Asian Journal of Chemistry; Vol. 23, No. 10 (2011), 4632-4634

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis and Characterization of Vanillin Semicarbazones

N. VENKATESHHAN[1,*], V. RAVICHANDIRAN[1], D. SELVAKUMAR[2] and V. LAVAKUMAR[1]

[1]Vel's College of Pharmacy, Pallavaram, Chennai-600 117, India
[2]Ultra College of Pharmacy, Vandiyur, Madurai-625 020, India

*Corresponding author: E-mail: nvenkatesh1976@yahoo.co.in

(*Received*: 14 January 2011; *Accepted*: 30 June 2011) AJC-10117

Semicarbazones have a great interest because of their chemistry and biological activities for the treatment of various human ailments. A series of seven vanillin semicarbazones (**3a-g**) were synthesized by reflux of aryl semicarbazides with appropriate carbonyl compound in the presence of glacial acetic acid. The aryl semicarbazides (**2a-g**) were synthesized from aryl carbamates by reacting with hydrazine hydrate and ethanol on hydrazinolysis. The aryl carbamates (**1a-g**) were obtained by the reaction between phenyl chloro formate and aniline/substituted aniline in anhydrous ether in the presence of sodium hydroxide. The structure of the newly synthesized compounds was established by various analytical techniques such as IR, ^{1}H NMR and MASS spectral studies.

Key Words: Vanillin semicarbazones, Synthesis, Aryl carbamates.

INTRODUCTION

Carbocyclic or heterocyclic ring systems comprise the core of chemical structures of the vast majority of therapeutic agents. Free-standing benzene rings have provided the core for a very large number of biologically active compounds[1]. Over the past few years, it has been established that several apparently quite unrelated drug classes owe their activity to effects on a shared biochemical system. Similar groups/structures often exhibit similar biological activities. However, they usually exhibit different potency. The traditional structure activity relationship investigations are a useful tool in the search for new drugs. However, structure activity relationship is usually determined by making minor changes to the structure of the existing compound and assessing the effect on its biological activity[2].

Vanillins are of considerable pharmacological interest since a number of derivatives have been reported to possess various biological activities. Semicarbazones have proved the efficiency and efficacy in combating various diseases[3]. It is of great interest because of their chemistry and potentially beneficial biological activities such as antinociceptive[4], anticonvulsant[5-7], antiarrhythmic[8], insulinmimic[9], uterotrophic[10], antiviral[11], antimalarial[12], antitubercular[13,14], cytotoxic[15], antibacterial and antifungal[16] activities.

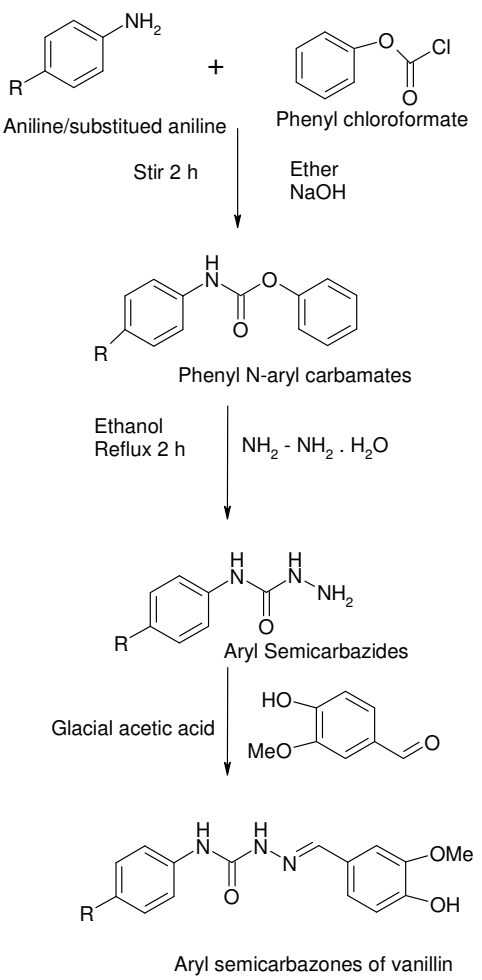
In consideration of diverse biological properties of this type of compounds and in continuation of the earlier work on semicarbazones derivatives, the present work was aimed to develop simple and efficient procedures for the synthesize of vanillin semicarbazones since there is no extensive and individual scientific reports are available for the incorporation of vanillin into aryl substituted semicarbazides. In this present investigation, a series of vanillin semicarbazones were synthesized by incorporation of vanillin into aryl substituted semicarbazides synthesized from aniline and substituted anilines.

EXPERIMENTAL

Melting points were determined on Veego melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was carried out on silica gel G coated plates using chloroform:methanol (9:1) as eluent and visualized by iodine vapours. The structure of the newly synthesized compounds was established by various analytical techniques such as IR, ^{1}H NMR and MASS spectral studies. IR spectra (KBr disc) were recorded on Shimadzu 8400 series FT-IR spectrophotometer. ^{1}H NMR spectra were obtained on Bruker AV spectrophotometer at 300 MHz in DMSO-d_6. Chemical shifts were reported in δ units (ppm) relative to an internal standard of tetramethylsilane. Mass spectra were recorded on JEOL GCmate. The general synthetic method was depicted in **Scheme-I**.

General procedure for the synthesis of vanillin semicarbazones[17]: A solution of phenyl chloroformate (0.01 mol) was added drop wise at 0 ºC to a well stirred solution of aniline/substituted aniline (0.01 mol) in 100 mL of anhydrous ether. During the second phase of addition, a solution of NaOH (0.01 mol) in 10 mL of distilled water was added simultaneously.

The mixture was stirred vigorously for 1 h at 0 ºC and again for 1 h at 20 ºC. The organic layer was washed with 25 mL of HCl 0.2 M and water. Finally it was dried over $MgSO_4$. Evaporation of the solvent yields the desired phenyl N-aryl carbamates (**1a-g**)[17]. A solution of respective carbamates (0.01 mol) was dissolved in a mixture of 4 mL of hydrazine hydrate (85 %) and 16 mL of ethanol separately and heated under reflux for 2 h. The solvent was evaporated under reduced pressure. The corresponding crystals of aryl semicarbazides (**2a-g**) obtained were recrystallized from alcohol. An equimolar quantity of aryl semicarbazides (0.01 mol) and the appropriate carbonyl compound (0.01 mol) with glacial acetic acid (1.0-1.5 mL) were refluxed for 30 min. The product obtained after cooling was filtered and recrystallized from 95 % ethanol to give titled compounds (**3a-g**). Thin layer chromatography (TLC) was run throughout the reactions to optimize the reactions for purity and completion[18].



Scheme-I: Synthesis of vanillin semicarbazones

(E)-1-(4-Hydroxy-3-methoxybenzylidene)-4-(4-chlorophenyl)semicarbazone (3a): m.p. 198-201ºC; IR (KBr, ν_{max}, cm^{-1}): 3427 (OH), 3311 (NH), 2900 (OCH_3), 1653 (CONH), 1609 (C=C), 1588 (C=N), 1231 (C-N),1091 (C-O), 730 (C-Cl); ^{1}H NMR (DMSO, 300 MHz) δ: 3.42 (s, 1H, CH), 3.85 (s, 3H, OCH_3), 6.79-7.74 (m, 7H, ArH), 7.84 (s, 1H, CONH), 8.97 (s, 1H, NH-N), 10.59 (s, 1H, OH); EI-MS m/z: 288.2 (M-31), 124, 89, 62.

(E)-1-(4-hydroxy-3-methoxybenzylidene)-4-(4-bromophenyl)semicarbazone (3b): m.p. 208-210 ºC; IR (KBr, ν_{max}, cm^{-1}): 3406 (OH), 3300 (NH), 2901 (OCH_3), 1652 (CONH), 1609 (C=C), 1583 (C=N), 1248 (C-N), 1071 (C-O), 682 (C-Br); ^{1}H NMR (DMSO, 300 MHz) δ: 3.43 (s, 1H, CH), 3.85 (s, 3H, OCH_3), 6.79-7.69 (m, 7H, ArH), 7.84 (s, 1H, CONH), 8.96 (s, 1H, NH-N), 10.60 (s, 1H, OH); EI-MS m/z: 243.6 (M-122), 167, 89, 62.

(E)-1-(4-hydroxy-3-methoxybenzylidene)-4-(4-fluorophenyl)semicarbazone (3c): m.p. 211-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 3469 (OH), 3249 (NH), 2886 (OCH_3), 1668 (CONH), 1600 (C=C), 1511 (C=N), 1240 (C-N), 1071 (C-O); ^{1}H NMR (DMSO, 300 MHz) δ: 3.32 (s, 1H, CH), 3.85 (s, 3H, OCH_3), 6.79-7.69 (m, 7H, ArH), 7.83 (s, 1H, CONH), 8.92 (s, 1H, NH-N), 10.58 (s, 1H, OH); EI-MS m/z: 303.9 (M^+), 274, 168, 125, 81, 54.

(E)-1-(4-hydroxy-3-methoxybenzylidene)-4-(4-nitrophenyl)semicarbazone (3d): m.p. 202-205 ºC; IR (KBr, ν_{max}, cm^{-1}): 3866 (OH), 3515 (NH), 3103 (OCH_3), 1725 (CONH), 1600 (C=C), 1491 (C=N), 1186 (C-N), 1061 (C-O); ^{1}H NMR (DMSO, 300 MHz) δ: 3.35 (s, 1H, CH), 3.87 (s, 3H, OCH_3), 6.80-8.224 (m, 7H, ArH), 8.229 (s, 1H, CONH), 9.49 (s, 1H, NH-N), 10.92 (s, 1H, OH); EI-MS m/z: 330.8 (M^+), 189, 125, 81, 67.

(E)-1-(4-Hydroxy-3-methoxybenzylidene)-4-(4-hyroxyl methyl)phenyl semicarbazone (3e): m.p. 224-226 ºC; IR (KBr, ν_{max}, cm^{-1}): 3792 (OH), 3412 (NH), 3074 (OCH_3), 1676 (CONH), 1600 (C=C), 1515 (C=N), 1115 (C-N), 1033 (C-O); ^{1}H NMR (DMSO, 300 MHz) δ; 3.32 (a, 1H, CH), 3.73 (s, 3H, OCH_3-Ar), 3.85 (s, 3H, OCH_3), 6.78-7.54 (m, 7H, ArH), 7.82 (s, 1H, CONH), 8.73 (s, 1H, NH-N), 10.47 (s, 1H, OH); EI-MS m/z: 315 (M^+), 279, 182, 123, 71, 53.

(E)-1-(4-Hydroxy-3-methoxybenzylidene)-4-*p*-tolyl-semicarbazone (3f): m.p. 214-216 ºC; IR (KBr, ν_{max}, cm^{-1}) : 3400 (OH), 3311 (NH), 2900 (OCH_3), 1653 (CONH), 1621 (C=C), 1593 (C=N), 1109 (C-N), 1024 (C-O); ^{1}H NMR (DMSO, 300 MHz) δ: 2.26 (s, 3H, CH_3), 3.32 (s, 1H, CH), 3.85 (s, 3H, OCH_3), 6.79-7.55 (m, 7H, ArH), 7.82 (s, 1H, CONH), 8.77 (s, 1H, NH-N), 10.53 (s, 1H, OH); EI-MS m/z: 198.9 (M-108), 134, 86.

(E)-1-(4-Hydroxy-3-methoxybenzylidene)-4-sulfonamido phenyl)semicarbazone (3g): m.p. 190-192 ºC; IR (KBr, ν_{max}, cm^{-1}): 3346 (OH), 3200 (NH), 2900 (OCH_3), 1682 (CONH), 1639 (C=C), 1586 (C=N), 1115 (C-N), 1030 (C-O); ^{1}H NMR (DMSO, 300 MHz) δ: 3.33 (s, 1H, CH), 3.86 (s, 3H, OCH_3), 6.80-7.86 (m, 7H, ArH), 7.87 (s, 2H, NH_2), 7.88 (s, 1H, CONH), 9.16 (s, 1H, NH-N), 10.70 (s, 1H, OH); EI-MS m/z: 256 (M-108), 138, 80.

RESULTS AND DISCUSSION

The synthesis of vanillin semicarbazones was achieved as depicted in **Scheme-I**. A same experimental condition was followed for synthesis of vanillin semicarbazones except for the difference in substituent. All the compounds were synthesized with good yield. The R_f value of the newly synthesized compounds indicted the formation of new chemical analogues

which was further confirmed by their different melting points. The structure of the synthesized compounds was established by spectral studies IR, ^{1}H NMR and MASS spectrums as well as elemental analysis data. IR spectra showed the C=N peak at 1593-1491 cm^{-1} and characteristic amide bonds at 3515-3200 cm^{-1} and 1725-1652 cm^{-1} for semicarbazone derivatives and the ^{1}H NMR spectrum revealed that the hydrazine (=N-NH) proton attached to the phenyl ring at 8.92-9.49. All the above data confirmed the formation of the vanillin semicarbazones.

Conclusion

The present study concluded that the structural modification on vanillin semicarbazones led to new compounds with a very interesting pharmacological profile. From these findings, it can be suggested that the designing of new chemical analogues with vanillin semicarbazones lead the necessity of further research.

ACKNOWLEDGEMENTS

The authors are thankful to the management, Vels University, Chennai, India for providing facilities, technical assistance funding, continuous encouragement and support.

REFERENCES

1. D. Lednicer, The Organic Chemistry of Drug Synthesis, New York: John Wiley & Sons, Vol. 7, p. 43 (2007).
2. S.S. Bahekar and D.B. Shinde, *Acta Pharm.*, **53**, 223 (2003).
3. S. Singh, A.K. Tiwari, H. Ojha, N. Kumar, B. Singh and A.K. Mishra, *Cancer Biother. Radiopharm*., **25**, 117 (2010).
4. L.T.S. Rocha, K.A. Costa, A.C.P. Oliveira, E.B. Nascimento, C.M. Bertollo, F. Araujo, L.R. Teixeira, S.P. Andrade, H. Beraldo and M.M. Coelho, *Life Sci.*, **79**, 499 (2006).
5. R. Thirumurugan, D. Sriram, A. Saxena, J. Stables and P. Yogeeswari, *Bioorg. Med. Chem.*, **14**, 3106 (2006).
6. P. Yogeeswari, D. Sriram, R. Thirumurugan, J.V. Raghavendran, K. Sudhan, R.K. Pavana and J. Stables, *J. Med. Chem.*, **48**, 6202 (2005).
7. A. Navneet and M. Pradeep, *J. Zhejiang Univ. Sci.*, **6B**, 617 (2005).
8. S. Wu, A. Fluxe, J.M. Janusz, J.B. Sheffer, G. Browning, B. Blass, K. Cobum, R. Hedges, M. Murawsky, B. Fang, G.M. Fadayel, M. Hare and L. Djandjighian, *Bioorg. Med. Chem. Lett.*, **16**, 5859 (2006).
9. A.M.B. Bastos, J.G. Silva, P.I.S. Maia, V.M. Deflon, A.A. Batista, A.V.M. Fer-reira, L.M. Botion, E. Niquet and H. Beraldo, *Polyhedron*, **27**, 1787 (2008).
10. O.M.A. Wafa, M.M.M. El-Din and A.M.M.E. Omar, *Steroids*, **57**, 199 (1992).
11. Y.J. Yang, J.H. Zhao, X.D. Pan and P.C. Zhang, *Chem. Pharm. Bull.*, **58**, 208 (2010).
12. R. Pingaew, S. Prachayasittikul and S. Ruchirawat, *Molecules*, **15**, 988 (2010).
13. F.R. Pavan, P.I.D.S. Maia, S.R.A. Leite, V.M. Deflon, A.A. Batista, D.N. Sato, S.G. Franzblau and C.Q.F. Leite, *Eur. J. Med. Chem.*, **45**, 1898 (2010).
14. D. Sriram, P. Yogeeswari, P. Senthilkumar and D. Sangaraju, *J. Enzym. Inhib. Med. Chem.*, **25**, 105 (2010).
15. V.S. Jevtovic, G. Pelosi, S. Ianelli, R.Z. Kovacevic and S.N. Kaišarevic, *Acta Chim. Slov.*, **57**, 363 (2010).
16. T. Hemalatha, P.K.M. Imran, A. Gnanamani and S. Nagarajan, *Nitric Oxide*, **19**, 303 (2008).
17. S.N. Pandeya, V. Mishra, I. Ponnilavarsan and J.P. Stables, *Polish J. Pharmacol.*, **52**, 283 (2000).
18. S.N. Pandeya, P. Yogeeswari and J. Stables, *Eur. J. Med. Chem.*, **35**, 879 (2000).