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Short Note

N,N′,N″-Tris[(5-methoxy-1*H*-indol-3-yl)ethyl]benzene-1,3,5-tricarboxamide

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Abstract: The title indole-based compound that enforces tripodal topology and is potential applicable for the use as artificial receptor, was prepared by a simple reaction of 1,3,5-benzenetricarbonyl trichloride with 5-methoxytryptamine. The compound was characterized by elemental analysis, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry.

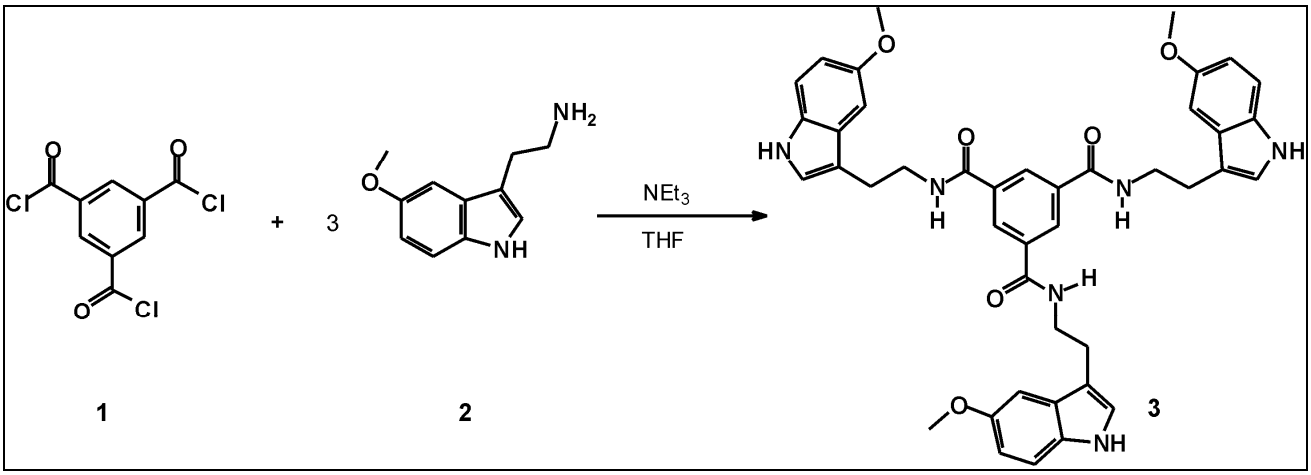
Keywords: indole; receptors; molecular recognition; ammonium ion

Introduction

The indole group was found to be a valuable building block for the construction of artificial receptors, which are able to bind both ionic [1–3] and neutral substrates, like some carbohydrates [4,5]. The design of indole-based carbohydrate receptors [6–10] was inspired by the binding modes of carbohydrate-binding proteins, which often use indole (Trp) and/or imidazole (His) groups to bind the carbohydrate substrate by hydrogen bonding and CH-π interactions [11].

In this paper we describe the simple synthesis of the methoxyindole-based compound **3** that enforces tripodal topology and is potential applicable for the use as artificial receptor. The synthesis of **3** involves the reaction of 1,3,5-benzenetricarbonyl trichloride (**1**) with 5-methoxytryptamine (**2**) (Scheme 1). A tripodal analogue of compound **3**, lacking the methoxy substituents, was previously reported as an anion receptor, showing preference for hydrogen sulfate over other anions [12]. In the

case of **3**, however, molecular modeling calculations indicated the ability of this compound to act as receptor for cations, such as NH_4^+ ion and other organic ammonium ions [13]. The complex with NH_4^+ ion can be stabilized by the formation of hydrogen bonding interactions with the methoxy groups of **3**, NH-π interactions with the indole rings as well as NH-π interaction with the central benzene ring of **3** (example of an energy-minimized structure of the 1:1 complex between **3** and NH_4^+ is shown in Figure 1). Proton NMR titration technique was employed to prove this suggestion. ^{1}H-NMR spectroscopic titrations of compound **3** with NH_4PF_6 in CD_3CN revealed movements of the signals of **3** (for example, upfield shifts of the benzene CH and amide NH of **3**) and provided indications for complex formation between the two binding partners. Titration data were analyzed using the WinEQNMR 2 program [14] and gave good fit only to the mixed 1:1 and 2:1 receptor-substrate binding model (K_{11} = 370 M^{-1}, K_{21} = 890 M^{-1}; average values from three titrations); the formation of complexes with 2:1 stoichiometry was further indicated by the mole ratio plot (see Figure S5).



Scheme 1. Synthesis of the title compound *N,N′,N″*-Tris[(5-methoxy-1*H*-indol-3-yl)ethyl]benzene-1,3,5-tricarboxamide (**3**).

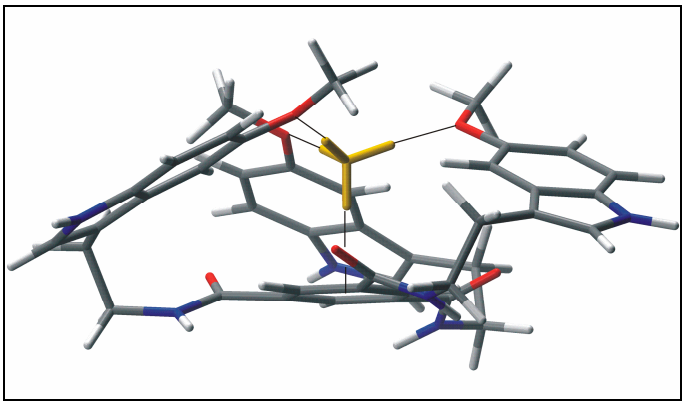


Figure 1. Energy-minimized structure of the 1:1 complex between **3** and NH_4^+ (MacroModel V.8.5, OPLS 2001 force field, MCMM, 50000 steps). Color code: receptor N, blue; O, red; C, gray; NH_4^+ is highlighted in yellow.

Experimental Section

1,3,5-Benzenetricarbonyl trichloride (**1**) (110 mg, 0.41 mmol) was dissolved in CH_2Cl_2/THF (3 mL/7 mL) and added dropwise to a mixture of 5-methoxytryptamine (**2**) (355 mg, 1.87 mmol) and triethylamine (0.35 mL, 252 mg, 2.49 mmol) in dry THF (20 mL). The reaction mixture was stirred for 48 h at room temperature. After addition of an additional amount of THF (20 mL), the solution was allowed to stand at room temperature and the formed precipitate, involving 5-methoxytryptamine and triethylamine hydrochlorides, was separated by filtration. Then, water (20 mL) was added, the mixture stirred for 60 minutes at room temperature and the organic solvents were removed under reduced pressure. The crude product was separated from the aqueous phase, dissolved in THF and dried over $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography (silica gel, $CHCl_3$/CH_3OH, 15:1, *v/v*). The product **3** was obtained as a white solid in 76% yield.

230 mg (0.32 mmol, 76%).

Mp = 122–123 °C.

R_f = 0.45 (silica gel, methanol/chloroform 1:15 v/v).

R_f = 0.57 (silica gel, methanol/chloroform 1:7 v/v).

^{1}H-NMR (400 MHz, THF-d_8): δ [ppm] = 3.01 (t, *J* = 7.3 Hz, 6H, CH_2), 3.67 (m, 6H, CH_2), 3.75 (s, 9H, OCH_3), 6.70 (dd, *J* = 8.7/2.4 Hz, 3H, H_{aryl}), 7.02 (d, *J* = 2.4 Hz, 3H, H_{aryl}), 7.11 (d, *J* = 2.4 Hz, 3H, H_{aryl}), 7.15 (d, *J* = 8.7 Hz, 3H, H_{aryl}), 8.09 (t, *J* = 5.8 Hz, 3H, NH), 8.43 (s, 3H, H_{aryl}), 9.78 (s, 3H, NH).

^{1}H-NMR (500 MHz, CD_3CN, [**3**] = 1 mM): δ [ppm] = 3.03 (t, *J* = 7.0 Hz, 6H, CH_2), 3.68 (m, 6H, CH_2), 3.77 (s, 9H, OCH_3), 6.79 (dd, *J* = 8.8 Hz/2.4 Hz, 3H, H_{aryl}), 7.12 (m, 6H, H_{aryl}), 7.24 (t, *J* = 5.4 Hz, 3H, NH), 7.30 (d, *J* = 8.8 Hz, 3H, H_{aryl}), 8.24 (s, 3H, H_{aryl}), 8.96 (s, 3H, NH).

^{13}C-NMR (100 MHz, THF-d_8): δ [ppm] = 26.6, 41.6, 55.8, 101.0, 112.4 (2C), 113.4, 123.7, 129.0 (2C), 133.1, 136.7, 154.8, 166.4.

HRMS (ESI) calcd. for $C_{42}H_{43}N_6O_6$ $[M + H]^+$ 727.323860. Found 727.323837.

Elemental Analysis: calcd. for $C_{42}H_{42}N_6O_6$: C, 69.40; H, 5.82; N, 11.57. Found: C, 69.33; H, 6.01; N, 11.34.

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