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Multicomponent Synthesis Of 4-H-Pyrimido [2, 1-b] Benzothiazole Derivatives Of Curcumin Using Hydrotalcite (Pb-Al-CO_3) As Catalyst.

[1]Rita Singh, [2]D.D. Agarwal & [3]M.C. Agarwal
[1,3]Deptt. of Chemistry, SMS Govt. Model Science College, Gwalior, M.P. India
[2]SOS Chemistry, Jiwaji University, Gwalior, M.P. India
Email- ritakrishna.singh3@gmail.com

Abstract
Synthesis of 4H-pyrimido [2,1-b]benzothiazole derivatives of curcumin by using multicomponent reaction using substituted aromatic aldehyde, 2-aminobenzothiazole and curcumin has been carried out in the presence of Al-Pb-CO_3hydrotalcite as a heterogeneous solid catalyst which is recyclable under solvent free condition. The hydrotalcite need short reaction time, non-toxic , reusable and easy to workup. Thus making this process environmentally friendly. 4H- pyrimido[2,1-b] benzothiazole derivatives of curcumin are potential molecules having good antibactaroal, anti-inflammatory, antimicrobial, and cancer preventive properties.
Keywords: Multicomponent synthesis, Al-Pb-CO_3hydrotalcite , solvent free condition.

1- INTRODUCTION

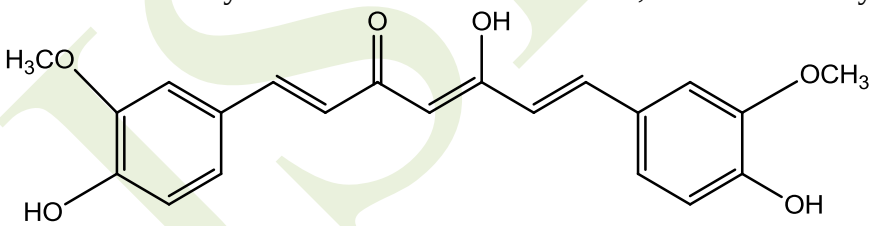
Multi-component Reaction (MCRs) is a one step reaction that combines two or more reactants to form an end product [(1-7)]. Since a MCR forms a product in one step; it generates considerably less waste than a multi- step synthesis. In a fastidious way, this diversity oriented multicomponent reactions have been found in broad applications in the pharmaceutical industry [(8)]. In the Consequence of this, systematic attempts are focused on multicomponent procedures for development of heterocyclic compounds libraries in the last few years on Diversity Oriented synthesis. As a one –pot reaction, multicomponent reactions usually provides excellent yield with shorter duration and are fundamentally different from two- component and many step reactions [(9)], and this allowed a rapid use to combination of complex organic compounds for an efficient lead structure identification and most effective use in drug discovery [(10)]. Importance from the point of view of green chemistry, multicomponent reactions are constituting a very useful class of tools for the synthesis of new compounds. Multicomponent reactions have been recently discovered a very good and attractive tool due to the formation of carbon – carbon and carbon – heteroatom in one – pots [(11-14)].

Hydrotalcites are a very absorbing metal hydrotalcites . They are extensively used as catalyst support and reagents [(15)]. The extreme significance, in multicomponent reactions is perceived in recent decades. It has been developed as combinatorial and medicinal –oriented chemistry. Since their high capability and advantages in comparison with multistage process. From this point of view, the scientific attempts are focused on multicomponent procedures for development of heterocyclic compounds, in last few decades [(16)].

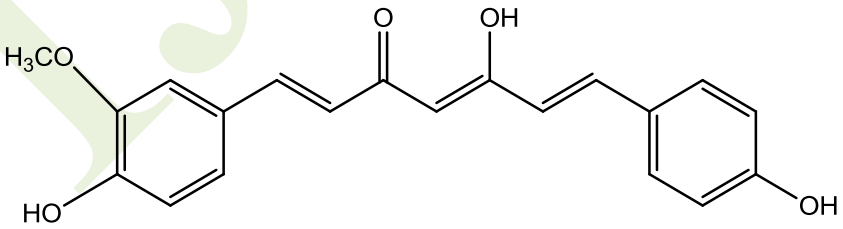
A model multicomponent reaction affects the simultaneous reagents, reactants and catalysts in the reaction formation, and

depends that all reactants couple in a selective ordered approaches under the same reaction condition [17]. The increasing attention from the last few decades towards the environmental conservation; and influenced the both academic and industrial areas. This elaborate the chemical processes, which gives excellent yield reduced the cost of raw materials, short time duration, use of non-toxic reagents and non-hazardous solvents. So one of the most important apparatus for such required of time is multicomponent reactions. This procedure consists of one or two systematic steps which carried out without any intermediate [19]. Thus, it is a simple procedure high bond energy saving and low expenditures are advantages of these reaction [18-20].

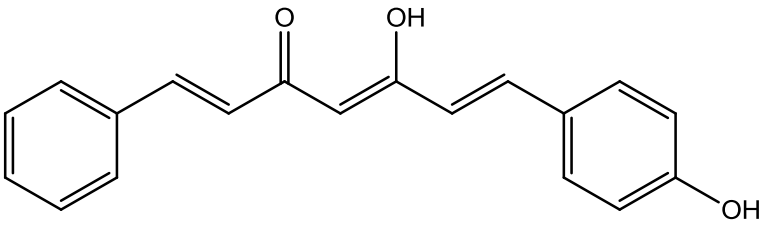
In this regard; multi-component reaction one of increasing importance to develop and synthesize the novel target compound in one –pot synthesis using easily available reactant material [21,22]. Multicomponent reactions are used in the syntheses of heterocyclic compounds that are a realm of classic carbonyl condensation chemistry [23]. Pyrimidines have attracted a notable interest because of their wide range of biological activities [24]. Some of which have anti-viral [25], anti-tumar[26], anti-inflammatory[27], anti-hypertensive activities[28-30], calcium channel modulators[31-34] and anti-microbial agents[35-39]. Curcumin was first isolated in **1815**, obtained in crystalline form, in 1870, and identified as 1,6,-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E-6E) or diferuloylmethane. The feruloylmethane skeleton, of curcumin was subsequently confirmed in **1910**. This is initially synthesised by **Lampe** [40]. The major curcuminoids present in turmeric are dimethoxycurcumin (curcuminll), bisdimethoxycurcumin(curcuminlll), and the recently identified cyclocurcumin (curcuminVl) (Scheme1). The curcuminnoid complex is also known as Indian saffron, yellow ginger, yellow root, kacchihaldi, ukon or natural yellow [41].



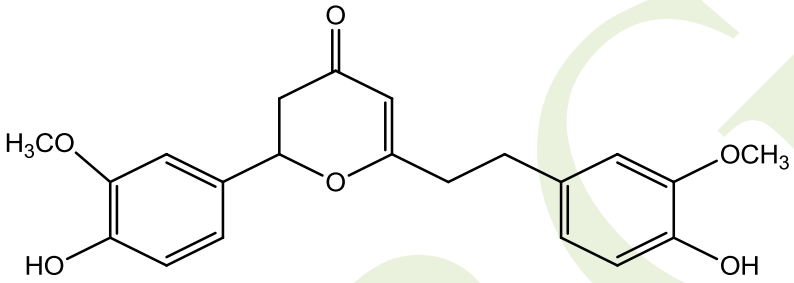
Curcumin curcumin(l)



Dimethoxycurcumin curcumin (ll)



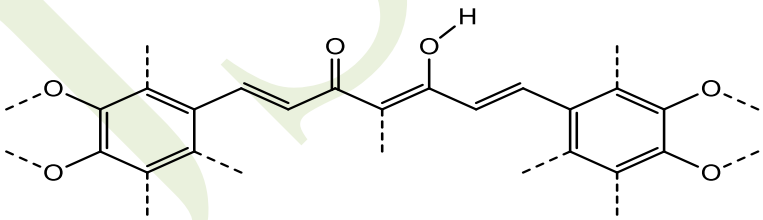
Bisdemethoxycurcumin curcumin (lll)



cyclocurcumin curcumin(lV)

Scheme 1: Various structure of curcumin present in curcuminoids form

Resent high- level, ab, initio and computationally intensive calculation have shown that the optimized structure of curcumin is planar or Linear [42]. The enol form has been found to be the stable ground state and in the optimized structure of the methoxy groups are seen pointing in the opposite direction with respect to the 1,3- keto – enol group as shown in scheme-2.



Scheme2: Possible sites for structural modification in curcumin and strategy for curcumin analogues preparation.

4-H-pyrimido benzothiazole derivatives of curcumin describes an important class of compound existence the main component of many commonly arising products, and are considerably used as cosmetic, antiseptic [43] and in pharmaceutical industry [44]. Derivatives of 4-H-benzothiazole derivatives of curcumin possess anti-inflammatory [45], anti-oxidant [46,47], anti-HIV protease [48], anti-microbial[49], acetyl cholinesterase[50], anti-malarial[51], antibacterial [52], and cancer preventive properties[53,54] . The comprehensive research has appeared that this polyphenol compound can both treat and prevent cancer disease [55-58].

These compounds are mostly prepared by curcumin in the absence of organic solvents. Currently a methodology is reported which depends on the use of hydrotalcite in the

synthesis of pyrimidine derivatives of curcumin[59]. From last few years, a lot of reactions have been performed under extensive verity of condition and several improvements for the experimental procedures have been made. Although it has been normally catalyzed by **Lewis** and **Bronsted**acid and base [60]. Such type of reaction has been catalyzed by various other catalysts such as Baker's yeast [61], Zeolites [62], ionic liquids [63] and metal oxides [64].

Elias *et al*[65] have reported the synthesis pyrimidine by microwave assisted reaction of curcumin with either primary amines or the amino acetate in the presence of montmorillonite K-10 as a catalyst with poor yield. **Shaabani*et al***[66] have synthesized 4H-pyrimido [2, 1-b] benzothiazole derivatives using an ionic liquid at $100^{O}C$ with poor yield. The disadvantage of ionic liquid is that they cannot be separated by distillation and their limited solubility in water. They are very costly and toxic for aquatic organism and humans [67]. **Rao*et al***[68] have also synthesized these types of derivatives, which suffer from drawbacks, such as toxic solvents, long reaction times, harsh reaction conditions and low yield. Various derivatives of curcumin has been synthesized and cross-examined for their anti-fungal and anti-bacterial activities [69, 70].

Literature survey exposed that researchers have synthesized the derivatives of curcumin i.e. 4-ethoxycarbonylethyl curcumin analogues [71], hydrozinocurcumin[72], mixed bio-conjugates of curcumin[73], knoevenagel condensates [74], pyrazoles and oxazoles[75], semicarbazones[76], but our interest lies in the development of curcumin derivatives using multicomponent reaction. Phenolic (–OH) and methylene hydrogen of curcumin exhibited the antioxidant activity by free radical reaction [77].

So the aim of the present multicomponent reaction is to use, like as biologically important component, curcumin and 2-aminobenzothiazole to convert it into another pyrimidine which is potential antibacterial. The synthesized molecules have efficient antibacterial activity (i.e. MIC value 2.5µm/ml). Thus our results are better than reported in literature for curcumin and that MIC values reported by **Mishra *et al***[78]. Our target molecules have shown good antibacterial activity (3µm/ml) against P. Aeruginosa as compared to activity was not shown by **Gin *et al***[79].

Therefore, We have developed a very clean and cost effective method for the synthesis of product 4-phenyl-4Hpyrimido [2,1-b][1,3]benzothiazolecurcumin by the condensation of aromatic aldehyde, curcumin and 2-amino benzothiazole using hydrotalcite as catalyst under solvent free condition. This procedure is very simple, easy work-up, short time duration and inexpensive catalyst is an important feature of this procedure.

2- EXPERIMENTAL SECTION

2.1- General Characterization Techniques

The ^{1}H NMR spectra are measured by BRUKER AVANCE II 400 NMR spectrometer with tetramethylsilane as an internal standard. ^{1}H NMR data are reported as follows: Chemical shift (ppm), integration, multiplicity (s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet and br-broad) and Coupling constant (Hz). Infra Red (IR) spectra are recorded by SHIMADZU IR spectrometer. The samples of IR spectrometer are dispersed in KBr pellets and are reported in terms of frequency of absorption (cm^{-1}). E-Merck Pre-coated TLC plates, Rankem silica gel G are used for the preparation of thin layer liquid chromatography. Melting points are determined in open capillaries and are uncorrected.

2.2- List of Chemical used and their Sources

Chemicals	**Source**
BenzaldehydeRankem	
3-Chlorobenzaldehyde	Himedia
2,4-dichlorobenzaldehyde	Himedia
2-nitrobenzaldehyde	Himedia
4-nitrobenzaldehyde	Himedia
3-hydroxybenzaldehyde	Himedia
p-hydroxybenzaldehydeHimedia	
4-methoxybenzaldehyde	Himedia
CurcuminHimedia	
2-Aminobenzothiozole	Sigma-Aldric
Aluminium chloride	Fisher Scientific
Sodium carbonate	Rankem
Lead hydroxide	Merck
Aluminium nitrate	Fisher Sientific
Nickel chloride	Rankem
Cerium nitrate	Merck
Sodium hydroxide	Fisher Sientific

Beside these chemicals we synthesized hydrotalcite for the use as catalyst.

2.3- Preparation of hydrotalcite Pb-Al-CO_3:

Hydrotalcite Pb-Al-CO_3 is prepared by one-pot co-precipitation reaction at 100^0C, autogenous pressure for 30-35 minutes and in aqueous medium and obtained a small and high surface area particles. In this procedure Pb-chloride and Al-chloride (in metallic ratio 3:1) are taken sodium carbonate was added and the pH of the reaction was maintained at 8.5. After this the slurry was aged for 12hours. After that mixture obtained white precipitate was filtered and washed many time with distill water to remove the alkali metal and anions. The solid was dried in oven at 100^0C for overnight.

M^{II}-X (aq) + M^{III}-X (aq) + Na_2CO / NaOH (aq)

100^0C ↓ p H-8.5

Hydrotalcite

Dried at 100^0C ↓(24hr.)

Hydrotalcite

(White powder form)

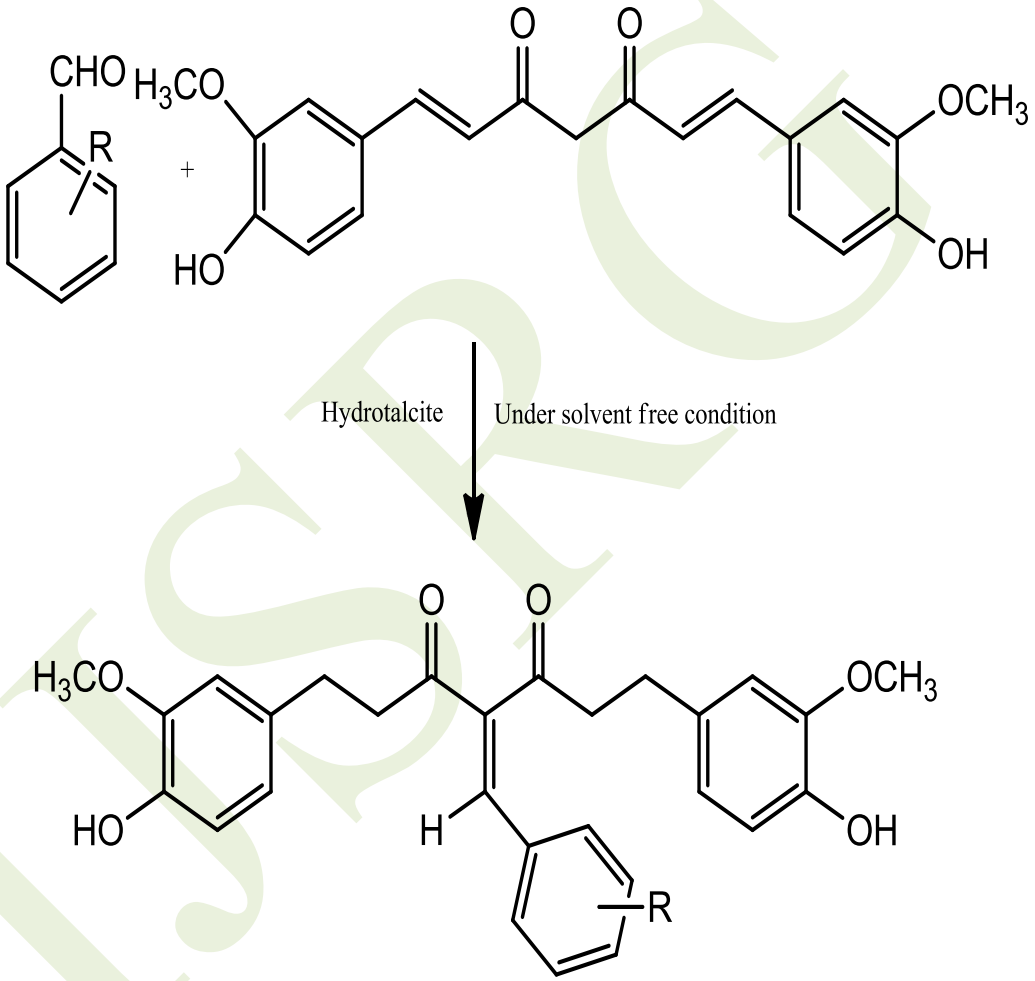
Scheme 3.1: Synthesis of hydrotalcite by co-precipitation method

2.4- Synthesis of 4H-pyrimido [2,1-b]benzothiazole derivatives of curcumin using hydrotalcite (Pb-Al-CO_3) as catalyst :

One-pot three component condensation reaction, A mixture of aromatic aldehyde (0.05 mol), 2-amino benzothiazole (0.05 mol) and curcumin (0.05 mol) was refluxed at 65-70^0C under solvent free condition in the presence of hydrotalcite Pb-Al-CO_3. The reaction was monitored by TLC. After completion the reaction, mixture was cooled at room temperature then poured into cold water and filtered. Product was purified by column chromatography with ethyl acetate and methanol (6:4). The solid was recrystallized by ethylacetate. The products of 4H-pyrimido benzothiazol derivatives of curcumin were collected as reddish yellow crystals.

2.5- Synthesis of intermediate

A mixture of aromatic aldehyde (0.05 ml) and curcumin (0.05 mol) was refluxed at 65-70^{0}C under solvent free condition using Pb-Al-CO_3 as a catalyst. The reaction was monitored by TLC (ethyl acetate / methanol 6:4). After completion the reaction product was washed with cold water and filtered. The product was purified by column chromatography using ethyl acetate and methanol (6:4). The solid mass was recrystallised by ethyl acetate. The intermediate product (scheme 3.2) was obtained as reddish yellow crystals. This was characterized by Mass, IR and NMR spectra.



Scheme 3.2 proposed intermediate reaction using hyrotalcite Pb-Al-CO_3

2.6- Recycling of the hydrotalcite catalyst

After the end of the reaction, the catalyst hydrotalcite (Pb-Al-CO_3) can be recovered by filtration. The obtained catalyst was washed several times with water and used second time in the reaction without a significant loss of yield. The reuse of catalyst reduced the cost of the total product yield. Thus, the product yield of the reaction after using this catalyst four times shows a small reduction.

Table 3.1 Recycling of the hydrotalcite catalyst (Pb-Al-CO_3)

Product	FreshCatalyst (Pb-Al-CO_3)	Catalyst (Pb-Al-CO_3) (1^{ST} Recycle)	Catalyst (Pb-Al-CO_3) (2^{nd} Recycle)	Catalyst (Pb-Al-CO_3) (3^{rd} Recycle)
3a	84 %	82%	81%	80%

Reaction condition: aromatic benzaldehyde (0.05mol), 2-amino-benzothiazol (0.05mol), curcumin (0.05mol) and 0.1mg hydrotalcite at 70^0C under solvent free condition.

3- RESULT AND DISCUSSION

3.1- Effect of Hydrotalcite catalysts

In the initial experiments, one-pot three component condensation reaction of aromatic aldehyde (0.05mol), 2-aminobenzothiazol (0.05mol) and curcumin (0.05mol) was refluxed under solvent free condition in the absence of catalyst, no product was obtained. In the presence of 0.1mg of catalyst hydrotalcite Pb-Al-CO_3 highest yield was obtained (84%). Although, Table 3:1 shows that minimum yield (10%) was obtained when hydrotalcite Al-Ca-SO_4 was used. The use of other hydrotalcites gave yield in the range of 35-60%. The reaction shows that the yield of the product is dependent on the nature of the metal (M^{+2} and M^{+3}) of the catalyst. Thus, this suggests that metal ions play an important role.

Table.3.2 Optimization of reaction condition using various catalysts.

Entry	Catalyst	Time (hours)	Yield (%)
1	No catalyst	8.00	No product
2	Ce-Ni-Cl_2	5.30	No product
3	Al-Ca-SO_4	6.45	15
4	Al-Ni-NO_3	6.30	42
5	Al-Mn-CO_3	7.00	59
6	Pb-Al- CO_3	4.00	84
7	Al-Mg-SO_4	8.00	35

Reaction condition: aromatic benzaldehyde (0.05mol), 2-amino-benzothiazol (0.05mol), curcumin (0.05mol) and 0.1mg hydrotalcite at 70^0C under solvent free condition.

3.2- Effect of Catalyst concentration on the reaction

In the initial experiments, In order to find out optimum amount of catalyst for the reactions. Different set of reactions containing various amount of catalyst were carried out from 0.05 to 0.2mg. For the imitation reaction between substituted aromatic aldehydes (0.05mol), 2-amino-benzothiazole (0.05mol) and curcumin (0.05mol) at 70^0C under solvent free condition for 4.00 hours. The yield of the target product increases phenomenally from 0.05mg-0.1mg with increase in catalyst amount. When the catalyst amount increased from 0.1-0.2mg no further improvement in the yield of the product was observed. Consequently, the most optimal amount of catalyst was 0.1g selected for all the subsequent reactions.

Table 3.3 Optimization of catalyst concentration

Entry	Catalyst (mg)	Yield (%)
1	0.050	15
2	0.075	45
3	0.085	75
4	0.10	84
5	0.50	84
6	0.20	84

Reaction condition: aromatic benzaldehyde (0.05mol), 2-amino-benzothiazol (0.05mol), curcumin (0.05mol) and 0.1mg hydrotalcite at 70^0C under solvent free condition

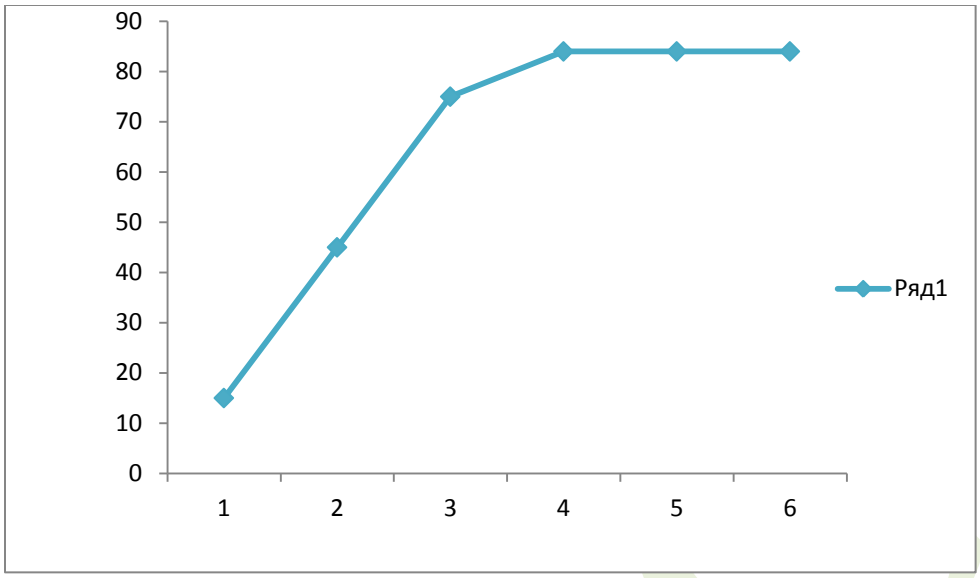


Fig. 3.1 Catalyst concentration effect on reaction

3.3- Effect of temperature on the reaction (^{0}C)

One-pot three component condensation reactions of substituted aromatic benzaldehyde (0.05mol), 2-amino-benzothiazol (0.05mol) and curcumin (0.05mol) using 0.1g hydrotalcite (Pb-Al-CO_3) at different temperature under solvent free condition have been studied and results are shown in table 3.4. At room temperature the product yield was 5%. In order to assess the applicable temperature system, the model reaction was carried out at 70^{0}C temperature. It was noticed that at this temperature the yield of the product was 84%. There was a sharp increase in the product yield at 60-70^{0}C. After 70^{0}C the yields of the product remain same.

Table 3.4 Temperature effect on reaction (^{0}C)

Entry	Temperature (^{0}C)	Yield (%)
1	35	25
2	45	50
3	55	59
4	60	68
5	65	71
6	70	84
7	75	84

Reaction condition: aromatic benzaldehyde (0.05mol), 2-amino-benzothiazol (0.05mol), curcumin (0.05mol) and 0.1mg hydrotalcite at 70^{0}C under solvent free condition.

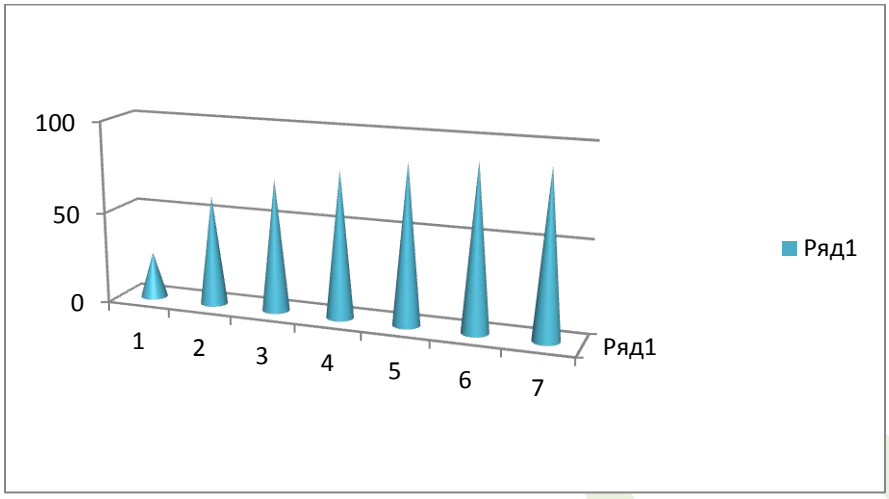


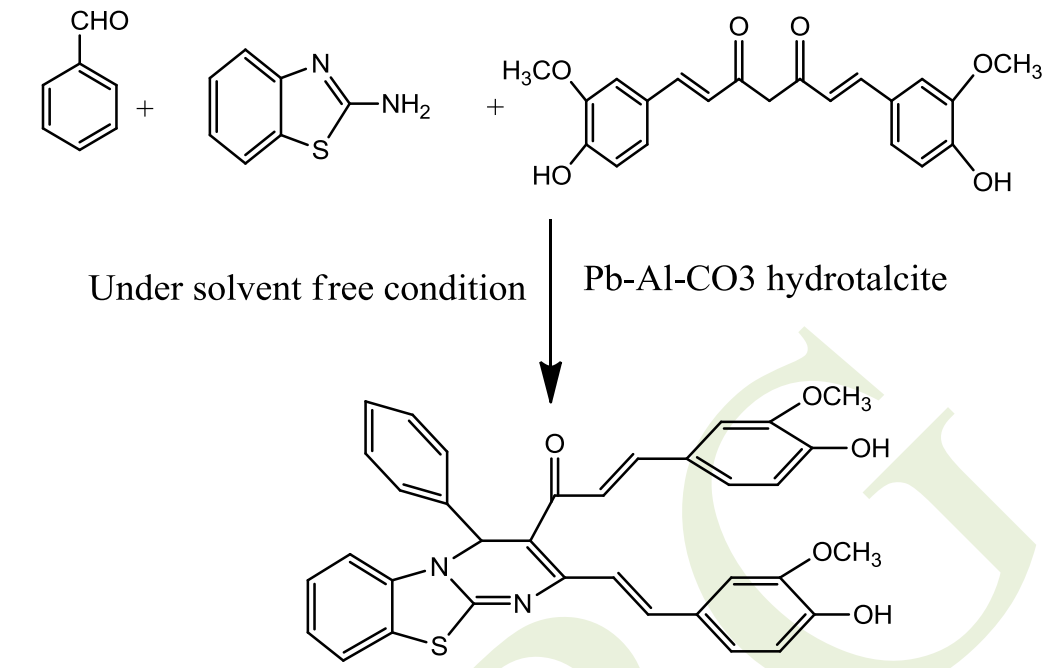
Fig. 3.2 Effect of Temperature on the reaction

3.4- Synthesis and characterization of 4H-pyrimido [2,1-b]benzothiazole derivatives of curcumin using various aromatic aldehydes :

On increasing the temperature of reaction leads to shorter time duration. The work has been developed to the synthesis of 4H-pyrimido[2,1-b]benzothiazol derivatives of curcumin using substituted aromatic aldehydes (0.05mol), 2-aminobenzothiazole (0.05mol), and curcumin (0.05mol) under solvent free condition resulting in product formation within 4.30-8.30hrs with excellent yields (Scheme 3.3).

The structure of 4H-pyrimido [2,1-b]benzothiazol derivatives of curcumin was confirmed by Mass, IR, ^{1}HNMR and C^{13} NMR spectral analysis. The NMR spectra of the products was characterized by singlet around 7.26 δ due to asymmetric C-H hydrogen and the multiplet (δ) between 7.61-3.93 for aromatic hydrogen of benzene ring of aromatic aldehyde and benzothiazole which is not showed by curcumin. Avariety of electon donating and electron withdrawing on aromatic aldehydes have been studied Table 3.3.

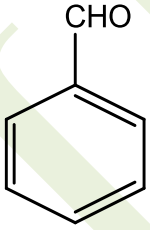
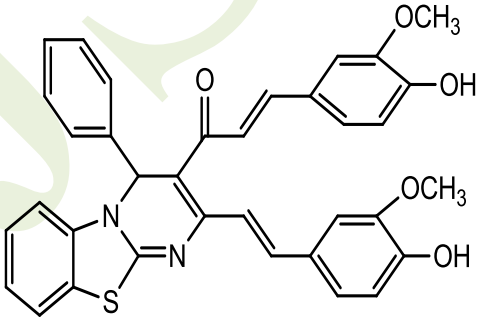
Various substituted aromatic aldhydes are electron donating and electron withdrawing substitiuent at ortho, meta, para position show equal dexterity towards the product formation in excellent yields. Thus the results show that highest yield (84%) is obtained with substituent 4- hydroxyl bezaldehyde. There was no significant effect of electron donating and electron withdrawing substituents.

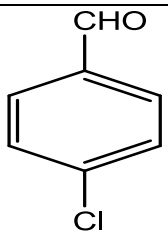
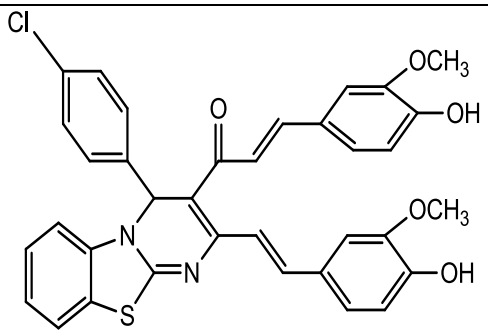
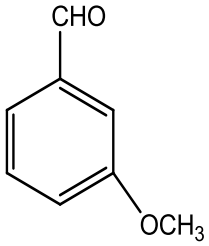
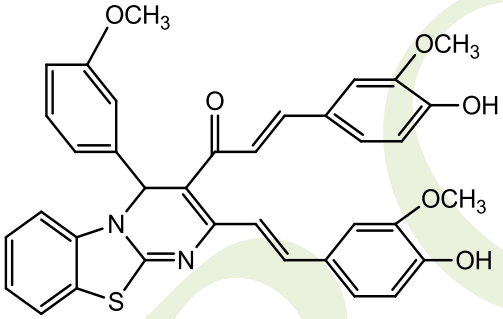
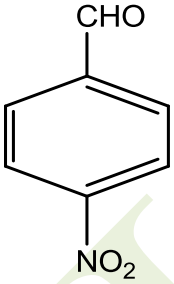
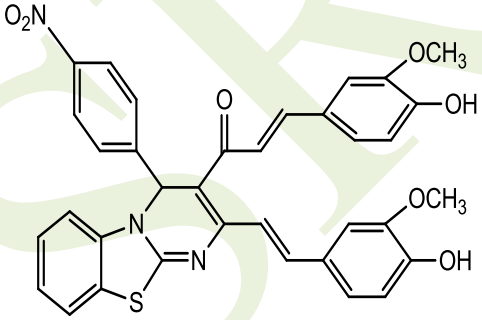
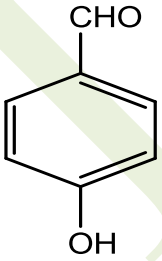
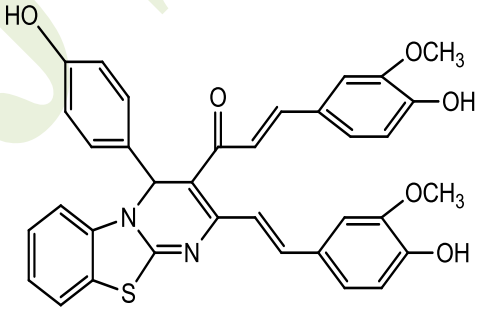


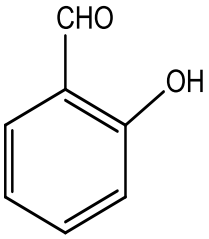
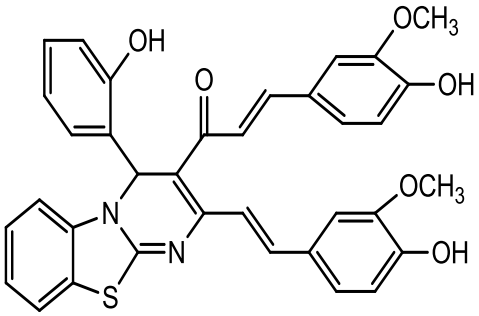
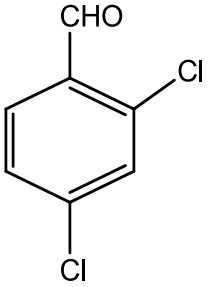
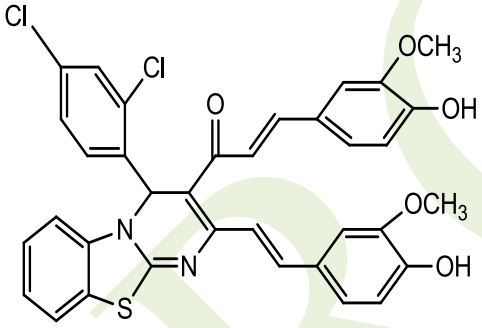
R=H, 4-OCH_3, 4-NO_2, 4-OH, 3-Cl, 2,4=Cl, 2-NO_2

Scheme 3.3 proposed reaction using hydrotalcite Pb-Al-CO_3

Table 3.5 One-pot synthesis of 4H-pyrimido[2,1-b]benzothiazole derivatives of curcumin using of hydrotalcite (Pb-Al-CO_3) :

Entry	Reactant	Product	Time (hours)	Yield (%)	M.P (0^0C)
3a			5.20	64	98-99

3b			6.00	75	111-113
3c			4.30	84	82-83
3d			8.15	80	86-87
3e			8.30	72	101-102

3f			4.50	70	101-102
3g			7.20	73	91-92

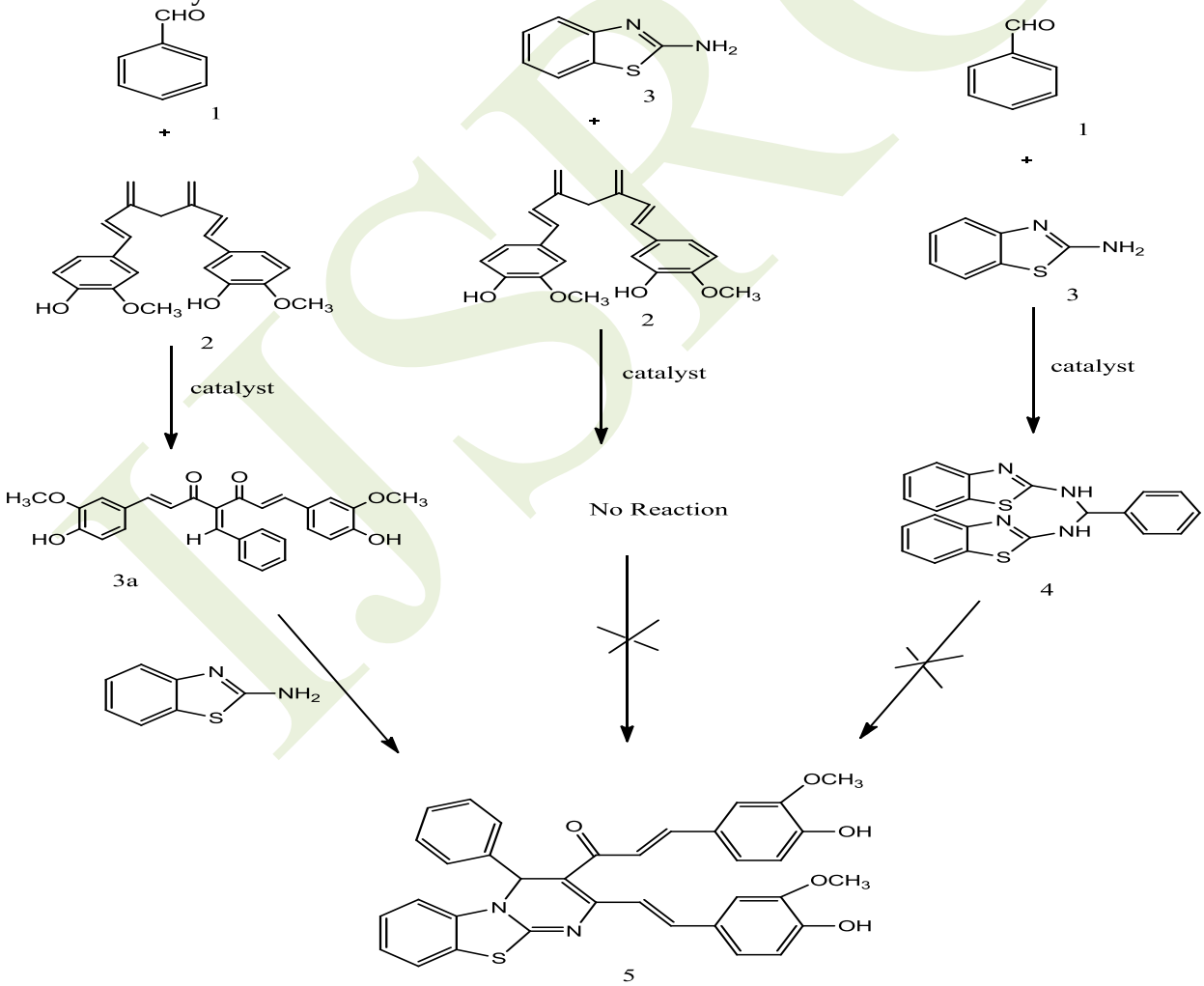
Reaction condition: aromatic benzaldehyde (0.05mol), 2-amino-benzothiazol (0.05mol), curcumin (0.05mol) and 0.1mg hydrotalcite at 70^0C under solvent free condition

4- MECHANISM

The proposed mechanistic pathway of one-pot three component reaction using aromatic aldehyde, 2-aminobenzothiazole and curcumin have not been reported in literature to such extent, this mechanism is for the first time reported in the basic metal hydrotalcite Pb-Al-CO_3, the proposed reaction proceeds very well. Literature survey shows that till now the intermediate compound of this three component condensation reaction has not been isolated and characterized.

For this reaction, the plausible mechanism has been intimated in scheme 3.4. On the basis of this proposed mechanism hydrotalcite Pb-Al-CO_3 can be discussed as an impressive catalyst for the formation of 4H-pyrimido [2,1-b]benzothiazolecurcumin. The mechanism of the product 4H-pyrimido [2,1-b]benzothiazolecurcumin has been studied in this chapter. For this, three set of reactions are carried out. Each set of reaction has two components. The intermediate was formed with aldehyde (1) and curcumin (2) was reacted with third component 2-aminobenzothiazol to form the product. The product was analyzed by mp, IR and mass spectral studies. From the above, it was found that only one set of reaction gave the product. **Sahu[(81)]have reported** the reaction proceeds in two steps, condensation of benzaldehyde (1) and curcumin (2) Knoevenagel type reaction. Then 2-aminobenzothiazol (3) reacted with intermediate (3a) through Michael addition type reaction to form pyrimidine derivative of curcumin. The product pyrimidine derivatives of curcumin having 4H-pyrimido[2,1-b]benzothiazolescurcumin in structure (5). All the synthesized products have been analyzed by melting point, mass, IR, ^{13}CNMR and ^{1}HNMR spectral studies.

The mass spectra of intermediate 3a shows the ion peak at 456. IR spectra of intermediate 3a, band due to ν (-OH) stretching vibration was observed at 2916 cm^{-1}. The other characteristics groups ν (C-H) and ν (-C=O) were observed at 2916, 1600cm^{-1} respectively. In the ^{13} C NMR spectra of intermediate (3a), has appeared the singlet at 10.11δ ppm has assigned due to carbon which is attached to benzene ring. The multiplet between 7.45-7.89 unsymmetrical due to hydrogens of benzaldehyde, which is not shown by the curcumin NMR spectra.Multiplet b/w 6.71-7.20 due to 5 hydrogen of two benzene ring of curcumin. This intermediate was first time isolated by Sahu et al. and which has been characterized and confirmed by comparing the data in literature survey [0]. Therefore, it has been suggested that it is the key intermediate for the proposed mechanistic study. We have been also isolated the intermediate (4a) successfully. The mass spectra of the intermediate (4a) show the ion peak at .In the ^{13} C NMR spectra of intermediate (4a) shows the triplet at 7.10 due to –CH, doublet at 7.27 due to tow identical hydrogen of –NH and multiplets was also observed between 7.45-8.11 due to five hydrogen of aromatic ring. This intermediate fail to produce the target intermediate, thus its involvement as intermediate for the target product can be ruled out.



Scheme 3.4 proposed mechanism for the synthesis of 4H- pyrimido [2,1-b] benzothiazole derivatives of curcumin

Shen*et al*. [80] have reported that the mechanism of three component reaction which easily proceeded with urea in different -2 system, when t-BuOK was used as catalyst. But they failed to characterized the intermediate

Kappe*et al.*[81] have reported that Lewis acid or protic acid-mediated three component reaction developed via iminium ion as a key intermediate usually them carbenium ion intermediate. But the intermediate of these three component condensations have not been isolated and characterized.

5- CHARACTERIZATION OF THE PRODUCT

The molecular ion peak is obtained at 588.67 **m/z** in mass spectra of the target compound (3a) which is matched with calculated molecular weight of the compound having structure as follows.

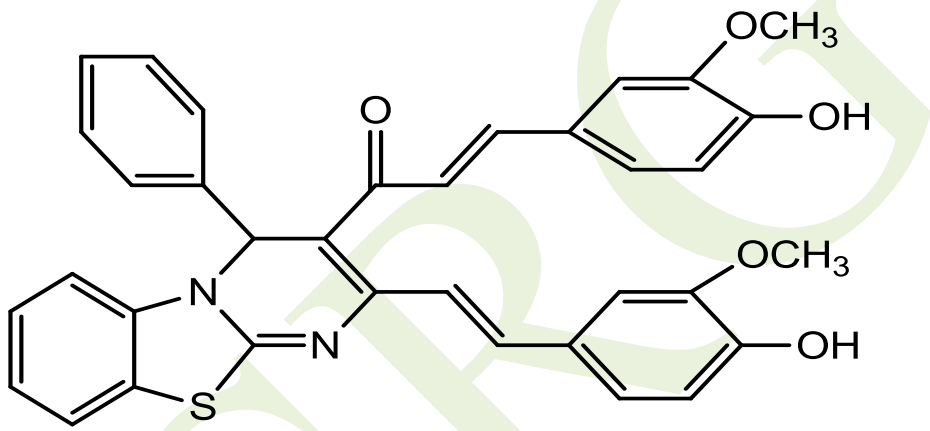


Fig. 3.3structure of 4-phenyl-4Hpyrimido [2,1-b][1,3] benzothiazolecurcumin

In the IR spectra of compound **(3a)** the band due to ν C-N and ν C-S stretching vibration are appeared at 1026 and 1153 cm^{-1} respectively [82]. The band due to ν C-OH stretching was observed at 3348 cm^{-1} and other characteristic groups like ν C-H and ν C=O are appeared at 2933 and 1625 cm^{-1} respectively.

In the ^{1}H NMR spectra of compound **(3a)** one singlet was appearing at 3.93 ppm assigned due to OCH_3. Many doublets were found at 6.44, 6.49, 6.87 and 8.56 due to C_6, C_5, C_7 and C_8 respectively.

In the ^{13}C NMR spectra of compound (3a) signals due to C_1-C_{10} aromatic and heterocyclic ring carbons and OCH_3 appeared as we expected in fig.[83] (3.10, 3.14, 3.18, 3.22, 3.26, 3.30, 3.34, 3.38).

6- CONCLUSION

The spectral data of the research supported in the formation of 4H-pyrimido [2,1-b] benzothiazole derivatives of curcumin (3a-3g) with different substisuted aromatic aldehydes (Table 3.4). The present protocol suggests several advantages such as simple research condition, short time duration, solvent free condition, easy workup and purification of target products by simply recrystallization. The catalyst 0.01g Pb-Al-CO_3 concluded in the formation of product in excellent yields (84%). When reaction is carried out in solvent (like acetonitrile, ethanol, hexane, and toluene) no product was obtained.

Spectroscopic data

Mass spectra of intermediate compound

4-benzylidedecurcumin (3): Calculated Mass ($C_{28}H_{24}O_6$), **MS** (m/z) (%): 456.49; **IR** (KBr), ν (cm^{-1}): 3736 (C-H), 2916 (C-H), 1621 (C=O), 1514 (C-H), 1274 (C-H); **^{13}C NMR** ($CDCl_3$, 400MHz) δ ppm: 182.82, 147.67, 145.97, 140.29, 139.88, 134.12,

129.83, 128.69, 129.22, 126.18, 125.88, 123.38, 122.64, 115.75, 110.36, 5544.

(3a)4-Phynyl-4H-pyrimido [2,1-b][1,3]benzothiazolecurcumin: Calculated Mass ($C_{35}H_{28}N_2O_5S$), **MS** (m/z) (%) : 588.7 (M^+), Elem. Anal.: C,71.41; H,4.97; N,4.76; O,13.59; S,5.45; orangish yellow crystal; **IR** (KBr), ν (cm^{-1}): 3348 (C-H), 2933 (C-H), 1625 (C=O), 1510 (C-H), 1273 (C-H), 1121 (C-S), 1026 (C-N), 962 (C-H); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 7.26 (s, 1H), 7.1-7.6 (m, 15H), 7.04 (d, 1H, C_7), 6.86 (d, 1H, C_8), 6.46 (d, 1H, C_5), 5.79 (d, 1H, C_6), 3.91 (s, 6H, OCH_3); **^{13}C NMR** ($CDCl_3$, 400MHz) δ ppm: 178.03, 148.55, 142.61, 141.56, 134.36, 123.60, 122.51, 122.38,117.65, 116.44, 108.99, 104.44,50.70.

(3b) 4-(2-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazolecurcumin: Calculated Mass ($C_{35}H_{27}N_2ClO_5S$), **MS** (m/z) (%) : 623.12 (M^+), Elem.Anal.: C,67.46; H,4.37; Cl,5.69; N,4.50; O,12.84; S,5.15; orangish yellow crystal; **IR** (KBr), ν (cm^{-1}): 3400 (OH), 3262 (C-H), 2926 (C-H), 1626 (C=O), 1563 (C-H), 1227 (C-H), 1126 (C-S), 1021 (C-N), 943-812 (C-H); **^{1}HNMR** ($CDCl_3$,400MHz): δ ppm: 7.24 (s, 1H), 7.1-7.7 (m, 14H), 7.04 (d,1H, C_7), 6.93 (d, 1H, C_8), 6.48 (d, 1H, C_5), 5.77 (d, 1H, C_6), 3.92 (s, 6H, OCH_3); **^{13}H NMR** ($CDCl_3$, MHz) δ ppm: 181.87, 149.11, 147.71, 140.35, 140.09, 129.76, 129.38, 129.35, 126.20, 125.60, 122.63, 120.76, 120.45, 115.77, 115.50, 110.58, 100.77, 55.45.

(3c) 4-(3-methoxyphenyl)-4H-pyrimido [2,1-b][1,3]benzothiazolecurcumin: Calculated Mass ($C_{36}H_{30}N_2O_6S$), MS (m/z) (%) : 618.78 (M^+), Elem.Anal.: C,69.89; H,4.89; N,4.53; O,15.52; S,5.18; orangish yellow crystal; **IR** (KBr), ν (cm^{-1}): 3737(OH), 2916 (C-H), 1681 (C=O), 1514 (C-H), 1418 (C-H), 1274 (C-H), 1133 (C-S), 1031 (C-N); **^{1}H NMR** ($CDCl_3$, 400MHz) δ ppm: 7.25 (s, 1H), 6.91-7.67 (m, 14H), 7.05 (d, 1H, C_7), 6.90 (d, 1H, C_8), 6.48 (d, 1H, C_5), 5.79 (d,1H, C_6), 3.97 (s, 6H, OCH_3); **^{13}C NMR** ($CDCl_3$, 400MHz) δ ppm: 182.92, 149.14, 147.77, 141.38, 126.22, 125.08, 122.76, 120.81, 120.59, 120.36, 117.67, 115,77, 115.53, 115.14, 110.72, 99.49, 55.51.

(3d) 4-(4-nitrophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazolecurcumin Calculated Mass ($C_{35}H_{27}N_3O_7S$), **MS** (m/z) (%) : 633.67 (M^+), Elem.Anal.: C,66.34; H,4.29; N,6.63; O,17.67; S,5.06; orangish yellow crystal; **IR** (KBr), ν (cm^{-1}): 3664 (C-H), 2926 (C-H), 1625 (C=O), 1519 (C-H), 1267 (C-H), 1122 (C-S), 1078 (C-N), 962-812 (C-H); **^{1}HNMR** ($CDCl_3$, 400MHz) δ ppm: 7.26 (s, 1H), 7.1-7.62 (m, 14H), 7.04 (d, 1H, C_7), 6.93 (d, 1H, C_8), 6.49 (d, 1H, C_5), 5.87 (d, 1H, C_5), 3.93 (s, 6H, OCH_3); **^{13}C NMR** ($CDCl_3$, 400MHz) δ ppm: 181.89, 149.13, 147.77, 140.37, 130.33, 129.80, 126.21, 123.45, 122.90, 120.78, 115.77, 115.51, 110.66, 100.79, 55.47.

(3e) 4-(4-hydroxyphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazolecurcumin

Calculated Mass ($C_{35}H_{28}N_2O_6S$), **MS** (m/z) (%) : 604.67 (M^+), Elem.Anal.: C,69.52; H,4.67; N,4.63; O,15.88; S,5.30; orangish yellow crystal; **IR** (KBr), ν (cm^{-1}): 3504 (OH), 1724 (C=O); 1508 (C-H), 1287 (C-H), 1154 (C-S), 1078 (C-N), 962-812 (C-H); **^{1}HNMR** ($CDCl_3$, 400MHz) δ ppm: 9.72 (s, 1H, OH), 7.06 (s, 1H, C-H), 6.85-7.57 (m, 14H), 7.05 (d, 1H, C_7), 6.85 (d, 1H, C_8), 6.49 (d, 1H, C_5), 5.81 (d, 1H, C_6), 3.92 (s, 6H, OCH_3); **^{13}C NMR** ($CDCl_3$, 400MHz) δ ppm: 182.89, 149.11, 147.75, 140.35, 129.87, 126.22, 122.79, 115.76, 115.53,100.79, 55.47.

(3f) 4-(2-hydroxyphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazolecurcumin Calculated Mass ($C_{35}H_{28}N_2O_6S$), **MS** (m/z) (%) : 604.67 (M^+), Elem.Anal.: C,69.52; H,4.67; N,4.63; O,15.88; S,5.30; orangish yellow crystal; **IR** (KBr), ν (cm^{-1}): 3504 (OH), 2941 (C-H), 1628 (C=O), 1508 (C-H), 1280 (C-

H), 11543(C-S), 1078 (C-N), 962-812 (C-H); **^{1}HNMR** ($CDCl_3$, 400MHz) δ ppm: 8.82 (s, 1H, OH), 7.26 (s, 1H), 7.1-7.7 (m, 14H), 7.04 (d, 1H, C_7), 6.87 (d, 1H, C_8), 6.48 (d, 1H, C_5), 5.77 (d, 1H, C_6), 3.93 (s, 6H, OCH_3); **^{13}C NMR** ($CDCl_3$, 400MHz) δ ppm: 182.88, 149.11, 147.73, 140.35, 129.80, 126.23, 122.70, 120.78, 115.77, 115.54, 110.63, 100.78, 55.47.

(3g) 4-(2,4-dichloro phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazolecurcumin Calculated Mass ($C_{35}H_{26}N_2O_5Cl_2S$), **MS** (m/z) (%) : 657.56 (M^+), Elem.Anal.: C,63.93; H,3.99; Cl,10.79; N,4.26; O,12.17; S,4.88; orangish yellow crystal; **IR** (KBr), ν (cm^{-1}): 3078 (C-H), 1716 (C=O); **^{1}HNMR** ($CDCl_3$, 400MHz) δ ppm: 7.74 (s, 1H), 7.06-7.58 (m, 6H), 6.76-7.02 (m, 7H), 6.53 (d, 1H, C_5), 5.86 (d, 1H, C_6),3.90 (s, 6H, OCH_3); **^{13}C NMR** ($CDCl_3$, 400MHz) δ ppm: 182.77, 148.91, 146.59, 140.25, 133.25, 129.56, 127.70, 126.21, 125.09, 122.54, 120.83, 120.23, 117.77, 115.71, 115.70, 115.39, 110.10, 100.71, 55.41.

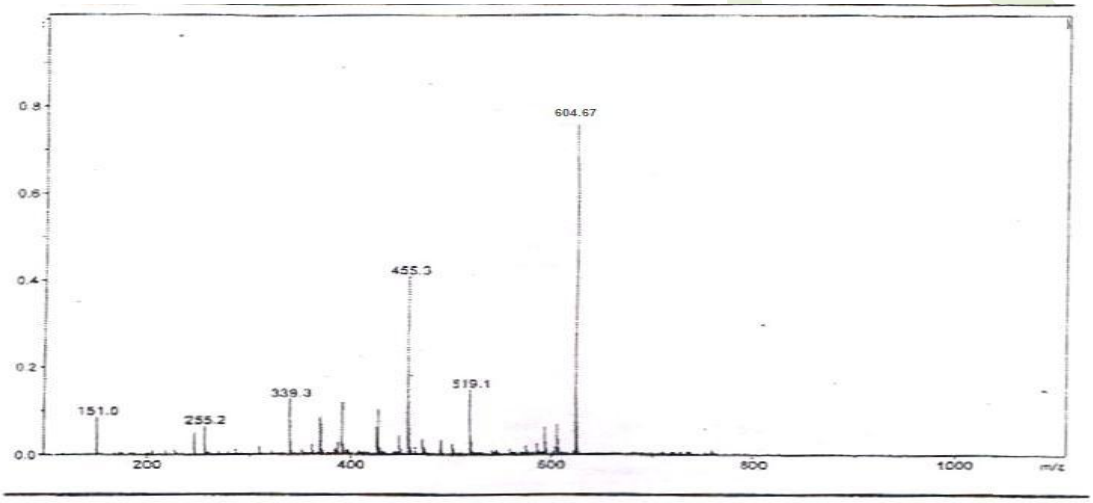


Fig.4 Mass spectra of 4-(4-hydroxyphenyl)-4H-pyrimido [2,1-b][1,3]benzothiazolecurcumin

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