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Recent advances on anticancer activity of coumarin derivatives

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ABSTRACT

Coumarin derivatives are important class of natural plant metabolites that offer variety of biological activities. They can also be derived synthetically, and a wide variety of synthetic coumarin derivatives (azoles, sulfonyl, furan, pyrazole etc) have shown promising anticancer, antitumor and anti-proliferative activities. Coumarin derivatives are not only effective anticancer agents, but also possess minimum side effects. On the basis of different substitution patterns, these potents have displayed tremendous capability to regulate the potential anticancer activities. In view of the above, efforts have been made by the scientists to develop its scaffolds that possess minimal side effects. This review article covers the recent developments of coumarin derivatives that are biologically active against various cancer cell lines. Further, it also highlights the evaluation of these active candidates via *in vivo*, *in vitro*, MTT assay. The ongoing developments in the discovery of novel anti-cancer agents and their effectiveness using Structural Activity Relationship is also discussed in detail.

1. Introduction

Cancer is a lethal disease, and it is responsible for the millions of deaths across the globe every year. According to the latest IARC reports, a total of 19.3 million cases and 10 million cancer deaths have occurred in 2020 globally [1]. In addition, the key sheet of WHO reported that cancer is responsible for about 9.6 million global demises in 2018, and one out of every sixth death is related to this [2]. Cancer is defined as the uncontrolled growth of abnormal cells in the body. When cancer is developed in the body, old cells do not die and instead grow out of control, forming new, abnormal cells. These abnormal cells cause rapid DNA replication and inhibit the protein secretion of normal cells. Some cancers such as lung cancer, breast cancer, cervical cancer and prostate cancer are the most common spreading among the people worldwide. Recent survey revealed that, lung cancer and breast cancers accounts for 1.8 and 0.6 million deaths respectively. Among the various cancer types, female breast cancer is the most leading cause of deaths in women and one out of every four women are suffering from this deadly disease [3]. Conventional therapies such as surgery, chemotherapy and radiotherapy are available for the cancer treatments to a significant extent, but they may damage normal cells [4].

Coumarins are oxygenated heterocyclic polyphenolic compounds that are extensively distributed in plant kingdom. About 1300 chemotypes have been recognised as secondary metabolites in plants, bacteria and fungi. Its derivatives occur in the roots (*Ferulago campestris)*, leaves *(Murraya paniculata)*, fruits *(Aegle marmelos)* and seeds (tonka beans) of plants [5]. These scaffolds play an intriguing role in the cancer treatments. The coumarin derivatives can trigger cell cycle arrest, angiogenesis inhibition, kinase inhibition, telomerase inhibition, carbonic anhydrase inhibition on various cancer cells [6]. The substitution patterns in the coumarin nucleus govern its therapeutic applications and pharmacological properties. The classification of coumarin is presented in Fig. 1.

In recent years, several studies reported the development of novel anticancer molecules and their detailed structure–activity relationship (SAR) studies. In a study, authors developed a series of new benzo[d] thiazole-hydrazones and examined their *in-vitro* inhibition of H+/K+ ATPase and anti-inflammatory effects. The study concluded that the synthesized compounds have displayed excellent inhibitory activity against H+/K+ ATPase. In addition to this, the synthesized compounds have exhibited good docking scores for inhibitory activity against H+/K+ ATPase [7]. Another study reported the synthesis of arylnaphthalene lactones from a wide range of different parts of plants. These arylnaphthalene lactones have provided significant biological activities and created them as potential candidates in drug discovery and development [8]. Furthermore, several review articles described the latest information about the development of effective drug analogues. The mechanism of action and the SAR of the latest potential anticancer molecules are broadly discussed [9–15]. However, the present review aims to provide

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Abbreviations

IARC	International agency for research on cancer
WHO	World health organisation
DNA	Deoxyribonucleic acid
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide;
CA	Carbonic anhydrase
HCA	Human carbonic anhydrase
TGFβ1	Transforming growth factor β1
Gal-1	Galactin-1
SAR	Structural activity relationship;
ALP	Alkaline phosphatise;
CDK2	Cyclin dependent kinase
ERα	Estrogen receptors alpha
EWG	Electron withdrawing group;
EDG	Electron donating group;
EGFR	Epidermal growth factor receptor
COX-2	Cyclooxygenase-2
DOX	Doxorubicin
ZBG	Zinc binding group;
HDACs	Histone deacetylases
ERMAs	Energy restriction mimetic agents
MCRs	Multicomponent reactions
hTERT	human telomerase reverse transcriptase
VEGFR-2	Vascular endothelial growth factor receptor 2
Ct-DNA	Calf thymus-DNA
5-LOX	5- Lipoxygenase
5-FU	5-Fluorouracil
TrxRs	Thioredoxin reductases
RTKs	Receptor tyrosine kinases
PI_3K	Phosphatidylinosito-3-kinase
MEK	Mitogen-activated Protein
MDR	Multi drug resistance
P-gp	P-glycoprotein
ERKs	Extracellular regulated protein kinases
HIFα	Hypoxia-inducible factor alpha
BMP2	Bone morphogenetic protein 2
RUNX 2	Runt-related transcription 2
c-myc	Cellular myelocytomatosis oncogene
MMP	Mitochondrial membrane potential
cyt(c)	Cytochrome C
HDAC 8	Histone deacetylase 8
MAPK 8	Mitogen activated protein kinase
mRNA	messenger ribonucleic acid
ROS	Reactive oxygen species
apaf-1	apoptotic protease activating factor-1

cutting-edge information on different coumarin-based anticancer scaffolds that have been reported in the last five years. Additionally, compilation of various research reports on natural and synthetic coumarin derivatives with anticancer activity and their SAR studies on coumarin core was extensively discussed. The overall objective of the present review is to describe the novel bioactive coumarin analogues that can overcome the side effects such as severe cytotoxicity and chemotherapeutic resistance.

2. Coumarin structure

The word coumarin has been derived from the French word "*coumarou*" for the Tonka bean and it was isolated as a natural product in 1820 for the first time [16]. It is extensively available in various parts of the plant kingdom, and its derivatives occur alternatively in the roots, stems, fruits and seeds of plants [5]. Usually, coumarins exist as free state in plants owing to their polar structure, and they exhibit blue fluorescence on UV-light absorption. Apart from the good pharmacological profile, coumarin derivatives are widely used in aroma enhancing in cosmetic industry. Particularly, extended conjugation in coumarin rings with electron rich and charge transfer properties enable this scaffold to interact with the molecules and ions. Its chemical structure arises from the fusion of benzene ring with pyran-2-one. Therefore, its systematic name is 2H-1-benzopyran-2-one [5]. Adoption of numbering can be overlooked and indexed. Oxygen holds 1 position, carbonyl carbon receives position 2 and so it goes around the ring.

3. Anticancer activity of selected coumarin derivatives

3.1. Coumarin azole hybrids

Azoles are an important class of nitrogen heterocycles that are present in various anticancer agents as fragments. The coumarin azole hybrids are promising biological agents that enhance the pharmacological activity. As a result, these hybrids have been chosen for the development of anticancer drugs [6]. The anticancer activity of a few triazole-based coumarins is discussed in the following sections (see Fig. 2).

3.1.1. Coumarin-triazole hybrids

Coumarin carrying triazole moiety has gained wide attention from the researchers and is largely used as anticancer scaffold [17]. Triazole moiety favours improvement in solubility and enhances binding affinity to the receptors and enzymes [18]. The chemical structures of various triazole based coumarin derivatives are presented in Fig. 3. In order to achieve good biological activity, triazolyl-coumarin based fluorescent probes were designed to evaluate cytotoxic activity against MCF-7 and HeLa cancer cell lines. The compounds **1a** and **1b** (MTT cytotoxicity) were turned out to be the most potent [19]. These unique templates played a major role in diagnosis and therapy.

CA isoforms play an active role in the mechanism of many diseases and the over expression of CA related proteins result tumor development in hypoxia [20]. Belma and co-workers designed **2a, b** (MTT assay) scaffolds as the highest inhibitors against hCA XII and IX respectively [21]. Whereas, the molecular docking revealed that the novel compound **3** effectively restrained the CA IX and CA XII expression. In the nutshell, these hybrids could inhibit CA expressions by forming hydrophobic interactions with targeted proteins [20]. Several reports highlighted that triazole nucleobases improve the solubility and generate synergistic activities. The candidate 4 (*in-vitro* antiproliferative activity) presented promising activity and down regulated the TGF β1 [18].

Notably, compound **5** (MTT assay) presented significant cytotoxicity by targeting Gal-1 protein apoptosis in cell treatment as compared to the positive control cisplatin [22]. In addition to this, coumarin tagged β-lactum triazole hybrids aided in DNA replication and controlled DNA damaging. SAR studies proposed that the presence of nitro and chloro group on phenyl at C-3 position favoured the anticancer activity as a result **6a**, **6b** exhibited substantial activity [23].

Other lead candidates of coumarinyl-triazolothiadiazene were designed as ALP inhibitors. Compound **7** expressed an apical inhibition and cytotoxicity as compared to the standard compound Cisplatin [17]. Docking analysis proposed feasible interaction of triazole-coumarin scaffold with CDK2 as well as presentable cytotoxicity profile. The extent of H-bonding and good electrostatic interaction improved the anticancer activity of compounds **8, 9** providing highest cytotoxic activity equipotent to test control [24]. However, these analogues imparted anticancer activity but their testing for toxicity is required. The SAR

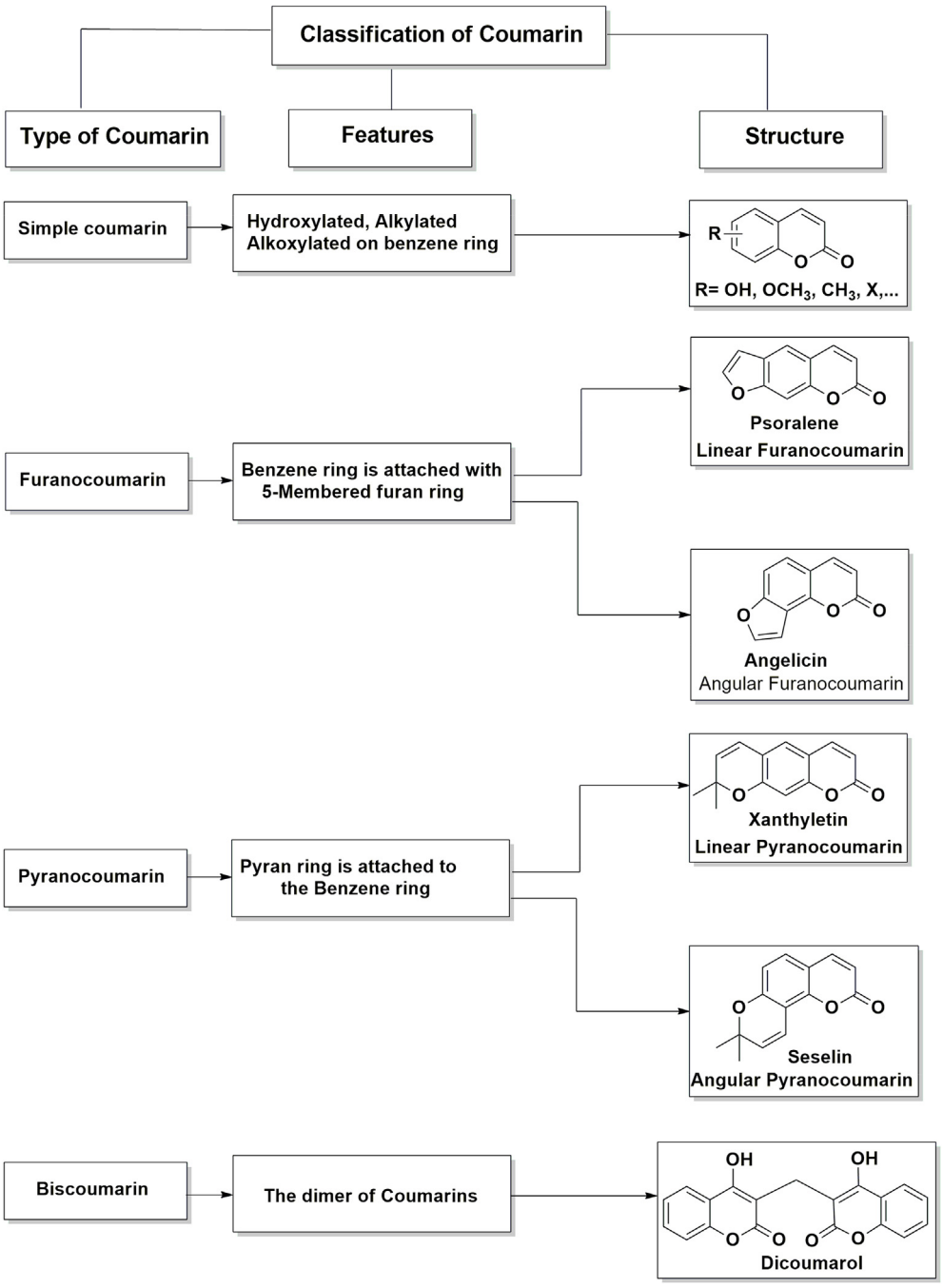


Fig. 1. Classification of coumarin based on its type, feature and structures.

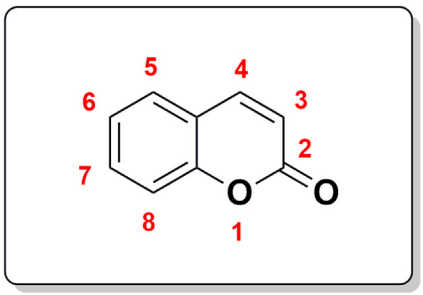
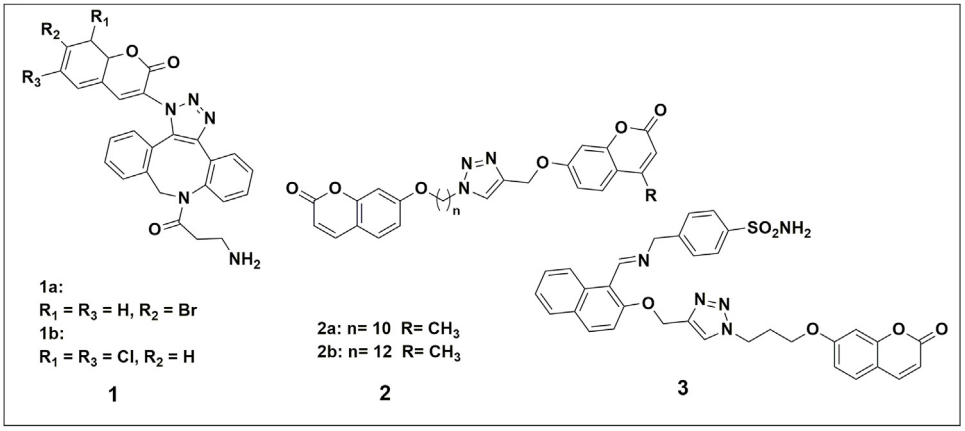


Fig. 2. The typical representation of coumarin structure formation.

indicated C-3, C-4 and C-8 as the favourable positions for substitution of aromatic heterocycles in the coumarin triazole moiety. Introduction of EWG (halogens, NO_2) enhanced cytotoxicity in compounds **1a,b,4,5** and **6a,b.** Whereas, the anticancer efficacy is greatly increased after the introduction of linker with EDG in compounds **2a,b,3,7,8** and **9.**

3.1.2. Coumarin thiazoles/oxazoles

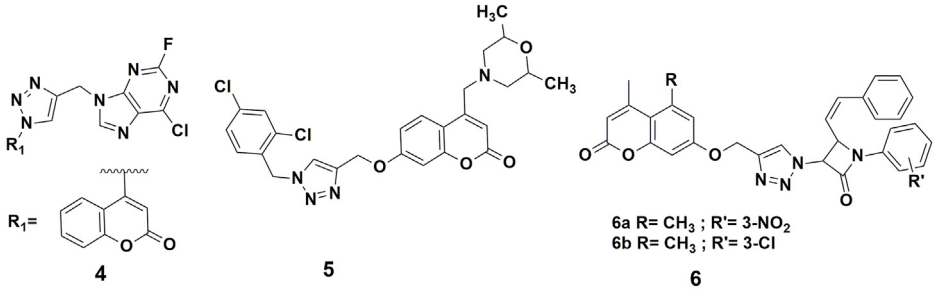
Thiazoles are the heterocycles consisting of two biologically active groups with N and S. They are available naturally and synthetically with diverse pharmacological activities. Their illustration with coumarin in the drug development has been proven as the promising anticancer agents. The chemical structures of important thiazole coumarin derivatives are presented in Fig. 4. The EGFR expression is present in malignant cancer cells such as lung, breast, colorectal and other cancers. In



Comp.	IC50 (μM)	
	MCF-7	HeLa
1a	10.65±0.68	18.24±1.15
1b	9.83±0.69	17.5±1.22
Cisplatin	18±0.5	10±0.6
Dioxorubicin	5.2±0.92	3.83±0.49

Comp.	IC50 (μM)	
	HepG2	769P
2a	4.739±0.015	3.194±0.011
2b	1.260±0.013	7.580±0.011
Dioxorubicin	0.820±0.090	0.450±0.040

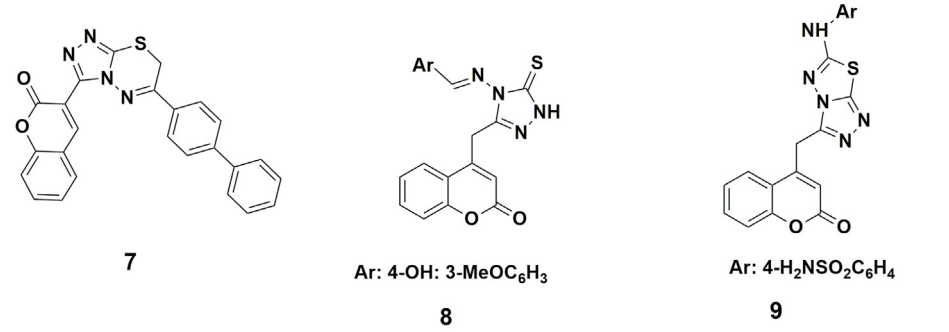
Comp.	IC50 (μM)	
	HT – 29	HEK293T
3	17.01±1.35	118.73±1.19
Dox	5.38±1.40	1.051±0.57



Comp.	IC50 (μM)	
	MGC-803	SGC-7901
4	2.86±0.46	1.28±0.08
5-FU	3.38±0.53	2.96±0.47

Comp.	IC50 (μM)
	MG-63
5	0.80±0.22
Cisplatin	17.42±0.77

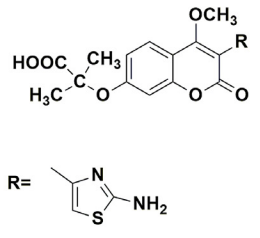
Comp.	IC50 (μM)
	MCF-7
6a	53.55
6b	58.62
Plumbagin	3.5



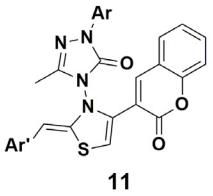
Comp.	IC50 (μM)
	H-157
7	1.01±0.12
Cisplatin	1.31±0.03

Comp.	IC50 (μM)
	HCT116
8	4.363
9	2.656
Doxorubicin	2.601

Fig. 3. The chemical structures of important coumarin-triazole hybrids.



10

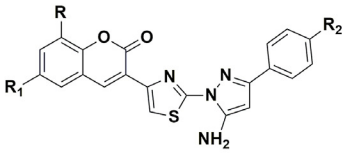


11

11a
Ar = -C_6H_5 ; Ar' = 4- Cl-C_6H_4
11b
Ar = 4- CH_3O- C_6H_4 ; Ar'= -C_6H_5
11c
Ar = 4- CH_3O- C_6H_4 ; Ar' = 4- Cl-C_6H_4
11d
Ar = 4- CH_3- C_6H_4 : Ar' = 4- CH_3O- C_6H_4
11e
Ar = 4- CH_3- C_6H_4 ; Ar'= 4- Cl- C_6H_4

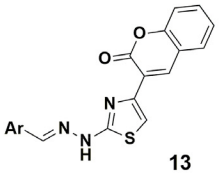
Comp.	IC_{50} (μM)	
	MDA-231	MCF-7
10	4.84±0.17	2.39 ±0.03
5-Fluorouracil	1.96±0.087	1.86±0.06
Doxorubicin	3.76±0.18	3.24±0.15

Comp.	IC_{50} (μM)			
	MDA MB-231	A549	K562	HeLa
11a	0.21	0.32	0.41	0.21
11b	0.22	0.39	0.31	0.29
11c	0.16	0.17	0.31	0.25
11d	0.20	0.52	0.36	0.32
11e	0.28	0.57	0.48	0.36
Doxorubicin	0.54	0.54	0.60	0.56

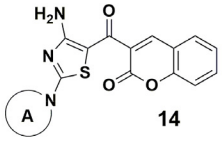


12

12a: R=R_1= -$C(CH_3)_3$: R_2= H
12b: R=R_2= H: R_2= -$N(CH_2CH_3)_2$

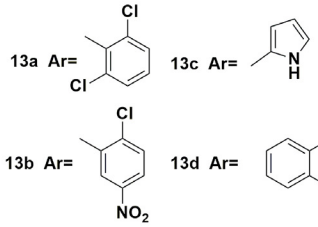


13



14

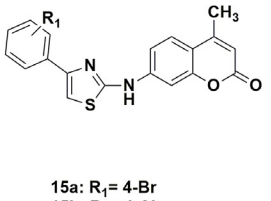
A: Thiomorpholino



Comp	IC_{50} (μM)	
	DU 145	MCF-7
12a	7±1	9±6
12b	8±1	8±2
Doxorubicin	4.2	3.0

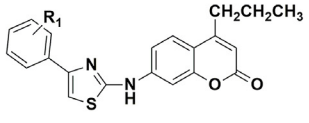
Comp.	IC_{50} (μM)	
	Hela	COS-7
13a	1.90	>50
13b	1.42	1.96
13c	6.25	12.50
13d	1.29	1.66
Doxorubicin	2.05	3.04

Comp.	IC_{50} (μM)		
	MCF-7	HepG2	SW480
14	7.5±0.7	16.9±0.7	13.0±0.6
Etoposide	3.1±0.6	6.2±0.5	7.7±1.5



15a: R_1= 4-Br
15b: R_1= 4-Cl
15c: R_1= 3-NO_2
15d: R_1= 2-OMe

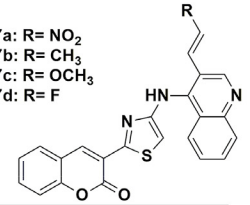
15



16a: R_1= 4-Br
16b: R_1= 4-Cl

16

17a: R= NO_2
17b: R= CH_3
17c: R= OCH_3
17d: R= F



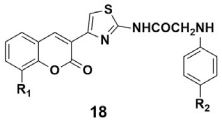
For A549: R=F at C-2 position in the acrydine increases the activity. For MDA-MB-231: R=OCH_3, CH_3 at C-2 position in the acrydine increases the activity.

17

Fig. 4. Chemical structures of important coumarin thiazole/oxazole hybrids.

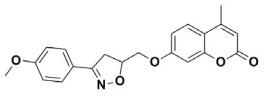
Comp	IC_{50} (μM)	
	HT-29	HCT-116
15a	0.38±0.044	0.53±0.077
15b	0.37±0.077	0.31±0.014
15c	0.37±0.017	0.32±0.041
16a	0.25±0.004	0.26±0.016
16b	0.33±0.032	0.34±0.0009
4-Hydroxycoumarin	>200	>200
OSU-CG5	10.14±0.373	2.85±0.111
OSU-CG12	10.82±1.259	3.4±0.581

Comp.	IC_{50} (μM)	
	MDA-MB-231	A-549
17a	14.06±1.12	17.13±1.23
17b	12.03±1.09	35.15±1.88
17c	08.03±0.81	31.11±1.79
17d	13.13±1.15	05.18±1.04
Cisplatin	04.13±1.07	02.14±1.03

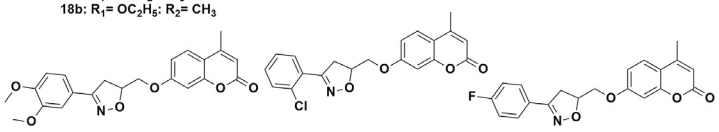


18

18a: R_1 = H: R_2=CH_3
18b: R_1= OC_2H_5: R_2= CH_3



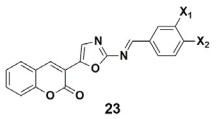
19



20 21 22

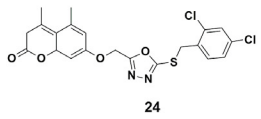
Compound	IC_{50} (μM)
	UACC 903
19	8.8
20	10.5
21	9.2
22	10.5

Comp.	IC_{50} (μM)
	Hep-G2
18a	1890
18b	15327
Cisplatin	11898

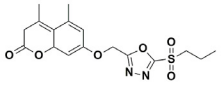


23

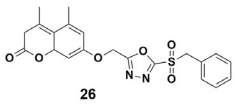
23a: X_1= H; X_2= Cl
23b: X_1=OH; X_2=OCH_3



24



25



26

Comp.	IC_{50} (μM)
	MCF-7
23a	74.1
Tamoxifen	4.3

Comp.	IC_{50} (μM)
	HCT116
23b	71.8
5-Fluorouracil	12.7

Comp.	IC_{50} (μM)
	MCF-7
24	<5
Tamoxifen	7.09

Comp.	IC_{50} (μM)
	MDA MB-231
25	7.07
26	7.07
Tamoxifen	47.1

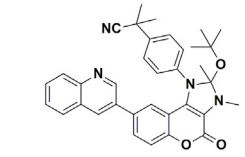
Fig. 4. (*continued*).

recent advances coumarin thiazole derivatives were docked onto EGFR and COX-2 enzyme. Compound **10 (***in vitro* Cytotoxicity) followed by the compounds **11a-e (***in-vitro* anticancer activity) and compounds **12a, b** (*in vitro* anticancer activity) formed stable complex with EGFR against the standard DOX [25–27].

On the other hand, hydrazinyl thiazoles showed zero or no violation of Lipinski's rule and were synthesized as new ZBG because HDACs undergo deacetylation by Zn^{2+} in ZBG catalyst. HDACs aberration was

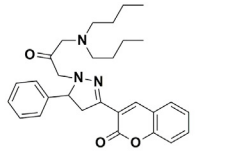
observed in HeLa and COS-7, therefore, compounds **13a-d (***in vitro* antitumor activity) manifested tremendous activity superior to DOX [28]. In a study, authors synthesized thiomorpholine coumarin derivatives out of which compound **14** (*in vitro* cytotoxic activity) successfully induced apoptotic cell death and caused G-1 phase arrest in cell cycle [29].

Anchoring aminotriazole thiazole in coumarin cage highlighted synergistic activity and targeted the cellular energy machinery in cancer cells. These ERMA leads **15a, 15b**, **15c**, **16a, b** verses OSU-CG5 and OSU-CG12 were highlighted as promising anticancer agents [30]. Likewise, momentous cytotoxicity was observed in the compounds **17a-d, 18a** and **18b** (*in-vitro* cytotoxic activity) equivalent to cisplatin [31,32]**.** SAR



Quinolin-3-yl at C-6 position, methyl and tert-butoxy at imidazole ring contributes in good inhibitory activity

27

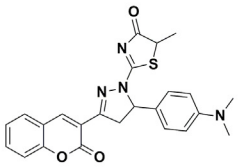


N-acetyl part connected with aliphatic amine substituent containing short-chain increase anticancer activity.

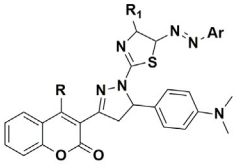
28

Comp.	IC50 (μM)				
	HCT116	MCF-7	SW620	CT26	A549
27	1.40±0.5	1.70±0.3	3.55±1.3	3.50±0.7	9.50±1.8
Cisplatin	12.30±2.9	4.50±1.8	12.40±2.6	15.10±2.6	9.97±2.1

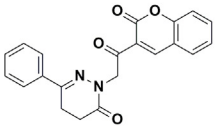
Comp.	IC50 (μM)			
	PC3	Bcap-37	MGC-803	HepG2
28	4.80±0.95	3.37±0.30	2.96±0.15	2.45±0.11
AMD	0.87±0.21	1.12±0.09	1.01±0.17	1.34±0.15



29



30

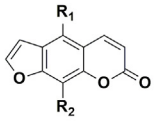


31

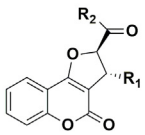
30a: R=H; R_1 = CH_3 Ar= 4-Cl-Ph
30b: R=OH; R_1 = Ph Ar= 4-CH_3-Ph
30c: R=H; R_1 = Ph Ar= 4-Cl-Ph
30d: R=OH; R_1 = Ph Ar= 4-Cl-Ph

IC50 (μM)	Comp.					
	29	30a	30b	30c	30d	Doxorubicin
MCF-7	10.75	8.61	6.56	6.51	5.41	6.73

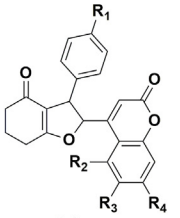
Comp.	IC50 (μM)	
	HCT-116	MCF-7
31	1.93±0.22	1.25±0.31
Doxorubicin	0.83±0.55	0.74±0.41



32



33



34

32a: R_1 ; R_2= H
32b: R_1 OCH_3 ; R_2=
32c: R_1 =OCH_3 ; R_2: OH

33a: R_1 : 3,4,5-OMe-C_6H_2; R_2= 4-OMe-C_6H_4
33b: R_1 : Phenethyl ; R_2= 4-OMe-C_6H_4

34a: R_1=R_3=H; R_2=R_4=Me
34b: R_1=R_2=R_4=H; R_3=OMe
34c: R_1=R_3=OMe; R_2=R_4=H
34d: R_1=Me; R_3=OMe; R_2=R_4=H

Comp.	IC50 (μM)	
	HepG2	HeLa
32a	8.19±0.64	17.77±1.17
32b	7.49±0.27	25.60±0.25
32c	7.46±0.03	13.48±0.85
5-Fu	3.13±0.52	3.73±0.58

IC50 (μM)	Comp.		
	33a	33b	Doxorubicin
A549	4.34	3.86	1.21
DU-145	2.13	1.99	2.14
HeLa	2.48	2.45	1.63
MCF-7	1.66	1.16	1.43

Comp.	IC50 (μM)
	A5493
34a	0.35
34b	0.28
34c	0.29
34d	0.32
Paclitaxel	0.35

Fig. 5. Chemical structures of coumarin based Coumarin pyrazole/furan hybrids.

revealed that the halogenated substituents at C_1, C_2 and C_3 provided excellent Cytotoxicity. This unique class of heterocycles have drawn much attention towards the anticancer drug discovery.

Isoxazolines have been described as an important class of heterocycles that are employed in pharmaceuticals and therapeutics [32]. The added triumph is that isoxazoline pharmacophore prospected synergetic effect with enriched affinity compared to the segments of parent structures **19–22** [33]. Wherein coumarin could act as a proactive by transporting and delivering active isoxazoline bioavailability of the active drug might be effectively inhibit the tumour growth [5].Coumarin appended oxazole derivatives **23a, b**(*in vitro* anticancer screening), **24**, **25** and **26** showed promising inhibition activity towards CDKs and ER-α respectively as compared to the posiitive controls [34,35]. Molecular hybridization and MCR approach has given positive results in solving the problem of toxicity as well as long reaction paths. SAR revealed that substitution of thiazoles and oxazoles at C-3 and C-7 position of coumarin played a crucial role in anticancer activity. Evidently, EWG group substitution at *ortho* and *para* position of phenyl ring in the compounds **11a** (against MDA MBA-231 and HeLa), **11c** (against A549 and HeLa), **11e** (against MDA MBA-231 and A549), **13a** (against HeLa), **13b** (against COS-7), **13c,d** (against HeLa and COS-7), **15a-c, 16a,b, 19–22, 23a** (against MCF-7), **24, 25, 26** (against MCF-7 and MDA MBA-231) expressed good anticancer activity. In addition to this, the incorporation of EWG at *meta* position of the phenyl ring in the compound **15c** also lead to increased efficacy towards anticancer activity. The SAR indication for the compounds **10, 11b, d, 12a d, 13c, 14, 15d, 18a, d,** and **20** displayed reduction in anticancer activities when the EDG groups were substituted.

Hence, these coumarin scaffolds have shown different types of molecular and pharmacological properties and therefore, these molecules pave the way to explore further in material as well as medicinal chemistry [26].

3.1.3. Coumarin pyrazoles/furans

Coumarin affixed pyrazoles have furnished diverse bioactivities and are potential anticancer agents. Particularly, counterfeit pyrazoles are reassuring cellular proliferation inhibitors and displayed antiproliferative activities on various human cancer cells. The synthesized compound **27 (***in vitro* evaluation) displayed an attractive anti-tumour activity as compared to positive test Cisplatin [1]. The chemical structures of important pyrazole derivatives are presented in Fig. 5.

Telomerase reverse transcriptase is the driving factor that affects the telomerase activity and the designed hTERT inhibitor **28** (*in vivo* studies) evaluated highly relative expression of anticancer activity [36]. Compounds **29, 30a-d** were witnessed as VEGFR inhibitors influenced the molecular orientation, ring size variations and the presence of heteroatoms providing H-bonding interactions with the VEGFR-2 binding pockets [37]. Whilst,*in vitro* evaluation of compound **31** was proved to be promising lead with the activity against HCT-116 and MCF-7 (43.0% and 59.2%) respectively superior to DOX (100% against both the cancer cell lines) [2]. A considerable attention has been drawn by furan, (five membered ring containing oxygen) and its combination with coumarin in demonstrating significant anticancer activity. Alkaloids of dihydrofuroquinolinone and furoquinoline are extensively dispersed in the nature and are biologically important. Keeping this in mind, the pharmacological importance of compounds **32a-c** (*in vitro*) synthesized from the roots of *Angelica dahurica* reported wide range of activities in contrast with drug resistants 5-FU [4].

Topo II breaks the DNA via catalytic enzyme activity and allows it for multiple recombination leading to the cell death. Therefore, compounds **33a, b** (cytotoxicity) were reported as topo inhibitors and displayed prominent cytotoxicity against the reported cell lines superior to DOX [38]. Surprisingly, compounds **34a-d** (cytotoxicity) were emerged as anti-inflammatory drugs as, inflammation damages DNA, unstable chromosomal fluctuation, strengthens tumour and metastasis [39]. According to the available data transcription and replication of DNA was effected by the binding mode of these drugs that inturn effected its physiological function and inhibited the tumour cell growth. Out of our expectation, molecular dynamics of the abovementioned chemotypes illustrated their good stability and Hydrogen bonding interactions. Therefore, these compounds can be counted as one of the best anticancer therapeutic agents.

As per SAR analysis C-3, C-4 and C-6 positions on coumarin demonstrated improvement in anticancer activity. In compounds **27, 28, 29, 30a, b, 31–34,** the substitution of EDG atoms on the various position of phenyl resulted excellent anticancer activity. But, in compound **30a, c, d** containing EWG at *para*-position in the phenyl moiety presented reduced efficiency.

3.2. Coumarin sulfonamides/benzamides

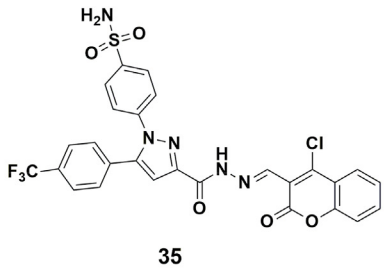
Sulfonamide derivatives are known for their antimicrobial, carbonase anhydrase and anticancer activities. On further exploration, the benzenesulfonamide congeners are potential COX-2 and 5-LOX inhibitors and found useful in cancer suppression [17]. Therefore, compound **35** was found to be more pronounced as COX-2 inhibitor superior to Celecoxib [40]. The uneven expression of either COX-2 or 5-LOX stimulates angiogenesis and blocks cell cycle apoptosis. Compound **36** (*in vitro* antiproliferative activity) modelled preliminary superiority as compared to the test control celecoxib **(0.41 ± 0.28 μM** for COX-2**)** and zileutin **(1.35 ± 0.24 μM** for 5-LOX**)** [41]. According to SAR results, the trio of the methoxy group enabled H-bonding with amino acid residues. Replacement of p-methyl with halogen also exhibited excellent anticancer activity evaluated by MTT assay.

Particularly, as shown in Fig. 6, the potential anticancer activity of compound **37** (Cytotoxic affect) was mainly attributed to the Ph-CONHN=CH- attached with C-3 position of Coumarin [42]. Other compounds **38a, b** (intrinsic binding constant = 2.64×10^4 $M^{-1}$and 8.29×10^5 M^{-1} respectively) displayed very good DNA binding (UV-based DNA titration) through intercalation and demonstrated remarkable anticancer activity (*in vitro)* [43].

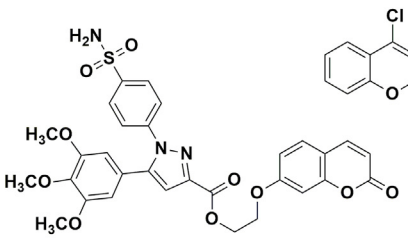
In some literature, Coumarin based benzamide **39** as the best HDAC inhibitor **(IC_{50} = 0.47 ± 0.02 μM)** were also investigated by performing SAR and *in vitro* studies. Substitution of benzyloxy was responsible for inhibiting HDAC more effectively [44]. Supported by the findings so far, these anticancer drugs could accelerate cancer cell apoptosis, inhibit proliferation, migration and invasion [40]. Besides, a significant outcome was observed by the coumarin-prolin sulfonamide hybrid derivatives. The anticancer data of the compound **40** was found to be active against MCF-7 versus 5- FU as the reference drug [45]. Known for its COX-2, LOX-5, HDAC inhibition, DNA intercalation, antioxidation and metastasis coumarin affixed sulfonamide agents have become the centre of attraction for the researches as well as the near future. The SAR results suggested that C-3 and C-7 positions of the coumarin were preferable for the heterocyclic substitution responsible for showing anticancer activity. In compounds **35, 38a,b** and **39** halogen substitution at 3, 4 positions provided very good anticancer activity. Whereas in compounds, **36, 37** and **40** EDG at benzenesulfonamide system also developed better activity.

3.3. Coumarin chalcones/furoxans

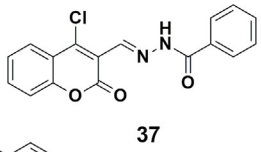
Chalcones (1, 3-diaryl-2-propene-1-ones) belongs to the flavonoid class of natural products containing two aromatic rings connected by α, β-unsaturated carbonyl group [20]. They reflect anticancer activity by forming the central core of the biologically active coumarin moiety. Therefore, they occupy an essential position in the discovery of the drugs. As presented in Fig. 7, the coumarin chalcone hybrids **41a-c (***in vitro* cytotoxicity) inhibited the telomerase cycle, increased caspases 3 and 9 and reduced oncogene phrase in HePG2 and K562) [46]. Interestingly, coumarin chalcone incorporated derivatives **42a, b** (*in vitro* antiproliferative activity) consisting urea and amide moieties provided



35



36

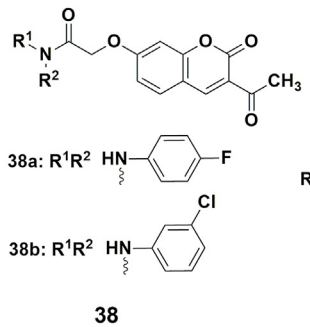


37

Comp.	IC_{50} (μM)
	HeLa
35	0.36±0.05
Celecoxib	7.79±0.84

Comp.	IC_{50} (μM)
	A549
36	4.48±0.57
Celecoxib	7.68±0.55

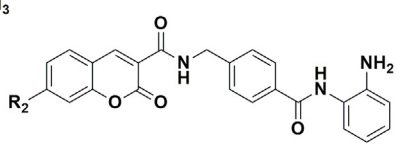
Comp.	IC_{50} (μM)			
	HL-60	KE-37	K-562	MDA-MB-231
37	2.9±0.4	5.3±1.1	7.2±0.9	9.1±1.2
Melphalan	14.9±3.3	17.3±2.7	25.7±2.5	21.4±4.2



38a: R^1R^2 HN–F

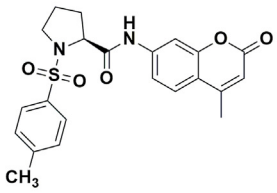
38b: R^1R^2 HN–Cl

38



R_2= 3,4-di-Cl-benzyloxy

39



40

Comp.	IC_{50}	
	HCT116	A2780
38a	0.16 nM	23.53 μM
38b	89.16 μM	84.8nM
5-Fluoro-uracil	11.13 μM	45.04 μM

Comp.	IC_{50} (μM)	
	HCT116	A2780
39	0.80±0.01	4.90±0.31
Entinostat	2.03±0.26	5.89±0.21

Comp.	IC_{50} (μM)
	MCF-7
40	1.07
5-Fluorouracil	45.04

Fig. 6. Typical chemical structures of coumarin sulfonamide/benzamide hybrids.

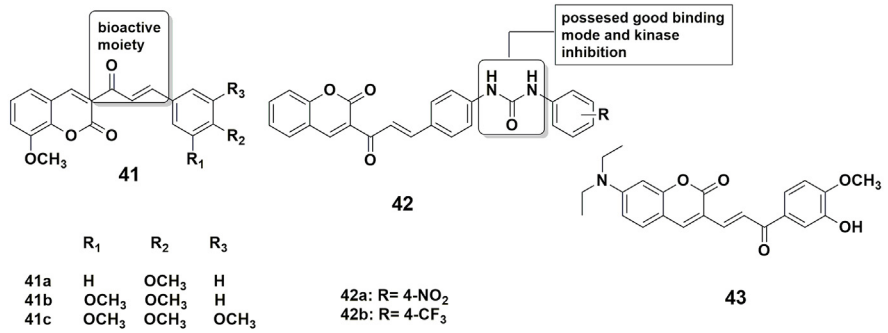
efficient binding with strong inhibitory activities against RTKs [47] (see Fig. 8).

Further, Compound **43** promoted ROS (determined by measuring the fluorescent signals using Image Express Micro Confocal analysis) accumulation in HCT116 cancer cells and down regulated anti-apoptotic proteins [48]. Therefore, compound **43** (antiproliferative activity by MTT assay) was found to be suitable for TrxR inhibition (western blot analysis) and had 8 fold improvement with robust anticancer activity compared to standard Xn [48]. On the other hand, compound **44** (*in vitro* anti proliferation) showed the best docking pose which effectively binded with tubulin protein and induced the cell cycle arrest at G2/M phase for the inhibition of tubulin polymerisation (molecular docking) [49].

Likewise, Furoxan is an influential NO donor that can inhibit the viability of cancer cells through down regulating both PI_3K/Akt and MEK/ERK pathways [50]. Apparently, a noteworthy activity was seen in compound **45**(antiproliferative activity by MTT assay) showed remarkable anticancer activity overcame MDR mediated P-gp overexpression [50]. Similarly in compound **46** (*in vitro* cytotoxicity) alkyl chain was played an important role to achieve stronger antitumor activity [51]. From the SAR data it could be concluded C-3 and C-7 substitution as the potent positions for better anticancer activity. The *para* position in the phenyl group was greatly influenced by the EWG in the compounds **42a, b, 45** and EDG (3-OH) in the compounds **43, 44** provided good anticancer activity. Morever, For the compound **41a-c** the presence of OMe group at 1,2,3 positions also showed excellent activity. The pharmakokinetic properties were well defined by evaluating cytotoxicity of coumarin backbone with two bioactive moieties: Chalcones and Furoxan. Structurally, furoxan assisted macrophage to inhibit tumour by producing high concentration of NO. Hence, These biochemically active molecules have been considered as the outstanding potents for the further drug optimization.

3.4. Dihydroxycoumarins

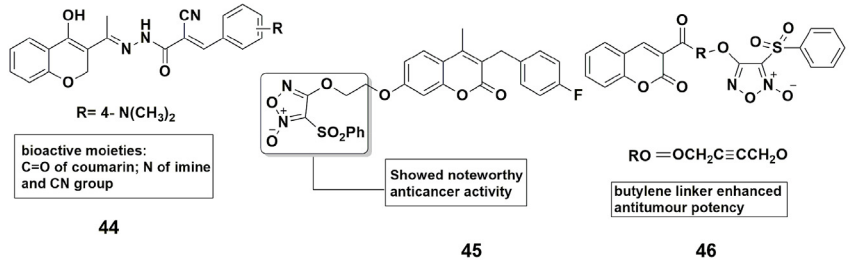
Dihydroxycoumarins are the important class of benzopyrones with different pharmacological properties like antimicrobial, anticancer.



Comp.	IC50 (μM)	
	HEPG2	K562
41a	0.65	1.09
41b	0.82	0.93
41c	2.06	1.36
Cisplatin	2.56	2.02
Combristatin	3.4	3.46
Doxorubicin	4.93	2.96

Comp.	IC50 (μM)	
	H4II2	HepG2
42a	13.06±1.44	2.326±0.23
42b	1.62±0.57	8.212±1.14
Sorafenib	3.45±0.68	7.522±1.05

Comp.	IC50 (μM)
	HCT116
43	3.60±0.06
Xn	27.60±1.50



IC50 (nM)	Comp.	
	44	Doxo
HeLa	8.36±0.12	7.01±0.015
MCF-7	8.20±0.18	9.86±0.12
A549	8.64±0.13	6.22±0.03
SKNSH	9.26±0.04	6.42±0.56

IC50 (nM)	Comp.		
	45	Cisplatin	Vincristine
HeLa	2.8	2741	NA
SKOV3	8.3	1440	NA
A549	3.7	13220	NA
OVCA429	3.9	7296	NA
OVCA433	3.3	24630	NA
A2780	6.6	2549	NA
MDA-MB-231	6.0	NA	0.65

IC50 (μM)	Comp.	
	46	Doxorubicin
SW620	1.86	2.32
HepG2	9.85	3.54
HCT116	3.46	0.48
MCF-7	7.92	3.25
HeLa	5.95	10.21

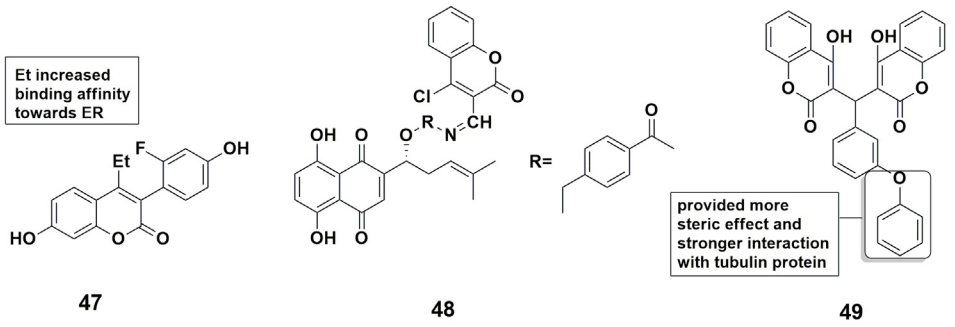
Fig. 7. Chemical structures of important coumarin-chalcone/furoxan hybrids.

Particularly, fluorescent imaging highlighted compound **47**(IC_{50} = 0.012 μM; antiproliferative activity) as the most potent ER-α antagonist and compound **48** as the potential anti-HIF-1α agent (Molecular docking evaluation) [52,53]. Owing to the ability of OH group interaction with tubulin protein, Chen and co-workers synthesized a series of dihydroxy coumarin congeners. The ability of forming hydrogen bonds with the tubulin protein played an important role in explaining the anticancer ability [54,55]. Out of the synthesized derivatives, compound **49** (*in vitro* cytotoxicity), **50a-c** (*in vitro* anticancer activity by MTT assay) and **51** (*in vitro* cytotoxicity) exhibited stronger interaction with tubulin with efficient anticancer activity [54–56]. Based on the SAR data, the substitution of EWG in compound **47** displayed the highest potency, while in compounds **49** and **51** EDG contributed for significant anticancer activity. According to SAR data, steric effect and substitution of various atom at phenyl governed the anticancer activity in compound **50a-c. 50a** (binding energy = −4.5 kcal/mol) proposed lowest activity due to large steric effect of methyl sulfonyl group, steric effect followed by electron withdrawing effect in compound **50b** (binding energy = −7.6 kcal/mol) contributed towards the highest activity, although in compound **50c** (binding energy = −6.8 kcal/mol) two Br atoms and their steric effect showed moderate anticancer activity.

Thus, dihydroxy coumarin based compounds could exert good cytotoxicity against different cancer cell lines with unique optical and pharmaceutical properties. On the basis of these studies, OH group interacted strongly with tubulin protein that explained its antiproliferation and paved the way for further exploration.

3.5. *Coumarin pyridine/pyrimidine/pipyridine derivatives*

Coumarin based pyridine derivatives have been appeared as potent anticancer agents, and the chemical structures of typical pyridine derivates are presented in Fig. 9. In recent studies, it was found that the synthesis of pyridine derivatives using microwave irradiation was extremely fast with enhanced anticancer activity along with good yields.



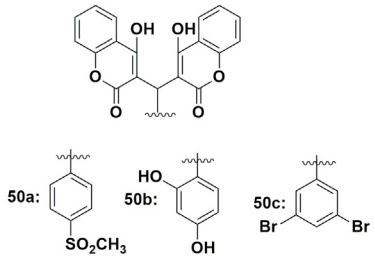
47 48 49

Comp.	IC_{50} (μM)
	MCF-7
47	16.1±0.7
4OHT	15.6±1.8

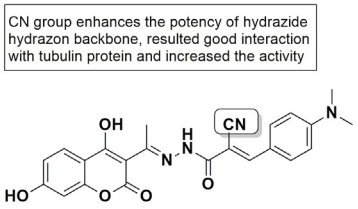
Comp.	IC_{50} (μM)
	HeLa
48	3.25±0.35
Doxorubicin	4.61±0.36

IC_{50} (μM)	Comp.	
	49	Doxorubicin
SMMC-7721	6±1.4	7±1.8
Bel-7402	8±2.0	6±2.6
MHCC97	7±1.7	8±2.0
Hep3B	9±2.0	7±1.5

Comp.	IC_{50} (μM)
	HL-60
50	25.78



50



51

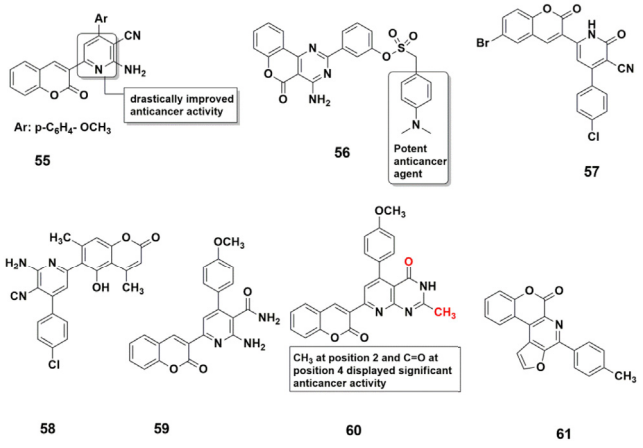
IC_{50} (μM)	Comp.			
	50a	50b	50c	Vinorebine
MDA-MB-231	45.1±1.2	25.3±2.3	35.3±1.6	30.2±1.9
MDA-MB-468	40.1±1.5	15.2±2.4	25.8±3.1	25.4±2.6
Hst578	40.3±1.8	25.7±2.2	30.4±1.6	35.1±1.8
HCC1937	45.9±2.5	20.2±3.0	35.5±1.8	35.6±2.3

IC_{50} (μM)	Comp.	
	51	Doxo
HeLa	5.14±0.16	7.01±0.015
MCF-7	3.42±0.52	9.16±0.12
A549	4.31±0.04	6.22±0.03
SKNSH	6.09±0.32	6.42±0.56

Fig. 8. Chemical structures of typical dihydroxycoumarins.

A study reported an increased oestrogenic expression (BMP2, RUNX2, COLI, OCN, mRNA determined by *in vitro* model of bone metastasis) in compound **52** and its excellent anticancer activity [57]. While, the anticancer activity against cancer cell lines was explained by the stronger interaction of the compound **53** (fluorescence lifetime $r_1 = 1.40$ ns and $r_2 = 4.41$ns) with Ct-DNA. In these hybrids, the extent of antiproliferative activity varied with basic amino group and the length of the linker. As a result, the compound **53** was found to be the most active and effectively binded with Ct-DNA [58]. Further, supported by Ct-DNA cleavage and fluorescence quenching study with transport protein BSA, compound **54a-b** was witnessed as the most potent towards anticancer activity [58].

The SAR activity showed that the presence of 6-methyl on coumarin pyridine hybrid **54a-b** expressed potent anticancer activity [59]. In 2017, El-naggar and co-workers synthesized pyridine based coumarin derivatives and evaluated their *in vitro* cytotoxicity. The screening results showed that most of the compounds had moderate cytotoxic activities. Nevertheless, compound **55** showed the most promising activity [60]. Subsequently, compound **56**(*in vitro* anticancer activity) suppressed tumour cell proliferation by shortening the telomerase length and in turn inhibited telomerase activity [61]. In continuation to our further investigation, substitution of C-3 and C6 position of pyridine of coumarin skeleton resulted strong activity in compounds **57** and **58** (*in vitro* anticancer activity) [62]. Compounds **59** and **60** upregulated the caspases 3 (8.35 and 7.54 folds respectively) activity and caused cell cycle arrest at G2/M phase in MCF-7 [63]. Surprisingly, the anticancer activity of compound **61** was found to be independent of ED/EW ability of the substituents. MTT assay revealed this scaffold as the most potent against MCF-7 [64].



Comp.	IC_{50} (μM)	
	HCT-116	MCF-7
55	14.1±1.14	9.9±0.82
5-FU	40±0.21	38.4±0.17

IC_{50} (μM)	Comp.	
	56	ADM
CNE2	1.92±0.13	2.12±0.56
KB	3.72±0.54	3.04±0.87
Cal27	1.97±0.51	1.56±0.64

Comp.	IC_{50} (μM)	
	HepG2	MCF-7
57	15.5	29.4
58	7.65	23.8
Cisplatin	3.67	5.71

Comp.	IC_{50} (μM)
	MCF-7
59	1.22±0.41
60	2.42±0.75
5-FU	7.76±0.46

Comp.	IC_{50} (μM)
	MCF-7
61	6.83
BG-45	34.33

Fig. 9. Chemical structures of coumarin pyridine/pyrimidine/piperidine derivatives.

The above results certified the title compounds as attractive templates for the development of potential anticancer drugs.

3.6. Anilinocoumarin derivatives

Recent investigations have proved aniline as an effective moiety when attached to the side chains of coumarin hybrids and such compounds were found to be potential anticancer agents. In addition to this, when aniline fused with coumarin, it could effectively target ERα binding and inhibit the tubulin polymerisation. As shown in Fig. 10, compound **62** (*in vitro* antiproliferative activity) displayed remarkable reduction in tumour cell growth, inhibited tubulin polymerisation by interacting with colchicines binding site and caused G2M phase arrest (immune-fluorescence staining, microtubule dynamic assays and competition assays with *N,N′*-ethylene-bis(iodoacetamide) [65]. SAR study reported that the methyl linker in the compound **62** was responsible for maintaining the anticancer activity. A plausible binding mode of Compounds **63a** (3-folds more potent) and **63b** (antiproliferative MTT assay) resulted down-regulation in ERα in MCF-7 and Ishikawa cells respectively [66]. The preliminary SAR data reported that the Substitution at C-7 position of coumarin decreased the cell growth inhibition in MCF-7 and this trend was completely reverse in ERα binding affinities. Interestingly, medium size basic groups such as piperidyl could increase ERα binding affinity as well as anticancer activity [66]. Similarly, a remarkable increase in the anticancer activity was seen in Compounds **64** and **65** possessing the most efficient cytotoxicity against MCF-7 [67]. Whereas, other promising leads **66** and **67** (*in vitro* cytotoxicity) showed much higher activity [68] (see Fig. 11).

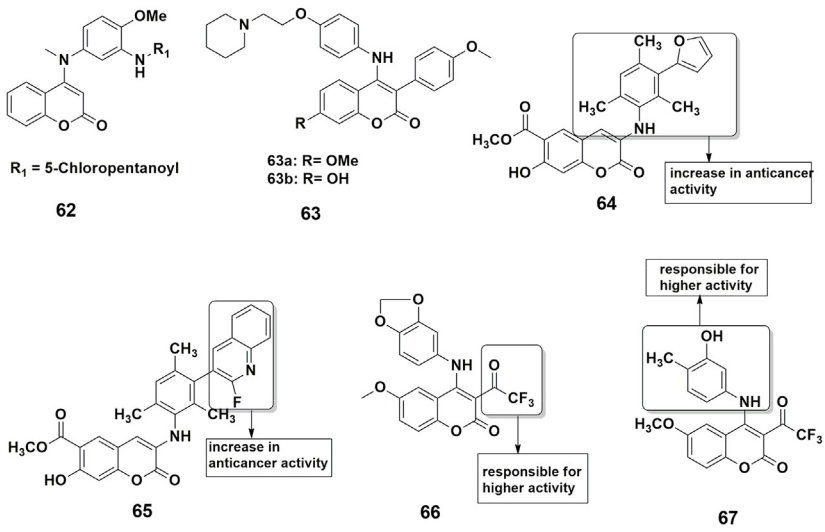
Accordingly, compounds **68a, b, c** were emerged as ER+ inhibitors and showed anticancer activity (MTT assay) at lowest concentrations [69]. Compound **69** was capable of inducing preG1 apoptosis cell growth arrest at G2/M, activated caspase 9, showed anti-VEGFR-2 kinase (IC_{50} = 0.36 μM) consistent with cytotoxicity [70]. According to the SAR data the substitution of ether linkage in the C-7 position of coumarin in compound **69** was beneficial for anticancer activity [71]. In continuation to this, compounds **70a-g, 71** and **72** exhibited good anticancer activities with strong cytotoxicity (*in vitro*) [71,72]. Being an active pharmaceutical ingredient, it became necessary to explore amino coumarin substituent. Therefore, more efforts are expected in further discovery of anilino and amino coumarin derivatives (see Fig. 12).

3.7. Coumarin based metal complexes

Metal complexes play a vital role in biochemical processes. The presence of metal ions accelerate the drug action providing better drug delivery. The pharmacology efficacy of the metal conjugated coumarin largely depends on the nature of coordination metal [73]. Two novel organotin carboxylate complexes **73** and **74** exhibited remarkable cytotoxic activity (*in vitro)*. These scaffolds accumulated in cytoplasm of HepG2 cells and induced apoptosis via ROS-mediated Mitochondrial dysfunction pathway [74].

The key compound **75** exhibited distinct telomerase inhibition (*in vitro* cytotoxicity) binding to c-myc promotor elements, lowered MMP of SKOV-3/DDP and arrested the cell cycle at G2/M phase (western blotting) [75]. In addition to this, Compound **76** also (*in vivo*) cogently fuelled antitumor affect. Besides this, the increase in cy(tc) caspases 3, apaf-1 and caspases 9 (western blot) indicated that the compound **76** induced mitochondria-mediated apoptosis in A549/DDP cells [76]. In a study, authors designed and synthesized coumarin appended Ir(III) complexes **77a-c** as the best theranostic anticancer agents that strictly overcame cisplatin resistance. All the three derivatives are witnessed as the best potent, but also prevented mitochondrial dysfunction in HeLa cells and ROS elevation (flow cytometric analysis [77].

In addition to this, organoselenium motifs **78, 79** underwent a strong interaction with the active site of HDAC8 (*in-silico* modelling) and altered tumor status by effectively inhibiting HDAC8 activity (*in vitro* assessment). Nevertheless, **78** escaped P-gp resistance while **79** resisted its P-gp (Rf = 12) overexpression (antiproliferative activity) [78]. On undergoing



IC50 (nM)	Comp.	
	62	Colchicine
SKOV3	3.5±0.1	51.9±3.2
HCT116	31.9±13.4	27.8±1.2
HepG2	27.3±11.0	42.8±0.8

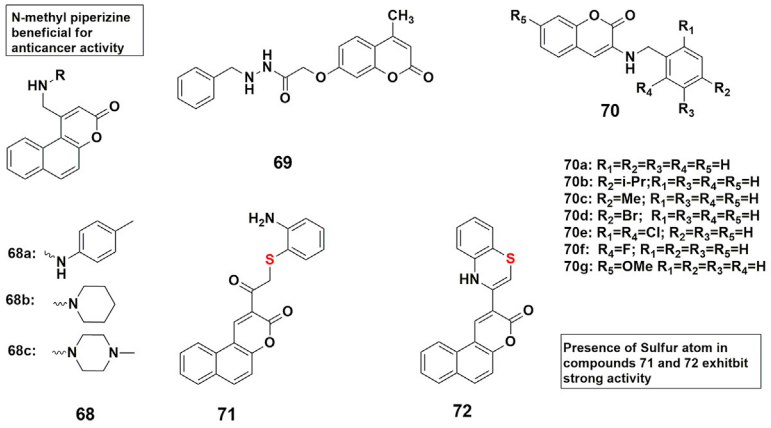
Comp.	IC50 (μM)	
	ISHIKAWA	MCF-7
63a	11.58±3.81	4.52±2.47
63b	8.43±1.06	7.31±2.121
Tamoxifen	16.47±2.04	11.35±3.13

Comp.	IC50 (μM)
	MCF-7
64	13.4±1.0
65	10.5±1.2
Doxrubicin	9.6±0.7

IC50 (μM)	Comp.		
	66	67	5-Fu
MCF-7	16.7	20.14	26.14
HCT116	4.42	4.62	38.30
HepG2	5.45	6.71	49.02
Panc-1	5.16	5.62	47.83

IC50 (μM)	Comp.			
	68a	68b	68c	5-Fluorouracil
MCF-7	5.17	0.83	14.24	45.04
A549	4.29	1.12	0.74	11.13
A375	9.02	5.26	13.61	-

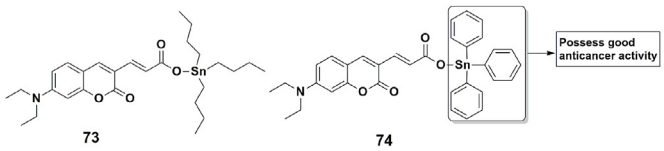
Comp.	IC50 (μM)
	MCF-7
69	1.24±0.06
Staurospiorine	8.81±0.39



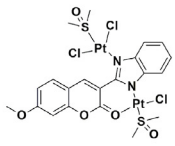
Comp.	IC50 (μM)		
	MGC-803	A549	NCI-H460
70a	19.49±1.51	15.53±1.16	17.36±0.76
70b	21.67±1.08	22.34±1.36	26.53±0.82
70c	17.58±1.60	18.45±0.93	20.22±1.32
70d	10.19±1.12	8.75±1.10	9.25±1.28
70e	24.90±1.25	19.37±1.05	21.16±0.74
70f	27.26±1.53	24.08±0.95	24.31±1.45
70g	16.07±0.82	14.32±0.77	18.44±0.69
5-Fu	46.89±1.09	39.37±0.78	44.17±0.54

Comp.	IC50 (μM)	
	HePG-2	MCF-7
71	7.10±1.21	10.42±0.83
72	8.05±0.91	12.41±0.64
5-Fu	2.34±0.14	6.58±0.09

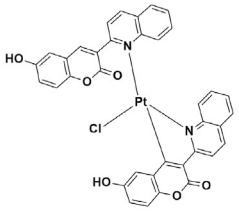
Fig. 10. Chemical structures of various anilino coumarins.



73 74



75

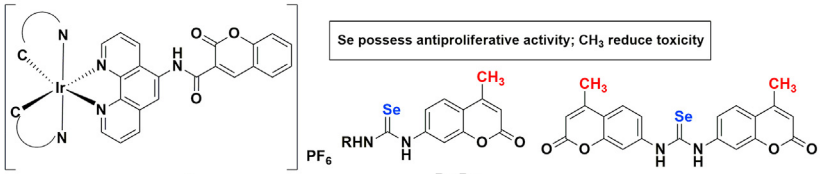


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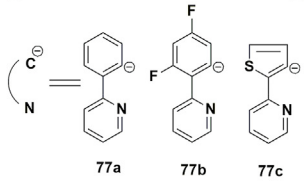
IC_{50} (μM)	Comp.		
	73	74	Cisplatin
HePG2	4.42±0.05	2.33±0.07	14.62±0.08
HeLa	1.24±0.08	0.94±0.06	9.89±0.11
A549	1.10±0.09	4.36±0.07	9.06±0.04

Comp.	IC_{50} (μM)
	SK-OV-3/DDP
75	0.5±0.2
Cisplatin	70.3±1.9

Comp.	IC_{50} (μM)
	HeLa
76	0.15±0.09
Cisplatin	12.09±0.24

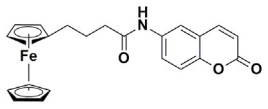


78 79



77a 77b 77c

77



80

IC_{50} (μM)	Comp.			
	77a	77b	77c	Cisplatin
HeLa	1.5±0.1	1.4±0.1	2.0±0.2	24.6±6.1
A549	1.1±0.1	0.62±0.05	0.80±0.07	14.5±1.5
A549R	0.5±0.04	0.30±0.02	0.45±0.04	76.9±7.5
HepG2	1.7±0.2	2.2±0.2	1.6±0.1	18.2±1.6
LO2	7.0±0.5	9.4±0.7	7.4±0.6	33.1±2.9

Comp.	GI_{50} (μM)
	HeLa
78	5.2±0.4
79	2.9±0.1
CDDP	1.8±0.5

Comp.	IC_{50} (μM)
	SGC-7901
80	3.56
CDDP	5.44

Fig. 11. Chemical structures of various coumarin based metal hybrids.

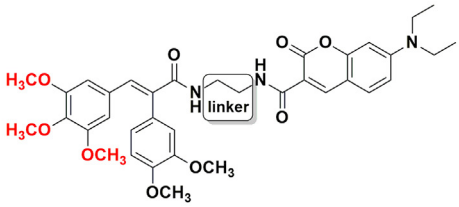
oxidation from Fc to Fc^{+} ROS is facilitated and its remarkable lipophilicity allowed Ferrocene-coumarin conjugate **80** to be served as promising anticancer agent. SAR analysis revealed that the introduction of methyl at C-4 position of coumarin ring and the amide linkage increase anticancer activity of the compound **80** [79].

Ascribe to great electropositivity and lipophilicity, metal based coumarin anticancer agents hold great promise for the formation of multifunctional therapeutic agents that can investigate the dynamic biological processes of living cells at subcellular level.

3.8. Miscellaneous coumarins

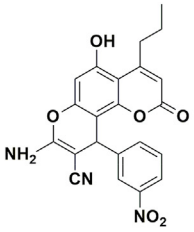
Coumarin derived cinnamamide derivative **81** expressed promising cytotoxicity and caused mitochondrial dysfunction by forming covalent bond with its thiol (evaluated by Fluoroscense imaging) [80]. From SAR results, the EDG on α-aryl were considered to be beneficial for the improvement of activity in the compound **81.**

Other privileged structures **82, 83a,b,84,85** demonstrated a good *in vitro* cytotoxic spectrum and compounds **86** and **87** displayed *in vitro* antiproliferative activity [81–84]. SAR studies showed that in compound **82** EWG substitution at C-3 position of phenyl moiety had a positive effect on cytotoxicity. Whereas in compounds **83a and b,** the EDG substitution at C-6 position of coumarin skeleton showed an excellent to moderate activity. In 2018, Kalairasi and co-workers synthesized coumarin derivatives **88a-d**. It was inferred that all the four compounds behaved as potent binders to Ct-DNA and resulted outstanding anticancer activity[85]. Another consistent result displayed compound **89** as potent anticancer agent (*in vitro)* [86]. SAR data revealed that by connecting EWG at the para position of phenyl played vital role in resulting higher activity.

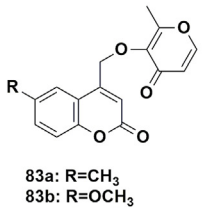


Tri methoxy group important for anticancer activity.
Linker provide optimum cytotoxicity.

81



82

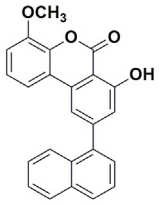


83

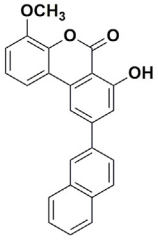
IC50 (μM)	Comp.
	81
HL-60	9.10

IC50 (μM)	Comp.	
	82	Doxorubicin
HCT-116	2.93	0.88
MCF-7	2.67	1.02
HEPG-2	5.56	1.19
A-549	3.97	0.91

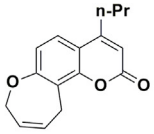
Comp.	IC50 (μM)	
	A549	HeLa
83a	2.47±0.14	3.98±0.27
83b	3.31±0.48	4.26±0.54
Cisplatin	1.92±0.07	2.86±0.16



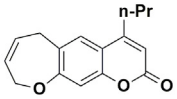
84



85



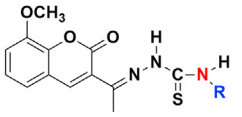
86



87

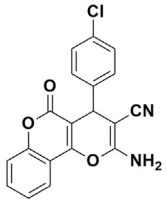
Comp.	IC50 (μM)		
	MCF-7	A549	HeLa
84	23.54±2.00	26.19±0.87	28.58±0.28
85	22.33±0.91	20.44±1.13	18.57±0.31
Cisplatin	17.59±1.36	11.72±0.70	7.75±0.42

Comp.	IC50 (μM)		
	Caco-2	HepG-2	SKBR-3
86	30.05±0.71	15.32±0.30	11.18±1.93
87	73.04±7.82	8.78±1.21	30.79±8.50
Tam	17.77±2.79	9.41±1.81	10.96±1.85

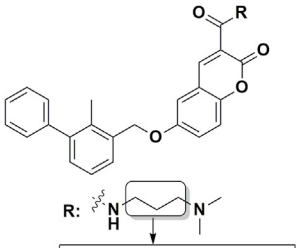


At terminal N atom the alkyl substitution improves anticancer activity.

88



89



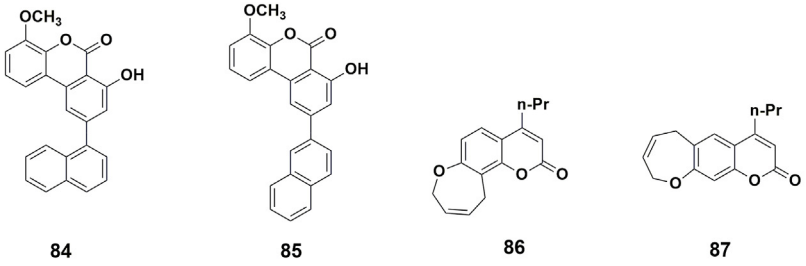
90

Comp.	IC50 (μM)	
	MCF-7	A549
88a	12.15±0.23	12.48±0.14
88b	11.77±0.29	11.98±0.19
88c	11.31±0.16	11.46±0.14
88d	12.19±0.20	12.65±0.16
Cisplatin	16.79±0.08	15.10±0.05

Comp.	IC50 (μM)	
	MCF-7	HeLa
89	7	19
ADR	<10	<10

IC50 (μM)	Comp.	
	90	Sorafenib
MCF-7	6.45±0.69	10.87±0.84
A549	8.65±1.04	11.24±1.04
H460	6.57±0.84	12.23±1.39
HT29	8.13±1.36	8.23±1.13

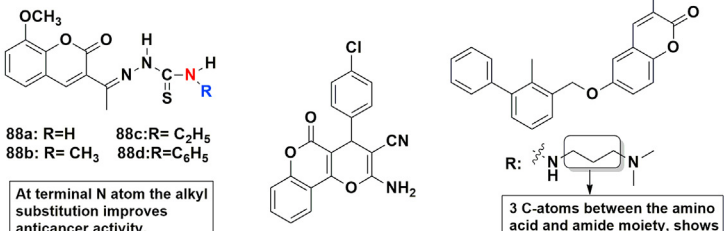
Fig. 12. Chemical structures of important coumarin hybrids.



84 85 86 87

Comp.	IC50 (μM)		
	MCF-7	A549	HeLa
84	23.54±2.00	26.19±0.87	28.58±0.28
85	22.33±0.91	20.44±1.13	18.57±0.31
Cisplatin	17.59±1.36	11.72±0.70	7.75±0.42

Comp.	IC50 (μM)		
	Caco-2	HepG-2	SKBR-3
86	30.05±0.71	15.32±0.30	11.18±1.93
87	73.04±7.82	8.78±1.21	30.79±8.50
Tam	17.77±2.79	9.41±1.81	10.96±1.85



88 89 90

Comp.	IC50 (μM)	
	MCF-7	A549
88a	12.15±0.23	12.48±0.14
88b	11.77±0.29	11.98±0.19
88c	11.31±0.16	11.46±0.14
88d	12.19±0.20	12.65±0.16
Cisplatin	16.79±0.08	15.10±0.05

Comp.	IC50 (μM)	
	MCF-7	HeLa
89	7	19
ADR	<10	<10

IC50 (μM)	Comp.	
	90	Sorafenib
MCF-7	6.45±0.69	10.87±0.84
A549	8.65±1.04	11.24±1.04
H460	6.57±0.84	12.23±1.39
HT29	8.13±1.36	8.23±1.13

Fig. 12. (*continued*).

Coumarin congener **90** could effectively inhibit the PD-1/PD-L1 binding by inducing the dimerization of PD-L1 protein (molecular docking) to exhibit stronger anticancer activity [87]. The SAR revealed that at C-6 position of coumarin the presence of 2-methylbiphenyl enhanced the potency of compound **90** by 5-folds. An excellent cytotoxicity of compounds **91a and b** occurred through the mechanisms associated with cell cycle arrest at G2/M and induction of apoptosis evaluated by dose responsive curve (PI staining) [88]. The SAR data analysis suggested that grafting a lipophilic EWG disubstitutents (2,4-F_2) and polysubstituents showed stronger anticancer activity 2,3,4,5,6-F_5. Much better activity was highlighted in compounds **91a, b** with therapeutic index of 10 and 13 respectively [88].

Subsequently, other target compounds **92**, **93** and **94** inhibited CDK2 activity by interacting with protein 1KE9 (molecular docking) [89]. Batran and co-workers synthesized an array of coumarin derivatives that could effectively inhibit VEGFR-2 kinase and p38 MAPK. Compounds **95** and **96** showed 94% inhibition in VEGFR-2 Kinase (molecular docking studies). Crystallographic structure illustrated a significant reduction in p38α MAPK phosphorylation by compound **97** (10 μM and 30 μM; 0.64±0.2) [90].

4. Future perspectives

The rate of cancer-related mortality is at alarming level due to the poor diagnosis, limited prevention options and lack of efficient treatment methods for cancers. Pertaining to its wide prevalence in many naturally occurring compounds, coumarin privileged scaffolds are endowed with outstanding anticancer profile. As a result, different classes of coumarin derivatives comprehensively investigated for their anticancer activity through diverse mechanisms of action. However, the new compounds isolated from natural sources such as plants and animals, and possible combination of these compounds with conventional chemotherapeutic agents seems to be important to improve the quality of life, especially in cancer patients. Additionally, the possible incorporation of steroids in the coumarin skeleton can be explored for further optimization. Preclinical trials include analysis for *in vivo*, toxicity, specificity and interaction of drugs. Therefore, many lead candidates are not cost effective for researchers of non-profit organisation. This has been altered by drug repositioning, which inturn give rise to other human pathologies. We have highlighted the potency of coumarin but the discovery of the therapeutic drugs of high specificity is still remaining. 3 and 4 positions have been considered as more prominent for the biological efficacy. The

redox features of dihydroxy group attached to simple coumarin may not be favourable for *in vivo* and lead to side effects. Further, a modification in pyrone rings is needed to overcome side effects. The new synthetic approaches such as MCR, microwave irradiation have not only provided the products with good yield but also showed multiple bioactivities. Above mentioned studies also lime lighted coumarin azole derivatives binding directly to DNA that can lead to further improvement in oxidative stress. Not to mention that complexes of longer absorption or emission will be constructed to make coumarin affixed organometals compatible for *in vivo* theragnostic optimization in upcoming future. Further, mechanistic and kinetic analysis involving the HDACs inhibition activity of thiazolyl appended coumarins will shed light on possible structural modifications required to obtain the more active antitumor agents.

5. Concluding remarks

The widespread distribution and excellent bioactivity of coumarins have led the scientists to carry out the research involving this ring system for decades. They have many biological activities including disease prevention, growth modulation and antioxidant properties. It has been shown in scientific studies that these compounds show antitumor effects depending on their effects on immune regulation, cell growth and differentiation. Although there are limitations on the use of most natural coumarins owing to their hepatotoxic effect, relatively safe analogues with higher potency have been obtained by molecular manipulations. In their structure–activity studies, significant positive results were obtained in anticancer activity screening with the addition of substituents at different positions of the coumarin core. In recent years, researchers have developed several coumarin derivatives that exhibit excellent anticancer activity. In this review, we have described various coumarin derivatives that have showed excellent anticancer activity in recent years. The structure-activity relationship among the different coumarins is well presented. Hybridisation of coumarin with different congeners has potential to become anticancer agents.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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