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Review article

Coumarins as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies

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ABSTRACT

Coumarins are fused benzene and pyrone ring systems which prompt biological investigation to assess their potential therapeutic significance. It possesses immeasurable anticancer potential with minimum side effects depending on the substitutions on the basic nucleus. Coumarins have a tremendous ability to regulate diverse range of cellular pathways that can be explored for selective anticancer activity. This is the first standalone review that emphasis on the assorted retrosynthetic approaches, important targets for molecularly targeted cancer therapy and structure activity relationship studies that highlight the chemical groups responsible for evoking the anticancer potential of coumarin derivatives reported from 2011 to 2014.

1. Introduction

Cancer being the second leading cause of death worldwide, a number of experiments have been going on to develop compounds having minor or no side effects; and coumarins were reported to exhibit negligible or mild side effects [1,2]. Coumarin (1,2-benzopyrone; 2*H*-1-benzopyran-2-one; phenylpropanoids; *cis-o*-coumarinic acid lactone; coumarinic anhydride; tonka bean camphor) belongs to an extensive class of compounds found abundantly in plants, bacteria and fungi [3,4]. Its name has been derived from a French word '*Coumarou*', the vernacular name of tonka beans (*Dipteryx odoranta* Wild; belonging to family Fabaceae) [5,6]. Coumarins are widely distributed in different parts of plants and have highest concentration in fruits [Bael fruit (*Aegle marmeleos*)], seeds [(tonka beans *Calophyllum inophyllum* Linn)], roots (*Ferulago campestris*) and leaves (*Murraya paniculata*) [7–9]. Coumarins have been previously considered as benzoic acid derivatives but the classical approach by W. H. Perkin, Sr. classified them as oxygenated heterocycles [10–12]. Various pharmacological activities of coumarins basically depend on the type of coumarin nucleus which includes antibacterial [13,14], cycloxygenase inhibiton [15], antimutagenic [16], scavanging of reactive oxygen species (ROS) [17,18], antiinflammatory [19,20], anticoagulant [21–23], lipoxygenase [24,25], CNS stimulants [26], antithrombotic [27,28], vasodilatory [29,30], and anticancer activity [31].

2. Synthetic strategies of coumarin

The synthesis of coumarins and their derivatives has attracted considerable attention in research and development to both organic and medicinal chemists. Keeping in view the importance of coumarins, we have compiled numerous synthetic strategies for the preparation of compound (**I**) from the year 2011 to 2014, as shown in Fig. 1. Many researchers have introduced various simple and efficient synthetic schemes by using reactant (**II**) in the presence of different catalysts to decrease the reaction time, by-products as well as to improve the percentage yield of (**I**). Albadi

Abbreviations: ARI, aromatase inhibitor; CAM, choriallanotoic membrane; CDC, cell cycle division protein; CDK2, cyclin dependent kinase 2; CDKN1A, cyclin-dependent kinase inhibitor 1A; CYP, cytochromes P450; DDIT4, DNA-damage-inducible transcript 4 protein; DHFR, dihydrofolate reductase; FGF-2, fibroblast growth factor-2; GDF-15, growth differentiation factor 15; hCA, human carbonic anhydrase; HSP 90, heat shock protein 90; hTERT, human telomerase reverse transcriptase; IC_{50}, 50% inhibitory concentration; MCT, monocarboxylate transporter; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; PI-3K, Phosphatidylinositide 3-kinases; RNR, ribonucleotide reductase; ROS, reactive oxygen species; SAR, structure activity relationship; STS, steroid sulfatase; VEGF, vascular endothelial growth factor.

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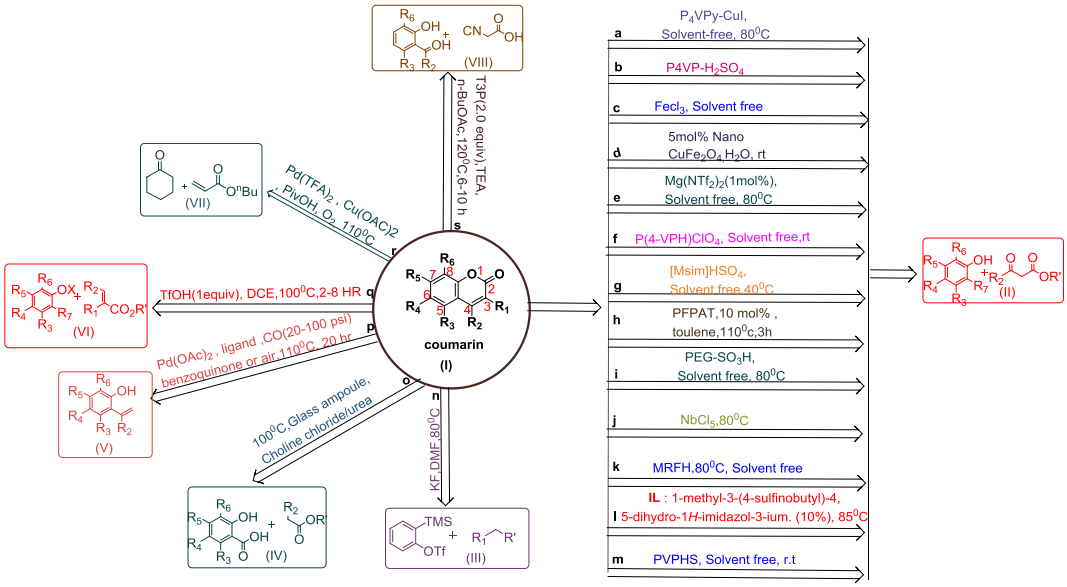


Fig. 1. Various retrosynthetic approaches for the synthesis of coumarin.

et al. performed (route a) solvent free synthesis by reacting (**II**) with poly (4-vinylpyridine) supported copper iodide and then, heating in oil bath for 80 °C to give compound (**I**). The catalyst 'poly(4-vinylpyridine)-supported copper iodide' can be recovered by simple filtration and recycled upto eight consecutive runs without loss of its efficiency [32]. Borah et al. (route b) have efficiently prepared (**I**) in good yield in microwave within few minutes by reacting (**II**) in the presence of poly(4-vinylpyridine)-supported sulfuric acid. The catalyst 'poly (4-vinylpyridine)-supported sulfuric acid' can be recovered and reused after activation [33]. On the other hand, ultrasonic assisted solvent free synthesis was carried out by Prousis et al. (route c) to afford excellent yield of (**I**) by reacting (**II**) under $FeCl_3$ catalyst which is an inexpensive, mild, and benign lewis acid catalyst [34]. Baghbanian et al. (route d) synthesized (**I**) by reacting (**II**) in the presence of $CuFe_2O_4$, H_2O at room temperature [35]. Wang carried (route e) out solvent free synthesis of (**I**) by reacting (**II**) in the presence of catalyst magnesium bis(trifluoromethane) sulfonamide at 80 °C [36]. Khaligh et al. carried (route f) out one pot synthesis of (**I**) with (**II**) in the presence of new and versatile solid acid catalyst poly(4-vinylpyridium)percolate under ultrasonic irradiation at room temperature [37]. Khaligh (route g) reacted (**II**) in the presence of an efficient, halogen free and reusable ionic liquid i.e. 3-methyl-1-sulfonic acid imidazolium hydrogen sulfate at 40 °C to yield (**I**) [38]. Montazeri et al. carried (route h) out efficient synthesis of (**I**) in presence of metal free catalyst pentafluorophenylammonium triflate (PFPAT) with (**II**) by Von Pechman reaction [39]. Nazeruddin et al. (route i) prepared (**I**) by reacting (**II**) in the presence of a mild and recyclable catalyst PEG-SO_3H at 80 °C [40]. S.T. Gao et al. (route j) carried out one pot synthesis of (**I**) by reacting (**II**) in the presence of $NbCl_5$ at 80 °C [41]. Rezaei et al. (route k) reacted (**II**) in the presence of a mild and inexpensive reagent i.e. melamine-formaldehyde resin supported H^+ to give efficient yield of (**I**) [42]. S. Das et al. synthesized (**I**) (route l) by reacting (**II**) in the presence of reusable ionic liquid as a catalyst at 85 °C [43]. N.G Khaligh conducted (route m) one pot synthesis of (**I**) in the presence of poly (4-vinylpyridium) hydrogen sulfate along with the use of reactant (**II**) [44]. Synthesis of compound (**I**) was performed under mild conditions with inherently low cost by many researchers using (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**) as reactants. Yoshida et al. (route n) performed three-component coupling using (**III**) in the presence of potassium fluoride, DMF at 80 °C to yield (**I**) [45]. Harishkumar et al. carried out (route l) solid phase synthesis of (**I**) by reacting (**IV**) in the presence of a choline chloride/urea as catalyst at 100 °C [46]. Ferguson et al. synthesized (**I**) (route p) in the presence of $Pd(OAc)_2$, low pressure of CO, benzoquinone or air and the reactant (**V**) [47]. Kim et al. obtained (**I**) by (route q) condensation of (**VI**) in the presence of TfOH and DCE at 100 °C for 2–8 h [48]. Kim et al. prepared (**I**) (route r) by reacting (**VII**) via Pd (II)-catalysed dehydrogenation-oxidative heck reaction [49]. Augustine et al., (route s) synthesized (**I**) from Perkin condensation by reacting (**VIII**) in the presence of Propylphosphonic anhydride (T3P), triethylamine (TEA), n-BuOAc at 120 °C for 6–10 h [50].

3. Anticancer activity of coumarins

Biological investigations of coumarins revealed the engrossment of innumerable pathways by which coumarins act as anticancer agents. Coumarins target a number of pathways in cancer such as kinase inhibition, cell cycle arrest, angiogenesis inhibition, heat shock protein (HSP90) inhibition, telomerase inhibition, antimitotic activity, carbonic anhydrase inhibition, monocarboxylate transporters inhibition, aromatase inhibition and sulfatase inhibition [51–53]. Furthermore, such research helped in derivation of structure activity relationship studies (SARs) which lead to the discovery of diverse substitution of coumarin nucleus, thereby enhancement/broadening of activity continuum.

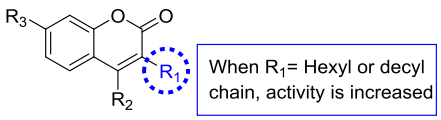
3.1. Kinase inhibitors

Kinases are the enzymes that catalyse the transfer of a phosphate group to the target protein. They play a critical role in the modulation of innumerable growth factor signalling. Activated forms of the kinases can cause increase in cell proliferation, prevent apoptosis, promote angiogenesis and metastasis in several cancers and its activation by the somatic mutation is a basic mechanism of tumour genesis. As all these effects are initiated by the activation of kinases, they are the key targets for inhibition by coumarins and their derivatives [54].

In 2014, Nasr et al. synthesized and evaluated coumarin derivatives for anticancer activity against resistant pancreatic cells

and drug sensitive cell lines such as Hep-G2 and CCRF. Compounds **1**–**4** were found to be more potent than the reference drug doxorubicin. Coumarin hydrazide–hydrazone pharmacophore was observed to display better activity than compounds having either coumarin or hydrazide–hydrazone pharmacophore. Caspase 3/7 assay suggested that compounds **1**–**4** activates caspases 3/7 and eventually induces apoptosis. Microarray analysis for finding out the molecular targets of coumarin derivatives indicated that compound **1** exhibits antiproliferative effect by up regulation of the cyclin-dependent kinase inhibitor 1A (CDKN1A), DNA-damage-inducible transcript 4 protein (DDIT4), growth differentiation factor 15 (GDF-15) and down regulation of the cell cycle division protein 2 (CDC2), cell cycle division protein (CDC20), and cyclin dependent kinase 2 (CDK2) genes. SAR assessment concluded that coumarin hydrazide–hydrazone backbone with bromine substitution is indispensible for the antitumour activity because of the electronegative effect of bromine on coumarin moiety. Moreover, comprehensive SAR features of the most active compounds are abridged below (Fig. 2) [55].

To develop potent anticancer agents, Kathuria et al. in 2011 synthesized six classes of coumarin derivatives which include 3-alkyl-4-methylcoumarins, pyranocoumarins, coumarin carboxamides, quaternary ammonium coumarins, 7-aminocoumarins, and 4-aminocoumarins. Along with Src kinase inhibitory activity, they also investigated antiproliferative activity of the compounds. It was suggested by the research group that there was poor correlation between the Src kinase inhibitory potency and the antiproliferative activity. It was inspected that **5** and **6** (Fig. 3) substituted with hexyl and decyl showed weak antiproliferative activity but maximum Src kinase inhibitory activity as compared to the standard protein kinase inhibitor, staurosporine, and a Src kinase inhibitor, PP2. Two more compounds including **7** and **8** of class 7-aminocoumarins have been found to show modest Src kinase activity [6]. Moreover, cell proliferation assay verified that among all screened classes, two compounds such as **9** and **10** of C-3 alkyl-substituted pyranocoumarins showed maximum antiproliferative activity but weak Src inhibition potency. It was observed that



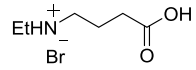
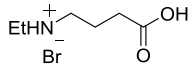
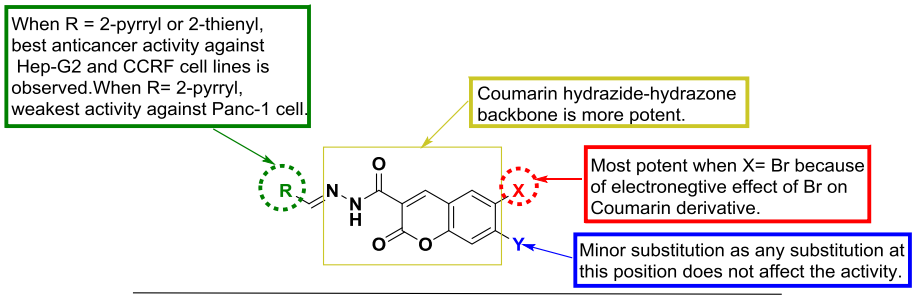
Compounds	R_1	R_2	R_3	IC_{50} (μM)
5	C_6H_{13}	CH_3		36.5
6	$C_{10}H_{21}$	CH_3		21.6
7	$C_{10}H_{21}$	CH_3	NH_2	73.5
8	H	CF_3	NH_2	30.9

Fig. 3. SAR study of quaternary ammonium derivatives and 7-aminocoumarin derivatives.

various substitution (Fig. 4) are responsible for the improved activity such as larger alkyl chain increases hydrophobicity, amidic linkage increases the solubility by participating in H-bonding, alkoxy group and amino acid conjugates at C-3 position increases the anticancer activity; while substitution of C-3 with carbonyl group decreases the activity [56].

Further, docking study and synthesis of coumarin substituted benzothiazole derivatives were accomplished in 2012 by Kini et al. They selected receptor tyrosine kinase as a target for anticancer activity for docking study. It was evaluated by SAR study that compound **11** was most active among all synthesized compounds (Fig. 5). It was investigated by docking simulation that **11** has not shown hydrogen bonding with the receptor but has found to form hydrophobic bonding by C-atom of allyloxy methylene group. Research group has reported various residues that are involved in



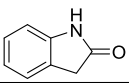
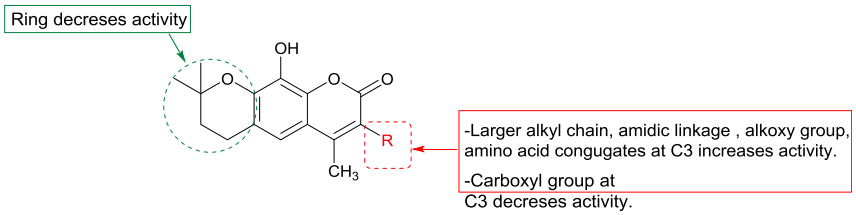
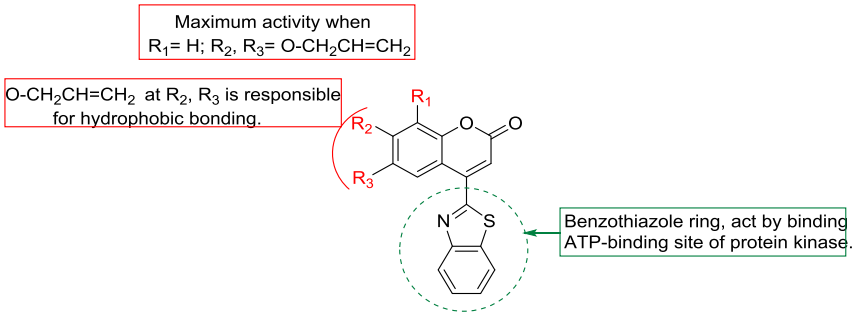
Compound	R	X	Y	IC_{50} (μM)		
				Hep-G2	Panc-1	CCRF
1		Br	H	3.60	6.50	5.15
2		Br	H	2.02	-	-
3		Br	H	4.18	-	9.02
4		Br	H	2.10	-	-

Fig. 2. SAR of coumarin substituted hydrazide–hydrazone derivatives.



Compound	R	% Cell proliferation		
		SiH_4	MDA-MB-468/MCF-7	SK-OV-3
9	C_2H_7	85%	45%	30%
10	$C_{10}H_{21}$	36%	57%	35%

Fig. 4. SAR study of C-3 alkyl-substituted pyranocoumarins.



11 R_1= H R_2=O-$CH_2CH=CH_2$ R_3= O-$CH_2CH=CH_2$

Compound	% Growth inhibition			
	10μM	50μM	100μM	200μM
11	18.54	25.34	43.78	70.34

Fig. 5. SAR study of coumarin substituted benzothiazole derivatives.

such interaction as shown in (Fig. 6) that includes Val53, Lys68, Glu81, Leu85, Thr96 and Gly177. It also exhibited extensive van der Waals bonding with Val53, Lys68, Glu81, Leu85, Thr96 and Gly177. Thus, **11** was found to have highest docking score (−64.67), which signified that **11** can fit well in the receptor cavity and making it potent inhibitor of receptor tyrosine kinase [57].

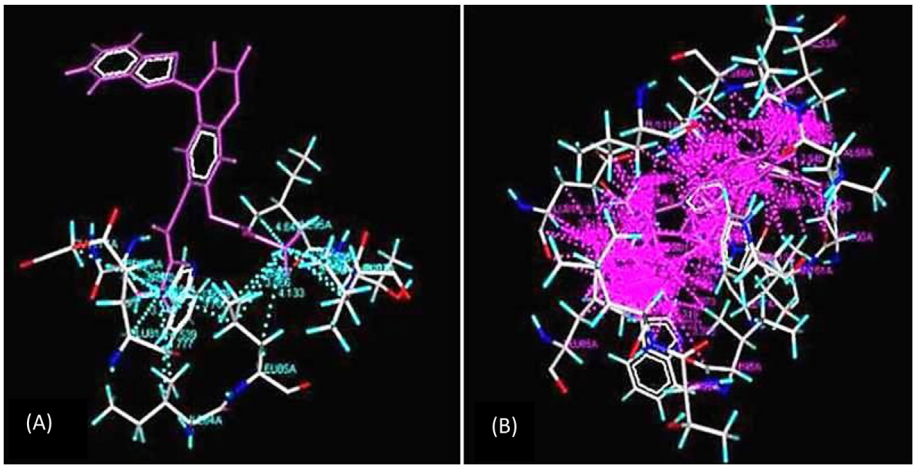


Fig. 6. (A) Green dotted lines indicating the hydrophobic interaction of **11** with the receptor residues by the C-atom of the allyloxy methylene group (B) Pink colour dotted lines indicating the van der waal's interaction of **11** with receptor residues [57]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

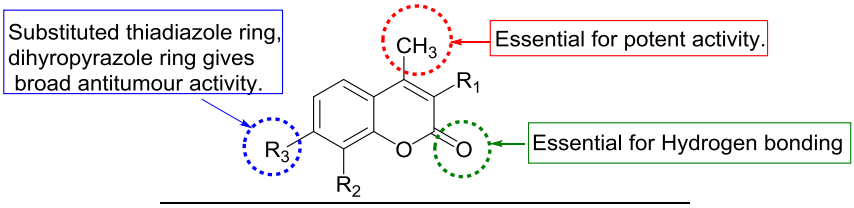
In 2014, El-Ansary et al. synthesized and executed docking simulation of some innovative benzopyrone derivatives. The synthesized compounds were evaluated for growth inhibition potential against six cancer cells lines such as CCR-CEM, HL-60, HOP-92, NCI-H460, HCT-116 and SF-295 as shown in (Fig. 7). Results of the *in-vitro* and SAR study revealed that **12**–**15** were the most potent compounds. Thus, displaying that coumarin nucleus with dihydropyrazole ring or thiadiazole ring has a broad anticancer activity. Docking simulation was performed to determine the binding modes of compounds within the binding site of casein kinase II. It was suggested that **14** and **15** have superior binding affinity and binding modes within the active site of casein kinase II as presented in (Fig. 8). Compound **14** displayed couple of hydrogen bonds, one between Asn118 with O atom of C═O of pyrone and another between Asp175 with H atom of NH. Further, **15** formed six hydrogen bonds with active site of CK2 enzyme, one H-bond between Tyr 50 and O atom of pyrazolone, another H-bond between Ser 51 and O of pyrazolone, two hydrogen bonds between Lys 68 with O of C═O of pyrone and O of pyrone moiety. Another two H-bond between Asp175 with O of C═O of pyrone and H of NH [58].

Novel coumarin-pyrazoline hybrids endowed with phenylsulfonyl moiety were synthesized in 2013 by Amin et al. Compounds were screened for its anticancer property towards a number of cell lines; and later PI3K (Phosphoinositol 3-Kinase) inhibitory activity was also inspected. They reported that compound **16** (Fig. 9) bearing unsubstituted phenyl ring at position 5 of the pyrazoline and Cl at R_1 position was found to have highest cytotoxicity with mild PI3K protein kinase inhibitory activity as compared to its reference compound wortmannin [59].

3.2. Cell cycle arrest

Coumarins are reported to arrest various phases of cell cycle such as G0, G1, S and M phase that eventually leads to apoptosis [60]. They are found to persuade apoptosis by caspase-dependent intrinsic pathway and alteration in the cellular level of Bcl-2 family proteins [61]. Mitochondrial potential gets highly depleted due to increased expression of proapoptotic Bax/Bak and intracellular reactive oxygen species (ROS). Further, it results in release of cytochrome c from the mitochondria which lowers the matrix metalloproteinase and translocate into the cytoplasm with the activation of initiator caspase-9 and extracellular caspases-3/7. Tumour suppressor proteins p53 and its transcriptional target PUMA are up regulated. PUMA interacts with antiapoptotic Bcl-2 family proteins, promotes the activation of Bax/Bak and have necessary role in multiple apoptotic models [62].

In 2013, Kumar et al. synthesized 3-(4,5-dihydro-1-phenyl-5-substituted phenyl-1H pyrazol-3-yl)-2H-chromen-2-one derivatives which were assessed for anticancer activity against 60 cancer cell lines. It was observed that, δ-lactone ring of the coumarin nucleus is the basic reason behind their impressive anticancer activity which resulted by induction of G1 arrest of cell cycle. Furthermore, assorted substitution of the coumarins was done to prevent hydrolysis of lactone in the circulation and allow the hydrolysis of the intact lactone ring only in the target tissue resulting in cell cycle arrest. These substitutions also resulted in increasing the total bioavailability of the drug. Hence, studying the chemical structure and *in-vitro* cancer screening revealed that compounds show a broad spectrum anticancer activity and



Compounds	R_1	R_2	R_3
12	CH_3	C_6H_5-HN, NH- (O)	OH
13	CH_3	H	C_2H_5-HN, N-N, S, O-
14	CH_3	H	C_6H_5-HN, N-N, S, O-
15	CH_3	H	H_3C, NH, N, O, O

Test Compounds and growth inhibition percentage				
Cell lines	12	13	14	15
CCR-CEM	34.32	13.42	27.41	27.69
HL-60	41.78	18.20	19.42	28.91
HOP-92	38.58	28.67	-	47.63
NCI-H460	27.42	-	10.68	10.43
HCT-116	26.99	14.14	21.17	18.83
SF-295	45.07	27.34	50.46	39.73

Fig. 7. SAR study of benzopyrone derivatives.

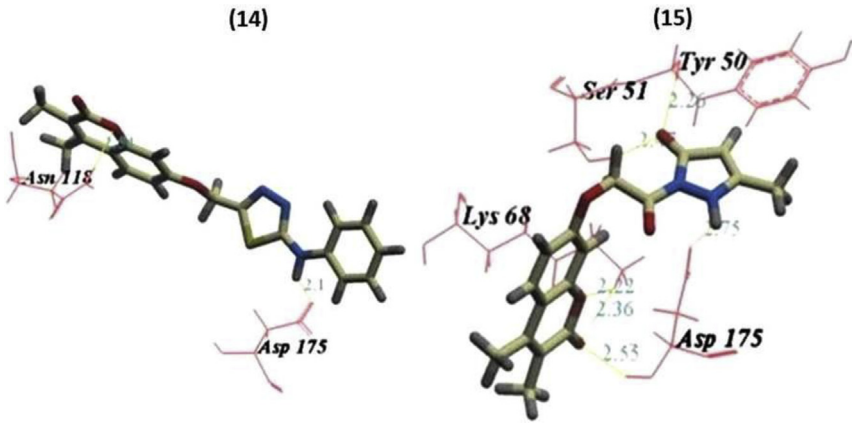
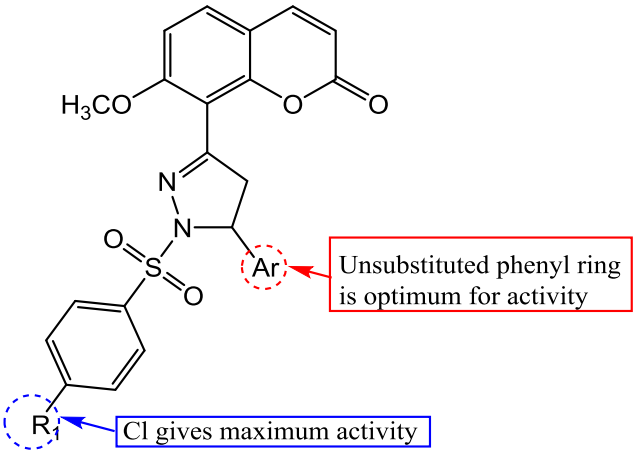


Fig. 8. Binding modes of compound 14 and 15 with the residues of binding site of casein kinase II [58].

compound **17** (Fig. 10) with 4-hydroxy substitution on the phenyl ring was found to be most potent anticancer agent with minimum mean growth percentage [63].

On the other hand, cytotoxic effects of eight acetoxycoumarins on A549 human lung cancer, CRL 1548 liver cancer, and CRL 1439 normal rat liver cell lines were investigated by Musa et al. in 2011. Cytotoxic activities of all compounds were gauged through crystal violet dye binding assay. Evaluation of CRL 1548 cancer cell line revealed that only compound **19** exhibited cytotoxicity with LD_{50} of 45.1 μM. Cell cycle analysis showed that concentration above 40 μM of compound **19** arrested A549 cells in S and G_2 phase but compound **18** arrested S and G_2 phase at lower concentration of 20 μM and G_1 phase with 40 as well as 60 μM. Thus, *in-vitro* results were



Compounds	Ar	R_1	IC $_{50}$(μM)
Doxorubicin	-	-	0.63
16	C_6H_6	Cl	0.01
			p 110α inhibition [%] IC $_{50}$(μM)
Wortmannin			-1.61
16			100(50.78)

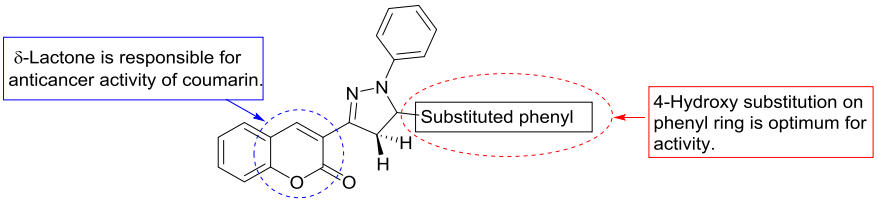
Fig. 9. SAR study of coumarin-pyrazoline hybrids.

helpful in concluding that **19** was highly toxic to all cancer cell lines and could be considered as a lead in development of potential anticancer agents but compound **18** was found to be less toxic and exhibited only tissue-specific toxicity. SAR features (Fig. 11) demonstrated that C-4 with phenyl ring, C-7 with diethylamino, and C-2 substitution with phenyl acetate on coumarin nucleus increased the cytotoxic activity [64].

A SAR study of *ortho*-dihydroxycoumarins with selective pro-apoptotic activity was conducted by Vazquez et al. in 2012. They monitored coumarins on cells viability, proliferation and pro-apoptotic activity. It was observed that compounds **20** and **21** were most active based upon the results of various assays, such as clonogenic assay and determination of apoptotic markers by cell cycle analysis, Annexin V binding assay, caspase-3, -8, -9, chemotaxis assay and clonogenic survival assay. Determination of apoptotic markers by cell cycle analysis revealed that **20** and **21** decrease the number of cells in G0/G1 phase of the cell cycle along with decrease in clonogenic capacity. SAR exploration (Fig. 12) demonstrated that compounds **20** and **21** with *ortho*-dihydroxy substitution (when R_3 & R_4 or R_2 & R_3 = OH) have highest activity than compounds with *meta*-dihydroxy substitution (when R_1 & R_4 = OH). Substitution of any one of the hydroxy group with methoxy, chloro or acetyl group resulted in compounds with diminished activity. Further, they also discovered that monoamine derivatives were found to be inactive [65].

Additionally, Hybrid molecular approach by Sashindhara et al., in 2012, developed coumarin-monastrol hybrid by combining two bioactive pharmacophore coumarin-monastrol as anticancer agents. Compound **22** displayed impressive activity against MCF-7 and MDB-MB-231 cell lines. SAR analysis revealed that there is a direct proportionality between the number of methoxy group and anticancer potential. Increase in the number of methoxy group on benzene ring attached to coumarin nucleus and the presence of tertiary butyl group on the benzene ring attached to coumarin segment amplified the activity. Apoptotic studies, caspase-3 activation assay and cell cycle analysis performed to evaluate the mechanism underlying anticancer activity of **22** revealed that it induces apoptosis by induction of caspase-3 activation in both primary and metastatic breast cancer cells irrespective of ER status. Moreover, cell cycle analysis showed that treatment of **22** at MCF-7 decreases the cells at S and G2 phase and arrest the cells at G-1 phase. SAR features (Fig. 13) demonstrated the basic substitution for increased anticancer activity [66].

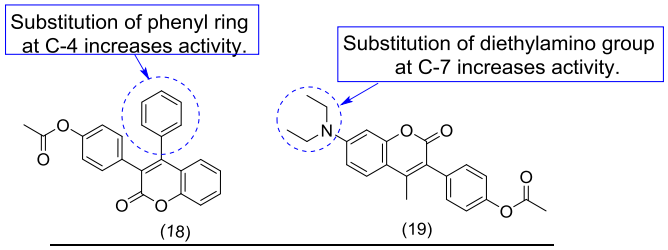
In another study, Benci et al., in 2012, synthesized coumarin derivatives containing 1,2,4-triazole; 4,5-dicyanoimidazole, and coumarin derivatives with purine moieties. They evaluated these



60 cell line assay in one dose of 10^{-5}concentration.

Compound	Substitution	Mean growth percentage	Range of growth percentage	Most sensative cell line	Growth of most sensitive cell line
17	-4hydroxy	77.59	-67.37 to 78.46	MDA-MB-231/ATCC	-67.37
		77.59	-65.18 to 78.46	CAK-1	-65.18
		77.59	-63.77 to 78.46	UO-31	-63.77
		77.59	-67.37 to 78.46	NCI-H522	-67.37

Fig. 10. SAR study of 3-(4,5-dihydro-1-phenyl-5-substituted phenyl-1H pyrazol-3-yl)-2H-chromen-2-one derivatives.

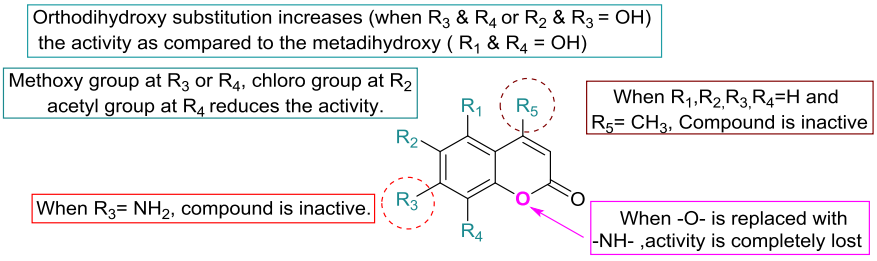


Compound	LD50 (Lethal Dose) (μM) A549 Lung cancer cell	CRL1548 Liver cancer cell	CRL 1439 Liver normal cell
18	89.3	>100	>100
19	48.1	45.1	49.1

Fig. 11. SAR of acetoxycoumarins derivatives.

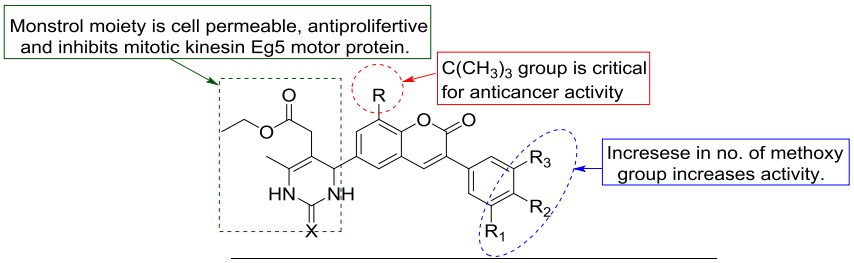
compounds for cytostatic activity assay on HeLa, HepG2 and SW620 cell lines. Among all the synthesized compounds only compounds **23** with 1,2,4-triazole moiety and **24** with purine moiety showed maximum ability to halt the cell multiplication and cell growth in the cell cycle (Fig. 14), but compounds with 4,5-dicyanoimidazole substitution did not show any remarkable results. Compound **23** exhibited stronger effects on HeLa cells because of the 1,2,4-triazole-3-carboxamide moiety. Compound **24** bearing 2-amino-6-chloropurine moiety exhibited higher effects on HepG2 and SW620 cells. Thus, it was found that coumarin derivatives with 1,2,4-triazole moiety having $R_1 = NH_2$ and $R_2 = OCH_3$ and coumarin derivatives with purine moiety with $R_2 = OH$, $R_3 = Cl$ and $R_4 = NH_2$ are essential for the optimum activity [67].

Recently, antitumour activity of 4-(1,2,3-triazol-1-yl) coumarin derivatives was assessed by Zhang et al. in 2014, against MCF-7, SW480 and A549 cell lines. MTT assay and flow cytometry assay were used for screening all the prepared derivatives and compound **25** was found to show maximum antitumour activity which is attributed to cell cycle arrest at G_2/M phase and induction of apoptosis. Substitution of coumarin nucleus drastically changed the activity. SAR study (Fig. 15) demonstrated that rotatable bonds facilitate the compound to bind to its receptor site. Different substitution at C-6 and C-7 of coumarin moiety were done to improve the potency but introduction of 4-fluorobezenesulfinate methyl-methanesulfonate resulted in complete loss of the activity. Further, replacement of 1, 2, 3 triazole and coumarin with piperazine and quinolone were performed respectively to measure the difference in biological activity. It was observed that replacement of these moieties resulted in the decrease in antitumour activity which



Compound	R_1	R_2	R_3	R_4	R_5	IC_{50}(μM) C195	CC_{50}(μM) C195
20	H	H	OH	OH	H	83.2	120.2
21	H	OH	OH	H	CH_3	97.4	76.0

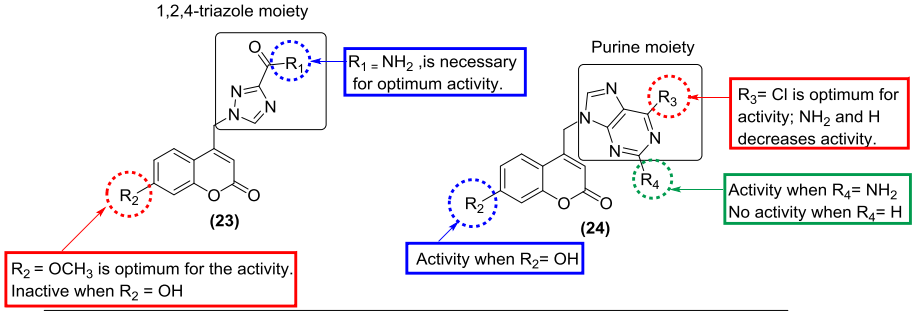
Fig. 12. SAR of *ortho*-dihydroxycoumarin derivatives.



Compound	R	R_1	R_2	R_3	X
22	$C(CH_3)_3$	OCH_3	OCH_3	OCH_3	S

	IC_{50} (μM)								
Cd	MCF-7	T47D	MDA-MB-231	DU-145	PC-3	A54	HepG2	NIH/3T3	Mouse skin fibroblast
22	2.42	3.13	3.978	>20	>20	>20	>20	>20	>20

Fig. 13. SAR study of coumarin-monastrol hybrid.



Compound	R_1	R_2	R_3	R_4	IC_{50} (μM) HeLa	HepG2	SW620
23	NH_2	OCH_3	-	-	35.5±13.5	-	-
24	-	OH	Cl	NH_2	34±8.4	25.6±12.6	35.4±3.7

Fig. 14. SAR of coumarin derivatives containing 1,2,4-Triazole and purine moieties.

concluded that coumarin nucleus is essential for the activity [68].

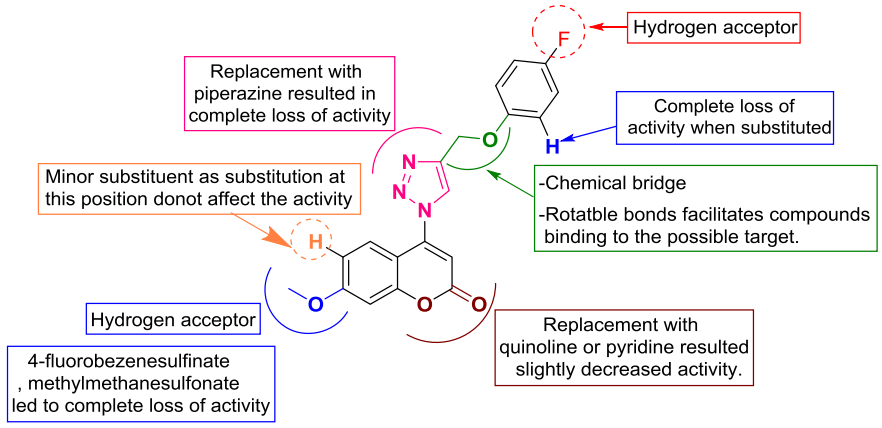
In 2014, Yang et al. synthesized and estimated the antiproliferative activity of hydroxylated 3-phenylcoumarins. SAR results (Fig. 16) illuminated that the antiproliferative activity is increased upon the introduction of electron-donating groups *such as ortho*-hydroxy-methoxy and *ortho*-dihydroxy groups on the aromatic ring A and B. Hence, compound **26** was 7 and 16 times more active as compared to resveratrol on HL-60 and A549 cells, respectively. It was found that **26** has shown the antiproliferative activity by cell cycle arrest at G2/M phase and apoptosis [69].

3.3. Angiogenesis inhibitors

Angiogenesis is also a foremost target of coumarin derivatives. They have been found to prevent angiogenesis by inhibiting fibroblast growth factor-2 (FGF-2) mediated proliferation, migration, and tubule formation. Furthermore, coumarin derivatives were observed to decrease the expression of vascular endothelial growth factor (VEGF) at mRNA level through nuclear factor-κB (NF-κB) and phosphorylation of IKKα; interestingly phosphatidylinositide 3-kinases (PI-3K)/Akt signalling pathway remain unaffected [70,71].

A number of angiogenesis inhibitors are being synthesized by researchers, such as novel benzophenone-conjugated coumarin analogues which were prepared in 2013 by Ranganatha et al. An array of assays were performed for evaluating its anticancer potential, such as trypan blue dye exclusion assay, MTT assay, choriallanotoic membrane (CAM) assay, PI3k assay, caspase activation assay and DNA fragmentation assay. CAM angiogenesis assay revealed that compounds **27**–**29** showed regression of newly formed microvessels, thus, proving these compounds to be admirable anti-angeogenesis agents. SAR study (Fig. 17) concluded that compound **27** possessing bromine group at *ortho* position of phenyl ring unveiled highest anti-angeogenesis activity followed by compound **28** having chloro and fluoro group at *ortho* position of phenoxy ring and methyl group at *para* position of benzoyl ring; and compound **29** with two chloro groups at *ortho* position of phenoxy ring [72].

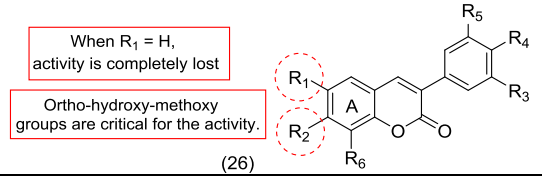
Novel N-[2-(2-benzoyl-4-methylphenoxy)-acetyl]-hydrazide methanone coumarin analogues targeting angiogenesis and apoptosis were developed by Avin et al. in 2014. They also accomplished *in vitro and in vivo* assay, and the results have



Compound 25

	IC_{50} (μM)		
Compound	MCF-7	SW480	A549
25	5.89 ± 0.14	1.99 ± 0.38	0.52 ± 0.21

Fig. 15. SAR study of 4-(1,2,3-triazol-1-yl) coumarin derivatives.



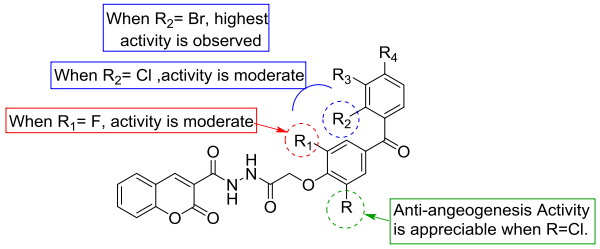
							IC_{50} (μM)	
Compound	R_1	R_2	R_3	R_4	R_5	R_6	HL-60	A549
26	OMe	OH	H	OH	H	H	5.2±0.6	7.5±0.6

Fig. 16. SAR study of hydroxylated 3-phenylcoumarins.

validated that compound **30** has excellent antiproliferative, anti-angiogenic effect with remarkable induction of apoptosis. It was also reported that **30** was a potent target specific antitumour agent as treatment with **30** was not cytotoxic to other organs. Further, on examining its SAR (Fig. 18) it was detected that bromine substituent at *ortho* position of benzoyl ring in benzophenone moiety is responsible for maximum activity [73].

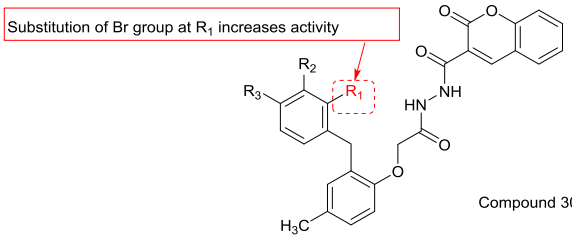
3.4. HSP90 inhibitors

A number of experiments are already been carried out and many are still in progress to inhibit all eight hallmarks of cancer by targeting HSP90. Coumarins are found to bind directly on HSP90 which is up-regulated in many cancers [74,75]. Many client proteins are also responsible for transformation of normal cells to cancerous cells. Coumarins degrade co-chaperone and client proteins which ultimately results in antiproliferative effect [76]. Coumarins are reported to cause *in vitro* and *in vivo* depletion of the key regulatory HSP 90-dependent kinases including Src, Raf-1 and ErBB2- a protein in humans encoded by ErBB2 gene [77].



Compound	R_1	R_2	R_3	R_4	R	Trypan blue assay IC_{50}value (μM)	MTT assay IC_{50}value (μM)	CAM Angeogenesis assay
27	H	Br	H	H	CH_3	7.7±0.09	7.6±0.10	Regression of microvessels
28	F	H	H	CH_3	Cl	9.4±0.02	9.3±0.04	Regression of microvessels
29	H	Cl	H	Cl	CH_3	10.4±0.08	10.2±0.12	Regression of microvessels
Standard						11.4±0.06	11.4±0.0	—

Fig. 17. SAR of benzophenone-conjugated coumarin analogues.



				EAC cells (IC_{50} values(μM))			DLA cells (IC_{50} values(μM))		
Compound	R_1	R_2	R_3	Tryptan blue assay	MTT assay	LDH release assay	Tryptan blue assay	MTT assay	LDH release assay

Fig. 18. SAR study of N-[2-(2-benzoyl-4-methylphenoxy)-acetyl]-hydrazide methanone coumarins derivatives.

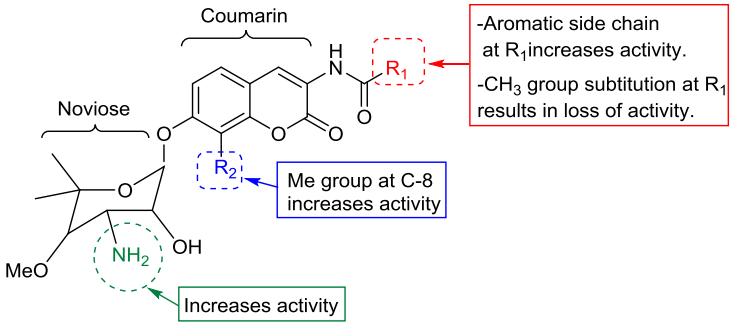
A study confirming this was performed by Zang et al. in 2013. The research group was foremost to synthetically realize 3′-amino isosteric replacement in the noviose moiety of HSP90 c-terminal inhibitors, contributing towards enhancement of cytotoxic activity. After SAR scrutiny (Fig. 19), they reported that incorporation of amino group into noviose moiety enhanced the anticancer activity of the compounds. Compounds having 3-benzamido substituent were observed to have high antiproliferative potency as compared to 3-acetoamino substituted analogues which were almost inactive. Further C-8 substitution and the replacement of 3′-OH with 3′-NH_2 were considered beneficial to be potent anticancer agents targeting HSP 90 c-terminus. Thus, they interpreted that compound **32** with R_2 as CH_3 group was a more active anticancer aminocoumarin analogues as compared to **31** having R_2 as Cl group [78].

Additionally, Zhao et al. in 2012, carried out the synthesis of 3-arylcoumarin derivatives as HSP 90 inhibitors. These derivatives were assessed for antiproliferative activity against various cell lines and thorough SAR study (Fig. 20) displayed that substitution of phenyl ring with electron deficient groups lead to enhancement of biological activity as compared to substitution with electron rich groups. It was observed that compounds such as **33**, **34** and **35** having substitution of bulky group at *para* position of the phenyl ring resulted in increased activity but substitution at *meta* or *ortho* position resulted in diminished activity. Further, it was evaluated that 8-methyl or 8-methyl-3-aryl substituted derivatives showed marked increase in activity as compared to the 8-desmethyl analogues. The compounds with substitution at C-3 position with bezo [b]thiophene ring exhibited higher activity against SKBR3 cell line at a concentration below 1 μM. Thus, it was concluded that compound **36** was the most potent agent to show antiproliferative activity by inhibition of HSP 90 and it does not degrade the non-HSP 90-dependent proteins [79].

3.5. Telomerase inhibitor

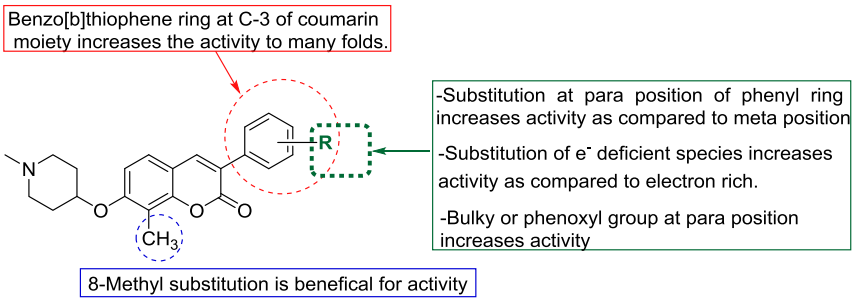
Telomerase is an enzyme which helps in maintaining the telomere length in human stem cells as well as cancer cells by adding TTAGGG repeats onto the telomeres. Telomerase activity is found only in tumour cells but not in adjacent normal cells. Different inhibitors including coumarins have been regarded for inhibition telomerase [80].

Xiao-Quin Wu et al. in 2013, prepared novel 1-(-3-substituted-5-phenyl-4,5-dihydropyrazol-1-yl)-2-thio-ethanone derivatives as potential telomerase inhibitors and also investigated their antiproliferative activity. Among all trifluoromethylphenyl-coumarin-dihyropyrazole derivatives compound **37** (Fig. 21) was found to possess high antiproliferative and telomerase inhibitory activity against various cell lines. Molecular docking of **37** (Fig. 22) on



			IC_{50}(μM)/L			
Compound	R_1	R_2	A2780	HeLa	Ketr-3	MCF-7
31	Ph	Cl	2.83	5.35	14.60	13.84
32	Ph	Me	7.52	2.89	2.14	8.12

Fig. 19. SAR study of aminocoumarin analogues containing noviose moiety.



Compound	Substitution at C-3	R	IC_{50} (μM) SKBR3	MCF-7
33	Aryl	*p*-Cl	8.24±1.59	3.89±0.61
34	Aryl	*p*-OCF_3	5.78±0.59	4.12±0.37
35	Aryl	*p*- OCH_3	29.93±15.44	16.92±2.34
36	Benzo[b]thiophene ring	-	0.98±0.01	0.81±0.02

Fig. 20. SAR study of 3-arylcoumarin derivatives.

binding site of telomerase was done to prepare a binding model derived from human telomerase reverse transcriptase (hTERT). Compound **37** was found to show intramolecular hydrogen bonding with the hydrogen atom of NH_2 group of Val 342. It was also observed that dihydropyrazole ring projects into a hydrophobic region comprising of Tyr 217, Leu 220, Thr 226, Ser 227 side chain which are essential for potent inhibitory activity of **37**. The 3D structure was more stable by the hydrophobic–hydrophobic interaction with thioether moiety at other end of the ATP binding pockets. Moreover, the introduction of fluorine atom increased the activity of **37** by distribution of the electrons in the molecule and strengthening dipole–dipole interaction [81].

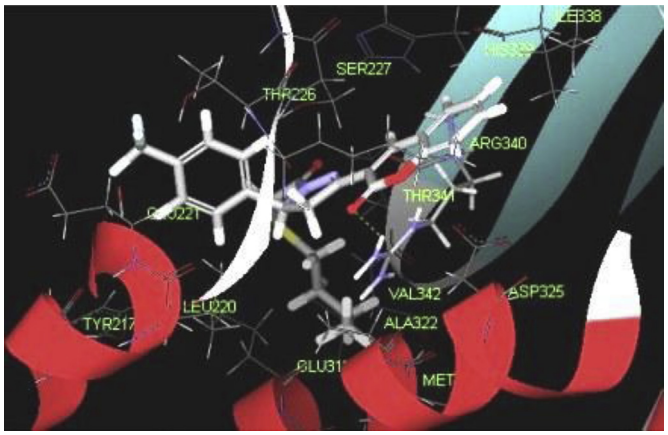
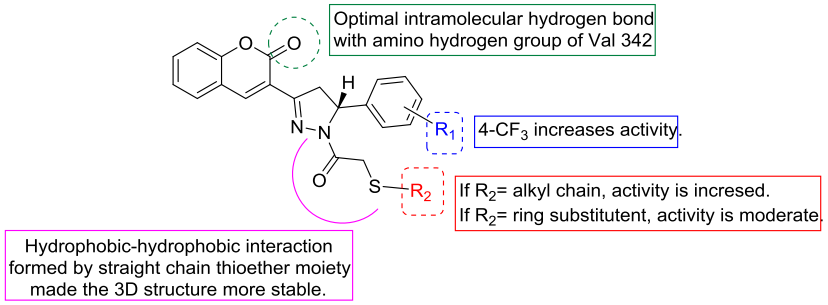


Fig. 22. Binding mode of compound **36** on the binding site of telomerase [81].

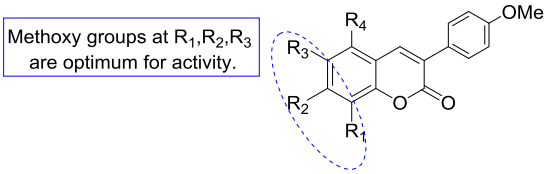
3.6. Antimitotic agents

Mitosis is a cell cycle process which occur both in normal and cancerous cells by which chromosomes are separated into two identical sets of chromosomes of its own nucleus and coumarin derivatives (pathway vi) inhibit cell division by acting directly on mitotic phase which primarily includes prometaphase and



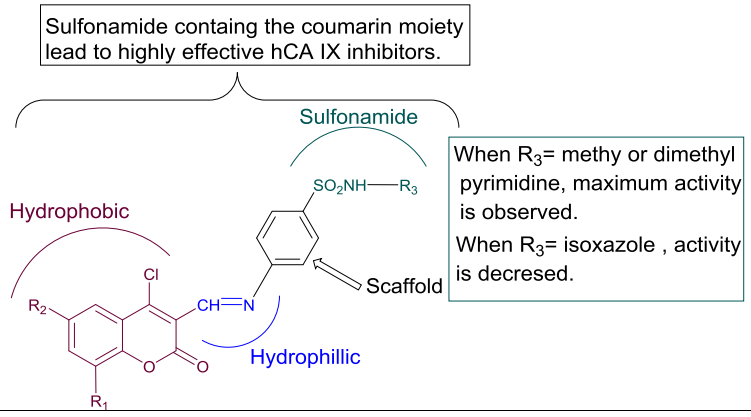
Compound	R_1	R_2	IC_{50}(μM) SGC-7901	MGC-803	Bcap-37	HEPG-2
37	4-CF_3	butane	2.91 ± 0.11	2.35±0.27	3.55 ± 1.00	8.68 ± 1.17

Fig. 21. SAR study of 1-(-3-substituted-5-phenyl-4,5-dihydropyrazol-1-yl)-2-thio-ethanone derivatives.



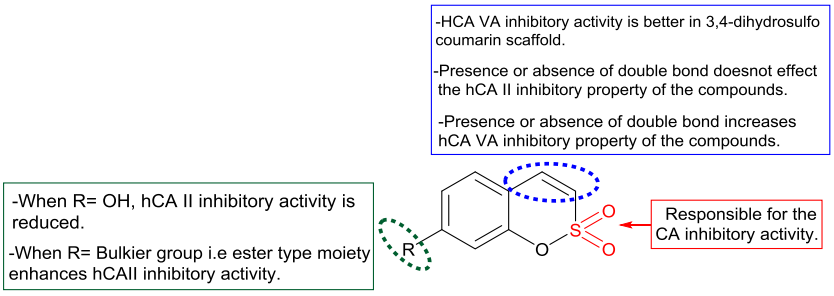
Compound	R1	R2	R3	R4	EC/μM$^{\alpha}$ Cleavage alterations	Cleavage arrest	Embryo spinning
38	OMe	OMe	OMe	H	0.2	4	>5

Fig. 23. SAR study of polyalkoxy-3(4-methoxyphenyl) coumarin.



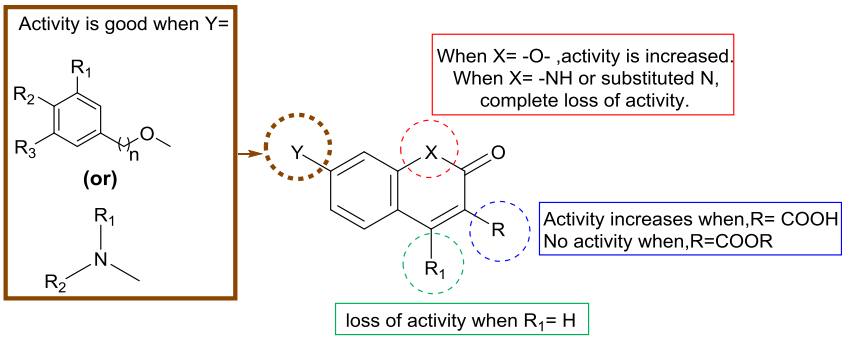
Compounds	R_1	R_2	R_3	IC_{50}(μM)^{a} B16-F10^{b}	MCF-7^{b}	hCAs II^{d}	hCA IX^{d}
39	H	H		0.17	0.020	0.023	0.124
40	$CH(CH_3)_3$	$CH(CH_3)_3$		0.19	0.032	0.063	0.024

Fig. 24. SAR of sulphonamides containing coumarin moiety.



Compound	Category	R	K_I(nM) hCA II	hCA VA
41	3,4-dihydrosulfocoumarin	OCH_3	2.4	91
42	sulfocoumarin	OCH_3	1.5	9960
43	3,4-dihydrosulfocoumarin	CH_3COO	1.5	1675

Fig. 25. SAR study of C-7 substituted sulfocoumarins and 3,4-dihydrosulfocoumarins.



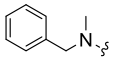
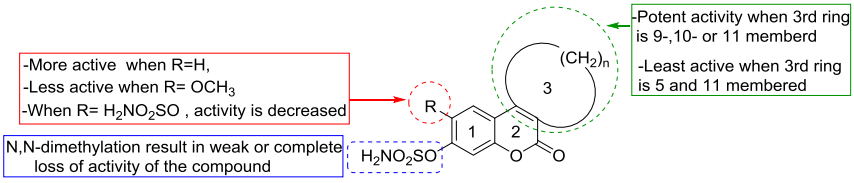
Compound	Y	X	R	R_1	Cytoxicity $EC_{50}(\mu M)$	Lactate uptake inhibition $IC_{50}(\mu M)$
44		-O-	COOH	H	0.22	0.059

Fig. 26. SAR study of carboxycoumarins.

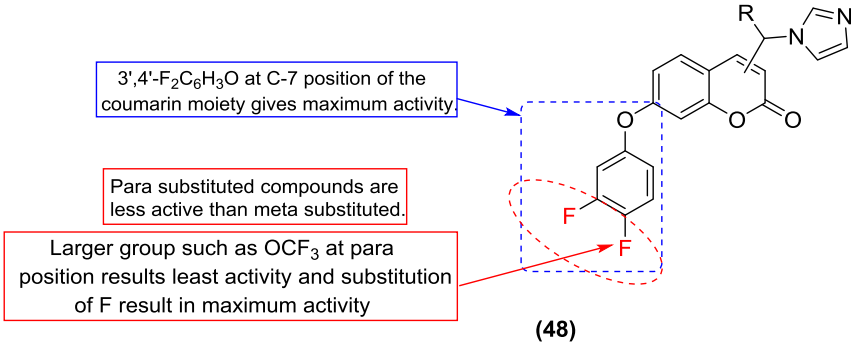


Compounds	R	n	PM $IC_{50}(nM)^{(a)}$	JEG-3 $IC_{50}(nM)$
45	H	7	2.4	0.022
46	H	8	1	0.025
47	H	9	13	0.015

Fig. 27. SAR study of steroid sulfatase inhibitors (Irosustats).

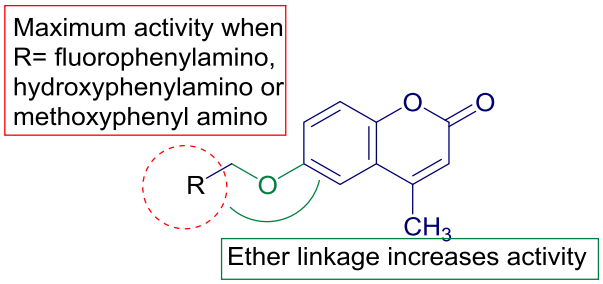
metaphase, thereby, enlightening that these derivatives targets microtubulin [82].

Further, antimitotic agents were developed by Tsyganov et al. in 2013. They semi-synthesized polyalkoxy-3(4-methoxyphenyl)coumarins from plant allylpolyalkoxybenzenes. The compounds were studied for their antimitotic activity by using the phenotypic sea urchin embryo assay. SAR study demonstrated (Fig. 23) that compound **38** was found to have evident antimitotic activity due to presence of methoxy group at C-5, C-6 and C-7 positions. It was reported that antimitotic effect of **38** was the result of targeting



Compound	R	CYP19(IC_{50})(μM)	CYP1 7Inhibition(%)
48	H	0.047	14

Fig. 28. SAR study of Imidazole derivatives of 4,7-disubstituted coumarins.



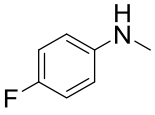
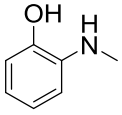
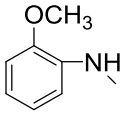
S.NO.	R	$IC_{50}(\mu M)$ Vero cells	Hep2 cells
49		30.731±0.92	3.621±0.10
50		22.880±0.79	4.196±0.12
51		21.254±0.83	5.432±0.15

Fig. 29. SAR study of 4-methyl-2h-chromen-2-one derivatives.

tubulin as at 4 μM dose cleavage arrest accompanied by formation of tuberculate eggs which is characteristic for microtubule destabilizers. Compound **38** was further tested in 60 human cancer cell lines at NCI, USA; and it has been observed that **38** caused inhibition of cancer cell growth with mean GI_{50} value of 3.981 [83].

3.7. Carbonic anhydrase inhibitors

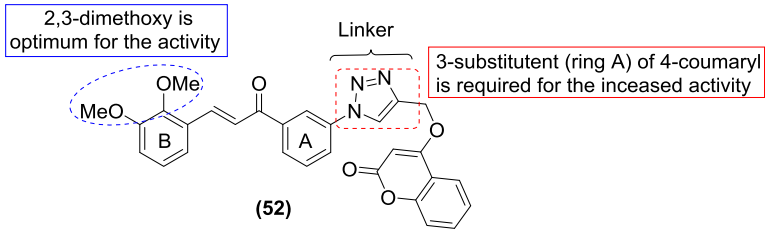
Carbonic anhydrase (CA) are controlled by the hypoxia-inducible transcription factor (HIF) and serves as an intrinsic maker of hypoxia in wide spectrum of cancer. Its expression is strongly linked to distinct types of cancer hypoxic cells. Carbonic anhydrases significantly catalyse the hydration of carbon dioxide to bicarbonates and protons contributing acidification of the tumour environment which results in acquisition of the metastatic phenotypes and chemoresistance to several anticancer drugs. Coumarins are reported to control the pH balance of tumour cells and inhibit the activity of tumour associated carbonic anhydrases in the management of hypoxic tumours [84].

Cancer-associated carbonic anhydrase inhibitors such as sulphonamides containing coumarin moiety were synthesized by Wang et al. in 2013. The synthesized derivatives were assessed for their ability to inhibit the enzymatic activity of the physiologically dominant isoenzyme human carbonic anhydrase II (hCA II) and tumour associated isoenzyme human Carbonic Anhydrase IX (hCA IX). SAR exploration (Fig. 24) verified that sulfonamide along with coumarin nucleus lead to the increased activity with high efficacy. Among all compounds, **39** and **40** having R_3 as pyrimidine moiety showed maximum activity while replacing it with isoxazole resulted in decreased activity. Most of the compounds having the unsubstituted moiety on the benzene ring of coumarin segment and the same moieties with substitution on the amino group were found to be more effective for high activity as hCA II inhibitors. But for hCA IX inhibitors the active gradient is CH_3 > t-Butyl > H [85].

In 2013, Tanc et al. developed a series of C-7 substituted sulfocoumarins and 3,4-dihydrosulfocoumarins by methanesulfonate of 2,4-dihydroxy- or 2-hydroxy-4-methoxbenzaldehyde followed by derivatization reaction, which were found to have carbonic anhydrase inhibitory activity. A number of new classes of coumarins of carbonic anhydrase inhibitors were reported as a lead; one such class is sulfocoumarins. SAR study (Fig. 25) indicated that substitution at C-7 position of coumarin nucleus strongly influence the human carbonic anhydrase VA (hCA VA) inhibition which suggests that bulkier moiety increases the activity but nature of these groups was not relevant for hCA II inhibition. It was also reported that presence or absence of double bond in the compound doesn't affect the hCA II inhibitory activity but its absence in **41** increases its hCA VA inhibitory activity. It was concluded that **41** was the most potent hCA VA inhibitor and **42**, **43** were potent hCA II inhibitor [86].

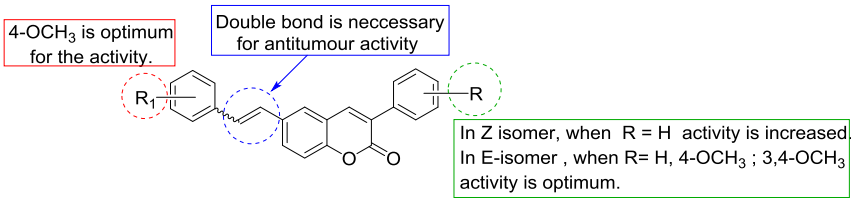
3.8. Monocarboxylate transporters (MCT) inhibitors

Coumarins are found to block lactate uptake Under hypoxia, cancer cells consume glucose and release lactate at a higher rate which is recaptured by oxygenated cancerous cells to fuel TCA cycle and enhance the tumour growth. Monocarboxylate transporters (MCTs) are the main lactate transporters and MCT1 as well as MCT4 are significantly expressed in cancer cells [87]. MCT1 has been found to show better affinity for lactate which allows the entry of



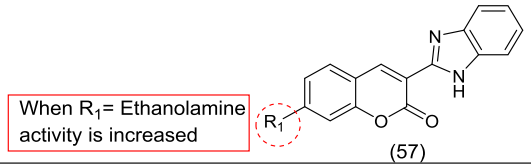
Compound	IC_{50} (μM) HuCCA-1	HepG2	A549	MOLT-3
52	2.36±0.14	4.26±0.29	18.06±1.07	0.53±0.08

Fig. 30. SAR of coumarin-chalcones hybrids.



Compound	Configuration	R	R_1	$IC_{50}(\mu M)$ MCF-7	HCT-28	K562
53	Z isomer	H	4-OCH_3	10.89	10.65	3.79
54	E isomer	H	4-OCH_3	7.32	3.78	13.02
55	E isomer	4-OCH_3	3,5-OCH_3	11.23	19.16	11.53
56	E isomer	3,4-OCH_3	4-OCH_3	4.23	7.14	8.76
	TMRV			8.41	4.83	6.39

Fig. 31. SAR of resveratrol-coumarin hybrid.



Compound	R_1	Percentages growth inhibition of compounds NCI-H23	SF-295	MALME-3M	OVCAR-4	CAKI-1
57	HO, NH_2 Ethanolamine	32.85	24.51	29.78	44.75	22.41
5-Fluorouracil		32.85	69.0	58.2	59.4	39.4

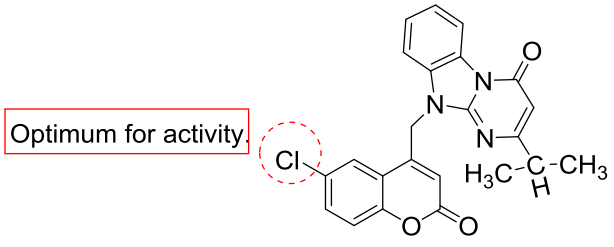
Fig. 32. SAR of coumarin-benzimidazole hybrids.

lactate into oxidative tumour cells while MCT4 shows low affinity but higher turnover rate and is expressed in glycolytic tumour cells as well as tumour-associated fibroblasts that export lactate [88]. Thus, MCTs blockade by coumarins prevent the use of lactate by oxygenated tumour cells and force them to depend on glucose. Hence, Hypoxic tumour cells which depend on glucose and have no access to replacement, die from the glucose deprivation [89].

Thus, in 2013 Draoui et al. synthesized carboxycoumarins and evaluated the lactate transport inhibitory activity of the compounds. A careful SAR examination (Fig. 26) revealed that carboxylic acid functionality was necessary for the activity and replacing it with ester group lead to the complete loss of the activity. O-benzyl and secondary amino group on the C-7 of carboxycoumarin resulted in improved activity. However, substitution of C-7 position with methyl group and replacement of lactone by lactam moiety provided an inactive compound. Thus, oxygen of carboxycoumarin and freedom at position 4 is indispensible for the impairment of lactate entry. Compound **44** with EC_{50} (μM) = 0.22 and IC_{50} = 0.059 on comparing with reference compound α-Cyano-4-hydroxycinnate (CHC) with EC_{50} (μM) = 10.7 and IC_{50} = 43.5 was found to be the most potent inhibitor of lactate uptake without any anticoagulant side effect and its *in vitro* ADME study indicated that **44** exhibited good aqueous solubility which is a problem with majority of the coumarin analogues [90].

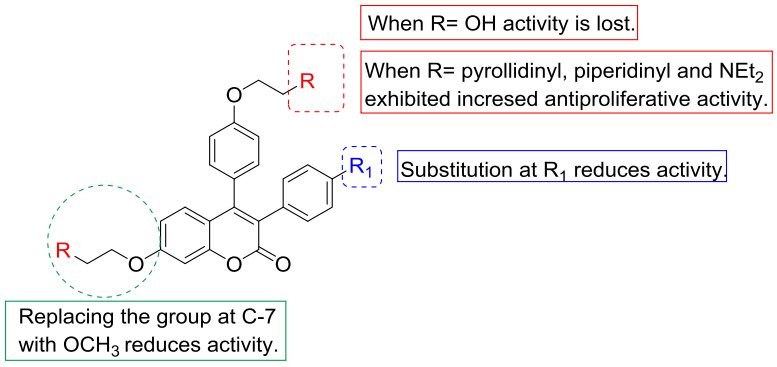
3.9. Aromatase/sulfatase inhibitors

Coumarin derivatives are also able to modulate several cancer specific enzymes such as aromatase and sulfatase [91,92]. Steroid sulfatase (STS) is responsible for converting oestrone sulphate to active hormones, therefore, inhibition of these enzymes by bicyclic and tricyclic coumates, decreases the biosynthesis of active hormones which are responsible for breast, endometrial and prostate cancer [93]. They also inhibit aromatase to prevent the conversion of other hormones such as androgens into oestrogen. Thus, inhibition of the aromatase also results in inhibiting the formation of genotoxic metabolites of oestrogen. Such metabolites include catechol oestrogens that induce mutations and inhibition of other



Compound	Number of cells Live	Dead	%of dead cells
58	12	88	88
5-Fluorouracil	12	88	88

Fig. 33. SAR study of dihydrobenzo [4,5]imidazo[1,2-a]pyrimidin-4-one derivative.



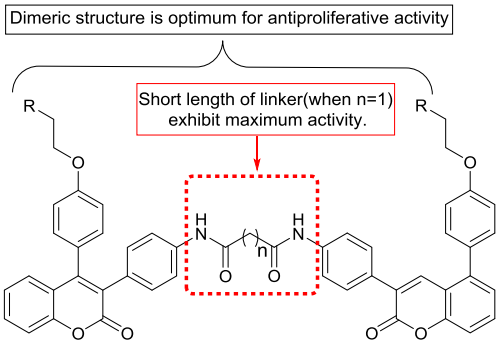
Compounds	R	R_1	IC_{50}(μM) A549	K562	MCF-7	Bel-7402
59		H	6.31 ± 0.42	4.58± 1.31	12.35±1.60	8.66±0.61
60		H	6.64±0.44	2.91±0.09	11.36±1.60	8.19±0.52
61		H	8.31±0.42	3.79±0.29	7.90±0.82	8.04±0.30

Fig. 34. SAR study of triphenylethylene-coumarin hybrids.

carcinogenic metabolites such as 2-hydroxyl-oestradiol and 4-hydroxy-oestradiol [94,95].

SAR studies (Fig. 27) on coumarin derivatives known as Irosustats (STX64, BN83495) were conducted by Woo et al. in 2011. This was the first class of steroid sulfatase inhibitors (STS) to enter clinical trials for patients with hormone-dependent cancer. It was observed that the main attention was shifted to the expansion of aliphatic ring, transfer of sulfamate group and N,N-dimethylation of sulfamate group. The most potent compounds found were **45**–**47** in which third ring was 9-, 10- and 11-membered respectively. N,N-dimethylation was found to be inactive during *in vitro* analysis. Reallocating of sulfamate group from C-7 to C-6 of coumarin moiety resulted in significant decrease in the activity and high inhibitory activity was resulted from conjugation of C-7 positioned sulfamate group with α,β-unsaturated lactone ring of coumarin nucleus. Introduction of methoxy group at C-6 rendered a feebly active compound. They also concluded that coumarin was the core moiety for the development of STS inhibitors [96].

In 2011, Stefanachi et al. synthesized imidazole derivatives of 4,7-disubstituted coumarin as aromatase inhibitors which were selective over 17-α-hydroxylase/C-17-20 lyase. Biological assays were done to test all the molecules for the inhibitory activities



Compounds	n	R	IC_{50} (μM) MCF-7	A549	K562	Hela
Cisplatin	-	-	9.26±1.14	8.37±1.08	5.69±0.83	8.06±0.95
62	1		3.52±0.48	7.73±0.93	3.23±0.39	42.49±5.05
63	1		8.57±0.42	8.44±0.96	0.98±0.08	7.82±0.82

Fig. 35. SAR study of dimeric compounds.

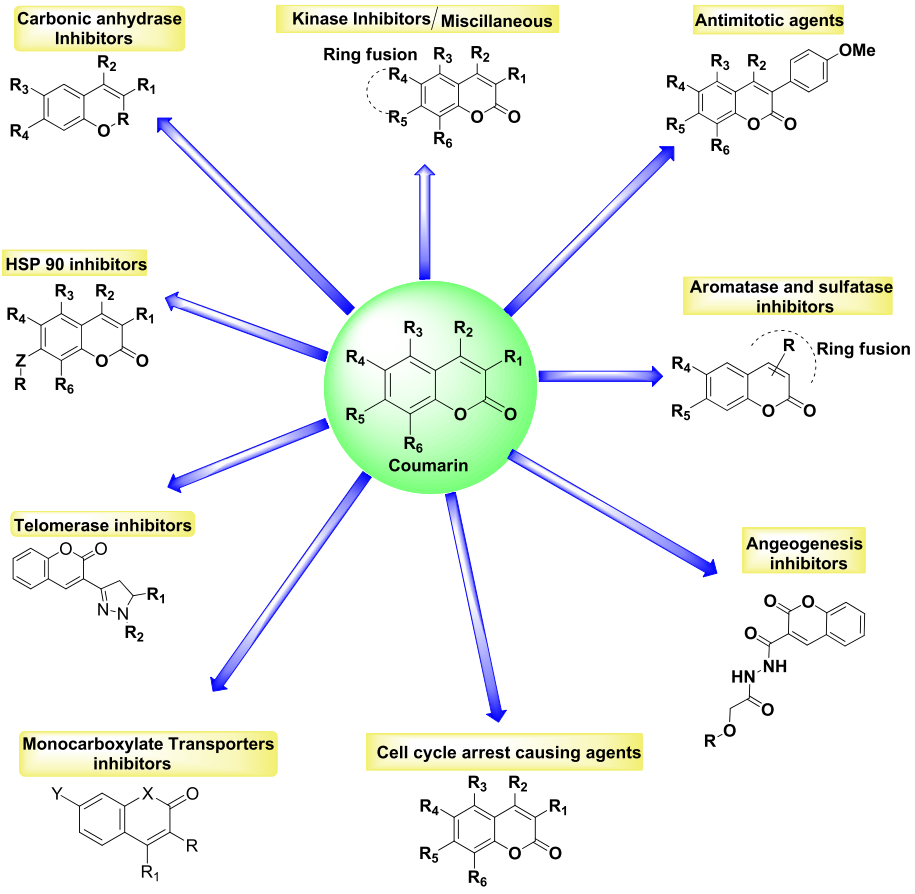


Fig. 36. Concerted summary of SAR studies of coumarin derivatives is represented.

against P450 enzymes i.e. AR (CYP19) and 17α-hydroxylase/C17, 20-lyase (CYP17) which are responsible for catalysing the final step in oestrogen and androgen biosynthesis respectively. A cautious SAR assessment (Fig. 28) confirmed that 3′4′-$F_2C_6H_3O$ substitution at C-7 position of the coumarin moiety is responsible for maximum anticancer activity and substitution at *meta* gives increased activity than *para* position. Further, substituting *para* position with larger group may lead to the decreased or complete loss of activity. Hence, compound **48** was found to be the most active and by the guidance of docking study **48** was taken to evaluate the selectivity of ARIs over other CYPs involved in biosynthesis of steroids [97].

3.10. Miscellaneous agents

Patel et al. in 2011, accomplished *in vitro* cytotoxic screening against Hep2 cell line and illustrated SAR study of 4-methyl-2h-chromen-2-one derivatives. Among all compounds, **49**–**51** were found to be most potent on comparison to their reference drug Methotrexate. IC_{50} value of Methotrexate was observed as 24.631 ± 0.67 and 9.798 ± 0.18 on vero and hep2 cells respectively. A vigilant SAR (Fig. 29) exploration verified that substitution of phenyl ring at position R with *para*-fluoro, *ortho*-OH and *ortho*-OCH_3 showed maximum activity. Compound **49** displayed maximum cytotoxic activity which suggested that the activity enhances on increasing the distance of substituents on phenyl ring [98].

In 2014, novel coumarin-chalcones hybrids were prepared by Pingaew et al., which were later on biologically appraised to explore anticancer activity against four cancer cell lines which included HuCCA-1, HepG2, A549 and MOLT-3. SAR analysis (Fig. 30) signified that higher cytotoxicity depends on the substitution pattern of different substituents on the ring A and B of the coumarin nucleus. Therefore, among all synthesized derivatives compound **52** exhibited higher efficacy of about 7 fold more active than etoposide (standard) because of the substitution of 2,3-dimethoxy on ring B and 3-substituent on ring A of the coumaryl analogue. It was also reported to exhibit some toxicity towards non-cancerous cells [99].

Resveratrol-coumarin hybrids were synthesized by Shen et al. in 2011, they further explored the SAR features (Fig. 31) on the basis of the biological results. It was observed that trans-6-substituted styryl hybrid compounds were more active than *cis*-6-substituted styryl hybrid compounds. It was reported that *trans* form hybrid compound get more easily fixed in the receptor than *cis* form hybrids. They also suggested that the steric conformation of the double bond at 6th position is necessary for the antitumour activity. Different substitutions played an important role in the inhibitory activity, such as 4-methoxy group is needed for activity while 3, 5-methoxyl group is unnecessary. Thus, it was concluded that compounds **53**–**56** showed higher degrees of growth inhibition [100].

Paul et al. in 2013 synthesized coumarin-benzimidazole hybrids. From the preliminary study of biological activity of coumarin-benzimidazole hybrids, they suggested that compound **57** exhibit better inhibitory activity towards most of the cell lines. SAR study (Fig. 32) authenticated that presence of ethanolamine at position-7 of the coumarin-benzimidazole hybrid resulted in a better activity. Further docking study showed that H-bonding in the active site of topoisomerases II, ribonucleotide reductase (RNR) and dihydrofolate

reductase (DHFR) also supports its activity [101].

In 2013, Puttaraju et al. synthesized coumarin-benzimidazole hybrids under microwave irradiation and evaluated its anticancer property. Compound **58** (Fig. 33) having 6-Cl substitution was found to be as potent as its reference compound 5-fluorouracil when tested for its *in vitro* evaluation by using trypan blue assay method [102].

In 2013, Chen et al. designed, synthesized and evaluated the antiproliferative activity of novel triphenylethylene-coumarin hybrids. They reported that compounds **59**–**61** demonstrated a broad-spectrum antiproliferative activity. Further SAR analysis (Fig. 34) suggested that the number of amino alkyl chain on 3,4-diphenylcoumarin have significant impact on antiproliferative property and the activity is enhanced by two side chains and presence of a weaker basic amino group on the side chain has a negative impact on the antiproliferative action [103].

Dimers of coumarin derivatives were synthesized by Tan et al. in 2014. They prepared dimeric compounds and evaluated antiproliferative activity by halting the cell growth and cell survival along with DNA binding property of coumarins by using cisplatin as positive control. It was observed by SAR investigation (Fig. 35) that compounds **62** and **63** with linker malonic amide (three carbons) exhibited significant antiproliferative activity without affecting normal cells, but as the linker is prolonged to five, six, or ten carbons the antiproliferative activities of the dimeric compounds decreases. This implies that when the two sole side chains of the dimeric compounds are close to each other the activity is increased drastically. Further, compound **62** was found to show highest binding affinity, thus, verifying that compound possessing linker of short length is beneficial for DNA binding [104].

Concerted summary of SAR studies of coumarin derivatives is represented in Fig. 36.

4. Conclusion

Coumarins are the small molecules that act as anticancer agents by targeting abundant mechanisms that appear to be involved in a variety of cancers. Researchers have explored for their inhibitory activity towards kinases, cell cycle arrest, angiogenesis, heat shock protein (HSP90), telomerase, mitosis, carbonic anhydrase, monocarboxylate transporters, aromatase and sulfatase. Investigators studied/developed their SAR as well as conformation and configurational requirements for binding site through docking simulation studies. There is still a lot to explore about the coumarin and its various interaction networks toward diverse targets. Currently existing data shows that all coumarins derivatives covered in this manuscript are reported to exhibit a tremendous anticancer potential. Analogues, such as 3-(4,5-dihydro-1-phenyl-5-substituted phenyl-1H pyrazol-3-yl)-2H-chromen-2-one derivatives which not only exhibit excellent anticancer activity but also show the increased bioavailability. Thus, such similar derivatives can be explored which may lead to the development of a potent anticancer pharmacophore.

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