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Synthesis, Characterization of 3-(Bromomethyl)-2-cyclopropyl-4-(4-fluorophenyl)quinoline and Its Crystal Structure

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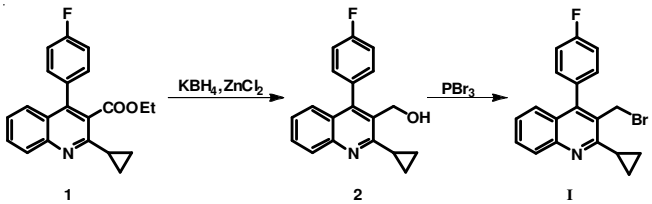
3-(Bromomethyl)-2-cyclopropyl-4-(4-fluorophenyl)quinoline (**I**), an important intermediate to synthesize pitavastatin calcium. It was prepared from ethyl 2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-carboxylate *via* reduction by $KBH_4/ZnCl_2$ and then bromide by PBr_3. The product was characterized by NMR and LC-MS. The crystal structure of compound **I** was investigated using X-ray diffraction and SHELXTL-97 software. The result indicated that compound **I** crystallized in the triclinic system, space group P-1 with a = 9.6150(19), b = 9.868 (2), c = 10.060(2) Å, V = 783.3 (4) Å^3; Z 2.

Keywords: 3-(Bromomethy)-2-cyclopropy-4-(4-fluorophenyl)quinolone, Synthesis, Characterization, Crystal structure.

INTRODUCTION

Pitavastatin calcium, a new treatment of high cholesterol statins[1,2]. It is used as HMG CoA reductase inhibitor by Nissan Chem Corporation and sold in Japan in 2003. It was proved to be a kind of long duration, good tolerance and high security drug to treat hyperlipidemia and high cholesterol statins, which have a broad market prospect.

3-(Bromomethyl)-2-cyclopropyl-4-(4-fluorophenyl)-quinoline(**I**) is widely concerned as the most important intermediate to synthesize pitavastatin calcium[3]. Now, some synthetic routes are reported about (**I**) in the literatures, such as, (**I**) could be prepared from 2-cyclopropyl-4-(4-fluorophenyl)-3-methylquinoline by NBS bromide in MeCN and CCl_4. But the yield is not high. Herein, we report the synthesis of (**I**) from ethyl 2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-carboxylate (**1**) with an overall yield of about 58.5 %. Meanwhile, the crystal structure of (**I**) was also investigated. The synthetic route of compound **I** was presented as **Scheme-I**.



1 2 I

Scheme-I: Route for the synthesis of compound **I**

EXPERIMENTAL

Ethyl 2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-carboxylate (**1**) was supplied by Well Chemical Co. Ltd of Jiangsu (Yancheng, People's Republic of China), its mass content is 98.5 % determined by GC. KBH_4, $ZnCl_2$ and PBr_3 was supplied by Sinopharm Chemical Reagent Co. Ltd of China. All other chemicals were of reagent grade and used without purification as received.

^{1}H NMR spectrum was obtained with Bruker AV-500 spectrometer at 500.13 MHz and measured in CD_3OD solution at 25 ± 0.5 °C. The sample was dissolved in a 5 mm diameter tube at a concentration of 20 mg/mL. X-ray diffraction was performed on a Bruker APEXII CCD diffractometer. Mass spectrum of (**I**) was analyzed using Trace DSQ LC/MS (Thermo Electron Co., USA).

Synthesis of compound I: In a 2 L four-necked flask, THF (30 mL), $ZnCl_2$ (3.15 g, 0.023 mol) and KBH_4 (2.45 g, 0.045 mol) were added, stirred for 2 h at room tempeature. ethyl 2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-carboxylate (**1**) (4.9 g, 0.015 mol) was dissolved in toluene and then it was added into the reaction vessel. The reaction system was heated slowly to the refluxing temperature. After 20 h, the system was cooled and filtered. The filter cake was washed and extracted by toluene. The organic layer was combined and washed with 0.1 mol/L sodium hydroxide solution and saturated brine until neutral. The product was collected by

evaporating the solvent under reduced pressure and recrystallized from a mixture of toluene. Compound **2** was obtained in the form of a white powder (2.8 g, 65 %, m.p. 129-130 °C).

Phosphorus tribromide (0.8 mL, 8.5 mmol) is added slowly to a solution of the compound **2** (1.25 g, 4.25 mmol) in dichloromethane (30 mL). Stirring is carried out in the ice bath for 4 h and 150 mL of water are then added. The remaining solution was washed by saturated sodium bicarbonate solution until pH is 8. Product was extracted with ethyl acetate and the organic phase is separated off and dried (using Na_2S0_4). The product was collected by evaporating the solvent under reduced pressure and recrystallized from a mixture of ethanol. By that means, 1.35 g (90 %, m.p. 133-135 °C) of the bromide (**I**) can be obtained in the form of a brown powder.

Crystals of **I** that suitable for X-ray diffraction were obtained by slow evaporation of 1,2-dichloroethane solution of **I**.

X-ray crystallography: A colourless block-like crystal of compound (**I**) grown in 1,2-dichloroethane with dimensions of 0.20 × 0.10 × 0.10 mm was used for structural determination. Diffraction data were collected on a Bruker APEXII CCD diffractometer by using graphite monochromated MoK_α radiation (λ = 0.71073 Å). The structure was solved by direct methods with SHELXS-97 and refined on the F^2 by full-matrix least-squares method with SHELXL-97. All non-hydrogen atoms were refined anisotropically[4-6].

RESULTS AND DISCUSSION

Identification of resonance in the spectra: ^{1}H NMR and LC-MS spectra of purified compound **I** were presented in Fig. 1.

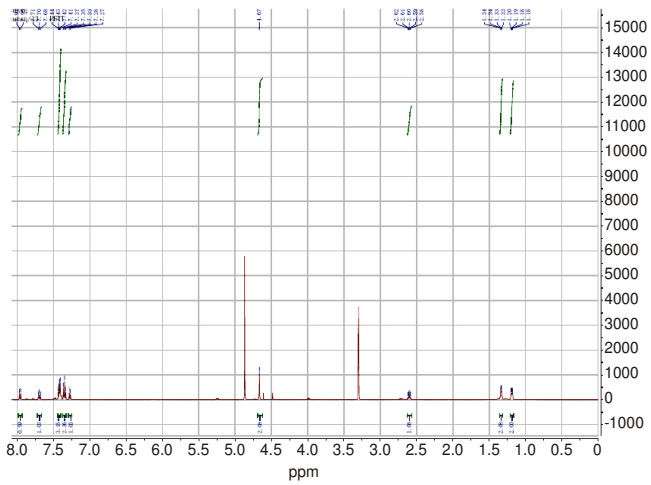


Fig. 1. ^{1}H NMR spectrum of compound **I**

In the ^{1}H NMR of Compound **I**, the peak at 4.67 ppm was ascribed to the proton of methylene which was substituted by atom Br. ^{1}H NMR-(CD_3OD): δ 1.19 (2H, m), 1.33 (2H, m), 2.58-2.62 (1H, m), 4.67 (2H, s), 7.27-7.44 (6H, m), 7.70 (1H, m), 7.90 (1H, m).

In the LC spectrum peak at 32.619 min ascribed to the Compound **I** (Fig. 2). In the MS spectrum, the existence of the peaks at right end showed the Compound **I**, *m/z* 355.75 was ascribed to molecular ion peak (M^+).

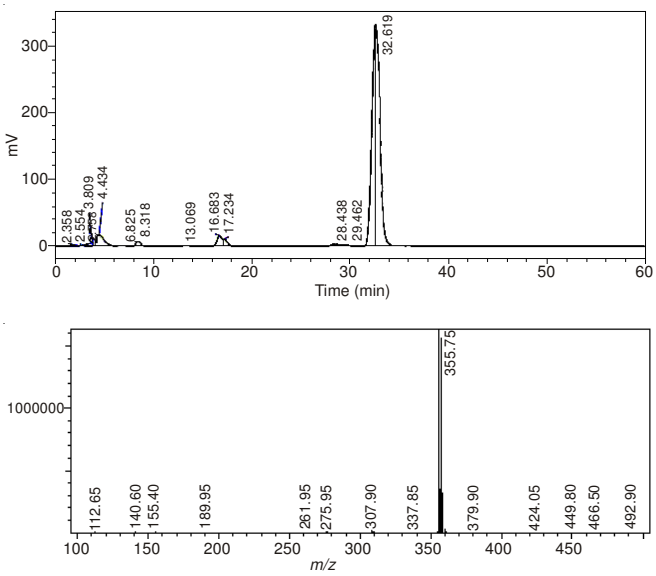


Fig. 2. LC-Mass spectrum of compound **I**

The crystal configuration of compound **I** was confirmed by X-ray structural analysis. X-ray data collection were presented in Table-1 and the geometric parameters for compound **I** were listed in Table-2. Molecular structure and packing plot of compound **I** were showed in Figs. 3 and 4, respectively.

TABLE-1
CRYSTALLOGRAPHIC DATA FOR COMPOUND (**I**)

ITEM	Data or Description
Formula	$C_{19}H_{15}BrFN$
Formula weight	356.22
Temperature (K)	293 (2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
a (Å)	9.6150(19)
b (Å)	9.868(2)
c (Å)	10.060(2)
Volume (Å^3)	783.3(4)
Z	2
Calculated density (g/cm^3)	1.510
Absorption coefficient (mm^{-1})	2.630
F(000)	360.0
Crystal size (mm)	0.20 × 0.10 × 0.10
Theta range for data collection (°)	2.17 to 25.83
Reflections collected/unique	2866 /1420 [R(int) = 0.0629]
Completeness to theta = 25.38 (%)	99.8
Max. and min. transmission	0.621 and 0.779
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1420/0/199
Goodness-of-fit on F^2	1.003
Final R indices [I>2σ(I)]	R1 = 0.0629, wR2 = 0.1679
R indices (all data)	R1 = 0.1415, wR2 = 0.1407
Largest diff. peak and hole (e. Å^{-3})	0.31 and -0.45

According to the data from X-ray crystallographic analysis, compound **I** crystallized in a P-1 space group of the triclinic system[7,8]. All H atoms were positioned geometrically and constrained to ride on their parent atoms, with C-H = 0.93 Å for aromatic H. Other H atoms were positioned geometrically and refined using a riding model, with C-H = 0.96 Å for alkyl H, with Uiso(H) = 1.2 Ueq(C) for aromatic H and Uiso(H)

TABLE-2
GEOMETRIC PARAMETERS FOR COMPOUND **I**

Bond	Distance (Å)	Bond	Distance (Å)
Br-C19	1.958 (6)	C8-C9	1.367 (8)
N-C4	1.314 (6)	C8-H8A	0.9300
N-C5	1.364 (6)	C9-C10	1.394 (7)
C1-C2	1.422 (10)	C9-H9A	0.9300
C1-C3	1.473 (9)	C10-C11	1.448 (7)
C1-H1A	0.9700	C11-C12	1.357 (7)
C1-H1B	0.9700	C11-C13	1.519 (7)
F-C16	1.364(6)	C12-C19	1.439(7)
C2-C3	1.460(8)	C13-C14	1.373(8)
C2-H2A	0.9700	C13-C18	1.375(8)
C2-H2B	0.9700	C14-C15	1.391(8)
C3-C4	1.496(8)	C14-H14A	0.9300
C3-H3A	0.9800	C15-C16	1.361(8)
C4-C12	1.422(7)	C15-H15A	0.9300
C5-C10	1.414(7)	C16-C17	1.342(8)
C5-C6	1.418(7)	C17-C18	1.390(8)
C6-C7	1.345(8)	C17-H17A	0.9300
C6-H6A	0.9300	C18-H18A	0.9300
C7-C8	1.412(8)	C19-H19B	0.9700
C7-H7A	0.9300	C19-H19C	0.9700
Angle	**Data** (º)	**Angle**	**Data** (º)
C4-N-C5	118.0 (4)	C8-C9-H9A	119.6
C2-C1-C3	60.5 (5)	C10-C9-H9A	119.6
C2-C1-H1A	117.7	C9-C10-C5	119.2 (5)
C3-C1-H1A	117.7	C9-C10-C11	124.6 (5)
C2-C1-H1B	117.7	C5-C10-C11	116.2 (5)
C3-C1-H1B	117.7	C12-C11-C10	119.2 (5)
H1A-C1-H1B	114.8	C12-C11-C13	121.9 (5)
C1-C2-C3	61.5 (5)	C10-C11-C13	118.9 (5)
C1-C2-H2A	117.6	C11-C12-C4	119.5 (5)
C3-C2-H2A	117.6	C11-C12-C19	120.6 (5)
C1-C2-H2B	117.6	C4-C12-C19	119.9 (5)
C3-C2-H2B	117.6	C14-C13-C18	119.5(5)
H2A-C2-H2B	114.7	C14-C13-C11	120.1(5)
C2-C3-C1	58.0(4)	C18-C13-C11	120.4(5)
C2-C3-C4	120.3(6)	C13-C14-C15	120.2(6)
C1-C3-C4	119.5(5)	C13-C14-H14A	119.9
C2-C3-H3A	115.6	C15-C14-H14A	119.9
C1-C3-H3A	115.6	C16-C15-C14	118.0(6)
C4-C3-H3A	115.6	C16-C15-H15A	120.1
N-C4-C12	123.3(5)	C14-C15-H15A	120.1
N-C4-C3	116.1(5)	C17-C16-C15	123.7(5)
C12-C4-C3	120.6(5)	C17-C16-F	118.8(6)
N-C5-C10	123.8(5)	C15-C16-F	117.4(6)
N-C5-C6	117.9(5)	C16-C17-C18	117.9(6)
C10-C5-C6	118.3(5)	C16-C17-H17A	121.1
C7-C6-C5	121.7(5)	C18-C17-H17A	121.1
C7-C6-H6A	119.1	C13-C18-C17	120.7(6)
C5-C6-H6A	119.1	C13-C18-H18A	119.6
C6-C7-C8	119.5(6)	C17-C18-H18A	119.6
C6-C7-H7A	120.3	C12-C19-Br	110.9(4)
C8-C7-H7A	120.3	C12-C19-H19B	109.5
C9-C8-C7	120.5(6)	Br-C19-H19B	109.5
C9-C8-H8A	119.8	C12-C19-H19C	109.5
C7-C8-H8A	119.8	Br-C19-H19B	109.5
C8-C9-C10	120.8(5)	H19B-C19-H19C	108.0
C1-C2-C3-C4	-107.9(7)	C10-C11-C12-C4	-0.1(8)
C2-C1-C3-C4	109.3(7)	C13-C11-C12-C4	-177.8(5)
C5-N-C4-C12	-0.7(8)	C10-C11-C12-C19	-179.5(5)
C5-N-C4-C3	179.9(5)	C13-C11-C12-C19	2.8(8)
C2-C3-C4-N	34.6(9)	N-C4-C12-C11	0.7(9)
C1-C3-C4-C12	147.2(7)	C3-C4-C12-C19	-0.5(8)
C4-N-C5-Cl0	0.1(8)	C12-C11-C13-C14	-101.2(6)
C4-N-C5-C6	179.0(5)	C10-C11-C13-C14	81.1(7)
N-C5-C6-C7	179.1(5)	C12-C11-C13-C18	76.5(7)
C10-C5-C6-C7	-2.0(8)	C10-C11-C13-C18	-101.2(6)

C5-C6-C7-C8	1.1(9)	C18-C13-C14-C15	-2.2(8)
C6-C7-C8-C9	0.3(10)	C11-C13-C14-C15	175.5(5)
C7-C8-C9-C10	-0.7(10)	C13-C14-C15-C16	0.5(9)
C8-C9-C10-C5	-0.2(9)	C14-C15-C16-C17	1.6(10)
C8-C9-C10-C11	179.8(5)	C14-C15-C16-F	-178.5(5)
N-C5-C10-C9	-179.6(5)	C15-C16-C17-C18	-1.9(9)
C6-C5-C10-C9	1.5(8)	F-C16-C17-C18	178.2(5)
N-C5-C10-C11	0.4(8)	C14-C13-C18-C17	1.9(9)
C6-C5-C10-C11	-178.5(5)	C11-C13-C18-C17	-175.8(5)
C9-C10-C11-C12	179.6(5)	C16-C17-C18-C13	0.1(9)
C5-C10-C11-C12	-0.3(7)	C11-C12-C19-Br	-101.2(5)
C9-C10-C11-C13	-2.6(8)	C4-C12-C19-Br	79.4(6)
C5-C10-C11-C13	177.4(5		

Symmetry code: (i) x, y, z (ii) -x, -y, -z

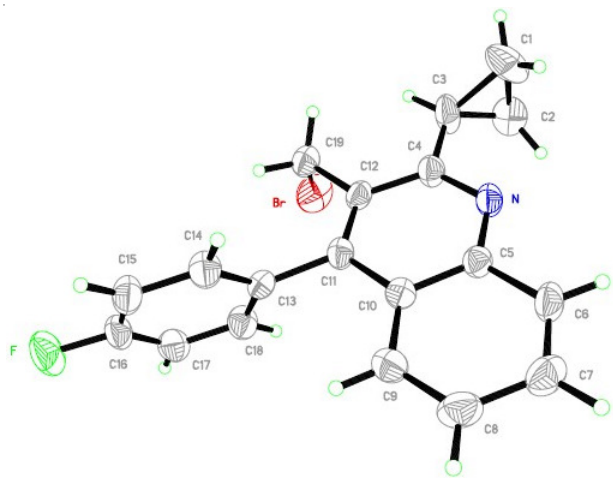


Fig. 3. General appearance of Compound **I** with the atoms represented by thermal vibration ellipsoids of 50 % probability

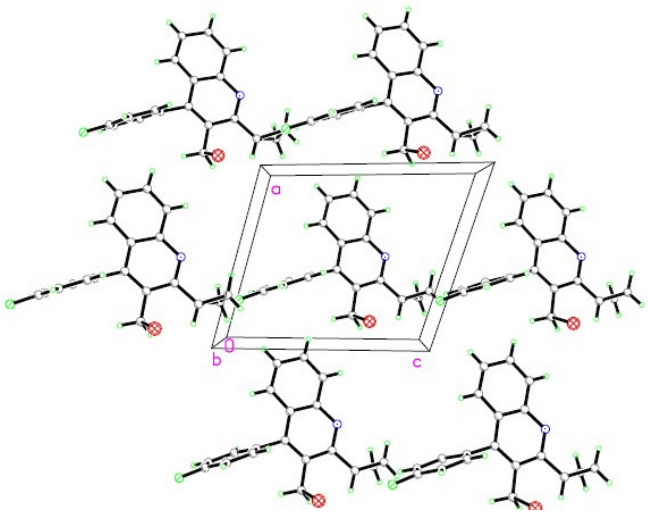


Fig. 4. Packing diagram for Compound **I**

= 1.5 Ueq(C) for other H. There are no intramolecular and intermolecular hydrogen bonds in the structure. Unit cell parameters: a = 9.6150(19), b = 9.868 (2), c = 10.060(2) Å, V = 783.3(4) Å^3; Z = 2.

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