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Functionalization of terpene alcohols with 1-sulfonyl-1,2,3-triazoles: synthesis of *N*-(2-terpenyloxyethenyl/ethyl)sulfonamides

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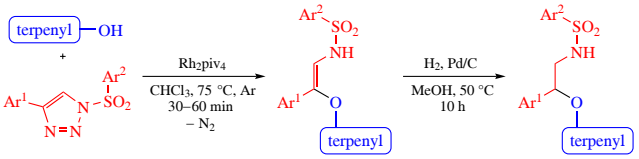
New *N*-(2-aryl-2-terpenyloxyethenyl)sulfonamides bearing two pharmacophoric terpenyloxy and sulfonamide groups linked through an ethylene bridge were synthesized by the reaction of *p*-menthol, allobetulin or isoborneol with 4-aryl-1-arylsulfonyl-1,2,3-triazoles in the presence of rhodium(II) pivalate. A significant part of the compounds obtained possessed low stability, which necessitated their hydrogenation into more stable *N*-(2-aryl-2-terpenyloxyethyl)-sulfonamides. Some of the synthesized compounds exhibited high antibacterial and moderate cytotoxic activity.



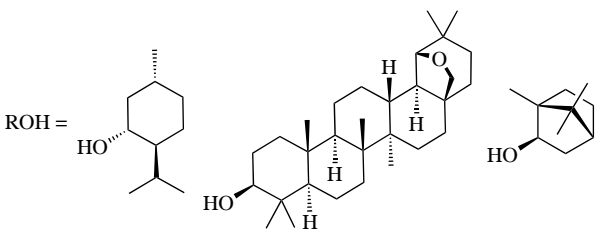
Ar^1 = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-thienyl; Ar^2 = 4-MeC_6H_4, 4-$MeOC_6H_4$

Keywords: terpene alcohols, 1,2,3-triazoles, rhodium(II) pivalate, azavinylcarbenes, OH insertion reactions, sulfonamides, antibacterial activity, cytotoxic activity.

Natural compounds play an exceptionally important role in the targeted synthesis of biologically active substances for medical purposes, which is due to their availability and high synthetic potential.[1–6] A special place among such compounds is occupied by terpenoids, in particular terpene alcohols, which are widespread in the plant kingdom and possess diverse and clearly expressed biological activity.[7,8] Derivatives of terpene alcohols obtained often surpass native substances in therapeutic efficacy. In this regard, in this work a chemical modification of terpene alcohols was carried out by introducing sulfonamide groups into their structure, which are among the well-known pharmacophoric groups. It was recently shown[9] that the sulfonamide derivative of cryptopleurin, a known antitumor and antiviral substance, exhibited 2–3 times greater activity against cancer cells than the original natural compound. In addition, improved pharmacokinetic properties, including higher clearance, longer biological half-life, and higher bioavailability, when taken orally, of this derivative compared to its parent natural product, have been noted. Potent inhibitors of butyrylcholinesterase, which probably plays an important role in Alzheimer's disease, have been obtained by synthesizing the sulfonamide derivatives of anthofin and cryptopleurin.[10,11] Recently, sulfonamides have been increasingly used in the development of multi-target drugs.[12]

In this work, we obtained a series of *N*-(2-aryl-2-terpenyloxyethenyl)sulfonamides whose molecules contained two linked pharmacophoric terpenyloxy and ethenylsulfonamide groups. The target compounds were prepared by the reaction of terpene alcohols **1** with 4-aryl-1-arylsulfonyl-1,2,3-triazoles **2** (Scheme 1).

The reactions represent the insertion of an enamide group at the O–H bond using rhodium azavinylcarbenes (α-imino carbenoids), which arise from 4-aryl-1-sulfonyl-1,2,3-triazoles upon heating in the presence of rhodium pivalate. Metal complexes of azavinylcarbenes are known to be reactive intermediates that are active in the formation of various carbo- and heterocycles, as well as unique acyclic nitrogen-containing compounds.[13] In particular, they undergo insertion reactions at the X–H bond (X = O, N), which is used in the synthesis of a wide range of compounds.[14] Thus, when studying these reactions involving alcohols, it was established that compounds were unstable upon isolation when ethanol was used as the reactant. However, when using secondary or tertiary alcohols (2-propanol, 1-phenylethanol, 1-adamantol, *p*-menthol), stable O–H insertion products, (2-alkoxy-2-phenylvinyl)arylsulfonamides, were obtained.[14] In other works,[15–17] propargyl, benzyl, allyl, furfuryl and other alcohols were also included in the range of



1a *p*-menthol (R = menthyl) **1b** allobetulin (R = allobetulinyl) **1c** isoborneol (R = isobornyl)

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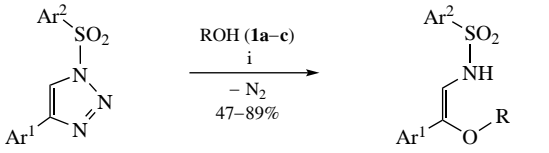


2a–e **3a–o** (**3a**,**j–l** stable)

2a Ar^1 = Ph, Ar^2 = 4-MeC_6H_4
2b Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4
2c Ar^1 = 4-BrC_6H_4, Ar^2 = 4-MeC_6H_4
2d Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$
2e Ar^1 = 2-thienyl, Ar^2 = 4-MeC_6H_4

3a Ar^1 = Ph, Ar^2 = 4-MeC_6H_4, R = menthyl
3b Ar^1 = Ph, Ar^2 = 4-MeC_6H_4, R = allobetulinyl
3c Ar^1 = Ph, Ar^2 = 4-MeC_6H_4, R = isobornyl
3d Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, R = menthyl
3e Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, R = allobetulinyl
3f Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, R = isobornyl
3g Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4, R = menthyl
3h Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4, R = allobetulinyl
3i Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4, R = isobornyl
3j Ar^1 = 4-BrC_6H_4, Ar^2 = 4-MeC_6H_4, R = menthyl
3k Ar^1 = 4-BrC_6H_4, Ar^2 = 4-MeC_6H_4, R = allobetulinyl
3l Ar^1 = 4-BrC_6H_4, Ar^2 = 4-MeC_6H_4, R = isobornyl
3m Ar^1 = 2-thienyl, Ar^2 = 4-MeC_6H_4, R = menthyl
3n Ar^1 = 2-thienyl, Ar^2 = 4-MeC_6H_4, R = allobetulinyl
3o Ar^1 = 2-thienyl, Ar^2 = 4-MeC_6H_4, R = isobornyl

Scheme 1 *Reagents and conditions*: i, Rh_2piv_4, $CHCl_3$, 75 °C, argon, 30–60 min.

alcohols studied, and it was found that in most cases the O–H insertion reactions were accompanied by rearrangements.

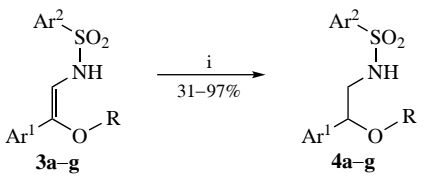
In our previous works,[18,19] we studied the NH-insertion reaction of 1-sulfonyl-1,2,3-triazoles with primary anilines. Herein, we turned to other available substrates such as secondary terpene alcohols, differing in the structure of the carbon framework: *p*-menthol **1a**, allobetulin **1b** and isoborneol **1c**. The starting 4-aryl-1-sulfonyl-1,2,3-triazoles **2a–e** were obtained by a known method[20] from the corresponding sulfonyl azides and alkynes under catalysis by copper(I) thiophene-2-carboxylate in toluene.

The reactions of terpene alcohols **1** with triazoles **2** were carried out in the presence of rhodium(II) pivalate under argon at 75 °C for 30–60 min (see Scheme 1). The reaction mixtures were subjected to column chromatography on silica gel. In all the reactions studied, the main products, according to ^{1}H NMR spectroscopy, were *N*-(2-aryl-2-terpenyloxyethenyl)sulfonamides **3**. Unfortunately, of the 15 compounds obtained, only four (**3a**,**j–l**) were stable when stored under normal conditions (room temperature, hermetically sealed package). It is noteworthy that compounds **3j–l** contain 4-bromophenyl substituent in position 2 at the sp^2-hybridized carbon atom. The other O–H insertion products are noticeably decomposed, probably due to hydrolysis, as evidenced by the appearance of signals in the ^{1}H NMR spectra that do not belong to arylethenylsulfonamides **3** when they are dissolved in $CDCl_3$ or DMSO-d_6.

It should be noted that the reactions of terpene alcohols **1** with triazoles **2** proceed with a high degree of stereoselectivity[14] providing *Z*-configuration of the alkenyl fragment, which was confirmed by the {^{1}H–^{1}H}-NOESY experiments.

The structures of compounds **3** (47–89% yields) were confirmed using mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy (when possible). The ^{1}H and ^{13}C NMR spectra contain signals for protons and carbon atoms of the terpenoid framework and the arylsulfonyl group with practically the same chemical shift values as in the starting reactants. The ^{1}H NMR spectra also contain signals for the alkenyl proton (δ_H 5.91–6.23 ppm) and the NH group proton (δ_H 6.38–6.63 ppm), and the ^{13}C NMR spectra show signals for the ethylene group carbon atoms: O–C= (δ_C 143–145 ppm) and =C–NH (δ_C 109–115 ppm).

To transform unstable compounds **3** into stable analogs that do not contain the C=C bond, we hydrogenated some of their representatives **3a–g** in a methanol solution (or a methanol–THF mixture for allobetulin derivatives) at 50 °C under a constant flow of hydrogen in the presence of Pd/C as a catalyst (Scheme 2). Crystalline *N*-(2-aryl-2-terpenyloxyethyl)sulfonamides **4a–g** were obtained in 31–97% yields. The emergence in these compounds of a new chiral atom at C^2 compared to the initial sulfonamides **3** is the cause for the formation of two diastereomers in approximately equal quantities, which is manifested by the doubling of all signals in the NMR spectra of the products. One of these compounds, *N*-(2-*p*-menthyloxy-2-phenylethyl)-sulfonamide **4a**, was obtained as an individual diastereomer by recrystallization from a mixture of light petroleum and ethyl acetate (20 : 1). The structures of compounds **4** were established by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. In particular, the ^{1}H NMR spectra contain signals for protons of the CH_2N (δ_H 3.07–3.19 ppm), $C_{terp.}HO$ (δ_H 2.74–2.98 ppm), ArCHO (δ_H 4.33–4.52 ppm), and NH (δ_H 4.47–4.88 ppm) groups, while the ^{13}C NMR spectra do not contain olefinic signals but those for a carbon of the ArCHO group (δ_C 75–86 ppm). Ethylsulfonamides **4** can be stored without visible changes for several months.



3a–g **4a–g**

a Ar^1 = Ph, Ar^2 = 4-MeC_6H_4, R = menthyl
b Ar^1 = Ph, Ar^2 = 4-MeC_6H_4, R = allobetulinyl
c Ar^1 = Ph, Ar^2 = 4-MeC_6H_4, R = isobornyl
d Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, R = menthyl
e Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, R = allobetulinyl
f Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, R = isobornyl
g Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4, R = menthyl

Scheme 2 *Reagents and conditions*: i, H_2 (1 atm), Pd/C, MeOH, 50 °C, 10 h.

Preliminary studies of the biological activity of the synthesized *N*-(2-aryl-2-terpenyloxyethyl)sulfonamides **4a–g** (Table 1) revealed high antibacterial activity of compounds **4a** and **4c** against *Staphylococcus aureus*, which was several times greater than the activity of the known drug sulfamethoxazole. In addition, the cytotoxic activity of compounds **4** (concentration 30 μmol, exposure 72 h, control – etoposide) against breast cancer cells (SK-BR-3), prostate adenocarcinoma (PC-3), lung carcinoma (A549), colorectal cancer cells (HCT116), melanoma cells (A375), and lung fibroblast cells (WI-26 VA4) was studied. All tested substances, with the exception of **4e**, exhibited moderate activity against cancer cells with less effect on normal cells (WI-26 VA4).

In conclusion, a series of *N*-(2-aryl-2-terpenyloxyethenyl)-sulfonamides and their hydrogenation products, *N*-(2-aryl-2-terpenyloxyethyl)sulfonamides, combining two pharmacophoric groups, terpenyloxy and sulfonamide, was synthesized by the

Table 1 Results of the study of biological activity of compounds **4a**,**c**–**g**.[a]

Compound	MIC[b]/mg ml^{-1}	Cell viability (%)					
		SK-BR-3	PC-3	A549	HCT116	A375	WI-26 VA4
4a	1	57	58	61	50	39	27
4c	1	26	46	40	41	74	41
4d	not active	54	49	46	46	72	82
4e	not active	88	88	91	105	99	105
4f	not active	29	46	27	76	77	91
4g	not active	54	43	39	73	60	113

[a] The substance **4b** did not dissolve in aqueous DMSO. [b] Minimum inhibitory concentration, against *S. aureus*.

reaction of terpene alcohols with 1-sulfonyl-1,2,3-triazoles. Some of the products, according to preliminary data, exhibit high antibacterial and moderate cytotoxic activity, which makes them promising for further studies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7712.

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