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Mendeleev Commun., 2022, **32**, 178–179

Mendeleev Communications

Synthesis of 1,4,2,6-dithiadiazinane 1,1-dioxide and study of its cytotoxic activity

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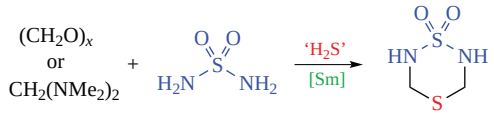
DOI: 10.1016/j.mencom.2022.03.008

Cyclothiomethylation of sulfamide using paraformaldehyde or bis(dimethylamino)methane, hydrogen sulfide or its sodium salts catalyzed by rare-earth salts affords 1,4,2,6-dithiadiazinane 1,1-dioxide. The heterocycle was found to exhibit a pronounced cytotoxic effect against suspension tumor cell lines (Jurkat, HL60, K562, and U937).



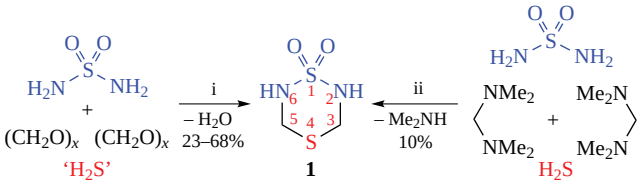
cytotoxic activity on tumor cell lines
Jurkat, K562, U937, HL60

Keywords: cyclothiomethylation, sulfamide, catalysis, hydrogen sulfide, sodium sulfide, samarium compounds, ytterbium compounds, 1,4,2,6-dithiadiazinane 1,1-dioxide, cytotoxic activity.

Previously,[1–3] we have reported on new promising cytotoxic N-, S- and O-heterocyclic compounds obtained by cyclothiomethylation and cycloaminomethylation reactions of carboxylic and sulfonic acid amides.[4–7] In this communication, we have studied the reaction between sulfamide, paraformaldehyde [or its chemical equivalent bis(dimethylamino)methane] and hydrogen sulfide (or NaHS, $Na_2S·9H_2O$) in the presence of catalysts based on salts and complexes of s- and d-elements.

The high interest in sulfamide derivatives is due to their wide applicability as antimicrobial, antioxidant agents,[8] carbonic anhydrase inhibitors,[9–11] drugs for the treatment of stomach ulcers,[12] 5HT-1A receptor antagonists,[13] and drugs for the treatment of asthma and chronic obstructive pulmonary disease.[14]

On the example of cyclocondensation of sulfamide with paraformaldehyde and hydrogen sulfide (Scheme 1), the effect of catalyst nature based on alkali (Na, K, Rb, Cs)[5] and transition (Ni, Cu, Fe, Sm, Yb) metals on the total yield of 1,4,2,6-dithiadiazinane 1,1-dioxide **1** was studied under the following conditions: sulfamide/$(CH_2O)_x$/H_2S/catalyst = 1 : 2.5 : 1 : 0.1, EtOH as the solvent, 70 °C, 4 h. Among the tested catalysts, salts $SmCl_3·6H_2O$, $Sm(NO_3)_3·6H_2O$, and YbF_3 were found to be the most efficient, which allowed us to obtain the target product **1** in 65, 59, and 68% yields, respectively. Without a catalyst, the cyclothiomethylation of sulfamide did not occur.



Scheme 1 *Reagents and conditions*: i, $(CH_2O)_x$, H_2S, NaHS or $Na_2S·9H_2O$, catalyst $SmCl_3·6H_2O$ or $Sm(NO_3)_3·6H_2O$ or YbF_3, EtOH, 70 °C, 4 h; ii, $CH_2(NMe_2)_2$, H_2S, $SmCl_3·6H_2O$ (catalyst), EtOH, 70 °C, 4 h.

† Deceased.

The replacement of gaseous hydrogen sulfide with more convenient for handling NaHS or $Na_2S·9H_2O$ [sulfamide/$(CH_2O)_x$/R_2S/catalyst = 1 : 2.5 : 1 : 0.1] provided product **1** in 23 and 65% yields, respectively. The replacement of paraformaldehyde by chemically equivalent bis(dimethylamino)-methane (10 mol% $SmCl_3·6H_2O$) brought about heterocycle **1** in less than 10% yield.

As for the most probable mechanism of cyclothiomethylation of sulfamide with formaldehyde and $Na_2S·9H_2O$, intermediate species $HOCH_2SNa$ may first be formed *in situ*, which then under the action of rare-earth salts ('hard' Lewis acids) leads to the formation of the desired 1,4,2,6-dithiadiazinane 1,1-dioxide **1** (see Online Supplementary Materials, Scheme S1).[15] The total chemical result of the process is obviously the formation of formaldehyde thio amino acetal. The identification of heterocycle **1** and intermediate $HOCH_2SNa$ was carried out using 1D (^1H, ^{13}C) and 2D (COSY, HSQC, HMBC) NMR experiments and mass spectrometry.

The resulted 1,4,2,6-dithiadiazinane 1,1-dioxide **1** and its precursor sulfamide have been investigated for their cytotoxic activity against the Jurkat, K562, U937 and HL60 tumor cell lines (Table 1). We have found that compound **1** exhibited cytotoxic activity which varied within 0.78–1.74 μM. In turn, the starting sulfamide is one order of magnitude less cytotoxic.

The study of the induction of apoptosis caused by the treatment of human T-lymphoblastic leukemia cells with 1,4,2,6-dithiadiazinane 1,1-dioxide **1** using flow cytometry has

Table 1 *In vitro* cytotoxicity (IC_{50}, μM) of 1,4,2,6-dithiadiazinane 1,1-dioxide **1** against different cell lines (Jurkat, K562, U937, and HL60) in comparison with sulfamide.

Compound	IC_{50}/μM			
	Cell lines			
	Jurkat	K562	U937	HL60
1	1.34 ± 0.12	0.98 ± 0.09	0.94 ± 0.08	0.78 ± 0.07
Sulfamide	24.58 ± 1.96	16.87 ± 1.51	14.73 ± 1.29	10.37 ± 1.18

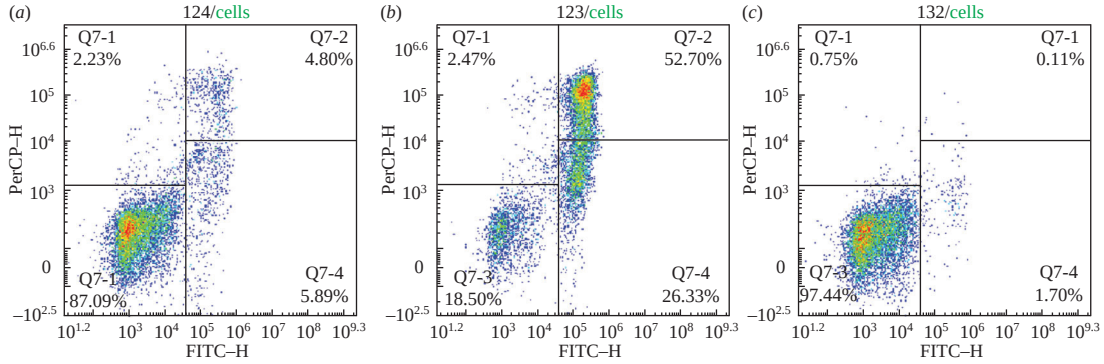


Figure 1 Plots of cytofluorometric analysis of the apoptosis-inducing activity of 1,4,2,6-dithiadiazinane 1,1-dioxide **1** on the Jurkat tumor cells: (*a*) 0.5 μM, (*b*) 1.5 μM, (*c*) control experiment. The incubation time of compound **1** with tumor cells was 24 h.

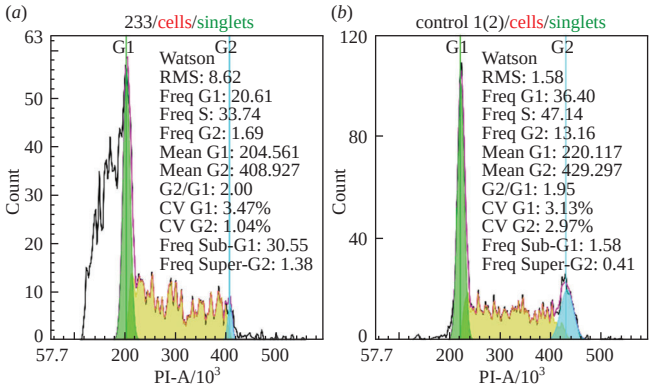


Figure 2 Cell cycle phases of the Jurkat cells after treatment with compound **1** at a concentration equal to IC_{50} during the 24 h incubation: (*a*) 1.5 μM concentration, (*b*) control experiment.

shown that the death of tumor cells occurs in accordance with the apoptotic pathway, *i.e.*, through the sequential passing of cells through the phases of early and late apoptosis (Figure 1).

The histograms of cell cycle phases in the Jurkat cells on exposure to compound **1** at a concentration equal to the IC_{50} show a pronounced rise in the hypodiploid cell population (sub-G1 phase) as compared to the control, which is an additional confirmation of the apoptotic pathway of cell death; the increase of the S-phase and the degradation of the G2 phase indicate a disruption of protein and DNA synthesis, which in turn significantly reduces the division of tumor cells (Figure 2).

In conclusion, the cyclothiomethylation of sulfamide with paraformaldehyde or bis(dimethylamino)methane, hydrogen sulfide or sodium (hydro)sulfide in the presence of catalysts based on f-elements is an efficient pathway to obtain 1,4,2,6-dithiadiazinane 1,1-dioxide. This compound reveals pronounced cytotoxic properties against suspension tumor cell lines (Jurkat, HL60, K562, and U937) in comparison with the cytotoxic effect of the starting sulfamide.

This study was carried out under the research plans of the IPC RAS on the subjects, State Registration nos. FMRS-2022-0079 and FMRS-2022-0074 (2022–2024), as well as with financial support from of the Russian Ministry of Education and Science (Federal target program no. 2021-0291-FP5-0001). The study of the structure of compounds **1** and **2** (see Online Supplementary Materials) were performed with the use of equipment from Collective Usage Centre ‘Agidel’ of Ufa Research Center of Russian Academy of Sciences at the Institute of Petrochemistry and Catalysis.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.008.

References

1 E. B. Rakhimova, V. Yu. Kirsanov, E. S. Mescheryakova, L. M. Khalilov, A. G. Ibragimov, L. U. Dzhemileva, V. A. D’yakonov and U. M. Dzhemilev, *ACS Med. Chem. Lett.*, 2019, **10**, 378.
2 N. Makhmudiyarova, I. Ishmukhametova, L. Dzhemileva, V. D’yakonov, A. Ibragimov and U. Dzhemilev, *Molecules*, 2020, **25**, 1874.
3 A. V. Evdokimova, A. A. Alexeev, E. V. Nurieva, E. R. Milaeva, S. A. Kuznetsov and O. N. Zefirova, *Mendeleev Commun.*, 2021, **31**, 288.
4 R. R. Khairullina, T. B. Tyumkina, G. A. Akhmetshina, M. F. Abdullin and A. G. Ibragimov, *Russ. Chem. Bull.*, 2021, **70**, 152.
5 R. R. Khairullina, A. R. Geniyatova, T. V. Tyumkina, D. S. Karamzina, A. G. Ibragimov and U. M. Dzhemilev, *Tetrahedron*, 2017, **73**, 7079.
6 V. R. Akhmetova, G. R. Nadyrgulova, Z. T. Niatshina, R. R. Khairullina, Z. A. Starikova, A. O. Borisova, M. Yu. Antipin, R. V. Kunakova and U. M. Dzhemilev, *Heterocycles*, 2009, **78**, 45.
7 G. A. Gazieva, A. N. Kravchenko, N. S. Trunova and N. N. Makhova, *Russ. Chem. Bull.*, 2007, **56**, 2272 (*Izv. Akad. Nauk, Ser. Khim.*, 2007, 2195).
8 J. R. Badgujar, D. H. More and J. S. Meshram, *Indian J. Microbiol.*, 2018, **58**, 93.
9 D. Vullo, A. Innocenti, I. Nishimori, J. Pastorek, A. Scozzafava, S. Pastoreková and C. T. Supuran, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 963.
10 D. Vullo, J. Voipio, A. Innocenti, C. Rivera, H. Ranki, A. Scozzafava, K. Kailab and C. T. Supuran, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 971.
11 E. Berrino, S. Bua, M. Mori, M. Botta, V. S. Murthy, V. Vijayakumar, Y. Tamboli, G. Bartolucci, A. Mugelli, E. Cerbai, C. T. Supuran and F. Carta, *Molecules*, 2017, **22**, 1049.
12 B. C. Ross, J. D. Michael and C. J. Cousins, *Patent EP 0104611 A3*, 1985.
13 A. Tait, A. Luppi, S. Franchini, E. Preziosi, C. Parenti, M. Buccioni, G. Marucci, A. Leonardi, E. Poggesi and L. Brasili, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1185.
14 A. Tait, A. Luppi, A. Hatzelmann, P. Fossa and L. Mosti, *Bioorg. Med. Chem.*, 2005, **13**, 1393.
15 R. G. Pearson, *J. Chem. Educ.*, 1968, **45**, 643.

Received: 8th July 2021; Com. 21/6608