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Novel Synthesis and Antimicrobial Activities of Thiazino-Oxazine Derivatives

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ABSTRACT

In the designing and synthesis of new heterocyclic compounds, containing two different pharmacophores, we have carried out new series of 3-(4-chlorophenyl)-4-methylidene-4,8-dihydro-2H,5H-1,3-thiazino[5,4-e]-1,3-oxazine-2,5,7(3H)-trione derivatives (5a-5k) in good yields from the cyclization of 5-[(1E)-N-(4-chlorophenyl)ethanimidoyl]-4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione derivatives (4a-4k) with triphosgene. All the synthesized compounds (5a-5k) were confirmed by spectral analysis. The synthesized compounds (5a-5k) were screened *in vitro* for their antibacterial activities against *S. subtilis* (gram positive) and *E. coli*. (gram negative) while antifungal activity against *C. albicans* by cup plate method. Some of the products of series were found to have quite good activities as compared to the standard drug streptomycin and flucanazole.

Keywords: Thiazine, Oxazine, Triphosgene, Antibacterial and antifungal activity.

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INTRODUCTION

The synthesis of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. [1] The increasing cases of microbial resistance pose a major concern to the scientific community and a threat for human life worldwide. [2] Moreover, invasive microbial infections caused by multi-drug - resistant Gram-positive bacteria and microbes are difficult to diagnose and treat. [3] There are the major cause of morbidity and mortality

especially in immune suppressed and hospital-acquired patients. [4] To overcome this problem, the development of new and safe antimicrobial agents with better effectiveness is urgently required. To this end, one of the best ways to design new antimicrobial agents is to generate hybrid molecules by combining two bioactive heterocyclic moieties in a single molecular scaffold. A number of thiazine derivatives exhibited various biological activities such as anticancer [5], antioxidant [6], antimicrobial [7-9] anticonvulsant [10] Selective

cyclooxygenase inhibitors [11], analgesic and anti-inflammatory [12], antimalarial. [13] In addition, benzoxazine derivatives also showed wide range of biological activities such as anticancer [14], progesterone receptor modulators [15], antimalarial [16], analgesic and anti-inflammatory [17], antimycobacterial [18], antibacterial and antiviral [19], antihyperlipidemic. [20] Owing to the above facts and in continuation of our research work on novel biologically active heterocycles and their increasing importance in pharmaceutical and biological field. Therefore we planned to synthesize a combined molecular framework that involves these two different chromophores, with the help of triphosgene and find out their antibacterial as well as antifungal activities.

MATERIALS AND METHODS

Solvents and reagents were commercially sourced from Sigma Aldrich and used without further purification. Melting points were determined in an open capillary and are uncorrected. Infrared spectra were obtained on Perkin Elmer FT-IR spectrometer. The samples were examined as KBr discs ~5 % w/w. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avon 400 MHz spectrometer using CDCl_3 , DMSO as solvent and TMS as internal reference, the chemical shift are reported in ppm. The synthesized compounds were subjected to antimicrobial screening using nutrient agar medium by well diffusion method. The antibacterial activity was tested against *B. subtilis* and *E. coli* bacteria as compared with standard drug (streptomycin) while antifungal activity was tested against *C. albicans* bacteria as compared with standard drug (flucanazole) the results are given in Table 4.

General procedure for synthesis of 5-acetyl-4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione (3a)

Acetic anhydride, 45ml, was added to a solution of 21 g of malonic acid in 100 ml of acetic acid. After 15 min stirring at 20-25°C, potassium thiocyanate, 19 g, was added in one portion. The mixture was stirred for 1h, allowed to stand at ~20°C for 48 h, and then diluted with 300 ml of water. The precipitate that formed was

filtered off, washed with water and recrystallized from absolute ethanol.

General procedure for synthesis of 5-[(1E)-N-(4-chlorophenyl) ethanemid oyl] -4-hydroxy- 2H-1,3-thiazine-2,6(3H)-dione derivatives (4a-4k)

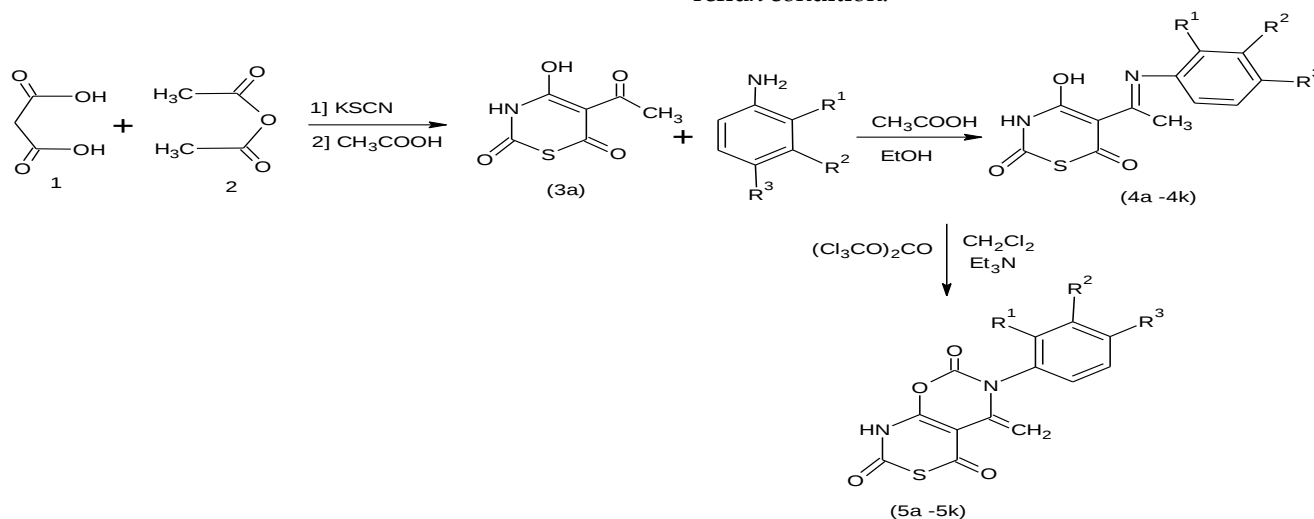
A mixture of compounds (3a) (0.01 mol) and different substituted aromatic amines (0.01 mol) in methanol (50 ml) was refluxed for 7 h, in the presence of few drop of glacial acetic acid. The progress and completion of reaction was checked by TLC. The reaction mixtures were distilled off cooled and then poured into ice water, filtered, washed with water and dried. The solid obtained was recrystallized by ethanol.

General procedure for synthesis of 3-(4-chlorophenyl)-4-methyldene-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazine-2,5,7(3H)-trione derivatives (5a-5k)

A solution of appropriate imines (4a-4k) (3 mmol) and 1 ml of triethylamine in 25 ml of dichloromethane was stirred under a nitrogen atmosphere. Triphosgene (1.5 mmol) in 10 ml of dichloromethane was added drop wise over a period of 15 min. The mixture was stirred at room temperature for 1 h and then refluxed for 3 h. Water was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (30 ml). The organic layer were dried over magnesium sulfate and evaporated to dryness. The solid was recrystallized from ethanol.

RESULTS AND DISCUSSION

Triphosgene is a stable, crystalline solid that has proved to be a useful substituent for phosgene. Triphosgene has long been repeatedly used in the construction of a variety of heterocyclic compounds. We have synthesized new series of 3-(4-chlorophenyl)-4-methyldene-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3] oxazine-2,5,7(3H)-trione derivatives (5a-5k) by cyclization of compounds (4a-4k) with triphosgene. The compounds (4a-4k) were prepared from the reaction of 5-acetyl-4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione (3a) and different substituted amine in the presence of catalytic amount of glacial acetic acid under reflux condition.



Scheme

The structures of the synthesized compounds were confirmed by IR, ^1H NMR, ^{13}C NMR spectral data. In IR spectra of all the synthesized compounds (5a-5k), an absorption band is observed in the region 3189–3324 cm^{-1} due to N-H stretching vibrations. The absorption band observed in the region 1722–1733 cm^{-1} due to >C=O stretching vibrations. In ^1H NMR spectra of compounds (5a-5k), two doublets are observed at δ , 5.10–5.25 ppm and δ , 5.20–5.42 ppm due to $=\text{CH}_2$ protons. The ^1H NMR spectra of all the synthesized compounds (5a-5k) exhibit a single sharp peak in the region δ , 7.95–8.06 ppm due to N-H proton. In ^1H NMR spectra of the synthesized compounds (5a-5k), a multiplet observed at δ , 6.75–8.40 ppm represents the presence of aromatic protons. In ^1H NMR spectra of (5b) singlet are observed at δ , 3.86 ppm due to $-\text{OCH}_3$ protons. In ^1H NMR spectra of (5c), a singlet is also observed at δ , 2.50 ppm due to $-\text{CH}_3$ proton. The compound (5f) in their ^1H NMR spectra shows a singlet at δ , 3.84 ppm due to $-\text{OCH}_3$ protons. In the ^1H NMR spectra of compound (5g), a singlet is observed at δ , 2.28 ppm due to $-\text{CH}_3$ proton. The ^1H NMR spectra of (5i), a singlet is observed at δ , 10.00 ppm due to $-\text{OH}$ group. The compounds (5j) in their ^1H NMR spectra show a singlet at δ , 3.82 ppm due to $-\text{OCH}_3$ proton. In the ^1H NMR spectra of compound (5k), a singlet is observed at δ , 2.22 ppm due to $-\text{CH}_3$ proton. The ^{13}C NMR spectra of all the synthesized compounds are in agreement with the proposed structures.

Spectral data of representative compounds

5-acetyl-4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione (Table 1, Entry 3a)

Yellow solid; mp 198–200°C.

IR (KBr): ν_{max} = 3408 ($-\text{OH}$), 3139 ($-\text{NH}$), 2802 ($-\text{C}-\text{H}$), 1655 ($>\text{C}=\text{O}$) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.73 (s, 3H, $-\text{CH}_3$), 8.06 (s, 1H, $-\text{NH}$), 10.49 (s, $-\text{OH}$) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 28.42 ($-\text{CH}_3$), 101.91, 164.13 ($-\text{CONH}$), 172.00 ($\text{CO}-\text{S}$), 179.88, 198.14 ($-\text{CO}$) ppm.

5-[(1E)-N-(4-chlorophenyl) ethanimidoyl] -4-hydroxy-2H-1,3- thiazine-2,6 (3H)-dione derivatives (Table 2, Entry 4a)

Orange solid; mp 218–220°C.

IR (KBr): ν_{max} = 3223 ($-\text{OH}$), 3105 ($-\text{NH}$), 3012 ($-\text{C}=\text{C}-\text{H}$), 2822 ($-\text{C}-\text{H}$), 1687 ($>\text{C}=\text{O}$), 1580 ($\text{Ar}-\text{C}=\text{C}$) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.42 (s, 3H, $-\text{CH}_3$), 7.23 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.97 (s, 1H, $-\text{NH}$), 11.72 (s, 1H, $-\text{OH}$) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 21.08 ($-\text{CH}_3$), 98.35, 127.80 (C-2), 129.97 (C-2), 133.68, 134.69, 163.80 ($-\text{CONH}$), 168.85, 173.92, 181.54 ($\text{CO}-\text{S}$) ppm.

4-hydroxy-5-[(1E)-N-(4-methoxyphenyl) ethanimidoyl]-2H-1,3-thiazine-2,6 (3H)-dione (Table 2, Entry 4b)

Yellow solid; mp 226–230°C.

IR (KBr): ν_{max} = 3417 ($-\text{OH}$), 3244 ($-\text{NH}$), 3015 ($-\text{C}=\text{C}-\text{H}$), 2905 ($-\text{C}-\text{H}$), 1687 ($>\text{C}=\text{O}$), 1610 ($\text{Ar}-\text{C}=\text{C}$) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.13 (s, 3H, $-\text{CH}_3$), 3.81 (s, 3H, $-\text{OCH}_3$), 6.90 (d, 2H, Ar-H), 7.19 (d, 2H, Ar-H), 7.99 (s, 1H, $-\text{NH}$), 10.71 (s, 1H, $-\text{OH}$) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 21.10 ($-\text{CH}_3$), 55.29 ($-\text{OCH}_3$), 91.47, 115.69 (C-2), 122.05 (C-2), 139.48, 154.13, 163.06 ($-\text{CONH}$), 169.41, 175.37, 181.86 ($\text{CO}-\text{S}$) ppm.

4-hydroxy-5-[(1E)-N-(4-methylphenyl) ethanimidoyl]-2H-1,3-thiazine-2,6 (3H)-dione (Table 2, Entry 4c)

Yellow solid; mp 238–240°C.

IR (KBr): ν_{max} = 3403 ($-\text{OH}$), 3243 ($-\text{NH}$), 3007 ($-\text{C}=\text{C}-\text{H}$), 2923 ($-\text{CH}$), 1687 ($>\text{C}=\text{O}$), 1607 ($\text{Ar}-\text{C}=\text{C}$) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.22 (s, 3H, $-\text{CH}_3$) 2.59 (s, 3H, $-\text{CH}_3$), 7.23 (d, 2H, Ar-H), 7.25 (d, 2H, Ar-H), 8.01 (s, 1H, $-\text{NH}$), 10.55 (s, 1H, $-\text{OH}$) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 19.89 ($-\text{CH}_3$), 21.78 ($-\text{CH}_3$), 85.41, 122.34 (C-2), 130.54 (C-2), 136.93, 148.53, 163.47 ($-\text{CONH}$), 168.36, 177.61, 183.49 ($\text{CO}-\text{S}$) ppm.

5-[(1E)-N-(4-bromophenyl) ethanimidoyl]-4-hydroxy-2H-1,3-thiazine-2,6 (3H)-dione (Table 2, Entry 4d)

Orange solid; mp 202–204°C.

IR (KBr): ν_{max} = 3385 ($-\text{OH}$), 3240 ($-\text{NH}$), 3012 ($-\text{C}=\text{C}-\text{H}$), 2921 ($-\text{C}-\text{H}$), 1687 ($>\text{C}=\text{O}$), 1613 ($\text{Ar}-\text{C}=\text{C}$) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.13 (s, 3H, $-\text{CH}_3$), 7.25 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H), 8.09 (s, 1H, $-\text{NH}$), 10.69 (s, 1H, $-\text{OH}$) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 21.43 ($-\text{CH}_3$), 83.97, 123.61, 124.82 (C-2), 133.04 (C-2), 149.93, 163.71, ($-\text{CONH}$), 167.09, 173.81, 181.44 ($\text{CO}-\text{S}$) ppm.

4-hydroxy-5-[(1E)-N-phenyl ethanimidoyl]-2H-1,3-thiazine-2,6(3H)-dione (Table 2, Entry 4e)

Orange solid; mp 206–208°C.

IR (KBr): ν_{max} = 3408 ($-\text{OH}$), 3179 ($-\text{NH}$), 3012 ($-\text{C}=\text{C}-\text{H}$), 2927 ($-\text{C}-\text{H}$), 1687 ($>\text{C}=\text{O}$), 1605 ($\text{Ar}-\text{C}=\text{C}$) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.17 (s, 3H, $-\text{CH}_3$) 6.99–7.49 (m, 5H, Ar-H) 7.95 (s, 1H, $-\text{NH}$), 10.62 (s, 1H, $-\text{OH}$) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 21.15 ($-\text{CH}_3$), 81.94, 118.93 (C-2), 127.34, 130.24 (C-2), 136.40, 163.47 ($-\text{CONH}$), 168.41, 174.33, 181.23 ($\text{CO}-\text{S}$) ppm.

4-hydroxy-5-[(1E)-N-(3-methoxyphenyl) ethanimidoyl]-2H-1,3-thiazine-2,6 (3H)-dione (Table 2, Entry 4f)

Yellow solid; mp 176–178°C.

IR (KBr): ν_{max} = 3401 ($-\text{OH}$), 3265 ($-\text{NH}$), 3010 ($-\text{C}=\text{C}-\text{H}$), 2924 ($-\text{CH}$), 1687 ($>\text{C}=\text{O}$), 1607 ($\text{Ar}-\text{C}=\text{C}$) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.14 (s, 3H, $-\text{CH}_3$), 3.82 (s, 3H, $-\text{OCH}_3$), 6.84–7.27 (m, 4H, Ar-H), 7.99 (s, 1H, $-\text{NH}$), 10.73 (s, 1H, $-\text{OH}$) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 22.30 ($-\text{CH}_3$), 55.67 ($-\text{OCH}_3$), 81.42, 107.83, 108.98, 115.57, 131.64, 151.06, 162.27, 163.22 ($-\text{CONH}$), 167.94, 175.22, 181.52 ($\text{CO}-\text{S}$) ppm.

4-hydroxy-5-[(1E)-N-(3-methylphenyl) ethanimidoyl] -2H-1,3- thiazine-2,6 (3H)-dione (Table 2, Entry 4g)

White solid; mp 172–174°C.

IR (KBr): ν_{max} = 3368 ($-\text{OH}$), 3205 ($-\text{NH}$), 3022 ($-\text{C}=\text{C}-\text{H}$), 2915 ($-\text{CH}$), 1687 ($>\text{C}=\text{O}$), 1619 ($\text{Ar}-\text{C}=\text{C}$) cm^{-1} .

Table 1: Synthesis of 5-acetyl-4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione (3a)

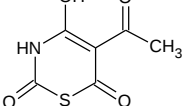
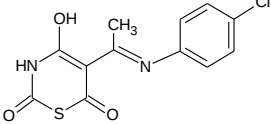
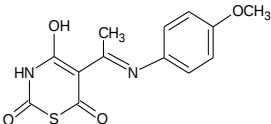
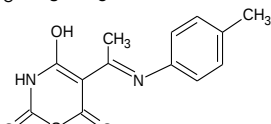
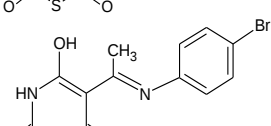
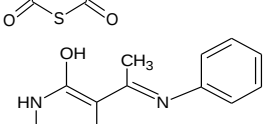
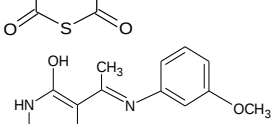
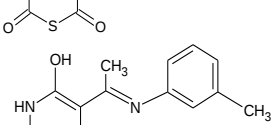
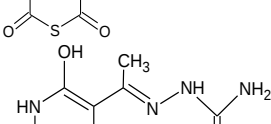
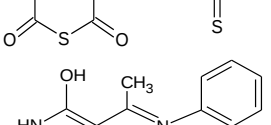
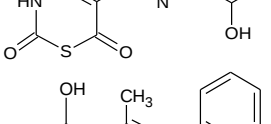
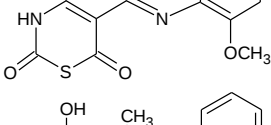
Entry	Compound	Yield (%)	M. P (°C)
3a		46	198-200

Table 2: Synthesis of 5-[(1E)-N-(4-chlorophenyl) ethanimidoyl] 4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione derivatives (4a-4k)

S. No	Entry	Compound	Yield (%)	M.P (°C)
1	4a		69	218-220
2	4b		63	226-230
3	4c		71	238-240
4	4d		70	203-205
5	4e		72	206-208
6	4f		67	176-178
7	4g		77	172-174
8	4h		75	232-234
9	4i		85	202-204
10	4j		72	214-216
11	4k		74	174-176

¹H NMR (400 MHz, DMSO): δ = 2.13 (s, 3H, -CH₃), 2.29 (s, 3H, -CH₃), 6.84-7.50 (m, 4H, Ar-H), 8.00 (s, 1H, -NH), 10.47 (s, 1H, -OH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 20.97 (-CH₃), 22.71 (-CH₃), 82.51, 119.20, 121.25, 124.19, 130.10, 139.76, 149.20, 163.69 (-CONH), 168.39, 175.32, 181.04 (CO-S) ppm.

(2E)-2-[1-(4-hydroxy-2,6-dioxo-3,6-dihydro-2H-1,3-thiazin-5-yl)ethylidene] hydrazine carbothioamide (Table 2, Entry 4h)

Yellow solid; mp 232-234°C.

IR (KBr): $\nu_{\max}$ = 3406 (-OH), 3337 (-NH), 3009 (-C=C-H), 1687 (>C=O), 1602 (Ar-C=C) cm⁻¹.

¹H NMR (400 MHz, DMSO): δ = 2.09 (s, 3H, -CH₃), 7.40 (s, 2H, -NH₂), 8.00 (s, 1H, -NH), 10.52 (s, 1H, -OH), 11.30 (s, 1H, -NH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 21.10 (-CH₃), 85.92, 154.47, 163.10 (-CONH), 173.39 (-C=S), 176.12, 181.40 (CO-S) ppm.

4-hydroxy-5-[(1E)-N-(2-hydroxyphenyl) ethanimidoyl]-2H-1,3-thiazine-2,6 (3H)-dione (Table 1, Entry 4i)

Orange solid; mp 202-204°C.

IR (KBr): $\nu_{\max}$ = 3418 (-OH), 3241 (-NH), 3017 (-C=C-H), 2905 (-CH), 1687 (>C=O), 1614 (Ar-C=C) cm⁻¹.

¹H NMR (400 MHz, DMSO): δ = 2.10 (s, 3H, -CH₃), 6.93-7.32 (m, 4H, -Ar-H), 8.02 (s, 1H, -NH), 9.86 (s, 1H, -OH), 10.43 (s, 1H, -OH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 19.10 (-CH₃), 81.54, 115.68, 120.42, 123.70, 129.78, 140.19, 152.30, 163.46 (-CONH), 168.22, 176.90, 181.74 (CO-S) ppm.

4-hydroxy-5-[(1E)-N-(2-methoxyphenyl) ethanimidoyl]-2H-1,3-thiazine-2,6 (3H)-dione (Table 2, Entry 4j)

Yellow solid; mp 214-216°C.

IR (KBr): $\nu_{\max}$ = 3415 (-OH), 3192 (-NH), 3019 (-C=C-H), 2927 (-CH), 1687 (>C=O), 1619 (Ar-C=C) cm⁻¹.

¹H NMR (400 MHz, DMSO): δ = 2.14 (s, 3H, -CH₃), 3.83 (s, 3H, -OCH₃), 6.64-7.56 (m, 4H, Ar-H), 8.02 (s, 1H, -NH), 10.59 (s, 1H, -OH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 19.96 (-CH₃), 55.81 (-OCH₃), 80.72, 115.17, 115.89, 122.39, 123.80, 136.47, 152.69, 163.71 (-CONH), 169.45, 175.10, 181.67 (CO-S) ppm.

4-hydroxy-5-[(1E)-N-(2-methylphenyl) ethanimidoyl]-2H-1,3-thiazine-2,6 (3H)-dione (Table 2, Entry 4k)

Yellow solid; mp 174-176°C.

IR (KBr): $\nu_{\max}$ = 3384 (-OH), 3246 (-NH), 3017 (-C=C-H), 2905 (-CH), 1687 (>C=O), 1612 (Ar-C=C) cm⁻¹.

¹H NMR (400 MHz, DMSO): δ = 2.10 (s, 1H, -CH₃), 2.38 (s, 1H, -CH₃), 7.02-7.35 (m, 4H, Ar-H), 8.00 (s, 1H, -NH), 10.45 (s, 1H, -OH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 19.14 (-CH₃), 20.40 (-CH₃), 80.63, 121.39, 127.50, 127.97, 128.90, 130.48, 147.00, 163.37 (-CONH), 167.96, 173.22, 181.58 (CO-S) ppm.

(3-(4-chlorophenyl)-4-methylidene-4,8-dihydro-2H,5H-[1,3] thiazino[5,4-e] [1,3] oxazine-2,5,7(3H)-trione (Table 3, Entry 5a)

Red solid; mp 90-92°C.

IR(KBr): $\nu_{\max}$ = 3189 (-NH), 3014 (-C=C-H), 1727 (-CO), 1619 (Ar-C=C) cm⁻¹.

Table 3: Synthesis of 3-(4-chlorophenyl)-4-methylidene-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazine-2,5,7(3H)-trione derivatives (5a-5k)

S. No.	Entry	Compound	Yield (%)	M.P (°C)
1	5a		70	90-92
2	5b		65	110-112
3	5c		68	168-170
4	5d		73	122-124
5	5e		86	100-102
6	5f		82	208-210
7	5g		77	160-162
8	5h		79	98-100
9	5i		85	92-94
10	5j		76	196-198
11	5k		69	94-96

¹H NMR (400 MHz, DMSO): δ = 5.25 (d, 1H, -CH), 5.42 (d, 1H, -CH), 7.27 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.95 (s, 1H, -NH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 88.79 (=CH₂), 101.97, 129.83 (C-2), 130.68 (C-2), 134.71, 135.44, 148.35 (-CO), 151.75, 153.23, 163.22 (-CONH), 181.32 (CO-S) ppm.

(3-(4-methoxyphenyl)-4-methylidene-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazine-2,5,7(3H)-trione (Table 3, Entry 5b)

Orange solid; mp 110-112°C.

IR (KBr): $\nu_{\max}$ = 3224 (-NH), 2994 (-C=C-H), 2841 (-C-H), 1722 (-C=O), 1607 (Ar-C=C) cm⁻¹.

¹H NMR (400 MHz, DMSO): δ = 3.86 (s, 3H, -OCH₃), 5.17 (d, 1H, -CH), 5.36 (d, 1H, -CH), 6.88 (d, 2H, Ar-H), 7.09 (d, 2H, Ar-H), 8.01 (s, 1H, -NH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 55.27 (-OCH₃), 88.48 (=CH₂), 101.67, 115.00 (C-2), 124.95, 129.00 (C-2), 144.19 (-CO), 154.46, 156.53, 159.68, 163.70 (-CONH), 181.86 (CO-S) ppm.

(4-methylidene-3-(4-methylphenyl)-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazine-2,5,7(3H)-trione (Table 3, Entry 5c)

Orange solid; mp 168-170°C.

IR (KBr): $\nu_{\max}$ = 3269 (-NH), 2995 (-C=C-H), 2927 (-CH), 1732 (-C=O), 1597 (Ar-C=C) cm⁻¹.

¹H NMR (400 MHz, DMSO): δ = 2.50 (s, 3H, -CH₃), 5.10 (d, 1H, -CH), 5.30 (d, 1H, -CH), 7.16 (d, 2H, Ar-H), 7.35 (d, 2H, Ar-H), 8.06 (s, 1H, -NH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 21.97 (-CH₃), 88.34 (=CH₂), 101.03, 126.41 (C-2), 129.00 (C-2), 130.33, 138.00, 143.47 (-C=O), 154.40, 157.36, 163.55 (-CONH), 181.78 (CO-S) ppm.

(3-(4-bromophenyl)-4-methylidene-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazine-2,5,7(3H)-trione (Table 3, Entry 5d)

Orange solid; mp 122-124°C.

IR (KBr): $\nu_{\max}$ = 3261 (-NH), 3015 (-C=C-H), 1730 (-C=O), 1619 (Ar-C=C) cm⁻¹.

¹H NMR (400 MHz, DMSO): δ = 5.12 (d, 1H, -CH), 5.20 (d, 1H, -CH), 7.46 (d, 2H, Ar-H), 8.40 (d, 2H, Ar-H), 8.05 (s, 1H, -NH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 88.63 (=CH₂), 101.46, 122.41, 127.42 (C-2), 129.74 (C-2), 130.13, 143.69 (-C=O), 154.00, 158.31, 164.57 (-CONH), 181.24 (CO-S) ppm.

(4-methylidene-3-phenyl-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazine-2,5,7(3H)-trione (Table 3, Entry 5e)

Brown solid; mp 100-102°C.

IR (KBr): $\nu_{\max}$ = 3239 (-NH), 3010 (-C=C-H), 1727 (-C=O), 1609 (Ar-C=C) cm⁻¹.

¹H NMR (400 MHz, DMSO): δ = 5.15 (d, 1H, -CH), 5.34 (d, 1H, -CH), 7.02 (t, 1H, Ar-H), 7.44 (d, 4H, Ar-H), 8.00 (s, 1H, -NH) ppm.

¹³C NMR (100 MHz, DMSO): δ = 88.71 (=CH₂), 101.97, 128.63, 129.83 (C-2), 130.68 (C-2), 133.01, 142.98 (-C=O), 153.23, 157.49, 163.22 (-CONH), 181.06 (CO-S) ppm.

(3-(3-methoxyphenyl)-4-methylidene-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazine-2,5,7(3H)-trione (Table 3, Entry 5f)

Yellow solid; mp 208-210°C.

IR (KBr): $\nu_{\max}$ = 3244 (-NH), 3016 (-C=C-H), 2852 (-CH), 1722 (-C=O), 1603 (Ar-C=C) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 3.84 (s, 3H, -OCH₃), 5.20 (d, 1H, -CH), 5.34 (d, 1H, -CH), 6.75 (d, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 7.02 (d, 1H, Ar-H), 7.11 (t, 1H, Ar-H), 7.98 (s, 1H, -NH) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 55.94 (-OCH₃), 88.89 (=CH₂), 101.22, 104.32, 117.04, 120.18, 128.94, 132.98, 143.00 (-C=O), 153.21, 157.21, 161.73, 164.52 (-CONH), 181.33 (CO-S) ppm.

(4-methylidene-3-(3-methylphenyl)-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazin-2,5,7(3H)-trione (Table 3, Entry 5g)

Red solid; mp 160-162°C.

IR (KBr): $\nu_{\max}$ = 3215 (-NH), 3009 (-C=C-H), 2845 (-CH), 1725 (-C=O), 1629 (Ar-C=C) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.28 (s, 3H, -CH₃), 5.16 (d, 1H, -CH), 5.31 (d, 1H, -CH), 6.80 (s, 1H, Ar-H), 7.02 (d, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 7.58 (d, 1H, Ar-H), 8.02 (s, 1H, -NH) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 21.26 (-CH₃), 88.70 (=CH₂), 101.20, 123.55, 125.67, 128.90, 129.96, 133.20, 138.78, 143.17 (-C=O), 153.64, 155.33, 163.01 (-CONH), 181.04 (CO-S) ppm.

(1-(4-methylidene-2,5,7-trioxo-7,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazin-3(4H)-yl)thiourea (Table 3, Entry 5h)

Yellow solid; mp 98-100°C.

IR (KBr): $\nu_{\max}$ = 3324 (-NH), 3011 (-C=C-H), 1732 (-C=O), 1631 (Ar-C=C) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.10 (s, 1H, -NH), 5.16 (d, 1H, -CH), 5.31 (d, 1H, -CH), 8.02 (s, 1H, -NH), 9.47 (s, 2H, -NH₂) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 89.92 (=CH₂), 101.95, 145.02 (-C=O), 151.75, 156.27, 163.19 (-CONH), 174.10 (C=S), 181.62 (CO-S) ppm.

(3-(2-hydroxyphenyl)-4-methylidene-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazin-2,5,7(3H)-trione (Table 3, Entry 5i)

Yellow solid; mp 92-94°C.

IR (KBr): $\nu_{\max}$ = 3405 (-OH), 3225 (-NH), 3024 (-C=C-H), 1733 (-C=O), 1622 (Ar-C=C) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 5.13 (d, 1H, -CH), 5.28 (d, 1H, -CH), 6.79 (d, 1H, Ar-H), 6.90 (t, 1H, Ar-H), 7.22 (d, 1H, Ar-H), 7.40 (t, 1H, Ar-H), 7.99 (s, 1H, -NH), 10.00 (s, 1H, -OH) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 88.90 (=CH₂), 101.45, 114.24, 122.74, 126.12, 126.76, 129.33, 143.00 (-C=O), 152.88 (C-2), 156.75, 161.79 (-CONH), 181.44 (CO-S) ppm.

(3-(2-methoxyphenyl)-4-methylidene-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazin-2,5,7(3H)-trione (Table 3, Entry 5j)

Brown solid; mp 196-198°C.

IR (KBr): $\nu_{\max}$ = 3236 (-NH), 3012 (-C=C-H), 2879 (-CH), 1732 (-C=O), 1621 (Ar-C=C) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 3.82 (s, 3H, -OCH₃), 5.14 (d, 1H, -CH), 5.32 (d, 1H, -CH), 6.75 (t, 1H, Ar-H),

6.92 (d, 1H, Ar-H), 7.19 (t, 1H, Ar-H), 7.39 (d, 1H, Ar-H), 8.04 (s, 1H, -NH) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 55.61 (-OCH₃), 88.57 (=CH₂), 101.51, 115.79, 116.75, 122.79, 125.40, 126.41, 130.19, 143.97 (-C=O), 153.00, 156.93, 161.81 (-CONH), 181.49 (CO-S) ppm.

4-methylidene-3-(2-methylphenyl)-4,8-dihydro-2H,5H-[1,3]thiazino[5,4-e][1,3]oxazin-2,5,7(3H)-trione (Table 3, Entry 5k)

Brown solid; mp 94-96°C.

IR (KBr): $\nu_{\max}$ = 3228 (-NH), 3018 (-C=C-H), 2835 (-CH), 1725 (-C=O), 1613 (Ar-C=C) cm^{-1} .

^1H NMR (400 MHz, DMSO): δ = 2.22 (s, 1H, -CH₃), 5.23 (d, 1H, -CH), 5.31 (d, 1H, -CH), 6.98 (t, 1H, Ar-H), 7.10 (t, 1H, Ar-H), 7.30 (d, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 8.02 (s, 1H, -NH) ppm.

^{13}C NMR (100 MHz, DMSO): δ = 19.84 (CH₃), 88.65 (=CH₂), 101.59, 125.00, 128.87, 129.49, 130.43, 134.13, 136.62, 142.99 (-C=O), 153.00, 156.76, 163.70 (-CONH), 181.42 (CO-S) ppm.

Table 4: Antimicrobial activity of Synthesized Compounds (5a-5k)

Comp. (100 $\mu\text{g/ml}$)	Antibacterial Activity		Antifungal Activity
	<i>B. subtilis</i>	<i>E. coli</i>	<i>C. albicans</i>
5a	19	17	15
5b	14	19	17
5c	15	18	19
5d	16	17	20
5e	19	15	17
5f	17	16	16
5g	15	17	18
5h	20	19	21
5i	19	17	14
5j	18	18	13
5k	19	19	17
Streptomycin	22	23	-
Flucanazole	-	-	25

The antimicrobial results were reported in Tables 4. The antibacterial and antifungal activity was comparable to the standard drugs streptomycin and flucanazole at 100 $\mu\text{g/ml}$.^[21] Against the bacterial strains, the compounds 5a, 5e, 5h, 5i, 5j, 5k have shown very good activity against *B. subtilis*. The compounds 5b, 5c, 5h, 5j, 5k were found to possess significant activity against *E. coli*. Against the fungal strains, the compounds 5c, 5d, 5g, 5h were found to possess even better antifungal activity against *C. albicans*. Remaining compounds exhibited moderate activity compared to the standard drugs Streptomycin and flucanazole.

The titles of compounds (5a-5k) were prepared from the appropriate imines and triphosgene. This synthetic protocol operates in short reaction time, atom economy and has benefit of easy workup. All the synthesized compounds were confirmed by IR, ^1H NMR, ^{13}C NMR spectral data and evaluated for their antimicrobial activities. Among the all the synthesized compounds, some compounds showed good activity compared to the standard drugs.

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