



## SYNTHESIS OF 2-AZETIDINONES SUBSTITUTED ISOCOUMARINS

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3-Formylisocoumarin condensed with aromatic primary amines to give Schiff bases (**2a-2d**). These Schiff bases are then reacted with acid chlorides in the presence of base in toluene to give 1,3,4-substituted 2-azetidinones.

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### INTRODUCTION

High throughput screening of the selected chemical libraries having heterocyclic or carbocyclic ring at their core is one of the most expeditious ways to search for useful medicinal activity. Heterocyclic lactones have long been a mainstay of organic synthesis due to their broad application to organic and medicinal chemistry. Isocoumarin or 1H-2-Benzopyran-1-ones constitute a small but significant group of naturally occurring lactones that is assuming growing importance in recent years. Isocoumarins constitute an important group of natural products. Equally important is the natural occurrence of 3,4-dihydro isocoumarin, the saturated lactones.

Isocoumarins have assumed importance in recent years<sup>1,2</sup> majority of the naturally occurring isocoumarins and dihydro Isocoumarins occur in fungi and other microorganism and are metabolic products of the host and therefore may be playing vital part in the metabolism of these microorganisms. Few observations reported in the literature regarding the physiological activity of some of them are quiet encouraging. The heteroatom improves binding and the rigid cyclic framework, imparts rigidity, enhancing the selectivity, Nitrogen atom being one of them. There are several examples reported in literature where the presence of nitrogen atom in compounds in various form has shown tremendous therapeutic applications.

$\beta$ -Lactam class of compounds has served as an important and highly successful role in the pharmaceutical industry. Miracle drugs such as Penicillins and Cephalosporins have significantly improved the human health and life expectancy. Although most Penicillin and Cephalosporin like compounds have been obtained by biosynthesis, by chemical modification of intermediates for bioassay of antibacterial activity because of growing resistance of bacteria against Penicillin and Cephalosporin like compounds and the need for medicines with more specific antibacterial activity.<sup>3,4</sup> Developments in the field of  $\beta$ -lactams<sup>5-8</sup> during the last decade have shown that the only essential

feature for the antibacterial activity in these compounds is the presence of  $\beta$ -lactam ring. Much attention was therefore focussed on this four membered cyclic amide and also the various substituents's attached directly to this system. The azetidinone derivatives have also been recognized as TACE inhibitors<sup>9</sup> and agents with new biological activities such as anticancer,<sup>10</sup> anticoccidal,<sup>11</sup> cardiovascular,<sup>12</sup> antiviral,<sup>13</sup> mutagenic property,<sup>14</sup> anticonvulsant and anti-inflammatory.<sup>15,16</sup>

The biological importance of the above heterocycles led us to introduce azetidinone ring on the isocoumarin ring with an aim to increasing their biological activity.

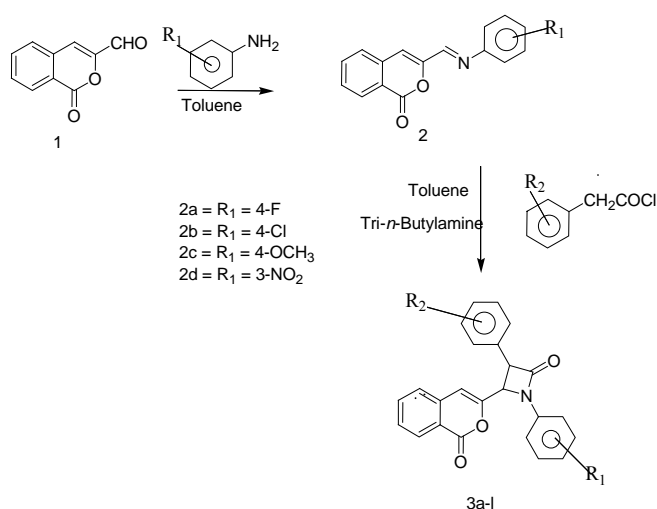
### RESULTS AND DISCUSSION

The 3-formylisocoumarin was condensed with various aromatic amines in toluene to yield Schiff's bases (**2a-2d**). Reaction was monitored by TLC. After completion of reaction the product was filtered and dried to get Schiff bases (**2a-2d**) and was characterized by their physical as well as spectral data. The IR spectra of compound (**2a-2d**) showed absorption for only one carbonyl group at 1717  $\text{cm}^{-1}$  and presence of  $\text{-CH=N-}$  band at 1618  $\text{cm}^{-1}$ . Some other bands were observed at 1493 and 1598  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) showed absence of aldehydic proton and the presence of  $\text{CH=N}$  proton at  $\delta$  8.17 ppm. These Schiff's bases (**2a-2d**) were then reacted with acid chlorides in the presence of base such as tri-n-butylamine to give 1,3,4- substituted 2-azetidinone (**3a-3l**). The IR spectra of compounds (**3a-3l**) showed absorption for two carbonyl groups at 1752 and 1739  $\text{cm}^{-1}$ . In the  $^1\text{H}$  NMR there were two doublets for  $\text{C}_3$  -H and  $\text{C}_4$ -H at 4.71 & 4.77 ppm. The envisaged reaction sequence is depicted in **Scheme 1**.

Structures of the compounds **3a-3l** were established by their IR and  $^1\text{H}$  NMR spectra. As reported in the literature cis isomer shows higher value of coupling constant than trans isomer.<sup>17</sup> Majority of isolated compounds are showing lower value of coupling constant confirming the trans azetidinone. One of the compound showing higher value of coupling constant confirming the presence of cis azetidinone. Few of them were showing mixture of both in which trans azetidinones containing small amount of cis azetidinones (Table 1).

**Table 1.** Stereochemistry of compounds (**3a-3l**)

Compound	R <sub>1</sub>	R <sub>2</sub>	Isolated isomer
3a	4-F	H	<i>Trans</i>
3b	4-Cl	H	<i>Trans: Cis (88: 12)</i>
3c	4-OCH <sub>3</sub>	H	<i>Trans</i>
3d	3-NO <sub>2</sub>	H	<i>Trans:Cis (91: 9)</i>
3e	4-F	4-OCH <sub>3</sub>	<i>Trans</i>
3f	4-Cl	4-OCH <sub>3</sub>	<i>Trans</i>
3g	4-OCH <sub>3</sub>	4-OCH <sub>3</sub>	<i>Trans</i>
3h	3-NO <sub>2</sub>	4-OCH <sub>3</sub>	<i>Trans</i>
3i	4-F	4-Cl	<i>Trans</i>
3j	4-Cl	4-Cl	<i>Trans</i>
3k	4-OCH <sub>3</sub>	4-Cl	<i>Cis</i>
3l	3-NO <sub>2</sub>	4-Cl	<i>Trans</i>



Scheme 1.

## EXPERIMENTAL SECTION

All the compounds were identified by examination of their spectral data and physical properties. Yields refer to the isolated yields of desired products. Melting points were determined on Buchi-545 melting point apparatus and are uncorrected. Progress of the reaction was monitored on TLC. IR spectra were recorded by Perkin Elmer Spectrum-1 (FTIR) using KBr discs, <sup>1</sup>H NMR and <sup>13</sup>C NMR was recorded in CDCl<sub>3</sub> using Avance 400 MHz Bruker spectrometer (chemical shift (δ) in ppm) with TMS as internal standard and mass spectra were recorded on a Thermofinigan Ion Trap GCMS Polaris Q. The dry reactions were carried out under nitrogen with magnetic/mechanical stirring.

### General procedure for the synthesis of 3-arylimino-1H-isochromen-1-ones (**2a-2d**)

An intimate mixture of 3-formyl isocoumarin (**1**) (10 mmol) and corresponding aromatic primary amine (11

mmol) was refluxed in toluene (30 ml) for 6-7 hours with azeotropic removal of the water formed during the reaction. The reaction was monitored by TLC. After reaction was completed the reaction mass was cooled down to 10°C the product was filtered and washed with cold toluene to get solid products.

**3-((4-fluorophenylimino)methyl)-1H-isochromen-1-one (2a):** Yellow solid; Yield: 80%; m.p. 197-198°C; Anal. Calcd. for C<sub>16</sub>H<sub>10</sub>FNO<sub>2</sub>; C, 71.91; H, 3.77; N, 5.24. Found: C, 71.93; H, 3.81; N, 5.30; IR (KBr, cm<sup>-1</sup>): 3072 (arom-CH), 1717 (>C=O), 1618; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.20 (s, 1H, C<sub>4</sub>-H), 7.10-8.39 (m, 8H, Ar-H), 8.17 (s, 1H, -CH=N-); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 112.9, 115.1, 121.6, 123.6, 127.9, 130.1, 130.5, 135.8, 136.6, 143.1, 150.0, 151.1, 159.4, 161.2; Mass (m/z): 267 [M<sup>+</sup>].

**3-((4-chlorophenylimino)methyl)-1H-isochromen-1-one (2b):** Yellow solid; Yield: 82%; m.p. 212-213°C; Anal. Calcd. for C<sub>16</sub>H<sub>10</sub>ClNO<sub>2</sub>; C, 67.74; H, 3.55; N, 4.94. Found: C, 67.75; H, 3.58; N, 4.97; IR (KBr, cm<sup>-1</sup>): 3070(arom-CH), 1723(>C=O), 1623; <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ: 7.23 (s, 1H, C<sub>4</sub>-H), 7.21-8.39 (m, 8H, Ar-H), 8.22 (s, 1H, -CH=N-); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 112.9, 115.1, 121.7, 123.6, 127.9, 130.2, 130.5, 135.8, 136.6, 143.2, 150.1, 151.1, 159.4, 161.3; Mass (m/z) : 283 [M<sup>+</sup>].

**3-((4-methoxyphenylimino)methyl)-1H-isochromen-1-one (2c):** Brown solid; Yield: 84%; m.p. 220-221°C; Anal. Calcd. for C<sub>17</sub>H<sub>13</sub>NO<sub>3</sub>; C, 73.11; H, 4.69; N, 5.02. Found: C, 73.14; H, 4.71; N, 5.05; IR (KBr, cm<sup>-1</sup>): 3067 (arom-CH), 1725 (>C=O), 1620; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.86 (s, 3H, -OCH<sub>3</sub>), 7.17 (s, 1H, C<sub>4</sub>-H), 6.95-8.36 (m, 8H, Ar-H), 8.19 (s, 1H, -CH=N-); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 55.7, 112.6, 114.9, 121.9, 123.4, 127.7, 129.6, 130.3, 135.7, 136.4, 143.1, 150.0, 151.1, 159.3, 161.2; Mass (m/z) : 279 [M<sup>+</sup>].

**3-((3-nitrophenylimino)methyl)-1H-isochromen-1-one (2d):** Yellow solid; Yield: 82 %; m.p. 228-229°C; Anal. Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>; C, 65.31; H, 3.43; N, 9.52. Found: C, 65.34; H, 3.48; N, 9.57; IR (KBr, cm<sup>-1</sup>): 3070 (arom-CH), 1719 (>C=O), 1616; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.25 (s, 1H, C<sub>4</sub>-H), 7.62-8.42 (m, 8H, Ar-H), 8.40 (s, 1H, -CH=N-); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 113.2, 115.3, 121.8, 123.8, 127.6, 130.4, 130.8, 135.9, 136.8, 144.0, 143.6, 150.2, 151.4, 155.6, 159.6, 161.3; Mass (m/z): 294 [M<sup>+</sup>].

### General procedure for the synthesis of 4-(1-oxo-1H-isochromen-3-yl)-1-aryl-3-phenylazetidin-2-ones (**3a-3l**)

A mixture of 3-iminoisocoumarin derivatives (10 mmol) (**2a-2d**), acid chlorides (20 mmol) and tri-*n*-butylamine (30 mmol) in toluene (50 ml) was refluxed for 3-4 hours. Reaction was monitored by TLC. After completion of the reaction it was then cooled to room temperature and 1:1 HCl (40-50 ml) was added. Organic layer was separated and washed with water followed by NaHCO<sub>3</sub> solution and finally with water and dried over

anhydrous sodium sulphate and solvent removed under reduced pressure. Compound was isolated using column chromatography (n-Hexane: Ethyl acetate = 90: 10) and thereafter it was crystallized from ethanol.

*1-(4-fluorophenyl)-4-(1-oxo-1H-isochromen-3-yl)-3-phenylazetididin-2-one (3a)*: White solid; Yield: 54%; m.p. 147-148°C; Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>FNO<sub>3</sub>; C, 74.8; H, 4.18; N, 3.63. Found: C, 74.64; H, 4.08; N, 3.74; IR (KBr, cm<sup>-1</sup>): 3060 (arom-CH), 1752 (>C=O), 1739 (>C=O), 1602 (C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.71 (d, 1H, *J*=2.4Hz, C<sub>3</sub>-H), 4.77 (d, 1H, *J*=2.4Hz, C<sub>4</sub>-H), 6.65 (s, 1H, -CH=C), 7.03-8.33 (m, 13H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 60.2, 61.3, 105.3, 114.6, 119.1, 121.3, 125.7, 127.6, 128.5, 129.3, 130.1, 130.8, 133.9, 135.6, 135.9, 138.1, 151.9, 156.7, 161.3, 164.2; Mass (m/z) : 385 [M<sup>+</sup>].

*1-(4-chlorophenyl)-4-(1-oxo-1H-isochromen-3-yl)-3-phenylazetididin-2-one (3b)*: White solid; Yield: 48 %; m.p. 162-163°C, Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>ClNO<sub>3</sub>; C, 71.73; H, 4.01; N, 3.49. Found: C, 71.85; H, 3.9; N, 3.37; IR (KBr, cm<sup>-1</sup>): 3064 (arom-CH), 1758 (>C=O), 1729 (>C=O), 1598(C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.71 (d, 1H, *J*=2.4Hz, C<sub>3</sub>-H), 4.78 (d, 1H, *J*=2.4Hz, C<sub>4</sub>-H), 6.65 (s, 1H, -CH=C), 7.30-8.34 (m, 13H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 60.2, 61.3, 105.3, 114.5, 119.2, 121.3, 125.7, 127.6, 128.6, 129.3, 130.1, 130.8, 133.9, 135.7, 135.9, 138.2, 151.9, 156.7, 161.3, 164.2; Mass (m/z) : 401 [M<sup>+</sup>].

*1-(4-methoxyphenyl)-4-(1-oxo-1H-isochromen-3-yl)-3-phenylazetididin-2-one (3c)*: White solid; Yield: 49%; m.p. 159-160°C, Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>NO<sub>4</sub>; C, 75.55; H, 4.82; N, 3.52. Found: C, 75.60; H, 4.88; N, 3.59; IR (KBr, cm<sup>-1</sup>): 3065 (arom-CH), 1759 (>C=O), 1731 (>C=O), 1603(C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.79 (s, 3H, -OCH<sub>3</sub>), 4.67 (d, 1H, *J*=2.4Hz, C<sub>3</sub>-H), 4.75 (d, 1H, *J*=2.4Hz, C<sub>4</sub>-H), 6.63 (s, 1H, -CH=C), 6.87-8.33 (m, 13H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 55.5, 60.2, 61.3, 105.3, 114.5, 118.4, 121.0, 125.9, 127.5, 128.2, 129.1, 129.9, 130.6, 133.8, 135.1, 136.0, 137.2, 152.0, 156.5, 161.6, 164.1; Mass(m/z) : 397 [M<sup>+</sup>].

*1-(3-nitrophenyl)-4-(1-oxo-1H-isochromen-3-yl)-3-phenylazetididin-2-one (3d)*: White solid; Yield: 46%; m.p. 165-166°C, Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>; C, 69.90; H, 3.91; N, 6.79. Found: C, 69.72; H, 3.75; N, 6.72; IR (KBr, cm<sup>-1</sup>): 3093 (arom-CH), 1759 (>C=O), 1733 (>C=O), 1604 (C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.83 (d, 1H, *J*=2.8Hz, C<sub>3</sub>-H), 4.89 (d, 1H, *J*=2.8Hz, C<sub>4</sub>-H), 6.70 (s, 1H, -CH=C), 7.39-8.30 (m, 13H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 60.2, 61.3, 105.3, 114.6, 118.6, 121.3, 125.9, 127.6, 128.3, 129.2, 130.1, 130.8, 133.8, 135.2, 136.1, 137.2, 138.2, 142.1, 152.1, 156.5, 161.7, 164.3; Mass (m/z) : 412 [M<sup>+</sup>].

*1-(4-fluorophenyl)-3-(4-methoxyphenyl)-4-(1-oxo-1H-isochromen-3-yl)azetididin-2-one (3e)*: White solid; Yield: 53%; m.p. 184-186°C, Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>FNO<sub>4</sub>; C, 72.28; H, 4.37; N, 3.37. Found: C, 72.17; H, 4.24; N, 3.30; IR (KBr, cm<sup>-1</sup>): 3074 (arom-CH), 1763 (>C=O), 1732 (>C=O), 1608 (C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.68 (s, 3H, -OCH<sub>3</sub>), 4.65 (d, 1H, *J*=2.4Hz, C<sub>3</sub>-H), 4.71 (d, 1H, *J*=2.4Hz, C<sub>4</sub>-H), 6.63 (s, 1H, -CH=C),

6.92-7.76 (m, 12H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 55.6, 60.2, 61.3, 105.4, 114.5, 118.6, 121.0, 125.9, 127.6, 128.3, 129.2, 129.9, 130.6, 133.9, 135.2, 136.1, 137.3, 153.0, 156.5, 161.6, 164.3; Mass (m/z) : 415 [M<sup>+</sup>].

*1-(4-chlorophenyl)-3-(4-methoxyphenyl)-4-(1-oxo-1H-isochromen-3-yl)azetididin-2-one (3f)*: White solid; Yield: 52%; m.p. 178-180°C, Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>ClNO<sub>4</sub>; C, 69.53; H, 4.20; N, 3.24. Found: C, 69.60; H, 4.08; N, 3.35; IR (KBr, cm<sup>-1</sup>): 3065 (arom-CH), 1766 (>C=O), 1732 (>C=O), 1607 (C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.81 (s, 3H, -OCH<sub>3</sub>), 4.65 (d, 1H, *J*=2.4Hz, C<sub>3</sub>-H), 4.71(d, 1H, *J*=2.4Hz, C<sub>4</sub>-H), 6.62 (s, 1H, -CH=C), 6.93-8.30 (m, 12H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 55.6, 60.2, 61.3, 105.4, 114.6, 118.7, 121.1, 125.9, 127.6, 128.3, 129.3, 129.9, 130.7, 133.9, 135.3, 136.1, 137.3, 153.0, 156.6, 161.2, 164.4; Mass (m/z) : 431 [M<sup>+</sup>].

*1,3-bis(4-methoxyphenyl)-4-(1-oxo-1H-isochromen-3-yl)azetididin-2-one (3g)*: White solid; Yield: 48%; m.p. 84-86°C, Anal. Calcd. for C<sub>26</sub>H<sub>21</sub>NO<sub>5</sub>; C, 73.06; H, 4.95; N, 3.28. Found: C, 72.90; H, 4.88; N, 3.17; IR (KBr, cm<sup>-1</sup>): 3068 (arom-CH), 1757(>C=O), 1725 (>C=O), 1610 (C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.80 (s, 3H, -OCH<sub>3</sub>), 3.83 (s, 3H, -OCH<sub>3</sub>), 4.61(d, 1H, *J*=4Hz, C<sub>3</sub>-H), 4.69 (d, 1H, *J*=4Hz, C<sub>4</sub>-H), 6.61 (s, 1H, -CH=C), 6.87-8.33 (m, 12H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 55.4, 55.6, 60.2, 61.3, 105.4, 114.4, 118.3, 121.2, 125.9, 127.7, 128.4, 129.4, 129.7, 131.0, 133.9, 135.4, 136.2, 137.3, 153.0, 156.6, 161.3, 164.6; Mass (m/z) : 427 [M<sup>+</sup>].

*3-(4-methoxyphenyl)-1-(3-nitrophenyl)-4-(1-oxo-1H-isochromen-3-yl)azetididin-2-one (3h)*: White solid; Yield: 55 %; m.p. 173-175 °C, Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>; C, 67.87; H, 4.10; N, 6.33. Found: C, 67.72; H, 3.97; N, 6.25; IR (KBr, cm<sup>-1</sup>): 3091 (arom-CH), 1763(>C=O), 1735 (>C=O), 1612 (C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.84 (s, 3H, -OCH<sub>3</sub>), 4.77 (d, 1H, *J*=2.8Hz, C<sub>3</sub>-H), 4.81 (d, 1H, *J*=2.8Hz, C<sub>4</sub>-H), 6.74 (s, 1H, -CH=C), 6.94-8.33 (m, 12H, Ar-H) ; <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 55.6, 60.2, 61.3, 105.6, 114.5, 118.4, 121.3, 126.1, 127.8, 128.2, 129.6, 129.7, 131.1, 133.9, 135.6, 136.2, 137.3, 138.1, 141.2, 153.1, 156.6, 161.3, 164.4; Mass (m/z) : 442 [M<sup>+</sup>].

*3-(4-chlorophenyl)-1-(4-fluorophenyl)-4-(1-oxo-1H-isochromen-3-yl)azetididin-2-one (3i)*: White solid; m.p. 150-152°C, Yield: 50%; Anal. Calcd. for C<sub>24</sub>H<sub>15</sub>ClFNO<sub>3</sub>; C, 68.66; H, 3.60; N, 3.34. Found: C, 68.76; H, 3.48; N, 3.25; IR (KBr, cm<sup>-1</sup>): 3075 (arom-CH), 1758 (>C=O), 1736 (>C=O), 1602 (C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.68 (d, 1H, *J*=2.4Hz, C<sub>3</sub>-H), 4.73 (d, 1H, *J*=2.4Hz, C<sub>4</sub>-H), 6.64 (s, 1H, -CH=C), 7.03-7.78 (m, 12H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 60.2, 61.3, 105.4, 114.6, 119.1, 121.3, 125.7, 127.6, 128.8, 129.6, 130.2, 131.1, 133.9, 135.7, 135.9, 138.3, 151.9, 156.8, 161.3, 164.3; Mass (m/z) : 419 [M<sup>+</sup>].

*1,3-bis(4-chlorophenyl)-4-(1-oxo-1H-isochromen-3-yl)azetididin-2-one (3j)*: White solid; Yield: 49%; m.p. 205-207°C, Anal. Calcd. for C<sub>24</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>3</sub>; C, 66.07; H, 3.47; N, 3.21. Found: C, 65.95; H, 3.35; N, 3.15; IR (KBr,

cm<sup>-1</sup>): 3081 (arom-CH), 1756 (>C=O), 1726 (>C=O), 1597(C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.69 (d, 1H, *J*=2.8Hz, C<sub>3</sub>-H), 4.73 (d, 1H, *J*=2.8Hz, C<sub>4</sub>-H), 6.64 (s, 1H, -CH=C), 7.31-7.78 (m, 12H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 60.2, 61.3, 105.4, 114.6, 119.2, 121.4, 125.8, 127.8, 128.9, 129.6, 130.3, 131.2, 133.9, 135.8, 135.9, 138.3, 151.8, 156.9, 161.4, 164.4; Mass (m/z) : 436 [M<sup>+</sup>].

*3-(4-chlorophenyl)-1-(4-methoxyphenyl)-4-(1-oxo-1H-isochromen-3-yl)azetidin-2-one (3k)*: White solid; Yield: 53%; m.p. 197-199°C, Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>ClNO<sub>4</sub>; C, 69.53; H, 4.20; N, 3.24. Found: C, 69.60; H, 4.04; N, 3.17; IR (KBr, cm<sup>-1</sup>): 3060 (arom-CH), 1751 (>C=O), 1725 (>C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.81 (s, 3H, -OCH<sub>3</sub>), 5.02 (d, 1H, *J*=6Hz, C<sub>3</sub>-H), 5.19 (d, 1H, *J*=6Hz, C<sub>4</sub>-H), 6.33 (s, 1H, -CH=C), 6.90-8.13 (m, 12H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 55.6, 60.2, 61.3, 105.6, 114.5, 118.5, 121.3, 126.1, 127.9, 128.2, 129.7, 129.9, 131.3, 133.9, 135.6, 136.3, 137.4, 138.3, 141.3, 151.3, 156.6, 161.4, 164.6; Mass (m/z) : 431[M<sup>+</sup>].

*3-(4-chlorophenyl)-1-(3-nitrophenyl)-4-(1-oxo-1H-isochromen-3-yl)azetidin-2-one (3l)*: White solid; Yield: 47%; m.p. 178-180°C; Anal. Calcd. for C<sub>24</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>5</sub>; C, 64.51; H, 3.38; N, 6.27. Found: C, 64.45; H, 3.25; N, 6.35; IR (KBr, cm<sup>-1</sup>): 3099 (arom-CH), 1755 (>C=O), 1730 (>C=O), 1603 (C-C aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.81 (d, 1H, *J*=2.4Hz, C<sub>3</sub>-H), 4.84 (d, 1H, *J*=2.4Hz, C<sub>4</sub>-H), 6.76 (s, 1H, -CH=C), 7.34-8.31 (m, 12H, Ar-H); <sup>13</sup>C-NMR (100.622 MHz, CDCl<sub>3</sub>, δ/ ppm): 60.2, 61.3, 105.3, 114.8, 118.7, 121.4, 126.1, 127.8, 128.5, 129.3, 130.2, 130.9, 134.1, 135.8, 136.3, 137.3, 138.6, 142.1, 152.2, 156.6, 161.8, 164.3; Mass (m/z) : 446 [M<sup>+</sup>].

## CONCLUSION

In conclusion, we have synthesized novel 4-(1-oxo-1H-isochromen-3-yl)-1-aryl-3-phenylazetidin-2-one derivatives starting from 3-formylisocoumarin under mild conditions.

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