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Importance of Imidazolidinone Motif in 4-Phenyl-*N*-arylsulfonylimidazolidinone for their Anticancer Activity†

Vinay K. Sharma, Ki-Cheul Lee, Cheonik Joo, Niti Sharma, and Sang-Hun Jung*

*College of Pharmacy and Institute of Drug Research and Development, Chungnam National University, Daejeon 305-764, Korea. *E-mail: jungshh@cnu.ac.kr*
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To investigate the possible isosteric replacement of imidazolidinone moiety in 4-phenyl-*N*-arylsulfonylimidazolidinone for broad and potent anticancer agents, a series of 4-phenyl-l(*N*)-arylsulfonylimidazolidinones **6a-k**, imidazolidinethione analogs **7a-i**, and imidazolidine oxime analogs **8a-c** were prepared and evaluated for their *in vitro* anticancer activity against four human cancer cell lines (human lung A549, human colon COLO205, human leukemia K562, human ovary SK-OV-3). Among all the derivatives of *N*-arylsulfonylimidazolidinone **6a-k**, compounds **6f** and **6g** showed the best inhibition comparable to doxorubicin against all cancer cell lines. Increasing the carbon chain on alkyl moieties of carbamates as shown in **6c-g** did not alter the activity. The imidazolidinethione analogs **7a-i** and imidazolidin-2-one oxime derivatives **8a-c** did not possess any good activity. Therefore, imidazolidinone moiety is the best pharmacophore among the 4-phenyl-*N*-arylsulfonylimidazolidinone derivatives.

Key Words : Arylsulfonylimidazolone, Anticancer activity, Antimitotic agent

Introduction

Microtubules have a crucial role in the cellular division thus are recognized as an important target for anticancer therapy.[1] A numerous naturally occurring compounds with anticancer activities have been identified, such as paclitaxel, vinblastine, combretastatin A-4P, dolastatin 10, epothilone A and colchicine, which act by interfering with the dynamics of tubulin polymerization and depolymerization, resulting in the mitotic arrest.[2] However, the clinical use of all these antitubulin agents is associated with the problems of drug resistance, toxicity, and bioavailability.[3]

According to the recent reports, some antitubulin agents binding at colchicine site like combretastatin A-4P (Fig. 1) acts as a vascular disrupting antitumor agent (VDA),[4] causing the vascular structure inside a solid tumor to collapse which starves the tumor to death.[5,6] In addition, some small molecules such as *N*-pyridinyl sulfonamide (ABT-751),[7-9] chloroindolyl sulfonamide[10] and styrylpridine *N*-oxide sulfonamide[11-13] (Fig. 1) have been reported as potent anticancer agents and are currently in clinical trials for different types of cancers.[14-18] Even though a large number of anticancer agents are under clinical trial, still there is an urgent need to find novel tubulin inhibitors which are effective in treatment of multidrug-resistant (MDR) tumors.

Jung and coworkers reported a novel 4-phenyl-l(*N*)-arylsulfonylimidazolidinones **1** (Fig. 2),[19] containing a sulfonylurea unit, which demonstrated highly potent anticancer activity against the various cancer cell lines.[20-23] The structure activity relationship studies revealed that 4-phenyl-l-benzenesulfonylimidazolidinone, a basic pharmacophore, was essential for the anticancer activity.[19, 24-28] Therefore, a numerous analogs of **1** have been studied by the substitutions on the phenyl group of sulfonyl moiety. Interestingly, the STERIMOL L parameter of these substituents at *p*-position seems to be well correlated with the activity[24] as the activity increases by increasing STERIMOL L values. Among the studied compounds, **1d** (Fig. 2)[19] with the longest acetamido group was the most potent. The fused bicyclic analog **2** containing indanyl group on sulfonyl group had also shown very good potency, comparable to doxorubicin. However, the compound **3** was less potent than **2**. These two factors were integrated into the design of **4**[29] analogs containing indoline moiety. As a result, these compounds exhibited a very good anticancer activity against various tumor cell lines. The potent inhibitory activity of **4** inspired us to go for more modifications on the indoline moiety and this led us to highly potent compound **5** (DW2282). The compound **5** was further studied for its antitumor efficacy in *in vitro* and *in vivo* models.[30] It not only showed potent inhibition for SW620 tumor cell growth in nude mice but also proved less toxic in comparison to the other analogs. In addition, it did not produce a series of toxic symptoms caused by the aniline metabolites of sulfonylureas, including hypoglycemia.[30] These results suggest that **5**, a S-isomer, could be a novel antitumor candidate with higher specificity and lower toxicity than other orally active sulfonylureas. Though the compound **5** showed very good profile, still the mechanism of action of these sulfonylurea derivatives was not clear. Therefore, later, our group[31] synthesized various derivatives of **5** and studied them for their mechanism of action. It was observed that the synthesized compounds are the potent inhibitors of tubulin polymerization and maintained a good

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

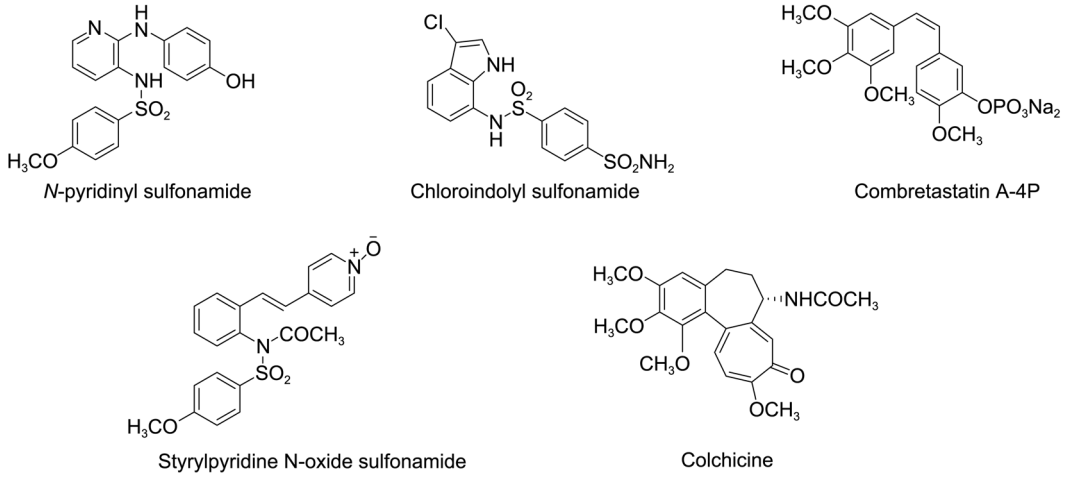


Figure 1. Known tubulin inhibitors.

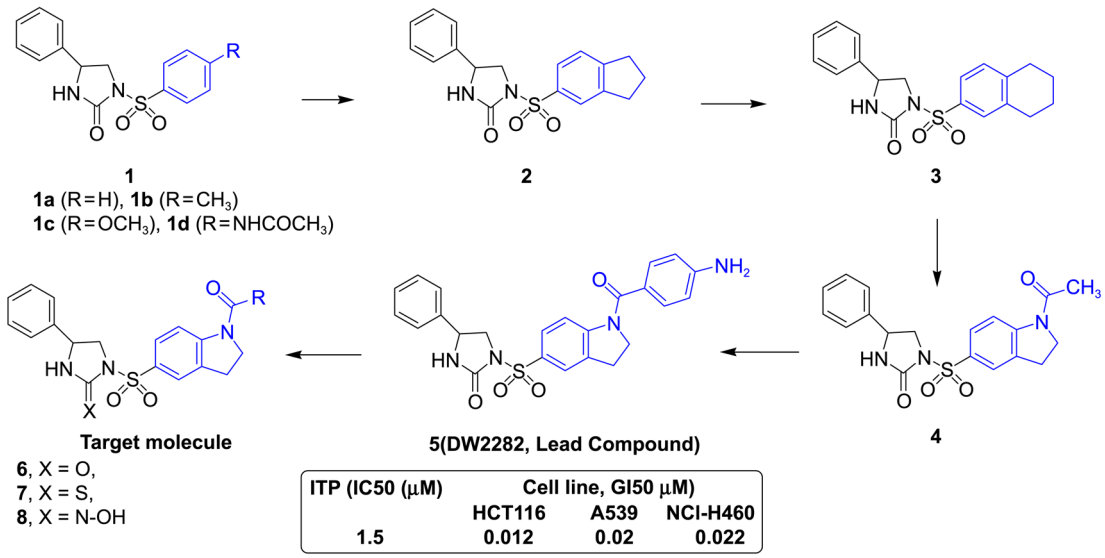


Figure 2. Structural modification at sulfonyl position of *N*-arylsulfonylimidazolones.

activity against multidrug resistant tumor cell lines. This implies that these are not the substrates for p-glycoprotein-mediated transport, like taxanes and vinca alkaloids derivatives. These findings encouraged us to continue our search for potent analogs. Therefore, here in the current article we have designed and synthesized analogs **6, 7** and **8** of **5** as shown in Fig. 2 for evaluating their *in vitro* inhibitory activities against four human cancer cell lines (human lung A549, human colon COLO205, human leukemia K562, human ovary SK-OV-3).

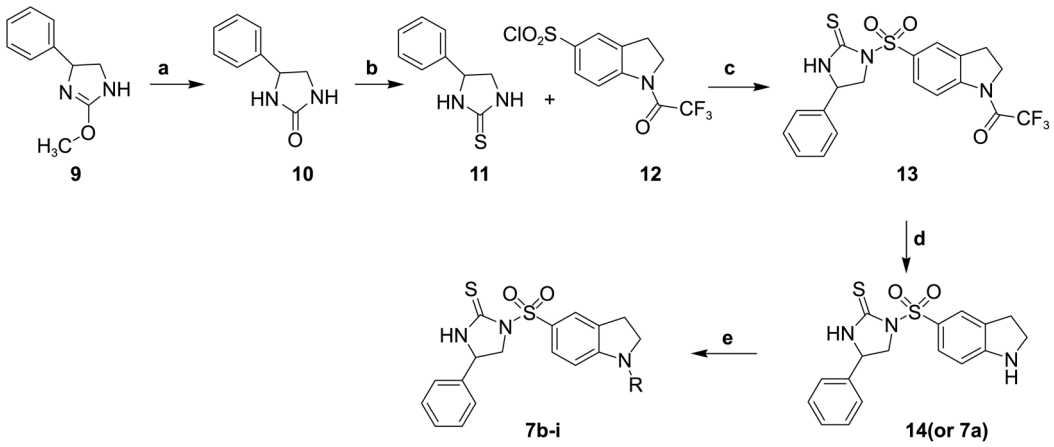
Chemistry

A series of *N*-arylsulfonylimidazolidinone analog **6a-k** was prepared by our earlier reported method[29] and the analogs **7a-i** and **8a-c** were prepared as illustrated in Scheme 1 and 2. The intermediate **9** was prepared by our previously reported procedure.[20,29] The compound **10** was prepared by stirring **9** in 10% HCl-methanol solution at 40-50 °C for 24 h. Intermediate **11** was obtained by the reaction of **10** with Lawesson's reagent in toluene. The intermediate **11** was further treated with the *N*-trifluoroacetylindolin-5-sulfonyl chloride (**12**)[20,29] in the presence of sodium hydride in THF to produce **13**. After the removal of trifluoroacetyl group of **13** using sodium hydroxide in aqueous acetone at room temperature, the resulting imidazolidinethione **14 (or 7a)** was finally treated with acetic anhydride, benzoyl chloride or aryl (or alkyl) chloroformate in acetonitrile at reflux temperature to produce *N*-arylsulfonylimidazolidinone analog **7b-g** (Scheme 1) as listed in Table 1. The compound **7h-i** was obtained by the reaction of intermediate **14 (or 7a)** with phenyl isocyanate or isopropyl isocyanate in anhydrous toluene at reflux for 24-72 h. The intermediate **15** was obtained by treating **11** with methyl iodide in presence of sodium hydroxide in acetone. Compound **16** was prepared by reacting intermediate **15** with *N*-trifluoroacetylindolin-5-

Table 1. *In vitro* anticancer activity of *N*-arylsulfonylimidazolones **6**, **7** and **8**

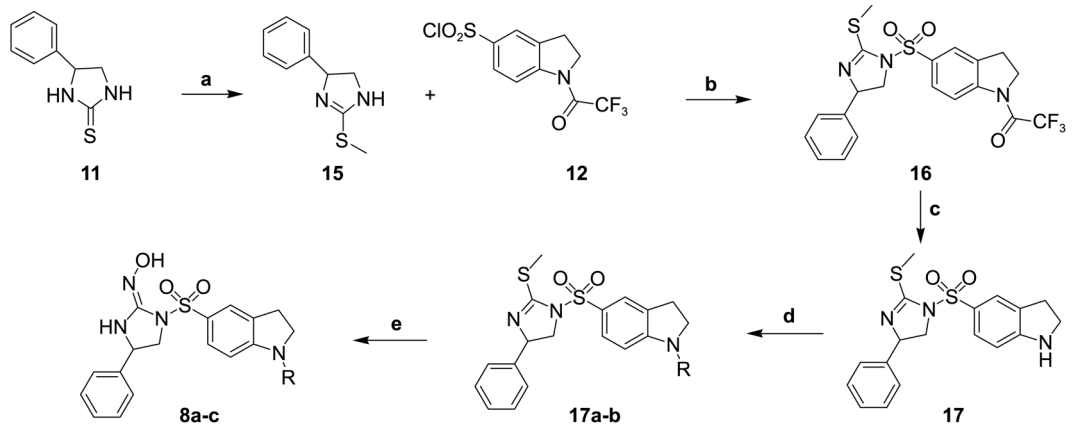
Compd. No.	R		IC_{50} (μM)[a]			
	X	R_1	A549	COLO205	SK-OV-3	K562
6a[19]	O	H	Nt[b]	>20	Nt	1.78
6b[19]	O	COMe	0.54	Nt	Nt	Nt
6c	O	COO-Me	2.65	2.12	Nt	>20
6d[31]	O	COO-Et	0.25	1.00	0.58	0.29
6e	O	COO-Pr-*n*	0.02	0.38	Nt	>20
6f	O	COO-Bu-*n*	0.05	0.11	3.37	3.98
6g	O	COO-Bu-*i*	0.04	0.11	2.03	5.32
6h	O	COO-C_6H_5	0.40	0.721	Nt	>20
6i	O	COO-$CH_2C_6H_5$	0.14	1.27	Nt	>20
6j[24]	O	CONHC_6H_5	0.18	1.26	0.16	<0.006
6k[24]	O	CONH-Pr-*i*	0.07	0.26	0.28	0.44
7a	S	H	>20	>20	>20	>20
7b	S	COMe	>20	18.30	17.79	9.14
7c	S	COO-Me	>20	3.08	25.31	17.27
7d	S	COO-Et	15.92	19.61	>20	13.83
7e	S	COO-Allyl	16.26	11.44	>20	9.16
7f	S	COO-Bu-*i*	13.59	7.73	19.98	7.80
7g	S	COC_6H_5	13.48	5.22	>20	6.29
7h	S	CONHC_6H_5	>20	3.77	16.61	4.54
7i	S	CONH-Pr-*i*	4.35	2.73	4.45	1.94
8a	N-OH	H	>20	>20	>20	>20
8b	N-OH	COO-Et	7.18	13.61	6.62	9.51
8c	N-OH	CONHC_6H_5	4.61	7.04	3.46	4.60
Sulofenur			>20	>20	19.20	>20
Doxorubicin			0.48	0.40	2.95	0.20

[a]IC_{50} values are taken as a mean from 3 experiments. [b]Nt; Not tested.



Scheme 1. Synthesis of *N*-arylsulfonylimidazolone **7**.
Reagents and condition: (a) HCl, methanol; (b) Lawesson's Reagent, Toluene; (c) NaH, THF; (d) NaOH, Acetone/H_2O; (e) RCOCl or RNCO, acetonitrile, reflux.

sulfonyl chloride (**12**)[20,29] in the presence of sodium bicarbonate in aqueous acetone at room temperature. The alkylthioimidazolines **17** was obtained by the same procedures as used for the preparation of **14**. The compound **17a-b** was resulted by the reaction of **17** in anhydrous acetonitrile with isocyanates (acyl halides or chloroformates) at room temperature. Finally the intermediates **17** and **17a-b** were reacted with hydroxylamine hydrochloride in anhydrous chloroform in the presence of triethylamine at room temperature. The reaction mixture was further refluxed for 72 h to yield the 4-phenylimidazolidin-2-one oximes **8a-c** (Scheme 2). All these synthesized compounds were characterized by physical and spectral analysis data that confirmed their assigned structures.



Scheme 2. Synthesis of *N*-arylsulfonylimidazolone **8**.
Reagents and condition: (a) NaOH, methyl iodide, acetone; (b) $NaHCO_3$, acetone-water (1:1); (c) NaOH, Acetone/H_2O; (d) RCOCl or RNCO, acetonitrile, reflux; (e) NH_2OH·HCl, TEA, chloroform.

Result and Discussion

The *in vitro* anticancer activity of compounds **6a-k**, **7a-i** and **8a-c** were measured against human lung carcinoma (A549), human colon (COLO205), human ovarian (SK-OV-3) and human leukemia (K562)cell lines using MTT assay.[32,33] The results from these tests were given as IC_{50} values in Table 1. Note that the order of IC_{50} values indicated below in parenthesis were as follows: A549, COLO205, SK-OV-3 and K562 cell lines.

To explore the structure-activity relationships of *N*-arylsulfonylimidazolidinone **5**, the aminobenzoyl group in **5** was replaced with carbamate moiety such as methyl **6c** (IC_{50} values; 2.65; 2.12; not tested and >20 μM), ethyl **6d** (IC_{50} values; 0.25; 1.00; 0.58 and 0.29 μM), propyl **6e** (IC_{50} values; 0.02; 0.38; not tested and >20 μM), butyl **6f** (IC_{50} values; 0.05; 0.11; 3.37 and 3.98 μM), isobutyl **6g** (IC_{50} values; 0.04; 0.11; 2.03 and 5.32 μM), phenyl **6h** ((IC_{50} values; 0.40; 0.721; not tested and >20 μM) and benzyl **6i** (IC_{50} values; 0.14; 1.27; not tested and >20 μM). The ethyl analog **6d** had the best potency against all cancer cell lines and carbamate analogs **6c-k** showed more potent activity than sulofenur and doxorubicin. Moreover, the analogs **6e**, **6f, 6g** and **6k** showed the similar level of activity to **5**, especially in case of A549 cell line.

Our previous studies[21,22,28,30] and the above results prove that the 4-phenyl-*N*-arylsulfonylimidazolidinones are potent anticancer agents. Therefore, to define the role of imidazolidinone moiety of **5** and **6**, isosteric imidazolidinethione analogs such as **7a-i** were prepared and tested against cancer cell lines as shown in Table 1. Most of these analogs showed poor inhibition except carbamoyl analogs **7i** (IC_{50} values; 4.35; 2.73; 4.45 and 1.94 μM) compared to the corresponding imidazolidinone analogs **6a-k**. These results supported the importance of imidazolidione moiety of **5** and **7** for their anticancer activity.

Finally, a series of 4-phenylimidazolidin-2-one oxime analogs **8a-c** were synthesized by replacing the ureido moiety of N-arylsulfonylimidazolidinones **6** with the hydroxy guanidine as a bioisoster. The compounds **8a** (IC_{50} values; >20; >20; >20 and >20), **8b** (IC_{50} values; 7.18; 13.61; 6.62 and 9.51) and **8c** (IC_{50} values; 4.61; 7.04; 3.46 and 4.60) showed poor activity compared to the corresponding imidazolidinone analogs **6**.

Conclusion

N-Arylsulfonylimidazolidinones **6d-k** showed the best inhibition comparable to doxorubicin against all cancer cell lines. In addition, increasing the carbon chain length on carbamate alkyl moieties as shown in **6c-g** did not alter the activity. The imidazolidinethione analogs **7a-i** and oxime derivatives **8a-c** did not possess any good activity. Therefore, on the basis of our previous [21,22,28,30] and current studies, it can be concluded that imidazolidinone moiety is a basic pharmacophore of 4-phenyl-*N*-arylsulfonylimidazolidinone.

Experimental

Chemistry. Melting points (mp) were determined on an Electro thermal 1A 9100 MK2 apparatus and are uncorrected. All commercial chemicals were used as obtained and all solvents were purified prior to use applying standard procedures.[34] Thin layer chromatography was performed on E Merck silica gel GF-254 pre-coated plates; identification was performed under UV illumination and colorization with 10% phosphomolybdic acid spray followed by heating. Flash column chromatography was performed on E Merck silica gel (230-400 mesh). Infrared spectra were recorded on a Nicolet 380 model FTIR. ^{1}H-NMR spectra were measured against the peak of tetramethylsilane using a Varian Unity Inova 400 NMR (400 MHz) spectrometer. High resolution mass spectrum (HRMS) was recorded on PE SCIEX API 2000 (triple quadrupole) mass spectrophotometer (Applied Biosystems, Foster City, CA, USA).

4-Phenylimidazolidin-2-one (10): Compound **9** (1.7 g, 0.011 mol) was dissolved in 10% solution of HCl-methanol

at room temperature. The reaction mixture was stirred 40-50 °C for 24 h and then removed the methanol. Now the residue was dissolved in dichloromethane and washed with sat. $NaHCO_3$. The organic layer was dried with anhydrous sodium sulfate and evaporated the solvent under vacuum. The crude product was recrystallized from acetone to give **10**.

Yield 90.0%; mp : 159.2-159.8 °C; white solid; IR (KBr) 3170, 1690 cm^{-1}; NMR (acetone-d_6) δ 3.20 (dd, J = 7.3 , 9.5 Hz, 1H), 3.83 (t, J = 8.4 Hz, 1H), 4.81 (dd, J = 7.3, 9.6 Hz, 1H), 7.38 (s, 5H).

4-Phenylimidazolidine-2-thione (11): The solution of compound **10** (3 g, 0.021 mol) in toluene was added to the Lawesson's reagent (4.66 g, 0.012 mol) at room temperature. The reaction mixture was refluxed for 30 minutes and then cooled at room temperature. The precipitate was filtered and recrystallized from acetone to give **11**.

Yield : 87.0%; mp : 185.2-186 °C; white solid; IR (KBr) 3220, 1520 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 3.48 (dd, J = 7.3 , 9.5 Hz, 1H), 4.12 (t, J = 8.6 Hz, 1H), 5.09 (dd, J = 7.3, 9.5 Hz, 1H), 7.38 (s, 5H).

2,2,2-Trifluoro-1-(5-(4-phenyl-2-thioxoimidazolidin-1-ylsulfonyl)indolin-1-yl)ethanone (13): The solution of compound **11** (606 mg, 3.4 mmol) in anhydrous tetrahydrofurane (30 mL) was added to sodium hydride (123 mg, 5.1 mmol) at 0 °C. To this solution was added *N*-trifluoroacetylindolin-5-sulfonyl chloride **12** (1.29 g, 4.1 mmol). The resulting mixture was stirred for 3 h at room temperature and then removed tetrahydrofurane. The residue was dissolved in dichloromethane and washed with waters. The organic layer was dried with anhydrous sodium sulfate and evaporated under vacuum. The residue was then separated by flash column chromatography to give **13.**

Yield: 36%; mp : 119.3-119.7 °C; yellow solid; IR (KBr) 3350, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.35 (t, J = 8.0 Hz, 2H), 4.07 (dd, J = 7.2, 10.2 Hz, 1H), 4.37 (t, J = 8.4 Hz, 2H), 4.64 (t, J = 8.6 Hz, 1H), 4.93 (dd, J = 7.2, 10.2 Hz, 1H), 7.05 (s, 1H), 7.21-7.23 (m, 2H), 7.36 -7.38 (m, 2H), 7.89-8.32 (m, 3H).

1-(Indolin-5-ylsulfonyl)-4-phenylimidazolidine-2-thione 14 (or 7a): The solution of compound **13** (0.4 g, 0.87 mmol) in acetone(30 mL) was added to the sodium hydroxide (55 mg, 1.31 mmol) and water (30 mL) at room temperature. The resulting mixture was stirred for 30 minutes and then added dichloromethane (20 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated under vacuum to give **14 (or 7a)**.

Yield : 98%; mp : 210.3-211.8 °C; yellow solid; IR (KBr) 3380, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.06 (t, J = 8.0 Hz, 2H), 3.70 (t, J = 8.4 Hz, 2H), 3.98 (dd, J = 7.3, 9.6 Hz 1H), 4.58 (t, J = 8.8 Hz, 1H), 4.96 (dd, J = 7.3, 9.6 Hz, 1H), 7.27-7.77 (m, 8H).

General Procedure of the Synthesis of 6a-k. These derivatives were synthesized by the same procedure as described previously.[29]

Methyl 5-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (6c): Yield 81.0%; White solid; mp 217.1-218.4 °C; IR (KBr) 3300, 1720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.08 (t, J = 8.0 Hz, 2H), 3.61 (t, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.98 (dd, J = 7.3, 9.6 Hz 1H), 4.58 (t, J = 9.2 Hz, 1H), 4.78 (dd, J = 7.2, 9.6 Hz, 1H), 7.19-7.31 (m, 5H),.7.66-7.79 (m, 2H), 8.16 (s, 1H); HRMS calcd for $C_{19}H_{19}N_3O_5S$ *m/z* 410.1045, found 401.1038.

Propyl 5-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (6e): Yield 73.0%; White solid; mp 182.1-184.9 °C; IR (KBr) 3310, 2950, 1725, 1680, 1360, 1180 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.98 (t, J = 7.0 Hz, 3H), 1.72 (m, 2H), 3.19 (t, J = 8.9 Hz, 2H), 3.48 (t, J =8.5 Hz, 2H), 3.99 (dd, J = 7.3, 9.2 Hz, 1H), 4.10 (t, J = 8.8 Hz, 2H), 4.34 (t, J = 9.6 Hz, 1H), 4.76 (dd, J = 7.3, 9.6 Hz, 1H), 7.18-7.42 (m, 5H),.7.74-7.78 (m, 2H), 8.14 (s, 1H); HRMS calcd for $C_{21}H_{23}N_3O_5S$ *m/z* 429.1358, found 429.1352.

Butyl 5-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (6f): Yield 83.0%; White solid; mp 147.1-148.3 °C; IR (KBr) 3400, 2950, 1720, 1180 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.95 (t, J = 8.2 Hz, 3H), 1.23-1.76 (m, 4H), 3.18 (t, J = 8.6 Hz, 2H), 3.49 (t, J = 8.5 Hz, 2H), 3.98 (dd, J = 7.3, 9.2 Hz, 1H), 4.20 (t, J = 8.8 Hz, 2H), 4.34 (t, J = 9.6 Hz, 1H), 4.78 (dd, J = 6.5, 8.4 Hz, 1H), 7.18-7.30 (m, 5H),.7.76 (m, 2H), 8.13 (s, 1H); HRMS calcd for $C_{22}H_{25}N_3O_5S$ *m/z* 443.1515, found 443.1508.

Isobutyl 5-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (6g): Yield 83.0%; White solid; mp 208.2-210.6 °C; IR (KBr) 3400, 2950, 1720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.98 (d, J = 6.6 Hz, 6H), 2.10 (m, 1H), 3.09 (t, J = 8.1 Hz, 2H), 3.58 (t, J = 8.2 Hz, 2H), 3.96 (dd, J = 7.3, 9.2 Hz, 1H), 4.10 (d, J = 6.6 Hz, 2H), 4.34 (t, J = 8.8 Hz, 1H), 4.78 (dd, J = 7.3, 8.6 Hz, 1H), 7.27 (s, 5H),.7.76 (s, 2H), 8.14 (s, 1H); HRMS calcd for $C_{22}H_{25}N_3O_5S$ *m/z* 443.1515, found 443.1510.

Phenyl 5-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (6h): Yield 75.0%; White solid; mp 175.1-176.5 °C; IR (KBr) 3320, 1730, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.28 (t, J = 8.6 Hz, 2H), 3.51 (t, J = 8.5 Hz, 2H), 3.91 (dd, J = 7.6, 9.5 Hz, 1H), 4.32 (t, J = 8.8 Hz, 1H), 4.77 (dd, J = 7.3, 9.7 Hz, 1H), 7.27-8.14 (m, 13H); HRMS calcd for $C_{24}H_{21}N_3O_5S$ *m/z* 463.1203, found 463.1197.

Benzyl 5-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (6i): Yield 77.0%; White solid; mp 199.1-200.8 °C; IR (KBr) 3400, 1730, 1700, 1360, 1180 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.22 (t, J = 8.6 Hz, 2H), 3.48 (t, J = 8.5 Hz, 2H) 3.89 (dd, J = 7.6, 9.6 Hz, 1H), 4.31 (t, J = 8.6 Hz, 1H), 4.73 (dd, J = 6.6, 7.7 Hz, 1H), 5.06 (t, J = 8.8 Hz, 2H), 7.20-8.05 (m, 13H); HRMS calcd for $C_{25}H_{23}N_3O_5S$ *m/z* 477.1358, found 477.1352.

General Procedure of the Synthesis of (7b-g). The solution of compound **14 or 7a** in acetonitrile was added to acetic anhydride, benzoyl chloride or aryl, alkyl chloroformate (1.1 eq). The reaction mixture was refluxed for 1-2 h and then removed the solvent under reduced pressure. The obtained residue was further separated by flash column chromatography to give **7b-g**.

1-(5-(4-Phenyl-2-thioxoimidazolidin-1-ylsulfonyl) indolin-1-yl) ethanone (7b): Yield : 55%; white solid; mp : 230.1-230.8 °C; IR (KBr) 3220, 1650 cm^{-1}; NMR($CDCl_3$) δ 2.22

(s, 3H), 3.27 (t, *J* = 8.4 Hz, 2H), 3.58 (t, *J* = 8.5 Hz, 2H) 3.92 (dd, *J* = 7.6, 9.6 Hz, 1H), 4.50 (t, *J* = 8.8 Hz, 1H), 4.92 (dd, *J* = 7.6, 9.8 Hz, 1H), 7.17-7.50(m, 5H), 7.79-8.00 (m, 2H), 8.21-8.36 (m, 1H); HRMS calcd for $C_{19}H_{19}N_3O_3S_2$ *m/z* 401.0868, found 401.0862.

Methyl 5-(4-phenyl-2-thioxoimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (7c): Yield : 71%; mp : 224.8-225.8 °C; white solid:; IR(KBr) 3300, 1700, 1480, 1320, 1180, 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.19 (t, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 3.60 (t, *J* = 8.5 Hz, 2H) 3.90 (dd, *J* = 7.6, 9.6 Hz, 1H) 4.63 (t, *J* = 9.4 Hz, 1H), 4.91 (dd, *J* = 7.7, 9.6 Hz, 1H), 7.26-7.43 (m, 5H), 7.87-7.99 (m, 3H); HRMS calcd for $C_{19}H_{19}N_3O_4S_2$ *m/z* 417.0817, found 417.0812.

Ethyl 5-(4-phenyl-2-thioxoimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (7d): Yield : 85%; mp : 204.8-205.6 °C; white solid; IR (KBr) 3400, 1690, 1300, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.1 Hz, 3H), 3.18 (t, *J* = 8.7 Hz, 2H), 3.62 (t, *J* = 9.5 Hz, 2H) 3.93 (dd, *J* = 7.6, 9.6 Hz, 1H), 4.44 (m, 2H), 4.63 (t, *J* = 9.5 Hz, 1H), 4.92 (dd, *J* = 7.8, 9.7 Hz, 1H), 7.38 (s, 5H), 7.87-7.92 (m, 3H); HRMS calcd for $C_{20}H_{21}N_3O_4S_2$ *m/z* 431.0973, found 431.0968.

Allyl 5-(4-phenyl-2-thioxoimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (7e): Yield : 76%; mp : 190.8-192 °C; white solid; IR(KBr) 3400, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$,) δ 3.19 (t, *J* = 8.7 Hz, 2H), 3.65 (t, *J* = 8.5 Hz, 2H) 3.97 (dd, *J* = 7.6, 9.6 Hz, 1H), 4.53 (t, *J* = 8.8 Hz, 1H), 4.95 (dd, *J* = 7.8, 9.7 Hz, 1H), 5.01 (m, 2H), 5.28 (m, 2H), 5.99 (dd, J = 5.7,11.3 Hz 1H), 7.31-7.42 (m, 5H), 7.88-7.93 (m, 3H); HRMS calcd for $C_{21}H_{21}N_3O_4S_2$ *m/z* 443.0973, found 443.0966.

Isobutyl 5-(4-phenyl-2-thioxoimidazolidin-1-ylsulfonyl) indoline-1-carboxylate (7f): Yield : 77%; mp : 168.2-170.6 °C; white solid; IR(KBr) 3400, 2950, 1690 cm^{-1}; NMR ($CDCl_3$) : δ 1.01(d, *J* = 6.6 Hz, 6H), 2.20 (m, 1H), 3.19 (t, *J* = 9.8 Hz, 2H), 3.62 (t, *J* = 9.3 Hz, 2H), 3.90 (dd, *J* = 7.6, 9.6 Hz, 1H), 4.23 (m, 2H), 4.63 (t, *J* = 9.4 Hz, 1H), 4.92 (dd, *J* = 7.8, 9.7 Hz, 1H), 7.31-7.42 (m, 5H), 7.86-7.92 (m, 3H); HRMS calcd for $C_{22}H_{25}N_3O_4S_2$ *m/z* 459.1286, found 459.1280.

Phenyl (5-(4-phenyl-2-thioxoimidazolidin-1-ylsulfonyl) indolin-1-yl) methanone (7g): Yield : 88%; mp : 214.2 - 214.8 °C; white solid; IR (KBr) 3250, 1640, 1470, 1370, 1150 cm^{-1}; NMR($CDCl_3$) : δ 3.19 (t, *J* = 8.3 Hz, 2H), 3.60 (t, *J* = 8.1 Hz, 2H), 3.91 (dd, *J* = 7.6, 9.6 Hz, 1H), 4.63 (t, *J* = 9.2 Hz, 1H), 4.91 (dd, *J* = 7.8, 9.7 Hz, 1H), 7.20-8.00(m, 13H); HRMS calcd for $C_{24}H_{21}N_3O_4S_2$ *m/z* 479.0973, found 479.0967.

General Procedure for the Synthesis 7h-i. The solution of compound **14 (or 7a)** in anhydrous toluene was added to phenyl isocyanate or isopropyl isocyanate (1.1 eq). The reaction mixture was refluxed for 24-72 h and then removed toluene. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried with anhydrous sodium sulfate and evaporated under vacuum. The residue was then separated by flash column chromatography to give **7h** & **7i**.

***N*-Phenyl-5-(4-phenyl-2-thioxoimidazolidin-1-ylsulfonyl) indoline-1-carboxamide (7h):** Yield : 85%; mp : 137.9-140.2 °C; white solid; IR (KBr) 3350, 1640, 1520, 1330, 1180 cm^{-1}; NMR(acetone-d_6) : δ 3.18 (t, *J* = 7.9 Hz, 2H), 3.64 (t, *J* = 8.0.5 Hz, 2H), 3.96 (dd, *J* = 7.6, 9.6 Hz, 1H), 4.59 (t, *J* = 9.4 Hz, 1H), 4. 98 (dd, *J* = 7.8, 9.7 Hz, 1H), 6.97-8.23(m, 13H); HRMS calcd for $C_{24}H_{22}N_4O_3S_2$ *m/z* 478.1133, found 478.1126.

***N*-Isopropyl-5-(4-phenyl-2-thioxoimidazolidin-1-ylsulfonyl) indoline-1-carboxamide (7i):** Yield : 55%; mp : 118.8-119.6 °C; white solid; IR (KBr) 3350, 2950, 1650, 1470, 1350, 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 1.24 (d, *J* = 6.3 Hz, 6H), 3.20 (t, *J* = 8.4 Hz, 2H), 3.66 (t, *J* = 8.5 Hz, 2H), 3.88 (m, 1H), 3.97 (dd, *J* = 7.6, 9.6 Hz, 1H), 4.60 (t, *J* = 8.4 Hz, 1H), 4. 91 (dd, *J* = 7.8, 9.7 Hz, 1H), 7.19-7.42 (m, 5H), 7.73-8.12(m, 3H); HRMS calcd for $C_{21}H_{24}N_3O_4S_2$ *m/z* 444.1290, found 444.1284.

2-(Methylthio)-4-phenyl-4,5-dihydro-1H-imidazole (15): The solution of compound **11** (0.5 g, 2.8 mmol) in acetone (20 mL) was added to the 1N NaOH (4 mL) at room temperature. The resulting mixture was stirred for 10 minutes and then added to methyl iodide (0.193 mL, 3.1 mmol). The resulting mixture was stirred for 30 minutes at room temperature and then removed acetone. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried with anhydrous sodium sulfate and evaporated under vacuum to give **15**.

Yield : 92%; mp :109.8-110.3 °C; white solid; IR (KBr) 3100, 1550 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.88 (dd, *J* = 7.3, 9.6 Hz, 1H), 4.65 (t, *J* = 9.6 Hz, 1H), 4.90 (t, *J* = 9.6 Hz, 1H), 7.32 (s, 5H).

General Procedure for the Synthesis of 16. The N-trifluoroacetylindolin-5-sulfonyl chloride **12** was added to the mixture of compounds **15** and sodium bicarbonate (1.5 eq) in acetone-water (1:1). The resulting mixture was stirred for 2 h at room temperature and then extracted with dichloromethane three times. The organic layer was dried with anhydrous sodium sulfate and evaporated under vacuum. The residue was then separated by flash column chromatography to give **16**.

2,2,2-Trifluoro-1-(5-(2-(methylthio)-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)indolin-1-yl)ethanone (16): Yield : 80%; mp : 160.4-161.5 °C; white solid; IR (KBr) 1670, 1580, 1470, 1320, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.51 (s, 3H), 3.21 (t, *J* = 8.4 Hz, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 3.84 (dd, *J* = 7.29, 9.5 Hz, 1H), 4.66 (t, *J* = 9.6 Hz, 1H), 4.88 (dd, *J* = 7.3, 9.5 Hz, 1H), 7.01-7.27 (m, 5H), 7.82-7.96 (m, 2H), 8.34 (d, *J* = 8.59 Hz, 1H).

General Procedure for the Synthesis of 17. The solution of compound **16** in acetone was added to the sodium hydroxide (1.05 eq) and water at room temperature. The resulting mixture was stirred for 0.5 h and then added dichloromethane. The organic layer was dried with anhydrous sodium sulfate and evaporated under vacuum to give **17**.

5-(2-(Methylthio)-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl) indoline (17): Yield 98%; yellow oil; IR (neat): 3380, 1600 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 2.44 (s, 3H), 3.21 (t, *J* =

8.4 Hz, 2H), 3.66 (t, *J* = 8.4 Hz, 2H), 3.79 (dd, *J* = 7.29, 9.5 Hz, 1H), 4.65 (t, *J* = 9.5 Hz, 1H), 4.89 (dd, *J* = 7.3, 9.5 Hz, 1H), 6.54-6.63(m, 1H), 7.04-7.65(m, 7H).

General Procedure of the Synthesis of 17a-b. The solution of compound **17** (1.0 eq) in anhydrous acetonitrile was added to isocyanates (acyl halides or chloroformates) (1.1 eq) at room temperature. The resulting mixture was stirred for 2 h, added water and then extracted with dichloromethane three times. The organic layer was dried with anhydrous sodium sulfate and evaporated under vacuum to give **17a-b**.

Ethyl 5-(2-(methylthio)-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)indoline-1-carboxylate (17a): yield : 71%; mp : 112.8-114.2 °C; white solid; IR(KBr) 1700, 1480 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 1.38(t, *J* = 8.0 Hz, 3H), 2.50 (s, 3H), 3.25 (t, *J* = 8.7 Hz, 2H), 3.66 (t, *J* = 9.5 Hz, 2H), 3.72 (dd, *J* = 7.3, 9.6 Hz, 1H), 4.02 (m, 2H), 4.65 (t, *J* = 8.8 Hz, 1H), 4.96 (dd, *J* = 7.3, 9.7 Hz, 1H), 6.97-7.21 (m, 5H), 7.69-7.91 (m, 3H).

5-(2-(Methylthio)-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-*N*-phenylindoline-1-carboxamide (17b): yield : 95%; mp : 178.2-180 °C; white solid; IR (KBr) 3370, 1670, 1430, 1320, 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 2.45(s, 3H), 3.21(t, *J* = 8.5 Hz, 2H), 3.66 (t, *J* = 8.5 Hz, 2H), 3.77 (dd, *J* = 7.3, 9.6 Hz, 1H), 4.63 (t, *J* = 8.8 Hz, 1H), 4.97 (dd, *J* = 7.3, 9.7 Hz, 1H), 6.49 (s, 1H), 7.09-7.82 (m, 12H), 8.07 (d, *J* = 8.5 Hz, 1H).

General Procedure for the Synthesis of 8a-c. The solution of compounds **17 and 17a-b** (1.0 eq) in anhydrous chloroform was added to triethylamine (3.0 eq) and hydroxylamine hydrochloride (2.5 eq) at room temperature. The resulting mixture was refluxed for 72 h and then cooled at room temperature. The precipitate was filtered and then washed with methylene chloride to give **8a-c**.

1-(Indolin-5-ylsulfonyl)-4-phenylimidazolidin-2-one oxime (8a): Yield: 64%; mp : 204.2204.6 °C; white solid; IR (KBr) 3370, 1690, 1600, 1320, 1120, 1060 cm^{-1}; ^{1}H-NMR (DMSO-d_6) : δ 3.20 (t, *J* = 8.5 Hz, 2H), 3.65 (t, *J* = 8.5 Hz, 2H), 2.97 (t, *J* = 8.54 Hz, 2H), 3.78 (dd, *J* = 7.3, 9.6 Hz, 1H), 4.60 (t, *J* = 8.8 Hz, 1H), 4.98 (dd, *J* = 7.3, 9.7 Hz, 1H), 6.47 (d, *J* = 9.03 Hz, 1H), 7.28-7.51(m, 7H), 8.88(s, 1H), 11.0(s, 1H); HRMS calcd for $C_{17}H_{18}N_4O_3S$ *m/z* 358.1100, found 358.1095.

Ethyl 5-(2-(hydroxyamino)-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)indoline-1-carboxylate (8b): yield: 13%; mp : 217.2-218.8 °C; white solid; IR (KBr) 3400, 1700, 1480, 1300, 1140 cm^{-1}; NMR(DMSO-d_6 + acetone-d_6) δ 1.32 (t, *J* = 7.1 Hz, 3H), 3.23 (t, *J* = 8.6 Hz, 2H), 3.68 (t, *J* = 8.5 Hz, 2H), 2.92 (t, *J* = 8.5 Hz, 2H), 3.80 (dd, *J* = 7.3, 9.6 Hz, 1H), 4.65 (t, *J* = 8.9 Hz, 1H), 4.91 (dd, *J* = 7.3, 9.7 Hz, 1H), 7.30(s, 5H), 7.72- 7.80(m, 3H), 8.99(s, 1H), 11.01(s, 1H); HRMS calcd for $C_{20}H_{22}N_4O_5S$ *m/z* 430.1311, found 430.1304.

5-(2-(Hydroxyamino)-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-N-phenylindoline-1-carboxamide (8c): yield : 49.7%; mp : 169.5-169.7 °C; white solid; IR (KBr) 3350, 1650, 1440, 1340, 1140 cm^{-1}; NMR (DMSO-d_6) : δ 3.20 (t, *J* = 8.6 Hz, 2H), 3.70 (t, *J* = 8.5 Hz, 2H), 2.93 (t, *J* = 8.5 Hz, 2H), 3.82 (dd, *J* = 7.3, 9.6 Hz, 1H), 4.67 (t, *J* = 8.8 Hz, 1H), 4.96 (dd, *J* = 7.3, 9.7 Hz, 1H), 7.04-7.75(m, 12H), 7.99(d, *J* = 9.0 Hz, 1H), 8.72 (s, 1H), 11.03(s, 1H); HRMS calcd for $C_{24}H_{23}N_5O_4S$ *m/z* 477.1471, found 477.1465.

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