European Journal of Medicinal Chemistry 185 (2020) 111788

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Recent developments on (−)-colchicine derivatives: Synthesis and structure-activity relationship

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ARTICLE INFO

Article history:
Received 20 June 2019
Received in revised form
12 October 2019
Accepted 12 October 2019
Available online 18 October 2019

Keywords:
(−)-Colchicine
(−)-Colchicine derivatives
Structure-activity relationship

ABSTRACT

(−)-Colchicine, an anti-microtubulin polymerization agent, is a valuable medication and the drug of choice for gout, Behçet's disease and familial Mediterranean fever. It has a narrow therapeutic index due to its high toxicity towards normal cells. Nonetheless, numerous (−)-colchicine derivatives have been synthesized and studied for their structure-activity relationship and preferential toxicity. Different functional groups such as amides, thioamides, *N*-arylurea and 8,12-diene cyclic have been incorporated into (−)-colchicine, resulting in derivatives (with moieties) that include electron-withdrawing and electron-donating groups. This review article focuses on recent developments in the chemical synthesis of (−)-colchicine derivatives, the substituents used, the functional groups linked to the substituents, the moieties and biological studies. Moreover, the current classification of derivatives based on the (−)-colchicine rings, namely ring A, B, and C (−)-colchicine derivatives, is discussed. This work demonstrates and summarizes the significance of (−)-colchicine derivatives in the biological field, and discusses their promising therapeutics for the future.

Contents

1. Introduction

The use of (−)-colchicine as part of a crude extract for the crucial treatment of gout dates back almost 2000 years. (−)-Colchicine is

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https://doi.org/10.1016/j.ejmech.2019.111788
0223-5234/

an alkaloid originating from the *Colchicum autumnale* plant [1]. It was first separated in 1820 by Pelletier and Caventou, and later, it was extracted in its pure form in 1883. Since then, (−)-colchicine has been continuously used in the production of amphidiploids and polyploids in plant breeding [2].

(−)-Colchicine is used in the treatment of different diseases such as cardiovascular disease, recurrent pericarditis, fibrotic disorders and Behcet's disease. In addition, the use of (−)-colchicine for the treatment of arrhythmia and ischemic heart disease is currently being investigated through clinical trials [3,4]. However, it has been reported to cause kidney and liver failure in patients due to its high toxicity [5,6]. Nevertheless, (−)-colchicine has also been reported to have an anti-inflammatory effects, which inhibit microtubule polymerization, and obstruct the functioning of neutrophils [7].

The full chemical name (IUPAC) of (−)-colchicine is *N*-[(7S)-1,2,3,10-tetramethoxy-9-oxo-6,7-dihydro-5H-benzo [a]heptalen-7-yl]acetamide. Its structure consists of tricyclic-membered rings, namely, ring A, with a trimethoxyl group; ring B, as a seven-membered ring with a 7-acetamide group; and ring C, which is a tropolonic ring (Fig. 1) [8,9]. (−)-Colchicine is available commercially as a light-sensitive, pale yellow powder with a molecular weight of 399.43 g/mol [8].

However, (−)-colchicine is not suitable for the treatment of cancer due to its high toxicity towards normal cells [10]. It is, therefore, imperative to develop derivatives of (−)-colchicine with increased potency and reduced toxicity that can serve as anti-tumour/anticancer agents. Over the past decade, several derivatives of (−)-colchicine with reduced toxicity and potential activity have been synthesized as part of structure-activity relationship (SAR) studies. Therefore, this review article evaluated the modifications to the (−)-colchicine rings, the chemical synthesis involved in the preparation of the derivatives, the SAR analysis, and the respective biological applications.

2. Structure-activity relationship of (−)-colchicine

Brossi et al. reported on the phenyl-tropolone atropisomerism of colchicine (natural and unnatural). They studied the configurations of colchicine related to bovine brain tubulin binding using NMR analysis and found that the "biaryl" moiety of natural (−)-colchicine exists in the "*S*"-configuration, while for unnatural (+)-colchicine, the "biaryl" moiety is in the "*R*"- configuration. In addition, unlike the unnatural (+)-colchicine with the "*R*"-configuration, natural (−)-colchicine with the "*S*"-configuration can bind to tubulin. This specific binding takes place at the hyper-homocysteinemic (CbsT/T) receptor, the interface between the α- and β-tubulin due to the methoxy group, which serves as a crucial player for the binding to take place, as revealed by studies into (−)-colchicine binding, where (−)-colchicine analogues, such as (−)-isocolchicine, lack a methoxy group. It has been shown that the binding of (+)-colchicide to tubulin is ineffective in contrast to that of (−)-colchicine analogues with a methoxy group (Fig. 2). *In vitro* and *in vivo* studies of the treatment of mice infected with L1210 and P388 leukaemia using (−)-colchicine and its analogues showed that (−)-colchicine analogues, such as (−)-thiocolchicine, are able to bind strongly to tubulin owing to the $-SCH_3$ group and not the $-OCH_3$ group on the C (10) of its tropolonic ring (Fig. 2). On the contrary, (−)-pesudothiocolchicine, which holds an $-SCH_3$ group at C (9), and (−)-isothiocolchicine, which possesses a $-SCH_3$ group at C (11), has been shown to have no binding affinity to tubulin. Additionally, the demethylation of the methoxy group on ring A poses a lower toxicity compared to (−)-colchicine. Moreover, the toxicity decreases in the order of the demethylation of the methoxy group; 3-OCH_3>2-OCH_3>1-OCH_3. For the 7-acetamide group, however, any change to C (7) has no impact on the binding and, as such, a variety of groups on C (7) can have an effect on the activity and toxicity of the analogues. Moreover, any group present on C (4) of ring A, such as the aldehyde group, can affect the toxicity, and thus, increase the potency of the compounds. Additionally, the demethylation metabolites of (−)-colchicine have been found to reduce the exposure of animals to hepatotoxicity through the

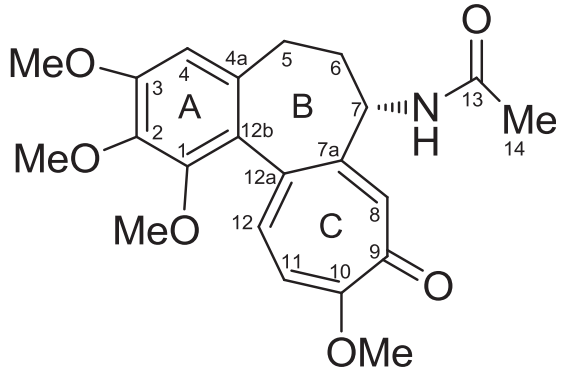


Fig. 1. (−)-Colchicine structure.

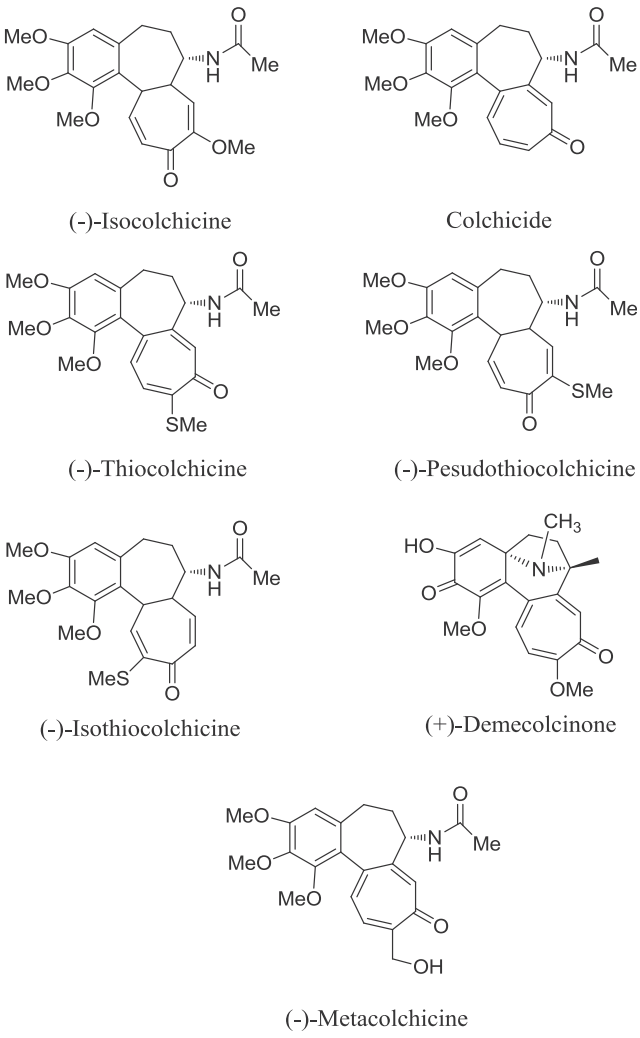


Fig. 2. Some structures of (−)-colchicine analogues.

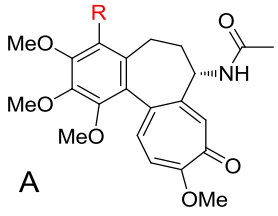
induction of the human gene, locus cytochrome P450 family 3 (CYP3A) compared to (−)-colchicine itself [11–14]. Newly-synthesized (+)-demecolcinone and (−)metacolchicine analogues of (−)-colchicine using the enantioselective method, have been proven to have a greater potency against A549, MDA-MB-231 and LoVo human cancer cell lines and a lower toxicity than (−)-colchicine (Fig. 2) [15,16].

3. (−)-Colchicine derivatives

The anti-tumour property of (−)-colchicine is derived from its ability to depolymerize microtubules through the formation of a tubulin-colchicine complex [17]. (−)-Colchicine can be a potential anti-tumour agent if its activity can be improved and, at the same time, its toxicity lowered. This section, therefore, discusses the possibilities of several (−)-colchicine derivatives that have been reported over the past decade [18,19].

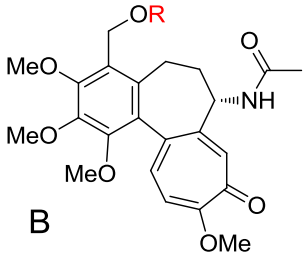
3.1. Ring A (−)-colchicine derivatives

Ring A (−)-colchicine is rich in electrons because of the three methoxy group substituents at C (1), C (2) and C (3), leaving C-4 as the only position that is available for substitution. Reports of substitutions at this position are not extensive because the reactions are difficult to perform since reagents with mild electrophilic properties are required. In addition, a 4-halo-(−)-colchicine synthesis on ring A was reported recently [20], whereby halogen substituents on (−)-colchicine C-4 (4-flouro-(−)-colchicine, 4-chloro-(−)-colchicine, 4-bromo-(−)-colchicine and 4-iodo-(−)-colchicine) were prepared for moderate to high yields by treating (−)-colchicine with NFSI, NCS, NBS and NIS, respectively, under acidic conditions so as to increase the potency and lower the toxicity of (−)-colchicine. Besides halo-(−)-colchicine derivatives, the preparation of several other (−)-colchicine C-4 substituents was also described, and the cytotoxic activity of the new derivatives



R	IC_{50} value (μM)		
	A549	HT29	HCT116
NO_2	0.073	0.031	0.038
OH	0.225	0.484	NT
CHO	1.007	0.128	0.054
COOH	NT	NT	NT
NH_2	2.185	1.550	NT
F	0.054	0.008	0.011
Cl	0.012	0.010	0.009
Br	0.014	0.006	0.007
I	0.032	0.006	0.007

NT: Not Tested



R	KB-31 IC_{50} (nM)	KB-8511 IC_{50} (nm)
H	260	> 1000
Tetrahydro-*2H*-pyran-(-2-*yl*)	> 1000	> 1000
-COMe	> 1000	> 1000

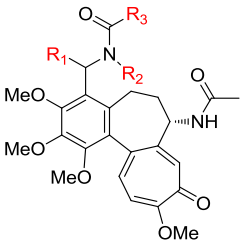
Fig. 3. A) *Yasobu* et al. C-4 (−)-colchicine derivatives. B) *Bensel* et al. C-4 (−)-colchicine derivatives.

was studied (Fig. 3A) [21]. However, among all these derivatives, only the 4-halo-(−)-colchicine derivatives showed strong activity against human lung adenocarcinoma A549, human colon adenocarcinoma HT29, and human colorectal carcinoma HCT116 cancer cell lines compared to other substituents. Additionally, the 4-halo-(−)-colchicine derivatives possesses a higher selectivity towards HT-29 compared to the other cell lines.

The substitution reaction on C-4 of (−)-colchicine can also take place with the possibility of electrophilic aromatic substitution *via* the reaction with aldehydes, acids or amide functional groups in an acidic medium [21]. An electrophilic substitution at C-4 of (−)-colchicine at room temperature with formaldehyde in H_2SO_4 produced the derivative, 4-hydroxymethyl-(−)-colchicine (Fig. 3B). Heating to 50 °C led to the dimerization of (−)-colchicine with a methylene bridge. Additionally, the use of AcOH resulted in the production of the derivative, 4-acetoxymethyl (−)-colchicine. Under the same conditions in AcOH, (−)-colchicine reacted with an amide to produce the derivative, 4-(acylamino)methyl (−)-colchicine, while it reacted with 4-(trifluoromethyl)benzaldehyde to produce a mixture of stereoisomers (Table 1). In terms of biological activity, only the 4-acetoxymethyl (−)-colchicine derivative showed antiproliferative activity towards HL-60 human epidermoid cancer cell lines.

(−)-Colchicine derivatives which are water-soluble have been synthesized (Table 2) [22]. Also, the treatment of 2-demethyl-(−)-colchicine with *N,N*-dimethylglycine and bis(2-oxo-3-oxazolidinyl)phosphinic chloride in a basic medium resulted in the formation of the derivative, 2-glcinate-(−)-colchicine, which can be converted into salt form *via* L-tartaric acid in an aqueous medium. Similarly, methylation reactions can take place at position 3 of 2,3-didemethyl-(−)-thiocolchicine *via* $TMSCHN_2$. However, the resulting derivatives have displayed little activity against human lung carcinoma (A549), human ovarian carcinoma (1A9), human epidermoid carcinoma of the nasopharynx (KB), and multi-drug-resistant KB subclone expressing P-glycoprotein (KB-V) cancer cell lines. However, 2-O-(*N,N*-Dimethylglycinyl)-2-demethyl-(−)-thiocolchicine and 2-O-(*N,N*-Dimethylglycinyl)-2-demethyl-(−)-thiocolchicine tartaric acid salt are more potent in tubulin polymerization than the analogues of (−)-colchicine (Table 3).

Table 1
Structure of position 4 of (−)-colchicine derivatives.



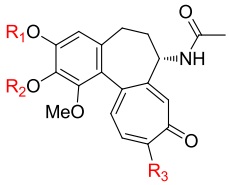
R_1	R_2	R_3
H	H	C_6H_5
H	H	Me
H	Me	Me
H	H	EtO
4-(F_3C)C_6H_4	H	Me

3.2. Ring B (−)-colchicine derivatives

Studies on the structure-activity relationships of (−)-colchicine analogues have demonstrated that ring B is not essential for tubulin binding and hence, antimitotic activity, but it modulates biophysical properties related to kinetics, association rates, activation energy and thermodynamics [7]. However, Ring B derivatives have been shown to enhance immunosuppressant activities using an allogenic mixed-lymphocyte reaction (MLR) assay. A novel immunosuppressant 7-amido-(−)-colchicine derivative was reportedly synthesized through a series of reactions, which included the initial deacetylation of acetamide on C-7 that resulted in the formation of 7-deacetyl-(−)-colchicine (Table 4). This was followed by an amidation reaction with an acyl chloride in a basic medium, with the subsequent substitution of the chloride with a nitrate. This, then, resulted in several 7-amido-(−)-colchicine derivatives. In addition, the effects of amide substituents were studied through the methylation of nitrogen on C-7 that was performed with iodomethane in tetahydrofuran (THF). The amide group might have experienced electronic and steric effects following the introduction of a phenyl ring, which had electrons withdrawing and donating substituents to different (−)-colchicine substituents. It has been shown that 7-amido-(−)-colchicine substituents with electron-donating substituents enhance immunosuppressive activity (Table 4). In contrast, (−)-colchicine derivatives with electron-withdrawing substituents are potent despite the electronic and steric effects [23].

Moreover, new colchicine derivatives (KR32160 and KR35345) have been reported as immunosuppressants [24]. T and B cells are lymphocyte cells in the immune system that are activated upon the entry of dangerous external antigens into the body or a

Table 2
Structures of positions 2 and 3 of Ring A (−)-colchicine derivatives.



Name	R1	R2	R3
2-Demthyl-(−)-colchicine	Me	H	OMe
2-Demthyl-(−)-thiocolchicine	Me	H	SMe
2-O-(*N,N*-Dimethylglycinyl)-2-demethyl-(−)-colchicine	Me	Me_2NCH_2CO-	OMe
2-O-(*N,N*-Dimethylglycinyl)-2-demethyl-(−)-thiocolchicine	Me	Me_2NCH_2CO-	SMe
2,3-Didemthyl-(−)-thiocolchicine	H	H	SMe
(−)-Thiocolchicine	Me	Me	SMe
3-O-(*N,N*-Dimethylglycinyl)-3-demethyl-(−)-thiocolchicine	Me_2NCH_2CO-	Me	SMe

Table 3
Ring A (−)-colchicine derivatives antitumor activity *in vitro*.

Compound	IC_{50} (μg/mL)/cell line			
	A549	1A9	KB	KB-V
2-Demthyl-(−)-colchicine	0.1	0.1	0.1	[24][a]
2-Demthyl-(−)-thiocolchicine	0.01	0.01	0.01	[56][a]
2-O-(*N*,*N*-Dimethylglycinyl)-2-demethyl-(−)-colchicine	0.44	0.04	0.09	[5][a]
2-O-(*N*,*N*-Dimethylglycinyl)-2-demethyl-(−)-thiocolchicine	0.05	0.05	0.02	[45][a]
2-O-(*N*,*N*-Dimethylglycinyl)-2-demethyl-(−)-colchicine tartaric acid salt	0.88	0.11	0.16	[4][a]
2-O-(*N*,*N*-Dimethylglycinyl)-2-demethyl-(−)-thiocolchicine tartaric acid salt	0.06	0.01	0.02	[28][a]

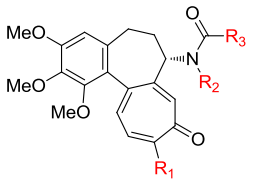
[a] % Inhibition of cell growth at 4 μg/mL.

transplanted organ, which is considered as a harmful antigen. The synthesized colchicine derivatives showed an ability to proliferate $CD4^+$ T-cells and regulate $CD8^+$ T-cells in rats through the inhibition of tubulin polymerization, the arrest of generation 2 (G2) in cell cycles, the reduced polymerization of mitochondria, and apoptosis (Fig. 4). Additionally, these derivatives inhibit the activation of T-cells by obstructing the pathway of STAT3 signalling and IL-2R activation compared to colchicine and traditional immunosuppressant drugs such as cyclosporine A (CsA), which have side effects. Accordingly, the synthesized derivatives have the potential to be considered as novel immunosuppressants.

The conversion of (−)-colchicine to a β-amino alcohol derivative can be performed following treatment with lithium perchlorate and propylene oxide in acetonitrile [19]. The isomers of C-7 amide carbonyl of (−)-colchicine and (−)-isocolchicine derivatives are the oxidized products of the alcohol derivatives using the Swern oxidation reaction. In addition, the effect of the replacement of the amide group with a thioamide group on the (−)-colchicine activity was investigated through the reaction with a thioacetylating reagent, thiobenzimidazolone, with a mixture of deacetyl-(−)-colchicine and deacetyl-(−)-isocolchicine isomers in acetonitrile. The resultant derivatives of these isomers were obtained in high yields. The 7-alkylamine deacetyl-(−)-colchicine and deacetyl-(−)-isocolchicine isomer derivatives were also prepared for the additional investigation of the effect of the amide carbonyl group on the bioactivities of (−)-colchicine (Fig. 4). Strong anti-microtubule and cytotoxicity effects against human prostate cancer (PC3) cell lines were evident in all the synthesized derivatives (Fig. 5).

In line with this, the investigation into a series of nitric oxide (NO)-releasing (−)-colchicine derivatives for a more potent antitumor activity was reported. These derivatives were prepared by coupling nitrates with *N*-methyl (−)-colchiceinamide (Fig. 6) [25]. Nitric oxide is produced in the body by the enzyme, NO synthase, and is involved in physiological roles such as neurotransmission and the immune system. It has been suggested that NO conjugates of cytotoxic agents display selective cytotoxicity for potential antitumour therapy. The SAR study of the NO conjugated colchicines that had been produced showed improved activity compared to

Table 4
Ring B (−)-colchicine derivatives.



R_1	R_2	R_3	IC_{50} (μM)
OMe	H	$-CH_2CH_2CH_2Cl$	4.70
		$-C_6H_4$(*m*-MeCl)	6.30
		$-C_6H_4$(*p*-MeCl)	0.32
OMe	H	$-CH_2CH_2CH_2ONO_2$	0.01
		$-C_6H_4$(*m*-$MeONO_2$)	0.25
		$-C_6H_4$(*p*-$MeONO_2$)	0.07
OMe	CH_3	$-CH_2CH_2CH_2ONO_2$	3.50
		$-C_6H_4$(*m*-$MeONO_2$)	>100
		$-C_6H_4$(*p*-$MeONO_2$)	>100
NMe	H	$-CH_2CH_2CH_2ONO_2$	6.60
		$-C_6H_4$(*m*-$MeONO_2$)	10.00
		$-C_6H_4$(*p*-$MeONO_2$)	2.50
SMe	H	$-CH_2CH_2CH_2ONO_2$	0.21
		$-C_6H_4$(*m*-$MeONO_2$)	0.07
		$-C_6H_4$(*p*-$MeONO_2$)	0.02

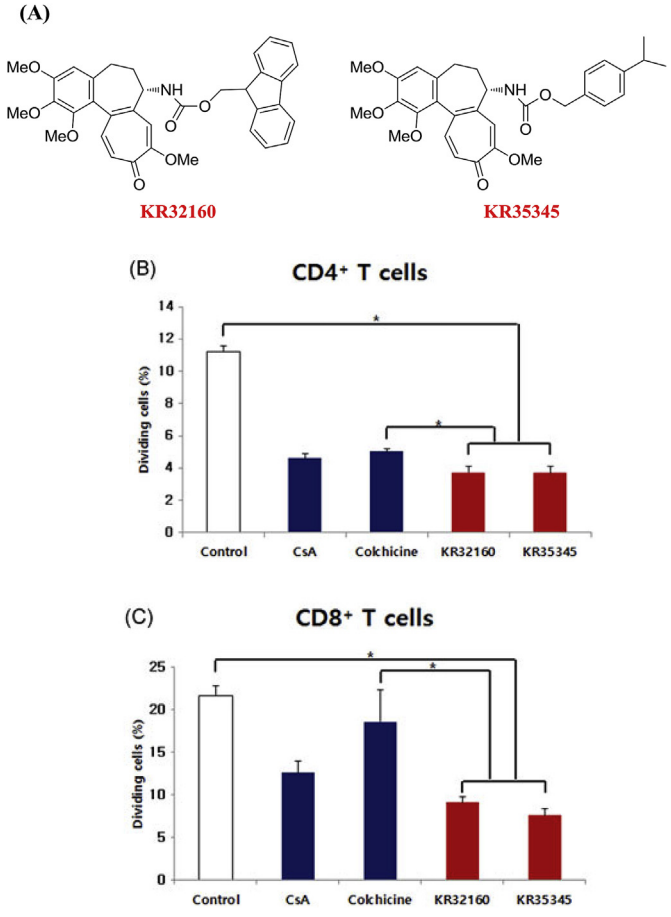


Fig. 4. (A) Structures of (−)-colchicine derivatives. *In vitro* suppressive effects on $CD4^+$ (B) and $CD8^+$ (C) T-cells proliferation by (−)-colchicine, CsA, KR32160 and KR35345 (Taxol is the Control). (Reproduced with permission from Ref. [24] © John Wiley & Sons 2019).

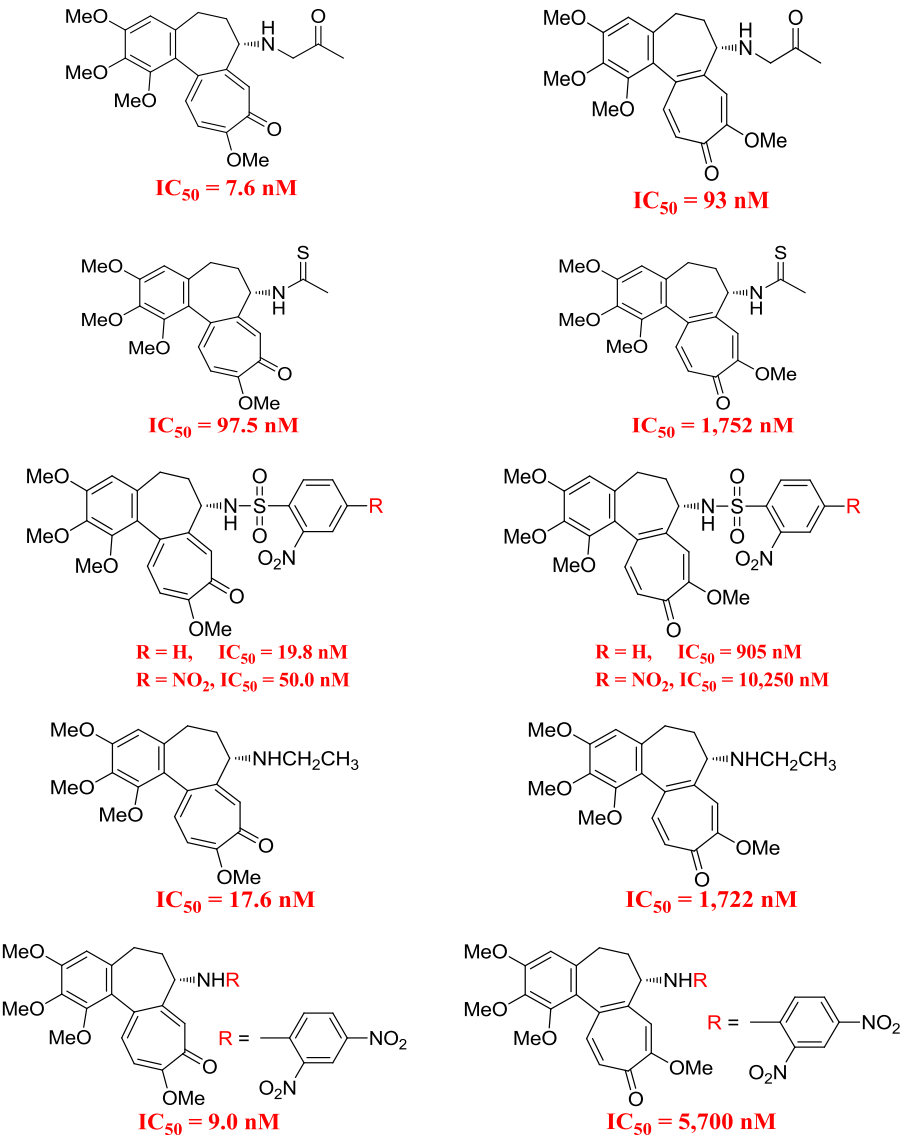


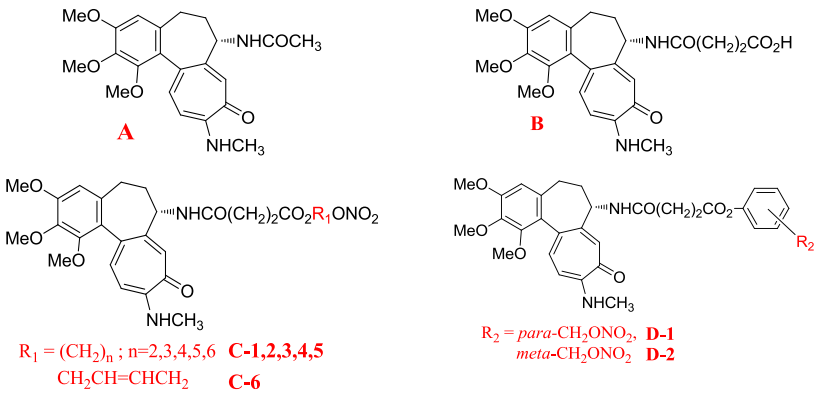
Fig. 5. Ring B (−)-colchicine and (−)-isocolchicine derivatives with IC_{50} (nM) cytotoxicity values against PC3 cell lines.

colchicine (Fig. 6). The cytotoxic activity of the *N*-methyl (−)-colchiceinamide derivatives with 1,3,4-thiadiazole moieties against various cancer cell lines such as human breast carcinoma (MCF-7), human lung cancer (A549), human ovary cancer (A2780) and human hepatoma (BEL7402) cell lines was reported. The SAR study discovered that the position of the substituents on the benzene ring of the benzene alkyl group plays an important role in the activity, where the *para*-substituted derivatives showed a higher activity than the *meta*-substituted derivatives. In addition, electron-withdrawing substituent derivatives showed a better activity compared to the ones with electron-donating groups [26].

Nicolaus N. et al. reported on the preparation of a library of triazole (−)-colchicine derivatives involving bioactive C-7 derivatives of (−)-colchicine using 7-azo-7-deacetyl (−)-colchicine as a precursor and Huisgen 1,3-dipolar cycloaddition. This was carried out using click chemistry in the presence of Cu(I) as the catalyst under microwave irradiation. Almost all the (−)-colchicine derivatives inhibited tubulin polymerization, and some of the derivatives targeted the (−)-colchicine binding site in the tubulin competition. The (−)-colchicine rearrangement under reflux in a basic medium produced all colchicine-type derivatives that were less active than colchicinoids [27].

Another biological study involving a series of 4-chloro-(−)-colchicine derivatives with *N*-alkanoyl, *N*-aroyl and hydroxyalkyl groups showed a reduction in the activity of those (−)-colchicine derivatives that possessed longer alkyl chains of amides. However, the potent cytotoxicity was maintained in the cycliccarboxiamide derivative. Notwithstanding the substituent positions, the derivatives of fluorophenyl amide and benzylamide showed good activity. It was shown that methoxy substituents on the benzene ring at the *meta* and *para*-positions displayed higher activity than the *ortho*-position substitution. In contrast to that, substitutions at the *meta*-position of the nitro substituents posed the highest activity compared to substitutions at the *ortho* and *para*-positions, possibly due to the hydrogen bonding interaction of the *meta*-group at the two positions of the tubulin binding site. Two α-hydroxy alkyl amide derivatives were shown to be potent *in vivo* for anti-tumour activity [28].

Recently, new designs of (−)-colchicine derivatives have been characterised by their dual potency, whereby their anti-tumour activity is coupled with the reduction of P-glycoprotein (P-gp) induction [29]. P-gp induction increases multidrug resistance (MDR),



Compounds	IC$_{50}$ (μM)/cell line			
	A2780	A549	BEL7402	MCF7
A	NT	NT	NT	NT
B	NT	NT	NT	NT
C-1	0.104	0.106	0.202	0.103
C-2	0.099	0.088	0.085	0.135
C-3	0.010	0.012	0.013	0.008
C-4	0.096	0.086	0.085	0.100
C-5	0.109	0.205	0.086	0.095
C-6	0.205	0.135	0.120	0.202
E-1	0.027	0.038	0.029	0.036
E-2	0.036	0.049	0.037	0.0058

NT: Not Tested

Fig. 6. Ring B (−)-colchicien derivatives with IC$_{50}$ value for A2780, A549, BEL7402 and MCF7 cell lines.

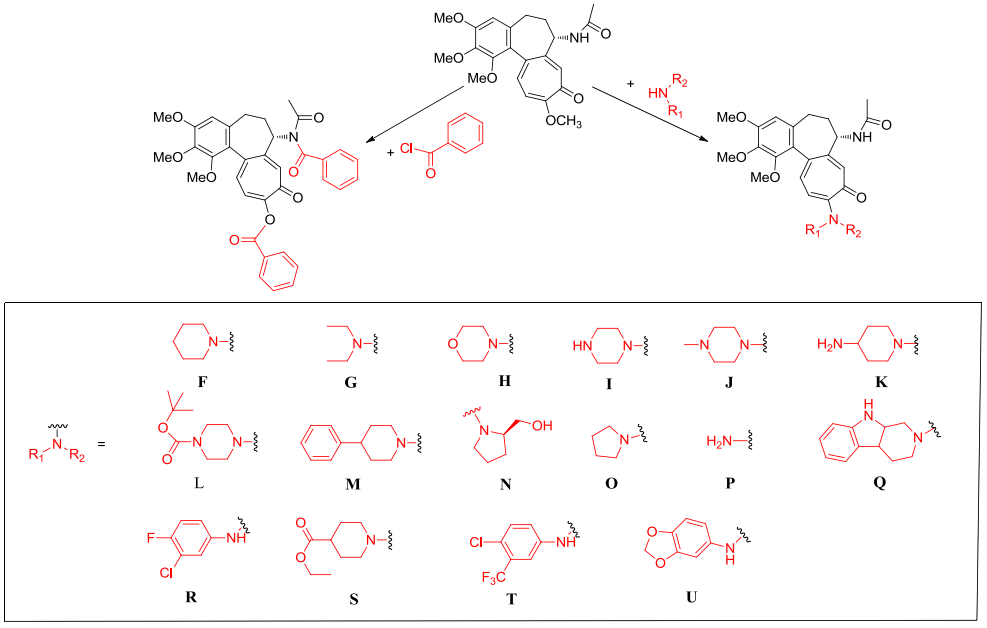


Fig. 7. Structure of *N*-benzylated (−)-colchicine derivatives.

thereby inhibiting the effectiveness of chemotherapy. This issue can be surmounted by making *N*-benzylated colchicine derivatives, which involve substituting the NH-acetyl side chain and replacing 10-OCH$_3$ with a series of *N*-linked functionalities (Fig. 7). This substitution has shown good anti-tumour activity in human colorectal carcinoma (HCT-116) (Fig. 8) and human colon carcinoma (Colo-205) cell lines, whilst displaying a reduction in P-gp induction (Table 5).

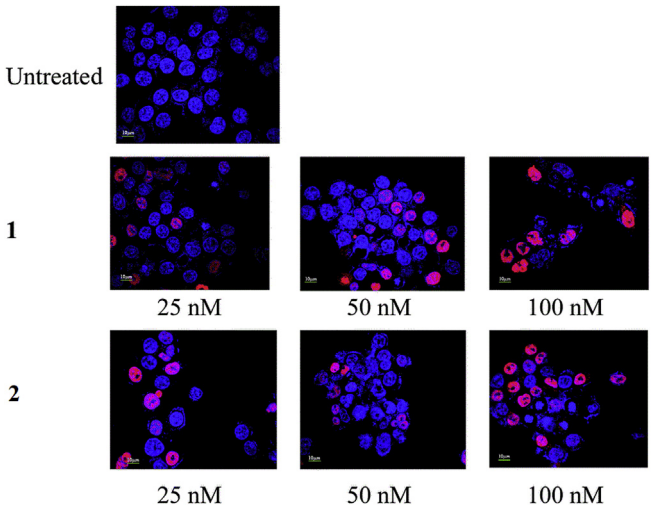


Fig. 8. Effect of colchicine (1) and [3-(trifluoromethyl)-4-chloro-phenylamino]-10-(−)-colchicine (2) on P-gp expression in HCT-116 cell lines (Reproduced with permission from Ref. [29] © Royal Society of Chemistry 2019).

Recently, a new library of *N*,*N*′-disubstituted urea (−)-colchicine derivatives with an aryl group has been synthesized *via* substitution reactions using aniline with electron-donating and electron-withdrawing groups. These *N*,*N*′-disubstituted urea (−)-colchicine derivatives have shown good cytotoxicity that inhibits oncogenes related to telomerase activation and the VEGF/VEGFR-2 autocrine process. Moreover, the presence of an *N*-arylurea group in (−)-colchicine enhanced its anti-tumour activity compared to an acetyl group. It was observed that *N*-arylurea substituents with electron-withdrawing groups exhibited higher potency than those with electron-donating groups (Fig. 9) [30].

3.3. Ring C (−)-colchicine derivatives

The tropolone moiety representing ring C (−)-colchicine is a structural feature that is crucial for high-affinity binding to tubulin [7]. Ring C derivatives are amenable to prodrug conjugations, and are synthesized with amines and heterocyclic amine substituents at the 10-OCH_3 position of colchicine through an alkylation reaction involving bromoalkylnitrile with cyclic secondary amines. This is followed by a reduction reaction with $LiAlH_4$, resulting in racemic and enantiomeric amines. Through the reaction of (−)-colchicine with prepared substituents, high yields of 10-amino-(−)-colchicine can be obtained (Fig. 10). A biological study showed a high-affinity binding to microtubule polymerization, and the inhibition of DLD-1 colorectal cancer cell lines by amino-(−)-colchicine derivatives owing to reduced entropy [31].

Huczyński et al. synthesized 10-amine (−)-colchicine derivatives using different amine substituents following a simple reflux reaction in acetonitrile. Different structures of amine substituents were involved such as saturated and unsaturated alkyl amines and alkyl amines containing oxygen atoms, an aromatic ring and morpholine rings (Fig. 11). Good yields of 10-amine-(−)-colchicine derivatives with a strong inhibition towards various human cancer cell lines (HL-60, HL-60/vinc, LoVo, LoVo/DX and BALAB/3T3) were obtained. The SAR study revealed that the small amine substituent-colchicine derivatives had potent anticancer activities compared to the larger amine substituents (Fig. 11) [18]. Subsequently, the antiproliferative activity of another series of C10-(−)-colchicine derivatives with an *N*,*N*′-disubstituted aryl group was studied using computational methods [32]. The calculated results of the antimitotic activity from the molecular docking of these derivatives to β-tubulin showed good agreement with the experimental results (Fig. 12). From Fig. 13, it can be seen that the interactions of (−)-colchicine (compound 1) with Glu 245 and Leu 245 of tubulin were the most important interactions, while the colchicine derivatives had other interaction positions, as shown in Table 6. Accordingly, the *N*,*N*′-disubstituted aryl group showed the effects of steric hindrance posed by the bulky moiety of the substituents, which hampered tubulin binding (as the bonding energy was higher than that of colchicine itself), hence, lowering the antiproliferative activity (Fig. 13). Additionally, the C10- amino acid derivatives of (−)-colchicine were prepared following the substitution reaction of the 10-OCH_3 group on ring C with the consistent amines (Fig. 14) [33].

New (−)-colchicine prodrugs have been synthesized as antiviral agents [34]. These prodrugs contain an ester link substituent, where cleavage occurs by the human enzyme, carboxylesterase-1 (hCE1), which is over-expressed in the immune cells of endothelial, hepatocyte cell and macrophages-monocytic cells. Upon cleavage of the (−)-colchicine prodrugs, the active drug is formed with a high polarity, low permeability of the cell membrane and a shift into the target site for accumulation. Huh-7 cells have shown a lower toxicity and higher activity at the micromolar level for antiviral activity against dengue (DENV) and the Zika (ZiKV) virus.

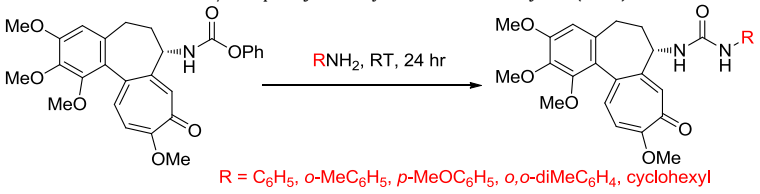
(−)-Colchicine analogues such as (−)-thiocolchicine, in which the $-OCH_3$ of C-10 is replaced with $-SCH_3$, have been shown to have a stronger inhibition to tubulin polymerization, [^{3}H](−)-colchicine binding and Burkitt lymphoma cell growth than (+)-thiocolchicine [35]. In another study, several synthesized (−)-thiocolchicine derivatives displayed reduced cytotoxicity towards cancer cell lines (A549, SK-OV-3, SK-MEL-2, HCT-15 and MCF-7) (Table 7) [36]. (−)-Thiocolchicine derivatives have also been produced *via* substitution reactions with alkyl nitrates and benzyl nitrates [23].

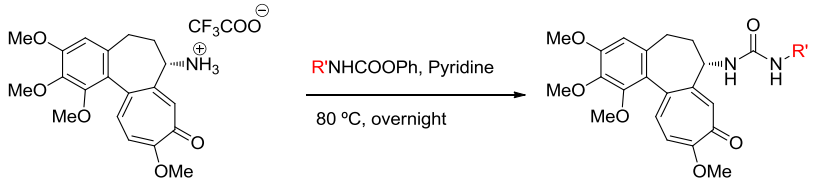
A new method of synthesizing 10-(−)-thiocolchicine with alkyl substituents involves the use of excess alkylthiolate salts in water under mild conditions. This method has a short reaction time and produces a high yield (Fig. 15) [37]. High cytotoxic activity has been observed against human cancer cell lines, namely the human DLD-1, LoVo, MCF-7 and MDA-MB-231 cell lines. SAR studies have shown that cytotoxicity is dependent on the length of the alkylthio chain, where the cytotoxicity increases as the chain length decreases.

Table 5
Cytotoxicity and P-gp induction activities of (−)-colchicine and *N*-benzylated (−)-colchicine derivatives.

(−)-Colchicine its derivatives[a]	P-gp induction activity[b]	IC_{50} (μM)/cell line	
		HCT-116	Colo-205
(−)-Colchicine	62.91	0.05	0.032
F	119.01	3.00	1.80
G	95.38	0.80	0.43
H	95.97	5.00	1.20
I	95.52	>10.0	8.00
J	102.82	3.00	1.00
K	102.04	10.00	5.00
L	90.94	4.00	3.00
M	101.03	1.00	0.80
N	86.53	10.00	8.00
O	107.12	0.30	0.24
P	107.41	0.15	0.12
Q	119.70	3.00	0.80
R	90.05	0.70	0.50
S	95.49	>10.0	8.00
T	90.29	0.04	0.03
U	102.66	4.00	3.00

[a] The derivatives from Fig. 6.
[b] % intracellular accumulation of Rh123/protein inside LS-180 cells at 100 nM. The increase in % intracellular accumulation of Rh123 indicates induction of P-gp.





R	IC50 (nM)/cell line			
	HT-29	MCF-7	HeLa	HEK-293
C_6H_5	11	12	12	10
o-MeC_6H_5	26	119	32	44
o-$MeOC_6H_5$	1200	1200	1400	1200
o,o-$diMeC_6H_4$	130	240	242	218
cyclohexyl	37	89	87	98
R'				
o-$CF_3C_6H_5$	15	25	18	19
p-FC_6H_5	5	10	10	13
o,o-$diClC_6H_4$	40	13	22	42
o-Cl-*p*-FC_6H_4	1.75	1.20	5	1.7
1-naphthyl	11.1	17	16	9

Fig. 9. Some structures of N-arylurea (−)-colchicine derivatives with cytotoxicity values against HT-29, MCF-7, HeLa and HEK-293 cell lines.

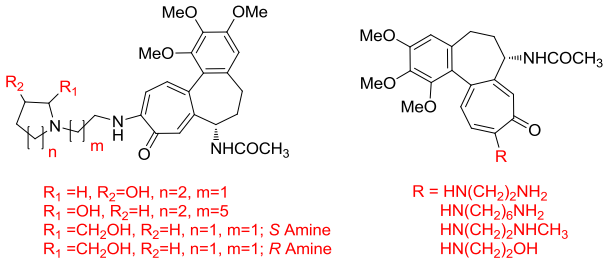


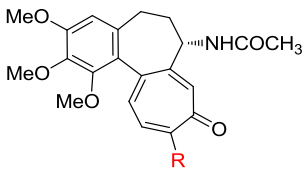
Fig. 10. Ring C amino-(−)-colchicine derivatives.

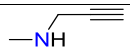
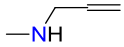
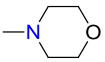
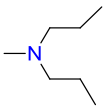
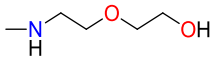
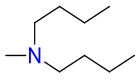
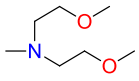
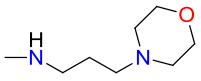
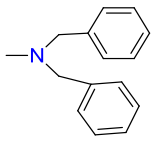
In addition, the synthesis of ring C (−)-colchicine derivatives with nitroso and iminonitroso agents was carried out using Diels-Alder cycloaddition reactions, which are highly stereo and regio-selective [38]. This was followed by the 8, 12-diene moiety of (−)-colchicine (Fig. 16), in which most derivatives have been shown to be active against the PC-3 and MCF-7 cancer cell lines with the ability to inhibit the (−)-colchicine-tubulin binding *in vitro* (Table 8). These derivatives, therefore, have the potential to be prodrugs following the retro Diels-Alder reactions.

4. Clinical applications of (−)-colchicine and its derivatives

As mentioned, (−)-colchicine is used in the treatment of acute gout, familial Mediterranean fever (FMF) and Behcet's disease. The Food and Drug Administration (FDA) of the United States first approved (−)-colchicine in 2009 under the unapproved drugs initiative once its medicinal properties became known [39]. Thus, many studies have been piloted by the use of (−)-colchicine for further applications including liver and heart diseases, and the treatment of tumours [40–42]. Randomized controlled trials (RCTs) have been used to evaluate (−)-colchicine for a wide spectrum of cardiac diseases [43,44] to study how (−)-colchicine can benefit some cardiac disease patients. The studies showed that there was a reduction in cardiovascular diseases, and (−)-colchicine was able to reduce the rate of post-pericardiotomy syndrome, periprocedural atrial fibrillation and recurrent pericarditis [45]. In addition, (−)-colchicine plays an important role in the prevention of cardiovascular disease by reducing the risk of the formation of cholesterol crystals, while preventing concomitant inflammatory responses through the disruption of neutrophil functions [46].

Cancer cells are more vulnerable than normal cells to extermination by (−)-colchicine because of the faster rate of mitosis. Hence, many researchers are fascinated by the use of (−)-colchicine and its analogues as anti-tumour drugs due to their anti-microtubule activity. Moreover, (−)-colchicine has a low therapeutic index with a restrained therapeutic value against cancer. Along with the destabilization of microtubuline, the toxicity of (−)-colchicine can cause anaemia, neutropenia, bone marrow damage, and gastrointestinal upset [47–49]. The toxicity of (−)-colchicine limits its clinical applications, while the oral administration of (−)-colchicine is safe when used properly. The



R	IC50 (μM)/cell line				
	HL-60	HL-60/vinc	LoVo	LoVo/DX	BALB/3T3
	0.018	0.95	0.21	1.77	0.16
	0.054	0.75	0.11	1.20	0.16
	0.66	80.05	7.46	71.56	14.08
	6.20	117.50	25.03	125.20	14.64
	5.76	54.24	10.09	48.87	14.18
	4.95	uv	150.80	uv	120.90
	4.29	24.29	8.37	7.04	53.74
	0.009	0.86	0.20	1.52	0.16
	47.60	uv	uv	Uv	133.00
	5.98	12.04	14.53	7.20	40.88
(-)-Colchicine	0.008	1.00	0.12	0.98	0.18
Doxorubicin	0.044	0.88	0.15	5.46	0.18
Cisplatin	1.00	6.87	3.70	5.20	5.30

uv - Un available in range of concentration used.

Fig. 11. Structures of (−)-colchicine and ring C amino (−)-colchicine derivatives with cytotoxicity values against HL-60, HL-60/vinc, LoVo, LoVo/DX and BALB/3T3 cell lines.

probability of using (−)-colchicine concentrations has been clinically studied for the treatment of gastric cancer. The study found that high clinically-acceptable concentrations of (−)-colchicine can be used for the treatment of gastric cancer [50,51]. The use of (−)-colchicine for the treatment of cancer is possible in clinically-tolerable doses in combination with a self-inhibitor. In addition, some (−)-colchicine derivatives possess anticancer properties [52]. Recently, a study on gout patients showed that (−)-colchicine is significantly capable of reducing the chances of the incidence of cancer in male patients with gout [53,54]. Additionally, (−)-colchicine and analogues can be used in inactive forms, such as prodrugs and codrugs, which can be activated by enzymes or physiological conditions, in the treatment of cancer [13]. Nevertheless, the use of (−)-colchicine in the clinical treatment of cancer is still being contended.

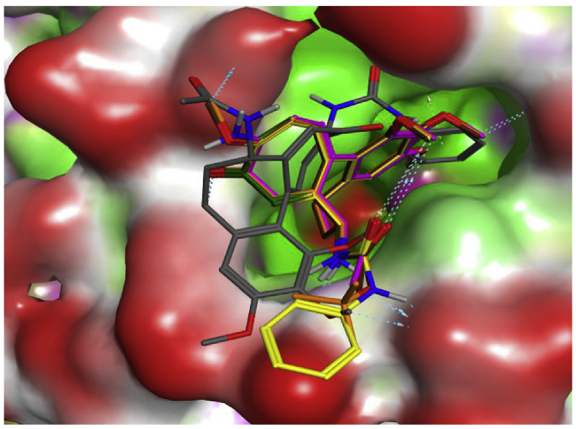


Fig. 12. (−)-Colchicine and *N,N′*-disubstituted aryl colchicine derivatives docked to the binding site in tubulin (Reproduced with permission from Ref. [32] © Elsevier 2016).

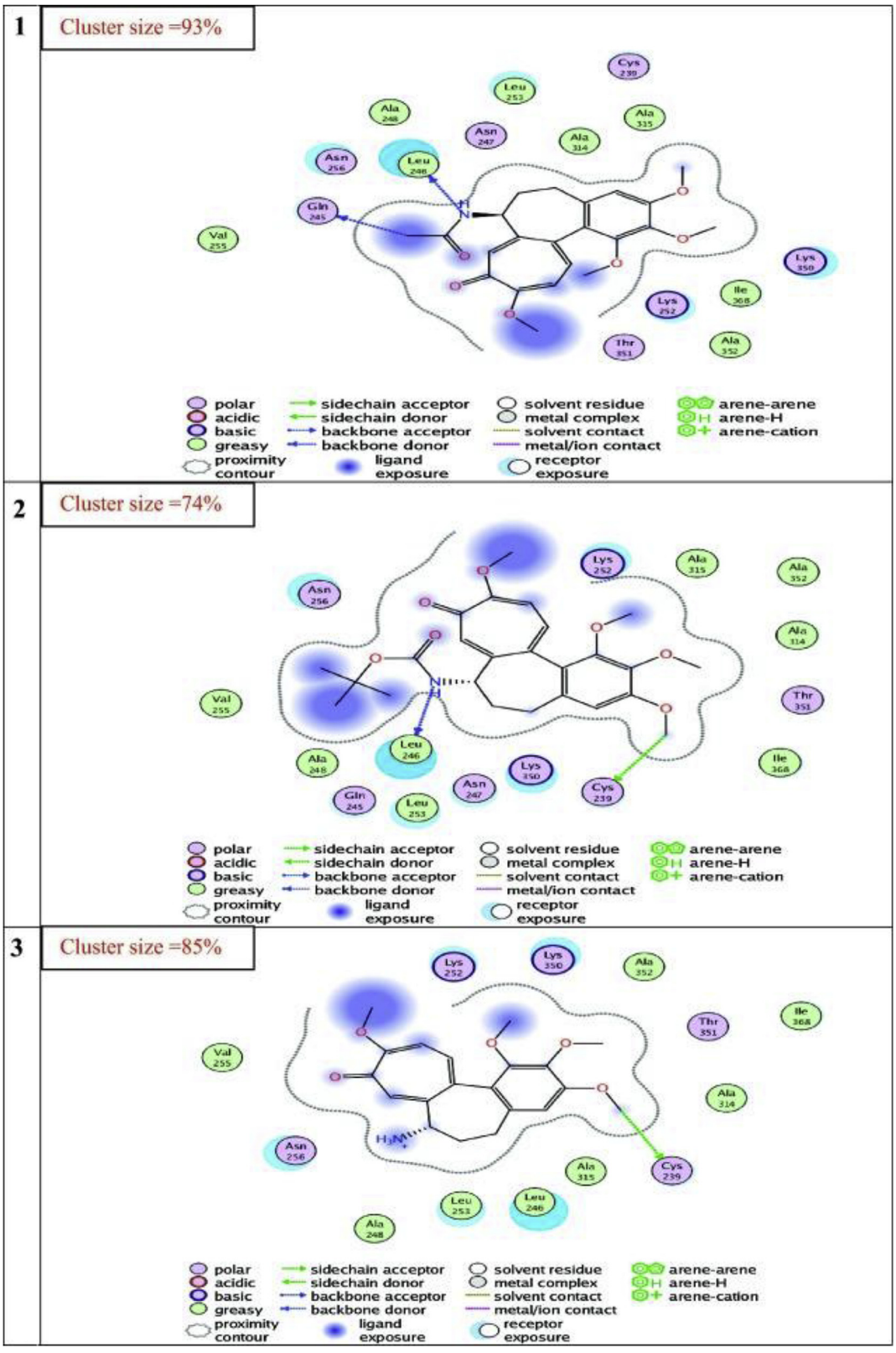


Fig. 13. Most dominant poses interaction diagrams of *N*,*N*′-disubstituted aryl (−)-colchicine derivatives to the binding site in tubulin (Reproduced with permission from Ref. [32] © Elsevier 2016).

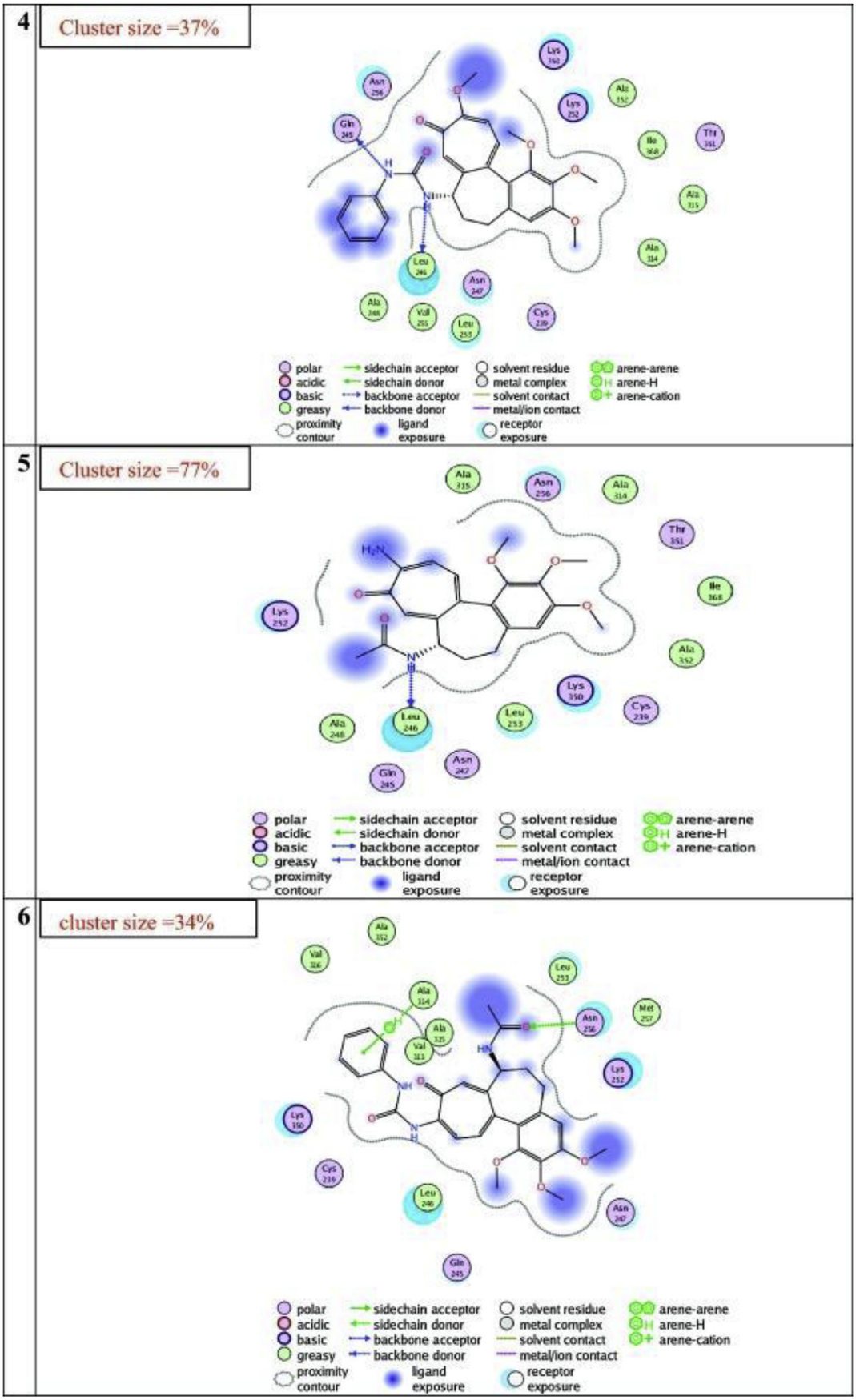


Fig. 13. (*continued*).

Table 6
(−)-Colchicine and (−)-colchicine derivatives tubulin binding locations and their bonding energies.

Compound[a]	Tubulin binding locations and positions	Bonding energy (kcal/mol)
(−)-Colchicine (1)	Leu 245 (backbone donor) and Glu 245 (backbine donor)	−6.45
2	Cys 239 (sidechain donor) and Leu 246 (backbone donor)	−6.52
3	Cys 239 (sidechain donor)	−6.23
4	Gln 245 (backbone donor) and Leu 246 (backbone donor)	−7.50
5	Leu 246 (backbone donor)	−6.17
6	Ala 314 (arene H) and Asn 256 (sidechain acceptor)	−8.5

[a] Based on compound number in Fig. 13.

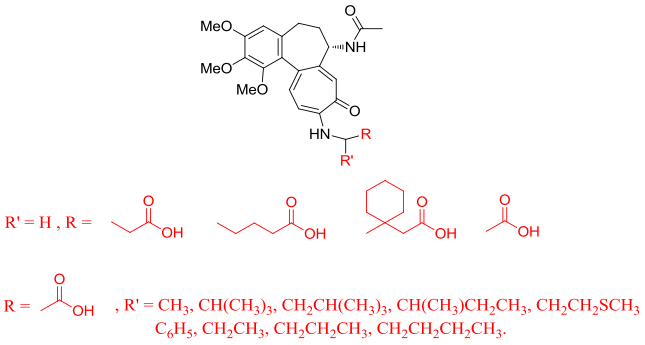


Fig. 14. Structures of 10-amino acid (−)-colchicine derivatives.

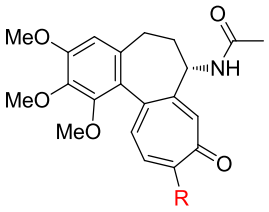
5. Future perspectives

Advancements have been made in the development of modified (−)-colchicine derivatives, particularly involving modifications on rings A and C of (−)-colchicine. Various studies have shown that synthesized (−)-colchicine derivatives that have been biologically evaluated in terms of their anti-tumour properties, have a high potential for clinical use as anticancer agents. The design of novel agents of (−)-colchicine derivatives using substituents should take into account the characteristics of the derivatives, namely their ability to be target-specific, their high affinity for tubulin binding, and their ability to inhibit microtubule polymerization. In addition, the derivatives should increase the efficacy of chemotherapy while reducing multidrug resistance as well as potential side effects.

Table 7
Cytotoxic activity for several (−)-thiocolchicine derivatives against cell lines.

Compounds	IC_{50} (nM)/cell line				
	A549	SK-OV-3	SK-MEL-2	HCT-15	MCF-7
N-[(4S)-Isopropenylcychlohexene-1-carboxyl]-(−)-deacetyl-10-(−)-thiocolchicine	7.50	17.20	17.90	8.10	5.20
Bis(N-deacetamidocolchicinyl)-7,12-bis(1-hydroxyethyl)-3,8,13,17- tetramethyl-21H,23H-porphine-2,18-dipropanamide	1684	2863	2837	4838	3215
N-(Pteroyl-5-L-glutamyl)-(−)-deacetyl-10-(−)-thiocolchicine	4955	NT[a]	NT	1162	697
N-[{2-(2,6-dichloroanilino)phenyl}acetyl] -(−)-deacetyl-10-(−)-thiocolchicine	520	1500	1050	306	296
N-(cis-4,7,10,13,16,19-Docosahexaenoyl)-(−)-deacetyl-10-(−)-thiocolchicine	917	2630	2005	392	494
N-[d-(+)-Gluconyl]-(−)-deacetyl-10-(−)-thiocolchicine	14.20	29.80	12.30	18.70	7.80
N-(trans-4-Hydroxy-3-methoxycinnamyl)-(−)-deacetyl-10-(−)-thiocolchicine	5.8	24.8	16.6	10.8	5.60
N-[(2R,3S,4R)-2-{(tert-Butoxycarbonyl) amino}-3,4-O-isopropylideneoctadecanoyl]-(−)-deacetyl-10-(−)-thiocolchicine	228	676	130	204	303
(−)-Colchicine[b]	21.00	18.00	6.00	9.00	> 300
Doxorubicin[b]	14.7	34.2	11.7	16.4	41.9

[a] NT-Not Tested.
[b] Reference materials.



R	IC_{50} (nM)/cell line			
	DLD-1	LoVo	MCF-7	MDA MB-231
SCH_3	4.2	13.6	55.5	81.2
SCH_2CH_3	51.2	19.5	56.1	148.3
$SCH_2CH_2CH_3$	71.8	56.1	764.4	704.2
$SCH(CH_3)_2$	177.3	149.6	564.2	1103.8
$SCH_2CH_2CH_2CH_3$	316.7	438.0	873.6	1773.3
(-)-Colchicine	43.0	118.8	41.3	25.3
Doxorubicin	510.6	520.2	1210.1	935.5

Fig. 15. Structures of 10-alkyl (−)-thiocolchicine with cytotoxicity values against DLD-1, LoVo, MCF-7 and MDA MB-231 cell lines.

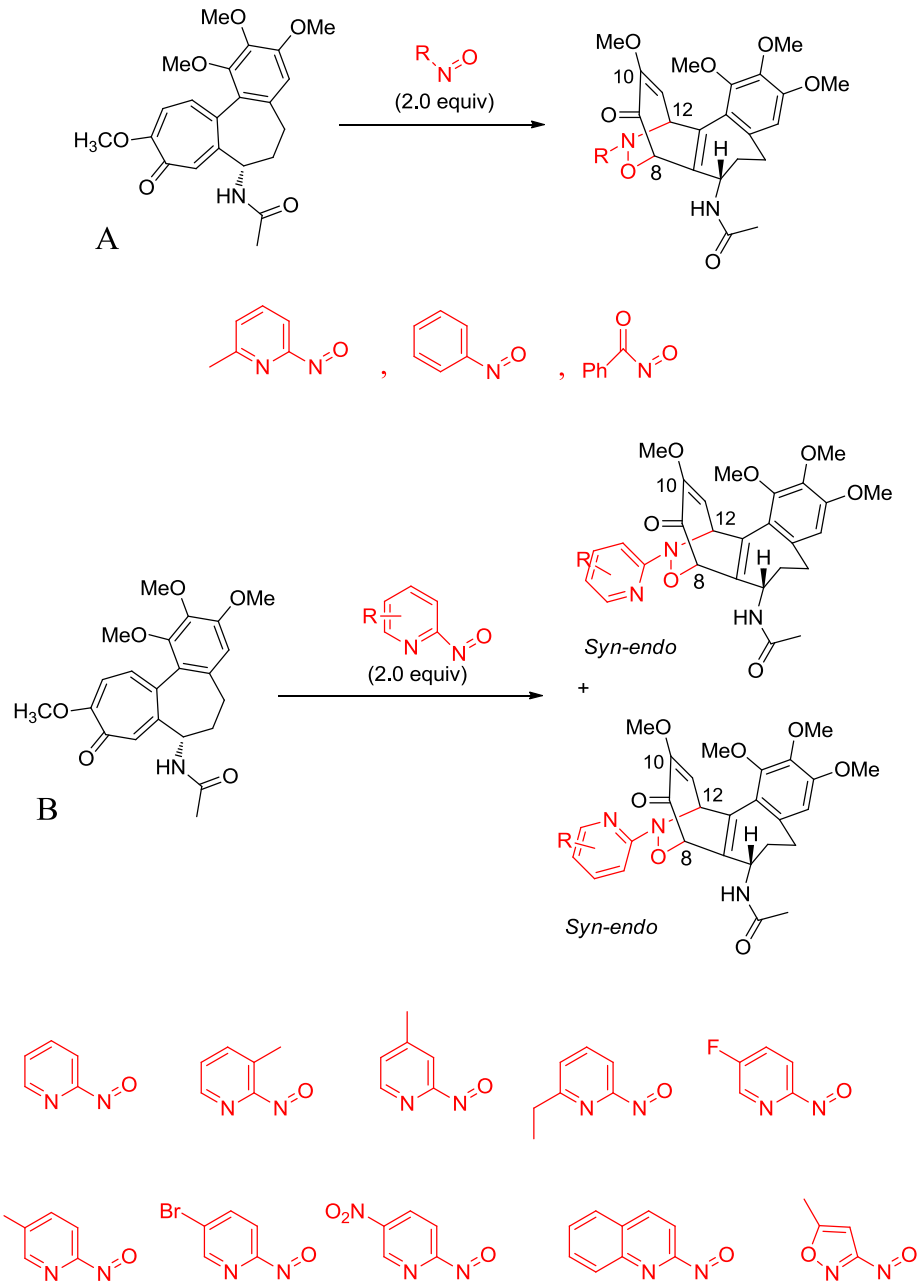


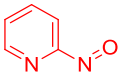
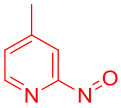
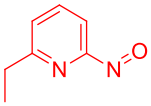
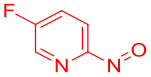
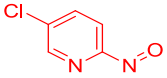
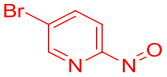
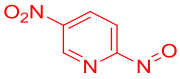
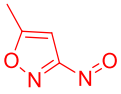
Fig. 16. A) Nitroso-(−)-colchicine derivatives. B) Iminonitroso-(−)-colchicine derivatives.

Moreover, the possibility of developing water-soluble (−)-colchicine derivatives and using nanotechnology for targeting their delivery into cancer cells without affecting normal cells offer a promising frontier for drug development.

6. Summary

In summary, (−)-colchicine offers a low therapeutic index in cancer treatment due to its high toxicity towards cancer cells as well as normal cells. Several (−)-colchicine derivatives have been synthesized and tested in terms of their biological activity against many different cancer cell lines in an attempt to reduce unselective cytotoxicity and improve therapeutic activity. Structure-activity relationship studies of these derivatives have shown that electron-donating and/or electron-withdrawing substituents affect the activity of the derivatives, as well as the steric and chain lengths. The potency of the derivatives will increase following replacement of the amide substituent on C-7 of (−)-colchicine with thioamide or thiobenzyl groups. Nitric oxide substituents provide the dual activity of physiological actions and cytotoxicity in cancer therapy. The presence of thiadiazole and triazole moieties on (−)-colchicine derivatives increase the inhibition of tubulin polymerization, as well as compete with the (−)-colchicine itself at the tubulin binding site. *Meta*-nitro substituents in the benzylamide group increase the activity of (−)-colchicine derivatives up to picomole levels and are able to form hydrogen bonds at the tubulin binding site. The *N*-benzyl substituent groups on C-10 of the (−)-colchicine derivatives confer a dual potency to the (−)-colchicine derivatives. High stereo- and regioselective derivatives can be obtained through Diels-Alder reactions by using the cycloaddition

Table 8
Cytotoxic activity for Iminonitroso derivatives of (−)-colchicine against PC-3 and MCF-7 cell line.

Iminonitroso derivatives of (−)-colchicine	IC_{50} (nM)/cell line	
	PC-3	MCF-7
	28	17
	14	10
	23	22
	15.6	15
	10	15.6
	24	20
	250	230
	250	190
(−)-Colchicine	20	12

of nitroso and iminonitroso agents with an 8,12-diene moiety of (−)-colchicine. This will result in retro Diels-Alder reactions of derivatives that can function as (−)-colchicine prodrugs.

Declaration of competing interest

The authors declare no competing financial interest.

Acknowledgments

The authors would like to acknowledge the Doctoral Research Scheme (DRS) scholarship from Universiti Malaysia Pahang, Malaysia.

Abbreviations used

1A9	Human ovarian carcinoma cell line
A2780	Human ovary cancer cell line
A549	Human lung carcinoma cell line
BEL 7402	Human hepatoma cell line
CbsT/T	hyperhomocysteinemic
Colo-205	Human colon carcinoma cell line
DLD-1	Colorectal cancer cell line
FDA	Food and Drug Administration
FMF	Familial Mediterranean Fever
HCT-116	Human colorectal carcinoma cell line
HCT-15	Human colon cancer cell line
HL-60	Human epidermoid cancer-cell line
HL-60/vinc	Human leukaemia vincristine-resistant subline
KB	Human epidermoid carcinoma of the nasopharynx cell line;
KB-31	Drug-sensitive
KB-8511	Multi-drug-resistant
KB-V	multi-drug resistant KB subclone expressing P-glycoprotein
LoVo	human colon adenocarcinoma cell line
LoVo/DX	doxorubicin resistant subline
MCF-7	Human breast carcinoma cell line
MDA-MB-231	human breast cancer cell line
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorodisulfoneimide
NIS	*N*-iodosuccinimide
PC3	Human prostate cancer cell line
RCTs	Randomized Controlled Trails
SAR	Structure-Activity Relationship
SK-MEL-2	Human malignant melanoma cell line
SK-OV-3	Human ovarian cancer cell line
THF	Tetrahydrofuran
$TMSCHN_2$	Trimethylsilyldiazomethane

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