

ENVIRONMENTALLY BENIGN MICROWAVE ASSISTED CATALYST FREE SYNTHESIS OF CURCUMIN PYRIMIDINONE AND THIOPYRIMIDINONE ANALOGUES

Abstract

Describe method consist of eco-friendly procedure for the preparation of Curcumin Pyrimidinone and Thiopyrimidinone analogues from Curcumin urea/thiourea

With the help of MW irradiation for appropriate time. Green impact of reaction significantly enhanced due to no use of catalyst and under MWI process. Good to excellent yield of products, simple working strategy and easy purification are the advantage of present methodology.

Keywords: Curcumin, Pyrimidinone, Thiopyrimidinone, MWI, Catalyst free, green methodology.

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I. INTRODUCTION

Nitrogen and Sulphur containing heterocycles have retained the interest of Medicinal organic chemist researchers along the historical development of Drug Chemistry. The presence of heteroatom or atoms results in remarkable change in cyclic structure due to presence of unshared paired of electron and change in electronegativity. Pauling scale of electronegativity for Nitrogen (3.04) and sulphur (2.58) itself explains different bonding and stability behavior of these heteroatom. High electronegativity bless with strong bonding and extra association with hydrogen atoms if present in, and gives overall stable structural geometry. Low electronegativity of Sulphur suffers from lack of association, these change in electronegativity significantly affect on numbers of available building blocks in laboratories. Figure 1 depicted with laboratory available building blocks for Nitrogen containing heterocycles and unavailable for Sulphur containing heterocycles.

Literature survey found reports on Curcumin Schiff base analogues for their biological activity. Curcumin benzylidene analogues formed imines with thiosemicarbazide and its copper complex exhibits potent antiblood cancer activity [1, 2]. Same synthetic strategies were used to obtain proteasomes inhibitors curcumin-copper complex consisting sulphur depicted in [Figure 2](#).

Complex nitrogen-sulphur containing Curcumin analogues were reported as anti-tumor compound [3]. An interesting report found with five spacer sulphur containing curcumin analogues as inhibitor of prostate cancer cell growth and androgen receptor activation [4]. Used method consist Methanol as an unavoidable solvent for obtaining desire product, which is well known toxic solvent.

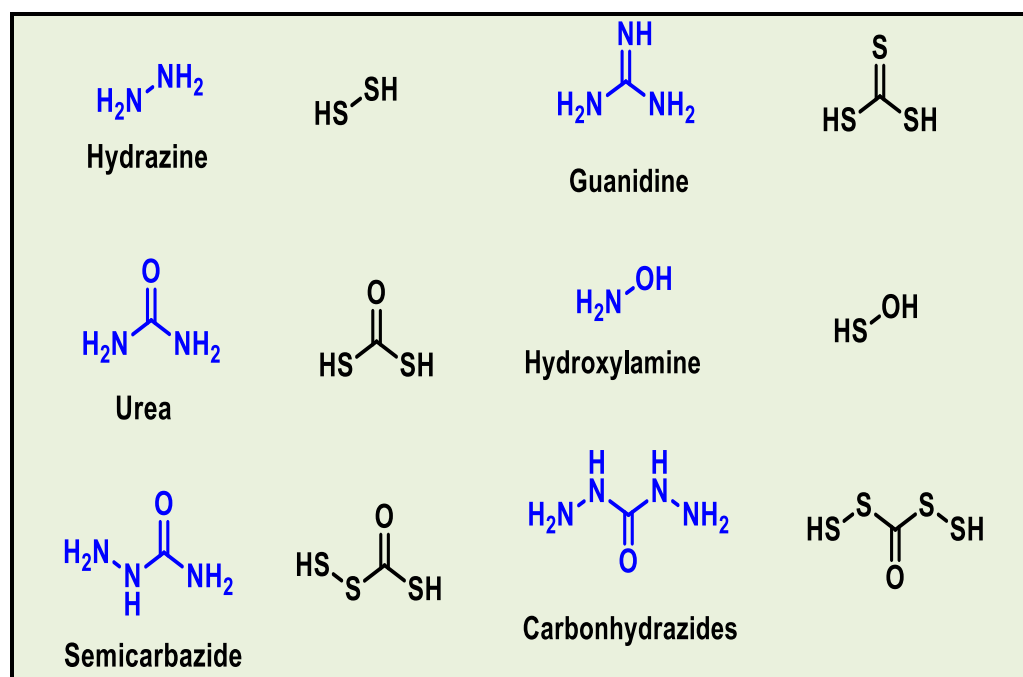


Figure 1: Laboratory available, cheap and stable Nitrogen containing building blocks and analogues hypothetical Sulphur consisting building blocks.

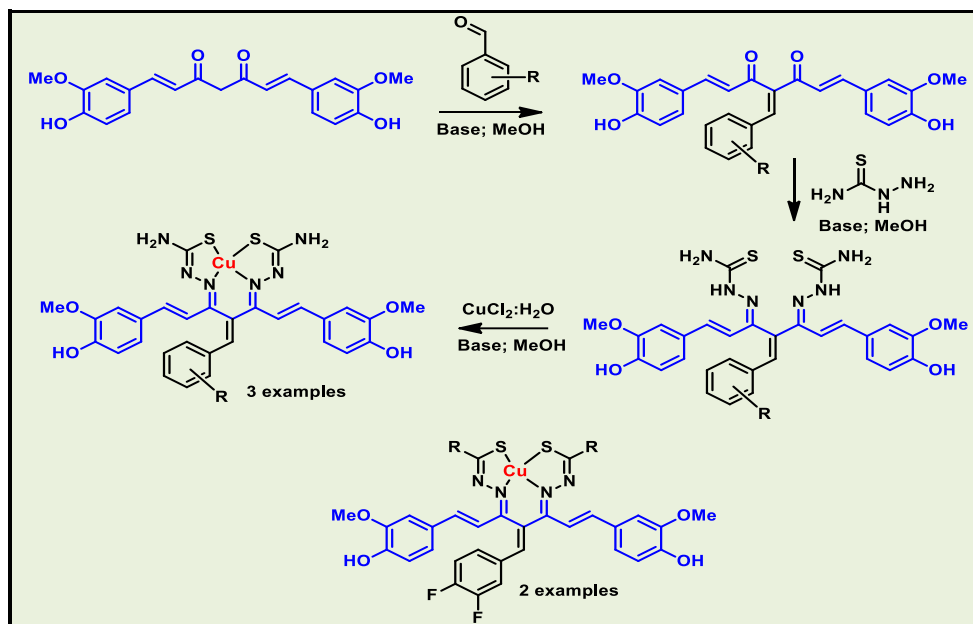


Figure 2: Curcumin-Sulphur-copper containing compounds exhibits as anti blood cancer and as proteasomes inhibitors. [1-2]

II. MATERIAL AND METHODS

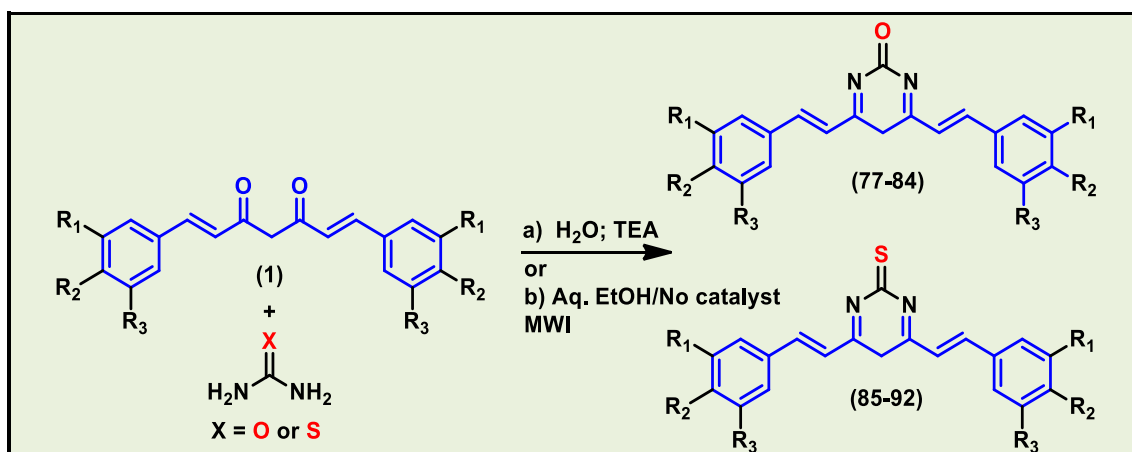
General: The commercial sample of curcumin was purchased from S. D. Fine Chemical Limited, Mumbai, and Maharashtra. Solvents used during experimentation were of Analytical grade purchased from Spectrochem of Loba, India and used further without distillation. During the laboratory work, starting materials were checked by Thin Layer Chromatography (TLC) for their purity purpose. Separation or formation of products was initially confirmed by TLC techniques. Mobile phase selected by trial and error method. Silica plate was used TLC Silica gel 60G, F₂₅₄ Plates by Merck.

IR was recorded for compounds synthesized in the laboratory and for validation of isolated curcumin from curcuminoids. Absorption spectra recorded in the range of 400-4000 cm⁻¹ with KBr pellets. Compounds synthesized during laboratory experimental work analyzed by using proton NMR and Carbon NMR. Deuterated solvents mostly used as DMSO-*d*₆, unless it is mentioned. Tetramethylsilane (TMS) was used as internal standard. Actual scanning was done by Bruker Advance DRX 300 FT-NMR.

Experimental

1. General method for Base catalyzed synthesis of Curcumin Pyrimidinone and Thiopyrimidinone analogues: Curcumin (1; 1mmol; 1 eq.) was taken in round bottom flask consisting 20 ml of aqueous alcohol (20%), to this urea/thiourea (1.5 mmol; 1.5 eq.) was added and allowed to stir at room temperature for 30 minutes for homogenous mixing. Cs₂CO₃ (15 mol%) was added in one portion. Yellow colour changes initially to

dark red and finally dark brown colour observed. Reaction mixture allowed to stir at room temperature, progress of reaction was monitor by TLC. After completion of reaction all reaction content pour to 25 ml of ice cold water and acidified with drop wise addition of dil. HCl using pH paper. All content set aside without further stirring for 1-2 hours. Thus obtained yellow solid was filter and washed with water, finally recrystallize from ethanol to obtained pure product, as depicted in **Scheme 1**.



Scheme 1 Protocol for synthesis of Thiopyrimidinone (77) and Pyrimidinone(78) analogues of Curcumin, conventional and MWI strategies were found fruitful.

- Microwave assisted catalyst free synthesis of Curcumin Pyrimidinone and Thiopyrimidinone analogues:** Curcumin (**1**; 1mmol; 1 eq.) was taken in round bottom flask consisting 50% of aqueous alcohol (20%), to this urea/thiourea (1.5 mmol; 1.5 eq.) was added and allowed to stir at room temperature for 30 minutes for homogenous mixing. After mixing reaction mixture MW irradiate at 600 Watt for appropriate time. After each 30 second of successive irradiation 5-6 second resting period was set to avoid overheating. Progress of reaction was monitor by TLC. After completion of reaction allowed cooling down and setting aside till solid mass settle down at bottom of RBF. Filter and recrystallize from hot ethanol to afford pure product.

Spectral Analysis of synthesized selected compounds

1. 4, 6-bis((E)-4-hydroxy-3-methoxystyryl)pyrimidin-2(2H)-one (77):

IR: (KBr) cm^{-1} : 3523 (OH), 3164 (NH), 1630 (C=O), 1563 (C=N), 1363 (C-N). ^1H NMR (300 MHz, DMSO- d_6): δ 3.74 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 5.88 (1H, s, H-4), 6.34 (2H, d, H-2,6), 6.69 (2H, d, H-1,7), 6.73–7.11 (m, ArH) ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 56.3 (-OCH₃), 56.8 (-OCH₃), 111.4 (C-4), 112.3 (ArC), 122.3, 122.8 and 122.9 (ArC and C-2,6), 127.6 ArC-1,1'), 142.6 (C-3), 147.5 and 147.9 (ArC-4,3), 151.1 (CO), 162.4 (N=C).

2. 4, 6-bis((E)-4-hydroxystyryl)pyrimidin-2(2H)-one (78):

IR: (KBr) cm^{-1} : 3545 (OH), 3113 (NH), 1636 (C=O), 1545 (C=N), 1379 (C-N). ^1H NMR (300 MHz, DMSO- d_6): δ 5.63 (1H, s, H-4), 6.57 (2H, d, H-2,6), 6.59 (4H, d, ArH), 6.72 (2H, d, H-1,7), 7.04 (m, ArH) ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 111.4 (C-4), 114.7

(ArC), 116.4 and 124.1 (C-2,6), 127.1(ArC-1,1'), 130.7 (ArC-2,5), 141.9(C-3), 156.1 (CO), 157.7 (ArC-4,4'), 162.3 (N=C).

3. 4, 6-di((E)-styryl)pyrimidin-2(1H)-one (79):

IR: (KBr) cm^{-1} : 3164 (NH), 1630 (C=O), 1563 (C=N), 1363 (C-N). ^1H NMR (300 MHz, DMSO- d_6): δ 5.57 (1H, s, H-4), 5.89 (2H, d, H-2,6), 6.79-6.82 (2H, d, H1,7), 7.23-7.38 (m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 111.9 (C-4), 116.7 (C6), 124.1 (C-2), 127.6-128.3 (ArC), 135.2 (C-1,7), 142.6 (ArC-3), 156.1 (CO), 162.1 (N=C).

4. 4, 6-bis((E)-4-methylstyryl)pyrimidin-2(1H)-one (80):

IR: (KBr) cm^{-1} : 3131 (NH), 1645 (C=O), 1578 (C=N), 1354 (C-N). ^1H NMR (300 MHz, DMSO- d_6): δ 2.33 (3H, s, CH₃), 2.37 (3H, s, CH₃), 5.55 (1H, s, H-4), 5.54 (1H, d, H-6), 6.62 (1H, d, H-7), 6.73 and 6.84 (2H, d, H-2,6), 7.11-7.23 (m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 20.9 (-CH₃), 21.3 (-CH₃), 111.5 (C-4), 113.4 (C6), 124.1 (C-2), 127.9-137.8 (ArC), 143.1 (C-3), 156.4 (CO), 160.1 (N=C).

5. 4, 6-bis((E)-4-nitrostyryl)pyrimidin-2(1H)-one (81):

IR: (KBr) cm^{-1} : 3177 (NH), 1656 (C=O), 1578 (C=N), 1365 (C-N). ^1H NMR (300 MHz, DMSO- d_6): δ 5.98 (1H, s, H-4), 6.90 (2H, d, H-2,6), 6.97 (2H, d, H-1,7), 7.69-8.21 (m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 114.1 (C-4), 117.5 (C-6), 123.1 (ArC), 124.6 (C-2), 129.7 (ArC), 142.7 (C-1,5), 147.5 and 147.9 (ArC-4,4'), 156.1 (CO), 164.5 (N=C).

6. 4, 6-bis((E)-4-bromostyryl)pyrimidin-2(1H)-one(82):

IR: (KBr) cm^{-1} : 3187 (NH), 1657 (C=O), 1549 (C=N), 1352 (C-N); ^1H NMR (300 MHz, DMSO- d_6): δ 5.45 (1H, s, H-4), 5.66 (2H, d, H-2,6), 6.71 (2H, d, H-1,7), 7.42-7.59 (m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 111.3 (C-4), 116.4 (C-6), 122.2 (ArC-4,4'), 124.3 (C-2), 128.6-131.2 (ArC), 142.6 (C-3), 147.5 and 147.9 (ArC), 154.2 (CO), 163.1 (N=C).

7. 4, 6-bis((E)-4-chlorostyryl)pyrimidin-2(1H)-one (83):

IR: (KBr) cm^{-1} : 3154 (NH), 1633 (C=O), 1555 (C=N), 1341 (C-N); ^1H NMR (300 MHz, DMSO- d_6): δ 5.43 (1H, s, H-4), 5.69 (2H, d, H-6), 6.69-6.84 (3H, d, H1,2,7), 7.44 and 7.56 (d, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 111.4 (C-4), 116.6 (C-6), 124.3 (C-2), 127.6, 132.4 and 133.1 (ArC), 137.9 (C-7), 142.1 (C-3), 153.4 (CO), 161.7 (N=C).

8. 4, 6-bis((E)-4-methoxystyryl)pyrimidin-2(1H)-one (84):

IR: (KBr) cm^{-1} : 3136 (NH), 1627 (C=O), 1555 (C=N), 1357 (C-N); ^1H NMR (300 MHz, DMSO- d_6): δ 3.77 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 5.39 (1H, s, H-4), 5.69 (2H, d, H-6), 6.69 (1H, d, H-7), 6.87 (2H, d, H-1,2), 6.92-7.21 (m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 55.7 (-OCH₃), 56.3 (-OCH₃), 111.7 (C-4), 113.4 (ArC), 116.9 (C-6), 127.3-130 (ArC), 135.1 and 138.2 (C-1,7), 142.6 (C-3), 154.9 (CO), 164.1 (N=C).

9. 4, 6-bis((E)-4-hydroxy-3-methoxystyryl)pyrimidin-2(1H)-thione (85):

IR: (KBr) cm^{-1} : 3511 (OH), 3119 (NH), 1577 (C=N), 1361 (C-N), 1270 (C=S); ^1H NMR (300 MHz, DMSO- d_6): δ 3.71 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 5.64 (1H, d, H-6), 6.09 (1H, s, H-4), 6.79-6.82 (2H, d, H-1,2), 6.87 (1H, d, H-7), 6.98-7.16 (6H, m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 54.4 (-OCH₃), 55.1 (-OCH₃), 109.6 (C-4), 118.7

(ArC), 120.3 and 120.4 (ArC and C-6), 127.3-130 (ArC), 135.1 and 138.2 (C-1,7), 152.8 (C-3), 161.9 (N=C), 174.9(S=C).

10. 4, 6-bis((E)-4-hydroxystyryl)pyrimidin-2(1H)-thione (86):

IR: (KBr) cm^{-1} : 3546 (OH), 3123 (NH), 1562 (C=N), 1354 (C-N), 1273 (C=S); ^1H NMR (300 MHz, DMSO- d_6): δ 5.66 (1H, d, H-6), 6.12 (1H, s, H-4), 6.65-6.72 (4H, d, ArH), 6.79-6.84 (3H, d, H-1,2 and 7), 7.54 (4H, d, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 109.2 (C-4), 118.7 (ArC), 115.9 (ArC), 116.3 and 123.1 (C-2 and C-6), 127.3130 (ArC), 135.1 and 138.2 (C-1,7), 152.8 (C-3), 162.1 (N=C), 174.5 (S=C).

11. 4, 6-di((E)-styryl)pyrimidin-2(1H)-thione (87):

IR: (KBr) cm^{-1} : 3121 (NH), 1557 (C=N), 1354 (C-N), 1264 (C=S); ^1H NMR (300 MHz, DMSO- d_6): δ 5.69 (1H, d, H-6), 6.12 (1H, s, H-4), 6.80-6.82 (2H, d, H-1,2), 6.84 (1H, d, H-7), 7.03-7.21 (10H, m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 109.2 (C-4), 117.3 (C-6), 124.1 (C-2), 127.9-128.7(ArC), 135.1 and 138.2 (C-1,7), 152.8 (C-3), 162.2 (N=C), 179.1(S=C).

12. 4, 6-bis((E)-4-methylstyryl)pyrimidin-2(1H)-thione (88):

IR: (KBr) cm^{-1} : 3109 (NH), 1564 (C=N), 1357 (C-N), 1276 (C=S); ^1H NMR (300 MHz, DMSO- d_6): δ 2.29 (3H, s, CH_3), 2.33 (3H, s, CH_3), 5.61 (1H, d, H-6), 6.11 (1H, s, H-4), 6.79-6.83 (2H, d, H-1,2), 6.84 (1H, d, H-7), 7.19-7.21 (6H, m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 22.1 ($-\text{CH}_3$), 24.3 ($-\text{CH}_3$), 110.1 (C-4), 118.4 (ArC), 121.6 and 121.9 (ArC and C-6), 127.7-131.2 (ArC), 134.3 and 135.7 (C-1,7), 152.0 (C3), 161.7 (N=C), 171.3(S=C).

13. 4, 6-bis((E)-4-nitrostyryl)pyrimidin-2(1H)-thione (89):

IR: (KBr) cm^{-1} : 3121(NH), 1560(C=N), 1515 (NO), 1360 (C-N), 1345 (NO), 1273 (C=S); ^1H NMR (300 MHz, DMSO- d_6): δ 5.87 (1H, d, H-6), 6.16 (1H, s, H-4), 6.876.99 (2H, d, H-1,2), 7.04 (1H, d, H-7), 7.09-8.19 (10H, d, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 110.2 (C-4), 119.4 (ArC), 121.7 and 122.1 (ArC and C-6), 129.7-132.1 (ArC), 136.9 and 138.6 (C-1,7), 153.4 (C-3), 163.3 (N=C), 177.1(S=C).

14. 4, 6-bis((E)-4-bromostyryl)pyrimidin-2(1H)-thione (90):

IR: (KBr) cm^{-1} : 3120(NH), 1563 (C=N), 1355 (C-N), 1248 (C=S), 551 (C-Br); ^1H NMR (300 MHz, DMSO- d_6): δ 5.11 (1H, d, H-6), 5.34 (1H, s, H-4), 5.49-5.58 (2H, d, H-1,2), 5.87 (1H, d, H-7), 6.11-6.57 (6H, m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 107.9 (C-4), 116.2 (ArC), 120.0 and 120.7 (ArC and C-6), 122.4-124.1 (ArC), 131.2 and 134.8 (C-1,7), 150.1 (C-3), 157.4 (N=C), 177.2(S=C).

15. 4, 6-bis((E)-4-chlorostyryl)pyrimidin-2(1H)-thione (91):

IR: (KBr) cm^{-1} : 3120(NH), 1563 (C=N), 1355 (C-N), 1248 (C=S), 678 (C-Cl); ^1H NMR (300 MHz, DMSO- d_6): δ 5.14 (1H, d, H-6), 5.22 (1H, s, H-4), 5.51-5.63 (2H, d, H-1,2), 5.88 (1H, d, H-7), 6.12-6.59 (8H, m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 105.2 (C-4), 115.4 (ArC), 121.6 and 122.1 (ArC and C-6), 123.0-123.9 (ArC), 133.7 and 134.6 (C-1,7), 149.7 (C-3), 156.5 (N=C), 176.9(S=C).

16. 4, 6-bis((E)-4-methoxystyryl)pyrimidine-2(1H)-thione (92):

IR: (KBr) cm^{-1} : 3133 (NH), 1567(C=N), 1360(C-N), 1275 (C=S); ^1H NMR (300 MHz, DMSO- d_6): δ 3.61 (3H, s, OCH₃), 3.69 (3H, s, OCH₃), 5.55 (1H, d, H-6), 6.00 (1H, s, H-4), 6.54-6.69 (2H, d, H-1,2), 6.89 (1H, d, H-7), 7.03–7.11 (8H, m, ArH); ^{13}C NMR (75 MHz, DMSO- d_6) ppm: 53.9 (-OCH₃), 54.1 (-OCH₃), 109.7 (C-4), 119.1 (ArC), 121.7 and 122.3 (ArC and C-6), 128.3-131.2 (ArC), 135.2 and 138.7 (C-1,7), 153.3 (C3), 160.2 (N=C), 177.1(S=C).

III. RESULTS AND DISCUSSIONS

Schiff base was first reported in the 19th Century and name after scientist Dr. Hugo Schiff who discovers the reaction [5]. Huge research work has been done to improve synthesis of Schiff base in form of productivity, smooth reaction completion with complex molecules, milder solvent-catalyst combination and respect to greener reaction profile. Early 21st Century it observed that efficient product formation depends upon nature of used carbonyl compound. Highly electrophilic carbonyl moiety and strong nucleophilic amines are the best starting material for Schiff base formation reaction. [6] In case of Schiff base synthesis, Curcumin play's carbonyl substrate role and being an-alter one. To improve electrophilicity of curcumin-carbonyl it was logical to search appropriate Lewis acid catalyst. Involvement of Lewis acid helps to eliminate water molecule at final step [6], especially in case of low electrophilic carbonyl compound. Various Lewis acid used as catalyst for synthesis of Schiff base like, ZnCl₂ [7], TiCl₄ [8], MgSO₄-PPTS [9], Ti(OR)₄ [10], MgSO₄ [11], H₂SO₄ [12], Ruthenium catalyzed [13], MgSO₄ [14], Mg(ClO₄)₂ [15], Er(OTf)₃ [16], P₂O₅/Al₂O₃ [17], Lanthanum, Thorium [18] and MCM-41-SO₃H [19].

To investigate proper solvent-catalyst combination series of reactions were carried out. During development of new synthetic protocol focus was remained maintained on room temperature reaction and OR non-conventional (specially, MWI) method. A greener reaction pathway has its own significant importance, hence while trial and error method purposefully green solvent and catalyst were explored. Water were taken as solvent and ethanol was added drop wise to know minimum amount of alcohol required to dissolved curcumin, and found 20% of aqueous alcohol is best combination and used further without any changes.

Table 1: Optimization of base catalyst for synthesis of (77) with respect to yield, used solvent is 20% of aqueous alcohol.

Entry	Base used	Stirring at RT	
		Time in hr.	Yield ^a
1.	Aq. NaHCO ₃ (sat.)	8 hours	29%
2.	Aq. Na ₂ CO ₃ (sat.)	8 hours	40%
3.	5% NaOH	8 hours	46%
4.	CS ₂ CO ₃	8 hours	82%
5.	K ₂ CO ₃	8 hours	54%
6.	Piperidine	8 hours	31%
7.	TEA	8 hours	39%
8.	Pyridine	8hours	27%
9.	Without catalyst	48 hours	Staring recover*

Isolated yield; MWI 600W; TLC Check,

As a model reaction strategy, Curcumin (1) and urea were chosen as fixed starting materials. Urea was taken as excess to assure complete transformation of curcumin into product. Another advantage of excess urea was it is water soluble and excess of urea will be easily removed with water work-up procedure. Various used base catalyst are depicted in Table 1.

Water and alcohol was taken as solvent hence inorganic bases were taken as best compatible catalytic partners, like bicarbonate, carbonates and hydroxide (**Table 1; Entry 1,2,4,5** and **3** respectively). Organic bases were tried for fair comparison with inorganic bases. But as expected organic bases does not found productive with aqueous alcoholic solvent combination. Cesium carbonate (**Table 1; Entry 4**) emerged as good catalyst with high productivity.

In concern with green aspect, most favorable catalytic condition is 'NO CATALYST' reaction. Throughout this research work attempted had been made to workout with either no catalyst or no solvent, whenever possible. Describe methodology is successful attempted of obtaining (77) without any catalyst in 20% of aqueous alcohol as solvent system. To achieve this, used MW irradiation technique found productive, and after performing series of reactions as depicted in **Table 2** 800W was found as optimum irradiation power.

Table 2: Optimization of MWI power for synthesis of (77), without catalyst with respect to yield, used solvent is 20% of aqueous alcohol.

Sr. No.	MWI (in Watt)	Without any catalyst	
		Time in Sec.	Yield ^a of products
1.	300	180	Starting recover
2.	400	180	Trace
3.	500	120	26%
4.	600	120	48%
5.	700	120	69%
6.	800	60	58%
7.	800	120	93%

Isolated yield

Optimum yield was obtained with irradiation at 800W energy for two minutes. To check effective irradiation time required for transformation, one minute's irradiation was done (**Table 2. Entry 6**) this gave 58% of productivity, hence two minutes irradiation was taken as final irradiation time.

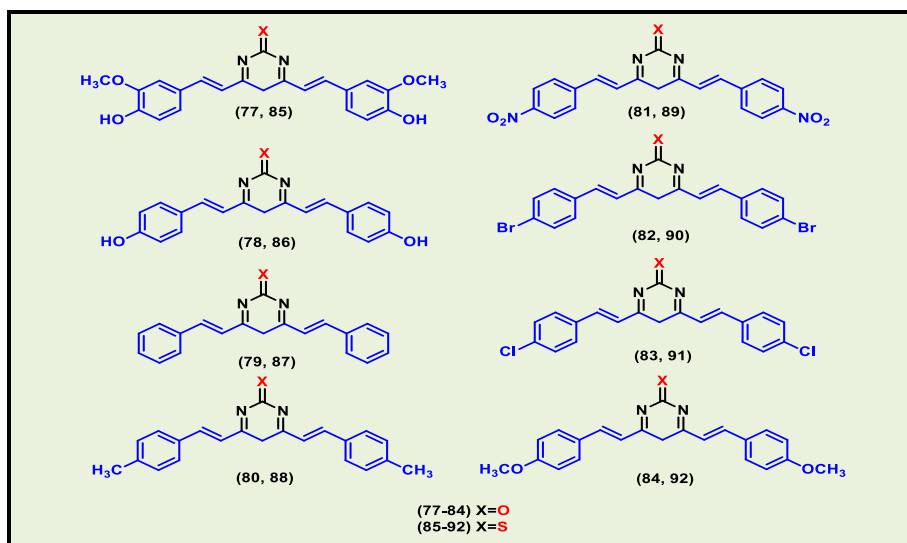


Figure 3: Synthesized curcumin Pyrimidinones/thiones analogues prepared by reaction of Curcumin analogues with Urea and Thiourea.

Finally effect of substituent on yield of product was done, by derivatisation method. Previously prepared curcumin analogues were taken as starting material for reaction with Urea and Thiourea. Comparison of both describe methods, stirring at room temperature and non-classical MWI method was done with respect to yield of product, as depicted in **Table 3**.

Structures of various synthesized analogues of pyrimidinone/thions are illustrated in **Figure 3**. It was observed that electron donating functionality elevates yields of product, whereas, electron withdrawing substituent responsible to fall down yields of product. Productivity of unsubstituted curcumin analogues (**79 and 87**) found in between these two. Better productivity obtained, when used MWI without any catalyst. At first glance this might be looking surprise, but due to unique tendency of MW irradiation to transfer huge amount of energy within no time, make possible to overcome various energy barriers and improve productivity of reaction.

In conclusions, describe method of curcumin-pyrimidinone/thione analogues by Cesium carbonate catalyzed and 20% of aqueous ethanol method has unique green concern. All chemical component used are environmentally benign. Easy reaction procedure and smoothly conversion of reactant to product are advantages of describe method. At work-up stage, simple filtration and recrystallization to obtained pure product increase importance of describe method.

**Table 3 Comparison of yield of product obtained
 by Cesium carbonates catalyzed room temperature with MWI method.**

Entry	Product No.	15mol% Cs ₂ CO ₃ as catalyst, Stirring at RT		No catalyst MWI (800W)	
		Time	Yield ^a	Time	Yield ^a
1.	(77)	8 hours	82	120 Sec.	93
2.	(78)	8 hours	87	120 Sec.	94
3.	(79)	8 hours	76	120 Sec.	91
4.	(80)	8 hours	90	120 Sec.	97
5.	(81)	12 hours	68	120 Sec.	74
6.	(82)	8 hours	86	120 Sec.	96
7.	(83)	8 hours	88	120 Sec.	94
8.	(84)	8 hours	89	120 Sec.	96
9.	(85)	8 hours	91	120 Sec.	96
10.	(86)	8 hours	93	120 Sec.	95
11.	(87)	8 hours	84	120 Sec.	97
12.	(88)	8 hours	89	120 Sec.	94
13.	(89)	12 hours	71	120 Sec.	80
14.	(90)	8 hours	91	120 Sec.	96
15.	(91)	8 hours	87	120 Sec.	90
16.	(92)	8 hours	91	120 Sec.	97

Isolated yield; Curcumin-isoxazole

To overcome long reaction time of previously proposed method, rapid scaffold was developed by using MWI techniques. Describe non-conventional MWI method fully catalyst free and rapid. All advantages of previous method are equally relevant with non-conventional MWI method.

IV. CONCLUSION

In conclusion, an efficient, green method for the synthesis of nitrogen and sulphur containing Curcumin analogues has been described using readily Potash alum as naturally occurring catalyst. The green reaction profile and mild reaction conditions are main advantage of this method. Reaction takes place at room temperature by simply stirring method, with operational simplicity offers excellent yields.

- 1. Conflict of Interest;** Author have no conflict of interest.
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