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Efficient and facile synthesis of heterocycles and their mechanistic consideration using kaolin

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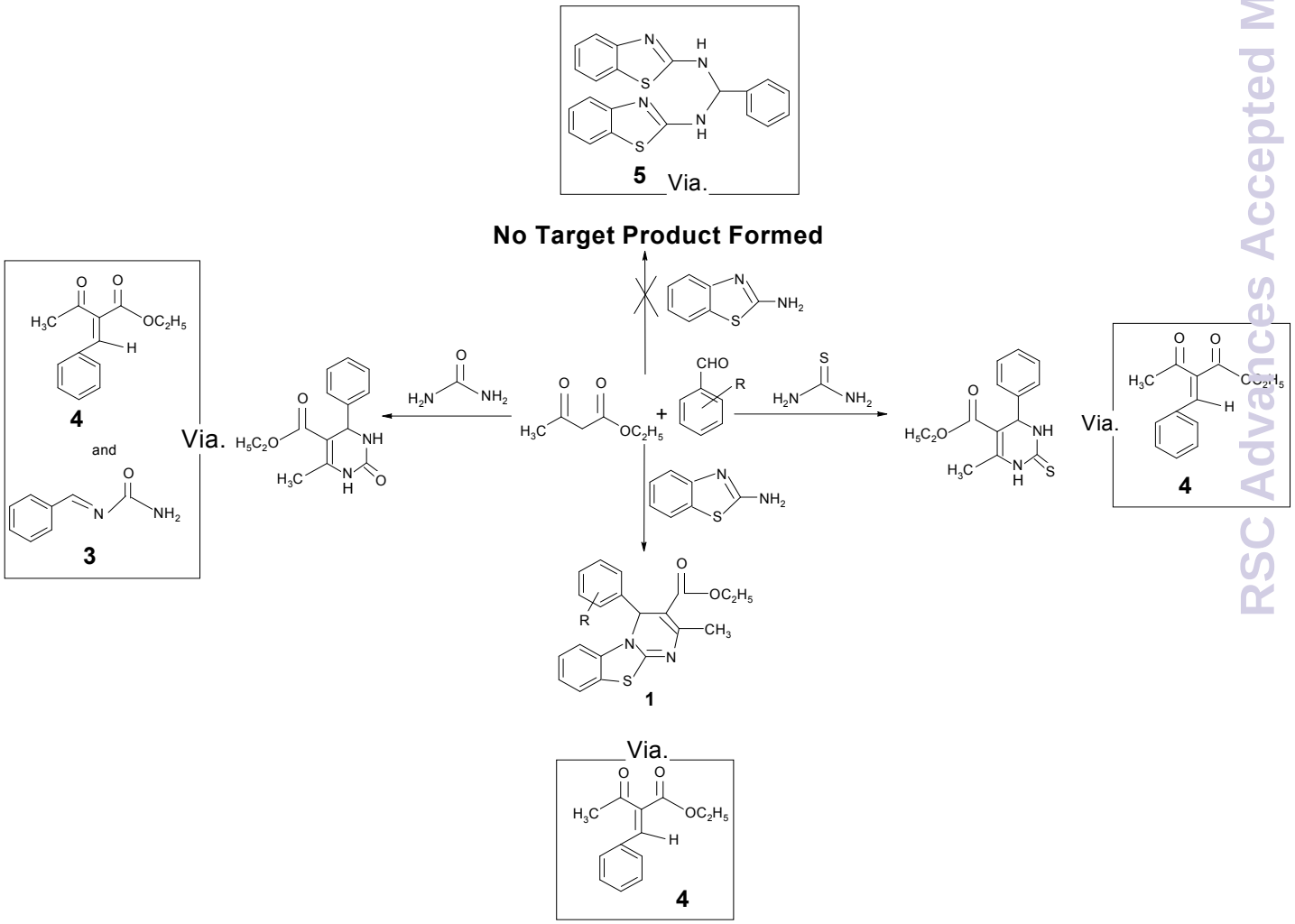
Graphical abstract



Abstract

Kaolin catalyzed solvent-free synthesis for new heterocyclic compounds are described. A series of heterocyclic compounds can be readily obtained using three-component reaction of diketone, aldehydes and 2-amino benzothiazole or urea or thiourea. Mechanism of three component kaolin catalyzed biginelli (using urea and thiourea) and biginelli like (using 2-amino benzothiazole) reaction has been investigated. This is first time that we have isolated and characterized the key intermediates using ^{1}H NMR, ^{13}C NMR and ESI-mass spectral characterization. Imine **3** and Knoevenagel type intermediate **4** were highly suggested as key intermediates for mechanistic study. The reaction is simple, clean and good yield is obtained within minutes.

Keywords: Mechanistic considerations, Isolation and Characterization of Key Intermediate, Kaolin, Solvent free conditions, Heterocycles.

Introduction

Multi-component reactions (MCRs)[1,2] are powerful tool and have attracted much attention of synthetic organic chemists because of the building of complex molecules with diverse range of complexity which can easily be achieved from readily available starting material. Dihydropyrimidines (DHPMs) exhibit interesting pharmacological activities such as anti-inflammatory,[3] anti-microbial,[4] anti-cardiiac,[5] antileishmanial,[6] calcium channel antagonist,[7] TRPV1 antagonists,[8] antimycobacterial,[9] antitubercular.[10] DHPMs also have been reported anticancer and anti HIV agents.[11] Recently many catalysts have been reported to catalyzed the Biginelli reaction such as metal catalysts,[12] iodine,[13] acid catalysts,[14] ultrasonication promoted,[15] lanthanide catalyzed,[16] Zeigler-Natta catalyst,[17] Lewis base,[18] zeolite catalyzed,[19] ionic liquid,[20] Baker's yeast,[21] Nefion-H,[22] Heteropoly acids[23] etc. The drawbacks of these reactions are harsh reaction conditions, long reaction time, lower yield, higher temperature etc.

In recent years, environmental benign industrial chemical process has been developed. In this sense, heterogeneous catalysts play a vital role in the development of cleaner technologies over homogeneous catalyst. These solid catalyst act as good supporting agents, entrain by products and ability to selectivity of product.[24] Aluminosilicate clays are well characterized by their surface acidities, which render them efficient, versatile supports, or catalysts.[25,26] There are extremely limited number of reactions in literature in which kaolin-based or kaolin-assisted reaction are to be reported as catalysts.[27-33] Kaolin, due to its acidic nature, can be a suitable replacement for various homogeneous catalysts. Kaolin has been used as solid catalyst in FCC additives,[27] fluid catalytic cracking catalysts,[28] alkylation,[29] protection reaction of carbonyl compounds,[30] halogenation,[31] biodiesel production,[32] esterification.[33]

Many research groups have developed solvent free synthesis using different catalysts,[34-39] but they have some drawbacks such as poor yield, long reaction time, high temperature, microwave and ultrasonication conditions etc. Although the ultrasonication technology has been shown feasible on a small scale, the commercialization of sonolysis is still a challenge due to its high energy requirement which makes ultrasonication an uneconomical technique.[40] Shaabani et al.[41(a)] have synthesized 4H-pyrimido[2,1-b]benzothiazole derivatives using ionic liquid at 100 ^{o}C with poor yields. Rao et al. have also synthesized these compounds with poor yield, higher reaction time and harsh reaction conditions. [41(b)] The drawback of ionic liquids is that it cannot be removed by distillation and their limited solubility in water restricts their use. They have high cost and also causes acute for aquatic organism and human.[42]

In view of the importance of heterogeneous solid acids as reusable catalysts in organic synthesis and in our continuation of ongoing research to develop heterocyclic compounds,[43] in the present research work, pyrimidines derivatives were synthesized using kaolin as novel solid

catalyst which is rapid, easy to separate, inexpensive and highly efficient. Kaolin used as catalyst led to formation of 82-95% yield. This paper reports this novel recyclable solid catalyst for multi-component reaction of diketone, aldehydes and 2-amino benzothiazole or urea or thiourea.

Results and Discussion

One-pot three component condensation reaction of ethyl acetoacetate, aromatic aldehyde and 2-amino benzothiazole using different catalysts and temperature under similar conditions has been studied to optimize the reaction conditions. Table 1 suggests that reaction took longer reaction time of 48 hours at 30 ^{o}C temperature without catalysts led to poor yield. Then reaction was carried out at 70 and 90 ^{o}C temperature. Hence 70 ^{o}C temperature was found to be optimum temperature. Best result was observed when kaolin as a catalyst was used (Table 1, entry 4). Different acidic and basic catalysts have been tried but most of them gave lower yield except acidic acid (Table 1, entry 12). Moderate yield was obtained when $CeCl_3$ and Al_2O_3 was used (Table 1, entry 10 and 18). Significance yields (55-69 %) were observed for other metal catalysts.

Table 1. Optimization of reaction conditions[a]

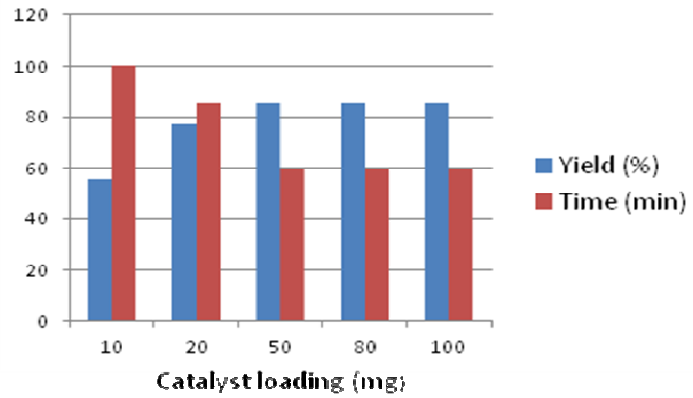
Entry	Catalyst (mol%)	Time (hrs)	Temperature (^{o}C)	Yield% of **1a**[b]
1	No Catalyst	48	30	15
2	No Catalyst	20	70	30
3	No Catalyst	15	90	30
4	Kaolin	1.0	70	85
5	$AlCl_3$	2.0	70	65
6	LiCl	1.1	70	68
7	$SnCl_2.2H_2O$	1.3	70	69
8	$ZnCl_2$	1.4	70	65
9	$Ni(NO_3)_2$	1.4	70	66
10	$CeCl_2$	2.0	70	70
11	$CuCl_2$	1.5	70	69
12	CH_3COOH	2.0	70	69
13	$AgNO_3$	2.0	70	65
13	$MgCl_2$	1.3	70	65
14	$Mg(OH)_2$	4.2	70	63
15	$Al(OH)_3$	3.5	70	69
16	$Ca(OH)_2$	4.0	70	68
17	MgO	5.0	70	65
18	Al_2O_3	4.2	70	71

19	CaO	5.2	70	61
20	$NaHCO_3$	6.0	70	55
21	KOH	6.0	70	59

[a]Condensation of benzaldehyde, ethyl acetoacetate and 2-amino benzothiazole in presence of various catalysts under solvent free conditions.
[b]Isolated yield

In order to evaluate the appropriate catalyst loading, a model reaction of benzaldehyde (0.0025 mol), ethyl acetoacetate (0.0025 mol) and 2-amino benzothiazole (0.0025 mol) was carried out using 10 mg, 20 mg, 50 mg, 80 mg, and 100 mg of kaolin as catalyst at 70 ^{o}C. The catalyst loading 50 mg was found to be the optimal quantity (Fig 2).

Fig 2. Optimization of kaolin as a catalyst



Catalyst was reused four times and the results show that the kaolin can be reused as such without significant loss in its catalytic activity (Table 2). The procedure was easy to work up, efficient and greatly reduced the role of solvent thus reducing environmental pollution.

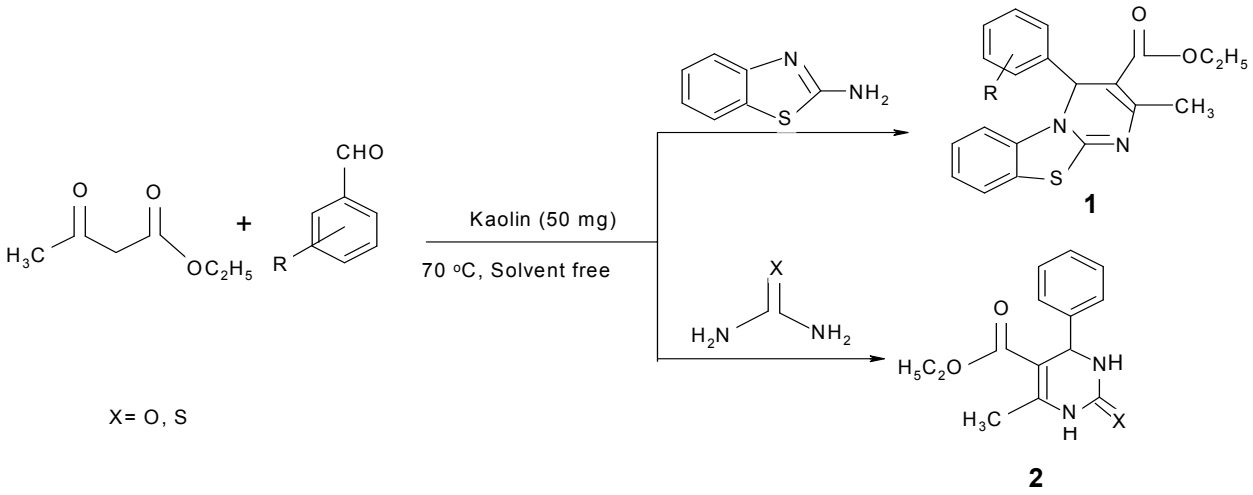
Table 2. Recyclability of Kaolin

Product	Fresh catalyst	Recycled (I)	Recycled (II)	Recycled (III)	Recycled (IV)
1a	85[a]	83[a]	83[a]	82[a]	81[a]

[a]Isolated yield

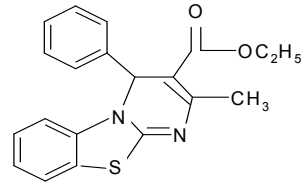
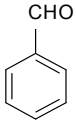
The methodology involves one-pot three component reaction of aldehydes (0.0025 mol), ethyl acetoacetate (0.0025 mol) and 2-amino benzothiazole (0.0025 mol) using kaolin as a catalyst under solvent free conditions at 70 ^{o}C (Scheme 1).

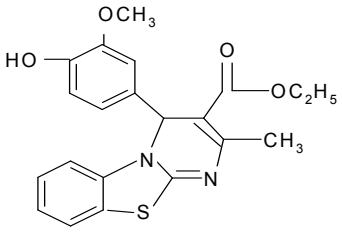
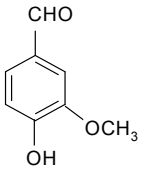
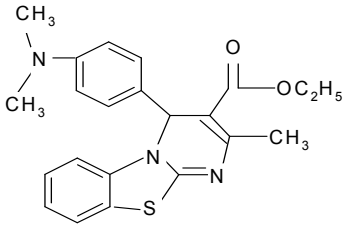
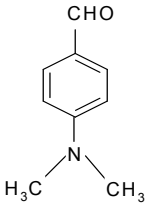
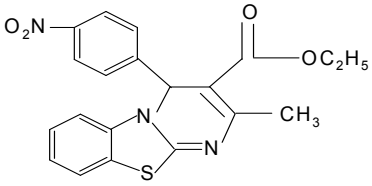
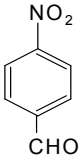
Scheme 1. Preparation of 4H-pyrimido [2,1-b] benzothiazole derivatives and 3,4-dihydropyrimidine-2 (1H)-ones/2 (1H) thione



Reaction was completed within 40-60 min with good yield (Table 3) and the structure of 4H-pyrimido[2,1-b][1,3]benzothiazole derivatives has been characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectra which support the probable structure of target compounds. Using the optimized reaction conditions, 3,4-dihydropyrimidin-2(1H)-one or thione were synthesized using benzaldehyde, ethyl acetoacetate and urea or thiourea (Scheme 1). A variety of electron donating and electron withdrawing groups on phenyl ring of aldehydes have been studied and found no significant effect of subsituents. The reaction using urea and thiourea was faster than that observed using 2-amino benzothiazole. It may be due to steric hinderance of benzothiazole moiety, as sterically hindered substrates proceed slowly.

Table 3. Kaolin catalyzed synthesis of 4H-pyrimido[2,1-b]benzothiazole (1a-1b) derivatives and 3, 4-dihydropyrimidine-2 (1H)-ones/(1H) thione (2a, 2b)

Entry	Products	aldehydes	Yield (%)[a]	Time (min)
1	 **1a**		85	60

2			88	50
	1b			
3			91	40
	1c			
4			89	40
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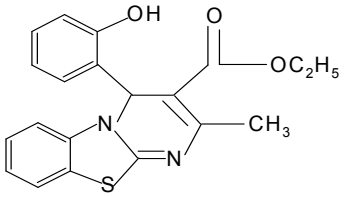
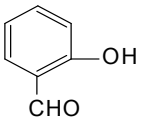
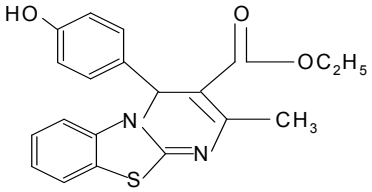
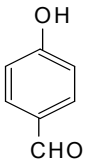
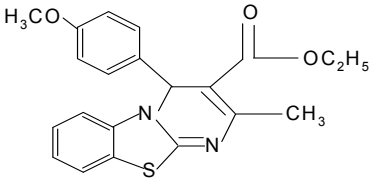
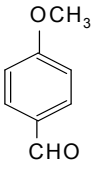
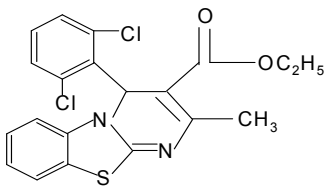
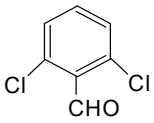
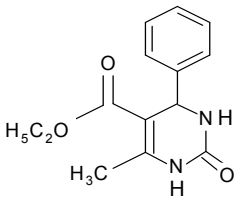
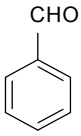
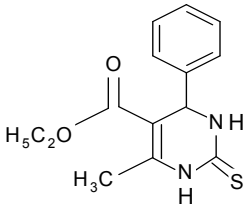
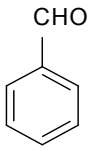
5			83	45
	1e			
6			88	55
	1f			
7			89	40
	1g			

8	 **1h**		82	45
9	 **2a**		95	25
10	 **2b**		93	25

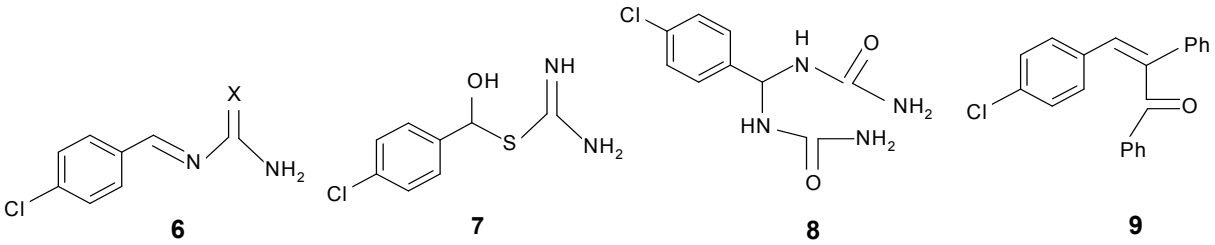
[a]Isolated yield

Mechanistic study

The mechanistic pathway of three components reaction using aldehyde, dicarbonyl and urea could not be established so far due to non characterization of intermediates. In a Previous report, Kappe proposed that Lewis acid or protic acid-mediated Biginelli reaction proceeded via the formation of an imine ion (formed by acid-catalyzed condensation of aldehyde with urea) as a key intermediate rather than carbenium ion intermediate (derived from the acid-catalyzed Aldol reaction of aldehyde and ethyl acetoacetate).[44] Shen et al.[45] have suggested that mechanism of Biginelli reaction proceeded in a different way using t-BuOK but they failed to isolate and characterize the intermediate **6** from the reaction (currently there is no report on the successful isolation of intermediate). Further they have synthesized the intermediate **9** (derived from the acid-mediated condensation of 4-chlorobenzaldehyde and 2-phenyl acetophenone) and intermediates **7** and **8** (using 4-chlorobenzaldehyde and thiourea or urea respectively) under

acidic conditions by the well known method documented in literature[46] (Fig 1) and these intermediates further reacts with third component to give the target product. Shen et al. have synthesized intermediate **8** in toluene solvent using acid-mediated conditions which gave target product with good yield but authors have reported that target product was formed with low yield (15%) in toluene that's why there is minimum possibility to form this type of intermediate in situ reaction because reaction does not proceed well in toluene solvent.

Fig 1. Possible reaction intermediates suggested by Shen et al.

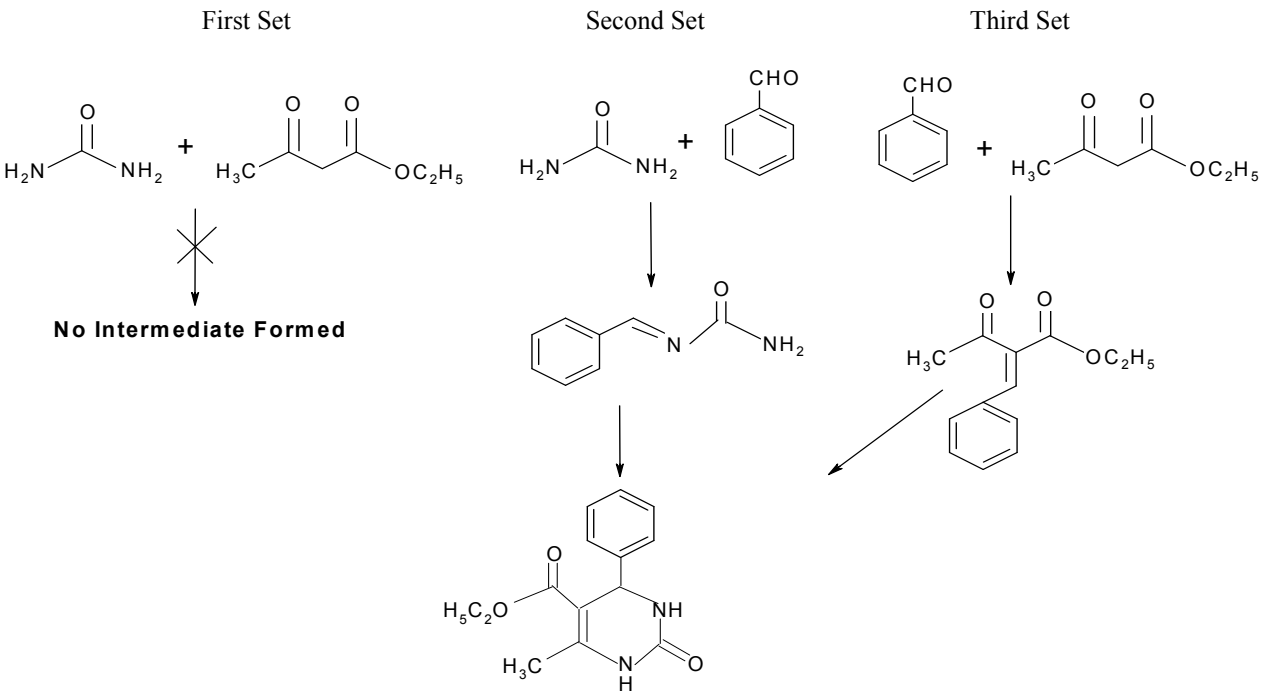


X= O, S

Intermediate **9** proposed by Shen et al. also was prepared in benzene but authors have reported that reaction proceeds well with high yield in protic solvents only hence there is also minimum possibility for this reaction to follow the mechanistic pathway as suggested by Shen et al. Thus author has synthesized all intermediates under different conditions as final product was formed. This shows that there is a need to look for mechanism and intermediates isolation. In the present article, Synthesis was tried with kaolin which is rapid, easy to separation, inexpensive and highly efficient. Reusability of catalyst makes very important criteria over cost and environment pollution. The utility of kaolin as catalyst led to formation of high yield.

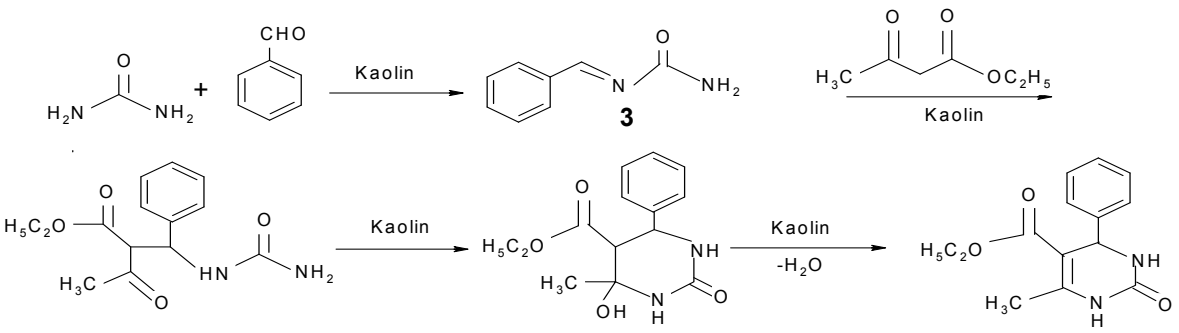
To prove the mechanism of this kaolin-mediated one-pot reaction for synthesis of 3,4-dihydropyrimidin-2(1H)-one/thione, each three set of reactions of two components were carried out (Scheme 2).

Scheme 2. Three set of reaction for preparation of 3,4-dihydropyrimidine-2 (1H)-ones/2 (1H) thione



The intermediate formed was reacted with third component and the product formed was characterized by mp. IR, NMR, and mass spectral studies. It was found that mechanism follow via two different pathway, which gives the product. First pathway i.e. the reaction proceeds in two steps: condensation of bezaldehyde and urea. Then ethyl acetoacetate was reacted with intermediate **3** (characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra) and gives the target product with 65% yield, which is as below;

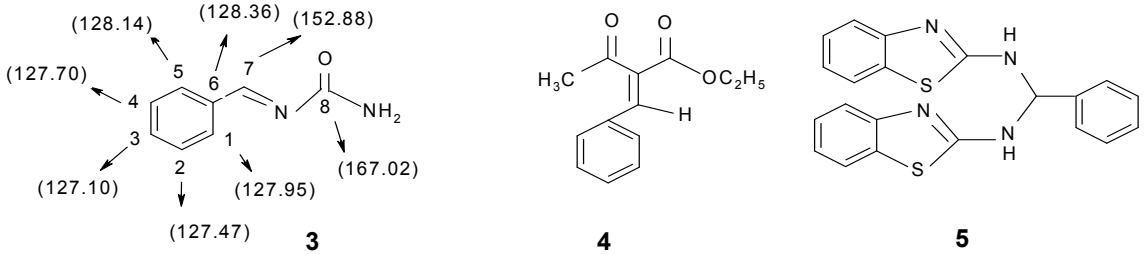
Scheme 3.



Plausible Mechanistic pathway using intermediate **3**

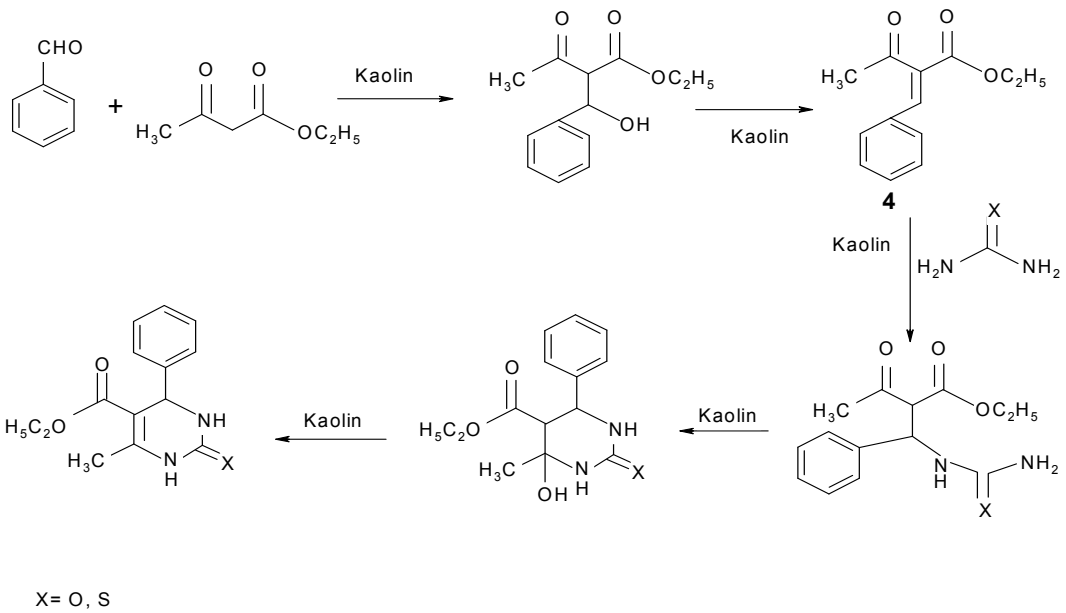
This is for the first time that we have isolated the intermediate **3** (prepared by condensation of benzaldehyde and urea) and the intermediate type **4** was prepared by condensation of ethyl acetoacetate and benzaldehyde and characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral study (Fig 3). Spectroscopic data has confirmed the proposed structure of intermediate **3** and **4**.

Fig 3. Key intermediate for mechanistic study



Second pathway i.e. condensation of aldehyde with ethyl acetoacetate, then urea is reacted with intermediate **4** (prepared by reaction of ethyl acetoacetate and benzaldehyde) and gives target product with 95% yield. Reaction scheme is as follow;

Scheme 4.



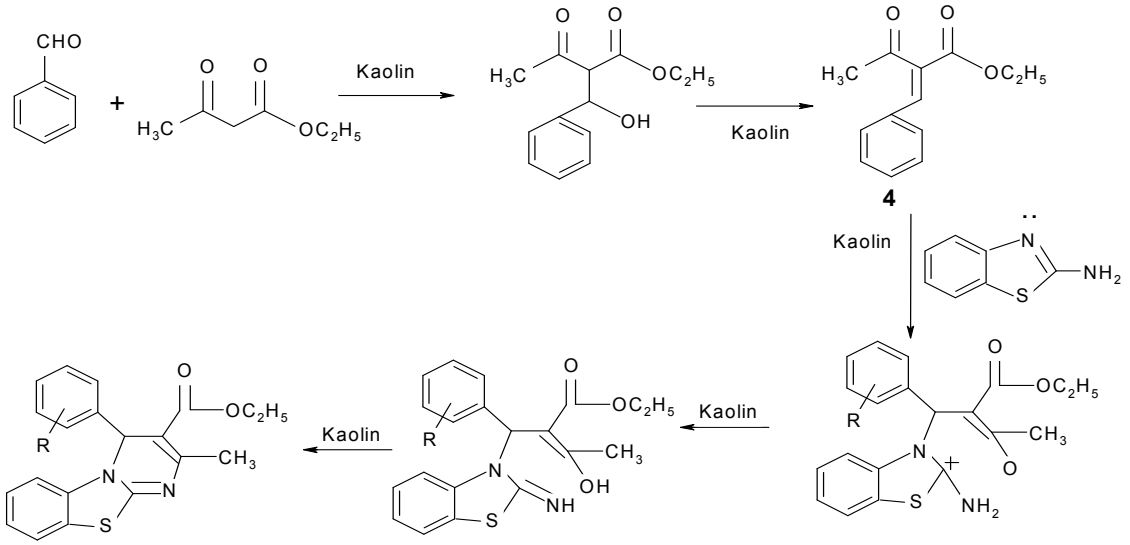
Plausible Mechanistic pathway using intermediate **4**

Characterization data of intermediate **4** was matched with literature.[47] This reveals that first mechanism pathway of reaction gives slightly low yield as compared to second. However, it is interesting that reaction mechanism followed these both routs using intermediates 3 and 4. This is first time that we have isolated and characterized the intermediate (prepared by condensation of benzaldehyde and urea) which is the key intermediate for mechanistic study (Fig 3). In case of dihydropyrimidin-2(1H)-thione, imine type of intermediate (prepared by condensation of benzaldehyde and thiourea) was not isolated and characterized. Sticky material was obtained with thiourea resultant intermediate could not be isolated and characterized. It may be due to the larger atomic size of sulhpur than oxygen in case of dihydropyrimidin-2(1H)-thione. Reaction with thiourea (larger atomic size of sulphur) may be proceeds with slow rate and kinetic of reaction which is not obtained under these reaction conditions. Interestingly this intermediate is not able to form the target product. Only intermediate **4** is formed the final product and follow the mechanistic pathway likewise to synthesis of dihydropyrimidin-2-(1H)-one using urea. It shows the different behavior of urea and thiourea. It may be due to the

difference between atomic size of oxygen and sulphur atoms. Larger atomic size of sulphur may create hindrance in mechanism to form the target molecule resultant reaction was not proceed further. It revealed the involvement of key intermediates which is formed in the first step and responsible for formation of target molecule.

In the similar pattern, three set of reactions of two components each were carried out for synthesis of 4H-pyrimido[2,1-b][1,3]benzothiazole. The intermediate formed was reacted with third component and the product formed was analyzed by mp, IR, NMR and mass spectral studies. It was found that only one set of reaction gave the product i.e. the reaction proceeds in two steps: condensation of bezaldehyde and ethyl acetoacetate according to Knoevenagel type reaction. Then 2-amino benzothiazole is reacted with condensate **4** through Michael addition (**4** characterized by IR, NMR and mass spectra) to afford the target product which is as follow:

Scheme 5.



Plausible Mechanistic pathway using intermediate **4** with 2-amino benzothiazole.

We have successfully isolated the product **5** (prepared by reacting benzaldehyde and 2-amino benzothiazole). The mass fragmentation of compound **5** show $[M-H]^+$ ion peak at 387. ^1H

NMR spectra shows the triplet at 6.99 (-CH), doublet at 7.19 due to two similar hydrogen of –NH and multiplet is observed between 7.37-8.02 due to hydrogen of aromatic rings. This intermediate failed to produce the target product, hence it involvement as intermediate can be ruled out.

Conclusion

It can be concluded that synthesis of compounds containing 4H-pyrimido[2,1-b][1,3]benzothiazole (**1a-1h**) derivatives and 3,4-dihydropyrimidin-2(1H)-one/thione **2a**, **2b** have carried out using one-pot three component reaction of aromatic aldehydes, 1,3-dicarbonyl and urea/thiourea/2-amino benzothiazole in the presence of kaolin as catalyst under solvent free conditions. The operational simplicity, availability of starting materials makes it a rather forward alternative procedure than traditional one. In addition, we have isolated and characterized the Intermediates **3** and **4**. 2-Amino benzothiazole and benzaldehyde has been reacted and resultant product **5** is formed which is successfully isolated and characterized. Overall study show that intermediate **3** and **4** are highly suggested key intermediates for reaction. We have tried the mechanistic study with amine scaffold and observed the different mechanistic behavior due to moiety of amine scaffold (urea/thiourea/2-amino benzothiazole). It shows the dependency of mechanistic behavior on amine scaffold which formed the intermediate in the first step of mechanism.

Experimental section

General

The ^{1}H NMR spectra were measured by BRUKER AVANCE II 400 NMR spectrometer with tretramethylsilane as an internal standard at 20-25 ^{o}C; data for ^{1}H NMR are reported as follow: chemical shift (ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m,

multiplet and br, broad), coupling constant (Hz). IR spectra were recorded by SHIMADZU, IR spectrometer of sample dispersed in KBr pellet and are reported in terms of frequency of absorption (cm^{-1}). E-Merck pre-coated TLC plates, RANKEM silica gel G for preparative thin-layer chromatography were used. Melting points were determined on electrical melting point apparatus in open capillary and were uncorrected. 2-Amino benzothiazole was purchased from Sigma Aldrich and other chemical were purchased from Himedia, Mumbai India.

One-pot three component reaction

Typical procedure. A mixture of aldehydes (0.0025 mol), dicarbonyl (0.0025 mol) and urea/thiourea/2-amino benzothiazole (0.0025 mol) were heated at 70 ^{o}C under solvent free conditions using kaolin (50 mg) as a catalyst. The time taken by different aldehydes in reaction was as mentioned in tables 2. After completion of the reaction (TLC analysis), the reaction mixture was cooled to room temperature and poured in cold water. The solid mass was filtered. It was dissolved in ethanol and filtered. The solid kaolin got separated as solid. The filtrate having product soluble in ethanol was concentrate to crystallize the product. Kaolin was washed with ethanol to remove any organic impurities that may has been present and used in next run.

Recyclability of catalyst

Recycled kaolin was reused for four times as such using benzaldehyde (0.0025 mol), ethyl acetoacetate (0.0025 mol) and 2-amino benzothiazole (0.0025 mol) heated at 70 ^{o}C under solvent free conditions without significant lose in activity.

Synthesis of intermediate 3

A mixture of benzaldehyde (0.0025 mol) and urea (0.0025 mol) were heated at 70 ^{o}C under solvent free conditions using kaolin (50 mg). The reaction was monitored by TLC. After completion of the reaction, mixture was cooled to room temperature and poured in cold water.

The solid mass obtained after filtration was dissolved in ethanol and contents stirred for 5 min. and resulting solution was filtered to separate kaolin. Crude product was recrystallized using methanol to give intermediate **3**.

Synthesis of intermediate 4

A mixture of ethyl acetoacetate (0.0025 mol) and benzaldehyde (0.0025 mol) were heated at 70 ^{o}C under solvent free conditions using kaolin (50 mg). After completion of the reaction (judged by TLC analysis), the reaction mixture was cooled to room temperature and poured in cold water. Filtered the solid mass and dissolved in ethanol to separate the kaolin.

Synthesis of compound 5

A mixture of 2-amino benzothiazole (0.0025 mol) and benzaldehyde (0.0025 mol) were heated at 70 ^{o}C under solvent free conditions using kaolin (50 mg). After completion of the reaction (judged by TLC analysis), the reaction mixture was cooled to room temperature and poured in cold water. Filtered the solid mass and dissolved in ethanol to separate the kaolin. Kaolin was washed ethanol to remove any organic impurities that may has been present.

Ethyl-2-methyl-4-(phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (1a).

Pale-yellow crystals, mp 178-180 ^{o}C, R_f= 0.47 (DCM:Toluene; 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3043 (C-H$_{str}$), 2968 (C-H$_{str}$ in CH_2CH_3), 1670 (C=O$_{str}$), 1589 (C=N$_{str}$), 1462 (C=C$_{str}$), 744 (C-H$_{def}$); ^{1}H-NMR (400 MHz, $CDCl_3$): H ppm 1.29 (3H, t, J_{HH} = 7.12 Hz, $CH_2\underline{CH_3}$), 2.46 (3H, s, $\underline{CH_3}$), 4.17 (2H, m, $\underline{CH_2}CH_3$), 6.39 (1H, s, -$\underline{CH}$), 7.07-7.43 (9H, m, ArH); ^{13}C NMR (100 MHz, DMSO): 165.44, 162.59, 154.04, 141.26, 137.43, 128.26, 126.79, 122.22, 111.65, 102.56, 59.35, 56.82, 23.17, 13.99; ESI-MS: m/z Calculated for $C_{20}H_{18}N_2O_2S$ 350.44, Found $[M+H]^+$ 351.2.

Ethyl-2-methyl-4-(4-hydroxy-3-methoxy phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (1b).

Pale-yellow powder, mp 192-194 ^{o}C, R_f = 0.53 (DCM:Toluene; 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3059 (C-H_{str}), 2983 (C-H_{str} in CH_2CH_3), 1703 (C=O_{str}), 1597 (C=N_{str}), 1504 (C=C_{str}), 740 (C-H_{def}); ^{1}H-NMR (400 MHz, $CDCl_3$): H ppm 1.31 (3H, t, J_{HH} = 7.12 Hz, $CH_2\underline{CH_3}$), 2.47 (3H, s, $\underline{CH_3}$), 3.8 (3H, s, Ar-O$\underline{CH_3}$), 4.12-4.19 (2H, m, $\underline{CH_2}CH_3$), 6.36 (1H, s, -$\underline{CH}$), 6.78 (1H, d, J_{HH} = 5.6 Hz, $\underline{ArH}$), 6.89-6.92 (2H, m, $\underline{ArH}$), 7.13-7.31 (4H, m, $\underline{ArH}$), 9.80 (1H, s, $\underline{OH}$); ^{13}C NMR (100 MHz, DMSO): 165.60, 162.34, 153.51, 147.12, 146.42, 137.61, 132.52, 126.37, 122.21, 115.18, 111.92, 110.88, 59.28, 55.43, 23.09, 14.08; ESI-MS: m/z Calculated for $C_{21}H_{20}N_2O_4S$ 396.49, Found $[M+H]^+$ 397.2.

Ethyl-2-methyl-4-(4-dimethylamino phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (1c).

Pale-yellow powder, mp 175-178 ^{o}C, R_f = 0.57 (DCM:Toluene; 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3059 (C-H_{str}), 2897 (C-H_{str} in CH_2CH_3), 1612 (C=O_{str}), 1581 (C=N_{str}), 1431 (C=C_{str}), 815-754 (C-H_{def}); ^{1}H-NMR (400 MHz, $CDCl_3$): H ppm 1.29 (3H, t, J_{HH} = 7.12 Hz, $CH_2\underline{CH_3}$), 2.86 (3H, s, $\underline{CH_3}$), 3.06 (6H, s, N($\underline{CH_3}$)$_2$), 4.15 (2H, m, $\underline{CH_2}CH_3$), 6.71-7.5 (4H, m, $\underline{ArH}$), 7.71-7.92 (4H, m, $\underline{ArH}$); ^{13}C NMR (100 MHz, DMSO): 166.39, 165.44, 153.95, 152.63, 133.43, 127.71, 125.91, 124.45, 121.63, 120.57, 23.13, 13.60; ESI-MS: m/z Calculated for $C_{22}H_{23}N_3O_2S$ 393.54, Found $[M+H]^+$ 394.2.

Ethyl-2-methyl-4-(4-nitro phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (1d).

Yellow powder, mp 170-172 ^{o}C, R_f = 0.52 (DCM:Toluene; 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3348 (C-H_{str}), 2933 (C-H_{str} in CH_2CH_3), 1625 (C=O_{str}), 1510 (C=N_{str}), 1267 (C=C_{str}), 962-812 (C-H_{def}); ^{1}H-NMR (400 MHz, $CDCl_3$): H ppm 1.31 (3H, s, $CH_2\underline{CH_3}$), 2.46 (3H, s, $\underline{CH_3}$), 4.15 (2H, m, $\underline{CH_2}CH_3$), 6.52 (1H, s, -$\underline{CH}$), 7.03-7.63 (8H, m, $\underline{ArH}$); ^{13}C NMR (100 MHz, $CDCl_3$): 166.25,

163.56, 155.83, 147.95, 147.62, 137.44, 128.06, 126.88, 124.43, 124.01, 123.73, 122.47, 111.36, 102.01, 60.42, 57.03, 23.97, 14.40; ESI-MS: m/z Calculated for $C_{20}H_{17}N_3O_4S$ 395.46, Found $[M+H]^+$ 396.4.

Ethyl-2-methyl-4-(2-hydroxy phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (1e).

Pale-yellow powder, mp 212-215 ^oC, R_f = 0.53 (DCM:Toluene; 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3028 ($C\text{-}H_{str}$), 2810 ($C\text{-}H_{str}$ in CH_2CH_3), 1668 ($C{=}O_{str}$), 1575 ($C{=}N_{str}$), 1485 ($C{=}C_{str}$), 837-750 ($C\text{-}H_{def}$); ^{1}H-NMR (400 MHz, DMSO): H ppm 1.29 (3H, t, J_{HH} = 4.76, $CH_2\underline{CH_3}$), 2.45 (3H, s, $\underline{CH_3}$), 4.1-4.19 (2H, m, $\underline{CH_2}CH_3$), 6.33 (1H, s, -CH), 6.66-7.92 (8H, m, ArH), 8.9 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO): 171.88, 165.92, 162.99, 157.23, 151.33, 133.73, 128.14, 126.08, 122.92, 116.07, 59.26, 56.23, 23.11, 14.04; ESI-MS: m/z Calculated for $C_{20}H_{18}N_2O_3S$ 367.34, Found $[M]^+$ 367.2.

Ethyl-2-methyl-4-(4-hydroxy phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (1f).

Pale-yellow powder, mp 210-212 ^oC, R_f = 0.59 (DCM:Toluene; 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3288 (OH_{str}), 3059 ($C\text{-}H_{str}$), 2897 ($C\text{-}H_{str}$ in CH_2CH_3), 1612 ($C{=}O_{str}$), 1581 ($C{=}N_{str}$), 1431 and 1377 ($C{=}C_{str}$), 815-754 ($C\text{-}H_{def}$); ^{1}H-NMR (400 MHz , $CDCl_3$): H ppm 1.25 (3H, t, J_{HH} = 4.76 Hz, $\underline{CH_3}CH_2$), 2.35 (3H, s, $\underline{CH_3}$), 4.04-4.12 (m, 2H, $CH_3\underline{CH_2}$), 6.30 (1H, s, -CH), 6.66 (2H, d, J_{HH} = 8.40 Hz, ArH), 7.13-7.59 (5H, m, ArH), 7.59 (1H, d, J_{HH} = 7.76 Hz, ArH), 9.26 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO): 165.55, 162.27, 157.22, 153.46, 137.56, 131.95, 128.13, 126.34, 123.57, 122.94, 122.20, 115.02, 111.80, 102.96, 59.27, 56.37, 23.09, 14.03; ESI-MS: m/z Calculated for $C_{20}H_{18}N_2O_3S$ 367.34, Found $[M]^+$ 367.2.

Ethyl-2-methyl-4-(4-methoxy phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate

(1g).

Pale-yellow powder, mp 130-132 ^{o}C, R_f = 0.53 (DCM:Toluene; 3:2); IR (KBr) (υ_{max}, cm^{-1}): 2941 (C-H_{str} in CH_2CH_3), 1627 (C=O_{str}), 1508 (C=N_{str}), 1280 (C=C_{str}), 962-813 (C-H_{def}); ^{1}H NMR (400 MHz, $CDCl_3$): H-ppm 1.28 (3H, t, J_{HH} = 4.76 Hz, $\underline{CH_3}CH_2$), 2.45 (3H, s, $\underline{CH_3}$), 3.71 (3H, s, Ar-O$\underline{CH_3}$), 4.11-4.21 (2H, m, $CH_3\underline{CH_2}$), 6.34 (1H, s, -CH), 6.78 (2H, d, J_{HH} = 8.64 Hz, ArH), 7.21-7.58 (6H, m, ArH); ^{13}C NMR (100 MHz, DMSO): 166.67, 163.27, 159.42, 154.51, 152.07, 138.06, 133.81, 128.51, 126.57, 123.88, 123.82, 122.14, 120.89, 119.04, 113.90, 111.80, 103.24, 60.09, 57.20, 55.18, 23.73, 14.40; ESI-MS: m/z Calculated for $C_{21}H_{20}N_2O_2S$ 380.47, Found $[M+H]^+$ 381.3.

Ethyl-2-methyl-4-(2, 6-dichloro phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (1h).

Pale-yellow powder, mp 150-152 ^{o}C, R_f = 0.56 (DCM:Toluene; 3:2);); IR (KBr) (υ_{max}, cm^{-1}): 3012 (C-H_{str}), 2922 (C-H_{str} in CH_2CH_3), 1625 (C=O_{str}), 1500 (C=N_{str}), 1278 (C=C_{str}), 960-812 (C-H_{def}); ^{1}H-NMR (400 MHz, DMSO): H ppm 1.09 (3H, t, J_{HH} = 4.76 Hz, $CH_2\underline{CH_3}$), 2.47 (3H, s, $\underline{CH_3}$), 4.04 (2H, m, $\underline{CH_2}CH_3$), 7.01-7.66 (7H, m, Ar-H); ^{13}C NMR (100 MHz, DMSO): 171.88, 165.92, 162.99, 151.33, 137.57, 133.73, 132.41. 129.14, 126.08, 125.57, 124.52, 122.97, 121.69, 117.66, 116.07, 59.26, 23.11, 14.04; ESI-MS: m/z Calculated for $C_{20}H_{16}N_2Cl_2O_2S$ 419.41, Found $[M]^+$ 419.6.

5-ethoxycarbonyl-4-pheyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 2a

Yellow powder, mp. 204-206 ^{o}C, R_f = 0.53 (DCM : Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3245, 3118, 2987, 1725, 1701, 1649; ^{1}H NMR (400 MHz, $CDCl_3$): H-ppm 1.06 (3H, t, J = 6.84 Hz, CH_3), 2.24 (3H, s, CH_3), 3.94 (2H, q, J = 6.75 Hz, CH_2,), 5.13 (1H, d, J = 3.06 Hz, H-4,), 7.21-7.37 (5H, m, Ar-H), 7.73 (1H, brs, NH), 9.19 (1H, brs, NH) ESI-MS: m/z Calculated for

$C_{14}H_{16}N_2O_3$ 260.32 Found $[M+H]^+$ 261.1.

Intermediate 3

Off white powder, mp 225-226 ^oC, Rf = 0.69 (toluene : ethyl acetate 2:3); ^1H-NMR (400 MHz, $CDCl_3$): H ppm 2.12 (2H, s, $-NH_2$), 2.54 (1H, s, -CH), 7.19-7.62 (5H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.02, 152.88, 128.36, 128.14, 127.95, 127.70, 127.47, 127.10; ESI-MS: m/z Calculated for $C_8H_8ON_2$ 148.3, Found $[M+H]^+$ 149.4.

Intermediate 4

Off white powder, mp 78-80 ^oC, Rf = 0.72 (hexane : methanol 2:3), ^1H-NMR (400 MHz, $CDCl_3$): H ppm 1.29 (3H, t, J = 14.24 Hz, CH_2CH_3), 2.46 (3H, s, CH_3), 4.17 (2H, m, CH_2CH_3), 6.39 (1H, s, =CH), 7.07-7.43 (5H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 200.71, 164.16, 140.09, 137.16, 134.65, 134.01, 132.73, 129.49, 128.75, 61.29, 29.72, 13.71; ESI-MS: m/z Calculated for $C_{13}H_{14}O_3$ 218.3, Found $[M+H]^+$ 219.5.

Intermediate 5

Off white crystal, mp 117-119 ^oC, Rf = 0.61 (Hexane : Methanol 1:1); ^1H-NMR (400 MHz, $CDCl_3$): H ppm 6.99 (1H, t, J = 6.96 Hz, -CH), 7.19 (2H, d, J = 6.72 Hz , NH), 7.37-8.02 (13H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 132.41, 130.86, 129.35, 128.15, 125.25, 120.77, 120.521, 117.69; ESI-MS: m/z Calculated for $C_{21}H_{16}N_4S_2$ 388.52, Found $[M-H]^+$ 387.2.

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Efficient and facile synthesis of heterocycles and their mechanistic consideration using kaolin

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Graphical abstract