Received: 30 November 2020 | Revised: 3 February 2021 | Accepted: 8 February 2021

DOI: 10.1002/jhet.4247

ARTICLE

JOURNAL OF HETEROCYCLIC CHEMISTRY WILEY

Synthesis and urease inhibition studies of some new quinazolinones

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Abstract

In this study, novel quinazolinones were designed, synthesized, characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR spectral data, and LC–MS. New compounds inhibitory activities on urease were assessed. All of the compounds exhibited potent urease inhibitory activities. Especially in the synthesized compounds, 2-benzyl-3-({5-[(4-nitrophenyl)amino]-1,3,4-thiadiazol2-yl}methyl)quinazolin-4(3*H*)-one has the best inhibitory effect against *Jack bean* urease with $IC_{50} = 3.30 \pm 0.09$ μg/mL. And also, *N*-(4-nitrophenyl)-2-[(4-oxoquinazolin-3(4*H*)-yl)acetyl] hydrazinecarbothioamide, *N*-(4-fluorophenyl)-2-[(4-oxoquinazolin-3(4*H*)-yl)acetyl] hydrazinecarbothioamide, and 2-benzyl-3-({5-[(4-fluorophenyl)amino]-1,3,4-thiadiazol-2yl} methyl)quinazolin-4(3*H*)-one have best activities among the synthesized compounds.

1 | INTRODUCTION

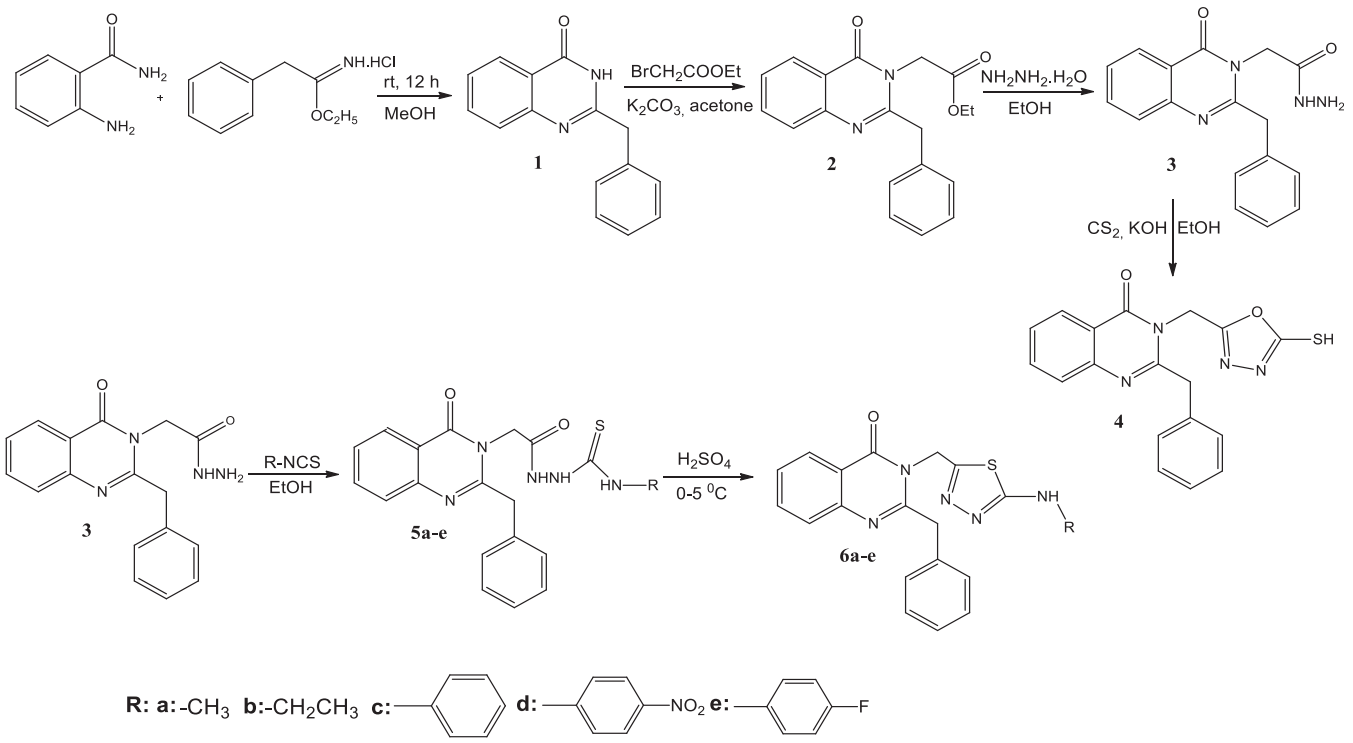
Quinazolines are a class of fused heterocycles that is of considerable interest because of their diverse pharmacological properties. Quinazolinones and quinazolines have important pharmacological activities are well documented attracted the scientists since 1888. It has been reported as antifungal,[1] antihypertensive, antimicrobial,[2] antiviral,[3] antitumor,[4] anti-HIV, anticonvulsant, antiinflammatory,[5] and anticancer activity, and so on.[6] According to recent studies, diverse quinazolinone derivates have antiurease activity with diverse side groups [7,8]. The inhibition of urease has significant roles, like therapy against bacterial urease, which induced human pathogenic states or to protect soil pH and controlling hydrolysis of urea in soil.

Among the heterocyclic systems, thiadiazole has a significant role in the modern medicinal chemistry. 1,3,4-Thiadiazoles are associated with diverse biopharmacological properties like antimicrobial, antifungal, antibacterial, antitumor, antiurease by the virtue of —N═C—S— grouping.[9] Five membered nitrogen or oxygen-containing heterocycles like as oxadiazole, furan, 1,3,4-triazoles, and 1,3,4-thiadiazoles are important classes of compounds in medicinal chemistry. Thiadiazoles are the common and useful structural core in biopharmacologically [10–12].

Urease is a well-recognized enzyme involved in the hydrolysis of urea to ammonia and carbon dioxide in living organisms [13]. Urease activity assays are widely applied in the biological sciences, environmental, agriculture studies, and medicine. Due to the role of urease in clinically important complications, it is necessary to regulate urease activity by using inhibitors. Several classes of different compounds have been reported as urease inhibitors [14]. The discovery of effective and safe urease inhibitors is crucial for pharmaceutical research because of association ureases with several pathological conditions especially agriculture applications [15]. Taking these into consideration, the aim of this work is to understand the effect of various quinazolinone derivatives and different alkyl and arly group effects on urease inhibition.

2 | RESULTS AND DISCUSSION

The synthetic strategy pathway for the intermediates and target compounds consisted of the reactions are outlined



SCHEME 1 The synthetic pathway of the synthesis of new quinazolinones

in Scheme 1. The starting iminoester was synthesized by the method reported in our previous study.[16]

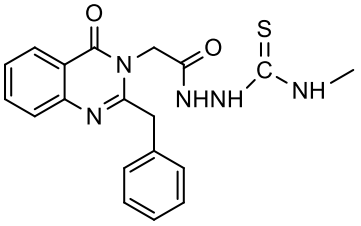
2-Aminobenzamide was reacted with iminoester hydrochloride in methanol to obtain compound **1**. Compound **2** was prepared by simple alkylation of compound **1** with ethylbromoacetate and K_2CO_3 in anhydrous acetone and then was transformed to hydrazide compound **3** by treatment with hydrazine monohydrate in ethanol. The ring closure reaction of molecule **3** with CS_2 in the presence of KOH resulted in the formation of compound **4,** which has oxadiazole ring. Compounds **5a-e,** which is thiosemicarbazide derivatives, were prepared by the nucleophilic addition of acid hydrazide to alkyl and arly derivates of isothiocyanates. The cyclization of compounds **5a-e** with cold concentrated sulfuric acid resulted in the formation of thiadiazole derivative compounds **6a-e**.

A new series of 2,3-disubstituted quinazolin-4(3*H*)-ones has been synthesized and then their antiurease activity has been screened. Urease inhibitory activity of the compounds was determined spectrophotometrically according to the method of Van Slyke and Archibald.[17] Most of the compounds showed excellent activity with IC_{50} values ranging between 30 ± 0.09 μg/mL and 10.20 ± 0.19 μg/mL compared with standard inhibitor, thiourea IC_{50} 20.33 ± 0.70 μg/mL

According to the results, all of the synthesized molecules are potent urease inhibitory. Quinazolinone molecules bearing thiadiazole rings **6a-e** showed excellent inhibitor activities against urease. Especially **6d** has best inhibition activity in this group. It has thiadiazole ring with —NO_2 molecule on phenyl ring at −4 position. And also, **5d, 5e, 6d, 6e** have shown the best antiurease activities compared with standard inhibitor, thiourea (Table 1). **5d** and **6d** have nitro molecule on phenyl ring, **5e** and **6e** have fluorine on phenyl ring at −4 position.

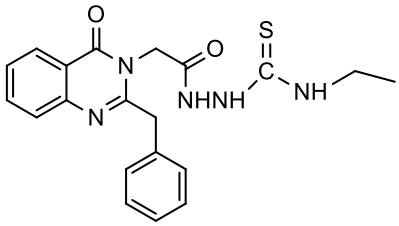
TABLE 1 IC_{50} values of the synthesized compounds and standard against Jack bean urease

Compound	IC_{50} (μg/mL)
1	10.20 ± 0.19
2	9.45 ± 0.20
3	8.90 ± 0.13
4	6.40 ± 0.15
5a	6.30 ± 0.10
5b	6.80 ± 0.20
5c	6.00 ± 0.17
5d	3.60 ± 0.15
5e	4.20 ± 0.10
6a	5.10 ± 0.11
6b	5.50 ± 0.18
6c	4.48 ± 0.11
6d	3.30 ± 0.09
6e	4.00 ± 0.08
Thiourea	20.33 ± 0.70



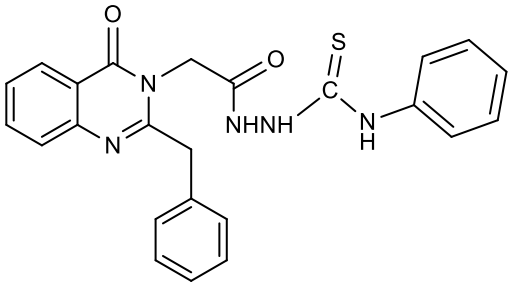
5a

IC_{50}= 6.30±0.10 μg/mL



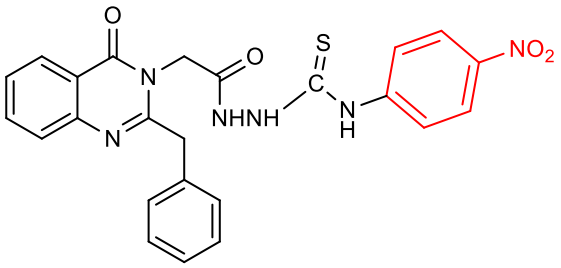
5b

IC_{50}= 6.80±0.20 μg/mL



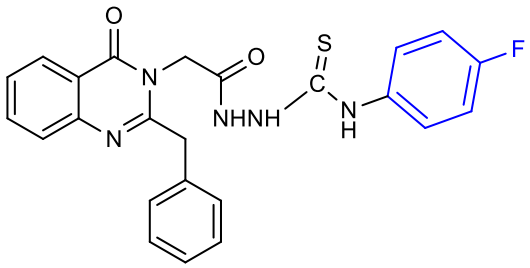
5c

IC_{50}= 6.00±0.17 μg/mL



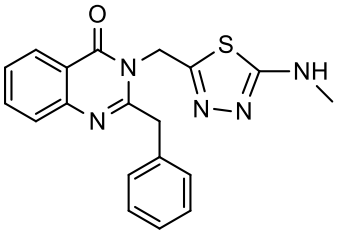
5d

IC_{50}= 3.60±0.15 μg/mL



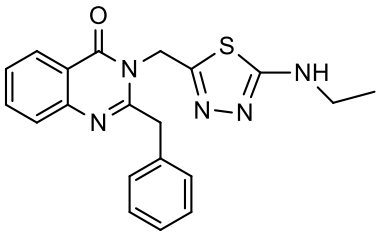
5e

IC_{50}= 4.20±0.10 μg/mL



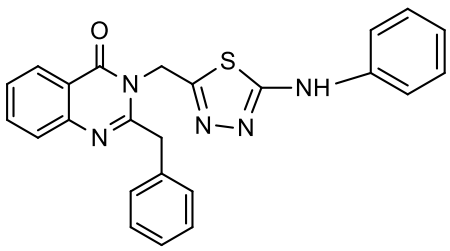
6a

IC_{50}= 5.10±0.11 μg/mL



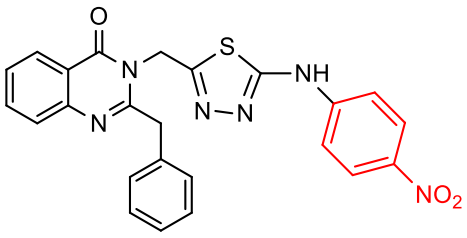
6b

IC_{50}= 5.50±0.18 μg/mL



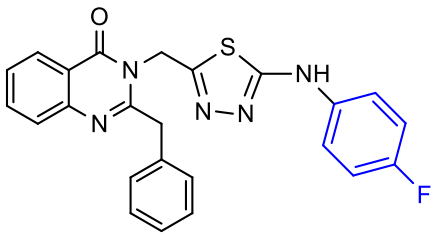
6c

IC_{50}= 4.48±0.11 μg/mL



6d

IC_{50}= 3.30±0.09 μg/mL



6e

IC_{50}= 4.00±0.08 μg/mL

3 | EXPERIMENTAL

3.1 | Synthesis of 2-benzylquinazolin-4 (3*H*)-one (1)

1.36 g 2-aminobenzamide and minister hydrochloride (0.01 mol) reacted with methanol for 12 hours at room temperature. The reaction was viewed by TLC (ethyl acetate-hexane, 3:1). The mixture was poured into water and the product was precipitated then filtered off. The product washed with water and recrystallized from ethanol-water 3:1. Yield 99%, Mp: 252–254°C, IR(ν_{max}, cm^{-1}): 3167 (NH), 1666 (C═O), 1600 (C═N). ^{1}H-NMR spectrum: 12.39 (1H, s, NH); 8.07 (1H, d, J = 7.6 Hz,

ArH); 7.74 (1H, t, J = 7.6 Hz, ArH); 7.59 (1H, d, J = 7.6 Hz, ArH); 7.46 (2H, d, J = 8.4 Hz, ArH); 7.37 (1H, t, J = 7.6 Hz, ArH); 7.31 (2H, d, J = 8.4 Hz, ArH); 3.91 (2H, s, CH_2). ^{13}C-NMR spectrum: 162.3 (C═O); 156.4 (C═N); ArC [149.3; 134.8; 129.3; 129.2; 128.9; 127.4; 127.2; 126.6; 126.1; 126.0; 121.2], 41.22 (CH_2). LC–MS, m/z: 236.96 $[M + H]^+$, 258.92 $[M + Na]^+$.

3.2 | Synthesis of ethyl (2-benzyl-4-oxoquinazolin-3(4*H*)-yl)acetate (2)

The solution of 2.4 g compound **1** (0.01 mol) in acetone, anhydrous K_2CO_3 2.76 g (0.02 mol) was added and the mixture was stirred for 15 minutes at room temperature. Ethyl bromoacetate (0.01 mol) was then added and the mixture was stirred for 12 hours. The end of the reaction was controlled by TLC (ethyl acetate-hexane, 3:1). The product was precipitated by the addition of water. White solid was filtered off, washed with water, and recrystallized from ethanol-water 3:2. Yield 70%, Mp: 96–98°C, IR(ν_{max}, cm^{-1}): 1738 (C═O), 1668 (C═O), 1587 (C═N), 1189 (C—O). ^{1}H-NMR spectrum: 8.09 (1H, t, J = 8.0 Hz, Ar H); 7.82 (1H, d, J = 7.6 Hz, Ar H); 7.67 (1H, d, J = 7.6 Hz, Ar H); 7.51 (1H, t, J = 8.0 Hz, Ar H); 7.28 (4H, m, Ar H); 5.11 (2H, s, NCH_2); 4.81 (2H, s, CH_2); 4.25 (2H, q, J = 7.2 Hz, OCH_2); 1.13 (3H, t, J = 7.2 Hz, CH_3). ^{13}C-NMR spectrum: 167.6; 161.7 (C═O); 155.8 (C═N); Ar C [147.2; 135.5; 135.3; 132.2; 129.4; 129.1; 128.6; 128.5; 127.5; 127.3; 126.6], 61.5 (OCH_2); 45.8 (CH_2); 14.2 (CH_3). LC–MS, m/z: 322.84 $[M + H]^+$, 344.96 $[M + Na]^+$.

3.3 | Synthesis of 2-(2-benzyl-4-oxoquinazolin-3(4*H*)-yl) acetohydrazide (3)

Hydrazine monohydrate (0.05 mol) was added to a solution of the compound **2** 2.90 g (0.01 mol) in ethanol. The mixture was stirred for 4 hours. The reaction was controlled by TLC (ethyl acetate-hexane, 3:1). The product was filtered off, washed, and recrystallized from ethanol. Yield: 80%, Mp: 240–242 °C, IR(ν_{max}, cm^{-1}): 3324 (NH-NH_2), 1659 (C═O), 1623 (C═O), 1593 (C═N). ^{1}H-NMR spectrum: 9.36 (1H, s, NH); 8.09 (1H, d, J = 8.0, Ar H); 7.8 (1H, t, J = 8.0, Ar H); 7.6 (1H, d, J = 8.0, Ar H); 7.5 (1H, t, J = 8.0, Ar H); 7.34–7.23 (5H, m, Ar H); 4.59 (2H, s, NCH_2); 4.24 (2H, s, NH_2); 4.13 (2H, s, CH_2). ^{13}C-NMR spectrum: 166.5; 161.8 (C═O); 156.3 (C═N); Ar C [147.3; 135.8; 134.4; 129.0; 127.4; 127.3; 127.1; 126.6; 120.3; 120.2], 44.8 (NCH_2); 41.5 (CH_2). LC–MS, *m/z*: 308.93 $[M + H]^+$, 330.77 $[M + Na]^+$.

3.4 | Synthesis of 2-benzyl-3-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl] quinazolin-4(3*H*)-one (4)

A solution of KOH 0.075 g (0.01 mol) in water (20 mL) and CS_2 (0.01 mol) was added to a solution of compound **3** 4 g (0.01 mol) in ethanol (20 mL) and then, the mixture of reaction was refluxed for 6 hours. The completed reaction was monitored by TLC (Ethyl acetate: Hexane, 3:1). The reaction mixture was cooled to room temperature and acidified to pH 6–7 with diluted HCl (4N). The precipitated product was filtrated, washed thoroughly with H_2O and recrystallized into ethanol. Yield 75%, Mp: 200–202°C, IR(ν_{max}, cm^{-1}): 3155 (NH), 1651 (C═O), 1590 (C═N). ^{1}H-NMR spectrum: 8.10 (1H, d, J = 7.6 Hz, Ar H), 7.82 (1H, t, J = 7.6 Hz, Ar H), 7.65 (1H, d, J = 8 Hz, Ar H), 7.52 (1H, t, J = 7.6 Hz, Ar H), 7.27 (2H, t, J = 7.6 Hz, Ar H), 7.12 (2H, t, J = 8.4 Hz, Ar H), 5.33 (2H, s, NCH_2), 4.32 (2H, s, CH_2). ^{13}C-NMR spectrum: 178.16 (oxadiazole C-5), 161.52 (C═O), 159.40 (oxadiazole C-2), 155.71 (C═N), Ar C [147.11; 135.55; 135.47; 129.11; 129.01; 127.72; 127.63; 127.54; 127.41; 127.33; 119.97]; 40.76 (NCH_2), 39.59 (CH_2). LC–MS, *m/z*: 350.65 $[M + H]^+$.

3.5 | Synthesis of compounds 5a-e

A mixture of hydrazide 4 g (0.01 mol) in ethanol (15 mL) and an appropriate isothiocyanate (0.011 mol) was refluxed for 3 hours. The solution was cooled and a white solid appeared. The precipitated product was filtrated and recrystallized from ethanol to obtain the desired pure products **5a-e**.

3.5.1 | *N*-methyl-2-[(4-oxoquinazolin-3 (4*H*)-yl)acetyl] hydrazinecarbothioamide (5a)

Yield: 52% Mp: 218–220°C, IR(v_{max}, cm^{-1}): 3324, 3208 (NH-NH), 1722 (C═O), 1655 (C═O), 1593 (C═N), 1167 (C═S). ^{1}H-NMR spectrum: 10.25 (1H, s, NH), 9.74 (1H, s, NH), 9.37 (1H, t, J = 8.0 Hz, Ar H), 8.57 (1H, s, NH), 8.09 (1H, t, J = 8.0 Hz, Ar H), 7.80 (2H, t, J = 8.0 Hz, Ar H), 7.60-7.51 (3H, m, Ar H), 7.24-7.31 (3H, m, Ar H), 4.80 (2H, s, NCH_2), 2,86 (2H, s, CH_2); 1.03 (3H, s,CH_3). ^{13}C-NMR spectrum: 14.78 (CH_3), 41.43 (CH_2), 44.84 (NCH_2), Ar C [120.08, 120.27, 126.66, 127.30, 127.38, 127.46, 129.05, 129.28, 135.17, 135.95, 136.12, 147.28], 156.49 (C═N), 164.24 (C═O), 167.32 (C═O), 179.55 (C═S). LC–MS, *m/z*: 381.82 $[M + H]^+$, 403.94 $[M + Na]^+$.

3.5.2 | *N*-ethyl-2-[(4-oxoquinazolin-3(4*H*)-yl)acetyl]hydrazinecarbothioamide (5b)

Yield 70%, Mp: 226-228°C, IR(ν_{max}, cm^{-1}): 3324-3300 (NH-NH), 1660-1612 (C═O), 1590 (C═N), 1182 (C═S). ^{1}H-NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.30 (1H, s, NH), 9.70 (1H, s, NH), 8.09 (1H, t, *J* = 7.6 Hz, Ar H), 7.90 (1H, s, NH), 7.81 (1H, t, *J* = 7.6 Hz, Ar H), 7.49-7.63 (2H, m, Ar H), 7.21-7.33 (3H, m, Ar H), 4.74 (2H, s, NCH_2), 4.56 (2H, m, CH_2), 4.15 (2H, s, CH_2), 1.02 (3H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6), δ, ppm: 14.67 (CH_3), 41.28 (CH_2), 41.62 (CH_2), 44.81 (NCH_2), Ar C [120.11, 126.57, 126.64, 127.27, 127.32, 128.99, 129.20, 135.20, 135.20, 135.38, 135.69, 147.16], 156.42 (C═N), 162.14 (C═O), 167.26 (C═O). LC-MS, *m/z*: 395.48 $[M + H]^+$, 417.94 $[M + Na]^+$.

3.5.3 | *N*-phenyl-2-[(4-oxoquinazolin-3(4*H*)-yl)acetyl] hydrazinecarbothioamide (5c)

Yield 64%, Mp: 240°C (dec.). IR(ν_{max}, cm^{-1}): 3310-3300 (NH-NH), 1656 (C═O), 1589 (C═N), 1179 (C═S), ^{1}H-NMR spectrum: 10.30 (1H, s, NH), 9.74 (1H, s, NH), 8.10 (2H, m, ArH), 7.85 (1H, s, NH), 7.80 (3H, m, Ar H), 7.65 (2H, t, *J* = 8.0 Hz, Ar H), 7.16-7.40 (5H, m, Ar H), 4.84 (2H, s, NCH_2), 4.32 (2H, t, *J* = 8.0 Hz, CH_2). ^{13}C-NMR spectrum: 40.78 (CH_2), 44.83 (NCH_2), Ar C [120.08, 126.57, 126.64, 127.33, 127.45, 128.99, 129.09, 129.24, 135.21, 135.38, 136.08, 139.38, 147.33], 156.43 (C═N), 164.14 (C═O), 166.51 (C═O), 179.90 (C═S). LC–MS, *m/z*: 443.94 $[M + H]^+$, 465.99 $[M + Na]^+$.

3.5.4 | *N*-(4-nitrophenyl)-2-[(4-oxoquinazolin-3(4*H*)-yl) acetyl] hydrazinecarbothioamide (5d)

Yield 55%, Mp: 210°C (dec.). IR(ν_{max}, cm^{-1}): 3462-3216 (NH-NH), 1671 (C═O), 1594 (C═N), 1176 (C═S). ^{1}H-NMR spectrum: 10.70 (1H, s, NH), 10.0 (1H, s, NH), 8.12 (1H, d, *J* = 8.0 Hz, Ar H), 7.93 (1H, s, NH), 7.82 (2H, t, *J* = 8.0 Hz, Ar H), 7.63–7.53 (1H, m, Ar H), 7.21–7.31 (4H, m, Ar H), 4.84 (2H, s, NCH_2), 4.21 (2H, s, CH_2). ^{13}C-NMR spectrum: 42.26 (CH_2), 46.83 (NCH_2), ArC [120.06, 126.57, 126.25, 127.28, 127.45, 129.17, 129.24, 135.21, 135.24, 135.95, 147.31], 156.29 (C═N), 161.74 (C═O), 164.62 (C═O). LC–MS, *m/z*: 489.16 $[M + H]^+$, 510.65 $[M + Na]^+$.

3.5.5 | *N*-(4-fluorophenyl)-2-[(4-oxoquinazolin-3(4*H*)-yl)acetyl] hydrazinecarbothioamide (5e)

Yield 65%, Mp: 238-240°C (dec.) IR(ν_{max}, cm^{-1}): 3301-3035 (NH-NH), 1657 (C═O), 1590 (C═N), 1178 (C═S). ^{1}H-NMR spectrum: 10.51 (1H, s, NH), 9.78 (1H, s, NH), 8.10 (1H, d, *J* = 8.0 Hz, Ar H), 7.90 (1H, s, NH), 7.82 (2H, t, *J* = 8.0 Hz, Ar H), 7.63-7.53 (1H, m, Ar H), 7.17–7.33 (4H, m, Ar H), 4.84 (2H, s, NCH_2), 4.19 (2H, s, CH_2). ^{13}C-NMR spectrum: 41.22 (CH_2), 41.83 (NCH_2), Ar C [115.52, 120.13, 126.57, 127.38, 127.49, 129.14, 129.29, 135.24, 135.44, 135.78, 136.12, 147.39], 156.53 (C═N), 159.90 (C-F, d, J_{CF} = 250 Hz), 166.38 (C═O), 167.56 (C═O). LC–MS, *m/z*: 461.80 $[M + H]^+$.

3.6 | Synthesis of compounds 6a-e

The compound derivates of thiosemicarbasite (0.01 mol) were dissolved with cold H_2SO_4 in the ice bath. The mixture was stirred in ice bath about an hour and then nearly an hour at room temperature too. At the end of this reaction, the mixture was taken in a beaker filled with ice and the product was precipitated by neutralized with NH_3. White solid products were filtered off and recrystallized from ethanol.

3.7 | 1. 2-benzyl-3-{[5-(methylamino)-1,3,4-thiadiazol-2-yl]methyl}quinazolin-4(3*H*)-one (6a)

Yield 55%, Mp: 154-156°C. IR(ν_{max}, cm^{-1}): 3334 (NH), 1660 (C═O), 1591-1568 (C═N). ^{1}H-NMR spectrum: 8.13 (1H, d, *J* = 8.0 Hz, Ar H); 7.80 (1H, s, Ar H); 7.72 (1H, s, NH); 7.62 (2H, d, *J* = 8.0 Hz, Ar H); 7.51 (1H, s, Ar H); 7.30 (4H, m, Ar H); 7.16 (2H, t, *J* = 7.2 Hz, Ar H); 5.31 (2H, s, NCH_2); 4.35 (2H, s, CH_2); 2.81 (3H, s, CH_3).

^{13}C-NMR spectrum: 31.68 (CH_3); 41.08 (CH_2); 42.51 (CH_2); Ar C [120.14, 126.70, 127.45, 128. 87, 129.03, 129.25, 135.18, 135.29, 135.87, 147.19]; 152.25 (thiadiazole C_2); 155.68 (C═N); 161.65 (C═O); 171.24 (thiadiazole C_5). LC-MS, *m/z*: 362.83 $[M + H]^+$, 399.86 $[M + Na]^+$.

3.7.1 | 2-benzyl-3-{[5-(ethylamino)-1,3,4-thiadiazol-2-yl]methyl}quinazolin-4(3*H*)-one (6b)

Yield 65%, Mp: 188-190°C. IR(ν_{max}, cm^{-1}): 3180 (NH), 1669 (C═O), 1590-1567 (C═N). ^{1}H-NMR spectrum: 8.13

(1H, d, J = 8.0 Hz, ArH); 7.80 (1H, s, ArH); 7.73 (1H, s, NH); 7.62 (2H, d, J = 8.0 Hz, Ar H); 7.51 (1H, s, Ar H); 7.28 (4H, m, Ar H), 5.30 (2H, s, NCH_2), 4.36 (2H, s, CH_2), 3.31 (2H, s, CH_2), 1.10 (3H, s, CH_3).^{13}C-NMR spectrum: 14.64 (CH_3); 40.06; 41.06 (CH_2); 42.49 (CH_2); Ar C [120.16, 126.71, 127.44, 129.07, 129.25, 135.20, 135.23, 135.28, 135.79, 135.91, 147.21]; 152.07 (thiadiazole C_2); 155.70 (C═N); 161.64 (C═O); 170.24 (thiadiazole C_5). LC–MS, m/z: 378.46 $[M + H]^+$, 399.86 $[M + Na]^+$.

3.7.2 | 2-benzyl-3-{[5-(phenylamino)-1,3,4-thiadiazol-2-yl]methyl}quinazolin-4(3*H*)-one (6c)

Yield 55%, Mp: 190°C dec. IR (ν_{max}, cm^{-1}): 3190 (NH), 1675 (C═O), 1592-1569 (C═N). ^{1}H-NMR spectrum: 10.47 (1H, s, NH); 8.15 (1H, d, J = 8.0 Hz, Ar H); 7.82 (1H, t, J = 8.0 Hz, Ar H); 7.64 (1H, d, J = 8.0 Hz, Ar H); 7.53 (3H, m, Ar H); 7.31 (5H, m, Ar H); 7.28 (4H, m, Ar H), 5.41 (2H, s, NCH_2), 4.38 (2H, s, CH_2). ^{13}C-NMR spectrum: 41.06 (CH_2); 42.54 (CH_2); Ar C [116.75; 117.92; 120.17, 122.42; 126.95, 127.46, 127.51, 129.11, 129.25; 135.35, 135.90, 140.96; 142.23; 147.24]; 154.43 (thiadiazole C_2); 155.73 (C═N); 161.72 (C═O); 166.02 (thiadiazole C_5). LC–MS, m/z: 425.80 $[M + H]^+$, 448.06 $[M + Na]^+$.

3.7.3 | 2-benzyl-3-({5-[(4-nitrophenyl)amino]-1,3,4-thiadiazol-2-yl}methyl)quinazolin-4-(3*H*)-one (6d)

Yield 68%, Mp: 183–185°C. IR (ν_{max}, cm^{-1}): 3203 (NH), 1671 (C═O), 1590–1575 (C═N). ^{1}H-NMR spectrum: 10.47 (1H, s, NH); 8.18 (1H, d, J = 8.0 Hz, Ar H); 8.14 (1H, d, J = 8.0 Hz, Ar H); 7.64 (1H, d, J = 8.0 Hz, Ar H); 7.52 (1H, t, J = 8.0 Hz, Ar H); 7.31 (3H, m, Ar H); 5.45 (2H, s, NCH_2), 4.38 (2H, s, CH_2). ^{13}C-NMR spectrum: 41.06 (CH_2); 42.54 (CH_2); Ar C [120.14, 120.44; 126.66, 126.70, 127.45, 128.87, 129.09; 129.30, 135.29, 135.87, 147.24]; 152.25 (thiadiazole C_2); 155.68 (C═N); 161.65 (C═O); 171.24 (thiadiazole C_5). LC–MS, m/z: 470.95 $[M + H]^+$, 493.00 $[M + Na]^+$.

3.7.4 | 2-benzyl-3-({5-[(4-fluorophenyl)amino]-1,3,4-thiadiazol-2-yl}methyl)quinazolin-4(3*H*)-one (6e)

Yield 68%, Mp: 250°C dec. IR (ν_{max}, cm^{-1}): 3219 (NH), 1673 (C═O), 1587–1589 (C═N). ^{1}H-NMR spectrum: 10.30 (1H, s, NH); 7.90 (1H, d, J = 8.0 Hz, Ar H); 7.68 (1H, d, J = 8.0 Hz, Ar H); 7.40 (1H, d, J = 8.0 Hz, Ar H); 7.45 (1H, t, J = 8.0 Hz, Ar H); 7.23 (3H, m, Ar H); 5.44(2H, s, NCH_2), 4.37 (2H, s, CH_2). ^{13}C-NMR spectrum: 41.02 (CH_2); 42.50 (CH_2); Ar C [119.10, 119.98; 125.12, 125.80, 126.05, 127.87, 128.97; 129.04, 134.99, 135.82, 146.94]; 152.20 (thiadiazole C_2); 155.61 (C═N); 160.10 (C-F, d, J_{CF} = 240 Hz), 161.63 (C═O); 171.24 (thiadiazole C_5). LC-MS, m/z: 444.00 $[M + H]^+$, 467.50 $[M + Na]^+$.

3.8 | Urease inhibitory assay

The method of Van Slyke and Archibald was used to assay urease inhibitory activity new compounds spectrophotometrically. Briefly, 500 µL of urease (*Jack bean*) solution (16 mg/mL urease solution was prepared in 100 mM pH 6.8 phosphate buffer) was added to 0.5 mL of the compounds and standard (0.01-0.00001 µg/mL). The mixture was incubated for 15 minutes at room temperature. After incubation, 0.4 mL phenol red solution which was prepared in urea-phosphate buffer (pH: 6.8) was transferred to the mixture. The absorbance was read at 570 nm. Thiourea was standard urease inhibitor. The assays were done in triplicate.[17]

4 | CONCLUSION

In this work, a novel series of quinazolin-4(3*H*)-one derivative has been synthesized and then their antiurease activity has been screened. Most of the compounds showed excellent activity with IC_{50} values ranging between 3.30 ± 0.09 and 10.20 ± 0.19 µg/mL compared with standard inhibitor, thiourea IC_{50} 20.33 ± 0.70 µg/mL. 2-benzyl-3-({5-[(4-nitrophenyl)amino]-1,3,4-thiadiazol-2-yl}methyl)quinazolin-4-(3*H*)-one has the best inhibitory effect against *Jack bean* urease with IC_{50} = 3.30 ± 0.09 µg/mL. The results show that quinazolinones with thiadiazole ring have positive effect on urease inhibitory activities.

DATA AVAILABILITY STATEMENT

Data available in article supplementary material

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Akyüz G. Synthesis and urease inhibition studies of some new quinazolinones. *J Heterocyclic Chem*. 2021;58: 1164–1170. https://doi.org/10.1002/jhet.4247