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Convenient way of synthesis and crystal structure of 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine, a histamine H_4 receptor antagonist

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Abstract

1-[(5-Chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine (JNJ 7777120) is the known histamine H_4 receptor reference compound. The convenient way of its synthesis and the crystal structure are described.

Keywords: 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine (JNJ 7777120); 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate; amide formation; crystal structure; histamine H_4 antagonist.

Introduction

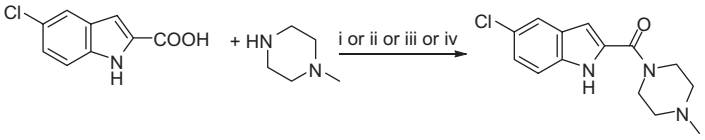
The histamine H_4 receptor (H_4R) was independently discovered in 2000 by a few groups (Oda et al., 2000; Liu et al., 2001; Morse et al., 2001; Nguyen et al., 2001; Zhu et al., 2001). The receptor H_4R shows homology with H_3R (58% for the transmembrane regions and 35% for overall) and is widely expressed in cells involved in immune response and inflammation (Parsons and Ganellin, 2006). Anti-H_4R ligands have been proposed to be useful in anti-inflammatory and immune modulating therapy (Dambaj et al., 2007; Zhang et al., 2007; Zampeli and Tiligada, 2009). 1-[(5-Chloro-1*H*-indol-2-yl) carbonyl]-4-methylpiperazine (JNJ 7777120) was described by Johnson&Johnson in 2003 (Jablonowski et al., 2003) as the first orally active, potent and selective H_4R antagonist. JNJ 7777120 displays a K_i value of 4 nM for the human H_4R, oral bioavailability of ~30% in rats, and 100% in dogs. JNJ 7777120 has become a commonly used H_4 antagonist for probing the physiological role of H_4R. For example, JNJ 7777120 has been reported to have anti-inflammatory activity *in vivo* (Thurmond et al., 2004), has shown inhibition of pruritus (Dunford et al., 2007), and has exhibited antinociception in animal models of inflammatory and neuropathic pain (Hsieh et al., 2010). The synthesis of JNJ 7777120 has been described by Jablonowski et al. (2003) (Scheme 1). In this method, 5-chloroindole-2-carboxylic acid was coupled with *N*-methylpiperazine in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU), 1-hydroxy-7-azabenzotriazole (HOAT), and *N*,*N*-diisopropylethylamine (DIPEA) in *N*,*N*-dimethylforamide (DMF).

Results and discussion

The reagents mentioned above are expensive and in this paper we report a new and more convenient way of preparation of the target compound. Thus, coupling reagents used were 1,1´-carbonyldiimidazole (CDI) (Paul and Anderson, 1960) (Scheme 1) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate (DMT/NMM/BF_4) (Kamiński et al., 2005) (Scheme 1). Because the crystal structure of JNJ 7777120 was not found in CSD (Allen and Motherwell, 2002), it was also solved.

The initial experiment was performed according to Jablonowski et al. (2003) with CDI in tetrahydrofuran (THF) solution. Purification of the crude product by column chromatography gave JNJ 7777120 in 39% yield. As the obtained yield was lower than 54% reported by Jablonowski et al. (2003), it was decided to use DMT/NMM/BF_4 as the coupling reagent (Kamiński et al., 2005). The crude product JNJ 7777120 was isolated in 81% yield after removal of the solvent. The ^{1}H NMR spectrum showed high purity of the obtained compound, even without any further purification. Then, the product JNJ 7777120 was synthesized again in the presence of CDI but this time in acetonitrile instead of THF. The experiments were conducted three times and, after crystallization, the yields ranged from 35% to 49%. The ^{1}H NMR spectrum and elemental analysis confirmed high purity of the compound, which allowed performance of crystallographic studies.

The results of X-ray structure analysis of 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine are shown in Figure 1. The structure independent unit consists of three molecules (A, B, and C) not fitting to each other exactly. From analysis of the geometrical details (Table 1), it is clear that these discrepancies in the structure of the three molecules are caused by rotary motion of piperazine and indole moieties around C7-N4 and C8-C7 bonds, respectively. Thus, three slightly



(i) HATU, HOAT, DIPEA, DMF, r.t. 48 h
(ii) (a) acid, CDI, THF, r.t. 1.5 h; (b) *N*-methylpiperazine, 0°C 0.5 h, r.t. 48 h
(iii) (a) acid, DMT/NMM/BF_4, CH_3CN, 0°C 1 h to 2.5 h; (b) *N*-methylpiperazine, 0°C 2 h, r.t. 24 h
(iv) (a) acid, CDI, CH_3CN, r.t. 1 h to 3 h; (b) *N*-methylpiperazine, 0°C 0.5 h, r.t. 48 h

Scheme 1 Synthetic routes to 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine.

altered arrangements of both rings with regard to central and planar amide group of C8-C7(O7)-N4 are 'frozen' in the structure. In the crystal, two types of dimers are arranged by means of three topologically analogous hydrogen bonds of N-H…O type (Figure 2). The first centrosymmetric dimer connects two B molecules by N16′-H16′…O7′=2.851(2) Å hydrogen bonds. The second non-centrosymmetric dimer is based on two different molecules of A and C and the following two hydrogen bonds: N16-H16…O7″=2.834(2) Å and N16″-H16″…O7=2.884(2) Å.

Conclusions

Two convenient methods of the synthesis of JNJ 7777120 are described. The most proficient synthesis involves the use of DMT/NMM/BF_4 as the coupling reagent, affording JNJ 7777120 in 81% yield. The preparation in the presence of CDI as the coupling reagent is less efficient. Both methods afford pure product and are cheaper than the method based on the use of HATU and HOAT. The 3-D properties of the examined compound are also described based on the X-ray structure analysis results.

Experimental section

Melting points are uncorrected and recorded on MEL-TEMP (Electrothermal). ^{1}H-NMR spectra were recorded on a Varian Mercury 300 (300 MHz) spectrometer.

Synthesis of 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine in the presence of CDI in THF

A mixture of CDI (0.35 g, 2.14 mmol) and 5-chloroindole-2-carboxylic acid (0.42 g, 2.14 mmol) in dry THF (5.0 ml) was stirred at room temperature for 1.5 h. The resultant solution was cooled to 0°C and treated dropwise with *N*-methylpiperazine (0.20 g, 2 mmol) in dry THF (5 ml). The mixture was stirred at 0°C for 0.5 h and then at room temperature for 48 h. Then the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate

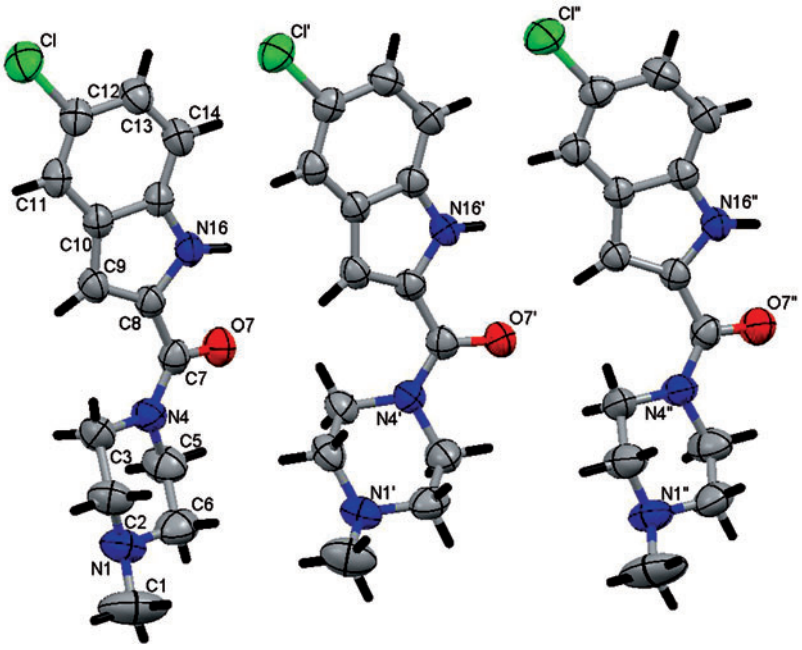


Figure 1 ORTHEP drawing for A, B, and C independent molecules of 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine.

Table 1 Selected geometrical details describing three independent molecules (A, B, and C) of 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine.

	A	B	C
Distance piperazine/indole (Å)	6.073	5.830	5.963
Angle piperazine/indole (°)	37.7	36.4	45.5
C8-C7-N4-C3 (°)	-2.9 (3)	5.2 (3)	1.5 (3)
N16-C8-C7-N4 (°)	165.3 (2)	-166.1 (2)	156.9 (2)
C8-C7 (Å)	1.482 (3)	1.482 (3)	1.484 (3)
C7-O7 (Å)	1.239 (3)	1.241 (3)	1.240 (3)
C7-N4 (Å)	1.345 (3)	1.342 (3)	1.338 (3)

(20 ml), washed with 1 M HCl (20 ml), saturated $NaHCO_3$ (20 ml), water (20 ml), brine (saturated solution of NaCl in water, 20 ml), and dried with Na_2SO_4. After concentration on a rotary evaporator, the residue was purified by silica gel column chromatography. The eluent was composed of CH_2Cl_2/CH_3OH (95:5) with eight drops of 25% ammonium hydroxide for 100 ml of solution. The yield was 0.22 g (39%) of light yellowish crystals; mp 189–190°C.

^{1}H-NHR ($CDCl_3$): δ 9.32 (br s, 1H, indole-1-*H*), 7.61 (d, *J*=2.0 Hz, 1H, indole-4-*H*), 7.34 (d, *J*=9.5 Hz, 1H, indole-7-*H*), 7.23 (d, *J*=2.0 Hz, 1H, indole-6-*H*), 6.70 (d, *J*=2.8 Hz, 1H, indole-3-*H*), 3.94 (br m, 4H, piperazine-1,6-*H*), 2.51 (t, *J*=5.1 Hz, 4H, piperazine-3,5-*H*), 2.35 (s, 3H, C*H*$_3$).

Synthesis of 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine in the presence of DMT/NMM/BF_4 in acetonitrile

A solution of DMT/NMM/BF_4 (0.33 g, 1 mmol) in absolute acetonitrile (5 ml) was cooled to 0°C, stirred, and treated with 5-chloroindole-2-carboxylic acid (019 g, 1 mmol) and *N*-methylmorpholine (0.11 ml, 1 mmol). The stirring was continued at 0°C for 2.5 h until the coupling reagent was consumed according to the TLC analysis [Merck silica gel, mobile phase CH_2Cl_2, visualization with 0.5% 4-(4-nitrobenzyl)pyridine in ethanol]. Then *N*-methylpiperazine (0.10 g, 1 mmol) was added and stirring of the mixture was continued for 2 h at 0°C and 24 h at room temperature. The solvent was removed under reduced pressure and the solid residue was dissolved in CH_2Cl_2. The solution was washed successively with water, saturated sodium bicarbonate and water again, dried with anhydrous $MgSO_4$, and then concentrated yielding light yellowish crystals (0.23 g, 81%); mp 189–190°C.

Synthesis of 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine in the presence of CDI in acetonitrile

A suspension of 5-chloroindole-2-carboxylic acid (1.02 g, 5.2 mmol) and CDI (0.84 g, 5.2 mmol) in 6 ml of absolute acetonitrile was stirred at room temperature for 3 h. The resultant solution was cooled to 0°C and treated dropwise with *N*-methylpiperazine (0.50 g, 5 mmol). The mixture was stirred at this temperature for 30 min and then at room temperature for 48 h. The precipitated solid product was filtered and crystallized from acetonitrile in the presence of activated carbon for decolorization yielding 1.03 g (49%) of light yellowish crystals; mp 189–190°C.

X-ray crystallographic study

Crystal data for 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine $C_{14}H_{16}N_3OCl$, M=277.75, monoclinic, space group $P2_1/n$, a=14.5725(10) Å, b=16.6208(12) Å, c=17.9608(13) Å, β=106.606(1)°, V=4168.8(5)Å^3, Z=12, D_x=1.328 g cm^{-3}, T=293 K, μ=0.271 mm^{-1}, λ=0.71073 Å, data/parameters=7381/517; final R_1=0.0391.

Crystals of JNJ7777120 were obtained by slow concentration (evaporation) of an acetonitrile solution. X-ray measurements of the crystals were performed on a SMART diffractometer with graphite-monochromated Mo Kα radiation (λ=0.71073 Å) at room temperature. The structures were solved by direct methods and refined with

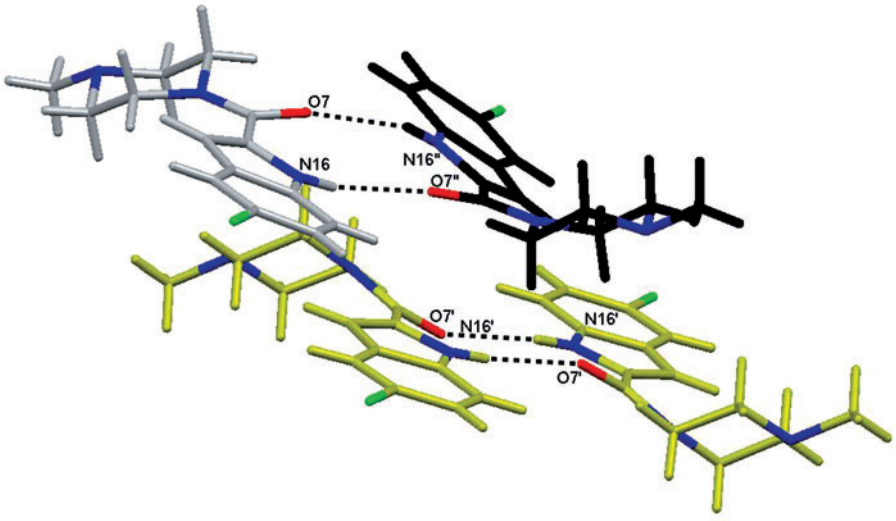


Figure 2 Two dimers in the structure of 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine created by H-bonds: centrosymmetric dimer (with two yellow B molecules), and non-centrosymmetric dimer (joining gray A molecule and black C molecule).

SHELXTL (Sheldrick, 2008). E-maps provided positions for all non-H-atoms. The full-matrix least-squares refinement was carried out on F^2s using anisotropic temperature factors for all non-H-atoms. All C-bound H-atoms were placed in idealized locations and refined using a riding model, with C-H=0.93 Å and $U_{iso}(H)=1.2U_{eq}(C)$. Crystallographic data for compound JNJ 7777120 (excluding structural factors) have been deposited at the Cambridge Crystallographic Data Center and allocated with the deposition number CCDC 798207. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, UK (Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk).

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Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

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