Rapid Construction of Substituted Dihydrothiophene Ureidoformamides at Room Temperature Using Diisopropyl Ethyl Ammonium Acetate: A Green Perspective

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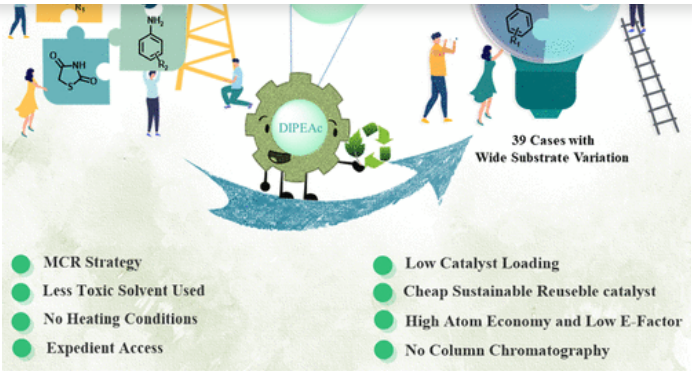
Cite this: *ACS Omega* 2020, 5, 45, 29055–29067
Publication Date: November 5, 2020
https://doi.org/10.1021/acsomega.0c03575

Abstract



An economic, sustainable, and straightforward environmentally friendly synthesis of highly diversified polyfunctional dihydrothiophenes is successfully achieved via diisopropyl ethyl ammonium acetate as a room-temperature ionic liquid. Multicomponent synthesis contains domino processes; the benefit of this present protocol is highlighted by its readily available starting materials, superior functional group tolerance, purity of synthesized compounds was checked by high-performance liquid chromatography results in up to 99.7% purity for the synthesized compounds, reaction mass efficiency, effective mass yield, and excellent atom economy. In addition, a series of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophene analogs were synthesized, and selected samples were chosen for testing their in vitro antibacterial and antifungal activities. Furthermore, a molecular docking study against sterol 14α-demethylase could provide valuable insight into the mechanism of antifungal action providing an opportunity for structure-based lead optimization.

Introduction

Jump To

Over the last few decades, ionic liquids (ILs) have received an excessive deal of attention in an extensive range of different areas, attainment from material synthesis to an alternative reaction as well as separation science media. (1−6) ILs can be considered as green substitutes for organic solvents. They differ from molecular solvents by their “structure and organization” and their idiomatic ionic character, which can lead to precise effects, building them multipurpose and tunable materials. (7−11) Also, ILs have been successfully used in many multicomponent reactions. (12−17)Therefore, ILs may be an ideal medium of multicomponent domino-type reactions without pressure-tight equipment and organic solvents.

Multicomponent reactions (MCRs) offer a chance for the combination of three or more flexible and straightforward building blocks in a one-pot operation, constructing complex structures by the

development of innovative and valuable organic compounds. (38−40)

Figure 1

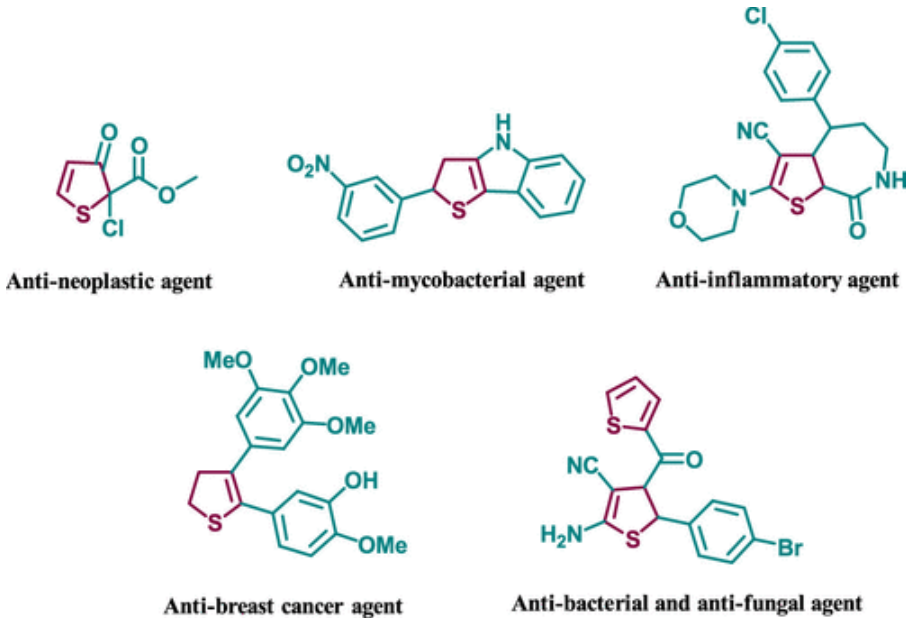
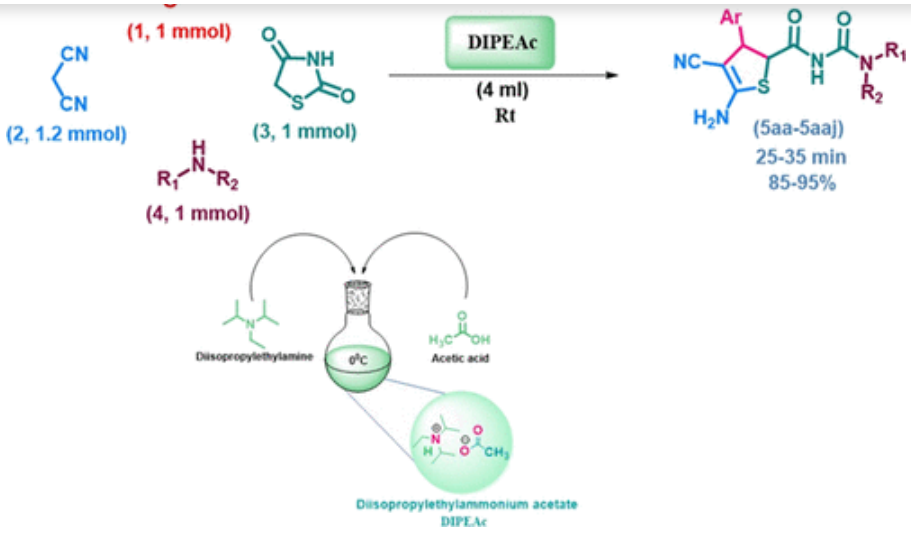


Figure 1. Chemical structures of some biologically active dihydrothiophenes.

In the past few decades, the careful study of the previously closely reported literature discloses pioneering work for the one-pot reaction of 1,3-thiazolidinedione, malononitrile, aldehyde, and aniline. In 2009, Sun et al. have reported the synthesis of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophenes by domino reactions of 1,3-thiazolidinedione in acetonitrile using organic amines as a catalyst. (41) In 2011, Shi et al. reported an improved synthesis of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophene derivatives under ultrasound irradiation. (42) Again in 2011, Lu et al. reported an efficient synthesis of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophene derivatives by domino reactions of 1,3-thiazolidinedione under catalyst-free conditions. (43) Whereas, in 2019, Kordnezhadian et al. carried out DBU-functionalized MCM-41-coated nanosized hematite (DBU-F-MCM-41-CNSH): a new magnetically separable basic nanocatalyst for the diastereoselective one-pot four-component synthesis of dihydrothiophene ureidoformamides. (44) Each of these reported procedures has its own merit, but all suffer from limitation of the synthesis to only a narrow range of dihydrothiophene ureidoformamides, a difficulty to isolate products or long reaction time, and harsh reaction conditions.

Thus, we wished to explore a more "eco-friendly" and expeditious protocol for the construction of



Scheme 1. One-Pot Four-Component Synthesis of 2-(*N*-Carbamoyl acetamide)-Substituted 2,3-Dihydrothiophenes (**5aa**–**5aaj**) in the Presence of DIPEAc as a New Room-Temperature Ionic Liquid

Results and Discussion

Jump To

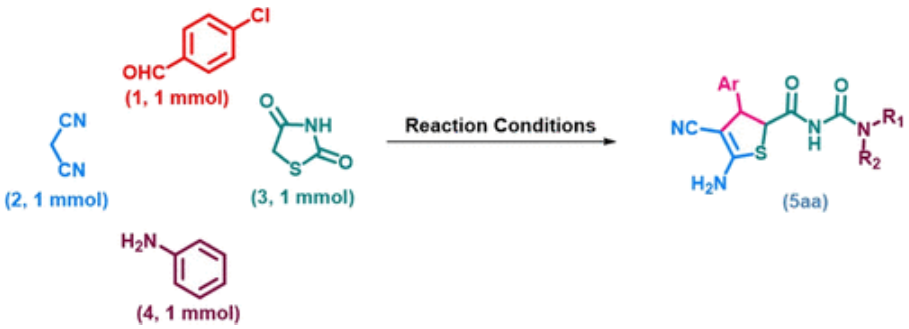
Chemistry

Nowadays, the selection of a suitable reaction medium is of crucial importance for the successful organic synthesis. Ionic liquids (ILs) have become quite a popular solvent and accelerant in the chemical community due to their new generations, which contain catalytic functional groups, especially acidic (3,45) and basic groups. (46−49) Among the ILs, room-temperature ionic liquids (RTILs) have been the prominence of multiple current scientific surveys because of the properties being non-explosive, non-volatile, easy to handle, thermally robust, and nearly-zero vapor pressures. (50) Our group has elaborated on the applications and syntheses of the ILs, (51) and we have wished to utilize them as a reaction media and a homogeneous catalyst support for a high-yield, rapid, and recyclable process for the synthesis of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophene.

Just following our goal to determine an innovative, sustainable, green, and synthetic path to choose the superior experimental conditions for the production of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophene, a model reaction was started with an equimolar (1:1:1:1) involving the four-component domino reaction between 4-chlorobenzaldehyde (**1a**) (1.0 mmol), malononitrile (**2**) (1.0 mmol), 1,3-thiazolidinedione (**3**) (1.0 mmol), and aniline (**4a**) (1.0 mmol). Scheme 2 is selected to elevate catalysts and conditions, reaction media, and catalyst dosage. As shown in Table 1, it was seen that when the reaction was performed in the absence of a catalyst in water, acetonitrile, and ethanol, the

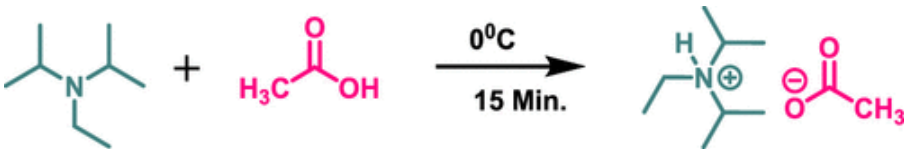
experiments and found the optimal reaction temperature (room temperature) (Table 1, entries 14–16, 18–22, and 28–38). In the presence of DIPEAc, this time, we have been seeing a new spot on the thin-layer chromatographic plate along with some unreacted 4-chlorobenzaldehyde (**1a**) and malononitrile (**2**) (Table 1, entries 13–22). Structural elucidation from ^{1}H NMR, ^{13}C NMR, and liquid chromatography–mass spectrometry (LC–MS) analysis of the isolated product gave an uncompleted Knoevenagel adduct because of the hygroscopic nature of malononitrile; then, we changed the equimolar ratio of malononitrile and optimized the model reaction, and we observed that the respective molar proportion for the model reaction between 4-chloro-benzaldehyde (**1a**) and malononitrile (**2**) changed from 1:1:1:1 to 1:1.2:1:1. This means that during the reaction, the molar proportion of malononitrile (**2**, 1.2 mmol) required was some more that of 4-chlorobenzaldehyde (**1**, 1 mmol), thiazolidinedione (**3**, 1 mmol), and aniline (**4**, 1 mmol). Employing this aspect, compound **5a** was isolated in 94% yield after only 30 min at room temperature. The model reaction in water using phase transfer catalysts was found to form the desired **5a** in less yields. Therefore, it can be thought that DIPEAc (Scheme 3) is a superior and green catalyst and solvent compared to the others shown in Table 1.

Scheme 2



Scheme 2. One-Pot Four-Component Reaction of 4-Chlorobenzaldehyde (**1a**, 1 mmol), Malononitrile (**2**, 1 mmol), 1,3-Thiazolidinedione (**3**, 1 mmol) and Aniline (**4a**, 1 mmol) under Different Conditions

Scheme 3



Scheme 3. Synthesis of Diisopropyl Ethyl Ammonium Acetate (DIPEAc)

Table 1. Efficiency Comparative Study of Various Catalysts for the Synthesis of 5-Amino-4-cyano-3-phenyl-*N*-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide (5a)[a]

3		(1:1:1:1)	CHCN
4	Cs_2CO_3	(1:1:1:1)	EtOH
5	p-TSA	(1:1:1:1)	H_2O
6	β-CD	(1:1:1:1)	H_2O
7	CTAB	(1:1:1:1)	H_2O
8	Et_3N	(1:1:1:1)	EtOH
9	$[Et_3NH][HSO_4]$	(1:1:1:1)	$[Et_3NH]$
10	[DBUH][OAc]	(1:1:1:1)	[DBUH][
11	ChCl:2urea	(1:1:1:1)	ChCl:2u
12	$ChCl:2ZnCl_2$	(1:1:1:1)	ChCl:2Z
13	PEG-400	(1:1:1:1)	PEG-40
14	PEG-400	(1:1:1:1)	H_2O
15	pyrrolidine ammonium acetate	(1:1:1:1)	pyrrolid
16	piperidine ammonium acetate	(1:1:1:1)	piperidi
17	triethyl ethylammonium acetate	(1:1:1:1)	triethyl
18	[bmim]Br	(1:1:1:1)	[bmim]E
19	DABCO	(1:1:1:1)	H_2O
20	dicationic ionic liquid	(1:1:1:1)	dicatior
21	DIPEAc	(1:1:1:1)	H_2O

25	DIPEAc	(1:1.2:1:1)	EtOH
26	**DIPEAc**	**(1:1.2:1:1)**	**DIPEAc**

[a]Reaction conditions: 4-chloro benzaldehyde (1.0 mmol), malononitrile (1.2 mmol), 1,3-thiazolidinedione (1.0 mmol), and aniline (1.0 mmol) in a medium (4 mL) stirred at room temperature.
[b]Isolated yields b: no condensation. Bold values are for highlighting the good result.

From this optimization of catalysts, we can conclude that DIPEAc gives a better yield of the desired product. After the effective optimization of the catalyst, we also investigated the catalyst loading in the model reaction DIPEAc for the synthesis of **5a**. To assure the volume of the DIPEAc, the model reaction was investigated by a number of trials by changing the catalyst loading from 1 to 5 mL; as the amount of DIPEAc rises progressively, there is a steady growth noticed in the product yield. Then, 4 mL of DIPEAc furnished the **5a** in 94% yield at room temperature (Table 2, entry 1) and completed an excellent renovation of the reactants into the product in room-temperature DIPEAc at room temperature for 30 min (HPLC = 98.81%). Further, an increase in the amount of DIPEAc showed no significant difference in reaction time and product yield. The model reaction was performed without any solvent and catalyst. The very small amount of the product was obtained after a prolonged period (Table 2, entry 1).

Table 2. Solvent Impact on the Reaction for Synthesis of 2-(N-Carbamoyl Acetamide)-Substituted 2,3dihydrothiophene Derivatives in Room Temperature DIPEAc[a]

entry	DIPEAc	temp. (°C)	solvent	time (min)	yield (%)[b]
1	0	room temp.		24 h	Trace
2	1 mL	room temp.		30	60
3	2 mL	room temp.		30	75
4	3 mL	room temp.		30	80
5	**4 mL**	**room temp.**		**30**	**94**
6	5 mL	room temp.		45	95
7	20 mol %	reflux	EtOH	220	80

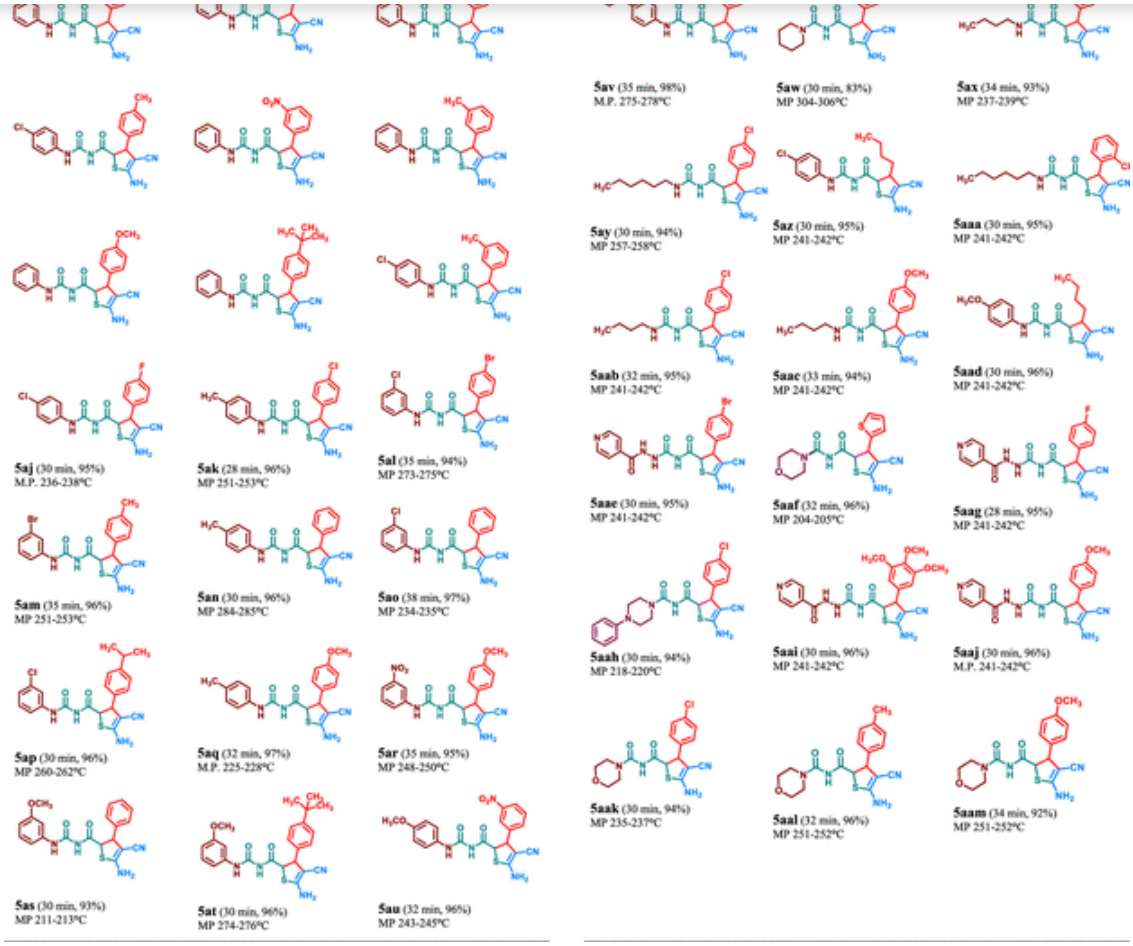
11	20 mol %	reflux	DMF	320	52
12	20 mol %	reflux	CH_2Cl_2	320	50

[a]Reaction conditions: 4-chloro benzaldehyde (1.0 mmol), malononitrile (1.2 mmol), 1,3-thiazolidinedione (1.0 mmol), and aniline (1.0 mmol) in a medium (4 mL) stirred at room temperature.
[b]Isolated yields b: no condensation. Bold values are for highlighting the good result.

Moreover, the performance of DIPEAc was examined by using 20 mol % DIPEAc in different solvents (Table 2, entries 7–12). In ethanol, we detect a preferred reaction medium, and no sticky reaction mass was formed. Still, the isolated reaction yield (73%, E-factor = 0.62) was not satisfactory than that of DIPEAc (94%, E-factor = 0.25), the reaction conversion with a readily superior yield. Meanwhile, in acetonitrile, water, methanol, CH_2Cl_2, DMF, and DCM reaction, output had lesser yields at reflux temperature. Not any of the solvents persist the superiority of yield and time over the non-solvent condition. Hence, the solventless condition was considered as excellent for the environmental suitability and cost.

As far as sustainable development is concerned, the fastest reaction time and highest efficiency for the formation of dihydrothiophene ureidoformamides were found at room temperature by using 4 mL of DIPEAc. Having excellent conditions in hand, the flexibility of the procedure was investigated for the synthesis of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophenes (**5aa**–**5aam**). We afterward examined the substrate scope by the reaction of different substituted aromatic/heteroaromatic aldehyde and aniline-subsumed methoxy, cyano, methyl, halogen (−Cl, −F, and −Br), hydroxyl, and nitro groups were used. The outcomes of all transformations carried out under these conditions are shown in Table 3. Aniline- and aldehyde-containing electron-withdrawing group like $-NO_2$ and electron-donating groups like −OMe and −Me on the aromatic ring was suited with this transformation, and comparable 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophenes (**5aa**–**5aam**) were achieved in good to high yields. To our enchantment, halogen-substituted 2-benzylidene malononitrile gave the products with high yields (**5ab**, **5ak**, and **5ao**). Furthermore, sterically crowded di- and trisubstituted benzaldehyde gave the desired outcomes in high yields (**5ah**, **5aai**, and **5aae**). The aliphatic aldehydes and heteroaryl aldehydes also remained under the current reaction medium without any trouble (**5ay**, **5aad**, and **5aah**).

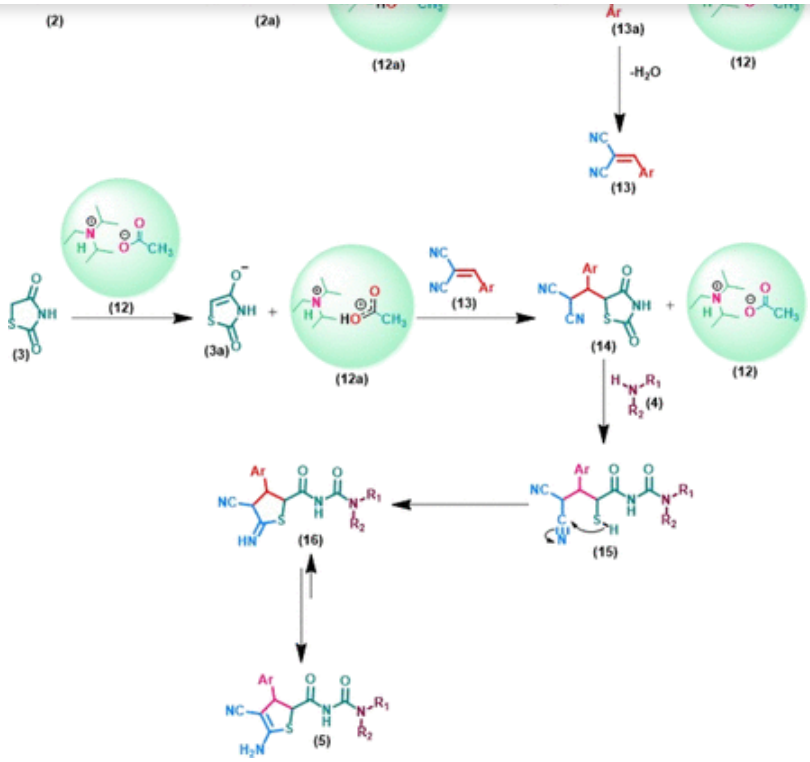
Table 3. Substrate Scope for Synthesis of 2-(*N*-Carbamoyl acetamide)-Substituted 2,3-Dihydrothiophene Derivatives in Room-Temperature DIPEAc[a]



[a]Reaction conditions: 4-chloro benzaldehyde (1.0 mmol), malononitrile (1.2 mmol), 1,3-thiazolidinedione (1.0 mmol), and aniline (1.0 mmol) in a medium (4 mL) stirred at room temperature. Isolated yields in parentheses: no condensation.

To describe the mechanism of this one-pot multicomponent reaction of aryl aldehyde (**1**), malononitrile (**2**), 1,3-thiazolidinedione (**3**), amines (**4**), and formation of 2- (N-carbamoyl acetamide)-substituted 2,3-dihydrothiophenes (**5aa–5aam**) in the presence of room-temperature DIPEAc (**12**), we suggest a plausible reaction mechanism, which is demonstrated in Scheme 4.

Scheme 4

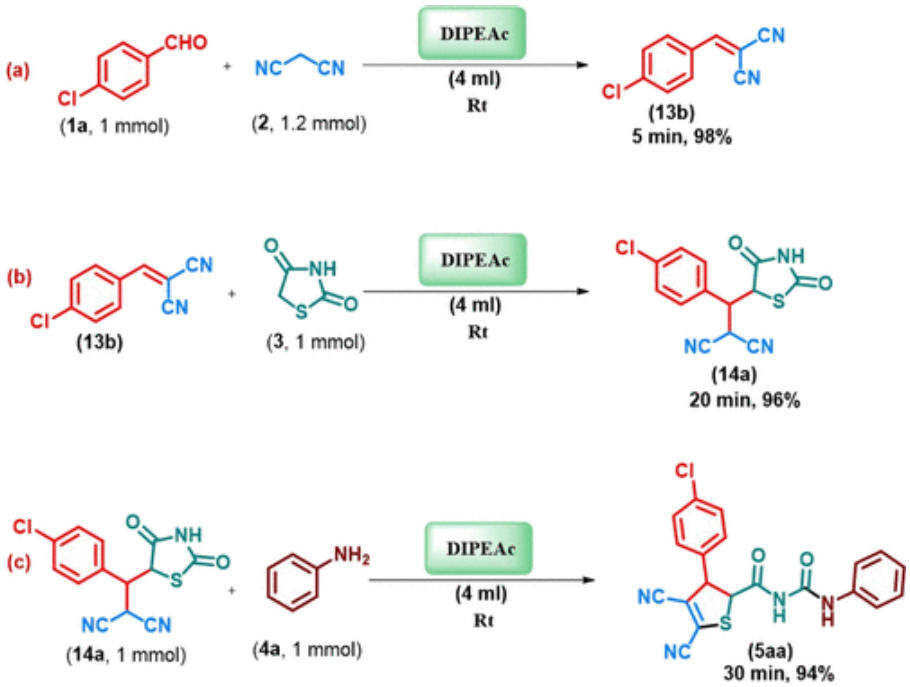


Scheme 4. Plausible Mechanism for the Formation of 2-(*N*-Carbamoyl acetamide)-Substituted 2,3-Dihydrothiophenes

The first step is the DIPEAc (**12**) catalyzing the synthesis of arylidene malononitrile (**13**) derived from the Knoevenagel condensation of the aromatic aldehyde (**1**) with malononitrile (**2**) after removing one molecule of water. In the next stage, 1,3-thiazolidinedione (**3**) in the existence of DIPEAc (**12**) transforms to its corresponding enolate (**3a**) and adds to the arylidene malononitrile (**13**) by Michael addition of the carbanion of 1,3-thiazolidinedione to arylidene cyanoacetamide (**14**). Then, the cyclic secondary amine (**4**) attacks the carbonyl group of 1,3-thiazolidinedione to open its ring and cause the formation of a sulfide anion (**15**) and the intramolecular addition of a sulfide anion to the cyano group in the intermediate (**16**). After this, at last thiophene (**5**) is produced by a dehydrogenation process in air. The DIPEAc medium was the best promoter for the preparation of dihydrothiophene derivatives; reasons for this could be explained as follows: (1) the use of DIPEAc raises the solubility of reagents, which results to a higher interfacial area and lower mass transfer resistance. (52) (2) The promoting impact of DIPEAc to the reaction could be credited to its hydrophobic, polarity, and hydrogen-bonding effects (53,54) (Scheme 4), making it easy to develop related products. It was revealed that only polar protic solvents could give the expected outcome, and the hydrogen-bonding effect is the main difference between other solvents and polar protic solvents, so the hydrogen-bonding effect may be the key factor to facilitate the

chlorobenzylidene)malononitrile (**13b**) was achieved in 98% yield after 5 min (Scheme 5a). In the next stage, the possibility of the Michael addition of 1,3-thiazolidinedione (**3**) to the arylidene malononitrile (**13b**) in the presence of DIPEAc was verified. Therefore, the newly synthesized 2-(4-chlorobenzylidene) malononitrile (**1** mmol) was treated with 1,3-thiazolidinedione (**3**, 1 mmol) in the presence of DIPEAc (4 mL) at room temperature and as expected, 2-((4-chlorophenyl) (2,4-dioxothiazolidin-5-yl) methyl) malononitrile (**14a**) was achieved in 95% yield after 20 min (Scheme 5b). Eventually, the synthesized 2-((4-chlorophenyl)-(2,4-dioxothiazolidin-5-yl) methyl) malononitrile (**14a**, 1 mmol) was treated with aniline (**4a**, 1 mmol) under the ideal reaction conditions, and the desired product (**5aa**) was achieved in 94% isolated yield after 30 min. (Scheme 5c)

Scheme 5



Scheme 5. Study of the Reliability of the Proposed Reaction Pathway for the Synthesis of 5-Amino-4-cyano-3-phenyl-*N*-(phenyl carbamoyl)-2,3-dihydrothiophene-2-carboxamide in the Presence of DIPEAc at Room Temperature

As far as sustainability is concerned, it is required to confirm the existing procedure with well-established "green metrics" such as the atom economy, reaction mass efficiency, E-factor, optimum efficiency, and practical mass yield. (56−59)

The E-factor is an extensively used green metric for chemical reactions. The lesser the value of the E-

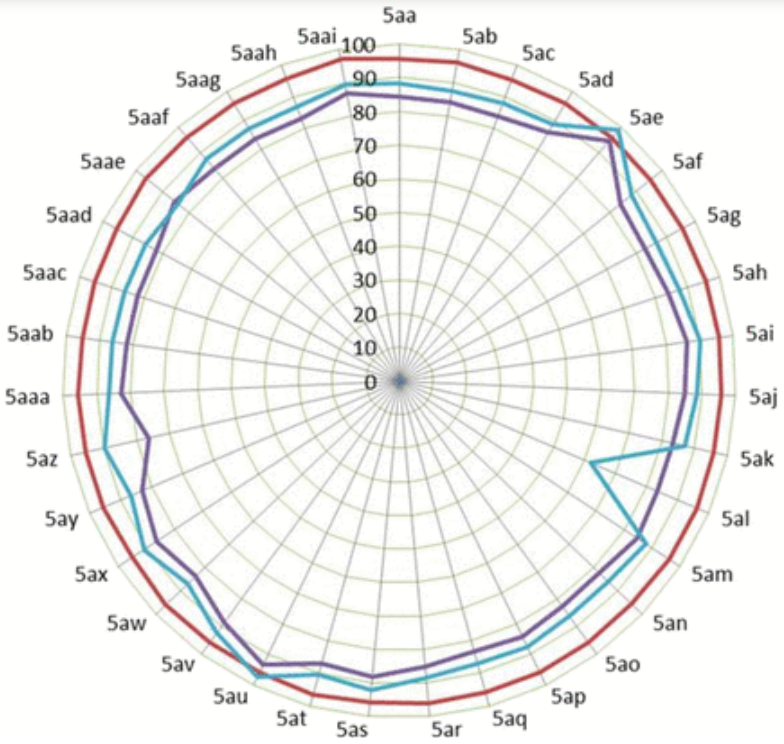


Figure 2. Radar chart of measured green metrics for the synthesis of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophenes (**5aa**–**5aam**).

Later, we measure the green chemistry metrics for both model reactions to afford **5aa** and **5ab** under optimized reaction conditions, as demonstrated in Table 4. The outcome revealed that the values of green chemistry metrics such as atom economy (AE), E-factor, optimum efficiency (OP), reaction mass efficiency (RME), and effective mass yield (EY) are nearly as close to their ideal values as demonstrated here (see the Supporting Information for detailed calculations).

Table 4. Quantitative Evaluation of Green Chemistry Metrics for 5aa and 5ab

sr. no.	green chemistry merits	ideal value	product (5aa)	product (5ab)
1	E-factor	0	0.20	0.18
2	atom economy (AE)	100%	95.67	96.02
3	reaction mass efficiency (RME)	100%	84.50	84.09

recovered catalyst were proven to be almost identical to the fresh one.

Figure 3

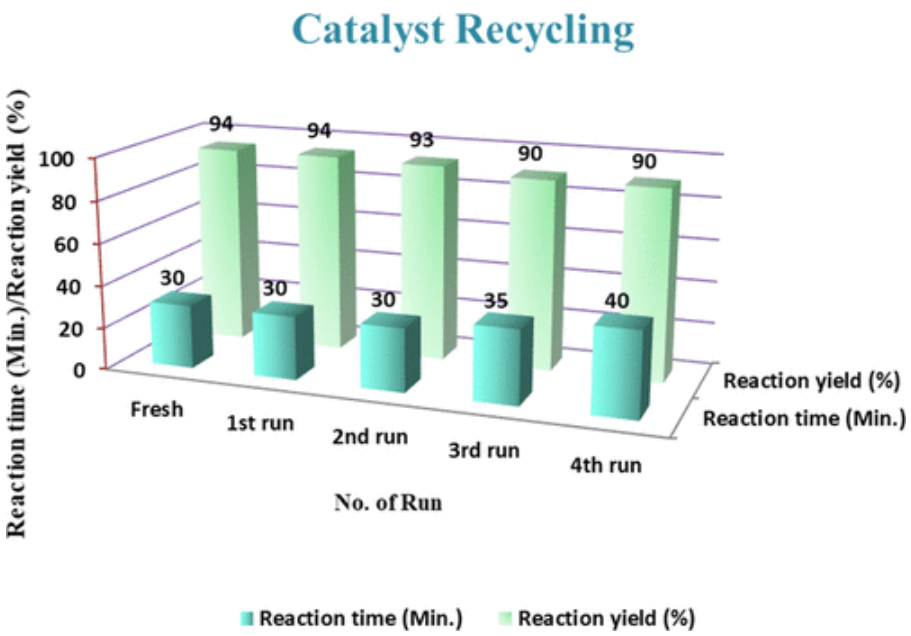
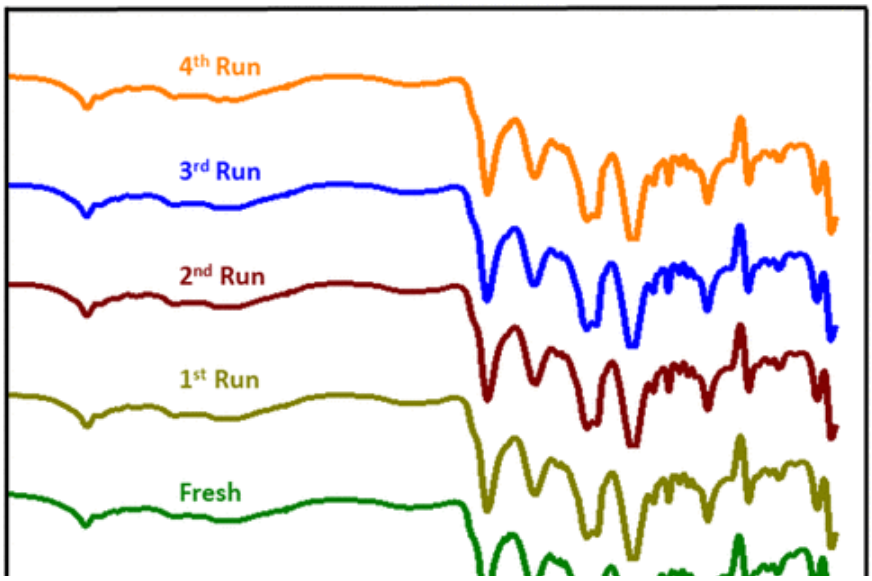


Figure 3. Recyclability of the catalyst.

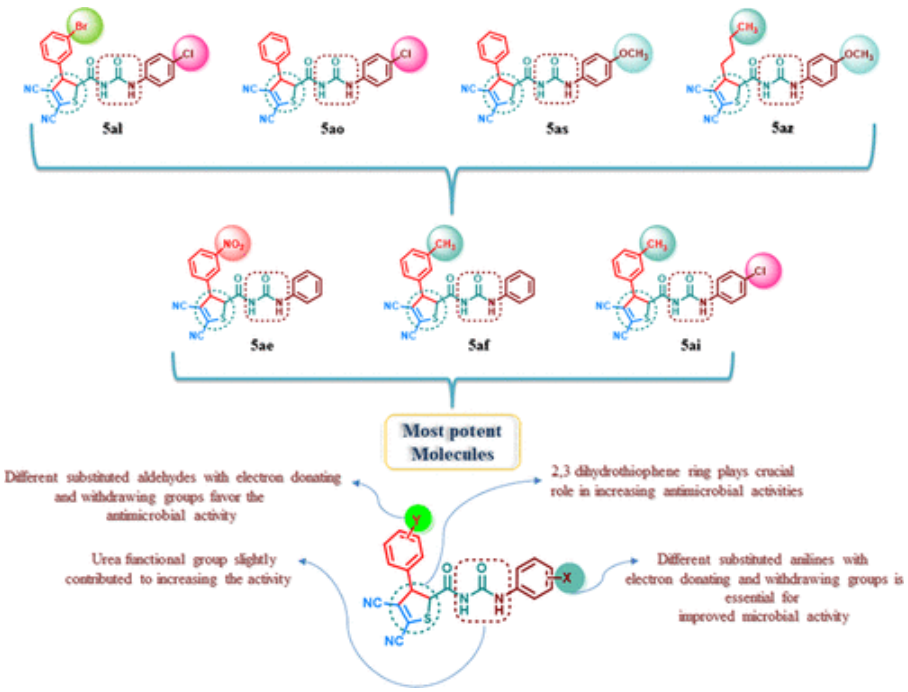
Figure 4



Antimicrobial Screening

In the route of identifying several novel antimicrobial agents, we are especially curious about the present work with novel 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophene derivatives. In this paper, the antimicrobial screening of 39 newly synthesized compounds was screened against four bacteria and four fungi using the agar well diffusion method. Zone of inhibition (μg/mL) values are displayed in Table 5. (60,61) The outcomes showed that majority of the synthesized compounds demonstrated antimicrobial activities against four bacteria *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*), *Bacillus subtilis* (*B. subtilis*), and *Staphylococcus aureus* (*S. aureus*) and four fungal strains *Aspergillus niger* (*A. niger*), *Aspergillus flavus* (*A. flavus*), *Fusarium oxysporum* (*F. oxysporum*), and *Candida albicans* (*C. albicans*). The standard drugs ampicillin, ciprofloxacin, miconazole, and fluconazole were used as standards for antibacterial and antifungal activities, respectively. The achieved results revealed that most of the compounds have demonstrated satisfactory to superb inhibitory activity against the four tested bacteria and fungi. The electronic property of the compounds has an adjacent correlation with their biological activity as illustrated in Figure 5. A stepwise molecular optimization to the scaffold of most potent compounds **5al**, **5ao**, **5as**, **5az**, **5ae**, **5af**, and **5ai** and the molecular area highlighted in Figure 5 explored the SAR.

Figure 5



1	**5aa**	76 ± 0.22	60 ± 0.34	31 ± 0.09	95 ± 0.75	100
2	**5ab**	39 ± 0.46	92.4 ± 0.28	98.3 ± 0.20	51.3 ± 0.81	55 ±
3	**5ac**	71 ± 0.38	96 ± 0.40	71.7 ± 0.61	66.1 ± 0.64	80 ±
4	**5ad**	95 ± 0.38	130.7 ± 0.87	100 ± 0.25	76 ± 0.39	70 ±
5	**5ae**	97.7 ± 0.65	65.7 ± 0.87	24.6 ± 0.95	97.2 ± 0.81	30 ±
6	**5af**	66.8 ± 0.34	68.6 ± 0.54	74.2 ± 0.19	88.9 ± 0.37	30 ±
7	**5ag**	92.1 ± 0.74	57.1 ± 0.34	75.2 ± 0.37	93.7 ± 0.64	*[b]
8	**5ah**	52.0 ± 0.63	88.1 ± 0.35	90.4 ± 0.76	55.8 ± 0.19	150
9	**5ai**	165.7 ± 0.54	166.7 ± 0.34	204.7 ± 0.33	191.5 ± 0.82	35 ±
10	**5aj**	77.38 ± 0.67	44.3 ± 0.34	64.2 ± 0.75	109.2 ± 0.44	60 ±
11	**5ak**	59.3 ± 0.33	82.3 ± 0.57	35.3 ± 0.63	84.5 ± 0.71	55 ±
12	**5al**	88.4 ± 0.31	92.3 ± 0.44	80 ± 0.17	122.3 ± 0.34	35 ±
13	**5am**	71.9 ± 0.30	102.5 ± 0.94	66.8 ± 0.90	48.3 ± 0.84	70 ±
14	**5an**	98.3. ± 0.74	104.6 ± 0 .09	83.0 ± 0.22	52.8 ± 0.10	2500
15	**5ao**	41.6 ± 0.90	79.3 ± 0.4	101.3 ± 0.62	88.1 ± 0.22	40 ±
16	**5ap**	168.1 ± 0.64	195.1 ± 0.37	108.5 ± 0.61	156.6 ± 0.78	60 ±
17	**5aq**	151.0 ± 0.64	188.7 ± 0.74	164.1 ± 0.31	139.7 ± 0.47	30 ±
18	**5ar**	165.7 ± 0.54	166.7 ± 0.34	204.7 ± 0.33	191.5 ± 0.82	50 ±
19	**5as**	32 ± 0.46	90.01 ± 0.28	98.3 ± 0.20	50.3 ± 0.81	50 ±

22	**5av**	61 ± 0.38	86 ± 0.40	61.7 ± 0.61	56.1 ± 0.64	50 ±
23	**5aw**	95.3. ± 0.74	108.6 ± 0 .09	73.0 ± 0.22	62.8 ± 0.10	40 ±
24	**5ax**	53.0 ± 0.73	98.1 ± 0.35	91.4 ± 0.77	56.8 ± 0.19	45 ±
25	**5ay**	72.9 ± 0.40	103.5 ± 0.94	56.8 ± 0.90	58.3 ± 0.84	60 ±
26	**5az**	76.8 ± 0.34	58.6 ± 0.54	84.2 ± 0.19	*	25 ±
27	**5aaa**	165.7 ± 0.54	166.7 ± 0.34	204.7 ± 0.33	191.5 ± 0.82	100
28	**5aab**	52.0 ± 0.63	88.1 ± 0.35	90.4 ± 0.76	55.8 ± 0.19	50 ±
29	**5aac**	59.3 ± 0.33	82.3 ± 0.57	35.3 ± 0.63	84.5 ± 0.71	150
30	**5aad**	165.7 ± 0.54	166.7 ± 0.34	204.7 ± 0.33	191.5 ± 0.82	80 ±
31	**5aae**	71 ± 0.38	96 ± 0.40	71.7 ± 0.61	66.1 ± 0.64	60 ±
32	**5aaf**	98.7 ± 0.77	104.6 ± 0.06	84.0 ± 0.46	88.1 ± 0.71	50 ±
33	**5aag**	98.7 ± 0.77	104.6 ± 0.06	84.0 ± 0.46	88.1 ± 0.71	25. ±
34	**5aah**	167.1 ± 0.64	193.1 ± 0.37	105.5 ± 0.61	152.6 ± 0.78	150
35	**5aai**	165.7 ± 0.54	166.7 ± 0.34	204.7 ± 0.33	191.5 ± 0.82	70 ±
36	**5aaj**	71 ± 0.38	96 ± 0.40	71.7 ± 0.61	66.1 ± 0.64	50 ±
37	**5aak**	165.7 ± 0.54	166.7 ± 0.34	204.7 ± 0.33	191.5 ± 0.82	100
38	**5aal**	61 ± 0.38	86 ± 0.40	61.7 ± 0.61	56.1 ± 0.64	60 ±
39	**5aam**	165.7 ± 0.54	166.7 ± 0.34	204.7 ± 0.33	191.5 ± 0.82	100
std	ampicillin	**100 ± 1.24**	**100 ± 2.14**	**250 ± 2.99**	**250 ± 0.88**	

std	fluconazole	**5 ± 2**

[a]Values are the average of three readings.
[b]All asterisks denote that no activity was observed up to 200 μg/mL.

The compounds **5ae**, **5af**, **5al**, **5ao**, and **5as** revealed good antibacterial activity against all four bacterial pathogens. The compounds **5ae**, **5af**, **5ai**, **5az**, **5aai**, and **5aag** showed excellent activity against all four fungal strains because of the presence of electron-withdrawing substituents ($-NO_2$, −Br, and −Cl) and electron-donating substituents ($-CH_3$ and $-OCH_3$) in the molecule. Compounds **5ae**, **5af**, and **5ai** showed good antibacterial and antifungal activity against the Gram-positive strains *E. coli,P. aeruginosa,S. aureus,B. subtilis,C. albicans,F. oxysporum,A. flavus*, and *A. niger.* We imagine that the presence of a 2,3-dihydrothiophene ring, $-NO_2$, $-CH_3$, and $-OCH_3$ moieties in the molecule contributes significantly to the antibacterial and antifungal activity.

Molecular Docking

To clarify the possible mechanism by which the dihydrothiophene ureidoformamides investigated herein can induce antifungal activity, and to further guide the SAR, an in silico binding study through molecular docking was performed against an important fungal target-sterol 14α-demethylase (CYP51), inhibition of which could prevent the conversion of lanosterol to ergosterol, causing the accumulation of 14α-methyl sterols in the cell and leading to impaired cell growth in fungi. This in silico molecular docking approach has now become an integral part of the drug discovery protocol, especially in the absence of available resources to perform the enzymatic assays, imparting knowledge on binding modes, affinities, and the associated thermodynamic interactions with the target enzyme that govern the inhibition of the causative pathogen. The Glide (grid-based ligand docking with energetics) module integrated into the Schrödinger molecular modeling package (Schrödinger, LLC, New York, NY, 2015) was used to predict the binding modes of dihydrothiophene ureidoformamides into the active site of the sterol 14α-demethylase (CYP51) enzyme. (62) The 3D crystal structure of sterol 14α-demethylase (CYP51) complexed with its inhibitor fluconazole (PDB code: 3KHM) was retrieved from the RCSB Protein Data Bank (PDB) (https://www.rcsb.org/pdb) and preprocessed using the protein preparation wizard applying the OPLS-2005 force field, which includes the elimination of all crystallographically observed water molecules (as there is no conserved interaction with the enzyme), appending the missing hydrogen/side-chain atoms corresponding to pH 7.0 considering the appropriate ionization states for the acidic and basic amino acid residues, identification of atom/residue overlaps, creating the disulfide bonds, assignment of reasonable charge and protonation state to the obtained structure, and finally energy minimization of the obtained structure until the average r.m.s.d. of non-hydrogen atoms converged to

of sterol 14α-demethylase using the extra precision (XP) Glide scoring function.

The enzyme–inhibitor complexation predicted by molecular docking showed that all these dihydrothiophene ureidoformamides could bind to CYP51 with a significant binding affinity adopting a similar orientation, and their complexes were stabilized by the formation of several bonded and non-bonded interactions. Their binding energies, which signify the binding relationship, were observed to be negative (−59.484 to −38.094 kcal/mol), while the average docking score was seen to be −7.841 kcal/mol. Furthermore, analysis of the per-residue interaction between these molecules and the active site residues of the enzyme was carried out to identify the most significantly interacting residues and their type of thermodynamic interactions, which is critical in lead optimization. This analysis is discussed for one of the most active analog **5aag** and is summarized in Table S1 (see in the Supporting Information) for the remaining molecules in the series.

The lowest energy-docked conformation of **5aag** (Figure 6) showed that it is deeply embedded into the active pocket of CYP51 with significant binding affinity, producing a Glide docking score of −9.702 and Glide binding energy of −59.484 kcal/mol. It could occupy the same coordinates as the native ligand engaging in a close network of bonded and non-bonded interactions with the residues forming the active site. It was found to be stabilized into the active site through a series of significant van der Waals interactions observed with Val461 (−2.854 kcal/mol), Met460 (−2.482 kcal/mol), Thr459 (−1.137 kcal/mol), Thr295 (−1.33 kcal/mol), His294 (−1.317 kcal/mol), Ala291 (−3.078 kcal/mol), Leu208 (−2.718 kcal/mol), Glu205 (−1.264 kcal/mol), Met106 (−3.171 kcal/mol), and Tyr103 (−3.504 kcal/mol) through the *N*-(5-amino-4-cyano-3-(4-flurophenyl)-2,3-dihydrothiophene core group, while the pyridine-linked carboxamide side chain showed a similar network of interactions with Cys422 (−1.111 kcal/mol), Leu356 (−2.936 kcal/mol), Ala287 (−1.553 kcal/mol), Leu127 (−1.254 kcal/mol), Tyr116 (−4.448 kcal/mol), Phe110 (−1.011 kcal/mol), and Ile105 (−1.124 kcal/mol) residues lining the active site. Furthermore, the enhanced binding affinity of **5aag** is also attributed to significantly favorable electrostatic interactions observed with Ala291 (−1.297 kcal/mol), Phe290 (−1.312 kcal/mol), Tyr 116 (−1.361 kcal/mol), and Glu101 (−1.015 kcal/mol) residues. Being a metalloprotein, CYP51 was expected to engage in a significant interaction with the ligand through the prosthetic Hem moiety, which was observed for **5aag** also wherein the compound showed significant van der Waals (−4.963 kcal/mol) and electrostatic (−3.696 kcal/mol) interactions with them contributing significantly to binding affinity. While the non-bonded (steric and electrostatic) interactions were observed to be the major driving force for the mechanical interlocking of **5aag**, the higher binding affinity is also supported by a prominent hydrogen-bonding interaction observed through Ala291 (2.419 Å), Phe290 (2.214 Å), and Tyr116 (2.679 Å).

Figure 6

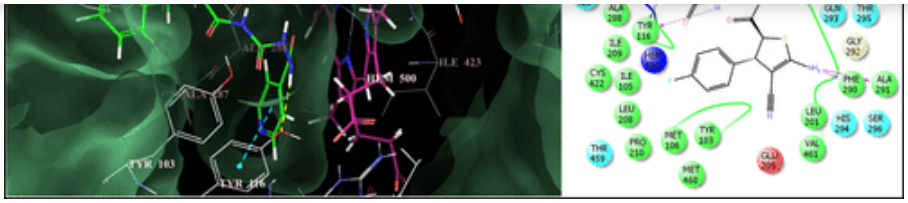


Figure 6. Binding mode of **5aag** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines represent the hydrogen bonding, while the green lines signify π−π stacking interactions).

Furthermore, a very close π−π stacking interaction was also observed with Tyr116 (2.68 Å). Such hydrogen-bonding and π-stacking interactions serve as an "anchor" guiding the orientation of the ligand into the 3D space of the enzyme active site and facilitate the steric and electrostatic interactions therein. A similar network of bonded and non-bonded interactions was observed for other molecules in the series, guiding their binding to CYP51 (see the Supporting Information, S1−S25). The inference derived from this in silico binding studies is now fruitfully utilized for the structure-based lead optimization to arrive at potent molecules with this scaffold.

Conclusions

Jump To

In conclusion, we have designed a very facile, simple, conveniently practical, and energy-efficient method for easy access of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophene derivatives in the presence of DIPEAc (diisopropyl ethyl ammonium acetate) as a reusable catalyst and reaction medium via a one-pot four-component domino reaction at room temperature. Operational simplicity, clean reaction profiles, mild reaction conditions, absence of tedious separation procedures, high atom economy, energy efficiency, excellent yields, and the use of a low-cost and environmentally sustainable ionic liquid are the main advantages of the present method. Likewise, recycling of the reaction media is an added superiority to this protocol. Keeping in mind that the synthetic significance of such pharmacologically relevant 2,3-dihydrothiophene scaffolds directly relates to medicinal chemistry, the present methodology with mild operational simplicity and reaction conditions offers the possibility of its use with cost-effective and environmentally friendlier ways for Gram-scale industrial syntheses as well. Also, a series of 2-(*N*-carbamoyl acetamide)-substituted 2,3-dihydrothiophene analogs were screened for their in vitro antibacterial and antifungal activities. Molecular docking studies of all new derivatives showed a high binding affinity toward sterol 14α-demethylase (CYP51). They provided clues for further modification of the scaffold to improve the activity and selectivity toward the target.

Experimental Section

Jump To

Avance DRX-250 and Bruker Avance DRX-400, respectively, in pure DMSO-d_6 or $CDCl_3$ solvents. IR spectroscopy (Shimadzu FT-IR 8300), in cm^{-1}, was employed for the characterization of the compounds. The HPLC analysis of all compounds was performed on an MS-Agilent 6120 quadrupole system.

General Procedure for the Synthesis of Diisopropyl Ethyl Ammonium Acetate (DIPEAc)

A mixture of anhydrous acetic acid (1 mmol) and *N*,*N*-diisopropylethylamine (1 mmol) was stirred at 0–10 °C for 20 min. The viscous liquid, diisopropyl ethyl ammonium acetate, was achieved. (16,26)

General Procedure for the One-Pot Four-Component Synthesis of 2-(*N*-Carbamoyl acetamide)-Substituted 2,3-Dihydrothiophenes (5aa–5aaj) in the Presence of DIPEAc

A mixture of appropriate aldehyde (1.0 mmol) and malononitrile (1.2 mmol, 0.06 g) was added to a 25 mL round-bottom flask containing a suspension of DIPEAc (4 mL), and the resulting mixture was stirred at room temperature for 2 min. Then, 1,3-thiazolidinedione (1.0 mmol, 0.11 g) and the amine (1.0 mmol) were added, and the reaction mixture was stirred at the same temperature, and use of the TLC followed the progress of the reaction. At the end of the reaction (indicated by thin-layer chromatography), the solvent was recovered, and 5 mL of distilled water was added to the crude product and allowed to stir at room temperature to make the catalyst soluble and for complete solidification of the final product. The precipitates were washed thoroughly twice with 5 mL of distilled water to afford the desired products in pure form. All synthesized compounds were fully characterized based on analytical and spectral studies such as IR, ^{1}H NMR, ^{13}C NMR, and HPLC analysis (for representative compounds **5aa** and **5ab**).

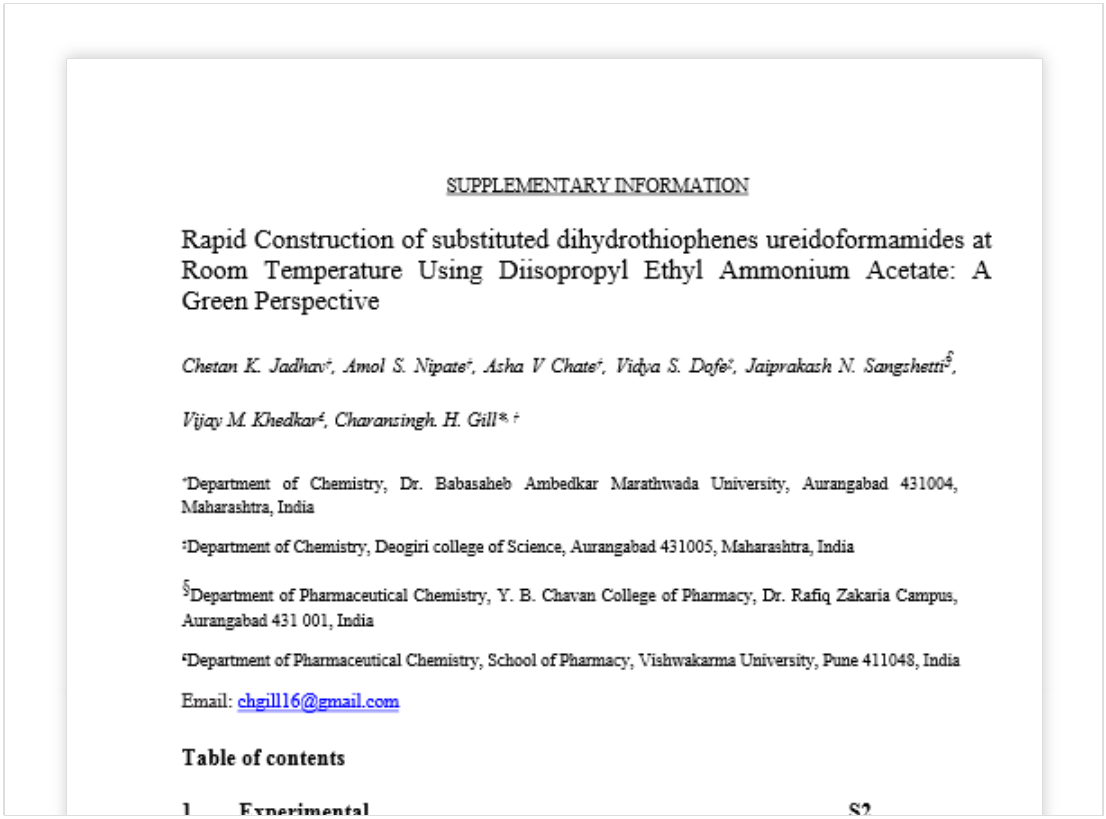
Supporting Information

Jump To

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03575.

- Analytical and spectroscopic data, a copy of ^{1}H NMR and ^{13}C NMR spectra, HPLC reports (**5aa**-**5ab**), and calculation of green metrics for compound **5aa** as a representative entry (PDF)

Room Temperature Using Diisopropyl Ethyl Ammonium Acetate: A Green Perspective



SUPPLEMENTARY INFORMATION

Rapid Construction of substituted dihydrothiophenes ureidoformamides at Room Temperature Using Diisopropyl Ethyl Ammonium Acetate: A Green Perspective

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Table of contents

1 Experimental S2

Terms & Conditions

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Notes

The authors declare no competing financial interest.
This work is dedicated to my beloved parents.

Acknowledgments

Jump To

The author C.K.J. is very much thankful to the Council for Scientific and Industrial Research (CSIR), New Delhi, for the award senior research fellowship. The author is also grateful to the Authority of Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad- 431004, India, for providing the laboratory facility. We are also thankful to SAIF, CSIR-CDRI, Lucknow, and BITS-Pilani, India for providing spectral analysis data.

References

Jump To

This article references 62 other publications.

1. Dong, K.; Liu, X.; Dong, H.; Zhang, X.; Zhang, S. Multiscale Studies on Ionic Liquids. *Chem. Rev.* **2017**, *117*, 6636− 6695, DOI: 10.1021/acs.chemrev.6b00776

| Google Scholar

4. Xin, B.; Hao, J. Imidazolium-Based Ionic Liquids Grafted on Solid Surfaces. *Chem. Soc. Rev.* **2014**, *43*, 7171– 7187, DOI: 10.1039/C4CS00172A

| Google Scholar

5. Welton, T. Ionic Liquids in Catalysis. *Coord. Chem. Rev.* **2004**, *248*, 2459– 2477, DOI: 10.1016/j.ccr.2004.04.015

| Google Scholar

6. Gordon, C. M. New Developments in Catalysis Using Ionic Liquids. *Appl. Catal. A Gen.* **2001**, *222*, 101– 117, DOI: 10.1016/S0926-860X(01)00834-1

| Google Scholar

7. Welton, T. Ionic Liquids in Green Chemistry. *Green Chem.* **2011**, *13*, 225, DOI: 10.1039/c0gc90047h

| Google Scholar

8. Wheeler, C.; West, K. N.; Eckert, C. A.; Liotta, C. L. Ionic Liquids as Catalytic Green Solvents for Nucleophilic Displacement Reactions. *Chem. Commun.* **2001**, 887– 888, DOI: 10.1039/b101202a

| Google Scholar

9. Tao, G.; He, L.; Liu, W.; Xu, L.; Xiong, W.; Wang, T.; Kou, Y. Preparation, Characterization and Application of Amino Acid-Based Green Ionic Liquids. *Green Chem.* **2006**, *8*, 639, DOI: 10.1039/b600813e

| Google Scholar

10. Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P. Green and Sustainable Solvents in Chemical Processes. *Chem. Rev.* **2018**, *118*, 747– 800, DOI: 10.1021/acs.chemrev.7b00571

| Google Scholar

11. Ghandi, K. A Review of Ionic Liquids, Their Limits and Applications. *Green Sustain. Chem.* **2014**, *04*, 44– 53,

13. Ranu, B. C.; Jana, R.; Sowmiah, S. An Improved Procedure for the Three-Component Synthesis of Highly Substituted Pyridines Using Ionic Liquid. *J. Org. Chem.* **2007**, *72*, 3152– 3154, DOI: 10.1021/jo070015g

| Google Scholar

14. Rahman, M.; Sarkar, A.; Ghosh, M.; Majee, A.; Hajra, A. Catalytic Application of Task Specific Ionic Liquid on the Synthesis of Benzoquinazolinone Derivatives by a Multicomponent Reaction. *Tetrahedron Lett.* **2014**, *55*, 235– 239, DOI: 10.1016/j.tetlet.2013.11.011

| Google Scholar

15. Mirhosseini-Eshkevari, B.; Esnaashari, M.; Ghasemzadeh, M. A. Novel Brönsted Acidic Ionic Liquids Confined in UiO-66 Nanocages for the Synthesis of Dihydropyrido[2,3- d]Pyrimidine Derivatives under Solvent-Free Conditions. *ACS Omega* **2019**, *4*, 10548– 10557, DOI: 10.1021/acsomega.9b00178

| Google Scholar

16. Jadhav, C. K.; Nipate, A. S.; Chate, A. V.; Songire, V. D.; Patil, A. P.; Gill, C. H. Efficient Rapid Access to Biginelli for the Multicomponent Synthesis of 1,2,3,4-Tetrahydropyrimidines in Room-Temperature Diisopropyl Ethyl Ammonium Acetate. *ACS Omega* **2019**, *4*, 22313– 22324, DOI: 10.1021/acsomega.9b02286

| Google Scholar

17. Patel, D. M.; Patel, H. M. Trimethylglycine-Betaine-Based-Catalyst-Promoted Novel and Ecocompatible Pseudo-Four-Component Reaction for Regioselective Synthesis of Functionalized 6,8-Dihydro-1' H ,5 H -Spiro[[1,3]Dioxolo[4,5- g]Quinoline-7,5'-Pyrimidine]-2',4',6'(3' H)-Trione Derivatives. *ACS Sustainable Chem. Eng.* **2019**, *7*, 18667– 18676, DOI: 10.1021/acssuschemeng.9b05184

| Google Scholar

18. Chate, A. V.; Dongre, R. M.; Khaire, M. K.; Bondle, G. M.; Sangshetti, J. N.; Damale, M. β-CD-Catalyzed Multicomponent Domino Reaction: Synthesis, Characterization, in Silico Molecular Docking and Biological Evaluation of Pyrano[2,3-d]-Pyrimidinone Derivatives. *Res. Chem. Intermed.* **2018**, *44*, 6119– 6136, DOI: 10.1007/s11164-018-3479-9

20. Lin, W.; Zheng, Y.-X.; Xun, Z.; Huang, Z.-B.; Shi, D.-Q. Microwave-Assisted Regioselective Synthesis of 3-Functionalized Indole Derivatives via Three-Component Domino Reaction. *ACS Comb. Sci.* **2017**, *19*, 708– 713, DOI: 10.1021/acscombsci.7b00126

| Google Scholar

21. Golchin, S.; Mosslemin, M. H.; Yazdani-Elah-Abadi, A.; Shams, N. DABCO-Catalyzed Multi-Component Domino Reactions for the One-Pot Efficient Synthesis of Diverse and Densely Functionalized Benzofurans in Water. *Res. Chem. Intermed.* **2017**, *43*, 1735– 1749, DOI: 10.1007/s11164-016-2726-1

| Google Scholar

22. Anusha Rani, M.; Vivek Kumar, S.; Malathi, K.; Muthu, M.; Almansour, A. I.; Suresh Kumar, R.; Ranjith Kumar, R. A One-Pot Multicomponent 1,3-Dipolar Cycloaddition Strategy: Combinatorial Synthesis of Dihydrothiophenone-Engrafted Dispiro Hybrid Heterocycles. *ACS Comb. Sci.* **2017**, *19*, 308– 314, DOI: 10.1021/acscombsci.6b00186

| Google Scholar

23. Safaei, S.; Mohammadpoor-Baltork, I.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V. SO3H-Functionalized MCM-41 as an Efficient Catalyst for the Combinatorial Synthesis of 1H-Pyrazolo-[3,4-b]Pyridines and Spiro-Pyrazolo-[3,4-b]Pyridines. *J. Iran. Chem. Soc.* **2017**, *14*, 1583– 1589, DOI: 10.1007/s13738-017-1099-8

| Google Scholar

24. Marshal, A.; Pradeep, K. G.; Music, D.; Zaefferer, S.; De, P. S.; Schneider, J. M. Combinatorial Synthesis of High Entropy Alloys: Introduction of a Novel, Single Phase, Body-Centered-Cubic FeMnCoCrAl Solid Solution. *J. Alloys Compd.* **2017**, *691*, 683– 689, DOI: 10.1016/j.jallcom.2016.08.326

| Google Scholar

25. Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G. New Multicomponent Domino Reactions (MDRs) in Water: Highly Chemo-, Regio- and Stereoselective Synthesis of Spiro{[1,3]Dioxanopyridine}-4,6-Diones and Pyrazolo[3,4-b]Pyridines. *Green Chem.* **2010**, *12*, 1357, DOI: 10.1039/c0gc00073f

| Google Scholar

27. Arumugam, N.; Almansour, A. I.; Kumar, R. S.; Altaf, M.; Mahalingam, S. M.; Periyasami, G.; Menéndez, J. C.; Ali Al-Aizari, A. J. M. Multicomponent Domino Protocol for the Stereoselective Synthesis of Novel Pyrrolo[3,2-c]Quinolinone Hybrid Heterocycles. *Tetrahedron Lett.* **2019**, *60*, 602– 605, DOI: 10.1016/j.tetlet.2019.01.035

| Google Scholar

28. Marsh, K. N.; Boxall, J. A.; Lichtenthaler, R. Room Temperature Ionic Liquids and Their Mixtures—a Review. *Fluid Phase Equilib.* **2004**, *219*, 93– 98, DOI: 10.1016/j.fluid.2004.02.003

| Google Scholar

29. Chate, A. V.; Kamdi, S. P.; Bhagat, A. N.; Jadhav, C. K.; Nipte, A.; Sarkate, A. P.; Tiwari, S. V.; Gill, C. H. Design, Synthesis and SAR Study of Novel Spiro [Pyrimido[5,4-b]Quinoline-10,5'-Pyrrolo[2,3-d]Pyrimidine] Derivatives as Promising Anti-cancer Agents. *J. Heterocycl. Chem.* **2018**, *55*, 2297– 2302, DOI: 10.1002/jhet.3286

| Google Scholar

30. Nipate, A. S.; Jadhav, C. K.; Chate, A. V.; Taur, K. S.; Gill, C. H. β-Cyclodextrin Catalyzed Access to Fused 1,8-dihydroimidazo[2,3- b]Indoles via One-pot Multicomponent Cascade in Aqueous Ethanol: Supramolecular Approach toward Sustainability. *J. Heterocycl. Chem.* **2020**, *57*, 820– 829, DOI: 10.1002/jhet.3828

| Google Scholar

31. Shao, W.; Kaldas, S. J.; Yudin, A. K. 3-Cyanoallyl Boronates Are Versatile Building Blocks in the Synthesis of Polysubstituted Thiophenes. *Chem. Sci.* **2017**, *8*, 4431– 4436, DOI: 10.1039/C7SC00831G

| Google Scholar

32. Barbarella, G.; Melucci, M.; Sotgiu, G. The Versatile Thiophene: An Overview of Recent Research on Thiophene-Based Materials. *Adv. Mater.* **2005**, *17*, 1581– 1593, DOI: 10.1002/adma.200402020

| Google Scholar

33. Hirbec, H.; Gaviria, M.; Vignon, J. Gacyclidine: A New Neuroprotective Agent Acting at the N-Methyl-D-Aspartate Receptor.

35. Kumar, A.; Gupta, G.; Srivastava, S. Functional Ionic Liquid Mediated Synthesis (FILMS) of Dihydrothiophenes and Tacrine Derivatives. *Green Chem.* **2011**, *13*, 2459, DOI: 10.1039/c1gc15410a

| Google Scholar

36. Wen, M.; Sun, P.-P.; Luo, X.; Deng, W.-P. Cu(II)-Catalyzed One-Pot Synthesis of Fully Substituted Dihydrothiophenes and Thiophenes from Thioamides and Enynones. *Tetrahedron* **2018**, *74*, 4168– 4173, DOI: 10.1016/j.tet.2018.02.035

| Google Scholar

37. Sun, J.; Xia, E.-Y.; Zhang, L.-L.; Yan, C.-G. Triethylamine-Catalyzed Domino Reactions of 1,3-Thiazolidinedione: A Facile Access to Functionalized Dihydrothiophenes. *European J. Org. Chem.* **2009**, *2009*, 5247– 5254, DOI: 10.1002/ejoc.200900845

| Google Scholar

38. Maruoka, H.; Yamazaki, M.; Tomioka, Y. Synthesis of Dihydrothieno[2,3- b]Pyridines Based on Titanium(IV) Chloride-Mediated Michael Reactions of 2-Amino-4,5-Dihydro-3-Thiophenecarbonitriles with α,β-Unsaturated Ketones. *J. Heterocycl. Chem.* **2004**, *41*, 641– 646, DOI: 10.1002/jhet.5570410428

| Google Scholar

39. Dofe, V. S.; Sarkate, A. P.; Shaikh, Z. M.; Jadhav, C. K.; Nipte, A. S.; Gill, C. H. Ultrasound-Assisted Synthesis of Novel Pyrazole and Pyrimidine Derivatives as Antimicrobial Agents. *J. Heterocycl. Chem.* **2018**, *55*, 756– 762, DOI: 10.1002/jhet.3105

| Google Scholar

40. Sun, J.; Zhang, L.-L.; Xia, E.-Y.; Yan, C.-G. Synthesis of Dihydrothiophenes or Spirocyclic Compounds by Domino Reactions of 1,3-Thiazolidinedione. *J. Org. Chem.* **2009**, *74*, 3398– 3401, DOI: 10.1021/jo900215a

| Google Scholar

41. Sun, J.; Zhang, Y.; Yan, C.-G. Tandem Four-Component Reaction for Efficient Synthesis of Dihydrothiophene with Substituted Amino Acid Ethyl Esters. *RSC Adv.* **2018**, *8*, 22498– 22505, DOI: 10.1039/C8RA03605E

43. Lu, G.; Zeng, L. Y.; Cai, C. An Efficient Synthesis of Dihydrothiophene Ureidoformamides by Domino Reactions of 1,3-Thiazolidinedione under Catalyst-Free Conditions. *Green Chem.* **2011**, *13*, 998, DOI: 10.1039/c0gc00884b

| Google Scholar

44. Kordnezhadian, R.; Shekouhy, M.; Khalafi-Nezhad, A. DBU-Functionalized MCM-41-Coated Nanosized Hematite (DBU-F-MCM-41-CNSH): A New Magnetically Separable Basic Nanocatalyst for the Diastereoselective One-Pot Four-Component Synthesis of 2-(N -Carbamoylacetamide)-Substituted 2,3-Dihydrothiophenes. *New J. Chem.* **2019**, *43*, 18559– 18570, DOI: 10.1039/C9NJ04714J

| Google Scholar

45. Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis, J. H. Novel Brønsted Acidic Ionic Liquids and Their Use as Dual Solvent–Catalysts. *J. Am. Chem. Soc.* **2002**, *124*, 5962– 5963, DOI: 10.1021/ja026290w

| Google Scholar

46. Zhang, Y.; Zhen, B.; Li, H.; Feng, Y. Basic Ionic Liquid as Catalyst and Surfactant: Green Synthesis of Quinazolinone in Aqueous Media. *RSC Adv.* **2018**, *8*, 36769– 36774, DOI: 10.1039/C8RA06378H

| Google Scholar

47. Xu, J.-M.; Liu, B.-K.; Wu, W.-B.; Qian, C.; Wu, Q.; Lin, X.-F. Basic Ionic Liquid as Catalysis and Reaction Medium: A Novel and Green Protocol for the Markovnikov Addition of N -Heterocycles to Vinyl Esters, Using a Task-Specific Ionic Liquid, [BmIm]OH. *J. Org. Chem.* **2006**, *71*, 3991– 3993, DOI: 10.1021/jo0600914

| Google Scholar

48. Welton, T. Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis. *Chem. Rev.* **1999**, *99*, 2071– 2084, DOI: 10.1021/cr980032t

| Google Scholar

49. Branco, L. C.; Rosa, J. N.; Moura Ramos, J. J.; Afonso, C. A. M. Preparation and Characterization of New Room Temperature Ionic Liquids. *Chem. - A Eur. J.* **2002**, *8*, 3671– 3677, DOI: 10.1002/1521-3765(20020816)8:16<3671::AID-CHEM3671>3.0.CO;2-9

51. Vekariya, R. L. A Review of Ionic Liquids: Applications towards Catalytic Organic Transformations. *J. Mol. Liq.* **2017**, *227*, 44– 60, DOI: 10.1016/j.molliq.2016.11.123

| Google Scholar

52. Hunt, P. A.; Ashworth, C. R.; Matthews, R. P. Hydrogen Bonding in Ionic Liquids. *Chem. Soc. Rev.* **2015**, *44*, 1257– 1288, DOI: 10.1039/C4CS00278D

| Google Scholar

53. Zhang, Q.; Zhang, S.; Deng, Y. Recent Advances in Ionic Liquid Catalysis. *Green Chem.* **2011**, *13*, 2619, DOI: 10.1039/c1gc15334j

| Google Scholar

54. Chen, S.-L.; Chua, G.-L.; Ji, S.-J.; Loh, T.-P. Ionic Liquid: A Green Solvent for Organic Transformations II. *ACS Symp. Ser.* **2007**, *950*, 177– 193, DOI: 10.1021/bk-2007-0950.ch014

| Google Scholar

55. Ramos, L. M.; Rodrigues, M. O.; Neto, B. A. D. Mechanistic Knowledge and Noncovalent Interactions as the Key Features for Enantioselective Catalysed Multicomponent Reactions: A Critical Review. *Org. Biomol. Chem.* **2019**, *17*, 7260– 7269, DOI: 10.1039/C9OB01088B

| Google Scholar

56. Sheldon, R. A. The E Factor: Fifteen Years On. *Green Chem.* **2007**, *9*, 1273, DOI: 10.1039/b713736m

| Google Scholar

57. Hudson, R.; Leaman, D.; Kawamura, K. E.; Esdale, K. N.; Glaisher, S.; Bishop, A.; Katz, J. L. Exploring Green Chemistry Metrics with Interlocking Building Block Molecular Models. *J. Chem. Educ.* **2016**, *93*, 691– 694, DOI: 10.1021/acs.jchemed.5b00696

| Google Scholar

Multicomponent Reaction for the Synthesis of Isothioureas through the Use of a Holistic CHEM21 Green Metrics Toolkit. *Green Chem.* **2017**, *19*, 249– 258, DOI: 10.1039/C6GC01928E

| Google Scholar

60. Thakur, A.; Ranote, S.; Kumar, D.; Bhardwaj, K. K.; Gupta, R.; Chauhan, G. S. Synthesis of a PEGylated Dopamine Ester with Enhanced Antibacterial and Antifungal Activity. *ACS Omega* **2018**, *3*, 7925– 7933, DOI: 10.1021/acsomega.8b01099

| Google Scholar

61. Felicetta, V. F.; Markham, A. E.; Peniston, Q. P.; McCarthy, J. L. A Study of Diffusion in Agar Gels by a Light Absorption Method. *J. Am. Chem. Soc.* **1949**, *71*, 2879– 2885, DOI: 10.1021/ja01176a089

| Google Scholar

62. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K., et al. A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *J. Med. Chem.* **2004**, *47*, 1739– 1749, DOI: 10.1021/jm0306430

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Assisted Synthesis, Antitubercular Activity, and Molecular Docking Studies of Pyrazole and Oxadiazole Hybrids. *ACS Omega* **2021**, *6* (42) , 28270-28284. https://doi.org/10.1021/acsomega.1c04411

4. Chetan Jadhav, Amol Nipate, Asha Chate, Charansingh Gill. Triethylammonium Hydrogen Sulfate [Et3NH][HSO4]-Catalyzed Rapid and Efficient Multicomponent Synthesis of Pyrido[2,3-d]pyrimidine and Pyrazolo[3,4-b]pyridine Hybrids. *ACS Omega* **2021**, *6* (28) , 18215-18225. https://doi.org/10.1021/acsomega.1c02093

5. Amol S. Nipate, Chetan K. Jadhav, Asha V. Chate, Prashant P. Dixit, Prachi Sharma, Charansingh H. Gill. Synthesis and Antimicrobial Activity of New Carbohydrazide Bearing Quinoline Scaffolds in Silico ADMET and Molecular Docking Studies. *Polycyclic Aromatic Compounds* **2024**, *44* (2) , 1348-1365. https://doi.org/10.1080/10406638.2023.2194653

6. Yong Tang, Kaifu Zhang, Yuelin Xu, Jinglin Ma, Hanqing Xie, Hongquan Zhang, Yanmin Jiang, Rui Zhao, Lei Wang. Lipase-catalyzed one-pot four-component reaction in water: green construction of substituted 2,3-dihydrothiophenes. *New Journal of Chemistry* **2023**, *47* (44) , 20316-20321. https://doi.org/10.1039/D3NJ03722C

7. Hiralben D. Atara, Gaurangkumar C. Brahmbhatt, Vishalkumar M. Parmar, Avinashkumar A. Barot, Tushar R. Sutariya, Narsidas J. Parmar. A chitosan N -ium acetate catalyzed Michael-aldol-dehydration-imino-Diels-Alder reaction: One-pot synthesis of new angular acridine-fused heterocycles. *Journal of Heterocyclic Chemistry* **2023**, *60* (9) , 1517-1529. https://doi.org/10.1002/jhet.4696

8. Chetan K. Jadhav, Amol S. Nipate, Asha V. Chate, Makrand V. Kulkarni, Charansingh H. Gill. Microwave-Assisted Chemistry: New Synthetic Application for the Rapid Construction of 1 H -Pyrazolo[1,2- b]Phthalazine-5,10-Dione Derivatives in Diisopropyl Ethyl Ammonium Acetate. *Polycyclic Aromatic Compounds* **2023**, *43* (1) , 895-914. https://doi.org/10.1080/10406638.2021.2021252

9. Chetan K. Jadhav, Amol S. Nipate, Asha V. Chate, Makrand V. Kulkarni, Vidya S. Dofe, Charansingh H. Gill. Rapid Multicomponent Tandem Annulation in Ionic Liquids: Convergent Access to 3-Amino-1-Alkylpyridin-2(1 H)-One Derivatives as Potential Anticancer Scaffolds. *Polycyclic Aromatic Compounds* **2022**, *42* (10) , 6946-6965. https://doi.org/10.1080/10406638.2021.1994427

12. S. Tasqeeruddin, Y. I. Asiri, S. Shaheen. Zirconium(IV) Oxychloride Octahydrate (ZrOCl2·8H2O): An Efficient Catalyst for the One-Pot Multicomponent Synthesis of Hexahydroquinoline Derivatives under Conventional Heating and Microwave Irradiation. *Russian Journal of Organic Chemistry* **2022**, *58* (7) , 1008-1014. https://doi.org/10.1134/S1070428022070107

13. Tejas M. Dhameliya, Prinsa R. Nagar, Kaushikkumar A. Bhakhar, Hevankumar R. Jivani, Bhavya J. Shah, Khushi M. Patel, Vaishnavi S. Patel, Archita H. Soni, Lipi P. Joshi, Normi D. Gajjar. Recent advancements in applications of ionic liquids in synthetic construction of heterocyclic scaffolds: A spotlight. *Journal of Molecular Liquids* **2022**, *348* , 118329. https://doi.org/10.1016/j.molliq.2021.118329

14. Brenno A. D. Neto, Rafael O. Rocha, Marcelo O. Rodrigues. Catalytic Approaches to Multicomponent Reactions: A Critical Review and Perspectives on the Roles of Catalysis. *Molecules* **2022**, *27* (1) , 132. https://doi.org/10.3390/molecules27010132

15. Kiran R. Khillare, Dipak S. Aher, Laxmikant D. Chavan, Sunil G. Shankarwar. Cesium salt of 2-molybdo-10-tungstophosphoric acid as an efficient and reusable catalyst for the synthesis of uracil derivatives via a green route. *RSC Advances* **2021**, *11* (54) , 33980-33989. https://doi.org/10.1039/D1RA05190C

16. Amol S. Nipate, Chetan K. Jadhav, Asha V. Chate, Tejshri R. Deshmukh, Aniket P. Sarkate, Charansingh. H. Gill. Synthesis and In Vitro Anticancer Activities of New 1,4-Disubstituted-1,2,3-triazoles Derivatives through Click Approach. *ChemistrySelect* **2021**, *6* (21) , 5173-5179. https://doi.org/10.1002/slct.202101035

17. Chetan K. Jadhav, Amol S. Nipate, Asha V. Chate, Pratiksha M. Kamble, Ganesh A. Kadam, Vidya S. Dofe, Vijay M. Khedkar, Charansingh H. Gill. Room temperature ionic liquid promoted improved and rapid synthesis of highly functionalized imidazole and evaluation of their inhibitory activity against human cancer cells. *Journal of the Chinese Chemical Society* **2021**, *68* (6) , 1067-1081. https://doi.org/10.1002/jccs.202000468