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Synthesis And Antitumor Potential Of New 7-Halocoumarin-4-Acetic Acid Derivatives

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Abstract

Compounds having their chemical structure based on coumarin framework have enticed much research concern not only because of the variance structural characteristic but also the pluralism of the bioactivities. In this report, four derivatives of 7-halo-4-coumarinylacetic acid referred to as **RY1**-**RY4** were synthesized, and their chemical backbones were confirmed via the employed spectrophotometers. The pharmacokinetic profiles of the synthesized halocoumarins were inspected *in silico* using a free online software named the pre-ADMET program. The potential of the synthesized halocoumarins as antitumor applicants was evaluated utilizing 5-fluorouracil as a reference drug and the well-authenticated protocol based on the MTT as a visible indicator against eight standard tumor-cell lines. The outcomes acquired from this assessment indicated that the synthesized halocoumarins, except **RY1**, have less impact as antitumor agents comparing with the standard drug. Also, the halocoumarins revealed roughly the same fashion of activity versus the test cell lines with the greatest inhibitory influence reported against MCF-7 and HeLa. From the calculated pharmacokinetic data and outcomes exhibited from antitumor assessment, the authors concluded that the synthesized halocoumarins, particularly **RY1**, offered potential applicants as antitumor agents with broad-ranged activity. Besides, the compounds **RY1** and **RY2** may provide highly valuable scaffolds for synthesizing agents with a powerful antitumor activity versus the breast and cervical cancer phenotypes.

Keywords: Halocoumarins; Synthesis; Antitumor; MTT assay; Pharmacokinetic parameters.

1. Introduction

Despite the continued advances in chemotherapy researches, cancer remains a big challenge for contemporary medicinal chemistry [1]–[3], which calls for the intensification of universal efforts for urgent development of more efficient anticancer agents with minimal side effects to combat this disease [4], [5].

Coumarins, a distinctive family of natural and synthetic products belonging to the benzo-α-pyrone class, the parent natural coumarin compound was first isolated from tonka beans (Dipteryx odorata) about two hundred years ago by Vogel [6]. Because of their versatile and unique oxygen-containing heterocyclic structure, coumarin-derived compounds occupy a prominent position in medicinal chemistry [7]. Various coumarins are in continual development as medicinal candidates with potent biological activity because of their high metabolism resistance, low toxicity, and good bioavailability. Owing to its basic structure, the coumarin framework can interact non-covalently with many receptor phenotypes resulting in this wide range of biological activities[8]. Among them, the antitumor effect has been extensively examined with encouraging results. Accordingly, coumarins can be exploited as scaffolds for promising cytotoxic agents [9]. Moreover, this family of compounds can meet Lipinski's rules of five and exhibit good cell membrane permeability, which are vital characteristics for drugs development [10]

Despite the development of different methods to synthesize coumarin-based derivatives, the Pechmann condensation reaction discovered by Hans von Pechmann in 1883, with its neoteric improvements, is still the most widely employed method [11]. This reaction has to attract a particular interest due to its simple, low-cost starting materials

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and produces high yields of various functionalized coumarins as desired [12].

This report aims to synthesize four derivatives of 7-halo-4-coumarinylacetic acid symbolized here as **RY1-RY4** by condensing 3-oxoglutaric acid with different 3-halophenols in a Pechmann-type reaction. The pharmacokinetic profiles of the synthesized compounds were studied *in silico* using a free online software named the pre-ADMET program. The antitumor activity of the prepared 7-halo-4-coumarinylacetic acids was investigated by applying the MTT-dependent protocol versus eight standard tumor-cell lines. These included HeLa (Epitheloid Cervix Carcinoma), SK-OV-3 (Caucasian Ovary Adenocarcinoma), AR42J (Rat Exocrine Pancreatic Tumor), MCF-7 (Caucasian Breast Adenocarcinoma), AB12 (Mouse Malignant Mesothelioma), KYSE-30 (Human Asian Esophageal Squamous Cell Carcinoma), LC540 (Rat Fischer Leydig Cell Testicular Tumor), and AMN3 (Murine Mammary Adenocarcinoma).

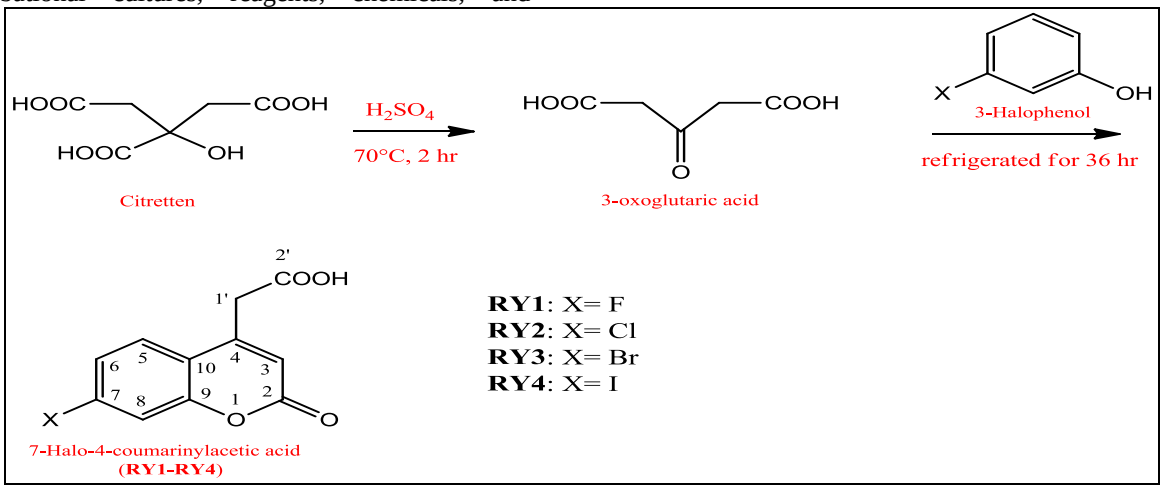
2. Experimental

2.1. General information

In this work, the tumor-lines and their incubational cultures, reagents, chemicals, and solvents used to conduct the synthesis and evaluating the antitumor potential were requested from some global suppliers such as Scharlau, Sigma-Aldrich, Bioworld, Labcorp, Chem-Lab, and Haihang. The electrothermal's IA9300 digital melting point apparatus was operated to report the melting points (mp) of the prepared 7-halo-4-coumarinylacetic acids on the base of the open-capillary technique. To observe the progress of the synthetic reactions and demonstrate the pureness of the prepared 7-halo-4-coumarinylacetic acids, thin-layer chromatography (TLC) technique was conducted. The mobile and stationary phases used in this technique were Millipore Sigma™ TLC-Silica Gel 60 (F254) and ether: MeOH (4:1) mixture, respectively. Spectrophotometers of analytical grade including Bruker-Avance III HD 600 MHz (DMSO-d6), Bruker FTIR-alpha-ATR, and Cary 300 UV-Vis Bio were utilized to figure the ^{1}H-NMR, ^{13}C-NMR, IR, and λmax scopes of the prepared 7-halo-4-coumarinylacetic acids.

2.2. Schedule of the chemical synthesis

The stairs rated for preparing the 7-halo-4-coumarinylacetic acids (RY1-RY4) are delineated in Scheme-1.



Scheme-1. Schematic trend that followed for the preparation of the 7-halo-4-coumarinylacetic acids **RY1-RY4**.

*2.3. General method for synthesizing 7-halo-4-coumarinylacetic acids (**RY1-RY4**)*

In a salt-ice bath, 10 ml of concentrated H_2SO_4 housed in a conical flask was cooled to 0°C. To this chilly acid, citretten (0.96 g, 5 mmol) was added slowly in the frequency governed by the reaction temperature that must be kept under 5°C. After 0.5 hr, the reaction mixture allowed to be stirred at 25°C and the temperature was carefully raised to 70°C. The factor controlled the rate of heating was the formation of foam and bubbles. The reaction mixture was housed in a salt-ice bath as a clear solution obtained. Concentrated H_2SO_4 (5 ml) followed by 3-halophenol (5 mmol) were added to the stirred mixture on condition of the reaction temperature kept under 10°C. The reaction mass was refrigerated for 36 hr, poured on a mixture of ice-water, filtered. The crude was sanitized from impurities by recrystallizing from ethyl acetic ester [13].

7-Fluoro-4-coumarinylacetic acid (RY1): mp=184-186°C; λ_{max} (EtOH)=282 nm; %yield=42; FTIR (ν, stretching, cm^{-1}): 3042 (C-H, alkene), 3001 (O-H, COOH), 2853 (C-H, alkane), 1726 (C=O, ester), 1702 (C=O, COOH), 1688 (C=C, alkene),

1582 (C=C, aromatic), 1171 (C-F); ^{1}H-NMR: δ= 11.17 (1H, s, OH-2'), 7.90 (1H, d, H-5, *J*=6 Hz), 7.11 (1H, d, H-6, *J*=6 Hz), 6.83 (1H, s, H-8), 6.41 (1H, s, H-3), 3.06 (2H, s, H-1') ppm; ^{13}C-NMR: δ= 173.6 (C, C-2'), 163.8 (C, C-7), 160.2 (C, C-2), 156.1 (C, C-4), 150.0 (C, C-9), 131.4 (CH, C-5), 116.8 (C, C-10), 114.1 (CH, C-3), 110.7 (CH, C-6), 108.2 (CH, C-8), 42.5 (CH_2, C-1') ppm.

7-Chloro-4-coumarinylacetic acid (RY2): mp=171-173°C; λ_{max} (EtOH)=281 nm; %yield=47; FTIR (ν, stretching, cm^{-1}): 3041 (C-H, alkene), 3003 (O-H, COOH), 2854 (C-H, alkane), 1725 (C=O, ester), 1701 (C=O, COOH), 1685 (C=C, alkene), 1586 (C=C, aromatic), 1095 (C-Cl); ^{1}H-NMR: δ= 11.17 (1H, s, OH-2'), 7.90 (1H, d, H-5, *J*=6 Hz), 7.14 (1H, d, H-6, *J*=6 Hz), 6.98 (1H, s, H-8), 6.41 (1H, s, H-3), 3.06 (2H, s, H-1') ppm; ^{13}C-NMR: δ= 173.5 (C, C-2'), 162.0 (C, C-2), 156.1 (C, C-4), 150.1 (C, C-9), 140.2 (C, C-7), 129.2 (CH, C-5), 127.4 (CH, C-6), 120.6 (CH, C-8), 119.8 (C, C-10), 114.5 (CH, C-3), 42.5 (CH_2, C-1') ppm.

7-Bromo-4-coumarinylacetic acid (RY3): mp=158-161°C; λ_{max} (EtOH)=283 nm; %yield=48; FTIR (ν, stretching, cm^{-1}): 3044 (C-H, alkene), 3006 (O-H, COOH), 2851 (C-H, alkane), 1722 (C=O, ester), 1698 (C=O, COOH), 1678 (C=C, alkene), 1577 (C=C, aromatic), 956 (C-Br); ^{1}H-NMR: δ= 11.15 (1H, s, OH-2'), 7.95 (1H, s, H-8), 7.84 (1H, d, H-5, *J*=6 Hz), 7.45 (1H, d, H-6, *J*=6 Hz), 6.40 (1H, s, H-3), 3.05 (2H, s, H-1') ppm; ^{13}C-NMR: δ= 173.2 (C, C-2'), 162.2 (C, C-2), 156.2 (C, C-4), 153.2 (C, C-9), 131.5 (CH, C-5), 130.1 (CH, C-6), 128.4 (C, C-7), 123.1 (C, C-10), 122.8 (CH, C-8), 114.6 (CH, C-3), 42.3 (CH_2, C-1') ppm.

7-Iodo-4-coumarinylacetic acid (RY3): mp=178-180°C; λ_{max} (EtOH)=283 nm; %yield=53; FTIR (ν, stretching, cm^{-1}): 3042 (C-H, alkene), 2995 (O-H, COOH), 2847 (C-H, alkane), 1727 (C=O, ester), 1709 (C=O, COOH), 1672 (C=C, alkene), 1579 (C=C, aromatic), 886 (C-Br); ^{1}H-NMR: δ= 11.13 (1H, s, OH-2'), 7.72 (1H, d, H-5, *J*=6 Hz), 7.66 (1H, d, H-6, *J*=6 Hz), 7.58 (1H, s, H-8), 6.42 (1H, s, H-3), 3.03 (2H, s, H-1') ppm; ^{13}C-NMR: δ= 171.0 (C, C-2'), 162.1 (C, C-2), 156.8 (C, C-4), 153.4 (C, C-9), 137.3 (CH, C-6), 130.2 (CH, C-5), 128.7 (CH, C-8), 122.2 (C, C-10), 114.4 (CH, C-3), 94.5 (C, C-7), 42.2 (CH_2, C-1') ppm.

2.4. Theoretical pharmacokinetic parameters

The pharmacokinetic parameters of the synthesized 7-halo-4-coumarinylacetic acids including absorption, distribution, metabolism, and excretion were evaluated *in silico* by using the online program named pre-ADMET software [14].

2.5. Antitumor potential

Tumor-line cells estimated 10000/pit were allowed to multiply for 24 hr on an expansion-advocated medium housed in a 96-pit plate. To each pit, a defined concentration of the investigated 7-halo-4-coumarinylacetic acids was positioned. From ancestor solution (1 μM) regarding every investigated coumarin, several double-reduced concentrations started from 200 μM and finished at 6.25 μM were prepared using DMSO as a thinner. The potential of the prepared 7-halo-4-coumarinylacetic acids to work as antitumor agents was evaluated in the next 72 hr by dismissing the expansion-advocated medium, pipetting 28 μl of MTT-dye (3.27×10^{3} μM), and inoculating for 90 min at 37°C. The resultant visible indication was measured using a multi-mode microplate reader (BioTik, Epoch/2) operated on 492 nm. The expansion suppression percent (ES%) regarding each 7-halo-4-coumarinylacetic acid was scored according to the following rule: ES%= visible absorbance of the unpatronized pit minus the visible absorbance of the patronized pit/visible absorbance of the. By figuring ES% values versus logarithmic concentrations and applying the nonlinear regression, the score of IC_{50} was calculated for each 7-halo-4-coumarinylacetic acid [15].

3. Results and discussion

3.1. Synthetic route

Among different synthetic models that are employed for preparing coumarin-derived compounds, the Pechmann-type condensation reaction may be considered as the widely applicable technique. This reaction involves the coupling of β-keto ester or acid with phenolic derivative under the influence of condensing agent. The nature of the reaction product, as well as the percentage of yield, depends on the types and reactivity of the reactants [16]. In the literate, there are few reports indicated the utilization of the halophenol as a reactant in this reaction phenotype since this kind of phenols characterized by a poor nucleophilicity that results from the deactivation impact of the attached halogen [17]. In this work, 3-oxyglutaric acid results *in situ* from the reaction of citretten with concentrated H_2SO_4 was condensed with various halophenols affording the target products, as shown in Scheme-1.

The percentages of yield were improved by the careful monitoring of the reaction steps to be ranged from 42% to 53%.

3.2. Theoretical Pharmacokinetic evaluation

Because of the complexity and diversity of the processes involved in drug discovery and development, several predictive in silico models have been constructed to provide informative data concerning the pharmacokinetic parameters of the investigated agents [18].

The analysis of the parameters reported in Table-1 indicated several enlightening issues; firstly, the synthesized coumarins have an excellent theoretical oral bioavailability that resulted from high HIA percentages ranging between 93.03%-98.23%. The weak-to-moderate permeability across the Caco2 cell of the investigated coumarins, as well as their freedom from the P-glycoprotein inhibition capacity, indicated that the excellent intestinal absorbability may arise from protein-mediated transport rather than passive diffusion [19]. Secondly, the ability of the synthesized coumarins to inhibit CYP2C9 may indicate that these coumarins have an anti-inflammatory potential since this enzyme metabolizes the arachidonic acid to the inflammatory signaling molecule named eicosatrienoic acid epoxide [20]. Thirdly, the synthesized coumarins have a high capacity for binding with plasma proteins resulting in the dropping of the distribution volume and consequently shorting their half-lives [21]. Finally, the poor inclusion through blood-brain barrier may indicate that these coumarins are free from the neurological side effects and this issue is highly important in the term of toxicity [22].

3.3. Antitumor potential

Investigating the potential of the prepared 7-halo-4-coumarinylacetic acids as antitumor applicants was performed according to the referenced schedule of MTT-based assessment. Through which, the tumor-line cells were handled with six serial double-reduced concentrations of a defined 7-halo-4-coumarinylacetic acid . Also, the employed positive and negative predictors were 5-fluorouracil (5-FU) and sulfinylbismethane (DMSO), respectively. Eight tumor-lines were appointed in this assessment, namely HeLa (*93021013*, Epitheloid Cervix Carcinoma), SK-OV-3 (*91091004*, Caucasian Ovary Adenocarcinoma), AR42J (*93100618*, Rat Exocrine Pancreatic Tumor), MCF-7 (*86012803*, Caucasian Breast Adenocarcinoma), AB12 (*10092306*, Mouse Malignant Mesothelioma), KYSE-30 (*94072011*, Human Asian Esophageal Squamous Cell Carcinoma), LC540 (*89031604*, Rat Fischer Leydig Cell Testicular Tumor), and AMN3 (Murine Mammary Adenocarcinoma).

Precise analyzing the IC_{50} scores, reported in Table-2 and displayed as diagrams in Figures 1a and 1b, concerning the 7-halo-4-coumarinylacetic acids revealed three informative perceptions; the first is the synthesized halocoumarins except one have a less antitumor effect versus the test tumor-cell lines than the standard drug. The one is the compound **RY1**, which has an antitumor effect greater than those of the other synthesized compounds and standard drug. This particular impact may be attributed to the presence of fluoride atom at position 7; this substituent with high electronegativity and small atomic size may enhance the aqueous solubility and cellular intake [23]. The second perception is the synthesized compounds displayed nearly the same trend of activity versus the investigated tumor-cell lines with superior inhibitory impact against two cell lines, namely MCF-7 and HeLa. The order of activity regarding the antitumor effect of the synthesized compounds was **RY1**, **RY2**, **RY4**, and **RY3**. The third perception is the decreased activity was remarkably parallel to the increment in the atomic weight of the substituent at position 7. Accordingly, the authors proposed that the intension in the atomic weight of the group grafted to this position may reveal a negative impact on the antitumor activity of the synthesized halocoumarins [24].

Table 1

Theoretical pharmacokinetic data gathered from testing the synthesized 7-halo-4-coumarinylacetic acids *in silico*.

Compound symbol	Caco2-P	PPB	CYP2C9	CYP2D6	CYTP3A4	Pggp-I
RY1	21.14	85.35%	Inhibitor	Non	Non	Non
RY2	21.17	79.49%	Inhibitor	Non	Non	Non
RY3	18.55	77.57%	Inhibitor	Non	Non	Non
RY4	11.20	77.36%	Inhibitor	Non	Non	Non

Caco2-P: In vitro Caco2 (Human colorectal carcinoma) cell permeability calculated in the term of nm/sec; **PPB**: In vitro plasma protein binding calculated as a percentage; **CYP2C9**: In vitro Cytochrome-P450 2C9 inhibitory effect; **CYP2D6**: In vitro Cytochrome-P450 2D6 inhibitory effect; **CYP3A4**: In vitro Cytochrome-P450 3A4 inhibitory effect; **Pggp-I**: In vitro P-glycoprotein inhibition capacity; **HIA**: Human intestinal absorption capability expressed as a percentage; **BBB-P**: In vitro blood-brain barrier penetration calculated as a ratio of the concentration of the agent in the brain over that in the blood.

Table 2

Results acquired from the antitumor estimation regarding the synthesized 7-halo-4-coumarinylacetic acids.

Tumor-line	5-FU	RY1	RY2	RY3	RY4
HeLa	13.11 ± 0.85	11.31 ± 0.73	12.14 ± 0.90	43.03 ± 0.76	36.24 ± 0.69
SK-OV-3	22.52 ± 0.75	20.13 ± 0.83	21.33 ± 0.88	44.14 ± 1.02	42.17 ± 0.92
AR42J	21.01 ± 0.95	21.05 ± 0.95	28.50 ± 1.06	39.67 ± 0.82	33.56 ± 0.80
MCF-7	12.46 ± 0.92	10.18 ± 0.87	10.67 ± 0.92	10.79 ± 1.03	10.70 ± 1.02
AB12	19.64 ± 1.05	16.40 ± 0.74	32.27 ± 1.11	47.69 ± 0.79	40.39 ± 1.04
KYSE-30	27.78 ± 1.00	26.08 ± 0.85	34.78 ± 0.98	39.46 ± 0.97	38.07 ± 0.82
LC540	21.11 ± 0.95	19.22 ± 0.79	26.12 ± 0.78	44.16 ± 0.84	43.67 ± 0.86
AMN3	23.62 ± 0.84	22.79 ± 0.81	29.32 ± 0.86	109.12 ± 0.94	20.37 ± 0.84

The outcomes were manifested in the format of IC50 (μM) ± SD (calculated for triple-independent trials).

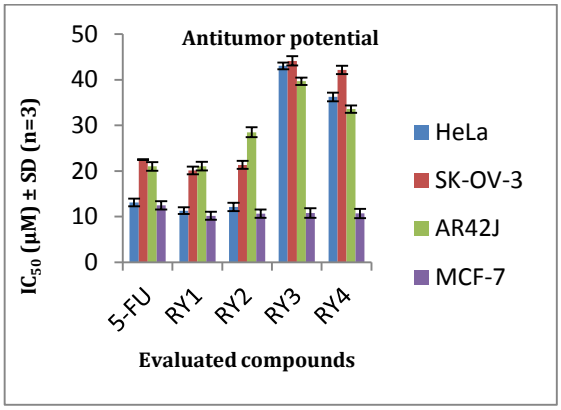


Figure-1a: Diagram explained graphically the impact of the synthesized 7-halo-4-coumarinylacetic acids as antitumor agents versus four tumor-cell lines, namely HeLa, SK-OV-3, AR42J, MCF-7

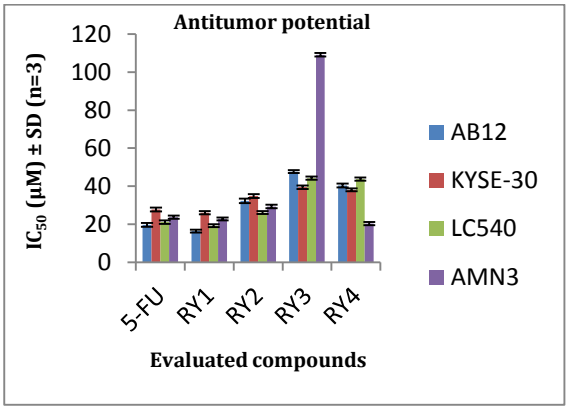


Figure-1b: Diagram displayed graphically the potential of the synthesized 7-halo-4-coumarinylacetic acids as antitumor agents versus four tumor-cell lines, namely AB12, KYSE-30, LC540, AMN3

4. Conclusions

This report demonstrated the synthesis and structural elucidation of four derivatives that belonged to the 7-halo-4-coumarinylacetic acid framework. From the calculated pharmacokinetic parameters, the authors concluded that the synthesized halocoumarins have appropriate drug-likeness properties as orally administrated agents. The antitumor assessment indicated that the synthesized products, with a preponderance activity contributed to **RY1**, have a good-to-excellent effect against the test tumor-cell lines with roughly the same mode of activity. Besides, the synthesized products showed a broad-ranged antitumor activity versus the tested lines with a privileged effect against MCF-7 and HeLa.

4. Conflicts of interest

There are no conflicts to declare.

5. Acknowledgments

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