International Journal of Medical, Pharmacy and Drug Research (IJMPD)
Article DOI: https://dx.doi.org/10.22161/ijmpd.7.5.1
Peer-Reviewed Journal
Int. J. Med. Phar. Drug Re., 7(5), 2023
ISSN: 2456-8015

Synthesis & Pharmacological Activity of Cytotoxicity Assay of Coumarins SVCM1-SVCM7

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Received: 09 Aug 2023; Received in revised form: 10 Sep 2023; Accepted: 20 Sep 2023; Available online: 01 Oct 2023

Abstract *— The therapeutic properties of natural and synthetic compounds against human illnesses have attracted a lot of interest. The pharmacological and biological effects of coumarins are widely exploited in medicine; they include anti-inflammatory, anticoagulant, antihypertensive, anticonvulsant, antioxidant, antibacterial, and neuroprotective properties. Signaling pathways affecting many cellular functions may also be modulated by coumarin derivates. Whether or not a coumarin has pharmacological, biochemical, or therapeutic characteristics is dependent on the nature of the replacement surrounding the coumarin core structure. The capacity to kill, repel, or otherwise impact the development of Anopheles arabiensis mosquitoes was evaluated using seven synthetic halogenated coumarins (SVCM1-SVCM7). The compounds SVCM1-SVCM7 were evaluated for their bactericidal and fungicidal activities using the disc diffusion method.*

Keywords *— **coumarin; antineoplastic; cancer therapy; docking.***

I. INTRODUCTION

More than two centuries have been devoted to learning about coumarins. They were initially isolated from Coumarouna odorata Aube (Dipteryx odorata), thus their name. A secondary metabolite, coumarin may be found in the oils of many different plant species. According to the nomenclature given by the International Union of Pure and Applied Chemistry (IUPAC), the fundamental nucleus of coumarin (Figure 1) is the molecule benzo-a-pyrone (2H-1-benzopyran-2-one). Natural coumarins have been identified, but the number of coumarins with intriguing biological effects has been augmented by synthetic derivatives resulting from substituents at various places in the chemical structures.

More than 60 different plants contain the coumarin 2H-chromen-2-one, 1,2-benzopyrone, which is a semi-volatile lactone with a low molecular weight and a pleasant aroma. Tobacco's cytotoxicity may also be attributed to the presence of coumarins, which were found in small concentrations.

II. COUMARINS AND THEIR PHARMACOLOGICAL ACTIVITY

The physicochemical characteristics and pharmacological applications of coumarins are affected by the wide range of biological activities to which they contribute due to their unique substitution pattern. Through their studies, Crum-Brown and Frasser advanced a notion that chemical makeup determines a substance's mode of action and pharmacological impact.

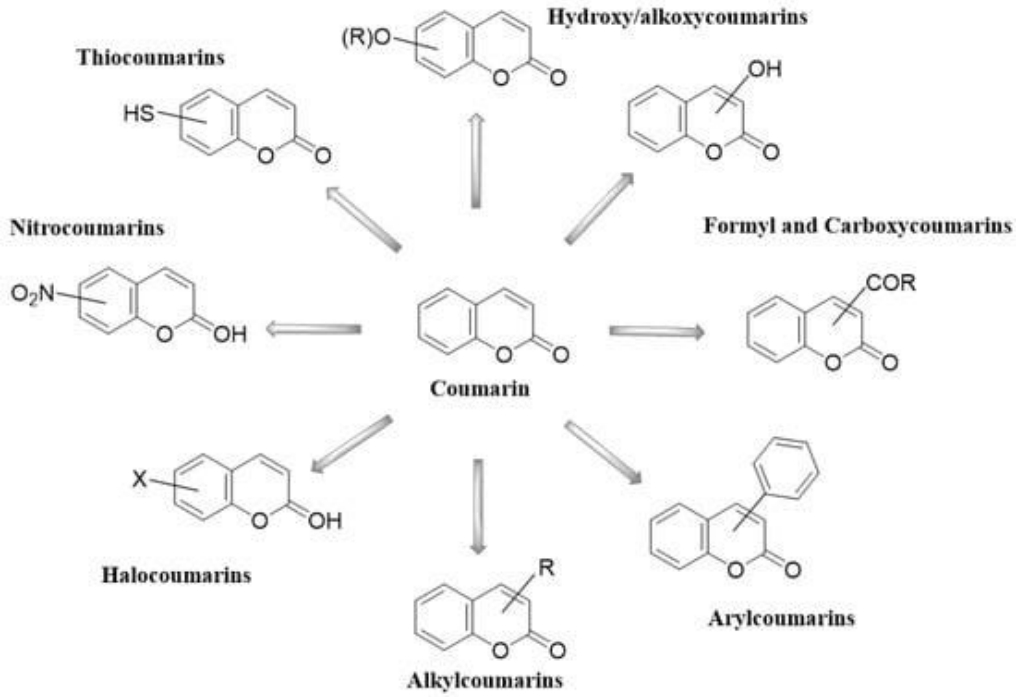

Fig.1. Coumarin as a basic nucleus for obtaining simple coumarins. Taken from Borges, F. et al. (2005). Accessed date 28 November 2022.

Evidence suggests that cytochrome P450 plays an inducing role in the oxidative metabolism of coumarins in the liver. The importance of the gut microbiota has also been shown. Rapid absorption and distribution throughout the body lead to widespread detection of coumarins, with the highest amounts seen in the liver and kidneys. It has not been shown if oral administration of coumarin or its metabolites leads to significant buildup of tissue. The coumarin's elimination pathway is context- and dose-specific. In the next paragraphs, we will discuss the primary medicinal applications of coumarins. Evidence suggests that cytochrome P450 plays an inducing role in the oxidative metabolism of coumarins in the liver. The importance of the gut microbiota has also been shown. Rapid absorption and distribution throughout the body lead to widespread detection of coumarins, with the highest amounts seen in the liver and kidneys. It has not been shown if oral administration of coumarin or its metabolites leads to significant buildup of tissue. The coumarin's elimination pathway is context- and dose-specific. In the next paragraphs, we will discuss the primary medicinal applications of coumarins. (Figure 2).

Scopoletin, esculetin, and osthole are the most well-described coumarins, and they have been shown to have a role in the regulation of several systems, including the cardiovascular and nervous ones. Coumarins are well-known for their cytotoxic effects against many cancers because to their many antineoplastic characteristics. N-(4-((2-((2-oxo-2H-chromen-4-yl)oxy)phenyl)-2-(piperidin-1-yl)acetamide) *9d; 3-(1H-benzo[d]imidazol-2-yl) *4d.-6-chloro-2H-chromen-2-one.

III. CYTOTOXICITY ASSAY OF COUMARINS SVCM1-SVCM7

The coumarin derivatives SVCM1-SVCM7 were tested for toxicity against UACC-62 (Melanoma), MCF-7 (Breast Cancer), and PBMC (Peripheral Blood Mononuclear Cell) cell lines using the MTT assay. Extremely harmful coumarin compounds have their IC50 values analyzed.

The most lethal compounds against both UACC-62 (Melanoma) and MCF-7 (Breast Cancer) cells were SVCM1, SVCM2, SVCM4, and SVCM5. UACC-62 (Melanoma) and MCF-7 (Breast Cancer) cell lines saw a 97.4, 97.9, 94.7, and 90.8% death rate at 50 g/ml and a 96.8, 90.9, 92.9, and 94.2% mortality rate, respectively. A summary of these results may be

seen in Tables 1 and 2. To demonstrate the chemicals' effects on healthy cells, we utilized PBMC (Peripheral Blood Mononuclear Cells) as a reference standard (Table 3).

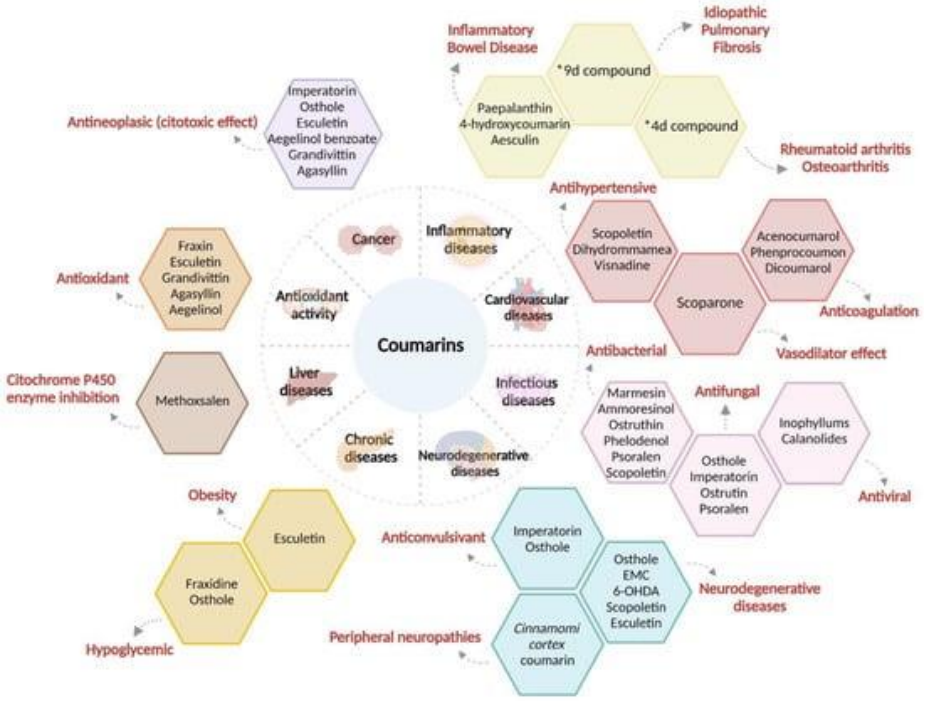

Fig.2. Properties and pharmacological effects of coumarins and coumarin derivatives against human diseases.

Table 1 Cell inhibition (%) of the synthetized coumarins against UACC-62 (Melanoma) cell atthe concentration of 100 µg/mL and 50 µg/ml

Compounds	100 µg/mL	50 µg/mL
SVCM1	98.5±0.003	**97.4±0.010**
SVCM2	91.5±0.012	**90.8±0.009**
SVCM3	50.0±0.08	**25.1±0.28**
SVCM4	98.0±0.003	**97.9±0.004**
SVCM5	95.9±0.017	**94.7±0.006**
SVCM6	50.8±0.06	**19.4±0.12**
SVCM7	29.6±0.06	**22.6±0.11**
Doxorubicin	--	**92.8±0.009**
Untreated	**--**	**2.8±0.195**

Values are mean ±SD (n=3)

Table 2: Cell inhibition (%) of the Synthetized coumarin against MCF-7 cells at theconcentration of 100 µg/mL and 50 µg/ml

Compounds	100 µg/mL	50 µg/mL
SVCM1	97.3±0.001	**96.8±0.003**
SVCM2	95.7±0.008	**94.2±0.011**
SVCM3	32±0.04	**26±0.07**
SVCM4	91.1±0.007	**90.9±0.008**
SVCM5	94.3±0.009	**92.9±0.002**
SVCM6	31.4±0.043	**28.6±0.03**
SVCM7	15.1±0.08	**14.2±0.06**
Doxorubicin	--	**90.3±0.008**
Untreated	**--**	**1.2±0.02**

Values are mean ±SD (n=3)

Table 3: Cell inhibition (%) of the Synthetized coumarin against PBMC cells at the concentration of 100 µg/mL and 50 µg/ml

Compounds	100 µg/mL	50 µg/mL
SVCM1	-151.53±0.006	**-95.95±0.005**
SVCM2	-154.08±0.016	**-98.23±0.005**
SVCM3	0.26±0.002	**-2.53±0.002**
SVCM4	-10.97±0.011	**-9.11±0.02**
SVCM5	-169.64±0.011	**-98.23±0.004**
SVCM6	4.85±0.002	**0.25±0.002**
SVCM7	7.14±0.004	**9.37±0.006**
Doxorubicin	18.11±0.002	**21.66±0.001**
Untreated	**--**	**-1.79±0.001**

Values are mean ±SD (n=3)

The IC50 values of the compounds SVCM1, SVCM2, SVCM4, and SVCM5 were determined using the UACC-62 (Melanoma) and MCF-7 cell lines. The IC50 for SVCM2 ranged from 28.78 to 30.93% across both cancer cell lines, as shown in Table 4. All of the compounds tested demonstrated selective effects on the cancer cell lines. Compared to the positive control, doxorubicin, the cytotoxic effects of SVCM1, SVCM4, and SVCM5 were much higher in UACC-62 (Melanoma) cancer cells.

Table 4: Table showing the IC_{50} (µg/ml) of compounds SVCM1, SVCM2, SVCM4, SVCM5 against UACC-62 (Melanoma) and MCF-7 cancer cells

Compounds	UCAA-62(Melanoma)	MCF-7
SVCM1	19.12±0.01	**20.73±0.02**
SVCM2	30.93±0.05	**28.78±0.02**
SVCM4	7.282±0.03	**15.39±0.01**
SVCM5	1.772±0.01	**21.96±0.04**
Doxorubicin	**0.09±0.01**	**1.61±0.01**

Values are mean ±SD (n=3)

Inhibitory concentrations (IC50 g/ml) of SVCM1, SVCM2, SVCM4, and SVCM5 against UACC-62 (Melanoma) and MCF-7 cancer cells are shown in Figures 3 and 4, respectively.

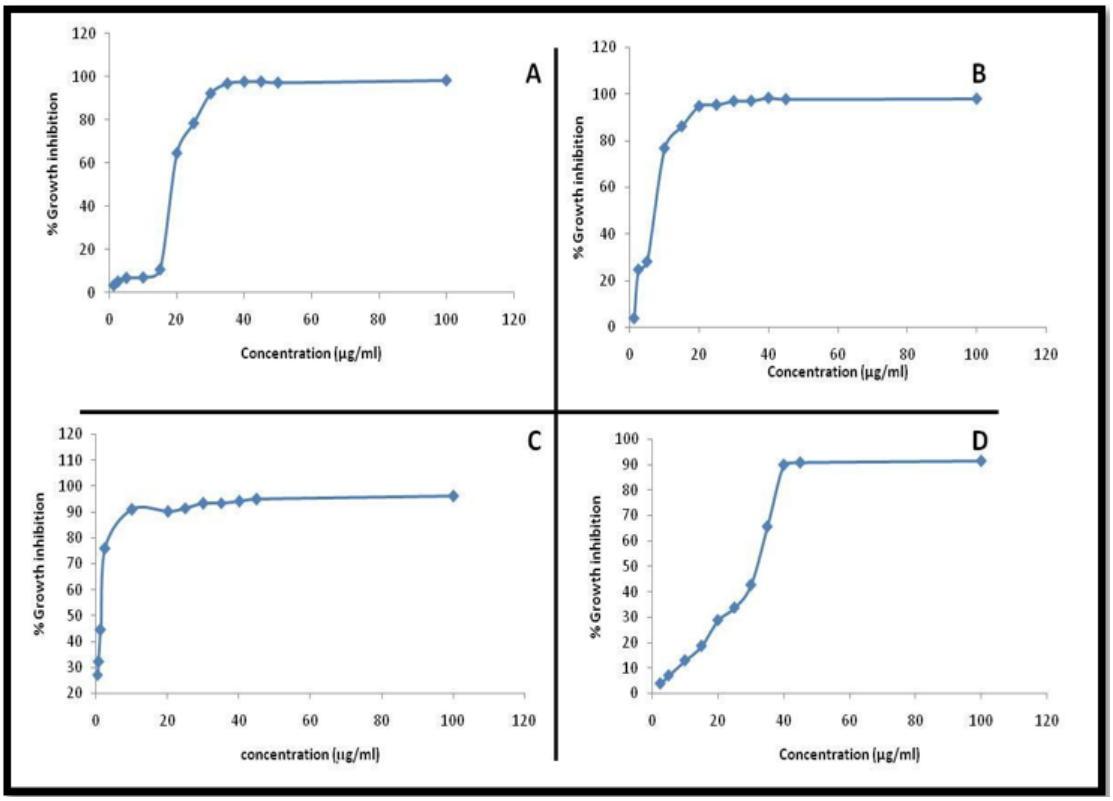

Fig.3 Inhibitory concentration of the substituted halogenated coumarins that killed cells by 50% (IC_{50}): (A) SVCM1; (B) SVCM4; (C) SVCM5; (D) SVCM2 against UACC-62 (Melanoma) cell line.

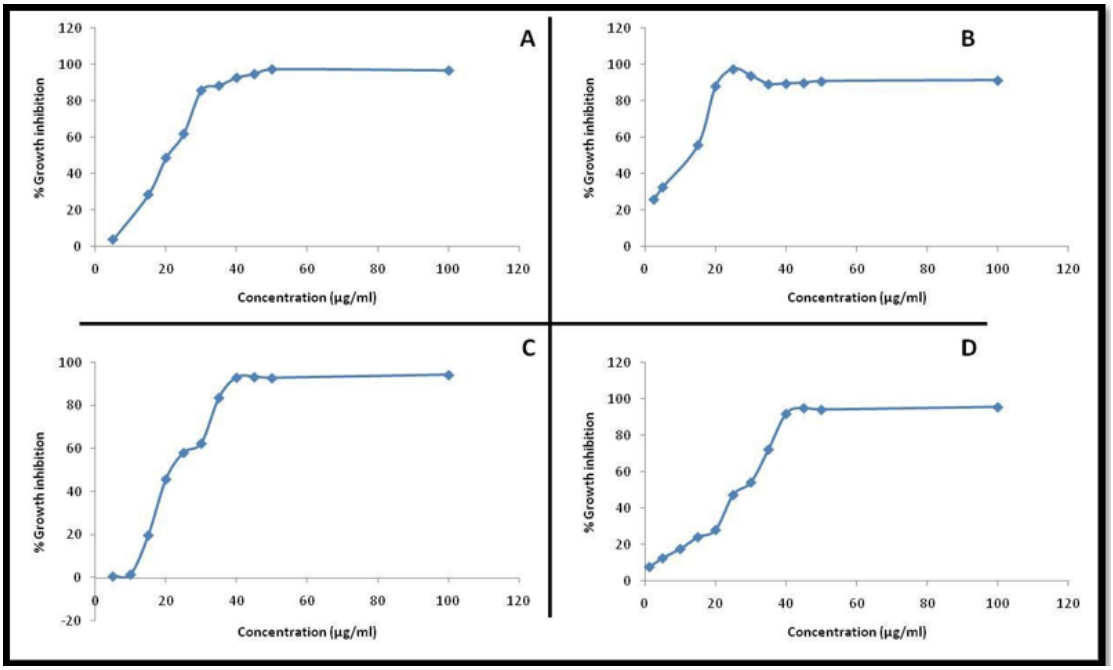

Fig.4 Inhibitory concentration of the substituted halogenated coumarins that killed cells by50% (IC_{50}): (A) SVCM1; (B) SVCM4; (C) SVCM5; (D) SVCM2 against MCF-7 (Breast) cell line.

IV. CONCLUSION

In an in vitro cytotoxicity assay, the compounds SVCM1, SVCM2, SVCM4, and SVCM5 were more effective than SVCM3, SVCM6, and SVCM7 against the melanoma and breast cancer cell lines UACC-62 and MCF-7. These compounds were shown to induce morphological changes, membrane modifications, and mitochondria membrane rupture in UACC-62 (Melanoma), hence activating the caspase-3 and causing apoptosis.

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