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Title: Organocatalysed Domino Synthesis of New Thiazole-Based Decahydroacridine-1,8-diones and Dihydropyrido[2,3-d:6,5-d']dipyrimidines in Water as Antimicrobial Agents

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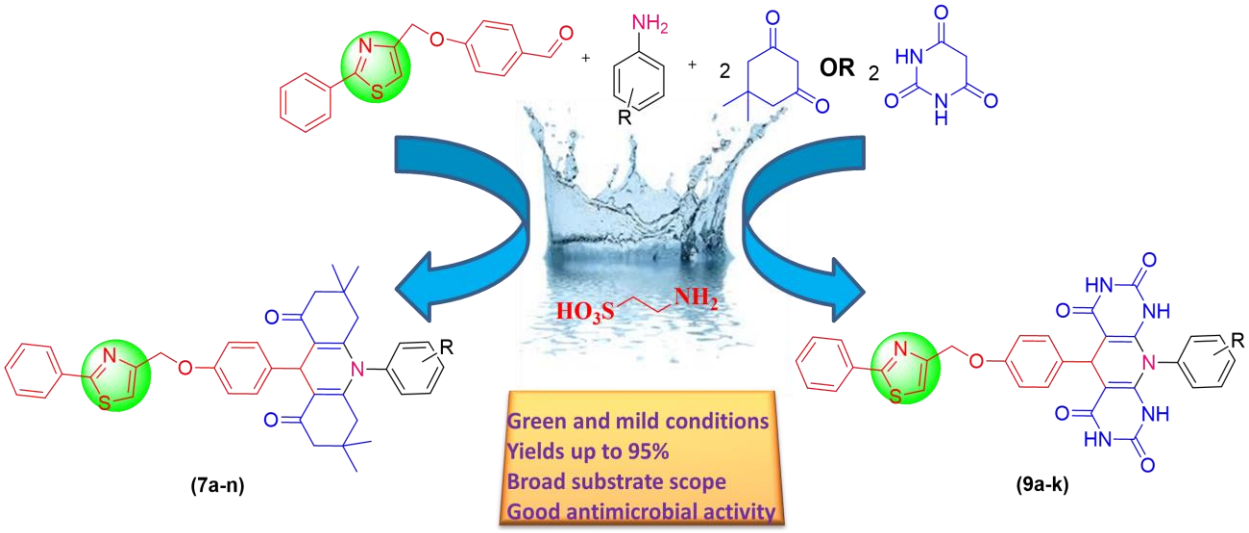
Graphical Abstract



OrganocatalysedDomino Synthesis of New Thiazole-Based Decahydroacridine-1,8-dionesand Dihydropyrido[2,3-d:6,5-d']dipyrimidines in Water as Antimicrobial Agents

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Abstract

Organopromoter, 2-aminoethanesulfonic acid catalyzed synthesis of series of structurally intriguing new hybrids thiazolyl acridine-1,8 (2*H*,5*H*)-diones and dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones for the first time. 2-Aminoethanesulfonic acid is a biobased organopromoter, used to generate four new bonds for the synthesis of new coupled thiazole-Based decahydroacridine-1,8-diones.Superior green credentials, operational simplicity, easy workup and recyclability of the catalyst are the key strengths of this method. Which attributes to broad substrate scope, mild reaction conditions, short reaction time, cost effectiveness, high atom economy and good to excellent yields make the present method a distinct improvement over existing methods. Spectral (IR,^{1}H NMR,^{13}C NMR, Mass) data, and elemental analyses confirmed the structures of the titled products. Series of thiazolyl acridine-1,8 (2*H*,5*H*)-diones and dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones were screened for their antimicrobial activity against four bacterial and three fungal strains.

Keywords Antimicrobial; Thiazolyl decahydroacridine-1,8-diones; Dihydropyrido[2,3-d:6,5-d']dipyrimidine; Multicomponent; Taurine

Introduction

Organocatalysis has been one of the fastest growing areas in synthetic chemistry in the last few years. It involved innate benefits in using small organic molecules of biological origin as promoters, which are typically non-toxic, insensitive to moisture and air, cost-effective, easily available, efficient and selective.[1-2] Organocatalyst corresponds to a low molecular weight organic molecule which in stoichiometric amounts catalyzes a chemical reaction.[3-5] Bio-organic catalysts are one of the organopromoter showing numerous excellent contributions in organic synthesis.[6-9] Bio-organic catalyst produces a line of proprietary product compositions, based upon its unique patented broad spectrum catalytic biochemistry, that establishes an entirely new platform technology for the chemical industry.[10] Organopromoters when used in combination with green solvents their real benefit are best realized.[11]

2-Aminoethanesulfonic acid (Taurine) is an organic compound that is widely distributed in animal tissues. It is a sulfur-containing semi-essential amino acid that exists in the human body and numerous other living creatures.[12-14] 2-Aminoethanesulfonic acid is in the zwitter ionic shape in water and this leads to essential biological and medicinal properties. Very few literature reports are available for 2-aminoethanesulfonic acid as catalyst. Recently Nader Daneshvar *et al* used 2-aminoethanesulfonic acid as a green bio-organic catalyst for the promotion of the Knoevenagel reaction and condensation reactions.[15,16] Silica gel supported 2-aminoethanesulfonic acid was also reported in the oxidation reaction of sulfides to their corresponding disulfides.[17]

The synthesis of acridine and analogues has attracted considerable attention from organic and medicinal chemists for many years, as a number of natural sources have been reported to have this heterocyclic nucleus. They are used in medicine and have enormous potential as pharmaceutical agents due to their biological activities (Figure 1) such as antiviral,[18] antibacterial,[19] anticancer,[20] anti-inflammatory activities[21] as well as efficiency in photodynamic therapy.[22] The chemical modifications of acridines by introducing different substitutions or heterocyclic rings were expanded the research on the structure activity relationship to afford new insight into molecular interactions at the receptor level.[23] Thiazole ring is a structural fragment of natural compounds such as thiamine (vitamin B1), thiamine pyrophosphate, epothilones, carboxylase, and the large family of macrocyclic thiopeptide antibiotics, thiostrepton and micrococcin P1.[24, 25] Thiazole derivatives are associated with a

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broad spectrum of biological properties, including anticancer, antitumor, anticonvulsant, antimicrobial, antituberculous and bacteriostatic activities (Figure 1).[26-29] Therefore we focused on attention to club theses heterocycles in one molecular framework to synthesize new hybrids thiazolyl acridinedione.

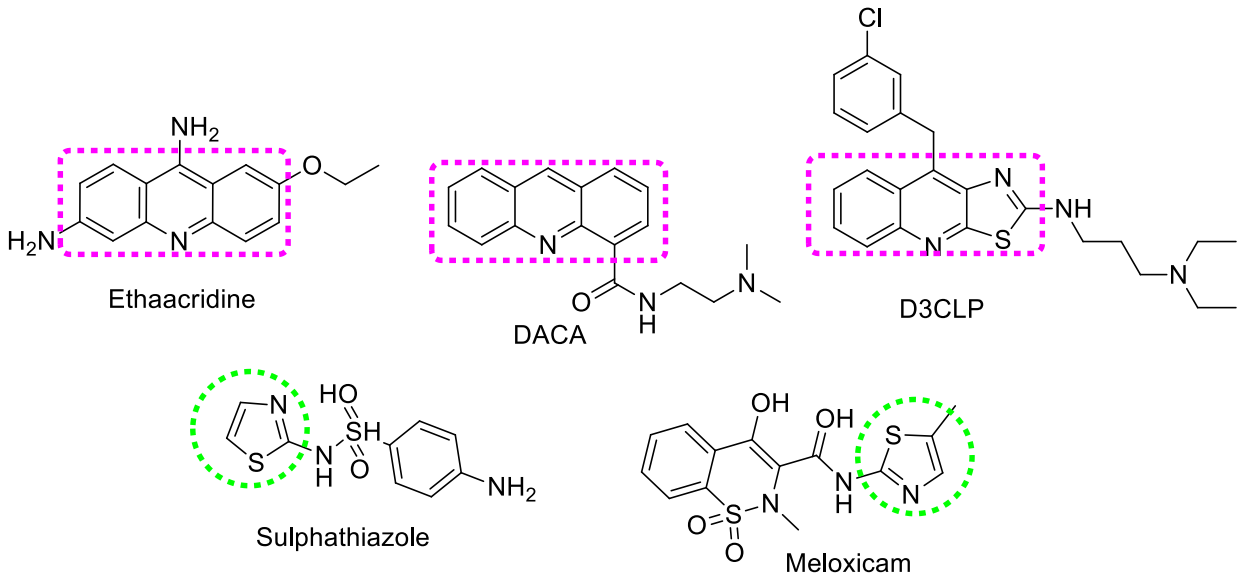


Figure 1: Biologically active molecules containing acridine and thiazole pharmacophore

There are many reported methods for the synthesis of acridinedione including multi-component condensation (MCR) of various aromatic aldehydes, cyclic diketones, and various aromatic amines in the presence of diverse catalysts Fe_3O_4@SiO_2-MoO_3H,[30] Pt NPs@rGO nanoparticles,[31] proline,[32] benzyltriethyl ammoniumchloride,[33] Fluorotailed acidic imidazolium salts,[34] 1-methylimidazolium trifluoroacetate [Hmim]TFA,[35] cericammonium nitrate,[36] silica-bonded *N*-propyl sulfamic acid,[37] amberlyst-15,[38] carbon-based solid acid,[39] 4-dodecylbenzenesulfonic acid,[40] and Vitamin B1.[41] Acridinediones are also synthesized by conventional heating in organic solvents and under MW irradiation.[42] However, all these methods have not been entirely satisfactory, owing to various side-effects associated with them *viz.*, unsatisfactory yield, long reaction times, laborious work-up procedures, the requirement for special apparatus and harsh reaction conditions.

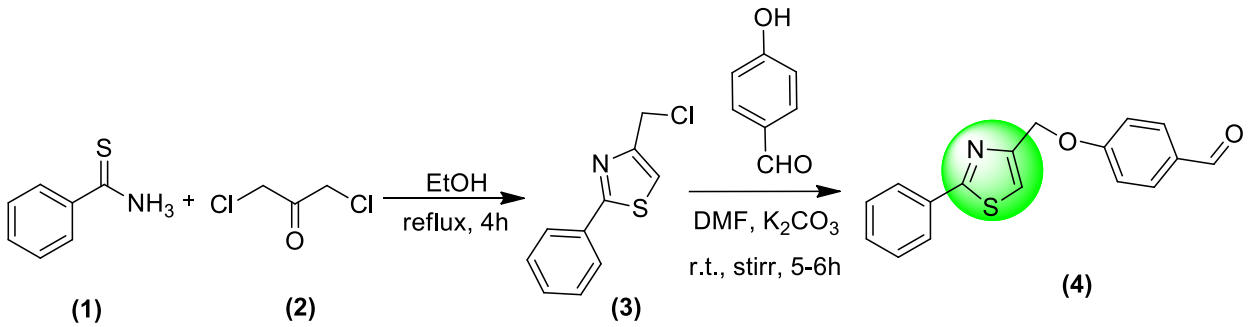
Consequently, in our continued pursuit towards the development of novel green synthetic routes for the construction of biologically important clubbed heterocycles,[43-46] we became

interested in the design of a new eco-friendly, efficient and versatile one pot multicomponent tandem synthesis of new hybrids thiazolyl decahydroacridine-1,8-dionesand dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones by using 2-aminoethanesulfonic acid as bio-organic promoter in water and evaluated for their antimicrobial activity.

Result and Discussion

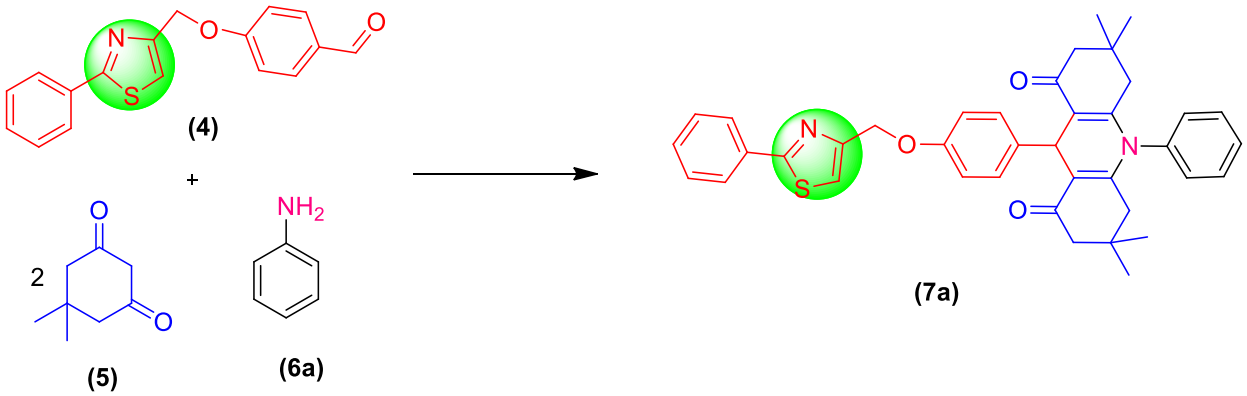
Chemistry

The basic requirement for the synthesis of these hybrids was the availability of the 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**4**). The synthesis of **4** (**Scheme 1**) was initiated by condensation of thioacetamide (**1**) and 1,3-dichloro acetone (**2**) in ethanol at reflux temperature. The resulting chloromethyl thazole (**3**) was then condensed with 4-hydroxy benzaldehyde in DMF/K_2CO_3 at room temperature for 5-6 h and obtained 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**4**) in 96 % yield.[47]



Scheme 1 Synthesis of4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **4**

To begin with, the one-pot synthesis of thiazolyl decahydroacridine-1,8-dione, was performed, whereby, well stirred solution of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(4a)** (1 mmol), cyclohexadione (**2**) (2 mmol) and aniline (**3a**) (1 mmol) was considered as model reaction.



Scheme 2 Synthesis of3,3,6,6-tetramethyl-10-phenyl-9-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione**7a**

To design more environmentally benign protocols, together with catalysts, there is need of cautious selection of the medium. Use of water as the reaction medium represents the most promising option in the search for cleaner, cheaper and more efficient technologies for organic transformations.[48-50] However, the implementation of aqueous media in organic reactions is often limited in scope due to the poor solubility of the organic precursors. To address this solubility issue, we sought to utilize different catalysts like β-Cyclodextrin, CTAB, tris(hydroxymethyl)aminomethane (THAM), *p*-TSA and 2-aminoethanesulfonic acid for the model reaction(**Scheme 2**). The reaction mixture of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(4a)**, cyclohexadione (**2**) and aniline (**5a**) was stirred at room temperature in water using above catalysts and obtained titled product thiazolyl decahydroacridine-1,8-dione **7a**, with 58, 62, 35, 59 and 73 % yield in 60 min. respectively (**Table 1, entries 1-5**). Therefore, considering the effective catalytic activity of 2-aminoethanesulfonic acid and for utilization of its applications in organic transformations, 2-aminoethanesulfonic acid was preferred as a catalyst of choice for subsequent optimization studies.

In order to improve the yield and rate of reaction, the effect of catalyst concentration and temperature was also investigated. To determine the exact requirement of catalyst for the reaction, we investigated the model reaction using different concentrations of 2-aminoethanesulfonic acid such as 10, 20, 30, and 40 mol %. During this, formation of the product was observed in 55, 73, 94 and 94% yield, respectively (**Table 1, entry 6**). This

indicated that 30 mol % of 2-aminoethanesulfonic acid was sufficient to carry out the reaction smoothly.

Model reaction in 2-aminoethanesulfonic acid at reflux was found to proceed with excellent yield (94%) to obtained thiazolyl decahydroacridine-1,8-dione **7a** in 60 min (**Table 1**). As temperature increased 40, 60, 80, 100 ^{o}C the yield of the product was also increased (71, 74, 90, 94 %). As expected, when the temperature was low, the catalytic system showed very poor activity, furnishing the desired product in low yields (**Table 1, entry 1**). However, on further raising the temperature, the yield was increased.

To evaluate the effect of solvent, model reaction was further performed using 2-aminoethanesulfonic acid in ethanol, water, ethanol:water (1:1), methanol, acetonitrile, chloroform and dichloromethane as solvent. Chloroform and dichloromethane did not bring the reaction to completion (**Table 1, entry 7**), but in contrast acetonitrile and methanol found to furnish the product in a moderate yields (**Table1, entry 6**). Reaction in ethanol and aqueous ethanol resulted in good yields 66% and 68%, respectively. Whereas, water brought the reaction to completion efficiently to furnish the product in excellent 94% yield (**Table 1, entry 5**).During the studies on the effect of the reaction medium, it was truly gratifying to notice an appreciable increase in the yield of the desired product, **7a** with the choice of water as the reaction medium. The reason for this result could be referred to the solubility of taurine. Since taurine is only soluble in water, use of ethanol removes this reagent from the homogeneous phase of the reaction.

Efficient recovery and reusability of the catalyst are other important features of our proposed protocol. Since 2-aminoethanesulfonic acid is soluble in water, it was easily separated from the products by simple filtration. The filtered solution was evaporated and thus obtained 2-aminoethanesulfonic acid reused for next two consecutive cycles for the synthesis of **7a**. As shown in there recyclability graph of catalytic efficiency of 2-aminoethanesulfonic acid, the isolated yields were almost similar until the third recycling (**Figure 2**). Recycled 2-aminoethanesulfonic acid was confirmed by FT-IR spectrum which determines structural information about the molecule. No change was observed in the IR spectra of 2-aminoethanesulfonic acid before the reaction and after third recycle (**Figure 3**).

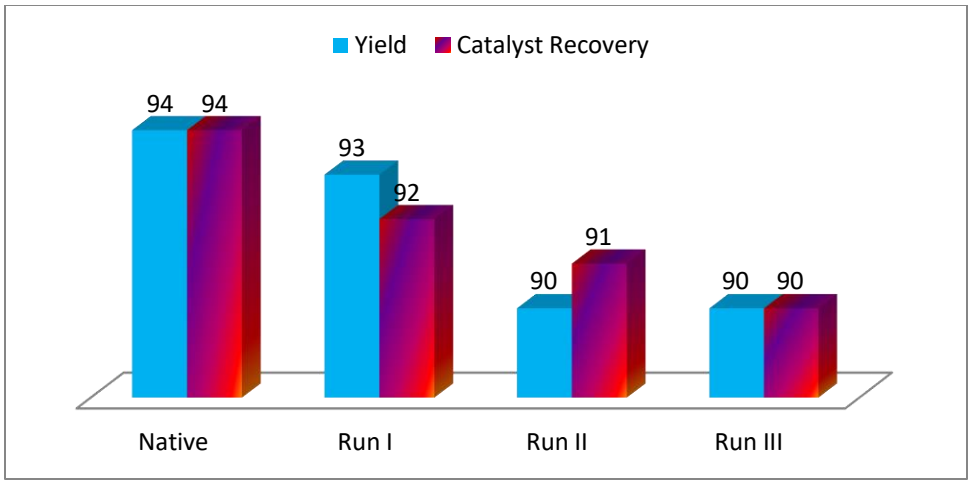


Figure 2 Recycle and recovery of 2-aminoethanesulfonic acid and its effect on yield.

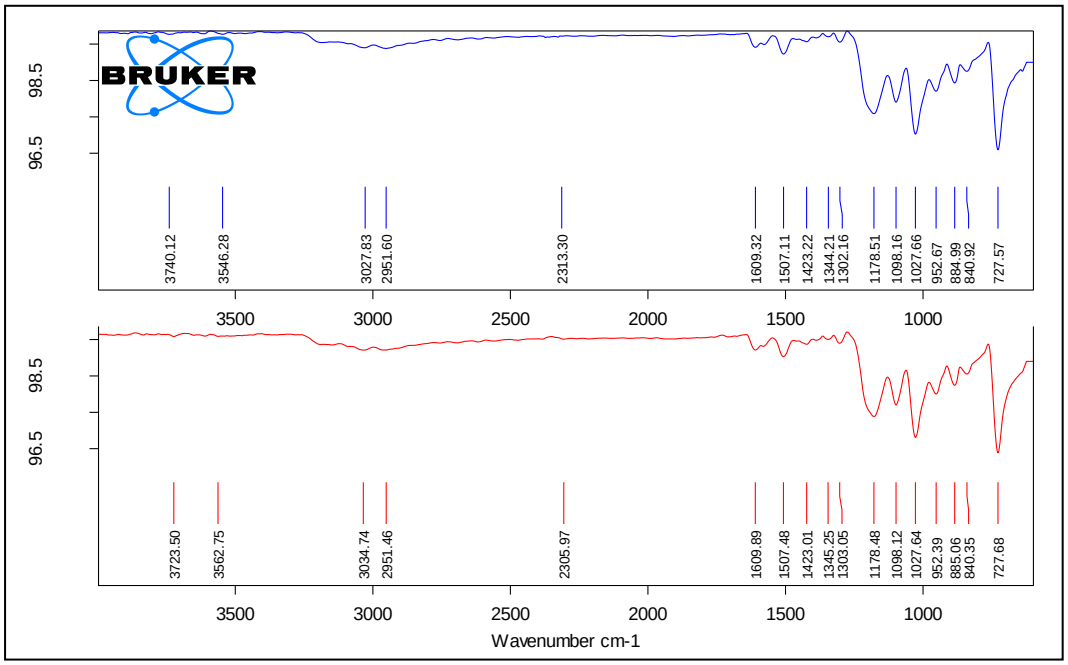
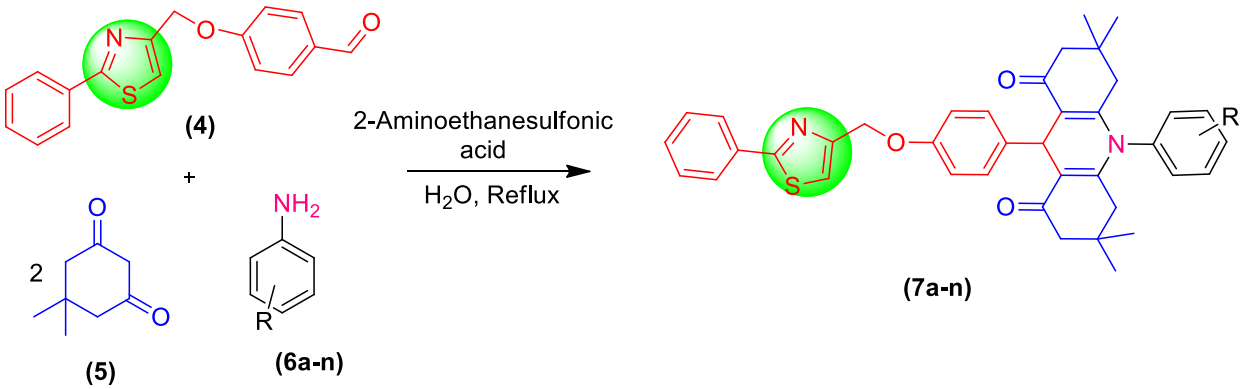


Figure 3 FT-IR spectra of 2-aminoethanesulfonic acid. Above Blue color: Fresh catalyst; Below Red color: After III recycle recovered catalyst

With optimized conditions in hand, we attempted to widen the scope of the designed protocol by reacting various substituted amines (aromatic and heterocyclic) with 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**4**) and 5,5-dimethyl-1,3-cyclohexanedione under aqueous medium in the presence of 2-aminoethanesulfonic acid. Pleasingly, in all cases, these components reacted successfully to form the corresponding thiazolyl decahydroacridine-1,8-

diones (**7a-n**) in good yields (**Scheme 3**). The results are summarized in **Table 2**. The results clearly revealed that the amines with electron-donating and electron-withdrawing functional groups at different positions reacted with 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**4)** and 5,5-dimethyl-1,3-cyclohexanedione smoothly and gave the corresponding product in good to excellent yields. The products were obtained in pure form, which avoided complicated purification operations, thus allowing the saving of both solvents and reagents.



Scheme 3 Synthesis of 10-(4-substituted phenyl)-3,3,6,6-tetramethyl-9-(4-((2-phenylthiazol-4 yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione **7a-n**

In addition, this procedure was successfully extended to synthesis of new thiazolyl dihydropyrido[2,3-d:6,5-d']dipyrimidines (**9a-k**) by the cyclocondensation of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(4),** barbituric acid **(8)** and aromatic amines (**6a-k**) (**Scheme 4**) using 2-aminoethanesulfonic acid as bio organopromoter in water.2-Aminoethanesulfonic acid catalyses the reaction efficiently and obtained desired thiazolyl dihydropyrido[2,3-d:6,5-d']dipyrimidines (**9a-k**) in good to excellent yields with short reaction time (**Table 3**).

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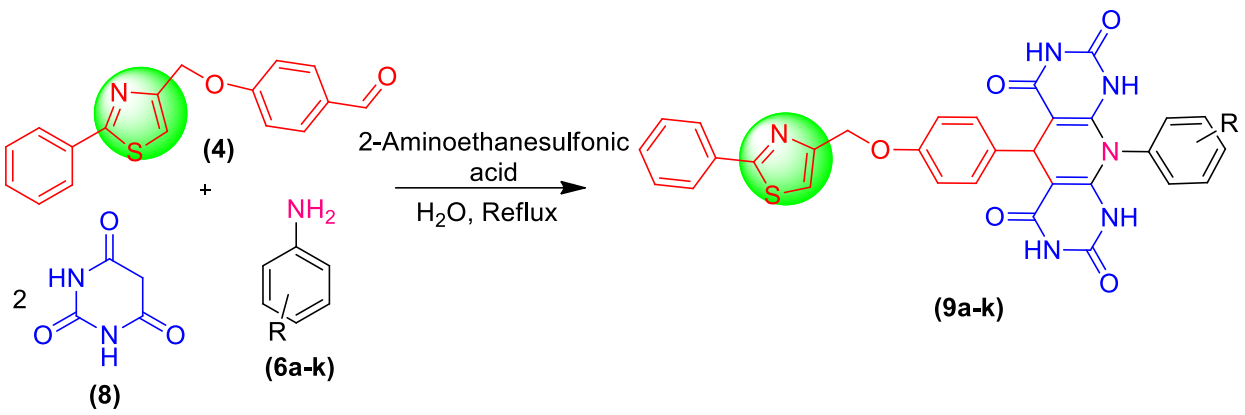

Scheme 4 Synthesis of10-(substituted phenyl)-5-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones **9a-k**

Plausible Mechanism of reaction

A probable mechanistic pathway for the formation of 1,8-decahydroacridine-1,8-dionesderivatives catalyzed by the 2-aminoethanesulfonic acid is outlined in **Scheme 5.** 2-aminothanesulfonic acid is a natural, green and commercially available amino acid containing a sulfonic acid group, in the acceleration of organic reactions.

The rate acceleration of this one pot four component cyclocondensation leading to N-substituted 1,8-decahydroacridine-1,8-diones is attributed to unique role of 2-aminothanesulfonic acid as a bifunctional donor-acceptor reagent and has binding capacity. Stronger hydrogen-bonding capabilities of 2-aminothanesulfonic acid might be assisting to enhance electrophilic character of carbonyl carbons of the reactants, *viz*; aldehydes and intermediate. It might also be increasing the rate of in situ formation of carbanion from dimedone. They may be causing rate acceleration resulting in high yields of the desired N-substituted 1,8-decahydroacridine-1,8-diones.

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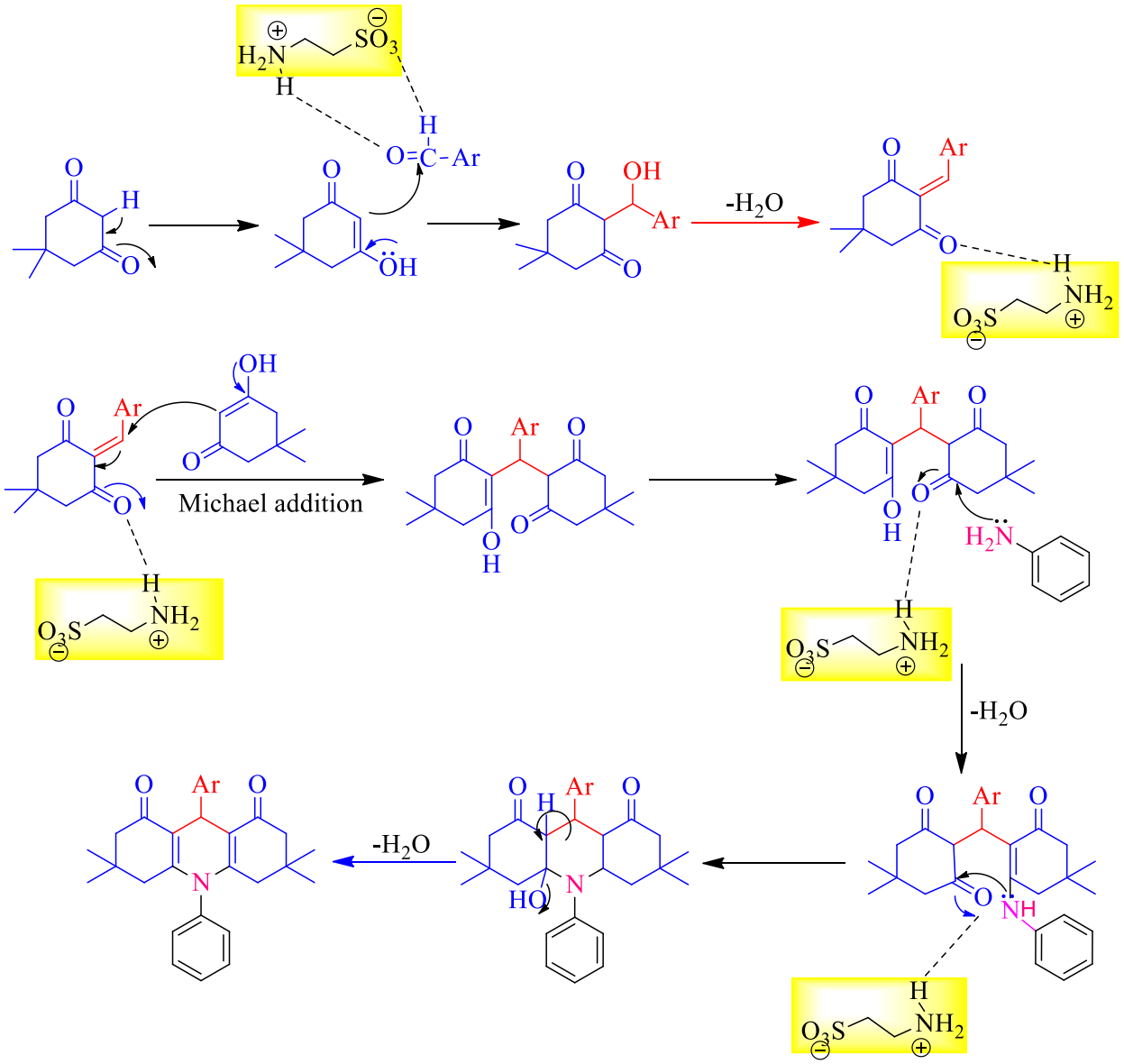

Scheme 5 Plausible reaction mechanism for the synthesis of thiazolyl decahydroacridine-1,8-diones**7a-n**

Antimicrobial activity

Newly synthesized thiazolyl decahydroacridine-1,8-diones (**7a-n**) and dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones (**9a-k**) were tested for the antimicrobial activity against four pathogenic bacteria and three fungi including, *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Candida albicans, Aspergillus Niger and Aspergillus Flavus* in vitro using Ampicillin, Ciprofloxacin and Miconazole used as positive

controls. The results are summarized in **Table 4** and **5**. Among the series thiazolyl decahydroacridine-1,8-diones, compounds **7a**, **7b**, **7d**, **7f**, **7g**, **7h**, **7j**, **7l** and **7n**showed significant antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis*. Among the thiazolyl dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones (**9a-k**) compounds **9d**, **9f**, **9i** and **9k** exhibited good inhibitory activity against selected all bacterial stains. Both the series of compounds showed poor activity against fungal strains when compared with standards.

Table1 Optimization of the reaction conditions for the synthesis of thiazolyl decahydroacridine-1,8-dione**7a**

Entry	**Catalyst**	**Solvent**	**Catalyst Loading (mol%)**	**Time (h)**	**Yield (%)[b]**
1	β-Cyclodextrin	H_2O	20	1	58
2	CTAB	H_2O	20	1	62
3	THAM	H_2O	20	1	35
4	*p*-TSA	H_2O	20	1	59
5	2-Aminoethanesulfonic acid	H_2O	20	1	73
6	2-Aminoethanesulfonic acid	H_2O	10, 20, 30, and 40	1	55, 73, 94 and 94
7	2-aminoethanesulfonic acid (40, 60, 80, 100 ^oC)	H_2O	30	1	71, 74, 90, 94
8	2-Aminoethanesulfonic acid	EtOH	30	1	66
9	2-Aminoethanesulfonic acid	EtOH:H_2O (1:1)	30	1	68
10	2-Aminoethanesulfonic acid	MeOH	30	1	42
11	2-Aminoethanesulfonic acid	$CHCl_3$	30	1	No reaction
12	2-Aminoethanesulfonic acid	CH_3CN	30	1	36
13	2-Aminoethanesulfonic acid	DCM	30	1	No reaction
14	-	H_2O	-	13	No reaction
[a]Reaction Conditions: 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (**1**) (4 mmol), Aniline (4 mmol), dimedone (8 mmol), Water (15 mL), 80^oC [b]Isolated yield					

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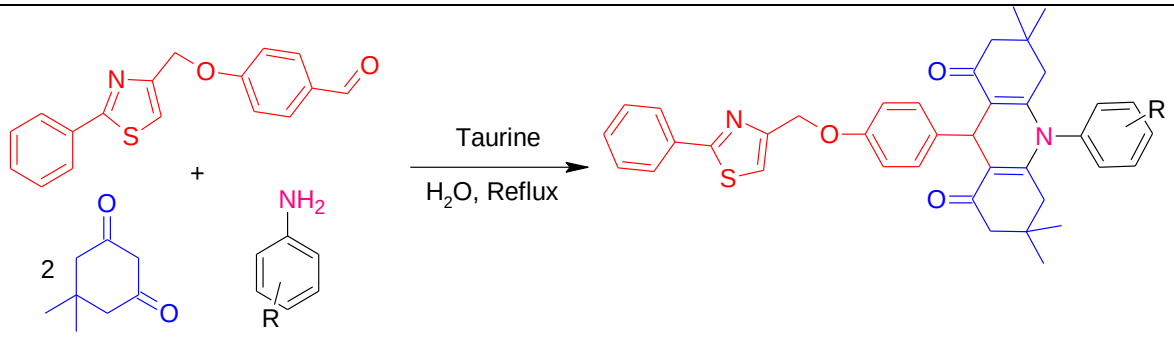
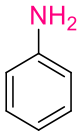
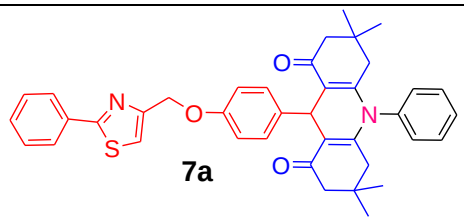
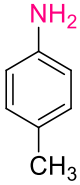
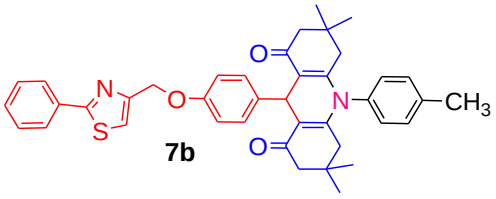
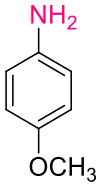
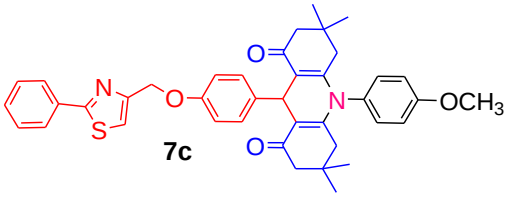
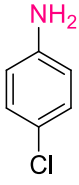
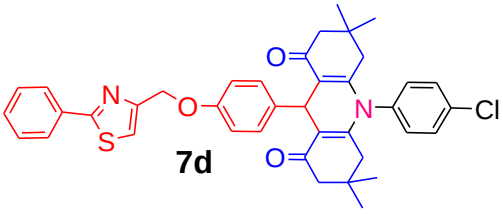
Table 2 Synthesis of 10-(4-substituted phenyl)-3,3,6,6-tetramethyl-9-(4-((2-phenylthiazol-4 yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-diones **7a-n**



Sr. No.	Aniline	Compound	Yield (%)	Melting Point (°C)
1		 **7a**	94	115-117
2		 **7b**	89	98-100
3		 **7c**	92	112-114
4		 **7d**	88	96-98

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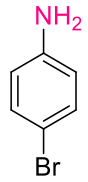
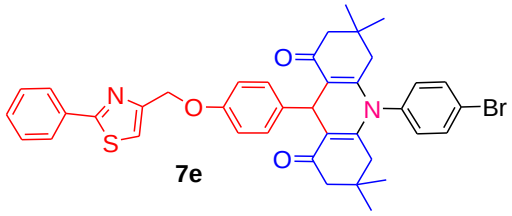
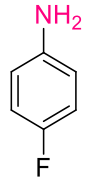
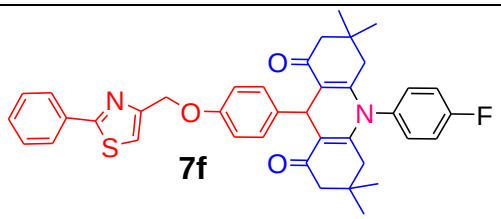
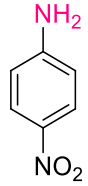
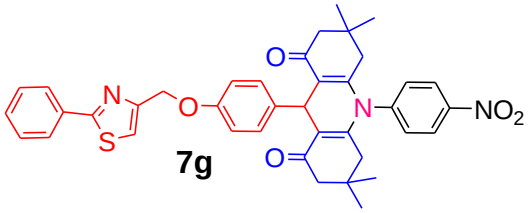
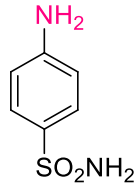
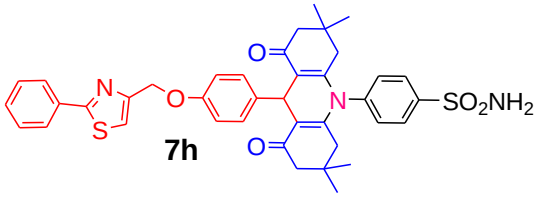
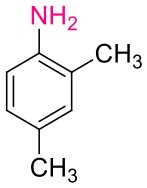
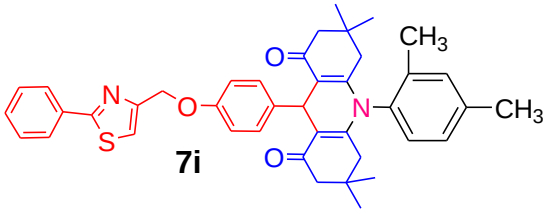
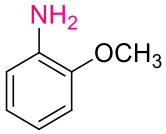
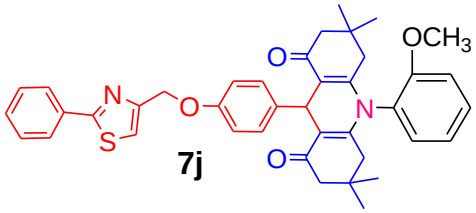
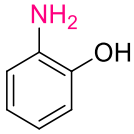
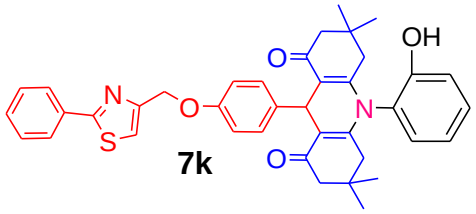
5		 **7e**	76	104-106
6		 **7f**	79	120-122
7		 **7g**	75	168-170
8		 **7h**	89	146-148
9		 **7i**	87	118-120
10		 **7j**	92	137-139
11		 **7k**	87	228-230

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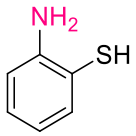
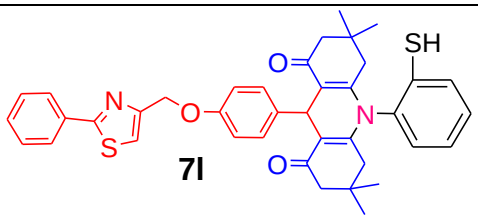
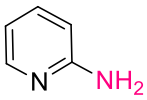
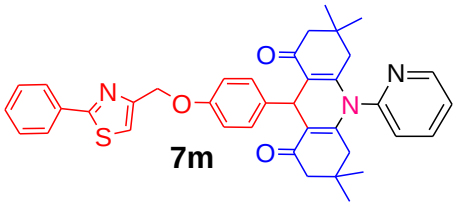
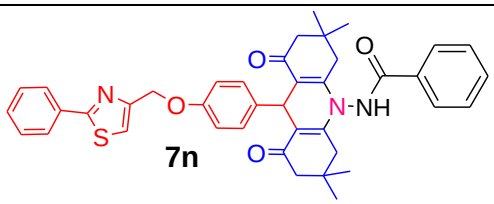
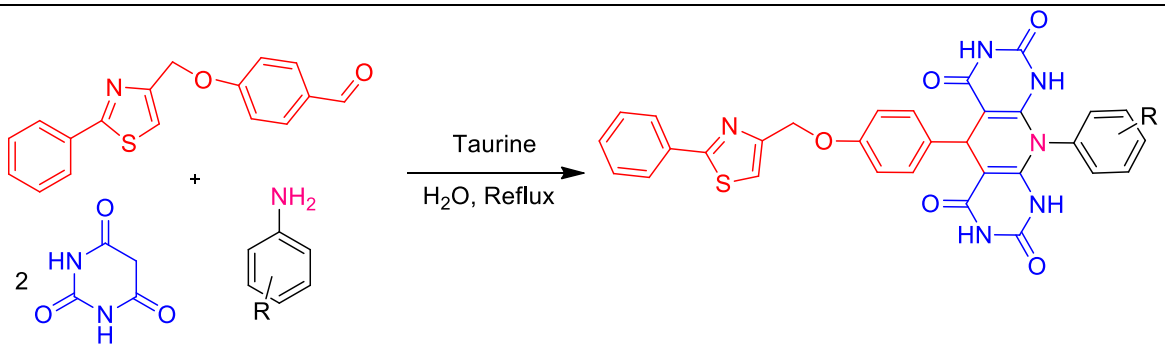
12		 **7l**	84	146-148
13		 **7m**	79	138-140
14		 **7n**	81	156-158

[a]Reaction Conditions: 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**4**) (4 mmol), dimedone (**5**) (8 mmol), substituted amines (**6a-n**) (4 mmol), 2-Aminoethanesulfonic acid (30 mol%), Water (15 mL) Reflux

[b]Isolated yield

Table 3 Synthesis of10-(substituted phenyl)-5-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones **9a-k**



Sr. No.	**Aniline**	**Compound**	**Yield (%)**	**Melting Point (°C)**

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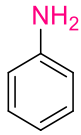
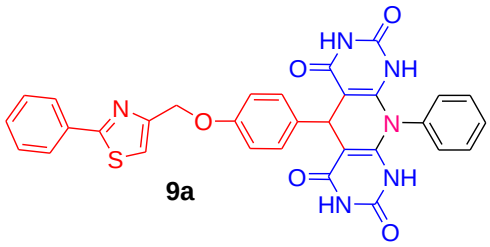
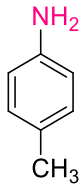
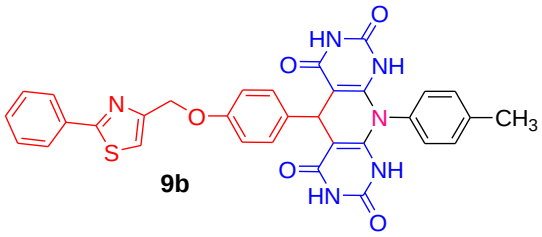
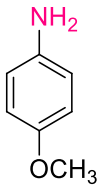
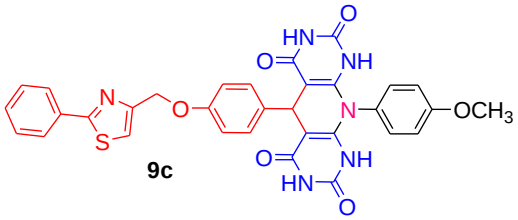
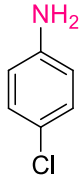
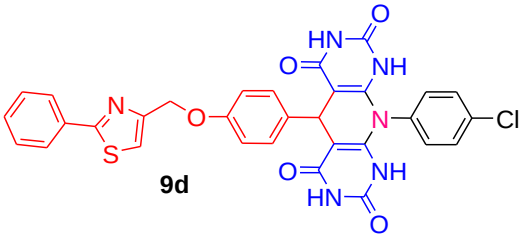
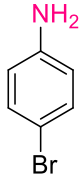
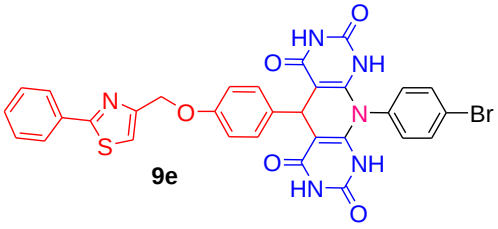
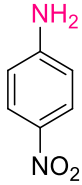
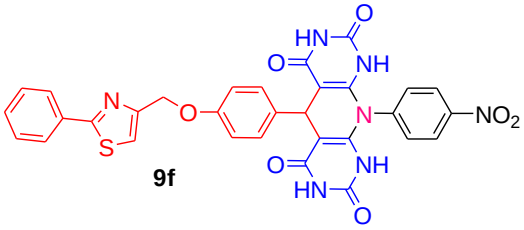
1		 **9a**	95	261-263
2		 **9b**	95	280-282
3		 **9c**	92	278-280
4		 **9d**	91	284-286
5		 **9e**	89	248-250
6		 **9f**	86	239-241

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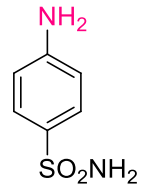
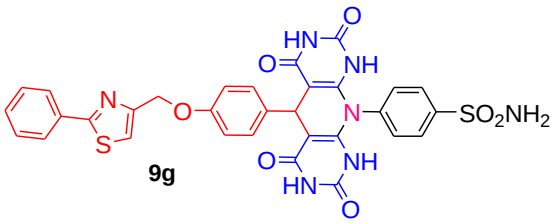
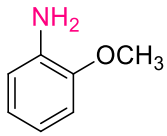
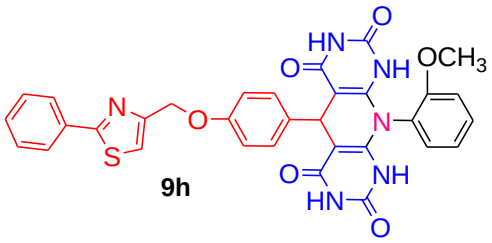
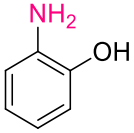
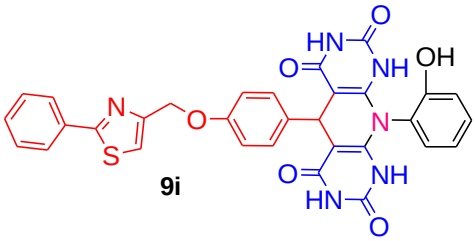
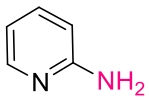
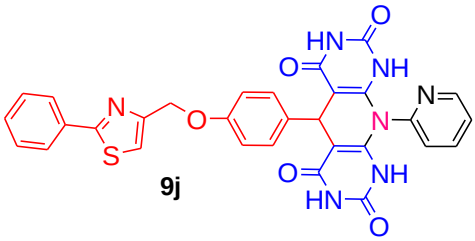
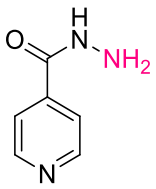
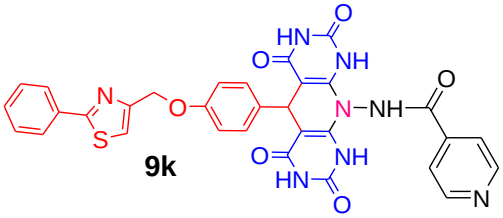
7		 **9g**	87	250-252
8		 **9h**	89	275-277
9		 **9i**	90	281-282
10		 **9j**	79	264-266
11		 **9k**	86	267-269

[a]Reaction Conditions: 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (**4**) (4 mmol), barbituric acid (**5**) (8 mmol), substituted amines (**6a-k**) (4 mmol), 2-Aminoethanesulfonic acid (30 mol%), Water (15 mL) Reflux

[b]Isolated yield

Table 4 MIC values of 10-(4-substituted phenyl)-3,3,6,6-tetramethyl-9-(4-((2-phenylthiazol-4 yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-diones **7a-n** after antimicrobial screening

Compound	MIC Values in µg/mL[a]				MIC Values in µg/mL[b]		
	Antibacterial Activity				Antifungal Activity		
	Escherichia coli	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus subtilis*	*Candida albicans*	*Aspergillus Niger*	*Aspergillus Flavus*
7a	165.8± 0.26	98.0± 0.31	79.0± 0.14	67.5± 0.85	48.5±0.36	77.3±0.22	91.5±0.37
7b	107.1± 0.38	188.4± 0.60	98.5± 0.08	108.0± 0.61	125.1±0.22	182.0±0.36	198.2±0.34
7c	165.9± 0.04	178.4± 0.24	186.3± 0.34	175.1± 0.38	102.1±0.33	142.1±0.66	138.3±0.56
7d	207.3± 0.34	ND	233.0± 0.64	204.1± 0.93	165.5±0.74	157.5±0.65	118.6±0.37
7e	219.4± 0.64	225.7± 0.38	ND	ND	240.1±0.24	198.3±22	205.1±0.38
7f	199.0± 0.52	178.1± 0.23	194.2.± 0.27	216.4± 0.75	212.0±0.76	195.4±067	229.3±0.27
7g	ND	ND	217.4± 0.09	241.3±0.70	208.7±0.81	265.7±0.24	193.1±0.30
7h	107.1±0.20	118.3±0.45	172.6± 0.24	91.22± 0.40	ND	239.1±0.21	243.3±0.71
7i	181.2± 0.25	ND	ND	144.7± 0.16	ND	ND	193.7±0.64
7j	97.5± 0.41	108.0± 0.97	185.4± 0.36	168.7± 0.55	225.1±0.03	192.2±0.40	160.5±0.33
7k	129.7± 0.34	182.7± 0.54	ND	ND	192.3±0.56	ND	238.1±0..56
7l	198.2± 0.74	97.6± 0.22	105.6± 0.50	272.5± 0.14	231.0±0.38	251.7±0.64	183.4±0.43
7m	146.3± 0.08	165.3± 0.34	ND	201.1± 0.30	196.1±0.17	187.4±0.62	175.3±0.56
7n	109.0± 0.51	140.6± .37	131.0± 0.22	161.1± 0.94	245.3±0.58	243.7±0.32	205.1±0.37
Ampicillin	100± 1.24	100± 2.14	250± 2.99	250± 0.88	-	-	-
Ciprofloxacin	25± 1.00	25± 1.15	50± 1.44	50± 0.96	-	-	-
Miconazole	-	-	-	-	25±1.17	25±1.11	12.5±0.98

[a]No activity reported up to 400 **µg/mL**for antibacterial
[b]No activity reported up to 250 **µg/mL**for antifungal, ND: No activity detected
Data are presented as mean±SD, n=3

Table 5 MIC values of 10-(substituted phenyl)-5-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones **9a-k** after antimicrobial screening

Compound	MIC Values in µg/mL[a]				MIC Values in µg/mL[b]		
	Antibacterial Activity				Antifungal Activity		
	Escherichia coli	*Pseudomona saeruginosa*	*Staphylococcus aureus*	*Bacillus subtilis*	*Candida albicans*	*Aspergillus Niger*	*Aspergillus Flavus*
9a	ND	101± 0.45	93± 0.08	85± 0.24	48±0.34	46±0.34	103±0.38
9b	130± 0.24	187.3± 0.64	115.7± 0.27	168.1± 0.47	38±0.47	64±0.53	49±0.08
9c	ND	98± 0.30	67± 0.41	ND	90±0.31	78±0.39	23±0.72
9d	97± 0.57	75± 0.36	82± 0.33	130± 0.63	84±0.22	ND	ND
9e	179± 0.38	191± 0.34	72.1± 0.51	164± 0.31	55±0.26	31±2.20	44.1±0.54
9f	76± 0.09	57± 0.11	101± 0.17	135± 0.60	107±0.22	39±0.11	41±0.90
9g	ND	ND	216± 0.34	1981± 0.38	131±0.24	106±0.22	155±0.76

9h	190± 0.06	174± 0.13	ND	ND	68±0.21	37±0.10	28±0.72
9i	ND	178.1± 0.57	129.6± 0.17	ND	243±0.38	105±0.71	136.7±0.37
9j	76± 0.85	91± 0.22	68± 0.34	111± 0.62	32±0.47	91±0.40	37±0.71
9k	68± 0.17	44± 0.92	98.1± 0.64	66.0± 0.74	43.1±0.55	62.9±0.36	29±0.88
Ampicillin	100± 1.24	100± 2.14	250± 2.99	250± 0.88	-	-	-
Ciprofloxacin	25± 1.00	25± 1.15	50± 1.44	50± 0.96	-	-	-
Miconazole	-	-	-	-	25±1.17	25±1.11	12.5±0.98

[a]No activity reported up to 400 **µg/mL**
[b]No activity reported up to 250 **µg/mL,** ND: No activity detected
Data are presented as mean±SD, n=3

Experimental

Reagents and instrumentation

All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with Bruker Avance 400 and Bruker Topspin spectrometer operating at 400 and 700MHz using $CDCl_3$ and DMSO solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm Mass spectra were recorded on a Sciex, Model; API 3000 LCMS/MS Instrument. CHNS Analysis was performed on Thermofisher Flash EA112 series Analyser. The purity of each compound was checked by TLC using silica-gel, $60F_{254}$ aluminum sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light.

Synthesis of 2-phenyl-4-chloromethylthiazole 3

In the first step, 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (4) was prepared according to the method already reported in our previous publication.35Thiobenzamide **(1)**(10 mmol) and 1,3-dichloro acetone **(2)** (10 mmol) were dissolved in ethanol. The reaction mixure was refluxed. The progress of the reaction was monitored by TLC. After 4h of the reflux, reaction mixture was cooled and solvent was removed under vacuum. The reaction residue was then poured on crushed ice. Thus obtained solid was filtered, washed with water, and crystallized from ethanol. Yield: 98%, M.P. 61-63ºC.[47]

Synthesis of 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde 4

A mixture of chloromethylthiazole (**3**) (10mmol), powdered potassium carbonate (20 mmol), and 4-hydroxybenzaldehyde (10 mmol) was added to *N,N*-dimethylformamide (20-30 mL). The reaction mixture was then stirred for 5-6 hr at r.t. After completion of the reaction, the reaction mixture was poured on crushed ice. Thus obtained solid was filtered, washed with water, and crystallized from ethanol. Yield: 97%, M.P. 100-102^{o}C.

General Procedure for the synthesis of 10-(4-substituted phenyl)-3,3,6,6-tetramethyl-9-(4-((2-phenylthiazol-4 yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-diones 7a-n

A mixture of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(4)** (1 mmol) and5,5-dimethylcyclohexane-1,3-dione (**2**) in water (20 mL) containing 2-aminothanesulfonic acid (30 mol%) was refluxed for 15 min. After that substituted anilines (**3a-n)** (1 mmole) was added and refluxed at 100℃. Progress of the reaction was monitored by thin layer chromatography using ethyl acetate:hexane (3:7) as solvent. After 60 min reaction mixture was cooled. Thus obtained solidwas filtered, dried and purified by crystallization.

General procedure for the synthesis of 10-(substituted phenyl)-5-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones 9a-k

A mixture of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(4)**(1 mmol) and barbituric acid(**2**) in water (20 mL) containing 2-aminothanesulfonic acid (30 mol%) was refluxed for 15 min. After that substituted anilines (**3a-k)** (1 mmole) was added and refluxed at 100℃. Progress of the reaction was monitored by thin layer chromatography using ethyl acetate:hexane (3:7) as solvent system. After 60 min reaction mixture was cooled. Thus obtained solid was filtered, dried and purified by crystallization.

4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde 4[47]

IR (ATR, υ cm^{-1}**)** Characteristic absorptions: 3117 (Ar-H stretch), 2830 (-C-H stretch), 1745 (C=O) and 1266 (C-O-C stretch). **^{1}H-NMR** (400 MHz, DMSO, δ ppm):5.33 (s, 2H, CH_2), 7.14-7.50 (m, 6H, Ar-H and thiazolyl-H), 7.82-8.00 (m, 4H, Ar-H) and 9.89 (s, 1H, -CHO). **MS** (Scanning mode, ESI^{+}): m/z (% intensity): 295.9 (M^{+}, 100)

9-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-10-phenylacridine-1,8(2H,5H,9H,10H)-dione 7a

IR (ATR, υ cm^{-1}**)** Characteristic absorptions: 3048, 2948, 2870, 1663, 1578, 1381, 1221, 882, 820, 783, 615.**^{1}H-NMR** (400 MHz, DMSO, δ ppm): 0.82 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.95-0.96 (m, 6H, CH_3), 2.15-2.45 (m, 8H, CH_2), 5.21 (s, 2H, CH_2), 5.34 (s, 1H, CH), 6.89-7.96 (m, 15H, Ar-H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.65, 168.74, 142.53, 141.80, 134.43, 132.90 (2C), 131.21 (2C), 130.53, 130.71 (2C), 129.87 (2C), 128.70 (2C), 127.69 (2C), 127.63, 125.82 (2C), 126.43 (2C), 124.74 (2C), 115.89, 114.31, 77.65, 66.76, 50.24, 49.65 , 44.21, 29.72; **MS** (Scanning mode, ESI^+): m/z 615.5 (M^+); Anal. calcd. For $C_{39}H_{38}N_2O_3S$: N, 4.56; C, 76.19; H, 6.23; S, 5.22 Found: N, 4.60; C, 76.13; H, 6.28; S, 5.21%.

10-(4-Methylphenyl)-3,3,6,6-tetramethyl-9-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione 7b

IR (ATR, υ cm^{-1}**)**Characteristic absorptions: 3053, 2959, 2868, 1670, 1582, 1367, 1245, 891, 834, 786, 617;^{1}H NMR (700 MHz, $CDCl_3$δ ppm):0.83-0.85 (m, 6H, CH_3), 1.19-1.27 (m, 9H, CH_3), 2.07-2.21 (m, 4H, CH_2), 2.27-2.51 (m, 4H, CH_2), 5.25 (s, 2H, CH_2), 5.38 (s, 1H, CH), 6.93-7.05 (m, 5H, Ar-H),7.06-.47 (m, 8H, Ar-H), 7.98 (d, 2H, *J=8 Hz*, Ar-H);^{13}C NMR (176 MHz, $CDCl_3$) δ 169.78, 168.51, 142.32, 141.78, 134.56, 132.23 (2C), 131.56 (2C), 130.87, 130.08 (2C), 129.93 (2C), 128.97 (2C), 127.89 (2C), 127.34, 125.76 (2C), 126.60 (2C), 124.86 (2C), 115.77, 114.39, 77.24, 66.47, 50.26, 49.92 , 44.61, 29.32, 27.43; **MS** (Scanning mode, ESI^+): m/z 629.3 (M^+); Anal. calcd. For $C_{40}H_{40}N_2O_3S$: N, 4.45; C, 76.40; H, 6.41; S, 5.10 Found: N, 4.48; C, 76.38; H, 6.50; S, 5.06%.

10-(4-Bromophenyl)-3,3,6,6-tetramethyl-9-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione 7e

IR (ATR, υ cm^{-1}**)** Characteristic absorptions: 3048, 2948, 2870, 1663, 1578, 1381, 1221, 882, 820, 783, 615; ^{1}H NMR (700 MHz, $CDCl_3$ δ ppm): 1.08-1.25 (m, 12H, CH_3), 2.27-2.52 (m, 8H, CH_2), 5.24 (s, 2H, CH_2), 5.35 (s, 1H, CH), 6.59-6.97 (m, 5H, Ar-H),6.89-7.13 (m, 2H, Ar-H), 7.21-7.95 (m, 7H, Ar-H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.57, 168.67, 142.32, 141.65, 141.02, 133.79, 132.78, 131.67, 130.92, 130.54 (2C), 128.29 (2C), 127.74 (2C), 126.28 (2C), 125.93 (2C), 124.10 (2C), 121.60, 120.58 (2C), 120.36, 119.61, 114.78, 77.45, 76.58, 66.45,

47.24, 40.87, 32.59, 29.62; **MS** (Scanning mode, ESI^+): m/z 693.5 (M^+); Anal. calcd. For $C_{39}H_{37}BrN_2O_3S$: N, 4.04; C, 67.53; H, 5.38; S, 4.62 Found: N, 4.11; C, 67.54; H, 5.42; S, 4.65%.

10-(4-Nitrophenyl)-3,3,6,6-tetramethyl-9-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione 7g

IR (ATR, υ cm^{-1}**)** Characteristic absorptions: 3074, 2992, 2875, 1670, 1565, 1388, 1254, 879, 825, 791, 630; ^{1}H NMR (700 MHz, $CDCl_3$ δ ppm):0.85-0.98 (m, 6H, CH_3), 1.14 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 2.18-2.50 (m, 8H, CH_2), 5.27 (s, 2H, CH_2), 5.38 (s, 1H, CH), 6.95-7.41 (m, 11H, Ar-H), 7.90-7.99 (m, 3H, Ar-H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.96, 168.64, 142.69, 141.34, 140.23, 133.85, 132.91, 131.43, 130.35, 130.09 (2C), 128.94 (2C), 127.89 (2C), 126.61 (2C), 125.12 (2C), 124.75 (2C), 121.78, 120.95 (2C), 120.34, 119.63, 114.42, 77.24, 76.88, 66.46, 47.09, 40.90, 32.65, 29.75; **MS** (Scanning mode, ESI^+): m/z 660.5 (M^+); Anal. calcd. For $C_{39}H_{37}N_3O_5S$: N, 6.37; C, 70.99; H, 5.65; S, 4.86 Found: N, 6.41; C, 70.93; H, 5.61; S, 4.90%.

10-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-9-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione 7k

IR (ATR, υ cm^{-1}**)** Characteristic absorptions: 3029, 2952, 2874, 1683, 1580, 1373, 1242, 879, 849, 776, 623; ^{1}H NMR (700 MHz, $CDCl_3$ δ ppm):1.13 (s, 6H, CH_3), 1.26 (s, 6H, CH_3), 2.33-2.44 (m, 8H, CH_2), 5.24 (s, 2H, CH_2), 5.37 (s, 1H, CH), 6.62-7.52 (m, 14H, Ar-H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.48 (2C), 143.56, 141.76, 140.72, 133.02, 132.05 (2C), 131.39, 130.36, 130.16, 129.03 (2C), 127.92 (2C), 126.57, 125.65 (2C), 124.21 (2C), 123.87, 122.35, 122.21, 121.70, 117.11, 115.76, 114.57, 77.25, 66.48, 47.08, 46.46, 31.43, 29.72; **MS** (Scanning mode, ESI^+): m/z 631.7 (M^+); Anal. calcd. For $C_{39}H_{38}N_2O_4S$: N, 4.44; C, 74.26; H, 6.07; S, 5.08 Found: N, 4.43; C, 74.27; H, 6.11; S, 5.01%.

10-(4-nitrophenyl)-5-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone 9f

IR (ATR, υ cm^{-1}**)** Characteristic absorptions: 3421, 3139, 2950, 2875, 1671, 1554, 1478, 1390, 1223, 886, 876, 721, 667. ^{1}H NMR (700 MHz, $CDCl_3$ δ ppm): 5.38 (s, 2H, CH_2).6.61 (s, 1H, CH), 7.22 (d, 2H, *J=8 Hz*, Ar-H), 7.46-7.59 (m, 4H, Ar-H), 7.87-8.39 (m, 8H, Ar-H), 11.21 (s, 2H, NH), 11.33 (s, 2H, NH); ^{13}C NMR (176 MHz, DMSO) δ 165.65 (2C), 164.39 (2C), 155.27,

150.76, 137.89, 133.32, 131.32, 131.42, 130.97, 129.94, 128.94 (2C), 127.21 (2C), 126.74, 124.09 (2C), 123.21 (2C), 122.01, 121.90 (2C), 120.54 (2C),119.65 (2C), 115.76, 89.41, 48.56; **MS** (Scanning mode, ESI^+): m/z 636.3 (M^+); Anal. calcd. For $C_{31}H_{21}N_7O_7S$: N, 15.43; C, 58.58; H, 3.33; S, 5.04 Found: N, 15.41; C, 58.62; H, 3.35; S, 5.02%.

N-(2,4,6,8-tetraoxo-5-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1,2,3,4,6,7,8,9-octahydropyrido[2,3-d:6,5-d']dipyrimidin-10(5H)-yl)isonicotinamide 9k

IR (ATR, υ cm^{-1}**)** Characteristic absorptions: 3459, 3139, 2950, 2863, 1668, 1565, 1435, 1389, 1243, 849, 765, 690. ^1H NMR (700 MHz, $CDCl_3$ δ ppm): 5.30 (s, 2H, CH_2), 5.37 (s, 1H, CH), 7.18-7.52 (m, 5H, Ar-H), 7.72-7.95 (m, 6H,Ar-H), 8.42-8.79 (m, 3H, Ar-H), 11.20 (s, 2H, NH), 11.29 (s, 2H, NH), 11.98 (s, 1H, NH); ^{13}C NMR (176 MHz, DMSO) δ 164.59 (2C), 163.92 (2C), 155.67, 151.07, 136.43, 133.76, 131.76, 131.21, 130.87, 129.93, 127.96 (2C), 127.41 (2C), 126.40, 124.64 (2C), 123.12 (2C), 122.87, 121.94 (2C), 120.34 (2C), 119.75 (2C), 115.67, 89.73, 48.21; **MS** (Scanning mode, ESI^+): m/z 635.7 (M^+); Anal. calcd. For $C_{31}H_{22}N_8O_6S$: N, 17.66; C, 58.67; H, 3.49; S, 5.05 Found: N, 17.65; C, 58.69; H, 3.42; S, 5.09%.

Conclusion

In this work, a highly efficient and environmentally green methodology has been developed for the synthesis of new hybrids thiazolyl acridine-1,8 (2*H*,5*H*)-dione and dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones using an inexpensive and recoverable bio-organopromoter, 2-aminothanesulfonic acid under aqueous conditions, which to the best of our knowledge has no precedents. The reaction system was significantly affected by catalyst loading, temperature and solvent. Therefore, the significant advantages of this procedure are low catalyst loading, short reaction times, high to excellent yields, elimination of toxic transition metals or organic solvents, simple workup, reusability of the catalyst and simple purification of the products. The developed catalytic system has ample scope to be utilized further towards the development of green methodologies. New thiazolyl acridine-1,8 (2*H*,5*H*)-dione and dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones showing moderate to good antimicrobial activity.

Conflicts of interest

There are no conflicts to declare.

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Author Contribution Statement

M. R. Bhosle conceived and designed the work. S. A. Kharote performed the experiments. G. M. Bondle contributed samples, reagents, analysis tools and analyzed the data. J. N. Sangshetti and S. A. Ansari carried out the antimicrobial assays. H. M. Alkahtani interpreted the spectral data.

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