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Article

Synthesis, Spectral Characterization and *In vitro* Antifungal Activity of New Naphthyl Thiazolidinones

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ABSTRACT

Microwave-assisted synthesis of naphthyl thiazolidinones (**4-6**) was successfully completed after reacting naphthyl thiosemicarbazones (**1-3**) with mercaptoacetic acid (1 mmol) in the presence of neutral alumina (Al_2O_3) and a few drops of piperidine under solvent-free conditions. The characterization of compounds (**4-6**) was done by spectral (IR, ^{1}H NMR, ^{13}C NMR and MS) and analytical data. The new compounds were screened for *in vitro* antifungal activity by Disk Diffusion Method during which compounds depicted moderate to good *in vitro* antifungal activity.

Key words: Antifungal activity, Microwave, Mercaptoacetic acid, Naphthyl thiazolidinones.

1. INTRODUCTION

Heterocyclic chemistry has been accredited with a tremendous attention over the decades by medicinal chemists for drug discovery. The interesting structural and stereochemical features of the heterocyclic compounds provide additional fascination to the researchers and thereby alterations in the skeleton have been envisaged to discover new chemical entities with a potential to afford some promising drugs of the future. The incorporation of heterocyclic moieties such as thiazolidinone, thiazole, or a heteroatom in the heterocyclic backbone affects their chemical properties and often results in useful alterations in their biological activities [1]. Therefore, researchers are on a continuous pursuit to design and produce better heterocyclic derivatives, by following natural models. The discovery of several biologically active heterocyclic derivatives with their wide applications in therapy has also brought about an interesting interest [1].

Thiazolidinone is a derivative of thiazole which belongs to five membered heterocyclic ring systems with multiple applications. Thiazolidinones have been reported to show versatile pharmacological activities. They have been reported as COX-1 inhibitor [2], anti-inflammatory [3], antiproliferative [4,5], antihistaminic [6], anti-HIV [7,8], hypnotic [9], anesthetic [10], antifungal [11], anthelmintic [12] and antiviral [13] agents as well as CNS [14] stimulants. 4-thiazolidinones, and their derivatives [15] exhibit unusually high activity against *Mycobacterium tuberculosis*. Recently, a number of 4-thiazolidinones derivatives found to exhibit highly potent and selective anti-platelet activating factor activity both *in vitro* and *in vivo* [16]. 2-Arylimino-4-thiazolidinone derivatives have also showed antibacterial [17,18], antifungal [19], and anticonvulsant activities [20,21]. Keeping in view the applications of heterocycles and in continuation of previous work [22], we herein report the microwave assisted synthesis of naphthyl thiazolidinone and *in vitro* antifungal studies.

2. EXPERIMENTAL

2.1. General

The Kofler apparatus was used to determine the melting points in degrees Celsius and is uncorrected. The PerkinElmer RXI Spectrophotometer was used to record the IR spectra on with and values are given in cm^{-1}. ^{1}H and ^{13}C NMR spectra were run in $CDCl_3$ on a JEOL Eclipse (400 MHz) instrument with TMS as internal standard and values are given in ppm (δ). Mass spectra were recorded on a JEOL SX 102/DA6000 Mass Spectrometer. The elemental analyses were performed using thermo EA 2110 series. For microwave irradiation, a microwave oven equipped with a turntable was used (LG smart chef MS-255R operating at 2450 MHz having maximum output of 900 W) for reaction. Thin-layer chromatography (TLC) plates were coated with silica gel G and exposed to iodine vapors to check the homogeneity as well as the progress of reaction. Petroleum ether refers to a fraction of boiling point 60–80°C. Sodium sulfate (anhydrous) was used as a drying agent. All the chemicals were purchased from Merck India and were used after distillation.

2.2. Microwave Assisted Synthesis of Naphthyl Thiazolidinones (4-6)

A mixture of compound (**1-3**) [23] (1.5 mmol), mercaptoacetic acid (1 mmol), and 1 gram of neutral alumina (Al_2O_3) irradiated in a microwave oven operating medium power (600 watts) for 50 s. The progress of a reaction was monitored by TLC using ethyl acetate: hexane (3:7) solvent system. After completion of a reaction, reaction mixture was cooled to room temperature and poured on crushed ice. Neutral alumina was recovered by simple filtration and re-crystallization was done in water which afforded respective products (**4-6**).

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2.2.1. 2-(4''-Chloro-1'', 2''-dihydronaphthyl)-3-carbothioc acid amidothiazolidin-4-one (4)

Yellow crystals; yield 87%; mp 144°C; IR (KBr, cm^{-1}): 3335 (NH, NH_2), 1665 (*CO*N), 1630 (C=C arom.), 1622 (C=C), 1230 (C=S), 1140 (N-N), 1020 (C-N), 740 (C-Cl), 630 (C-S). ^{1}H NMR ($CDCl_3$) *δ*: 7.4–7.11 (m, 4H, arom.), 6.7 (s, 1H, N*H*, exchangeable with D_2O), 3.2 (s, 2H, CH_2), 3.0 (s, 1H, C*H*-N), 2.5 (t, 2H, CH_2), 2.3 (t, 2H, CH_2), 2.1 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$), *δ*: 183 (C=S), 167 (*C*=O), 130 ($C_{3''}$), 125 ($C_{4''}$), 122–128 (6C, Arom.), 64.0, 61 (2×*C*H_2), 43 (*C*-Cl), 53 (*C*-N). Anal. Calcd for $C_{14}H_{14}N_3OS_2Cl$: C, 49.48, H, 4.15, N, 12.36 found: C, 49.15, H, 4.02, N, 12.07; ESI MS: *m/z* 339/341 [M^+].

2.2.2. 2-(4''-Hydroxy-1'', 2''-dihydronaphthyl)-3-carbothioc acid amidothiazolidin-4-one (5)

Off-white crystals; yield 84%; mp 149°C; IR (KBr, cm^{-1}): 3553 (OH), 3328 (NH), 1662 (*CO*N), 1634 (C=C arom.), 1625 (C=C), 1232 (C=S), 1137 (N-N), 1083 (C-O), 1020 (C-N), 632 (C-S). ^{1}H NMR ($CDCl_3$) *δ*: 7.52–7.21 (m, 4H, arom.), 7.03 (s, 1H, OH, exchangeable with D_2O), 6.5 (s, 1H, N*H*, exchangeable with D_2O), 3.2 (s, 1H, C*H*-N), 3.0 (s, 2H, CH_2), 2.52 (t, 2H, CH_2), 2.36 (t, 2H, CH_2), 2.12 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$), *δ*: 182 (C=S), 168 (*C*=O), 131 ($C_{3''}$), 121 ($C_{4''}$), 124-130 (6C, Arom.), 64.0, 62 (2×*C*H_2), 72 (*C*-O), 55 (*C*-N). Anal. Calcd for $C_{14}H_{15}N_3O_2S_2$: C, 52.32, H, 4.70, N, 13.07 found: C, 52.02, H, 4.33, N, 12.87; ESI MS: *m/z* 321 [M^+].

2.2.3. 2-(1'', 2''-Dihydronaphthyl)-3-carbothioc acid amidothiazolidin-4-one (6)

Off-white crystals; yield 84%; mp 151°C; IR (KBr, cm^{-1}): 3330 (NH), 1668 (*CO*N), 1633 (C=C arom.), 1623 (C=C), 1234 (C=S), 1129 (N-N), 1025 (C-N), 633 (C-S). ^{1}H NMR ($CDCl_3$) *δ*: 7.51–7.21 (m, 4H, arom.), 6.8 (s, 1H, N*H*, exchangeable with D_2O), 5.2 (s, 1H, C_4-*H*), 3.2 (s, 1H, C*H*-N), 3.0 (s, 2H, CH_2), 2.52 (t, 2H, CH_2), 2.36 (t, 2H, CH_2), 2.23 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$), *δ*: 184 (C=S), 168 (*C*=O), 130 ($C_{3''}$), 127 ($C_{4''}$), 122–126 (6C, Arom.), 65.2, 63 (2×*C*H_2), 51 (*C*-N). Anal. Calcd for $C_{14}H_{15}N_3OS_2$: C, 55.06, H, 4.95, N, 13.76 found: C, 54.83, H, 4.72, N, 13.60; ESI MS: *m/z* 305 [M^+].

2.3. In vitro Antifungal Activity

The Disk Diffusion Method [24,25] was employed to screen the compounds (**4-6**) for assaying *in vitro* antifungal activity. The strains of *Candida albicans*, *Candida krusei*, *Candida parapsilosis*, and *Cryptococcus neoformans* were inoculated in Sabouraud Dextrose broth medium (Hi-Media Mumbai) and incubated for 24 h at 35°C, and subsequently a suspension of about 10^6 CFU Ml^{-1} was prepared in sterile saline solution according to the McFarland protocol. Autoclaved Sabouraud Dextrose Agar (SDA) was poured on to 9 cm diameter plates in laminar flow cabinet and then with the help of sterilized cotton swabs the suspension of each fungal cell was streaked on to SDA plates. Five paper disks of 6.0 mm diameter were put onto SDA plate. 1 mg of each test compound was dissolved in 100 µl dimethyl sulfoxide (DMSO) to get ready stock solution and from this stock solution varied concentrations 10, 20, 25, 50, and 100 µg/µl of all trial compounds were set. Subsequently, the compounds of varied concentrations were poured over disk plate on to it. The disk of Fluconazole (30 µg) was used as a positive control and DMSO poured disk as a negative control. The susceptibility of different fungal strains against test compounds was assessed on the basis of diameter of zone of inhibition after 48 h of incubation at 35°C. The diameters of Zones of inhibition for different fungal strains are shown in Table 1 and MIC results for fungal strains are shown in Table 2.

Table 1: Antifungal activity naphthyl thiazolidinone derivatives-Positive control (Fluconazole), and Negative control (DMSO) measured by the Halo Zone Test (Unit, mm)

Compounds	Corresponding effect on microorganism			
	CA[a]	CK[b]	CP[c]	CN[d]
4	15.4±0.5	14.2±0.5	15.2±0.5	11.1±0.5
5	20.5±0.2	17.8±0.4	17.1±0.2	16.2±0.4
6	17.5±0.5	17.1±2.0	15.1±0.2	14.2±0.5
Fluconazole	20.0±0.5	20.0±0.5	18.0±0.5	19.0±0.5
DMSO	-	-	-	-

[a]*Candida albicans*, [b]*Candida krusei*, [c]*Candida parapsilosis*, [d]*Cryptococcus neoformans*. DMSO: Dimethyl sulfoxide

Table 2: MIC of naphthyl thiazolidinone derivatives, positive control (Fluconazole)

MIC (µg/ml)	Compounds			Positive Control
Strains	4	5	6	
Candida albicans	16	1	4	1.0
Candida krusei	512	128	128	64.0
Candida parapsilosis	32	16	32	8.0
Cryptococcus neoformans	128	16	32	8.0

MIC: Minimum inhibition concentration

3. RESULTS AND DISCUSSION

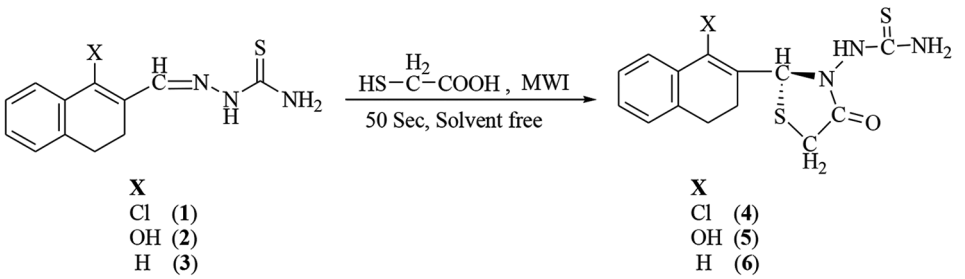
3.1. Chemistry

In the view of the pharmacological importance of thiazolidinones [2-14], and in continuation of ongoing research on organic synthesis under solvent-free conditions [26], we again describe an expeditious, convenient and solvent free microwave accelerated approach for the rapid synthesis of naphthyl thiazolidinones. The naphthyl thiosemicarbazone derivatives (**1-3**) (1 mmol) on reaction with mercaptoacetic acid (1 mmol) and 1 g of neutral alumina (Al_2O_3) using dry conditions yielded corresponding naphthyl thiazolidinones (Scheme 1). The procedure was carried out by varying microwave power from 150 watts to 700 watts. It was observed that by increase in power up to 560 watts; there was increase in yield and shortened reaction time. Beyond the 560 watts, there was no significant change in reaction time and yield.

The tentative mechanism for the formation of thiazolidinones (**4-6**) has been proposed in Scheme 2. The mechanism depicts clearly the formation of hydrazone *in situ* first by simple condensation which later undergo cyclization with merceptoacetic acid hence leads to the formation of the products. The structures of these compounds were characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR, MS) and analytical methods.

3.2. Stereochemistry

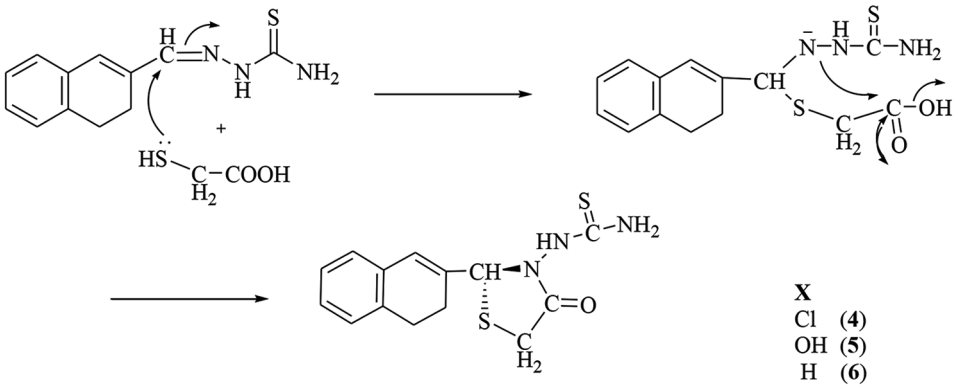
The stereo-selectivity of these thiazolidinones can be explained by considering that there is a considerable amount of steric hindrance to ring-closure from one side of the ring at carbonyl carbon which might be explained on the basis that the sulfur atom is bulkier than nitrogen during cyclization. Thus, the thiazolidinone ring closes at carbonyl carbon, by the attack of sulfur of mercaptoacetic acid moiety, preferentially from the front (*β*, axial) so that the nitrogen has an



X
Cl **(1)**
OH **(2)**
H **(3)**

X
Cl **(4)**
OH **(5)**
H **(6)**

Scheme 1: Pathway for the formation of Naphthyl thiazolidinones **4-6.**



X
Cl **(4)**
OH **(5)**
H **(6)**

Scheme 2: Mechanism for the formation of naphthyl thiazolidinones (**4-6**).

equatorial orientation (*α*, equatorial) to avoid steric repulsion, giving minimum steric hindrance and maximum stability. This is further supported by the fact that during cyclization the nitrogen already attached to carbonyl carbon is moved towards the back (α, equatorial) side to reduce the steric hindrance, and leaving the front (*β*, axial) side for the attack of nucleophile to close the thiazolidinone ring. Therefore, the only product of this reaction with **R** stereochemistry was selectively obtained. The dreiding models also suggest the attack of sulfur from the β-side which pushes the nitrogen to the less hindered α-side. Hence, the formulation of the compound as **R** is preferred over its isomer **S**.

3.3. Pharmacology

The *in vitro* antifungal activities of compounds (**4-6**) were tested using the fungal cultures of *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. neoformans* by the disk diffusion method [24,25] and then the minimum inhibitory concentrations (MICs) of all the compounds were determined. Fluconazole was used as a positive control, while the disk poured in DMSO was used as negative control. The MIC was assessed by the macro dilution test using standard inoculums of 10^5CFU Ml^{-1}. Initially, the compounds were dissolved in DMSO after that serial dilution of the test compounds were set to final concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 mg/mL to each tube was added 100 mL of 24 h old inoculums. The MIC is the lowest concentration of the test compound, which can restrain the apparent growth after 18 h incubation at 37°C. The MIC was determined visually after incubation for 18 h, at 37°C. The *in vitro* study results verified that the compound **5** was found to be the most active antifungal agent among the three compounds. Zone of inhibition was visualized after 18 h of incubation at 36°C. The susceptibility was assessed on the basis of diameter of zone of inhibition against Gram-positive and Gram-negative strains of fungi. The zones of inhibition (mm) of every compound against Gram-positive and Gram-negative strains of fungi are shown in Table 1 while as the MIC results for fungal strains are shown in Table 2. From the data given in Tables 1 and 2, the compound **5** showed impressive behavior for being almost equally potent in case of *C. albicans.*

4. CONCLUSION

We have conveniently prepared new naphthyl thiazolidinones through green and solvent-free strategy. Another advantage of this method is potential yields in lesser reaction time with high purity of the products. The antifungal activity investigation revealed that one of these compounds depicted potential antifungal behavior. The results revealed that these compounds have better prospectus to act as antifungal candidate, which warrants further *in vivo* microbiological investigations.

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