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Synthesis, Characterization and Crystal Structure of (4-Amino-2-ethoxy-5-nitrophenyl)(piperidin-1-yl) methanone

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ABSTRACT

*The biological importance of piperidine and carboxamides derivatives in different disciplines of medicines have received considerable attention owing to their wide range of biological and pharmacological activities. The present study has been carried out on newly synthesized 4-Amino-2-ethoxy-5-nitrophenyl) (piperidin-1-yl) methanone (**3**) by hydrolysis of ester (**1**) to acid (**2**) with sodium hydroxide in methanol and followed by acid-amine coupling with piperidine in presence of HATU, triethylamine to obtain compound (**3**). The newly synthesized, (4-Amino-2-ethoxy-5-nitrophenyl) (piperidin-1-yl) methanone (**3**) is characterized by Mass, IR, ^{1}H & ^{13}C NMR studies. The structure is further confirmed by single crystal XRD data. Compound (**3**) crystallizes in monoclinic centrosymmetric P21/c space group with a = 11.968(6) Å, b = 8.992(4) Å, c = 16.175(6) Å, β = 122.16(3) °, V = 1473.6(12) Å^3 and Z = 4. The dihedral angle between the phenyl and piperidine rings is 86.52°. In the crystal structure of compound (**3**), there exists a one dimensional chain along crystallographic c-axis formed by strong N–H···O intermolecular hydrogen bonding interaction, two such chains interact through weak C–H···O intermolecular hydrogen bonding interactions.*

Keywords: (4-Amino-2-ethoxy-5-nitrophenyl) (piperidin-1-yl) methanone, Synthesis, Characterization, Single Crystal, N–H···O and C–H···O hydrogen bonds.

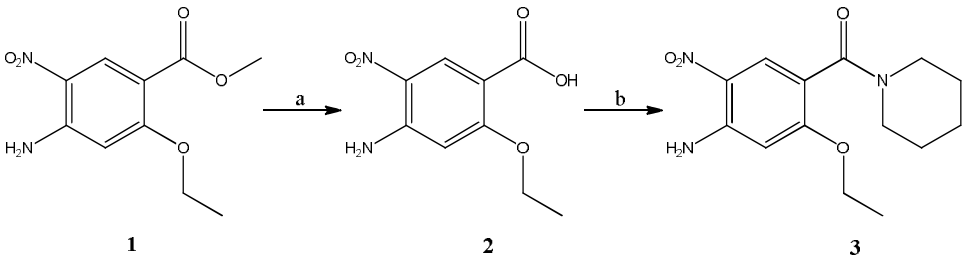
INTRODUCTION

Piperidine is naturally obtained from *Pipernigrum* L [1], different other methods have also been reported for its synthesis [2]. Researchers have notified that the substituted piperidine derivatives possessed a broad spectrum of pharmacological applications. Especially, the piperidine-carboxamides have received considerable attention owing to their wide range of biological and pharmacological activities [3]. The physiological activity of many substituted piperidines prompted the scientists to design simple methods for the synthesis of piperidine and carboxamide derivatives. Carboxamides of piperidine have been reported to

exhibit anti-hypertensive and spasmolytic activities [4-5]. In the current decade, numerous piperidine-carboxamide derivatives have been synthesized by our research fellows with diverse biological activities [6-14]. Also, several quinoxaline amide derivatives have been tested for anti-bacterial activity against Gram-negative & Gram-positive bacteria [15, 19-22] and various crystal studies [16, 23]. Due to the broad range of applications and encouraged by these reported activities the research work is aspired to synthesize and develop a single crystal of a new hybrid of Piperidine-Carboxamide compound (4-Amino-2-ethoxy-5-nitrophenyl) (piperidin-1-yl) methanone (**3**). The single crystal was developed by the method of slow evaporation in dimethylformamide to understand the structural features of compound (**3)**. The crystal structure revealed the formation of (4-Amino-2-ethoxy-5-nitrophenyl) (piperidin-1-yl) methanone (**3**) and was supported by Mass, IR, ^{1}H & ^{13}C NMR data.

MATERIALS AND METHODS

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated Plates (silica gel 60 F254) were used and spots were visualized with UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting Point (MP) determinations were performed by using Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded in Varian MR-400 MHz instrument. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal standard and the signals were reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and coupling constants in Hz. The mass spectra were recorded on Agilent ion trap MS. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer. Single crystal X-ray diffraction studies were carried out on Bruker Smart Apex CCD Diffractometer.



1 **2** **3**

Experimental Conditions: a) NaOH, MeOH, HCl; b) HATU, THF, Piperidine, TEA.

Scheme-1: Synthesis of compound (4-Amino-2-ethoxy-5-nitrophenyl) (piperidin-1-yl) methanone (**3**)

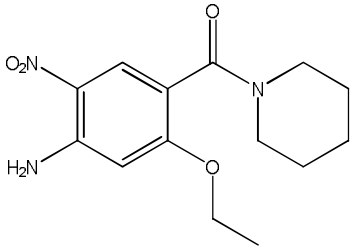
Synthesis of 4-Amino-2-ethoxy-5-nitrobenzoic acid (2): Compound (**2)** was synthesized by refluxing the mixture of compound (**1)** with aq. sodium hydroxide and methanol for 3 h. Evaporated the reaction mixture and acidify with dilute hydrochloric acid. The obtained solid was filtered, dried and recrystallized.

Synthesis of (4-Amino-2-ethoxy-5-nitrophenyl) (piperidin-1-yl) methanone (3): Compound **3** was synthesized by treating compound **2** with HATU (1-[Bis(dimethylamino) methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxidhexafluorophosphate), TEA and THF and stirred at room temperature for 30 min and then added piperidine to the resultant solution and stirred for additional 2 h. Extracted the reaction mass with ethyl acetate and wash with water and brine solution, dried over sodium sulphate and evaporated the solvent under reduced pressure and isolated the pale yellow solid in hexanes as pure compound **(3)**. The physical and characterization data are tabulated in table 1.

RESULTS AND DISCUSSION

Compound (**3)** was synthesized according to the **Scheme 1** and characterized by IR, Mass, ^{1}H & ^{13}C NMR and Single Crystal X-ray diffraction studies. Spectral data's of compound (**3)** are interpreted in table 1 and are in agreement with the proposed structure.

Table 1: Physical and Spectral data of Compound (3)

Compound Structure	
Chemical Name	(4-Amino-2-ethoxy-5-nitrophenyl)(piperidin-1-yl) methanone
Molecular Formula	$C_{14}H_{19}N_3O_4$
Molecular Weight	293.31
Color	pale yellow
Nature	Crystalline
MR (^{o} C)	174-178^{o}C (dec)
Mass : *m/z*	294.20 (M+1)
IR: υ max/cm^{-1}	3463.96, 3298.88, 3182.12, 2984.38, 2984.38, 2935.93, 2856.58, 1638.15, 1604.80, 1568.04, 1508.43, 1489.63, 1452.79, 1466.25, 1392.20, 1318.66, 1250.24, 1130.93, 1117.89, 1077.58, 1038.98, 925.34, 846.53, 822.68, 652.12, 517.85, 472.99
^{1}H NMR (400 MHz, DMSO-d6) (δ ppm):	7.76 (s, 1H), 7.61 (s, 2H), 6.50 (s, 1H), 4.07 (q, 2H), 3.53 (t, 2H), 3.12 (t, 2H), 1.58 – 1.38 (m, 6H), 1.33 (t, 3H).
^{13}C NMR (400 MHz, DMSO-6) (δ ppm):	14.18, 23.98, 25.26, 25.87, 41.97, 47.36, 64.14, 98.40, 116.87, 124.18, 125.69, 148.57, 159.82, 164.43

Crystal Structure Determination of Compound (3): Plate like pale yellow colored single crystals of compound (**3)** were obtained from slow evaporation of the solution of the compound (**3**) in dimethylformamide. A single crystal of compound (**3)** with dimensions 0.39 × 0.22 × 0.18 mm was chosen for X-ray diffraction study. X-ray intensity data were collected at room temperature (298K) on a Bruker Smart Apex CCD diffractometer using graphite monochromated Mo-Kα radiation (λ= 0.71073 Å). Data integration and reduction were processed with SAINT software [17] and an empirical absorption correction was applied to the collected reflections with SADABS [17]. The structure was solved by direct methods using SHELXS97 [18] and refinement was carried out by full-matrix least-squares technique using SHELXL97. Anisotropic displacement parameters were calculated for all non-hydrogen atoms.

Technical details of data acquisition and selected refinement results are listed in table 2. Further, the details of X-ray structure determination are deposited at the CSD (deposition number CCDC 1016708).

Table 2: The Crystallographic Data and Structure Refinements of Compound (3)

Parameter	**Compound (3)**
CCDC Reference number	1016708
Empirical formula	$C_{14}H_{19}N_3O_4$
Formula weight	293.32
Temperature/K	298
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	11.968(6)
b/Å	8.992(4)
c/Å	16.175(6)
α/°	90
β/°	122.16(3)
γ/°	90
Volume/Å^3	1473.6(12)
Z	4
ρ_{calc}g/cm^3	1.322
μ/mm^{-1}	0.098
F(000)	624
Crystal size/mm^3	0.39 × 0.22 × 0.18
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.02 to 49.998
Index ranges	-14 ≤ h ≤ 14,
	-10 ≤ k ≤ 10,
	-19 ≤ l ≤ 19

Reflections collected	13641
Independent reflections	2585 [R_{int} = 0.0481, R_{sigma} = 0.0377]
Data/restraints/parameters	2585/0/199
Goodness-of-fit on F^2	1.049
Final R indexes [I>=2σ (I)]	R_1 = 0.0798, wR_2 = 0.2019
Final R indexes [all data]	R_1 = 0.1045, wR_2 = 0.2184
Largest diff. peak/hole / e $Å^{-3}$	0.54/-0.19

Compound (**3)** crystallizes in the centrosymmetric monoclinic $P2_1/c$ space group with all atoms located in general positions. The X-ray crystal structure shows a single molecule of Compound (**3)** in its asymmetric unit (Figure 1) and there are four molecules in the unit cell (Z=4) (Figure 2). The observed C–C, C–N, C–O, C=O and N=O bond lengths and bond angles are in the normal range. The selected bond lengths and bond angles are tabulated in table 3 and 4 respectively.

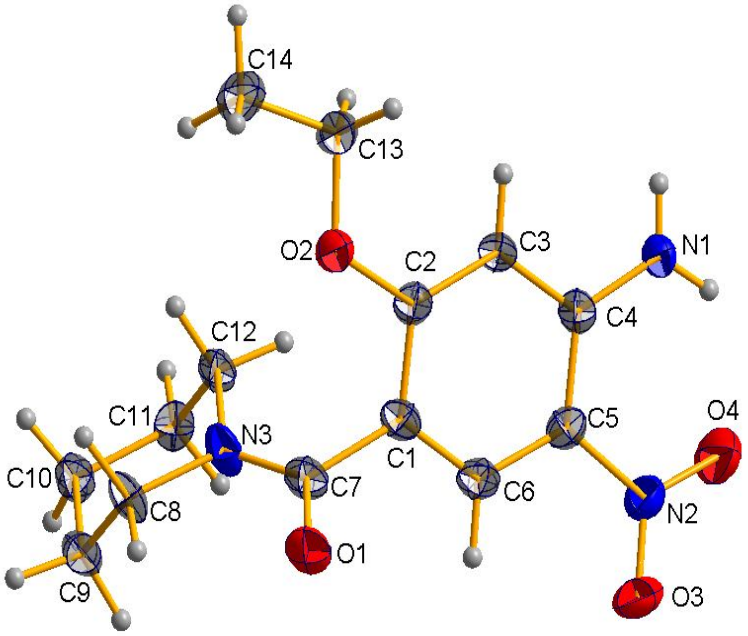


Fig 1: Thermal ellipsoidal plot of Compound **3**, showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 30% probability level except for the H atoms, which are shown as solid globs.

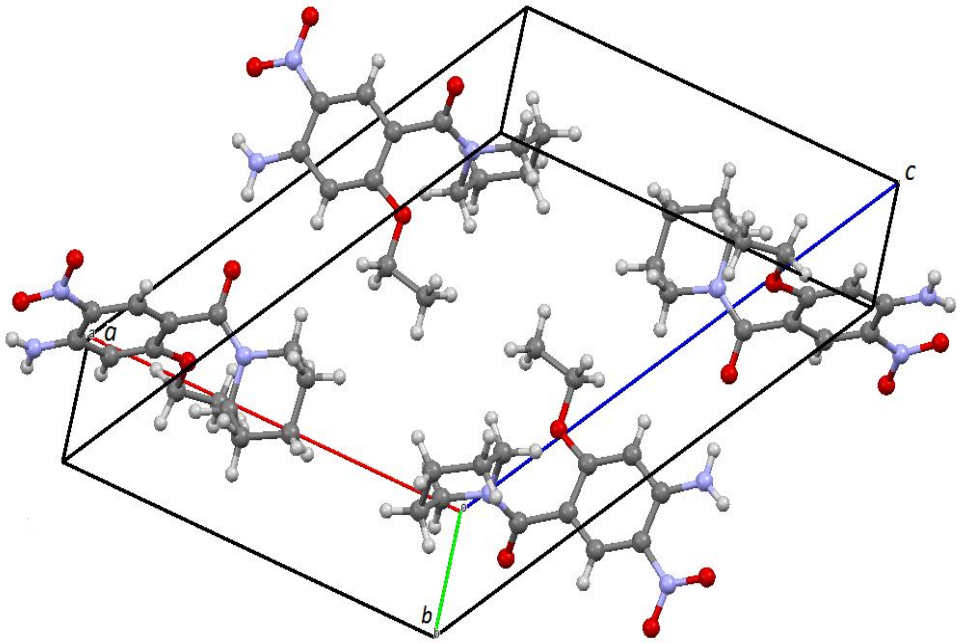


Fig 2: Packing diagram of Compound **3**, shown four molecules in the unit cell.

Table 3: Bond Lengths (Å) observed in Compound (3)

Parameter	Length/Å	Parameter	Length/Å
C(1)-C(7)	1.506(4)	C(13)-C(14)	1.488(5)
C(2)-C(1)	1.415(4)	N(1)-C(4)	1.336(4)
C(3)-C(2)	1.363(4)	N(2)-C(5)	1.425(4)
C(3)-C(4)	1.401(4)	N(3)-C(7)	1.328(4)
C(5)-C(4)	1.411(4)	N(3)-C(8)	1.463(4)
C(5)-C(6)	1.391(5)	N(3)-C(12)	1.472(4)
C(6)-C(1)	1.353(4)	O(1)-C(7)	1.224(4)
C(8)-C(9)	1.468(6)	O(2)-C(2)	1.354(4)
C(10)-C(9)	1.511(6)	O(2)-C(13)	1.428(4)
C(10)-C(11)	1.513(6)	O(3)-N(2)	1.221(4)
C(12)-C(11)	1.475(6)	O(4)-N(2)	1.224(4)

Table 4: Bond Angles (°) observed in Compound (3)

Parameter	Angle/°	Parameter	Angle/°
C(2)-C(1)-C(7)	122.3(3)	O(1)-C(7)-C(1)	119.3(3)
C(6)-C(1)-C(2)	117.6(3)	O(1)-C(7)-N(3)	122.4(3)
C(6)-C(1)-C(7)	120.0(3)	N(3)-C(8)-C(9)	111.3(3)
C(3)-C(2)-C(1)	121.1(3)	C(8)-C(9)-C(10)	111.7(4)
O(2)-C(2)-C(1)	114.4(3)	C(9)-C(10)-C(11)	111.0(4)
O(2)-C(2)-C(3)	124.4(3)	C(12)-C(11)-C(10)	111.9(3)
C(2)-C(3)-C(4)	121.9(3)	N(3)-C(12)-C(11)	109.7(3)
C(3)-C(4)-C(5)	116.2(3)	O(2)-C(13)-C(14)	107.0(3)
N(1)-C(4)-C(3)	118.6(3)	O(3)-N(2)-C(5)	118.7(3)
N(1)-C(4)-C(5)	125.1(3)	O(3)-N(2)-O(4)	121.7(3)
C(4)-C(5)-N(2)	121.4(3)	O(4)-N(2)-C(5)	119.6(3)
C(6)-C(5)-C(4)	121.1(3)	C(7)-N(3)-C(8)	122.0(3)
C(6)-C(5)-N(2)	117.6(3)	C(7)-N(3)-C(12)	125.5(3)
C(1)-C(6)-C(5)	121.9(3)	C(8)-N(3)-C(12)	112.6(3)
N(3)-C(7)-C(1)	118.3(3)	C(2)-O(2)-C(13)	118.3(2)

Single Crystal X-ray studies reveal that there are four hydrogen bonding interactions, out of which two intramolecular (one N–H···O, one C–H···O) and two intermolecular (one N–H···O, one C–H···O) type. The relevant hydrogen bonding interactions are tabulated in table 5. Both the hydrogen atoms of amine moiety involved in N–H···O hydrogen bonding interactions, one intramolecular and another intermoleular.

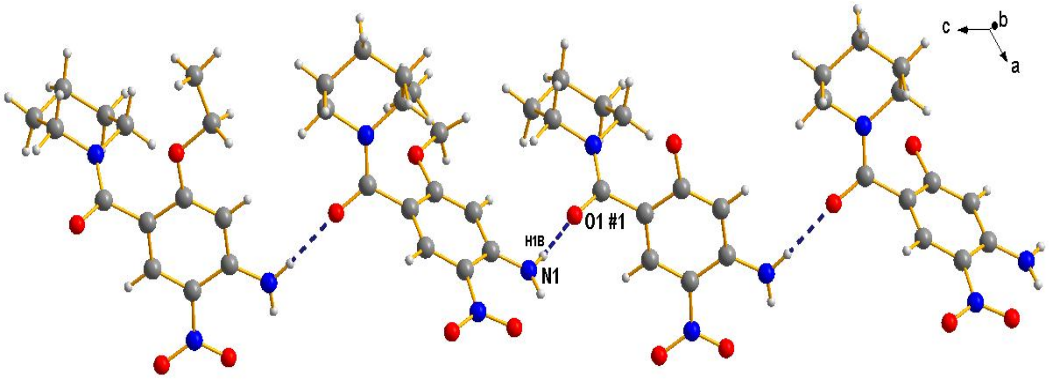


Fig 3: N–H···O Intermolecular hydrogen bonding interactions along crystallographic *c*-axis, symmetry transformation #1: **x, 3/2-y, 1/2+z**.

Table 5: Hydrogen bonding parameters (Å, deg) of Compound (3).

D–H···A	*d*(D–H)	*d*(H···A)	D(D···A)	∠DHA
N1–H1A···O4	0.87	2.03	2.631	125
N1–H1B···O1#1	0.87	2.02	2.884(5)	174
C8–H8A···O3#2	0.99	2.60	3.227(6)	122
C8–H8B···O1	0.99	2.36	2.768	104

Symmetry transformations: #1: x, 3/2-y, 1/2+z; #2: -x, -1/2+y, 1/2-z.

The intermolecular hydrogen bonding interaction which involved H1B of amine group interacts (N1–H1B···O1) with oxygen of amide group with H···O bond distance of 2.02 Å leads to form a chain along crystallographic *c*-axis shown in Figure 3. Two such chains interacts through intermoleular C–H···O hydrogen bonding interactions (C8–H8A···O3) with H···O bond distance of 2.60 Å to form an extanded network as shown in Figure 4. All the hydrogen bonding parameters are listed in table 5.

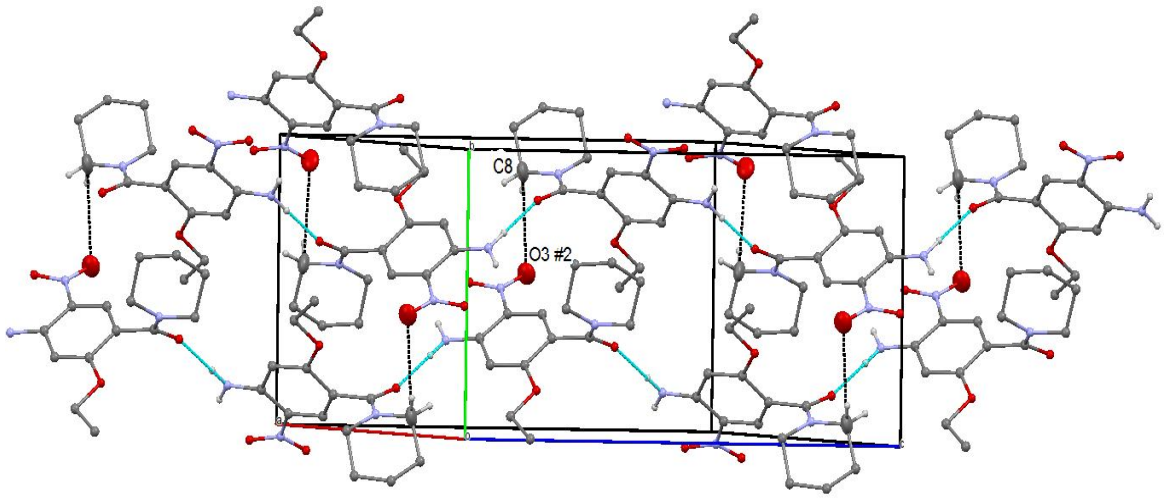


Fig 4: Extended hydrogen bonding network formed using intermoleular C–H···O hydrogen bonding interactions, symmetry transformation #2: **-x, -1/2+y, 1/2-z.**

Supplementary Materials: CCDC 1016708 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ UK; fax (+44) 1223 336 033.

APPLICATIONS

(4-Amino-2-ethoxy-5-nitrophenyl)(piperidin-1-yl) methanone (**3**) is the precursor for various heterocyclic compounds like benzimiadazoles, benzotriazoles, quinoxalines, benzodiazepine etc., which exhibits various biological activities and studying their molecular and crystal structure might give an insight to the mechanisms of their biological actions.

CONCLUSIONS

The newly synthesized Piperidine-Carboxamide namely (4-Amino-2-ethoxy-5-nitrophenyl) (piperidin-1-yl) methanone (**3**) was well characterized by IR, Mass, ^{1}H and ^{13}C NMR and by Single Crystal XRD data.

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