Synthesis and crystal structure studies of (2*RS*)-3-[(2*RS*)-2-(1-hydroxy-cyclohexyl)-2-(4-methoxyphenyl)ethyl]-2-(pyridin-3-yl)thiazolidin-4-one

Chandagirikoppal V. Kavitha[a], Basappa[a], Kempegowda Mantelingu[a], Sundararaj I. Doreswamy[b], Javaregowda Shashidhara Prasad[b] and Kanchugarakoppal S. Rangappa[a]

Department of Studies in [a]Chemistry and [b]Physics, University of Mysore, Manasagangothri, Mysore-570006, INDIA

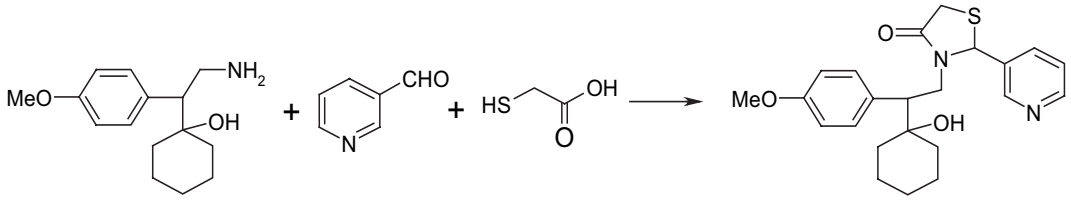
The compound (2*RS*)-3-[(2*RS*)-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl]-2-(pyridin-3-yl)-thiazolidin-4-one **4** was synthesised via one-pot three-component system in three different methods, such as conventional (DCC), MW irradiation with solvent and MW irradiation without solvent methods. Among them, MW irradiation without solvent has the advantage of short time with high yield and environmentally benign. The synthesised compound was characterised by spectroscopic technique and finally confirmed by X-ray diffraction. The compound crystallises in the triclinic crystal system with $Z = 2$ in the space group $P\bar{1}$. The cell parametres are $a = 10.317(9)$ Å, $b = 10.280(1)$ Å, $c = 11.408(6)$ Å, $\alpha = 73.824(6)°$ $\beta = 70.122(5)°$ $\gamma = 70.293(3)°$ and $R_1 = 0.0527$ for 10124 reflections [$I > 2\sigma(I)$]. The cyclohexane ring of the molecule is in chair conformation. The molecule exhibits intermolecular hydrogen bonds of type N–H...O and C–H...O.

Keywords: 4-thiazolidinone, venlafaxine analogs, crystal structure, pharmacological activity

Many naturally occurring and synthetic compounds containing the pyridine scaffold possess interesting pharmacological properties.[1] Among them, 2-pyridyl substituted 4-thiazolidinones are found to exhibit highly potent and selective anti-platelet activating factor activity both *in vitro* and *in vivo*.[2] Therefore, the synthesis of 4-thiazolidinone bearing pyridine moiety continues to attract interest in bioorganic and medicinal chemistry. Many other derivatives of 4-thiazolidinones have been reported to exhibit diverse pharmocological activities such as anti-inflammatory,[3] antiviral,[4] antimycobacterial, anti-microbial,[5] anti-cancer,[6] anti-fungal.[7] Consequently, several protocols have been developed that allows the synthesis of 4-thiazolidinone skeletons.

Microwave activation as a non-conventional energy source has become an important method that can be used to carryout a wide range of reactions within short time with higher yields, especially in the absence of solvents.[8-10] There are several advantages associated with the use of solvent free system over using organic solvent. These include: (i) there is no reaction media to collect, dispose of or purify and recycle; (ii) in a laboratory preparative scale, require no need of specialised equipments; (iii) extensive and expensive purification procedures can often be avoided; (iv) greater selectivity is observed; (v) reaction times can be rapid with increased yields and lower energy usage; and (vi) economic considerations, since cost savings can be associated with the non use of solvents requiring disposal or recycling. Not surprisingly, solvent free microwave approach to multi-component reactions has recently drawn the attention for high-speed parallel synthesis of the library of medicinal compounds.[11,12] Earlier, we have reported the synthesis of various 4-thiazolidinone anologs using 1-[2-amino-1-(4-methoxyphenyl)ethyl]-cyclohexanol **1**, an intermediate of the drug venlafaxine (a new class of anti-depressant medications that affect the chemical messengers called neurotransmitters within the brain) under both conventional (DCC) and microwave irradiation technique.[13] The yields were in the range of 65–70 % and 80–90 % for DCC method and microwave technique respectively with greater than 98 % purity. It is indeed prompted us to synthesise the title compound **4**, from 1-(2-amino)-1-(4-methoxyphenylethyl)-cyclohexanol **1**, pyridin-3-carboxaldehyde **2** and thioglycollic acid **3** by one-pot, three components under microwave irradiation without solvent and is successfully achieved in excellent yields at short reaction time.

Condensation of 1-(2-amino)-1-(4-methoxyphenylethyl)-cyclohexanol **1**, pyridin-3-carboxaldehyde **2** with thioglycollic acid **3** either in THF at room temperature for 4 hours or MW irradiation with DMF as a solvent for 70 seconds at 20 % power level or MW irradiation without solvent for 40 seconds at 20 % power level generated **4** with 68 %, 85 %, 97 % yield respectively (Scheme 1, Table 1).



Scheme 1

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

Sl.No	Method	Time taken for reaction	Yield/ %
1	Conventional (DCC)	4 h	68
2	MW irradiation with solvent	70 s	85
3	MW irradiation without solvent	40 s	97

* Correspondent. E-mail: rangappaks@yahoo.com

It is seen that the microwave irradiation without solvent has the advantage of short routine, good yields, convenient workup and environmentally benign process.

The Ortep[14] of compound **4** is shown in Fig. 1. The cyclohexane ring is in chair conformation with weighted average ring bond distance 1.5283 (11,31) Å. The dihedral angle between the planes comprising of atoms N(18)–O(20)–C(21)–C(19)–S(22)–C(23) and C(24)–C(25)–C(26)–C(27)–N(28)–C(29) is 89.3(1)°, which indicate that they are perpendicular to each other and the dihedral angle between the planes with atoms C(24)–C(25)–C(26)–C(27)–N(28)–C(29) and O(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8) is 29.3(1)°. Also, the dihedral angle between the planes comprising of atoms N(18)–O(20)–C(21)–C(19)–S(22)–C(23) and O(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8) is 60.10(9)°. The molecule exhibits intermolecular hydrogen bonds of type N–H...O and C–H...O. The crystal data are given in Table 2.

Experimental

The melting point was recorded on SELACO-650 hot stage apparatus and is uncorrected. IR (KBr) spectra were recorded on a Jasco FT/IR-4100 FTIR spectrometre. ^{1}H NMR were recorded on Shimadzu AMX 400, spectrometre using $CDCl_3$ as solvent and TMS as an internal standard (Chemical shift in ppm). Elemental analysis was carried out on a vario-EL instrument. TLC was conducted on 0.25 mm silica gel plates ($60F_{254}$, Merck). All extracted solvents were dried over Na_2SO_4 and evaporated under reduced pressure.

Synthesis of (2RS)-3-[(2RS)-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl]-2-(pyridin-3-yl)-thiazolidin-4-one **4**

Method 1. Conventional (DCC)

A mixture of 1-[2-amino-1-(4-methoxyphenyl)ethyl] cyclohexanol **1** (1.00 g, 4.016 mmol), and pyridine-3-carboxaldehyde **2** (0.5161 g 4.819 mmol) in dry THF was stirred with ice cooling for 5 minutes, followed by the addition of thioglycollic acid **3** (0.5548 g, 6.024 mmol). After 5 minutes, DCC (1.6572 g, 8.03 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for about 4 hrs at room temperature to complete the reaction. The residue, dicyclohexylurea was filtered off, the filtrate was concentrated to dryness under the reduced pressure. Demineralised water was added to the residue and extracted with dichloromethane. The organic layer was washed with 5 % $NaHCO_3$ solution/citric acid solution and dried over Na_2SO_4. The crude solid was recrystallised from methanol to furnish crystalline solid **4**. A good quality single crystal was obtained from slow evaporation technique by using methanol as solvent m.p. 116 °C.

IR ν_{max} *(KBr)*: 3324.6, 2928.4, 2851.2, 1508, 1686.4, 803 cm^{-1}. ^{1}H NMR *($CDCl_3$)* δ: 1.0–1.8 (m, 10H, cycl–H), 5.33 (s, 1H, C(2–H), 4.62 (s, 1H, –OH), 6.82–6.93 (dd, 2H, Ar–H), 7.08–7.19 (d, *J* = 6 Hz, 1H, Ar–H), 7.24–7.32 (m, 1H, Ar–H), 7.4–7.44 (d, 1H, Ar–H), 8.06–8.18 (s, 1H, Ar–H), 8.52–8.65 (dd, 1H, Ar–H), 3.8–3.88 (s, 3H, –O–CH_3), 3.6–3.74 (dd, 2H, *J* = 6 Hz, C(5)–H), 2.92–3.1 (q, 1H,–CH–), 3.3–3.8 (d, 2H, $–CH_2$. CHNS analysis: Anal Calcd for $C_{23}H_{28}N_2O_3S$ C. 66.96, H. 6.84, N. 6.78, S. 7.78. Found: C. 66.96, H. 6.84, N. 6.79, S. 7.77 %.

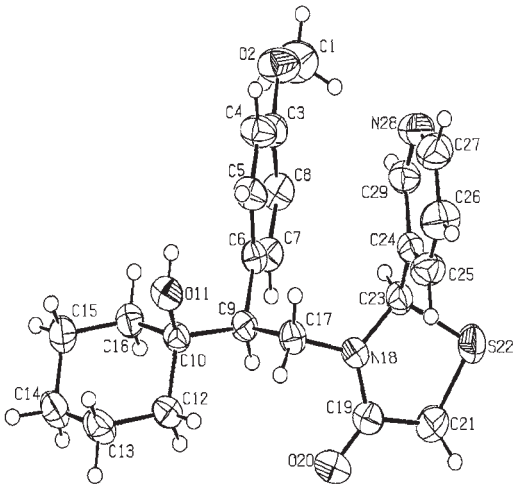


Fig. 1 ORTEP diagram of the molecule 4 at 50 % probability.

Method 2. MW irradiation in DMF solvent

A 25 ml conical flask charged with 1-(2-amino)-1-(4-methoxyphenyl-ethyl) cyclohexanol **1** (1 g, 4.016 mmol), pyridin-3-carboxaldehyde **2** (0.5161 g 4.819 mmol), thioglycollic acid **3** (0.5548 g, 6.024 mmol) and DMF (5 ml) was irradiated in the microwave oven at 20 % power level for 70 seconds. After completion of the reaction (tlc), a ten equivalent of demineralised water was added to the cooled (rt) contents of the flask and extracted with dichloromethane. The title compound **4** was isolated in pure form using the workup procedure as mentioned in the method 1.

Method 3. MW irradiation without solvent

A 25 ml conical flask charged with 1-(2-amino)-1-(4-methoxyphenyl-ethyl) cyclohexanol **1** (1 g, 4.016 mmol), pyridin-3-carboxaldehyde **2** (0.5161 g 4.819 mmol) thioglycolic acid **3** (0.5548 g, 6.024 mmol) was made slurry and irradiated in the microwave oven at 20 % power level for 40 seconds. The title compound **4** was obtained in 97 % yield. The workup procedure was simple as mentioned in the method 1.

Single crystal X-ray crystallography: A single crystal of size 0.2 × 0.30 × 0.2 mm was chosen for single crystal X-ray diffraction studies. The X-ray diffraction data were collected on a DIPLABO Image Plate system at room temperature, in oscillation mode with a range of 5°. The data were reduced using *DENZO*[15] and processed using *Scalepack*. No absorption corrections were applied. The structure was solved by direct methods using SHELXS-97.[16] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at chemically acceptable positions and allowed to ride on the parent atoms. Refinements were done using SHELXL-97.[17] Full Crystallographic details are deposited at Cambridge Crystallographic Database Centre (CCDC NO. 283878).

In summary, we have synthesised the title compound **4** in three different methods. Solvent-free MW irradiated method with high yield, short time and environmentally benign process was achieved. Further, the single crystal X-ray crystallographic studies of the possible biologically active compound **4** is reported.

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Table 2 Crystallographic details of molecule **4**

Compound name	3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)-2-(pyridin-3-yl)-thiazolidin-4-one 4
CCDC no.	283878
Empirical formula	$C_{23}H_{28}N_2O_3S$
Formula weight	412.53
Temperature	293(2)K
Wavelength	0.71073Å
Crystal system	*Triclinic*
Space group	$P\bar{1}$
Cell dimensions	
a	10.317(9)Å
b	10.280(1)Å
c	11.408(6)Å
α	73.824(6)°
β	70.122(5)°
γ	70.293(3)°
Volume	1052.7(2)Å^3
Z	2
Density (calculated)	1.302 Mg/m^3
F_{000}	440
θ range for data collection	2.61° to 32.49°
Reflections collected	10124
Independent reflections	6255 [Rint = 0.0331]
Data/restraints/parametres	6255/0/264
Goodness of fit on F^2	0.99
Final R indices [I>2σ(I)]	R1 = 0.0527, wR2 = 0.1450
R indices (all data)	R1 = 0.0807, wR2 = 0.1717
Largest diff. peak and hole	0.302 & -0.468 e.Å^{-3}

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