3.1. Introduction

Promising adenosine $A_{2A}$ receptor affinity has been illustrated for the 2-aminopyrimidine scaffold (Figure 3.1), as discussed in Chapter 1. To further explore the structure activity relationships of this scaffold, related to adenosine receptor affinity, the following design strategies were employed in this study:

a) To further investigate substitution of the phenyl ring (B), analogues substituted in the 4', instead of the 3' position (as previously synthesised by Robinson, 2013) were synthesised,

b) the aromatic substituent on position 4 ($R^2$) was varied and

c) a thiazole moiety was introduced in the phenylamide side chain ($R^3$).

Figure 3.1: General structure of synthesised 2-aminopyrimidines.

3.2. Results and Discussion

The synthetic strategy followed for the synthesis of the 2-aminopyrimidines was based on a method that was successfully used in our laboratories in a previous study (Robinson, 2013). Compounds were thus synthesised over three steps starting from the commercially available 3- or 4-formyl benzoic acids and aromatic ketones as illustrated in Scheme 3.1.
Firstly, a Claisen-Schmidt condensation of equimolar quantities of the ketones and aldehydes in the presence of sodium hydroxide (Raeppl et al., 2004), yielded the intermediate 3- or 4-(3-oxopropenyl)benzoic acid derivatives (37a - 37f, 37h and 37i). The amides (38a - 38f, 38h - 38n) were subsequently formed using carbonyldiimidazole to effect coupling (Miagnan et al., 1989). Coupling reagents that were investigated included 1,1'-carbonyldiimidazole (CDI), thionyl chloride, oxalyl chloride and N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC). CDI was selected as its use resulted in the highest yields, while also being affordable.

For this reaction, a coupling reagent, such as CDI, is required in order to replace the carboxylic acid hydroxyl group with a better leaving group, thus activating it (Scheme 3.2) (Clayden et al., 2012). When CDI is used, the hydroxyl group is replaced by an imidazole, which is easily displaced by the amine nucleophile (Montalbetti and Falque, 2005).
Scheme 3.2: Mechanism of amide formation using CDI as coupling reagent (adapted from Montalbetti and Falque, 2005).

Generally, 2-aminopyrimidines are prepared by the reaction of chalcones with guanidine hydrochloride or nitrate, under basic conditions. Bases and solvents that have been used include sodium or potassium hydroxide, in ethanol or water (Yejella et al., 2011, Kanagarajan et al., 2010, Thanh and Mai, 2009, Chang et al., 2004), sodium methoxide in DMF (dimethylformamide) (Agarwal et al., 2005) and sodium hydride in DMF (Sharma et al., 2009). Since several attempts at using sodium hydroxide in ethanol (Thanh and Mai, 2009) were unsuccessful (it resulted in a complicated mixture of products from which it was not possible to isolate the desired 2-aminopyrimidines), the 2-aminopyrimidines of this study were formed by cyclisation of amide intermediates (38a – 38n) with guanidine hydrochloride in the presence of sodium hydride (Sharma et al., 2009).

A reaction mechanism (Scheme 3.3) proposed by Singh and co-workers (2011) for the above reaction, involved the following: Firstly guanidine hydrochloride (A) is activated by sodium hydride and the resulting free guanidine undergoes conjugate Michael addition on an alkene bond of the enone (B) to form intermediate (C). The amine and ketone groups then react to afford cyclic intermediate (D) which undergoes dehydration, resulting in dihydropyrimidine (E). Since the most acidic tertiary proton is abstracted easily in the presence of NaH in DMF, spontaneous aerial oxidation of (F), a tautomer of (E) occurs, finally yielding the desired 2-aminopyrimidine (G).
As indicated previously, the first objective of this study was to investigate the effect of an amide substituent in position 4' of the phenyl ring (39a). A piperidine substituent was selected as starting point, since it was associated with optimal adenosine A<sub>2A</sub> receptor affinity in the 3' series, as demonstrated by 15 (synthesised in a previous study; Robinson, 2013).

**Scheme 3.3:** Mechanism of aminopyrimidine formation (Singh et al., 2011).
Preliminary screening however, revealed that 39a, (and analogues 40 and 41, synthesised in a related project) did not exhibit affinity for either of the receptor subtypes (see Chapter 4), and further synthesis of this series was abandoned.

Synthesis of the derivatives aimed at achieving the second objective, namely incorporation of different heterocyclic moieties on position 4 of the pyrimidine ring thus commenced. A piperidine substituent (R1) was again selected due to the optimal affinity previously identified for this substituent (Robinson, 2013). Compounds 39b – 39f were synthesised successfully, although in low yields, using the synthetic route illustrated in Scheme 3.1.
For these derivatives, the temperature had to be monitored carefully during the final reaction step, due to the heat sensitivity of the amide intermediates. Heating above 80 °C, in most cases, resulted in decomposition and reaction failure, while no reaction occurred at temperatures below 60 °C. Synthesis of derivatives substituted with the following heterocyclic groups: 2-methylpyrazine, 2-(5-chlorothiophene), 5-phenylfuran, 2-(5-chlorofuran), 2-(5-bromofuran), 2-(5-nitrofuran) and 2-(1-methylpyrrole) were unsuccessful (Figure 3.2).

Figure 3.2: Examples of 2-aminopyrimidines for which synthesis was unsuccessful.

In order to investigate whether these reactions were feasible if the functionalities of the aldehydes and ketones were interchanged (in other words starting with 3-acetylbenzoic acid instead of 3-formylbenzoic acid), the synthesis of a number of derivatives was attempted using the alternative route illustrated in Scheme 3.4. Although the reagents employed in this alternative route were more expensive, the variety of different heteroaryl groups that could be incorporated (due to availability of additional aldehydes), was increased. The strategy however, proved to be unsuccessful as only one derivative (39g) was obtained using this route.
Scheme 3.4: Alternative synthesis of 2-aminopyrimidines. Reagents and conditions: a) NaOH, MeOH, rt, 8 h. b) CDI, CH₂Cl₂, NHR, rt, 5 h. c) Guanidine hydrochloride, NaH, DMF, 80 °C, 24 h. Ar= heteroaromatic substituent.

Due to the ease of synthesis and good in vitro affinity (obtained during preliminary screening) demonstrated by the 5-methylthiophene derivative 39f, further methylthiophene derivatives (39h – 39j) were synthesised. The availability of these derivatives would provide the opportunity to assess the effect of different amide substituents on affinity, selectivity and cell viability.

39f $R^1 = 1$-piperidinyl; $R^2 = 2$-(5-methylthienyl) [Yield = 15%]

39h $R^1 = 4$-ethyl-1-piperazinyl; $R^2 = 2$-(5-methylthienyl) [Yield = 16%]

39i $R^1 =$ morpholinyl; $R^2 = 2$-(5-methylthienyl) [Yield = 24%]

39j $R^1 =$ pyrrolidinyl; $R^2 = 2$-(5-methylthienyl) [Yield = 21%]
Since the synthesis of the 5-bromofuran derivative, 4-(5-bromofuran-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (Figure 3.2), failed using both synthetic routes (Scheme 3.1 and 3.4), the synthesis of a piperazine substituted analogue, 4-(5-bromofuran-2-yl)-6-[3-(4-ethylpiperazine-1-carbonyl)phenyl]pyrimidin-2-amine was attempted. This was done to investigate whether changing the amide substituent would have any effect on reaction success. Interestingly, for this particular derivative, debromination of the furan ring occurred during aminopyrimidine formation (as confirmed by NMR, IR and MS), resulting in the formation of 39k.

\[
\begin{align*}
39k & \quad R^1 = 4\text{-ethyl-1-piperazinyl;} \quad R^2 = 2\text{-furanyl} \quad [\text{Yield} = 10\%]
\end{align*}
\]

A final attempt at the synthesis of 4-(5-bromofuran-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine was done by reacting compound 39d with N-bromosuccinimide (Ismail et al., 2004), but this resulted in complete degradation of the 2-aminopyrimidine (Scheme 3.5).

\[
\begin{align*}
39d \quad \text{(a)} & \quad \Rightarrow \quad 39d \quad \text{(b)}
\end{align*}
\]

Scheme 3.5: Alternative synthesis of 4-(5-bromofuran-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine. Reagents and conditions a) NBS, DMF, rt.

Having synthesised derivatives that incorporated six different heterocyclic groups in position 4, we proceeded with the synthesis of compounds aimed at achieving objective three, which was the incorporation of a thiazole moiety. This series (39l – 39m) also included a 4′ substituted analogue (39l).
The synthesis of derivatives substituted in the 3' position, was challenging (six of the eight compounds attempted, failed), and in most cases, even though the preliminary acid precursors were obtained, yields of the amides were either poor or coupling failed. In several instances, aminopyrimidine formation (the final step) was also unsuccessful (Figure 3.3). It is suspected that the poor solubility of the amide intermediates (in most solvents) contributed to reaction failure.

**Figure 3.3:** Examples of thiazole derivatives for which synthesis failed.

The use of different coupling reagents was reinvestigated, in an attempt to improve the yields of the amide intermediates. Yields obtained in the synthesis of \( N-(4\)-methyl-1,3-thiazol-2-yl\)-3-[(1\(E\))-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzamide using oxalyl chloride (yield = 3%), thionyl chloride (yield = 11%), EDAC (yield = 28%) and CDI (yield =
40%) indicated that CDI was still the most effective coupling agent. Upscaling the first step (e.g. 2.5 g of formylbenzoic acid for 37i, versus 1 g for 37f) to increase the amount of amide available for the last step resulted in the successful synthesis of only two derivatives (39m and 39n).

A total of fourteen structurally diverse 2-aminopyrimidines were thus successfully synthesised. All compounds were characterised primarily by NMR spectroscopy while infrared spectroscopy and mass spectrometry data provided additional structural confirmation. Assignment of NMR signals were based on interpretation of both 1D (1H, 13C, DEPT) and 2D (HSQC, HMBC, COSY) NMR spectra. Mass data obtained for all compounds correlated well with calculated values. As examples, the characterisation of compounds 37f, 38f, 38k, 39f and 39k will be discussed in further detail.

![37f](image)

In the 1H NMR spectrum of benzoic acid derivative 37f (Appendix, p. 134), 10 signals were present, accounting for 12 protons, as was expected. These included the protons of the hydroxyl group, the methyl group, the double bond and aromatic protons of the phenyl and thiophene rings. Proton signals were assigned using chemical shifts, integration, multiplicities, coupling constants as well as correlations observed in COSY, HSQC and HMBC spectra (as detailed in Table 3.1). The signal at 13.18 ppm was thus assigned as the hydroxyl group while the doublets at 7.73 and 7.91 ppm were assigned as H-1 and H-2 respectively, with the coupling constant of 15.6 Hz characteristic of a trans double bond (Pavia et al., 2009, Silverstein et al., 2005). The four proton signals of the 1,3-disubstituted aromatic ring were further assigned as δH 8.37 (H-2′), 8.12 (H-6′), 7.99 (H-4′) and 7.58 (H-5′). The characteristic triplet signal of H-5′ is due to ortho coupling with both H-4′ and H-6′ and has a typical coupling constant of 7.7 Hz (Silverstein et al., 2005). The aromatic protons of the methylthiophene ring occurred at 7.05-7.00 ppm and 8.23 ppm for H-4″ and H-3″, respectively. As expected, the signal of the more deshielded H-3″ is found downfield from H-4″. The signal of the methyl group is further present at 2.54 ppm.

The 13C NMR spectrum confirmed the presence of 15 carbons. Analysis of the 13C NMR spectrum in conjunction with the DEPT 135 and DEPT 90 spectra indicated six quaternary, one methyl and eight CH carbons. Assignment of carbon signals was further done based on
chemical shifts and observed 2D correlations (Table 3.1). The six quaternary carbons (181.0, 167.0, 150.7, 143.3, 135.1, 131.6 ppm), were assigned as C-3 (the ketone), the carboxylic acid carbon, C-5", C-2", C-1' and C-3' respectively. The HMBC correlation between C-1' (135.1 ppm) and the double bond protons at H-1 (7.73 ppm) and H-2 (7.91 ppm) for example, were used to determine the assignments of C-1' and C-3'. The signals at 122.8 and 141.6 ppm were assigned to the double bond, while the carbon signals of the aromatic ring were present between 129.3 and 135.1 ppm. The signals at 127.8 and 134.8 ppm were assigned to C-4" and C-3", respectively while the methyl signal occurred at 15.8 ppm.

The presence of an OH group in 37f is further confirmed by the characteristic broad peak at 3064 - 2562 cm\(^{-1}\) in the infrared spectrum (Appendix, p. 172). The peak at 1682 cm\(^{-1}\), is further indicative of the C=O group. These characteristic peaks were present in the infrared spectra of all the acid intermediates. The mass observed at 273.0565 amu ([M+H]) in the mass spectrum of 37f, further corresponded well with the value of 273.0580 calculated for C\(_{15}\)H\(_{13}\)O\(_3\)S.
Table 3.1: NMR spectroscopic data and HMBC correlations of 3-[(1E)-3-(5-methylthiophen-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37f):

![Chemical Structure]

<table>
<thead>
<tr>
<th>Atom no.</th>
<th>(^1)H-NMR shift in ppm (multiplicity, J in Hz)</th>
<th>(^{13})C-NMR shift in ppm (Type)</th>
<th>HMBC ((\delta_H) to (\delta_C))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.73 (d, 15.6)</td>
<td>141.6 (CH)</td>
<td>2′ and/or 5′, 1′, 6′, 3</td>
</tr>
<tr>
<td>2</td>
<td>7.91 (br d, 15.6)</td>
<td>122.8 (CH)</td>
<td>1′ and/or 3′, 1, 3</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>181.0 (C)</td>
<td></td>
</tr>
<tr>
<td>1′</td>
<td></td>
<td>135.1 (C)</td>
<td></td>
</tr>
<tr>
<td>2′</td>
<td>8.37 (br s)</td>
<td>129.5 (CH)</td>
<td>1′,1, acid C=O, 3′ and/or 4′ and/or 6′</td>
</tr>
<tr>
<td>3′</td>
<td></td>
<td>131.6 (CH)</td>
<td></td>
</tr>
<tr>
<td>4′</td>
<td>7.99 (br d, 7.7)</td>
<td>131.0 (CH)</td>
<td>2′ and/or 5′, 6′, acid C=O</td>
</tr>
<tr>
<td>5′</td>
<td>7.58 (t, 7.7)</td>
<td>129.3 (CH)</td>
<td>3′ and/or 4′ and/or 6′, 1′, 1</td>
</tr>
<tr>
<td>6′</td>
<td>8.12 (br d, 7.7)</td>
<td>132.9 (CH)</td>
<td>3′ and/or 4′, 1</td>
</tr>
<tr>
<td>1″</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2″</td>
<td></td>
<td>143.3 (C)</td>
<td></td>
</tr>
<tr>
<td>3″</td>
<td>8.23 (t, 3.0)</td>
<td>134.8 (CH)</td>
<td>4″, 2″, 5″, 3</td>
</tr>
<tr>
<td>4″</td>
<td>7.01 (br s)</td>
<td>127.8 (CH)</td>
<td>3″, 2″, 5″</td>
</tr>
<tr>
<td>5″</td>
<td></td>
<td>150.7 (C)</td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>2.54 (s)</td>
<td>15.8 (CH₃)</td>
<td>4″, 3″, 2″, 5″</td>
</tr>
<tr>
<td>Acid C=O</td>
<td></td>
<td>167.0 (C)</td>
<td></td>
</tr>
<tr>
<td>OH</td>
<td>13.18 (br s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The NMR data of the other acid intermediates (37b – 37i) were similar, except for 37a, which is a 4′ substituted derivative. For compound 37a, the two doublet signals at 7.97 and 7.94
ppm, integrating for 2 protons each, confirmed the presence of the para-disubstituted benzene ring. These protons further showed HSQC correlations to the carbon signals at 129.8 and 128.8 ppm.

Assignments of the NMR spectra of the other acid derivatives were done using the same approach as discussed for 37f. Differences observed in the NMR spectra were largely due to the variations in the 4-aryl/heteroaryl substituents. The observed shifts of the five membered ring systems are given in Table 3.2, in comparison with shifts and assignments of similar systems, as found in literature. Note that deuterated dimethylsulfoxide (DMSO-d$_6$) was used as solvent for observed spectra and that literature NMR spectra were obtained in the presence of either deuterated chloroform (CDCl$_3$) or DMSO-d$_6$.

**Table 3.2:** Comparison of observed and literature chemical shifts of five membered ring systems and the 2-benzofuran ring:

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Observed δ$_H$ shift in ppm (DMSO-d$_6$)</th>
<th>Literature values δ$_H$*</th>
<th>Observed δ$_C$ (ppm) (DMSO-d$_6$)</th>
<th>Literature values δ$_C$*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-methylfuranyl (37i)</td>
<td>3” 7.83  4” 6.44  CH$_3$ 2.41</td>
<td>3” 7.37 – 7.73  4” 6.38 – 6.43  CH$_3$ 2.31-2.40</td>
<td>2” 151.8  3” 121.9  4” 109.6  5” 158.8  CH$_3$ 13.8</td>
<td>2” 151.8  3” 121.9  4” 109.6  5” 158.8  CH$_3$ 13.8</td>
</tr>
<tr>
<td>2-furanyl (37e)</td>
<td>3” 7.90  4” 6.80  5” 8.14-8.06</td>
<td>3” 7.35 – 7.90  4” 6.60 – 6.83  5” 7.66 – 8.11</td>
<td>2” 152.8  3” 120.0  4” 112.8  5” 148.6</td>
<td>2” 152.7–153.9  3” 116.4–122.9  4” 112.7–113.0  5” 146.6–152.5</td>
</tr>
<tr>
<td>2-(5-methylthiophenyl) (37f)</td>
<td>3” 8.23  4” 7.01  CH$_3$ 2.54</td>
<td>3” 7.60  4” 6.80  CH$_3$ 2.53</td>
<td>2” 143.3  3” 134.8  4” 127.8  5” 150.7  CH$_3$ 15.8</td>
<td>2” 149.5  3” 132.8  4” 126.8  5” 142.1  CH$_3$</td>
</tr>
<tr>
<td>2-(5-bromofuranyl) (37h)</td>
<td>3” 8.02-7.93  4” 6.95</td>
<td>3” 7.38  4” 6.93</td>
<td>2” 154.6  3” 122.2  4” 115.0  5” 129.8</td>
<td>2” 154.4  3” 118.9  4” 114.3  5” 128.2  CDCl$_3$</td>
</tr>
<tr>
<td>Substituent</td>
<td>Observed δ&lt;sub&gt;H&lt;/sub&gt; shift in ppm (DMSO-&lt;em&gt;d&lt;/em&gt;&lt;sub&gt;6&lt;/sub&gt;)</td>
<td>Literature values δ&lt;sub&gt;H&lt;/sub&gt;*</td>
<td>Observed δ&lt;sub&gt;c&lt;/sub&gt; (ppm) (DMSO-&lt;em&gt;d&lt;/em&gt;&lt;sub&gt;6&lt;/sub&gt;)</td>
<td>Literature values δ&lt;sub&gt;c&lt;/sub&gt;*</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>2-benzofuranyl (37g)</td>
<td>3'' 7.55-7.53 5'' &amp; 8'' 7.78-7.64 6'' &amp; 7'' 7.49-7.64</td>
<td>3'' 7.36 5'', 6'', 7'' &amp; 8'' 7.29, 7.36, 7.42, 7.62 (signals not assigned)</td>
<td>2'' 152.7 3'' 113.6 4'' 128.2 9'' 155.1</td>
<td>5'', 6'', 7'', 8'' 129.5-111.5</td>
</tr>
</tbody>
</table>

*Obtained from a combination of the following sources: \(^a\)Lam et al., 2012; \(^b\)Robinson, 2013; \(^c\)Sharma et al., 2013; \(^d\)Altenhöner et al., 2010; \(^e\)Dvornikova et al., 2003; \(^f\)Zheng et al., 2011; \(^g\)Ismail et al., 2004; \(^h\)Obushak, et al., 2008.

Carbon-fluorine coupling was further observed in the \(^{13}\)C NMR spectrum of the 4-fluorophenyl derivative (37e). This coupling occurred for the carbons present at δ<sub>c</sub> 165.1 (d, \(J_{C-F} = 250.9\) Hz, C-4''), 134.1 (d, \(J_{C-F} = 2.6\) Hz, C-1''), 131.7 (2C, d, \(J_{C-F} = 9.8\) Hz, C-2'', C-6'') and 115.8 (2C, d, \(J_{C-F} = 20.3\) Hz, C-3'', C-5'') and correlated well with coupling constants of \(^1J = 245\) Hz, \(^2J = 21\) Hz, \(^3J = 7.7\) and \(^4J = 3.3\) Hz as described by Silverstein and co-workers for compounds containing the 4-fluorophenyl group (2005).

The characterisation of 38f will henceforth be discussed as an example of the amide intermediates (38a – 38n).
In the $^1$H NMR spectrum of amide 38f (Appendix, p. 136) the disappearance of the OH signal at 13.18 ppm indicated *inter alia* that the carboxylic acid was no longer present. Signals observed at 3.72 (br s, 2H), 3.35 (br s, 2H) and 1.78 -1.68 ppm (m, 6H), showing HSQC correlations with carbons at 48.8, 43.2, 26.5, 25.5 and 24.5 ppm, confirmed the presence of the piperidine moiety. The change in environment caused a downfield shift of C-3’ from 131.6 ppm to 137.2 ppm, while the shift of C-1’ remained unchanged (135.2 ppm in comparison with 135.1 ppm, as in 38f).

Furthermore, 19 signals were observed in the $^1$H NMR spectrum, which corresponded to 21 protons. Protons were assigned as previously discussed and 2D correlations are provided in Table 3.3. The protons of the double bond were present at 7.45 – 7.36 and 7.68 ppm, while the aromatic protons of the phenyl and methylthiophene rings were observed between 7.70 – 7.36 and 7.70 – 6.85 ppm, respectively. The signal of the methyl group was observed at 2.56 ppm, correlating in the HSQC with the carbon at 16.2 ppm.

The $^{13}$C NMR spectrum confirmed the presence of 20 carbons while analysis of the DEPT 90 spectrum (in conjunction with the $^{13}$C NMR spectrum) showed the presence of six quaternary, one CH$_3$, five CH$_2$ and eight CH carbons, as expected. The six quaternary carbons (181.3, 169.5, 150.4, 143.2, 137.2, 135.2 ppm), were assigned as C-1 (the ketone), the amide carbonyl, C-2” and C-5” (in no particular order), C-3’ and C-1’, respectively. The signals of the double bond occur at 122.4 ppm and 142.3 ppm for C-2 and C-3 respectively, similar to that observed for these carbons in compound 37f. The carbon signals for the phenyl ring are found between 137.2 ppm and 122.4 ppm, while the CH methylthiophene carbon signals (C-3” and C-4”) are present at 132.6 ppm and 127.0 ppm respectively.

The mass spectrum showed the expected increase in mass with the $[M]^+$ ion of 339.1267 amu, correlating well with the calculated value of 339.1288 for C$_{20}$H$_{21}$NO$_2$S. On the IR spectrum of this compound, the disappearance of the OH and carboxylic acid C=O peaks is clearly visible, as well as the appearance of a new set of peaks, due to the amino group of the amide, between 3044 – 2853 cm$^{-1}$, which corresponds with literature (Patel et al., 2011), further indicating that the synthesis of the amide was successful.
Table 3.3: NMR spectroscopic data and HMBC correlation of (2E)-1-(5-methylthiophen-2-yl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38f):

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Atom no.</th>
<th>$^1$H-NMR (shift, $J$ in Hz)</th>
<th>$^{13}$C-NMR (Type)</th>
<th>HMBC ($\delta_H$ to $\delta_C$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>181.3 (C)</td>
<td></td>
</tr>
<tr>
<td>2 and 5' and 4'</td>
<td>7.46-7.36</td>
<td>122.4 (CH)</td>
<td>1, amide C=O, 3, 3', 1', 4', 5', 6', 2'</td>
</tr>
<tr>
<td>3</td>
<td>7.78 (d, 15.6)</td>
<td>142.3 (CH)</td>
<td>1, 1', 5', 6', 2', 2'</td>
</tr>
<tr>
<td>1'</td>
<td></td>
<td>137.2</td>
<td></td>
</tr>
<tr>
<td>2' and 3''</td>
<td>7.70-7.65 (m)</td>
<td>126.4</td>
<td>1, amide C=O, 5'', 2'', 3, 4', 5', 6', 4''</td>
</tr>
<tr>
<td>3''</td>
<td></td>
<td>135.2</td>
<td></td>
</tr>
<tr>
<td>6'</td>
<td>7.63 (dt, 7.7, 1.5 Hz)</td>
<td>129.5</td>
<td>3, 4', 5', 2'</td>
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<tr>
<td>1''</td>
<td></td>
<td>150.4</td>
<td></td>
</tr>
<tr>
<td>2''</td>
<td></td>
<td>150.4</td>
<td></td>
</tr>
<tr>
<td>4''</td>
<td>6.85 (dd, 3.9, 1.2)</td>
<td>127.0</td>
<td>5'', 2'', 3'', CH$_3$</td>
</tr>
<tr>
<td>5''</td>
<td></td>
<td>143.2</td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>3.56 (d)</td>
<td>16.2</td>
<td>5'', 2'', 3'', 4''</td>
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<tr>
<td>Amide C=O</td>
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<td>169.5</td>
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</tr>
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R

<table>
<thead>
<tr>
<th>$^1$H-NMR (shift, $J$ in Hz)</th>
<th>$^{13}$C-NMR (Type)</th>
<th>HMBC ($\delta_H$ to $\delta_C$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.72 (s) &amp; 3.35 (s)</td>
<td>43.2 &amp; 48.8</td>
<td></td>
</tr>
<tr>
<td>1.78 – 1.68 (m)</td>
<td>26.5, 25.5, 24.5</td>
<td>CONCH$_2$ &amp; piperidine CH$_2$</td>
</tr>
</tbody>
</table>

Differences observed in the NMR spectra of the amide intermediates were again largely due to the variations in the aryl/heteroaryl substituents (which were similar to the acids, see table...
and also due to variations in the amine substituents. $^1$H and $^{13}$C NMR spectroscopic shifts of the different amine substituents, compared to literature values obtained for similar systems, is given in Table 3.4.

**Table 3.4:** Comparison of observed and literature shifts of amine substituents:

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Observed $\delta$$_H$ (CDCl$_3$)</th>
<th>Literature values $\delta$$_H$</th>
<th>Observed $\delta$$_C$ (CDCl$_3$)</th>
<th>Literature values $\delta$$_C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R - \text{N} - \text{N}$</td>
<td>$\text{CH}_2^<em>$ 3.72 and 3.35 $\text{CH}_2^</em>$ region of 2.74 $\text{CH}_2^*$ 48.8 and 43.2</td>
<td>$\text{CH}_2^<em>$ region of 1.50 $\text{CH}_2^</em>$ 26.5, 25.5, 24.5</td>
<td>$\text{CH}_2^<em>$ 47.9 $\text{CH}_2^</em>$ 25.9, 27.8, 27.8</td>
<td>$\text{CH}_2^<em>$ 48.9 $\text{CH}_2^</em>$ 52.4 $\text{NCH}_2\text{CH}_3$ 52.4 $\text{CH}_3$ 11.9 $\text{CDCl}_3$.</td>
</tr>
<tr>
<td>(38f)</td>
<td>$\text{CH}_2^*$ 1.78 – 1.68</td>
<td>$\text{CH}_2^*$ region of 1.50</td>
<td>$\text{CH}_2^*$ 1.04 – 1.07</td>
<td>$\text{CH}_2^*$ 1.09 $\text{CDCl}_3$.</td>
</tr>
<tr>
<td>$R - \text{N} - \text{N} - \text{N}$</td>
<td>$\text{CH}_2^<em>$ 3.82 and 3.45 $\text{CH}_2^</em>$ 2.60 – 2.32 $\text{NCH}_2\text{CH}_3$ 2.80 – 2.32</td>
<td>$\text{CH}_2^<em>$ 3.10 – 3.13 $\text{CH}_2^</em>$ 2.51 – 2.54 $\text{NCH}_2\text{CH}_3$ 2.37 – 2.43</td>
<td>$\text{CH}_2^<em>$ 4.77 and 42.3 $\text{CH}_2^</em>$ 53.1 and 52.3 $\text{NCH}_2\text{CH}_3$ 52.2</td>
<td>$\text{CH}_2^<em>$ 48.9 $\text{CH}_2^</em>$ 52.4 $\text{NCH}_2\text{CH}_3$ 52.4 $\text{CH}_3$ 11.9 $\text{CDCl}_3$.</td>
</tr>
<tr>
<td>(38h)</td>
<td>$N - \text{O}$</td>
<td>$\text{CH}_2^<em>$ 3.91 – 3.35 $\text{CH}_2^</em>$ 4.69, 3.82, 2.67, 3.39</td>
<td>$\text{CH}_2^<em>$ 48.2, 42.6 $\text{CH}_2^</em>$ 66.8</td>
<td>$\text{CH}_2^<em>$ 45.0-49.7 $\text{CH}_2^</em>$ 63.1 -68.3 $\text{CDCl}_3$.</td>
</tr>
<tr>
<td>(38i)</td>
<td>$\text{CH}_2^<em>$ &amp; $\text{CH}_2^</em>$ 1.98 and 1.89</td>
<td>$\text{CH}_2^<em>$ region of 2.75 $\text{CH}_2^</em>$ region of 1.59</td>
<td>$\text{CH}_2^<em>$ 49.6 and 46.3 $\text{CH}_2^</em>$ 26.4 and 24.4</td>
<td>$\text{CH}_2^<em>$ 56.7 $\text{CH}_2^</em>$ 24.4 $\text{CDCl}_3$.</td>
</tr>
</tbody>
</table>
| (38j) | Obtained from a combination of the following sources: $^a$Silverstein et al. (2005); $^b$Riganas et al. (2012); $^c$Katritzky et al. (2005). For the thiazole derivatives, (38l – 38n) the protons of the thiazole moiety were present in the aromatic region between 8.18 and 7.15 ppm, corresponding with reported data (Sakarya et al., 2012; Karim et al., 2013).
The characterisation of the 2-aminopyrimidines is exemplified by the discussion of compound 39f. When the $^1$H NMR spectrum of compound 39f (Appendix, p. 147) is compared to that of 38f, it is clear that the protons of the double bond are no longer present, while two singlets at 7.28 and 5.23 ppm are indicative of the presence of H-5 (the pyrimidine ring proton) and the NH$_2$ group, respectively. In the $^{13}$C NMR spectrum, the most downfield signal observed for 38f (181.3 ppm), correlating to the ketone group, is no longer present in 39f, while the appearance of the shifts at 164.8, 163.6 and 160.9 ppm accounts for the quaternary carbons (6, 2 and 4) of the pyrimidine ring.

Furthermore, in the $^1$H NMR spectrum, 10 signals, corresponding to 22 protons were present. The remaining signals were assigned as follows: 3.74 - 4.12 ppm as the piperidine protons, 7.58 - 6.84 ppm as the methylthiophene ring protons, 8.09 - 7.43 ppm as the phenyl protons and 2.53 ppm as the CH$_3$ protons. Observed 2D correlations and assignments are given in detail in Table 3.5.

Inspection of the $^{13}$C NMR spectrum in conjunction with the DEPT 135 spectrum further indicated the presence of one CH$_3$, five CH$_2$, seven CH and eight quaternary carbons. The quaternary carbons ($\delta_C$ 169.8, 164.8, 163.3, 160.9, 144.56, 140.2, 138.0, 136.9 ppm) were identified as the amide carbonyl, C-6, C-2, C-4, C-5", C-2", C-1' and C-3' respectively. Similar to the $^{13}$C NMR spectrum of the amide precursor (39f), the carbon signals of the methylthiophene ring, namely C-3" and C-4" (127.4, 126.6 ppm), the phenyl ring (138.0, 136.9, 128.7, 128.5, 127.9, 125.6 ppm) as well as the piperidine moiety (48.8, 43.8, 26.5, 25.6, 24.5 ppm) were still present.
Table 3.5: NMR data and HMBC correlations of 4-(5-methylthiophen-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (39f):

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Atom no.</th>
<th>$^1$H-NMR (shift, J in Hz)</th>
<th>$^{13}$C-NMR (Type)</th>
<th>HMBC (δ_H to δ_C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7.28 (s)</td>
<td>102.0</td>
<td>6, 4, 2&quot;, 1'</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>164.8</td>
<td></td>
</tr>
<tr>
<td>1' or 3'</td>
<td></td>
<td></td>
<td>138.0</td>
</tr>
<tr>
<td>2' and 6'</td>
<td>8.09-8.02 (m)</td>
<td>125.6</td>
<td>C=O, 6, 4', 5', 6', 2'</td>
</tr>
<tr>
<td>1' or 3'</td>
<td></td>
<td></td>
<td>136.9</td>
</tr>
<tr>
<td>4' and 5'</td>
<td>7.53-7.43 (m)</td>
<td>128.8 or 128.5</td>
<td>C=O, 1', 3', 4', 5', 6', 2'</td>
</tr>
<tr>
<td>1&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2&quot;</td>
<td></td>
<td>140.2</td>
<td></td>
</tr>
<tr>
<td>3&quot;</td>
<td>7.58 (d, 3.7)</td>
<td>127.4</td>
<td>4, 5&quot;, 2&quot;, 4&quot;</td>
</tr>
<tr>
<td>4&quot;</td>
<td>6.80 (dd, 3.6)</td>
<td>126.6</td>
<td>5&quot;, 2&quot;, 3&quot;, CH₃</td>
</tr>
<tr>
<td>5&quot;</td>
<td></td>
<td>144.6</td>
<td></td>
</tr>
<tr>
<td>NH₂</td>
<td>5.23 (s)</td>
<td></td>
<td>4, 6</td>
</tr>
<tr>
<td>C=O</td>
<td></td>
<td>169.8</td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>2.53 (br d)</td>
<td>15.8</td>
<td>5&quot;, 4&quot;</td>
</tr>
<tr>
<td>R</td>
<td>3.74 (s) &amp; 3.36 (s)</td>
<td>43.8 &amp; 48.8</td>
<td>-</td>
</tr>
<tr>
<td>R</td>
<td>1.72-1.42 (m)</td>
<td>26.5, 25.6, 24.5</td>
<td>CONCH₂ &amp; piperidine CH₂</td>
</tr>
</tbody>
</table>
The purity of the 2-aminopyrimidines was assessed by HPLC and (4-ethylpiperazine-1-carbonyl)phenylpyrimidin-2-amine as expected (Figure 3.4). The IR spectrum of \(1664 \text{ cm}^{-1}\) when compared to that of \(38f\) indicated the presence of the \(\text{NH}_2\) group, while the amide peak as observed in \(38f\) is still present at 3167 – 2851 cm\(^{-1}\). The ketone peak present at 1664 cm\(^{-1}\) in the spectrum of \(38f\) disappeared, with only the amide carbonyl peak remaining at 1624 cm\(^{-1}\) in the spectrum of \(39f\). The mass spectrum of \(39f\) exhibited a molecular ion at 378.1489 amu, which correlated well with the calculated value of 378.1509 for \(\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_5\). The purity of the 2-aminopyrimidines was assessed by HPLC and \(39f\) was found to be 91% pure.

The NMR and IR spectra of \(39a\) – \(39n\) were very similar and assignments of NMR and IR spectra were done in the same manner, while mass data correlated well with calculated values.

Interestingly, when the characterisation of compound \(39k\) was done, analysis of the NMR and mass data in particular revealed that \(39k\) formed, instead of 4-(5-bromofuran-2-yl)-6-[3-(4-ethylpiperazine-1-carbonyl)phenyl]pyrimidin-2-amine as expected (Figure 3.4).

![Figure 3.4: Synthesis of 2-aminopyrimidine 39k.](image)

The analytical data of \(38k\) was revisited, in order to ascertain that the bromine substituent was indeed present in the amide precursor. In the \(^1\text{H}\) NMR spectrum of \(38k\) (Appendix, p. 139) it was clear that there were only two furan ring protons, present at 7.27 and 6.55 ppm (H-3" and H-4"). The shift of C-5" (128.4 ppm) in the \(^{13}\text{C}\) NMR spectrum, was further indicative of bromine substitution in this position, when compared to a shift of 144.6 ppm observed for C-5" in the \(^{13}\text{C}\) NMR spectrum of \(39k\) (Appendix, p. 155). The mass found at 416.0718 amu further correlated with the calculated value of 416.0730 for \(\text{C}_{20}\text{H}_{21}\text{BrN}_2\text{O}_3\). In the IR spectrum the peak of the C-Br group was present at 769 cm\(^{-1}\), in the area where signalling of bromine substituents generally occur (Silverstein et al., 2005).
The first inconsistency observed during the characterisation of \textbf{39k} was the appearance of an additional proton signal in the $^1$H NMR spectrum at 7.59 ppm. Although the $^1$H NMR spectrum of this compound demonstrated all the characteristics of a 2-aminopyrimidine (the presence of the NH$_2$ and H-5 signals, with loss of the double bond signals), the proton signals integrated for 20 protons, instead of the expected 19. Coupling observed in the COSY spectrum between the protons identified as H-3", H-4" and later H-5", clearly showed that H-5" was present on the furan ring. Inspection of the $^{13}$C NMR spectrum in conjunction with the DEPT 135 and HSQC further revealed the presence of the C-5" (CH) carbon at 144.6 ppm, instead of the quaternary carbon expected at approximately 128 ppm. The strong C-Br signal as observed in the IR spectrum of \textbf{38k} was also absent. Lastly, in the mass spectrum, the mass of 378.1903 amu ([M+H]), correlating with the calculated value of 378.1898 confirmed the molecular formula of C$_{21}$H$_{24}$N$_5$O$_2$. It was thus clear that debromination occurred.

Literature indicates that, although relatively harsh ionic, catalytic or radical conditions are needed, the replacement of an aromatic bromine by hydrogen is indeed possible. It is also well known that bromine is easier to remove from aromatic systems than chlorine and fluorine (Zhang \textit{et al}., 1997, Choi and Chi, 2001). Reports indicate that higher temperatures lead to more rapid debromination and that this reaction usually involves a catalyst or a strong reducing agent such as a metal hydride (Choi and Chi, 2001). In some instances rearrangement, isomerisation and disproportionation of bromine substituted aromatic systems have also been observed, sometimes in the presence of strong Lewis acids or at elevated temperatures, but occasionally even under milder conditions. For example, O'Bara and co-workers (1970) demonstrated that the reversal of bromination can occur in non-polar solvents at a temperature as low as 25 °C (O'Bara \textit{et al}., 1970). Reductive dehalogenation of aryl halides by sodium hydride was further carried out by Zang and co-workers (1997), and although this reaction took place in the presence of a catalyst, it indicates the ability of sodium hydride to cause reductive dehalogenation of aryl halides. In this particular investigation, chlorobenzene was dehalogenated in THF at a temperature of 66 °C in the presence of lanthanide chloride as catalyst. All the previously mentioned factors (bromine being a good leaving group, NaH being a strong base and the high reaction temperature) could therefore very well contribute to the dehalogenation of the bromofuran ring to yield \textbf{39k}. A possible nucleophilic aromatic substitution reaction mechanism is proposed in Scheme 3.6.
Scheme 3.6: Proposed mechanism for dehalogenation of the 2-bromofuran group by sodium hydride at high temperatures.

3.3. Summary

Fourteen 2-aminopyrimidines were successfully synthesised according to standard literature procedures and characterisation of final compounds and intermediates were done by NMR spectroscopy, mass spectrometry, infrared spectroscopy, while melting points were also determined. Purity of the final compounds was assessed by HPLC.

In this chapter the design, synthesis and characterisation of compounds were discussed. The biological evaluation of the synthesised compounds will be discussed in Chapter 4.

3.4. Experimental

3.4.1. Materials and methods

Starting materials and reagents were obtained from Sigma-Aldrich, and used without further purification. Solvents for reactions and chromatography were acquired from Rochelle and Merck. Dichloromethane was distilled over calcium hydride when required. Deuterated solvents for nuclear magnetic resonance (NMR) spectroscopy were purchased from Merck.

Thin layer chromatography

Reactions were monitored routinely by thin layer chromatography (TLC) on precoated Kieselgel 60 F254 plates obtained from Merck. Detection of TLC plates was done by UV at a wavelength of 254 nm. Various mobile phases were used: Dichloromethane: methanol (9:1) or dichloromethane: ethyl acetate (8:2) were used for the acid and amide intermediates while dichloromethane: methanol (98:2) or dichloromethane: ethyl acetate (8:2) were used for the 2-aminopyrimidines.
Melting points

Melting points were determined with a Buchi B-545 apparatus and are uncorrected.

Mass spectrometry (MS)

Mass spectra were obtained with a Brucker micrOTOF-QII mass spectrometer in APCI (atmospheric-pressure chemical ionisation) and positive ionisation mode.

Nuclear magnetic resonance (NMR) spectroscopy

Proton ($^1$H) and carbon ($^{13}$C) NMR spectra were routinely recorded on a Bruker Avance III 600 spectrometer at frequencies of 600 MHz and 150 MHz respectively. In addition, compounds 39i - 39n were sent to the University of KwaZulu-Natal, Pietermaritzburg for further NMR spectroscopic analysis. Spectra for these compounds were recorded on a Bruker Avance III 500 spectrometer with a 5 mm BBO-Z probe at frequencies of 500 MHz and 125 MHz for $^1$H and $^{13}$C NMR spectra respectively. Deuterated chloroform (CDCl$_3$) and deuterated dimethylsulfoxide (DMSO-$d_6$) were used as solvents. MestReNova 8.1 was used to process the data.

The $^1$H NMR spectra are reported as chemical shift (δ) in ppm, and the integration (e.g. 2H or 1H), the multiplicity and the coupling constant (J) in Hz are also provided. Abbreviations used are: s (singlet), br s (broad singlet), d (doublet), br d (broad doublet), dd (doublet of doublets), t (triplet), br t (broad triplet), q (quartet), p (pentet) or m (multiplet). Chemical shifts are referenced to the residual solvent signal at 7.26 and 77.0 ppm for $^1$H and $^{13}$C respectively, in CDCl$_3$ and 3.5 and 39.5 ppm for $^1$H and $^{13}$C respectively, in DMSO-$d_6$.

High performance liquid chromatography (HPLC)

HPLC analysis of the final 2-aminopyrimidines was performed, to determine purity. An Agilent 1100 HPLC system equipped with a quaternary pump and an Agilent 1100 series diode array detector were utilized. HPLC grade acetonitrile (Merck) and Milli-Q water (Millipore) were used for chromatography. A Venusil XBP C18 column (4.60 x 150 mm, 5 µm) with an initial mobile phase (70% MilliQ water: 30% acetonitrile) at a flow rate of 1ml/min was employed. The concentration of acetonitrile in the mobile phase was linearly increased over a period of 5 minutes to a final concentration of 85%. The time allowed for equilibration between runs was 5 minutes and the duration of each HPLC run was 15 minutes. The concentration of the test compounds injected varied (20 µl of 1 mM to 20 µl of 0.25 mM). The eluent was monitored at wavelengths of 210, 254 and 300 nm.
Infrared spectrometry

A Bruker Alpha (platinum ATR) infrared spectrometer was used to record infrared spectra and the Opus® mentor software platform to process data.

3.4.2. Synthetic procedures

General procedure for the synthesis of acid intermediates (37a-37i)

To a stirred suspension of the aldehyde (17 mmol, 1 equivalent) in 100 ml methanol, the ketone (17 mmol, 1 equivalent) was added and stirred at room temperature. Thereafter, 0.5 equivalents of a NaOH (40% w/v) solution was added dropwise (pH of approximately 11). The reaction mixture was stirred overnight where after it was acidified with concentrated hydrochloric acid to a pH of approximately 1. The resulting precipitate was filtered and rinsed with water. Recrystallization was done with methanol.

General procedure for the synthesis of amide intermediates (38a-38n)

The chalcones (37a -37i) (1 equivalent), obtained in the previous step were suspended in dry dichloromethane (50 ml) and 1,1'-carbonyldiimidazole (1.2 equivalents) added to the reaction mixture. The reaction was stirred under nitrogen at room temperature for 4 h. The selected amine (1.2 equivalents) was then added and the reaction was stirred for a further 3 h – 24 h, while periodically monitoring the reaction with thin layer chromatography. After completion, the reaction was quenched by the addition of brine and the organic and aqueous layers were separated. The aqueous layer was further extracted twice more with dichloromethane. The organic fractions were combined and washed with sodium hydrogen carbonate and brine where after the organic fraction was concentrated (in vacuo). Purification was done with column chromatography using either (dichloromethane: methanol [98:2]; dichloromethane: methanol [9:1] or dichloromethane: ethyl acetate [8:2]). The polarity of these solvent systems was occasionally increased during column chromatography. Final purification was done by recrystallization from ethanol.

General procedure for the synthesis of 2-aminopyrimidines

A small amount of N,N-dimethylformamide (8 – 10 ml) was used to dissolve guanidine hydrochloride (1.5 equivalents). The amide intermediates (38a – 38n) (1 equivalent) obtained during the previous step and sodium hydride (3 equivalents) were then added while stirring under nitrogen. The reaction mixture was heated (60 – 120 °C) while under nitrogen. Discolouration (usually to black) at this stage was usually indicative of decomposition of the intermediate. The reaction mixture was stirred for 24 h under nitrogen and then allowed to cool, where after it was diluted with equal volumes of water and ethyl acetate. The aqueous
and organic layers were separated and the aqueous phase was extracted with ethyl acetate (four times) where after the organic layers were combined. The combined organic fractions were washed with brine to remove all dimethylformamide and then concentrated (in vacuo). The crude product was purified by column chromatography using (dichloromethane: methanol [98:2], dichloromethane: methanol [9:1] or dichloromethane: ethyl acetate [8:2]). Final purification was done by recrystallizing from ethanol with care due to temperature sensitivity of some of the 2-aminopyrimidines.

3.4.3 Spectroscopic and Physical data of compounds

4-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37a)

The title compound was prepared from 1-(5-methyl-2-furyl)ethanone and 4-formyl benzoic acid in a yield of 79%: mp 117.9 – 118.0 °C (methanol), cream solid. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 7.97 (d, $J = 8.5$ Hz, 2H, H-2′ and H-6′ or H-3′ and H-5′), 7.94 (J = 8.5 Hz, 2H, H-2′ and H-6′ or H-3′ and H-5′), 7.81 (d, $J = 3.5$ Hz, 1H, H-3″), 7.76 (d, $J = 15.8$ Hz, H-2), 7.71 (d, $J = 15.8$ Hz, H-1), 6.46 – 6.41 (m, 1H, H-4″), 2.40 (s, 3H, CH$_3$). $^{13}$C NMR (151 MHz, DMSO-$d_6$) δ 175.5 (C-3), 166.9 (COOH), 159.0 (C-5″), 151.8 (C-2″), 140.7 (C-1), 138.7 (C-1′), 132.0 (C-4″), 129.8, 128.8 (4C, C-2′, C-3′, C-5′, C-6′), 124.2 (C-2), 122.1 (C-3″), 109.7 (C-4″), 13.8 (CH$_3$). IR $v_{\text{max}}$ (cm$^{-1}$): 3103 – 2544 (br, OH); 1685 (COOH); 1654 (C=O); 1601; 1509; 1428; 1315; 1288; 1064; 928; 845; 772 (Ar). HRMS-APCI m/z: found 256.0730 [M$^+$], [C$_{15}$H$_{12}$O$_4$]: 256.0736 calcd.

3-[(1E)-3-oxo-3-(pyridine-2-yl)prop-1-en-1-yl]benzoic acid (37b)

The title compound was prepared from 1-(pyridine-2-yl)ethanone and 3-formylbenzoic acid in a yield of 10%: mp 177.1 – 177.2 °C (methanol), blue-grey solid. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 13.21 (br s, OH), 8.81 (ddd, $J = 4.7$, 1.6, 0.9 Hz, 1H, H-6″), 8.35 – 8.28 (m, 2H, H-2 and H-2′), 8.10 (dt, $J = 7.9$, 1.1 Hz, 1H, H-3″), 8.07 – 8.02 (m, 2H, H-6′, H-4″), 8.00 (dt, $J = 7.8$, 1.1 Hz, 1H, H-1″), 7.78 (d, $J = 8.5$ Hz, 2H, H-2′ and H-6′ or H-3′ and H-5′), 7.74 (d, $J = 15.8$ Hz, H-2), 7.70 (d, $J = 15.8$ Hz, H-1), 6.46 – 6.41 (m, 1H, H-4″), 2.40 (s, 3H, CH$_3$). $^{13}$C NMR (151 MHz, DMSO-$d_6$) δ 175.5 (C-3), 166.9 (COOH), 159.0 (C-5″), 151.8 (C-2″), 140.7 (C-1), 138.7 (C-1′), 132.0 (C-4″), 129.8, 128.8 (4C, C-2′, C-3′, C-5′, C-6′), 124.2 (C-2), 122.1 (C-3″), 109.7 (C-4″), 13.8 (CH$_3$). IR $v_{\text{max}}$ (cm$^{-1}$): 3103 – 2544 (br, OH); 1685 (COOH); 1654 (C=O); 1601; 1509; 1428; 1315; 1288; 1064; 928; 845; 772 (Ar). HRMS-APCI m/z: found 256.0730 [M$^+$], [C$_{15}$H$_{12}$O$_4$]: 256.0736 calcd.
1.4 Hz, 1H, H-4′), 7.90 (d, J = 16.1 Hz, 1H, H-1), 7.69 (ddd, J = 7.5, 4.7, 1.3 Hz, 1H, H-5″), 7.59 (t, J = 7.7 Hz, 1H, H-5″).

13C NMR (151 MHz, DMSO-d6) δ 188.5 (C-3), 166.9 (COOH), 153.2 (C-2″), 149.2 (C-6″), 142.8 (C-1), 137.8 (C-4″), 135.0 (C-1′), 133.0 (C-6′), 131.6 (C-3″), 131.3 (C-4′), 129.5 (C-5′), 128.8 (C-2″), 127.8 (C-5″), 122.5 (C-3″), 121.8 (C-2). IR v max (cm⁻¹): 3095 – 2513 (br, OH); 1716 (N); 1672 (COOH); 1611 (C=O); 1586; 1586; 1273; 1195; 1097; 1035; 1009; 751 (Ar).

HRMS-APCI m/z: found 253.0729 [M]+, [C₁₅H₁₁NO₃]: 253.0739 calcd.

3-[(1E)-3-oxo-3-phenylprop-1-en-1-yl]benzoic acid (37c)

The title compound was prepared from 1-phenylethan-1-one and 3-formylbenzoic acid in a yield of 71%: mp 200.2 – 201.0 °C (methanol), white solid. 1H NMR (600 MHz, DMSO-d6) δ 13.17 (br s, 1H, OH), 8.37 (br s, 1H, H-2′), 8.20 – 8.11 (m, 3H, H-2″, H-6″, H-6′), 8.04 – 7.96 (m, 2H, H-4′, H-2), 7.79 (d, J = 15.6 Hz, 1H, H-1), 7.69 – 7.63 (m, 1H, H-4″ or H-5′), 7.61 – 7.53 (m, 3H, H-3″, H-5″, H-4″ or H-5′). 13C NMR (151 MHz, DMSO-d6) δ 189.1 (C-3), 167.0 (COOH), 143.0 (C-1), 137.4 (C-1′), 135.1 (C-1″), 133.2 (C-5′ or C-4″), 132.4 (C-6″), 131.7 (C-3″), 131.1 (C-4′), 129.5, 129.2 (C-2″, C-4″ or C-5′)*, 128.8, 128.6 (4C, C-2″, C-6″, C-3″, C-5″)*, 123.1 (C-2). IR v max (cm⁻¹): 3062 – 2535 (br, OH); 1671 (COOH); 1605 (C=O); 1445; 1413; 1368; 1289; 1212; 754; 685 (Ar). HRMS-APCI m/z: found 253.0859 [M+H]+, [C₁₆H₁₃O₃]: 253.0865 calcd. *In no particular order.

3-[(1E)-3-(furan-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37d)

The title compound was prepared from 1-(furan-2-yl)ethan-1-one and 3-formylbenzoic acid in a yield of 34%: mp 211.4 – 211.5 °C (methanol), white crystals. 1H NMR (600 MHz, DMSO-d6) δ 8.36 (t, J = 1.7 Hz, 1H, H-2′), 8.14 – 8.06 (m, 2H, H-6′, H-5″), 8.00 (dt, J = 7.7, 1.4 Hz, 1H, H-4″), 7.90 (br d, J = 3.6 Hz, 1H, H-3″), 7.81 – 7.75 (m, 2H, H-1 and H-2), 7.59 (t, J = 7.7 Hz, 1H, H-5″), 6.80 (dd, J = 3.6, 1.7 Hz, 1H, H-4″). 13C NMR (151 MHz, DMSO-d6) δ 176.5 (C-3), 167.0 (COOH), 152.8 (C-2″), 148.6 (C-5″), 141.8 (C-1), 134.9 (C-1″), 132.9 (C-6″),
131.7 (C-3’), 131.1 (C-4’), 129.3 (2C, C-2’, C-5’), 123.0 (C-2), 120.0 (C-3'”), 112.8 (C-4’’). IR νmax (cm⁻¹): 3124 – 2552 (br, OH); 1678 (COOH); 1607 (C=O); 1465; 1394; 1281; 985; 754 (Ar). HRMS-APCI m/z: 243.0655 found [M+H]+, [C₁₄H₁₁O₄]: 243.0657 calcd.

3-[(1E)-3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl]benzoic acid (37e)

The title compound was prepared from 1-(4-fluorophenyl)ethan-1-one and 3-formyl benzoic acid in a yield of 97%: mp 207.8 – 209.0 °C (methanol), white solid. 1H NMR (600 MHz, DMSO-d₆) δ 8.37 (br s, 1H, H-2’), 8.27 (dd, J = 8.6, 5.5 Hz, 2H, H-2”, H-6’”), 8.10 (d, J = 7.6 Hz, 1H, H-6’), 8.04 – 7.97 (m, 2H, H-2, H-4’), 7.79 (d, J = 15.6 Hz, 1H, H-1), 7.55 (t, J = 7.7 Hz, 1H, H-5’), 7.39 (t, J = 8.6 Hz, 2H, H-3”, H-5’’”). 13C NMR (151 MHz, DMSO-d₆) δ 187.7 (C-3), 167.4 (COOH), 165.1 (d, J_C-F = 250.9 Hz, C-4””), 143.4 (C-1), 134.8 (C-1’), 134.1 (d, J_C-F = 2.6 Hz, C-1””), 133.1 (C-3’), 132.4 (C-6’), 131.7 (2C, d, J_C-F = 9.8 Hz, C-2”, C-6’’”), 131.2 (C-4”), 129.6 (C-2”), 129.1 (C-5”), 122.7 (C-2), 115.8 (2C, d, J_C-F = 20.3 Hz, C-3”, C-5’’”). IR νmax (cm⁻¹): 2958 – 2548 (br, OH); 1681 (COOH); 1599 (C=O); 1507; 1296; 1211; 1157; 1096 (C-F); 837; 755; 694 (Ar). HRMS-APCI m/z: 271.0756 found [M+H]⁺, [C₁₆H₁₂FO₃]: 271.0770 calcd.

3-[(1E)-3-(5-methylthiophen-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37f)

The title compound was prepared from 1-(5-methylthiophen-2-yl)ethan-1-one and 3-formylbenzoic acid in a yield of 98%: mp 207.8 – 209.0 °C (methanol), white solid. 1H NMR (600 MHz, DMSO-d₆) δ 13.19 (br s, 1H, OH), 8.37 (br s, 1H, H-2’), 8.23 (t, J = 3.0 Hz, 1H, H-3’”), 8.12 (br d, J = 7.7 Hz, 1H, H-6’), 7.99 (br d, J = 7.7 Hz, 1H, H-4’”), 7.91 (br d, J = 15.7 Hz, 1H, H-2”), 7.73 (d, J = 15.6 Hz, 1H, H-1), 7.58 (t, J = 7.7 Hz, 1H, H-5’”), 7.01 (br s, 1H, H-4”), 2.54 (s, 3H, CH₃). 13C NMR (151 MHz, DMSO-d₆) δ 181.0 (C-3), 167.0 (COOH), 150.7 (C-5’”), 143.3 (C-2”), 141.6 (C-1), 135.1 (C-1’), 134.8 (C-3””), 132.9 (C-6’), 131.6 (C-3’), 131.0 (C-4’), 129.5 (C-2’ or C-5’), 129.3 (C-2’ or C-5”), 127.8 (C-4’”), 122.8 (C-2), 15.8 (CH₃).
**IR** $v_{\text{max}}$ (cm$^{-1}$): 3064 – 2562 (Br, OH); 1682 (COOH); 1645 (C=O); 1592; 1453; 1236; 974; 755; 666 (Ar). **HRMS-APCI** $m/z$: 273.0565 found [M+H]$^+$, [C$_{15}$H$_{13}$O$_3$S: 273.0580 calcd].

3-[(2E)-3-(1-benzofuran-2-yl)prop-2-enoyl]benzoic acid (37g)

The title compound was prepared from 1-benzofuran-2-carbaldehyde and 3-acetylbenzoic acid in a yield of 19%: mp 230.1 – 230.2 °C (methanol), yellow solid. **$^1$H NMR** (600 MHz, DMSO-$d_6$) δ 13.34 (br s, 1H, OH), 8.55 (t, $J$ = 1.8 Hz, 1H, H-2'), 8.35 (dt, $J$ = 7.8, 1.5 Hz, 1H, H-6'), 8.21 (dt, $J$ = 7.7, 1.4 Hz, 1H, H-4'), 7.78 – 7.64 (m, 5H, H-2, H-3, H-5', H-5'', H-8''), 7.55 – 7.53 (m, 1H, H-3''), 7.39 – 7.38 (m, 1H, H-6'' or H-7''), 7.34 – 7.26 (m, 1H, H-6'' or H-7''). **$^{13}$C NMR** (151 MHz, DMSO-$d_6$) δ 187.9 (C-1), 166.7 (COOH), 155.1 (C-9''), 152.7 (C-2''), 137.5 (C-1''), 133.7 (C-4''), 132.6 (C-6''), 131.5 (C-3''), 131.2 (C-2 or C-3), 129.5 (C-5' or C-5''), 128.9 (C-2''), 128.2 (C-4''), 127.2 (C-6'' or C-7''), 123.7 (C-6'' or C-7''), 122.3 (C-5' or C-5''), 121.3 (C-2 or C-3), 113.6 (C-3''), 111.5 (C-8''). **IR** $v_{\text{max}}$ (cm$^{-1}$): 3067 – 2553 (br, OH); 1693 (COOH); 1603 (C=O); 1586; 1419; 1281; 1204; 974; 742; 668 (Ar). **HRMS-APCI** $m/z$: 292.0722 found [M]$^+$, [C$_{18}$H$_{12}$O$_4$: 292.0736 calcd].

3-[(1E)-3-(5-bromofuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37h)

The title compound was prepared from 1-(5-bromofuran-2-yl)ethanone and 3-formylbenzoic acid in a yield of 45%: mp 117.3 – 117.4 °C (methanol), pale cream coloured crystals. **$^1$H NMR** (600 MHz, DMSO-$d_6$) δ 8.36 (t, $J$ = 1.7 Hz, 1H, H-2'), 8.08 (dt, $J$ = 7.8, 1.5 Hz, 1H, H-6'), 8.02 – 7.93 (m, 2H, H-4', H-3''), 7.80 (d, $J$ = 15.8 Hz, 1H, H-1), 7.73 (d, $J$ = 15.7 Hz, 1H, H-2), 7.58 (t, $J$ = 7.7 Hz, 1H, H-5'), 6.95 (d, $J$ = 3.6 Hz, 1H, H-4''). **$^{13}$C NMR** (151 MHz, DMSO-$d_6$) δ 175.3 (C-3), 167.0 (COOH), 154.6 (C-2''), 142.4 (C-1), 134.8 (C-1''), 132.9 (C-6'), 131.9 (C-3''), 131.3 (C-4''), 129.8 (C-5''), 129.4 (C-2' or C-5'), 129.3 (C-2' or C-5'), 121.4 (C-2); 119.7(C-3''), 114.9 (C-4''). **IR** $v_{\text{max}}$ (cm$^{-1}$): 3082 – 2519 (br, OH); 1654 (COOH); 1601
(C=O); 1450; 1272; 1243; 1203; 1021; 982; 824; 752; 664 (C-Br). **HRMS-APCI** m/z: 320.9740 found [M+H]^+; [C_{14}H_{10}BrO_4]: 320.9757 calcd.

3-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37i)

![Chemical structure](image)

The title compound was prepared from 1-(5-methyl-2-furyl)ethanone and 3-formyl benzoic acid in a yield of 48%: mp 116.8 – 116.9 °C (methanol), white-yellow crystals. **1H NMR** (600 MHz, DMSO-d$_6$) δ 8.34 (br s, 1H, H-2′), 8.08 (br d, J = 8.0 Hz, 1H, H-6′), 7.99 (dt, J = 7.8, 1.4 Hz, 1H, H-4′), 7.83 (d, J = 3.5 Hz, 1H, H-3″), 7.79 – 7.69 (m, 2H, H-1 and H-2), 7.58 (t, J = 7.7 Hz, 1H, H-5′), 6.44 (dd, J = 3.7, 1.1 Hz, 1H, H-4″), 2.41 (s, 3H, CH$_3$). **13C NMR** (151 MHz, DMSO-d$_6$) δ 175.62 (C-3), 167.0 (COOH), 158.8 (C-5″), 151.8 (C-2″), 141.2 (C-1), 135.0 (C-1′), 132.8 (C-6″), 131.7 (C-3’), 131.0 (C-4′), 129.3 (C-2′ or C-5′), 129.2 (C-2′ or C-5′), 123.1 (C-2), 121.9 (C-3″), 109.6 (C-4″), 13.8 (CH$_3$). **IR v$_{max}$ (cm$^{-1}$):** 2923 (br, OH), 1664 (COOH); 1586 (C=O); 1509; 1448; 1285; 1205; 792; 751 (Ar). **HRMS-APCI** m/z: 257.0797 found [M+H]^+; [C$_{15}$H$_{13}$O$_4$]: 257.0814 calcd.

(2E)-1-(5-methylfuran-2-yl)-3-[4-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38a)

![Chemical structure](image)

The title compound was prepared from 4-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37a) in a yield of 73%: mp 152.1 – 153.0 °C (ethanol), white crystals. **1H NMR** (600 MHz, CDCl$_3$) δ 7.83 (d, J = 15.7 Hz, 1H, H-3), 7.66 (d, J = 8.1 Hz, 2H, H-2′, H-6′), 7.45 – 7.38 (m, 3H, H-3′, H-5′, H-2), 7.27 (d, J = 3.4 Hz, 1H, H-3″), 6.23 (dd, J = 3.6, 1.1 Hz, 1H, H-4″), 3.71 (br s, 2H, CONCH$_2$), 3.34 (br s, 2H, CONCH$_2$), 2.44 (s, 3H, CH$_3$), 1.75 – 1.43 (m, 6H, 3 x piperidine CH$_2$). **13C NMR** (151 MHz, CDCl$_3$) δ 176.9 (C-1), 169.5 (amide C=O), 158.3 (C-5″), 152.4 (C-2″), 142.1 (C-3), 138.1 (C-4′), 135.8 (C-1′), 128.4 (C-2′, C-6′), 127.4 (C-3′, C-5′), 122.2 (C-2), 119.8 (C-3″), 109.4 (C-4″), 48.7, 43.2 (2 x CONCH$_2$), 26.5, 25.5, 24.5 (3 x piperidine CH$_2$), 14.2 (CH$_3$). **IR v$_{max}$ (cm$^{-1}$):** 3110 – 2851 (N-tertiary); 1729; 1708;
1657 (C=O); 1620; 1599 (C=O); 1508; 1432; 1371; 1334; 1268; 1113; 1066; 987; 808; 7667 (Ar). **HRMS-APCI m/z:** 324.1573 found [M+H]^+; [C_{20}H_{22}O_{3}] calculated 324.1600.

**(2E)-3-[3-(piperidine-1-carbonyl)phenyl]-1-(pyridin-2-yl)prop-2-en-1-one (38b)**

The title compound was prepared from 3-[(1E)-3-oxo-3-(pyridine-2-yl)prop-1-en-1-yl]benzoic acid (37b) in a yield of 24%; green oil. **H NMR** (600 MHz, CDCl$_3$) δ 8.73 (ddd, J = 4.7, 1.5, 0.8 Hz, 1H, H-6”), 8.32 (d, J = 16.0 Hz, 1H, H-2), 8.17 (dt, J = 7.9, 1.1 Hz, 1H, H-3”), 7.93 – 7.84 (m, 2H, H-2’, H-6’), 7.73 (m, 2H, H-2’, H-6’), 7.45 – 7.38 (m, 2H, H-4’, H-5’), 3.72 (br s, 2H, CONCH$_2$), 3.34 (br s, 2H, CONCH$_2$), 1.73 – 1.45 (m, 6H, 3 x piperidine CH$_2$). **C NMR** (151 MHz, CDCl$_3$) δ 189.3 (C-1), 169.5 (amide C=O), 153.9 (C-2”), 148.8 (C-6”), 143.6 (C-3), 137.2 (C-3”), 137.0 (C-4”), 135.4 (C-1”), 129.6 (C-2' or C-6'), 128.5 (C-4' or C-5'), 128.9 (C-4' or C-5'”), 127.0, 126.9 (C-2' or C-6' and C-5”) 122.9 (C-3'”), 121.8 (C-2), 48.8, 43.1 (2 x CONCH$_2$), 26.5, 25.5, 24.5 (3 x piperidine CH$_2$). **IR** v$_{max}$ (cm$^{-1}$): 2933; 2854 (N-tertiary); 1672 (C=O); 1606 (C=O); 1437; 1327; 1260; 1216; 1026; 1008; 789; 745 (Ar). **HRMS-APCI m/z:** 320.1505 found [M]^+; [C_{20}H_{20}N_{2}O_{2}] calculated 320.1525.

**(2E)-1-phenyl-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38c)**

The title compound was prepared from 3-[(1E)-3-oxo-3-(pyridine-2-yl)prop-1-en-1-yl]benzoic acid (37c) in a yield of 20%; mp 120.5 – 121.3 °C (ethanol), light yellow solid. **H NMR** (600 MHz, CDCl$_3$) δ 8.05 – 7.99 (m, 2H, H-2”, H-6”), 7.79 (d, J = 15.7 Hz, 1H, H-3), 7.71 – 7.62 (m, 2H, H-2’ and H-6’ or H-4’), 7.62 – 7.53 (m, 2H, H-2, H-4’), 7.51 (br t, J = 7.7 Hz, 2H, H-3”, H-5”), 7.48 – 7.38 (m, 2H, H-5’ and H-4’ or H-6’), 3.73 (br s, 2H, CONCH$_2$), 3.35 (br s, 2H, CONCH$_2$), 1.73 – 1.46 (m, 6H, 3 x piperidine CH$_2$). **C NMR** (151 MHz, CDCl$_3$) δ 190.2 (C-1), 169.4 (amide C=O), 143.7 (C-3), 137.9 (C-1”), 137.3 (C-3”), 135.2 (C-1’), 132.9 (C-4”), 129.4 (C-4’ or C-5’ or C-6’), 129.0 (C-4’ or C-5’ or C-6’), 128.6 (C-3” and C-5” or C-2” and C-
6\textsuperscript{"o}), 128.51 (C-4\textsuperscript{'} or C-5\textsuperscript{'} or C-6\textsuperscript{'}), 128.48 (C-3\textsuperscript{"} or C-2\textsuperscript{"} and C-6\textsuperscript{"}), 126.5 (C-2\textsuperscript{'}, 122.7 (C-2), 48.8, 43.2 (2 x CONCH\textsubscript{2}), 26.6, 25.5, 24.5 (3 x piperidine CH\textsubscript{2}). \textbf{IR} \textit{v}_{\text{max}} (cm\textsuperscript{-1}): 3058 – 2846 (N-tertiary); 1665 (C=O); 1621; 1604; 1577 (C=O); 1441; 1338; 1226; 1220; 1021; 981; 813 (Ar). \textbf{HRMS-APCI} \textit{m/z}: 318.1477 found [M-H]\textsuperscript{+}, [C\textsubscript{21}H\textsubscript{20}NO\textsubscript{2}]: 318.1494 calcd.

(\textit{2E})-1-(furan-2-yl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38d)

The title compound was prepared from 3-([(1\textit{E})-3-(furan-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37d) in a yield of 25\%: mp 156.2 – 156.3 °C (ethanol), white solid. \textbf{\textit{1H NMR}} (600 MHz, CDCl\textsubscript{3}) \textit{\delta} 7.84 (d, \textit{J} = 15.8 Hz, 1H, H-3), 7.70 – 7.62 (m, 3H, H-2\textsuperscript{'}, H-5\textsuperscript{"}, H-6\textsuperscript{'}), 7.50 – 7.37 (m, 3H, H-2, H-4\textsuperscript{'}, H-5\textsuperscript{'}), 7.33 (d, \textit{J} = 3.5 Hz, 1H, H-3\textsuperscript{"}), 6.59 (dd, \textit{J} = 3.6, 1.7 Hz, 1H, H-4\textsuperscript{"}), 3.72 (br s, 2H, CONCH\textsubscript{2}), 3.34 (br s, 2H, CONCH\textsubscript{2}), 1.73 – 1.44 (m, 6H, 3 x piperidine CH\textsubscript{2}). \textbf{\textit{13C NMR}} (151 MHz, CDCl\textsubscript{3}) \textit{\delta} 177.7 (C-1), 169.4 (amide C=O), 153.5 (C-2\textsuperscript{"}), 146.7 (C-5\textsuperscript{"}), 142.8 (C-3), 137.2 (C-3\textsuperscript{'}), 135.0 (C-1\textsuperscript{'}), 129.5, 129.0, 128.6 (C-4\textsuperscript{'}, C-5\textsuperscript{'} and C-6\textsuperscript{'} or C-2\textsuperscript{'})\textsuperscript{*}, 126.5 (C-2\textsuperscript{'} or C-6\textsuperscript{'}), 122.0 (C-2), 117.7 (C-3\textsuperscript{"}), 112.6 (C-4\textsuperscript{"}), 48.7, 43.1 (2 x CONCH\textsubscript{2}), 26.5, 25.5, 24.5 (3 x piperidine CH\textsubscript{2}). \textbf{IR} \textit{v}_{\text{max}} (cm\textsuperscript{-1}): 3110 – 2852 (N-tertiary); 1952; 1627 (C=O); 1591 (C=O); 1462; 1396; 1273; 1050; 995; 779 (Ar). Mass spectrum not obtained due to decomposition of sample. *In no particular order.

(\textit{2E})-1-(4-fluorophenyl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38e)

The title compound was prepared from 3-([(1\textit{E})-3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl]benzoic acid (37e) in a yield of 22\%: mp 133.6 – 133.8 °C (ethanol), yellow crystals. \textbf{\textit{1H NMR}} (600 MHz, CDCl\textsubscript{3}) \textit{\delta} 8.09 – 8.02 (m, 2H, H-2\textsuperscript{"}, H-6\textsuperscript{"}), 7.80 (d, \textit{J} = 15.6 Hz, 1H, H-3), 7.69 (br s, 1H, H-2\textsuperscript{'}), 7.65 (br d, \textit{J} = 7.6 Hz, 1H, H-6\textsuperscript{'}), 7.53 (d, \textit{J} = 15.7 Hz, 1H, H-2), 7.48 – 7.39 (m, 2H, H-4\textsuperscript{'}, H-5\textsuperscript{'}), 7.21 – 7.14 (m, 2H, H-3\textsuperscript{"}, H-5\textsuperscript{"}), 3.73 (br s, 2H, CONCH\textsubscript{2}), 3.35 (br s, 2H, CONCH\textsubscript{2}), 1.75 – 1.45 (m, 6H, 3 x piperidine CH\textsubscript{2}). \textbf{\textit{13C NMR}} (151 MHz, CDCl\textsubscript{3}) \textit{\delta}
188.5 (C-1), 169.4 (amide C=O), 165.7 (d, $J_{C,F} = 255.0$ Hz, C-4''), 143.9 (C-3), 137.3 (C-3'), 135.2 (C-1'), 134.3 (d, $J_{C,F} = 3.0$ Hz, C-1''), 131.1 (d, $J_{C,F} = 9.1$ Hz, 2C, C-2'', C-6''), 129.5, 129.0, 128.6 (C-4', C-5', C-6'')*, 126.5 (C-2'), 122.4 (C-2), 115.8 (d, $J_{C,F} = 21.1$ Hz, 2C, C-3'', C-5''), 48.8, 43.2 (2 x CONCH$_2$), 26.6, 25.6, 24.5 (3 x piperidine CH$_2$). IR $v_{\text{max}}$ (cm$^{-1}$): 3061 – 2857 (N-tertiary); 1667 (C=O); 1597 (C=O); 1426; 1335; 1208; 1160; 1007; 884; 810; 746 (Ar). HRMS-APCI m/z: 388.1554 found [M+H]$^+$, [C$_{21}$H$_{21}$FNO$_2$: 388.1556 calcd]. *In no particular order.

(2E)-1-(5-methylthiophen-2-yl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38f)

The title compound was prepared from 3-[(1E)-3-(5-methylthiophen-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37f) in a yield of 48%: orange oil. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 15.6$ Hz, 1H, H-3), 7.70 – 7.65 (m, 2H, H-3'' and H-2''), 7.63 (br d, $J = 7.7$, 1H, H-6''), 7.46 – 7.36 (m, 3H, H-5'', H-4', H-2), 3.72 (br s, 2H, CONCH$_2$), 3.35 (br s, 2H, CONCH$_2$), 2.56 (br s, 3H, CH$_3$), 1.78 -1.68 (m, 6H, 3 x piperidine CH$_2$). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 181.3 (C-1), 169.5 (amide C=O), 150.4 (C-5''), 143.2 (C-2''), 142.3 (C-3), 137.2 (C-3'), 135.2 (C-1'), 132.6 (C-3''), 129.5, 129.0, 128.4 (C-4', C-5', C-6''), 127.0 (C-4''), 126.4 (C-2'), 122.4 (C-2), 48.8, 43.2 (2 x CONCH$_2$), 26.5, 25.5, 24.5 (3 x piperidine CH$_2$), 16.1 (CH$_3$). IR $v_{\text{max}}$ (cm$^{-1}$): 3044 – 2853 (N-tertiary); 1644 (C=O); 1623 (C=O); 1592; 1433; 1316; 1232; 1065; 998; 803 (Ar). HRMS-APCI m/z: 339.1267 found [M]$^+$, [C$_{20}$H$_{21}$NO$_2$S: 339.1288 calcd]. *In no particular order.

(2E)-3-(1-benzofuran-2-yl)-1-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38g)

The title compound was prepared from 3-[(2E)-3-(1-benzofuran-2-yl)prop-2-enoyl]benzoic acid (37g) in a yield of 40%: yellow oil. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.12 – 8.06 (m, 2H, H-2', H-6'), 7.75 – 7.67 (m, 2H, H-2, H-3), 7.64 – 7.59 (m, 2H, H-5'', H-4''), 7.56 – 7.49 (m, 2H, H-4'').
H-5’, H-8”), 7.38 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H, H-6” or H-7”), 7.30 – 7.20 (m, 1H, H-6" or H-7”), 7.04 (s, 1H, H-3”), 3.73 (s, 2H, CONCH$_2$), 3.34 (s, 2H, CONCH$_2$), 1.80 – 1.42 (m, 6H, 3 x piperidine CH$_2$). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 188.8 (C-1), 169.3 (amide C=O), 155.6 (C-9”), 152.8 (C-2”), 138.1 (C-1’ or C-3’), 137.0 (C-1’ or C-3’), 131.3, 131.1 (C-2 or C-3 and C-4’ or C-5’)*, 129.4, 128.9 (C-5’ or C-6’ or C-2’ or C-3’)*, 128.5, 127.0 126.9, 123.4 (C-6’ or C-2’ and C-6” or C-7”)*, 121.9, 121.5 (C-2 or C-3 and C-4’ or C-5’), 112.9 (C-3”), 111.4 (C-8”), 48.8, 43.2 (2 x CONCH$_2$), 26.5, 25.5, 24.5 (3 x piperidine CH$_2$). IR $\nu$$_{max}$ (cm$^{-1}$): 2918 – 2852 (N-tertiary); 1662 (C=O); 1625; 1596 (C=O); 1444; 1253; 1204; 1124; 964; 804 (Ar). HRMS-APCI m/z: 360.1595 found [M+H]$^+$, [C$_{23}$H$_{22}$NO$_3$: 360.1600 calcd]. *In no particular order.

(2E)-3-[3-(4-ethylpiperazine-1-carbonyl)phenyl]-1-(5-methylthiophen-2-yl)prop-2-en-1-one (38h)

The title compound was prepared from 3-[(1E)-3-(5-methylthiophen-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37f) in a yield of 89%: orange oil. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.78 (d, J = 15.5 Hz, 1H, H-3), 7.70 – 7.62 (m, 3H, H-2′, H-6′, H-3”), 7.44 (t, J = 7.6 Hz, 1H, H-5’), 7.42 – 7.35 (m, 2H, H-4’ and H-2), 6.85 (dd, J = 3.8, 1.2 Hz, 1H, H-4”), 3.82 (br s, 2H, CONCH$_2$), 3.45 (br s, 2H, CONCH$_2$), 2.60 – 2.32 (m, 9H, 2 x CH$_2$NCH$_2$CH$_3$, NCH$_2$CH$_3$, thiophene CH$_3$), 1.09 (t, J = 7.2 Hz, 3H, NCH$_2$CH$_3$). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 181.3 (C-1), 169.5 (amide C=O), 150.5 (C-5”), 143.2 (C-2”), 142.1 (C-3), 136.5 (C-3’), 135.3 (C-1’), 132.7 (C-3”), 129.7 (C-6”), 129.0 (C-5’), 128.6 (C-4’), 127.0 (C-4”), 126.6 (C-2”), 122.5 (C-2’), 53.1, 52.3 (2 x CH$_2$NCH$_2$CH$_3$), 52.2 (NCH$_2$CH$_3$), 47.7, 42.3 (2 x CONCH$_2$), 16.1 (thiophene CH$_3$), 11.8 (NCH$_2$CH$_3$). IR $\nu$$_{max}$ (cm$^{-1}$): 3112 – 2821 (N-tertiary); 1921 (C=O); 1447; 1061; 808; 744 (Ar). HRMS-APCI m/z: 369.1631 found [M+H]$^+$, [C$_{21}$H$_{26}$N$_2$O$_2$S: 369.1637 calcd].
(2E)-1-(5-methylthiophen-2-yl)-3-[3-(morpholine-4-carbonyl)phenyl]prop-2-en-1-one (38i)

The title compound was prepared from 3-[(1E)-3-(5-methylthiophen-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37f) in a yield of 12%: mp 151.8 – 152.0 °C (ethanol), white crystals. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.78 (d, $J = 15.6$ Hz, 1H, H-3), 7.70 – 7.67 (m, 2H, H-2′, H-3′), 7.66 (br d, $J = 7.7$ Hz, 1H, H-6′), 7.46 (t, $J = 7.6$ Hz, 1H, H-5′), 7.42 – 7.38 (m, 2H, H-4′ en H-2), 6.86 (dd, $J = 3.8$, 1.2 Hz, 1H, H-4″), 3.91 – 3.35 (m, 8H, morpholine, CH$_2$), 2.57 (br s, 3H, CH$_3$). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 181.2 (C-1), 169.7 (amide C=O), 150.6 (C-5″), 143.1 (C-2″), 142.0 (C-3), 136.1 (C-3′), 135.4 (C-1″), 132.7 (C-3″), 129.9 (C-6′), 129.1 (C-5′), 128.5 (C-4′), 127.0 (C-4″), 126.7 (C-2′), 122.6 (C-2), 66.8, 48.2, 42.6 (4C, morpholine CH$_2$), 16.1 (CH$_3$). IR $v_{\text{max}}$ (cm$^{-1}$): 2965 – 2952 (N-tertiary); 1638 (C=O); 1594 (C=O); 1449; 1329; 1258; 1215; 1107; 1060; 976; 798 (Ar). HRMS-APCI m/z: 341.1080 found [M]$^+$, [C$_{19}$H$_{19}$NO$_3$S: 341.1086 calcd].

(2E)-1-(5-methylthiophen-2-yl)-3-[3-(pyrrolidine-1-carbonyl)phenyl]prop-2-en-1-one (38j)

The title compound was prepared from 3-[(1E)-3-(5-methylthiophen-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37f) in a yield of 8%: mp 150.9 – 151.0 °C (ethanol), white solid. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.82 – 7.76 (m, 2H, H-3, H-2′), 7.69 (d, $J = 3.8$ Hz, 1H, H-3″), 7.64 (br d, $J = 7.8$, 1H, H-6′), 7.53 (dt, $J = 7.8$, 1.4 Hz, 1H, H-4′), 7.46 – 7.38 (m, 2H, H-5′, H-2), 6.86 (dd, $J = 3.9$, 1.1 Hz, 1H, H-4″), 3.67 (t, $J = 7.0$ Hz, 2H, CONCH$_2$), 3.44 (t, $J = 6.7$ Hz, 2H, CONCH$_2$), 2.57 (s, 3H, CH$_3$), 1.98 (p, $J = 6.8$ Hz, CH$_2$CH$_2$CH$_2$), 1.89 (p, $J = 6.6$ Hz, 2H, CH$_2$CH$_2$CH$_2$). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 181.4 (C-1), 169.0 (amide C=O), 150.4 (C-5″), 143.1 (C-2″), 142.0 (C-3), 136.1 (C-3′), 135.4 (C-1″), 132.7 (C-3″), 129.9 (C-6′), 129.1 (C-5′), 128.5 (C-4′), 127.0 (C-4″), 126.7 (C-2′), 122.6 (C-2), 66.8, 48.2, 42.6 (4C, morpholine CH$_2$), 16.1 (CH$_3$).
143.2 (C-2’”), 142.3 (C-3), 138.0 (C-3’), 135.1 (C-1’), 129.9 (C-6’), 128.9 (C-5’ or C-4’), 128.7 (C-4’ or C-5’), 127.0 (C-4’’), 126.6 (C-2’), 122.4 (C-2), 49.6, 46.3 (2 x CONCH₂), 26.4, 24.4 (2 x CH₂CH₂CH₂), 16.1 (CH₃). IR ν_max (cm⁻¹): 3050 – 2869 (N-tertiary); 1621 (C=O); 1591 (C=O); 1428; 1318; 1233; 1004; 795 (Ar).

HRMS-APCI m/z: 326.1184 found [M+H]^+, [C₁₉H₂₀NO₂S: 326.1215 calcd].

(2E)-1-(5-bromofuran-2-yl)-3-[3-(4-ethylpiperazine-1-carbonyl)phenyl]prop-2-en-1-one (38k)

The title compound was prepared from 3-[(1E)-3-(5-bromofuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37h) in a yield of 59%; mp 140.1 – 141.0 °C (ethanol), white to light yellow crystals. ¹H NMR (600 MHz, CDCl₃) δ 7.85 (d, J = 15.7 Hz, 1H, H-3), 7.71 (br s, 1H, H-2’), 7.67 (dt, J = 7.5, 1.6 Hz, 1H, H-6’), 7.49 – 7.39 (m, 3H, H-4’, H-5’, H-2), 7.27 (d, J = 3.6 Hz, 1H, H-3’’), 6.55 (d, J = 3.6 Hz, 1H, H-4’’), 3.83 (br s, 2H, CONCH₂), 3.45 (br s, 2H, 2H,CONCH₂), 2.55 (s, 2H,CH₂NCH₂), 2.49 – 2.38 (m, 4H, CH₂CH₃ and CH₂NCH₂CH₃), 1.10 (t, J = 7.2 Hz, 3H, CH₃). ¹³C NMR (151 MHz, CDCl₃) δ 176.4 (C-1), 169.4 (amide C=O), 155.2 (C-2’’), 143.3 (C-3), 136.6 (C-3’), 135.0 (C-1’), 129.9 (C-6’), 129.1 (C-4’ or C-5’), 129.0 (C-4’ or C-5’), 128.4 (C-5’’), 126.9 (C-2’), 121.4 (C-2), 119.6 (C-3’’), 114.8 (C-4’’), 53.1, 52.4 (2 x CH₂NCH₂CH₃), 52.2 (CH₂CH₃), 47.8, 42.2 (2 x CONCH₂), 11.9 (CH₃). IR ν_max (cm⁻¹): 3086 – 1765 (N-tertiary); 1661(C=O); 1605 (C=O); 1453; 1418; 1295; 1205; 1063; 1012; 824; 793 (Ar) 745 (C-Br). HRMS-APCI m/z: 416.0718 found [M]^+, [C₂₀H₂₁BrN₂O₃: 416.0730 calcd].

N-(1,3-benzothiazol-2-yl)-4-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzamide (38l)
The title compound was prepared from 4-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37a) in a yield of 42%: mp 234.9 – 235.3 °C (ethanol), yellow solid. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 12.94 (s, NH), 8.20 (d, $J = 8.4$ Hz, 2H, H-2', H-6'), 8.05 – 7.97 (m, 3H, H-5', H-3', H-4* or H-7*), 7.86 – 7.69 (m, 4H, H-3", H-2, H-3, H-4* or H-7*), 7.50 – 7.44 (m, 1H, H-5* or H-6*), 7.37 - 7.31 (m, 1H, H-5* or H-6*), 6.46 (d, $J = 3.4$ Hz, 1H, H-4"), 2.41 (s, 3H, CH$_3$). HRMS-APCI m/z: 389.0925 found [M+H]$^+$, [C$_{22}$H$_{17}$N$_2$O$_3$S: 389.0960 calcd]. This sample decomposed upon standing and impurities were present in the NMR spectra. Interpretation of the $^{13}$C NMR spectrum was further complicated by its poor quality (due to insufficient scans run) which prevented the unambiguous assignment of $^{13}$C NMR signals and these data are therefore not presented. Proton and mass data are however in agreement with the proposed structure, and the expected 2-aminopyrimidine product was obtained successfully from this starting material, verifying its presence.

$N$-(1,3-benzothiazol-2-yl)-3-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzamide (38m)

The title compound was prepared from 3-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37i) in a yield of 21%: mp 251.1 – 252.0 °C (ethanol), white solid. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 8.58 (br s, 1H, H-2'), 8.14 (br d, $J = 7.7$ Hz, 1H, H-6'), 8.08 (br d, $J = 7.8$ Hz, 1H, H-4'), 8.02 (br d, $J = 7.9$ Hz, 1H, H-4* or H-7*), 7.81 – 7.75 (m, 4H, H-3", H-2, H-3, H-4* or H-7*), 7.64 (t, $J = 7.7$ Hz, 1H, H-5'), 7.49 – 7.42 (m, 1H, H-5* or H-6*), 7.39 – 7.28 (m, 1H, H-5* or H-6*), 6.47 (d, $J = 3.2$ Hz, 1H, H-4"), 2.42 (s, 3H, CH$_3$). $^{13}$C NMR (151 MHz, DMSO-$d_6$) δ 175.7 (C-1), 158.7 (C-5") 151.9 (C-2"), 141.2 (C-3), 133.1 (C-1'), 131.7 (C-4'), 129.8 (C-6'), 129.3 (C-5'), 128.0 (C-2'), 126.3 (C-5* or C-6*), 123.8 (C-5* or C-6*), 123.6 (C-2 or C-3"), 121.8 (C-4* or C-7*), 109.7 (C-4"), 13.8 (CH$_3$). IR v$_{\text{max}}$ (cm$^{-1}$): 3051; 2921 (N-tertiary); 1667 (C=O); 1645 (C=O); 1515; 1439; 1274; 1208; 1055; 1027; 988; 913; 748 (Ar). HRMS-APCI m/z: 388.0865 found [M]$^+$, [C$_{22}$H$_{16}$N$_2$O$_3$S: 388.0881 calcd]. Several quaternary carbons were not clearly visible on $^{13}$C NMR spectrum, presumably due to long relaxation times and a HMBC was not obtained for this sample.
**N-(6-chloro-1,3-benzothiazol-2-yl)-3-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzamide (38n)**

The title compound was prepared from 3-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (37i) in a yield of 7%: mp 269.6 – 270.0 °C (ethanol), white solid. **1H NMR** (600 MHz, DMSO-d₆) δ 13.02 (s, 1H, NH), 8.57 (br s, 1H, H-2'), 8.17 (d, J = 2.2 Hz, 1H, H-7*), 8.13 (d, J = 7.8 Hz, 1H, H-6'), 8.09 (d, J = 7.9 Hz, 1H, H-4'), 7.81 – 7.69 (m, 4H, H-2, H-3, H-4*, H-3''), 7.64 (t, J = 7.7 Hz, 1H, H-5'), 7.49 (dd, J = 8.6, 2.2 Hz, 1H, H-5*), 6.48 – 6.43 (m, 1H, H-4''), 2.42 (s, 3H, CH₃). **13C NMR** (151 MHz, DMSO-d₆) δ 175.6 (C-1), 166.0 (amide C=O), 158.9 (C-5''), 151.8 (C-2''), 141.1 (C-3), 135.0 (C-3'), 133.3 (C-1'), 133.1 (C-4'), 132.6 (C-4a* or C-7a*), 130.1 (C-6'), 129.4 (C-5'), 128.0 (C-2'), 127.8 (C-6'), 126.6 (C-5'), 123.4, 121.8, 121.7, 121.5 (C-2, C-4*, C-7*, C-3''), 109.7 (C-4''), 13.8 (CH₃). **IR** v max (cm⁻¹): 3172 – 2852 (N-tertiary); 1981; 1655 (C=O); 1595 (C=O); 1556; 1444; 1299; 1263; 1211; 1068; 981; 818 (Ar). **HRMS-APCI m/z**: 422.0453 found [M]⁺, [C₂₂H₁₅ClN₂O₃S: 422.0491 calcd]. In no particular order.

**4-(5-methylfuran-2-yl)-6-[4-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (39a)**

The title compound was prepared from (2E)-1-(5-methylfuran-2-yl)-3-[4-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38a) in a yield of 11%: mp 190.8 – 191.0 °C (ethanol), dark brown crystals. **1H NMR** (600 MHz, CDCl₃) δ 8.08 (d, J = 8.4 Hz, 2H, H-6', H-2'), 7.50 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.35 (s, 1H, H-5), 7.11 (d, J = 3.3 Hz, 1H, H-3''), 6.17 (dd, J = 3.3, 1.2 Hz, 1H, H-4''), 5.22 (s, 2H, NH₂), 3.72 (br s, 2H, CONCH₂), 3.34 (br s, 2H, CONCH₂)
2.43 (br s, 3H, CH₃), 1.75 – 1.44 (m, 6H, 3 x piperidine CH₂). ¹³C NMR (151 MHz, CDCl₃) δ 169.7 (C=O), 164.9 (C-6), 163.3 (C-2), 157.2 (C-4), 155.3 (C-5"), 150.5 (C-2"), 138.5 (C-1' or C-4"), 138.3 (C-1' or C-4'), 127.2, 127.1 (4C, C-2', C-6', C-3', C-5'), 113.3 (C-3"), 108.8 (C-4"), 101.7 (C-5), 48.7, 43.1 (2 x CONCH₂), 26.5, 25.6, 24.5 (3 x piperidine CH₂), 14.02 (CH₃).

IR νmax (cm⁻¹): 3520 – 3344 (NH₂); 2922 – 2853 (N-tertiary); 1598 (C=O); 1597 1519 (NH); 1442; 1260; 1001; 830 (Ar). HRMS-APCI m/z: 363.1812 found [M+H]⁺, [C₂₁H₂₃N₄O₂: 363.1821 calcd]. Purity (HPLC): 97%.

4-[3-(piperidine-1-carbonyl)phenyl]-6-(pyridin-2-yl)pyrimidin-2-amine (39b)

The title compound was prepared from (2E)-3-[3-(piperidine-1-carbonyl)phenyl]-1-(pyridin-2-yl)prop-2-en-1-one (38b) in a yield of 30%: mp 181.0 – 181.1 °C (ethanol), yellow crystals. ¹H NMR (600 MHz, CDCl₃) δ 8.72 (dt, J = 4.7, 1.3 Hz, 1H, H-6"), 8.37 (dt, J = 7.9, 1.1 Hz, 1H, H-6"), 8.18 (dt, J = 7.4, 1.7 Hz, 2H, H-2', H-6'), 8.14 (s, 1H, H-5), 7.84 (td, J = 7.7, 1.8 Hz, 1H, H-4"), 7.54 – 7.46 (m, 2H, H-4', H-5'), 7.39 (ddd, J = 7.5, 4.7, 1.2 Hz, 1H, H-5"), 5.25 (brs, 2H, NH₂), 3.74 (brs, 2H, CONCH₂), 3.37 (s, 2H, CONCH₂), 1.74 – 1.48 (m, 6H, 3 x piperidine CH₂). ¹³C NMR (151 MHz, CDCl₃) δ 169.8 (C=O), 165.7 (C-6), 164.9 (C-4), 163.4 (C-2), 154.5 (C-1"), 149.4 (C-2"), 137.8 (C-1'), 137.0 (C-3'), 128.8 (C-4' or C-5'), 128.7 (C-4' or C-5'), 128.1 (C-2' or C-6'), 125.8 (C-2' or C-6'), 125.1 (C-5"), 121.6 (C-3"), 104.4 (C-5), 48.8, 43.2 (2 x CONCH₂), 26.5, 25.6, 24.5 (3 x piperidine CH₂). IR νmax (cm⁻¹): 3392 – 3209 (NH₂); 2293 – 2852 (N-tertiary); 1617 (C=O); 1541; 1449; 1429; 784 (Ar). HRMS-APCI m/z: 359.1724 found [M⁺], [C₂₁H₂₃N₄O₂: 359.1754 calcd]. Purity (HPLC): 96%.

4-phenyl-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (39c)
The title compound was prepared from (2E)-1-phenyl-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38c) in a yield of 19%: mp 209.2 – 209.3 °C (ethanol), cream coloured crystals. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.14 – 8.07 (m, 2H, H-2’, H-6’), 8.08 – 8.01 (m, 2H, H-2”, H-6”), 7.55 – 7.45 (m, 6H, H-4’, H-5’, H-3”, H-4”, H-5”, H-5), 5.30 (s, 2H, NH$_2$), 3.75 (br s, 2H, CONCH$_2$), 3.38 (br s, 2H, CONCH$_2$), 1.82 – 1.37 (m, 6H, 3 x piperidine CH$_2$).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 169.8 (C=O), 166.4 (C=O), 165.3 (C-6), 163.6 (C-2), 138.0, 137.5, 137.0 (C-1’, C-3’, C-1'”), 130.5, 128.8, 128.8 (2C), 128.6, 128.0 (6 x Ar-C), 127.1 (C-2” and C-6”), 125.7 (C-2’), 104.2 (C-5), 48.8, 43.2 (2 x CONCH$_2$), 26.5, 25.6, 24.5 (3 x piperidine CH$_2$). IR $\tilde{v}$ max (cm$^{-1}$): 3389 – 3206 (NH$_2$); 2920 – 2850 (N-tertiary); 1612 (C=O); 1539; 1442; 1346; 1280; 803; 769 (Ar). HRMS-APCI m/z: 359.1849 found [M+H$^+$], [C$_{22}$H$_{23}$N$_4$O: 359.1866 calcd]. Purity (HPLC): 99%. *In no particular order; Ar-C = C-4’, C-5’, C-6’, C-3”, C-4”, C-5”.

4-(furan-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (39d)

The title compound was prepared from (2E)-1-(furan-2-yl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38d) in a yield of 9%: mp 178.2 – 178.3 °C (ethanol), dark brown crystals. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.12 – 8.07 (m, 2H, H-2′, H-6′), 7.59 (d, $J = 1.4$ Hz, 1H, H-5”), 7.54 – 7.46 (m, 2H, H-4’, H-5’), 7.42 (s, 1H, H-5), 7.19 (d, $J = 3.4$ Hz, 1H, H-3”), 6.56 (dd, $J = 3.4$, 1.7 Hz, 1H, H-4”), 5.27 (s, 2H, NH$_2$), 3.74 (br s, 2H, CONCH$_2$), 3.37 (br s, 2H, CONCH$_2$), 1.78 – 1.44 (m, 6H, 3 x piperidine CH$_2$). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 169.8 (C=O), 165.2 (C-6), 163.4 (C-2), 157.2 (C-4), 152.1 (C-2””), 144.6 (C-5”), 137.8, 137.0 (C-1’, C-3’), 128.8 (C-4’ or C-5’), 128.7 (C-4’ or C-5’), 127.9 (C-2’ or C-6’), 125.7 (C-2’ or C-6’), 112.3 (C-4”), 102.1 (C-5), 48.8, 43.2 (2 x CONCH$_2$), 26.5, 25.6, 24.5 (3 x piperidine CH$_2$). IR $\tilde{v}$ max (cm$^{-1}$): 3419 – 3219 (NH$_2$); 2933 – 2856 (N-tertiary); 1612 (C=O); 1560.5; 1449; 1245; 800; 738 (Ar). HRMS-APCI m/z: 348.1581 found [M$^+$], [C$_{20}$H$_{20}$N$_2$O$_2$: 348.1586 calcd]. Purity (HPLC): 94%.
4-(4-fluorophenyl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (39e)

The title compound was prepared from (2E)-1-(4-fluorophenyl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38e) in a yield of 11%: mp 141.9 – 142.3 °C (ethanol), light yellow to white crystals. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.13 – 8.03 (m, 4H, H-2′, H-6′, H-2″, H-6″), 7.55 – 7.47 (m, 2H, H-4′, H-5′), 7.42 (s, 1H, H-5), 7.21 – 7.13 (m, 2H, H-3″, H-5″), 5.24 (s, 2H, NH$_2$), 3.75 (s, 2H, CONCH$_2$), 3.38 (s, 2H, CONCH$_2$), 1.74 – 1.47 (m, 6H, 3 x piperidine CH$_2$). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 169.8 (C=O), 165.4 (C-2 or C-4 or C-6), 165.2 (C-2 or C-4 or C-6), 164.9 (d, $J_{C-F}$ = 251.7 Hz, C-4″), 163.5 (C-2 or C-4 or C-6), 138.0 (C-1′ or C-3′), 137.0 (C-1′ or C-3′), 133.6 (d, $J_{C-F}$ = 3.2 Hz, C-1″), 129.1 (d, $J_{C-F}$ = 8.8 Hz, C-2″ and C-6″), 128.8, 128.6 (C-4′ and C-5′), 128.0 (C-6″), 125.8 (C-2″), 115.8 (d, $J_{C-F}$ = 20.2 Hz, C-3″ and C-5″), 103.8 (C-5), 48.8, 43.2 (2 x CONCH$_2$), 26.6, 25.6, 24.5 (3 x piperidine CH$_2$). IR $\nu_{\text{max}}$ (cm$^{-1}$): 3061 – 2997 (NH$_2$); 2945 – 2857 (N-tertiary); 1667 (C=O); 1597; 1426; 1207; 1160; 1007 (C-F); 844; 810; 746 (Ar). HRMS-APCI $m/z$: 377.1773 found [M+H]$^+$, [C$_{22}$H$_{22}$FN$_4$O: 377.1772 calcd]. Purity (HPLC): 92%.

4-(5-methylthiophen-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (39f)

The title compound was prepared from (2E)-1-(5-methylthiophen-2-yl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38f) in a yield of 15%: mp 215.4 – 215.8 °C (ethanol), light orange-yellow crystals. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.09 – 8.02 (m, 2H, H-2′, H-6′), 7.58 (d, $J = 3.7$ Hz, 1H, H-3″), 7.53 – 7.43 (m, 2H, H-4′, H-5′), 7.28 (s, 1H, H-5), 6.80 (dd, $J = 3.6$, 1.3 Hz, 1H, H-4″), 5.23 (s, 2H, NH$_2$), 3.74 (s, 2H, CONCH$_2$), 3.36 (s, 2H, CONCH$_2$), 2.53 (br s, 3H, CH$_3$), 1.72 – 1.42 (m, 6H, 3 x piperidine CH$_2$ ). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 169.80
(C=O), 164.8 (C-6), 163.6 (C-2), 160.9 (C-4), 144.6 (C-5′), 140.2 (C-2″), 138.0 (C-1′ or C-3′), 136.9 (C-1′ or C-3′), 128.8 (C-4′ or C-5′), 128.5 (C-4′ or C-5′), 127.9 (C-6′), 127.4 (C-3″), 126.6 (C-4″), 125.6 (C-2′), 102.0 (C-5), 48.8, 43.2 (2 x CONCH₂), 26.5, 25.6, 24.5 (3 x piperidine CH₂), 15.8 (CH₃). IR νmax (cm⁻¹): 3369 – 3303 (NH₂); 3167 – 2851 (N-tertiary); 1618 (amide C=O); 1565; 1535; 1455; 1233; 790 (Ar). HRMS-APCI m/z: 378.1489 found [M]+, [C₂₁H₂₂N₄O₃]: 378.1509 calcd.

Purity (HPLC): 91%.

4-(1-benzofuran-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (39g)

The title compound was prepared from (2E)-3-(1-benzofuran-2-yl)-1-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (38g) in a yield of 19%: mp 184.7 – 185.0 °C (ethanol), light brown crystals. ¹H NMR (600 MHz, CDCl₃) δ 8.18 – 8.13 (m, 2H, H-2′, H-6′), 7.67 (d, J = 7.7 Hz, 1H, H-5″), 7.64 (s, 1H, H-5), 7.60 (d, J = 8.3 Hz, 1H, H-8″), 7.58 – 7.49 (m, 3H, H-3″, H-4′, H-5″), 7.39 (t, J = 7.7 Hz, 1H, H-7″ or H-6″), 7.28 (t, J = 7.5 Hz, 1H, H-7″ or H-6″), 5.34 (s, 2H, NH₂), 3.76 (br s, 2H, CONCH₂), 3.39 (br s, 2H, CONCH₂), 1.76 – 1.45 (m, 6H, 3 x piperidine CH₂). ¹³C NMR (151 MHz, CDCl₃) δ 169.8 (C=O), 165.5 (C-6), 163.4 (C-2), 157.4 (C-4), 155.5 (C-9″), 153.5 (C-2″), 137.7 (C-1′ or C-3′), 137.0 (C-1′ or C-3′), 128.8 (C-4′ and C-5′), 128.2 (C-4″), 128.0 (C-2′ or C-6″), 126.2 (C-7″ or C-6″), 125.8 (C-2′ or C-6″), 123.4 (C-7″ or C-6″), 122.1 (C-5″), 111.7 (C-8″), 107.7 (C-3″), 103.2 (C-5), 48.9, 43.2 (2 x CONCH₂), 26.6, 25.5, 24.5 (3 x piperidine CH₂). IR νmax (cm⁻¹): 3416 – 3209 (NH₂); 3055 – 2851 (N-tertiary); 1603 (C=O); 1501 (amine); 1445; 812; 743 (Ar). HRMS-APCI m/z: 398.1778 found [M]+, [C₂₄H₂₂N₄O₂]: 398.1767 calcd. Purity (HPLC): 99%.
4-[3-(4-ethylpiperazine-1-carbonyl)phenyl]-6-(5-methylthiophen-2-yl)pyrimidin-2-amine (39h)

The title compound was prepared from (2E)-3-[3-(4-ethylpiperazine-1-carbonyl)phenyl]-1-(5-methylthiophen-2-yl)prop-2-en-1-one (38h) in a yield of 16%: mp 191.0 – 191.8 °C (ethanol), light yellow crystals. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.10 – 8.04 (m, 2H, H-2′, H-6′), 7.54 – 7.46 (m, 2H, H-4′, H-5′), 7.28 (s, 1H, H-5), 6.80 (dd, \(J = 3.7, 1.3\) Hz, 1H, H-4″), 5.23 (s, 2H, NH\(_2\)), 3.84 (s, 2H, CONCH\(_2\)), 3.48 (s, 2H, CONCH\(_2\)), 2.57 – 2.37 (m, 9H, thiophene CH\(_3\), NCH\(_2\)CH\(_3\), 2 x CH\(_2\)NCH\(_2\)CH\(_3\)), 1.09 (t, \(J = 7.2\) Hz, 3H, CH\(_2\)CH\(_3\)). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 169.8 (C=O), 164.7 (C-6), 163.3 (C-2), 160.9 (C-4), 144.6 (C-5′), 140.2 (C-2″), 138.1 (C-1′ or C-3′), 136.2 (C-1′ or C-3′), 128.8 (C-4′ or C-5′), 128.7 (C-4′ or C-5′), 128.2 (C-6′), 127.4 (C-3″), 126.6 (C-4″), 125.9 (C-2″), 102.0 (C-5), 53.1 (CH\(_2\)NCH\(_2\)CH\(_3\)), 52.4 (CH\(_2\)NCH\(_2\)CH\(_3\)), 52.2 (CH\(_2\)CH\(_3\)), 47.8 (CONCH\(_2\)), 42.1 (CONCH\(_2\)), 15.8 (thiophene CH\(_3\)), 11.9 (CH\(_2\)CH\(_3\)). IR \(v_{\text{max}}\) (cm\(^{-1}\)): 3388 – 3180 (NH\(_2\)); 2971 – 2804; (N-tertiary); 1624 (C=O); 1565; 1531; 1439; 1242; 1012; 805 (Ar). HRMS-APCI \(m/z\): 408.1832 found [M+H]\(^{+}\), [C\(_{22}\)H\(_{26}\)N\(_5\)OS: 408.1853 calcd]. Purity (HPLC): 96%.

4-(5-methylthiophen-2-yl)-6-[3-(morpholine-4-carbonyl)phenyl]pyrimidin-2-amine (39i)

The title compound was prepared from (2E)-1-(5-methylthiophen-2-yl)-3-[3-(morpholine-4-carbonyl)phenyl]prop-2-en-1-one (38i) in a yield of 24%: mp 212.0 – 212.2 °C (ethanol), red crystals. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.12 – 8.06 (m, 2H, H-2′ and H-6′), 7.58 (d, \(J = 3.6\) Hz, 1H, H-3″), 7.55 – 7.47 (m, 2H, H-4′, H-5′), 7.28 (s, 1H, H-5), 6.81 (dd, \(J = 3.5, 1.4\) Hz, 1H, H-4″), 5.20 (s, 2H, NH\(_2\)), 3.89 – 3.44 (m, 8H, morpholine CH\(_2\)), 2.54 (s, 3H, CH\(_3\)). \(^{13}\)C NMR
The title compound was prepared from \((2E)-1-(5\text{-methylthiophen}-2\text{-yl})-3-[3-(\text{pyrrolidine-1-carbonyl})\text{phenyl}]\text{prop-2-en-1-one (38j)}\) in a yield of 21%: mp 254.6 – 254.7 °C (ethanol), cream coloured crystals. \(^1\text{H NMR (600 MHz, DMSO-}d_6\text{)} \delta 8.31 \text{(br s, 1H, H-2′), 8.26 \text{(br d, } J = 7.9 \text{ Hz, 1H, H-6′), 7.96 \text{(d, } J = 3.6 \text{ Hz, 1H, H-3′), 7.68 \text{(s, 1H, H-5), 7.62 \text{(br d, } J = 7.5 \text{ Hz, 1H, H-4′), 7.57 \text{(t, } J = 7.6 \text{ Hz, 1H, H-5′), 6.92 \text{(d, } J = 3.6 \text{ Hz, 1H, H-4′), 6.72 \text{(s, 2H, NH}_2\text{)}, 3.58 – 3.19 \text{(m, 4H, CONCH}_2\text{), 1.93 – 1.78 \text{(m, 4H, CH}_2\text{CH}_2\text{CH}_2\text{)}}\text{.} \ ^{13}\text{C NMR (151 MHz, DMSO-}d_6\text{)} \delta 168.0 \text{(C=O), 163.6 \text{(C-2 or C-6), 163.4 \text{(C-2 or C-6), 160.4 \text{(C-4), 143.8 \text{(C-5′), 140.6 \text{(C-2′), 137.8 \text{(C-1′ or C-3′), 137.2 \text{(C-1′ or C-3′), 128.7, 128.6, 128.5 \text{(C-4′, C-5′, C-3″), 127.9 \text{(C-6′), 127.0 \text{(C-4”), 125.4 \text{(C-2”), 99.8 \text{(C-5), 49.0, 45.9 \text{(2 x CONCH}_2\text{), 26.0, 24.0 \text{(2 x CH}_2\text{CH}_2\text{CH}_2\text{)), 15.4 \text{ (CH}_3\text{).) IR } v_{\text{max}} \text{(cm}^{-1}\text{): 3340 – 3169 \text{(NH}_2\text{); 2877 \text{(N-tertiary); 1642 \text{(C=O); 1565; 1551; 1446; 892; 791 \text{(Ar). HRMS-APCI } m/z: 380.1290 \text{ found } [M^+]^+, [C_{20}H_{20}N_4O_2S: 380.1301 \text{ calcd]. Purity (HPLC): 94}.% \text{.* In no particular order.}}\text{.} \end{quote}

\[4-(5\text{-methylthiophen-2-yl})-6-[3-(\text{pyrrolidine-1-carbonyl})\text{phenyl}]\text{pyrimidin-2-amine (39j)}\]
The title compound was prepared from (2E)-1-(5-bromofuran-2-yl)-3-[3-(4-ethylpiperazine-1-carbonyl)phenyl]prop-2-en-1-one (38k) in a yield of 10%: mp 177.3 – 178.0 °C (ethanol), dark brown crystals. \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 8.10 (m, 2H, H-2', H-6'), 7.59 (d, \(J = 1.7\) Hz, 1H, H-5''), 7.55 – 7.45 (m, 2H, H-5', H-4'), 7.41 (s, 1H, H-5), 7.19 (d, \(J = 3.4\) Hz, 1H, H-3''), 6.56 (dd, \(J = 3.4, 1.7\) Hz, 1H, H-4''), 5.31 (s, 2H, NH\(_2\)), 3.84 (s, 2H, CONCH\(_2\)), 3.48 (s, 2H, CONCH\(_2\)), 2.54 (s, 2H, CH\(_3\)NCH\(_2\)CH\(_3\)), 2.48 – 2.37 (m, 4H, CH\(_2\)CH\(_3\), CH\(_2\)NCH\(_2\)CH\(_3\)), 1.09 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) δ 169.7 (C=O), 165.0 (C-6), 163.3 (C-2), 157.2 (C-4), 152.0 (C-2''), 144.6 (C-5''), 137.9 (C-1' or C-3'), 136.3 (C-1' or C-3'), 128.9, 128.8, 128.2 (C-4', C-5', C-6''), 125.9 (C-2''), 112.3 (C-4''), 111.8 (C-3'''), 102.0 (C-5), 53.1, 52.4 (2 x CH\(_2\)NCH\(_2\)CH\(_3\)), 52.2 (CH\(_3\)CH\(_3\)), 47.7 (CONCH\(_2\)), 42.1 (2 x CONCH\(_2\)), 11.9 (CH\(_3\)). IR \(v_{\text{max}}\) (cm\(^{-1}\)): 3303 – 3188 (NH\(_2\)); 2605 – 2753 (N-tertiary); 1624 (C=O); 1559.62 (NH); 1430; 1012; 724 (Ar). HRMS-APCI \(m/z\): found 378.1903 [M+H]\(^+\), [C\(_{21}\)H\(_{24}\)N\(_5\)O\(_2\): 378.1898 calcd].

Purity (HPLC): 94%.* In no particular order.

4-[2-amino-6-(5-methylfuran-2-yl)pyrimidin-4-yl]-N-(1,3-benzothiazol-2-yl)benzamide (39l)

The title compound was prepared from \(N\)-(1,3-benzothiazol-2-yl)-4-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzamide (38l) in a yield of 10%: mp 289.2 – 289.5 °C, yellow solid. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) δ 12.99 (s, 1H, NH), 8.34 – 8.25 (m, 4H, H-2', H-6', H-3', H-5'), 8.03 (d, \(J = 7.9\) Hz, 1H, H-4* or H-7*), 7.80 (d, \(J = 8.1\) Hz, 1H, H-4* or H-7*), 7.54 – 7.44 (m, 2H, H-5, H-5* or H-6*), 7.35 (t, \(J = 7.6\) Hz, 1H, H-5* or H-6*), 7.26 (d, \(J = 3.3\) Hz, 1H, H-3''), 6.80 (s, 2H, NH\(_2\)), 6.34 (d, \(J = 3.5\) Hz, 1H, H-4''), 2.41 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) δ 165.7 (C=O), 163.8 (C-2 or C-6), 163.0 (C-2 or C-6), 158.6 (C-2*), 156.8 (C-4), 154.7 (C-5''), 150.3 (C-2''), 148.2 (C-4a* or C-7a*), 141.0 (C-1'), 133.2 (C-4'), 131.0 (C-4a* or C-7a*), 128.7, 126.8 (4C, C-2', C-6', C-3', C-5'), 126.2 (C-5* or C-6*), 123.7 (C-5* or C-6*), 121.7 (C-4* or C-7*), 120.4 (C-4* or C-7*), 113.5 (C-3''), 108.9 (C-4''), 100.0 (C-5), 13.6 (CH\(_3\)). IR \(v_{\text{max}}\) (cm\(^{-1}\)): 3328 (NH\(_2\)); 3175 (N-tertiary); 1648 (C=O); 1561; 1510; 1451; 1278;
HRMS-APCI $m/z$: found 428.1176 [$M+H]^+$, [C$_{23}$H$_{18}$N$_5$O$_2$S: 428.1181 calcd]. **Purity** (HPLC): 81%.

3-[2-amino-6-(5-methylfuran-2-yl)pyrimidin-4-yl]-N-(1,3-benzothiazol-2-yl)benzamide (39m)

![Chemical Structure]

The title compound was prepared from N-(1,3-benzothiazol-2-yl)-3-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzamide (38m) in a yield of 16%: mp 242.3 – 242.0 °C, cream solid. **$^1$H NMR** (500 MHz, DMSO-$_d_6$) $\delta$ 13.04 (s, 1H, NH), 8.86 (br s, 1H, H-2′), 8.41 (d, $J = 7.8$ Hz, 1H, H-6′), 8.25 (br d, $J = 7.8$ Hz, 1H, H-4′), 8.04 (d, $J = 7.9$ Hz, 1H, H-4* or H-7*), 7.81 (d, $J = 8.1$ Hz, 1H, H-4* or H-7*), 7.72 (t, $J = 7.8$ Hz, 1H, H-5′), 7.55 (s, 1H, H-5), 7.49 (ddd, $J = 8.3$, 7.2, 1.3 Hz, 1H, H-5* or H-6*), 7.36 (td, $J = 7.6$, 1.2 Hz, 1H, H-5* or H-6*), 7.23 (d, $J = 3.3$ Hz, 1H, H-3″), 6.79 (s, 2H, NH$_2$), 6.36 (dd, $J = 3.3$, 1.2 Hz, 1H, H-4″), 2.43 (s, 3H, CH$_3$). **$^{13}$C NMR** (125 MHz, DMSO-$_d_6$) $\delta$ 165.7 (C=O), 163.8 (C-2 or C-6), 163.4 (C-2 or C-6), 158.8 (C-2*), 156.7 (C-4), 154.7 (C-5″), 150.4 (C-2″), 148.6 (C-4a* or C-7a*), 137.6 (C-1′), 132.3 (C-4a* or C-7a*), 131.6 (C-3′), 130.9 (C-6′), 130.1 (C-4′), 129.0 (C-5′), 126.7 (C-2′), 126.2 (C-5* or C-6*), 123.7 (C-5* or C-6*), 121.7 (C-4* or C-7*), 120.6 (C-4* or C-7*), 113.1 (C-3″), 108.9 (C-4″), 99.6 (C-5), 13.6 (CH$_3$). **IR** $\nu_{max}$ (cm$^{-1}$): 3504 (NH$_2$); 3123 (N-tertiary); 1602 (C=O); 1523; 1443; 1276; 1229 (Ar). **HRMS-APCI** $m/z$: found 428.1166 [$M+H]^+$, [C$_{23}$H$_{18}$N$_5$O$_2$S: 428.1176 calcd]. **Purity** (HPLC): 96%.
3-[2-amino-6-(5-methylfuran-2-yl)pyrimidin-4-yl]-N-6-chloro-1,3-benzothiazol-2-yl]benzamide (39n)

The title compound was prepared from \( N\)-(6-chloro-1,3-benzothiazol-2-yl)-3-\[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl\]benzamide (38n) in a yield of 29\%: mp 118.1 – 118.5 °C, cream solid. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 13.13 (s, 1H, NH), 8.85 (s, 1H, H-2′), 8.41 (d, \( J = 7.9 \) Hz, 1H, H-6′), 8.24 (d, \( J = 7.9 \) Hz, 1H, H-4′), 8.18 (d, \( J = 2.6 \) Hz, 1H, H-7*), 7.80 (d, \( J = 8.6 \) Hz, 2H, H-4*), 7.72 (s, 1H, H-5′), 7.54 (s, 1H, H-5), 7.50 (br d, \( J = 6.8 \) Hz, 1H, H-5*), 7.23 (d, \( J = 3.3 \) Hz, 1H, H-3″), 6.79 (s, 2H, NH₂), 6.35 (d, \( J = 3.6 \) Hz, 1H, H-4″), 2.42 (s, 3H, CH₃).

\(^1\)C NMR (125 MHz, DMSO-\(d_6\)) \( \delta \) 166.0 (C=O), 163.8 (C-2 or C-6), 163.4 (C-2 or C-6), 159.7 (C-2*), 156.7 (C-4), 154.7 (C-5′), 150.4 (C-2″), 147.3 (C-4a* or C-7a*), 137.6 (C-1′), 133.2 (C-3′ or C-4a* or C-7a*), 132.3 (C-3′ or C-4a* or C-7a*), 131.0 (C-6′), 130.2 (C-4′), 129.1 (C-5′), 127.7 (C-6*), 126.7 (C-2′ or C-5′), 126.5 (C-2′ or C-5*), 121.6 (C-4* or C-7*), 121.4 (C-4* or C-7*), 113.1 (C-3′), 108.9 (C-4″), 99.6 (C-5), 13.6 (CH₃). IR \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3172 – 3104 (NH₂); 2923 – 2852 (N-tertiary); 1681; 1655 (C=O); 1595 ;1556; 1510; 1444; 1370; 1299; 1068; 818 (Ar); 792 (C-Cl). HRMS-APCI \( m/z \): found 462.0756 \([M+H]^+\), \([C_{23}H_{17}ClN_5O_2S] \): 462.0752 calcd. Purity (HPLC): 72\%.