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Mendeleev Commun., 2021, **31**, 204–206

Mendeleev Communications

Antibacterial activity of new silatrane pyrrole-2-carboxamide hybrids

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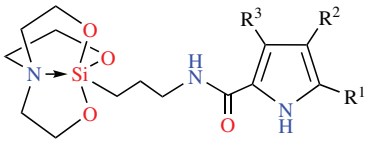
DOI: 10.1016/j.mencom.2021.03.019

Silatrane-1*H*-pyrrole-2-carboxamide hybrids conjugated *via* propane-1,3-diyl linker have been synthesized by the reaction of 1-(3-aminopropyl)silatrane with 2-(trichloroacetyl)pyrroles. Their *in silico* screening would predict their antitumor activity. Their *in vitro* screening for antimicrobial activity revealed the representative with $R^1 = R^2 = R^3 = H$ to be the most potent against Gram-positive microorganisms such as *E. durans*, *B. subtilis* and *E. coli*.



$R^1 = R^2 = R^3 = H$ or Me
$R^1 = Ph$, $R^2 = R^3 = H$
$R^1 + R^2 = (CH_2)_4$, $R^3 = H$

Keywords: silatranes, pyrrolecarboxamides, hybrids, antitumor activity, antimicrobial action.

Silatranes, $R–Si(OCH_2CH_2)_3N$, belong to the class of tricyclic compounds of hypervalent silicon with an intramolecular transannular donor–acceptor bond Si←N.[1] These compounds possess intriguing physical-chemical properties (high dipole moment, easy polarizability of the R–Si bond, resistance to hydrolysis)[1,2] and valuable biological (physiological, pharmacological) activity.[3] The latter is obviously caused by easier (due to the formation of hydrogen bonds and dipole–dipole coupling) adsorption of silatranes (and their congeners) on the surface of cell membranes and active transport of their molecules into the cells,[3] which is critical to drug discovery and design.

The broad utility of silatranes has sparked interest in the modification of their exocyclic functional substituents. For example, amino- and thioalkylsilatranes are known to be precursors for the synthesis of new compounds exhibiting extremely beneficial properties, which are widely sought after in materials science,[4] biology, and medicine.[5]

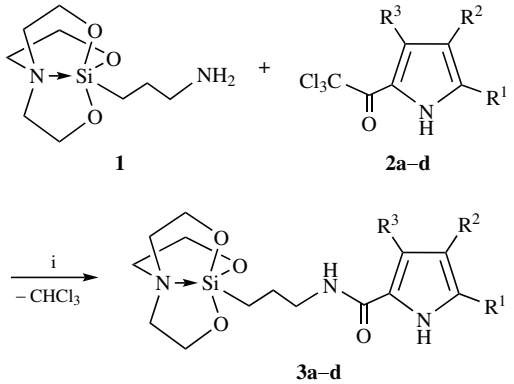
On the other hand, pyrroles and their derivatives,[6] in particular, pyrrole carboxamides, find extensive application in therapeutically active drugs, including anti-HIV,[7] antitumor,[8] fungicidal,[9] insecticidal[10] and antibacterial[11] ones.

Molecular hybridization is a method of combining two or more pharmacophoric units into one molecule[12] being popular in design of multifaceted compounds. This was successfully employed to access, in particular, new silatrane hybrids with anticancer, anti-inflammatory, antimicrobial, and other activities.[13]

In the present work, we report on the synthesis of silatranyl-pyrrole conjugates which combine the unique properties of silatranes and the biological activity of pyrroles. 1-(3-Aminopropyl)silatrane, $H_2N(CH_2)_3Si(OCH_2CH_2)_3N$ **1**, and 2-(trichloroacetyl)pyrroles **2a–d** were used as precursors to obtain hitherto unknown 1*H*-R-pyrrole-2-carboxamide-silatrane hybrids **3a–d** (Scheme 1).†

Usually, pyrrole-2-carboxamides are synthesized by the classical reaction of amines with pyrrole-2-carboxylic acids, or directly with 2-(trichloroacetyl)pyrroles. However, in the former case, the activating reagents (thionyl chloride, *N*,*N*′-dicyclohexylcarbodiimide, *N*,*N*′-carbonyldiimidazole, *etc*.) are required, which leads to undesirable waste. In the latter, the reaction gives the target products only in 27–52% yields.[14] In our hands, the reaction of aminosilatrane **1** with 2-(trichloroacetyl)pyrroles **2** affords products **3** in much higher yields (up to 96%). This fact can be explained by the powerful electron-donating effect of the silatranyl group, which increases basicity of the nitrogen atom and, as a consequence, dramatically enhances reactivity of the amino silatranes in comparison with organic amines.[15]

Pyrrolecarboxamide-silatrane hybrids **3a–d** are coloured (yellow to red) powders soluble in DMSO, acetonitrile and $CHCl_3$ (when heated). Their structure has been established by elemental analysis, IR, ^1H, ^{13}C, ^{15}N, ^{29}Si, 1D and 2D NMR spectroscopy, mass spectrometry and X-ray diffraction (see Online Supplementary Materials). The FT-IR spectra of silatranes **3a–d** show characteristic absorption bands of silatranyl group at 588–590 cm^{-1} (N→Si),



1 **2a–d**

3a–d

a $R^1 = R^2 = R^3 = H$
b $R^1 = R^2 = R^3 = Me$
c $R^1 = Ph$, $R^2 = R^3 = H$
d $R^1 + R^2 = (CH_2)_4$, $R^3 = H$

Scheme 1 *Reagents and conditions*: i, THF, 65 °C, 1 h.

† For experimental details, see Online Supplementary Materials.

761–775 and 1051–1054 cm^{-1} (Si–O), 1266–1271 cm^{-1} (O–CH_2), and 1359–1375 cm^{-1} (CH_2–N).[1] The absorption bands in the regions of 1520–1542 and 1609–1629 cm^{-1} are assigned to the C=C and C=O stretching vibrations of the pyrrole ring and carbonyl group, respectively.[16] The absorption bands at 3221–3271 cm^{-1} (NH-amide) and 3321–3404 cm^{-1} (NH-pyrrole) are due to N–H bending vibrations of the pyrrolecarboxamide-linked silatranes **3a**–**d**.

The ^{1}H NMR spectra of hybrids **3a**–**d** contain characteristic triplets of the silatranyl moiety representing the NCH_2 and OCH_2 groups in narrow ranges of 2.76–2.77 and 3.59–3.60 ppm (*J* 5.7 Hz), respectively.[1] The broad singlets assigned to the CO–NH group at 6.94–7.89 ppm are observed for pyrrole-linked silatranes **3a**–**d**. Singlets at 10.52–11.53 ppm correspond to the pyrrole NH protons. The peaks of the phenyl fragment in the region of 6.53–7.76 ppm additionally confirm the structure of compound **3c**. In the ^{13}C NMR spectra, silatranyl NCH_2 and OCH_2 carbons resonate at 49.95–51.82 and 56.67–57.44 ppm, respectively. The peaks of the pyrrole ring carbons (C2, C3, C4, C5) appear at 108.30–130.47 ppm. The ^{15}N NMR spectra display signals for the nitrogen of the silatranyl ring (NSil), CO–NH, and NH groups in the regions from −356 to −357 ppm, from −270 to −273 ppm and from −221 to − 230 ppm, respectively. The ^{29}Si NMR spectra of compounds **3a**–**d** contain peaks for the silatranyl moiety in a very narrow region from −70.33 to −70.50 ppm. Such values are indicative of an intramolecular transannular Si←N dative bond.[1] The high-resolution mass spectra of hybrids **3a**–**d** consist of base peaks corresponding to the $[M + H]^+$.

The synthesized pyrrolecarboxamide-silatrane hybrids **3a**–**d** have been screened for physico-chemical and pharmacokinetic properties, pharmacological (see Online Supplementary Materials, Tables S1–S3) and antimicrobial activity (Table 1). The prediction of *in silico* ADME (absorption, distribution, metabolism and excretion)[17] properties reveals that products **3a**–**d** have significant drug-likeness based on Lipinski's rules[18(*a*)] and other important characteristics (see Table S1).[18(*b*)] Compounds **3a**–**d** exert low skin permeation (see Table S2) and, at the same time, they are water-soluble and possess high gastrointestinal absorption as well as bioavailability.

Probable pharmacological activity profiles of compounds **3a**–**d** have been studied *in silico* using the PASS program.[19] For each investigated activity, PASS calculates two probabilities, Pa (active) and Pi (inactive). Pa and Pi values vary from 0.000 to 1.000 (or Pa/Pi). The calculated screening indicates that the starting pyrroles **2a**–**d** almost do not have antitumor activity (Pa/Pi ~ 0.230/0.220). At the same time, compounds **3a**–**d** may exert very high antitumor activity: Pa/Pi ~ 0.956/0.004, *i.e.* with a probability ~95–96% (see Table S3). Thus, the data obtained by the SwissADME and PASS programs, confirm that the synthesized silatranes **3a**–**d** can be good candidates for pharmacological trials.

The antimicrobial activity and minimal inhibitory concentration (MIC) have been determined using the broth microdilution method.[20] The starting silatrane **1** and pyrrolecarboxamide-linked silatranes **3a**–**d** were tested *in vitro* for antimicrobial activity against bacterial strains of Gram-positive *Enterococcus durans* B-603, *Bacillus subtilis* B-407 and Gram-negative *Escherichia coli* B-1238 (Table 1).

It was established that pyrrole silatranes **3a**–**c** exhibited moderate to excellent activity with respect to Gram-positive microorganisms. Meanwhile, tetrahydroindole silatrane **3d** was effective against Gram-negative *E. coli*. The MICs of silatranes **3b**–**d** are two times lower or comparable for *E. durans*, *B. subtilis* and 8–16 times lower for *E. coli* as compared with the starting silatrane **1**. Maximum antibacterial activity (MIC, 3.1 and 6.2 μg ml^{-1}) against *E. durans* and *B. subtilis* is demonstrated by compound **3a** as compared to standard aminoglycoside antibiotic, Gentamicin (MIC, 25 and 50 μg ml^{-1}). Thus, hybrid **3a** is the most potent among the studied compounds against Gram-positive bacterial strains.

Table 1 Antibacterial activities of silatranes **3a**–**d**.[a]

Compound	MIC / μg ml^{-1}		
	E. durans B-603 (G+)	*B. subtilis* B-407(G+)	*E. coli* B-1238 (G–)
1	125	500	>1,000
3a	3.1	6.2	125
3b	62.5	250	125
3c	125	500	>1,000
3d	500	500	62.5
Gentamicin	25	50	100

[a] Bacteria were provided by All-Russian Collection of Micro-organisms, VKM.

In conclusion, novel silatrane hybrids have been synthesized from 1-(3-aminopropyl)silatrane and 2-(trichloroacetyl)pyrroles. These compounds of pentacoordinated silicon are equipped with 1*H*-R-pyrrole-2-carboxamide group. The calculated *in silico* ADME profile and high antitumor action (PASS Online service) as well as *in vitro* investigated antimicrobial activity (MIC to 3.1 μg ml^{-1}) make these compounds prospective objects for further research.

The main results were obtained using the equipment of Baikal Analytical Center of Collective Using, Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.019.

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Received: 12th November 2020; Com. 20/6365