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# SYNTHESIS AND ANTICONVULSANT EVALUATION OF SEMICARBAZONES OF ACETOPHENONE MANNICH BASES

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Several semicarbazones of acetophenone and *p*-chloroacetophenone Mannich bases were designed and synthesized to meet the pharmacophore requirements essential for anticonvulsant activity. Mannich bases of acetophenone and *p*-chloroacetophenone were prepared by reacting formaldehyde with various secondary amines and then condensed with several aryl semicarbazides to yield the corresponding semicarbazones. All compounds were evaluated for their anticonvulsant activity by maximal electroshock (MES) and by subcutaneous metrazole (ScMet) and strychnine (ScSty) induced seizure methods, and their neurotoxic effects were determined using the rotorod test. The title compounds were also investigated for antidepressant and sedative-hypnotic potentiation properties. It is established that 3-[3-chlorophenyl(β-dimethylaminopropiophenone)semicarbazone] has excellent anticonvulsant activity in MES, ScSty, and ScMet tests and exhibits a potent antidepressant effect in the absence of sedative-hypnotic potentiation. The present study has proved our earlier hypothesis concerning the pharmacophore model with essential binding sites for semicarbazones. The inclusion of an additional moiety ($CH_2$–$CH_2$–N<) at the electron donor acceptor group retained the anticonvulsant activity.

## *Introduction*

Epilepsy is a complex and chronic neurological disorder characterized by the unpredictable recurrence of unprovoked seizures and is associated with high degree of morbidity and mortality. A seizure is the clinical expression of abnormal neuronal firing within the brain that occurs with or without the loss of consciousness. Both genders are affected equally, but the incidence of epilepsy is highest during childhood, reaches a plateau until the age of 65, and increases thereafter [1]. Approximately 2.5 million people [2] including 340,000 children in the United States and about 45 – 100 million people worldwide suffer from epilepsy and its sequelae [3]. Prior to 1990, the medical treatment of patient with epilepsy was accomplished by using one or combination of classical [4] antiepileptic drugs (AEDs) such as phenytoin, carbamazepine, and valproate. All these established drugs have failed to control seizures in 25 – 30% patients and are proved to cause intolerable adverse effects (like neurotoxicity, fatal idiosyncratic disorders, etc.) in patients receiving either monotherapy or polytherapy.

In the past decade, a group of new AEDs including felbamate, gabapentin, lamotrigine, oxcarbazepine and some other have been made available to the patients with epilepsy, but yet not all of them have had their seizures controlled or their adverse effects completely eliminated. Recently, several investigational AEDs including ganoxolone, ramacemide, rufinamide, etc. [5] have been put into clinical trials and only limited data on their efficacy and safety against a particular seizure type are available till date. Although the diagnosis of seizure type and treatments are complicated, the therapy of patients with epilepsy has been accomplished in current clinical practice by administering one or combination of classical and new epileptic drugs, however, they still suffer from unwanted side effects like sedation, which stimulates the search for safer, better and more effective AEDs.

Mannich bases in general have been identified as potential therapeutic agents for a wide variety of diseases. They have shown anticonvulsant [6], anticancer and cytotoxic properties [7], and anti-HIV [8], analgesic and anti-inflammatory activity [9]. Semicarbazones of several aldehydes and ketones have emerged as new chemical entities with potential anticonvulsant properties [10]. Recently Dimmock et al. [11, 12] and Pandeya et al. [13] proposed a hypothetical pharmacophore model for the anticonvulsant activity of semicarbazones, which comprises two hydrophobic aryl binding sites, a hydrogen-bonding region, and an electron-donor acceptor system (Fig. 1).

In view of these facts and in continuation of our search for new potential anticonvulsants, we attempted to synthesize a new series of semicarbazones of acetophenone and 4-chloroacetophenone Mannich bases. This was done with the objective that semicarbazones of Mannich bases would meet the structural requirements essential for anticonvulsant activity. In the present study, acetophenone and *p*-chloroacetophenone were condensed with formaldehyde and several secondary amines to give Mannich bases. These Mannich bases were reacted with various substituted aryl semicarbazides, which resulted in the formation of semicarbazones of Mannich bases. The chemical structures of the synthesized compounds were confirmed by UV, IR and NMR spectral data and elemental analyses. The title compounds were tested for their anticonvulsant and antidepressant properties and the effect on sedative-hypnotic activity of phenobarbitone.

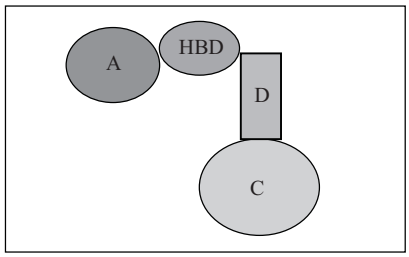



**Fig. 1**. Proposed pharmacophore model for anticonvulsant activity: (**A**, **C**) hydrophobic binding sites; (**HBD**) hydrogen-bonding site; (**D**) electron donor group.

*Results and Discussion*

All the synthesized compounds (**1 – 10**) gave satisfactory elemental analyses (within ± 0.4%) for C, H and N. The UV, IR and NMR spectra were consistent with the proposed chemical structures. In the initial anticonvulsant screening in mice, the synthesized compounds were administered by intraperitoneal route at a dose of 30, 100 and 300 mg/kg and the maximal electroshock (MES) and subcutaneous metrazole (ScMet) and strychnine (ScSty) induced seizure tests were performed for each compound.

According to test results, seven out of ten compounds showed significant anticonvulsant activity in the initial screening. Compounds **1**, **3** and **4** showed good anticonvulsant activity at a dose of 300 mg/kg in MES and ScMet tests, whereas compound **8** was active in ScMet and ScSty and compound **9** was active in MES and ScSty tests at a dose of 300 mg/kg. In comparison to phenytoin and carbamazepine, compound **3** exhibited superior activity by protecting against the MES and ScMet induced seizure up to 4 h at a dose of 300 mg/kg, while the other compounds were less active than these reference drugs. In general, semicarbazones of 4-chloroacetophenone Mannich bases (**4**, **5**, **8** and **10**) showed higher activity than acetophenone Mannich bases. The activity demonstrated by compounds **3**, **4**, **8** and **10** in at least two tests revealed that chloro substituent at the 4th position favored a broad spectrum of activity. In particular, compound **8** showed activity in both MES and ScSty tests at a dose of 100 mg/kg and was comparable with carbamazepine.

In the subsequent screening, the most active compounds (**3** and **4**) were administered by oral route at a dose of 30 mg/kg in rats, and the activity was evaluated before and 0.25, 0.5, 1, 2 and 4 h after treatment. Compound **3** exhibited excellent activity by protecting the test rats up to 4 h after administration, while compound **4** protected animals only within 0.5 h and showed only moderate activity.

According to the binding site hypothesis proposed by Dimmock et al. [10, 11] for the anticonvulsant activity of semicarbazones, there should be two aryl binding site at both ends and a hydrogen bonding site in the middle. Recently, we proposed a modified pharmacophore model [13], which includes an additional binding site besides three according to the model of Dimmock et al. [10, 11]. In the present series, the most active compounds **3** and **4** possess all essential pharmacophore requirements proposed earlier (Fig. 2). It was established that the N,N-disubstituted amino ethyl group introduced at the electron donor moiety did not change their activity. Further, the chloro substituent at any one end of aryl ring favored the activity, which confirmed that and electronegative substituent in the aryl-binding moiety becomes essential for activity.

Thus, the present study has further proved our earlier hypothesis on the anticonvulsant activity of semicarbazones [17 – 19]. In addition, the inclusion of an additional moiety ($CH_2$–$CH_2$–N<) at the electron donor acceptor group retained the activity. From the results demonstrated by compounds **3**, **4**, **8** and **10**, it is evident that there should be an electronegative substituent at one end of aryl binding region for optimal anticonvulsant activity.

Compounds **2**, **3**, **4** and **10** showed no significant effect on the phentobarbitone-induced sleep, which confirmed that these compounds lacked sedative-hypnotic activity.

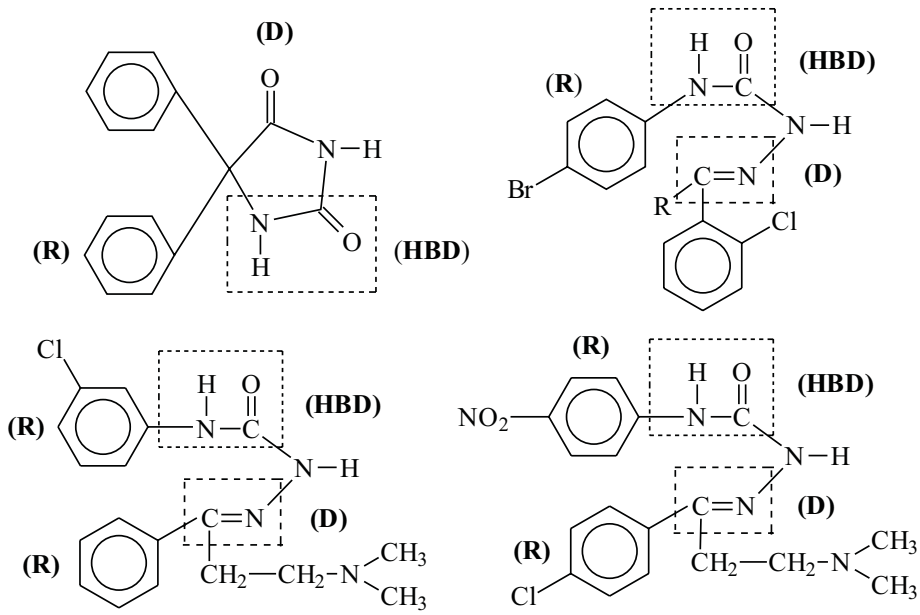
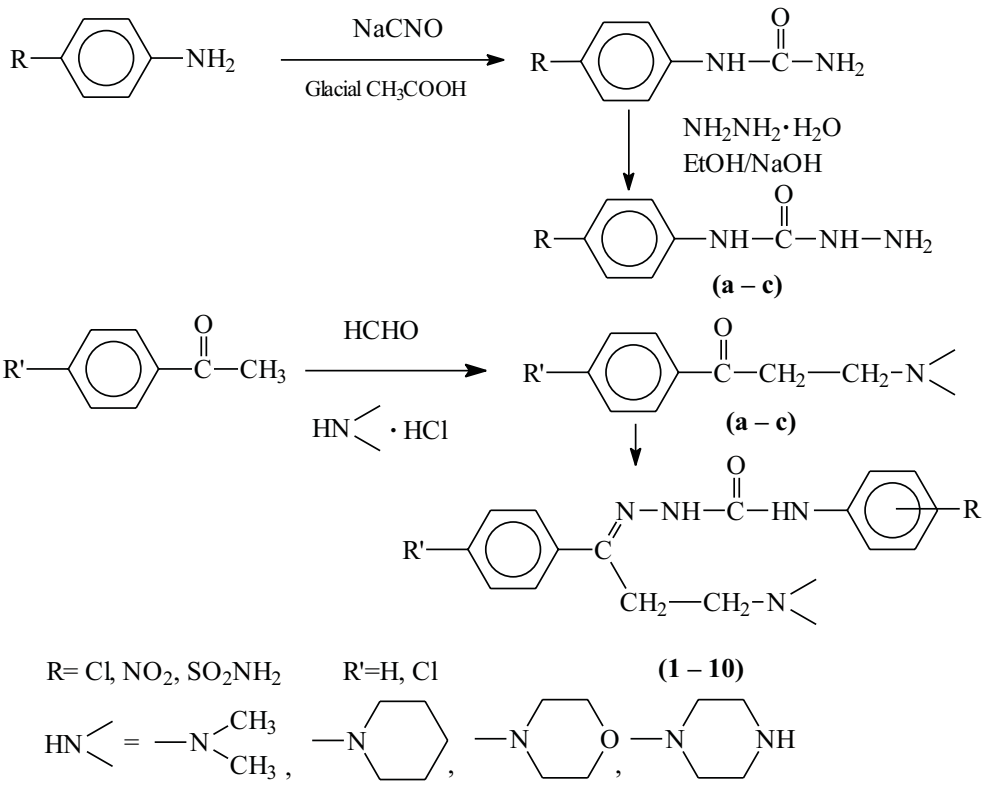



**Fig. 2**. Structures of anticonvulsants showing the general pharmacophore model for anticonvulsant activity.

**Scheme 1**




Compounds **5**, **6**, **7** and **8** exhibited, despite their poor anticonvulsant activity, a significant sedative-hypnotic action. In antidepressant screening, compounds **3**, **4** and **10** were more active than the reference drug imipramine. The above results show that compound **3** (3-chlorophenyl[β-dimethylaminopropiophenone]semicarbazone) is a potential anticonvulsant with no sedative properties and is the most interesting compound in the present series. However, the additional antidepressant activity of this compound is not related to its anticonvulsant activity.

*Experimental Section*

The purity of the synthesized compounds was checked by TLC using silica gel G as a stationary phase and methanol – chloroform (9 : 1) mixture as the mobile phase. Melting points were determined in open capillary tubes using Thomas – Hoover melting point apparatus and are uncorrected. The structures of all compounds were confirmed by recording their UV, IR and $^1$H NMR spectra on UV 7500, JASCO FT-IR 5300, and JEOL FX 90Q FT NMR spectrometers, respectively. Elemental analyses were performed in Heraeus CHN rapid analyzer.

**Synthesis of initial semicarbazides (a–c)**. The substituted semicarbazides (a-c) were prepared from the corresponding anilines by following the method described in [14]. First, the substituted aniline was converted into phenyl urea by treating with sodium cyanate in the presence of glacial acetic acid. Then, phenyl urea was treated with an equimolar amount of hydrazine hydrate to give the target semicarbazide.

Mannich bases of acetophenone and *p*-chloroacetophenone were prepared by condensing with formaldehyde and various secondary amines according to a method described in [15] and schematically depicted in Scheme 1.

N,N-Dimethylaminopropiophenone: m.p., 148 – 152°C (publ., 152 – 155°C); N,N-dimethylamino-*p*-chloropropiophenone: m.p.. 169 – 172°C (publ., 173 – 175°C [16]; 1-piperidino-*p*-chloropropiophenone: m.p., 187 – 189°C (publ., 186 – 187°C); 1-Piperazino-*p*-chloropropiophenone, m.p. 180 – 182°C.

**Synthesis of semicarbazones of Mannich bases (1 – 10). General procedure**. To a warm ethanol solution of Mannich base, an appropriate semicarbazide was added and the mixture was heated on a water bath until complete dissolution of semicarbazide. A few milliliters of glacial acetic acid was then added, and the heating was continued with occasional stirring. The target semicarbazone was precipitated either by cooling the concentrated solution in ice bath or by adding a few lumps of ice while the solution was hot, after which the mixture was kept in ice overnight. The precipitate was filtered and dried at room temperature. The yields and physicochemical constants of synthesized compounds are presented in Table 1.

**Anticonvulsant screening**. The synthesized compounds were evaluated for their CNS properties such as anticonvulsant, antidepressant, sedative-hypnotic potentiation and neurotoxicity. Preliminary anticonvulsant screening was performed in mice by using MES, ScMet, and ScSty tests and the activity was established by following the anticonvulsant drug development (ADD) program protocol [20, 21]. The drugs were administered intraperitoneally in a volume of 0.01 ml/g body weight at doses of 30, 100 and 300 mg/kg (each test group consisted of four mice). The activities of compounds in the MES, ScMet, and

ScSty tests are presented in Table 2. The most active compounds were additionally examined for the activity (MES) in rats at a dose of 30 mg/kg.

**Neurotoxicity (NT) screening**. The minimal motor impairment was measured in mice using the rotorod test. The mice were trained to stay on an accelerating rotorod with a

Table 1.

**Physicochemical constants of synthesized compounds**

| Compound | Chemical Name and Physico Chemical Data |
|---|---|
| **1** | **4-Nitrophenyl-(β-dimethylaminopropiophenone)semicarbazone**: Yield: 71%, m.p.: 122°C, UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 375.5, 235. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1430 (–NH–CO–NH), 1617 (C=N), 2940 (–$CH_2$–). $^1H$ NMR (DMSO, δ): 1.3 – 1.6 (s, 6H, N-dimethyl protons), 2.8 – 3.9 (m, 4H, –$CH_2$–$CH_2$), 5.9 – 6.4 (s, 1H, –NH), 6.9 – 8.28 (m, 9H, Ar-H), 9.0 (s, 1H, =N–NH).$C_{18}H_{23}N_5O_3$. |
| **2** | **4-Sulphonamidophenyl-(β-dimethylaminopropiophenone)semicarbazone**: Yield: 62 %, m.p.:152 – 155°C, UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 262.5, 206.5. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1354 ($SO_2$), 1600 (NH–CO–NH), 1670 (C=N), 2935 (–$CH_2$–), 3360 ($SO_2NH_2$). $^1H$ NMR (DMSO, δ): 1.3 – 1.6 (s, 6H, N-dimethyl protons), 2.8 – 3.9 (m, 4H, –$CH_2$–$CH_2$), 5.9 – 6.4 (s, 1H, –NH), 6.9 – 8.28 (m, 9H, Ar–H), 9.0 (s, 1H, =N–NH). $C_{18}H_{23}N_5O_3S$. |
| **3** | **3-Chlorophenyl-(β-dimethylaminopropiophenone)semicarbazone**: yield: 62%, m.p. 125 – 128°C. UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 278, 239, 210. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1590 (NH–CO–NH), 1660 (C=N), 2860 (>$CH_2$). $^1H$ NMR (DMSO, δ): 1 – 1.3 (s, 6H, dimethyl protons), 2.8 – 3.9 (m, 4H, –$CH_2$–$CH_2$), 5.9 – 6.4 (s, 1H, NH–Ar), 6.9 – 8.3 (m, 9H, Ar–H), 9.1 – 9.3 (s, 1H, =N–NH–). $C_{18}H_{21}N_4O$. |
| **4** | **4-Nitrophenyl-(β-dimethylamino-4-chloropropiophenone)semicarbazone**: Yield: 73%, m.p. 80°C. UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 376, 250, 209. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1610 (NH–CO–NH), 1655 (C=N), 2930 (>$CH_2$). $^1H$ NMR (DMSO, δ): 1 – 1.7 (s, 6H, dimethyl protons), 2.5 – 3.8 (m, 4H, –$CH_2$–$CH_2$), 5.4 – 5.9 (s, 1H, NH–Ar), 7.2 – 8.4 (m, 9H, Ar–H), 9.2 – 9.4 (s, 1H, =N–NH–). $C_{18}H_{20}ClN_5O_3$. |
| **5** | **4-Sulphonamidophenyl-(β-dimethylamino-4-chloropropiophenone)semicarbazone**: Yield: 57%, m.p. 120 – 124°C. UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 267, 206. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1350 ($SO_2$), 1612 (NH–CO–NH), 1650 (C=N), 2930 (>$CH_2$), 3360 ($SO_2NH_2$). $^1H$ NMR (DMSO, δ): 1 – 1.7 (s, 6H, dimethyl protons), 2.5 – 4.0 (m, 4H, –$CH_2$–$CH_2$), 5.4 – 5.8 (s, 1H, NH–Ar), 7.0 – 8.4 (m, 9H, Ar–H), 9.3 (s, 1H, =N–NH–). $C_{18}H_{22}ClN_5O_3S$. |
| **6** | **4-Nitrophenyl-(β-piperidinylpropiophenone)semicarbazone**: yield: 67%, m.p. 85 – 88°C. UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 372, 228. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1608 (NH–CO–NH), 1650 (C=N), 2940 (>$CH_2$). $^1H$ NMR (DMSO, δ): 1.4 – 2.6 (m, 10H, piperidinyl), 2.7 – 4.0 (m, 4H, –$CH_2$–$CH_2$), 6.0 – 6.4 (s, 1H, NH–Ar), 7.0 – 7.9 (m, 9H, Ar–H), 9.5 (s, 1H, =N–NH–). $C_{21}H_{25}N_5O_3$. |
| **7** | **4-Nitrophenyl-(β-morpholinylpropiophenone)semicarbazone**: yield: 65%, m.p. 138°C. UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 377, 373, 227. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1610 (NH–CO–NH), 1644 (C=N), 2935 (>$CH_2$). $^1H$ NMR (DMSO, δ): 1.5 – 2.4 (m, 8H, morpholinyl), 2.8 – 3.8 (m, 4H, –$CH_2$–$CH_2$), 5.9-6.2 (s, 1H, NH–Ar), 7.3 – 8.2 (m, 9H, Ar–H), 9.1 – 9.3 (s, 1H, =N–NH–). $C_{20}H_{23}N_5O_4$. |
| **8** | **4-Nitrophenyl-(β-morpholinyl-4-chloropropiophenone)semicarbazone**: yield: 63%, m.p. 110°C. UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 373, 327, 209. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1610 (NH–CO–NH), 1654 (C=N), 2942 (>$CH_2$). $^1H$ NMR (DMSO, δ): 1.5 – 2.1 (m, 8H, morpholinyl), 2.5 – 3.3 (m, 4H, –$CH_2$–$CH_2$), 5.8 – 6.2 (s, 1H, NH–Ar), 7.0 – 8.3 (m, 9H, Ar–H), 9.1 (s, 1H, =N–NH–). $C_{20}H_{22}ClN_5O_4$. |
| **9** | **4-Nitrophenyl-(β-piperazinylpropiophenone)semicarbazone**: yield: 75%, m.p. 148 – 150°C. UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 337, 302, 208. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1610 (NH–CO–NH), 1658 (C=N), 2920 (>$CH_2$), 3380 (secondary NH). $^1H$ NMR (DMSO, δ): 3.0 – 3.5 (m, 8H, piperazinyl), 2.4 – 2.9 (m, 4H, –$CH_2$–$CH_2$), 4.8 – 5.0 (s, 1H, NH–Ar), 6.8 – 8.3 (m, 9H, Ar–H), 9.2 (s, 1H, =N–NH–). $C_{20}H_{24}N_6O_3$. |
| **10** | **4-Nitrophenyl-(β-piperazinyl-4-chloropropiophenone)semicarbazone**: yield: 75%, m.p. 220 – 222°C. UV spectrum in $C_2H_5OH$ ($\lambda_{max}$, nm): 327, 307, 211. IR spectrum ($\nu_{max}$, $cm^{-1}$): 1610 (NH–CO–NH), 1652 (C=N), 2922 (>$CH_2$), 3376 (secondary NH). $^1H$ NMR (DMSO, δ): 2.3 – 2.8 (m, 8H, piperazinyl), 2.4 – 2.9 (m, 4H, –$CH_2$–$CH_2$), 4.7 – 5.0 (s, 1H, NH–Ar), 6.8 – 8.0 (m, 8H, Ar–H), 9.1 (s, 1H, =N–NH–). $C_{20}H_{23}ClN_6O_3$. |

Table 2

**Anticonvulsant Evaluation after Intraperitoneal Injection in Mice and Oral Administration in Rats**

| Comound | Intraperitoneal injection in mice* | | | | | | | Oral administration in rats | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MES | | ScMet | | ScSty | NT | | MES | | | | |
| | 0.5 h | 4 h | 0.5 h | 4 h | | 0.5 h | 4 h | 0.25 h | 0.5 h | 1 h | 2 h | 4 h |
| 1 | 300 | – | 300 | – | – | 300 | – | - | - | - | - | - |
| 3 | 300 | 300 | 300 | 300 | – | 300 | 300 | 30 | 30 | 30 | 30 | 30 |
| 4 | 300 | – | 300 | – | – | 100 | – | 30 | 30 | - | - | - |
| 6 | – | – | 300 | – | – | 300 | – | - | - | - | - | - |
| 8 | – | – | 100 | – | 100 | 300 | – | - | - | - | - | - |
| 10 | 300 | – | – | – | 300 | – | – | - | - | - | - | - |
| PTN | 30 | 30 | 30 | – | – | 100 | 100 | - | - | - | - | - |
| CBZ | 30 | 100 | 100 | 300 | – | 100 | 300 | - | - | - | - | - |
| VPA | – | – | 300 | – | – | – | – | - | - | - | - | - |

* Doses of 30, 100 and 300 mg/kg of each compound were administered; figures in the table indicate the dose, whereby bioactivity was demonstrated in half or more of test mice; animals were examined 0.5 and 4 h after injections were made. The (–) sign indicates absence of activity and the (-) sign indicates "not tested". Compounds **2**, **5**, **7** and **9** were inactive at doses 30, 100 and 300 mg/kg in all tests.

diameter of 3.2 cm, which rotates at 10 rpm. Trained animals were injected intraperitoneally with the test compounds at a dose of 30, 100 and 300 mg/kg. Neurotoxicity was indicated by the inability of animals to maintain equilibrium on the rod for at least one minute in each of three trails. The results are shown in Table 2. The reference drugs were phenytoin (PTN), carbamazepine (CBZ), and valproate (VPA).

**Antidepressant screening**. The compounds were tested for their antidepressant activity at a dose of 20 mg/kg by Porsolt despair swim test [22]. The mice were administered intraperitoneally with test compounds and were allowed to swim in a restricted space. The duration of immobility was monitored as a measure of the antidepressant activity, and the results (Table 3) were compared with those for the reference drug imipramine (IMP).

**Evaluation of sedative-hypnotic potentiation**. The potentiation or antagonism of synthesized compounds with respect to the phenobarbitone (PBN) induced narcosis in mice was evaluated using the righting reflex method [21]. The loss of righting reflex was measured as the criterion for activity.

Table 3

**Antidepressant and Sedative-Hypnotic Potentiation Screening**

| Compound | Antidepressant screen* | Sedative-hypnotic potentiation screen |
|---|---|---|
| | Immobility period | Duration of sleep |
| **1** | 71.67 ± 2.35 | 78.33 ± 4.50 |
| **2** | 13.33 ± 2.35 | 69.40 ± 8.12 |
| **3** | 5.00 ± 3.33 | 70.80 ± 9.18 |
| **4** | 3.33 ± 2.35 | 58.00 ± 7.57 |
| **5** | 198.33 ± 10.26 | 169.33 ± 8.18 |
| **6** | – | 185.16 ± 8.11 |
| **7** | – | 178.66 ± 6.74 |
| **8** | 120.00 ± 8.81 | 104.80 ± 4.58 |
| **9** | 88.33 ± 4.71 | 78.66 ± 7.76 |
| **10** | 1.67 ± 2.35 | 70.80 ± 9.18 |
| IMP | 8.3 ± 2.36 | – |
| PBN | – | 60.33 ± 9.60 |

* Compounds **6** and **7** produced sleep without losing righting reflex and were not tested.

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## СИНТЕЗ И ПРОТИВОСУДОРОЖНАЯ АКТИВНОСТЬ СЕМИКАРБАЗОНОВ ОСНОВАНИЯ МАННИХА АЦЕТОФЕНОНА

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Синтезирован ряд производных семикарбазонов оснований Манниха ацетофенона и *n*-хлорацетофенона, удовлетворяющих необходимым требованиям к фармакофорам соединений, обладающих противосудорожной активностью. Исходные основания Манниха ацетофенона и *n*-хлорацетофенона были получены реакцией формальдегида с различными аминами, а затем подвергнуты конденсации с арилсемикарбазидами для получения целевых семикарбазонов. Синтезированные соединения были испытаны на противосудорожную активность посредством тестов, использующих максимальный электрошок и конвульсии, вызванные подкожным введением метразола и стрихнина. Также исследована нейротоксичность (с помощью теста на вращающемся стержне) и седативные и антидепрессантные свойства веществ. Установлено, что 3-[3-хлорфенил(β-диметиламинопропиофенон)семикарбазон] обладает значительной активностью как антидепрессант при отсутствии седативного действия. Результаты подтвердили предложенную ранее модель фармакофора, содержащую места связывания семикарбазонов. Противосудорожная активность сохраняется при включении дополнительного электрон-донорного фрагмента ($CH_2$–$CH_2$–N<).