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AN UPDATED REVIEW ON COUMARIN WITH SPECIAL EMPHASIS ON ANTICANCER ACTIVITY

[1]Astha, [2]Anju Goyal*, [3]Monika Gupta and [2]Rakesh K Sindhu
[1]Laureate Institute of Pharmacy, Kangra, Himachal Pradesh, India
[3]Chitkara College of Pharmacy, Chitkara University, Punjab, India
[3]A.S.B.A.S.J.S. Memorial College of Pharmacy, Bela Punjab, India

#Author for Correspondence:
"Dr. Anju Goyal, Professor and Head (Pharmaceutical Chemistry)
Chitkara College of Pharmacy, Chitkara University, Punjab, India"
E-mail: anju.goyal@chitkara.edu.in; anju_goyal2003@rediffmail.com

ABSTRACT

Coumarin moieties can be divided into two categories natural or synthetic. It has become a compelling subject of research for many investigators due to their broad spectrum of pharmacological potency. Coumarin scaffold has been reported to have inhibitory effect on number of cell lines serving as a pharmacophore of utmost importance for anticancer drug development. Coumarins act on tumour cells through different types of mechanisms and few of them have been reported to possess high selectivity towards the cancer cell lines. In present work, the role of coumarins as potential anticancer drugs has been briefly reviewed which may serves as a magnificent tool for future explorations of design, synthesis and biological studies of these kind of derivatives.
***Keywords*: Coumarin, Benzopyrones, Anticancer**

Introduction

"Cancer is a major public health burden both in the developed and developing countries". About one in four persons is suffering from cancer during his or her lifetime and at present about one in five of all deaths is due to cancer (Sharma *et al.*, 2017). From the literature survey, researchers reported that coumarin play an important role in the anticancer activity. Coumarins are wide class of natural and synthetic compounds exhibiting versatile pharmacological actions (Han *et al.*, 2015). Coumarin belong to benzopyrone family of medicinal agents, in which benzene ring and pyrone ring are joined together. The benzopyrones (Figure 1) can be subdivided into the benzo-α-pyrone (1a), benzo-γ-pyrone (1b).

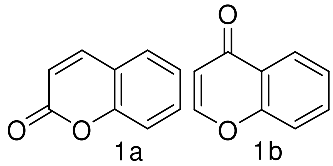


Fig. 1 : Types of coumarin

They differ from each other only in the position of carbonyl group in heterocyclic ring. The benzo-α-pyrone is also known as coumarins (Wang *et al.*, 2006). Coumarin was first synthesized in 1868 (Holagunda *et al.*, 2014). Coumarin can be synthesized by pechmann condensation, Perkin, Knoevenagel, witting. Several studies have investigated the possible use of simple coumarin such as Scopoletin (Figure2), "7-hydroxycoumarin" (Figure 3) in treatment of cancer cells (Yadagiri *et al.*, 2014). Coumarin exhibited antitumor activity at different stage of cancer formation through various mechanisms.

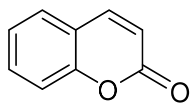


Fig. 2 : Scopoletin

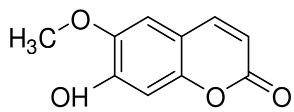
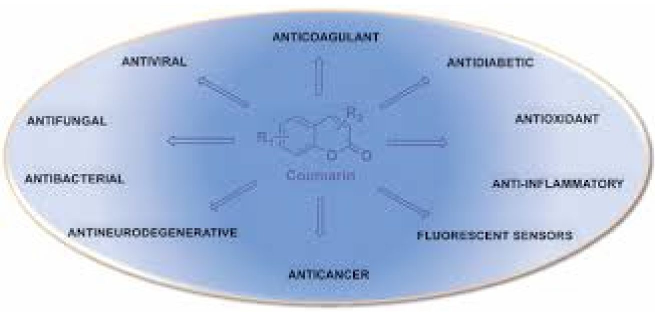


Fig. 3 : 7-Hydroxycoumarin

Mechanism of action

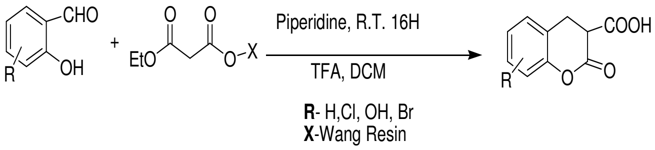
Depending upon the structure of Coumarins, they act on several tumors' cells by discrete mechanisms *viz.* inhibition of the tolemerase enzyme, inhibition of protein kinases and down regulation of oncogenes expression or induction of apoptosis mediated by caspase-9which overpower proliferation of cancer cells and arrests "cell cycle in G0/G1 phase, G2 /M phase". (Nawrot-Modranka *et al.*, 2006).

Biological activity of coumarin



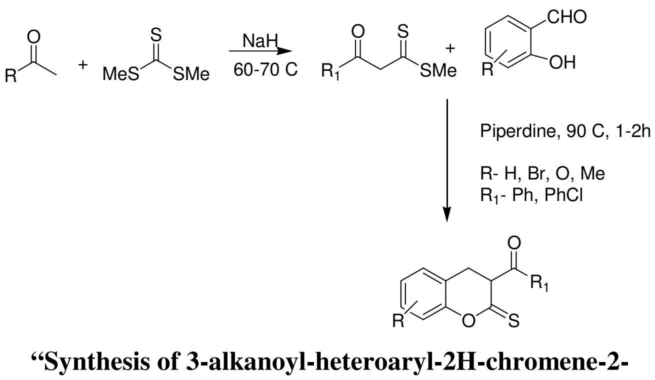
SYNTHESIS OF COUMARINS

Watson *et al.* (2020) discover and synthesis coumarin catalyzed by piperdiene, compassionate synthesis of substitute "coumarin-n-carboxylic acid derivatives by using Knoevenagel condensation reaction between ethyl malonate" hydroxybenzaldehydesat room temperaturein the presence of pyridine (Birkenkamp *et al.,* 2008). Carboxylic acid is commonly used resin in peptide synthesis. Ethylmalonate was firstly bounded with carboxylic acid and then it re-joined with hydroxybenzaldehydes, "which produced coumarin-n-carboxylic acid derivatives" (Moreira *et al.,* 2007).



Synthesis of coumarin-n-carboxylic-acid

"Singh *et al.* (2020) discovered and" synthesized coumarin of a "3-alkanoyl-heteroaroyl-2H-chromene-2-thiones using b-oxodithioesters" and few hydroxybenzaldehydes in the presence of piperidine under solvent (Aslam *et al.,* 2010). B-oxodithioesters synthesized by ketones and dimethyl tri thiocarbonate. The various "solvents such as dimethyl sulfoxide, dimethyl formamide, and acetonitrile" can be used for synthesis (Frosch *et al.,* 2002).



"Synthesis of 3-alkanoyl-heteroaryl-2H-chromene-2-thiones"

Anticancer activity of coumarin

Ravindra K. Rawal *et al.* (2020) reviewed an illustration of various coumarin hybrid molecules with their SAR. They reviewed that breast cancer is second major route cause of mortality in women after lung cancer. This become the major reason for continuous development of advanced and hybrid therapeutic agent which are capable to treat breast cancer partially or completely in recent year and still in progress. The literature review reveal that advanced coumarin derivatives possess remarkable potency for treatment of breast cancer.

Maja Molnar *et al.* (2020) "Coumarins", common or engineered, because of their wide scope of natural exercises, have gotten a fascinating subject of examination for some analysts (Stefenachi *et al*., 2011). "Coumarin" framework has demonstrated to have a significant job in anticancer medication improvement because of a reality that a considerable lot of its subsidiaries have indicated "an anticancer movement on different cell lines". Activity of "coumarins on tumor cells" is done by means of various components and some of them show generally excellent selectivity toward the disease cells(Dandriyal *et al.,*2016).

Laura Anaissi-Afonso *et al* (2020) A multicomponent response from sweet-smelling aldehydes, "4-Hydroxycoumarin" and "2-Hydroxynaphthoquinone" used to incorporate a progression of naphthoquinone-coumarin conjugates (Sarma *et al*., 2011). Topoisomerase II docking investigations of naphthoquinone subsidiaries occurred. The half and half "structures were assessed against the isoform of human topoisomerase II, Escherichia coli DNA Gyrase and *E.coli* Topoisomerase I" (Alshafeiy *et al*., 2019). Every single tried compound hindered interceded unwinding of contrarily supercoiled roundabout DNA in the low micromolar go. This hindrance was vague to "DNA Gyrase nor Topoisomerase I". Naphthoquinone-coumarins act by chemically hindering appeared by Cleavage examines (Madonna *et al*., 2010). ATPase tests and sub-atomic docking concentrates additionally called attention to that the method of activity is identified with the ATP-restricting site.

GovindaiahPilli *et al.* (2020) Tuberculosis (TB) is as yet a requesting overall medical issue and "*mycobacterium tuberculosis* (MTB) stays one of the most harmful human microbes". In quest for looking through "new antitubercular and antimicrobial specialists", subbed "coumarin and phenyl-1,2,4-triazolidine-3-thiones 4a-I and 5a-e" have been combined and assessed for their antitubercular and antimicrobial exercises (Singh *et al*., 2008). The Substituted "coumarin and phenyl-1,2,4-triazolidine-3-thiones" demonstrated greatest movement against Mycobacterium tuberculosis (H37Rv). The title mixes have shown astounding in vitro antibacterial action against the *S. aureus*, Bacillus and *E. coli* shows low least inhibitory fixations (MIC) for example 0.4 to 1.6 µg/mL (Lee *et al*., 2014). "*In vitro* antifungal" movement indicated that the mixes "4a-I and 5a-e are astounding antifungal operators against" "*Candida albicans*, *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus"* treat parasitic stains with the estimations of "low least inhibitory fixations (MIC)" going from 0.4 to 6.25 µg/mL. Atomic "docking study was performed" for all the integrated mixes with "*E. coli* as antibacterial and *Mycobacterium tuberculosis*" DprE1 as antituberculosis (Petit *et al.,*1995).

Ravindra K. Rawal *et al.* (2019) there is ceaseless headway in the advancement of helpful specialists against bosom disease as of late and it is still in progress (Shashidhar *et al.,* 2012). Advancement of half and half atoms by consolidating diverse pharmacophores to get critical organic movement is a great methodology (Rahim *et al*., 2016). Coupling of coumarin ring with different moieties shows the structure of more current mixes against bosom malignant growth. These unmistakable pharmacophores have an assorted method of activity just as selectivity (Bano *et al*., 2015). It has been accounted for in the writing that coumarin half breeds have huge strength against bosom malignant growth by official to different natural targets which are related with bosom disease. Coumarin half and halves because of low harmfulness profile on different organ frameworks, having more consideration of specialists to examine their helpful capacity against bosom malignant growth. In this survey, shows different Coumarin half and half alongside their basic movement connections. The coumarin half and half coupling with isoxazole, thiazole, monastrol, chalcone, triazole, sulphonamide, triphenylethylene, benzimidazole, pyran, imidazole, stilbene, estrogen, phenyl sulphonylfuroxan, and so on. (Milanese *et al.,* 2011).

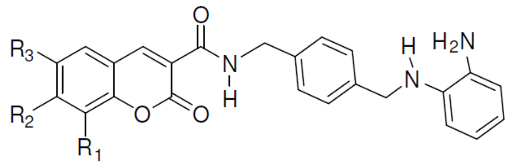
Ahmed Sabt *et al* (2019) plan and amalgamation of coumarin-6-sulfonamide subordinates having various capacities, and in-vitro investigation of their development inhibitory movement towards the expansion of three disease cell lines; HepG2 (hepatocellular carcinoma), MCF-7 (bosom malignancy), and Caco-2 (colon malignant growth). The most touchy cells HepG2 (hepatocellular carcinoma) shows impact to the objective coumarins (Zhang *et al*., 2010). Mixes 13a and 15a rose as the most dynamic individuals “against HepG2 cells (IC50¼3.48±0.28 and 5.03±0.39mM”, separately). We ready to initiate “apoptosis in HepG2 cells”, as guaranteed “by the up regulation of the Bax and down regulation” of the Bcl-2, other than boosting caspase-3 levels. Plus, compound actuated a critical increment in the level of cells at Pre-G1 by 6.4-folds, with simultaneous noteworthy capture “in the G2-M” stage by “5.4-folds” contrasted with “control” (Aiello *et al.,* 2012).

Chengzhe Wu *et al.* (2018) structured and blend a significant enthusiasm for growing new SERMs as multifunctional specialists in ladies' wellbeing. The double particular “estrogen receptor modulators/ VEGFR-2 inhibitors (SERMs/V-2I) has been” utilized for the revelation of new bosom malignancy restorative specialists (Badshah *et al*., 2018). The strong estrogen receptor restricting partiality and against proliferative adequacy appeared in past examination prompts the readiness of a progression of “3-aryl-4-anilino-2H-chromen-2-ones” (Zhou *et al*., 2012). In this ongoing investigation, basically correlated“3-aryl-4-anilino/aryloxy-2H-chromen-2-one” moieties were structured, incorporated and assessed as another “chemo”-kind of double “ERα” and VEGFR-2 inhibitors. The subsidiaries showed powerful exercises were found in both enzymatic and cell examines (Damu *et al.,* 2014).

Tamer Nasr *et al.* (2018) planned and blend new arrangement of “hydrazide-hydrazone and amide subbed coumarin” subordinates were orchestrated and assessed “*in vitro* for their antitumor” movement (Riveiro *et al*., 2010). Bromocoumarinhydrazidehydrazone subordinate demonstrated amazing movement against safe “pancreatic carcinoma (Panc-1), hepatocellular carcinoma (HepG2) and leukemia (CCRF) cell lines and its” instrument of activity was explored (Chadha *et al*., 2015). Likewise, compound 11b had the option to fill in as a concoction transporter “for 99mTc” and the 99mTc-11b “*in vivo* bio-distribution study” uncovered a momentous focusing on capacity of “99mTc into” strong “tumor” indicating that “99mTc-11b” may be a “promising radiopharmaceutical imaging operator” for malignancy (Peng *et al.,* 2010).

Soniya D. Naika *et al.* (2018) structured progression of new “coumarin” connected with pyrimidine subsidiaries have been combined by means of microwave light (Lacy *et al.,* 2004). Structures of the combined mixes were described by “IR, 1H NMR, 13C NMR, GC-MS and CHN” investigation strategies (Ploypradith *et al*., 2004). All recently orchestrated mixes screened for their in-vitro against microbial and hostile to malignant growth exercises (Hela and A549 Cell lines). Further DNA cleavage contemplated and reports uncovered that the majority of the blended mixes restrain the development of the pathogenic creature by genome cleavage as no hints of DNA were found (Ploypradith *et al*., 2004). The current examination brings up that the integrated coumarin-pyrimidine analogs are promising in focused medication conveyance frameworks, can be utilized for malignant growth treatment. “Docking results” likewise upheld the examinations (Kontogiorgis *et al.,* 2008).

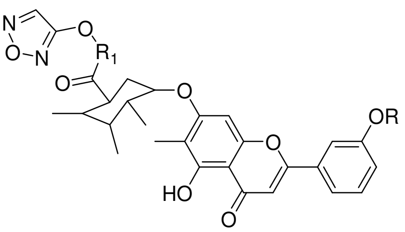
T. Abdizadehet*al. (*2017) designed and synthesis a novel arrangement of “coumarin based benzamides” as HDAC inhibitors. Histone deacetylase (HDACS) are alluring restorative objective for the treatment of malignant growth and different illnesses (Dall'Acqua *et al*., 2007). It has four classes among them class 1isozyme are associated with advancing tumor cells multiplication, angiogenesis, separation, intrusion and metastasis and furthermore reasonable focuses for disease treatment (Santana *et al*., 2000). The cytotoxicity action of the combined mixes was tried against various human malignant growth cell lines including HCT116, A2780, MCF-7, PC3, HL60, A549 and a solitary typical cell line. In the examination done by the scientists the four mixes (2a, 2b, 2c, 2d) (Figure 5) showed cytotoxic with IC50 (Guiotto *et al*., 2004). Among every one of them compound 2u show a higher intensity for HDAC1 restraint with IC50 esteem.



S.No.	R_1	R_2	R_3
2a	H	OCH_2CH_3	H
2b	H	4-Br-Benzyloxy	H
2c	H	4-OCH_3-Benzyloxy	H
2d	H	3,4Di-D-Benzyloxy	H

Fig. 5 : Coumarin based benzamides derivatives

XUE *et al. (*2017) planned a synthesisof a progression of NO-giving Scutellarin subsidiaries and the antiproliferative action against MCF-7, HCT-116, PC-3 and HepG2 disease cell lines (Ploypradith *et al*., 2004). Among every one of, the mixes 3a-c (Figure6) displayed antiproliferative action. The compound 3c was the most dynamic and shown low harmfulness against typical human liver L-O2 cells with an IC50. They show great selectivity among ordinary and harmful liver cell (Pisklak *et al*., 2003). The compound 3bacted anticancer by initiating apoptosis and cell cycle capture at S-stage and prompted mitochondrial brokenness in the HepG2 and PC-3 cell lines further human apoptosis protein cluster unit could instigate apoptosis through down – controlling the degree of procaspse-3 and repressing the statement of enduring, C-1AP1, HSP27, HSP60, HSP70, in HepG2 cell lines (Mohareb *et al.,* 2001).



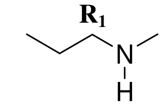
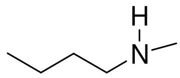
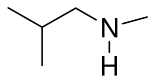
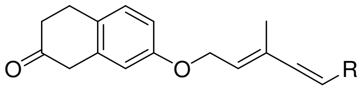
S. NO.	R	R_1
3a	Bn	
3b	Bn	
3c	Bn	

Fig. 6 : Scutellarin derivatives

Bisi *et al.* (2017) The multipotent specialist has been gotten by little library of coumarins conveying butynyl-amino chains in the field of MDR returning operators (Micke *et al.*, 2003). By the examination done by the analysts the detailed anticancer and chemo preventive common item 7-isopentenyloxy coumarin was connected to various terminals amines (Borges *et al.*, 2010). The anticancer conduct and MDR returning capacity of new mixes were assessed on human colon malignancy cell, especially inclined to build up the MDR phenotype. Among every one of, the mixes 4a-e (Figure 7), the compound 4e rose as the most fascinating of arrangement demonstrating a multipotent natural profile and conjugation of a suitable coumarin with an appropriately chose "butynyl-amino chain" permitted to get novel half and half atoms with improved *in vitro* antitumor movement (Hamacher *et al.,* 2010).



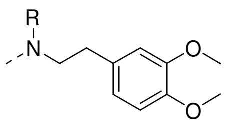
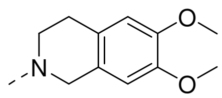
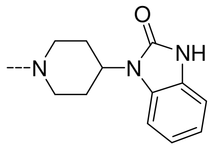
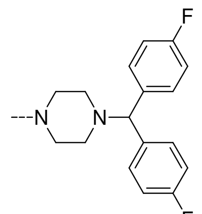
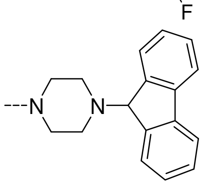
S.NO	R
4a	
4b	
4c	
4d	
4e	

Fig. 7 : 7-Isopentenyloxy "coumarin derivatives"

Zoidis *et al.* (2017) synthesized of "indeno (1, 2c) cinnoline-11-one" (Figure 8) derivatives. By the investigation of the researchers the inhibition of human topoisomerase and antiproliferative assay MCF-7 cancer celllines (Hamacher *et al.,* 2008).

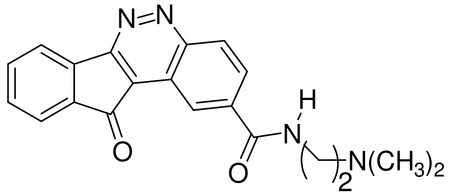
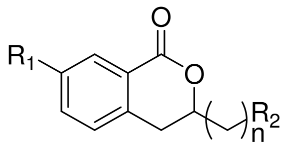


Fig. 8 : Indeno [1, 2-C] Cinnoline-11-one

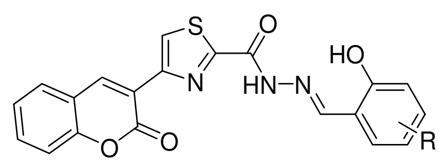
Keller *et al.* (2016) structured and union a progression of novel isocoumarin subsidiaries by utilizing Castro Stephens cross coupling. A tale "3, 4 dihydroisocoumarin" subordinates were acquired by reactant hydrogenation of relating "isocoumarin" antecedents (Youns *et al*., 2011). The antiproliferative action of all mixes 5a-h (Figure 9) was assessed in vitro in various tumor cell. The "3, 4 – dihydroisocoumarin" subordinates of compound structures hydrogen bond with Ser190 and Gln 192 buildups of Kallikrein5 (KLK5) (Efferth *et al*., 2009). The compound 5b is the most dynamic compound in the arrangement with powerful antiproliferative movement and high selectivity list against bosom malignant growth cell.



S.NO	n	R_1	R_2
5a	1	H	OH
5b	1	OCH_3	OH
5c	3	OCH_3	OH
5d	3	OCH_3	O-*n*-Pentyl
5g	3	OCH_3	1-phenyl-1*H*-tetrazole-5-thiol
5h	3	OCH_3	5-phenyl-1*H*-tetrazole

Fig. 9 : 3, 4 –Dihydroisocoumarin derivatives

Wang *et al.* (2016) synthesis of coumarin thiazole compounds "for their α-glucosidaseactivity". "The majority of the screened compounds displayed potent inhibitory activities with IC_{50}values". Among all of the tested moleculesfrom 6a-e (Figure 10), compound 6e was most active compound of coumarin thiazolecompounds. The binding interaction of compound 6e with the "active site of α-glucosidase was confirmed through molecular" (Youns *et al.,* 2010).



S.NO	R
6a	4-OCH_3
6b	2-OH
6c	4-OH
6d	3, 5-tBu_2, 2-OH
6e	3, 5-Cl_2

Fig. 10 : 3-Thiazole substituted Coumarin derivatives

Vaarla *et al.* (2015) one-pot multicomponent approach has been utilized for the blend of novel arrangement of coumarin subbed "thiazolyl - 3-aryl pyrazole-4-carbaldehyde" (Figure 11) including "3(2-bromoacetyl) coumarin" and subbed acetophenones using Vielsmeir-haack response condition (Heravi*et al*., 2011). The compound 6 showed critical cytotoxic action with IC50 values against Hela-cell lines.

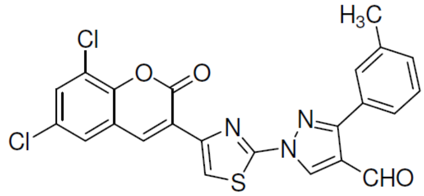
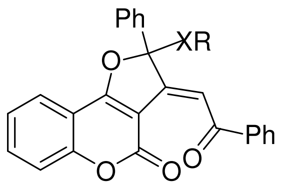


Fig. 11 : Coumarin substitutedThiazolyl -3-aryl pyrazole-4-carbaldehyde

Rajabi *et al.* (2015) "designed and synthesis" a furo (2-c) coumarin compound 7a-d (Figure 12) and assessed their anticancer potencies against bosom and colon malignant growth cell lines utilizing sulforhodamine B measure Compound 7b and 7d demonstrated higher antiproliferative action. UV spectroscopy utilizing for BSA restricting the compound 7b and 7dgive over all liking consistent.



S.NO	X	R
7a	O	CH_3
7b	O	CH_2CH_3
7c	N	CH_3CH_2
7d	N	$CH_2CH_2CH_2CH_2$

Fig. 12 : Furo [3, 2-C] Coumarin derivatives

Lung *et al.* (2014) designed and synthesized a novel "series of" "4-(1,2,3-triazol-1-yl) coumarinconjugates" **(Figure 13)** and "were" evaluated for "anticancer" potencies *in vitro*on3 human cell lines of cancer which includescolon carcinoma, human breast carcinoma "and lung carcinoma" to elevate the pharmacological "potency, optimization" campaign of structures were carried out which emphasized specially on the "1, 2, 3-triazole C-4 position and C-6 and C-7 position of coumarin".

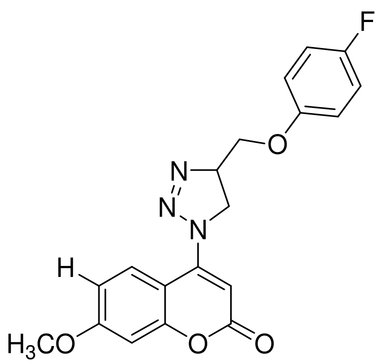


Fig. 13 : 4-(1,2,3-triazol-1-yl) coumarin conjugate

Amin *et al.* (2014) structured and amalgamation antiproliferative intensity of coumarin and pyrazoline subsidiaries, bearing subbed moieties. By the examination of the specialists the objective subsidiaries were combined from the "8 acetyl-7-methoxy-coumarin" (Figure 14) by Claisen Schmidt buildup using a few aldehydes to given the chalcones, they show intense action after responding with "phenyl hydrazine, hydrazine hydrate or semi carbazide" under suitable condition.

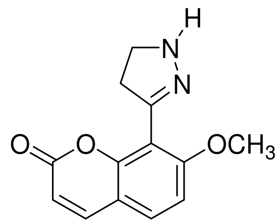


Fig. 14 : 8-Pyrazolyl-7-methoxy-coumarin

Conclusion

The current work gives an abstract of the anticancer intensity of enhanced subordinatespfcoumarin. The coumarin core has been demonstrated to be a fundamental pharmacophore for a few bioactive subsidiaries. During most recent couple of years, coumarin have shown a huge situation in anticancer exploration by follow up on a few tumors' phones by discrete instruments. Coumarins have been exhibited to have a few pharmacological exercises, for example, "antiasthmatic, calming, antitumor, antimicrobial, antiviral, antihyperlipidemic, cancer prevention agent, antinociceptive, energizer, hostile to HIV, antituberculosis", against flu. This paper gives a compressed version of system of the anticancer exercises of different coumarin subsidiaries. Along these lines, this paper has been controlling for the improvement of coumarin as hostile to malignancy operators, which can be a lead core for future advancements to get more secure and powerful mixes.

References

Adronov, A.; Gilat, S.L.; Frechet, J.M.; Ohta, K.; Neuwahl, F.V. and Fleming, G.R. (2000). Light harvesting and energy transfer in laser-dye-labeled poly (aryl ether) dendrimers. Journal of the American Chemical Society, 122(6): 1175-1185.

Alshafeiy, H.; Ibrahim, B.M.; Safar, M.M.; El-Shenawy, S.; Yassin, N.A. and Kenawy, S. (2019). Fluconazole, a Fungal Cytochrome P450 Enzyme Inhibitor: The Potential Role in Augmenting Hepatotoxicity and Hyperinsulinemia Induced by Dexamethasone in Rats. Egyptian Journal of Chemistry, 62(10): 1895-1906.

Amin, K.M.; Abou-Seri, S.M.; Awadallah, F.M.; Eissa, A.A.M.; Hassan, G.S. and Abdulla, M.M. (2015). European Journal of Medicinal Chemistry, 90: 221-231.

Aslam, K.; Khosa, M.K.; Jahan, N. and Nosheen, S. (2010). Short communication: synthesis and applications of Coumarin. Pakistan Journal of Pharmaceutical Sciences. 23(4): 449-454.

Badshah, S.L. and Ullah, A. (2018). New developments in non-quinolone-based antibiotics for the inhibition of bacterial gyrase and topoisomerase IV. European Journal of Medicinal Chemistry, 152: 393-400.

Bakhchinian, R.; Terrier, F.; Kirkiacharian, S.; Resche-Rigon, M.; Bouchoux, F. and Cérède, E. (2003).

Synthesis and relative binding affinity to human steroid receptors of substituted 3-aryloxycoumarins. Il Farmaco, 58(11): 1201-1207.

Bano, S.; Alam, M.S.; Javed, K.; Dudeja, M.; Das, A.K. and Dhulap, A. (2015). Synthesis, biological evaluation and molecular docking of some substituted pyrazolines and isoxazolines as potential antimicrobial agents. European Journal of Medicinal Chemistry, 95: 96-103.

Birkenkamp, K.U.; Dokter, W.H.; Esselink, M.T.; Jonk, L.J.; Kruijer, W. and Vellenga, E. (1999). A dual function for p38 MAP kinase in hematopoietic cells: involvement in apoptosis and cell activation. Leukemia, 13: 1037–1045.

Borges, M.F.M.; Roleira, F.M.F.; Milhazes, N.J.S.P.; Villare, E.U. and Penin, L.S. (2010). Simple coumarins: privileged scaffolds in medicinal chemistry. Frontiers in Medicinal Chemistry, 4: 23-85.

Buragohain, P.; Saikia, B.; Surineni, N.; Barua, N.C.; Saxena, A.K. and Suri, N. (2014). Synthesis of a novel series of artemisinin dimers with potent anticancer activity involving Sonogashira cross-coupling reaction. Bioorganic & Medicinal Chemistry Letters, 24(1): 237-239.

Buragohain, P.; Saikia, B.; Surineni, N.; Barua, N.C.; Saxena, A.K. and Suri, N. (2014). Synthesis of a novel series of artemisinin dimers with potent anticancer activity involving Sonogashira cross-coupling reaction. Bioorganic & Medicinal Chemistry Letters, 24(1): 237-239.

Chadha, N.; Bahia, M.S.; Kaur, M. and Silakari, O. (2015). Thiazolidine-2, 4-dione derivatives: Programmed chemical weapons for key protein targets of various pathological conditions. Bioorganic & Medicinal Chemistry, 23(13): 2953-2974.

Dall'Acqua, F. (1995). The molecular basis of psoralen photochemotherapy. CRC Handbook of Organic Photochemistry and Photobiology. 1341-1350.

Damu, G.L.; Cui, S.F.; Peng, X.M.; Wen, Q.M.; Cai, G.X. and Zhou, C.H. (2014). Synthesis and bioactive evaluation of a novel series of coumarinazoles. Bioorganic &Medicinal Chemistry Letters, 24(15): 3605-3608.

Dandriyal, J.; Singla, R.; Kumar, M. and Jaitak, V. (2016). Recent developments of C-4 substituted coumarin derivatives as anticancer agents. European Journal of Medicinal Chemistry, 119: 141-168.

Das, K.; Panda, U.; Datta, A.; Roy, S.; Mondal, S.; Massera, C.; Askun, T.; Celikboyun, P.; Garribba, E.; Sinha, C. and Anand, K. (2015). An enolato-bridged dinuclear Cu (II) complex with a coumarin-assisted precursor: a spectral, magnetic and biological study. New Journal of Chemistry, 39(9): 7309-7321.

Frosch, P.J.; Johansen, J.D.; Menné, T.; Pirker, C.; Rastogi, S.C.; Andersen, K.E.; Bruze, M.; Goossens, A.; Lepoittevin, J.P. and White, I.R. (2002). Further important sensitizers in patients sensitive to fragrances: II. Reactivity to essential oils. Contact Dermatitis, 47(5): 279-287.

Gazivoda, T.; Šokcˇević, M.; Kralj, M.; Šuman, L.; Pavelić, K.; De Clercq, E.; Andrei, G.; Snoeck, R.; Balzarini, J.; Mintas, M. and Raić-Malić, S. (2007). Synthesis and antiviral and cytostatic evaluations of the new C-5 substituted pyrimidine and furo [2, 3-d] pyrimidine 4 ‘, 5 ‘-didehydro-L-ascorbic acid derivatives. Journal of Medicinal Chemistry, 50(17): 4105-4112.

Guiotto, A.; Chilin, A.; Manzini, P.; Dall'Acqua, F.; Bordin, F. and Rodighiero, P. (1995). Synthesis and antiproliferative activity of furocoumarin isosters. Farmaco, 50(6): 479.

H Zhou, C. and Wang, Y. (2012). Recent researches in triazole compounds as medicinal drugs. Current Medicinal Chemistry, 19(2): 239-280.

Hamacher, R.; Schmid, R.M.; Saur, D. and Schneider, G. (2008). Apoptotic pathways in pancreatic ductal adenocarcinoma. Molecular Cancer, 7(1): p.64.

Heravi, R.E.; Hadizadeh, F.; Sankian, M.; Afshari, J.T.; Taghdisi, S.M.; Jafarian, H. and Behravan, J. (2011). Novel selective Cox-2 inhibitors induce apoptosis in Caco-2 colorectal carcinoma cell line. European Journal of Pharmaceutical Sciences, 44(4): 479-486.

Jameel, E.; Umar, T.; Kumar, J. and Hoda, N. (2016). Coumarin: a privileged scaffold for the design and development of ant neurodegenerative agents. Chemical Biology & Drug Design, 87(1): 21-38.

Kempen, I.; Hemmer, M.; Counerotte, S.; Pochet, L.; De Tullio, P.; Foidart, J.M.; Blacher, S.; Noël, A.; Frankenne, F. and Pirotte, B. (2008). 6-Substituted 2-oxo-2H-1-benzopyran-3-carboxylic acid derivatives in a new approach of the treatment of cancer cell invasion and metastasis. European journal of medicinal chemistry, 43(12): 2735-2750.

Khilya, O.V.; Frasinyuk, M.S.; Turov, A.V. and Khilya, V.P. (2001). Chemistry of 3-hetarylcoumarins. 1. 3-(2-benzazolyl) coumarins. Chemistry of Heterocyclic Compounds, 37(8): 1029-1037.

Kontogiorgis, C.; Litinas, K.E.; Makri, A.; Nicolaides, D.N.; Vronteli, A.; Hadjipavlou-Litina, D.J.; Pontiki, E. and Siohou, A. (2008). Synthesis and biological evaluation of novel angular fused Pyrrolocoumarins. Journal of Enzyme Inhibition and Medicinal Chemistry, 23(1): 43-49.

Lacy, A. and O'Kennedy, R. (2004). Studies on coumarins and coumarin-related compounds to determine their therapeutic role in the treatment of cancer. Current Pharmaceutical Design, 10(30): 3797-3811.

Lee, H.Y.; Tsai, A.C.; Chen, M.C.; Shen, P.J.; Cheng, Y.C.; Kuo, C.C.; Pan, S.L.; Liu, Y.M.; Liu, J.F.; Yeh, T.K. and Wang, J.C. (2014). Azaindolyl sulfonamides, with a more selective inhibitory effect on histone deacetylase 6 activity, exhibit antitumor activity in colorectal cancer HCT116 cells. Journal of Medicinal Chemistry, 57(10): 4009-4022.

Lessene, G.; Czabotar, P.E. and Colman, P.M. (2008). BCL-2 family antagonists for cancer therapy. Nature Reviews Drug Discovery, 7(12): 989-1000.

Li, B.; Pai, R.; Di, M.; Aiello, D.; Barnes, M.H.; Butler, M.M.; Tashjian, T.F.; Peet, N.P.; Bowlin, T.L. and Moir, D.T. (2012). Coumarin-based inhibitors of *Bacillus anthracis* and *Staphylococcus aureus* replicative DNA helicase: chemical optimization, biological evaluation, and antibacterial activities. Journal of Medicinal Chemistry, 55(24): 10896-10908.

Li, X.; Yao, Z.; Jiang, X.; Sun, J.; Ran, G.; Yang, X.; Zhao, Y.; Yan, Y.; Chen, Z.; Tian, L. and Bai, W. (2020). Bioactive compounds from Cudrania tricuspidata: A natural anticancer source. Critical Reviews in Food Science and Nutrition, 60(3): 494-514.

Li, Y.Q.; Ho, K.Y. and Zuo, X.L. (2012). Atlas of Gastrointestinal Endomicroscopy. World Scientific, 145-165.

Li, Z.J.; Wu, Z.S. and Li, H.Y. (2011). Analysis of electromagnetic scattering by uniaxial anisotropic bispheres. Journal of optical Society of America A, 28(2): 118-125.

Ling, L.L.; Schneider, T.; Peoples, A.J.; Spoering, A.L.; Engels, I.; Conlon, B.P.; Mueller, A.; Schäberle, T.F.; Hughes, D.E.; Epstein, S. and Jones, M. (2015). A new antibiotic kills pathogen without detectable resistance. Nature, 517(7535): 455-459.

Liu, H.; Ren, Z.L.; Wang, W.; Gong, J.X.; Chu, M.J.; Ma, Q.W.; Wang, J.C. and Lv, X.H. (2011). Novel coumarin-pyrazole carboxamide derivatives as potential topoisomerase II inhibitors: Design, synthesis and antibacterial activity. European Journal of Medicinal Chemistry, 157: 81-87.

Madonna, S.; Béclin, C.; Laras, Y.; Moret, V.; Marcowycz, A.; Lamoral-Theys, D.; Dubois, J.; Barthelemy-Requin, M.; Lenglet, G.; Depauw, S. and Cresteil, T. (2010). Structure–activity relationships and mechanism of action of antitumor bis 8-hydroxyquinoline substituted benzylamines. European Journal of Medicinal Chemistry, 45(2): 623-638.

Micke, G.A.; Moraes, E.P.; Farah, J.P. and Tavares, M.F. (2003). Assessing the separation of neutral plant secondary metabolites by micellar electrokinetic chromatography. Journal of Chromatography A, 1004(1-2): 131-143.

Milanese, A.; Gorincioi, E.; Rajabi, M.; Vistoli, G. and Santaniello, E. (2011). New synthesis of 6 [3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid and evaluation of the influence of adamantyl group on the DNA binding of a naphthoic retinoid. Bioorganic Chemistry, 39(4): 151-158.

Mohamed, K.O.; Nissan, Y.M.; El-Malah, A.A.; Ahmed, W.A.; Ibrahim, D.M.; Sakr, T.M. and Motaleb, M.A. (2014). Design, synthesis and biological evaluation of some novel sulfonamide derivatives as apoptosis inducers. European Journal of Medicinal Chemistry, 135: 424-433.

Mohareb, R.M.; El‐Omran, F.A. and Ho, J.Z. (2001). The reaction of 2-amino-3-cyano-4, 5, 6, 7-tetrahydrobenzo [b]‐thiophene with diethyl malonate: synthesis of coumarin, pyridine, and thiazole derivatives. Heteroatom Chemistry: An International Journal of Main Group Elements, 12(3): 168-175.

Moreira, M.D.; Picanço, M.C.; Barbosa, L.C.D.A.; Guedes, R.N.C.; Campos, M.R.D.; Silva, G.A. and Martins, J.C. (2007). Plant compounds insecticide activity against Coleoptera pests of stored products. Pesquisa Agropecuária Brasileira, 42(7): 909-915.

Myung, N.; Connelly, S.; Kim, B.; Park, S.J.; Wilson, I.A.; Kelly, J.W. and Choi, S. (2013). Bifunctional coumarin derivatives that inhibit transthyretin amyloid genesis and serve as fluorescent transthyretin folding sensors. Chemical Communications, 49(80): 9188-9190.

Nawrot-Modranka, J.; Nawrot, E. and Graczyk, J. (2006). In vivo antitumor, in vitro antibacterial activity and alkylating properties of phosphorohydrazine derivatives of coumarin and chromone. European journal of medicinal chemistry, 41(11): 1301-1309.

Peng, X.M.; Cai, G.X. and Zhou, C.H. (2013). Recent developments in azole compounds as antibacterial and antifungal agents. Current Topics in Medicinal Chemistry, 13(16): 1963-2010.

Peng, X.M.; Kumar, K.V.; Damu, G.L. and Zhou, C.H. (2016). Coumarin-derived azolyl ethanols: synthesis, antimicrobial evaluation and preliminary action mechanism. Science China Chemistry, 59(7): 878-894.

Petit, P.X.; Lecoeur, H.; Zorn, E.; Dauguet, C.; Mignotte, B. and Gougeon, M.L. (1995). Alterations in mitochondrial structure and function are early events of dexamethasone-induced thymocyte apoptosis. The Journal of Cell Biology, 130(1): 157-167.

Pisklak, M.; Maciejewska, D.; Herold, F. and Wawer, I. (2003). Solid state structure of coumarin anticoagulants: warfarin and sintrom. 13C CPMAS NMR and GIAO DFT calculations. Journal of Molecular Structure, 649(1-2): 169-176.

Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S. and Ruchi Rawat, S. (2004). A highly efficient synthesis of lamellarins K and L by the Michael addition/ring-closure reaction of benzyl dihydro isoquinoline derivatives with ethoxycarbonyl-β-nitrostyrenes. Angewandte Chemie International Edition, 43(7): 866-868.

Rahim, F.; Ullah, H.; Taha, M.; Wadood, A.; Javed, M.T.; Rehman, W.; Nawaz, M.; Ashraf, M.; Ali, M.; Sajid, M. and Ali, F. (2016). Synthesis and in vitro acetylcholinesterase and butyrylcholinesterase inhibitory potential of hydrazide-based Schiff bases. Bioorganic Chemistry, 68: 30-40.

Riveiro, M.E.; De Kimpe, N.; Moglioni, A.; Vazquez, R.; Monczor, F.; Shayo, C. and Davio, C. (2010). Coumarins: old compounds with novel promising therapeutic perspectives. Current Medicinal Chemistry, 17(13): 1325-1338.

Sánchez-Recillas, A.; Estrada-Soto, S.; Navarrete-Vázquez, G.; Millán-Pacheco, C.; Ortiz-Andrade, R.; Villalobos-Molina, R.; Ibarra-Barajas, M. and Gallardo-Ortiz, I.A. (2019). Functional relaxant effect of 6, 7-dipropoxy-2H-chromen-2-one is mainly by calcium channel blockade in ex vivo assay of tracheal rings. Medicinal Chemistry Research, 28(8): 1197-1204.

Santana, L.; Uriarte, E.; Dalla Via, L. and Gia, O. (2000). A new benzo angelicin with strong photobiological activity. Bioorganic & Medicinal Chemistry Letters, 10(2): 135-137.

Sarma, R. and Prajapati, D. (2011). Microwave-promoted efficient synthesis of dihydroquinolines. Green Chemistry, 13(3): 718-722.

Sashidhara, K.V.; Kumar, A.; Kumar, M.; Srivastava, A. and Puri, A. (2010). Synthesis and antihyperlipidemic activity of novel coumarin bisindole derivatives. Bioorganic & Medicinal Chemistry Letters, 20(22): 6504-6507.

Sharma, A. and Gupta, M. (2017). Underlying mechanisms of Anticancer Coumarins: An over view. 2212-9553.

Shashidhar, K.V.; Kumar, A.; Dodda, R.P.; Krishna, N.N.; Agarwal, P.; Srivastava, K. and Puri, S.K. (2012). Coumarin–trioxane hybrids: Synthesis and evaluation as a new class of antimalarial scaffolds. Bioorganic & Medicinal Chemistry Letters, 22(12): 3926-3930.

Singh, R.K.; Lange, T.S.; Kim, K.K.; Shaw, S.K. and Brard, L. (2008). A novel indole ethyl isothiocyanate (7Me-

IEITC) with anti-proliferative and pro-apoptotic effects on platinum-resistant human ovarian cancer cells. Gynecologic oncology, 109(2): 240-249.

Stefenachi, A.; Favia, A.D.; Nicolotti, O.; Leonetti, F.; Pisani, L.; Catto, M.; Zimmer, C.; Hartmann, R.W. and Carotti, A. (2011). Design, synthesis, and biological evaluation of imidazolyl derivatives of 4, 7-disubstituted coumarins as aromatase inhibitors selective over 17-α-hydroxylase/C17− 20 lyase. Journal of Medicinal Chemistry, 54(6): 1613-1625.

Thompson, J.S.; Asmis, R.; Glass, J.; Liu, H.; Wilson, C.; Nelson, B.; Brown, S.A. and Stromberg, A.J. (2006). P53 status influences regulation of HSPs and ribosomal proteins by PDTC and radiation. Biochemical and Biophysical Research Communications, 343(2): 435-442.

Tiftikci, E. and Erk, C. (2004). The synthesis of novel crown ethers, part X, 4-propyl-and 3-ethyl-4-methylchromenone-crown ethers. Journal of Heterocyclic Chemistry, 41(6): 867-871.

Turner, N.A.; Sharma-Kuinkel, B.K.; Maskarinec, S.A.; Eichenberger, E.M.; Shah, P.P.; Carugati, M.; Holland, T.L. and Fowler, V.G. (2011). Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research. Nature Reviews Microbiology, 17(4): 203-218.

Wang, S.J.; Sun, B.; Cheng, Z.X.; Zhou, H.X.; Gao, Y.; Kong, R.; Chen, H.; Jiang, H.C.; Pan, S.H.; Xue, D.B. and Bai, X.W. (2011). Dihydroartemisinin inhibits angiogenesis in pancreatic cancer by targeting the NF pathway. Cancer chemotherapy and Pharmacology, 68(6): 1421-1430.

Wang, T.H.; Chan, Y.H.; Chen, C.W.; Kung, W.H.; Lee, Y.S.; Wang, S.T.; Chang, T.C. and Wang, H.S. (2006). Paclitaxel (Taxol) upregulates expression of functional interleukin-6 in human ovarian cancer cells through multiple signaling pathways. Oncogene, 25(35): 4857-4866.

Wen, X.Y.; Wu, S.Y.; Li, Z.Q.; Liu, Z.Q.; Zhang, J.J.; Wang, G.F.; Jiang, Z.H. and Wu, S.G. (2009). Ellagitannin (BJA3121): an anti-proliferative natural polyphenol compound, can regulate the expression of MiRNAs in HepG2 cancer cells. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 23(6): 778-784.

Yadagiri, B.; Holagunda, U.D.; Bantu, R.; Nagarapu, L.; Kumar, C.G.; Pombala, S. and Sridhar, B. (2014). Synthesis of novel building blocks of benzosuberone bearing coumarin moieties and their evaluation as potential anticancer agents. European Journal of Medicinal Chemistry, 79: 271-272.

Yadagiri, B.; Holagunda, U.D.; Bantu, R.; Nagarapu, L.; Kumar, C.G.; Pombala, S. and Sridhar, B. (2014). Synthesis of novel building blocks of benzosuberone bearing coumarin moieties and their evaluation as potential anticancer agents. European Journal of Medicinal Chemistry, 79: 260-265.

Youns, M. and Fathy, G.M. (2013). Upregulation of extrinsic apoptotic pathway in curcumin-mediated antiproliferative effect on human pancreatic carcinogenesis. Journal of Cellular Biochemistry, 114(12): 2654-2665.

Youns, M.; Efferth, T. and Hoheisel, J.D. (2011). Transcript profiling identifies novel key players mediating the growth inhibitory effect of NS-398 on human pancreatic cancer cells. European Journal of Pharmacology, 650(1): 170-177.

Youns, M.; Efferth, T.; Reichling, J.; Fellenberg, K.; Bauer, A. and Hoheisel, J.D. (2009). Gene expression profiling identifies novel key players involved in the cytotoxic effect of Artesunate on pancreatic cancer cells. Biochemical Pharmacology, 78(3): 273-283.

Youns, M.; Hoheisel, J.D. and Efferth, T. (2010). Toxicogenomics for the prediction of toxicity related to herbs from traditional Chinese medicine. Planta Medica, 76(17): 2019-2025.

Zhang, W.; Li, Z.; Zhou, M.; Wu, F.; Hou, X.; Luo, H.; Liu, H.; Han, X.; Yan, G.; Ding, Z. and Li, R. (2014). Synthesis and biological evaluation of 4-(1, 2, 3-triazol-1-yl) coumarin derivatives as potential antitumor agents. Bioorganic & Medicinal Chemistry Letters, 24(3): 799-807.

Zhong, H.; Zhao, X.; Zuo, Z.; Sun, J.; Yao, Y.; Wang, T.; Liu, D. and Zhao, L. (2016). Combating P-glycoprotein-mediated multidrug resistance with 10-O-phenyl dihydroartemisinic ethers in MCF-7 cells. European Journal of Medicinal Chemistry, 108: 720-729.