Synthesis and X-ray crystal structure analysis of 4-(3,4-dichlorophenyl)-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-naphthalen-1(2*H*)-one: Sertraline key intermediate analog

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The novel bioactive compound 4-(3,4-dichlorophenyl)-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-naphthalen-1(2*H*)-one was synthesised in three different methods, namely, conventional, MW irradiation with solvent and MW irradiation without solvent. The synthesised compound was characterised by spectroscopic techniques and finally confirmed by X-ray crystal structure analysis.

Keywords: antidepressant, sertraline, 4-(3,4-dichlorophenyl)tetralone, crystal structure

Tetralones are the versatile building blocks for the construction of molecules of biological interest.[1-4] Derivatives of tetralones are found to exhibit their binding affinities at dopamine D_2, serotonin 5-HT_{2A} and 5-HT_{2C} receptors, potential atypical antipsychotic profile,[5] promising inhibitory activity versus kidney mitochondrial 25-hydroxyvitamin D_3 24-hydroxylase (CYP24).[6] Some tosylates of tetralone derivatives are found to be the key intermediates in the synthesis of new CNS drugs.[7] Furthermore, the other derivative of tetralone namely, 4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalen-1(2*H*)-one is used to synthesise a sertraline hydrochloride. Sertraline hydrochloride (Fig. 1) was found to be a selective and potent competitive inhibitor of synaptosomal serotonin uptake and used for the treatment of depression, as well as dependency and other anxiety related disorders.[8-10]

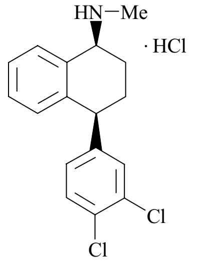
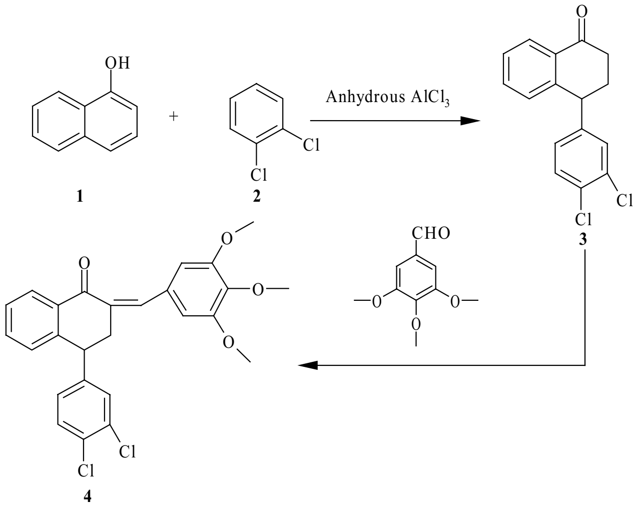


Fig. 1 Sertraline hydrochloride.

In light of the above observations, we have synthesised the novel possible bioactive 4-(3,4-dichlorophenyl)-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydro-naphthalen-1(2*H*)-one **4** using the sertraline hydrochloride key intermediate, 4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalen-1(2*H*)-one **3**. The incorporation of the trimethoxy phenyl ring to the active tetralone nucleus may possibly enhance the biological properties.

Nowadays microwaves (MW) have been employed in organic chemistry to reduce the reaction time from hours to minutes, to increase the yields and greater selectivity.[11] Particularly with solvent-free conditions, MW methods result in efficient and safe technology, "green chemistry".[12] As a part of our continued effort towards the synthesis of bioactive analogs, herein we have reported the synthesis and X-ray crystal structure analysis of a possible bioactive, 4-(3,4-dichlorophenyl)-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-naphthalen-1(2*H*)-one **4**.



Scheme 1

The compound 4-(3,4-dichlorophenyl)-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-naphthalen-1(2*H*)-one **4** was obtained by the Knoevenagel condensation reaction of 4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalen-1(2*H*)-one **3** with 3,4,5-trimethoxy benzaldehyde as shown in Scheme 1. The precursor **3** was synthesised by the reaction of naphthalen-1-ol with 1,2-dichlorobenzene in the presence of anhydrous aluminium chloride.[13] In order to increase the yield of the title compound **4** which may serve as a possible antidepressant, we have carried out the reaction under microwave heating using different conditions. It can be seen from Table 1 that the Knoevenagel condensation reaction has proceeded smoothly with excellent yields, in short time under microwave irradiation without solvent. Irradiation powers were varied between 20 and 50% and examined for the condensation of 4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalen-1(2*H*)-one **3** with 3,4,5-trimethoxy benzaldehyde to find the optimal reaction condition. It was found that the irradiation at 50% power level gave the highest yield of compound **4** with greater than 99% purity (Scheme 1, Table 1).

The ORTEP plot[14] of compound **4** is shown in Fig. 2. The crystal data are given in Table 2. The 3,4-dihydro-naphthalen-1(2*H*)-one ring is in nearly orthogonal position to

Table 1 The different methods used for the synthesis of title compound **4**.

Sample No.	Method	Reaction time	Yield/%
1	Conventional	4 h	65
2	MW irr. with solvent	90 s	82
3	MW irr. without solvent	60 s	96

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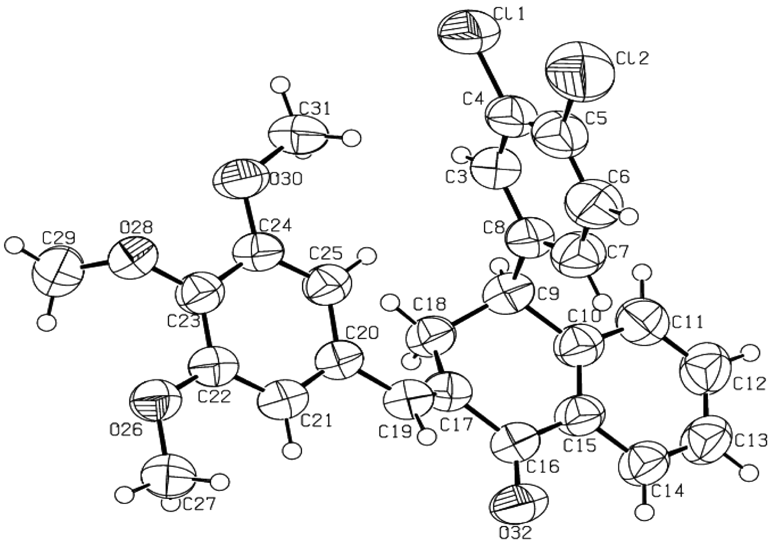

Fig. 2 ORTEP diagram of molecule **4** at 50% probability.

the 4-(3,4-dichlorophenyl) ring with the dihedral angle 87.2(3)°. The 3,4-dihydro-naphthalen-1(2*H*)-one ring adopts a half chair conformation with atom C18 deviating from the Cremer and Pople plane[15] defined by the atoms C9, C10, C11, C12, C13, C14, C15, C16, and C17 by –0.450(53) Å. The puckering amplitude is 0.5441(54) Å. The bond lengths and bond angles have normal values. The structure exhibits intramolecular and intermolecular hydrogen bonding of the type C–H...O. The intermolecular hydrogen bonding of the type C–H...O is with a bond length of 3.421(7) Å and a bond angle 159° with the symmetry code $\{1 + x, 1 + y, z\}$. The packing of the molecules when viewed down the *c* axis indicates that the molecules are interlinked by hydrogen bonds. The packing of the compound **4** is shown is Fig. 3.

Experimental

The melting points were determined on SELACO-650 hot stage apparatus and are uncorrected. IR (KBr) spectra were recorded on a Jasco FT/IR-4100 Fourier transform infrared spectrometer, ^{1}H NMR were recorded on Shimadzu AMX400, spectrometer by using $CDCl_3$ as solvent and TMS as an internal standard (Chemical shift in ppm). Elemental analyses were obtained on a vario-EL instrument. Thin layer chromatography (TLC) was conducted on 0.25 mm silica gel plates ($60F_{254}$, Merck). Visualisation was made with UV light. All extracted solvents were dried over Na_2SO_4 and evaporated with a BUCHI rotary evaporator. Reagents were obtained commercially and used as received.

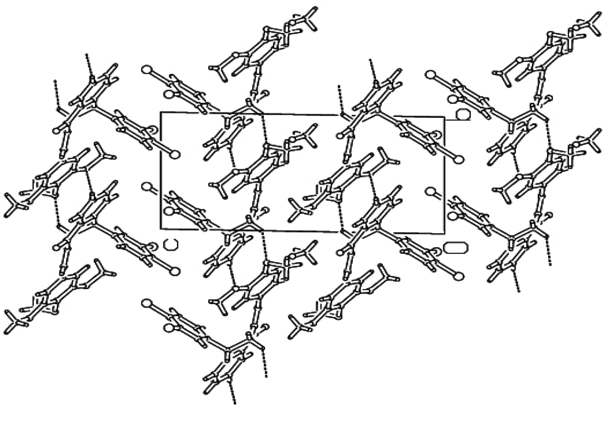

Fig. 3 Packing of molecule **4** along *C*-axis.

Table 2 Crystallographic details of molecule **4**

Empirical formula	$C_{26}H_{22}Cl_2O_4$
Formula weight	469.37
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	*Triclinic*
Space group	$P\bar{1}$
Cell dimensions	a = 7.871(2)Å
	b = 8.875(2)Å
	c = 16.890(4)Å
	α = 86.218(1)°
	β = 80.620(5)°
	γ = 73.877(1)°
Volume	1118.0(4)Å^3
Z	2
Density (calculated)	1.394 Mg/m^3
Absorption coefficient	0.322 mm^{-1}
F_{000}	488
Crystal size	0.3 × 0.25 × 0.25 mm
Index ranges	$-9 \leq h \leq 9$
	$-9 \leq k \leq 9$
	$-20 \leq l \leq 20$
θ range for data collection	2.39° to 25.02°
Reflections collected	4838
Independent reflections	3302 [R(int) = 0.0370]
Absorption correction	None
Max. and min. transmission	None and none
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3302/0/290
Goodness of fit on F^2	1.281
Final R indices [I>2σ(I)]	R_1 = 0.1029, wR_2 = 0.2850
R indices (all data)	R_1 = 0.1300, wR_2 = 0.3377
Extinction coefficient	0.006(8)
Largest diff. peak and hole	1.186 and –0.484 e.Å^{-3}

Synthesis and characterisation

General procedure for the preparation of 4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalen-1(2H)-one **3**

To a stirred solution of naphthalen-1-ol **1** (1 g, 6.94 mmol) in 1,2-dichlorobenzene **2** (0.78 ml, 6.94 mmol) anhydrous $AlCl_3$ (1.85 g, 13.87 mmol) was added. The reaction mixture was heated to 100°C and stirred at this temperature for 1 h. The reaction mixture was then cooled to room temperature and poured into ice and concentrated hydrochloric acid (3 ml), followed by the addition of dichloromethane (10 ml). The organic layer was separated, and the aqueous layer was extracted twice with dichloromethane (20 ml). The combined organic layers were washed with water (10 ml) and stirred with celite (1 g) and activated carbon (1 g) and filtered; the solvents were then evaporated in vacuum. To the oily residue, methanol (3 ml) was added. The product was crystallised, filtered, and then washed twice with methanol. Yield: 1.6 g (80%). M.p. 99–101°C.

Synthesis of 4-(3,4-dichlorophenyl)-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-naphthalen-1(2H)-one **4**

Method 1. Conventional

A mixture of 4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalen-1(2*H*)-one **3** (1 g, 3.43 mmol), 3,4,5-trimethoxybenzaldehyde (0.674 g, 3.43 mmol) was refluxed for 3–4 h with 10 ml of absolute ethanol containing ammonium acetate (0.529 g, 2 eq). After completion of the reaction (benzene: ethyl acetate: 7 : 3 used for TLC), ethanol was removed under vacuum. Deionised water was added to the residue and extracted with ethyl acetate (15 × 3 ml). The organic layer was dried over anhydrous sodium sulfate and solvent was evaporated under reduced pressure. The crude product was recrystallised from methanol. M.p. 103°C IR ν_{max} (KBr): 1670, 1620, 1133, 1005 cm^{-1} ^{1}H NMR: 7.3–7.5 (d, 5H, Ar–H), 3.7 (t, 1H, cyclohexane), 3.35–3.38(d, 2H, cyclohexane), 6.05–6.15 (s, 1H, C =CH–), 8.1–8.2 (d, H, Ar–H), 7.8–7.9 (s, 1H, Ar–H), 6.65–6.78 (s, 2H, Ar–H), 3.78 (s, 9H, $-OCH_3$). CHNS analysis: Anal Calcd for (C_{26} H_{22} Cl_2 O_4) C. 66.53, H. 4.72 Found: C. 66.53, H. 4.73%.

Method 2. MW irradiation with solvent

A mixture of 4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalen-1(2*H*)-one **3** (1 g, 3.43 mmol), trimethoxybenzaldehyde (0.674 g, 3.43 mmol) and ammonium acetate (0.529 g, 2 eq) moistened with water was taken in a 25 ml Erlenmeyer flask. It was irradiated in the microwave oven at 50% power level for 90 seconds. The reaction mixture was cooled, poured into water and extracted with ethyl acetate (15 × 3 ml). The combined solvent was concentrated in vacuum and the crude product was recrystallised using methanol to get pure crystalline solid **4**.

Method 3. MW irradiation without solvent

A 25 ml Erlenmeyer flask charged with equimolar mixture of 4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalen-1(2*H*)-one **3** (1 g, 3.43 mmol), trimethoxybenzaldehyde (0.674 g, 3.43 mmol) and ammonium acetate (0.529 g, 2 eq) was made slurry and irradiated in the microwave oven at 50% power level for 60 s. Using the above workup procedure we have obtained the pure compound **4**.

X-ray structure determination of compound **4**

A single crystal of the title compound with dimensions of 0.3 × 0.25 × 0.25 mm was chosen for X-ray diffraction studies. The measurements were made on a DIPLABO Image Plate system with graphite-monochromated Mo*Kα* radiation. Thirty-six frames of data were collected in oscillation mode with an oscillation range of 5°. Image processing and data reduction were done by using *DENZO*.[16] The reflections were merged with *Scalepack*. The peaks were successfully indexed with primitive triclinic lattice. The structure was solved using maXus.[17-19] All the non-hydrogen atoms were revealed in the first map itself. Initially, full-matrix least-squares refinement for 4838 reflections with isotropic temperature factors for all the nonhydrogen atoms was carried out. Subsequent refinements were carried out with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for hydrogen atoms, which were placed at chemically acceptable positions. The residuals finally converged to $R1 = 0.1029$. Full crystallographic details are deposited at Cambridge Crystallographic Database Centre (CCDC NO.616506).

In summary, we have synthesised a novel bioactive 4-(3, 4-dichlorophenyl)-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-naphthalen-1(2*H*)-one **4** by three different methods. Solvent-free microwave irradiation in presence of ammonium acetate at 50% power level resulted in high yield under shorter time and greater than 99% purity. And also environmentally benign process was achieved. Further, the single crystal X-ray crystallographic analysis of the possible biologically active compound **4** is reported.

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