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Original article

Structure–activity relationship studies of novel arylsulfonylimidazolidinones for their anticancer activity

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ABSTRACT

To define the SAR, a series of novel *N*-arylsulfonylimidazolidinone derivatives were evaluated for their *in vitro* anticancer activity against five human tumor cell lines, including A549, COLO205, KATO III, K562, SK-OV-3 and murine leukemia (P288D1) cell line. Among them, *N*-(2-chloroacetyl)-6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (**4m**) and *N*-cyclohexyl-6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (**4n**) exhibited comparable *in vitro* anticancer activity to doxorubicin against A549, KATO III and K562 cell lines and gave superior xenographic results against NCI-H23 and SW620 cancer cell lines. Regarding the structure–activity relationship, two critical points were discovered; the steric congestion at 4-position of *N*-arylsulfonylimidazolidinone scaffold abolishes the activity and the bulkiness or hydrophobicity of acyl groups at 3,4-dihydroquinoline of **4**, especially with carbamoyl moiety, enormously enhances the activity.

1. Introduction

For several decades, the antimitotic agents are being used for the treatment of cancer [1,2]. These agents interfere with the dynamics of tubulin polymerization and depolymerization, resulting in the inhibition of chromosome segregation during mitosis and consequently the inhibition of cell division [3–5]. Although antimitotic compounds such as taxanes and vinca alkaloids have been clinically used as essential chemotherapeutics in the treatment of different type of cancers, a major drawback of these compounds in clinical application is the development of drug resistance through the expression of efflux pumps, including P-glycoprotein (P-gp) and multi-drug resistance associated protein MRP [6,7]. Therefore, it is essential to find and develop novel antimitotic agents which will be effective in treating multi-drug resistant (MDR) tumors.

Keeping these facts in mind, Jung and coworkers discovered a novel 4-phenyl-l(*N*)-arylsulfonylimidazolidinones **3** (Fig. 1) [8], which contains a sulfonylurea unit and demonstrated highly potent anticancer activity against the various cancer cell lines [9–12]. The structure–activity relationship studies revealed 4-phenyl-1-benzenesulfonylimidazolidinone as a basic pharmacophore [8,13–16] required for the anticancer activity. Therefore, a numerous analogs of **3** have been studied by the substitutions around the phenyl group on sulfonyl moiety. Interestingly, the STERIMOL L parameter of these substituents at *p*-position seems to be well correlated with the activity [13]. Among the compounds studied, **3d** (Fig. 1) [8] with the longest acetamido group was most potent. The fused bicyclic analog **3e** (Fig. 1) [8] containing indanyl on sulfonyl had also shown very good potency, which is comparable to doxorubicin. However, the compound **3f** (Fig. 1) [8] was less potent than **3e** (Fig. 1) [8]. This may imply that substituents of a small volume at the 3-position additionally increase the activity. These two factors were integrated into the design of **3g** (Fig. 1) [17] analogs containing indoline moiety. As a result, these compounds exhibited a very good anticancer activity against various tumor cell lines. Later, our group [18] synthesized various derivatives of **3g** and studied them for their antitumor activity. It was observed that the synthesized compounds are not only the potent inhibitors of tubulin polymerization but also maintain activity against multi-drug resistant tumor cell lines, which implies that they are not a substrate for P-glycoprotein mediated transport, like taxanes and vinca alkaloids derivatives. These findings were very much encouraging for us to continue our search for potent analogs. Therefore in this study, we have replaced indoline moiety in **3g** with 3,4-dihydroquinoline to design and synthesize a number of analogs of **4** and evaluated their *in vitro* inhibitory activities against five human cancer cell lines (human lung A549, human

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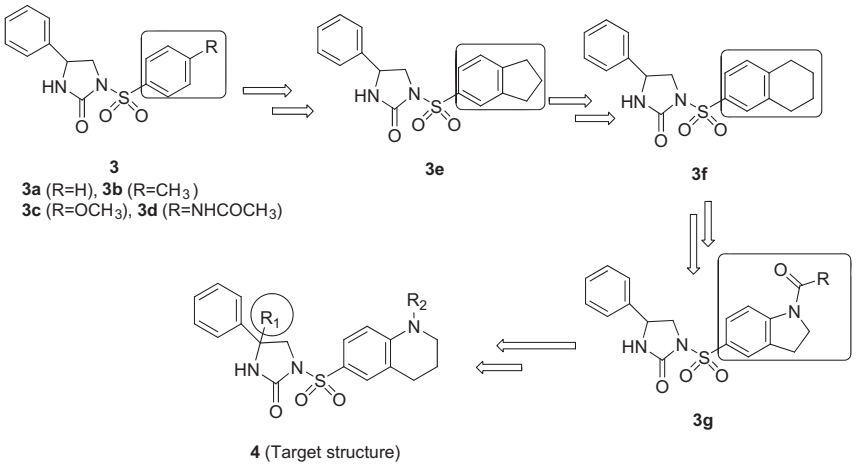


Fig. 1. Structural modification on *N*-arylsulfonylimidazolidinones.

colon COLO205, human stomach KATO III, human leukemia K562, human ovary SK-OV-3) and one murine leukemia cell line P388D1. Highly active compounds **4m** and **4n** were subjected to *in vivo* study.

2. Chemistry

A series of *N*-arylsulfonylimidazolones **4** were prepared as illustrated in Scheme 1. Intermediate **7a** [9] was prepared with previously reported method and **7b** was prepared from the 2-phenyl-1-propene **5b** according to the procedure for preparation of **7a**. The treatment of **5b** with *N*-bromosuccinimide and cynamide in dichloromethane gave *N*-(1-bromo-2-phenylpropan-2-yl)cyanamide **6b** in 65.3% isolated yield after flash column chromatography. Compounds **6b** can be stored at −10 °C without major decomposition for at least one week. Compound **6b** was treated with methanol containing 5% hydrochloride at 35–40 °C for 6–8 h to form *in situ* isourea intermediate and the resulting reaction mixture was then stirred with 2 equivalent of sodium carbonate at room temperature overnight to give the compound **7b**. Reaction of **7** with the corresponding arylsulfonyl chlorides **8** [18] in the presence of sodium bicarbonate in acetone–water (1:1) produced regioisomers **9** and **10** with an approximate ratio of 3:7 in favor of 1-sulfonylated product **10** as shown in the case of **9c** and **10c**. Since in our previous studies [17] 1-arylsulfonylimidazolidinones **3g** (Fig. 1) was the active isomer, we only isolated regioisomer **10** in most of the cases, which was subsequently hydrolyzed to the final *N*-arylsulfonylimidazolidinones **4** as listed in Table 1.

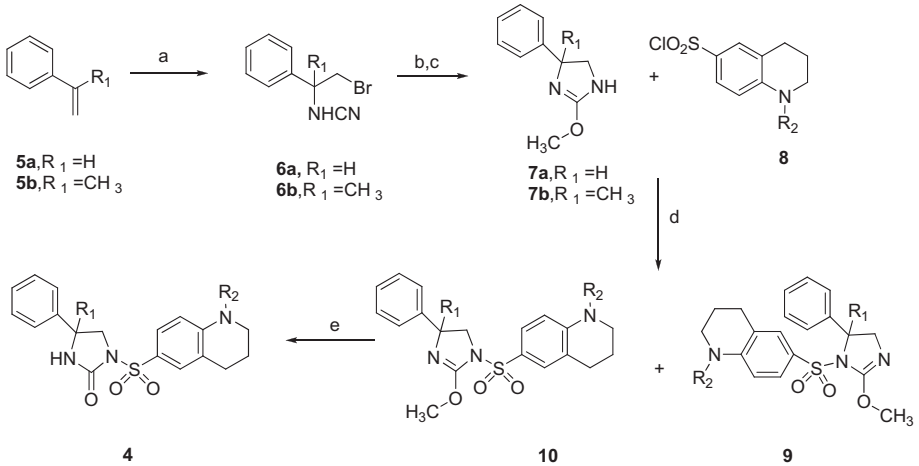
3. Pharmacology

3.1. In vitro anticancer activity

The *in vitro* anticancer activity of compounds **4a**–**q** was measured against human lung carcinoma (A549), human colon (COLO205), human stomach (KATO III), human leukemia (K562), human ovarian (SK-OV-3), and murine leukemia (P288D1) cancer cell lines using MTT assay [19,20]. The results from these tests are given as IC_{50} values in Table 2.

3.2. In vivo anticancer activity

The *in vivo* anticancer activity evaluation of **4m** and **4n** was performed against human lung carcinoma (NCI-H23) and human colon carcinoma (SW620) xenograft tumor models in mice using the previously reported procedure [12,21]. The results are shown in Table 3. To evaluate the antitumor activity of **4m**, **4n** and doxorubicin, NCI-H23 cells (6×10^6/mouse) and SW620 cells (2×10^6/



Scheme 1. Synthesis of *N*-arylsulfonylimidazolidinones **4a**–**q** (a) NBS, NH_2CN, CH_2Cl_2; (b) HCl, methanol; (c) Na_2CO_3; (d) $NaHCO_3$, acetone/H_2O, and then arylsulfonyl chloride; (e) HCl, methanol. Note = substituents (R_1 and R_2) are indicated in Table 1.

Table 1
The substituent of *N*-arylsulfonylimidazolidinones **4a**–**q**

Compound No.	R_1	R_2	Compound No.	R_1	R_2
4a	H	H	**4j**	H	COPh
4b	H	$COOCH_3$	**4k**	H	$COCF_3$
4c	H	COOEt	**4l**	H	$CONH_2$
4d	H	COO*n*Pr	**4m**	H	$CONHCOCH_2Cl$
4e	H	COO*i*Bu	**4n**	H	$CONHC_6H_{11}$
4f	H	COO*n*Bu	**4o**	CH_3	$COCF_3$
4g	H	$COOCH_2CH{=}CH_2$	**4p**	CH_3	CONHPh (*p*-SCH_3)
4h	H	$COOCH_2CH_2Cl$	**4q**	CH_3	CONHPh(*p*-OCH_3)
4i	H	$COCH_2Cl$			

mouse) were injected subcutaneously into the right flank of the nude mice. The compounds **4m** or **4n** were orally administered after dissolving in propylene glycol (Dose: 65 mg/kg/2day × 6 for NCI-H23 and SW620) on days 2, 4, 6, 8, 10 and 12 after tumor cell transplantation. Doxorubicin was intraperitoneally administered every day as 1 mg/kg on days 1–11, 2 mg/kg on days 12–14, and 3 mg/kg on days 15–18. Doxorubicin was dissolved in sterilized saline prior to administration (Table 3). On the final day, tumors were excised and weighed. Mean tumor weights were determined and used to calculate the tumor growth inhibition (TGI) expressed as a percentage:

$$\%\mathrm{TGI} = [1 - (\text{mean final tumor weight}_{\text{treated}}/\text{mean final tumor weight}_{\text{control}})] \times 100$$

4. Result and discussion

4.1. Structure–activity relationship

As shown in Table 2, the synthesized compounds **4a**–**n** exhibited comparable or superior activities to sulofenur against almost all tested cancer cell lines [22]. In particular, compounds **4c** ($IC_{50} = 0.344$ μM), **4m** ($IC_{50} = 0.449$ μM) and **4n** ($IC_{50} = 0.231$ μM) possess most potent anticancer activity against A549 cell lines comparable to doxorubicin.

In our previous studies, we observed that the bicyclic system at sulfonyl group of **3g** is important for the anticancer activity [17].

Table 2
Anticancer activity of *N*-arylsulfonylimidazolidinones **4a**–**q** against human cancer cell lines.

Compd. No.	IC_{50} (μM)[a]					
	A549	COLO205	KATO III	K562	SK-OV-3	P388D1
4a	>20	7.232	>20	>20	10.385	4.246
4b	1.145	4.015	16.535	>20	3.482	2.264
4c	0.344	2.782	11.181	>20	2.877	1.425
4d	1.034	1.418	3.304	>20	3.924	2.023
4e	>20	3.721	2.745	2.377	5.650	1.245
4f	>20	4.106	4.010	3.675	9.573	2.084
4g	4.310	6.585	5.046	0.473	2.747	0.945
4h	>20	2.821	8.676	10.619	9.797	1.212
4i	Nt[b]	11.193	3.464	1.095	Nt[b]	Nt[b]
4j	8.142	19.302	14.290	1.218	8.558	5.340
4k	>20	10.727	13.079	>20	19.595	4.717
4l	2.535	>20	3.588	3.655	>20	12.266
4m	0.449	9.905	2.535	0.515	6.139	3.870
4n	0.231	3.893	8.920	0.813	1.840	8.161
4o	>20	>20	>20	>20	>20	>20
4p	>20	>20	Nt[b]	>20	>20	>20
4q	5.303	>20	Nt[b]	12.427	9.474	15.889
Sulofenur	>20	23.060	31.400	19.200	78.200	>100
Doxorubicin	0.477	0.400	4.380	0.198	2.947	0.338

[a] IC_{50} values are taken as a mean from 3 experiments.
[b] Nt* = not tested.

Thus in the current study, the indoline moiety of **3g** was replaced with 3,4-dihydroquinoline at this position of *N*-arylsulfonylimidazolidinones. In addition, we studied the effect of substitutions with alkoxycarbonyl, acyl and most importantly carbamoyl groups at 1-position of 3,4-dihydroquinoline of the *N*-arylsulfonylimidazolidinones.

Interestingly, carbamate compounds **4b**–**j** gave far better activity than **4a** or sulofenur, toward almost all cell lines and some of them showed even comparable activity to doxorubicin. However, the activity of carbamate analogs **4b**–**j** varied each other with cell lines. The compound **4c** showed the best activity against A549 and SK-OV-3(IC_{50} value; 0.334, 2.877 μM, respectively), so did **4d** (against COLO205), **4e** (against KATO III) and **4g** (against K562 and P388D1). The activity of **4c** against A549 and SK-OV-3 and the compounds **4d**, **4e** and **4f** toward human stomach KATO III have comparable activity to those of doxorubicin. The compound **4g** (IC_{50} value; 0.473; 2.747 and 0.945 μM, respectively) showed comparable activity to doxorubicin against human leukemia K562, human ovary SK-OV-3 and murine leukemia P388D1.

Introduction of various acyl substitutions at 1-position of 3,4-dihydroquinoline of **4** also showed very potent anticancer activity. Especially, chloroacetyl analog **4i** (IC_{50} value; 3.464 μM) gave comparable activity to doxorubicin against human stomach KATO III. The benzoyl analog **4j** exhibited better activity than acetyl analogs **4i** and **4k** against human lung A549 and leukemia P388D1 cell lines.

Further, introduction of carbamoyl substitutions at this position enhances the activity considerably. Compounds **4m** and **4n** have shown nearly comparable activity to doxorubicin against human lung A549, human stomach KATO III and human leukemia K562. These findings confirm that the carbamoyl moiety enhances the potency of **4** toward the various cell lines. In addition, comparison of the activity of **4m** and **4n** to that of **4l** reveals that the increment of lipophilicity of urea moiety is also important for activity enhancement. Taken together, on increasing the bulkiness or lipophilicity of *N*-arylsulfonylimidazolidinones **4** with the introduction of alkoxycarbonyl, acyl or most importantly carbamoyl groups at 1-position of 3,4-dihydroquinoline enhances their anticancer activity.

To explore the influence of the substitution on imidazolidinone ring of **4**, a methyl group was introduced at 4-position of imidazolidinone group as shown in **4o**–**q**. Surprisingly, the activities of **4o**, **4p** and **4q** show very weak inhibition against all cell lines. As compared to **4k**, the disappearance of activity of **4o** indicates that the steric congestion at this position is unfavorable for the activity.

Table 3
Xenografic Studies of *N*-arylsulfonylimidazolidinones **4m** and **4n**.

Tumor[a]	Mice[b]	Agent	Dose (mg/kg)	Administered route	Body weight change[c] (g)	TGI[d] (%)
NCI-H23	HTXM[e]	Vehicle only		p.o.	1.2	
		4m	65	p.o.	−0.6	58.5
		4n	65	p.o.	1.6	65.2
		Doxorubicin	1, 2, 3	i.p.	−1.6	39.6
SW620	HTXM	Vehicle only		p.o.	1.1	
		4m	65	p.o.	1.0	67.0
		4n	65	p.o.	2.0	72.6
		Doxorubicin	1, 2, 3	i.p.	−2.3	45.0

[a] NCI-H23: human carcinoma, SW620: human colon carcinoma.
[b] Numbers of mice used were 7 per group for NCI-H23 and SW620.
[c] Body weight change was calculated from day 0 to day 20.
[d] Tumor growth inhibition (TGI %) was determined at day 19 for NCI-H23 and SW620 after transplantation.
[e] Human tumor xenograft mice (HTXM: BALB/c-nu/nu mice) were purchased from Charles River Laboratories in Japan and used as 5 weeks old female.

Thus, phenylimidazolidinone motif should be the main pharmacophore of **4**.

4.2. Anticancer activity

Such remarkable *in vitro* activity of compounds **4m** and **4n** led us to investigate its antitumor activities *in vivo* against human lung carcinoma (NCI-H23) and human colon carcinoma (SW620) xenograft tumor models in mice. The results are shown in Table 3. Without any significant change of body weight of mice, compound **4m** (Dose: 65 mg/kg/2day × 6) showed 58.5 and 67.0% TGI against NCI-H23 and SW620 xenograft tumor models in mice, respectively. Compound **4n** (Dose: 65 mg/kg/2day × 6) showed 65.2 and 72.6% TGI against NCI-H23 and SW620 xenograft tumor models in mice, respectively. These antitumor activities of **4m** and **4n** are superior to doxorubicin, which was intraperitoneally administered at its toxicity-limiting dose. Therefore, compounds **4m** and **4n** are considered to be valuable candidates for the development of new anticancer agents containing sulfonylurea pharmacophore.

5. Conclusion

On the basis of our previous [17] and current studies, the structural requirements of *N*-arylsulfonylimidazolidinone analogs for their anticancer activity against tested cell lines are as follows; (i) 4-phenyl-1-benzenesulfonylimidazolidinone as a basic pharmacophore, (ii) steric congestion at 4-position of *N*-arylsulfonylimidazolidinone scaffold abolishes the activity, (iii) the bicyclic system is important at sulfonyl function and (iv) increasing the bulkiness or hydrophobicity at bicyclic system of acyl groups, especially with carbamoyl moiety enormously enhances the activity.

6. Materials and method

6.1. Chemistry

Melting points (mp) were determined on Electro thermal 1A 9100 MK2 apparatus and are uncorrected. All commercial chemicals were used as obtained and all solvents were purified by the standard procedures prior to use [23]. Flash column chromatography was performed with E Merck silica gel (230–400 mesh). FT-IR spectrum was recorded by Nicolet – 380 model. ^{1}H and ^{13}C NMR spectra were measured against the peak of tetramethylsilane by Varain Unity Inova (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometers. High resolution mass spectrum (HRMS) was recorded on PE SCIEX API 2000 (triple quadrupole) mass spectrophotometer (Applied Biosystems, Foster City, CA, USA).

6.1.1. *N-(1-Bromo-2-phenylpropan-2-yl)cyanamide (**6b**)*

This compound was synthesized by the same procedure as described previously [9] using α-methylstyrene instead of styrene. Yield 65.3%; Colorless liquid; IR (KBr) 3150, 2950, 2200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73(s, 3H), 3.66(s, 2H), 3.63(d, J = 6.0 Hz, 1H), 5.24(bs, exchangeable with D_2O, 1H), 7.36(s, 5H); HRMS calcd for $C_{10}H_{11}BrN_2$ m/z 238.0106, found 238.0101.

6.1.2. *2-Methoxy-4-methyl-4-phenyl-4,5-dihydro-1H-imidazole (**7b**)*

This compound was synthesized by the same procedure as described previously [9] using compound **6b**.Yield 88.0%; Yellowish liquid; IR (KBr) 3250, 2950, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3H), 3.70 (s, 2H), 3.91 (s, 3H), 7.26–7.37 (s, 5H); HRMS calcd for $C_{11}H_{14}N_2O$ m/z 190.1106, found 190.1098.

6.2. General procedure of the synthesis of N-aryl-sulfonylimidazole (**9**) and (**10**)

These derivatives were synthesized by the same procedure as described previously [9]. In brief, an appropriate amount of arylsulfonyl chlorides **8** (1.0 equivalent) were added to the mixture of compounds **7** and sodium bicarbonate (1.5 equivalents) 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 dehydrated with anhydrous sodium sulfate and evaporated under vacuum. The compounds **9** and **10** were then separated from the residue by flash column chromatography.

6.2.1. *6-(2-Methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-1,2,3,4-tetrahydroquinoline (**10a**)*

Yield 100%; Pale yellowish liquid; IR (KBr) 3370, 2900, 1640, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.91 (quin, J = 6.1 Hz, 2H), 2.73 (t, J = 6.2 Hz, 2H), 3.37 (t, J = 6.2 Hz, 2H), 3.61 (dd, J = 7.2, 9.5 Hz, 1H), 3.89 (s, 3H), 4.20 (dd, J = 7.2, 9.5 Hz, 1H), 4.55 (bs, exchangeable with D_2O, 1H), 4.86 (dd, J = 7.4, 9.4 Hz, 1H), 6.70–7.47 (m, 8H); HRMS calcd for $C_{19}H_{21}N_3O_3S$ m/z 371.1304, found 371.1298.

6.2.2. *Methyl 6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**10b**)*

Yield 46.2%; Colorless liquid; IR (KBr) 2940, 1705, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.96 (quin, J = 5.9 Hz, 2H), 2.81 (t, J = 6.0 Hz, 2H), 3.72 (dd, J = 7.2, 9.8 Hz, 1H), 3.82 (t, J = 5.9 Hz, 2H), 3.85 (s, 3H), 3.97 (s, 3H), 4.32 (dd, J = 7.2, 9.8 Hz, 1H), 4.91 (dd, J = 7.1, 9.2 Hz, 1H), 7.05–7.32 (m, 5H), 7.62–8.01(m, 3H); HRMS calcd for $C_{21}H_{23}N_3O_5S$ m/z 429.1358, found 429.1346.

6.2.3. *Ethyl 6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**10c**); ethyl 6-(2-methoxy-5-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**9c**)*

10c; Yield 47.5%; Colorless liquid; IR (KBr) 2940, 1700, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.3 Hz, 3H), 1.96 (quin, J = 6.4 Hz, 2H), 2.80 (t, J = 6.4 Hz, 2H), 3.72 (dd, J = 7.1, 9.5 Hz, 1H), 3.81 (t, J = 6.4 Hz, 2H), 3.97 (s, 3H), 4.30 (q, J = 7.3 Hz, 2H), 4.31 (dd, J = 7.3, 9.5 Hz, 1H), 4.90 (dd, J = 7.2, 9.4 Hz, 1H), 7.05–8.09 (m, 8H); HRMS calcd for $C_{22}H_{25}N_3O_5S$ m/z 443.1515, found 443.1504. **9c**; Yield 13.9%; Colorless liquid; IR (KBr) 2940, 1700, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.3 Hz, 3H), 1.96 (m, 2H), 2.02–2.21 (m, 2H), 2.64 (t, J = 6.4 Hz, 2H), 3.34 (t, J = 6.0 Hz, 2H), 3.82 (s, 3H), 5.34 (dd, J = 7.1, 9.5 Hz, 1H), 4.15 (t, J = 6.4 Hz, 2H), 7.05–7.94 (m, 8H), HRMS calcd for $C_{22}H_{25}N_3O_5S$ m/z 443.1515, found 443.1506.

6.2.4. *Propyl 6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**10d**)*

Yield 37.7%; Colorless liquid; IR (KBr) 2950, 1700, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7.4 Hz, 3H), 1.64–1.87 (m, 2H), 1.97 (quin, J = 6.2 Hz, 2H), 2.81(t, J = 6.4 Hz, 2H), 3.72 (dd, J = 7.3, 9.7 Hz, 1H), 3.82 (t, J = 7.4 Hz, 2H), 3.97 (s, 3H), 4.21 (t, J = 6.9 Hz, 2H), 4.32 (dd, J = 7.3, 9.7 Hz, 1H), 4.91 (dd, J = 7.5, 9.7 Hz, 1H), 7.05–7.31 (m, 5H), 7.62–8.08 (m, 3H); HRMS calcd for $C_{23}H_{27}N_3O_5S$ m/z 457.1671, found 457.1664.

6.2.5. *Isobutyl 6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**10e**)*

Yield 43.7%; Colorless liquid; IR (KBr) 2950, 1700, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 6.6 Hz, 6H), 2.00 (quin, J = 6.2 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 3.75 (dd, J = 7.4, 9.7 Hz, 1H), 3.87 (t, J = 6.2 Hz, 2H), 4.00 (s, 3H), 4.07 (d, J = 6.6 Hz, 2H), 4.36 (dd, J = 7.4, 9.7 Hz, 1H), 4.94 (dd, J = 7.2, 9.4 Hz, 1H), 7.08–8.15 (m, 8H); HRMS calcd for $C_{24}H_{29}N_3O_5S$ m/z 471.1828, found 471.1820.

*6.2.6. Butyl 6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**10f**)*

Yield 27.2%; Colorless liquid; IR (KBr) 2950, 1700, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 6.3 Hz, 3H), 1.22–1.74 (m, 4H), 1.91 (quin, J = 6.5 Hz, 2H), 2.75 (t, J = 6.6 Hz, 2H), 3.67 (dd, J = 7.3, 9.8 Hz, 1H), 3.76(t, J = 6.6 Hz, 2H), 3.92 (s, 3H), 4.19 (t, J = 6.4 Hz, 2H), 4.27(dd, J = 7.3, 9.7 Hz, 1H), 4.86 (dd, J = 7.5, 9.2 Hz, 1H), 7.00–8.05 (m, 8H); HRMS calcd for $C_{24}H_{29}N_3O_5S$ m/z 471.1828, found 471.1822.

*6.2.7. Allyl 6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**10g**)*

Yield 100.0%; Colorless liquid; IR (KBr) 2950, 1720, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94 (m, 2H), 2.77 (t, J = 6.3 Hz, 2H), 3.62 (m, 2H), 3.76 (m, 2H), 3.85 (s, 3H), 4.25 (dd, J = 7.3, 9.0 Hz, 1H), 4.74 (d, J = 5.3 Hz, 2H), 4.74 (m, 1H), 5.24–5.46 (m, 2H), 5.82–6.23 (m, 1H), 7.22–8.06 (m, 8H); HRMS calcd for $C_{23}H_{25}N_3O_5S$ m/z 455.1515, found 455.1508.

*6.2.8. 2-Chloroethyl 6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**10h**)*

Yield 26.5%; Colorless liquid; IR (KBr) 2950, 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (quin, J = 6.0 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H), 3.65 (dd, J = 7.3, 9.7 Hz, 1H), 3.77 (t, J = 5.9 Hz, 2H), 3.86 (t, J = 6.4 Hz, 2H), 3.97 (s, 3H), 4.32 (dd, J = 7.3, 9.7 Hz, 1H), 4.50 (t, J = 6.4 Hz, 2H), 4.91 (dd, J = 7.3, 9.4 Hz, 1H), 7.06–8.09 (m, 8H); HRMS calcd for $C_{22}H_{24}ClN_3O_5S$ m/z 477.1125, found 477.1120.

*6.2.9. 2-Chloro-1-(6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinolin-1(2H)-yl)ethanone (**10i**)*

Yield 26.6%; Colorless liquid; IR (KBr) 2940, 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (quin, J = 6.4 Hz, 2H), 2.86 (t, J = 6.4 Hz, 2H), 3.87 (t, J = 6.4 Hz, 2H), 3.75 (dd, J = 7.0, 9.4 Hz, 1H), 3.99 (s, 3H), 4.26 (s,2H), 4.34 (dd, J = 7.3, 9.7 Hz, 1H), 4.88 (dd, J = 7.1, 9.5 Hz, 1H), 7.15–7.82 (m, 8H); HRMS calcd for $C_{21}H_{22}ClN_3O_4S$ m/z 447.1020, found 447.1012.

*6.2.10. (6-(2-Methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinolin-1(2H)-yl)(phenyl)methanone (**10j**)*

Yield 100.0%; Colorless liquid; IR (KBr) 3270, 2910, 1720, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (quin, J = 6.4 Hz, 2H), 2.92 (t, J = 6.5 Hz, 2H), 3.45 (m, 1H), 3.78 (t, J = 6.4 Hz, 2H), 4.27 (m, 1H), 4.80 (m, 1H), 7.15–7.77 (m, 13H), 8.22 (bs, exchangeable with D_2O, 1H); HRMS calcd for $C_{26}H_{25}N_3O_4S$ m/z 475.1566, found 475.1558.

*6.2.11. 2,2,2-Trifluoro-1-(6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinolin-1(2H)-yl)ethanone (**10k**)*

Yield 10.8%; Colorless liquid; IR (KBr) 2950, 1695, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (quin, J = 6.1 Hz, 2H), 3.74 (dd, J = 7.2, 9.5 Hz, 1H), 3.84 (t, J = 6.1 Hz, 2H), 3.98 (s, 3H), 4.34 (dd, J = 7.3, 9.5 Hz, 1H), 4.94 (dd, J = 7.3, 9.3 Hz, 1H), 7.07–7.38 (m, 5H), 7.72–7.98 (m, 3H); HRMS calcd for $C_{21}H_{20}F_3N_3O_4S$ m/z 467.1127, found 467.1120.

*6.2.12. 6-(2-Methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxamide(**10l**)*

Yield 00.0%; Colorless liquid; IR (KBr) 3380, 3200, 3150, 2920, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (quin, J = 5.9 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 3.43 (bs, exchangeable with D_2O, 2H), 3.63 (t, J = 5.9 Hz, 2H), 4.26 (dd, J = 7.3, 9.5 Hz, 1H), 4.80(m, 1H), 6.68 (bs, exchangeable with D_2O, 1H), 7.28–7.81 (m, 8H), 8.19 (bs, exchangeable with D_2O, 1H); HRMS calcd for $C_{20}H_{22}N_4O_4S$ m/z 414.1362, found 414.1356.

*6.2.13. N-(2-Chloroacetyl)-6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxamide (**10m**)*

Yield 75.5%; Colorless liquid; IR (KBr) 3300, 2950, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (quin, J = 6.4 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 3.74 (dd, J = 7.2, 9.4 Hz, 1H), 3.81 (t, J = 6.4 Hz, 2H), 3.98 (s, 3H), 4.34 (dd, J = 7.3, 9.4 Hz, 1H), 4.52 (s, 2H), 4.94 (dd, J = 7.2, 9.2 Hz, 1H), 7.09–7.81 (m, 8H), 8.40 (bs, exchangeable with D_2O, 1H); HRMS calcd for $C_{22}H_{23}ClN_4O_5S$ m/z 490.1078, found 490.1066.

*6.2.14. N-Cyclohexyl-6-(2-methoxy-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxamide (**10n**)*

Yield 13.6%; Colorless liquid; IR (KBr) 3250, 3100, 2950, 1700, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11–1.67 (m, 11H), 1.96 (quin, J = 5.9 Hz, 2H), 2.78 (t, J = 6.0 Hz, 2H), 3.72 (t, J = 6.0 Hz, 2H), 3.73 (dd, J = 7.2, 9.5 Hz, 1H), 3.98 (s, 3H), 4.32 (dd, J = 7.2, 9.5 Hz, 1H), 4.92 (dd, J = 7.2, 9.4 Hz, 1H), 7.07–7.35 (m, 5H), 7.63(s, 3H); HRMS calcd for $C_{26}H_{32}N_4O_4S$ m/z 496.2144, found 496.2138.

*6.2.15. 1-(N-Trifluoroacetyl-1,2,3,4-tetrahydroquinoline-6-sulfonyl)-2-methoxy-4-methyl-4-phenyl-4,5-dihydroimidazole (**10o**)*

Yield 43.6%; Colorless liquid; IR (KBr) 3050,2930, 1680, 1660 cm^{-1}; ^1H NMR (CDCl3) δ 1.54 (s, 3H), 2.09 (quin, J = 6.2 Hz, 2H), 2.89 (t, J = 7.0 Hz, 2H), 3.86 (t, J = 6.4 Hz, 2H), 3.90 (d, J = 9.5 Hz, 1H), 3.99 (s, 3H), 4.09 (d, J = 9.2 Hz, 1H), 7.27 (s, 5H), 7.66–7.93 (m, 3H); HRMS calcd for $C_{22}H_{22}F_3N_3O_4S$ m/z 481.1283, found 481.1274.

*6.2.16. 6-(2-Methoxy-4-methyl-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-N-(4-(methylthio)phenyl)-3,4-dihydroquinoline-1(2H)-carboxamide(**10p**)*

Yield 43.3%; Colorless liquid; IR (KBr) 3270, 2900, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55(s, 3H), 2.00 (quin, J = 6.4 Hz, 2H), 2.46 (s, 3H), 2.80 (t, J = 7.1 Hz, 2H), 3.81 (t, J = 6.4 Hz, 2H), 3.89 (d, J = 10.0 Hz, 1H), 4.00 (s, 3H), 4.10 (d, J = 9.0 Hz, 1H), 6.95–7.64 (m, 12H); HRMS calcd for $C_{28}H_{30}N_4O_4S_2$ m/z 550.1708, found 550.1706.

*6.2.17. 6-(2-Methoxy-4-methyl-4-phenyl-4,5-dihydroimidazol-1-ylsulfonyl)-N-(4-methoxyphenyl)-3,4-dihydroquinoline-1(2H)-carboxamide (**10q**)*

Yield 28.8%; Colorless liquid; IR (film) 3280, 2930, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H), 1.99 (quin, J = 6.2 Hz, 2H), 2.79 (t, J = 6.2 Hz, 2H), 3.71 (t, J = 5.9 Hz, 2H), 3.79 (s, 3H), 3.91 (d, J = 5.9 Hz, 1H), 4.00 (s, 3H), 4.11 (m, 1H), 6.81–7.71 (m, 12H); HRMS calcd for $C_{28}H_{30}N_4O_5S$ m/z 534.1937, found 534.1930.

*6.3. General procedure of the synthesis of imidazolidinones (**4**)*

These imidazolidinones **4** derivatives were synthesized by the same procedure with little modification as described previously [9]. In brief, the corresponding compounds **10** were dispersed in ether and then hydrochloride (3 equivalent) in methanol (>5% w/w concentration) was added. The resulting mixture was stirred for 3 h at room temperature. During the reaction, the reaction mixture become clear solution and then re-precipitated. The white solid was collected, washed with ether, and dried in vacuum oven below 60 °C to give **4**.

*6.3.1. 4-Phenyl-1-(1,2,3,4-tetrahydroquinolin-6-ylsulfonyl)imidazolidin-2-one (**4a**)*

Yield 100.0%; White solid; mp 198.5–199.4 °C; IR (KBr) 3100, 2950, 2350, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.79 (quin, J = 5.1 Hz, 2H), 2.68 (t, J = 5.1 Hz, 2H), 3.25 (t, J = 5.0 Hz, 2H), 3.40 (dd, J = 7.3, 9.8 Hz, 1H), 4.17 (t, J = 9.6 Hz, 1H), 4.74 (dd, J = 7.3, 9.5 Hz, 1H), 6.48–6.74 (m, 3H), 7.17–7.44 (m, 5H), 8.06 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 155.5, 146.9,

140.2, 129.6, 128.9, 128.4, 127.4, 125.9, 125.7, 116.3, 52.5, 41.5, 40.3, 39.5, 26.3, 20.1; HRMS calcd for $C_{18}H_{19}N_3O_3S$ *m*/*z* 357.1147, found 357.1138.

*6.3.2. Methyl 6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**4b**)*

Yield 41.8%; White solid; mp 209.0–209.5 °C; IR (KBr) 3210, 3100, 2930, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.88 (quin, J = 6.0 Hz, 2H), 2.81(t, J = 5.9 Hz, 2H), 3.52 (dd, J = 7.3, 9.2 Hz, 1H), 3.68 (dd, J = 7.3, 9.8 Hz, 2H), 3.76 (s, 3H), 4.27 (dd, J = 9.6 Hz, 1H), 4.81 (dd, J = 7.2, 9.3 Hz, 1H), 7.19–8.01 (m, 8H), 8.22 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 155.1, 154.3, 143.4, 139.6, 132.1, 130.8, 129.6, 129.3, 126.4, 125.9, 124.1, 66.1, 53.3, 52.7, 45.7, 27.9, 22.9; HRMS calcd for $C_{20}H_{21}N_3O_5S$ *m*/*z* 415.1202, found 415.1206.

*6.3.3. Ethyl 6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**4c**)*

Yield 79.3%; White solid; mp 213.9–214.6 °C; IR (KBr) 3210, 3100, 2920, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.27 (t, J = 7.0 Hz, 3H), 1.88 (quin, J = 5.9 Hz, 2H), 2.81(t, J = 5.9 Hz, 2H), 3.52 (dd, J = 7.2, 9.8 Hz, 1H), 3.75 (t, J = 5.9 Hz, 2H), 4.21(q, J = 7.0 Hz, 2H), 4.29 (t, J = 9.5 Hz, 1H), 4.81 (dd, J = 7.2, 9.4 Hz, 1H), 7.19–8.02 (m, 8H), 8.22 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 155.4, 154.8, 143.7, 139.5, 131.4, 130.4, 129.3, 129.0, 129.0, 126.1, 125.9, 123.7, 62.5, 53.0, 52.8, 45.2, 27.7, 22.7, 14.5; HRMS calcd for $C_{21}H_{23}N_3O_5S$ *m*/*z* 429.1358, found 429.1350.

*6.3.4. Propyl 6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**4d**)*

Yield 63.4%; White solid; mp 213.9–214.8 °C; IR (KBr) 3320, 3100, 2940, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.94 (t, J = 6.8 Hz, 3H), 1.64 (m, 2H), 1.89(quin, J = 6.8 Hz, 2H), 2.82 (t, J = 6.6 Hz, 2H), 3.52 (dd, J = 7.2, 9.5 Hz, 1H), 3.77 (t, J = 6.6 Hz, 2H), 4.13 (t, J = 6.2 Hz, 2H), 4.30 (t, J = 9.6 Hz, 1H), 4.81 (dd, J = 7.3, 9.4 Hz, 1H), 7.20–8.02 (m, 8H), 8.21(bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 155.4, 154.8, 143.3, 139.4, 132.2, 129.6, 129.3, 126.9, 126.1, 125.4, 124.1, 68.8, 53.7, 52.6, 45.4, 27.1, 22.1, 21.6, 9.9; HRMS calcd for $C_{22}H_{25}N_3O_5S$ *m*/*z* 443.1515, found 443.1502.

*6.3.5. Isobutyl 6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**4e**)*

Yield 62.6%; White solid; mp 190.0–191.0 °C; IR (KBr) 3220, 3100, 2950, 1720, 1700, cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.94 (d, J = 6.6 Hz, 6H), 1.89 (quin, J = 6.4 Hz, 2H), 2.81(t, J = 6.4 Hz, 2H), 3.51 (dd, J = 7.2, 9.2 Hz, 1H), 3.78 (t, J = 6.4 Hz, 2H), 3.96 (d, J = 6.6 Hz, 2H), 4.30 (t, J = 9.6 Hz, 1H), 4.81 (dd, J = 7.2, 9.2 Hz, 1H), 7.34–8.01 (m, 8H), 8.22 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 155.9, 154.9, 143.6, 139.9, 131.5, 130.4, 129.3, 128.9, 126.2, 126.0, 123.7, 72.7, 53.0, 52.8, 45.3, 28.0, 27.8, 22.8, 19.3; HRMS calcd for $C_{23}H_{27}N_3O_5S$ *m*/*z* 457.1671, found 457.1666.

*6.3.6. Butyl 6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**4f**)*

Yield 49.2%; White solid; mp 145.5–146.0 °C; IR (KBr) 3220, 3100, 2950, 1720, 1700, cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90 (t, J = 6.2 Hz, 3H), 1.16–1.71 (m, 4H), 1.86 (quin, J = 5.7 Hz, 2H), 2.79 (t, J = 6.1 Hz, 2H), 3.50 (dd, J = 7.2, 9.5 1H), 3.74 (t, J = 6.2 Hz, 2H), 4.16 (t, J = 6.4 Hz, 2H), 4.27 (t, J = 9.4 Hz, 1H), 4.78 (dd, J = 7.2, 9.3 Hz, 1H), 7.17–7.99 (m, 8H), 8.20 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 155.3, 154.2, 142.7, 139.4, 132.5, 131.0, 129.6, 129.2, 126.9, 126.1, 125.8, 125.1, 67.0, 56.2, 55.4, 45.2, 30.2, 27.0, 23.1, 18.5, 13.4; HRMS calcd for $C_{23}H_{27}N_3O_5S$ *m*/*z* 457.1671, found 457.1662.

*6.3.7. Allyl 6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**4g**)*

Yield 40.8%; White solid; mp 139.8–141.2 °C; IR (KBr) 3400, 3050, 2930, 1740, 1700, cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.89 (quin, J = 5.6 Hz, 2H), 2.81 (t, J = 6.5 Hz, 2H), 3.51 (dd, J = 7.3, 9.8 Hz, 1H), 3.78 (t, J = 6.4 Hz, 2H), 4.29 (t, J = 9.2 Hz, 1H), 4.65–4.74 (m, 2H), 4.80 (dd, J = 7.2, 9.5 Hz, 1H), 5.18–5.47 (m, 2H), 5.81–6.24 (dd, 11.3, 5.7, H), 7.18–8.01 (m, 8H), 8.20 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 154.9, 154.0, 143.1, 139.0, 131.9, 131.2, 130.0, 128.9, 128.6, 125.7, 125.5, 123.3, 118.2, 66.6, 52.6, 52.3, 44.9, 27.2, 22.3; HRMS calcd for $C_{22}H_{23}N_3O_5S$ *m*/*z* 441.1358, found 441.1356.

*6.3.8. 2-Chloroethyl 6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**4h**)*

Yield 28.3%; White solid; mp 178.3–179.4 °C; IR (KBr) 3210, 3100, 2950, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90 (quin, J = 6.1 Hz, 2H), 2.82 (t, J = 6.1 Hz, 2H), 3.63 (dd, J = 7.2, 9.8 Hz, 1H), 3.78 (t, J = 6.2 Hz, 2H), 3.93 (t, J = 4.8 Hz, 2H), 4.29 (dd, J = 8.3, 8.9 Hz, 2H), 4.43 (t, J = 4.8 Hz, 1H), 4.81 (dd, J = 7.0, 9.3 Hz, 1H), 7.27–7.92 (m, 8H), 8.22 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 154.9, 153.7, 142.8, 139.0, 131.5, 130.2, 128.9, 128.6, 126.4, 125.7, 123.5, 65.5, 53.4, 52.7, 45.0, 41.6, 27.3, 22.3; HRMS calcd for $C_{21}H_{22}ClN_3O_5S$ *m*/*z* 463.0969, found 463.0962.

*6.3.9. 1-(1-(2-Chloroacetyl)-1,2,3,4-tetrahydroquinolin-6-ylsulfonyl)-4-phenylimidazolidin-2-one (**4i**)*

Yield 14.8%; White solid; mp 207.8–208.8 °C; IR (KBr) 3100, 2950, 2350, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.04 (quin, J = 6.2 Hz, 2H), 2.90 (t, J = 6.2 Hz, 2H), 3.59 (dd, J = 7.0, 9.5 Hz, 1H), 3.82 (t, J = 6.2 Hz, 1H), 4.29 (t, J = 9.6 Hz, 1H), 4.81 (dd, J = 7.3, 9.5 Hz, 1H), 7.13–7.98 (m, 8H), 8.06 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 166.7, 155.9, 143.9, 138.8, 133.2, 129.6, 129.4, 128.8, 126.6, 126.0, 125.0, 52.6, 52.2, 45.5, 44.3, 25.8, 23.3; HRMS calcd for $C_{20}H_{20}ClN_3O_4S$ *m*/*z* 433.0863, found 433.0856.

*6.3.10. 1-(1-Benzoyl-1,2,3,4-tetrahydroquinolin-6-ylsulfonyl)-4-phenylimidazolidin-2-one (**4j**)*

Yield 96.0%; White solid; mp 213.1–214.5 °C; IR (KBr) 3270, 2910, 1720, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.96 (quin, J = 6.2 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 3.49 (m, 1H), 3.78 (t, J = 6.4 Hz, 2H), 4.27 (t, J = 9.2 Hz, 1H), 4.80 (dd, J = 7.2, 8.9 Hz, 1H), 7.15–7.77 (m, 13H), 8.22 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 171.0, 155.5, 144.2, 139.4, 135.3, 133.9, 131.1, 130.9, 129.0, 128.9, 128.4, 128.3, 125.8, 125.2, 125.1, 52.7, 52.5, 45.4, 26.9, 23.1; HRMS calcd for $C_{25}H_{23}N_3O_4S$ *m*/*z* 461.1409, found 461.1398.

*6.3.11. 4-Phenyl-1-(1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinolin-6-ylsulfonyl)imidazolidin-2-one (**4k**)*

Yield 74.8%; White solid; mp 166.7–171.1 °C; IR (KBr) 3210, 3110, 2910, 1730, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.03 (quin, J = 6.2 Hz, 2H), 2.93 (t, J = 6.2 Hz, 2H), 3.55 (dd, J = 7.2, 9.3 Hz, 1H), 3.88 (t, J = 6.3 Hz, 2H), 4.33 (t, J = 9.4 Hz, 1H), 4.83 (dd, J = 7.2, 9.5 Hz, 1H), 7.17–7.46 (m, 5H), 7.83 (s, 3H), 8.27 (bs, exchangeable with D_2O, 1H); ^{13}C (DMSO-d_6) δ = 155.9, 155.2, 141.7, 139.3, 134.9, 129.5, 129.2, 128.9, 125.9, 125.6, 125.1, 117.8, 114.94, 52.9, 52.6, 45.0, 26.0, 22.8; HRMS calcd for $C_{20}H_{18}F_3N_3O_4S$ *m*/*z* 453.0970, found 453.0962.

*6.3.12. 6-(2-Oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxamide (**4l**)*

Yield 70%; White solid; mp 168.8–170.4 °C; IR (KBr) 3350, 3200, 3100, 2900, 1750, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (quin, J = 5.9 Hz, 2H), 2.75 (t, J = 6.2 Hz, 2H), 3.43 (bs, exchangeable with D_2O, 2H), 3.63 (t, J = 5.9 Hz, 2H), 4.26 (t, J = 9.5 Hz, 1H), 4.80 (dd, J = 7.2, 9.4 Hz, 1H), 6.68 (bs, exchangeable with D_2O, 1H), 7.28–7.81

(m, 8H), 8.19 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 156.2155.3, 141.8, 139.7, 134.2, 129.9, 129.3, 126.2, 125.8, 125.5, 123.2,53.2, 52.9, 49.3, 25.8, 23.4; HRMS calcd for $C_{19}H_{20}N_4O_4S$ *m*/*z* 400.1205, found 400.1202.

*6.3.13. N-(2-Chloroacetyl)-6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxamide (**4m**)*

Yield 22.2%; White solid; mp 179.2–179.8 °C; IR (KBr) 3330, 2940, 1720, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.91 (quin, J = 5.6 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H), 3.50 (dd, J = 7.2, 9.5 Hz,1H), 3.70 (t, J = 6.2 Hz, 2H), 4.29 (t, J = 9.3 Hz, 1H), 4.54 (s, 2H), 4.81 (dd, J = 7.0, 9.3 Hz, 1H), 7.24–7.70 (m, 8H), 8.22 (bs, exchangeable with D_2O, 1H), 10.61 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 168.9, 155.3, 155.0, 140.1, 139.5, 132.5, 130.2, 129.3, 129.0, 125.9, 125.8, 125.5, 123.5, 53.2, 52.6, 45.2, 42.1, 27.5, 22.5; HRMS calcd for $C_{21}H_{21}ClN_4O_5S$ *m*/*z* 476.0921, found 476.0912.

*6.3.14. N-Cyclohexyl-6-(2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxamide (**4n**)*

Yield 49.2%; White solid; mp 145.5–146.0 °C; IR (KBr) 3220, 3100, 2950, 1720, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90 (t, J = 6.2 Hz, 3H), 1.16–1.71 (m, 4H), 1.86 (quin, J = 5.7 Hz, 2H), 2.79 (t, J = 6.1 Hz, 2H), 3.50 (dd, J = 7.2, 9.3 Hz, 1H), 3.74 (t, J = 6.2 Hz, 2H), 4.16 (t, J = 6.4 Hz, 2H), 4.27 (t, J = 9.1 Hz, 1H), 4.78 (dd, J = 7.2, 9.1 Hz, 1H), 7.17–7.99 (m, 8H), 8.20 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 156.0, 155.51,148.5, 139.8, 129.4, 129.0, 128.7, 128.5, 127.6, 125.9, 121.1, 113.6, 52.6, 49.5, 41.4, 33.2, 26.6, 25.4, 24.6, 20.5; HRMS calcd for $C_{25}H_{30}N_4O_4S$ *m*/*z* 482.1988, found 482.1980.

*6.3.15. 4-Methyl-4-phenyl-1-(1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinolin-6-ylsulfonyl)imidazolidin-2-one (**4o**)*

Yield 19.0%; White solid; mp 189.1–190.4 °C; IR (KBr) 3230, 2900, 1720, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.52 (s, 3H), 2.01 (q, J = 6.1 Hz, 2H), 2.90 (t, J = 6.5 Hz, 2H), 3.89 (m, 2H), 3.90 (d, J = 9.1 Hz, 1H), 4.08 (d, J = 9.4 Hz, 1H), 7.35 (s, 5H), 7.77–7.82 (m, 3H), 8.50 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 155.4, 154.8, 143.7, 141.0, 135.3, 130.0, 129.0, 128.5, 128.4, 126.3, 125.9, 124.8, 116.9, 58.8, 57.7, 50.7, 45.3, 29.9 26.4, 23.2; HRMS calcd for $C_{21}H_{20}F_3N_3O_4S$ *m*/*z* 467.1127, found 467.1122.

*6.3.16. 6-(4-Methyl-2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-N-(4-(methylthio)phenyl)-3,4-dihydroquinoline-1(2H)-carboxamide (**4p**)*

Yield 30.8%; White solid; mp 179.1–179.7 °C; IR (KBr) 3340, 3240, 2900, 1720, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.56 (s, 3H), 1.96 (quin, J = 5.9 Hz, 2H), 2.44 (s, 3H), 2.82 (t, J = 5.7 Hz, 2H), 3.33 (s, 3H), 3.77 (t, J = 4.8 Hz, 2H), 3.77 (d, J = 9.6 Hz, 1H), 4.02 (d, J = 9.5 Hz, 1H), 7.15–7.63 (m, 12H), 8.42 (bs, exchangeable with D_2O, 1H), 9.23 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 155.6, 154.5, 143.4, 140.7, 135.5, 134.9, 132.1, 131.2, 129.1, 128.9, 128.6, 126.8, 126.7, 126.4, 125.7, 124.6, 120.6, 55.4, 50.7, 45.4, 29.7,27.4, 23.1,14.6; HRMS calcd for $C_{27}H_{28}N_4O_4S_2$ *m*/*z* 536.1552, found 536.1544.

*6.3.17. N-(4-Methoxyphenyl)-6-(4-methyl-2-oxo-4-phenylimidazolidin-1-ylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxamide (**4q**)*

Yield 27.6%; White solid; mp 183.2–184.1 °C; IR (KBr) 3340, 3220, 3100, 2940, 1720, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.52 (s, 3H), 1.91 (quin, J = 5.1 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H), 3.72 (s, 3H), 3.77 (m, 2H), 3.79 (d, J = 9.1, 1H), 4.09 (d, J = 9.2 Hz, 1H), 6.82–7.70 (m, 12H), 8.44 (bs, exchangeable with D_2O, 1H), 9.10 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ = 159.3, 155.6, 154.5, 143.3, 140.7, 135.4, 131.2, 129.1, 128.9, 128.6, 126.8, 126.7, 126.4, 125.7, 124.6, 114.3,56.5, 55.5, 50.7, 45.5, 29.7, 27.4, 22.8; HRMS calcd for $C_{27}H_{28}N_4O_5S$ *m*/*z* 520.1780, found 520.1784.

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