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A Simple and Efficient Carbodiimide Mediated One-pot Synthesis of Novel 2-(2- hydroxynaphthalen-1-yl)-3-phenyl-1,3-thiazolidin-4-one derivatives: A Potent Antimicrobial Agent

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Abstract: A new and efficient method for the preparation of 2-(2-hydroxynaphthalen-1-yl)-3-phenyl-1,3-thiazolidin-4-one derivatives have been assembled by DCC mediated three-component one pot reaction of amine, aldehyde and mercaptoacetic acid. The final compounds were obtained in quantitative yields within 30 min. The synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H-NMR, and mass electronic spectral data. The established compounds were screened for antimicrobial activity.
Keywords:2-hydroxynaphthalene-1-carbaldehyde, DCC, 1,3-thiazolidinones, Mercaptoacetic acid, One pot synthesis, Past reaction, Antimicrobial agent.

Introduction

The structural and therapeutic diversity coupled with commercial viability of small heterocyclic molecules has fascinated organic and medicinal chemists. In recent years, 4-thiazolidinones and oxazolidinones are the most extensively investigated class of compounds. While oxazolidinones are emerging as new class of antibiotics represented by Linezolid, 4-thiazolidinones have many interesting activity profiles namely COX-1 inhibitors, inhibitors of the bacterial enzyme MurB, non-nucleoside inhibitors of HIV-RT and anti-histaminic agents [1-6]. Consequently, many different protocols have been developed, that allow the synthesis of 4-thiazolidinone skeletons. These methods employ a one-pot three-component condensation or a two step synthesis[7]. The reaction was believed to proceed via imine formation in the first step followed by attack of sulfur nucleophile on the imine carbon and finally intramolecular cyclization with the elimination of water. The latter step seems to be critical for obtaining high yields of 4-thiazolidinones. Therefore, variations have been made in the removal of water during the cyclization. Most commonly followed protocols[8] use either azeotropic distillation or molecular sieves. In addition, there are scattered reports of using anhydrous $ZnCl_2$ or sodium sulphate[9] as desiccant. In all the above-mentioned methods, the reaction requires prolonged heating at high temperatures (70–80 ºC) for nearly 17–20 h.

Surrey, at al reported that the reaction was performed in sealed vessels at 70 ºC using molecular sieves[10]. These protocols tend to be limited by yields ranging from moderate to very good depending on the reactants. Secondly, it is desirable to avoid the use of another solid component like molecular sieves and/or $ZnCl_2$ particularly in solid phase synthesis. In order to circumvent these difficulties we have chosen a

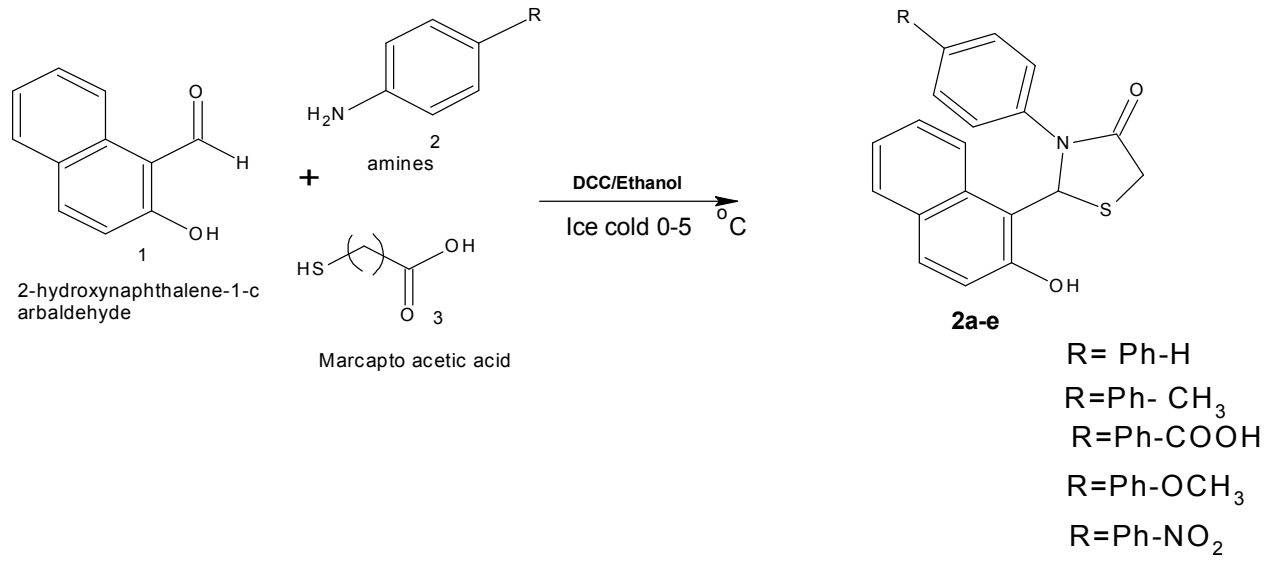
radically different approach to generate 4-thiazolodinone scaffolds by simpler methods in quantitative yields. The protocol was ideally suited for the synthesis of a thiazolidinone library[11-13]. A variety of desiccants namely, trimethylorthoformate, molecular sieves, sodium sulphate and azeotropic distillation have been reported in the literature for the preparation of thiazolidinones. It was generally believed that the first step in the annulation was the addition of sulfur nucleophile to the imine centre followed by attack of the nitrogen on the carboxylic moiety with the expulsion of water giving the cyclized product. The rate-limiting step appears to be the attack of the amine nitrogen at the carbonyl carbon. If this could be enhanced, one could rapidly obtain the thiazolidinones in high yields. Bearing this in mind we utilized that carbodiimides, which are extensively used in peptide synthesis for dehydration leading to peptide bond formation [14-18] could be an ideal candidate to activate the carboxyl group of the adduct obtained by the sulfur addition to the imine thereby facilitating cyclization.

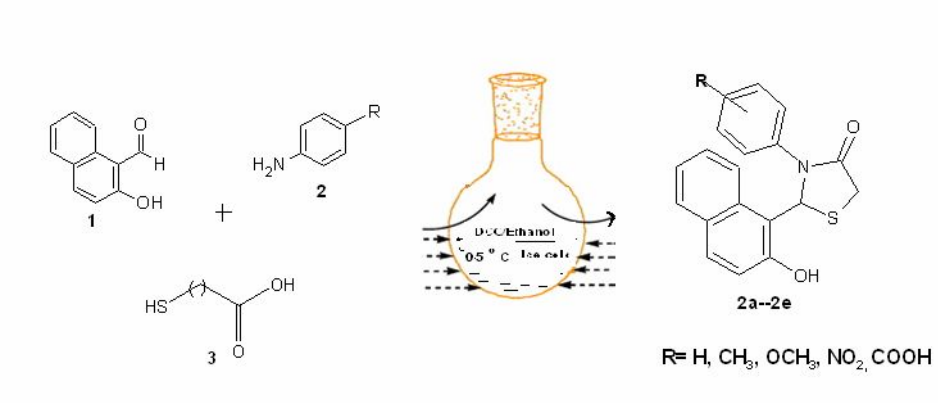
In continuation of our research program [3, 20-23] toward the synthesis of potentially bioactive agent by simple and practical approach, herein we report a rapid and efficient method for the synthesis of novel 2-(2-hydroxynaphthalen-1-yl)-3-phenyl-1,3-thiazolidin-4-One derivative *via* one-pot three-component condensation with quantitative yield. The synthesized compounds exhibit significant antimicrobial activity.

Results and Discussion

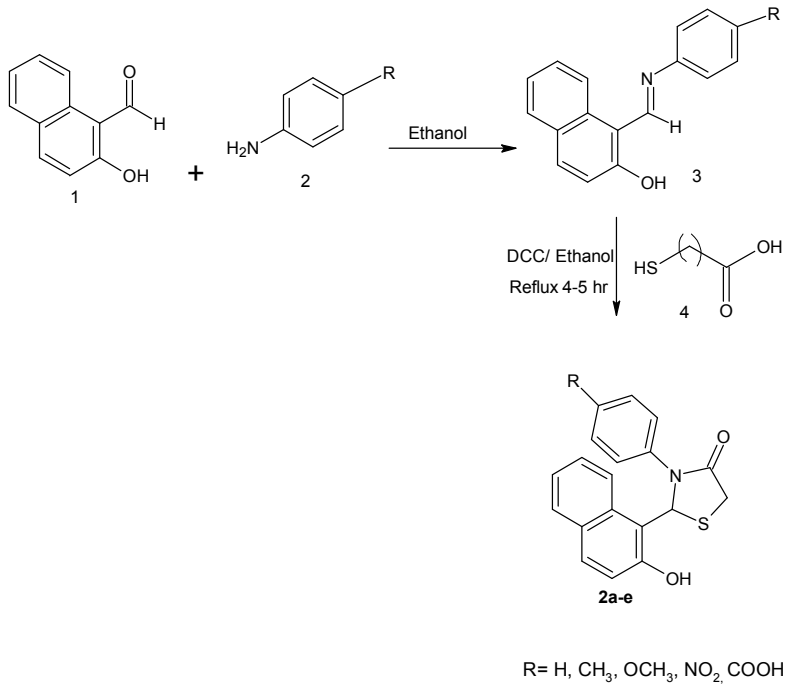
The chemistry using amine, aldehyde and mercaptoacetic acid proceeded uneventfully and the product was isolated in quantitative yield after work up. To optimize the ratio of reactants, experiments were carried out using different proportions of the reactants. It was observed that the ratio of reactants using at 1:2:3 for amine, aldehyde and mercapto acetic acid, respectively gave almost quantitative yields. This is in agreement with the earlier observation reported by Holmes et al.[7] In a typical experiment, amine and aldehyde were stirred in THF under ice cooling for 5 min, followed by addition of mercaptoacetic acid and DCC the reaction mixture is stirred for an additional 20-30 min. The DCC, which was precipitated, was removed by filtration and the usual work-up gave the desired products in almost quantitative yields. We have observed that addition of DCC in ice cold conditions gives better yields as compared with the reaction carried out at refluxed on water bath and ambient room temperature.

Our mechanistic investigations using spectral studies gave proof of cyclized products. From the IR spectra compound (**2a)** showed the absence of carbonyl stretching vibration in napthadehyde and generation of a new sharp band in the region of 1741 cm^{-1} to 1658 cm^{-1} which is corresponding to cyclized product of thiadiazols. In addition to that a broad peak obtained in the region of 3428 cm^{-1} which is corresponding to phenolic OH present in aromatic napthadehyde. Finally a weak band observed in region of 2926 cm^{-1} which is due to aromatic CH stretching vibration. The structure was further confirmed by H-NMR spectra. The H NMR spectra show the broad peak at 16.11 ppm – 15.55 ppm which is due to phenolic OH present at second position of napthadehyde. A resonate doublets exhibits peak at 5.52-5.58 ppm which is due to the aliphatic CH_2 present in thiadiazole ring. In addition to this a resonate multiplets observed in the region of 6.98-8.55 ppm which is corresponding to resonate signals of aromatic proton. The structure was further assigned by mass spectra which give the molecular ion peak [M/z= 322.69]. Due to simple and efficient synthesis of desired compounds we have to try for the synthesis of thiadiazoles derivatives in a short time hence due to its vital importance and easy reaction pathway we have to synthesize few more title derivatives which will exhibit the similar spectral data where presented experimental section.[19-23]





Scheme -1.1: Synthesis of 2-(2-hydroxynaphthalen-1-yl)-3-phenyl-1,3-thiazolidin-4-one derivatives



Scheme -1.2: Synthesis of 2-(2-hydroxynaphthalen-1-yl)-3-phenyl-1,3-thiazolidin-4- one derivative

Under Ice cold condition

Table- 1. Physical and analytical data 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4-one derivative carried out under Ice cold condition.

Com	Color	Yield %	M.P °C	Cryst solvent	Molecular Formula mol/wt	Analysis Calcd (Found) % C	H	N	S
2a	Yellowish	92.42	192-193	Ethyle acetate	$C_{19}H_{15}NO_2S$ (321.39).	71.00 (71.08)	4.70 (4.63)	4.36 (4.62)	9.98 (9.85)
2b	Yellowish	85.23	179-180	Ethyle acetate	$C_{20}H_{17}NO_2S$ (335.42).	71.62 (71.52)	5.11 (5.19)	4.18 (4.12)	9.56 (9.62)
2c	Yellowish	80.69	178-179	Ethyle acetate	$C_{20}H_{17}NO_3S$ (351.40).	68.36 (68.43)	4.88 (4.96)	3.99 (4.06)	9.12 (9.03)
2d	Yellowish	82.56	204-205	Ethyl acetate	$C_{20}H_{15}NO_4S$ (343.40).	65.74 (65.64)	4.14 (4.23)	3.83 (3.96)	8.78 (8.62)
2e	Reddish	90.45	181-182	Ethyl acetate	$C_{19}H_{14}N_2O_4S$ (366.39).	62.28 (62.21)	3.85 (3.93)	7.65 (7.52)	8.75 (8.64)

Under thermal cold condition

Table- 2. Physical and analytical data 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4- one derivative carried out under thermal cold condition.

Com	Color	Yield%	M.P °C	Cryst solvent	Molecular Formula mol/wt	Analysis Calcd (Found) % C	H	N	S
2a	Yellowish	62.52	192-194	Ethyle acetate	$C_{19}H_{15}NO_2S$ (321.39).	71.00 (71.07)	4.70 (4.60)	4.36 (4.62)	9.98 (9.84)
2b	Yellowish	75.22	179-182	Ethyle acetate	$C_{20}H_{17}NO_2S$ (335.42).	71.62 (71.54)	5.11 (5.16)	4.18 (4.13)	9.56 (9.62)
2c	Yellowish	60.60	178-179	Ethyle acetate	$C_{20}H_{17}NO_3S$ (351.40).	68.36 (68.42)	4.88 (4.98)	3.99 (4.10)	9.12 (9.05)
2d	Yellowish	72.51	203-204	Ethyl acetate	$C_{20}H_{15}NO_4S$ (343.40).	65.74 (65.68)	4.14 (4.26)	3.83 (3.94)	8.78 (8.62)
2e	Reddish	68.42	182-183	Ethyl acetate	$C_{19}H_{14}N_2O_4S$ (366.39).	62.28 (62.25)	3.85 (3.90)	7.65 (7.57)	8.75 (8.62)

Electronic Spectra

The electronic spectra of all the synthesized thadiazole derivatives were recorded in polar and non polar solvent in the concentration of $\mathbf{3\times10^5}$, the visible spectral result of all the compound was summarized in table 3 and 4. The absorption maxima of all the compound can be exhibited due to π-π* transitions. The UV-spectrum of compounds **2a** to **2e** was tested in different solvents where the absorption maxima of all the thiadiazoles derivatives can shows bathochromic shifts in all non polar solvents the absorption maxima of compounds **2c** and **2e** exhibits two transitions higher maxima at **443.56, 318.55** and **450.27,335.19** respectively due to the deep colour and conjugation of above derivatives.

Similarly the visible spectral maxima of compounds **2a, 2b** and **2d** was exhibits a lower λ_{max} may due to the effect of conjugation with in the molecules. Finally the visible spectral result shows that all the thiadiazole derivatives was shifted to bathochromic shift(red shift) due to non polar solvents than that of polar solvents and protocol was summarized in table-3 and 4.

Table-3: Electronic spectra of 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4-one derivative

compounds	solvent	λ_{max} in nm	Absorbance(A)	Log ε
2a	Methanol	422.13, 312.6	0.41, 0.32	4.22, 3.12
2b	Methanol	438.44, 317.5	0.435, 0.34	4.38, 3.17
2c	**Methanol**	**443.56,319.55**	**0.79, 0.34**	**4.43, 3.19**
2d	Methanol	442.4, 316.20	0.676, 0.638	4.42, 3.16
2e	Methanol	**450.27, 335.19**	**0.467, 0.466**	**4.50, 3.35**

The above compounds were tested in methanol.

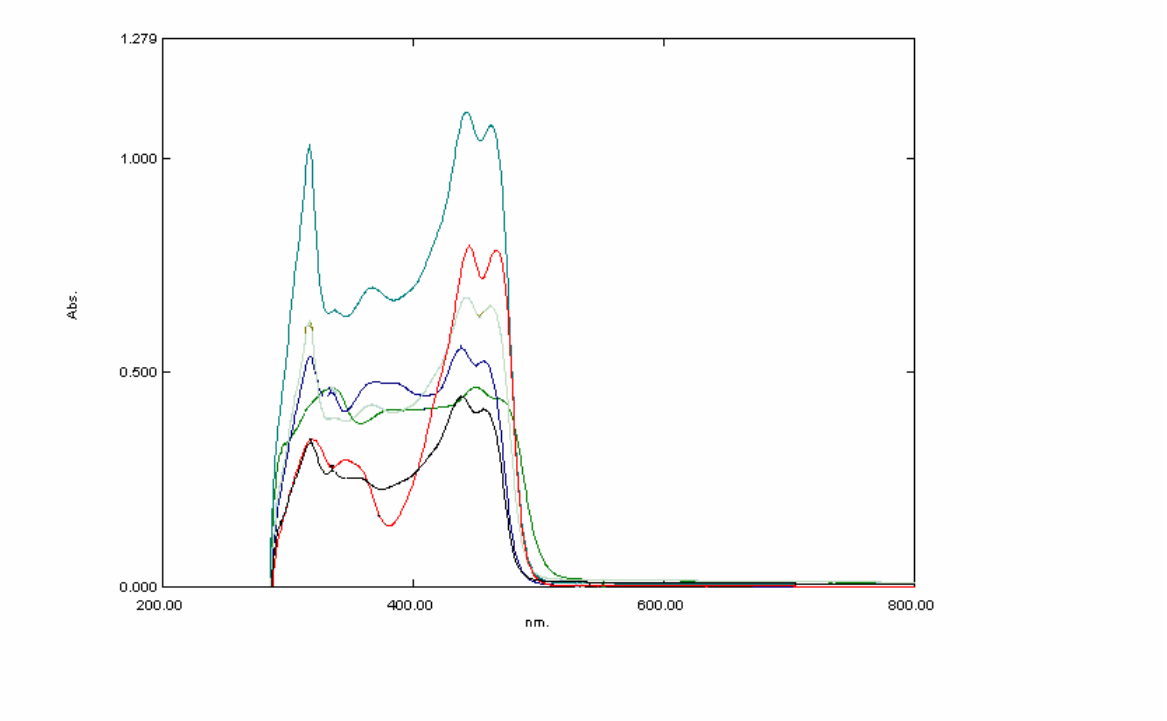


Fig-1: Electronic spectra of the 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4-one derivatives in methanol

Table-4: Electronic spectra of 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4-one derivative

Compounds	solvent	λ_{max} in nm	Absorbance(A)	Log ε
2a	DMF	300.12, 310.26	0.866, 079	3.00, 3.10
2b	DMF	320.43, 381.72	0.957,0.954	3.20, 3.81
2c	DMF	**468.24, 446.81**	**1.58, 1.54**	**4.68, 4.46**
2d	DMF	319.15, 390.2	1.08, 0.967	3.19,3.90
2e	**DMF**	**410.05, 340.78**	**0.809,0.644**	**4.10, 3.40**

The above compounds were tested in DMF.

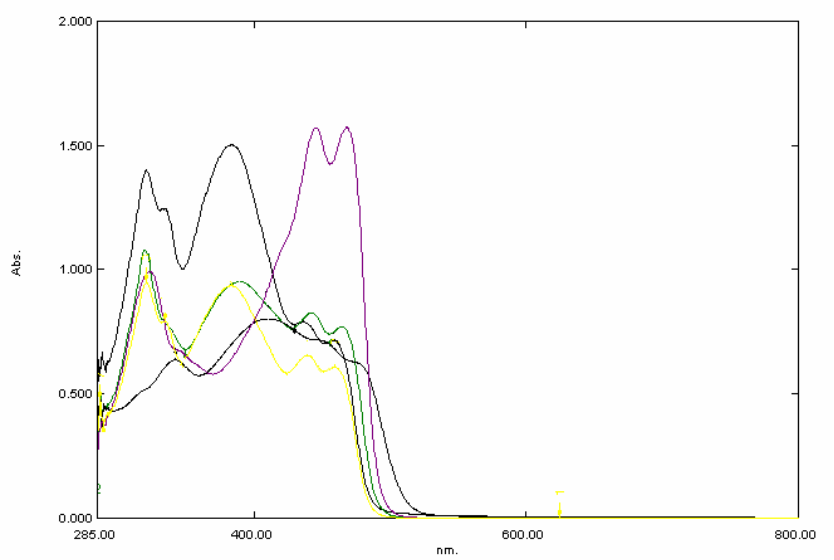


Fig-2: Electronic spectra of the 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4-one derivatives in DMF

Experimental Section

All organic solvents used for the synthesis were of analytical grade. The TLC was performed on Baker-Flex silica gel 1B-F (1.55) plates using ethyl acetate and petroleum ether (1:8). Melting points were determined on a Mel-Temp apparatus and were uncorrected. IR spectra were recorded in the matrix of KBr with Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra was recorded on Jeol spectrometer (400 MHz), and chemical shifts (δ) given in ppm relative to the TMS in $CDCl_3$ solvent. Mass spectra were recorded by electron ionization (EI) on a finnigan MAT 312 spectrometer. C, H and N analysis were performed at Cochin University, Sophisticated Test & Instrumentation Center, Kochi, Kerala, India. Column chromatography separations were obtained on silica gel (60–120 mesh).

General synthesis: Under Ice cold condition:

1. Synthesis of 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4-one (2a)

The appropriate amine (1.07 mL, 0.01 mol) and aldehyde (1.74 gm, 0.01 mol) were stirred in ethanol under ice cold conditions for 15 min, followed by addition of mercaptoacetic acid (0.91 mL, 0.01 mol). After 5 min DCC (1.94gm, 0.01mol) was added to the reaction mixture at 0-5 °C and the reaction mixture stirred for an additional 50 min at room temperature the compounds was precipitate in R. B flask. The resulting DCC was removed by filtration the crude product was purified by column chromatography on silica gel using ethyl acetate-pt ether as eluent. Similarly same procedure was used for all the thiazolidine derivatives. This compound was obtained as yellowish solid in 91.42% yield.

Under thermal cold condition:

The 1.07 mL, of amine (0.01 mol) and aldehyde (1.74 gm, 0.01 mol) were reflux in ethanol under thermal conditions for 1hr, followed by addition of mercaptoacetic acid (0.91 mL, 0.01 mol). After 5 min DCC (1.94gm, 0.01mol) was added to the reaction mixture reflux for an additional 4-5hr on water both the compounds was precipitate in R. B flask. The resulting DCC was removed by filtration the crude product was purified by column chromatography on silica gel using ethyl acetate-pt ether as eluent. Similarly same procedure was used for all the thiazolidine derivatives. This compound was obtained as yellowish solid in 62.42% yield.

Spectral data:

1. Synthesis of 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4-one (2a)

This compound was obtained as yellowish solid with yield% 91.42%; IR cm^{-1} (KBr), 3264 (-OH-), 3062, 2924 (Ar-CH), 1676 (C=O), 1395 (C=C), 1212 (C-N), 1567, 1086, 813, 670. 15.96 (s, 1H, -OH-), 9.63-9.65 (d, 1H –CH- Thiazolidine ring), 3.56-3.63 (t, 2H, CH_2 Thiazolidine ring), 6.98-7.56 (m, 6H, Ar-H), 7.77-8.49 (m, 4H, Ar-H phenyl ring). FAB Mass M/Z =322.69. UV-Visible in Methanol λ_{max}= 422, 312. In DMF λ_{max}= 300, 310.

2. Synthesis 2-(2-hydroxy-1-naphthyl)-3-(4-methylphenyl)-1,3-thiazolidin-4-one(2b)

This compound was obtained as yellowish solid with yield% 85.23%, IR cm^{-1} (KBr); 3264 (-OH-), 3062, 2924 (Ar-CH), 1676 (C=O), 1395 (C=C), 1212 (C-N), 1567, 1086, 813, 670. 15.95 (s, 1H, -OH-), 9.63-9.65 (d, 1H –CH- Thiazolidine ring), 3.56-3.63 (t, 2H, CH_2

Thiazolidine ring), 6.98-7.56 (m, 6H, Ar-H), 7.77-8.49 (m, 4H, Ar-H phenyl ring) 2.35 (s, 3H, $-CH_3$). FAB Mass M/z =356.83. UV-Visible in Methanol λ_{max}= 438, 317. In DMF λ_{max}= 320, 381.

3. Synthesis of 2-(2-hydroxy-1-naphthyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one(2c)

This compound was obtained as yellowish solid with yield% 80.69%, IR cm^{-1} (KBr); 3428.5(-OH-), 3061.7, 2960.6, 2926.9 (Ar-CH), 1711.4(C=O), 1349.7(C=C), 1197.9(C-N), 1492, 1264, 1022, 696. 15.95 (s, 1H, -OH-), 9.63-9.65 (d, 1H –CH- Thiazolidine ring), 3.56-3.63 (t, 2H, CH_2 Thiazolidine ring), 6.98-7.56 (m, 6H, Ar-H), 7.77-8.49 (m, 4H, Ar-H phenyl ring) 3.35 (s, 3H, $-OCH_3$). FAB Mass M/z =352.62. UV-Visible in Methanol λ_{max}= 443, 319. In DMF λ_{max}= 468, 446.

4. Synthesis of 4-[2-(2-hydroxy-1-naphthyl)-4-oxo-1,3-thiazolidin-3-yl]benzoic acid(2d)

This compound was obtained as yellowish solid with yield% 82.59%, IR cm^{-1} (KBr); 3224.5(-OH-), 3050.7, 2924.4(Ar-CH), 1676.5(C=O), 1574.6(C=C), 1219.9(C-N), 1367, 1086, 741, 665. 15.54(s, 1H, phenolic-OH-), 13(s, 1H, acidic-OH-), 9.69-9.67(d, 1H, -CH- Thiazolidine ring), 5.56-5.58(t, 2H, CH_2 Thiazolidine ring), 7.94-8.04(m, 6H, Ar-H), 7.73-7.80(m, 4H, Ar-H phenyl ring). FAB Mass M/z =345.21. UV-Visible in Methanol λ_{max}= 442, 316. In DMF λ_{max}= 319, 390.

5. Synthesis of 2-(2-hydroxy-1-naphthyl)-3-(4-nitrophenyl)-1,3-thiazolidin-4-one(2e)

This compound was obtained as reddish solid with yield% 90.45%, IR cm^{-1} (KBr); 3264 (-OH-), 3062, 2924 (Ar-CH), 1676 (C=O), 1395(C=C), 1567 (NO_2), 1212 (C-N), 1567, 1086, 813, 670. 15.96 (s, 1H, -OH-), 9.63-9.65 (d, 1H –CH- Thiazolidine ring), 3.56-3.63 (t, 2H, CH_2 Thiazolidine ring), 6.98-7.56 (m, 6H, Ar-H), 7.77-8.49 (m, 4H, Ar-H phenyl ring). FAB Mass M/z =367.63. UV-Visible in Methanol λ_{max}= 450, 335. In DMF λ_{max}= 410, 340.

Evaluation of Antimicrobial Activity

The *in vitro* antimicrobial activity was carried out against 24 hr old cultures of two bacteria and two fungi by cup-plate method [24]. Complexes have been tested for their antibacterial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans.* Nutrient agar and potatodextrose agars were used to culture the bacteria and fungus respectively. The compounds were tested at a concentration of 0.005 mol / ml in DMSO solution. The solution of Chloramphenicol (2mg/ ml) and Flucanazole (2 mg/ ml) were prepared in sterilized water and used as standards for comparison of antibacterial and antifungal activities respectively. The compounds were tested at varied concentration. The minimum inhibition concentration was found to be 0.001mol/ ml in DMSO against all organisms. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria at 28 ºC and 48 h for fungus at 35ºC. Each experiment was repeated thrice and the average of the three independent determinations was recorded. The established derivatives give significant activity towards the tested bacteria and obtained protocol was summerised in Table-5. The compound **2a 2d** and **2e** were exhibited more significant activity towards the bacteria than that of compound **2b** and **2c**. Similarly, from the obtained protocol the compounds **2a, 2b** and **2c** show promising antifungal activity than that of the compounds **2d** and **2e**. The significant antimicrobial activity of given synthesized compounds reveals a very good antimicrobial agent, the all synthesized compounds exhibits very good activity is due to the thiazolidine ring different and functional group used for the synthesis of thiazolidine derivatives [25].

Table-5. Evaluation of antimicrobial activity of 2-(2-hydroxynaphthalen-1-yl)-3-phenyl-1,3-thiazolidin-4- one derivative

Compounds	Antibacterial activity Zone of inhibition in cm		Antifungal activity Zone of inhibition in cm	
	Staphylococcus	*E. coli*	*A. niger*	*C. albicans*
2a	2.1 cm	2.6 cm	3.1 cm	2.6 cm
2b	1.5 cm	1.5 cm	3.5 cm	3.3 cm
2c	1.8 cm	1.9 cm	3.8 cm	3.9 cm
2d	2.6 cm	2.9 cm	2.6 cm	2.9 cm
2e	2.0 cm	2.3 cm	3.0 cm	3.3cm
Chloramphenicol	3.8 cm	3.8 cm	--	--
Flucanazole	-	-	4.0 cm	4.0 cm

Conclusion

We developed simple and efficient approach for the synthesis of 2-(2-hydroxy-1-naphthyl)-3-phenyl-1,3-thiazolidin-4-one dervatives. The efficiency and simple methodology based on three component one pot synthesis and utility of DCC catalyzed reaction. The efficiency of the reaction employed was explained by fact that the energy required to conversion of desired molecule can be explained by the role of DCC as a dehydrating agent. The spectroscopy characterization of given compounds obtained in high purity and Eco-friendly method. The visible spectroscopy of present compounds shows bathochromic shift (red shift) due to high conjugation in thiazolidine derivatives with respective substituted functional groups. From antimicrobial activity results the compound containing simple amines **2a** and methoxy **2d** and **2e** towards antibacterial and the compounds **2a, 2b** and **2c** shows more activity towards antifungal than that of antibacterial activity. Overall antimicrobial results shows reported thiazolidine derivatives will exhibits significant antimicrobial activity.

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