Organocatalyzed Synthesis and Antibacterial Activity of Novel Quinolino Annulated Analogues of Azepinones

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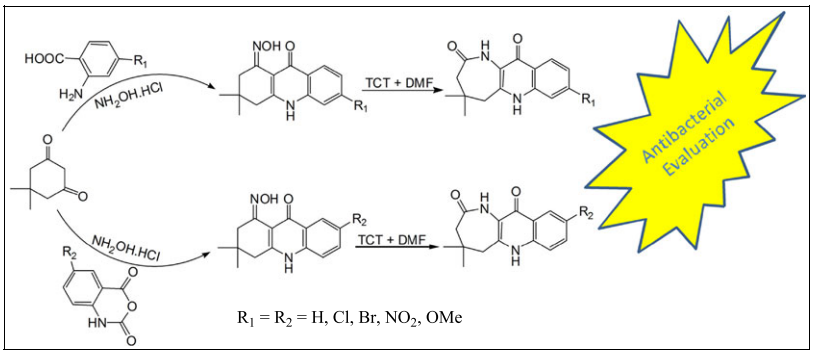


Starting from dimedone, two methodologies for synthesizing novel quinolino annulated azepinones have been reported. The protocol involves azepinone synthesis by the action of a newly synthesized organocatalyst derived from the reaction of TCT and DMF on oxime derivatives (**5** and **9**), which were obtained by the reaction of acridine dione derivatives (**4** and **8**) with hydroxylamine hydrochloride. The derivatives **4** and **8** were obtained by the reaction of **1** with anthranilic acid **2** and isatoic anhydride **7**, respectively. The synthesis of all the compounds was confirmed initially by TLC followed by spectral analysis through IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis. The results that emanated on the evaluation of the antibacterial activity of azepinones against two Gram-positive and two Gram-negative test organisms using disc diffusion method have also been discussed. Compounds **6c**, **6d**, **6e**, **10c**, and **10e** have been found to display better inhibitory activity than standard drugs streptomycin and tetracycline. The minimum inhibitory concentration and IC_{50} values for the compounds under study as well as of standard drugs were calculated. The maximum inhibition by bacterial strains was observed at 150 μg/mL.

INTRODUCTION

The onset of new epidemic diseases and the renaissance of several microbes that had been controlled coupled with the increase in microbial resistance have necessitated the requisition of development of new antimicrobials. Various heterocyclic compounds show antimicrobial potential, and among them quinoline nucleus forms the most desirable motifs having prominent antimicrobial activity [1]. Quinoline and its derivatives, chiefly quinolones, are medicinally important, as they show immense pharmacological activities like antimicrobial [2], anticancer [3], antiviral [4], and anti-inflammatory [5]. For instance, antibiotic chloroquine is used in the treatment of malaria. It is also reported that chloroquine is used in treating amoebic liver abscess and some major autoimmune disorders like rheumatoid arthritis and lupus erythematosus.

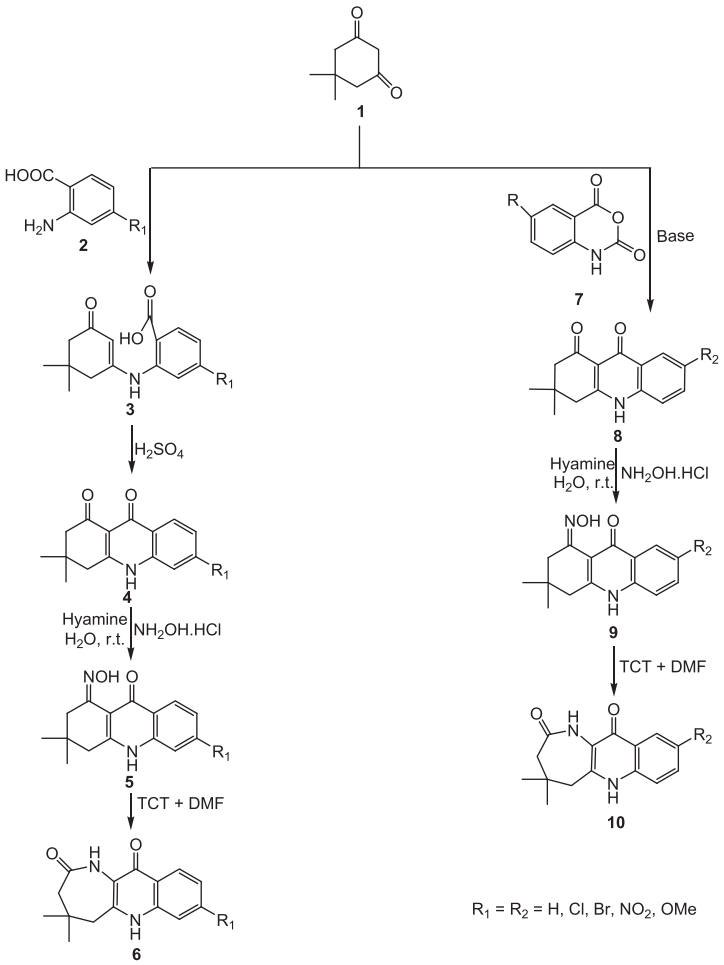
The utilization of drugs to cure diseases caused by the microbes has been increased so much that the microbes have become resistant to them. The dangerous effects of drug molecules on human life include hypersensitivity, immune suppression, and allergic reactions. For example, using mefloquine for a prolonged time has been rarely found to cause neuropsychiatric effects [6]. Despite a large number of quinoline nucleus-based drugs, that is, ciprofloxacin, sparfloxacin, ofloxacin, norfloxacin, and gatifloxacin, have been available for treatment of various infections, efforts have been made to improve the pharmacokinetic profile and therapeutic index and to remove the side effects caused due to these and antibiotics. This situation forces to the search for new antimicrobials.

Quinoline, being significantly important for treatment of various infectious diseases, has been selected in this communication for synthesis of novel quinolino annulated azepinone derivatives followed by their antibacterial drug designing under *in vitro* conditions with an effort to provide better treatment of various pathogenic microorganisms.

RESULTS AND DISCUSSION

Synthetic route shown in Scheme 1 was followed to accomplish the preparation of target compounds **6**(**a**–**e**)

Scheme 1. Synthesis of quinolino annulated analogues of azepinones.



and **10**(**a**–**e**). The acridones **4** [7] and **8** [8,9] were synthesized according to the reported procedures in the literature. At room temperature, the synthesized acridone (**4** or **8**) was stirred with hydroxylamine hydrochloride in water and in the presence of Hyamine catalyst to obtain the corresponding oximes (**5** or **9**), respectively. The rate of reaction was also found to be significantly affected by the amount of catalyst used and the temperature at which the reaction was carried out. Various concentrations of catalyst were loaded on to substrate out of which 60 mol% was found to be optimum as shown in Table 1. The rate and yield of reaction remain unchanged on increasing the amount of catalyst while it decreased on decreasing catalyst concentration. Similarly, stirring at higher or lower temperature led to the formation of undesired products or left the reaction incomplete. Thus, 60 mol% Hyamine at room temperature under aqueous conditions was chosen as the optimum reaction conditions. Further, the effect of various solvents in the transformation was also evaluated. It was found that solvents like $CHCl_3$, CH_3CN, EtOH, and EtOH–H_2O took much more time for the completion of reaction and still no desired product was formed. The transformation occurred in least amount of time when the catalyst was applied under aqueous conditions. The complete illustration of effect of different reaction conditions on yield of reaction has been depicted in Table 2.

Table 1

Effect of various concentration of Hyamine catalyst on the synthesis of **5** and **9**.

S. No.	Catalyst (mol%)	Time (min)	Yield (%)
1	No	65	19
2	30	71	62
3	40	82	69
4	50	78	87
5	60	55	99
6	70	60	97

The generated oxime (**5** or **9**) upon subsequent addition of a newly synthesized organocatalyst derived from the reaction of TCT and DMF underwent Beckmann rearrangement to produce the corresponding quinolino

Table 2

Effect of various reaction conditions on yield of reaction.

S. No.	Reaction conditions	Yield (%)
A	Solvent free, no catalyst, r.t.	10
B	$CHCl_3$, Hyamine, reflux	29
C	$CHCl_3$, Hyamine, r.t.	62
D	CH_3CN, Hyamine, reflux	33
E	CH_3CN, Hyamine, r.t.	55
F	EtOH, Hyamine, reflux	38
G	EtOH, Hyamine, r.t.	69
H	H_2O, Hyamine, reflux	20
I	H_2O, Hyamine, r.t.	99
J	EtOH–H_2O, Hyamine, reflux	52
K	EtOH–H_2O, Hyamine, r.t.	78
L	Solvent-free, Hyamine, r.t.	80

annulated azepinones (**6** or **10**), respectively. The Beckmann rearrangement usually involves the use of harmful acids, so alternative pathways have been searched where it is carried out under moderate conditions [10]. Recently, the use of organocatalysts has attracted the attention of the researchers because of their efficiency, good catalytic activity, and easy method of their handling during the operation of the process of rearrangement. In this category of catalysts, the cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) has emerged as one of the highly active, first [11–13] organocatalyst in effecting the *Beckmann rearrangement*.

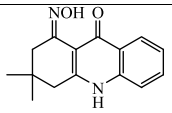
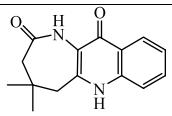
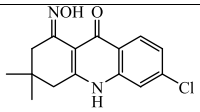
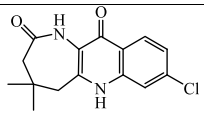
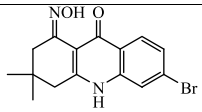
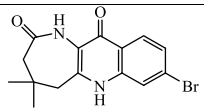
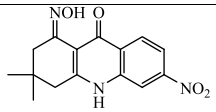
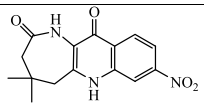
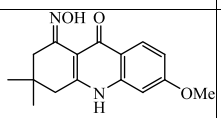
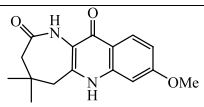
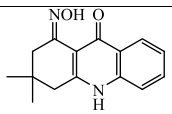
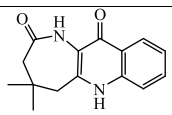
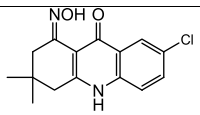
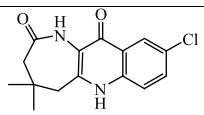
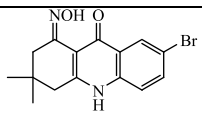
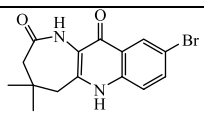
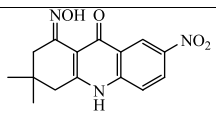
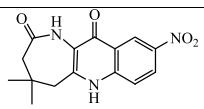
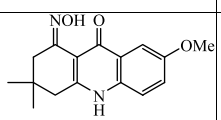
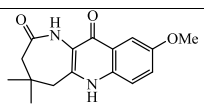
In the present communication, it has been found that the synthesized organocatalyst has a mild effect and it gives product with high purity unlike other catalysts that are rather strong acids or bases. Besides requiring high temperature, the latter reactions also produce huge amounts of hazardous by-products [14,15]. Synthesis of nylon-6 from ϵ-caprolactam is one such example that employs the use of fuming sulfuric acid and produces ammonium sulfate as by-product [16,17].

It was found out that the reaction worked equally well with all the substituents whether electron releasing or electron withdrawing. Scheme 2 summarizes the optimization study of the synthesis of oximes **5** and **9** and their further conversion into azepinones **6** and **10**, respectively. A probable mechanism for the synthesis of quinolino annulated azepinones has been described in Scheme 3.

The synthesis of quinolino annulated analogues of azepinones **6** and **10** was confirmed initially via thin-layer chromatography (TLC) and finally through spectral and elemental analyses. During spectral analysis, the authors depicted some distinctive peaks characteristic of particular groups, such as the following: The IR spectra illustrate the presence of absorption band at 3359 cm^{-1} due to NH stretching, and a twin peak at 1673 cm^{-1} and 1646 cm^{-1} due to C=O stretching respectively denoted the formation of compound **4a** or **8a**. Besides IR, the appearance of signal at 7.19–8.08 ppm due to the four aromatic protons, at 1.91 ppm due to NH protons, and at 160.76 and 195.85 ppm due to C of two C=O groups further confirmed its formation. In the same way, the appearance of absorption band at 3273, 1671, and 919 cm^{-1} due to OH, C=N, and N–O stretching, respectively, and at 4.39 ppm due to OH protons marked the formation of compound **5a** or **9a**. Similarly, the formation of compound **6a** or **10a** was ascertained through IR spectra, which showed absorption bands at 3565 cm^{-1} due to NH stretching, doublet at 1700–1648 cm^{-1} due to overlapping of amide I and amide II bands, and at 1338 cm^{-1} due to amide III band. The study of NMR again contributed to its formation by displaying peaks at 11.12 ppm due to NH protons of amide group and at 161.85 ppm due to C of amide group. The compounds **6b** and **10b** displayed peaks similar to **6a** and **10a**, respectively, except the presence of an additional absorption band at 753 cm^{-1} due to C–Cl stretching was observed. On similar grounds, the remaining compounds **6c–6e** and **10c–10e** were interpreted. The latter compounds displayed different absorption bands in IR due the the substitution of their aromatic ring with different groups such as the following: An absorption band at 685 cm^{-1} was observed because of C–Br stretching in **6c** and **10c**, while the formation of compounds **6d** and **10d** was ascertained by the appearance of absorption bands at 1530 and 1349 cm^{-1} due to asymmetric and symmetric stretching of NO_2. The compounds **6e** and **10e** were confirmed by 1219 cm^{-1} (asym. Str. of C–O–C) and 1016 cm^{-1} (sym. Str. of C–O–C) absorption bands in addition to the presence of tall singlet at 3.73 ppm (–OCH_3). The isotopic peaks were observed in the mass spectrum of compounds **6b–6c** and **10b–10c**. A little variation in the ^1H and ^{13}C NMR values of aromatic ring was observed in compounds **6b–6e** and **10b–10e** again because of the attachment of different groups.

Biological studies. Followed by synthesis, the novel azepinones were evaluated for their efficiency against two Gram-positive, that is, *Staphylococcus aureus* and *Bacillus subtilis*, and two Gram-negative, that is, *Escherichia coli* and *Enterobacter cloacae*, test organisms by employing disc diffusion method and taking 50, 100, and 150 μg/mL concentrations of the test compounds. Streptomycin and tetracycline were taken as standard. Streptomycin was put in the Petri plates containing test compounds **6a** to **6e** containing *S. aureus* and *E. coli* test organisms and test compounds **10a** to **10e** containing *B. subtilis* and *E. cloacae* test organisms. Tetracycline was put in the Petri plates containing test compounds **6a** to **6e** containing *B. subtilis* and *E. cloacae* test organisms and test compounds **10a** to **10e** containing *S. aureus* and *E. coli* test organisms. The results of MIC

Scheme 2. Optimization study of the synthesized products. [Color figure can be viewed at wileyonlinelibrary.com]

Product	Structure	Time (h)	Yield (%)	Product	Structure	Time (h)	Yield (%)
5a		8	99	**6a**		12	90
5b		10	85	**6b**		15	79
5c		10	81	**6c**		15	75
5d		10	79	**6d**		18	63
5e		8	88	**6e**		12	81
9a		8	99	**10a**		14	90
9b		10	83	**10b**		13	76
9c		9	84	**10c**		14	71
9d		10	82	**10d**		20	59
9e		8	93	**10e**		15	80

and IC_{50} screening are summarized in Table 3 and Figure 1, respectively.

These novel derivatives demonstrated varying antibacterial activities against different strains. Compound **10a** being unsubstituted and compound **10d** bearing nitro group at 9 position showed remarkable activity against *S. aureus*, whereas the unsubstituted compound **6a** showed moderate activity against

Scheme 3. Mechanism for the synthesis of quinolino annulated azepinones. [Color figure can be viewed at wileyonlinelibrary.com]

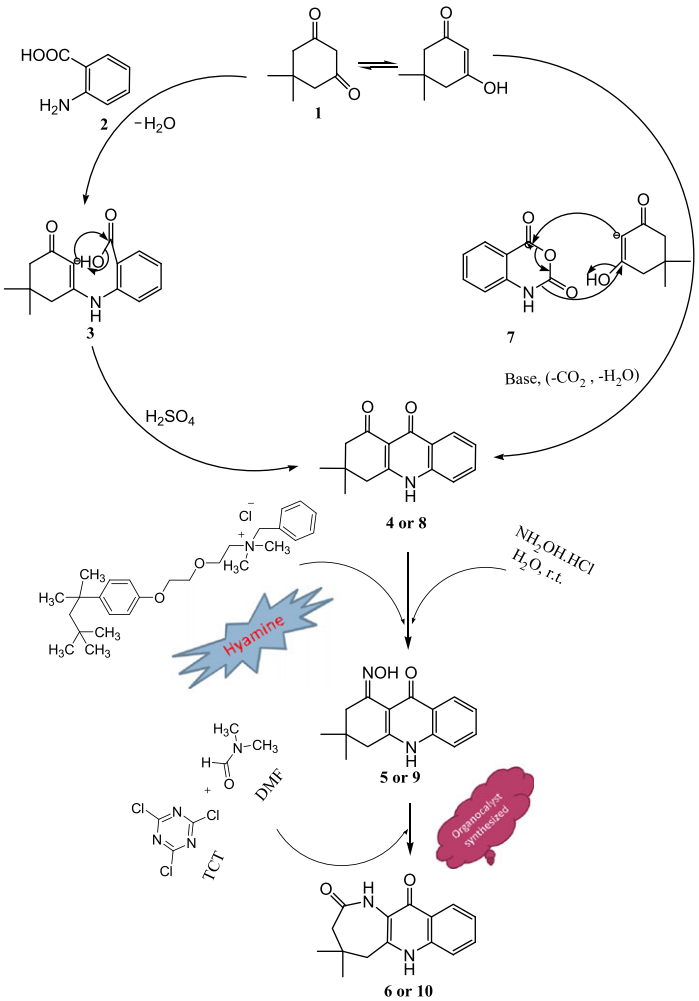


Table 3

Minimum inhibitory concentration in μg/mL against *S. aureus*, *B. subtilis*, *E. coli*, and *E. cloacae* bacterial strains.

Products	*S. aureus*	*B. subtilis*	*E. coli*	*E. cloacae*
6a	30	100	15	90
6b	80	155	90	100
6c	15	105	05	10
6d	120	10	55	115
6e	35	45	25	20
10a	80	35	70	60
10b	55	100	20	25
10c	25	90	01	185
10d	145	60	110	25
10e	15	75	35	40
Streptomycin	20	40	55	20
Tetracycline	50	30	25	55
Control	-	-	-	-

S. aureus. In case of *B. subtilis*, compound **6b** bearing chlorine atom at 8 position depicted significant antibacterial activity. Compounds **10b** and **10d** bearing chlorine atom and nitro group at 9 position showed good antibacterial activity against *B. subtilis*. Compounds **10a**, **10c**, and **10e** showed moderate antibacterial activity. In the same way, compounds **10a** and **10d** in case of *E. coli* and compound **6a** in case of *E. cloacae* depicted significant antibacterial activity. In case of *S. aureus*, compounds **6c** and **10e** showed MIC of 15 μg/mL, which means it was more potent than standard drug streptomycin. In a similar way, in case of *B. subtilis*, compound **6d** bearing nitro group at 8 position showed MIC of 10 μg/mL and depicted it to be more potent than standard drugs streptomycin (40 μg/mL) and tetracycline (30 μg/mL). Compounds **6c** and **10c** bearing chlorine atom at positions 8 and 9 respectively showed significant MIC (05 and 01 μg/mL, respectively) than standard streptomycin (55 μg/mL) and tetracycline (25 μg/mL). In the same way, compounds **6c** and **6e** showed significant MIC (10 and 20 μg/mL, respectively) as compared with standard streptomycin (20 μg/mL) and tetracycline (55 μg/mL).

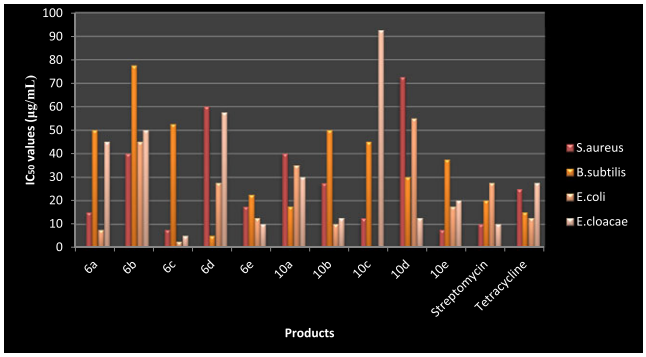


Figure 1. IC_{50} values of synthesized azepinones. [Color figure can be viewed at wileyonlinelibrary.com]

CONCLUSIONS

Synthetic protocols conceived in the present work provided an elegant heteroannulation of the quinoline ring with dimedone to produce the corresponding azepinone analogues of biological interest. *In vitro* evaluation of newly synthesized compounds revealed an improved therapeutic effectiveness as compared with the parent drugs. Some derivatives showed equipotent antibacterial activities against the selected strains. Experimental data reveal that the synthesized novel derivatives of quinolino annulated azepinones have remarkable antibacterial potential.

EXPERIMENTAL

General. All the chemicals and solvents used in this study were laboratory grade and procured from E. Merck (Germany), Sigma-Aldrich, Alfa Aeaser, Molychem, and Loba. All the solvents were distilled and dried before use. The compounds were synthesized using feasible procedures reported in the literature. Before analysis, the synthesized compounds were purified through column chromatography. The TLC plates (Silica Gel G) were used to confirm the purity of commercial grade reagents and the synthesized compounds. The IR spectra of synthesized compounds were obtained on a PerkinElmer IR spectrophotometer (KBr pellet). ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker AVANCE II 400 NMR spectrometer, and chemical shifts are expressed as δ (ppm) using tetramethylsilane as an internal standard and $CDCl_3$ or DMSO as a solvent, from SAIF/CIL, Punjab University, Chandigarh. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), m (multiplet), and q (quartet). Mass spectra of compounds were recorded on Waters, Q-TOF Micromass (LC–MS) mass spectrometer from SAIF/CIL, Punjab University, Chandigarh. The microanalysis and spectral (IR, ^{1}H NMR, and MS) data of all the compounds were found to be consistent to the structures assigned to the molecules. All the bacterial strains were procured from MTCC, Chandigarh, India.

Chemistry. ***General procedure for the preparation of 6-substituted-3,3-dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione (4) [7].*** The acridone **4** was prepared according to the protocol given in the literature in which anthranilic acid **2** (0.1 mol, 13.7 g) on reaction with **1** (0.1 mol, 14.0 g) in the presence of absolute alcohol (4.6 mL) gave enamine **3**, which upon dehydration with sulfuric acid (9.8 mL) underwent cyclization to form acridone **4**.

Spectral data of compound 4a. ***3,3-Dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione.*** Yield: 98% (yellow solid powder), mp 343–345°C, IR ν_{max} (KBr, in cm^{-1}): 3359, 3132, 1673, 1646, 1610, 1348; ^{1}H NMR (400 MHz; DMSO-d_6, δ): 1.10 (6H, s, $2CH_3$), 1.91 (1H, s, NH), 2.51–2.59 (2H, m, CH_2), 3.45–3.65 (2H, m, CH_2), 7.19–8.08 (4H, m, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): 21.89, 25.67, 43.94, 53.29, 120.31, 128.30, 129.33, 132.08, 137.26, 138.91, 152.22, 155.46, 160.76, 195.85; MS (EI): m/e = 241.26 [M+]; *Anal*. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81; O, 13.26. Found: C, 74.69; H, 6.23; N, 5.79; O, 13.23.

General procedure for the preparation of 7-substituted-3,3-dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione (8) [8,9]. Dimedone **1** (15 mmol, 210 mg) and sodium hydride (15 mmol, 360 mg) upon distillation were stirred in 40-mL DMF for 10 min followed by heating at 50°C for 6 min. The second step involved stirring along with heating at 90–100°C for 4 h after the addition of isatoic anhydride **7** (14 mmol, 228 mg) in the reaction mixture. DMF was then distilled off, and water (50 mL) and acetic acid (pH 5) were then added in the obtained residue. The product was then precipitated out and filtered through suction. The washing of precipitate was performed with ethanol, and recrystallization was performed with DMF.

Spectral data of compound 8b. ***7-Chloro-3,3-dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione.*** Yield: 95% (yellow solid powder), mp 302–306°C, IR ν_{max} (KBr, in

cm^{-1}): 3370, 3132, 1684, 1646, 1620, 1317, 800; ^{1}H NMR (400 MHz; DMSO-d_6, δ): 1.12 (6H, s, $2CH_3$), 1.91 (1H, s, NH), 2.61–2.68 (2H, m, CH_2), 3.42–3.63 (2H, m, CH_2), 7.05–8.17 (3H, m, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): 21.47, 23.96, 49.63, 59.08, 121.72, 129.01, 129.34, 130.17, 133.58, 146.29, 149.32, 149.67, 163.63, 195.11; MS (EI): m/e = 277.45 (1) [M+2], 275.45 (3) [M+]; *Anal*. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; Cl, 12.86; N, 5.08; O, 11.61. Found: C, 65.31; H, 5.09; Cl, 12.82; N, 5.09; O, 11.60.

General procedure for the preparation of 6-substituted-3,3-dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione-1-oxime (5) and 7-substituted-3,3-dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione-1-oxime (9). The reaction involved the stirring of mixture of dione **4** (2 mmol, 482 mg) and hydroxylamine hydrochloride (2.5 mmol, 174 mg) in water (4 mL) in the presence of Hyamine (60 mol%). TLC was performed to check the completion of reaction. As the precipitate came in the reaction mixture, it was filtered out and dried to obtain the pure oxime **5**. Same procedure was applied in the preparation of **9** from **8**.

Spectral data of some representative drugs. ***6-Chloro-3,3-dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione-1-oxime (5b).*** Yield: 85% (yellow solid powder), mp 319°C, IR ν_{max} (KBr, cm^{-1}): 3386, 3200, 3010, 1680, 1673, 1592, 1380, 942, 750; ^{1}H NMR (400 MHz; DMSO-d_6, δ): 1.12 (6H, s, $2CH_3$), 1.94 (1H, s, NH), 2.12–2.32 (2H, m, CH_2), 2.63–2.72 (2H, m, CH_2), 4.43 (1H, s, OH), 7.23–8.12 (3H, m, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.02, 31.38, 42.91, 52.36, 120.71, 124.84, 127.14, 130.03, 138.44, 140.59, 148.13, 149.35, 165.49, 198.04; MS (EI): m/e = 292.45 (1) [M+2], 290.45 (3) [M+]; *Anal*. Calcd for $C_{15}H_{15}ClN_2O_2$: C, 61.97; H, 5.20; Cl, 12.19; N, 9.64; O, 11.01. Found: C, 61.99; H, 5.22; Cl, 12.16; N, 9.63; O, 11.04.

3,3-Dimethyl-6-nitro-3,4-dihydro-2H,10H-acridine-1,9-dione-1-oxime (5d). Yield: 79% (yellow solid powder), mp 324–326°C, IR ν_{max} (KBr, cm^{-1}): 3380, 3210, 3023, 1685, 1652, 1581, 1522, 1378, 1340, 932; ^{1}H NMR (400 MHz; DMSO-d_6, δ): 1.14 (6H, s, $2CH_3$), 1.97 (1H, s, NH), 2.19–2.40 (2H, m, CH_2), 2.68–2.80 (2H, m, CH_2), 4.46 (1H, s, OH), 7.76–8.69 (3H, m, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): 24.98, 36.13, 46.45, 56.24, 120.11, 129.65, 129.93, 135.63, 139.04, 148.43, 152.34, 152.71, 163.86, 192.65; MS (EI): m/e = 301.44 [M+]; *Anal*. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95; O, 21.24. Found: C, 59.81; H, 5.05; N, 13.92; O, 21.26.

3,3-Dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione-1-oxime (9a). Yield: 99% (yellow solid powder), mp 330°C, IR ν_{max} (KBr, cm^{-1}): 3379, 3273, 3010, 1676, 1671, 1583, 1375, 919; ^{1}H NMR (400 MHz; DMSO-d_6, δ): 1.10 (6H, s, $2CH_3$), 1.92 (1H, s, NH), 2.06–2.26 (2H, m, CH_2), 2.59–2.72 (2H, m, CH_2), 4.39 (1H, s, OH), 7.16–8.01 (4H, m, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): 21.36, 39.38, 46.11, 58.09, 120.53, 128.34, 129.37, 132.83, 137.67, 141.01, 144.64, 145.37, 170.98, 190.87; MS (EI): m/e = 256.23 [M+]; *Anal*. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93; O, 12.48. Found: C, 70.27; H, 6.27; N, 10.96; O, 12.46.

7-Bromo-3,3-dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione-1-oxime (9c). Yield: 84% (yellow solid powder), mp 292–294°C, IR ν_{max} (KBr, cm^{-1}): 3370, 3260, 3020, 1682, 1673, 1593, 1372, 938, 685; ^{1}H NMR (400 MHz; DMSO-d_6, δ): 1.13 (6H, s, $2CH_3$), 1.95 (1H, s, NH), 2.09–2.31 (2H, m, CH_2), 2.61–2.80 (2H, m, CH_2), 4.46 (1H, s, OH), 7.03–8.51 (3H, m, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.49, 33.92, 43.17, 59.66, 122.54, 131.35, 132.05, 136.52, 137.61, 143.28, 149.77, 152.22, 160.94, 198.71; MS (EI): m/e = 336.9 (1) [M+2], 334.9 (1) [M+]; *Anal*. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; Br, 23.84; N, 8.36; O, 9.55. Found: C, 53.72; H, 4.52; Br, 23.85; N, 8.34; O, 9.54.

7-Methoxy-3,3-dimethyl-3,4-dihydro-2H,10H-acridine-1,9-dione-1-oxime (9e). Yield: 93% (yellow solid powder), mp 352°C, IR ν_{max} (KBr, cm^{-1}): 3375, 3267, 2843, 2815, 1678, 1675, 1583, 1386, 1210, 1036, 948; ^{1}H NMR (400 MHz; DMSO-d_6, δ): 1.08 (6H, s, $2CH_3$), 1.87 (1H, s, NH), 2.03–2.21 (2H, m, CH_2), 2.57–2.79 (2H, m, CH_2), 3.73 (3H, s, OCH_3), 4.39 (1H, s, OH), 7.01–7.99 (3H, m, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): 24.28, 36.85, 49.23, 52.47, 79.66, 121.39, 130.13, 130.46, 132.17, 136.23, 141.56, 143.87, 153.20, 167.29, 193.47; MS (EI): m/e = 286.53 [M+]; *Anal*. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78; O, 16.76. Found: C, 67.11; H, 6.31; N, 9.75; O, 16.75.

Synthesis of organocatalyst. The first step for the synthesis of organocatalyst was the addition of DMF (2 mL) on TCT (1.84 g, 0.01 mol). The temperature of the reaction mixture was maintained at 25°C. As the white solid was obtained, TLC was taken to ensure that TCT and DMF have completely reacted to synthesize the organocatalyst.

General procedure for the synthesis of 8-substituted-4,4-dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,2-b]quinoline-2,11-dione (6) and 9-substituted-4,4-dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,2-b]quinoline-2,11-dione (10). The synthesized organocatalyst was subsequently added to the mixture of oxime **5** (1 mmol, 256 mg) in DMF (1.5 mL). The reaction mixture was then stirred till precipitate was obtained. TLC was performed to confirm the synthesis of azepinone. The reaction work up was performed through ice in which residue obtained was filtered. The precipitate obtained was dried and recrystallized in ethanol to give **6**. Same procedure was applied in the preparation of **10** from **9**.

Spectral data of some representative drugs. ***4,4-Dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,3-b]quinoline-2,11-dione (6a or 10a).*** Yield: 90% (yellow solid powder), mp 361–363°C, IR ν_{max} (KBr, cm^{-1}): 3565, 3447, 3029, 1700, 1648, 1617, 1578, 1395, 1338; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.08 (6H, s, $2CH_3$), 1.91 (1H, s, NH), 2.50–2.58 (2H, m, CH_2), 3.18–3.38 (2H, m, CH_2), 7.19–8.08 (4H, m, Ar–CH), 11.12 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 27.80, 31.84, 47.25, 53.27, 123.18, 128.10, 128.14, 132.07, 136.65, 146.70, 148.79, 149.88, 161.85, 197.17; MS (EI): m/e = 272.22 [M+]; *Anal*. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93; O, 12.48. Found: C, 70.26; H, 6.25; N, 10.95; O, 12.46.

8-Chloro-4,4-dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,2-b] quinoline-2,11-dione (6b). Yield: 79% (yellow solid powder), mp 381°C, IR ν_{max} (KBr, cm^{-1}): 3560, 3377, 3062, 1684, 1646, 1617, 1573, 1383, 1337, 753; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.09 (6H, s, $2CH_3$), 1.94 (1H, s, NH), 2.60–2.69 (2H, m, CH_2), 3.17–3.32 (2H, m, CH_2), 7.26–8.01 (3H, m, Ar–CH), 11.10 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 26.71, 33.67, 44.09, 53.19, 120.71, 124.44, 127.74, 130.01, 138.49, 145.98, 149.57, 149.97, 167.43, 196.77; MS (EI): m/e = 292.45 (1) [M+2], 290.45 [M+]; *Anal*. Calcd for $C_{15}H_{15}ClN_2O_2$: C, 61.97; H, 5.20; Cl, 12.19; N, 9.64; O, 11.01. Found: C, 61.93; H, 5.18; Cl, 12.22; N, 9.62; O, 11.04.

8-Bromo-4,4-dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,2-b] quinoline-2,11-dione (6c). Yield: 75% (yellow solid powder), mp 365°C, IR ν_{max} (KBr, cm^{-1}): 3573, 3378, 3062, 1674, 1639, 1627, 1576, 1380, 1333, 685; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.10 (6H, s, $2CH_3$), 1.96 (1H, s, NH), 2.62–2.73 (2H, m, CH_2), 3.20–3.43 (2H, m, CH_2), 7.29–8.06 (3H, m, Ar–CH), 11.14 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 24.39, 32.43, 42.82, 63.74, 123.87, 127.17, 127.46, 128.03, 130.82, 138.79, 140.32, 141.41, 162.64, 198.27; MS (EI): m/e = 336.89 (1) [M+2], 334.89 (1) [M+]; *Anal*. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; Br, 23.84; N, 8.36; O, 9.55. Found: C, 53.72; H, 4.48; Br, 23.87; N, 8.34; O, 9.52.

4,4-Dimethyl-8-nitro-1,4,5,6-tetrahydro-3H-azepino[3,2-b] quinoline-2,11-dione (6d). Yield: 63% (yellow solid powder), mp 388–390°C, IR ν_{max} (KBr, cm^{-1}): 3573, 3369, 3060, 1676, 1634, 1614, 1562, 1530, 1386, 1336, 1349; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.08 (6H, s, $2CH_3$), 2.01 (1H, s, NH), 2.69–2.80 (2H, m, CH_2), 3.26–3.41 (2H, m, CH_2), 7.73–8.62 (3H, m, Ar–CH), 11.18 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.92, 34.92, 47.68, 54.38, 125.42, 129.15, 129.55, 132.79, 135.23, 142.76, 146.83, 149.04, 161.69, 195.72; MS (EI): m/e = 301.92 [M+]; *Anal*. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95; O, 21.24. Found: C, 59.76; H, 5.05; N, 13.98; O, 21.23.

8-Methoxy-4,4-dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,2-b]quinoline-2,11-dione (6e). Yield: 81% (yellow solid powder), mp 393–395°C, IR ν_{max} (KBr, cm^{-1}): 3560, 3360, 3052, 2848, 1670, 1642, 1611, 1557, 1372, 1332, 1219, 1016; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.09 (6H, s, $2CH_3$), 1.92 (1H, s, NH), 2.51–2.60 (2H, m, CH_2), 3.20–3.43 (2H, m, CH_2), 3.73 (3H, s, OCH_3), 7.09–7.99 (3H, m, Ar–CH), 11.10 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 29.63, 37.68, 43.62, 54.15, 65.94, 121.65, 125.90, 129.36, 129.96, 136.72, 139.11, 142.42, 146.65, 166.28, 194.43; MS (EI): m/e = 286.49 [M+]; *Anal*. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78; O, 16.76. Found: C, 67.10; H, 6.38; N, 9.72; O, 16.71.

9-Chloro-4,4-dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,2-b] quinoline-2,11-dione (10b). Yield: 76% (yellow solid powder), mp 381°C, IR ν_{max} (KBr, cm^{-1}): 3560, 3377, 3062, 1684, 1646, 1617, 1573, 1383, 1337, 753; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.09 (6H, s, $2CH_3$), 1.94 (1H, s, NH), 2.60–2.69 (2H, m, CH_2), 3.17–3.32 (2H, m, CH_2), 7.05–8.17 (3H, m, Ar–CH), 11.10 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 26.71, 33.67, 44.09, 53.19, 121.11, 122.47, 131.39, 132.66, 140.62, 145.36, 145.98, 149.57, 167.43, 196.77; MS (EI): m/e = 292.45 (1) [M+2], 290.45 [M+]; *Anal*. Calcd for $C_{15}H_{15}ClN_2O_2$: C, 61.97; H, 5.20; Cl, 12.19; N, 9.64; O, 11.01. Found: C, 61.93; H, 5.18; Cl, 12.22; N, 9.62; O, 11.04.

9-Bromo-4,4-dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,2-b] quinoline-2,11-dione (10c). Yield: 71% (yellow solid powder), mp 365°C, IR ν_{max} (KBr, cm^{-1}): 3573, 3378, 3062, 1674, 1639, 1627, 1576, 1380, 1333, 685; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.10 (6H, s, $2CH_3$), 1.96 (1H, s, NH), 2.62–2.73 (2H, m, CH_2), 3.20–3.43 (2H, m, CH_2), 7.03–8.51 (3H, m, Ar–CH), 11.14 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 24.39, 32.43, 42.82, 63.74, 116.23, 121.92, 129.23, 133.78, 137.29, 138.79, 141.41, 145.64 162.64, 198.27; MS (EI): m/e = 336.89 (1) [M+2], 334.89 (1) [M+]; *Anal*. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; Br, 23.84; N, 8.36; O, 9.55. Found: C, 53.72; H, 4.48; Br, 23.87; N, 8.34; O, 9.52.

4,4-Dimethyl-9-nitro-1,4,5,6-tetrahydro-3H-azepino[3,2-b] quinoline-2,11-dione (10d). Yield: 59% (yellow solid powder), mp 388–390°C, IR ν_{max} (KBr, cm^{-1}): 3573, 3369, 3060, 1676, 1634, 1614, 1562, 1530, 1386, 1336, 1349; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.08 (6H, s, $2CH_3$), 2.01 (1H, s, NH), 2.69–2.80 (2H, m, CH_2), 3.26–3.41 (2H, m, CH_2), 7.91–9.49 (3H, m, Ar–CH), 11.18 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.92, 34.92, 47.68, 54.38, 115.31, 122.56, 123.36, 132.26, 146.83, 149.04, 151.23, 159.29, 161.69, 195.72; MS (EI): m/e = 301.92 [M+]; *Anal*. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95; O, 21.24. Found: C, 59.76; H, 5.05; N, 13.98; O, 21.23.

9-Methoxy-4,4-dimethyl-1,4,5,6-tetrahydro-3H-azepino[3,2-b]quinoline-2,11-dione (10e). Yield: 80% (yellow solid powder), mp 393–395°C, IR ν_{max} (KBr, cm^{-1}): 3560, 3360, 3052, 2848, 1670, 1642, 1611, 1557, 1372, 1332, 1219, 1016; ^1H NMR (400 MHz; DMSO-d_6, δ): 1.09 (6H, s, $2CH_3$), 1.92 (1H, s, NH), 2.51–2.60 (2H, m, CH_2), 3.20–3.43 (2H, m, CH_2), 3.73 (3H, s, OCH_3), 7.01–7.99 (3H, m, Ar–CH), 11.10 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 29.63, 37.68, 43.62, 54.15, 65.94, 101.66, 106.95, 133.43, 136.27, 139.11, 142.19, 146.65, 150.48 166.28, 194.43; MS (EI): m/e = 286.49 [M+]; *Anal*. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78; O, 16.76. Found: C, 67.10; H, 6.38; N, 9.72; O, 16.71.

Biological evaluation. ***Antibacterial assay.*** Disc diffusion method [18,19] was adopted to assess the antibacterial potential of the synthesized compounds under *in vitro* conditions against randomly chosen bacterial strains, namely, *S. aureus*, *B. subtilis* (Gram positive), and *E. cloacae*, *E. coli* (Gram negative), taking streptomycin and tetracycline as standard. The MIC and IC_{50} values of all the synthesized compounds and of the standard drugs were determined.

Disc diffusion assay. The biological assay started with the synthesis of nutrient agar media. The latter was autoclaved and put (approx. 40 mL) in different Petri plates and left undisturbed for some time to let it settle down and get solidified. With the help of micropipette approx. 100 μL bacteria was put in the center of each Petri plate, which was spread on the entire Petri plate with the help of an L-shaped glass rod. The Petri plates were then bored to produce four wells of approx. 6 mm diameter each. Three milligrams of each compound was dissolved in DMSO and was kept as a stock solution from which 50, 100, and 150 μg/mL dilutions were prepared.[20] Out of the four wells, the three wells were filled with 50, 100, and 150 μg/mL concentrations of the compounds to be evaluated. The fourth well was filled only with the solvent, and this well was used as blank. Then streptomycin was put in the Petri plates containing test compounds **6a** to **6e** containing *S. aureus* and *E. coli* test organisms and test compounds **10a** to **10e** containing *B. subtilis* and *E. cloacae* test organisms. Tetracycline was put in the Petri plates containing test compounds **6a** to **6e** containing *B. subtilis* and *E. cloacae* test organisms and test compounds **10a** to **10e** containing *S. aureus* and *E. coli* test organisms. Then all the Petri plates were covered and were tightly packed with a paraffin film and were kept undisturbed in laminar air flow for 15 min so that the compounds could completely diffuse into agar. The plates were then kept in an incubator at 37°C for approx. 24 h. Finally, the diameter of zone of inhibition was measured to determine the antibacterial activity. Each test was performed in triplicates [21].

Calculation of minimum inhibitory concentration and IC_{50}. After measuring zone of inhibition, the values of MIC and IC_{50} were calculated for which serial dilution method was adopted. It depicted the minimum concentration, where no microbial growth was observed. A stock solution of 3 mg/mL of each compound was prepared in DMSO and further diluted to obtain a final concentration ranging from 200 to 0.05 μg/mL. Microorganisms were then added to each dilution in a 1:1 ratio. The prepared test tubes were then incubated for 24 h at 27°C. The lowest concentration where no growth of microorganisms was observed was noted as MIC. Dose–response curves were computed to obtain the concentrations where 50% inhibition of bacteria growth (IC_{50}) was observed. For some compounds, streptomycin was used as a standard, and for some other compounds, tetracycline was used as standard.

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