International Journal of Pharmacology and Pharmaceutical Technology

Volume 1 | Issue 2 Article 9

January 2017

Synthesis and anticonvulsant activity of some 1-cyclohexylidine/ cycloheptylidine-4-substitued semicarbazide derivatives

Asmita Gajbhiye
Department of Pharmaceutical Sciences, Dr. H. S. Gour Central University, Sagar (M.P.) India.,
asmitapatil27@rediffmail.com

Synthesis and anticonvulsant activity of some 1-cyclohexylidine/ cycloheptylidine-4-substitued semicarbazide derivatives

Alok Jain, Shailendra Patil & Asmita Gajbhiye

Department of Pharmaceutical Sciences, Dr. H. S. Gour Central University, Sagar (M.P.) India.
E-Mail : asmitapatil27@rediffmail.com

Abstract **-** Aryl semicarbazide derivatives are reported to possess anticonvulsant activity. On the other hand unsubstituted and small substituents (less than 3 carbon atom) containing cyclohexanones prevented both pentylenetetrazole and MES induced seizures. Similarly cycloheptanone fused with benzodiazepine and furan produced anticonvulsant compounds. Therefore looking into the above facts in the present study, we have synthesized 12 derivatives of 1-cyclohexylidine/cycloheptylidine-4-substitued semicarbazide derivatives and screened them for anticonvulsant activity.

The synthesis of compounds was achieved as follows: The various para substituted (H, CH_3, F,Cl,Br, I) anilines were converted to aryl ureas by reacting with sodium cyanate in the presence of glacial acetic acid. These aryl ureas and aryl semicarbazides were synthesized by allowing them to react with hydrazine hydrate. Finally the aryl semicarbazides were condensed with cyclohexanone/ cycloheptanone in the presence of sodium acetate to give title compounds. All the synthesized compounds were evaluated for anticonvulsant activity by MES method using carbamazepine as standard and it was observed that all the compounds possess anticonvulsant activity comparable to carbamazepine. Carbamazepine had shown the abolition in the hind limb extensor tonic convulsion after 2 sec. whereas few compounds i.e. 1-cyclohexylidine-4-(4-fluorophenyl) semicarbazide, 1-cycloheptylidine-4-(4-fluorophenyl) semi-carbazide and 1-cycloheptylidine-4-phenylsemicarbazide were more active than standard. Overall it was found that cycloheptyl containing compounds were more active than cyclohexyl containing compounds. The unsubstitued compounds were more active than halo derivatives i.e. electron withdrawing groups, and halo compounds were more active than methyl derivatives i.e. electron donating group (CH_3). The order of activity for cyclohexanone and cycloheptanone derivatives is as follows: H >F >Cl >Br >I >CH_3. Among the halo derivatives, the activity decreased with increasing molecular weight of halo substituents.

Keywords- *cyclohexylidine; anticonvulsant; semicarbazide; cyproheptylidine***.**

I. INTRODUCTION

Epilepsy is a neurological disorder characterized by unprovoked seizures that affect millions of people worldwide. It is estimated that 25% of the epileptic population have seizures that are not responsive to presently available medical therapies. **[1].**

Conventional antiepileptic drugs (AEDs) phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide and benzodiazepine, are widely used but exhibit an unfavorable side effect profile and failure to adequately control seizures **[2].** It is estimated that available medication controls the seizures in only 50% of patients or decrease incidence in only 75% of patients. These facts make the field of anticonvulsant drug discovery a high priority **[3].** The long-established AEDs control seizures in 50% of patients developing partial seizures and in 60-70% of those developing generalized seizures **[4].** Hence, there is an urgent need to develop new AEDs.. Symptoms of depression were significantly more likely to appear in patients taking vigabatrin. These results triggered the search for newer anticonvulsants **[5].**

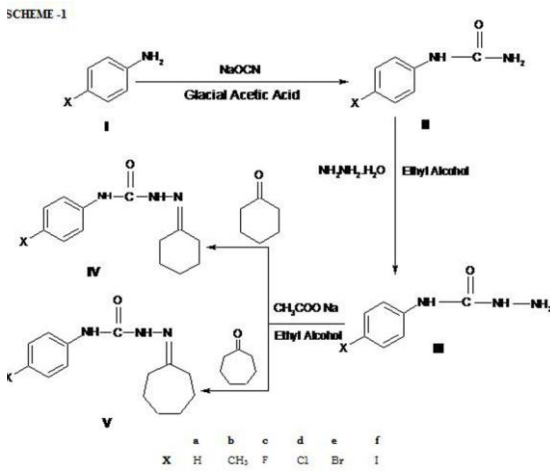
A number of aryl semicarbazones elicited anti-Maximal Electroshock (MES) activity, as a result of interaction of aryl ring and the semicarbazone group (HNCONHN=) at aryl binding site and a hydrogen bonding area respectively. Various p-substituted (Cl, Br) phenylsemicarbazones were synthesized to confirm the role of primary amino group in hydrogen bonding at the receptor site.

Semicarbazones as the lipophilic moiety resulted in compounds with broad spectrum of anticonvulsant activity and therefore, they may be utilized for the future development of novel anticonvulsants with broad spectrum of anticonvulsant activity **[6, 7].** The anticonvulsant activity of unsubstituted and mono-alkyl-substituted cyclohexanones was examined by testing the ability of the compounds to inhibit seizures induced by pentylenetrazol- and maximal electroshock in mice **[8].** The unsubstituted cyclohexanone prevented both pentylenetrazol- and maximal electroshock-induced

seizures. On the other hand, cycloheptanone is used to produce anticonvulsant compounds **[9]**. It is also used to produce other anticonvulsant agents such as furan-2(3H), 1'-cycloheptane]-3-one oxime maleate and furan-2(3H), 1'-cycloheptane] hydrochloride. In the present study we have converted semicarbazides to semicarbazones by reacting with cyclic aldehydes or ketones i.e. cyclohexanone and cycloheptanone.

II. MATERIALS AND METHODS

Melting points were determined in open capiliry tubes and are uncorrected on melting point apparatus. IR spectra were recorded on Perkin Elmer Bx-1 IR spectrometer. ^{1}H NMR on Jeol-300D (300 MHz) using TMS as internal standard.



A. *Synthesis of arylurease*

The syntheses of arylurease **(II a-f)** were achieved as per scheme-1 **[10]**. Aniline and/or p-substituted aniline (CH_3, F, Cl, Br, I; 0.1 mol; **I a-f**) was dissolved in glacial acetic acid (10 mL) and diluted with water (upto 100 mL). To this solution an equimolar (0.1 mol) quantity of sodium cyanate in warm water (50 mL) was added with stirring.

The reaction mixture was allowed to stand for 30 min, and then compounds **(II a-f)** were filtered, washed with water and dried after recrystallization from boiling water.

B. *Synthesis of arylsemicarbazides*

The syntheses of arylsemicarbazides **(IIIa-f)** were achieved as per scheme-1 **[10]**.To an aqueous solution of arylureas (**II a-f;** 0.1 mol); an equimolar quantity of hydrazine hydrate was added. Ethanol (2 mL) was added to this solution. The reaction mixture was refluxed for 30 min and cooled in ice. For p-substituted phenylsemicarbazides (**III a-f**) NaOH (4 g) was added to make the reaction mixture alkaline, before refluxing. The product (**III a-f**) was filtered under suction and recrystallized from ethanol.

C. *Synthesis of Cyclohexylidine semicarbazide derivatives*

Semicarbazides (**III a-f;** 0.1 mol) and sodium acetate were dissolved in water in the molar ratio of 1:1.5 and then cyclohexanone (0.1 mol) was added to the solution. The prepared solution was stirred well for an hour at 35°C. The final solution appeared to be a turbid mixture, then, ethanol was added to get a clear solution. The volume of the reaction mixture was reduced to one half by using rotary evaporator. The solution was left overnight. The product so formed (**IV a-f**) was filtered and recrystallized from ethanol. The characterization data of compounds **IVa-f** is given in Table 1.

.

TABLE 1: Characterization data of 1-Cyclohexylidine-4-substituted semicarbazides (**IV a-f)**

Comp. No.	X	IUPAC name	% yield	M.P. (°C)	IR (cm^{-1})	NMR δ (ppm)
IV-a	H	1-Cyclohexylidine-4-phenylsemicarbazide	64	180-183	3423.4 NH Stretching Vibration (C-NH-C), 3207.5 NH Stretching Vibration (C-NH-N), 1654.2 C=O Stretching, 1585.6 C=N Stretching 917.9 -1009.7Cyclohexyl Structural Vibration	-
IV-b	CH_3	1-Cyclohexylidine-4-p-tolysemicarbazide	65	195-198	3423.3 NH Stretching Vibration (C-NH-C), 3207.4 NH Stretching Vibration (C-NH-N), 2905.3 CH Stretching of methyl group, 1654.2 C=O Stretching, 1585.1 C=N Stretching, 917.8 -1009.6Cyclohexyl	-

					structural Vibration	
IV-c	F	1-Cyclohexylidine-4- (4-fluorophenyl) semicarbazide	58	205-209	3423.5 NH Stretching Vibration (C-NH-C), 3207.6 NH Stretching Vibration (C-NH-N), 1654.3 C=O Stretching, 1585.8 C=N Stretching, 1160.3 C-F Stretching, 917.1 – 1009.5 Cyclohexyl Structural Vibration	8.33 s, 1H, C-NH-N, 6.89 – 7.41m, 4H, aromatic ring protons 6.09 s, 1H, C-NH-C,1.09 – 1.48m, 10H, Cyclohexyl ring protons
IV-d	Cl	4-(4-chlorophenyl) 1-Cyclohexylidine semicarbazide	69	220-224	3423.1 NH Stretching Vibration (C-NH-C) 3207.3 NH Stretching Vibration (C-NH-N), 1654.4 C=O Stretching,1585.3 C=N Stretching, 917.5 – 1009.4 Cyclohexyl Structural Vibration, 815.9 C-Cl Stretching.	8.38s, 1H, C-NH-N,6.89 – 7.41,m, 4H, aromatic ring protons, 6.12s, 1H, C-NH-C 1.09 – 1.48m,10H, Cyclohexyl ring protons
IV-e	Br	4-(4-bromophenyl) 1-Cyclohexylidine semicarbazide	62	229-234	3423.6NH Stretching Vibration (C-NH-C),3207.1NH Stretching Vibration (C-NH-N), 1654.2C=O Stretching 1585.8 C=N Stretching 917.9 -1009.1Cyclohexyl Structural Vibration 547.3C-Br Stretching	-
IV-f	I	1-Cyclohexylidine-4-(4-iodophenyl) semicarbazide	63	240-245	3423.6 NH Stretching Vibration (C-NH-C), 3207.1 NH Stretching Vibration (C-NH-N), 1654.6 C=O Stretching, 1585.2 C=N Stretching, 917.8 – 1009.3Cyclohexyl Structural Vibration, 510.3 C-I Stretching.	-

TABLE 2: Characterization data of 1- Cycloheptylidine-4-substituted semicarbazides (**V a-f)**.

Comp. No.	**X**	**IUPAC name**	**% yield**	**M.P. (°C)**	**IR**	**NMR**
V-	H	1-Cycloheptylidine-4-phenylsemicarbazide	64	185-189	3423.5 NH Stretching Vibration (C-NH-C), 3207.6 NH Stretching Vibration (C-NH-N), 1654.3 C=O Stretching,1585.6 C=N Stretching, 917.6 – 1009.7 Cycloheptyl Structural Vibration	-
V-b	CH_3	1-Cycloheptylidine-4-p-tolysemicarbazide	58	195-198	3423.3 NH Stretching Vibration (C-NH-C), 3207.5 NH Stretching Vibration (C-NH-N), 2845.3 CH	-

					Stretching of methyl group, 1654.2 C=O Stretching, 1585.6 C=N Stretching, 917.8– 1009.3Cycloheptyl Structural Vibration	
V-c	F	1-Cycloheptylidine-4-(4-fluorophenyl) semicarbazide	56	205-207	3423.7 NH Stretching Vibration (C-NH-C), 3207.9 NH Stretching Vibration (C-NH-N), 1654.3C=O Stretching, 1585.1C=N Stretching 1162.3 C-F Stretching,917.7 – 1009.4 Cycloheptyl Structural Vibration	8.35 s, 1H, C-NH-N, 6.89 – 7.41m, 4H, aromatic ring protons, 6.18 s, 1H, C-NH-C,1.09 – 1.48 m, 12H, Cycloheptyl ring protons
V-d	Cl	4-(4-chlorophenyl) 1-Cycloheptylidine semicarbazide	51	215-219	3423.6 NH Stretching Vibration (C-NH-C), 3207.8 NH Stretching Vibration (C-NH-N), 1654.1 C=O Stretching, 1585.2C=N Stretching 917.9 – 1009.5Cycloheptyl Structural Vibration, 815.9 C – Cl Stretching.	8.37s, 1H, C-NH-N, 6.89 – 7.41m, 4H, aromatic ring protons, 6.14,s, 1H, C-NH-C,1.09 – 1.48 m, 12H, Cycloheptyl ring protons
V-e	Br	4-(4-bromophenyl) 1-Cycloheptylidine semicarbazide	59	225-228	3423.7 NH Stretching Vibration (C-NH-C), 3207.4 NH Stretching Vibration (C-NH-N), 1654.2 C=O Stretching, 1585.5 C=N Stretching, 917.9 – 1009.6 Cycloheptyl Structural Vibration, 547.3 C-Br Stretching.	-
V-f	I	1-Cycloheptylidine-4-(4-iodophenyl) semicarbazide	58	236-240	3423.9 NH Stretching Vibration (C-NH-C), 3207.5 NH	-

					Stretching Vibration (C-NH-N), 1654.4 C=O Stretching, 1585..6C=N Stretching, 917.9 – 1009.3 Cycloheptyl Structural Vibration, 510.3C-I Stretching.	

.

D. Synthesis of Cycloheptylidine semicarbazide derivative

Semicarbazides (**III a-f;** 0.1 mol) and sodium acetate were dissolved in water in the molar ratio of 1:1.5 and then cycloheptanone (0.1 mol) was added to the solution. The prepared solution was stirred well for an hour at 35°C. The final solution appeared to be a turbid mixture, then, ethanol was added to get a clear solution. The volume of the reaction mixture was reduced to one half by using rotary *evaporator. The solution was left overnight. The product so formed (**V a-f**) was filtered and recrystallized from ethanol. The characterization data of compounds **V a-f** is given in Table 2.*

E. Pharmacological Screening of synthesized compounds

All the synthesized semicarbazide compounds have been screened for their possible anticonvulsant activity on albino rats using the apparatus Techno Electrocunvulsiometer with eye (corneal) electrodes, etc.

Suspension of all synthesized compounds were made (0.008 mol), according to their molecular weight, by using sodium carboxymethylcellulose (as suspending agent) in water and 0.3 mL of this suspension was injected intraperitoneally in albino rats.

Groups of 3 albino rats were used. The test was started 30 min. after i.p. injection with the test compounds or the vehicle or standard drug (carbamazepine). Techno Electrocunvulsiometer apparatus with corneal electrodes was used to deliver the stimuli. The intensity of stimulus is dependent on the apparatus 15mA, 75Hz for 0.2 sec. Under these conditions all vehicles/ standard drug (carbamazepine)/ compounds treaded mice showed the characteristic extensor tonus. The animals were observed closely for 2 min. Disappearance of hind limb extensor tonic convulsion was used as positive criterion.

The abolition of hind limb extensor of synthesized compounds treated groups were compared with that of controlled and standard drug (carbamazepine) treated groups. The data is given in Table 3.

III. RESULTS, DISCUSSION AND CONCLUSION

All the title compounds were synthesized successfully and were characterized by IR and NMR. The characterization data of compounds **IVa-f** and **V a-f** is given in Table 1 and 2 respectively.

Anticonvulsant activity was performed by using abolition time of hind limb extensor in albino rats. The result of anticonvulsant activity is shown in Table 3.

All synthesized compounds showed anticonvulsant activity comparable to that of standard drug (carbamazepine). Carbamazepine had shown abolition in hind limb extension after 2 seconds. Few compounds showed activity equal to carbamazepine and even better than that of carbamazepine. Other compounds showed moderate activity, little lesser but comparable to that of carbamazepine. The most active compound **V-c** had shown abolition in hind limb extension after 1 second, which had F at aromatic ring and cycloheptyl moiety. The least active compound **IV-b** had shown abolition in hind limb extension after 4 seconds, which had CH_3 at aromatic ring and cyclohexyl moiety.

F. Cyclohexylidine semicarbazide derivatives

The unsubstituted compound is more active than electron-donating group (CH_3) substituted compound but is less active than electron withdrawing group (F, Cl, Br, I) substituted compounds. In halo substituted compounds, the fluoro derivative is most active than chloro, bromo and iodo derivatives. The anticonvulsant activity is in the following order for the halo derivatives of cyclohexanone i.e. F > Cl > Br > I **(IV c > IV d > IV e > IV f).** The activity decreased with increasing molecular weight of halo substituents.

G. Cycloheptylidine semicarbazide derivatives

The unsubstituted compound is more active than electron donating group (CH_3) substituted compound

but is less active than electron withdrawing group (F, Cl, Br, I) substituted compounds. In halo substituted compounds, the fluoro derivative is most active than chloro, bromo and iodo derivatives. The anticonvulsant activity is in the following order for the halo derivatives of cycloheptanone i.e. F > Cl > Br > I **(V c > V d > V e > V f).** The activity decreased with increasing molecular weight of halo substituents.

In general, it was found that the cycloheptyl moiety containing compounds are more active than cyclohexyl moiety containing compounds.

ACKNOWLEDGMENT

The authors are thankful to the Head, Department of Pharmaceutical sciences, dr. H. S. Gour Central University, Sagar, Madhya Pradesh for providing the facilties for performing this research work. Authors are grateful to UGC for providing the financial assistance in the form of JRF to Alok Jain.

REFERENCES

1. H. Beraldo, D. Gambino, "Wide pharmacological versatility of semicarbazones thiosemicarbazones and their metal complexes" **Mini Rev. Med. Chem,** Vol. 4, pp 159-165, 2004,
2. L.J.M. Lopes, "The new drugs and strategies to manage epilepsy" **Curr. Pharmac. Design,** Vol. 6, pp 873-878, 2000.
3. R.J. Porter, M.A. Rogawski, "New antiepileptic drugs: from serendipity to rational discovery." **Epilepsia,** pp 33, 1992.
4. M. Berk, J. Segal, L. Janet, M. Vorster, "Emerging options in the treatment of bipolar disorders." **Drugs,** Vol. 61, pp 1407-1414, 2001.
5. T.W. Rall, L.S. Schleifer, "Drugs effective in the treatment of epilepsies: Goodman and Gilman's The Pharmacological Basis of Therapeutics." 6th edition, Macmillan Publishing Co, INC, New York, pp 448-474, 1980.
6. S.N. Pandeya, V. Mishra, I. Ponnilavarsan, J.P. Stables, "Anticonvulsant activity of p-chlorophenyl substituted aryl semicarbazones – the role of primary terminal amino group." **Pol. J. Pharmacol.,** Vol. 52, pp 283–290, 2000.
7. N. Aggarwal, P. Mishra, "Synthesis of 4-aryl substituted semicarbazones of some terpenes as novel anticonvulsants." **J. Pharm. Pharmaceut. Sci. (www.ualberta.ca/~csps),** Vol. 7(2), pp 260-264, 2004.
8. K.D.Holland,D.K.Naritoku, A.C McKeon, J.A. Ferrendelli, D.F. Covey**,** "Convulsant and anticonvulsant cyclopentanones and cyclohexanones" **Mol. Pharmacol.**, Vol. 37, pp 98-103, 1990.
9. B.M. Reddy, M. Pavani, P.M. Sreekanth, "An efficient synthesis of 1,5-benzodiazepine derivatives catalyzed by a solid superacid sulfated zirconia." **Tetrahedron Letters Pergamon,** Vol. 44, pp 4447–4449, 2003.
10. S.N. Pandeya, S. Kohli, N. Siddiqui, J.P. Stables, "Synthesis and anticonvulsant activities of 4-N-substituted arylsemicarbazones" **Pol. J. Pharmacol,** Vol. 55, pp 565–571, 2003

◈◈◈