

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-thiadiazole was introduced in condensation reactions with both terephthaldehyde and 4-dimethylaminobenzaldehyde to yield imine derivatives 1a and 1b respectively. The resulting imine 1a was treated with amino acids L-valine and L-cysteine, also the imine 1b was reacted with amino acids L-cysteine, L-isoleucine and L-tyrosine to obtain five new imidazolidine derivatives 2a-e respectively. 2-amino-5-mercapto-1,3,4-thiadiazole was also converted to the corresponding azoaldehyde derivative 3 through coupling reaction of its diazonium salt with 4-hydroxybenzaldehyde dissolved in sodium hydroxide solution. The resulting azoaldehyde 3 was reacted with 2-amino-5-mercapto-1,3,4-thiadiazole to 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 derivatives 5a-c respectively.

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, cardiotoxic⁽⁴⁾, antibacterial activity against *Klebsiella pneumoniae*⁽⁵⁾, antitubercular^(6,7), anticonvulsant⁽⁸⁾, antileishmanial, analgesic⁽⁹⁾, anti-inflammatory⁽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 moiety^(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 as anti-inflammatory, 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 from Merck, BDH, sigma Aldrich and CDH and were used without further

purification. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F₂₅₄). 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. ¹H NMR spectra were collected on NMR spectrometer, Bruker 2009 spectrometer at 400 MHz in DMSO-d₆ 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

Synthesis of 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, 10 mmol) was added. The reaction mixture was refluxed with stirring on a water bath at 65°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} (ν N-H, thione form and ν C-H, benzene, vib. coupling), 2972 and 2885 (ν N-H, intramolecularly hydrogen bonded, thione form), 1691 (ν C=N, imine), 1562 and 1508 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1051 (ν C=S, thione form), 750 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 2.5 (DMSO solvent), 3.4 (H₂O 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, 5 mmol) 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} (ν N-H, thione form and ν C-H, benzene, vib. coupling), 2953 and 2885 (ν C-H3 and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1597 (ν C=N, imine), 1529 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1060 (ν C=S, thione form), 775 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 2.49 (DMSO solvent), 3.02 (s, 6H, 2×N-CH₃), 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 °C 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, dried and 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} (ν N-H, imidazolidine, ν N-H, thione form and ν C-H, benzene, vib. coupling), 2962 and 2887 (ν C-H3 and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1597 (ν C=O, amide, imidazolidine), 1504 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1041 (ν C=S, thione form), 773 and 680 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 0.9 (d, 12H, 4×CH₃), 1.8 (m, 2H, 2×CH(CH₃)₂), 2.48 (DMSO solvent), 3.34 (H₂O in DMSO), 3.64 (s, 2H, 2×O=C-CH-N, imidazolidine), 4.2 (s, 2H, 2×SH), 5.26 (s, 2H, 2×N-CH-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 C₂₂H₂₆N₈O₂S₄: 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} (ν N-H, imidazolidine and ν N-H, thione form, vib. coupling), 3053 and 3032 (ν C-H, benzene), 2939 and 2877 (ν C-H2 and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1612 (ν C=O, amide, imidazolidine), 1568 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1053 (ν C=S, thione form), 844 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 1.4 (s, 2H, 2×CH₂-SH), 1.8 (m, 4H, 2×CH₂-SH), 2.5 (DMSO solvent), 3.3 (H₂O in DMSO), 3.6 (s, 2H, 2×O=C-CH-N, imidazolidine), 4.2 (s, 2H, 2×SH, thiadiazole), 5.26 (s, 2H, 2×N-CH-N, imidazolidine), 7.09–7.38 (m, 4H, Ar-H), 8.16 (s, 2H, 2×N-H, imidazolidine). Anal. Calcd. for C₁₈H₁₈N₈O₂S₆: 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 the synthesis 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 °C 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, dried and recrystallized from ethanol.

2-(4-(dimethylamino)phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-5-(mercaptomethyl)imidazolidin-4-one 2c: IR (cm⁻¹):3080_{br} (ν N-H, imidazolidine, ν N-H, thione form and ν C-H, benzene, vib. coupling), 2993 and 2887 (ν C-H3 and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 2958 and 2825 (ν C-H2), 1593 (ν C=O, amide, imidazolidine), 1533 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1058 (ν C=S, thione form), 817 and 775 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 1.4 (s, 1H, CH₂-SH), 2.31 (s, 1H, CH₂-SH), 2.48–2.49 (DMSO solvent), 3.02 (s, 6H, 2×N-CH₃), 3.37 (s, 1H, O=C-CH-N, imidazolidine), 6.7 (s, 1H, N-CH-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 C₁₄H₁₇N₅O₃S₃: 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} (ν N-H, imidazolidine, ν N-H, thione form and ν C-H, benzene, vib. coupling), 2962 and 2889 (ν C-H3 and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 2615 (ν S-H, thiol form), 1591 (ν C=O, amide, imidazolidine), 1516 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1058 (ν C=S, thione form), 775 and 671 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 0.9 (m, 6H, CH₃-CH₂ and CH₃-CH), 1.5 (m, 2H, CH₂), 1.9 (m, 1H, CH₃CH-CH₂), 2.5 (DMSO solvent), 3.02 (s, 6H, 2×N-CH₃), 3.5 (s, 1H, O=C-CH-N, imidazolidine), 6.7 (s, 1H, N-CH-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 C₁₇H₂₃N₅O₂S₂: 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} (ν O-H), 3203 (ν N-H, imidazolidine), 3091 (ν N-H, thione form), 3018 (ν C-H, benzene), 2956 and 2867 (ν C-H3 and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 2600 (ν S-H, thiol form), 1589 (ν C=O, amide, imidazolidine), 1531 and 1514 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1080 (ν C=S, thione form), 777 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 2.5 (DMSO solvent), 3.02 (ss, 6H, 2×N-CH₃), 3.38 (s, 1H, O=C-CH-N, imidazolidine), 6.70 (s, 1H, N-CH-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 C₁₉H₁₉N₅O₂S₂: 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-2-yl)diazenyl)benzaldehyde 3: was prepared following the method described by Acton⁽²¹⁾ as dark orange solid, mp 129–131°C, yield 55%; IR (cm⁻¹): 3284_{br} (ν O-H), 3095 (ν N-H, thione form and ν C-H, benzene, vib. coupling), 2962 and 2899 (ν N-H, intramolecularly hydrogen bonded, thione form), 2829 and 2700 (ν C-H, aldehyde), 1627 (ν C=O, aldehyde), 1552 and 1498 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1039 (ν 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} (ν O-H), 3099 (ν N-H, thione form and ν C-H, benzene, vib. coupling), 2949 and 2802 (ν N-H, intramolecularly hydrogen bonded, thione form), 1610 (ν C=N, imine), 1554 and 1502 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1061 (ν C=S, thione form), 715 (δ_{o.o.p.} C-H, benzene rings); ¹H NMR: δ = 2.48 (DMSO solvent), 3.7 (H₂O 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 °C 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, dried and 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} (ν O-H, ν N-H, imidazolidine, ν N-H, thione form and ν C-H, benzene, vib. coupling), 2968 and 2877 (ν C-H₂, imidazolidine and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1566 (ν C=O, amide, imidazolidine), 1514 and 1452 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1047 (ν C=S, thione form), 715 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 2.5 (DMSO solvent), 3.6 (m, 2H, O=C-CH₂-N, imidazolidine), 6.5 (s, 1H, N-CH-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 C₁₃H₁₀N₈O₂S₄: 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} (ν O-H, ν N-H, imidazolidine, ν N-H, thione form and ν C-H, benzene, vib. coupling), 2960 and 2879 (ν C-H₃, and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1568 (ν C=O, amide, imidazolidine), 1504 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1041 (ν C=S, thione form), 775 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 0.9 (m, 6H, CH(CH₃)₂), 2.48 (DMSO

solvent), 2.86 (m, 1H, CH(CH₃)₂), 3.69 (m, 1H, O=C-CH-N, imidazolidine), 5.3 (s, 1H, N-CH-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 C₁₆H₁₆N₈O₂S₄: 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.

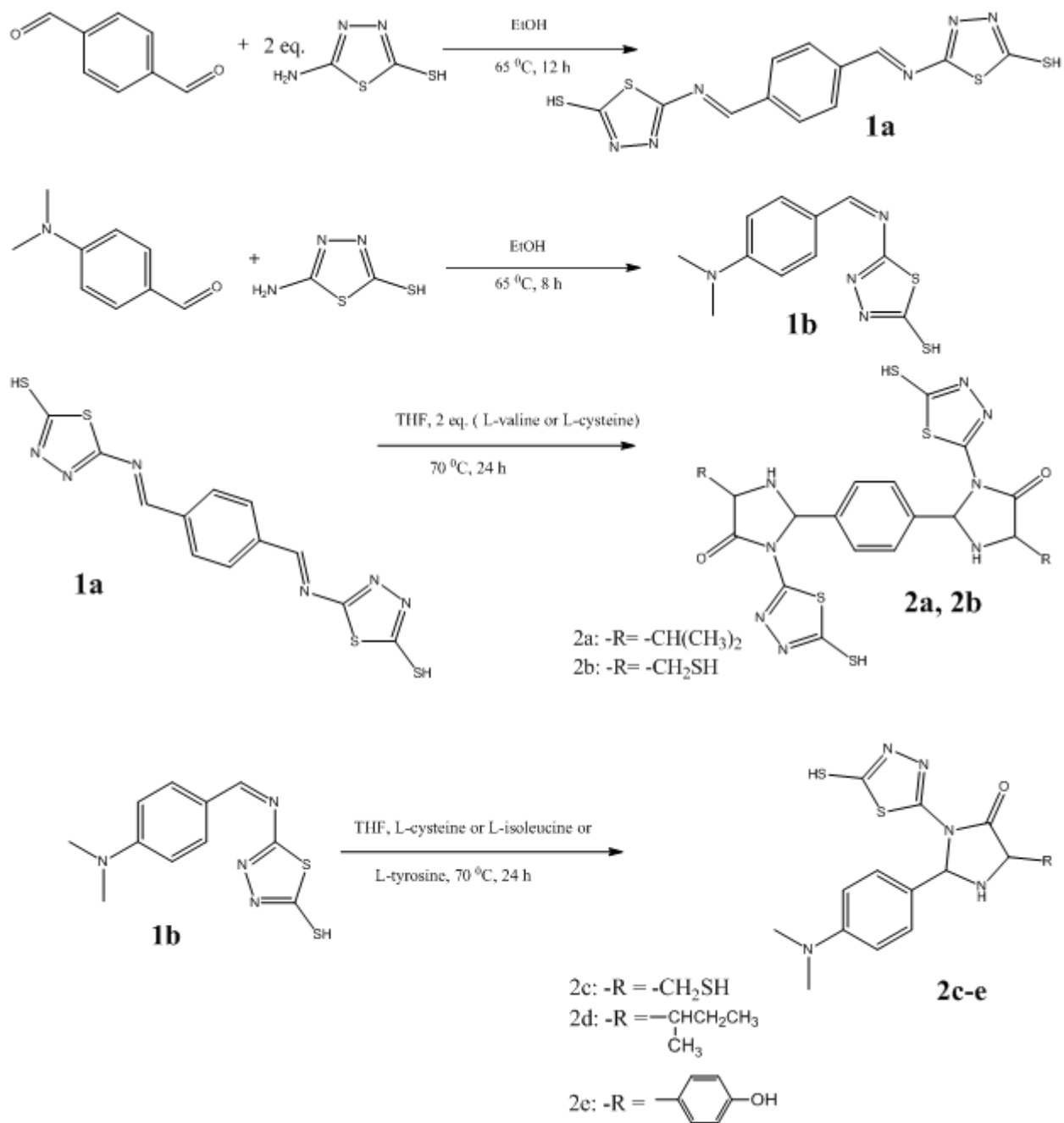
(E)-2-(4-hydroxy-3-((5-mercapto-1,3,4-thiadiazol-2-yl) diazenyl) phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-5-(mercaptomethyl) imidazolidin-4-one 5c: IR (cm⁻¹): 3381_{br} (ν O-H), 3232 (ν N-H, imidazolidine, ν N-H, thione form and ν C-H, benzene, vib. coupling), 2949 and 2877 (ν C-H₂ and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1566 (ν C=O, amide, imidazolidine), 1527 and 1487 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1043 (ν C=S, thione form), 845 (δ_{o.o.p.} C-H, benzene); ¹H NMR: δ = 1.8 (s, 2H, CH₂-SH), 2.1 (s, 2H, CH₂-SH), 2.49 (DMSO solvent), 3.7 (s, 1H, O=C-CH-N, imidazolidine), 5.4 (s, 1H, N-CH-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 C₁₄H₁₂N₈O₂S₅: 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

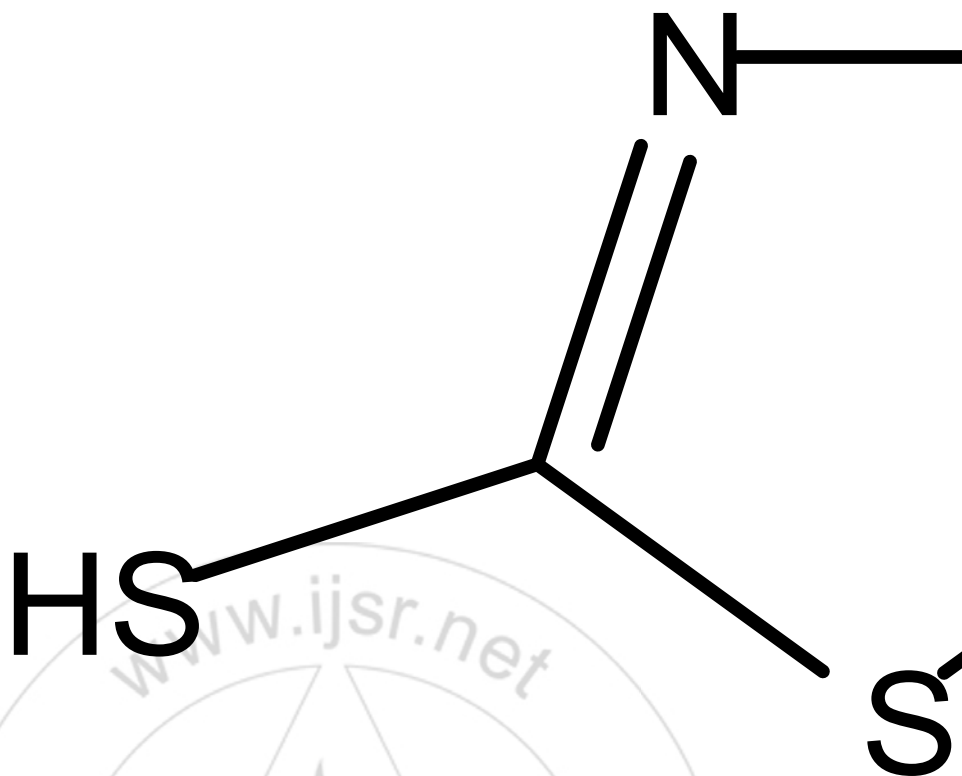
3.1 Chemistry

The precursors imines **1a** and **1b** were synthesized by reacting the aromatic aldehydes (terephthalaldehyde 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 with L-valine and L-cysteine, also the imine derivative **1b** was treated with L-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 newly imidazolidines were confirmed by IR, ¹H 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 1597 cm⁻¹, respectively, while the absorption bands due to (NH₂) group at 3336 and 3267 cm⁻¹ have disappeared. The broad absorption band at 3194 and 3090 cm⁻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 1060 cm⁻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 ring at 1597 and 1612 cm⁻¹, respectively. The stretching absorption band for (N-H, imidazolidine) appeared at 3134 and 3356 cm⁻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 1589 cm⁻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 3446 cm⁻¹ assigned to the stretching of (OH) function.

The ¹H NMR spectra of imines **1a** and **1b** showed the (CH=N) proton as a singlet at δ 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 as a singlet at 3.02 ppm.

The ¹H NMR spectra of imidazolidine compounds **2a** and **2b** showed the disappearance of the (CH=N) protons at 10.12 ppm, the (O=C-CH-N) proton of imidazolidine appeared as a singlet at 3.6 ppm, the (N-CH-N) proton of imidazolidine as a singlet at 5.26 ppm, 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 thiazazole as a singlet at 4.2 ppm. The ¹H NMR spectrum of compound **2a** showed the (N-H) proton of thione form at 8.19 ppm, the four methyl protons as doublet at 0.9 ppm, while the CH(CH₃)₂ protons appeared as a multiplet at 1.8 ppm. The ¹H NMR spectrum of compound **2b** showed the two methylene protons at 1.8 ppm, the sulfhydryl (CH₂-SH) proton as a singlet at 1.4 ppm.

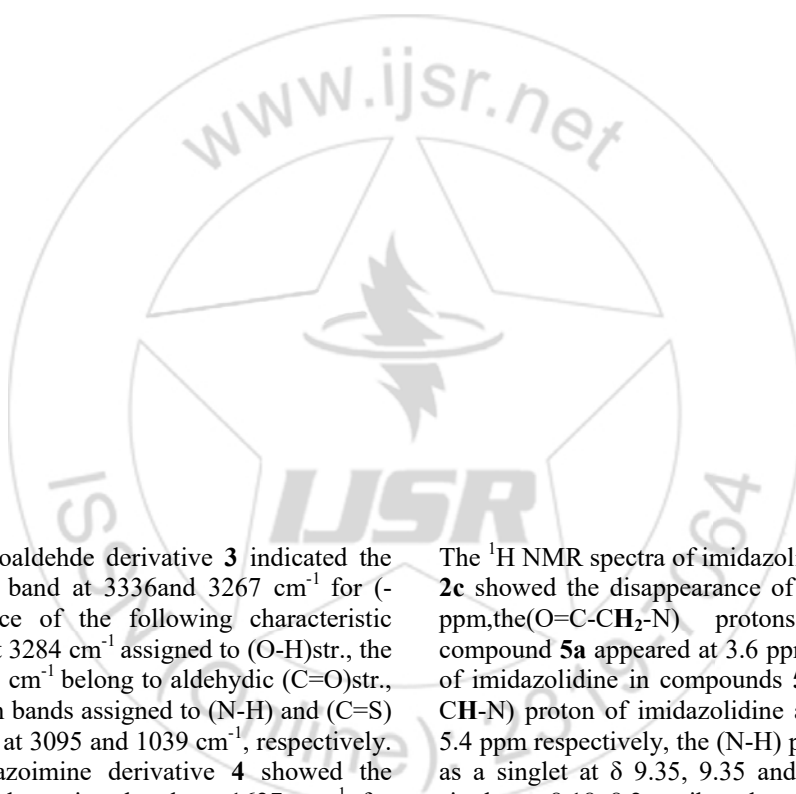
The ¹H NMR spectra of imidazolidine compounds **2c**, **2d** and **2e** showed the absence of the intense signal due to the (CH=N) proton at 9.60 ppm, the peak for the two methyl N(CH₃)₂ protons appeared at 3.02 ppm, the (O=C-CH-N) proton of imidazolidine appeared as a singlet at 3.37, 3.5 and 3.38 ppm respectively, the (N-CH-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 ¹H NMR spectrum of compound **2c** showed the (CH₂-SH) proton at 1.4 ppm, the methylene protons at 2.31 ppm. The ¹H NMR spectrum of compound **2d** showed the two methyl protons, methylene protons and methine proton in (CH₃-CH₂-CH-CH₃) as multiplets at 0.9, 1.5 and 1.9 ppm, respectively. The ¹H NMR spectrum of compound **2e** showed the (O-H) proton as a broad signal at 9.63 ppm.

The azoaldehyde derivative **3** was synthesized by reacting the diazonium salt of 2-amino-5-mercapto-1,3,4-thiadiazole with alkaline solution of 4-hydroxybenzaldehyde using the method described by acton⁽²¹⁾ as shown in Scheme 3. The resulting azoaldehyde **3** was condensed with 2-amino-5-mercapto-1,3,4-thiadiazole in absolute ethanol to give

azoimine derivative **4**. The resulting imine **4** was allowed to react with glycine, 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 proven by IR, ¹H 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 azoaldehyde derivative **3** indicated the absence of the doublet band at 3336 and 3267 cm⁻¹ for (-NH₂)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 (-NH₂)str. in 2-amino-5-mercapto-1,3,4-thiadiazole at (3336, 3267) cm⁻¹, while the absorption band attributed to (C=N)str. appeared at 1610 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 ¹H 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 singlets at 8.7 and 8.8 ppm, the (Ar-H) protons at δ 6.8–7.7 ppm.

The ¹H NMR spectra of imidazolidine compounds **5a**, **5b** and **2c** showed the disappearance of the (CH=N) proton at δ 9.6 ppm, the (O=C-CH₂-N) protons of imidazolidine in compound **5a** appeared at 3.6 ppm, the (O=C-CH-N) proton of imidazolidine in compounds **5b** and **5c** at 3.7 ppm, the (N-CH-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 appeared as a singlet at 13.2–13.3 ppm, the (Ar-H) protons recorded at δ 7.10–7.85 ppm; additionally the ¹H NMR spectrum of compound **5b** showed the two methyl protons as a multiplet at 0.9 ppm, while the CH(CH₃)₂ proton at 2.86 ppm. Also, the ¹H NMR spectrum of compound **5c** showed the (CH₂-SH) proton as a singlet at 1.8 ppm, the methylene protons as a singlet at 2.1 ppm.

Table 1: Physical Properties of the Synthesized Compounds

Product	Physical state	R _f (developer)	m.p. (°C)	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

4. Acknowledgements

We are highly thankful to staff of the central laboratory, University of Kashan, Iran for their significant assistance in ¹H NMR and Elemental Analysis measurements of the target compounds.

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