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Synthesis, Crystal Structure, and Spectroscopic Properties of 5-Ethoxycarbonyl-4-[(4-methoxy-carbonyl)phenyl] -6-methyl-3,4-dihydropyrimidin2(1H)-ones

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The title compound, 5-ethoxycarbonyl-4-[(4-methoxycarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (1), was synthesized from the one-pot, three-component condensation reactions and characterized by FTIR, ^{1}H NMR, HRMS, and single crystal X-ray diffraction. The compound (1) crystallizes in a triclinic system, space group P-1 with $a = 6.1874(12)$, $b = 7.5715(15)$, $c = 17.369(4)$Å, $\alpha = 80.24(3)$, $\beta = 81.15(3)$, $\gamma = 76.93(3)^\circ$, and $Z = 2$. The molecules are linked by hydrogen bonds N–H···O and C–H···O to generate a 2D network. In addition, UV-visible and fluorescence spectral measurements prove that it shows positive solvatochromic effect as the solvent polarity was increased.

Keywords Crystal structure; 3,4-dihydropyrimidin-2(1H)-ones; fluorescence; solvatochromic effect; synthesis

Introduction

Recently, heterocyclic compounds have been extensively investigated because of their significant properties and applications in organic and medicinal chemistry. Among these compounds, dihydropyrimidinones and their derivatives have gained the remarkable importance in recent years due to their wide range biological activities, such as calcium channel blockers [1], antitumor [2], antiviral [3], antioxidant [4], anti-HIV [5], antimicrobial [6], antihypertensive, and anti-inflammatory actions [7, 8]. In addition, several alkaloids containing the dihydropyriminone-5-carboxylate core unit have been isolated from marine sources, which also possess interesting biological properties [9, 10]. Moreover, 3,4-dihydropyrimidin-2(1H)-ones and their derivatives has been used as sequence-selective DNA-binding agents by fluorescence and ultraviolet spectroscopy techniques

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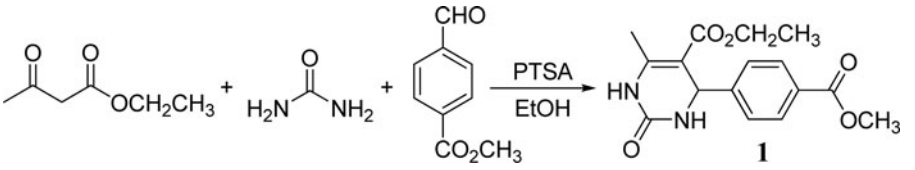

Scheme 1. Synthesis route of 5-ethoxycarbonyl-4-[(4-methoxycarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (1).

[11, 12]. Additionally, the interactions between 3, 4-dihydropyrimidin-2(1H)-ones and bovine serum albumin were also investigated by fluorescence and ultraviolet spectroscopy method [13].

Based on important application of dihydropyrimidinone compounds, we herein report that a 3,4-dihydropyrimidinone derivatives, 5-ethoxycarbonyl-4-[(4-methoxycarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (1) has been synthesized by the one-pot, three-component condensation reactions (Scheme 1) and the structure was characterized by FTIR, ^{1}H NMR, HRMS, and single-crystal X-ray diffraction. Meanwhile, the photophysical properties were also investigated by UV-visible and fluorescence spectroscopy.

Experimental

Materials and Instruments

All reagents and solvents for synthesis and analyses were of analytical grade and used without further purification. Melting points were determined on X4 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded in KBr disks on Nicolet 6700 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 MHz spectrometer using TMS as internal standard and DMSO as a solvent. HRMS spectra were obtained on Thermo Scientific Exactive Plus Mass spectrometer. UV-visible and fluorescence spectra were measured on Mapada UV-3300 and F-7000 fluorescence spectrophotometers in different polar organic solvents.

Synthesis of 5-ethoxycarbonyl-4-[(4-methoxycarbonyl)phenyl]-6-methyl -3,4-dihydropyrimidin-2(1H)-ones

A stirred mixture of ethyl acetoacetate (2 mmol), methyl 4-formylbenzoate (2 mmol), urea (2 mmol), and p-toluenesulfonic acid (0.2 mmol) were refluxed in ethanol (10 mL) until the reaction completed. After cooling, the resulting solid product was filtered and recrystallized from ethanol to afford pure compounds, yield 82%. mp.191∼193°C. IR (KBr), ν(cm^{-1}): 3240, 3111, 2987, 1731, 1706, 1652, 1605, 1287, 1221, 1092. ^{1}H NMR(DMSO-d_6, 400 MHz): 9.27 (s, 1H, -NH), 7.93 (d, 2H, J = 8.0 Hz, Ar-H), 7.82 (s, 1H, -NH), 7.38 (d, 2H, J = 8.0 Hz, Ar-H), 5.22 (d, 1H, J = 3.2 Hz, CH), 3.99∼3.96 (m, 2H, -OCH_2), 3.83 (s, 3H, -OCH_3), 2.26 (s, 3H, -CH_3), 1.08 (t, 3H, J = 7.2 Hz, -OCH_2CH_3). HRMS calcd for [M + H]$^+$ $C_{16}H_{18}N_2O_5$: 319.1249, found 319.1261.

Table 1. Crystal and structure refinement data for compound (**1**)

Compound	**1**
CCDC number	981746
Empirical formula	$C_{16}H_{18}N_2O_5$
Formula weight	318.32
Temperature	293(2)
Wavelength	0.71073
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions(Å, °)	$a = 6.1874(12)$; $\alpha = 80.24(3)$ $b = 7.5715(15)$; $\beta = 81.15(3)$ $c = 17.369(4)$; $\gamma = 76.93(3)$
Volume(Å^3), Z	775.5(3); 2
Calculated density (g cm^{-3})	1.363
Absorption coefficient μ(mm^{-1})	0.102
F(000)	336
Crystal size (mm^3)	0.30 × 0.26 × 0.20 mm
Theta range for data collection (°)	3.19 to 25.00
Limiting indices	$-7 <= h <= 7$, $-8 <= k <= 8$, $-20 <= l <= 20$
Reflections collected	5966
Independent reflection	2717 [R(int) = 0.0370]
Completeness to theta	97.1
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2648/0/216
Goodness-of-fit on F^2	1.103
Final R indices [$I > 2$sigma(I)]	$R1 = 0.0511$, $wR2 = 0.1526$
R indices (all data)	$R1 = 0.0853$, $wR2 = 0.1799$
Largest diff. peak and hole	0.271 and −0.302

Crystal Structure Determination and Refinement

Single crystals of the compounds (**1**) suitable for X-ray diffraction analysis were grown by slow evaporation of the ethanol solution at the room temperature. The colorless block crystal with dimensions of 0.30 mm × 0.26 mm × 0.20 mm was selected for X-ray diffraction analysis. The intensity data was collected at 293(2) K on a Rigaku Weissenbery IP diffractometer equipped with a graphite monochromated Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å) by using an $\omega/2\theta$ scan mode. The structure was solved by direct methods using SHELXS-97 program [14] and refined by full-matrix least-squares techniques on F^2 using SHELXL-97 [15]. Hydrogen atoms of C–H were generated geometrically. The crystal data and structure refinement details are reported in Table 1. The selected bond lengths and bond angles for compound **1** are listed in Table 2. The hydrogen bond lengths and bond angles of compound **1** are presented in Table 3.

Results and Discussion

Synthesis

The synthetic rout for the preparation of compound (**1**) is depicted in Scheme 1. The compound (**1**) was obtained in good yield through one-pot**,** three-component Biginelli

Table 2. Selected bond lengths (Å) and bond angles (°)

Bond	Dist.	Bond	Dist.	Bond	Dist.
N(1)-C(10)	1.339(3)	N(1)-C(9)	1.464(4)	N(2)-C(10)	1.361(3)
N(2)-C(11)	1.382(4)	O(1)-C(2)	1.334(4)	O(1)-C(1)	1.445(4)
O(2)-C(2)	1.195(4)	O(3)-C(10)	1.227(3)	O(4)-C(15)	1.215(3)
O(5)-C(15)	1.345(3)	O(5)-C(14)	1.433(4)	C(2)-C(3)	1.486(4)
C(3)-C(4)	1.375(4)	C(3)-C(8)	1.387(4)	C(4)-C(5)	1.378(4)
C(5)-C(6)	1.382(3)	C(6)-C(7)	1.381(4)	C(6)-C(9)	1.519(4)
C(7)-C(8)	1.368(4)	C(9)-C(12)	1.520(3)	C(11)-C(12)	1.345(4)
C(11)-C(13)	1.490(3)	C(12)-C(15)	1.466(4)	C(14)-C(16)	1.498(4)
Angle	(°)	Angle	(°)	Angle	(°)
C(10)-N(1)-C(9)	125.4(2)	C(10)-N(2)-C(11)	124.3(2)	C(2)-O(1)-C(1)	117.0(3)
C(15)-O(5)-C(14)	116.6(2)	O(2)-C(2)-O(1)	124.0(3)	O(2)-C(2)-C(3)	124.3(3)
O(1)-C(2)-C(3)	111.8(3)	C(4)-C(3)-C(8)	118.6(3)	C(4)-C(3)-C(2)	119.1(2)
C(8)-C(3)-C(2)	122.2(3)	C(3)-C(4)-C(5)	120.6(2)	C(4)-C(5)-C(6)	121.1(2)
C(5)-C(6)-C(7)	117.7(2)	C(5)-C(6)-C(9)	121.1(2)	C(7)-C(6)-C(9)	121.2(2)
C(8)-C(7)-C(6)	121.6(2)	C(7)-C(8)-C(3)	120.3(3)	N(1)-C(9)-C(12)	109.6(2)
N(1)-C(9)-C(6)	109.5(2)	C(12)-C(9)-C(6)	113.1(2)	O(3)-C(10)-N(1)	123.4(2)
O(3)-C(10)-N(2)	120.6(2)	N(1)-C(10)-N(2)	116.0(3)	C(12)-C(11)-N(2)	119.3(2)
C(12)-C(11)-C(13)	128.3(3)	N(2)-C(11)-C(13)	112.4(2)	C(11)-C(12)-C(15)	121.2(2)
C(11)-C(12)-C(9)	120.6(2)	C(15)-C(12)-C(9)	118.2(2)	O(5)-C(14)-C(16)	108.0(2)
O(4)-C(15)-O(5)	121.5(3)	O(4)-C(15)-C(12)	127.2(2)	O(5)-C(15)-C(12)	111.2(2)

condensation reactions using p-toluenesulfonic acid as catalyst. The procedure offers several advantages, including high yields, a short reaction time, milder conditions, and environmental friendly procedure, as well as easy isolation of products.

Spectroscopic Properties

The structures of the pure products (**1**) were confirmed by IR, ^{1}H NMR, and HRMS spectroscopic techniques. Its FTIR spectrum (Fig. 1) shows two absorption bands at 3240 and 3111 cm^{-1} suggesting the present of two NH groups. Three strong absorption bands appeared at 1731, 1706, and 1652 cm^{-1} that correspond to stretching vibrations of three –C=O groups. Furthermore, a weak absorption band around 1605 cm^{-1} may be contributed to the C=C stretching vibrations, conforming the formation of dihydropyrimidinone ring. The ^{1}H NMR of products (**1**) are presented in Fig. 2. The appearance of signals at 9.27

Table 3. Hydrogen bond lengths (Å) and bond angles (°)

D-H···A	d(D-H)	d(H···A)	d(D···A)	∠DHA(°)
N(1)-H(1)···O(4)[a]	0.82	2.31	3.1663	173
N(2)-H(2)···O(3)[b]	0.83	2.02	2.8494	179
C(13)-H(13A)···O(3)[b]	0.96	2.58	3.4403	150

Symmetry codes: (a) x, –1+y, z; (b) 3–x,1–y,–z.

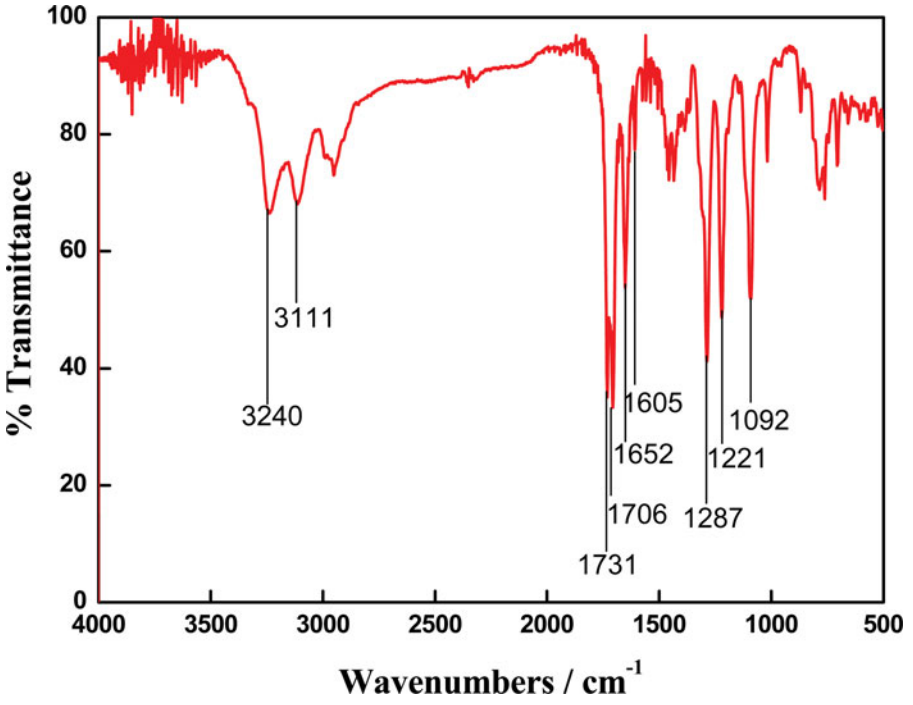

Figure 1. FT IR spectrum of compound (**1**).

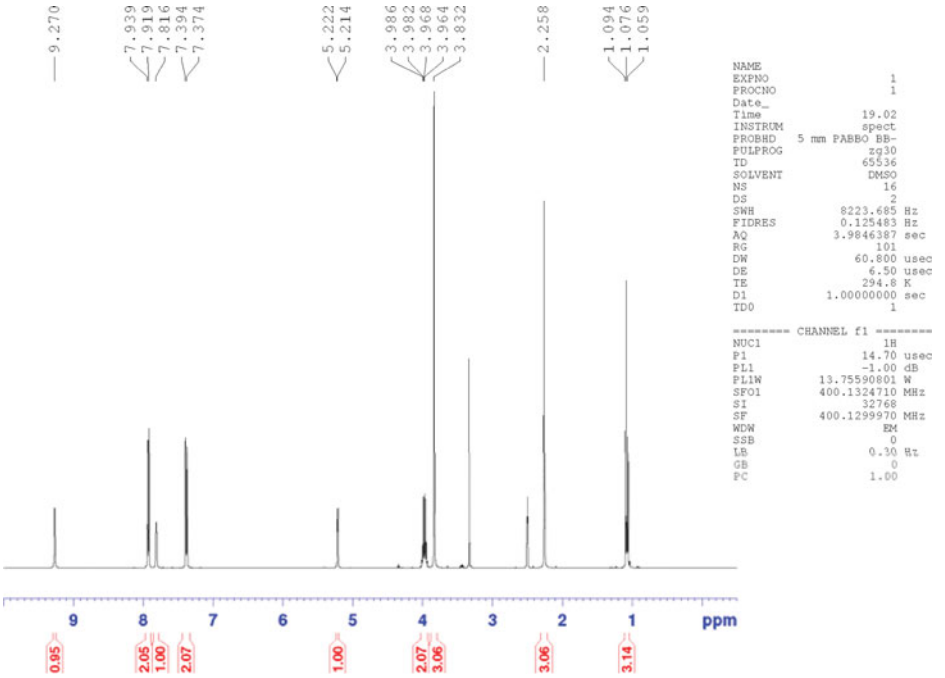

Figure 2. ^{1}H NMR spectrum of compound (**1**) in DMSO-d_6.

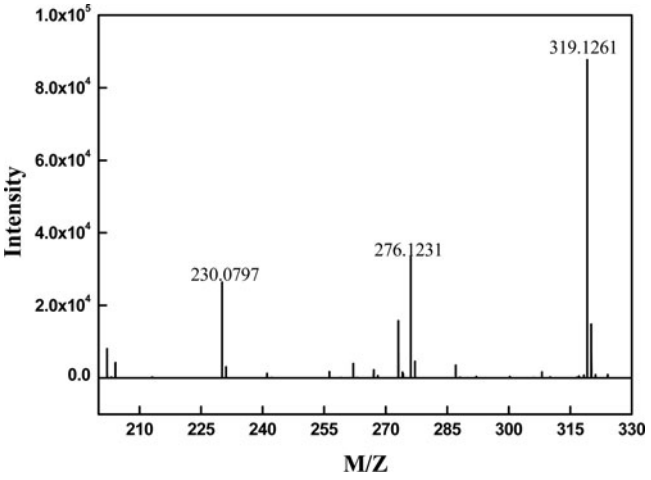

Figure 3. HRMS spectrum of compound (**1**).

and 7.82 ppm are assigned to two NH protons. The benzylic proton appeared as doublet signals around 7.93 and 7.38 ppm. The signals are observed at 5.22 ppm due to –CH- protons and the signals at 3.83 ppm is contributed to $-CH_3$ protons of methoxyl group. The $-CH_3$ protons of methyl group connected to dihydropyrimidinone ring was found at 2.26 ppm. While triplet and quadrate signals at 3.97 and 1.08 ppm are assigned to $-CH_2$- and $-CH_3$ protons of ethoxyl group, respectively. Finally, its structure was confirmed by HRMS spectral analysis and the experimentally obtained mass 319.1261 $[M + H]^+$ is in agreement with that of the calculated mass 319.1249 (Fig. 3).

Crystal Structure Description of the Compound (1)

As depicted in Fig. 4, the structure of **1** consists of a dihydropyrimidinone ring with an ethoxycarbonyl group and benzene ring with a methoxycarbonyl group. Bond lengths and angles are within normal ranges and comparable to a related structure [16]. The dihydropyrimidinone ring is nonplanar, which forms a twist-boat configuration, as indicated by the largest displacement at atom N1 from the least-squares plane −0.105(3) Å and the C(10)-N(1)-C(9)-C(12) torsion angle 24.0(1)° [17, 18]. The benzene ring is planar and constructs a dihedral angle of 8.0(5)° with the carboxyl connected to it. The benzene ring connected with dihydropyrimidinone ring by single bond of C(6)-C(9). The center of C(9) is belong to sp^3 configuration from the angles of N(1)-C(9)-C(6), N(1)-C(9)-C(12), H(9)-C(9)-C(6), and H(9)-C(9)-C(12) are 109.5(2)°, 109.6(2)°, 108.2(0)°, and 108.1(8)°, respectively. The carbonyl group C15 = O4 exists in an s-cis conformation with respect to the C11 = C12 double bond [19].

Figure 5 presents all main Hydrogen bonds in crystal structures of compound **1**. These bonds are formed between NH donor group and oxygen atoms as acceptors. Besides the N–H···O bonds, the weak Hydrogen bonds of the type C–H···O are also formed. The crystal packing is built up from the interaction of intermolecular hydrogen bonds to generate a 2D structure as shown in Fig. 6.

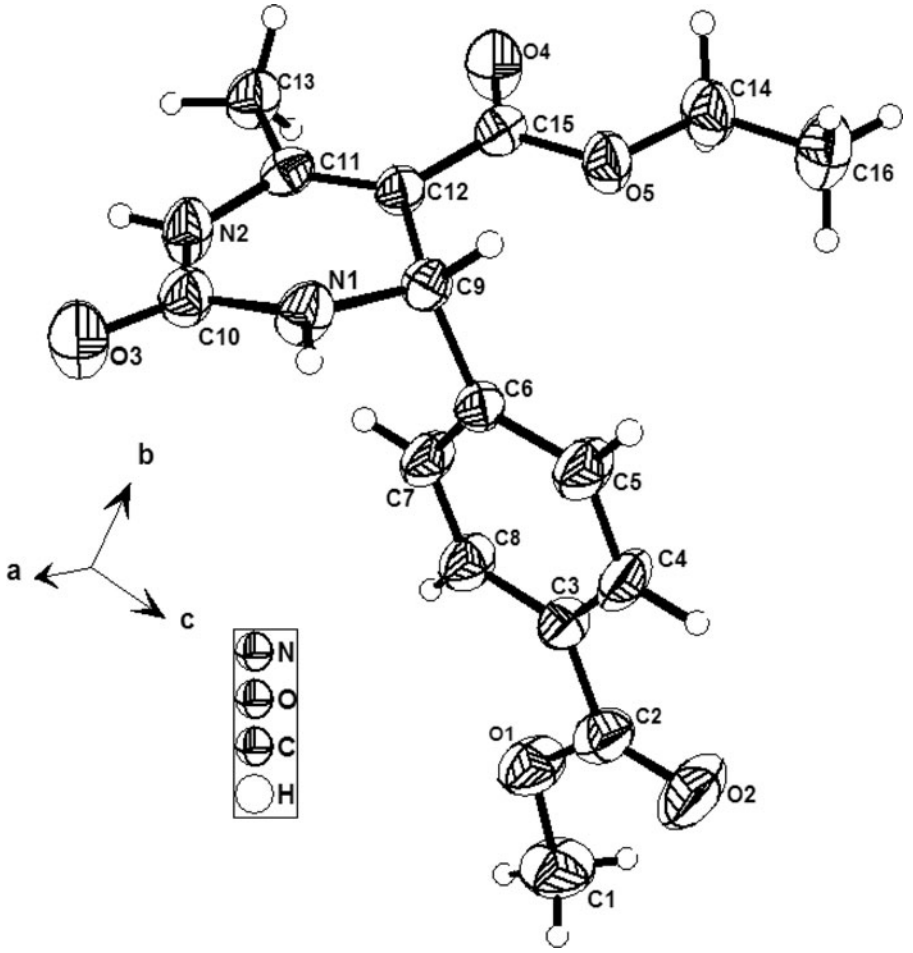

Figure 4. Molecular structure of compound (**1**).

Photophysical Properties

In order to study the photophysical properties of compound **1**, we have investigated the UV–visible absorption and fluorescence emission spectra of compound **1** in chloroform($CHCl_3$), tetrahydrofuran (THF), methanol (MeOH), dimethylformamide (DMF), and dimethyl sulfoxide (DMSO). These solvents were selected on the basis of increasing order of their dielectric constant values [20]. The relevant absorption and fluorescence spectral data along with the dielectric constants of solvents are presented in Table 4. Figure 7 shows the UV-visible absorption spectra at the concentration of 1×10^{-4} mol L^{-1} in different solvents and Fig. 8 shows the fluorescence emission spectra at the concentration of 1×10^{-5} mol L^{-1} in different solvents using an excitation wavelength of 282 nm.

In its UV-visible absorption spectra, the compound **1** display an intense broad band in the range 276–383 nm in different solvents. These absorption bands were ascribed to π-π^*electronic transition. The absorption maxima shifts were observed at solvent polarities

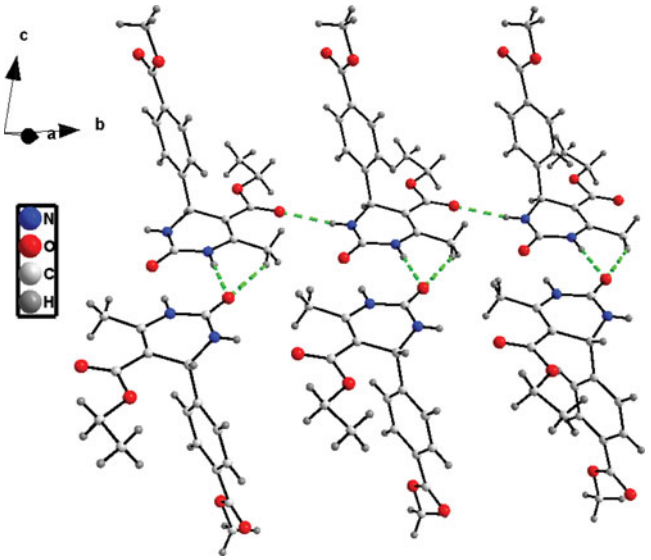

Figure 5. Interaction of intermolecular hydrogen bonds of compound (**1**).

changing from 1 nm to 6 nm. The absorption spectrum undergoes a redshift as the solvent polarity is increased from $CHCl_3$ to DMSO.

In its fluorescence spectra, an intense emission band has been observed in the region 319–344 nm in all the above mentioned solvents and the fluorescence spectra of compound **1** showed significantly larger solvatochromic effect. There was an appreciable change in emission maxima with the variation of solvent systems from polar ($CHCl_3$) to highly polar (DMF) solvent, with Stokes shift of 43–61 nm. The observed red shifting of emission bands in the absorption and emission spectra suggests the possibility of the enhanced intermolecular interactions between the fluorescent molecule and the solvent molecules. However, in case of DMSO no such observation was made due to its weak interactions with the fluorescent molecule.

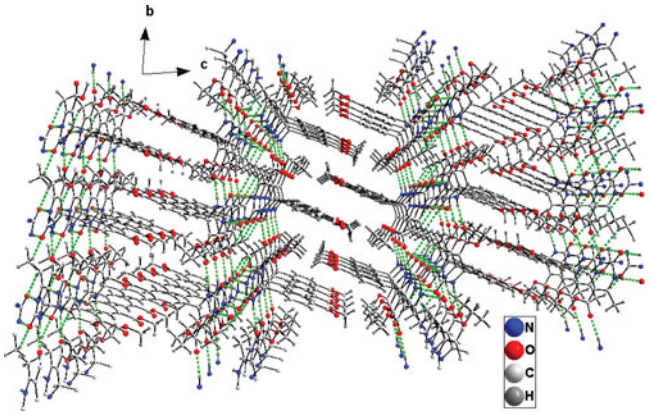

Figure 6. The crystal packing of compound (**1**), showing intermolecular hydrogen-bonding interactions as green dashed.

Table 4. Dielectric constant, photophysical properties, and Stoke shift values of compound (**1**) in different solvents

Solvent	Dielectric constant	λ_{abx} (nm)	λ_{em} (nm)	Stoke shift (nm)
$CHCl_3$	4.81	276	319	43
THF	7.58	282	330	48
MeOH	32.66	282	336	54
DMF	36.71	283	344	61
DMSO	46.45	283	340	57

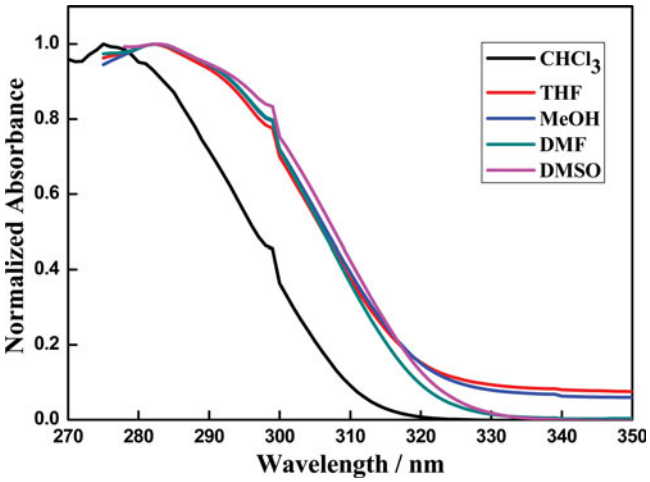

Figure 7. UV-visible spectra of compound (**1**) in different solvents.

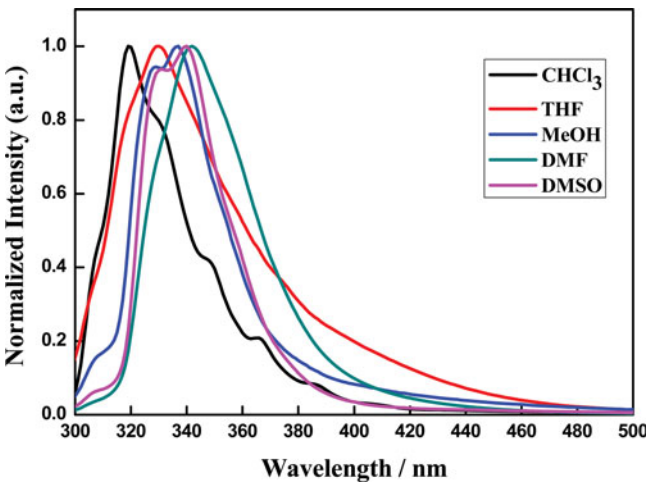

Figure 8. Fluorescence spectra of compound (**1**) in different solvents.

Conclusions

In the present study, 5-ethoxycarbonyl-4-[(4-methoxycarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (1) was successfully synthesized using a simple method and was characterized by spectral techniques. The crystal packing is built up from the interactions of intermolecular hydrogen bonds to generate a 2D structure. In addition, its photophysical measurements indicate that it exhibits good absorbent and fluorescent properties with positive solvatochromic behavior in different solvents.

Funding

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Supplementary Material

Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 981746. Copies of available material 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).

Supplemental data for this article can be accessed at http://www.tandfonline.com/gmcl

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