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An efficient ultrasound assisted synthesis of (*Z*)-3-(3-(amino)acryloyl)-2*H*-chromen-2-ones

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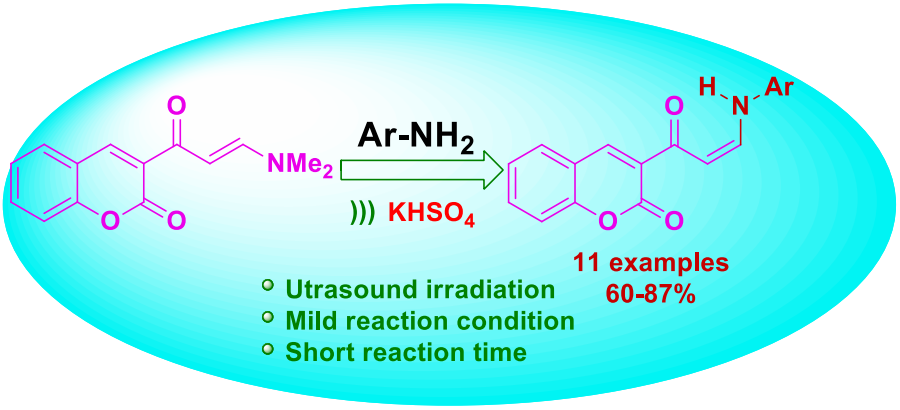
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Abstract

A series of coumarin-enaminones were synthesized by a facile ultrasound assisted protocol, affording the products in good to high yields ranging from 60% to 87%. The reaction was completed in a short time with high specificity yielding exclusively the *Z*-isomer of the enaminones. In addition, the method is simple, environment friendly, and cost effective employing the use of aqueous solvent and inexpensive reagent. The structures were established with the help of spectral analyses such as FT-IR, MS/HR-MS, ^{1}H NMR, and ^{13}C NMR.



Keywords: Coumarin, enaminones, ultrasound irradiation, Michael addition

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Introduction

Coumarins are a large class of naturally occurring benzopyrone derivatives, chemically characterized by a fused benzene and α-pyrone ring systems.[1] They are regarded as privileged structural frameworks in medicinal chemistry because of their ability to interact with a wide range of biological targets.[2] This versatility renders them as valuable starting scaffold for the rational design and development of novel therapeutic agents across multiple disease domains.[3] The rigid fused-ring structure of coumarin derivatives further imparts wide-ranging applicability, extending beyond medicinal chemistry to fields such as bromatology, material science, and supramolecular chemistry.[4] In particular, coumarin-based compounds have garnered significant attention in drug research, as their remarkable potential in disease prevention and therapy has positioned them as a prominent focus of contemporary medicinal chemistry investigations.[5] Numerous natural and synthetic coumarins have been established as active pharmaceutical ingredients, owing to their well-demonstrated and remarkable therapeutic potential such as, anticoagulant,[6] anticancer,[7] antioxidants,[8] antimicrobial,[9,10] antiviral,[11] antiparasitic,[12] anti-inflammatory, and analgesic,[13] antidiabetic,[14] antidepressant,[15] anti-Alzheimer's,[16] and anti-Parkinson's properties.[17]

On the other hand, enaminones are versatile and easily accessible reagents that have attracted significant interest in recent years.[18] They are well recognized as fundamental building blocks in the field of organic chemistry for the development of novel drug molecular hybrids.[19] In particular, the reactivity and synthetic utility of *N,N*-dimethyl enaminones as a pivotal intermediates have been comprehensively summarised in a review by Huang and Yu. *N,N*-Dimethyl enaminones allow further elaboration through a range of facile chemical transformations.[20] In addition to their synthetic utility, compounds containing the enaminone moiety have demonstrated a wide spectrum of pharmacological activities.[21] Various enaminone-based analogues have shown promising biological effects and have been explored in several therapeutic areas such as antibiotic, anti-inflammatory, antitubercular, antinociceptive, anticonvulsants, antitumor, antifungal, antimicrobial and antidepressants activities.[22]

Coumarin-based enaminones have been explored for their synthetic versatility and promising pharmacophoric properties like anti-microbial,[23] cytotoxicity,[24] anti-proliferative,[25] anticancer,[26] antioxidant,[27] and applications as chemo-dosimeters in fluorescent molecular probes.[28] Furthermore, a series of (*Z*) coumarin-enaminones carrying biologically active sulfonamide scaffold was designed, synthesized and reported to function as aromatase inhibitors and apoptosis enhancers.[26] Recent literature has also highlighted new synthetic approach for the preparation of coumarin enaminone analogues, along with an evaluation of their anticancer properties. This study mentions the importance of developing innovative methodologies to access structurally diverse coumarin derivatives, since such modifications often enhance biological activity and expand therapeutic potential.[29] However, despite these initial investigations, the current literature on coumarin enaminones and their derivatives is relatively scarce and their comprehensive biological potential is not substantially explored, thus highlighting the need for further studies.

Our research group has previously reported the synthesis of various enaminones and evaluated their biological activities.[30,31] In line with our ongoing interest in investigating the synthetic accessibility of coumarin enaminones, we herein report the synthesis of coumarin enaminone derivatives.

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Results and Discussion

3-Acetylcoumarin (**1**) was subjected to formylation by reacting it with *N,N*-dimethylformamide dimethylacetal (DMF-DMA) following the reported procedure, to give the corresponding formylated compound (**2**).[32] The synthesis of enaminones **4** was taken up subsequently. Initially, to a solution of aniline (**3a**:1 mmol) and compound **2** (1 mmol) in ethanol (3 mL), a solution of $KHSO_4$ (2 mmol) dissolved in 3 mL of water was added in one lot. The resulting mixture was then subjected to ultrasound irradiation. During the course of the reaction, the product precipitated out and at the end of 22 minutes, the reaction went to completion giving a solid product in 80% yield. The reaction of compound **2** with other aromatic amines (**3b-k**) proceeded smoothly under similar conditions affording the desired enaminones **4b-k** in overall yields ranging from 60% to 87% (Scheme 1). The structures of the compounds were established based on the spectral and analytical data (Experimental). Unfortunately, this reaction failed with alkyl and aralkyl amines. All our attempts under various conditions, like, refluxing ethanol, acetic acid and MW irradiation gave disappointing results and no product could be isolated from the complex reaction mixture.

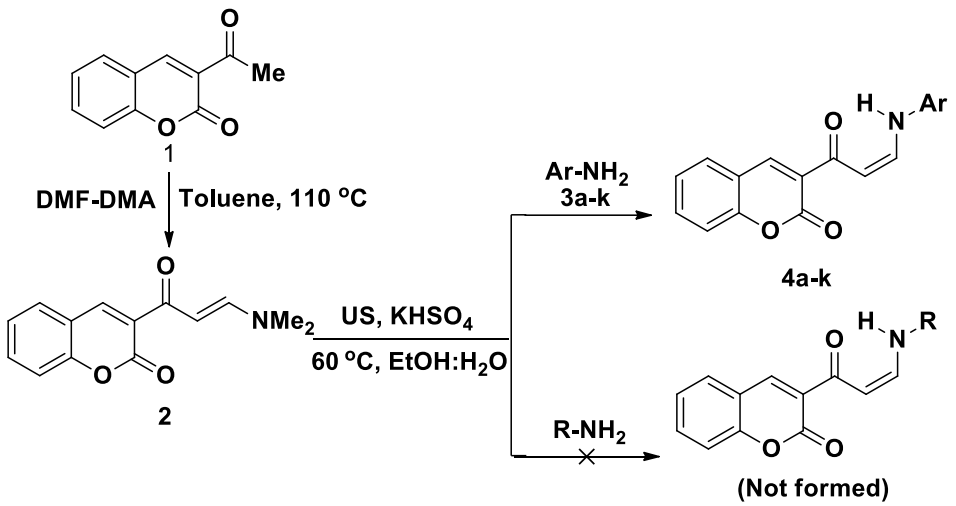
The synthetic protocol features the prominent and highly reactive nature of *N,N*-dimethylamino leaving group that form a part of the intermediate enaminones (**2**), a core structural feature whose synthetic utility is described extensively in the literature.[20] The transformations involving *N,N*-dimethylamino building block proceed through three synthetic strategies (1) direct C(sp^2)–H *β* functionalization reactions, (2) difunctionalization reactions through C=C double bond cleavage, and (3) cascade cyclization reactions.[20] The presence of the dimethylamino group polarizes the conjugated π-system through resonance which modulates the incoming nucleophilic amine attack at the *β*-carbon. Under our strategic protocol based on the same foundational dimethylamino activation in ultrasound irradiation assisted by $KHSO_4$, the addition-elimination at the *β*-carbon is drastically accelerated, by-passing the long reaction time, formation of isomers and conventional protocols. The rate of reaction was observed to be dependent on the electronic effects exerted by the groups attached to the phenyl ring as well as the quinolinyl groups at the *β*-carbon. The electron-donating groups (EDGs) like methyl and methoxy led to the completion of the rection within 12 minutes. This can be attributed to the fact that the EDGs enhance the electron density at the *β*-carbon that facilitates the intramolecular push required to expel the dimethylamino group forming the corresponding coumarin-enaminones. Conversely, the electron-withdrawing groups (EWGs) such as Cl, Br, F, NO_2, at the para position of the phenyl, the quinolinyl and phenyl groups at *β*-positions took 24-27 minutes, which decreases the electron density at the *β*-carbon, thereby stabilizing the intermediate and delaying the elimination step and hence longer reaction time as observed.

In a previous report by Bollikala and coworkers, the synthesis of coumarin enaminones such as **4a**, **4b**, **4d** and **4f** was obtained by the reaction of formylated coumarin (**2**) with aromatic amines catalysed by camphorsulphonic acid in dimethylsulphoxide at 80 °C for 1-2 h. The methodology suffers significant stereochemical limitations leading to *E*/*Z* isomeric mixtures. This methodology also failed with aliphatic amines, limiting the methodology to aromatic amines.[33]

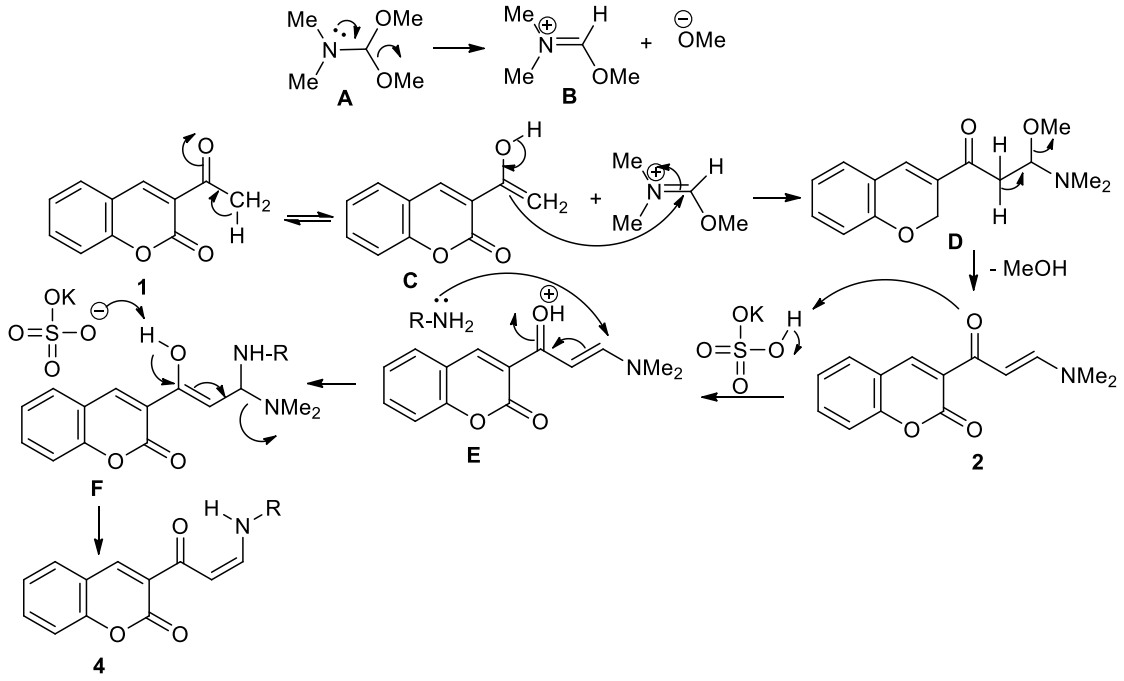
In contrast, our protocol smoothly resulted in a series of coumarin-enaminones including compounds **4a**, **4b**, **4d** and **4f** overcoming the formation of mixtures and forming exclusively the *Z*-isomer. In addition, it employs low-toxic, readily available reagent – $KHSO_4$ in an aqueous water-ethanol solvent system with ultrasound-assisted activation, minimizing energy consumption, high yields (60-87%), purity, short reaction times (12-24 min), and operational simplicity without harsh conditions. We thus present the synthesis of enaminones **4a-4k** as shown in Scheme 1 with the pictorial presentation of the synthesized compounds in figure 1. The mechanistic pathway for the formation of the coumarin-enaminones are presented in Scheme 2.

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The process is initiated by the assistance of the lone pair of electrons on nitrogen atom, whereby DMF-DMA (**A**) undergoes thermal decomposition to give the iminium ion (**B**). **B** is then attacked by the enolized acetyl coumarin (**1**) to form an intermediate **D** which loses a methanol molecule yielding the formylated acetyl coumarin (**2**). Compound **2** subsequently undergoes *aza*-Michael addition-elimination reaction in the presence of $KHSO_4$. Thus, the carbonyl oxygen atom of **2** is protonated to give an intermediate **E** thereby making the *β*-carbon highly electron deficient and more susceptible to attack by a nucleophile. Consequently, **E** is attacked by the amine to produce the intermediate **F** which finally loses dimethylamine to yield the enaminone **4**.



Scheme 1. Synthesis of coumarin-enaminone derivatives **4a-k.**



Scheme 2. A plausible mechanism of coumarin-enaminone.

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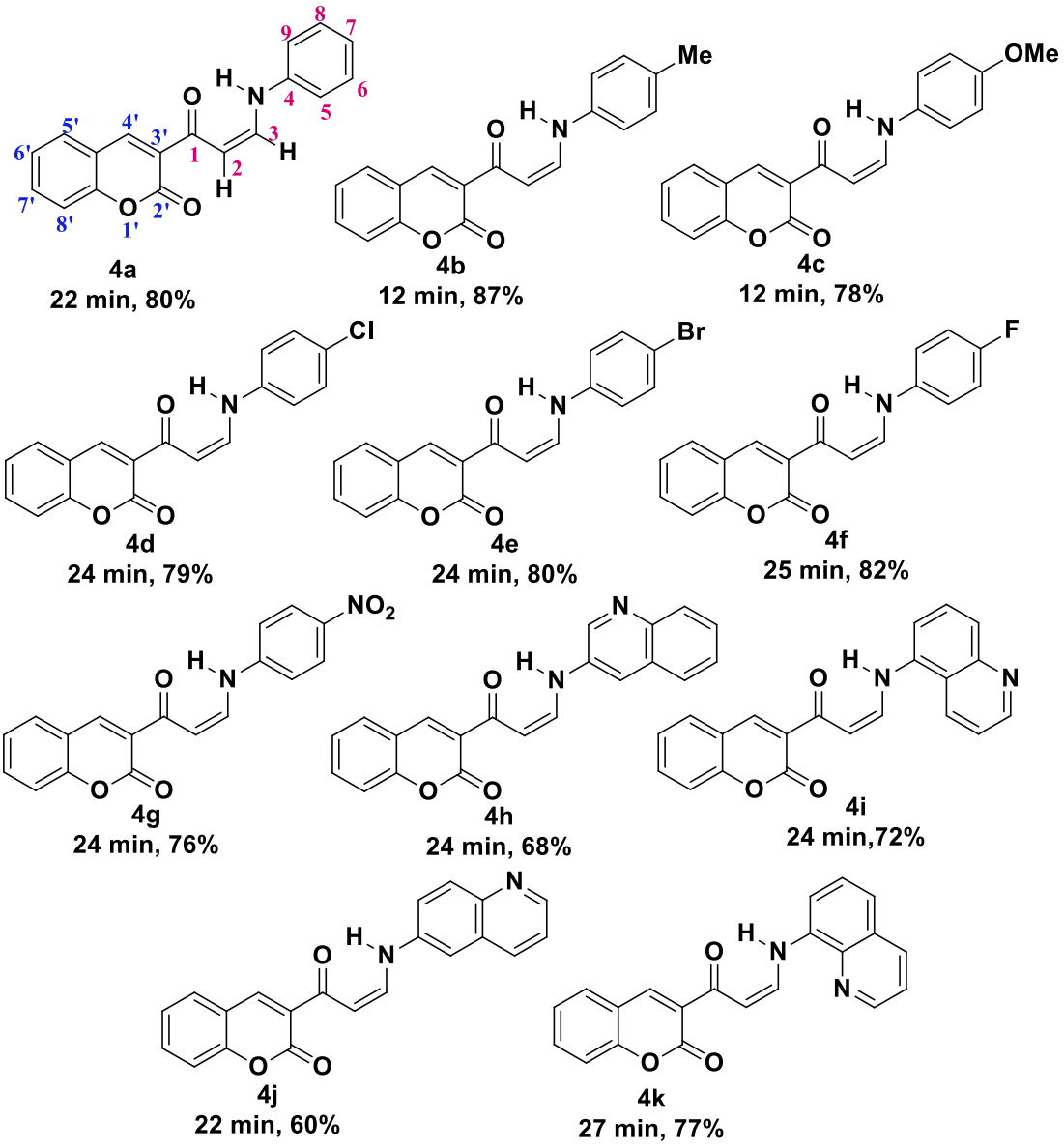


Figure 1. Synthesized coumarin-enaminones **4a-k.**

The structures of the synthesized compounds (**4a-k**) were established by a combination of spectral and analytical techniques. Thus, the IR spectra of **4b** displayed characteristic absorptions corresponding to N–H stretching at 3441 cm^{-1} and two distinct C=O stretching vibrations, attributable to the lactone and acetyl carbonyl groups at 1729 and 1605 cm^{-1} respectively, thereby confirming the formation of the target products. High-resolution mass spectrometry (HR-MS) further supported these assignments by providing the peak at 306.1126 consistent with the calculated molecular weight $[MH]^+$: 306.1130.

In the ^1H NMR spectrum of compound **4b**, a singlet was observed at δ 2.33 ppm corresponding to three protons of the CH_3 group. Two doublets appearing at δ 7.03 ppm and δ 7.16 ppm were attributed to the four protons of the phenyl ring, each with a coupling constant of 8.0 Hz. For the coumarin group, the $C_{4'}$ displayed a singlet at δ 8.59 ppm, while the $C_{5'}$ proton resonated at δ 7.64 ppm as a doublet with a coupling constant of 7.5 Hz. The other protons appeared as multiplets in the region δ 7.30-7.36 ppm and δ 7.58-7.61 ppm. The vinylic protons at C_2 and C_3 positions along with the NH proton establish a characteristic splitting pattern providing a definitive spectral confirmation of the cis-configuration. The C_2 proton resonated as a clean

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doublet at δ 6.61 ppm with coupling constant J = 7.5 Hz. The adjacent C_3 proton undergoes simultaneous vicinal coupling with both C_2 and NH resolving into a double doublet at δ 7.55 ppm with coupling constants of 7.5 Hz and 12.5 Hz. The coupling constants of C_2 and C_3 protons at 7.5 Hz are indicative of the cis-orientation, confirming the *Z*-isomer and ruling out the *E*-isomer (J = 12.0 Hz). The coupling extended to the NH proton which is subsequently split into a doublet at δ 12.29 ppm with a coupling constant of 12.5 Hz. This downfield shift of the NH proton can be attributed to the intramolecular hydrogen bonding with the carbonyl oxygen atom. The intramolecular hydrogen bonding is possible only when the amine and the carbonyl group are on the same side of the vinylic double bond. This unequivocally establishes the *Z*-conformation of the coumarin-enaminones. The ^{13}C NMR spectrum of compound **4b** displayed a distinct peak for methyl carbon at δ 20.82 ppm. A characteristic signal for the lactone carbonyl and carbonyl carbon at δ 159.38 and 189.17 ppm respectively and the aromatic carbons resonated at their expected region. In the same manner, the structures of the other compounds were also well accounted for by the spectroscopic data.

Interestingly, compound **4g** presented a distinct exception and was found to exist as an inseparable mixture of both the (*E*) and the (*Z*) isomers in the ratio 77:23. For the *Z*-isomer, the C_2 proton revealed a clear doublet splitting at δ 6.56 ppm with coupling constant J = 8.4 Hz. The C_3 proton being split by both the neighbouring C_2 and NH protons, resolved into a distinct double doublet at δ 8.04 ppm (J = 8.4 Hz, 12.4 Hz). The NH proton in turn resonated as a doublet at δ 11.99 ppm (J = 12.8 Hz). The *E*-configuration exhibits a much larger vinylic coupling constant of 13.2 Hz for C_2 doublet splitting (δ 6.75 ppm). The C_3 proton displayed as a multiplet at 7.95-7.98 ppm, while the NH proton appeared as a doublet at 10.80 ppm (J = 13.6 Hz). The proton signals corresponding to the coumarinyl group appear as parallel, overlapping resonance reflecting the coexistence of the isomers. The splitting pattern, the divergence in the coupling constants and the NH electronic environments allow a vivid distinction between the *E*- and the *Z*-isomers.

Conclusions

A series of 11 coumarin-enaminones were successfully synthesized employing ultrasound as an efficient tool assisted by $KHSO_4$ in aqueous media. The protocol offers improved reaction rate, with mild conditions in aqueous solvent. A significant highlight of the strategy is the consistent formation of *Z*-isomeric products avoiding the formation of isomers and side products except in compound **4g** where the *E*/*Z* mixtures was also detected. Overall, the method provides a practical and efficient approach for the synthesis of coumarin-enaminone derivatives.

Experimental Section

General. All reagents and chemicals were purchased from TCI and Sigma-Aldrich and were used directly without any further purification. Infrared (IR) spectra were recorded on a Fourier-transform infrared (FT-IR) spectrometer using KBr pellets. Melting points were measured by the open capillary method and are reported as uncorrected values. Electrospray ionization mass spectra (ESI-MS) were obtained on a THERMO Finnigan LCQ Advantage Max ion trap spectrometer. High-resolution mass spectrometric (HRMS) data were collected on a Xevo G2-XS QTof mass analyzer (Waters) operated with MassLynx version 4.1 software. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400, 500 MHz spectrometer in $CDCl_3$, with tetramethyl silane (TMS) as the internal reference, DMSO-d_6. Chemical shifts are reported in δ (ppm). Signal multiplicities are

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indicated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet) with coupling constants (*J*) given in hertz (Hz). Ultrasound irradiation was carried out in an EQUITRON Digital Ultrasonic Cleaner (2.5 L, model 8425.025.424) operating at 170 W and 50 Hz. Column chromatography was performed on SRL silica gel (60–120 mesh) using an ethyl acetate–hexane (1:4) eluent system.

Synthesis of (*E*)-3-(3-(dimethylamino)acryloyl)-2*H*-chromen-2-one (2). A mixture of 3-Acetylcoumarin (**1**) (940 mg, 5 mmol) and *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) (1.3 mL, 10 mmol) taken in a round bottom flask was refluxed in toluene (5 mL) under dry conditions for 4 hours. On completion of the reaction (TLC), the solvent was sucked dry under reduced pressure to give a gum which on trituration with hexane gave a practically pure solid enaminone **2** in 95% yield which was collected by filtration, washed with hexane and dried. This was then subsequently used for the synthesis of coumarin enaminones (**4**) derivatives without purification.

General procedure for the synthesis of (*Z*)-3-(3-(amino)acryloyl)-2*H*-chromen-2-ones. Enaminone **2** (1 mmol) and primary amine **3** (1 mmol) were dissolved in 2 mL of EtOH and to this solution was added 2 mmol of $KHSO_4$ dissolved in 2 mL water in one lot and the resultant mixture was irradiated in US bath at 60 ℃ for 20-22 minutes. The progress of the reaction was monitored consistently (TLC) and the precipitated product was collected by filtration, washed with EtOH:H_2O solvent and dried to give the enaminones **4** in overall 68-90% yields. Purification for analytical purposes was carried out using column chromatography with silica gel 60-120 mesh and ethylacetate:hexane (1:4) as eluent.

(*Z*)-3-(3-(Phenylamino)acryloyl)-2*H*-chromen-2-one[33] (**4a**). Orange solid; yield: 80%; mp 181-182 ℃ [225-228 ℃]; FT-IR (ν_{max}, cm^{-1}): 3415, 1726, 1609.

(*Z*)-3-(3-(*p*-Tolylamino)acryloyl)-2*H*-chromen-2-one[33] (**4b**). Orange solid, yield: 87%; mp 200-201 ℃ [232-234 ℃]; FT-IR (ν_{max}, cm^{-1}): 3441, 1729, 1605; ^{1}H NMR (500 MHz, $CDCl_3$), ppm: 2.33 (s, 3H, CH_3), 6.61 (d, 1H, *J* = 7.5 Hz), 7.03 (d, 2H, *J* = 8 Hz), 7.16 (d, 2H, *J* = 8 Hz), 7.30-7.36 (m, 2H), 7.55 (dd, 1H, *J* = 7.5, 12.5 Hz), 7.58-7.61 (m, 1H), 7.64 (d, 1H, *J* = 7.5 Hz), 8.59 (s, 1H), 12.29 (d, 1H, NH, *J* = 12.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), ppm: 20.82, 96.55, 116.48, 116.83, 118.96, 124.69, 125.62, 130.35, 133.36, 134.25, 137.39, 145.84, 146.85, 154.74, 159.39, 184.17. $C_{19}H_{15}NO_3$, HRMS (ESI) *m/z*: found: $[MH]^+$ 306.1126, Calculated: 306.1130.

(*Z*)-3-(3-((4-Methoxyphenyl)amino)acryloyl)-2*H*-chromen-2-one (**4c**). Orange solid; yield: 78%; mp 180-181 ℃; FT-IR (ν_{max}, cm^{-1}): 3453, 1724, 1607; ^{1}H NMR (300 MHz, $CDCl_3$), ppm: 3.80 (s, 3H, OCH_3), 6.59 (d, 1H, *J* = 7.5 Hz), 6.90 (d, 2H, *J* = 9 Hz), 7.07 (d, 2H, *J* = 9.0 Hz), 7.28-7.31 (m, 1H), 7.33-7.36 (m, 1H), 7.49 (dd, 1H, *J* = 7.5 Hz, 12.6 Hz), 7.56-7.65 (m, 2H), 8.58 (s, 1H), 12.35 (d, 1H, NH, *J* = 12.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), ppm: 55.75, 96.42, 115.22, 116.61, 118.53, 119.13, 124.83, 125.79, 129.70, 133.46, 145.84, 147.48, 154.85, 157.00, 159.57, 183.97. $C_{19}H_{15}NO_4$, HRMS [ESI]: Found *m/z*: $[MH]^+$ 322.1076, Calculated: 322.1079.

(*Z*)-3-(3-((4-Chlorophenyl)amino)acryloyl)-2*H*-chromen-2-one[33] (**4d**). Brown solid; yield: 79%; mp 217- 218 ℃ [215-217 ℃]; FT-IR (ν_{max}, cm^{-1}): 3453, 1724, 1607; ^{1}H NMR (500 MHz, $CDCl_3$), ppm: 6.67 (d, 1H, *J* = 8.0 Hz), 7.05 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.34-7.37 (m, 2H), 7.50 (dd, 1H, *J* = 8.0 Hz, 12.0 Hz), 7.59-7.66 (m, 1H), 8.59 (s, 1H), 12.24 (d, 1H, NH, *J* = 12.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), ppm: 97.46, 116.54, 117.88, 118.87, 124.77, 125.39, 129.42, 129.67, 123.89, 133.59, 138.54, 146.00, 146.21, 154.83, 159.31, 184.94. $C_{19}H_{15}NO_4$, HRMS [ESI]: Found, *m/z*: $[MH]^+$. 326.0581, Calculated: 326.0578.

(*Z*)-3-(3-((4-Bromophenyl)amino)acryloyl)-2*H*-chromen-2-one (**4e**). Orange solid; yield: 80%; mp 214-215 ℃, FT-IR (ν_{max}, cm^{-1}): 3427, 1718, 1610; ^{1}H NMR (500 MHz, $CDCl_3$), ppm: 6.67 (d, 1H, *J* = 8 Hz) 7.00 (d, 2H, *J* = 8.5 Hz), 7.31-7.37 (m, 2H), 7.46 (d, 2H, *J* = 8.5 Hz), 7.49-7.52 (m, 1H), 7.60-7.65 (m, 2H), 8.58 (s, 1H), 12.21 (d, 1H, NH, *J* = 12.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 97.55, 116.54, 116.89, 118.22, 118.86, 124.78, 124.38,

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129.68, 132.81, 133.62, 139.01, 145.85, 146.25, 154.83, 159.31, 186.01. $C_{18}H_{12}BrNO_3$, HRMS [ESI]: Found, *m/z*: [MH]+ 372.0061, Calculated: 372.0053.

(*Z*)-3-(3-((4-Fluorophenyl)amino)acryloyl)-2*H*-chromen-2-one[33] (**4f**). Yellow solid; yield: 82%; mp 201-202 ℃ [203-205 ℃]; FT-IR (ν_{max}, cm^{-1}): 3433, 1736, 1565. $C_{18}H_{12}FNO_3$, HRMS [ESI]: Found, *m/z*: $[M-H]^+$ 308.0715, Calculated: 308.0723.

(*E*/*Z*)-3-(3-((4-Nitrophenyl)amino)acryloyl)-2*H*-chromen-2-one (**4g**). Orange solid; yield: 76%; mp 225-227 ℃; FT-IR (ν_{max}, cm^{-1}): 3453, 1708, 1596; ^{1}H NMR (400 MHz, DMSO-d_6), ppm: 6.56 (d, 1H, *J* = 8.4 Hz), 6.75 (d, 1H, *J* = 13.2 Hz), 7.36 (d, 2H, *J* = 9.6), 7.39-7.47 (m, 3H), 7.58 (d, 1H, *J* = 9.2 Hz), 7.70-7.74 (m, 1H), 7.92-7.94 (m, 1H), 7.95-7.98 (m, 1H), 8.04 (dd, 1H, *J* = 8.4 Hz, 12.4 Hz), 8.18 (d, 2H, *J* = 9.2 Hz), 8.22-8.27 (m, 1H), 8.58 (s, 1H), 8.71 (s, 1H), 10.80 (d, 1H, NH, *J* = 13.6 Hz), 11.99 (d, 1H, NH, *J* = 12.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) ppm: 99.05, 116.79, 119.03, 125.05, 127.33, 128.12, 128.65, 129.40, 130.01, 134.00, 143.23, 145.78, 146.85, 155.13, 159.49. 185.82. $C_{18}H_{12}N_2O_5$, HRMS [ESI]: Found, *m/z*: $[MH]^+$ 337.0825, Calculated: 337.0819.

(*Z*)-3-(3-(Quinolin-3-ylamino)acryloyl)-2*H*-chromen-2-one (**4h**). Orange solid; yield: 68%; mp 220-221 ℃; FT-IR (ν_{max}, cm^{-1}): 3439, 1721, 1604; ^{1}H NMR (400 MHz, $CDCl_3$), ppm: 6.81 (d, 1H, *J* = 7.6 Hz), 7.32-7.38 (m, 3H), 7.54-7.57 (m, 1H), 7.61-7.68 (m, 4H), 7.77-7.81 (m, 1H), 8.10 (d, 1H, *J* = 8.0 Hz), 8.63 (s, 1H), 8.85 (s, 1H), 12.41 (d, 1H, NH, *J* = 12.4 Hz). $C_{21}H_{14}N_2O_3$, HRMS [ESI]: Found, *m/z*: $[MH]^+$ 343.1088, Calculated: 343.1077.

(*Z*)-3-(3-(Quinolin-5-ylamino)acryloyl)-2*H*-chromen-2-one (**4i**). Maroon solid; yield: 72%; mp 210-212 ℃; FT-IR (ν_{max}, cm^{-1}): 3456, 1737, 1605; ^{1}H NMR (500 MHz, $CDCl_3$), ppm: 6.83 (d, 1H, *J* = 8.0 Hz), 7.32-7.39 (m, 3H), 7.55 (dd, 1H, *J* = 8.5 Hz, 13.0 Hz), 7.60-7.67 (m, 2H), 7.69-7.77 (m, 2H), 7.95 (d, 1H, *J* = 8.5 Hz), 8.56 (d, 1H, *J* = 8.5 Hz), 8.67 (s, 1H), 9.02 (s, 1H), 13.22 (d, 1H, NH, *J* = 12.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 98.60, 112.08, 116.58, 118.86, 120.25, 121.49, 124.85, 125.26, 125.60, 129.70, 129.80, 133.74, 135.22, 136.22, 136.23, 146.25, 147.32, 148.55, 151.13, 154.89, 159.29, 185.52. $C_{21}H_{14}N_2O_3$, HRMS [ESI]: Found, m/z: $[MH]^+$ 343.1085, Calculated: 343.1077.

(*Z*)-3-(3-(Quinolin-6-ylamino)acryloyl)-2*H*-chromen-2-one (**4j**). Brown solid; yield: 60%; mp 213-215 ℃; FT-IR (ν_{max}, cm^{-1}): 3743, 1716, 1607; ^{1}H NMR (500 MHz, $CDCl_3$), ppm: 6.75 (d, 1H, *J* = 8.0 Hz), 7.33-7.38 (m, 3H), 7.41 (dd, 1H, *J* = 8.5 Hz, 12.5 Hz), 7.46 (s, 1H), 7.52-7.54 (m, 1H), 7.62-7.69 (m, 2H), 8.09-8.13 (m, 2H), 8.62 (s, 1H), 8.83 (s, 1H), 12.42 (d, 1H, NH, *J* = 12.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 98.60, 112.08, 116.58, 118.86, 120.25, 121.49, 124.85, 125.26, 125.60, 129.70, 129.80, 133.74, 135.22, 136.22, 136.23, 146.25, 147.32, 148.55, 151.13, 154.89, 159.29, 185.52. $C_{21}H_{14}N_2O_3$, HRMS [ESI]: Found, *m/z*: $[MH]^+$ 343.1084, Calculated: 343.1077.

(*Z*)-3-(3-(Quinolin-8-ylamino)acryloyl)-2*H*-chromen-2-one (**4k**). Orange solid; yield: 77%; mp 225-227 ℃; FT-IR (ν_{max}, cm^{-1}): 3452, 1716, 1602; ^{1}H NMR (500 MHz, $CDCl_3$), ppm: 6.82 (d, 1H, *J* = 8.0 Hz), 7.28-7.35 (m, 3H), 7.45-7.50 (m, 3H), 7.56-7.60 (m, 1H), 7.62-7.64 (m, 1H), 7.78 (dd, 1H, *J* = 8.0 Hz, 13.0 Hz), 8.12-8.14 (m, 1H), 8.77 (s, 1H), 9.01-9.02 (m, 1H), 13.41 (d, 1H, NH, *J* = 13.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 98.50, 109.92, 116.45, 119.04, 121.90, 122.13, 124.69, 125.49, 126.75, 128.80, 129.68, 133.41, 165.95, 136.84, 138.65, 146.68, 148.48, 149.53, 154.85, 159.56, 184.58. $C_{21}H_{14}N_2O_3$, HRMS [ESI]: Found, *m/z*: $[MH]^+$ 343.1081, Calculated: 343.1077.

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Supplementary Material

Supplementary data associated with this article is available in the Supplementary Material.

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