Chapter 5

Transition-Metal-Free C–N Cross-Coupling of Coumarins Enabled by a Multifunctional Reagent

5. Transition-Metal-Free C–N Cross-Coupling of Coumarins Enabled by a Multifunctional Reagent

5.1 Introduction

Easy synthetic access to variably functionalized coumarins is of utmost importance as this chemical motif serves as a crucial component of various natural products along with the benefits of a multitude of biological activities and tunable photophysical properties.[1-5] Among the wide palette of fluorophores, coumarins have been selected multiple times as resourceful bioimaging tools for their high quantum yields and biocompatibility, and minor synthetic adjustments can lead to modulation of their fluorescent properties. It has been established that 7-aminocoumarins are more preferred central scaffolds for fluorescence imaging applications than 7-hydroxycoumarins due to their better quantum yield, photostability, wider pH range stability, and better scope for synthetic modification.[3-6] Traditionally, 7-aminocoumarins are constructed from their corresponding aminophenols via Pechmann and other traditional condensation reactions, such as Perkin, Knoevenagel, etc. (figure 5.1i). Although fairly simple and less technical, such condensation pathways for the synthesis of coumarins are restricted by harsh reaction conditions and lack of substrate availability. Besides, metal-catalyzed approaches have also been adopted using Buchwald Hartwig coupling reactions with coumarin sulfonates, which have helped to extend the substrate scope of aminocoumarins (figure 5.1ii).[7-8] Several metal-free alternatives have also been reported that curtail the generation of sensitive intermediates and provide better chemoselectivity. Recently, the utilization of Smiles rearrangement for the introduction of nitrogen functionalities to a moiety has gained much attention. Kumar *et al.* synthesized *N*-arylated coumarin scaffolds based on Smiles rearrangement of *O*-arylated coumarin constructed from 4-bromo coumarin and 2-amino phenols under mild reaction conditions.[9] Lippe and group prepared a number of *N*-alkyl and *N*-aryl 7-aminocoumarins from their respective coumarin acetamide precursors in a

single step via Smiles rearrangement without the employment of metals (Figure 5.1iii).[10]Although these methods show great potential in terms of mild reaction conditions, excellent substrate tolerability, and simple and hassle-free techniques, in all cases, the availability of corresponding precursors and the feasibility of their synthesis becomes a limiting factor. In order to eliminate the requirement of any precursor, we sought to develop a reaction methodology for incorporating nitrogen functionality using a multifunctional reagent, dichloro-dicyanopyrazine, which utilizes phenols and amines as coupling partners.[11] With our continuing interests in the development of new-age 7-aminocoumarin fluorescent molecules,[4,5] herein, we report the design of a one-pot transition-metal-free reaction protocol for the accessible synthesis of 7-aminocoumarin derivatives from β-methyl umbelliferone. The net impact of induced proximity of nucleophile and electrophile and electronic rearrangement drives the reaction.

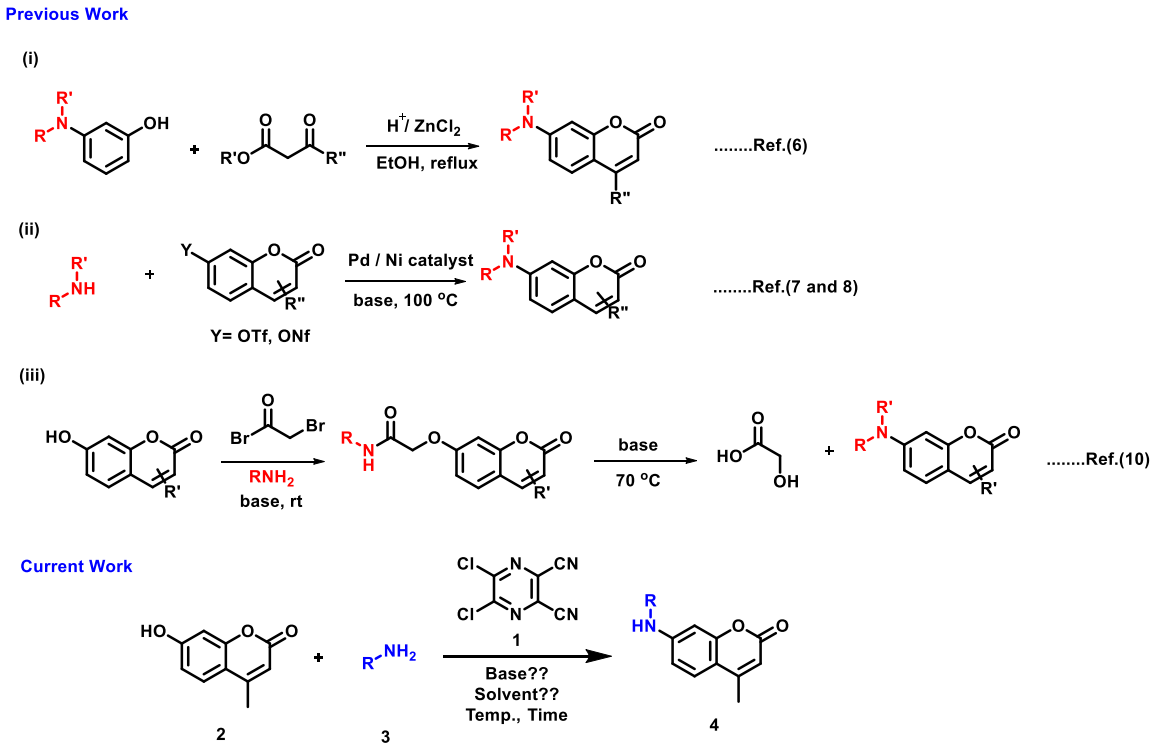


Figure 5.1: Synthetic methodologies for constructing 7-aminocoumarins using (i) Pechmann condensation of aminophenols, (ii) Buchwald–Hartwig C-N cross-coupling of sulfonylated

hydroxycoumarins, (iii) amination of coumarin ethers via Smiles rearrangement followed by hydrolysis and (iv) current approach of transition metal-free C-N bond cross coupling using multifunctional reagent.

5.2 Results and Discussion

To check the feasibility of the perceived methodology, we first started with simple nucleophilic aromatic substitution (S_NAr) of the multifunctional dichlorodicyanopyrazine (**1**) with aniline (**3a**) as the model amine (scheme 5.1, table 5.1). **3a** (1 mmol) was reacted with **1** (1 equiv.) in the presence of K_3PO_4 (1.2 equiv.) in ACN at a slightly elevated temperature of 50 ^oC for 2h to produce the corresponding aminated product **IIIa** in about 51% yield (Table 5.1, entry 1). Raising the quantity of base to 1.5 and 2 equivalences led to an increase in the yield of **IIIa** (59% and 67%) (entries 2-3). However, a further increase to 2.5-3 equivalents led to a decrease in the yield of **IIIa** (45%) with the simultaneous formation of the undesired disubstituted byproduct (**IVa**) in 32% yield (entry 4). Next, to check the solvent effect, the reaction was carried out in other solvents, such as THF, DMF, DMSO and 1,4-dioxane (entries 5-8). In THF and DMF, the yield was moderately improved to 88% and 76%, respectively, but in DMSO, it was reduced drastically to almost 5%. In 1,4-dioxane, the formation of intermediate **IIIa** was found to be maximum (98%). After optimizing the solvent, our next goal was to check the effect of different bases on the yield, so we replaced K_3PO_4 with K_2CO_3, KOH, Cs_2CO_3, KO*t*Bu and NaH keeping the rest of the conditions the same as above (entries 9-13). The yield of **IIIa** was found to be decreased in all the cases (49%, 72%, 84%, 78% and 69%, respectively) as compared to the K_3PO_4 triggered reaction. With these optimized conditions in hand, we then sought to carry out the second S_NAr reaction of the intermediate **IIIa** with β-methylumbelliferone (**2**). After ensuring the complete conversion of **3a** to **IIIa** using thin-layer chromatography (TLC), we then added **2** (0.76

equiv. w.r.t. **3a**) to the reaction mixture with another 3 equiv. of K_3PO_4 and refluxed the resultant reaction mixture at 100 ^oC for another 30 mins. The requirement of excessive base was to enable the occurrence of the second S_NAr and stipulated Smiles rearrangement in a single step. However, to our utter dismay, we discovered the desired product **Va** was not formed due to certain solubility issues (entry 14). Usually, high polarity solvents like DMSO are used to promote rearrangement. So, to find a common solvent system for smooth proceeding of both nucleophilic substitutions as well as the rearrangement, we thought of using a mixture of solvents. After a few hits and trials and with the help of literature support, we used a mixture of 1,4-dioxane and DMSO (1:2) and to our delight, the formation of desired product **Va** was obtained in 98% yields (entry 15). Finally, the reduction of Va with Zn/acetic acid led to cleavage of the multifunctional reagent and release of final product **4a** in 95% yield**.**

Scheme 5.1: Synthetic scheme for one-pot synthesis of 7-aminocoumarins.

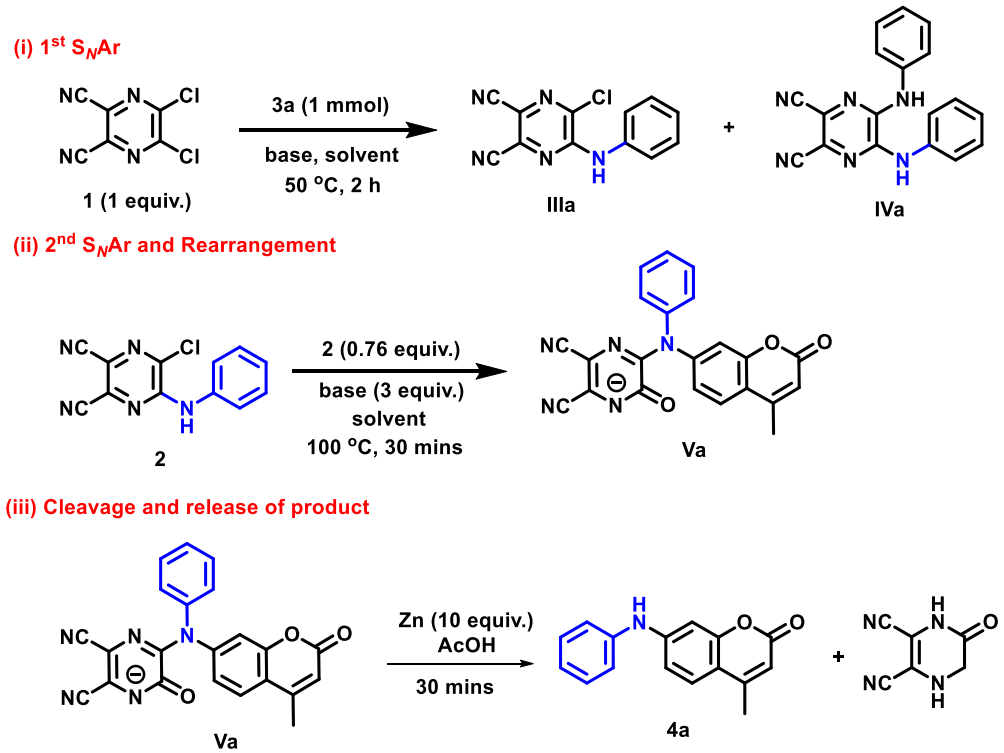


Table 5.1: Optimisation table for reaction conditions

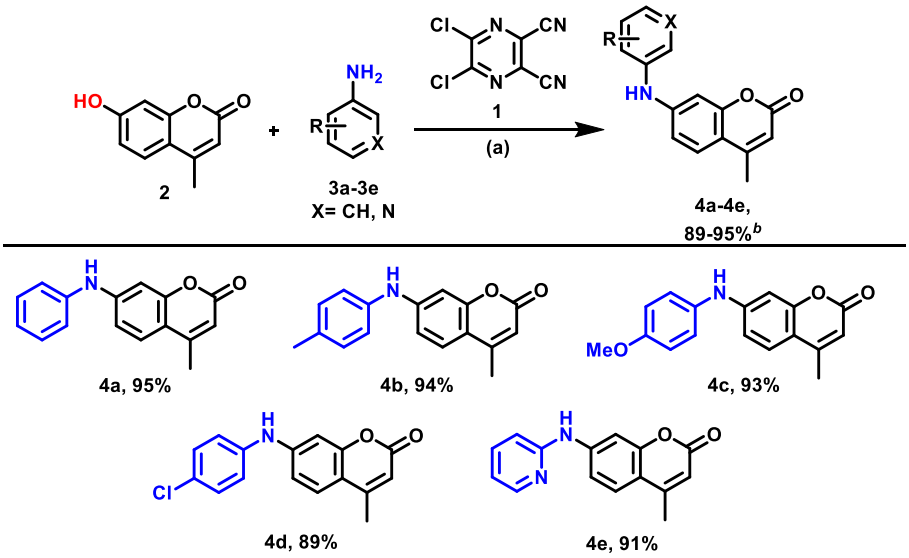
Entry	Base (equiv.)	Solvent	Temp(°C) /Time (h)	Yield of IIIa (%)[a]	Yield of Va (%)[c]
(i) For 1st aromatic nucleophilic substitution reaction (S_NAr)					
1	K_3PO_4 (1.2)	ACN	50 / 2	51	-
2	K_3PO_4 (1.5)	ACN	50 / 2	59	-
3	K_3PO_4 (2)	ACN	50 / 2	67	-
4	K_3PO_4 (2.5-3)	ACN	50 / 2	45 (32)[b]	-
5	K_3PO_4 (2)	THF	50 / 2	88	-
6	K_3PO_4 (2)	DMF	50 / 2	76	-
7	K_3PO_4 (2)	DMSO	50 / 2	5	-
8	K_3PO_4 (2)	1,4-Dioxane	50 / 2	98	-
9	K_2CO_3	1,4-Dioxane	50 / 2	49	-
10	KOH (2)	1,4-Dioxane	50 / 2	72	-
11	Cs_2CO_3 (2)	1,4-Dioxane	50 / 2	84	-
12	KO*t*Bu (2)	1,4-Dioxane	50 / 2	78	-
13	NaH (2)	1,4-Dioxane	50 / 2	69	-
(ii) **For 2nd aromatic nucleophilic substitution reaction (S_NAr) and rearrangement step**					

14	K_3PO_4 (2)	1,4-Dioxane	100 / 0.5	-	0
15	K_3PO_4 (2)	1,4-Dioxane:DMSO (1:2)	100 / 0.5	-	98

Reagents and Conditions. (i) **1** (1equiv.) **3a** (1 mmol), solvent (3 mL), heat at 50 °C for 2 h. (ii) **2** (0.76 equiv.), base (3 equiv.), solvent (6 mL), heat at 100 °C for 30 mins. (iii) Zn dust (10 equiv.), AcOH (8 mL), heat at 80 °C for 30 mins. [a]Isolated yields of IIIa, [b]Isolated yields of IVa, [c]Isolated yields of Va.

After optimisation of the total synthetic scheme, our next objective was to evaluate the substrate scope of the designed methodology. For this, we selected several aromatic amines and subjected them to reaction with **2** using the optimised reaction conditions (scheme 5.2). A total of 5 aromatic amines were chosen and all of them produced the desired compounds **4a-4e** in excellent yields (89-95%). The presence of both electron-donating **(4b-4c)** and electron withdrawing **(4d)** groups seem to be well tolerated by the reaction. Moreover, heteroatom containing aromatic amines, as in aminopyridines, are also well tolerated and give desired product **4e** in about 91% yield.

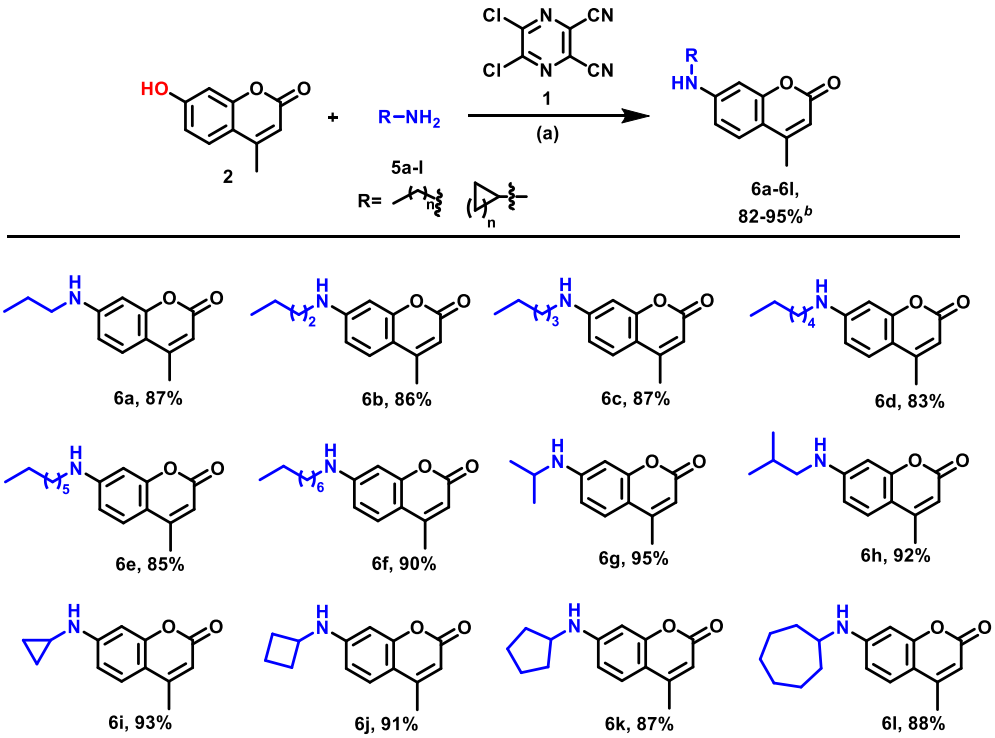
Scheme 5.2: Substrate scope of aromatic amines.[a]



[a]Reagents and Conditions: (a) **1** (1 equiv.) **3a-3e** (1 mmol), K_3PO_4 (2 equiv.), 1,4-dioxane, heat at 50 °C for 2 h followed by addition of **2** (0.76 equiv.), K_3PO_4 (3 equiv.) DMSO (1:2), heat at 100 °C for 30 mins. Finally, addition of Zn dust (10 equiv.), AcOH (8 mL) with heating at 80 °C for another 30 mins. [b]Isolated yields.

Delighted with the success of the method with aromatic amines, we then sought to extend its substrate scope to variable aliphatic and alicyclic amines (scheme 5.3). Aliphatic amines starting from propyl to octylamines showed good tolerability along with moderate yields of the desired products (**6a-6f**, 83-90%). Branched chain alkyl amines like isopropyl- and isobutylamines showed greater affinity to the reaction with better yields (92-95%) of the corresponding aminated products **6g** and **6h**. Alicyclic amines ranging from cyclopropyl- to cycloheptyl amines showed decent tolerance to the methodology and their corresponding 7-cycloalkylaminocoumarin derivatives **(6i-6l)** were afforded in good to excellent yields (88-93%).

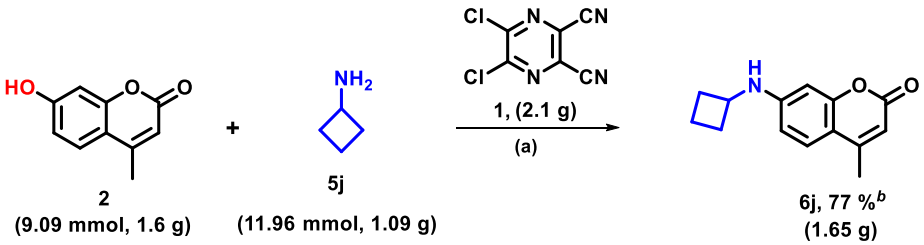
Scheme 5.3: Substrate scope of aliphatic and alicyclic amines.[a]



[a]Reagents and Conditions: (a) **1** (1 equiv.) **5a-5l** (1 mmol), K_3PO_4 (2 equiv.), 1,4-dioxane, heat at 50 °C for 2 h followed by addition of **2** (0.76 equiv.), K_3PO_4 (3 equiv.), 1,4-dioxane:DMSO (1:2), heat at 100 °C for 30 mins. Finally, the addition of Zn dust (10 equiv.), AcOH (8 mL) with heating at 80 °C for another 30 mins. [b]Isolated yields.

After exploring the substrate scope, we proceeded to evaluate the robustness of the methodology. We carried out a gram scale synthesis of compound **6j** (Scheme 5.4)**,** which has been reported to be a very efficient and bright 7-aminocoumarin fluorophore,[4] using the optimised reaction protocol. After completion of the reaction, we found that **6j** was produced in 77% yield (1.65 g).

Scheme 5.4: Gram Scale synthesis of compound **6j**.[a]

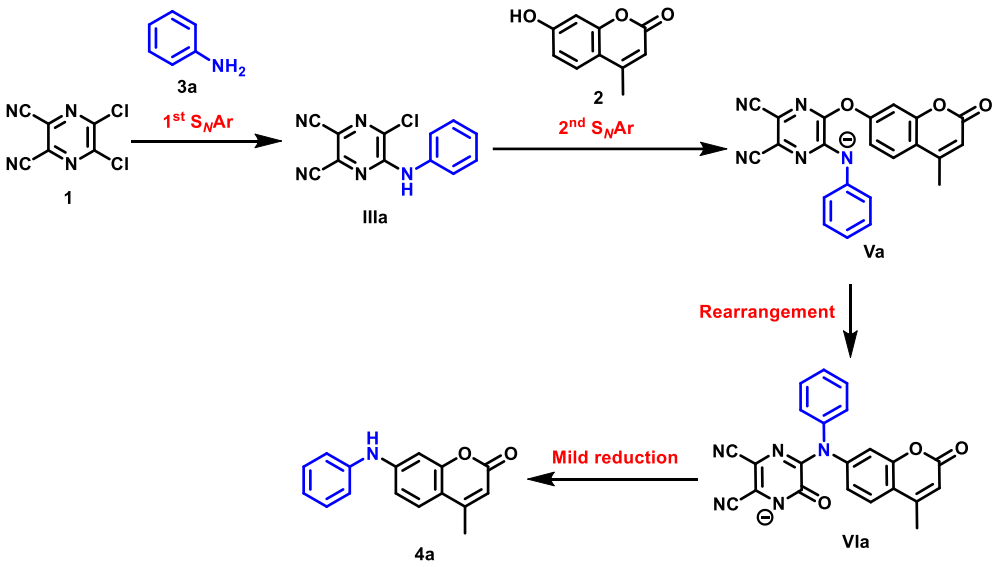


[a]Reagents and Conditions: (a) **1** (1 equiv., 2.1 g) **5j** (1 equiv., 11.96 mmol, 1.09 g), K_3PO_4 (2 equiv.), 1,4-dioxane: (1:2), heat at 50 °C for 2 h followed by addition of **2** (0.76 equiv., 9.09 mmol, 1.6 g), K_3PO_4 (3 equiv.), DMSO, heat at 100 °C for 30 mins. Finally, addition of Zn dust (10 equiv.), AcOH (8 mL) with heating at 80 °C for another 30 mins. [b]Isolated yield of **6j**.

With the help of literature report and above findings, a plausible reaction mechanism has been proposed (scheme 5.5). The multifunctional reagent undergoes S_NAr substitution with aniline (3a) in presence of a base to produce the intermediate IIIa. Due to deactivation of the pyrazine ring by the attachment of the electron rich aniline portion, the chances of further substitution with another molecule of aniline are usually prevented. Next, addition of **2** to the reaction along with more base leads to a second S_NAr substitution of **IIIa** to produce intermediate **Va**

which undergoes internal rearrangement to intermediate **VIa.** Ultimately, mild reduction of **VIa** yields the desired cross coupled product **4a** in a transition metal-free single pot reaction method.

Scheme 5.5: Plausible reaction mechanism.



5.3 Conclusion

In summary, we have demonstrated a single pot transition metal-free method for synthesis of *N*-aryl or *N*-alkyl 7-aminocoumarins **(4a-4e** and **6a-6l)** from readily available and inexpensive precursor β-methyl umbelliferone. The reaction curtails the requirement of expensive transition metals, pre-activated substrates and expensive reaction set up. It provides the benefits of easy reaction conditions, moderate temperatures, broader substrate scope and decent functional group tolerance. The reaction is triggered by the total effect of induced proximity of nucleophile and electrophile followed by electronic rearrangement for net dehydrative C–N coupled products.

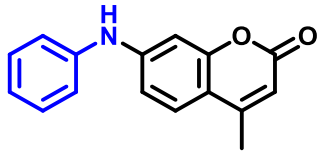
5.4 Experimental section

5.4.1 General procedure for synthesis of 7-aminocoumarins (4a-4e and 6a-6l): To a screw-cap vial equipped with a stir bar were added amine (**3**, 1.3 equiv), anhydrous 1,4-Dioxane (4.0

mL per mmol of **3**), 5,6-dichloropyrazine-2,3-dicarbonitrile (**1**, 1.2 equiv), and anhydrous K_3PO_4 powder (5.0 equiv). The reaction mixture was heated at 50 °C for 2 h during which time the amine and 5,6- dichloropyrazine-2,3-dicarbonitrile were converted to the S_NAr adduct. Next, DMSO (8.0 mL per mmol of **3**) and coumarin (**2**, 1.0 equiv) were added, and the resulting mixture was heated at 100 °C for 30 minutes to induce the Smiles rearrangement. The reaction mixture was cooled to room temperature and treated with AcOH (12.0 mL per mmol of **2**) and zinc (10.0 equiv). The resulting mixture was heated at 80 °C for 30 minutes to ensure full reductive cleavage of the rearranged intermediate. After complete conversion, the reaction mixture was diluted with EtOAc, filtered, and washed with water three times. The organic was dried with $MgSO_4$, concentrated to dryness, and the crude residue was purified by silica gel chromatography eluting with EtOAc in hexanes to afford the corresponding aminated product **4a**.

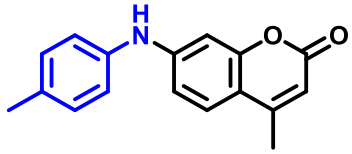
5.4.2 Gram-scale procedure for the synthesis of compound 6j: To a round bottom flask equipped with a stir bar were added amine (**5j**, 11.06 mmol), anhydrous 1,4-Dioxane (4.0 mL per mmol of **3**), 5,6-dichloropyrazine-2,3-dicarbonitrile (**1**, 1.2 equiv), and anhydrous K_3PO_4 powder (5.0 equiv). The reaction mixture was heated at 50 °C for 2 h. Next, DMSO (8.0 mL per mmol of **2**) and coumarin (**2**, 1.0 equiv) were added, and the resulting mixture was heated at 100 °C for 30 minutes. The reaction mixture was cooled to room temperature and treated with AcOH (12.0 mL per mmol of **2**) and zinc (10.0 equiv). The resulting mixture was heated at 80 °C for 30 minutes and the reaction mixture was diluted with EtOAc, filtered, and washed with water three times. The organic was dried with $MgSO_4$, concentrated to dryness, and the crude residue was purified by silica gel chromatography eluting with EtOAc in hexanes to afford the corresponding aminated product **6j**.

5.5 Analytical Data of Synthesized Compounds



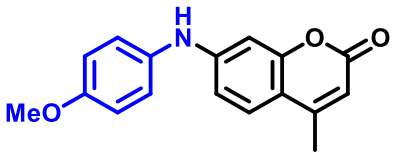
4-Methyl-7-(phenylamino)-2H-chromen-2-one (4a)

The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **4a** was obtained as a yellow solid with 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.6 Hz, 1H), 7.40–7.32 (m, 2H), 7.23–7.17 (m, 2H), 7.14–7.07 (m, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.15 (br s, 1H), 6.07 (d, *J* = 1.1 Hz, 1H), 2.38 (d, *J* = 1.2 Hz, 3H).



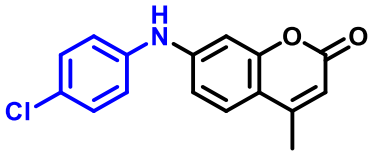
4-Methyl-7-(*m*-tolylamino)-2*H*-chromen-2-one (4b)

The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **4b** was obtained as a yellow solid with 94% yield. ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.81 (br s, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.25–7.20 (m, 1H), 7.02–6.95 (m, 3H), 6.85 (d, J = 2.1 Hz, 1H), 6.85–6.82 (m, 1H), 6.05 (d, J = 1.2 Hz, 1H), 2.35 (d, J = 2.1 Hz, 3H), 2.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d^6) 160.4, 155.0, 153.4, 148.0, 141.0, 138.8, 129.2, 126.4, 123.0, 120.0, 116.7, 112.2, 111.3, 109.3, 99.9, 21.1, 18.0. HRMS (EI) m/z: [M+] calcd for $C_{17}H_{15}NO_2$, 265.1103; found, 265.1099.



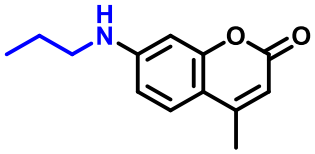
7-((4-Methoxyphenyl)amino)-4-methyl-2H-chromen-2-one (4c)

The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **4c** was obtained as a yellow solid with 93% yield. ^{1}H NMR (400 MHz, DMSO-d^6, ppm): δ 8.63 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 9.1 Hz, 2H), 6.95 (d, J = 9.1 Hz, 2H), 6.83 (dd, J = 8.7, 2.3 Hz, 1H), 6.67 (d, J = 2.3 Hz, 1H), 6.00 (d, J = 1.1 Hz, 1H), 3.75 (s, 3H), 2.33 (d, J = 1.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 160.5, 155.4, 155.2, 153.5, 149.5, 133.6, 126.4, 122.9, 114.7, 111.2, 110.5, 108.7, 98.4, 55.2, 18.0. HRMS (EI) m/z: [M+] calcd for $C_{17}H_{15}NO_3$, 281.1052; found, 281.1054.



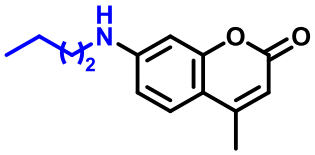
7-((4-chlorophenyl)amino)-4-methyl-2H-chromen-2-one (4d)

The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **4d** was obtained as a yellow solid with 89% yield. ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.23 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.21–7.09 (m, 3H), 6.49 (bd, J = 8.1 Hz, 2H), 6.07 (br s, 1H), 5.95 (d, J = 1.1 Hz, 2H), 2.31 (d, J = 1.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d^6, ppm): δ 160.5, 155.5, 153.6, 151.0, 136.8, 136.0, 128.5, 126.5, 126.5, 109.9, 109.8, 108.2, 97.1, 18.0, 17.8. HRMS (EI) m/z: [M+] calcd for $C_{16}H19NO_2$, 279.1259; found, 279.1254.



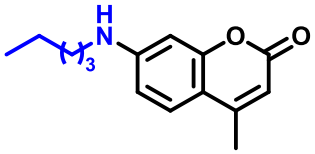
4-methyl-7-(propylamino)-*2H*-chromen-2-one (**6a**)

The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **6a** was obtained as a yellowish brown solid with 87% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.75 Hz, 1H), 6.51 (dd, *J* = 2 Hz, 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 5.97 (s, 1H), 4.29 (s, 1H), 3.15 (q, *J* = 7 Hz, 2H), 2.35 (s, 3H), 1.72–1.65 (m, 2H), 1.02 (t, *J* = 7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 156.0, 153.0, 151.7, 125.4, 110.3, 110.2, 109.2, 97.9, 45.2, 22.3, 18.5, 11.5. HRMS (ESI) *m/z* calculated for $C_{13}H_{15}O_2N$ $[M + H]^+$ calculated as 218.1176, found 218.1182.



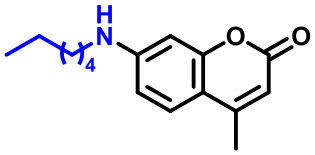
4-methyl-7-(butylamino)-*2H*-chromen-2-one (**6b**)

The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **11** was obtained as a green solid with 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 1H), 6.51 (dd, *J* = 2 Hz, 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 5.99 (s, 1H), 4.26 (s, 1H), 3.18 (t, *J* = 7.0 Hz, 2H), 2.35 (s, 3H), 1.64 (quint, *J* = 7.5 Hz, 2H), 1.49–1.42 (m, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 156.0, 153.0, 151.7, 125.4, 110.4, 110.2, 109.3, 97.9, 43.2, 31.2, 20.2, 18.5, 13.8. HRMS (ESI) *m/z* calculated for $C_{14}H_{17}O_2N$ $[M + H]^+$ calculated as 232.1332, found 232.1340.



4-methyl-7-(pentylamino)-*2H*-chromen-2-one (6c)

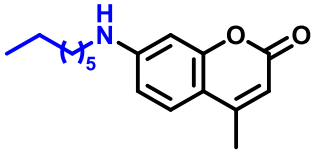
The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **6c** was obtained as a brownish yellow solid with 87% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9.0 Hz, 1H), 6.51 (dd, *J* = 2.5 Hz, 2.5 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.98 (d, *J* = 1 Hz, 1H), 4.26 (s, 1H), 3.17 (t, *J* = 7 Hz, 2H), 2.35 (d, *J* = 1 Hz, 3H), 1.66 (quint, *J* = 7.5 Hz, 2H), 1.42–1.38 (m, 4H), 0.94 (t, *J* = 7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 156.0, 152.9, 151.7, 125.4, 110.3, 110.2, 109.2, 97.9, 43.4, 29.1, 28.8, 22.4, 18.5, 13.9. HRMS (ESI) *m/z* calculated for $C_{15}H_{19}O_2N$ $[M + H]^+$ calculated as 246.1489, found 246.1479.



4-methyl-7-(hexylamino)-*2H*-chromen-2-one (6d)

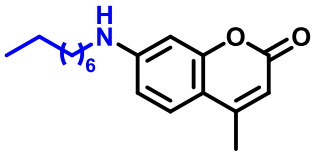
The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **6d** was obtained as a brown solid with 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 1H), 6.51 (dd, *J* = 2.5 Hz, 2.5 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.99 (s, 1H), 4.23 (s, 1H), 3.18 (q, *J* = 6.5 Hz, 2H), 2.36 (s, 3H), 1.69–1.63 (m, 2H), 1.36–1.30 (m, 6H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 155.0, 152.0, 150.6, 124.4,

109.3109.2, 108.2, 96.9, 42.5, 28.6, 28.1, 25.7, 21.5, 17.5, 13.0. HRMS (ESI) *m/z* calculated for $C_{16}H_{21}O_2N$ $[M + H]^+$ calculated as 260.1645, found 260.1654.



4-methyl-7-(heptylamino)-*2H*-chromen-2-one (6e)

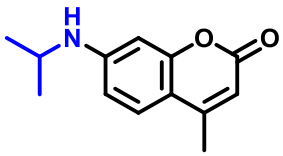
The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **6e** was obtained as a dark brown solid with 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9 Hz, 1H), 6.51 (dd, *J* = 2.0 Hz, 2.5 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.98 (d, *J* = 1 Hz, 1H), 4.24 (s, 1H), 3.19–3.15 (m, 2H), 2.35 (d, *J* = 1 Hz, 3H), 1.69–1.63 (m, 2H), 1.35–1.30 (m, 8H), 0.91 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.1, 156.0, 153.0, 151.7, 125.4, 110.3, 110.2, 109.1, 97.8, 43.5, 31.8, 29.1, 29.0, 27.0, 22.6, 18.5, 14.0. HRMS (ESI) *m/z* calculated for $C_{17}H_{23}O_2N$ $[M + H]^+$ calculated as 273.1729, found 273.1735.



4-methyl-7-(octylamino)-*2H*-chromen-2-one (6f)

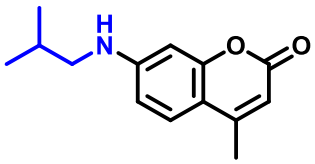
The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **6f** was obtained as a dark brown solid with 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9.0 Hz, 1H), 6.51 (dd, *J* = 2.5 Hz, 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 5.98 (s, 1H), 4.25 (s, 1H), 3.17–3.15 (m, 2H), 2.35 (s, 3H), 1.65 (quint, *J* = 7.5 Hz, 2H), 1.43–1.27 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 156.0, 153.0, 151.6,

125.4, 110.4, 110.2, 109.3, 97.9, 43.5, 31.8, 29.3, 29.2, 29.1, 27.0, 22.6, 18.5, 14.1. HRMS (ESI) *m/z* calculated for $C_{18}H_{25}O_2N$ $[M + H]^+$ as 288.1958, found 288.1968.



4-methyl-7-(isopropylamino)-*2H*-chromen-2-one (6g)

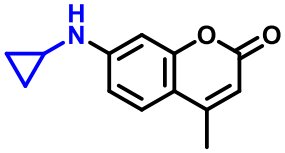
The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **6e** was obtained as a greenish brown solid with 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 1H), 6.48 (dd, *J* = 2.5, 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 5.99 (s, 1H), 4.06 (s, 1H), 3.73–3.66 (m, 1H), 2.36 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 156.0, 152.9, 150.6, 125.5, 110.6, 110.2, 109.2, 98.2, 44.2, 22.7, 18.5. HRMS (ESI) *m/z* calculated for $C_{13}H_{15}O_2N$ $[M + H]^+$ calculated as 218.1176, found 218.1182.



4-methyl-7-(isobutylamino)-*2H*-chromen-2-one (6h)

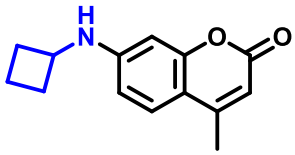
The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **6h** was obtained as a brownish yellow solid with 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9 Hz, 1H), 6.52 (dd, *J* = 2 Hz, 2.5 Hz, 1H), 6.45 (d, *J* = 2 Hz, 1H), 5.98 (s, 1H), 4.31 (s, 1H), 3.01 (d, *J* = 6.5 Hz, 2H), 2.35 (s, 3H), 1.98–1.90 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 156.0, 152.9, 151.7, 125.4, 110.3, 110.2, 109.2,

97.9, 51.2, 28.0, 20.3, 18.5. HRMS (ESI) *m/z* calculated for $C_{14}H_{17}O_2N$ $[M + H]^+$ calculated as 232.1332, found 232.1339.



7-(cyclopropylamino)-4-methyl-2H-chromen-2-one (**6i**)

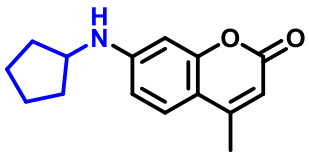
The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound 6 was obtained as an orange solid with 93% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 9.0 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.63 (dd, *J* = 2.0 Hz, 2.0 Hz, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 4.68 (s, 1H), 2.53–2.49 (m, 1H), 2.36 (s, 3H), 0.85–0.81 (m, 2H), 0.59–0.56 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 155.7, 153.1, 152.1, 125.3, 110.9, 110.6, 109.6, 99.0, 24.8, 18.6, 7.6. HRMS (ESI) m/z calculated for $C_{13}H_{13}O_2N$ [M + H]+ calculated as 216.1019, found 216.1028.



7-(cyclobutylamino)-4-methyl-2H-chromen-2-one (**6j**)

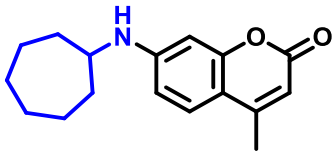
The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **6j** was obtained as a greenish yellow solid with 91% yield. 1H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 9 Hz, 1H), 6.47 (dd, *J* = 2.4 Hz, 2.4 Hz, 1H), 6.38 (d, *J* = 1.8 Hz, 1H), 5.95 (s, 1H), 4.68 (s, 1H), 3.96–3.91 (m, 1H), 2.47–2.42 (m, 2H), 2.32 (s, 3H), 1.91–1.80 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.2, 155.9, 153.2, 150.5, 125.5, 110.5, 110.4, 109.1, 98.2, 48.4, 30.8, 18.6,

15.3. HRMS (ESI) m/z calculated for C14H15O2N $[M + H]^+$ calculated as 230.1176, found 230.1197.



7-(cyclopentylamino)-4-methyl-2H-chromen-2-one (**6k**)

The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 35% ethyl acetate:hexane. Compound **6k** was obtained as a brownish yellow solid with 87% yield. 1H NMR (500 MHz, CDCl3) δ 7.34 (d, J = 8.5 Hz, 1H), 6.50 (dd, J = 2.0 Hz, 2.0 Hz, 2H), 6.46 (d, J = 2.5 Hz, 1H), 5.97 (d, J = 1Hz, 1H), 4.28 (s, 1H), 3.83 (t, J = 5.5 Hz, 1H), 2.35 (s, 3H), 2.34–2.04 (m, 2H), 1.77–1.66 (m, 4H), 1.55–1.48 (m, 2H). 13C NMR (151 MHz, CDCl3) δ 162.2, 155.9, 153.2, 153.1, 151.3, 125.4, 110.7, 110.1, 108.9, 98.3, 54.4, 33.3, 24.1, 18.6. HRMS (ESI) m/z calculated for $C_{15}H_{17}O_2N$ $[M + H]^+$ calculated as 244.1332, found 244.1361.

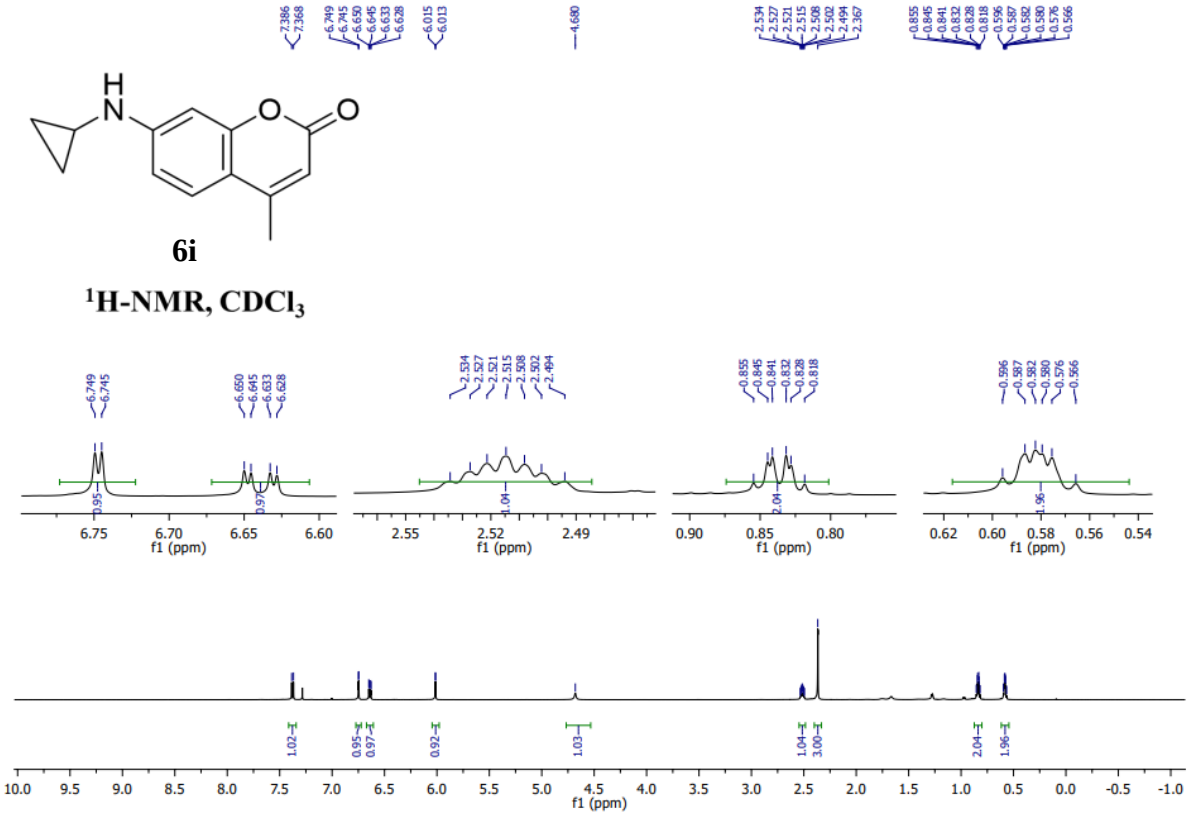


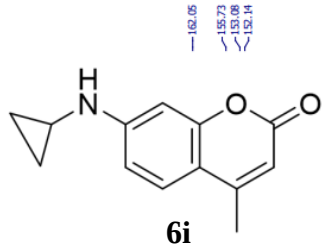
7-(cycloheptylamino)-4-methyl-2H-chromen-2-one (**6l**)

The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **6l** was obtained as a whitish yellow solid with 88% yield. ^{1}H NMR (500 MHz, CDCl3) δ 7.35 (d, J = 9.0 Hz, 1H), 6.46 (dd, *J* = 2.0 Hz, 2.5 Hz, 1H), 6.39 (d, *J* = 2.0 Hz, 1H), 5.98 (d, *J* = 1.0 Hz, 1H), 4.20 (s, 1H), 3.51–3.49 (m, 1H), 2.35 (d, *J* = 1.0 Hz, 3H), 2.06–2.01 (m, 2H), 1.74–1.49 (m, 10H). 13C NMR (125 MHz, $CDCl_3$) δ 162.1, 156.1, 152.9, 150.5, 125.5, 110.8, 110.1,

109.1, 98.3, 53.7, 34.6, 28.1, 24.3, 18.5. HRMS (ESI) m/z calculated for $C_{17}H_{21}O_2N$ $[M + H]^+$ calculated as 272.1645, found 272.1671.

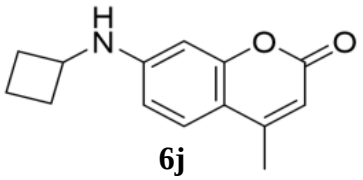
5.6 Spectral data of synthesised compounds





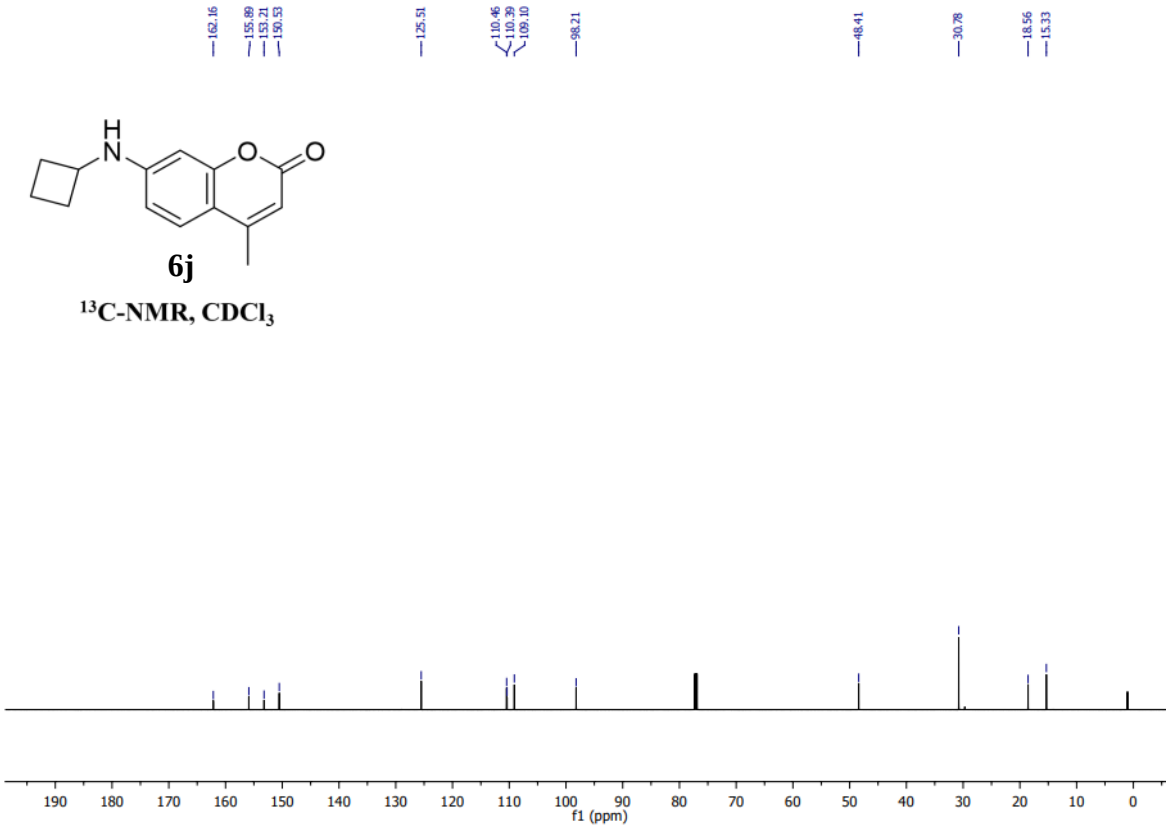
6i

^{13}C-NMR, $CDCl_3$



6j

^{1}H-NMR, $CDCl_3$



6j

^{13}C-NMR, $CDCl_3$

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