SOLID $\text{SiO}_2\text{-H}_3\text{PO}_4$ IS AN EFFICIENT CATALYST FOR CYCLIZATION OF ENONES UNDER SOLVENT-FREE CONDITION: SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF SOME OXAZINE DERIVATIVES

GANESAMOORTHY THIRUNARAYAN^{1,*} AND VELAYUTHAM RENUKA²

¹Department of Chemistry, Annamalai University, Annamalainagar-608002, India.

²Department of Chemistry, National College, Tiruchirappalli-620 001.

ABSTRACT

A series of some 1, 3-oxazine amine derivatives including 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines has been synthesised by solid $\text{SiO}_2\text{-H}_3\text{PO}_4$ catalyzed solvent-free cyclization of aryl chalcones and urea under microwave irradiation. The yields of the oxazines were more than 80%. The synthesised oxazine amines were characterized by their physical constants, analytical and spectroscopic data. The antimicrobial activities of these oxazine derivatives have been studied using Bauer-Kirby method.

Key words: Oxazine amines, Enones, $\text{SiO}_2\text{-H}_3\text{PO}_4$, Solvent-free synthesis.

INTRODUCTION

The unsaturated oxazine and its derivatives are important bio-active six membered heterocyclic compounds possess one oxygen and one nitrogen atom¹. Depending upon the relative position of these two atoms and the double bond, they show some isomeric structures such as 1, 2 or 1, 3 or 1, 4 oxazines². These oxazines were medicinally important due to the presence of oxygen, nitrogen heteroatoms along with a double bond in their structural moieties³. The important medicinal activities of these oxazines are anti-bacterial, anti-fungal³⁻⁵, anti-plasmodial⁶, anti-cancer⁷, anti-depressants⁸, cytotoxicity⁹, anti-osteoplastic¹⁰, anti-tumour¹¹, anti-oxidant¹², anti-tuberculosis¹³, anti-neoplastic¹⁴, antagonists¹⁵, anti-inflammatory¹⁶, anti-infectants¹⁷, IKB kinase beta¹⁸ and PTP-1B inhibition¹⁹. These oxazine derivatives were applied for improving the super resolution microscope²⁰, synthesis of eosinophils²¹, identification and separation of neutrophils²². Many oxazine derivatives were used as dyes²³. These oxazine derivatives are used as intermediate for synthesis of N-acylamides of β -ketoacids²⁴, amides²⁵, halosubstituted aryl methyl ketones²⁶ and uracils²⁷. Numerous solvent assisted and solvent-free synthetic methods were available for synthesis of oxazine derivatives²⁸. Currently scientists and organic chemists paid much more interest for solvent-free synthesis^{4, 29-31, 32}. Hetero Diels-alder reaction³, ring closure³⁰, cycloaddition of the types (6+0)³³, (4+2)³⁴ and (3+3)³⁵, Betti base induced condensation³⁰, Mannich type condensation-cyclization⁴ and cyclization of chalcones⁵ were used for synthesis of oxazine derivatives. Verma et. al.²⁹ have synthesised some benzoxazine/oxazine fused isoquinolines and naphthyridines by solvent-free method. Elarfi and Al-difar⁵ have synthesised some 1, 3-oxazine derivatives by solvent-assisted method from chalcones and urea. More than 75% of dihydro-2H-benzo- and naphtho-1, 3-oxazine derivatives were synthesized by Mathew et al.,⁴ using solvent-free method. Efficient synthesis of some 1, 3-oxazine-4-thiones synthesised by N-methylimidazole promoted solvent-free conditions. Sapkal et al., have investigated the role of ammonium acetate for solvent-free synthesis of 1,3-disubstituted-2,3-dihydro-1H-naphthyl oxazines³¹. Within the above view, there is no information available in the literature for the solvent-free synthesis and the study of antimicrobial activities of 1-naphthyl based oxazine 2-amine derivatives. Therefore, the authors taken efforts to synthesize some aryl unsaturated oxiranes including 1-naphthyl based oxazine-2-amine derivatives and studied the antimicrobial activities using Bauer-Kirby in-vitro disc diffusion method.

EXPERIMENTAL

General

All chemical and reagents used in this present study were purchased from Sigma-Aldrich and Merck Chemical companies. Samsung GW73BD model microwave oven(100-700W, 230V, 50Hz, 2450Hz) is used for synthesising the oxazine derivatives. The melting points of the oxazine derivatives were determined using a Mettler FP51 melting point apparatus in open glass capillaries and are uncorrected. The SHIMADZU Fourier transform

spectrophotometer was used for recording infrared spectra (KBr, 4000-400 cm^{-1}) of all oxazines in KBr discs. The NMR spectra of oxazines were recorded in Bruker AV400 series type NMR spectrometer, operating at 400MHz for ¹H and 100 MHz for ¹³C spectra in CDCl_3 solvent using TMS as internal standard. The SHIMADZU mass spectrometer was used for recording mass spectra of all synthesised oxazines using chemical ionization technique.

Preparation of $\text{SiO}_2\text{-H}_3\text{PO}_4$ catalyst

The $\text{SiO}_2\text{-H}_3\text{PO}_4$ catalyst was prepared according to literature procedure³⁶. In a 50mL Borosil beaker, 2 g of silica (10-20 μ) 2 mL of ortho phosphoric acid were taken and mixed thoroughly with glass rod. This mixture was heated on a hot air oven at 85°C for 1h, cooled to room temperature, stored in a borosil bottle and tightly capped.

Synthesis of 4-(aryl)-5,6-dihydro-6-(substituted phenyl)-4H-1,3-oxazine-2-amines.

Equi-molar quantities of chalcones (2 mmol), urea(2mmol) and 0.4 g of $\text{SiO}_2\text{-H}_3\text{PO}_4$ were taken in a 50 mL beaker, closed with the lid. This reaction mixture was subjected to microwave irradiation for 2-4 minutes at 650W (Scheme 1) (Samsung, Microwave Oven.). The completion of reaction was monitored by Thin layer Chromatogram. After completion of reaction, about 20 mL of dichloromethane was added, followed by simple filtration. The solution was concentrated and the residue was purified by re-crystallization. The solid catalyst was reused for further reaction runs. The synthesised oxazines were characterized by their physical constants, IR, NMR and Mass spectral data. Analytical and Mass spectral data of these oxazine derivatives were presented in Table 1.

Scheme 1. Synthesis of 4-aryl-5,6-dihydro-6-(substituted phenyl)-4H-1,3-oxazine-2-amines by $\text{SiO}_2\text{-H}_3\text{PO}_4$ catalyzed cyclization of aryl chalcones and urea under microwave irradiation.

RESULTS AND DISCUSSION

The authors attempts to synthesize oxazine derivatives by cyclization of chalcones possessing electron withdrawing as well as electron donating group as substituents and urea in the presence of solid acidic catalyst $\text{SiO}_2\text{-H}_3\text{PO}_4$ under microwave irradiation. Hence the authors have synthesized some substituted 1,3-oxazine derivatives by the cyclization of 2 mmole of chalcone, 2 mmole of urea under microwave irradiation with 0.4g of $\text{SiO}_2\text{-H}_3\text{PO}_4$ catalyst at 550W for 4-6 minutes (Samsung Grill, GW73BD Microwave oven, 230V A/c, 50Hz, 2450Hz, 100-750W (IEC-705), (Scheme 1). During the course of this reaction $\text{SiO}_2\text{-H}_3\text{PO}_4$ catalyses cyclization between chalcones and urea followed by rearrangement gave the 1, 3-oxazine amines. The yield of the oxazine in this reaction is more than 80%. The chalcone containing electron donating substituent (OCH_3) gave higher yields than electron-withdrawing (halogens, NO_2) substituents. Further we have investigated this cyclization reaction with equimolar quantities of the styryl 1-naphthyl ketone (entry 10) and urea under the same condition mentioned as above. In this reaction the obtained yield was 90%. The effect of catalyst on this reaction was investigated

by varying the catalyst quantity from 0.1 g to 1 g. As the catalyst quantity is increased from 0.1 g to 1 g, the percentage of yield of product was increased from 82 to 90%. There is no increase the percentage of product after adding 0.4 g of catalyst. The results, analytical and mass spectral data are summarized in Table 1. The reusability of this catalyst was studied for the cyclization of styryl 1-naphthyl ketone, and urea (entry 10) the result is presented in Table 2. From the Table 2, first two runs gave 90% product. The third, fourth and fifth runs of reactions gave respectively the yields 89.5%, 89.5% and 89% of oxazines. There was no appreciable loss in its effect of catalytic activity observed up to the fifth run. The effect of solvents on the yield was also studied with methanol, ethanol, dichloromethane and tetrahydrofuran from each component of the catalyst (entry 10). Similarly the effect of microwave irradiation was studied on each component of the catalyst. The effect of solvents on the yield of oxazine derivatives presented in Table 3. From the table highest yield of oxazine obtained from the cyclization of chalcones and urea with the catalyst $\text{SiO}_2\text{-H}_3\text{PO}_4$ in microwave irradiation. The infrared and nmr spectroscopic data of these oxazine amine derivatives are summarized in Table 4.

Table 1. Analytical, physical constants, yield and mass fragment of 4-aryl-5,6-dihydro-6(substituted phenyl)-4H-1,3-oxazine-2-amines.

Entry	R	R'	M.W.	Yield (%)	m.p.(°C)	Mass (m/z)
1			252	88	134-136	252[M ⁺], 236, 175, 160, 84, 77, 43, 42, 16
2			268	85	144-145 (145-146) ^[27]	268[M ⁺], 252, 251, 236, 175, 160, 99, 93, 84, 77, 43, 42, 16
3			295	87	65-66 (65-66) ^[27]	295[M ⁺], 280, 265, 279, 251, 236, 175, 160, 118, 84, 77, 44, 43, 42, 30, 16, 15
4			282	89	122-123	282[M ⁺], 266, 251, 236, 205, 190, 175, 160, 107, 91, 84, 77, 43, 42, 31, 16
5			288	85	115-116	286[M ⁺], 288[M ²⁺], 270, 266, 251, 175, 160, 111, 107, 99, 84, 77, 43, 42, 35, 16
6			282	89	132-133	282[M ⁺], 266, 251, 256, 236, 205, 190, 175, 160, 107, 91, 84, 77, 43, 42, 31, 16
7			266	88	112-113	266[M ⁺], 251, 250, 175, 160, 91, 84, 77, 43, 42, 31, 16, 15
8			297	85	141-142	297[M ⁺], 281, 251, 175, 168, 160, 122, 84, 77, 45, 43, 42, 16
9			340	90	115-116	340[M ⁺], 324, 248, 165, 84, 77, 43, 44, 16
10			302	86	109-110	302[M ⁺], 286, 356, 225, 210, 175, 159, 127, 99, 91, 84, 77, 52, 43, 42, 16
11			302	90	98-99	302[M ⁺], 286, 225, 210, 159, 127, 99, 84, 77, 52, 43, 42, 16

12			375	85	117-118	375[M ⁺], 377[M ²⁺], 358, 339, 263, 175, 165, 118, 111, 84, 77, 43, 35, 16,
13			375	85	112-113	375[M ⁺], 377[M ²⁺], 358, 339, 263, 248, 209, 175, 165, 118, 111, 84, 77, 58, 43, 35, 16,
14			419	85	121-123	419[M ⁺], 421[M ²⁺], 403, 339, 248, 209, 175, 118, 111, 84, 77, 58, 43, 35, 16,
15			375	85	119-120	375[M ⁺], 377[M ²⁺], 358, 263, 248, 209, 175, 118, 84, 77, 58, 43, 42, 35, 16,
16			383	87	125-126	383[M ⁺], 368, 353, 339, 263, 254, 165, 147, 106, 91, 77, 58, 44, 43, 42, 16, 15
17			356	86	115-116	356[M ⁺], 340, 339, 263, 248, 165, 99, 93, 84, 77, 58, 43, 42, 16,
18			370	91	102-104	370[M ⁺], 339, 354, 290, 263, 205, 165, 148, 107, 91, 77, 58, 43, 42, 31, 16
19			354	90	119-120	354[M ⁺], 339, 354, 291, 262, 205, 229, 175, 148, 107, 91, 77, 58, 43, 42, 31, 16
20			386	85	131-132	386[M ⁺], 339, 369, 327, 263, 248, 205, 84, 91, 77, 46, 43, 41, 16,
21			386	85	122-123	386[M ⁺], 339, 369, 248, 205, 165, 84, 77, 46, 43, 41, 16,
22			386	85	134-135	386[M ⁺], 339, 369, 248, 205, 165, 84, 77, 46, 43, 41, 16,
23			355	85	116-117	355[M ⁺], 324, 263, 248, 190, 165, 99, 92, 77, 43, 41, 16,

Table 2. Reusability of $\text{SiO}_2\text{-H}_3\text{PO}_4$ catalyst on cyclization cum acetylation of styryl 1-naphthyl ketone (2 mmol) with urea (2 mmol) under microwave irradiation(**entry 11**).

Run	1	2	3	4	5
Yield	90	90	89.5	89.5	89

Table 3. The effect of solvents in conventional heating and without solvent in microwave irradiation on yield of oxazine amine (entry 11).

Solvents															Microwave irradiation
MeOH			EtOH			DCM			THF						
FA	SA	FASA	FA	SA	FASA	FA	SA	FASA	FA	SA	FAPA	FA	SA	FASA	
63	42	77	61	43	80	63	44	78	65	43	86	78	69	90	

MeOH=Methanol; EtOH=Ethanol; DCM= Dichloromethane; THF=Tetrahydrofuran; FA=fly-ash; SA=Sulphuric acid; FASA=fly-ash; H_2SO_4

Table 4. Infrared and NMR spectroscopic data of 4-aryl-5,6-dihydro-6(substituted phenyl)-4H-1,3-oxazine-2-amines

Entry	IR(ν , cm^{-1})				$^1\text{H}(\delta$, ppm)						$^{13}\text{C}(\delta$, ppm)		
	NH	C=N	C-O-C	Substt.	NH(δ)	H ₃ (dd)	H ₃ (dd)	H ₅ (dd)	H ₆ (dd)		Substt.	C ₂	C ₄
1	3534	1598	1234	---	2.345	2.625	2.425	2.214	4.257	6.545-7.345	---	165.33	52.56
2	3564	1628	1245	3564 (OH)	2.295	2.598	2.465	2.201	4.351	6.289-7.258	---	164.82	51.36
3	3526	1614	1264	---	2.214	2.491	2.458	2.269	4.451	6.358-7.298	3.658 N(CH ₃) ₂	164.35	52.36
4	3514	1610	1236	1238 (OCH ₃)	2.361	2.412	2.542	2.230	4.652	6.257-7.987	4.023 (OCH ₃)	164.03	52.28
5	3536	1599	1265	---	2.173	2.918	2.350	2.113	4.714	7.174-7.291	---	164.17	52.07
	3525	1621	1218	1225 (OCH ₃)	2.277	2.753	2.299	2.217	4.593	6.781-7.352	3.997 (OCH ₃)	163.21	52.19
7	3536	1593	1214	---	2.197	2.807	2.245	2.172	4.673	6.917-7.352	2.514 (CH ₃)	164.44	52.84
8	3558	1624	1265	---	2.317	2.897	2.436	2.223	4.709	7.273-8.165	---	165.23	52.78
19	3565	1613	1243	---	2.215	2.267	2.157	2.267	4.297	6.413-7.607	---	165.32	53.29
10	3526	1598	1215	---	2.291	2.301	2.221	2.245	4.252	6.325-7.852	---	165.02	52.01
11	3523	1589	1212	---	2.295	2.384	2.201	2.236	4.652	6.259-7.962	---	164.99	51.36
12	3554	1596	1212	3348 (NH ₂)	2.112	2.232	2.215	2.313	4.654	6.423-7.967	4.898 (NH ₂)	165.76	52.81
13	3550	1588	1222	3354 (NH ₂)	2.111	2.203	2.216	2.329	4.665	6.434-7.925	4.859 (NH ₂)	165.58	52.95
14	3548	1589	1226	3335 (NH ₂)	2.234	2.214	2.256	2.028	4.643	6.723-7.767	---	164.37	52.36
15	3545	1612	1223	---	2.243	2.212	2.256	2.029	4.634	6.722-7.789	---	164.37	52.80
16	3545	1608	1212	---	2.153	2.255	2.260	2.053	4.697	6.851-7.894	---	165.18	52.11

17	3555	1612	1212	---	2.012	2.211	2.309	2.123	4.723	6.634-7.989	3.736	164.47	52.33
18	3545	1592	1213	3540 (OH)	2.209	2.333	2.378	2.153	4.298	6.655-7.880	---	165.33	52.22
19	3535	1606	1210	1213 (OCH ₃)	2.227	2.238	2.355	2.111	4.337	6.813-7.978	4.046 (OCH ₃)	164.37	52.31
20	3544	1601	1223	---	2.221	2.235	2.254	2.134	4.454	6.232-7.887	2.657 (CH ₃)	164.52	52.74
21	3555	1615	1215	---	2.320	2.227	2.378	2.098	4.658	6.858-7.590	---	165.37	52.99
22	3557	1615	1211	---	2.314	2.232	2.371	2.093	4.653	6.859-7.598	---	165.36	52.97
23	3550	1618	1213	---	2.189	2.211	2.343	2.019	4.626	6.544-7.959	---	165.29	52.32
Entry	¹³ C(δ, ppm)												
	C ₅	C ₆	Ar-C	Substt.									
1	47.33	65.90	125.36-142.25	---									
2	47.98	66.25	126.25-139.38	---									
3	47.01	65.98	122.68-139.25	44.38 N(CH ₃) ₂									
4	48.74	65.39	121.36-141.25	62.38 (OCH ₃)									
5	47.95	67.03	126.43-139.40	---									
6	47.94	66.79	114.54-137.36	56.78(OCH ₃)									
7	47.17	66.84	125.77-139.04	25.37(CH ₃)									
8	48.26	67.25	126.37-142.10	---									
9	47.29	66.25	124.37-146.02	---									
10	48.02	66.36	125.36-146.28	---									
11	48.62	67.25	124.29-154.35	---									
12	47.96	66.38	121.87-139.25	---									
13	47.34	66.25	121.26-139.98	---									
14	47.37	66.44	121.34-139.98	---									
15	47.22	67.29	121.25-138.32	---									
16	47.29	67.29	121.35-139.35	---									
17	47.04	67.28	121.35-141.29	45.33 N(CH ₃) ₂									
18	47.29	66.93	118.35-139.32	---									
19	47.22	66.85	115.36-158.34	59.67(OCH ₃)									
20	47.21	66.28	114.28-148.68	24.84(CH ₃)									
21	47.33	66.84	115.36-159.72	---									
22	47.93	66.82	115.36-159.72	---									
23	48.22	66.29	116.38-157.29	---

Figure 1. Effect of catalyst loading.

Table 5. Antibacterial activities of substituted styryl 3-thienyl ketones(entries 11-23).

Entry	X	<i>E.coli</i>	<i>S.aures</i>	<i>Pseudomonas</i>	<i>Klebsiella</i>	<i>P.vulgaris</i>	<i>Enterococcus faecalis</i>
11	H	+	---	+	±	++	++
12	3-NH ₂	---	++	+	++	+	±
13	4-NH ₂	---	++	++	++	+	±
14	3-Br	+	+	++	++	+	++
15	3-Cl	++	±	++	+	+	+
16	4-Cl	++	+	++	+	++	+
17	4-N(CH ₃) ₂	---	++	+	++	---	++
18	4-OH	±	+	+	---	±	+
19	4-OCH ₃	+	+	±	---	++	±
20	4-CH ₃	+	+	±	---	++	±
21	2-NO ₂	---	+	+	+	+	---
22	3-NO ₂	+	+	+	+	+	---
23	4-NO ₂	+	+	+	+	+	--

Disc size: 6.35 mm; Duration: 24-45 h; Standard: Ampicillin (30-33 mm) and Streptomycin(20-25 mm); Control: Methanol; ---: No activities; ±: Active(8-12 mm); +: Moderately active(13-19 mm); ++: Active(20-24 mm).

Antimicrobial activities

Antibacterial sensitivity assay

Antibacterial sensitivity assay of all 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines (entries 11-23) was performed using Kirby-Bauer³⁰ disc diffusion technique. In each Petri plate about 0.5 mL of the test bacterial sample was spread uniformly over the solidified Mueller Hinton agar using sterile glass spreader. Then the discs with 5mm diameter made up of Whatmann No.1 filter paper, impregnated with the solution of the compound were placed on the medium using sterile forceps. The plates were incubated for 24 h at 37°C by keeping the plates upside down to prevent the collection of water droplets over the medium. After 24 h, the plates were visually examined and the diameter values of the zone of inhibition were measured. Triplicate results were recorded by repeating the same procedure.

The antibacterial activities of all prepared 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines (entries 11-23) have been studied against two gram positive pathogenic strains *Staphylococcus aureus*, *Enterococcus faecalis* and four gram negative strains *Escherichia coli*, *Klebsiella species*, *Pseudomonas* and *Proteus vulgaris*. The disc diffusion technique was followed using the Kirby-Bauer³⁰ method, at a concentration of 250 µg/mL with Ampicillin and Streptomycin used as the standard drugs. The measured antibacterial activities of all 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines (entries 11-23) are presented in Table 5. Compound 15 and 16 showed maximum zone of inhibition against *Escherichia coli*, with greater than 20 mm compared to the chalcones 11, 14, 16, 19-22 and they are moderately active in 13-19 mm of zone of inhibition. Oxazine-2-amine 18 was active with in 8-12 mm of zone of inhibition. The oxazine-2-amines 12, 13 and 17 were found to be effective against *S. aureus* within 20-24

mm of zone of inhibition. Compounds 18-53, 14 and 16 are moderately active within 13-19 mm of zone of inhibition. The oxazine 15 was active within 8-12 mm of zone of inhibition. The chalcone derivatives 14-16 were more active against *Pseudomonas* a showing greater than 20 mm zone of inhibition and the other derivatives showed the zone of inhibitions between 12-19 mm. The oxazines 11-13, 17, 8, 21-13 were showed active with in 13-19 mm maximum zone of inhibition. The oxazine derivative 19 and 20 were active within 8-12 mm of zone of inhibition. The oxazine derivatives 12-14 were effective against *Klebsiella* with 20-24 mm zone of inhibition while the other ketones showed a moderate activity. The compounds 11, 16, 19 and 20 were active when it is screened against *P. vulgaris* and the other compounds are less effective. The oxazines 11, 14 and 17 showed activities against *E.faecalis* when they are screened with 20-24 mm zone of inhibition.

Antifungal sensitivity assay

Antifungal sensitivity assay all 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines (entries 11-23) were performed using Kirby-Bauer³⁰ disc diffusion technique. PDA medium was prepared and sterilized as above. It was poured (ear bearing heating condition) in the Petri-plate which was already filled with 1 mL of the fungal species. The plate was rotated clockwise and counter clock-wise for uniform spreading of the species. The discs were impregnated with the test solution. The test solution was prepared by dissolving 15 mg of the chalcone in 1mL of DMSO solvent. The medium was allowed to solidify and kept for 24 h. Then the plates were visually examined and the diameter values of zone of inhibition were measured. Triplicate results were recorded by repeating the same procedure.

The study of antifungal activities of all 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines (entries 11-23) has been done with

Candida albicans as the fungal strain using the disc diffusion technique and the other two strains *Penicillium* species and *Aspergillus niger*, the dilution method was adopted. The drug dilution was kept as 50 µg/mL. *Griseofulvin* has been taken as the standard drug. The observed antifungal activities of all all 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines (entries 11-23) were presented in Table 6. The study of antifungal activities of all all 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines (entries 11-23) against *C. albicans*, showed that the five compounds **1**, **18**, **21-23** are effective with 20 mm as the zone of inhibition in 250 µg/disc while oxazine-2-amines **12**, **13**, **16**, **17**, and **20** are active with 13-19

mm zone of inhibition and the compound **11** was the least active with 8-12 mm zone of inhibitions. The oxazine derivatives **16** and **22** are more visible against *Penicillium* species, in the development of the fungal colony and 2-3 colonies are recorded for the compounds **11-13**, **15** and **20**. The inhibition of oxazine-2-amines against *A. niger* was more active in two compounds **1** and **18**. The compounds **11-14**, **16**, **19**, **22** and **23** are active with 8-12 mm zone of inhibitions. Presence of a methoxy, methyl, dimethyl, chloro, bromo and nitro substituents are responsible for antimicrobial activities of 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines

Table 6. Antifungal activities of substituted styryl 3-thienyl ketones(entries 11-23).

Entry	X	Disc diffusion technique (250µg/mL) <i>Candida albicans</i>	Drug dilution method (50µg/mL)	
			<i>Penicillium</i>	<i>Aspergillus niger</i>
11	H	±	+	+
12	3-NH ₂	+	+	+
13	4-NH ₂	+	+	+
14	3-Br	---	±	+
15	3-Cl	++	+	++
16	4-Cl	+	++	+
17	4-N(CH ₃) ₂	+	±	±
18	4-OH	++	---	++
19	4-OCH ₃	---	---	+
20	4-CH ₃	+	+	---
21	2-NO ₂	++	±	---
22	3-NO ₂	++	++	+
23	4-NO ₂	++	±	+

Standard: Griseofulvin and Gentamycin; Duration : 72 h; Control: Methanol; Medium: Potato dextrose agar; ++: No fungal colony; +: One fungal colony; ±: Two-three fungal colonies; ---: Heavyfungalcolony.

CONCLUSIONS

Some oxazine amine derivatives including 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines have been synthesised by solvent-free cyclization of aryl chalcones and urea in presence of SiO₂-H₃PO₄ catalyst under microwave irradiation. The yields of these oxazines were more than 80%. This synthetic methodology offers solvent-free cyclization, non-hazardous, easy-workup procedure, shorter reaction time and better yields. These oxazine derivatives were characterized by their physical constants and spectral data. The antimicrobial activities of synthesised 4-(1-naphthyl)-5,6-dihydro-6-(substituted phenyl)-oxazine-2-amines have been evaluated. The compounds possess methoxy, methyl, dimethyl, chloro, bromo and nitro substituents were showed appreciable antimicrobial activities.

ACKNOWLEDGEMENT

The authors thank DST NMR facility, Department of Chemistry, Annamalai University, Annamalaiagar-608002 for recording NMR spectral of compounds.

REFERENCES

- (a) A. Banerjee, S. Ganguly, T. Chattopadhyay, K. S. Banu, A. Patra, S. Bhattacharya, E. Zangrando, D. Das, *Inorg. Chem.* **48**(18), 8695 (2009); (b) P. Jacob, N. L. Benowitz, L. Yu, A. T. Shulgin, *Anal. Chem.* **58**(11), 2218, (1986); (c) I. P. Yakovlev, A. V. Prep'yalov, B. A. Ivin, *Chem. Heterocycl. Compd.* **30**(3), 255, (1994)
- M. K. Manjula, K. M. L. Rai, S. L. Gaonkar, K. A. Raveesha, S. Satish, *Eur. J. Med. Chem.* **44**, 280, (2009)
- B. P. Mathew, A. Kumar, S. Sharma, P. K. Shukla, M. Nath, *Eur. J. med. Chem.* **45**, 1502, (2010)
- M. J. Elarfi, H. A. Al-Difar, *Sci. Rev. Chem. Commun.* **2**(2), 103, (2012)
- V. Tiwari, J. Meshram, P. Ali, J. Sheikh, U. Tripathi, *J. Enzyme Inhib. Med. Chem.* **26**(4), 569, (2011)
- B. C. Das, A. C. Madhukumar, J. Anguiano, S. Mani, *Bioorg. Med. Chem. Lett.* **19**(15), 4204, (2009)
- D. Zhou, B. L. Harrison, U. Shah, T. H. Andree, G. A. Hornby, R. Scerni, *Bioorg. Med. Chem. Lett.* **16**(5), 1338, (2006)
- S. Wang, Y. Li, Y. Liu, A. Lu, Q. You, *Bioorg. Med. Chem. Lett.* **18**(14), 4095, (2008)
- Y. Ando, K. Ando, M. Yamaguchi, J. Kunitomo, M. Koida, R. Fukuyama, *Bioorg. Med. Chem. Lett.* **16**(22), 5849, (2006)
- L. Benameur, Z. Bouaziz, P. Nebois, M. H. Bartoli, M. Boitard, H. Fillion, *Chem. Pharm. Bull. (Tokyo)*. **44**(3), 605, (1996)
- K. Roy, I. Mitra, A. *Chem. Biol. Drug. Des.* **74**(5), 507, (2009)
- A. Blaser, B. D. Palmer, H. S. Sutherland, I. Kmentova, S. G. Franzblau, B. Wan, *J. Med. Chem.* **55**(1), 312, (2012)
- L. Seal, D. Von Hoff, R. Lawrence, E. Izbicke, R. M. Jamison, *Invest. New Drugs.* **15**(4), 289, (1997)
- B. Brudeli, L. R. Moltzau, K. W. Andressen, K. A. Krobert, J. Klaveness, F. O. *Bioorg. Med. Chem.* **18**(24), 8600, (2010)
- M. Akhter, A. Husain, N. Akhter, M. S. Y. Khan, *Indian J. Pharm. Sci.* **73**, 101, (2011)
- Gothi D, Joshi J M. Resistant TB: Newer Drugs and Community Approach. *Recent Pat Antiinfect Drug Discov.* **6**(1), 27, (2011)
- K. S. Oh, S. Lee, J. K. Choi, B. H. *Comb. Chem. High. Throughput Screen.* **13**(9), 790, (2010)
- S. Y. Cho, J. Y. Baek, S. S. Han, S. K. Kang, J. D. Ha, J. H. Ahn, *Bioorg. Med. Chem. Lett.* **16**(3), 499, (2006)
- S. F. Lee, Q. Vérollet, A. Fürstenberg, *Angew. Chem. Inter. Ed.* **52**(34), 8948, (2013)
- L. Kass. *Biotech Histochem.* **70**(1), 19, (1995)
- L. Kass. *Biotech Histochem.* **70**(1), 29, (1995)
- C. Jung, B. K. Müller, D. C. Lamb, F. Nolde, K. Müllen, C. Bräuchle, *J. Am. Chem. Soc.* **128**(15), 5283, (2006)

23. J. H. MacMillan, S. S. Washburne, Detailed Synthetic Procedure for 4-(4-bromophenyl)-1,3(3H) Oxazine-2,6-Dione and related 4 and 5-aryl substituted -1,3(3H) Oxazine-2,6-Diones. Spectroscopic and analytical data are included. Temple University, <http://www.archive.org>. (2013)
24. E. Ziegler, G. Kollenz, G. Kriewitz, W. Ott, *Liebigs Ann. Chem.* 1751, (1977)
25. N. P. Gambryan, Yu. V. Zeifman, *Izv. Akad. Nauk SSSR, Ser. Khim.* **9**, 2059 (1969)
26. B. A. Arbuzov, N. N. zobova, F. B. Balabanova, *Izv. Akad. Nauk SSSR, Ser. Khim.* **3**, 577 (1971)
27. H. I. Sculnick, H. W. Smith, R. J. Smith, W. Wierenga, *US Pat. No. 4495349, C. A.* **102**, 185093, (1985)
28. A. K. Verma, D. Chioudhary, R. K. Saunthwal, V. Rustagi, M. Patel, R. K. Tiwari, *J. Org. Chem.* **78(13)**, 6657, (2013)
29. M. A. Khalilzadeh, I. Yavari, Z. Hossaini, H. Sadeghifar, *Monatsch Chem.* **140**, 467, (2009)
30. S. B. Sapkal, K. F. Shelke, A. H. Kategaonkar, M. S. Shingare, *Green Chem. Lett.* **2(2)**, 57, (2009)
31. Z. Turgut, E. Pelit, A. Koycil, *Molecules.* **12**, 345, (2007)
32. R. Arulkumaran, S. Vijayakumar, S. P. Sakthinathan, D. Kamalakkannan, K. Ranganathan, R. Suresh, R. Sundararajan, G. Vanangamudi. G. Thirunarayanan, *J. Chil. Chem. Soc.* **58(2)**, 1684 (2013)
33. L. Capuano, W. Fischer, W. Scheidt, M. Schneider, *Chem. Ber.* **111**, 2497 (1978)
34. Yu. S. Andreichikov, D. D. Nekrasov, M. A. Rudenko, V. E. Kolla, A. L. Tregubov, *Khim. Farm. Zh.* No.9, 38, (1991)
35. V. E. Zakhs, I. P. Yakovlev, N. A. Smorygo, V. A. Gindin, B. A. Ivin, *Khim. Geterots. Seod*, No. 3, 386, (1987)
36. P. Janaki, K. G. Sekar, G. Thirunarayanan, *Org. Chem. An Indian J.* **9(1)**, 68, (2013)
37. A. W. Bauer, W. M. Kirby, J. C. Sherris, M. Truck, *Am. J. Clin. Pathol.* **45**, 493, (1966)