

## Synthesis and anti-microbial / anti-malarial activity of a new class of chromone-dihydroquinazolinone hybrid heterocycles

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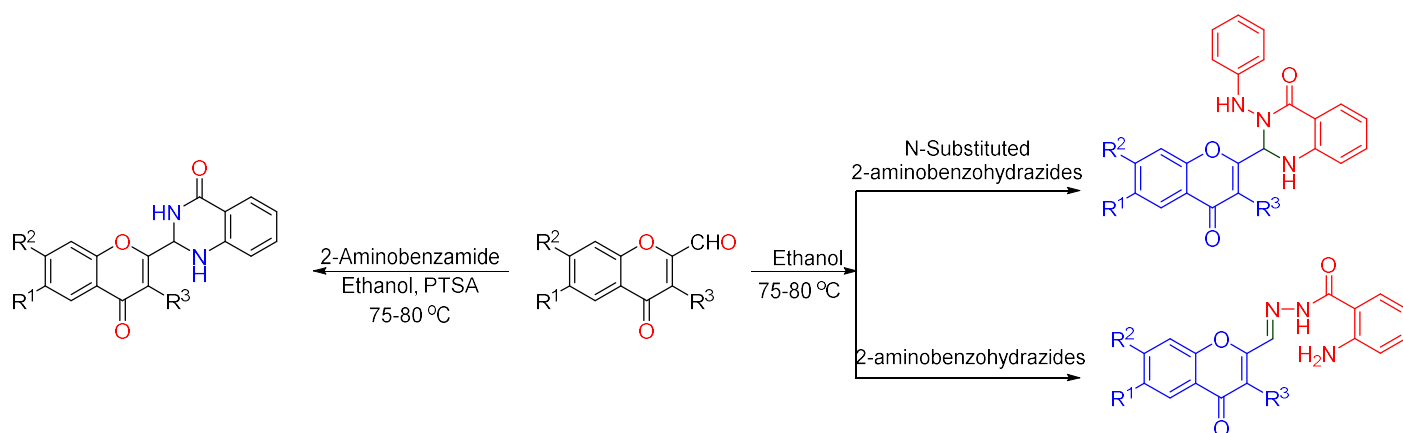
Received 09-29-2017

Accepted 01-16-2018

Published on line 03-15-2018

### Abstract

A new series of chromone-2,3-dihydroquinazolin-4-one hybrid heterocycles are synthesized from chromone-2-carbaldehydes by coupling with 2-aminoarylamides and hydrazides without oxidizing agents. The newly synthesized products exhibited moderate to good antimicrobial activity.



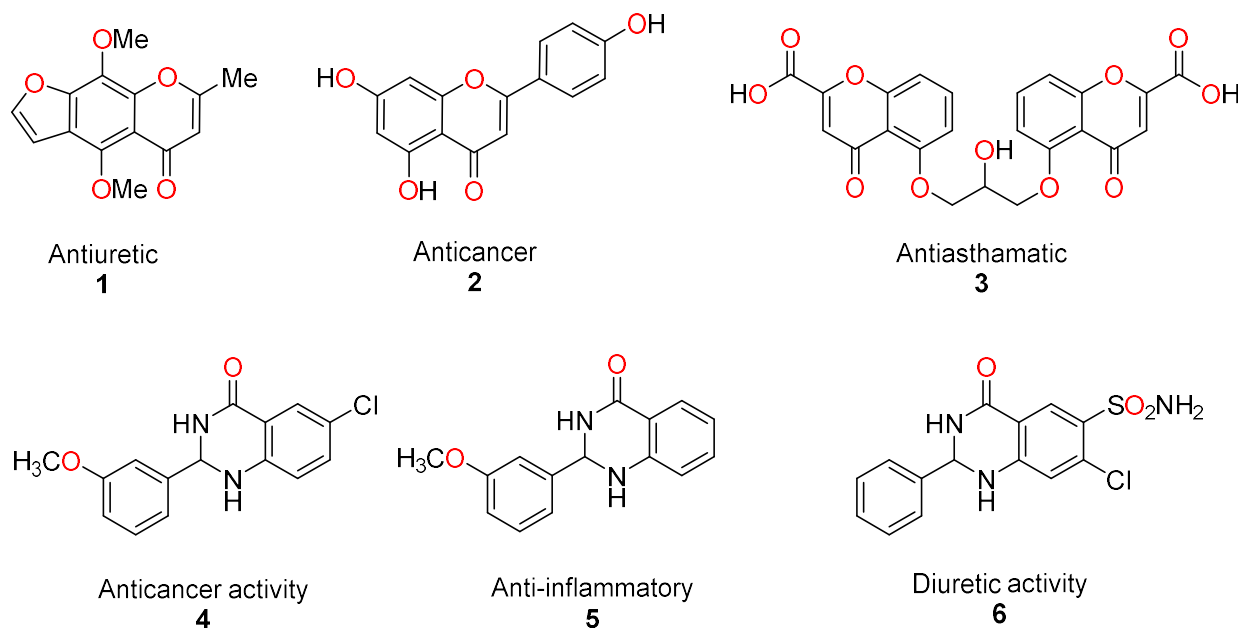
**Keywords:** Chromone-2-carbaldehydes, 2-aminobenzamide, 2-aminobenzohydrazide, 2,3-dihydroquinazolin-4-ones, antimicrobial activity, antimalarial activity

## Introduction

Chromones and their derivatives are well-known naturally occurring oxygen heterocyclic compounds which exhibit important biological functions in nature. The rigid bicyclic chromone is a privileged moiety in drug discovery with activities such as anti-inflammatory, antitumor and anticancer activity.<sup>1-3</sup> Simple, non-hydroxylated chromones were discovered to be selective inhibitors of p56lck tyrosine kinase.<sup>4</sup> Thus, a simple, efficient synthesis of chromone molecular hybrids remains an important research topic.

Nitrogen-containing heterocyclic compounds are also reported to be significantly important because of their diverse biological and pharmacological activities such as antibacterial, antifungal,<sup>5-8</sup> anticancer,<sup>9-11</sup> antiparkinson,<sup>12</sup> antidepressant,<sup>13</sup> analgesic,<sup>14</sup> diuretic<sup>15,16</sup> and antihistamine activity.<sup>17</sup> These compounds also act as vasodilating agents,<sup>18</sup> antihypertensive,<sup>19,20</sup> and CNS stimulant.<sup>21</sup> Other major pharmacological activities include, antianxiety,<sup>22</sup> tranquilizing,<sup>23</sup> antifibrillatory,<sup>24</sup> and anticonvulsant<sup>25</sup> effects. Some of the important chromone and 2,3-dihydroquinazolin-4-one scaffold drug candidates are presented in Figure 1.<sup>26-31</sup>

The heterocyclic molecular hybrids have advantages, such as, the potential to reduce the development of drug resistance and undesired side effects.<sup>32-39</sup> Chromone scaffold based hybrid heterocyclic products exhibited a wide range of biological activity.<sup>40-45</sup>



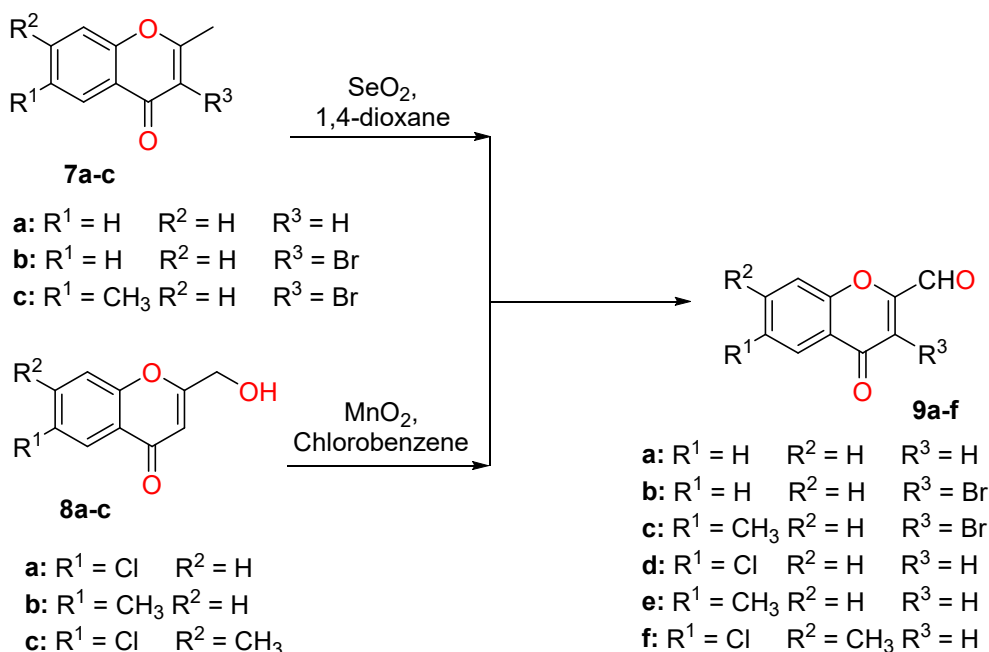
**Figure 1.** Chromone and 2,3-dihydroquinazolin-4-one drugs

In view of the interesting biological activities exhibited by chromones and 2,3-dihydroquinazolin-4-ones, structural modification of chromones has been attempted. The present work describes the design, synthesis and evaluation of antimicrobial and antimalarial activity of novel chromone-2,3-dihydroquinazolinone hybrid molecules. These novel scaffolds have been prepared by coupling 4-oxo-4*H*-chromene-2-carbaldehydes with 2-aminobenzamide and 2-aminobenzohydrazide derivatives. During the synthesis, formation of new intermediates has also been realized.

Literature survey has shown that while extensive studies have been carried out on chromone-3-carbaldehyde<sup>46-47</sup>, there is not much work on the synthesis and chemistry of chromone-2-carbaldehydes, probably due to the complexity in synthetic procedures.

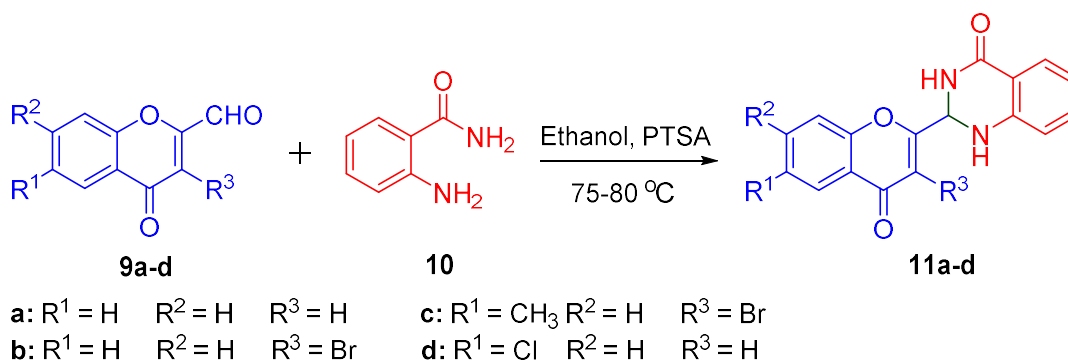
## Results and Discussion

4-Oxo-4*H*-chromen-2-carbaldehydes **9a-f** were synthesized using reported procedures<sup>48-50</sup> (1) by SeO<sub>2</sub> oxidation of 2-methyl-4*H*-chromen-4-ones **7a-c**, (2) by MnO<sub>2</sub> oxidation of 2-(hydroxymethyl)-4*H*-chromen-4-ones **8a-c** (Scheme 1). Approach 2 was specific for 6-substituted chromones as approach 1 resulted in very low yields of compounds **9e-f**.



**Scheme 1.** Synthesis of 4-oxo-4*H*-chromene-2-carbaldehydes (**9a-f**)

4-Oxo-4*H*-chromene-2-carbaldehydes **9a-d** were reacted with 2-aminobenzamide **10** in ethanol at 75-80 °C using PTSA as a catalyst for 3 hrs. The reaction was monitored for completion by TLC. The compounds 2-(4-oxo-4*H*-chromen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-ones **11a-d** were isolated by column chromatography (Scheme 2). Under the present reaction conditions, formation of two compounds (the desired cyclized compound and an imine intermediate) was possible, but only the desired cyclized compounds **11a-d** were obtained in excellent yields.

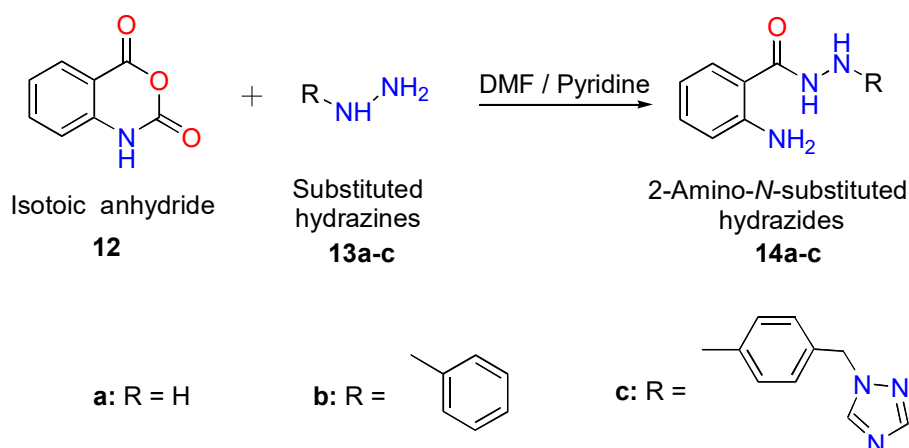


**Scheme 2.** Synthesis of 2-(4-oxo-4*H*-chromen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (**11a-d**)

The IR (solid, KBr) spectrum of 2-(4-oxo-4*H*-chromen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one **11a** exhibited absorption bands at 3318 cm<sup>-1</sup> (NH), 1721 cm<sup>-1</sup> (CO, chromone) and 1672 cm<sup>-1</sup> (CO, amide). The <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of the compound **11a** showed ten signals corresponding to twelve protons. The aldehyde proton of 4-oxo-4*H*-chromen-2-carbaldehyde **9a** was absent. Exchangeable protons were identified

by D<sub>2</sub>O exchange analysis at  $\delta_H$  8.67 ppm (d,  $J$  2.8 Hz, 1H, NH amide) and  $\delta_H$  7.5 ppm. Characteristic CH proton signals (H-2) appeared at  $\delta_H$  5.76 ppm (t,  $J$  2.8 Hz, 1H). This observation suggested the formation of a cyclized compound **11a**. The <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **11a** showed seventeen signals. Of the seventeen signals, one was observed in the aliphatic region at  $\delta_C$  63.32 ppm, which can be correlated with the aliphatic proton at  $\delta_H$  5.76 ppm. The remaining 16 signals were observed between  $\delta_C$  108.07 and 176.97 ppm. The positive-ion ESI-MS and HRMS data of **11a** showed a protonated molecular ion at  $m/z$  293.09 [M+H]<sup>+</sup> and  $m/z$  293.0936 [M+H]<sup>+</sup>, respectively.

Following the above observations, the study was extended to 2-aminobenzohydrazides **14a-c** which were synthesized using commercially available isatoic anhydride **12** and different hydrazine's **13a-c** in DMF (Scheme 3).

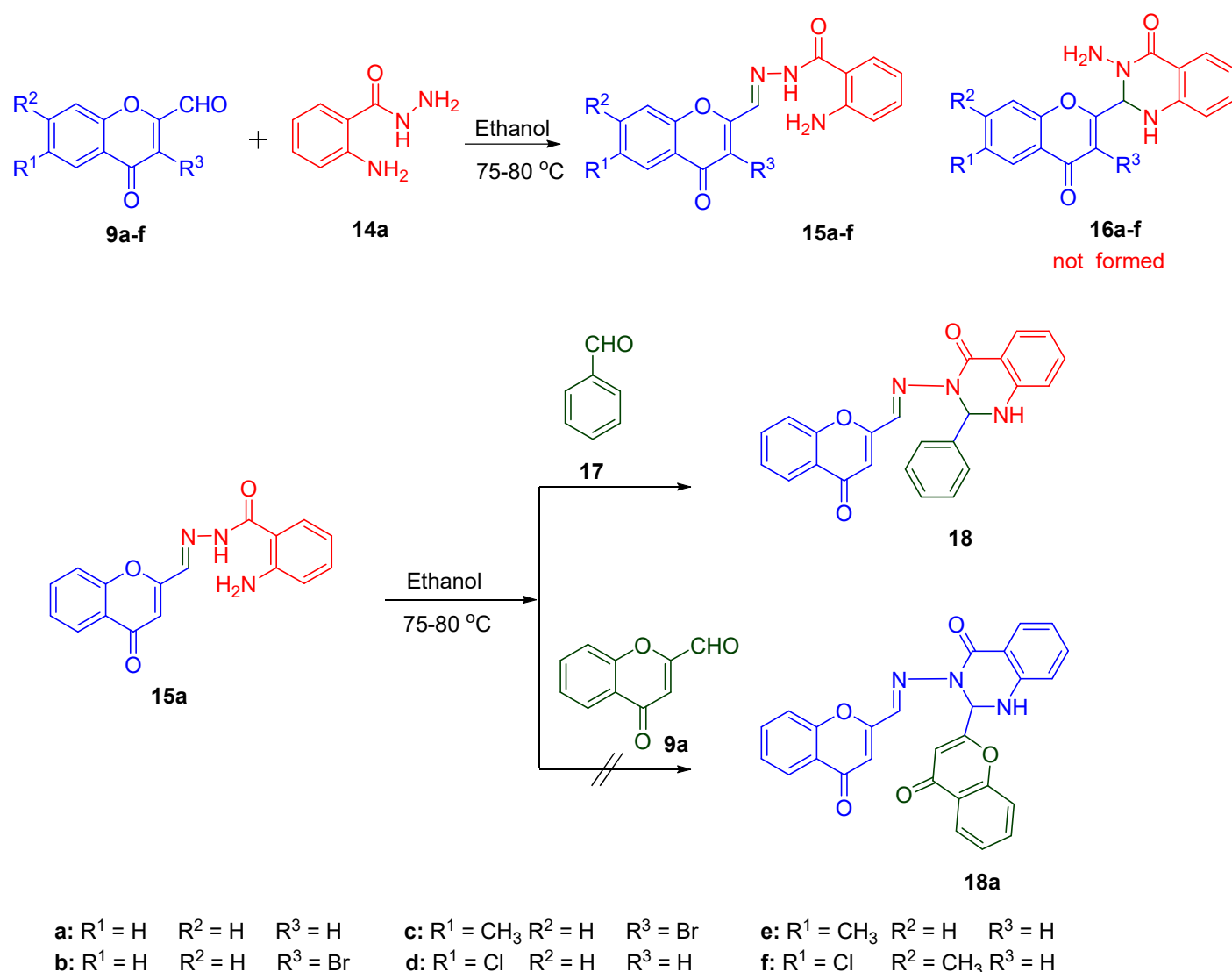


**Scheme 3.** Synthesis of 2-amino-*N*-substituted hydrazides (**14a-c**)

The reaction of 4-oxo-4*H*-chromene-2-carbaldehyde **9a-f** with 2-aminobenzohydrazide **14a** gave imine intermediates **15a-f** and the desired cyclized products **16a-f** were not observed even under forcing experimental conditions (Scheme 4). Literature survey supported the imine formation from aldehydes with 2-aminobenzohydrazide.<sup>51</sup>

The IR (solid, KBr) spectrum of 2-amino-*N*'-[(4-oxo-4*H*-chromen-2-yl)methylene]benzohydrazide **15a** exhibited absorption bands at 3466 cm<sup>-1</sup> (NH, primary amine), 3351 cm<sup>-1</sup> (NH, secondary amine), 1738 cm<sup>-1</sup> (CO, chromone) and 1663 cm<sup>-1</sup> (CO, amide). The <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **15a** showed twelve signals corresponding to thirteen protons. The aldehyde proton of **9a** had disappeared. D<sub>2</sub>O exchange analysis showed exchangeable protons at  $\delta_H$  12.2 (s, 1H, amide NH) and  $\delta_H$  6.52 ppm (s, 2H, NH<sub>2</sub>). Presence of two amine protons suggested the involvement of only the hydrazide NH<sub>2</sub> in the reaction. The absence of a proton in the aliphatic region suggested that the compound formed was an imine, but not the expected cyclic product. The <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) of **15a** showed seventeen signals between  $\delta_C$  111.71 ppm and 176.84 ppm. The absence of aliphatic carbons correlates with the absence of aliphatic protons in <sup>1</sup>H NMR. The positive ESI-MS and HRMS data of **15a** showed the molecular ion at  $m/z$  308.1 [M+H]<sup>+</sup> and 308.1046 [M+H]<sup>+</sup>, respectively. From the HSQC data of **15a**, the absence of correlations for the protons at  $\delta_H$  12.2 and 6.52 ppm confirmed that these are not attached to any carbon. This data supported the D<sub>2</sub>O exchange information. The HSQC data showed that there are ten methine groups and seven quaternary carbons, two of them corresponding to carbonyl carbons. HOMO COSY of **15a** showed two singlets at  $\delta_H$  8.25 and 6.72 ppm which did not show any correlations. From the <sup>1</sup>H NMR study on 4-oxo-4*H*-chromene-2-carbaldehydes, the proton at  $\delta_H$  6.72 ppm was assigned to the H-3 olefin proton. The other proton at  $\delta_H$  8.25 ppm which correlated with the

carbon at  $\delta_c$  138.7 ppm (HSQC) was predicted to be from an imine. This was supported by the double bond equivalence (DBE) from HRMS data.



**Scheme 4.** Synthesis of 2-amino-N'-[(4-oxo-4H-chromen-2-yl)methylene]benzohydrazide (**15a-f**)

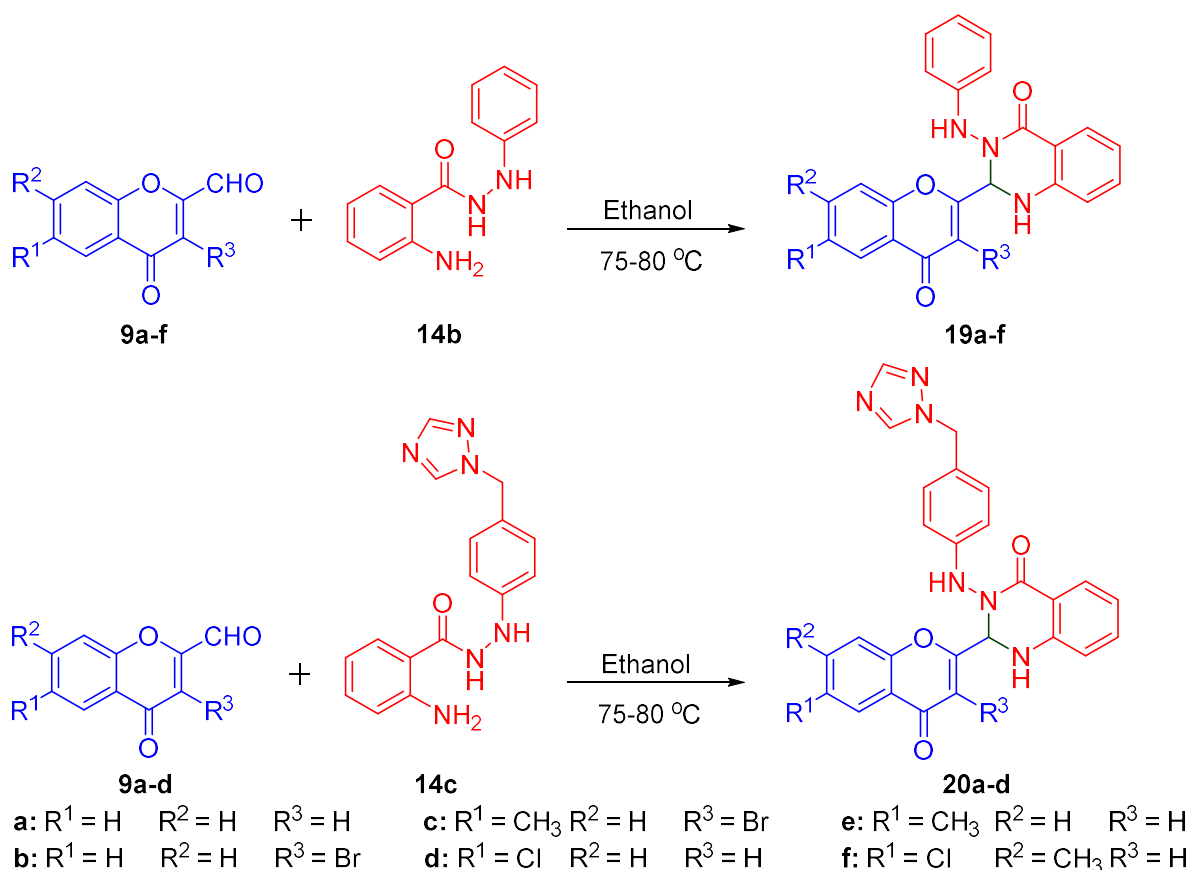
The results can be explained based on the difference in nucleophilicity of the  $NH_2$  of hydrazide and aniline. The lone pair of electrons on the amino group corresponding to aniline **14a** are conjugated with the aromatic nuclei and also the carbonyl group at the ortho position. Hence, these electrons are not freely available for the reaction when compared to the lone pair of electrons on the  $NH_2$  of hydrazide **14a**.

The imine compound **15a** was further reacted with benzaldehyde **17**. Interestingly, the reaction yielded the novel cyclic product 3-[[[(4-oxo-4H-chromen-2-yl)methylene]amino]-2-phenyl-2,3-dihydroquinazolin-4(1H)-one **18** (Scheme 4). In the  $^1H$  NMR spectrum of **18**, the characteristic peak of cyclic compound H-2' appeared at  $\delta_H$  6.67 ppm and corresponding  $^{13}C$  signal of C-2' appeared at  $\delta_C$  76.32 ppm. When the same reaction was carried out using 4-oxo-4H-chromene-2-carbaldehyde **9a**, the reaction did not occur (Scheme 4), probably due to steric hindrance.

Further reaction was carried out using the N-substituted 2-aminobenzohydrazides **14b,c**. Interestingly, the compounds obtained were the desired cyclic products **19a-f** (Scheme 5). In the  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )

spectra of the obtained compounds **19a-f**, a characteristic signal of H-2 was observed at  $\delta_H$  5.93 – 6.41 ppm and the corresponding carbon signal was observed at  $\delta_C$  71.4 – 72.2 ppm in  $^{13}C$  NMR. In the case that the free  $NH_2$  of hydrazide **14a** was substituted with a phenyl **14b** (where the lone pair is conjugated with the phenyl ring), the NH of the amide participated in the reaction, resulting in cyclized compounds having two heterocyclic moieties.

In order to develop hybrid triazole heterocyclic skeletons **20a-d**, 4-oxo-4*H*-chromene-2-carbaldehydes **9a-d** were reacted with *N'*-{4-[(1*H*-1,2,4-triazol-1-yl)methyl]phenyl}-2-aminobenzohydrazide **14c** (Scheme 5).



**Scheme 5.** Synthesis of 2-(4-oxo-4*H*-chromen-2-yl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-ones (**19a-f**) and 3-({4-[(1*H*-1,2,4-triazol-1-yl)methyl]phenyl}amino)-2-(4-oxo-4*H*-chromen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (**20a-d**)

## Biological Activity

### In vitro antibacterial activity

The hybrid molecules synthesized were tested against Gram-positive bacteria *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), and Gram-negative bacteria *Escherichia coli* (MTCC 443), and *Pseudomonas aeruginosa* (MTCC 741) (Table 1). Compounds **11b**, **19a-c**, **20b** showed very good activity against the gram-positive organism *Staphylococcus aureus* compared to the standard drug Ampicillin. The compound **19b** exhibited higher activity against gram-negative organism *Escherichia coli* when compared with the drug Ampicillin.

**Table 1.** Antimicrobial activity results of the synthesized compounds

Minimal inhibition concentration ( $\mu\text{g/ml}$ )					
S. No	Compound	<i>E.coli</i> MTCC 443	<i>P. aeruginosa</i> MTCC 441	<i>S. aureus</i> MTCC 96	<i>S. pyogenus</i> MTCC 442
	Ampicillin	100	100	250	100
	Ciprofloxacin	25	25	50	50
1	<b>11a</b>	200	250	250	250
2	<b>11b</b>	500	125	62.5	125
3	<b>15a</b>	250	250	250	200
4	<b>19a</b>	500	500	125	250
5	<b>19b</b>	62.5	100	100	125
6	<b>19c</b>	100	125	125	125
7	<b>19e</b>	125	200	200	250
8	<b>19f</b>	250	125	250	200
9	<b>20a</b>	125	200	200	125
10	<b>20b</b>	500	200	100	200
11	<b>20c</b>	200	200	200	500
12	<b>20d</b>	250	250	200	250

**In vitro antifungal activity**

The *in vitro* antifungal activity of the synthesized compounds were tested against fungal strains, *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) (Table 2). The compounds **15a**, **19e-f**, **20c** showed more activity against *Candida albicans* when compared to the standard drug Griseofulvin.

**Table-2.** Antifungal activity results of the synthesized compounds

Minimal fungicidal concentration ( $\mu\text{g/ml}$ )				
S. No	Compound	<i>C. albicans</i> MTCC 227	<i>A. niger</i> MTCC 282	<i>A. clavatus</i> MTCC 1323
Test Std.	Griseofulvin	500	100	100
1	<b>11a</b>	500	>1000	>1000
2	<b>11b</b>	500	500	500
3	<b>15a</b>	250	>1000	>1000
4	<b>19a</b>	500	1000	1000
5	<b>19b</b>	1000	>1000	>1000
6	<b>19c</b>	1000	>1000	>1000
7	<b>19e</b>	250	>1000	>1000
8	<b>19f</b>	200	>1000	>1000
9	<b>20a</b>	1000	>1000	>1000
10	<b>20b</b>	>1000	250	500
11	<b>20c</b>	250	>1000	>1000
12	<b>20d</b>	>1000	250	250

### Antimalarial activity

The antimalarial activity of the synthesized compounds was evaluated and compared with standard drugs Chloroquine and quinine. Activity of all the synthesized compounds was found to be lower than the standard drugs.

### Conclusion

In summary, we have developed a simple, efficient and convenient method for the synthesis of novel chromone / 2,3-dihydroquinazolin-4-one hybrid heterocycles by coupling of 2-aminobenzamide / 2-amino-benzohydrazides with chromone-2-carbaldehydes. Some of the synthesized compounds were found to exhibit moderate to very good antimicrobial activity. Hence, derivatives of chromone / 2,3-dihydroquinazolin-4-ones can be utilized in the future for the development of potent antimicrobial drugs.

### Experimental Section

**General.** Electrospray ionization and tandem mass spectrometry experiments were performed using a triple quadrupole mass spectrometer (PE Sciex model API 3000). The positive and negative electrospray data were obtained by switching the capillary voltage between +5000 and -4500 V, respectively. For HRMS, UPLC-TOF-MS system consisted of an Acquity™ Ultra Performance Liquid Chromatography system and Micromass LCT Premier XE Mass Spectrometer (High sensitivity orthogonal time-of-flight instrument; Waters, Milford, USA) equipped with an ESI lock spray source for accurate mass values. Leucine-enkephalin was used as reference compound, was introduced via the lock spray channel.

The NMR experiments were performed on Varian spectrometers operating at 400 and 500 MHz in DMSO-*d*<sub>6</sub> at 30 °C. The <sup>1</sup>H chemical shift values were reported on the  $\delta$  scale in ppm, relative to TMS ( $\delta$  = 0.00) and the <sup>13</sup>C chemical shift values were reported relative to DMSO ( $\delta$  = 40 ppm) as internal standard. Standard pulse sequences provided by Varian were used for distortionless enhancement by polarization transfer (DEPT), gradient double quantum filtered correlation spectroscopy (gDQCOSY), and gradient heteronuclear single quantum coherence spectroscopy (gHSQC).

Biological activity measurements were performed at M/s Microcare Laboratories, Surat, India. Antibacterial activity: Minimum inhibitory concentration (MIC) assay of the hybrid molecules synthesized was done by broth dilution method in tubes for macro dilution and in plates for micro dilution. Muller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test bacteria. DMSO was used as diluent to get the desired concentration of synthesized compounds. Standard drugs ampicillin and ciprofloxacin were used for comparison.

*Antifungal activity* was performed against the fungal strains *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323). Fungal growth was done with *Sabourauds dextrose* broth at 28.8 °C in aerobic condition for 48 hrs. 2% DMSO and sterilized distilled water were used as negative control and Griseofulvin (1 U strength) was used as positive control. Results were recorded in the form of primary and secondary screening.

*Antimalarial Activity.* The *in vitro* antimalarial assay was carried out in 96 well microtitre plates according to the micro assay protocol reference. Chloroquine and Quinine were taken as the reference drug for comparison.



**General procedure for synthesis of 4-oxo-4H-chromen-2-carbaldehydes (9a-c)**

1,4-dioxane (10 volumes), 2-methyl-4H-chromene-4-ones (**7a-c**) (160 mg, 1.0 mmol) and a catalytic amount of hydrogen peroxide were placed in a three-necked flask and selenium dioxide (177.5 mg, 1.6 mmol) was added under stirring and heated to 100-105 °C. After completion of the reaction (16 h.; TLC monitoring), the reaction mass was cooled to 25-35 °C and the selenium salts were removed by filtration. The filtrate was concentrated and the crude compound was purified by silica gel column chromatography. Elution of the column with ethyl acetate/petroleum ether 15:85 gave compounds **9a-c** in 60% yield.

**General procedure for synthesis of 4-oxo-4H-chromen-2-carbaldehydes (9d-f)**

Chlorobenzene (15 volumes), 2-(hydroxymethyl)-4H-chromene-4-one (**8a-c**) (176 mg, 1.0 mmol) and MnO<sub>2</sub> (348 mg, 4.0 mmol) were placed in a three-necked flask and heated to 130-135 °C. After completion of the reaction (24 h. TLC monitoring), the reaction mass was cooled to 25-35 °C and the manganese salts were removed by filtration. The filtrate was concentrated and the crude compound was purified by silica gel column chromatography. Elution of column with ethyl acetate/petroleum ether 15:85 gave compounds **9d-f** in 70% yield.

**General procedure for synthesis of 2-(4-oxo-4H-chromen-2-yl)-2,3-dihydroquinazolin-4(1H)-ones (11a-d)**

4-Oxo-4H-chromene-2-carbaldehyde (**9a-d**) (1.0 mmol), ethanol (10 volumes) and PTSA (catalytic amount) were placed in a three-necked flask and 2-aminobenzamide (1.2 mmol) was added under stirring and heated to 75-80 °C. After completion of the reaction (3 h. TLC monitoring), the reaction mass was cooled to 20-25 °C and filtered. The crude compound was purified by silica gel column chromatography. Elution of column with ethyl acetate/petroleum ether 20:80 gave compounds **11a-d**.

**2-(4-Oxo-4H-chromen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (11a).** Off-white crystalline solid (195 mg, 67%). Mp 282-285 °C. IR (solid, KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3318 (NH, sec amine), 1721 (C=O, ketone), 1672 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  8.67 (d, *J* 2.8 Hz, 1H, H-3', amide NH), 8.00 (dd, *J*<sub>1</sub> 7.60 Hz, *J*<sub>2</sub> 0.8 Hz, 1H, H-5), 7.78 (dt, *J*<sub>1</sub> 8.4 Hz, *J*<sub>2</sub> 1.6 Hz, 1H, H-7), 7.64 (d, *J* 6.8 Hz, 1H, H-5'), 7.50 (m, 3H, H-6, H-8 and 1'H-NH), 7.31 (dt, *J*<sub>1</sub> 8.4 Hz, *J*<sub>2</sub> 1.6 Hz, 1H, H-7'), 6.83 (d, *J* 8.0 Hz, 1H, H-8'), 6.72 (t, *J* 7.6 Hz, 1H, H-6'), 6.28 (s, 1H, H-3), 5.76 (t, *J* 3.2 Hz, 1H, H-2'). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  176.9 (C-4, C=O), 166.9 (C-2), 162.9 (C-4', amide C=O), 155.6 (C-8a), 146.5 (C-8'a), 134.7 (C-7'), 133.7 (C aromatic), 127.4 (C aromatic), 125.7 (C aromatic), 124.9 (C-5), 123.1 (C aromatic), 118.3 (C aromatic), 117.8 (C-8), 114.7 (C aromatic), 114.5 (C aromatic), 108.1 (C-3) and 63.3 ppm (C-2'). ESI-MS *m/z*: 293.093. HRMS (ESI): *m/z* calcd for C<sub>17</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 293.0926; found: 293.0936.

**2-(3-Bromo-4-oxo-4H-chromen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (11b).** Yellow crystalline solid (260 mg, 70%). mp 235-238 °C. IR (solid, KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3297 (NH, sec amine), 1740 (C=O, ketone), 1672 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  8.44 (d, *J* 1.6 Hz, 1H, H-3', amide NH), 8.07 (dd, *J*<sub>1</sub> 6.8 Hz, *J*<sub>2</sub> 1.2 Hz, 1H, H-5), 7.8 (m, 1H, H-7), 7.72 (d, *J* 6.4 Hz, 1H, H-5'), 7.52 (t, *J* 6.4 Hz, 1H, H-6), 7.42 (s, 1H, H-1', NH), 7.28 (dt, *J*<sub>1</sub> 6.4 Hz, *J*<sub>2</sub> 1.2 Hz, 1H, H-7'), 7.16 (d, *J* 6.8 Hz, 1H, H-8), 6.76 (t, *J* 6.0 Hz, 1H, H-6'), 6.74 (d, *J* 6.8 Hz, H-8') and 6.27 ppm (t, *J* 2.4 Hz, 1H, H-2'). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  171.9 (C-4, C=O), 165.7 (C-2), 161.9 (C-4', amide C=O), 152.9 (C-8a), 145.9 (C-8'a), 135.7 (C-7'), 134.9 (C aromatic), 128.4 (C aromatic), 125.7 (C aromatic), 124.7 (C-5), 123.1 (C aromatic), 118.1 (C aromatic), 117.8 (C-8), 114.8 (C aromatic), 114.5 (C aromatic), 108.1 (C-3) and 63.3 ppm (C-2'). ESI-MS *m/z*: 371.0033 [M+H]<sup>+</sup>, *m/z* 373.0013 [M+2+H]<sup>+</sup>. HRMS (ESI): *m/z* calcd for C<sub>17</sub>H<sub>12</sub>BrN<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 371.0031; found: 371.0033.

**2-(3-Bromo-6-methyl-4-oxo-4H-chromen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (11c).** Brown crystalline solid (270 mg, 70%). mp 250-252 °C. IR (solid, KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3317 (NH, sec amine), 1738 (C=O, ketone), 1672 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  8.43 (d, *J* 2.0 Hz, 1H, H-3', amide NH), 7.85 (d, *J* 1.2 Hz, 1H, H-5), 7.71 (dd, *J*<sub>1</sub> 6.0 Hz, *J*<sub>2</sub> 1.2 Hz, 1H, H-5'), 7.60 (dd, *J*<sub>1</sub> 6.8 Hz, *J*<sub>2</sub> 1.2 Hz, 1H, H-7), 7.41 (s, 1H, H-1'-NH), 7.27 (dt,

$J_1$  6.8 Hz,  $J_2$  1.2 Hz, 1H, H-7'), 7.07 (d,  $J$  6.8 Hz, 1H, H-8), 6.76 (t,  $J$  6.4 Hz, 1H, H-6'), 6.72 (d,  $J$  6.4 Hz, 1H, H-8'), 6.26 (t,  $J$  2.4 Hz, 1H, H-2') and 2.36 ppm (s, 3H, H-6a).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  172.1 (C-4, C=O), 165.0 (C-2), 161.6 (C-4', amide C=O), 153.6 (C-8a), 144.9 (C-8'a), 135.0 (C-7'), 134.3 (C aromatic), 133.7 (C aromatic), 127.9 (C aromatic), 124.7 (C-5), 123.2 (C aromatic), 118.3 (C aromatic), 117.9 (C-8), 114.7 (C aromatic), 114.5 (C aromatic), 108.1 (C-3), 63.7 (C-2') and 20.6 ppm (C-6a). ESI-MS  $m/z$ : 385.0185  $[\text{M}+\text{H}]^+$ ,  $m/z$  387.018  $[\text{M}+2+\text{H}]^+$ . HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{14}\text{BrN}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 385.0188; found: 385.0193.

**2-(6-Chloro-4-oxo-4H-chromen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (11d).** Yellow crystalline solid (180 mg, 55%). mp 260-262 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3296 (NH, sec amine), 1738 (C=O, ketone), 1688 (C=O, amide).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  8.69 (d,  $J$  2.8 Hz, 1H, H-3', amide NH), 7.93 (d,  $J$  2.8 Hz, 1H, H-5), 7.85 (dd,  $J_1$  9.6 Hz,  $J_2$  3.2 Hz, 1H, H-5'), 7.63 (dd,  $J_1$  6.0 Hz,  $J_2$  1.6 Hz, 1H, H-7), 7.55 (d,  $J$  8.8 Hz, 1H, H-8), 7.51 (s, 1H, H-1' NH), 7.30 (dt,  $J_1$  8.4 Hz,  $J_2$  1.2 Hz, 1H, H-7'), 6.83 (d,  $J$  7.6 Hz, 1H, H-8'), 6.73 (t,  $J$  8.0 Hz, 1H, H-6'), 6.32 (s, 1H, H-3) and  $\delta_{\text{H}}$  5.77 ppm (t,  $J$  3.2 Hz, 1H, H-2').  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  175.8 (C-4, C=O), 165.8 (C-2), 162.6 (C-4', amide C=O), 154.2 (C-8a), 147.5 (C-8'a), 134.6 (C-7'), 134.2 (C aromatic), 129.7 (C aromatic), 127.3 (C aromatic), 125.7 (C aromatic), 123.9 (C aromatic), 118.2 (C-8), 117.9 (C aromatic), 114.7 (C aromatic), 114.2 (C aromatic), 108.9 (C-3) and 63.8 ppm (C-2'). ESI-MS  $m/z$ : 327.05  $[\text{M}+\text{H}]^+$ ,  $m/z$  329.04  $[\text{M}+2+\text{H}]^+$ . HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{12}\text{ClN}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 327.0536; found: 327.0533.

#### Synthesis of 2-amino-N'-[(4-oxo-4H-chromen-2-yl)methylene]benzohydrazides (15a-f)

4-Oxo-4H-chromene-2-carbaldehydes (**9a-f**) (1.0 mmol), ethanol (10 volumes) were placed in a three-necked flask and 2-aminobenzohydrazide (**14a**) (1.2 mmol) was added under stirring and heated to 75-80 °C. After completion of the reaction (3 h. TLC monitoring), the reaction mass was cooled to 20-25 °C and the compound was filtered and dried at 70 °C for 4 h.

**2-Amino-N'-[(4-oxo-4H-chromen-2-yl)methylene]benzohydrazide (15a).** Yellow crystalline solid (245 mg, 80%). mp 188-192 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3466 (NH, primary amine), 3351 (NH, sec amine), 1738 (C=O, ketone), 1663 (C=O, amide).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  12.16 (s, 1H, H-1'b, amide NH), 8.24 (s, 1H, H-2a), 8.06 (dd,  $J_1$  8.4 Hz,  $J_2$  2.0 Hz, 1H, H-5), 7.86 (m, 1H, H-7), 7.73 (d,  $J$  8.0 Hz, 1H, H-8), 7.62 (dd,  $J_1$  8.0 Hz,  $J_2$  1.2 Hz, 1H, H-2'), 7.53 (dt,  $J_1$  7.6 Hz,  $J_2$  0.8 Hz, 1H, H-6), 7.26 (dt,  $J_1$  8.4 Hz,  $J_2$  1.2 Hz, 1H, H-4'), 6.78 (d,  $J$  8.0 Hz, 1H, H-5'), 6.72 (s, 1H, H-3), 6.61 (dt,  $J_1$  8.4 Hz,  $J_2$  0.8 Hz, 1H, H-3') and 6.53 ppm (s, 2H, H-6'a, NH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  176.8 (C-4, C=O), 165.7 (C1'a, C=O amide), 159.2 (C-2), 155.5 (C-8a), 150.6 (C aromatic), 138.7 (C-2a), 134.7 (C-7), 132.9 (C4'), 128.5 (C-2'), 125.6 (C-6), 124.9 (C-5), 123.8 (C aromatic), 118.5 (C-8), 116.6 (C-5'), 114.6 (C-3'), 112.2 (C aromatic), and 111.7 ppm (C-3). ESI-MS  $m/z$ : 308.1  $[\text{M}+\text{H}]^+$ , HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{N}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 308.1035; found: 308.1046.

**2-Amino-N'-[(3-bromo-4-oxo-4H-chromen-2-yl)methylene]benzohydrazide (15b).** Yellow crystalline solid (270 mg, 70%). mp 254-257 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3471 (NH, primary amine), 3357 (NH, sec amine), 1739 (C=O, ketone), 1635 (C=O, amide).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  12.4 (s, 1H, H-2'b, amide NH), 8.87 (s, 1H, H-2a), 8.00 (d, 1H,  $J$  8.0 Hz, H-5), 7.90 (t,  $J$  8.0 Hz, 1H, H-7), 7.74 (d,  $J$  8.8 Hz, 1H, H-8), 7.65 (d,  $J$  8.0 Hz, 1H, H-2'), 7.56 (t,  $J$  7.6 Hz, 1H, H-6), 7.26 (t,  $J$  8.0 Hz, 1H, H-4'), 6.80 (d,  $J$  8.4 Hz, 1H, H-5') and 6.60 ppm (t,  $J$  7.6 Hz, 3H, H-3', H-6'a, NH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  171.9 (C-4, C=O), 165.6 (C1'a, C=O), 155.4 (C-2), 154.6 (C-8a), 150.8 (C aromatic), 138.0 (C-2a), 135.2 (C-7), 133.1 (C4'), 128.5 (C-2'), 126.0 (C-6), 125.4 (C-5), 121.6 (C aromatic), 118.3 (C-8), 116.6 (C-5'), 114.5 (C-3'), 111.9 (C aromatic) and 111.8 ppm (C-3). ESI-MS  $m/z$ : 386.01  $[\text{M}+\text{H}]^+$ , 388.01  $[\text{M}+2+\text{H}]^+$ , HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{13}\text{BrN}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 386.0140; found: 386.0139.

**2-Amino-N'-[(3-bromo-6-methyl-4-oxo-4H-chromen-2-yl)methylene]benzohydrazide (15c).** Yellow crystalline solid (292 mg, 73%). mp 236-239 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3464 (NH, primary amine), 3350 (NH, sec amine), 1739 (C=O, ketone), 1661 (C=O, amide).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  + DMSO- $d_6$ ):  $\delta_{\text{H}}$  12.32 (s, 1H, H-1'b, amide NH), 8.91 (s, 1H, H-2a), 7.91 (s, 1H, H-5), 7.64 (m, 3H, H-7, H-8 and H-2'), 7.22 (t, 1H, H-4'), 6.81 (d,  $J$  8.4

Hz, 1H, H-5'), 6.59 (t, 1H, H-3') 6.50 (s, 2H, H-6'a, NH<sub>2</sub>) and 2.48 ppm (s, 3H, H-6a). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 171.8 (C-4, C=O), 165.9 (C1'a, C=O), 155.3 (C-2), 152.9 (C-8a), 150.7 (C aromatic), 138.1 (C-2a), 136.3 (C-6), 135.8 (C-7), 133.1 (C-4'), 128.5 (C-2'), 124.6 (C-5), 121.4 (C aromatic), 118.1 (C-8), 116.6 (C-5'), 114.5 (C-3'), 111.8 (C aromatic), 111.8 (C-3) and 20.4 ppm (C-6a). ESI-MS *m/z*: 400.0 [M+H]<sup>+</sup>, 402.0 [M+2+H]<sup>+</sup>, HRMS (ESI): *m/z* calcd for C<sub>18</sub>H<sub>15</sub>BrN<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 400.0297; found: 400.0302.

**2-Amino-N'-[(6-Chloro-4-oxo-4H-chromen-2-yl)methylene]benzohydrazide (15d).** Yellow crystalline solid (240 mg, 71%). mp 218-220 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3459 (NH, primary amine), 3349 (NH, sec amine), 1742 (C=O, ketone), 1673 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 12.21 (s, 1H, H-1'b, amide NH), 8.19 (s, 1H, H-2a), 7.97 (s, 1H, H-5), 7.82 (dt, *J*<sub>1</sub> 1.6 Hz, *J*<sub>2</sub> 8.8 Hz, 1H, H-7), 7.79 (d, *J* 8.0 Hz, 1H, H-8), 7.61 (dd, *J*<sub>1</sub> 1.6 Hz, *J*<sub>2</sub> 8.4 Hz, 1H, H-2'), 7.25 (dt, *J*<sub>1</sub> 1.2 Hz, *J*<sub>2</sub> 8.4 Hz, 1H, H-4'), 6.72 (d, *J* 8.4 Hz, 1H, H-5'), 6.70 (s, 1H, H-3), 6.61 (dt, *J*<sub>1</sub> 1.2 Hz, *J*<sub>2</sub> 8.4 Hz, 1H, H-3') and 6.48 ppm (s, 2H, H-6'a, NH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 175.9 (C-4, C=O), 165.5 (C1'a, C=O amide), 160.2 (C-2), 155.5 (C-8a), 150.2 (C aromatic), 138.3 (C-2a), 134.1 (C-7), 133.1 (C-4'), 129.5 (C aromatic), 128.5 (C-2'), 125.6 (C aromatic), 123.9 (C aromatic), 118.3 (C-8), 116.8 (C-5'), 114.1 (C-3'), 112.5 (C aromatic), and 111.6 ppm (C-3). ESI-MS *m/z*: 342.1 [M+H]<sup>+</sup>, 344.1 [M+2+H]<sup>+</sup>. HRMS (ESI): *m/z* calcd for C<sub>17</sub>H<sub>13</sub>ClN<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 342.1049; found: 342.1055.

**2-Amino-N'-[(6-methyl-4-oxo-4H-chromen-2-yl)methylene]benzohydrazide (15e).** Yellow crystalline solid (275 mg, 85%). mp 249-251 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3463 (NH, primary amine), 3345 (NH, sec amine), 1800 (C=O, ketone), 1661 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 12.14 (s, 1H, H-1'b, amide NH), 8.23 (s, 1H, H-2a), 7.84 (s, 1H, H-5), 7.65 (m, 3H), 7.26 (dt, *J*<sub>1</sub> 8.4 Hz, *J*<sub>2</sub> 1.6 Hz, 1H, H-4'), 6.79 (d, *J* 7.6 Hz, 1H, H-5'), 6.67 (s, 1H, H-3) 6.61 (t, *J* 8.0 Hz, 1H, H-3'), 6.51 (s, 2H, H-6'a, NH<sub>2</sub>) and 2.44 ppm (s, 3H, H-6a). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 176.5 (C-4, C=O), 165.8 (C1'a, C=O), 159.2 (C-2), 153.2 (C-8a), 150.5 (C aromatic), 138.3 (C-2a), 136.3 (C-6), 135.8 (C-7), 132.8 (C-4'), 128.3 (C-2'), 124.1 (C-5), 123.9 (C aromatic), 118.1 (C-8), 116.5 (C-5'), 114.4 (C-3'), 111.9 (C aromatic), 111.7 (C-3) and 20.2 ppm (C-6a). ESI-MS *m/z*: 322.11 [M+H]<sup>+</sup>, HRMS (ESI): *m/z* calcd for C<sub>18</sub>H<sub>16</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 322.1192; found: 322.1184.

**2-Amino-N'-[(6-chloro-7-methyl-4-oxo-4H-chromen-2-yl)methylene]benzohydrazide (15f).** Yellow crystalline solid (230 mg, 65%). mp 246-248 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3484 (NH, primary amine), 3370 (NH, sec amine), 1673 (C=O, ketone), 1630 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 12.16 (s, 1H, H-1'b, amide NH), 8.22 (s, 1H, H-2a), 7.96 (s, 1H, H-5), 7.83 (s, 1H, H-8), 7.62 (d, *J* 7.6 Hz, 1H, H-2'), 7.25 (t, *J* 7.2 Hz, 1H, H-4'), 6.78 (d, *J* 8.4 Hz, 1H, H-5'), 6.72 (s, 1H, H-3), 6.59 (t, *J* 8.0 Hz, 1H, H-3'), 6.52 (s, 2H, H-6'a, NH<sub>2</sub>) and 2.45 ppm (s, 3H, H-7a). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 175.6 (C-4, C=O), 165.6 (C1'a, C=O), 159.3 (C-2), 154.0 (C aromatic), 150.6 (C aromatic), 143.1 (C aromatic), 138.5 (C-2a), 132.9 (C4'), 130.8 (C-6), 128.5 (C-2'), 124.1 (C-5), 123.1 (C aromatic), 120.8 (C aromatic), 116.5 (C-5'), 114.5 (C-3'), 112.1 (C aromatic), 111.4 (C-3) and 20.1 ppm (C-6a). ESI-MS *m/z*: 356.07 [M+H]<sup>+</sup>, *m/z* 358.07 [M+2+H]<sup>+</sup>, HRMS (ESI): *m/z* calcd for C<sub>18</sub>H<sub>15</sub>ClN<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 356.0802; found: 356.0797.

### Synthesis of 3-[[[(4-oxo-4H-chromen-2-yl)methylene]amino]-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (18).

2-Amino-N'-[(4-oxo-4H-chromen-2-yl)methylene]benzohydrazide (**15a**) (307 mg, 1.0 mmol), ethanol (10 volumes) were placed in a three-necked flask and benzaldehyde (127 mg, 1.2 mmol) was added under stirring and heated to 75- 80 °C. After completion of reaction (3 h. TLC monitoring), reaction mass was cooled to 20-25 °C and compound was filtered and dried at 70 °C for 4 h. to obtain a yellow crystalline solid (325 mg, 82%). mp 285-288 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3298 (NH, sec amine), 1740 (C=O, ketone), 1630 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 8.81 (s, 1H, H-2a), 8.14 (d, *J* 3.2 Hz, 1H, NH), 8.04 (dd, *J*<sub>1</sub> 8.0 Hz, *J*<sub>2</sub> 1.2 Hz, 1H, H-5), 7.81 (dt, *J*<sub>1</sub> 8.8 Hz, *J*<sub>2</sub> 1.6 Hz, 1H, H-7), 7.74 (d, *J* 7.2 Hz, 1H, CH aromatic), 7.68 (d, *J* 8.8 Hz, 1H, H-8), 7.50 (t, *J* 8.0 Hz, 1H, H-6), 7.4-7.3 (m, 6H, CH aromatic), 6.83 (d, *J* 8.0 Hz, 1-H, CH aromatic), 6.76 (t, *J* 7.6 Hz, 1H, CH aromatic), 6.70 (s, 1H, H-3) and 6.67 ppm (d, *J* 2.8 Hz, 1H, H-2'). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 178.2 (C-4,

C=O), 162.5 (C-1'a, C=O), 159.9 (C-2), 156.1 (C-8a), 145.1 (C aromatic), 143.7 (C aromatic), 139.1 (C-2a), 134.9 (C-7), 134.0 (C-4'), 129.3 (C aromatic), 129.1 (C aromatic), 128.8 (C-3' and C-5'), 126.6 (C-2' and C-6'), 125.7 (C-6), 125.0 (C aromatic), 124.5 (C-5), 120.2 (C-8), 118.3 (C-5'), 116.2 (C-3'), 115.2 (C aromatic), 110.9 (C-3) and 76.4 ppm (C-2'). ESI-MS  $m/z$ : 396.2 [M+H]<sup>+</sup>.

#### Synthesis of 2-(4-oxo-4H-chromen-2-yl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-ones (19a-f)

4-Oxo-4H-chromene-2-carbaldehyde (**9a-f**) (1.0 mmol), and ethanol (10 volumes) were placed in a three-necked flask and 2-amino-N'-phenylbenzohydrazide (**14b**) (1.2 mmol) was added under stirring and heated to 75-80 °C. After completion of the reaction (3 h. TLC monitoring), the reaction mass was cooled to 20-25 °C and filtered. The crude compound was purified by silica gel column chromatography. Elution of the column with ethyl acetate/petroleum ether 20:80 gave compounds **19a-f**.

**2-(4-Oxo-4H-chromen-2-yl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (19a).** Off white crystalline solid (306 mg, 80%). mp 153-155 °C. IR (solid, KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3279 (NH, sec amine), 1649 (C=O, ketone), 1607 (C=O amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  8.61 (s, 1H, H-3'a), 8.00 (dd,  $J_1$  8.0 Hz,  $J_2$  1.6 Hz, 1H, H-5), 7.88 (d,  $J$  3.2 Hz, 1H, H-1', NH), 7.79 (m, 1H, H-7), 7.70 (dd,  $J_1$  8.4 Hz,  $J_2$  1.2 Hz, 1H, H-5'), 7.47 (dt,  $J_1$  8.0 Hz,  $J_2$  1.2 Hz, 1H, H-6), 7.42 (d,  $J$  8.4 Hz, 1H, H-8), 7.34 (dt,  $J_1$  8.4 Hz,  $J_2$  1.6 Hz, 1H, H-7'), 7.19 (t,  $J$  8.4 Hz, 2H, H-3', H-5'), 6.8 (m, 5H, CH aromatic), 6.42 (s, 1H, H-3) and 5.95 ppm (d,  $J$  3.2 Hz, 1H, H-2'). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  176.9 (C-4, C=O), 165.3 (C-2), 162.5 (C-4', C=O), 155.6 (C-8a), 147.6 (C-8'a), 146.3 (C aromatic), 134.5 (C aromatic), 134.0 (C aromatic), 128.9 (C-3', 5'), 127.5 (C aromatic), 125.7 (C aromatic), 124.9 (C-5), 123.2 (C aromatic), 119.4 (C aromatic), 118.4 (C-8), 118.2 (C aromatic), 114.7 (C aromatic), 114.3 (C aromatic), 112.3 (C-2' and C-6'), 108.9 (C-3) and 71.6 ppm (C-2'). ESI-MS  $m/z$ : 384.13 [M+H]<sup>+</sup>, HRMS (ESI):  $m/z$  calcd for C<sub>23</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 384.1348; found: 384.1333.

**2-(3-Bromo-4-oxo-4H-chromen-2-yl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (19b).** Off white crystalline solid (322 mg, 70%). mp 259-262 °C. IR (solid, KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3300 (NH, sec amine), 1678 (C=O, ketone), 1664 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  8.33 (s, 1H, H-3'a, NH), 8.06 (dd,  $J_1$  8.4 Hz,  $J_2$  1.6 Hz, 1H, H-5), 7.85 (d,  $J$  2.8 Hz, 1H, H-1', NH), 7.78 (m, 2H, H-7, H-5'), 7.52 (t,  $J$  8.0 Hz, 1H, H-6), 7.33 (t,  $J$  6.8 Hz, 1H, H-7'), 7.17 (t,  $J$  8.0 Hz, 2H, H-3', H-5'), 7.07 (d,  $J$  8.4 Hz, 1H, H-8), 6.80 (m, 5H, CH aromatic) and 6.41 ppm (d,  $J$  2.8 Hz, 1H, H-2'). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  171.6 (C-4, C=O), 163.0 (C-2), 161.5 (C-4', C=O), 154.3 (C-8a), 147.2 (C-8'a), 145.9 (C aromatic), 135.1 (C aromatic), 133.9 (C-7'), 129.0 (C-3', 5'), 127.3 (C-7), 126.3 (C aromatic), 125.5 (C aromatic), 121.2 (C aromatic), 119.5 (C aromatic), 118.1 (C-8), 117.9 (C aromatic), 114.3 (C aromatic), 113.9 (C aromatic), 112.3 (C-2'' and C-6''), 107.3 (C-3) and 71.9 ppm (C-2'). ESI-MS  $m/z$ : 462.04 [M+H]<sup>+</sup>,  $m/z$  464.04 [M+2+H]<sup>+</sup>, HRMS (ESI):  $m/z$  calcd for C<sub>23</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>Br [M+H]<sup>+</sup>: 462.0453; found: 462.0432.

**2-(3-Bromo-6-methyl-4-oxo-4H-chromen-2-yl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (19c).** Yellow crystalline solid (284 mg, 60%). mp 225-227 °C. IR (solid, KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3372 (NH, sec amine), 1683 (C=O, ketone), 1639 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  8.34 (s, 1H, H-3'a, NH), 7.83 (s, 2H, H-5, H-1', NH), 7.75 (d,  $J$  7.6 Hz, 1H, H-7), 7.62 (d,  $J$  8.4 Hz, 1H, H-5), 7.33 (t,  $J$  7.2 Hz, 1H, H-7'), 7.15 (t,  $J$  7.6 Hz, 2H, H-3', H-5'), 6.97 (d,  $J$  8.4 Hz, 1H, H-8), 6.80 (m, 5H, CH aromatic), 6.38 (d,  $J$  2.8 Hz, 1H, H-2') and 2.41 ppm (s, 3H, H-6a). <sup>13</sup>C NMR (100 Hz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  171.5 (C-4, C=O), 163.0 (C-2), 161.3 (C=O, C-4', amide), 152.6 (C-8a), 147.2 (C-8'a), 145.9 (C aromatic), 136.2 (C-6), 136.0 (C aromatic), 133.9 (C aromatic), 128.9 (C-3', 5'), 127.3 (C aromatic), 124.6 (C aromatic), 121.0 (C aromatic), 119.5 (C aromatic), 118.1 (C-8), 117.8 (C aromatic), 114.3 (C aromatic), 113.9 (C aromatic), 112.3 (C-2' and C-6'), 107.2 (C-3), 71.9 (C-2') and 20.4 ppm (C-6a). ESI-MS  $m/z$ : 476.05 [M+H]<sup>+</sup>, 478.05 [M+2+H]<sup>+</sup>, HRMS (ESI):  $m/z$  calcd for C<sub>24</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>Br [M+H]<sup>+</sup>: 476.0610; found: 476.0591.

**2-(6-Chloro-4-oxo-4H-chromen-2-yl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (19d).** Yellow crystalline solid (258 mg, 62%). mp 198-200 °C. IR (solid, KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3289 (NH, sec amine), 1645 (C=O, ketone), 1602 (C=O, amide). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  8.59 (s, 1H, H-3'a), 7.89 (d,  $J$  2.8 Hz, 1H, H-5),

7.85 (d,  $J$  2.8 Hz, 1H, H-1', NH), 7.79 (t,  $J$  6.0 Hz, 1.6 Hz, 1H, H-7), 7.72 (dd,  $J_1$  8.4 Hz,  $J_2$  1.2 Hz, 1H, H-5'), 7.55 (d,  $J$  8.4 Hz, 1H, H-8), 7.31 (dt,  $J_1$  8.4 Hz,  $J_2$  1.6 Hz, 1H, H-7'), 7.10 (t,  $J$  8.4 Hz, 2H, H-3', H-5'), 6.77 (m, 5H, CH aromatic), 6.44 (s, 1H, H-3) and 5.91 ppm (d,  $J$  3.2 Hz, 1H, H-2').  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  175.9 (C-4, C=O), 164.9 (C-2), 162.2 (C-4', C=O), 155.1 (C-8a), 147.0 (C-8'a), 146.1 (C aromatic), 134.5 (C aromatic), 134.0 (C aromatic), 129.7 (C aromatic), 128.9 (C-3', 5'), 127.6 (C aromatic), 124.9 (C-5), 123.2 (C aromatic), 119.4 (C aromatic), 118.4 (C-8), 118.3 (C aromatic), 114.8 (C aromatic), 114.3 (C aromatic), 112.3 (C-2' and C-6'), 108.8 (C-3) and 71.6 ppm (C-2'). ESI-MS  $m/z$ : 418.08  $[\text{M}+\text{H}]^+$ , 420.08  $[\text{M}+2+\text{H}]^+$ , HRMS (ESI):  $m/z$  calcd for  $\text{C}_{23}\text{H}_{17}\text{ClN}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 418.0912; found: 418.0812.

**2-(6-Methyl-4-oxo-4H-chromen-2-yl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (19e).** Pale yellow crystalline solid (278 mg, 70%). mp 213–215 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3329 (NH, sec amine), 1653 (C=O, ketone), 1603 (C=O, amide).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  8.57 (s, 1H, H-3'a, NH), 7.84 (d,  $J$  3.2 Hz, 1H, 1'-H, NH), 7.77 (d,  $J$  1.2 Hz, 1H, H-5), 7.70 (d,  $J$  8.0 Hz, 1H, H-7), 7.61 (dd,  $J_1$  8.0 Hz,  $J_2$  2.0 Hz, 1H, H-5'), 7.33 (m, 2H, H-8, H-7'), 7.19 (t,  $J$  8.0 Hz, 2H, H-3', H-5'), 6.85 (m, 5H, CH aromatic), 6.38 (s, 1H, H-3), 5.93 (d,  $J$  2.8 Hz, 1H, H-2') and 2.44 ppm (s, 3H, H-6a).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  177.3 (C-4, C=O), 165.7 (C-2), 163.0 (C-3'a, amide C=O), 154.4 (C-8a), 148.1 (C aromatic), 146.0 (C aromatic), 136.0 (C-6), 135.9 (C aromatic), 133.8 (C-7'), 128.7 (C-3' and C-5'), 127.3 (C-7), 124.0 (C-5), 123.4 (C aromatic), 119.2 (C aromatic), 118.0 (C-8), 118.0 (C aromatic), 114.8 (C aromatic), 114.5 (C aromatic), 112.0 (C-2' and C-6'), 108.4 (C-3), 71.4 (C-2') and 20.2 ppm (C-6a). ESI-MS  $m/z$ : 398.14  $[\text{M}+\text{H}]^+$ , HRMS (ESI):  $m/z$  calcd for  $\text{C}_{24}\text{H}_{20}\text{N}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 398.1505; found: 398.1490.

**2-(6-Chloro-7-methyl-4-oxo-4H-chromen-2-yl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (19f).** Pale yellow crystalline solid (327 mg, 76%). mp 276–278 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3285 (NH, sec amine), 1645 (C=O, ketone), 1604 (C=O, amide).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  8.56 (s, 1H, H-3'a, NH), 7.91 (s, 1H, H-5), 7.84 (d,  $J$  3.2 Hz, 1H, H-1', NH), 7.70 (d,  $J$  7.2 Hz, 1H, H-5'), 7.48 (s, 1H, H-8), 7.34 (t,  $J$  8.4 Hz, 1H, H-7'), 7.19 (t, 8.0 Hz, 2H, H-3', H-5'), 6.80 (m, 5H), 6.43 (s, 1H, H-3), 5.96 (d,  $J$  2.8 Hz, 1H, H-2') and 2.44 ppm (s, 3H, H-7a).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  177.3 (C-4, C=O), 165.7 (C-2), 162.9 (C-3'a, amide C=O), 154.4 (C-8a), 148.2 (C-8'a), 146.8 (C aromatic), 136.2 (C aromatic), 135.9 (C aromatic), 133.9 (C-7'), 130.5 (C aromatic), 128.8 (C-3' and C-5'), 127.4 (C aromatic), 124.0 (C-5), 119.9 (C aromatic), 119.3 (C aromatic), 118.0 (C-8), 117.9 (C aromatic), 114.5 (C aromatic), 112.0 (C-2' and C-6'), 109.2 (C-3), 72.3 (C-2') and 21.0 ppm (C-6a). ESI-MS  $m/z$ : 432.11  $[\text{M}+\text{H}]^+$ , 434.10  $[\text{M}+2+\text{H}]^+$ , HRMS (ESI):  $m/z$  calcd for  $\text{C}_{24}\text{H}_{19}\text{ClN}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 432.1115; found: 432.1102.

### Synthesis of 3-({4-[(1H-1,2,4-triazol-1-yl)methyl]phenyl}amino)-2-(4-oxo-4H-chromen-2-yl)-2,3-dihydroquinazolin-4(1H)-ones (20a-d)

4-Oxo-4H-chromene-2-carbaldehyde (**9a-d**) (1.0 mmol), ethanol (10 volumes) were placed in a three-necked flask and N'-{4-[(1H-1,2,4-triazol-1-yl)methyl]phenyl}-2-aminobenzohydrazide (**14c**) (1.2 mmol) was added under stirring and heated to 75–80 °C. After completion of the reaction (3 h. TLC monitoring), the reaction mass was cooled to 20–25 °C and filtered. The crude compound was purified by silica gel column chromatography. Elution of the column with ethyl acetate/petroleum ether 20:80 gave compounds **20a-d**.

**3-({4-[(1H-1,2,4-Triazol-1-yl)methyl]phenyl}amino)-2-(4-oxo-4H-chromen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (20a).** Pale yellow crystalline solid (255 mg, 55%). mp 160–163 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3259 (NH, sec amine), 1741 (C=O, ketone), 1651 (C=O, amide).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  8.66 (s, 1H, H-3'a), 8.57 (s, 1H, H-5'''), 7.99 (dd,  $J_1$  8.0 Hz,  $J_2$  1.6 Hz, 1H, H-5), 7.92 (s, 1H, H-3'''), 7.84 (d,  $J$  2.4 Hz, 1H, H-1', NH), 7.77 (m, 1H, H-7), 7.69 (dd,  $J_1$  7.6 Hz,  $J_2$  1.2 Hz, 1H, H-5'), 7.48 (dt,  $J_1$  7.6 Hz,  $J_2$  0.8 Hz, 1H, H-6), 7.40 (d,  $J$  8.4 Hz, 1H, H-8), 7.34 (dt,  $J_1$  8.4 Hz,  $J_2$  1.6 Hz, 1H, H-7'), 7.17 (d,  $J$  8.4 Hz, 2H, H-3', H-5'), 6.80 (m, 4H), 6.40 (s, 1H, H-3), 5.93 (d,  $J$  3.2 Hz, 1H, H-2') and 5.26 ppm (s, 2H, H-4'a).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  176.8 (C-4, C=O), 165.2 (C-2), 162.4 (C-4', C=O, amide), 155.6 (C-8a), 151.5 (C-3'''), 147.4 (C-8'a), 146.3 (C aromatic), 143.7 (C-5'''), 134.5 (C aromatic), 134.0 (C-7'), 129.1 (C-3', C-5'), 127.5 (C aromatic), 127.0 (C aromatic), 125.7 (C aromatic), 124.9 (C

aromatic), 123.2 (C-5), 118.4 (C aromatic), 118.2 (C aromatic), 114.7 (C aromatic), 114.2 (C aromatic), 112.3 (C-2' and C-6'), 108.9 (C-3), 71.6 (C-2'') and 51.9 ppm (C-4'a). ESI-MS  $m/z$ : 465.16  $[M+H]^+$ , HRMS (ESI):  $m/z$  calcd for  $C_{26}H_{21}N_6O_3$   $[M+H]^+$ : 465.1675; found: 465.1688.

**3-({4-[(1*H*-1,2,4-Triazol-1-yl)methyl]phenyl}amino)-2-(3-bromo-4-oxo-4*H*-chromen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (20b).** Green crystalline solid (245 mg, 45%). mp 260-264 °C. IR (solid, KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3323 (NH, sec amine), 1736 (C=O, ketone), 1675 (C=O, amide).  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H$  8.59 (s, 1H, H-3'a, NH), 8.44 (s, 1H, H-5''), 8.06 (dd,  $J_1$  8.0 Hz,  $J_2$  1.2 Hz, 1H, H-5), 7.93 (s, 1H, H-3''), 7.85 (d,  $J$  2.8 Hz, 1H, H-1', NH), 7.77 (m, 2H, H-7, H-5'), 7.52 (t,  $J$  7.6 Hz, 1H, H-6), 7.35 (dt,  $J_1$  8.8 Hz,  $J_2$  2.0 Hz, 1H, H-7'), 7.15 (d,  $J$  8.0 Hz, 2H, H-3', H-5'), 7.06 (d,  $J$  8.4 Hz, 1H, H-8), 6.80 (m, 4H, CH aromatic), 6.40 (d, 2.4 Hz, 1H, H-2') and 5.26 ppm (s, 2H, H-4'a).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C$  171.6 (C-4, C=O), 163.0 (C-2), 161.4 (C-4', C=O amide), 154.3 (C aromatic), 151.5 (C-3''), 147.1 (C aromatic), 146.0 (C aromatic), 143.8 (C-5''), 135.2 (C aromatic), 134.0 (C-7'), 129.2 (C-3', C-5'), 127.3 (C aromatic), 127.1 (C-7), 126.3 (C-6), 125.6 (C aromatic), 121.2 (C-5), 118.1 (C aromatic), 118.0 (C aromatic), 114.3 (C aromatic), 113.8 (C aromatic), 112.2 (C-2' and C-6'), 108.0 (C-3), 72.0 (C-2') and 51.9 ppm (C-4'a). ESI-MS  $m/z$ : 543.07  $[M+H]^+$ , 545.07  $[M+2+H]^+$ , HRMS (ESI):  $m/z$  calcd for  $C_{26}H_{20}BrN_6O_3$   $[M+H]^+$ : 543.0780; found: 543.0799.

**3-({4-[(1*H*-1,2,4-Triazol-1-yl)methyl]phenyl}amino)-2-(3-bromo-6-methyl-4-oxo-4*H*-chromen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (20c).** Pale brown crystalline solid (278 mg, 50%). mp 248-250 °C. IR (solid, KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3252 (NH, sec amine), 1736 (C=O, ketone), 1668 (C=O, amide).  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H$  8.59 (s, 1H, H-3'a, NH), 8.41 (s, 1H, H-5''), 8.06 (s, 1H, H-5), 7.90 (s, 1H, H-3''), 7.77 (d,  $J$  2.8 Hz, 1H, H-1', NH), 7.71 (d,  $J$  7.6 Hz, 1H, H-7), 7.65 (d, 8.4 Hz, 1H, H-5'), 7.31 (dt,  $J_1$  8.8 Hz,  $J_2$  2.0 Hz, 1H, H-7'), 7.15 (d,  $J$  8.0 Hz, 2H, H-3', H-5'), 7.06 (d,  $J$  8.4 Hz, 1H, H-8), 6.80 (m, 4H, CH aromatic), 6.40 (d, 2.4 Hz, 1H, H-2'), 5.25 ppm (s, 2H, H-4'a) and 2.49 ppm (s, 3H, H-6a).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C$  176.1 (C-4, C=O), 164.9 (C-2), 162.3 (C=O amide), 155.2 (C-8a), 151.0 (C-3''), 147.1 (C-8'a), 145.9 (C aromatic), 143.3 (C-5''), 134.5 (C aromatic), 134.1 (C-7'), 133.9 (C-6), 128.7 (C-3', C-5'), 127.1 (C aromatic), 126.9 (C aromatic), 124.9 (C aromatic), 123.2 (C-5), 117.9 (C aromatic), 118.2 (C aromatic), 114.7 (C aromatic), 114.3 (C aromatic), 112.3 (C-2' and C-6'), 108.9 (C-3), 71.4 (C-2'), 51.8 (C-4'a) and 29.9 ppm (C-6a). ESI-MS  $m/z$ : 557.09  $[M+H]^+$ ,  $m/z$  559.09  $[M+2+H]^+$ , HRMS (ESI):  $m/z$  calcd for  $C_{27}H_{22}BrN_6O_3$   $[M+H]^+$ : 557.0937; found: 557.0944.

**3-({4-[(1*H*-1,2,4-Triazol-1-yl)methyl]phenyl}amino)-2-(6-chloro-4-oxo-4*H*-chromen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (20d).** Yellow crystalline solid (224 mg, 45%). mp 255-260 °C. IR (solid, KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3269 (NH, sec amine), 1741 (C=O, ketone), 1647 (C=O, amide).  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H$  8.66 (s, 1H, H-3'a, NH), 8.57 (s, 1H, H-5''), 7.92 (s, 1H, H-5), 7.91, (s, 1H, H-3''), 7.84 (s, 1H, H-1', NH), 7.82 (d,  $J$  2.0 Hz, 1H, H-7), 7.69 (d,  $J$  4.8 Hz, 1H, H-5'), 7.48 (d,  $J$  7.2 Hz, 1H, H-8), 7.34 (t, 1H, H-7'), 7.17 (d,  $J$  6.8 Hz, 2H, H-3', H-5'), 6.80 (m, 4H), 6.40 (s, 1H, H-3), 5.93 (d,  $J$  2.4 Hz, 1H, H-2') and 5.26 ppm (s, 2H, H-4'a).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C$  175.8 (C-4, C=O), 165.8 (C-2), 162.4 (C-4', C=O amide), 154.2 (C aromatic), 151.5 (C-3'), 147.4 (C aromatic), 146.3 (C aromatic), 143.7 (C-5''), 134.5 (C aromatic), 134.1 (C-7'), 130.1 (C-6) 129.2 (C-3', C-5'), 127.6 (C aromatic), 127.1 (C-7), 124.3 (C aromatic), 123.9 (C-5), 120.9 (C aromatic), 118.3 (C aromatic), 114.8 (C aromatic), 114.2 (C aromatic), 112.3 (C-2' and C-6'), 108.9 (C-3), 71.5 (C-2') and 51.6 ppm (C-4'a). ESI-MS  $m/z$ : 499.12  $[M+H]^+$ ,  $m/z$  501.12  $[M+2+H]^+$ , HRMS (ESI):  $m/z$  calcd for  $C_{26}H_{20}ClN_6O_3$   $[M+H]^+$ : 499.1285; found: 499.1290.

## Acknowledgements

The authors are thankful to the management of Dr. Reddy's laboratories and Department of Chemistry, Osmania University for facilitating the research work.

## Supplementary Material

Supplementary material ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS spectrum for the compounds **11a**, **15a**, **19a** and **20a**) associated with this article can be found in the website.

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