

# Sulfur-containing monoterpenoids as potential antithrombotic drugs: Research in the molecular mechanism of coagulation activity using pinanyl sulfoxide as an example

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## Abstract

© 2018 Nikitina, Kiselev, Startseva, Bodrov, Azizova, Shipina, Fedyunina, Boichuk, Lodochnikova, Klochkov, Galiullina and Khaliullina. In this article we present the synthesis of enantiomerically pure sulfoxide and study the influence of this compound on hemostasis. Detailed NMR studies and molecular dynamics simulations using sodium dodecyl sulfate (SDS) membrane models indicated that the bicyclic fragment of sulfoxide was embedded into the SDS micelle whereas the -SO(CH<sub>2</sub>)<sub>2</sub>OH fragment remained on the surface of the micelle and was in contact with the solvent. We also found that the pro-coagulative activity of sulfoxide was due to its ability to inhibit platelet activation and inhibited the catalytic activity of phospholipid surface which was involved in formation of coagulation clotting factor complexes.

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## Keywords

Coagulation activity, Molecular mechanism of coagulation activity, Platelets aggregation, Sulfoxides, Terpenes

## References

- [1] Abraham, M. J., van der Spoel, D., Lindahl, E., and Hess, B. (2014). GROMACS User Manual version 5.0.1. Available online at: [www.gromacs.org](http://www.gromacs.org)
- [2] Alfonso, V. A., Bredikhin, A. A., Bredikhina, Z. A., Eliseenkova, R. M., Kataeva, O. N., Litvinov, I. A., et al. (2008). First examples of the cocrystallization of diastereomers of chiral phosphorus compounds. *Struct. Chem.* 19, 873-878. doi: 10.1007/s11224-008-9353-4
- [3] Anderson, K. M., Afarinkia, K., Yu, H.-W., Goeta, A. E., and Steed, J. W. (2006). When Z' = 2 is better than Z' = 1 supramolecular centrosymmetric hydrogen-bonded dimers in chiral systems. *Cryst. Growth Des.* 6, 2109-2113. doi: 10.1021/cg0603265
- [4] Annunziata, R., Cinquini, M., Cozzi, F., and Farina, S. (1987). Synthesis of configurationally stable allylic sulphoxides via diastereoselective oxidation. *Tetrahedron Lett.* 43, 1013-1018. doi: 10.1016/S0040-4020(01)90039-0
- [5] Arai, Y., Matsui, M., and Koizumi, T. J. (1991). Powerful dienophiles for asymmetric Diels-Alder reactions:  $\alpha$ -(2-exo-hydroxy-10-bornylsulfinyl)maleimides. *Org. Chem.* 56, 1983-1985. doi: 10.1021/jo00006a005
- [6] Aversa, M. C., Barattucci, A., and Bonaccorsi, P. (2002). Synthesis and Diels-Alder reactivity of sulfinyl homo- and hetero-dienes obtained via enantio-pure sulfenic acids. *ARKIVOC* 17, 79-98. doi: 10.3998/ark.5550190.0003.b09
- [7] Balick, M., Duke, J., Kaptchuk, T., Mc Coleb, R., Pavek, R., Pellin, C., et al. (1994). *Herbal Medicine*. Washington, DC: National Institutes of Health
- [8] Berendsen, H. J. C., Postma, J. P. M., Gunsteren, W. F., and Hermans, J. (1981). "Interaction models for water in relation to protein hydration," in *Intermolecular Forces*, ed B. Pullman (Dordrecht: Reidel), 331-342
- [9] Binns, M. R., Goodridge, R. J., and Haynes, R. K. (1985). Preparation of stable, camphor-derived, optically active allylic sulfoxides. *Tetrahedron Lett.* 26, 6381-6384. doi: 10.1016/S0040-4039(01)84604-9

- [10] Born, G. (1962). Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 194, 927-929. doi: 10.1038/194927b0
- [11] Bruce, C. D., Berkowitz, M. L., Perera, L., and Forbes, M. D. E. (2002). Molecular dynamics simulation of sodium dodecyl sulfate micelle in water: micellar structural characteristics and counterion distribution. *J. Phys. Chem.* 106, 3788-3793. doi: 10.1021/jp013616z
- [12] Caillon, L., Lequin, O., and Khemtémourian, L. (2013). Evaluation of membrane models and their composition for islet amyloid polypeptide-membrane aggregation. *Biochim. Biophys. Acta* 1828, 2091-2098. doi: 10.1016/j.bbamem.2013.05.014
- [13] Carreno, M. C., Hernandez-Torres, G., Ribagorda, M., and Urbano, A. (2009). Enantiopure sulfoxides: recent applications in asymmetric synthesis. *Chem. Commun.* 41, 6129-6144. doi: 10.1039/b908043k
- [14] Cutsforth, G. A., Whitaker, R. N., Hermans, J., and Lentz, B. R. (1989). A new model to describe extrinsic protein binding to phospholipid membranes of varying composition: application to human coagulation proteins. *Biochemistry* 28, 7453-7461. doi: 10.1021/bi00444a045
- [15] Demakova, M. Y., Sudarikov, D. V., Rubtsova, S. A., Popov, A. V., Frolova, L. L., Slepukhin, P. A., et al. (2012a). Synthesis and asymmetric oxidation of caranylsulfanylimidazoles. *Helv. Chim. Acta* 5, 940-950. doi: 10.1002/hlca.201100484
- [16] Demakova, M. Y., Sudarikov, D. V., Rubtsova, S. A., Slepukhin, P. A., and Kutchin, A. V. (2012b). Reaction of 1-methyl-2-terpenylsulfanylimidazoles with chlorine dioxide. *Russ. J. Org. Chem.* 1, 113-118. doi: 10.1134/S1070428012010186
- [17] Eschler, B., Haynes, R. K., and Kremmydas, S. J. (1988). A simple route to (R)-(+)-4-t-butoxycyclopent-2-enone. *Chem. Soc. Chem. Commun.* 137-138. doi: 10.1039/c39880000137
- [18] Finegold, J. A., Asaria, P., and Francis, D. P. (2013). Mortality from ischemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. *Int. J. Cardiol.* 168, 934-945. doi: 10.1016/j.ijcard.2012.10.046
- [19] Fucke, K., Qureshi, N., Yufit, D. S., Howard, J. A. K., and Steed, J. W. (2010). Hydrogen bonding is not everything: extensive polymorphism in a system with conserved hydrogen bonded synthons. *Cryst. Growth Des.* 10, 880-886. doi: 10.1021/cg901224f
- [20] Galiullina, L. F., Blokhin, D. S., Aganov, A. V., and Klochkov, V. V. (2012). Investigation of cholesterol+model of biological membrane complex by NMR spectroscopy. *MRSej.* 14:12204. Available online at: <https://www.scopus.com/inward/record.uri?eid=2-s2.0-84871625991&partnerID=40&md5=54fa000ff2c16e23dbaa04259fa29fff>
- [21] Galiullina, L. F., Rakhmatullin, I. Z., Klochkova, E. A., Aganov, A. V., and Klochkov, V. V. (2015). Structure of pravastatin and its complex with sodium dodecyl sulfate micelles studied by NMR spectroscopy. *Magn. Reson. Chem.* 53, 110-114. doi: 10.1002/mrc.4146
- [22] Gasparyan, A., Yu Watson, T., and Lip, G. Y. H. (2008). The role of aspirin in cardiovascular prevention: implications of aspirin resistance. *J. Am. Coll. Cardiol.* 51, 1829-1843. doi: 10.1016/j.jacc.2007.11.080
- [23] Gavrilov, V. V., Startseva, V. A., Nikitina, L. E., Lodochnikova, O. A., Gnezdilov, O. I., Lisovskaya, S. A., et al. (2010). Synthesis and antifungal activity of sulfides, sulfoxides, and sulfones based on (1S)-(-)- $\beta$ -pinene. *Pharm. Chem. J.* 44, 126-129. doi: 10.1007/s11094-010-0413-x
- [24] Grant, D. J. W. (1999). "Theory and origin of polymorphism," in *Polymorphism in Pharmaceutical Solids*, ed H. G. Brittain (New York, NY: Marcel Dekker Inc.), 1-34
- [25] Henry, G. D., and Sykes, B. D. (1994). Methods to study membrane protein structure in solution. *Meth. Enzymol.* 239, 515-535. doi: 10.1016/S0076-6879(94)39020-7
- [26] Humphrey, W., Dalke, A., and Klaus, S. (1996). VMD-Visual Molecular Dynamics. *J. Mol. Graph.* 14, 33-38. doi: 10.1016/0263-7855(96)00018-5
- [27] Ishmuratov, G. Y., Yakovleva, M. P., Tukhvatshin, V. S., Talipov, R. F., Nikitina, L. E., Artemova, N. P., et al. (2014). Sulfurcontaining derivatives of mono-and bicyclic natural monoterpenoids. *Chem. Nat. Compd.* 50, 22-47. doi: 10.1007/s10600-014-0862-7
- [28] Iversen, L. V., Ostergaard, O., Nielsen, C. T., Jacobsen, S., and Heegaard, N. H. (2013). A heparin-based method for flow cytometric analysis of microparticles directly from platelet-poor plasma in calcium containing buffer. *J. Immunol. Methods* 388, 49-59. doi: 10.1016/j.jim.2012.12.001
- [29] Kiselev, S. V., Nikitina, L. E., Startseva, V. A., Artemova, N. P., Bodrov, A. V., Boichuk, S. V., et al. (2017). Hemocoagulation activity of sulfur-containing pinane-type terpenoids. *Pharm. Chem. J.* 51, 78-82. doi: 10.1007/s11094-017-1611-6
- [30] Komatsu, N., Hashizume, M., Sugita, T., and Uemura, S. (1993). Catalytic Asymmetric oxidation of sulfides with tert-Butyl hydroperoxide using binaphthol as a chiral auxiliary. *J. Org. Chem.* 58, 4529-4533. doi: 10.1021/jo00069a009
- [31] Krudysz-Amblo, J., Mann, K. G., and Butenas, S. (2015). "Tissue factor structure and coagulation," in *Thrombosis and Inflammation in Acute Coronary Syndromes*, eds E. Ercan and G. Ece (Sharjah: Bentham Science Publishers), 23-57
- [32] Lawrie, A. S., Albanyan, A., Cardigan, R. A., Mackie, I. J., and Harrison, P. (2009). Microparticle sizing by dynamic light scattering in fresh frozen plasma. *Vox Sang.* 96, 206-212. doi: 10.1111/j.1423-0410.2008.01151.x
- [33] Lhermusier, T., Chap, H., and Payrastre, B. (2011). Platelet membrane phospholipid asymmetry: from the characterization of a scramblase activity to the identification of an essential protein mutated in Scott syndrome. *J. Thromb. Haemost.* 9, 1883-1891. doi: 10.1111/j.1538-7836.2011.04478.x
- [34] Lodochnikova, O. A., Krivolapov, D. B., Startseva, V. A., Nikitina, L. E., Bodrov, A. V., Artemova, N. P., et al. (2015). S = O.S = O interactions as a driving force for low-temperature conformational rearrangement of stable H-bonding (S(O)-CH<sub>2</sub>-CH<sub>2</sub>-OH...)<sub>2</sub> synthon in two modifications of diastereomeric pinanyl sulfoxides co-crystal. *Phosphorus Sulfur Silicon Relat. Elem.* 190, 2222-2231. doi: 10.1080/10426507.2015.1072185
- [35] Lubecka, E., Kwiatowska, A., Ciarkowski, J., and Sikorska, E. (2010). NMR studies of new arginine vasopressin analogs modified with  $\alpha$ -2-indanylglycine enantiomers at position 2 bound to sodium dodecyl sulfate micelles. *Biophys. Chem.* 151, 139-148. doi: 10.1016/j.bpc.2010.06.002
- [36] MacKerell, A. D. Jr. (1995). Molecular dynamics simulation analysis of a sodium dodecyl sulfate micelle in aqueous solution: decreased fluidity of the micelle hydrocarbon interior. *J. Phys. Chem.* 99, 1846-1855. doi: 10.1021/j100007a011
- [37] Malde, A. K., Zuo, L., Breeze, M., Stroet, M., Poger, D., Nair, C. P., et al. (2011). An automated force field topology builder (ATB) and repository: version 1.0. *J. Chem. Theory Comput.* 7, 4026-4037. doi: 10.1021/ct200196m

- [38] Nikitina, L. E., Akulina, I. V., Garaev, R. S., Artemova, N. P., Dorofeeva, L. Y., Startseva, V. A., et al. (2012a). Synthesis and anti-inflammatory and antipyretic activity of 2-(1'-hydroxy-4'-isopropenyl-1'-methylcyclohexyl-2'-thio)-methylethanoate. *Pharm. Chem. J.* 46, 20-22. doi: 10.1007/s11094-012-0727-y
- [39] Nikitina, L. E., Artemova, N. P., and Startseva, V. A. (2011). *Natural and Thiomodified Monoterpenoids*. Saarbrücken: LAP LAMBERT
- [40] Nikitina, L. E., Artemova, N. P., Startseva, V. A., Fedyunina, I. V., and Klochkov, V. V. (2017a). Biological activity of S-containing monoterpenoids. *Chem. Nat. Compd.* 5, 811-819. doi: 10.1007/s10600-017-2131-z
- [41] Nikitina, L. E., Dieva, S. A., Plemenkov, V. V., Lodochnikova, O. A., Gubaidullin, A. T., Kataeva, O. N., et al. (2001). 7,7-Dimethyl-2,10-epoxybicyclo[3.1.1]heptane. Synthesis, structure, and products of epoxide ring cleavage. *Russ. J. Gen. Chem.* 8, 1233-1237. doi: 10.1023/A:1013251021230
- [42] Nikitina, L. E., Kiselev, S. V., Bodrov, A. V., Startseva, V. A., Artemova, N. P., Klochkov, V. V., et al. (2017b). Development of approaches to the study of the interaction of biologically active thioterpenoids with model membranes. *BioNanoScience* 7, 600-607. doi: 10.1007/s12668-017-0432-0
- [43] Nikitina, L. E., Lodochnikova, O. A., Startseva, V. A., Bodrov, A. V., Artemova, N. P., Klimovitskii, A. E., et al. (2017c). Extraordinary behavior of  $\beta$ -hydroxy sulfoxides and sulfone of pinane series. *Phosphorus Sulfur Silicon Relat. Elem.* 192, 187-191. doi: 10.1080/10426507.2016.1255619
- [44] Nikitina, L. E., Startseva, V. A., Artemova, N. P., Dorofeeva, L., Yu Kuznetsov, I. V., Lisovskaya, S. A., et al. (2012b). Synthesis and antifungal activity of the carane series. *Pharm. Chem. J.* 45, 664-667. doi: 10.1007/s11094-012-0699-y
- [45] Nikitina, L. E., Startseva, V. A., Dieva, S. A., Vakulenko, I. A., and Shamov, G. A. (2006). Reaction of  $\beta$ -pinene and thiols in the presence of Lewis acids. *Chem. Nat. Compd.* 2, 178-181. doi: 10.1007/s10600-006-0072-z
- [46] Nikitina, L. E., Startseva, V. A., Dorofeeva, L. Y., Artemova, N. P., Kuznetsov, I. V., Lisovskaya, S. A., et al. (2010). Antifungal activity of bicyclic monoterpenoids and terpenesulfides. *Chem. Nat. Compd.* 46, 28-32. doi: 10.1007/s10600-010-9517-5
- [47] Nikitina, L. E., Startseva, V. A., Vakulenko, I. A., Khismatulina, I. M., Lisovskaya, S. A., Glushko, N. P., et al. (2009). Synthesis and antifungal activity of compounds of the pinane series. *Pharm. Chem. J.* 43, 251-254. doi: 10.1007/s11094-009-0282-3
- [48] Niks, M., and Otto, M. (1990). Towards an optimized MTT-assay. *J. Immunol. Meth.* 130, 149-151. doi: 10.1016/0022-1759(90)90309-J
- [49] Pyne, S. G., Bloem, P., and Griffith, R. (1989). Conjugate addition of amines to (Rs)-10-isobornyl vinyl sulfoxides. *Tetrahedron Lett.* 45, 7013-7022. doi: 10.1016/S0040-4020(01)89169-9
- [50] Rakhmatullin, I. Z., Galiullina, L. F., Klochkova, E. A., Latfullin, I. A., Aganov, A. V., and Klochkov, V. V. (2016). Structural studies of pravastatin and simvastatin and their complexes with SDS micelles by NMR spectroscopy. *J. Mol. Struct.* 1105, 25-29. doi: 10.1016/j.molstruc.2015.10.059
- [51] Santos, M. R. V., Moreira, F. V., Fraga, B. P., De Sousa, D. P., Bonjardim, L. R., and Quintans-Junior, L. J. (2011). Cardiovascular effects of monoterpenes: a review. *Rev. Bras. Farmacogn.* 21, 764-771. doi: 10.1590/S0102-695X2011005000119
- [52] Shitikova, A. S. (2000). *Thrombocytic Hemostasis*. Saint Petersburg: Publishing house of Saint Petersburg State Medical University
- [53] Siess, W. (1989). Molecular mechanism of platelet activation. *Physiol. Rev.* 69, 58-78. doi: 10.1152/physrev.1989.69.1.58
- [54] Startseva, V. A., Nikitina, L. E., Lodochnikova, O. A., Klimovitskii, A. E., Aref'ev, A. V., Artemova, N. P., et al. (2014). Study of "Racemic Compound-Like" behavior of diastereomeric mixture of pinanyl sulfoxides by X-ray diffraction, IR spectroscopy, and DFT calculations. *Phosphorus Sulfur Silicon Relat. Elem.* 189, 615-629. doi: 10.1080/10426507.2013.843003
- [55] Usachev, K. S., Filippov, A. V., Filippova, E. A., Antzutkin, O. N., and Klochkov, V. V. (2013). Solution structures of Alzheimers amyloid A $\beta$ 13-23 peptide: NMR studies in solution and in SDS. *J. Mol. Struct.* 1049, 436-440. doi: 10.1016/j.molstruc.2013.06.043
- [56] Vargas-Díaz, M. E., Lagunas-Rivera, S., Joseph-Nathan, P., Tamariz, J., and Zepeda, L. G. (2005). Efficient and highly diastereoselective preparation of a myrtenal derived bis-sulfoxide and its preliminary evaluation as chiral acyl donor. *Tetrahedron Lett.* 46, 3297-3300. doi: 10.1016/j.tetlet.2005.03.104
- [57] Wojaczynska, E., and Wojaczynski, J. (2010). Enantioselective synthesis of sulfoxides: 2000-2009. *Chem. Rev.* 110, 4303-4356. doi: 10.1021/cr900147h
- [58] Yang, T. K., Chen, R.-Y., and Lee, D.-S. (1994). Application of new camphor-derived mercapto chiral auxiliaries to the synthesis of optically active primary amines. *J. Org. Chem.* 59, 914-921. doi: 10.1021/jo00083a037