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Synthesis, Characterization and Antimicrobial Activity of Some New Thiazines

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Cyclohexanone on Claisen-Schmidt condensation with various aromatic aldehydes in presence of dilute sodium hydroxide affords the corresponding 2,6-diarylidene cyclohexanones (**1**). Further, these compounds (**1**) were subjected to cyclocondensation with thiourea, catalyzed by aqueous potassium hydroxide to form 4-aryl-8-arylidene-2-imino-5,6-dihydro-4H,7H-(3,1)benzothiazines (**2**). The structures of synthesized compounds were characterized by their spectral studies and the antimicrobial activity of **2** was also evaluated.

Key Words: Synthesis, Thiazines, Antimicrobial activity.

INTRODUCTION

Thiazines are an important class of heterocyclic compounds being studied by many researchers[1–9] and reported to possess a wide spectrum of biological properties such as antibacterial[10], antifungal[11], antimycobacterial[12], anthelminthic[13], anti-HIV[14], herbicidal[15], pesticidal[16], analgesic[17], antiinflammatory[18], antiserotinin[19] and anticonvulsant[20] activities. Moreover, thiazine nucleus is a pharmacophore of cephalosporins that occupy a very important place in the field of antibiotics[21] and the antifungal activity of thiazine nucleus is due to the presence of thiourea linkage in its structure[22]. In view of these observations, a series of new 4-aryl-8-arylidene-2-imino-5,6-dihydro-4H,7H-(3,1) benzothiazines **(Scheme-1)** with an aim to obtain potential antibacterial and antifungal agents were synthesized.

EXPERIMENTAL

All melting points were determined in open capillary tubes using a liquid paraffin bath and are uncorrected. The purity of compounds was checked by TLC. UV (λ_{max}, nm) spectra were obtained on a Shimadzu visible spectrophotometer. IR (ν_{max}, cm^{-1}) spectra were run on a Shimadzu 8700 spectrophotometer in potassium bromide pellets. ^1H NMR spectra were taken on an Amx-400 spectrophotometer in $CDCl_3$ using tetramethylsilane as reference. Mass spectra were recorded on a Finigan Mat spectrophotometer by GC-MS.

General procedure for the preparation of 2,6-diarylidenecyclohexanones[23]: A mixture of 10% sodium hydroxide (30 mL), ethyl alcohol (50 mL), cyclohexanone (0.01 mol) and aromatic aldehyde (0.02 mol) was stirred at 20–25°C for 2 h. Later, the reaction mixture was kept in an ice chest overnight. The product was filtered, washed with ice-cold water followed by ice-cold ethanol, dried and recrystallized from dimethyl formamide. The physical data of these

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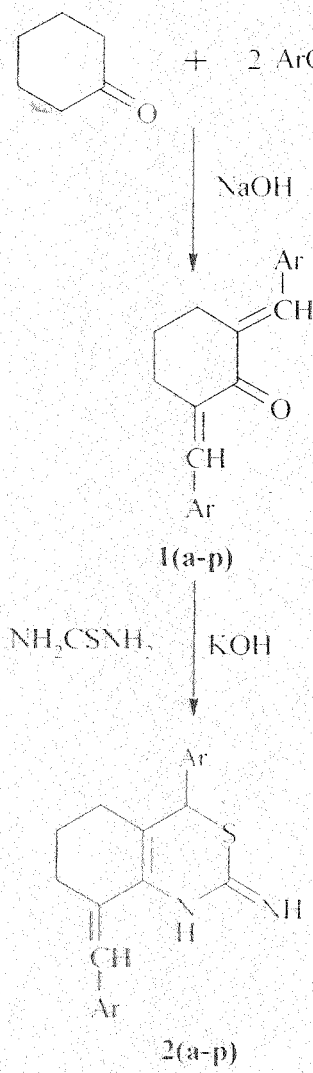

Scheme-1

compounds **1(a–p)** is given in Table-1. UV of **1a**: 393, IR of **1d**: 1658 ν(C═O) 1593, 1556, 1504, 1458 ν(aromatic), 831 ν(C═C); ^{1}H NMR of **1a**: δ 1.5–2.0 (m, CH_2, 2H), δ 2.7–3.1 (m, $(CH_2)_2$, 4H), δ 7.2–7.6 (m, ArH, 10H), δ 7.9 (s, 2 × methine, 2H). Mass of **1c**: 360 (M^+), 227, 133, 94.

General procedure for the preparation of 4-aryl-8-arylidene-2-imino-5,6-dihydro-4H,7H-(3,1)benzothiazines[24]: A mixture of 2,6-diarylidene cyclohexanone (0.01 mol), thiourea (0.015 mol) and potassium hydroxide (0.01 mol) dissolved in 10 mL of water was refluxed in isopropyl alcohol for 14 h. Later, the solvent was removed under reduced pressure and the residue obtained was treated with ice-cold water, filtered, dried and recrystallized from ethanol. The physical data of these compounds **2(a–p)** is given in Table-1. UV of **2a**: 286, IR of **2d**: 3436 ν(imine), 3193 ν(cyclic NH), 1604 ν(C═N), 1506, 1475 ν(aromatic), 1028 ν(C—N).

^{1}H NMR of **2a**: δ 1.5–2.2 (m, $(CH_2)_2$, 4H), δ 2.3–2.9 (m, CH_2, 2H), δ 4.9 (s, —CH—S, 1H), δ 6.5 (s, imine, 1H), δ 7.0 (s, cyclic NH, 1H), δ 7.2–7.5 (m, ArH, 10H), δ 7.8 (s, methine, 1H).

TABLE-1
PHYSICAL DATA OF **1(a-p)** AND **2(a-p)**

Compd.	Ar	m.f.	m.w.	m.p. (°C)	Yield (%)
1a	Phenyl	$C_{20}H_{18}O$	274	116–118	74
1b	*m*-Nitrophenyl	$C_{20}H_{16}N_2O_5$	364	206–208	69
1c	*p*-Dimethylaminophenyl	$C_{24}H_{28}N_2O$	360	82–84	56
1d	*p*-Methoxyphenyl	$C_{22}H_{22}O_3$	334	158–160	81
1e	3,4-Dimethoxyhenyl	$C_{24}H_{26}O_5$	394	142–144	86
1f	3,4,5-Trimethoxyphenyl	$C_{26}H_{30}O_7$	454	210–212	98
1g	*p*-Chlorophenyl	$C_{20}H_{16}OCl_2$	342	150–152	88
1h	*p*-Tolyl	$C_{22}H_{22}O$	302	172–174	92
1i	2,3,4-Trimethoxyphenyl	$C_{26}H_{30}O_7$	454	180–182	97
1j	2-Furfurly	$C_{16}H_{14}O_3$	254	146–148	78
1k	*p*-Fluorophenyl	$C_{20}H_{16}OF_2$	310	148–149	79
1l	*m*-Tolyl	$C_{22}H_{22}O$	302	83–84	78
1m	Styryl	$C_{24}H_{22}O$	326	181–182	82
1n	1-Naphthyl	$C_{28}H_{22}O$	374	208–209	85
1o	*p*-Ethoxyphenyl	$C_{24}H_{26}O_3$	362	145–146	81
1p	*p*-Isopropylphenyl	$C_{26}H_{30}O$	358	140–141	85
2a	Phenyl	$C_{21}H_{20}N_2S$	332	192–194	74
2b	*m*-Nitrophenyl	$C_{21}H_{18}N_4O_4S$	422	190–191	79
2c	*p*-Dimethylaminophenyl	$C_{25}H_{30}N_4S$	418	110–112	40
2d	*p*-Methoxyphenyl	$C_{23}H_{24}N_2O_2S$	392	196–198	75
2e	3,4-Dimethoxyhenyl	$C_{25}H_{28}N_2O_4S$	452	223–225	68
2f	3,4,5-Trimethoxyphenyl	$C_{27}H_{32}N_2O_6S$	512	213–215	78
2g	*p*-Chlorophenyl	$C_{21}H_{18}N_2SCl_2$	400	235–236	88
2h	*p*-Tolyl	$C_{23}H_{24}N_2S$	360	218–220	91
2i	2,3,4-Trimethoxyphenyl	$C_{27}H_{32}N_2O_6S$	512	187–189	94
2j	2-Furfurly	$C_{17}H_{16}N_2O_2S$	312	179–181	86
2k	*p*-Fluorophenyl	$C_{21}H_{18}N_2F_2S$	368	188–189	79
2l	*m*-Tolyl	$C_{23}H_{24}N_2S$	360	175–176	40
2	Styryl	$C_{25}H_{24}N_2S$	384	192–193	75
2n	1-Naphthyl	$C_{29}H_{24}N_2S$	432	225–226	68
2o	*p*-Ethoxyphenyl	$C_{25}H_{28}N_2O_2S$	420	201–202	78
2p	*p*-Isopropylphenyl	$C_{27}H_{32}N_2S$	416	192–193	88

2d: δ 1.6–2.0 (m, $(CH_2)_2$, 4H), δ 2.4–2.8 (m, CH_2, 2H), δ 3.8 (s, 1 × OCH_3, 3H), δ 3.9 (s, 1 × OCH_3, 3H), δ 4.9 (s, CH—S, 1H), δ 6.5 (s, imine, 1H), δ 6.7 (s, cyclic NH, 1H), δ 6.9–7.3 (m, ArH, 8H), δ 7.6 (s, methine, 1H).

2e: δ 1.6–2.0 (m, $(CH_2)_2$, 4H), δ 2.5–2.8 (m, CH_2, 2H), δ 3.9 (s, 4 × OCH_3, 12H), δ 4.9 (s, CH—S, 1H), δ 6.5 (s, imine, 1H), δ 6.7 (s, cyclic NH, 1H), δ 6.8–6.9 (m, ArH, 6H), δ 7.6 (s, methine, 1H).

2f: δ 1.6–2.0 (m, $(CH_2)_2$, 4H), δ 2.5–2.8 (m, CH_2, 2H), δ 3.9 (s, 6 × OCH_3, 18H), δ 4.9 (s, CH—S, 1H), δ 6.5 (s, imine and ArH, 1H and 4H), δ 6.6 (s, cyclic NH, 1H), δ 7.6 (s, methine, 1H).

2g: δ 1.6–2 (m, $(CH_2)_2$, 4H), δ 2.4–2.7 (m, CH_2, 2H), δ 4.9 (s, CH—S, 1H), δ 6.5 (s, imine, 1H), δ 6.9 (s, cyclic NH, 1H), δ 7.1–7.4 (m, ArH, 8H), δ 7.6 (s, methine, 1H).

2h: δ 1.6–2.0 (m, $(CH_2)_2$, 4H), δ 2.3 (s, 2 × CH_3, 6H), δ 2.4–2.7 (m, CH_2, 2H), δ 4.9 (s, CH—S, 1H), δ 6.5 (s, imine and 1H), δ 6.6 (s, cyclic NH, 1H), δ 7.1–7.2 (d, ArH, 8H), δ 7.55 (s, methine, 1H).

2i: δ 1.6–2.0 (m, $(CH_2)_2$, 4H), δ 2.5–2.8 (m, CH_2, 2H), δ 3.8 (s, 4 × OCH_3, 12H), δ 3.87 (s, 1 × OCH_3, 3H), δ 3.95 (s, 1 × OCH_3, 3H), δ 5.2 (s, CH—S, 1H), δ 6.5 (s, imine, 1H), δ 6.6–6.7 (m, cyclic NH and ArH, 1H and 2H), δ 6.8–6.9 (m, ArH, 2H), δ 7.6 (s, methine, 1H).

2k: δ 1.6–2.0 (m, $(CH_2)_2$, 4H), δ 2.4–2.7 (m, CH_2, 2H), δ 4.95 (s, CH—S, 1H), δ 6.5 (s, imine, 1H), δ 6.95 (s, cyclic NH, 1H), δ 7.0–7.3 (m, ArH, 8H), δ 7.6 (s, methine, 1H).

2l: δ 1.6–2.0 (m, $(CH_2)_2$, 4H), δ 2.35 (s, 2 × CH_3, 6H), δ 2.5–2.8 (m, CH_2, 2H), δ 4.9 (s, CH—S, 1H), δ 6.5 (s, imine, 1H), δ 6.65 (s, cyclic NH, 1H), δ 7.0–7.3 (m, ArH, 8H), δ 7.6 (s, methine, 1H).

Mass of **2a**: 332 (M^+ = 100%), 255, 91, 77. **2g**: 400 (M^+ = 100%), 404 (M+4), 289, 125. **2h**: 360 (M^+ = 100%), 269, 125, 91.

Antimicrobial activity

The newly synthesized 4-aryl-8-arylidene-2-imino-5,6-dihydro-4H,7H-(3,1) benzothiazines **2(a–p)** were screened for *in vitro* antimicrobial activity using two Gram positive organisms, *viz.*, *Staphylococcus aureus* and *Bacillus subtilis*, two Gram negative organisms, *viz.*, *Escherchia coli* and *Pseudomonas aeruginosa* and two fungal organisms, *viz.*, *Asperagillus niger* and *Candida albicans* by agar cup plate method[25] at 100 μg . The zone of inhibition was measured in mm and the values of antibacterial and antifungal activity of **2(a-p)** were compared against standard references, ampicillin and amphotericin B, respectively (Table-2).

TABLE-2
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF **2(a–p)**

Compound	Antibacterial activity			Antifungal activity		
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
2a	20	19	20	17	13	13
2b	16	16	15	14	11	NA
2c	17	18	17	16	10	NA
2d	24	22	20	21	14	14
2e	21	21	20	15	13	13
2f	17	17	14	12	10	11
2g	23	24	20	20	16	14
2h	23	23	16	17	14	13
2i	18	17	11	13	9	11

Compound	Antibacterial activity			Antifungal activity		
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
2j	23	21	17	15	14	13
2k	26	25	24	19	15	15
2l	17	15	13	12	11	11
2m	21	18	17	15	13	12
2n	21	19	20	18	14	11
2o	20	21	17	14	12	16
2p	17	18	13	10	11	13
Ampicillin	38	32	33	30	—	—
Amphotericin B	—	—	—	—	18	16

RESULTS AND DISCUSSION

The structures of new compounds prepared during the present investigation have been authentically established by their UV, IR, NMR and mass spectral studies. In the following section the spectral studies of some selected compounds were dealt.

The compounds **1(a–p)** were prepared by reaction of cyclohexanone with aromatic aldehydes which is an example for Claisen-Schmidt condensation. The formation of **1a** from cyclohexanone was indicated by its UV spectrum. The cyclohexanone exhibited λ_{max} at 262. The compound **1a** exhibited λ_{max} at 393. This clearly indicates that the bathochromic shift was because of =CHAr chromophore. The formation of **1d** from cyclohexanone was indicated by its IR spectrum. The cyclohexanone exhibited ν_{max} at 1715 (C=O). The compound **1d** exhibited ν_{max} at 1658 (C=O). The appearance of a band at 1658 is mainly due to the presence of two =CHAr chromophores[26]. This clearly indicates the formation of **1d**. The formation of **1a** was also confirmed by its ^{1}H NMR spectrum. The presence of signals at δ 1.5–2.0 (m, CH_2, 2H), δ 2.7–3.1 (m, $(CH_2)_2$, 4H), δ 7.2–7.6 (m, ArH, 10H) and δ 7.9 (s, 2 × methine, 2H) clearly shows the formation of **1a**.

The compounds **2(a–p)** were prepared by cyclocondensation of **1(a–p)** with thiourea. The formation of **2a** from **1a** was indicated by its UV spectrum. The λ_{max} of **1a** was 393. The λ_{max} of **2a** was 286. These indicate that the hypsochromic shift was attributed because of cyclocondensation. The formation of **2d** from **1d** was confirmed by its IR spectrum. The compound **1d** exhibited ν_{max} at 1658 (C=O). The compound **2d** exhibited ν_{max} at 3436 and 3193 (imine and cyclic NH). The absence of 1658 and presence of 3436 and 3193 in **2d** clearly indicates its formation. The formation of **2a** was confirmed by its ^{1}H NMR spectrum. The presence of signals at δ 1.5–2.2 (m, $(CH_2)_2$, 4H), δ 2.3–2.9 (m, CH_2, 2H), δ 4.9 (s, —CH—S, 1H), δ 6.5 (s, imine, 1H), δ 7.0 (s, cyclic NH, 1H), δ 7.2–7.5 (m, ArH, 10H), δ 7.8 (s, methine, 1H) clearly shows the formation of **2a**. The compounds **2d**, **2e**, **2f**, **2g**, **2h**, **2i**, **2k** and **2l** were also confirmed by their ^{1}H NMR spectra. The formation of **2a** was also elucidated by its mass spectrum. The molecular ion peak of **2a** was observed at m/e 332, which was in good agreement with the calculated molecular weight of the compound. The compounds **2g** and **2h** were also confirmed by their mass spectra.

The compounds **2(a–p)** exhibited antibacterial activity against Gram + ve and

Gram –ve organisms. Among these compounds with *p*-fluorophenyl **2k** and *p*-methoxyphenyl **2d** substitutions showed the maximum activity against *S. aureus*, *B. subtilis*, *E. coli* and *Ps. aeruginosa*, respectively, while other compounds showed moderate and poor activity. All thiazines **2(a–p)** showed antifungal activity against *A. niger*. Among these compounds with *p*-chlrophenyl substitution **2g** exhibited the highest activity against *A. niger*, while compound with *p*-dimethylaminophenyl substitution **2c** showed the least activity. The compounds except **2b** and **2c**, also showed activity against *C. albicans*. The compound with *p*-ethoxyphenyl **2o** substitution exhibited good activity against *C. albicans*, while others showed moderate and poor activity. However, none of these compounds had greater activity than standard references, Ampicillin and Amphotericin B.

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