INTERNATIONAL JOURNAL OF DRUG DEVELOPMENT AND RESEARCH

INT.J.DRUG DEV & RES., SEP-DEC 2009;1(1):126-135

RESEARCH ARTICLE

STRUCTURE ACTIVITY RELATIONSHIP STUDIES OF CONJUGATED DIAMIDES OF VARIABLE ATOMIC ELECTRONEGATIVITY FOR SLEEPING TIME SYNERGISTIC ACTIVITY

HARDIK ARVINDBHAI PATEL, KIRAN MANUBHAI PATEL, DHRUBO JYOTI SEN AND DILIPKUMAR RAMJIBHAI CHAVDA

Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Hemchandracharya North Gujarat University, Arvind Baug, Mehsana-384001, Gujarat, India

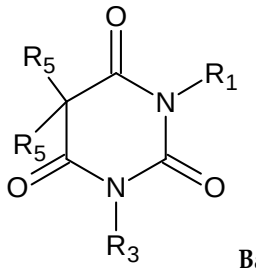
ABSTRACT

The idea has been generated for CNS depression from the rational drug design from the structure of benzodiazepines and barbiturates in which there are closed chain urea moiety having two nitrogens in heterocyclic rings. Our objective was to synthesis such molecule in which this type of linkage must be in closed chain as well as in side chain. The synthesised molecule has three variables of three hetero atoms O/S/N and the CNS depression study has been done with respect to the standard sedative drug and found that the CNS depression activity persists in only urea moiety and there was no CNS depression activity in thiourea and guanidine linkage, but the sleeping time potentiation has been found in all the three compounds are as follows: ***Compound-A: X=O (urea derivative)*** *>* ***Compound-C: X=NH (guanidine derivative)*** *>* ***Compound-B: X=S (thiourea derivative)*** *because electronegativity of oxygen for urea X:O=3.5 and of sulfur for thiourea X:S=2.4 and of nitrogen for guanidine X:NH=3.1. So the X=O shows the maximum electronegativity with two lone pair of electrons whereas X=S has also two lone pairs but X=NH has one lone pair of electrons, but in case of NH moiety the electronegativity of hetero element (N) is in between the hetero elements (O) for X:O and (S) for X:S. So, the affinity for GABA receptor binding capacity for urea is maximum to block the chloride channel.*

KEY WORDS: *Conjugated Diamides, electronegativity, CNS depression, GABA receptor, Synergistic Activity*

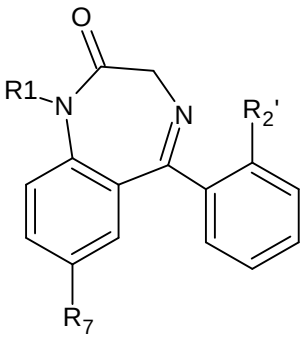
OBJECTIVE

Screening for structure activity relationship has been implemented by the structural tailoring of cyclic amide chain of CNS depressants drugs like barbiturates and benzodiazepines into open chain amide linkage in the synthesized molecules[1]. Here open chain diamides have been synthesized by keeping X variable (X=O: Urea, X=S: Thiourea and X=NH: Guanidine). There are two nitrogen atoms present in the six membered barbiturates (pyrimidine ring) as well as in seven membered benzodiazepines (diazepine ring) in closed ring structure, whereas our synthesized molecules have two nitrogen in five membered ring (pyrazole ring) as well as in open chain moiety –CO-NH-C(=X)-NH– to possess CNS depression by GABA receptor inhibition and chloride channel blocking[2].



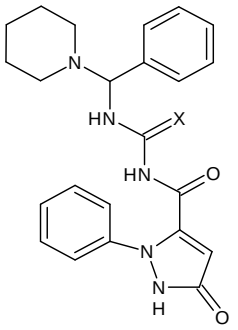
Barbiturate

*Corresponding Author: e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,
Received on: 14-10-09 ; Accepted on: 28-12-09



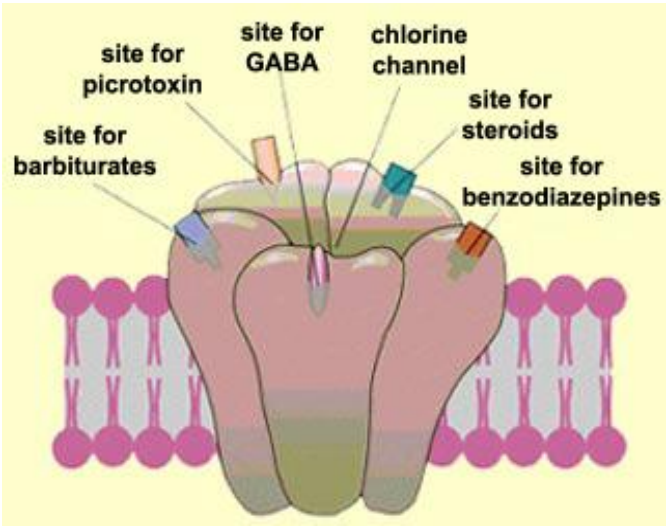
Benzodiazepine

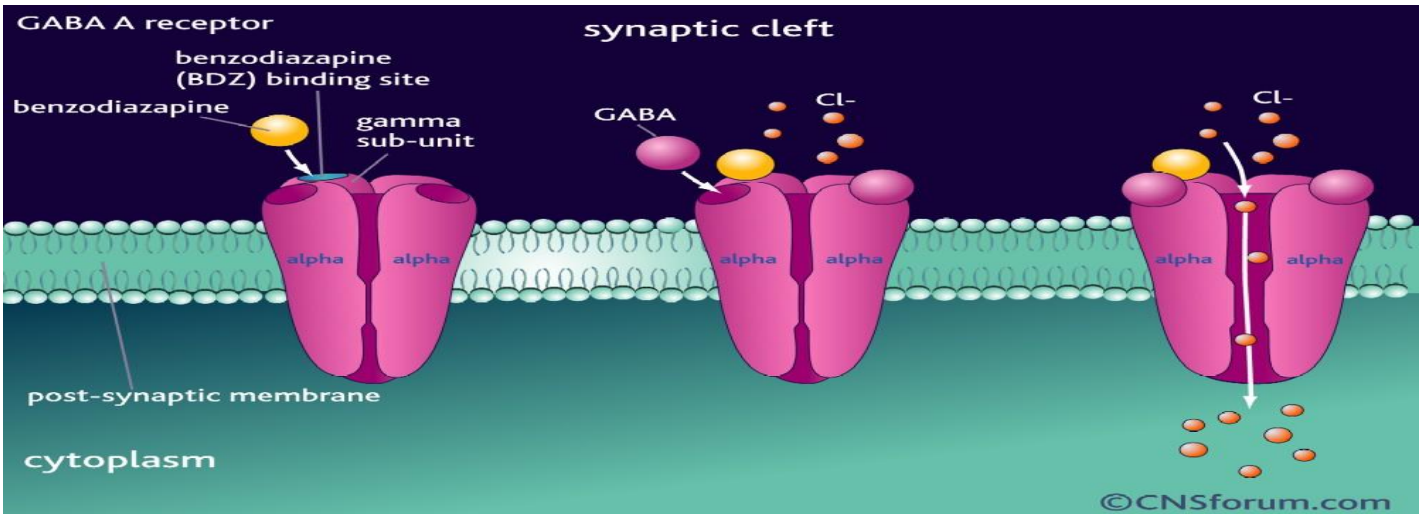
X=O: Urea, X=S: Thiourea, X=NH: Guanidine



Chemical Design

ETIOLOGY OF CNS DEPRESSION

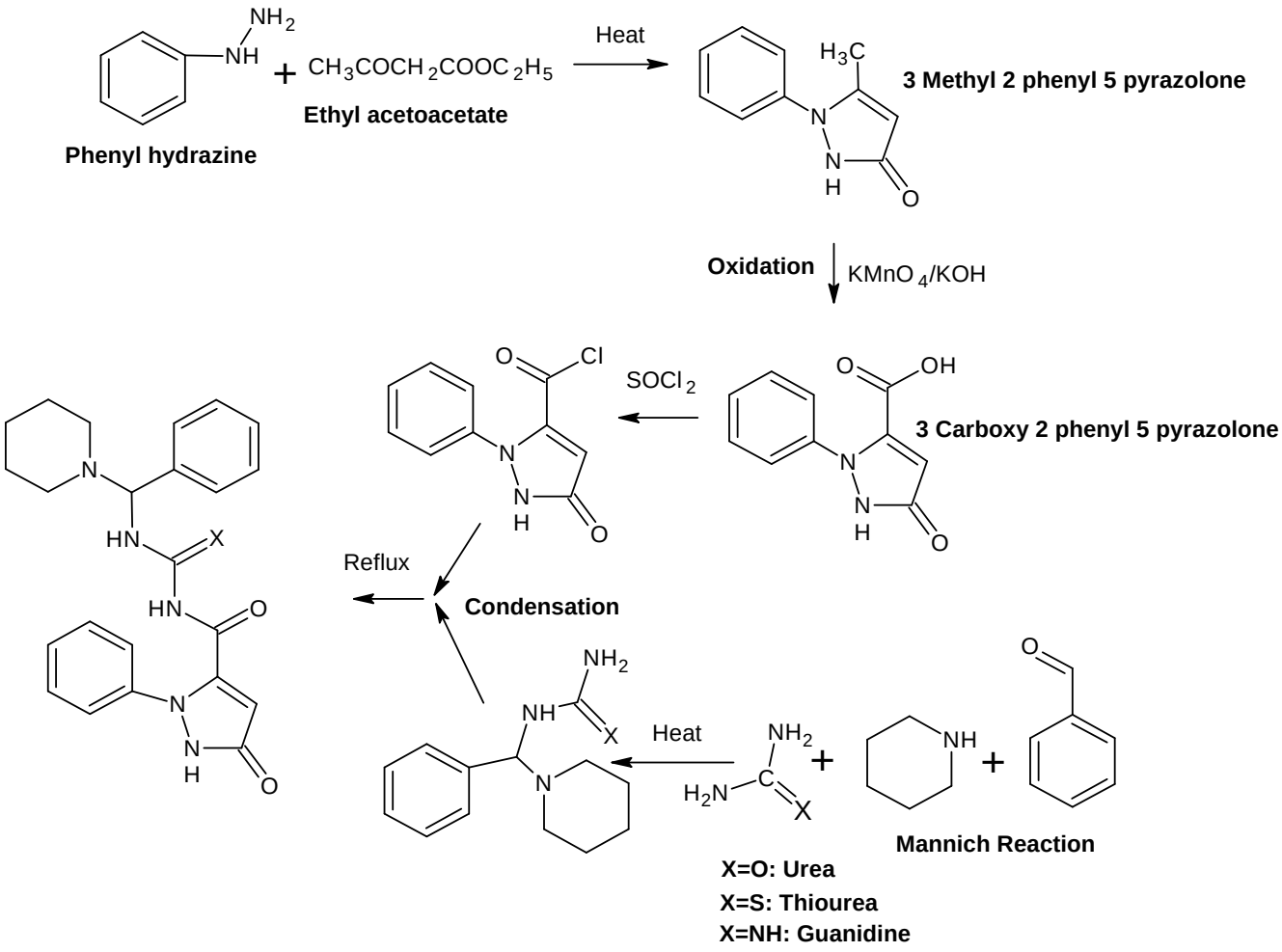




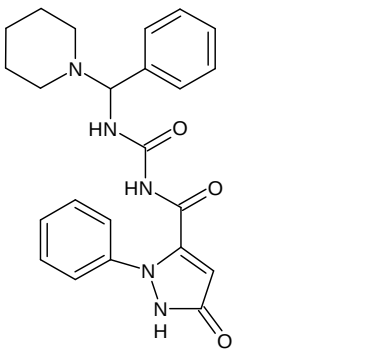
***Corresponding Author:** *e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*

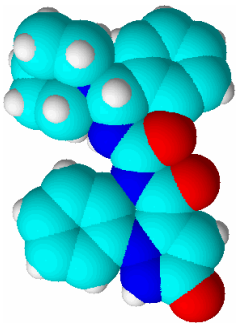
Received on: 14-10-09 ; Accepted on: 28-12-09

SCHEME

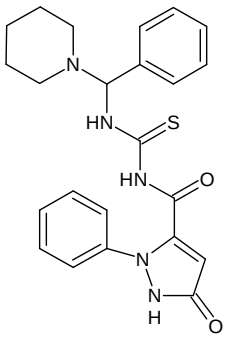


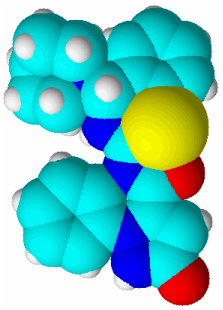
SYNTHESISED COMPOUNDS





Compound-A
$C_{23}H_{25}N_5O_3$

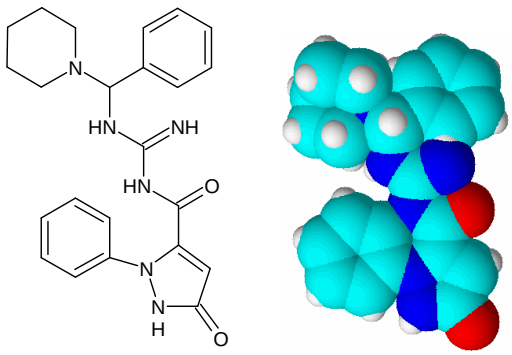




Compound-B
$C_{23}H_{25}N_5O_2S$

***Corresponding Author:** *e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*

Received on: 14-10-09 ; Accepted on: 28-12-09



Compound-C

$C_{23}H_{26}N_6O_2$

CHEMISTRY

The desired moiety has been synthesized by condensation of phenyl hydrazine with ethylacetoacetate to get the 2-phenyl-3-methyl-5-pyrazolone entity which on alkaline $KMnO_4$ oxidation produced free carboxylic acid by oxidation of methyl group. This carboxylic acid has been converted into acid chloride by thionyl chloride and condensed with the Mannich bases prepared by the reaction between benzaldehyde, piperidine and urea/thiourea/guanidine to get the desired molecules[3-6]. All the three have molecules been characterized by elemental microanalysis (N%) and spectral studies for structural confirmation.

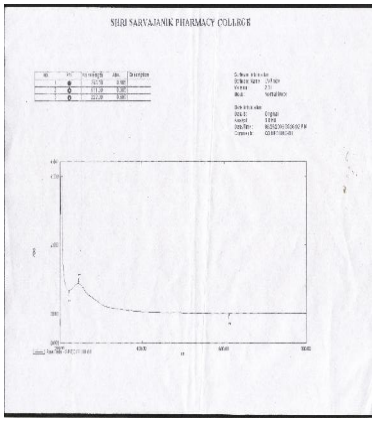
PHYSICOCHEMICAL PARAMETERS

COMPOUNDS	% YIELD	M.P. °C	POLARITY	MOL. FORMULA	N% CALCD	N% FOUND
Compound-A : X=O	87.71	220	Semipolar	$C_{23}H_{25}N_5O_3$	16.70	17.06
Compound-B : X=S	42.89	235-238	Semipolar	$C_{23}H_{25}N_5O_2S$	16.08	16.68
Compound-C : X=NH	33.83	80-82	Semipolar	$C_{23}H_{26}N_6O_2$	20.08	20.52

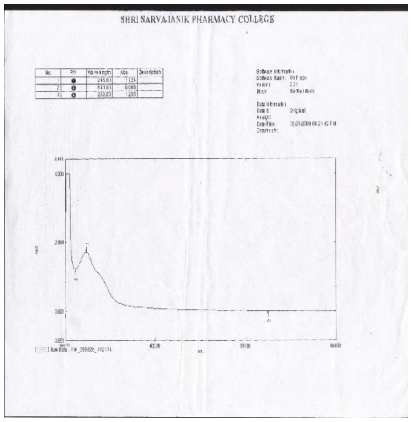
***Corresponding Author:** *e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*

Received on: 14-10-09 ; Accepted on: 28-12-09

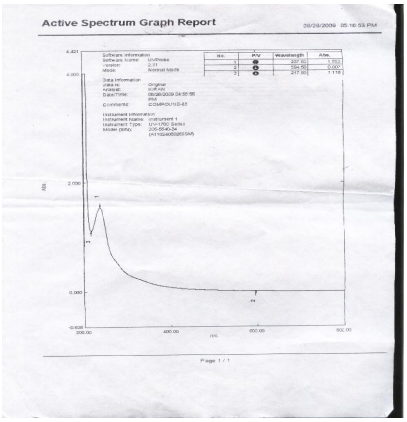
ULTRAVIOLET SPECTRAS OF SYNTHESISED COMPOUNDS



Compound-A : X=O
λ_{max}= 246nm

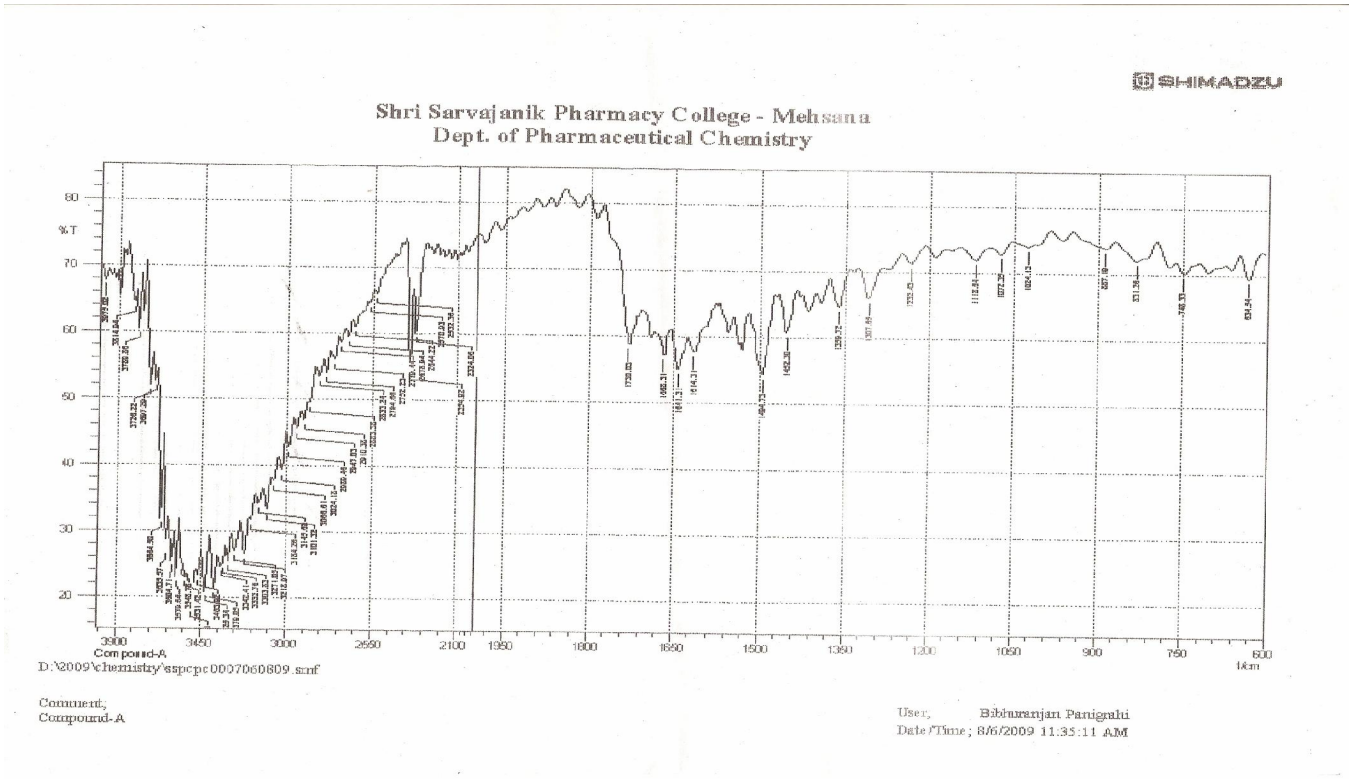


Compound-B : X=S
λ_{max}= 246.50nm



Compound-C : X=NH
λ_{max}= 237.50nm

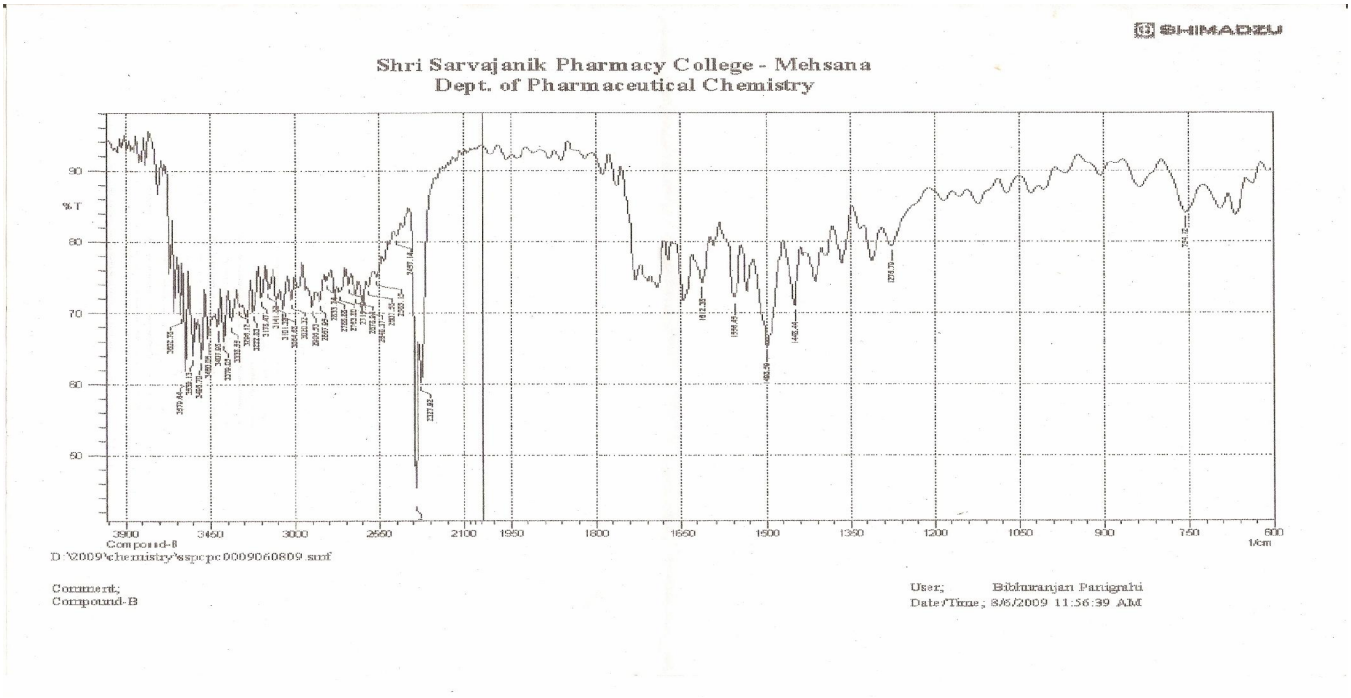
INFRA RED SPECTRAS OF SYNTHESISED COMPOUNDS



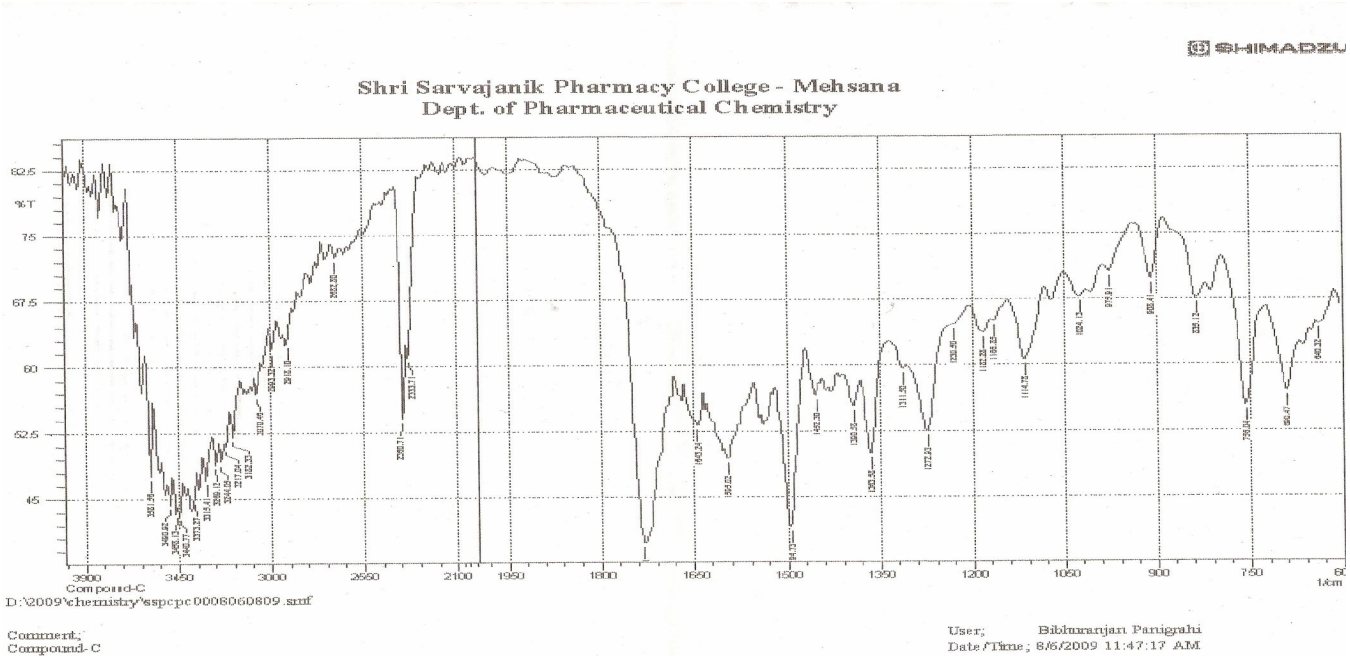
Compound-A: X=O

***Corresponding Author:** *e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*

Received on: 14-10-09 ; Accepted on: 28-12-09



Compound-B : X=S

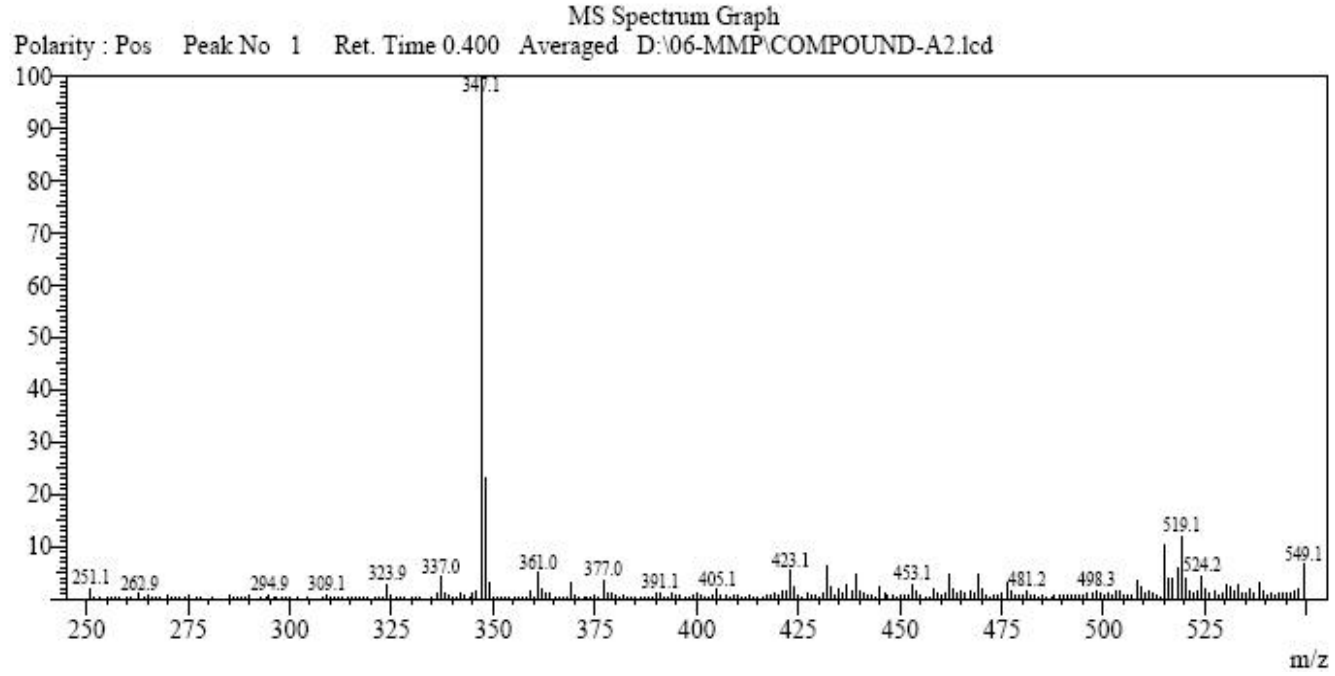


Compound-C: X=NH

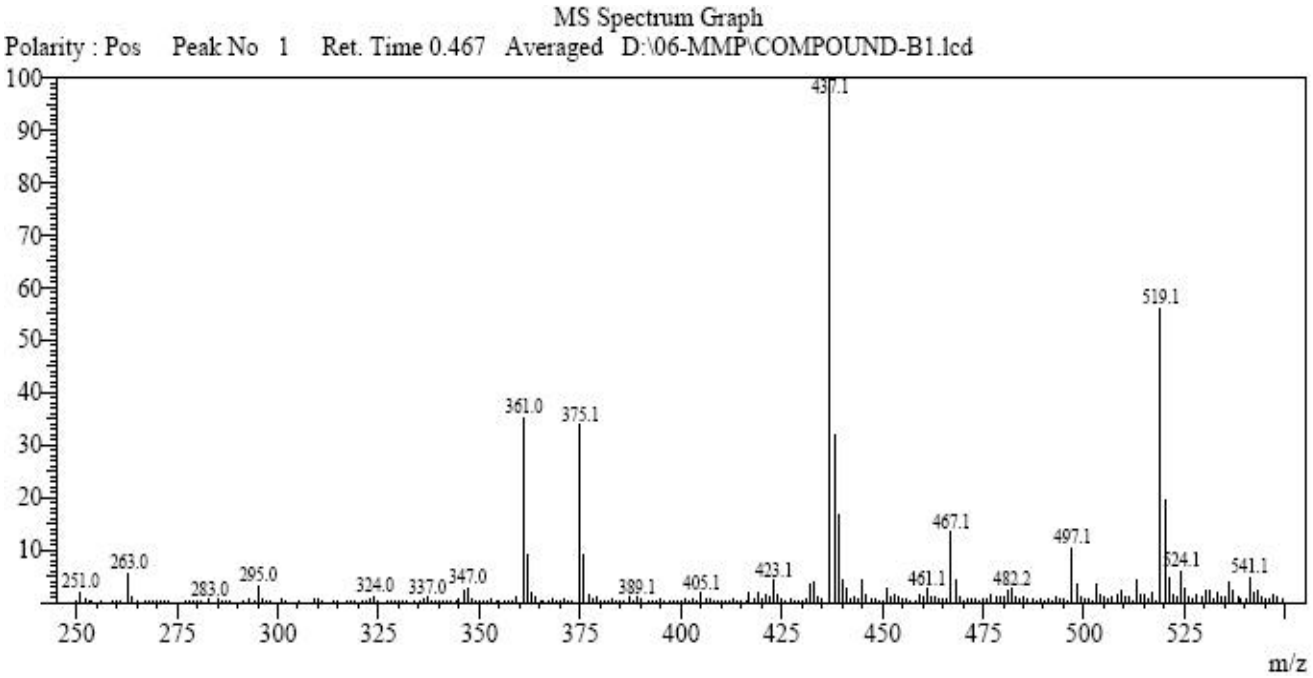
***Corresponding Author:** *e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*

Received on: 14-10-09 ; Accepted on: 28-12-09

MASS SPECTRAS OF SYNTHESISED COMPOUNDS



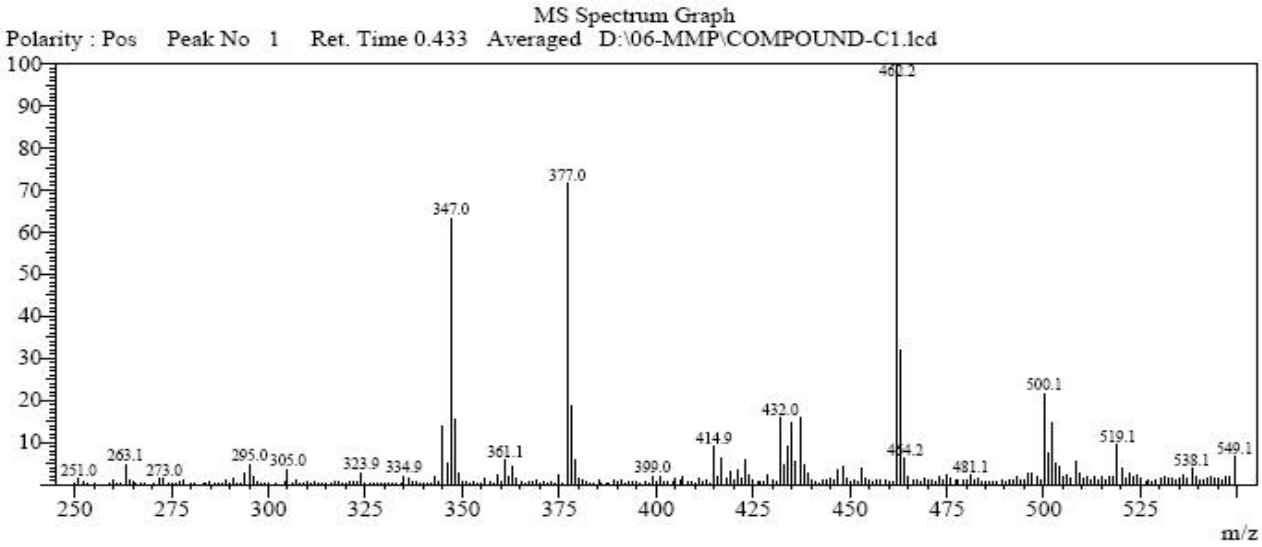
Compound-A: X=O



Compound-B : X=S

***Corresponding Author:** e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*

Received on: 14-10-09 ; Accepted on: 28-12-09



Compound-C: X=NH

PHARMACOLOGY

All the synthesized molecules have been characterized for their structural conformity by chromatography, spectral datas and by elemental microanalysis for N%. CNS depression study has been done by intraperitoneally for these compounds alone (0.5mg/kg), compounds (0.5mg/kg) + diazepam (5mg/kg) and diazepam (5mg/kg) by dissolving in propylene glycol to screen the duration of sleeping time and potentiation effect by synergistic activity in mice. It has been found that Compound-A (urea derivative) only has sleep inducing property but the synergistic action by the combination effect of all compounds+diazepam showed much more duration of sleep rather than diazepam[7-10].

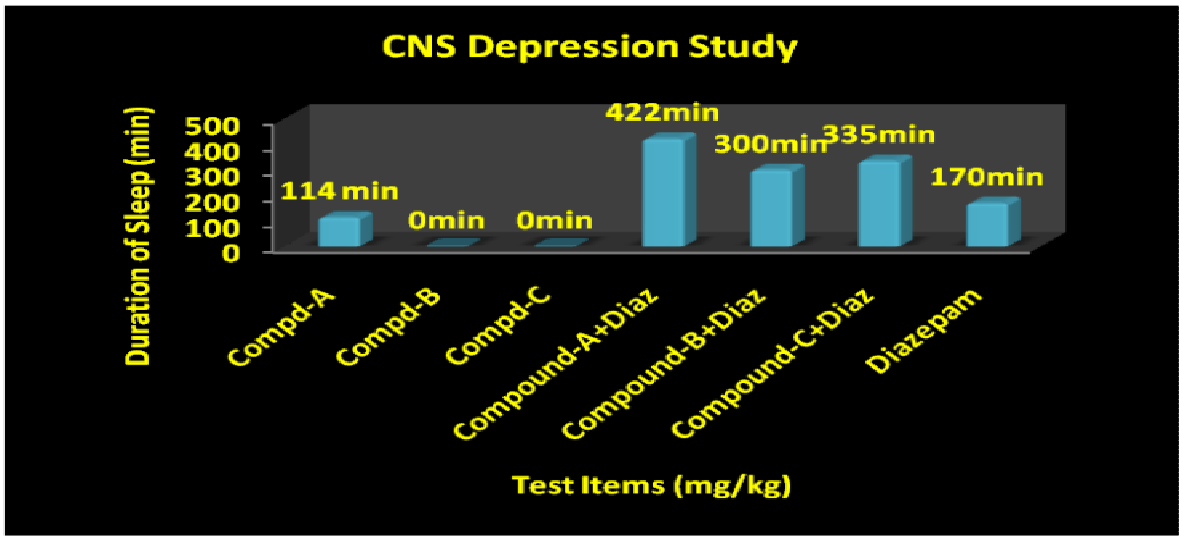
1. Compounds (0.5mg/kg)
2. Compounds (0.5mg/kg) + Diazepam (5mg/kg)
3. Diazepam (5mg/kg)

Test item	Duration of sleep (Minutes±SE)	Potentiation time (Minutes±SE)
Compound:A	114 ± 0.73	00
Compound:B	00	00
Compound:C	00	00
Diazepam+Compound:A	422 ± 0.76	252 ± 0.53
Diazepam+Compound:B	300 ± 0.62	130 ± 0.47
Diazepam+Compound:C	335 ± 0.64	165 ± 0.67
Diazepam	170 ± 088	----------

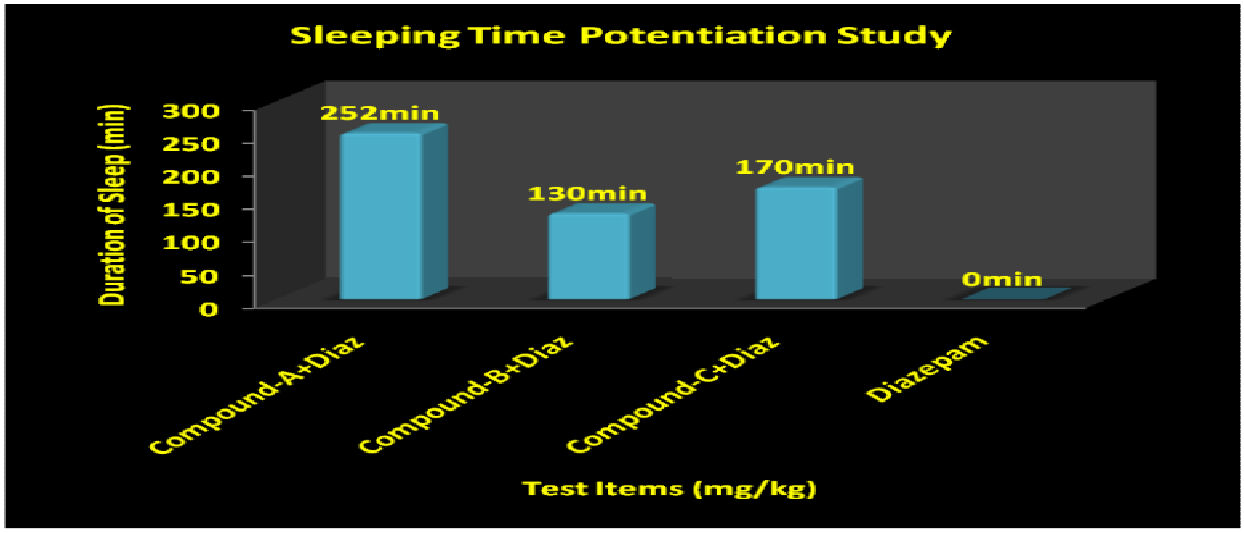
***Corresponding Author:** *e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*

Received on: 14-10-09 ; Accepted on: 28-12-09

CNS DEPRESSION STUDY



SLEEPING TIME POTENTIATION STUDY



RESULT

All the synthesized molecules have been characterized for their structural conformity by chromatography, spectral datas and by elemental microanalysis for N%. CNS depression study has been done by intraperitoneally for these compounds alone (0.5mg/kg), compounds (0.5mg/kg) + diazepam (5mg/kg) and diazepam (5mg/kg) by dissolving in propylene glycol to screen the duration of sleeping time and potentiation effect by synergistic activity in mice. It has been found that Compound-A (urea derivative) only has sleep inducing property but the synergistic action by the

***Corresponding Author:** *e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*
Received on: 14-10-09 ; Accepted on: 28-12-09

combination effect of all compounds+diazepam showed much more duration of sleep rather than diazepam[11-12].

DISCUSSION

Potentiation time: Compound-A: X=O (urea derivative) > Compound-C: X=NH (guanidine derivative) > Compound-B: \X=S (thiourea derivative). Electronegativity of oxygen for urea X:O=3.5 and of sulfur for thiourea X:S=2.4 and of nitrogen for guanidine X:NH=3.1. So the X=O shows the maximum electronegativity with two lone pair of electrons whereas X=S has also two lone pairs but X=NH has one lone pair of electrons, but in case of NH moiety the electronegativity of hetero element (N) is in between the hetero elements (O) for X:O and (S) for X:S. So, the affinity for GABA receptor binding capacity for urea is maximum to block the chloride channel. The chemical structure of the synthesized molecule and diazepam create a synergistic action in blockage of GABA receptor as well as chloride channel in-vivo to possess long duration of sleep. Determination of 'P' value and 't' value by statistical parameters showed the authenticity of experimental work[13,14].

ACKNOWLEDGEMENT

All the authors are thankful to the project guide Prof. (Dr.) Dhrubo Jyoti Sen : D.Pharm., B.Sc.(Hons), B.Pharm.(Hons), M.Pharm., Ph.D., FICS, CChem FIC(India), CChem MRSC(UK), Department of Pharmaceutical and Medicinal Chemistry and the staff members of Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India to fulfill the project work successfully.

REFERENCES

1. *Prabhu G.V. and Venkappayya D., (1995**),** J.Indian Chem.Soc., **72**, 681-684.*
2. *Dandiya P.C., Sharma P.K. and Menon M.K. (1962): Ind. J. Med. Res. **50**, 752-760.*
3. *A.I. Vogel, Vogel's Textbook of Practical Organic Chemistry 3rd Edition (1956), Longmans, Green and Co Ltd, London.*
4. *Sen D.J. (2000), PhD thesis, Jadavpur University.*
5. *Misra A.K., Dandiya P.C. and Kulkarni S. K. (1973): Ind. J. Pharmac. **5**, 449-450.*
6. *Wincor M.Z (1993): U.S. Pharmacist. **18**, 1-17.*
7. *Greenblatt D.J. (1998), Clin.Pharmacol.Ther, **64**, 553-561.*
8. *Fujimoto J.M. (1960), J.Pharmacol, **129**, 139.*
9. *Kinard W.J. and Carr C.J. (1957), J.Pharmacology, **121**, 354.*
10. *Dews P.B., (1953), Brit.J.Pharmacol, **8**, 46.*
11. *Roy A., (1981), Eur.J.Pharmac, **73**, 217.*
12. *Turner, R.A.(1965). Depressants of the central nervous system. In Turner, R.A. (Ed) Screening methods in pharmacology, Academic Press, New York and London, pp. 69-86.*
13. *Singh J., Khosla P., Srivastava P.K. (2000), Nimodipine potentials anesthetic effects of ethanol, pentobarbitone and ketamine in rats. Indian J Pharmacol; 32: 206–209.*
14. *Ghosh M.N., Fundamentals of Experimental Pharmacology, 2nd edition, (Scientific Book Agency, Calcutta), 1984, p: 153-157, 190.*

****

Source of Support: NIL
Conflict of Interest: NONE

***Corresponding Author:** *e-mail: : dhrubosen69@yahoo.com; Phone: 00-91-2762-247711 (Ext-306); Fax: 00-91-2762-247712,*
Received on: 14-10-09 ; Accepted on: 28-12-09