# Anticancer effects of Coumarin Sulfonamides

Subjects: Biochemical Research Methods

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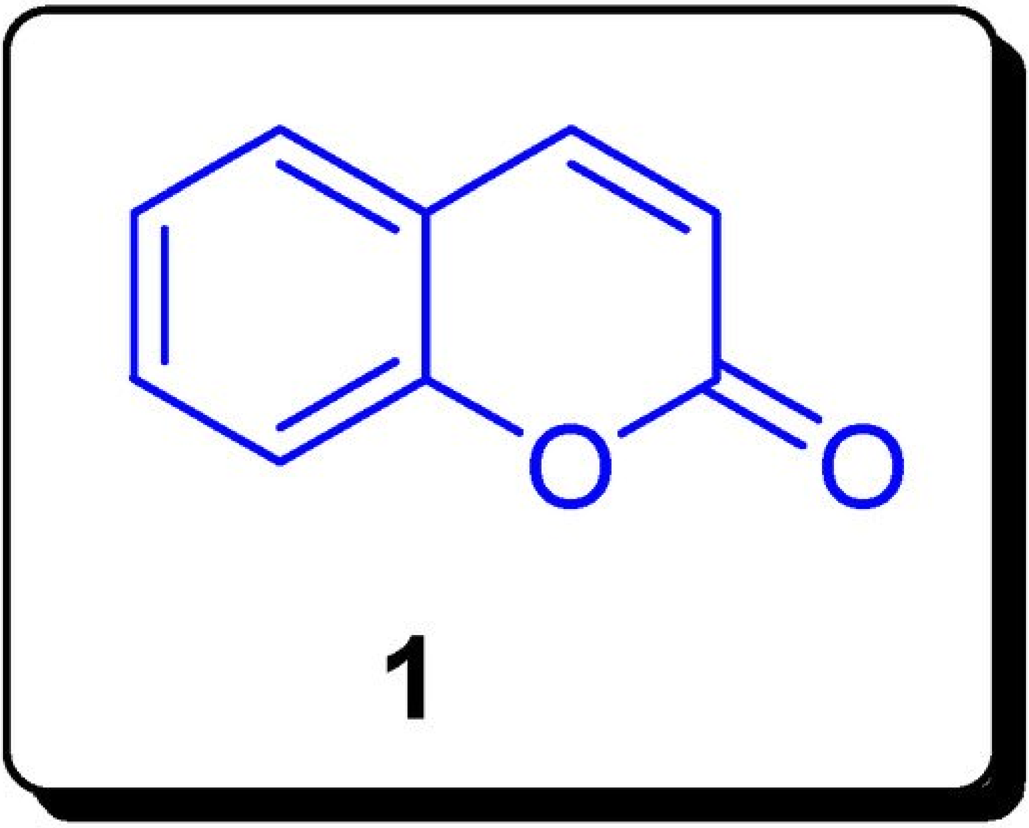
Coumarin is an important six-membered aromatic heterocyclic pharmacophore, widely distributed in natural products and synthetic molecules. The versatile and unique features of coumarin nucleus, in combination with privileged sulfonamide moiety, have enhanced the broad spectrum of biological activities. The research and development of coumarin, sulfonamide-based pharmacology, and medicinal chemistry have become active topics, and attracted the attention of medicinal chemists, pharmacists, and synthetic chemists. Coumarin sulfonamide compounds and analogs as clinical drugs have been used to cure various diseases with high therapeutic potency, which have shown their enormous development value. The diversified and wide array of biological activities such as anticancer, antibacterial, anti-fungal, antioxidant and anti-viral, etc. were displayed by diversified coumarin sulfonamides.

coumarin sulfonamide anticancer agents

## 1. Introduction

Ever since the first time that coumarin **1** was isolated from natural source tonka bean (*Dipteryx odorata*), commonly known as cumaru, in 1820 by Vogel [1][2]. Coumarin is an old, important, and diversified oxygen containing six membered heterocyclic classes of 1,2 benzopyrones, which naturally occur in plants and many other species, such as fungi (*Armillariella tabescens, Fomitopsis officinalis*) and bacteria (*Streptomyces niveus, Escherichia coli*) [3][4]. More than 1300 coumarins are present in plants, which play vital role in physiology and overall functioning of plants [1]. The general structure of coumarin **1** is given below (**Figure 1**). In the mid-nineteenth century, the research and development of coumarin-based compounds and hybrid structures began via the famous Perkin condensation reaction between acetic anhydride and salicylaldehyde. The different synthetic classical techniques, such as Knoevenagel, Perkin and Pechmann reactions, are applied to achieve simple coumarins [5][6][7]. The rapid developments in the synthetic chemistry of coumarins have been made, due to their wide therapeutic potential as medicinal drugs. The coumarin scaffolds displayed an array of biological activities, such as coumarin chalcone derivatives, coumarin aryl sulfonamides, and coumarin hydrazine–hydrazone hybrids, etc., which were screened to investigate their anticancer activities [8][9][10][11][12]. Coumarin scaffolds are extensively studied for their antioxidant [13][14][15][16], antibacterial [17][18][19][20], anti-fungal [21][22][23], anti-inflammatory [24][25], anti-diabetic [26], vasorelaxant [27], analgesic [28], anti-HIV [29], antimicrobial [30], anti-coagulation [31], and anti-pyretic [32] activities, etc.



**1**

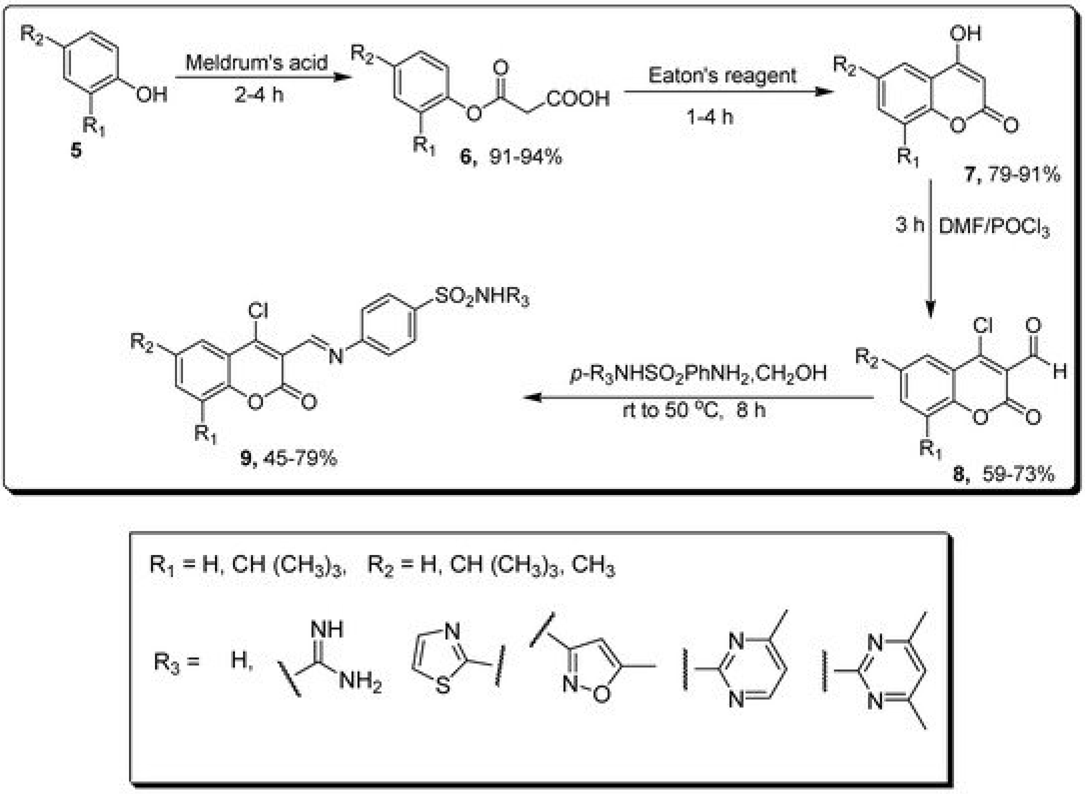
**Figure 1.** Structure of coumarin **1**.

## 2. Coumarin Sulfonamides as Anti-Cancer Agents and Carbonic Anhydrase Inhibitors

Cancer is one of the most lethal, notable complex and serious threats to human health, and has attracted attention worldwide. All over the world, about 7.6 million people die due to cancer every year, and around 13 million people will likely die before 2030. In 2020, globally, almost 10 million people died due to cancer [33][34]. Extensive research and development work have been conducted in the field of oncology to develop anticancer therapeutic agents, and large breakthroughs and great strides have been made over past 60 years [35]. Coumarin sulfonamide derivatives and analogs have therapeutic potential against different types of cancer cell lines and CAs (carbonic anhydrases). CAs are also known as carbonate dehydratases [36]. CAs are metalloenzymes which are present in all life forms, and are essential for equilibria between different simple but significant reaction species, such as carbon dioxide, proton, and bicarbonate [37][38][39][40][41]. In 1933, 88 years ago, these enzymes were discovered, and are still an extraordinary example of convergent evolution, and extensively studied and investigated for biomedical inhibitory activities. CAs were found in bacteria, archaea and eukarya; genetically, at least eight (α-, β-, γ-, δ-, ζ-, η-, θ- and ι-CAs) distinct families [37][38][39][40][41][42]. The α-CAs family is present in vertebrates, and the bacteria, algae, and cytoplasm of green plants, while β-CAs are found in bacteria, the chloroplasts of monodicotyledons and dicotyledons, and algae. The γ-CAs are mainly present in archaea and some bacteria, the δ-, ζ- and θ-CAs are present in some marine diatoms, and the η-CAs are present in protozoa. The ι-CAs were discovered in marine phytoplankton, as well as in some bacteria [42][43][44][45][46][47][48][49][50][51][52]. There are five membrane-bound isozymes: CA-IV, CA-IX, CA-XII, CA-XIV, and CA-XV), five cytosolic forms CA-I, CA-II, CA-III, CA-VII, and CA-XIII, a secreted CA isozyme CA-VI, and two mitochondrial forms, CA-VA and CA-VB [53][54][55][56][57]. CAs inhibition mechanism with coumarins was unraveled with kinetic and X-ray crystallographic techniques. The first natural product, coumarin, was bound to human isoform hCA-II, but the formation of the enzyme inhibitor complex is not a rapid process, it takes 6 h for incubation period, while other classes take just 15 min for the incubation period [58][59][60][61][62][63]. The coumarin sulfonamides' anticancer and CAs inhibition activities are discussed below in more detail.

## 2.1. Benzenesulfonamide-Based Coumarins as Carbonic Anhydrases II and IX Inhibitors

Wang and coworkers designed a solvent-free green methodology to synthesize substituted coumarin containing sulfonamides derivatives, and screened for carbonic anhydrase inhibitory activities. In this synthetic strategy, Meldrum's acid was reacted with various substituted phenol **5** to achieve substituted malonic acid-based mono phenol esters **6** in (91–94%) yield, which further cyclized with Eaton's reagent under mild conditions to yield 4-hydroxycoumarin **7** in (79–91%) yield. In the next step, substituted 3-formyl-4-chlorocoumarin **8** (59–73%) was obtained by Vilsmeiere Haack reactions in dimethylformamide (DMF) and phosphoryl chloride. Derivative **8** was treated with substituted sulfonamides in ethanol at room temperature (rt) to 50 °C, leading to the formation of final coumarin sulfonamide derivative **9** in (45–79%) yield (Scheme 1) [64].



**Scheme 1.** Synthesis of coumarin containing sulfonamide derivative **9**.

The benzenesulfonamide coumarins' eighteen derivatives were afforded and screened for their in vitro anticancer activity against mouse melanoma cells (B16–F10) and breast carcinoma cell lines (MCF-7), and two human carbonic anhydrase against hCAs II (cytosolic off target isoform) and hCAs IX (trans-membrane tumor-associated isoform). The $IC_{50}$ calculations were done by using Origin 8.6 software using an inhibitory model with the sum of squares of the residuals minimized. The most active derivative was substituted dimethyl pyrimidine-based coumarin benzene sulfonamide **9a** (**Figure 2**), which displayed the highest and remarkable significant anticancer potential against MCF-7 cell lines with $IC_{50}$ 0.0088 µM when compared with the reference drugs doxorubicin $IC_{50}$ 0.072 µM and semaxanib $IC_{50}$ 0.012 µM. Both the virtual screening and anticancer activity results for MCF-7 showed that the over-expressed CA might be the most active therapeutic candidate that coumarin sulfonamides interacted with. The substituted pyrimidine-based coumarin benzene sulfonamide **9b** (**Figure 2**) and di-*tert*-butyl substituted coumarin benzenesulfonamide containing pyrimidine **9c** (**Figure 2**) displayed strong inhibition against hCAs II and hCAs IX isoforms with $IC_{50}$ values of 0.063 µM and 0.124 µM (**Table 1**) respectively, when compared with standard drugs acetazolamide (AAZ) and sulfanilamide (SA). The SAR studies investigated that the introduction of thiazole and methyl pyrimidine substitutions in the benzenesulfonyl ring of the coumarin enhanced the anticancer and carbonic anhydrase inhibition activities of the below-mentioned coumarin derivatives [64].

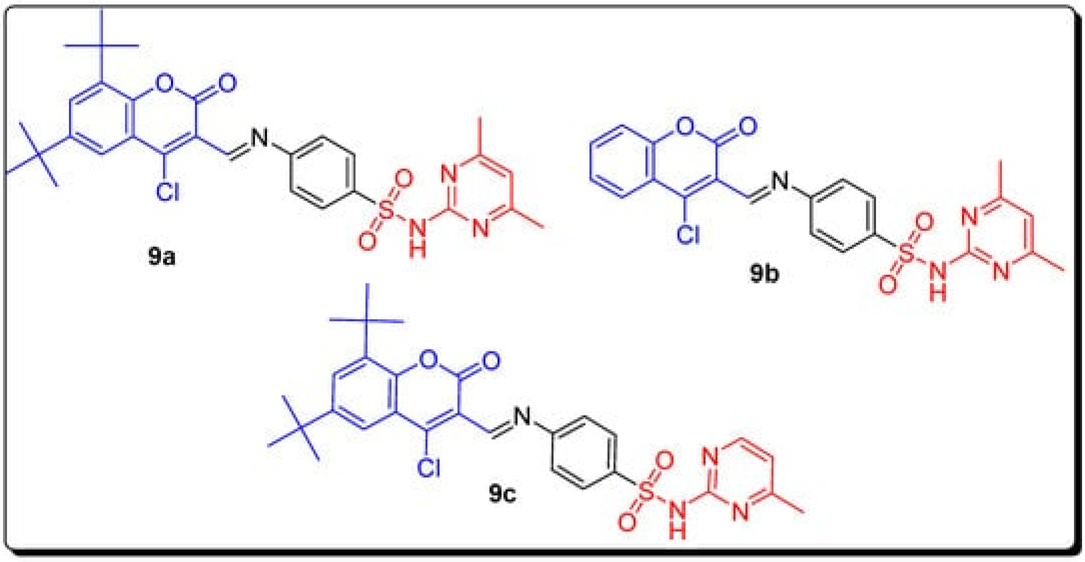


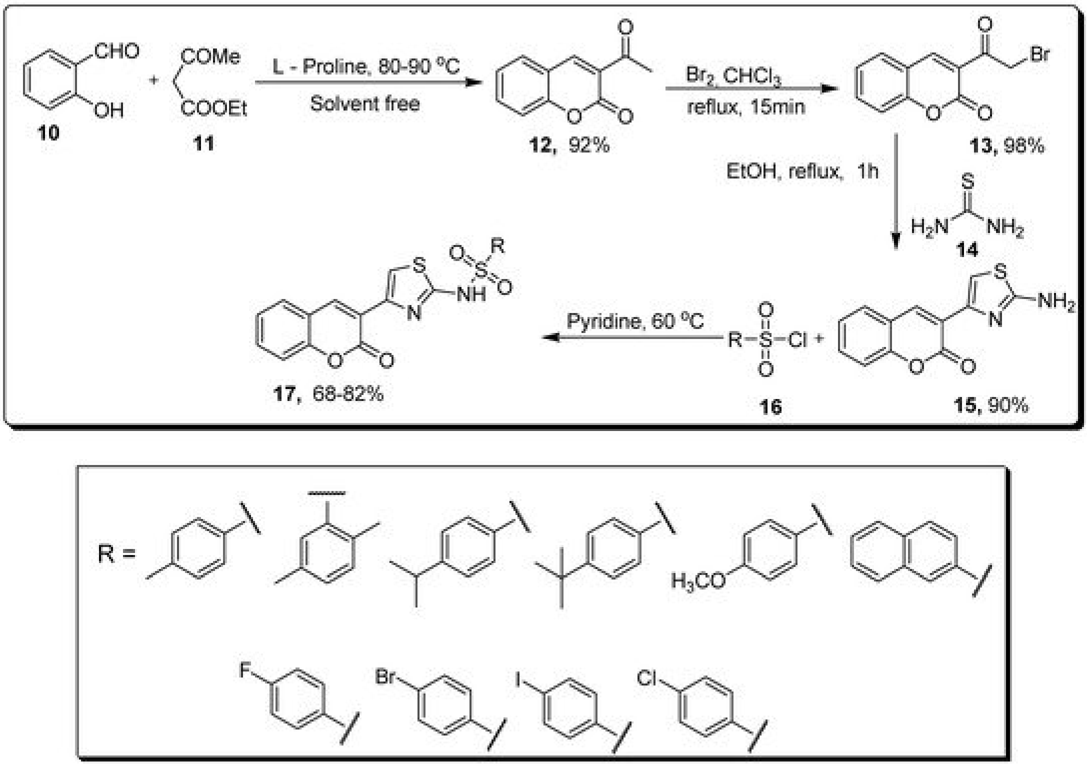
**Figure 2.** Structure of the most active anticancer and CA inhibitors coumarin sulfonamides **9a**–**9c**.

**Table 1.** Anticancer data of compound **9a** and CAs inhibition data of compounds **9b** and **9c**.

| Compound | MCF-7 µM | Compounds | hCAs II µM | hCAs IX µM |
|---|---|---|---|---|
| **9a** | 0.0088 | **9b** | - | 0.124 |
| **Doxorubicin** | 0.065 | **9c** | 0.063 | - |
| **Semaxanib** | 0.0031 | **AAZ** | 0.016 | 0.028 |
| **-** | - | **SA** | 0.26 | 0.29 |

## 2.2. Thiazole-Sulfonamide Coumarin Hybrids as hCA I and hCA II Inhibitors

Kurt and colleagues developed a solvent-free approach to achieve the unsubstituted thiazole-based coumarin sulfonamides **17** by the reaction of 2-hydroxybenzaldehyde **10**, L-proline and ethyl 3-oxobutanoate **11**, by heating for 0.5 h at a temperature of 80–90 °C to obtain 3-acetylcoumarin **12** in 92% yield, which further refluxed for 15 min in chloroform and bromine solutions to obtain 3-(bromoacetyl) coumarin **13** in 98% yield. Refluxing compound **13** with thiourea **14** in ethanol for 1 h gives 2-amino coumarin thiazolyl derivatives **15** (90% yield) that were further treated with benzenesulfonyl chloride **16** derivatives at 60 °C in pyridine, which led to the synthesis of thiazole-based coumarin sulfonamides **17** in 68–82% yield (Scheme 2) [65].



**Scheme 2.** Solvent-free synthesis of coumarin sulfonamide derivatives **17**.

The thiazole ring of acetazolamide was combined with coumarin moiety to afford biologically active, substituted benzenesulfonamide-based coumaryl thiazole hybrids, and was screened for its anticancer activity against hCA I and hCA II (human carbonic anhydrase isoforms). Among all these compounds, the scaffold coumarin-thiazole-based naphthalene-2-sulpho-namide **17a** (**Figure 3**) displayed the strongest inhibition against hCA I and hCA II with the $IC_{50}$ values 5.63 µM and 8.48 µM (**Table 2**), respectively. The SAR showed that bulky substituents such as s *tert*-butyl, naphthalene and iodine increase inhibitory activity, so compound **17a** showed the most potent inhibitory activity due to the steric effect of bulky group substitution, such as naphthalene on sulfonyl group against hCA I and hCA II [65].

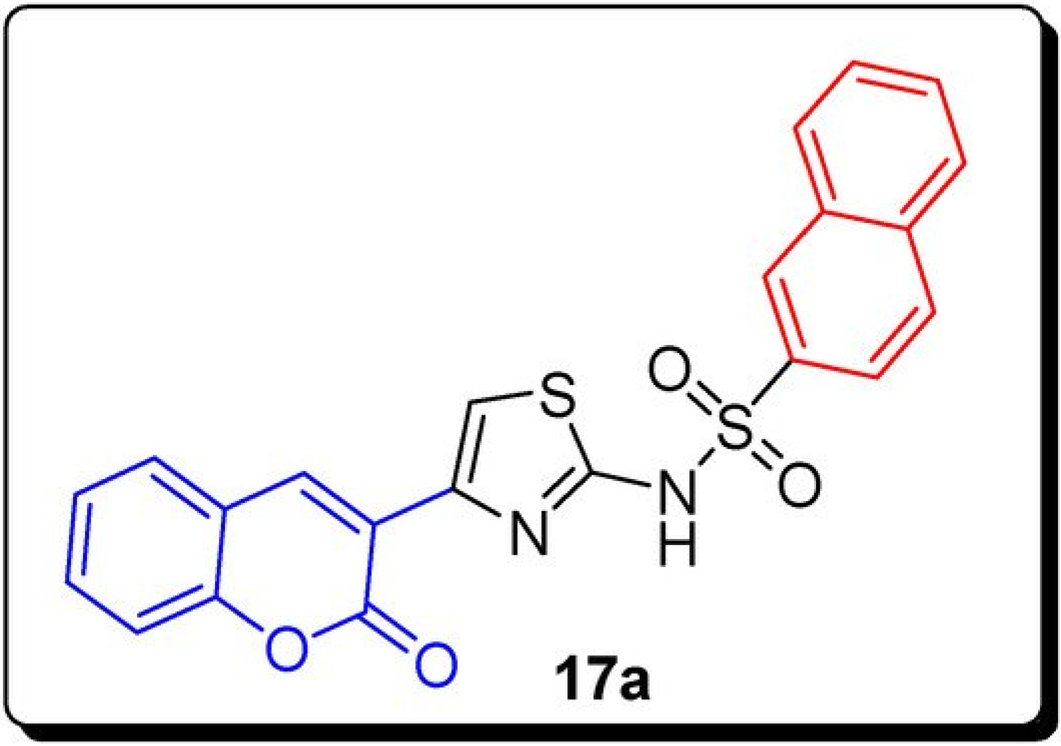


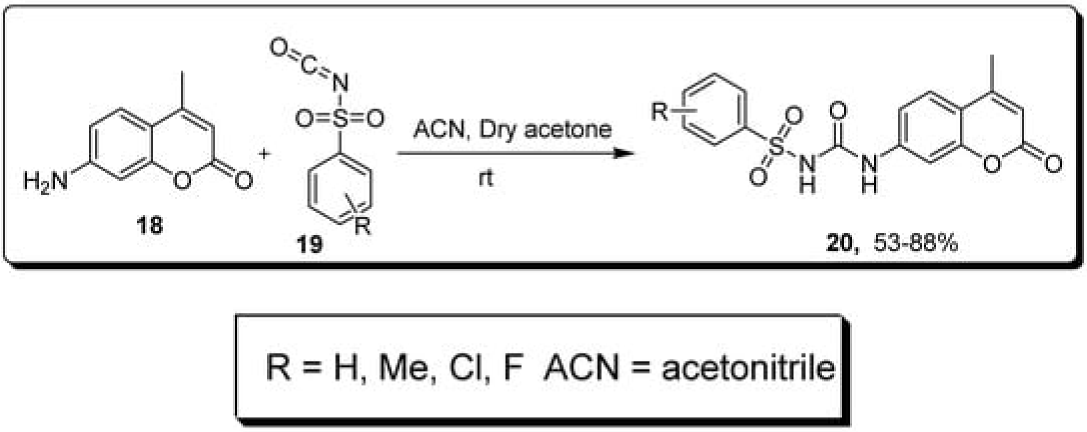
**Figure 3.** Structures of the most active antioxidant and CA inhibitors coumarin sulfonamides **17a**.

**Table 2.** CAs inhibition data and antioxidant data of compounds **17a**–**17b**.

| Compound | hCA I $IC_{50}$ (μM) | hCA II $IC_{50}$ (μM) |
|---|---|---|
| **17a** | 5.63 | 8.48 |

### 2.3. Sulfonyl Ureido Coumarins Hybrids as Carbonic Anhydrase Inhibitors

Bozdag and collogues described a single step reaction to afford substituted sulfonyl ureido coumarins **20** in 53–88% yield by the treatment of coumarin **18** and sulfonyl ureido isocyanates **19** in acetonitrile (ACN) or dry acetone (Scheme 3) [66].



**Scheme 3.** Synthesis of substituted sulfonyl ureido coumarins **20**.

The ary lsulfonylureido coumarin derivatives were evaluated for their inhibitory activity against hCA **I** and **II** (carbonic anhydrase cytosolic inhibitor) and hCA IX and XII (tumor-associated isoforms). The 4-chloro-substituted coumarin benzenesulfonamide **20a** (**Figure 4**) exhibited the highest inhibitory activity with a $K_I$ value 20.2 nM against hCA IX and 6.0 nM against hCA XII (**Table 3**). Acetazolamide (AAZ) was used as a standard reference drug with $K_I$ = 25.0 nM and $K_I$ = 5.7 nM (**Table 3**) against hCA IX and hCA XII, respectively. The SAR showed that analogue **20a** was the most potent due to the presence of electron withdrawing Cl atom in the benzene ring of the sulfonyl ureido group [66].

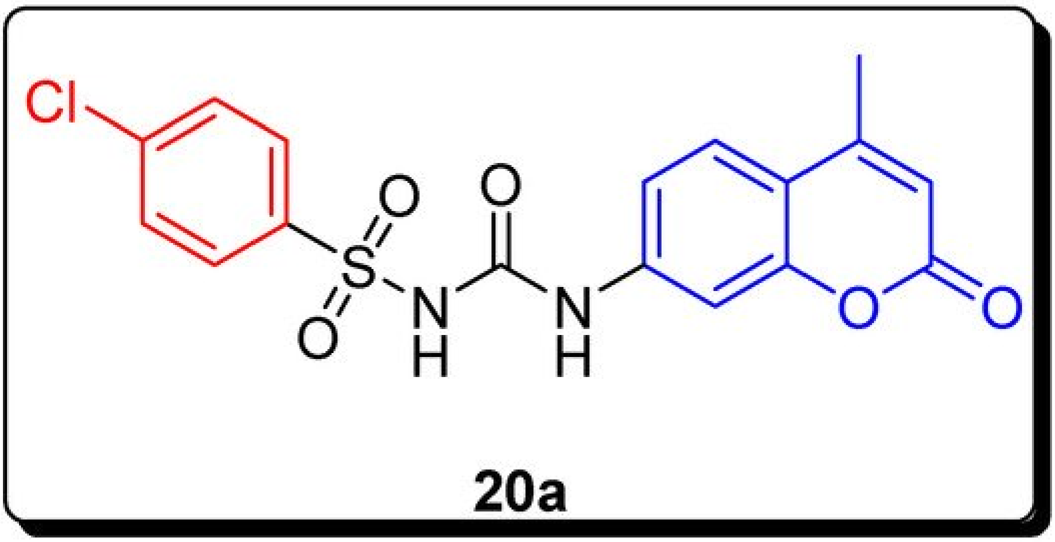


**Figure 4.** Structures of the most active coumarin sulfonamide CA inhibitor **20a**.

**Table 3.** CAs inhibition data compound **20a**.

| Compound | hCA IX<br>$K_I$ (nM) | hCA XII<br>$K_I$ (nM) |
|---|---|---|
| **20a** | 20.2 | 6.0 |

| Compound | hCA IX<br>$K_I$ (nM) | hCA XII<br>$K_I$ (nM) |
|---|---|---|
| **AAZ** | 25.0 | 5.7 |

### 2.4. Benzene Sulfonamido-Coumarinyl Hydrazones Hybrids as CA Inhibitors

Chandak et al., in 2016, synthesized sulfonamide bearing coumarin derivatives by a Hantzsch thiazole synthetic approach as shown in Scheme 4. In this synthetic strategy, the thiazolyl hydrazine methylidene pyrazole **31** derivatives were achieved from 4-hydrazinobenzenesulfonamide hydrochloride, further converted into pyrazole-based carbaldehyde bearing thiosemicarbazones, and finally reacted to substituted bromoacetyl-based coumarins **30** by condensation reaction. In the second step, different 6-substituted 3-bromoacetylcoumarins **30** and 4-thioureido-benzenesulfonamide achieved 2-amino-substituted-coumarinylthiazoles **32** by condensation reaction. In the next step, heterocyclic series **33** containing three IBTs prepared by treatment of 2-aminobenzothiazole-6-sulfonamide that first obtained from sulfanilamide and 6-substituted-3-bromoacetylcoumarins. On the other hand, the derivatives of series 4, different 3-acetylcoumarins **29** and 4-hydrazinobenzenesulfonamide hydrochloride **34** by refluxing together in aqueous ethanol with anhydrous sodium acetate give benzenesulfonamido-coumarinyl hydrazones, **35** (Scheme 4) [67].

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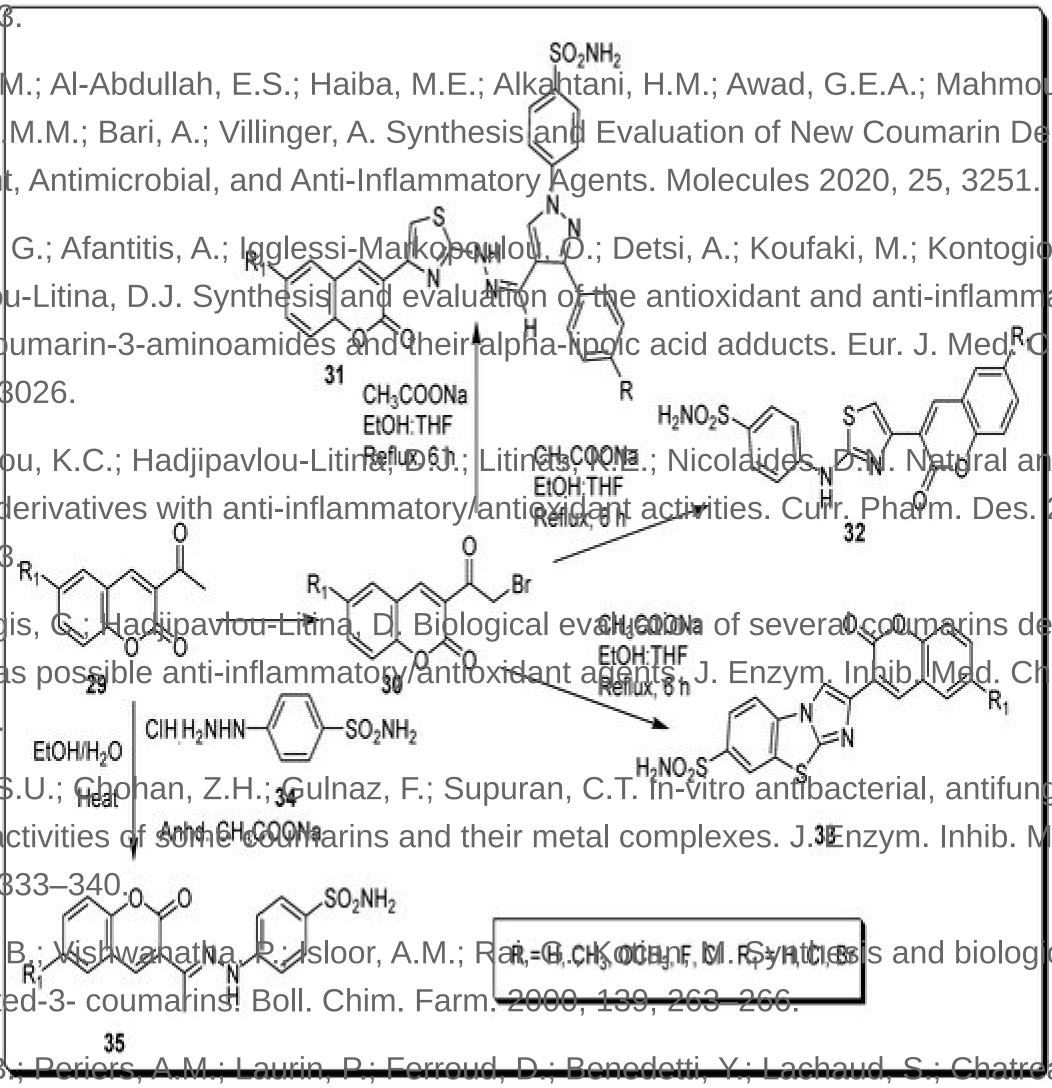

**Scheme 4.** Synthesis of sulfonamide-bearing coumarin derivatives **31**–**35**.

The following sulfonamide-bearing coumarin scaffold consisted of twenty-four compounds evaluated for the inhibition of hCA I, II, IX and XII (human carbonic anhydrase isoforms). Among all of these, the **32a** compound (**Figure 5**) exhibited strong potent inhibitory activity with a $K_I$ value 2.28 nM (**Table 4**) against hCA IX, as compared to standard compound AZA with a $K_I$ range 25.0 nM. Moreover, analogues **32a** and **32b** were most potent with $K_I$ values 0.54 nM against hCA XII when compared to AZA with a $K_I$ value 5.7 nM. The hybrid structure 4-{2-[1-(2-oxo-2*H*-chromen-3-yl)ethylidene]hydrazino} benzenesulfonamide **35a** revealed the highest activity $K_I$ = 13.23 nM for hCA II in comparison with reference drug AZA with $K_I$ value 12.1 nM. The compound 4-{2-[1-(6-bromo-2-oxo-2*H*-chromen-3-yl)ethylidene]hydrazino}benzenesulfonamide **35b** (**Figure 5**) screened potent inhibitory activity with a $K_I$ value 21.95 nM against hCA I, as compared to standard compound AZA (acetazolamide) with a $K_I$ range 250.0 nM (**Table 4**). The SAR showed that the introduction of bromo and unsubstituted H-atom on coumarin increase the carbonic anhydrase inhibitory activity of derivatives **35a** and **35b** (**Figure 5**), while the presence of electron-withdrawing group and unsubstituted H-atom enhances the inhibitory activity of compounds **32a** and **32b** [67].

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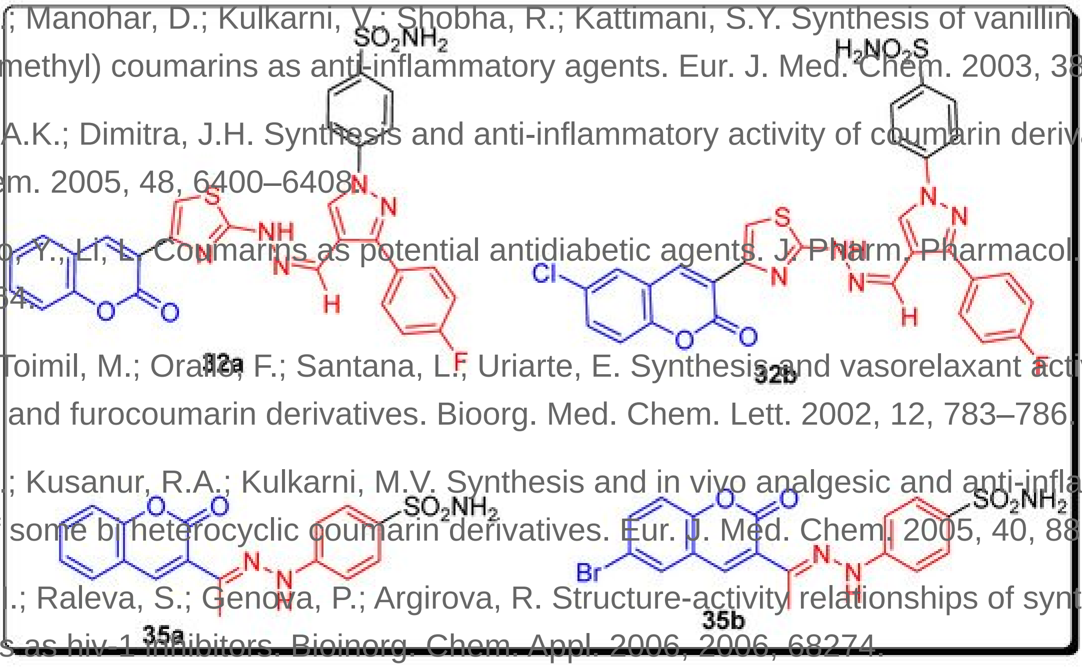

**Figure 5.** Structures of the most active coumarin sulfonamide CA inhibitors **32a**–**32b** and **35a**–**35b**.

**Table 4.** Coumarin sulfonamide as CA inhibitors **32a**–**32b** and **35a**–**35b**.

| Compound Number | hCA I $K_I$ (nM) | hCA II $K_I$ (nM) | hCA IX $K_I$ (nM) | hCA XII $K_I$ (nM) |
|---|---|---|---|---|
| **32a** | 263.49 | 21.20 | 2.28 | 0.54 |
| **32b** | 349.63 | 17.46 | 2.54 | 0.54 |
| **35a** | 220.13 | 13.23 | 58.61 | 4.4 |
| **35b** | 21.95 | 1751.72 | 23.59 | 0.62 |
| **AZA** | 250.0 | 12.1 | 25.0 | 5.7 |

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