Biological Forum – An International Journal **15(5a): 398-407(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Synthesis, Characterization and Antioxidant Activity of 7, 8-Benzoflavone Derivatives

Nahate N.R.[1*], Bhandarkar S.E.[2] and Khobragade B.P.[3]
[1]Department of Chemistry, Shri Shivaji Arts,
Commerce and Science College, Akot, (Maharashtra), India.
[2]Department of Chemistry, GVISH, Amravati, (Maharashtra), India.
[3]Department of Chemistry, R.D.I.K. and N.K.D. College, Badnera, (Maharashtra), India.

(Corresponding author: Nahate N.R.)*
(Received: 05 April 2023; Revised: 24 April 2023; Accepted: 03 May 2023; Published: 15 May 2023)
(Published by Research Trend)

ABSTRACT: Heterocyclic compounds are widely known for their medicinal properties. Flavonoids have gained significant attention due to their potent pharmacological behaviour. Flavones among them have been reported to be an important class of heterocyclic compounds possessing a wide range of biological activities. The synthesis of 7,8-benzoflavone derivatives can be challenging due to the complexity of the molecular structure. The precise manipulation of chemical reactions to achieve the desired substitutions at specific positions requires careful planning and optimization. In present work series of ten novel 7,8-benzoflavone have been synthesized by reported literature and tested for antioxidant potential. Structural analysis carried by FTIR, 1HNMR and GCMS. It was found that structural modification and substitution effects on the pharmacological potency. The primary objective of this study is to assess the impact of functional groups on the chemical behavior of benzoflavone derivatives. The present study shows that electron-donating groups exhibit better antioxidant potential and increase radical scavenging. This work introduces new 7,8-benzoflavone derivatives, expanding the chemical diversity of this class of compounds. This contributes to the pool of potential bioactive molecules for further exploration. Depending on the antioxidant activity observed, these novel derivatives might have potential applications in pharmaceuticals, nutraceuticals, or functional foods.

Keywords: Acylation, Esterification, 7,8-Benzoflavone, Antioxidant, Baker-Venkataraman rearrangement, Flavones.

INTRODUCTION

Benzoflavone derivatives are a class of compounds that have gained significant attention in the field of medicinal chemistry due to their diverse pharmacological activities and potential therapeutic applications (Singh *et al.,* 2017; Yahiaoui *et al.,* 2008; Dhawan, 2003; Juvale *et al.,* 2013). The benzoflavone scaffold consists of fused benzene and flavone ring system, which imparts unique structural and chemical properties to these derivatives (Singh *et al.,* 2019; Dong *et al*., 2020; Wang *et al.,* 2008; Rishita *et al*., 2021). This structural design, combined with the flexibility for functional group modifications, offers numerous opportunities for designing and developing novel compounds with enhanced biological activity.

The flavone backbone, commonly found in natural products and plant extracts, possesses a wide range of biological effects, including antioxidant (Stermitz *et al.,* 2001), anti-inflammatory (Boek *et al.,* 2001), anticancer (Ji-Tai *et al.,* 2007; Eisinger *et al.,* 1981; Gupta *et al.,* 2010; Zampieri *et al.,* 2008; Jayashankara *et al*., 2008), antimicrobial (Sharma *et al.,* 2014; Desai *et al*., 2014), and neuroprotective activities (Abid *et al.,* 2009). The incorporation of a benzene ring into the flavone structure further extends the potential pharmacological properties of benzoflavone derivatives. The presence of the benzene ring confers lipophilicity, enabling these compounds to interact with specific cellular targets and exhibit improved drug-like properties.

The biological activities of benzoflavone derivatives have been extensively studied in various disease models and cell-based assays. For instance, these derivatives have shown promising antioxidant potential by scavenging free radicals and inhibiting oxidative stress-induced damage. Moreover, their anti-inflammatory properties have been attributed to the modulation of key inflammatory mediators, such as cytokines, enzymes, and transcription factors.

In addition to their antioxidant and anti-inflammatory effects, benzoflavone derivatives have exhibited significant anticancer activity. They have been reported to inhibit the proliferation of cancer cells, induce apoptosis, and interfere with various signaling pathways involved in tumor growth and metastasis. Furthermore, benzoflavone derivatives have demonstrated antimicrobial activity against both Gram-positive and Gram-negative bacteria, as well as antifungal properties.

The neuroprotective potential of benzoflavone derivatives has also been investigated extensively. These compounds have shown the ability to protect neuronal cells against oxidative stress, neuroinflammation, and neurodegenerative processes.

Furthermore, benzoflavone derivatives have been explored as potential candidates for the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease.

Given the broad spectrum of pharmacological activities exhibited by benzoflavone derivatives, they represent an attractive class of compounds for the development of novel therapeutics. However, despite the considerable research efforts in this field, there is still a need for a deeper understanding of the structure-activity relationships and the underlying mechanisms of action of benzoflavone derivatives.

Overall, the study of benzoflavone derivatives offers an exciting opportunity to contribute to the field of medicinal chemistry and drug discovery. By harnessing the unique structural features and biological activities of these compounds, we can pave the way for the development of novel therapeutic agents with enhanced efficacy and reduced side effects, ultimately benefiting patients and improving their quality of life.

MATERIAL AND METHODS

Benzaldehyde (99.5 %), Ethanol, Methanol, acetonitrile was acquired from Avra. 4-nitrobenzaldehyde (98%), Zinc chloride, acetic acid, Benzoic acid (99.9%), 4-chloro benzoic acid (98%), 4-nitro benzoic acid (98%) , 4-methoxy benzoic acid (97%) and 4-bromo benzoic acid were purchased from S D Fine-Chem Ltd. Acetonitrile and Ethyl Acetate (99%) were obtained from Sisco Research Laboratories Pvt. Ltd. All of these reagents were used as received without any further purification.

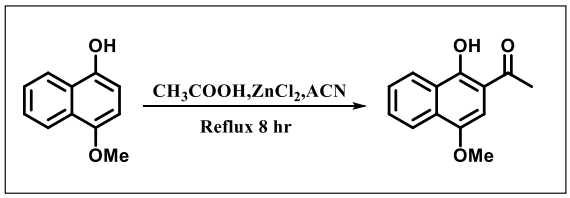
Characterization Techniques. The structure of synthesized compounds was determined by chemical properties elemental analysis and spectral data. The IR spectra were recorded on KBr pellet on SHIMADZU-400 FTIR spectrometer at Shri Shivaji Science College, Amravati, Maharashtra (India). 1H-NMR spectra were recorded on BRUKER AVANCE NEO 500 MHz spectrometer using CDCl3 solvent and TMS as internal standards at SAIF, Punjab University, Chandigarh (India). Chemical shifts are expressed in ppm. Mass spectrums were recorded on Thermo Scientific TSQ 8000 Gas Chromatogram.

Experimental

Stepwise synthesis of benzoflavone

a) Preparation of 1-(1-hydroxy-4-methoxynaphthalen-2-yl)ethan-1-one (1a)

There are different methods for the acetylation of α-naphthol. Here modified Nenchi's method is used for the acetylation reaction (Stoughton, 1935; Blicke et al., 1932; Wadodkar, 1977; Jamode, 1977).Fused zinc chloride (5g) was added in hot glacial acetic acid (34 mmol) and reflux, till dissolved then finely powdered 4-methoxynaphthalen-1-ol (2 mmol) was added with constant stirring and the mixture, was refluxed further for 8 hrs. Then the reaction mixture was cooled and poured in ice cold acidulated water. The solid obtained was filtered, washed with brine solution, and sodium sulphate and recrystallized from rectified spirit **(Scheme 1).**



Scheme 1: Preparation of (1a).

FT-IR: (KBr, ν/cm): 420.43, 485.03, 570.93, 678.94, 790.81, 856.39, 983.70, 1020.34, 1083.99, 1147.65, 1207.44, 1263.37, 1334.74, 1384.89, 1460.11, 1624.06 (C=O, acyl), 1745.58, 1836.23, 1880.60, 1963.53, 2048.40, 2100.48, 2231.64, 2297.22, 2657.91, 2694.56, 2735.06, 2827.64, 2922.16, 3059.10, 3228.84, 3745.76, 3909.71 ,4087.16, 4145.03 ,4281.97, 4415.06, 4642.66. HRMS (m/z): Cal. Mol. Wt.:216.12, Mol. Wt. (Found): 216.08. 1H NMR (ppm): (500 MHz, CDCl3): δ 13.98 (s,1H), 8.411-8.413 (t,1H), 8.394-8.396 (t,1H), 7.66-7.68 (d,1H), 7.54-7.57 (m,1H), 7.44-7.48 (s,1H), 3.45 (s,3H), 2.59 (s,3H)

Plausible mechanism of Acylation. Stepwise mechanism of acylation as shown in Fig. 1. According to literature reports phenols interacts with Lewis's acid $ZnCl_2$ and simultaneously, the acetic acid comes in vicinity via chelation. Due to chelation the electrophilic nature of carbonyl carbon of acetic acid increases.

Then the nucleophilic attack of the pi-bond on the carbonyl carbon generates the unstable tetrahedral intermediate.

Lastly, the unstable tetrahedral intermediate undergoes rearrangement to forms desired product by removal of water molecule and deprotonation (Fig. 1).

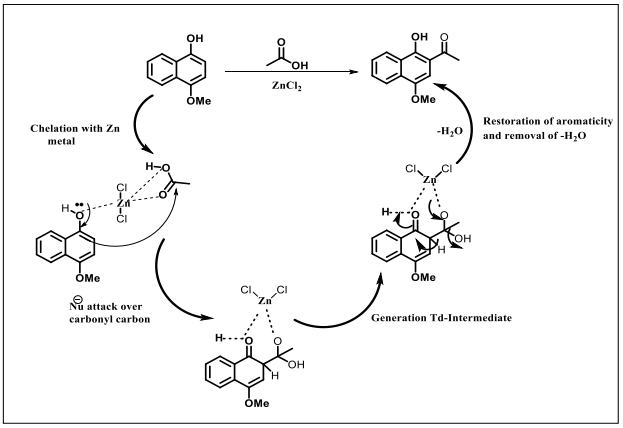
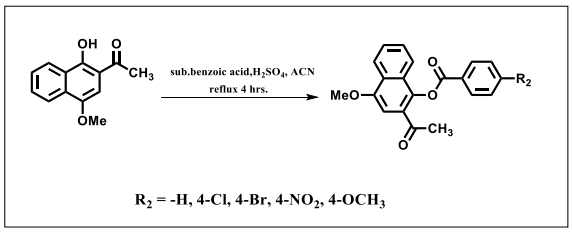


Fig. 1. Plausible mechanism of Acylation.

b) Esterification of 1-(1-hydroxy-4-methoxynaphthalen-2-yl)ethan-1-one with substituted aromatic acids to obtain esters (2a-e)

Esterification is a chemical reaction that involves the formation of an ester from a carboxylic acid and an alcohol, typically in the presence of an acid catalyst. Numbers of methods are available for esterification of phenols and alcohols with organic acids (Wadodkar *et al*., 1972; Doyle *et al*., 1948; Doifode, 1965). Esterification reactions are often conducted under reflux conditions, where the reactants are heated in the presence of an acid catalyst, such as sulfuric acid or hydrochloric acid. The acid catalyst protonates the carboxylic acid, making it more reactive towards the

alcohol. Products are confirmed by FTIR, NMR and GCMS characterization. General scheme for the synthesis of esters is given as below **(Scheme 2).** Structures of synthesized esters are shown in Table 1.



Scheme 2: Preparation of (2a-e)

a) 2-acetyl-4-methoxynaphthalen-1-yl benzoate (2a). FT-IR: (KBr, ν/cm): 420.48, 495.71, 559.36, 684.73, 794.67, 858.32, 931.62, 979.84, 1018.41, 1082.07, 1139.93, 1199.72, 1276.88, 1321.24, 1406.11, 1618.28 (C=O, Acyl), 1683.86 (C=O, benzoyl) , 1926.89, 2094.69, 2304.94, 2566.33, 2669.48, 2748.56, 2835.36, 2914.44, 3061.03, 3736.12, 3880.78, 4067.87, 4143.10, 4193.25, 4264.61, 4405.42, 4494.14, 4573.22. GCMS (m/z):Cal. Mol. Wt.: 321.03 Mol. Wt. (Found): 320.06. ^{1}H NMR (ppm): (500 MHz, $CDCl_3$): δ 14.05 (s,1H), 12.25 (s,1H), 8.47-8.48 (s,1H), 8.16-8.17 (d,2H), 7.74-7.76 (d,1H), 7.60-7.64 (t,2H), 7.51-7.58 (m,1H), 7.48-7.49 (d,1H), 7.23 7.25 (d,1H), 3.45 (s,3H), 2.67(s,3H)

b) 2-acetyl-4-methoxynaphthalen-1-yl 4-chlorobenzoate (2b). FT-IR: (KBr, ν/cm): 384.55, 418.55, 476.42, 563.21, 677.01, 798.53, 852.54, 929.69, 979.84, 1022.27, 1089.78, 1134.14, 1203.58, 1284.59, 1323.17, 1409.96, 1620.21 (C=O, Acyl) , 1681.93 (C=O, benzoyl), 1878.67, 1932.67, 2102.41, 2154.49, 2297.22, 2571.11, 2669.48, 2835.36, 2999.48, 2835.36, 2929.87, 3014.74, 3061.03, 3734.19, 3880.78, 4079.45, 4164.31, 4270.40, 4335.98, 4378.41, 4407.34, 4478.71, 4570.10**.** GCMS (m/z): Cal. Mol. Wt.: 353.12
Mol. Wt. (Found): 354.44. ^{1}H NMR (ppm): (500 MHz, $CDCl_3$): δ 13.99 (s,1H), 8.41-8.43 (s,1H), 7.70-7.71 (d,1H), 7.55-7.60 (m,2H), 7.47-7.50 (m,1H), 7.19-7.23 (t,1H), 3.45 (s,3H), 2.63(s,3H)

c) 2-acetyl-4-methoxynaphthalen-1-yl 4-bromobenzoate (2c). FT-IR: (KBr, ν/cm): 353.95, 420.50, 474.51, 564.20, 678.97, 800.49, 856.43, 927.80, 985.67, 1015.57, 1081.15, 1134.19, 1278.86, 1234.19, 1411.95, 1617.38, 1684.80, 1830.52, 1880.68, 1938.54, 2100.57, 2244.27, 2299.25, 2574.12, 2675.38, 2841.27, 2920.35, 3021.02, 3062.13, 3721.81, 3767.14, 3914.70, 3970.64, 4075.76, 4150.99, 4269.62, 4330.38, 4416.21, 4573.42
GCMS (m/z):Cal. Mol. Wt.: 400.01, Mol. Wt. (Found): 399.71.^{1}H NMR (ppm): (500 MHz, $CDCl_3$): δ 14 (s,1H), 8.43-8.45 (m,1H), 7.73-7.74 (d,1H), 7.59-7.62 (q,2H), 7.50-7.53 (m,1H), 7.24-7.25 (d,1H), 3.45 (s,3H), 2.67 (s,3H).

d) 2-acetyl-4-methoxynaphthalen-1-yl 4-nitrobenzoate (2d). FT-IR: (KBr, ν/cm): 422.21, 511.14, 567.07, 678.94, 719.45, 798.53, 860.25, 931.62, 981.77, 1020.43, 1126.43, 1207.44, 1286.52, 1328.95, 1415.75, 1614.42 (C=O, acyl), 1691.57 (C=O, benzoyl), 1824.66, 1876.74, 1957.75, 2090.84, 2144.84, 299.15,2 553.75,2 667.55,2 841.15,2 924.09,3 010.88,3 064.89, 3111.18, 3741.90, 3886.56, 4046.66, 4094.88, 4299.88, 4287.76, 4335.98, 4413.13, 4494.14, 4582.87.GCMS (m/z):Cal. Mol. Wt.: 364.15, Mol. Wt. (Found): 365.30.^{1}H NMR (ppm):(500 MHz, $CDCl_3$): δ14.03 (s,1H), 8.47-8.49 (d,1H), 7.76-7.78 (d,1H), 7.63-7.65 (t,2H), 7.53-7.56 (t,1H), 7.27-7.28 (d,1H), 3.45 (s,3H), 2.71(s,3H)

e) 2-acetyl-4-methoxynaphthalen-1-yl 4-methoxybenzoate (2e). FT-IR: (KBr, ν/cm): 419.54, 479.33, 563.24, 682.83, 745.52, 796.64, 862.22, 896.94, 980.84, 1024.25, 1086.93, 1149.62, 1271.14, 1308.76, 1408.10, 1461.14, 1621.24 (C=O, acyl), 1682.96 (C=O, benzoyl), 1832.45, 1963.62, 2094.78, 2301.18 2667.06, 2922.28, 3063.09, 3732.42, 3880.94, 3960.03, 4103.73, 4193.43, 4281.19, 4340.99, 4414.26, 4499.16.GCMS (m/z): Cal. Mol. Wt.: 349.29. Mol. Wt. (Found): 350.02

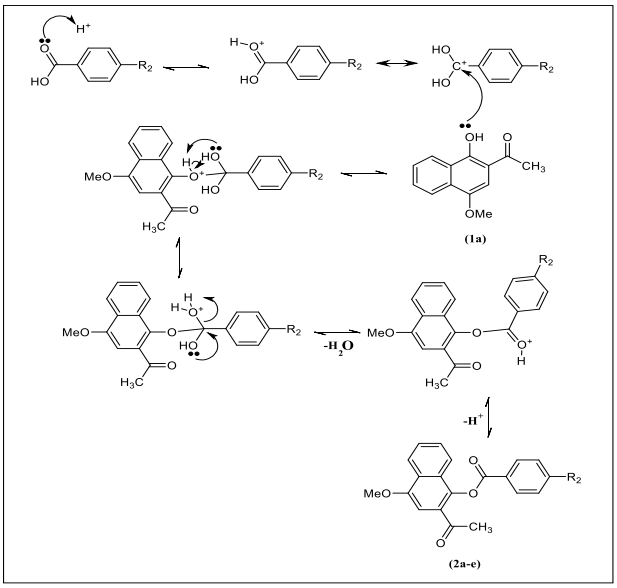


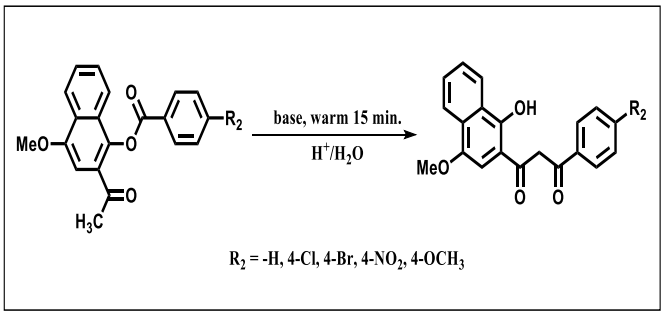
Fig. 2. Plausible mechanism of aromatic acids.

Plausible mechanism of esterification of aromatic acids. Esterification, in general is an acid catalysed process which involves an addition elimination mechanism. Carboxyl oxygen gets protonated by

H_2SO_4 to give delocalized carbocation making the carbocation a better electrophile. A proton is transferred to one of the hydroxyl groups to form a good leaving group. The hydroxy group's alcohol oxygen atom donates a pair of electrons to a carbon atom which makes a π bond by eliminating water. This reaction is possible only at reflux temperature (Fig. 2).

c) The Baker-Venkatraman transformation of esters to obtain (3a-e). Baker-Venkataraman is a base catalysed intramolecular Claisen condensation between ester and methyl ketone. Many bases have been reported but pyridine is found most suitable (Bourne *et al.,* 1949; Kumar *et al.,* 1999; Maiti *et al.,* 2011; Sarda *et al.,* 2006; Pandya *et al.,* 2012). This step involves the conversion of ester into diketones in presence of basic medium. This step follows Baker-Venkataraman rearrangement mechanism **(Scheme 3).**

Structures and spectral data of compounds (3a-e) is shown in Table 2.



Scheme 3: Preparation of (3a-e)

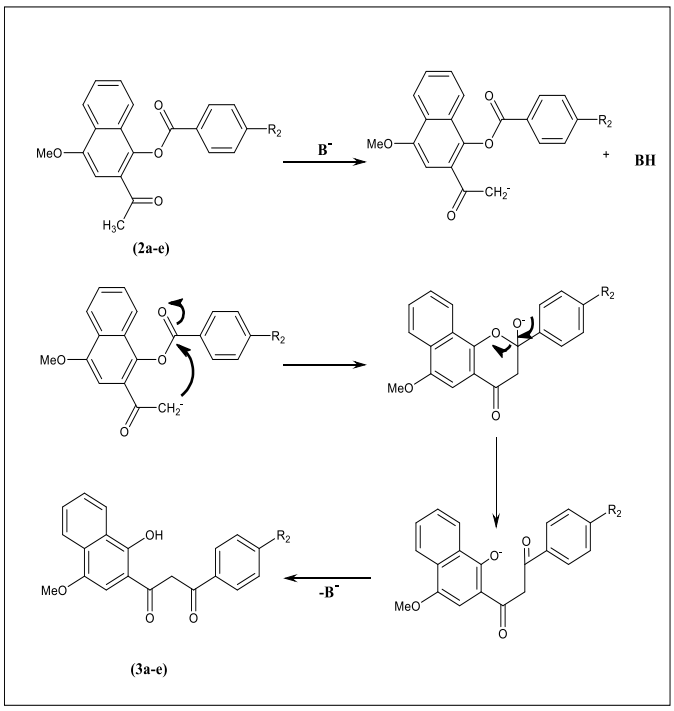
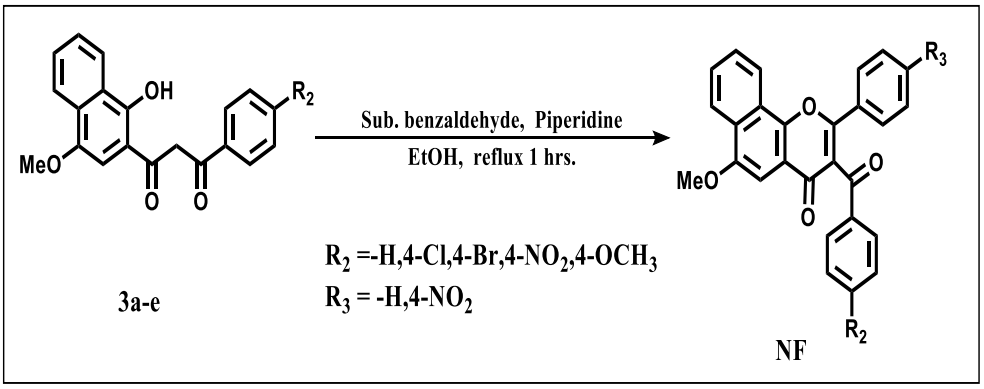


Fig. 3. Plausible mechanism of Baker-Venkataraman rearrangement.

Plausible mechanism of Baker-Venkatraman rearrangement. This mechanism involves an intramolecular Claisen Condensation between an ester and methyl ketone (Khanapur *et al*., 2015). Base abstracts α-proton to form enolate which subsequently attack on carbonyl of ester to form tetrahedral intermediate. Upon workup it forms β-diketones (Fig. 3).

d) Synthesis of benzoflavone derivatives (NF1-NF10). Literature survey already showed that there are various synthetic routs for 7,8-benzoflavone synthesis. Structure modification plays significant role in enhancing the biological potential (Yahiaoui *et al.,* 2008; Rokade *et al.,* 2009; Cushnie *et al.,* 2011; Yoon *et al*., 2012; Juvale *et al.,* 2013; Singh *et al.,* 2017; Vhanale *et al.,* 2019). To a mixture of glacial acetic acid and fused zinc chloride 4-methoxynaphthalen-1-ol was added under reflux condition to form 1-(1-hydroxy-4-methoxynaphthalen-2-yl)ethan-1-one **(1a)**, which further on acid catalyzed esterification with variously substituted benzoic acids gives benzoylated products **(2a-e)**. Under Baker-Venkataraman reaction condition esters are rearranged to 1, 3-diketones **(3a-e)**. Diketones on reaction with substituted aromatic aldehydes under aldol conditions followed by cyclization using suitable cyclizing agent converted to 7,8-benzoflavones **(Scheme 4).**



Scheme 4. Synthesis of Benzoflavones.

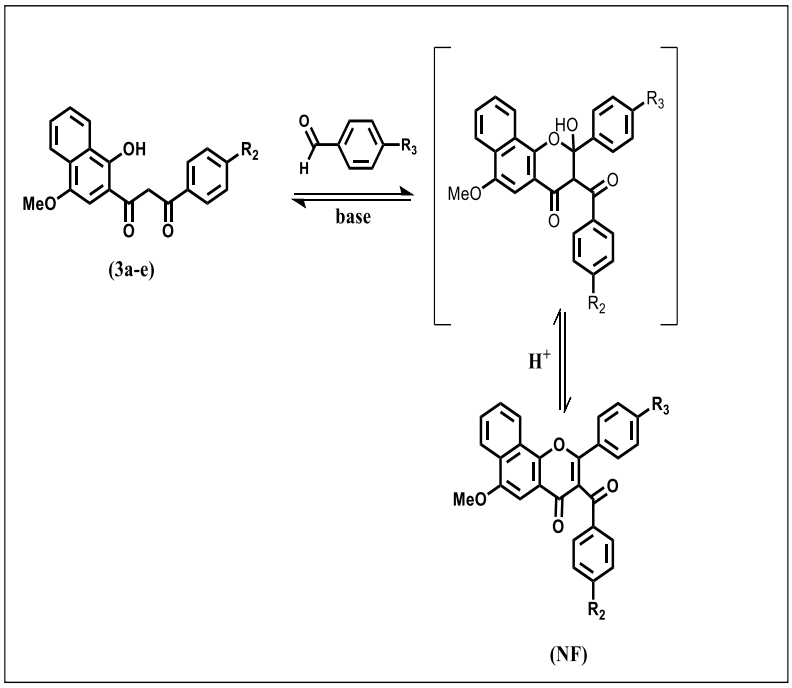


Fig. 4. Plausible mechanism of benzoflavone synthesis.

Structures and spectral data of compounds (NF1-NF10) are shown in Table 3.

Plausible Mechanism of benzoflavone synthesis. It was reported the possibility of the formation of an α-aroylchalcone as an intermediate which under the experimental conditions cyclizes to give the flavone (Chicholkar, 1981). Flavones are usually synthesized from β-diketones by refluxing them with acetic acid and H_2SO_4. This method involves base catalyzed piperidine cyclization. Structures are confirmed by spectral data. The reaction probably proceeds via intermediate flavanone which decomposes to flavone (Fig. 4).

Biological Investigation of benzoflavone derivatives.

Antioxidant activity. An antioxidant may be defined as "any substance that when present at low concentration, compared with those of the oxidizable substrate significantly delays or inhibits oxidation of that substrate."

Method: DPPH Free Radical Scavenging Assay.

Preparation of Sample: The free-radical scavenging activity was estimated by DPPH assay. The reaction mixture contained 10 µl of test sample and positive control ascorbic acid with 10 mg concentration and 190 µl of methanolic solution of 0.1 mM DPPH radical. The mixture was then shaken vigorously and incubated at 37 °C for 5 min. The absorbance was measured at 517 nm on ELISA plate reader indicated higher free radical scavenging activity, which was calculated using the following equation:

Antioxidant Potential of synthetic compounds. The antioxidant activities of benzoflavone derivatives were successfully assessed using the free radical scavenging assay. The results are shown in the Table 4 and Fig. 5.

$$\frac{(\%)\ \text{Free radical scavenging effect [Control Absorbance(Ac) - Sample Absorbance(As)]}}{\text{Control Absorbance(Ac)}} \times 100$$

Table 1: Structure of compounds (2a-2e).

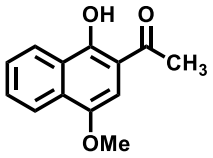
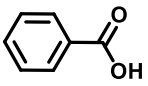
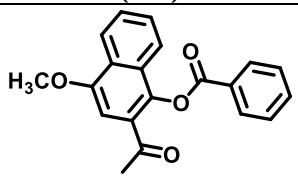
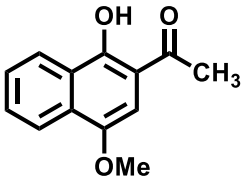
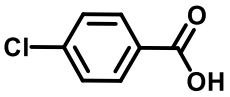
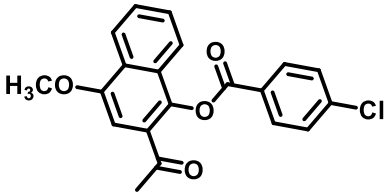
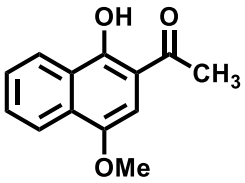
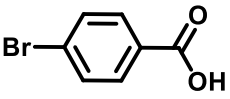
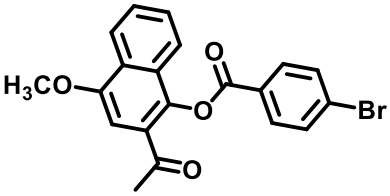
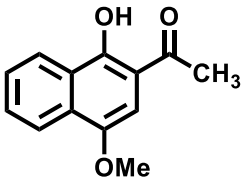
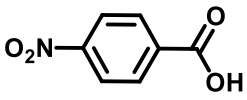
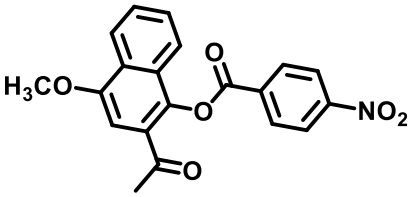
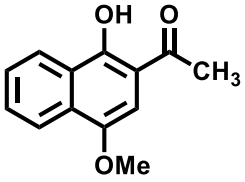
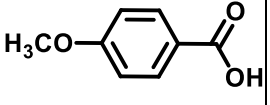
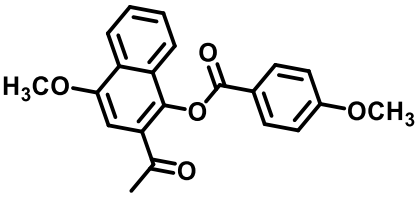
(1a)	(R_2)	(2a-e)
		 (2a)
		 (2b)
		 (2c)
		 (2d)
		 (2e)

Table 2: Confirmation of compounds by ^{1}HNMR and GCMS.

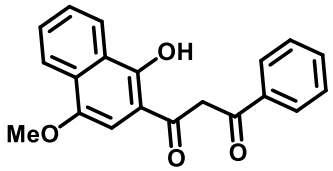
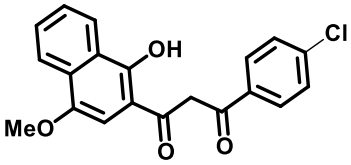
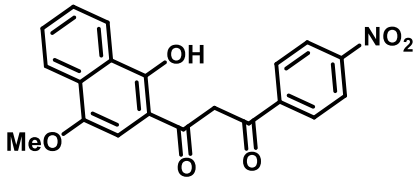
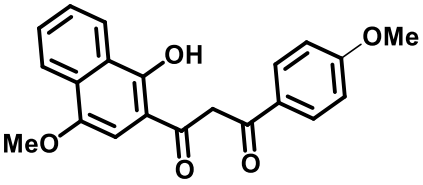
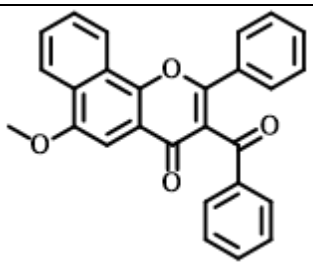
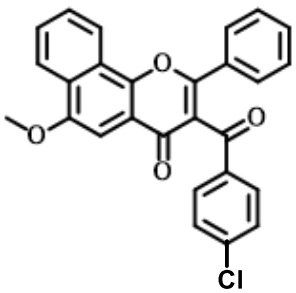
Structure and code of product	Confirmation by ^{1}HNMR and GCMS
 **(3a)**	^{1}H NMR (ppm): (500 MHz, $CDCl_3$): δ 11.04 (s, 1H), 8.59 (s,1H), 8.38 (s,2H), 7.96 (s,1H), 7.82-7.39 (m, 3H), 6.02 (s,1H), 3.81 (s,2H), 3.79 (s,3H).GCMS(m/z): Cal.Mol.Wt.: 320.00 Mol. Wt. (Found): 320.57
 **(3b)**	GCMS (m/z): Cal. Mol. Wt.: 355.01 Mol. Wt. (Found): 354.02
 **(3d)**	^{1}H NMR (ppm): (500 MHz, $CDCl_3$): δ 11.03 (s,1H), 8.40 (d,2H), 8.31-8.32 (d,2H), 7.37-7.40 (t,2H), 7.26-7.27 (d,2H) 6.69-7.00 (d,2H) ,6.02 (s,1H), 3.81 (s,2H), 3.74 (s,3H)
 **(3e)**	GCMS (m/z): Cal. Mol. Wt.: 351.02 Mol. Wt. (Found): 350.35

Table 3: Confirmation of compounds by ^{1}H NMR and GCMS.

Structure and code of product	Confirmation by ^{1}HNMR and GCMS
 **NF1**	^{1}H NMR (ppm): (500 MHz, $CDCl_3$): δ 8.12-8.13 (d,2H), 8.11-8.12 (d,2H), 7.97-7.99 (t,3H), 7.89-7.88 (d,1H), 7.65-7.69 (m,5H), 7.03-7.06 (d,1H), 5.70 (s,1H), 3.64 (s,3H) GCMS (m/z): Cal. Mol. Wt.: 406.04 Mol. Wt. (Found): 405.11
 **NF2**	**GCMS (m/z):** Cal. Mol. Wt.: 440.08 Mol. Wt. (Found): 440.31

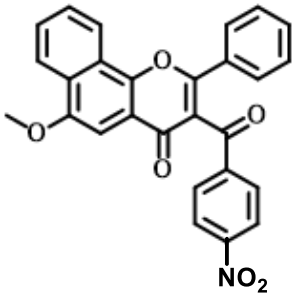
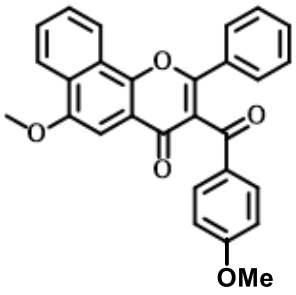
 **NF3**	^{1}H NMR (ppm): (500 MHz, $CDCl_3$): δ 8.32-8.33 (d,2H), 8.29-8.30 (d,2H), 8.12-8.13 (d,2H), 8.11-8.12 (d,2H), 7.89-7.99 (m,4H), 7.65-7.69 (M,1H), 7.03-7.09 (d,2H), 5.70 (s,1H), 3.64 (s,3H)
 **NF4**	**GCMS (m/z):** Cal. Mol. Wt.: 451.11 Mol. Wt. (Found): 450.22

Table 4: % Antioxidant Potential using DPPH Assay Method (Conc. used 1 mg).

Compound Code	R		Antioxidant Potential (%) (Mean±SD)
	R^2	R^3	
NF1	-H	-H	34.265±1.32
NF2	4-Cl	-H	16.552±1.56
NF3	4-Br	-H	30.2.06±2.11
NF4	4-NO_2	-H	18.065±0.55
NF5	4-OCH_3	-H	36.546±1.22
NF6	-H	4-NO_2	12.852±1.45
NF7	4-Cl	4-NO_2	12.323±1.58
NF8	4-Br	4-NO_2	13.121±1.45
NF9	4-NO_2	4-NO_2	39.125±1.14
N10	4-OCH_3	4-NO_2	-
Standard	+Ve Control (Ascorbic acid)		86.78±2.15

*All the data statistically analyzed with mean±SD (n=3)

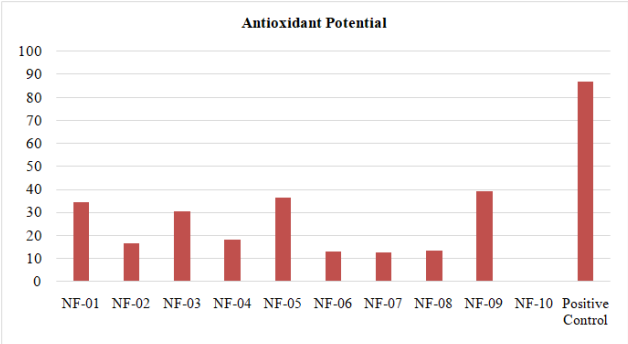


Fig. 5. Graphical representation of antioxidant potential of benzoflavones.

RESULTS AND DISCUSSION

The synthesis of novel 7,8-benzoflavone derivatives was successfully achieved through a multi-step synthetic routes. Structural characterization was carried out using a combination of spectroscopic techniques.

The antioxidant activity of the synthesized 7,8-benzoflavone derivatives was assessed using DPPH assay method. The observed antioxidant activity suggests that the modifications made to the benzoflavone scaffold influence its ability to scavenge free radicals and mitigate oxidative stress.

CONCLUSIONS

In the present work, we investigated that the benzo ring at the C-7 and C-8 positions of the flavone structure is a promising moiety that can synthesize compounds such as 7,8-benzoflavone derivatives that are likely to exhibit promising biological activities. Furthermore, the benzo

ring inflection of the 7,8-benzoflavones structure intentionally incorporation of methoxy (OMe) and hydroxyl (-OH) group over the ring. Which enhances the strong biological activities.

FUTURE SCOPE

On the basis of reported literature and present work, we have synthesized the 7,8-benzoflavone but in future researchers could take the advantages to this protocol to synthesized novel benzoflavones.

Acknowledgement. The authors are thankful to The Director, Government Vidarbha Institute of Science and Humanities, Amravati for providing research facilities. Authors are very much thankful to the Director, SAIF, Punjab University Chandigarh for providing spectral data.
Conflict of Interest. None.

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How to cite this article: Nahate N.R., Bhandarkar S.E. and Khobragade B.P. (2023). Synthesis, Characterization and Antioxidant Activity of 7, 8-Benzoflavone Derivatives. *Biological Forum – An International Journal*, *15*(5a): 398-407.

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