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RESEARCH ARTICLE

Exploring aminomethylcoumarins: versatile synthesis, structural diversity, and ADME prediction

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Abstract: This research presents a highly efficient method for synthesizing diverse aminomethylcoumarin libraries through the interaction of Mannich bases of coumarins and primary amines. The developed amination process demonstrated versatility and compatibility with various substituents. Reactions were completed within short timeframes, yielding high-purity products with substantial yields, as well as facilitating the scale-up of the process. The synthesized derivatives exhibited structural diversity, incorporating carboxylic and amino groups, as well as amide, hydrazide, and hydroxamic acid moieties. *In silico* ADME predictions highlighted the potential of these aminomethylcoumarins as promising candidates for further optimization in the development of oral chemotherapeutic agents.

Keywords: coumarin; amine; aminomethylcoumarin; amination; ADME.

Introduction

Synthetic transformations of bioactive plant metabolites represent a current focal point in modern organic chemistry. These transformations involve the synthesis of new biologically active compounds and compounds of novel structural motifs, which hold promise for medicinal chemistry. Coumarin derivatives are widely distributed in the plant kingdom and, due to the presence of hydroxyl, methoxyl, and acetyl groups, serve as versatile starting materials for functionalization. On the other hand, it is well-documented that the introduction of primary amino functionality into the coumarin ring often leads to the emergence of new types of biological activity or the enhancement of biological effects. Comprehensive exploration of their physicochemical properties, including fluorescence, opens up new application avenues. The Mannich reaction is recognized as one of the methods for structurally modifying drug-like substrates, particularly benzopyran-2-ones. This reaction results in the incorporation of a pharmacophoric primary aminomethyl function into the coumarin system [1]. It is worth noting that aminomethyl derivatives of coumarins can readily be transformed into the corresponding ammonium salts, which exhibit enhanced solubility in aqueous environments. This

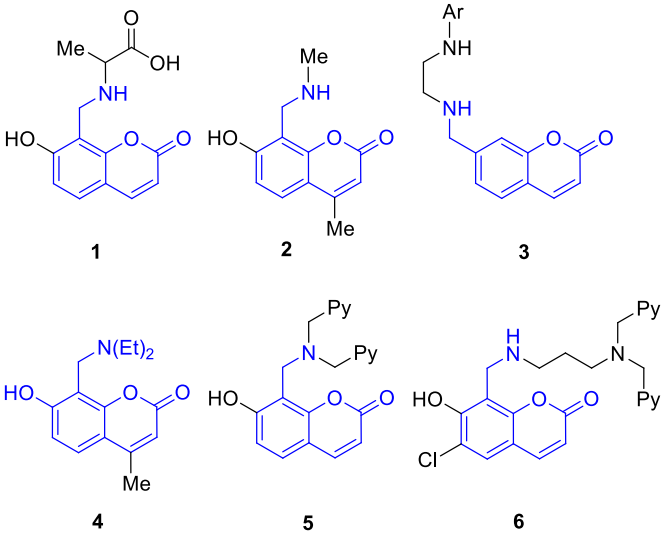

Figure 1. Examples of aminomethyl derivatives of coumarins that have found practical applications in various area.

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attribute holds significant importance in medicinal chemistry. Figure 1 illustrates only a limited selection of aminomethyl derivatives of coumarins; for instance, coumarins **1** and **2** are utilized as antimicrobial agents [2]. Another noteworthy example is coumarin **3**, which impacts the human nervous system and finds application in medical practice for the treatment of psychoses and schizophrenia [3]. Additionally, coumarin **4** is employed as a plant growth regulator [4]. Furthermore, coumarin-based Zn^{2+} probes, compounds **5** and **6**, have been utilized for ratiometric fluorescence imaging [5]. Hence, considering the diverse biological activities of aminomethyl derivatives of coumarins, the development of effective synthesis methods and targeted functionalization, as well as the investigation of the physicochemical properties of the obtained compounds, represents a practically beneficial endeavor.

Simultaneously, a meticulous assessment of Absorption, Distribution, Metabolism, and Excretion (ADME) parameters, coupled with extensive investigations into the biological activities of these derivatives, will facilitate the discernment of a diverse array of compounds suitable for applications in medicinal chemistry, agrochemistry, and allied fields.

In our previous work, we developed an efficient methodology for the synthesis of aminomethyl derivatives of coumarins, their acetoxy derivatives [6], as well as formyl/acetyl derivatives of coumarins and furocoumarins [7]. In this study, we investigated the interaction of aminomethyl derivatives of coumarins **7***{1-10}* with structurally diverse primary amines, demonstrating the synthetic attractiveness of the resulting derivatives and conducting an assessment of ADME parameters.

Results and Discussion

As an initial model reaction to assess key reaction parameters, we examined the amination reaction of dimethylaminocoumarin **7***{1a}* ($N(Alk)_2 = N(Me)_2$) and diethylaminocoumarin **7***{1b}* ($N(Alk)_2 = N(Et)_2$) with commercially available benzylamine **8***{1}*. This allowed us to primarily evaluate the impact of the leaving group in this transformation. We conducted initial tests of the reaction of starting materials (**7***{1a}* or **7***{1b}*, and **8***{1}*) in the presence of various solvents to optimize the reaction conditions (see Table 1). It is important to note that the progress of this reaction at room temperature was very slow, as indicated by LCMS data. Therefore, further investigations aimed at optimizing the methodology were carried out at the boiling point of the respective solvent. Indeed, upon the interaction of the starting reagents in a molar ratio of 1:1.5 in 10 ml of MeOH under reflux conditions for 2.5 hours, the reaction yielded the product **9***{1-1}* with a 23% yield for **7***{1a}* and 31% for **7***{1b}* (Entry 1, Table 1). The product **9***{1-1}* also formed in relatively low yields when using EtOH (28% for **7***{1a}* and 38% for **7***{1b}*, respectively) and AcCN (21% for **7***{1a}* and 26% for **7***{1b}*, respectively) (Entry 2 and 4, Table 1). Conducting the reaction in *i*-PrOH allowed us to obtain the product **9***{1-1}* with yields of 43% for **7***{1a}* and 54% for **7***{1b}*, respectively (Entry 3). Therefore, the most favorable approach, primarily based on the yield of the key reaction product, was to perform the reaction in *i*-PrOH under reflux conditions for 2.5 hours. We also observed that when the reaction was carried out under these conditions with an increased molar ratio of the starting reagents (1:2 and 1:3), the yield of **9***{1-1}* increased as well (Entry 5 and 6), and at a 1:4 ratio, the product **9***{1-1}* formed with moderate yields (38% for **7***{1a}* and 43% for **7***{1b}*, respectively), along with unidentified mixtures of complex products (Entry 7). Hence, the optimal methodology for conducting the amination reaction involved using a molar ratio of reagents of 1:3 in *i*-PrOH under reflux conditions. It is noteworthy that in all cases, the yield of the target product was higher when the corresponding **7***{1b}* was used as the starting compound. Therefore, in subsequent experiments, diethylaminocoumarin derivatives were chosen as the starting substrates.

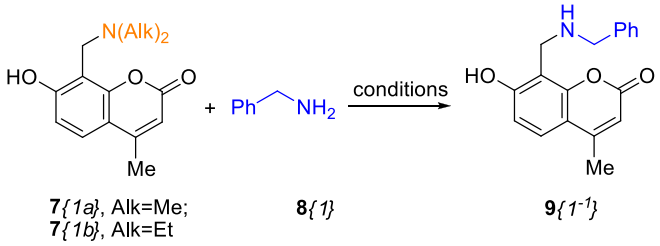
With the optimized reaction conditions established, we embarked on the exploration of substituted diethylaminocoumarins **7***{1-10}* (10 examples) and various

Table 1. Optimization of the reaction conditions on the example of compound **7***{1a}* and **7***{1b}* synthesis.

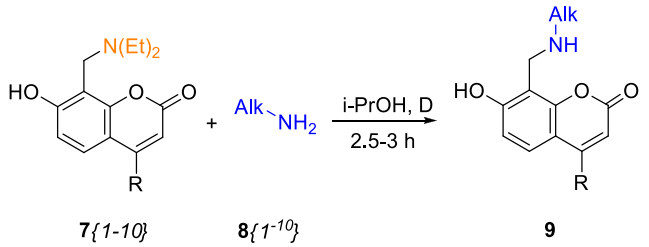
Entry	Aminomethyl coumarin (1 eq.)	Amount of benzylamine (eq.)[a]	Solvent	Reaction time (h)	Yield of product **9***{1-1}* (%)[b]
1	**7***{1a}* / **7***{1b}*	1.5	MeOH	2.5	23 / 31
2	**7***{1a}* / **7***{1b}*	1.5	EtOH	2.5	28 / 38
3	**7***{1a}* / **7***{1b}*	**1.5**	***i*-PrOH**	**2.5**	**43 / 54**
4	**7***{1a}* / **7***{1b}*	1.5	AcCN	2.5	21 / 26
5	**7***{1a}* / **7***{1b}*	2	*i*-PrOH	2.5-3	51 / 63
6	**7***{1a}* / **7***{1b}*	**3**	***i*-PrOH**	**2.5-3**	**68 / 84**
7	**7***{1a}* / **7***{1b}*	4	*i*-PrOH	2-2.5	38 / 43

[a] Reaction conditions: **7***{1a}* or **7***{1b}* (1.0 eq.) and benzylamine (1.5-4 eq.), appropriate solvent (10 ml), reflux;
[b] Yields of isolated compound **9***{1-1}*;

structurally diverse primary amines **8***{1-10}* (10 examples), which were selected randomly to obtain a variety of product **9** in this reaction (Scheme 2). As a result, 98 experiments were conducted, allowing us to achieve the target product **9** with a high success rate of 86%, and with good purity (>95% according to HPLC). In the majority of cases, the yields fell within the range of 36-83%, and for more than 50% of the representative set, the yield exceeded 70%.



Scheme 1. Investigation of the amination reaction of dimethylaminocoumarins **7***{1a,b}* and benzylamine **8***{1}* as a model reaction.



Scheme 2. The aminomethylcoumarins **9** library generation.

The representative substrates, diethylaminocoumarins **7***{1-10}* and primary amines **8***{1-10}*, are listed in Figure 2. First, we examined the compatibility of various primary amines in these amination reactions. To our delight, a wide range of alkyl groups in the case of primary amines **8***{1-10}* including methyl, ethyl, propyl, cyclopropyl, cyclopentyl, allyl, propargyl, benzyl, and ester, were found to be well-suited for this transformation. Substituted diethylaminocoumarins **7***{1-10}* with methyl, ethyl, and propyl substituents were also tolerated in this procedure, illustrating the generality of the method. However, higher yields were observed for 4-Ph substituted diethylaminocoumarins **7***{6-10}*. As an example, using coumarin **7***{6}* and amine **8***{6}*, we successfully scaled up the synthesis method and obtained aminomethylcoumarin **9***{6-6}* in a quantity of 15 grams; after crystallization from EtOH, the product yield reached 74%. Additionally, the synthetic potential of the obtained derivatives was demonstrated using aminomethylcoumarin **9***{6-9}* as example. Contrary to our expectations, the hydrolysis of **9***{6-9}* under acidic conditions failed to produce the desired product, both at room temperature and under reflux conditions. However, conducting the hydrolysis under basic conditions, using 1M NaOH in *i*-PrOH at 50 °C for 4 hours, resulted in the formation of the corresponding acid **10** with a yield of 67% (Scheme 3). We also explored the direct amidation of aminomethylcoumarin **9***{6-9}* with ester group. The amidation of **9***{6-9}* with *i*-PrNH$_2$, as well as with 1,2-binucleophilic reagents, hydrazine hydrate, and hydroxylamine, yielded amide **11**, hydrazide **12**, and hydroxamic acid **13** with yields of 56%, 78%, and 67%, respectively (Scheme 3). Considering that the treatment of benzopyran-2-ones under basic conditions results in the opening of the coumarin system, in this case, both hydrolysis and interaction with *N*-,*N*- and *N*-,*O*-binucleophiles proceeded while preserving the coumarin ring. This is confirmed by the presence of a singlet signal at 6.13-6.19 ppm in the ^{1}H NMR spectra.

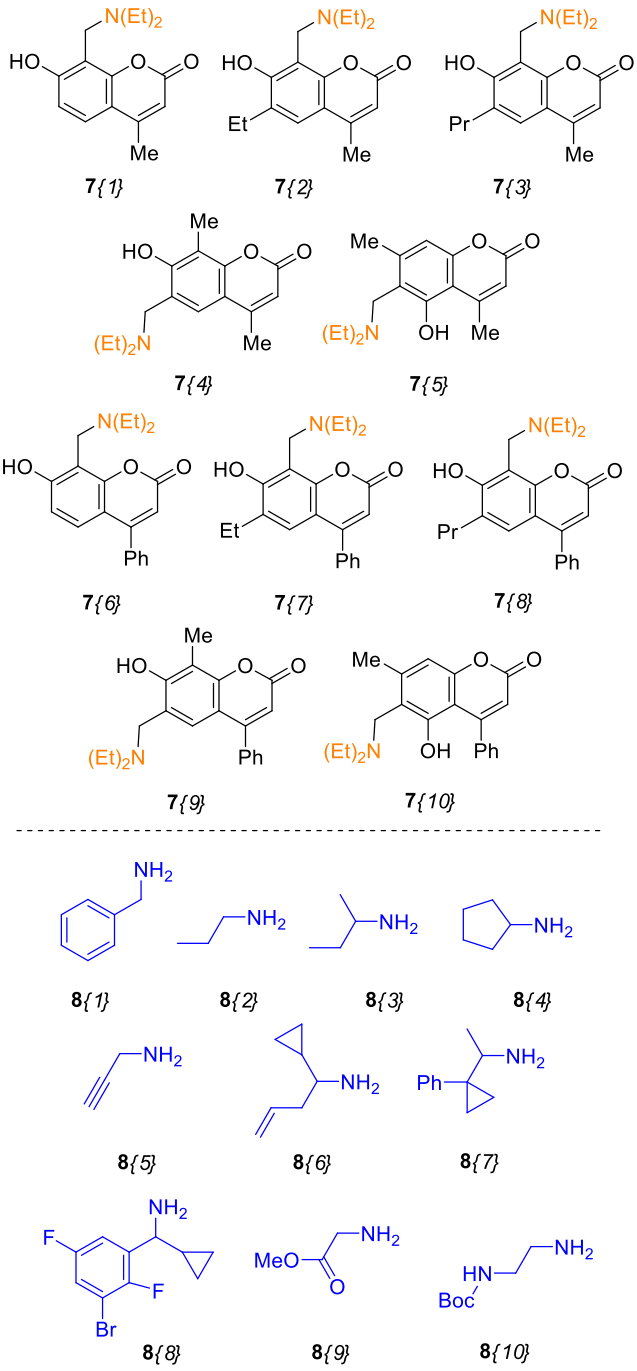
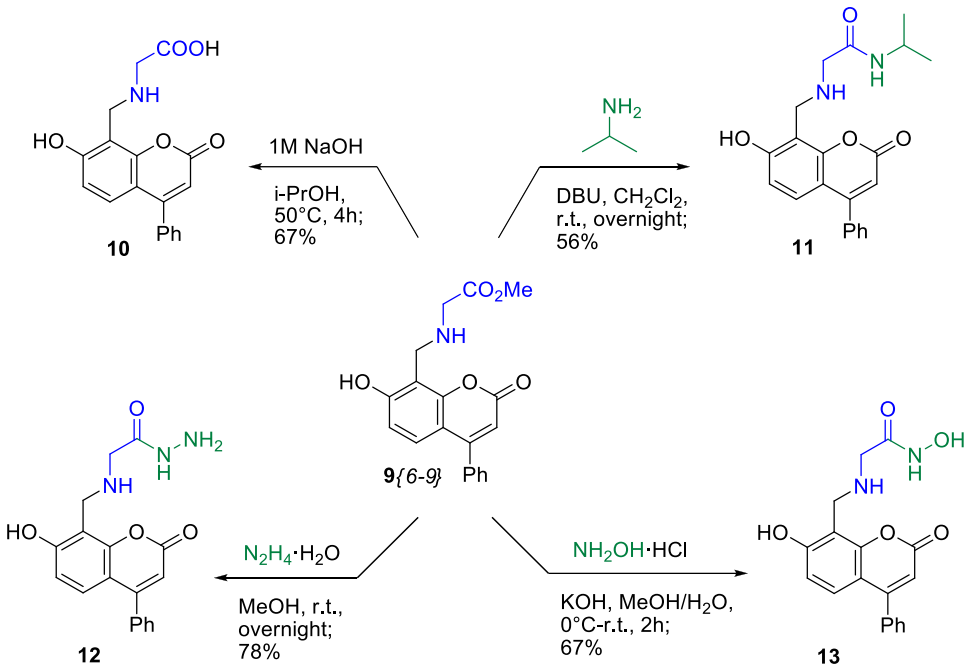


Figure 2. Scope of diethylaminocoumarins **7***{1-10}* and primary amines **8***{1-10}*.

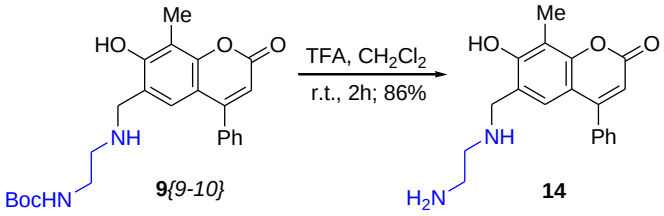
Additionally, the synthetic potential of the obtained derivatives was demonstrated using aminomethylcoumarin **9***{6-9}* as example. Contrary to our expectations, the hydrolysis of **9***{6-9}* under acidic conditions failed to



Scheme 3. Synthetic utility of aminomethylcoumarin **9***{6-9}*.

produce the desired product, both at room temperature and under reflux conditions. However, conducting the hydrolysis under basic conditions, using 1M NaOH in *i*-PrOH at 50 °C for 4 hours, resulted in the formation of the corresponding acid **10** with a yield of 67% (Scheme 3). We also explored the direct amidation of aminomethylcoumarin **9***{6-9}* with ester group. The amidation of **9***{6-9}* with *i*-PrNH$_2$, as well as with 1,2-binucleophilic reagents, hydrazine hydrate, and hydroxylamine, yielded amide **11**, hydrazide **12**, and hydroxamic acid **13** with yields of 56%, 78%, and 67%, respectively (Scheme 3). Considering that the treatment of benzopyran-2-ones under basic conditions results in the opening of the coumarin system, in this case, both hydrolysis and interaction with *N*-,*N*- and *N*-,*O*-binucleophiles proceeded while preserving the coumarin ring. This is confirmed by the presence of a singlet signal at 6.13-6.19 ppm in the ^{1}H NMR spectra.

The hydrolysis of aminomethylcoumarin **9***{9-10}* with a *Boc*-group under anhydrous acidic conditions led to the formation of aminomethylcoumarin **14** with an 86% yield, which contained an additional free amino group (Scheme 4).



Scheme 4. The hydrolysis of aminomethylcoumarin **9***{9-10}*.

In contemporary drug discovery, the exploration of absorption, distribution, metabolism, and excretion (ADME) plays a pivotal role. The early assessment of these properties is crucial in identifying compounds with favorable pharmacokinetic characteristics for further drug development. In this study, the *in silico* ADME screening systems were employed to anticipate the performance of synthesized aminomethylcoumarins **9** in an *in vivo* setting. The estimation encompassed physicochemical attributes, pharmacokinetic properties, and ADME parameters, and was conducted using the SwissADME free web tool [8]. The results of the calculations are presented in Table S1-S2 (see Supplemental Materials) and Figure 3.

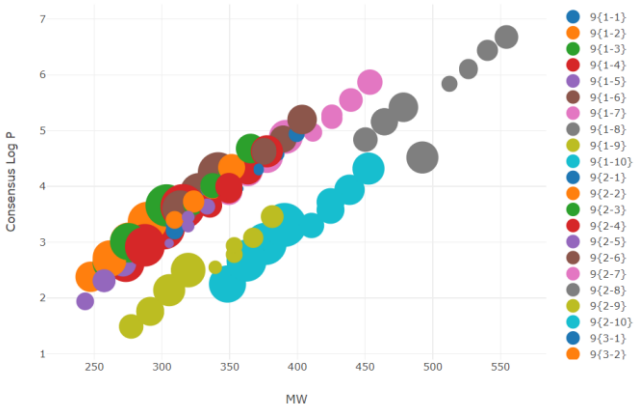


Figure 3. Dependence of log*P* from Molecular Weight (MW) and C(sp^3) for aminomethylcoumarins **9** library.

The analysis of the obtained data reveals that the synthesized aminomethylcoumarins **9** exhibit favorable physicochemical properties. Overall, there is a consistent pattern of increasing theoretical log*P* with rising molecular weight, aligning with expectations given the structural similarity of the substructural fragments of coumarin derivatives **7**. However, the impact of sp^3-hybridized carbons on lipophilicity is relatively modest. Another

observed trend, with an unaltered amine, demonstrates an increase in log*P* with a higher percentage of sp^3-hybridized carbons for coumarins **7***{1, 4, 5, 2, 3}*, attributed to alkyl substituents in the phenyl ring. Subsequently, there is a sharp decline in the share of sp^3-hybridized carbons upon transitioning from substructural fragment **7***{3}* to **7***{6}* (introduction of a phenyl substituent in position 4), followed by a linear dependence of log*P* on the number of sp^3-hybridized carbons for derivatives **7***{6, 9, 10, 7, 8}*. Compounds featuring the *N*-Boc fragment of diamine **8***{10}* demonstrate a substantial decrease in calculated lipophilicity (1-2 orders of magnitude). Conversely, the presence of a glycine fragment deviates from the general trend and is predicted to significantly enhance the hydrophilicity of the compound. Additionally, in comparison to amine derivatives **8***{7}*, compounds with the **8***{8}* substructure exhibit approximately 0.8-0.9 times higher calculated lipophilicity (attributed to the presence of halogens in the phenyl nucleus). This deviation from the anticipated linear trend, where the extrapolated difference should be around two orders of magnitude, suggests a unique influence of the specific structural features on the lipophilic nature of these compounds.

Conclusions

In conclusion, we have successfully demonstrated an efficient and practical method for synthesizing libraries of structurally diverse aminomethylcoumarins through the interaction of Mannich bases of coumarins and primary amines. This amination process was effective for both Mannich bases of coumarins and primary amines, as evidenced by the successful outcomes in 86 out of 98 experiments. The reactions were completed in short reaction times (2.5-3 hours) with high purity and good yields (ranging from 36% to 83%, and for over 50% of the representative set, the yield exceeded 70%). The versatility of this protocol was demonstrated by its compatibility with a wide range of substituents, allowing for the practical synthesis of target compounds with diverse substituents. The developed synthesis methodology also facilitated the scale-up of the process, with 15 grams of product obtained in a single step. We explored the synthetic potential of the obtained derivatives, resulting in the generation of products containing carboxylic and amino groups, as well as amide, hydrazide, and hydroxamic acid moieties within their structures. The *in silico* prediction of physicochemical and pharmacokinetic characteristics of the new synthesized aminomethylcoumarins indicated their potential as promising candidates for further refinement in the quest for oral chemotherapeutic agents.

Experimental section

The solvents were purified according to the standard procedures. All materials were purchased from commercial sources and used without further purification. Reaction flow and identity of obtained compounds was controlled with TLC on Merck F_{254} plates using $CHCl_3$: MeOH (9:1, *v*/*v*) system as eluents. The success rate was calculated as the number of successful experiments divided by the total number of experiments. NMR spectra were recorded on a Mercury-400 spectrometer (spectrometer frequency for ^{1}H: 400 MHz, ^{13}C: 100 MHz) from DMSO-d_6 solutions. The TMS signal was used as an internal standard. Mass spectra were recorded on Agilent 1100 LC/MSD instrument with chemical ionization (CI). Melting points were determined using a *Kofler*-type Leica Galen III micro hot stage microscope. Elemental analyses for C, H, and N were conducted using Perkin-Elmer C, H, N Analyzer, their results were found to be in good agreement (± 0.2%) with the calculated values.

The Experimental Section describes 25 compounds selected in random manner, which corresponds to generally accepted approaches in combinatorial chemistry (according to ACS standards).

The starting diethylaminocoumarins **7***{1-10}* were synthesized previously [6].

The molecular structures for the compound library **9** were introduced in simplified molecular-input lineentry specification (SMILES) nomenclature into the SwissADME web tool. The results of the calculations are presented in Table S1-S2 (see Supplemental Materials).

*General procedure for the preparation of amino-methylcoumarins **9***

To a solution of **7***{1-10}* (1 mmol) in 10 mL of *i*-PrOH, 3 mmol of the corresponding primary amine **8***{1-10}* was added. The reaction mixture was refluxed for 2.5-3 hours (the reaction progress was monitored by TLC). After the completion of the reaction, the mixture was allowed to cool, and the resulting precipitate was filtered. In cases where no precipitate formed, the reaction mixture was evaporated, and the residue was crystallized from EtOH. All products **9** were obtained as yellow-orange needle-shaped crystals.

*8-((Benzylamino)methyl)-7-hydroxy-4-methyl-2H-chromen-2-one (**9**{1-1})*

Yield: 543 mg, 88%. Mp 211-213 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (1H, br.s., OH), 7.81 (1H, d, *J* 7.6 Hz), 7.35 (2H, d, *J* 7.7 Hz), 7.26-7.29 (3H, m), 6.98 (1H, d, *J* 7.6 Hz), 6.17 (s, 1H), 5.58 (m, NH), 4.02 (2H, d, *J* 4.6 Hz), 3.89 (2H, d, *J* 4.6 Hz), 2.46 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4, 153.8, 155.4, 151.4, 141.3, 129.3×2, 126.5, 127.4, 128.1×2, 118.6, 112.8, 113.4, 112.1, 58.6, 44.2, 21.6. HPLC (CI) m/z $(M+H)^+$ 296.4.

*8-((sec-Butylamino)methyl)-7-hydroxy-4-methyl-2H-chromen-2-one (**9**{1-3})*

Yield: 486 mg, 73%. Mp 183-184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (1H, br.s., OH), 0.89 (3H, d, *J* 3.8 Hz), 7.84 (1H, d, *J* 7.6 Hz), 7.03 (1H, d, *J* 7.6 Hz), 6.13 (1H, s), 5.56 (m, NH), 4.06 (2H, d, *J* 4.2 Hz), 2.76 (1H, m), 2.48 (3H, s), 1.54 (2H, m), 1.10 (3H, d, *J* 3.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 155.6, 154.6, 151.3, 126.2, 118.4, 112.8, 113.6, 112.3, 56.0, 42.1, 33.1, 22.4, 18.6, 12.6. HPLC (CI) m/z $(M+H)^+$ 262.4.

*8-(((1-Cyclopropylbut-3-en-1-yl)amino)methyl)-7-hydroxy-4-methyl-2H-chromen-2-one (**9**{1-6})*

Yield: 538 mg, 83%. Mp 181-182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (1H, br.s., OH), 7.61 (1H, d, *J* 7.6 Hz), 6.94 (1H, d, *J* 7.6 Hz), 6.18 (1H, s), 5.52 (m, NH), 4.9-5.4 (m, 3H), 4.21 (2H, d, *J* 4.2 Hz), 2.51-2.53 (1H, m), 2.46 (3H, s), 2.11 (2H, m), 1.54 (2H, m), 1.04 (4H, m), 0.22-0.29 (4H, m). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.9, 153.7, 155.1, 151.2, 137.6, 125.8, 116.7, 112.8, 117.0, 113.3, 112.1, 66.4, 41.6, 39.4, 20.8, 18.2, 4.6×2. HPLC (CI) m/z $(M+H)^+$ 300.5.

*8-((Cyclopentylamino)methyl)-6-ethyl-7-hydroxy-4-methyl-2H-chromen-2-one (**9**{2-4})*

Yield: 551 mg, 89%. Mp 188-189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (3H, d, *J* 3.6 Hz), 1.63-1.74 (8H, m), 2.48 (3H, s), 2.51 (2H, d, *J* 3.6 Hz), 2.67 (1H, m), 3.88 (2H, d, *J* 4.2 Hz), 5.64 (m, NH), 6.16 (1H, s), 7.43 (1H, s), 10.52 (1H, br.s., OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4, 153.9, 152.6, 149.3, 123.8, 124.5, 116.1, 114.2, 113.1, 58.4, 42.1, 36.4×2, 23.7, 24.2×2, 21.6, 16.1. HPLC (CI) m/z $(M+H)^+$ 302.5.

*6-Ethyl-7-hydroxy-4-methyl-8-((prop-2-yn-1-ylamino)-methyl)-2H-chromen-2-one (**9**{2-5})*

Yield: 460 mg, 74%. Mp 188-189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (1H, br.s., OH), 7.48 (1H, s), 6.19 (1H, s), 5.72 (m, NH), 3.84 (2H, d, *J* 4.6 Hz), 3.38 (2H, d, *J* 4.2 Hz), 3.16 (1H, d, *J* 4.2 Hz), 2.52 (2H, d, *J* 3.6 Hz), 2.46 (3H, s), 1.16 (3H, d, *J* 3.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.2, 153.4, 152.3, 149.1, 124.6, 124.3, 116.8, 113.7, 113.1, 82.9, 74.6, 43.7, 41.3, 23.4, 21.2, 16.3. HPLC (CI) m/z $(M+H)^+$ 272.4.

*6-Ethyl-7-hydroxy-4-methyl-8-(((1-(1-phenylcyclo-propyl)ethyl)amino)-methyl)-2H-chromen-2-one (**9**{2-7})*

Yield: 546 mg, 84%. Mp 197-198 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (1H, br.s., OH), 7.42 (2H, m), 7.38 (1H, s), 7.36 (2H, m), 7.22 (1H, m), 6.16 (1H, s), 5.61 (m, NH), 4.21 (2H, d, *J* 4.2 Hz), 3.40 (1H, m), 3.10 (3H, d, *J* 3.8 Hz), 2.54 (2H, d, *J* 3.6 Hz), 2.48 (3H, s), 1.14-1.18 (2H, m), 0.84-0.96 (4H, m). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4, 153.7, 152.8, 151.6, 149.5, 129.8×2, 127.3, 7.4×2, 126.1×2, 124.9, 124.6, 116.4, 113.8, 113.1, 71.4, 15.6, 42.3, 32.3, 23.2, 21.4, 17.4. HPLC (CI) m/z $(M+H)^+$ 378.6.

*8-((((3-Bromo-2,5-difluorophenyl)(cyclopropyl)methyl)-amino)methyl)-7-hydroxy-4-methyl-6-propyl-2H-chromen-2-one (**9**{3-8})*

Yield: 564 mg, 91%. Mp 215-216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.42-0.48 (4H, m), 1.08 (3H, t, *J* 3.6 Hz), 1.14 (1H, m), 1.74 (2H, m), 2.51 (3H, s), 2.68 (2H, d, *J* 3.8 Hz), 3.86 (1H, m), 4.12 (2H, d, *J* 4.6 Hz), 5.56 (m, NH), 6.18 (1H, s), 6.93 (1H, s), 7.38 (1H, s), 7.46 (2H, s), 10.61 (1H, br.s., OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 4.3×2, 16.1, 19.4, 22.1, 26.7, 36.1, 41.8, 62.4, 110.1, 111.9, 113.2, 114.6, 116.7, 117.3, 120.9, 122.6, 125.3, 153.4, 154.0, 160.8, 161.2, 162.3. HPLC (CI) m/z $(M+H)^+$ 493.5.

*6-((Cyclopentylamino)methyl)-7-hydroxy-4,8-dimethyl-2H-chromen-2-one (**9**{4-4})*

Yield: 544mg, 84%. Mp 179-180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (1H, br.s., OH), 7.54 (1H, s), 6.17 (1H, s), 5.68 (m, NH), 3.86 (2H, d, *J* 4.2 Hz), 2.66 (1H, m), 2.46 (3H, s), 2.18 (3H, s), 1.62-1.74 (8H, m). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.9, 154.3, 153.4, 151.9, 125.1, 121.4, 118.6, 114.3, 113.1, 59.3, 46.9, 24.6×2, 36.1×2, 28.4, 21.6. HPLC (CI) m/z $(M+H)^+$ 288.2.

*tert-Butyl (2-(((7-hydroxy-4,8-dimethyl-2-oxo-2H-chromen-6-yl)methyl)-amino)ethyl)carbamate (**9**{4-10})*

Yield: 436 mg, 72%. Mp 176-177 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (1H, br.s., OH), 7.49 (1H, s), 6.89 (1H, d, *J* 4.4 Hz), 6.14 (1H, s), 5.56 (m, NH), 3.84 (2H, d, *J* 4.2 Hz), 3.32 (2H, m), 2.69 (2H, m), 2.49 (3H, s), 2.19 (3H, s), 1.46 (9H, s). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.9, 156.3, 153.4, 152.8, 151.6, 125.3, 121.8, 118.1, 113.8, 113.2, 80.4, 50.1, 49.3, 41.6, 31.2, 29.5, 29.3×2, 20.6. HPLC (CI) m/z $(M+H)^+$ 363.2.

*6-((Benzylamino)methyl)-5-hydroxy-4,7-dimethyl-2H-chromen-2-one (**9**{5-1})*

Yield: 465 mg, 91%. Mp 192-193 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (1H, br.s., OH), 7.46 (2H, m), 7.32 (3H, m), 6.77 (1H, s), 6.13 (1H, s), 5.68 (m, NH), 3.83 (2H, d, *J* 4.3 Hz), 3.78 (2H, d, *J* 4.2 Hz), 2.48 (3H, s), 2.34 (3H, s). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.8, 158.3, 156.4, 151.1, 143.2, 138.5, 129.4×2, 128.3×2, 127.8, 121.7, 113.3, 112.1, 111.2, 59.1, 47.3, 25.1, 20.9. HPLC (CI) m/z $(M+H)^+$ 310.4.

*7-Hydroxy-4-phenyl-8-((propylamino)methyl)-2H-chromen-2-one (**9**{6-2})*

Yield: 476 mg, 73%. Mp 186-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (1H, br.s., OH), 7.69 (1H, d, *J* 7.2 Hz), 7.38-7.41 (5H, m), 6.93 (1H, d, *J* 7.2 Hz), 6.19 (1H, s), 4.58 (1H, m, NH), 3.83 (2H, d, *J* 3.4 Hz), 2.59 (2H, m), 1.52 (2H, m), 1.12 (3H, d, *J* 3.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.3, 166.1, 154.9, 138.4, 129.3×2, 128.9×2, 128.1, 126.7, 118.1, 113.9, 113.1, 112.6, 52.8, 51.7, 44.6, 25.1, 14.6. HPLC (CI) m/z $(M+H)^+$ 310.2.

*Methyl ((7-hydroxy-2-oxo-4-phenyl-2H-chromen-8-yl)-methyl)glycinate (**9**{6-9})*

Yield: 480 mg, 76%. Mp 183-184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (1H, br.s., OH), 7.71 (1H, d, *J* 7.2 Hz), 7.36-7.38 (5H, m), 6.94 (1H, d, *J* 7.2 Hz), 6.17 (1H, s), 4.66 (1H, m, NH), 4.01 (3H, s), 3.86 (2H, d, *J* 3.4 Hz), 3.48 (2H, d, *J* 3.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.3, 160.9, 156.2, 155.4, 151.6, 136.8, 129.9×2, 129.1×2, 128.3, 127.7, 118.3, 113.9, 113.1, 112.8, 52.8, 49.6, 43.9. HPLC (CI) m/z $(M+H)^+$ 340.1.

*8-((Benzylamino)methyl)-6-ethyl-7-hydroxy-4-phenyl-2H-chromen-2-one (**9**{7-1})*

Yield: 546 mg, 85%. Mp 186-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (1H, br.s., OH), 7.53 (1H, s), 7.38-7.41 (5H, m), 7.31-7.34 (5H, m), 6.19 (1H, s), 5.38

(1H, m, NH), 3.84 (2H, d, *J* 3.4 Hz), 3.78 (2H, d, *J* 3.4 Hz), 2.51 (2H, d, *J* 3.2 Hz), 1.19 (3H, d, *J* 3.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.8, 156.4, 152.3, 148.7, 136.7, 141.4, 131.9, 131.2, 130.5×2, 129.1×2, 128.2, 127.9×2, 127.1, 126.3, 124.6, 113.4, 112.9, 116.6, 58.6, 24.6, 16.8. HPLC (CI) m/z $(M+H)^+$ 386.2.

*7-Hydroxy-4-phenyl-8-((prop-2-yn-1-ylamino)methyl)-6-propyl-2H-chromen-2-one (**9**{8-5})*

Yield: 482 mg, 71%. Mp 186-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (1H, br.s., OH), 7.54 (1H, s), 7.32-7.35 (5H, m), 6.19 (s, 1H), 4.89 (1H, m, NH), 3.86 (2H, d, *J* 3.4 Hz), 3.32 (2H, s), 3.11 (1H, s), 2.68 (2H, d, *J* 3.2 Hz), 1.72 (2H, m), 1.12 (3H, d, *J* 3.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.8, 156.8, 154.1, 149.3, 136.7, 129.1×2, 128.4×2, 127.2, 125.4, 118.1, 113.4, 112.9, 84.3, 74.6, 42.7, 40.9, 34.6, 26.3, 15.1. HPLC (CI) m/z $(M+H)^+$ 348.4.

*6-((Benzylamino)methyl)-7-hydroxy-8-methyl-4-phenyl-2H-chromen-2-one (**9**{9-1})*

Yield: 564 mg, 92%. Mp 197-198 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (1H, br.s., OH), 7.58 (1H, s), 7.38-7.41 (5H, m), 7.31-7.34 (5H, m), 6.17 (s, 1H), 5.14 (1H, m, NH), 3.79 (4H, m), 2.24 (3H, s). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.3, 156.8, 153.7, 151.7, 141.3, 136.4, 130.2×2, 129.4×2, 128.8×2, 128.1, 127.9×2, 127.3, 125.3, 121.4, 118.6, 113.4, 112.8, 58.3, 56.1, 29.4. HPLC (CI) m/z $(M+H)^+$ 372.5.

*6-(((1-Cyclopropylbut-3-en-1-yl)amino)methyl)-7-hydroxy-8-methyl-4-phenyl-2H-chromen-2-one (**9**{9-6})*

Yield: 514 mg, 72%. Mp 184-185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (1H, br.s., OH), 7.61 (1H, s), 7.32-7.36 (5H, m), 6.19 (s, 1H), 5.26 (1H, m, NH), 4.93-5.13 (3H, m), 3.89 (2H, d, *J* 3.4 Hz), 2.48 (1H, m), 2.21 (3H, s), 1.96-1.98 (2H, m), 1.12 (1H, m), 0.86-0.89 (4H, m). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.9, 156.8, 153.4, 151.7, 137.3, 136.4, 129.3×2, 128.6×2, 128.1, 125.3, 121.3, 118.4, 116.7, 113.8, 113.1, 66.1, 48.3, 39.6, 29.3, 18.7, 6.4×2. HPLC (CI) m/z $(M+H)^+$ 376.6.

*7-Hydroxy-8-methyl-4-phenyl-6-(((1-(1-phenylcyclopropyl)ethyl)amino)-methyl)-2H-chromen-2-one (**9**{9-7})*

Yield: 536 mg, 81%. Mp 186-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (1H, br.s., OH), 7.54 (1H, s), 7.41-7.45 (5H, m), 7.32-7.35 (5H, m), 6.19 (1H, s), 5.74 (1H, m, NH), 4.18 (2H, d, *J* 4.2 Hz), 3.21 (1H, m), 2.24 (3H, s), 1.15 (3H, d, *J* 3.6 Hz), 0.86-0.98 (4H, m). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.9, 156.8, 153.4, 151.6, 150.3, 136.7, 129.8×2, 129.1×2, 128.3×2, 127.6, 125.9, 125.4×2, 124.8, 121.8, 118.6, 113.3, 112.8, 71.2, 44.3, 32.7, 26.4, 17.6, 7.6×2. HPLC (CI) m/z $(M+H)^+$ 426.4.

*tert-Butyl (2-(((7-hydroxy-8-methyl-2-oxo-4-phenyl-2H-chromen-6-yl)-methyl)amino)ethyl)carbamate (**9**{9-10})*

Yield: 490 mg, 73%. Mp 183-184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (1H, br.s., OH), 7.51 (1H, s), 7.34-7.37 (5H, m), 6.94 (1H, d, *J* 4.4 Hz), 6.16 (1H, s), 1.48 (9H, s), 5.58 (1H, m, NH), 3.84 (2H, d, *J* 4.2 Hz), 3.34 (2H, m), 2.68 (2H, m), 2.21 (3H, s). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.9, 156.4, 153.5, 152.8, 151.9, 136.7, 128.8×2, 128.4×2, 127.7, 125.4, 121.6, 118.3, 113.9, 113.2, 80.6, 50.4, 49.6, 41.8, 31.4, 29.4, 29.1. HPLC (CI) m/z $(M+H)^+$ 425.6.

*5-Hydroxy-7-methyl-4-phenyl-6-((propylamino)methyl)-2H-chromen-2-one (**9**{10-2})*

Yield: 481 mg, 71%. Mp 186-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (1H, br.s., OH), 7.39-7.42 (5H, m), 6.72 (1H, s), 6.21 (1H, s), 4.58 (1H, m, NH), 3.84 (2H, d, *J* 3.4 Hz), 2.61 (2H, m), 2.36 (3H, s), 1.54 (2H, m), 1.14 (3H, d, *J* 3.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 170.3, 163.0, 156.5, 155.7, 145.0, 134.7, 131.3, 126.2, 125.9, 125.9, 125.4, 123.9, 123.6, 121.7, 119.2, 109.6, 69.7, 67.5, 58.4, 39.2, 28.0, 27.3. HPLC (CI) m/z $(M+H)^+$ 324.4.

*6-(((Cyclopentylamino)methyl)-5-hydroxy-7-methyl-4-phenyl-2H-chromen-2-one (**9**{10-4})*

Yield: 474 mg, 79%. Mp 178-179 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (1H, br.s., OH), 7.54 (1H, s), 7.38-7.41 (5H, m), 6.17 (1H, s), 5.68 (1H, m, NH), 3.86 (2H, d, *J* 4.2 Hz), 2.66 (1H, m), 2.46 (3H, s), 2.18 (3H, s), 1.62-1.74 (8H, m). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 170.3, 163.0, 156.5, 155.7, 145.0, 134.7, 131.3, 126.2, 125.9, 125.9, 125.4, 123.9, 123.6, 121.7, 119.2, 109.6, 69.7, 67.5, 58.4, 39.2, 28.0, 27.3. HPLC (CI) m/z $(M+H)^+$ 350.5.

*((7-Hydroxy-2-oxo-4-phenyl-2H-chromen-8-yl)methyl)-glycine (**10**)*

Compound **9**{6-9} (1 equiv.) was dissolved in *i*-PrOH, and a 1M solution of NaOH (1.2 equiv.) was added. The mixture was then stirred at 50 °C for 4 hours. After cooling, reaction mixture acidified to pH 3-4 with concentrated HCl. The resulting precipitate was filtered and crystallized from *i*-PrOH. Yield: 276 mg, 71%. Mp 173-174 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (1H, br.s., OH), 7.71 (1H, d, *J* 7.2 Hz), 7.36-7.38 (5H, m), 6.94 (1H, d, *J* 7.2 Hz), 6.17 (1H, s), 4.66 (1H, m, NH), 4.01 (3H, s), 3.86 (2H, d, *J* 3.4 Hz), 3.48 (2H, d, *J* 3.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 170.3, 163.0, 156.5, 155.7, 145.0, 134.7, 131.3, 126.2, 125.9, 125.9, 125.4, 123.9, 123.6, 121.7, 119.2, 109.6, 69.7, 67.5, 58.4, 39.2, 28.0, 27.3. HPLC (CI) m/z $(M+H)^+$ 326.3.

*2-(((7-Hydroxy-2-oxo-4-phenyl-2H-chromen-8-yl)-methyl)amino)-N-iso-propylacetamide (**11**)*

A mixture of ester **9**{6-9} (1.0 mmol), isopropylamine (5.0 mmol), and DBU (0.2 mmol) was stirred at room temperature for 48 hours. Ethyl acetate (15 mL) was added, and the organic phase was washed with saturated aqueous NH_4Cl solution (4 × 15 mL), dried over Na_2SO_4, evaporated, and the residue was crystallized from acetone. Yield: 283 mg, 75%. Mp 181-182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (1H, br.s., OH), 7.71 (1H, d, *J* 7.2 Hz), 7.36-7.38 (5H, m), 6.94 (1H, d, *J* 7.2 Hz), 4.66 (1H, m, NH), 4.01 (3H, s), 6.17 (1H, s), 3.86 (2H, d, *J* 3.4 Hz), 3.48 (2H, d, *J* 3.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1,

170.3, 163.0, 156.5, 155.7, 145.0, 134.7, 131.3, 126.2, 125.9, 125.9, 125.4, 123.9, 123.6, 121.7, 119.2, 109.6, 69.7, 67.5, 58.4, 39.2, 28.0, 27.3. HPLC (CI) m/z $(M+H)^+$ 367.5.

*2-(((7-Hydroxy-2-oxo-4-phenyl-2H-chromen-8-yl)-methyl)amino)aceto-hydrazide (**12**)*

Ester **9***{6-9}* (1 mmol) was dissolved in methanol (20 mL), and hydrazine hydrate (1.5 mmol) was added. The mixture was allowed to stand overnight at 25 °C. The resulting product was separated, collected by suction filtration, washed with methanol, and recrystallized from acetone. Yield: 296 mg, 83%. Mp 175-176 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (1H, br.s., OH), 7.71 (1H, d, *J* 7.2 Hz), 7.36-7.38 (5H, m), 6.94 (1H, d, *J* 7.2 Hz), 6.17 (1H, s), 4.66 (1H, m, NH), 4.01 (3H, s), 3.86 (2H, d, *J* 3.4 Hz), 3.48 (2H, d, *J* 3.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 170.3, 163.0, 156.5, 155.7, 145.0, 134.7, 131.3, 126.2, 125.9, 125.9, 125.4, 123.9, 123.6, 121.7, 119.2, 109.6, 69.7, 67.5, 58.4, 39.2, 28.0, 27.3. HPLC (CI) m/z $(M+H)^+$ 340.2.

*N-hydroxy-2-(((7-hydroxy-2-oxo-4-phenyl-2H-chromen-8-yl)methyl)-amino)acetamide (**13**)*

To a mixture of ester **9***{6-9}* (1 mmol) and $NH_2OH{\cdot}HCl$ (0.204 g, 3 mmol) in H_2O (3 mL) at 0-5 °C, a solution of KOH (0.392 g, 7 mmol) in H_2O (1 mL) was added dropwise with stirring. The reaction mixture was stirred at room temperature for 1-4 hours, then acidified to pH 5-6 with concentrated HCl. The resulting precipitate was collected by filtration, washed with water, and dried to yield product **13**. Yield: 265 mg, 79%. Mp 178-179 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (br. s, 2H), 10.03 (br. s, 1H), 7.58 (d, *J* 6.8 Hz, 1H), 7.36-7.39 (m, 2H), 7.32-7.34 (m, 3H), 6.93 (d, *J* 6.8 Hz, 1H), 6.19 (s, 1H), 4.75-4.76 (m, 1H), 3.81-3.83 (d, *J* 5.6 Hz, 2H), 3.17-3.19 (d, *J* 5.6 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.2, 160.6, 156.7, 155.8, 155.3, 151.4, 136.3, 129.5×2, 128.7×2, 128.1, 127.3, 117.3, 113.6, 112.9, 49.7, 42.1. HPLC (CI) m/z $(M+H)^+$ 341.4.

*6-(((2-Aminoethyl)amino)methyl)-7-hydroxy-8-methyl-4-phenyl-2H-chromen-2-one (**14**)*

To a solution of ester **9***{6-9}* (1 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL). The reaction mixture was stirred for 2h at room temperature, after which time the solvents were removed *in vacuo*. The resulting material was triturated with MTBE to provide the product as an white solid. Yield: 216 mg, 87%. Mp 186-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (br. s, 1H), 7.56 (s, 1H), 7.40-7.42 (m, 2H), 7.36-7.37 (m, 3H), 6.24 (s, 1H), 5.63-5.66 (m, 2H), 4.54-4.56 (m, 1H), 3.86-3.88 (d, *J* 5.6 Hz, 2H), 2.66-2.68 (m, 2H), 2.53-2.55 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.9, 155.7, 153.2, 150.6, 136.1, 128.6×2, 128.1×2, 127.1, 125.6, 121.7, 118.3, 113.1, 112.3, 52.7, 49.3, 42.4, 29.6. HPLC (CI) m/z $(M+H)^+$ 325.6

Notes

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Дослідження амінометилкумаринів: універсальний синтез, структурна різноманітність, прогнозування ADME параметрів

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Резюме: В роботі розроблено ефективний метод синтезу бібліотеки структурно-різноманітних амінометилкумаринів при взаємодії основ Манніха на основі кумаринів з первинними амінами. Розроблена процедура амінування продемонструвала універсальність підходу та його сумісність з різними замісниками. Реакції завершувались утворенням продуктів з високими виходами та проходили за короткий час, що дозволило масштабувати розроблену методику. На основі отриманих похідних продемонстрована можливість проведення структурної модифікації, що дозволило отримати похідні з різноманітними функціональними групами, зокрема карбоксильною, аміно-, амідною, гідразидною та гідроксамовою групами. Проведення *in silico* досліджень ADME параметрів підтвердило потенціал отриманих амінометилкумаринів як перспективних кандидатів для подальшої оптимізації при розробці лікарських засобів.

Ключові слова: кумарин; амін; амінометилкумарин; амінування; ADME.