RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2017, **7**, 36977

The value of pyrans as anticancer scaffolds in medicinal chemistry†

Dinesh Kumar,*[a] Pooja Sharma,[ae] Harmanpreet Singh,[a] Kunal Nepali,[a] Girish Kumar Gupta,*[b] Subheet Kumar Jain[a] and Fidele Ntie-Kang *[cd]

Pyran is an oxygen-containing heterocyclic moiety, which exhibits an array of pharmacological properties. Pyran is also one of the important structural subunits found widely in natural products, *e.g.* coumarins, benzopyrans, sugars, flavonoids, xanthones, *etc.* The diverse anticancer capabilities of pyrans have been additionally evidenced by the fact that this heterocycle has recently been a focal point for researchers worldwide. This review provides a summary of pyran-based anticancer compounds, with emphasis on the past 10 years. It focuses on advancements in the field of naturally occurring pyrans as anticancer agents. The discussion also includes structure–activity relationships, along with the structures of the most promising molecules, their biological activities against several human cancer cell lines, as well as mechanistic insights discovered through the pharmacological evaluation and molecular modeling of pyran-based molecules. The promising activities revealed by these pyran-based scaffolds undoubtedly place them at the forefront for the discovery of prospective drug candidates. Thus, they could therefore be of great interest to researchers working on the synthesis of antitumour drug candidates.

Received 14th May 2017
Accepted 17th July 2017

DOI: 10.1039/c7ra05441f

rsc.li/rsc-advances

[a]*Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab-143005, India. E-mail: dinesh_arora_81@yahoo.co.in; Tel: +91-9988902489*

[b]*Department of Pharmaceutical Chemistry, M. M. College of Pharmacy, Maharishi Markandeshwer University, Mullana, 133203, Haryana, India. E-mail: girish_pharmacist92@rediffmail.com; Tel: +91-80599-30169; +91-72069-30164*

[c]*Department of Chemistry, Faculty of Science, University of Buea, P.O. Box 63, Buea, Cameroon. E-mail: fidele.ntie-kang@ubuea.cm; Tel: +237 677915473*

[d]*Institute for Pharmacy, Martin-Luther-Universität Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, 06120 Halle (Saale), Germany. E-mail: ntiekfidele@gmail.com; fidele.ntie-kang@pharmazie-uni-halle.de; Tel: +49 3455525043*

[e]*Sri Sai College of Pharmacy Manawala, Amritsar, 143115, Punjab, India*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra05441f

Dinesh Kumar graduated in pharmacy in 2005 from the Punjab Technical University, occupying the 4th position in the entire university. In 2008 he obtained his Master's degree in pharmaceutical chemistry from the Guru Nanak Dev University, Amritsar, Punjab, India. He is currently a Ph.D. candidate in pharmaceutical sciences from the Guru Nanak Dev University, Amritsar, where he works on the synthesis and evaluation of chalconoid hybrids as potent anti-proliferative agents. In 2014 he became Assistant Professor of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar. His current research is focused on the synthesis and evaluation novel heterocycles, along with their application in medicinal chemistry.

Pooja Sharma is a graduate in pharmacy from the Punjab Technical University (2005), later obtaining her Master's degree in Pharmacognosy (Phytochemistry) in 2008 from the Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar. During her graduate studies, she emerged 2nd position in the university. She also worked in the Council of Scientific & Industrial Research (CSIR) laboratory of India at Jammu, focusing on the phytochemical investigation and standardization of extracts from Boerhaavia diffusa. *She later became Assistant Professor in Sri Sai College of Pharmacy, Manawala, Amritsar, Punjab, India. Currently she is Head of Department at Sri Sai College of Pharmacy, Manawala, Amritsar, Punjab, India, where she focuses on the extraction and isolation of phytochemical constituents of pharmaceutical interest.*

1 Introduction

The expression "tumour" induces fear, particularly when one considers recent statistics of cancer cases worldwide.[1] Another cause for concern is the mammoth task that physicians must carry out in order to attempt to save patients' lives. A tumour is depicted by the uncontrolled development and spread of abnormal cells. While normal body cells grow, divide and die in an orderly fashion, cancer cells do not follow this norm. They rather continue to grow and divide in a disorderly fashion. The weapons used for this fight generally include specialised surgical operations, radiation therapy and chemotherapy. Despite continued research efforts towards the development of anticancer (chemotherapeutic) drugs, cancer remains a primary cause of death. It is estimated that the number of cancer cases may reach up to 15 million at the end of 2020.[2–6]

According to the World Health Organization (WHO), more than 80% of the world's population relies on traditional medicines for their essential health care needs.[7,8] Plants have a long history of their utilization in the treatment of tumors and it is estimated that more than 60% of presently utilised anticancer agents are obtained from nature.[8] Heterocyclics represent the most abundant compound classes present among known drugs. Typically, the former need to be decorated with suitable

Harmanpreet Singh studied pharmacy at the Punjab Technical University between 2006 and 2010. His post graduate work was within the field of pharmaceutics (ISF college of Pharmacy), where he worked on the transmucosal delivery of docetaxel using nanofiber as a carrier system for the treatment of buccal cancer. He started his Ph.D. in 2014 at the Guru Nanak Dev University, Amritsar, India, where he is currently working on the development of different carrier system for increasing the bioavailability, shelf life and effective delivery of the docosahexanoic acid (DHA).

Girish Kumar Gupta graduated in pharmacy in 2006 from Guru Jambheswar University of Science and Technology, Hisar, India. In 2009 he obtained his Master's degree in pharmaceutical chemistry from the University Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana, India. Currently working as Assistant Professor in M. M. College of Pharmacy, Maharishi Markandeshwar University, Mullana, Ambala, India, he has more than 8 years of research experience in pharmaceutical field including academic and industrial research and teaching. He has over 60 publications in the field of heterocyclic chemistry in peer reviewed high impact journals. He is also a member of many pharmaceutical associations and societies. He is also an editorial board member, editor, guest editor and reviewer of many reputed international and national journals. His area of research encompasses drug design, molecular modelling, green synthesis related to nitrogen containing heterocycles.

Kunal Nepali obtained his Master's degree in pharmaceutical chemistry from ISF college of Pharmacy Moga, Punjab in 2008. He later obtained his Ph.D. in pharmaceutical chemistry from the Punjab Technical University. His research is focused on designing bioactive products based on SAR studies, developing synthetic methodologies for multi-component synthesis and molecular modeling studies of xanthine oxidase and tubulin inhibitors. In 2011 he became Assistant Professor at the Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar. He has attended many national and international conferences and has published his research in journals of international repute.

Subheet Kumar Jain obtained his M. Pharmacy in pharmaceutics from Dr H. S. Gour University, Sagar in 2000. He later obtained his Ph.D. in pharmaceutical sciences from the same university in 2004. Currently, he is working as Professor & Head in the Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar. His areas of interest include novel drug delivery systems, anticancer drug delivery using nano carrier approaches, dermal drug delivery using carrier approaches, and gastro-retentive drug delivery. He has published his research in many national and international journals.

substituents in order to obtain their appropriate biological effects.[9]

Tremendous progress has been made in the war against cancer, with the development of many novel chemotherapeutic agents. However, due to toxicity and drug-resistance problems encountered with many currently available treatments, it remains a great challenge to discover and develop more effective drugs to treat cancer. We present the structure–activity relationships and their mechanistic insights established during the pharmacological evaluation of selected potent pyrans. The structures of the designed and synthesised molecules discussed in this compilation clearly highlight the interesting and promising anticancer profiles of the compounds. An overview of selected molecular modeling studies has also been incorporated, with the aim of providing insight into the possible binding sites. This classification of the pyrans discussed in this study is based on one of the core functionalities of their chemical architecture. The classification is as follows:

- Benzopyrans and fused pyran-based anticancer scaffolds.
- Flavones and fused flavone-based anticancer scaffolds.
- Coumarins and fused coumarin-based anticancer scaffolds.
- Xanthones and xanthene-based anticancer scaffolds.
- Other scaffolds.

A summary of the most potent compounds have been presented in the ESI (Table S1†).

2 Benzopyrans and fused pyran-based anticancer scaffolds

The pyran ring is the core unit of benzopyran, chromone, flavanoids, coumarin, xanthones, and naphthoquinones, which exhibit diverse pharmacological activities. Pyran heterocycles are both prevalent across compounds classified as of 'natural origin' and 'man-made'. Numerous naturally occurring compounds containing pyrans and benzopyrans, show fascinating therapeutic activities. These have spurred considerable awareness of the synthetic arena based on their structure, reactivity, synthesis and biological properties. The classification of pyran heterocyclic compounds depends on the presence of the 2*H* or 4*H* pyran scaffold (Fig. 1). Thus, the benzo derivative of *2H*-pyran is named 2*H*-1-benzopyran (commonly *2H*-chromene) and the benzo analogue of 4*H*-pyran is called 4*H*-1-benzopyran (commonly 4*H*-chromene).[10] Interrelated naphthyl derivatives are exemplified by 2*H*-naphtho[1,2,*b*]pyran and xanthenes. Ketones obtained from pyrans are called pyranones (likewise regularly pyrones), the parent molecules being pyran-2-one and pyran-4-one.[11–13] Paltry names are utilised for the related benzo analogues; coumarin, dihydrocoumarin, chromone, xanthone, and chromanone or chroman-4-one.

It is well established that small heterocyclic molecules are predominant building blocks for biologically active compounds,[14,15] while an increasing number of structural frameworks have been described as privileged structures.[16] Pyran skeletons are important structural units found widely in natural products, *e.g.* sugars, coumarins,[17] flavonoids,[18] anthraquinones,[19] *etc.* Examples include flavonoid-based pyran derivatives (Fig. 2), including epicalyxins F and G along with calyxins F, G, L and I (Fig. 2), isolated from the seeds of *Alpinia blepharocalyx*. Epicalyxin F is the most potent member of this class, as an anticancer agent against human HT-1080 fibrosarcoma and murine 26-L5 carcinoma.[20]

The bioactive metabolite, β-lapachone (**20**, Fig. 3), is a typical example of a pyran derivative, which generally shows diverse biological activities (*e.g.* anticancer, antibacterial and anti-inflammatory activities), making it important for drug development. Zanamivir (**22**, Fig. 3), for example, was approved for prevention of influenza A and B. Moreover, zanamivir was the first commercially developed neuraminidase inhibitor. This drug is currently marketed by GlaxoSmithKline under the trade name of "Relenza". Laninamivir octanoate is a prodrug of laninamivir (**23**, Fig. 3), which is structurally similar to zanamivir and is administered orally.[21,22] Pyran-based drugs, which are commercially available and/or are in preclinical/clinical trials have been shown in Fig. 3. A literature survey has shown the abundance of commercially available therapeutic agents containing the pyran unit. Benzopyrans and fused pyran-based are an important class of structural motif for many natural and synthetic compounds, possessing high activity profiles, due to their wide range of biological activities, including anticancer properties.[23–25]

Madda *et al.* synthesised new chromeno-annulated *cis*-fused pyrano[3,4-*c*]benzopyran and naphtho pyran analogues, and tested these compounds against different human cancer cell lines. It was shown that compounds **27** and **28** (Fig. 4) had exceptionally high cytotoxicity towards human cervical malignant cells (HeLa). Compound **27**, for example, exhibited pronounced inhibitory action against both breast cancer cell lines (MDA-MB-231 and MCF-7). Furthermore, compound **29** displayed high cytotoxicity against only MDA-MB-231, while

Fidele Ntie-Kang studied Chemistry at the University of Douala in Cameroon between 1999 and 2004, leading to BSc and MSc degrees. His Ph.D. work at the Centre for Atomic Molecular Physics and Quantum Optics (CEPAMOQ) was based on the computer-aided design of antitubercular agents. He has an experience in molecular modeling and has been involved in the design and management of databases of natural products from African flora for virtual screening. Fidele has formerly worked as a Scientific Manager/Senior Instructor at the Chemical and Bioactivity Information Centre (CBIC), hosted at the Chemistry Department of the University of Buea, Cameroon. He is currently a Senior Scientist in the group of Prof. Wolfgang Sippl, sponsored by the Alexander von Humboldt Foundation, Germany, under a Georg Forster fellowship.

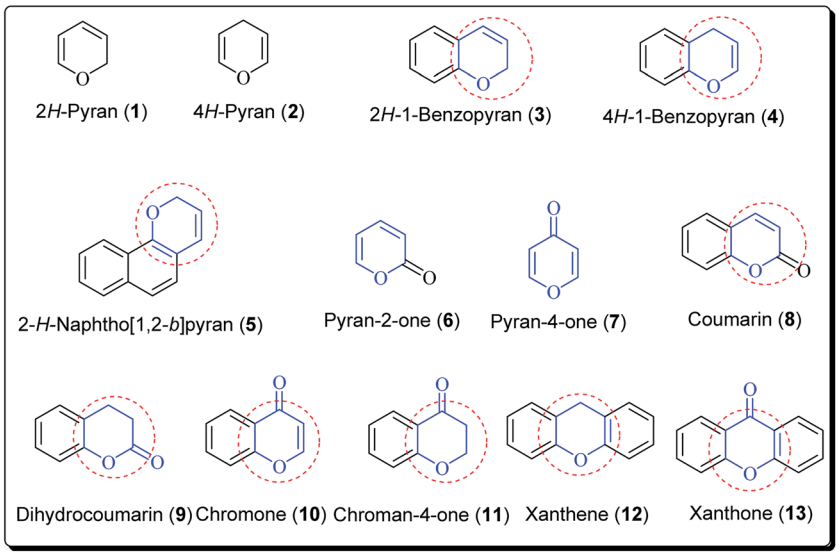


Fig. 1 Pyran-based heterocycles.

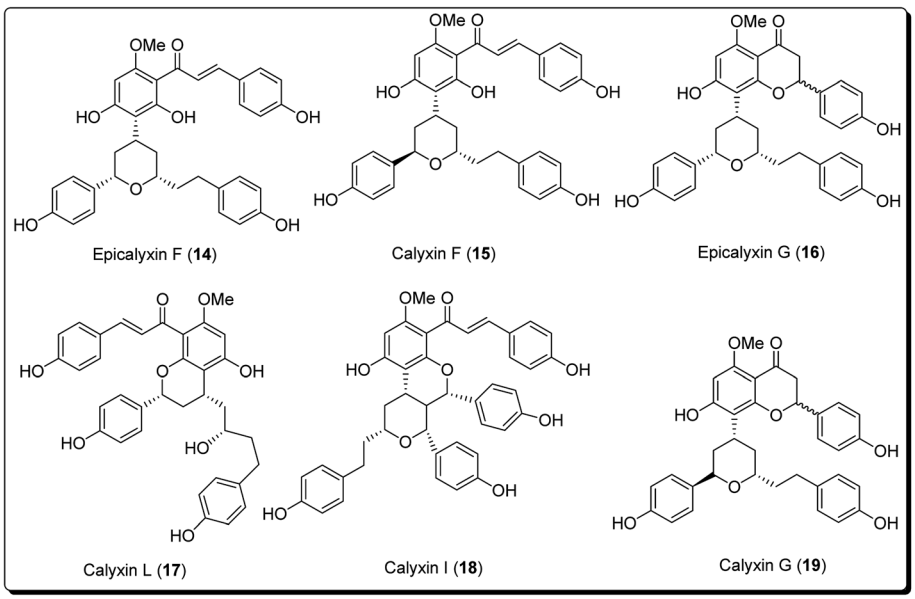


Fig. 2 Pyran-based derivatives obtained from natural origin with cell damage potential.

compound **28** demonstrated promising effects against human lung cancer cell line, A549 with an IC_{50} value of 2.53 μM.[26] Additionally, Morales *et al.* discovered 5-morpholino-7*H*-thieno[3,2-*b*]pyran-7-ones as potential prospective PI3K inhibitors. Substitution of the thiophene for the phenyl core in compound **30** resulted in compound **31**, which showed a comparative or better PI3K and mTOR enzymatic inhibition profile than compound **30** (Fig. 5). The former also showed a marginally better aqueous solubility, cell porosity, and better activity when tested in a PC3 cell expansion, while down-regulating the PI3K pathway as shown by restraining pAKT-S473 levels.[27]

The 4*H*-pyrano-[2,3-*b*]naphthoquinone scaffold is known to be a mimetic of an assorted assembly of naturally occurring pyranonaphthoquinones and their engineered analogues, with promising anticancer potentials.[28] Natural products within this class include rhinacanthin O (**34**, Fig. 6) from the Asian medicinal plant *Rhinocanthus nasutus*, pyranokunthone B (**35**, Fig. 6) from a marine actinomycete, α- and β-lapachones (**21** and **20**), isolated from the heartwood of the trees of Bignoniaceae, among others.[29] β-Lapachone has been examined for the treatment of tumors connected with hoisted NADH quinone oxidoreductase levels. The compound is currently in stage II clinical trials for the treatment of pancreatic tumour.[28–35] Magedov *et al.*

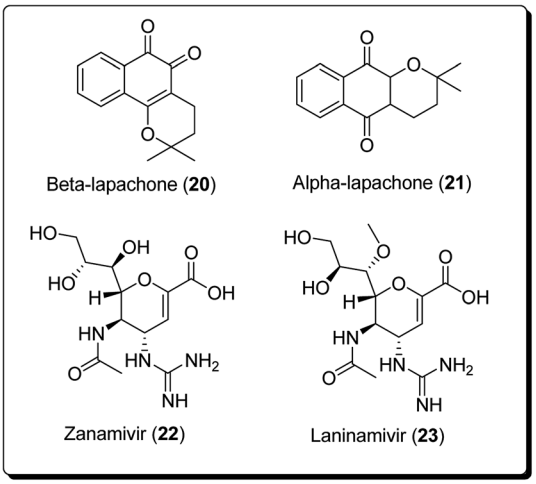


Fig. 3 Pyran-based natural and synthetic marketed drugs in preclinical/clinical trials.

screened a synthesised library of molecules, exhibiting low micromolar antiproliferative activity and initiated apoptosis in human cancerous cells, towards a set of malignant cells.[34] Selected analogues exhibited promising activities against cancer cell lines impervious to professional apoptotic stimuli, thus exhibiting their potential in treating tumors with grim anticipations. It was found that compound **36** and **37** showed antiproliferative effects better than those of α-lapachone, even though the latter was optional to the regioisomeric β-lapachone.[34]

Naturally occurring (dihydro) pyranonaphthoquinones can be found in bacteria, fungi, and higher plants, pointing to their biochemical relevance in nature. Many of these pyranonaphthoquinone derivatives have indeed been found to possess diverse and pronounced biological activities, including antimicrobial, antiparasitic, antiviral and anticancer properties.[35] Eleutherin (**38**, Fig. 7) and psychorubrin (**39**) and pentalongin (**40**) are typical examples of this class of compounds. Thi *et al.* carried out the synthesis of new (dihydro) pyranonaphthoquinones (**41**–**44**) and their epoxy analogues. The most potent compound (**44**) showed an IC_{50} value of 1.5 μM against KB and 3.6 μM in Hep-G2 cell lines.[35]

Natural products bearing the furanone-fused pyranonaphthoquinone skeleton, with the tricyclic pharmacophore (Fig. 8)

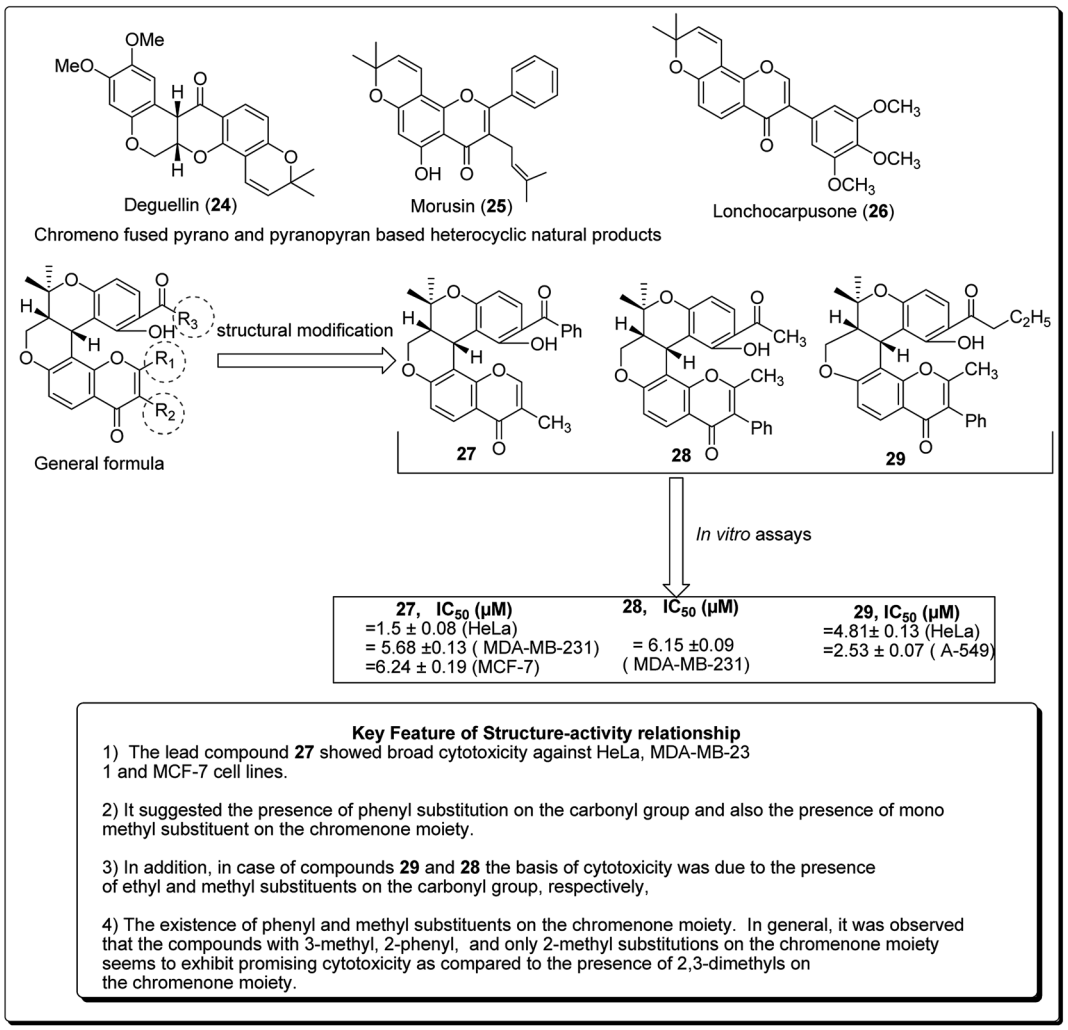


Fig. 4 Novel chromeno-annulated *cis*-fused pyrano[3,4-*c*]benzopyran and naphtho pyran derivatives along with their SAR.

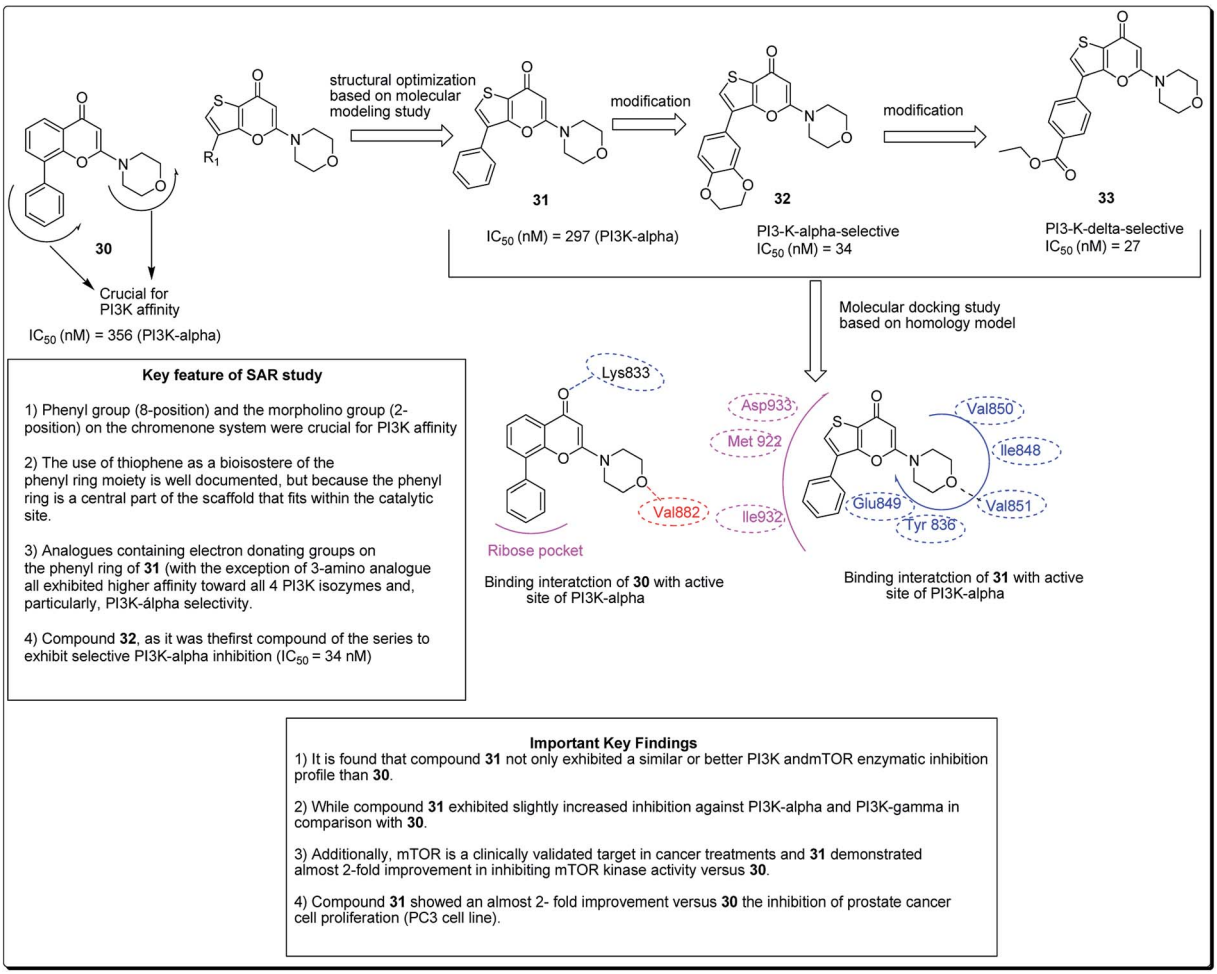


Fig. 5 5-Morpholino-7*H*-thieno[3,2-*b*]pyran-7-ones designed as next generation PI3K inhibitors along with SARs.

also play an important role in medicinal chemistry, *e.g.* kalafungin (**45**), medermycin (**46**), griseusin (**47**) and granaticin (**48**). Kalafungin, for example, has shown activity against L5178Y mouse leukemic cells, as well as against AKT kinase.[36] Meanwhile, medermycin was shown to possess several biological activities, including cytotoxicity against K562 human myeloid leukemia, P-388 murine leukemia and L5178Y murine lymphoblastoma cell lines.[37] Griseusin and granaticin also have proven antiprotozoal, antibacterial, and cytotoxic activities.[38–40] Based on these evidences, Jiang *et al.* synthesised several compounds bearing this quinone–pyran–lactone tricyclic pharmacophore and evaluated their anticancer properties against several cell lines, including squamous carcinoma KB cells, vincristine-resistant KB/VCR cells, human lung cancer A549 cells, and human leukemia HL60 cells.[41] The most promising compounds were the stereoisomers with the

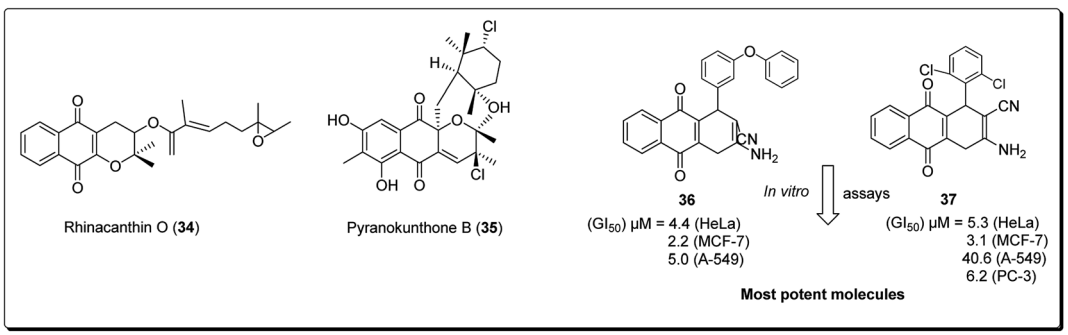


Fig. 6 4*H*-Pyrano-[2,3-*b*]naphthoquinones with anticancer activity.

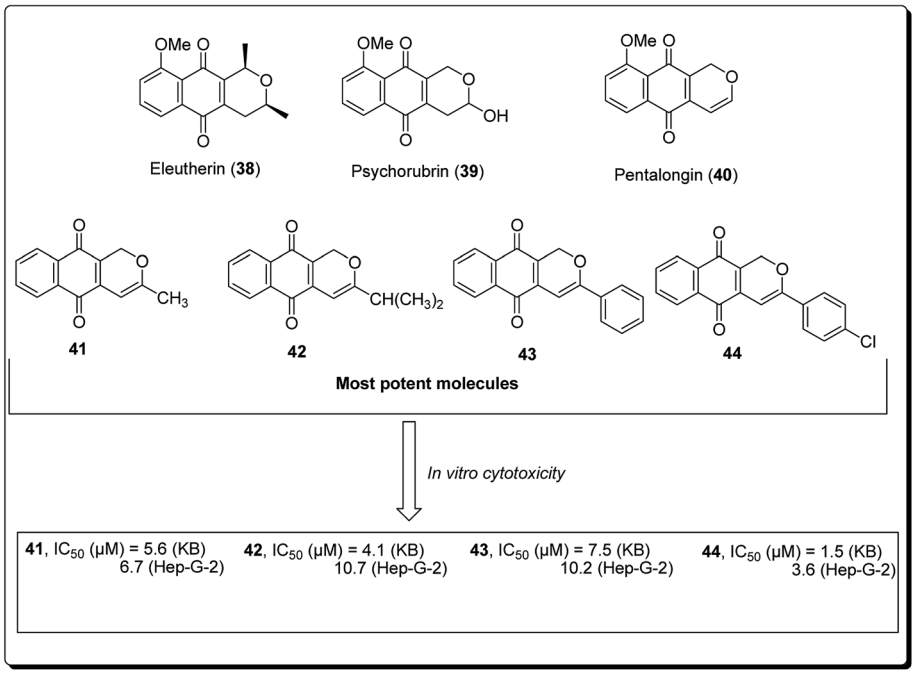


Fig. 7 Bioactive (dihydro)pyranonaphthoquinone-derived natural and synthetic anticancer agents.

aliphatic amino(piperazinyl) substituent on the tricyclic pharmacophore (**49** and **50**), with inhibitory potencies in the lower and sub micromolar ranges.[41] Meanwhile, fluoro substituted benzo[*b*]pyran derivated analogues of 6-flurobenzo[*b*]pyran-4-one (**51**, Fig. 9) have shown activities against NCI-H460 (lung), MCF7 (breast) and SF-268 (CNS) cancer cell lines.[42]

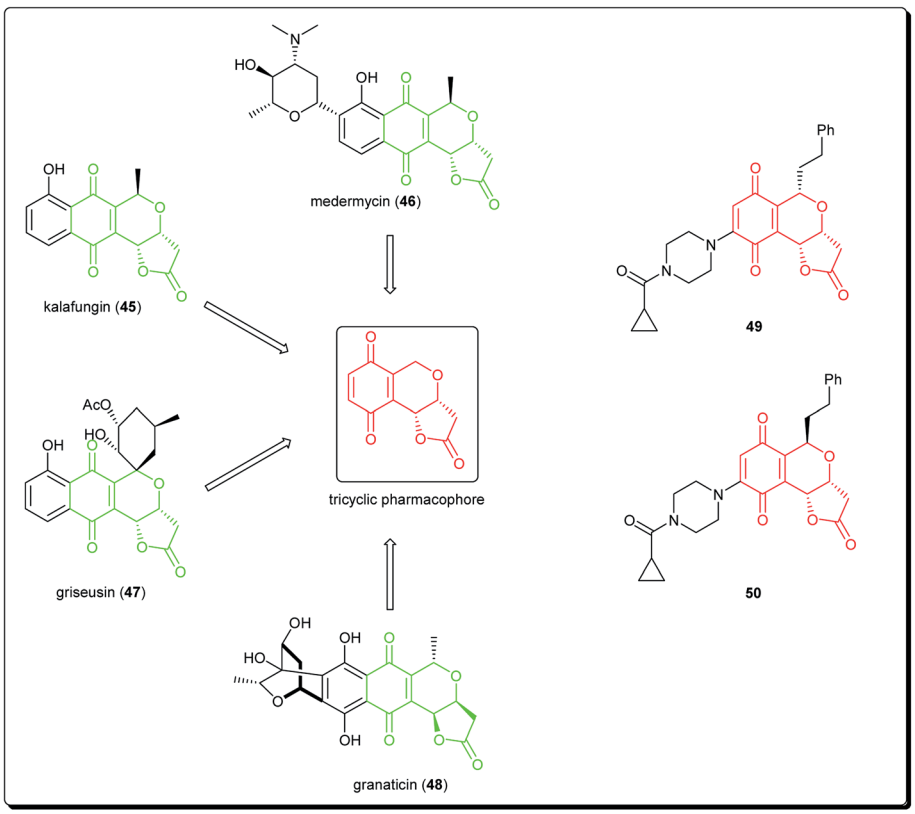
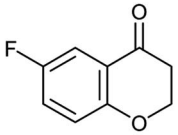


Fig. 8 Natural products bearing the furanone-fused pyranonaphthoquinone skeleton with tricyclic pharmacophore, along with synthesized anticancer derivatives.

3 Flavone-based scaffolds

The term "flavonoid" refers to a huge class of plant secondary metabolites, which are biosynthesised from common chalcone precursors.[43] Flavonoids are members of a much bigger family of more than 5000 naturally occurring polyphenolics, present in several foods of plant origin, which are known to be a rich source of anticancer drugs.[44,45] These compounds are often characterised by the presence of a common phenylbenzopyrone linkage (C6–C3–C6) in their structures. Several flavonoid subclasses exist, depending on the saturation level and opening of the central pyran ring, including; flavones, isoflavones, flavonols, flavanonols, flavanols, flavanones and pterocarpans.[45,46] Flavonoids exhibit a broad range of biological activities, *e.g.* anti-mutagenic, antiproliferative and antioxidant activities.[47–49] The antioxidants are usually involved in cell signaling, cell cycle regulation, and angiogenesis.[50–53]



6-flurobenzo[b]pyran-4-one (**51**)

Fig. 9 Fluorinated pyran-4-one scaffold used for designing potent anticancer agents.

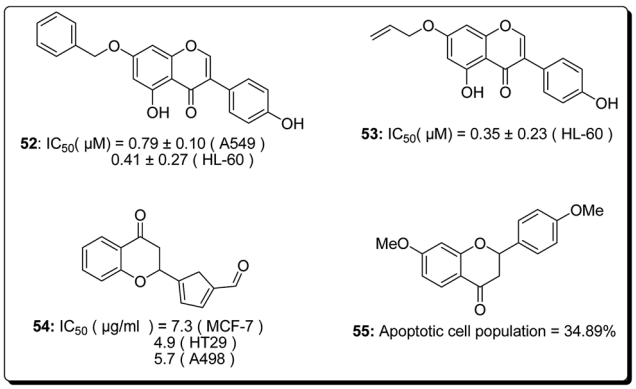


Fig. 10 The cell killing potential of some flavonoid-based anticancer agents.

Flavanones have been thought to be quite promising in the search for new lead compounds in the field of cancer chemotherapy. About a decade ago, Hsiao *et al.* established that flavanone and 2′-OH flavanone inhibited cell growth of A549, LLC, AGS, SK-Hepl and HA22T malignant cells, whereas other flavanones (4′-OH flavanone, 6-OH flavanone) showed little or no inhibition.[54] Moreover, Choi *et al.* later reported that 4′,7-dimethoxyflavanone exhibits persuasive anticancer activity by inducing cell cycle arrest and apoptosis in human breast cancer MCF-7 cells.[55] The results of another study, published soon afterwards, explored the antiproliferative effects of synthetic flavanone derivatives on human breast cancer cells by way of p53-mediated apoptosis and the induction of cell cycle arrest at the G1 phase.[56] Usman *et al.* had previously reported the cytotoxic activities of flavanones isolated from the bark of *Cryptocarya costata*.[57] A study of eight flavanones on colorectal carcinoma cells indicated that 2′-OH flavanone showed the most potent cytotoxic effect on these cancer cells, and cell death

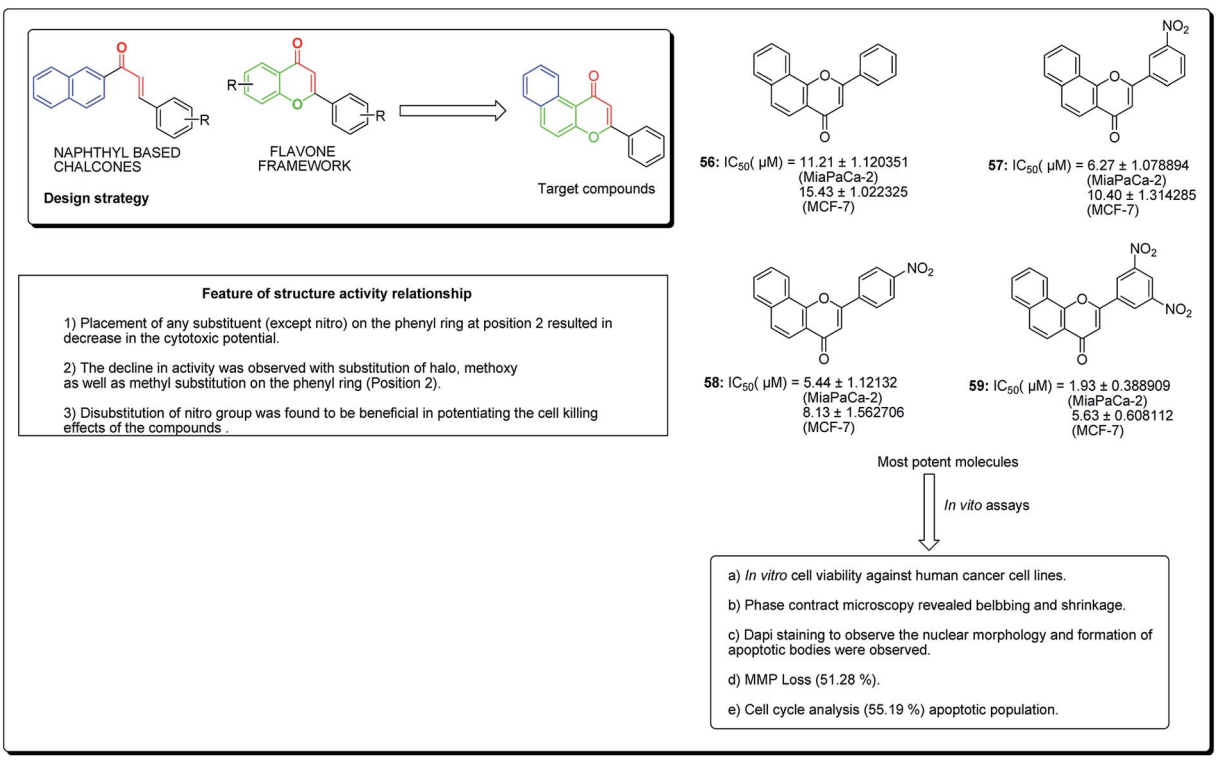


Fig. 11 Anticancer potential of most potent naphthoflavone along with their SARs.

induced by 2′-OH flavanone, was *via* the occurrence of DNA ladders, apoptotic bodies, and hypodiploid cells, all characteristics of apoptosis.[58] Flavonoids (Fig. 10) are also important ingredients of human diet.[56,59–62]

Kumar *et al.* established the design and synthesis of naphthoflavones (**56–59**, Fig. 11). All the synthesised compounds were screened towards a panel of human malignant cells. Compound **59** displayed noteworthy cytotoxicity towards MiaPaCa-2 cell lines, with IC_{50} values of 1.93 μM and 5.63 μM against MCF-7 cell lines. Compound **59** was found to prompt apoptosis, confirmed through phase contrast microscopy, DAPI staining and mitochondrial membrane potential loss (MMP). The cell phase division study demonstrates an increase from 11.26% (control test) to 55.19% (treatment with compound **59** at 20 μM) in the apoptotic population.[63]

Myricetin (**60**, Fig. 12), one of the flavonoids, is available in a wide assortment of natural sources. Strikingly, those myricetin subordinates are thought to indicate anticancer action, which could diminish pancreatic malignancy development by means of acceptance of cell apoptosis.[64,65] On the basis of the previous findings, Xue *et al.* established a sequence of new myricetin analogues.[83] It was experimentally demonstrated that compound **62** affects the growth of human breast cells MDA-MB-231. Results from the telomerase inhibition assay also demonstrated that compound **62** acts against human bosom cells MDA-MB-231, with an IC_{50} value of 0.91 μM. The docking simulation of compound **75**, towards the target site, was performed to get the likely binding mode. The docking pose showed that the heterocyclic ring was profoundly embedded into the dynamic site, forming hydrophobic associations with build-ups of Phe568, Pro627, with four methoxy groups having hydrophobic collaborations with residues Phe568, Pro627, Lys902, Val904 and Pro929 (Fig. 12).[66]

Safavi *et al.* further carried out the synthesis and testing of the cytotoxicity of halogenated flavanones against a panel of human cancer cell lines.[67] Among the synthesised compounds, 3′,7-dichloroflavanone (**65**) showed the highest activity against MCF-7, LNCaP, PC3, Hep-G2, KB and SK-NMC cells. However,

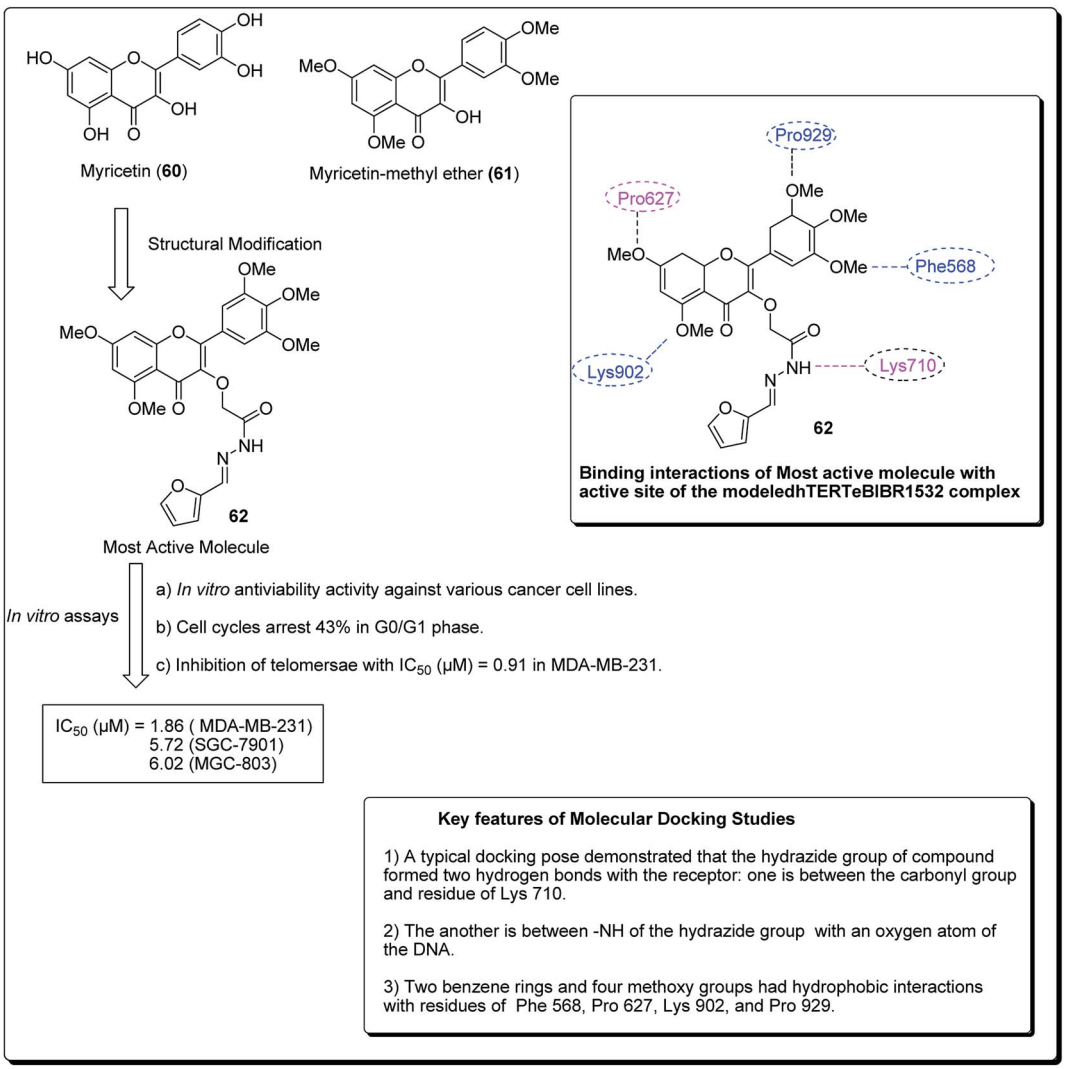


Fig. 12 Structure of most active novel myricetin anticancer analogs along with their molecular docking features.

3′,6-dichloroflavanone (**66**, Fig. 13), with an IC_{50} value of 2.9 μM, was the most potent compound against MDA-MB-231 cells, being approximately 12 times more potent, when compared with the reference drug (etoposide). It has been demonstrated that the modulation of the flavanone structure could increase antitumor activity. Thus, chlorine substitution on the chromanone ring and on the C-2 attached phenyl ring was used for structural modification and modulation of the basic pharmacophore of flavanones. Among the synthesised compounds (Fig. 13), 3′,7-dichloroflavanone (**65**) showed the better profile of cytotoxicity. However, 3′,6-dichloroflavanone (**66**) with IC_{50} value of 2.9 μM, was the most potent compound against MDA-MB-231 cells, as previously mentioned. According to the flow-cytometric analysis, compound **66** could be shown to induce apoptosis by 66.19 and 21.37% in PC3 and MDA-MB-231 cells, respectively. The results of acridine orange/ethidium bromide staining and TUNEL assays suggested that the cytotoxic activity of this compound in PC3 and MDA-MB-231 cells occurs *via* apoptosis.[67] Topoisomerases are known to play essential roles in maintaining DNA topology during the processes of DNA

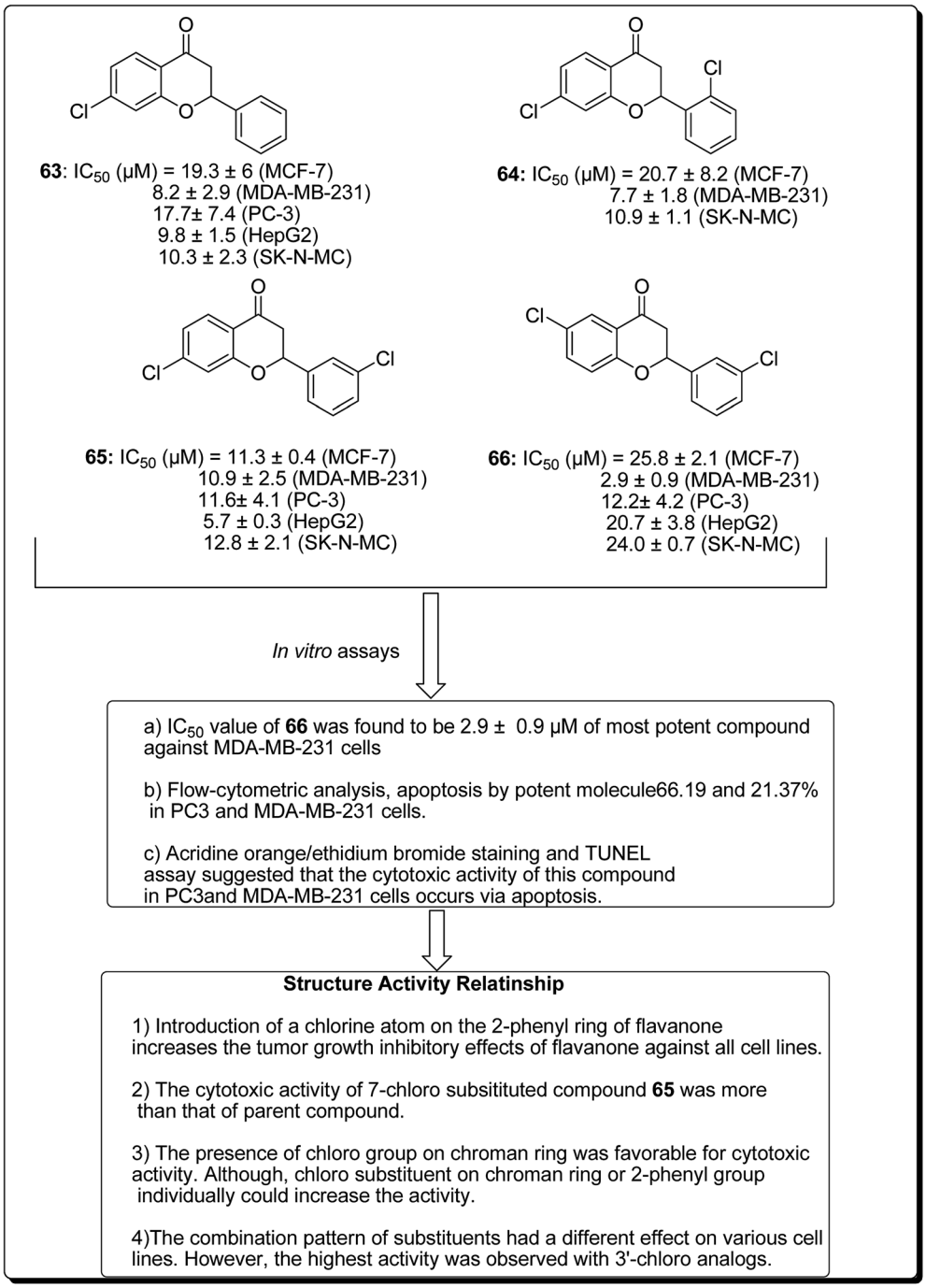


Fig. 13 Structure of halogenated flavanones as potential apoptosis-inducing agents along with their SAR studies.

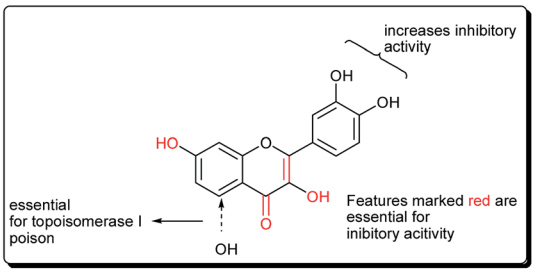


Fig. 14 Key structural features essential for inhibitory topoisomerase activity.

replication, transcription and recombination. Thus, topoisomerase inhibitors are cytotoxic agents that bind to free topoisomerase and prevent the formation of a covalent enzyme–DNA complex, and are thereby referred to as topoisomerase antagonists or "topoisomerase poisons". A number of flavonoids and other polyphenolic compounds are known to inhibit and poison mammalian topoisomerase I and II. These include quercetin, acacetin, apigenin, kaempferol, morin and luteolin.[45] The structural features of flavonoids essential for the inhibition of topoisomerase have been described (Fig. 14).[45]

4 Coumarin-based scaffolds

Coumarins and pyrans form an exceptional class of oxygen-containing heterocyclic compounds, which play a key role in medicinal chemistry, due to their structural diversity and pharmaceutical properties.[68] Coumarins play a special role in nature.[69,70] Coumarins scaffolds are present in natural phytoconstituents, exhibiting diverse biological activities, including anticancer properties through diverse mechanisms,[71–73] thus making it a privileged structure. These abilities have been explored in detail.[74] Coumarin scaffolds have also been explored through the formation of diverse hybrids, with promising biological activities (Fig. 15).[75–79] Among the coumarin hybrids from natural sources are pyranocoumarin derivatives, having several structural arrangements between the coumarin and the pyran rings. The few important pyranocoumarins include xanthyletin (**74**) (predominantly isolated from *Zanthoxylum americanum*), khellactone (**73**) (isolated from *Ligusticum elatum*), arisugacins (**75**), and pyripyropenes (**76**) (Fig. 16).[80]

Kumar *et al.* designed and synthesised 2,4-diarylpyrano[3,2-*c*]chromen-5(4*H*)-ones.[81] The design strategy involved the fusion of coumarin and chalcone, employing pyran as a linker. Among the obtained derivatives, compound **77** (Fig. 17) revealed momentous effects in HCT 116 cell lines, with IC_{50} values of 1.4 and 4.3 μM towards "MiaPaCa-2" cell lines. This compound was shown to initiate apoptosis as revealed by Hoechst 33258 staining, phase contrast microscopy, and mitochondrial membrane potential (MMP) loss. The cell phase division study indicated that the apoptotic population amplified from 10.22% in the control to 57.19% in a sample treated with compound **77** at a concentration of 20 μM.[81]

Hussain *et al.* further conducted a novel synthesis of coumarin derivatives as potent anti-breast cancer agents against ER +ve and ER −ve cell lines.[82] Compound **85** was found to be ER-α selective and most dynamic from all synthesised molecules, exhibiting prospective antiproliferative activity. The

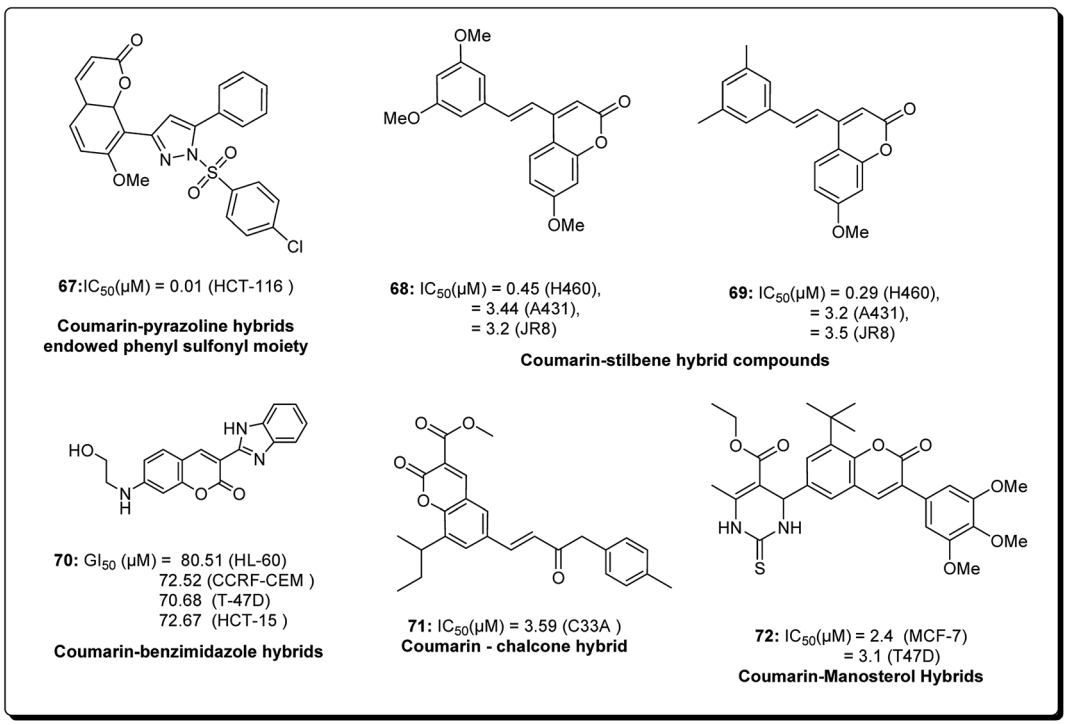


Fig. 15 Structure of coumarin hybrids along with their IC_{50} values against various cancer cell lines.

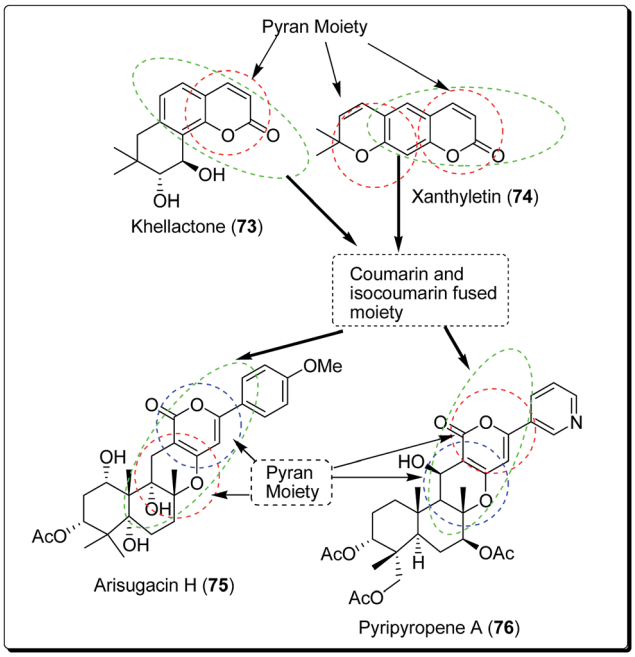


Fig. 16 Natural agents containing coumarin and pyran moieties.

docking simulation showed that compound **85** could favorably fit well in the receptor cavity of ER-α, following the binding pattern similar to the standard drug. The coumarin nucleus and the *p*-methoxyphenyl group at the third position formed a hydrophobic interaction with the residues Glu353, Arg394, Phe404 and Leu349. The aroyl substituent at the fourth position, having the amino alkoxy chain, anchored the piperidine ring by forming hydrophobic contacts with Trp383, Asp351, Leu354, Leu536 and Thr347. The methoxy group of coumarin at the seventh position interacted with Glu353 and Arg394 (Fig. 18). Compound **85** had a similar (but non-standard) binding pattern for ER-β binding, the coumarin pharmacophore forming hydrophobic interactions different from that observed in ER-α, *i.e.* interacting with Glu305, Arg346, Leu301, Leu339, and Leu343. At the third position, the 4-methoxyphenyl group forms a hydrophobic interaction with the amino residues Met421, Gly472, His575, Leu298, Phe356, Met340, and Ile373, which are essential features for ER-β binding.[82]

Coumarin is a modification of the benzopyran-2-one by directed introduction of a heterocyclic substituent. In most cases, a heteroaryl substituent is introduced at position 3 or 4 of the coumarin ring. Thus, 3- and 4-heteroarylcoumarins are reported to exhibit significant biological activities, including inhibiting the growth of several cancer types.[83] Prompted by this, Yana *et al.* reported the synthesis and anticancer evaluation of a series of novel 6-pyrazolinylcoumarins *via* NCI60-cell line assay. The outcome of the study revealed that compound **87** showed the highest level of anti-mitotic activity with a mean GI_{50} value of 10.20 μM and a sensitivity profile toward the Leukemia cell lines CCRF-CEM and MOLT-4 (GI_{50} values 1.88 μM and 1.92 μM), respectively, as represented in Fig. 19. The SAR study indicated that the antitumor activity of the synthesised compounds depends on substituent at third and fourth positions of the coumarin core. Moreover, it was found that compounds bearing the 3-methoxy-4 hydroxyphenyl and the 4-hydroxyphenyl substituents at position 5 of the pyrazoline fragment were more active than the other analogues.[84]

Another study was carried out on the design and synthesis of coumarin derivatives with improved anticancer activity. Among them, oligomerization (di/tri) of coumarin is one of the effective ways.[85,86] The derived dimeric natural product was shown to be more effective than the monomeric species (with IC_{50} ~70 μmol L^{-1}).[87,88] With this inspiration, the concept of molecular oligomerization led to the discovery of two novel series of dimeric derivatives of triphenylethylene–coumarin hybrids.[89,90] The dimeric compounds had potent anti-tumor activities, possibly by acting on DNA *via* the intercalative mode, and higher than their corresponding monomeric compounds,[91,92] respectively. The positive results inspired interests to explore the trimeric variants of the triphenylethylene–coumarin hybrid in an effort to produce more efficient antitumour agents. Zhang *et al.* further discovered new trimers of triphenylethylene–coumarin hybrids, containing two amino side chains. The trimeric compound **88** (Fig. 20) exhibited significant antiproliferative activity against three cancer cells at IC_{50} of nearly 10 μmol L^{-1}. The outcome of the DNA photocleavage studies revealed that compound **88** had significant interaction with Ct-DNA by the intercalative mode. Overall, the presence of extended linker and piperidinyl substitutions on the side chains were found to be favourable for DNA binding and the antitumour activity.[93]

5 Xanthones and xanthene-based scaffolds

Xanthones are an outstanding class of oxygenated tricyclic compounds, which display different fascinating pharmacological properties, relying on the nature and types of substitutions.[94–96] Recently, xanthones have been valued as having an effective pharmacophore in the field of medicinal chemistry world.[97] Prior to this, xanthones were shown to be present in bug sprays, larvicides and ovicides.[98] Shortly afterward, several experimental studies established that xanthone analogues could stop the growth of tumor cells and could also possess antioxidant and anti-inflammatory properties.[99] Xanthones are mainly found in plants of the Bonnetiaceae and Clusiaceae, in addition to the Podostemaceae, Guttiferae and Gentianaceae.[100]

Many naturally-occurring and man-made xanthene derivatives have been reported to exhibit antitumor activities,[101–104] among others. In the recent past, there has been a renewed interest in the synthesis of this class of compounds as the number of its applications have increased, both in the field of medicinal chemistry and material science. Particularly, xanthones (9*H*-xanthen-9-ones) are well explored heterocyclic derivatives with the dibenzo-γ-pyrone skeleton.[105–108] Some xanthone-containing plant extracts are directly used in traditional medicines. Analogous thioxanthone derivatives are also present in anticancer drugs.[109–113] Moreover, there are some

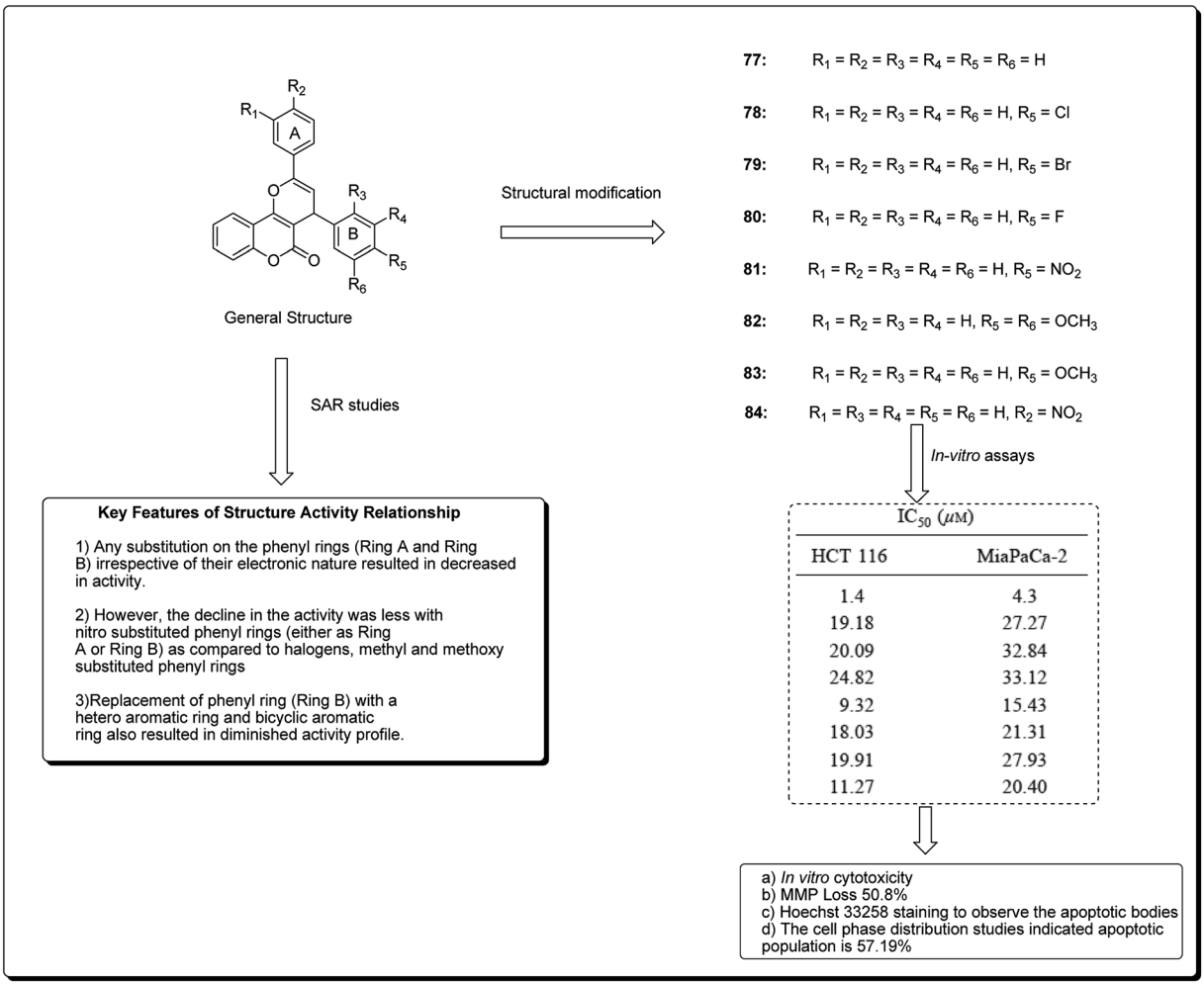


Fig. 17 Most potent coumarins scaffolds along with their IC_{50} values and SARs.

marketed formulations having xanthone derivatives (**89–97**, Fig. 21) as one of their active ingredients.

Lee *et al.* isolated three coumarin derivatives, theraphins (**98–101**) are recognised xanthones such as 2-hydroxyxanthone, 1,7-dihydroxyxanthone and 5-hydroxy-1-methoxyxanthone (Fig. 22), from the bark of *Kayea assamica* (Clusiaceae).[114] These were analysed for their cytotoxic activities, based on a panel of human cancer cell lines. Among these compounds, **99–101** displayed cytotoxic action against Col-205, KB, and LNCaP cell lines with IC_{50} values ranging from 3.5 to 13.1 μM. Meanwhile, the coumarin subsidiaries demonstrated modest effects, with IC_{50} values in the range 9.7–11.1 μM against the D6 clone, and IC_{50} values in the range 5.1–10.4 μM against the W2 clone. The result of the study demonstrated that the 7-hydroxycoumarins had an inhibitory impact on human malignant cell lines.[110]

Laphookhieo *et al.* isolated 5-*O*-methylcelebixanthone (**102**), along with six compounds; celebixanthone (**103**), 1,3,7-trihydroxy-2,4-di(3-methylbut-2-enyl)xanthone, cochinchinone A (**104**), α-mangostin (**90**), β-mangostin (**92**) and cochinchinone C (**105**) from roots of *Cratoxylum cochinchinense*.[115] These analogues were screened for their cytotoxic effects in NCI-H187 (human lung cancer) cell line. Among these, compounds **90**, **103** and **104** showed cytotoxic activities with IC_{50} values ranging from 0.65 to 5.2 μg mL^{-1}.[111] Chantarasriwong *et al.* also established the series of caged *Garcinia* xanthones and evaluated them for their anticancer activity using cell proliferation and apoptosis assays against human colon and leukemic HCT-116 and HL-60 cell lines respectively. Compound **106** proved to be the most active compound against colon cancer cells, with an IC_{50} value of 0.2 μM against HCT-116, while compound **107** was the most active against HL-60 (Leukemia), having an IC_{50} value 0.4 μM, Fig. 23.[116]

In a similar study, Matsumoto *et al.* confirmed that all xanthones obtained from *Garcinia mangostana* (Fig. 24) demonstrated a noteworthy anticancer activity.[117] However, α, β and γ-mangostins (**90–92**) were particularly active at 10 μM. The most active compound at this concentration was α-mangostin. The anticancer effect of α-mangostin was also shown in other leukemia cell lines: K562, NB4 and U937. Cell development of all these leukemia cell lines was hindered by α-mangostin at 5–10 μM.[117] Chiang *et al.* reported that the heated water concentrate of mangostin-organic product pericarp showed an intense antileukemic activity, with IC_{50} values of 61

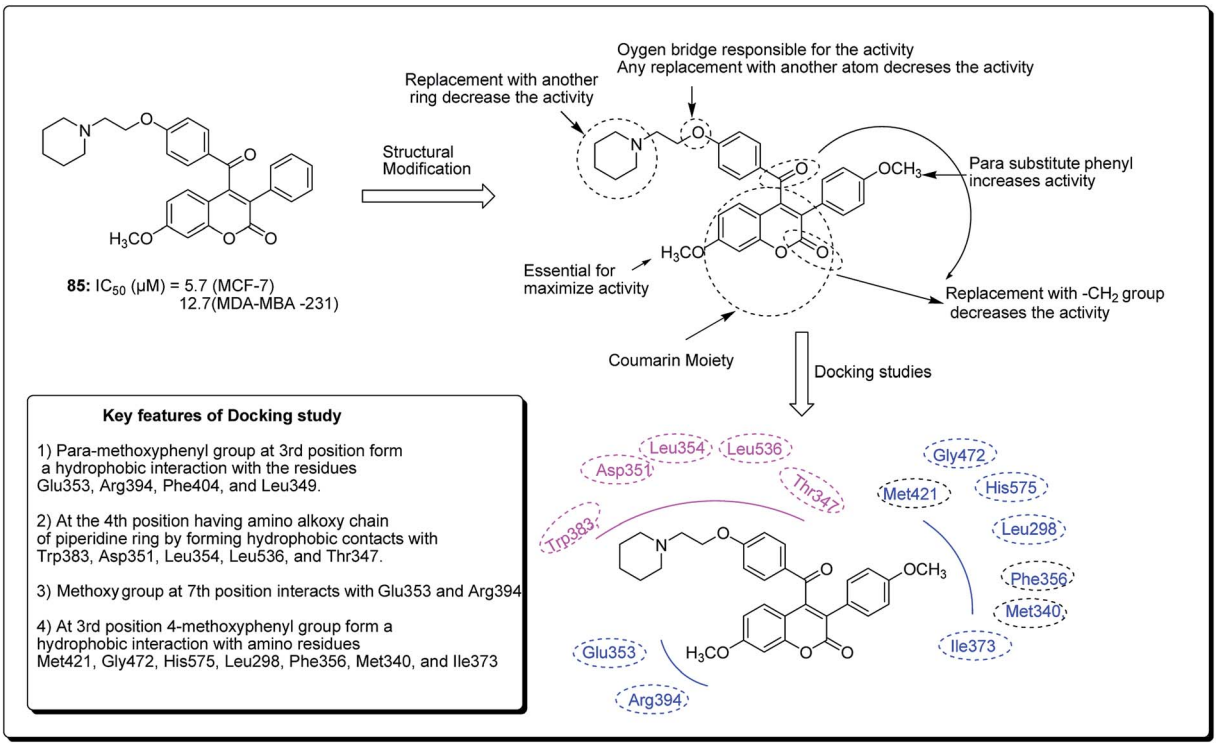


Fig. 18 Structure of most potent ERα/ERβ selective coumarin derivative along with their docking study.

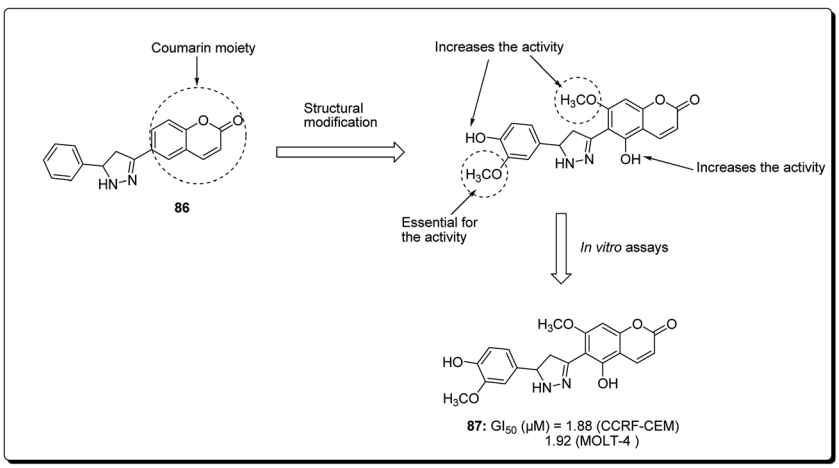


Fig. 19 Structure of most active 6-pyrazolinylcoumarin analogue as anticancer agent.

and 159 μg mL^{-1} against K562 and Raji cells, respectively.[118] Balunas *et al.* have also screened α, β and γ-mangostins by using a non-cell, chemical based the microsomal aromatase hindrance assay with an IC_{50} value 4.97 μM against SK-BR-3 breast cancer cell lines.[119] Recently, Jung *et al.* determined the antitumor properties of these compounds in pre-neoplastic injuries induced with 7,12-dimethylbenz[*a*]anthracene (DMBA) in a mouse mammary organ development. It was observed that α-mangostin restrained DMBA-induced preneoplastic sores with an IC_{50} of 2.44 μM.[120] Suksamrarn *et al.* separated distinctive xanthones from mangosteen fruit pericarp and tested them for antineoplastic activity against three diverse human malignant cells, *e.g.* mouth carcinoma (KB), breast cancer (BC-1) and small cell lung cancer (NCI-H187), with IC_{50} values of 2.8, 3.53 and 3.72 μg mL^{-1}, respectively.[121] Nonetheless, α-mangostin (**90**) showed the most pronounced effect on BC-1 cells, with an IC_{50} value of 0.92 μg mL^{-1}. It was found that an action of α-mangostin was further noteworthy than the standard medication ellipticine (IC_{50} = 1.46 μg mL^{-1}).[121]

Chen *et al.* verified that α- and γ-mangostins appreciably subdued lipopolysaccharide-stimulated NO˙ production and cytotoxic effects when applied to RAW 264 cells.[122] The quantity of NO˙ fabrication at 3 to 25 μM was continuously calculated, and the IC_{50} values were found to be 12.4 and 10.1 μM for α- and

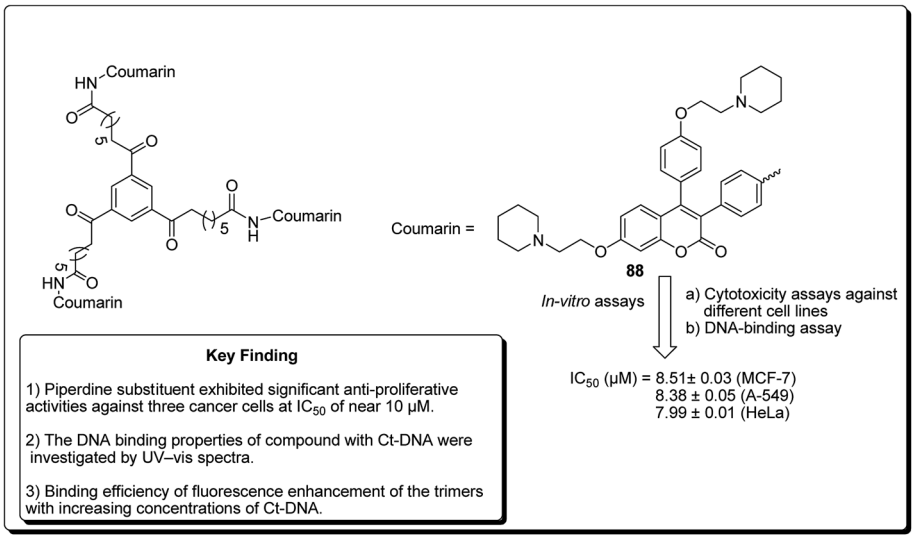


Fig. 20 Structure of most potent trimers of triphenylethylene–coumarin hybrids.

γ-mangostins, respectively.[122] Watanapokasin *et al.* examined the antiproliferative effects of mangostin xanthones, focusing on colon malignancy.[123] Nutritional administration of α-mangostin altogether hindered the acceptance and improvement of unusual grave foci in an artificially instigated rodent model of colon carcinogenesis. The development of COLO 205 xenografts was totally stifled when mice were infused intraperitoneally with 3 mg of a mangostin extract containing α- and γ-mangostin. In addition, minor doses of the extract were decreased the tumor volume. Atomic component kappa-B (NF-κB) action was also diminished by 30%. The balb/c mice bearing colon tumor NL-17 xenografts indicated 50–70% lessening in tumor size when intraperitoneal treated with a concentrate from mangosteen pericarp containing 25% α-mangostin.[123–126]

Cao *et al.* isolated two new cytotoxic xanthones; termicalcicolanone A (**108**) and termicalcicolanone B (**109**, Fig. 25) from the ethanolic extract of the Madagascan plant *Terminalia calcicola*.[127] These compounds were evaluated for their

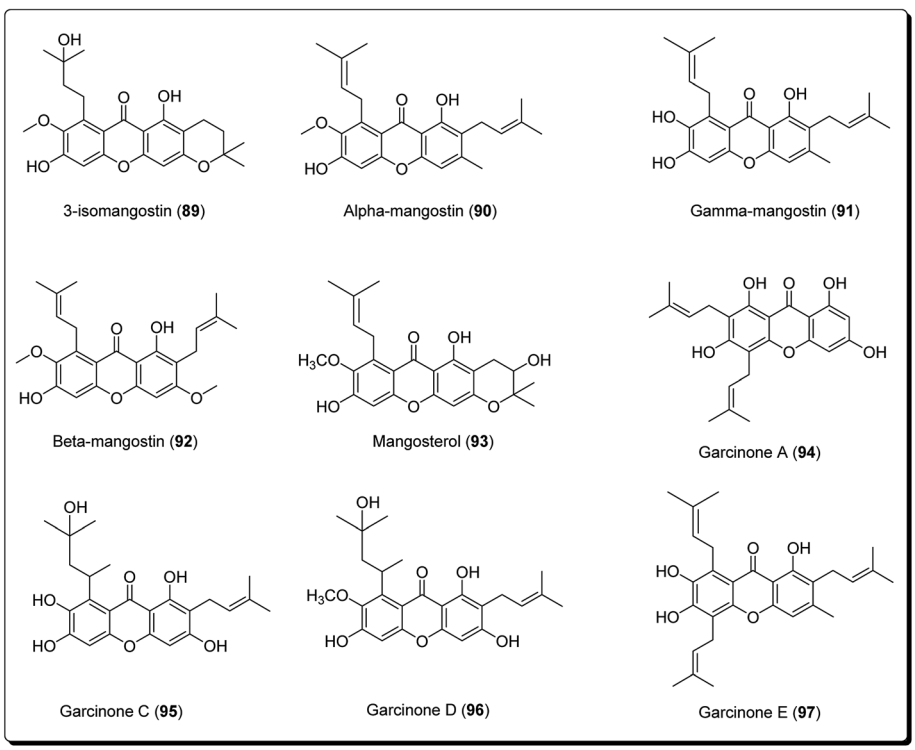


Fig. 21 Structure of natural xanthones in marketed formulations.

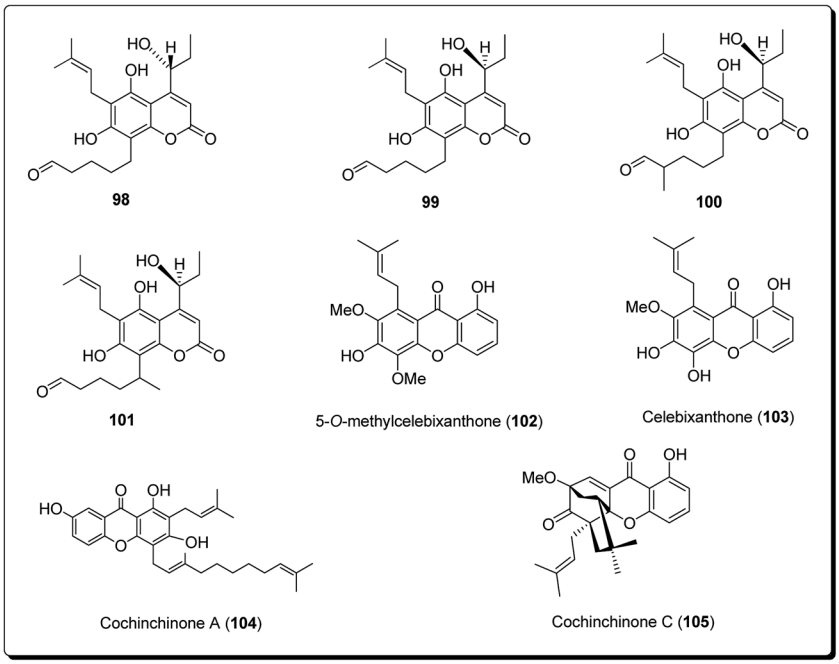


Fig. 22 Some potent cytotoxic coumarins and xanthones (98 to 105).

antiproliferative activity in the A2780 human ovarian cancer cell line assay and had IC_{50} values of 40.6 and 8.1 μM, respectively.[127] Han *et al.* isolated three new prenylated xanthones, along with ten known compounds, from the stem bark of *Garcinia lancilimba*.[128] These analogues were tested for their apoptotic effects against HeLa-C3 cells, which produce a biosensor proficient in detecting caspase-3 activation and it had been found out that 7,9,12-trihydroxy-2,2-dimethylpyrano [3,2-*b*]xanthen-6(2*H*)-one (**110**, Fig. 25), also arresting cell mitosis by interfering with microtubule formation and then induce apoptotic cell death.[128] Tao *et al.* isolated new xanthones, a pair of new natural products and known related compounds (Fig. 25) from the resin of *Garcinia hanburyi*.[129] These compounds were evaluated for their cytotoxicity against HeLa cervical carcinoma cells, with adriamycin as the positive control and all except compound **111** (IC_{50} = 111 μM) was found to display most potent cytotoxicity (Fig. 25).[129]

Garcinia hanburyi, resin (named gamboge) is originally used as pigment and folk medicine. In recent years, a special group of xanthones, caged *Garcinia* xanthones, which have been identified as bioactive compounds with potent biological properties, *e.g.* antitumor, anti-HIV-1, antibacterial, and anti-inflammatory activities. The compounds occur naturally in the resin, fruit, and other parts of the plant. Han *et al.* reported 40 different xanthones from *G. hanburyi*. Furthermore, multiple mechanisms of cytotoxic activity have been reported, such as cell cycle

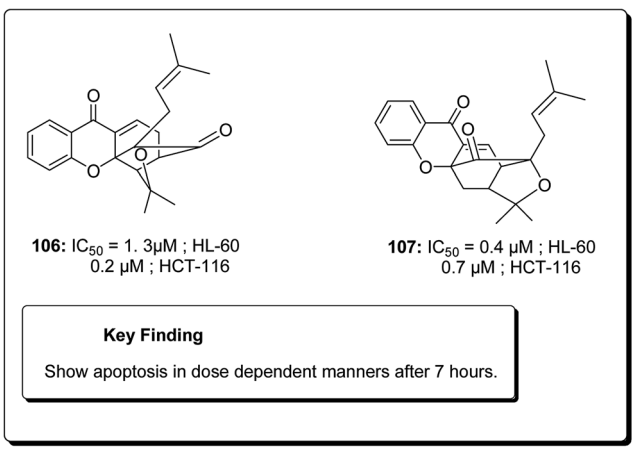


Fig. 23 Some potent xanthones (106 and 107).

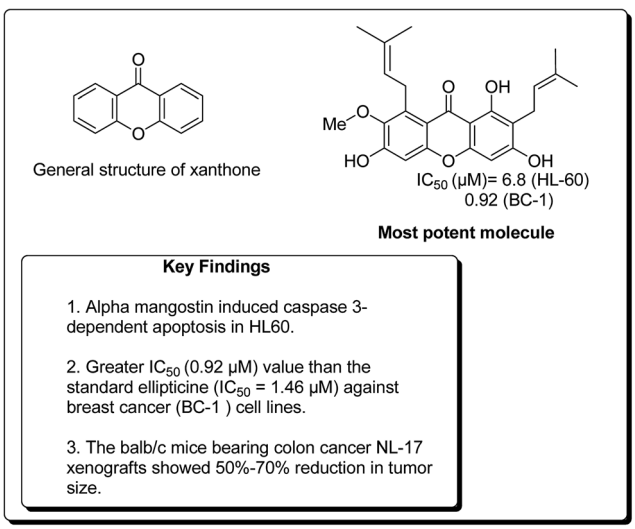


Fig. 24 Xanthone nucleus and structure of a potent xanthone.

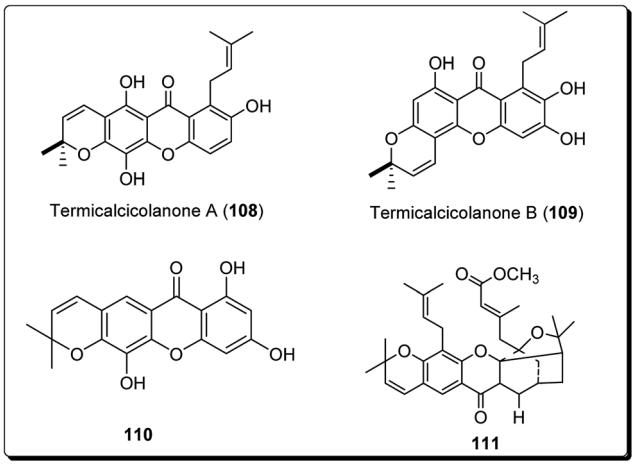


Fig. 25 Some potent antiproliferative compounds (**108** to **111**).

arrest, apoptosis induction, telomerase inhibition, and anti-angiogenesis.[130] Mu *et al.* established an oxidative analogue of gambogic acid as a potential antitumor compound by inducing apoptosis in HepG2 cells. Caged xanthones isolated from *G. hanburyi* were screened cytotoxic activities against many cell lines, such as human lung carcinoma cells (A 549), henrietta lacks cervical carcinoma tumor cells (HeLa), human hepatoma (SMMC-7221), human leukemia K 562 (K 562/S), doxorubicin-resistant K 562 (K 562/R), human colon carcinoma cells (HCT 116), human breast carcinoma cells (SK-BR-3), human hepatocellular carcinoma cells (HepG2), human liver cancer cells (Hep3B), human liver cancer cells (Huh7), and human neuroblastoma cells (SH-SY5Y).[131,132] The modified xanthones were found to exhibit the most potent antitumor activities by inducing apoptosis in HepG2 cell lines in a dose-dependent manner.[133] It was found that the efficiency of cell growth inhibition increased dramatically when the concentration of modified xanthones was increased.[131,132] Jang *et al.* reported that modified xanthones (Fig. 26) were selective agonist for TrkA receptor, showing a strong neurotrophic activity by selectively binding to TrkA, inducing its tyrosine phosphorylation, provoking outgrowth in PC12 cells, eliciting PI3-kinase/Akt and MAPK activation, thus preventing neuronal cell death.[133]

Zelefack *et al.* isolated butyraxanthones A–D, along with four known xanthones (**114–117**) and a triterpenoid (lupeol) from the shoot bark of *Pentadesma butyracea*.[134] These compounds were evaluated for their *in vitro* antiplasmodial action towards *Plasmodium falciparum* chloroquine-resistant strain and for the cytotoxic effect in human breast tumor cell line (MCF-7). It was found out that among all tested compounds, only butyraxanthone D (**114**) was inactive (IC_{50} > 10 μg mL^{-1}) but another isolated compound **115** showed the best potency.[134]

Mosoophon *et al.* also extracted ruguloxanthones A–C, 14-methoxytajixanthone and tajixanthone ethanoate, a new bicyclo[3.3.1]nona-2,6-diene analogue, rugulosone and seven known compounds, shamixanthone, tajixanthone, 14-methoxytajixanthone-25-acetate, tajixanthone hydrate, tajixanthone methanoate, isoemericellin, and ergosterol, from the fungus *Emericella rugulosa*. Compound **118** (rugulosone, Fig. 27) also exhibited cytotoxicity against the BC1, KB, and NCI-H187 cancer cell lines, with IC_{50} values of 1.3, 2.6 and 1.3 μg mL^{-1}, respectively.[135]

Bhattacharya *et al.* synthesised xanthenes from the one-pot condensation of β-naphthol with aryl aldehydes catalysed by $TaCl_5$ under solvent-free conventional heating.[136] The synthesised xanthenes (Fig. 28) were evaluated against a group of six human tumor lines such as SW-620, 502713 and Colo-205 (colon), SKNSH (CNS), A-549 (lung) and PC-3 (prostate), using

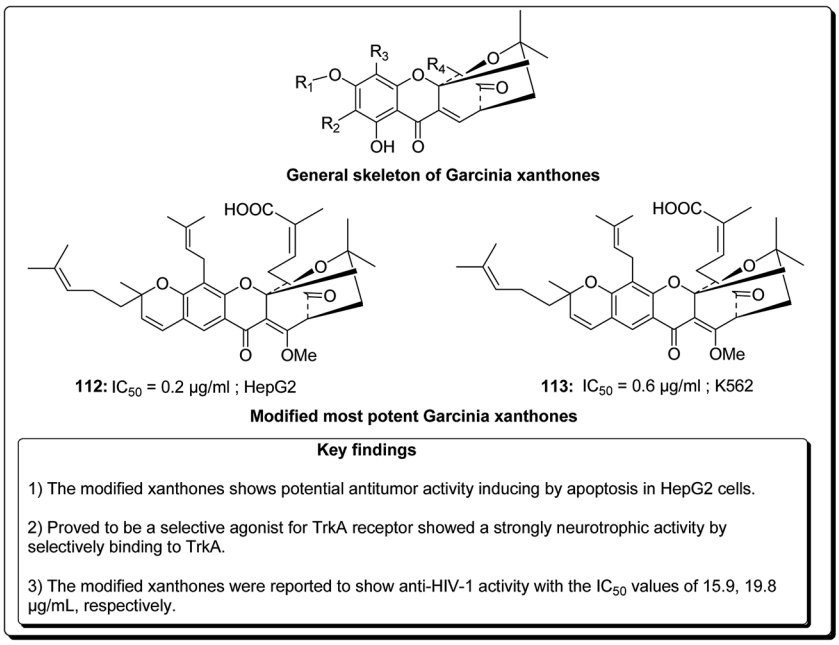


Fig. 26 Some reported potent cytotoxic compounds (**112** and **113**).

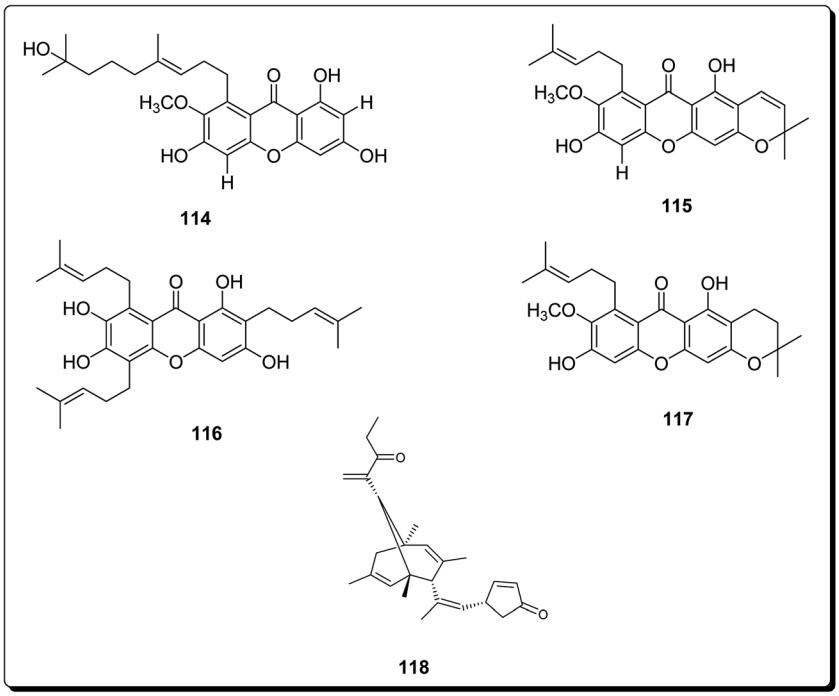


Fig. 27 More potent cytotoxic analogues (**114** to **118**).

sulforhodamine B. Compound **119** showed IC_{50} of 37.9 and 41.3 μM against Colo-205 and 502713 respectively, whereas compound **120** showed an IC_{50} of 41.9 μM against Colo-205 cell line.[136] Niu *et al.* isolated 1,4,5,6-tetrahydroxanthenes and bracteaxanthenes, together with 26 known compounds from the ethanol extract of stem bark of *Garcinia bracteata*. These compounds were evaluated for their cell growth inhibiting effect against human leukaemic HL-60 cell lines. The prenylated xanthones (Fig. 28) showed more potent effects. Compounds **121–123** were found most effective *via* the inhibition of HL-60 cell growth with GI_{50} values of 2.8, 3.4 and 3.1 μM, respectively.[137] Caxanthones A–E, with anticancer properties, which were identified from *Codonopsis ovata*.[139] While coxanthone B showed significant inhibitory activity against SF-295 and MDAMB-435 (IC_{50} values of 7.0 and 15.0 μM, respectively), coxanthone A showed cytotoxicity against the A549 cell line (IC_{50} value of 22.5 μM). Meanwhile, the cytotoxic activity of 1-hydroxy-3,5-dimethoxyxanthone, swertiperenine and 1,7,8-trihydroxy-3-methoxyxanthone were shown to be with IC_{50} values of 3.0, 5.0 and 21.0 μM against A549, MDAMB-435, and A549 cell lines, respectively.[138] Among synthesised xanthones with promising anticancer properties, Mulakayala *et al.* showed

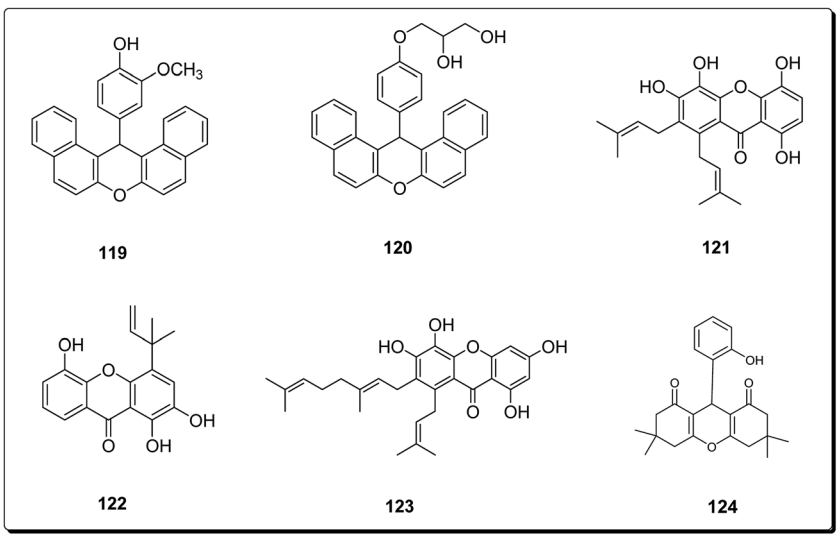


Fig. 28 Selected potent anticancer synthesized compounds (**119** to **124**).

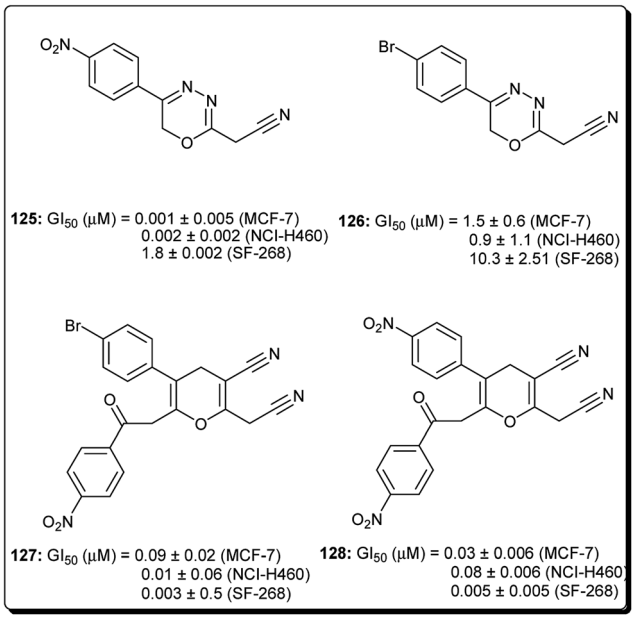


Fig. 29 Selected potent 1,3,4-oxadiazine pyran derivatives (**125** to **128**).

that 9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**124**) and its analogues could be good starting points for anticancer drug discovery programs, as this compound and its analogues showed good antiproliferative properties *in vitro* against three cancer cell lines (with IC_{50} values between 23 and 38 μM).[139]

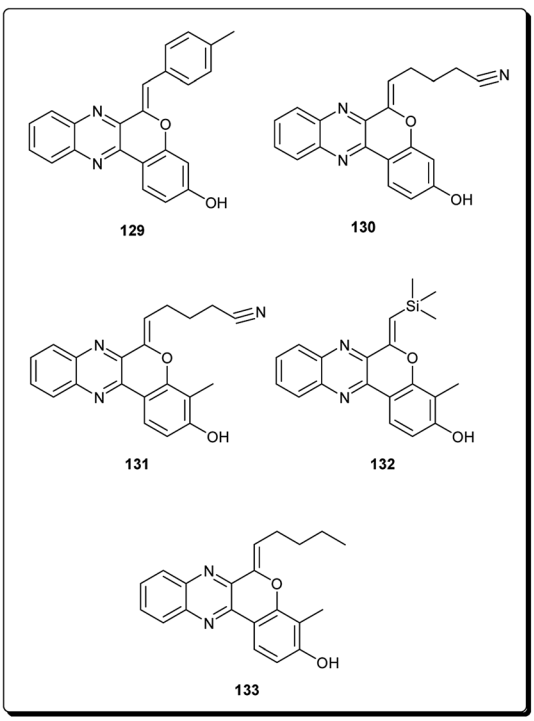


Fig. 30 Selected potent chromeno[4,3-*b*]quinoxaline derivatives (**129** to **133**).

6 Other scaffolds

Mohareb and Schatz described 1,3,4-oxadiazine pyran derivatives with highly potent activities against breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268), some of which showed better inhibitory effect towards three cell lines than the standard drug doxorubicin, among which compounds **125** to **128** (Fig. 29) showed submicromolar activities.[140] Kumar *et al.* also designed and synthesised a number of chromeno[4,3-*b*]quinoxaline derivatives with activities against human metastatic breast cancer cells (MDA-MB 231) and human chronic myeloid leukemia cells (K562).[141] The most potent compounds (**129** to **133**, Fig. 30) inhibited the growth of the cancer cells up to about 50% at 1 μM.

7 Conclusions

The pyran scaffold has received much attention of researchers both from the pharmaceutical industries and academic organizations in the recent past. As evident from numerous cited papers, the pyran scaffold is the building block of various coumarins, xanthones and flavonoids present in various natural plants. Numerous compounds containing pyran nucleus have displayed inhibitory activities with IC_{50} values in the micromolar range. The overall conclusion is that pyran being one of the privileged heterocycles has shown a wide array of biological activities, particularly against cancer. There is abundant evidence that the utilization of diversely substituted pyran analogues has provided the platform for identification of new chemical entities which could be drug candidates with diverse biological properties. The *in vitro*, *in vivo*, and *in silico* experiments have shown pyrans to be molecules with potentially exploitable structures for the development of new cytotoxic and anticancer agents. Moreover, structures of designed and synthesised molecules discussed in this compilation clearly highlight the interesting and promising anticancer profiles along with their structure–activity relationships. A discussion of the key interactions with the amino acid in selected binding sites, as demonstrated by molecular modeling studies, has also been provided.

Acknowledgements

Authors are thankful to Prof. Ajaib Singh Brar, Vice-chancellor of Guru Nank Dev University, Amritsar for their encouragements. One of the authors Mr Dinesh Kumar is thankful to UGC, New Delhi for providing research fellowship under UPE (Focus Area-Health Care, Drug Development, and Sports Medicines) Scheme (Sanction No. 25994/Estt./A-11). FNK is currently a Georg Forster fellow of the Alexander von Humboldt Foundation, Germany.

Notes and references

1 J. Ferlay, I. Soerjomataram, M. Ervi, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D. M. Parkin, D. Forman and

F. Bray, *GLOBOCAN, 2012, v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11*, International Agency for Research on Cancer, Lyon, France, 2013, http://globocan.iarc.fr, accessed on 29 January 2017.

2 A. Nakhi, R. Adepu, D. Rambabu, R. Kishore, G. R. Vanaja, A. M. Kalle and M. Pal, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4418–4427.

3 R. L. Siegel, K. D. Miller and A. Jemal, *Ca-Cancer J. Clin.*, 2016, **66**, 7–30.

4 J. M. Winter, M. F. Brennan, L. H. Tang, M. I. D'Angelica, R. P. DeMatteo, Y. Fong, D. S. Klimstra, W. R. Jarnagin and P. J. Allen, *Ann. Surg. Oncol.*, 2012, **19**, 169–175.

5 E. Deutsch, L. Maggiorella, P. Eschwege, J. Bourhis, J. C. Soria and B. Abdulkarim, *Lancet Oncol.*, 2004, **5**, 303–313.

6 M. J. Alvarez-Cubero, M. Saiz, L. J. Martinez-Gonzalez, J. C. Alvarez, J. A. Lorente and J. M. Cozar, *Urol. Oncol.*, 2013, **31**, 1419–1429.

7 W. C. Willett, *Science*, 1994, **264**, 532–537.

8 V. Duraipandiyan, M. Ayyanar and S. Ignacimuthu, *BMC Complementary Altern. Med.*, 2006, **6**, 35.

9 D. Kumar and S. K. Jain, *Curr. Med. Chem.*, 2016, **23**, 4338–4394.

10 S. R. Jaggavarapu, A. S. Kamalakaran, J. Nanubolu, V. P. Jalli, S. K. Gangisetty and G. Gaddamanugu, *Tetrahedron Lett.*, 2014, **55**, 3670–3673.

11 R. Pal, V. Kumar, A. K. Gupta, V. Beniwal and G. K. Gupta, *Med. Chem. Res.*, 2014, **23**, 4060–4069.

12 G. K. Gupta, V. Kumar and A. Mittal, *Lett. Org. Chem.*, 2014, **11**, 273–286.

13 A. Kumar, P. Lohan, G. K. Gupta, D. Kaushik and O. Prakash, *Eur. J. Med. Chem.*, 2012, **50**, 81–89.

14 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136.

15 D. Enders, C. Grondal and M. R. M. Huttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581.

16 B. Kazemi, S. Javanshir, A. Maleki, M. Safari and H. R. Khavasi, *Tetrahedron Lett.*, 2012, **53**, 6977–6981.

17 K. C. Nicolaou, J. A. Pfefferkorn and G. Q. Cao, *Angew. Chem., Int. Ed.*, 2000, **39**, 734–739.

18 Y. Moumou, J. Vasseur, F. Trotin and J. Dubois, *Phytochemistry*, 1992, **31**, 1239–1241.

19 I. E. Soria-Mercado, A. Prieto-Davo, P. R. Jensen and W. J. Fenical, *J. Nat. Prod.*, 2005, **68**, 904–910.

20 M. B. Gewali, Y. Tezuka, A. H. Banskota, M. S. Ali, I. Saiki, H. Dong and S. Kadota, *Org. Lett.*, 1999, **1**, 1733–1736.

21 K. Koyama, M. Takahashi, M. Oitate, N. Nakai, H. Takakusa, S. Miura and O. Okazaki, *Antimicrob. Agents Chemother.*, 2009, **53**, 4845–4851.

22 M. Kiso, S. Kubo, M. Ozawa, Q. M. Le, C. A. Nidom, M. Yamashita and Y. Kawaoka, *PLoS Pathog.*, 2010, **6**, e1000786.

23 D. R. da Rocha, A. C. de Souza, J. A. Resende, W. C. Santos, E. A. dos Santos, C. Pessoa, M. O. de Moraes, L. V. Costa-Lotufo, R. C. Montenegro and V. F. Ferreira, *Org. Biomol. Chem.*, 2011, **9**, 4315–4322.

24 Y. Dong, Q. Shi, K. Nakagawa-Goto, P. C. Wu, S. L. Morris-Natschke, A. Brossi, K. F. Bastow, J. Y. Lang, M. C. Hung and K. H. Lee, *Bioorg. Med. Chem.*, 2010, **18**, 803–808.

25 J. M. Doshi, D. Tian and C. Xing, *J. Med. Chem.*, 2006, **49**, 7731–7739.

26 J. Madda, A. Venkatesham, B. N. Kumar, K. Nagaiah, P. Sujitha, C. G. Kumar, T. P. Rao and N. J. Babu, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4428–4434.

27 G. A. Morales, J. R. Garlich, J. Su, X. Peng, J. Newblom, K. Weber and D. L. Durden, *J. Med. Chem.*, 2013, **56**, 1922–1939.

28 I. E. Soria-Mercado, A. Prieto-Davo, P. R. Jensen and W. Fenical, *J. Nat. Prod.*, 2005, **46**, 904–910.

29 P. Siripong, K. Kanokmedakul, S. Piyaviriyagul, J. Yahuafai, R. Chanpai, S. Ruchirawat and N. Oku, *J. Tradit. Med.*, 2006, **23**, 166–172.

30 H. Hussain, K. Krohn, V. U. Ahmad, G. A. Miana and I. R. Greend, Lapachol: an overview, *ARKIVOC*, 2007, **2**, 145–171.

31 A. J. da Silva, C. D. Netto, W. Pacienza-Lima, E. C. Torres-Santos, B. Rossi-Bergmann, S. Maurel, A. Valentin and P. R. Costa, *J. Braz. Chem. Soc.*, 2009, **20**, 176–182.

32 S. Jiinnez-Alonso, H. C. Orellana, A. Estevez-Braun, A. G. Ravelo, E. Perez-Sacau and F. Machin, *J. Med. Chem.*, 2008, **51**, 6761–6772.

33 M. S. Bentle, E. A. Bey, Y. Dong, K. E. Reinicke and D. E. Boothman, *J. Mol. Histol.*, 2006, **37**, 203–218.

34 I. V. Magedov, A. S. Kireev, A. R. Jenkins, N. M. Evdokimov, D. T. Lima, P. Tongwa, J. Altig, W. F. Steelant, S. van Slambrouck, M. Y. Antipin and A. Kornienko, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5195–5198.

35 T. A. D. Thi, T. H. V. Thi, H. T. Phuong, T. H. Nguyen, C. P. The, C. V. Duc, Y. Depetter, T. V. Nguyen and M. D'hooghe, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3355–3358.

36 E. J. Salaski, G. Krishnamurthy, W.-D. Ding, K. Yu, S. S. Insaf, C. Eid, J. Shim, J. I. Levin, K. Tabei, T.-B. Lourdes, W.-G. Zhang, L. A. McDonald, E. Honores, C. Hanna, A. Yamashita, B. Johnson, Z. Li, L. Laakso, D. Powell and T. S. Mansour, *J. Med. Chem.*, 2009, **52**, 2181.

37 N. Tanaka, T. Okabe, F. Isono, M. Kashiwagi, K. Nomoto, M. Takahashi, A. Shimazu and T. Nishimura, *J. Antibiot.*, 1985, **38**, 1327.

38 N. Tsuji, M. Kobayashi, Y. Wakisaka, Y. kawamura, M. Mayama and K. Matsumoto, *J. Antibiot.*, 1976, **29**, 7.

39 H. G. Floss, P. Soong and C.-T. Chang, *J. Antibiot.*, 1975, **28**, 156.

40 R. Corbaz, L. Ettlinger, E. Gaumann, J. Kalvoda, W.-K. Schierlein, F. Kradolfer, B.-K. Manukian, L. Neipp, V. Prelog, P. Reusser and H. Zahner, *Helv. Chim. Acta*, 1957, **40**, 1262.

41 X. Jiang, M. Wang, S. Song, Y. Xu, Z. Miao and A. Zhang, *RSC Adv.*, 2015, **5**, 27502–27508.

42 A. E. G. Hammam, O. I. A. El-Salam, A. M. Mohamed and N. A. Hafez, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2005, **44**, 1887–1893.

43 K. Kowalski, A. K. Chyła, L. Szczupak, P. Hikisz, J. Bernasińska, A. Rajnisz, J. Solecka and B. Therrien, *J. Organomet. Chem.*, 2013, **741**, 153–161.
44 M. K. Chahar, N. Sharma, M. P. Dobhal and Y. C. Joshi, *Pharmacogn. Rev.*, 2011, **5**, 1–12.
45 D. Ravishankar, A. K. Rajora, F. Greco and H. M. I. Osborn, *Int. J. Biochem. Cell Biol.*, 2013, **45**, 2821–2831.
46 W. Y. Huang and Y. Z. Cai, *Nutr. Cancer*, 2010, **62**, 1–20.
47 H. De Groot and U. Rauen, *Fundam. Clin. Pharmacol.*, 1998, **12**, 249–255.
48 J. E. Middleton, *Adv. Exp. Med. Biol.*, 1998, **439**, 175–182.
49 J. S. Yoon, M. K. Lee, S. H. Sung and Y. C. Kim, *J. Nat. Prod.*, 2006, **69**, 290–291.
50 M. L. Neuhouser, *Nutr. Cancer*, 2004, **50**, 1–7.
51 L. W. Min, *Cancer Treat. Rev.*, 2009, **35**, 57–68.
52 Y. Akao, T. Itoh, K. Ohguchi, M. Iinuma and Y. Nozawa, *Bioorg. Med. Chem.*, 2008, **16**, 2803–2810.
53 J. R. Mays, S. A. Hill, J. T. Moyers and B. S. Blagg, *Bioorg. Med. Chem.*, 2010, **18**, 249–266.
54 Y. C. Hsiao, Y. S. Hsieh, W. H. Kuo, H. L. Chiou, S. F. Yang, W. L. Chiang and S. C. Chu, *J. Biomed. Sci.*, 2007, **14**, 107–119.
55 E. J. Choi, J. I. Lee and G. H. Kim, *Int. J. Mol. Med.*, 2010, **25**, 293–298.
56 E. J. Choi, J. I. Lee and G. H. Kim, *Arch. Pharmacal Res.*, 2011, **34**, 2125–2130.
57 H. Usman, E. H. Hakim, T. Harlim, M. N. Jalaluddin, Y. M. Syah, S. A. Achmad and H. Takayama, *Z. Naturforsch., C: J. Biosci.*, 2006, **61**, 184–188.
58 S. C. Shen, C. H. Ko, S. W. Tseng, S. H. Tsai and Y. C. Chen, *Toxicol. Appl. Pharmacol.*, 2004, **197**, 84–95.
59 S. Y. Liao, J. C. Chen, L. Qian, Y. Shen and K. C. Zheng, *Eur. J. Med. Chem.*, 2008, **43**, 2159–2170.
60 M. Hirunuma, Y. Shoyama, K. Sasaki, S. Sakamoto, F. Taura, Y. Shoyama, H. Tanaka and S. Morimoto, *Phytochemistry*, 2011, **72**, 752–760.
61 M. Switalska, G. Grynkiewicz, L. Strzadala and J. Wietrzyk, *Nutr. Cancer*, 2013, **65**, 874–884.
62 Y. Murti and P. Mishra, *Indian J. Pharm. Sci.*, 2014, **76**, 163–166.
63 D. Kumar, O. Singh, K. Nepali, P. M. S. Bedi, A. Qayum, S. Singh and S. K. Jain, *Anti Canc. Agents Med. Chem.*, 2016, **16**, 881–890.
64 A. Aghdassi, P. Phillips, V. Dudeja, D. Dhaulakhandi, R. Sharif, R. Dawra, M. M. Lerch and S. Saluja, *Cancer Res.*, 2007, **67**, 616–625.
65 M. Mouria, A. S. Gukovskaya, Y. Jung, P. Buechler, O. J. Hines, H. A. Reber and S. J. Pandol, *Int. J. Cancer*, 2002, **98**, 761–769.
66 W. Xue, B. A. Song, H. J. Zhao, X. B. Qi, Y. J. Huang and X. H. Liu, *Eur. J. Med. Chem.*, 2015, **97**, 155–163.
67 M. Safavi, N. Esmati, S. K. Ardestani, S. Emami, S. Ajdari, J. Davoodi, A. Shafiee and A. Foroumadi, *Eur. J. Med. Chem.*, 2012, **58**, 573–580.
68 A. Al-Kawkabani, B. Boutemeur-Kheddis, M. Makhloufi-Chebli, M. Hamdi, O. Talhi and A. M. Silva, *Tetrahedron Lett.*, 2013, **54**, 5111–5114.
69 Y. Shi and C. Zhou, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 956–960.
70 S. Y. Hur, T. E. Kim, Y. G. Park, J. R. Kim and J. W. Kim, *Exp. Mol. Med.*, 2005, **37**, 436–446.
71 T. Devji, C. Reddy, C. Woo, S. Awale, S. Kadota and D. Carrico-Moniz, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5770–5773.
72 N. S. Reddy, M. R. Mallireddigari, S. Cosenza, K. Gumireddy, S. C. Bell, E. P. Reddy and M. V. Reddy, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4093–4097.
73 J. Klenkar and M. Molnar, *J. Chem. Pharm. Res.*, 2015, **7**, 1223–1238.
74 K. Nepali, S. Sharma, D. Kumar, A. Budhiraja and K. L. Dhar, *Recent Pat. Anti-Cancer Drug Discovery*, 2014, **9**, 303–339.
75 K. M. Amin, A. A. Eissa, S. M. Abou-Seri, F. M. Awadallah and G. S. Hassan, *Eur. J. Med. Chem.*, 2013, **60**, 187–198.
76 F. Belluti, G. Fontana, L. Dal Bo, N. Carenini, C. Giommarelli and F. Zunino, *Bioorg. Med. Chem.*, 2010, **18**, 3543–3550.
77 K. Paul, S. Bindal and V. Luxami, *Bioorg. Med. Chem.*, 2013, **23**, 3667–3672.
78 K. V. Sashidhara, A. Kumar, M. Kumar, J. Sarkar and S. Sinha, *Bioorg. Med. Chem.*, 2010, **20**, 7205–7211.
79 K. V. Sashidhara, S. R. Avula, K. Sharma, G. R. Palnati and S. R. Bathula, *Eur. J. Med. Chem.*, 2013, **60**, 120–127.
80 A. K. Bagdi, A. Majee and A. Hajra, *Tetrahedron Lett.*, 2013, **54**, 3892–3895.
81 D. Kumar, F. Malik, P. M. S. Bedi and S. Jain, *Chem. Pharm. Bull.*, 2016, **64**, 399–409.
82 M. K. Hussain, M. I. Ansari, N. Yadav, P. K. Gupta, A. K. Gupta, R. Saxena, I. Fatima, M. Manohar, P. Kushwaha and V. Khedgikar, *RSC Adv.*, 2014, **4**, 8828–8845.
83 O. G. Ganina, E. Daras, V. Bourgarel-Rey, V. Peyrot, A. N. Andresyuk, J. P. Finet, A. Y. Fedorov, I. P. Beletskaya and S. Combes, *Bioorg. Med. Chem.*, 2008, **16**, 8806–8812.
84 Y. Garazd, M. Garazd and R. Lesyk, *Saudi Pharm. J.*, 2017, **25**, 214–223.
85 H. P. Zhao, A. C. Donnelly and B. R. Kusuma, *J. Med. Chem.*, 2011, **54**, 3839–3853.
86 Z. N. Siddiqui, T. N. M. Musthafa, A. Ahmad and A. U. Khan, *Arch. Pharm.*, 2011, **344**, 394–401.
87 B. R. Kusuma, L. B. Peterson, H. Zhao, G. Vielhauer, J. Holzbeierlein and B. S. Blagg, *J. Med. Chem.*, 2011, **54**, 6234–6253.
88 J. A. Burlison and B. S. J. Blagg, *Org. Lett.*, 2006, **8**, 4855–4858.
89 G. H. Tan, Y. C. Yao, Y. J. Gu, S. Li, M. Lv, K. Wang, H. Chen and X. Li, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2825–2830.
90 M. Zhu, L. K. Zhou, Y. C. Yao, S. Li, M. Lv, K. Wang, X. Li and H. Chen, *Med. Chem. Res.*, 2015, **24**, 2314–2324.
91 L. Zhao, Y. C. Yao, S. M. Lv, H. Chen and X. Li, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 900–904.
92 H. Chen, S. Li, Y. C. Yao, L. Zhou, J. Zhao, Y. Gu, K. Wang and X. Li, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4785–4789.

93 L. Zhang, Y. C. Yao, M. Y. G. R. X. Rong, K. R. Wang, L. Xiao-Liu and H. Chen, *Chin. Chem. Lett.*, 2016, **27**, 1708–1716.
94 S. M. Kupchan, D. R. Streelman and A. T. Sneden, *J. Nat. Prod.*, 1980, **43**, 296–301.
95 D. K. Winter, D. L. Sloman and J. A. Porco Jr, *Nat. Prod. Rep.*, 2013, **30**, 382–391.
96 C. N. Lin, S. J. Liou, T. H. Lee, Y. C. Chuang and S. J. Won, *J. Pharm. Pharmacol.*, 1996, **48**, 539–544.
97 C. A. Chen, R. H. Yeh and D. S. Lawrence, *J. Am. Chem. Soc.*, 2002, **124**, 3840–3841.
98 L. F. Steiner and S. A. Summerland, *J. Econ. Entomol.*, 1943, **36**, 435–439.
99 J. H. Cheng, A. M. Huang, T. C. Hour, S. C. Yang, Y. S. Pu and C. N. Lin, *Eur. J. Med. Chem.*, 2011, **46**, 1222–1231.
100 M. Chase, Angiosperm phylogeny group, *Bot. J. Linn. Soc.*, 2003, **141**, 399–436.
101 J. K. Burmester, Xanthene compounds for cancer chemotherapy, *US Pat.* WO, 2006102102 A2, 2006.
102 Y. Xiao and R. Ottenbrite, Tumor necrosis factor inhibitors, *US Pat.* WO, 2006083869, 2006.
103 M. I. Greene, R. Murali, X. Cheng, R. Ottenbrite and Y. Xiao, *US Pat.* WO, 2006083970, 2006.
104 M. R. Campos-Esparza, M. V. Sanchez-Gomez and C. Matute, *Cell Calcium*, 2009, **45**, 358–368.
105 A. Martinez, A. Galano and R. Vargas, *J. Phys. Chem. B*, 2011, **115**, 12591–12598.
106 J. Pedraza-Chaverri, L. M. Reyes-Fermin, E. G. Nolasco-Amaya, M. Orozco-Ibarra, O. N. Medina-Campos, O. Gonzalez-Cuahutencos, I. Rivero-Cruz and R. Mata, *Exp. Toxicol. Pathol.*, 2009, **61**, 491–501.
107 M. Buelna-Chontal, F. Correa, S. Hernandez-Resendiz, C. Zazueta and J. Pedraza-Chaverri, *J. Med. Food*, 2011, **14**, 1370–1374.
108 L. M. Reyes-Fermín, S. González-Reyes, N. G. Tarco-Álvarez, M. Hernández-Nava, M. Orozco-Ibarra and J. Pedraza-Chaverri, *Nutr. Neurosci.*, 2012, **15**, 34–41.
109 M. K. Schwaebe, T. J. Moran and J. P. Whitten, *Tetrahedron Lett.*, 2005, **46**, 827–829.
110 K. Matsumoto, Y. Akao, H. Yi, K. Ohguchi, T. Ito, T. Tanaka, E. Kobayashi, M. Iinuma and Y. Nozawa, *Bioorg. Med. Chem.*, 2004, **12**, 5799–5806.
111 M. Pedro, F. Cerqueira, M. E. Sousa, M. S. J. Nascimento and M. Pinto, *Bioorg. Med. Chem.*, 2002, **10**, 3725–3730.
112 C. Gnerre, U. Thull, P. Gailland, P. A. Carrupt, B. Testa, E. Fernandes, F. Silva, M. Pinto, J. L. Wolfender, K. Hostettmann and G. Cruciani, *Helv. Chim. Acta*, 2001, **84**, 552–570.
113 S. Poondru, S. Zhou, J. Rake, G. Shackleton, T. H. Corbett, R. E. Parchment and B. R. Jasti, *J. Chromatogr. B: Biomed. Sci. Appl.*, 2001, **759**, 175–178.
114 K. H. Lee, H. B. Chai, P. A. Tamez, J. M. Pezzuto, G. A. Cordell, K. K. Win and M. Tin-Wa, *Phytochemistry*, 2003, **64**, 535–539.
115 S. Laphookhieo, J. K. Syers, R. Kiattansakul and K. Chantrapromma, *Chem. Pharm. Bull.*, 2006, **54**, 745–747.
116 O. Chantarasriwong, W. C. Cho, A. Batova, W. Chavasiri, C. Moore, A. L. Rheingold and E. A. Theodorakis, *Org. Biomol. Chem.*, 2009, **7**, 4886–4894.
117 K. Matsumoto, Y. Akao, E. Kobayashi, K. Ohguchi, T. Ito, T. Tanaka, M. Iinuma and Y. Nozawa, *J. Nat. Prod.*, 2003, **66**, 1124–1127.
118 L. C. Chiang, H. Y. Cheng, M. C. Liu, W. Chiang and C. C. Lin, *LWT–Food Sci. Technol.*, 2004, **37**, 539–544.
119 M. J. Balunas, B. Su, R. W. Brueggemeier and A. D. Kinghorn, *J. Nat. Prod.*, 2008, **17**, 1161–1166.
120 H. A. Jung, B. N. Su, W. J. Keller, R. G. Mehta and A. D. Kinghorn, *J. Agric. Food Chem.*, 2006, **54**, 2077–2082.
121 S. Suksamrarn, O. Komutiban, P. Ratananukul, N. Chimnoi, N. Lartpornmatulee and A. Suksamrarn, *Chem. Pharm. Bull.*, 2006, **54**, 301–305.
122 L. G. Chen, L. L. Yang and C. C. Wang, *Food Chem. Toxicol.*, 2008, **46**, 688–693.
123 R. Watanapokasin, F. Jarinthanan, A. Jerusalmi, S. Suksamrarn, Y. Nakamura, S. Sukseree, W. Uthaisang-Tanethpongtamb, P. Ratananukul and T. Sano, *Appl. Biochem. Biotechnol.*, 2010, **162**, 1080–1094.
124 A. F. Aisha, K. M. Abu-Salah, Z. Ismail and A. M. S. A. Majid, *BMC Complementary Altern. Med.*, 2012, **12**, 104.
125 N. Kosem, K. Ichikawa, H. Utsumi and P. Moongkarndi, *J. Nat. Med.*, 2013, **67**, 255–263.
126 S. J. Kim, E. H. Hong, B. R. Lee, M. H. Park, J. W. Kim, A. R. Pyun, Y. J. Kim, S. Y. Chang, Y. W. Chin and H. J. Ko, *Immune Netw.*, 2012, **12**, 253–260.
127 S. Cao, P. J. Brodie, J. S. Miller, R. Randrianaivo, F. Ratovoson, C. Birkinshaw, R. Andriantsiferana, V. E. Rasamison and D. G. Kingston, *J. Nat. Prod.*, 2007, **70**, 679–681.
128 Q. B. Han, H. L. Tian, N. Y. Yang, C. F. Qiao, J. Z. Song, D. C. Chang, K. Q. Luo and H. X. Xu, *Chem. Biodiversity*, 2008, **5**, 2710–2717.
129 S. J. Tao, S. H. Guan, W. Wang, Z. Q. Lu, G. T. Chen, N. Sha, Q. X. Yue, X. Liu and D. A. Guo, *J. Nat. Prod.*, 2009, **72**, 117–124.
130 Q. B. Han and H. X. Xu, *Curr. Med. Chem.*, 2009, **16**, 3775–3796.
131 R. Mu, N. Lu, J. Wang, Y. Yin, Y. Ding, X. Zhang, H. Gui, Q. Sun, H. Duan, L. Zhang and Y. Zhang, *Eur. J. Cancer Prev.*, 2010, **19**, 61–67.
132 W. Zhou, B. Cai, J. Shan, S. Wang and L. Di, *AAPS PharmSciTech*, 2015, **16**, 28812–28840.
133 S. W. Jang, M. Okada, I. Sayeed, G. Xiao, D. Stein, P. Jin and K. Ye, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 16329–16334.
134 F. Zelefack, D. Guilet, N. Fabre, C. Bayet, S. Chevalley, S. Ngouela, B. N. Lenta, A. Valentin, E. Tsamo and M. G. Dijoux-Franca, *J. Nat. Prod.*, 2009, **72**, 954–957.
135 P. Moosophon, S. Kanokmedhakul, K. Kanokmedhakul and K. Soytong, *J. Nat. Prod.*, 2009, **72**, 1442–1446.
136 A. K. Bhattacharya, K. C. Rana, M. Mujahid, I. Sehar and A. K. Saxena, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5590–5593.
137 S. L. Niu, Z. L. Li, F. Ji, G. Y. Liu, N. Zhao, X. Q. Liu, Y. K. Jing and Y. M. Hua, *Phytochemistry*, 2012, **77**, 280–286.

138 A. A. Dar, N. A. Dangroo, A. Raina, A. Qayum, S. Singh, A. Kumar and P. L. Sangwan, *Phytochemistry*, 2016, **132**, 102–108.
139 N. Mulakayala, P. V. N. S. Murthy, D. Rambabu, M. Aeluri, R. Adepu, G. R. Krishna, C. M. Reddy, K. R. S. Prasad, M. Chaitanya, C. S. Kumar, M. V. B. Rao and M. Pal, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2186–2191.
140 R. M. Mohareb and J. Schatz, *Bioorg. Med. Chem.*, 2011, **19**, 2707–2713.
141 K. S. Kumar, D. Rambabu, B. Prasad, M. Mujahid, R. Krishna, M. V. B. Rao, C. M. Reddy, G. R. Vanaja, A. M. Kallee and M. Pal, *Org. Biomol. Chem.*, 2012, **10**, 4774–4781.