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FULL-LENGTH PAPER

Synthesis and antitumor evaluation of novel sulfonylcycloureas derived from nitrogen mustard

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Abstract A new series of sulfonylcycloureas derivatives have been synthesized and evaluated in vitro for their antitumor activity against four cancer cell lines (A431, Jurkat, U266, and K562). These compounds were prepared by the condensation of several sulfonamides (**2a–m**) with ethyl bis(2-chloroethyl)carbamate (**1a**). The relative cytotoxicity of these new derivatives in comparison to chlorambucil is reported.

Keywords Cancer · Sulfonamides · Nitrogen mustard · Sulfonylcycloureas · Antitumor

Introduction

Cancer is a major public health problem and a leading cause of death worldwide [1]. More than half of all cancer cases and 60 % of deaths from cancer appear in less developed countries [2]. Potent antitumor drugs, such as nitrogen mustards (e.g., chlorambucil, melphalan, and mechlorethamine) [3], have been widely used in cancer chemotherapy for many years. These compounds were identified as DNA-targeted alkylating agents due to formation of cross links within the DNA chain of tumor cells. The development of these compounds bears several challenges and has received much attention in order to overcome drawbacks including high chemical reactivity inducing bone marrow toxicity or reduction of cytotoxicity via DNA repair mechanism. In the last decade, many structural modifications have been envisioned to increase cytotoxicity, stability, and selectivity for targeting the DNA of tumor cells [4–10].

After the discovery of Sulofenur (LY186641(A), Fig. 1) an antineoplastic sulfonylurea [11], an extensive range of novel compounds containing sulfonamides [12–19] and diaryl sulfonylurea [20–25] moieties have attracted considerable attention and been evaluated against various types of cancer. Later, El-Deeb et al. synthesized several novel cyclic arylsulfonylureas ((B), Fig. 1) and evaluated their antitumor activity against different human solid tumors [26]. In addition, other sulfonylurea derivatives with important pharmaceutical activities, such as hypoglycemic ((C), Fig. 1) [27], H_3 receptor antagonists [28] ((D), Fig. 1), and antimalarial [29] ((E), Fig. 1) activity, were recently described.

In the current study, our aim is to explore new selective DNA-directed alkylating agents, less toxic and more stable. We have synthesized a novel series of sulfonylcyclourea derivatives (**4a–m**) containing a nitrogen mustard moiety using commercially available chlorosulfonyl isocyanate and N,N-bis(2-chloroethyl)amine as the starting material. These new derivatives were evaluated for their in vitro antitumor activity against four cancer cell lines (A431, Jurkat, U266, and K562).

Electronic supplementary material The online version of this article (doi:10.1007/s11030-015-9647-6) contains supplementary material, which is available to authorized users.

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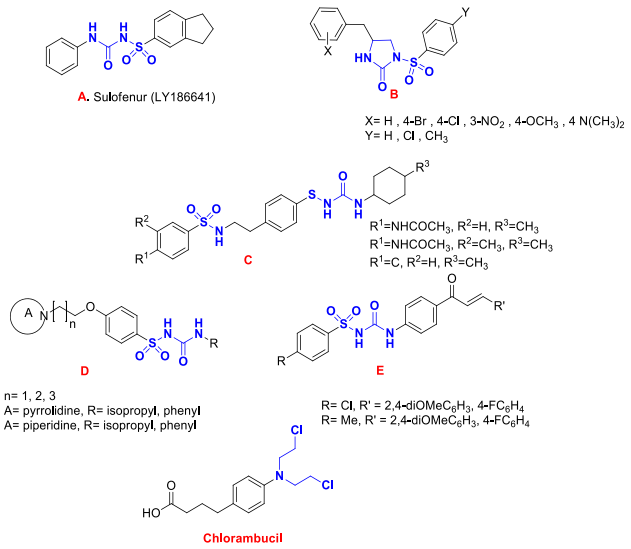
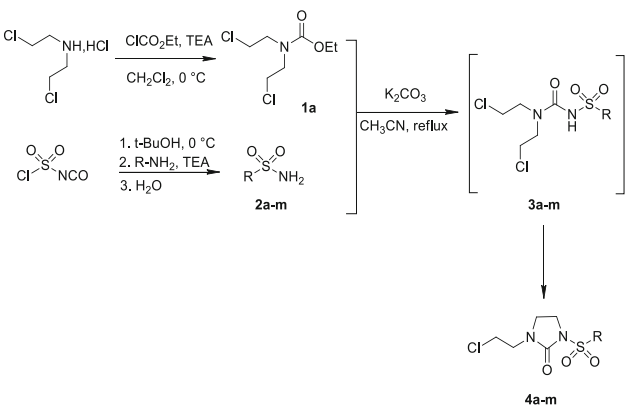


Fig. 1 Examples of bioactive sulfonylurea derivatives

Results and discussion

Chemistry

Our synthetic route for the preparation of sulfonylcyclourea derivatives (**4a–m**) is outlined in Scheme 1. The synthesis of sulfonamide derivatives (**2a–m**) [30–35] was carried out in three steps, by carbamoylation of chlorosulfonyl isocyanate with *tert*-butanol in anhydrous conditions to form the *N*-chlorosulfonyl carbamate, which was then reacted with various amines (sulfamoylation). Removal of the *tert*-butyloxycarbonyl (BOC) protecting group was accomplished under mild conditions in water according to a previously described procedure [36]. Ethyl bis(2-chloroethyl)carbamate (**1a**) was prepared in excellent yield by direct acylation of commercially available *N,N*-bis(2-chloroethyl)amine with ethyl chloroformate in the presence of triethylamine in anhydrous dichloromethane at 0 °C. The condensation of ethyl



Scheme 1 Synthesis of novel sulfonylcyclourea derivatives (**4a–m**)

bis(2-chloroethyl)carbamate (**1a**) sulfonamides (**2a–m**) in acetonitrile using K_2CO_3 as a base under refluxing conditions for 3–5 h generated intermediates (**3a–m**). The strong acidity of the N**H** proton between SO_2 and C=O facilitates the intermolecular cyclization leading to the desired products (**4a–m**) in good yields. The physical data and yields of the final products are listed in Table 1.

Antitumor activity

The cytotoxic effects of the new products were determined in T-lymphoma cells (Jurkat), Chronic Myelogenous Leukemia cells (K562), Myeloma cells (U266), and Epidermoid carcinoma cells (A431) by MTT assay. Chlorambucil was used as reference. IC_{50} values were calculated by logistic regression analysis of dose–response curves plotting between percentage of viability and the concentration of the test compounds. The results are summarized in Table 2. Compounds **4c** and **4d** showed some cytotoxicity. For compound **4c**, the IC_{50} value is 422 μM for Jurkat, 482 μM for K562, 908 μM for U266, and 638 μM for A431. Interestingly, compound **4d** displayed higher cytotoxicity than **4c**. For this compound, the IC_{50} value is 390 μM, 464 μM, 473 μM, and 315 μM, respectively, for Jurkat, K562, U266, and A431. Further investigations are currently in progress to evaluate the impact on cancer cell cycle by these structures and the cell death pathway involved.

Conclusion

In the present work, we have developed the synthesis of a new series of sulfonylcyclourea derivatives containing a nitrogen mustard moiety, starting from commercially available compounds. The antitumor activity of these molecules was evaluated against 4 different cancer cell lines (Jurkat, K562, U266, and A431) using Chlorambucil as reference. Compound **4d** showed higher cytotoxicity than compound **4c**; however, when compared to chlorambucil, its biological activity remained modest.

Experimental procedure

Chemistry

Chemical materials, solvents, and reagents were reagent grade and were used without purification. Melting points were recorded using a Büchi® melting point apparatus Model B-540 and are uncorrected. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25-mm Merck F-254 silica gel glass plates. Column

Table 1 Physical properties, yields, and molecular structures of products (**4a–m**)

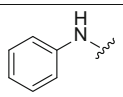
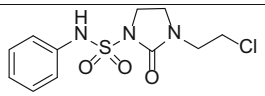
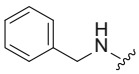
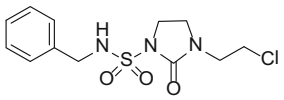
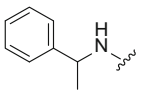
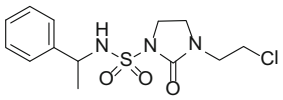
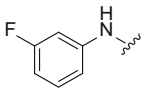
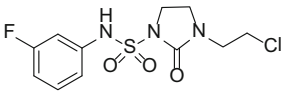
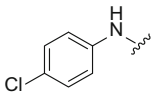
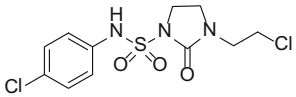
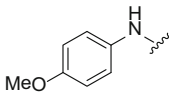
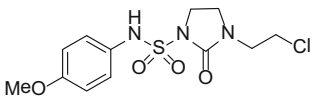
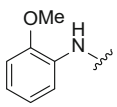
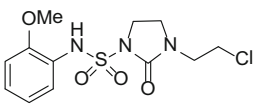
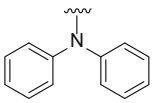
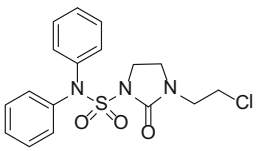
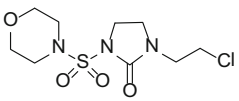
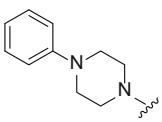
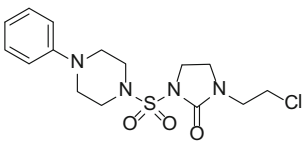
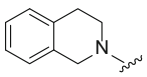
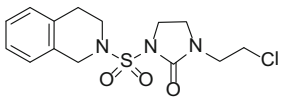
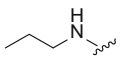
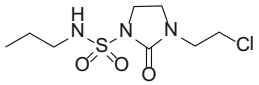
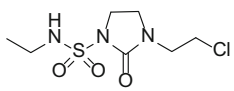
Entry	R	Compound	Time(hours)	Yield (%)	m.p. (°C)
4a			3	86	90–92
4b			3.5	83	96–98
4c			5	90	83–84
4d			3	88	101–103
4e			3.5	81	99–101
4f			5	77	91–92
4g			4.5	73	100–102
4h			3.5	82	111–113
4i			5	89	104–106
4j			4	92	110–111
4k			4	90	101–102
4l			5	87	97–99
4m			5	88	98–100

Table 2 Antitumor profile of compounds (**4c**, **4d**)

	IC_{50} (μM)			
	A431	Jurkat	U266	K562
Chlorambucil	68	113	143	159
4c	638	422	908	482
4d	315	390	473	464

chromatography was performed using silica gel 60 Å (63–200 μm). ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer and chemical shifts were reported in parts per million (ppm) using tetramethylsilane as internal standard with coupling constants (J) reported in Hertz (Hz). NMR signals are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Elemental analyses were performed using a Perkin–Elmer 2400 C, H, N analyzer, and the determined values were within the acceptable limits of the calculated values. IR spectra were recorded on a Perkin Elmer Spectrum Version10.4.1 RX-I spectrometer using KBr disks.

*General procedure for the synthesis of ethyl bis(2-chloroethyl)carbamate (***1a***)*

The *N*-acylation reaction of bis(2-chloroethyl)amine (0.5 g, 2.8 mmol) with ethyl chloroformate (0.45 g, 0.39 mL, 1.5 equiv) was carried out in anhydrous dichloromethane at 0 °C for 1.5 h in the presence of triethylamine (1.5 equiv). The organic phase was washed with HCl (0.1 N), then with water, and then dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the product was obtained as an oil in excellent yield.

*General procedure for the synthesis of sulfonamide derivatives (***2a–m***)*

Sulfonamide derivatives were obtained by slowly adding *tert*-butanol (0.85 g, 1.09 mL, 11.48 mmol) to a stirred solution of chlorosulfonyl isocyanate (CSI) (1.62 g, 1 mL, 11.48 mmol) in anhydrous methylene chloride (10 mL) at 0 °C. After 30 min, the resulting solution of *N*-chlorosulfonyl carbamate (1.75 mL, 1.1 equiv.) was slowly added to a solution of primary amine (1 equiv) in anhydrous methylene chloride (10 mL) at 0 °C in the presence of triethylamine. Stirring was continued for 2 h. The reaction mixture was diluted with methylene chloride (30 mL) and subsequently washed with 0.1 N HCl (20 mL) and then with water (25 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give the desired sulfonamide derivatives (**2a–m**) in excellent yields.

*General procedure for the synthesis of sulfonylcyclourea derivatives (***4a–m***)*

A mixture of ethyl bis(2-chloroethyl)carbamate (**1a**) and 1 equiv of sulfonamides derivatives (**2a–m**) in the presence of K_2CO_3 (1.5 equiv) was heated to reflux in acetonitrile under stirring for 3–5 h. The progress of the reaction was monitored by TLC using dichloromethane and methanol (9.9:0.1). The reaction mixture was evaporated and diluted with methylene chloride (30 mL) and then washed with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography using CH_2Cl_2 as eluent.

Bis(2-chloroethyl)carbamate (**1a**) Yellow oil; 99 % Yield; R_f = 0.6 (CH_2Cl_2/MeOH, 9:1); IR (KBr, cm^{-1}) ν: 1633 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.15 (q, 2H, J = 6.03, CH_2–O), 3.69–3.50 (m, 8H, 2($2CH_2$–Cl)), 1.22 (t, 3H, J = 5.95, CH_3–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.8, 61.8, 51.0, 41.9, 14.5; ESI-MS m/z: 214 $[M+1]^+$; Anal Calcd for $C_{13}H_{18}ClN_3O_3S$: C 39.27, H 6.12, N 6.54; found: C 39.15, H 6.09, N 6.58.

N-chloroethyl,N′-(1-phenyl)sulfamoyl,imidazolidine-2-one (**4a**) White powder; 86 % Yield; R_f = 0.63 (CH_2Cl_2/MeOH, 9:1); m.p. 90–92 °C, IR (KBr, cm^{-1}) ν: 3228 (NH), 1630 (C=O), 1327, 1160 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.05–7.37 (m, 5H, Ar–H), 6.70 (S, 1H, NH), 4.60 (t, J = 8.24 Hz, 2H, Cl–CH_2), 3.90 (t, J = 7.20 Hz, 2H, NH–CH_2), 3.57–3.61 (m, 4H, $(CH_2)_{cyc}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.5, 140.3, 129.3, 123.7, 121.8, 68.9, 49.0, 47.0; ESI-MS m/z: 304 $[M+1]^+$; Anal Calcd for $C_{11}H_{14}ClN_3O_3S$: C 43.49, H 4.65, N 13.83, S 10.56; found: C 43.41, H 4.59, N 13.87, S 10.44.

N-chloroethyl,N′-(1-benzyl)sulfamoyl,imidazolidine-2-one (**4b**) White powder; 83 % Yield; R_f = 0.65 (CH_2Cl_2/MeOH, 9:1); m.p. 96–98 °C; IR (KBr, cm^{-1}) ν: 3237 (NH), 1641 (C=O), 1335, 1171 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11–7.43 (m, 5H, Ar–H), 6.77 (S, 1H, NH), 4.61 (t, J = 8.24 Hz, 2H, Cl–CH_2), 3.92 (t, J = 7.20 Hz, 2H, NH–CH_2), 3.62–3.59 (m, 4H, $(CH_2)_{cyc}$), 4.04 (d, J = 6.1, CH_2–Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 143.3, 128.3, 121.7, 119.8, 68.9, 49.3, 46.9, 43.5; ESI-MS m/z: 318 $[M+1]^+$; Anal Calcd for $C_{12}H_{16}ClN_3O_3S$: C 45.35, H 5.07, N 13.22, S 10.09; found: C 45.29, H 5.03, N 13.16, S 10.11.

N-chloroethyl,N′-(1-methylbenzyl)sulfamoyl,imidazolidine-2-one (**4c**) White powder; 90 % Yield; R_f = 0.61 (CH_2Cl_2/MeOH, 9:1); m.p. 83–84 °C; IR (KBr, cm^{-1}) ν: 3230 (NH), 1639 (C=O), 1311, 1142 (O=S=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.48–7.22 (m, 5H, Ar–H), 4.70 (t, J = 7.39, 1H, CH_2),4.50 (t, J = 7.46, 1H, CH_2), 4.40 (t, J = 7.71, 1H, CH_2), 4.20 (t, J = 8.12, 1H, CH_2), 3.70 (q,

J = 7.38 Hz, 1H, *CH–Ph), 3.60–3.20 (m, 4H, $(CH_2)_{cyc}$), 1.4 (d, J = 6.9 Hz, 3H, CH_3–*CH); ^{13}C NMR (60 MHz, CDCl3) δ: 164.1, 141.9, 128.2, 127.1, 125.6, 66.1, 53.4, 47.1, 46.9, 40.3; ESI-MS m/z: 332 $[M+1]^+$; Anal Calcd for $C_{13}H_{18}ClN_3O_3S$: C 47.06, H 5.47, N 12.66, S 9.66; found: C 47.02, H 5.44, N 12.61, S 9.60.

N-chloroethyl,N′-(3-fluorophenyl)sulfamoyl,imidazolidine-2-one (**4d**) White powder; 88 % Yield; R_f = 0.66 (CH_2Cl_2/MeOH, 9:1); m.p. 101–103 °C; IR (KBr, cm^{-1}) ν: 3219 (NH), 1620 (C=O), 1322, 1159 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20–7.03 (m, 4H, Ar–H), 4.55 (t, J = 6.23 Hz, 2H, Cl–CH_2), 3.85 (t, J = 6.50 Hz, 2H, N-CH_2), 3.60–3.51 (m, 4H, $(CH_2)_{cyc}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 140.1, 136.2, 123.7, 114.5, 66.1, 47.0, 46.9; ESI-MS m/z: 322 $[M+1]^+$; Anal Calcd for $C_{11}H_{13}ClFN_3O_3S$: C 41.06, H 4.07, N 13.06, S 9.97; found: C 41.00, H 4.12, N 13.03, S 9.92.

N-chloroethyl,N′-(4-chlorophenyl)sulfamoyl,imidazolidine-2-one (**4e**) White powder; 81 % Yield; R_f = 0.63 (CH_2Cl_2/MeOH, 9:1); m.p. 99–101 °C; IR (KBr, cm^{-1}) ν: 3226 (NH), 1619 (C=O), 1315, 1149 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22–7.12 (m, 4H, Ar–H), 4.62 (t, J = 6.23 Hz, 2H, Cl–CH_2), 3.81 (t, J = 6.50 Hz, 2H, N–CH_2), 3.66–3.58 (m, 4H, $(CH_2)_{cyc}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5, 139.1, 131.2, 124.7, 113.5, 68.1, 49.0, 45.9; ESI-MS m/z: 338 $[M+1]^+$; Anal Calcd for $C_{11}H_{13}C_{l2}N_3O_3S$: C 39.06, H 3.87, N 12.42, S 9.48; found: C 39.10, H 3.82, N 12.39, S 9.52.

N-chloroethyl,N′-(4-methoxyphenyl)sulfamoyl,imidazolidine-2-one (**4f**) White powder; 77 % Yield; R_f = 0.66 (CH_2Cl_2/MeOH, 9:1); m.p. 91–92 °C; IR (KBr, cm^{-1}) ν: 3239 (NH), 1627 (C=O), 1330, 1169 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (d, J = 8.8 Hz, 2H, Ar–H), 6.85 (d, J = 8.8 Hz, 2H, Ar–H), 4.60 (t, J = 6.23 Hz, 2H, Cl–CH_2), 3.85 (t, J = 6.50 Hz, 2H, N–CH_2), 3.75(s, 1H, CH_3–O), 3.60–3.55 (m, 4H, $(CH_2)_{cyc}$); ^{13}C NMR (100 MHz, CDCl3) δ: 161.5, 140.2, 135.1, 123.7, 114.5, 67.1, 47.2, 47.05, 41.5; ESI-MS m/z: 334 $[M+1]^+$; Anal Calcd for $C_{12}H_{16}ClN_3O_4S$: C 43.18, H 4.83, N 12.59, S 9.61; found: C 43.22, H 4.79, N 12.52, S 9.55.

N-chloroethyl,N′-(2-methoxyphenyl)sulfamoyl,imidazolidine-2-one (**4g**) White powder; 73 % Yield; R_f = 0.66 (CH_2Cl_2/MeOH, 9:1); m.p. 100–102 °C; IR (KBr, cm^{-1}) ν: 3230 (NH), 1625 (C=O), 1325, 1163 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, J = 8.1 Hz, 2H, Ar–H), 6.99 (d, J = 8.1 Hz, 2H, Ar–H), 4.53 (t, J = 7.10 Hz, 2H, Cl–CH_2), 3.99 (t, J = 6.20 Hz, 2H, N–CH_2), 3.81(s, 1H, CH_3–O), 3.65–3.59 (m, 4H, $(CH_2)_{cyc}$); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 165.0, 143.4, 133.5, 121.8, 112.3, 65.7, 49.3, 46.9, 39.9; ESI-MS m/z: 334 $[M+1]^+$; Anal Calcd for $C_{12}H_{16}ClN_3O_4S$: C 43.18, H 4.83, N 12.59, O 19.17, S 9.61; found: C 43.23, H 4.80, N 12.53, S 9.58.

N-chloroethyl,N′-(1-diphenyl)sulfamoyl,imidazolidine-2-one (**4h**) White powder; 82 % Yield; R_f = 0.71 (CH_2Cl_2/MeOH, 9:1); m.p. 111–113 °C; IR (KBr, cm^{-1}) ν: 3235 (NH), 1635 (C=O), 1340, 1180 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17–6.65 (m, 10H, Ar–H), 4.57 (t, J = 8.01 Hz, 2H, Cl–CH_2), 3.88 (t, J = 6.66 Hz, 2H, NH–CH_2), 3.49–3.57 (m, 4H, $(CH_2)_{cyc}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 139.5, 128.4, 124.1, 122.3, 69.1, 49.5, 47.1; ESI-MS m/z: 380 $[M+1]^+$; Anal Calcd for $C_{17}H_{18}ClN_3O_3S$: C 53.75, H 4.78, N 11.06, S 8.44; found: C 53.70, H 4.81, N 11.00, S 8.49.

N-chloroethyl,N′-(morpholin-4-yl)sulfamoyl,imidazolidine-2-one (**4i**) White powder; 89 % Yield; R_f = 0.71 (CH_2Cl_2/MeOH, 9:1); m.p. 104–106 °C; IR (KBr, cm^{-1}) ν: 1611 (C=O), 1338, 1178 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.64 (t, J = 8.46 Hz, 2H, Cl–CH_2), 3.90 (t, J = 7.17 Hz, 2H, N–CH_2), 3.77 (t, J = 4.50Hz, 4H, $2CH_2$–O), 3.71–3.67 (m, 4H, $(CH_2)_{cyc}$), 3.16 (t, J = 4.71 Hz, 4H, $2CH_2$–N); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 66.9, 65.0, 49.0, 47.0, 44.2; ESI-MS m/z: 298 $[M+1]^+$; Anal Calcd for $C_9H_{16}ClN_3O_4S$: C 36.30, H 5.42, N 14.11, S 10.77; found: C 36.26, H 5.48, N 14.09, S 10.63.

N-chloroethyl,N′-(4-phenylpiperazin-1-yl)sulfamoyl,imidazolidine-2-one (**4j**) Yellow powder; 92 % Yield; R_f = 0.71 (CH_2Cl_2/MeOH, 9:1); m.p. 110–111 °C; IR (KBr, cm^{-1}) ν: 1629 (C=O), 1320, 1166 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.85–7.34 (m, 5H, Ar–H), 4.68 (t, J = 8.2 Hz, 2H, Cl–CH_2), 3.87 (t, J = 8.16Hz, 2H, N–CH_2), 3.70–3.65 (m, 4H, $(CH2)_{cyc}$), 3.35–3.25 (2m, 8H, 2(N–CH_2– CH_2–N)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 137.2, 129.3, 117.2, 116.7, 66.9, 53.1, 49.0, 47.0, 44.8; ESI-MS m/z: 373 $[M+1]^+$; Anal Calcd for $C_{15}H_{21}ClN_4O_3S$: C 48.32, H 5.68, N 15.03, S 8.60; found: C 48.27, H 5.71, N 15.09, S 8.54.

N-chloroethyl,N′-(1,2,3,4-tetrahydroisoquinolin2-yl)sulfamoyl,imidazolidine-2-one (**4k**) White powder;90 % Yield; R_f = 0.71 (CH_2Cl_2/MeOH, 9:1); m.p. 101–102 °C; IR (KBr, cm^{-1}) ν: 1632 (C=O), 1302, 1150 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18–7.05 (m, 4H, Ar–H), 4.60 (t, J = 8.28 Hz, 2H, Cl–CH_2), 4.40 (s, 1H, Ph–CH_2–N), 3.80 (t, J = 7.14 Hz, 2H, N–CH_2), 3.60–3.45 (m, 6H, $(CH_2)_{cyc}$ + CH_2–N), 2.97 (t, J = 6.03 Hz, 2H, Ph–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 134.2, 127.5, 126.5, 67.9, 49.6, 48.0, 46.5, 41.7, 25.3; ESI-MS m/z: 344 $[M+1]^+$; Anal Calcd for $C_{14}H_{18}ClN_3O_3S$: C 48.91, H 5.28, N 12.22, S 9.33; found: C 49.00, H 5.32, N 12.16, S 9.25.

N-chloroethyl,N′-(1-propyl)sulfamoyl,imidazolidine-2-one (**4l**) Yellow powder; 87 % Yield; R_f = 0.71 (CH_2Cl_2/MeOH, 9:1); m.p. 97–99 °C; IR (KBr, cm^{-1}) ν: 3249 (NH), 1615

(C=O), 1307, 1140 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.65 (t, J = 7.35 Hz, 2H, Cl–CH_2), 4.22 (t, J = 6.03 Hz, 1H, NH), 3.71–3.60 (m, 4H, $(CH_2)_{cyc}$), 3.08 (q, J = 6.96 Hz, 2H, CH_2–NH), 1.57 (m, 2H, CH_2), 0.94 (t, J = 7.35 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9, 67.1, 47.0, 46.8, 45.0, 41.3, 22.0, 10.0; ESI-MS m/z: 270 $[M+1]^+$; Anal Calcd for $C_8H_{16}ClN_3O_3S$: C 35.62, H 5.98, N 15.58, S 11.89; found: C 35.57, H 6.01, N 15.50, S 11.93.

N-chloroethyl,N′-(1-ethyl)sulfamoyl,imidazolidine-2-one (**4m**) Yellow powder; 88 % Yield; R_f = 0.66 (CH_2Cl_2/MeOH, 9:1); m.p. 98–100 °C; IR (KBr, cm^{-1}) ν: 3240 (NH), 1622 (C=O), 1310, 1146 (O=S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.70 (t, J = 7.20 Hz, 2H, Cl–CH_2), 4.15 (t, J = 6.22 Hz, 1H, NH), 3.85–3.71 (m, 4H, $(CH_2)_{cyc}$), 2.88 (m, J = 7.36 Hz, 2H, NH–CH_2), 1.01 (t, J = 7.35 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.1, 68.3, 47.5, 46.4, 44.9, 40.8, 12.5; ESI-MS m/z: 256 $[M+1]^+$; Anal Calcd for $C_7H_{14}ClN_3O_3S$: C 32.88, H 5.52, N 16.43, S 12.54; found: C 32.93, H 5.46, N 16.38, S 12.49.

Antitumor activity

Cell lines and culture conditions

Jurkat (acute T cell Leukemia, ATCC TIB-152), K562 (chronic myelogenous leukemia, ATCC CLL-243) and U266 (multiple myeloma, ATCC TIB-196) were routinely cultured in RPMI-1640 supplemented with 10 % Fetal Bovine Serum (FBS, IDBIO, Limoges, France), 100 U/mL penicillin, 100 µg/mL streptomycin, 2 mM L-glutamine, 1 mM sodium pyruvate, 1 % vitamins, and 1 % non-essentials amino-acids. A431 (vulvar epidermoid carcinoma, ATCC CRL-1555) was cultured in DMEM supplemented with 10 % FBS, 100 U/mL penicillin, 100 µg/mL streptomycin, 2 mM L-glutamine, and 1 mM sodium pyruvate. The cells were cultured at 37 °C in a fully humidified 5 % CO_2 incubator. All reagents for cell culture were purchased from Gibco-BRL Life Technologies, Cergy-Pontoise, France.

Cell viability assay

Cytotoxicity activity was evaluated using the MTT assay (3-(4,5-dimethylthiazol-2-yl)-phenyl-tetrazolium bromide). Briefly, tumor cell lines were added into 96-well tissue culture plates in culture medium. Compounds were prepared at a concentration of 4000 µM in 10 % DMSO in complete culture medium (v/v). The solutions were used at concentration range from 2000 µM to 3.9 µM. Cells were incubated with or without drugs for 72 h. Then, the MTT solution was added at a final concentration of 0.5 mg/mL per well and cells were incubated for 3 h at 37 °C. The purple formazan crystals were dissolved by adding 200 µL DMSO. The absorbance was read using a microplate spectrophotometer (Triad, Dynex Technologies) at 595 nm. All measurements were carried in triplicates. The results were compared with those of a control reference plate fixed on the treatment day, and the growth inhibition percentage was calculated for each drug contact period. The concentration required for 50 % inhibition of cell viability (IC_{50}) was calculated using the software Origin Pro (Origin Lab, Northampton, USA). Assays were performed in hexaplicate on three independent experiments.

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