

***N*-(5-(Dichloromethylene)-2-oxoimidazolidin-4-ylidene)sulfonamides: Small molecules with big synthetic capabilities**Svitlana A. Chumachenko<sup>a</sup>, Oleh V. Shablykin<sup>a,b\*</sup>, Svitlana V. Shishkina<sup>c,d</sup>, Andrii V. Kozytskyi<sup>b,e</sup> and Olga V. Shablykina<sup>a,e</sup><sup>a</sup>*V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Academician Kukhar Str., 1, Kyiv, 02094, Ukraine*<sup>b</sup>*Enamine Ltd., Winston Churchill Str., 78, Kyiv, 02094, Ukraine*<sup>c</sup>*SSI “Institute for Single Crystals” National Academy of Sciences of Ukraine, Nauky Ave., 60, Kharkiv, 61001, Ukraine*<sup>d</sup>*Institute of Organic Chemistry National Academy of Sciences of Ukraine, Academician Kukhar Str., 5, Kyiv, 02660, Ukraine*<sup>e</sup>*Taras Shevchenko National University of Kyiv, Volodymyrska Str., 64/13, Kyiv, 01601, Ukraine***CHRONICLE***Article history:*

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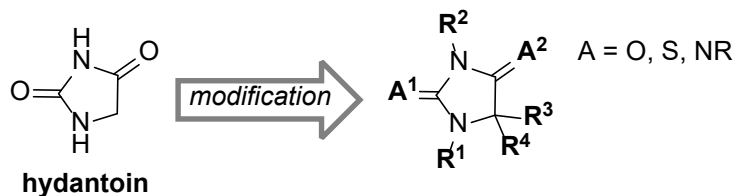
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Hydantoin**Heterocyclization**Alkylation**Arylation***ABSTRACT**

A number of 5-dichloromethylidene-4-sulfonyliminohydantoin were synthesized by the reaction of 2-amino-3,3-dichloroacrylonitrile (ADAN) with aryl and alkyl isothiocyanates. These products are polyfunctional molecules that are considered as initial materials for the synthesis of bioactive compounds. The method of such derivatives multigram synthesis was optimized; also, the features of purification were described, and the main products of reaction mixture alcoholysis (acyclic carbamates) were identified for the first time. A number of modifications was carried out on the example of 5-dichloromethylidene-4-tosyliminohydantoin, namely: alkylation, hydrolysis of the amino group with subsequent arylation, substitution reaction with *S*-nucleophile, Suzuki – Miyaura coupling, and reduction of the dichloromethylidene fragment to the methyl group. The anticancer activity of 5-dichloromethylidene-4-tosyliminohydantoin was shown.

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**1. Introduction**

Since its discovery (1861), the heterocyclic core of hydantoin has had invariable attention from medicinal chemistry. As a basis for the construction of compact bioactive molecules<sup>1</sup>, hydantoin has completely justified the optimistic expectations, which were based on the features of its structure. This unique combination of  $\alpha$ -amino acid and urea fragments in a small cycle is not only relatively stable: there are quite enough approaches to the synthesis of hydantoin derivatives, and this fact provides different directions of variation of substituents in the basic heterocyclic nucleus<sup>2-4</sup>.

**Scheme 1.** The possibilities of hydantoin core modifications

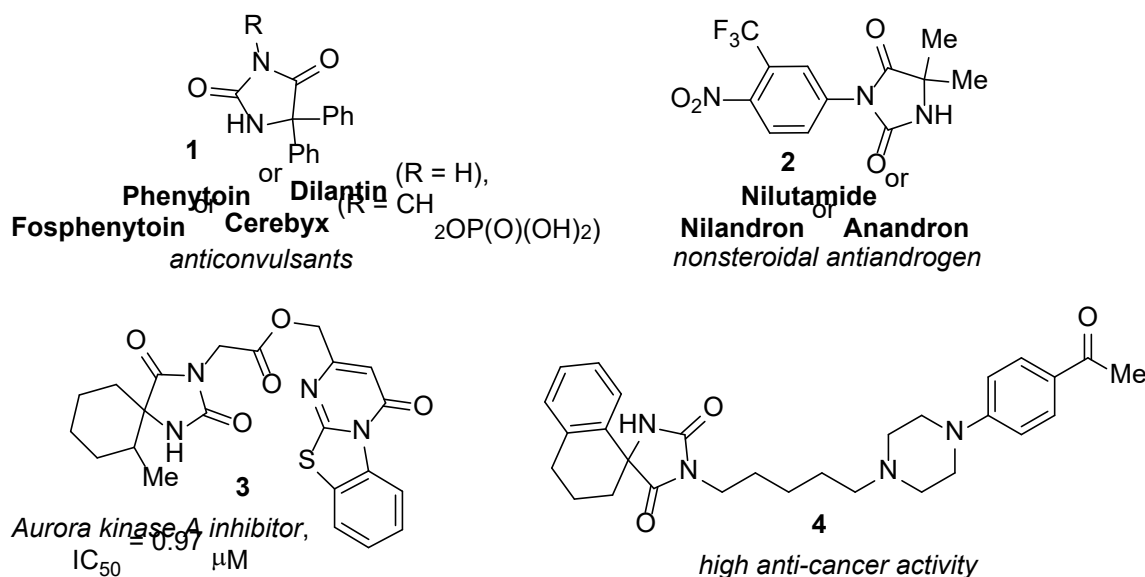
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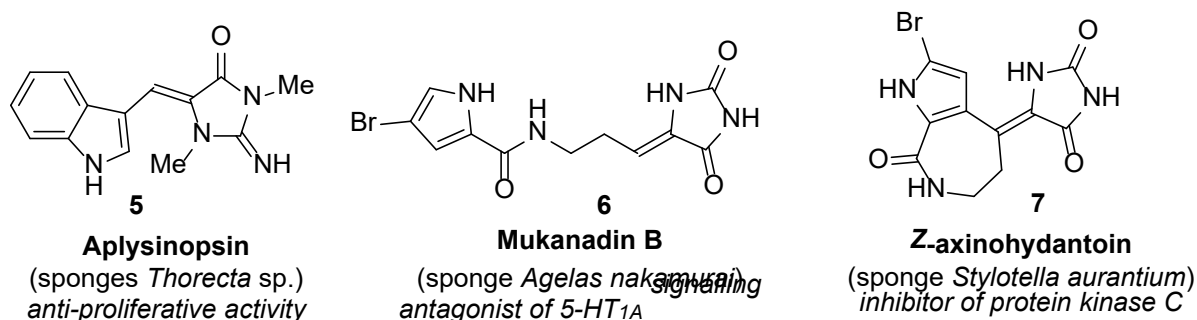
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There are a number of 5,5-disubstituted derivatives (including spiro compounds) among the practically valuable hydantoins. Many of these molecules are now well-known “classical” drugs (**Fig. 1**, structures **1**, **2**)<sup>2</sup>, the biological action of others has been discovered only recently (**Fig. 1**, structures **3**<sup>5</sup>, **4**<sup>6</sup>).



**Fig. 1.** Biologically active 5,5-disubstituted hydantoins

But 5-methylidene derivatives of hydantoin are also worth attention, especially due to presence of this motif in a number of natural compounds related to alkaloids, mainly extracted from marine organisms (**Fig. 2**, structures **5**<sup>7, 8</sup>, **6**<sup>9, 10</sup>, **7**<sup>11</sup>).

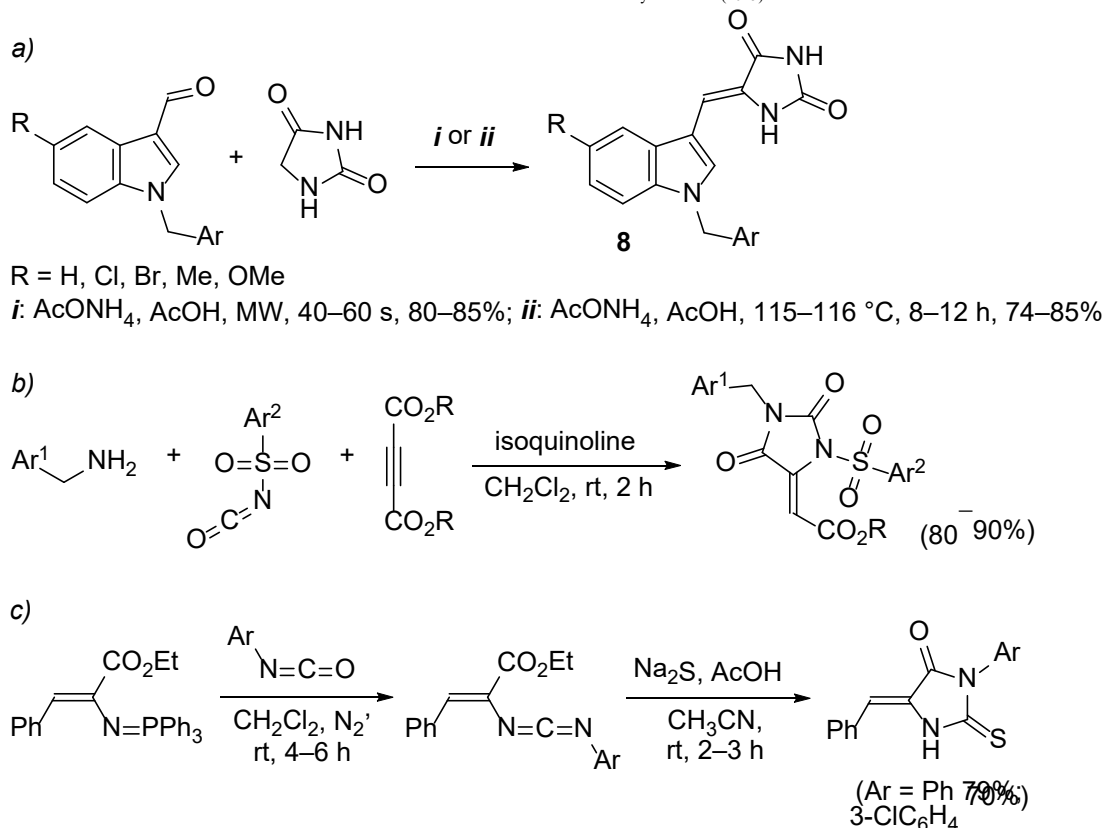


**Fig. 2.** Natural 5-methylidenehydantoins

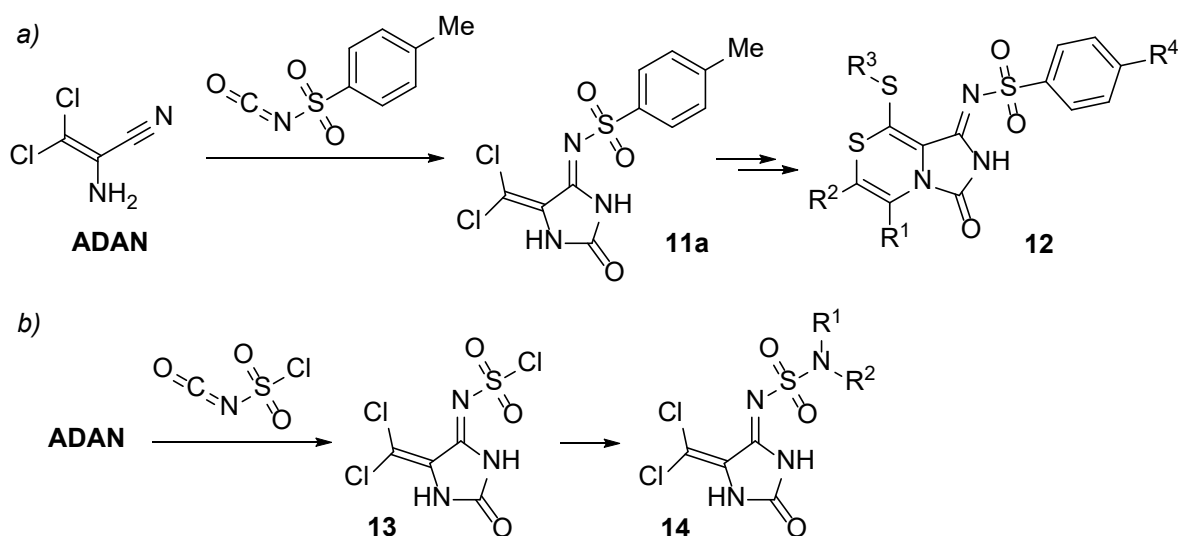
Therefore, 5-methylidene derivatives of hydantoin can be considered as promising compounds from a perspective of their biological properties. Approaches to the synthesis of such compounds are quite capable of providing their diversity, which is sufficient for the medicinal chemistry requirements. Of course, most of such derivatives are synthesized by direct condensation of aldehydes and the active methylene unit of hydantoin. For example, a set of Aplysinopsin analogues (**Scheme 2a**, general formula **8**) with anticancer activity was synthesized in such a way<sup>12</sup>.

However, synthetic options, where the formation of the hydantoin core is the final stage (**Scheme 2b**<sup>4, 13</sup> and **Scheme 2c**,<sup>2, 14</sup>), are also possible. To realize this approach, on the one hand, functional groups such as iso(thio)cyanate are required, and on the other hand, unsaturated fragments such as alkynes or enamines have to be involved.

In our opinion, one of the most interesting substrates in this group is 2-amino-3,3-dichloroacrylonitrile (ADAN). Since its creation, this unique polyfunctional reagent has demonstrated an extremely wide range of synthetic possibilities for the preparation of functionalized heterocycles<sup>15-17</sup>. For example, the interaction of ADAN with tosyl isocyanate led to the hydantoin derivative **11a** (**Scheme 3a**)<sup>18</sup>. In this work, substance **11a** became the basis for the construction of compounds of general formula **12**, and some of them confirmed their activity as Hsp90 Inhibitors, which can be used, in particular, for the treatment of osteoarthritis.



**Scheme 2.** Different approaches to the 5-methylidenehydantoin synthesis (literature data)



**Scheme 3.** Synthesis of 5-dichloromethylidene-4-sulfonyliminohydantoin: a) literature data; b) our previous works

In its turn, we previously synthesized sulfonyl chloride **13** (Scheme 3b) by a similar reaction, which, reacting with various primary and secondary amines, allowed us to obtain a fairly wide range of sulfamides **14** with significant anticancer<sup>19, 20</sup> and antiviral activity<sup>20</sup>, studied *in vitro*. In addition, compounds **14** showed a fairly low overall cytotoxicity<sup>21</sup>.

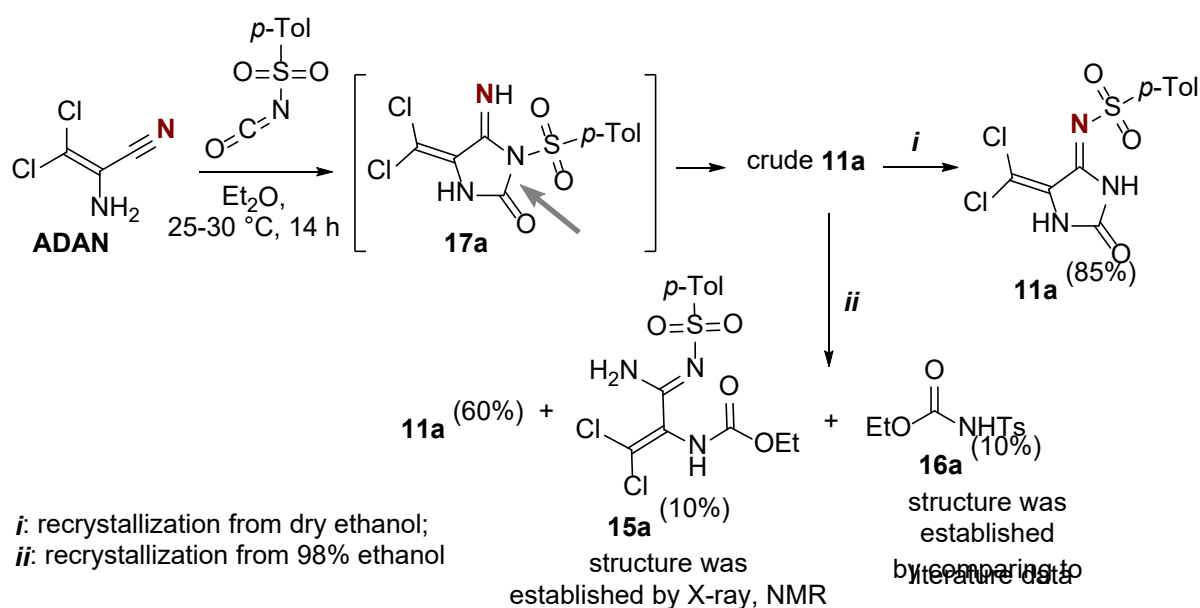
These data confirm that chemical transformations of 5-dichloromethylidene-4-sulfonyliminohydantoin are a productive source of bioactive compounds. Therefore, in this study, we aimed to investigate the possibilities of compounds type **11** modifying, focusing on the following areas: 1) the efficiency of ADAN and various arylsulfonylisocyanates interaction; 2) reactions of iminohydantoin moiety; 3) reactions of dichloromethylidene moiety.

## 2. Results and Discussion

### 2.1. Synthesis of *N*-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)sulfonamides

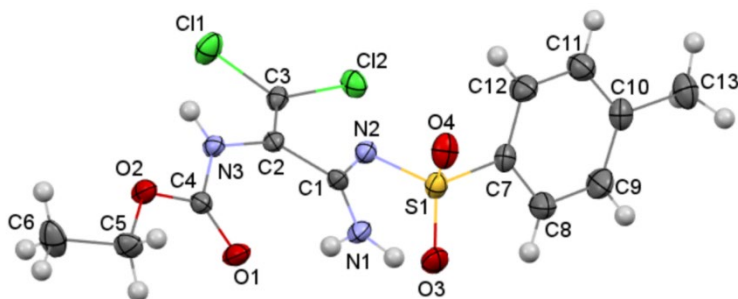
At the first part of the study, we attempted to reproduce the synthesis of substance **11a** according to Scheme 4a. The reaction was carried out by adding TsNCO to a solution of ADAN in diethyl ether and subsequent prolonged stirring at room temperature, which was in full agreement with previous data<sup>18,19</sup>. It is worth reminding about an interesting detail of the isocyanates interaction with ADAN: the resulting sulfonamide is a product of migration of the sulfonyl residue to the Nitrogen atom, which was the part of nitrile group (this atom is marked in colour below in **Scheme 4**).

We have discovered several important practical aspects of this transformation. The reaction is efficient both in small (about 5 mmol) and multigram quantities; the product is weakly soluble in Et<sub>2</sub>O and crystallizes well from the reaction mixture. However, we have found that the yellowish colour of the precipitate indicates the presence of a certain amount of impurities. Colourless crystals of compound **11a** can be obtained after recrystallization from ethanol with non-prolonged boiling, but the solvent would be to dry. The use of rectified ethanol (97–98%) for recrystallization leads to a decrease in the yield from approximately 85% to 60%.



**Scheme 4.** The formation of product **11a** and the structure of main by-products

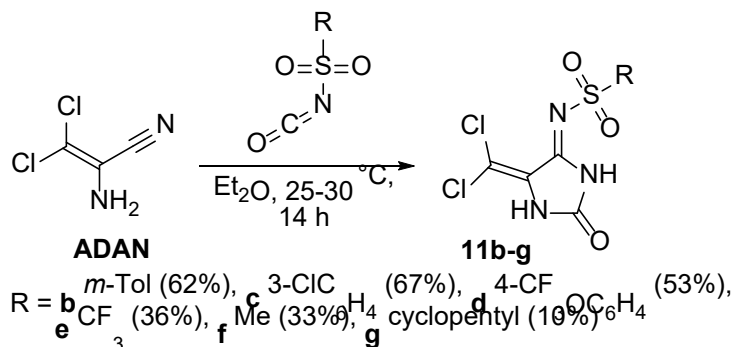
To better appreciate the processes that may be responsible for product losses, we analysed the mother liquor after recrystallization of the crude product **11a** from rectified ethanol. Two compounds **15a**, **16a** were isolated, and their structures were reliably established (Scheme 4). In particular, X-ray analysis of substance **15a** (**Fig. 3**) showed the *cis*-position of the amino group and the *p*-tolylsulfonyl substituent at the C1=N2 double bond (torsion angle N1–C1–N2–S1 -3.4(3)°). The dichloromethylene group is oriented almost orthogonally to the C1=N2 double bond (torsion angle C3–C2–C1–N2 102.3(2)°). The *para*-tolyl substituent is in the *+sc*-conformation to the C1–N2 bond and is significantly rotated to the N2–S1 bond (torsion angles C1–N2–S1–C7 76.4(2)°, N2–S1–C7–C12 69.6(2)°). The carboxyl moiety of the ester group is in the *sp*-position to the C1–C2 bond and coplanar with the C2–N3 bond (torsion angles C1–C2–N3–C4 -27.8(3)°, C2–N3–C4–O1 -5.6(3)°), and the ethyl group is antiperiplanar to the C4–O2 bond (torsion angle C4–O2–C5–C6 -159.6(2)°).



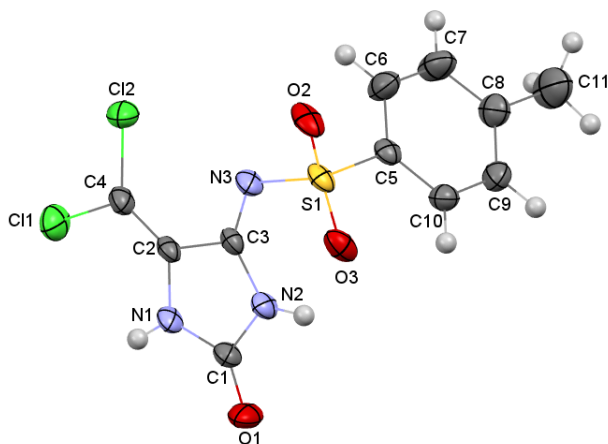
**Fig. 3.** Molecular structure of compound **15a** according to X-ray diffraction data. Thermal ellipsoids of non-hydrogen atoms are shown at 50% probability level

We assume that heating in ethanol during the recrystallization contributes to the completion of the initial sulfamide **17a** rearrangement into the product **11a**, and the decrease in yield is associated with a significantly lower resistance of compound **17a** to the action of nucleophilic solvents (in **Scheme 4**, the bond that is cleaved as a result of solvolysis by ethanol is marked with a gray arrow). This suggestion is supported by the fact that the isolated and purified substance **11a** does not undergo solvolysis during boiling in ethanol.

The reaction with ADAN was realized with the other aryl sulfonyl isocyanates participation, and, with the correct procedure, the yields of purified products **11b-d** were at least 50% (**Scheme 5**). Not only aromatic sulfonyl isocyanates can effectively react with ADAN: iminohydantoin **11e-g** with, respectively, a triflyl, mesyl and cyclopentylsulfonyl residue were obtained, but their yields were not high. Obviously, the activity of the isocyanate should be optimal for rapid cyclization and formation of a product of type **11**, otherwise the destruction of the substrates occurs.



Before discussing further transformations, it is worth clarifying one aspect of the compound's **11** structure (which was not considered in previous works), namely the configuration of the C=N bond. Unfortunately, due to the small number of Hydrogen atoms in the molecules type **11** and their derivatives, the use of heteronuclear NMR correlations to establish the configuration rarely gives an unambiguous result. Previously<sup>19</sup> the *Z*-configuration of analogous bonds was determined by X-ray for one of sulfamides **14**. The X-ray diffraction data obtained during this study also demonstrates the *Z*-configuration of the C=N fragment in molecule **11a** (**Fig. 4**).

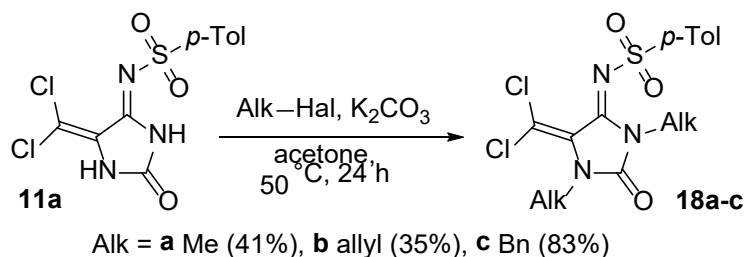


**Fig. 4.** Molecular structure of compound **11a** according to X-ray diffraction data. Thermal ellipsoids of non-hydrogen atoms are shown at 50% probability level

Although it seems reasonable to assume that the corresponding bond has a *Z*-configuration in all compounds of a similar structure, henceforth we will indicate the configuration index in the compounds names only for molecules in which it is reliably determined.

## 2.2. Synthetic modifications of *N*-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)sulfonamides via *N*-alkylation

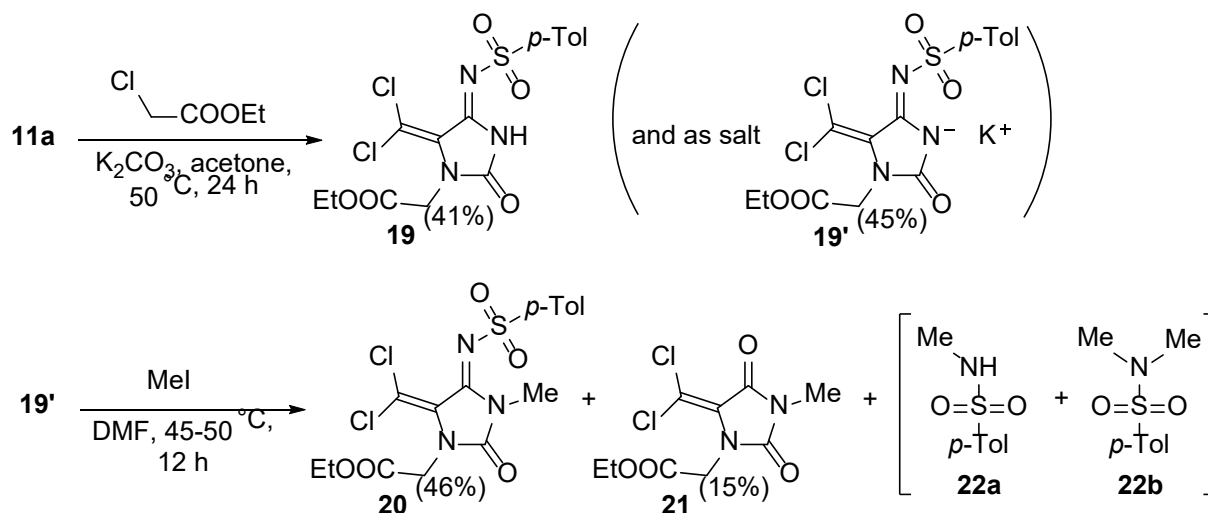
In the next step of our research the processes of alkylation of the hydantoin fragment were investigated. First, the reaction occurred in acetone solution with potash as a base. The use of sufficiently active alkylating agents (methyl iodide, allyl and benzyl chloride) resulted in the complete alkylation of both NH fragments and the formation of products **18a-c** (**Scheme 6**). However, in the case of the allylic derivative, a significant amount of unidentified by-products was formed, and the extensive purification seriously reduced the yield of product **18b**.



**Scheme 6.** The alkylation of substrate **11a**

Alkylation with chloroacetic acid ester (a less active agent) allowed us to stop at the stage of monoalkyl derivative **19** (**Scheme 7**). The NH fragment near the dichloromethylidene group turned out to be more active. The structure of this compound was confirmed by NMR techniques (see Experimental part and SI, copies of spectra). Surprisingly, this substance can be isolated both in the form of NH-acid and in the form of its potassium salt **19'** (see Experimental part, procedure for the synthesis).

The action of MeI in dry DMF was used to methylate the NH group of compounds **19**. The usage of potassium salt **19'** was a pretty convenient method for this transformation; although the standard procedure, i.e. the combination of NH-acid **19** with  $K_2CO_3$ , was also effective and gave a similar result. The relatively low yield of methylated product **20** was caused by partial hydrolysis of the imine fragment and the formation of hydantoin **21** (**Scheme 7**). Iminohydantoin **20** and hydantoin **21** were extracted and separated chromatographically; other methylated products of the hydrolysis (sulfamides **22a,b**) were detected in the mixture by HPLC.

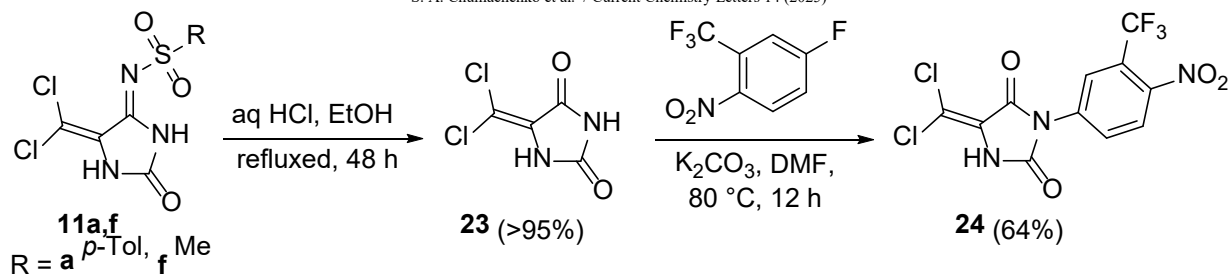


**Scheme 7.** The synthesis of monoalkyl derivative and non-symmetric dialkyl derivative of **11a**

We observed the hydrolysis of such an imine fragment for the first time, since through the synthesis of dialkyl derivatives **18a-c** no probable hydrolysis products were found in the reaction mixture. However, the possibility of hydrolysis of the imine group with preservation of the hydantoin cycle encouraged us to accomplish the directed hydrolysis of some products type **11**.

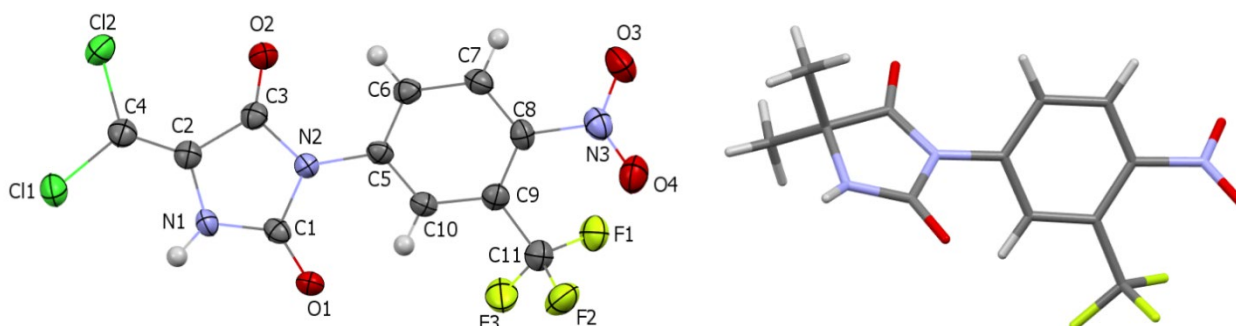
Actually, prolonged acid hydrolysis of sulfonamides **11a** and **11f** yielded a previously undescribed, the simplest one among of 5-dichloromethylidenehydantoin, namely compound **23** (**Scheme 8**). In both cases, the yield of substance **23** was more than 95%, but for preparative purposes, hydrolysis of the mesyl derivative **11f** is more appropriate, as it is easier in this case to purify the product from water-soluble mesylamine.

For the examination the synthetic possibilities of hydantoin **23**, this molecule was arylated by the action of 4-fluoro-1-nitro-2-(trifluoromethyl)benzene: as a result, an analogue of Nilutamide (compound **24**) was synthesized (**Scheme 8**). Note that in this reaction the NH fragment surrounded by two C=O groups is more active, rather than NH surrounded by C=O and C=CCl<sub>2</sub>. In contrast, in the reaction with ethyl chloroacetate the O=C–NH–C=CCl<sub>2</sub> fragment is more active, rather than O=C–NH–C=N; it shows that the activating force of the dichloromethylidene group in such cycles is intermediate between the activating force of the imine and carbonyl groups.



**Scheme 8.** The hydrolysis of **11a** imine moiety. The synthesis of Nilutamide analogue

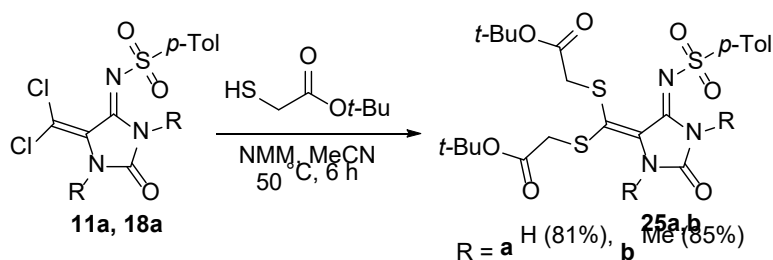
**Fig. 5** shows the structure of compound **24** (determined by X-ray diffraction) in comparison to Nilutamide, and the geometric parameters of both structures are expectedly very close.



**Fig. 5.** Molecular structure of: a) compound **24** according to X-ray diffraction data; thermal ellipsoids of non-hydrogen atoms are shown at 50% probability level; b) Nilutamide according to X-ray diffraction data, Refcode LANLET<sup>22</sup>

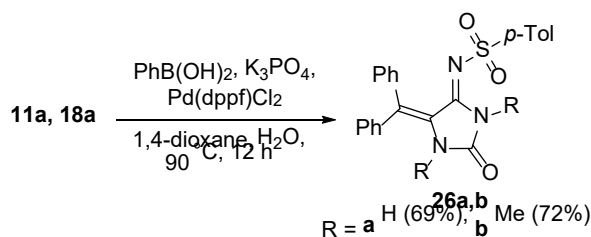
### 2.3. Synthetic modifications of *N*-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)sulfonamides by involving C=CCl<sub>2</sub> fragment

Next, as part of the compound 5-dichloromethylidene-4-sulfonyliminohydantoin's chemical properties, the replacement of Chlorine atoms in the C=CCl<sub>2</sub> group was examined. According to literature data<sup>18</sup> (**Scheme 3a**), the Chlorine atoms in compound **11a** can be substituted by *S*-nucleophiles. We successfully carried out the reaction with thioglycolic acid ester for both compound **11a** and its dimethyl derivative **18a** (**Scheme 9**). It is interesting that the time and efficiency of the transformation for both substrates were almost the same; therefore, it is possible to provide modifications of iminohydantoin **11** sequentially at several reaction centres.



**Scheme 9.** The interaction of compounds **11a, 18a** with thioglycolic acid ester

Not only nucleophilic substitution: the Pd-catalyzed cross-coupling reaction of compounds **11a** and **18a** with phenylboronic acid was experienced (**Scheme 10**). More than 2 eq of phenylboronic acid was used, and the possible by-product of one Chlorine atom substitution was not observed.



**Scheme 10.** Compounds **11a, 18a** in Suzuki reaction

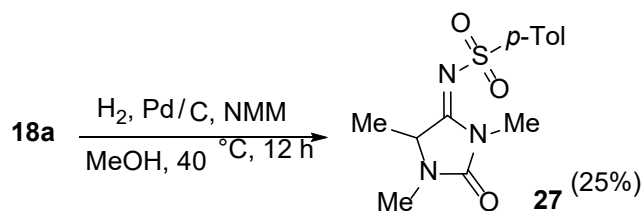
In this case, close reaction time was also observed for both substrates. This fact was easily verified by analysing LCMS spectra of the equal amounts of substances **11a** + **18a** mixture after the coupling was implemented. The details of this analysis are shown in **Table 1**.

**Table 1.** The mixture of **11a** + **18a** behaviour<sup>1</sup> in the coupling with PhB(OH)<sub>2</sub> (conditions see in Scheme 10)

Initial substrate, mol %		Amount of target products in crude reaction mixture, mol %			
<b>11a</b>	<b>18a</b>	<b>11a</b>	<b>18a</b>	<b>26a</b>	<b>26b</b>
100	0	0	–	43	–
0	100	–	0	–	42
50	50	0	0	29	27

<sup>1</sup> according to LCMS data

Another obvious transformation of the C=CCl<sub>2</sub> moiety was a reduction. Pd-catalyzed hydrogenation was applied to compounds **11a** and **18a**, but only derivative **18a** formed the target product (**Scheme 11**), although in low yield. As a result of imine **11a** hydrogenation (according to LC-MS data) a complicated mixture formed, in which the analogue of product **27** was not detected.



**Scheme 11.** Pd-catalyzed hydrogenation of **18a**

#### 2.4. Biological investigation

It was mentioned above that a compound **11a** was used for the synthesis of bioactive substances<sup>18</sup>. We assumed that compounds of type **11** could exhibit biological activity too. In cooperation with the National Cancer Institute (NCI, Bethesda, Maryland, USA), a single-dose test of the anticancer activity of the compound **11a** was carried out on a panel of 60 cancer cell lines. According to the results of the test, it was found that substance **11a** has a pronounced tendency to slow down and cause death of cancer cells, because the Mean Growth Percent is expressed as a negative number (-27%). In relation to individual lines Colon Cancer, Melanoma, Ovarian Cancer, Renal Cancer (**Table 1**), the studied substance showed high lethality with a GP index of less than -90%. At the same time, a five-dose test gave a slightly different list of cell lines most susceptible to the action of the compound **11a** (**Table 2**). In addition, the dependence of the effectiveness on concentration was not clear. For example, for some lines rather low GI<sub>50</sub> was established, but at the same time much higher concentrations of compound **11a** were required for their complete inhibition or for their death. In **Table 2**, among the data set, the cases where growth retardation was most effective are marked in colour.

**Table 2.** Anticancer activity of the compound **11a**: One and Five Dose Assay Data

	Growth Percent according to One Dose Assay, C = 10 <sup>-5</sup> M, % (Mean GP -27%)	Five Dose Assay Data		
		lg GI <sub>50</sub> (MID -5.62)	lg TGI (MID -5.13)	lg LC <sub>50</sub> (MID -4.61)
<i>Leukemia</i>				
RPMI-8226	5.48	-6.18	> -4.00	> -4.00
<i>Colon Cancer</i>				
COLO 205	-92.4	-5.75	-5.48	-5.21
KM12	-3.57	-6.46	-5.78	-4.83
<i>Melanoma</i>				
LOX IMVI	-94.7	-5.80	-5.52	-5.25
<i>Ovarian Cancer</i>				
OVCAR-3	-95.1	-5.68	-5.34	-4.99
<i>Renal Cancer</i>				
ACHN	-90.7	-5.50	-5.00	-4.49
CAKI-1	-91.0	-5.72	-5.38	-5.04
<i>Breast Cancer</i>				
MCF7	11.6	-5.98	-4.76	> -4.00
MDA-MB-468	-54.8	-6.02	-5.59	-5.16

### 3. Conclusions

Thus, we have shown that sulfonyl isothiocyanates with different substituents can be involved in the reaction with ADAN to produce 5-dichloromethylidene-4-sulfonyliminohydantoin. The transformations involving aromatic sulfonyl isothiocyanates are the most effective; but aliphatic derivatives can also provide an acceptable yield of the target products. The improved method of isolation and purification of these substances allows to minimize their losses due to certain side processes that were detected after studying the reaction mixture.

At the example of 5-dichloromethylidene-4-tosyliminohydantoin, it is shown that such substrates can be easily modified by: 1) alkylation reactions of the Nitrogen atoms of the hydantoin core, 2) hydrolysis of the imine fragment, 3) reactions with thioglycolic acid ester, 4) Pd-catalyzed cross-coupling with phenylboronic acid. The last two transformations occur in high yield with the participation of both the initial NH-hydantoin and its dimethyl derivative, which provides broad synthetic opportunities for diversifying the library of 5-dichloromethylidene-4-sulfonyliminohydantoin in the future. In addition, for 1,3-dimethyl-5-dichloromethylidene-4-tosyliminohydantoin, the possibility of reducing the dichloromethylidene group to the methyl group has been shown. The anticancer activity of 5-dichloromethylidene-4-tosyliminohydantoin has been exposed, which confirms the value of this class of compounds not only as starting synthetic material, but also as independent drugs.

### Acknowledgements

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### Disclaimer

This material should not be interpreted as representing the viewpoint of the U.S. National Institutes of Health, or the National Cancer Institute.

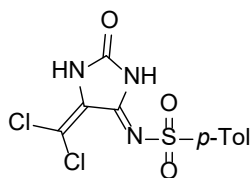
## 4. Experimental part

### 4.1. Material and Methods

All chemical reagents and solvents were kindly provided by Enamine Ltd. as a support of Ukrainian science. The reaction progress was monitored using the thin-layer chromatography (TLC) method on Silica gel 60 F254 Merck. Flash chromatography was carried out using Silica gel (200–300 mesh). Melting points were determined using an automated melting point System Opti Melt. NMR spectra of obtained products were recorded on Varian Unity Plus 400 spectrometer (400 MHz for  $^1\text{H}$  and 101 MHz for  $^{13}\text{C}$ ), Bruker 170 spectrometer (500 MHz for  $^1\text{H}$  and 126 MHz for  $^{13}\text{C}$ ), and Agilent ProPulse 600 spectrometer (600 MHz for  $^1\text{H}$ , 151 MHz for  $^{13}\text{C}$ ), with chemical shifts reported in ppm using the solvent residual signal as an internal standard ( $^1\text{H}$ ,  $^{13}\text{C}$ ). High-resolution mass spectra (HRMS) were acquired using an Agilent LC/MSD TOF mass spectrometer *via* electrospray ionization time of flight reflectron experiments.

### 4.2. General procedure for the synthesis *N*-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)- sulfonamides **11a-g** (5 mmol scale)

Appropriate chlorosulphonyl isocyanate (5 mmol) was added dropwise with stirring to a solution of ADAN (5 mmol) in absolute  $\text{Et}_2\text{O}$  (25 mL) at  $-10$ – $-5$  °C, then cooling bath was removed and the mixture was stirred at  $25$ – $30$  °C for 14 h. The resulting precipitate was collected by filtration and washed with  $\text{Et}_2\text{O}$ . Crude product was purified by recrystallization from dry ethanol.

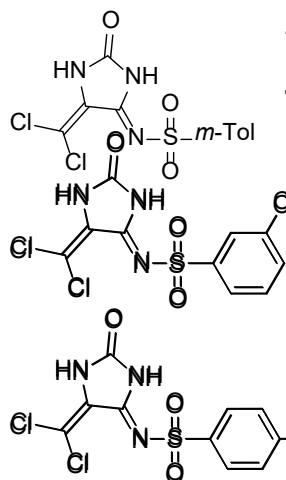


**(Z)-N-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)-4-methylbenzenesulfonamide (11a).** White solid; mp  $245$ – $247$  °C;  $R_f$  (MTBE) 0.25;  $R_f$  (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) 0.7; yield 1.23 g (74 %).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.75 (br. s, 1H), 11.20 (s, 1H), 7.85 (d,  $J = 8.0$  Hz, 2H), 7.40 (d,  $J = 8.0$  Hz, 2H), 2.38 (s, 3H) ppm;  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ )  $\delta$  152.2, 151.7, 143.4, 138.2, 129.9, 129.6 $\times$ 2, 126.4 $\times$ 2, 108.3, 21.0 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 333.9820, found: 333.9809.

**X-ray diffraction study of 11a.** The colourless crystals of **11a** ( $\text{C}_{11}\text{H}_9\text{Cl}_2\text{N}_3\text{O}_3\text{S}$ ) are monoclinic. At 173 K  $a = 14.685(9)$ ,  $b = 12.126(9)$ ,  $c = 17.086(11)$  Å,  $\beta = 115.29(2)^\circ$ ,  $V = 2751(3)$  Å $^3$ ,  $M_r = 334.17$ ,  $Z = 8$ , space group  $C2/c$ ,  $d_{\text{calc}} = 1.614$  g/cm $^3$ ,  $\mu(\text{MoK}\alpha) = 0.633$  mm $^{-1}$ ,  $F(000) = 1360$ . Intensities of 10312 reflections (2425 independent,  $R_{\text{int}} = 0.0682$ ) were measured on the Bruker APEX II diffractometer (graphite monochromated  $\text{MoK}\alpha$  radiation, CCD detector,  $\varphi$ - and  $\omega$ -scanning,  $2\theta_{\text{max}} = 50^\circ$ ). The structure was solved by direct method using OLEX2 $^{23}$  package with SHELXT $^{24}$  and SHELXL modules $^{25}$ . Positions of the hydrogen atoms were located from electron density difference maps and refined using “riding” model with  $U_{\text{iso}} = nU_{\text{eq}}$  ( $n = 1.5$  for methyl group and  $n = 1.2$  for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against  $F^2$  in anisotropic approximation for non-hydrogen atoms using

2425 reflections was converged to  $wR_2 = 0.1035$  ( $R_1 = 0.0399$  for 2058 reflections with  $F > 4\sigma(F)$ ,  $S = 1.055$ ). The final atomic coordinates, and crystallographic data for molecule **11a** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2424957).

**N-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)-3-methylbenzenesulfonamide (11b)**. White solid; mp 187–189 °C; yield 1.03 g (62 %).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.78 (br. s, 1H), 11.22 (s, 1H), 7.84–7.70 (m, 2H), 7.54–7.43 (m, 2H), 2.39 (s, 3H) ppm;  $^{13}\text{C NMR}$  (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  152.2, 151.8, 140.9, 138.9, 133.6, 129.9, 129.0, 126.5, 123.5, 108.4, 20.8 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 333.9820, found: 333.9809.



**3-Chloro-N-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)benzenesulfonamide (11c)**. Light yellow solid; mp 189–191 °C; yield 1.19 g (67 %).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.82 (br. s, 1H), 11.26 (s, 1H), 8.02 (s, 1H), 7.91 (d,  $J = 7.9$  Hz, 1H), 7.75 (d,  $J = 7.9$  Hz, 1H), 7.64 (t,  $J = 7.9$  Hz, 1H) ppm;  $^{13}\text{C NMR}$  (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  152.6, 152.2, 142.8, 133.7, 132.9, 131.3, 130.0, 126.0, 125.2, 108.9 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{10}\text{H}_7\text{Cl}_3\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 353.9274, found: 353.9264.

**N-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)-4-(trifluoromethoxy)benzenesulfonamide (11d)**. White solid; mp 222–224 °C; yield 1.07 g (53 %).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.93 (br. s, 1H), 11.26 (s, 1H), 8.11 (d,  $J = 8.4$  Hz, 2H), 7.59 (d,  $J = 8.4$  Hz, 2H) ppm;  $^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  152.5, 152.4, 151.2, 140.0, 130.0 $\times$ 2, 129.1 $\times$ 2, 121.5, 108.9 ppm,  $\text{OCF}_3$  signal is not determined due to the low intensity;  $^{19}\text{F NMR}$  (376 MHz,  $\text{DMSO-}d_6$ )  $\delta$  -57.25 ppm. HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{11}\text{H}_7\text{Cl}_2\text{F}_3\text{N}_3\text{O}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 403.9486, found:

403.9475.

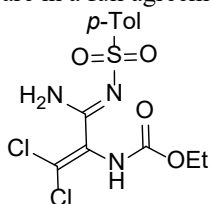
**N-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)-1,1,1-trifluoromethanesulfonamide (11e)**. White solid; mp 198–200 °C; yield 0.56 g (36 %).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.49 (s, 1H) ppm, another NH signal is not determined due to the exchange processes;  $^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  155.6, 152.0, 130.0, 118.9 (q,  $J = 319.8$  Hz), 111.7 ppm;  $^{19}\text{F NMR}$  (376 MHz,  $\text{DMSO-}d_6$ )  $\delta$  -79.71 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_5\text{H}_3\text{Cl}_2\text{F}_3\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 311.9224, found: 311.9218.

**N-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)methanesulfonamide (11f)**. White solid; mp 257–259 °C; yield 0.425 g (33 %).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.66 (br. s, 1H), 11.17 (s, 1H), 3.10 (s, 3H) ppm;  $^{13}\text{C NMR}$  (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  152.3, 151.7, 129.8, 107.8, 41.6 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_5\text{H}_6\text{Cl}_2\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 257.9507, found: 257.9500.

**N-(5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)cyclopentanesulfonamide (11g)**. White solid; mp 202–204 °C; yield 0.160 g (10 %).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.65 (br. s, 1H), 11.15 (s, 1H), 3.62 (p,  $J = 8.0$  Hz, 1H), 2.03–1.85 (m, 4H), 1.74–1.63 (m, 2H), 1.62–1.51 (m, 2H) ppm;  $^{13}\text{C NMR}$  (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  152.3, 151.5, 129.9, 107.4, 62.0, 27.5 $\times$ 2, 25.6 $\times$ 2 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_9\text{H}_{12}\text{Cl}_2\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 311.9976, found: 311.9968.

#### 4.3. Interaction of ADAN with TosNCO (0.2 mol scale)

TsNCO (35.51 g, 0.2 mol) was added dropwise with stirring to a solution of ADAN (24.66 g, 0.2 mol) in absolute  $\text{Et}_2\text{O}$  (400 mL), and the mixture was stirred at 25–30 °C for 14 h. The resulting precipitate was collected by filtration and washed with  $\text{Et}_2\text{O}$  (100 mL). Crude product was purified by recrystallization from dry ethanol (400 mL, 5–10 min boiling). The ethanol solution (filtrate after crystallization) was evaporated and residue was purified by flash chromatography (eluent  $\text{CH}_2\text{Cl}_2$ –MTBE, gradient 0–100%) to isolate compounds **15a**, **16a**. The data of **15a** is given below; the properties of **16a** are in a full agreement with literature source<sup>26</sup>.



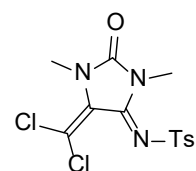
**Ethyl (Z)-(3-amino-1,1-dichloro-3-(tosylimino)prop-1-en-2-yl)carbamate (15a)**. Light beige solid; melting point: 167–169 °C;  $R_f$  (MTBE) 0.6; yield 6.85 g (10 %).  $^1\text{H NMR}$  (600 MHz,  $\text{DMSO-}d_6$ )  $\delta$  9.40 (br. s, 1H), 9.13 (br. s, 1H), 8.40 (br. s, 1H), 7.69 (d,  $J = 8.0$  Hz, 2H), 7.32 (d,  $J = 8.0$  Hz, 2H), 3.88 (br. q,  $J = 7.3$  Hz, 2H), 2.36 (s, 3H), 1.09 (br. t,  $J = 7.3$  Hz, 2H) ppm;  $^{13}\text{C APT NMR}$  (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  158.7 (C), 152.8 (C), 142.2 (C), 139.4 (C), 130.6 (C), 129.0 $\times$ 2 (CH), 126.2 $\times$ 2 (CH), 61.0 (CH<sub>2</sub>), 20.9 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>) ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{16}\text{Cl}_2\text{N}_3\text{O}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 380.0239, found: 380.0228.

**X-ray diffraction study of 15a**. The colourless crystals of **15a** ( $\text{C}_{13}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_4$ ) are triclinic. At 173 K  $a = 8.7642(3)$ ,  $b = 9.3401(4)$ ,  $c = 11.3447(5)$  Å,  $\alpha = 82.501(2)^\circ$ ,  $\beta = 87.803(2)^\circ$ ,  $\gamma = 63.268(2)^\circ$ ,  $V = 822.09(6)$  Å<sup>3</sup>,  $M_r = 380.24$ ,  $Z = 2$ , space group  $P\bar{1}$ ,  $d_{\text{calc}} = 1.536$  g/cm<sup>3</sup>,  $\mu(\text{MoK}\alpha) = 0.544$  mm<sup>-1</sup>,  $F(000) = 392$ . Intensities of 12155 reflections (3777 independent,  $R_{\text{int}} = 0.0353$ ) were measured on the Bruker APEX II diffractometer (graphite monochromated  $\text{MoK}\alpha$  radiation, CCD detector,  $\varphi$ - and  $\omega$ -scanning,  $2\theta_{\text{max}} = 50^\circ$ ). The structure was solved by direct method using OLEX2<sup>23</sup> package with SHELXT<sup>24</sup> and SHELXL modules<sup>25</sup>. Positions of the hydrogen atoms were located from electron density difference maps and refined using “riding” model with  $U_{\text{iso}} = nU_{\text{eq}}$  ( $n = 1.5$  for methyl groups and  $n = 1.2$  for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against  $F^2$  in anisotropic approximation for non-hydrogen atoms using

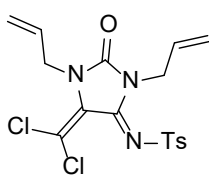
3777 reflections was converged to  $wR_2 = 0.0970$  ( $R_1 = 0.0387$  for 3059 reflections with  $F > 4\sigma(F)$ ,  $S = 1.051$ ). The final atomic coordinates, and crystallographic data for molecule **15a** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2424958).

#### 4.4. General procedure for the synthesis of compounds **18a-c**

Compound **11a** (0.5 g, 1.5 mmol) was dissolved in acetone (25 mL) and milled  $K_2CO_3$  (1.03 g, 7.5 mmol) with KI (cat.) were added. The reaction mixture was stirred at 25–30 °C for 30 min, and then alkyl halide (7.5 mmol) was added. Reaction mixture was stirred at 50 °C for 24 h (until full conversion according to LCMS), then the acetone was evaporated from the reaction mixture, 5% aq HCl was added to pH 5–6, and product extracted with  $CH_2Cl_2$  (2×20 mL). Combined extracts were dried, and the solvent was evaporated to produce crude product which was purified by flash chromatography (hexane–MTBE, gradient 0–100%).

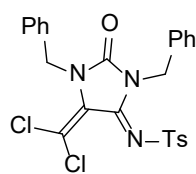


**N-(5-(dichloromethylene)-1,3-dimethyl-2-oxoimidazolidin-4-ylidene)-4-methylbenzenesulfonamide (18a)**. White solid; mp 219–221 °C;  $R_f$  (MTBE) 0.8;  $R_f$  (5% MeOH in  $CH_2Cl_2$ ) 0.6; yield 0.22 g (41 %).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.83 (d,  $J = 8.0$  Hz, 2H), 7.28 (d,  $J = 8.0$  Hz, 2H), 3.74 (s, 3H), 3.52 (s, 3H), 2.42 (s, 3H) ppm;  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  153.7, 149.0, 143.1, 140.0, 129.3×2, 129.0, 126.6×2, 113.5, 32.0, 31.8, 21.6 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $C_{13}H_{14}Cl_2N_3O_3S$   $[M+H]^+$ : 362.0133, found: 362.0122.



**N-(1,3-diallyl-5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)-4-methylbenzenesulfonamide (18b)**. Light beige solid; mp 78–80 °C;  $R_f$  (MTBE) 0.9;  $R_f$  ( $CH_2Cl_2$ ) 0.35; yield 0.22 g (35 %).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.84 (d,  $J = 8.1$  Hz, 2H), 7.28 (d,  $J = 8.1$  Hz, 2H), 6.09 (ddt,  $J = 16.8, 10.2, 5.8$  Hz, 1H), 5.83 (ddt,  $J = 17.1, 10.6, 5.1$  Hz, 1H), 5.36 (d,  $J = 17.1$  Hz, 1H), 5.30 (d,  $J = 10.2$  Hz, 1H), 5.25 (d,  $J = 10.6$  Hz, 1H), 5.16 (d,  $J = 16.8$  Hz, 1H), 4.94 (d,  $J = 5.8$  Hz, 2H), 4.64 (dt,  $J = 5.1, 1.7$  Hz, 2H), 2.42 (s, 3H) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  153.2, 147.2, 143.2, 139.7, 131.9, 130.9, 129.3×2, 127.9, 126.6×2, 119.5, 118.1, 113.7, 46.8, 45.6, 21.7 ppm;

HRMS (ESI-TOF):  $m/z$  calcd. for  $C_{17}H_{18}Cl_2N_3O_3S$   $[M+H]^+$ : 414.0446, found: 414.0436.



**N-(1,3-dibenzyl-5-(dichloromethylene)-2-oxoimidazolidin-4-ylidene)-4-methylbenzenesulfonamide (18c)**. Light yellow solid; mp 116–118 °C;  $R_f$  (MTBE) 0.9;  $R_f$  ( $CH_2Cl_2$ ) 0.3; yield 0.64 g (83 %).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.86 (d,  $J = 8.4$  Hz, 2H), 7.47 (d,  $J = 7.4$  Hz, 2H), 7.39 (t,  $J = 7.4$  Hz, 2H), 7.35–7.29 (m, 4H), 7.28 (d,  $J = 8.4$  Hz, 2H), 7.10 (br. d,  $J = 7.5$  Hz, 2H), 5.63 (s, 2H), 5.26 (s, 2H), 2.42 (s, 3H) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  154.0, 147.3, 143.3, 139.7, 136.0, 135.0, 129.3×2, 129.0×2, 128.6×2, 128.1, 128.0, 128.0, 127.9×2, 126.6×2, 126.4×2, 114.5, 48.2, 47.0, 21.7 ppm;  $^{13}C$  APT NMR (101 MHz,  $CDCl_3$ )  $\delta$  154.0 (C), 147.3 (C), 143.3 (C), 139.7 (C), 136.0

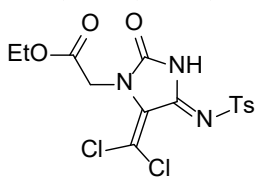
(C), 135.0 (C), 129.3×2 (CH), 129.0×2 (CH), 128.6×2 (CH), 128.1 (CH), 128.0 (CH), 128.0 (C), 127.9×2 (CH), 126.6×2 (CH), 126.4×2 (CH), 114.5 (C), 48.2 (CH<sub>2</sub>), 47.0 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>) ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $C_{25}H_{22}Cl_2N_3O_3S$   $[M+H]^+$ : 514.0759, found: 514.0750.

#### 4.5. Procedure of the interaction of compound **11a** with ethyl 2-chloroacetate

Compound **11a** (0.5 g, 1.5 mmol) was dissolved in DMF (20 mL) and milled potassium carbonate  $K_2CO_3$  (1.03 g, 7.5 mmol) with KI (cat.) were added. The reaction mixture was stirred at 25–30 °C for 30 min, then ethyl 2-chloroacetate (0.8 mL, 0.92 g, 7.5 mmol) was added. Reaction mixture was stirred at 50 °C for 24 h (until starting compound disappears by LCMS). Reaction mixture then poured into water (100 mL), the precipitate was filtered and washed with water (10 mL) and MTBE (20 mL) to obtain product **19** as K-salt **19'**. MTBE from filtrate (water – MTBE suspension) was evaporated; water solution was acidified by 35% aq HCl. The compound **19** precipitate, which was formed after acidification, was filtered off and washed with water (10 mL).

K-salt of **19'** can easily be transferred quantitatively to **19** by addition 5% aq HCl into its 5% aq solution with subsequent DCM extraction.

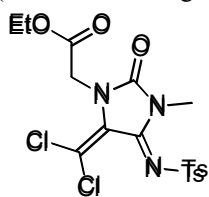
**Salt 19'**. White solid; yield 0.31 g (45 %).  $^1H$  NMR (600 MHz,  $DMSO-d_6$ )  $\delta$  7.74 (d,  $J = 8.0$  Hz, 2H), 7.24 (d,  $J = 8.0$  Hz, 2H), 4.53 (s, 2H), 4.11 (q,  $J = 7.1$  Hz, 2H), 2.33 (s, 3H), 1.17 (t,  $J = 7.1$  Hz, 3H) ppm;  $^{13}C$  NMR (151 MHz,  $DMSO-d_6$ )  $\delta$  169.2, 167.8, 165.1, 141.3, 140.6, 133.8, 128.4×2, 127.0×2, 101.8, 60.9, 43.3, 20.9, 14.0 ppm.



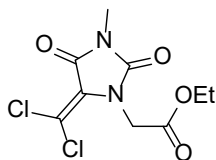
**Ethyl 2-(5-(dichloromethylene)-2-oxo-4-(tosylimino)imidazolidin-1-yl)acetate (19)**. White solid; mp 163–165 °C; yield 0.26 g (41 %) from reaction mixture; yield 0.54 g (86 %) combined with acidified salt.  $^1H$  NMR (600 MHz,  $DMSO-d_6$ )  $\delta$  7.86 (d,  $J = 7.8$  Hz, 2H), 7.42 (d,  $J = 8.0$  Hz, 2H), 4.70 (s, 2H), 4.17 (q,  $J = 7.1$  Hz, 2H), 2.39 (s, 3H), 1.19 (t,  $J = 7.1$  Hz, 3H) ppm, NH don't observed due to exchange processes;  $^{13}C$  NMR (151 MHz,  $DMSO-d_6$ )  $\delta$  168.0, 152.9, 151.4, 143.7, 138.0, 129.7×2, 128.7, 126.5×2, 111.1, 61.6, 43.9, 21.0, 13.9 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $C_{15}H_{16}Cl_2N_3O_5S$   $[M+H]^+$ : 420.0188, found: 420.0177.

#### 4.6. Procedure of the compound **19** alkylation with MeI

Salt **19'** (0.5 g, 1.1 mmol) was dissolved in DMF (5 mL) and MeI (0.09 mL, 0.20 g, 1.3 mmol) was added. The reaction mixture was heated with stirring at 45–50 °C until full conversion of the substrate, and poured into water (50 mL). The products mixture was extracted with MTBE (3×15 mL). Combined extracts were dried, and the solvent was evaporated to produce crude products (iminohydantoin **20** and hydantoin **21**), which were separated and purified by flash chromatography (hexane–MTBE, gradient 0–100%).



**Ethyl 2-(5-(dichloromethylene)-3-methyl-2-oxo-4-(tosylimino)imidazolidin-1-yl)acetate (20).** White solid; mp 125–127 °C;  $R_f$  (MTBE) 0.8; yield 0.218 g (46 %).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (d,  $J = 8.2$  Hz, 2H), 7.29 (d,  $J = 8.2$  Hz, 2H), 4.79 (s, 2H), 4.25 (q,  $J = 7.1$  Hz, 2H), 3.78 (s, 3H), 2.42 (s, 3H), 1.28 (t,  $J = 7.1$  Hz, 3H) ppm;  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  167.5, 153.5, 148.6, 143.3, 139.6, 129.4×2, 127.6, 126.6×2, 113.9, 62.4, 45.0, 31.9, 21.7, 14.2 ppm;  $^{13}\text{C APT NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  167.5 (C), 153.5 (C), 148.6 (C), 143.3 (C), 139.6 (C), 129.4×2 (CH), 127.6 (C), 126.6×2 (CH), 113.9 (C), 62.4 (CH<sub>2</sub>), 45.0 (CH<sub>2</sub>), 31.9 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>); HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{N}_3\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 434.0344, found: 434.0335.

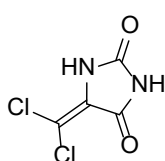


**Ethyl 2-(5-(dichloromethylene)-3-methyl-2,4-dioxoimidazolidin-1-yl)acetate (21).** White solid; mp 114–116 °C;  $R_f$  (MTBE) 0.8;  $R_f$  ( $\text{CH}_2\text{Cl}_2$ ) 0.7; yield 0.045 g (15 %).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.74 (s, 2H), 4.23 (q,  $J = 7.1$  Hz, 2H), 3.12 (s, 3H), 1.28 (t,  $J = 7.1$  Hz, 3H) ppm;  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.8, 159.7, 153.6, 126.1, 112.8, 62.2, 43.5, 25.6, 14.3 ppm;  $^{13}\text{C APT NMR}$  (151 MHz,  $\text{CDCl}_3$ )  $\delta$  167.8 (C), 159.7 (C), 153.6 (C), 126.2 (C), 112.8 (C), 62.2 (CH<sub>2</sub>), 43.5 (CH<sub>2</sub>), 25.6 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>); HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_9\text{H}_{11}\text{Cl}_2\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 281.0096, found:

281.0087.

#### 4.7. Obtaining of compound **23**

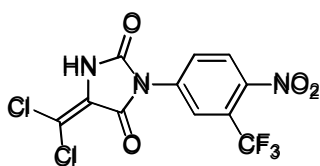
To the suspension of compound **11a** or **11f** (1 mmol) in 96% EtOH (10 mL) and 36% aq HCl (0.17 mL, 2 mmol) was added. The mixture was refluxed for 48 h; then the solvent was evaporated. In the case of substrate **11a**, the residue was treated by flash chromatography (hexane–MTBE, gradient 0–100%) to separate the target product **23** from 4-methylbenzenesulfonamide. In the case of substrate **11f**, the residue was treated by water (10 mL) to separate water-soluble methanesulfonamide. In both cases the yield of **23** is almost quantitative, and it can be reduced only due to mechanical losses.



**5-(Dichloromethylene)imidazolidine-2,4-dione (23).** Light beige solid; subl. >260 °C;  $R_f$  (MTBE) 0.8.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.40 (s, 1H), 10.79 (s, 1H) ppm;  $^{13}\text{C NMR}$  (151 MHz,  $\text{DMSO}-d_6$ )  $\delta$  160.8, 153.1, 128.9, 105.9 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_4\text{H}_3\text{Cl}_2\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 180.9572, found: 180.9566.

#### 4.8. Arylation of compound **23**

To the solution of initial compound **23** (0.5 g, 2.8 mmol) in dry DMF (5 mL) 4-fluoro-1-nitro-2-(trifluoromethyl)benzene (0.59 g, 2.8 mmol) and  $\text{K}_2\text{CO}_3$  (0.42 g, 3 mmol) were added. The mixture was heated with stirring at 80 °C for 12 h, and poured into water (50 mL). The product was extracted with MTBE (3×15 mL). Combined extracts were dried, and the solvent was evaporated to produce crude product, which was purified by flash chromatography (hexane–MTBE, gradient 0–100%).

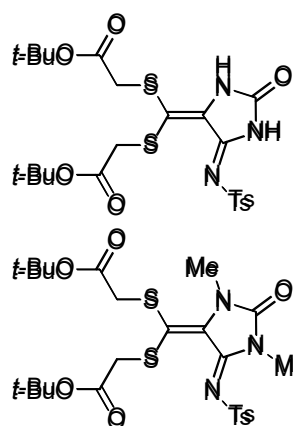


**5-(Dichloromethylene)-3-(4-nitro-3-(trifluoromethyl)phenyl)imidazolidine-2,4-dione (24).** White solid; mp 216–218 °C;  $R_f$  (MTBE) 0.7;  $R_f$  (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) 0.5; yield 0.65 g (64 %).  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.63 (s, 1H), 8.35 (d,  $J = 8.7$  Hz, 1H), 8.16 (s, 1H), 8.05 (d,  $J = 8.7$  Hz, 1H) ppm;  $^{13}\text{C NMR}$  (126 MHz,  $\text{DMSO}-d_6$ )  $\delta$  158.1, 150.8, 145.7, 135.6, 131.6, 127.3, 126.6, 125.5 (q,  $J = 5.6$  Hz), 122.1 (q,  $J = 34.1$  Hz), 121.7 (q,  $J = 273.4$  Hz), 108.5 ppm;  $^{13}\text{C APT NMR}$  (126 MHz,  $\text{DMSO}-d_6$ )  $\delta$  158.1 (C), 150.8 (C), 145.7 (C), 135.6 (C), 131.6 (CH), 127.3 (C), 126.6 (CH), 125.5 (q,  $J = 5.6$  Hz) (CH), 122.1 (q,  $J = 34.1$  Hz) (C), 121.7 (q,  $J = 273.4$  Hz) (C), 108.5 (C) ppm;  $^{19}\text{F NMR}$  (376 MHz,  $\text{DMSO}-d_6$ )  $\delta$  -59.60 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{11}\text{H}_5\text{Cl}_2\text{F}_3\text{N}_3\text{O}_4$   $[\text{M}+\text{H}]^+$ : 369.9609, found: 369.9602.

**X-ray diffraction study of 24.** The colourless crystals of **24** ( $\text{C}_{11}\text{H}_4\text{Cl}_2\text{F}_3\text{N}_3\text{O}_4$ ) are monoclinic. At 173 K  $a = 13.0116(5)$ ,  $b = 16.2142(6)$ ,  $c = 12.8661(5)$  Å,  $\beta = 101.137(2)^\circ$ ,  $V = 2663.28(18)$  Å<sup>3</sup>,  $M_r = 370.07$ ,  $Z = 8$ , space group  $P2_1/c$ ,  $d_{\text{calc}} = 1.846$  g/cm<sup>3</sup>,  $\mu(\text{MoK}\alpha) = 0.549$  mm<sup>-1</sup>,  $F(000) = 1472$ . Intensities of 36809 reflections (4698 independent,  $R_{\text{int}} = 0.0747$ ) were measured on the Bruker APEX II diffractometer (graphite monochromated  $\text{MoK}\alpha$  radiation, CCD detector,  $\varphi$ - and  $\omega$ -scanning,  $2\theta_{\text{max}} = 50^\circ$ ). The structure was solved by direct method using OLEX2<sup>23</sup> package with SHELXT<sup>24</sup> and SHELXL modules<sup>25</sup>. Positions of the hydrogen atoms were located from electron density difference maps and refined using “riding” model with  $U_{\text{iso}} = 1.2U_{\text{eq}}$  of the carrier atom. Full-matrix least-squares refinement against  $F^2$  in anisotropic approximation for non-hydrogen atoms using 4698 reflections was converged to  $wR_2 = 0.1177$  ( $R_1 = 0.0487$  for 3307 reflections with  $F > 4\sigma(F)$ ,  $S = 1.026$ ). The final atomic coordinates, and crystallographic data for molecule **24** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2424959).

#### 4.9. General procedure for the compounds **25a,b** synthesis

To the suspension of compound **11a** or **18a** (1 mmol) and NMM (0.275 mL, 0.253 g, 2.5 mmol) in absolute MeCN (10 mL) *tert*-butyl 2-mercaptoacetate (0.36 mL, 0.37 g, 2.5 eq) was added dropwise with stirring. Reaction mixture was stirred at 50 °C for 6 h, then the solvent was evaporated in vacuo. Water (10 mL) was added to residue and precipitate was formed, which was filtered off, washed with the mixture MeCN – water 1 : 1 (2×5 mL), dried and recrystallized from EtOH.

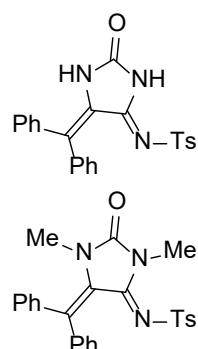


**Di-tert-butyl 2,2'-(((2-oxo-5-(tosylimino)imidazolidin-4-ylidene)methylene)bis(sulfaneyl))diacetate (25a).** Yellow solid; mp 140–142 °C;  $R_f$  (MTBE) 0.55; yield 0.45 g (81 %).  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  11.52 (br. s, 1H), 10.72 (s, 1H), 7.83 (d,  $J$  = 8.3 Hz, 2H), 7.35 (d,  $J$  = 8.0 Hz, 2H), 3.73 (s, 2H), 3.55 (s, 2H), 2.34 (s, 3H), 1.31 (s, 9H), 1.26 (s, 9H) ppm;  $^{13}\text{C NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$  168.0, 167.5, 152.7, 151.1, 143.2, 138.5, 131.8, 129.5×2, 126.5×2, 122.7, 81.5, 81.3, 37.1, 36.9, 27.5×3, 27.4×3, 21.0 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{32}\text{N}_3\text{O}_7\text{S}_3$   $[\text{M}+\text{H}]^+$ : 558.1402, found: 558.1388.

**Di-tert-butyl 2,2'-(((1,3-dimethyl-2-oxo-5-(tosylimino)imidazolidin-4-ylidene)methylene)bis(sulfaneyl))diacetate (25b).** Yellow solid; mp 132–134 °C;  $R_f$  (MTBE) 0.8; yield 0.50 g (85 %).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 (d,  $J$  = 7.4 Hz, 2H), 7.28 (d,  $J$  = 7.4 Hz, 2H), 3.77 (s, 3H), 3.57 (s, 2H), 3.54 (s, 3H), 3.32 (s, 2H), 2.42 (s, 3H), 1.42 (s, 9H), 1.39 (s, 9H) ppm;  $^{13}\text{C NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$  167.5, 167.3, 154.7, 149.4, 142.6, 139.9, 130.8, 129.2×2, 126.8, 126.0×2, 81.7, 81.4, 38.4, 38.3, 32.2, 31.0, 27.5×6, 21.1 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{25}\text{H}_{36}\text{N}_3\text{O}_7\text{S}_3$   $[\text{M}+\text{H}]^+$ : 586.1715, found: 586.1700.

#### 4.10. General procedure for the compounds **26a,b** synthesis

To the suspension of compound **11a** or **18a** (1 mmol) in the mixture of 1,4-dioxane –  $\text{H}_2\text{O}$  4 : 1 (10 mL)  $\text{PhB}(\text{OH})_2$  (0.27 g, 2.2 mmol),  $\text{K}_3\text{PO}_4$  (1.02 g, 4.8 mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (0.075 g, 0.1 mmol) were added. Reaction mixture was stirred at 90 °C for 12 h, then the solvent was evaporated in vacuo. The residue was poured into water (50 mL); and the product was extracted with MTBE (3×15 mL). Combined extracts were dried, and the solvent was evaporated to produce crude product, which was purified by flash chromatography (hexane–MTBE, gradient 0–100%).

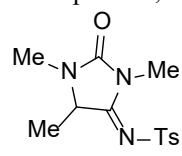


**N-(5-(Diphenylmethylene)-2-oxoimidazolidin-4-ylidene)-4-methylbenzenesulfonamide (26a).** Yellow solid; mp 158–160 °C;  $R_f$  (MTBE) 0.35;  $R_f$  (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) 0.65; yield 0.29 g (69 %).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.80 (s, 1H), 7.82 (s, 1H), 7.42–7.29 (m, 6H), 7.25–7.18 (m, 6H), 7.13 (d,  $J$  = 7.2 Hz, 2H), 2.43 (s, 3H) ppm;  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  152.8, 152.4, 143.6, 138.6, 137.6, 137.2, 133.6, 130.5×2, 129.6, 129.3×2, 129.3×2, 129.3×2, 128.6, 128.1×2, 126.9×2, 125.9, 21.7 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{20}\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 418.1225, found: 418.1214.

**N-(5-(Diphenylmethylene)-1,3-dimethyl-2-oxoimidazolidin-4-ylidene)-4-methylbenzenesulfonamide (26b).** Yellow solid; mp 195–197 °C;  $R_f$  (MTBE) 0.8; yield 0.32 g (72 %).  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  7.40–7.31 (m, 3H), 7.16–7.09 (m, 4H), 7.09–6.93 (m, 7H), 3.57 (s, 3H), 2.54 (s, 3H), 2.36 (s, 3H) ppm;  $^{13}\text{C NMR}$  (126 MHz, DMSO- $d_6$ )  $\delta$  155.1, 151.9, 141.6, 139.9, 139.8, 139.5, 132.4, 130.1×2, 129.7×2, 129.5, 128.8×2, 128.6, 128.1×2, 127.6×2, 127.6, 125.4×2, 32.0, 31.1, 20.8 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 446.1538, found: 446.1525.

#### 4.11. Reduction of the compound **18a**

To the suspension of compound **18a** (0.362 g, 1 mmol) and NMM (0.275 mL, 0.253 g, 2.5 mmol) in MeOH (25 mL) cat. amount of 10% Pd / C (0.05 g) was added; and the mixture was stirred under  $\text{H}_2$  (20 atm) at 40 °C for 12 h. After that catalyst was filtered off, and the solvent was evaporated in vacuo. The residue was poured into water (50 mL); and the product was extracted with MTBE (3×15 mL). Combined extracts were dried, and the solvent was evaporated to produce crude product, which was purified by flash chromatography (hexane–MTBE, gradient 0–100%).



**4-Methyl-N-(1,3,5-trimethyl-2-oxoimidazolidin-4-ylidene)benzenesulfonamide (27).** White solid; mp 186–188 °C;  $R_f$  (MTBE) 0.3; yield 0.075 g (25 %).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (d,  $J$  = 8.4 Hz, 2H), 7.30 (d,  $J$  = 8.4 Hz, 2H), 4.89 (q,  $J$  = 6.7 Hz, 1H), 3.03 (s, 3H), 2.98 (s, 3H), 2.43 (s, 3H), 1.73 (d,  $J$  = 6.7 Hz, 3H) ppm;  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.3, 154.3, 143.3, 139.1, 129.5×2, 126.7×2, 57.3, 27.5, 26.9, 21.6, 17.8 ppm; HRMS (ESI-TOF):  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{18}\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 296.1069, found: 296.1061.

#### 4.12. Biological Assay

The anticancer activity of the compound **11a** was tested according to the International Program of the National Institutes of Health – DTP (Developmental Therapeutic Program, <https://dtp.cancer.gov>) of the National Cancer Institute (NCI, Bethesda, Maryland, USA) on 60 cancer cell lines; the details of the technique are also given<sup>27</sup>.

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