Scientific paper

Synthesis, Antimicrobial and Molecular Docking Studies of Some New Derivatives of 2,3-Dihydroquinazolin-4(1*H*)-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(1*H*)-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 the catalyst and in H_2O as the solvent and characterized by spectroscopic data and analytical methods. Antibacterial and antifungal activity of the title compounds were evaluated against two Gram positive and two Gram negative bacterial strains and strains of fungi and compared with ▪standard drugs, using well diffusion method minimum bactericidal/fungicidal concentration were determined. The potential α-amylase and α-glucosidase inhibitory activity of compounds **4a**–**l** were investigated *in silico* using molecular docking simulation method. Therefore, these 2,3-dihydroquinazolin-4(1*H*)-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(1*H*)-one, antibacterial activity, antifungal activity, anti-diabetic activity.

1. Introduction

The 2,3-dihydroquinazolin-4(1*H*)-one (DHQ) is an important nitrogen-containing heterocyclic scaffold. DHQ ring system is a distinguished scaffold in drug design. DHQ in medicinal chemistry acting 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 inhibitory,[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 are known to possess interesting biological properties such as antibacterial,[18,19] antifungal,[20–22] anticancer,[23–25] antihypertensive[26,27] activities. 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 carbons 2 and 3. Due to their attractive properties, 2-substituted DHQs are becoming prominent synthetic intermediates for organic chemists and pharmacologist.

Based on the above observations we report here the synthesis of a new series of 2,3-dihydroquinazolin-4(1*H*)-one derivatives **4a**–**l** with structure modifications involving incorporation of 5-phenyl-1,3,4-thiadiazol-2-amine (**3**) at position 3 and aromatic aldehydes **2a**–**l** at position 2 of DHQ ring system. In the present study, various aryl aldehyde 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 dextrose and agar/broth) were obtained from Merck, Germany and used without any additional filtration. Microbiological tests were performed using a Memmert INC153T2T3 incubator. Melting points were determined in Philip Harris

C4954718 melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet Nexus-670 FTIR spectrophotometer, using potassium bromide pellets and the frequencies are expressed in cm^{-1}. The ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer, using TMS as the internal reference, with DMSO-d_6 as the solvent. 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, 70 eV). Elemental analysis was 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 7.53 g (85%); m.p. 225–227 °C; IR (KBr, cm^{-1}): ν_{max} 3267.45, 3062.96 (NH), 1629.53 (C=N), 1510.55 (strong bending NH), 664.71 (C–S); ^1H NMR (500 MHz, DMSO-d_6) δ 7.42 (s, 2H, NH), 7.44–7.46 (m, 3H, ArH), 7.74 (d, J = 7.7 Hz, 2H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 126.7 (2CH), 129.6 (2CH), 130.0 , 131.4 , 156.8 (C=N), 169.0 (C=N). MS m/z 177.1 (M^+ + H). Anal. Calcd for $C_8H_7N_3S$: 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(1*H*)-ones 4a–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] See Tables 1 and 2 and Scheme 1.

2-Phenyl-3-(5-Phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4a)

This compound was obtained as light brown solid in a yield 0.3113 g (81%); m.p. 171–173 °C. IR (KBr, cm^{-1}): ν_{max} 3364.47 (NH), 3033.20 (C–H), 1633.86 (C=O), 1500.59 (C=N), 1448.65 (strong bending NH), 1386.63 (C–N), 1180.94 (N–N), 689.71 (C–S). ^1H NMR (500 MHz, DMSO-d_6): δ 6.81 (t, J = 7.5 Hz, 1H, NH), 6.93 (d, J = 8.2 Hz, 1H, CH), 7.32 (m, 5H, ArH), 7.41 (t, J = 3.8 Hz, 1H, ArH), 7.44 (d, J = 0.58 Hz, 1H, ArH), 7.55 (m, 3H, ArH), 7.82 (d, J = 7.9 Hz, 1H, ArH), 7.98 (d, J = 6.5 Hz, 2H, ArH), 8.34 (d, J = 0.2 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 69.0 (N-C-N), 113.2, 116.2, 118.9, 126.1 (2CH), 127.5 (2CH), 128.9, 128.9, 129.1 (2CH), 129.9 (2CH), 130.4, 131.3, 136.2, 139.8, 147.3, 158.2 (C=O), 160.9 (C=N), 164.3 (C=N). 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-Chlorophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4b)

This compound was obtained as brownish yellow solid in a yield 0.3518 g (84%); m.p. 210–212 °C. IR (KBr, cm^{-1}): ν_{max} 3324.17 (NH), 3056.76 (C–H), 1661.58 (C=O), 1615.33 (C=N), 1506.09 (strong bending NH), 1439.22 (C–N), 1245.53 (N–N), 748.42 (C–Cl), 685.60 (C–S). ^1H NMR (500 MHz, DMSO-d_6): δ 6.86 (t, J = 7.6 Hz, 1H, NH), 6.90 (d J = 8.2 Hz, 1H, CH), 7.07 (d, J = 7.8 Hz, 1H, ArH), 7.20 (t, J = 7.7 Hz, 1H, ArH), 7.33 (t, J = 7.6 Hz, 1H, ArH), 7.41 (t, J = 7.8 Hz, 1H, ArH), 7.53 (t, J = 3.3 Hz, 3H, ArH), 7.57 (d, J = 7.9 Hz, 1H, ArH), 7.60 (d, J = 3.3 Hz, 1H, ArH), 7.93 (t, J = 7.4 Hz, 3H, ArH), 8.11 (d, J = 4.2 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 67.2 (N–C–N), 112.5, 116.5, 119.1, 125.8, 127.5 (2CH), 128.1, 128.8, 129.9 (2CH), 130.3, 130.9 (2CH), 131.4 (C–Cl), 132.1, 136.3, 136.9, 146.1, 157.4 (C=O), 160.9 (C=N), 164.5 (C=N). 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-(4-Chlorophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4c)

This compound was obtained as greenish yellow solid in a yield 0.3560 g (85%); m.p. 227–229 °C. IR (KBr, cm^{-1}): ν_{max} 3377.68 (NH), 3053.97 (C–H), 1650.19 (C=O), 1613.78 (C=N), 1488.61 (strong bending NH), 1447.76 (C–N), 1253.00 (N–N), 756.40 (C–Cl), 684.14 (C–S). ^1H NMR (500 MHz, DMSO-d_6): δ 6.82 (t, J = 7.4 Hz, 1H, NH), 6.94 (d, J = 8.2 Hz, 1H, CH), 7.33 (d, J = 8.2 Hz, 2H, ArH), 7.39 (d, J = 8.3 Hz, 2H, ArH), 7.43 (d, J = 8.6 Hz, 2H, ArH), 7.54 (t, J = 4.0 Hz, 3H, ArH), 7.82 (d, J = 7.9 Hz, 1H, ArH), 8.0 (m, 2H, ArH), 8.31 (d, J = 4.0 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 68.5 (N–C–N), 113.2, 116.3, 119.1, 127.5 (2CH), 128.1 (2CH), 129.0, 129.2 (2CH), 129.9 (2CH), 130.4, 131.3 (C–Cl), 133.6, 136.3, 138.8, 147.1, 158.1 (C=O), 160.7 (C=N), 164.4 (C=N). 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-Nitrophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4d)

This compound was obtained as yellow solid in a yield 0.3521 g (82%); m.p. 199–201 °C. IR (KBr, cm^{-1}):

ν_{max} 3356.94 (NH), 3063.28 (C–H), 1660.59 (C=O), 1615.85 (C=N), 1509.00 (strong bending NH), 1438.99 (C–N), 1509.00 and 1338.31 (NO_2), 1248.33 (N–N), 687.14 (C–S). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.88 (t, *J* = 0.5 Hz, 1H, NH), 7.27 (d, *J* = 7.4 Hz, 1H, CH), 7.41 (t, *J* = 8.08 Hz, 1H), 7.47 (d, *J* = 6.82 Hz, 1H), 7.52 (t, *J* = 1.98 Hz, 3H), 7.59 (t, *J* = 8.7 Hz, 2H, ArH), 7.92 (m, 4H, ArH), 8.02 (d, *J* = 0.8 Hz, 1H, ArH), 8.12 (d, *J* = 7.6 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 65.9 (N–C–N), 112.7, 117.2, 119.6, 126.2, 126.5, 127.5 (2CH), 128.8, 129.8 (2CH), 130.2, 130.7, 131.4, 134.6, 134.8, 136.4, 146.0, 147.8 (C–NO_2), 157.5 (C=O), 160.6 (C=N), 164.6 (C=N). 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-(3-Nitrophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4e)

This compound was obtained as brownish yellow solid in a yield 0.3649 g (85%); m.p. 226–228 °C. IR (KBr, cm^{-1}): ν_{max} 3353.50 (NH), 3065.72 (C–H), 1659.93 (C=O), 1613.78 (C=N), 1519.31 (strong bending NH), 1444.15 (C–N), 1519.31 and 1357.73 (NO_2), 1300.09 (N–N), 686.53 (C–S). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.84 (t, *J* = 7.6 Hz, 1H, NH), 6.98 (d, *J* = 8.2 Hz, 1H, CH), 7.44 (t, *J* = 7.5 Hz, 1H, ArH), 7.56 (t, *J* = 3.5 Hz, 3H, ArH), 7.58 (d, *J* = 3.9 Hz, 1H, ArH), 7.62 (d, *J* = 8.0 Hz, 1H, ArH), 7.68 (d, *J* = 7.8 Hz, 1H, ArH), 7.85 (d, *J* = 3.3 Hz, 1H, ArH), 7.98 (m, 2H, ArH), 8.14 (d, *J* = 8.1 Hz, 1H, ArH), 8.30 (s, 1H, ArH), 8.43 (d, *J* = 4.0 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 68.3 (N–C–N), 113.1, 116.4, 119.4, 121.3, 124.0, 127.5 (2CH), 129.0, 129.9 (2CH), 130.3, 130.9, 131.4, 132.4, 136.4, 142.1, 146.8, 148.5 (C–NO_2), 158.0 (C=O), 160.5 (C=N), 164.6 (C=N). 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-(4-Nitrophenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4f)

This compound was obtained as light green solid in a yield 0.3606 g (84%); m.p. 190–192 °C. IR (KBr, cm^{-1}): ν_{max} 3371.85 (NH), 3058.92 (C–H), 1657.13 (C=O), 1609.39 (C=N), 1520.35 (strong bending NH), 1441.98 (C–N), 1490.12 and 1347.08 (NO_2), 1306.95 (N–N), 693.16 (C–S). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.85 (t, *J* = 7.6 Hz, 1H, NH), 6.96 (d, *J* = 8.3 Hz, 1H, CH), 7.44 (t, *J* = 8.0 Hz, 1H, ArH), 7.56 (m, 3H, ArH), 7.59 (m, 3H, ArH), 7.83 (t, *J* = 4.0 Hz, 1H, ArH), 7.99 (d, *J* = 3.6 Hz, 2H, ArH), 8.20 (d, *J* = 8.4 Hz, 2H, ArH), 8.41 (d, *J* = 3.7 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 68.5 (N–C–N), 113.2, 116.4, 119.4, 124.4 (2CH), 127.5 (2CH), 127.6 (2CH), 129.0, 129.9 (2CH), 130.3, 131.4, 136.4, 146.8, 147.0 (C–NO_2), 148.0, 158.0 (C=O), 160.5 (C=N), 164.5 (C=N). 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-Hydroxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4g)

This compound was obtained as green solid in a yield 0.3123 g (78%); m.p. 218–220 °C. IR (KBr, cm^{-1}): ν_{max} 3380.01 (NH), 3060.60 (O–H), 2946.15 (C–H), 1665.55 (C=O), 1609.81 (C=N), 1496.30 (strong bending NH), 1456.32 (C–N), 1312.71 (N–N), 1236.41(C–O), 687.01 (C–S). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.61 (t, *J* = 7.4 Hz, 1H, NH), 6.75 (d, *J* = 8.5 Hz, 1H, CH), 6.90 (t, *J* = 8.6 Hz, 2H, ArH), 7.12 (m, 1H, ArH), 7.35 (t, *J* = 7.8 Hz, 1H, ArH), 7.48 (d, *J* = 7.0 Hz, 2H, ArH), 7.53 (m, 2H, ArH), 7.77 (m, 2H, ArH), 7.86 (d, *J* = 8.1 Hz, 1H, ArH), 7.93 (d, *J* = 5.0 Hz, 2H, ArH), 10.23 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 66.0 (N–C–N), 112.4, 116.1, 116.2, 118.4, 119.0, 125.4, 125.6, 127.4 (2CH), 128.7, 129.8 (2CH), 130.0, 130.4, 131.2, 135.9, 147.2, 155.2 (C–OH), 157.6 (C=O), 161.4 (C=N), 164.2 (C=N). 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-(3-Hydroxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4h)

This compound was obtained as brown solid in a yield 0.3203 g (80%); m.p. 207–209 °C. IR (KBr, cm^{-1}): ν_{max} 3275.51(NH), 3075.36 (O–H), 2910.10 (C–H), 1601.72 (C=O), 1505.26 (C=N), 1505.26 (strong bending NH), 1448.04 (C–N), 1379.91 (N–N), 1216.41(C–O), 683.43 (C–S). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.68 (t, *J* = 1.3 Hz, 1H, NH), 6.79 (d, *J* = 7.0 Hz, 1H, CH), 6.93 (m, 1H, ArH), 7.13 (t, *J* = 4.4 Hz, 3H, ArH), 7.42 (t, *J* = 8.7 Hz, 4H, ArH), 7.72 (d, *J* = 8.1 Hz, 1H, ArH), 7.83 (m, 2H, ArH), 7.99 (d, *J* = 8.1 Hz, 2H, ArH), 9.93 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 68.9 (N–C–N), 115.4, 115.8, 116.2, 116.9, 118.8, 127.5 (2CH), 128.9, 129.9 (2CH), 130.4, 131.3, 131.6, 134.2, 136.2, 141.3, 145.9, 147.4 (C–OH), 157.9 (C=O), 164.3 (C=N), 170.0 (C=N). 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-(4-Hydroxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4i)

This compound was obtained as red solid in a yield 0.3203 g (80%); m.p. 210–212 °C. IR (KBr, cm^{-1}): ν_{max} 3281.73 (NH), 3152.73 (O–H), 2929.54 (C–H), 1616.59 (C=O), 1582.00 (C=N), 1526.97 (strong bending NH), 1501.20 (C–N), 1299.01 (N–N), 1258.42 (C–O), 678.90 (C–S). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.69 (m, 2H, NH, CH), 6.95 (d, *J* = 8.5 Hz, 2H, ArH), 7.13 (t, *J* = 4.0 Hz, 3H, ArH), 7.33 (t, *J* = 3.0 Hz, 1H, ArH), 7.55 (m, 2H, ArH), 7.78 (m, 2H, ArH), 7.98 (d, *J* = 7.6 Hz, 2H, ArH), 8.23 (d, *J* = 1.4 Hz, 1H, ArH), 9.80 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 68.8 (N–C–N), 113.1, 116.2, 118.7, 126.9 (2CH), 127.5 (2CH), 128.6 (2CH), 128.9, 129.7 (2CH), 130.5, 136.1, 138.2, 146.0, 147.4, 158.0 (C–

OH), 163.8 (C=O), 164.2 (C=N), 169.3 (C=N). 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-(3-Methoxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4j)

This compound was obtained as greenish yellow solid in a yield 0.3149 g (76%); m.p. 192–194 °C. IR (KBr, cm^{-1}): ν_{max} 3259.27 (NH), 3012.24 (C–H), 1653.97 (C=O), 1615.35 (C=N), 1510.68 (strong bending NH), 1441.67 (C–N), 1295.99 (N–N), 1260.28 (C–O), 685.30 (C–S). ^{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* = 8.1 Hz, 1H, ArH), 6.94 (d, *J* = 9.4 Hz, 2H, ArH), 7.22 (t. *J* = 8.1 Hz, 1H, ArH), 7.42 (d, *J* = 6.5 Hz, 2H, ArH), 7.54 (m, 3H, ArH), 7.83 (d, *J* = 8.0 Hz, 1H, ArH), 7.98 (d, *J* = 6.2 Hz, 2H, ArH), 8.32 (d, *J* = 1.0 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.5 (CH_3), 68.8 (N–C–N), 112.8, 113.2, 113.6, 116.2, 118.2, 118.9, 127.5 (2CH), 128.9, 129.8 (2CH), 130.3, 130.4, 131.3, 136.2, 141.4, 147.4, 158.2 (C–OCH_3), 159.8 (C=O), 160.9 (C=N), 164.3 (C=N). 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-(4-Methoxyphenyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (4k)

This compound was obtained as brownish yellow solid in a yield 0.3232 g (78%); m.p. 220–222 °C. IR (KBr, cm^{-1}): ν_{max} 3397.48 (NH), 3057.61 (C–H), 1660.24 (C=O), 1609.56 (C=N), 1504.27 (strong bending NH), 1455.58 (C–N), 1300.42 (N–N), 1242.84 (C–O), 686.93 (C–S). ^{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* = 8.1 Hz, 2H, ArH), 7.13 (d, *J* = 8.0 Hz, 1H, ArH), 7.42 (m, 1H, ArH), 7.55 (m, 5H, ArH), 7.82 (d, *J* = 8.3 Hz, 2H, ArH), 7.98 (m, 2H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.5 (CH_3), 68.7 (N–C–N), 113.2, 114.4 (2CH), 116.2, 118.76, 127.0 (2CH), 128.6 (2CH), 128.9, 129.9 (2CH), 131.2, 131.7, 132.2, 136.2, 147.4, 158.1 (C–OCH_3), 159.7 (C=O), 160.9 (C=N), 164.2 (C=N). 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.

3-(5-Phenyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (4l)

This compound was obtained as brownish yellow solid in a yield 0.2868 g (72%); m.p. 208–210 °C. IR (KBr, cm^{-1}): ν_{max} 3373.40 (NH), 3052.07 (C–H), 1649.00 (C=O), 1613.00 (C=N), 1494.77 (strong bending NH), 1448.97 (C–N), 1290.22 (N–N), 682.73 (C–S). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 6.80 (t, *J* = 8.07 Hz, 1H, NH), 6.92 (d, *J* = 8.2 Hz, 1H, CH), 7.11 (m, 2H, ArH), 7.14 (d, *J* = 7.8 Hz, 2H, ArH), 7.19 (d, *J* = 7.8 Hz, 2H, ArH), 7.39 (d, *J* = 0.3 Hz, 1H, ArH), 7.55 (m, 3H, ArH), 7.82 (d, *J* = 0.6 Hz, 1H, ArH), 7.97 (d, *J* = 6.4 Hz, 2H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.0 (CH_3), 68.9 (N–C–N), 113.2, 116.2, 126.0 (2CH), 127.5 (2CH), 128.9, 129.6 (2CH), 129.9 (2CH), 130.4, 136.2, 136.9, 138.3, 138.3 (C–CH_3), 147.4, 158.2, 160.9 (C=O), 164.2 (C=N), 169.4 (C=N). 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.

2. 3. Antibacterial Activity (*In vitro*)

The antibacterial activity of synthesized compounds **4a–l** was 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). Ciprofloxacin was employed as the 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, 24 h. 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 are shown in Table 3.

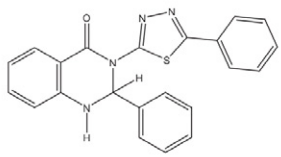
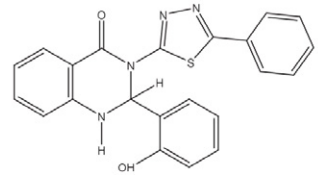
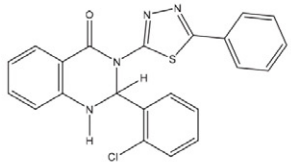
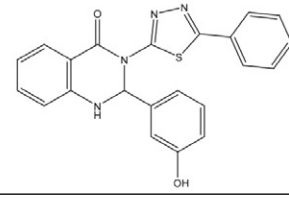
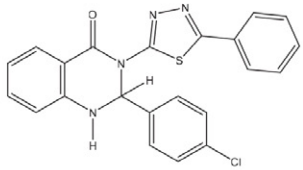
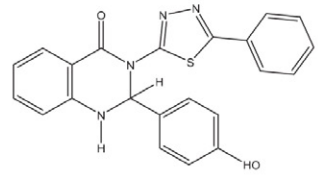
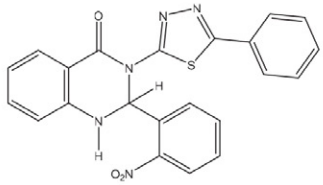
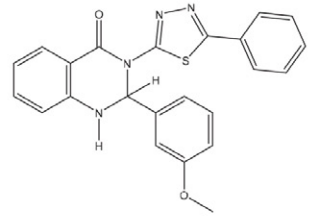
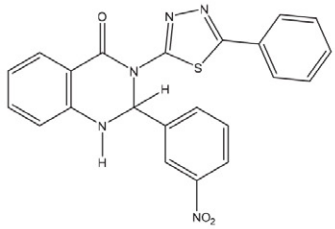
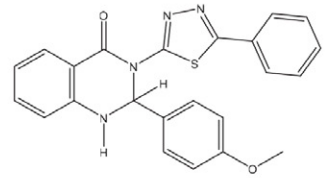
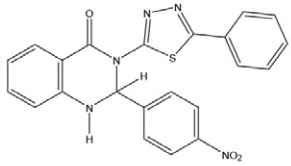
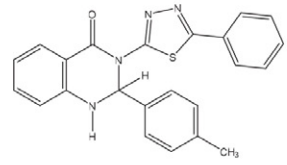
2. 4. Antifungal Activity (*In vitro*)

Also the antifungal activity of synthesized compounds **4a–l** was 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 the 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 Sabouraud dextrose broth at 37 °C and stored at 4 °C for further use. Sabouraud dextrose broth was used for the preparation of inoculums of the fungi and Sabouraud dextrose agar and broth were used for the screening method[21] and their results are presented in Table 4.

Table 1. Groups (X) attached to benzaldehyde

4 and 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–l**

4a		**4g**	
4b		**4h**	
4c		**4i**	
4d		**4j**	
4e		**4k**	
4f		**4l**	

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 α-amylase (PDB ID: 1hny) and α-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 **4a–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 assigning 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 **4a–l** were performed against the active site of α-amylase and α-glucosidase, finally Discovery Studio 4.5 Client was used to visualize docking results, which are shown in Table 5 and Figure 1.

3. Results and Discussion

3. 1. Chemistry

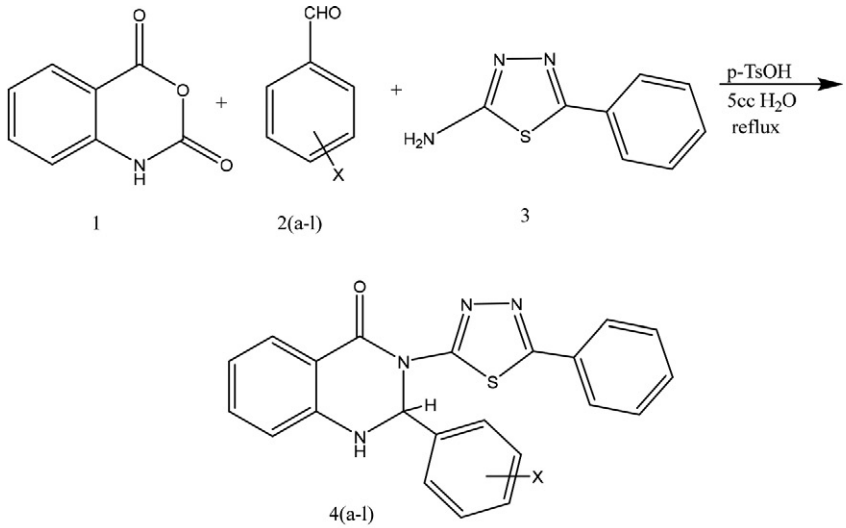
Considering the importance of 2,3-dihydroquinazolin-4(1*H*)-ones several methods have been revealed for the synthesis of these compounds.[30–32] In this study compounds 2-(substituted phenyl)-3-(5-phenyl-1-3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one **4a–l** were obtained by refluxing isatoic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

Compounds **4a–l** contain a chiral center at the carbon 2 that is formed during the reaction. Hence, these compounds are in the form of racemate. Racemates consist of an equimolar mixture of two enantiomers. About more than half of the drugs currently in use are chiral compounds and near 90% of the last ones are marketed as racemates. Indeed, numerous studies have demonstrated that drug enantiomers may interact differently with biological macromolecules. Replacing existing racemates with unichiral drugs may result in improved safety and efficacy profile of various racemates.[33,34]

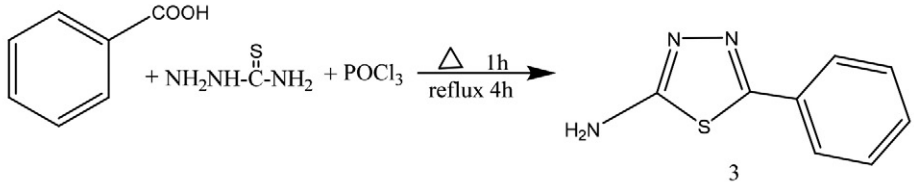
5-Phenyl-1,3,4-thiadiazol-2-amine (**3**) was obtained by refluxing benzoic acid and thiosemicarbazide in phosphorous oxychloride (Scheme 2).

Different spectroscopic data were used to confirm 2-(substituted phenyl)-3-(5-phenyl-1-3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-ones **4a–l**. All of the newly synthesized products **4a–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 **4a–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(1*H*)-one ring appeared as a broad signal at 8.36–7.03 ppm and C–H proton of position 2 appeared at 5.8–6.5 ppm.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(1*H*)-ones.



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



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

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 Gram positive bacteria: *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 (Gram positive bacteria), compound **4k** has the highest performance compared with ciprofloxacin 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 Gram negative bacteria: *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 (Gram negative bacteria), **4l** has shown the highest performance compared with ciprofloxacin 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 compounds **4a**–**l**, it can be concluded that the synthesized compounds that have substituted phenyl groups along with thiadiazol and quinazoline **4a**–**l** compared to other compounds in this study, can perform well in eliminating human bacterial pathogens.

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 **4a**–**l** compared with amphotericin B in this study, can perform well in eliminating human fungal pathogens.

3. 4. Anti-diabetic Activity (*In silico*)

In this section, it has been performed docking simulation of the newly synthesized derivatives **4a**–**l** binding the active site of the α-amylase (PDB ID: 1hny) and α-glucosidase (PDB ID: 2ze0). The docking result of the tested compounds **4c**, **4d** and **4g** showed lowest ΔG_{bind} with α-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 α-glucosidase. The binding energies, inhibition constants and residues involved in H-bonding are presented in Table 5 and Figures 1 and 2.

Table 3. Antibacterial activity of compounds **4a**–**l**

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

	Gram positive bacteria						**Gram negative bacteria**					
	***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

Table 4. Antifungal activity of compounds **4a–l**

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

	C .albicans **PTCC5027**			***A .niger*** **PTCC5320**		
compounds	**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

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

compounds	**Total Energy (Kcal/mol)**	**α-amylase PDB ID: 1hny**		**α-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	—

4. Conclusion

In summary, in the present study target molecules **4a–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 **2a–l** using *p*-TsOH as the 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 α-glucosidase and compounds **4c** and **4g** showed the lowest ΔG_{bind} results (–10.0 kcal/mol) against α-amylase.

Acknowledgments

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Supplementary Data

Copies of IR, ^{1}H NMR, ^{13}C NMR and MS spectra of compounds **4a–l** are provided in supplementary material via the "Supplementary Content" section of this article's webpage.

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Povzetek

V tej študiji predstavljamo serijo novih 2-(substituiranih fenil)-3-(5-fenil-1,3,4-tiadiazol-2-il)-2,3-dihidrokinazolin-4(1*H*)-onskih derivatov, ki smo jih pripravili s pomočjo refluktiranja izatojskega anhidrida, 5-fenil-1,3,4-tiadiazol-2-amina in aromatskih aldehidov v prisotnosti *p*-TsOH kot katalizatorja in v H_2O kot topilu. Spojine smo karakterizirali s pomočjo spektroskopskih in analitskih metod. Določili smo antibakterijsko aktivnost proti dvema Gram pozitivnima in dvema Gram negativnima bakterijama ter aktivnost proti glivam; v vseh primerih smo izvedli tudi primerjavo s standardnimi učinkovinami. Z uporabo metode difuzije smo določili minimalno baktericidno oz. fungicidno koncentracijo. Morebitno inhibitorno aktivnost spojin **4a**–**l** za α-amilazo in α-glukozidazo smo raziskovali *in silico* s pomočjo metode molekulskega sidranja. Ugotovili smo, da so pripravljeni 2,3-dihidrokinazolin-4(1*H*)-onski derivati obetavni kandidati za nadaljnji razvoj novih razredov učinkovin, ki bodo imele delovanje proti mikrobom in diabetesu.