



Review article

Recent insight into the biological activities of synthetic xanthone derivatives



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ABSTRACT

Xanthenes are a class of oxygen containing heterocyclic compounds with a broad range of biological activities, and they have prominent significance in the field of medicinal chemistry. Xanthone is an attractive scaffold for the design and development of new drugs due to its promising biological activities, primarily as anticancer, antimalarial, antimicrobial, anti-HIV, anticonvulsant, anticholinesterase, anti-oxidant, anti-inflammatory, and as inhibitors of several enzymes like α -glucosidase, topoisomerase, protein kinase, aromatase, etc. In this review, we have compiled and discussed recent developments on the pharmacological profile of synthetic xanthone derivatives for different therapeutic targets. The review highlights the therapeutic significance of xanthenes and offers support in the development of new xanthone derivatives as therapeutic agents.

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1. Introduction

Xanthenes (**1**) are a class of oxygen-heterocycles containing γ -pyron moiety condensed with two benzene rings (Fig. 1). They are widely distributed in nature and exhibit different biological activities depending on their chemical structure and position of substituents on the aromatic ring [1,2]. Their interesting structural scaffold and pharmacological importance have encouraged scientists to isolate these compounds from natural products and to synthesize them as novel drug candidates. In the last two decades, xanthenes have attracted researchers in the field of medicinal chemistry. Numerous naturally occurring and synthetic xanthone derivatives have been reported in the literature with several beneficial heterogeneous pharmacological activities [3–6]. In view of the importance of xanthone derivatives in medicinal chemistry, we have made efforts to briefly summarize the different biological activities of synthetic xanthone derivatives reported in the literature over the last decade. The focus of this review article is to highlight the significance of synthetic xanthenes as anticancer, antimicrobial, antimalarial, anti-HIV, anticonvulsant, anticholinesterase, antioxidant, anti-inflammatory, and antimalarial agents and to discuss their inhibitory activity on different enzymes, including α -glucosidase, topoisomerase, protein kinase C, miRNA, intestinal P-glycoprotein, acyl-CoA:cholesterol acyltransferase, xanthine oxidase, and aromatase.

2. Biological activities of xanthenes

2.1. Anticancer activity of xanthenes

In modern society, cancer is one of the leading causes of death and continuous efforts are being made by researchers to develop novel drugs for cancer treatment [7]. Recently, several articles on synthetic xanthenes with a focus on the anticancer activity have been reported [5,8,9]. Considering the antiproliferative activity of xanthone derivatives and hydrazine system [10], Lembege et al., in 2008 synthesized a series of aryl- and heteroaryl-hydrazones derived from xanthone carbaldehyde and reported their antiproliferative activity. The position of aldehyde function at different positions leads to three sets of compounds, bearing the hydrazonomethyl chain at positions 5, 6, or 7 on the xanthone nucleus, respectively. The compounds were evaluated for *in vitro* antiproliferative activity against two cancer cell lines, i.e., MCF-7 (breast adenocarcinoma) and KB 3.1 (squamous cell oral carcinoma). Four compounds of the series showed a significant growth inhibitory effect against both cell lines with IC₅₀ in the micromolar range, and the most promising compound was the xanthone derivative **2** (Fig. 2) [11].

In 2009, Castanheiro et al. reported the synthesis and antitumor activity of pyranoxanthenes and two prenylated xanthenes against the breast adenocarcinoma MCF-7 cells. The pyranoxanthenes with a rigid dihydropyran ring was inactive, whereas the C-prenylated xanthenes **3** and **4** (Fig. 2) bearing the lipophilic prenyl group in C-2

of the xanthone scaffold exhibited the moderate growth inhibitory activity against MCF 7 cell lines [12]. Next, Fernandes et al. developed the methodology for the synthesis of a series of new chiral derivatives of xanthenes (CDX) in an enantiomerically pure form and reported their inhibition effect on the *in vitro* growth of three human tumor cell lines, that is, A375-C5 (melanoma), MCF-7 (breast adenocarcinoma), and NCI-H460 (non-small cell lung cancer). Some CDX showed cell type selectivity, and in particular cases the growth inhibitory activity was dependent on the stereochemistry of the CDXs. The results revealed that the growth inhibitory effect on human tumor cell lines was dependent on the nature and position of substituents on the xanthone scaffold and the stereochemistry of the CDXs. The most active compound of the series was **5** (Fig. 2), which was active in all human tumor cell lines in the micromolar range [13].

Encouraged by the reports showing antitumor activity of dihydroxy xanthenes [14,15], Palmeira et al., in 2010 synthesized 3,4-dihydroxy xanthone derivatives by performing prenylation and other modifications in order to increase the cytotoxicity. All the compounds showed improved cytotoxicity in leukemia cells, and the fused xanthone, i.e., 3,4-dihydro-12-hydroxy-2,2-dimethyl-2H,6H-pyrano [3,2-b]xanthene-6-one (**6**) (Fig. 2), was the most potent with promising antiproliferative and apoptotic effects in leukemia cell lines [16].

In 2011, Wang et al. reported a natural-product-like caged xanthone (**7**) (Fig. 2) with a simple structure that showed potent cytotoxicity *in vitro* but poor efficacy *in vivo* due to its poor drug-like properties, such as aqueous solubility and cell membrane permeability [17,18]. Further to improve the *in vitro* antitumor activity and drug-like properties, a novel series of natural-product-like caged xanthenes were synthesized through activity and property based optimization of the prenyl moiety of the main compound **7**. The series exhibited improved *in vitro* antitumor activity and drug-like properties. Among the synthesized series of natural-product-like caged xanthone, the most promising compound on the basis of antitumor activity and drug-like properties was dimethyl amino group bearing compound **8**, and it was selected for *in vivo* efficacy experiments. The compound **8** exhibited more potency than compound **7** in *in vivo* experiments and subsequently was considered as a potent and promising antitumor agent for clinical developments [19].

In 2013, Luo et al. synthesized a series of aminoalkoxy substituted benzo[b]xanthone derivatives and reported their *in vitro* antitumor activity in five human tumor cell lines. Most of the compounds of the series exhibited moderate to good inhibitory activity, and the compounds **9** and **10** (Fig. 2) showed the most promising antitumor activity against most cell lines. The structure activity relationship studies suggested that a four or five carbon spacer and a terminal dimethyl amino group at position C-3 of the benzo[b]xanthone scaffold were advantageous for growth inhibitory activity [20].

The α -mangostin is a xanthone-derived natural product that is isolated from tropical fruit mangosteen, *Garcinia mangostana* L. (Clusiaceae) [21,22]. Several reports describing the synthetic and medicinal chemistry of α -mangostin derivatives for anticancer activity have been reported [23–25]. Considering the limited aqueous solubility of α -mangostin, efforts were made by Fei et al., in 2014 to increase their aqueous solubility and anti-cancer activity by introducing polar solubility groups on α -mangostin. A series of novel xanthone analogues based on α -mangostin were synthesized and evaluated as anticancer agents by cytotoxic activity using 5 human cancer cell lines. Several compounds of this series showed promising activity in the μ M range on all the cell lines, and a structure activity relationship study suggested that phenol groups on C3 and

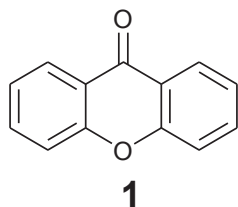


Fig. 1. Xanthone: an oxygen containing heterocyclic compound.

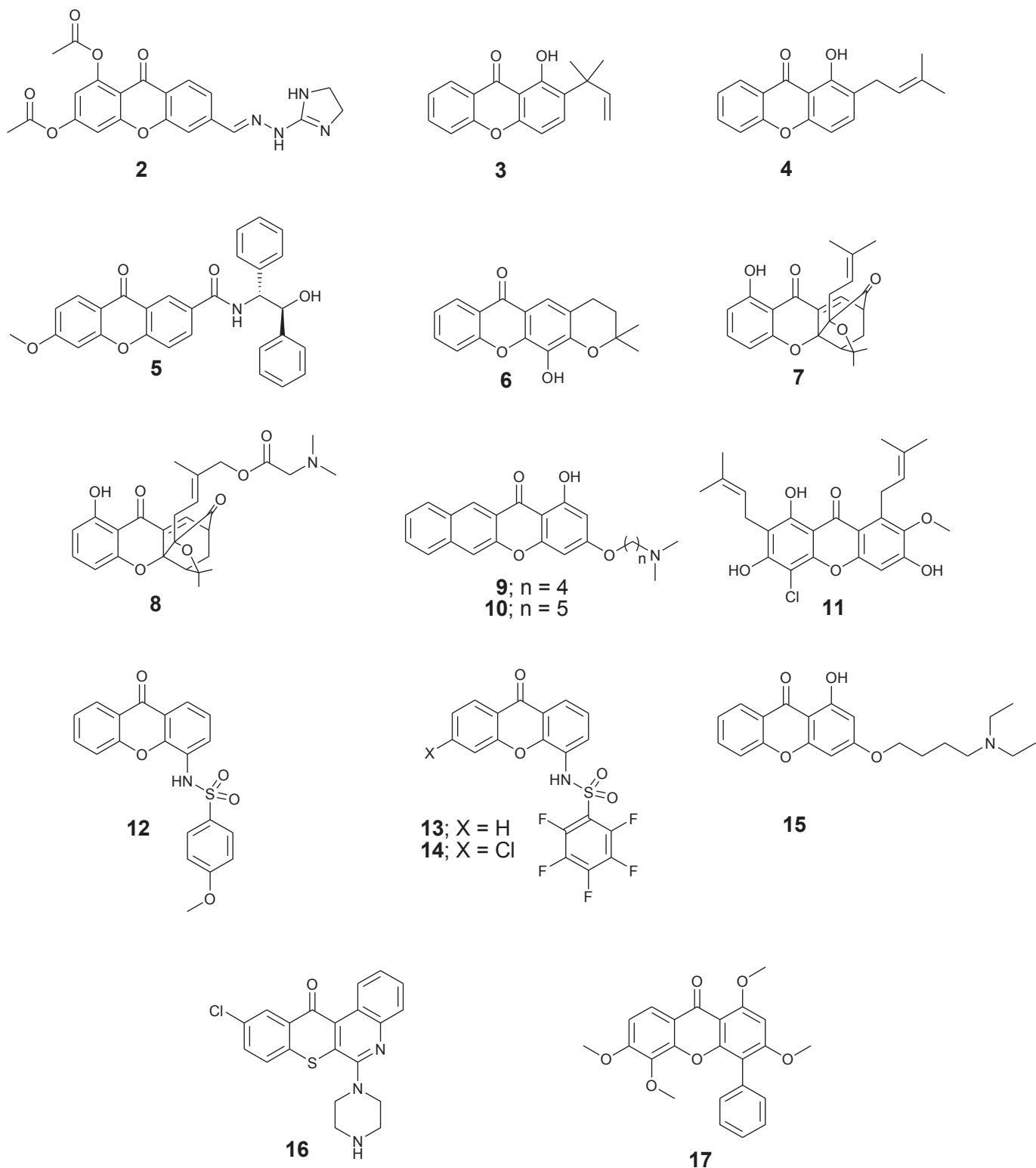


Fig. 2. Xanthone derivatives as anticancer agents.

C6 are critical to inhibition activity to cancer cell lines and that C4 modification increases the activity and drug like properties. The compound **11** (Fig. 2) bearing the chloro group at C4 showed good potency and increased solubility by several times compared to α -

mangostin [26].

Based on the antiproliferative activity of sulfonamide derivatives and xanthone analogues, Motavallizadeh et al., in 2014 designed and synthesized a series of novel hybrid compounds

bearing xanthone and sulfonamide moiety in the same molecule. A series of novel N-(9-oxo-9H-xanthen-4-yl)benzenesulfonamide derivatives were synthesized, and their antiproliferative activity was evaluated against a panel of cancer cell lines. The 4-methoxy-N-(9-oxo-9H-xanthen-4-yl)benzenesulfonamide (**12**) (Fig. 2) containing a 4-methoxy group on the phenyl ring showed the maximum antiproliferative activity against MDA-MB-231, T-47D, and SK-N-MC cells. The pentafluoro derivatives **13** and **14** (Fig. 2) exhibited promising antiproliferative activity against CCRF-CEM and MDA-MB-468 cells [27].

In 2014, Yang et al. introduced the nitrogen-containing side chain on 1,3-dihydroxyl xanthenes, synthesized a series of novel 1-

hydroxyl-3-aminoalkoxy xanthone derivatives, and evaluated for *in vitro* anticancer activities against four human cancer cell lines. Most of the compounds exhibited promising cytotoxic activities against the four tested cancer cell lines with IC_{50} in the micromolar range. The most active compound of the series was diethylamine substituted compound **15** (Fig. 2), which showed excellent broad spectrum anti-cancer activity and dose- and time-dependent anticancer effects on human gastric carcinoma MGC-803 cells through apoptosis [28].

In view of the significance of tetracyclic and tricyclic scaffold, primarily anthraquinone based heterocyclic derivatives as anti-cancer agents [29,30], Chen et al., in 2015 reported the synthesis

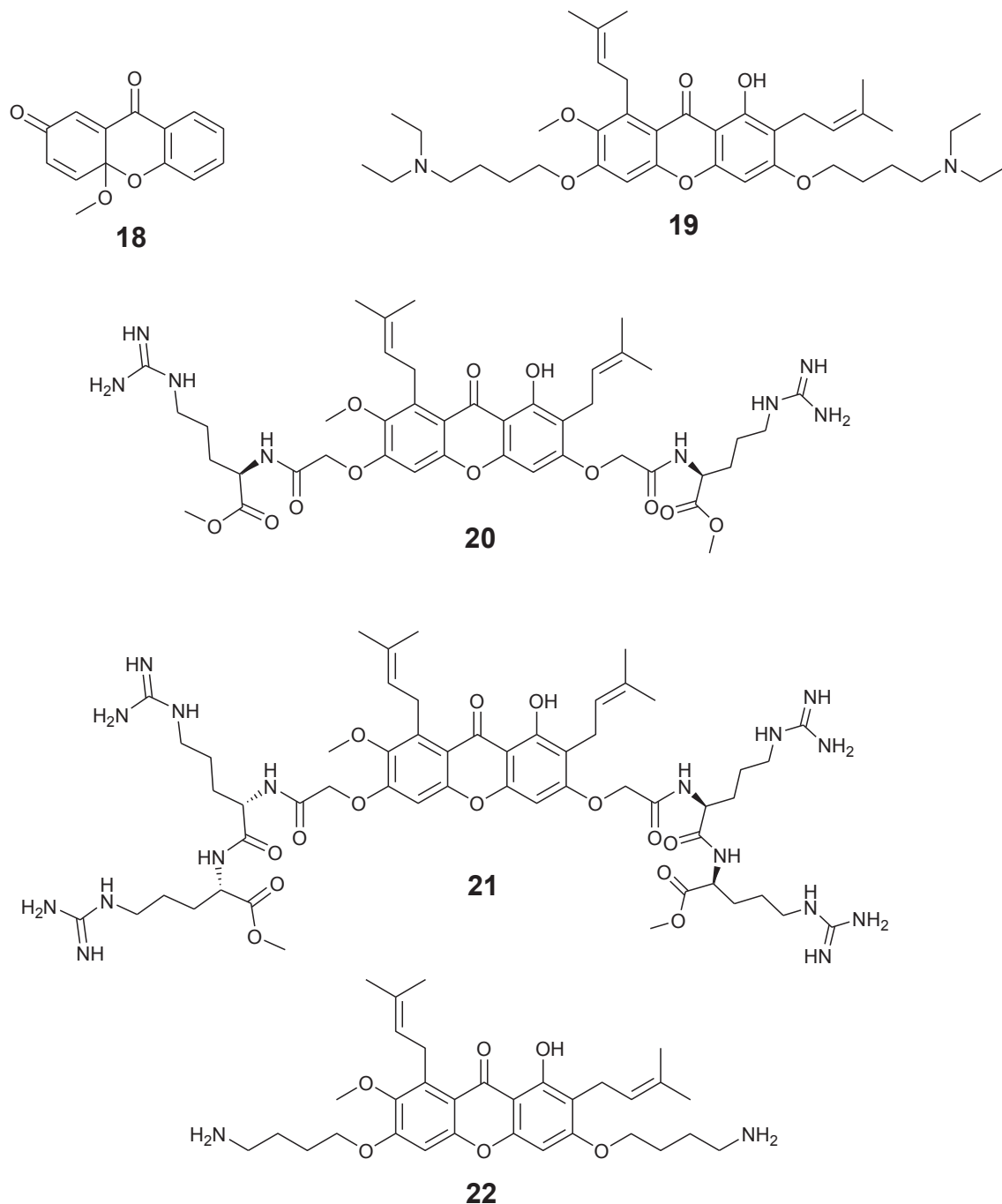


Fig. 3. Xanthone derivatives as antimicrobial agents.

and antitumor activity of a series of novel tetracyclic heterocyclic azathioxanthone analogues. Several compounds of the series exhibited significance cytotoxicity, and among these compounds, compound **16** (Fig. 2) with a piperazinyl group as side chain showed not only outstanding cytotoxic activity but also exhibited the inhibitory effect against topoisomerases and significant increase of apoptotic cells. The result suggested that the terminal NH group plays an important role in cytotoxic activity and topoisomerase inhibition [31].

Human hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide [32]. In view of the previous reports describing the cytotoxicity activity results of naturally occurring xanthone dimers and synthesized biphenyl scaffold with two allyl groups [33,34], Dai et al., in 2013 designed and synthesized a series of phenyl substituted tetramethoxy xanthone derivatives and evaluated their potential cytotoxic activity against HCC cells. The structure activity relationship study of the synthesized series revealed that the electronic effects in the phenyl ring played a vital role in the antiproliferative activity, and the bulky substituent has an unfavorable effect on the inhibition. The 3-phenylxanthone **17** (Fig. 2) with no substituent on the phenyl ring showed the high frequency apoptosis in human HCC QGY-7703 cells and better cytotoxic selectivity for HCC cells [35].

2.2. Antimicrobial activity of xanthenes

Several articles have been published highlighting the antimicrobial activity of xanthone analogues [36–38]. In 2011, Omolo et al. reported the synthesis and antimicrobial activity of xanthenes, xanthenediones, and spirobenzofurans. Xanthenes and related diones displayed promising antimicrobial activity, particularly against the yeasts *Cryptococcus neoformans* and *Candida albicans*; among them, the dione **18** (Fig. 3) was the most potent [39].

The antimicrobial activity and selectivity of α -mangostin, a natural product bearing hydrophobic xanthone scaffold, towards Gram-positive bacteria were improved by the modification of amphiphilic conformation of α -mangostin by Zou et al. in 2013. A series of xanthone derivatives were designed and synthesized by cationic modification of the free C3 and C6 hydroxyl group of α -mangostin with cationic group, i.e., amino groups of different pKa values. The xanthone analogues bearing moieties with high pKa values exhibited excellent antimicrobial properties against Gram positive bacteria, whereas the compounds with low pKa value had reduced antimicrobial activity. The most potent compound of the series was **19** (Fig. 3), which exhibited a four-member carbon chain with diethyl amino groups at C-3 and C-6 positions of xanthone skeleton and kills the bacteria rapidly, and it showed no sign of resistance or cross resistance in laboratory assays [40]. In view of the unsatisfactory toxicity results of the compound, next efforts were made to identify the components that mimic the action of an antimicrobial cationic peptide with the intention to reduce toxicity and improve bacterial membrane selectivity while sustaining the

in vivo antimicrobial activity. On a xanthone template, several effective membrane-targeting small molecules with promising membrane selectivity were designed and synthesized. To explore the effect of isoprenyl groups or lipophilic chains on antimicrobial activity, six compounds with different isoprenyl groups at the C2 and C8 positions on the xanthone core were synthesized. To investigate the role of cationic amino acid residues in antimicrobial activity, several compounds were synthesized by modifying the hydrophobic xanthone core at the C3 and C8 positions with cationic amino acids. Among the series, xanthone derivatives **20** and **21** (Fig. 3) displayed the most promising antimicrobial activity against some of the most serious forms of Gram-positive bacteria, low toxicity, and activity in a mouse model of corneal infection [41]. Later, inspired by the antimicrobial activity of nonpeptidic xanthone **18** and aiming to identify the more potent xanthone derivatives with lower hemolytic activity and greater membrane selectivity, a series of 46 nonpeptidic amphiphilic xanthone derivatives were designed, synthesized, and evaluated for antimicrobial activity and selectivity. The compounds of the series were classified into four groups based on spacer length, cationic moieties, lipophilic chains, and triarm functionalization. The compound **22** (Fig. 3) bearing two primary amine groups was the most potent xanthone derivative with acceptable selectivity and lower hemolytic activity [42].

2.3. Antimalarial activity of xanthenes

Hydroxyxanthenes are considered as novel antimalarial agents with activity against multidrug-resistant *Plasmodium* parasites. These compounds are assumed to exert their activity by complexation to the heme and inhibition of hemozoin formation [43]. In 2002, Kelly et al. synthesized a series of 3,6-bis- ω -diethylaminoalkoxyxanthenes by attaching R-groups bearing 2 to 8 carbon atoms in a chain and protonatable nitrogen atoms to improve their heme affinity through ionic interactions with the propionate side chains of the metalloporphyrin and to enable drug accumulation in the parasite food vacuole. The two compounds **23** and **24** (Fig. 4), having 5 and 6 carbon side chain with diethyl amino group, respectively, at C3 and C6 positions of the xanthone core, showed promising activity with IC₅₀ in the nanomolar range against strains of chloroquine-susceptible and multidrug-resistant *Plasmodium falciparum* *in vitro* [44].

In 2007, Portela et al. reported the synthesis and antimalarial activity of chlorinated 9H-xanthenes bearing a [2-(diethylamino)ethyl]amino group in position 1. All the compounds of the series were active against the strains 3D7 and Dd2 of *P. falciparum*. Their antiplasmodial action is most likely due to the inhibition of hemozoin formation, allowing the development of toxicity to the parasite by free haematin. The most potent compound of the series was 6-chloro-1-[[2-(diethylamino)-ethyl]amino]-9H-xanthen-9-one (**25**) (Fig. 4) with chloro atom and a substituted amino side chain in the same relative positions as those in the potent

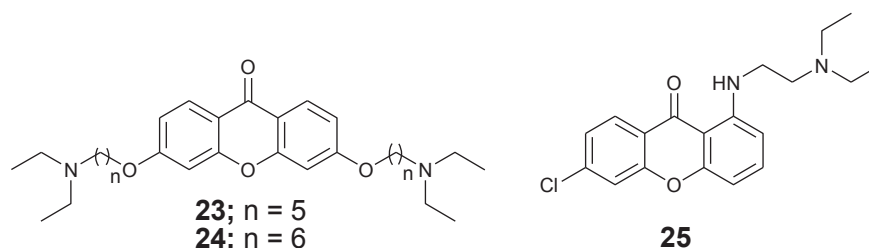


Fig. 4. Xanthone derivatives as antimalarial agents.

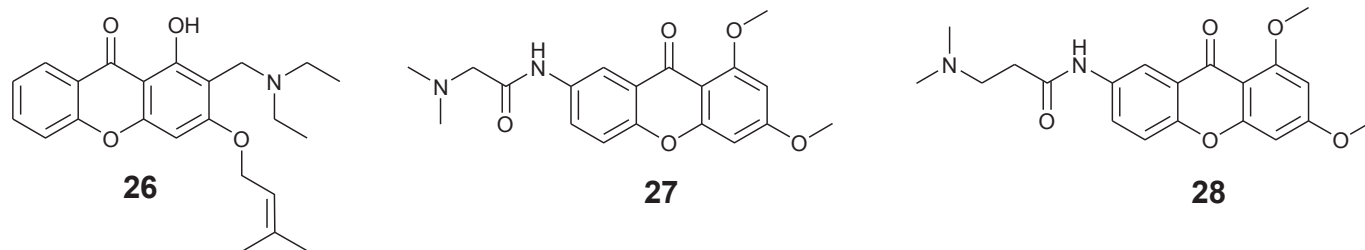


Fig. 5. Xanthone derivatives as anticholinesterase agents.

antimalarial drug chloroquine [45].

2.4. Anticholinesterase activity of xanthenes

One of the severe problems among aged populations all over the world is Alzheimer's disease (AD), which is a progressive and degenerative disorder. The most predominant treatment strategy for AD is the use of cholinesterase inhibitor drugs. The xanthone derivatives' ability to inhibit acetylcholinesterase (AChE) and block the acetylcholinesterase-induced β -amyloid aggregation [46,47] and increased biological potency of Mannich bases [48] motivated Qin et al., in 2013 to design dual inhibitors of two major forms of cholinesterase enzyme, i.e., AChE and butyrylcholinesterase (BuChE), by conjugating xanthone with Mannich bases. A series of Mannich bases of 1,3-dihydroxyxanthone derivatives were synthesized and evaluated for anti-cholinesterase activity on both the enzymes. The results revealed that most of the compounds exhibited moderate to good inhibitory activities with the IC_{50} values at micromolar level concentrations against both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Among the series, the compounds with diethylamine methyl at the end of the side chain in position 2 of xanthone exhibited maximum activity, and the compound 2-((diethylamino)methyl)-1-hydroxy-3-(3-methylbut-2-enyloxy)-9H-xanthen-9-one (**26**) (Fig. 5) showed potent inhibitory activity against AChE and the best inhibitory activity against BuChE [49].

In 2014, Qu et al. identified xanthone compound **27** (Fig. 5) with good AChE inhibitory activity through high-throughput screening. Further, to optimize the inhibitory activity of compound **27** through structure activity relationship analysis, a series of xanthone derivatives were designed, synthesized, and evaluated for AChE inhibitory activity. Several compounds showed promising inhibitory activity to AChE, and the most potent compound among the series was xanthone derivative **28** (Fig. 5), which inhibited AChE in micromolar range and exhibited good AChE/BuChE inhibition selectivity. The computational docking studies of **27** to the active site of AChE suggested that the molecule could fit in the hydrophobic pocket of AChE, and amide bond could generate hydrogen bonding interactions [50].

2.5. Anticonvulsant activity of xanthenes

Anticonvulsants are also known as antiepileptic agents used in the treatment of epileptic seizures. Furthermore, the use of anti-epileptic drugs is also known to have multiple and serious side effects, and for several of them the mechanism of action is not fully understood [51]. Thus, discovery of new compounds with anticonvulsant activity is still very important. In view of the reported anticonvulsant activity of xanthone derivatives, [52] Marona et al., in 2008 designed and synthesized a series of alkanolamine and amide derivatives of xanthenes and evaluated their anticonvulsant activity using maximal electroshock (MES) and subcutaneous pentylenetetrazole (scMet) induced seizures and for neurotoxicity (TOX) using the rotarod test on mice and rats. The aminoalkanol derivatives of 6-chloroxanthone showed promising activity and among which the *R*-(–) and *S*-(+)-2-amino-1-propanol derivatives of 6-chloro-2-methylxanthone (**29**) (Fig. 6) displayed the maximum activity [53].

Next, Szkaradek et al. reported the synthesis and anticonvulsant activity of a series of aminoalkanol derivatives of 6-methoxy- or 7-chloro-2-methylxanthone and 6-methoxy-4-methylxanthone with the intention of exploring the effect of position and type of substituent on anticonvulsant activity. All compounds showed activity in the MES screen, which is recognized as one of the two most widely used seizures models for early identification of candidate anticonvulsants. The 6-methoxy substituted xanthone derivatives bearing 2-aminobutan-1-ol moiety at position 2 (**30**) (Fig. 6), which exhibited promising activity; the *S* isomer of **30** was the most potent comparison to *R* isomer and racemic mixture [54]. Later, to explore the effect of the piperazine moiety with a methylene linker on xanthone skeleton, a series of xanthone derivatives with a piperazine moiety was synthesized and evaluated for anticonvulsant activity. The most promising compound of the series for anticonvulsant activity was 6-methoxy-2-[[4-benzyl]piperazin-1-yl]methyl]-9H-xanthen-9-one (**31**) (Fig. 6), having substitution at C2 and C6 position of xanthone [55].

2.6. Anti-HIV activity of xanthenes

HIV has claimed 34 million lives so far and continues to be a major global public health issue [56]. The drug resistant problem

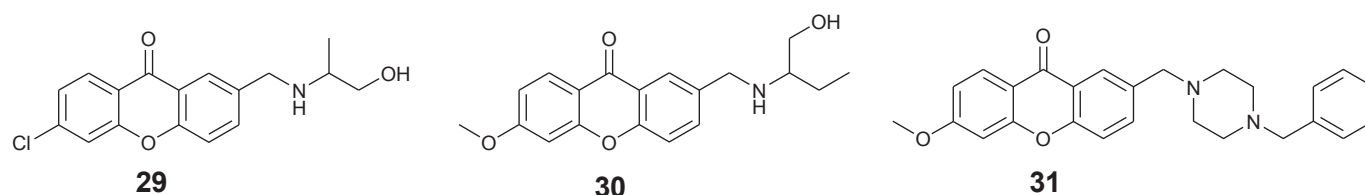


Fig. 6. Xanthone derivatives as anticonvulsant agents.

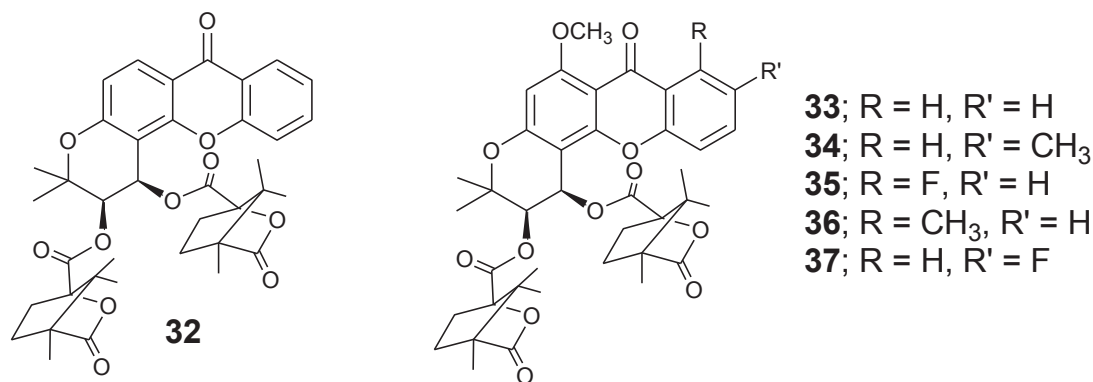


Fig. 7. Xanthone derivatives as anti-HIV agents.

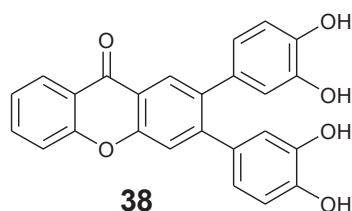


Fig. 8. Xanthone derivative as antioxidant agent.

associated with current anti-HIV agents has dramatically reduced their efficacy and encouraged researchers to discover new anti-HIV agents with higher potency or novel mechanism [57,58]. In 2012, Zhou et al. designed a series of tri-aryl conjugated compounds with xanthen-9-one moiety in order to explore the interaction of a target protein binding pocket with a compound planar ring. Twenty four 1*R*, 2*R*-dicamphanoyl-3,3-dimethyldihydropyrano- [2,3-*c*]xanthen-7(1*H*)-one (DCX) (**32**) derivatives were synthesized and evaluated against both wild type and drug resistant HIV strains. The three DCX compound (**33–35**) (Fig. 7) showed promising activity against both HIV strains with an EC₅₀ of micromolar range. The structure activity relationship studies of the reported compounds revealed that the extended conjugated system of the pyranoxanthone skeleton enables the interaction of small DCX molecules within the viral building pocket, therefore leading to improved anti-HIV activity and selectivity [59].

Further, to identify anti-HIV and chemosensitizing dual function agents, 19 dicamphanoyl-dihydropyranochromone (DCP) and dicamphanoyl-dihydropyranoanthone (DCX) derivatives were evaluated for their activity to reverse multidrug resistance (MDR) in cancer cell lines over-expressing P-glycoprotein (P-gp). Few

compounds fully reversed resistance to vincristine and exhibited a 20-fold enhancement compared to the first generation chemosensitizer, verapamil at micromolar concentration. The DCX derivatives **36** and **37** (Fig. 7) showed promising activities by acting as dual inhibitor of HIV replication and chemoresistance mediated by P-gp and thus considered beneficiary in combination therapy to overcome P-gp-associated drug resistance for AIDS treatment [60].

2.7. Antioxidant activity of xanthenes

Development of effective antioxidants for food, cosmetic, and pharmaceutical purposes is still a challenge. In the last few decades, the active participation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in some physiopathologies and in cellular signaling systems has attracted researchers. Considering the antioxidant activity of xanthone derivatives reported in previous articles [61,62], Santos et al., in 2010 synthesized 2,3-diarylxanthone derivatives and evaluated their scavenging activity for reactive oxygen species (ROS), including superoxide radicle (O₂⁻), hydrogen peroxide (H₂O₂), singlet oxygen (¹O₂), peroxyradical (ROO⁻), and hypochlorous acid (HOCl) as well as reactive nitrogen species (RNS), including nitric oxide (NO) and peroxynitrite anion (ONOO⁻). The 2,3-diarylxanthenes showed promising ROS and RNS scavenging properties with IC₅₀ in the nanomolar to micromolar range. Xanthenes with two catechol rings **38** (Fig. 8) were the most potent scavengers of all tested ROS and RNS [63].

2.8. Anti-inflammatory activity of xanthenes

Based on previous reports exhibiting the anti-inflammatory activity of xanthone derivatives [64], Yen et al., in 2012 designed and synthesized a prenyl and pyrano derivatives structure related to 1,3,6-trihydroxy-9*H*-xanthen-9-one, a basic skeleton of

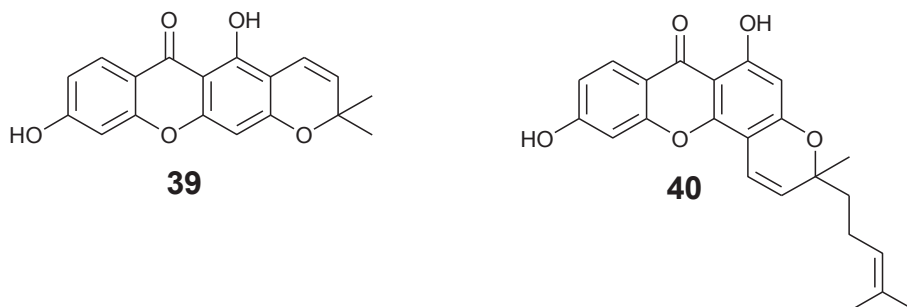


Fig. 9. Xanthone derivatives as anti-inflammatory agents.

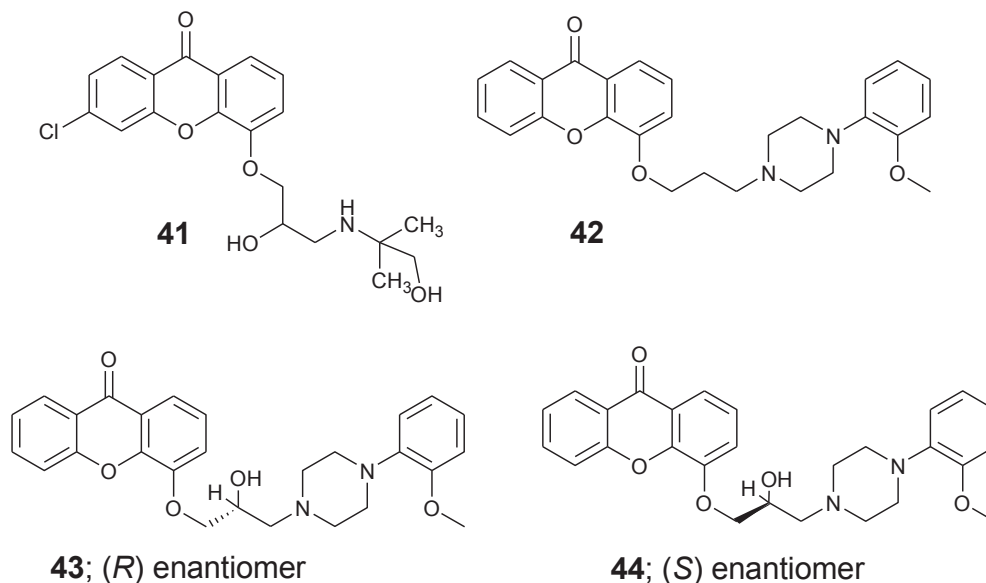


Fig. 10. Xanthone derivatives with cardiovascular activity.

gambogic acid (GA). The series was evaluated for anti-inflammatory activity toward superoxide anion generation and elastase release by human neutrophils in response to fMLP/CB and *in vitro* cytotoxic effect against four human cancer cell lines. A linear 3,3-dimethylpyranoxanthone **39** (Fig. 9) showed substantial potency in both anti-inflammatory assays, and an angular 3-methyl-3-prenylpyranoxanthone **40** (Fig. 9) was most potent in the elastase release assay [65].

2.9. Cardiovascular activity of xanthenes

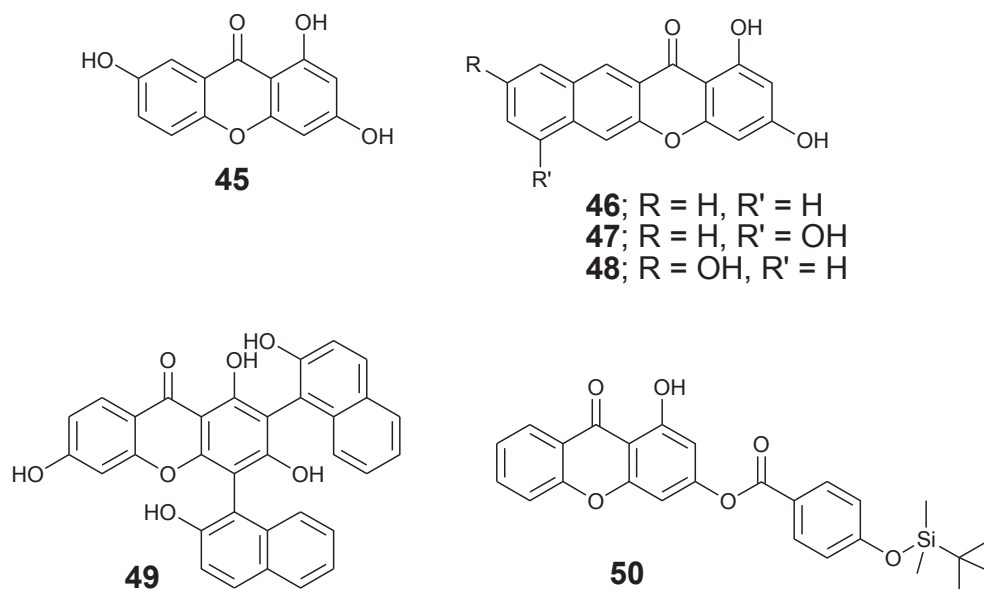
Hypertension and arrhythmia are the main factors responsible for cardiovascular mortality. Undoubtedly, several antiarrhythmic and hypotensive drugs are available in the market, but due to their severe side effects there is still a need for new agents with improved potency and minimal side effects [66]. In 2009, Marona et al. reported the synthesis of a series of xanthone derivatives bearing aminoalcohols side chain and evaluated them for electrocardiographic, antiarrhythmic, hypotensive, anticonvulsant activities, and α_1 - and β_1 -adrenergic binding affinities. Compound **41** (Fig. 10) showed most potent hypotensive activity and antiarrhythmic activity in the adrenaline-induced model of arrhythmia [67].

Furthermore, based on the literature reports approving the significance of xanthone derivatives and piperazine moiety for cardiovascular activity [68,69], Szkaradek et al., in 2013 designed and synthesized a series of nine piperazine derivatives of xanthenes and evaluated their cardiovascular activity. All compounds were *in vitro* screened for their affinity for chosen adrenoreceptors, and then *in vivo* antiarrhythmic and hypotensive activity of the structures were tested. These compounds showed nanomolar affinity for α_1 -adrenoreceptor and promising cardiovascular activity in animal models. The most potent compound of the series was 4-(3-(4-(2-methoxyphenyl)piperazine-1-yl)propoxy)-9H-xanthen-9-one hydrochloride (**42**) (Fig. 10). The pharmacological results and binding studies of these compounds revealed that antiarrhythmic and hypotensive activities were related to adrenolytic properties [70]. Next, 6 new xanthone derivatives were synthesized and screened *in vitro* for their affinity for chosen adrenoreceptors. The series was also tested for *in vivo* antiarrhythmic and hypotensive

activity. Two compounds exhibited nanomolar affinity for α_1 -adrenoreceptor as well as the highest cardiovascular efficacy in the animal models. The most promising compounds were (R)-4-(2-hydroxy-3-(4-(2-methoxyphenyl)piperazine-1-yl)propoxy)-9H-xanthen-9-one hydrochloride (**43**) and (S)-4-(2-hydroxy-3-(4-(2-methoxyphenyl)piperazine-1-yl)propoxy)-9H-xanthen-9-one hydrochloride (**44**) (Fig. 10) [71].

2.10. Xanthenes as α -glucosidase inhibitors

In biological systems, the final step of carbohydrate digestion is catalyzed by enzyme α -glucosidase, and the inhibitors of α -glucosidase have wide applications in medicinal chemistry. These inhibitors have played an important role in explaining the action mechanism of α -glucosidase at molecular levels and in developing chemotherapeutics for clinical use in the treatment of carbohydrate mediated diseases, such as diabetes, cancer, HIV, hepatitis, hyperlipoproteinemia, and obesity [72]. Bearing in mind the α -glucosidase inhibitory activity of xanthone derivatives reported in the literature [73], Yan et al., in 2006 designed novel α -glucosidase inhibitors by using a xanthone scaffold. A series of hydroxylxanthenes and their acetoxy and alkoxy derivatives were synthesized and evaluated for α -glucosidase inhibition activity. These xanthone derivatives inhibited the α -glucosidase *in vitro* with moderate to good activity. Among these, polyhydroxylxanthenes exhibited the highest activities, and compound **45** (Fig. 11) bearing hydroxyl group on C1, C3 and C7 position of xanthone core was the most potent [74]. Next to discover the effect of conjugated π system to the inhibitory activity, a series of xanthone derivatives with extended π -system, that is, benzoxanthenes and their structurally perturbed analogues were synthesized as α -glucosidase inhibitors. The benzoxanthone **46**, **47**, and **48** (Fig. 11) inhibited the *in vitro* α -glucosidase 17–28 fold more strongly than the xanthone derivatives bearing a smaller conjugated π system. Benzoxanthone, bearing angularly fused rings and reduced bezoxanthenes, showed decreased activities, suggesting that the linearly π -conjugated system plays an important role in the α -glucosidase inhibition process. The structure activity relationship study of this series indicated that the π -stacking effect and hydrogen bonding plays a crucial role in inhibiting the α -glucosidase [75]. Furthermore, to provide more insight into the correlation

Fig. 11. Xanthone derivatives as α -glucosidase inhibitors.

between structure and inhibitory activities of xanthenes, multiple linear regression was employed to establish QSAR models for 43 xanthone derivatives. The results revealed that α -glucosidase inhibitory activity of xanthone derivatives can be regulated by H bond forming substituents, π -stacking forming aromatic rings, and softness values on the xanthone skeleton [76].

In 2011, Li et al. reported the α -glucosidase inhibition activity of a series of novel xanthone derivatives having non-coplanar and flexible structures. Compound bearing one or two naphthol moieties exhibited promising activity, and compound **49** (Fig. 11) was

reported as the most potent α -glucosidase inhibitor. Structure activity and relationship studies of the series revealed that α -glucosidase inhibition was due to the multiple interactions with the enzyme, including π -stacking, hydrophobic effect, and conformational flexibility due to the structural non-coplanarity [77]. Next, to explore the inhibitory and binding mechanism of xanthone-based inhibitors towards α -glucosidase, two xanthone derivatives, that is, 1,3,7-trihydroxy xanthone (**45**) (Fig. 11) and 1,3-dihydroxy benzo-xanthone (**46**) (Fig. 11), were selected for various experimental and theoretical studies. The results showed that both the

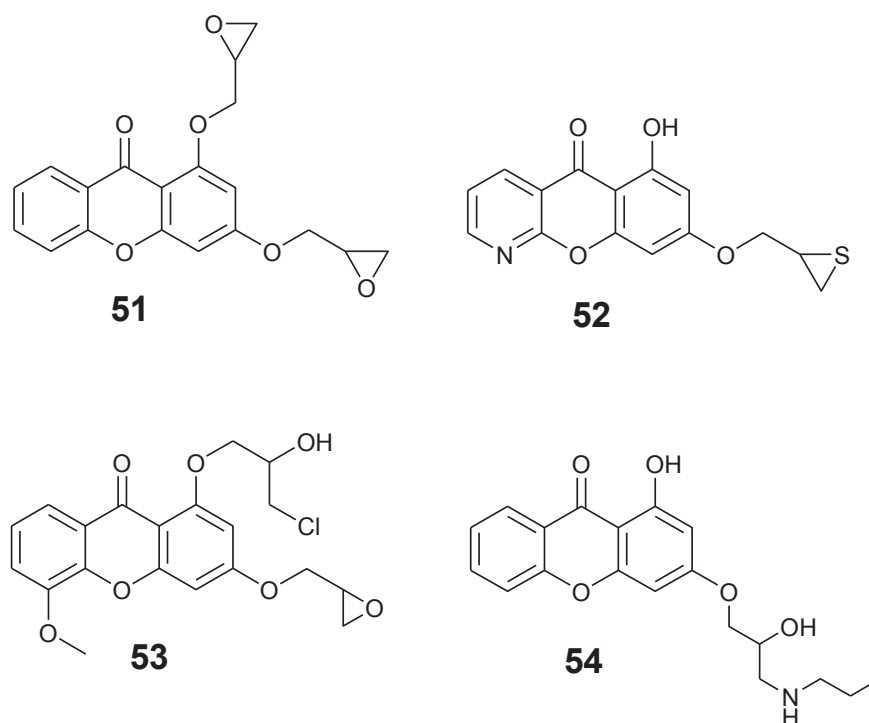


Fig. 12. Xanthone derivatives as topoisomerase inhibitors.

compounds act as non-competitive inhibitors and induce the loss of α -helix in α -glucosidase. Docking studies revealed the significance of polyhydroxy groups and expanded aromatic ring for H-bonding and π - π interactions with α -glucosidase [78]. Later, to study the effect of addition of aromatic moieties at the 3-position of xanthone skeleton on α -glucosidase inhibitory activity, a series of xanthone derivatives bearing different 3-aryloxy groups were synthesized and evaluated for α -glucosidase inhibition activity. The 3-aryloxy derivatives showed promising activity comparison to parent 1,3-dihydroxyxanthone, and among the series compound **50** (Fig. 11) was the most potent. The addition of aromatic moieties at the 3-position of 1,3-dihydroxyxanthone increases the inhibitory activity against α -glucosidase. The structure activity relationship analysis revealed that substituents on the addition aromatic ring influenced the inhibition, and the oxygen and nitrogen containing groups like hydroxyl, methoxy, methaminy, and alkylsilyloxy increased the α -glucosidase inhibitory activities. Docking studies suggested that hydrophobic effects were responsible for the enhanced inhibitory activities of the 3-aryloxy xanthone derivatives [79].

2.11. Xanthenes as topoisomerase inhibitors

Topoisomerase are critical cellular enzymes necessary for cell proliferation by solving topological hurdles in the process of DNA replication and are considered as one of the major targets in anticancer drug development. They are generally classified as type I and type II [80,81]. In 2007, Woo et al. synthesized epoxy group conjugated xanthone analogues and evaluated their topoisomerase II inhibitory activity. Among the tested compounds, the bis oxirane substituted xanthone derivative **51** (Fig. 12) was the most potent [82]. Next, to explore the effect of oxiran or thiiran substituents on the xanthone core, a series of oxiranylmethoxy or thiiranylmethoxy group substituted 5-azaxanthenes and -acridone analogues were designed, synthesized, and tested for their biological activities for cancer cell lines and topoisomerase I and II inhibition. The most potent compound of the series was 3-thiiranylmethoxy-1-hydroxy-5-azaxanthone (**52**) (Fig. 12), which showed substantial topoisomerase I inhibitory activity [83]. To study the effect of the methoxy group in the xanthone core and the methyl group in the oxiranyl part, several methyloxiranylmethoxyxanthone analogues were synthesized and evaluated for cytotoxic and topoisomerase II inhibitory activity. The compounds bearing the halohydrin group at the C3 position and the methoxy group at the C5 position exhibited comparable topoisomerase II inhibitory activities to etoposide at 100 μ M concentration, and the most active compound was **53** (Fig. 12) [84].

In 2011, Jun et al. designed and synthesized eight novel heteroatom nucleophilic epoxide ring-opened xanthone derivatives and evaluated them for topoisomerase I and II inhibitory activity. Compound **54** (Fig. 12) bearing NH in the side chain of the xanthone core was the most efficient topoisomerase II α inhibitors. Structure activity relationship study suggests that inhibitory activity of these

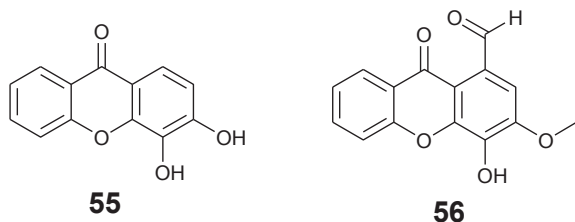


Fig. 13. Xanthone derivatives as protein kinase C inhibitors.

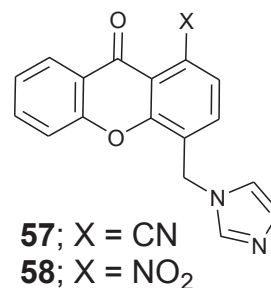


Fig. 14. Xanthone derivatives as aromatase inhibitors.

compounds were dependent upon the nucleophiles substituted in the side chain ($\text{NH} > \text{N} > \text{S} > \text{O}$) and those at the end of the side chain ($\text{CH}_3 > \text{CH}_2\text{OH} > \text{CH}_2\text{Cl}$), whereas the carbon length in the side chain had no significant effect. The hydrogen donor group, i.e., NH, in the side chain plays significant role in the topoisomerase inhibitory II α activity of the xanthone core compound [85].

2.12. Xanthenes as protein kinase C inhibitors

Protein kinase C (PKC) is a family of serine–threonine kinases and plays key roles in cellular functions, such as growth, differentiation, tumor promotion, and apoptosis. The PKC family consists of several isoforms and is grouped into three families: the classical PKCs (cPKCs), novel PKCs (nPKCs), and atypical PKCs (aPKCs), which includes the isoforms α , β I, β II and γ ; δ , ϵ , θ , and η ; and λ and ξ , respectively [86,87]. In view of the PKC inhibitory activity of xanthone derivatives [88,89], Saraiva et al. designed and synthesized a new series of xanthone derivatives bearing mono or dioxygenated groups in one or two aromatic ring of xanthone nucleus and studied their effect on PKC isoforms α , β I (cPKCs), δ and η (nPKCs), and ξ (aPKCs) using phenotypic assay. The compounds of the series exhibited modulatory activity on PKC isoforms, and most of them cause an effect compatible with PKC activation [90]. Next, two xanthone derivatives, that is, 3,4-dihydroxyxanthone (**55**) (Fig. 13) and 1-formyl-4-hydroxy-3-methoxyxanthone (**56**) (Fig. 13), were tested on isoforms of protein kinase C. Both xanthenes caused an effect compatible with PKC inhibitors and presented a difference on their potency towards the individual PKC isoforms tested; therefore, they are considered an important scaffold to develop new isoform selective PKC inhibitors [91].

2.13. Xanthenes as aromatase inhibitors

Aromatase, a cytochrome P450 enzyme complex present in breast tissues, plays a significant role in the biosynthesis of important endogenous estrogens from androgens. The source of estrogen production in breast cancer tissues is intra-tumoral

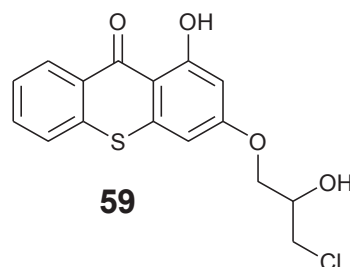


Fig. 15. Xanthone derivative as intestinal P-glycoprotein inhibitor.

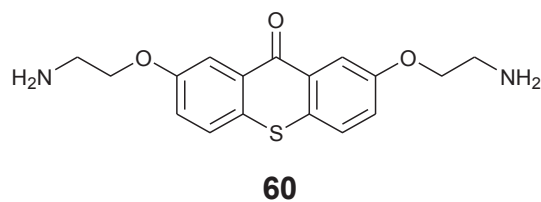


Fig. 16. Thioxanthone derivative as miRNA inhibitor.

aromatase, and inhibition of aromatase may inhibit the growth stimulation effect of estrogens in breast cancer tissues. Consequently, aromatase is considered a useful therapeutic target in the treatment and prevention of estrogen-dependent breast cancer [92]. Recanatini et al. reported a new series of nonsteroidal AIs with xanthone nuclei bearing H-bond accepting function and heterocyclic ring linked by methylene unit to the aromatic ring. The most interesting AIs of the series were **57** and **58** (Fig. 14), which showed good aromatase inhibitory activity [93].

2.14. Xanthenes as intestinal P-glycoprotein inhibitors

Intestinal P-glycoprotein (P-gp) is an efflux transporter that belongs to the superfamily of ATP-binding cassette transporters. P-gp-mediated drug efflux is suggested to be important in expressing multidrug resistance (MDR) in various cancers [94]. P-gp substrate includes anticancer drugs, antibiotics, immunosuppressant, HIV protease inhibitors, and calcium channel blockers and P-gp function modulators [95]. To study the P-gp modulating function of xanthone analogues, Chae et al., in 2015 synthesized xanthone and thioxanthone analogues and evaluated *in vitro* and *in vivo* P-gp inhibitory activity. The 3-(3-chloro-2-hydroxypropoxy)-1-hydroxy-9H-thioxanthen-9-one (**59**) (Fig. 15) exhibited promising intestinal

P-gp inhibition activity via increasing the cellular accumulation and efflux of daunomycin (DNM) and the oral exposure of paclitaxel (PTX) [96].

2.15. Xanthenes as miRNA inhibitors

A micro RNA is a small non-coding RNA molecule that is involved in many biological processes such as development, differentiation, and carcinogenesis through translation repression by binding to a target mRNA [97–99]. The compounds that modulate the miRNA pathway can be used as a biological tool to explain the mechanisms of miRNA-mediated gene regulation and as a drug lead for miRNA related diseases. Considering the previous studies highlighting the significance of xanthone and thioxanthone derivatives as the fluorescent indicators for detecting the interactions between RNA and small molecules [100], Murata et al., in 2013 synthesized a series of aminoalkoxy-substituted thioxanthone derivatives and studied their inhibitory activity against the dicing reaction upon their binding to pre-miRNA. Among the series, the most potent inhibitor for dicing reaction of pre-miR-29a processing was compound **60** (Fig. 16) [101].

2.16. Xanthenes as acyl-CoA:cholesterol acyltransferase inhibitors

The absence of acyl-CoA:cholesterol acyltransferase (ACAT) affects the absorption and transformation of cholesterol, indirectly resulting in the reduction of cholesteryl ester accumulation in blood vessels. Thus, acyl-CoA:cholesterol acyltransferase are considered to be useful anti-atherogenic agents [102]. During the high-throughput screening of synthesized xanthone analogues, Hu et al. identified a xanthone sulfonamide **61** (Fig. 17) with ACAT inhibitory activity. To optimize the inhibitory effect of this compound through its structure activity relationship, a series of

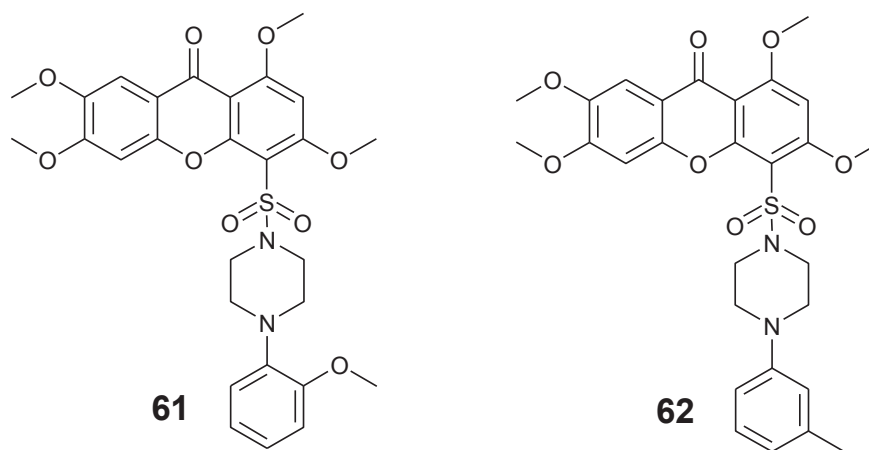


Fig. 17. Xanthone derivatives as acyl-CoA: cholesterol acyltransferase inhibitors.

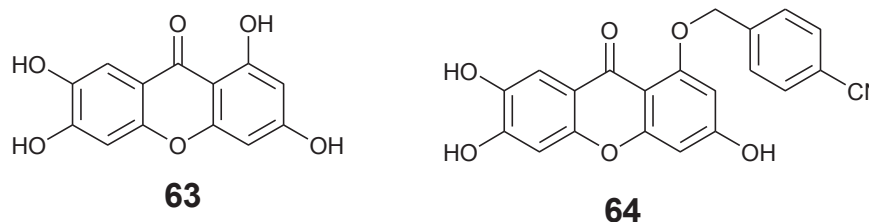


Fig. 18. Xanthone derivatives as xanthine oxidase inhibitors.

xanthone sulfonamides were synthesized and evaluated for ACAT inhibition activity. Among the series, several xanthone derivatives were potent ACAT inhibitors, and compound **62** (Fig. 17) was the most potent; also, docking studies suggested that it could fit into the hydrophobic pocket of ACAT-2 [103].

2.17. Xanthenes as xanthine oxidase inhibitors

Xanthine oxidase is an enzyme that generates reactive oxygen species and catalyzes the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. Xanthine oxidase inhibitor reduces the production of uric acid by inhibiting the xanthine oxidase and thus can be used for the treatment of hyperuricemia and related medical conditions including gout [104]. Hu et al. identified the xanthone analogue **63** (Fig. 18), having four hydroxy groups, with good inhibitory activity against xanthine oxidase but with very poor solubility in most solvents. To explore the new xanthone derivatives with better physicochemical properties, a series of compounds by simple chemical modification of parent compound (**63**) were synthesized and evaluated for xanthine oxidase inhibitor activity. Compounds bearing methyl, chloro, or cyano groups at *ortho/para* position of benzyl moiety, which is present at C-1 position of xanthone nucleus, showed good inhibition against xanthine oxidase. The most potent compound of the series was **64** (Fig. 18), having the cyano group at the para position of benzyl moiety [105].

3. Conclusion

From the above discussion, it is clearly evident that xanthenes possess diversified biological activities and have immense potentiality in the field of medicinal chemistry. In modern drug discovery xanthenes are important pharmacophore and several research laboratories worldwide are focusing on the synthesis of different xanthone derivatives for the development of novel and more potent drugs. This review article is focused on the pharmacological activities of synthetic xanthone derivatives for various therapeutic targets reported recently. The present survey indicates that xanthenes have been targeted for their anticancer, antimicrobial, antimalarial, anticholinesterase, anti-HIV, anti-inflammatory, anticonvulsant, antioxidant and cardiovascular properties. Furthermore, their potential as inhibitors of enzymes such as α -glucosidase, topoisomerase, protein kinase C, aromatase, intestinal P-glycoprotein, miRNA, acyl-CoA: cholesterol acyltransferase, xanthine oxidase have also been investigated. There is much scope in this promising xanthone moiety for other therapeutic targets, future investigations of this scaffold could give some more encouraging results in the field of medicinal chemistry. It is anticipated that the information compiled in this review article not only update researchers with the recent reported biological activities of synthetic xanthone derivatives, but also motivate them to design and synthesize promising xanthenes with improved medicinal properties.

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