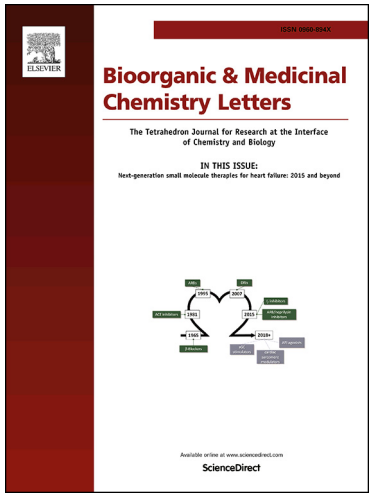

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Optimization of Substituted Cinnamic Acyl Sulfonamide Derivatives as Tubulin Polymerization Inhibitors with Anticancer Activity

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Keywords:

Cinnamic acid

Sulfonamide

Antiproliferative activity

Molecular docking

Anti-tubulin polymerization

A new series of novel cinnamic acyl sulfonamide derivatives were designed and synthesized and evaluated their anti-tubulin polymerization activities and anticancer activities. One of these compounds, compound **5a** with a benzdioxan group, was observed to be an excellent tubulin inhibitor (IC_{50} = 0.88 μM) and display the best antiproliferative activity against MCF-7 with an IC_{50} value of 0.17 μg/mL. Docking simulation was performed to insert compound **5a** into the crystal structure of tubulin at colchicine binding site to determine the probable binding model. 3D-QSAR model was also built to provide more pharmacophore understanding that could be used to design new agents with more potent anti-tubulin polymerization activity.

HER-2: human epidermal growth factor receptor 2

Hsp90:heat shock protein 90

SAR:structure-activity relationship

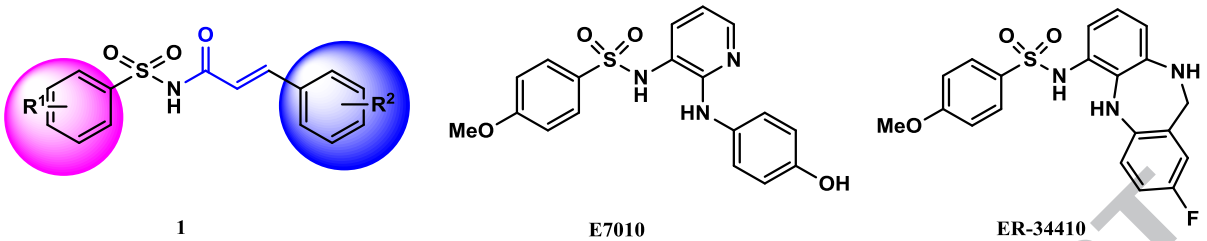
DMAP:4-dimethyaminopyridine

EDCI:1-[3-(dimethyamino)-propyl]-3- ethylcarbodiimide hydrochloride

ELISA:enzyme linked immunosorbent assay

Oxygen-bearing heterocycles especially 1,3-benzodioxole and 1,4-benzodioxan have been observed to display potent anticancer activity as tubulin [1, 2], human epidermal growth factor receptor 2 (HER-2) [3], topoisomerase II [4], heat shock protein 90 (Hsp90) inhibitors [5] and 5-HT_{1A} receptor Agonist [6, 7]. Sulfonamides have reported to display broad biological activity as carbonic anhydrase [8], tubulin [9-11], matrix metalloproteinase [12], gelatinase A [13], HIV-1 protease [14], potassium ion channel [15], alkaline phosphatase inhibitor [16] and so on. Recently the main research field about sulfonamides is to evaluate their anticancer activities. In a previous paper, we have reported the potent *in vitro* anticancer activities of a series of cinnamic acyl sulfonamides (Fig. 1) [17]. Besides, our group also reported another series of compounds containing sulfonamide scaffold with tubulin polymerization activities as anticancer agents[10]. These findings encouraged us to continuously design new sulfonamides bearing oxygen-bearing heterocycles as anticancer agents.

Tubulin, the major component of microtubule and cytoskeleton, has become the most important molecular target for cancer chemotherapeutic agents. A number of sulfonamide derivatives have been identified as inhibitors of tubulin polymerization. Yoshino *et al* screened out compound E7010 (Fig. 1) which was demonstrated to be an outstanding tubulin inhibitor with IC_{50} values of 0.06-0.8 μg/mL against cancer cell lines [18]. Based on the result, they modified the chemical structure of E7010 and discovered ER-34410 (Fig. 1) which displayed much better anticancer activity than E7010 [19]. After that, Owa *et al* reported another series of novel anticancer sulfonamides with E7070 as a lead compound [20]. These compounds were demonstrated to bind to the colchicine binding site on β-tubulin reversibly [19]. While there are no anticancer agents that bind to the colchicine site of tubulin in clinic, the above mentioned sulfonamide derivatives are currently in clinical trials [21].

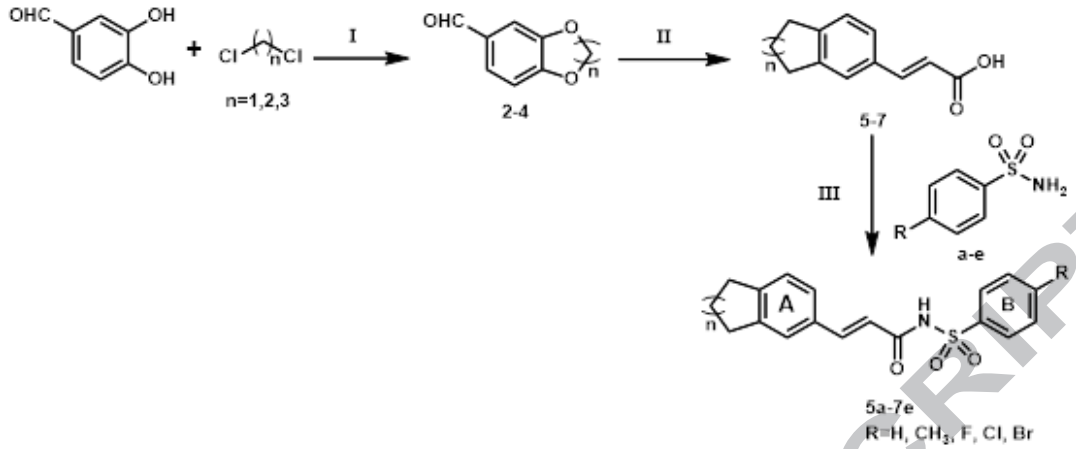


1 E7010 ER-34410

Figure 1. Chemical structures of compound **1**, **E7010** and **ER-34410**.

In this paper, we have prepared a series of novel sulfonamide derivatives, which arised from the structure-activity relationship (SAR) study, explored their antiproliferative and anti-tubulin activities, investigated the inhibitor-protein interaction by docking study and built a 3D-QSAR model to provide more pharmacophore understanding. All the results mentioned above demonstrated that the synthesized sulfonamide derivatives could be a new class of potent anti-tubulin agents with anticancer activity.

The general synthetic route for the novel cinnamic acyl sulfonamide derivatives **5a-7e** is depicted in Scheme 1 as reported by our group [17]. 3, 4-Dihydroxybenzaldehyde, substituted alkanes and benzenesulfonamides were commercially available. Compounds **2-4** were prepared by substitution reaction of 3, 4-dihydroxybenzaldehyde and dichloromethane (1, 3-dichloroethane or 1, 4-dichloropropane). The cinnamic acids **5-7** were obtained from the reaction of compounds **2-4** and malonic acid. In a similar manner with previous paper [17], cinnamic acids **5-7** and sulfonamides **a-e** were added together with 4-dimethyaminopyridine (DMAP) and 1-[3-(dimethyamino)-propyl]-3-ethylcarbodiimide hydrochloride (EDCI) as catalyst to get the target compounds **5a-7e**. The related experimental details were summarized in Supporting Information. Based on the results of ^{1}H NMR spectroscopy and X-ray determination, the configuration of sulfonamides was determined. The crystal structure of compound **5b** (CCDC number: 1559627) and **6c** (CCDC number: 1559632) are shown in Figure 2. Crystallographical and experimental data of compounds **5b** and **6c** were summarized in Table 3 of Supplementary Material.



Scheme 1. General synthesis of cinnamic acid sulfonamide derivatives (**5a**-**7e**). Reagents and conditions: (I) K_2CO_3，acetone，reflux，29 h; (II) piperidine, pyridine, 80-90 °C, 24 h; (III) substituted benzenesulfonamides, CH_2Cl_2, EDCI, DMAP, overnight

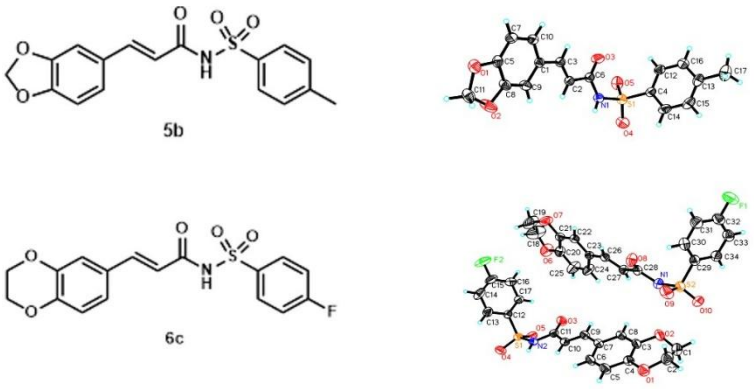


Figure 2. Crystal structure of compounds **5b** and **6c**.

The synthesized sulfonamides were screened for their antiproliferative activities toward MCF-7 human breast cancer cells. The results are summarized in Table 1 with colchicine as control. The data showed that some of the tested compounds displayed significant antiproliferative activity toward MCF-7 cell lines. Compound **5a** (IC_{50} = 0.17 μg/ml), which had benzdioxan group on A ring and no substituent on B benzene ring, was even more potent than colchicine (IC_{50} = 0.33 μg/ml). Compared with **5a, c**ompounds **5b**-**7e** didn't exhibit significant antiproliferative activity, indicating that substituents on B benzene ring had a deleterious decreasing effect on activity. In particular, a methyl replacement of *para*-position of B benzene ring, represented by

5b (IC_{50} = 48.95 μg/ml), leaded to weaker activity. Other compounds (**5c**, **5d** and **5e**) (IC_{50} = 74.05 μg/mL, 47.27 μg/mL and 89.01 μg/mL) with substituted *para*-halogen exhibited approximately antiproliferative activities with the same order of magnitude.

From the data presented in Table 1, it could conclude that in the case of same substituents on B ring, change of oxygen-bearing heterocycle on A ring could also affect the antiproliferative activities of the compounds. The sulfonamide derivatives containing 1, 3-benzodioxole scaffold (**5a**–**5e**) displayed better antiproliferative activities whereas the derivatives containing 1, 4-benzodioxan and 1, 5-benzodioxepine groups, in general, displayed relatively weaker activities. Overall, the results indicated that the structure of heterocycles and aromaticity of benzene ring could influence antiproliferative activity of these synthesized compounds.

Table 1. Antiproliferative activities and anti-tubulin activities of **5a**-**7e** against MCF-7 cells.

Compd	n	R	MCF-7 IC_{50}[a] (μg/ml)	ITP IC_{50}[b] (μM)
5a	1	H	0.17	0.88
5b	1	CH_3	48.95	40.85
5c	1	F	74.05	76.90
5d	1	Cl	47.27	94.72
5e	1	Br	89.01	51.59
6a	2	H	2.16	5.47
6b	2	CH_3	>100	93.33
6c	2	F	52.13	27.46
6d	2	Cl	51.31	87.92
6e	2	Br	>100	>100
7a	3	H	53.87	49.01
7b	3	CH_3	>100	>100
7c	3	F	>100	>100
7d	3	Cl	>100	>100
7e	3	Br	>100	>100
Colchicine			0.33	1.36

[a] IC_{50} was determined by the concentration of compounds required for 50% inhibition of cell growth (MCF-7). Cells were treated with compounds for 48 h, and cytotoxicity was determined by MTT assay. [b] IC_{50} values were determined by in vitro tubulin polymerization assay and represented the concentration of compounds for 50% inhibition of the maximum tubulin polymerization levels.

To examine whether the compounds interact with tubulin and inhibit tubulin polymerization *in vitro*, we performed the tubulin polymerization assay. As shown in Table 1, compounds **5a** which was most potent in antiproliferative assay also showed best tubulin polymerization inhibition activity (IC_{50} = 0.88 μM). Besides, the tubulin polymerization inhibition activities of other compounds were also relative to antiproliferative activity. The calculated Pearson Product-Moment Correlation Coefficient of the values was 0.831, which indicated a strong positive correlation between the two sets of data. This result indicated the antiproliferative activity was probably produced by direct interaction of tubulin with the compound. Overall，**5a** could be a promising lead for the further development of novel tubulin inhibitor.

In order to explore probable interaction model of inhibitors with target protein, molecular docking was performed to simulate a binding model derived from tubulin crystal structure (PDB ID: 1SA0). All docking runs were applied CDOCKER protocol of Discovery Studio 3.1. The 2D and 3D binding model of compound **5a** and tubulin was depicted in Figure 3. In this model, compound **5a** was docked into the colchicine binding site of tubulin with binding free energy of -35.24 KJ mol^{-1}, One hydrogen bond was observed (CYS241: S-H…O: 2.4 Å, Angel: 147.8). Also other residues shown in Figure 3 interacted with compound 5a through Van der Waals force. These residues influenced the accessibility of the hydrophobic pocket and their size could be important in controlling tubulin selectivity. Overall, these results suggested that compound **5a** could be well inserted into tubulin, similar with colchicine.

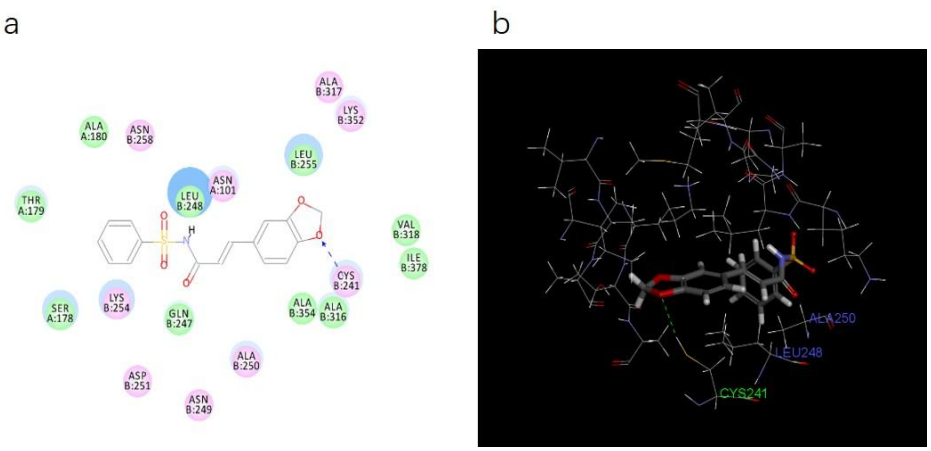


Figure 3. Binding model of compound 5a with tubulin (PDB: 1SA0). a) 2D structure of the binding model (H-bonds are displayed as dashed lines.) The purple circles showed the amino acids which participate in hydrogen bonding, electrostatic or polar interactions and the green circles show the amino acids which participate in the van der Waals interactions b) 3D structure of the binding model.

Based on previous and current results, in order to provide more statistically correlation between structure and activity and acquire more potent inhibitors, we developed a 3D-QSAR model of the cinnamic acyl sulfonamide derivatives. Twenty-five compounds randomly selected from the previous paper [14] and ten compounds **5a-6d** and **7a** from this paper which exhibited anti-tubulin activity with IC_{50} less than 100 μM were selected as the mimic objects. The whole process was initiated by a 3D-QSAR protocol of Discovery Studio 3.1. The data combined the predicted pIC_{50} values and experimental pIC_{50} values were listed in Table 2.

Table 2. Experimental and predicted inhibitory activities of compounds by 3D-QSAR models

	Experimental pIC_{50}	Predicted pIC_{50}	Residual error
5a[a]	6.05551	6.53081	-0.00793
5b	4.38881	4.38557	0.00324
5c	4.11407	4.11089	0.00318
5d	4.02365	4.02257	0.00108
5e	4.28819	4.14673	0.14146
6a	5.26201	4.29668	-0.01766
6b	4.03012	4.01317	0.01695
6c	4.56225	4.43078	0.13147
6d	4.05601	4.01896	0.03705
7a	4.30971	3.82286	-0.25358
10a[b]	5.34679	5.33442	0.01237
10b	4.39794	4.39059	0.00734
10c	5.61979	5.72511	-0.10531
10e	5.24413	5.23332	0.01081
11a	5.27572	5.07505	0.20067
11c	5.05061	5.04861	0.00199
11d	5.03152	4.99216	0.03936

11e	5.16749	5.17213	-0.00463
12b	3.86328	3.88493	-0.02165
12c	5.42022	5.46658	-0.04636
12d	4.25964	4.32116	-0.06151
12e	4.27572	4.25123	0.02448
13b	3.83565	3.82084	0.01481
13d	4.28400	4.20282	0.08118
14d	4.85387	4.77873	0.07513
14e	4.46852	4.42690	0.04162
15a	4.30103	4.51751	-0.21647
15b	3.82102	4.12619	-0.30517
15c	5.20066	4.87134	0.32931
15e	3.78781	3.73222	0.05558
16a	4.13077	4.30604	-0.17526
16b	3.9914	4.01146	-0.02006
16c	4.16115	4.18798	-0.02683
16d	4.10791	4.15459	-0.04667
16e	3.87290	3.92235	-0.04944

[a] Bold fonts represented compounds from this paper. [b]No bold fonts represented compounds from previous paper.

In this model, we selected (E)-N-(methylsulfonyl)but-2-enamide (Fig. 4a) as substructure to build alignment conformation before QSAR analysis, then applied CDOCKER protocol to explore each molecule with lowest energy before alignment conformation. Then the process of QSAR analysis was conducted following previous protocol [22], the initial set of compounds has been randomly divided into training set and test set in QSAR protocol. Predicted pIC_{50} values and residual errors of all compounds were calculated by this QSAR model had been summarized in Table 2. The fitting curve of the observed pIC_{50} vs. the predicted data was shown in Figure 4b. As shown, the correlation coefficient r^2 between observed and predicted activity of training set was found to be 0.990, while that of test set was found to be 0.893, which proved this QSAR model was acceptable.

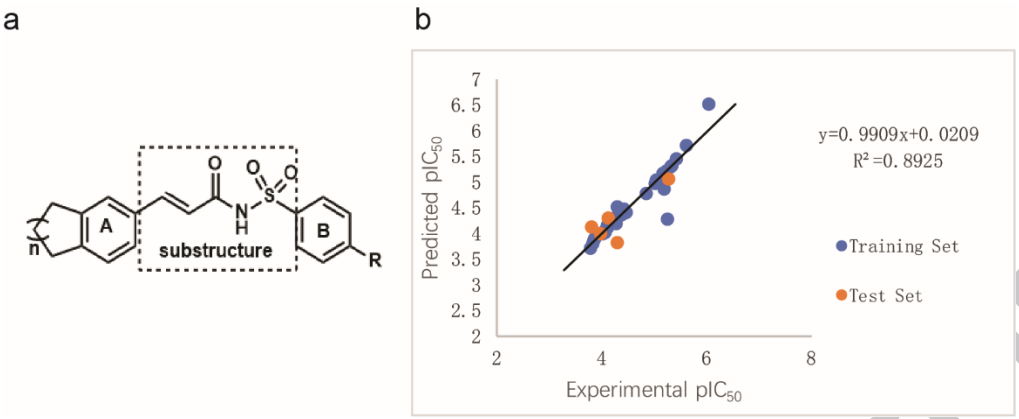


Figure 4. (a) E)-N-(methylsulfonyl)but-2-enamide as substructure for QSAR analysis. (b) The fitting curve of the observed pIC_{50} vs. the predicted pIC_{50}

The aligned molecules with the iso-surfaces from the 3D-QSAR model on van der Waals grids (Fig. 5b) and electrostatic potential grids (Fig. 5a) were shown. As described in previous paper, electrostatic map indicated red contours around regions where high electron density (negative charge) was expected to increase activity, and blue contours represent areas where low electron density (partial positive charge) was expected to increase activity [22]. Steric map derived from van der Waals analysis indicates areas where steric bulk was predicted to increase (green) or decrease (yellow) activity [22].

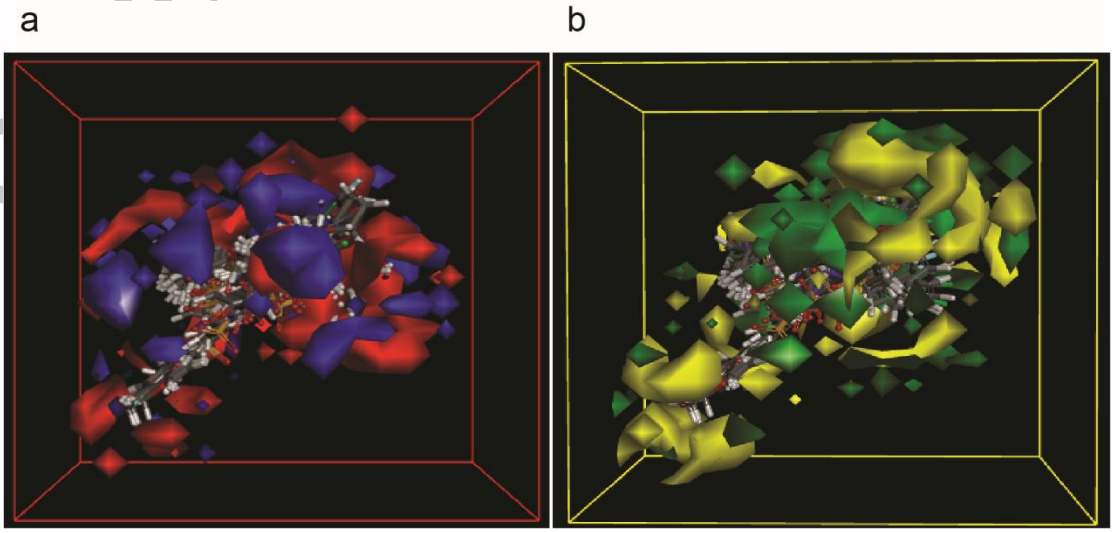


Figure 5. (a) 3D-QSAR model coefficients on electrostatic potential grids. Blue represents positive coefficients; red represents negative coefficients. (b) 3D-QSAR

model coefficients on van der Waals grids. Green represents positive coefficients; yellow represents negative coefficients

According to the maps in Figure 5, it suggested that the compounds with negative charged and small groups on B benzene ring showed better activity, indicating that no substituent or small negative charged group on B ring might be better choice than other substituents. Whereas, oxygen-bearing heterocycle group on A ring was surrounded by yellow grids ring, which suggested that the molecule size on A ring would benefit activity promotion, however, for the electron density it seemed that the electronegativity didn't influence the activity obviously.

In this paper, a series of cinnamic acyl sulfonamides **(5a-7a**) had been synthesized and evaluated their biological activities as novel tubulin polymerization inhibitors. These compounds exhibited potent tubulin polymerization inhibition activities and antiproliferative activities against MCF-7 human breast cancer cell line. Compound **5a** showed the most potent antiproliferative activity with IC_{50} value of 0.17 μg/ml against MCF-7 and anti-tubulin polymerization activity with IC_{50} of 0.88 μM. Molecular simulation was performed to predict probable inhibitor-tubulin protein interaction model. Besides, through 3D-QSAR study, the model was built to provide more pharmacophore understanding that could be used to design other novel agents. Overall, the information provided by this work might be helpful for the design and synthesis of tubulin polymerization inhibitors with better activities.

The main work on the synthesis of target compounds, evaluation of their biological activities, data analysis, and manuscript preparation were performed by Yin Luo and Yang Zhou. Yanhua Song and Guo Chen contributed to manuscript revision. Yu-Xiang Wang, Ye Tian and Wei-Wei Fan contributed to the synthesis. Yu-Shun Yang and Tao Cheng contributed to the 3D QSAR and molecular docking. Hai-Liang Zhu and Yin Luo are the corresponding authors.

The content of the manuscript is original and has not been submitted for publication

elsewhere. There is no conflict of interest in the manuscript.

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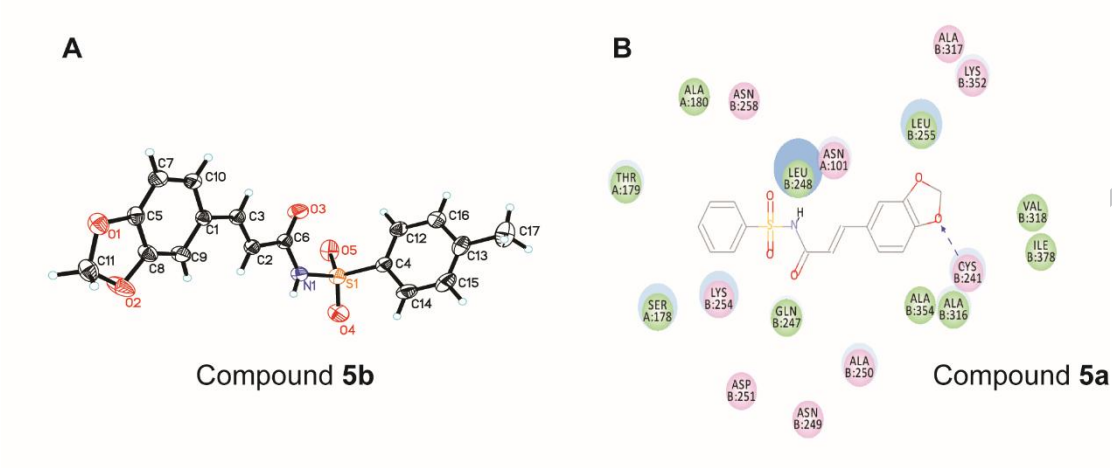

Compounds of novel cinnamic acyl sulfonamide derivatives as tubulin polymerization inhibitors were designed, synthesized and evaluated for the inhibitory activity against tubulin polymerization and cancer cell inhibitory activity. Docking simulation and 3D-QSAR of these compounds were also conducted.

- 15 novel cinnamic acyl sulfonamide derivatives have been synthesized.
- Their biological activities were as potential tubulin polymerization inhibitors.
- Compound **5a** showed the most inhibitory activity against tubulin and cancer cells.
- Crystal structures of compounds **5b** and **6c** were determined.