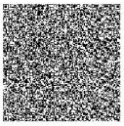

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Synthesis of a New Series of Quinolinoxymethylcoumarins as Potent Anticancer Agents

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Abstract

4-Bromomethylcoumarins (**1a-f)** were reacted with 8-hydroxyquinoline to yield quinolinoxymethylcoumarins (**2a-f)**. The structure of all the synthesized compounds were confirmed by spectral studies and screened for their anticancer activities against Dalton's Ascitic lymphoma (DAL) and Ehrlich Ascites Carcinoma (EAC) cell lines. Out of these, compound **(2b)** (R = 6-OMe) was found to be the most potent cytotoxic compound against DAL and EAC cell lines.

Keywords: 4-Bromomethylcoumarins, Coumarins, Quinoline, Cytotoxic activity.

1. Introduction

A large number of naturally occurring compounds possessed heterocyclic rings as an important part of their structure. Such compounds including indole, quinoline, benzimidazole, coumarins

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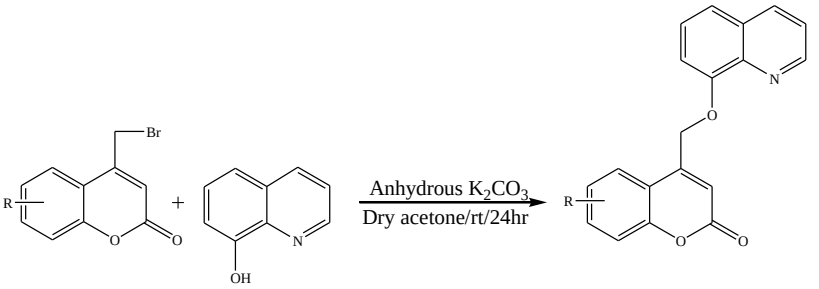
and imidazopyridines are widely used as medicines. Among them, quinoline and its derivatives exhibited remarkable activities such as antimalarial [1], antiproliferative [2], photosynthesis-inhibiting [3], proteasome inhibitors [4] and antioxidative activities [5]. They also act as antifungal [6], antibacterial [7], antiprotozoic drugs as well as exhibit antineoplastics [8] and antischistosomal activity [9].

Compounds containing coumarin rings have remarkable medicinal value due to their potential anticancer [10], antimicrobial [11] and antiulcerogenic effect [12] properties. They also act as fluorescent probes [13]. In addition, 4-heteroaryloxymethylcoumarins are reported to exhibit significant biological activities such as antibacterial [14], antifungal [15], antimicrobial [16], antidiuretic [17] and anti-inflammatory activity [18].

On the basis of these literature studies, we set out to synthesize a new series of biologically active compounds containing both of these two important pharmacophores. This study presents the synthesis, characterization and *in vitro* cytotoxic activities of these new quinolinoxymethylcoumarins

1.1 Chemistry

4-Bromomethylcoumarins [19] **(1a-f)** were synthesized by the Pechmann cyclisation of phenols with 4-bromoethylacetoacetate [20]. 6-Methyl-4-bromomethylcoumarin reacted with 8-hydroxyquinoline in the presence of anhydrous K_2CO_3 to give 6-methyl-4-(quinolin-8-yloxymethyl)-chromone-2-one [21]. We have extended the same method to other substituent of 4-bromomethylcoumarins **(1a-f) (Scheme 1).**



1(a-f) **2(a-f)**

R = a; 7-CH_3, b; 6-OMe, c; 5,6-Benzo, d; 6-Cl, e; 6-Br, f; 6-F.

Scheme 1.

2. Results and Discussion

2.1 *In vitro* anticancer screening

The newly synthesized compounds were evaluated for their *in vitro* cytotoxic activity against Dalton's Lymphoma Ascites (DAL) and Ehrlich Ascites Carcinoma (EAC) Cells using Dhamija method [22]. *5-Fluorouracil* which is one of the most effective anticancer agents was used as the reference drug in this study.

The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of Dalton's Lymphoma Ascites (DAL) and Ehrlich Ascites Carcinoma (EAC) cells. The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. The IC_{50} of the synthesized compounds compared to the reference drug are shown in Table 1 and the results are represented graphically in Figure 1.

The investigation of *in vitro* cell cytotoxicity (Table 1) against DAL cell revealed that the most of the tested compounds exhibited good activity. The Compound **(2b)** (R = 6-OCH_3) was found to be the most potent against DAL cell with IC_{50} value of 50.76 µg/mL. The compound **(2e)** (R= 6-Br) was found to be highly active against DAL cell with IC_{50} value of 65.87 µg/mL. The compounds **(2a)** (R= 7-CH_3), **(2c)** (R= 5,6-Benzo) and **(2d)** (R= 6-Cl) showed moderate activity against DAL cell with IC_{50} between 78.01 and 84.54 µg/mL.

The compound **(2f)** (R= 6-F) showed poor activity against DAL cell with IC_{50} 104.25 µg/mL.

The investigation of *in vitro* cell cytotoxicity (Table-1) against EAC cell revealed that the most of the tested compounds exhibited good activity. The Compound **(2b)** (R = 6-OCH_3) was the most potent compound in this screening against EAC cell with IC_{50} value of 41.25 µg/mL. The compounds **(2d)** (R = 6-Cl) and **(2f)** (R = 6-F) were found to be highly active against EAC cell with IC_{50} value between 69.96 and 56.41 µg/mL. The compounds **(2a)** (R = 7-CH_3), **(2c)** (R = 5,6-Benzo) and **(2e)** (R = 6-Br) showed poor activity against EAC cell with IC_{50} between 104.67 and 115.23 µg/mL.

Compound	R	DAL IC_{50}	EAC IC_{50}
2a	7-CH_3	84.54	110.34
2b	6-OCH_3	50.76	41.25
2c	5,6-Benzo	78.01	104.67
2d	6-Cl	81.25	69.96
2e	6-Br	65.87	115.23
2f	6-F	104.25	56.41
5-Flurouracil		41.60	41.60

Table 1: Result of *in vitro* cytotoxic activity of the synthesized compounds against DAL & EAC cells.

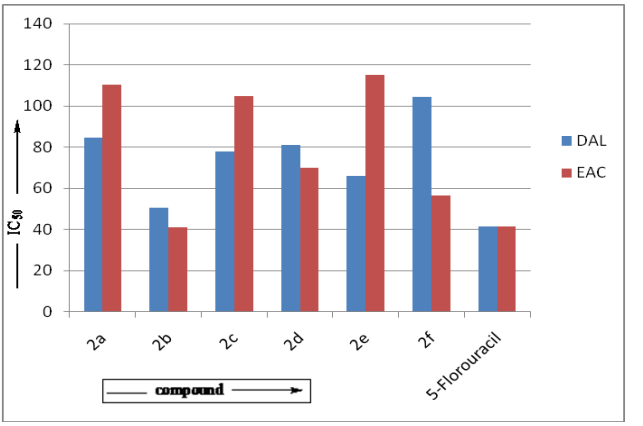


Figure 1: IC_{50} µg/mL of the synthesized compounds and *5-Flourouracil* against DAL & EAC cells.

3. Experimental section

3.1 General

The melting points were determined by open capillary method using electric melting point apparatus and are uncorrected. The IR spectra (KBr disc) were recorded on a Shimadzu-8400S FT-IR Spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker 400 MHz spectrometer by using $CDCl_3$ as a solvent and TMS as an internal standard. The chemical shifts are expressed in δ ppm. The purity of the compound was checked by TLC.

3.2. General procedure for the synthesis of 4-(quinolin-8-yloxymethyl)-chromone-2-one (2a-f).

8-Hydroxyquinoline (0.493g, 3.4 mmol) and anhydrous K_2CO_3 (1.38g, 10 mmol) were stirred in 25 ml of dry acetone for 30 min. One of the 4-bromomethylcoumarins **1(a-f)** (3.4 mmol) was added and stirring was continued for 24 h. The reaction mixture was concentrated to one fourth volume and poured on to crushed ice. The solid separated was filtered and washed with 10 ml of 5% HCl. Then, it was washed with 50 ml of cold water. The crude product was dried and recrystallised from ethanol.

7-Methyl-4-(quinolin-8-yloxymethyl)-chromen-2-one. **(2a)**

Yield 95%; colorless solid; m.p. 227 - 230 ^{0}C; IR (KBr, cm^{-1}) 1725 cm^{-1} (lactone C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H, 7-CH_3), 5.64 (s, 2H, OCH_2), 6.71(s, 1H, C_3-H), 7.0 - 8.99 (m, 9H, Ar-H): ^{13}C NMR (400 MHz, $CDCl_3$): δ 21.26, 67.20, 110.94, 114.12, 117.41, 117.61, 121.79, 122.43, 123.79, 126.91, 130.17, 133.47, 134.65, 136.69, 140.58, 149.99, 150.10, 152.33, 153.73, 161.17.

6-Methoxy-4-(quinolin-8-yloxymethyl)-chromen-2-one. **(2b)**

Yield 90%; yellow solid; m.p. 155 - 160 ^{0}C; IR (KBr, cm^{-1}) 1735 cm^{-1} (lactone C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 5.67 (s, 2H, OCH_2), 6.75 (s, 1H, C_3-H), 7.0 – 8.10 (m, 9H, Ar-H).

1-(Quinolin-8-yloxymethyl)-benzo(f)chromen-3-one .**(2c)**

Yield 85%; yellow solid; m.p. 185 - 188 °C; IR (KBr, cm^{-1}) 1720 cm^{-1} (lactone C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.0 (s, 2H, OCH_2), 6.96 - 9.0 (m, C_3-H & 12H, Ar-H).

6-Chloro-4-(quinolin-8-yloxymethyl)-chromen-2-one. (**2d)**

Yield 70%; colorless solid; m.p. 225 - 227 ˚C; IR (KBr, cm^{-1}) 1725 cm^{-1} (lactone C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.55 (s, 2H, OCH_2), 6.80 (s, 1H, C_3-H), 7.10 - 9.01 (m, 9H, Ar-H).

6-Bromo-4-(quinolin-8-yloxymethyl)-chromen-2-one. **(2e)**

Yield 73%; brown solid; m.p. 202 – 207 ^{0}C; IR (KBr, cm^{-1}) 1721 cm^{-1} (lactone C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.65 (s, 2H, OCH_2), 6.79 (s, 1H, C_3-H), 7.10 - 9.0 (m, 9H, Ar-H).

6-Fluoro-4-(quinolin-8-yloxymethyl)-chromen-2-one. **(2f)**

Yield 40%; colorless solid; m.p. 229 - 232 ^{0}C; IR (KBr, cm^{-1}) 1722 cm^{-1} (lactone C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.57 (s, 2H, OCH_2), 6.80 (s, 1H, C_3-H), 7.09 - 9.0 (m, 9H, Ar-H).

4. Conclusion

The methoxy substitution at 6-position of coumarin moiety was found to enhance the *in vitro* cytotoxicity against both DAL and EAC cell lines.

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