International Journal of Research
Available at http://internationaljournalofresearch.org/
p-ISSN: 2348-6848
e-ISSN: 2348-795X
Volume 02 Issue 03
April 2015

Cytotoxic Activity of Coumarin Derivatives and Their Complexes

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Abstract

Coumarin consists of a natural compounds group, which is found in different plants. Those Coumadin's, which are secluded from the plant, displayed that their compounds had a pasmolytic and hypotensive state, which has a vital role in plant biochemistry and physiology, by acting not only as antioxidants and enzyme inhibitors but as a precursor of toxic elements as well. Furthermore, these compounds have an essential role to play as plant growth hormones, growth regulators, respiratory control, and photosynthesis and as a defence mechanism against any kind of disease. They also play a role at various levels of cancer development since some of them have cytostatic characteristics, while others have cytotoxic effects on the organism. Thus shown, that the ancient correlation of plant coumarins with different animal and other species during evolution is the reason for the extensive spectrum in biochemical and pharmacological effects of these chemicals in biological arrangements. Metalo proteins, which are the hub of enzymatic process, which display an important role in biological arrangements. They discover the structure of active locations and play their part as biological redox assisters. Various cases proved that metal complexes of coumarin exhibited increased biological activities as compared to their ligands. As a result of their half-filled orbitals, transition metal display different oxidation states, and a diversity of coordination structures and ligand spheres.

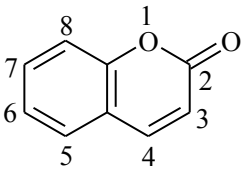
Key words: Coumarin derivatives, Complexes, Cytotoxic activity.

Introduction

The broad advancements of science are relevant to the materialization of bioinorganic chemistry. It is a subject matter which incorporates both biology and inorganic chemistry, according to (Jr &

Banci, 2002). This area of study includes the observations of metal ions and their complexes in a biological arrangement: how they operate, how they develop and their storage and application (Broderick & Coucouvanis, 2003). In order to carry and store oxygen in the body, iron prophyrin complex, which is a part of the haemoglobin, is essential. Similarly, in order to carry out the photosynthetic process of transporting an electron or for cross membrane proteins; iron and copper centres have proved to be fundamentally important (Kaim & Schwederski, 1994). Cobalt, another metal, which is necessary for transporting alkyl groups from a single molecule to the next in a biological arrangement, is found in coenzyme, B12 (Roat & Malone, 2007). In various enzymes, manganese, a metal, participates as a redox centre. Thus, this proves that metals prove a vital part in biological arrangements and are necessary in order to execute different actions.

The latest developments in bioinorganic chemistry have incorporated in them the usage of metal ions so that therapeutic and imaging agents can be established. One of the most fundamental goals of bioinorganic chemistry field is the advancements of coordination complexes which can then be adjusted to the biological arrangements. According to Sadler & Guo (1998), the pharmacological actions carried about by the metal complexes are dependent on the metal ion, its ligands and the infrastructure of the complex. In the studyh of bioinorganic chemistry, azo and bis azo Coumarin transition metal complexes have proved a fascinating compound. Coumarin (1,2-benzopyrone), which is the molecule from which coumarin has been acquired, is an elementary compound in a huge class of phenolic substances, which not only materialize uniformly, but consist of fused benzene and α-pyronering, according to (Keating & Kennedy, 1997). These compoundsm are an element of the benzopyrone class, which is fundamentally important in two ways: the diversity in both its infrastructure and its biology.



Coumarins, higher than 1300 in numbers, have been found from the habitual origins. These habitual origins and compounds are essential for progressive arrangements and synthesis of the increasingly effective parallels. Coumarins, both natural and unnatural, were confirmed to have anti-

inflammatory, anticoagulation, estrogenic, dermal photosensitizing, vasodilator, molluscicidal, antihelmintic, sedative, hypnotic, hypothermic and antiulcer roles. Included in the coumarin nucleus are various components which energetically control the biological motion of the emerging derivatives (Hsiang lin et al., 2011). Included in the characteristics of coumarins are their cytotoxic effects, which have been minutely analysed. Their wide area of effects on tumours is obvious by different sorts of examinations carried out in vitro and in vivo, and in scientific analysis. Therefore, the cytotoxic coumarins show a susceptible source of advanced anticancer agents. These agents could probably assist in side-toxicity and the resistance phenomena. Thus, it can be said that coumarins have different characteristic and can have completely varied effects on the various cellular arrangements in the body. Coumarin consists of a natural compounds group which is found in different plants. Those coumarins which are secluded from the plant displayed that their compounds had a pasmolytic and hypotensive state, which has a vital role in plant biochemistry and physiology, by acting not only as antioxidants and enzyme inhibitors but as a precursor of toxic elements as well. Furthermore, these compounds have an essential role to play as plant growth hormones, growth regulators, respiratory control, and photosynthesis and as a defence mechanism against any kind of disease (Kostove et al., 2001). 7-hydroxy coumarin is the operating metabolite of coumarin Kostova et al. (2001) for human malignant cell lines, for instance A549, HL-60, MCF7, coumarin and 7-hydroxy coumarin were both discovered to be cytostatic that is, growth inhibitors and preventers. This derivative has been acknowledged for its antibiotic and antifungal processes and the coumarin derivatives have also been widely adopted for analytical use.

Complexes of Coumarin

A lot of fascination has occurred due to the complexes of transition metal ions. The capability of coumarins to attach to metal icons shows another way of modulating their pharmacological feedback. 3d transition metal ions have become a widely known area of interest and importance in bioinorganic and coordination chemistry. It is due to the fact that they have the required competence for chelates formation with various cations, which are followed by a colour change at different levels of pH. The

main characteristic of the chelate formation is its increased stability, since it has a structure of six membered rings. According to (Kostova et al., 2005). In order to advance the efficiency of the compound an addition of hydroxyl components in coumarin rings would assists while, on the other hand, an addition of azo group to hydroxyl coumarins would assist in raising its chelating impulse. Furthermore, monohydroxy compounds, which consist of a coumarin nucleus, also have a huge significance. Metalo proteins, which are the hub of enzymatic process, which display an important role in biological arrangements. They discover the structure of active locations and play their part as biological redox assisters. Various cases proved that metal complexes of coumarin exhibited increased biological activities as compared to their ligands, as described by (Kostova & Momekov, 2006). As a result of their half-filled orbitals, transition metal display different oxidation statrs, and a diversity of coordination structures and ligand spheres. A huge variety of coordination compounds and the workings of cytotoxic actions have been carried out in reference to the advancement of the advanced antitumor agents. Recently, various researches have shown the binding of complexes coumarin derivatives with metals which have the characteristics of biological activity. According to Kostova & Stefanova (2010) the research regarding the binding characteristics of coumarin derivatives to various metal ions is an extremely essential area of study in order to completely appreciate the determinants influencing their biological activities. It has also been discovered that the attachments of a metal to a coumarin derivate not only sustains its biological activity but, in fact, boosts it. The capability of complexation of 6-hydroxy-4-methyl coumarin derivatives with transition metal ions has not been announced up till now. However, it is predicated that metal complexes of this compound will not only sustain but also boost their biological activity similar to the process of transition metal complexes with hydroxycoumarin derivatives.

2 Biological Activity of Coumarin

One of the foremost causes of fatality in developed countries happens to be cancer and agents capable of cytotoxic action which are being hunt down. Indicating to be an important source of motivation for the design of structural analogues with better pharmacological profile, are natural products with their capacity to interact with more than one target. On behalf of their

extraordinary range of biological activities, generally coupled with low toxicity, coumarins are a vital family of natural and synthetic origin that has been drawing great interest lately. Cell proliferation, as shown, is repressed by 4-hydroxycoumarins derivatives bearing an aryl group in the 3 position of the coumarin skeleton. According to a fresh study, it has been revealed that without affecting a non-tumoralfibroblastic cell line the most simple 4-hydroxycoumarin results in selective cytoskeleton disorganization in melanoma cells (Serra et al., 2012). Anti-mutagenic anti-bacterial, anti-thrombotic, lipoxygenase and cyclooxygenase inhibition, scavenging of reactive oxygen species, vasodilatory, and anti-tumour are the biological effects seen. Coumarin derivatives, according to some studies, having a substituted hydroxy group at the position 7 are responsible for antibiotic and antifungal activities while the hydroxyl group on the coumarin ring is essential for its anti-cancer activity. The influence of the coumarin skeleton and substitutions at Positions 3 and 7 on antitumor activities has been confirmed by earlier studies. 7-hydroxycoumarin and coumarin are powerful cytotoxic and cytostatic agents according to the in-vitro effects of coumarins on the augmentation of renal cell carcinoma-derived cell lines. Cancer cell viability can be diminished and DNA synthesis can be halted by hydroxylated derivatives containing substituted carboxylic group at Position 3 as suggested by some studies (Hong.Li et al., 2014). Via refluxing Coumarin-4-carboxaldehyde and o-aminothiophenolin acetic acid, a series of Coumarin substituted benzothiazoles have been synthesized and IR, ^{1}H NMR and mass spectroscopy characterizes these compounds. Reasonable to first-class anti-breastcancer activity was revealed by most of the compounds after all the compounds were checked for their anticancer activity against MCF-7 breast cancer cell line with MTT assay. It was discovered that the activity of the compounds was augmented after 48 hours as compared to 24 hours when cytotoxicity was checked at both durations (Kini et al., 2012). Goel et al. (2009) on account of the influence of its thiocoumarin derivative 7,8-diacetoxy-4-methylthiocoumarin (DAMTC) and the antioxidant coumarin 7, 8-diacetoxy-4-kmethylcoumarin (DAMC) itself on human non-small cell lung cancer A549 cells, makes it the subject under examination. The outcomes reveal that apoptosis was also fostered along with the reticence of cell propagation by both DAMC and DAMTC, and this apoptosis as established by flow

cytometric analysis, morphological examination and annexin-V assay, was with an IC50 of 160µg/ml. Fascinatingly, it was seen that these two induced apoptosis in malignant cells but showed evidence of modest cytotoxicity towards peripheral blood mononuclear cells.

The synthesized compounds, as a result, showed reasonable to powerful antimicrobial activity against E. coli and S. aureus in the antimicrobial activity of the synthesized compounds of coumarinsassessed against a panel of nine bacterial strains using broth micro-dilutionmethods (Medyouni et al., 2013). In conjunction with benzo[5,6]coumarin-3-carboxylicacid(**1**a) and 7-(*N,N′*-diethylamino)-coumarin-3-carboxylic acid (**2**a), against the SGC-7901 cell lines determined by Sulforhodamine B(SRB) assay, some novel dicoumarin derivatives, triethylene-glycol dibenzo[5,6] coumarin-3-carboxylate(**1**a), triethylene-glycol di[7-(*N,N′*-diethylamino)]-coumarin-3-carboxylate(**2**a) synthesis and the cytotoxic effect of these compounds. 50% inhibition of the cell viability of SGC-7901 cells at micromolar concentrations was induced by the investigated dicoumarinderivatives as a result of the initial cytotoxicity screening process. Agent with PEG moiety has a greatr role in cell-killing ability of the molecules than the rest of the agents. As compared to compound **1**a, compound **2**a was proved superior consistent with the attained IC50 values (Zhang et al., 2009). Evaluation of their anti-tumour activity and preparation of novel compounds that have both coumarin and chalcones bodies in one molecule are next. Preparation of target compounds resulted from several 3-acetylcoumarin with methoxybenzyloxy moiety in 6 or 7 position of coumarin ring synthesized by aldol condensation of 3-acetylcoumarins with a variety of aldehydes. H, C-NMR and Mass spectra characterized all of the target compounds. Fine to outstanding activity for these compounds was shown by assessment of manufactured compound for their anti-tumour activity (Molaverdi et al., 2012). To scrutinize chemical and biological properties of the products of the reaction of methylchromone-3-carboxylate,3-formyl-4-hydroxycoumarin,3-formylchromone and ch- romone 3-carbonyl chloride with phosphorushydrazides was what this work aimed to achieve. ^{1}H, ^{13}C, NMR spectroscopy was used was put to use for structure and keto-enoltautomerism analyses. In reaction of phosphorus hydrazides with chromone-3-carbonyl chloride and 3-formylchromone, the

chromone series and was obtained. The solution was dominated by the ring transformation species consisting of the coumarin ring. Antitumor and antibacterial activity of some compounds was checked and in vitro antitumor activity against P388 leukemia was displayed by them. Using L1210 murine leukemia, antineoplastic activity of the compounds united with methotrexate was confirmed. In-vitro Preussmann test (NBP test) determined alkylating activity of phosphorohydrazides of coumarin and chromone (Nawrot Modranka et al., 2006). 50% inhibitory concentration (IC50 values) of 18 coumarins and four cinnamic acid derivatives were deliberated to examine the structure–activity association of coumarins for the inhibitory activity on mushroom tyrosinase. Esculetin had the best inhibitory activity (IC50 =543µM) on mushroom tyrosinase among these and addition of a hydroxy group to the C6 and C7 positions of the coumarin ring and no substitutionon the lactone ring played a vital role in this. Without upsetting cell growth, 5µM considerably repressed the production of melanin in murine B16 melanoma cells. Moreover, as compared to that in the control, the number of 3,4-dihydroxyphenylalanine (DOPA)-positive melanocytes in the split-epidermal sheets treated with 0.05% or 0.1% esculetin was considerably lesser. These results compelled us to conclude that in vitro, esculetin has stopping effects on tyrosinase activity (Masatomo et al., 2003). Elemental analysis, IR, ^{1}HNMR, ^{13}C NMR, ^{19}F NMR, EI-MS, and FAB-MS characterized all the freshly synthesized compounds Kalkhambkar et al. (2008) studied anti-microbial, anti-inflammatory and analgesic activities new fluorinated coumarins and azocoumarins and the presence of fluorine were synthesized and tremendous anti-inflammatory and potential anti-bacterial and anti-fungal activities contrasted to the other halogenated compounds were displayed by them according to the results of bioassay. Basing on the spectral data (^{1}H,^{13}C-NMR, UV, IR and EI mass), the 6 new 4-methylcoumarins with performances which are unlike each other for instance amino, hydroxy, N-acetyl, acetoxy and nitro have been produced and established. On behalf of their influence on liver microsomal lipid peroxidation which is NADPH reliant in vitro, they were for the first time inspected and the results were compared with other model 4-methylcoumarinderivatives. This was done in order to determine the structure–activity relationship. A remarkable inhibition of lipid peroxidation occurs by the substitution

of the hydroxyl group for antioxidant property. Highest antioxidant and radical scavenging activities were possessed by ortho dihydroxy and ortho hydroxy-amino coumarins (Tyagi et al., 2005).

Since this study proceeded in stages, preparing and diagnosing four compounds of Schiff's-bases through condensing 3-amino coumarin with aldehyde aromatic was the first stage. The reaction of the prepared Schiff's-bases with the compound 4-hydroxy coumarin formed the second one. Study of the biological effects of the prepared compounds towards Staphylococcus aureu, Bacillus subtilis, Bacillus cereus, Psedomonaseaeruginosa which are some Gram positive bacteria and Gram negative bacteria. Against Aspergllusniger, penicilliumitalicum and fusariumoxysporum too which are some fungi (Abdkhadom, 2007). To screen their anticoagulant activity in rabbits so as to define in more precise expressions the structural features that are accountable for the anticoagulant activity of coumarins, the synthesis of three series of new coumarin derivatives was done. To give derivatives, esterification of the 7-hydroxycoumarin with benzoic acid, salicylic acid and 5-amino salicylic acid was carried out for first series. Construction of amide linkage between 6-aminocoumarin and benzoic acid, salicylic acid and 5-amino salicylic acid to provide derivatives resulted in the second series synthesis. Esterification of the coumarin-6-carboxylic acid with phenol, resorcinol and *m*-chlorophenol to give new derivatives formed the third series. Through Quick's one-stage method, the anticoagulant activity of these derivatives was scrutinized in rabbits. Prior to and subsequent to dispensing through mouth, kept under deliberation was the prime influence of every derivative on the time of prothrombine for 5 rabbits. In order to typify the chemical structure of these derivatives, spectroscopic and physical modus operandi e.g. FTIR, UV and ^{13}C-NMR spectra were put into practice. Through escalating the prothrombine time, the derivatives showed significant anticoagulant activity depending on prothrombin time measurements. Separated from a hydroxyl group by short carbon side chain showing anticoagulant activity, according to this study, the coumarin derivatives had an esterlinkage at position 6 or 7 (Mustafa, 2012). Verified productively under mild reaction conditions is the universal, easy and clear-cut approach to fresh substituted coumarin derivatives using Betti's condensation reaction of aromatic aldehydes, coumarin and

ammonia precursors. Structures intended to intermingle with both Gram positive and Gramnegative bacteria, reported the design and calculated molecular properties of some coumarin derivatives on the basis of hypothetical antibacterialpharmacophores and IR, ^{1}H NMR, ^{13}C NMR, Mass spectrometry and elemental data characterized all the synthesized molecules. Explained and confirmed experimentally are the activities, relationship of these compounds regarding molecular modelling, correlation of structure, Lipinski rule of five, drug likeness, toxicity profiles and other physico-chemical properties of drugs (Parvez et al., 2010). By difference in vitro models e.g. (DPPH) free radical-scavenging activity, linoleic acid emulsion model system, plummeting power assay and phosphomolybdenum method, a series of imino and amino derivatives of 4-hydroxycoumarins were synthesised and assessed for antioxidant potential. Antimicrobial activity of acquired coumarins, evaluated against eight fungi and 13 bacteria was also included. Among the map-nitrophenol derivatives with IC 50 at 25.9 µM possessed radical-scavenging activity analogous to BHT and high-quality antioxidant activity were all owned by the entire set of compound prepared. While imines showed improved antifungal properties, all tested amino derivatives displayed strong antibacterial activity according to the observed data (Vukovic et al., 2010). By intermolecular condensation reaction of 2-hydroxyacetophenones and 2-hydroxybenzaldehyde with imidazolylphenylacetic acid energetic intermediates, a series of coumarin analogues having a substituted phenyl ring on position 3 were synthesized by a novel methodology. Two dissimilar antioxidant assays (radicalscavenging capability of DPPH stable free radical and inhibition of lipid peroxidation encouraged by the thermal free radical AAPH) the in vitro antioxidant activity of the synthesized compounds was estimated. The aptitude of the compounds to hinder soybean lipoxygenase, a sign of potential anti-inflammatory activity was also a part of this (Roussaki et al., 2010). For c-carboxylation of key glutamicacid residues in blood clotting proteins by vitamin K-reliant carboxylase, Vitamin K happens to be an indispensable cofactor and coumarin anti-coagulants are well thought-out as anti-vitamin K in nature. Vitamin K is rehabilitated from the active form to vitamin K 2, 3-epoxide throughout catalysis. To preserve the coagulation cycle, this must be recycled to the active form by vitamin K epoxide reductase

(VKOR). 9, 10 4-hydroxy coumarins provoke VKOR and prevent vitamin K recycling and hence an accretion of anomalous form of coagulation protein called des-γ-carboxyprothrombin(DCP) occurs. If not, then proteins induced by vitamin K antagonism (PIVKA-II) are accumulated. The VKOR antagonistic effects check the action of the coumarin-type drugs and related compounds. Twenty 3-pyridinyl, pyrimidinyl and pyrazolyl-4-hydroxycoumarin derivatives have been synthesized in this study and they have poles apart anticoagulant activities. This was shown by comparative analysis between vivo (CT, PT determination) and in vitro (measurement of PIVKA-II levels) with regard to warfarin. 3-pyrazolyl-4-hydroxy coumarin derivatives presented to be the most potential compounds (Abdelhafez et al., 2010). New drugs can be prepared for which hybrid molecules formed by merging various pharmacophores can be created and hence a number of compounds may be manufactured possessing an appealing biological character. Lately, by utilizing agents with changed working methods, combination chemotherapy happens to be one of the techniques being implemented to treat cancer. Hence for the treatment of cancer, a single molecule enclosing more than one pharmacophore, each with a changed mode of action could be very advantageous. Consequently, as reported, hybrid molecules by pairing coumarins with different bioactive molecules like: resveratrol, maleimide and alphalipoicacid have resulted in new compounds carrying antiplatelet, antioxidantand anti-inflammatory activities after taking on this approach. Anti-cancer activities of stilbene-coumarin hybrid compounds have also been investigated thoroughly. Moreover, a series of coumarin-chalcone hybrids represented noteworthy taxol resistant cancersinhibition. After being aspired by this study a number of fresh compounds comprising both coumarin and chalcones units embodied in a single molecule and possessing the capability to perform antitumor activity are being drafted and composed. A round of coumarin-chalcone hybrids have been manufactured and reviewed for their in vitro cytotoxicity in opposition to regular fibroblasts (NIH3T3) along with a team of 4 homo-sapiens cancer cell lines. 3 composites displayed an IC50 range lying in the midst of 3.59 to 17.97 μM out of the 21 composites that were monitored. The best compound displayed about 30-fold additional percipience en route for C33A (cervical carcinoma) cells as compared to regular fibroblast NIH3T3

cells with 3.59 µM being their IC50 value (Sashidhara et al., 2010). Found in wine, vegetables, seeds, nuts, fruit, coffee, and tea, the Benzopyrones are a group of compounds whose members comprise coumarins and flavonoids. Nutritional exposure to benzopyrones is noteworthy. 1g/day of mixed benzopyrones are there in a regular western diet. This is the reason why research into their pharmacological and therapeutic properties is in continuous progress. Owing to its metabolites, (e.g. 7-hydroxycoumarin) coumarin is a natural substance that has displayed anti-tumour activity in vivo. For this reason, these relevant compounds and their therapeutic importance is highlighted. The release of Cyclin D1, which is over-expressed in various types of cancer, is inhibited by 7-hydroxycoumari. The G1 phase in HL-60 leukaemia cells consequential from the reticence of retinoblastoma protein phosphorylation is seized and hence esculetin brings development and cell cycle succession to a halt. From the treatment of leukaemia to that of patients with human immunodeficiency virus, modern studies exploring the prospective of flavonoids being utilized as curative agents have revealed that they may have use in a range of remedial situations. Being a tyrosine kinase inhibitor and a renowned isoflavone, studies suggest that genistein may be a possible contender for cancer treatment since it kindles hampering effects on cell growth of different cancer cell-cultures. Investigation of the effects of coumarins and coumarin-related compounds on a panel of cell-lines has also been done. MCF-7 a breast carcinoma and A549 a lung carcinoma are two cell lines involved in this. Via a biosensor called the Cytosensormicrophysiometer, microtitre assays were carried out along with real-time examination of cell viability. The most powerful inhibitory effect on cell growth in contrast to the other two compounds, according to the studies, was displayed by genistein and esculetin (Lacy& Kennedy, 2004).Via the microculturetetrazolium (MTT) assay with IC50 values exceeding 100 µM, the cytotoxicity of 22 natural and semi-synthetic simple coumarins estimated in GLC4, and in COLO 320 was checked. COLO 320 happens to be a human colorectal cancer cell line while GLC4 is a human small cell lung cancer cell line. Noteworthy potencies were shown by a number of compounds despite the fact that most coumarins showed evidence of merely squat cytotoxicity when subjected to MTT assay and subsequent continuous (96 h) incubation. It is evident that each and every one of the possibly active natural

compounds has no less than two phenolic groups in the 6, 7 or 6, 8 locations as regards the interests of structure-cytotoxicity relationship. Also, carefully considering the significance of no less than two polar purposes for high cytotoxicity, the 5-formyl-6-hydroxy substituted semi-synthetic analogue was revealed to be quite effective (Kostova, 2005). A sequence of chosen 4-methylcoumarins (4-methyl-2H-1-benzopyran-2-ones) underwent synthesis and testing for radical-scavenging capability and for this purpose the stable 1,1-diphenyl-2-picrylhydrazyl radical was used, while for reducing power ability the test was performed on the basis of reduction of ferric to ferrous cation. Each of the compounds under study were found to be showing activity similar to that of Trolox (6-hydroxy-2, 5, 7, 8-tetramethylchroman-2-carboxylicacid), which is a common antioxidant and is frequently used in most of the testing methods. The interpretations from the research were put forward after considering the structural characteristics which the compounds' behaviour was dependent upon. The first to present the antioxidant activity of 4-methylcoumarin representatives, and besides that it also adds to the current information regarding the range of important biological activities and probable roles in therapy and for food preservation that have a connection with the aforementioned group of compounds (Cavar et al., 2009). Synthesis of several novel 3-bromo-4-methyl-7-methoxy-8-amino substituted coumarins and 2-substituted 7-bromo-6-methyl-8H-pyrano-benzimidazoles, benzoxazoles and or benzoxazine-8-ones was performed in order to use them in pharmacological evaluation. From certain representative compounds was discovered antitumor activity in vitro on Ehrlich ascites carcinoma during the initial stage of testing (Nofal et al., 2000). The process whereby new blood vessels are formed from the already present host vasculatures through stimulation by biochemical stimulators is known as angiogenesis. Angiogenesis has a part to play in healing of wounds, development of embryos, and the female reproductive cycle, which undergoes complex regulations in normal vascular system. Nevertheless, malignant angiogenesis has a very important part to play in a number of fatal diseases, which include cancer, vascular insufficiency, diabetic retinopathy, and rheumatoid arthritis, by having oxygen and nutrients reach the cells and tissues via a normal delivering mechanism. The growth of solid tumours, their invasion and metastasis is most affected by tumour angiogenesis

which are triggered by angiogenic inducers, it is very important that angiogenesis are controlled during its early stage as that allows for a possibility of a more promising therapeutic strategy for the concerned diseases. This study will focus on the systemic screening of the antiangiogenic activity of coumarins and the synthesizing of a series of 7-dialkylamino-3,4-substituted coumarin derivatives. These compounds underwent the cell proliferation inhibitory test against cell lines like U87 MG, B16BL6, HeLa, DLD-1, SiHa, NIH 3T3, and HUVEC. One specific finding from comparing the growth inhibition activity next to HUVEC and other cell lines was that cyano groups when at the 4-position lead to increased bioactivity. Specifically, the compounds were found to be clearly inhibiting the different cancer cell lines from proliferating, and a high selectivity for HUVEC was seen. Thus, these coumarin molecules may substitute as lead compounds and nontoxic angiogenesis inhibitors and small molecular ligands can be developed through them for targeting HUVEC (Lee et al., 2006).

In order to find out the fundamental characteristics of the structure that determined the novel multidrug resistance (MDR) reversal activity, it was important that an introductory investigation was conducted of coumaric derivatives as MDR modulators. A fair reversal of MDR (fluorescence activity ratio (FAR) values >1) was induced by 14 compounds out of a 44 coumarins. 6-hydroxy-3-(2-hydroxyethyl)-4-methyl-7-methoxycoumarn was the most active compound and had a similar potency with that of a MDR modulator verapamil. The resultant findings point toward a link present between the chemical structure and MDR-reversal effect on tumour cells. The cytotoxicity of each of the coumarins tested was found to be more towards tumour cells as compared to toward normal ones. It was found that a number of these compounds showed powerful cytotoxic activities (CC5015-29 µg/mL in HSC cells) in comparison with that of gallic acid (CC50=24 µg/mL). The most tumour-specific cyto toxicity was found in both 6-hydroxy-7-methoxy-4-methyl-3-isopropylcoumarin and3-ethyl-6-hydroxy-7-methoxy-4-methyl-Coumarin (SI value=4.1 and 3.6, respectively). Coumarins come under the classification of strong new MDR modulators and are not very toxic to normal cells. The way their structure and potency are connected can be understood further as that will allow for the designing of optimal agents. When normal

tissues have been affected by the cytotoxicity and the tumours resist the drug, efficiency decreases. The main concentration of such researches has been molecular cancer chemotherapeutics, more toward drug resistance and tumour-specific cytotoxic drugs (Kawase et al., 2005). The application of a semiempirical molecular orbital method (CACHe) was done to explain the link between cytotoxicity against the human squamous cell carcinoma line HSC-2 (evaluated by 50% cytotoxic concentration, CC50) of 20 coumarin (2H-pyran-2-one) derivatives and twelve physical parameters, for whose calculation the CONFLEX/PM3 method is used. An extremely important link was found present between the CC50 and ionization potential, the highest occupied molecular orbital (HOMO) energy, variance between electron energy of HOMO and electron energy of lowest unoccupied molecular orbital (LUMO), or complete hardness (r^2=0.756~0.802). In contrast, no major link was found to be present between the CC50 and heat of formation, stability of hydration, dipole moment, electron affinity, or LUMO energy (r^2=0.13~0.36). On plotting CC50 vs. log P a parabolic curve was seen, and from the curve the maximum cytotoxicity (or the least CC50value) was found to be at log P of 2.5. From the current research it was found that, besides the property of electrons that makes them accept and donate, hardness and softness also have a significant role in the estimation of cytotoxic activity of coumarin derivatives. Nature has an extremely wide variety of coumarin (2H-pyran-2-one) and its derivatives and, therefore, they display an extensive pharmacological profile, which also includes anticancer activity plus the scavenging activity of superoxide anions whose generation is triggered by activated neutrophils. When substituents were introduced at C-2, C-4 or C-7 of the heterocyclic ring of coumarin, different biological activities were stimulated. Through an increase in the cytosolic translocation of cytochrome C and activating the cysteine protease 32 kD aproenzyme they have been found to stimulate apoptosis in human leukaemia cells. In spite of it all, not a lot of work was done for determining a link between the structure and cytotoxic activity of coumarins. The present study examined the link present between the 50% cytotoxic concentration (CC50) of 20 coumarin derivatives against the HSC-2 cell line and twelve physical parameters whose calculation was done using the CONFLEX/PM3 method (Ishihara et al., 2006). For this current research a number

of substituted hydroxycoumarin derivatives underwent synthesis. A link was formed between different alkyl and prenyl groups and the benzopyrone ring of three hydroxycoumarin scaffolds through the phenoxy group by means of an ether bond. This was done for examining their cytotoxic activity as novel anti-austerity agents. Synthesis of a sequence of hydroxycoumarin derivatives was carried out which were then assessed in relation with human pancreatic PANC-1 cancer cells under nutrient-deprived conditions. Examination of a number of compounds found that under nutrition-deficient conditions they showed 100% preferential cytotoxicity at low micromolar concentrations while cytotoxicity was absent under nutrient-rich conditions. The current research found novel geranylated coumarin derivatives to be having the most cytotoxic activity of 6.25 µM within 24 h. The favoured behaviour of the compounds against PANC-1 with regard to the anti-tumour activity under low oxygen and nutrient conditions shows that it can potentially turn out to be a very promising lead structure in developing novel agents to help fight against pancreatic (Devji et al., 2011). Several natural compounds are potentially therapeutic in nature but due to the toxic side effects that they exhibit, they need to be chemically modified. An examination was conducted of structural parameters which may be having an effect upon the cytotoxicity of isocoumarins similar to 9,10-dihydroxy-5,7-dimethoxy-1H-naphtho(2,3c) pyran-1 one (paepalantine1). Anti-microbial activity was found in Paepalantine1. The substance also had major in vitro cytotoxic effects in the McCoy cell line. Neutral red assay was the method used for testing, on the same cell line, two other natural and two semi-synthetic isocoumarins with similar formations acquired from the capitula of Paepalanthus bromelioides. The cytotoxicity of these compounds was reduced by substituting the 9 and/or 10-OH group. From the examination of the chemical structure/biological activity of the coumarins it was found that when a cathecolic group was added to the basic structure it lead to higher cytotoxic activity in tumour cell lines. The hydroxyls present in paepalantine 1 are located at positions 9 and 10 of the aromatic ring and this structure makes it like the cathecolic system. The cytotoxicity of isocoumarins is decreased when the free hydroxyls are substituted at positions 9 or 10. The structure of isocoumarins keeps changing because different kinds of substitutions keep occurring, and this affects their

biological activity (Devienne et al., 2002). Synthesis of several new coumarin and N-amino-2-quinolone derivatives was carried out. Coumarin (1) was reacted with excess of Hydrazine hydrate 98% and the yield was made up of 1-amino-2-quinolone (2). The reaction of Compound (2) with different Sulfonyl chloride yielded Sulfonamides [N-(2-oxoquinolin-1(2H)-yl) methane sulfonamide (3), N-(2-oxoquinolin-1(2H)-yl) Benzene sulfonamide (4) and 4-methyl-N-(2-oxoquinolin-1(2H)-yl) benzene sulfonamide (5)]. 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetic acid (6) was reacted with different amines yielding compounds 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2-oxoquinolin-1(2H)-yl) acetamide (7) N-(5-methyl-1,3,4-thiadiazol-2-yl) -2- (4-methyl-2-oxo-2H-chromen-7yloxy) acetamide (8) via amide linkage. TLC was used for checking the reactions and the purity level of the products formed. In order to make sure that the final compounds and their intermediates were correct and of the required structures, tests were performed to check their melting points, IR spectroscopy, and elemental microanalysis. The coumarin and N-amino-2-quinolone derivatives were assessed in order to check if any antibacterial and antifungal activity was present in them (Saour, 2012). In a research by Al-bayati et al. (2012), synthesis of 4-hydroxycoumarin was carried out to be used as the initial reactant, and was reacted with acetyl chloride, using pyridineas a base to form 3-acetyl-4-hydroxy coumarin 2. Following that Schiff bases were produced by treating 2 and hydrazine derivatives in boiling absolute ethanol. The last step of the experiment was the synthesis of pyrazole derivates by ring closure reaction of schiff bases with a little concentrated sulphuric acid being used as a catalyst. In order to make sure that the required and correct compounds had been formed they were undergone tests of FT-IR-spectra and CHN-analysis through which the proposed structures were verified. Some of the test compounds were then examined in vitro to get to know about their biological activity against certain bacterial and fungal microorganisms. Coumarin that had Schiff bases showed a good antimicrobial activity against Gram (+) bacteria while those having pyrazole derivatives were found to be having only a reasonable antibacterial activity against Gram (-) E.coli. A study by Manojkumar et al. (2009) aimed at synthesizing coumarinyl heterocycles and clarifying that these compounds could be acting antioxidants and cytotoxic agents against Dalton's lymphoma ascites tumour

cells (DLA) and Ehrlich ascites carcinoma cells (EAC). The report showed a synthesis of coumarin derivatives containing pyrazole, pyrazolone, thiazolidin-4-one, 5-carboxymethyl-4-thiazolidinone and3-acetyl-1,3,4-oxadiazole ring. A reaction was carried out of 4-Methylcoumarinyl-7-oxyacetic acid hydrazide (1) and arylazo propanes or hydrazono-3-oxobutyrate derivatives, resulting in the formation of pyrazole .and pyrazolone derivatives. When Schiff's bases of (1) with thioglycolic acid, thiomalic acid or acetic anhydride underwent heterocyclisation, it resulted in novel heterocyclic derivatives 4-thiazolidinones 5-carboxymethyl- 4-thiazolidinones and oxadiazoles respectively. Excellent potential antioxidant activity in vitro was found in certain compounds and cytotoxic activity against DLA cells and EAC cells.

Conclusion

The chemical syntheses and structural modifications of Coumarin derivatives and their complexes are of interest due to their biological activities and characteristic conjugated molecular architecture. This review summarized the recent synthetic approaches to coumarin derivatives and their complexes and the current state of research into their biological activities.

Acknowledgemnt

The authors would like to thank Faculty of Science and Technology, Universiti Sains Islam Malaysia (USIM) for providing the facilities for the research work.

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