Research Article

Synthesis, Crystal Structure, and Theoretical Studies of N-(4-((4-chlorobenzyl)oxy)phenyl)-4-(trifluoromethyl)pyrimidin-2-amine

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The title compound ($C_{18}H_{13}ClF_3N_3O$) were synthesized and recrystallized from CH_3OH . The compound was characterized by 1H NMR, MS, HRMS, and X-ray diffraction. The compound crystallized in the monoclinic space group $P2(1)/n$ with $a = 8.2354$ (14), $b = 12.686$ (2), $c = 16.633$ (3) Å, $\alpha = 90^\circ$, $\beta = 97.951$ (3), $\gamma = 90^\circ$, $V = 1721.0$ (5) Å³, $Z = 4$, and $R = 0.0376$ for 1933 observed reflections with $I > 2\sigma(I)$. X-ray analysis reveals that intermolecular N-H...N interactions exist in the adjacent molecules. Theoretical calculation of the title compound was carried out with HF/6-31G (d,p), B3LYP/6-31G (d,p). The full geometry optimization was carried out using 6-31G (d,p) basis set and the frontier orbital energy. The optimized geometric bond lengths and bond angles obtained by using HF and DFT (B3LYP) showed the best agreement with the experimental data.

1. Introduction

Heterocyclic compounds are commonly used as scaffolds on which pharmacophores are arranged to provide potent and selective medicines or pesticides [1–3]. Usually, pyrimidine and their derivatives have been proved to be effective biological activities [4]. Some of them had been developed to commercial agrochemicals and medicines, such as Sulfo-meturon-Methyl, Bensulfuron-Methyl, Chlorimuron-Ethyl, Pyrazosulfuron-Ethyl, Nicosulfuron, Flazasulfuron, Azimsulfuron, Primisulfuron-Methyl, Amidosulfuron, Flumetsulam, Metosulam, diclosulam, florasulam, Penoxsulam, and 5-FU. Also phenoxy group always exhibited diversity activities, such as antibacterial, antifungal, anti-HIV, antioxidant, and anti-inflammatory activities [5, 6].

In view of these facts mentioned above, and also as a part of our work on the synthesis of bioactive lead compounds for drug discover, the title compounds were designed, synthesized, and characterized by 1H NMR, FTIR, MS, and HRMS. The single crystal structure of the title compound was determined by X-ray diffraction.

2. Results and Discussion

2.1. Synthesis and Spectra. The 1-chloro-4-((4-nitrophenoxymethyl)benzene was synthesized easily from the starting materials 4-nitrophenol and 1-chloro-4-(chloromethyl)benzene with mild condition. The 1-chloro-4-((4-nitrophenoxymethyl)benzene was reduced by Raney Ni to regarding 4-((4-chlorobenzyl)oxy)aniline. We also used Fe/HCl, $SnCl_2$ to reduce, but the yield and purity are low. In the process of title compound, some conditions were tried, but the reaction can not work, such as different base (K_2CO_3 , NaOH, Et_3N , NaH), different solvent (EtOH, THF, Acetone), and different reaction temperature. Surprisingly, it is reported that acid can synthesize N-phenylpyrimidin-2-amine. So the title compound was synthesized under the catalyst 4-methylbenzenesulfonic acid. The proton magnetic resonance spectra of the title compound have been recorded in $CDCl_3$. The NH proton of chemical shift is at δ 7.24 as a singlet. The signal of CH_2 protons was observed at δ 5.02 ppm as a singlet. The chemical shifts at 8.58 and 6.97 ppm are the proton of pyrimidine. The ESI-MS spectrum showed that the m/z of

TABLE 1: Selected bond lengths [$\text{\AA}$] and theoretical calculations for the title compound.

Bond	X-ray crystal	HF	DFT
Cl(1)–C(3)	1.736 (2)	1.744	1.759
O(1)–C(8)	1.370 (2)	1.354	1.370
O(1)–C(7)	1.413 (2)	1.401	1.420
N(1)–C(14)	1.350 (3)	1.352	1.365
N(1)–C(11)	1.411 (3)	1.412	1.410
N(2)–C(15)	1.317 (3)	1.305	1.325
N(2)–C(14)	1.353 (3)	1.340	1.359
N(3)–C(17)	1.325 (3)	1.318	1.334
N(3)–C(14)	1.336 (3)	1.319	1.342
C(1)–C(6)	1.373 (3)	1.390	1.400
C(1)–C(2)	1.379 (3)	1.383	1.393
C(8)–C(13)	1.372 (3)	1.383	1.402
C(8)–C(9)	1.381 (3)	1.391	1.397
C(15)–C(16)	1.386 (3)	1.395	1.402
C(16)–C(17)	1.363 (3)	1.371	1.387
C(17)–C(18)	1.503 (3)	1.514	1.518
C(18)–F(2)	1.301 (8)	1.322	1.346

TABLE 2: Selected bond angles [$^\circ$] and theoretical calculations for the title compound.

Angle	X-ray crystal	HF	DFT
C(8)–O(1)–C(7)	117.89 (16)	119.754	118.259
C(14)–N(1)–C(11)	127.94 (18)	130.245	132.287
C(15)–N(2)–C(14)	115.91 (18)	116.704	116.152
C(17)–N(3)–C(14)	115.80 (18)	116.592	115.998
C(6)–C(1)–C(2)	120.8 (2)	120.784	120.858
C(4)–C(3)–Cl(1)	120.1 (2)	119.560	119.483
C(1)–C(6)–C(7)	119.9 (2)	120.999	120.812
O(1)–C(7)–C(6)	108.99 (17)	109.037	108.863
O(1)–C(8)–C(9)	115.84 (18)	115.904	125.197
C(13)–C(8)–C(9)	119.17 (19)	119.071	119.092
C(12)–C(11)–N(1)	118.26 (18)	117.364	116.555
N(3)–C(14)–N(1)	119.37 (19)	120.361	120.410
N(3)–C(14)–N(2)	125.20 (19)	125.137	125.685
N(2)–C(15)–C(16)	123.8 (2)	123.320	123.299
N(3)–C(17)–C(18)	114.1 (2)	114.203	114.515

molecular ion was 381, according to its molecular formula $\text{C}_{13}\text{H}_{12}\text{F}_3\text{N}_5$. The elemental analysis result is according to the calculated results.

2.2. Crystal Structure. The selected bond lengths and bond angles are shown in Tables 1 and 2. The molecular structure of the title compound is shown in Figure 1. The molecular packing of the molecule is shown in Figure 2. The hydrogen-bond distances ($\text{\AA}$) of the title compound are listed in Table 3.

The title compound consists of pyrimidine ring and two benzene rings according to X-ray single-crystal structure determination. Generally, the average bond lengths and bond angles of ring system (phenyl and pyrimidine) are normal

TABLE 3: Hydrogen-bond distance ($\text{\AA}$) of the title compound.

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(1)–H(1)...N(2)#1	0.86	2.23	3.071(2)	167.7

Symmetry transformations used to generate equivalent atoms: #1 $-x + 1, -y + 1, -z$.

TABLE 4: Total energy and frontier orbital energy.

	DFT	HF
$E_{\text{total}}/\text{Hartree}^b$	–1692.951	–1685.229
$E_{\text{HOMO}}/\text{Hartree}$	–0.200	–0.287
$E_{\text{LUMO}}/\text{Hartree}$	–0.058	0.088
$\Delta E^a/\text{Hartree}$	0.142	0.375

^a $\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$.

^b1 Hartree = $4.35974417 \times 10^{-18}$ J = 27.2113845 eV.

ranges. The C14–N1 bond [1.350 (3) $\text{\AA}$] is shorter than the general C–N bond length of 1.47 $\text{\AA}$, but it is similar to the bond (N(2)–C(14) (1.353 (3) $\text{\AA}$), N(3)–C(14) (1.336 (3) $\text{\AA}$), C(10)–C(11) (1.388 (3) $\text{\AA}$), C(11)–C(12) (1.380 (3) $\text{\AA}$). It is indicated that the C–N–C form a p - π conjugated with pyrimidine and benzene ring. The bond angle of C5–N2–C6 is 102.82 ($^\circ$). In Tables 1 and 2, it can be easily seen that DFT and HF have good coherence with the crystal diffraction. Only the bond length of C3–C4 > C2–C3 > C1–C2 is different with the calculation structure. The torsion angle of ether group C8–O1–C7–C6 is 173.68 ($^\circ$).

As shown in Figure 1, the pyrimidine ring (C14, N2, C14, C16, C17, N3) and two phenyl ring (C1, C2, C3, C4, C5, C6 and C12, C13, C14, C15, C16, C17) are fairly planar with plane equation $7.475x + -4.398y + 1.810z = 1.3485$ ($7.233x + -3.932y + 3.978z = 2.1245$ and $4.729x + -4.552y + 10.801z = 0.5328$), and the largest deviation from the least squares plane is 0.0023 nm (0.0010 nm and 0.0031 nm). Also the pyrimidine ring is nearly planar with phenyl ring (C1, C2, C3, C4, C5, C6) with the dihedral angle of 7.8° and two phenyl ring with the dihedral angle of 27.9° , 34.9° .

The title compound has an extensive network of hydrogen bonding. In the ab plane, they are linked together by N–H...N hydrogen bonds. This hydrogen-bonding sequence is repeated to form a ring. The ring is shaped like a decagon and has two N1 and two H1 atoms at the vertices, leading to a hydrogen-bond network defining cyclic motifs denoted R_2^2 (8). The slight discrepancy of crystal structures is probably the consequence of the weakness of this hydrogen bond and van der Waals interactions in the solid-state structure.

2.3. Molecular Total Energies and Frontier Orbital Energy Analysis. Molecular total energy and frontier orbital energy levels are listed in Table 4. It is seen that the results of HF and MP2 methods have good consistency. Energy gap between HOMO and LUMO calculated by B3LYP is smaller than those calculated by HF.

The HOMO and LUMO levels of title compound were deduced using DFT method, as shown in Figure 3. The HOMO and LUMO diagrams of title compound show that

FIGURE 1: The molecular structure of the title compound.

FIGURE 2: The molecular packing of the molecule.

the compound is likely to exhibit an efficient electron transfer from the pyrimidine ring of HOMO to the whole pyrimidine molecular skeleton of LUMO if electronic transitions occur. The HOMO for the title compound is mainly localized at the benzene ring and pyrimidine ring, whereas the LUMO is localized at CF_3 group, benzene ring, and pyrimidine ring. Therefore, when electrons transfer from HOMO to LUMO, the electron density significantly decreases in the electron-donating benzene ring system, accompanied by an increase in the electron density of the electron accepting the whole molecule system.

3. Materials and Methods

3.1. Instruments. Melting points were determined using an X-4 apparatus and uncorrected. ^1H NMR spectra were

measured on a Bruker AV-400 instrument using TMS as an internal standard and CDCl_3 as the solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analysis was performed on a Vario EL elemental analyzer. All the reagents are of analytical grade or freshly prepared before use.

3.2. Theoretical Calculations. According to the above crystal structure, a crystal unit was selected as the initial structure, while HF/6-31G (d, p), DFT-B3LYP/6-31G (d, p), and MP2/6-31G (d, p) methods in Gaussian 03 package [7] were used to optimize the structure of the title compound. Vibration analysis showed that the optimized structures were in accordance with the minimum points on the potential energy surfaces, which means no virtual frequencies, proving that the obtained optimized structures were stable.

FIGURE 3: Frontier molecular orbitals of 5: (a) HOMO of 5; (b) LUMO of 5.

SCHEME 1: The synthetic route of title compound.

All the convergent precisions were the system default values, and all the calculations were carried out on the Nankai Stars supercomputer at Nankai University.

3.3. General Procedure. The title compounds were synthesized according to the route shown in Scheme 1, and the yields were not optimized. The pyrimidine 4 was synthesized according to the references.

To a solution of 4-nitrophenol (15 mmol), K_2CO_3 (2.96 g, 0.02 mol), and KI (0.2 g) in EtOH (15 mL), 1-chloro-4-(chloromethyl)benzene (16 mmol) was added. The resulting mixture was stirred at refluxing for 7 h. After cooling, the precipitate formed was collected after filtration. The pure product 2 was obtained by recrystallization from a mixture of petroleum ether/acetone to give in good yields. White crystal, yield, 84%; mp, 113–114°C. Then the mixture of compound 2 (70 mL), $NH_2NH_2 \cdot H_2O$ (75 mL, 80%), and Raney Ni (0.5 g) was refluxing in methanol, the mixture was filtrated after refluxing 1 h, and the solvent was evaporated to afford white solid. The compound 3 was recrystallization in methanol. Yield, 96%; mp, 109–110°C. 1H NMR (400 MHz, $CDCl_3$), 7.28–7.43 (m, 4H, Ph–H), 6.80 (d, J = 6.6 Hz, 2H, Ph–H), 6.40 (d, J = 6.6 Hz, 2H, Ph–H), 4.95 (s, 2H, OCH_2). To a solution of compound 3 (3.6 mmol) and 4 (3 mmol) in 1,4-dioxane (20 mL), 4-methylbenzenesulfonic acid (0.46 g, 2.4 mmol) was added. The mixture was refluxed for 5 h. After the reaction was completed, the 1,4-dioxane was evaporated and the residue was washed with saturated $NaHCO_3$ solution and extracted several times with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4 , and evaporated. The remainder was purified by chromatography on silica gel using petroleum ether (60–90°C) and ethyl

acetate as the eluent to afford the compound 5. Yellow crystal, yield 79.6%, m.p. 132–133°C, 1H NMR ($CDCl_3$, 400 MHz), δ : 8.58 (d, J = 4.8 Hz, 1H, Pyrimidine–H), 7.49 (d, J = 8.8 Hz, 2H, Ph–H), 7.34–7.38 (m, 4H, Ph–H), 7.24 (br, 1H, NH), 6.97 (s, 1H, Pyrimidine–H), 6.95 (d, J = 9.2 Hz, 2H, Ph–H), 5.02 (s, 2H, OCH_2). MS (ESI), m/z : 381 $[M+H]^+$. Elemental anal. (%), calculated: C, 56.93; H, 3.45; N, 11.06; found: C, 57.05; H, 3.49; N, 11.10.

3.4. Structure Determination. The cube-shaped single crystal of the title compound was obtained by recrystallization from EtOH. The crystal with dimensions of 0.20 mm $\times$ 0.16 mm $\times$ 0.10 mm was mounted on a Rigaku Saturn diffractometer with a graphite-monochromated $MoK\alpha$ radiation (λ = 0.71073 Å) by using a Phi scan modes at 294 (2) K in the range of $2.03^\circ \leq \theta \leq 25.01^\circ$. A total of 8720 reflections were collected, of which 3027 were independent (R_{int} = 0.0376) and 1933 were observed with $I > 2\sigma(I)$. The calculations were performed with SHELXS-97 program [8], and the empirical absorption corrections were applied to all intensity data. The nonhydrogen atoms were refined anisotropically. The hydrogen atoms were determined with theoretical calculations and refined isotropically. The final full-matrix least squares refinement gave R = 0.0419 and wR = 0.1069 ($w = 1/[\sigma^2(F_o^2) + (0.0718P)^2 + 0.0256P]$ where $P = (F_o^2 + 2F_c^2)/3$), S = 1.03, $(\Delta/\sigma)_{max}$ = 0.003, $\Delta\rho_{max}$ = 0.200, and $\Delta\rho_{min}$ = $-0.25 e \text{ Å}^{-1}$. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-Ray Crystallography [9]. A summary of the key crystallographic information was given in Table 5.

TABLE 5: Crystal structure and data refinement parameters.

Empirical formula	$C_{18}H_{13}ClF_3N_3O$
Formula weight	379.76
Temperature	294 (2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
	$a = 8.2354 (14) \text{ Å}$ $\alpha = 90 \text{ deg.}$
Unit cell dimensions	$b = 12.686 (2) \text{ Å}$ $\beta = 97.951 (3) \text{ deg.}$
	$c = 16.633 (3) \text{ Å}$ $\gamma = 90 \text{ deg.}$
Volume	$1721.0 (5) \text{ Å}^3$
Z, calculated density	4, 1.466 Mg/m ³
Absorption coefficient	0.265 mm^{-1}
$F(000)$	776
Crystal size	$0.20 \times 0.16 \times 0.10 \text{ mm}$
Theta range for data collection	2.03 to 25.01 deg.
Limiting indices	$-9 \leq h \leq 8, -12 \leq k \leq 15,$ $-19 \leq l \leq 19$
Reflections collected/unique	8720/3027 [$R(\text{int}) = 0.0376$]
Completeness to theta = 25.01	99.90%
Absorption correction	Semiempirical from equivalents
Max. and min. transmission	0.9740 and 0.9490
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	3027/6/263
Goodness of fit on F^2	1.028
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0419, wR_2 = 0.1069$
R indices (all data)	$R_1 = 0.0784, wR_2 = 0.1302$
Largest diff. peak and hole	0.201 and -0.247 e.Å^{-3}

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Conflict of Interests

The author(s) declare(s) that there is no conflict of interests regarding the publication of this paper.

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