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EFFICIENT SYNTHESIS OF COUMARIN-BASED α-ACYLOXY AMIDES AS PROMISING STARTING MATERIALS FOR DIVERSE POST-CONDENSATION REACTIONS

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Abstract:
In this paper, the Passerini three-component reaction for the straightforward synthesis of coumarin-based α-acyloxy amides, by employing 4-chloro-3-formylcoumarin, has been described. This reaction is compatible with various isocyanides and carboxylic acids. Furthermore, synthesized products could be rendered as potential starting materials for divergent post-condensation reactions and can be efficiently converted into precious follow-up structures. Simple and available starting materials, catalyst-free selective process, valuable and diverse structures, and easy purification are some highlighted advantages of the synthesized coumarin-based α-acyloxy amides.

Key words: 4-Chloro-3-formylcoumarin, isocyanide, carboxylic acid, passerini three-component reaction, post-condensation reaction.

Introduction

It is of highly interest to prepare various chemical structures based on outstanding scaffolds from the perspective of synthetic or medicinal chemistry. Coumarin scaffold is one of the most privileged ring systems which occurs in nature as the secondary metabolism products of plants[I]. Natural and synthetic coumarin-based compounds possess various pharmacological activities such as antioxidant,[II] antibacterial,[III] antiviral,[IV] anti-inflammatory,[V] and antiantidepressant[VI] activities. For example, some pharmaceutically active coumarins have shown in Figure 1. Warfarin[VII] and acenocoumarol[VIII] are prescription drugs used as natural anticoagulant agents and reduce blood clotting. Novobiocin[IX] is a clinical antibiotic. Coumarin-based azoles emerge antifungal activities[X]. Additionally, the synthesized coumarin-3-(*N*-aryl)carboxamides have cytotoxic activity against cancer cells[XI].

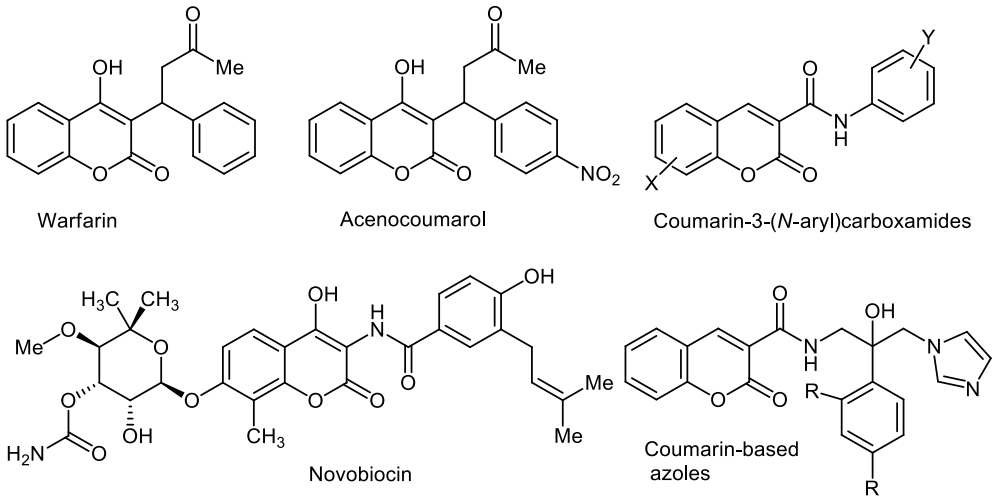
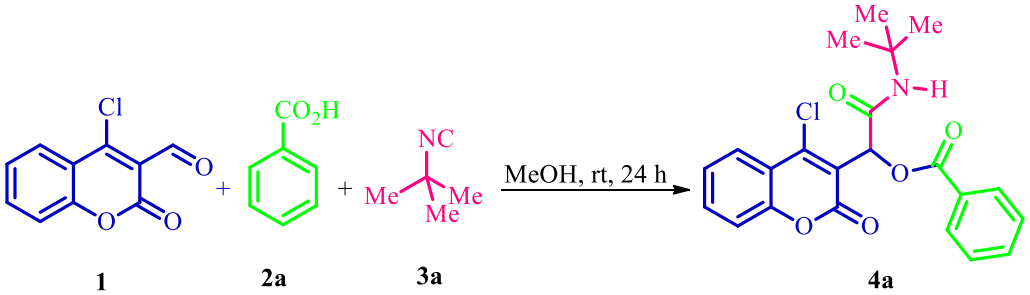


Figure 1 Structures of some coumarin-based bioactive compounds.

On the other hand, isocyanide-based multicomponent reactions[XII] are potent and suitable tools to generate functionalized chemical compounds with excellent diversity and complexity. Among various IMCRs, Ugi[XIII] four-component reaction and Passerini[XIV] three-component reaction are versatile manners for the synthesis of polyfunctional *bis*-amides and *α*-acyloxy amides, these motifs have similar structures to peptides and depsipeptides which are prominent biological scaffolds. Also synthesized *bis*-amides and *α*-acyloxy amides are excellent starting materials for the post condensation reactions[XV-XVI]. Coumarin-based bis-amides and *α*-acyloxy amides can be obtained by utilizing coumarins in these types of reactions. Due to the importance of *bis*-amides and *α*-acyloxy amides, remarkable efforts have been made for the design and synthesis of these structures. In recent years some reports employed coumarin-3-carboxylic acid in Ugi 4CR. for example, Che *et al.* have demonstrated the preparation of chromeno[3,4-*c*]pyrrole-3,4-diones by one-pot Ugi 4CR and intramolecular Michael addition[XVII]. Kumar *et al*. have established a strategy for the construction of coumarin-based Knoevenagel-Ugi products[XVIII]. Furthermore, the synthesis of 3-substituted coumarin-3-carboxamides have been reported by Balalaie and co-workers[XI].

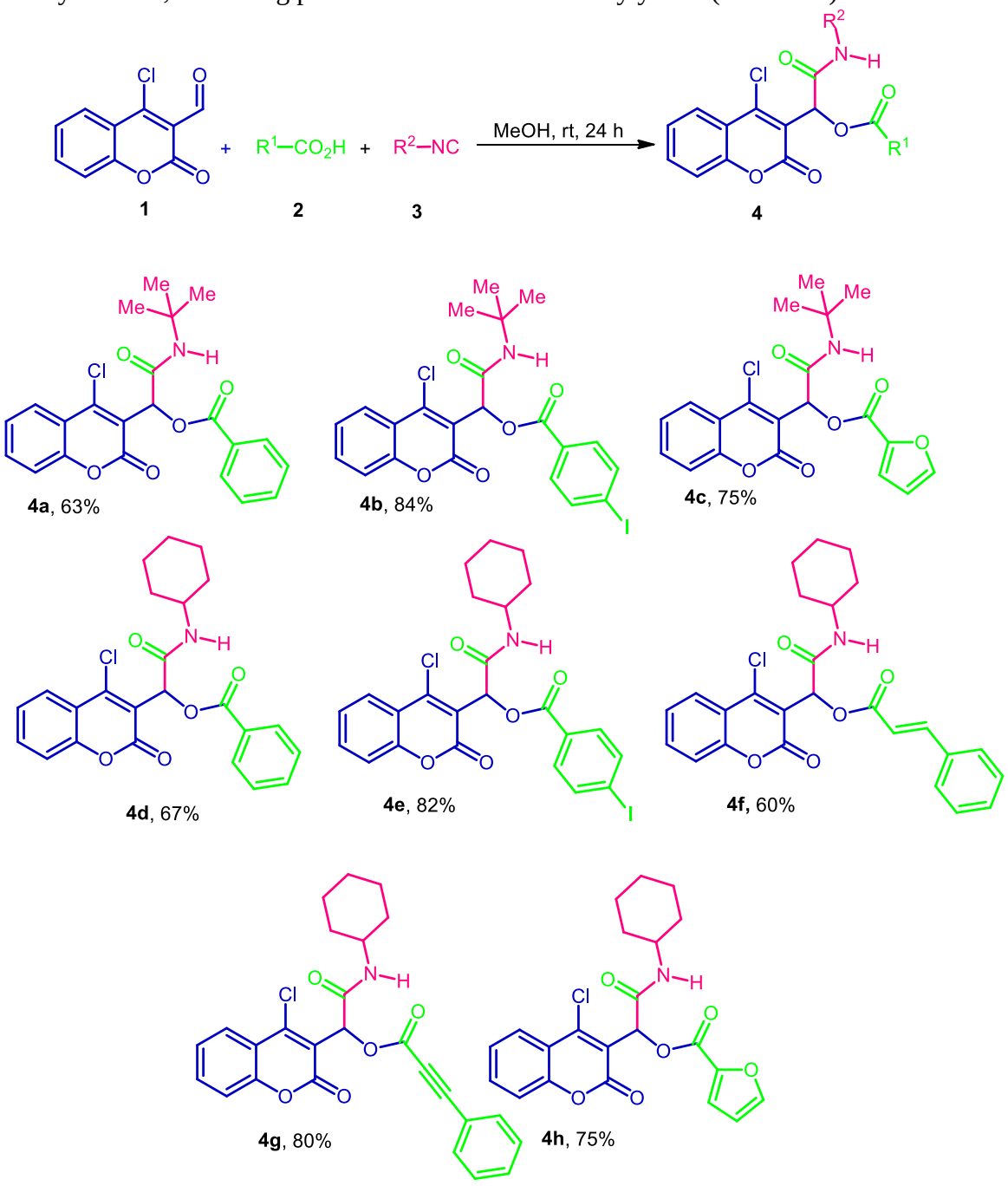
Results and Discussion

Stimulated by this proposal, we decided to utilize 4-chloro-3-formylcoumarin in Ugi four-component reaction, but immediate replacement of chlorine atom in the structure of 4-chloro-3-formylcoumarin with aliphatic amines complicated the reaction[XXI,XXII] and according to the literature, the reaction of 4-chloro-3-formylcoumarin with aromatic amines produces distinct products[XXII]. Therefore, we decided to investigate the Passerini 3CR of 4-chloro-3-formylcoumarin with *tert*-butyl isocyanide and benzoic acid. To our delight, this reaction proceeded smoothly, affording the expected coumarin-based *α*-acyloxy amide **4a** in 65% yield within 24 h (Scheme 1).



Scheme 1 Synthesis of coumarin-based α-acyloxy amide **4a**.

After accomplishing this synthesis, we decided to extend the scope of this synthetic route. Therefore, the generality of this reaction was investigated by probing different isocyanides and carboxylic acids, delivering products **4b**-**4h** in satisfactory yields (Scheme 2).



Scheme 2 Synthesis of coumarin-based α-acyloxy amides **4a**-**4h**.

The structure of compounds **4a-4h** were identified using usual spectroscopic methods including mass, IR, NMR, and elemental analysis. The mass spectrum of **4a** showed a molecular ion peak at *m/z* = 414. In the IR spectrum of **4a**, the absorption bands at 1743 and 1678 cm^{-1} were attributed to the stretching frequencies of esteric and amidic carbonyl groups. ^1H NMR spectrum of **4a** displayed a singlet at 1.42 ppm, which was related to the hydrogens of *tert*-butyl group. The broad singlet at 6.42 ppm was recognized as amidic NH group. The next singlet peak at 6.84 ppm belonged to CH^1. Nine aromatic hydrogens appeared at 7.30-8.09

ppm. The existence of nineteen peaks in ^{1}H-decoupled ^{13}C NMR spectrum of **4a** was in complete agreement with the proposed structure for it. Peaks at 28.57 and 51.86 ppm were related to the *tert*-butyl group. The Peak of CH[1] appeared at 70.31 ppm. Ten aromatic signals gave rise at 116.70-133.90 ppm. In addition, peaks at 164.59, 165.82, and 177.04 were attributed to the amidic and esteric carbonyl groups.
It is noteworthy that at least four potential active sites exist in the structure of the synthesized coumarin-based α-acyloxy amides (Figure 2).

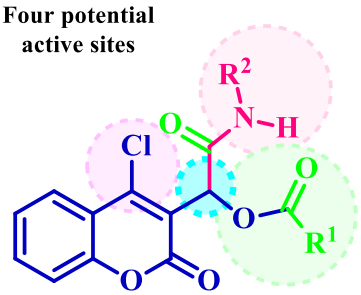


Figure 2 Potential active sites of the synthesized coumarin-based α-acyloxy amides.

Furthermore, this possibility that the chlorine atom of these products can be replaced by various nucleophiles,[XXIII-XXXII] make them convenient starting materials for further transformations. In this regard, by choosing the proper carboxylic acids, isocyanides, and post-condensation chemical reactions, various coumarin-based heterocycles can be prepared. For example, **4g** and **4f** offer great potential for intramolecular Sonogoshira coupling[XXXIII] and intramolecular Heck reaction,[XXXIV] respectively. Moreover, products **4c**, **4f**, **4g**, and **4h** could be rendered as suitable starting materials for Diels-Alder reaction. Additionally, halogen functionality on the acid component could provide a possibility for further coupling reactions in the cases of **4b** and **4e**[XXXV]. Interestingly, Balalaie and co-workers have described a post-transformational reaction to prepare triazolo-diazepinones, and product **4g** is a convenient substrate to generate these types of heterocycles[XXXVI]. Recently Shiri and co-workers have utilized 3-chloro-2-formylquinolines in the Passerini three-component reaction. They also develop efficient methods for the preparation of quinoline-based α-hydroxy, α-oxy, and α-oxo amides using Passerini adducts. Similar transformations are possible for the synthesized compounds **4a-4h**[XXXVII].

Conclusion

In conclusion, we present a selective Passerini three-component reaction to generate differently substituted coumarin-based α-acyloxy amides. We also believe that the construction of these products is a significant endeavor in synthetic organic chemistry due to the presence of this framework in a wide spectrum of natural bioactive compounds. Additionally, the synthesized coumarin-based α-acyloxy amides offer potential applications as starting materials for post-condensation transformations, and further investigations to assay their reactions are in progress in our research group.

Experimental Section

General

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded as KBr pellets on a Nicolet FTIR 100 spectrophotometer. ^{1}H NMR (500 MHz, 300 MHz) and ^{13}C NMR (125 MHz, 75 MHz) spectra were obtained using Bruker DRX-500 Avance and Bruker DRX-300 Avance spectrometers. All NMR spectra were recorded at r.t. in $CDCl_3$. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference.

Coupling constants (*J* values) are reported in hertz (Hz), and standard abbreviations were used to indicate spin multiplicities. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. All chemicals and solvents were purchased from Merck or Aldrich and were used without further purification. Starting materials were synthesized according to the procedures reported in the literature[XIX].

General procedure for the preparation of 4a-4h.

To a solution of 4-chloro-3-frormylcoumarin (1 mmol) and carboxylic acid (1 mmol) in anhydrous MeOH was added isocyanide (1 mmol). The reaction mixture was stirred at ambient temperature for 24 h. After completion of the reaction, a white solid was formed which isolated by simple filtration and washed with EtOH 96% twice to obtain the desired product.

2-(*tert*-Butylamino)-1-(4-chloro-2-oxo-2*H*-chromen-3-yl)-2-oxoethyl benzoate (4a):

White powder, mp = 161-165 °C, 0.26 g, yield: 63%. IR (KBr): 3440 (N-H), 1743 (C=O of ester), 1678 (C=O of amide), 1608 and 1526 (C=C of Ar) cm^{-1}. Anal. calcd. for $C_{22}H_{20}ClNO_5$ (413.85): C, 63.85 H, 4.87, N, 3.38%. Found: C, 63.81 H, 4.85, N, 3.38%. MS (EI, 70 eV): *m/z* (%) = 414 (M^+, 1), 340 (4), 313 (30), 208 (81), 104 (100), 77 (95). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (9H, s, $3CH_3$ of *tert*-butyl), 6.43 (1H, s, NH), 6.84 (1H, s, CH^1), 7.31 (1H, dd, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 1.2 Hz, CH^8 of coumarin), 7.35 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, CH^6 of coumarin), 7.48 (2H, t, $^3J_{HH}$ = 7.5 Hz, 2CH of Ph), 7.59 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH of Ph), 7.61 (1H, t, $^3J_{HH}$ = 8.2 Hz, CH^7 of coumarin), 7.95 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 1.5 Hz, CH^5 of coumarin), 8.09 (2H, d, $^3J_{HH}$ = 8.0 Hz, 2CH of Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.5 ($3CH_3$ of *tert*-butyl), 51.8 (C of *tert*-butyl), 70.3 (CH^1), 116.7 (CH^8 of coumarin), 118.0 (C^{4a}), 121.9 (C^3), 124.9 (CH^6 of coumarin), 126.5 (CH^5 of coumarin), 128.7 (2CH of Ph), 128.8 (C of Ph), 129.9 (2CH of Ph), 133.4 (CH of Ph), 133.9 (CH^7 of coumarin), 150.6 (C^4), 152.2 (C^{8a}), 158.0 (CO_2 of coumarin), 164.5 (CO_2 of ester), 165.8 (CO of amide).

2-(*tert*-Butylamino)-1-(4-chloro-2-oxo-2*H*-chromen-3-yl)-2-oxoethyl 4-iodobenzoate (4b):

White powder, mp = 188-190 °C, 0.45 g, yield: 84%. IR (KBr): 3415 (N-H), 1735 (C=O of ester), 1680 (C=O of amide), 1607 and 1518 (C=C of Ar) cm^{-1}. Anal. calcd. for $C_{22}H_{19}ClNO_5$ (539.75): C, 48.96 H, 3.55, N, 2.60%. Found: C, 48.94 H, 3.45, N, 2.58%. MS (EI, 70 eV): *m/z* (%) = 539 (M^+, 1), 466 (6), 439 (37), 230 (100), 208 (93). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (9H, s, $3CH_3$ of *tert*-butyl), 6.34 (1H, s, NH), 6.82 (1H, s, CH^1), 7.33 (1H, d, $^3J_{HH}$ = 8.3 Hz, CH^8 of coumarin), 7.37 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz CH^6 of coumarin), 7.61 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz CH^7 of coumarin), 7.78 (2H, d, $^3J_{HH}$ = 8.6 Hz, 2CH of Ar), 7.85 (2H, d, $^3J_{HH}$ = 8.6 Hz, 2CH of Ar), 7.96 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 1.5 Hz, CH^5 of coumarin). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.5 ($3CH_3$ of *tert*-butyl), 51.9 (C of *tert*-butyl), 70.5 (CH^1), 101.9 (C_{ipso}-I), 116.7 (CH^8 of coumarin), 118.0 (C^{4a}), 121.6 (C^3), 124.9 (CH^6 of coumarin), 126.5 (CH^5 of coumarin), 128.2 (C of Ar), 131.1 (2CH of Ar), 133.5 (CH^7 of coumarin), 138.1 (2CH of Ar), 150.7 (C^4), 152.2 (C^{8a}), 158.0 (CO_2 of coumarin), 164.2 (CO_2 of ester), 165.5 (CO of amide).

2-(*tert*-Butylamino)-1-(4-chloro-2-oxo-2*H*-chromen-3-yl)-2-oxoethyl furan-2-carboxylate (4c):

White powder, mp = 182-185 °C, 0.30 g, yield: 75%. IR (KBr): 3391 (N-H), 1744 (C=O of ester), 1712 (C=O of coumarin), 1674 (C=O of amide), 1606 and 1535 (C=C of Ar) cm^{-1}. Anal. calcd. for $C_{20}H_{18}ClNO_5$ (403.81): C, 59.49 H, 4.49, N, 3.47%. Found: C, 59.47 H, 4.45, N, 3.48%. MS (EI, 70 eV): *m/z* (%) = 403 (M^+, 1), 317 (4), 303 (31), 208 (100), 94 (73). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (9H, s, $3CH_3$ of *tert*-butyl), 6.47 (1H, s, NH), 6.54 (1H, t, $^3J_{HH}$ = 1.5 Hz, CH of Ar), 6.73 (1H, s, CH^1), 7.30 (1H, d, $^3J_{HH}$ = 8.5 Hz CH^8 of coumarin), 7.31 (1H, d, $^3J_{HH}$ = 2.0 Hz, CH of Ar), 7.34 (1H, t, $^3J_{HH}$ = 7.8 Hz, CH^6 of coumarin), 7.59 (1H, t, $^3J_{HH}$ = 8.1 Hz, CH^7 of coumarin), 7.62 (1H, d, $^3J_{HH}$ = 2.0 Hz, CH of Ar), 7.93 (1H, d, $^3J_{HH}$ = 8.0 Hz,

CH^5 of coumarin). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.5 ($3CH_3$ of *tert*-butyl), 51.8 (C of *tert*-butyl), 70.1 (CH^1), 112.2 (CH of furan), 116.6 (CH^8 of coumarin), 118.0 (C^{4a}), 119.8 (CH of furan), 121.6 (C^3), 124.9 (CH^6 of coumarin), 126.5 (CH^5 of coumarin), 133.4 (CH^7 of coumarin), 143.2 (C of Ar), 147.3 (CH of Ar), 150.8 (C^4), 152.2 (C^{8a}), 156.4 (CO_2 of coumarin), 157.8 (CO_2 of ester), 165.5 (CO of amide).

1-(4-Chloro-2-oxo-2*H*-chromen-3-yl)-2-(cyclohexylamino)-2-oxoethyl benzoate (4d):

White powder, mp = 157-159 °C, 0.25 g, yield: 67%. IR (KBr): 3360 (N-H), 1736 (C=O of ester), 1670 (C=O of amide), 1604 and 1525 (C=C of Ar) cm^{-1}. Anal. calcd. for $C_{24}H_{22}ClNO_5$ (439.89): C, 65.53 H, 5.04, N, 3.18%. Found: C, 65.51 H, 5.05, N, 3.20%. MS (EI, 70 eV): *m/z* (%) = 439 (M^+, 2), 313 (22), 208 (37), 105 (100). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17-2.06 (10 H, m, $5CH_2$ of cyclohexyl), 3.81-3.93 (1H, m, CH of cyclohexyl), 6.47 (1H, d, $^3J_{HH}$ = 8.4 Hz, NH), 6.91 (1H, s, CH^1), 7.31 (1H, dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 0.8 Hz, CH^8 of coumarin), 7.35 (1H, td, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.1 Hz, CH^6 of coumarin), 7.48 (2H, t, $^3J_{HH}$ = 7.8 Hz, 2CH of Ph), 7.59 (1H, td, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.5 Hz, CH^7 of coumarin), 7.61 (1H, tt, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.3 Hz, CH of Ph), 7.94 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 1.6 Hz, CH^5 of coumarin), 8.09 (2H, dd, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 1.1 Hz, 2CH of Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 24.7, 25.5, 32.6, 32.7 ($5CH_2$ of cyclohexyl), 48.4 (CH of cyclohexyl), 70.2 (CH of cyclohexyl), 116.7 (CH^8 of coumarin), 118.0 (C^{4a}), 121.8 (C^3), 124.9 (CH^6 of coumarin), 126.5 ($CH^5$of coumarin), 128.7 (2CH of Ph), 128.7 (C of Ph), 129.9 (2CH of Ph), 133.4 (CH of Ph), 133.9 (CH^7 of coumarin), 150.5 (C^4), 152.2 (C^{8a}), 158.0 (CO_2 of coumarin), 164.6 (CO_2 of ester), 165.6 (CO of amide).

1-(4-Chloro-2-oxo-2*H*-chromen-3-yl)-2-(cyclohexylamino)-2-oxoethyl 4-iodobenzoate (4e):

White powder, mp = 155-157 °C, 0.46 g, yield: 82%. IR (KBr): 3403 (N-H), 1730 (C=O of ester), 1678 (C=O of amide), 1604 and 1531 (C=C of Ar) cm^{-1}. Anal. calcd. for $C_{24}H_{21}ClINO_5$ (565.78): C, 50.95 H, 3.74, N, 2.48%. Found: C, 50.91 H, 3.75, N, 2.50%. MS (EI, 70 eV): *m/z* (%) = 565 (M^+, 1), 439 (42), 247 (46), 231 (100), 209 (85). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20-2.04 (10H, m, $5CH_2$ of cyclohexyl), 3.80-3.92 (1H, m, CH of cyclohexyl), 6.40 (1H, d, $^3J_{HH}$ = 8.5 Hz, NH), 6.88 (1H, s, CH^1), 7.32 (1H, d, $^3J_{HH}$ = 8.7 Hz, CH^8 of coumarin), 7.36 (1H, t, $^3J_{HH}$ = 8.5 Hz, CH^6 of coumarin), 7.61 (1H, t, $^3J_{HH}$ = 8.2 Hz, CH^7 of coumarin), 7.78 (2H, d, $^3J_{HH}$ = 8.2 Hz, 2CH of Ar), 7.84 (2H, d, $^3J_{HH}$ = 8.2 Hz), 7.95 (1H, d, $^3J_{HH}$ = 8.9 Hz, CH^5 of coumarin). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 24.7, 25.5, 30.8, 32.7 ($5CH_2$ of cyclohexyl), 48.5 (CH of cyclohexyl), 70.4 (CH^1), 101.9 (C_{ipso}-I), 116.7 (CH^8 of coumarin), 118.0 (C^{4a}), 121.5 (C^3), 124.9 (CH^6 of coumarin), 126.5 (CH^5 of coumarin), 128.2 (C of Ar), 131.2 (2CH of Ar), 133.5 (CH^7 of coumarin), 138.1 (2CH of Ar), 150.6 (C^4), 152.2 (C^{8a}), 158.0 (CO_2 of coumarin), 164.2 (CO_2 of ester), 165.4 (CO of amide).

1-(4-Chloro-2-oxo-2*H*-chromen-3-yl)-2-(cyclohexylamino)-2-oxoethyl cinnamate (4f):

White powder, mp = 100-105 °C, 0.28 g, yield: 60%. IR (KBr): 3404 (N-H), 1735 (C=O of ester), 1663 (C=O of amide), 1604 and 1532 (C=C of Ar) cm^{-1}. Anal. calcd. for $C_{26}H_{24}ClNO_5$ (465.93): C, 67.02 H, 5.19, N, 3.01%. Found: C, 67.01 H, 5.15, N, 3.03%. MS (EI, 70 eV): *m/z* (%) = 465 (M^+, 3), 339 (14), 255 (67), 208 (92), 185 (45). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18-2.07 (10H, m, $5CH_2$ of cyclohexyl), 3.84-3.90 (1H, m, CH of cyclohexyl), 6.47 (1H, d, $^3J_{HH}$ = 8.4 Hz, NH), 6.58 (1H, d, $^3J_{HH}$ = 16 Hz, CH=*CH*-CO), 6.80 (1H, s, CH^1), 7.34 (1H, d, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 0.8 Hz, CH^8 of coumarin), 7.38 (1H, td, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 0.9 Hz, CH^6 of coumarin), 7.40-7.43 (3H, m, 3CH of Ph), 7.56 (2H, d, $^3J_{HH}$ = 7.7 Hz, 2CH of Ph), 7.62 (1H, td, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 1.3 Hz, CH^7 of coumarin), 7.80 (1H, d, $^3J_{HH}$ = 16 Hz, *CH*=CH-CO), 7.97 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 1.5 Hz, CH^5 of coumarin). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 24.8, 25.5, 29.6, 32.6 ($5CH_2$ of cyclohexyl), 48.5 (CH of cyclohexyl), 70.0 (CH^1), 116.1 (CH=*CH*-CO), 116.7 (CH^8 of coumarin), 118.1 (C^{4a}), 121.9 (C^3), 124.9 (CH^6 of

coumarin), 126.5 (CH^5 of coumarin), 128.3 (2CH of Ph), 129.0 (2CH of Ph), 130.9 (CH of Ph), 133.4 (CH^7 of coumarin), 133.8 (C of Ph), 147.3 *(CH*=CH-CO), 150.6 (C^4), 152.2 (C^{8a}), 158.0 (CO_2 of coumarin), 165.0 (CO_2 of ester), 165.7 (CO of amide).

1-(4-Chloro-2-oxo-2*H*-chromen-3-yl)-2-(cyclohexylamino)-2-oxoethyl 3-phenylpropiolate (4g):

White powder, mp = 183-185 °C, 0.37 g, yield: 80%. IR (KBr): 3403 (N-H), 2230 (C≡C), 1724 (C=O of ester), 1678 (C=O of amide), 1603 and 1526 (C=C of Ar) cm^{-1}. Anal. calcd. for $C_{26}H_{22}ClNO_5$ (463.91): C, 67.31 H, 4.78, N, 3.02%. Found: C, 67.33 H, 4.75, N, 3.05%. MS (EI, 70 eV): *m/z* (%) = 464 (M^+, 1), 338 (13), 209 (70), 129 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17-2.06 (10H, m, $5CH_2$ of cyclohexyl), 3.80-3.90 (1H, m, CH of cyclohexyl), 6.51 (1H, d, $^3J_{HH}$ = 8.4 Hz, NH), 6.74 (1H, s, CH^1), 7.33 (1H, d, $^3J_{HH}$ = 8.5 Hz, CH^6 of coumarin), 7.37 (1H, t, $^3J_{HH}$ = 8.1 Hz, CH^8 of coumarin), 7.38 (2H, t, $^3J_{HH}$ = 7.5 Hz, 2CH of Ph, and), 7.47 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH of Ph), 7.59-7.63 (3H, m, 2CH of Ph and CH^7 of coumarin), 7.94 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH^5 of coumarin). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 24.9, 25.5, 32.6, 32.8 ($5CH_2$ of cyclohexyl), 48.7 (CH of cyclohexyl), 70.9 (CH^1), 79.5 (C of CO-*C*≡C), 89.2 (C of CO-C≡*C*), 116.7 (CH^8 of coumarin), 118.0 (C^{4a}), 118.9 (C of Ph), 121.2 (C^3), 125.0 (CH^6 of coumarin), 126.6 (CH^5 of coumarin), 128.6 (2CH of Ph), 131.2 (CH of Ph), 133.1 (2CH of Ph), 133.6 (CH^7 of coumarin), 151.1 (C^4), 151.9 (C^{8a}), 152.2 (CO_2 of coumarin), 157.9 (CO_2 of ester), 164.9 (CO of amide).

1-(4-Chloro-2-oxo-2*H*-chromen-3-yl)-2-(cyclohexylamino)-2-oxoethyl furan-2-carboxylate (4h):

White powder, mp = 152-155 °C, 0.32 g, yield: 75%. IR (KBr): 3354 (N-H), 1738 (C=O of ester), 1671 (C=O of amide), 1604 and 1528 (C=C of Ar) cm^{-1}. Anal. calcd. for $C_{22}H_{20}ClNO_6$ (429.85): C, 61.74 H, 4.69, N, 3.26%. Found: C, 61.70 H, 4.66, N, 3.28%. MS (EI, 70 eV): *m/z* (%) = 430 (M^+, 5), 303 (33), 209 (100), 95 (82). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.19-2.04 (10H, m, $5CH_2$ of cyclohexyl), 3.85-3.87 (1H, m, CH of cyclohexyl), 6.52 (2H, d, $^3J_{HH}$ = 8.4 Hz, NH_2), 6.54 (1H, t, $^3J_{HH}$ = 1.9 Hz, CH of Ar), 6.80 (1H, s, CH^1), 7.29 (1H, d, $^3J_{HH}$ = 8.3 Hz, CH^6 of coumarin), 7.30 (1H, d, $^3J_{HH}$ = 3.5 Hz, CH of Ar), 7.35 (1H, t, $^3J_{HH}$ = 8.4 Hz, CH^8 of coumarin), 7.59 (1H, t, $^3J_{HH}$ = 8.3 Hz, CH^7 of coumarin), 7.63 (1H, d, $^3J_{HH}$ = 1.9 Hz, CH of Ar), 7.93 (1H, d, $^3J_{HH}$ = 8.0 Hz, CH^5 of coumarin). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 24.5, 24.6, 25.4, 32.5, 32.7 ($5CH_2$ of cyclohexyl), 48.4 (CH of cyclohexyl), 70.0 (CH^1), 112.2 (CH of furan), 116.6 (CH^8 of coumarin), 118.0 (C^{4a}), 119.7 (CH of furan), 121.5 (C^3), 124.9 (CH^6 of coumarin), 126.5 (CH^7 of coumarin), 133.4 (CH^5 of coumarin), 143.2 (C of furan), 147.3 (CH of furan), 150.7 (C^4), 152.2 (C^{8a}), 156.4 (CO_2 of coumarin), 157.8 (CO_2 of ester), 165.3 (CO of amide).

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