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Synthesis of new conjugated coumarin–benzimidazole hybrids and their anticancer activity

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ABSTRACT

A series of novel coumarin–benzimidazole hybrids, 3-(1*H*-benzo[*d*]imidazol-2-yl)-7-(substituted amino)-2*H*-chromen-2-one derivatives of biological interest were synthesized. Six out of the newly synthesized compounds were screened for in vitro antitumor activity against preliminary 60 tumor cell lines panel assay. A significant inhibition for cancer cells was observed with compound **8** (more than 50% inhibition) compared with other compounds and active known drug 5-fluorouracil (in some cell lines) as positive control. Compound **8** displayed appreciable anticancer activities against leukemia, colon cancer and breast cancer cell lines.

Coumarin and its derivatives are important compounds due to their presence in naturally occurring products and their wide-range applications in agrochemicals, drugs and pharmaceuticals[1–5] such as anticancer,[6,7] anti-HIV,[8] antituberculosis,[9] anti-influenza,[10] anti-alzheimer,[11,12] anti-inflammatory,[13] antiviral[14] and antimicrobial agents.[15] Coumarin derivatives have also been shown to be novel lipid lowering agents that possess moderate triglyceride lowering activity.[16] Many coumarin derivatives have unique ability to scavenge reactive oxygen species such as hydroxyl free radicals, superoxide radicals, or hypochlorous acid to prevent free radical injury.[17] Certain coumarin derivatives have been shown to function as HIV integrase inhibitors and evaluated in the treatment of HIV infection,[18] whereas others evaluated as anti-invasive compounds due to their inhibitory activity against some serine proteases and matrix metalloproteases (MMPs).[19] 6-Nitro-7-hydroxy coumarin acts as a selective anti-proliferative agent by activating p38, stress activated protein kinase (SAPK), p21WAF1/CIP1 cyclin dependent kinase inhibitor and human renal cell carcinoma cell line, A-498.[20,21] Coumarin showed the inhibition of polymerization of tubulin and arrest cells in mitotic phase by inhibiting microtubule formation.[22] The benzimidazole moiety also exist in many biologically active natural products, synthetic compounds[23] and are well known for clinical values toward tumor cells,[24–26] and antiviral agents.[27–31] 2-Arylbenzimidazole-5-carboxylic acids were shown to inhibit the HCV NS5B RNA polymerase.[32,33] Coumarin–benzimidazole hybrids showed diverse biological activity with significant clinical potential, such as anti-angiogenesis[34] and antihepatitis.[35]

Despite numerous attempts in search for more effective antitumor agents, coumarin still remains as one of the most versatile class of compound against cancer cell lines and are an important component among the molecules in drug discovery. Most of hybrid molecules have been reported where both coumarin and benzimidazole moieties were attached via spacer[35] as shown in Figure 1(A–C). Still, rare examples are known for coumarin–benzimidazole hybrids as antitumor agents. Here, we reported the synthesis, evaluation and molecular docking of combinations of two biological active coumarin and benzimidazole moiety without any linkage or spacer and the corresponding amines at position 7 of coumarin moiety that exhibit better anticancer activity.

The synthetic strategy to obtain the targets **5**, **7**–**14** and **18** are depicted in Schemes 1 and 2. In order to synthesize compounds of amino substituted coumarin–benzimidazole hybrids, we began with the commercially available starting material 5-bromosalicylaldehyde (**1**) and diethylmalonate (**2**). 5-Bromosalicylaldehyde (**1**) was refluxed with diethylmalonate in the presence of piperidine, acetic acid and ethanol for 3 h gave 7-bromo-2-oxo-2*H*-chromene-3-carboxylic acid ethyl ester (**3**) with 86% yield followed by hydrolysis with NaOH at room temperature to obtain 7-bromo-2-oxo-2*H*-chromene-3-carboxylic acid (**4**) with 63% yield. Compound **4** was refluxed with *o*-phenylenediamine in polyphosphoric acid (PPA) for 12 h gave two types of products **5** and **6** and separated through column chromatography in 62% and 20% yields, respectively. Compound **5** was substituted with different primary amines at 7-position of coumarin ring in ethanol using triethyl-

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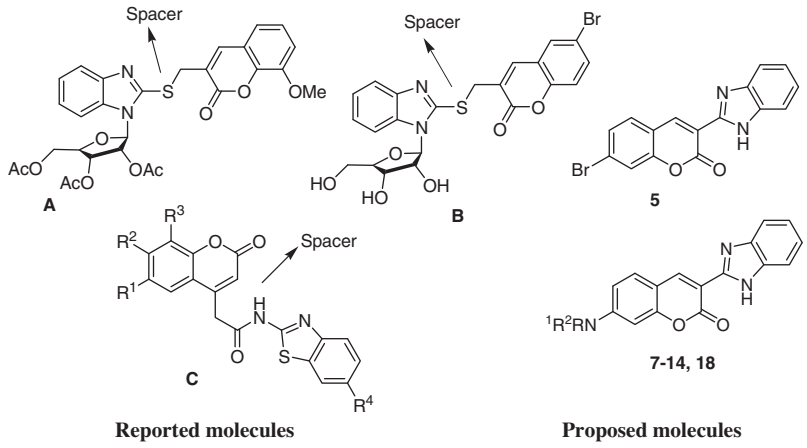
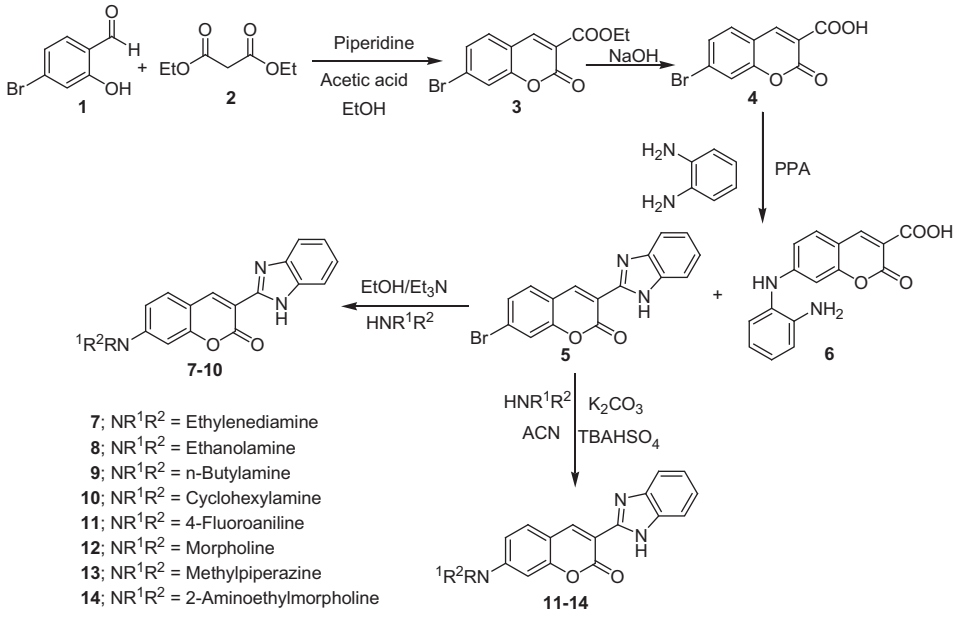
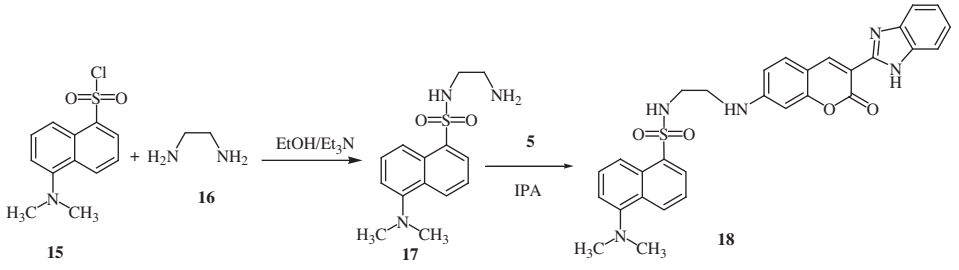


Figure 1. Reported and proposed coumarin–benzimidazole hybrids.



Scheme 1. Synthesis of 3-(1*H*-benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-one analogs (**7**–**14**).



Scheme 2. Synthesis of 5-dimethylamino-naphthalene-1-sulfonic acid {2-[3-(1*H*-benzimidazol-2-yl)-2-oxo-2*H*-chromen-7-ylamino]ethyl}-amide (**18**).

amine as base to obtain compounds **7**–**10**. Compounds **11**–**14** were not synthesized via this methodology and used alternate phase transfer catalyzed approach to synthesize these compounds (Scheme 1).

Compound **5** was refluxed with primary and secondary amines using K_2CO_3 as base and $TBAHSO_4$ as catalyst in acetonitrile for 6–8 h, gave compounds **11**–**14** with moderate to good yields.

Treatment of 5-dimethylamino-naphthalene-1-sulfonyl chloride (**15**) with excess of ethylenediamine (**16**) in ethanol using triethylamine at refluxing conditions for 7 h gave 5-dimethylamino-naphthalene-1-sulfonic acid-(2-amino-ethyl)-amide (**17**) and used further without purification. Compound **17** was refluxed with 3-(1*H*-benzimidazol-2-yl)-7-bromo-chromen-2-one (**5**) in isopropyl alcohol (IPA) for 8 h and after work up gave brown crystals of