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Synthesis of Derivatives of methoxy substituted Flavone

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ABSTRACT
An efficient synthesis of 3-methoxy substituted Flavone and Flavanone derivatives has been achieved. Flavanone is obtained by cyclization of 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) propane-1,3-dione with various substituted aromatic benzaldehyde by using a catalytic amount of piperidine under solvent of ethanol. Flavanone derivative was oxidized using I_2/DMSO to give Flavone. The entire reported compound has 72–80 percentage of isolated yield. Nitro group containing Flavone obtained more yield than another compound. All Synthesized compounds were characterized by H NMR, IR, and Mass Spectroscopy.
Keywords: *Flavonoids,Flavone, Flavanone, Aromatic aldehyde, BVT, Pyridine.*

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INTRODUCTION

Medicinal activities of the plants are recognized owing to the existence of various flavonoid. They contains polyphenolic compounds existent in varied plants occur naturally in foods of plant origin into flavanones, flavone, isoflavones, and flavanonols. Flavanone are an assortment of common and natural compounds that are widely found in the plant kingdom and they give taste and color to plant. Flavonoid derivatives are premeditated for variety of pharmacological activities to delight unalike diseases. Flavone is a member of flavonoids and a class of natural products and exhibits anti-oxidant. Flavone derivatives are gifted to irritable the blood-brain barrier and amend the brain function. Flavones inhabit a distinctive place in the natural and synthetic organic chemistry owing to their useful biological activities. It was observed that plant-based flavanones in a diet are undeniably non-toxic and have no confrontational effect [1-5]. Flavanones exhibits various pharmacological activities such as antioxidant which help to a justification for research worried to modulate events complicated in the mechanisms of cancer and cardiovascular dysfunction. Some flavones have potent antioxidant activity and the antioxidant activity of flavones in different materials varies because of their different chemical structures [6-11] Flavones occupy a special place in the realm of natural and synthetic organic chemistry owing to their useful biological activities such as activities of these polyphenolic compounds. activities of these polyphenolic compounds. Flavones have been enumerated as an efficient influence in healthy food. Zhao and co-worker deliberate the structure-activity relationships of flavone and found that 40 -OH was important for inhibitory activity. Golub et al. synthesized novel flavone hydroxyl group-containing derivatives, and screened for anticancer activities. The 4-hydroxy group-containing compound exhibits good activities than the natural lead compound. The author also designed a series of flavone derivatives with alkanes substituted in 4 -OH to generate ether [12-16].

The various number of compounds containing Flavone and Flavanone moiety exhibits good antioxidant activities of medicinal plants which is due to, flavonoids and phenolic acids, then carotene and vitamins. So large number of researcher studies on antioxidant activities last few years. These activities of Flavones are accompanied by other biological activities such as anti-virus, bacteriostatic, anti-aging, and anti-cancer activities. Some flavones show antioxidant activities different materials varies due to their different chemical structures. Flavones in POD are mostly categorized as high iso-flavones. Last few years POD has been used as raw material for the preparation of fermented foods, such as wine, bread, cake, tea, beverage, sauce, candy, etc. The compound containing iso-flavones derivatives has antioxidant activities due to the number of phenolic hydroxyl groups in their structure. Flavonoids have been the

attention of numerous research in the search for discovering anti-COVID-19 drug candidates and involved considerable interest as potential SARS-CoV-2 inhibitor [17-20].
The compound containing flavones derivatives has antioxidant activities due to the number of phenolic hydroxyl groups in their structure. Flavonoids have been the attention of numerous research in the search for discovering anti-COVID-19 drug candidates and involved considerable interest as potential SARS-CoV-2 inhibitor. Some of the flavones derivatives have shown antioxidant activity and the antioxidant activity of flavones in different materials varies due to different chemical structures. Flavones play an important role in the ecology of plants by making flowers and fruits attractive to bees and birds. Many naturally occurring and synthetic flavanones are known to have remarkable biological activities. The anti-inflammatory, and anti-viral activities of flavanones have been reported by the various researcher, Flavanone exhibits various biological activities likes antimicrobial, cytotoxicity, anti-inflammatory, improvement of cardiac function after ischemia.

Reaction Scheme:

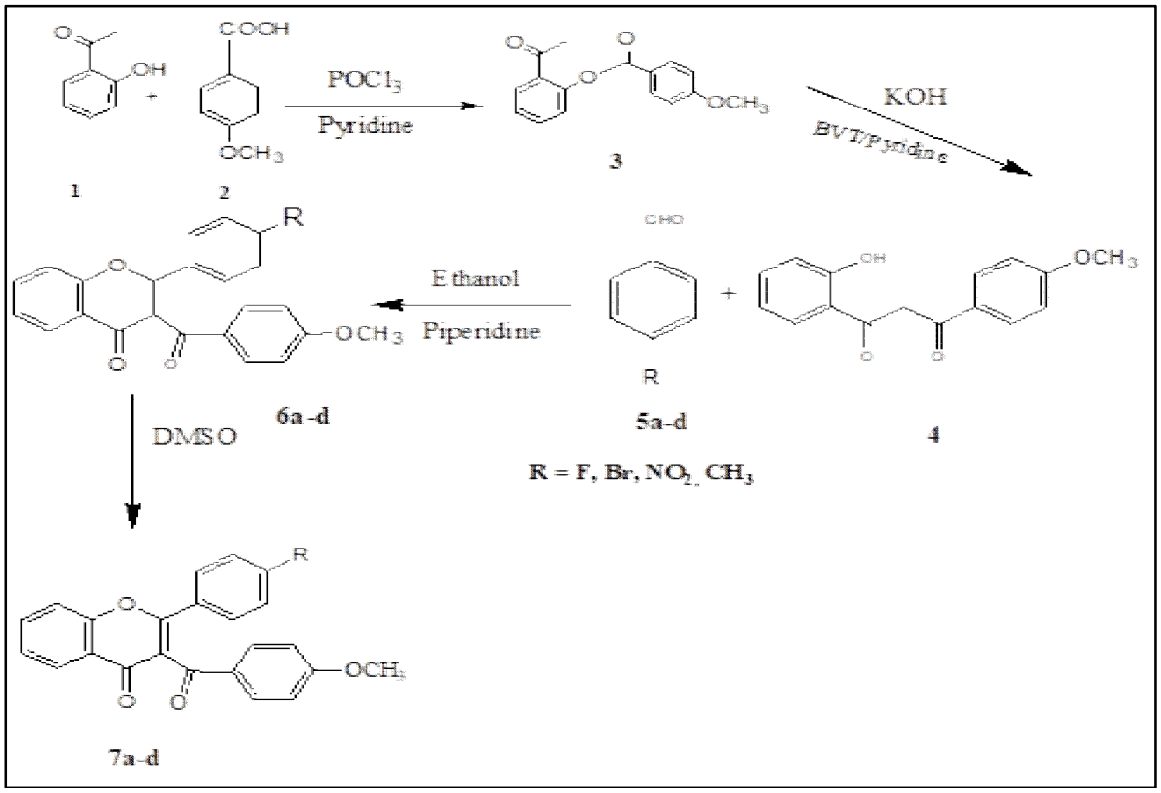

Fig. 1: Reaction Scheme

We have reported 3-methoxy substituted Flavone and Flavanone derivatives in the above mention scheme. Starting from o-hydroxy acetophenone with anisic acid with catalic amount of dry pyridine to 2-acetyl phenyl 4-methoxybenzoate. This compound was reacted with BVT in Pyridine to form 2-acetyl phenyl 4-methoxybenzoate.3-Aroylflavanone obtained from cyclization of 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) propane-1,3-dione with 4-substituted aldehyde in the piperidine in ethanol. We have obtained obtained 3-anisoyl-2(3-substituted phenyl) flavone derivative by reduction of 3-Aroylflavanone derivative by using iodine crystal in solvent DMSO [21-25].

MATERIAL AND METHODS

General methods and materials

All solvents and reagents were picked up since Merck India Ltd and are of AR Grade and recycled without further purification. Melting Points were unwavering by the open capillary method and were uncorrected. Thin-layer chromatography (TLC) was implemented on silica. The spots were visualized by exposure to iodine vapor Nuclear magnetic resonance (NMR) spectra were recorded on a 400-MHz spectrometer for a HNMR. IR spectra of the compounds accomplished in potassium bromide (KBr) disks on a Bruker IR spectrometer. Mass spectra were recorded on a Waters ZQ-4000 spectrometer. The yields of the synthesized compounds were revealed for the isolated product.

Preparation of 2-acetyl phenyl 4-methoxybenzoate (3)
o-hydroxy acetophenone (0.05 mmol) and anisic acid(0.005) were suspended in dry pyridine (30 ml) and this POCl3 (3 ml) was added drop-wise with constant stirring and cooling. The reaction mixture was kept overnight and worked up dilution and acidification with ice-cold HCl (50 %) neutralizing pyridine. Thus, the solid product obtained was filtered washed with water followed by sodium carbonate (10%) washing and finally again with water. It was crystallized from ethanol to obtain 2-acetyl phenyl 4-methoxybenzoate m.p. 110° C, yield 76 %.

Preparation of 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)propane-1,3-dione. (4)
2-acetyl phenyl 4-methoxybenzoate was dissolved in dry pyridine (40 ml) in 50 ml RBF. The solution warmed at the temperature of 60° C. Then crushed KOH (15 g) was added slowly with constant stirring at R.T. Reaction. Progress of the reaction was monitored by using a TLC plate. After four hours of heating, the reaction mixture was acidified by adding ice-cold dip. HCl (1:1). The brownish-yellow solid product thus separated was filtered, washed with $NAHCO_3$ (10%). Then wash again with cold water. Recrystallized using ethanol acetic acid mixture to acquire 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)propane-1,3-dione m.p. 112° C, yield 74 %.

Preparation of 3-Aroylflavanone.
1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)propane-1,3-dione (0.012 mol) mixed with 4-substituted aldehyde (0.012 mol) in 25 ml of ethanol and piperidine (0.5 mol) in the 250 RBF. It was refluxed for 15-20 min. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mass was cooled toR.T. It was acidified with dil. HCl (1:1) and the desired product were separated. Recrystallized from ethanol-acetic acid mixture to get the product (6a).

Preparation of 3-anisoyl-2(3-substituted phenyl)flavone.
A mixture of 3-Aroylflavanone (6a) (0.01mol) and iodine crystal was reflexed in DMSO (20 ml) for about 10 min in 250 ml RBF. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mixture was cooled to R.T. The solid product was obtained, separated, it was washed with sodium thiosulphate solution. Finally, recrystallize from ethanol acetic acid mixture to get the 3-benzoyl-2 (4 Fluro phenyl) 4-cholrophenyl flavone**.** (7a).

RESULTS AND DISCUSSION

Table 1. Physical data of synthesized compounds 6(a-d).

Entry	Compound	R	Reaction Time (Min)	Yield (%)	M.P. (°C)
1	6a	NO_2	10	82	233
2	6b	Br	12	79	241
3	7c	F	12	76	167
4	7d	CH_3	14	72	163

Table 2. Physical data of synthesized compounds 7(a-d).

Entry	Compound	R	Reaction Time (Min)	Yield (%)	M.P. (°C)
1	7a	NO_2	10	84	162
2	7b	Br	12	78	117
3	7c	F	12	72	133
4	7d	CH_3	14	76	141

We herein report the synthesis of various anisoyl-2(3-substituted phenyl) flavone derivatives. This synthetic approach signifies the most efficient route to a diverse synthesis of flavone reported in the literature. The synthesis occupations readily available starting materials and simple procedures make this method very attractive and convenient for the synthesis of various substituted flavone derivatives. The desired substituted flavone derivative 7(a–d) was prepared in good yield through a multi-step reaction by using3-anisoyl-2(3-substituted phenyl) flavone according to the procedure outlined in the reaction Scheme.2-acetyl phenyl 4-methoxybenzoatewas prepared from hydroxy acetophenone and anisic acid by using a standard method. 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)propane-1,3-dione was prepared by 2-acetyl phenyl 4-methoxybenzoate using potassium hydroxide in pyridine .1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)propane-1,3-dione was reacted with 4 substituted benzaldehyde in ethanol using a catalytic amount of piperidine and acetic acid to gives substitutedflavanone. Flavanone derivative was oxidized using I_2/DMSO to give flavone. The formation of methoxy substituted flavone derivatives was confirmed by recording their IR, ^{1} H NMR, and mass spectra.IR spectrum of Flavone 7a showed an absorption band at 3447 cm^{-1} which is due to the aromatic stretching. An absorption band at

1672 is due to the C-O stretching of flavone which confirms the formation of flavone ring. The absorption band at 1661 cm^{-1} is due to the stretching of the NO2group. The absorption band that appeared at 1596 cm^{-1} is due to C=O (carbonyl group). The ^{1} H NMR spectrum of 7a showed multiplet appeared at, 6.8 . Is due to aromatic proton. Similarly, a singlet appeared at 3.3 is due to the three protons of the methoxy group. The mass spectrum of 7a showed a molecular ion peak at m/z 390, which is in agreement with the molecular formula $C_{23}O_6H_{15}N$.

Spectral data of methoxy substituted flavone derivative

3-benzoyl-2 (4 nitro phenyl) 4-methoxyphenyl flavone (7a)

Molecular formula:$C_{23}O_6H_{15}N$ yield: 84**%.** m.p. 163^{o}C**,** IR (KBr) cm−^{1}: 3447 (-CH Aromatic str), 1596(>C=O str),); 1672 (C-O of Flavone); 1161 (Ar-NO_2 str); ^{1} H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.3 (s, 3H, OCH_3), 6.8(d, 4H), 7.34 (d, 4H), 7.5 (m, 2H), 7.91(m,2H), mass: 390 (M+1).

3-benzoyl-2 (4 bromo phenyl) 4-methox phenyl flavone (7b)

Molecular formula $C_{23}O_4H_{15}Br$: yield: 78**%**, m.p. 117^{o}**C**IR (KBr) cm−^{1}: 3479 (-CH Aromatic str), 1583(>C=O str), 1630 (C-O of Flavone); 530 (Ar-Br str);; ^{1} H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.5 (s, 3H,OCH_3), 6.6(m, 3H), 6.7(m, 1H), 7.0(d, 2H), 7.5 (d, 4H), 8.0 (d, 2H), mass: 436 (M+1).

3-benzoyl-2 (4 Fluro phenyl) 4-methox phenyl flavone (7c)

Molecular formula $C_{23}O_4H_{15}F$: yield: 72 **%**, m.p.133 oC**,,**IR (KBr) cm−^{1} : 3014 (-CH Aromatic str), 1601(>C=O str), 1161 (Ar-F str);; ^{1} H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.4 (s, 3H,OCH_3), 6.8(m, 3H), 7.2(d, 4H), 7.3 (d, 2H), 7.9 (d, 2H), 8.4 (m, 1H), mass: 375 (M+1).

3-benzoyl-2 (4-methyl phenyl) 4-methox phenyl flavone (7d)

Molecular formula $C_{24}O_4H_{18}$: yield: 76 %, m.p. 141^{o}C**,** IR (KBr) cm−^{1} : 3108 (-CH Aromatic str), 1591(>C=O str), 1503(C-O of Flavone) ; mass: 371 (M+1).

CONCLUSION

In Conclusion, we have synthesized a series of methoxy substituted Flavoneand Flavanone by multistep reaction starting with hydroxy acetophenone and anisic acid by using a standard method. The compound containing nitro group at para position exhibit the highest yield among synthesized compound. All synthesized compounds are characterized by IR, ^{1}HNMR, Mass spectroscopic techniques.

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