CHAPTER 3

Design and synthesis of 4,6-disubstituted 2-aminopyrimidines and chalcones

3.1. Design of compounds

The first objective of this study was to select potential adenosine A_{2A} antagonists for synthesis that would fit literature pharmacophore models, and at the same time, incorporate structural features associated with activity, selectivity and without potential metabolic liabilities (see section 2.5.2.5 and 1.3). The 2-aminopyrimidine scaffold (**17**) was thus selected as it has the required H-bond donor acceptor motif and heterocyclic aromatic ring (Figure 3.1).

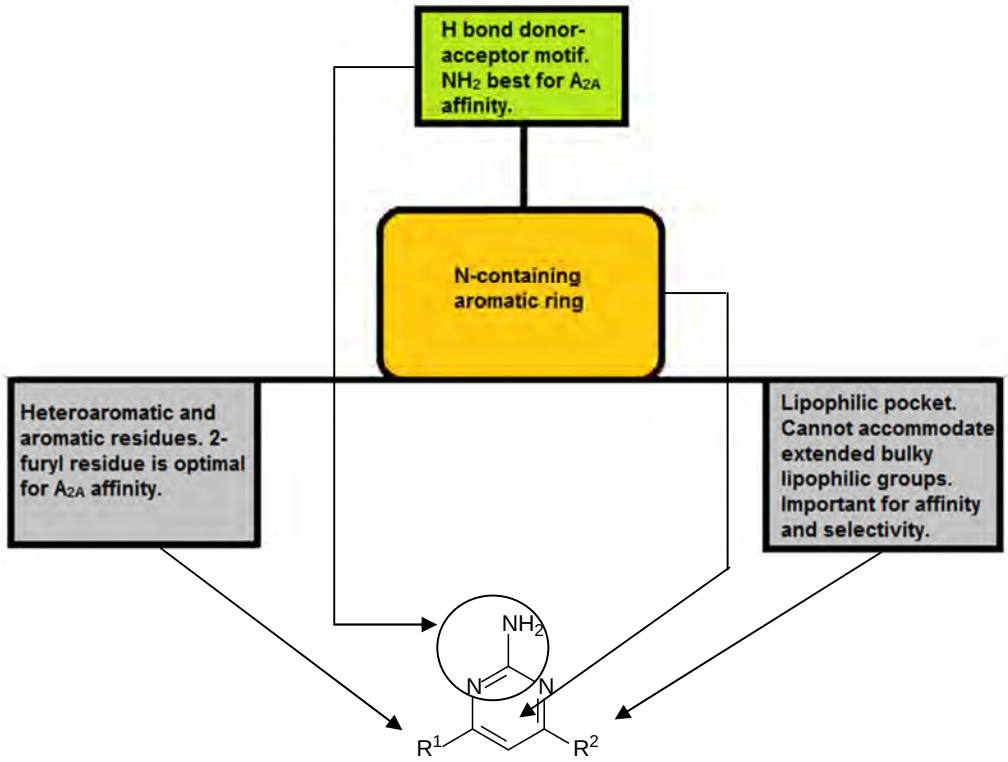
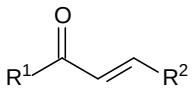
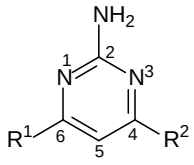
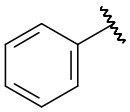
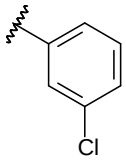
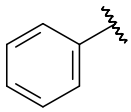
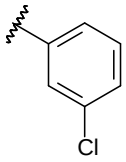
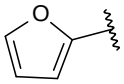
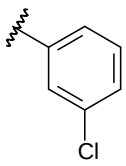
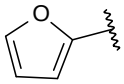
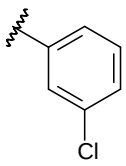
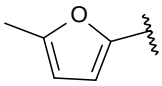
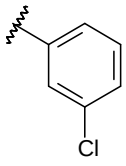
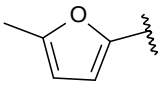
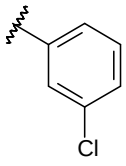
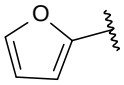
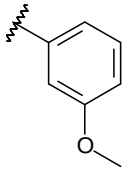
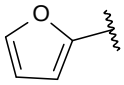
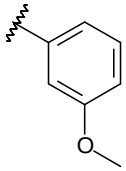
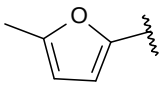
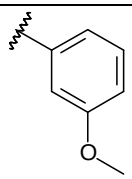
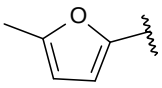
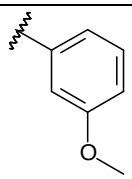


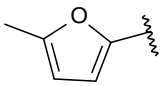
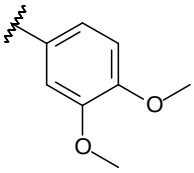
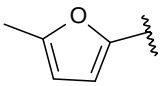
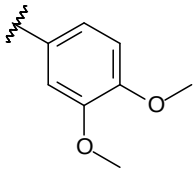
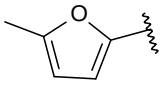
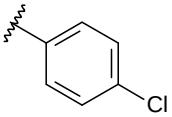
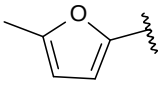
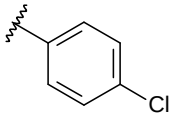
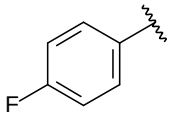
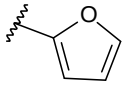
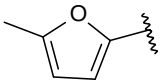
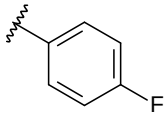
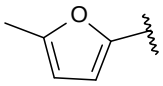
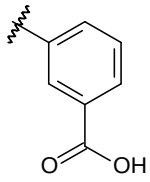
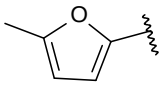
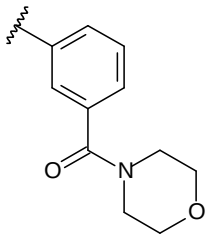
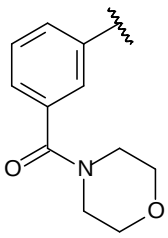
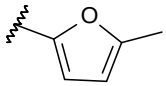
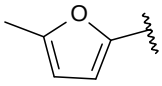
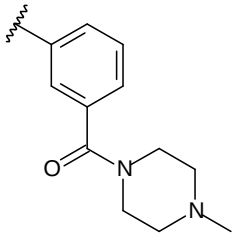
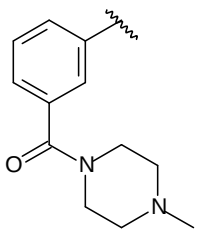
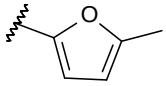
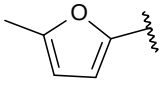
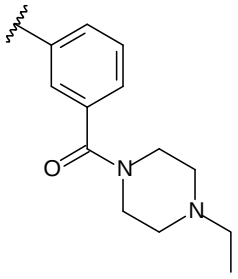
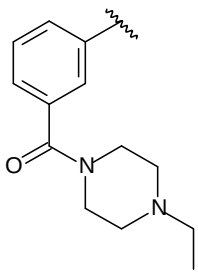
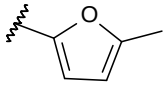
Figure 3.1: The 2-aminopyrimidine scaffold containing important features as indicated by literature pharmacophores (Mantri *et al.,* 2008; Borroni *et al.,* 2005).

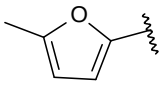
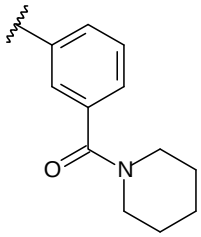
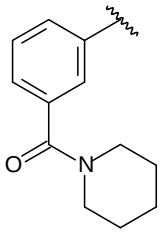
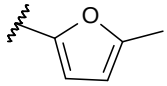
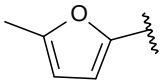
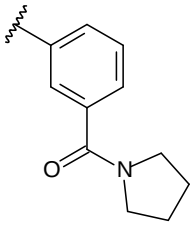
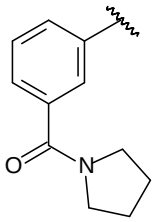
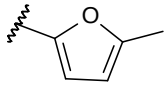
As previously discussed, the furan moiety is often associated with adenosine A_{2A} affinity, and it was therefore decided that one of the substituents should be a furan or substituted furan (substitution of the furan ring results in improved metabolic stability). Lastly, a substituted phenyl

was selected as the other lipophilic moiety (Figure 3.1). Several 2-aminopyrimidines with these features (Table 3.1) were thus designed.

Table 3.1 Structures of proposed 2-aminopyrimidines and their chalcone intermediates

No.	Chalcone intermediate		No.	4,6-Disubstituted 2-aminopyrimidine	
					
	R^1	**R^2**		**R^1**	**R^2**
1a			**2a**		
1b			**2b**		
1c			**2c**		
1d			**2d**		
1e			**2e**		

1f			**2f**		
1g			**2g**		
1h			**2h**		
1i					
1j			**2j**		
1k			**2k**		
1l			**2l**		

1m			**2m**		
1n			**2n**		

To verify whether furan substitution (e.g. compounds **2b**, **2c**) did indeed result in improved binding affinity over phenyl substitution, compound **2a**, with a 6-phenyl substituent was included in this study. The following substitutions on the phenyl ring were explored to investigate their effect on activity: For compounds **2a** – **2h**, various electron withdrawing and electron donating substituents were included. The phenylamide substituent, as present in compounds **2j** to **2n**, was selected as a larger alternative (this type of substituent were previously included in structurally similar arylindenopyrimidines with activity) and in some instances (e.g. **2k** and **2l**), the effect of the additional nitrogen, as present in the piperazine ring, could be explored.

These structures were then docked into the crystal structure of the adenosine A_{2A} receptor to further investigate the feasibility of these compounds as antagonists of this receptor.

3.1.1 Molecular modelling

3.1.1.1 Introduction

Molecular modelling is a computational tool which can be used for numerous applications, for example, the design of novel compounds for a specific receptor target, to investigate important interactions between the ligand and active site, or to gain additional insight into the binding modes of inhibitors to an active site.

3.1.1.2 Method

Molecular docking studies were carried out in Windows based Accelrys® Discovery Studio (DS 3.1). The crystal structure of the adenosine A_{2A} receptor [Protein Data Bank (PDB) code 3EML],

co-crystalised with the known A_{2A} antagonist ZM 241385 was used for molecular modelling studies. This receptor was prepared with the 'Clean protein' function to correct problems such as incomplete amino acid side chains and typed with the CHARMm force field. A fixed atom constraint was applied to the backbone and a minimisation was then carried out using the Generalised Born approximation with Molecular Volume (GBMV) as the solvent model to obtain a receptor at energetic minimum. A binding sphere with a radius of 5 Å was defined using the existing ligand (ZM 241385) before it was removed from the receptor. Selected inhibitors were drawn in Discovery Studio and prepared for docking with the 'Prepare ligand' protocol to correct valences and remove duplicates whereafter ligands were visually inspected and remaining errors removed. All waters of crystallization were removed. ZM 241385 was then docked (allowing a maximum of ten conformers) to ensure docking validity using the CDOCKER protocol (MMFF used as ligand partial charge method). The same protocol was used for the docking of ligands. Orientation, CDOCKER and C-DOCKER_INTERACTION energies of the ten different conformers of each ligand were considered and the best conformation for each ligand selected. An *in situ* ligand minimisation was then performed on the selected conformers.

3.1.1.3 Results and Discussion

To ensure docking validity, ZM 241385 was docked into the active site and the root square mean deviation (RSMD) of 1.43 Å calculated for the most suitable pose of the ligand in the docking experiment and the ligand from the crystal structure (Figure 3.2). As the misalignment of the two structures was mostly due to of the flexible side chain, this result was considered acceptable.

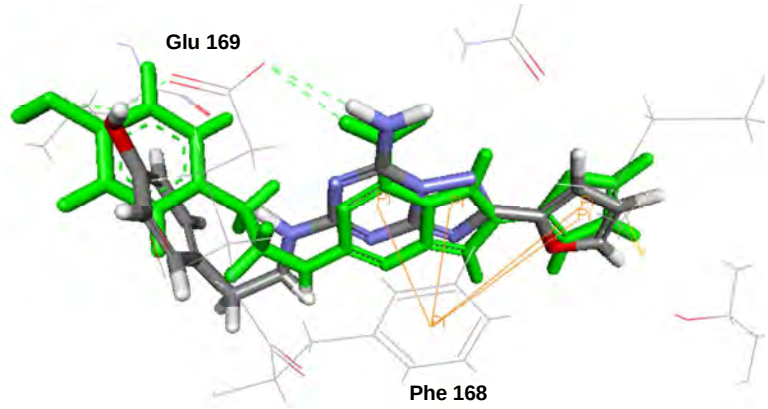


Figure 3.2: ZM 241385 from the original crystal structure (in green), superimposed on ZM 241385 docked within the active site of the prepared human A_{2A} receptor. Green lines: hydrogen bonding interactions; Orange lines: π stacking

All fifteen proposed 2-aminopyrimidines were then successfully docked, indicating that these compounds would fit into the active site. The orientation of the selected 2-aminopyrimidine conformers was similar to that of ZM 241385 with the exocyclic amino group in the direction of the amino acid residues Asn 253 and Glu 169, allowing hydrogen bonding between the amino group and at least one of these residues. Anchoring of the heterocyclic aminopyrimidine ring by an aromatic stacking interaction with Phe 168 was another important interaction, similar to that seen for the bicyclic triazolotriazine core of ZM 241385. Additional interactions observed include π-π stacking of the furan and phenyl substituents with Phe 168 (Figure 3.3). The furan or methylfuran substituent of the selected pose of all compounds was ~3 Å away from the highly conserved Trp 246 (Figure 3.3) which is an important residue in receptor activation as discussed in chapter 2 (paragraph 2.5.2.4).

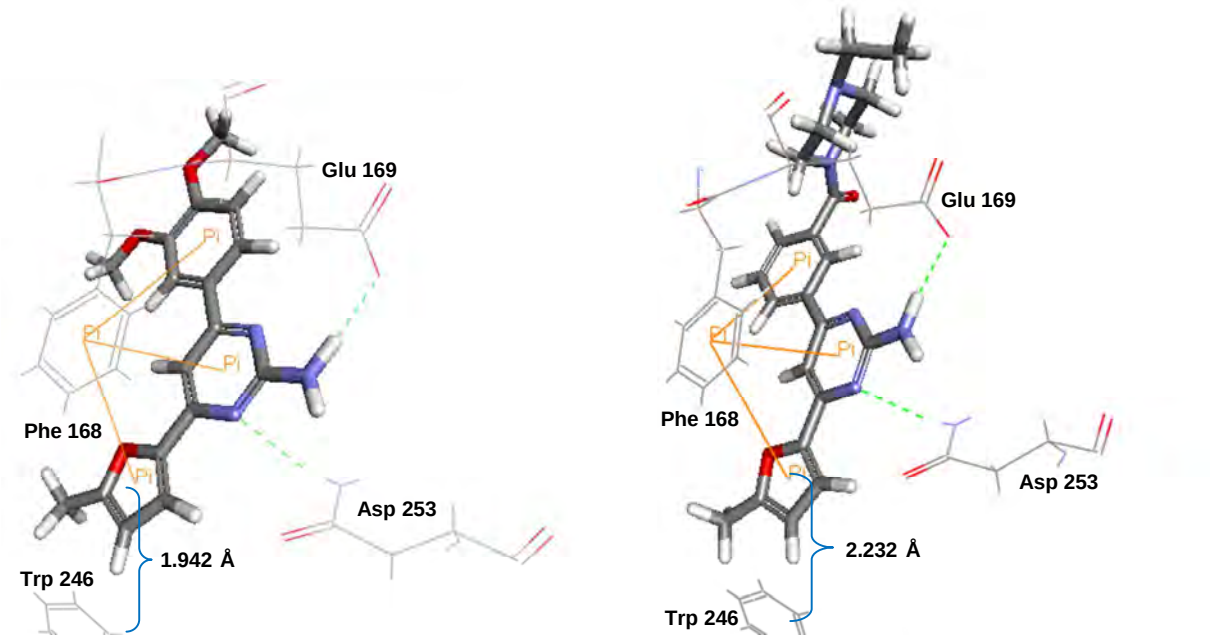


Figure 3.3: Compound **2f** (A) and Compound **2l** (B) docked within adenosine A_{2A} receptor. The model used was without water of crystallisation. Green lines: hydrogen bonding interactions; Orange lines: π stacking.

Since docked compounds had similar interactions with the adenosine A_{2A} receptor as ZM 241385, it was concluded that it was indeed feasible to screen these 2-aminopyrimidines as antagonists of the adenosine A_{2A} receptor.

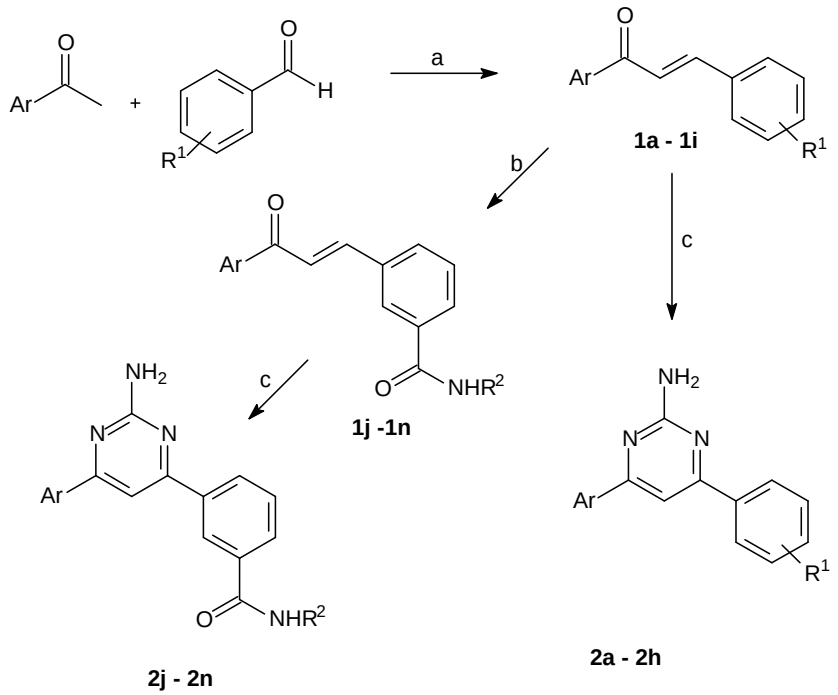
3.2 Chalcone intermediates

Since the monoamine oxidase inhibitory activity of chalcones have been reported (Chimenti *et al.,* 2009), it was decided that selected chalcones that would be obtained as intermediates during the synthesis of the 2-aminopyrimidines (Table 3.1) would be screened as inhibitors of monoamine oxidase.

3.3 Chemistry

2-Aminopyrimidines are classically prepared by the reaction of substituted chalcones with guanidine under basic conditions, e.g. NaOH in ethanol (Thanh & Mai, 2009). However, under these particular conditions, a complicated mixture of products was obtained, and in this study, the 4,6-disubstituted 2-aminopyrimidines were thus prepared by reacting substituted chalcones and guanidine hydrochloride in the presence of sodium hydride (Sharma *et al.,* 2009). The intermediate chalcones were obtained by a Claisen-Schmidt condensation between commercially available ketones and aldehydes under basic conditions (Cocconcelli *et al*., 2008). For the phenylamide derivatives (compounds **2j** – **2n**) the Claisen-Schmidt condensation reaction was followed by an amide coupling reaction where various amines were coupled to the acid group in the presence of 1,1'-carbonyldiimidazole (CDI) (Maignan *et al.,* 1989) before aminopyrimidine formation (Scheme 3.1).

The general synthetic approach followed for the synthesis of the 2-aminopyrimidines is illustrated in Scheme 3.1.



Scheme 3.1: Synthesis of 4,6-disubstituted 2-aminopyrimidines. Reagents and conditions: (a) NaOH, EtOH/MeOH, rt, 3 h; (b) CDI, CH_2Cl_2, NHR^2, rt, 5 h; (c) Guanidine hydrochloride, NaH, DMF, 110 °C, 24 h. Ar = Phenyl, furan or 5-methylfuran.

3.3.1 Materials and instrumentation

Chemicals were purchased from Sigma-Aldrich, and used without further purification. Solvents for reactions and chromatography were obtained from Rochelle, while deuterated solvents for nuclear magnetic resonance (NMR) spectroscopy were purchased from Merck.

Thin layer chromatography (TLC):

Reactions were routinely monitored on TLC using precoated Kieselgel 60 F254 plates (Merck) and detection done by UV at a wavelength of 254 nm. The mobile phase used for detection of aminopyrimidines (**2a** - **2h)**, as well as their chalcone intermediates (**1a** - **1h**) was ethyl acetate: petroleum ether (1:4). For the phenylamide derivatives (**2j** - **2n**) and their chalcone intermediates (**1i** - **1n**) a mobile phase of dichloromethane: methanol (9:1) was used.

Melting points:

All melting points were determined using a Buchi B-545 apparatus, and are uncorrected.

Mass spectrometry (MS):

Most of the compounds were sent to the University of the Witwatersrand for analysis. These samples were run on a dual focusing DFS magnetic sector mass spectrometer in EI+ mode. Samples were introduced via a heated direct insertion probe. The source was operated at 150 ℃ and electron energy was set to 70 eV. The mass spectrum for compound **1n** was obtained with a Bruker micrOTOF-QII mass spectrometer in atmospheric-pressure chemical ionisation (APCI) mode.

Nuclear magnetic resonance (NMR) spectroscopy:

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker Avance III 600 spectrometer at frequencies of 600 MHz and 150 MHz, respectively. Samples were dissolved in either deuterochloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-*d6*). Data obtained were processed and analysed with MestReNova2. ^{1}H NMR data is reported indicating the chemical shift (δ) in ppm, the integration (e.g. 1H), the multiplicity and the coupling constant (J) in Hz. The following abbreviations are used: 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/quintet) or m (multiplet). Chemical shifts are referenced to the residual solvent signal ($CDCl_3$ 7.26 and 77.0 ppm for ^{1}H and ^{13}C respectively; DMSO-*d*6: 2.5 and 39.5 ppm for ^{1}H and ^{13}C, respectively).

High performance liquid chromatography (HPLC):

HPLC analyses were conducted with an Agilent 1100 HPLC system equipped with a quaternary pump and an Agilent 1100 series diode array detector to determine the purity of the synthesized compounds. HPLC grade acetonitrile (Merck) and Milli-Q water (Millipore) was used for the chromatography. A Venusil XBP C18 column (4.60 × 150 mm, 5 µm) was used with 30% acetonitrile and 70% MilliQ water as the initial mobile phase at a flow rate of 1 ml/min. A solvent gradient program was initiated at the start of each HPLC run, the concentration of acetonitrile in the mobile phase was linearly increased up to 85% over a period of 5 min. Each HPLC run lasted 15 min and a time period of 5 min was allowed for equilibration between runs. The test compound was injected (20 µl, 1 mM) into the HPLC system and the eluent was monitored at wavelengths of 210, 254 and 300 nm.

3.3.2 Synthetic procedures

*General procedure for the synthesis of chalcones (***1a** – **1h***)*

Ketone (8.57 mmol, 1 equiv) and benzaldehyde (8.57 mmol, 1 equiv) was dissolved in ethanol, and stirred at room temperature. To this mixture, a solution of 40% (w/v) sodium hydroxide (0.5 equiv) was added dropwise. After the reaction mixture was stirred at room temperature for 3 hours, the residue that formed was filtered and washed with cold ethanol. The resulting solid was recrystalised from ethanol (Cocconcelli *et al*., 2008).

Procedure for the synthesis of 3-[(1E)-3-(5-methylfuran-2-yl)-3-oxoprop-1-en-1-yl]benzoic acid (**1i**)

A solution of 4% (w/v) sodium hydroxide (34.4 mmol, 2 equiv) was added to a suspension of 3-formylbenzoic acid (**1i**) (17.2 mmol 1 equiv) and an acetophenone derivative (17.2 mmol, 1 equiv) in methanol (100 ml). The mixture was stirred at room temperature for 24 h and acidified with concentrated hydrochloric acid to a pH of 1-2. The precipitate that formed was filtered, rinsed with water and recrystalised with methanol (Raeppel *et al*., 2007).

General procedure for the synthesis of chalcones (**1j** – **1n**)

1,1'-Carbonyldiimidazole (7.00 mmol, 1.2 equiv) was added to a suspension of the acid (5.83 mmol, 1 equiv) in dichloromethane (70 ml). After the reaction mixture was stirred under nitrogen at room temperature for 2 h, the amine (7.00 mmol, 1.2 equiv) was added. The mixture was then stirred for a further 3 h. The reaction was quenched by the addition of brine and extraction of the aqueous phase was done with dichloromethane (2×20ml). The combined organic fractions were washed once with saturated sodium hydrogen carbonate and twice with brine. The organic fraction was concentrated (*in vacuo*), purified with column chromatography (dichloromethane: methanol (98:2) and recrystalised from methanol.

General procedure for the synthesis of 2-aminopyrimidines

Guanidine hydrochloride (4.61 mmol, 1.5 equiv) was dissolved in a small amount of DMF (15 ml), and chalcone (3.07 mmol, 1 equiv) and sodium hydride (9.22 mmol, 3 equiv) were added while stirring. The reaction mixture was heated (110 ˚C) for 24 h under nitrogen, allowed to cool down and then diluted with equal volumes of ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (twice) and the organic layers combined. All traces of DMF were removed by washing the combined organic layers with water (4 times). The organic layer was

concentrated *in vacuo* and the crude product was purified with column chromatography [petroleum ether: ethyl acetate (4:1)] and recrystalised with ethanol.

3.3.3 Results and Discussion

Characterisation of compounds was primarily done by NMR which involved the analysis of 1D (^{1}H, ^{13}C, DEPT) and 2D (HSQC, HMBC, COSY) spectra as well as the consideration of NMR data as reported for known compounds (eg. for compounds **1a**). Mass spectrometry was further used in conjunction with melting points as final confirmation of structures. The experimental values obtained in mass spectrometry experiments correlated well with the calculated values. For all of the synthesised compounds, except for compound **2n**, the difference between these two values are less than 5 ppm. The characterisation of a few compounds will be discussed below in more detail.

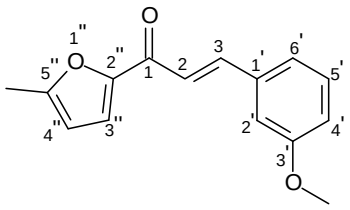
*Compound **1e**:*

The ^{13}C NMR spectrum of chalcone **1e** revealed the presence of 15 carbons. After examining the DEPT 90/135 in conjunction with the ^{13}C spectrum, eight methine, two methyl and five quaternary carbons were identified. Assignment of carbon signals were based on their chemical shifts, multiplicity and observed 2D correlations. The five quaternary carbons (δ_C 177.1, 159.5, 158.2, 152.4, 136.1), were assigned as C-1 (carbonyl carbon), C-3', C-2'', C-5'' and C-1' respectively. Important to note here is the correlation between C-2'' (δ_C 158.2) and the furan methyl group at (δ_H 14.1) which was used to distinguish between carbons 2'' and 5''. The correlation between C-3' (δ_C 159.5) and the OCH_3 (δ_H 3.83) was used *inter alia* in the assignment of this carbon. The signals of the double bond occur at δ_C 121.5 and δ_C 143.1, while the carbons of the aromatic ring are found between δ_C 113.4 and 129.8. The signals at δ_C 119.6 and 109.3 were further assigned to C-3'' and C-4'' of the furan ring, while the methoxy carbon is present at δ_C 55.3 and the furan methyl at δ_C 14.1 (Table 3.2).

The ^{1}H NMR spectrum showed signals for 14 protons comprising of signals of the double bond, the furan and the phenyl moieties as well as the methyl groups. Protons were assigned using chemical shifts, integration, multiplicities and coupling constants as well as observed COSY, HSQC and HMBC correlations (Table 3.2). For example, the doublets at δ_H 7.79 and δ_H 7.35 were assigned as H-3 and H-2 respectively, with the coupling constant of 16.1 Hz being indicative of a trans-double bond (Pavia *et al.,* 2009). The four aromatic signals at δ_H 7.31 (br t, 8.0 Hz, H-5'), 7.22 (br d, *J* = 7.7 Hz, H-6'), 7.13 (br s, H-2'), 6.94 (dd, *J* = 2.6, 8.2 Hz, H-4'),

confirm the presence of a 1,3-disubstituted aromatic ring. The protons at δ_H 7.24 and δ_H 6.20 were assigned as H-3" and H-4" of the furan ring, while the methyl groups occur at δ_H 3.83 (methoxy) and δ_H 2.43 (furan methyl) (Table 3.2). The molecular formula of $C_{15}H_{14}O_3$ was further confirmed with high-resolution mass spectrometry (m/z 242.09396). ^1H and ^{13}C NMR assignments of chalcones (**1a** - **1h**) were all done in a similar manner and differences in the spectra were primarily observed in the signals of the phenyl ring, due to the presence of the electron donating or withdrawing substituent.

Table 3.2: NMR data and HMBC correlations of (2*E*)-3-(3-methoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1e**)

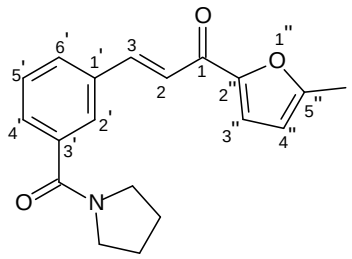


Atom no.	δ_H (multiplicity, *J* in Hz)	δ_C (Type)	HMBC (δ_H to δ_C)
1		177.1 (C)	
2	7.35 (d, 16.1)	121.5 (CH)	1', 6', 3, 1
3	7.79 (d, 16.1)	143.1 (CH)	1', 2', 2/6', 1
1'		136.1 (C)	
2'	7.13 (br s)	113.4 (CH)	3', 4', 2/6', 3
3'		159.8 (C)	
4'	6.94 (dd, 2.6, 8.2)	116.0 (CH)	2', 3', 2/6'
5'	7.31 (t, 8.0)	129.8 (CH)	1', 3', 4'
6'	7.22 (br d, 7.7)	121.0 (CH)	2', 4', 3
1''			
2''		152.4 (C)	
3''	7.24 (d, 1H, 3.5)	119.6 (CH)	2'', 4'', 5''
4''	6.20 (dd, 0.8, 3.4)	109.3 (CH)	2'', 3'', 5''
5''		158.2 (C)	
OCH_3	3.83 (s)	55.3 (CH_3)	3'
CH_3	2.43 (s)	14.1 (CH_3)	3'', 4'', 5''

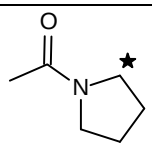
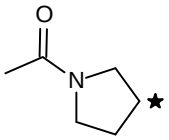
*Compound **1n**:*

The molecular formula for chalcone **1n** was established as $C_{19}H_{19}NO_3$ by high resolution mass spectrometry. The ^{13}C NMR spectrum revealed the presence of 19 carbons while concomitant inspection of the DEPT90/135 spectrum indicated the presence of one CH_3, four CH_2, eight CH and six quaternary carbons. The ^1H NMR spectrum showed signals for 19 protons. Shifts and assignments of protons and carbons of the chalcone scaffold of compound **1n** are very similar to that observed for compound **1e**. In addition to the signals associated with the chalcone scaffold, the CH_2 signals of the pyrrolidine ring appear as two characteristic pentets (δ_H 1.95 and 1.86) and triplets (δ_H 3.63 and 3.41) in the ^1H NMR spectrum. Carbon peaks associated with the pyrrolidine amide substituent include the amide carbonyl (δ_C 168.9) and the four CH_2 carbons (δ_C 49.5, 46.2, 26.3 and 24.3). After further analysis of the COSY, HSQC and HMBC spectra, the structure of compound **1n** was confirmed as (2*E*)-1-(5-methylfuran-2-yl)-3-[3-(pyrrolidine-1-carbonyl)phenyl]prop-2-en-1-one. NMR assignments of compounds **1i** - **1n** was all done in a similar manner with spectra largely differing in the signals associated with the carboxylic acid and phenylamide substituents.

Table 3.3: NMR data and HMBC correlations of (2*E*)-1-(5-methylfuran-2-yl)-3-[3-(pyrrolidine-1-carbonyl)phenyl]prop-2-en-1-one (**1n**)



Atom no.	δ_H (multiplicity, *J* in Hz)	δ_C (Type)	HMBC (δ_H to δ_C)
1		176.9 (C)	
2 and 5'	7.44 – 7.37 (m)	122.1 (CH)	1, 3, 1', 2', 3', 6'
3 and 2'	7.82 – 7.76 (m)	142.1 (CH)	1, 2, 3, 1', 2', 4'/5', 6', CON
1'		135.0 (C)	
2' and 3	7.82 – 7.76 (m)	126.6 (CH)	1, 2, 3, 2', 4'/5', 6', CON
3'		137.8 (C)	
4'	7.49 (br d, 7.7)	128.8 or 128.6 (CH)	2', 4'/5', 6', CON

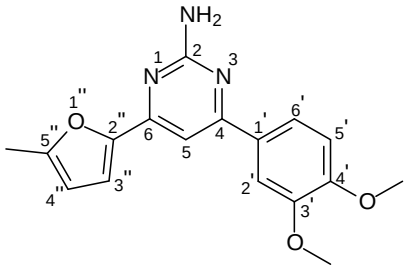
5' and 2	7.44 – 7.37 (m)	128.8 or 128.6 (CH)	1, 1', 2', 3', 6'
6'	7.62 (br d, 7.7)	129.9 (CH)	3, 2', 4'/5'
1''			
2''		152.3 (C)	
3''	7.24 (d, 3.5)	119.8 (CH)	2'', 4'', 5''
4''	6.2 (d, 3.5)	109.4 (CH)	2'', 3'', 5''
5''		158.3 (C)	
amide C=O		168.9 (C)	
CH_3	2.41 (s)	14.1 (CH_3)	3'', 4'', 5''
	3.63 (t, 7.1) 3.41 (t, 6.6)	49.5 (CH_2) 46.2 (CH_2)	$CH_2\underline{C}H_2CH_2$, $CON\underline{C}H_2$
	1.95 (p, 6.9) 1.86 (p, 6.7)	26.3 (CH_2) 24.3 (CH_2)	$CH_2\underline{C}H_2CH_2$, $CON\underline{C}H_2$

*Compound **2f**:*

In the ^{1}H NMR and ^{13}C NMR spectra of 2-aminopyrimidine (**2f**), 17 protons and carbons are present. Inspection of the ^{13}C NMR and DEPT 90/135 spectra established that there are eight quaternary, six CH and three CH_3 carbons. The carbon signals can be grouped as follows: δ_C 14.0 (furan methyl), δ_C 56.0 and 55.9 (2 x OMe), the very characteristic CH of the pyrimidine ring at δ_C 100.8 (C-5), δ_C 112.8 and 108.7 (CH carbons of the furan ring), δ_C 110.7 – 120.1 (aromatic CH carbons), δ_C 130.2 – 155.0 (furan and phenyl quaternary carbons) and δ_C 156.7 – 165.2 (quaternary pyrimidine carbons) (Table 3.3).

In the ^{1}H NMR spectrum the singlets at δ_H 7.29 (1H), 5.35 (2H), 3.98 (3H), 3.93 (3H) and 2.43 (3H) were assigned as H-5, the -NH_2, the two methoxy groups and the CH_3 of the furan ring, respectively. The signals of the aromatic ring occur between δ_H 6.93 – 7.68 while the signals at δ_H 6.15 and 7.08 were assigned as H-3'' and H-4'' of the furan ring. These assignments were made as previously indicated (analysis of 1D and 2D spectra) (Table 3.4). Compound **2f** further has a molecular formula of ($C_{17}H_{17}N_3O_3$) as deduced from the molecular ion peak at (m/z 311.1262) in the high resolution mass spectrum. Assignment of compounds **2a** - **2h** was done in a similar manner.

Table 3.4: NMR data and HMBC correlations of 4-(3,4-dimethoxyphenyl)-6-(5-methylfuran-2-yl)pyrimidin-2-amine (**2f**):



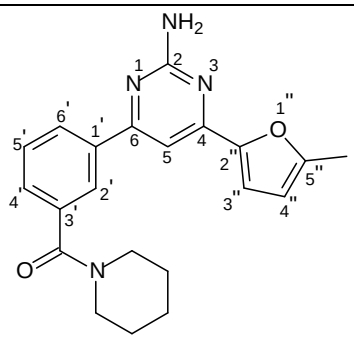
Atom no.	δ_H (multiplicity, *J* in Hz)	δ_C (Type)	HMBC (δ_H to δ_C)
1			
2		163.3 (C)	
3			
4		165.2 (C)	
5	7.29 (s)	100.8 (CH)	4, 6, 1', 3'/4'/2''
6		156.7 (C)	
1'		130.2 (C)	
2'	7.68 (d, 2.0)	109.8 (CH)	4,1', 3'/4'/2'', 6'
3'		151.1 or 150.6 or 149.0 (C)	
4'		151.1 or 150.6 or 149.0 (C)	
5'	6.93 (d, 8.4)	110.7 (CH)	4, 1', 2', 3'/4'/2'', 6'
6'	7.61 (dd, 2.1, 8.4)	120.1 (CH)	4, 2', 3'/4'/2''
1''			
2''		151.1 or 150.6 (C)	
3''	7.08 (d, 33)	112.8 (CH)	3'/4'/2'', 4'', 5''
4''	6.15 (dd, 0.8, 3.3)	108.7 (CH)	3'/4'/2'', 3'', 5''
5''		155.0 (C)	
NH_2	5.35 (s)		4, 6
CH_3	2.43 (s)	14.00 (CH_3)	4'', 5''
OCH_3	3.98 (s)	56.0 (CH_3)	2', 3'/4'/2'', 5'
OCH_3	3.93 (s)	55.9 (CH_3)	2', 3'/4'/2'', 5'

*Compound **2m**:*

Inspection of the ^{1}H and ^{13}C NMR spectra of compound **2m** revealed that this compound was a 2-aminopyrimidine with structural similarities to compound **2f**. ^{13}C NMR and DEPT 90/135 spectra indicated one CH_3, five CH_2, seven CH and eight quaternary carbons. In the aliphatic region, peaks at δ_C 48.8, 43.1, 26.5, 25.5 and 24.5 corresponds to the five CH_2 carbons of the piperidine ring, while the methyl group of the furan ring is located at δ_C 14.0 ppm. Due to small difference in shifts observed for the peaks at δ_C 164.9 and 163.4, as well as for the phenyl peaks (δ_C 128.7, 128.5, 127.9 and 125.7) the unambiguous assignment of these peaks to a particular carbon was not possible. Individual CH_2 carbons of the piperidine ring were also not assigned due to the limited correlations observed for these peaks while assignment for all other carbons are indicated in Table 3.5.

The ^{1}H NMR spectrum showed 21 protons, comprising of signals for protons of the piperidine (δ_H 3.73 – 1.39), phenyl (δ_H 8.12 – 7.44), pyrimidine (δ_H 7.35) and furan (δ_H 6.15 and 7.09) moieties. NMR assignments were further done after careful consideration of COSY, HSQC and HMBC spectra. The spectroscopic data as well as the high-resolution mass results (m/z 362.1729), indicating a molecular formula of $C_{21}H_{22}N_4O_2$, were in agreement with the proposed structure. The NMR data of 2-aminopyrimidines **2j** - **2n** were very similar to that of compound **2m** with differences primarily observed in the signals of the different amide substituents.

Table 3.5: NMR data and HMBC correlations of 4-(5-methylfuran-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (**2m**)

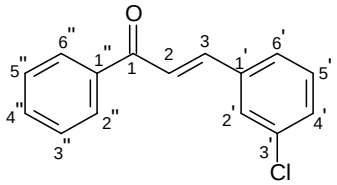


Atom no.	δ_H (multiplicity, *J* in Hz)	δ_C (Type)	HMBC (δ_H to δ_C)
1			

2		164.9 or 163.4 (C)	
3			
4		157.2 (C)	
5	7.35 (s)	101.6 (CH)	2/6, 4, 1'/3', 2', 4', 5', 6', 2''
6		164.9 or 163.4 (C)	
1'		137.9 (C)	
2'	8.12 – 8.05 (m)	128.7 or 128.5 or 127.9 or 125.7 (CH)	2/6, 2', 4', 5', 6', C=O
3'		136.8 (C)	
4'	7.52 – 7.44 (m)	128.7 or 128.5 or 127.9 or 125.7 (CH)	2', 4', 5', 6', 1'/3', C=O
5'	7.52 – 7.44 (m)	128.7 or 128.5 or 127.9 or 125.7 (CH)	2', 4', 5', 6', 1'/3', C=O
6'	8.12 – 8.05 (m)	128.7 or 128.5 or 127.9 or 125.7 (CH)	2/6, 2', 4', 5', 6', C=O
1''			
2''		150.4 (C)	
3''	7.09 (d, 3.4)	113.1 (CH)	2'', 4'', 5''
4''	6.15 (dd, 1.1, 3.4)	108.7 (CH)	2'', 3'', 5''
5''		155.2 (C)	
NH_2	5.35 (s)		2, 4, 6
CH_3	2.42 (s)	14.00 (CH_3)	4'', 5''
C=O		169.8 (C)	
CON$\underline{CH_2}$	3.73 (br s)	48.8 (CH_2)	CON$\underline{CH_2}$
CON$\underline{CH_2}$	3.36 (br s)	43.1 (CH_2)	CON$\underline{CH_2}$
3 x piperidine CH_2	1.77 – 1.39 (m)	26.5, 25.5, 24.5 (CH_2)	CON$\underline{CH_2}$, CON$\underline{CH_2}$, piperidine CH_2

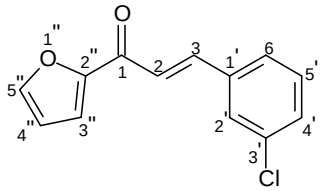
Physical data of chalcones

(2*E*)-3-(3-chlorophenyl)-1-phenylprop-2-en-1-one (**1a**)



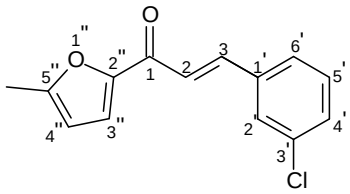
The title compound was prepared from acetophenone and 3-chlorobenzaldehyde in a yield of 34%: mp 74.7-75.1 ℃ (ethanol) (lit. Rueping *et al*., 2011, 72 – 73 ℃), pale yellow crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H, H-2'', H-6''), 7.73 (d, *J* = 15.7 Hz, 1H, H-3), 7.65 – 7.57 (m, 2H, H-2', H-4''), 7.56 – 7.47 (m, 4H, H-2, H-3'', H-5'', H-6'), 7.40 – 7.32 (m, 2H, H-4', H-5');^{13}C NMR (151 MHz, $CDCl_3$) δ 190.0 (C-1), 143.0 (C-3), 137.8 (C-1''), 136.7 (C-1'), 134.9 (C-3'), 133.0 (C-4''), 130.3, 130.2 (C-4', C-5'), 128.7, 128.5 (C-2'', C-6'' and C-3'', C-5''), 127.9 (C-2'), 126.8 (C-6'), 123.2 (C-2). EI-HRMS m/z: calcd for $C_{15}H_{11}ClO$, 242.0498, found 242.04878; Purity (HPLC): 93%.

(2*E*)-3-(3-chlorophenyl)-1-(furan-2-yl)prop-2-en-1-one (**1b**)



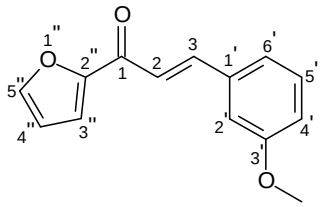
The title compound was prepared from 2-acetylfuran and 3-chlorobenzaldehyde in a yield of 17%: mp 76.2-77.1 ℃ (ethanol), light yellow crysta ls. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 15.8 Hz, 1H, H-3), 7.67 – 7.65 (m, 1H, H-5''), 7.62 (br t, *J* = 1.9 Hz, 1H, H-2') 7.49 (br dt, *J* = 1.6, 7.3 Hz, 1H, H-6'), 7.43 (d, *J* = 15.8 Hz, 1H, H-2), 7.39 – 7.31 (m, 3H, H-4', H-5', H-3''), 6.60 (dd, *J* = 1.7, 3.6 Hz, 1H, H-4''); ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5 (C-1), 153.5 (C-2''), 146.7 (C-5''), 142.2 (C-3), 136.5 (C-1'), 134.9 (C-3'), 130.4, 130.1 (C-4', C-5'), 127.9 (C-2'), 126.9 (C-6'), 122.3 (C-2), 117.8 (C-3''), 112.6 (C-4''). EI-HRMS m/z: calcd for $C_{13}H_9ClO_2$, 232.0291, found 232.02796; Purity (HPLC): 92%.

(2*E*)-3-(3-chlorophenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1c**)



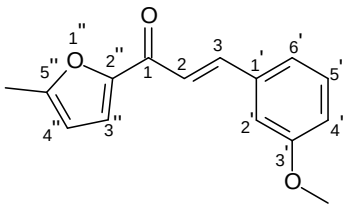
The title compound was prepared from 1-(5-methyl-2-furyl)ethanone and 3-chlorobenzaldehyde in a yield of 12%: mp 91.4-92.3 ℃ (ethanol), orang e crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 15.7 Hz, 1H, H-3), 7.65 – 7.61 (m, 1H, H-2'), 7.52 – 7.47 (m, 1H, H-6'), 7.41 – 7.32 (m, 3H, H-4', H-5', H-2), 7.31 – 7.27 (m, 1H, H-3''), 6.24 (m, 1H, H-4''), 2.46 (s, 3H, C$\underline{H_3}$).^{13}C NMR (151 MHz, $CDCl_3$) δ 176.7 (C-1), 158.4 (C-2'' or C-5''), 152.3 (C-2'' or C-5''), 141.4 (C-3), 136.6 (C-1'), 134.8 (C-3'), 130.2, 130.1 (C-4' and C-5'), 127.7 (C-2'), 126.8 (C-6'), 122.5 (C-2), 119.9 (C-3''), 109.4 (C-4''), 14.2 ($\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{14}H_{11}ClO_2$, 246.0448, found 246.0444; Purity (HPLC): 100%.

(2*E*)-1-(furan-2-yl)-3-(3-methoxyphenyl)prop-2-en-1-one (**1d**)



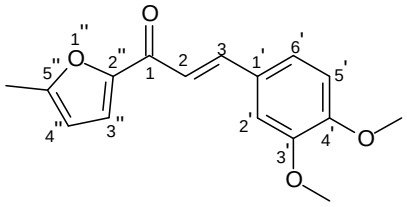
The title compound was prepared from 2-acetylfuran and 3-methoxybenzaldehyde in a yield of 22%: mp 65.4-66.4 ℃ (ethanol), amber crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 15.8 Hz, 1H, H-3), 7.65 (dd, *J* = 0.8, 1.7 Hz, 1H, H-5''), 7.42 (d, *J* = 15.8 Hz, 1H, H-2), 7.35 – 7.29 (m, 2H, H-5', H-3''), 7.25 – 7.22 (br d, 7.5 Hz, 1H, H-6'), 7.15 (br t, *J* = 2.0 Hz, 1H, H-2'), 6.95 (ddd, *J* = 0.9, 2.6, 8.2 Hz, 1H, H-4'), 6.59 (dd, *J* = 1.7, 3.6 Hz, 1H, H-4''), 3.84 (s, 3H, OC$\underline{H_3}$).^{13}C NMR (151 MHz, $CDCl_3$) δ 177.9 (C-1), 159.8 (C-3'), 153.6 (C-2''), 146.5 (C-5''), 143.9 (C-3), 136.0 (C-1'), 129.9 (C-5'), 121.3 (C-6' or C-2), 121.1 (C-6' or C-2), 117.6 (C-3''), 116.3 (C-4'), 113.4 (C-2'), 112.5 (C-4''), 55.3 (O$\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{14}H_{12}O_3$, 228.0786, found 228.07796; Purity (HPLC): 94%.

(2*E*)-3-(3-methoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1e**)



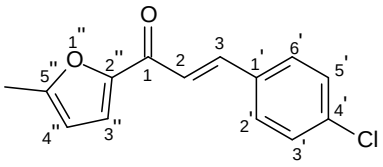
The title compound was prepared from 1-(5-methyl-2-furyl)ethanone and 3-methoxybenzaldehyde in a yield of 46%: mp 96.9-97.5 ℃ (ethanol), yellow crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 16.1 Hz, 1H, H-3), 7.35 (d, *J* = 16.1 Hz, 1H, H-2), 7.31 (t, *J* = 8.0 Hz, 1H, H-5'), 7.24 (d, 1H, *J* = 3.5 Hz, H-3''), 7.22 (br d, 1H, *J* = 7.7 Hz, H-6'), 7.13 (br s, 1H, H-2'), 6.94 (dd, *J* = 2.6, 8.2 Hz, 1H, H-4'), 6.20 (dd, *J* = 0.8, 3.4 Hz, 1H, H-4''), 3.83 (s, 3H, $OC\underline{H}_3$), 2.43 (s, 3H, $C\underline{H}_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 177.1 (C-1), 159.8 (C-3'), 158.2 (C-5''), 152.4 (C-2''), 143.1 (C-3), 136.1 (C-1'), 129.8 (C-5'), 121.5 (C-2), 121.0 (C-6'), 119.6 (C-3''), 116.0 (C-4'), 113.4 (C-2'), 109.3 (C-4''), 55.3 ($O\underline{C}H_3$), 14.1 ($\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{15}H_{14}O_3$, 242.0943, found 242.09396; Purity (HPLC): 100%.

(2*E*)-3-(3,4-dimethoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1f**)



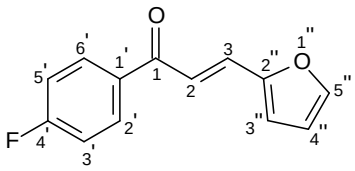
The title compound was prepared from 1-(5-methyl-2-furyl)ethanone and 3,4-dimethoxybenzaldehyde in a yield of 35%: mp 116.3-117 ℃ (ethanol), yellow crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (br d, *J* = 15.7 Hz, 1H, H-3), 7.26 – 7.16 (m, 3H, H-6', H-2, H-3''), 7.11 (br s, 1H, H-2'), 6.85 (br d, *J* = 8.4 Hz, 1H, H-5'), 6.19 (br s, 1H, H-4''), 3.93 (s, 3H, $OC\underline{H}_3$), 3.90 (s, 3H, $OC\underline{H}_3$), 2.40 (s, 3H, $C\underline{H}_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2 (C-1), 157.8 (C-5''), 152.5 (C-2''), 151.2 (C-3' or C-4'), 149.1 (C-3' or C-4'), 143.3 (C-3), 127.7 (C-1'), 123.0 (C-2), 119.1 (C-6' or C-3''), 119.2 (C-6' or C-3''), 111.0 (C-5'), 110.1 (C-2'), 109.2 (C-4''), 55.9 ($O\underline{C}H_3$), 55.9 ($O\underline{C}H_3$), 14.1 ($\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{16}H_{16}O_4$, 272.1049, found 272.1045; Purity (HPLC): 90%.

(2*E*)-3-(4-chlorophenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1g**)



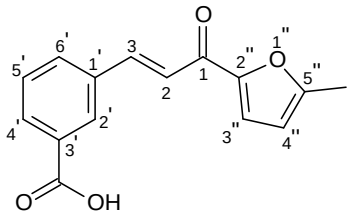
The title compound was prepared from 1-(5-methyl-2-furyl)ethanone and 4-chlorobenzaldehyde in a yield of 41%: mp 151.4-151.9 ℃ (ethanol), pal e yellow solid.^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 15.7 Hz, 1H, H-3), 7.49 (m, 2H, H-2', H-6'), 7.29 – 7.24 (m, 3H, H-2, H-3', H-5'), 7.18 (d, *J* = 3.4 Hz, 1H, H-3''), 6.14 (dd, *J* = 0.9, 3.4 Hz, 1H, H-4''), 2.36 (s, 3H, C<u>H</u>$_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 176.9 (C-1), 158.3 (C-5''), 152.4 (C-2''), 141.7 (C-3), 136.2 (C-4'), 133.3 (C-1'), 129.5 (C-2', C-6' or C-3', C-5'), 129.1(C-2', C-6' or C-3', C-5'), 121.7 (C-2), 119.7 (C-3''), 109.4 (C-4''), 14.2 (<u>C</u>H$_3$). EI-HRMS m/z: calcd for $C_{14}H_{11}ClO_2$, 246.0448, found 246.0441; Purity (HPLC): 96%.

(2*E*)-1-(4-fluorophenyl)-3-(furan-2-yl)prop-2-en-1-one (**1h**)



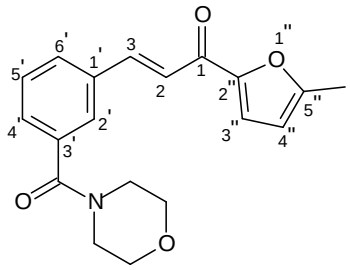
The title compound was prepared from 1-(4-fluorophenyl)ethanone and furan-2-carbaldehyde in a yield of 40%: mp 59.9-60.5 ℃ (lit. Tsukerman *et al.,* 1968, 116 ℃) (ethanol), dark orange solid.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 2H, H-2', H-6'), 7.59 (d, *J* = 15.3 Hz, 1H, H-3), 7.52 (d, *J* = 1.7 Hz, 1H, H-5''), 7.42 (d, *J* = 15.3 Hz, 1H, H-2), 7.19 – 7.12 (m, 2H, H-3', H-5'), 6.72 (d, *J* = 3.4 Hz, 1H, H-3''), 6.51 (dd, *J* = 1.7, 3.4 Hz, 1H, H-4'').^{13}C NMR (151 MHz, $CDCl_3$) δ 188.0 (C-1), 165.5 (d, $J_{C\text{-}F}$ = 253.5 Hz, C-4'), 151.5 (C-2''), 145.0 (C-5''), 134.4 (d, $J_{C\text{-}F}$ = 3.2 Hz, C-1'), 130.96 (d, $J_{C\text{-}F}$ = 9.6 Hz, C-2', C-6'), 130.8 (C-3), 118.7 (C-2), 116.4 (C-3''), 115.6 (d, $J_{C\text{-}F}$ = 21.9 Hz, C-3', C-5'), 112.7 (C-4''). EI-HRMS m/z: calcd for $C_{13}H_9FO_2$, 216.0587, found 216.0581; Purity (HPLC): 91%.

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



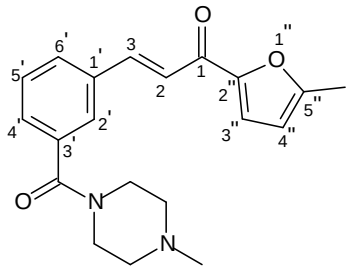
The title compound was prepared from 1-(5-methyl-2-furyl)ethanone and 3-formylbenzoic acid in a yield of 68%: mp 191.7-194.1 ℃ (methanol), pale yellow crystals. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 13.20 (br s, 1H, O<u>H</u>), 8.33 (br s, 1H, H-2'), 8.07 (br d, *J* = 7.8 Hz, 1H, H-6'), 7.98 (dt, *J* = 1.4, 7.7 Hz, 1H, H-4'), 7.82 (d, *J* = 3.5 Hz, 1H, H-3''), 7.75 (d, *J* = 16.0 Hz, 1H, H-7 or H-8), 7.71 (d, *J* = 16.0 Hz, 1H, H-7 or H-8), 7.57 (t, *J* = 7.7 Hz, 1H, H-5'), 6.42 (dd, *J* = 1.1, 3.5 Hz, 1H, H-4''), 2.40 (s, 3H, C<u>H</u>$_3$).^{13}C NMR (151 MHz, DMSO-*d6*) δ 175.6 (C-1), 167.0 (acid C=O), 158.8 (C-5''), 151.8 (C-2''), 141.2 (C-3), 135.0 (C-1'), 132.8 (C-6'), 131.6 (C-3'), 131.0 (C-4'), 129.2 (C-2', C-5'), 123.1 (C-2), 121.9 (C-3''), 109.6 (C-4''), 13.8 (<u>C</u>H$_3$). EI-HRMS m/z: calcd for $C_{15}H_{12}O_4$, 256.0736, found 256.0729; Purity (HPLC): 100%.

(2*E*)-1-(5-methylfuran-2-yl)-3-[3-(morpholine-4-carbonyl)phenyl]prop-2-en-1-one (**1j**)



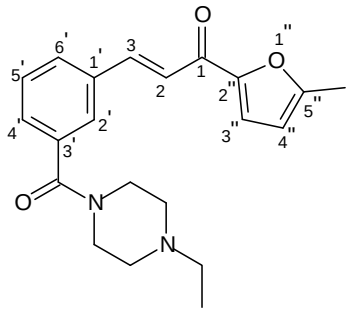
The title compound was prepared from (1*E*)-1-(5-methylfuran-2-yl)-3-[3-oxoprop-1-en-1-yl]benzoic acid (**1i**) and morpholine in a yield of 54%: mp 149.1-149.9 ℃ (methanol), pale yellow crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 15.8 Hz, 1H, H-3), 7.69 (br t, *J* = 1.6 Hz, 1H, H-2'), 7.65 (dt, *J* = 1.6, 7.7 Hz, 1H, H-6'), 7.47 – 7.36 (m, 3H, H-2, H-5', H-4'), 7.25 (br d, *J* = 3.4 Hz, 1H, H-3''), 6.21 (dd, *J* = 1.0, 3.4 Hz, 1H, H-4''), 3.93 – 3.31 (m, 8H, 4 x morpholine C<u>H</u>$_2$), 2.43 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.8 (C-1), 169.6 (amide C=O), 158.4 (C-5''), 152.3 (C-2''), 141.8 (C-3), 136.0 (C-1' or C-3'), 135.4 (C-1' or C-3'), 129.9 (C-6'), 129.1, 128.5 (C-4', C-5')*, 126.6 (C-2'), 122.4 (C-2), 119.8 (C-3''), 109.4 (C-4''), 66.8, 48.2, 42.5 (morpholine <u>C</u>H$_2$). EI-HRMS m/z: calcd for $C_{19}H_{19}NO_4$, 325.131, found 325.130; Purity (HPLC): 100%. * In no particular order.

(2*E*)-1-(5-methylfuran-2-yl)-3-[3-(4-methylpiperazine-1-carbonyl)phenyl]prop-2-en-1-one (**1k**)



The title compound was prepared from (1*E*)-1-(5-methylfuran-2-yl)-3-[3-oxoprop-1-en-1-yl]benzoic acid (**1i**) and 1-methylpiperazine in a yield of 67 %: mp 131.0-132.2 ℃ (methanol), yellow crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 15.8 Hz, 1H, H-3), 7.68 (br t, *J* = 1.6 Hz, 1H, H-2'), 7.63 (dt, *J* = 1.6, 7.7 Hz, 1H, H-6'), 7.45 – 7.35 (m, 3H, H-4', H-5', H-2), 7.25 (d, *J* = 3.5 Hz, 1H, H-3"), 6.20 (d, *J* = 3.5 Hz, 1H, H-4"), 3.81 (br s, 2H, CONC$\underline{H}_2$), 3.44 (br s, 2H, CONC$\underline{H}_2$), 2.50-2.27 (m, 10H, 2 x $\underline{C}H_2NCH_3$, 2 x $C\underline{H}_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 176.8 (C-1), 169.5 (amide C=O), 158.3 (C-5"), 152.3 (C-2"), 141.9 (C-3), 136.5 (C-1' or C-3'), 135.3 (C-1' or C-3'), 129.7 (C-6'), 129.0 (C-4' or C-5'), 128.5 (C-4' or C-5'), 126.6 (C-2'), 122.3 (C-2), 119.8 (C-3"), 109.4 (C-4"), 55.2 ($\underline{C}H_2NCH_3$), 54.6 ($\underline{C}H_2NCH_3$), 47.6 (CON$\underline{C}H_2$), 45.9 (piperazine $\underline{C}H_3$,), 42.0 (CON$\underline{C}H_2$), 14.1 (furan $\underline{C}H_3$,). EI-HRMS m/z: calcd for $C_{20}H_{22}N_2O_3$, 338.163, found 338.163; Purity (HPLC): 97%.

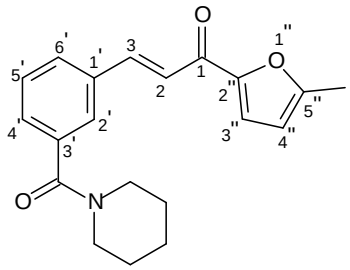
(2*E*)-3-[3-(4-ethylpiperazine-1-carbonyl)phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1l**)



The title compound was prepared from (1*E*)-1-(5-methylfuran-2-yl)-3-[3-oxoprop-1-en-1-yl]benzoic acid (**1i**) and 1-ethylpiperazine in a yield of 63%: mp 98.5-98.8 ℃ (methanol), orange solid.^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 15.9 Hz, 1H, H-3), 7.68 (br s, 1H, H-2'), 7.63 (br d, *J* = 7.6 Hz, 1H, H-6'), 7.45 – 7.36 (m, 3H, H-4', H-5', H-2), 7.25 (d, *J* = 3.5 Hz, 1H, H-3"), 6.21 (d, *J* = 3.5 Hz, 1H, H-4"), 3.81 (br s, 2H, CONC$\underline{H}_2$), 3.44 (br s, 2H, CONC$\underline{H}_2$), 2.55 – 2.33 (m, 9H, 2 x C$\underline{H}_2$NCH$_3$, NC$\underline{H}_2$CH$_3$, furan C$\underline{H}_3$), 1.08 (t, *J* = 7.2 Hz, 3H, NCH$_2$C$\underline{H}_3$).^{13}C NMR (151

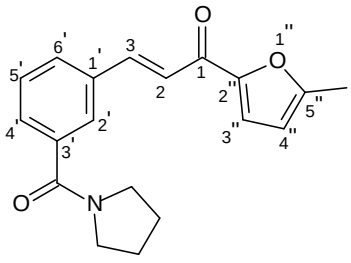
MHz, $CDCl_3$) δ 176.8 (C-1), 169.4 (amide C=O), 158.3 (C-5''), 152.3 (C-2''), 141.9 (C-3), 136.5 (C-1' or C-3'), 135.3 (C-1' or C-3'), 129.8 (C-6'), 129.0 (C-4' or C-5'), 128.5 (C-4' or C-5'), 126.6 (C-2'), 122.3 (C-2), 119.8 (C-3''), 109.4 (C-4''), 53.1 ($\underline{C}H_2NCH_2$), 52.3 ($\underline{C}H_2NCH_2$), 52.2 ($N\underline{C}H_2CH_3$), 47.7 ($CON\underline{C}H_2$), 42.1 ($CON\underline{C}H_2$), 14.1 (furan $\underline{C}H_3$), 11.8 (piperazine $\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{21}H_{24}N_2O_3$, 352.179, found 352.178; Purity (HPLC): 98%.

(2*E*)-1-(5-methylfuran-2-yl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (**1m**)



The title compound was prepared from (1*E*)-1-(5-methylfuran-2-yl)-3-[3-oxoprop-1-en-1-yl]benzoic acid (**1i**) and piperidine in a yield of 78%: mp 144.2-144.4 ℃ (methanol), pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 15.8 Hz, 1H, H-3), 7.68 (br s, 1H, H-2'), 7.63 (br d, *J* = 7.8 Hz, 1H, H-6'), 7.45 – 7.35 (m, 3H, H-4', H-5', H-2), 7.25 (d, 1H, *J* = 3.4 Hz, H-3''), 6.21 (d, *J* = 3.4 Hz, 1H, H-4''), 3.71 (s, 2H, $CONC\underline{H}_2$), 3.33 (s, 2H, $CONC\underline{H}_2$), 2.43 (s, 3H, $C\underline{H}_3$), 1.71 – 1.42 (m, 6H, 3 x piperidine $C\underline{H}_2$).^{13}C NMR (151 MHz, $CDCl_3$) δ 176.9 (C-9), 169.5 (amide C=O), 158.3 (C-5''), 152.3 (C-2''), 142.1 (C-3), 137.2 (C-3'), 135.2 (C-1'), 129.5 (C-6'), 128.9 (C-4' or C-5'), 128.3 (C-4' or C-5'), 126.4 (C-2'), 122.2 (C-2), 119.8 (C-3''), 109.4 (C-4''), 48.7 ($CON\underline{C}H_2$), 43.1 ($CON\underline{C}H_2$), 26.5, 25.5, 24.5 (3 x piperidine $\underline{C}H_2$), 14.2 ($\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{20}H_{21}NO_3$, 323.152, found 323.151; Purity (HPLC): 96%.

(2*E*)-1-(5-methylfuran-2-yl)-3-[3-(pyrrolidine-1-carbonyl)phenyl]prop-2-en-1-one (**1n**)

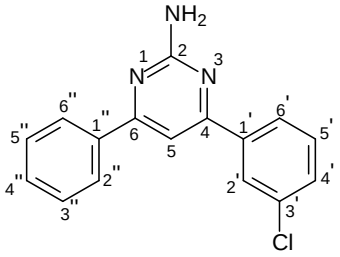


The title compound was prepared from (1*E*)-1-(5-methylfuran-2-yl)-3-[3-oxoprop-1-en-1-yl]benzoic acid (**1i**) and pyrrolidine in a yield of 74%: mp 120.8-122.6 ℃ (methanol), yellow

crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 2H, H-2', H-3), 7.62 (br d, *J* = 7.7 Hz, 1H, H-6'), 7.49 (br d, *J* = 7.7 Hz, 1H, H-4'), 7.44 – 7.37 (m, 2H, H-5', H-2), 7.24 (d, *J* = 3.5 Hz, 1H, H-3''), 6.2 (d, *J* = 3.5 Hz, 1H, H-4''), 3.63 (t, *J* = 7.1 Hz, 2H, CONC$\underline{H_2}$), 3.41 (t, *J* = 6.6 Hz, 2H, CONC$\underline{H_2}$), 2.41 (s, 3H, CH_3), 1.95 (p, *J* = 6.9 Hz, 2H, $CH_2C\underline{H_2}CH_2$), 1.86 (p, *J* = 6.7 Hz, 2H, $CH_2C\underline{H_2}CH_2$).^{13}C NMR (151 MHz, $CDCl_3$) δ 176.9 (C-1), 168.9 (amide C=O), 158.3 (C-5''), 152.3 (C-2''), 142.1 (C-3), 137.8 (C-3'), 135.0 (C-1'), 129.9 (C-6'), 128.8 (C-4' or C-5'), 128.6 (C-4' or C-5'), 126.6 (C-2'), 122.1 (C-2), 119.8 (C-3''), 109.4 (C-4''), 49.5 (CON$\underline{C}H_2$), 46.2 (CON$\underline{C}H_2$), 26.3 ($CH_2\underline{C}H_2CH_2$), 24.3 ($CH_2\underline{C}H_2CH_2$), 14.1 ($\underline{C}H_3$). APCI-HRMS m/z: calcd for $C_{19}H_{19}NO_3$ $(M + H)^+$, 310.1443, found 310.1448; Purity (HPLC): 93%.

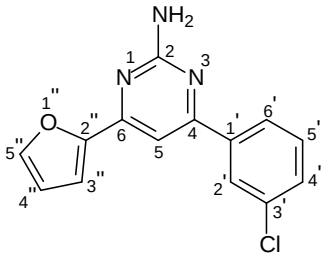
Physical data of 2-aminopyrimidines

4-(3-chlorophenyl)-6-phenylpyrimidin-2-amine (**2a**)



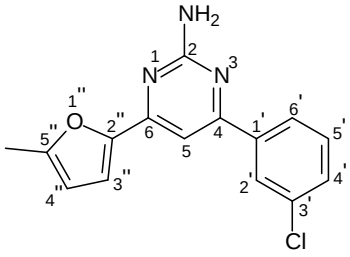
The title compound was prepared from (2*E*)-3-(3-chlorophenyl)-1-phenylprop-2-en-1-one (**1a**) in a yield of 15%: mp 128.6-131.4 ℃ (ethanol), white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (m, 3H, Ar-H), 7.92 (dt, *J* = 1.5, 7.6 Hz, 1H, H-4'/6'), 7.53 – 7.39 (m, 6H, Ar-H, H-5), 5.42 (s, 2H, N$\underline{H_2}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.5, 164.64, 163.6 (C-2, C-4, C-6)*, 139.5, 137.4, 134.8 (C-1', C-1'', C-3'')*, 130.6, 130.3, 130.0, 128.8 (2C), 127.2, 127.1 (2C), 125.1 (Ar-C), 104.1 (C-5). EI-HRMS m/z: calcd for $C_{16}H_{12}ClN_3$, 281.0719, found 281.0717; Purity (HPLC): 99%.* In no particular order.

4-(3-chlorophenyl)-6-(furan-2-yl)pyrimidin-2-amine (**2b**)



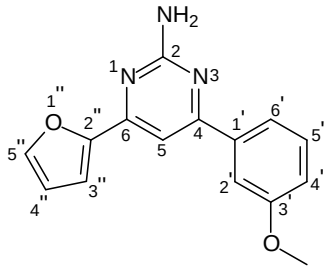
The title compound was prepared from (2*E*)-3-(3-chlorophenyl)-1-(furan-2-yl)prop-2-en-1-one (**1b**) in a yield of 22%: mp 144.1-144.4 ℃ (ethanol), light yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (br t, *J* = 1.9 Hz, 1H, H-2'), 7.91 (dt, *J* = 1.45, 7.6 Hz, 1H, H-6'), 7.59 (dd, *J* = 0.8, 1.8 Hz, 1H, H-5''), 7.42 (ddd, *J* = 8.0, 2.1, 1.2 Hz, 1H, H-4'), 7.38 (br t, *J* = 7.8 Hz, 1H, H-5'), 7.34 (s, 1H, H-5), 7.20 (dd, *J* = 0.8, 3.5 Hz, 1H, H-3''), 6.56 (dd, *J* = 1.8, 3.5 Hz, 1H, H-4''), 5.41 (s, 2H, N$\underline{H_2}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6 (C-2 or C-4), 163.4 (C-2 or C-4), 157.24 (C-6), 152.0 (C-2''), 144.6 (C-5''), 139.3 (C-1'), 134.8 (C-3'), 130.4 (C-4' or C-5'), 129.9 (C-4' or C-5'), 127.2 (C-2'), 125.1 (C-6'), 112.3 (C-3'' or C-4''), 111.80 (C-3'' or C-4''), 101.94 (C-5). EI-HRMS m/z: calcd for $C_{14}H_{10}ClN_3O$, 271.0512, found 271.05049; Purity (HPLC): 98%.

4-(3-chlorophenyl)-6-(5-methylfuran-2-yl)pyrimidin-2-amine (**2c**)



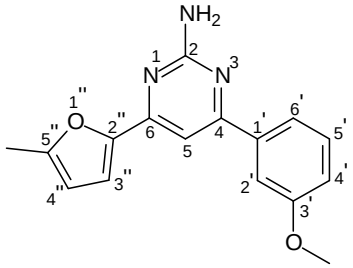
The title compound was prepared from (2*E*)-3-(3-chlorophenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1c**) in a yield of 45%: mp 170.5-172.1℃ (ethanol), yellow solid.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (br s, 1H, H-2'), 7.92 (d, *J* = 7.6 Hz, 1H, H-6'), 7.46 – 7.37 (m, 2H, H-4', H-5'), 7.31 (s, 1H, H-5), 7.11 (br s, 1H, H-3''), 6.17 (br s, 1H, H-4''), 5.26 (s, 2H, N$\underline{H_2}$), 2.43 (s, 3H, C$\underline{H_3}$).^{13}C NMR (151 MHz, $CDCl_3$) δ 164.3 (C-2 or C-4), 163.3 (C-2 or C-4), 157.3 (C-6), 155.4 (C-5''), 150.5 (C-2''), 139.4 (C-1'), 134.8 (C-3'), 130.3 (C-4' or C-5'), 129.9 (C-4' or C-5'), 127.2 (C-2'), 125.1 (C-6'), 113.3 (C-3''), 108.8 (C-4''), 101.6 (C-5), 14.0 (C$\underline{H_3}$). EI-HRMS m/z: calcd for $C_{15}H_{12}ON_3Cl$, 285.0669, found 285.0656; Purity (HPLC): 100%.

4-(3-methoxyphenyl)-6-(furan-2-yl)pyrimidin-2-amine (**2d**)



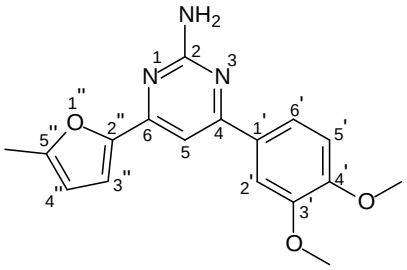
The title compound was prepared from (2*E*)-1-(furan-2-yl)-3-(3-methoxyphenyl)prop-2-en-1-one (**1d**) in a yield of 19%: mp 113.8-116.8 ℃ (ethanol), dark brown crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 – 7.57 (m, 3H, H-2',H-4',H-5''), 7.40 – 7.37 (m, 2H, H-5, H-5'), 7.19 (dd, *J* = 0.82, 3.4 Hz, 1H, H-3''), 7.03 (ddd, *J* = 0.96, 2.59, 8.1 Hz, 1H, H-6'), 6.55 (dd, *J* = 1.7, 3.4 Hz, 1H, H-4''), 5.41 (s, 2H, N$\underline{H}_2$), 3.89 (s, 3H, OC$\underline{H}_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 165.92 (C-4), 163.35 (C-2), 159.96 (C-3'), 156.43 (C-6), 152.15 (C-2''), 144.51 (C-5''), 138.89 (C-1'), 129.68 (C-5'), 119.47 (C-4'), 116.54 (C-6'), 112.21 (C-2'/C-3''/C-4''), 112.21 (C-2'/C-3''/C-4''), 112.07 (C-2'/C-3''/C-4''), 102.18 (C-5), 55.37 (O$\underline{C}$H$_3$). EI-HRMS m/z: calcd for $C_{15}H_{13}N_3O_2$, 267.1008, found 267.0920; Purity (HPLC): 92%.

4-(3-methoxyphenyl)-6-(5-methylfuran-2-yl)pyrimidin-2-amine (**2e**)



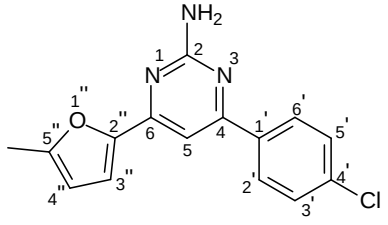
The title compound was prepared from (2*E*)-3-(3-methoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1e**) in a yield of 43%: mp 149.0 -150.6 ℃ (ethanol), light orange crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H, H-2', H-4'), 7.38 (br t, *J* = 7.9 Hz, 1H, H-5'), 7.33 (s, 1H, H-5), 7.09 (d, *J* = 3.3 Hz, 1H, H-3''), 7.02 (dd, *J* = 2.6, 8.2 Hz, 1H, H-6'), 6.15 (dd, *J* = 0.9, 3.3 Hz, 1H, H-4''), 5.44 (s, 2H, N$\underline{H}_2$), 3.88 (s, 3H, OC$\underline{H}_3$), 2.44 (s, 3H, C$\underline{H}_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6 (C-4), 163.4 (C-2), 159.9 (C-3'), 157.0 (C-6), 155.1 (C-5''), 150.6 (C-2''), 139.1 (C-1'), 129.6 (C-5'), 119.4 (C-4'), 116.3 (C-6'), 113.0 (C-3''), 112.1 (C-2'), 108.7 (C-4''), 101.7 (C-5), 55.4 (O$\underline{C}$H$_3$), 14.0 ($\underline{C}$H$_3$). EI-HRMS m/z: calcd for $C_{16}H_{15}N_3O_2$, 281.1163, found 281.1156 ; Purity (HPLC): 100%.

4-(3,4-dimethoxyphenyl)-6-(5-methylfuran-2-yl)pyrimidin-2-amine (**2f**)



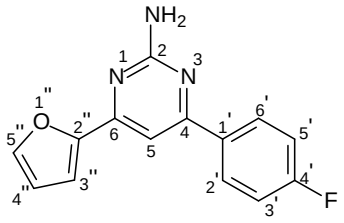
The title compound was prepared from (2*E*)-3-(3,4-dimethoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1f**) in a yield of 27%: mp 167.4-168.1 ℃ (ethanol), d ark yellow crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.0 Hz, 1H, H-2'), 7.61 (dd, *J* = 2.1, 8.4 Hz, 1H, H-6'), 7.29 (s, 1H, H-5), 7.08 (d, *J* = 3.3 Hz, 1H, H-3''), 6.93 (d, *J* = 8.4 Hz, 1H, H-5'), 6.15 (dd, *J* = 0.8, 3.3 Hz, 1H, H-4''), 5.35 (s, 2H, $N\underline{H}_2$), 3.98 (s, 3H, $OC\underline{H}_3$), 3.93 (s, 3H, $OC\underline{H}_3$), 2.42 (s, 3H, $C\underline{H}_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 165.2 (C-4), 163.3 (C-2), 156.7 (C-6), 155.0 (C-5''), 151.1, 150.6 (C-4' or C-3' and C-2'')*, 149.0 (C-3' or C-4'), 130.2 (C-1'), 120.1 (C-6'), 112.8 (C-3''), 110.7 (C-5'), 109.8 (C-2'), 108.7 (C-4''), 100.8 (C-5), 56.0 ($OC\underline{H}_3$), 55.9 ($OC\underline{H}_3$), 14.00 ($C\underline{H}_3$). EI-HRMS m/z: calcd for $C_{17}H_{17}N_3O_3$, 311.1267, found 311.1262; Purity (HPLC): 100%* In no particular order.

4-(4-chlorophenyl)-6-(5-methylfuran-2-yl)pyrimidin-2-amine (**2g**)



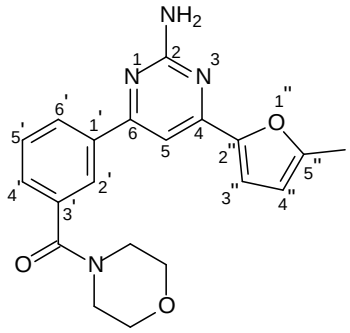
The title compound was prepared from (2*E*)-3-(4-chlorophenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1g**) in a yield of 30%: mp 205-205.1℃ (ethanol), dark yellow powder. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 8.14 (d, *J* = 8.6 Hz, 2H, H-2', H-6'), 7.56 (d, *J* = 8.6 Hz, 2H, H-3', H-5'), 7.39 (s, 1H, H-5), 7.21 (d, *J* = 3.3 Hz, 1H, H-3''), 6.76 (s, 2H, $N\underline{H}_2$), 6.32 (dd, *J* = 1.0, 3.3 Hz, 1H, H-4''), 2.37 (s, 3H, $C\underline{H}_3$).^{13}C NMR (151 MHz, DMSO-*d6*) δ 163.9 (C-2 or C-4), 163.1 (C-2 or C-4), 156.7 (C-6), 154.7 (C-5''), 150.4 (C-2''), 136.0 (C-1'), 135.2 (C-4'), 128.8 (C-2', C-6' or C-3', C-5'), 128.6 (C-2', C-6' or C-3', C-5'), 113.3 (C-3''), 108.9 (C-4''), 99.4 (C-5), 13.7 ($\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{15}H_{12}ClN_3O$, 285.0669, found 285.0663; Purity (HPLC): 99%.

4-(4-fluorophenyl)-6-(5-methylfuran-2-yl)pyrimidin-2-amine (**2h**)



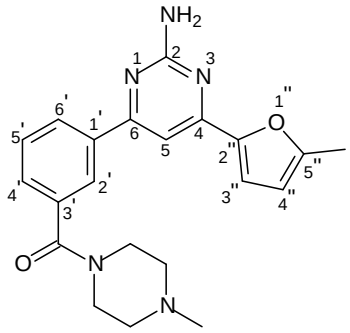
The title compound was prepared from (2*E*)-1-(4-fluorophenyl)-3-(furan-2-yl)prop-2-en-1-one (**1h**) in a yield of 41%: mp 162.3-162.5 ℃ (ethanol), faded yellow crystals.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 – 8.03 (m, 2H, H-2',H-6'), 7.59 (dd, *J* = 0.8, 1.8 Hz, 1H, H-5''), 7.37 (s, 1H, H-5), 7.19 – 7.13 (m, 3H, H-3'', H-3', H-5'), 6.57 (dd, *J* = 1.8, 3.4 Hz, 1H, H-4''), 5.28 (s, 2H, N$\underline{H}_2$).^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0 (C-2 or C-4), 164.4 (d, $J_{C\text{-}F}$ = 250.5 Hz, C-4'), 163.3 (C-2 or C-4), 157.1 (C-6), 152.2 (C-2''), 144.6 (C-5''), 133.5 (d, $J_{C\text{-}F}$ = 3.5 Hz, C-1'), 129.1 (d, $J_{C\text{-}F}$ = 8.5 Hz C-2', C-6'), 115.7 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3', C-5'), 112.3 (C-3''), 111.6 (C-4''), 101.7 (C-5). EI-HRMS m/z: calcd for $C_{14}H_{10}FN_3O$, 255.0808, found 255.0798; Purity (HPLC): 100%.

4-(5-methylfuran-2-yl)-6-[3-(morpholine-4-carbonyl)phenyl]pyrimidin-2-amine (**2j**)



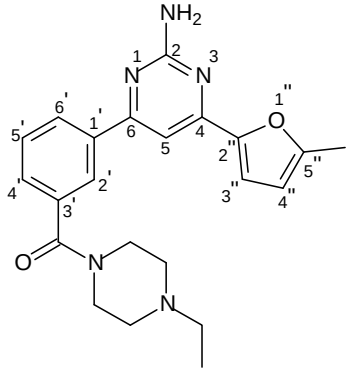
The title compound was prepared from (2*E*)-1-(5-methylfuran-2-yl)-3-[3-(morpholine-4-carbonyl)phenyl]prop-2-en-1-one (**1j**) in a yield of 20%: mp 205-205.1 ℃ (methanol), yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (m, 2H, H-2', H-6'), 7.55 – 7.46 (m, 2H, H-4', H-5'), 7.35 (s, 1H, H-5), 7.09 (d, *J* = 3.4 Hz, 1H, H-3''), 6.16 (br d, *J* = 3.4 Hz, 1H, H-4''), 5.32 (s, 2H, N$\underline{H}_2$), 3.87 – 3.43 (m, 8H, morpholine C$\underline{H}_2$), 2.42 (s, 3H, C$\underline{H}_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 170.0 (C=O), 164.6 (C-2 or C-6), 163.4 (C-2 or C-6), 157.3 (C-4), 155.3 (C-5''), 150.4 (C-2''), 138.1 (C-1'), 135.7 (C-3'), 128.8, 128.7, 128.4, 125.9 (C-2', C-4', C-5', C-6')*, 113.2 (C-3''), 108.7 (C-4''), 101.5 (C-5), 66.8, 48.2, 42.6 (morpholine $\underline{C}H_2$) 14.0 ($\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{20}H_{20}N_4O_3$, 364.1535, found 364.1529; Purity (HPLC): 92%. * In no particular order.

4-(5-methylfuran-2-yl)-6-[3-(4-methylpiperazine-1-carbonyl)phenyl]pyrimidin-2-amine (**2k**)



The title compound was prepared from (2*E*)-1-(5-methylfuran-2-yl)-3-[3-(4-methylpiperazine-1-carbonyl)phenyl]prop-2-en-1-one (**1k**) in a yield of 57%: 194.3-194.4 ℃ (methanol), cre am solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 – 8.07 (m, 2H, H-2', H-6'), 7.53 – 7.45 (m, 2H, H-4', H-5'), 7.35 (s, 1H, H-5), 7.09 (d, *J* = 3.4 Hz, 1H, H-3''), 6.15 (br d, *J* = 3.4 Hz, 1H, H-4''), 5.30 (s, 2H, $N\underline{H}_2$), 3.83 (br s, 2H, CONC$\underline{H}_2$), 3.46 (br s, 2H, CONC$\underline{H}_2$), 2.60 – 2.19 (m, 10H, 2 x $\underline{C}H_2NCH_3$, 2 x $C\underline{H}_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8 (C=O), 164.7 (C-2 or C-6), 163.4 (C-2 or C-6), 157.3 (C-4), 155.3 (C-5''), 150.5 (C-2''), 138.1 (C-1'), 136.2 (C-3'), 128.8, 128.7, 128.2, 125.9 (C-2', C-4', C-5', C-6')*, 113.2 (C-3''), 108.8 (C-4''), 101.6 (C-5), 55.2 ($\underline{C}H_2NCH_3$), 54.6 ($\underline{C}H_2NCH_3$), 47.7 (CON$\underline{C}H_2$), 46.0 (piperazine $\underline{C}H_3$), 42.1 (CON$\underline{C}H_2$), 14.0 (furan $\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{21}H_{23}N_5O_2$, 377.1852, found 377.1842; Purity (HPLC): 85%. *In no particular order.

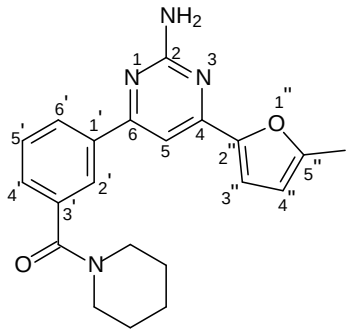
4-(5-methylfuran-2-yl)-6-[3-(4-ethylpiperazine-1-carbonyl)phenyl]pyrimidin-2-amine (**2l**)



The title compound was prepared from (2*E*)-3-[3-(4-ethylpiperazine-1-carbonyl)phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (**1l**) in a yield of 16%: 178.1-178.4 ℃ (methanol), lig ht orange solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 – 8.07 (m, 2H, H-2', H-6'), 7.52 – 7.44 (m, 2H, H-4', H-5'), 7.34 (s, 1H, H-5), 7.08 (d, *J* = 3.4 Hz, 1H, H-3''), 6.14 (dd, *J* = 1.0, 3.4 Hz, 1H, H-4''), 5.38 (s,

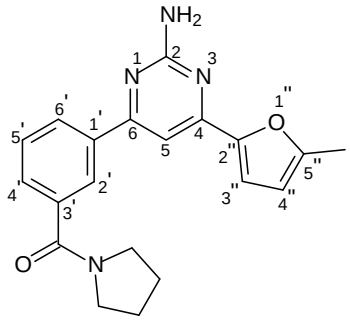
2H, N$\underline{H}_2$), 3.83 (br s, 2H, CONC$\underline{H}_2$), 3.46 (s, 2H, CONC$\underline{H}_2$), 2.62 – 2.21 (m, 9H, 2 x C$\underline{H}_2$NCH$_3$, NC$\underline{H}_2$CH$_3$, furan C$\underline{H}_3$), 1.07 (t, *J* = 7.4 Hz, 3H, NCH$_2$C$\underline{H}_3$).^{13}C NMR (151 MHz, CDCl$_3$) δ 169.7 (C=O), 164.7 (C-2 or C-6), 163.4 (C-2 or C-6), 157.2 (C-4), 155.2 (C-5''), 150.4 (C-2''), 138.0 (C-1'), 136.2 (C-3'), 128.7, 128.7, 128.2, 125.9 (C-2', C-4', C-5', C-6')*, 113.1 (C-3''), 108.7 (C-4''), 101.5 (C-5), 53.0 (C$\underline{H}_2$NCH$_2$), 52.3 (C$\underline{H}_2$NCH$_2$), 52.2 (NC$\underline{H}_2$CH$_3$), 47.7 (CONC$\underline{H}_2$), 42.1 (CONC$\underline{H}_2$), 14.0 (furan C$\underline{H}_3$), 11.8 (NCH$_2$C$\underline{H}_3$). EI-HRMS m/z: calcd for $C_{22}H_{25}N_5O_2$, 391.2008, found 391.2005; Purity (HPLC): 100%. *In no particular order.

4-(5-methylfuran-2-yl)-6-[3-(piperidine-1-carbonyl)phenyl]pyrimidin-2-amine (**2m**)



The title compound was prepared from (2*E*)-1-(5-methylfuran-2-yl)-3-[3-(piperidine-1-carbonyl)phenyl]prop-2-en-1-one (**1m**) in a yield of 56%: 179.2-180.5 ℃ (methanol), ora nge crystals. ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.12 – 8.05 (m, 2H, H-2', H-6'), 7.52 – 7.44 (m, 2H, H-4', H-5'), 7.35 (s, 1H, H-5), 7.09 (d, *J* = 3.4 Hz, 1H, H-3''), 6.15 (dd, *J* = 1.1, 3.4 Hz, 1H, H-4''), 5.35 (s, 2H, NH$_2$), 3.73 (br s, 2H, CONC$\underline{H}_2$), 3.36 (br s, 2H, CONC$\underline{H}_2$), 2.42 (s, 3H, C$\underline{H}_3$), 1.77 – 1.39 (m, 6H, 3 x piperidine C$\underline{H}_2$).^{13}C NMR (151 MHz, CDCl$_3$) δ 169.8 (C=O), 164.9 (C-2 or C-6), 163.4 (C-2 or C-6), 157.2 (C-4), 155.2 (C-5''), 150.4 (C-2''), 137.9 (C-1'), 136.8 (C-3'), 128.7, 128.5, 127.9 125.7 (C-2', C-4', C-5', C-6'), 113.1 (C-3''), 108.7 (C-4''), 101.6 (C-5), 48.8 (CONC$\underline{H}_2$), 43.1 (CONC$\underline{H}_2$), 26.5, 25.5, 24.5 (3 x piperidine C$\underline{H}_2$), 14.00 (C$\underline{H}_3$). EI-HRMS m/z: calcd for $C_{21}H_{22}N_4O_2$, 362.1743, found 362.1729; Purity (HPLC): 97%.

4-(5-methylfuran-2-yl)-6-[3-(pyrrolidine-1-carbonyl)phenyl]pyrimidin-2-amine (**2n**)



The title compound was prepared from (2*E*)-1-(5-methylfuran-2-yl)-3-[3-(pyrrolidine-1-carbonyl)phenyl]prop-2-en-1-one (**1n**) in a yield of 27%: 213.7-213.8 ℃ (methanol), yel low crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (t, *J* = 1.8 Hz, 1H, H-2'), 8.10 (dt, *J* = 1.5, 7.8 Hz, 1H, H-6'), 7.59 (dt, *J* = 1.4, 7.7 Hz, 1H, H-4'), 7.49 (t, *J* = 7.7 Hz, 1H, H-5'), 7.36 (s, 1H, H-5), 7.08 (d, *J* = 3.4 Hz, 1H, H-3''), 6.14 (dd, *J* = 1.2, 3.3 Hz, 1H, H-4''), 5.37 (s, 2H, $N\underline{H_2}$), 3.66 (t, *J* = 7.0 Hz, 2H, $CONC\underline{H_2}$), 3.44 (t, *J* = 6.7 Hz, 2H, $CONC\underline{H_2}$), 2.41 (s, 3H, $C\underline{H_3}$), 1.95 (p, *J* = 7.0 Hz, 2H, $CH_2C\underline{H_2}CH_2$), 1.86 (p, *J* = 6.7 Hz, 2H, $CH_2C\underline{H_2}CH_2$).^{13}C NMR (151 MHz, $CDCl_3$) δ 169.2 (C=O), 164.8 (C-2 or C-6), 163.4 (C-2 or C-6), 157.2 (C-4), 155.2 (C-4''), 150.5 (C-1''), 137.7 (C-1' or C-3'), 137.6 (C-1' or C-3'), 128.8, 128.5, 128.3, (C-4', C-5', C-6')*, 125.9 (C-2'), 113.1 (C-3''), 108.7 (C-4''), 101.5 (C-5), 49.6 ($CON\underline{C}H_2$), 46.2 ($CON\underline{C}H_2$), 26.3 ($CH_2\underline{C}H_2CH_2$), 24.4 ($CH_2\underline{C}H_2CH_2$), 14.0 ($\underline{C}H_3$). EI-HRMS m/z: calcd for $C_{20}H_{20}N_4O_2$, 348.1586, found 348.1573; Purity (HPLC): 95%. *In no particular order.

3.4 Summary

In this chapter the design, synthesis and characterisation of the 2-aminopyrimidines and their chalcone intermediates were described. The designed 2-aminopyrimidines were docked within the active site of the adenosine A_{2A} receptor to investigate the binding orientations of compounds and interactions between compounds and residues in the active site. The results indicated that all screened compounds have the necessary features to potentially be good adenosine A_{2A} antagonists.

All compounds were synthesised according to literature procedures and were fully characterised by NMR spectroscopy and mass spectrometry. HPLC was also used to determine the purity of all synthesised compounds.