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Synthesis and structural study of new substituted chiral sulfamoyl oxazolidin-2-ones

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ABSTRACT

The synthesis of new series of oxazolidinones having sulfonamide moieties is described. These compounds are synthesized in good yield starting prochiral 1,3-dichloro-2-propanol and chlorosulfonyl isocyanate. This strategy involves the formation of carboxylsulfamide by carbamoylation–sulfamoylation reaction followed by intermolecular cyclization. In order to determine the enantioselectivity during the cyclization step, X-ray studies of products are performed.

1. Introduction

The emergence of bacterial resistance to the antibiotics poses a serious concern for medical professionals during the last decades. In particular, multi-drug-resistant Gram-positive bacteria are of major concern. Oxazolidinones, exemplified by Linezolid,[1,2] are a novel class of totally synthetic antibacterial agents that have been successfully implemented in the clinic. The literature reveals that extensive chemical programmes exist.[3,4] Previously, we reported the synthesis of the *N*,*N*′-sulfonyl bis-oxazolidin-2-ones.[5] In this work, we describe the synthesis and structural study of oxazolidinones having sulfonamide moieties. The sulfonamide group is considered as a pharmacophore, which is present in number of biologically active molecules, particularly antimicrobial agents.[6] It was shown that sulfonamide moieties can enhance largely the activity of antibacterial agents especially against both Gram-positive and Gram-negative bacteria.[7] In addition, the sulfonamide derivatives constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial,[8] antitumor,[9] anticarbonic anhydrase,[10] anticonvulsant[11] or protease inhibitory activity[12] among others. Based on this fact, a positive effect to sulfonamide moieties on the activity of oxazolidinone was anticiped.

In this paper, we report the synthesis and the structural analysis of compound (**2a**), a racemic mixture of (5*R*) and (5*S*)chloromethyl-2-oxo-oxazolidine-3-sulfonic acid (3) fluorophenyl-amide and structural analysis of compound (**2b**), also a racemic mixture of (5*R*) and (5*S*) chloromethyl-3-(3,4 dihydro-1*H*-isoquinoline-2-sulfonyl)-oxazolidin-2-one. Packings of the two crystal structures presented herein are the results of individually weak but synergistic non covalent interactions like typical N–H···O=C hydrogen bonds or π/π stacking effects.

A search in the Cambridge Structural Database[13] for sulfonyl *N*-oxazolidinone fingerprint revealed 45 hits but a restriction on sulfonamide derivatives focused only on position 5 substitution revealed two hits, namely 2-oxo-3-oxazolidinesulfonamide (CSD ref code FUWMOZ[14]) and the symmetric sulfonyl-bis(*N*-oxazolidinone) (CSD ref code PEQDAQ[15]). Scheme 1 resumes the structures of the CSD hits and the two compounds detailed in this paper.

2. Results and discussion

2.1. Preparation of substituted sulfamoyl-oxazolidinones

The synthesis of sulfamides is usually performed by reacting an amine with a substituted sulfonyl chloride or anhydride often in the presence of a buffering base in an aprotic solvent. The yields are variable, but can be improved after optimization. A number of synthesis procedures have been reported for the preparation of sulfonamides from acids using coupling reagents, such as EDC, DCC,

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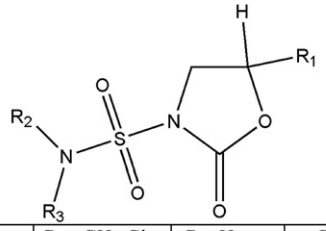


2a	R_1= CH_2-Cl	R_2=H	R_3=*m*-F-Ph
2b	R_1 = CH_2-Cl	R_2 to R_3 = 3,4-benzopiperidine	
FUWMOZ	R_1=H	R_2= H	R_3= Ph
PEQDAQ	R_1 = H	R_2 to R_3 = -CH_2-CH_2-O-C=O-	

Scheme 1. Chemical formulas for the two compound (**2a**) and (**2b**) analyzed in this paper and the two analogous CSD hits (ref code FUWMOZ and PEQDAQ) discussed herein.

CDI or Mukaiyama's reagent.[16] However, those approaches can be limited by drastic reaction conditions, the formation of secondary products, long times, and low yields.

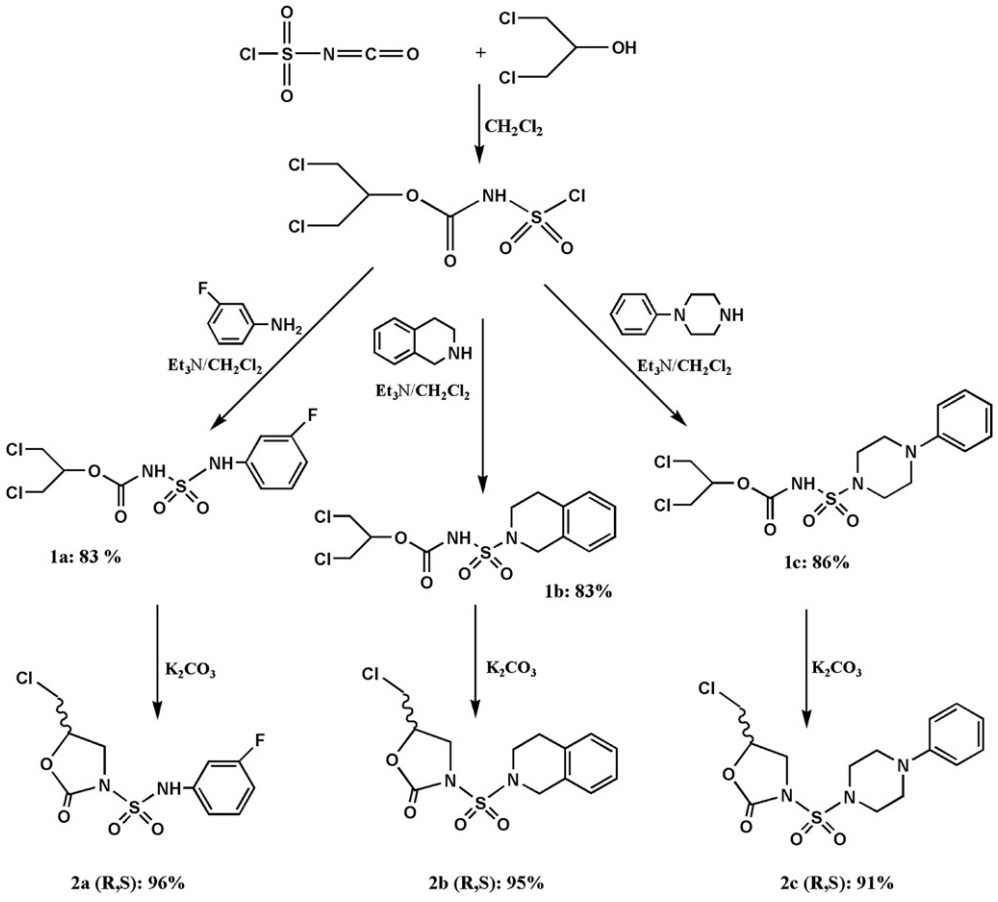
Chlorosulfonyl isocyanate (CSI) has been found to be a versatile reagent in organic synthesis with great interest in heterocyclic chemistry.[17] In our previous works, we have established that CSI is a suitable reagent allowing the introduction a sulfonamide moiety in biomolecules.[18] CSI is also the reagent of choice for the preparation of sulfamoyl oxazolidin-2-ones. In this case CSI contains the required sulfonyl group and the nitrogen, which is necessary for the formation of oxazolidin-2-ones.

The synthetic pathway followed for the preparation of the title compounds was accomplished by a three-steps sequence as shown in Scheme 2. Firstly, the prochiral alcohol, 1,3-dichloro-2-propanol, reacted smoothly with chlorosulfonyl isocyanate in the presence of dichloromethane to easily give carbamate. In the second step, condensation of the carbamate with commercially available corresponding amines (3-fluoroaniline, 1-phenyl piperazine and 1,2,3,4-tetrahydroisoquinoline) in the presence of triethylamine at 0 °C afford substituted sulfamides (**1a**–**c**) in good yields. These products were purified by chromatography on silica gel (eluted with DCM/MeOH: 9.1). In the next stage of the synthesis, compounds **1a**–**c** were subjected to the intramolecular cyclization in diluted basic medium under solvent reflux. The cyclization were attempt with potassium carbonate in acetone or acetonitrile at room temperature yielding 5-chloromethyl-2-oxazolidinone derivatives with a chiral center at the 5-position. A probable mechanism of the cyclization-reaction course is shown in Scheme 3.

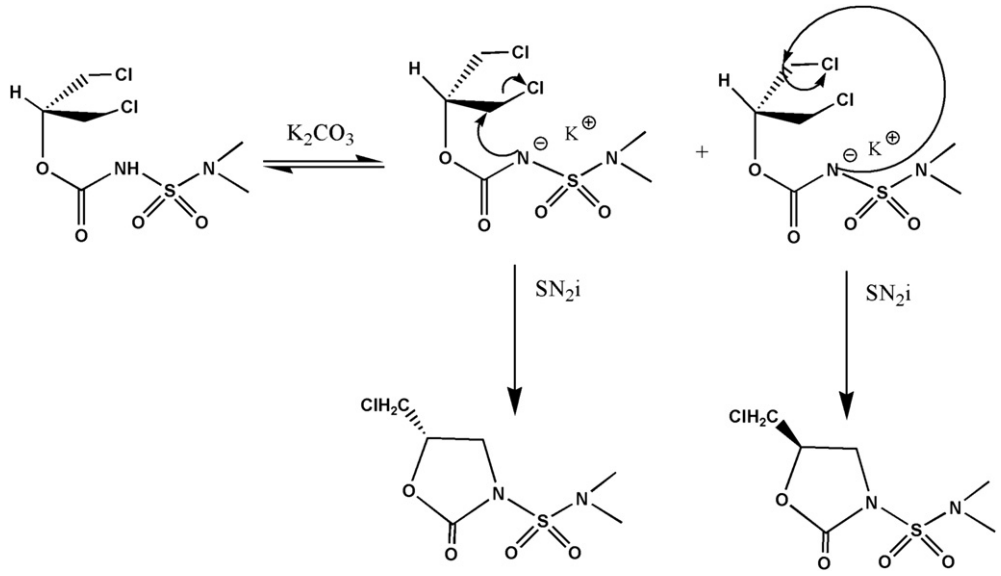
Identification of all isolated products (**1a**–**c**) and (**2a**–**c**) was accomplished by ^{1}H and ^{13}C NMR and mass spectrometry. The compounds 2**a** and 2**b** were submitted to X-ray crystallographic analysis, which gave the structures shown in Fig. 1.

2.2. X-ray structural analyses

The compounds 2**a** and 2**b** are racemic mixture, both crystallize in the centrosymmetric $P2_1/c$ space group (n°14) (Table 1). The asymmetric units are only composed of one molecule; an ORTEP view with numbering scheme of the asymmetric entities for the two crystal structures is given on Fig. 1. For the two crystal structures, the sum of angles at N(1) [S(1)–N(1)–C(1)+S(1)–N(1)–C(2)+C(1)–N(1)–C(2)] are both 360° consistent with trigonal planar geometry at nitrogen N(1) (Table 2).



Scheme 2.



Scheme 3.

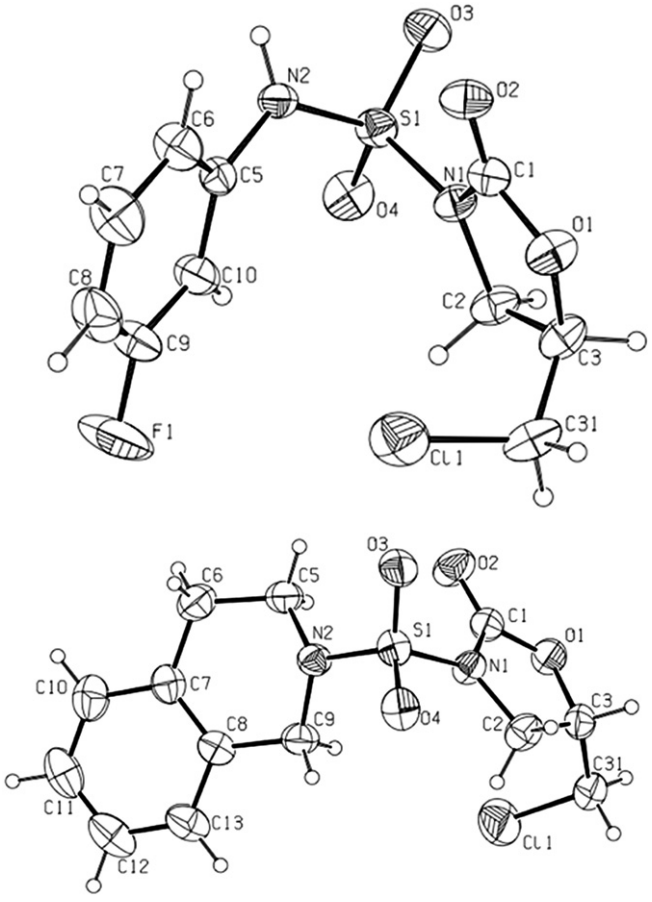


Fig. 1. ORTEP diagram of the asymmetric unit content of **2a** (top) and **2b** (bottom). Displacement ellipsoïds are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radii.

The oxazolidinone rings are arranged in a flat conformation, the angles at O(1) are 111.15° and 111.23°, respectively, for the two compounds and are typical trigonal planar geometry at oxygen, while angles around tetrahedral C(2) and C(3) range between

Table 1
Crystallographic data for compound (**2a**) and (**2b**) and refinement data

Compound reference	Compound **2a**	Compound **2b**
Chemical formula	$C_{10}H_{10}ClFN_2O_4S$	$C_{13}H_{15}ClN_2O_4S$
Formula mass	308.8 g mol^{-1}	330.8 g mol^{-1}
Crystal system	Monoclinic	Monoclinic
a (Å)	9.1300 (3)	14.5010 (12)
b (Å)	8.9369 (2)	9.3963 (12)
c (Å)	16.3629 (5)	10.6178 (12)
α (°)	90	90
β (°)	97.4100(18)	93.340 (7)
γ (°)	90	90
Unit cell volume (Å^3)	1323.96 (7)	1444.3 (3)
Temperature (K)	293 (2)	293 (2)
Space group	$P2_1/c$	$P2_1/c$
Z	4	4
Radiation:	Mo Kα (λ=0.71073 Å)	Mo Kα (λ=0.71073 Å)
θ range for data collection:	1.0–26.4°	0.41–24.13°
Reflections collected/ unique/with [$I>2\sigma(I)$]:	19,795/3240/2310	14,474/2440/1728
Data/restraints/parameters:	3036/0/172	2275/0/190
Goodness of fit on F^2:	1.036	1.116
Final R indices [$I>2\sigma(I)$]:	$R1$=0.0435, $wR2$=0.1102	$R1$=0.0448, $wR2$=0.1044
R indices (all data):	$R1$=0.0623, $wR2$=0.1211	$R1$=0.0640, $wR2$=0.1164
$(\Delta\rho)_{max}$:	0.32 e Å^{-3}	0.17 e Å^{-3}
$(\Delta\rho)_{min}$:	−0.38 e Å^{-3}	−0.28 e Å^{-3}
CCDC deposition number	885193	885192

101.24 and 105.66°. These led to torsion angle around C(2)–C(3) bond extremely small (Table 2). So, molecules are characterized by the planarity of the pentagonal ring in which N(1) behave a sp^2 hybridization character favorable to a conjugation of O(1) C(1) O(2) N(1) system. This latter enable a diminution of the bond lengths around the C(1) in regards of standard values.[19] Another consequence is the significant difference between the S(1)–N(1) and S(1)–N(2) bond distances (Δl=0.062 and 0.0676 Å).

At a molecular scale, comparison shows a close similarity in the ring conformation and angles in the molecules with the two similar structures already present in the CSD (Fig. 2).

Local environment around a central molecule gives rise to dimers in the crystal packing, the two (+) (−) enantiomers facing each other. Details of the local organization around a dimer in the crystal structure of (**2a**) and (**2b**) are given on Fig. 3. Both crystal

Table 2
Selected bond distances (Å), bond angles (°) and torsion angles (°)

Compound reference	Compound **2a**	Compound **2b**
N(2)–S(1)	1.5993 (18)	1.6076 (23)
S(1)–N(1)	1.6613 (16)	1.6752 (23)
C(1)–O(2)	1.1993 (27)	1.1983 (36)
C(1)–O(1)	1.3317 (24)	1.3379 (36)
S(1)–N(1)–C(1)	123.79 (0.14)	−124.06 (0.19)
S(1)–N(1)–C(2)	123.47 (0.13)	−123.59 (0.19)
C(1)–N(1)–C(2)	112.74 (0.17)	112.35 (0.21)
C(1)–O(1)–C(3)	111.15 (0.16)	111.23 (0.21)
O(1)–C(3)–C(2)	105.66 (0.19)	105.27 (0.22)
N(1)–C(2)–C(3)	101.24 (0.16)	101.76 (0.23)
C(1)–O(1)–C(3)–C(2)	0.99 (0.23)	4.53 (0.29)
O(1)–C(3)–C(2)–N(1)	−1.49 (0.21)	−2.98 (0.27)
C(2)–N(1)–C(1)–O(1)	−1.11 (0.24)	2.10 (0.31)

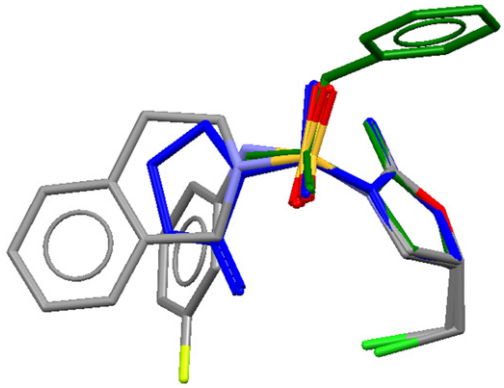


Fig. 2. Superposition of the two compound **2a** and **2b** analyzed in this paper (in gray) and the two analogous CSD hits (ref code FUWMOZ in green and PEQDAQ in blue). The common sulfonyl *N*-oxazolidinone structure is highlighted by atom-type colors.

structures are described in the centrosymmetric space group $P2_1/c$, thus these structures are composed of a racemic mixture of *R* and *S* configuration at carbon C(3), with respect numbering scheme of the cif file, which indicates the absence of enantioselectivity during the cyclization process. Two symmetric entities of (**2a**) form a dimer via two mutual short intermolecular NH/O═C hydrogen bond that link N(2) of the first molecule to O(2) of the second and vice versa (Table 3). On the other hand, arrangement of aromatic rings is a parallel-displaced alignment with an interplanar distance of 3.138 Å. But π/π intermolecular parallel stacking interactions between fluoro-benzene cannot be really taken into account because of the too large offset distance between centroids, almost 4 Å in comparison with a typical offset distance of 1.6–1.8 Å for this kind of interaction, observed in benzene dimer, and despite an expected stacking distance.[20] This crystal structure can be described as a sandwich structure with slices pile up along the *a* direction. Hydrophobic slices are made of aromatic rings with van der Waals interactions, and more thin hydrophilic slices are made of oxazolidinone rings linked by hydrogen bond.

In the crystal structure of **2b** a dimer organization is also observed with weak favorable face-to-face π/π interactions between aromatic rings with distance of 3.815 Å between the centroids of aromatic rings. Typical distances between centroids range from 3.3 to 3.8 Å for π/π face-to-face or parallel staking interactions in the crystal structure benzene taken as reference. [21] This dimer is connected tri-dimensionally to other dimers via T-shaped π/π interactions. Distance of 5.307 Å between the centroids is typical distance observed for the most favorable interactions T-shaped observed in the crystal structure of benzene.[21] In **2b**, the tridimensional organization is made of 'zig-zag' π/π ribbons connected themselves via π/π effects.

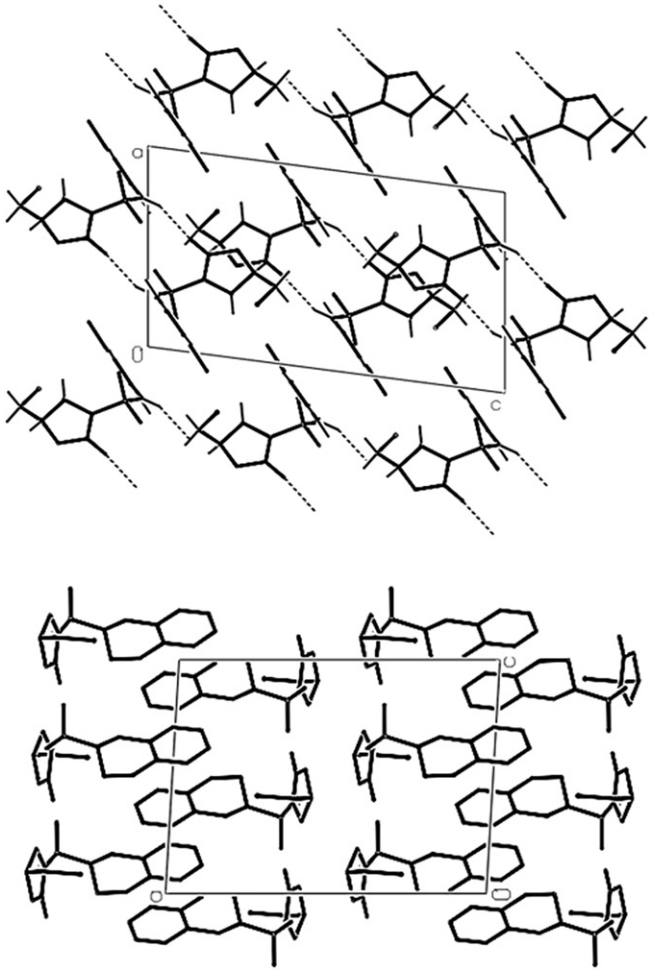


Fig. 3. Molecular packing of compounds **2a** (top) and **2b** (bottom) projected along the crystallographic *b-axis* (PLUTO diagram from PLATON).[22] For the compound **2a**, H bonds showing the formation of dimers are represented as dashed lines. Aromatics rings stack antiparallel and form slices parallels to *c axis*. For compound **2b**, layers of hydrophobic regions that enclose the benzopiremidic ring and layers of polar regions are stacked parallel to the *c-axis* (H atoms are omitted for clarity).

Table 3
Intermolecular NH–O hydrogen bond parameters (distances in Å and angles in °) for compound **2a**

D–H	*d* (D–H)	*d* (H···A)	DHA	*d* (D···A)	A
N(2)–H(2N)	0.860	2.101	157.08	2.912	O(2)···[−*x*+1; −*y*, −*z*+2]

3. Conclusion

X-ray structure comparison shows a close similarity at the molecular scale in the ring conformation and angles in the molecules with the two similar structures already present in the CSD. The mutual presence of the two enantiomers in the crystal structures gives rise to local organization in dimers connected either by H-bond, either by parallel π/π interactions. The study of the crystal structures emphasizes weak intermolecular interaction network, crucial for the crystal cohesion. This structural study shows that the synthesis process is efficient but non-enantioselective.

4. Experimental section

4.1. General

Melting points were determined in open capillary tubes on an Electro thermal apparatus and uncorrected. IR spectra were recorded

on a Perkin–Elmer FT-600 spectrometer. Proton nuclear magnetic resonance was determined with a 360 WB or AC 250-MHz Bruker spectrometer using DMSO-d_6 and $CDCl_3$ as a solvent and TMS as an internal standard. Chemical shifts are reported in δ units (parts per million). All coupling constants J are reported in hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and combination of these signals. Electron ionization mass spectra (30 eV) were recorded in positive or negative mode on a Water MicroMass ZQ. HRMS were recorded on a JEOL JMS DX-300 using NBA as matrix in FAB^+ ionization mode. All reactions were monitored by TLC on silica Merck h60 F_{254} (Art. 5554) precoated aluminum plates and were developed by spraying with ninhydrin solution. Visualization was made with ultraviolet light. Column chromatographies were performed on Merck silica gel 60H (Art. 9385).

4.2. General procedure for the synthesis of carboxylsulfamides

To a stirred solution of chlorosulfonyl isocyanate (CSI) (1.62 g, 11.44 mmol) in (10 mL) of anhydrous dichloromethane at 0 °C was added (1.47 g, 11.39 mmol) of 1,3-dichloropropanol-2 in the same solvent. After a period of 30 min, the resulting solution and (1.75 mL, 1.1 equiv) of triethylamine was slowly added into a solution containing 1 equiv of primary or secondary amine in (10 mL) of dichloromethane. The reaction did not rise above 5 °C. The resulting reaction solution was allowed to warm up to room temperature for over 2 h. The reaction mixture diluted with 30 mL of dichloromethane, washed with HCl 0.1 N and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to give the crude product. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH: 9.9/0.1) to give a carboxylsulfamides in good yields.

*4.2.1. 3-Fluoroanilyn, 1,3-dichloropropan-2-yl sulfonamide carbamate (**1a**).* Yield: 83%, white solid, mp: 139–140 °C, R_f=0.71 (CH_2Cl_2/MeOH, 9:1). ^1H NMR ($CDCl_3$, δ ppm): 8.2 (s, 1H, N*H*), 4.0 (s, 1H, N*H*-ph), 6.9–7–7.2 (m, 4H, *H*–Ar), 3.8 (d, J=5.25 Hz, 4H, 2CH_2), 5.2 (m, 1H, C*H*–$(CH_2)_2$–Cl_2). ^{13}C NMR ($CDCl_3$, δ ppm): 159.9, 159, 130.2, 124.6, 112.5, 78.8, 45. IR (KBr, cm^{-1}): 3219 and 3284 (NH), 1716 (C=O), 1139 and 1351 (SO_2). MS ESI^+ 30 eV m/z: 367 $[M+Na]^+$. HRMS m/z (MNa^+) 366.9705 (calcd for $C_{10}H_{11}Cl_2FN_2O_4S$: 366.9698).

*4.2.2. 1,2,3,4-Tétrahydroisoquinolyn, 1,3-dichloropropan-2-yl sulfonamide carbamate (**1b**).* Yield: 83%, oil, R_f=0.63 (CH_2Cl_2). ^1H NMR ($CDCl_3$, δ ppm): 7.8 (s, 1H, N*H*), 7.2–7.0 (m, 4H, *H*–Ar), 5.1 (m, 1H, C*H*–CH_2), 4.6 (s, 2H, CH_2–N), 3.6–3.8 (m, 6H, CH_2–N-cyc+2CH_2–Cl_2), 2.9 (t, J=5.8 Hz, 2H, CH_2-ph). ^{13}C NMR ($CDCl_3$, δ ppm): 159, 136.1, 134.1, 127.5, 126.9, 126.3, 125.7, 78.8, 47.4, 45, 44.3, 28.1. IR (CCl_4, cm^{-1}): 3262 (NH), 1751(C=O), 1374 and 1159 (SO_2). MS ESI^+ 30 eV m/z: 367.1 $[M+H]^+$. HRMS m/z (MH^+) 367.0295 (calcd for $C_{13}H_{16}Cl_2N_2O_4S$: 367.0286).

*4.2.3. Phenylpiperazin, 1,3-dichloropropan-2-yl sulfonamide carbamate (**1c**).* Yield: 86%, white solid, mp: 136–137 °C, R_f=0.68 (CH_2Cl_2/MeOH, 9:1). ^1H NMR ($CDCl_3$, δ ppm): 8.0 (s, 1H, N*H*), 7.0–6.9 (m, 5H, *H*–Ar), 5.2 (m, 1H, C*H*–CH_2), 3.9 (d, J=5.2 Hz, 4H, 2CH_2–Cl), 3.5 (t, J=5.2 Hz, 4H, 2CH_2–N), 3.2 (t, J=5.4 Hz, 4H, 2CH_2–N). ^{13}C NMR ($CDCl_3$, δ ppm): 159, 149.6, 129.6, 121.9, 114.3, 78.8, 51.5, 45.8, 45. IR (KBr): 3028 (NH), 1739 (C=O), 1372 and 1167 (SO_2) cm^{-1}. MS ESI^+ 30 eV m/z: 396 $[M+H]^+$. HRMS m/z (MH^+) 396.0559 (calcd for $C_{14}H_{19}Cl_2N_3O_4S$: 396.0551).

4.3. General procedure for the synthesis of sulfamoyl-oxazolidinones

A solution of carboxylsulfamides (0.47 g, 1.28 mmol) in dry CH_3CN (20 mL) or acetone was added a K_2CO_3 (0.17 g, 1.23 mmol) a one fraction. The reaction mixture was stirred at room temperature under inert atmosphere. Progress of the reaction is monitored by TLC, which indicates complete disappearance of carboxylsulfamide within 1.5 h. Then the reaction mixture was filtered and concentrated under vacuum to give the crude product. Crystals were grown from dichloromethane/diethylether solution of the compounds at ambient temperature.

*4.3.1. 5-Chloromethyl-N-(3-fluorophenyl)-2-oxo-1,3-oxazolidinone-3-sulfonamide (**2a**).* Yield: 96%, white solid. Colorless crystals from dichloromethane/diethylether, mp: 191–192 °C, R_f=0.75 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (DMSO-d_6, δ ppm): 4.0 (s, 1H, C*H*–Ph), 6.9–7–7.2 (m, 4H, *H*–Ar), 3.9 (m, 2H, CH_2-cyc), 4.9 (m, 1H, *C*H*), 3.6–3.8 (part of ABX, J_{AB}=5.69 Hz, J_{Bx}=9.00 Hz, 2H, CH_2Cl). ^{13}C NMR (DMSO-d_6, δ ppm): 151.9, 149.6, 129.6, 121.9, 114.3, 81.4, 50.3, 43.7. IR (KBr, cm^{-1}): 1752 (C=O), 1362 and 1391 (SO_2). MS ESI^+ 30 eV m/z: 309.2 $[M+H]^+$. HRMS m/z (MH^+) 309.0118 (calcd for $C_{10}H_{10}ClFN_2O_4S$: 309.0112).

*4.3.2. 1,2,3,4-Tétrahydroisoquinolyn, 5-(chloromethyl), oxazolidin-2-one-3-sulfonamide (**2b**).* Yield: 95%, white solid. Colorless crystals from dichloromethane/diethylether, mp: 92–93 °C, R_f=0.67 (CH_2Cl_2). ^1H NMR (DMSO-d_6, δ ppm): 3.0 (t, J=2H, CH_2–Ph), 3.6 (t, 2H, CH_2–N-cyc), 4.6 (s, 2H, CH_2–N-cyc), 7.3 (m, 4H, *H*–Ar), 4.8 (m, 1H, *C*H*), 4.1–4.2 (part of ABX, J_{AB}=5.26 Hz, J_{Bx}=9.13 Hz, 2H, CH_2Cl). ^{13}C NMR (DMSO-d_6, δ ppm): 167.7, 151.9, 131.1, 115, 110.5, 104.8, 81.4, 43.3, 32.6. IR (KBr): 1750 (C=O), 1360 and 1389 (SO_2) cm^{-1}. MS ESI^+ 30 eV m/z: 331.2 $[M+H]^+$. HRMS m/z (MH^+) 331.0525 (calcd for $C_{13}H_{15}ClN_2O_4S$: 331.0519).

*4.3.3. Phenylpeperazin, 5-(chloromethyl), oxazolidin-2-one-3-sulfonamide (**2c**).* Yield: 91%, white solid. mp: 126–127 °C, R_f=0.72 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (DMSO-d_6, δ ppm): 3.1 (t, 4H, N–CH_2-ph), 3.2 (t, 4H, N–CH_2–CH_2), 3.9 (m, 2H, CH_2-cyc), 7.3 (m, 5H, *H*–Ar), 4.9 (m, 1H, *C*H*), 3.6–3.8 (part of ABX, J_{AB}=3.78 Hz, J_{Bx}=4.16 Hz, 2H, CH_2Cl). ^{13}C NMR (DMSO-d_6, δ ppm): 151.9, 149.9, 129.6, 121.9, 114.3, 81.4, 50.3, 43.7, 43.3, 32.9. IR (KBr, cm^{-1}): 1739 (C=O), 1143 and 1310 (SO_2). MS ESI^+ 30 eV m/z: 360.1 $[M+H]^+$. HRMS m/z (MH^+) 360.0793 (calcd for $C_{14}H_{18}ClN_3O_4S$ 360.0784).

4.4. X-ray structure determination

Suitable crystals were mounted for measurements. Data collection was performed at 293 on a Nonius KappaCCD diffractometer using Mo Kα (λ=0.71073 Å) radiation and processed with the HKL package of programs.[23] The crystal structure was solved with direct methods using *SHELXS-97* and final refinement, based on F^2, was carried out by full matrix least squares with *SHELXL-97* software.[24,25] Refinement was performed anisotropically for all non-hydrogen atoms. In general, in the final stages of least-squares refinement, hydrogen atoms were assigned to idealized positions and were allowed to ride with thermal parameters fixed at 1.2 U eq of the parent atom. The residual electron densities were of no chemical significance.

*4.4.1. X-ray crystal data for **2a**.* $C_{10}H_{10}ClFN_2O_4S$, monoclinic space group $P2_1/c$: a=9.1300(3), b=8.9369(2), c=16.3629(5) Å, β=97.4100(18)°; V=1323.96(7) Å^3, Z=4, D_{calcd}=1.549 g/cm^3; μ=0.469 mm^{-1}; $F(000)$=632.0. A total of 19,795 reflections were integrated in the θ-range of 1.00–26.4° of which 3240 were unique, leaving an overall R-merge of 0.043 and an overall redundancy of 6.1. For solution and refinement, 3036 were considered as unique after merging for Fourier. The final agreement factors were $R1$=0.0435 for 2310 reflections with $F>4\sigma(F)$; $R1$=0.0623 and $wR2$=0.1211 for all the 2310 data; GOF=1.036.

The residual electron density in the final difference Fourier does not show any feature above 0.32 e $Å^{-3}$ and below −0.38 e $Å^{-3}$.

4.4.2. X-ray crystal data for ***2b****.* $C_{13}H_{15}ClN_2O_4S$, monoclinic space group $P2_1/c$: a=14.5010(12), b=9.3963(12), c=10.6178 (12) Å, β=93.340 (7)°; V=1444.3 (3) $Å^3$, Z=4, D_{calcd}=1.521 g/cm^3; μ=0.426 mm^{-1}; $F(000)$=688.0. A total of 14,474 reflections were integrated in the range of $0.41°<\theta<24.13°$ of which 2440 were unique, leaving an overall R-merge of 0.052 and an overall redundancy of 5.9. For solution and refinement, 2275 were considered as unique after merging for Fourier. The final agreement factors were $R1$=0.0448 for 1728 reflections with $F>4\sigma(F)$; $R1$=0.0640 and $wR2$=0.1164 for all the 2275 data; GOF=1.116. The residual electron density in the final difference Fourier does not show any feature above 0.17 e $Å^{-3}$ and below -0.28 e $Å^{-3}$.

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Supplementary data

The crystal structures corresponding to **2a** and **2b** have been deposited at the Cambridge Crystallographica Data Centre and respectively allocated the deposition number CCDC 885193 and 885192. These detailed X-ray crystallographic data can obtained free of charge on application to the Cambridge Crystallographic Data Center, 12 Union Road Cambridge CB2 1EZ, UK. Email: deposit@ccdc.cam.ac.uk.

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