Crystal structure of 2-(3-methoxyphenylethynyl)-6-methylpyridine, $C_{15}H_{13}NO$, *M-MPEP* – a *mGluR5* antagonist

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Abstract

$C_{15}H_{13}NO$, monoclinic, $P12_1/c1$ (no. 14),
 $a = 15.986(3)$ Å, $b = 6.760(1)$ Å, $c = 11.415(2)$ Å,
 $\beta = 104.63(3)^\circ$, $V = 1193.5$ Å³, $Z = 4$,
 $R_{\text{gt}}(F) = 0.055$, $wR_{\text{ref}}(F^2) = 0.139$, $T = 183$ K.

Source of material

Preparation of the title compound was achieved by a Sonogashira cross coupling between 2-ethynyl-6-methylpyridine (4 g, 14.3 mmol) and 3-bromoanisole (2.0 mL, 15.7 mmol) in the presence of tetrakis(triphenylphosphine)palladium (1.65 g, 1.4 mmol) and lithium chloride (20 mg, 0.4 mmol) in 100 mL degassed *N,N*-dimethylformamide. The resulting mixture was warmed to 110 °C and stirred at this temperature for 4 h. After cooling, 50 mL of H₂O was added and the resulting solution was extracted with EtOAc (4 × 30 mL). The organic layer was washed with saturated NaCl (3 × 20 mL), dried over Na₂SO₄ and evaporated. Purification of the residue by column chromatography (toluene/ether 9/1) led to a mixture that was separated by chromatography (hexane/EtOAc 9/1) to yield 1.91 g (60 %) of title compound as a colorless oil. The colorless oil was dissolved in a mixture methanol/H₂O (5:1) and the resulting solution was allowed to stand at r.t. for 2 days before collection of the colorless monocrystal suitable for X-ray analysis. Spectroscopic data obtained from NMR, mass and micro analysis support the proposed structure.

Discussion

Glutamate is the major excitatory neurotransmitter in brain and such involved in several physiological and pathological conditions [1]. Glutamate acts at two classes of receptors, the ionotropic and the metabotropic glutamate receptors (mGluRs) [2]. Metabotropic glutamate receptors comprise a family of eight G protein coupled receptors (mGluR1–8) that are activated by

glutamate and can modulate fast excitatory responses evoked by glutamatergic stimulation of ionotropic receptors [3]. The eight mGluR subtypes are subdivided into three groups principally based on sequence homology, but also on signal transduction pathway and agonist selectivity [4]. Group I mGluRs (mGluR1 and mGluR5 subtypes) exhibit a regional pattern of expression in the CNS suggesting distinct functional roles for each receptor [5]. Recent work in transgenic mice indicates a powerful regulatory role for the mGluR5 in mediating a variety of cocaine-induced behaviors. Specifically, mGluR5 knock-out mice were insensitive to the locomotor activating effects of cocaine and failed to acquire cocaine self-administration [6]. With the purpose of identifying a novel series of mGluR5 noncompetitive antagonists for use in brain imaging and/or addiction therapy, we decided first to obtain detailed information about the molecular conformation in solid state of the most potent and selective antagonist of mGluR5 described in the literature [2].

In the solid-state, the molecule is nearly planar with a mean deviation of only 0.046(2) Å despite the possibility of free rotation about the C6—C7 and C8—C9 bonds and no preferred orientation of the methoxy group. The two rings are offset by only 4.9 Å and the peripheral methyl and methoxy ligands are in *trans*-like arrangement. The alkynyl backbone is linear with angles measured at 177.6° (C6—C7—C8) and 179.6° (C7—C8—C9). The torsion angles between the two rings also demonstrate the molecular planarity with *cis*-type angles of 3.9° and 5.6°, and *trans*-type angles of 175.1° and 175.4°. Significant π -stacking, propagating along the *b* axis, exists in the crystal lattice with intermolecular separations of 3.7 Å. There are no significant intermolecular contacts.

Table 1. Data collection and handling.

Crystal:	colorless block, size 0.25 × 0.25 × 0.30 mm
Wavelength:	Mo K_{α} radiation (0.71073 Å)
μ :	0.78 cm ^{−1}
Diffractionmeter, scan mode:	Nonius KappaCCD, ω
$2\theta_{\text{max}}$:	54.96°
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$:	4475, 2724
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 1708
$N(\text{param})_{\text{refined}}$:	154
Program:	SHELXTL [7]

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Table 2. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	x	y	z	U _{iso}
H(1A)	4e	0.2317	-0.2591	0.4457	0.039
H(2A)	4e	0.1583	-0.5384	0.3580	0.042
H(3A)	4e	0.0832	-0.7349	0.4641	0.040
H(5A)	4e	0.1556	-0.3691	0.7522	0.037
H(10A)	4e	0.3092	0.1942	0.9228	0.041
H(11A)	4e	0.3838	0.4869	0.9942	0.045
H(12A)	4e	0.4408	0.6772	0.8618	0.045

Table 2. Continued.

Atom	Site	x	y	z	U _{iso}
H(14A)	4e	0.0007	-0.9129	0.7004	0.062
H(14B)	4e	0.0652	-0.9436	0.6151	0.062
H(14C)	4e	-0.0200	-0.8119	0.5694	0.062
H(15A)	4e	0.4266	0.5363	0.5516	0.068
H(15B)	4e	0.5017	0.6183	0.6615	0.068
H(15C)	4e	0.4130	0.7383	0.6175	0.068

Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
O(1)	4e	0.07321(8)	-0.6790(2)	0.6912(1)	0.0465(8)	0.0343(7)	0.0388(7)	-0.0044(5)	0.0156(6)	-0.0131(6)
N(1)	4e	0.36030(9)	0.3249(2)	0.6751(1)	0.0295(8)	0.0303(8)	0.0289(7)	0.0017(6)	0.0077(6)	-0.0019(6)
C(1)	4e	0.2013(1)	-0.3379(3)	0.4902(2)	0.032(1)	0.036(1)	0.0296(9)	0.0024(8)	0.0075(7)	-0.0006(8)
C(2)	4e	0.1578(1)	-0.5037(3)	0.4385(2)	0.035(1)	0.044(1)	0.0263(9)	-0.0038(8)	0.0083(7)	0.0023(9)
C(3)	4e	0.1135(1)	-0.6211(3)	0.5013(2)	0.033(1)	0.032(1)	0.0331(9)	-0.0074(8)	0.0050(8)	0.0005(8)
C(4)	4e	0.1135(1)	-0.5716(2)	0.6190(1)	0.0284(9)	0.0306(9)	0.0309(9)	0.0004(7)	0.0086(7)	0.0013(7)
C(5)	4e	0.1564(1)	-0.4037(2)	0.6718(1)	0.035(1)	0.0305(9)	0.0282(9)	-0.0043(7)	0.0092(8)	-0.0006(8)
C(6)	4e	0.2007(1)	-0.2851(2)	0.6081(1)	0.0279(9)	0.0283(9)	0.0310(9)	0.0016(7)	0.0064(7)	0.0024(7)
C(7)	4e	0.2450(1)	-0.1093(3)	0.6622(1)	0.034(1)	0.033(1)	0.0325(9)	0.0030(8)	0.0107(8)	0.0014(8)
C(8)	4e	0.2819(1)	0.0399(3)	0.7033(1)	0.032(1)	0.031(1)	0.0323(9)	0.0017(8)	0.0106(8)	-0.0014(8)
C(9)	4e	0.3262(1)	0.2183(2)	0.7516(1)	0.0278(9)	0.0284(9)	0.0307(9)	0.0010(7)	0.0077(7)	0.0016(7)
C(10)	4e	0.3336(1)	0.2733(3)	0.8711(2)	0.037(1)	0.036(1)	0.0304(9)	0.0027(8)	0.0111(8)	-0.0003(8)
C(11)	4e	0.3773(1)	0.4457(3)	0.9128(2)	0.042(1)	0.039(1)	0.0306(9)	-0.0069(8)	0.0077(8)	-0.0001(9)
C(12)	4e	0.4112(1)	0.5572(3)	0.8350(2)	0.041(1)	0.030(1)	0.040(1)	-0.0057(8)	0.0053(8)	-0.0026(8)
C(13)	4e	0.4018(1)	0.4924(3)	0.7169(1)	0.0289(9)	0.030(1)	0.035(1)	0.0040(8)	0.0053(7)	0.0001(8)
C(14)	4e	0.0261(1)	-0.8502(3)	0.6400(2)	0.038(1)	0.035(1)	0.050(1)	-0.0007(9)	0.0087(9)	-0.0066(9)
C(15)	4e	0.4390(1)	0.6062(3)	0.6293(2)	0.044(1)	0.043(1)	0.048(1)	0.0070(9)	0.0119(9)	-0.0099(9)

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