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

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**ABSTRACT**

Synthesis of 1,2,3-thiadiazolyl 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<sub>4</sub> gives 5-(bromomethyl)-4-(4-substituted phenyl)-1,2,3-thiadiazole. This product again reacted with N-nitroimidazolidin-2-imine, K<sub>2</sub>CO<sub>3</sub> and CH<sub>3</sub>CN 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,<sup>1-4</sup> antimalarial,<sup>5</sup> antibacterial,<sup>6,7</sup> anticancer,<sup>8</sup> anti-inflammatory<sup>9</sup> and anticytokine agents.<sup>10</sup> Moreover, many literature reviews<sup>11-13</sup> 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 bithiouras.<sup>14</sup> The nitroimidazoles compounds are very interesting therapeutically<sup>15-17</sup>. We have many papers to describe their potentials in negligence's disease like amoebic, trichomonal, giardial



and anaerobic bacterial infections.<sup>18,19</sup> However the certain nitroimidazoles are demonstrated in experimental animals of the mutagenic and carcinogenic properties.<sup>20,21</sup> Nitroimidazole and metronidazole are nitro heterocyclic that, like other nitro compounds, exhibit antibacterial, antiprotozoal and radio sensitizing properties.<sup>22</sup> These properties have been related to their electron affinity and more precisely to the reduction potential of the one-electron transfer pair  $ArNO_2/ArNO$  involved in the corresponding redox chain.<sup>22,23</sup> Derivative Cl. 64855 (2-amino-3-(1-methyl-3-nitro-2-imidazolyl)-1,3,4-thiadiazole) (figure 1), megarol, is a nitroimidazole that is very effective against *Trypanosoma cruzi*, a parasite responsible for Chagas disease in South America<sup>24-26</sup>; 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 nitroimidazole and benzimidazole, the only available drug megarol 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.<sup>28,29</sup>

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,<sup>30-32</sup> and anticancer. Also, thiazole ring present in many drugs such as Nizatidine, Abafungin, and Amphiphenazole.

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

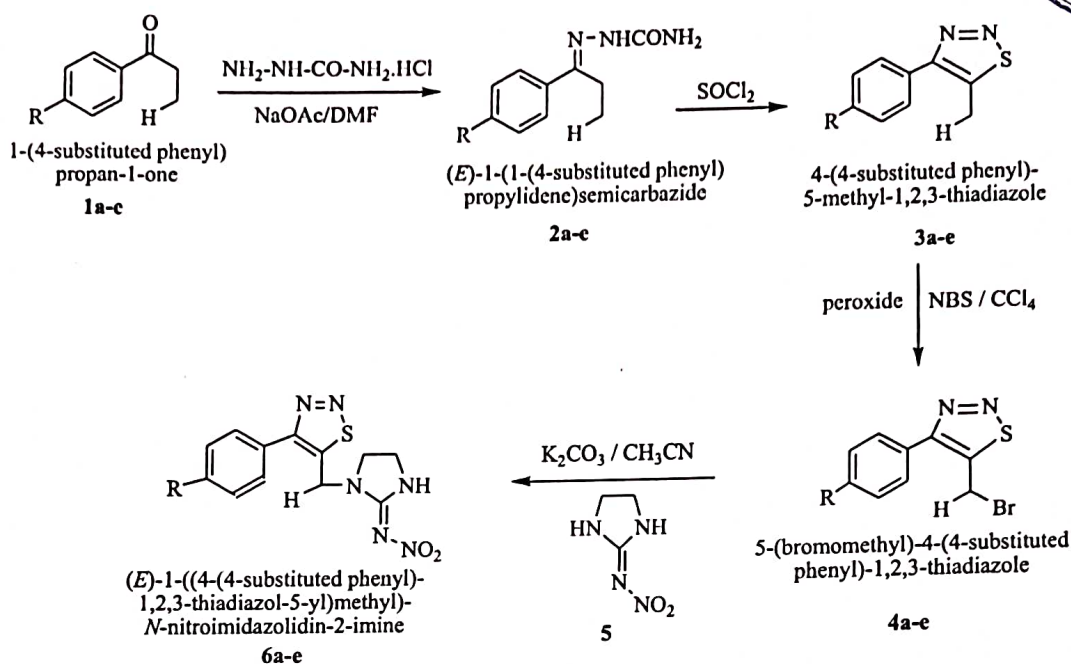
## EXPERIMENTAL SECTION

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, <sup>1</sup>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 II 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-nitroimidazolidin-2-imine (6a-e) and its derivatives**

Synthesis of 1,2,3-thiadiazolyl 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<sub>4</sub> gives 5-(bromomethyl)-4-(4-substituted phenyl)-1,2,3-thiadiazole (4a-e). This product again reacted with N-nitroimidazolidin-2-imine (5), K<sub>2</sub>CO<sub>3</sub> and CH<sub>3</sub>CN 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 °C

IR: (KBr / cm<sup>-1</sup>): 3380 (N-H), 3112 (Ar-H), 1620 (C=N), 1495 (-N=N-), 1338 & 1515 (-NO<sub>2</sub>);  
<sup>1</sup>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<sub>12</sub>H<sub>12</sub>N<sub>6</sub>O<sub>2</sub>S, 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 °C

IR: (KBr / cm<sup>-1</sup>): 3372 (N-H), 3110 (Ar-H), 1614 (C=N), 1487 (-N=N-), 1330 & 1511 (-NO<sub>2</sub>);  
<sup>1</sup>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<sub>12</sub>H<sub>11</sub>ClN<sub>6</sub>O<sub>2</sub>S, 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 °C

IR: (KBr / cm<sup>-1</sup>): 3365 (N-H), 3108 (Ar-H), 1610 (C=N), 1485 (-N=N-), 1331 & 1513 (-NO<sub>2</sub>);  
<sup>1</sup>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<sub>12</sub>H<sub>11</sub>BrN<sub>6</sub>O<sub>2</sub>S, 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 °C



IR: (KBr /  $\text{cm}^{-1}$ ): 3360 (N-H), 3111 (Ar-H), 1611 (C=N), 1480 (-N=N-), 1330 & 1510 (-NO<sub>2</sub>);  
<sup>1</sup>H-NMR : (DMSO) :  $\delta$  7.46 (d 2H Ar-H),  $\delta$  7.03 (d 2H Ar-H),  $\delta$  3.81 (s 2H -CH),  $\delta$  2.77 (t 4H -CH),  $\delta$  2.00 (s 1H N-H); MS: (m/z: RA %): = 323 (M+1); Elemental analysis : C<sub>12</sub>H<sub>11</sub>FN<sub>6</sub>O<sub>2</sub>S, 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 °C

IR: (KBr /  $\text{cm}^{-1}$ ): 3364 (N-H), 3110 (Ar-H), 1608 (C=N), 1475 (-N=N-), 1331 & 1502 (-NO<sub>2</sub>);  
<sup>1</sup>H-NMR : (DMSO) :  $\delta$  7.37 (d 2H Ar-H),  $\delta$  6.83 (d 2H Ar-H),  $\delta$  3.81 (s 2H -CH),  $\delta$  3.73 (s 3H -CH),  $\delta$  2.77 (t 4H -CH),  $\delta$  2.00 (s 1H N-H); MS: (m/z: RA %): = 335 (M+1); Elemental analysis : C<sub>13</sub>H<sub>14</sub>FN<sub>6</sub>O<sub>3</sub>S, Calculated: (%) C 46.70, H 4.22, N 25.14, O 14.36, S 9.59 Found (%) : C 46.65, H 4.20, N 25.14, 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 100  $\mu$ /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.

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