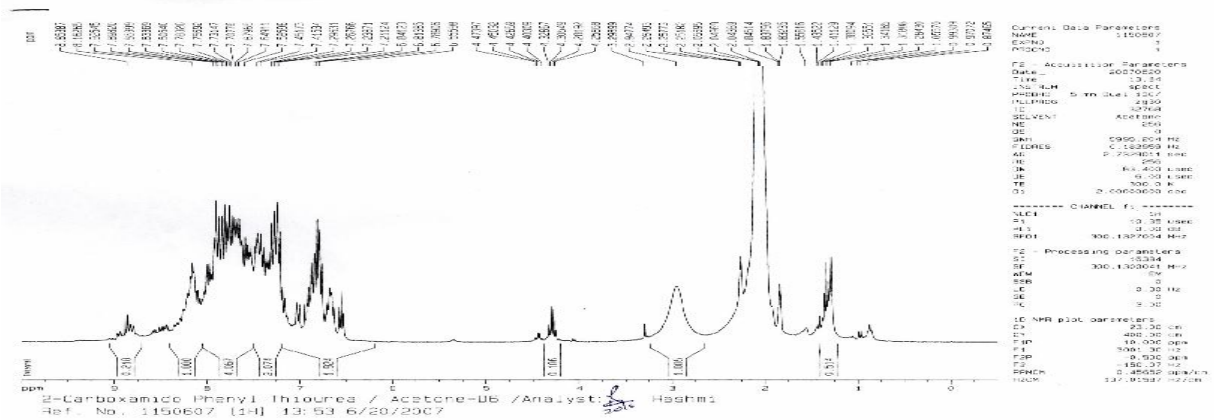
COMPOUND-3 (2-CARBOXY PHENYL THIOUREA)



Interpretation:

^{1}H NMR: δ, 6.58-8.12 (4H, Aryl), 1.000 (H_1A- Aromatic), 1.261 (Aromatic Triplet), 1.197 (Amide- Broad Peak).

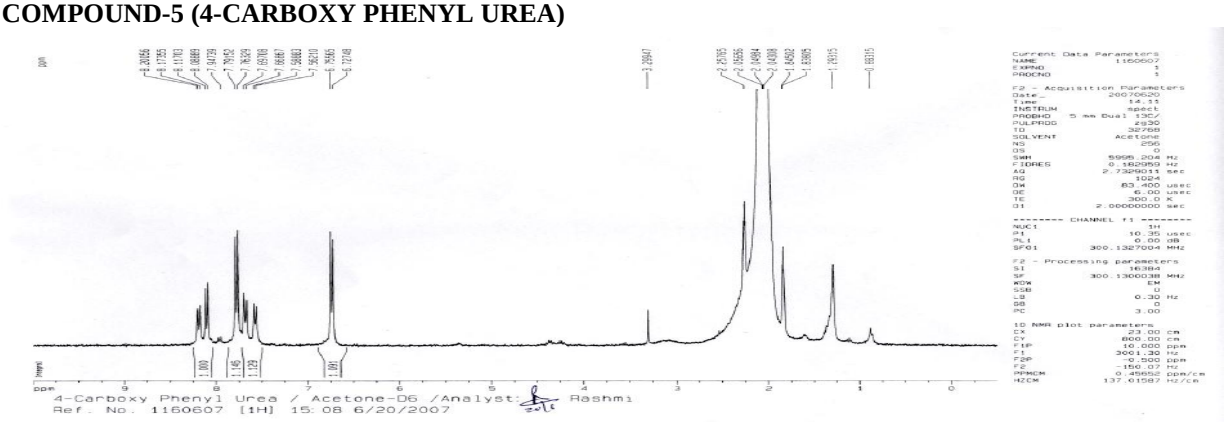
COMPOUND-4 (2-CARBOXAMIDO PHENYL THIOUREA)



Interpretation:

- ✓ ^{1}H NMR: δ, 6.58-8.12 (4H, Aryl), 1.000 & 2.074 (Reaction not done Properly), 1.005 (Water of Acetone), δ, 2 (Acetone- Long Peak).

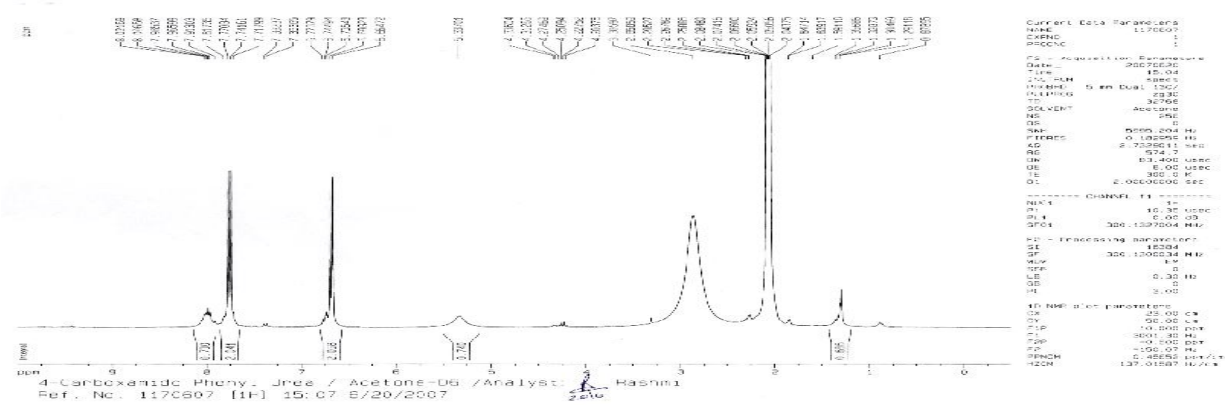
COMPOUND-5 (4-CARBOXY PHENYL UREA)



Interpretation:

- ✓ ^{1}H NMR: δ, 6.58-8.25 (4H, Aryl), 1.000 (H_1A of Benzene-NH-CO-NH_2), 1.146 (H_2A), 1.129 (H_2B), 1.129 (H_2B- Four Peaks), 1.091 (-NH-NH_2).

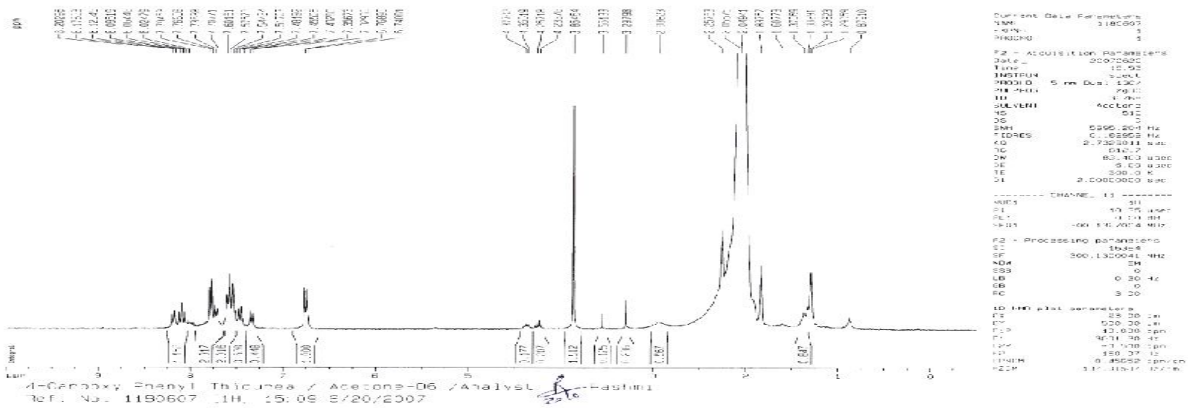
COMPOUND-6 (4-AMIDO PHENYL UREA)



Interpretation:

- ✓ ^{1}H NMR: δ, 5.25-8.12 (4H, Aryl), 0.700 (-NH_2), 2.041 (HA of -NH-CO-NH_2), 2.058 (HB- 2 Proton at Upper), 0.740 (-NH).

COMPOUND-7 (4-CARBOXY PHENYL THIOUREA)

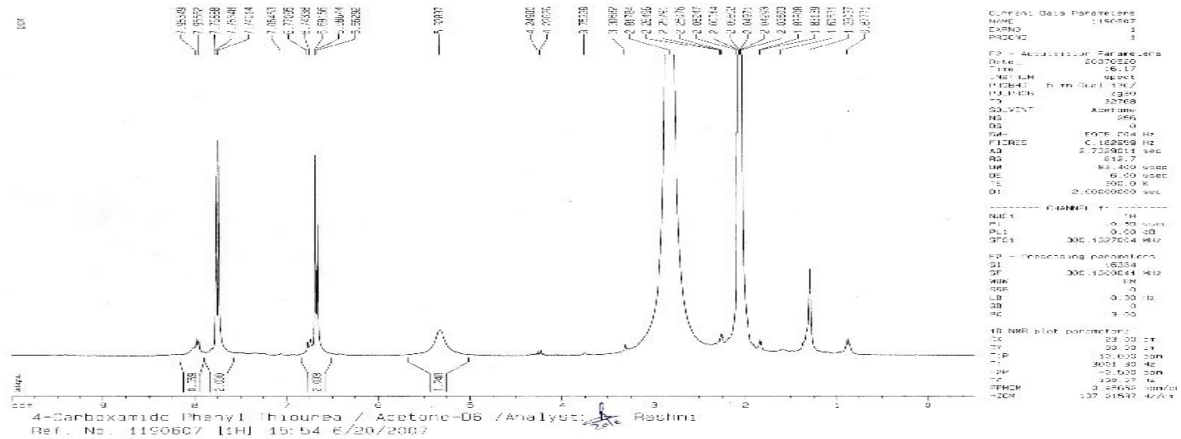


Interpretation:

- ✓ ^{1}H NMR: δ, 6.58-8.25 (4H, Aryl), 1.000 (H_1A of Benzene-NH-CO-NH_2), 2.017 (Aromatic Doublet), 2.016 (Aromatic Triplet).

1.515 (Water of Acetone).

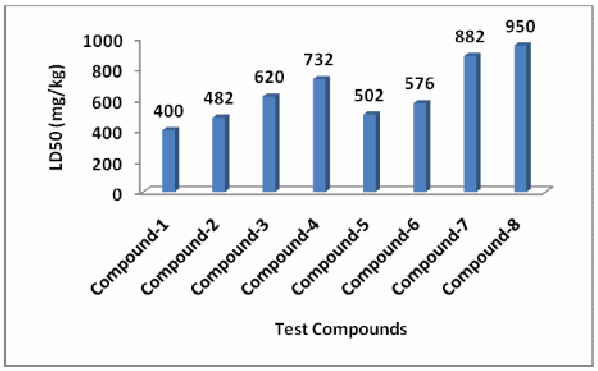
COMPOUND-8 (4-AMIDO PHENYL THIOUREA)



Interpretation:

- ✓ ^{1}H NMR: δ, 6.58-8.25 (4H, Aryl), 0.359 (-NH), 2.000 & 2.093 (Aromatic), 1.248 (Amide).

Pharmacological Work[13]:



Histogram of LD_{50}

Acute Toxicity:-

The acute toxicological studies of the compounds were done by determination of LD_{50} intraperitoneally by mg/kg dose in propylene glycol in 18 hours fasting mice and found that LD_{50} was as follows in between 400-950 mg/kg, which shows that thiourea derivatives are more toxic than urea linkages and 2-substituted derivatives are lesser than 4-substitition as bond energy in ortho is higher than para substitution:

Compound-1 < Compound-2 < Compound-5 < Compound-6 < Compound-3 < Compound-4 < Compound-7 < Compound-8

CNS Depression Studies:-

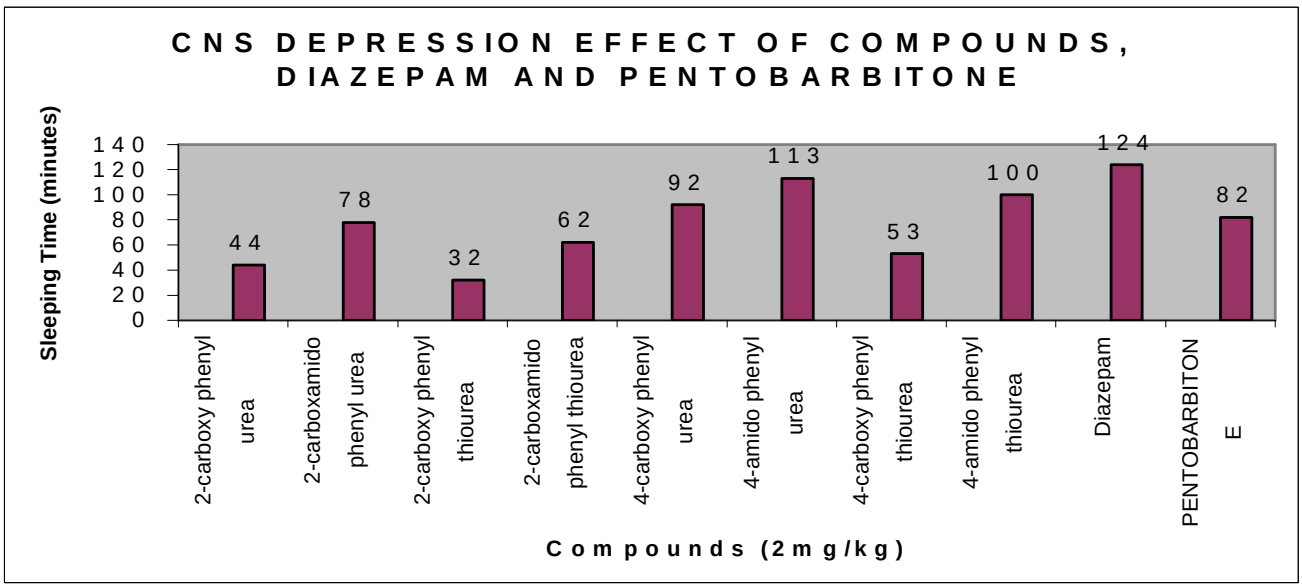
The CNS depression study of all the synthesized compound were carried out by administering intraperitoneally the various doses of the test compounds in mg/kg dose in 18 hours fasting male albino mice using propylene glycol as an inert vehicle. The loss of righting reflex and regaining of it was noted for each compound to determine the sleeping time. It has been found that all the test compounds have sleep inducing property due to the presence of urea/thiourea linkage and the urea/thiourea diamide derivatives were found longer duration of sleep inducing property due to the presence of two amide linkages and out of which the thiourea derivative and thiourea diamide derivatives showed lesser duration than urea and urea diamide linkage. Sleeping time potentiation effect was studied for the test compounds by using pentobarbitone as barbiturates and alprazolam as benzodiazepines on male albino mice. The 2-sustituted derivatives were found less active than 4-substituted derivatives due to the steric hindrance and ortho effect. All the observations were noted for four groups of mice and the bioassay result was tabulated after statistical parameters for significance of pharmacological screening: Student's-t-test and P-value. All the test results were found significant to a high extent for the structure activity relationship

studies of the synthesized molecules and the maximum activity has been shown by the COMPOUND-6 (4-Amido phenyl urea) having two amide group[14-16].

Pharmacological Screening:

CNS depression studies have been done on male albino mice (25-35 gms) in 18 hours fasting condition. The test compounds and the standard drugs have been administered intraperitoneally in propylene glycol medium in six groups of animals and biological response has been tabulated in minutes ± SE (Standard Error) for statistical parameters[17]. Student's-t-test have been recorded and P-value has been determined for the authenticity of the pharmacological response and that has been found satisfactory: P < 0.001%= a; P < 0.01%= b; P < 0.1%=c.

CNS Depression Effect of Compounds, Diazepam and Pentobarbitone



CNS Depression Effect of Compounds and By Diazepam

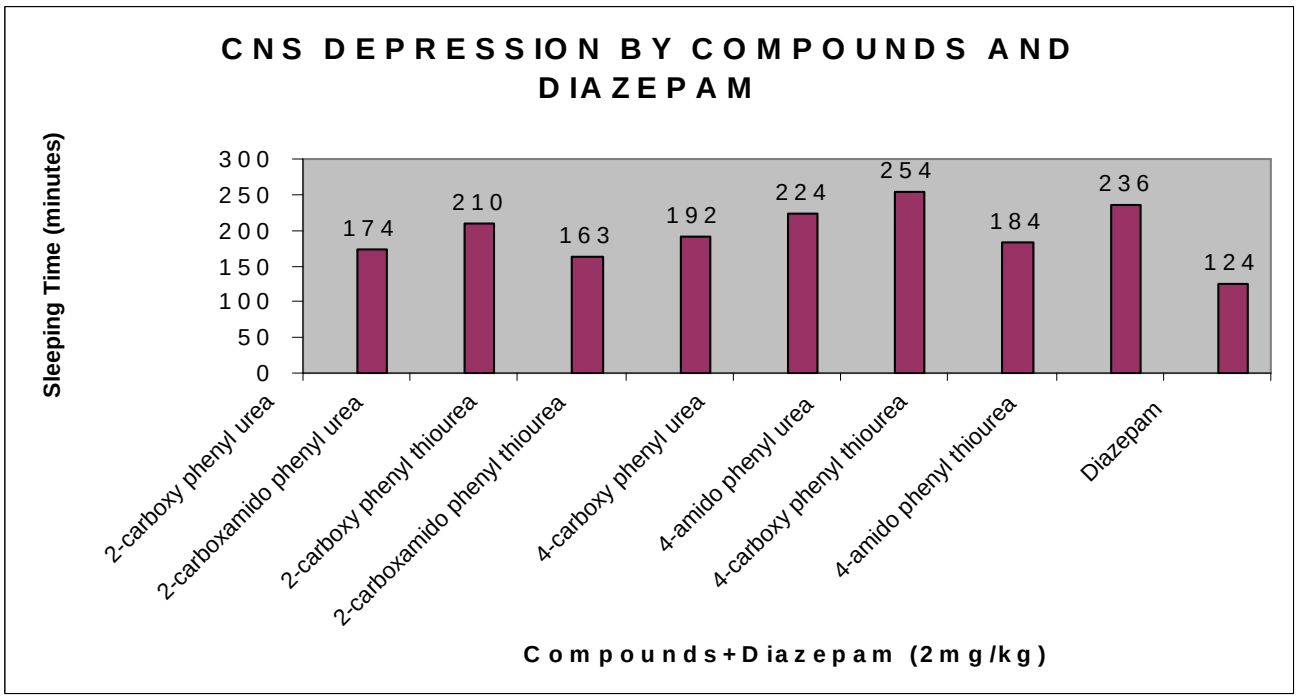
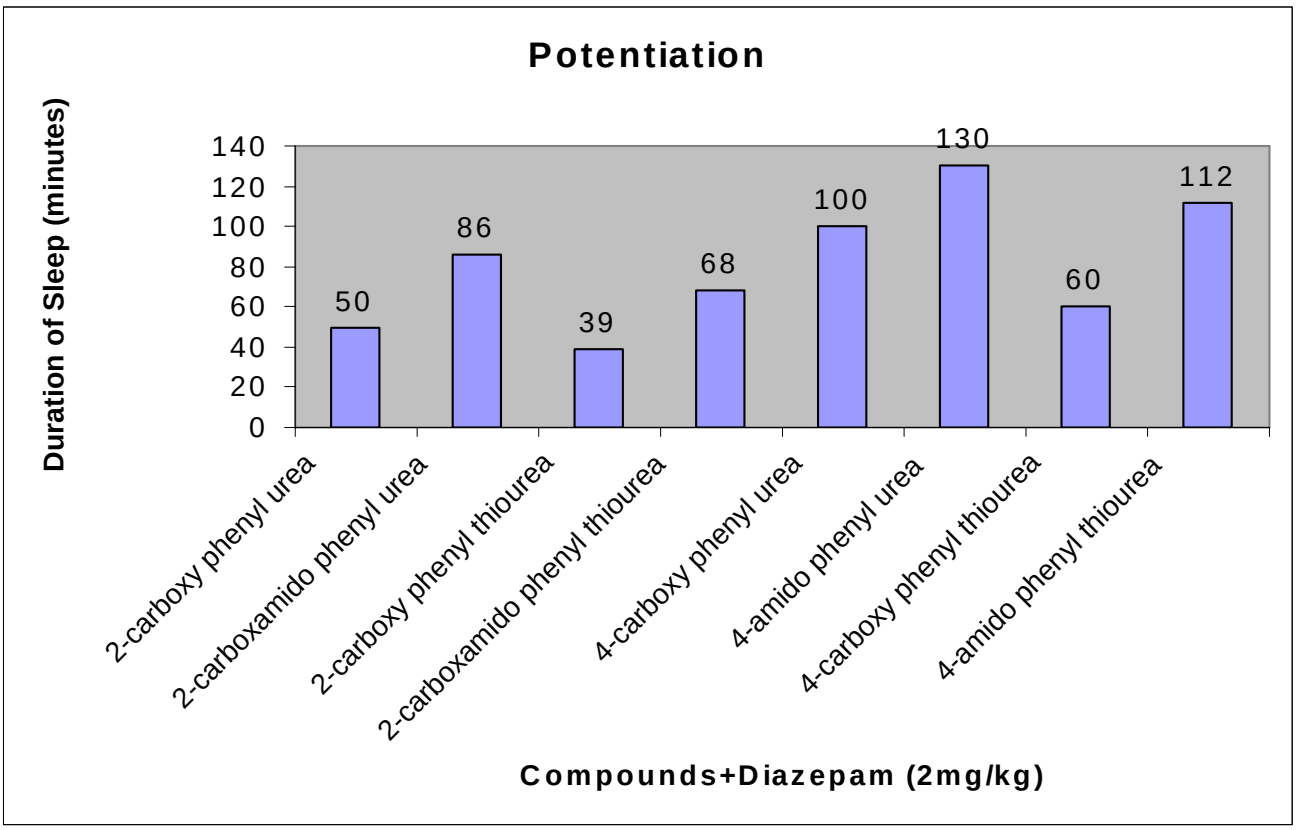
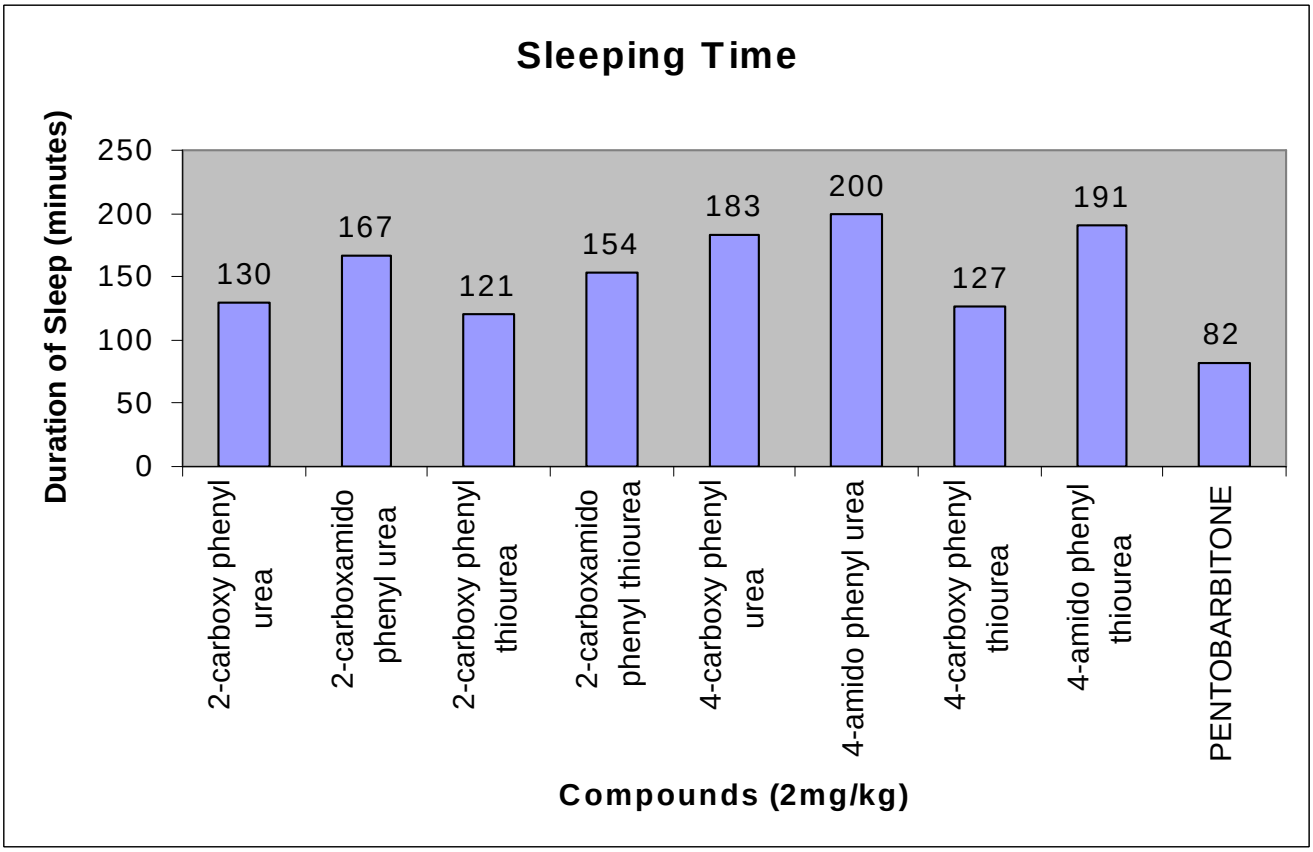


Table-4

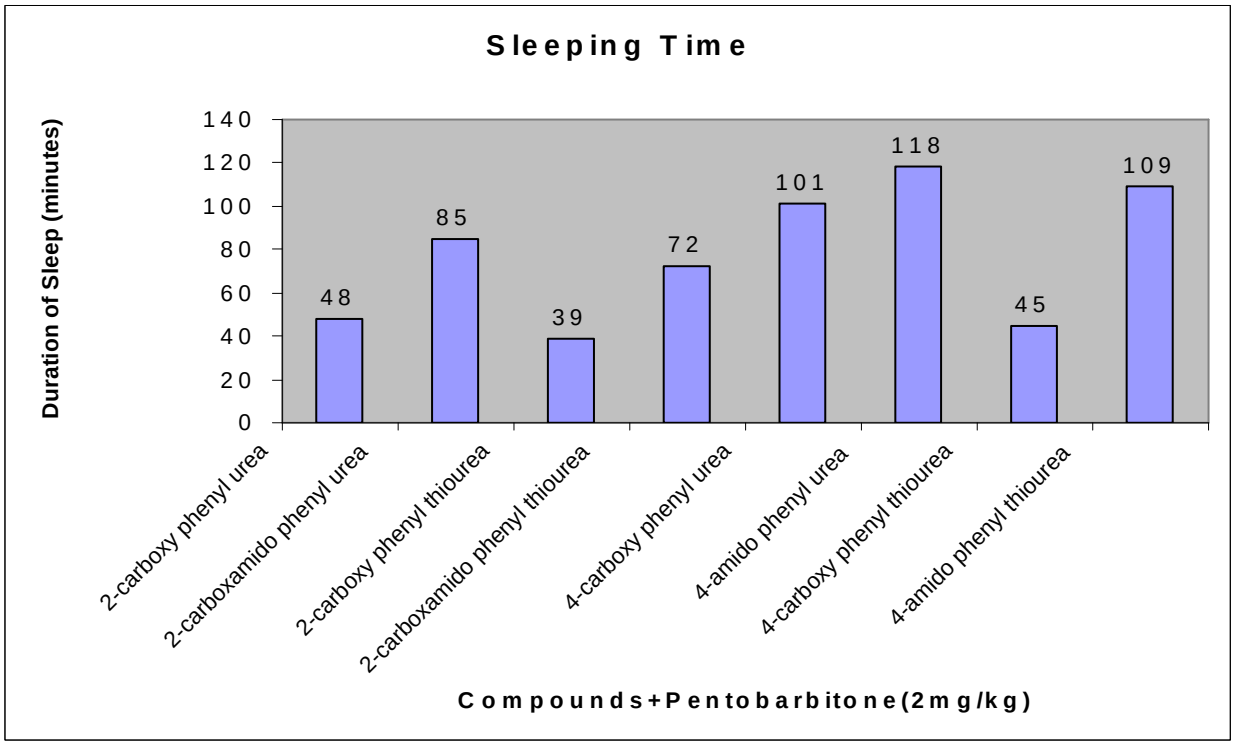
Compounds	Dose (mg/ kg)	Sleeping Time (Minutes) ± SE	Compounds + Diazepam (Minutes) ± SE	Potentiation (Minutes) ± SE: Diazepam	Compounds + Pentobarbitone ± SE (Minutes)	Potentiation (Minutes) ± SE: Pentobarbitone
2-carboxy phenyl urea	2	44 ± 0.23^{a}	174 ± 0.65^{a}	50 ± 0.49^{b}	130 ± 0.66^{a}	48 ± 0.32^{a}
2-carboxamido phenyl urea	2	78 ± 0.31^{c}	210 ± 0.39^{c}	86 ± 0.65^{a}	167 ± 0.21^{b}	85 ± 0.34^{a}
2-carboxy phenyl thiourea	2	32 ± 0.64^{b}	163 ± 0.92^{a}	39 ± 0.46^{a}	121 ± 0.49^{a}	39 ± 0.56^{c}
2-carboxamido phenyl thiourea	2	62 ± 0.58^{a}	192 ± 0.24^{b}	68 ± 0.78^{b}	154 ± 0.12^{a}	72 ± 0.47^{a}
4-carboxy phenyl urea	2	92 ± 0.43^{a}	224 ± 0.47^{a}	100 ± 0.45^{a}	183 ± 0.13^{b}	101 ± 0.36^{b}
4-amido phenyl urea	2	113 ± 0.21^{b}	254 ± 0.87^{c}	130 ± 0.42^{c}	200 ± 0.34^{a}	118 ± 0.47^{b}
4-carboxy phenyl thiourea	2	$53 \pm 0.86b^{a}$	184 ± 0.54^{c}	60 ± 0.42^{b}	127 ± 0.46^{b}	45 ± 0.76^{b}
4-amido phenyl thiourea	2	100 ± 0.12^{c}	236 ± 0.35^{b}	112 ± 0.76^{c}	191 ± 0.76^{b}	109 ± 0.77^{a}
Diazepam	2	124 ± 0.25^{a}	----			
Pentobarbitone	2	82 ± 0.64^{a}	----			



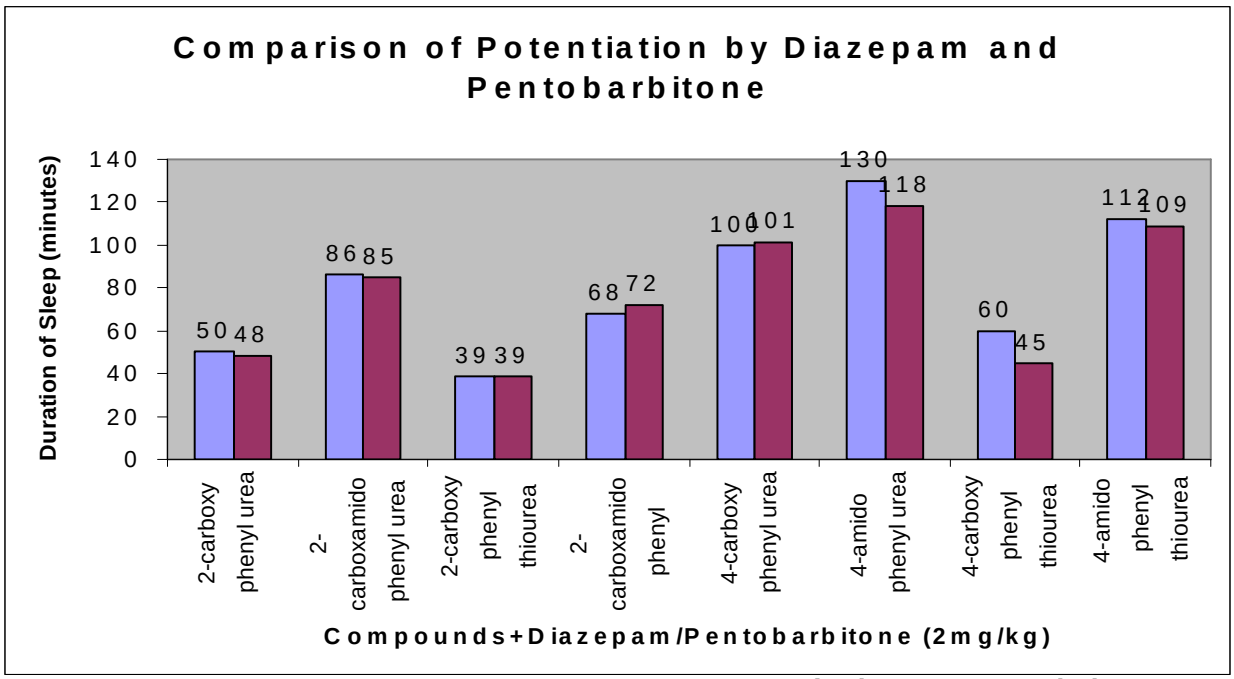
CNS Depression Effect Of Compounds and By Pentobarbitone



Sleeping Time Potentiation By Pentobarbitone



Comparison of Sleeping Time Potentiation By Diazepam/Pentobarbitone With Compounds

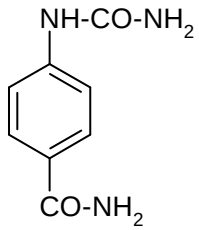


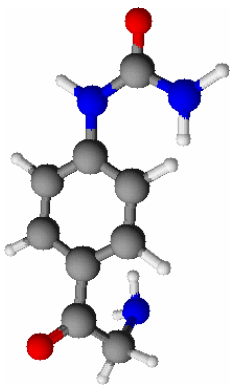
Conclusion:-

It has been found that all the test compounds have sleep inducing property due to the presence of open chain urea/thiourea linkage and the urea/thiourea diamide derivatives were found longer duration of sleep inducing property due to the presence of two test compounds by using pentobarbitone as barbiturates and diazepam as benzodiazepines on male albino mice. The 2-sustituted derivatives were found less active than 4-substituted derivatives due to the steric hindrance and ortho effect. All the observations were noted for four groups of mice and the bioassay result was tabulated after statistical

parameters for significance of pharmacological screening: Student's-t-test and P-value. The CNS depression occurs due to the action on GABA receptor having free NH_2 and COOH groups: H_2N-CH_2-CH_2-CH_2-CH_2-COOH (γ-amino butyric acid). The synthesized compounds which have free –C(O/S)-NH_2 (urea/thiourea) groups and –COOH groups shows the CNS depression effect and the maximum activity has been shown by the compound-6 in which amido as well as urea

linkages are in para position to each other which blocks the GABA receptor and results CNS depression. The same attachment shows lesser action in case of ortho substitution due to ortho effect and steric hindrance.





COMPOUND-6 **3D-STRUCTURE**

All the test results were found significant to a high extent for the structure activity relationship studies of the synthesized molecules and the maximum activity has been shown by the **COMPOUND-6 (4-Amido phenyl urea)** having two amide groups.

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Author Information: Ravikumar V. Modi did this project under the guidance of Prof Dr Dhrubo Jyoti Sen at Shri Sarvajanik Pharmacy College, Mehsana, Gujarat during his M.Pharm. Degree course (2005-2007) and at present Mr. Modi is a final year student of MBA in USA.

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