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COMPARISON OF PHARMACOLOGICAL SCREENING OF CNS DEPRESSANT ACTION OF FUSED RING HETEROCYCLIC ADDUCT WITH FUSED RING AROMATIC WITH BENZODIAZEPINE AS STANDARD

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ABSTRACT

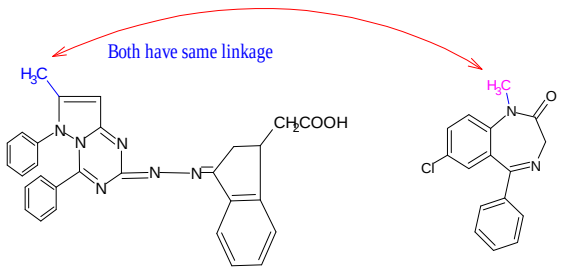
CNS depression screening has been performed for synthesised molecule having fused ring heterocyclic adduct with fused ring nonheterocyclic moiety with benzodiazepine as reference standard as well as a herbal formulation having sleep inducing property. It has been found that the synthsesied compound has CNS depression property with comparison to benzodiazepine as well as the herbal formulation.

Objective of the Work

The aim of the work was to perform the pharmacological screening of the herbal formulation (I) containing various herbs with reported CNS depressant action and for compound (II) using *Diazepam* induced mice method and by the "spontaneous motor activity" method. The herbal formulation as having lower adverse effects can be put into use with lower risk factors and also the other drawbacks of the diazepam can be avoided. At the same time the lab synthesized adduct is having the pyrazole and the indole acetic acid moieties fused with each other with a Schiff's base linkage between them. The purpose to synthesize it was to produce CNS depressant effect rather than the anti-inflammatory effects as has been reported already and accepted globally for the moieties mentioned above. The tailoring of the benzodiazepine moiety was done according to the following correlation between the compound (II) & diazepam[1-6].

Comparison between the Compound (II) and Diazepam:-

1



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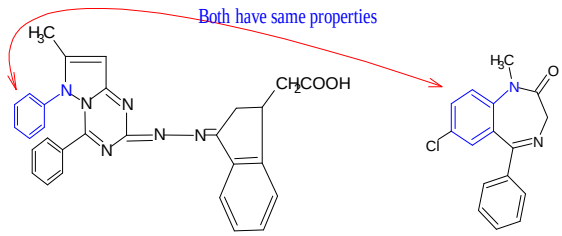

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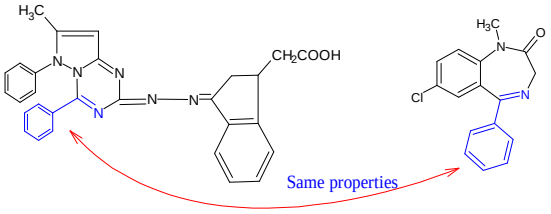

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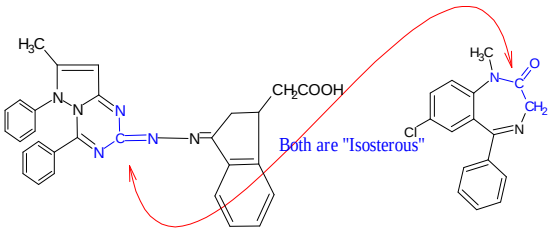

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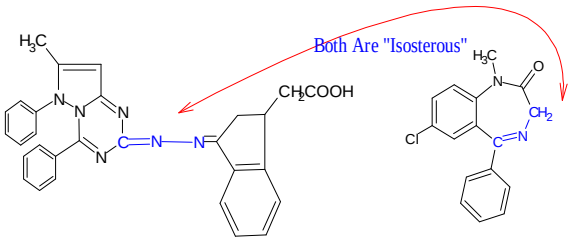

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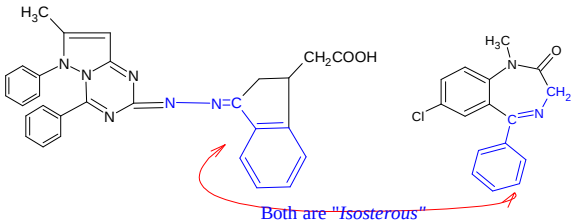

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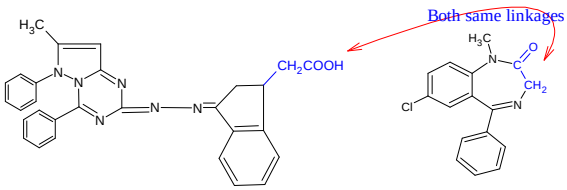
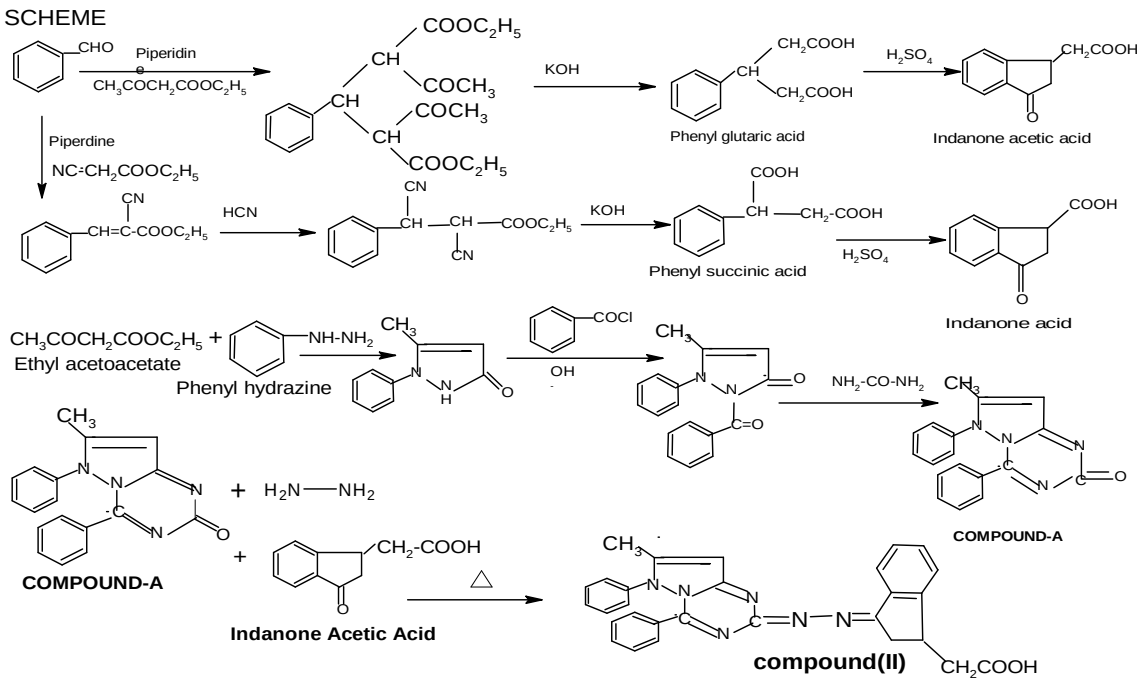


Materials and Methods

The work was started with the diazepam induced groups of mice which were given the dose of 2.5mg t.i.d human dose of diazepam intra peritoneally using sterile glass syringe normally use for VAT BOTULINUM ENDOTOXIN vaccination, which had been diluted to obtain the animal dose with the help of propylene glycol solution. The groups of 6 animals were made by selecting randomly having 25gms of weight each and 6 such groups were made to avoid the repetitive dose to the same group. The polyherbal formulation(I) is having the herbs, which have already been accepted for their CNS depressant action like Brahmi, Rauwolfia, Jatamansi, Pepper, and Valerian. The mentioned drug was present in the poly herbal formulation (I) as powdered form and then was formulated in a pill form. As it is available in the powdered pills, it had to be given as oral suspension with the help of 24# needle for oral feeding. The doses for the formulation (I) were pre-calculated according the human dose (300-600mg at bed time) and then the doses were administered and observed for the sedative action. The doses were also been given in order to check the potentiation in the pre-administered diazepam induced groups of mice. The lab-synthesized molecule, compound (II) was synthesized in the following scheme[7-12].

The dose for the compound (II) was also been taken similarly as for diazepam and calculated accordingly for the dose of mice. The dilution of the compound (II) was done with the propylene glycol solution in order to maintain the homogeneity with diazepam and also to make a clear solution for the i.p. administration. The doses of diazepam were given in two groups, in first, 2.5mg and in the other, 5mg of diazepam having 0.5 mg/ml concentration. Herbal formulation (I) was started with the human dose of 300 mg and then consecutively various groups were administered various doses of the same drug. The doses were planned for the human doses of 600mg, 800mg, and 1gm and converted into mice doses and then administered orally as a suspension made in simple water. The compound (II) was administered in the doses of 5mg, 7.5 mg, 8mg, and 10mg of human dose and then checked for the sedative action. Also the potentiation of the sedative

action of diazepam was checked for the herbal formulation (I) and the compound (II) by both the methods mentioned previously. For the measurement of spontaneous motor activity an instrument called photoactometer was used. The mice were administered the doses of various drugs and then put into photo actometer for 5 min at the interval of 30 min each and then the counts on the display were noted for each mice. The data was then interpreted for the said action and then the action of the drug on the animals was predicted accordingly at various doses. The comparative studies were done by interpreting the data tabulated in the forthcoming tables drawn by applying students T-table method and also by the graphical representation of the same data as plotted in the forthcoming section[13-15].



Results and Discussion

The doses of the drugs were given and the sedation was produced on the diazepam induced mice and the onset and the duration of action observed for Formulation (1) and Compound (2) are tabulate in the following tables.

Table-1 shows the simple effects of various doses of the \

Table-1 Effects of various drugs in various doses.

Drug	Dose	Effect
Formulation(I)	2.5 mg	Drowsiness
	5 mg	Drowsiness
	6.5 mg	Drowsiness
	8 mg	Drowsiness
Compound(II)	5 mg	Drowsiness
	7.5 mg	Drowsiness
	8 mg	Induces Sleep
	10 mg	Induces Sleep but mortality (4 out of 6)

The other table, Table-2, shown below shows the Onset of action, Duration of action. All the data are interpreted from the student's T-table statistical method. Here they are presented in the ± SEM values[16,17].

Table-2

Treatment	Onset of Action (min)	Recovery (min)	Duration of action (min)
Diazepam (5 mg)	11.67 ± 1.054	189.2 ± 7.897	185 ± 7.528
Diazepam (5 mg) + Compound(2) (2.5mg)	7.5 ± 1.118	322.2 ± 11.3	315.8 ± 11.06
Diazepam (5 mg) + Compound(2) (5 mg)	7.5 ± 1.118	397.5 ± 4.233	390 ± 4.282
Diazepam (5 mg) + Formulation(1) (25mg)	10 ± 1.291	431.7 ± 19.18	421.7 ± 18.29
Diazepam (5 mg) + Formulation(1) (50mg)	11.67 ± 1.054	475 ± 4.83	467.5 ± 8.539

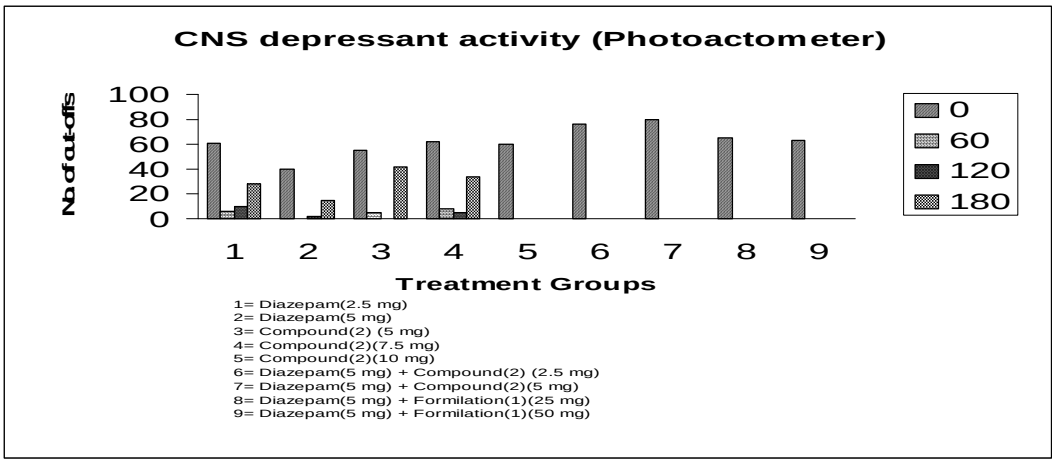
The CNS depressant action of the mentioned dugs was also screened by the *'spontaneous motor*

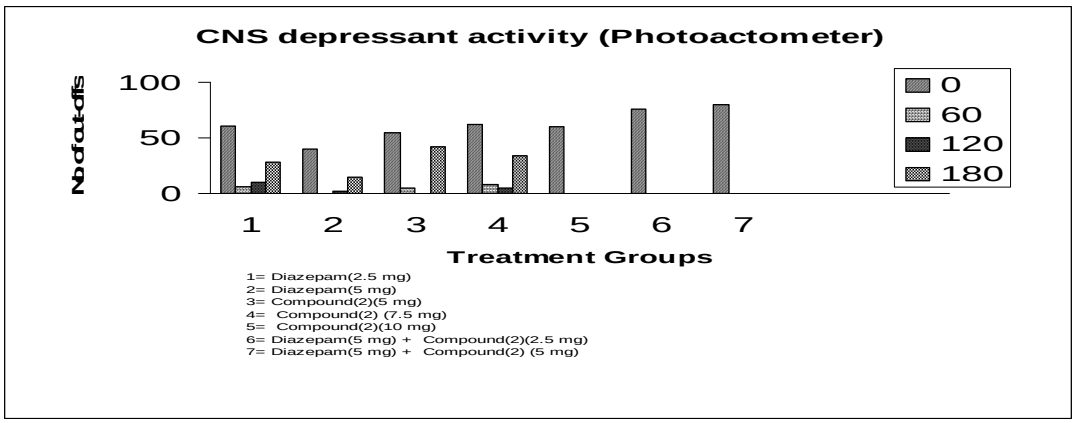
activity" model. The data obtained by that screening are shown in the Table-3.

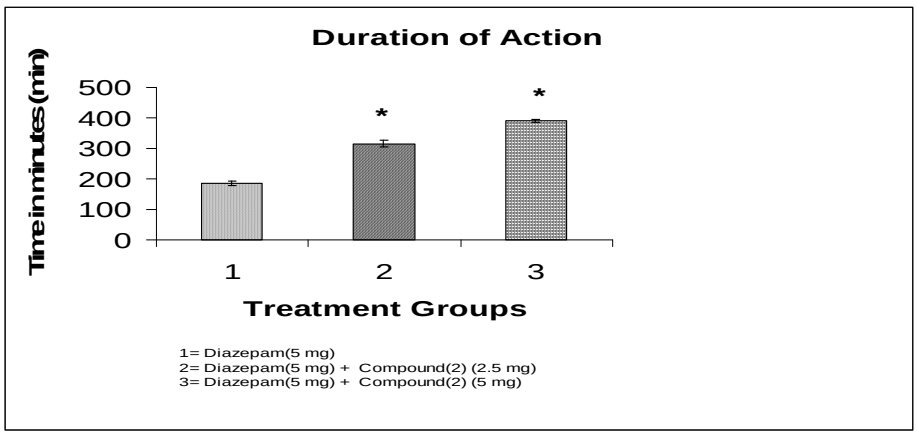
Table-3 Data obtained from "*spontaneous motor activity"* model.

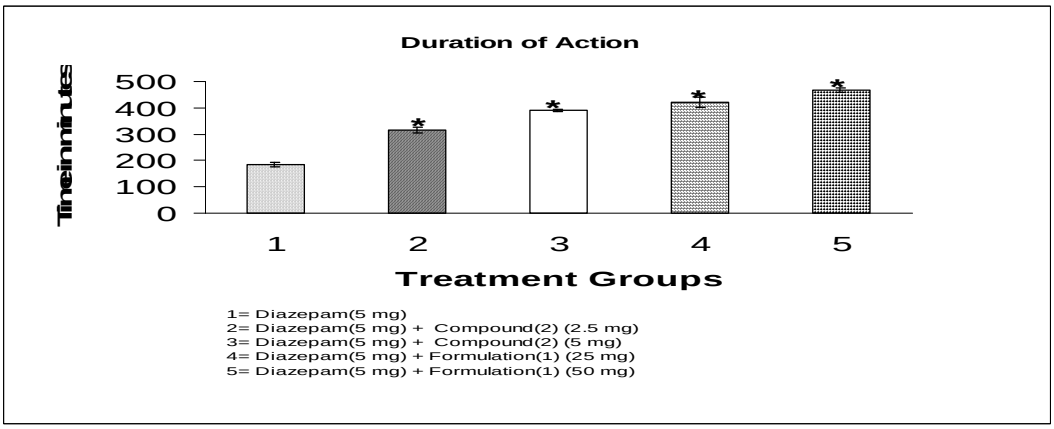
Drug	Dose	Time	0	30	60	90	120	180	240	300
Diazepam	2.5mg/kg		61	16	6	4	10	28	0	0
	5mg/kg		40	0	0	0	0	2	15	30
Compound (II)	5mg/kg		55	23	5	3	0	42	0	0
	7.5mg/kg		62	20	8	7	5	34	0	0
	10mg/kg		60	0	0	0	0	0	0	0
Diazepam + compound (II)	5mg/kg 2.5mg/kg		76	0	0	0	0	0	0	0
Diazepam + Compound (II)	5mg/kg 5mg/kg		80	0	0	0	0	0	0	0
Diazepam + Formulation (I)	5mg/kg 25mg/kg		65	0	0	0	0	0	0	0
Diazepam + Formulation (I)	5mg/kg 50mg/kg		63	0	0	0	0	0	0	0

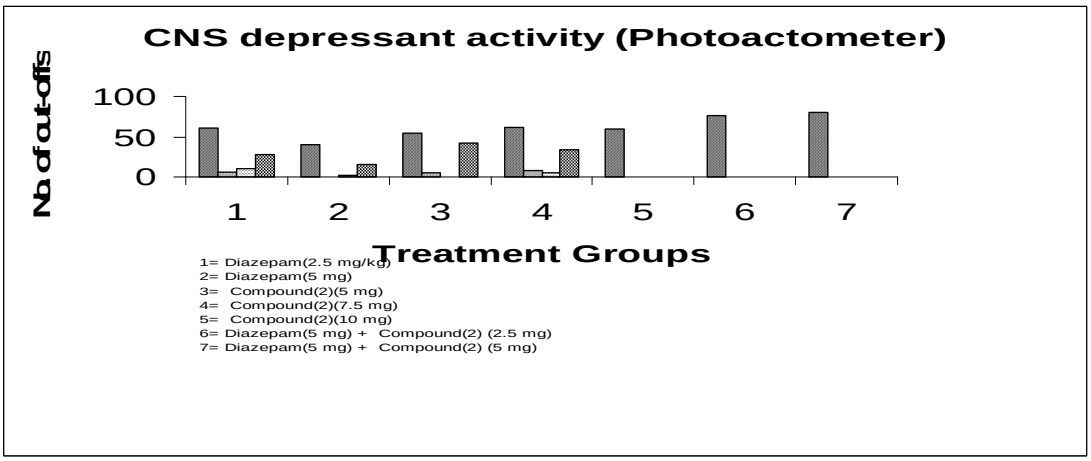
The data obtained above has also been plotted in various graphs which are shown in the following comparisons. From the data tabulated in the table 2 various comparisons have also been made with the standard doses of diazepam and the compound (II) and diazepam with the formulation (I), which are shown in the following graphs.

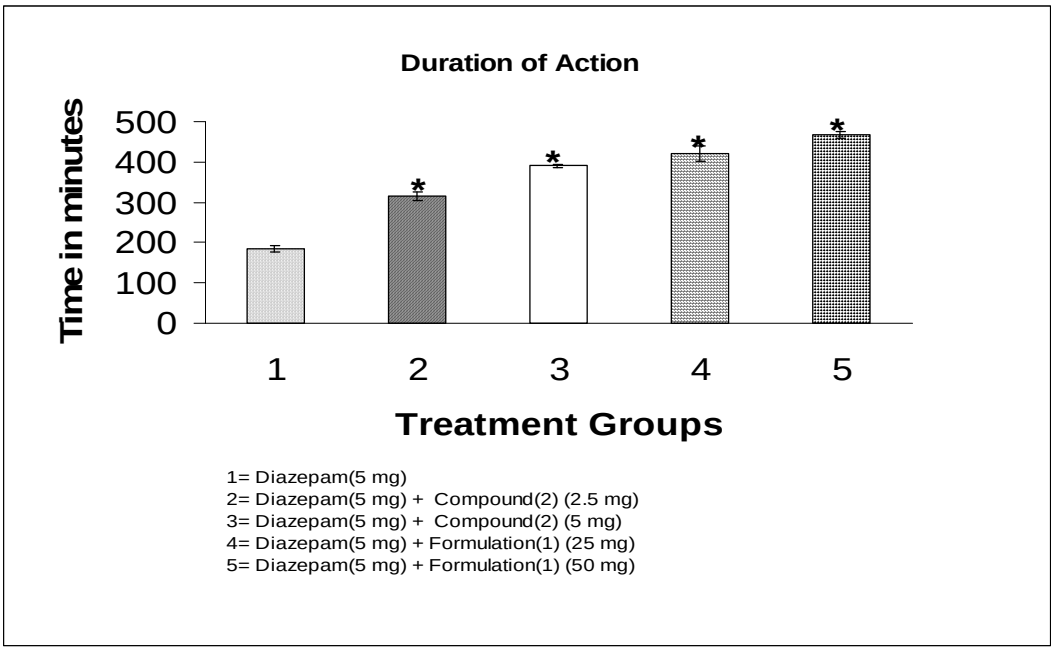


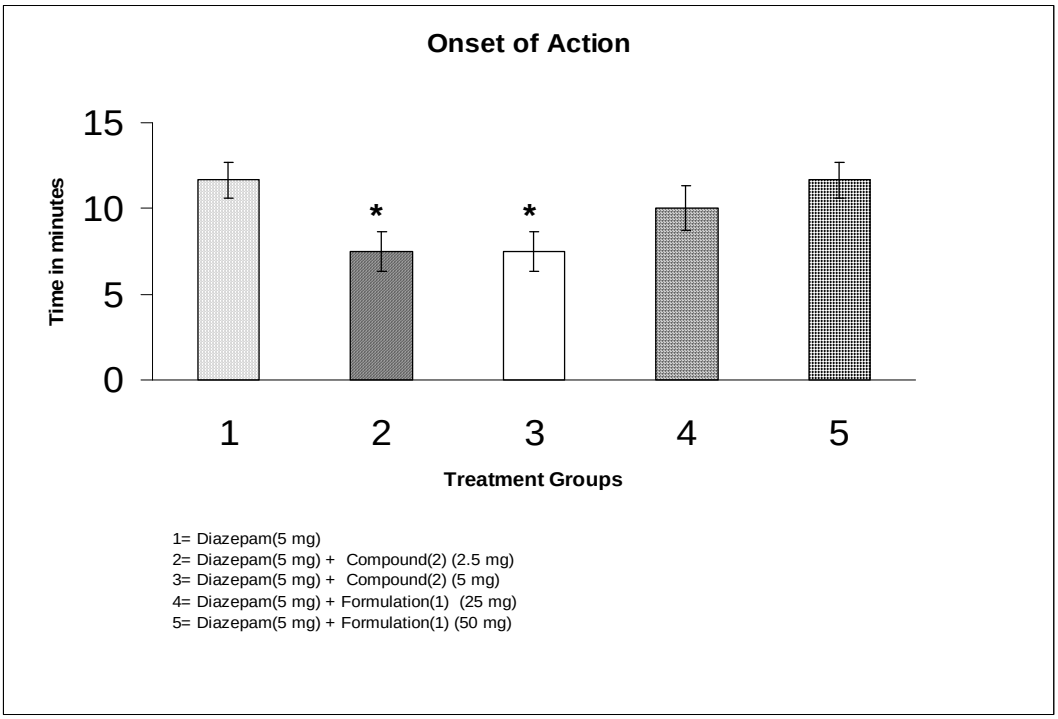


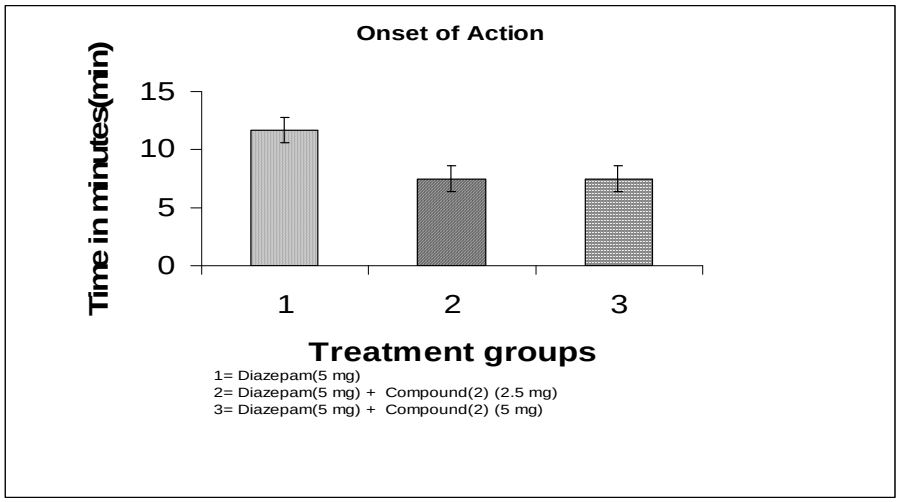

Duration of Action
Time in minutes (min)
500
400
300
200
100
0
*
*
1
2
3
Treatment Groups
1= Diazepam(5 mg)
2= Diazepam(5 mg) + Compound(2) (2.5 mg)
3= Diazepam(5 mg) + Compound(2) (5 mg)


Duration of Action
Time in minutes
500
400
300
200
100
0
*
*
*
*
1
2
3
4
5
Treatment Groups
1= Diazepam(5 mg)
2= Diazepam(5 mg) + Compound(2) (2.5 mg)
3= Diazepam(5 mg) + Compound(2) (5 mg)
4= Diazepam(5 mg) + Formulation(1) (25 mg)
5= Diazepam(5 mg) + Formulation(1) (50 mg)


CNS depressant activity (Photoactometer)
No of cut-offs
100
50
0
1
2
3
4
5
6
7
Treatment Groups
1= Diazepam(2.5 mg/kg)
2= Diazepam(5 mg)
3= Compound(2)(5 mg)
4= Compound(2)(7.5 mg)
5= Compound(2)(10 mg)
6= Diazepam(5 mg) + Compound(2) (2.5 mg)
7= Diazepam(5 mg) + Compound(2) (5 mg)


Duration of Action
Time in minutes
500
400
300
200
100
0
1
2
3
4
5
Treatment Groups
1= Diazepam(5 mg)
2= Diazepam(5 mg) + Compound(2) (2.5 mg)
3= Diazepam(5 mg) + Compound(2) (5 mg)
4= Diazepam(5 mg) + Formulation(1) (25 mg)
5= Diazepam(5 mg) + Formulation(1) (50 mg)


Onset of Action
Time in minutes
15
10
5
0
1
2
3
4
5
Treatment Groups
1= Diazepam(5 mg)
2= Diazepam(5 mg) + Compound(2) (2.5 mg)
3= Diazepam(5 mg) + Compound(2) (5 mg)
4= Diazepam(5 mg) + Formulation(1) (25 mg)
5= Diazepam(5 mg) + Formulation(1) (50 mg)



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