European Scientific Journal November 2013 edition vol.9, No.33 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431

SYNTHESIS AND STRUCTURAL STUDIES OF 1-[(8-NITRONAPHTHO[2,1-B]FURAN-2-YL) CARBONYL] PIPERIDINE

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Abstract

Naphtho [2,1-b] furan-2-carboxyazide has been synthesized from ethyl 8-nitronaphtho [2,1-b] furan-2-carboxylate, by first converting into 8-nitronaphtho [2,1-b] furan-2-carboxyhydrazide , followed by diazotization. The reaction of carboxyazide with piperidine resulted in nucleophilic substitution reaction giving 1- [(8-nitronaphtho [2, 1-*b*] furan-2-yl) carbonyl] piperidine (NNFCP). The compound has been characterized by FT-IR, ^{1}HNMR, Mass spectral data and X-ray diffraction analysis.

Keywords: Synthesis, Naphtho[2,1-b]furan, Piperidine, Carboxamide and Crystal structure

1. Introduction

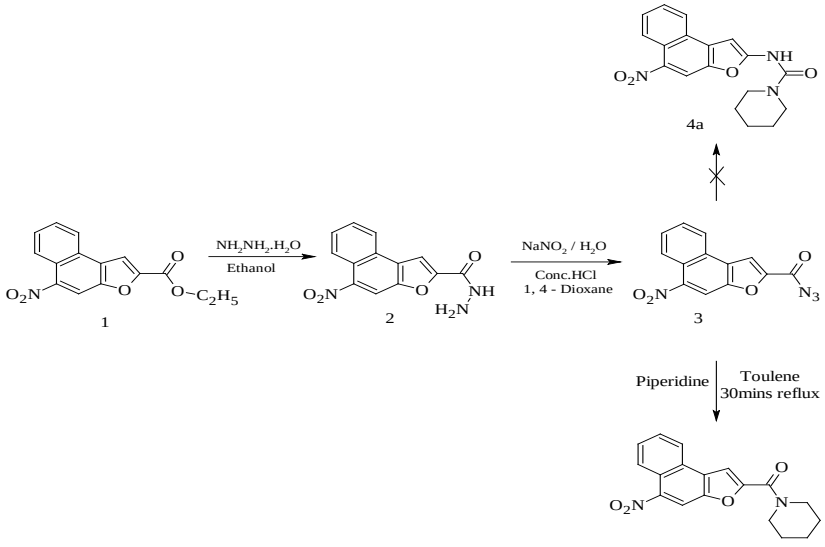
Naphtho[2,1-b]furan derivatives are known to exhibit various biological and pharmacological activities such as antimicrobial, anti inflammatory, analgesic, anthelmintic and antipyretic (Joshi, 2010; Ravidra, 2006; Shashikala Devi, 2011, 2010; Kumaraswamy, 2008). Carboxamides owing to their wide range of biological activities have received considerable attention. Carboxamide group containing piperidine ring have been used as antiviral, PARP-1 inhibitor, antimicrobial, antidepressant and antioxidants (Wieslaw M. Kazmierski,2011; Sunkyung Lee, 2012; Neelottama Kushwaha, 2011; Deepali gupta, 2011; Vaidya, 2012). The compounds with carboxamide functionality are also used as fungicides (Yukihiro Yoshikawa, 2011).

Encouraged by these reports it was contemplated to synthesize compound encompassing naphtho [2,1-b]furan, piperidine and carbonyl functionality in a single molecular frame work. We herein report the synthesis of 1-[(8-nitronaphtho[2,1-*b*]furan-2-yl)carbonyl]piperidine and its crystal structure analysis.

2. Experimental

2.1. Materials and physical measurements

Melting points were recorded on open capillary tube and are uncorrected. Elemental analysis was recorded on Heraeus CHN rapid analyzer. UV spectrum was recorded on UV-Vis-Spectrophotometer (Model - Ocean Optics USB-4000, USA). IR spectra were recorded on FT-Bruker Spectrophotometer using KBr pellet. ^{1}HNMR spectrum was recorded on Bruker 300MHz in DMSO-d_6 solution using TMS as an internal standard. Mass spectrum was recorded on Agilent Quadrupole LC-MS System. Reaction was monitored by thin layer chromatography and spots were visualized with UV light and recrystallization was carried out by using toluene. The single crystal X-ray data collection of the compound was carried out using Bruker Axs kappa APEX II CCD diffractometer.



Scheme-1 Synthesis of 1- [(8-nitronaphtho [2,1-*b*] furan-2-yl) carbonyl] piperidine

The compounds **1, 2** and **3** were prepared according to the procedure in the literature (Vaidya, 2011).

Synthetic procedure of NNFCP

8-Nitronaphtho [2,1-b] furan-2-carboxyazide (0.57 g, 0.002 mol) was refluxed with piperidine (0.85 ml, 0.01 mol) in toluene (10ml) for 30 mins,

excess of solvent was removed under reduced pressure and the reaction mixture was cooled, and the solid separated was filtered, washed with warm toluene. It was recrystallized from toluene to obtain NNFCP , with m.p. 152-154 ^{0}C.

Yield = 0.35 g (53.8%). Elemental analysis data for compound NNFCP ($C_{18}H_{16}N_2O_4$): found: C – 66.62%, H – 4.94%, N – 8.60%, calculated: C – 66.65, H – 4.97, N – 8.63.

2.2. Crystal structure determination of NNFCP

Single crystal suitable for diffraction was obtained by slow evaporation of a solution of the compound in toluene. The yellow crystal of the compound having appropriate dimensions of 0.30 mm x 0.20 mm x 0.20 mm was mounted on a fine-focus sealed tube for X-ray crystallographic study. A Bruker Axs-kappa APEX II CCD diffractometer equipped with a graphite monochromated Mo Kα (λ = 0.71073Å) radiation was used for the measurement of data. The structure was solved by direct methods and refined by full matrix least squares on F^2 (SHELXL 97) program package (Sheldrick,1998). Non-hydrogen atoms were refined by anisotropic displacement parameters and the positions of all H-atoms were fixed geometrically and included in estimated positions using a riding model. The final full matrix least-squares refinements including 218 parameters for 2673 reflections with I>2sigma(I) gave R1 = 0.0409, wR2 = 0.1036. Molecular graphics employed include ORTEP 3 (Farrugia,1997) and CAMERON (Watkin,1993).

The title compound crystallizes in triclinic P-1 with a = 4.83580(10) Å , b = 12.9391(3) Å, c = 13.7923(4) Å and α = 62.3850(10)º, β = 88.494(2)º, γ = 82.286(2)º, V = 757.13(3) Å^3, Z = 2, d=1.423 Mg/m^3 .The crystallographic XRD data is given in Table 1.

Table 1 Crystal Data and Structure Refinement of the title compound

Empirical formula	$C_{18}H_{16}N_2O_4$
Formula weight	324.33
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system,	Triclinic
Space group	P-1
Unit cell dimensions	a = 4.83580(10) Å α= 62.3850(10)º b = 12.9391(3) Å β = 88.494(2)º c = 13.7923(4) Å γ = 82.286(2)º
Volume	757.13(3) A^3
Z, Calculated density	2, 1.423 Mg/m^3
Absorption coefficient	0.102 mm^-1
F (000)	340
Crystal size	0.20 x 0.20 x 0.15 mm
Theta range for data collection	1.79 to 25.00 deg.

Limiting indices	-5<=h<=5, -13<=k<=15, -15<=l<=16
Reflections collected / unique	13431 / 2673 [R (int) = 0.0282]
Completeness to theta = 25.00	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9934 and 0.9356
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2673 / 0 / 218
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.1036
R indices (all data)	R1 = 0.0489, wR2 = 0.1115
Extinction coefficient	0.030(4)
Largest diff. peak and hole	0.246 and -0.276 e.A^{-3}

Full Crystallographic data (cif file) relating to the crystal structure have been deposited with the Cambridge Crystallographic Data Center as CCDC 903318 which contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

3. Results and Discussion

There are two pathways of reaction by which 8-nitronaphtho[2,1-b]furan-2-carboxyazide **3** can undergo on treatment with amines. In one of the pathways it can undergo Curtius rearrangement to yield *N*-(8-nitronaphtho [2,1-*b*] furan-2-yl) piperidine-1-carboxamide **4a**. In second pathway it can undergo nucleophilic substitution reaction with elimination of hydrazoic acid [16-17] to give 1- [(8-nitronaphtho [2,1-*b*] furan-2-yl) carbonyl] piperidine. In the present investigation the carboxyazide **3** underwent nucleophilic substitution reaction and produced the compound **4**. The product obtained was recrystallized from toluene. Spectral studies and single crystal X-ray analysis confirmed the structure.

3.1. Spectral studies of NNFCP

The UV-Visible spectrum showed peaks at λ_{max} 350.85 nm due to carbonyl group and λ_{max} 436.00 nm due to extended aromatic conjugation (Fig.1).

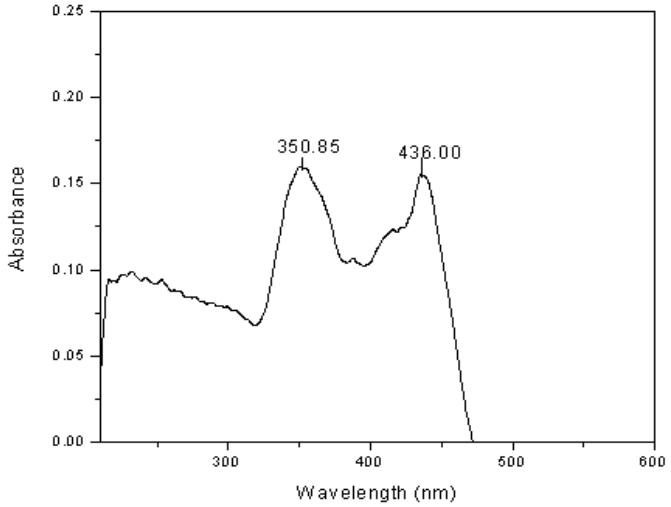


Fig 1 - UV Spectrum of 1-[(8-nitronaphtho[2,1-*b*]furan-2-yl)carbonyl]piperidine

The FT-IR Spectrum of compound **4** (Fig.2) exhibited the strong bands at 1318.4 cm^{-1} and 1543.8 cm^{-1} can be assigned to the NO_2 asymmetric and symmetric stretch respectively. Strong band at 1606.9 cm^{-1} is due to aromatic C=C stretch. The strong band at 1739.2cm^{-1} due to C=O stretching frequency. Medium band appeared at 2920.8 cm^{-1} due to aliphatic C-H stretching frequency and band at 1436.5 cm^{-1} can be assigned to C-H aliphatic bending frequency. The bands at 3011.7 cm^{-1} and 3110.6 cm^{-1} can be attributed to aromatic C-H stretch and strong band at 750.9 cm^{-1} is due to aromatic C-H bending.

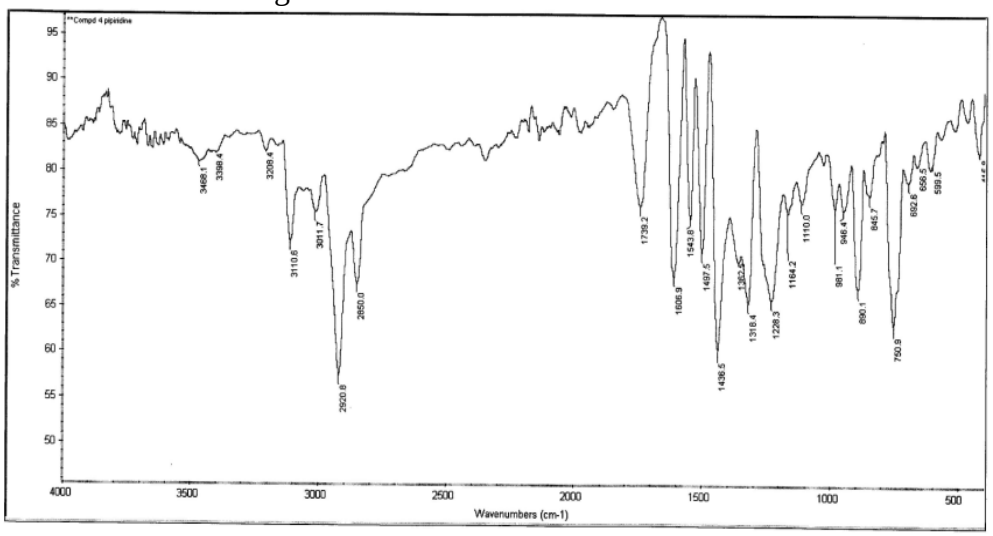


Fig 2 - IR Spectrum of 1-[(8-nitronaphtho [2,1-*b*] furan-2-yl) carbonyl] piperidine.

The ^{1}HNMR spectrum (Fig.3 and Fig.4) showed two peaks at δ 1.63 integrated for six protons and at δ 3.70 integrated for four protons. These peaks are attributed to protons at C-15, C-16 and C-17 and protons at C-14 and C-18 respectively of piperidine ring system. Two singlets were observed at δ 8.25 (1H, C-11) and δ 8.83 (1H, C-10) which confirmed the substitution of nitro group at C-1 atom. Two doublets appeared at δ 8.44 and δ 8.65 for aromatic protons of C-6 and C-3 and multiplet (doublet of doublet) appeared at δ 7.84 which integrated for protons of C-4 and C-5 respectively. (Numbering of carbon atoms is present in Fig.6)

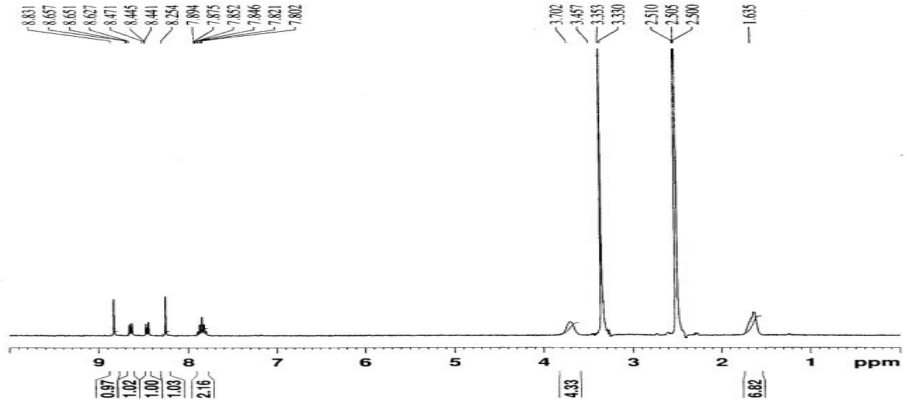


Fig 3 - ^{1}HNMR spectrum of 1-[(8-nitronaphtho[2,1-*b*]furan-2-yl)carbonyl]piperidine

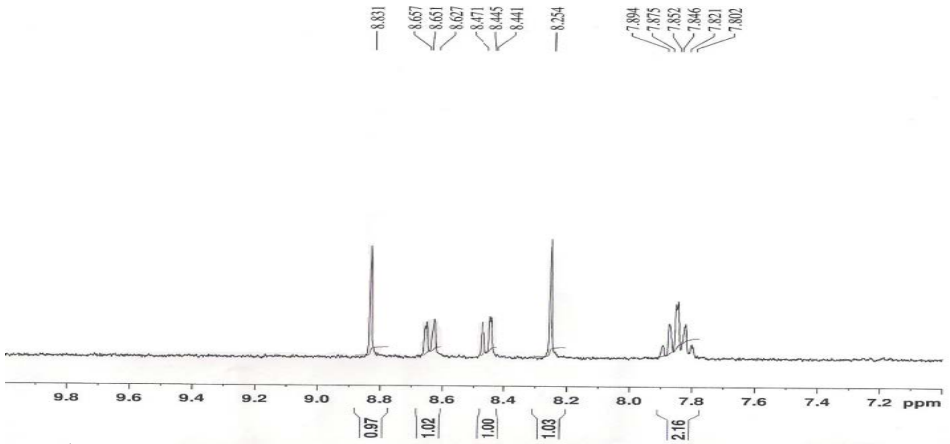


Fig 4 - ^{1}HNMR expanded aromatic region of 1-[(8-nitronaphtho[2,1-*b*]furan-2-yl) carbonyl] piperidine.

The mass spectrum of the compound shows molecular ion peak at m/z = 324.8 (M^{+}) (Fig. 5), which corresponds to molecular weight of compound **4** with molecular formula $C_{18}H_{16}N_2O_4$.

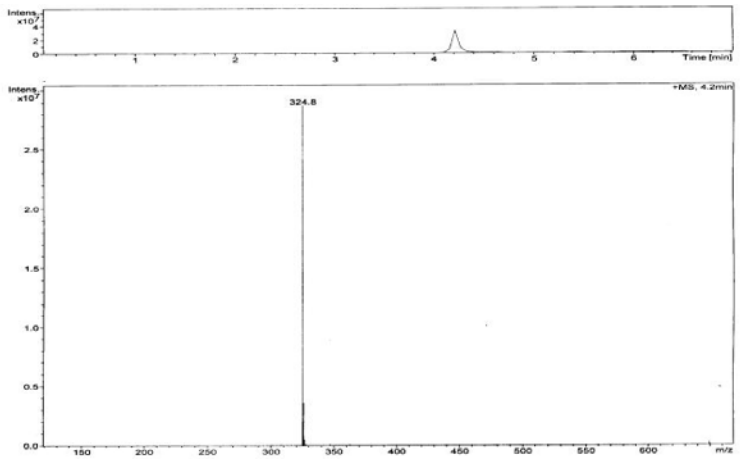


Fig 5 - Mass spectrum of 1-[(8-nitronaphtho[2,1-*b*]furan-2-yl)carbonyl]piperidine

3.2 Crystal structure of NNFCP

3.1.1. **Conform*ational Features***

The selected bond length, bond angle and torsional angles is reported in Table 2. Fig.6 shows the molecular structure of the present compound. The N2-C13 bond length is 1.342 (Allen et al 1.346 A) which is in close agreement to the standard values. The C13-O4 has a bond length of 1.2284(19) Å which is shorter (Allen et al C=O is 1.333) (Orpen,1992). All other bond length and bond angle values are consistent with those of other reported structures of naphthofuran derivatives. The O3-C12-C11 is 111.51(13) (the value in other related structure is110.17); this slight increase in value is due to the electron withdrawing carbonyl group.C10-C1-C2 is 123.33(15) (121.73 close to aromatic bond angle), this increase in the bond angle at C1 atom may be due to the presence of the electron withdrawing nitro group. The nitro group present is also known to lie in-plane with that of the naphthofuran fragment.

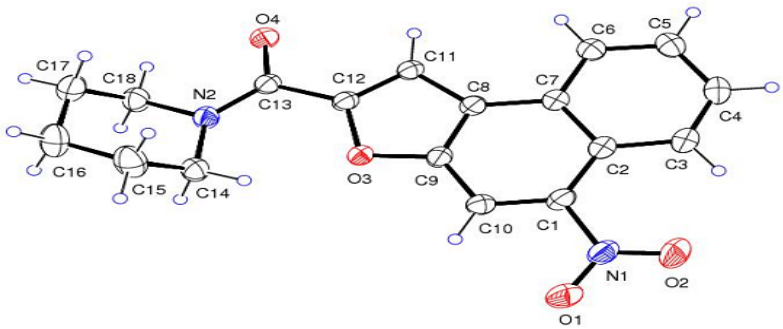


Fig 6 - The thermal ellipsoid plot of the title compound, drawn at 40% probability

The naphthofuran unit is essentially planar, and the dihedral angle between the piperidyl ring and the mean plane of the naphthofuran fragment is -179.54(16)° indicates the two moieties are coplanar. N-Substituted piperidine have been the subject to several X-ray crystallographic investigations and most of them were found to adopt a nearly planar conformation (that is with the N-C=O group lying in the mean plane of the piperidyl ring). Such a conformation would not be preferred in terms of non-bonded interactions alone and is to be ascribed to restricted rotation of freedom with the aromatic naphthofuran ring around the N-C partial double bond, as can be easily proved by comparing the observed N-C distances with those expected for a pure single bond. The piperidyl ring tends to be coplanar with the amide group owing to the partial double bond character of the C(13)-N(2) bond. This is evident from the comprehensive discussion of the C (sp2)-N (piperidyl) bond by Gilli and Bertolasi (Gilli,1979). In the piperidyl ring, the atom N2 is at the apex from the plane comprising the other 4 atoms C14/ C15/C17/C18 of the ring and its deviation is 0.2405Å and the C16 atom is below the plane of the ring and its deviation is found to be -0.2181 Å. The piperidine ring exhibits a perfect chair conformation (Cremer, 1975) with puckering parameters QT= 0.5620(2) Å, θ = 2.02(0)° and ψ2 = -12.75(0.12)°.The asymmetry parameter (PARST) (Nardelli,1983,1985) for the piperidine ring ΔCs is -1.30896. There is a fairly large spread in the endocyclic torsion angles at N in the piperidyl moiety N2-C14-C15-C16 = 55.3°(2), C14-C15-C16-C17 = -53.6°(3), C15-C16-C17-C18 = +53.4°(3), C16-C17-C18-N2 = -56.2°(2), C15-C14-N2-C13 = 113.5°(2), C15-C14-N2-C18 = -58.5°(2). This variation in the values of torsion angles are attributed to the packing effects. Packing effects will influence torsion angles more than bond angles or bond lengths.

Table 2 Selected Bond lengths (Å) and torsional angles (°) of NNFCP

Bond lengths (Å)	
C(1)-C(10)	1.365(2)
C(1)-N(1)	1.469(2)
C(2)-C(3)	1.413(2)
C(2)-C(7)	1.428(2)
C(3)-C(4)	1.362(3)
C(4)-C(5)	1.394(3)
C(5)-C(6)	1.361(2)
C(6)-C(7)	1.409(2)
C(7)-C(8)	1.423(2)
C(8)-C(9)	1.373(2)
C(8)-C(11)	1.427(2)
C(9)-O(3)	1.3639(18)
C(9)-C(10)	1.382(2)
C(11)-C(12)	1.347(2)
C(12)-O(3)	1.3775(18)
C(12)-C(13)	1.486(2)

C(13)-O(4)	1.2284(19)
C(13)-N(2)	1.342(2)
C(14)-N(2)	1.462(2)
C(14)-C(15)	1.505(3)
C(15)-C(16)	1.513(3)
C(16)-C(17)	1.517(3)
C(17)-C(18)	1.496(3)
C(18)-N(2)	1.461(2)
N(1)-O(2)	1.193(2)
N(1)-O(1)	1.204(2)
Torsional angles (°)	
C(11)-C(12)-C(13)-N(2)	-179.54(16)
O(3)-C(12)-C(13)-N(2)	5.3(2)
N(2)-C(14)-C(15)-C(16)	55.3(2)
C(14)-C(15)-C(16)-C(17)	-53.6(3)
C(15)-C(16)-C(17)-C(18)	53.4(3)
C(16)-C(17)-C(18)-N(2)	-56.2(2)
O(4)-C(13)-N(2)-C(18)	4.7(3)
C(12)-C(13)-N(2)-C(18)	-173.15(15)
O(4)-C(13)-N(2)-C(14)	-166.95(18)
C(12)-C(13)-N(2)-C(14)	15.2(3)
C(17)-C(18)-N(2)-C(13)	-113.24(18)
C(17)-C(18)-N(2)-C(14)	59.7(2)
C(15)-C(14)-N(2)-C(13)	113.5(2)
C(15)-C(14)-N(2)-C(18)	-58.5(2)

3.1.2. Packing Features

The crystal packing is mainly governed by intra and intermolecular C-H···O interactions. An intramolecular hydrogen bond acting as conformational lock is found between nitro O1 and naphtho H13 atom. This hydrogen bond creates a virtual ring which may be the key feature of this drug. The molecular structure is further stabilized by C14-H14···O3 and C10-H10···O1 interactions. Etter's graph set analysis classifies the motif generated as S(6) and S(5) corresponding to C14-H14···O3 and C10-H10···O1 respectively (Etter,1990)

The O1 of the nitro group is forming a bifurcated bond thus acting as an acceptor from two H - donors H14A and H10. The packing diagram showing the binary graph set of weak intra and inter molecular interactions is as in Fig.7.

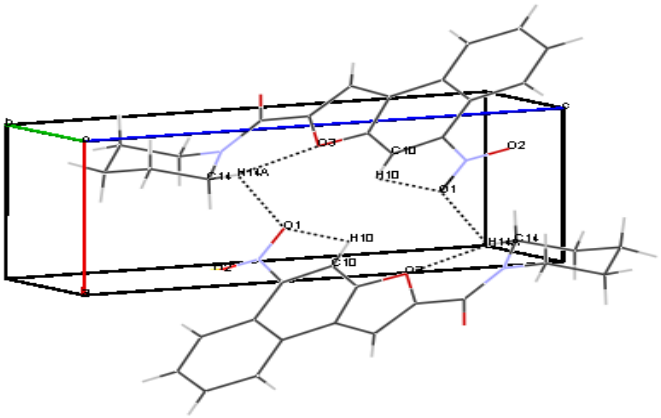


Fig.7 The packing diagram showing the binary graph set of weak intra and inter molecular interactions

In the crystal structure, within the selected asymmetric unit, the two molecules are linked by two C-H···O hydrogen bonds forming centrosymmetric inversion dimer exhibiting a graph set motif of $R^2_2(22)$ as shown in Fig.8. The non-bonded interactions and the possible hydrogen bonds in the crystal structure are reported in Table 3. This bimolecular aggregate can be regarded as the basic building block within the supramolecular structure which dictates the crystal packing. There are no direction-specific interactions between adjacent sheets. In particular, C-H···π (arene) hydrogen bonds and aromatic π- π stacking interactions are absent from the structure of the title compound.

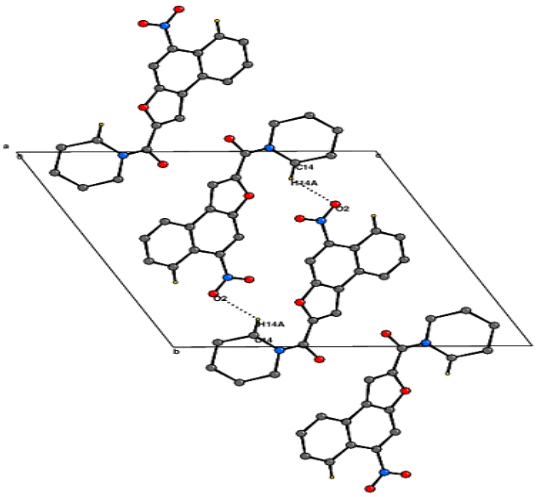


Fig 8. The C-H···O interactions making a graph set of $R^2_2(22)$ inversion dimers

Table 3 Nonbonded interactions and possible hydrogen bonds (Å and °) of NNFCP *(D-donor; A-acceptor; H-hydrogen)*

D—H· · ·A	D—H	H· · ·A	D· · ·A	D—H· · ·A
C3-H3···O2 (0)	0.930	2.149	2.769	123.10
C14-H14A···O3 (0)	0.970	2.096	2.850	133.28
C6-H6···O4 (1)	0.930	2.504	3.426	171.49
C11-H11···O4 (1)	0.930	2.320	3.215	161.27
C14-H14A···O (2)	0.970	2.684	3.412	132.19
C10-H10···O1 (2)	0.930	2.654	3.421	140.22
C15-H15A···O2 (3)	0.970	2.888	3.497	121.77
C16-H16A···O2 (4)	0.970	2.702	3.568	148.98
C18-H18A···O4 (5)	0.970	2.741	3.511	136.68

Symmetry code: (0) x,y,z (1) -x-1,-y,-z+1 (2) -x+1,-y-1,-z+1 (3) -x,-y-1,-z+1
(4) x,+y+1,+z-1 (5) x+1,+y,+z

4. Conclusion

The compound 1- [(8-Nitronaphtho [2, 1 - b] furan – 2-yl) carbonyl] piperidine has been synthesised and characterized by UV, FT-IR, ^{1}HNMR, Mass spectral data and X-ray Crystallographic analysis. Single crystal X-ray analysis reveals the absence of C-H…π (arene) and π- π stacking interactions in the packing of the molecules. It also explains the role of C-H…O interactions playing a dominant role in determining the crystal packing and molecular conformation of the title compound.

Acknowledgements

The authors are thankful to SAIF, IIT Madras for single crystal result. The authors are thankful to Professor and Chairman, Department of Chemistry, Kuvempu University for providing laboratory facilities. One of the authors is thankful to UGC for financial assistance. CRG and SS thank RSST and Principal, SSMRV Degree college for their encouragement and support.

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