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RESEARCH ARTICLE

SYNTHESIS OF BIS-PYRIMIDO IMIDAZOLE FUSED RING HETEROCYCLIC ADDUCT WITH UREAS OF MANNICH BASE FOR CNS DEPRESSION

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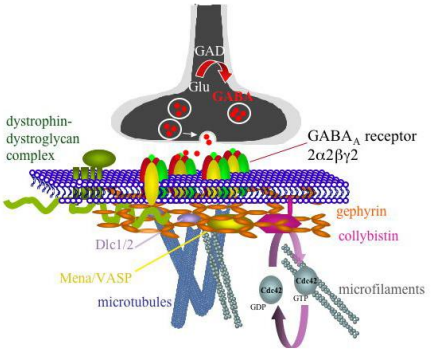
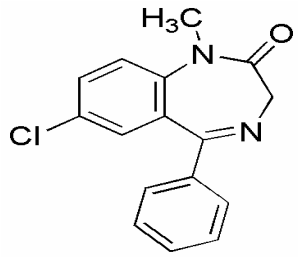
ABSTRACT

Mannich bases as well as urea derivatives have potent CNS depression activity. In our project work we have chosen a CNS drug which blocks the GABA receptor as well as chloride channel. Benzodiazepines have closed chain amide linkage which acts on GABA (gamma amino butyric acid) receptor and produces CNS depression with the blockage of chloride channel. This receptor has free amino and carboxylic acid functional group which produces amide linkage in-vivo.

Keywords:





This idea has been implemented by keeping open chain amide linkage instead of closed chain into the desired molecule with pyrimido-imidazole fused ring heterocyclic entity at the place of benzodiazepine nucleus to posses the CNS depression activity. Phenytoin is used as antiepileptic drug which has imidazole ring and that been synthesized by reacting between benzil with urea and alcoholic KOH to possess Benzilic acid rearrangement and which on benzoylation in basic medium produced di-benzoyl derivative substituted at imide group which on condensation with urea produced tetraphenyl bis-pyrimido imidazole fused ring heterocyclic molecule. This is now condensed with the Mannich bases of benzaldehyde, piperidine and urea/thiourea/guanidine to get three desired moiety of Schiff's base. All the three compounds have same structural similarity except variable X=O/S/NH and -C=N-C=(X)-NH-CH- linkage [1].

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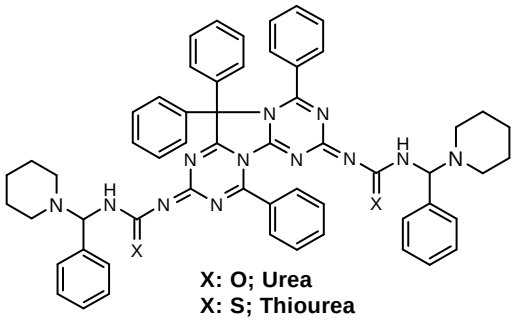
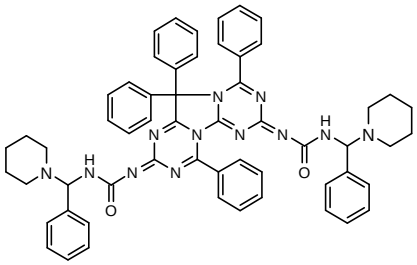
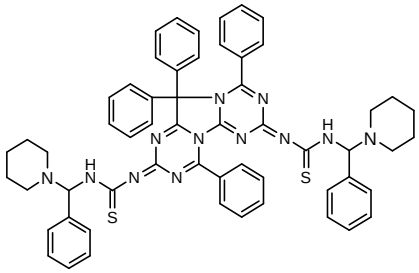


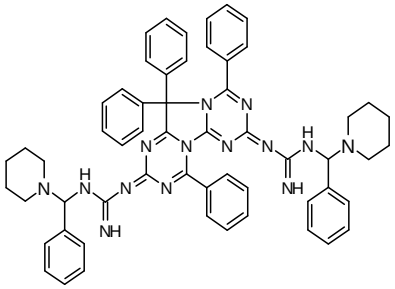
Synthesized molecule:



X =O: Urea Derivative



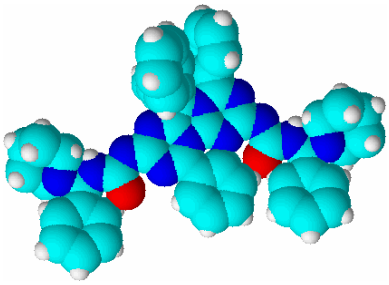
X = S: Thiourea Derivative



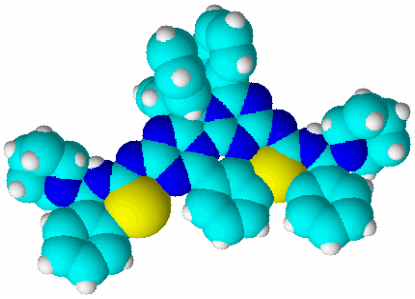
X = NH: Guanidine Derivative

Chemistry:

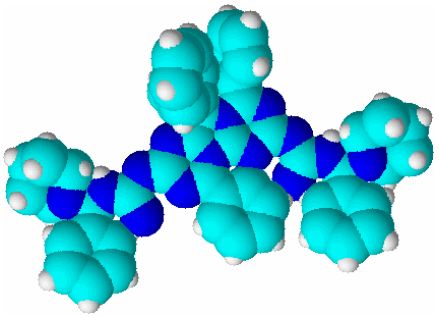
Diazepam as Benzodiazepine class of drug has azepine ring having two nitrogen atoms and by keeping this idea bis-pyrimido imidazole molecule adduct with Mannich base adduct by variable substitution at X has been performed where X=O (urea), S (thiourea) and NH (guanidine) by following Schiff's base formation [2]. All these steps have been performed by following the synthetic steps:



COMPOUND-1



COMPOUND-2



COMPOUND-3

3D-VIEW

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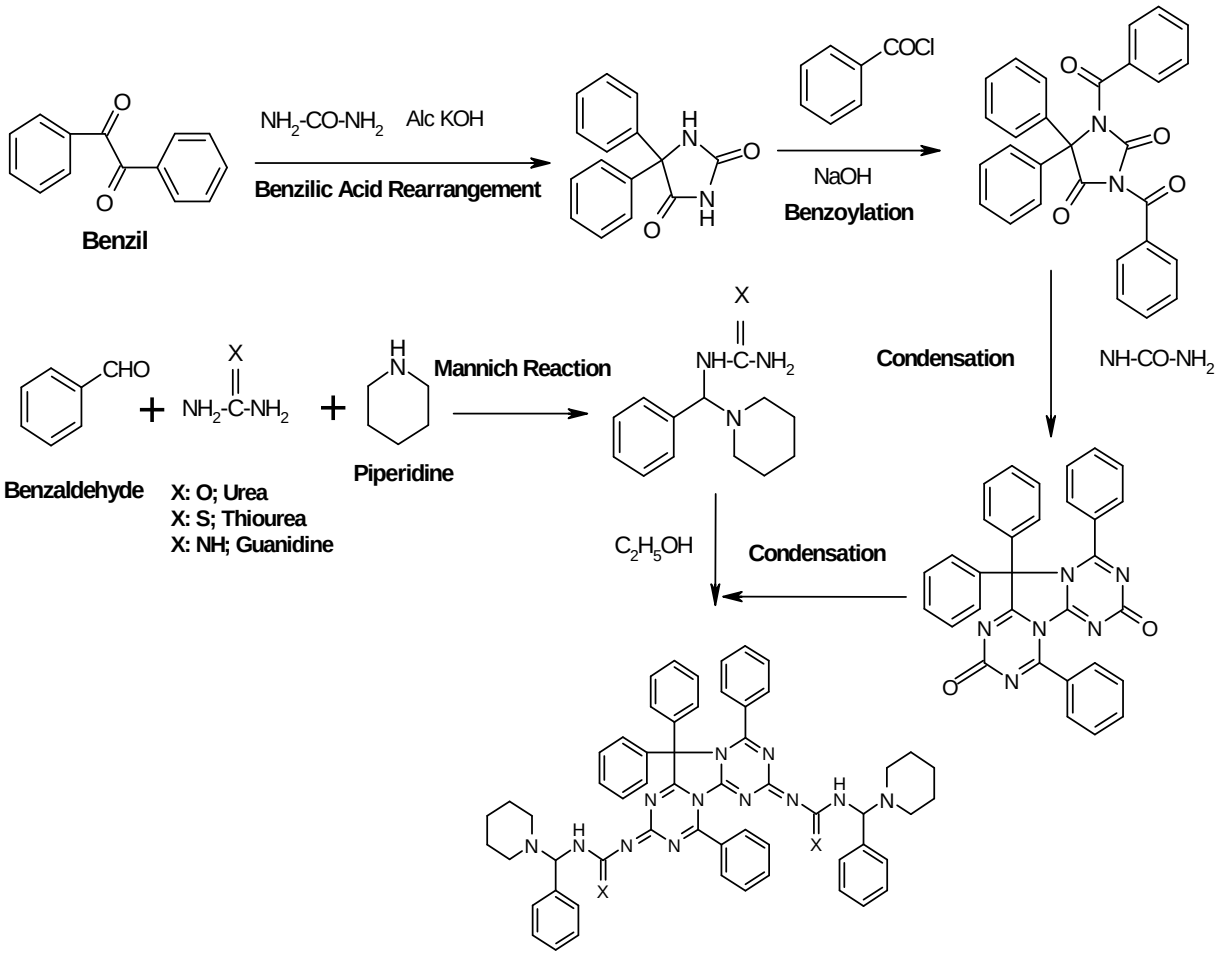
SCHEME



PHYSICOCHEMICAL PARAMETERS

COMPOUNDS	% YIELD	M.P. ºC	POLARITY	MOL. FORMULA	N% CALCD	N% FOUND
Compound-1 : X=O	54	87-90	Semipolar	C57H54N12O2	17.90	17.86
Compound-2 : X=S	48	150-152	Semipolar	C57H54N12S2	17.31	17.28
Compound-3 : X=NH	64	116-120	Semipolar	C57H56N14	20.90	21.02

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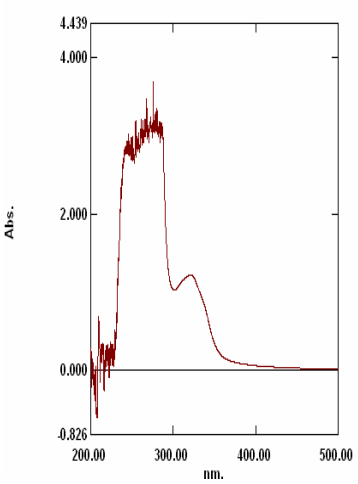
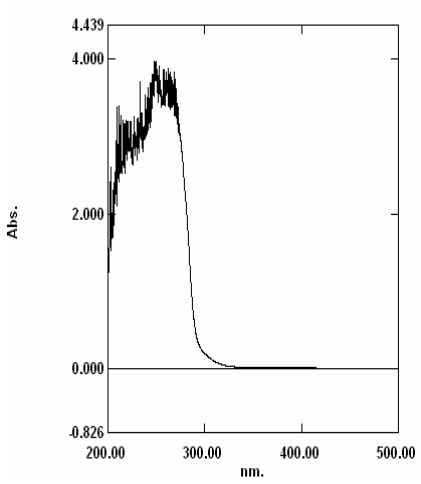
ULTRAVIOLET SPECTRAS OF SYNTHESISED COMPOUNDS



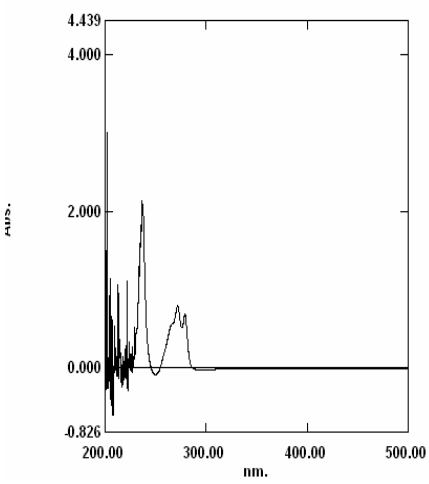
Compound-1 : X=O

λmax= 276nm



Compound-2 : X=S

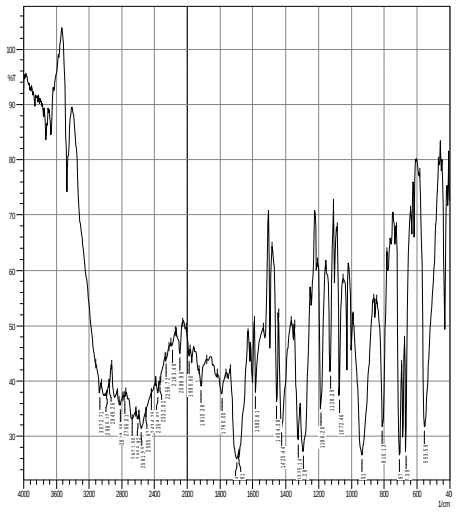
λmax= 248nm



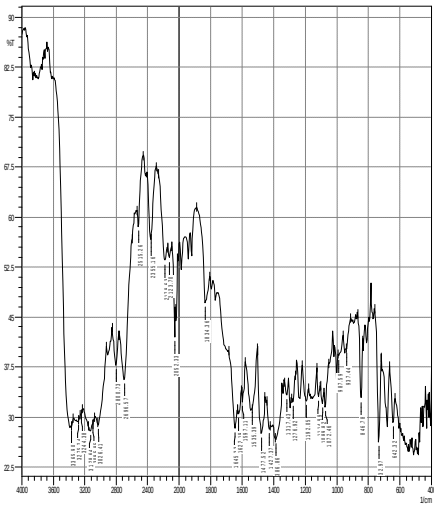
Compound-3 : X=NH

λmax= 239nm

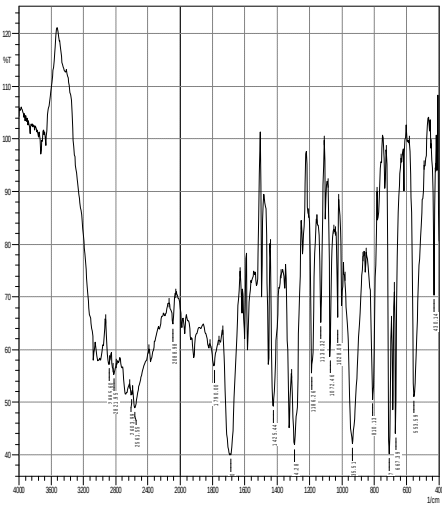
INFRA RED SPECTRAS OF SYNTHESISED COMPOUNDS



Compound-1 : X=O



Compound-2 : X=S



Compound-3 : X=NH

Pharmacology:

The structural authenticity has been done by elemental microanalysis, physicochemical parameters and by spectral studies. This big molecule has open chain urea linkage having variable X: O, S and NH. These agents were then tested for CNS depression activity by sleeping time and potentiation activity by combination effect with compound+diazepam [3]. The in-vivo testing has been done by intraperitoneally by three sets in mice in propylene glycol medium:

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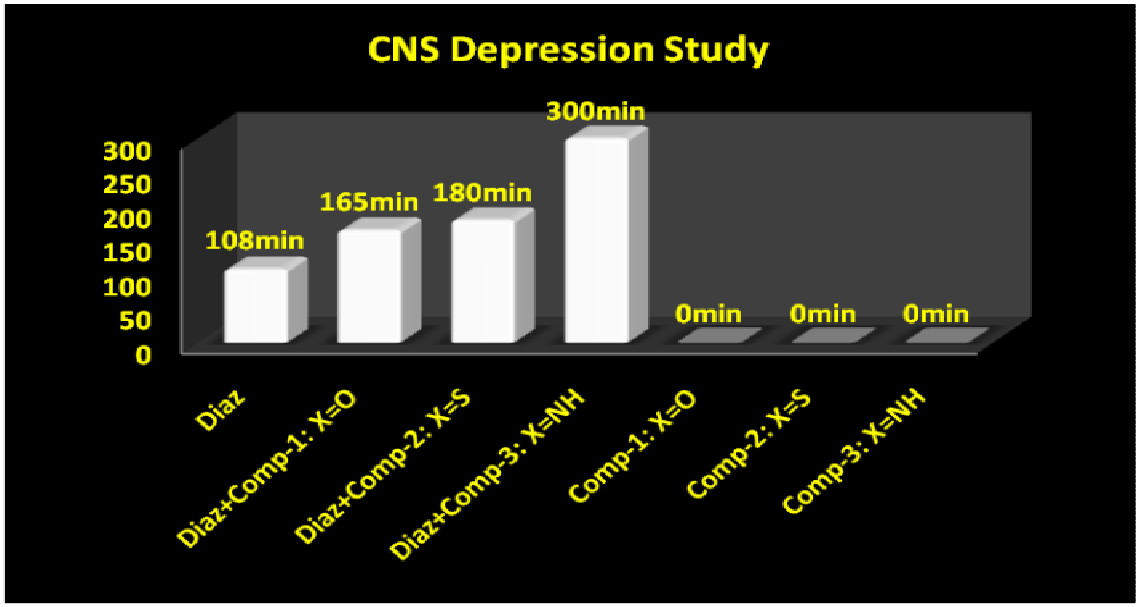
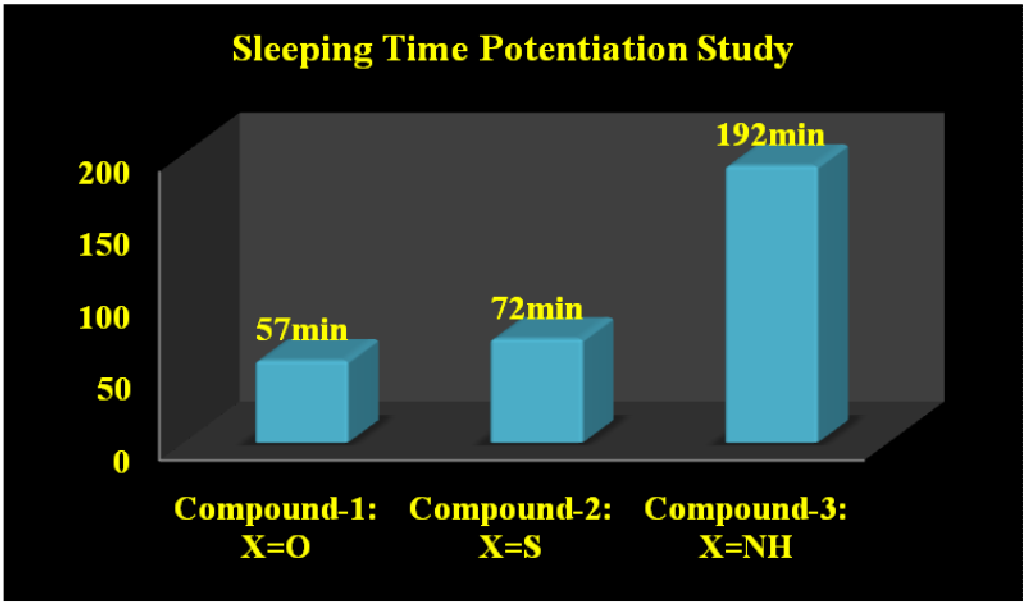
1. Compounds (0.5mg/kg) 2. Compounds (0.5mg/kg) + Diazepam (5mg/kg) 3. Diazepam (5mg/kg)



Compound-3: X=NH (guanidine derivative) > Compound-2: X=S (thiourea derivative) > Compound-1: X=O (urea derivative)

Sleeping Time Potentiation



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CONCLUSION:

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 all the synthesized compounds did not show the CNS depression property but the synergistic action by the combination effect of compound+diazepam showed much more duration of sleep rather than diazepam.

Potentiation time for the compound-3: X=NH (guanidine derivative) > compound-2: X=S (thiourea derivative) > compound-1: X=O (urea derivative)

Electronegativity of oxygen for urea X:O=3.5 and of sulfur for thiourea X:S=2.4 and of nitrogen+hydrogen for guanidine X:NH=3.1+2.2=5.3. So the X=NH shows the maximum electronegativity with one lone pair of electrons whereas X=O and X=S both have two lone pairs of electrons but the affinity for GABA receptor binding capacity for guanidine 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 [4].

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References:

1. Dandiya P.C., Sharma P.K. and Menon M.K. (1962): Ind. J. Med. Res. 50, 752-760.

2. A.I. Vogel, Vogel's Textbook of Practical Organic Chemistry 3rd Edition (1956), Longmans, Green and Co Ltd, London.

3. Sen D.J. (2000), PhD thesis, Jadavpur University.

4. Misra A.K., Dandiya P.C. and Kulkarni S. K. (1973): Ind. J. Pharmac.. 5. 449-450.

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Conflict of Interest: NONE

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