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Synthesis, Characterization and Crystal Structure of 4-Amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide

Keesari Srinivas [1,2]*, Pallepogu Raghavaiah[3], Vurimidi Himabindu[1] and Ghanta Mahesh Reddy[4]

1. Institute of Science and Technology, Center for Environmental Science, J.N.T.University, Kukatpally, Hyderabad-500 072, Telangana State, **INDIA**
2. Green Evolution Laboratories, Wangapally Village, Nalgonda-500 085, Telangana State, **INDIA**
3. Department of Chemistry, Dr. Harisingh Gour University, Sagar-470 003, Madhya Pradesh, **INDIA**
4. Mecleods Pharmaceuticals Ltd, G-2, Shanthi Nagar, Andheri East, Mumbai-400 093, Maharashtra, **INDIA**

Email: keesarisrinivas2014@gmail.com

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ABSTRACT

*The amide functionality is a familiar feature in small or complex synthetic or natural molecules and plays a key role for medicinal chemists. And in-depth analysis of the comprehensive medicinal chemistry database revealed that the carboxamide group appears in more than 25% of known drugs. This can be expected, since carboxamides are neutral, are stable and have both hydrogen-bond accepting and donating properties. The newly synthesized 4-amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide (**3**) by hydrolysis of ester (**1**) to acid (**2**) with sodium hydroxide in methanol and followed by acid-amine coupling with dibenzylamine to obtain compound **3**. The newly synthesized, 4-amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide **3** is characterized by LC-MS, 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 = 8.9255(5) Å, b = 17.2482(12) Å, c = 13.5773(8) Å, β = 95.171(6) ° V = 2081.7(2) Å^3 and Z = 4. The dihedral angle between the two phenyl rings which is 6.91°. In the crystal structure of compound **3**, there exists a one dimensional chain along crystallographic a axis formed by strong N–H···O hydrogen bonding interaction, it also consists weak C–H···O intramolecular hydrogen bonding interactions.*

Keywords: 4-amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide, synthesis, characterization, single crystal, N–H···O hydrogen bonds.

INTRODUCTION

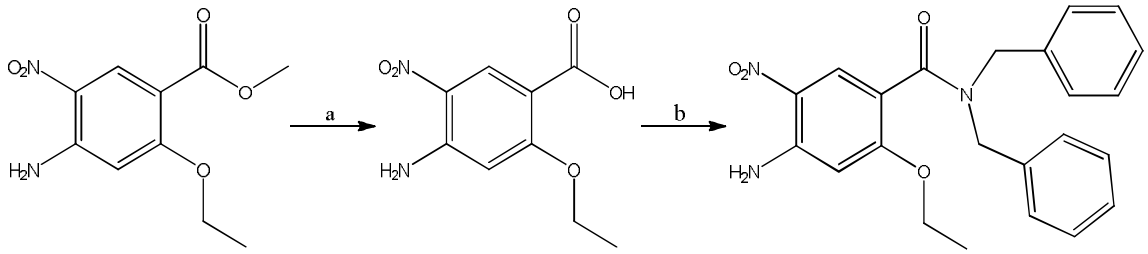
Amide derivatives are of considerable importance because of their diverse biological activities such as tuberculosis [1], anticonvulsant [2], analgesic anti-inflammatory [3], insecticidal [4], antifungal [5], and antitumor [6] properties. Also, they have wide spectrum of antimicrobial activity, anthelmintic, bactericidal, insecticidal activity [7, 27-28] and show anti-platelet activity [8]. They are also involved as an intermediate product in the synthesis of therapeutic agents and in-depth analysis of the comprehensive

medicinal chemistry database revealed that the carboxamide group appears in more than 25% of known drugs [9]. Among them, quinoxaline amide derivatives have a diverse pharmacological activities ranging from antibacterial [10-14], antifungal [15], anti-tubercular [16-18], analgesic [19], anti-inflammatory [10] and anti-ulcerative agent [20-21]. Also, several quinoxaline amide derivatives have been tested for antibacterial activity against Gram-negative & Gram-positive bacteria [22, 29-30] and various crystal studies [23-24].

Due to the broad range of applications, amide derivative compounds have aroused the attention of the scientific community. Encouraged by these reported activities, we have synthesized a new compound, 4-Amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide (**3)** and crystallized 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-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide (**3**) and was supported by IR, LC-MS, ^{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. ^{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 Oxford (Agilent) X Calibur, Gemini diffractometer equipped with EOS CCD detector.



Experimental Conditions: a) NaOH, MeOH, HCl; b) $SOCl_2$, DCM, Dibenzylamine, NaOH.

Scheme-1: Synthesis of compound 4-Amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide

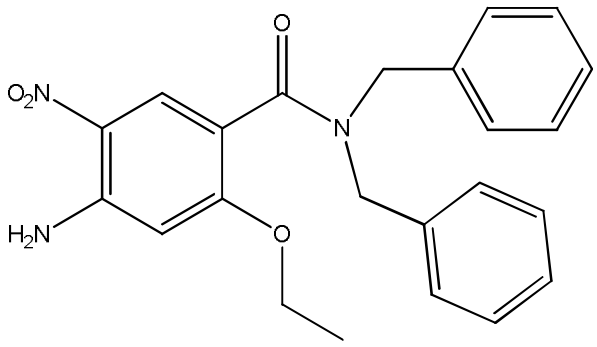
Synthesis of 4-amino-2-ethoxy-5-nitrobenzoic acid (2): Compound **2** was synthesized by refluxing the mixture of compound **1** with aq. sodium hydroxide and methanol for 3 h. Evaporated the reaction mixture and acidify with dilute hydrochloric acid. The obtained solid was filtered, dried and recrystallized.

Synthesis of 4-Amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide (3): Compound **3** was synthesized by refluxing the compound **2** with thionyl chloride for 6 h. Evaporate the reaction mixture completely under reduced pressures and dilute with dichloromethane and the resultant solution was added to dibenzylamine and stirred for 12 h. Filtered the unwanted solid and basify the filtrate with aq. sodium hydroxide solution. Evaporate the solvent under reduced pressure and isolated the solid in hexanes as pure compound **3** as pale yellow solid. 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, LC-MS, ^{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-N,N-dibenzyl-2-ethoxy-5-nitrobenzamide
Molecular Formula	$C_{23}H_{23}N_3O_4$
Molecular Weight	405.45
Color	pale yellow
Nature	Crystalline
MP (^{o}C)	165-170^{o}C (dec)
LC-MS : *m/z*	406.30 (M+1)
IR: υ max/cm^{-1}	3455.53, 3335.55, 2938.64, 1635.50, 1597.54, 1559.64, 1462.62, 1450.60, 1390.67, 1380.0, 1326.66, 1249.50, 1084.65, 1029.68, 818.70, 698.65, 658.72.
^{1}H NMR (δ ppm) (400 MHz, DMSO-d_6):	7.84(s, 1H), 7.63(s, 2H), 7.37-7.27(m, 8H), 7.12(s, 1H), 7.10(s, 1H), 6.54(s, 1H), 5.3-3.9(m, 6H), 1.35(t, *J* = 7.2 Hz, 3H).
^{13}C NMR (δ ppm) (400 MHz, $CDCl_3$):	13.5, 45.6, 50.2, 63.9, 97.6, 116.2, 125.9, 126.3(2C), 126.4, 126.8, 127.1, 127.5(2C), 127.7(2C), 127.8(2C), 135.0, 135.5, 146.6, 159.5, 166.9.

Crystal Structure Determination of Compound 3: Plate like pale yellow single crystals of compound **3** were obtained from slow evaporation of the solution of compound in dimethylformamide. A single crystal of compound **3** with dimensions 0.42 × 0.36 × 0.32 mm was chosen for X-ray diffraction study. X-ray intensity data were collected at room temperature (298K) using Oxford (Agilent) X Calibur, Gemini diffractometer equipped with EOS CCD detector. Monochromatic Mo Kα radiation (λ= 0.71073 Å) was used for the measurements. Data were collected and reduced by using the ''CrysAlis PRO'' program[25]. An empirical absorption correction using spherical harmonics was implemented in ''SCALE3 ABSPACK'' scaling algorithm. The structure was solved by direct methods using SHELXS97[26] and refinement was carried out by full-matrix least-squares technique using SHELXL97[26]. Anisotropic displacement parameters were calculated for all non-hydrogen atoms. H atoms attached to the N atom were located from difference Fourier map and refined isotropically. 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 1010701).

Table 2: The crystallographic data and structure refinements of compound **3**

Parameter	**Compound 3**
CCDC Reference number	1010701
Empirical formula	$C_{23}H_{23}N_3O_4$
Formula weight	405.44
Temperature/K	298
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	8.9255(5)
b/Å	17.2482(12)
c/Å	13.5773(8)
α/°	90
β/°	95.171(6)
γ/°	90
Volume/Å^3	2081.7(2)
Z	4
ρ_{calc}g/cm^3	1.294
μ/mm^{-1}	0.09
F(000)	856
Crystal size/mm^3	0.42 × 0.36 × 0.32
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.602 to 52.738
Index ranges	-11 ≤ h ≤ 10
	-21 ≤ k ≤ 12
	-9 ≤ l ≤ 16
Reflections collected	8872
Independent reflections	4248 [R_{int} = 0.0318, R_{sigma} = 0.0607]
Data/restraints/parameters	4248/4/279
Goodness-of-fit on F^2	1.02
Final R indexes [I>=2σ (I)]	R_1 = 0.0574, wR_2 = 0.1094
Final R indexes [all data]	R_1 = 0.1164, wR_2 = 0.1364
Largest diff. peak/hole / e Å^{-3}	0.20/-0.13

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 tables 3 and 4 respectively.

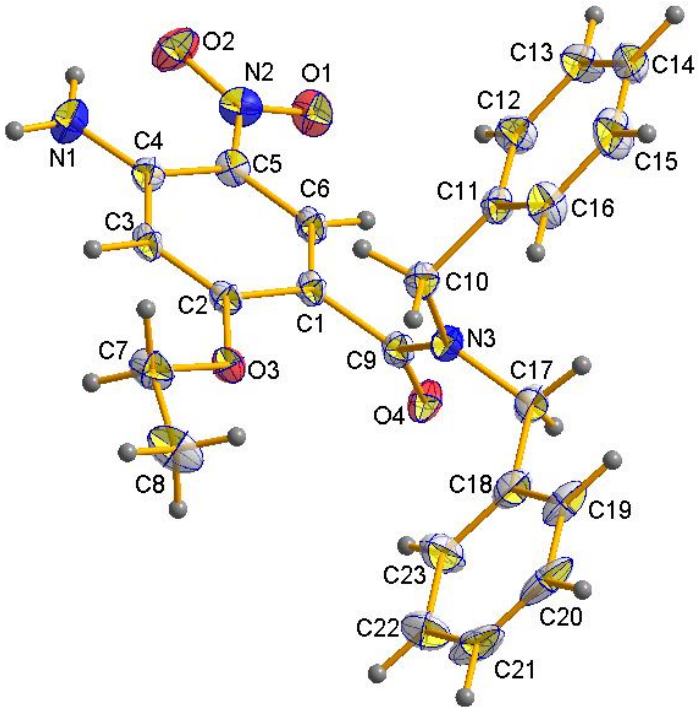


Fig 1: Crystal structure of compound **3**, thermal ellipsoids are drawn at 30% probability level excepting for H atoms, which are shown as circles of arbitrary radius.

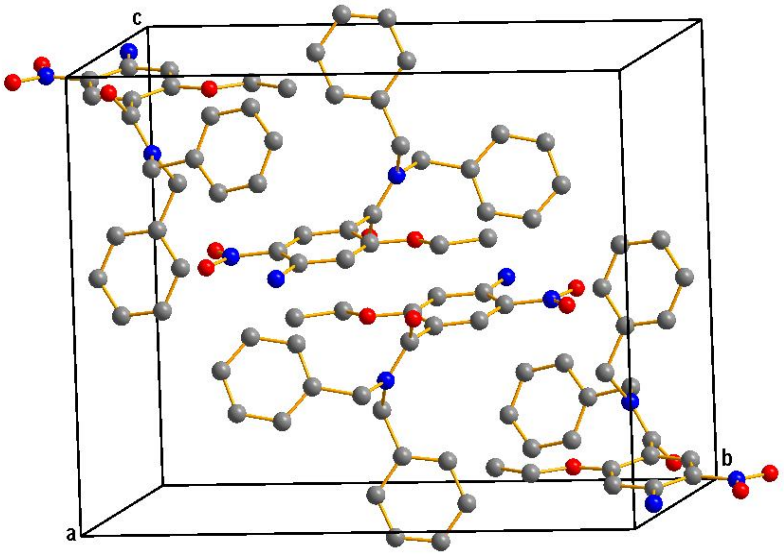


Fig 2: Packing diagram of compound **3**, hydrogens atoms are omitted for clarity.

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

Parameter	Length/Å	Parameter	Length/Å
C(1)-C(2)	1.419(3)	C(11)-C(12)	1.372(3)
C(1)-C(6)	1.371(3)	C(11)-C(16)	1.388(3)
C(1)-C(9)	1.499(3)	C(12)-C(13)	1.386(3)
C(2)-C(3)	1.368(3)	C(13)-C(14)	1.366(4)
C(2)-O(3)	1.357(3)	C(14)-C(15)	1.370(4)
C(3)-C(4)	1.414(3)	C(15)-C(16)	1.389(3)
C(4)-C(5)	1.410(3)	C(17)-C(18)	1.504(3)
C(4)-N(1)	1.354(3)	C(17)-N(3)	1.465(3)
C(5)-C(6)	1.392(3)	C(18)-C(19)	1.371(4)
C(5)-N(2)	1.432(3)	C(18)-C(23)	1.362(4)
C(7)-C(8)	1.503(3)	C(19)-C(20)	1.379(5)
C(7)-O(3)	1.441(3)	C(20)-C(21)	1.356(7)
C(9)-N(3)	1.352(3)	C(21)-C(22)	1.335(7)
C(9)-O(4)	1.235(2)	C(22)-C(23)	1.396(6)
C(10)-C(11)	1.514(3)	N(2)-O(1)	1.238(2)
C(10)-N(3)	1.465(2)	N(2)-O(2)	1.241(2)

Table 4: Bond Angles (^{o}) observed in compound 3

Parameter	Angle/°	Parameter	Angle/°
C(2)-C(1)-C(9)	124.5(2)	C(11)-C(12)-C(13)	121.0(3)
C(6)-C(1)-C(2)	117.5(2)	C(14)-C(13)-C(12)	120.0(3)
C(6)-C(1)-C(9)	117.81(19)	C(13)-C(14)-C(15)	120.0(3)
C(3)-C(2)-C(1)	121.1(2)	C(14)-C(15)-C(16)	120.3(3)
O(3)-C(2)-C(1)	114.6(2)	C(11)-C(16)- C(15)	120.0(3)
O(3)-C(2)-C(3)	124.2(2)	N(3)-C(17)-C(18)	113.0(2)
C(2)-C(3)-C(4)	121.7(2)	C(19)-C(18)-C(17)	120.6(3)
C(5)-C(4)-C(3)	116.7(2)	C(23)-C(18)-C(17)	120.7(3)
N(1)-C(4)-C(3)	119.6(2)	C(23)-C(18)-C(19)	118.7(3)

N(1)-C(4)-C(5)	123.7(2)	C(18)-C(19)-C(20)	120.6(4)
C(4)-C(5)-N(2)	122.5(2)	C(21)-C(20)-C(19)	120.7(6)
C(6)-C(5)-C(4)	120.8(2)	C(22)-C(21)-C(20)	118.8(6)
C(6)-C(5)-N(2)	116.7(2)	C(21)-C(22)-C(23)	121.9(6)
C(1)-C(6)-C(5)	122.1(2)	C(18)-C(23)-C(22)	119.4(4)
O(3)-C(7)-C(8)	106.8(2)	O(1)-N(2)-C(5)	119.3(2)
N(3)-C(9)-C(1)	119.31(18)	O(1)-N(2)-O(2)	121.2(2)
O(4)-C(9)-C(1)	118.6(2)	O(2)-N(2)-C(5)	119.5(2)
O(4)-C(9)-N(3)	122.0(2)	C(9)-N(3)-C(10)	125.16(18)
N(3)-C(10)- C(11)	112.75(17)	C(9)-N(3)-C(17)	119.55(17)
C(12)-C(11)-C(10)	120.7(2)	C(17)-N(3)-C(10)	115.29(17)
C(12)-C(11)-C(16)	118.7(2)	C(2)-O(3)-C(7)	119.07(19)
C(16)-C(11)-C(10)	120.5(2)		

Single crystal x-ray studies reveal that there are five intramolecular (one N–H···O, one N–H···N and three C–H···O) and one intermolecular (N–H···O) hydrogen bonding interactions in the crystal structure of compound **3**. The relevant hydrogen bonding interactions are tabulated in table 5. Both the hydrogens of amine moiety involved in N–H···O hydrogen bonding interactions, one intramolecular and another intermoleular. The intermoleular interaction which involved H1B of amine interacts (N1–H1B···O4) with oxygen of C=O group with H···O bond distance of 2.16 Å leads to form a chain along crystallographic *a* axis is shown in **Figure 3**. The other hydrogen atom (H1A) of amine involved in intramolecular hydrogen bonding interactions (N1–H1A···O1) with H···O bond distance of 1.96 Å. There are three C–H···O hydrogen bonding interactions (intramolecular) and the parameters are listed in table 5.

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···O1	0.90	1.96	2.636	131
N1–H1A···N2	0.90	2.59	2.932	104
N1–H1B···O4 #1	0.92(3)	2.16(4)	2.938(3)	142(3)
C6–H6···O1	0.93	2.34	2.672	101
C10–H10B···O3	0.97	2.54	3.053	113
C17–H17B···O4	0.97	2.34	2.741	104

Symmetry transformations: #1: -1+x,y,z.

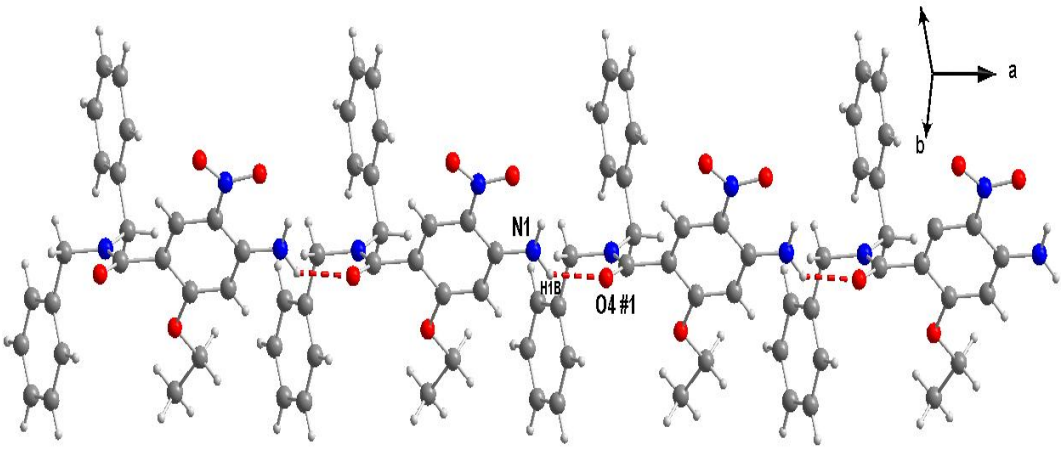


Fig 3: N–H···O Intermolecular hydrogen bonding interactions along crystallographic *a* axis, Symmetry transformation: #1: -1+x, y, z.

Supplementary Materials: CCDC 1010701 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; or e-mail:deposit@ccdc.cam.ac.uk.

APPLICATIONS

4-amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide (**3**) is the precursor for various heterocyclic compounds like quinoxalines, benzimiadazoles, benzotriazoles, 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 dibenzylbenzamide namely 4-Amino-N, N-dibenzyl-2-ethoxy-5-nitrobenzamide **(3)**, was synthesized and well characterized by IR, LC-MS, ^{1}H and ^{13}C NMR and by single crystal XRD data.

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