Asian Journal of Chemistry Vol. 20, No. 5 (2008), 3805-3810

Synthesis of Novel 3-Chloro-2-methylphenyl Substituted Methylene Bridged Aryl Semicarbazones with Potential Anticonvulsant Activity

ABDOLRASOUL H. EBRAHIMABADI*†, MOHAMMAD GERAYESH BORAZJANIAN‡ and EBRAHIM H. EBRAHIMABADI†
Kerman Neuroscience Research Center, Kerman University of Medical Sciences
P.O. Box 76175-113, Kerman, Iran
Fax: (98)(341)2111010
E-mail: aebrahimabadi@kashanu.ac.ir; rebrahimabadi@hotmail.com

A series of 2-(3-chloro-2-methylphenylamino) N-substituted acetohydrazide derivatives (**3a-f**) have been synthesized as potential anticonvulsant agents. The 2-(3-chloro-2-methylphenylamino)acetamide (**1**) was obtained from the reaction of 3-chloro-2-methylaniline with 2-chloroacetamide. The treatment of compound **1** with hydrazine hydrate afforded 2-(3-chloro-2-methylphenylamino)acetohydrazide (**2**) intermediate. Reaction of compound **2** with appropriate aldehyde or ketone in absolute ethanol led to the synthesis of target compounds **3a-f**. The structure of intermediates and final compounds was confirmed by elemental analysis, IR and ^{1}H NMR spectra.

Key Words: Semicarbazones, Anticonvulsant, 3-Chloro-2-methyl substituted aryl semicarbazones, Epilepsy.

INTRODUCTION

Epilepsy is a general term including over 40 different types of human seizure disorders[1]. Approximately 4 % of the world population experiences this serious neurological disorder over its lifetime[2]. Although the current drugs provide adequate seizure control in many patients, it is roughly estimated that up to 28-30 % of patients are poorly treated with the available antiepileptic drugs[3]. Moreover, due to lifelong medication, many currently available antiepileptic drugs have serious side effects[4].

In past decade, a novel group of aryl semicarbazones with potent anticonvulsant activity have been designed[5-10]. These compounds are structurally dissimilar from many common anticonvulsants containing the dicarboximide

†Essential Oils Research Center, Kashan University, Post Code: 87317-51167, Kashan, Iran. Fax: (98)(361)5552930
‡Department of Medicinal Chemistry, Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran.

function (CONRCO), which may contribute to their toxic side effects[11]. Aryl semicarbazones skeleton consist of three main parts: a lipophilic aryl or alkyl (cyclic or acyclic) group which connect to receptor by hydrophobic interactions, a semicarbazone moiety capable of making several hydrogen bonds to the receptor and an auxiliary aryl binding site (Fig. 1)[12]. Several research groups have synthesized a remarkable amount of derivatives of this compounds by changing the lipophilic and/or auxiliary aryl binding site to obtain more active and less toxic anticonvulsants[5-15]. This study reports the synthesis of some aryl semicarbazone derivatives with a methylene bridge between N_1 and the carbonyl group C_2 of the semicarbazone moiety (**Scheme-I**, **3a-f**). This methylene group will give a center of flexibility (sp^3 carbon) to all conjugated semicarbazone portion of the molecule resulting a possible better fitting to the receptor. It also improves the distances between the center of lipophilic binding site and the carbonyl (C_2), N_3 and N_4 atoms of semicarbazone part. These distances have a critical rule in anticonvulsant potency of this derivatives[16]. 3-Chloro-2-methylphenyl fragment is chosen as auxiliary aryl binding site according to a previous report regarding good anticonvulsant activity of aryl semicarbazone derivatives containing this fragment[17].

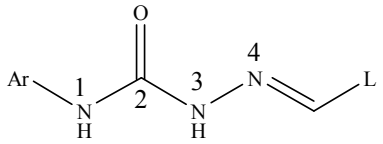
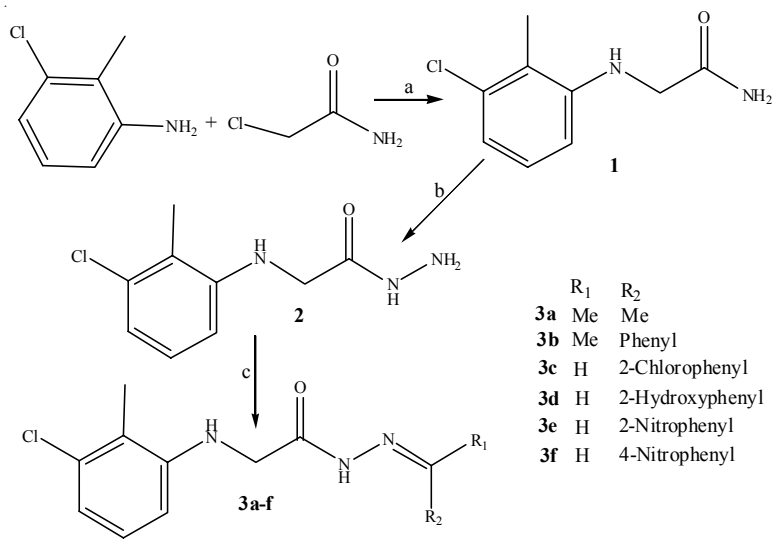


Fig. 1. General structure of aryl semicarbazone anticonvulsants: (Ar) auxiliary aryl binding site, (L) lipophilic binding site

EXPERIMENTAL

Melting points were measured in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. Infrared and proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded for the compounds on Mgna-IR-550 (KBr) and Brucker Advance (400 MHz) instruments, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Chemical shift values are given in δ scale. Elemental analyses (C, H, N) were undertaken with Perkin-Elmer model 240C analyzer. The homogeneity of the compounds was monitored by ascending thin-layer chromatography on silica gel G (Merck) coated aluminum plates, visualized by iodine vapour and UV light. Column chromatography was performed on (Merck) Silica gel 60 (particle size 0.06-0.20 mm).

Preparation of 2-(3-chloro-2-methylphenylamino)acetamide (1): In a flask containing 200 mL of absolute ethanol was added 3-chloro-2-methylaniline (39 mL, 0.32 mol), sodium carbonate (16.96 g, 0.16 mol)



Scheme-I: Synthesis of aryl semicarbazone derivatives (**3a-f**). Reagents and conditions: (a) Na_2CO_3, EtOH, Reflux, 24 h; (b) NH_2NH_2, H_2O, EtOH, Reflux, 24 h; (c) appropriate aldehyde or ketone, EtOH, room temperature, 4 h, then Reflux, 2 h

and 2-chloroacetamide (29.92 g, 0.16 mol) and resulting mixture was refluxed with stirring for 24 h. The solvent was removed by rotary evaporator and 40 mL distilled water was added. The resulting white precipitate was filtered and washed with 20 mL extra water and dried. Recrystallization of precipitate in 90 % ethanol led to the formation of white needle crystals. Yield 45 %, m.p. 153-154 ºC. IR (KBr, ν_{max}, cm^{-1}): 3452 (NH), 1664 (CO); ^1H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 4.25 (brs, 1H, NH), 6.33 (d, 1H, phenyl), 6.58 (d, 1H, phenyl), 6.81 (m, 1H, phenyl), 8.91 (brs, 2H, NH_2); Elemental analysis (%), found C: 54.48, H: 5.63, N: 14.14, calculated C: 54.52, H: 5.58, N: 14.10.

Preparation of 2-(3-chloro-2-methylphenylamino)acetohydrazide (2): A clear solution of compound **1** (20 g, 0.1 mol) in 50 mL ethanol was added steadily to a flask containing 48.5 mL hydrazine hydrate 80 % with stirring. The reaction mixture was refluxed for 24 h. The solvent and extra hydrazine was removed by rotary evaporator and 50 mL distilled water was added. The precipitate was filtered, washed with extra water, dried in vacuum oven and recrystallized from 90 % ethanol to give white cubic crystals. Yield 75 %, m.p. 162-163 ºC. IR (KBr, ν_{max}, cm^{-1}): 3380 (NH), 1657 (CO); ^1H NMR (400 MHz, $CDCl_3$) δ: 2.19 (s, 3H, CH_3), 3.30 (brs,

2H, NH_2), 4.13 (s, 2H, CH_2), 4.25 (brs, 1H, NH), 6.33 (d, 1H, phenyl), 6.58 (d, 1H, phenyl), 6.81 (m, 1H, phenyl), 8.91 (brs, 1H, CONH); Elemental analysis (%), found C: 50.55, H: 5.63, N: 19.66, calculated C:50.59, H: 5.66, N:19.67.

General procedure for the preparation of 2-(3-chloro-2-methylphenylamino)-N-X-acetohydrazides (3a-f): To a stirring solution of compound **2** (1.6 g, 7 mmol) in absolute ethanol at room temperature was added drop wise 7 mmol of appropriate aldehyde or ketone in 20 mL absolute ethanol. The resulting mixture was stirred for 4 h and refluxed for additional 2 h. The reaction mixture was cooled to room temperature and filtered. The crude products were purified by column chromatography on silica gel eluting with ethyl acetate-ethanol (95:5) and recrystallized from ethanol to give **3a-f**.

2-(3-Chloro-2-methylphenylamino)-N-(propan-2-ylidene)acetohydrazide (3a): Yield 90.6 %, m.p. 198-199 ºC. IR (KBr, ν_{max}, cm^{-1}): 3413 (NH), 1673 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.09 (s, 3H, $ArCH_3$), 4.03 (s, 2H, CH_2), 4.25 (brs, 1H, NH), 6.33 (d, 1H, phenyl), 6.58 (d, 1H, phenyl), 6.81 (m, 1H, phenyl), 8.91 (brs, 1H, CONH); Elemental analysis (%), found C: 56.78, H: 6.32, N: 16.55, calculated C: 56.80, H: 6.36, N: 16.56.

2-(3-Chloro-2-methylphenylamino)-N-(1-phenylethylidene)acetohydrazide (3b): Yield 86 %, m.p. 219-220 ºC. IR (KBr, ν_{max}, cm^{-1}) 3428 (NH), 1680 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (s, 3H, $ArCH_3$), 2.14 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 6.46 (m, 1H, Phenyl), 6.65 (m, 1H, Phenyl), 6.86 (m, 1H, phenyl), 7.24 (m, 3H, phenyl), 7.57 (m, 2H, phenyl), 9.12 (s, 1H, CONH); Elemental analysis (%), found C: 64.63, H: 5.72, N: 13.33, calculated C:64.66, H: 5.75, N: 13.31.

2-(3-Chloro-2-methylphenylamino)-N-(2-chlorobenzylidene)acetohydrazide (3c): Yield 77.7 %, m.p. 224-225 ºC. IR (KBr, ν_{max}, cm^{-1}): 3411 (NH), 1679 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.29 (s, 3H, CH_3), 4.11 (s, 2H, CH_2), 5.04 (s, 1H, ArNH), 6.13 (m, 1H, phenyl), 6.42 (m, 1H, phenyl), 6.73 (m, 1H, phenyl), 7.10-7.83 (m, 4H, phenyl), 8.18 (s, 1H, imine), 11.55 (brs, 1H, CONH); Elemental analysis (%), found C: 57.11, H: 4.52, N: 12.46, calculated C:57.16, H: 4.50, N:12.50.

2-(3-Chloro-2-methylphenylamino)-N-(2-hydroxybenzylidene)-acetohydrazide (3d): Yield 82.7 %, m.p. 243-244 ºC. IR (KBr, ν_{max}, cm^{-1}) 3436 (NH), 1676 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.05 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 6.14 (m, 1H, phenyl), 6.45 (m, 1H, phenyl), 6.66 (m, 1H, phenyl), 6.77 (m, 1H, phenyl), 7.03 (m, 1H, phenyl), 7.27 (m, 1H, phenyl), 7.52 (m, 1H phenyl), 8.25 (s, 1H, imine), 10.91 (brs, 1H, OH), 11.45 (brs, 1H, CONH); Elemental analysis (%), found C: 60.44, H: 5.05, N: 13.20, calculated C: 60.47, H: 5.08, N: 13.22.

2-(3-Chloro-2-methylphenylamino)-N-(2-nitrobenzylidene)-acetohydrazide (3e): Yield 83 %, m.p. 218-219 ºC. IR (KBr, ν_{max}, cm^{-1}): 3409 (NH), 1684 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.95 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 5.08 (brs, 1H, ArNH), 6.12 (m, 1H, phenyl), 6.41 (m, 1H, phenyl), 6.69 (m, 1H, phenyl), 7.19-7.75 (m, 4H, phenyl), 8.19 (s, 1H, imine), 11.6 (s, 1H, CONH); Elemental analysis (%), found C: 55.42, H: 4.40, N: 16.22, calculated C: 55.42, H: 4.36, N: 16.16.

2-(3-Chloro-2-methylphenylamino)-N-(4-nitrobenzylidene)acetohydrazide (3f): Yield 85 %, m.p. 241-242 ºC. IR (KBr, ν_{max}, cm^{-1}): 3419 (NH), 1682 (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.29 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 6.13 (m, 1H, phenyl), 6.42 (m, 1H, phenyl), 6.72 (m, 1H, phenyl), 7.67 (d, 2H, phenyl), 7.86 (s, 1H, imine), 7.98 (d, 2H, phenyl), 11.66 (s, 1H, CONH); Elemental analysis (%), found C: 55.39, H: 4.33, N: 16.18, calculated C: 55.42, H: 4.36, N: 16.16.

RESULTS AND DISCUSSION

The synthetic pathway for the preparation of intermediates (**1**, **2**) and target molecules (**3a-f**) is presented in **Scheme-I**.

The reaction of 3-chloro-2-methylaniline with 2-chloroacetamide in ethanol in the presence of Na_2CO_3 (as proton acceptor) led to the formation of 2-(3-chloro-2-methylphenylamino)acetamide (**1**) by a S_N^2 reaction[18]. Treatment of compound **1** with hydrazine hydrate afforded related acetohydrazide intermediate **2** in good yield[8]. Final compounds **3a-f** were obtained from the reaction of appropriate aldehyde or ketone with compound **2** in ethanol by hydrazone formation reaction[19].

ACKNOWLEDGEMENT

The authors thank to Kerman Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran for supporting the experiment.

REFERENCES

1. D.A. McCormick and D. Contreras, *Ann. Rev. Physiol.*, **63**, 815 (2001).
2. T.R. Brown and G.L. Holmes, *N. Eng. J. Med.*, **344**, 1145 (2001).
3. K.J. Meador, *J. Clin. Psychiatry*, **64**, 30 (2003).
4. Z. Lin and P.K. Kadaba, *Med. Res. Rev.*, **17**, 537 (1997).
5. J.R. Dimmock, K.K. Sindhu, R.S. Thayer, P. Mack, M.J. Duffy and R.S. Reid, *J. Med. Chem.*, **36**, 2243 (1993).
6. J.R. Dimmock, R.N. Puthucode, J.M. Smith, M. Hetherington, J.W. Quail and U. Pugazhenthi, *J. Med. Chem.*, **39**, 3984 (1996).
7. J.R. Dimmock, H.A. Sample, S. John, M.A. Beazely and G.D. Abrams, *Pharmazie*, **54**, 260 (1999).
8. S.N. Pandeya, N. Aggarwal and J.S. Jain, *Pharmazie*, **54**, 300 (1999).
9. J.R. Dimmock and G.B. Baker, *Epilepsia*, **35**, 645 (1994).

10. J.R. Dimmock, S.C. Vashishta and J.P. Stables, *Eur. J. Med. Chem.*, **35**, 241 (2000).
11. P.K. Kadaba, *J. Pharm. Sci.*, **73**, 850 (1984).
12. J.R. Dimmock, S.N. Pandeya, J.W. Quail, U. Pugazhenthi, T.M. Allen, G.Y. Kao, J. Balzarini and E. De Clercq, *Eur. J. Med. Chem.*, **30**, 303 (1995).
13. J.R. Dimmock, K.K. Sidhu, S.D. Tumber, S.K. Basran, M. Chen and J.W. Quail, *Eur. J. Med. Chem.*, **30**, 287 (1995).
14. S.N. Pandeya, I. Ponnilavarasan, A. Pandey, R. Lakhan and J.P. Stables, *Pharmazie*, **54**, 923 (1999).
15. S.N. Pandeya, P. Yogeeswari and J.P. Stables, *Eur. J. Med. Chem.*, **35**, 879 (2000).
16. P. Yogeeswari, D. Sriram, R. Thirumurugan, J.V. Raghavendran, K. Sudhan, R.K. Pavana and J. Stables, *J. Med. Chem.*, **48**, 6202 (2005).
17. P. Yogeeswari, R. Thirumurugan, R. Kavya, S.J. Selwyn and J.P. Stables, *Eur. J. Med. Chem.*, **39**, 729 (2004).
18. R.T. Morrison and R.N. Boyd, Organic Chemistry, Prentice-Hall, Inc., p. 172 (1992).
19. M.W. Beukers, M.J. Wanner, J.K.V.F.D. Kunzel, E.C. Klaasse, A.P. Ijzerman and G.J. Koomen, *J. Med. Chem.*, **46**, 1492 (2003).

(*Received*: 24 September 2007; *Accepted*: 8 February 2008) AJC-6315