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SYNTHESIS OF SUBSTITUTED TRIAZOLO-PYRROLE FUSED RING ADDUCT WITH BENZYLIDENE PIPERIDYL UREA/THIOUREA BRIDGE AND SCREENING FOR CNS DEPRESSION

[1]VIKRAMKUMAR VISHNUBHAI PATEL* AND [2]PROF DR DHRUBO JYOTI SEN

1DEPARTMENT OF PHARMACEUTICAL AND MEDICINAL CHEMISTRY, SHRI SARVAJANIK PHARMACY COLLEGE, HEMCHANDRACHARYA NORTH GUJARAT UNIVERSITY, ARVIND BAUG, MEHSANA-384001, GUJARAT, INDIA

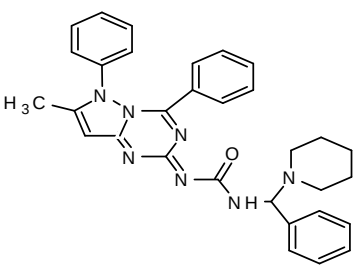
Phone: 00-91-2762-247711, Fax: 00-91-2762-247712, Email: dhrubosen69@yahoo.com2

2DEPARTMENT OF QUALITY ASSURANCE, S.K. PATEL COLLEGE OF PHARMACEUTICAL EDUCATION AND RESEARCH, GANPAT UNIVERSITY, MEHSANA-GOZARIAHIGHWAY, KHERVA-382711, TA. & DIST: MEHSANA (N.G.)

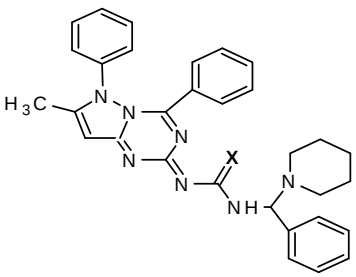
Abstract: *The molecular design of two molecules have been derived from the tailoring of the benzodiazepine moiety in which the amide group is in cyclic form as well as bioisosteric ($CH_2 \approx NH$) and we have incorporated the same amide linkage in open chain by keeping the triazolo-pyrrole ring having Mannich base of urea/thiourea linkage with piperidine nucleus for CNS depression activity. Phenyl substituted 5-pyrazolone has been synthesized by the reaction between phenyl hydrazine and ethyl acetoacetate and substituted trizolo-pyrrole fused ring has been synthesized by condensation of benzoylated phenyl substituted 5-pyrazolone with urea. This on reaction between Mannich base which has been synthesized by the reaction between benzaldehyde with piperidine and urea/thiourea produced amide bridge having variable atom X=O: Urea and X=S: Thiourea. The two components were characterized for their structural confirmation by IR spectra and elemental microanalysis.*

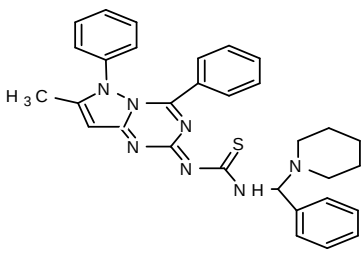
Synthesized Molecule:

X=Oxygen: Urea derivative; X=Sulphur: Thiourea derivative



X=O: Urea derivative (Compound-1)





X=S: Thiourea derivative (Compound-2)

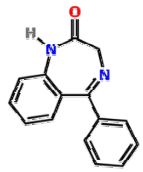
The toxicological behavior of the two compounds were observed for LD_{50} study in propylene glycol medium in mg/kg dose intraperitoneally and found in this order: ***Compound-1 (280mg/kg) > Compound-2 (210mg/kg)****. The CNS depression study for the synthesized compounds were screened on mice through intraperitoneally in three different sets and compared with the sleeping time with diazepam (Benzodiazepine) as standard drug: (1) Only standard drug (2) Only test compounds and (3) Test compounds + standard drug. The CNS depression activity on mice has been noted for diazepam. This CNS depression activity has been found in the two test compounds by*

observation of the sleeping time by the duration of loss of righting reflex and regaining of it. The sleeping time potentiation effect was observed by the duration of sleeping time produced by diazepam + test compounds. It has been found that the sleeping time and synergistic activity for ***Compound-1 (urea derivative) > Compound-2 (thiourea derivative)*** *and this is due to the electronegativity of Urea X:O=3.44 and Thiourea X:S=2.07. Both of compounds have same structural similarity except variable X=O/S and -C=N-C=(X)-NH-CH- 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 and that effect on the activity of the synthesized compounds as well as with diazepam (benzodiazepine) and produces CNS depression.*

Keywords: Fused ring heterocyclic (Triazolo-pyrrole), Urea/Thio urea bridge, CNS depression, Benzodiazepines, Molecular design, Bioisosteric

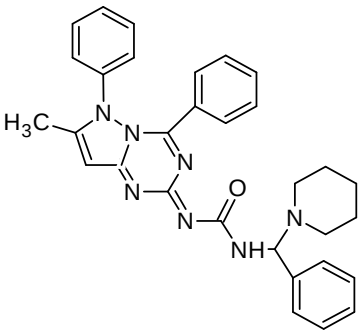
OBJECTIVE:

The molecular design of two molecules have been derived from the tailoring of the benzodiazepine and barbiturate moiety in which the amide group is in cyclic form and we have incorporated the same amide linkage in open chain by keeping the triazolo-pyrrole ring of having Mannich base of urea/thiourea linkage with piperidine nucleus for CNS depression activity [1].

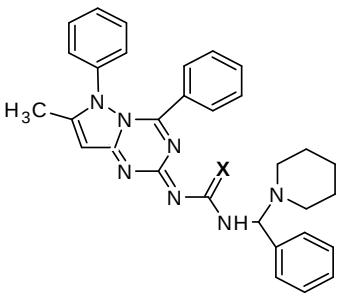


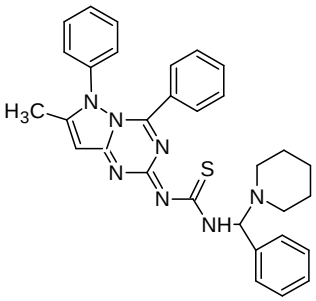
Benzodiazepine

MOLECULAR DESIGN



COMPOUND – 1





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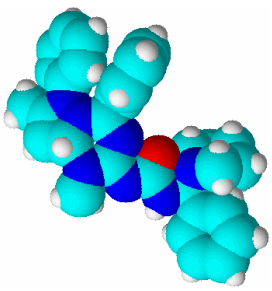
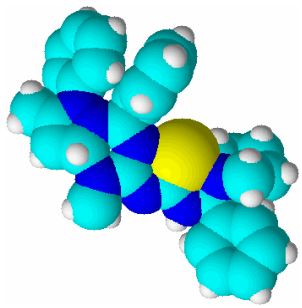
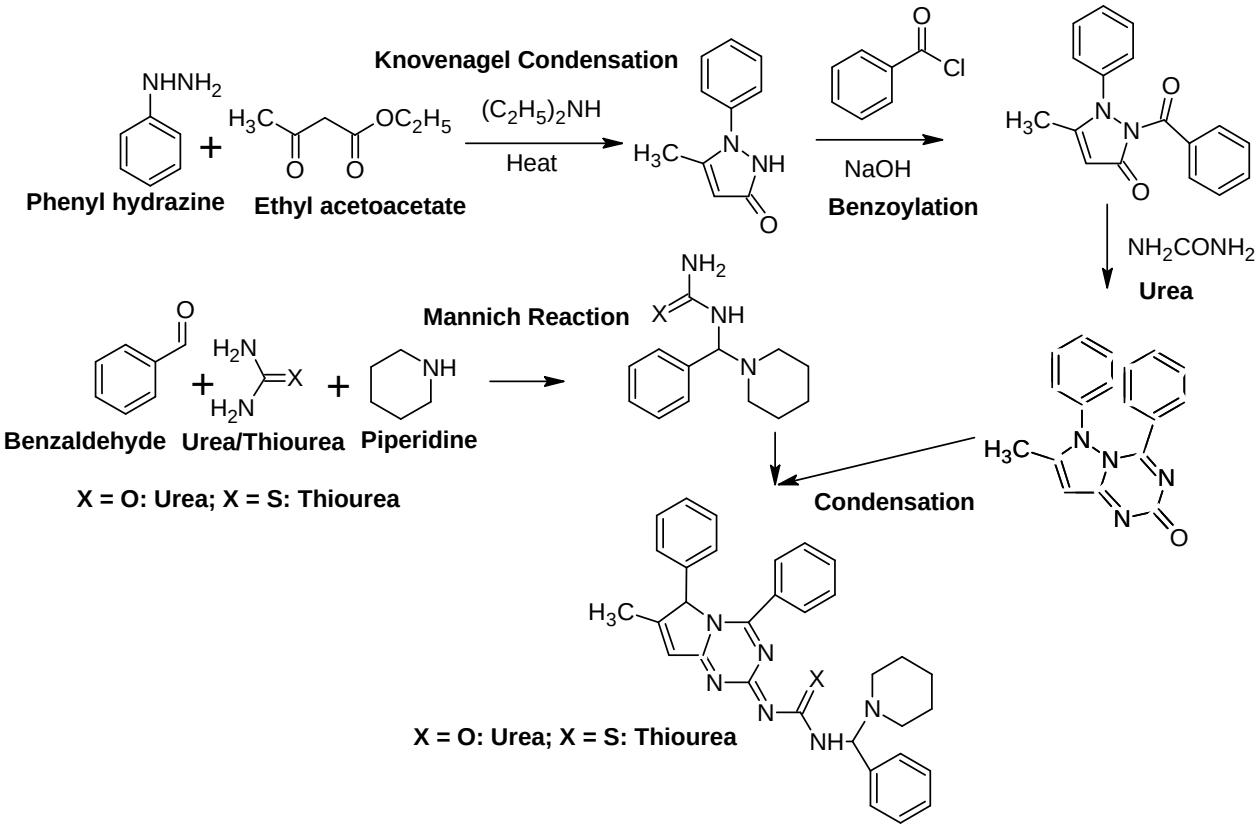




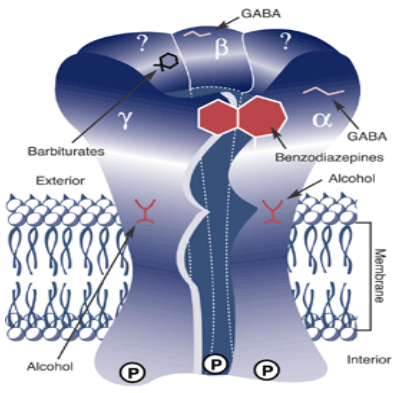
3-D STRUCTURE

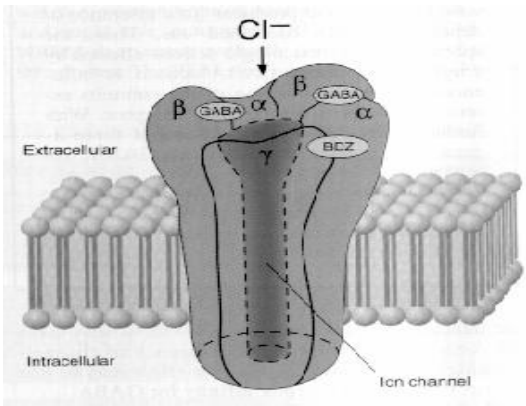
SCHEME



Phenyl substituted 5-pyrazolone has been synthesized by the reaction between phenyl hydrazine and ethyl acetoacetate and substituted trizolo-pyrrole fused ring has been synthesized by condensation of benzoylated phenyl substituted 5-pyrazolone with urea. This on reaction between Mannich base which has been synthesized by the reaction between benzaldehyde with piperidine and urea/thiourea produced amide bridge having variable atom X=O: Urea and X=S: Thiourea. The two components were characterized for their structural confirmation by IR spectra and elemental microanalysis [2,3].

ETIOLOGY OF CNS DEPRESSION



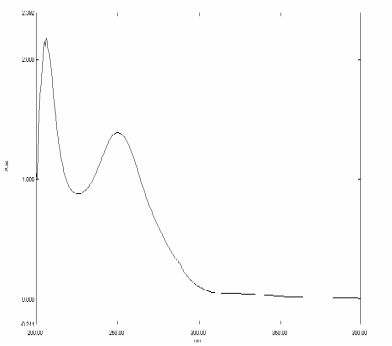


PHYSICOCHEMICAL PARAMETERS

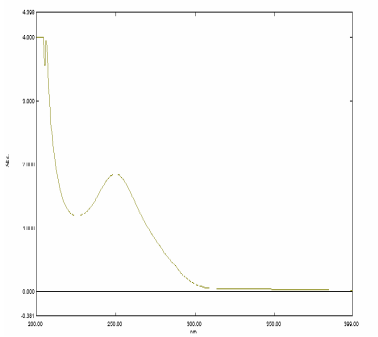
Test Items	% YIELD	M.P. ºC	POLARITY	MOL. FORMULA	N% CALCD	N% FOUND
Compound-1 : X=O	54	170-172	Semipolar	$C_{32}H_{35}N_7O$	13.11	13.23

Compound-2 : X=S	48	128-130	Semipolar	$C_{32}H_{35}N_7S$	12.73	12.68
Urea Derivative	64	78-80	Semipolar	$C_{13}H_{19}N_3O$	18.02	18.34
Thiourea Derivative	58	130-132	Semipolar	$C_{13}H_{19}N_3S$	16.86	16.88
5-Pyrazolone	67	100-105	Semipolar	$C_{10}H_{10}N_2O$	16.09	16.12
Benzoyl-5-Pyrazolone	78	70-75	Semipolar	$C_{17}H_{14}N_2O$	10.07	9.98
Triazolo-pyrrole	82	80-82	Semipolar	$C_{20}H_{14}N_4O$	17.17	17.23

ULTRAVIOLET SPECTRAS OF SYNTHESISED COMPOUNDS

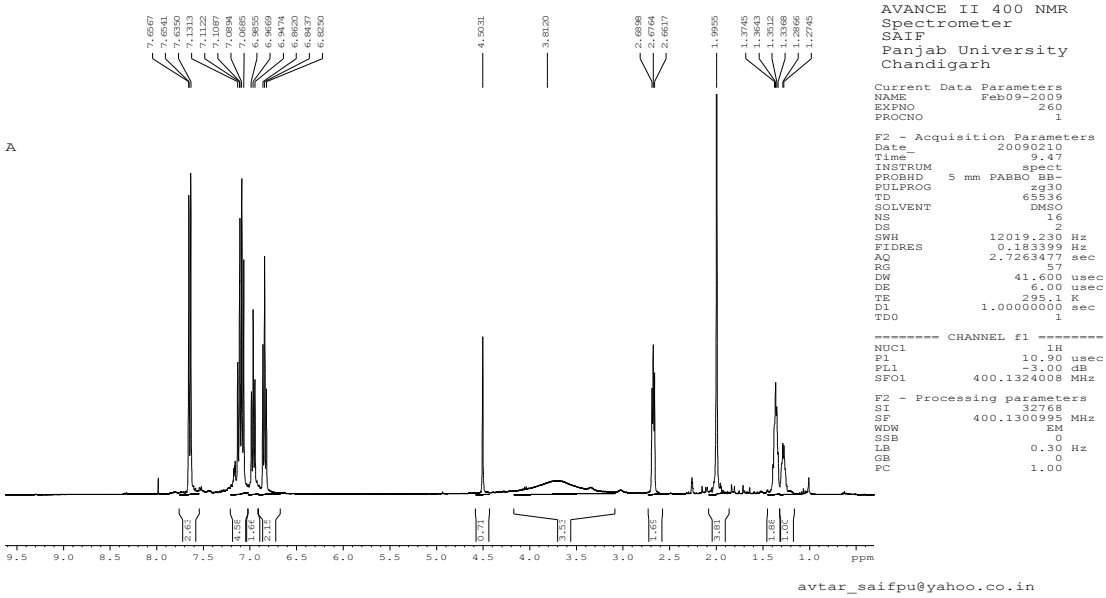


COMPOUND-1 **λ_{max} 250nm**



COMPOUND-2

NMR SPECTRAS OF SYNTHESISED COMPOUNDS

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BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME          Feb09-2009
EXPNO                260
PROCNO                 1

F2 - Acquisition Parameters
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Time                9.47
INSTRUM            spect
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PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   16
DS                    2
SWH           12019.230 Hz
FIDRES        0.183399 Hz
AQ            2.7263477 sec
RG                   57
DW               41.600 usec
DE                6.00 usec
TE                295.1 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1               10.90 usec
PL1              -3.00 dB
SFO1        400.1324008 MHz

F2 - Processing parameters
SI                32768
SF          400.1300995 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
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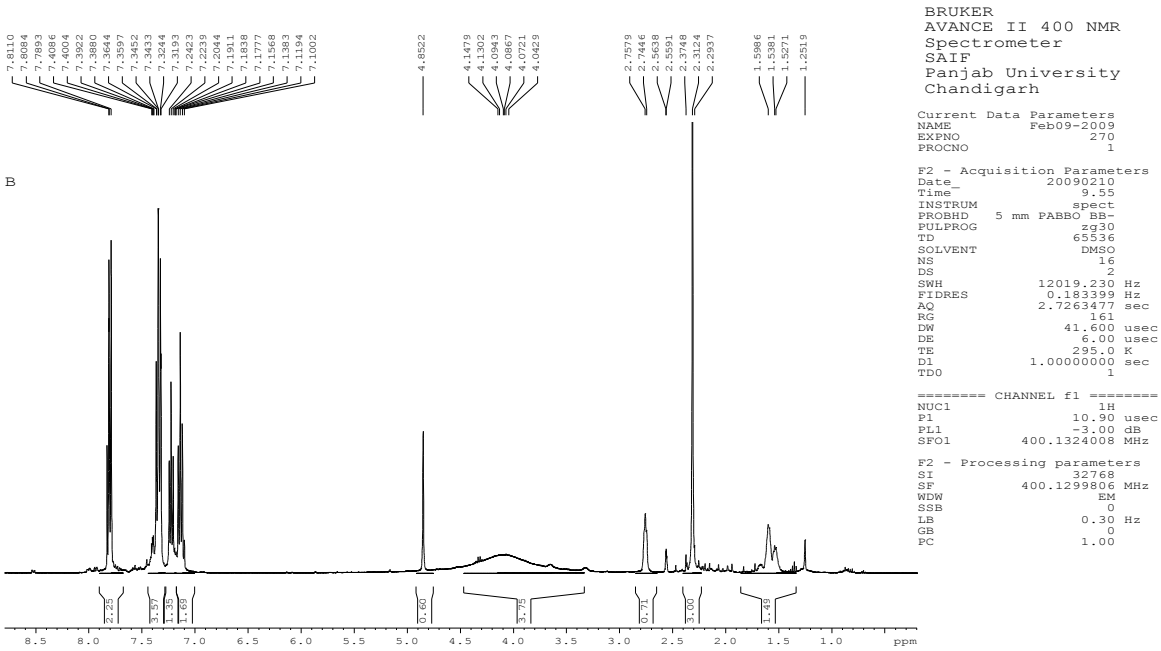
avtar_saifpu@yahoo.co.in

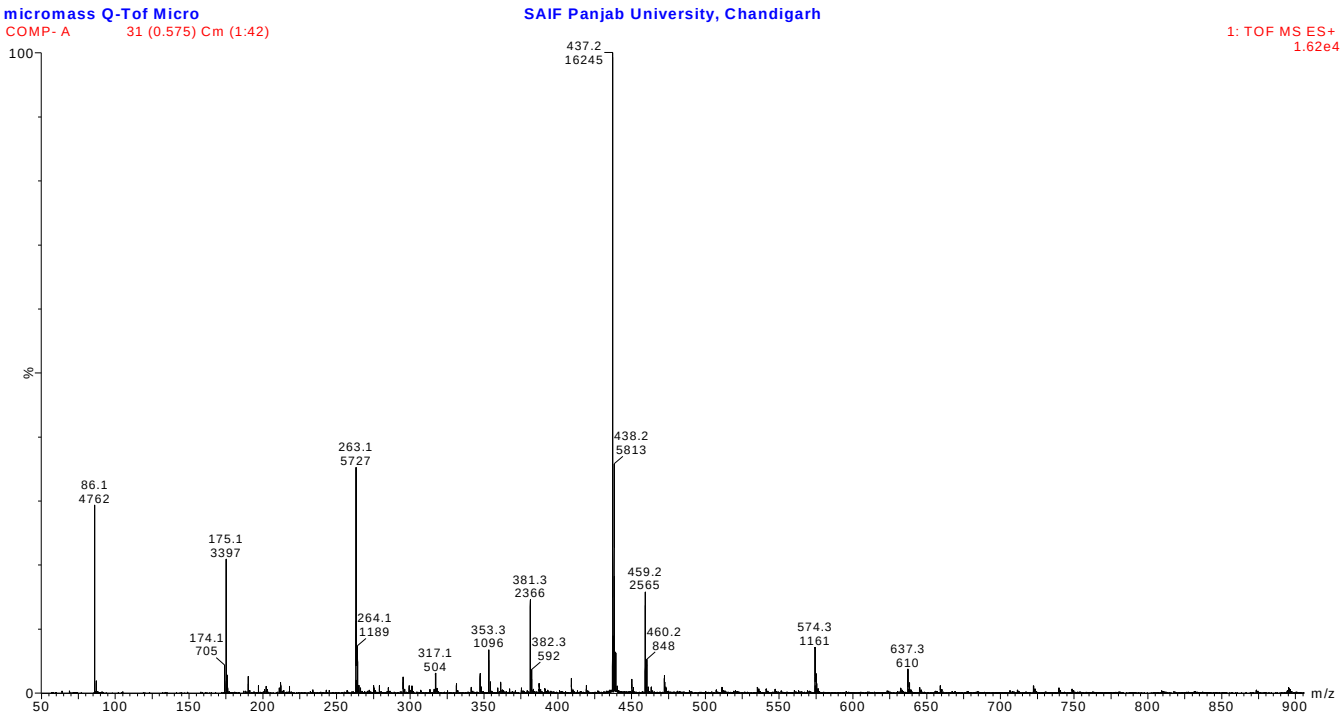
COMPOUND-1 X: O



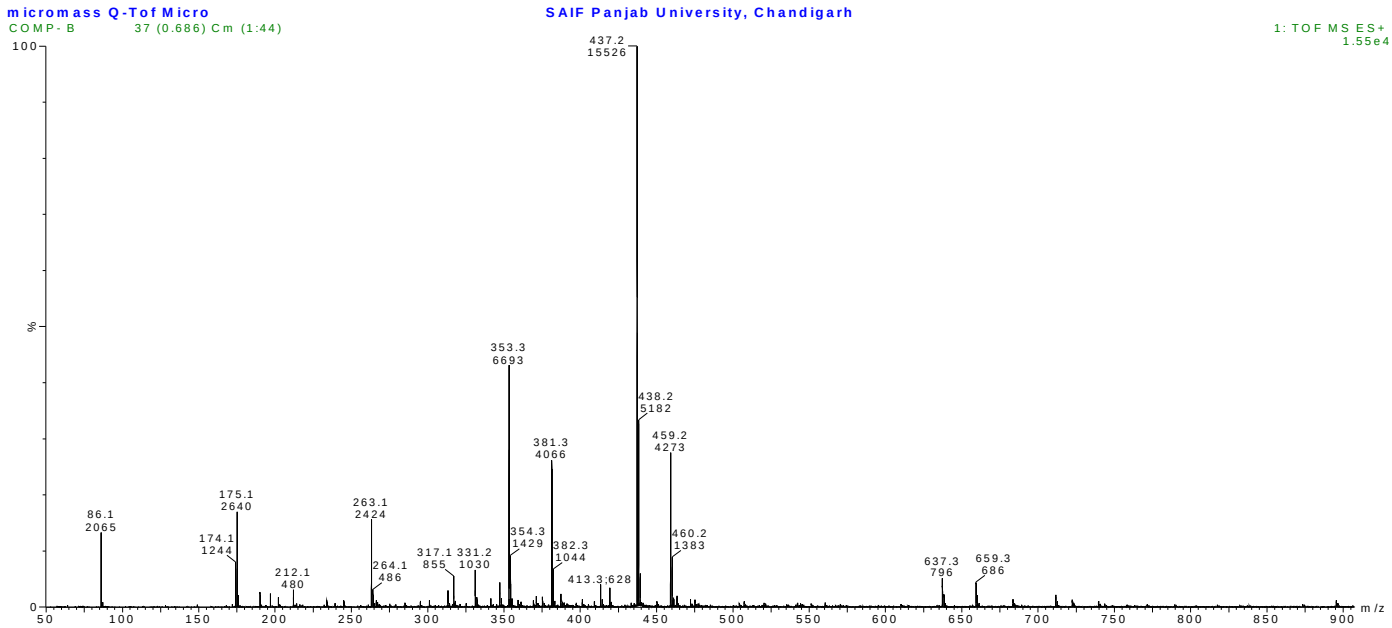
avtar_saifpu@yahoo.co.in

COMPOUND-2 X: S

MASS SPECTRAS OF SYNTHESISED COMPOUNDS

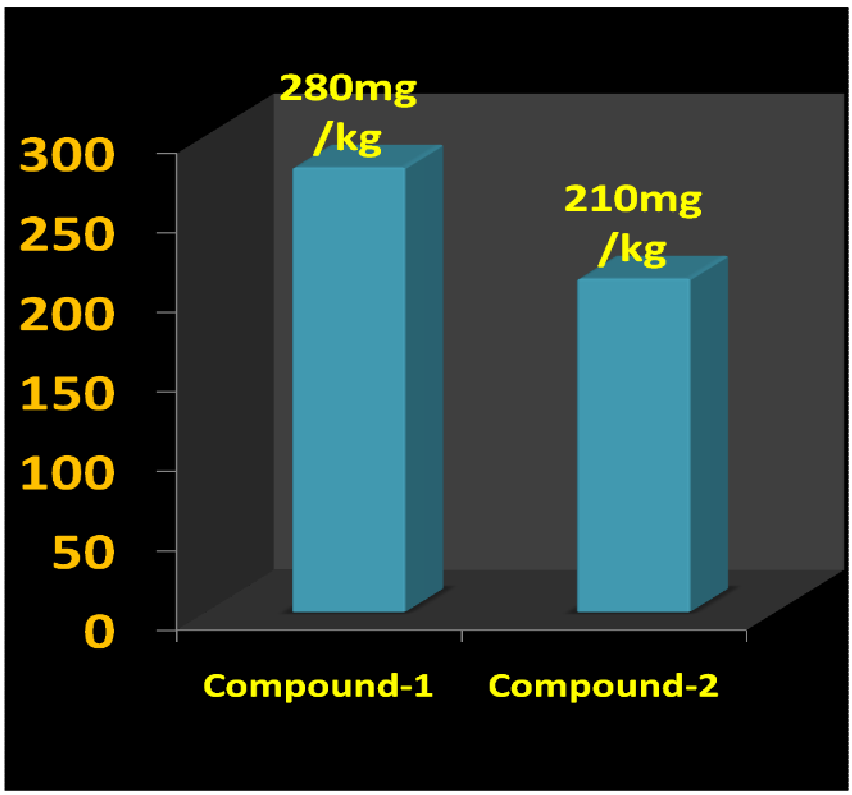


COMPOUND-1 = X: O

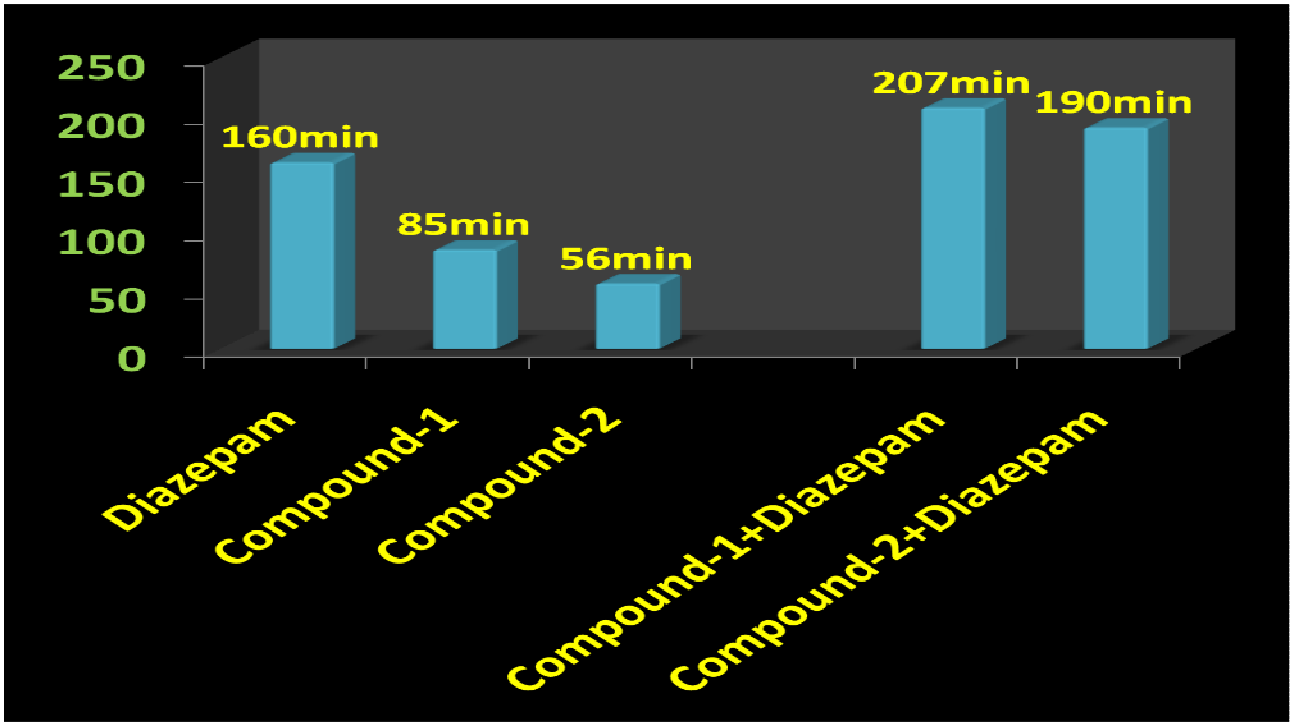


COMPOUND-2 = X: S

ACUTE TOXICITY OF THE SYNTHESISED COMPOUNDS



CNS DEPRESSION AND SLEEPING TIME POTENTIATION EFFECT



RESULT AND DISCUSSION

The CNS depression study for the synthesized compounds were screened on mice through intraperitoneally in three different sets and compared with the sleeping time with diazepam (Benzodiazepine): (1) Only standard drug (5mg/kg) (2) Only test compounds (0.5mg/kg) and (3) Test compounds (0.5mg/kg) + standard drug (5mg/kg) by dissolving in propylene glycol to screen the duration of sleeping time and potentiation effect by synergistic activity in mice. The CNS depression activity on mice has been noted for diazepam. This CNS depression activity has been found in the two test compounds by observation of the sleeping time by the duration of loss of righting reflex and regaining of it. The sleeping time potentiation effect was observed by the duration of sleeping time produced by diazepam + test compounds. It has been found that the sleeping time and synergistic activity for Compound-1 (urea derivative) > Compound-2 (thiourea derivative) and this is due to the electronegativity of Urea X:O=3.44 and Thiourea X:S= 2.07. Both of compounds have same structural similarity except variable X=O/S and -C=N-C=(X)-NH-CH- linkage which acts on GABA receptor and produces CNS depression with the blockage of chloride channel. This receptor has free amino and carboxylic acid functional group which produce amide linkage in-vivo and that effects on the activity of the synthesized compounds as well as diazepam (benzodiazepine) and produces CNS depression [4].

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