Synthesis, Antimicrobial and Molecular Docking studies of Some New Derivatives of 2,3-dihydroquinazolin-4(1H)-one

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Abstract

In the present study a series of novel 2-(substituted phenyl)-3-(5-phenyl-1-3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one derivatives were synthesized by refluxing Isatoic anhydride, 5-phenyl-1,3,4-thiadiazol-2-amine and aromatic aldehydes in the presence of p-TsOH as catalyst and in H_2O as solvent and characterized by spectral data and analytical methods. Antibacterial and antifungal activity of the title compounds are evaluated against two gram positive and two gram negative bacterial strains and strains of fungi Compared with standard drugs, using well diffusion method, minimum bactericidal/fungicidal concentration methods. The potential Alpha-amylase and Alpha-glucosidase inhibitory activity of compounds 4(a-l) were investigated in silico using molecular docking simulation method. Therefore, these 2,3-dihydroquinazolin-4(1H)-one derivatives may be considered as promising candidates for the development of new classes of antimicrobial and antidiabetic drugs.

Keywords: Isatoic anhydride, 2,3-dihydroquinazolin-4(1H)-one , antibacterial activity, antifungal activity, anti-diabetic activity.

1. Introduction

The 2,3-dihydroquinazolin-4(1H)-one (DHQ) is an important nitrogen-containing heterocyclic scaffold. DHQ ring system is a distinguished scaffold in drug design. DHQ in medicinal chemistry as an important pharmacophore has drawn much attention due to its broad spectrum of

pharmaceutical activities, which include antibacterial,[1,2] antifungal,[3-5] anticancer,[6-8] Antidiabetic,[9] anti-tuberculin,[10] anti-inflammatory,[11-13] Cholinesterase inhibitor,[14] antihypertensive activities[15,16] and insecticidal activity[17].

On the other hand, 2-Amino-1,3,4-thiadiazole and its derivatives have drawn attention of many organic chemists during recent years, since many of these compounds known to possess interesting biological properties such as antibacterial,[18,19] antifungal,[20-22] anticancer,[23-25] antihypertensive[26,27] activities. With Considering the reactivity of the amine group in the derivatization process, 2-amino-1,3,4-thiadiazole moiety is a good scaffold for drug synthesis.

Most of the DHQ derivatives are substituted on the carbon 2 and 3. Due to their attractive properties, 2-substituted DHQs are becoming a prominent synthetic intermediate for organic chemists and pharmacologist.

Based on the above observations we report here the synthesis of a new series of 2,3-dihydroquinazolin-4(1H)-one derivatives **4(a-l**) with structure modifications involving incorporation of 5-phenyl-1,3,4-thiadiazol-2-amine ***3*** at position 3 and aromatic aldehydes **2(a-l)** at position 2 of DHQ ring system. In the present study, various aryl aldehydes groups were specifically incorporated at position 2 of the DHQ scaffold with the aim of new antibacterial, antifungal and anti diabetic drugs.

2. Experimental

Starting materials, solvents, and culture environments (nutrient agar/broth, sabouraud dextroseand agar/broth) were obtained from Merck, Germany and used without any more filtration. Microbiological tests were performed using a Memmert- INC153T2T3 incubator. Melting points are determined in Philip Harris C4954718 melting point apparatus and are uncorrected. IR spectra are recorded on a Thermo Nicolet Nexus-670 FTIR spectrophotometer, using potassium bromide pellets and the frequencies are expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra are recorded with a Bruker Avance-400MHz spectrometer, using TMS as the internal reference, with DMSO-d_6 as solvent, The chemical shifts are reported in parts per million (ppm). Mass spectra were obtained on a 5973 Network Mass Selective Detector instrument using electron impact ionization ((EI) 70eV). Elemental analysis is performed on FlashEA 1112 series (Thermo Finnigan) CHNS analyzer.

2.1. Synthesis of 5-phenyl-1,3,4-thiadiazol-2-amine. (3)

A stirring mixture of benzoic acid (50 mmol), thiosemicarbazide (50 mmol) and phosphorus oxychloride ($POCl_3$) (15 ml) was heated at 75 °C for 1 h. After cooling to room temperature, water was added; the reaction mixture was further refluxed for 4 h. After cooling, the mixture was basified to pH 8 by the dropwise addition of 50% potassium hydroxide solution under stirring. thus, obtained precipitate was filtered and recrystallized from ethanol.[28]

This compound was obtained as yellow solid in a yield of 85%; m.p.: 225-227 °C;

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 (S, 2H, NH), 7.44-7.46 (m, 3H, ArH), 7.74 (d, j = 7.73 Hz, 2H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 126.74 (2CH), 129.56 (2CH), 130.00 , 131.43 , 156.84 (C=N), 168.98 (C=N).

IR (KBr, ν , cm^{-1}); 3267.45, 3062.96 (ν_{NH}), 1629.53 ($\nu_{C=N}$),1510.55 (strong bending ν_{NH}), 664.71(ν_{C-S});

MS (m/z): 177.1 (M^+ + H)

Anal. Calcd for C8H7N3S (%): C, 54.22; H, 3.98; N, 23.71; S, 18.09. Found: C, 54.23; H, 3.99; N, 23.74; S, 18.13.

2.2. General procedure for the synthesis of compounds 2-substituted phenyl-3-(5-phenyl-1-3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one 4(a-l).

To a round-bottom flask containing H_2O (5 mL) was added isatoic anhydride (1 mmol, 0.1631 g), relevant aldehyde (1 mmol), 1,3,4-thiadiazol-2-amine (1.1 mmol, 0.1949 g), and p-TsOH (Our inventory was its monohydrate) (0.6 mmol, 0.1141 g). The mixture was heated under reflux for 2 hours. The precipitate was filtered and recrystallized from EtOH.[29]

According to Table 1&2 and Scheme 1.

2.2.1. 2-phenyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4a):

This compound was obtained as light brown solid in a yield of 81%; m.p.: 171-173 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.81 (t, j = 7.48 Hz,1H, NH), 6.93 (d, j = 8.15 Hz, 1H, CH), 7.32 (m, 5H, ArH), 7.41 (t, j = 3.75 Hz, 1H, ArH), 7.44 (d, j= 0.58 Hz, 1H, ArH), 7.55 (m, 3H, ArH), 7.82 (d, j = 7.92 Hz, 1H, ArH), 7.98 (d, j = 6.47 Hz, 2H, ArH), 8.34 (d, j = 0.18 Hz, 1H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 68.95 (N-C-N), 113.19, 116.22, 118.90, 126.13 (2CH), 127.49 (2CH), 128.87, 128.94, 129.12 (2CH), 129.87 (2CH), 130.37, 131.32, 136.21, 139.80, 147.29, 158.17 (C=O), 160.87 (C=N), 164.32 (C=N).

IR (KBr, *v*, cm^{-1}); 3364.47 (v_{NH}), 3033.20 (v_{C-H}), 1633.86 ($v_{C=O}$), 1500.59 ($v_{C=N}$), 1448.65 (strong bending v_{NH}), 1386.63 (v_{C-N}), 1180.94 (v_{N-N}), 689.71 (v_{C-S}).

MS (m/z): 384.2 (M^+ + H)

Anal. Calcd for $C_{22}H_{16}N_4OS$ (%): C, 68.73; H, 4.20; N, 14.57; S, 8.34. Found: C, 68.77; H, 4.25; N, 15.02; S, 8.29.

2.2.2. 2-(2-chlorophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4b):

This compound was obtained as brownish yellow solid in a yield of 84%; m.p.: 210- 212 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.86 (t, j = 7.55 Hz, 1H, NH), 6.90 (d j = 8.22 Hz, 1H, CH), 7.07 (d, j = 7.80 Hz, 1H, ArH), 7.20 (t, j = 7.67 Hz, 1H, ArH), 7.33 (t, j = 7.63 Hz, 1H, ArH), 7.41 (t, j = 7.78 Hz, 1H, ArH), 7.53 (t, j = 3.29 Hz, 3H, ArH), 7.57 (d, j = 7.87 Hz, 1H, ArH), 7.60 (d, j = 3.34 Hz, 1H, ArH), 7.93 (t, j = 7.44 Hz, 3H, ArH), 8.11 (d, j = 4.25 Hz, 1H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 67.21 (N-C-N), 112.54, 116.50, 119.10, 125.79, 127.48 (2CH), 128.07, 128.85, 129.86 (2CH), 130.27, 130.89 (2CH), 131.35 (C-Cl), 132.06, 136.32, 136.88, 146.07, 157.35 (C=O), 160.93 (C=N), 164.49 (C=N).

IR (KBr, *v*, cm^{-1}); 3324.17 (v_{NH}), 3056.76 (v_{C-H}), 1661.58 ($v_{C=O}$), 1615.33 ($v_{C=N}$), 1506.09 (strong bending v_{NH}), 1439.22 (v_{C-N}), 1245.53 (v_{N-N}), 748.42 (v_{C-Cl}), 685.60 (v_{C-S}).

MS (m/z): 418.2 (M^+ + H)

Anal. Calcd for $C_{22}H_{15}ClN_4OS$ (%): C, 63.08; H, 3.61; N, 13.38; S, 7.65. Found: C, 63.05; H, 3.62; N, 13.45; S, 7.77.

2.2.3. 2-(4-chlorophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4c):

This compound was obtained as greenish yellow solid in a yield of 85%; m.p.: 227- 229 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.82 (t, j = 7.44 Hz, 1H,NH), 6.94 (d, j = 8.25 Hz. 1H, CH), 7.33 (d, j = 8.18 Hz, 2H, ArH), 7.39 (d, j = 8.26 Hz, 2H, ArH), 7.43 (d, j = 8.62 Hz, 2H, ArH), 7.54 (t, j = 4.03 Hz, 3H, ArH), 7.82 (d, j = 7.88 Hz, 1H, ArH), 7.97 (m, 2H, ArH), 8.31 (d, j = 3.95 Hz, 1H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 68.47 (N-C-N), 113.19, 116.30, 119.08, 127.50 (2CH), 128.11(2CH), 128.99, 129.15 (2CH), 129.87 (2CH), 130.36, 131.33 (C-Cl), 133.60, 136.28, 138.84, 147.09, 158.09 (C=O), 160.67 (C=N), 164.40 (C=N).

IR (KBr, *v*, cm^{-1}); 3377.68 (v_{NH}), 3053.97 (v_{C-H}), 1650.19 ($v_{C=O}$), 1613.78 ($v_{C=N}$), 1488.61 (strong bending v_{NH}), 1447.76 (v_{C-N}), 1253.00 (v_{N-N}), 756.40 (v_{C-Cl}), 684.14 (v_{C-S}).

MS (m/z): 418.2 (M^+ + H)

Anal. Calcd for $C_{22}H_{15}ClN_4OS$ (%): C, 63.08; H, 3.61; N, 13.38; S, 7.65. Found: C, 63.07; H, 3.60; N, 13.41; S, 7.76.

2.2.4. 2-(2-nitrophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4d):

This compound was obtained as yellow solid in a yield of 82%; m.p.: 199- 201 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.88 (t, j = 0.50 Hz. 1H, NH), 7.27 (d, j = 7.43 Hz, 1H, CH), 7.41 (t, j= 8.08Hz, 1H), 7.47 (d, j= 6.82Hz, 1H), 7.52 (t, j= 1.98Hz, 3H), 7.59 (t, j = 8.67 Hz, 2H, ArH), 7.92 (m, 4H, ArH), 8.02 (d, j = 0.77 Hz, 1H, ArH), 8.12 (d, j = 7.55 Hz, 1H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 65.87 (N-C-N), 112.68, 117.17, 119.60, 126.25, 126.46, 127.50 (2CH), 128.82, 129.85 (2CH), 130.21, 130.69, 131.39, 134.64, 134.77, 136.35, 145.98, 147.84 (C-NO_2), 157.51 (C=O), 160.63 (C=N), 164.57 (C=N).

IR (KBr, *v*, cm^{-1}); 3356.94 (v_{NH}), 3063.28 (v_{C-H}), 1660.59 ($v_{C=O}$), 1615.85 ($v_{C=N}$), 1509.00 (strong bending v_{NH}), 1438.99 (v_{C-N}), 1509.00 & 1338.31 (v_{No2}), 1248.33 (v_{N-N}), 687.14 (v_{C-S}).

MS (m/z): 429.1 (M^+ + H)

Anal. Calcd for $C_{22}H_{15}N_5O_3S$ (%): C, 61.53; H, 3.52; N, 16.31; S, 7.47. Found: C, 61.50; H, 3.55; N, 16.38; S, 7.41.

2.2.5. 2-(3-nitrophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4e):

This compound was obtained as brownish yellow solid in a yield of 85%; m.p.: 226- 228 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.84 (t, j = 7.55 Hz, 1H, NH), 6.98 (d, j = 8.17 Hz, 1H, CH), 7.44 (t, j = 7.52 Hz, 1H, ArH), 7.56 (t, j = 3.50 Hz, 3H, ArH), 7.58 (d, j = 3.91 Hz, 1H, ArH), 7.62 (d, j = 8.03 Hz, 1H, ArH), 7.68 (d, j = 7.81 Hz, 1H, ArH), 7.85 (d, j = 3.32 Hz, 1H, ArH), 7.98 (m, 2H, ArH), 8.14 (d, j = 8.12 Hz, 1H, ArH), 8.30 (s, 1H, ArH), 8.43 (d, j = 4.04 Hz, 1H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 68.28 (N-C-N), 113.13, 116.43, 119.36, 121.28, 123.96, 127.52 (2CH), 129.05, 129.87 (2CH), 130.29, 130.88, 131.39, 132.39, 136.43, 142.12, 146.82, 148.47 (C-NO_2), 158.05 (C=O), 160.53 (C=N), 164.58 (C=N).

IR (KBr, *v*, cm^{-1}); 3353.50 (v_{NH}), 3065.72 (v_{C-H}), 1659.93 ($v_{C=O}$), 1613.78 ($v_{C=N}$), 1519.31(strong bending v_{NH}), 1444.15 (v_{C-N}), 1519.31 & 1357.73 (v_{No2}), 1300.09 (v_{N-N}), 686.53 (v_{C-S}).

MS (m/z): 429.2 (M^+ + H)

Anal. Calcd for $C_{22}H_{15}N_5O_3S$ (%): C, 61.53; H, 3.52; N, 16.31; S, 7.47. Found: C, 61.55; H, 3.50; N, 16.36; S, 7.59.

2.2.6. 2-(4-nitrophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4f):

This compound was obtained as light green solid in a yield of 84%; m.p.: 190- 192 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.85 (t, j = 7.59 Hz, 1H, NH), 6.96 (d, j = 8.32 Hz, 1H, CH), 7.44 (t, j = 8Hz, 1H, ArH), 7.56 (m, 3H, ArH), 7.59 (m, 3H, ArH), 7.83 (t, j = 3.98 Hz, 1H, ArH), 7.99 (d, j = 3.58 Hz, 2H, ArH), 8.20 (d, j = 8.45 Hz, 2H, ArH), 8.41 (d, j = 3.69 Hz, 1H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 68.46 (N-C-N), 113.15, 116.40, 119.35, 124.40 (2CH), 127.52 (2CH), 127.63 (2CH), 129.04, 129.90 (2CH), 130.29, 131.41, 136.40, 146.82, 147.02 (C-NO_2), 147.96, 158.04 (C=O), 160.53 (C=N), 164.54 (C=N).

IR (KBr, *v*, cm^{-1}); 3371.85 (v_{NH}), 3058.92 (v_{C-H}), 1657.13 ($v_{C=O}$), 1609.39 ($v_{C=N}$), 1520.35(strong bending v_{NH}), 1441.98 (v_{C-N}), 1490.12 & 1347.08 (v_{No2}), 1306.95 (v_{N-N}), 693.16 (v_{C-S}).

MS (m/z): 429.2 (M^+ + H)

Anal. Calcd for $C_{22}H_{15}N_5O_3S$ (%): C, 61.53; H, 3.52; N, 16.31; S, 7.47. Found: C, 61.50; H, 3.54; N, 16.30; S, 7.38.

2.2.7. 2-(2-hydroxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4g):

This compound was obtained as green solid in a yield of 78%; m.p.: 218- 220 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.61 (t, j = 7.39 Hz, 1H, NH), 6.75 (d, j = 8.46 Hz, 1H, CH), 6.90 (t, j = 8.57 Hz, 2H, ArH), 7.12 (m, 1H, ArH), 7.35 (t, j = 7.77 Hz, 1H, ArH), 7.48 (d, j = 7.03 Hz, 2H, ArH), 7.53 (m, 2H, ArH), 7.77 (m, 2H, ArH), 7.86 (d, j = 8.10 Hz, 1H, ArH), 7.93 (d, j = 4.99 Hz, 2H, ArH), 10.23 (s, 1H, OH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 66.04 (N-C-N), 112.38, 116.11, 116.24, 118.40, 119.05, 125.45, 125.61, 127.44 (2CH), 128.70, 129.84 (2CH), 130.00, 130.38, 131.25, 135.94, 147.24, 155.25 (C-OH), 157.58 (C=O), 161.40 (C=N), 164.21 (C=N).

IR (KBr, *v*, cm^{-1}); 3380.01 (v_{NH}), 3060.60 (v_{O-H}), 2946.15 (v_{C-H}), 1665.55 ($v_{C=O}$), 1609.81 ($v_{C=N}$), 1496.30(strong bending v_{NH}), 1456.32 (v_{C-N}), 1312.71 (v_{N-N}), 1236.41(v_{C-O}), 687.01 (v_{C-S}).

MS (m/z): 400.2 (M^+ +H)

Anal. Calcd for $C_{22}H_{16}N_4O_2S$ (%): C, 65.99; H, 4.03; N, 13.99; S, 8.01. Found: C, 66.07; H, 4.01; N, 13.95; S, 8.25.

2.2.8. 2-(3-hydroxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4h):

This compound was obtained as brown solid in a yield of 80%; m.p.: 207- 209 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.68 (t, j = 1.30 Hz, 1H, NH), 6.79 (d, j = 7.05 Hz, 1H, CH), 6.93 (m, 1H, ArH), 7.13 (t, j = 4.41 Hz, 3H, ArH), 7.42 (t, j = 8.68 Hz, 4H, ArH), 7.72 (d, j = 8.11 Hz, 1H, ArH), 7.83 (m, 2H, ArH), 7.99 (d, j = 8.11 Hz, 2H, ArH), 9.93 (s, 1H, OH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 68.89 (N-C-N), 115.44, 115.80, 116.19, 116.86, 118.80, 127.50 (2CH), 128.94, 129.88 (2CH), 130.41, 131.31, 131.64, 134.19, 136.17, 141.32, 145.87, 147.38 (C-OH), 157.94 (C=O), 164.26 (C=N), 169.97 (C=N).

IR (KBr, *v*, cm^{-1}); 3275.51(v_{NH}), 3075.36 (v_{O-H}), 2910.10 (v_{C-H}), 1601.72 ($v_{C=O}$), 1505.26 ($v_{C=N}$), 1505.26(strong bending v_{NH}), 1448.04 (v_{C-N}), 1379.91 (v_{N-N}), 1216.41(v_{C-O}), 683.43 (v_{C-S}).

MS (m/z): 400.2 (M^+ + H)

Anal. Calcd for $C_{22}H_{16}N_4O_2S$ (%): C, 65.99; H, 4.03; N, 13.99; S, 8.01. Found: C, 66.02; H, 4.04; N, 14.05; S, 8.13.

2.2.9. 2-(4-hydroxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4i):

This compound was obtained as red solid in a yield of 80%; m.p.: 210- 212 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.69 (m, 2H, NH, CH), 6.95 (d, j = 8.50 Hz, 2H, ArH), 7.13 (t, j = 4.02 Hz, 3H, ArH), 7.33 (t, j = 2.98 Hz, 1H, ArH), 7.55 (m, 2H, ArH), 7.78 (m,2H, ArH), 7.98 (d, j = 7.61 Hz, 2H, ArH), 8.23 (d, j = 1.45 Hz, 1H, ArH), 9.80 (s, 1H, OH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 68.84 (N-C-N), 113.13, 116.17, 118.68, 126.93 (2CH), 127.48 (2CH), 128.58 (2CH), 128.90, 129.71(2CH), 130.50, 136.13, 138.24, 145.96, 147.45, 157.97 (C-OH), 163.78 (C=O), 164.18 (C=N), 169.26 (C=N).

IR (KBr, *v*, cm^{-1}); 3281.73(v_{NH}), 3152.73 (v_{O-H}), 2929.54 (v_{C-H}), 1616.59 ($v_{C=O}$), 1582.00 ($v_{C=N}$), 1526.97(strong bending v_{NH}), 1501.20 (v_{C-N}), 1299.01 (v_{N-N}), 1258.42(v_{C-O}), 678.90 (v_{C-S}).

MS (m/z): 400.2 (M^+ + H)

Anal. Calcd for $C_{22}H_{16}N_4O_2S$ (%): C, 65.99; H, 4.03; N, 13.99; S, 8.01. Found: C, 65.90; H, 4.06; N, 13.92; S, 7.87.

2.2.10. 2-(3-methoxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4j):

This compound was obtained as greenish yellow solid in a yield of 76%; m.p.: 192- 194 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 3.68 (s, 3H, CH_3), 6.81 (m, 2H, NH, CH), 6.85 (d, j = 8.14 Hz, 1H, ArH), 6.94 (d, j = 9.37 HJz, 2H, ArH), 7.22 (t. j = 8.08 Hz, 1H, ArH), 7.42 (d, j = 6.50 Hz, 2H, ArH), 7.54 (m, 3H, ArH), 7.83 (d, j = 7.95 Hz, 1H, ArH), 7.98 (d, j = 6.15 Hz, 2H, ArH), 8.32 (d, j = 0.98 Hz, 1H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 55.50 (CH_3), 68.85 (N-C-N), 112.78, 113.22, 113.61, 116.21, 118.18, 118.91, 127.51 (2CH), 128.93, 129.85 (2CH), 130.26, 130.40, 131.30, 136.19, 141.43, 147.36, 158.16 (C-OCH_3), 159.84(C=O), 160.89 (C=N), 164.34 (C=N).

IR (KBr, *v*, cm^{-1}); 3259.27(ν_{NH}), 3012.24 (ν_{C-H}), 1653.97 ($\nu_{C=O}$), 1615.35 ($\nu_{C=N}$), 1510.68(strong bending ν_{NH}), 1441.67 (ν_{C-N}), 1295.99 (ν_{N-N}), 1260.28(ν_{C-O}), 685.30 (ν_{C-S}).

MS (m/z): 414.2 (M^+ + H)

Anal. Calcd for $C_{23}H_{18}N_4O_2S$ (%): C, 66.65; H, 4.38; N, 13.52; S, 7.73. Found: C, 66.90; H, 4.34; N, 13.83; S, 7.57.

2.2.11. 2-(4-methoxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4k):

This compound was obtained as brownish yellow solid in a yield of 78%; m.p.: 220- 222 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 3.67 (s, 3H, CH_3), 6.81 (m, 2H, NH, CH), 6.92 (d, j = 8.07 Hz, 2H, , ArH), 7.13 (d, j = 7.99 Hz, 1H, ArH), 7.42 (m, 1H, ArH), 7.55 (m, 5H, ArH), 7.82 (d, j = 8.33 Hz, 2H, ArH), 7.98 (m, 2H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 55.52 (CH_3), 68.70 (N-C-N), 113.16, 114.43 (2CH), 116.20, 118.76, 127.00 (2CH), 128.58 (2CH), 128.90, 129.86 (2CH), 131.20, 131.73, 132.25, 136.15, 147.38, 158.14 (C-OCH_3), 159.66 (C=O), 160.87 (C=N), 164.23 (C=N).

IR (KBr, *v*, cm^{-1}); 3397.48(ν_{NH}), 3057.61 (ν_{C-H}), 1660.24 ($\nu_{C=O}$), 1609.56 ($\nu_{C=N}$), 1504.27(strong bending ν_{NH}), 1455.58 (ν_{C-N}), 1300.42 (ν_{N-N}), 1242.84(ν_{C-O}), 686.93 (ν_{C-S}).

MS (m/z): 414.2 (M^+ + H)

Anal. Calcd for $C_{23}H_{18}N_4O_2S$ (%): C, 66.65; H, 4.38; N, 13.52; S, 7.73. Found: C, 66.73; H, 4.47; N, 13.43; S, 7.88.

2.2.12. 3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-one (4l):

This compound was obtained as brownish yellow solid in a yield of 72%; m.p.: 208- 210 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 6.80 (t, j= 8.07Hz, 1H, NH), 6.92 (d, j = 8.20 Hz, 1H, CH), 7.11 (m, 2H, ArH), 7.14 (d, j = 7.85 Hz, 2H, ArH), 7.19 (d, j = 7.85 Hz, 2H, ArH), 7.39 (d, j = 0.31 Hz, 1H, ArH), 7.55 (m, 3H, ArH), 7.82 (d, j = 0.60 Hz, 1H, ArH), 7.97 (d, j = 6.41 Hz, 2H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6) δ 21.02 (CH_3), 68.86 (N-C-N), 113.23, 116.22, 125.98 (2CH), 127.49 (2CH), 128.90, 129.61 (2CH), 129.88 (2CH), 130.40, 136.16, 136.86, 138.26, 138.30 (C-CH_3), 147.37, 158.16, 160.91 (C=O), 164.25 (C=N), 169.39 (C=N).

IR (KBr, *v*, cm^{-1}); 3373.40 (v_{NH}), 3052.07 (v_{C-H}), 1649.00 ($v_{C=O}$), 1613.00 ($v_{C=N)}$, 1494.77 (strong bending v_{NH}), 1448.97 (v_{C-N}), 1290.22 (v_{N-N}), 682.73 (v_{C-S}).

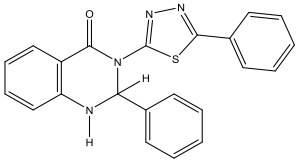
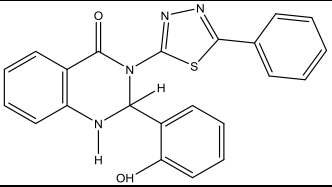
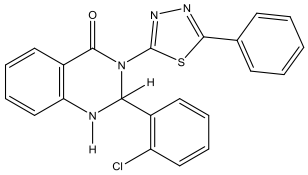
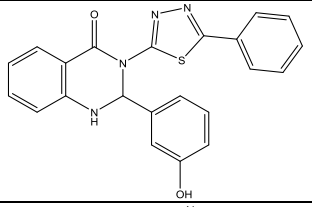
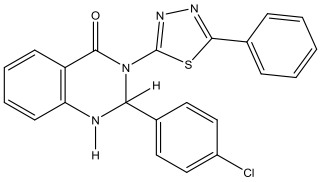
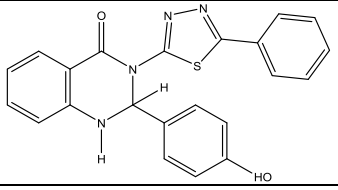
MS (m/z): 398.2 (M^+ + H)

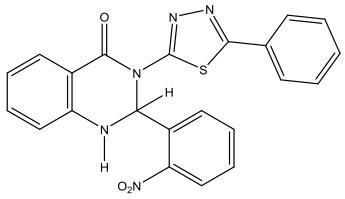
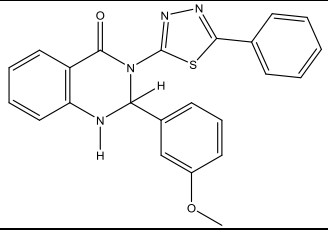
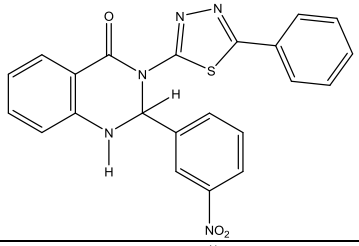
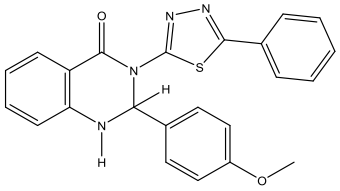
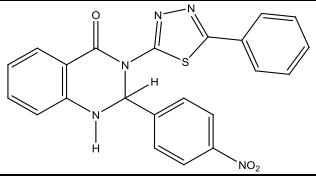
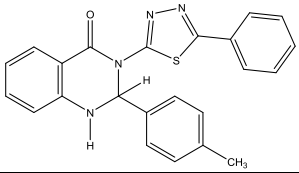
Anal. Calcd for $C_{23}H_{18}N_4OS$ (%): C, 69.33; H, 4.55; N, 14.06; S, 8.05. Found: C, 69.63; H, 4.59; N, 14.16; S, 8.23.

Table 1. groups (X) attached to benzaldehyde

4 & 2:	a	b	c	d	e	f	g	h	i	j	k	l
X:	H	2-Cl	4-Cl	2-NO_2	3-NO_2	4-NO_2	2-OH	3-OH	4-OH	3-OCH_3	4-OCH_3	4-CH_3

Table 2. Structure of compounds

4a		**4g**	
4b		**4h**	
4c		**4i**	

4d		**4j**	
4e		**4k**	
4f		**4l**	

2.3. Antibacterial activity (*In vitro*)

The antibacterial activity of synthesized compounds 4(a-l) were evaluated against two Gram positive and two-gram negative bacteria by using the well diffusion method, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC). Ciprofloxaasin was employed as a standard drug to compare the results. Strains of *Staphylococcus aureus* PTCC1826, *Staphylococcus epidermidis* PTCC1856, *Escherichia coli* PTCC1789, and *Pseudomonas aeruginosa* PTCC1950, were taken from the iranian industrial microorganisms collection center (lyophilized). The bacterial cultures were developed by selective nutrient broth at 37 °C, 24h. Nutrient broth was used for the preparation of inoculums of the bacteria and nutrient agar and broth were used for the screening method[21] and their results were tabulated in Table 3.

2.4. Antifungal activity (*In vitro*)

Also, the antifungal activity of synthesized compounds 4(a-l) were evaluated against two fungal strains by using the well diffusion method, minimum inhibitory concentration (MIC), and minimum fungicidal concentration (MFC). Amphotericin B was employed as a standard drug to compare the results. Strains of *Candida albicans* PTCC5027 and *Aspergillus niger* PTCC5320, were taken from the iranian industrial microorganisms collection center. The fungal cultures were developed by selective Saboroud dextrose broth at 37 °C and stored at 4 °C for further use.

Saboroud dextrose broth was used for the preparation of inoculums of the fungi and Saboroud dextrose agar and broth were used for the screening method[21] and their results were tabulated in Table 4.

2.5. Anti-diabetic propertises by molecular docking (*In silico*)

AutoDock Vina v.1.2.0 was used to perform all docking simulations. A set of new quinazolin derivatives were subjected to docking with Alpha-amylase (PDB ID: 1hny) and Alpha-glucosidase (PDB ID: 2ze0) from the protein data bank (RCSB) (http://www.rcsb.org/pdb). To carry out in silico studies, the 2D structures of the synthesized ligands 4(a-l) were drawn by ChemDraw 19.1.1 and converted to energy minimized 3D structures in the pdb file format using Chem3D. By removing the heteroatoms, water molecule and cofactors, the target protein file was prepared by leaving the associated residue with protein by using Discovery Studio 4.5 Client. Preparation of target protein file AutoDockTools-1.5.6 has been done, which involves the assing of Gasteiger charges for all the atoms of molecules converting into AD4 type. Grid box for 1hny was 64×64×64 and for 2ze0 was 72×72×72. Docking simulations for the compounds 4(a-l) were performed against the active site of Alpha-amylase and Alpha-glucosidase, finally Discovery Studio 4.5 Client was used to visualize docking results tabulated in Table 5 and Figure 1.

3. Results and Discussion

3.1. Chemistry

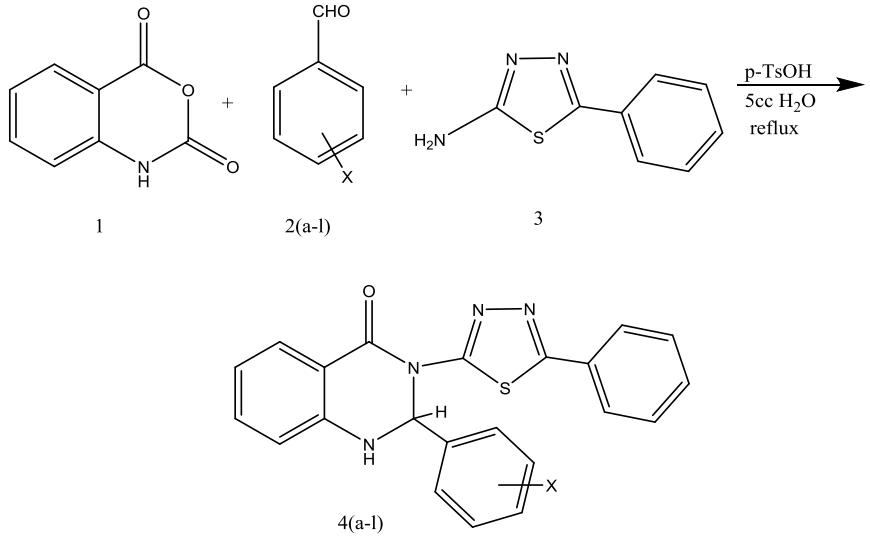
Considering the importance of 2,3-dihydroquinazolin-4(1H)-ones several methods have been revealed for synthesis of these compounds[30-32] In this study the compounds of 2-(substituted phenyl)-3-(5-phenyl-1-3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one 4(a-l) were obtained by refluxing Isatoic anhydride 1, 5-phenyl-1,3,4-thiadiazol-2-amine 3 and aromatic aldehydes 2(a-l) in the presence of p-TsOH as catalyst in H_2O as solvent as shown in scheme 1.

5-phenyl-1,3,4-thiadiazol-2-amine 3 was obtained by refluxing Benzoic acid and thiosemicarbazide in phosphorous oxychloride according to scheme 2.

Different spectral data were used to confirm 2-(substituted phenyl)-3-(5-phenyl-1-3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one 4(a-l). All of the newly synthesized products 4(a-l) were characterized by FT-IR spectroscopy, ^{1}H and ^{13}C NMR spectra, mass spectrometry and elemental analysis. In the FT-IR spectra of compounds 4(a-l) the strong and sharp absorption bands due to

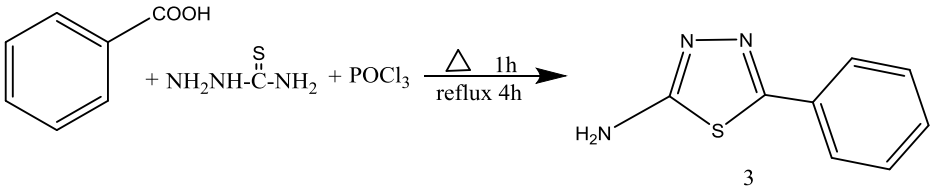
NH and (N-CO) groups were observed at around 3379–3282 cm^{-1} and 1655–1608 cm^{-1}, respectively.

Also, in the ^{1}H NMR spectra, the NH proton of the 2,3- dihydroquinazolin-4(1H)-one ring appeared as a broad signal at 8.36-7.03 ppm and C-H proton of position 2 appeared at 5.8-6.5ppm.The ^{13}C NMR spectra showed a signal at 171–162 ppm assigned to the (N-C=O) group and a signal for C-H at 66-70 ppm that confirmed the synthesis of 2,3-dihydroquinazolin-4(1H)-ones.



X : H, 4-NO_2 , 3-NO_2 , 2-NO_2 , 4-OH, 3-OH, 2-OH , 4-Cl , 2-Cl , 4-OCH_3 , 3-OCH_3 , 4-CH_3

Scheme 1. Synthesis of 2-substituted-2,3-dihydroquinazolin-4(1H)-one derivatives



Scheme 2. Synthesis of 5-phenyl-1,3,4-thiadiazol-2-amine

3.2. Antibacterial activity (*In vitro*)

As illustrated by the inhibition zone in Table 3, all tested compounds showed antibacterial activity against all Gram-positive and Gram-negative strains. The greatest effects of all compounds in bacteria samples were observed against *E. coli*. The best effect of the compounds against Gr^{+} bacteria's: *S. aureus*: 4k: (IZ = 26±0.52), (MIC = 250), (MBC = 500). *S.*

epidermidis: 4j: (IZ = 28±0.31), (MIC = 125) (MBC = 250). In this group (Gr+), compound 4k has the highest performance compared with ciprofloxasin than the other compounds, 4k probably works well in penetrating the membrane of these bacteria and causes more degradation of peptidoglycans than the other synthetic structures. The best effect of the compounds against Gr- bacteria's: *E. coli*: 4l: (IZ = 31±0.96), (MIC = 125) (MBC = 250). *P. aeruginosa*: 4i*:* (IZ = 26±0.14), (MIC = 250) (MBC = 500). In this group (Gr-), 4l has shown the highest performance compared with ciprofloxasin than the other compounds. This compound is likely to penetrate and destroy these bacteria by destroying the inner and outer membranes. According to the results obtained from the antibacterial activity of the compounds, it can be concluded that the synthesized compounds that have substituted phenyl groups along with thiadiazol and quinazoline 4(a-l) compared to other compounds in this study, can perform good in eliminating human bacterial pathogens.

Table 3. Antibacterial activity of compounds 4(a-l)

Concentration of compounds: 1mg/ml
Inhibition Zone (IZ): mm
Minimum Inhibitory Concentration (MIC): 0-1000µg/ml
Minimum Bactericidal Concentration (MBC): 0-1000µg/ml
±: average three times
Cip: Ciprofloxacin
Well diameter: 9mm

	Gr+						**Gr-**					
	***S. aureus* PTCC1826**			***S. epidermidis* PTCC1856**			***E. coli* PTCC1789**			***P. aeruginosa* PTCC1950**		
compounds	**IZ**	**MIC**	**MBC**	**IZ**	**MIC**	**MBC**	**IZ**	**MIC**	**MBC**	**IZ**	**MIC**	**MBC**
4a	19±0.22	500	1000	21±0.23	500	1000	17±0.33	1000	1000	21±0.02	500	1000
4b	21±0.21	250	500	22±0.26	250	500	19±0.42	1000	1000	21±0.21	500	1000
4c	17±0.96	500	1000	14±0.75	1000	1000	16±0.78	1000	1000	20±0.48	500	1000
4d	14±0.33	1000	1000	15±0.34	1000	1000	12±0.92	1000	1000	16±0.92	1000	1000
4e	16±0.28	500	1000	19±0.67	500	1000	14±0.28	1000	1000	14±0.35	1000	1000
4f	16±0.66	500	1000	17±0.33	500	1000	19±0.34	1000	1000	19±0.46	1000	1000
4g	16±0.66	500	1000	16±0.33	1000	1000	18±0.39	1000	1000	19±0.44	1000	1000
4h	19±0.56	500	1000	22±0.42	250	500	21±0.37	500	1000	25±0.23	500	1000
4i	18±0.41	500	1000	19±0.22	500	1000	22±0.82	500	1000	**26±0.14**	**250**	**500**
4j	24±0.76	250	500	**28±0.31**	**125**	**250**	24±0.47	500	1000	21±0.29	500	1000
4k	**26±0.52**	**250**	**500**	25±0.57	250	500	26±0.33	500	1000	24±0.68	250	500
4l	24±0.19	250	500	27±0.29	125	250	**31±0.96**	**125**	**250**	24±0.16	250	500
Cip	41±0.35	15.62	31.25	46±0.21	7.81	15.625	37±0.33	31.25	62.50	34±0.66	62.50	125

3.3. Antifungal activity (*In vitro*)

It was found that the synthesized compounds exhibited varied antifungal effects against two fungal strains (Table 4). The highest number of compounds affecting antifungal activity was observed against *C .albicans*. The best effect of the compounds against Fungal specimens: *C. albicans*: 4j (IZ = 26±0.33), (MIC = 250), (MBC = 500) and *A. niger*: 4k (IZ = 21±0.66), (MIC = 500), (MBC = 1000). According to the results obtained from the antifungal activity of the

compounds, it can be concluded that the synthesized compounds that have substituted phenyl groups along with thiadiazol and quinazoline 4(a-l) compared with Amphotericin-B in this study, can perrform good in eliminating human fungal pathogens.

Table 4. Antifungal activity of compounds 4(a-l).

Concentration of compounds: 1mg/ml
Inhibition Zone (IZ): mm
Minimum Inhibitory Concentration (MIC): 0-1000µg/ml
Minimum Fungicidal Concentration (MFC): 0-1000µg/ml
±: average three times
AB: Amphotericin B
NA: No Activity
Well diameter: 9mm

compounds	*C .albicans* PTCC5027			*A .niger* PTCC5320		
	IZ	**MIC**	**MFC**	**IZ**	**MIC**	**MFC**
4a	21±0.33	500	1000	17±0.66	1000	1000
4b	23±0.33	500	1000	20±0.66	500	1000
4c	20±0.33	500	1000	14±0.66	1000	1000
4d	14±0.33	1000	1000	11±0.66	NA	NA
4e	19±0.33	1000	1000	15±0.66	1000	1000
4f	19±0.33	1000	1000	16±0.66	1000	1000
4g	17±0.33	1000	1000	12±0.66	NA	NA
4h	21±0.33	500	1000	19±0.66	1000	1000
4i	20±0.33	500	1000	14±0.66	1000	1000
4j	**26±0.33**	**250**	**500**	20±0.66	500	1000
4k	25±0.33	500	1000	**21±0.66**	**500**	**1000**
4l	21±0.33	500	1000	19±0.66	1000	1000
AB	36±0.33	62.50	125	34±0.66	62.50	125

3.4. Anti-diabetic (*In silico*)

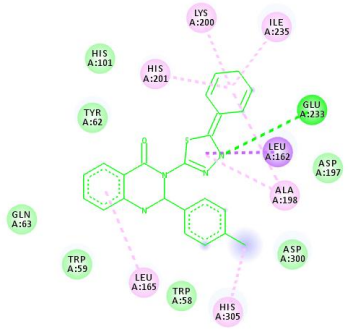
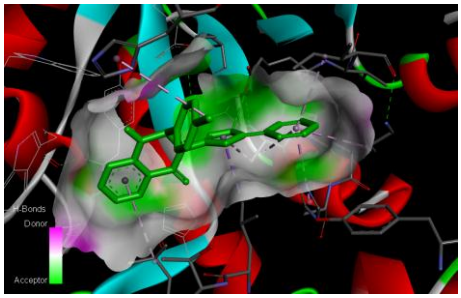
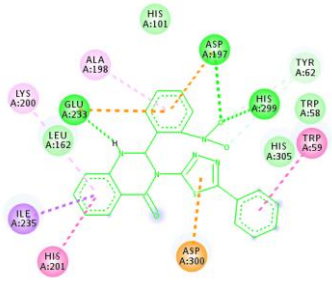
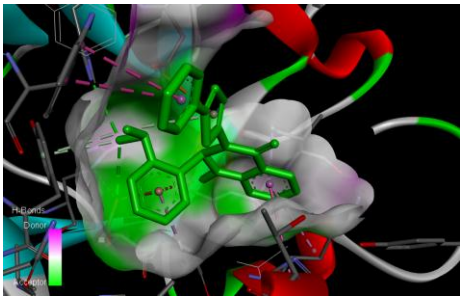
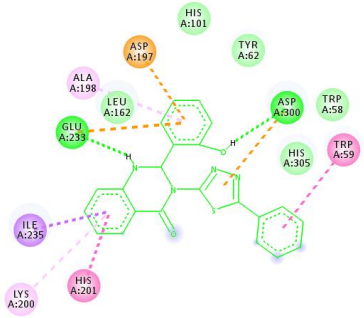
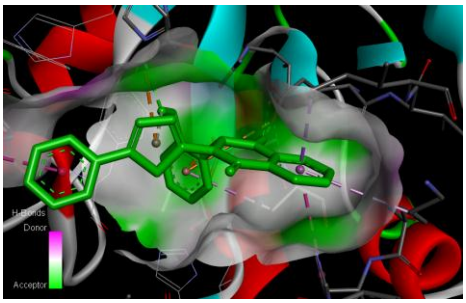
In this section, it has been performed docking simulation of the newly synthesized derivatives **4(a–l)** binding the active site of the Alpha-amylase (PDB ID: 1hny) and Alpha-glucosidase (PDB ID: 2ze0). The docking result of the tested compounds **4c**, **4d** and **4g** showed lowest ΔG_{bind} with Alpha-amylase by -10.0 kcal/mol, and compounds **4e**, **4f** and **4i** showed lowest ΔG_{bind} , Respectively -10.6, -9.5 and -10.1 with Alpha-glucosidase. The binding energies, inhibition constants, and residues involved in H-bonding are tabulated in Table 5 and Figure 1 & 2.

Table 5- Molecular docking reports for compounds *4(a-l)* against protein 1hny and 2ze0.

compounds	Total Energy (Kcal/mol)	Alpha-amylase PDB ID: 1hny		Alpha-glucosidase PDB ID: 2ze0	
		Affinity (Kcal/mol)	**H-Bond**	**Affinity (Kcal/mol)**	**H-Bond**
4a	11.3828	-9.6	-	-8.9	Arginine: 407
4b	13.3308	-9.1	-	-9.4	Arginine: 407
4c	11.6324	**-10.0**	**Glutamic acid: 233**	-9.2	Valine: 383

4d	-12.5194	**-10.0**	**Aspartic acid: 197 Glutamic acid: 233 Histidine: 299**	-9.1	Arginine: 407
4e	-2.1596	-9.1	-	**-10.6**	**Arginine: 407 Glutamine: 167**
4f	7.2655	-8.7	-	**-9.5**	**Arginine: 197 Asparagine: 324**
4g	7.8283	**-10.0**	**Glutamic acid: 233 Aspartic acid: 300**	-9.0	Arginine: 407
4h	9.9999	-9.1	-	-9.0	Arginine: 407
4i	10.1567	-9.5	-	**-10.1**	**Arginine: 407 Glutamine: 167**
4j	16.9915	-9.1	-	-9.1	Arginine: 407
4k	17.1349	-9.5	-	-9.0	-
4l	11.1987	-9.8	-	-9.3	-

362

compounds	**Alpha-amylase, PDB ID: 1hny**	
	2D	**3D**
4c		
4d		
4g		

363 **Fig 1. Ligand–Protein 2D and 3D interaction on the active site of 1hny.**

364

compounds	**Alpha-glucosidase, PDB ID: 2ze0**	
	2D	**3D**

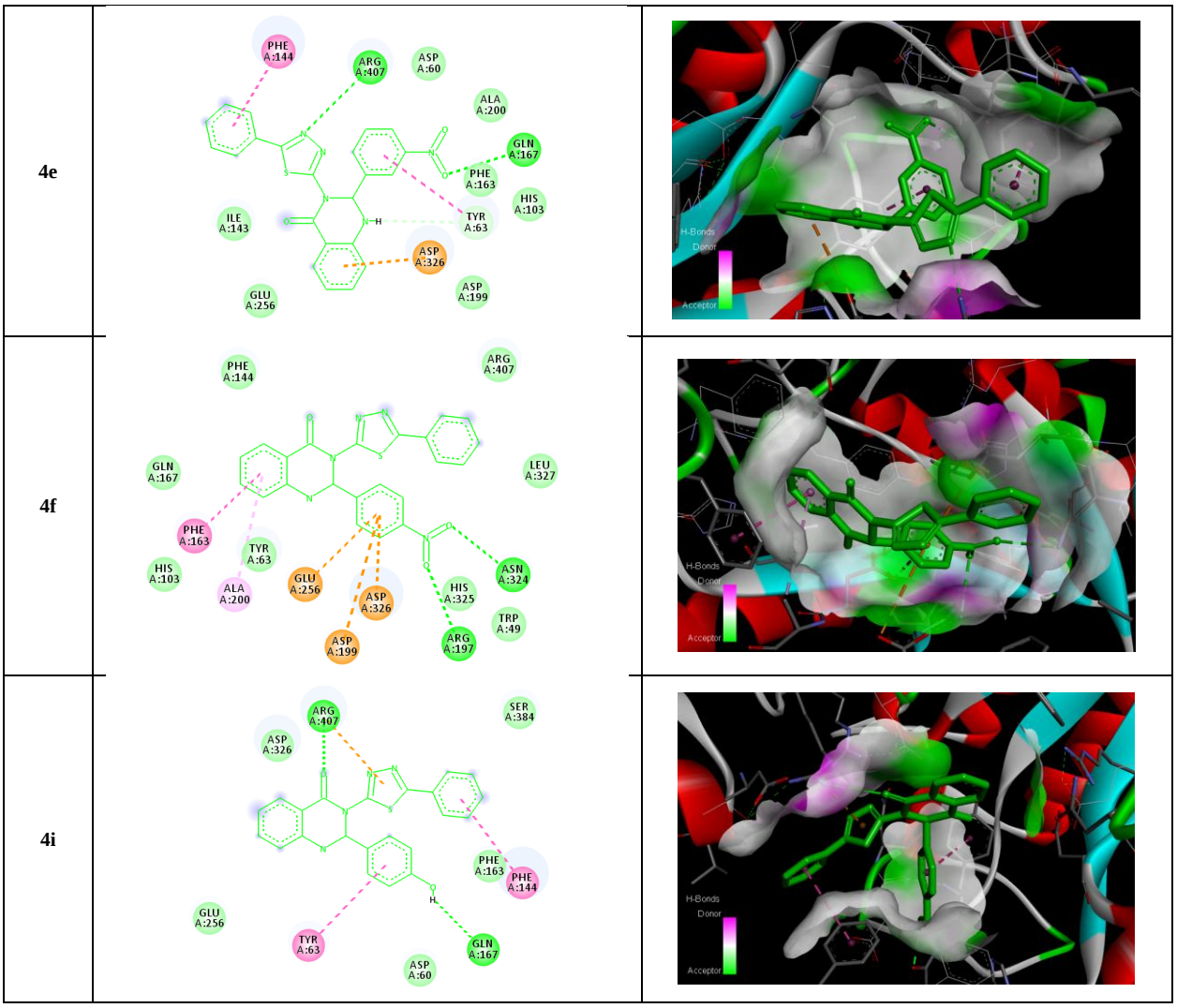


Fig 2. Ligand–Protein 2D and 3D interaction on the active site of 2ze0.

4. Conclusion

In summary, in the present study target molecules 4(a-l) were synthesized via a one-pot condensation reaction between isatoic anhydride 1 and 5-phenyl-1,3,4-thiadiazol-2-amine 3 with aromatic aldehydes 2(a-l) using p-TsOH as a catalyst in refluxing water. The newly synthesized compounds were characterized by Mass, FT- IR, ^{1}H NMR,^{13}C NMR spectra and analytical methods. The antibacterial activities of the synthesized compounds showed that compounds 4k against *S. aureus*, 4j against *S. epidermidis*, 4l against *E. coli*, and 4i against *P. aeruginosa* have comparable inhibitory effects with the standards used. also, The antifungal activities of the synthesized compounds showed that compounds 4j against *C .albicans* and 4k against *A .niger* have comparable inhibitory effects with the standards used. All compounds showed good results

especially compound 4e showed the lowest ΔG_{bind} results (-10.6 Kcal/mol) against Alpha-glucosidase and compounds 4c and 4g showed the lowest ΔG_{bind} results (-10.0 Kcal/mol) against Alpha-amylase.

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