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A Novel 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine ($C_{21}H_{26}N_2O_8$): Microwave-Irradiated Hantzsch Ester Synthesis, Characterization and Molecular Crystal

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The novel 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine was synthesized through multicomponent one pot Hantzsch ester synthesis using 4,5-dimethoxy-2-nitrobenzaldehyde, ethyl 3-oxobutanoate, and ammonium carbonate under microwave irradiation and subsequently characterized by several spectroscopic techniques, i.e., ESI mass, IR, ^1H, and ^{13}C NMR along with single crystal X-ray diffraction method. The single crystal of 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine ($C_{21}H_{26}N_2O_8$) was developed in 0.35 × 0.30 × 0.25 mm dimension in methanol. The crystal structure parades only intermolecular hydrogen bonding of the N(2)-H(2A) . . . O(2) type and the boat conformation of the dihydropyridine ring.

Keywords Crystal structure; microwave-irradiated Hantzsch ester synthesis; single-crystal X-ray diffraction study; symmetric 1,4-DHP

1. Introduction

1,4-Dihydropyridines (1,4-DHPs) are most versatile, interesting and important research moiety for the investigators in synthetic, therapeutic, and bioorganic chemistry since the first synthesis of 1,4-DHPs reported by Hantzsch in 1882, which provides the convenient course of reaction for the synthesis of the symmetric 1,4-DHPs [1]. The development of 1,4-DHP-based drugs for the treatment of cardiovascular diseases has drawn considerable attention owing to their calcium antagonists activity or more specifically because they are persuasive L-type of calcium channel activators and blockers [2, 3]. Furthermore, 1,4-DHPs have been extensively used as PAF-acether antagonists [4], thromboxane synthetase inhibitors [5], antithrombotic antihypertensive agents [6], in the treatment of multidrug resistance during the cancer chemotherapy [7] together with the therapeutic treatment of cerebral and peripheral vascular disorders, congestive heart failure, arrhythmias, cardiomyopathy, atherosclerosis, and angina [8, 9].

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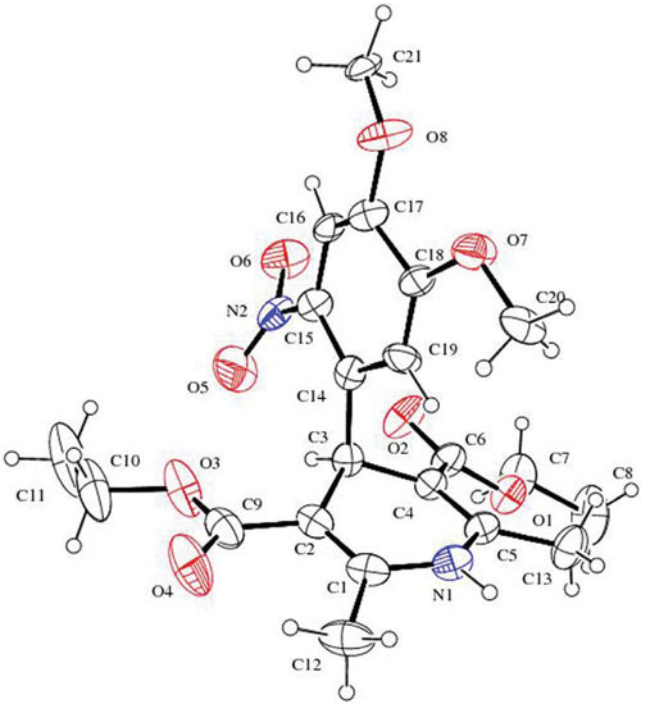


Figure 1. The molecular structure of the title compound ($C_{21}H_{26}N_2O_8$) showing the atom-labeling scheme (ORTEP).

Drugs based on 1,4-DHP (i.e., nisoldipine, nifedipine, aranidipine, nitrendipine, nimodipine, nilvadipine, etc.) nucleus and having axial ortho/meta-nitrophenyl substitution at the third C(3) position, are significantly valuable molecules for the treatment of cardiovascular disorder as the calcium channel antagonists. Accordingly, change in substitution on the second C(2) and fourth C(4) position of 1,4-DHP leads to a wide variety of symmetric as well as asymmetric structures [10] (Fig. 1). The structure activity relationships (SARs) study of 1,4-DHPs are prime area of interest for the development of efficient biological and pharmacological molecules and plausible explanations for the structural requirements for optimum activity have been provided [11–13]. The calcium channel antagonists activity of 1,4-DHPs is driven by the SARs, which is influentially dependent on the nature and position of the substitutions present on the phenyl ring [14, 15]. The SAR study of nifedipine suggests that the substitution available at the second C(2), third C(3), and fourth C(4) atoms diverges the activity and the tissue selectivity [16, 17]. Significant to mention here, that the SAR is independent of the electron donating or withdrawing nature of the substituent on the phenyl ring, rather highly dependent on the bulkiness of the substituent. The size, nature, and position of the substitutions on the phenyl ring are the vital points of voltage-dependent calcium channel antagonist activity [18, 19].

Literature reports reveal that most of the 1,4-DHP compounds with symmetric functionalities having esters, sulphonyl, nitrile, or acyl groups at second C(2) and fourth C(4) position, and a phenyl ring at third C(3) position of the 1,4-DHP ring are the essential requirement for the therapeutic activity [20–22].

The single-crystal X-ray diffraction studies of 1,4-DHPs indicates that the degree of puckering could be stimulus by the various substitution available on the phenyl ring at the

third C(3) position of 1,4-DHP ring and confine the free rotation of the phenyl ring because of the second C(2) and fourth C(4) position which becomes a purpose for a more favorable conformation for drug receptor interaction [23, 24].

Keeping the key information about symmetric 1,4-DHPs in mind and continuing with our previous report on the crystal structure studies of 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbmethoxy-1,4-dihydropyridine ($C_{19}H_{22}N_2O_8$) [25], which was synthesized by the conventional Hantzsch synthetic method, we have decided to focus our research interest for the synthesis of the title compound under microwave irradiation.

The title compound is structurally similar to nifedipine drug, however, differs in substituent present at second C(2) and fourth C(4) positions, i.e., 3,5-dicarbethoxy instead of 3,5-dicarbmethoxy additionally with two methoxy groups on the ortho nitrophenyl ring at the third position C(3) of DHP ring. Accordingly, the title compound was synthesized by the Hantzsch synthesis and characterized by means of suitable physical and spectroscopy techniques. The single crystal of 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine ($C_{21}H_{26}N_2O_8$) have been developed in a mixture of acetonitrile and methanol (1:1 v/v ratio) by the crystallization method and confirmed by single-crystal diffraction method.

2. Experimental

2.1. Chemicals and Reagents

All Reagents and solvents were commercially available from Spectrochem (India) and Merck and were used as received without further purification.

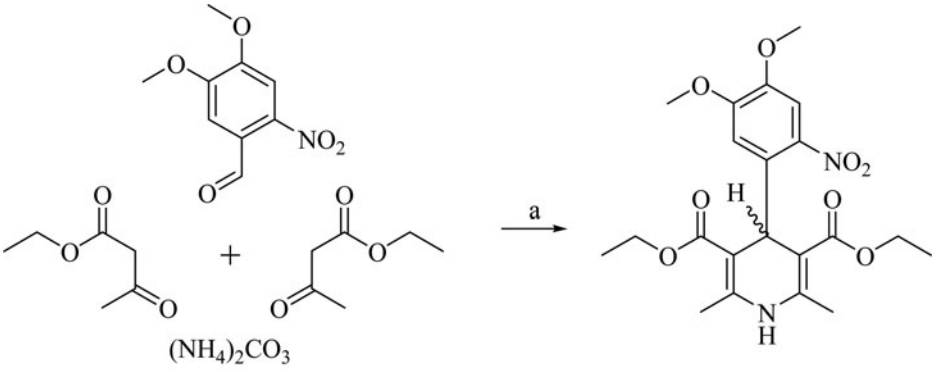
2.2. Physical Measurements

Analytical TLC was performed on silica gel-G using benzene:acetone (7:3) as solvent system. Synthesis of the compound was carried out in domestic microwave oven, Whirlpool AKL260, 400 W. Melting point was determined in open capillaries on a melting point apparatus purchased from JSGW and is uncorrected. The synthesized compound was micro analyzed satisfactorily for C, H, and N in EURO EA Elemental Analyzer, EA-3000, RS-232. The IR spectra were recorded on Shimadzu FT-IR 8400 spectrophotometer using KBr discs. The ESI mass spectra were recorded on Micromass Q-Tof Micro having mass Range of 4000 amu in quadruple and 20000 amu in ToF. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Av 500 spectrophotometer. The chemical shifts are reported in δ ppm scale, using the TMS as an internal standard. The single crystal XRD was obtained on Enraf Nonius CAD4-MV_{31} diffractometer.

2.3. Synthesis of 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1, 4-dihydropyridine ($C_{21}H_{26}N_2O_8$)

A fusion mixture of 4,5-dimethoxy-2-nitrobenzaldehyde (10 mmol), ethyl 3-oxobutanoate (0.025 mol), and ammonium carbonate (0.015 mol) in 10 mL methanol was transferred into a 25 mL round bottom flask and was then irradiated at 400 W in a domestic microwave oven for 15 min. The progress of reaction was monitored by TLC using benzene:acetone (7:3) solvent system. After completion of reaction, the resulting reaction mixture was cooled to room temperature and treated with little quantity of methanol and then poured into the

crushed ice followed by filtration through suction. The solid thus obtained was washed with small amount of water and dried in air under vacuum to give the product as lemon yellow color powder (Scheme 1).



[a]Reagents and conditions: Methanol; Microwave irradiation; 400 W; 15 minute

Scheme 1. Reaction scheme for the synthesis of 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine ($C_{21}H_{26}N_2O_8$).

Yield 98%, m.p. 205–215°C, elemental analysis: ($C_{21}H_{26}N_2O_8$) calcd. C, 58.06; H, 6.03; N, 6.45; O, 29.46; found C, 57.91; H, 5.88; N, 6.31; O, 29.33, mass: $m/z = 433.31$, IR (KBr, ν cm^{-1}): 3421–3288 (N-H stretching), 3091, and 3047 (C-H stretching of aromatic), 2978 (C-H asymmetric stretching of $–CH_3$), 2910 (C-H symmetric stretching of $–CH_3$), 2856 (C-H asymmetric stretching of $–CH_2$), 2781 (C-H symmetric stretching of $–CH_2$), 1739 and 1697 (C = O stretching of ester), and 1217 and 1037 (C-table O-C stretching of $–OCH_3$). ^{1}H NMR (δ ppm, $CDCl_3$ + 500 MHz): 1.17 (t, $J = 15$ Hz, 6H, $-CH_3$), 2.34 (s, 6H, $-CH_3$), 3.84 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 3.98–4.01 (m, 2H, $-CH_2$), 4.10–4.14 (m, 2H, $-CH_2$), 5.70 (s, 1H, -NH), 6.01 (s, 1H, -CH), 6.95 (s, 1H, Ar-H) and 7.38 (s, 1H, Ar-H). ^{13}C NMR (δ ppm, $CDCl_3$ + 125 MHz): 14.11, 19.57, 34.53, 55.93, 56.20, 60.09, 104.43, 107.31, 112.37, 137.36, 140.38, 144.23, 147.08, 152.71, 167.30.

2.4. Single-Crystal Development Method

In a 100 mL beaker, 1 g quantity of dried pure product was taken along with sufficient amount of mixture of acetonitrile and methanol in 1:1 v/v ratio and heated on hot plate till solid product gets dissolved, 1 g of charcoal was added and heated again then filtered the hot solution through Whatman 42 filter paper in 50 mL stopper conical flask and cover the stopper a little opened. The filtered solution was allowed to stand at room temperature for 4–6 weeks to form lemon yellow-colored crystals by slight evaporation. The crystals thus obtained were filtered and washed with very small quantity of methanol and analyzed by single-crystal X-ray diffraction method. The structure, achieved by X-ray crystallographic analysis, is provided in Fig. 1.

3. Results and Discussion

The symmetric, 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine ($C_{21}H_{26}N_2O_8$) compound have been synthesized via Hantzsch synthesis

Table 1. Crystal data and structure refinement for title compound ($C_{21}H_{26}N_2O_8$)

Identification code	Shelxl
Empirical formula	C_{21} H_{26} N_2O_8
Formula weight	434.44
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 8.2977(3)$ Å $\alpha = 90^\circ$
	$b = 18.3410(7)$ Å $\beta = 91.9540(10)^\circ$
	$c = 14.5295(5)$ Å $\gamma = 90^\circ$
Volume	2209.93(14) A^3
Z	4
Calculated density	1.306 mg/m^3
Absorption coefficient	0.101 mm^{-1}
$F(000)$	920
Crystal size	0.35 × 0.30 × 0.25 mm
Theta range for data collection	2.22° to 24.06°
Limiting indices	$-9 \le h \le 9$
	$-21 \le k \le 19$
	$-16 \le l \le 11$
Reflections collected/unique	18220/3495 [R(int) = 0.0254]
Completeness to theta = 24.06	99.9%
Absorption correction	Semiempirical from equivalents
Max. and min. transmission	0.9752 and 0.9156
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3495/285/478
Goodness-of-fit on F^2	1.023
Final R indices [$I > 2$sigma(I)]	$R_1 = 0.0376$, $wR_2 = 0.1010$
R indices (all data)	$R_1 = 0.0554$, $wR_2 = 0.1140$
Extinction coefficient	0.0087(11)
Largest diff. peak and hole	0.158 and −0.111 e. $Å^{-3}$

by using microwave oven in excellent yield (98%). The synthetic route used for the synthesis of title compound is sketched out in Scheme 1. The reaction involves a multicomponent cyclocondensation of ethyl 3-oxobutanoate, 4,5-dimethoxy-2-nitrobenzaldehyde and ammonium carbonate in methanol. The IR, ESI mass, ^{1}H, and ^{13}C NMR spectral data, given in experimental part are in full agreement of the newly synthesized 1,4-DHP's structure.

The IR spectral data shows the characteristic N-H stretching at 3421–3288 cm^{-1} of 1,4-DHP ring and C=O stretching at 1739 and 1697 cm^{-1} of ester group available on C(6) and C(9) carbon atoms. Asymmetric and symmetric stretching bands of $–CH_3$ obtained at 2978 and 2910 cm^{-1}, respectively, available on C(1) and C(5) carbon atoms. The ESI mass spectral data show the value of molecular ion peak at 433.31 *m/z* suggesting the total molecular weight of the title compound. The ^{1}H NMR spectral data shows characteristic singlet peaks at 7.38, 5.70, 3.90, and 2.34 δ ppm corresponds to –NH, -CH, -OCH_3, and

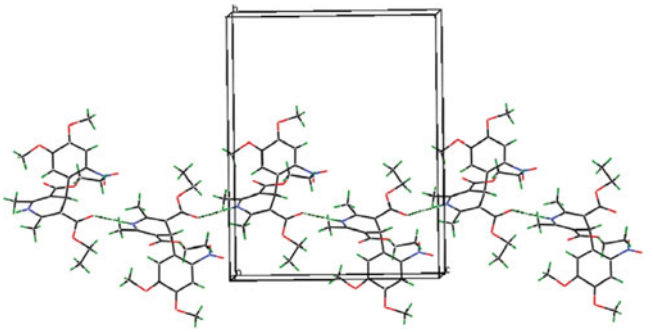


Figure 2. The unit cell content of $C_{21}H_{26}N_2O_8$ showing hydrogen bonding interactions.

–CH_3 groups. The ^{13}C NMR data display the characteristic dihydro carbon peak of 1,4-DHP motif at 104.43 and 152.71 δ ppm.

3.1. Crystal Structure

The crystal structure of the title compound was cracked by direct method SHELXS-97 [26] and determined by full matrix least-squares on F^2 with program system SHELXL-97 [27]. The monoclinic single-crystal system of the title compound was obtained in 0.35 × 0.30 × 0.25 mm dimensional crystal size and analyzed at 293(2) K temperature for the collection of crystal data. The intensity data of crystal of the title compound having shelxl identification code were collected using graphite monochromated Mo $K\alpha$ radiation (0.71073 Å) in the ω-2θ scan mode. The title compound crystallizes in the monoclinic $P2_1/c$ space group with unit cell dimensions $a = 8.2977(3)$ Å, $b = 18.3410(7)$ Å, and $c = 14.5295(5)$ Å, $\alpha = 90$, $\beta = 91.9540(10)$, $\gamma = 90$. The crystal data and final refinement details of the title compound are given in Table 1. The equivalent isotropic displacement parameters and atomic coordinates of all nonhydrogen atoms for title compound ($C_{21}H_{26}N_2O_8$) are enumerated in Table S1. The bond lengths and bond angles between atoms, observed through single crystal analysis are in sync with the previously reported symmetric 1,4-DHP crystal structures [28] and the data are given in Table S2.

The anisotropic displacement parameters of title compound for all atoms except hydrogen atoms are listed in Table S3. The hydrogen atoms were refined riding on their bonded atoms with a global isotropic temperature factor are given in Table S4.

The N(1) atom of pyridyl ring shows an sp^2 hybridization [29], which can be understood from the observed values of the bond angles of the title compound, C(1)-N(1)-C(5) at 123.56(14), C(1)-N(1)-H(1) at 119.2(12), and C(5)-N(1)-H(1) at 115.9(12) and the equal orientation observed for the N(2) atom of nitro group in the phenyl ring O(5)-N(2)-O(6) at 123.3(9) (Table S2).

A closer look on the literature reports suggest that, if carbonyl groups are involved in hydrogen bonding then they makes an *antiperiplanar* (ap/trans) conformation, whereas the carbonyl groups, not involved in the hydrogen bonding would be defined as *synperiplanar* (sp/cis) [30, 31]. The C(1)-C(2)-C(9)-O(4) and C(5)-C(4)-C(6)-O(2) torsion angles are 14.8(7) and -172.5(9), respectively (Table S5), showing that C(5)-C(4)-C(6)-O(2) carbonyl group is *antiperiplanar* (ap/trans) to the respective endocyclic (C=C) double bonds of the 1,4-DHP ring (Fig. 2) [32].

Table 2. Hydrogen bonds [Å and °] for $C_{21}H_{26}N_2O_8$

D-H ... A	d(D-H)	d(H ... A)	d(D ... A)	<(DHA)
N(2)-H(2A) ... O(2)[a]	0.88(2)	2.22(2)	3.062(2)	160.8(18)

Where, a = Symmetry transformations used to generate equivalent atoms: x, y-1, z.

Whereas, the previously reported analogous DHP compound is *synperiplanar* having hydrogen bonding with the N(2) atom of the nitro group available on C(15) carbon atom [25].

The crystal structure of title compound shows intermolecular hydrogen bond of N(1)-H(1) ... O(2) atoms, having $(x, -y + \frac{1}{2}, z - \frac{1}{2})$ symmetry code with 2.114(17) Å length and 173.7(17) angle (Table 2). The same is reflected in enhanced stability of the crystal structure and might also play crucial role in its desired calcium antagonist effect [33–35].

Differing from the earlier reported 1,4-DHPs [36], the intermolecular distances and size of bond angles between two atoms in title compound are shorter, which resulted in the increase stability of the crystal structure. The substituted phenyl ring of the newly synthesized 1,4-DHP have planar conformation (pseudoaxial conformation). However, angles C(4)-C(3)-C(2) and C(1)-N(1)-C(5) of pyridyl ring are observed at 110.04(13) and 123.56(14) from the mean plane with the help of rest of the carbon atoms which describes the boat type arrangement of the DHP ring. The plane of phenyl ring of the title compound is apparently perpendicular to DHP planar ring (Fig. 1) and dihedral angle between phenyl ring and DHP ring is C(4)-C(3)-C(14) at 110.37(13) and C(2)-C(3)-C(14) at 111.10(13). Data compiled in Table S2 also advocates for the presence of co-planarity of the phenyl ring in the title compound. The dimension of the torsion angles is directly reflected by the degree of ring distortions of DHP ring at N(1) and C(3) atoms. The torsion angle value of C(1)-C(2)-C(3)-C(4) at 25.0(2) is higher in the DHP ring, which indicates that C(3) atom has greater puckering than at N(1) atom. This gives confirmation for a flat boat conformation by the DHP ring in the title compound. The flattened boat-type conformation of 1,4-DHP and the perpendicular orientation of the substituted phenyl ring C(14), C(15), C(16), C(17), C(18), C(19) with respect to the dihydropyridine ring is most suitable conformation for the calcium channel antagonist activity [37, 38]. A similar report of almost boat type conformation has also been documented in path breaking 1,4-DHPs-based drug molecules nisoldipine and nifedipine [39]. The distance between C(3) and N(1) atoms and the perpendicular orientation of phenyl ring on C(3) atom further gives evidences for the flattened boat-type conformation of the dihydropyridine ring.

4. Conclusion

The 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine ($C_{21}H_{26}N_2O_8$) has been successfully synthesized by microwave irradiation. The flattened boat-type molecular structure of the title compound have been confirmed by single crystal X-ray diffraction crystallographic method having perpendicular phenyl ring at the fourth position of DHP ring. Moreover, functional groups and molecular weight were determined by the IR, ^{1}H-, ^{13}C- NMR, and Mass spectroscopic methods.

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Supplementary Data

Crystallographic data for the structure reported in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-957556 for the 4-(4,5-dimethoxy-2-nitrophenyl)-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine ($C_{21}H_{26}N_2O_8$). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk, www: http://www.ccdc.cam.ac.uk).

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