Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 10 [8] July 2021 : 137-148

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Multicomponent Synthesis and evaluation of Antioxidant activity of Curcumin Derivatives by using Hydrotalcites as Green Catalyst

Goyal Rupendra*, Jain Suman[1], Agarwal D D[2].
*Assistant Professor, SOS in Pharmaceutical Sciences, Jiwaji University, Gwalior (M.P.)
[1]Director, SOS in Pharmaceutical Sciences, Jiwaji University, Gwalior (M.P.)
[2]Professor, SOS in Chemistry, Jiwaji University, Gwalior (M.P.)
*** Corresponding author's** E-mail: goyalrk09@gmail.com

ABSTRACT
The synthesis of 1H- Pyrazole-2(3H)-yl-pyridine-4-yl- Methanone (B1-B6) and substituted hydrazine derivatives (D1-D6) of curcumin by Multicomponent reactions using Substituted aldehydes and Hydrazines has been carried out using Mg-Al-CO3 as efficient catalyst. As hydrotalcites need short reaction time, non toxic and recyclable. Hence hydrotalcites made this process green as well as environment friendly. Heterocycles synthesized by this process evaluated for Antioxidant activity that shows promising antioxidant activity against standard Ascorbic acid and Butylated Hydroxy Anisole.
Keywords: *Curcumin; Multicomponent synthesis; Antioxidant activity; Hydrotalcites; Green Catalyst.*

Received 29.06.2021 Revised 26.06.2021 Accepted 13.07.2021

INTRODUCTION

Curcumin and its derivatives have been extensively studied in past due to their promising activity as protectors in cardiovascular [1], Alzheimer's and Parkinson's diseases [2-5] and cancer inhibition [6-10]. These derivatives have also been used as antibacterial, fungi [11], antiviral [12], antidiabetic [13], anti-inflammatory [14-15] and antioxidant [16, 17]. Examples of success involving the Curcumin family which is attracting are CNBOO1 as protector/activator of memory, and chicoric acid and 3,5- dicaffeoyl quinic acid are two specific selective HIV Integrase inhibitors [18]. Although Curcumin and its derivatives have been used in different biological evaluations by various groups around the world while in all these high experimental screening, POM bioinformatics approaches like petra/osiris/molinspiration (POM) analyses to predict molecular properties for these compounds with multi potential bioactivity were missing throughout in previous studies. Once again and curiously, little attention has been paid to the identification of type of pharmacophore sites of Curcumin (CURC-D), especially the bioavailability and toxicity risks of the series never been established. It is evident for Computational group that this poly-activity can be generated from CURC-D tautomerism/isomerism/conformism or co-existence of two independent pharmacophore sites [19-21] in the same molecule. Most of drugs are the subject of pharmacological properties change in solution. The bioinformatist/ pharmacologist should take in consideration the resulting principal active tautomer/isomer/ conformer which is the real responsible of bioactivity not always the parent molecule.

MCRs represent as an efficient and effective tool for generating libraries of small molecule compounds and also exhibit indispensability for the studies of SAR i.e. structure activity relationship. Some of the uncommon scaffolds are generated via MCRs, their utility in biological realm is explored by the key of exhibiting the ability to functionalize or modify them [22]. These MCRs are most preferred because of their effectiveness and efficiency in synthesizing highly functionalized organic molecules. The availability of their starting materials is also easy which are further combined in one pot process including synthesizing the product and keeping diversity and complexity leading to time, cost as well as reduction of waste effluents [23-24].

Antioxidants are materials capable of scavenging ROS and protecting from oxidative damage. Antioxidant has been shown to prevent destruction of β-cells by inhibiting peroxidation chain reaction and thus provide protection against the development of diabetes. Plant contains natural antioxidants (tannins, flavonoids, polyphenols etc.) can preserve β-cell function and prevent diabetes induced ROS formation. A Number of synthetic antioxidants such as butylated hydroxyl anisole (BHA), butylated hydroxyl toluene (BHT), propyl galate (PG) and tert- butyl hydro quinone (TBHQ) has been added to food stuffs although

these synthetic antioxidants are efficient and cheap, there are some disadvantages because they are suspected of having some toxic properties such as liver damage and mutagenesis is a problem of worry however the natural antioxidants, particularly phenolics and flavonoids are safe. So, in modern years, extensive attention has been directed towards identification of medicinal plants with antioxidant capability that may be used for human utilization. The search for raw materials containing potent antioxidants continues to attract the attention of researchers. Fruit, vegetables and spices are all known to be rich sources of natural antioxidants and medicinal plants are another important source for a wide variety of natural antioxidants [25].

hydrotalcite is rapid, less corrosive to the reactor, easy to separate, inexpensive and highly efficient [26]. The reusability of the catalyst is a very important criteria over cost and environmental pollution. The utility of hydrotalcite as a catalyst led to formation of high yields [27].

MATERIAL AND METHODS

Material and instrument used:

All chemicals were obtained from Merck, High media and SD fine chemicals ltd. All solvents were redistilled and dried before use. Reactions were routinely monitored by thin layer chromatography and spots were visualized by exposure to iodine vapour or UV light. All the synthesized compounds were purified by column chromatography followed by recrystallization. Melting points were determined by using open capillary method and are uncorrected. Fourier Transform Infra Red spectra (FTIR) were recorded on Shimadzu FTIR-8400S spectrophotometer using potassium bromide pellets and sodium chloride cell. Nuclear Magnetic Resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded on JEOL-300 MHz spectrophotometer in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm). Mass spectra were recorded on HEWLETT 180017, PACKARD GCD System mass spectrophotometer using electron ionization detector.

Synthetic scheme- I:

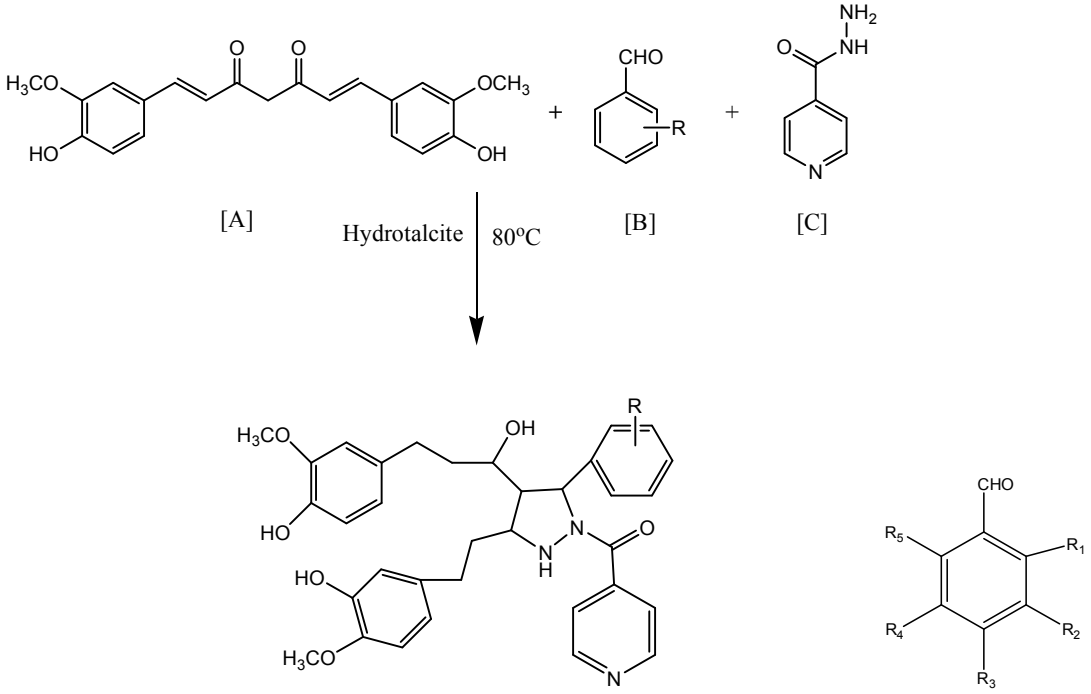


Fig 1: Synthetic scheme of aldehyde derivatives of curcumin moiety and R-substituted aromatic aldehyde derivatives

Synthetic Schemes-II:

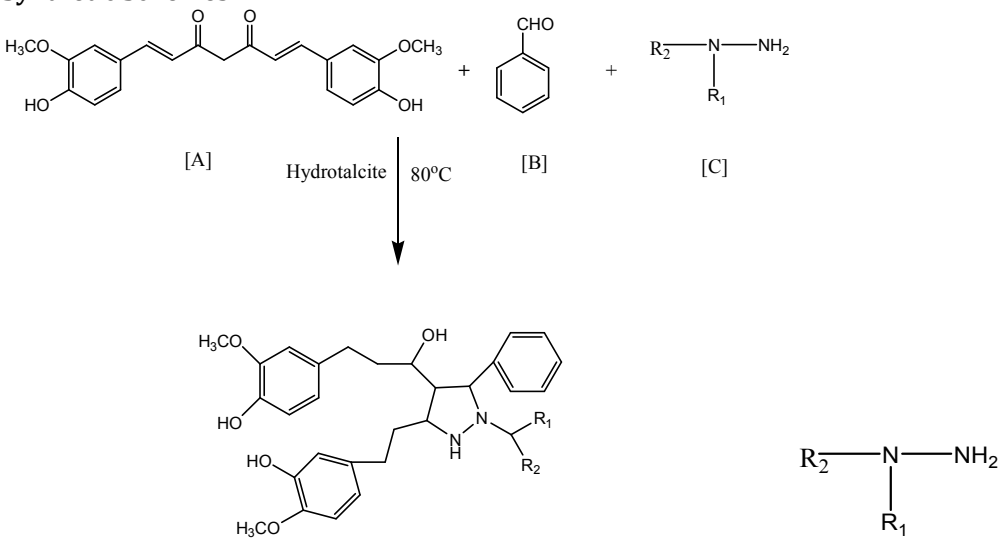
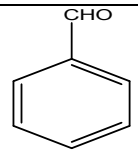
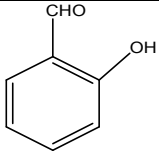
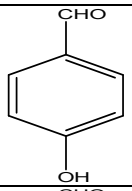
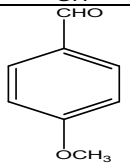
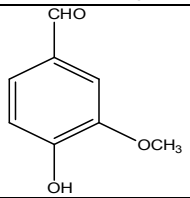
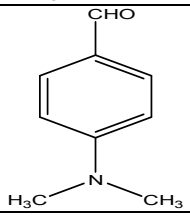


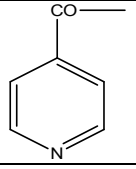
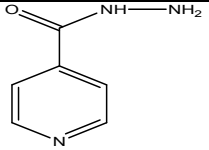
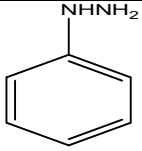
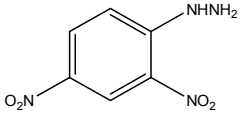
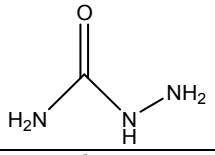
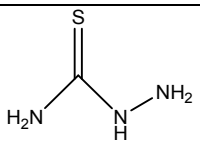
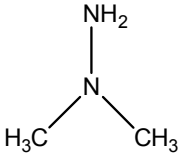
Fig 2: Synthetic scheme of hydrazine derivatives of curcumin moiety and R-Substituted hydrazine derivatives

Table 1: Targeted aldehyde derivatives

ComP, code	R_1	R_2	R_3	R_4	R_5	Structure of substrate	Substrate name
B1	-H	-H	-H	-H	-H		Benzaldehyde
B2	-OH	-H	-H	-H	-H		o-Salicylaldehyde
B3	-H	-H	-OH	-H	-H		p- Salicylaldehyde
B4	-H	-H	$-OCH_3$	-H	-H		4-methoxybenzaldehyde
B5	-H	$-OCH_3$	-OH	-H	-H		vanillin or (4-hydroxy-3-methoxybenzaldehyde)
B6	-H	-H	$-N(CH_3)_2$	-H	-H		4-(dimethylamino) benzaldehyde

General Synthetic Procedure for Compounds B1-B6:
A solution of substituted benzaldehyde (0.01mol) in ethanol along with curcumin (0.01mol) and Isoniazide (0.01mol) in the presence of hydrotalcite was refluxed for 4 hours upto 80°C. The excess solvent was distilled off under reduced pressure. The cooled residual mass was washed with distilled water. It was filtered and dried. The crude product was recrystallised from methanol to yield compound B1 to B6 reaction was monitored by TLC.

Table 2: Targeted hydrazine derivatives

Comp Code	R′	R″	Structure of substrate	Substrate name
D1	-H			Isoniazid
D2	-H	$-C_6H_4$		Phenyl hydrazine
D3	-H	$-C_6H_3(NO_2)_2$		2,4-Dinitro phenyl hydrazine
D4	-H	$-CONH_2$		Semicarbazide
D5	-H	$-CSNH_2$		Thiosemicarbazide
D6	$-CH_3$	$-CH_3$		1,1-Dimethyl hydrazine

General Synthetic Procedure for Compounds D1-D6:
A solution of substituted hydrazine (0.01mol) in ethanol and benzaldehyde (0.01mol) with curcumin (0.01mol) in the presence of hydrotalcite was refluxed for 4 hours up to 80°C. The excess solvent was distilled off under reduced pressure. The cooled residual mass was washed with distilled water. It was filtered and dried. The crude product was recrystallised from methanol to yield compound D1 to D6 reaction. The reaction was monitored by TLC.

RESULT AND DISCUSSION
Reaction of curcumin, 4- methoxy benzaldehyde and Isonicotinohydrazide at 80^0 C in the absence of catalyst fails to give product. Under this study we used hydrotalcite as a catalyst. In order to evaluate appropriate hydrotalcite as catalyst a model reaction using solution of substituted benzaldehyde (0.01 mole) in ethanol along with curcumin (0.01 mole) and isoniazid (0.01 mole) was carried out using various hydrotalcite as catalyst up to 80^0 C (Fig 1). The reaction was optimized also for a scheme II (Fig 2). It was found that out of various hydrotalcite Mg-Al-Co_3 was found to be catalyst that gives product in better yield at optimise temperature 80^0 C.
The multicomponent reaction of a solution of substituted benzaldehyde (0.01 mole) in ethanol along with curcumin (0.01 mole) and isoniazid (0.01 mole) in the presence of Mg-Al-Co_3 was refluxed for 4 hours at 80^0 C resulted the formation of product with yield ranges from 57.13 to 89.64% (scheme I) and from 46.02 to 78.58% (scheme II). The structure of 3-phenyl-1H-Pyrazol-2 -(3H) –yl- Pyridin-4-yl-methanone

derivatives of curcumin was confirmed by FTIR, NMR and Mass spectral analysis. The ^{1}H NMR spectra of the product B1 to B6 were characterized by singlet around 7.5 δ due to asymmetric C-H Hydrogen and the multiplet at 7.05 to 7.77 δ with unsymmetric pattern for aromatic Hydrogens of Pyridine and Benzene ring of aldehyde which is not shown by curcumin. Mass spectra of product B1 shows the the [M +] molecular ion peak at 583.7 and other peaks at 188.9, 264.9, 370.8 for corresponding fragments that support the probable structure of product B1.

Optimised reaction conditions in hand lead us to synthesize the hydrazene derivatives of curcumin using solution of substituted hydrazine (0.01 mole) in ethanol benzaldehyde (0.01 mole) with curcumin (0.01 mole) in the presence of optimised Hydrotalcite under optimum temperature condition that is 80^{0} C. Synthesized Pyrazole derivatives have been characterized by FTIR, 1H NMR, ^{13}C NMR and Mass spectral study.

The reaction using organic catalyst is harmful to nature as well as researcher. Hence there is a need to find out green, environmental as well as human friendly catalyst as Hydrotalcite. This reaction greatly reduce the environmental pollution by eliminating organic solvent/ catalyst. Various substituted aromatic aldehyde and hydrazines containing electron withdrawing and electron donating group shows equal ease towards the product formation in high yield.

The one pot three component strategy of hydrazide substituted benzaldehyde was used for the synthesis of curcumin derivatives. In this work the synthesis of curcumin derivatives was done using an environmental friendly procedure via Mg-Al-CO3 hydrotalcite which have been used as efficient catalysts. These catalysts are inexpensive and non-toxic powders. Data of Spectra and other analytical technique supported identification of synthesized curcumin derivatives. The present work offers many merits such as the reaction conditions were extremely simple, there was operational simplicity, reaction time was short, easy to work up and purification was also easy for the products via simple means of re-crystallization.

Effect of physicochemical parameter on synthesized derivatives

Effect of catalyst:

The reaction using different hydrotalcitesas catalysts were studied and the product yield was analyzed. The product yield is definitely affected by the type of catalysts[28]. The Highest yield of product (89.64%) was obtained with Mg-Al-CO3 hydrotalcites. It was followed by Ca-Al-CO3 giving 81% yield and lowest yield of the product (32.51%) was obtained with Al-Mn-Cu-CO3. No product formation were obtained in the absence of catalysts. The result shows the hydrotalcites having basic metals give highest yield.

Table 3 Effect of various catalysts in the product yield

S.N.	Catalysts	Yield (%)
1	Ca-Al- CO3	81.05
2	Zn-Al- CO3	78.13
3	Mg-Al-CO3	89.64
4	Ni-Al- CO3	74.26
5	Ni-Fe- CO3	71.88
6	Ni-Cu-Al- CO3	67.07
7	Ni-Ca-La- CO3	60.01
8	Ni-Ca-Al- CO3	48.26
9	Ni-Zn-Al-Fe- CO3	41.38
10	Al-Mn-Cu- CO3	32.51
11	No catalyst	0

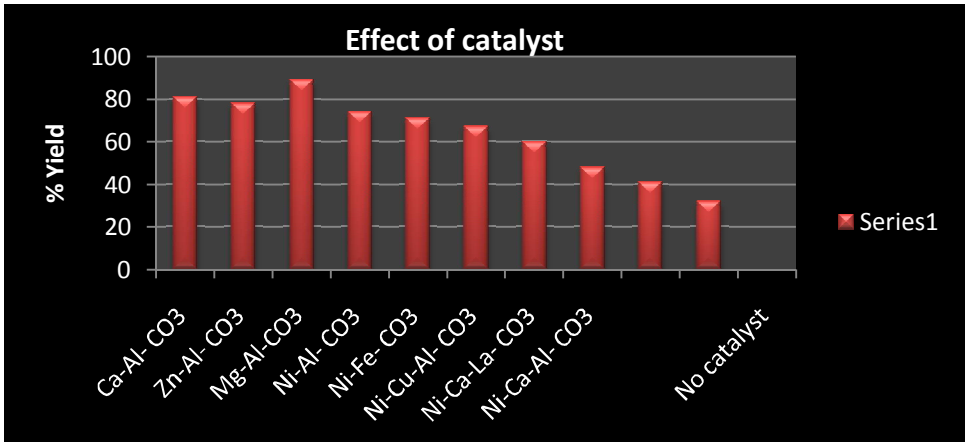


Figure 3: Effect of various catalysts on % yield

Effect of temperature:

The yield at various temperature ranges from room temperature to 100°C was studied. The reaction was highly sensitive to temperature. When temperature is raised to 50°C the yield was 67%. Increase in temperature further increased the yield. Higher yield (89.64%) was obtained at 80°C [29]. when temperature was further raised the yield decreases hence 80°C was considered as optimum temperature for future studies.

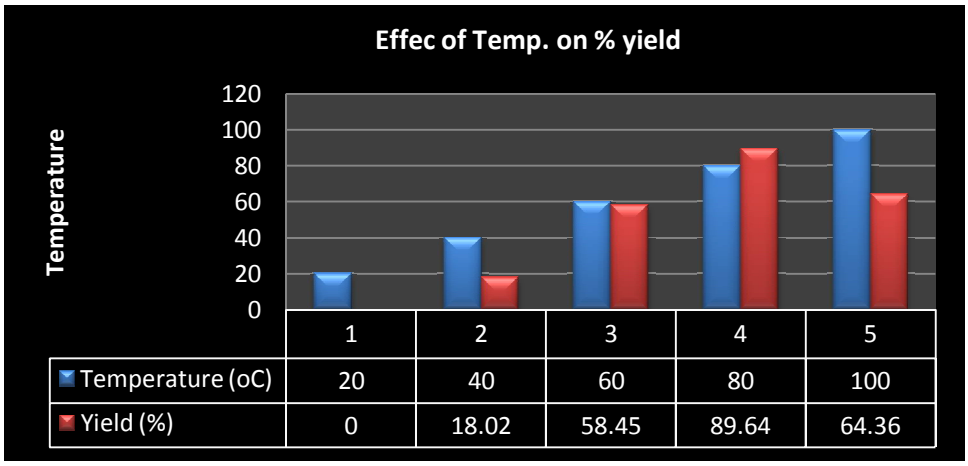


Figure 4: Effect of temperature on % yield

Effect of catalysts concentration:

The effect of concentration of optimized catalyst on the formation ofcurcumin derivatives was studied. Concentration of catalyst range from 50 to 150 mg and observed the % yield of product[30]. The highest yield (89.64%) was observed at 100 mg weight of hydrotalcites.

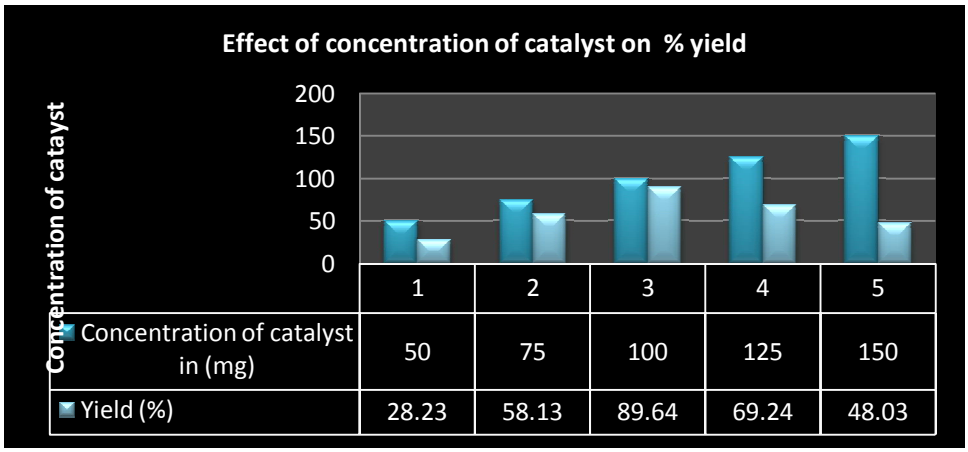


Figure 5: Effect of Concentration of catalyst on % yield

Recyclability of catalyst:

Catalyst can be used again with small reduction in the weight of catalysts and without any loss in their ability. The stability of catalyst in recyclability upon 2nd recycle products yield was 82%. This can be either some loss of catalyst during workup[31-33]. The 3rd recycle shows yield 69%. This shows slight loss of yield. So hydrotalcites found stable as recyclable catalyst.

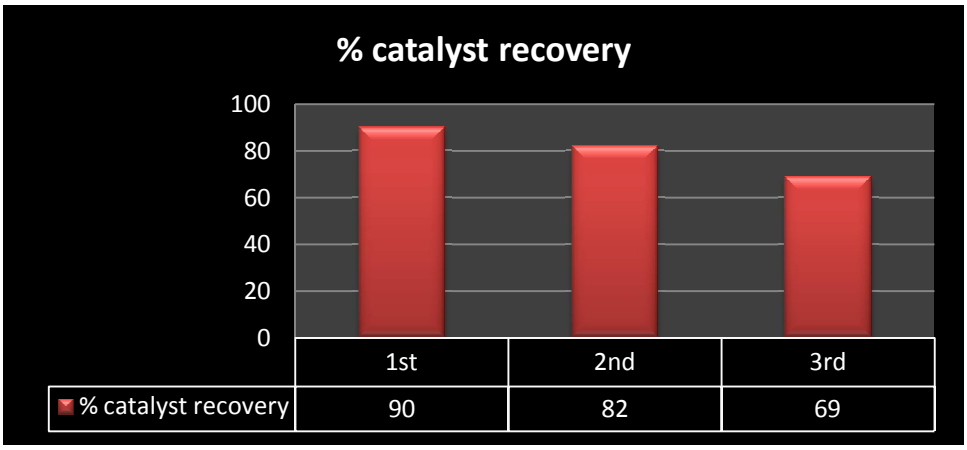


Figure 6: Recyclability of catalyst

So the final optimized condition for the synthesis of curcumin derivatives as benzaldehyde (0.01mol) in ethanol, curcumin (0.01mol) and hydrazine (0.01mol) in the presence of hydrotalcite 100 mg was refluxed for 4 hours upto 80°C.

Table 4: Physiochemical data of synthesized compound

Compound	% yield	*Rf value	Mol. Formula	Mol. Mass g/mol
B1	89.64	0.65	$C_{34}H_{37}N_3O_6$	583
B2	72.64	0.71	$C_{34}H_{37}N_3O_7$	599
B3	73.27	0.82	$C_{34}H_{37}N_3O_7$	599
B4	78.62	0.58	$C_{35}H_{39}N_3O_7$	613
B5	67.48	0.52	$C_{35}H_{39}N_3O_8$	629
B6	57.13	0.70	$C_{36}H_{42}N_4O_6$	626
D1	71.36	0.63	$C_{34}H_{37}N_3O_6$	583
D2	78.58	0.50	$C_{34}H_{38}N_2O_5$	554
D3	56.12	0.49	$C_{34}H_{36}N_4O_9$	644
D4	64.36	0.81	$C_{29}H_{35}N_3O_6$	521
D5	46.02	0.55	$C_{29}H_{35}N_3O_5S$	537
D6	58.14	0.69	$C_{30}H_{39}N_3O_5$	521

Characterization of synthesized compounds:

CMP-B1:(5-(3-hydroxy-4-methoxyphenethyl)-4-(1-hydroxy-2-(3,methoxy4hydroxyyphenyl) ethyl)-3-phenyl-1H-pyrazol-2(3H)-yl)(pyridin-4-yl)methanone structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group CN, NH, C=O and OH,(3379, 2265, 1680, 3254,1106 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 583.7(M^+) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m7.064-7.170) Ar-CH (4H, m7.180-7.182) Benz-CH (5H, m 7.6420-7.8386) NH(1H,s 5.881) CHO(1H, s11.441) Ar-NH(s 4.7488) Ar-OCH_3 amide (0H,s 6.001).

CMP-B2: (5-(3-hydroxy-4-methoxyphenethyl)-4-(1-hydroxy-2-(3, methoxy 4 hydroxyyphenyl) ethyl)-3-(1-hydroxyphenyl-1H-pyrazol-2(3H)-yl)(pyridin-4-yl)methanone structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH,(3254,1715, 3545 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 599.1(M^+) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m6.8745-7.4578) Ar-CH (4H, m 7.2365-7.3459) Benz-CH (5H, m 7.6875-7.8564)NH(1H,s 4.6985) CHO(1H, s 10.6236) Ar-NH(s 4.6254) Ar-CO amine (0H,s 5.8745).

CMP-B3: (5-(3-hydroxy-4-methoxyphenethyl)-4-(1-hydroxy-2-(3, methoxy 4 hydroxyyphenyl) ethyl)-3-(3-hydroxyphenyl-1H-pyrazol-2(3H)-yl)(pyridin-3-yl)methanone structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3452, 1622, 3326 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 599.1 (M^+) which matches to calculated molecular

weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m 7.6541-7.7845) Ar-CH Indole (4H, m 7.265-7.3256) Benz-CH (5H, m 7.4525-7.5021) NH(1H,s 5.784) CHO(1H, s 9.2354) Ar-NH(s 4.7154), Ar-NH^{2} (0H,s 5.1254).

CMP-B4: (5-(3-hydroxy-4-methoxyphenethyl)-4-(1-hydroxy-2-(3, methoxy 4 hydroxyyphenyl) ethyl)-3-(3-Methoxyyphenyl-1H-pyrazol-2(3H)-yl)(pyridin-3-yl)methanone structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3356, 1635, 3478 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 614.0 (M^{+}) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m 7.302-7.6384) Ar-CH (4H, m 7.231-7.282) Benz-CH (5H, m 7. 6874-7.6987) NH(1H,s 5.698) CHO(1H, s 9.2365) Ar-NH(s 4.8457) Ar-NH_2 (2H,s 6.1250).

CMP-B5: (5-(3-hydroxy-4-methoxyphenethyl)-4-(1-hydroxy-2-(3, methoxy 4 hydroxyyphenyl) ethyl)-3-(2-hydroxy3-Methoxyyphenyl-1H-pyrazol-2(3H)-yl)(pyridin-3-yl)methanone structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3345, 1662, 3471 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 630(M^{+}) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m 7.0365-7.2145) Ar-CH (4H, m 7.326-7.378) Benz-CH (5H, m 7. 524-7.586) NH(1H,s 5.457) COH(1H, s 9.1547) Ar-NH(s 4.7254) Ar-NH_2 (0H,s 5.2451).

CMP-B6: (5-(3-hydroxy-4-methoxyphenethyl)-4-(1-hydroxy-2-(3, methoxy 4 hydroxyyphenyl) ethyl)-3-(3-N,N-dimethylphenyl-1H-pyrazol-2(3H)-yl)(pyridin-3-yl)methanone structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3365, 1702, 3459 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 629.1 (M^{+}) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m 7.065-7.214) Ar-CH Indole (4H, m 7.345-7.425) Benz-CH (5H, m 7.578-7.648) NH(1H,s 5.469) CHO(1H, s 9.3251)Ar-NH(s 4.6587) Ar-NH_2 (0H,s 5.124).

CMP-D1: (5-(3-hydroxy-4-methoxyphenethyl)-4-(1-hydroxy-2-(3, methoxy 4 hydroxyyphenyl) ethyl)-3-(3-phenyl-1H-pyrazol-2(3H)-yl)(pyridin-3-yl)methanone structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3254, 1719, 3510 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 583.7 (M^{+}) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m 7.0874-7.1265) Ar-CH_3 (3H, m 7.324-7.394) Benz-CH (5H, m 7.578-7.682) NH(1H,s 5.657) CHO(1H, s 9.0245) Ar-NH(s 4.751) Ar-NH_2 (2H,s 5.326).

CMP-D2: 5-(2-(4-(1-hydroxy-3-(3-methoxy 4 hydroxyphenyl) propyl)-1,5-diphenylpyrazolidin-3-yl)ethyl)-2-methoxyphenol structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3345, 1652, 3425 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 554.1 (M^{+}) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m 7.154-7.215) Ar-CH (4H, m 7.356-7.482) Benz-CH (5H, m 7.548-7.6302) NH(1H,s 5.547) CHO(1H, s 9.4257) Ar-NH(s 4.7514) Ar-NH_2 (0H,s 5.324).

CMP-D3: 5-(2-(4-(1-hydroxy-3-(3-methoxy 4 hydroxyphenyl) propyl)-1,5-diphenylpyrazolidin-3-yl)ethyl)-2-phenyl2,4-dinitro structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3379, 1680, 3536 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 644.1 (M^{+}) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first carbon Ar-CH (4H, m 7.157-7.265) Ar-CH (4H, m 7.365-7.425)Benz-CH (5H, m 7.458-7.598) NH(1H,s 5.568) CHO(1H, s 8.457) Ar-NH(s 4.6587) Ar-NH_2 (2H,s 5.547).

CMP-D4: 5-(2-(4-(1-hydroxy-3-(3-methoxy 4 hydroxyphenyl) propyl)-1,5-diphenylpyrazolidin-3-yl)ethyl)-2-amide structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3365, 1698, 3525 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 521.6 (M^{+}) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first proton Ar-CH (4H, m 7.0658-7.254) Ar-CH (4H, m 7.352-7.347) Benz-CH (5H, m 7.678-7.854) NH(1H,s 5.758) CHO(1H, s 9.325) Ar-NH(s 4.7541) Ar-NH_2 (2H,s 5.451).

CMP D5: 5-(2-(4-(1-hydroxy-3-(3-methoxy 4 hydroxyphenyl) propyl)-1,5-diphenylpyrazolidin-3-yl)ethyl)-2-thiamide structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3335, 1672, 3565 cm-1) identified by the FTIR spectra. The molecular ion peak is obtained at 537.1 (M^{+}) which matches to calculated molecular weight of the proposed structure. The ^{1}H NMR spectra exhibit signal of first proton Ar-CH (4H, m 7.187-7.214) Ar-CH (4H, m 7.331-7.386) Benz-CH (5H, m 7.457-7.566) NH(1H,s 5.651) CHO(1H, s 9.255) Ar-NH(s 4.514)Ar-NH_2 (2H,s 5.741).

CMP D6: 5-(2-(4-(1-hydroxy-3-(3-methoxy 4 hydroxyphenyl) propyl)-1,5-diphenylpyrazolidin-3-yl)ethyl)-2-N,N-dimethyl structure is confirmed by FTIR, ^{13}C and ^{1}H NMR. This structure has functional group NH, C=O and OH, (3335, 1672, 3565 cm-1) identified by the FTIR spectra. The molecular ion peak is

obtained at 537.1 (M^+) which matches to calculated molecular weight of the proposed structure. The ^1H NMR spectra exhibit signal of first proton Ar-CH (4H, m 7.236-7.254) Ar-CH (4H, m 7.365-7.421) Benz-CH (5H, m 7.642-7.684) NH(1H,s 5.745) CHO(1H, s 10.265) Ar-NH(s 4.678) Ar-NH (1H,s 5.265).

Antioxidant Activity of synthesized compounds:

Free radical scavenging is one of the best known mechanisms by which antioxidants inhibit lipid oxidation. DPPH, hydroxyl, nitric oxide, and superoxide radical scavenging activity evaluations are standard assays in antioxidant activity studies[32]. The antioxidant activity of the synthesized curcumin derivatives **(B1-D6)** were determined by Two methods using ascorbic acid (AA) and butylated hydroxy anisole (BHA) as standards.

DPPH Radical Scavenging Activity:

The *in-vitro* antioxidant activities of compounds (B1-D6) were determined spectro photometrically by DPPH radicals, and the results are given in below table. DPPH radicals are stable free radicals, and in the presence of molecules capable of donating H atoms, their radical character is neutralized. The reduction capacity of DPPH radicals was determined by the decrease in its absorbance at 517 nm, which is induced by antioxidants. On the other hand, it is well established that organic molecules incorporating an electron donating groups (amine, hydroxyl, and methoxy) can act as free radical trapping agents and are capable of opposing oxidative challenges. It can be seen from present Table that compounds **B1**, **B3** and **B5** present the highest scavenging activity on DPPH•, whereas the compounds **B4**, **B6**, **D1**, and **D6** exhibit moderate and **B2**, **D2**, **D3**, **D4** and **D5** showed very low scavenging activity on DPPH•, respectively.

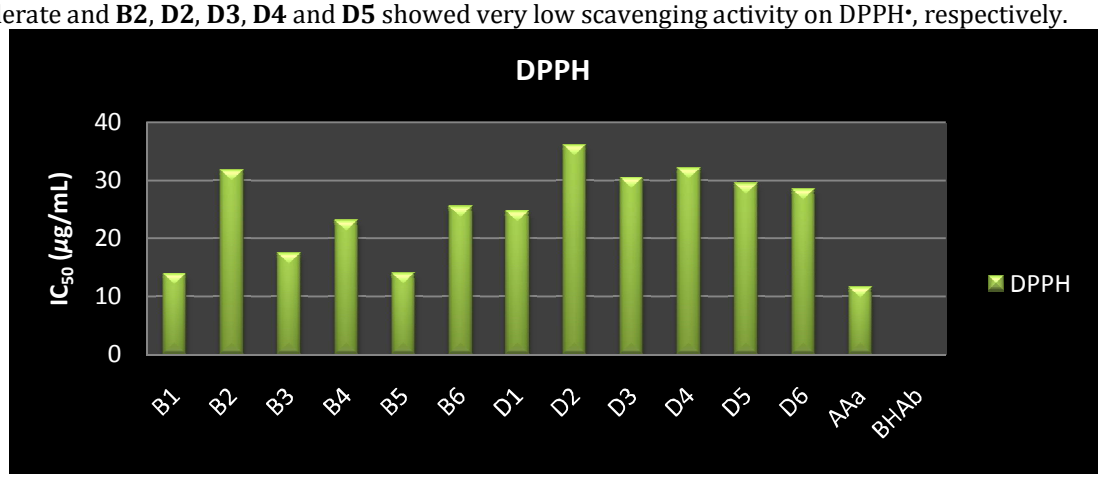


Fig 7: DPPH Radical Scavenging Activity

Hydroxyl Radical Scavenging Activity:

The IC_{50} values of compounds **(B1-D6)** in this assay were in the range of 16.9 to 42.2 μg/mL. The IC_{50} values obtained are more than that of the standard. The compounds **B1** and **B5** were found to show better inhibition compared to other compounds with IC_{50} values 16.9 and 17.00 μg/mL, respectively. The compounds **D2**, **D3**, and **D4** showed poor radical scavenging activity compared to the standard. The results were compared with standard BHA (15.3 μg/mL) which was more effective than the compounds tested.

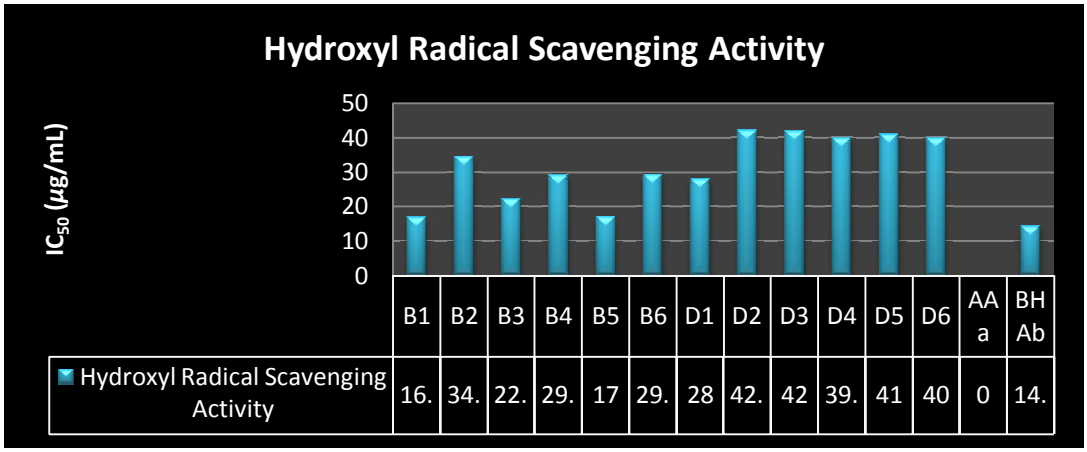


Fig 8: Hydroxyl Radical Scavenging Activity

Table 6: IC_{50} values for evaluated antioxidant assays of examined

Compounds Code	DPPH	HO^-
B1	13.9±0.10	16.9±0.11
B2	31.8±0.15	34.6±0.16
B3	17.4±0.65	22.2±0.14
B4	23.1±0.10	29.1±0.16
B5	14.0±0.17	17.0±0.11
B6	25.5±0.10	29.3±0.62
D1	24.7±0.44	28.0±0.47
D2	36.1±0.10	42.2±0.36
D3	30.5±0.25	42.0±0.01
D4	32.1±0.18	39.9±0.11
D5	29.5±0.25	41.0±0.01
D6	28.5±0.64	40.0±0.26
AA[a]	11.6±0.14	-
BHA[b]	-	14.3±0.11

CONCLUSION

All the compounds **(B1-D6)** showed comparable or slight less activity to the standard (ascorbic acid). Compounds **B1** to **D6** bearing a hydroxyl group (electron donating group) at para position showed dominant DPPH activity. The presence of nitro group (electron withdrawing group) **D3** instead of a hydroxyl group in the same position exhibits less activity compared to compounds **B3** and **B5**. When methoxy groups are added in the 2, 3, or 4 positions on the phenyl ring, the antioxidant activity is increased (**B1**, **B3**, and **B5**). This activity may be correlated with the introduction of electron donor substituent which stabilizes the generated radical during oxidation.

In conclusion, a series of new curcumin derivatives (B1-D6) were synthesized in good yield and were characterized by different spectral studies. The synthesized compounds showed a wide range of potentially promising antioxidant activities. Compounds **B1**, **B3**, and **B5** showed significant scavenging effect against the tested free radicals.

ACKNOWLEDGMENT

Authors are highly acknowledge to Central Instrument Facility lab of Jiwaji University, Gwalior for providing help to characterize compounds and also acknowledge to Faculty and Research Scholars of Department of Pharmacy.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest

REFERENCES

1. Wongcharoen W, Phrommintikul A, The protective role of curcumin in cardiovascular diseases. Int J Cardiol 133 (2009) 145–151
2. Maher P, Akaishi T, Schubert D, Abe K A, pyrazole derivative of curcumin enhances memory. Neurobiol Aging 31 (2010) 706–709
3. Shen L, Zhang HY, Ji HF, A theoretical study on Cu(II)- chelating properties of curcumin and its implications for curcumin as a multipotent agent to combat Alzheimer's disease. J Mol Struct THEOCHEM 757 (2005) 199–202
4. Gomez G, Mansouraty G, Gardea J, Narayan M, Acceleration of oxidative protein folding by curcumin through novel nonredox chemistry. Biochem Biophys Res Co 364 (2007) 561–566
5. Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL, A potential role of the curry spice curcumin in Alzheimer's disease. Curr Alzheimer Res 2 (2005) 131–136
6. Lopez-Lazaro M, Anticancer and carcinogenic properties of curcumin: considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. Mol Nutr Food Res 52 (2008) 103–127
7. Aggarwal BB, Kumar A, Bharti AC, Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res 23 (2003) 363–398
8. Patel BB, Sengupta R, Qazi S, Vachhani H, Rishi AK, Majumdar APN, Yu Y, Curcumin enhances the effects of 5-fluorouracil and oxaliplatin in mediating growth inhibition of colon cancer cells by modulating EGFR and IGF-1R. Int J Cancer 122 (2008) 267–273
9. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB, Curcumin and cancer: an ''old-age'' disease with an ''age-old'' solution. Cancer Lett 267 (2008) 133–164
10. Lin CL, Lin JK, Curcumin: a potential cancer chemopreventive agent through suppressing NF-jB signaling. J Cancer Mol 4 (2008) 11–16

11. Sahu PK, Gupta SK, Thavaselvam D, Agarwal DD, Synthesis and evaluation of antimicrobial activity of 4H-pyrimido[2,1-b]benzo. Eur J Med Chem 54 (2012) 366–378
12. Rai D, Yadav D, Bamzarini J, De Clercq E, Singh RK, Design and development of curcumin bioconjugates as antiviral agents. Nucleic Acids Symp 52 (2008) 599–600
13. Kuhad A, Chopra K, Curcumin attenuates diabetic encephalopathy in rats: behavioral and biochemical evidences. Eur J Pharmacol 576 (2007) 34–42
14. Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee RK, Turmeric and curcumin: biological actions and medicinal applications. Curr Sci 87 (2004) 44–53
15. Chainani-Wu N, Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa). J Altern Complement Med 9 (2003) 161–168
16. Sharma OP, Antioxidant activity of curcumin and related compounds. Biochem Pharmacol 25 (1976) 1811–1812
17. Balogun E, Hoque M, Gong P, Killeen E, Green CJ, Foresti R, Alam J, Motterlini R, Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. Biochem J 371 (2003) 887–895
18. Santo RD, Costi R, Artico M, Tramontano E, Colla PL, Pani A, HIV-1 integrase inhibitors that block HIV-1 replication in infected cells. Planning synthetic derivatives from natural products. Pure Appl Chem 75 (2003) 195–206
19. Hadda TB, Ali MA, Masand V, Gharby S, Fergoug T, Warad I, Tautomeric origin of dual effects of N1-nicotinoyl-3-(40- hydroxy-30-methyl phenyl)-5-[(sub)phenyl]-2-pyrazolines on bacterial and viral strains: POM analyses as new efficient bioinformatics' platform to predict and optimize bioactivity of drugs. Med Chem Res 22 (2013) 1438–1449
20. Sheikh J, Hadda TB, Antibacterial, antifungal and antioxidant activity of some new water-soluble b-diketones. Med Chem Res 22 (2013) 964–975
21. Chohan ZH, Youssoufi MH, Jarrahpour A, Hadda TB, Identification of inhibition: indolenyl sulphonamide derivatives. Eur J Med Chem 45 (2010) 1189–1199
22. Domling A, Wang W, Wang K. Chemistry and biology of multicomponent reactions. Chemical reviews. 2012 Jun 13;112(6):3083-135.
23. Toure BB, Hall DG. Natural product synthesis using multicomponent reaction strategies. Chemical reviews. 2009 Sep 9;109(9):4439-86.
24. Tejedor D, Garcia-Tellado F. Chemo-differentiating ABB′ multicomponent reactions. Privileged building blocks. Chemical Society Reviews. 2007;36(3):484-91.
25. Saha MR, Hasan SM, Akter R, Hossain MM, Alam MS, Alam MA, Mazumder ME. In vitro free radical scavenging activity of methanol extract of the leaves of Mimusopselengi Linn. Bangladesh Journal of Veterinary Medicine. 2008;6(2):197-202.
26. A.Corma, S. Iborra, S. S. Miquel and J. Primo, J. Catal., 1998, 173, 315.
27. Sahu P. K., Sahu P. K., Jain R., Yadav R. and Agarwal D. D., Hydrotalcite: recyclable, novel heterogeneous catalyst for facile, environmentally benign and high yielding multi-component synthesis and mechanistic study undersolvent free conditions, Catal. Sci. Tech. (2012). 2465-2475.
28. Robu M, Tanase C, Boscornea C, Tomas S, Albulescu R. Curcumin derivatives with potential biological activity. circulation. 2009 Jan 1;4:5.
29. Alshehri SM, Naushad M, Ahamad T, Alothman ZA, Aldalbahi A. Synthesis, characterization of curcumin based ecofriendly antimicrobial bio-adsorbent for the removal of phenol from aqueous medium. Chemical Engineering Journal. 2014 Oct 15; 254:181-9.
30. Khan AT, Lal M, Ali S, Khan MM. One-pot three-component reaction for the synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst. Tetrahedron Letters. 2011 Oct 12;52(41):5327-32.
31. Bratu MG. Synthesis of curcumin derivatives. Acta Universitatis Cibiniensis Series E: Food Technology. 2005;9(1):11.
32. Patel Rajesh M, Patel Natvar J. In vitro antioxidant activity of coumarin compounds by DPPH, Super oxide and nitric oxide free radical scavenging methods. Journal of advanced pharmacy education & research. 2011;1: 52-68.

CITATION OF THIS ARTICLE

G Rupendra, J Suman, Agarwal D D. Multicomponent Synthesis and evaluation of Antioxidant activity of Curcumin Derivatives by using Hydrotalcites as Green Catalyst. Bull. Env. Pharmacol. Life Sci., Vol10[8] July 2021 : 137-148