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## Letter to the Editor

### Anticonvulsant activity of novel Schiff bases of thiadiazole derivatives

Sir,

Heterocyclic compounds containing Schiff bases have been explored which played an important role in heterocyclic chemistry. Schiff bases are structurally similar to biological compounds due to their flexible nature. This happens due to N=CH- group which is responsible for transformation and racemisation in living systems (Prasad et al., 2011).

Epilepsy is a disease which includes disorders of brain function having symptoms of periodic and unpredictable seizures. Epilepsy is very common and affects around 1-2% of the world population (Hirtz et al., 2007).

There is a disadvantage in treating epilepsy currently because about 25% of epileptics are inefficiently controlled by medication (Cascino, 1994). Thus, there is a need for newer anticonvulsant drugs which are both safe and effective. Various study indicated the development of 1,3,4-thiadiazole as anticonvulsant drug.

The present study was carried out to look into the anticonvulsant activity of novel Schiff bases (10a-f) by maximal electroshock method (MES). The neurotoxicity of the compounds was also assessed for the compounds at the experimental dose levels.

Test compounds were synthesized in laboratory and compounds were checked for purity by TLC, IR, <sup>1</sup>H NMR and elemental analysis (Pandey et al., 2016; Pandey et al., 2018). Test compounds are as follows: 5-(2-Hydroxyphenyl)-2-[N-(4-hydroxy-3-methoxybenzylidene)-2-aminophenyl]-1,3,4-thiadiazole (**10a**), 5-(2-mercaptophenyl)-2-[N-(4-hydroxy-3-methoxybenzylidene)-2-aminophenyl]-1,3,4-thiadiazole (**10b**), 5-(2-hydroxyphenyl)-2-[N-(4-hydroxy-3-methoxybenzylidene)-3-aminophenyl]-1,3,4-thiadiazole (**10c**), 5-(2-mercaptophenyl)-2-[N-(4-hydroxy-3-methoxybenzylidene)-3-aminophenyl]-1,3,4-thiadiazole (**10d**), 5-(2-hydroxyphenyl)-2-[N-(4-hydroxy-3-methoxybenzylidene)-4-aminophenyl]-1,3,4-thiadiazole (**10e**), 5-(2-mercaptophenyl)-2-[N-(4-hydroxy-3-methoxybenzylidene)-4-aminophenyl]-1,3,4-thiadiazole (**10f**).

Wistar rats of either sex were divided into the groups of 6 animals per group (OECD., 2001). Synthetic deriva-

tives were administered once orally at a dose of 50 mg/kg body weight to a group. The rats then critically observed for clinical signs, gross behavioural changes and mortality after 30 min, 1 hour, 2 hours, 3 hours and then after 24 hours. These observations were continued for a period of 7 days. After observing mortalities and behavioral profile for the stipulated time, the maximal safe dose for the study was found out. Further, in accordance with the OECD guidelines, the doses for the study were narrowed out. The results are summarized in Table I.

Adult Wistar rats were used to evaluate anticonvulsant activity of Schiff bases using MES pattern test (Rajak et al., 2011). The test compound and the reference drug suspended in a vehicle (Tween 80) were administered orally to a group of 6 rats (50 mg/kg in 1% Tween 80) 60 min before the test. The control animals were admi-

Table I

LD <sub>50</sub> (mg/kg body weight) of Schiff bases			
Compound	24 hours	48 hours	7 days
10a	1275	1275	1035
10b	1295	1295	925
10c	1520	1520	1235
10d	1236	1236	984
10e	2395	2395	2125
10f	2405	2405	2215

Table II

Anticonvulsant activity of novel Schiff bases		
Treatment	Duration of tonic hind limb extension (sec)	Recovery
Tween 80 (2 mL/kg)	17.5 ± 0.8	Yes
10a (50 mg/kg)	4.9 ± 0.3	Yes
10b (50 mg/kg)	5.6 ± 0.4	Yes
10c (50 mg/kg)	5.4 ± 0.6	Yes
10d (50 mg/kg)	6.2 ± 0.4	Yes
10e (50 mg/kg)	3.8 ± 0.5	Yes
10f (50 mg/kg)	4.6 ± 0.5	Yes
Phenytoin (5 mg/kg)	6.2 ± 0.9	Yes

Data are mean ± SEM; n=6



nistered the vehicle. An increased electric current were applied, initial current of 1 mA, increment of 0.1 mA/0.2 sec at 50 Hz. Tonic extension of hind limbs was taken as the end point. The mean threshold current for electroshock-induced tonic hind limb extensor seizure was calculated for each drug. The results are summarized in Table II.

Standard rotarod test was used to measure minimal motor impairment in rats (Rajak et al., 2011; Deacon, 2013). Before the experiment, rats were placed on rotarod rotating at 6 rpm, in two training sessions that last 10 and 13 min respectively. The animals under investigation were injected i.p. (50 mg/kg in 1% Tween 80) in three groups, each of six rats. The control group received 1% Tween 80 as a vehicle. One hour later, the animals were again tested on the rotarod to assess the locomotor coordination and neurological deficit like ataxia, sedation, hyper-excitability), which were reflected by the inability of the animal to maintain equilibrium on the rod after the administration of selected candidate. The endpoint for minimal neurotoxicity assessment was reflected by the inability of rat to maintain their equilibrium for at least 1 min in each of the three trails.

**10e** was found to be least sedative. Animals were found to maintain equilibrium on rotarod for 300 sec but some percentage of animals failed like 16.6% for **10a**, 0% for **10e** and 33.3 for **10f**.

Chemical compounds having hydroxyl, methoxy, mercapto or combination of these groups on terminal phenyl ring presented good result in MES test. These groups can be replaced with other groups having compounds with less anticonvulsant activity. The hydroxyl group substituted with phenyl group increases the activity because of increase in the size of the molecule. Increased size possess extra van der Waal bonding due to which activity increases.

The anticonvulsant activity of the compounds is mainly due to presence of more than one phenyl substituent in

thiadiazole ring. The presence of electron donar atom also played important role in the activity. Any substitution in the terminal phenyl group modifies the anti-convulsant activity of the compounds.

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