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Design and synthesis of semicarbazones and their bio-isosteric analogues as potent anticonvulsants: The role of hydrogen bonding

SURENDRA N. PANDEYA[1]*
ANIL K. AGARWAL[1]
ANITA SINGH[2]
JAMES P. STABLES[3]

[1] *Department of Pharmaceutics Institute of Technology, Banaras Hindu University, Varanasi – 221005, India*

[2] *Department of Pharmacy Kumaon University Uttaranchal, India*

[3] *National Institute of Neurological Disorders and Stroke, NIH, USA*

A series of *p*-nitrophenyl substituted semicarbazones (**4a-c**) and phenoxy/*p*-bromophenoxy acetyl hydrazones (**8a-q**) were synthesized and their anticonvulsant activity was screened against maximal electroshock seizure (MES), subcutaneous metrazole (ScMet) and subcutaneous strychnine (ScSty) tests. Compounds **4a-c** with –NHCO– were found to be the most active in all these tests. These compounds were also active in the MES test after oral administration in rats. On the other hand, compounds **8a-q** with $–OCH_2–$ were devoid of anticonvulsant activity. The studies revealed that the hydrogen bonding domain in semicarbazones, adjacent to the lipophilic aryl ring, is essential for the anticonvulsant activity.

Keywords: semicarbazones, hydrazones, anticonvulsant, hydrogen bonding domain, aryl ring (lipophilic)

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Epilepsy is a major neurological disorder throughout the world (1). Although some new drugs, such as vigabatrin, fosphenytoin and levetiracetam, have appeared on the market, the development of novel agents, particularly compounds effective against complex partial seizures remain a major focus of antiepileptic drug research. Recently, Unverferth *et al.* (2) suggested a pharmacophore model for structurally different anticonvulsants containing aryl rings and electron donor and hydrogen bond donor/acceptor functions. During the last five years, semicarbazones emerged as novel anticonvulsant entities in the laboratories of Dimmock (3, 4) and Pandeya (5, 6). The structural requirements in the semicarbazone series are: a lipophilic aryl ring, a distal aryl ring and a hydrogen-bonding domain (HBD). The lipophilic aryl ring with chloro, bromo or nitro groups has been found to be essential for anticonvulsant activity. The distal aryl ring is also implicated at the binding site. The HBD in semicarbazone series has been suggested by Dimmock to be the terminal $–NHCONH_2$. Pandeya *et al*. (7) suggested this HBD to be adjacent to the lipophilic aryl ring, but it was not confirmed as some of the compounds with $–CH_2–$ in place of –NH– were showing activity.

* Correspondence, e-mail: amill1909@rediffmail.com

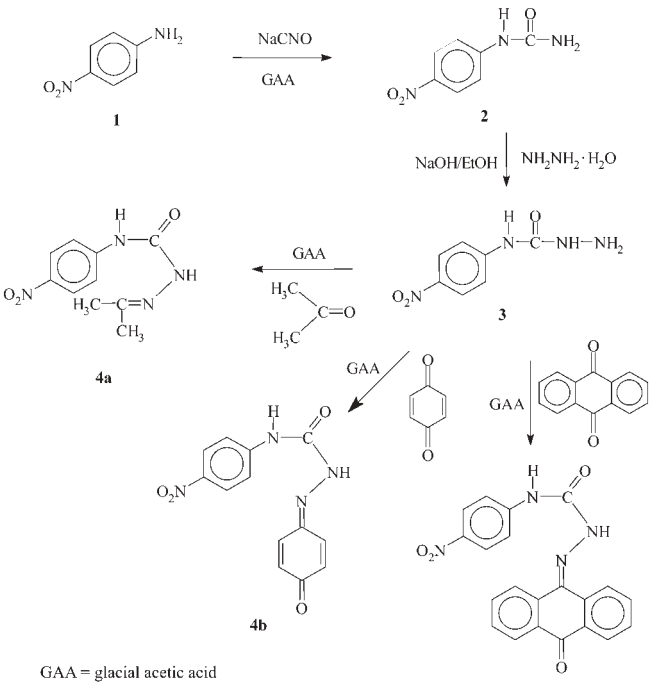
In this paper, we have synthesized some compounds with the lipophilic aryl ring and the hydrogen bonding pharmacophore having –NHCONH–. Further, in order to confirm the essentiality of this HBD, bio-isosteric modifications have been attempted. The –NHCO– pharmacophore has been replaced by $–OCH_2–$ group, which cannot form a hydrogen bond. This has been done to test whether the activity still remains or not.

EXPERIMENTAL

Chemistry

Melting points of the synthesized compounds were taken by the open capillary method and are uncorrected. UV, IR and ^1H NMR spectra were taken on Jasco Model 7800 (Jasco, Japan Spectroscopic Co., Japan), Jasco FT/IR-5300 and Jeol FX90Q FT (Jeol, Japan) instruments, respectively, and were consistent with the assigned structures. Purity of the synthesized compounds was checked by TLC using silica gel G (Merck, Germany) and chloroform/methanol (9:1) solvent systems.

Synthesis of p*-nitrophenyl semicarbazide (**3**).* – *p*-Nitrophenyl semicarbazide was prepared according to the literature (8) (Scheme 1).



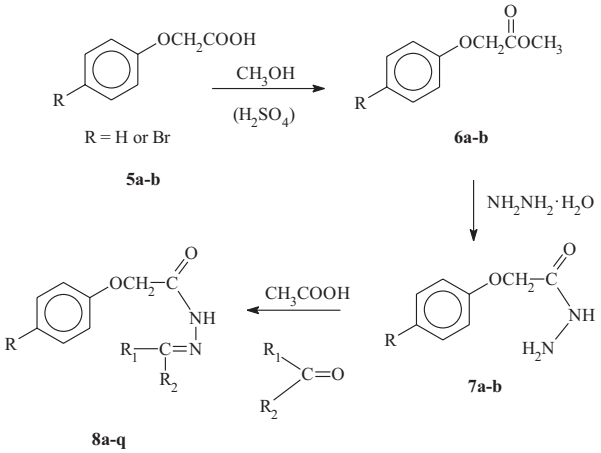
Scheme 1

*Synthesis of semicarbazone derivatives (**4a-c**).* – A solution of *p*-nitrophenyl semicarbazide (**3**) (0.01 mol) and an equimolar quantity of the appropriate carbonyl compound were refluxed for 30 minutes in the presence of glacial acetic acid (1–1.5 mL). The product obtained after cooling was filtered and recrystallized from 95% ethanol to give pure compounds **4a-c** (Scheme 1).

*Synthesis of phenoxy/*p*-bromophenoxy methyl esters* (**6a-b**). – A solution of phenoxy/*p*-bromophenoxy acetic acid (**5a-b**) (0.01 mol), concentrated sulphuric acid (0.002 mol, 0.1 mL) and methanol (10 mL) was heated under reflux with stirring for 24 h. On cooling, sodium bicarbonate solution (0.01 mol, 0.84 g) was added to neutralize any acid present. Extraction with diethyl ether and evaporation of organic solvents produced the methyl ester, which was used directly.

*Synthesis of phenoxy/*p*-bromophenoxy acetyl hydrazides* (**7a-b**). – The methyl ester (**6a-b**) (0.01 mol) and hydrazine hydrate (0.01 mol, 0.5 mL) in 95% ethanol (50 mL) were refluxed under stirring for 1 h. On cooling, the precipitate was collected. The identity of the hydrazides was confirmed by IR spectroscopy.

*Synthesis of phenoxy/*p*-bromophenoxy acetyl hydrazone derivatives (**8a-q**).* – An ethanolic solution of the hydrazides (**7a-b**) (0.01 mol) and the appropriate carbonyl compound (0.01 mol) and a few drops of glacial acetic acid were refluxed under stirring for 1 h. On cooling, the precipitate was collected, dried and recrystallized from ethanol (95%) to give the pure compounds **8a-q** (Scheme 2).



Scheme 2

Anticonvulsant screening

Compounds **4a-c** and **8a-q** were screened for anticonvulsant activity in maximal electroshock seizure (MES), subcutaneous metrazole (ScMet) and subcutaneous strychnine (ScSty) tests in mice (9). The data in Table IV (except ScSty test) were generated by the National Institute of Neurological Disorders and Stroke, NIH (USA), using their proto-

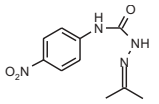
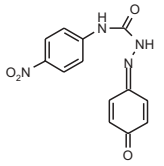
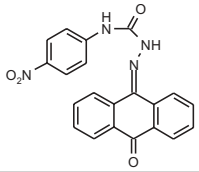
cols (10). Compounds **4a-c** were also administered orally to Sprague Dawley rats for MES screening and the results were noted at the end of 0.25, 0.5, 1, 2 and 4-h periods (Table V). The figures in Table IV reveal the lowest dose at which bioactivity was demonstrated and the lines indicate the absence of anticonvulsant activity.

Strychnine seizure pattern test (ScSty). – Animals of either sex, weighing between 22.5 to 24.5 g, of the control group received polyethylene glycol vehicle (PEG). Drug solution was administered intraperitoneally to the other groups. After 1 h, the animals of both groups were injected subcutaneously with strychnine (2 mg kg^{-1} body mass) and observed for 45 minutes. The dose at which the hind leg tonic extensor component was abolished was noted (Table III).

Neurotoxicity screening

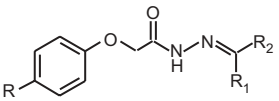
Minimal motor impairment was measured in mice by the rotorod test. The mice were trained to stand on an accelerating rotorod that rotated at 10 rev min^{-1}. The rod diameter was 3.2 cm. Trained animals were given intraperitoneal (*i.p.*) injections of the test compounds in doses of 30, 100 and 300 mg kg^{-1} body mass. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 minute in each of the three trials.

Table I. Physical properties of p*-nitrophenyl semicarbazones (**4a-c**)*

Compound No.	Structure	M.p. (°C)	Yield (%)	R_f[a]	Molecular formula (M_r)	Analysis (%) Calc./Found		
						C	H	N
4a		143	64	0.84	$C_{10}H_{12}N_4O_3$ (236.23)	50.84 50.72	5.12 5.21	23.71 24.10
4b		145	70	0.44	$C_{13}H_{10}N_4O_4$ (286.23)	54.54 54.23	3.52 3.71	19.57 19.24
4c		188	62	0.48	$C_{21}H_{14}N_4O_4$ (386.36)	65.28 65.13	3.65 3.52	14.50 14.83

[a] TLC (chloroform/methanol, 9:1)

*Table II. Physical properties of phenoxy/*p*-bromophenoxy acetyl hydrazones (**8a-q**)*



Compound No.	R	R_1	R_2	M.p. (°C)	Yield (%)	R_f[a]	Molecular formula (M_r)	Analysis (%) Calc./Found		
								C	H	N
8a	H	H	2-OH-C_6H_4	160	83	0.66	$C_{15}H_{14}N_2O_3$ (270.28)	66.65 66.38	5.22 4.95	10.36 10.42
8b	H	H	-C_6H_5	142	78	0.78	$C_{15}H_{14}N_2O_2$ (254.28)	70.85 71.25	5.55 5.42	11.01 10.84
8c	H	H	4-CH_3O-C_6H_4	122	80	0.68	$C_{16}H_{16}N_2O_3$ (284.31)	67.59 67.12	5.67 5.25	9.85 10.20
8d	H	CH_3	-C_6H_5	163	74	0.50	$C_{16}H_{16}N_2O_2$ (268.31)	71.62 71.92	6.01 5.85	10.44 10.53
8e	H	H	2-Cl-C_6H_4	110	67	0.55	$C_{15}H_{13}ClN_2O_2$ (288.73)	62.39 61.98	4.53 4.91	9.70 9.81
8f	H	CH_3	4-Cl-C_6H_4	165	84	0.52	$C_{16}H_{15}ClN_2O_2$ (302.76)	63.47 63.58	4.99 4.84	9.25 9.11
8g	Br	H	2-OH-C_6H_4	180	85	0.79	$C_{15}H_{13}BrN_2O_3$ (349.18)	51.59 51.48	3.75 4.05	8.02 7.86
8h	Br	H	-C_6H_5	187	71	0.65	$C_{15}H_{13}BrN_2O_2$ (333.18)	54.07 53.67	3.93 3.73	8.40 8.68
8i	Br	H	4-CH_3O-C_6H_4	170	51	0.77	$C_{16}H_{15}BrN_2O_3$ (363.216)	52.91 52.60	4.16 3.98	7.71 7.31
8j	Br	CH_3	-C_6H_5	126	60	0.86	$C_{16}H_{15}BrN_2O_2$ (347.21)	55.34 54.44	4.35 4.31	8.06 8.26
8k	Br	H	4-Cl-C_6H_4	150	64	0.83	$C_{15}H_{12}BrClN_2O_2$ (367.62)	49.00 49.21	3.29 3.24	7.62 7.32
8l	H	CH_3	4-NH_2-C_6H_4	134	76	0.72	$C_{16}H_{17}N_3O_2$ (283.33)	67.82 67.98	6.64 6.34	14.83 15.02
8m	H	H	4-$N(CH_3)_2$-C_6H_4	148	82	0.69	$C_{17}H_{19}N_3O_2$ (297.35)	68.66 69.36	6.44 6.27	14.13 14.23
8n	H	CH_3	4-OH-C_6H_4	200	84	0.83	$C_{16}H_{16}N_2O_3$ (284.31)	67.59 67.37	5.67 5.37	9.85 9.46
8o	H	CH_3	4-$C_6H_5CH_2O$-C_6H_4	172	68	0.73	$C_{23}H_{22}N_2O_3$ (374.44)	73.77 73.89	5.92 5.71	7.48 7.39
8p	Br	CH_3	4-$C_6H_5CH_2O$-C_6H_4	149	62	0.70	$C_{23}H_{21}BrN_2O_3$ (453.33)	60.93 61.22	4.67 4.35	6.18 5.89
8q	Br	CH_3	4-NO_2-C_6H_4	190	79	0.82	$C_{16}H_{14}BrN_3O_4$ (392.20)	48.99 49.25	3.59 3.92	10.71 10.44

[a] TLC (chloroform/methanol, 9:1)

Table III. Spectral data of p*-nitrophenyl semicarbazones (**4a-c**) and phenoxy/*p*-bromophenoxy acetyl hydrazones (**8a-q**)*

Compound No.	UV (EtOH) λ_{max} (nm)[a]	IR (KBr), ν_{max} (cm^{-1})[b]	^1H NMR ($DMSD_6$), δ (ppm)[c]
4a	270	3365, 1635, 1572, 1475	5.1 (s, 6H), 6.0 (s, 1H), 7.1–7.21 (m, 4H), 8.8 (s, 1H)
4b	265	3375, 1620, 1570, 1472	3.8–4.5 (m, 4H), 6.2 (s, 1H), 7.08–7.22 (m, 4H), 8.56 (s, 1H)
4c	259	3365, 1635, 1575, 1475	6.1 (s, 1H), 7.12–7.23 (m, 4H), 7.35–8 (m, 8H), 8.78 (s, 1H)
8a	288	2968, 1678, 1618, 848	4.8 (s, 2H), 5.21 (s, 1H), 7.02–7.21 (m, 5H), 7.4–7.9 (m, 4H), 8.76 (s, 1H), 11.3 (s, 1H)
8b	282	2968, 1682, 1599, 833	4.76 (s, 2H), 5.28 (s, 1H), 7.08–7.28 (m, 5H), 7.38–7.58 (m, 5H), 8.4 (s, 1H)
8c	290.5	2961, 1678, 1604, 844	3.9 (s, 3H), 4.75 (s, 2H), 5.2 (s, 1H), 7.0–7.26 (m, 5H), 7.38–7.6 (m, 4H), 8.8 (s, 1H)
8d	273.5	2916, 1701, 1597, 844	2.67 (s, 3H), 4.85 (s, 2H), 7.11–7.19 (m, 5H), 7.38–7.59 (m, 5H), 9.54 (s, 1H)
8e	281	2924, 1701, 1604, 825	4.82 (s, 2H), 5.26 (s, 1H), 7.03–7.28 (m, 5H), 7.4–7.92 (m, 4H), 8.78 (s, 1H)
8f	269	2922, 1705, 1608, 830	3.81 (s, 3H), 4.84 (s, 2H), 7.12–7.21 (m, 5H), 7.39–7.8 (m, 4H), 9.23 (s, 1H)
8g	271	2924, 1678, 1494, 840	4.84 (s, 2H), 5.28 (s, 1H), 7.02–7.21 (m, 4H), 7.4–7.93 (m, 4H), 9.22 (s, 1H), 11.61 (s, 1H)
8h	278.5	2924, 1684, 1490, 826	4.8 (s, 2H), 5.24 (s, 1H), 7.02–7.26 (m, 4H), 7.38–7.9 (m, 5H), 9.31(s, 1H)
8i	280	2924, 1678, 1608, 825	3.91 (s, 3H), 4.78 (s, 2H), 5.28 (s, 1H), 7.02–7.24 (m, 4H), 7.4–7.8 (m, 4H), 8.78 (s, 1H)
8j	263.5	2924, 1696, 1488, 814	2.62 (s, 3H), 4.86 (s, 2H), 7.14–7.2 (m, 4H), 7.4–7.6 (m, 5H), 9.47 (s, 1H)
8k	280.5	2924, 1694, 1610, 820	4.81 (s, 2H), 5.20 (s, 1H), 7.02–7.27 (m, 4H), 7.39–7.94 (m, 4H), 8.82 (s, 1H)
8l	310	2924, 1678, 1599, 845	2.68 (s, 3H), 4.21 (s, 2H), 4.76 (s, 2H), 7.1–7.21 (m, 5H), 7.38–7.61 (m, 4H), 9.48 (s, 1H)
8m	235	2920, 1678, 1604, 818	3.0 (s, 6H), 4.82 (s, 2H), 5.24 (s, 1H), 7.02–7.19 (m, 5H), 7.59–7.67 (m, 4H), 8.78 (s, 1H)
8n	284.5	2924, 1680, 1605, 835	2.59 (s, 3H), 4.84 (s, 2H), 7.08–7.18 (m, 5H), 7.37–7.68 (m, 4H), 9.39 (s, 1H), 10.81 (s, 1H)
8o	286	2924, 1678, 1494, 840	2.46 (s, 3H), 2.76 (s, 2H), 4.93 (s, 2H), 7.01–7.23 (m, 4H), 7.42–7.96 (m, 10H), 9.36 (s, 1H)
8p	285	2924, 1692, 1492, 832	2.28 (s, 3H), 2.59 (s, 2H), 5.28 (s, 2H), 7.0–7.24 (m, 4H), 7.57–7.99 (m, 9H), 9.59 (s, 1H)
8q	313	2924, 1685, 1580, 1496	2.64 (s, 3H), 4.82 (s, 2H), 7.09–7.19 (m, 4H), 7.28–7.88 (m, 4H), 8.86 (s, 1H)

[a] All compounds exhibited absorbtion bands due to the aromatic ring (benzenoid band), which is formed by $\pi \rightarrow \pi^*$ transition, in the region of 250–313 nm. A bathochromic effect is seen on substitution of auxochromes on the aromatic ring.

[b] 3365–3375 (secondary amine –NH, aryl –NH stretch), 2916–2968 (> CH_2 stretch), 1620–1705 (–C=O stretch), 1472–1620 (C=N stretch), 1570–1580 (aryl –NO_2 stretch), 814–848 (aryl –H stretch)

[c] s – singlet, m – multiplet, EtOH – ethanol, KBr – potassium bromide, ppm – parts per million

RESULTS AND DISCUSSION

p-Nitrophenyl semicarbazones (**4a-c**) were prepared by the reaction of semicarbazide (**3**) with the appropriate carbonyl compound following the literature procedure (11). Preparation of phenoxy/*p*-bromophenoxy acetyl hydrazones (**8a-q**) was carried out according to the method described in literature (7). Structural, physical and spectral data of the synthesized compounds are summarized in Tables I–III. The data on anticonvulsant activity are given in Tables IV and V.

Table IV. Anticonvulsant activity of 4-nitrophenyl semicarbazones and phenoxy/p-bromophenoxy acetyl hydrazones in mice[a]

Compound[b] No.	Concentration (mg kg^{-1} body mass)[c]						
	MES		ScMet		TOX		ScSty
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	0.5 h
4a	300	–	100	–	100	–	100
4b	300	–	100	–	30	–	100
4c	300	–	300	–	100	–	100
8a	–	–	–	–	100	–	–
8c	–	–	–	–	100	100	–
8d	–	–	–	300	100	100	100
8e	–	–	–	–	–	100	–
8f	–	–	–	–	300	100	–
8g	–	–	–	–	100	100	–
8h	–	–	–	–	–	100	–
8i	–	–	–	–	100	–	–
8k	–	–	–	–	100	300	–
8l	–	–	–	–	30	–	–
8m	–	–	–	–	300	–	–
Phenytoin	30	30	–	–	100	100	NT
Carbamazepine	30	100	100	300	100	300	NT
Valproic acid	–	–	300	–	–	–	NT

MES – maximal electroshock seizure
ScMet – subcutaneous metrazole
TOX – neurotoxicity
ScSty – subcutaneous strychnine
– no activity
NT – not tested

[a] Intraperitoneally administration to mice,
[b] For MES, ScMet and ScSty screen the number of animals used: 1 (dose 30, 100 and 300 mg kg^{-1}). For TOX screen, the number of animals used: 4 (dose 30 mg kg^{-1}), 8 (dose 100 mg kg^{-1}) and 4 (dose 300 mg kg^{-1}). Vechicle: 2% aqueous methylcellulose.
[c] The minimum dose exhibiting activity in half or more mice is given 0.5 or 4 h after injection.

*Table V. Evaluation of compounds **4a-c** in the MES test upon oral administration (dose 30 mg kg^{-1}) in rats*[a]

Time (h)	**4a**		**4b**		**4c**	
	MES	TOX	MES	TOX	MES	TOX
0.25	0/4	0/4	0/4	0/4	0/4	0/4
0.50	2/4	0/4	2/4	0/4	0/4	0/4
1	1/4	0/4	1/4	0/4	1/4	0/4
2	0/4	0/4	2/4	0/4	1/4	0/4
4	0/4	0/4	2/4	0/4	3/4	0/4

[a] Number of animals protected/number of animals used
For abreviations see Table III.

The results are summarized along with the literature data of clinically used drugs in Table IV. Compounds **4a-c** exhibited anticonvulsant activity in MES test at 300 mg kg^{-1} body mass, whereas compounds **8a-q** did not show any anticonvulsant activity in the MES test even up to 300 mg kg^{-1}. In the ScMet screen also compounds **4a-c** showed activity, but compounds **8a-q** failed to give any anticonvulsant activity except for compound **8d.** In the ScSty test, the pattern of activity in the MES test was repeated. In the neurotoxicity screen, compound **8f** was found to be the least toxic (up to a dose of 300 mg kg^{-1}), whereas compounds **4a, 4c, 8a, 8c, 8d, 8g, 8i,** and **8k** were the toxic at a dose of 100 mg kg^{-1}. Compounds **4b** and **8l** were the most toxic ones.

Compounds **4a-c** were further evaluated by the MES test upon oral administration to rats (Table V). At a dose of 30 mg kg^{-1}, compound **4a** showed 25% protection up to 1 h and 50% protection after 0.5 h. Compound **4b** showed 50% protection up to 4 h and 25% protection after 1 h. However, compound **4c** afforded 25% protection up to 2 h and 75% after 4 h. These compounds exhibited no acute neurotoxicity at this dose throughout the interval tested (4 h).

From the results it is apparent that semicarbazones **4a-c**, having a lipophilic group and a HBD, represented by the pharmacophore –NHCO– exhibit anticonvulsant activity even better than valproic acid both in MES and ScMet screenings. These compounds are also active orally in the MES test, showing 50–75% protection at a dose of 30 mg kg^{-1} body mass. Replacement of this HBD –NHCO– group by a non-hydrogen bonding pharmacophore –OCH_2– completely abolishes the activity in both MES and ScMet tests.

CONCLUSIONS

The anticonvulsant activity in arylsemicarbazones requires a hydrogen bonding domain (–NHCO–) adjacent to the lipophilic aryl ring, whereas replacement of this –NHCO– group by non-hydrogen bonding entities abolishes the anticonvulsant activity.

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S A Ž E T A K

Dizajniranje i sinteza semikarbazona i njihovih bioizostera kao snažnih antikonvulziva – uloga vodikovih veza

SURENDRA N. PANDEYA, ANIL K. AGARWAL, ANITA SINGH i JAMES P. STABLES

Sintetizirana je serija *p*-nitrofenil supstitutiranih semikarbazona (**4a-c**) i fenoksi/*p*-bromofenoksi acetil hidrazona (**8a-q**). Njihovo antikonvulzivno djelovanje evaluirano je elektrošok testom (MES) i testovima subkutanog metrazola (ScMet) i subkutanog strihnina (ScSty). Spojevi **4a-c** sa –NHCO– skupinom bili su najaktivniji u svim testovima. Ti spojevi su aktivni i u MES testu nakon peroralne primjene u štakora. Nasuprot tome,

spojevi **8a-q** sa $–OCH_2–$ skupinom nisu djelovali antikonvulzivno. Istraživanja su pokazala da su vodikove veze u susjedstvu lipofilnog arilnog prstena bitne za antikonvulzivno djelovanje.

Ključne riječi: semikarbazoni, hidrazoni, antikonvulziv, vodikove veze, arilni prsten (lipofilan)

Department of Pharmaceutics, Institute of Technology, Banaras Hindu University Varanasi – 221005, India

Department of Pharmacy, Kumaon University, Uttaranchal, India

National Institute of Neurological Disorders and Stroke, NIH, USA