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Encouraging Effects of Ethacrynic Acid Derivatives Possessing a Privileged α, β-Unsaturated Carbonyl Structure Scaffold

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Abstract

α, β-unsaturated carbonyl unit has remarkable utility in the development of biologically active and therapeutically relevant compounds in medicinal chemistry. In recent years, a number of Ethacrynic acid (EA) derivatives containing α, β-unsaturated carbonyl group were reported, which displayed versatile biological activities, such as antitumor activity, antimalarial effects, antiviral activity and reducing intraocular pressure. In this review, we summed up a number of derivatives regarding Ethacrynic acid as the lead and α, β-unsaturated carbonyl moiety as the functional group, researching on structure-activity relationship and evaluating their various biological activities in recent years. By summarizing the structure-activity relationships of these derivatives, we aimed to demonstrate α, β-unsaturated carbonyl group is a privileged scaffold in these structures and we should pay more attention to α, β-unsaturated carbonyl group to the development of more effectively bioactive new compounds.

Keywords: α, β-Unsaturated carbonyl; Ethacrynic acid; Derivatives; Biological activities

Introduction

α, β-unsaturated carbonyl group is attractive to medicinal chemists due to its peculiar chemical properties and biological activities. It carries out Michael addition reactions with cysteine residues in ATP-binding pocket [1]. Although prominent progress has been made on these compounds with α, β-unsaturated carbonyl group, more efforts are ongoing to discover new compounds with potent biological activities. In the development of ErbB inhibitors, the introduction of an acrylamide fragment on a heterocyclic scaffold of a reversible EGFR/ErbB-2 conjugate produces irreversible ErbB inhibitors [2] such as Canertinib (Figure 1). Afatinib (Figure 1), an ATP-competitive anilinoquinazoline derivative, harbors a reactive acrylamide group and can block enzymatically active ErbB receptor family members irreversibly. It binds to the target leading to the inhibition of ErbB-4 [3]. Ibrutinib (Figure 1) is a potent inhibitor which can covalently bind to Cys481 amino acid of Bruton's tyrosine kinase (BTK) enzyme [4]. It has been found to inhibit many processes such as tumor-cell migration, ERK signaling and NF-κB DNA binding [5] in preclinical studies. Some small molecule inhibitors of HER2 tyrosine kinase exhibit activity in the populations of trastuzumab-resistant breast cancer including Neratinib [6] (Figure 1). Except α, β-unsaturated carbonyl group, a lot of alternative electrophilic groups has been investigated including butynamides, vinylsulfonamides, and epoxides [7] but with lower reactivity. Therefore, in order to develop more effectively bioactive new compounds, we should pay more attention to α, β-unsaturated carbonyl group.

As we all know, Ethacrynic acid (EA) (Figure 1), is clinically used as diuretic drug and is used to treat high blood pressure and the swelling caused by diseases [8]. It possesses α, β-unsaturated carbonyl unit, a privileged scaffold which was often employed in the design of enzyme inhibitors [9]. In the published articles, it was not difficult to find that α, β-unsaturated carbonyl group played a significant role in biological activities of the EA derivatives. These derivatives displayed exceptional chemical properties and versatile biological activities, such as antitumor activity, antimalarial effects, antiviral activity and reducing intraocular pressure. This review summed up some EA derivatives with α, β-unsaturated carbonyl moiety as the functional group, researching on SAR and information available on the pharmacological activities. Through structure-activity relationships of these EA derivatives, it demonstrated that α, β-unsaturated carbonyl group was a privileged scaffold in these structures.

Biological Evaluation and Discussion

Antitumor activity

Cancer is one of the most life-threatening diseases which threaten millions of people's lives around the world. And in the treatment of cancer, chemotherapy is still the main clinical treatment. However, many chemotherapeutic drugs recently used in clinic have serious side effects or low specificity [10]. Except that, one important obstacle must be taken into consideration is multidrug resistance (MDR)

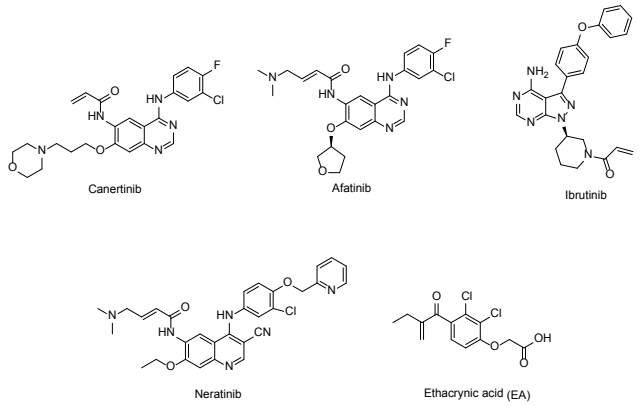

Figure 1: Representative chemical structures containing α, β-unsaturated carbonyl group.

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against anticancer drugs in cancer treatment [11]. Up to now, several mechanisms have been suggested to provide explanation to the phenomenon, and one of them is that GSTs are a kind of prevalent proteins in many solid tumors and overexpress in cancer cells resistant to drugs [12]. Glutathione transferases which can also be called glutathione S-transferases or GSTs, are members of Phase II detoxification enzymes expressed in most plants and animals [13]. Their high expression is associated with the drug resistance of cancers. Particularly, GST π, a special isozyme, is prevalent and expressed at high levels in different human cancerous and precancerous tissues (particularly liver, pancreas, ovarian, non-small cell lung, breast, lymphomas and colon) [14].

Ethacrynic acid (EA), one of the first generation of GST π inhibitors, has been found to improve the cytotoxicity of the chemotherapeutic drugs. Because EA contains α, β-unsaturated carbonyl group, a Michael receptor, it can combine to Glutathione (GSH) to form a complex that inhibits GST π by Michael addition. So the ability of EA to inhibit GST π is derived from α, β-unsaturated carbonyl group, and its primary diuretic side effect results from carboxyl group. But due to its high side effect of diuretic properties and lack of isozyme specificity, EA has limited utility in clinical applications [15] and it shown inhibition on cell growth and induction of apoptosis only at high concentrations [16].

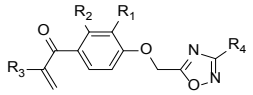
A great deal of reported EA derivatives possessed antitumor activity, and can be divided into three categories according to their scaffolds.

EA derivatives containing a heterocyclic ring: Yang et al. [17] has reported a series of EA derivatives containing a heterocyclic oxadiazole ring by replacing the carboxyl group and the data revealed their inhibitory ability on GST π activity and proliferation of HL-60 cells. Halogen and methyl groups were introduced at the R_1- and R_2- positions of the aromatic ring. Compounds with one chlorine substituent at R_2- position exhibited greater GST π inhibitory activity. Analyzing substituents on the heterocyclic oxadiazole ring, it indicated that the effect of phenyl group was superior to methyl substitution. However, when the oxadiazole ring of compound had an electron-withdrawing or electron-donating group (example: F, CF_3 and CH_3), it inhibited GST π activity much weakly than the compounds with non-substituted benzene ring in oxadiazole ring. And compounds 6r, 6s and 6u performed more potent anti-proliferative activity, even though 6u did not show GST π inhibitory activity (Table 1).

Except heterocyclic oxadiazole substituents, Li et al. [18] synthesized and reported a series of thiazole derivatives. The structures of thiazole derivatives and their inhibition on GST π activity as well as proliferation of HL-60 cells were shown in Table 2.

Among all the synthesized compounds, 9a, 9b and 9c were the most effective ones containing a phenyl-substituted thiazole ring and a methyl at R_3- position and among the three compounds, the inhibitory effect of 9b was the best. The inhibitory efficiency to GST π of EA was 65.1% at the concentration of 5 μM, however, the inhibitory rates of the three compounds were respectively 54.1%, 73.1% and 44.0% at the concentration of 1 μM. Compounds with a methyl substitute at R_3- position were more efficient than those with an ethyl substitute at the same position. And the larger substituent (example: 4-CF_3 phenyl, 2-naphthyl and 4-NO_2 phenyl) the thiazole ring had, the poorer inhibitory effect the compound possessed.

The anti-proliferative activity of all thiazole derivatives on HL-60 cells was similar to that of EA oxadiazole analogues, implying that the anti-proliferative ability of these compounds were independent of their inhibition on GST π activity.



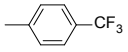
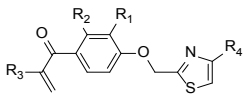
Code	R_1	R_2	R_3	R_4	IC_{50} (μM) for inhibiting GST π activity	GI_{50} (μM) for inhibiting HL-60 cell growth
EA	Cl	Cl	C_2H_5	–	3.4 ± 0.7	45.0 ± 1.1
6r	Cl	Cl	C_2H_5	CH_3	4.0 ± 0.3	2.3 ± 0.2
6s	Cl	Cl	C_2H_5		3.6 ± 0.7	1.7 ± 0.1
6u	Cl	Cl	C_2H_5		>40	1.1 ± 0.2

Table 1: EA analogues with oxadiazole substituents and their effects on inhibiting GST π activity and proliferation of HL-60 cells.



Code	R_1	R_2	R_3	R_4	GST π activity inhibition (%, 5 μM)	GST π activity inhibition (%, 1 μM)	GI_{50} (μM) for HL-60
EA	Cl	Cl	C_2H_5	–	65.1	24.2	44.2
9a	CH_3	CH_3	CH_3		100	54.1	3.4
9b	H	Cl	CH_3		100	73.1	6.4
9c	H	CH_3	CH_3		100	44.0	4.7

Table 2: EA analogues with thiazole substituents and their effects on inhibiting GST π activity and proliferation of HL-60 cells.

EA amide derivatives: Ethacrynic acid, once used to be a loop diuretic drug, did show cytotoxicity to primary chronic lymphocytic leukemia (CLL) cells in previous reports. However, EA was not ideal as chemotherapeutic agents treating chronic lymphocytic leukemia (CLL), the most common adult leukemia in the United States due to its diuretic properties and relative lack of potency. What's more, the growing evidence has demonstrated that Wnt signaling pathway was activated in CLL cells, and deregulation of Wnt/β-catenin pathway is directly related to tumorigenesis [19] namely Wnts, a large family of secreted glycoproteins which are involved in cell proliferation, differentiation, and oncogenesis, are highly expressed in CLL [20]. The uncontrolled Wnt signaling may contribute to the defect in apoptosis which is characteristic of this malignancy [21]. Thus, Wnt signaling could be attractive in the therapy of CLL. Jin et al. [19] reported and synthesized a series of amide derivatives of EA and evaluated their inhibition on Wnt signaling pathway and ability to reduce the survival of CLL cells.

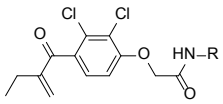
All of the compounds in the article contained α, β-unsaturated carbonyl moiety, while the hydrogenation of α, β-unsaturated carbonyl group contributed to the decreased survival of CLL cells and elimination of Wnt signal transduction of EA (compounds with hydrogenated α, β-unsaturated carbonyl group were not shown in the Table). Hence, α, β-unsaturated carbonyl moiety was still necessary and some compounds were effective in reducing the survival of CLL cells and antagonizing Wnt signaling pathway even at low micromolar concentrations. The data shown in Table 3 suggested that amide derivatives possessed enhanced inhibitory potency on Wnt signaling pathway and survival of CLL compared to EA. And aromatic-containing amides were superior to aliphatic amides in activity. Among all aromatic-containing amides derivatives, one with larger substitution (example: phthalimide, benzothiazole and naphthyl carboxylic acid) revealed good inhibition on both of them. Besides, it's worth noting that the EC_{50} for inhibition of CLL survival were invariably higher than the IC_{50} for inhibition of Wnt signaling with the exceptions of most of the aromatic carboxylic acids, suggesting there may be other target receptors in the cells for the active EA derivatives.

Mignani et al. [22] also designed and synthesized some series of EA amide derivatives whose modifications were focused on carboxyl group. And *in vivo*, the resulting compounds were tested for the capacity to inhibit the growth of three kinds of cells: human epidermal carcinoma (KB), human leukemic HL-60 and the non-dividing quiescent endothelial progenitor cells (EPC) with rapid proliferative capacity from Cyprinuscarpio. In addition, these compounds were tested against the non-dividing quiescent endothelial progenitor cells (EPC) to form a selectivity index (SI), and may indicate that these chemicals specifically acted on cells with rapid proliferation.

Obviously, compounds listed in Table 4 showed better activities than EA. Compound A5 with 2-phenylethylamine chain exhibited good anti-proliferative activity to KB and HL-60 cells but low activities against EPC cells indicating its specific effect on rapid proliferative cell lines. This result led to designing more EA amide derivatives. The 4-position of benzene ring contained phosphate groups or cyclic phosphates can moderately increase the anti-proliferative activity of EA derivatives. And it was noteworthy that compound B11 and compound B17, two of the most potent compounds, expressed promising SI.

Ethacrynic acid derivatives of transition metalcomplexes: Amongst the various kinds of GST enzymes, GST π is one of the more cysteine-rich GST isozymes, with four cysteine residues. And it's known that transition metals, such as ruthenium, had high binding affinity to sulfur groups [23]. So that's indeed a meaningful point for the study whether the inhibitory activity of the organometallic ruthenium fragment on GST can be mediated by coupling with EA. Here, we listed the coupling compounds of organometallic ruthenium–arene fragments regarding imidazole as the linker in Figure 2.

In the process of experiment, the effect of treating GST π with equimolar ratios of EA and ruthenium complexes was investigated and monitored their activity in 30 minutes. It could be observed that compounds 2, 3 and 4 reacted rapidly with GST π leading to the loss of enzymatic activity. Nevertheless, EA inactivated GST π more slowly, taking 12 min to reduce to 50% of its original rate for the residual activity. Besides, the efficacy of the three compounds to inhibit cell growth was evaluated against the cisplatin-sensitive A2780 and the cisplatin-resistant A2780cisR human ovarian carcinoma cell lines and the results were shown in Table 5. And RAPTA-C (Figure 3), a prototypical one of ruthenium (II)-arene compounds



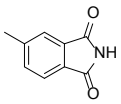
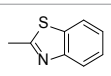
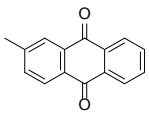
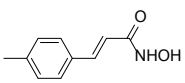
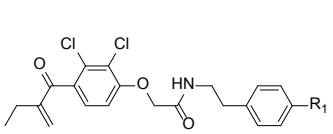
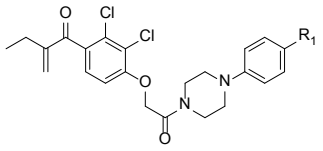
Code	R	EC_{50} (μM) for CLL inhibition	IC_{50} (μM) for Wnt inhibition
EA	–	9.9	32.7
12		2.5	4.88
13		1.5	4.86
32		2.1	2.97
40		2.6	1.81

Table 3: Structures and inhibition of Wnt signaling and CLL survival by EA derivatives.



series A



series B

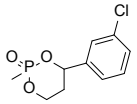
Code	R_1	IC_{50} (μM) for KB	IC_{50} (μM) for HL-60	IC_{50} (μM) for EPC	SI KB/HL-60
EA	–	11 ± 2	46 ± 12	>100	>9/>2
A5	H	0.6 ± 0.2	1.3 ± 0.3	4.2 ± 0.7	7/3
A10		0.4 ± 0.1	1.2 ± 0.1	0.7 ± 0.2	1.75/0.58
A14		0.5 ± 0.1	1.2 ± 0.2	3.4 ± 0.1	6.8/2.8
B11		0.17 ± 0.1	0.8 ± 0.1	2.9 ± 0.1	17/3.6
B15		0.2 ± 0.1	0.35 ± 0.05	1.25 ± 0.05	6.25/3.6
B17		0.4 ± 0.1	0.9 ± 0.1	7.8 ± 1.4	21/8.7

Table 4: Anti-proliferative activities of EA and its amide derivatives.

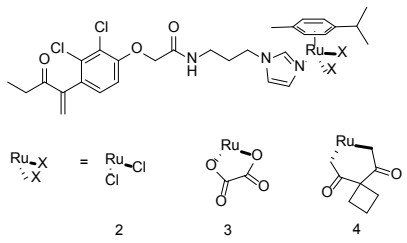


Figure 2: The structures of organometallic ruthenium–arene Ethacrynic acid–imidazole complexes.

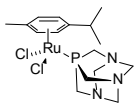


Figure 3: The structure of RAPTA-C.

Code	IC_{50} (μM) for A2780	IC_{50} (μM) for A2780cisR
EA	57.9 ± 1.1	54.5 ± 1.4
2	10.3 ± 2.1	12.9 ± 1.1
3	16.6 ± 1.4	9.4 ± 0.4
4	15.6 ± 0.9	9.8 ± 0.6
RAPTA-C	>200	>200

Table 5: Inhibition of viability of A2780 and A2780 cisR ovarian carcinoma cell lines with the treatment of three compounds.

was also investigated. Apparently, it exhibited nearly no effect to GST π even at high concentration. In contrary, the three compounds were highly active in inhibiting the growth of both ovarian cancer cell lines: they were 3-5 folds more efficient than EA on molar basis and 10 fold more efficient than the well-established RAPTA-C.

Anti-plasmodial activity

Plasmodium falciparum causes the most lethal form of malaria, which is a devastating disease that gives rise to vast morbidity and loss of life [24]. The need of new strategies to treat plasmodium falciparum deserves more attention due to the increase of drug resistance and lack of effective vaccine. The plasmodium falciparum cysteine proteases, also known as falcipains, participate in different erythrocytic cycle processes of the malaria parasite such as the hydrolysis of host haemoglobin, erythrocyte invasion and rupture. And falcipain-2 and falcipain-3 are two of the four biochemical characterizations which were essential haemoglobinases. In the early and late trophozoite stages of the parasite life, falcipain-2 is an important cysteine protease in the acidic food vacuole of the parasite [25]. The development of parasites is suspended when inhibiting falcipain-2 to block the hemoglobin hydrolysis, many studies *in vivo* have confirmed that [26]. Due to the biochemical similarity of falcipain-3 and falcipain-2, falcipain-3 can also play a significant role in hemoglobin hydrolysis and may be more potent than falcipain-2 [27]. So some compounds were synthesized targeting falcipain-2 and -3 which is a current focus for the research. Furthermore, two *P. falciparum* strains 3D7 and W2 were investigated. And in the work, non-peptidic cysteine protease inhibitors derived from the EA as a lead compound were evaluated for their inhibition to falcipain-2 and falcipain-3 [28]. The result was shown in Table 6.

By comparing a series of compounds in the report, compound 9, the ethyl ester of EA, was more effective than EA both for falcipain-2 and falcipain-3. Nearly all the amide derivatives expressed better inhibitory effect than EA itself. Compound 23, with a long acidic side chain which can exceedingly improve the activities displayed value of IC_{50} 18.8 μM against Plasmodia, was one of the most active inhibitors in the series. Apparently, compound 24, the biotinylateddichloro-substituted EA amide was the best one to inhibit falcipains and *P. falciparum* with value of IC_{50} 9.0 μM. It was remarkable that one with α, β-unsaturated system appeared to be in favor of activity against falcipains.

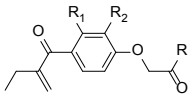
Activity against elevated intraocular pressure (IOP)

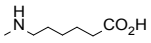
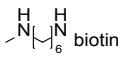
In glaucoma eye diseases, the elevated intraocular pressure (IOP) can lead to blindness, and is one of the risk factors for axonal injury in the optic nerve and retinal ganglion cell death. In order to relieve or control IOP, an amount of drugs have been applied such as epinephrine, pilocarpine, and β-adrenergic receptor antagonists [29], whereas some of them are not ideal. In general, anti-glaucoma drugs play a role in reducing intraocular pressure by inhibiting aqueous-humor production or an increase of conventional or unconventional outflow. In human eyes, the route of conventional outflow is considered as the main one [30]. It has been observed that EA, a sulfhydryl (SH) -reactive diuretic can enhance the aqueous effluent outflow facility both in the enucleated calf eyes and human eyes targeting trabecular meshwork. For example, intrauterine injection of up to 3 mM can produce IOP-lower effect but once the concentration of EA was higher than 3 mM, some side effects occurred. So there is a must for EA derivatives with better efficiency, ocular safety and corneal penetration. According to different protocol for optimization of EA, Atsushi et al. [31] reported some derivatives with various scaffolds, and their potency was evaluated based on these requirements (Table 7).

Among all synthesized compounds, the efficacy and cytotoxicity of EA disappeared after acryloyl group converting to an alkylacryloyl, alkyloyl or hydroxyacryloyl group. The introduction of aromatic groups at the 2-position of the acryloyl moiety enhanced cell efficacy and cytotoxicity due to its electron-withdrawing properties to increase the positive charge on the C-3 of the acryloyl moiety. The cytoskeleton regulatory function and the cytotoxicity of these compounds may be related to the reactivity of the acryloyl moiety of C-3. And there is no doubt that α, β-unsaturated carbonyl group was a key structure. SA9000 and SA9622 have proven to have about 100 folds greater potency than EA respectively; meanwhile, compound SA8999 displayed higher safety than EA. So it can be observed that the cytoskeleton regulatory function was not only related to the properties of the 2-position of the acryloyl moiety but also to α, β-unsaturated carbonyl group and aromatic ring. All in all, the structural modification of EA led to improved potency and safety especially compound SA9000, a most promising candidate for further investigation.

Antiviral activity

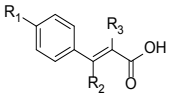
Coronavirus can cause infections in human, other mammals and birds. They are highly common and serious pathogens causing severe respiratory and gastrointestinal infections such as SARS-CoV and transmissible gastroenteritis virus (TGEV). Coronavirus is a positive strand RNA virus. In the expression and replication of genes, protease M^{pro}, a cysteine protease featuring a two-β-barrel fold [32] plays an

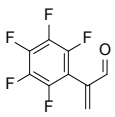


Code	R_1	R_2	R	IC_{50} (μM) for Falcipain-2	IC_{50} (μM) for Falcipain-3	IC_{50} (μM) for 3D7/W2
8 (EA)	Cl	Cl	OH	443 ± 17	Ni	Ni
9	Cl	Cl	OC_2H_5	60.6 ± 4.2	163 ± 5.6	Ni
23	Cl	Cl		57.1 ± 13	96.5 ± 0.6	18.8 ± 0.9
24	Cl	Cl		3.0 ± 1.1	11.9 ± 1.1	9.0 ± 0.4

Ni, no inhibition

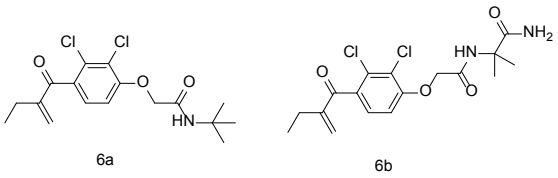
Table 6: Inhibitory effect of compounds on Falcipain-2, Falcipain-3 as well as antiplasmodial activity.



Code	R_1	R_2	R_3	Cell area EC_{50} (μM)	MTS assay LC_{50} (μM)	Safety Margin (LC_{50}/EC_{50})
EA	–	–	–	62	158	2.6
SA8999		H	H	41	260	6.3
SA9000		H	H	0.81	16	20
SA9622		H	H	0.66	3.6	5.5
SA9753		H	H	>30	>100	ND

ND, no determined

Table 7: Structures, Cytotoxicity and LC_{50}/EC_{50} Ratio (Safety Margin) for EA derivatives.



6a 6b

Code	TGEV M^{pro}	SARS-CoVM^{pro}
5a(EA)	+	+ (100 μM)
		+++ (100 μM)
6a	+++	++ (50 μM)
		++ (20 μM)
		+++ (100 μM)
6b	+++	++ (50 μM)
		++ (20 μM)

Table 8: Inhibition of 6a and 6b on TGEV M^{pro} and SARS-CoVM^{pro} in the HPLC-Based Assay.

important role in the proteolytic hydrolysis of polyproteins. So M^{pro} is recognised as an attractive target for new antiviral drugs. Because EA contains an electrophilic group that acts on the cysteine residue, it has developed as nonpeptide cysteine protease inhibitor. However, it was weakly active in the assay, and its derivatives exhibited better antiviral activity as Ulrich et al. reported [32].

As we can see from Table 8, the inhibitory effects of 6a and 6b were equipotent (>80% inhibition) between 20 μM and 100 μM in the HPLC-based assay on SARS-CoVM^{pro}. And in these derivatives, 6b was the most potent one. Except amide derivatives, other EA derivatives were also evaluated in HPLC assay (data not shown), and the results suggested that only the amide derivatives had an inhibitory effect on SARS-CoVM^{pro}.

Conclusion

Until now, the EA has been modified into various derivatives with diverse activities, and it is undoubted that α, β-unsaturated carbonyl group is an essential group of activity of EA derivatives. Based on the activities of EA derivatives containing α, β-unsaturated carbonyl group summarized here, we can conclude that α, β-unsaturated carbonyl unit has remarkable utility in the development of biologically active and therapeutically relevant compounds, for example, the development of irreversible inhibitors that form covalent bonds with cysteine or other nucleophilic residues. And in the design of irreversible inhibitors, α, β-unsaturated carbonyl group is just like an electrophilic "warheads", Michael addition reaction is the most widely used to achieve irreversible binding [33]. Some compounds have been marketed and used as anticancer agents. Such inhibitors have a potential advantage in terms of effectiveness and selectivity inhibition.

In general cytotoxic mechanism, the electrophilic α, β-unsaturated carbonyl group selectively forms adducts with reactive nucleophilic cysteine residues specifically associated with the active sites of proteins [24]. And chemical derivatization can lead to the loss of protein function, so the specialized cysteine residues are toxicologically relevant molecular targets. Although the inhibitive efficiency on tumor cell proliferation or cell growth or selected target responds well to a certain number of EA derivatives, some issues can't be neglected and further investigations should be deserved.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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