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Synthesis of thioalkylated-4-aryltetrahydroquinazolinone derivatives and their antibacterial activity

Ravibabu Velpula[1], Janardhan Banothu[1], Acharya Nagarjun Pyde[2] and Rajitha Bavantula[1*]

[1]*Department of Chemistry, National Institute of Technology, Warangal-506004, A.P., India*
[2]*Department of Microbiology, Osmania University, Hyderabad-500007, A.P., India*

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Abstract: A series of 2-[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethylsulfanyl]-4-aryl-4,6,7,8-tetrahydro-3*H*-quinazolin-5-ones **(7a-f)** and 2-[2-oxo-2-(3-oxo-3*H*-chromen-2-yl)-ethylsulfanyl]-4-aryl-4,6,7,8-tetrahydro-3*H*-quinazolin-5-ones **(9a-f)** were synthesized and screened for their *in vitro* antibacterial activity against *Staphylococcus aureus, Bacillus thuringiensis* (Gram positive), *Escherichia coli and Klebsiella pneumonia* (Gram negative) bacterial strains. Among all the compounds, **7b** and **7d** were shown highest activity against all the tested bacterial strains compared to the standard drug Gentamicin. These two quinazolinone derivatives (**7b** and **7d**) could be considered as useful templates for further development of potential antibacterial agents.

Keywords: Antibacterial activity; 3-(2-bromoacetyl)-2*H*-chromen-2-one; 2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one; thioalkylated-4-aryltetrahydroquinazolinones.

1. Introduction

Tetrahydroquinazolinone having dihydropyrimidinone (DHPMs) core, which is a popular motif present in variety of natural products and found to possessed broad range of biological activities that include antibacterial, antiviral, antitumor, calcium channel modulators, mitotic kinesine inhibitors and α_{1a}-adrenergic receptor antagonists[1]. Recently, DHPM derivatives present in batezelladine alkaloids were found as potent HIV gp-120-CD4 inhibitors[2]. Due to their versatile pharmacological properties, much attention has been focused on the modification of their core by template decoration strategies. The nucleophilic centers of DHPMs allow a variety of alkylation, acylation as well as cyclization reactions[3-7]. On the other hand, coumrain derivatives were reported as antimicrobial[8, 9], anti-inflammatory[10], anticoagulant[11], antitumor[12] and anti-HIV[13] agents. They also widely used as additives in foods, perfumes, cosmetics, optical brighteners, and dispersed fluorescence and lasers dyes[14, 15]. Some of the thioalkylated DHPMs having calcium channel activating properties has shown in Figure 1.

In view of the above therapeutic properties as well as from our earlier communication on the synthesis coumarin incorporated quinazoline derivatives and their antimicrobial activity[16], prompted us to undertake the synthesis of thioalkylated quinazolinone derivatives and to evaluate their antibacterial activity.

*Corresponding author: E-mail: rajitabhargavi@yahoo.com; Tel: 0091-0870-2459445, Fax: 0091-0870-2459547

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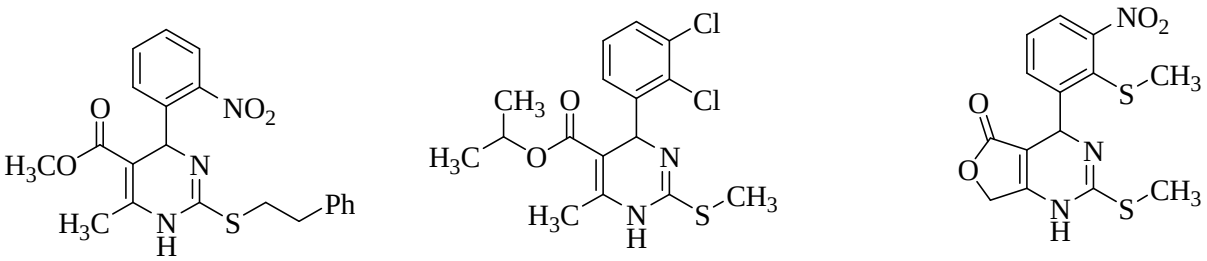


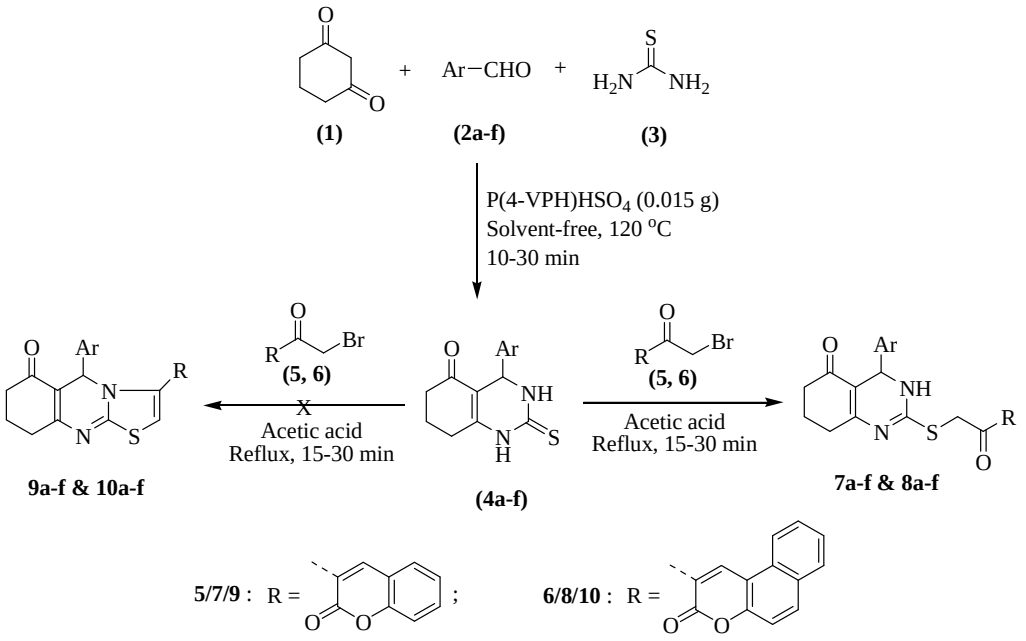
Figure 1. Biologically potent thioalkylated DHPMs.

2. Results and discussion

The intermediates, 4-aryl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-ones **(4a-f)** were synthesized *via* one-pot multicomponent condensation of 1,3-cyclohexanedione (**1**), aryl aldehydes (**2a-f**) and thiourea (**3**) utilizing poly(4-vinylpyridinium)hydrogen sulfate [P(4-VPH)HSO_4] as catalyst under solvent-free conditions with excellent yields (88-94%)[17]. The title compounds **7a-f** and **8a-f** were obtained by the reaction of **4a-f** with 3-(2-bromoacetyl)-2*H*-chromen-2-one (**5**) and 2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (**6**) in acetic acid under the reflux conditions with good to excellent yields (80-95%).

Balkan and co-workers[18] reported the synthesis of thiazolo[3,2-*a*]pyrimidine derivatives by the treatment of methyl-4-(4-aryl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate with phenacyl bromide in acetic acid under reflux conditions. Under similar reaction conditions, we aimed to synthesize thiazolo[2,3-*b*]quinazolinone derivatives using 3-(2-bromoacetyl)-2*H*-chromen-2-one/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one instead of phenacyl bromide. Thus, we carried out the reaction utilizing equimolar quantities of 4-phenyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one **(4a)** and 3-(2-bromoacetyl)-2*H*-chromen-2-one **(5)**. The presence of a broad band at 3424 cm^{-1} (NH) and sharp bands at 1711, 1656 cm^{-1} (C=O of lactone and ketone) from the IR spectrum, doublets at δ 3.55 and δ 4.12 ppm (methylene CH_2) from the ^{1}H NMR, and molecular ion peak from the mass spectrum as well as elemental analysis confirmed the product formed as 2-((2-oxo-2-(2-oxo-2*H*-chromen-3-yl)ethyl)thio)-4-phenyl-3,4,7,8-tetrahydroquinazolin-5(6*H*)-one **(7a)** but not the expected product, 3-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-8,9-dihydro-5*H*-thiazolo[2,3-*b*] quinazolin-6(7*H*)-one **(9a)**. The same reaction was also carried with 2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one **(6)** and observed the corresponding acyclic product **(8a).** Therefore we ruled out the formation of thiazolo[2,3-*b*] quinazolinone derivatives **(9a-f & 10a-f)**.

A series of 2-((2-oxo-2-(2-oxo-2*H*-chromen-3-yl)ethyl)thio)-4-aryl-3,4,7,8-tetrahydroquinazolin-5(6*H*)-ones **(7a-f)** and 2-((2-oxo-2-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)ethyl)thio)-4-aryl-3,4,7,8-tetrahydroquinazolin-5(6*H*)-ones **(8a-f)** were synthesized by varying 4-aryl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one **(4a-f)** with compounds (**5** & **6)** separately in refluxing acetic acid (Figure 1) with good yields (Table 1). All the synthesized compounds were characterized by their analytical and spectral studies.



a: Ar = C_6H_5 **b**: Ar = 4-$OCH_3C_6H_4$ **c**: Ar = 3,4-$(OCH_3)_2C_6H_3$

d: Ar = 3,4,5-$(OCH_3)_3C_6H_2$ **e**: Ar = 3-$NO_2C_6H_4$ **f**: Ar = 2-ClC_6H_4

Figure 1. Synthesis of thioalkylated-4-aryltetrahydroquinazolinone derivatives

Table 1. Synthesis of thioalkylated-4-aryltetrahydroquinazolinone derivatives **(7a-f & 8a-f)**.

Entry[a]	Aldehyde	Product	Time (min)	Yield[b] (%)
1	Benzaldehyde	**7a**	20	85
2	4-Methoxybenzaldehyde	**7b**	25	90
3	3,4-Dimethoxybenzaldehyde	**7c**	25	95
4	3,4,5-trimethoxybenzaldehyde	**7d**	20	95
5	3-Nitrobenzaldehyde	**7e**	15	80
6	2-Chlorobenzaldehyde	**7f**	30	83
7	Benzaldehyde	**8a**	15	85
8	4-Methoxybenzaldehyde	**8b**	25	92
9	3,4-Dimethoxybenzaldehyde	**8c**	20	94
10	3,4,5-trimethoxybenzaldehyde	**8d**	15	95
11	3-Nitrobenzaldehyde	**8e**	15	82
12	2-Chlorobenzaldehyde	**8f**	25	86

[a]**Reaction conditions**: 4-Aryl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-ones (1 mmol), 3-(2-bromoacetyl)-2*H*-chromen-2-one/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (1 mmol), glacial acetic acid (5 mL), reflux.
[b]Isolated yields.

3. Antibacterial activity:

Compounds (**7a-f** & **8a-f**) were screened for their in vitro antibacterial activity against Gram positive bacterial strains: Staphylococcus aureus (*Sa*) and Bacillus thuringiensis (*Bt*) and Gram negative bacterial strains: Escherichia coli (*Ec*) and Klebsiella pneumonia (*Kp*) with respect to Gentamicin as positive control drug.

Zone of inhibition (in mm) values for analogs (250 µg/mL) and positive control drug Gentamicin (30 µg/mL) were determined by Agar disc diffusion method[19, 20]. All the compounds as well as standard were dissolved in DMSO. The plate was incubated at 37 ^{o}C for 24 h, and the resulting zone of inhibition was measured **(Table-2)**. From the antibacterial data, 2*H*-chromen-2-one derivatives possessing methoxy substitutions i.e. **7b, 7c** and **7d** have shown prominent activity against *Staphylococcus aureus* and *Escherichia coli* whereas compound **7a** was active only against *Staphylococcus aureus*, **7e** and **7f** were inactive against all the bacterial strains. All the substituents of 3*H*-benzo[*f*]chromen-3-one except **8f** showed good activity against *Staphylococcus aureus* but inactive against *Escherichia coli* and *Klebsiella pneumonia*. Among all the compounds, **7b** and **8e** showed maximum zone of inhibition (10 mm) against *Staphylococcus aureus* and *Bacillus thuringiensis* respectively, therefore these compounds were useful as potent pharmacophores for further development of antibacterial agents for the treatment of bacterial infections.

Table 2. Zone of inhibition values of compounds **7a-f & 8a-f** at 250 µg/mL and positive control drug Gentamicin at 30 µg/mL against different bacterial strains.

Entry	Product	Zone of Inhibition in mm			
		Gram positive		Gram negative	
		Sa	Bt	Ec	Kp
1	**7a**	6	-	-	-
2	**7b**	10	6	10	8
3	**7c**	8	-	7	-
4	**7d**	8	7	8	6
5	**7e**	-	-	-	-
6	**7f**	-	-	-	-
7	**8a**	7	7	-	-
8	**8b**	6	-	-	-
9	**8c**	8	7	-	-
10	**8d**	8	8	-	-
11	**8e**	8	10	-	-
12	**8f**	-	-	-	-
13	**Gentamicin**	15	17	15	14

Bacterial strains:- Sa: Staphylococcus aureus, Bt: Bacillus thuringiensis, Ec: Escherichia coli and Kp: Klebsiella pneumonia.
'-' Not active.

4. Experimental Section:

All the solvents and chemicals were purchased from Aldrich/Merck and used without further purifications. Melting points were determined in open capillaries using Stuart SMP30 melting point apparatus and are uncorrected. The progress of the reactions as well as purity of the compounds was monitored by thin layer chromatography, and the developed chromatogram was visualized with UV light and iodine vapors. IR spectra were recorded on Perkin-Elmer 100S spectrophotometer using KBr disk. ^{1}H NMR spectra were recorded on Bruker-400 MHz spectrometer using TMS as an internal standard. The C, H and N analyses of the compounds were done on a Carlo Erba modal EA1108 and mass spectra were recorded on a Jeol JMSD-300 spectrometer.

4.1. General procedure for synthesis of 4-aryl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (4a-f):

To a mixture of 1,3-cyclohexanedione (1 mmol), aromatic aldehyde (1 mmol) and thiourea (1.2 mmol); P(4-VPH)HSO_4 (0.015 g) was added and heated at 120 ^{o}C under solvent-free conditions. After completion of the reaction as indicated by TLC, 5 mL of water was added and the mixture was stirred at room temperature for additional 10 min. The solid separated out was filtered washed with water and recrystallized from methanol to afford the pure product. The aqueous layer containing catalyst was recovered under reduced pressure, washed with dichloromethane, dried and reused in subsequent reactions.

4.2. General procedure for the synthesis of 7a-f:

A mixture of 4-aryl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (1 mmol) and 3-(2-bromoacetyle)-2*H*-chromen-2-one (1 mmol) were dissolved in 5 mL of glacial acetic acid and heated at reflux temperature for 15-30 min. After completion of the reaction monitored by TLC, the solid separated out was filtered and washed with hot acetic acid, furnished the analytically pure product without recrystallization.

4.2.1.2-((2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl)thio)-4-phenyl-3,4,7,8-tetrahydroquinazolin-5(6H)-one (7a): White solid; mp. 232-234 ºC; IR (KBr, cm^{-1}) υ_{max}: 3424, 3121, 2898, 2785, 1711, 1656, 1624, 1606, 1516, 1376, 1176, 1055, 771, 697; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81-1.99 (m, 2H), 2.17-2.30 (m, 2H), 2.64-2.69 (m, 2H), 3.55 (d, *J* = 12.4 Hz, 1H), 4.12 (d, *J* = 12.8 Hz, 1H), 5.66 (s, 1H), 6.78-6.86 (m, 4H), 6.98 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.39-7.43 (m, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.89-7.91 (m, 1H), 8.44 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.2, 25.3, 36.0, 54.5, 95.1, 112.5, 115.5, 118.0, 124.5, 124.6, 127.3, 127.9, 128.7, 129.6, 133.0, 138.4, 142.4, 153.3, 157.4, 166.5, 193.6; MS (ESI) *m/z*: 445 (M+1); Anal. Calcd. for $C_{25}H_{20}N_2O_4S$: C, 67.55, H, 4.54, N, 6.30. Found: C, 67.76; H, 4.36; N, 6.41.

4.2.2.4-(4-Methoxyphenyl)-2-((2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl)thio)-3,4,7,8 tetrahydroquinazolin-5(6H)-one (7b): Pale yellow solid; mp. 236-238 ºC; IR (KBr, cm^{-1}) υ_{max}: 3441, 3163, 2893, 2850, 2784, 1716, 1660, 1627, 1607, 1509, 1376, 1245, 1178, 1069,771; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-2.30 (m, 4H), 2.62-2.68 (m, 2H), 3.49 (s, 3H), 3.53 (d, *J* = 12.8 Hz, 1H), 4.08 (d, *J* = 12.8 Hz, 1H), 5.63 (s, 1H), 6.30 (d, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.40-7.43 (m, 1H), 7.64 (t, *J* = 6.8 Hz, 1H), 7.89-7.91 (m, 1H), 8.39 (s, 1H), 8.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.2, 25.3, 36.1, 54.1, 54.8, 95.1, 112.4, 112.7, 115.4, 118.2, 124.6, 125.0, 129.6, 130.1, 130.4, 132.8, 141.8, 153.3, 157.3, 158.7, 166.0, 193.7; MS (ESI) *m/z*: 475 (M+1); Anal. Calcd. for $C_{26}H_{22}N_2O_5S$: C, 65.81, H, 4.67, N, 5.90. Found: C, 65.96; H, 4.42; N, 5.98.

4.2.3.4-(3,4-Dimethoxyphenyl)-2-((2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl)thio)-3,4,7,8-tetrahydroquinazolin-5(6H)-one (7c): Pale yellow solid; mp. 251-253 ºC; IR (KBr, cm^{-1}) υ_{max}: 3424, 3189, 2926, 2804, 1716, 1659, 1631, 1608, 1572, 1526, 1327, 1275, 1252, 1144, 1024, 766; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-2.28 (m, 4H), 2.60-2.67 (m, 2H), 3.47 (s, 6H), 3.73 (d, *J* = 13.2 Hz, 1H), 4.07 (d, *J* = 13.2 Hz, 1H), 5.61 (s, 1H), 6.32-6.81 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.42-7.59 (m, 2H), 7.88-7.90 (m, 1H), 8.37 (s, 1H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.2, 25.4,

36.2, 54.4, 54.7, 55.4, 95.1, 110.9, 112.4, 112.6, 115.5, 118.1, 124.6, 124.9, 129.6, 131.0, 132.9, 141.9, 148.5, 153.3, 157.5, 166.1, 193.7; MS (ESI) *m/z*: 505 (M+1); Anal. Calcd. for $C_{27}H_{24}N_2O_6S$: C, 64.27, H, 4.79, N, 5.55. Found: C, 64.36; H, 4.56; N, 5.58.

4.2.4.2-((2-Oxo-2-(2-oxo-2H-chromen-3-yl)ethyl)thio)-4-(3,4,5-trimethoxyphenyl)-3,4,7,8-tetrahydroquinazolin-5(6H)-one (7d): Yellow solid; mp. 213-215 ºC; IR (KBr, cm^{-1}) υ_{max}: 3422, 3180, 2932, 2798, 1714, 1662, 1627, 1615, 1575, 1528, 1331, 1273, 1248, 1151, 1019, 759; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-1.97 (m, 2H), 2.24-2.31 (m, 2H), 2.60-2.69 (m, 2H), 3.55 (s, 9H), 3.56 (d, *J* = 12.8 Hz, 1H), 4.09 (d, *J* = 12.8 Hz, 1H), 5.75 (s, 1H), 7.31 (d, *J* = 9.2 Hz, 1H), 7.46-7.49 (m, 1H), 7.68-7.73 (m, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.73 (s, 1H), 9.02 (s, 1H); MS (ESI) *m/z*: 535 (M+1); Anal. Calcd. for $C_{28}H_{26}N_2O_7S$: C, 62.91, H, 4.90, N, 5.24. Found: C, 63.02; H, 4.82; N, 5.12.

4.2.5.4-(3-Nitrophenyl)-2-((2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl)thio)-3,4,7,8-tetrahydroquinazolin-5(6H)-one (7e): White solid; mp. 241-243 ºC; IR (KBr, cm^{-1}) υ_{max}: 3124, 2892, 2781, 1710, 1657, 1618, 1602, 1522, 1371, 1170, 1061, 768, 704; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81-1.93 (m, 2H), 2.18-2.33 (m, 2H), 2.61(m, 2H), 3.61 (d, *J* = 12.4 Hz, 1H), 4.08 (d, *J* = 12.4 Hz, 1H), 5.66 (s, 1H), 6.61 (s, 2H), 6.89 (s, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 8 Hz, 1H), 8.43 (s, 1H); MS (ESI) *m/z*: 490 (M+1); Anal. Calcd. for $C_{25}H_{19}N_3O_6S$: C, 61.34, H, 3.91, N, 8.58. Found: C, 61.47; H, 3.85; N, 8.62.

4.2.5.4-(2-Chlorophenyl)-2-((2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl)thio)-3,4,7,8-tetrahydroquinazolin-5(6H)-one (7f): White solid; mp. 231-233 ºC; IR (KBr, cm^{-1}) υ_{max}: 3436, 3099, 2896, 2787, 1709, 1659, 1623, 1606, 1567, 1514, 1375, 1282, 1267, 1176, 1053, 763; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-1.98 (m, 2H), 2.14-2.28 (m, 2H), 2.61-2.67 (m, 2H), 3.53 (d, *J* = 12.8 Hz, 1H), 3.99 (d, *J* = 12.8 Hz, 1H), 6.07 (s, 1H), 6.95-6.99 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.22-7.40 (m, 4H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 8.50 (s, 1H), 8.73 (s, 1H). MS (ESI) *m/z*: 479 (M+1); Anal. Calcd. for $C_{25}H_{19}ClN_2O_4S$: C, 62.69, H, 4.00, N, 5.85. Found: C, 62.86; H, 3.91; N, 5.79.

4.3.General procedure for synthesis of 8a-f:

To a mixture of 4-aryl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (1 mmol) and 2-(2-bromoacetyl)-3*H* benzo[*f*]chromen-3-one (1 mmol); 5 mL of glacial acetic acid was added and refluxed for 15-30 min. After completion of the reaction shown by TLC, the solid separated out was filtered and washed with hot acetic acid, furnished the analytically pure product without recrystallization.

4.3.1. 2-((2-Oxo-2-(3-oxo-3H-benzo[f]chromen-2-yl)ethyl)thio)-4-phenyl-3,4,7,8-tetrahydro-quinazolin-5(6H)-one (8a): Yellow solid; mp. 236-238 ºC; IR (KBr, cm^{-1}) υ_{max}: 3419, 3118, 2904, 2782, 1712, 1658, 1623, 1610, 1517, 1381, 1175, 1052, 769, 692; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80-1.96 (m, 2H), 2.15-2.28 (m, 2H), 2.61-2.66 (m, 2H), 3.54 (d, *J* = 12.4 Hz, 1H), 4.11 (d, *J* = 12.8 Hz, 1H), 5.62 (s, 1H), 6.76-6.84 (m, 4H), 6.99 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.40-7.45 (m, 3H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.90-7.92(m, 1H), 8.43 (s, 1H), 8.79 (s, 1H); MS (ESI) *m/z*: 495 (M+1); Anal. Calcd. for $C_{29}H_{22}N_2O_4S$: C, 70.43, H, 4.48, N, 5.66. Found: C, 70.49; H, 4.41; N, 5.68.

4.3.2. 4-(4-Methoxyphenyl)-2-((2-oxo-2-(3-oxo-3H-benzo[f]chromen-2-yl)ethyl)thio)-3,4,7,8-tetrahydroquinazolin-5(6H)-one (8b): Pale yellow solid; mp. 205-207 ºC; IR (KBr, cm^{-1}) υ_{max}: 3444, 3158, 2887, 2849, 2777, 1714, 1663, 1622, 1612, 1514, 1379, 1242, 1184, 1075, 776; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-1.95 (m, 2H), 2.18-2.29 (m, 2H), 2.63-267 (m, 2H), 3.47 (s, 3H), 3.57 (d, *J* = 12.4 Hz, 1H), 4.12 (d, *J* = 12.8 Hz, 1H), 5.71 (s, 1H), 6.27 (d, *J* = 6.4 Hz, 2H), 6.74 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 9.2 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.83 (t, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.85 (s, 1H), 9.05 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.2, 20.9, 25.7, 36.1, 54.8, 95.3, 112.2, 112.5, 112.6, 115.8, 122.2, 124.3, 126.2, 128.4, 128.6, 128.9, 129.1, 129.8, 130.0, 130.8, 134.3, 137.1, 153.3, 157.2, 158.6, 166.2, 171.8, 193.6; MS

(ESI) *m/z*: 525 (M+1); Anal. Calcd. for $C_{30}H_{24}N_2O_5S$: C, 68.69, H, 4.61, N, 5.34. Found: C, 68.81; H, 4.48; N, 5.42.

4.3.3.4-(3,4-Dimethoxyphenyl)-2-((2-oxo-2-(3-oxo-3H-benzo[f]chromen-2-yl)ethyl)thio)-3,4, 7,8-tetrahydroquinazolin-5(6H)-one (8c): Pale yellow solid; mp. 226-228 ºC; IR (KBr, cm^{-1}) υ_{max}: 3419, 3181, 2916, 2794, 1714, 1664, 1627, 1614, 1567, 1522, 1331, 1279, 1248, 1142, 1017, 767; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-1.98 (m, 2H), 2.18-2.29 (m, 2H), 2.65 (d, *J* = 18.8 Hz, 2H), 3.53 (s, 6H), 3.71 (d, *J* = 13.6 Hz, 1H), 4.10 (d, *J* = 12.4 Hz, 1H), 5.61 (s, 1H), 6.31 (s, 1H), 6.43 (s, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.63-7.67 (m, 1H), 7.88 (d, *J* = 6.8 Hz, 1H), 8.40 (s, 1H), 8.75 (s, 1H). MS (ESI) *m/z*: 555 (M+1); Anal. Calcd. for $C_{31}H_{26}N_2O_6S$: C, 67.13, H, 4.73, N, 5.05. Found: C, 67.25; H, 4.62; N, 5.11.

4.3.4. 2-((2-Oxo-2-(3-oxo-3H-benzo[f]chromen-2-yl)ethyl)thio)-4-(3,4,5-trimethoxyphenyl)-3,4,7,8-tetrahydroquinazolin-5(6H)-one (8d): Pale yellow solid; mp. 245-247 ºC; IR (KBr, cm^{-1}) υ_{max}: 3436, 3099, 2924, 2799, 1717, 1656, 1632, 1589, 1563, 1532, 1322, 1127, 749; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-1.96 (m, 2H), 2.23-2.30 (m, 2H), 2.61-2.69 (m, 2H), 3.57 (s, 9H), 3.65 (d, *J* = 12.8 Hz, 1H) 4.17 (d, *J* = 12.8 Hz, 1H), 5.77 (s, 1H), 6.15 (s, 2H), 7.37 (d, *J* = 9.2 Hz, 1H), 7.66-7.69 (m, 1H), 7.79-7.83 (m, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.86 (s, 1H), 9.07 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.2, 25.6, 36.2, 54.9, 59.7, 95.5, 106.5, 112.1, 116.1, 122.2, 124.0, 126.3, 128.6, 128.9, 129.8, 134.4, 137.1, 137.5, 151.9, 153.3, 157.6, 166.4, 193.7; MS (ESI) *m/z*: 585 (M+1); Anal. Calcd. for $C_{32}H_{28}N_2O_7S$: C, 65.74, H, 4.83, N, 4.79. Found: C, 65.62; H, 4.92; N, 4.61.

4.3.5.4-(3-Nitrophenyl)-2-((2-oxo-2-(3-oxo-3H-benzo[f]chromen-2-yl)ethyl)thio)-3,4,7,8-tetrahydroquinazolin-5(6H)-one (8e): White solid; mp. 230-232 ºC; IR (KBr, cm^{-1}) υ_{max}: 3118, 2886, 2776, 1712, 1661, 1615, 1598, 1520, 1367, 1173, 1065, 771, 708; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-2.18 (m, 3H), 2.25-2.66 (m, 3H), 3.72 (d, *J* = 13.2 Hz, 1H) 4.15 (d, *J* = 13.2 Hz, 1H), 5.94 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.34 (s, 1H), 7.52 (s, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 12.4 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 8.60 (d, *J* = 8.8 Hz, 1H), 8.86 (d, *J* = 9.6 Hz, 1H), 9.17 (s, 1H); MS (ESI) *m/z*: 540 (M+1); Anal. Calcd. for $C_{29}H_{21}N_3O_6S$: C, 64.55, H, 3.92, N, 7.79. Found: C, 64.72; H, 3.81; N, 7.63.

4.3.6.4-(2-Chlorophenyl)-2-((2-oxo-2-(3-oxo-3H-benzo[f]chromen-2-yl)ethyl)thio)-3,4,7,8-tetrahydroquinazolin-5(6H)-one (8f): White solid; mp. 224-226 ºC; IR (KBr, cm^{-1}) υ_{max}: 3401, 3128, 2899, 2838, 2776, 1713, 1647, 1606, 1579, 1511, 1374, 1276, 1224, 772; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-1.97 (m, 2H), 2.15-2.28 (m, 2H), 2.60-2.66 (m, 2H), 3.54 (d, *J* = 12.4 Hz, 1H), 4.00 (d, *J* = 12.4 Hz, 1H), 6.06 (s, 1H), 6.93-6.98 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.21-7.39 (m, 5H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 8.51 (s, 1H), 8.74 (s, 1H). MS (ESI) *m/z*: 430 (M+1); Anal. Calcd. for $C_{29}H_{21}ClN_2O_4S$: C, 65.84, H, 4.00, N, 5.30. Found: C, 65.92; H, 3.90; N, 5.42.

5. Conclusion

We have synthesized a series of thioalkylated-4-aryltetrahydroquinazolinone derivatives under conventional heating in acetic acid with good to excellent yields in short reaction times. All the compounds were evaluated for their *in vitro* antibacterial activity. The activity data revealed that the compound possessing simple coumarin and 4-methoxy group **(7b)** has shown maximum zone of inhibition, and it may consider as a lead compound for further development of antibacterial agent for the treatment of bacterial infection.

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