Heterocyclic Letters
Vol. 11| No.3|403-408| May-July|2021
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

NOVEL SYNTHESIS AND CHARACTERIZATION OF (E)-1-((4-(4-SUBSTITUTED PHENYL)-1,2,3-THIADIAZOL-5-YL) METHYL)-N-NITRO IMIDAZOLIDIN-2-IMINE DERIVATIVES

Anil Bhagwatrao Chidrawar*

**PG Department & Research Center of Chemistry, Degloor College, Degloor, Dist. Nanded, S.R.T.M.University, Nanded, Maharashtra, INDIA.*
Email: anilchidrawar74@gmail.com,

ABSTRACT
Synthesis of 1,2,3-thiadazolyl imidazole derivatives as neo nicotinic insecticides. Synthesis of this by following steps. 1-(4-substituted phenyl) propan-1-one reacted with semi carbazide hydrochloride in sodium acetate and DMF gives (E)-1-(1-(4-substituted phenyl) propylidene) semi carbazide. This semi carbazide cyclized with thionyl chloride to obtained 4-(4-substituted phenyl)-5-methyl-1,2,3-thiadiazole. Which on further reacted with peroxide, NBS and CCl_4 gives 5-(bromomethyl)-4-(4-substituted phenyl)-1,2,3-thiadiazole. This product again reacted with N-nitroimidazolidin-2-imine, K_2CO_3 and CH_3CN gives (E)-1-((4-(4-substituted phenyl)-1,2,3-thiadiazol-5-yl) methyl)-N-nitroimidazolidin-2-imine.

KEY WORDS
1,2,3-thiadiazole, 2-nitroimino imidazole, semi cabzones, valerophenone

INTRODUCTION
Nitrogen, oxygen and sulfur containing heterocyclic compounds are key building blocks used to develop compounds of biological or medicinal interest to chemists. A vast number of nitrogen containing heterocyclic building blocks have applications in pharmaceuticals and agrochemical research and drug discovery. Heterocyclic compounds also have a practical use as components in dyes, antioxidants, copolymers, bases, and ligands.
There are plenty of imidazole containing drugs, such as angiotensin II antagonistic,[1–4] antimalarial,[5] antibacterial,[6,7] anticancer,[8] anti-inflammatory[9] and anticytokine agents.[10] Moreover, many literature reviews[11–13] showed that the 1,3,4-thiadiazole nuclei and annulated 1,3,4-thiadiazoles have antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radio protective, and antileishmanial activities. These important biological activities encouraged several research groups to find out different methods for synthesis of new thiadiazoles using different synthons, such as thiosemicarbazones, thiocarbazides, dithiocarbonates, thio-acylhydrazines, arylhydrazines, and bithioureas.[14]
The nitroimidazoles compounds are very interesting therapeutically [15–17]. We have many papers to describe their potentials in negligence's disease like amoebic, trichomonal, giardial

and anaerobic bacterial infections.[18,19] However the certain nitroimidazoles are demonstrated in experimental animals of the mutagenic and carcinogenic properties[20,21]. Nifurtimox and metronidazole are nitro heterocyclic that, like other nitro compounds, exhibit antibacterial, antiprotozoal and radio sensitizing properties8. These properties have been related to their electron affinity and more precisely to the reduction potential of the one-electron transfer pair ArNO2./ArNO2 involved in the corresponding redox chain.[22,23] Derivative CL 64855 (2-amino-5-(1-methyl-5-nitro-2- imidazolyl)-1,3,4-thiadiazole) (figure 1), megazol, is a nitroimidazole that is very effective against Trypanosoma cursi, a parasite responsible for Chagas disease in South America[24–27]; the compound is of particular interest since it is active on all strains of the parasite. Owing to the rather low efficiency and severe side effects of nifurtimox and benznidazole, the only available drugs megazol represents a promising alternative. More recently it has been shown that this compound is also highly active against Trypanosoma brucei in association with suramin or melarsoprol.[28,29]

Identification of novel structure leads that may be of use in designing new, potent, selective and less toxic anticancer agents remains a major challenge for medicinal chemistry researchers. Compounds containing thiazole core have diverse biological activities as antihypertension, antifungal, antimicrobial, anti-inflammatory, antioxidant, antitubercular,[30-36] and anticancer. Also, thiazole ring present in many drugs such as Nizatidine, Abafungin, and Amiphenazole

The present work explains synthesis of thiadiazol, isoxazole, benzimidazole, dihydropyridines, and benzodiazepine derivatives, and their biological importance such as insecticidal and fungicidal properties.

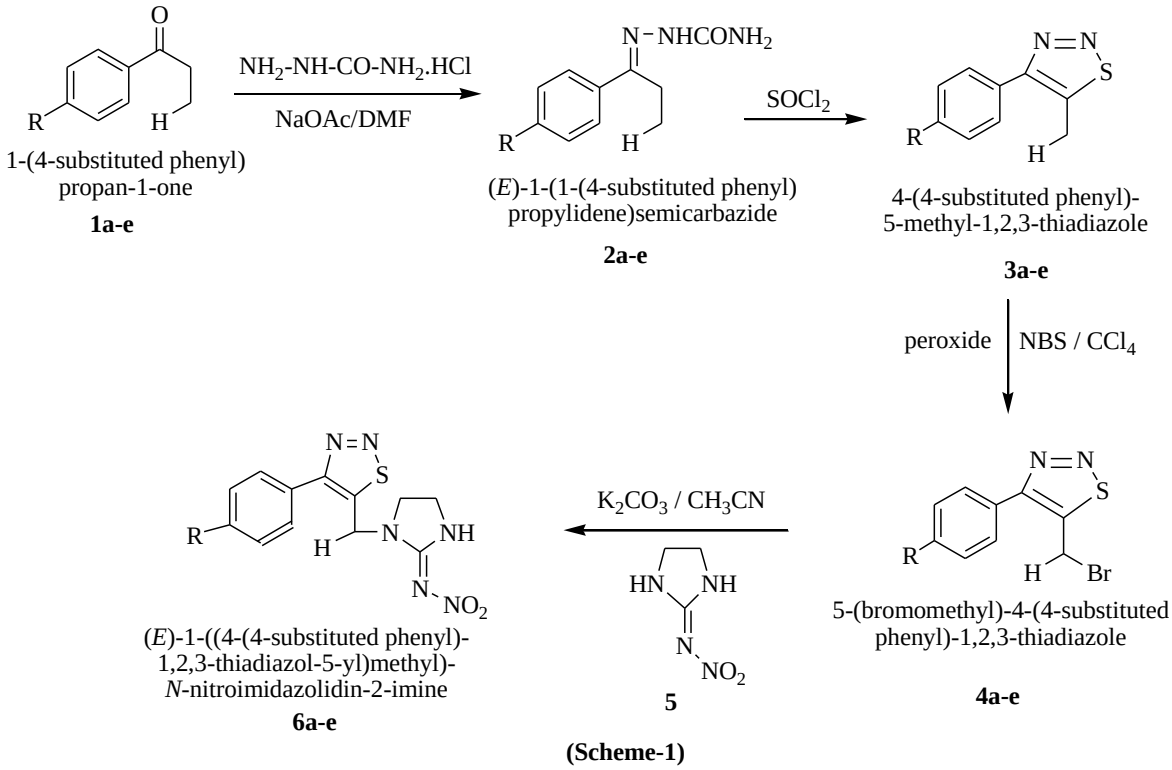
EXPERIMENTAL SECTION

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by Thin layer chromatography.

MATERIAL AND METHODS

Synthesis of (E)-1-((4-(4-substituted phenyl)-1,2,3-thiadiazol-5-yl)methyl)-N-nitroimidazo lidin-2-imine (6a-e) and its derivatives

Synthesis of 1,2,3-thiadazolyl imidazole derivatives as neo nicotinic insecticides. Synthesis of this by reacting 1-(4-substituted phenyl) propan-1-one (1a-e) with semi carbazide hydrochloride in sod. acetate and DMF gives (E)-1-(1-(4-substituted phenyl) propylidene) semi carbazide (2a-e). This semi carbazide cyclized with thionyl chloride to obtained 4-(4-substituted phenyl)-5-methyl-1,2,3-thiadiazole (3a-e). Which on further reacted with peroxide, NBs and CCl_4 gives 5-(bromomethyl)-4-(4-substituted phenyl)-1,2,3-thiadiazole (4a-e). This product again reacted with N-nitroimidazolidin-2-imine (5), K_2CO_3 and CH_3CN gives (E)-1-((4-(4-substituted phenyl)-1,2,3-thiadiazol-5-yl)methyl)-N-nitroimidazolidin-2-imine (6a-e). The sequence of synthetic methodology is depicted in Scheme 1.



(Scheme-1)

R = H, -Cl, -Br, -F, -OMe

1) (E)-1-((4-(4- phenyl)-1,2,3-thiadiazol-5-yl) methyl)-N-nitroimidazolidin-2-imine (6a)

Yield : 66 % , m.p. : 156 ^{0}C

IR: (KBr / cm^{-1}): 3380 (N-H), 3112 (Ar-H), 1620 (C=N), 1495 (-N=N-), 1338 & 1515 (-NO_2); ^{1}H-NMR : (DMSO) : δ 7.48 (d 2H Ar-H), δ 7.32 (d 2H Ar-H), δ 7.22 (d 1H Ar-H), δ 3.81 (s 2H -CH), δ 2.81 (t 4H -CH), δ 2.00 (s 1H N-H); MS: (m/z : RA %): = 305 (M+1); Elemental analysis : $C_{12}H_{12}N_6O_2S$, Calculated: (%) C 47.36, H 3.97, N 27.62, O 10.51, S 10.54 Found (%) : C 47.30, H 3.93, N 27.60, O 10.47, S 10.51

2) (E)-1-((4-(4-chlorophenyl)-1,2,3-thiadiazol-5-yl)methyl)-N-nitroimidazolidin-2-imine (6b)

Yield : 57 % , m.p. : 149 ^{0}C

IR: (KBr / cm^{-1}): 3372 (N-H), 3110 (Ar-H), 1614 (C=N), 1487 (-N=N-), 1330 & 1511 (-NO_2); ^{1}H-NMR : (DMSO) : δ 7.42 (d 2H Ar-H), δ 7.33 (d 2H Ar-H), δ 3.81 (s 2H -CH), δ 2.77 (t 4H -CH), δ 2.00 (s 1H N-H); MS: (m/z : RA %): = 339 (M+1); Elemental analysis : $C_{12}H_{11}ClN_6O_2S$, Calculated: (%) C 42.54, H 3.27, Cl 10.47, N 24.81, O 9.45, S 9.47 Found (%) : C 42.50, H 3.25, Cl 10.43, N 24.78, O 9.41, S 9.44

3) (E)-1-((4-(4-bromophenyl)-1,2,3-thiadiazol-5-yl)methyl)-N-nitroimidazolidin-2-imine (6c)

Yield : 51 % , m.p. : 179 ^{0}C

IR: (KBr / cm^{-1}): 3365 (N-H), 3108 (Ar-H), 1610 (C=N), 1485 (-N=N-), 1331 & 1513 (-NO_2); ^{1}H-NMR : (DMSO) : δ 7.49 (d 2H Ar-H), δ 7.37 (d 2H Ar-H), δ 3.81 (s 2H -CH), δ 2.81 (t 4H -CH), δ 2.00 (s 1H N-H); MS: (m/z : RA %): = 384 (M+1); Elemental analysis : $C_{12}H_{11}BrN_6O_2S$, Calculated: (%) C 37.61, H 2.89, Br 20.85, N 21.93, O 8.35, S 8.37 Found (%) : C 37.58, H 2.85, Br 20.80, N 21.91, O 8.32, S 8.35

4) (E)-1-((4-(4-fluorophenyl)-1,2,3-thiadiazol-5-yl)methyl)-N-nitroimidazolidin-2-imine (6d)

Yield : 53 % , m.p. : 165 ^{0}C

IR: (KBr / cm^{-1}): 3360 (N-H), 3111 (Ar-H), 1611 (C=N), 1480 (-N=N-), 1330 & 1510 ($-NO_2$); ^{1}H-NMR : (DMSO) : δ 7.46 (d 2H Ar-H), δ 7.03 (d 2H Ar-H), δ 3.81 (s 2H -CH), δ 2.77 (t 4H -CH), δ 2.00 (s 1H N-H); MS: (m/z: RA %): = 323 (M+1); Elemental analysis : $C_{12}H_{11}FN_6O_2S$, Calculated: (%) C 44.72, H 3.44, F 5.89, N 26.07, O 9.93, S 9.95 Found (%) : C 44.70, H 3.41, F 5.85, N 26.03, O 9.90, S 9.92

5) (E)-1-((4-(4-methoxyphenyl)-1,2,3-thiadiazol-5-yl)methyl)-N-nitroimidazolidin-2-imine (6e)

Yield : 71 % , m.p. : 155 ^{0}C

IR: (KBr / cm^{-1}): 3364 (N-H), 3110 (Ar-H), 1608 (C=N), 1475 (-N=N-), 1331 & 1502 ($-NO_2$); ^{1}H-NMR : (DMSO) : δ 7.37 (d 2H Ar-H), δ 6.83 (d 2H Ar-H), δ 3.81 (s 2H -CH), δ 3.73 (s 3H -CH), δ 2.77 (t 4H -CH), δ 2.00 (s 1H N-H); MS: (m/z: RA %): = 335 (M+1); Elemental analysis : $C_{13}H_{14}FN_6O_3S$, Calculated: (%) C 46.70, H 4.22, N 25.14, O 14.36, S 9.59 Found (%) : C 46.65, H 4.20, N 21.14, O 14.32, S 9.55

RESULT AND DISCUSSION

Multistep synthesis is the process of taking a readily available compound (one you can buy) and converting it into the compound you need using chemical reactions. Multistep syntheses require more than one step (reaction), and so one or more intermediate compounds are formed along the way. In present work, we report multistep synthesis of novel (E)-1-((4-(4- phenyl)-1,2,3-thiadiazol-5-yl)methyl)-N-nitroimidazolidin-2-imine (6a) by reacting starting with 1-(4-phenyl) propan-1-one, (E)-1-((4-(4-chlorophenyl)-1,2,3-thiadiazol-5-yl)methyl)-N-nitroimidazolidin-2-imine (6b) by reacting starting with 1-(4-chloro phenyl) propan-1-one, (E)-1-((4-(4-bromophenyl)-1,2,3-thiadiazol-5-yl) methyl)-N-nitroimidazolidin-2-imine (6c) by reacting starting with 1-(4-bromo phenyl) propan-1-one, (E)-1-((4-(4-fluorophenyl)-1,2,3-thiadiazol-5-yl) methyl)-N-nitroimidazolidin-2-imine (6d) by reacting starting with 1-(4-fluoro phenyl) propan-1-one and (E)-1-((4-(4-methoxy phenyl)-1,2,3-thiadiazol-5-yl) methyl)-N-nitroimidazolidin-2-imine (6e) by reacting starting with 1-(4-methoxy phenyl) propan-1-one respectively with semi carbazide hydrochloride in sod. acetate and DMF.

CONCLUSIONS

In conclusion a facile multistep synthesis has been developed for the title compounds using readily available starting materials. All the five newly synthesized compounds were screened for antibacterial activity studies at a concentration of 100µ/ml using DMSO as a control and Streptomycin used as standard against gram positive and gram-negative bacteria. Some compounds were found to possess a broad-spectrum activity. However, the activities of the tested compounds are much less than those of standard antibacterial agents used.

ACKNOWLEDGEMENTS

The authors are thankful to the Principal, Degloor College, Degloor for providing laboratory facilities and the Director, Indian Institute of Chemical Technology, Hyderabad for providing spectra.

REFERENCES

i. Guo X.-Z., Shi L., Wang R., Liu X.-X., Li B.-G., Lu X.-X., Bioorg. Med. Chem., 16, 10301–10310 (2008).

ii. Roumelioti P., Polevaya L., Zoumpoulakis P., Giatas N., Mutule I., Keivish T., Zoga A., Vlahakos D., Iliodromitis E., Kremastinos D., Grdadolnik S. G., Mavromoustakos T., Matsoukas J., Bioorg. Med. Chem. Lett., 12, 2627–2633 (2002).

iii. Shafiee A., Hadi zadeh F., Noori S.-B., J. Heterocycl. Chem., 37, 1015–1018 (2000).
iv. Farghaly T. A., Gomha S.-M., Abdalla M.-M., Arch. Pharm. Res., 37, 306–314 (2014).
v. Pfaller M. A., Krogstad D.-J., Am. J. Trop. Med. Hyg., 32, 660– 665 (1983).
vi. Gomha S.-M., Hassaneen H. M. E., Molecules, 16, 6549–6560 (2011).
vii. Khabnadideh S., Rezaei Z., Khalafi-Nez had A., Ba hrinajafi R., Mohamadi R., Farrokhroz A. A., Bioorg. Med. Chem. Lett., 13, 2863–2865 (2003).
viii. Li W.-T., Hwang D. R., Song J.-S., Chen C. P., Chuu J.-J., Hu C. B., Lin H. L., Huang C. L., Huang C. Y., Tseng H. Y., Lin C. C., Chen T. W., Lin C. H., Wang H. S., Shen C. C., Chang C. M., Chao Y. S., Chen C. T., J. Med. Chem., 53, 2409–2417 (2010).
ix. Lombardino J. G., Wiseman E. H., J. Med. Chem., 17, 1182–1188 (1974).
x. Laufer S. A., Striegel H. A., Gerd K. W., J. Med. Chem., 45, 4695–4705 (2002).
xi. Kushwaha N., Kushwaha S. K. S., Rai A. K., Inter. J. Chem. Res., 4, 517–531 (2012).
xii. Singh A. K., Mishra G., Jyoti K., J. App. Pharm. Sci., 1, 44–49 (2011).
xiii. Siddiqui N., Ahuja P., Ahsan W., Pandeya S. N., Alam M. S., J. Chem. Pharm. Res., 1, 19–30 (2009).
xiv. Shawali A. S., J. Adv. Res., 5, 1–17 (2014).
xv. Nair M D & Nagarajan K. Nitroimidazoles as chemotherapeutic agent. Progress in Drug Research, 27, 163- 252 (1983).
xvi. Edwards D., J. Antimicrob. Chemother., 31, 1, 9-20 (1993)
xvii. Al-Soud Y. A. Al-Masoudi, N. A., Clercq, E. De, Paneccoque C., Heteroatom Chemistry, 18, 4, 333-340 (2007)
xviii. Global Plan to Combat Neglected Tropical Diseases 2008–2015. World Health Organization WHO 2007
xix. De Castro, S.L., The challenge of Chagas disease chemotherapy: an update of drugs assayed against, Trypanosoma cruzi.Acta Tropica, 53, 83-98 (1993)
xx. López M.M.N. and Carballo M.A., Toxicology Letters, 180, 46–52 (2008)
xxi. Buschini A., Ferrarini L., Franzoni S., Galati S., Lazzaretti M., Mussi F., Albuquerque C.N., Zucchi T. M. A. D., Poli P., Journal of Parasitology Research, 1, 11 (2009).
xxii. Raether W, Hanel H., Parasitology research, 90, 1, 19-39 (2003).
xxiii. Viode C., De Albuquerque C., Chauviere G., Houee-Levin C., Perie J., New Journal of Chemistry, 21, 1331-1338 (1997).
xxiv. Asato, G., Berkellhammer, G. Science, 162, 1146 (1968) Cristina Northfleet de Albuquerque et al. Asian Journal of Biomedical and Pharmaceutical Sciences; 4 ,31, 10-14 (2014).
xxv. Asato G., Berkellhammer G., Journal Medicinal Chemistry, 15, 10, 1086-1088 (1972).
xxvi. Albright J.D., Shepherd R.G., Journal Heterocyclic Chemistry, 10, 6, 899- 907 (1973)
xxvii. Albuquerque C. N., Perie J. J., Brazilian Journal of Pharmaceutical Sciences, 35, 1, 57-64 (1999).
xxviii. Enanga B, Keita M, Chauviere G, Dumas M, Bouteille B., Tropical medicine & international health: TM & IH, 3, 9, 736-741 (1998).
xxix. Darsaud A., Chevrier C., Bourdon L., Dumas M., Buguet A., Bouteille B., Tropical Medicine & International Health, 9, 1, 83-91 (2004).
xxx. Karegoudar P, Karthikeyan M. S., Prasad D.J., Mahalinga M, Holla B.S., Kumari N.S., Eur J Med Chem, 43, 261–267 (2008).
xxxi. Gomha S. M., Kheder N. A., Abdelaziz M. R., Mabkhot Y. N., Alhajoj A. M., Chem. Central J., 11, 25, (2017).
xxxii. Gomha S. M., Abdel-Aziz H. A., Bull Kor Chem Soc, 33, 2985–2990 (2012).
xxxiii. Kheder N. A., Riyadh S. M., Asiry A. M., Chem Pharm Bull, 61, 504–510 (2013).

xxxiv. Sharma P. K., Sawhney S. N., Gupta A., Singh G.B., Bani S., Indian J Chem, 37B, 376–381 (1998).
xxxv. Shih M. H., Ying K. F., Bioorg Med Chem, 12, 4633–4643 (2004).
xxxvi. Shiradkar M., Kumar G. V. S., Dasari V., Tatikonda S., Akula K. C., Shah R., Eur J Med Chem, 42, 807–816 (2007).

Received on May 30, 2021.