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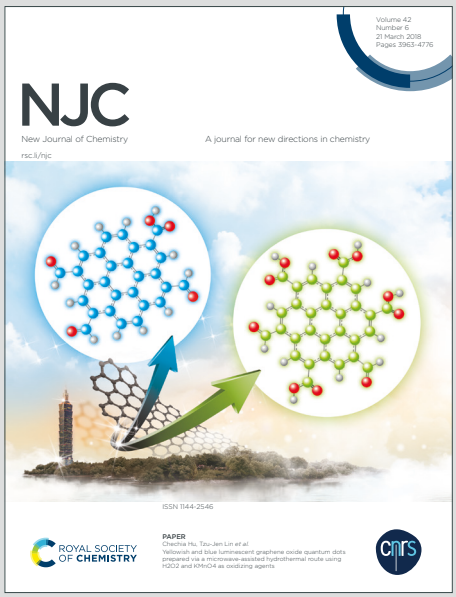

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ARTICLE

NHC-catalyzed green synthesis of functionalized chromones: DFT mechanistic insights and *in vitro* activities in cancer cells

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An efficient synthesis of 3-aminochromones and 3-alkylchromones by N-heterocyclic carbene (NHC) catalyzed intramolecular hydroacylation reaction of corresponding salicylaldehyde derived nitrile and activated alkynes respectively in ionic liquid under microwave condition is reported. This protocol has the rewards of environmental friendliness, higher yields, shorter reaction times, and convenient operation using the commercially available thiazolium catalyst. The origin of chemical reactivity of NHC-catalyzed intramolecular hydroacylation reaction of nitrile is studied with Density Functional Theory (DFT). The results suggest that 3-aminochromone formation occurs *via* an acyl anion intermediate called the Breslow intermediate (**INT2**) through TS2. Breslow intermediate (**INT2**) forms a carbon-carbon bond with the nitrile carbon to produce an imine intermediate **INT3** *via* **TS3**, which further undergoes imine to amine tautomerism to give an end product. Some of the derivatives of 3-aminochromone are subjected to amine functionalization in one pot to obtain a library of compounds for anticancer activity. Among the investigated compounds, **2c** (**SVM-2**), **4c** (**SVM-4**) and **2d** (**SVM-9**) show IC_{50} values of 5.18, 4.89 and 27.3 µM respectively in HeLa S3 cancer cells. Compound **5c** (**SVM-5**) shows IC_{50} values of 13.3 and 14.2 µM in A549 and HeLa S3 cancer cells, respectively. Compounds **2c** (**SVM-2**) and **4c** (**SVM-4**) produced morphological changes and controlled the colony formation in HeLa S3 cells, which indicate that these small molecules are potential candidates for anticancer drugs.

Introduction

N-heterocyclic carbene (NHC) catalysis has emerged as an efficient and selective strategy for organic transformations in modern chemistry.[1] They are heavily used owing to their *umpolung* reactivity and usefulness in forming important carbon-carbon bonds.[2-4] Of the heterocycles, chromones are among the most prevalent scaffolds found in natural products and pharmaceuticals.[5-8] In the last few decades, a wealth of research has been focused on the construction of these chromones.[9] Nonetheless, access to chromones with desirable substitution patterns using sustainable route remains a challenge when traditional multi-step approaches are applied.[10-11] Though classic synthetic protocols are available for chromone core construction, substituent patterns of these chromones are largely dictated by the activating groups that are required for reactivity.[12-15] Recently, chromones derived by intramolecular hydroacylation of alkene, nitrile, alkyne and activated alkyne have received much attention because of broad availability of the salicylaldehyde based starting materials, and several reports highlight the recent advances in this field.[14,16-21] Green approaches to diversely substituted chromones in shorter reaction time are highly desirable as chromones are well-known for their wide-range of pharmacological and biological activities. This heterocyclic motif especially 3-aminochromone has repeatedly been found in compounds exhibiting anti-inflammation, anti-rheumatic, anti-leukemic, anti-mutagenic and selectively inhibition of v-*abl* tyrosine protein kinases properties (Figure 1).[22-33] These motivate us to devise sustainable methodologies for its synthesis using NHC catalysis. In this regard, based on the earlier communications,[34,35] an intramolecular hydroacylation was employed using commercially available thiazolium salt in ionic liquid under microwave condition. From which, 3-aminochromones were generated, which were highly valuable building blocks for further functionalization that leads to a series of 3-aminochromone derivatives for anticancer activity.[22-33]

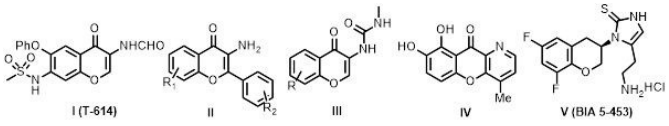

Figure 1. Biologically active 3-aminochromones.

Recently, the combinatorial syntheses of various new small organic molecules using NHC based organocatalytic approach were experimented with considerable success using various organic solvents.[34-38] To avoid the disadvantages such as volatility and toxicity of many organic solvents, inherently, we have employed

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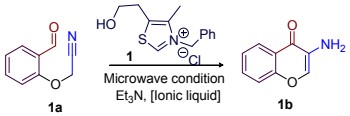
ionic liquids as a green medium for this intramolecular hydroacylation reaction. Ionic liquids have attracted our interest as using it is one of the four principal methods to avoid conventional organic solvents.[39,40] As organic salts with melting points below ambient temperature, they lack a measurable vapor pressure and have high chemical and thermal stabilities, which mark them as an environmentally benign reaction media.[41-43] Microwave activation is another green synthetic approach that has emerged as a powerful promoter of a variety of reactions, including organic reactions.[44-47] The irradiation of microwaves on the reaction mixture significantly reduces reaction time, enhances conversions and boasts environmental advantages as well as the induction of reactions under dry conditions.[44] In this article, we are presenting the achieved sustainable synthesis of chromone derivatives in line with the earlier communications on intramolecular hydroacylation chemistry[34,35] using commercially available thiazolium catalyst in ionic liquids under microwave condition. In earlier studies, chromone synthesis has been achieved using dry organic solvent with longer reaction time. Hence, we have undertaken an investigation using commercially available thiazolium (**1**) catalyst, salicyladehyde derived nitrile or activated alkyne as the reacting species in ionic liquid under microwave condition. Our computational studies elucidated the origin of intramolecular hydroacylation reactivity of nitrile. We also provide insights on the Breslow intermediate (**INT2**) favored reaction pathway. The resulting 3-aminochromones were further subjected to amine functionalization using one pot protocol or reaction with isolated 3-aminochromones to obtain a library of 3-aminochromone derivatives in good to excellent yields. In this case, a series of amide linked compounds was prepared by the reaction of amine with bromoacetylbromide followed by N-alkylation with morpholine or piperidine at 0 °C to rt. Successively, the isolated 3-aminochromones reacted with 3-formylchromone in various alcohols, formed a new class of three component addition products. Some of the amine functionalized compounds were subjected to *in vitro* anticancer activity using HeLa S3 and A549 cancer cell lines. Additionally, morphological changes and controlled colony formation in HeLa S3 cells have been studied using the active compounds. Furthermore, the developed sustainable reaction condition was applied to salicylaldehyde derived activated alkynes which delivered the 3-alkylchromones in good to excellent yields.

Results and discussion

We were pleased to find the green intramolecular hydroacylation reaction of 2-(2-formylphenoxy)acetonitrile (**1a**) using 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (**1**) as a catalyst, Et_3N as a base and 1 equivalent of commercially available ionic liquid as solvent under microwave condition (Table 1). Without the catalyst, in 1 equivalent of [bmim][BF_4], the reaction afforded only a trace amount of the product (**1b**) under microwave condition at 80 °C (entry 1) in one hour. When the amount of thiazolium salt **1** was increased along with the equal ratio of triethylamine (5, 10, 15 and 20 mol %), the yield of 3-aminochromone **1b** was improved (65, 77, 83 and 92 %) (entries 2-5). The use of 20 mol% of the catalyst (**1**) gave good yield (92 %) (entry 5). Further, decrease of reaction time (30 and 15 min) lowered the yield of **1b** from 92 % to 75 % and 63 % respectively (entries 6 and 7). Raising the reaction temperature from 80 to 100 °C did not improve the yield of **1b** (entry 8).

Table 1. Optimization of the reaction condition.

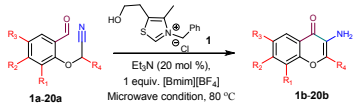


S. No.	**1** [mol %]	Solvent[a]	Et_3N [mol %]	Tem. [°C]	Time [min]	Yield [%][b]
1	0	[bmim][BF_4]	20	80	60	5
2	5	[bmim][BF_4]	5	80	60	65
3	10	[bmim][BF_4]	10	80	60	77
4	15	[bmim][BF_4]	15	80	60	83
5	**20**	[bmim][BF_4]	**20**	**80**	**60**	**92**
6	20	[bmim][BF_4]	20	80	15	63
7	20	[bmim][BF_4]	20	80	30	75
8	20	[bmim][BF_4]	20	100	60	91
9	20	[bmim][Cl]	20	80	60	82
10	20	[bmim][Br]	20	80	60	80

Reaction condition: [a]1 mole equiv. of ionic liquid was used w.r.t. starting material. [b]Isolated yield of **1b**

With other ionic liquids such as [bmim][Cl] and [bmim][Br] under entry 5 condition, the reaction provided moderate yields (entries 9 and 10). Finally, 0.2 equiv. of catalyst **1** and 0.2 equiv. of triethylamine in 1 equiv. of [bmim][BF_4] were employed at 80 °C over 60 min microwave irradiation to achieve **1b** (entry 5). With the optimized sustainable reaction condition in hand (Table 1, entry 5) for the synthesis of 3-aminochromone, we explored the generality of this reaction (Table 2). A broad range of differently substituted salicylaldehyde derived nitriles bearing electron-neutral, electron-donating, and electron-withdrawing substituent on aromatic rings were examined. Our results showed that the reaction can be effectively adopted for various salicylaldehyde derivatives (Table 2). The electron-neutral alkyl substituted aldehydes exhibited prominently good yields (**1b–5b**, 83–92 %). An electron-donating methoxy substituent in the aromatic ring was suitable for the reaction with no apparent change in reactivity and provided good to excellent yields (**6b–10b**, 80–94 %). Substrate with an electron-withdrawing nitro substituent in the aromatic ring showed a moderate yield of 78 % (**11b**). Further exploration revealed that the substrates with halo substituent(s) on the ring can give good to excellent yields (**12b–20b**, 81–93 %). Thus, scope of the reaction is wide, allowing the facile generation of a variety of 3-aminochromones in a sustainable manner with excellent yields. Our results showed that the intramolecular hydroacylation of nitrile can be adopted for various salicylaldehyde derived nitrile compounds. Furthermore, the reaction proceeded well with the compounds having active alkyne group (**1e–15e**) to obtain the corresponding 3-alkyl chromone derivatives (**1f–15f**) in good to excellent yields (Table 6). But the compound with 1-adamantane carbonyl group (**16e**) did not produce the desired product due to steric hindrance.

Table 2. Substrate scope of 3-aminochromones.[a]



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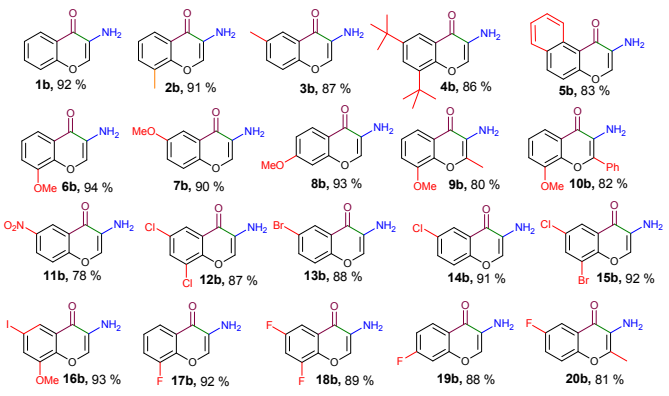
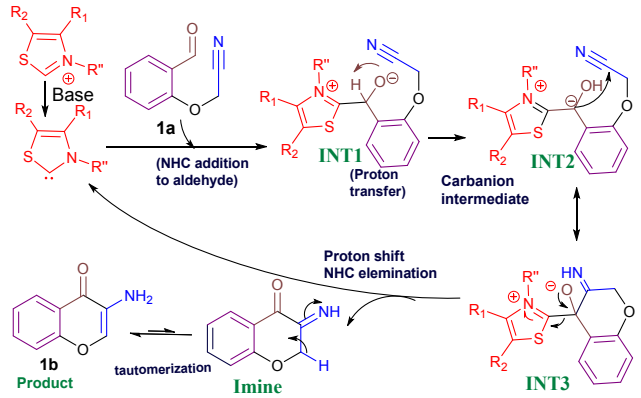


[a]Isolated yields of **1b-20b**

Density functional theory (DFT) calculation

Umpolung reactivity is an essential synthetic strategy in organic chemistry because it can offer an unconventional technique for conventional bond formation. Numerous NHC-catalyzed reactions have been developed by using the umpolung strategy such as benzoin condensation, Stetter reaction and cycloaddition/annulation reactions.[1-4] In accordance with the mechanistic studies of those reactions, we understood that the umpolung which triggered the whole catalytic cycle, did it by nucleophilic addition of the carbene carbon to the electrophilic carbon of the aldehyde, ketene, etc.[3b-j] The initial step of the title reaction was proposed to be the nucleophilic addition of the carbene carbon in the NHC (generated *in situ* from the deprotonation of the thiazolium cation by base) to the aldehyde, which resulted in the formation of a NHC-aldehyde adduct **INT1** (**INT**-intermediate) as shown in Scheme 1.



Scheme 1. Reaction mechanism based on the DFT calculation.

The reaction was accomplished *via* three stages, *i.e.* the formation of Breslow intermediate **INT2**, intramolecular hydroacylation of nitrile to give imine **INT3**, and imine-amine tautomerization. The calculated Gibbs free energy profile of the mechanism is shown in Figure 2**.** The free energy of the aldehyde + NHC was set as 0.0 kcal/mol. All the optimized structures and geometrical parameters are displayed in SI.[48] The B3LYP-DFT method has been successfully applied to gain better insights on the intramolecular hydroacylation reaction within the Breslow intermediate (**INT2**) catalyzed by NHC. The stable conformation (minimum free energy) of the starting materials, products, intermediates and transition states are shown in Figures 3-6. We have studied the hydroacylation reaction of 2-(2-formylphenoxy)acetonitrile (**1a**) using benzyl thiazolium catalyst (**1**). The mechanism proposed for this NHC-catalyzed transformation contained three intermediates and three transition states.

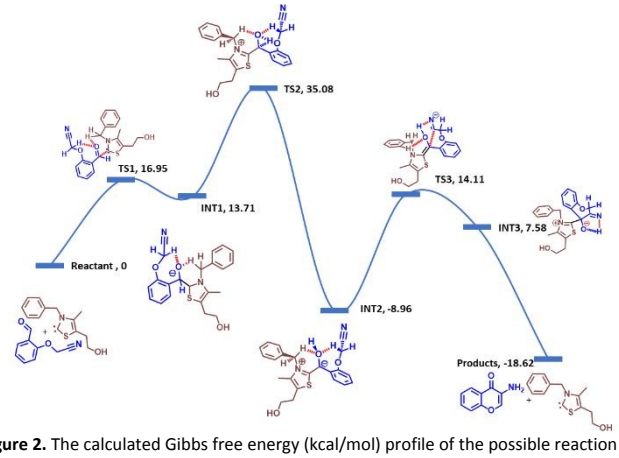


Figure 2. The calculated Gibbs free energy (kcal/mol) profile of the possible reaction pathway.

During the C–C bond formation between the catalyst and aldehyde, **TS1** (**TS** = Transition state) occurred, which showed two strong hydrogen bonding [H···O···H] interactions between the catalyst and reactant. Nucleophilic addition to the aldehyde formed **INT1** and negative charge on oxygen was stabilized through a hydrogen bond. Furthermore, an acyl anion intermediate (**INT2**) (–8.96 kcal/mol) was formed *via* **TS2** (35.08 kcal/mol). The barrier energy of **TS2** was found to be higher; however, the inclusion of solvation effect (Et_3N) substantially reduced the barrier to 19.46 kcal/mol. Also, we tracked down the base (Et_3N) incorporated transition state (See the stabilized TS in the SI). From this, we confirmed that the polarity of the carbonyl carbon had changed and umpolung strategy was attained. A close look on **INT2** revealed that this intermediate had two strong hydrogen bonding interactions involving methylene hydrogen atom present in the catalyst and the nitrile counterpart, which in turn stabilized the intermediate (Figure 5). Then hydroacylated product was formed through **TS3** (14.11 kcal/mol). Partial C–C bond cleavage was explained in **INT3** structure. After the tautomerization, **INT3** gave thermodynamically stable hydroacylated product 3-aminochromone which had the lowest Gibbs free energy (–18.62 kcal/mol) compared with the starting materials.

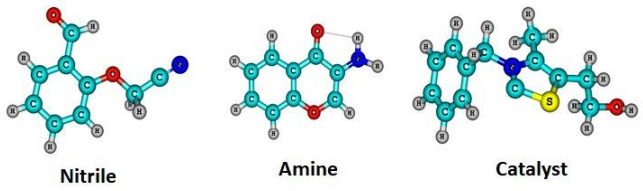


Figure 3. Minimum energy stable conformation of the nitrile, thiazolium catalyst and 3-aminochromone calculated at the B3LYP/6-31g (d,p) level of theory.

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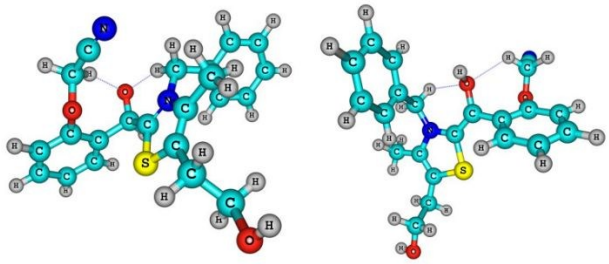


Figure 4. Minimum energy stable conformation of the intermediates (**INT1** and **INT2**) that occur during the formation of Breslow intermediate, calculated at the B3LYP/6-31g (d,p) level of theory.

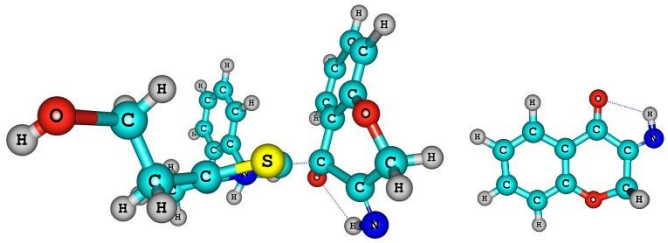


Figure 5. Minimum energy stable conformation of the imine intermediate (**INT3**) and imine calculated at the B3LYP/6-31g (d,p) level of theory .

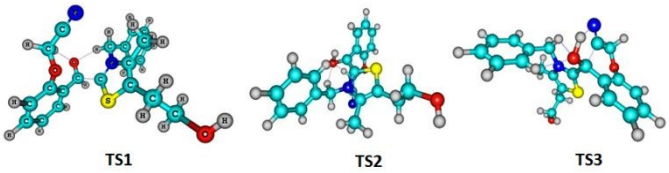
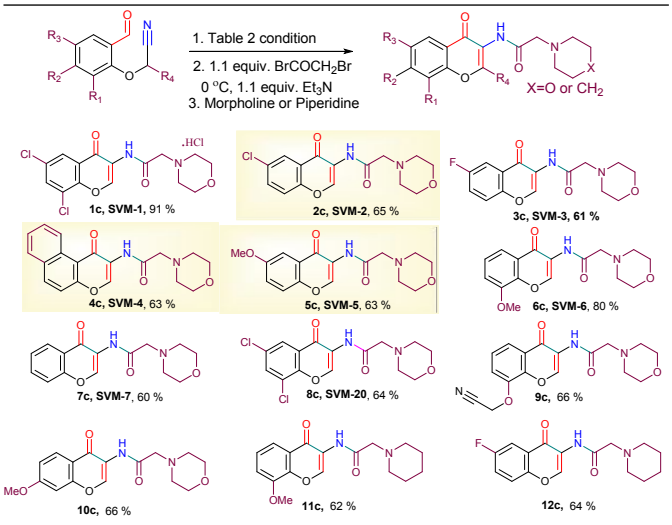


Figure 6. Minimum energy stable conformation of transition states **TS1**, **TS2** and **TS3**, calculated at the B3LYP/6-31g (d,p) level of theory.

Formation of 3-aminochromone derivatives

Table 3. Substrate scope for the amine functionalized 3-aminochromone.[a]



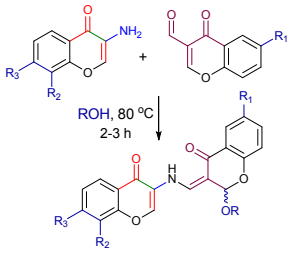
[a]Isolated yields of **1c-12c**

Functionalized 3-aminochromones showed various biological and pharmaceutical activities[22-33] which envisage us to make a new class of compounds for cancer treatment by functionalizing the amine part. After the formation of 3-aminochromones (Table 2 condition), they were reacted with 1.1 equiv. of bromoacetylbromide in presence of 2 equiv. of Et_3N for 30 min. The amine compounds were converted to amide derivatives which further reacted with morpholine or piperidine for another 2-10 h at room temperature to form morpholine or piperidine based N-functionalized 3-aminochromones in moderate yield. In this process, we have synthesized a series of compounds (**1c**-**12c**) easily in one pot using various 3-aminochromone derivatives under Table 2 condition (Table 3).

Three component reactions

During the course of amine functionalization, we intended to synthesize an another series of molecules for cancer treatment by carrying out one-pot three component addition reactions (Table 4). In this case, 1 equiv. of 3-aminochromone, 1 equiv. of 3-formylchromone and an excess amount of alcohol were refluxed (~80 °C) for 2 h to produce (*Z*)-3-(((2-alkoxy-4-oxochroman-3-ylidene)methyl)amino)-4H-chromen-4-one as yellow precipitate upon cooling. The compound was obtained selectively in one diasteromeric form which has been characterized by NMR and single crystal X-ray analyses. Crystal structure of **1d** is given in Figures 7 and 8. We explored the generality of the reaction by using various 3-formylchromones, 3-aminochromones and alcohols to obtain the desired three-component products (**1d**–**12d**) in moderate yields (65-78 %) (Table 4). The isolation of pure products was achieved by simple filtration of the precipitate and then washing with cold ethanol.

Table 4. Substrate scope for the amine functionalized 3-aminochromone.[a]

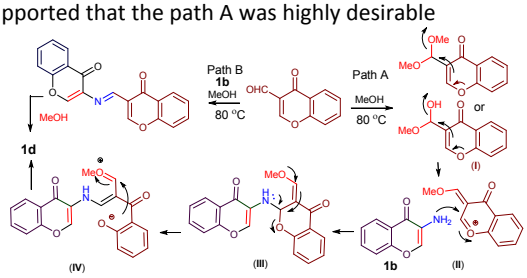


1d, (SVM-8) 68 % R=Me;R_1=R_2=R_3=H
2d, (SVM-9) 78 %; R= Et, R_1=R_2=R_3=H
3d, (SVM-19), 68 %; R= Isopropyl,R_1=R_2=R_3=H
4d, (SVM-10), 72 %; R= Et, R_1=Me;R_2=R_3=H
5d, (SVM-11), 77 %; R= Me, R_1=R_3=H; R_2=OMe
6d, (SVM-12), 73 %; R= R_1=Me, R_3=H; R_2=OMe
7d, (SVM-13), 75 %; R= Et; R_1=R_3=H; R_2=OMe
8d, (SVM-14), 65 %; R= Et, R_1=Me, R_3=H; R_2=OMe
9d, (SVM-15), 72 %; R= Me, R_1=R_2=H, R_3=OMe
10d, (SVM-16), 71 %; R= Et, R_1=R_2=H, R_3=OMe
11d, (SVM-17), 76 %; R= R_1=Me, R_2=H, R_3=OMe
12d, (SVM-18), 69 %; R= Et, R_1=Me, R_2=H, R_3=OMe

[a]Isolated yields of **1d-12d**

The possible reaction pathway is depicted in Scheme 2. The reaction of 3-formylchromone with alcohol (methanol) produced acetal or hemiacetal (**I**) which further eliminated methanol or water molecule to obtain the intermediate (**II**). The intermediate (**II**) reacted with the amine part of 3-aminochromone to produce an another intermediate (**III**). Amine donated its lone pair of electrons to the chromone ring, which favoured a ring opening intermediate (**IV**) which on ring closure furnished the corresponding product (**1d**) at 80 °C. In order to identify the reaction pathway, we have prepared the methylacetal protected 3-formylchromone and carried out the same reaction with 3-aminochromone to obtain similar three component product (**1d**). The result confered that the reaction might proceeded through acetal or hemiacetal formation[48] from 3-formylchromone and alcohol, followed by 3-aminochromone addition (Path A). Also, imine formation followed by Michael addition with alcohol can produce three component adduct **1d** through path way B. We have tested this possibility using high molecular weight alcohol. The

reaction did not produce the desired three component adduct, which supported that the path A was highly desirable



Scheme 2. Plausible reaction pathway.

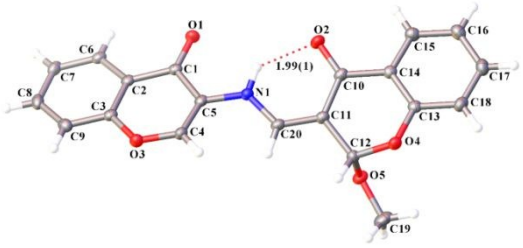


Figure 7. Solid thermal ellipsoid plot of the compound **1d** with 50 % probability level. Selected bond lengths (Å) and angles (°): O1–C11.2311(15), O2–C10 1.2489(15), O3–C3 1.3689(15), O3–C4 1.3520(16), O4–C12 1.4349(15), O4–C13 1.3710(15), O5–C12 1.4073(14), O5–C19 1.4312(16), N1–C5 1.3945(16), N1–C20 1.3453(16), O1–C1–C5 121.79(12), O1–C1–C2 124.30(11), C3–O3–C4 118.78(10), C5–N1–C20 125.76(11), C12–O4–C13 116.14(9), C12–O5–C19 113.13(10), O2–C10–C11 123.01(12), O2–C10–C14 121.14(11). Hydrogen bond distance (Å): N1–H…O2 2.6638(14)

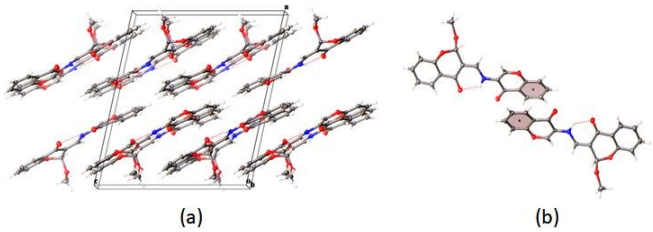


Figure 8. (a) Crystal packing viewed down the b-axis showing N1–H…O2 intramolecular interaction in compound **1d**. (b) Molecular packing diagram of compound **1d** exhibiting π–π stacking interaction.

In vitro anticancer activity of the functionalized 3-aminochromones (SVM-1 to 20)

The anticancer activity of the selected compounds (**SVM-1** to **SVM-20**) was tested against human cervical (HeLa S3) and human lung (A549) cancer cell lines by MTT assay. The plots of % of cell survival *versus* log concentration are displayed in Figures 9 and 10; the obtained IC_{50} values are given in Table 5. The IC_{50} values clearly indicated that the compounds **SVM-2** (5.18 µM) and **SVM-4** (4.89 µM) can exhibit potential anticancer activity against HeLa S3 cells. In the same cell line, compounds **SVM-1**, **SVM-5**, and **SVM-9** displayed moderate anticancer activity with IC_{50} values of 12.1, 14.2 and 27.3 µM respectively, while the other compounds showed less activity (IC_{50} > 36 µM). Besides, compound **SVM-5** showed a significant anticancer activity in A549 cancer cells with an IC_{50} value of 13.3 µM while all the other compounds displayed moderate activity (Table 5).

Table 5. IC_{50} values of the compounds against HeLa S3 and A549 cancer cells.

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Compound	A549 IC_{50} (µM)	HeLa S3 IC_{50} (µM)	Compound	A549 IC_{50} (µM)	HeLa S3 IC_{50} (µM)
SVM-1	>100	12.1	**SVM-12**	71.2	41.6
SVM-2	>100	5.18	**SVM-13**	>100	43.2
SVM-3	>100	>100	**SVM-14**	73.7	44.7
SVM-4	75.2	4.89	**SVM-15**	>100	36.6
SVM-5	13.3	14.2	**SVM-16**	>100	36.2
SVM-6	>100	70.7	**SVM-17**	>100	47.7
SVM-7	>100	>100	**SVM-18**	86.7	42.3
SVM-8	>100	42.9	**SVM-19**	>100	44.3
SVM-9	>100	27.3	**SVM-20**	>100	82.3
SVM-10	>100	91.8	Cisplatin[a]	15.1	21.3
SVM-11	>100	42.6	-	-	-

[a] Literature values[49,50]

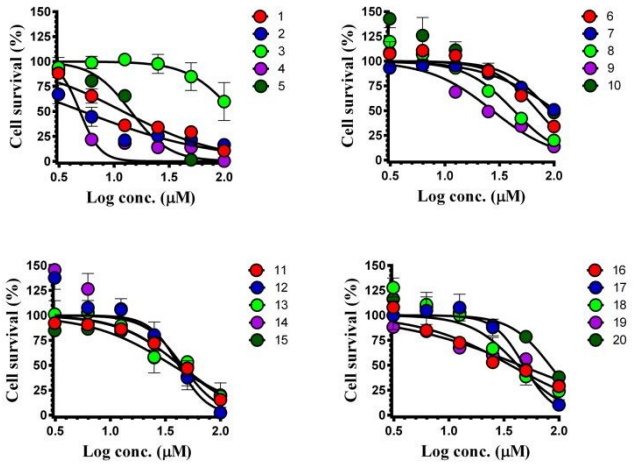


Figure 9. Anticancer property of the compounds (**SVM-1** to **SVM-20**) against HeLa S3 cells after 24 h. The experiments were conducted in triplicate and data was calculated by mean ± SD.

The results obtained here are comparable with those of cisplatin which has an IC_{50} value of 21.3 µM in HeLa S3, and 15.1 µM in A549 cancer cell lines.[49,50] Based on the structure-activity relationship (SAR), compound **SVM-4** which has a benzene ring substituent at 5th and 6th carbons of 3-aminochromone showed enhanced activity in HeLa S3 cancer cells. Analogously, **SVM-2** that has a chloro substituent at 6th carbon of 3-aminochromone showed the lowest IC_{50} value in HeLa S3 cells. Similarly, the compound with methoxy substituent at 6th carbon of 3-aminochromone showed an excellent *in vitro* activity against both HeLa S3 and A549 cells. Further, morpholine attached compounds showed enhanced activity towards cancer cell lines compared with the three component products. However, few three component products showed moderate activity when compared to the standard drug cisplatin.

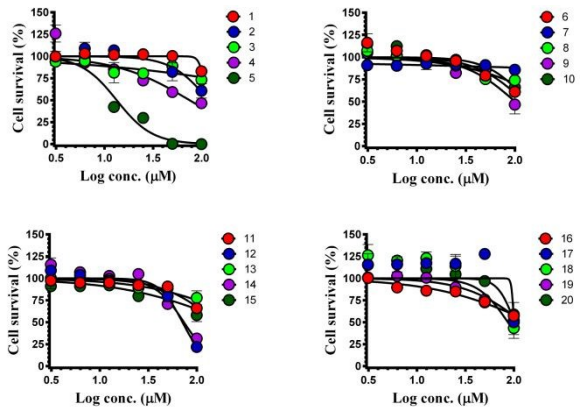


Figure 10. Anticancer property of the compounds (**SVM-1** to **SVM-20**) against A549 cells after 24 h. The experiments were conducted in triplicate and data was calculated by mean ± SD.

Morphological changes in HeLa S3 cancer cells

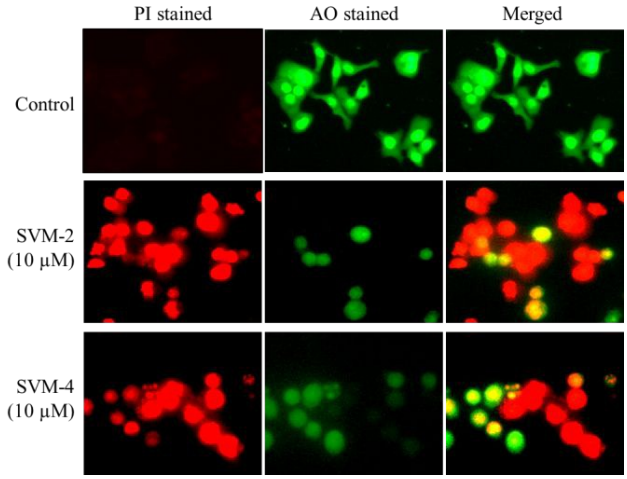


Figure 11. Morphological changes and nuclear condensation were observed by fluorescence probes after the treatment of **SVM-2** and **SVM-4** in HeLa S3 cells. AO indicates live cells and PI indicates dead cells. Images were captured under fluorescence microscope (Biorevo, BZ-9000, Keyence).

AO (acridine orange)/PI (propidium iodide) staining was evaluated to see the morphological changes associated with apoptotic mode of cell killing. Acridine orange is used as a dye that could stain nucleic acids (DNA and RNA) with an intact cell membrane, and propidium iodide is also a dye which penetrates only damaged cell membrane. The morphological changes in HeLa S3 cancer cells after the treatment of compounds **SVM-2** and **SVM-4** (10 μM) are displayed in Figure 11. Treatment of compounds **SVM-2** and **SVM-4** caused dramatic changes in morphology, nuclear condensation, membrane blebbing and irregularity in shape in cancer cells (Figure 11). AO/PI staining studies clearly confirmed that the compounds showed significant morphological changes and induced cell death.

Colony formation studies

Effect of **SVM-2** and **SVM-4** on colony formation was investigated in HeLa S3 cells. As shown in Figure 12, the treatment of 10 μM of **SVM-2** and **SVM-4** significantly inhibited the colony formation in HeLa S3 cells. Therefore, **SVM-2** and **SVM-4** not only showed anticancer activity in HeLa S3 cells but also controlled the colony formation ability.

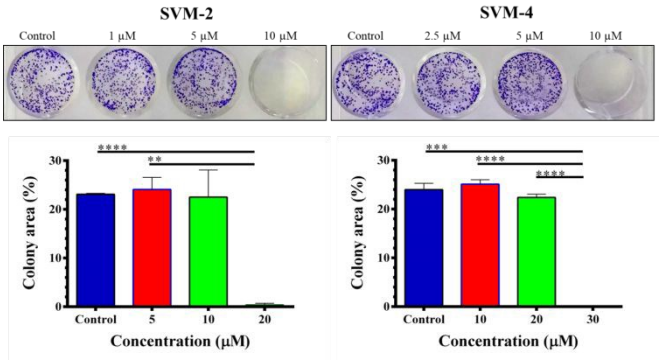
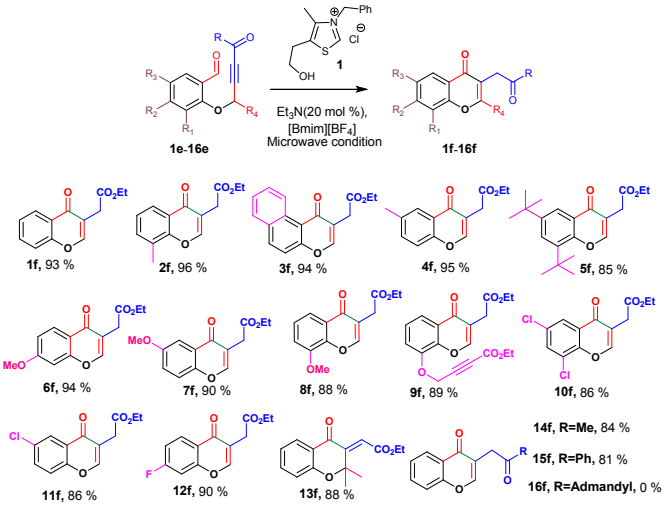


Figure 12. Colony formation study in HeLa S3 cells after the exposure of **SVM-2** and **SVM-4**. The data was calculated by mean±SD using ImageJ software with three replications. Significance was compared with treated and untreated groups **** $p < 0.0001$, *** $p < 0.0008$ and ** $p<0.0091$.

Table 6. Substrate scope of 3-alkylchromones.[a]



[a]Isolated yields of **1d-12d**

Conclusions

In summary, we have developed a highly efficient and environmentally benign synthesis of 3-aminochromones and 3-alkylchromones *via* an intramolecular hydroacylation reaction of aldehyde-nitrile and aldehyde-activated alkyne respectively using thaizolium catalyst in ionic liquid under microwave condition. The DFT studies showed that the formation of 3-aminochromone was achieved *via* an acylanion intermediate (**INT2**) which was the driving force for the reactivity. Furthermore, a series of 3-aminochromone derivatives was constructed by using a scaffold modification strategy. 3-Aminochromones were reacted with bromoacetylbromide and morpholine or piperidine to obtain morpholine or piperidine fuctionalized 3-aminochromone derivatives in moderate to good yields through one pot protocol. In addition, we have developed a

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new type of three-component adduct library by reacting 3-aminochromones with 3-formyl chromones in alcohol. From this library, twenty compounds were evaluated for anticancer activity in HeLa S3 and A549 cell lines. Among which, **SVM-2**, **SVM-4** and **SVM-9** showed IC_{50} values of 5.18, 4.89 and 27.3 μM respectively in HeLa S3 cells. Compound **SVM-5** showed IC_{50} values of 13.3 and 14.2 μM in A549 and HeLa S3 cells respectively. The most potent compounds **SVM-2** and **SVM-4** produced morphological changes and controlled the colony forming ability in HeLa S3 cells, which indicated that these molecules are potential candidates for anticancer activity.

Experimental

General methods: All the reactions were conducted in a flame or oven dried glassware under nitrogen atmosphere with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Evaporation of organic solvents was achieved by rotary evaporation at a temperature below 40 ℃. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using base solution of potassium permanganate. Technical grade solvents were used for chromatography and were distilled prior to use. NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300, 400 MHz Bruker DPX 400, 500 MHz Bruker AMX 500 or 400 MHz JEOL ECA 400 NMR spectrometer. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premier™ mass spectrometer. Single crystal X-ray analysis was done on a Bruker X8 CCD diffractometer.

Materials*:* All the starting materials were purchased from commercial suppliers and used without further purification. The thazolium catalyst (**1**) was purchased from a commercial supplier and used directly for hydroacylation reaction. All the ionic liquids used were purchased from a commercial supplier and used without further purification. Starting materials (**1a**-**21a**; **1e**-**16e**) were purified through silica gel column and perfectly dried prior to use.

Experimental procedures:

Synthesis of 1a-20a:[35] In a round-bottom flask, salicylaldehyde (100 mg, 0.825 mmol, 1 equiv.) was dissolved in dry DMF (0.5 mL) and stirred with anhydrous K_2CO_3 (169 mg, 1.23 mmol, 1.5 equiv.) for 15 minutes at ambient temperature under nitrogen atmosphere. After the formation of potassium salt of salicylaldehyde, bromoacetonitrile (125 mg, 0.98 mmol, 1.2 equiv.) was added and stirring was continued for 18-24 h. The reaction progress was monitored using TLC. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate (10 mL), washed with water (3x10 mL), brine (2x5 mL), and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by flash chromatography on silica (Yield 80-98 %).

Synthesis of 3-aminochromone and 3-alkylchromone (**1b-21b, 1f-15f**)***:*** Thiazolium precatalyst (**1**) (23 mg, 0.124 mmol, 0.2 equiv.) and 2-(2-formylphenoxy)acetonitrile[35] (**1a**) (100 mg, 0.621 mmol, 1 equiv.) were suspended in [bmim][BF_4] (116 μL, 0.621 mmol, 1 equiv.) in a microwave sealed tube under nitrogen atmosphere. Triethylamine (18 μL, 0.124 mmol, 0.2 equiv.) was added *via* syringe to the reaction mixture which was allowed to stir at 80 ℃ under microwave condition for 1 h (CEM Microwave synthesizer was used) to produce 3-aminochromone as a pale-yellow precipitate. Upon 100 % conversion (as judged by thin layer chromatography, 30 % ethyl acetate/hexane), water (30 mL) was added to the reaction mixture and the precipitate was extracted with ethylacetate (3×20 mL) and washed with brine (2×10 mL), and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by flash chromatography on silica to obtain 3-amino-4*H*-chromen-4-one (**1b**)[35] as pale yellow solid (Yield 92 mg, 92 %). m. p. 107–109 ℃ (lit.[35] 108 ℃); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, J = 8 Hz, 1H), 7.78 (s, 1H), 7.63–7.60 (m, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.35 (dd, J_1 = 8 Hz, J_2 = 7.5 Hz, 1H), 3.64 (brs, 2H, -NH_2).

3-Amino-8-methyl-4H-chromen-4-one (2b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-6-methylphenoxy)acetonitrile (**2a**) (100 mg, 0.571 mmol, 1 equiv.), **1** (30 mg, 0.114 mmol, 0.2 equiv) and triethylamine (16 μL, 0.114 mmol, 0.2 equiv) in [bmim][BF_4] (106 μL, 0.571 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 91 mg, 91 %). m. p. 127–129 ℃ (lit.[35] 127 ℃); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.92 (d, J = 8 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 4.54 (brs, 2H, -NH_2), 2.41 (s, 3H).

3-Amino-6-methyl-4H-chromen-4-one (3b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-4-methylphenoxy)acetonitrile (**3a)** (100 mg, 0.571 mmol, 1 equiv.), **1** (30 mg, 0.114 mmol, 0.2 equiv) and triethylamine (16 μL, 0.114 mmol, 0.2 equiv) in [bmim][BF_4] (106 μL, 0.571 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 87 mg, 87 %). m. p. 87–89 ℃ (lit.[35] 88 ℃); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.77 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 3.64 (brs, 2H, -NH_2), 2.46 (s, 3H).

3-Amino-6,8-di-tert-butyl-4H-chromen-4-one (4b):[35] The title compound was prepared according to the general procedure using 2-(2,4-di-tert-butyl-6-formylphenoxy)acetonitrile (**4a**) (100 mg, 0.366 mmol, 1 equiv.), **1** (19 mg, 0.073 mmol, 0.2 equiv) and triethylamine (10 μL, 0.073 mmol, 0.2 equiv.) in [bmim][BF_4] (68 μL, 0.366 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 86 mg, 86 %). m. p. 120–122 ℃ (lit.[35] 121 ℃}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 2.0 Hz, 1H), 7.84 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 3.43 (brs, 2H, -NH_2), 1.47 (s, 9H), 1.37 (s, 9H).

2-Amino-1H-benzo[f]chromen-1-one (5b):[35] The title compound was prepared according to the general procedure using 2-(1-formylnaphthalen-2-yloxy)acetonitrile (**5a**) (100 mg, 0.473 mmol, 1 equiv.), **1** (25 mg, 0.094 mmol, 0.2 equiv.) and triethylamine (13 μL, 0.094 mmol, 0.2 equiv) in [bmim][BF_4] (88 μL, 0.473 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 83 mg, 83 %). m. p. 125–127 ℃ (lit.[35] 125 ℃); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 9.2 Hz, 1H), 8.07–8.03 (m, 2H), 7.77–7.73 (m, 1H), 7.67–7.61 (m, 1H), 4.66 (brs, 2H, -NH_2).

3-Amino-8-methoxy-4H-chromen-4-one (6b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-6-methoxyphenoxy)acetonitrile (**6a**) (100 mg, 0.523 mmol, 1 equiv.), **1** (28 mg, 0.104 mmol, 0.2 equiv) and triethylamine (14 μL, 0.104 mmol, 0.2 equiv) in [bmim][BF_4] (97 μL, 0.523 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 94 mg, 94 %). m. p. 130–132 ℃ (lit.[35] 132 ℃); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.60 (t, J = 4.8 Hz, 1H), 7.28 (d, J = 4.4 Hz, 1H), 4.56 (brs, 2H, -NH_2), 3.93 (s, 3H).

3-Amino-6-methoxy-4H-chromen-4-one (7b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-

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4-methoxyphenoxy)acetonitrile (**7a**) (100 mg, 0.523 mmol, 1 equiv.), **1** (28 mg, 0.104 mmol, 0.2 equiv.) and triethylamine (14 µL, 0.104 mmol, 0.2 equiv) in [bmim][BF_4] (97 µL, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 90 mg, 90 %). m. p. 96–98 °C (lit.[35] 96 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (s, 1H), 7.51 (d, J = 9.2 Hz, 1H), 7.41 (d, J = 2.8 Hz, 1H), 7.29 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 4.52 (brs, 2H, -NH_2), 3.83 (s, 1H).

3-Amino-7-methoxy-4H-chromen-4-one (8b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-5-methoxyphenoxy)acetonitrile (**8a**) (100 mg, 0.523 mmol, 1 equiv.), **1** (28 mg, 0.104 mmol, 0.2 equiv.) and triethylamine (14 µL, 0.104 mmol, 0.2 equiv.) in [bmim][BF_4] (97 µL, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 93 mg, 93 %). m. p. 160–162 °C (lit.[35] 160 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.9 Hz, 1H), 7.62 (s, 1H), 6.86 (dd, J_1 = 9 Hz, J_2 = 2.0 Hz, 1H), 3.82 (brs, 2H, -NH_2), 3.81 (s, 3H).

3-Amino-8-methoxy-2-methyl-4H-chromen-4-one (9b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-6-methoxyphenoxy)propanenitrile (**9a**) (100 mg, 0.487 mmol, 1 equiv.), **1** (26 mg, 0.097 mmol, 0.2 equiv.) and triethylamine (13 µL, 0.097 mmol, 0.2 equiv.) in [bmim][BF_4] (110 µL, 0.487 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 80 mg, 80 %). m. p. 172–174 °C (lit.[35] 172 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 8 Hz, 1H), 6.97 (d, J = 7.2 Hz, 1H), 3.88 (s, 3H), 3.50 (brs, 2H, -NH_2), 2.37 (s, 3H).

3-Amino-8-methoxy-2-phenyl-4H-chromen-4-one (10b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-6-methoxyphenoxy)-2-phenylacetonitrile[35] (**10a**) (100 mg, 0.374 mmol, 1 equiv.), **1** (20 mg, 0.075 mmol, 0.2 equiv.) and triethylamine (10 µL, 0.075 mmol, 0.2 equiv,) in [bmim][BF_4] (70 µL, 0.374 mmol, 1 equiv.). The product was obtained as pale yellow solid; (85 mg, 85% yield); m.p. 123–125 °C {lit.[35] 125 °C}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (d, J = 8.4 Hz, 2H), 7.62 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 1H), 7.60–7.56 (m, 2H), 7.51–7.49 (m, 1H), 7.35–7.33 (m, 2H), 4.73 (brs, 2H, -NH_2), 3.95 (s, 3H).

3-Amino-6-nitro-4H-chromen-4-one (11b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-4-nitrophenoxy)acetonitrile (**11a**) (100 mg, 0.485 mmol, 1 equiv.), **1** (26 mg, 0.097 mmol, 0.2 equiv.) and triethylamine (13 µL, 0.097 mmol, 0.2 equiv.) in [bmim][BF_4] (90 µL, 0.485 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 78 mg, 78 %). m. p. 168–170 °C (lit.[35] 168 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (d, J = 2 Hz, 1H), 8.40 (dd, J_1 = 9.2 Hz, J_2 = 2 Hz, 1H), 8.01 (s, 1H), 7.78 (d, J = 9.2 Hz, 1H), 4.81 (brs, 2H, -NH_2).

3-Amino-6,8-dichloro-4H-chromen-4-one (12b):[35] The title compound was prepared according to the general procedure using 2-(2, 4-dichloro-6-formylphenoxy)acetonitrile (**12a**) (100 mg, 0.434 mmol, 1 equiv.), **1** (23 mg, 0.086 mmol, 0.2 equiv.) and triethylamine (12 µL, 0.086 mmol, 0.2 equiv.) in [bmim][BF_4] (81 µL, 0.434 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 87 mg, 87 %). m. p. 180–182 °C (lit.[35] 182 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 4.77 (brs, 2H, -NH_2).

3-Amino-6-bromo-4H-chromen-4-one (13b):[35] The title compound was prepared according to the general procedure using 2-(4-bromo-2-formylphenoxy)acetonitrile (**13a**) (50 mg, 0.208 mmol, 1 equiv.), **1** (11 mg, 0.041 mmol, 0.2 equiv.) and triethylamine (6 µL, 0.041 mmol, 0.2 equiv.) in [bmim][BF_4] (39 µL, 0.208 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 44 mg, 88 %). m. p. 162–164 °C (lit.[35] 162 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (d, J = 2.4 Hz, 1H), 7.97 (s, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H), 4.64 (brs, 2H, -NH_2).

3-Amino-6-chloro-4H-chromen-4-one (14b):[35] The title compound was prepared according to the general procedure using 2-(4-chloro-2-formylphenoxy)acetonitrile (**14a**) (50 mg, 0.256 mmol, 1 equiv.), **1** (13 mg, 0.051 mmol, 0.2 equiv.) and triethylamine (7 µL, 0.051 mmol, 0.2 equiv.) in [bmim][BF_4] (57 µL, 0.256 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 45.5 mg, 91 %). m. p. 174–176 °C (lit.[35] 175 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 2.4 Hz, 1H), 7.78 (s, 1H), 7.52 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 7.39 (d, J = 9.2 Hz, 1H), 3.67 (brs, 2H, -NH_2).

3-Amino-8-bromo-6-chloro-4H-chromen-4-one (15b):[35] The title compound was prepared according to the general procedure using 2-(2-bromo-4-chloro-6-formylphenoxy)acetonitrile (**15a**) (50 mg, 0.182 mmol, 1 equiv.), **1** (10 mg, 0.036 mmol, 0.2 equiv.) and triethylamine (5 µL, 0.036 mmol, 0.2 equiv.) in [bmim][BF_4] (34 µL, 0.182 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 46 mg, 92 %). m. p. 191–193 °C (lit.[35] 192 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 8.01 (d, J = 2.4 Hz, 1H), 4.77 (brs, 2H, -NH_2).

3-Amino-6-iodo-8-methoxy-4H-chromen-4-one (16b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-4-iodo-6-methoxyphenoxy)acetonitrile (**16a**) (100 mg, 0.315 mmol, 1 equiv.), **1** (66 mg, 0.063 mmol, 0.2 equiv.) and triethylamine (9 µL, 0.063 mmol, 0.2 equiv.) in [bmim][BF_4] (58 µL, 0.315 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 93 mg, 93 %). m. p. 209–211 °C (lit.[35] 209 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.87 (d, J = 1.6 Hz, 1H), 7.48 (d, J = 1.2 Hz, 1H), 4.63 (brs, 2H, -NH_2), 3.92 (s, 1H).

3-Amino-8-fluoro-4H-chromen-4-one (17b):[35] The title compound was prepared according to the general procedure using 2-(2-fluoro-6-formylphenoxy)acetonitrile (**17a**) (30 mg, 0.167 mmol, 1 equiv.), **1** (9 mg, 0.033 mmol, 0.2 equiv.) and triethylamine (5 µL, 0.033 mmol, 0.2 equiv.) in [bmim][BF_4] (31 µL, 0.167 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 27 mg, 92 %). m. p. 163–165 °C (lit.[35] 165 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (td, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 7.81 (s, 1H), 7.38 (ddd, J_1 = 10.4 Hz, J_2 = 8 Hz, J_3 = 1.2 Hz, 1H), 7.28 (dd, J_1 = 9 Hz, J_2 = 4.4 Hz, 1H), 3.69 (brs, 2H, -NH_2).

3-Amino-6,8-difluoro-4H-chromen-4-one (18b):[35] The title compound was prepared according to the general procedure using 2-(2,4-difluoro-6-formylphenoxy)acetonitrile (**18a**) (20 mg, 0.101 mmol, 1 equiv.), **1** (5 mg, 0.02 mmol, 0.2 equiv.) and triethylamine (3 µL, 0.02 mmol, 0.2 equiv.) in [bmim][BF_4] (19 µL, 0.101 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 17 mg, 89 %). m. p. 150–152 °C (lit.[35] 149 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.81 (ddd, J_1 = 10.8 Hz, J_2 = 8.4 Hz, J_3 = 2.8 Hz, 1H), 7.57 (td, J_1 = 8.4 Hz, J_2 = 2 Hz, 1H), 4.73 (brs, 2H, -NH_2).

3-Amino-7-fluoro-4H-chromen-4-one (19b):[35] The title compound was prepared according to the general procedure using 2-(5-fluoro-2-formylphenoxy)acetonitrile (**19a**) (100 mg, 0.558 mmol, 1 equiv.), **1** (30 mg, 0.111 mmol, 0.2 equiv.) and triethylamine (15 µL, 0.111 mmol, 0.2 equiv.) in [bmim][BF_4] (104 µL, 0.558 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 88 mg, 88 %). m. p. 172–174 °C (lit.[35] 172 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, J_1=

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9.6 Hz, J_2 = 6.4 Hz, 1H), 7.74 (s, 1H), 7.11–7.06 (m, 2H), 3.64 (brs, 2H, -NH_2).

3-Amino-6-fluoro-2-methyl-4H-chromen-4-one (20b):[35] The title compound was prepared according to the general procedure using 2-(5-fluoro-2-formylphenoxy)propanenitrile (**20a**) (60 mg, 0.31 mmol, 1 equiv.), **1** (16 mg, 0.062 mmol, 0.2 equiv.) and triethylamine (8 µL, 0.062 mmol, 0.2 equiv.) in [bmim][BF_4] (58 µL, 0.31 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 48 mg, 81 %). m. p. 165−167 °C (lit.[35] 165 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H), 7.61 (dd, J_1 = 9.2 Hz, J_2 = 4.8 Hz, 1H), 7.54 (dt, J_1 = 8 Hz, J_2 = 2.8 Hz, 1H), 4.41 (brs, 2H, -NH_2), 2.39 (s, 1H).

3-Amino-6-(trifluoromethoxy)-4H-chromen-4-one (21b):[35] The title compound was prepared according to the general procedure using 2-(2-formyl-4-(trifluoromethoxy)phenoxy)acetonitrile (**21a**) (50 mg, 0.204 mmol, 1 equiv.), **1** (10 mg, 0.04 mmol, 0.2 equiv.) and triethylamine (6 µL, 0.04 mmol, 0.2 equiv.) in [bmim][BF_4] (38 µL, 0.204 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 43 mg, 87 %). m. p. 107−109 °C (lit.[35] 108 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (s, 1H), 7.92 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.72 (dd, J_1 = 9.2 Hz, J_2 = 1.1 Hz, 1H), 4.67 (brs, 2H, -NH_2).

Ethyl-2-(4-oxo-4H-chromen-3-yl)acetate (1f): [34] The title compound was prepared according to the general procedure using ethyl-4-(2-formylphenoxy)but-2-ynoate (**1e**) (100 mg, 0.431 mmol, 1 equiv.), **1** (23 mg, 0.086 mmol, 0.2 equiv.) and triethylamine (12 µL, 0.086 mmol, 0.2 equiv) in [bmim][BF_4] (97 µL, 0.431 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 93 mg, 93 %). m. p. 78−80 °C (lit.[34] 80 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (dd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, 1H), 7.94 (s, 1H), 7.65 (ddd, J_1 = 8.7 Hz, J_2 = 7.2 Hz, J_3 = 1.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.41–7.38 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.47 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H).

Ethyl-2-(8-methyl-4-oxo-4H-chromen-3-yl)acetate (2f):[34] The title compound was prepared according to the general procedure using ethyl-4-(2-formyl-6-methylphenoxy)but-2-ynoate (**2e**) (100 mg, 0.406 mmol, 1 equiv.), **1** (22 mg, 0.081 mmol, 0.2 equiv.) and triethylamine (11 µL, 0.081 mmol, 0.2 equiv.) in [bmim][BF_4] (91 µL, 0.406 mmol, 1 equiv.). The product was obtained as pale white solid (Yield 96 mg, 96 %). m. p. 80−82 °C (lit.[34] 82 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.6 Hz, 1H), 7.99 (s, 1H), 7.50 (d, J = 6.8 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 4.19 (q, J = 6.8 Hz, 2H), 3.48 (s, 2H), 2.47 (s, 3H), 1.28 (t, J = 6.8 Hz, 3H).

Ethyl-2-(1-oxo-1H-benzo[f]chromen-2-yl)acetate (3f):[34] The title compound was prepared according to the general procedure using ethyl-4-(1-formylnaphthalen-2-yloxy)but-2-ynoate (**3e**) (100 mg, 0.354 mmol, 1 equiv.), **1** (19 mg, 0.070 mmol, 0.2 equiv.) and triethylamine (10 µL, 0.070 mmol, 0.2 equiv) in [bmim][BF_4] (75 µL, 0.354 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 94 mg, 94 %). m. p. 114−116 °C (lit.[34] 116 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.00 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.73 (dd, , J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.62–7.58 (m, 1H), 7.48 (d, J = 8.8 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.54 (s, 2H), 1.29 (t, J = 7.2 Hz, 3H).

Ethyl-2-(6-methyl-4-oxo-4H-chromen-3-yl)acetate (4f):[34] The title compound was prepared according to the general procedure using ethyl-4-(2-formyl-4-methylphenoxy)but-2-ynoate (**4e**) (100 mg, 0.406 mmol, 1 equiv.), **1** (22 mg, 0.081 mmol, 0.2 equiv.) and triethylamine (11 µL, 0.081 mmol, 0.2 equiv.) in [bmim][BF_4] (91 µL, 0.406 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 95 mg, 95 %). m. p. 73−75 °C (lit.[34] 75 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.91 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.46 (s, 2H), 2.43 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H).

Ethyl-2-(6,8-di-tert-butyl-4-oxo-4H-chromen-3-yl)acetate (5f):[34] The title compound was prepared according to the general procedure using ethyl-4-(2,4-di-tert-butyl-6-formylphenoxy)but-2-ynoate (**5e**) (100 mg, 0.290 mmol, 1 equiv.), **1** (15 mg, 0.058 mmol, 0.2 equiv.) and triethylamine (8 µL, 0.058 mmol, 0.2 equiv.) in [bmim][BF_4] (54 µL, 0.290 mmol, 1 equiv.). The product was obtained as pale white solid (Yield 85 mg, 85 %); m. p. 92−94 °C (lit.[34] 92 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 2 Hz, 1H), 8.01 (s, 1H), 7.69 (d, J = 1.6 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.48 (s, 2H), 1.48 (s, 9H), 1.36 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H).

Ethyl-2-(7-methoxy-4-oxo-4H-chromen-3-yl)acetate (6f):[34] The title compound was prepared according to the general procedure using ethyl-4-(2-formyl-5-methoxyphenoxy)but-2-ynoate (**6e**) (100 mg, 0.381 mmol, 1 equiv.), **1** (20 mg, 0.076 mmol, 0.2 equiv.) and triethylamine (11 µL, 0.076 mmol, 0.2 equiv.) in [bmim][BF_4] (71 µL, 0.381 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 94 mg, 94 %). m. p. 103−104 °C (lit.[34] 104 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.8 Hz, 1H), 7.86 (s, 1H), 6.95 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1H), 6.81 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.44 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Ethyl-2-(6-methoxy-4-oxo-4H-chromen-3-yl)acetate (7f):[34] The title compound was prepared according to the general procedure using ethyl-4-(2-formyl-4-methoxyphenoxy)but-2-ynoate (**7e**) (100 mg, 0.381 mmol, 1 equiv.), **1** (20 mg, 0.076 mmol, 0.2 equiv.) and triethylamine (11 µL, 0.076 mmol, 0.2 equiv.) in [bmim][BF_4] (71 µL, 0.381 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 90 mg, 90 %); m. p. 94−96 °C (lit.[34] 95 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.57 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 9.2 Hz, 1H), 7.27–7.24 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.48 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H).

Ethyl-2-(8-methoxy-4-oxo-4H-chromen-3-yl)acetate (8f):[34] The title compound was prepared according to the general procedure using ethyl-4-(2-formyl-6-methoxyphenoxy)but-2-ynoate (**8e**) (100 mg, 0.381 mmol, 1 equiv.), **1** (20 mg, 0.076 mmol, 0.2 equiv.) and triethylamine (11 µL, 0.076 mmol, 0.2 equiv.) in [bmim][BF_4] (71 µL, 0.381 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 88 mg, 88 %). m. p. 125−127 °C (lit.[34] 127 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.77 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 7.31 (t, J = 8 Hz, 1H), 7.16 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.47 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Ethyl-4-(3-(2-ethoxy-2-oxoethyl)-4-oxo-4H-chromen-8-yloxy)but-2-ynoate (9f):[34] The title compound was prepared according to the general procedure using diethyl-4,4'-(3-formyl-1,2-phenylene)bis(oxy)dibut-2-ynoate (**9e**) (100 mg, 0.279 mmol, 1 equiv.), **1** (15 mg, 0.056 mmol, 0.2 equiv.) and triethylamine (8 µL, 0.056 mmol, 0.2 equiv.) in [bmim][BF_4] (52 µL, 0.279 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 89 mg, 89 %). m. p. 113−115 °C (lit.[34] 114 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.87 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 7.34 (d, J = 8 Hz, 1H), 7.28 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 4.99 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 3.48 (s, 2H), 1.30 (t, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 2H).

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Ethyl-2-(6,8-dichloro-4-oxo-4H-chromen-3-yl)acetate (10f):[34] The title compound was prepared according to the general procedure using ethyl-4-(2,4-dichloro-6-formylphenoxy)but-2-ynoate (**10e**) (100 mg, 0.322 mmol, 1 equiv.), **1** (17 mg, 0.066 mmol, 0.2 equiv.) and triethylamine (9 µL, 0.066 mmol, 0.2 equiv.) in [bmim][BF_4] (62 µL, 0.322 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 86 mg, 86 %). m. p. 103−105 ℃ (lit.[34] 105 ℃); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 2.4 Hz, 1H), 8.01 (s, 1H), 7.70 (d, J = 2.4 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.47 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Ethyl-2-(6-chloro-4-oxo-4H-chromen-3-yl)acetate (11f):[34] The title compound was prepared according to the general procedure using ethyl-4-(4-chloro-2-formylphenoxy)but-2-ynoate (**11e**) (100 mg, 0.375 mmol, 1 equiv.), **1** (20 mg, 0.075 mmol, 0.2 equiv.) and triethylamine (10 µL, 0.075 mmol, 0.2 equiv.) in [bmim][BF_4] (70 µL, 0.375 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 86 mg, 86 %). m. p. 87−89 ℃ (lit.[34] 88 ℃); ^{1}H NMR (400 MHz, $CDCl_3$): 8.17 (d, J = 2.4 Hz, 1H), 7.94 (s, 1H), 7.60 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.47 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H).

Ethyl-2-(7-fluoro-4-oxo-4H-chromen-3-yl)acetate (12f):[34] The title compound was prepared according to the general procedure using ethyl-4-(5-fluoro-2-formylphenoxy)but-2-ynoate (**12e**) (100 mg, 0.4 mmol, 1 equiv.), **1** (21 mg, 0.08 mmol, 0.2 equiv.) and triethylamine (11 µL, 0.08 mmol, 0.2 equiv.) in [bmim][BF_4] (74 µL, 0.4 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 90 mg, 90 %). m. p. 101−103 ℃ (lit.[34] 102 ℃); ^{1}H NMR (400 MHz, $CDCl_3$): 8.22 (dd, J_1 = 9.6 Hz, J_1 = 6.4 Hz, 1H), 7.91 (s, 1H), 7.13 (d, J = 6.4 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.45 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H).

(E)-Ethyl-2-(2,2-dimethyl-4-oxochroman-3-ylidene)acetate (13f):[34] The title compound was prepared according to the general procedure using ethyl-4-(2-formylphenoxy)-4-methylpent-2-ynoate (**13e**) (50 mg, 0.192 mmol, 1 equiv.), **1** (10 mg, 0.038 mmol, 0.2 equiv.) and triethylamine (5 µL, 0.038 mmol, 0.2 equiv.) in [bmim][BF_4] (35 µL, 0.192 mmol, 1 equiv.). The product was obtained as yellow viscous oil (Yield 44 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.19 (s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.62 (s, 6H), 1.32 (t, J = 7.2 Hz, 3H).

3-(2-Oxopropyl)-4H-chromen-4-one (14f):[34] The title compound was prepared according to the general procedure using 2-(4-oxopent-2-ynyloxy)benzaldehyde (**14e**) (100 mg, 0.495 mmol, 1 equiv.), **1** (26 mg, 0.099 mmol, 0.2 equiv.) and triethylamine (14 µL, 0.099 mmol, 0.2 equiv.) in [bmim][BF_4] (92 µL, 0.495 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 84 mg, 84 %). m. p. 96−98 ℃ (lit.[34] 97 ℃); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 7.6 Hz, 1H), 7.88 (s, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 3.56 (s, 2H), 2.33 (s, 3H).

3-(3,3-Dimethyl-2-oxobutyl)-4H-chromen-4-one (15f):[34] The title compound was prepared according to the general procedure using 2-((4-oxo-4-phenylbut-2-yn-1-yl)oxy)benzaldehyde (**15e**) (100 mg, 0.378 mmol, 1 equiv.), **1** (20 mg, 0.075 mmol, 0.2 equiv.) and triethylamine (10 µL, 0.075 mmol, 0.2 equiv.) in [bmim][BF_4] (70 µL, 0.378 mmol, 1 equiv.). The product was obtained as a pale white solid (Yield 81 mg, 81 %). m. p. 131−133 ℃ (lit.[34] 132 ℃); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 2H), 7.97 (s, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.50–7.44 (m, 3H), 7.39 (t, J = 7.6 Hz, 1H), 4.15 (s, 2H).

Synthesis of 2-((4-(adamantan-2-yl)-4-oxobut-2-yn-1-yl)oxy) benzaldehyde (16e): Step 1. In a round-bottom flask, salicylaldehyde tethered with the propargyl group 2-(prop-2-yn-1-yloxy)benzaldehyde (300 mg, 1.87 mmol, 1 equiv.) was dissolved in dry ethanol (10 mL) under nitrogen atmosphere. Triethyl orthoformate (0.60 mL, 3.20 mmol, 1.7 equiv.) and PPTS (5 mg, 0.02 mmol, 0.01 equiv.) were added and the resulting solution was refluxed for 3 h. The progress of the reaction was monitored using TLC. Upon completion, the reaction mixture was quenched with few drops of Et_3N (0.05 equiv.) and concentrated. The oil was diluted with ethyl acetate (50 mL), washed with 10 % $NaHCO_3$ (2×20 mL), followed by brine (2×10 mL) and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was dried under vacuum. The obtained protected salicylaldehyde derivative was used for the next step.

Step 2. In a round-bottom flask, under nitrogen atmosphere, the acetal protected salicylaldehyde derivative (1-(diethoxymethyl)-2-(prop-2-yn-1-yloxy)benzene from step 1) (439 mg, 1.88 mmol, 1 equiv.) was dissolved in dry THF (10 mL). The solution was stirred at –78 ℃ (dry ice-acetone bath) for 10 min, butyl lithium (2 M in cyclohexane) (1.40 mL, 2.82 mmol, 1.5 equiv.) was slowly added to the flask over 10 min and stirred for another 30 min at the same temperature. 1-Adamantanecarbonylchloride in dry THF (631 mg, 3.20 mmol, 1.7 equiv.) was slowly added to the reaction mixture and stirring was continued for another 30-60 min. The progress of the reaction was monitored using TLC. Upon completion, the reaction mixture was allowed to warm to ambient temperature and quenched with saturated NH_4Cl (20 mL). Then the reaction mixture was diluted with ethyl acetate (50 mL), washed with water (3×50 mL), followed by brine (2×10 mL), and then dried over Na_2SO_4. The solvent was evaporated and the crude product was dissolved in $CHCl_3$ (20 mL), then water (10 mL) and 50 % TFA (3 mL) were added, and stirred the biphasic mixture for 15 to 30 min. The progress of deprotection was monitored by using TLC. Upon completion, the reaction mixture was diluted with ethyl acetate (50 mL), washed with aqueous $NaHCO_3$ (2×50 mL), water (3×50 mL), followed by brine (2×10 mL), and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by flash column chromatography to obtain **16e** as a viscous oil (Yield 480 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.46 (s, 1H), 7.83 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.54–7.50 (m,1H), 7.10–7.03 (m, 2H), 4.89 (s, 2H), 1.98 (s, 1H), 1.86 (s, 2H), 1.78 (d, 2.16 Hz, 3H), 1.68 (q, 12.0 Hz, 4H), 1.57 (s, 4H), 1.37 (d, 11.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 189.6, 174.4, 159.7, 135.6, 128.4, 125.5, 121.5, 113.6, 83.4, 80.0, 72.8, 56.5, 42.1, 41.4, 38.6, 38.5, 36.5, 36.4, 36.1, 28.1, 27.8.

Amine functionalization of 3-aminochromones for active drug candidates (1c-12c): Stepwise process; Procedure A: In a round-bottom flask, under nitrogen atmosphere, 3-aminochromone **1b** (200 mg, 1.24 mmol, 1 equiv.) was dissolved in acetonitrile (5 mL) and stirred the reaction mixture with Et_3N (346 µL, 2.48 mmol, 2 equiv.) at 0 ℃. Bromoacetylbromide (118 µL, 1.36 mmol, 1.1 equiv.) was added *via* syringe over 5 min at 0 ℃ and the reaction mixture was allowed to stir for another 30 min at room temperature. After the formation of amide bond (judged by TLC), morpholine (321 µL, 3.726 mmol, 3 equiv.) was added and stirring was continued for 12

h. The progress of the reaction was monitored using TLC. After the completion of the reaction, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3x30 mL). The combined organic layer was washed with brine (2×10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by flash chromatography on silica to obtain 2-morpholino-*N*-(4-oxo-4*H*-chromen-3-yl)acetamide (**7c**) as a white solid (over two steps) (Yield 232 mg, 65 %). m. p. 150−152 ℃ {lit.[35] 150 ℃}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.72 (s, 1H, -NH), 9.31 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 3.77 (t, J = 4 Hz, 4H), 3.13 (s, 2H), 2.57 (t, J = 4 Hz, 4H).

One pot process; Procedure B: After the completion of microwave reaction for the synthesis of **1b** using **1a** (100 mg, 0.621 mmol), the microwave tube was kept at 0 ℃, triethylamine (141 µL, 1.242 mmol, 2 equiv.) followed by bromoacetylbromide (59 µL, 0.683 mmol, 1.1 equiv.) were added using syringe and stirred the reaction mixture for 30 min at room temperature. After the formation of amide bond (judged by TLC), morpholine (160 µL, 1.863 mmol, 3 equiv.) was added and stirring was continued for 12 h. The progress of the reaction was monitored using TLC. After the completion of the reaction, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3x30 mL). The combined organic layer was washed with brine (2×10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by flash chromatography on silica to obtain 2-morpholino-*N*-(4-oxo-4*H*-chromen-3-yl)acetamide (**7c**) as a white solid (over three steps) (Yield 107 mg, 60 %).

N-(6-Chloro-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (2c): The title compound was prepared according to procedure B using 2-(4-chloro-2-formylphenoxy)acetonitrile (**14a**) (100 mg, 0.512 mmol), triethylamine (142 µL, 1.02 mmol, 2 equiv.), bromoacetylbromide (49 µL, 0.564 mmol, 1.1 equiv.) and morpholine (132 µL, 1.53 mmol, 3 equiv.). The product was obtained as pale white solid (Yield 107 mg, 65 %). m. p. 215–217 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 9.38 (s, 1H), 8.21 (d, J = 2.5 Hz, 1H), 7.63 (dd, J_1 = 9 Hz, J_2 = 2.5 Hz, 1H), 7.48, (d, J = 9 Hz, 1H), 3.83 (t, J = 4.5 Hz, 4H), 3.18 (s, 2H), 2.62 (t, J = 4.5 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.9, 168.8, 154.1, 145.2, 134.2, 130.9, 125.0, 124.1, 123.1, 120.3, 67.0, 62.1, 53.8. FT-IR (KBr): ν_{max} 3285, 2855, 1685, 1631, 1606, 1531, 1111, 831 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{15}H_{16}N_2O_4Cl$: 323.0720, found: 323.0719.

N-(6-Fluoro-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (3c): The title compound was prepared according to procedure B using 2-(4-fluoro-2-formylphenoxy)acetonitrile (100 mg, 0.558 mmol), triethylamine (155 µL, 1.117 mmol, 2 equiv.), bromoacetylbromide (53 µL, 0.614 mmol, 1.1 equiv.) and morpholine (144 µL, 1.675 mmol, 3 equiv.). The product was obtained as dirty white solid (Yield 104 mg, 61 %). m. p. 202–204 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 9.39 (s, 1H), 7.87 (dd, J_1 = 8.1 Hz, J_2 = 3 Hz, 1H), 7.53 (dd, J_1 = 9.2 Hz, J_2 = 4.2 Hz, 1H), 7.45–7.40 (m, 1H), 3.83 (t, J = 4.5 Hz, 4H), 3.18 (s, 2H), 2.63 (d, J = 4.3 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.8, 159.4 (d, $^1J_{CF}$ = 241 Hz), 152.1, 145.3, 123.6, 123.0 (d, $^4J_{CF}$ = 7.3 Hz), 122.6, 122.3, 120.7 (d, ^{3}JCF = 8.0 Hz), 110.3 (d, ^{2}JCF = 23.6 Hz) 67.0, 62.1, 53.8; FT-IR (KBr): ν_{max} 3244, 3059, 2961, 2859, 2821, 1690, 1636, 1581, 1485, 1111, 833 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{15}H_{16}N_2O_4F$: 307.1094, found: 307.1093.

2-Morpholino-N-(1-oxo-1H-benzo[f]chromen-2-yl)acetamide (4c): The title compound was prepared according to procedure B using 2-((1-formylnaphthalen-2-yl)oxy)acetonitrile (**5a**) (100 mg, 0.473 mmol), triethylamine (132 µL, 0.947 mmol, 2 equiv.), bromoacetylbromide (45 µL, 0.521 mmol, 1.1 equiv.) and morpholine (122 µL, 1.421 mmol, 3 equiv.). The product was obtained as dirty white solid (Yield 100 mg, 63 %); m. p. 155–157 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.00 (d, J = 8.3 Hz, 2H), 9.42 (s, 1H), 8.06 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.78 (t, J = 7.3 Hz, 1H), 7.64 (t, J = 7.0 Hz, 1H), 7.51 (d, J = 8.9 Hz, 1H), 3.89 (s, 4H), 3.23 (s, 2H), 2.66 (s, 4H); ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.7, 168.9, 157.1, 142.6, 135.7, 130.5, 130.2, 129.4, 128.4, 126.9, 126.7, 125.9, 117.8, 115.5, 67.1, 62.3, 53.8. FT-IR (KBr): ν_{max} 3267, 2918, 2816, 1683, 1643, 1600, 1514, 1116, 829 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{19}H_{19}N_2O_4$: 339.1345, found: 339.1346.

N-(6-Methoxy-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (5c): The title compound was prepared according to procedure B using 2-(2-formyl-4-methoxyphenoxy)acetonitrile (**7a**) (100 mg, 0.523 mmol), triethylamine (145 µL, 1.047 mmol, 2 equiv.), bromoacetylbromide (50 µL, 0.575 mmol, 1.1 equiv.) and morpholine (135 µL, 1.57 mmol, 3 equiv.). The product was obtained as pale yellow solid (Yield 111 mg, 67 %); m. p. 170–172 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.83 (s, 1H), 9.36 (s, 1H), 7.57 (d, J = 3.0 Hz, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.29 (dd, J_1 = 9.2 Hz, J_2 = 3 Hz, 1H), 3.89 (s, 3H), 3.84 (t, J = 4.6 Hz, 4H), 3.18 (s, 2H), 2.63 (t, J = 4.6 Hz, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 171.6, 168.7, 156.7, 150.8, 144.9, 124.5, 123.1, 122.7, 119.9, 104.1, 67.1, 62.1, 55.9, 53.8; FT-IR (KBr): ν_{max} 3278, 2959, 2854, 1680, 1631, 1587, 1491, 1113, 868 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{16}H_{19}N_2O_5$: 319.1294, found: 319.1294.

N-(8-Methoxy-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (6c): The title compound was prepared according to procedure B using 2-(2-formyl-3-methoxyphenoxy)acetonitrile (**6a**) (100 mg, 0.523 mmol), triethylamine (145 µL, 1.047 mmol, 2 equiv.), bromoacetylbromide (50 µL, 0.575 mmol, 1.1 equiv.) and morpholine (135 µL, 1.57 mmol, 3 equiv.). The product was obtained as pale yellow solid (Yield 116 mg, 70 %). m. p. 145–147 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 9.35 (s, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 3.92 (s, 3H), 3.75 (t, J = 4.5 Hz, 4H), 3.10 (s, 2H), 2.55 (t, J = 4.3 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.7, 168.7, 148.9, 146.3, 144.8, 124.6, 124.1, 123.1, 116.1, 114.0, 67.0, 62.1, 56.3, 53.8; FT-IR (KBr): ν_{max} 3307, 1689, 1573,1392, 1060, 812 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{16}H_{19}N_2O_5$: 319.1294, found: 319.1296.

N-(6,8-Dichloro-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (8c) & (1c, HCl salt): The title compound was prepared according to procedure B using 2-(2,4-dichloro-6-formylphenoxy)acetonitrile (**12a**) (100 mg, 0.434 mmol), triethylamine (121 µL, 0.869 mmol, 2 equiv.), bromoacetylbromide (41 µL, 0.478 mmol, 1.1 equiv.) and morpholine (112 µL, 1.304 mmol, 3 equiv.). The product was obtained as dirty white solid (Yield 107 mg, 69 %); m. p. 170–172 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 9.47 (s, 1H), 8.12 (d, J = 2.3 Hz, 1H), 7.75 (d, J = 2.3 Hz, 1H), 3.84 (t, J = 4.4 Hz, 4H), 3.20 (s, 2H), 2.64 (t, J = 4.4 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.4, 168.9, 150.0, 145.1, 134.0, 130.5, 124.8, 124.3, 123.8, 123.7, 67.0, 62.1, 53.8; FT-IR (KBr): ν_{max} 3337, 1694, 1628, 1599, 1495, 1182, 866 cm^{-1}. HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{15}H_{15}N_2O_4Cl_2$: 357.0345, found: 357.0342. Compound **8c** (50 mg, 0.14 mmol) was dissolved in ethanol (0.2 ml)

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and added 2 M HCl solution in diethyl ether (2 mL) and stirred the reaction mixture for 10 min. After slow evaporation with needle pressure of nitrogen gas followed by high vacuum drying yielded quantitative amount of HCl salt (**1c**). The product was obtained as white solid (Yield 50 mg, 91 %); m. p. 107–109 °C; ^{1}H NMR (500 MHz, DMSO-d_6 & 3-drops of CD_3OD): δ 9.44 (s, 1H), 8.29 (s, 1H), 8.15 (s, 1H), 4.15 (bs, 2H), 4.05 (bs, 2H), 3.41 (s, 2H), 3.13 (s, 2H). ^{13}C{^{1}H} (126 MHz, DMSO-d_6 & 3-drops of CD_3OD): δ 170.3, 164.1, 150.0, 148.1, 134.3, 130.1, 124.5, 124.4, 124.1, 123.8, 63.4, 57.2, 52.3.

N-(8-(Cyanomethoxy)-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (9c): The title compound was prepared according to procedure B using 2,2'-((3-formyl-1,2-phenylene)bis(oxy))diacetonitrile (100 mg, 0.465 mmol), triethylamine (129 µL, 0.93 mmol, 2 equiv.), bromoacetylbromide (44 µL, 0.511 mmol, 1.1 equiv.) and morpholine (120 µL, 1.395 mmol, 3 equiv.). The product was obtained as pale yellow solid (Yield 104 mg, 66 %). m. p. 159–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 9.78 (s, 1H), 9.41 (d, *J* = 3.5 Hz, 1H), 7.95 (dd, J_1 = 6.8 Hz, J_2 = 2.8 Hz, 1H), 7.39–7.33 (m, 2H), 4.95 (s, 2H), 3.81 (t, *J* = 4.6 Hz, 4H), 3.17 (s, 2H), 2.61 (t, *J* = 4.5 Hz, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): *δ* 171.2, 168.8, 146.7, 145.5, 144.6, 124.5, 124.3, 123.6, 119.9, 117.9, 114.2, 66.9, 62.0, 55.0, 53.7; FT-IR (KBr): ν_{max} 3298, 2989, 2843, 1686, 1627, 1582, 1454, 1109, 868 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{17}H_{18}N_3O_5$: 344.1246, found: 344.1244.

Synthesis of 2,2'-((3-formyl-1,2-phenylene)bis(oxy))diacetonitrile: In a round-bottom flask, under nitrogen atmosphere, 2,3-dihydroxybenzaldehyde (200 mg, 1.449 mmol, 1 equiv.) was stirred with anhydrous K_2CO_3 (599 mg, 4.347 mmol, 3 equiv.) in dry DMF (1 mL) for 15 min at room temperature. After formation of yellow precipitate, bromoacetonitrile (240 µL, 3.478 mmol, 2.4 equiv.) was added and stirring was continued for 24 h. The progress of the reaction was monitored using TLC. After the completion of the reaction, the reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3×20 mL), washed with brine (2×5 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography on silica to obtain white solid (Yield 274 mg, 88 %). m. p. 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 10.35 (s, 1H), 7.60 (dd, J_1 = 9.3 Hz, J_2 = 4.1 Hz, 1H), 7.34–7.30 (m, 2H), 4.93 (s, 2H), 4.89 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 188.3, 149.4, 148.6, 130.7, 126.4, 123.6, 120.7, 114.7, 114.3, 58.7, 54.9.

N-(7-Methoxy-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (10c): The title compound was prepared according to procedure B using 2-(2-formyl-5-methoxyphenoxy)acetonitrile (**8a**) (100 mg, 0.523 mmol), triethylamine (145 µL, 1.047 mmol, 2 equiv.), bromoacetylbromide (50 µL, 0.575 mmol, 1.1 equiv.) and morpholine (135 µL, 1.57 mmol, 3 equiv.). The product was obtained as pale yellow solid (Yield 109 mg, 66 %). m. p. 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.76 (s, 1H), 9.26 (s, 1H), 8.10 (dd, J_1 = 8.9Hz, J_2 = 2.1Hz, 1H), 6.96 (dd, J_1 = 9.2Hz, J_2 = 2.3Hz, 1H), 6.84 (d, *J* = 2.3 Hz, 1H), 3.88 (d, *J* = 1.8Hz, 3H), 3.81 (t, *J* = 3.7 Hz, 4H), 3.15 (s, 2H), 2.60 (s, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): *δ* 171.8, 168.8, 149.0, 146.4, 144.9, 124.7, 124.1, 123.2, 116.5, 114.1, 67.0, 62.1, 56.4, 53.8; FT-IR (KBr): ν_{max} 3273, 3132, 2972, 2853, 1672, 1631, 1524, 1440, 1115, 864 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{16}H_{19}N_2O_5$: 319.1294, found: 319.1292.

N-(8-Methoxy-4-oxo-4H-chromen-3-yl)-2-(piperidin-1-yl)acetamide (11c): The title compound was prepared according to procedure B using 2-(2-formyl-3-methoxyphenoxy)acetonitrile (**6a**) (100 mg, 0.523 mmol), triethylamine (145 µL, 1.047 mmol, 2 equiv.), bromoacetylbromide (50 µL, 0.575 mmol, 1.1 equiv.) and piperidine (154 µL, 1.57 mmol, 3 equiv.). The product was obtained as pale yellow solid (Yield 102 mg, 62 %). m. p. 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.94 (s, 1H), 9.43 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.32–7.25 (m, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 3.98 (s, 3H), 3.09 (s, 2H), 2.52 (s, 4H), 1.70 (p, *J* = 5.4Hz, 4H), 1.47 (d, *J* = 4.7Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 171.8, 169.9, 148.9, 146.3, 144.8, 124.5, 124.3, 123.3, 116.5, 113.9, 62.5, 56.3, 55.0, 26.2, 23.6; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{17}H_{21}N_2O_4$: 317.1501, found: 317.1501.

N-(6-Fluoro-4-oxo-4H-chromen-3-yl)-2-(piperidin-1-yl)acetamide (12c): The title compound was prepared according to procedure B using 2-(4-fluoro-2-formylphenoxy)acetonitrile (100 mg, 0.558 mmol), triethylamine (155 µL, 1.117 mmol, 2 equiv.), bromoacetylbromide (53 µL, 0.614 mmol, 1.1 equiv.) and piperidine (144 µL, 1.675 mmol, 3 equiv.). The product was obtained as pale yellow solid (Yield 108 mg, 64 %). m. p. 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.92 (s, 1H) 9.40 (s, 1H), 7.86 (dd, J_1 = 8.2 Hz, J_2 = 3 Hz, 1H), 7.51 (dd, J_1 = 9.2Hz, J_2 = 4.2Hz, 1H), 7.43–7.38 (m, 1H), 3.10 (s, 2H), 2.53 (s, 4H), 1.70 (p, *J* = 5.6Hz, 4H), 1.48 (d, *J* = 5.1 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 170.0, 159.1 (d, $^1J_{CF}$ = 245.5 Hz), 152.1, 145.2, 123.8, 123.2 (d, $^4J_{CF}$ = 7.9 Hz), 122.4, 122.2, 120.7 (d, $^3J_{CF}$ = 8 Hz), 110.3 (d, $^2J_{CF}$ = 23.7 Hz), 62.5, 55.0, 26.2, 23.6; FT-IR (KBr): ν_{max} 3294, 2936, 2855, 1692, 1643, 1582, 1483, 1159, 827 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{16}H_{18}N_2O_3F$: 305.1301, found: 305.1302.

Procedure for three component addition reaction; Procedure C: 3-aminochromone (**1b**) (100 mg, 0.621 mmol, 1 equiv.) was dissolved in methanol (5 mL) and reacted with 3-formylchromone (108 mg, 0.621 mmol, 1 equiv.) at 80 °C for about 2 h. The three component adduct was precipitated upon cooling to room temperature. The obtained solid was filtered off, washed with cold methanol (3×3 mL) and then *vacuum* dried to obtain pure form of (*Z*)-3-(((2-methoxy-4-oxochroman-3-ylidene)methyl)amino)-4H-chromen-4-one (**1d**) as pale yellow solid (Yield 147 mg, 68 %); m. p. 244–246 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.57 (d, *J* = 12.9 Hz, 1H), 8.84 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 12.9 Hz, 1H), 7.86 (dd, J_1 = 17.3 Hz, J_2 = 8.0 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.54 (q, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 5.77 (s, 1H), 3.40 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 181.3, 177.6, 156.6, 149.1, 147.5 (2C), 144.1, 142.8, 141.6, 136.0, 126.2, 122.8 (2C), 122.7, 120.0, 118.8, 115.4, 107.1, 101.6, 55.4; FT-IR (KBr): ν_{max} 3442, 2933, 1643, 1471, 1205 cm^{-1}; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{20}H_{16}NO_5$: 350.1028, found: 350.1034. (Note: ^{13}C{^{1}H} NMR experiments of compounds **1d**-**12d** suffered solubility issues during the sample preparation in both $CDCl_3$ and DMSO-d_6. The maximum solubility of the compounds was found to be 4 mg/0.5 mL of the solvent. In some cases, a mixture of solvents such as $CDCl_3$ and 3 drops of CD_3OD was necessary to dissolve the compounds on slight pre-heating of the NMR tube. The additional signals are believed to be obtained due to the diastereomeric nature of the compounds and partial decomposition of the compound due to heat.

(Z)-3-(((2-Ethoxy-4-oxochroman-3-ylidene)methyl)amino)-4H-chromen-4-one (2d): The title compound was prepared according to procedure C using **1b** (100 mg, 0.621 mmol), ethanol (5 mL) and 3-formylchromone (108 mg, 0.621 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 175 mg, 78 %); m. p. 256–258 °C; FT-

IR (KBr): ν_{max} 3445, 2967, 1644, 1471, 1207 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.55 (d, *J* = 12.8 Hz, 1H), 8.85 (s, 1H), 8.19–8.17 (m, 1H), 7.95 (d, *J* = 13.2 Hz, 1H), 7.87–7.83 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.56–7.52 (m, 2H), 7.16–7.07 (m, 2H), 5.87 (s, 1H), 3.80–3.64 (m, 2H), 1.10 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR: (100 MHz, DMSO-d_6) δ 180.9, 171.30, 156.0, 155.9, 144.38, 143.07, 135.0, 134.9, 126.40, 126.20, 125.9, 125.7, 123.0, 122.4, 122.3, 119.1, 118.4, 104.9, 100.4, 63.5, 15.4.; HR-MS (ESI) m/z $[M+H]^+$: calcd. for $C_{21}H_{18}NO_5$: 364.1185, found: 364.1181.

(Z)-3-(((2-Isopropoxy-4-oxochroman-3-ylidene)methyl)amino)-4H-chromen-4-one (3d): The title compound was prepared according to procedure C using **1b** (100 mg, 0.621 mmol), isopropanol (5 mL) and 3-formylchromone (108.8 mg, 0.621 mmol, 1 equiv.). The product was obtained as yellow solid (Yield 159 mg, 68 %). m. p. 244–246 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 11.52 (d, *J* = 13.2 Hz, 1H), 8.85 (s, 1H), 8.18 (dd, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 1H), 7.92–7.83 (m, 3H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.55–7.52 (m, 2H), 7.15–7.11 (t, *J* = 7.2 Hz, 1H), 7.05 (d, 8.4 Hz, 1H), 5.96 (s, 1H), 4.13–4.07 (m, 1H), 1.19 (d, *J* = 6 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): *δ* 181.1, 171.3, 156.2, 155.9, 144.0, 143.0, 135.0, 134.8, 126.4, 126.2, 125.9, 125.7, 123.0 (2C), 122.2, 119.1, 118.5, 105.3, 99.1, 70.1, 23.6, 22.5; FT-IR (KBr): ν_{max} 3448, 2966, 1644, 1472, 1212 cm^{-1}; HR-MS (ESI) m/z $[M+H]^+$: calcd. for $C_{22}H_{20}NO_5$: 378.1341, found: 378.1341.

(Z)-3-(((2-Ethoxy-6-methyl-4-oxochroman-3-ylidene)methyl)amino) -4H-chromen-4-one (4d): The title compound was prepared according to procedure C using **1b** (100 mg, 0.621 mmol), ethanol (5 mL) and 3-formyl-6-methylchromone (116 mg, 0.621 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 170 mg, 72 %). m. p. 260–262 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 11.52 (d, *J* = 12.8 Hz, 1H), 8.85 (s, 1H), 8.18 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 1H), 7.93–7.83 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.56–7.52 (m, 1H), 7.34 (dd, J_1 = 6.4 Hz, J_2 = 2.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.83 (s, 1H), 3.78–3.62 (m, 2H), 2.32 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 181.1, 171.3, 155.8, 154.0, 144.1, 142.9, 135.8, 134.8, 131.3, 126.4, 126.0, 125.7, 125.5, 122.7, 122.2, 119.1, 118.3, 105.1, 100.3, 63.4, 20.6, 15.4; FT-IR (KBr): ν_{max} 3449, 2959, 1648, 1467, 1216 cm^{-1}; HR-MS (ESI) m/z $[M+H]^+$: calcd. for $C_{22}H_{20}NO_5$: 378.1341, found: 378.1339.

(Z)-8-Methoxy-3-(((2-methoxy-4-oxochroman-3-ylidene)methyl) amino)-4H-chromen-4-one (5d): The title compound was prepared according to procedure C using **6b** (100 mg, 0.523 mmol), methanol (5 mL) and 3-formylchromone (91 mg, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 181 mg, 77 %). m. p. 270–272 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 11.53 (d, *J* = 13.0 Hz, 1H), 8.83 (s, 1H), 7.92 (d, *J* = 13 Hz, 1H), 7.83 (dd, J_1 = 7.9, J_2 = 1.6 Hz, 1H), 7.64 (ddd, J_1 = 12.8 Hz, J_2 = 7.4 Hz, J_3 = 2.1 Hz, 1H), 7.60–7.48 (m, 2H), 7.48–7.36 (m, 3H), 7.18–7.02 (m, 1H), 5.74 (s, 1H), 3.93 (d, *J* = 6.9 Hz, 3H), 3.36 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$ & 3-drops of CD_3OD): δ 187.8, 180.8, 160.1, 154.8, 147.8, 137.2, 134.0, 133.6, 125.4, 124.2, 123.0, 121.2, 116.9, 115.8, 115.4, 113.4, 112.1, 105.1, 100.6, 55.4, 54.4; FT-IR (KBr): ν_{max} 3446, 2970, 1640, 1487, 1212, 1018 cm^{-1}; HR-MS (ESI) m/z $[M+H]^+$: calcd. for $C_{21}H_{18}NO_6$: 380.1134, found: 380.1132.

(Z)-8-Methoxy-3-(((2-methoxy-6-methyl-4-oxochroman-3-ylidene) methyl)amino)-4H-chromen-4-one (6d): The title compound was prepared according to procedure C using **6b** (100 mg, 0.523 mmol), methanol (5 mL) and 3-formyl-6-methylchromone (98 mg, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 150 mg, 73 %); m. p. 316–318 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 11.51 (dd, J_1 = 13 Hz, J_2 = 2.3 Hz, 1H), 8.82 (d, *J* = 3.0 Hz, 1H), 7.89 (dd, J_1 = 13.0 Hz, J_2 = 3.0 Hz, 1H), 7.71–7.56 (m, 2H), 7.50–7.38 (m, 2H), 7.33 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.98 (dd, J_1 = 8.2 Hz, J_1 = 3.2 Hz, 1H), 5.70 (d, *J* = 3.4 Hz, 1H), 3.94 (d, *J* = 3.4 Hz, 3H), 3.34 (d, *J* = 3.6 Hz, 3H), 2.29 (d, *J* = 2.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$ & 3 drops of CD_3OD): δ 187.9, 181.0, 160.1, 152.7, 147.9, 136.9, 134.5, 131.3, 130.7, 125.2, 124.2, 123.0, 122.7, 116.7, 115.8, 113.4, 103.9, 103.9, 55.4, 54.3, 19.5; FT-IR (KBr): ν_{max} 3424, 2937, 1652, 1488, 1218, 1070 cm^{-1}; HR-MS (ESI) m/z $[M+H]^+$: calcd. for $C_{22}H_{20}NO_6$: 394.1291, found: 394.1286.

(Z)-3-(((2-Ethoxy-4-oxochroman-3-ylidene)methyl)amino)-8-methoxy-4H-chromen-4-one (7d): The title compound was prepared according to procedure C using **6b** (100 mg, 0.523 mmol), ethanol (5 mL) and 3-formylchromone (91 mg, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 184 mg, 75 %); m. p. 230–232 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 11.52 (d, *J* = 13.0 Hz, 1H), 8.83 (s, 1H), 7.91 (d, *J* = 12.9 Hz, 1H), 7.83 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.66 (dd, J_1 = 7.2 Hz, J_2 = 2.1 Hz, 1H), 7.58–7.47 (m, 1H), 7.42 (q, *J* = 7.7 Hz, 2H), 7.28–6.98 (m, 3H), 5.85 (s, 1H), 3.94 (s, 3H), 3.77–3.50 (m, 2H), 1.06 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$ & 3 drops of CD_3OD): δ 188.7, 181.7, 161.0, 155.9, 148.8, 143.7, 143.5, 141.6, 134.9, 134.5, 126.4, 125.1, 124.7, 122.2, 117.8, 116.8, 114.3, 104.6, 101.5, 56.3, 55.3, 14.0. FT-IR (KBr): ν_{max} 3446, 2974, 1651, 1468, 1205, 1019 cm^{-1}; HR-MS (ESI) m/z $[M+H]^+$: calcd. for $C_{22}H_{20}NO_6$: 394.1291, found: 394.1310.

(Z)-3-(((2-Ethoxy-6-methyl-4-oxochroman-3-ylidene)methyl)amino) -8-methoxy-4H-chromen-4-one (8d): The title compound was prepared according to procedure C using **6b** (100 mg, 0.523 mmol), ethanol (5 mL) and 3-formyl-6-methylchromone (98 mg, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 165 mg, 65 %); m. p. 290–292 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 11.49 (d, *J* = 12.9 Hz, 1H), 8.80 (s, 1H), 7.87 (d, *J* = 12.9 Hz, 1H), 7.75–7.54 (m, 2H), 7.48–7.35 (m, 2H), 7.31 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1H), 7.02–6.83 (m, 1H), 5.80 (s, 1H), 3.93 (s, 3H), 3.76–3.54 (m, 2H), 2.28 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 189.1, 176.5, 160.5, 154.5, 148.7, 143.5, 137.5, 135.9, 125.5, 124.9, 124.8, 123.8, 123.0, 120.2, 118.7, 118.3, 118.1, 116.7, 112.8, 56.3, 56.3, 29.7, 21.0; FT-IR (KBr): ν_{max} 3444, 2970, 1640, 1487, 1212, 1066 cm^{-1}; HR-MS (ESI) m/z $[M+H]^+$: calcd. for $C_{23}H_{22}NO_6$: 408.1447, found: 408.1459.

(Z)-7-Methoxy-3-(((2-methoxy-4-oxochroman-3-ylidene)methyl) amino)-4H-chromen-4-one (9d): The title compound was prepared according to procedure C using **8b** (100 mg, 0.523 mmol), methanol (5 mL) and 3-formylchromone (91 mg, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 170 mg, 72 %); m. p. 282–284 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 11.64–11.30 (m, 1H), 8.75 (s, 2H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.86 (ddd, J_1 = 10.4 Hz, J_2 = 9.2 Hz, J_3 = 3.2 Hz, 2H), 7.59–7.43 (m, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 7.17–6.98 (m, 2H), 5.83 (s, 1H), 3.88 (s, 3H), 3.32 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 188.7, 176.1, 160.5, 137.2, 136.9, 135.9 (2C), 131.1, 127.8, 127.5, 127.0, 125.5 (2C), 118.6, 118.3, 116.2, 114.3, 100.0, 99.7, 55.7, 55.7; HR-MS (ESI) m/z $[M+H]^+$: calcd. for $C_{21}H_{18}NO_6$: 380.1134, found: 380.1124.

(Z)-3-(((2-Ethoxy-4-oxochroman-3-ylidene)methyl)amino)-7-methoxy-4H-chromen-4-one (10d): The title compound was prepared according to procedure C using **8b** (100 mg, 0.523 mmol),

ethanol (5 mL) and 3-formylchromone (91 mg, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 174 mg, 71 %). m. p. 292–294 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.48 (d, J = 13.0 Hz, 1H), 8.74 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 13.0 Hz, 1H), 7.83 (dd, J_1 = 7.8 Hz, J_2 = 1.7 Hz, 1H), 7.51 (ddd, J_1 = 8.2 Hz, J_2 = 7.3 Hz, J_3 = 1.8 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.16–7.00 (m, 3H), 5.83 (s, 1H), 3.88 (s, 3H), 3.79–3.55 (m, 2H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$ & few drops of CD_3OD): δ 181.6, 171.4, 164.4, 157.7, 155.7, 143.8, 141.4, 135.0, 134.4, 127.1, 126.1, 125.9, 122.6, 122.1, 117.7, 115.2, 104.3, 101.4, 100.0, 55.7, 55.1, 13.6; HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{22}H_{20}NO_6$: 394.1291, found: 394.1299.

(Z)-7-Methoxy-3-(((2-methoxy-6-methyl-4-oxochroman-3-ylidene) methyl)amino)-4H-chromen-4-one (11d): The title compound was prepared according to procedure C using **8b** (100 mg, 0.523 mmol), methanol (5 mL) and 3-formyl-6-methylchromone (98 mg, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 186 mg, 76 %). m. p. 266–268 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (d, J = 13.0 Hz, 1H), 8.72 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 13.1 Hz, 1H), 7.61 (d, J = 1.3 Hz, 1H), 7.39–7.25 (m, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.08 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 7.03–6.91 (m, 1H), 5.68 (s, 1H), 3.88 (s, 3H), 3.38 (s, 3H), 2.68 (s, 3H); ^{13}C{1H} NMR (126 MHz, $CDCl_3$): δ 188.7, 176.1, 163.5, 160.5, 157.9, 154.5, 137.2, 135.9, 127.0, 125.5, 125.0, 120.2, 118.3, 116.2, 114.6, 114.3,101.1, 99.7, 55.8, 55.7, 29.7, 21.0. HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{22}H_{20}NO_6$: 394.1291, found: 394.1279.

(Z)-3-(((2-Ethoxy-6-methyl-4-oxochroman-3-ylidene)methyl) amino)-7-methoxy-4H-chromen-4-one (12d): The title compound was prepared according to procedure C using **8b** (100 mg, 0.523 mmol), ethanol (5 mL) and 3-formyl-6-methylchromone (98 mg, 0.523 mmol, 1 equiv.). The product was obtained as pale yellow solid (Yield 175 mg, 69 %). m. p. 244–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.45 (d, J = 13.0 Hz, 1H), 8.74 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 13.0 Hz, 1H), 7.62 (d, J = 1.8 Hz, 1H), 7.31 (dd, J = 8.3, 2.3 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.08 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 5.79 (s, 1H), 3.88 (s, 3H), 3.81–3.53 (m, 2H), 2.29 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 188.7, 176.0, 172.9, 163.5, 160.5, 154.5, 137.2, 136.9, 135.9, 127.0, 125.5, 125.0, 120.2, 118.3, 118.1, 117.7, 116.2, 114.32, 100.0, 55.8, 55.7, 21.0, 20.5. HR-MS (ESI) m/z [M+H]$^+$: calcd. for $C_{23}H_{22}NO_6$: 408.1447, found: 408.1459.

Computational studies

All the calculations were carried out using the Gaussian09 quantum chemical program.[48] Geometry optimization of the reactants, intermediates and transition states were performed using the B3LYP[51-55] functional in conjunction with the basis set 6-31G**. Frequency calculations have been done to confirm that the optimized structures were minima on the potential energy surface. For the stable structures, no imaginary frequency was observed. For the transition states, one imaginary frequency on the reaction path was observed. Further intrinsic reaction coordinate (**IRC**) energy profiles have been calculated to confirm that the tracked transition states (**TS**) were the correct ones.

Anticancer activity

HeLa S3 and A549 cancer cells were cultured and maintained in standard DMEM (Dulbecco's modified eagle medium) with 10 % fetal bovine serum. The cancer cells were stored at 37 °C under humidified condition (5 % of CO_2 and 95 % of air). Briefly, cells were seeded in 96-well plates (2×10^4/plate) and incubated with fresh DMEM at 37 °C under 5% CO_2 and 95% air for 24 h. After the cells were washed twice with PBS (phosphate buffered saline), the medium was changed to serially diluted test samples in DMEM (100 µL) with a control and blank in each test plate. After 24 h of treatment, the cells were washed twice with PBS and incubated with 100 µL of DMEM containing MTT solution (5 mg/mL). Then, the cells were incubated for 3-4 h at 37 °C and DMSO (100 µL) was added to each well. Addition of DMSO gave purple colored precipitate due to the formation of formazan in live cells. After 3-4 h of incubation at 37 °C, it formed purple colored precipitate due to the formation of formazan in live cells. For quantifying the precipitate, the absorbance at 570 nm was measured (BioRad).[56] Cell viability was calculated from the mean values of data from three wells by using the following equation:

Cell viability (%) = [Abs $_{(Test\ sample)}$ – Abs $_{(Blank)}$]/ [Abs $_{(Control)}$ – Abs $_{(Blank)}$] x 100

Fluorescence study

1×10^5 HeLa S3 cancer cells were seeded in 30 mm plates; cells were treated with compounds **SVM-2** (50 µM) and **SVM-4** (10 µM), and incubated for 24 h. After treatment, cells were stained with AO/PI (10 µM) solution for 15 min at dark condition. The images were captured under fluorescence microscope.[56-58]

Colony formation study

Freshly prepared HeLa S3 cells (2×10^3/well) were plated in 24-well plates and incubated for overnight under condition (5 % of CO_2 and 95 % of air) for cell attachment. Next day, HeLa S3 cells were treated with different concentrations of **SVM-2** (1, 5 and 10 µM) and **SVM-4** (2.5, 5 and 10 µM) for 24 h, and washed twice with PBS. Then, cells were incubated with freshly prepared DMEM for 10 days to grow colonies. After 10 days of incubation, cells were washed with distilled H_2O and incubated with crystal violet solution for 15-20 min at room temperature. Cells were then washed with distilled H_2O and dried. The images were captured and colony area was calculated by ImageJ software.

Conflicts of interest

There are no conflicts to declare

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Table of Content:

NHC catalyzed green synthesis of functionalized chromones: DFT mechanistic insights and *in vitro* activities in cancer cells

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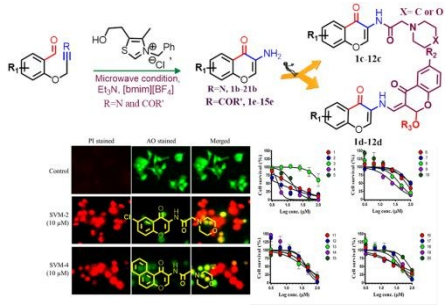

A simple green protocol for the synthesis of 3-aminochromone derivatives using NHC catalyzed intramolecular hydroacylation reaction was developed. Further functional 3-aminochromes was subjected to anticancer activites.