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Synthesis of alkyl *N*-(aminocarbonyl)arylcarbohydrazonates and *N*-(aminocarbonyl)arylcarbohydrazonamides, potential anticonvulsants

© **Alexey O. Menkov**,*+ and **Yury I. Smushkevich**
D. Mendeleev University of Chemical Technology of Russia. Miusskaya Sq. 9. Moscow, 125047. Russia.
Phone: +7 (495) 495-24-15. E-mail: aomenkov@bk.ru

*Supervising author; +Corresponding author

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Abstract

The exploration trend of the anticonvulsant activity of semicarbazones has developed since the 90s of the twentieth century. So far, a large group of semicarbazones has been researched on the anticonvulsant activity on generalized tonic-clonic and myoclonic seizure is also an absence seizure. The influence of semicarbazones on the level of GABA in brain cells of rodents is determined. The proposed site for binding semicarbazones with the active site of the ferment enhancing the activity of inhibitory neurons has also been researched. Atomic charges were calculated and contribution of each atom to binding with the ferment was appraised on the basis of this model. The pharmacophoric model of semicarbazones was elucidated. Basic requirements for the structure of semicarbazones for a demonstration of anticonvulsant activity are described. The main regularities of the material structure and activity of semicarbazones are revealed. Experimental data have been compared with data on the activity of drugs widely used in medical practice, such as phenytoin, carbamazepine, valproic acid, and phenobarbital. Some semicarbazones surpass these preparations by exerting the least neurotoxicity thus providing high defense and high protection indices. In this work, we report synthesis structural analogues of semicarbazones – alkyl *N*-(aminocarbonyl)-arylcarbohydrazonates. We also research the elucidation of the influence on the environment to the reaction between alkoxy benzocarboxy-imidoate hydrochlorides and semicarbazide hydrochloric acid on the formation of *N*-(aminocarbonyl)-arylcarbohydrazonates or *N*-(aminocarbonyl)benzocarbohydrazonamide. On the basis of quantum-chemical calculations of the received compounds and comparing results with the previously-reported information, we can decide the potentially high anticonvulsant activity of these compounds due to the presence of additional electron-donating groups in the binding region with the active site of the ferment and the presence of a hydrophobic alkyl substituent in the binding region with the hydrophobic part of the ferment.

References

[1] H. Kaur, B. Kumar, B. Medhi. Antiepileptic drugs in development pipeline: A recent update. *eNeurologicalSci.* **2016**. Vol.4. P.42-51. DOI: 10.1016/j.ensci.2016.06.003
[2] R. Sridharan, B.N. Murthy. Prevalence and pattern of epilepsy in India *Epilepsia*. **1999**. Vol.40. No.5. P.631-636. DOI:10.1111/j.1528-1157.1999.tb05566.x
[3] G.F. Carl, M.L. Smith. Phenytoin-Folate Interactions: Differing Effects of the Sodium Salt and the Free Acid of Phenytoin *Epilepsia.* **1992**. Vol.33. No.2. P.372-375. DOI: 10.1111/j.1528-1157.1992.tb02330.x
[4] P. Kwan, M.J. Brodie. Phenobarbital for the treatment of epilepsy in the 21st century: a critical review *Epilepsia.* **2004**. Vol.45. No.9. P.1141-1149. DOI: 10.1111/j.0013-9580.2004.12704.x
[5] N. Calcaterra, J. Barrow. Classics in chemical neuroscience: diazepam *ACS Chemical Neuroscience*. **2014**. Vol.5. P.253-260. DOI: 10.1021/cn5000056
[6] S.D. Shorvon. Drug treatment of epilepsy in the century of the ILAE: the second 50 years, 1959-2009 *Epilepsia.* **2009**. Vol.50. No.s3. P.93-130. DOI: 10.1111/j.1528-1167.2009.02042.x
[7] J.M. Rho, S.D. Donevan, M.A. Rogawski Barbiturate-like actions of the propanediol dicarbamates felbamate and meprobamate *Journal of Pharmacology and Experimental Therapeutics.* **1997**. Vol.280. No.3. P.1383-1391.
[8] J. Riss, J. Cloyd, J. Gates, S. Collins. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics *Acta Neurol Scand.* **2008**. Vol.118. P.69-86. DOI: 10.1111/j.1600-0404.2008.01004.x

[9] R.H. Levy et al. Valproic acid: chemistry, biotransformation and pharmacokinetics *Antiepileptic drugs*. **2002**. Vol.5. P.780-800.
[10] A. Birnbaum, S. Marina, B. Boureois. Valproate. *Treatment of Epilepsy: Principles and Practice. - 5th ed. - Philadelphia: Lippincott Williams & Wilkins*. **2011**. P.622-629.
[11] M. Bialer et al. Progress report on new antiepileptic drugs: a summary of the Twelfth Eilat Conference (EILAT XII) *Epilepsy research*. **2015**. Vol.111. P.85-141. DOI: 10.1016/j.eplepsyres.2015.01.001
[12] J. Dimmock, K. Sidhu, R. Thayer, P. Mack, M. Duffy, R. Reid, J. Quail, U. Pugazhenthi. Anticonvulsant activities of some arylsemicarbazones displaying potent oral activity in the Maximal Electroshock Screen in rats accompanied by high Protection Indices. *J. Med. Chem*. **1993**. Vol.36. P.2243-2252. DOI: 10.1021/jm00068a001
[13] F. Azam, B. El-gnidi, I. Alkskas. Combating oxidative stress in epilepsy: Design, synthesis, quantum chemical studies and anticonvulsant evaluation of 1-(substituted benzylidene ethylidene)-4-(naphthalen-1-yl)semicarbazides. *Eur. J. Med. Chem*. **2010**. Vol.45. P.2817-2826. DOI: 10.1016/j.ejmech.2010.02.063
[14] V.I. Ilyin et al. V102862 (Co 102862): a potent, broad-spectrum state-dependent blocker of mammalian voltage-gated sodium channels *British journal of pharmacology*. **2005**. Vol.144. No.6. P.801-812. DOI: 10.1038/sj.bjp.0706058
[15] N.C. Lam. Sodium channel blocker compositions and the use thereof. *Pat.* W0 006 11 88, 19 Oct. **2000**.
[16] P. Yogeeswari et al. Discovery of N-(2,6-Dimethylphenyl)-Substituted Semicarbazones as Anticonvulsants: Hybrid Pharmacophore-Based Design. *J. Med. Chem.* **2005**. Vol.48. P.6202-6211 DOI: 10.1021/jm050283b
[17] J. Dimmock, S. Vashishthaa, J. Stablesb. Anticonvulsant properties of various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds *Eur. J. Med. Chem.* **2000**. Vol.35. P.241-248. DOI: 10.1016/S0223-5234(00)00123-9
[18] O. Alam et al. Synthesis, anticonvulsant and toxicity screening of newer pyrimidine semicarbazone derivatives. *Eur. J. Med. Chem*. **2010**. Vol.45. No.6. P.2467-2472. DOI: 10.1016/j.ejmech.2010.02.031
[19] H. Rajak et al. Novel semicarbazones based 2,5-disubstituted-1,3,4-oxadiazoles: One more step towards establishing four binding site pharmacophoric model hypothesis for anticonvulsant activity *Bioorganic & medicinal chemistry letters*. **2010**. Vol.20. No.14. P.4168-4172. DOI: 10.1016/j.bmcl.2010.05.059
[20] F. Azam et al. Synthesis of some novel N-4-(naphtha [1,2-d] thiazol-2-yl)semicarbazides as potential anticonvulsants. *Eur. J. Med. Chem.* **2009**. Vol.44. No.1. P.203-211. DOI:10.1016/j.ejmech.2008.02.007
[21] A. Pinner, F. Klein. Umwandlung der nitrile in imide. *Eur. J. Inorg. Chem*. **1877**. Vol.10. No.2. P.1889-1897. DOI:10.1002/cber.187701002154