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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).

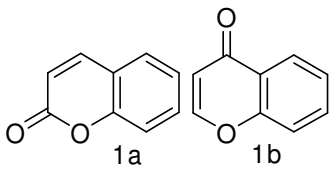


Fig. 1 : Types of coumarin

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.

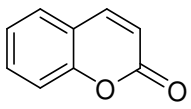


Fig. 2 : Scopoletin

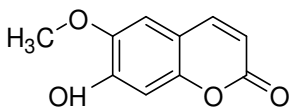
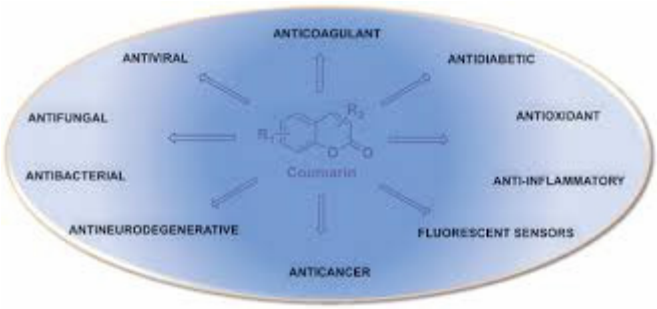


Fig. 3 : 7-Hydroxycoumarin

Mechanism of action

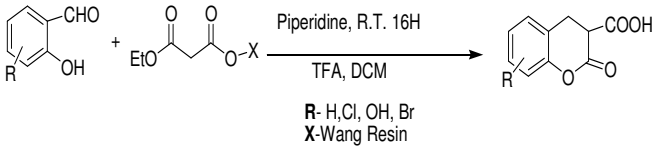
Depending upon the structure of Coumarins, they act on several tumors' cells by discrete mechanisms *viz.* inhibition of the tolemerase enzyme, inhibition of protein kinases and down regulation of oncogenes expression or induction of apoptosis mediated by caspase-9which overpower proliferation of cancer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

Biological activity of coumarin



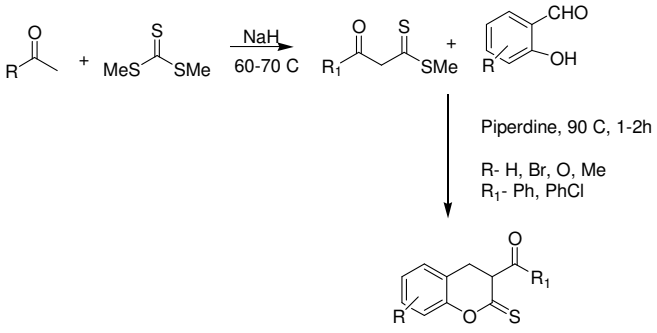
SYNTHESIS OF COUMARINS

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).

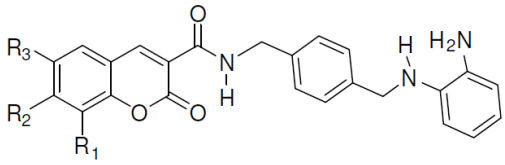
Ahmed Sabt *et al* (2019) plan and amalgamation of coumarin-6-sulfonamide subordinates having various capacities, and in-vitro investigation of their development inhibitory movement towards the expansion of three disease cell lines; HepG2 (hepatocellular carcinoma), MCF-7 (bosom malignancy), and Caco-2 (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).

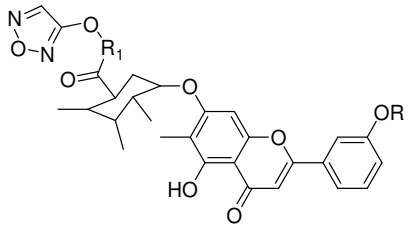
T. Abdizadehet*al. (*2017) designed and synthesis a novel arrangement of "coumarin based benzamides" as HDAC inhibitors. Histone deacetylase (HDACS) are alluring restorative objective for the treatment of malignant growth and different illnesses (Dall'Acqua *et al*., 2007). It has four classes among 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).



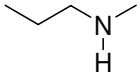
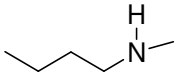
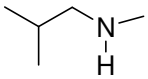
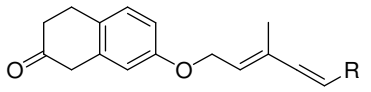
S. NO.	R	R_1
3a	Bn	
3b	Bn	
3c	Bn	

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).



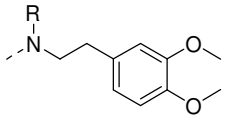
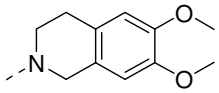
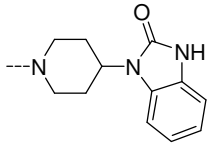
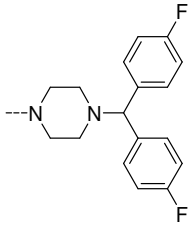
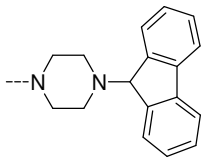
S.NO	R
4a	
4b	
4c	
4d	
4e	

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).

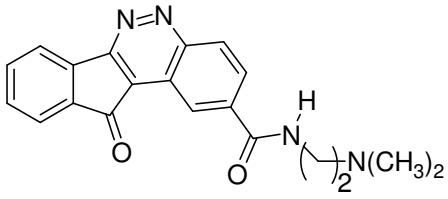
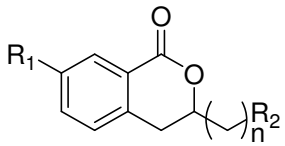


Fig. 8 : Indeno [1, 2-C] Cinnoline-11-one

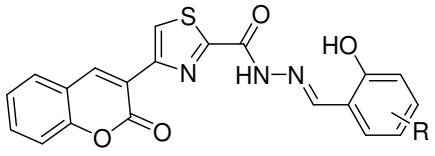
Keller *et al.* (2016) structured and union a progression of novel isocoumarin subsidiaries by utilizing Castro Stephens cross coupling. A tale "3, 4 dihydroisocoumarin" subordinates were acquired by reactant hydrogenation of relating "isocoumarin" antecedents (Youns *et al*., 2011). The antiproliferative 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.

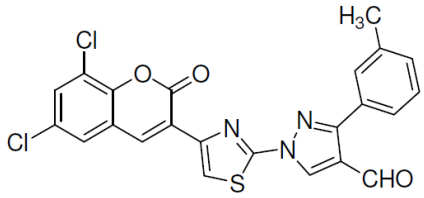
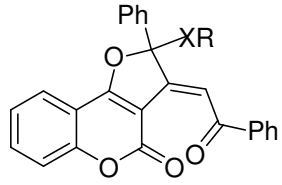


Fig. 11 : Coumarin substitutedThiazolyl -3-aryl pyrazole-4-carbaldehyde

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".

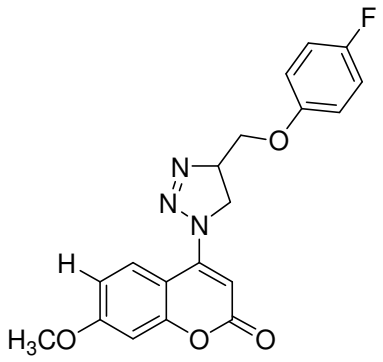


Fig. 13 : 4-(1,2,3-triazol-1-yl) coumarin conjugate

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.

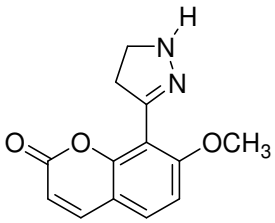


Fig. 14 : 8-Pyrazolyl-7-methoxy-coumarin

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.

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