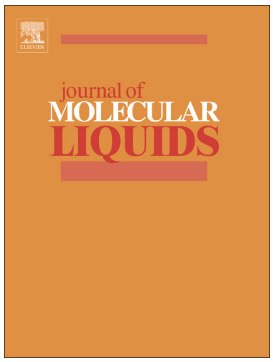

Low melting mixture glycerol:proline as an innovative designer solvent for the synthesis of novel chromeno fused thiazolopyrimidinone derivatives: An excellent correlation with green chemistry metrics

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Low Melting Mixture Glycerol: Proline as an Innovative Designer Solvent for the Synthesis of Novel Chromeno Fused Thiazolopyrimidinone Derivatives: An Excellent Correlation with Green Chemistry Metrics

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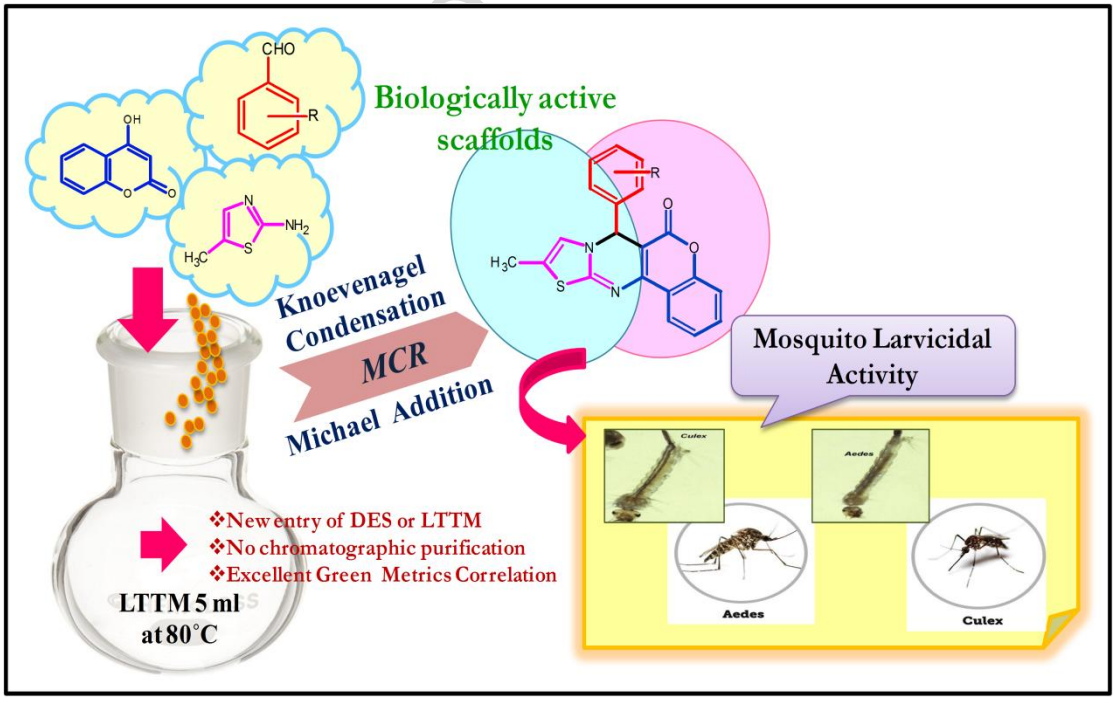
Graphical Abstract



Abstract

The expansion of proficient and environmentally benign synthetic protocols has engrossed increasing attention in recent organic syntheses in view of the mounting concern over the environment. As part of this green concept, our group designed novel LTTM by using Glycerol and proline (1:1) at reflux condition, and effectiveness of novel DES or LTTM has been studied for the synthesis of 7-(aryl)-10-methyl-6*H*,7*H*-chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-6-one derivatives *via* Multicomponent reaction. The synthetic methodology with the use of novel LTTM as green solvent and inexpensive, biodegradable, plays a dual role (recyclable catalyst and solvent) with its operational simplicity and maximum greener synthetic efficiency with green chemistry metrics calculations will be attractive for academic and industrial research. The synthesized derivatives have been evaluated for mosquito larvicidal bioassay using two mosquito species namely *Aedes aegypti* and *Culex quinquefasciatus*.

Keywords

Low Transition Temperature Mixture; Green Metrics; Multicomponent Reactions; chromene; Green Chemistry

1. Introduction

Within the scope of green chemistry, green solvents occupy an imperative position. Green solvents are accomplished as green medium; because they have been meeting the criteria of twelve green chemistry principles such as availability, non-toxicity, biodegradability, reusability, economical, etc [1]. Ionic liquids are highlighted as green solvents and extensively used in different synthetic methods. To overcome the drawbacks of the ionic liquid, Deep Eutectic Solvents (DES) have been arising as an eco-friendly solvent as well as catalyst for several organic transformations over the years [2]. They have been well known to make progress in MCR with excellent green metrics such as high atom economy and low E factor [3].

Deep Eutectic Solvent (DES) or Low Transition Temperature Mixtures (LTTMs) were introduced by A. P. Abott in this century [4] and work has been continued by M. C. Kroon and coworkers. This new designer solvent LTTM is a mixture of Hydrogen Bond Donor (HBD) and Acceptor (HBA) which has been proved as bio-solvents [5]. Preparation of LTTM is very simple, eco-friendly and straightforward and 100% atom economic, inexpensive and non-toxic materials. In several organic transformations LTTM acts as catalyst as well as solvent due to physical properties such as low vapor pressure, non-inflammability, biocompatibility, biodegradability and cost efficiency [6-9]. Other than this, LTTMs or DESs are accounted as innovative and sustainable solvent and has several applications [10-13]. Each LTTM has its own properties which make them suitable as green solvent [14, 15].

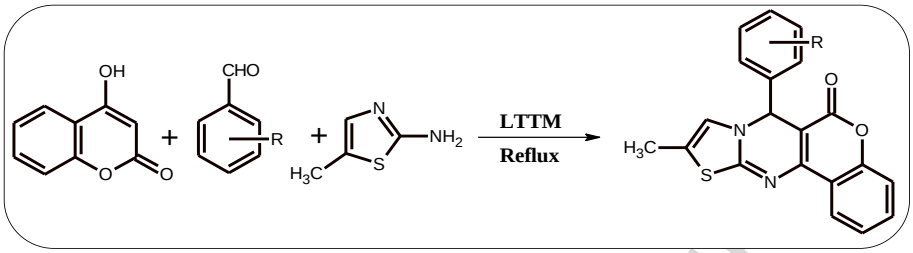
Chromene ring widely present in plant products including edible vegetables and fruits [16]. Also, various chromene-based bioactive natural products have been recognized, and associated with the capacity to prevent diseases [17]. Even though, it shows wide applications in laser dyes and fluorescence, pigments and cosmetics [18-20]. Chromene fused derivatives

are vital class of natural compounds because of its bioactivity in pharmaceutical and agrochemicals field [21]. Chromene scaffolds with thiazolopyrimidine moiety have also wide applications in heterocyclic chemistry [22] such as anticancer [23-27] activities, anti-tuberculotic [28], anti-microbial [29-34], anti-inflammatory [33] and analgesic [35], insecticidal [36], herbicidal [37, 38], antioxidant [34, 39], acetylcholinesterase inhibitors [40], antimalarial [41], anti-HIV [42]. Reddy *et al.* have been reported the synthesis of chromeno fused thiazolopyrimidine molecules [43]. However, these methods have been reported with some limitations such as use of expensive reagents and solvents, longer reaction time, and lower selectivity of catalyst, environmental hazards and catalyst reusability problem. To overcome these limitations, it is necessary to implement versatile alternatives and new strategies for the development of sustainable chemical processes in the framework of green chemistry principles [44].

Taking into consideration, the significance of LTTMs and in search for new eco-friendly and bio-renewable solvents, thus our group has been taking efforts towards synthesis of several organic reactions and novel bioactive molecules by using biodegradable ionic liquid, DES or LTTM [45-51]. LTTM of glycerol and proline have been explored in this work. By selecting easily available, cost effective starting materials such as glycerol and proline with proportion (1:1) LTTM is prepared. The physical and thermal properties of novel LTTM were studied. Similarly the catalytic efficiency and the role LTTM or DES as a reaction promoting medium were investigated for the synthesis of chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin motifs.

Considering reviews on LTTM or DES, it is applicable for several multicomponent reactions (MCRs). MCRs represents environmentally and eco-friendly pathway with high atom economy [52, 53]. In extension of our constant efforts in the development of novel synthetic methodologies for the synthesis of bioactive scaffolds, we report an expedient

synthesis of chromeno fused thiazolopyrimidne derivatives (Scheme 1) and performed *in-vitro* mosquito larvicidal bioassay of selected motifs using two well known species of mosquitoes, *Aedes aegypti* and *Culex quinquefasciatus*.



Scheme 1 Glycerol: Proline (1:1) LTTM mediated synthesis of chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin derivatives

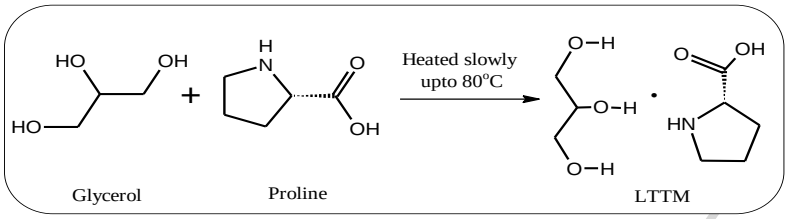
2. Experimental

All the chemicals were purchased from Alfa Aesar and Spectrochem (PVT. Ltd, Mumbai, India), Sigma Aldrich and used without purification. The reaction was monitored by TLC. The desired structures of the synthesized compounds were confirmed by their relevant spectral data. The melting points were determined in open glass capillary method and are uncorrected. The Compounds were confirmed by IR, ^{1}H NMR and ^{13}C NMR. The IR spectra were recorded on a JASCO FT-IR 4600 spectrum spectrophotometer and the values are expressed as ν max cm^{-1}. The ^{1}H NMR and ^{13}C NMR, DEPT spectra were recorded on Bruker Spectrospin Avance II-300 MHz and 75 MHz spectrophotometer relative to TMS as an internal standard using DMSO-*d6* as a solvent. Thermal analysis of newly prepared LTTM was performed on (SDT Q600 V20.9 Build 20) instrument.

2.1 General synthetic procedure for the preparation of Glycerol: Proline (1:1) LTTM

The LTTM have been prepared by selecting glycerol as a hydrogen bond donor and proline as a hydrogen bond acceptor. A mixture of glycerol (100 mmol, 9.2 g) and proline (100 mmol, 11.5 g) in the ratio 1:1was heated at 80˚C with continuous stirring for 30 min (Scheme 2). The resulting LTTM forms dark yellowish viscous liquid with an excellent atom economy, was subsequently allowed to cool at room temperature and was used for the

synthesis of chromeno fused thiazolo[3,2-*a*]pyrimidin derivatives without further purification.



Scheme 2 Preparation of Glycerol: Proline (1:1) LTTM

2.2 General synthetic procedure for the synthesis of chromeno[4,3-d]thiazolo[3,2 a]pyrimidin

A mixture of 4-Hydroxycoumarin (1 mmol, 0.162 g) and 4-chlorobenzaldehyde (1 mmol, 0.140 g), with 5ml LTTM was taken in a 50 ml round bottomed flask at room temperature to form the Knoevenagel product, monitored by TLC and then 2-mino 5-methyl thiazole (1 mmol, 0.106 g) were added and continued at reflux condition for 20 min. The progress of the reaction was monitored by TLC using petroleum ether- ethyl acetate (8:2 v/v). After completion, the reaction mixture was cooled to room temperature. Water was added to the reaction mixture and the product was collected by simple filtration, washed with hot ethanol and diethyl ether. Finally, the crude product was recrystallized from ethanol to obtain the pure product (Scheme 1).

3. Result and Discussion

A new LTTM is formed by glycerol and proline with proportion (1:1). Generally, glycerol is obtained from plant and animal sources, occurs as triglycerides. The hydrolysis, saponification or trans-esterification of triglycerides produces glycerol and fatty acids. On the other side, proline is α amino acid, oftenly used as an asymmetric catalyst in organic synthesis. To replace volatile organic solvents, LTTMs has been used as a catalyst or solvent in the advancement of green sustainable synthetic chemistry. Combining the applicability of

multicomponent reactions with interesting features of LTTM, with a complete study on physical and thermal properties of new LTTM has been developed.

3.1 Characterization of Glycerol: Proline (LTTM)

3.1.1 TGA analysis of new LTTM-GP (1:1)

TGA is a conventional and most popular technique used to study the thermal stability and decomposition of the materials. TGA is performed of LTTM G: P (1:1) to evaluate the thermal stability by means of the degradation temperature. The thermal decomposition process is affected by the operating parameters and conditions such as the rate of heating, temperature, pressure, surrounding environment and moisture content and composition of the heated sample. The LTTM sample was heated from room temperature to 350˚C under continuous nitrogen flow. The weight loss of LTTM during the long runs could be endorsed to the amount of moisture content and volatiles present in the sample.

Figure 1 show that TGA and DTG curves of the glycerol and proline mixture. These curves reveal two main weight loss regions. The first weight loss is about 13 wt % in the 50–175˚C temperature range may be due to the loss of physically adsorbed and bound water. This temperature range is sufficient to promote and catalyze organic synthesis. The second weight loss of about 81 wt % in the temperature range about 175–300˚C, corresponds to the thermal degradation/ decomposition of glycerol and proline moiety. The decomposition values (T_{dcp}) of LTTM G: P (1:1) in range from 58.42˚C to 344.34˚C. We can conclude that, the LTTM stay intact under experimental conditions as a solvent.

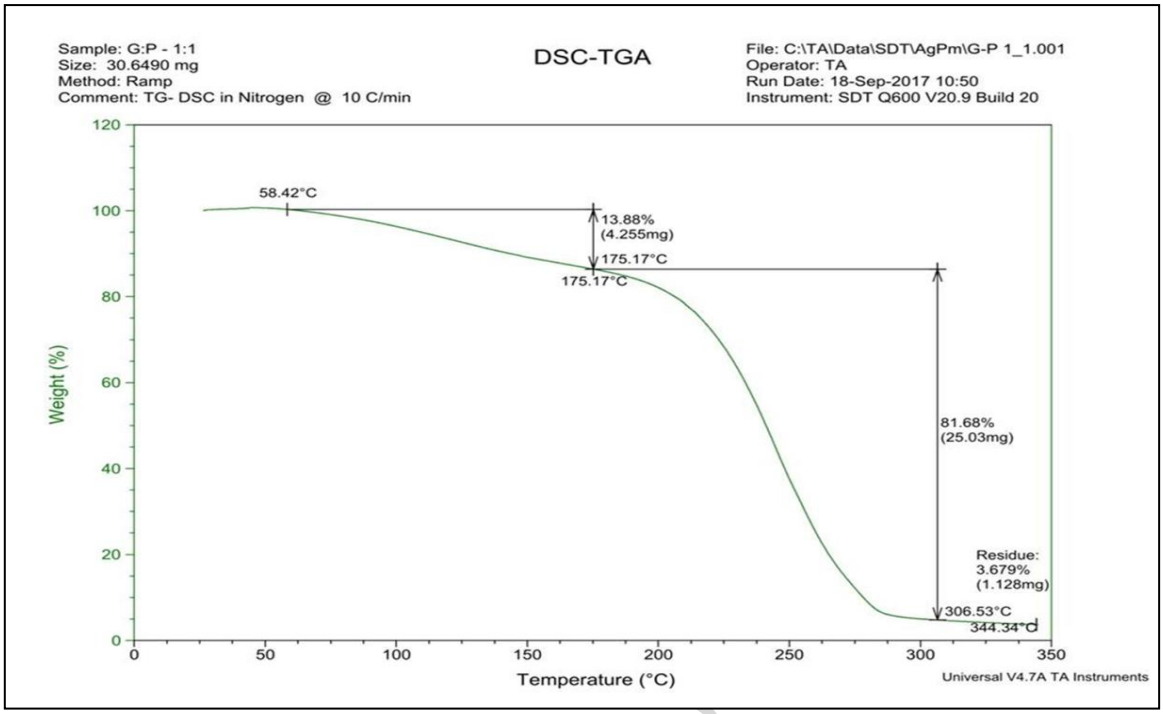


Fig. 1 TGA analysis of new LTTM-GP (1:1)

3.1.2 DSC analysis of LTTM-GP (1:1)

Plot of heat flow vs. temperature (Fig. 2) range between 25˚C and 350˚C obtained by DSC. A broad endothermic peak ~116˚C is observed in the DSC curves on heating the glycerol-proline mixture. This is associated with water content in the mixture and its interaction with the LTTM and the exothermic events that start to appear at about ~237˚C, associated with the degradation backbone of LTTM.

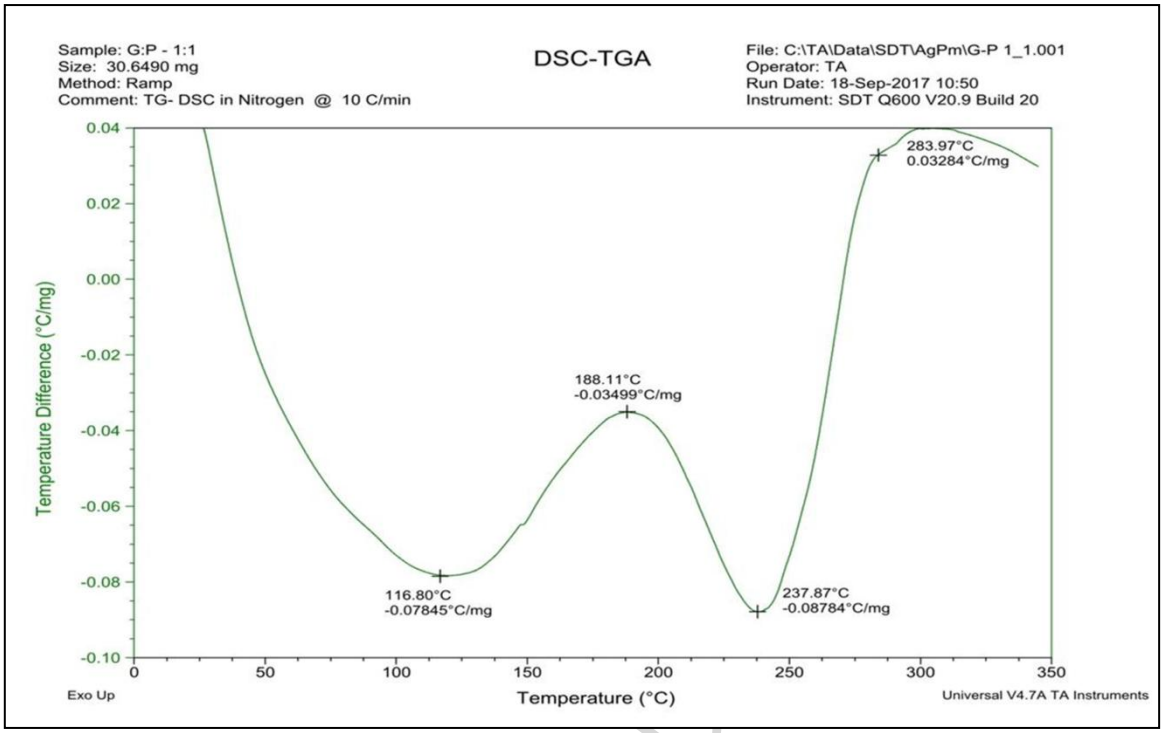


Fig.2 DSC curve of LTTM-GP (1:1)

3.1.3 FT-IR and NMR Spectral analysis of LTTM-GP (1:1)

The possible structure of LTTM-GP (1:1) was investigated with FT-IR, NMR spectral analysis to explore the type of interaction and atoms involved in interactions in the given ratio of components. The FT-IR spectra (Fig. 3) of LTTM of glycerol, proline (molar ratio 1:1) were recorded at room temperature. In glycerol, the stretching vibration band of –OH observed at ν_{max}3303 and C=O at 1650 cm^{-1}. In proline, stretching vibration band of C=O observed at 1614 cm^{-1} and C-OH at 3151 and 3357 cm^{-1}. The mixture of LTTM-GP (1:1) shows stretching band corresponding to C-OH at 3325cm^{-1} and the another stretching band observed at 2360 and 2138cm^{-1}which indicates the formation of a hydrogen bonding (O=C-O-H----N).

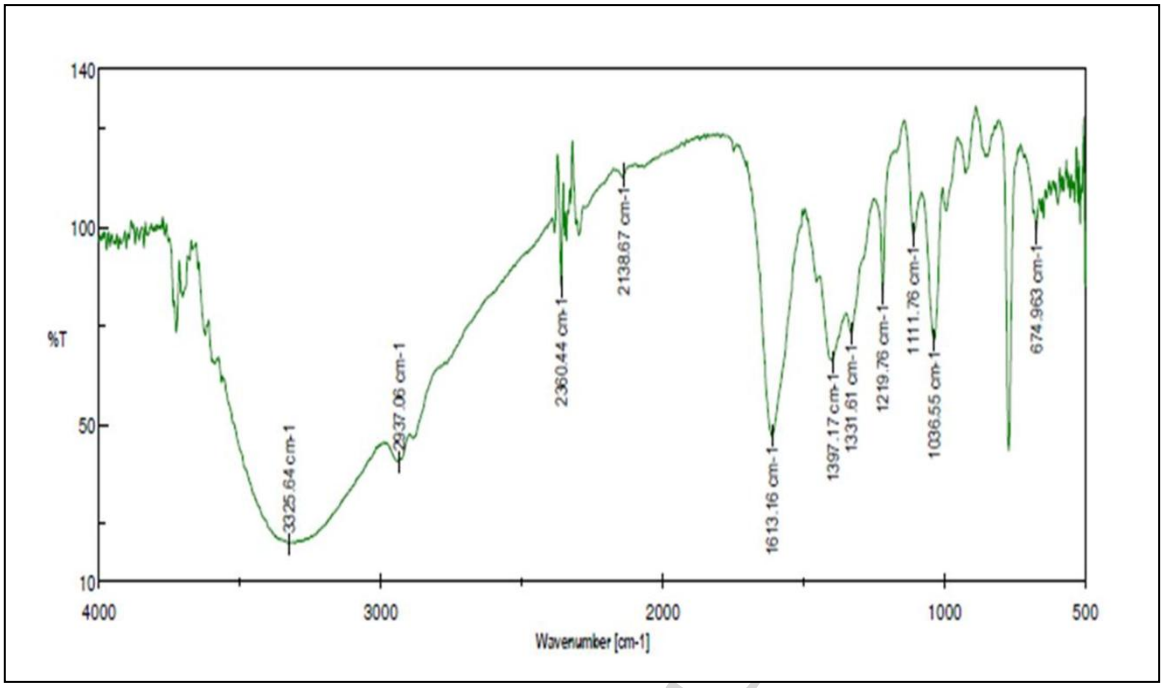


Fig. 3 FT-IR spectrum of LTTM-GP (1:1)

The ^{1}HNMR analysis of glycerol and proline LTTM mixture (molar ratio 1:1) was recorded. The ^{1}H NMR (Fig. 4) showed a singlet at δ,4.158 ppm due to (R-OH) proton which confirms hydrogen bonding between two reactants and δ, 4.867 ppm represents (Ar-OH) proton of proline in the same mixture. The signals that appeared between δ, 3.267 ppm and 3.471 ppm represent the aliphatic protons (R-H).

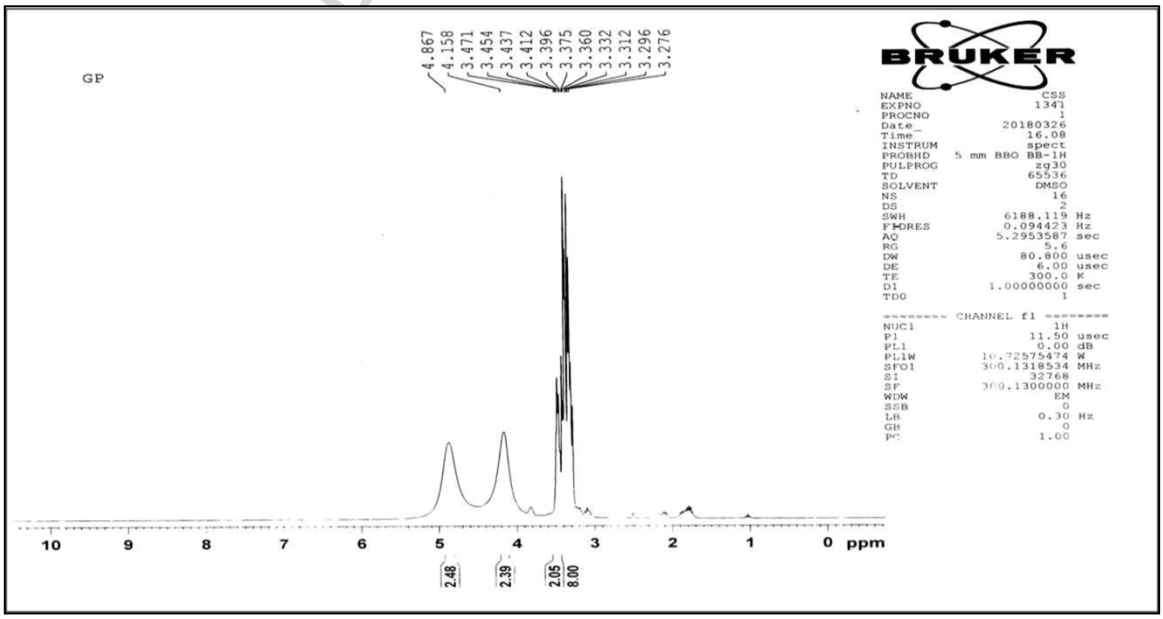


Fig. 4 NMR Spectrum of LTTM-GP (1:1)

3.2 Chemistry

In the view of bioactive applications of 7-(aryl)-10-methyl-*6H,7H*-chromeno[4,3 *d*]thiazolo[3,2-*a*]pyrimidin-6-one derivatives, our current focus has been targeted, to synthesize these novel scaffolds using simple environmental friendly, facile protocol based on green chemistry principles. We initially investigated the preliminary reaction of 4-hydroxy coumarin (1mmol, 0.162 g), 4-chlorobenzaldehyde (1mmol, 0.140 g) and 2-amino 5-methyl thiazole (1mmol, 0.106 g) using different reaction conditions.

The choice of solvent is also an important aspect in every reaction to prove the greenness of the protocol. To study the solvent efficiency, the reaction was carried out in a variety of polar and non-polar solvents at different conditions. Water was used for this reaction, but according to our expectations, the reaction does not proceed further beyond the Knoevenagel product and desired product was not obtained. When ethanol was used as a solvent, the desired product was obtained in 42% yield under reflux conditions (Table 1 Entry 3b). Then, we endeavor same reaction in a combination of water/ethanol mixture and other organic solvents like DCM, methanol, glycerol at reflux condition, but the desired product is obtained in very poor yield (Table 1 Entry 4-7). As a new designer solvent, LTTM was used for the same reaction at reflux condition, astonishingly the yield of the product increased up to 94% in shorter reaction time (Table 1 Entry 8). We screened the reaction using various number of LTTM, however the yield of the product was poor (Table 1 Entry 9-11). After testing various solvents and solvent-free conditions, it is observed that a Glycerol: Proline (1:1) (LTTM) leads to the formation of the product with better yield (Table 1 Entry 8). The results are summarized in Table 1.

Table 1 Optimization of solvent for the synthesis of chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-6-one

Sr. No.	Solvent	Temp. Condition (˚C)	Reaction time (mins.)	Yield[b](%)
1	Solvent free	30	300	Knoevenagel product
2a.	Water	30	180	Knoevenagel product
2b.	Water	80	120	Knoevenagel product
3a.	Ethanol	30	320	Knoevenagel product
3b.	Ethanol	80	180	42
4.	Water : Ethanol (1:1)	80	120	46
5.	DCM	80	120	40
6.	Methanol	80	300	52
7.	Glycerol	80	90	56
8.	**Glycerol: Proline (1:1)**	**80**	**30**	**94**
9.	Glycerol: Proline (1:2)	80	80	70
10.	Choline chloride: oxalic acid (1:1)	80	60	60
11.	Choline chloride: oxalic acid (1:2)	80	75	42

Highest yield in shortest reaction time shown in bold

a. Reaction condition: 4-hydroxy coumarin (1mmol), 4-chloro benzaldehyde (1mmol) and 2-amino 5-methyl thiazole (1mmol) heated at 80˚C in 5 ml of respective solvent.

b. Yields refer to pure isolated products.

Further to evaluate the catalytic effect in order to establish the reaction conditions, then model reaction was carried out in different catalysts (20mol %) such as citric acid, PTSA, acetic acid, NaOH and proline but unfortunately inferior results were obtained. The results are summarized in Table 2.

Table 2 Optimization of catalysts for the synthesis of chromeno[4,3 d]thiazolo[3,2-a]pyrimidin-6-one

Sr. No.	Catalyst	Catalyst Load (mol %)	Temp. Conditions (˚C)	Time (mins.)	Yield[b] (%)
1.	Citric acid	20	80	180	44
2.	PTSA	20	80	120	40
3.	Acetic acid	20	80	180	38
4.	NaOH	20	80	120	40
5.	Proline	20	80	120	68
6.	**Glycerol: Proline (1:1)**	-	80	**30**	**94**

Highest yield in shortest reaction time shown in bold

a. Reaction condition: 4-hydroxy coumarin (1mmol), 4-chloro benzaldehyde (1mmol) and 2-amino 5-methyl thiazole (1mmol) heated at 80˚C in 5 ml of respective solvent.

b. Yields refer to pure isolated products.

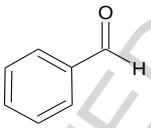
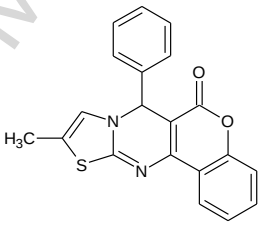
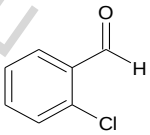
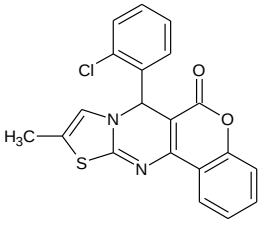
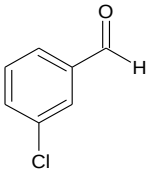
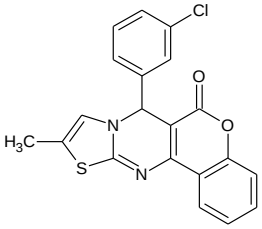
After the study of effect of solvent and catalyst, it is clear from table 2, the desired product of 7-(aryl)-10-methyl-6*H*,7*H*-chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-6-one was obtained an excellent yield in Glycerol: Proline (1:1)(LTTM) (Table No. 2, Entry 6).The results shown in table no.1 and 2 indicate that Glycerol: Proline (1:1)(1:1) LTTM can act as suitable, eco-friendly reaction promoting medium. Remarkably, the workup procedure for this reaction involves only simple filtration and washing of residue with hot ethanol and diethyl ether to result in pure products.

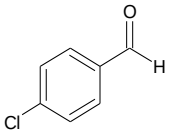
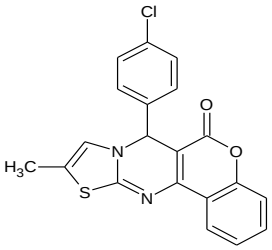
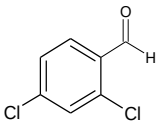
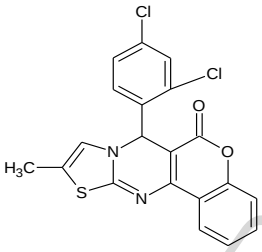
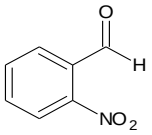
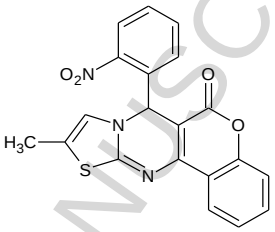
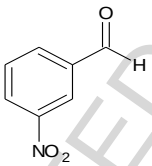
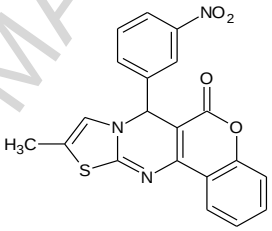
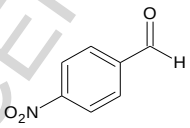
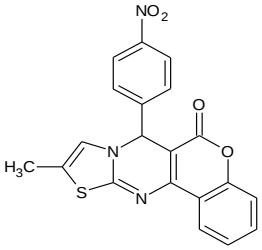
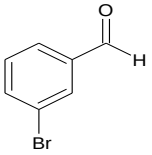
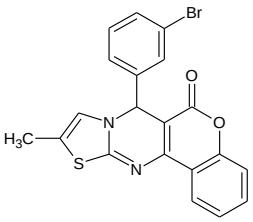
The structures of the products were confirmed on the basis of spectroscopic data. The infrared (IR) spectra of the compound code **CA-4** showed the characteristic band at 1666.20, 1608.34 cm^{-1} due to the presence of a carbonyl group. The ^{1}H NMR showed a singlet at δ, 6.252 due to benzylic (-CH) proton which confirms the cyclization. The signals appeared between δ, 6.95 and 7.82 ppm represent the aromatic protons. In the ^{13}C NMR spectrum the signal appeared at δ, 22.50, 36.11, 58.70, 103.57, 115.80, 120.08, 120.71, 122.59, 129.25,

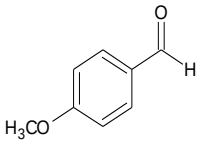
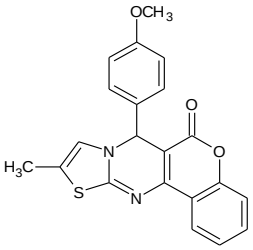
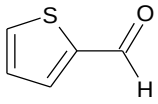
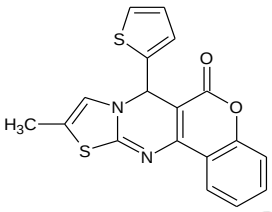
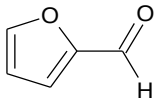
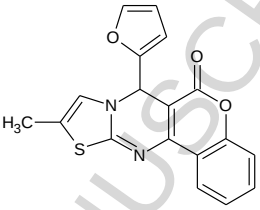
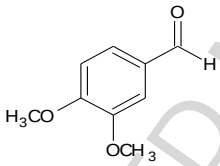
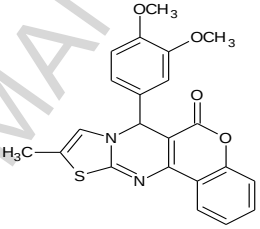
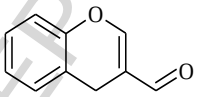
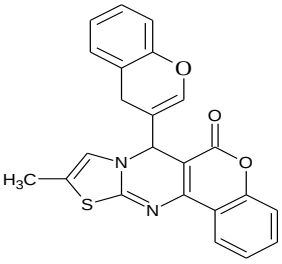
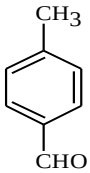
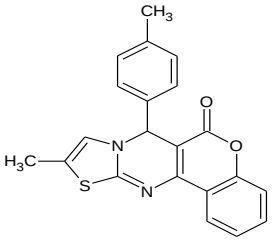
124.51, 127.82, 128.70, 130.12, 131.28, 141.20, 152.81, 165.78, 168.70, 169.72 ppm indicate the presence of aromatic carbons. Characteristic carbonyl carbons appeared at δ, 165.78, 168.70 ppm. Mass spectra of the compound show a molecular ion peak at *m/z* 380 (Mþ) which confirmed the proposed structure.

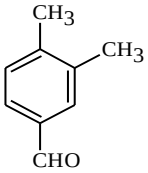
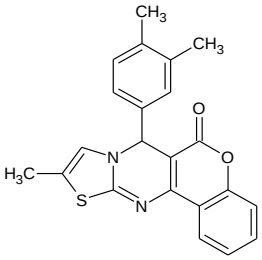
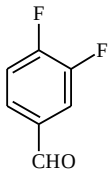
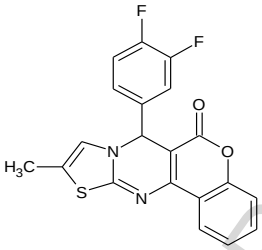
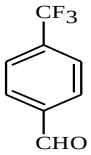
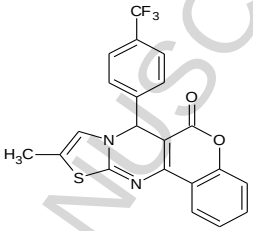
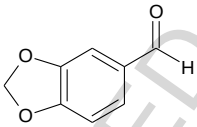
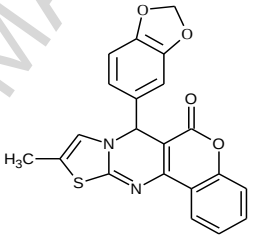
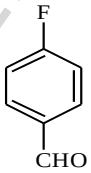
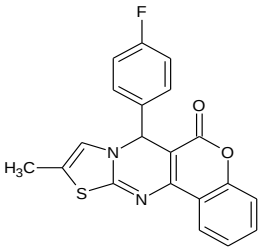
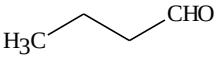
Using these optimized reaction conditions, a series of 7-(aryl)-10-methyl-6*H*,7*H*-chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-6-one derivatives were synthesized in moderate to an excellent yields from different aromatic aldehydes having electron donating as well as electron-withdrawing groups. These substrate scopes are listed in Table No. 3.

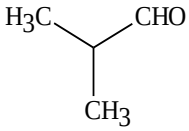
Table 3 Synthesis of chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-6-one derivatives using LTTM **(Entry 1-20)**[a]

Entry No.	Code	Aldehyde	Product[c] (Structure)	Time (mins.)	Yield[b] (%)	M.P. (˚C)
1.	CA-1			30	92	260
2.	CA-2			35	92	242
3.	CA-3			30	92	243

4.	CA-4			30	94	243
5.	CA-5			40	88	256
6.	CA-6			40	82	254
7.	CA-7			45	82	254
8.	CA-8			35	86	252
9.	CA-9			38	92	258

10.	CA-10			45	84	262
11.	CA-11			35	84	200
12.	CA-12			35	80	228
13.	CA-13			45	88	264
14.	CA-14			45	88	276
15.	CA-15			30	92	235

16.	CA-16			35	86	>300
17.	CA-17			35	94	280
18.	CA-18			40	82	238
19.	CA-19			45	90	258
20.	CA-20			45	92	246
21.	CA-21		--	720	--	--

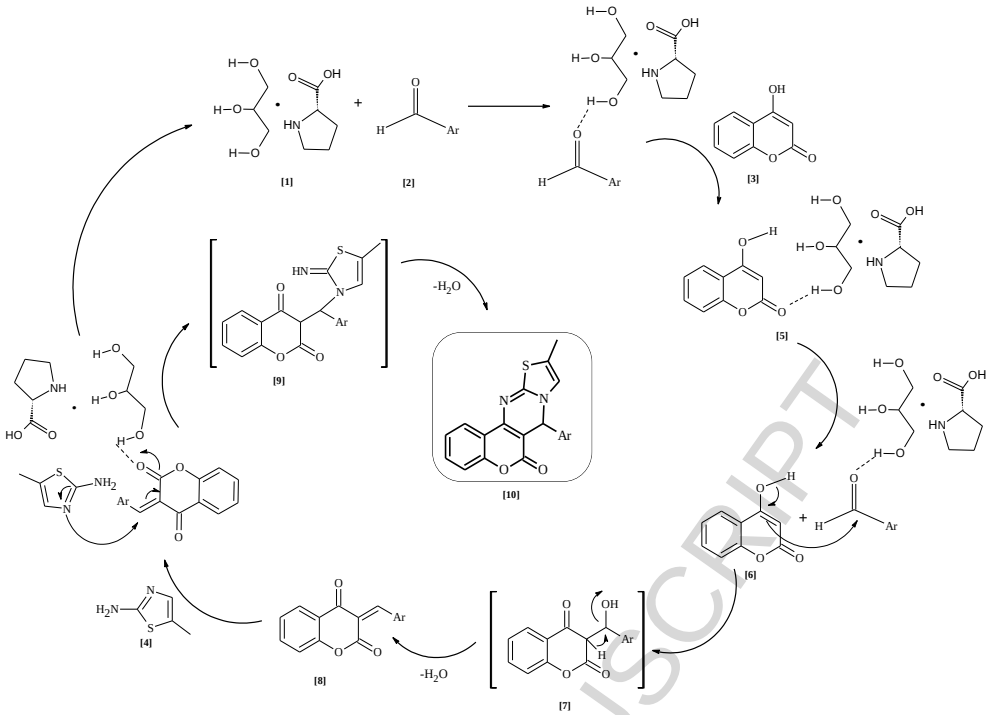
22.	CA-22		--	720	--	--

a. Reaction condition: 4-hydroxy coumarin (1mmol), Aromatic aldehyde (1mmol) and 2-amino 5-methyl thiazole (1mmol) heated at 80˚C in 5 ml of Glycerol: Proline (1:1) LTTM.

b. Yields refer to pure isolated products.

c. Products prepared for first time.

It is noteworthy to reveals that this methodology worked well for hetero-aromatic aldehydes (Table 3). A plausible mechanism for the synthesis of 7-(aryl)-10-methyl-*6H,7H*-chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-6-one derivatives **(10)** is depicted in (Scheme 3). The reaction may proceed through the formation of the Knoevenagel condensation of the aromatic aldehyde **(2)** and 4-hydroxycoumarin **(3)** in glycerol: proline as a catalyst and solvent generates an intermediate. The 2-amino 5-methyl thiazole **(4)** then undergoes subsequent aza Michael addition reaction followed by intra-molecular cyclization with carbonyl group of 4-hydroxycoumarin and amino group of 2-amino 5-methyl thiazole to give Michael adduct undergoes dehydration to afford the desired product (10). The catalyst may be increases the electrophilicity of the carbonyl groups in the reaction.



Scheme 3 Mechanistic pathway of the 7-(aryl)-10-methyl-6*H*,7*H*-chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-6-one

4. Reusability of LTTM

The reusability of the catalyst is exceptionally important aspect of green chemistry. In the present study, reusability of the LTTM was evaluated by using the reaction of 4-Hydroxycoumarin (1 mmol), 4-Chlorobenzaldehyde (1 mmol), and 2-Amino 5-methyl thiazole (1 mmol) in the Glycerol: Proline (1:1) LTTM under optimized conditions. After completion of the reaction, as indicated by TLC, 10 ml of water was added to the reaction mixture and the crude reaction product was separated by simple filtration. The LTTM was recovered by evaporating the water at 80˚C under vacuum. The recycled LTTM was successively reused for the next reaction and recycled another time (Fig. 5).

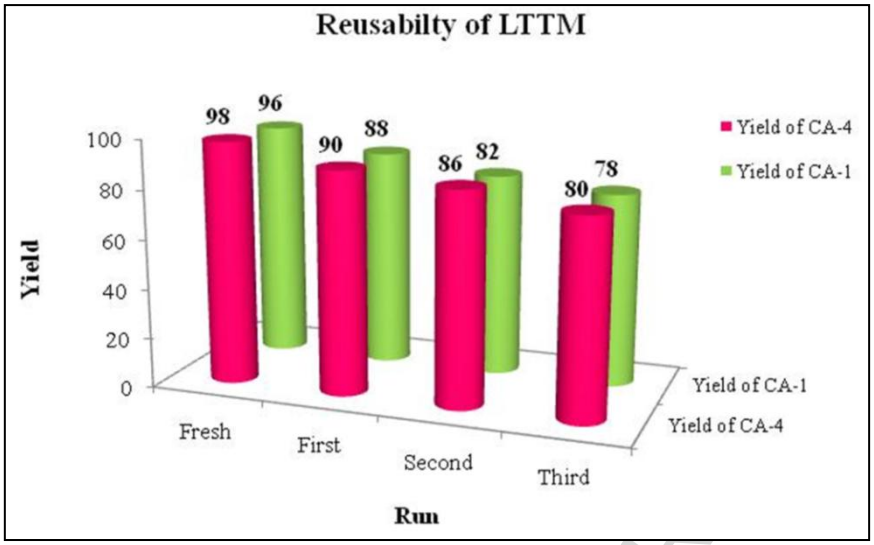


Fig.5 Reusability of LTTM

5. Green Metric Calculations

Compliant with principles of green chemistry, green metrics such as Mass Intensity (MI), Reaction Mass Efficiency (RME), Carbon Efficiency (CE), and Atom Economy (AE) and E Factor have been considered as a gauge of greenness and environmental sustainability in diminishing the amount of theoretical waste [54].

In ideal condition MI ≈ 1%, RME ≈ 100%, %CE ≈ 100 and %AE ≈ 100 and E-factor ≈ 0 is expected. To reveal the greenness of the present protocol, we have explored the results in terms of reported green metric parameters [55].

The high yield of the product shows that the significant RME values and moderate yield generate moderate RME values. In addition to this, all carbon atoms in the reactants are present in the product shows excellent values of % CE. MI values and E factor of the reaction are very close to the ideal values. The percent atom economy of each scaffold indicates maximum conversion of starting materials into product and minimum waste exclusion. Mass of catalyst is excluded as it is recyclable. (Fig. 6)

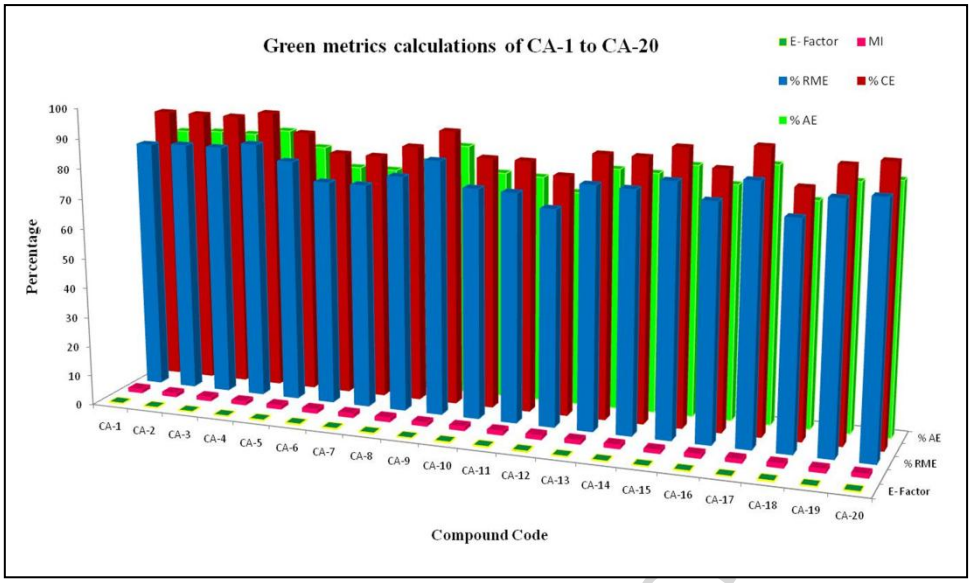


Fig. 6 Green metrics calculations (The exact values are mentioned in the supporting information). E- factor, *MI* mass intensity, *% RME* percentage reaction mass efficiency, *% CE* percentage carbon efficiency, *% AE* percentage atom economy.

6. Mosquito Larvicidal Bioassay of synthesized chromeno[4,3 d]thiazolo[3,2-*a*]pyrimidin derivatives

Mosquito is serious household pest in the society and mosquito borne diseases such as, malaria, dengue fever, filariasis, yellow fever causing millions of death every year [56]. In recent years, various numbers of heterocyclic scaffolds exhibited significant insecticidal activity for the control of insect pests and vectors. Considering all the aspects, we performed mosquito larvicidal bioassay of synthesized chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin derivatives.

Insects rearing

Laboratory colony of mosquito species *Aedes aegypti* and *Culex quinquefasciatus* were reared and maintained in plastic container containing water and the experiments were carried out at $27^0 \pm 30^0$ C and 50-90% relative humidity. Larvae were fed a diet of rabbit feed.

Larvicidal bioassay

During preliminary screening in the laboratory trial, the larvae of *Aedes aegypti* and *Culex quinquefasciatus* were collected from the insect rearing cage. During the study 5 different concentrations was prepared at the range of 25 µg/ml, 50µg/ml, 100µg/ml, 125µg/ml, 250µg/ml and 500µg/ml. The larvicidal bioassay was performed by the procedure of WHO guidelines. Groups of 10, some 2^{nd} and 3^{rd} instars larvae of *Aedes aegypti* and *Culex quinquefasciatus* were released in different plastic cups contain 50 ml water and compounds with different concentrations were added from stock solution. Three replicates were maintained for the individual compound along with the simultaneous control and untreated groups. A control group was set up with DMSO-distilled water. During this experiment no food was offered to larvae. Mortalities of treated larvae were determined after an exposure period of 24 hrs. The larvae were considered dead, if they were unable to move or respond when stimulated by probing with a needle. The experimental means in which 100% mortality of larvae occurs, were selected for dose-response bioassay.

Dosage-response bioassay

Initially, all these synthesized compounds investigated at low to high concentrations**.** The control was taken separately. The experiment replicated thrice. The results are expressed in terms of percent mortality.

Based on the preliminary screening results, preliminary active compounds were subjected to dose-response bioassay for larvicidal activity against the larvae of *Aedes aegypti* and *Culex quinquefasciatus*. Again, the numbers of dead larvae were counted after 24 hrs of exposure, and the percentage of mortality was reported from the standard of three replicates.

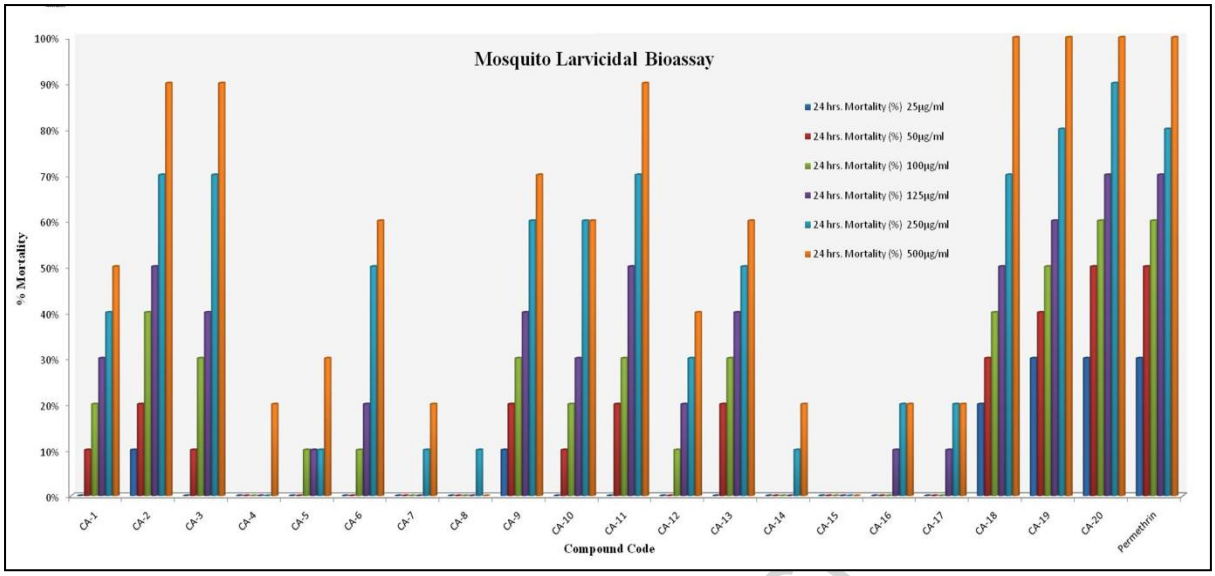


Fig.7 Larvicidal assay against 3rd instars larvae of *Aedes aegypti*

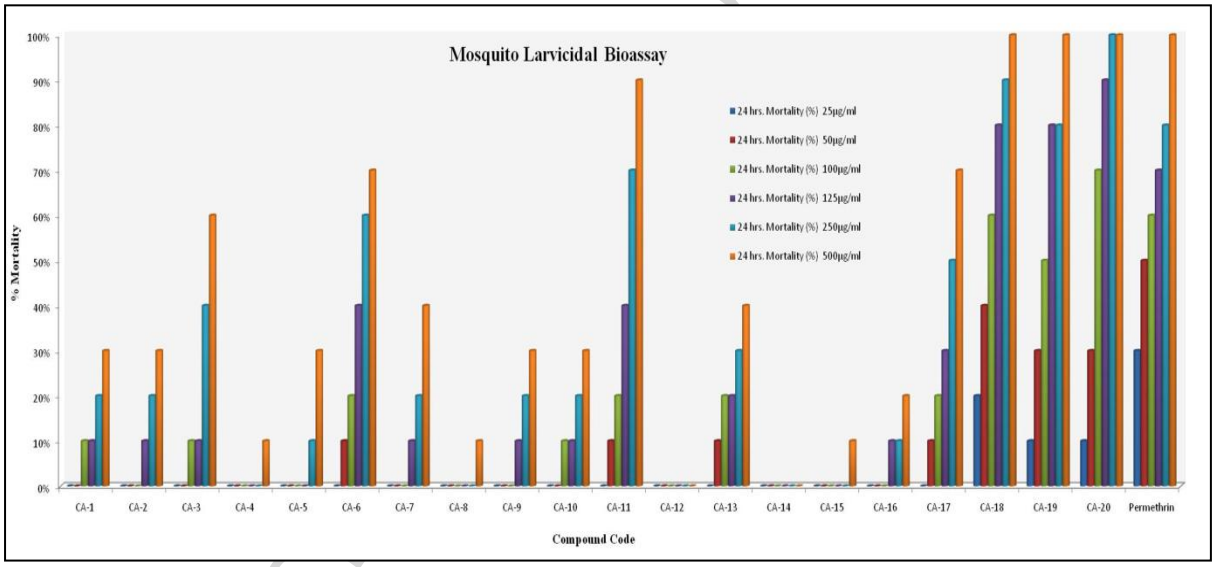


Fig.8 Larvicidal assay against 3rd instars larvae of *Culex quinquefasciatus*

Statistical Analysis

The average larval mortality data were subjected calculating LC_{50}, LC_{99}, and other statistics as fiducial limits and Regression equation (table 4 and 5) were calculated using the SPSS software [57].

The results from the study showed that the chromeno fused scaffolds exhibited larvicidal activity. No mortality was observed in control. All the compounds possesses

moderate to excellent mosquito larvicidal activity. Compound **CA-17** with LC_{50} value 68.41, 74.99 ppm and LC_{99} value 370.363, 170.77 ppm showed the highest larvicidal activity against 3rd and 4th instar larvae of both species *Aedes aegypti*, *Culex quinquefasciatus* respectively. Compound code **CA-2** and **CA-20** compounds also exhibited larvicidal activity against *Aedes aegypti* with LC_{50} value 141.64 ppm, 98.17 ppm and LC_{99} value 503.28 ppm, 465.38 ppm respectively. Whereas **CA-2** and **CA-20** compounds showed larvicidal activity against *Culex quinquefasciatus* with LC_{50} value 79.78 ppm, 107.42 ppm and LC_{99} value 391.89 ppm, 371.63 ppm respectively.

Table 4 Statistical data of mosquito larvicidal bioassay of selected derivatives

Statistical data of *Aedes aegypti*						
Entry No.	**Compd. Code**	**LC_{50}**	**Fiducial Limit**	**LC_{99}**	**Fiducial Limit**	**Regression equation**
1.	CA-2	141.64	123.88 – 181.00	503.28	440.61 – 593.84	Y= 0.006 + 0.911 log x
2.	CA-4	181.73	104.01 – 290.05	641.94	454.74 – 1285.67	Y= 0.005 + 0.191 log x
3.	CA-5	207.99	124.62 – 356.35	612.27	425.90 – 1367.50	Y= 0.006 + 1.193 log x
4.	CA-9	375.69	240.09 – 1017.74	898.82	584.67– 7511.33	Y= 0.004 + 1.671 log x
5.	CA-12	271.68	165.60 – 523.26	976.71	647.94 – 2573.86	Y= 0.003 + 0.896 log x
6.	CA-17	68.41	50.18 – 83.95	370.36	318.57 – 450.66	Y= 0.008 + 0.527 log x
7.	CA-19	274.09	184.75 – 453.742	931.05	518.03 – 1506.17	Y= 0.005 + 1.395 log x
8.	CA-20	98.17	79.17 – 116.11	465.38	401.56 – 561.73	Y= 0.006 + 0.622 log x
9.	Control	--	--	--	--	--

LC_{50} =Lethal concentration 50 at which 50% of target population died.

LC_{99} = Lethal concentration 99 at which 99% of target population died.

Table 5 Statistical data of mosquito larvicidal bioassay of selected derivatives

Statistical data of *Culex quinquefasciatus*						
Entry No.	**Compd. Code**	**LC_{50}**	**Fiducial Limit**	**LC_{99}**	**Fiducial Limit**	**Regression equation**
1.	CA-2	79.78	25.30 – 120.78	391.89	230.58 – 648.49	Y= 0.010 + 0.773 log x
2.	CA-5	400.41	298.76 – 681.28	893.09	636.76 – 1871.23	Y= 0.005 + 1.891 log x
3.	CA-9	294.40	152.85 – 1019.19	856.55	532.74 – 4963.81	Y= 0.004 + 1.218 log x
4.	CA-15	320.57	271.33 – 583.77	876.83	602.24 – 2042.08	Y= 0.004 + 1.341 log x
5.	CA-17	74.99	68.97 – 81.01	170.77	156.37 – 190.28	Y= 0.024 + 1.822 log x
6.	CA-20	107.42	11.18 – 245.87	371.63	298.71 – 2203.36	Y= 0.009 + 0.946 log x
7.	Control	--	--	--	--	--

LC_{50} =Lethal concentration 50 at which 50% of target population died.

LC_{99} = Lethal concentration 99 at which 99% of target population died.

7. Conclusion

In summary, Glycerol: proline (1:1) LTTM was successively reported and also used for one pot multi-component synthesis of chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin derivatives as a biocompatible solvent/ catalyst. The LTTM plays a dual role such as solvent/catalyst with better reusability. This protocol has major advantages such as operational simplicity, green, efficient protocol in designer solvents, easy work-up procedure, and good to excellent yields, column chromatography-free technique and an excellent correlation with green metrics calculations. Hence, by providing a greener alternative route, a highly efficient protocol was developed which can easily replace existing methods. The present methodology will be attractive, convenient, and green alternative path for simple catalytic organic transformations to develop bioactive molecules with structural diversity and molecular complexity. Also, chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin derivatives were found to have mosquito larvicidal bioassay in laboratory condition with moderate to excellent results in terms of LC_{50} and LC_{99} and percentage mortality after 24hrs.

8. Spectroscopic data of the synthesized compound

7-(4-chlorophenyl)-10-methyl-6*H*,7*H*-chromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-6-one (Table 3 Entry 4, compd. code CA-4)

White powder; yield 94%; mp 243˚C; IR (ν max): 2915.84, 1666.2, 1608.34, 1518.67, 1484.92, 1397.17, 1179.26, 1035.59 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d*6): δ, 2.223 (s, 3H, CH_3), 6.252 (s, 1H, -CH), 6.954 (s, 1H, Ar-H), 7.129–7.209 (t, 4H, Ar-H), 7.431–7.454 (d, 1H, Ar-H, *J*=6.9 Hz), 7.798–7.823 (d, 2H, Ar-H, *J*=7.5 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-*d*6): δ, 22.50, 36.11, 58.70, 103.57, 115.80, 120.08, 120.71, 122.59, 129.25, 124.51, 127.82, 128.70, 130.12, 131.28, 141.20, 152.81, 165.78, 168.70, 169.72 ppm; DEPT90: 75 MHz, DMSO-*d*6): δ, 36.085, 115.796, 122.240, 123.238, 124.581, 127.863, 128.555, 131.188 ppm; mass (*m/z*): 380.84742 (M^+). Anal. calcd. For $C_{20}H_{13}ClN_2O_2S$: C, 63.07; H, 3.44; N, 7.36%; Found: C, 63.02; H, 3.40; N, 7.32%.

(Remaining all spectral data of synthesized compounds mentioned in supporting information)

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Highlights:

- New entry of DES or LTTM.
- Products with excellent yield with non-chromatographic purification, shorter reaction time.
- Successively reused LTTM on the basis of Green chemistry.
- Admirable green metric correlation with synthesized scaffolds with high atom economy.
- Synthesized derivatives exhibit an excellent mosquito larvicidal activity.