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 (16). 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), antineoplastic, antidepressant, cardiotonic (4), antimicrobial activity (5), antidepressant, cardiotonic (4), anticonvulsant (8), antileishmanial (6), antitubercular (7), analgesic (9), antiinflammatory (10), anticancer (11), antimetabolite (12) and effect on Tyrosinase (13). Thiadiazoles are easily metabolized by biochemical reactions and they are non-carcinogenic in nature. Thiadiazoles and their derivatives exhibit wide range of pharmacological activities such as antimicrobial activity (3), antineoplastic, antidepressant, cardiotonic (4), antimicrobial activity (5), antidepressant, cardiotonic (4), anticonvulsant (8), antileishmanial (6), antitubercular (7), analgesic (9), antiinflammatory (10), anticancer (11), antimetabolite (12) and effect on Tyrosinase (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; while the isomer does not 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 antitumour, antiviral, antifungal, antihypertensive, antibacterial and antifungal activities (19,20). Thus, in this article, we reported here the synthesis of 1,3,4-thiadiazole derivatives containing biologically active imidazolidine moieties, 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 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. 1H NMR spectra were collected on a Bruker 200 MHz NMR spectrometer, Bruker 500 MHz NMR spectrometer. IR spectra were recorded on a Perkin Elmer 300A Elemental Analyzer at Kashan University, Iran. Elemental Analysis (CHNS.) was carried out with Perkin Elmer 300A Elemental Analyzer at Kashan University, Iran.

2.2. Chemical Methods

Synthesis of (Z)-5-((4-(dimethylamino) benzylidene) bis(azanylidenediene)) 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-mercaptot-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 decrystallized from ethanol: IR (cm−1): 3194 (C–H, aromatic), 2927 and 2885 (C–H, aliphatic), 1691 (C=C, aromatic), 1562 and 1508 (C=C, aromatic), 750 (C=S, aromatic). 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 5,5’-(((1E,1’E)-1,4-phenylenebis(methanlylidene))bis(azanylidenediene)) bis(1,3,4-thiadiazole-2-thiol) 1b:

Dimethylaminobenzaldehyde (0.745 g, 5 mmol) was dissolved in (30 mL) of absolute ethanol, then 2-Amino-5-mercaptop-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 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 (C–H, aromatic), 2972 and 2885 (C–H, aliphatic), 1691 (C=C aromatic), 1562 and 1508 (C=C aromatic), 750 (C=S, aromatic). 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).
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): 3090w (ν N-H, imidazolidine), 2933and 2887 (ν C-H and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1597 (ν C=N, benzene), 1529 (ν C=C, benzene and ν C=C, 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), 3.62-3.64 (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 (4 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 evaporated under reduced pressure to give colored solid, dried and recrystallized from ethanol.

2,2′-(1,4-phenylene)bisis(5-isopropyl-3-(5-mercapto-1,3,4-thiadiazol-2-yl)imidazolidin-4-one) 2a:IR (cm⁻¹): 3134w (ν N-H, imidazolidine), 2933and 2887 (ν C-H and ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 1579 (ν C=N, benzene), 1520 (ν C=C, benzene and ν C=C, thiadiazole, vib. coupling), 1041 (ν C-S, thione form), 775 (δ_o.o.p. C-H, benzene); 1H NMR: δ = 0.9 (d, 6H, 2×CH₃), 1.8 (m, 4H, 2×CH₂), 1.28 (s, 6H, 2×CH₂), 2.48 (DMSO solvent), 3.34 (H₂O in DMSO), 3.64 (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, 19.60; S, 22.79. Found C, 47.28; H, 4.62; N, 19.19; S, 22.79.

2,2′-(1,4-phenylene)bisis(3-(5-mercapto-1,3,4-thiadiazol-2-yl)-5-(mercaptomethyl) imidazolidin-4-one) 2b:IR (cm⁻¹): 3355w (ν N-H, imidazolidine and ν N-H, thione form, vib. coupling), 3053 and 3032 (ν C-H, benzene), 2933and 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 = 2.1 (s, 2H, 2×CH₂-SH), 1.8 (m, 4H, 2×CH₂-SH), 2.5 (DMSO solvent), 3.3 (H₂O in DMSO), 3.64 (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 C₁₉H₁₉N₅O₂S₄: C, 55.19; H, 4.63; N, 16.94; S, 15.59. 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)diazeyl)benzaldehyde 3: was prepared following the method described by Acton[21] as dark orange solid, mp 129-131°C, yield 55%, IR (cm⁻¹): 3284w(ν O-H), 3040s (ν N-H, thione form and ν C-H, benzene, vib. coupling), 2962 and 2899 (ν N-H, intramolecularly hydrogen bonded, thione form, vib. coupling), 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 O=H, thione form), 837 (δ_o.o.p. C-H, benzene rings).

Synthesis of 2-(E)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazeyl)-4-((E)-(5-mercapto-1,3,4-thiadiazol-2-yl)(dimethyl)pheno 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, 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): 3267 br (O-H), 3099 (U N-H, thione form and U C-H, benzene, vib. coupling), 2949 and 2802 (U N-H, intramolecurally hydrogen bonded, thione form), 1610 (U C=O, amide, imidazolidine), 1554 and 1502 (U C=N, benzene and U C=N, thiadiazole, vib. coupling), 1061 (U C=S, thione form), 715 (δ o.o.p. C-H, benzene, vib. coupling), 715 (δ o.o.p. C-H, benzene ring), 2960, 2877 (ʋ C-H2 and ʋ C-H3, and ʋ C=C, benzene and ʋ C=C, thione forms), 9.3 (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-mercaptomethyl)imidazolidin-4-one 5c:IR (cm⁻¹): 3381 br (O-H), 3232 (U N-H, imidazolidine, U N-H, thione form and U C-H, benzene, vib. coupling), 2949 and 2877 (U C=H2 and U N-H, intramolecurally hydrogen bonded, thione form, vib. coupling), 1566 U C=O, amide, imidazolidine), 1527 and 1487 (U C=C, benzene and U C=N, thiadiazole, vib. coupling), 1043 (U 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), 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 C₁₃H₂₃N₃O₄S₂: 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 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 newlyimidazolidines 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, 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-C=H-N) proton of imidazolidine appeared as a singlet at 3.37, 3.5 and 3.38 ppm respectively, the (N-H, imidazolidine) 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 2e showed the (CH₂-SH) proton at 1.4 ppm, the methylene protons at 2.31 ppm. 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 spectra of imidazolidine compounds 5a, 5b and 2c showed the disappearance of the (CH=N) proton at 69.6 ppm, the (O=C-C₂H₂-N) protons of imidazolidine in compound 5a appeared at 3.6 ppm, the (O=C-C₂H₂-N) proton of imidazolidine in compounds 5b and 5c at 3.7 ppm, the (N-C₂H₂-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 CH₂(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 | Rf (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      | Brown solid    | 0.77 (Toluene/ EtOH, 7:3) | 114-116 | 67        |

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