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Synthesis and Characterization of New 1, 3, 4-Thiadiazoles Substituted with Imidazolidine Moiety

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Abstract: ***2-amino-5-mercapto-1,3,4-thiadiazolewas introduced in condensation reactions with both terephthaldehyde and 4-dimethylaminobenzaldehyde to yield imine derivatives1a and 1b respectively. The resulting imine1awas treated with amino acids L-valine and L-cysteine, also the imine 1b wasreacted with amino acids L-cysteine, L-isoleucine and L-tyrosine to obtain five new imidazolidine derivatives2a-erespectively.2-amino-5-mercapto-1,3,4-thiadiazolewas also converted to the corresponding azoaldehyde derivative3 through coupling reaction of its diazonium salt with 4-hydroxybenzaldehyde dissolved in sodium hydroxide solution. The resulting azoaldehyde 3 was reacted with2-amino-5-mercapto-1,3,4-thiadiazoleto give the corresponding azoimine derivative 4. Treatment of the resulting azoimine 4 with amino acids glycine, L-valine and L-cysteine afforded three new imidazolidine derivatives5a-crespectively.***

Keywords: 1,3,4-thiadiazoles, imines, imidazolidines

1. Introduction

Thiadiazoles are clear to yellowish liquids which are soluble in alcohol, ether and slightly soluble in water; they are starting material for numerous chemical compounds including sulphur drugs[(1)]. Thiadiazoles are easily metabolized by biochemical reactions and they are non-carcinogenic in nature[(2)]. Thiadiazoles and their derivatives exhibit wide range of pharmacological activities such as antimicrobial activity[(3)], antidepressant, cardiotonic[(4)], antibacterial activity against *Klebsiella pneumonia*[(5)], antitubercular[(6,7)],anticonvulsant[(8)], antileshmanial , analgesic[(9)],antiinflammtory[(10)], anticancer[(11)], phosphodiesterase inhibitors[(12)] and effect on Tyrosinase enzyme[(13)].This diversity of biological activity may be due to the presence of -N=C-S moity[(14,15)]. There are four isomers of thiadiazole , among these four isomers 1,3,4-thiadiazole is the most thermally stable; which is only isomer doesn´t contain any sulphur- nitrogen bond[(16)]. 1,3,4-thiadiazole relatively stable in aqueous acid solutions but the nucleus can undergo ring cleavage by aqueous base solutions[(17)].

Imidazolidines are compounds of highly conserved five-membered ring nitrogen-containing pharmacophores; and thus imidazolidines have attracted attention due to their important roles as building blocks in the synthesis of biologically active compounds[(18)]. Imidazolidine derivatives possess some interesting biological activities such asantiinflammtory, antiviral, antifungal,antihypertensive, antigastrohelcosis and antiasthmatic[(19,20)]. Thus, in this article, we reported here the synthesis of 1,3,4-thiadiazole derivatives containing biologically active imidazolidine moiety, which might have some biological activity.

2. Experimental

2.1. General

The chemicals used were purchased fromMerck, BDH, sigma Aldrich and CDH and were used without further purification. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F_{254}). The progress of reactions were monitored by TLC and visualized by development of the TLC plates with iodine vapor. Melting points were determined on an Electro thermal Stuart SMP 30 capillary melting point apparatus. Infrared spectra were recorded on SHIMADZU FTIR-8400S Infrared Spectrophotometer as potassium bromide discs. ^{1}H NMR spectra were collected on NMR spectrometer, Bruker 2009 spectrometer at 400 MHz in DMSO-d_6 as solvent and TMS as an internal standard at Kashan University, Iran.Elemental Analysis (CHNS.) was carried out with Perkin Elmer 300A Elemental Analyzer at Kashan University, Iran.Azoaldehyde derivative**4**was prepared following the method described by Acton [(2)].

2.2. Chemical Methods

Synthesisof5,5'-(((1E,1'E)-1,4-phenylenebis(methanylidene))bis(azanylylidene))bis(1,3,4-thiadiazole-2-thiol) 1a:
Terephthaldehyde(0.67 g, 5 mmol) was dissolved in (35 mL) of absolute ethanol, then 2-Amino-5-mercapto-1,3,4-thiadiazole (1.33 g , 10mmol) was added. The reaction mixture was refluxed with stirring on a water bath at 65^{o}C for 12 h and monitored by TLC. The mixture was then allowed to cool down to room temperature , the colored precipitate was filtered and recrystallized from ethanol: IR (cm^{-1}):3194$_{br}$ (υ N-H, thione form and υ C-H, benzene, vib. coupling), 2972and 2885 (υ N-H, intramolecularly hydrogen bonded, thione form), 1691(υ C=N, imine), 1562and 1508(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling), 1051 (υ C=S, thione form), 750 ($\delta_{o.o.p.}$ C-H, benzene)); ^{1}H NMR: δ =2.5 (DMSO solvent), 3.4 (H_2O in DMSO),7.09–7.96(m, 4H, Ar-H), 8.10 (s, 2H,2×N-H, thione forms), 10.12 (s, 2H,2×CH=N, imine).

Synthesis of (Z)-5-((4-(dimethylamino) benzylidene) amino)-(1,3,4-thiadiazole-2-thiol) 1b:
4-Dimethylaminobenzaldehyde(0.745 g, 5 mmol) was dissolved in (30 mL) of absolute ethanol, then 2-Amino-5-mercapto-1,3,4-thiadiazole (0.665 g , 5mmol) was added.

The reaction mixture was refluxed with stirring on a water bath at 65°C for 8 h and monitored by TLC. The mixture was then allowed to cool down to room temperature , the colored precipitate was filtered and recrystallized from ethanol: IR (cm^{-1}):3090_{br} (υ N-H, thione form and υ C-H, benzene, vib. coupling), 2953and 2885 (υ C-H3 andυ N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1597(υ C=N, imine), 1529(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling), 1060 (υ C=S, thione form), 775 ($\delta_{o.o.p.}$ C-H, benzene); ^{1}H NMR: δ =2.49 (DMSO solvent), 3.02 (s, 6H, 2×N-CH_3), 6.62–6.64(m, 2H, Ar-H), 7.59–7.68 (m, 2H,Ar-H), 8.20 (s, 1H, N-H, thione form), 9.60 (s, 1H, CH=N, imine).

General procedure for the synthesis of imidazolidine derivatives (2a,2b):

A mixture of bisimine derivative**1a** (0.729 g, 2 mmol) and L-valine or L-cysteine (4mmol) in tetrahydrofuran (25 mL**)** was refluxed on a water bath at 70 ºC for about 24 h and monitored by TLC. The mixture was then allowed to cool down to room temperature, the solvent was evaporated under reduced pressure to give colored solid, driedand recrystallized from ethanol.

2,2'-(1,4-phenylene)bis(5-isopropyl-3-(5-mercapto-1,3,4-thiadiazol-2-yl)imidazolidin-4-one)2a:IR (cm^{-1}):3134_{br} (υ N-H, imidazolidine,υ N-H, thione form and υ C-H, benzene, vib. coupling), 2962and 2887 (υ C-H3 and υ N-H, intramolecularly hydrogen bonded, thione form, vib.coupling), 1597(υ C=O, amide, imidazolidine), 1504(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling), 1041 (υ C=S, thione form), 773 and 680 ($\delta_{o.o.p.}$ C-H, benzene); ^{1}H NMR: δ =0.9 (d, 12H, 4×CH_3), 1.8 (m, 2H, 2×C**H**$(CH_3)_2$), 2.48 (DMSO solvent), 3.34 (H_2O in DMSO),3.64 (s, 2H, 2×O=C-C**H**-N, imidazolidine), 4.2 (s, 2H, 2×SH), 5.26 (s, 2H, 2×N-C**H**-N, imidazolidine), 7.10–7.93(m, 4H, Ar-H), 8.19 (s, 2H,2×N-H, thione forms), 8.30 (s, 2H,2×N-H, imidazolidine).Anal. Calcd. for $C_{22}H_{26}N_8O_2S_4$: C, 46.96; H, 4.66; N, 19.91; S, 22.79 Found C, 47.28; H, 4.62; N, 20.22; S, 22.47.

2,2'-(1,4-phenylene)bis(3-(5-mercapto-1,3,4-thiadiazol-2-yl)-5-(mercaptomethyl) imidazolidin-4-one) 2b:IR (cm^{-1}):3356_{br} (υ N-H, imidazolidine andυ N-H, thione form, vib. coupling),3053 and 3032(υ C-H, benzene), 2939and 2877 (υ C-H2 and υ N-H, intramolecularly hydrogen bonded, thione form, vib. coupling),1612(υ C=O, amide, imidazolidine), 1568 (υ C=C, benzene and υ C=N, thiadiazole, vib. coupling), 1053 (υ C=S, thione form), 844 ($\delta_{o.o.p.}$ C-H, benzene);^{1}H NMR: δ =1.4 (s, 2H,2×CH_2-S**H**),1.8 (m, 4H, 2×C**H**$_2$-SH), 2.5 (DMSO solvent), 3.3 (H_2O in DMSO),3.6 (s, 2H, 2×O=C-C**H**-N, imidazolidine),4.2 (s, 2H, 2×SH, thiadiazole), 5.26 (s, 2H, 2×N-C**H**-N, imidazolidine), 7.09–7.38(m, 4H, Ar-H),8.16 (s, 2H, 2×N-H, imidazolidine). Anal. Calcd. for $C_{18}H_{18}N_8O_2S_6$: C, 37.88; H, 3.18; N, 19.63; S, 33.71 Found C, 38.09; H, 3.26; N, 19.74; S, 34.03.

General procedure for thesynthesis of imidazolidine derivatives (2c,2d,2e):

A mixture of mine derivative**1b** (0.525 g, 2 mmol) and L-cysteine or L-isoleucine or L-tyrosine (2mmol) in tetrahydrofuran (25 mL**)** was refluxed on a water bath at 70 ºC for about 24 h and monitored by TLC. The mixture was then allowed to cool down to room temperature, the solvent was removed under reduced pressure to give colored solid, driedand recrystallized from ethanol.

2-(4-(dimethylamino)phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-5-(mercaptomethyl)imidazolidin-4-one2c:IR (cm^{-1}):3080_{br} (υ N-H, imidazolidine,υ N-H, thione formand υ C-H, benzene, vib. coupling), 2993and 2887 (υ C-H3 andυ N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 2958 and 2825 (υ C-H2),1593(υ C=O, amide, imidazolidine), 1533(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling), 1058 (υ C=S, thione form), 817 and 775 ($\delta_{o.o.p.}$ C-H, benzene); ^{1}H NMR: δ =1.4 (s, 1H,CH_2-S**H**),2.31 (s, 1H, C**H**$_2$-SH), 2.48-249(DMSO solvent), 3.02 (s, 6H, 2×N-CH_3), 3.37 (s, 1H, O=C–C**H**-N, imidazolidine),6.7 (s, 1H, N-C**H**-N, imidazolidine), 7.10(m, 2H, Ar–H), 7.65–7.67 (m, 2H, Ar–H), 8.4(s, 1H, N–H, thione form)9.65, (s, 1H, N–H, imidazolidine); Anal. Calcd. for $C_{14}H_{17}N_5OS_3$: C, 45.75; H, 4.66; N, 19.05; S, 26.17 Found C, 46.05; H, 4.79; N, 19.22; S, 26.41.

5-(sec-butyl)-2-(4-(dimethylamino)phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)imidazolidin-4-one 2d:IR (cm^{-1}):3084_{br} (υ N-H, imidazolidine,υ N-H, thione formand υ C-H, benzene, vib. coupling), 2962and 2889 (υ C-H3 andυ N-H, intramolecularly hydrogen bonded, thione form, vib. coupling),2615(υ S-H,thiol form),1591(υ C=O, amide, imidazolidine), 1516(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling), 1058 (υ C=S, thione form), 775 and 671 ($\delta_{o.o.p.}$ C-H, benzene); ^{1}H NMR: δ =0.9 (m, 6H, C**H**$_3$-CH_2 andC**H**$_3$-CH), 1.5 (m, 2H,CH_2), 1.9 (m, 1H,CH_3C**H**-CH_2), 2.5(DMSO solvent),3.02 (s, 6H, 2×N-CH_3),3.5 (s, 1H, O=C-C**H**-N, imidazolidine),6.7 (s, 1H, N-C**H**-N, imidazolidine),), 7.10 (m, 2H, Ar-H), 7.54–7.67 (m, 2H, Ar-H), 8.1 (s, 1H, N–H, thione form)9.65, (s, 1H, N-H, imidazolidine); Anal. Calcd. for $C_{17}H_{23}N_5OS_2$: C, 54.09; H, 6.14; N, 18.55; S, 16.99 Found C, 54.43; H, 6.26; N, 18.39; S, 16.71.

2-(4-(dimethylamino)phenyl)-5-(4-hydroxyphenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl) imidazolidin-4-one 2e:IR (cm^{-1}): 3446_{br}(υ O-H),3203 (υ N-H, imidazolidine),3091(υ N-H, thione form),3018(υ C-H, benzene), 2956and 2867 (υ C-H3 andυ N-H, intramolecularly hydrogen bonded, thione form, vib. coupling),2600(υ S-H,thiol form),1589(υ C=O, amide, imidazolidine), 1531and1514(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling),1080 (υ C=S, thione form), 777($\delta_{o.o.p.}$ C-H, benzene); ^{1}H NMR: δ = 2.5 (DMSO solvent), 3.02 (ss, 6H, 2×N-CH_3), 3.38 (s, 1H, O=C–C**H**-N, imidazolidine),6.70(s, 1H, N-C**H**-N, imidazolidine), 6.88–7.72(m, 8H, Ar-H),8.04(s, 1H, N-H, thione form), 9.63 (s, 1H, O-H),9.65, (s, 1H, N-H, imidazolidine). Anal. Calcd. for $C_{19}H_{19}N_5O_2S_2$: C, 55.19; H, 4.63; N, 16.94; S, 15.51 Found C, 55.40; H, 4.57; N, 17.29; S, 15.39.

Synthesis of 4-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-yl)diazenyl)benzaldehyde3:was prepared followingthe method described by Acton[21] as dark orange solid, mp 129-131°C, yield55**%**;IR **(**cm^{-1}): 3284_{br} (υ O-H),3095 (υ N-H, thione form and υ C-H,benzene, vib. coupling), 2962 and 2899 (υ N-H, intramolecularly hydrogen bonded, thione form), 2829 and 2700 (υ C-H, aldehyde),1627 (υ C=O, aldehyde), 1552 and 1498(υ C=C,benzene and υ C=N, thiadiazole, vib. coupling), 1039($\upsilon_{C=S}$, thione form),837 (δ o.o.p. C-H, benzene rings).

Synthesis of 2-((E)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)-4-((E)-((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)phenol 4:

Azoaldehyde derivative **3**(1.33 g, 5 mmol) was dissolved in (30 mL) of absolute ethanol, then 2-Amino-5-mercapto-1,3,4-thiadiazole (0.665 g , 5mmol) was added. The reaction

mixture was refluxed with stirring on a water bath at 65°C for 8 h and monitored by TLC. The mixture was then allowed to cool down to room temperature , the colored precipitate was filtered and recrystallized from ethanol. IR (cm^{-1}):3267_{br} (υ O-H),3099 (υ N-H, thione form and υ C-H, benzene, vib. coupling), 2949 and 2802 (υ N-H, intramolecularly hydrogen bonded, thione form),1610 (υ C=N, imine), 1554 and 1502(υ C=C,benzene and υ C=N, thiadiazole, vib. coupling), 1061(υC=S, thione form), 715 (δ o.o.p. C-H, benzene rings); ^{1}H NMR: δ = 2.48 (DMSO solvent), 3.7 (H_2O in DMSO)6.8–7.7(m, 3H, Ar-H), 8.7 and 8.8 (ss, 2H, 2×N-H, thione forms), 9.6 (s, 1H,CH=N, imine),10.60 (s, 1H, O-H).

General procedure for the synthesis of imidazolidine derivatives (5a-c):

A mixture of azomine derivative**4** (0.762g, 2 mmol) and glycine,L-valine or L-cysteine (2 mmol) in tetrahydrofuran (25 mL**)** was refluxed on a water bath at 70 ºC for about 24 h and monitored by TLC. The mixture was then allowed to cool down to room temperature, the solvent was removed under reduced pressure to give colored solid, driedand recrystallized from ethanol.

(E)-2-(4-hydroxy-3-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl) imidazolidin-4-one 5a:IR (cm^{-1}): 3255_{br}(υ O-H, υ N-H, imidazolidine, υ N-H, thione form and υ C-H, benzene, vib. coupling), 2968and 2877 (υ C-H2, imidazolidine and υ N-H , intramolecularly hydrogen bonded, thione form, vib. coupling), 1566(υ C=O, amide, imidazolidine), 1514and1452(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling),1047 (υ C=S, thione form), 715 ($\delta_{o.o.p.}$ C-H, benzene);^{1}H NMR: δ = 2.5 (DMSO solvent), 3.6 (m, 2H, O=C–C**H$_2$**-N, imidazolidine),6.5(s, 1H, N-C**H**-N, imidazolidine), 7.10–7.85(m, 3H, Ar-H), 8.18(s, 2H, 2×N-H, thione forms),9.3 (s, 1H, N-H, imidazolidine), 13.2 (s, 1H, O-H). Anal. Calcd. for $C_{13}H_{10}N_8O_2S_4$: C, 35.61; H, 2.30; N, 25.55; S, 29.25 Found C, 35.78; H, 2.23; N, 25.92; S, 29.19.

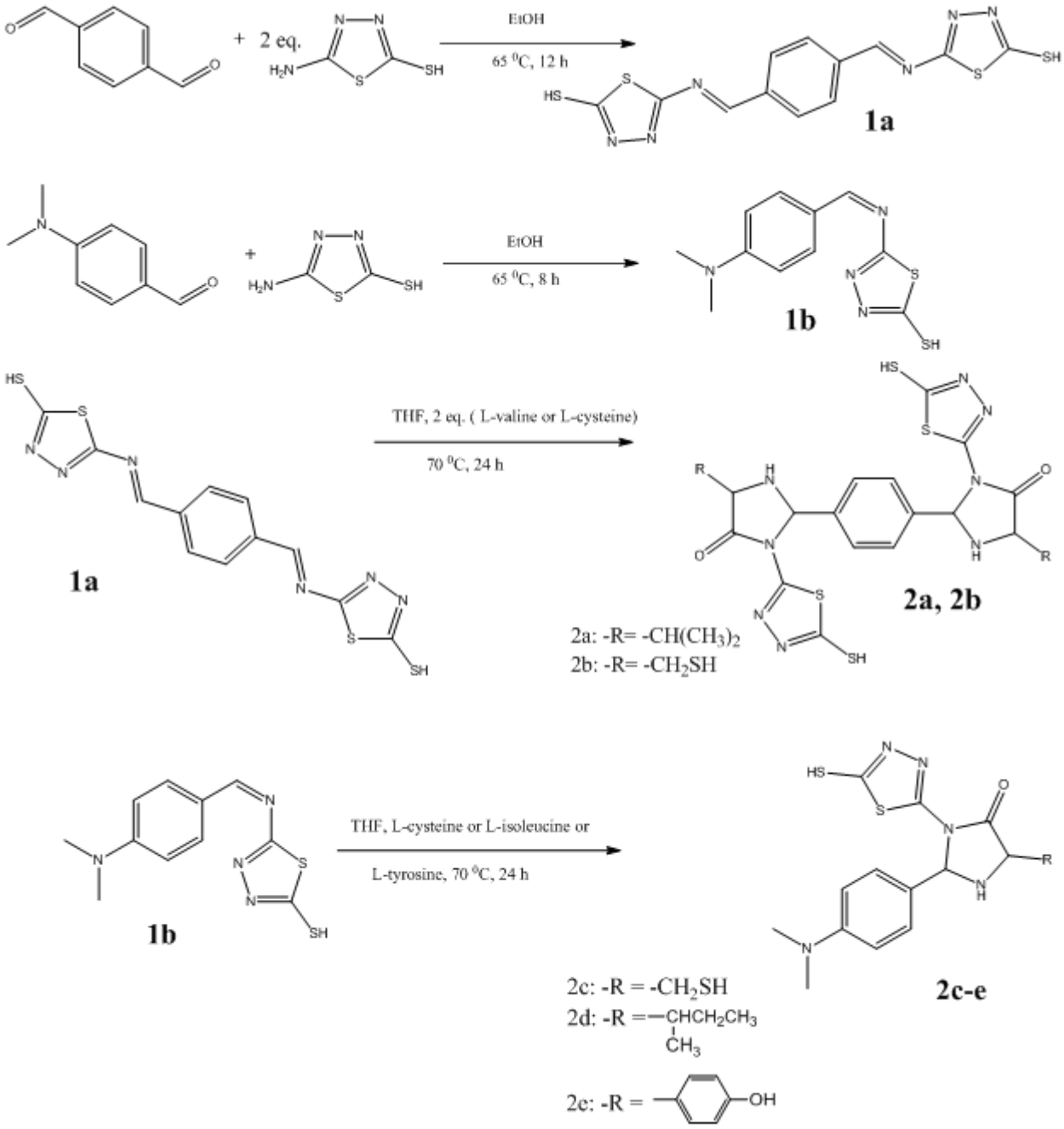
2-(4-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-5-isopropyl-3-(5-mercapto-1,3,4-thiadiazol-2-yl)imidazolidin-4-one 5b:IR (cm^{-1}): 3188_{br}(υ O-H, υ N-H, imidazolidine, υ N-H, thione form and υ C-H, benzene, vib. coupling), 2960and 2879 (υ C-H3, and υ N-H , intramolecularly hydrogen bonded, thione form, vib. coupling), 1568(υ C=O, amide, imidazolidine), 1504(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling),1041 (υ C=S, thione form), 775 ($\delta_{o.o.p.}$ C-H, benzene);^{1}H NMR: δ = 0.9 (m, 6H, CH(C**H$_3$**)$_2$, 2.48 (DMSO solvent), 2.86 (m, 1H,C**H**(CH_3)$_2$, 3.69 (m, 1H, O=C-C**H**-N, imidazolidine),5.3 (s, 1H, N-C**H**-N, imidazolidine), 7.10–7.82(m, 3H, Ar-H), 8.18(s, 2H, 2×N–H, thione forms)9.3, (s, 1H, N-H, imidazolidine),13.3 (s, 1H, O-H). Anal. Calcd. for $C_{16}H_{16}N_8O_2S_4$: C, 39.99; H, 3.36; N, 23.31; S, 26.69 Found C, 39.78; H, 3.31; N, 23.10; S, 26.85.

(E)-2-(4-hydroxy-3-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-5-(mercaptomethyl)imidazolidin-4-one 5c:IR (cm^{-1}): 3381_{br}(υ O-H), 3232(υ N-H, imidazolidine, υ N-H, thione formandυ C-H, benzene, vib. coupling), 2949and 2877 (υ C-H2 and υ N-H , intramolecularly hydrogen bonded, thione form, vib. coupling), 1566(υ C=O, amide, imidazolidine), 1527and1487(υ C=C, benzene and υ C=N, thiadiazole, vib. coupling),1043 (υ C=S, thione form), 845 ($\delta_{o.o.p.}$ C-H, benzene); ^{1}H NMR: δ =1.8 (s, 2H, CH_2-S**H)**, 2.1 (s, 2H, **CH_2**-SH),2.49 (DMSO solvent), 3.7 (s, 1H, O=C-C**H**-N, imidazolidine),5.4 (s, 1H, N-C**H**-N, imidazolidine), 7.1–7.8(m, 3H, Ar-H), 8.2(s, 2H, 2×N–H, thione forms),9.7(s, 1H, N-H, imidazolidine),13.2 (s, 1H, O-H). Anal. Calcd. for $C_{14}H_{12}N_8O_2S_5$: C, 34.70; H, 2.50; N, 23.12; S, 33.08 Found C, 35.04; H, 2.26; N, 23.29; S, 32.91.

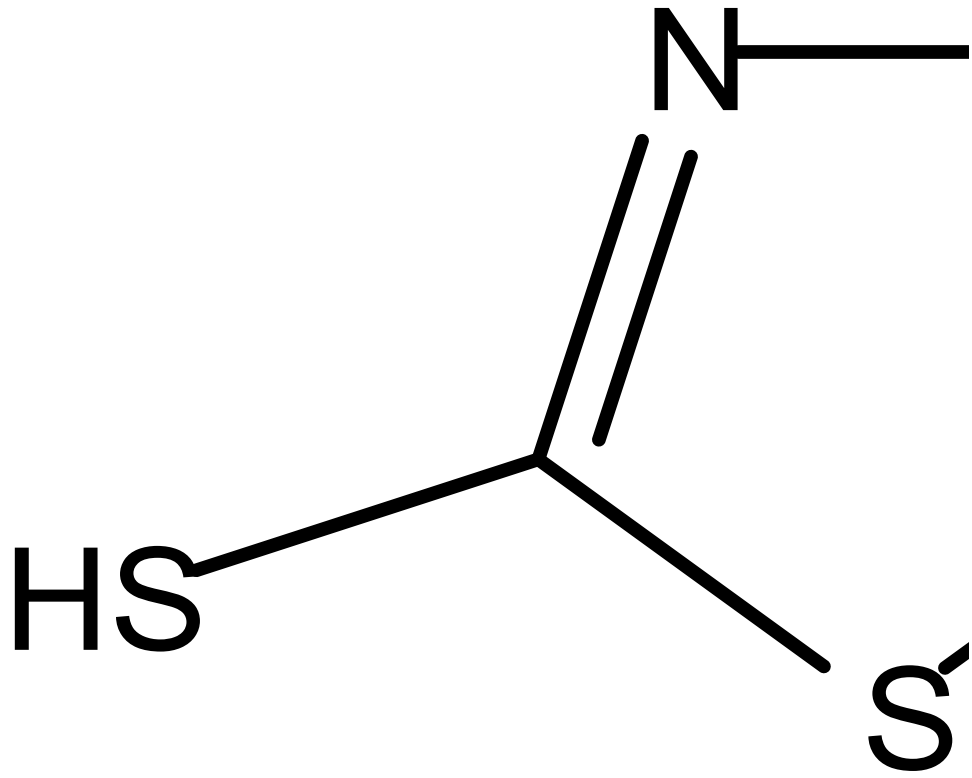
3. Results and Discussion

3.1 Chemistry

The precursors imines **1a** and**1b** were synthesized by reacting the aromatic aldehydes (terephthaldehyde and 4-dimethylaminobenzaldehyde) with 2-amino-5-mercapto-1,3,4-thiadiazole in absolute ethanol as indicated in Scheme 1. The synthesized imine **1a** was reacted withL-valine and L-cysteine, also the imine derivative **1b**was treatedwithL-cysteine, L-isoleucine and L-tyrosine to give the target imidazolidine-1,3,4-thiadiazole derivatives**2a-e** respectively (Scheme 1). The proposed mechanism for the addition of amino acids to imines was shown in Scheme 2.
The chemical structures of these newlyimidazolidines were confirmedby IR, ^{1}H NMR spectral measurements and (CHNS) elemental analysis and were in good agreement with the proposed structures. The biological activity of the synthesized imidazolidines**2a-e** will be measured in subsequent study.



Scheme 1. Synthesis of imidazolidines **2a-e**



The IR spectra of imines**1a** and **1b**showed the stretching absorption band of the (C=N) function at 1691 and 1597cm^{-1}, respectively, while the absorption bands due to (NH_2) group at 3336 and 3267cm^{-1} have disappeared. The broad absorption band at 3194 and 3090cm^{-1}attributed to the (N-H)str. in thione form, respectively. The stretching band of (C=S) function in thione form appeared as strong band at 1051 and 1060cm^{-1}, respectively. The IR spectra of compounds **2a** and **2b** indicated the absence of (C=N) absorption band and the appearance of (C=O, amide)str. for imidazolidine ringat1597 and 1612cm^{-1}, respectively. The stretching absorption band for (N-H, imidazolidine) appeared at 3134 and 3356cm^{-1}, respectively. In the IR spectra of compounds **2c, 2d** and **2e,** the (C=O, imidazolidine) stretching absorption band was found at 1593, 1591 and 1589cm^{-1}, respectively, while the absorption band due to (C=N)has disappeared. The band appearing at 3080, 3084 and 3203 cm^{-1} was for (N-H, imidazolidine) stretching, respectively. Moreover, the IR spectrum of compound**2e** showed a characteristic broad band at 3446cm^{-1} assigned to the stretching of (OH) function.

The ^{1}H NMR spectra of imines **1a** and **1b**showed the (CH=N) proton as a singlet atδ 10.12 and 9.60 ppm respectively, the (N-H) proton of thione form appeared as a singlet at 8.10 and 8.20 ppm respectively, the (Ar-H) protons at δ 6.62 –7.96 ppm. Moreover, the spectrum of compound **1b** showed the two methyl protons asa singlet at 3.02 ppm.

The ^{1}H NMR spectra of imidazolidine compounds **2a** and **2b** showed the disappearance of the (CH=N) protonsat 10.12 ppm, the(O=C-C**H**-N) proton of imidazolidine appeared as a singlet at 3.6 ppm,the(N-C**H**-N) proton of imidazolidine as a singlet at5.26ppm, the (N-H) proton of imidazolidine ring as a singlet at δ 8.30 and 8.16 ppm, respectively, The (Ar-H) protons at δ 7.09 –7.93 ppm, The (S-H) proton of thiadiazole as a singlet at 4.2 ppm. The ^{1}H NMR spectrum of compound**2a** showed the (N-H) proton of thione format 8.19 ppm, the fourmethyl protons as doublet at 0.9 ppm, while the **CH**(CH_3)$_2$protons appeared asa multiplet at 1.8 ppm.The ^{1}H NMRspectrum of compound**2b** showed the two methylene protons at 1.8 ppm, the sulfhydryl (CH_2-S**H)** proton as a singlet at 1.4 ppm.

The ^{1}H NMR spectra of imidazolidine compounds **2c, 2d**and **2e** showed the absence of the intense signal due to the(CH=N) proton at 9.60 ppm,the peak for the two methyl N(CH_3)$_2$ protons appeared at 3.02 ppm, the(O=C-C**H**-N) proton of imidazolidine appeared as a singlet at 3.37, 3.5 and 3.38 ppm respectively, the(N-C**H**-N) proton of imidazolidine as a singlet at 6.7 ppm, the (N-H) proton of imidazolidine ring as a singlet at δ 9.65 ppm, the singlet at 8.4, 8.1 and 8.04 attributed to the (N-H) proton in thione form respectively, the (Ar-H) protons at δ 6.88–7.72 ppm.The ^{1}H NMR spectrum of compounds**2c**showedthe (CH_2-S**H**) proton at 1.4 ppm, themethylene protons at 2.31 ppm.The ^{1}H NMR spectrum of compound**2d** showedthe two methylprotons, methylene protons and methine proton in (CH_3-CH_2-CH-CH_3)as multiplets at 0.9, 1.5 and 1.9 ppm, respectively.The ^{1}H NMR spectrum of compound**2e** showedthe (O-H) proton as a broad signal at 9.63 ppm.

Theazoaldehyde derivative**3**was synthesized by reacting the diazonium salt of2-amino-5-mercapto-1,3,4-thiadiazolewith alkaline solution of 4-hydroxybenzaldehyde using the method described by acton[21]as shown in Scheme 3.The resulting azoaldehyde **3**wascondensed with2-amino-5-mercapto-1,3,4-thiadiazole in absolute ethanol to give

azoimine derivative **4**. The resulting imine**4**was allowed to react withglycine, L-valine and L-cysteine leading to the formation of imidazolidine-1,3,4-thiadiazole derivatives **5a-c** respectively (Scheme 3).

The structures of the target compounds synthesized were provenbyIR,^{1}H NMR spectral measurements and (CHNS) elemental analysis and were in good agreement with the proposed structures. The biological activity of the synthesized imidazolidines **5a-c** will be measured in subsequent study.

The IR spectrum of azoaldehde derivative **3** indicated the absence of the doublet band at 3336and 3267 cm^{-1} for (-NH_2)str. and appearance of the following characteristic bands: the broad band at 3284 cm^{-1} assigned to (O-H)str., the absorption band at 1627 cm^{-1} belong to aldehydic (C=O)str., the stretching absorption bands assigned to (N-H) and (C=S) in thione form appeared at 3095 and 1039 cm^{-1}, respectively. The IR spectrum of azoimine derivative **4** showed the disappearance of the absorption band at 1627 cm^{-1} for aldehydic (C=O)str., also disappearing the doublet band for (-NH_2)str. in2-amino-5-mercapto-1,3,4-thiadiazole at (3336, 3267) cm^{-1}, while the absorption band attributed to (C=N)str.appeared at1610 cm^{-1}. In the IR spectra of imidazolidine compounds **5a, 5b** and **5c,** the stretching absorption band due to (C=O, imidazolidine) was found at 1566, 1568 and 1566 cm^{-1}, respectively, while the absorption band due to (C=N) at 1610 cm^{-1}has disappeared.The band appearing at 3080, 3084 and 3203 cm^{-1} was for (N-H, imidazolidine) stretching, respectively.

The ^{1}H NMR spectrum of azoimine compound **4** showed the (O-H) proton as a broad peak at 10.60 ppm,the (CH=N) proton as a singlet at δ 9.6 ppm, the two (N-H) protons of thione forms appeared as a singlets at 8.7 and 8.8 ppm, the (Ar-H) protons at δ 6.8–7.7 ppm.

The ^{1}H NMR spectra of imidazolidine compounds **5a, 5b**and **2c** showed the disappearance of the (CH=N) proton atδ9.6 ppm,the(O=C-C**H$_2$**-N) protons of imidazolidine in compound **5a** appeared at 3.6 ppm , the(O=C-C**H**-N) proton of imidazolidine in compounds **5b** and **5c**at3.7ppm, the(N-C**H**-N) proton of imidazolidine as a singlet at 6.5, 5.3 and 5.4 ppm respectively, the (N-H) proton of imidazolidine ring as a singlet at δ 9.35, 9.35 and 9.7 ppm respectively, the singlet at 8.18–8.2 attributed to the (N-H) proton in thione form, the signal of (O-H) proton appearedas a singlet at 13.2-13.3 ppm, the (Ar-H) protons recorded at δ 7.10–7.85 ppm; additionally the ^{1}H NMR spectrum of compound **5b** showed the two methyl protons as a multiplet at 0.9 ppm, while the C**H**(CH_3)$_2$ proton at 2.86 ppm. Also, the ^{1}H NMR spectrum of compound**5c**showedthe (CH_2-S**H**) proton as a singlet at 1.8 ppm, themethylene protons as a singlet at 2.1 ppm.

Table 1: Physical Properties of the Synthesized Compounds

Product	Physical state	R_f(developer)	m.p. (^oC)	Yield (%)
1a	Yellow solid	0.64 (Toluene/ EtOH, 7:3)	186-188	79
1b	Orange solid	0.77 (Toluene/ EtOH, 7:3)	174-176	82
2a	Dark orange solid	0.74(Toluene/ EtOH, 7:3)	115-117	71
2b	Dark orange solid	0.80(Toluene/ EtOH, 7:3)	108-110	68
2c	Light brown solid	0.82(Toluene/ EtOH, 7:3)	151-153	83
2d	Light orange solid	0.76(Toluene/ EtOH, 7:3)	159-161	75
2e	Orange solid	0.74(Toluene/ EtOH, 7:3)	165-167	78
3	Dark orange solid	0.49(Toluene/ EtOH, 7:3)	129-131	55
4	Orange solid	0.73(Toluene/ EtOH, 7:3)	178-180	71
5a	Brown solid	0.75(Toluene/ EtOH, 7:3)	111-113	74
5b	Brown solid	0.68(Toluene/ EtOH, 7:3)	117-119	73
5c	Brownsolid	0.77(Toluene/ EtOH, 7:3)	114-116	67

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