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Review article

Research progress in the biological activities of 3,4,5-trimethoxycinnamic acid (TMCA) derivatives

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ABSTRACT

TMCA (3,4,5-trimethoxycinnamic acid) ester and amide are privileged structural scaffolds in drug discovery which are widely distributed in natural products and consequently produced diverse therapeutically relevant pharmacological functions. Owing to the potential of **TMCA** ester and amide analogues as therapeutic agents, researches on chemical syntheses and modifications have been carried out to drug-like candidates with broad range of medicinal properties such as antitumor, antiviral, CNS (central nervous system) agents, antimicrobial, anti-inflammatory and hematologic agents for a long time. At the same time, SAR (structure-activity relationship) studies have draw greater attention among medicinal chemists, and many of the lead compounds were derived for various disease targets. However, there is an urgent need for the medicinal chemists to further exploit the precursor in developing chemical entities with promising bioactivity and druggability. This review concisely summarizes the synthesis and biological activity for **TMCA** ester and amide analogues. It also comprehensively reveals the relationship of significant biological activities along with SAR studies.

Contents

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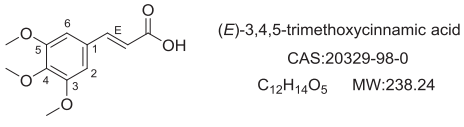
1. Introduction

TMCA is a cinnamic acid substituted by multi-methoxy groups (Fig. 1). It is considered as an active metabolite of the root of *Polygala tenuifolia* Wild. (Polygalaceae), which have been used as traditional medicine in China for treating insomnia, headache and epilepsy [1,2]. **TMCA** has been reported to show anticonvulsant and sedative activity in former studies, and mechanism research reveal that it act as a GABAA/BZ receptor agonist for anti-seizure and insomnia therapy [3,4]. The appealing structural scaffold and pharmacological importance of **TMCA** has encouraged researches to synthesize its drivatives as novel drug candidates. Up to now, **TMCA** derivatives have attracted great attention and interest from researchers in the field of medicinal chemistry [5].

TMCA acts as a precursor to construct a large number of structural frameworks for diverse applications. The carboxyl group of **TMCA** is the most frequently concerned group for modification. Additionally, ester and amide derivatives are the most important analogues to report in this review. The substitution point at C=C bond and methoxy groups are also briefly mentioned in this article [6–9]. The modifications in these frameworks lead to the broadening of activity continuum of **TMCA** analogues [10,11].

As for the pharmacology researches, this review is focus on the properties of **TMCA** esters and amides as antitumor, antiviral, CNS agnets, antimicrobial, anti-inflammatory and hematologic agents. We summarized advances in natural products of **TMCA** analogues (**N1-9**) and synthetic derivatives (**S1-74**). As for the synthetic derivatives, both the investigations that **TMCA** as core nucleus or as active substituent are reviewed. When using **TMCA** as substituent, the analogues are compared to the most potent compound according to SAR. For these points of view, this review is dedicated to accomplish an urgent need of compilation and summarization of natural products, biological activities and SAR that could be helpful for researchers to design some new potentially active of **TMCA** analogues.

With the development of society, health problems arouse more and more attention worldwide. Side effects and multidrug-resistant exist in clinical utilizations of modern drugs have forced researchers to set their sights to natural products to seek precursors with more safety and efficiency. TCM (Traditional Chinese Medicine), a cluster of time-honored herb medicine, has attracted much attention in developing new drugs. Our research group has made unremitting effort to seek promising lead compounds from TCM, not only **TMCA** from *P. tenuifolia*, but also α-asarone from *Acorus gramineus*, salvianic acid A from *Salvia miltiorrhiza* and vanillyl alcohol from *Gastrodia elata* have been absorbed into the investigation [12,13]. Combination of Traditional Chinese Medicine Chemistry, CTCMC, is our main drug design strategy (Fig. 2), which means to integrate active constituents based on TCM theory. Accordint to the strategy CTCMC, we have developed potential lead compounds including DBZ (tanshinol borneol ester) [14,15], 2-hydroxypyrrolobenzodiazepine-5,11-dione analogues [16] and **TMCA-**α-asaronol ester [17,18]. We believe that this strategy is benefit to the innovation of new drugs from natural products. Moreover, we consider that this strategy can be helpful to decrease the costs during screening the test compounds and the blindness existing in the structural modification of natural products.



(*E*)-3,4,5-trimethoxycinnamic acid
CAS:20329-98-0
$C_{12}H_{14}O_5$ MW:238.24

Fig. 1. Structure of 3,4,5-trimethoxycinnamic acid (**TMCA**).

2. Biological activities of natural TMCA ester and amide derivatives

2.1. TMCA esters and amide isolated from natural products

TMCA esters are widely distributed in several types of medicinal plants. The genus *Polygala*, containing spiecs *P. tenuifolia*, is the richest resource for **TMCA** esters [19]. Additionally, **TMCA** esters also exist in the genus *Erythroxylum* [20] and *Rauwolfia* [21].

3,6′-disinapoyl sucrose (**N1**), an active oligosaccharide acyl component obtained from the roots of *P. tenuifolia*., is recorded as the standards for quality control of *P. tenuifolia* using the HPLC (high performance liquid chromatography) determination method according to the 2015 edition of Chinese pharmacopoeia (Fig. 3) [22]. **TMCA** has been demonstrated to be the metabolite of **N1** [23]. The latter showed antidepressant activity mediating *via* the inhibiting of MAO (monoamine oxidase)-A and MAO-B activity, reducing plasma cortisol and MDA levels, increasing SOD (superoxide dismutase) activity [24]. Tenuifoliside A (**N2**), another active **TMCA** ester isolated from *P. tenuifolia*, possessed antidepressant-like, cognitive enhancement and cerebral protective effects [25,26]. In addition, **N2** was proved to promote the viability of rat glioma cells C6 through BDNF (brain derived neurotrophic factor)/TrkB-ERK (extracellular signal-regulated kinase)/PI3KCREB signaling pathway [27].

Bioactivity-guided fractionation of root extract of *P. tenuifolia* yielded some constituents with soluble epoxide hydrolase inhibitory activity (Table 1.), including esters **N2**, **N3**, **N4** and **N5** [28]. Thereinto, ester **N5** displayed the most potent inhibition of soluble epoxide hydrolase with the IC_{50} (half maximal inhibitory concentration) value of 6.4 μM. Ester **N2**, which was structurally similar to ester **N5**, performed best interaction between the soluble epoxide hydrolase in molecular docking (RCSB Protein Data Bank ID: 3ANS).

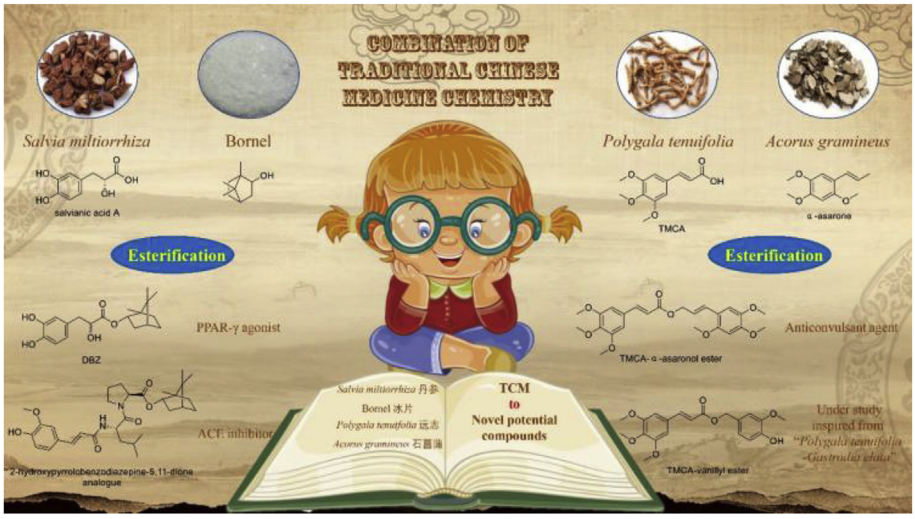


Fig. 2. Drug design strategy: based on Combination of Traditional Chinese Medicine Chemistry (CTCMC).

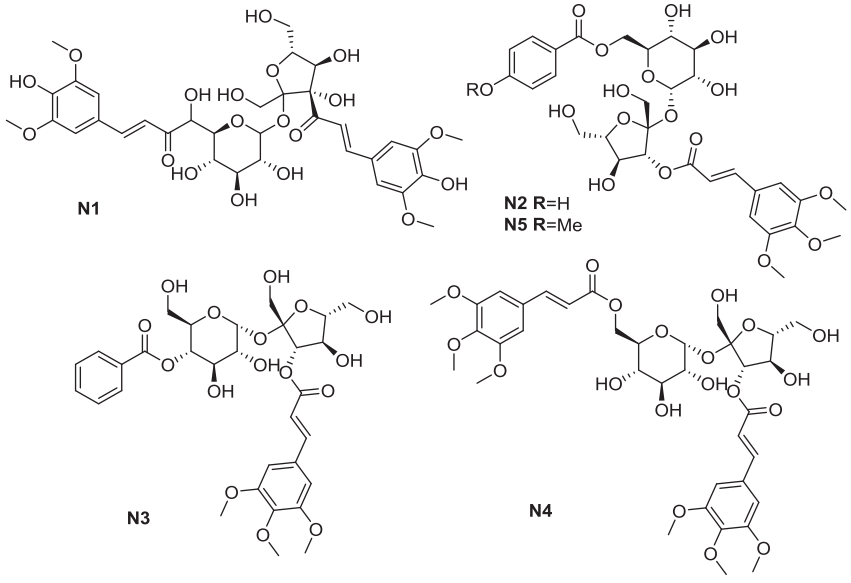


Fig. 3. TMCA esters isolated from *P. tenuifolia*.

Table 1
Inhibitory activity of soluble epoxide hydrolase and interaction for ester **N2**, **N3**, **N4** and **N5**.

Com.	Inhibitory activity			Interaction and Autodock score	
	100 μM (%)	IC_{50} (μM)	Type	Hydrogen bonds (Å)	Binding energy[b]
N2	>100	9.1	a	Tyr343(2.68), Gln384(2.79), Asn378(2.62), Met503(3.22)	−7.36
N3	>100	18.0	a	Thr360(2.71), Gln384(3.06)	−6.79
N4	97.4	27.2	a	Gln384(2.91)	−8.27
N5	>100	6.4	a	Asp335(3.30), Gln384(3.14)	−7.87
AUDA[c]		4.4			

a: competitive; b: kcal/mol; c: positive control.

As for the SAR, research results demonstrated that the substituted benzoic acid esterification on the pyranose was helpful for the compounds to interact with active site of soluble epoxide hydrolase.

In 2013, Zhao et al. [29] presented that one of the major metabolite of *P. tenuifolia* in rat, 3,4,5-trimethoxycinnamate (**N6**), at the dosage of 15–30 μM markedly shortened APD50 (action potential duration at 50% repolarization) and APD90 (action potential duration at 90% repolarization) in cardiomyocytes in a concentration-dependent and a reversible manner (Fig. 4). Moreover, ester **N6** suppressed L-type calcium current, but showed effect on neither I_{to} (transient outward potassium current) nor $I_{K,SS}$ (steady-state potassium current). Furthermore, **N6** abolished isoprenaline and BayK8644-induced EADs (early afterdepolarizations), suppressed

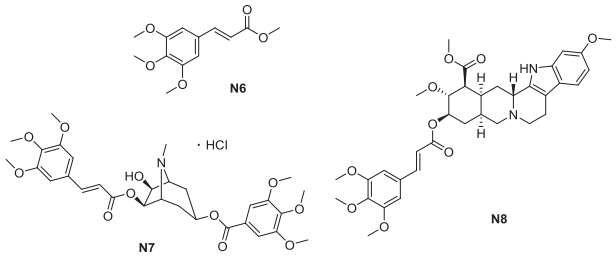


Fig. 4. TMCA esters isolated from other natural products.

DADs (delayedafterdepolarizations) and Tas (triggered activities). The phenomenon revealed that **N6** protected heart from arrhythmias *via* its inhibitory effect on calcium channel. Ester **N6** was also described to probe the active site of esterase named FAE-III, with the Km (substrate concentration at which the reaction rate is half of V_{max}) value of 1.63, and Kcat (limiting rate of any enzyme-catalyzed reaction at saturation) value of 1063 [30].

Pervilleine A (**N7**) was isolated and characterized from *Erythroxylum pervillei* (Fig. 4) [20]. Cholinergic and adrenergic effects of **N7** were investigated. Ester **N7** (30 μM) non-competitively inhibited cholinergic response in the guinea-pig ileum and did not affect the carbachol-induced contraction of the rat anococcygeus smooth muscle. Further research indicated that **N7** exhibited weak vascular antiadrenergic and nonspecific anticholinergic effects. Subsequently, compounds structurally similar to **N7** were obtained from *Erythroxylum pervillei*. The cytotoxicity of isolated components as MDR (multi-drug resistant) inhibitors were speculated according to the SAR as well, suggesting that **TMCA** group at C-6 was necessary for cytotoxicity [31].

Rescinnamine (**N8**) isolated from *Rauvolfia*, known as moderil or anaprel, was considered as an angiotensin-converting enzyme inhibitor used as an antihypertensive drug clinically (Fig. 4) [21]. This ester exhibited significant inhibition against SARS (severe acute respiratory syndrome) as well. The minimal concentration of inhibition toward SARS-CoV (SARS coronavirus) was approached to be 10 μM [32]. As the analogue of reserpine, ester **N8,** which beared a substituted cinnamate in place of a substituted benzoate, was reported to modulate MDR [33]. Ester **N8** enhanced the cytotoxic activity of natural product antitumor drugs in CEM/VLB_{100} cells on different dosages. Structure-function relationship revealed that compounds that retained the pendant benzoyl function in an appropriate spatial orientation all modulated MDR.

2.2. TMCA amides isolated from natural products

Piplartine (**N9**), also known as piperlongumine, is the most frequently reported **TMCA** amide isolated from *Piper* plants (Fig. 5). Piplartine has shown effective against various ailments including cancer, neurogenerative disease, arthritis, melanogenesis, lupus nephritis, and hyperlipidemic [34]. Several related molecular targets have been disclosed such as NF-κB (nuclear transcription factor-κB), MAPK (mitogen-activated protein kinase), IL-6 (interleukin-6), JAK (janus kinase) etc.

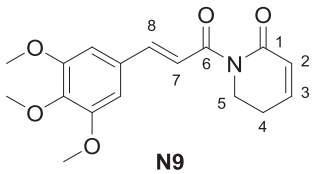


Fig. 5. Structure of piplartine.

3. Bioactivities of synthetic TMCA ester and amide derivatives

The structure of **TMCA** could be prepared by several kinds of reactions for the synthesis cinnamic acid including Perkin and Knoevenagel reaction. For the synthesis of **TMCA** ester and amide derivatives, coupling reactions were utilized widely. Catalysts including DCC (dicyclohexylcarbodiimide)/DMAP (4-dimethylaminopyridine), DMAP/EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) were commonly chosen. Sometimes **TMCA** was converted into cinnamoyl chloride to increase the activity of reaction.

To date, numerous **TMCA** ester and amide analogues have been synthesized and evaluated the bioacitivities. The largely unexplored derivatives possess a variety of pharmacological activities, ranging from antitumor, antiviral, CNS agnets, antimicrobial, anti-inflammatory and hematologic agents. Next, these derivatives were discussed one by one in the following paragraphs.

3.1. Antitumor activity of synthetic TMCA derivatives

Nowadays, cancer is one of the leading causes of death and unremitting efforts being made by researches to develop antitumor agents with more efficiency and safety [35]. So far, various **TMCA** ester and amide derivatives with antitumor effect have been reported. We summarized the progress of these active compounds as follow.

3.1.1. Synthetic TMCA esters as antitumor agents

The antitumor evaluation of a series of olive secoiridoids derivatives was carried out by Busnena and coworkers [36]. **TMCA** was introduced to give esterification product with tyrosol, which was the e major olive phenolic in olive oil. The result of *in vitro* activity demonstrated that ester **S1** (Fig. 6) showed moderate antitumor activity against the MDA-MB231 human breast cancer cells (IC_{50}: 46.7 μM) with the c-MET (tyrosine-protein kinase Met) inhibition as the possible mechanism. The SAR studies indicatited that function groups positioned with more hydrogen bond donor binding role of the hydroxyl groups were more conducive to the inhibitory activity compared with 3,4,5-trimethoxyl group on aromatic ring.

MDR is a major obstacle to successful cancer chemotherapy. Ester **S2**, inspired by the lead compound quercetin, processed antitumor activity against MDR by modulating activity of P-gp (P-glycoprotein 1) (Fig. 6) [37]. At 1.0 μM, ester **S2** showed high P-gp and BCRP- modulating activities. When ester **S2** was used along to evaluate the cytotoxicity for the mentioned cell lines, no significant cytotoxicity was observed ($IC_{50} > 100$ μM). According to SAR investigation, **TMCA** moiety showed stronger P-gp-modulating and BCRP- modulating activities than subtittued benzoic acid esters, suggesting that the extra C=C bond on cinnamic acid group was important for the activity.

Ester **S3** was also explored as MDR modulator. A series of analogues were synthesized and split as *cis-trans* isomer (Fig. 6) [38]. Among them, the ester **S3** with the configuration for *trans/cis* displayed most potent MDR modulating activity, with the $[I]_{0.5}$ value of 0.01 μM.

Ester **S4**, which was a ester derivative of methylated epigallocatechin, possessed most promising P-gp inhibition among the synthetic methylated epigallocatechin analogues (Fig. 6) [39]. Noncytotoxic ester **S4** reversed drug resistance of P-gptransfected breast cancer cell line LCC6MDR (EC_{50}: 123–195 nM). Futher study demonstrated that ester **S4** inhibited the active drug efflux of P-gp transporter. The SAR investigation revealed that the derivatives substituted with **TMCA** group exhibited favourable activity in both *cis*-methylated epigallocatechin derivatives and *trans*-methylated

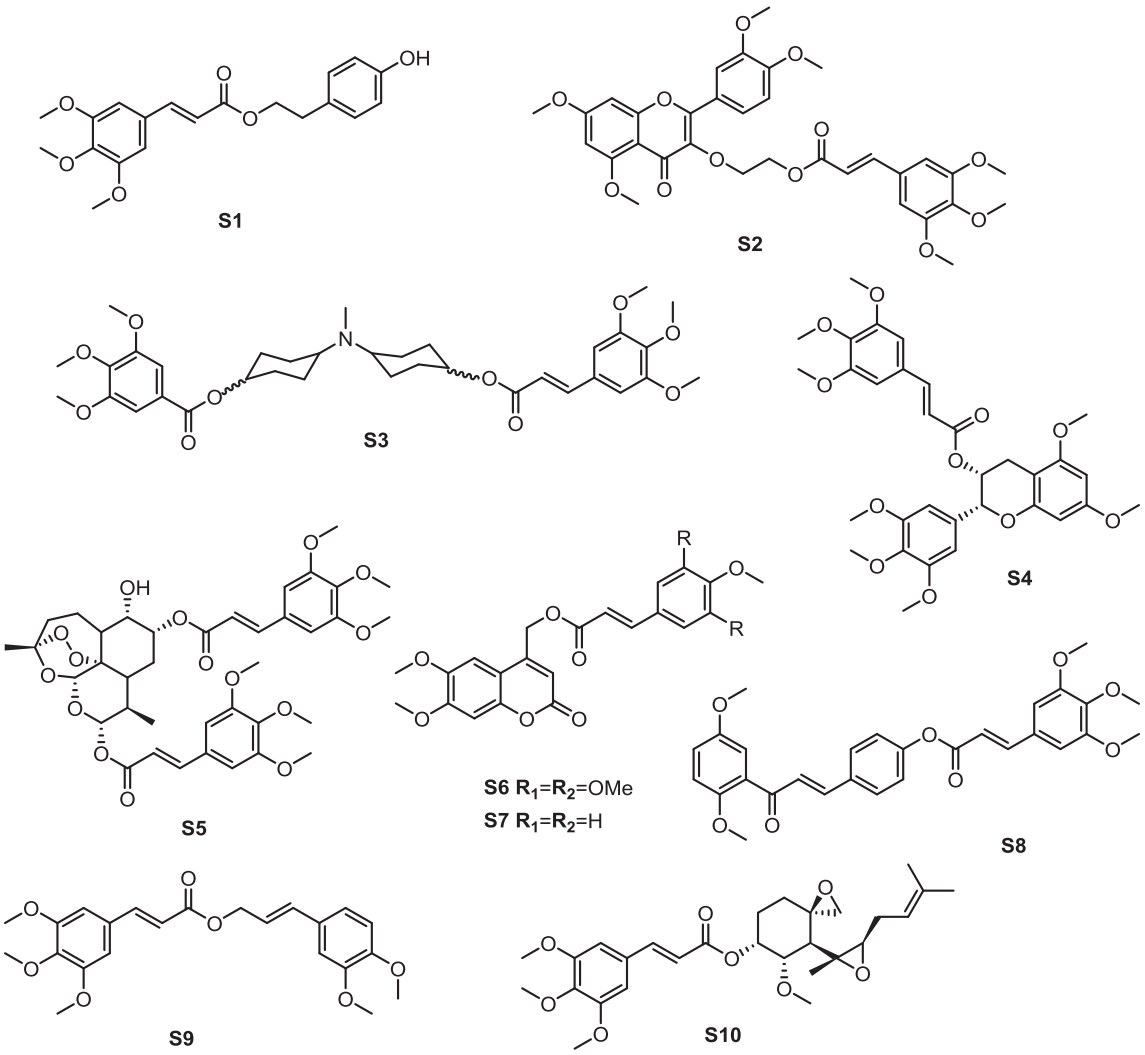


Fig. 6. Structure of synthetic **TMCA** ester derivatives as antitumor agents (**S1**-**S10**).

gallocatechin derivatives, suggesting the potential of **TMCA** group promitting the activity of lead compounds.

The structure of **TMCA** ester was widely used for the modify of natural products. Ester **S5**, which was the structure of dihydroartemisinin esterified with **TMCA**, exhibited significant antitumor activity (Fig. 6) [40], with The IC_{50} values of ester **S5** against cell lines: PC-3, SGC-7901, A549 and MDA-MB-435s were 17.22, 11.82, 0.50 and 5.33 μM, respectively. The cytotoxicities of ester **S5** on normal hepatic L-02 cells was weak (IC_{50}: 58.65 μM). Meanwhile, the SI (selective index) (IC_{50} normal/IC_{50} cancer) value was 117.30. As for the SAR, on the one hand, multi-methoxyl group substituted cinnamic acid esters performed better than other substituted cinnamic acid esters. On the other hand, diester derivatives exhibited stronger inhibitory activity than compounds with bare hydroxy on the C-9 of dihydroartemisinin in general according to the pharmacological results.

Nam et al. [41] executed the esterification of 4-senecioyloxymethyl-6, 7-dimethoxycoumarin, which was a metabolite of the plant plant *Crinum latifolium*. Ester **S6** showed moderate cytotoxicity on B16 and HCT116 cell lines with the IC_{50} values of 6.74 and 8.31 μg/mL (Fig. 6) [30]. The most promising ester was the 4-methoxycinnamoyl substituted derivative **S7**, which was structurally similar to ester **S6**.

Based on the structure of the precursor 2′,5′-dimethoxychalcone, a series of ester derivatives were synthesized [42]. Among them, ester **S8** possessed broad spectrum antitumor activity in different cell lines (Fig. 6). When ester **S8** was added in cell lines including A549, Hep 3B, HT-29 and MCF-7, the IC_{50} values were 36.7, 23.2, 23.8 and 6.4 μM, respectively. Further research suggested that this cluster of esters could mediate cancer cell apoptosis *via* G2/M arrest.

Ester **S9** was designed based on a cytotoxic natural ester isolated from *Piper sintenense* (Fig. 6) [43]. In several cell models including PC-3, Hela, A549 and BEL7404, ester **S9** possessed cytotoxicity with the IC_{50} values of 80, 64, 172 and 212 μM, respectively.

Han et al. [44] synthesized fumagillin analogues according to molecular modeling with MetAP2 (human methionine aminopeptidase-2). Among them, ester **S10** exhibited the strongest antitumor activity in EL-4 and CPAE cells, with the IC_{50} values of 0.15 and 0.03 μg/mL (Fig. 6), respectively. Ester **S10** interacted well with MetAP2 according to the docking study. In subsequent study, ester **S10** was demonstrated to inhibit MetAP2 significantly with the IC_{50} value of 0.96 nM [45]. The SAR of the synthetic fumagillin analogues could be summarized as that the aromatic ring of the derivatives should be positioned to contact with the Leu447 of human MetAP-2 for maximizing hydrophobic interaction, and the activity of *cis*-cinnamic acid ester derivative was much less than *trans*-cinnamic acid ester derivatives.

3.1.2. Synthetic TMCA amides as antitumor agents

Piplartine was modified on heterocyclic ring *via* Baylis-Hillman reaction. The derivatives were determined anticancer activity [46]. In HeLa and IMR-32 cells, amides **S11**–**13** were demonstrated to enforced cell cycle inhibition arresting cells in G2-M phase of the cell cycle (Fig. 7). The enhanced ERK1/2, MAPK activation was significant when the potent compounds were used along or combined with chemotherapeutic drugs. In the combination treatment with colcemid and hydroxyurea, the enhanced elongation and inhibition of cell adhesion in both the cells were observed.

Multiple piplartine analogues with alkyl or halogen substituents at C-7 and morpholine substituents at C-2 were prepared by Wu et al. [7]. All the compounds showed modest selectivity for WI38 human fetal lung normal cells and MRC-5 human lung normal cells. Among the synthetic compounds, amide **S14** (Fig. 7) displayed most potent inhibitory against four cancer cells *in vitro* (Table 2). Subsequently, amide **S14** exerted significant antitumor potency in ROS (reactive oxygen species) elevation and excellent. SAR suggested that 2-Halo-7-alkylpiperlongumines retained *in vitro* anticancer activity, while analogue with morpholine substituents at position 7 of piplartine exhibited diminished cytotoxicity.

Table 2
Antitumor activity of **S14** *in vitro*.

Amides	IC_{50} (μM)				
	A549	HCT116	MDA-MB-231	Hep3B	WI38
S14	3.94	9.85	6.07	16.69	19.60
Piplartine	5.90	21.80	19.53	69.46	26.78

Based on the structure of piplartine and cenocladamide, a series of analogues were synthesized by Santos et al. [47]. Amide **S15** was identified as the most promising compound against MDA-MB-231 cells (IC_{50}: 6.6 μM) (Fig. 7). Additionally, amide **S15** also induced apoptosis on several tested cell lines (efficacy: 15%–80% of apoptosis), which was superior to the positive control doxorubicin. The proliferating inhibition also showed selectivity, because amide **S15** was proved to be unconspicuous cytotoxicity to the non-tumorigenic cells including iHMEC and MCF10A.

Zeng et al. [48] synthesized multiple N, N-disubstituted thiourea analogues as the inhibitors of HSP70 (heat shock protein 70). Amides **S16** and **S17** (Fig. 7), which were the molecules contained **TMCA** amide group, exhibited favourable inhibition against HSP70

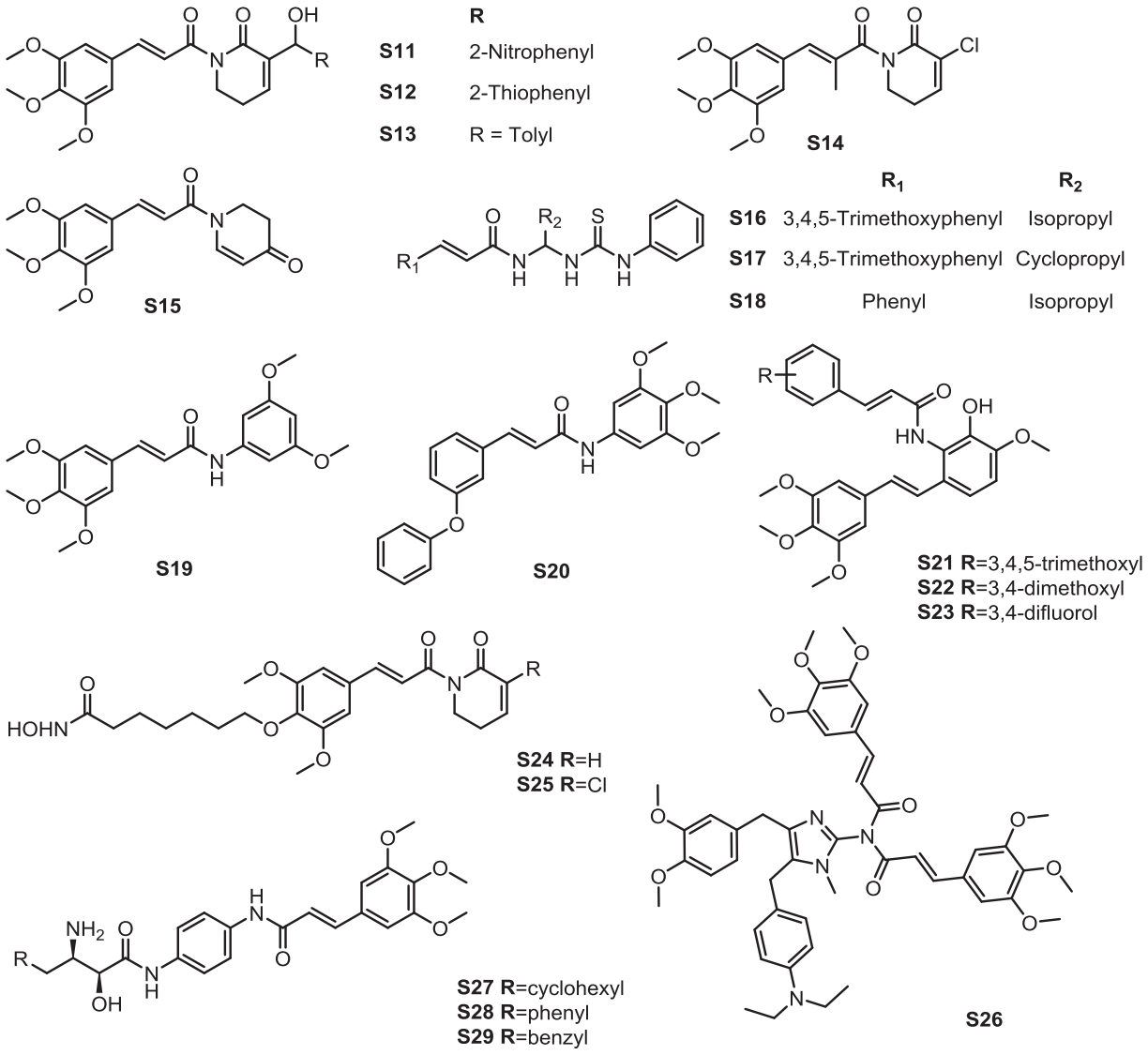


Fig. 7. Structure of synthetic **TMCA** amide derivatives as antitumor agents (**S11**-**S29**).

with the ratio of 50.42% and 50.45% in 200 μM. Amide **S18** was the most potent compound with the percentages of inhibition of 65.36. Furthermore, amide **S18** induced M-phase arrest in HL-60/VCR cells and was proved that it was not the substrate of P-glycoprotein drug transporters.

A series of phenylcinnamides were synthesized and assessed the antitumor activity [49]. Among them, amide **S19** showed moderate antitumor effect against U-937 and HeLa cells with IC_{50} values of 9.7 and 38.9 μM (Fig. 7), respectively. The most potent amide **S20**, C-4 position on benzene etherification analogue, exerted apoptosis effect with IC_{50} values of 1.8 and 2.1 μM for the mentioned two kinds of cell lines, respectively.

According to the structure of Combretastatin A-4, a precursor exhibited cytotoxic effect against murine lymphocytic leukemia, a series of derivatives with higher aqueous solubility were designed and synthesized [50]. Among them, amide **S21** (Fig. 7), a **TMCA** amide, showed favourable antitumor activity against several kinds of cell lines (Table 3). The most potent amides **S22** and **S23** were structurally similar to **S21**. SAR indicated that 3,4-substituted on benzene of the cinnamide was helpful to promote apoptosis activity.

Inspired by the structure of piplartine and suberoylanilide hydroxamic acid, which was a kind of HDACi (histone deacetylase inhibitor), active antileukemic amides **S24** and **S25** were synthesized (Fig. 7) [8]. Amide **S24** were reported to mediate DNA damage and apoptosis. Subsequently, amide **S25**, which was an analogue introduced C2-chloro substituent to **S25**, improved apoptosis activity but redcued selectivity in noncancerous MCF-10A cell lines. amides **S24** and **S25** also performed antileukemic activity through mediating pro-apoptotic proteins expression, inhibiting DNA repair and pro-survival proteins expression, and interfering cellular GSH (glutathione) defense.

Zhang et al. developed a Namidine scaffold framework as MDR modulator [51]. Amides **S26**, which was an analogue with two units of 3-(3,4,5-trimethoxyphenyl)acryloyl in the molecule structure, was proved to be the most potential compound among the derivatives (Fig. 7). Amide **S26** (1 mM) sensitized LCC6MDR cells toward Taxol 24.5 folds (EC_{50}: 210.5 nM), which was more potent than verapamil.

TMCA amides were considered to be bestatin-based inhibitor of MetAP2 and inhibitor against HUVECs (human umbilical vein endothelial cells) [52]. A series of α-hydroxy-β-amino amide analogues were synthesized and evaluated inhibition against MetAP2 and HUVEC growth. Amides **S27-29** (Fig. 7), which were **TMCA** amide analogues, exhibited significant inhibitory effect (Table 4.). When the R group was substituted with benzyl group, both MetAP2 and HUVEC growth inhibition were favourable. When **TMCA** moiety were replaced with other group, the inhibition against MetAP2 and HUVEC growth can not be ensured at same time.

3.2. Antiviral activity of synthetic TMCA derivative

A variety of virus widely exist in the nature and threaten public health. **TMCA** is using to design antiviral agents, involving to anti-HBV (hepatitis B virus), anti-SARS and anti-influenza A agents. To date, nearly all the reported effective antiviral analogues are **TMCA** esters.

Table 4
Enzyme and cellular activities of amides **S27**, **S28** and **S29**.

Com.	IC50 MetAP2 (nM)	GI50 HUVEC (μM)	GI @ 5 μM HUVEC (%)
S27	177	0.67	>98
S28	755	–	93
S29	67	0.85	>98

Sixteen phenylpropionic acid analogues were prepared and screened for the anti-HBV effect [53]. Ester **S30** (Fig. 8) displayed the outstanding HBV inhibitory, with the CC_{50} (half cytotoxicity concentration) value of 506.99 μM in HepG2 2.2.15 cells, and IC_{50} values of HBsAg (hepatitis B surface antigen) and HBeAg (hepatitis Be Antigen) were 107.19 and 74.80 μM, respectively.

Research group of Jijun Chen synthesized numerous of natural-based compounds and measured their anti-HBV activity, several **TMCA** esters exhibited anti-HBV activity in the studies (Table 5). Caudatin, an effective anti-HBV precursor tetracyclic triterpenoid separated from *Cynanchum bungee*, was modified with cinnamic acid and measured for anti-HBV activity. Ester **S31** (Fig. 8) exhibited most potent for anti-HBV activity, with the CC_{50} value of 1821.75 μM in HepG2 2.2.15 cells, and both the IC_{50} values of HBsAg and HBeAg were 5.52 μM. With the highest SI value of 330. The IC_{50} value of **S31** inhibiting HBV DNA replication was 53.1 μM [54]. Ester **S32** (Fig. 8), which was an esterified derivative from andrographolide, also performed moderate anti-HBV effect, with the CC_{50} value of 211 μM in HepG2 2.2.15 cells, and the IC_{50} values of HBsAg and HBeAg were 753 and 518 μM, respectively. The IC_{50} value of **S32** inhibiting HBV DNA replication was 53.1 μM. **TMCA** was considered as one of the group which was favourable to enhance anti-HBV activity according to SAR [55].

p-Hydroxyacetophenone, isolated from *Artemisia capillaris*, was explored as the precursor for the anti-HBV agent. A series of anlogues were synthesized and identificated through the Mitsunobu reaction on the primary hydroxyl group of pyranose. Among the synthetic compounds, ester **S33** (Fig. 8) exhibited strongest anti-HBV DNA replication effect, with the CC_{50} value of 1821.75 μM in HepG2 2.2.15 cells, meanwhile, the IC_{50} value of **S33** inhibiting HBV DNA replication was 5.8 μM, SI = 330 [56]. The SAR can be concluded that glycosides showed stronger inhibitory activity than aglycones in general, meanwhile, the cinnamic acid analogues positioned with methoxyl or fluoro group exhibited more potential activity than other substituted analogues.

According to the structure of effective ester tetrapeptide aldehyde against SARS, a series of derivatives were synthesized. Ester **S34** (Fig. 8) showed weak anti-SARS CoV 3CL R188I mutant protease effect (IC_{50}: 250 μM) [57]. Interestingly, according to another research result from the author [58], **TMCA** amide analogue was reported to be the most promising compound among the designed derivatives. The author considered that planar aromatic ring and its hydrophobic functionality on the structure of substituted group were essential for the inhibitory activity.

Inspired by the structure of penta-*O*-galloyl-β-D-glucose, several derivatives were synthesized and determined for the anti-influenza A activity [59]. Compared with 3,4,5-trimethoxy benzoic acid

Table 3
Cytotoxic activity (Concentration of drug causing 50% inhibition of cell growth) data of amides, **S21**, **S22**, **S23** and CA-4 by SRB method.

Com.	MCF7	DU145	HOP62	HeLa	K562	SK-OV-3	Colo205	MIA-PaCa-2
S21	0.079	0.095	24.8	14.9	28.0	20.9	76.0	64.5
S22	0.056	0.060	0.090	7.5	0.094	0.099	0.099	29.9
S23	0.031	0.045	43.6	29.2	0.099	29.8	74.9	74.0
CA-4	0.033	0.046	0.15	0.008	0.031	31.6	0.025	–

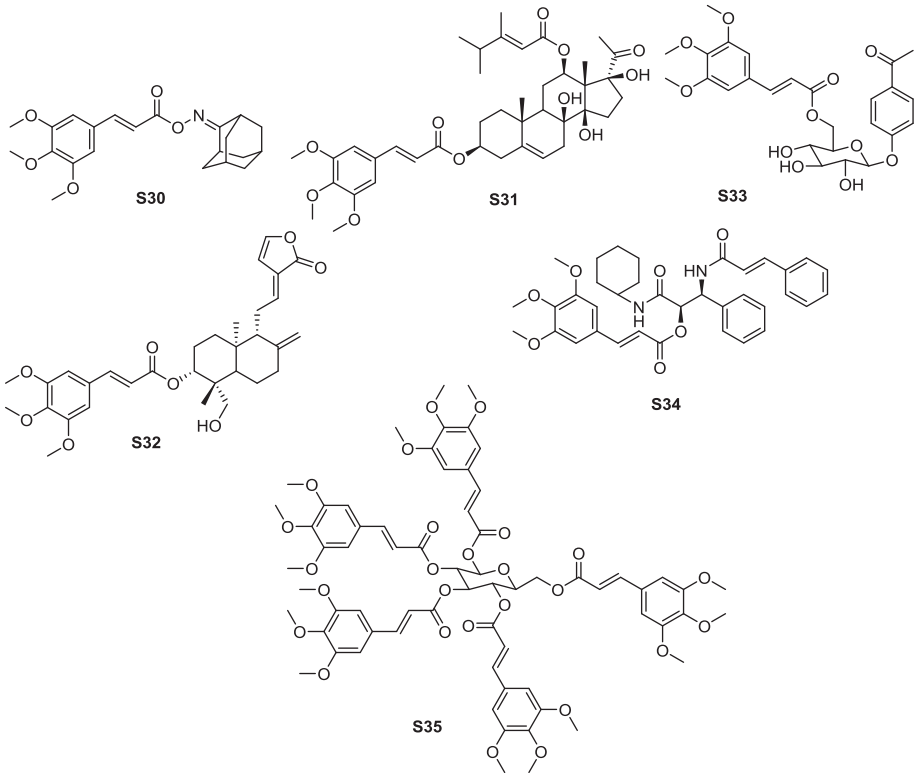


Fig. 8. Structure of synthetic **TMCA** derivatives as antivival agents (**S30-S35**).

Table 5
Anti-HBV activity and cytotoxicity of esters **S30, S31, S32** and **S33**.

Com.	CC_{50} (μM)	HBsAg		HBeAg		DNA replication	
		IC_{50} (μM)	SI	IC_{50} (μM)	SI	IC_{50} (μM)	SI
S30	506.99	107.19	4.73	74.80	6.78	141.46	3.58
S31	>1821.75	5.52	>330.0	5.52	>330.0	2.44	>746.6
S32	211	753	–	518	1.6	53.1	3.0
S33	>2423.5	285.7	>8.5	>2423.5	–	114.9	>21.1

substituted derivatives, ester **S35** showed stronger inhibition against influenza A. Ester **S35** (Fig. 8), which was composed by D-Mannose and five units of **TMCA**, showed most potent anti-influenza A effect. As for the configuration, ester **S35** was the mixture of α- and β-anomer, with the ratio of α/β = 63/37.

3.3. CNS agents of synthetic TMCA derivative

CNS disorders, which are made up of multiple diseases whose symptoms contain cognitive impairment and maniac or depressive behavior, affected millions of people around the world [60]. Because of the complexity of pathogenesis, development of CNS agents is high investment but low returns. Coherent with the bioactivity of precursor **TMCA**, **TMCA** ester and amide analogues have been reported to show CNS activity including antinarcotic, neuroprotective anti-Alzheimer and anticonvulsant effect. Several targets are involved to such as 5-HT (5-hydroxytryptamine), Ache (acetylcholine), BuChe (butyrocholinesterase), Aβ (1–42), EP2 and Nrf2 (nuclear factor 2).

3.3.1. Synthetic TMCA esters as CNS agents

In 2013, a series of **TMCA** analoges were synthesized and examined the antinarcotic activity [61]. Ester derivatives were synthesized by acyl chlorination of **TMCA**, among which ester **S36** (Fig. 9) exhibited moderate antinarcotic *in vivo* and *in vitro*. At the dose of 20 kg/mg, **S36** suppressed naloxone-stimulated jumping behavior in morphine-dependent mice. Moreover, **S36** inhibited 5-HT_{1A} with the IC_{50} value of 9.4 μM.

According to the structure of Sintenin, a lignanoid isolated from *Piper sintenense*, Jung et al. [62] synthesized multiple ester analogues. The neuroprotective effect of the synthetic esters was determined in *in vitro* models. Ester **S37** (Fig. 9) showed moderate neuroprotective activity in DPPH (1,1-Diphenyl-2-picrylhydrazylradical2,2-Diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl) radicals scavenging model, with the inhibition for 18.60% at 50 μg/mL, which was higher than the positive control quercetin. Further study revealed that caffeic acid substituted ester showed the most potent neuroprotective effect through suppressing the H_2O_2-induced oxidative injury in PC12 cells.

Ester **S38** (Fig. 9), which was a esterified derivative of active lead compound-tacrine, was confirmed to show potential against

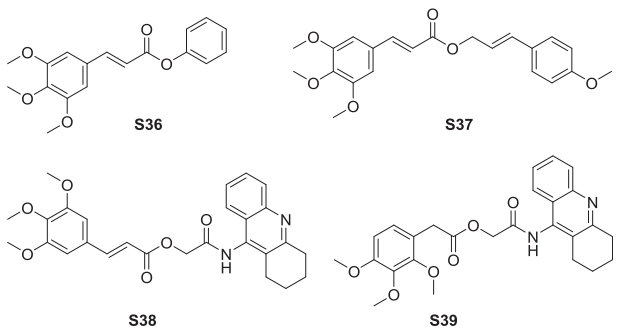


Fig. 9. Structure of synthetic **TMCA** ester derivatives as CNS agents (**S36-S39**).

Alzheimer's disease [63]. To detail, **S38** showed inhibitor against AChe, BuChe and Aβ (1–42) aggregation with IC_{50} values of 16.88, 298.9 and 45.88 μM, respectively. The most active ester **S39**, which also containing trimethoxybenzene moiety, showed AChe inhibition (IC_{50}: 5.63 μM, 13 times stronger than tacrine). The SAR investigation suggested that electron-withdrawing substituents on the benzene ring of cinnamate were not conductive to improve the inhibitory activity of AChe, BuChe and Aβ (1–42) aggregation.

Table 6
Serotonin (5-HT) receptor and transporter binding afnities of amides **S40** and **S41**.

Compound	Receptor binding affinity (IC50, μM)					
	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	5-HT transporter
S40	1.2	>10	8.8	>10	>10	>10
S41	2.1	6.8	4.5	5.0	5.6	6.7
TMCA	7.6	>10	2.5	>10	>10	>10

3.3.2. Synthetic TMCA amides as CNS agents

Jung et al. [5] synthesized several **TMCA** amides and measured the antinarcotic activity. The reaction details about preparation of **TMCA** were described. Among the homologous, amides **S40** and **S41**(Fig. 10) were the most potential amides *in vivo* and *in vitro*. At the dose of 5 mg/kg (i.p.), **S40** and **S41** significantly decreased the naloxone-induced jumping behavior in morphine-dependent mice, with the inhibition ratio values of 88% and 80%, respectively. *In vitro*, **S40** and **S41** exhibited favourable binding affinity to serotonergic receptors such as 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7, and the 5-HT transporter (Table 6). Amide **S40** displayed the most significant binding affinity to the 5-HT_{1A} receptor. Additionally, **S41** possessed different binding affinity to mentioned receptors. Ability of activating the pERK expression for the amides was also determined. The result indicated that amides **S40** and **S41** moderately increased the expression of pERK.

Amide **S42** (Fig. 10) was reported to be effective in inhibiting seizure-induced mediation of neuronal injury by PGE2 (prostaglandin E2) receptor subtype EP2 [64]. As the most potent molecular in the synthetic analogues, **S42** possessed competitive antagonism of EP2 receptor (K_B: 2.4 nM), meanwhile, the EP4 (prostaglandin E2 receptor 4) receptor K_B value was 11.4 μM, and the SI was 4730. Furhermore, **S42** as a brain-permeant agent inhibted the up-regulation of COX-2 (prostaglandin-endoperoxide synthase 2) mRNA in rat cultured microglia activated by EP2 and markedly decreased neuronal injury in hippocampus when administered in mice beginning 1 h after termination of pilocarpine-induced status epilepticus. The result revealed that **S42** was effective in treating inflammation-related brain injury. Based on the structure of **S42**, amide **S43** was synthesized and evaluated the selectivity against prostanoid receptor EP2 and DP1.

A series of piplartine analogues were synthesized and measured cytoprotection against hydrogen peroxide- and 6-hydroxydopamine-induced neuronal cell oxidative damage in PC12 cells [65]. Amides **S44** and **S45** (Fig. 10) showed low cytotoxicity and confer potent protection of PC12 cells from the oxidative injury *via* upregulation of a panel of cellular antioxidant molecules. Genetically silencing the transcription factor Nrf2, a master regulator of the cellular stress responses, suppresses the cytoprotection, indicating the critical involvement of Nrf2 for the cellular action of **S44** and **S45** in PC12 cells.

Cinepazide (**S46**) (Fig. 10) is a marketed drug using for the treatment of cardiovascular and cerebrovascular diseases, and peripheral vascular diseases. Cinepazide can also be regarded as a **TMCA** amide analogue. Amide **S46** was suggested to protect PC12 neuronal cells by affecting mitochondrial functions [66]. To detail, **S46** inhibited OGD (oxygen–glucose deprivation)-induced oxidative stress, as supported by its capability of reducing intracellular reactive oxygen species and malondialdehyde production and enhancing superoxide dismutase activity. Furthermore, **S46** was found to sustain the function of mitochondrial function *via* stabilizing mitochondrial membrane potential, promoting OGD-induced suppression of mitochondrial respiratory complex activities and enhancing ATP (adenosine-triphosphate) production.

Jung and coworkers [67] presented a simple synthesis **TMCA** amides and evaluated the bioactivities. All the synthesic amides were determined the radical scavenging activity, neurotoxicity inhibition and antinarcotic activity. No significant radical scavenging activity was observed for the tested amides compared to the reference material *in vitro*. Amide **S47** (Fig. 10) showed most potent neuroprotective activity in glutamate-induced primary cortical neuronal cells at the doses ranging from 5 to 20 μM. Meanwhile, all the analogues showed antinarcotic property *in vivo*. Amide **S48** displayed strongest inhibition among the examed amides, which indicated that **TMCA** moiety was essential for the enhancement of antinarcotic activty.

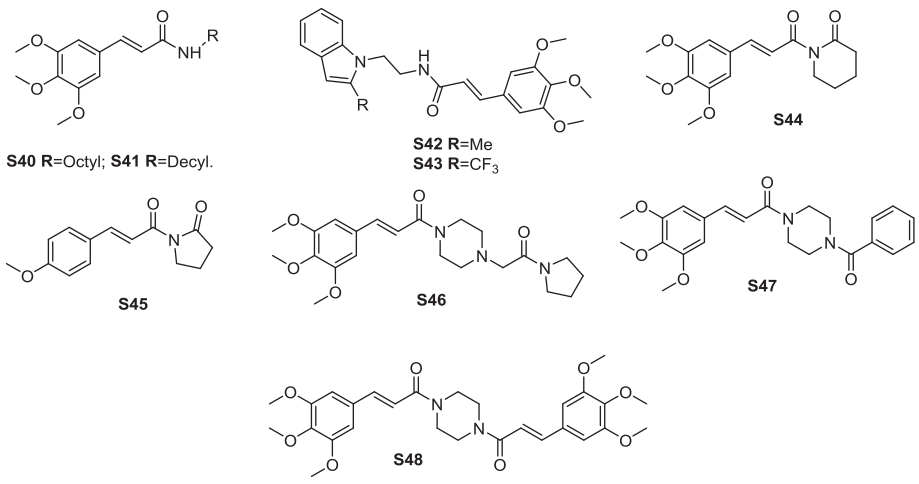


Fig. 10. Structure of synthetic **TMCA** amide derivatives as CNS agents (**S40**-**S48**).

3.4. Antimicrobial activity of synthetic TMCA derivatives

TMCA ester ester and amide analogues are applied to synthesize antimicrobial agents as well. Active derivatives have been reported to suppressed the growth of strains including *Ustilaginoidea oryzae*, *Pyricularia oryzae*, *P. falciparum*, *S. aureus*, *C. krusei* and *Trypanosoma cruzi*.

3.4.1. Synthetic TMCA esters as antimicrobial agents

Trichodermin cinnamic acid ester derivatives were prepared and by Zheng et al. [68]. Among the obtained compounds, ester **S49** (Fig. 11) exhibited moderate inhibition against *Ustilaginoidea oryzae* and *Pyricularia oryzae in vitro*, with the EC_{50} values of 11.04, and 11.07 μM, respectively. Ester **S50**, which was a derivative substituted with ortho-fluorine cinnamic acid, exhibited prodominent inhibition against mentioned strains, with the EC_{50} values of 0.56, and 0.53 μM, respectively. The effect was even better than the marketed drug prochloraz, which could be related with the function of the fluorine moiety in inhibiting microbials [69].

Several studies have reported esters including **TMCA** moiety possessed antimalarial effect, which indicated that **TMCA** could be an important group for developing antimalarial agents. As an analogue of neolignane, ester **S51** (Fig. 11) was identified and measured the antimalarial activity *in vitro* [70]. The result revealed that **S51** exhibited moderate antimalarial activity against blood forms of chloroquine-resistant *P. falciparum* with both the IC_{50} values for ^{3}H-hypoxantine and HRPII were 127.9 μM.

In an anticipation of powerful antimalarial activity, Aratikatla et al. [71] exploited a series of syncarpamide analogues and investigated the efficacy *in vivo* and *in vitro*. Among the synthetic compounds, ester **S52** (Fig. 11) displayed the strongest inhibition for 3D7 and K1 strains of *P. falciparum*, with the IC_{50} values of 1.89 and 1.93 μM, respectively. Unfortunately, there was no significant effect for **S52** inhibiting N-67 strain of *Plasmodium in vivo*.

Dai et al. [72] modified the structure of Kniphofiones A and B, which were two lead compounds separated from *Kniphofia ensifolia*. Ester **S53** (Fig. 11) was reported to show marked antiplasmodial effect against Dd2 chloroquine-resistant strain of *P. falciparum* (IC_{50}: 2.7 μM). The most potent ester **S54** was structurally similar to **S53**, and the IC_{50} value of **S54** was 1.3 μM. Ester **S54** exerted 7 and 20 times the efficiency of Kniphofiones A and B.

3.4.2. Synthetic TMCA amides as antimicrobial agents

Fregnan et al. [73] synthesized several analogues of piplartine and evaluated the antimicrobial activity of the analogues. Amides **S55** and **S56** (Fig. 12) were the most potent amides (Table 7). Amide **S55** displayed three-fold more potent than piplartine in antibacterial evaluation against *S. aureus* and five-fold less toxic than piplartine. Amide **S56** possessed fourfold more potent in antifungal evaluation against *C. krusei* and five-fold less toxic than piplartine. As for the SAR, it was possible to note that an aromatic ring lacking methoxyl moieties is important for the antibacterial activity of these compounds. On the other hand, trimethoxyphenyl group substituted on benzene ring was imperative for the antifungal activity.

Carvalho et al. [74] synthesized several cinnamic N-acylhydrazones and measured the antitrypanosomal effect. Amide **S57** (Fig. 12) exhibited modest antitrypanosomal activity against trypomastigote forms of *Trypanosoma cruzi* with the IC_{50} value of 18.4 μM. The value of SI of **S57** was the highest of 134. Moreover, possessed favourable cruzain inhibition with the IC_{50} value of 45.9 μM.

Derivatives of 4″-*O*-(*trans*-*β*-arylacrylamido)carbamoyl azithromycin were synthesized and assessed for their antibacterial effect against nine significant pathogens [75]. Amide **S58** (Fig. 12) exhibited moderate antibacterial effect against susceptible and resistant strains (Table 8). The most potent amide **S59** was structurally close to **S58**, which revealed that 3,4-dimethoxyl substituted moiety enhanced the antibacterial activity for the lead compound.

3.5. Anti-inflammatory activity of synthetic TMCA derivatives

Inflammation is body's natural response against external infection. [76]. **TMCA** ester and amide derivatives have been reported to show anti-inflammatory activity through the targets including TNF-*α* (tumor necrosis factor), NO (nitric oxide) and NF-*κ*B.

3.5.1. Synthetic TMCA esters as anti-inflammatory agents

Ku et al. [61] combined carbazole with cinnamoyl group and measured the vascular barrier protective effects of derivatives.

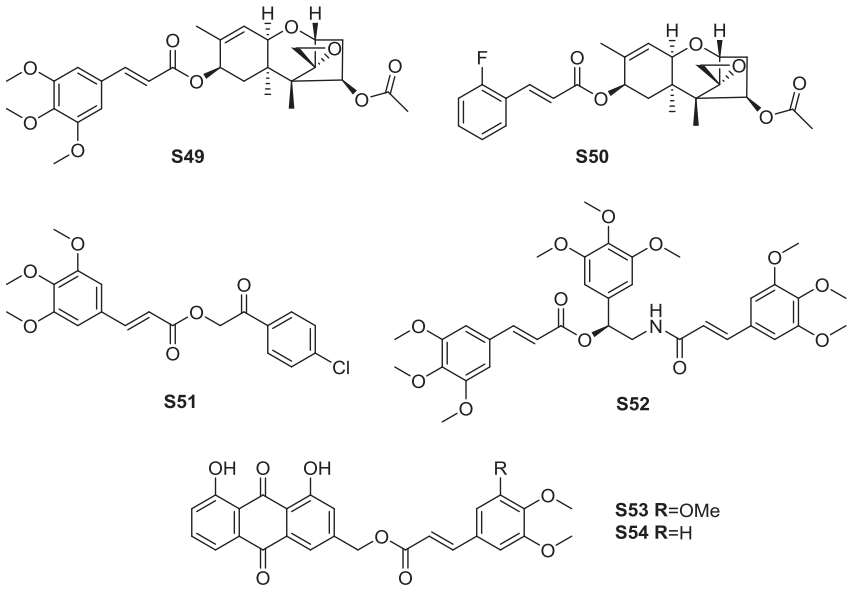


Fig. 11. Structure of synthetic **TMCA** amide derivatives as antimicrobial agents (**S49**-**S54**).

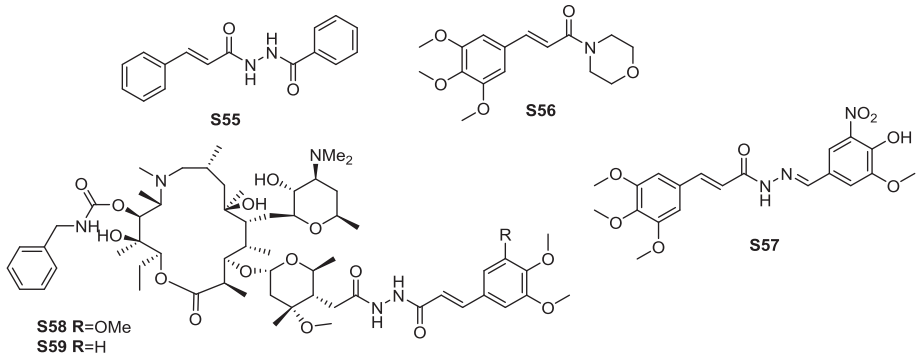


Fig. 12. Structure of synthetic **TMCA** amide derivatives as antimicrobial agents (**S55**-**S59**).

Table 7
Antimicrobial activity of amides **S55** and **S56**.

Com.	Fungus					Bacteria	CC_{50}
	C. albicans ATCC 10231	*C. tropicalis* ATCC 750	C. krusei ATCC 6258	C. glabrata ATCC 90030	C. parapsilosis ATCC 22019	*S. aureus* ATCC 6538	BHK-21
S55	375.79 (0.61)[a]	375.79 (0.61)	-[b]	375.79 (0.61)	375.79 (0.61)	85.20 (2.71)	231.71
S56	–	97.67 (1.89)	48.83 (3.79)	–	–	–	185,55
Piplartine	94.60 (0.42)	–	189.20 (0.21)	189.20 (0.21)	94.60 (0.42)	315.33 (0.12)	40.14

[a] IC_{50} (SI).
[b] Inactive at highest evaluated concentration.

Table 8
Antimicrobial activity of amides **S58** and **S59**.

Com.	*S. aureus* ATCC25923	*S. pneumoniae* ATCC49619	*S. pyogenes* S2	*S. aureus*	*S. aureus ATCC*29213	*S. pyogenes* R2	*S. pneumoniae* A22072	*S. pneumoniae* AB11	*S. pyogenes* R2
S58	1	0.5	1	4	4	32	2	16	64
S59	0.5	0.06	0.25	2	4	64	2	64	64
Azithromycin	0.25	0.03	0.25	0.12	1	128	4	256	≥128

Ester **S60** (Fig. 13) exhibited marked inhibition on HMGB1 (high mobility group box-1 protein)-mediated hyperpermeability. At the dose of 10 μM, **S60** inhibited hyperpermeability with the most remarkable inhibition of 70.2% and ELISA OD_{650} value of 0.158. On mice model, also suppressed HMGB1-mediated hyperpermeability with the inhibition of 58.9%. The result demonstrated that **S60** could be a potent agent for inhibiting HMGB1-mediated inflammatory responses.

Kumar et al. [77] reported that ester **S61** (Fig. 13) isolated from *Piper longum* inhibited ICAM-1 (intercellularcelladhesionmolecule-1), VCAM-1 and E-selectin by the induction of TNF-α. As one of the thionocinnamate homologs, **S62** exhibited better inhibition than **S61**. On the concentration of 20 μg/mL, **S62** exerted 95% inhibition of ICAM-1 expression (IC_{50}: 10 μg/mL). Consequently, **S62** abolished adhesion of neutrophils to endothelial monolayer by the induction of TNF-α. SAR investigation indicated that the critical role of the chain-length of the alkyl moiety in the alcohol moiety, number of methoxy groups in the aromatic ring of the cinnamoyl moiety and the presence of the α, β- C-C double bond in the thiocinnamates and thionocinnamates.

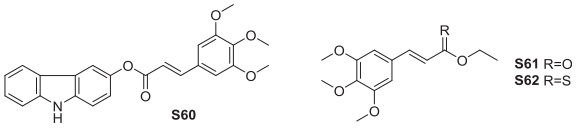


Fig. 13. Structure of synthetic **TMCA** ester derivatives as anti-inflammatory agents (**S60**-**S62**).

3.5.2. Synthetic TMCA amides as anti-inflammatory agents

A series analogues of piplartine (**S63**) were synthesized and investigated the anti-inflammatory activity [76]. Among them, amide **S63-66** (Fig. 14) exhibited better inhibition. At the dose of 10 μM, LPS (lipopolysaccharide)-induced NO production was inhibited by four mentioned amides with the inhibition of 91%, 46%, 65% and 41%, respectively. Additionally, the cytotoxicity of four amides in RAW264.7 macrophages was measured with the IC_{50} values of 3, 6, 14 and 17 μM, respectively.

Sun et al. [78] designed and synthesized several piplartine derivatives. Analogue **S67** (Fig. 14), which was the ketone analogue with amide group replaced by carbonyl to increase its electrophilicity, was certified to show more potential than the lead amide piplartine in blocking LPS-induced secretion of NO and PGE2 as well as COX-2 and iNOS (inductive nitric oxide synthase) expressions in RAW264.7 macrophages.

3.6. Hematologic activity of synthetic TMCA derivatives

TMCA amides have been revealed to show hematologic activity, in which anti-aggregatory and haemostatic effect are the relative effects.Substituted cinnamoyl-tyramine analogues were synthesized and evaluated the platelet anti-aggregatory activity [79]. Among the synthetic derivatives, amides **S68** and **S69** (Fig. 15) exhibited moderate platelet anti-aggregatory activity. At the dosage of 20 μg/mL, amides **S68** and **S69** suppressed PAF (platelet-activating factor) receptor binding to rabbit platelet with the inhibition of 12 and 19%, respectively (Table 9). On the concentration of 30 μg/mL, **S68** and **S69** inhibited PAF induced platelet aggregation with

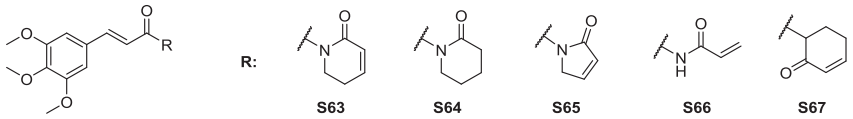


Fig. 14. Structure of synthetic **TMCA** amide derivatives as anti-inflammatory agents (**S63**-**S67**).

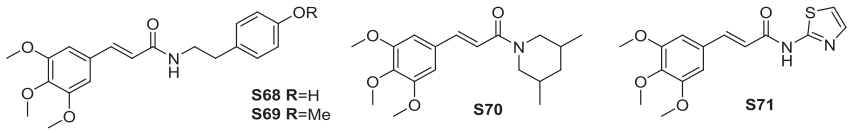


Fig. 15. Structure of synthetic **TMCA** derivatives as hematologic agents (**S68**-**S71**).

the inhibition of 28.8 and 39.3%, respectively. In addition, at the dose of 50 μg/mL, amides **S68** and **S69** inhibited PAF induced platelet aggregation with the inhibition of 24.4 and 29.1%, respectively. SAR suggested that 3,4-dimethoxycinnamoyl group could be the beneficial for the platelet anti-aggregatory activity.

To investigate the aggregation inhibition of piplartine and its analogues, a seires of derivatives of piplartine were synthesized by Park et al. [80]. Among the derivatives, amide **S70** (Fig. 15) displayed the most promising platelet aggregation inhibitory effect in different models (Table 10). SAR research revealed that adding a methyl group to the C-2 position of the piperidine ring exerted mixed effects, promoting inhibitory effect for thrombin and collagen-induced platelet aggregation but reducing inhibition to arachidonic acid-induced platelet aggregation.

Ten new cinnamamide derivatives containing a 2-aminothiazole substructure were presented as potent haemostatic agents [81]. Among the studied series, amide **S71** (Fig. 15) exhibited coagulation activity to a certain extent. Amide **S71** promoted platelet aggregation (IC_{50}: 18.09 μmol/L) more potent than etamsylate. Amide **S71** showed lowest TT (thrombin time) value among the analogues, moreover, **S71** improved platelet aggregation relative to etamsylate while promoting APTT (activated partial thromboplastin time) and PT (prothrombin time), suggesting that **S71** showed haemostatic activity by stimulating fibrinogen or promoting fibrin and activating platelet aggregation.

3.7. Other activities of synthetic TMCA derivatives

Apart from the bioactivity described above, **TMCA** amide derivatives exhibited ACAT (O-acyltransferase) and ALR2 (aldose reductase) inhibitory as well. A series of Yakuchinone B derivatives were synthesized and assessed the lipid-lowering activity [9]. As the most promising amide, *in vivo*, amide **S72** (Fig. 16) inhibited rat hepatic cholesterol ACAT more significant than positive control and it exerted remarkable hypocholesterolemic activity. Subsequent research implicated that **S72** from male rats could be better metabolized than those from females [82]. Sex-related different CYP3A2 expression in the toxicology research relevant to decreased accumulation and metabolism of **S72** in female rats.

Piplartine was proved to suppress recombinant human ALR2 (IC_{50}: 160 μM) [6]. To improve the activity, multiple derivatives were prepared by modificating styryl/aromatic and heterocyclic ring functionalities. **S73** and **S74**(Fig. 16) synthesized by Michael addition exhibited aldose reductase inhibitor effect, with the IC_{50} value for 4 μM. Notably, according to SAR study, double bond and 3,4,5-trimethoxy substitutions at aromatic ring are important characteristics for ARI effect.

4. Conclusion

Up to now, esterification and amidation still play a significant role in discovering and developing new drugs. Amide bond formation dominated the most frequently used reaction to give the production even though the new synthetic reactions are spring up [83]. Compared with other modifications, esterification and amidation are easy to exert the metabolic characteristic of lead compounds, moreover, esterification and amidation can be easily controlled for industrial scale production for the targets compounds. Currently, the difficulty to develop new drugs is to discover novel lead compounds instead of synthsis.

As for the promising precursor **TMCA**, it is clearly evident that **TMCA** ester and amide analogues possess diversified biological activities and have immense potentiality in the field of medicinal chemistry from the above discussion. This review article is focused on the pharmacological activities of natural and synthetic **TMCA** ester and amide derivatives for various therapeutic targets reported recently. The present survey indicates that **TMCA** ester and amide derivatives have been targeted for their antitumor, antiviral, CNS agnets, antimicrobial, anti-inflammatory and hematologic agents. There is much scope in this potent **TMCA** ester and amide moiety for other therapeutic targets, future investigations of the scaffolds could give some more encouraging results in the field of medicinal chemistry. It is not to be neglected that esters generally perform poor pharmacokinetics and limited druggability [84], so there are still gaps waiting for overcoming when **TMCA** derivatives are developed to the marketed drugs.

It is anticipated that the information compiled in this review article not only update researchers with the recent reported biological activities of **TMCA** ester and amide analogues derivatives, but also motivate them to design and synthesize promising **TMCA**

Table 9
Platelet anti-aggregatory activity of amides **S68** and **S69**.

Com.	Inhibition (%)		
	PAF receptor binding to rabbit platelet	ADP induced platelet aggregation	PAF induced platelet aggregation
Dose	20 μg/mL	30 μg/mL	50 μg/mL
S68	12	24.4	28.8
S69	19	29.1	39.3

Table 10
Platelet anti-aggregatory activity of amide **S70**.

Com.	Conc. (μM)	Inhibition (%)			
		Collagen (2 μg/mL)	Arachidonic acid (100 μM)	PAF (10 nM)	Thrombin (100 μM)
S70	300	98.6	100	94.8	–
	150	97.2	100	56.9	–
Piplartine	300	100	100	100	23.5
	150	100	76.4	100	–
Acetylsalicylic acid	300	5.8	100	0.3	–
	150	–	75	0.3	–

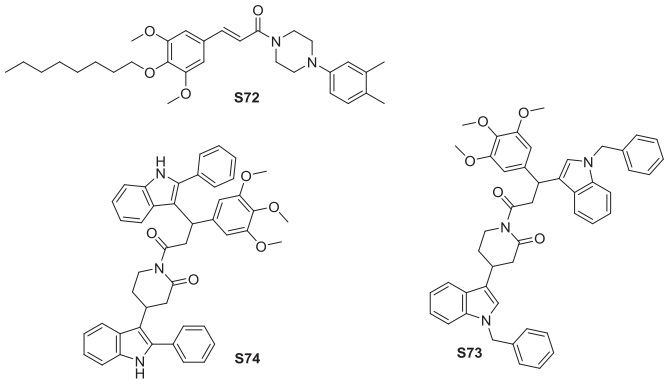


Fig. 16. Structure of synthetic **TMCA** derivatives for other activities (**S72**-**S74**).

ester and amide with improved medicinal properties.

Disclosure

None of the authors have any conflict of interest to disclose.

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Abbreviations

5-HT 5-hydroxytryptamine
AChe acetylcholine
ATP adenosine-triphosphate
APTT activated partial thromboplastin time
ACAT O-acyltransferase
ALR2 aldose reductase
APD_{50} action potential duration at 50% repolarization
APD_{90} action potential duration at 90% repolarization
BuChe butyrocholinesterase
BDNF brain derived neurotrophic factor
CC_{50} half cytotoxicity concentration
COX-2 prostaglandin-endoperoxide synthase 2
C.krusei Candida krusei
CNS central nervous system
c-Met tyrosine-protein kinase Met
DCC Dicyclohexylcarbodiimide
DMAP 4-dimethylaminopyridine
DADs delayedafterdepolarizations
DPPH 1,1-Diphenyl-2-picrylhydrazylradical2,2-Diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl
ERK extracellular signal-regulated kinase
EADs early afterdepolarizations
EDCI 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EC_{50} half effective concentration
EP4 prostaglandin E2 receptor 4
GSH glutathione
HPLC high performance liquid chromatography
HMGB1 high mobility group box-1 protein
HSP70 heat shock protein 70
HDACi histone deacetylase inhibitor
HBV hepatitis B virus
HBsAg hepatitis B surface antigen
HBeAg hepatitis Be Antigen
HUVECs human umbilical vein endothelial cells
ICAM-1 intercellularcelladhesionmolecule-1
IC_{50} half maximal inhibitory concentration
iNOS inductive nitric oxide synthase
IL-6 interleukin- 6
I_{to} transient outward potassium current
$I_{K,SS}$ steady-state potassium current
i p intraperitoneal injection
JAK janus kinase
K_m substrate concentration at which the reaction rate is half of V_{max}
K_{cat} limiting rate of any enzyme-catalyzed reaction at saturation
LPS lipopolysaccharide
MAO monoamine oxidase
MAPK mitogen-activated protein kinase
MDR multi-drug resistant
MetAP2 human methionine aminopeptidase-2
NF-κB nuclear transcription factor-κB
NO nitric oxide
Nrf2 nuclear factor 2
OGD oxygen–glucose deprivation
P. falciparum Plasmodium falciparum
PAF platelet-activating factor
PGE2 prostaglandin E2
PT prothrombin time
P-gp P-glycoprotein 1
P. tenuifolia *Polygala tenuifolia* Willd. (Polygalaceae)
ROS reactive oxygen species
SAR structure-activity relationship
SARS severe acute respiratory syndrome
SARS-CoV SARS coronavirus
SI selective index
SOD superoxide dismutase
TCM traditional Chinese medicine
TNF-α tumor necrosis factor
TT thrombin time
TMCA 3-(3,4,5-trimethoxyphenyl) acrylic acid
TAs triggered activities

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