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Review Of Research

DESIGN, SYNTHESIS, CHRACTERIZATION AND ANTIOXIDANT EVALUATION OF NOVEL ASYMMETRICAL METHOXY CURCUMIN ANALOGUES CONTAINING CHROMONE MOIETY

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ABSTRACT

Structurally novel series mono-carbonyl curcumin analogues have been designed and synthesized as Asymmetrical Methoxy Chromone Curcumin Analogues (AMCCAs) 8a–c & 9a-c from various substituted amide ketones(5a-c &7a-c) and 3- formyl 6- Methoxy Chromone aldehyde (2) by using polyethylene glycol (PEG-400) as a green reaction medium and tested for their in vitro anti-oxidant activity by (H_2O_2, DPPH, Ferrous reducing power scavenging activity). Many synthetic modifications of curcumin have been studied and modified intensively in order to develop a molecule with enhanced bioactivities. All the synthesized compounds were characterized by IR, ^{1}HNMR. Among the tested series, compounds 8b ,8c, 9b and 9c exhibited excellent, whereas compounds 8a ,9a showed moderate scavenging activity to hydrogen peroxide scavenging activity as compared to the standard butylated hydroxy toluene (BHT), DPPH free radical scavenging activity and ferrous-reducing power activity, against standard ascorbic acid.

KEYWORDS: *3- Formyl chromone aldehyde, 3- Formyl 6- methoxy chromone aldehyde, Asymmetical Methoxy Chromone Curcumin(AMCCA), PEG-400, Antioxidant activity.*

INTRODUCTION:

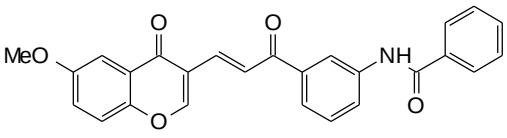
Naturally Curcumin is popular carbon analogue, polyphenolic or diferuloylmethane molecule, extracted from the rhizome of the herb Curcuma longa (turmeric)[1-3] which has been used for centuries as a dietary pigment and widely used as a food colorant.[4] Curcumin is a β-diketone component of the turmeric, a yellow pigment of spice used as curry ingredient and has been used for centuries in Ayurvedic, and Hindu as habitual medicine in India, China and Southeast Asia. It is reachable natural product of compounds which were found to be good source of novel and potent bioactive compounds with negligible side effects in vivo[5-7]. Curcumin has a potent antioxidant activity [8-9]and various curcumin related phenols have also been found in edible or medicinal plants, especially in Zingiberaceae. Curcumin has a unique conjugated structure including two methoxylated phenols and an enol form β-diketone. The antioxidant mechanism of curcumin has attracted much attention. [10]

Many investigations have shown that curcumin and its derivatives have several biological activities. The main pharmacological effects include anti-oxidation[11], anti-inflammatory[12], anti-fungal[13], anti-bacterial[14] anti-tumor and anticancer[15] activities. During the last decade, synthetic modifications of curcumin, which were aimed at enhancing its bioactivities, have been intensively studied. However few of these studies were focused on the improvement of its pharmacokinetic profiles. It is suggested that the stability and metabolic profiles of curcumin could be enhanced by deleting the β--diketone moiety. Although curcumin is remarkably non-toxic natural product.

Poly ethylene glycols of different molecular weights are comprehensively used as solvents in diverse pharmaceutical industries. The use of PEG as a green and alternative reaction medium in organic reactions is relatively recent is the great success of the development of new selective eco-friendly methodologies[16-19] in the preparation of biologically active compounds. Synthesis of asymmetrical methoxyc chromone curcumin analogues (AMCCAs) using aq. NaOH in PEG-400 as green alternative reaction medium and evaluate them as antioxidant agent. To the best of our knowledge, this is the first report of this synthesis as antioxidant evaluation of newly synthesized of Chromone curcumin analogues (CCAs).

CHEMISTRY:

Though Curcumin is non toxic and biologically active moiety, up till now many curcumin analogues have been synthesized. Robinson et al.[20] have synthesized enone and dienone analogues. Bandgar et al.[21] have synthesized novel curcumin mimics containing olefin as well as aromatic, alicyclic or heteroaromatic amide moieties and evaluated for antioxidant, cytotoxic and antimicrobial activity. Bandgar et al.[22] have also synthesized novel curcumin analogues and evaluated as anti-inflammatory, anticancer and antioxidant agents. Herein, we have synthesized the new curcumin methoxy analogues containing enone and amide including chromone moiety. The title compounds asymmetrical methoxy chromone curcumin analogues (AMCCAs) were prepared by the acylation of 3-amino acetophenone and 4- amino acetophenone with methoxy and fluoro benzoyl chloride to afford corresponding amide (5a-c) and (7a-c) which on Claisen-Schmidt condensation with 3- formyl 6- methoxy chromone aldehydes (2) and NaOH in PEG-400 prepared AMCCAs (8a–c & 9a-c) in good to excellent yields (Scheme 3a & -3b). The completion of the reaction was monitored by TLC. The substituted 3- formyl 6- methoxy chromone aldehydes (2) was prepared by the Vilsmeier–Haack reaction[23] from 2-hydroxy 5- methoxy acetophenone (1) using DMf/$POCl_3$. All the synthesized compounds were characterized by IR, ^{1}HNMR.



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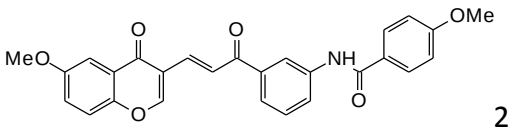

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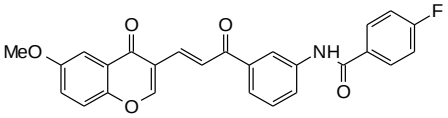

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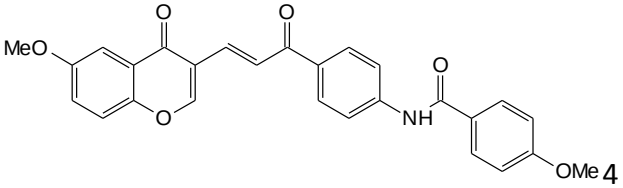

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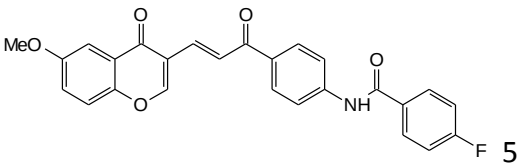

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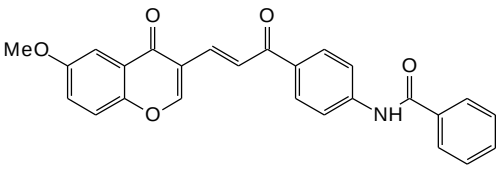

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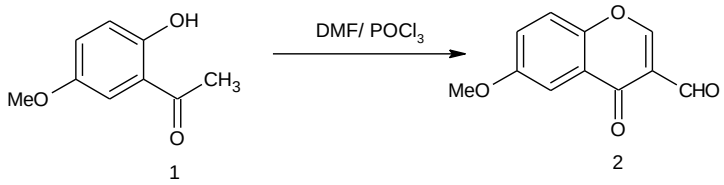
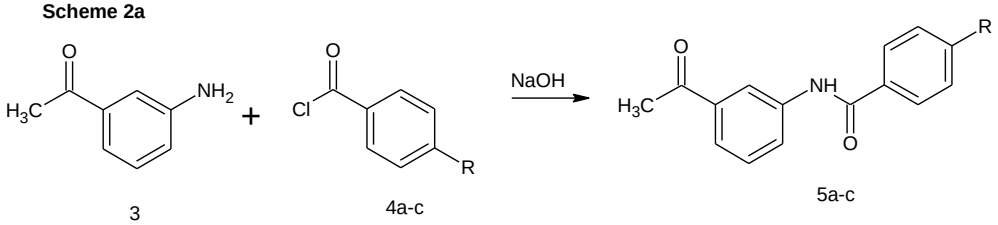
Scheme 1



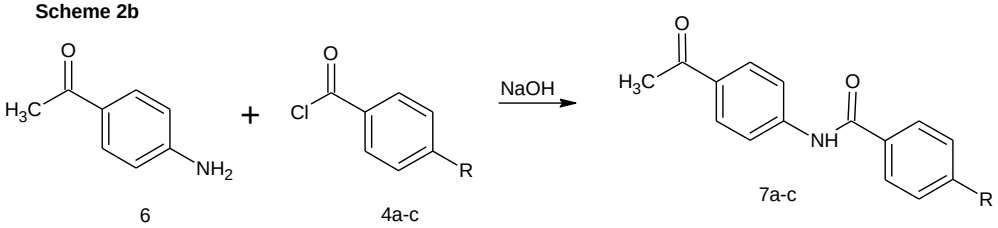
1 2

Scheme 2a



3 4a-c 5a-c

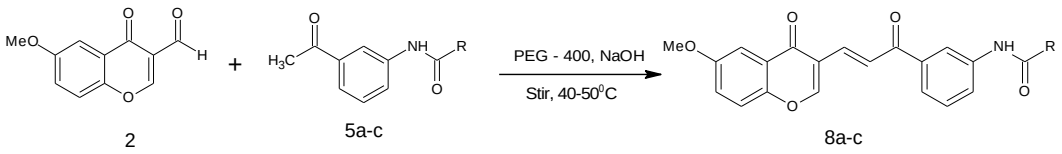
Scheme 2b



6 4a-c 7a-c

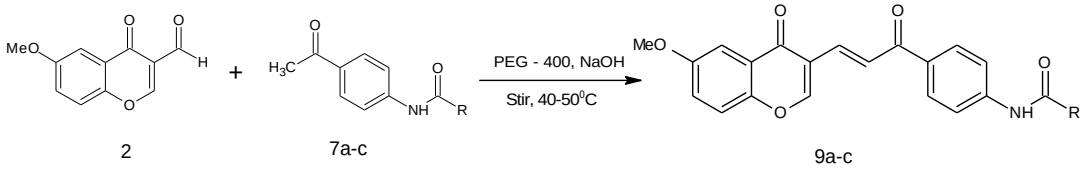
R = -H, -OMe, -F

Scheme 3 a



2 5a-c 8a-c

Scheme 3b



2 7a-c 9a-c

R = -Ph, 4-OMe-Ph, 4-F-Ph

GENERAL INSTRUMENTATION:

IR spectra were recorded on FT-IR spectrometer (Perkin Elmer, Maharashtra, India) using KBr disk method. 1HNMR spectra were recorded on 1HNMR (Varian-NMR-mercury 300 MHz) spectrometer in $CDCl_3$ as solvent. All chemical shifts (d) are quoted in parts per million downfield from TMS and coupling constants (J) are given in hertz. Abbreviations used in the splitting pattern were as follows: s = singlet, d = doublet, t = triplet, q = quintet and m = multiplet. All the reagents and solvents were used of analytical grade and used as supplied unless otherwise stated. Thin layer chromatography was performed on silica gel coated plates for monitoring the reactions. The spots could be visualized easily under UV light.

General procedure for synthesis of 3- formyl methoxy chromone aldehyde 2 :

In dry DMF (60 ml) in three neck flask, POCl3 (37.5 ml) was added slowly with vigorous stirring at 50 ^{0}C. Heating and stirring was continued for 2 hrs at 45-55 ^{0}C. The solution of 2- hydroxyl 5-methoxy acetophenone (9.12 gm) in DMF (12.5 ml) was then slowly added with stirring at 50 ^{0}C and stirring was continued for 2 hrs.[24-25] After cooling the mixture was kept overnight at room temperature and diluted slowly by adding ice cold water (250 ml) and was stirred for 6hrs. The red crystalline product separated was filtered and recrystallised from alcohol

General procedure for the preparation N-(3-Acetylphenyl)- 4-hydro/methoxy/fluoro-benzamide (5a-c):

1-(3-Amino-phenyl) ethanone 1 (1 g, 7.40 mM) was suspended in 20 mL of 5% of sodium hydroxide solution in round bottom flask and added 2 mL 4-substituted (R= H, & OMe & F) benzoyl chloride, 0.5 mL at a time, with constant shaking and stirred vigorously for 10 min, reaction mixture was heated under reflux on water bath at 70–80 °C for 30 min until the odor of the 4-substituted (R= H, & OMe & F) benzoyl chloride was disappeared. Make sure that the mixture has an alkaline pH. Filter off the solid benzoyl erivative and recrystallized it from petroleum ether and ethyl acetate to obtain compound (5a-c).

General procedure for the preparation N-(4-Acetylphenyl) - 4- hydro/methoxy/fluoro-fluoro-benzamide (7a-c):

1-(4-Amino-phenyl) ethanone 1 (1 g, 7.40 mM) was suspended in 20 mL of 5% of sodium hydroxide solution in round bottom flask and added 2 mL 4-substituted (R= H, OMe & F) benzoyl chloride, 0.5 mL at a time, with constant shaking and stirred vigorously for 10 min, reaction mixture was heated under reflux on water bath at 70–80 °C for 30 min until the odor of the 4-substituted (R= H, OMe & F) benzoyl chloride was disappeared. Make sure that the mixture has an alkaline pH. Filter off the solid benzoyl erivative and recrystallized it from petroleum ether and ethyl acetate to obtain compound(7a-c).

Synthesis of Asymmetrical methoxy Chromone Curcumin Chalcones (8a-c) :

A mixture of different substituted amide ketones N-(3-Acetylphenyl)- 4-hydro/methoxy/fluoro-benzamide (5a-c) and 3- formyl chromone carbaldehyde 2 (1 mmol) was dissolved in 15 ml PEG-400. To this mixture, sodium hydroxide (20%, 1ml) was added and the reaction mixture was stirred at 40-50 ^{0}C temperature for 1 hr.[26] The reaction mixture was then poured into 100 ml ice cold water. The product was separated out, it was filtered and processed out. The obtained products were recrystallised (8a-c) from ethanol to afford pure compounds.

Synthesis of asymmetrical methoxy chromone Curcumin Chalcones (9a-c) :

A mixture of different substituted amide ketones N-(4-Acetylphenyl)- 4-hydro/ methoxy/fluoro-benzamide (7a-c) and 3- formyl chromone carbaldehyde 2 (1 mmol) was dissolved in 15 ml PEG-400. To this mixture, sodium hydroxide (20%, 1ml) was added and the reaction mixture was stirred at 40-50 ^{0}C temperature for 1 hr.[26] The reaction mixture was then poured into 100 ml ice cold water. The product was separated out, it was filtered and processed out. The obtained products were recrystallised (9a-c) from ethanol to afford pure compounds.

The spectral data of synthesized compounds (8a-c & 9a-c):

8a. : *N*-(3-((2*E*)-3-(6-methoxy-4-oxo-4*H*-chromen-3-yl)acryloyl)phenyl)benzamide

1H NMR (CDCl3, 300 MHz):

δ 3.73 (s, 3H), **Aromatic protons -** δ 7.15 (d, 1H, ArH), δ 6.88 (d,1H, ArH), δ 6.81 (d, 1H, ArH), δ7.22 (s,1H, ArH, near to 'O' of Chromone), **Unsaturated C=C-C=O -** δ 7.76 (d, 1H) & δ 7.82 (d, 1H), J= 15.5Hz.

Aromatic protons - δ 8.19 (d, 1H), 7.55 (d,1H), δ7.43 (d,1H), δ7.92 (d,1H) δ8.0(s,1H) – N-H of Amide**.** ArH - δ 7.95 (d,1H) J=6.5Hz. , δ 7.44 (d,1H), δ7.51 (d,1H), δ 7.44 (d,1H) J=6.4Hz, δ 7.95 (d,1H).

8b : 4-**methoxy-*N*-(3-((2*E*)-3-(6-methoxy-4-oxo-4*H*-chromen-3-l)acryloyl)phenyl)benzamide**

1H NMR (CDCl3, 300 MHz):

δ 3.73 (s, 3H), **Aromatic protons -** δ 7.15 (d, 1H, ArH), δ 6.88 (d,1H, ArH), δ 6.81 (d, 1H, ArH), δ7.22 (s,1H, ArH, near to 'O' of Chromone), **Unsaturated C=C-C=O -** δ 7.76 (d, 1H) & δ 7.82 (d, 1H), J= 15.5Hz.

Aromatic protons - δ 8.19 (d, 1H), 7.55 (d,1H), δ7.43 (d,1H), δ7.92 (d,1H) δ8.0(s,1H) – N-H of Amide**.** ArH - δ 7.84 (d,1H)) J=6.5Hz , δ 6.95 (d,1H), δ3.75 (s,1H) for OMe methoxy protons, δ 6.95 (d,1H) J=6.4Hz, , δ 7.84 (d,1H).

8c: 4-fluoro-*N*-(3-((2*E*)-3-(6-methoxy-4-oxo-4*H*-chromen-3-yl)acryloyl)phenyl)benzamide

1H NMR (CDCl3, 300 MHz):

δ 3.73 (s, 3H), **Aromatic protons -** δ 7.15 (d, 1H, ArH), δ 6.88 (d,1H, ArH), δ 6.81 (d, 1H, ArH), δ7.22 (s,1H, ArH, near to 'O' of Chromone), **Unsaturated C=C-C=O -** δ 7.76 (d, 1H) & δ 7.82 (d, 1H), J= 15.5Hz.

Aromatic protons - δ 8.19 (d, 1H), 7.55 (d,1H), δ7.43 (d,1H), δ7.92 (d,1H) δ8.0(s,1H) – N-H of Amide**.** ArH - δ 7.93 (d,1H)) J=6.5Hz , δ 7.15 (d,1H), δ 7.15 (d,1H) J=6.4Hz, , δ 7.93 (d,1H) near to electronegative F.

9a : *N*-(4-((2*E*)-3-(6-methoxy-4-oxo-4*H*-chromen-3-yl)acryloyl)phenyl)benzamide

1H NMR (CDCl3, 300 MHz):

δ 3.73 (s, 3H), **Aromatic protons -** δ 7.15 (d, 1H, ArH), δ 6.88 (d,1H, ArH), δ 6.81 (d, 1H, ArH), δ7.22 (s,1H, ArH, near to 'O' of Chromone), **Unsaturated C=C-C=O -** δ 7.76 (d, 1H) & δ 7.82 (d, 1H), J= 15.5Hz.

Aromatic protons - δ 7.79 (d, 1H), 7.79 (d,1H), δ7.83 (d,1H), δ7.83 (d,1H), δ8.0(s,1H) – N-H of Amide**.** ArH - δ 7.95 (d,1H)) J=6.5Hz , δ 7.44 (d,1H), δ 7.51 (d,1H), δ 7.44 (d,1H) J=6.4Hz, δ 7.95 (d,1H) .

9b:4-methoxy-*N*-(4-((2*E*)-3-(6-methoxy-4-oxo-4*H*-chromen-3-yl)acryloyl)phenyl)benzamide

1H NMR (CDCl3, 300 MHz):

δ 3.73 (s, 3H), **Aromatic protons -** δ 7.15 (d, 1H, ArH), δ 6.88 (d,1H, ArH), δ 6.81 (d, 1H, ArH), δ7.22 (s,1H, ArH, near to 'O' of Chromone), **Unsaturated C=C-C=O -** δ 7.76 (d, 1H) & δ 7.82 (d, 1H), J= 15.5Hz.

Aromatic protons - δ 7.79 (d, 1H), 7.79 (d,1H), δ7.83 (d,1H), δ7.83 (d,1H), δ8.0(s,1H) – N-H of Amide**.** ArH - δ 7.84 (d,1H)) J=6.5Hz , δ 6.95 (d,1H), δ 3.73 (s,3H) for OMe methoxy substitutent, δ 6.95 (d,1H) J=6.4Hz, , δ 7.84 (d,1H) .

9c : 4-fluoro-*N*-(4-((2*E*)-3-(6-methoxy-4-oxo-4*H*-chromen-3-yl)acryloyl)phenyl)benzamide

1H NMR (CDCl3, 300 MHz):

δ 3.73 (s, 3H), **Aromatic protons -** δ 7.15 (d, 1H, ArH), δ 6.88 (d,1H, ArH), δ 6.81 (d, 1H, ArH), δ7.22 (s,1H, ArH, near to 'O' of Chromone), **Unsaturated C=C-C=O -** δ 7.76 (d, 1H) & δ 7.82 (d, 1H), J= 15.5Hz.

Aromatic protons - δ 7.79 (d, 1H), 7.79 (d,1H), δ7.83 (d,1H), δ7.83 (d,1H), δ8.0(s,1H) – N-H of Amide**.** ArH **-** δ 7.93 (d,1H)) J=6.5Hz, δ 7.15 (d,1H), due to 'F' fluoro substitutent δ 7.15 (d,1H), δ 7.93 (d,1H) .

BIOLOGICAL STUDIES:

IN *VITRO ANTI-OXIDANTACTIVITY* :

Hydrogen Peroxide (H_2O_2) Scavenging Activity :

The hydrogen peroxide scavenging assay was performed by the reported method [27]. A solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (pH 7.4). The 1 mM concentrations of various compounds (8a–c) & (9a-c) were added to a hydrogen peroxide solution (0.6 mL, 40 mM). Absorbance of hydrogen peroxide at 230 nm was determined after 10 min. against a blank solution containing phosphate buffer without drug. The percentage scavenging of hydrogen peroxide of synthetic compounds and standard compounds was calculated using the following formula:

% scavenged ½ H_2O_2 = [(A_0- A_1) / A_0]

here, A_0 = the absorbance of the control.

A_1 = the absorbance in the presence of the sample of MO and standards.

Dpph Radical Scavenging Activity :

The ability of compounds to scavenge DPPH radical was assessed using literature method with slight modification. Briefly, 1 mL of synthesized compounds (8a-c & 9a-c) as 100 mM was mixed with 3.0 mL DPPH (0.5 mmol/L in methanol), the resultant absorbance was recorded at 517 nm after 30 min. incubation at 37 °C. The percentage of scavenging activity was derived using the following formula,

Percentage of inhibition (%) = [(A control – A sample) / A control] x 100

Where A control - absorbance of DPPH

A sample - absorbance reaction mixture (DPPH with Sample).

Ferrous Reducing Power :

The reducing ability of compounds was measured according to the reported method [27]. 100 mM of the synthesized compounds (1.0 mL) was mixed with 2.5 mL of phosphate buffer (0.2 M, pH 6.6) and 2.5 mL of potassium ferricyanide (1%). The mixture was incubated at 50 °C for 20 min. with TCA (10%: 2.5 mL). Then mixture was centrifuged at 1209.6 rcf. for 10 min. The supernatant (2.5 mL) was mixed with 2.5 mL of distilled water and 0.5 mL of ferric chloride (1%), and the absorbance was measured at 700 nm. Higher absorbance of the reaction mixture indicated greater reducing power. The reducing power of compounds was compared with that of standard antioxidant.

Table-1 : In vitro antioxidant activity of compounds.

Entry	% Inhibition Antioxidant activity in vitro		
	H_2O_2	DPPH	Ferrous reducing power (%)
8a	41.03	24.84	33.76
8b	57.12	32.85	31.22
8c	54.34	24.82	22.65
9a	55.65	35.66	38.52
9b	**75.66**	**40.67**	**43.28**
9c	**81.52**	**41.23**	**45.34**
BHT	**86.62**	---	--
Ascorbic acid	---	**42.77**	**42.44**

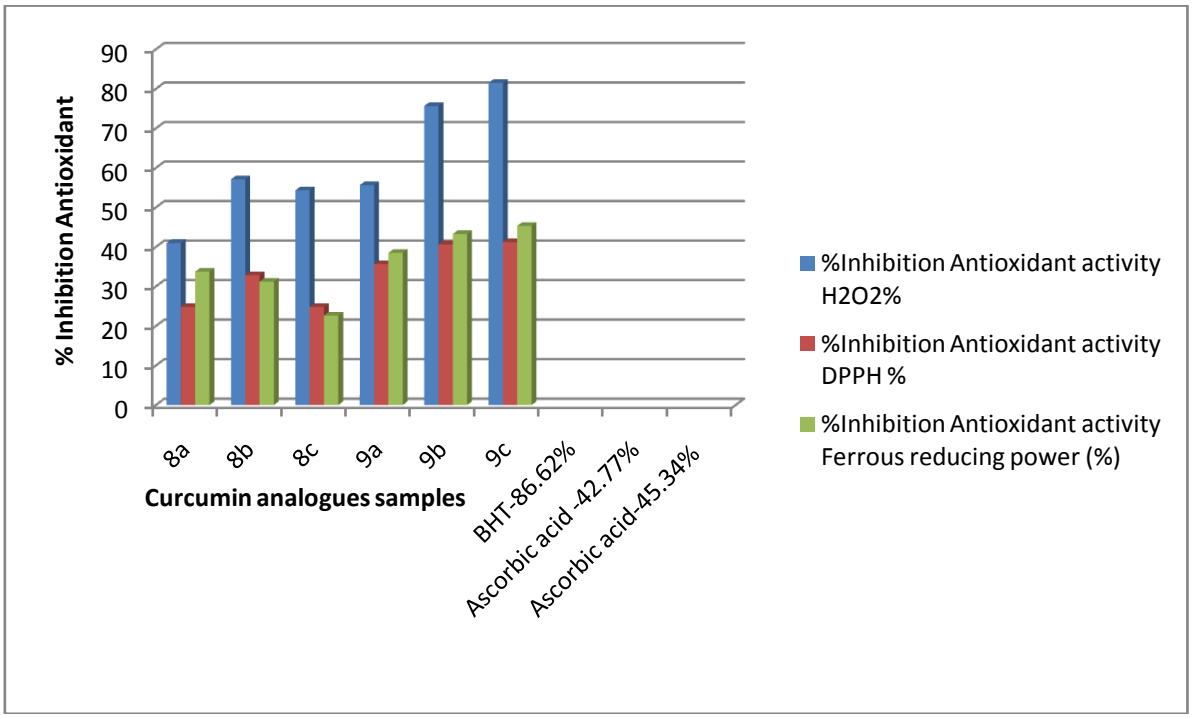


Figure 1- Comparison between % inhibition antioxidant activity of H_2O_2, DPPH and Ferrous reducing power.

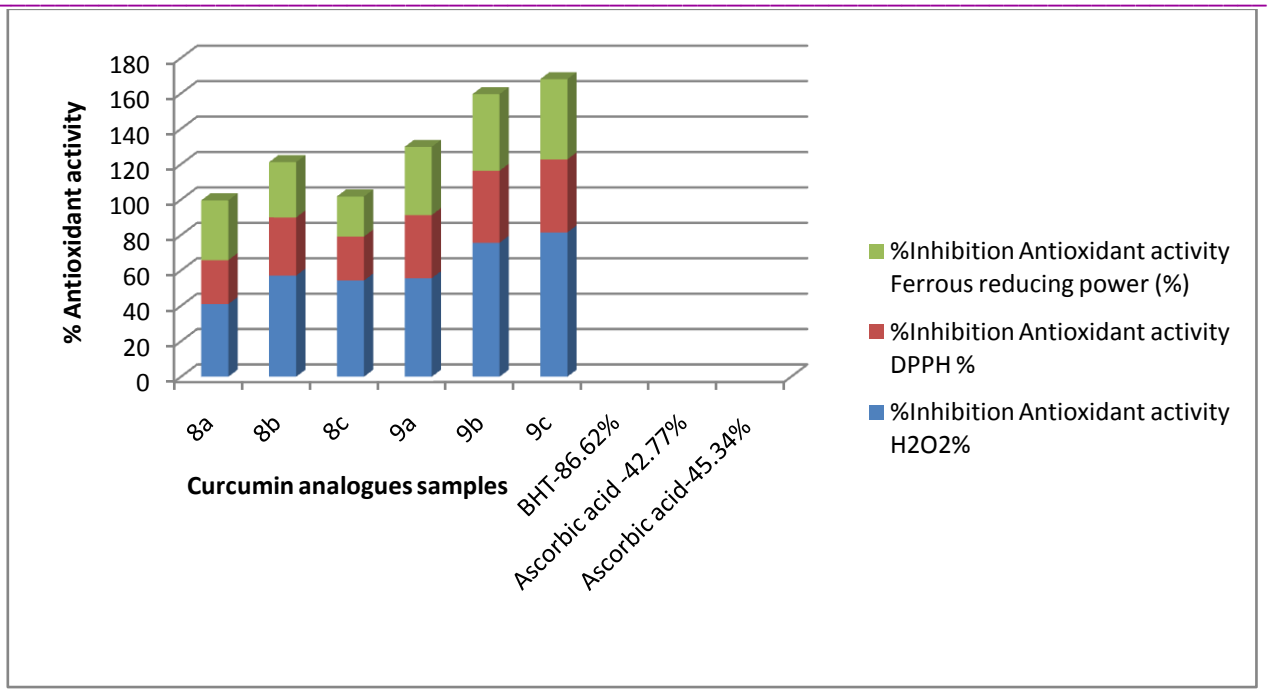


Figure 2- Extent of % inhibition antioxidant activity of H_2O_2, DPPH and Ferrous reducing power.

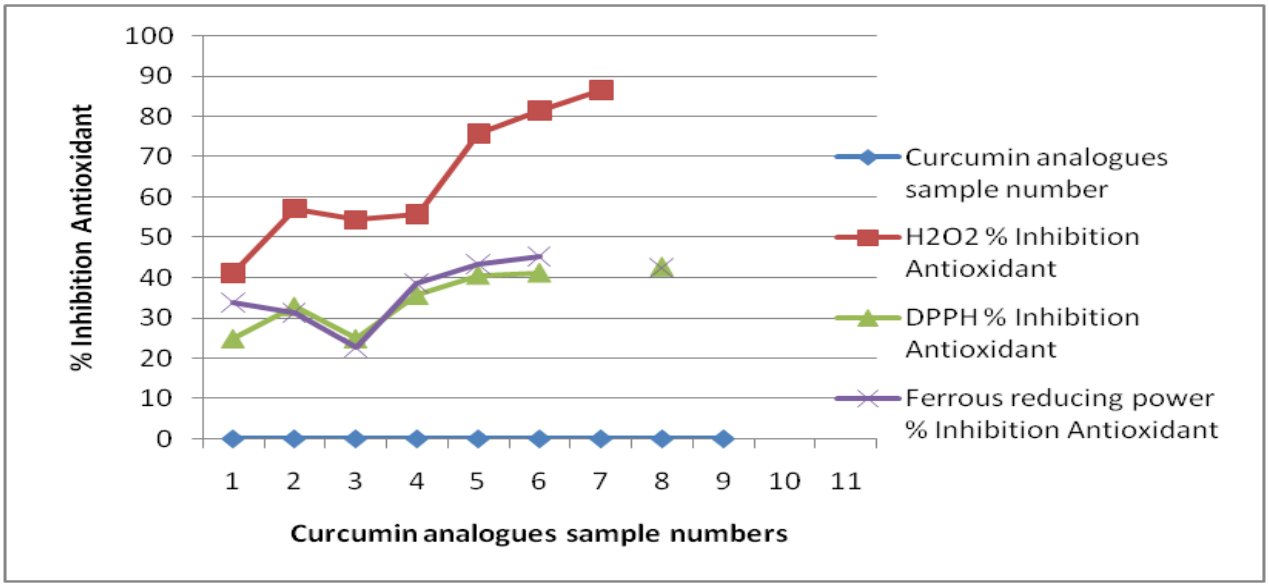


Figure 3 – Difference in % inhibition antioxidant activity due to H_2O_2, DPPH and Ferrous reducing power.

In Vitro Antioxidant Activity :

We have determined antioxidant activity of synthesized asymmetrical methoy pyrazole curcumin analogues (AMPCAs) against reactive oxygen species such as hydrogen peroxide, DPPH, ferrous reducing power. Results are shown in Table 1. All the synthesized compounds showed good to moderate scavenging activity against hydrogen peroxide. The antioxidant activity result revealed that the compound [28-29] 9b & 9c (75.66 & 81.52 %) was found to possess excellent inhibition of H_2O_2. scavenging activity as compared to the BHT (86.62%). The remaining compounds 8a, 8b, 8c, and 9a showed (44–55%) moderate inhibition of H_2O_2 scavenging activity.

In case of DPPH free radical scavenging activity, compounds 8a, 8b, 8c and 9a exhibited good activity (24 – 35 %) as compared to standard ascorbic acid (42.77%), whereas rest of the compounds showed moderate activity. Compounds 9b & 9c showed (43.28-45.34%) excellent ferrous reducing power activity as compared to standard ascorbic acid (42.77%), whereas the remaining compounds 8a, 8b, 8c & 9c showed moderate activity (31.22–45.34 %)

RESULT AND DISCUSSION:

Spectral analysis:

All the synthesized compounds were characterized by IR, ^{1}HNMR. were evaluated for their anti-oxidant activity. In the present study, the synthesis of title compounds of Asymmetrical methoxy Chromone Curcumin analogues (AMCCAs) Chalcones (8a-c & 9a-c) by Claisen Schmidt condensation has been carried out successfully by using selected heterocyclic amide ketones containing prepared from 3 - and 4- amino acetophenone with 3- formyl chromone carbaldehyde 2 (1 mmol) was dissolved in 15 ml PEG-400 according to literature methods (Scheme 1) . The purity of the newly synthesized compounds was recognized by TLC. The characterization of all the listed synthesized Chalcones were made by IR , NMR spectral analysis. The IR spectrum of the titled compounds showed absorption due to –NH stretching at ~3380- 3350 cm^{-1}, CH=CH shows at 1607 cm^{-1} Due to amide carbonyl group at ~1647 cm^{-1}, C-N shows at 1340 cm^{-1}.

^{1}H NMR spectrum (300MHz) recorded in DMSO-d_6 showed a typical singlet at δ 9–10 (for -NH) and a typical 1H-1H coupling constant in between 15.5 Hz showing trans stereochemistry of the double bond. Chalcones showed the IR absorptions characteristics of carbonyl >C=O (1685-1600 cm-1) and aromatic C=C (1580-1400 cm^{-1}). The ^{1}H NMR spectra of chalcones displayed multiplet due to aromatic protons at 7.2- 8.0 δ (m, Ar-H).and unsaturation at 7.5- 6.5 δ due to unsaturated C=C-C==O. Remaining all data and about the methods and conditions are described in experimental section.

It is observed that 3-formyl 6- metoxy chromones generally possess several magnifying biological activities[30] which strongly depend on the nature and position of substituents. In addition to that chromones exhibiting excellent medicinally properities, though is is low toxic in nature. The presence of electron-withdrawing formyl group at C-3 position 3- formylchromones are highly reactive species, more sensible, therefore it is more potent to better antioxidant , other many more like properties.

The results of antoxidant activity exposed that the compounds (8a-c & 9a-c) exhibited moderate to considerable activity when compared with reference standard. Compounds 8a is plane but compound 8b & 8c is methoxy and fluoro substituted and there is amino group is meta to acetyl in the amido chalcone made from 3- amino acetophenone. Also compound 9a is plane, but 9b and 9c these are further methoxy and fluoro substituted and there is amino is para substituted to acetyl group in the amido chalcone which is made from 4- amino acetophenone . Due to these situation in 8b, 8c carrying methoxy and fluoro at 3-position and in 9b ,9c carrying methoxy and fluoro at 4- position on the aromatic ring-B showed remarkable activity.[30] which is considerable with the standard, suggesting that electron withdrawing and electron donating groups at the meta position in the compounds have less scavenging activity in compared with at para position have more scavenging activity for H_2O_2, DPPH and Ferous reducing power . All the other compounds (8a, 9a) with were found to have intermediate activity[31] here also para substituted 9a have some comparable good scavenging activity than meta susubsituted compound(8a).

CONCLUSIONS:

In conclusion, we have successfully developed the synthesis of title compounds of Asymmetrical Methoxy Chromone Curcumin analogues (AMCCAs) Chalcones (8a-c & 9a-c) by Claisen Schmidt condensation in good yields without producing any side products by using PEG-400 as an alternative green reaction medium. The developed method is operationally simple and could be used efficiently for the preparation of biologically important Chromone Curcumin Chalcones and were characterized by IR, ^{1}H NMR. All the newly synthesized compounds were evaluated for their antioxidant biological activity , and found to be more potent. In case of antioxidant activity, compounds 9b & 9c was found to be potent, whereas compound 8b, 8c & 9a was found to be having differenciable H_2O_2 scavenging activity to standard Butylated hydroxytoluene (BHT). The compounds 9b & 9c were found to be excellent in DPPH free radical scavenging activity as compared to standard ascorbic acid as well as in ferrous reducing power activity.

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Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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