International Journal of Engineering Science Invention (IJESI)
ISSN (Online): 2319 – 6734, ISSN (Print): 2319 – 6726
www.ijesi.org ||Volume 7 Issue 7 Ver III || July 2018 || PP 12-23

Synthesis, Characterization and Antimicrobial screening of some new bipyridinyl substituted coumarin

Jigar Patel[1,2*]
[1]*Department of Chemistry, SSR College of Arts, Commerce and Science (Affiliated with SavitribaiPhule Pune University, Pune, Maharastra), Sayli Road, Silvassa, Dadra and Nagar Haveli-396230.*
[2]*Department of Chemistry, Sardar Patel University, V V Nagar.*
Corresponding Auther: Jigar Patel

Abstract:*The synthesis of various 7-methoxy-4-methyl-8-(4'-aryl-2',2''-bipyridin-6'-yl)coumarins* ***(5a-c)****; 7-methoxy-4-methyl-8-(4'-aryl-2',3''-bipyridin-6'-yl)coumarins* ***(6a-c)*** *and 7-methoxy-4-methyl-8-(4'-aryl-2',4''-bipyridin-6'-yl) coumarins* ***(7a-c)*** *has been carried out by the reaction of 4-methyl-7-methoxy-8-coumarinoyl methyl pyridinium bromide salt* ***(1)*** *with various 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones* ***(2a-c),*** *3-aryl-1-(pyridin-3-yl)prop-2-en-1-ones* ***(3a-c)*** *and 3-aryl-1-(pyridin-4-yl)prop-2-en-1-ones* ***(4a-c)*** *respectively in the presence of ammonium acetate in refluxing acetic acid* ***(Scheme 1)****under Krohnke's reaction condition. The required chalcones 3-aryl-1-(pyridin-2-yl)-prop-2-ene-1-ones* ***(2a-c)****, 3-aryl-1-(pyridin-3-yl)-prop-2-ene-1-ones* ***(3a-c)*** *and 3-aryl-1-(pyridin-4-yl)-prop-2-ene-1-ones* ***(4a-c)*** *were prepared by the reaction of respective 2-acetyl pyridine, 3-acetyl pyridine and 4-acetyl pyridine with various p-substituted benzaldehydes in the presence of sodium hydroxide in ethanol.The synthesis of compounds 7-methoxy-4-methyl-8-(6'-aryl-4',2''-bipyridin-2'-yl)coumarins* ***(11a-c)****; 7-methoxy-4-methyl-8-(6'-aryl-4',3''-bipyridin-2'-yl)coumarins* ***(12a-c)*** *and 7-methoxy-4-methyl-8-(6'-aryl-4',4''-bipyridin-2'-yl)coumarins* ***(13a-c)*** *has been carried out by the reaction of 4-methyl-7-methoxy-8-coumarinoyl methyl pyridinium bromide salt* ***(1)*** *with various 1-aryl-3-(pyridin-2-yl)prop-2-en-1-ones* ***(8a-c)****,1-aryl-3-(pyridin-3-yl)prop-2-en-1-ones* ***(9a-c)*** *and 1-aryl-3-(pyridin-4-yl)prop-2-en-1-ones* ***(10a-c)****respectively in the presence of ammonium acetate in refluxing acetic acid under Krohnke's reaction condition.****(Scheme 3)****. The required chalcones****(8a-c),(9a-c) and (10a-c)*** *were prepared by the reaction of various p-substituted acetophenones with 2-formyl pyridine, 3-formyl pyridine and 4-formyl pyridine respectively in the presence of sodium hydroxide in ethanol. The structures of all the compounds synthesized, have been supported by analytical and spectral data. All the synthesized compounds were screened for their antimicrobial activity.*

Keywords: *Coumarins, Bypyridinyl-Coumarins, Krohnke's reaction and Antimicrobial activity.*

Date of Submission: 27-06-2018 Date of acceptance: 12-07-2018

I. Introduction

Coumarins are the best known aromatic lactones [1]. The isolation of coumarin was first reported by Vogel in Munich in 1820 [2].The coumarin ring system has an easy acceptability in the biological system compared to its isomeric chromones and flavones nucleus [3] and is widely distributed in nature [4-7]. Several biological activities have been claimed for compounds comprising both coumarins and coumarins fused to pyridine ring. For instance, coumarin nucleus is present in promising drug candidates as nonpeptidic HIV protease inhibitors1 such as topoisomerase-II [8] and tyrosine kinase [9] inhibitors. Coumarins joined to pyridines have been reported to possess several important biological activities. Among the heterocyclic substituted coumarins, pyridylcoumarins have a special importance due to their diverse physiological actions.Srenivasulu et al [10] have synthesized some 3-(3-pyridyl)coumarinderivatives. The compounds were synthesized by reacting substituted salicylaldehyde/o-hydroxyacetophenone with 3-pyridine acetic acid or its sodium salt under Perkin reaction conditions. These compounds were reported to have fish toxicity and bactericidal activities. A number of coumarin derivatives having pyridine substituted mainly at 3rd or 4th position of the coumarin possess CNS depressant activity, R B Moffett [11-13] synthesized number of 3-pyridyl and 4-pyridyl coumarins using modified Pechmann, Knoevenagel and Perkin reactions of pyridine acetic acid or pyridoyl acetic acid with substituted phenols and salicylaldehydes.Bipyridines are molecules which results when two pyridine nuclei are connected by a carbon-carbon single bond. Large number of bipyridines and substituted bipyridines are widely used in the complexation of inorganic metal ions. Their use as ligands in coordination and supramolecular chemistry is also reported in literature [14]. The transition metal complexes of bipyridines are reported to have important applications like photocatalysis [15], chemosensors [16] and luminescent probes for biomolecular systems [17]. In addition to their use as ligands in metal complexes, the bipyridines are also

reported to have other interesting applications. Some of the bipyridines are used as building blocks for the construction of efficient molecular and macromolecular nonlinear optical (NLO) chromophores [18]. Certain bipyridines are also reported to have important medicinal applications, e.g. 5-aryl-2,2′-bipyridines are reported to have a strong fungicidal activity against different plant diseases [19]. Certain bipyridine derivatives are used as cardiotonic drugs[20]. Thus, considering the importance of above bipyridinederiva- tives and in continuation of our interest in synthesizing newer modified pyridyl substituted coumarin derivatives, it was thought worthwhile to incorporate bipyridine nucleus in coumarin moiety as a substituent group and therefore in the present work, synthesis of various bipyridinyl substituted coumarins have been carried out. The syntheses of all newer compounds have been developed using Krohnke's pyridine synthesis [21-22].

II. Materials and Methods

All chemicals were purchased from Sigma-Aldrich, German. Melting points were determined by the open capillary method and were uncorrected. FTIR spectra of the synthesized compounds were recorded on a Shimadzu-8400S, using KBr pellets in 10^{-4} resolution and 30 scans. ^{1}H NMR spectra were recorded on a Varian spectrometer, USA at 400 MHz or BrukerAvance 400 spectrometer at room temperature. Samples were prepared in CD_3COCD_3, CD_3OD, $CDCl_3$ and DMSO-d_6 containing TMS as an internal standard. Splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift values were given in parts per million (ppm). ^{13}C NMR were recorded on Varian 400 spectrometer, operating at 400 MHz. The Liquid Chromatography Mass Spectra (LC-MS) were recorded on a Varian Inc, USA, 410Prostar Binary LC with 500 MS IT PDA detectors.

Experimental

Synthesis of 7-methoxy-4-methyl-8-(4'-aryl-2',2''-bipyridin-6'-yl)coumarins (5a-c); 7-methoxy-4-methyl-8-(4'-aryl-2',3''-bipyridin-6'-yl)coumarins (6a-c) and 7-methoxy-4-methyl-8-(4'-aryl-2',4''-bipyridin-6'-yl)coumarins (7a-c) (Scheme-1)

The synthesis of compounds 7-methoxy-4-methyl-8-(4'-aryl-2',2"-bipyridin-6'-yl)coumarins **(5a-c)**; 7-methoxy-4-methyl-8-(4'-aryl-2',3"-bipyridin-6'-yl)coumarins **(6a-c)** and 7-methoxy-4-methyl-8-(4'-aryl-2',4"-bipyridin-6'-yl) coumarins **(7a-c)** has been carried out by the reaction of 4-methyl-7-methoxy-8-coumarinoyl methyl pyridinium bromide salt **(1)** with various 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones **(2a-c)**, 3-aryl-1-(pyridin-3-yl)prop-2-en-1-ones **(3a-c)** and 3-aryl-1-(pyridin-4-yl)prop-2-en-1-ones **(4a-c)** respectively in the presence of ammonium acetate in refluxing acetic acid **(Scheme 1)**.

The following general procedure was used.

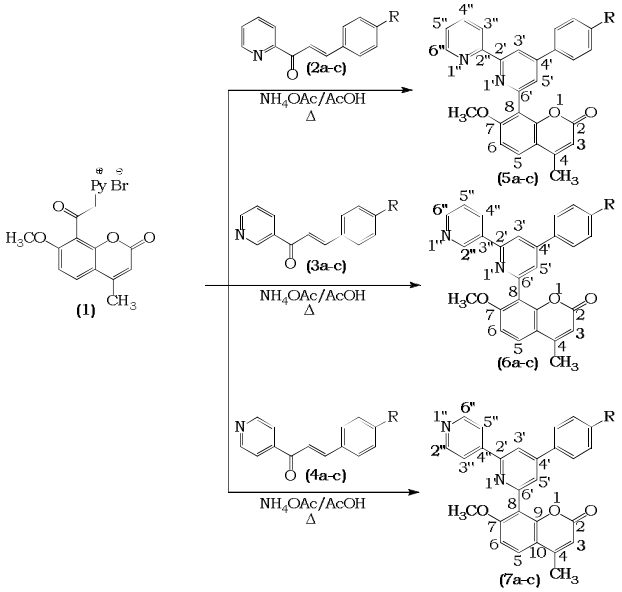
In a 100 mL round bottom flask equipped with a magnetic needle,4-methyl-7-methoxy-8-coumarinoyl methyl pyridiniumbromide salt **(1)** (0.003 mol) in glacial acetic acid (15 mL) was taken. To this ammonium acetate (0.03 mol) was added with stirring at room temperature. Then a solution of an appropriate 3-aryl-1-(pyridin-2-yl)prop-2-en-1-one **(2a-c)** (0.003 mol) or 3-aryl-1-(pyridin-3-yl)prop-2-en-1-one **(3a-c)** (0.003 mol)or3-aryl-1-(pyridin-4-yl)prop-2-en-1-one **(4a-c)** (0.003 mol) in glacial acetic acid (15 mL) was added with stirring at room temperature during 15 minutes. The reaction mixture was further stirred for 30 minutes and then refluxed for 8 hours at 140˚C. It was then allowed to come to room temperature and was poured into ice-cold water (75 mL). A crude solid obtained was extracted with chloroform (3 x 30 mL). The organic layer was washed with 5% sodium bicarbonate solution (3 x 20 mL), water (2 x 20 mL) and dried over anhydrous sodium sulfate. The removal of chloroform under reduced pressure gave gummy material which was subjected to column chromatography using silica gel and chloroform-pet.ether (60-80) (9:1) as an eluent to give appropriate products **(5a-c)** or **(6a-c)** or **(7a-c)**. The compounds were recrystallized from chloroform-hexane.

The structures of all the compounds **(5a-c)**, **(6a-c)** and **(7a-c)**were confirmed by analytical and spectral data. The formation of compounds **(5a-c)**,**(6a-c)** and **(7a-c)** follows Krohnke's pyridine synthesis mechanism**(Scheme 2)**.

Characterizations of synthesized compoundscompounds (5a-c), (6a-c) and (7a-c) (Scheme-1)

7-methoxy-4-methyl-8-(4-p-tolyl-2,2'-bipyridin-6-yl)-coumarin(5a)

R = CH_3, Yield = 63%, mp265-266°C, IR (cm^{-1}), ν_{max}1727 (C=O stretching of δ-lactone of coumarin), 1602 and 1516 (aromatic C=C and C=N stretchings), 831 (C-H bending vibrations of p-disubstituted benzene ring), 2938 (aliphatic C-H stretching), 3058 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.43 and 2.46 (6H, two singlet, 2 × CH_3),3.88 (3H, singlet, OCH_3), 6.17 (1H, singlet,proton at C_3), 7.00-8.57 (11H, multiplet, aromatic protons except proton at C_6"), 8.83 (1H, poorly resolved doublet of doublet, proton at C_6"). ^{13}C NMR (δ, ppm) ($CDCl_3$) 19.40(CH_3), 21.31(CH_3), 56.14(OCH_3), 107.84(CH), 112.50(CH), 113.86(C), 115.64(CH), 118.06(CH), 118.11(C), 121.45(CH), 123.66(CH), 124.40(CH), 127.31(CH), 129.50(CH), 132.26(C), 137.26(CH), 139.35(C), 147.14(C), 149.21(CH), 152.00(C), 152.71(C), 155.26(C), 155.37(C), 155.95(C), 157.01(CO of coumarin) and 160.85(CO of coumarin). Anal.Calcd.for$C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45%. Found: C, 77.29; H, 4.98; N, 6.27%.



	R		R		R
5a	CH_3	**6a**	CH_3	**7a**	CH_3
5b	OCH_3	**6b**	OCH_3	**7b**	OCH_3
5c	Cl	**6c**	Cl	**7c**	Cl

Scheme-1

7-methoxy-8-(4-(4-methoxyphenyl)-2,2'-bipyridin-6-yl)-4-methyl-coumarin(5b)

R = OCH_3, Yield = 68%, mp248°C, IR (cm^{-1}), ν_{max}1730 (C=O stretching of δ-lactone of coumarin), 1597 and 1498 (aromatic C=C and C=N stretchings), 817 (C-H bending vibrations of p-disubstituted benzene ring), 2977 (aliphatic C-H stretching), 3028 (aromatic C-H stretching). ^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (3H, singlet, CH_3), 3.86 and 3.88 (6H, two singlets, 2 × OCH_3), 6.17 (1H, singlet,proton at C_3), 7.01-8.58 (11H, multiplet, aromatic protons except proton at C_6"), 8.85 (1H, poorly resolved doublet of doublet, proton at C_6"). ^{13}C NMR (δ, ppm) ($CDCl_3$) 19.40(CH_3), 55.84(OCH_3), 56.14(OCH_3), 107.84(CH), 112.50(CH), 113.86(C), 114.84(CH), 115.64(CH), 118.06(CH), 118.11(C), 121.45(CH), 123.66(CH), 124.40(CH), 129.61(CH), 134.67(C), 137.26(CH), 147.14(C), 149.21(CH), 152.00(C), 152.71(C), 155.26(C), 155.35(C), 156.95(C), 157.11(C), 158.49(C), 160.95(CO of coumarin).Anal.Calcd.for$C_{28}H_{22}N_2O_4$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.59; H, 4.89; N, 6.17%.

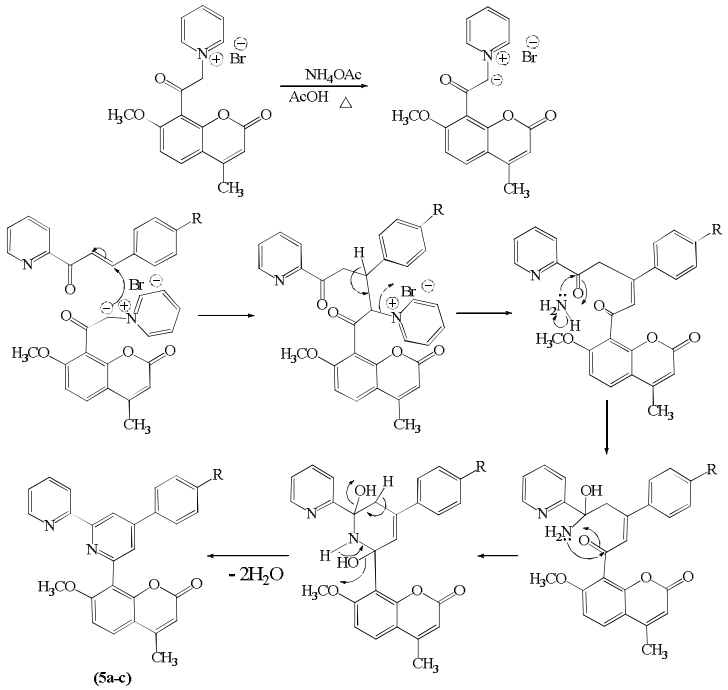
8-(4-(4-chlorophenyl)-2,2'-bipyridin-6-yl)-7-methoxy-4-methyl-coumarin(5c)

R = Cl, Yield = 70%, mp210-211°C, IR (cm^{-1}), ν_{max}1728 (C=O stretching of δ-lactone of coumarin), 1597 and 1498 (aromatic C=C and C=N stretchings), 817 (C-H bending vibrations of p-disubstituted benzene ring), 2947 (aliphatic C-H stretching), 3066 (aromatic C-H stretching). ^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (3H, singlet, CH_3), 3.88 (3H, singlet, OCH_3), 6.17 (1H, singlet,proton at C_3), 7.04-8.65 (11H, multiplet, aromatic protons except proton at C_6"), 8.96 (1H, poorly resolved doublet of doublet, proton at C_6"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 56.14(OCH_3), 107.84(CH), 112.51(CH), 113.86(C), 115.63(CH), 118.06(CH), 118.11(C), 121.44(CH), 123.65(CH), 124.41(CH), 128.79(C), 129.31(CH), 134.86(CH), 137.24(CH), 139.31(C), 147.14(C), 149.22(CH), 152.00(C), 152.71(C), 155.26(C), 155.34(C), 155.94(C), 157.01(C), 160.85(CO of coumarin). Anal.Calcd.for$C_{27}H_{19}N_2O_3Cl$: C, 71.29; H, 4.21; N, 6.16%. Found: C, 71.25; H, 4.16; N, 6.13%.

7-methoxy-4-methyl-8-(4-p-tolyl-2,3'-bipyridin-6-yl)-coumarin(6a)

R = CH_3, Yield = 67%, mp 213°C, IR (cm^{-1}), ν_{max}1726 (C=O stretching of δ-lactone of coumarin), 1603 and 1381 (aromatic C=C and C=N stretchings), 811 (C-H bending vibrations of p-disubstituted benzene ring), 2928 (aliphatic C-H stretching), 3058 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.43 and 2.46 (6H, two singlets, 2 × CH_3), 3.88 (3H, singlet, OCH_3), 6.16 (1H, singlet,proton at C_3), 6.99-8.36(10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.63 (1H, poorly resolved doublet of doublet, proton at C_6"), 9.21 (1H, meta coupled doublet, J = 1.6 Hz, proton at C_2"). ^{13}C NMR (δ, ppm) 19.40(CH_3), 21.31(CH_3), 56.14(OCH_3), 107.83(CH), 112.50(CH), 113.85(C), 114.07(CH), 118.11(C), 118.21(CH),

124.26(CH), 124.41(CH), 127.32(CH), 129.51(CH), 132.27(C), 134.38(CH), 134.56(C), 139.34(C), 147.16(C), 149.12(CH), 149.21(CH), 152.01(C), 152.38(C), 152.69(C), 155.26(C), 157.01(C), 160.79(CO of coumarin). Anal.Calcd.for$C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45%. Found: C, 77.29; H, 5.04; N, 6.37%.



Scheme-2

7-methoxy-8-(4-(4-methoxyphenyl)-2,3'-bipyridin-6-yl)-4-methyl-coumarin(6b)

R = OCH_3, Yield = 69%, mp 240°C, IR (cm^{-1}), ν_{max}1728 (C=O stretching of δ-lactone of coumarin), 1597 and 1381 (aromatic C=C and C=N stretchings), 816 (C-H bending vibrations of p-disubstituted benzene ring), 2942 (aliphatic C-H stretching), 3033 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (3H, singlet, CH_3), 3.86 and 3.88 (6H, two singlets, 2 × OCH_3), 6.18 (1H, singlet,proton at C_3), 7.01-8.38 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.65 (1H, poorly resolved doublet of doublet, proton at C_6"), 9.22 (1H, meta coupled doublet, J = 1.6 Hz, proton at C_2").^{13}C NMR (δ, ppm) 19.38(CH_3), 55.79(OCH_3), 56.14(OCH_3), 107.83(CH), 112.49(CH), 113.86(C), 115.63(CH), 118.07(CH), 118.10(C), 121.39(CH), 123.65(CH), 124.38(CH), 128.79(C), 129.32(CH), 134.86(C), 137.25(CH), 139.94(C), 147.13(C), 149.22(CH), 149.25(CH), 152.69(C), 155.25(C), 155.36(C), 155.38(C), 157.01(C), 160.82(CO of coumarin). Anal.Calcd.for$C_{28}H_{22}N_2O_4$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.56; H, 4.87; N, 6.19%.

8-(4-(4-chlorophenyl)-2,3'-bipyridin-6-yl)-7-methoxy-4-methyl-coumarin(6c)

R = Cl, Yield = 71%, mp242-243°C, IR (cm^{-1}), ν_{max}1724 (C=O stretching of δ-lactone of coumarin), 1604 and 1497 (aromatic C=C and C=N stretchings), 837 (C-H bending vibrations of p-disubstituted benzene ring), 2937 (aliphatic C-H stretching), 3059 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (3H, singlet, CH_3), 3.88 (3H, singlet, OCH_3), 6.17(1H, singlet,proton at C_3), 7.04-8.37 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.64 (1H, doublet of doublet, J = 4.6 and 1.2 Hz, proton at C_6"), 9.21 (1H, meta coupled doublet, J = 1.6 Hz, proton at C_2"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 56.10(OCH_3), 107.83(CH), 112.50(CH), 113.86(C), 114.84(CH), 115.64(CH), 118.09(C), 118.11(CH), 121.46(CH), 124.11(C), 124.41(CH), 129.63(CH), 134.68(C), 137.26(CH), 147.14(C), 149.21(CH), 149.41(CH), 152.26(C), 155.27(C), 155.34(C), 156.96(C), 157.12(C), 158.48(C), 160.87(CO of coumarin).Anal.Calcd.for$C_{27}H_{19}N_2O_3Cl$: C, 71.29; H, 4.21; N, 6.16%. Found: C, 71.24; H, 4.17; N, 6.12%.

7-methoxy-4-methyl-8-(4-p-tolyl-2,4'-bipyridin-6-yl)-coumarin(7a)

R = CH_3, Yield = 66%, mp202°C, IR (cm^{-1}), ν_{max}1727 (C=O stretching of δ-lactone of coumarin), 1599 and 1514 (aromatic C=C and C=N stretchings), 820 (C-H bending vibrations of p-disubstituted benzene ring), 2938 (aliphatic C-H stretching), 3059 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.43 and 2.46 (6H, two singlets, 2 × CH_3), 3.88(3H, singlet, OCH_3), 6.17 (1H, singlet,proton at C_3), 7.01-7.94 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.70 (2H, ortho coupled doublet, J = 4.4 Hz, protons at C_2" and C_6").^{13}C NMR (δ, ppm) 19.41(CH_3), 21.31(CH_3), 56.13(OCH_3), 107.85(CH), 112.51(CH), 113.80(C), 115.60(CH), 115.62(CH), 118.11(C), 121.40(CH), 124.39(CH), 127.31(CH), 129.54(CH), 132.21(C),

139.34(C), 145.72(C), 147.13(C), 149.83(CH), 152.00(C), 152.71(C), 153.60(C), 155.21(C), 157.00(C), 160.83(CO of coumarin). Anal.Calcd.for$C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45%. Found: C, 77.27; H, 5.03; N, 6.37%.

7-methoxy-8-(4-(4-methoxyphenyl)-2,4'-bipyridin-6-yl)-4-methyl-coumarin(7b)

R = OCH_3, Yield = 70%, mp189-190°C, IR (cm^{-1}), ν_{max}1724 (C=O stretching of δ-lactone of coumarin), 1604 and 1497 (aromatic C=C and C=N stretchings), 837 (C-H bending vibrations of p-disubstituted benzene ring), 2936 (aliphatic C-H stretching), 3059 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (3H, singlet, CH_3), 3.88 (6H, singlet, 2 × OCH_3), 6.17 (1H, singlet,proton at C_3), 7.01-7.94 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.70 (2H, poorly resolved ortho coupled doublet, protons at C_2" and C_6").^{13}C NMR (δ, ppm) 19.41(CH_3), 55.83(OCH_3), 56.13(OCH_3), 107.85(CH), 112.51(CH), 113.80(C), 114.81(CH), 115.59(CH), 115.59(CH), 118.11(C), 121.40(CH), 124.37(CH), 129.59(CH), 134.58(C), 145.70(C), 147.12(C), 149.79(CH), 152.03(C), 152.69(C), 153.59(C), 155.19(C), 157.01(C), 158.79(C), 160.82(CO of coumarin).Anal.Calcd.for$C_{28}H_{22}N_2O_4$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.57; H, 4.87; N, 6.16%.

8-(4-(4-chlorophenyl)-2,4'-bipyridin-6-yl)-7-methoxy-4-methyl-coumarin(7c)

R = Cl, Yield = 69%, mp218°C, IR (cm^{-1}), ν_{max}1726 (C=O stretching of δ-lactone of coumarin), 1604 and 1498 (aromatic C=C and C=N stretchings), 828 (C-H bending vibrations of p-disubstituted benzene ring), 2938 (aliphatic C-H stretching), 3058 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (3H, singlet, CH_3), 3.88 (3H, singlet, OCH_3), 6.17 (1H, singlet,proton at C_3), 7.01-7.99 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.75 (2H, ortho coupled doublet, J = 4.8 Hz, protons at C_2" and C_6").^{13}C NMR (δ, ppm) 19.41(CH_3), 56.13(OCH_3), 107.86(CH), 112.51(CH), 113.81(C), 115.61(CH), 115.62(CH), 118.11(C), 121.40(CH), 124.39(CH), 128.73(CH), 129.32(CH), 134.84(C), 140.41(C), 145.73(C), 147.14(C), 149.83(CH), 152.00(C), 152.71(C), 153.61(C), 155.21(C), 157.01(C), 160.83(CO of coumarin).Anal.Calcd.for$C_{27}H_{19}N_2O_3Cl$: C, 71.29; H, 4.21; N, 6.16%. Found: C, 71.20; H, 4.17; N, 6.10%.

Synthesis of 7-methoxy-4-methyl-8-(6'-aryl-4',2''-bipyridin-2'-yl)coumarins (11a-c); 7-methoxy-4-methyl-8-(6'-aryl-4',3''-bipyridin-2'-yl)coumarins (12a-c) and 7-methoxy-4-methyl-8-(6'-aryl-4',4''-bipyridin-2'-yl)coumarins (13a-c).

The synthesis of compounds 7-methoxy-4-methyl-8-(6'-aryl-4',2"-bipyridin-2'-yl)coumarins**(11a-c)**;7-methoxy-4-methyl-8-(6'-aryl-4',3"-bipyridin-2'-yl)coumarins **(12a-c)** and7-methoxy-4-methyl-8-(6'-aryl-4',4"-bipyridin-2'-yl)coumarins**(13a-c)** has been carried out by the reaction of 4-methyl-7-methoxy-8-coumarinoyl methyl pyridinium bromide salt **(1)** with various 1-aryl-3-(pyridin-2-yl)prop-2-en-1-ones **(8a-c)**,1-aryl-3-(pyridin-3-yl)prop-2-en-1-ones**(9a-c)** and1-aryl-3-(py-ridin-4-yl)prop-2-en-1-ones **(10a-c)** respectivelyin the presence of ammonium acetate in refluxing acetic acid **(Scheme 3).**

The following general procedure was used.

In a 100 mL round bottom flask equipped with a magnetic needle,4-methyl-7-methoxy-8-coumarinoyl methyl pyridinium bromide salt **(1)** (0.003 mol) in glacial acetic acid (15 mL) was taken. To this ammonium acetate (0.03 mol) was added with stirring at room temperature. Then a solution of an appropriate 1-aryl-3-(pyridin-2-yl)prop-2-en-1-one **(8a-c)** (0.003 mol) or 1-aryl-3-(pyridin-3-yl)prop-2-en-1-one **(9a-c)** (0.003 mol)or1-aryl-3-(pyridin-4-yl)prop-2-en-1-one **(10a-c)** (0.003 mol) in glacial acetic acid (15 mL) was added with stirring at room temperature during 15 minutes. The reaction mixture was further stirred for 30 minutes and then refluxed for 8 hours at 140˚C. It was then allowed to come to room temperature and was poured into ice-cold water (75 mL). A crude solid obtained was extracted with chloroform (3 x 30 mL). The organic layer was washed with 5% sodium bicarbonate solution (3 x 20 mL), water (2 x 20 mL) and dried over anhydrous sodium sulfate. The removal of chloroform under reduced pressure gave gummy material which was subjected to column chromatography using silica gel and chloroform-pet.ether (60-80) (9:1) as an eluent to give appropriate products **(11a-c)** or **(12a-c)** or **(13a-c)**. The compounds were recrystallized from chloroform-hexane.

The structures of all the compounds products **(11a-c)**, **(12a-c)** and **(13a-c)**were confirmed by analytical and spectral data.The formation of compounds products **(11a-c)**, **(12a-c)** and **(13a-c)** follows Krohnke's pyridine synthesis mechanism similar to **Scheme 2**.

Characterizations of synthesized compoundscompounds (11a-c), (12a-c) and (13a-c) (Scheme-3)

7-methoxy-4-methyl-8-(6'-p-tolyl-2,4'-bipyridin-2'-yl)-coumarin (11a)

R = CH_3, Yield = 65%, mp 242°C, IR (cm^{-1}), ν_{max}1730 (C=O stretching of δ-lactone of coumarin), 1597 and 1497 (aromatic C=C and C=N stretchings), 817 (C-H bending vibrations of p-disubstituted benzene ring), 2923 (aliphatic C-H stretching), 3059 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.45 and 2.46 (6H, two singlet, 2 × CH_3), 3.88 (3H,singlet,OCH_3), 6.18 (1H, singlet,proton at C_3), 7.00-8.85 (11H, multiplet, aromatic protons except proton at C_6"), 8.97 (1H, poorly resolved doublet of doublet, proton at

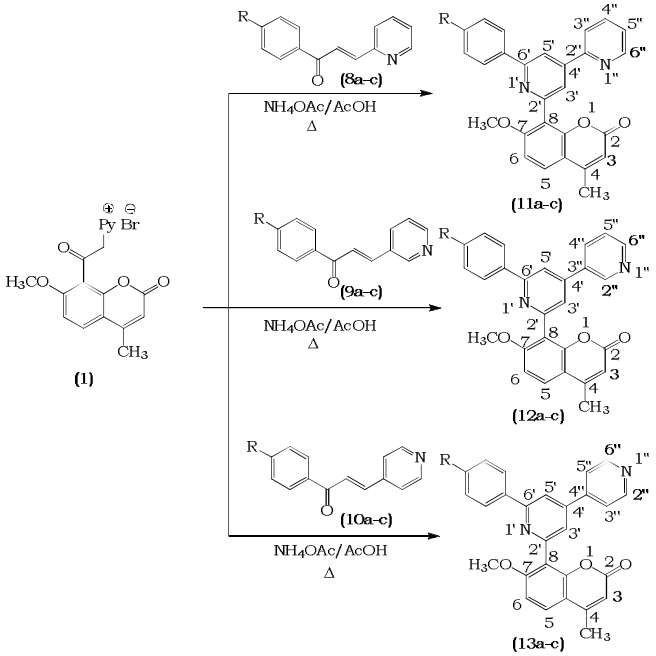
C_6"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 21.31(CH_3), 56.12(OCH_3), 107.81(CH), 112.53(CH), 113.81(C), 118.12(C), 118.73(CH), 118.74(CH), 120.51(CH), 123.33(CH), 123.62(CH), 124.46(CH), 129.49(CH), 130.31(C), 136.02(C), 137.21(CH), 147.14(C), 149.21(CH), 149.35(C), 152.70(C), 153.77(C), 154.64(C), 155.32(C), 157.02(CO of coumarin) and 160.81(CO of coumarin).Anal.Calcd.for$C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45%. Found: C, 77.33; H, 5.01; N, 6.33%.

7-methoxy-8-(6'-(4-methoxyphenyl)-2,4'-bipyridin-2'-yl)-4-methyl-coumarin (11b)

R = OCH_3, Yield = 68%, mp 230-231°C, IR (cm^{-1}), ν_{max}1728 (C=O stretching of δ-lactone of coumarin), 1598 and 1498 (aromatic C=C and C=N stretchings), 817 (C-H bending vibrations of p-disubstituted benzene ring), 2940 (aliphatic C-H stretching), 3067 (aromatic C-H stretching).^1H NMR (δ, ppm) ($CDCl_3$) 2.45 (3H, singlet, CH_3), 3.88 (6H, two singlets, 2 × OCH_3), 6.15 (1H, singlet,proton at C_3), 6.99-8.84 (11H, multiplet, aromatic protons except proton at C_6"), 8.96 (1H, poorly resolved doublet of doublet, proton at C_6"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 55.85(OCH_3), 56.13(OCH_3), 107.81(CH), 112.53(CH), 113.81(C), 114.82(CH), 118.12(C), 118.74(CH), 118.74(CH), 120.52(CH), 123.61(CH), 124.45(CH), 128.66(CH), 131.33(C), 137.21(CH), 147.11(C), 149.21(CH), 149.35(C), 152.71(C), 153.77(C), 154.64(C), 155.31(C), 157.02(C), 159.22(C), 160.81(CO of coumarin). Anal.Calcd.for$C_{28}H_{22}N_2O_4$: C, 74.65; H, 6.22; N, 7.13%. Found: C, 74.60; H, 4.87; N, 6.19%.

8-(6'-(4-chlorophenyl)-2,4'-bipyridin-2'-yl)-7-methoxy-4-methyl-coumarin (11c)

R = Cl, Yield = 65%, mp 238°C, IR (cm^{-1}), ν_{max}1725 (C=O stretching of δ-lactone of coumarin), 1597 and 1491 (aromatic C=C and C=N stretchings), 819 (C-H bending vibrations of p-disubstituted benzene ring), 2978 (aliphatic C-H stretching), 3064 (aromatic C-H stretching).^1H NMR (δ, ppm) ($CDCl_3$) 2.45 (3H, singlet, CH_3), 3.85 (3H, singlet, OCH_3), 6.15 (1H, singlet,proton at C_3), 7.01-8.31 (11H, multiplet, aromatic protons except proton at C_6"), 8.75 (1H, poorly resolved doublet of doublet, proton at C_6"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 56.12(OCH_3), 107.82(CH), 112.52(CH), 113.82(C), 118.13(C), 118.74(CH), 118.74(CH), 120.50(CH), 123.61(CH), 124.45(CH), 129.02(CH), 129.31(CH), 132.91(C), 137.13(C), 137.21(CH), 147.14(C), 149.21(CH), 149.35(C), 152.70(C), 153.78(C), 154.63(C), 155.32(C), 157.02(C), 160.82(CO of coumarin). Anal.Calcd.for$C_{27}H_{19}N_2O_3Cl$: C, 71.29; H, 4.21; N, 6.16%. Found: C, 71.24; H, 4.16; N, 6.12%.



	R		R		R
11a	CH_3	**12a**	CH_3	**13a**	CH_3
1b	OCH_3	**12b**	OCH_3	**13b**	OCH_3
11c	Cl	**13c**	Cl	**13c**	Cl

Scheme-3

7-methoxy-4-methyl-8-(6'-p-tolyl-3,4'-bipyridin-2'-yl)-coumarin (12a)

R = CH_3, Yield = 70%, mp 214°C, IR (cm^{-1}), ν_{max}1728 (C=O stretching of δ-lactone of coumarin), 1600 and 1498 (aromatic C=C and C=N stretchings), 826 (C-H bending vibrations of p-disubstituted benzene ring), 2943 (aliphatic C-H stretching), 3067 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (6H, singlet, 2 × CH_3), 3.88 (3H, singlet, OCH_3), 6.17 (1H, singlet,proton at C_3), 7.01-7.93 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.59 (1H, poorly resolved doublet of doublet, proton at C_6"), 8.96 (1H, meta coupled doublet, J = 1.6 Hz, proton at C_2"). ^{13}C NMR (δ, ppm) 19.40(CH_3), 21.31(CH_3), 56.14(OCH_3), 107.32(CH), 112.51(CH), 113.82(C), 116.20(CH), 116.21(CH), 118.10(C), 123.31(CH), 124.03(CH), 124.45(CH), 129.51(CH), 130.34(C), 133.00(C), 134.07(CH), 136.02(C), 147.11(C), 147.62(C), 147.93(CH), 148.91(CH), 152.74(C), 153.72(C), 155.32(C), 157.03(C), 160.81(CO of coumarin).Anal.Calcd.for$C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45%. Found: C, 77.36; H, 5.07; N, 6.40%.

7-methoxy-8-(6'-(4-methoxyphenyl)-3,4'-bipyridin-2'-yl)-4-methyl-coumarin (12b)

R = OCH_3, Yield = 71%, mp225-226°C, IR (cm^{-1}), ν_{max}1728 (C=O stretching of δ-lactone of coumarin), 1600 and 1498 (aromatic C=C and C=N stretchings), 826 (C-H bending vibrations of p-disubstituted benzene ring), 2939 (aliphatic C-H stretching), 3066 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.45 (3H, singlet, CH_3), 3.88 (6H, two singlets, 2 × OCH_3), 6.15 (1H, singlet,proton at C_3), 6.99-8.03 (10H, multiplet, aromatic protons except protons at C_2" and C_6"),8.84 (1H, poorly resolved doublet of doublet, proton at C_6"), 8.96 (1H, meta coupled doublet, J = 1.6 Hz, proton at C_2"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 55.81(OCH_3), 56.14(OCH_3), 107.32(CH), 112.52(CH), 113.83(C), 114.82(CH), 116.20(CH), 116.21(CH), 118.11(C), 124.02(CH), 124.44(CH), 128.63(CH), 131.30(C), 133.01(C), 134.06(CH), 147.11(C), 147.62(C), 147.93(CH), 148.92(CH), 152.74(C), 153.71(C), 155.33(C), 157.02(C), 159.23(C), 160.81(CO of coumarin).Anal.Calcd.for$C_{28}H_{22}N_2O_4$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.57; H, 4.85; N, 6.16%.

8-(6'-(4-chlorophenyl)-3,4'-bipyridin-2'-yl)-7-methoxy-4-methyl-coumarin (12c)

R = Cl, Yield = 72%, mp246-247°C, IR (cm^{-1}), ν_{max}1725 (C=O stretching of δ-lactone of coumarin), 1603 and 1473 (aromatic C=C and C=N stretchings), 837 (C-H bending vibrations of p-disubstituted benzene ring), 2939 (aliphatic C-H stretching), 3066 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.45 (3H, singlet, CH_3), 3.86 (3H, singlet, OCH_3), 6.15(1H, singlet,proton at C_3), 7.00-8.03 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.03 (1H, poorly resolved doublet of doublet, proton at C_6"), 8.71 (1H, meta coupled doublet, J = 1.6 Hz, proton at C_2").^{13}C NMR (δ, ppm) 19.40(CH_3), 56.14(OCH_3), 107.31(CH), 112.52(CH), 113.79(C), 116.21(CH), 116.21(CH), 118.09(C), 124.00(CH), 124.44(CH), 129.00(CH), 129.29(CH), 132.91(C), 133.10(C), 134.07(CH), 137.12(C), 147.11(C), 147.62(C), 147.94(CH), 148.92(CH), 152.74(C), 153.73(C), 155.33(C), 157.02(C), 160.81(CO of coumarin).Anal.Calcd.for$C_{27}H_{19}N_2O_3Cl$: C, 71.29; H, 4.21; N, 6.16%. Found: C, 71.19; H, 4.14; N, 6.11%.

7-methoxy-4-methyl-8-(6-p-tolyl-4,4'-bipyridin-2-yl)-coumarin (13a)

R = CH_3, Yield = 64%, mp 230°C, IR (cm^{-1}), ν_{max}1730 (C=O stretching of δ-lactone of coumarin), 1598 and 1383 (aromatic C=C and C=N stretchings), 817 (C-H bending vibrations of p-disubstituted benzene ring), 2938 (aliphatic C-H stretching), 3028 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.40 and 2.43 (6H, two singlets, 2 × CH_3), 3.88(3H, singlet, OCH_3), 6.16 (1H, singlet,proton at C_3), 7.01-7.93 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.73 (2H, ortho coupled doublet, J = 4.8 Hz, protons at C_2" and C_6"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 21.31(CH_3), 56.12(OCH_3), 107.81(CH), 112.53(CH), 113.81(C), 118.12(C), 118.74(CH), 118.74(CH), 121.13(CH), 123.33(CH), 124.46(CH), 129.49(CH), 130.31(C), 136.02(C), 144.45(C), 147.14(C), 149.35(C), 149.82(CH), 152.70(C), 153.77(C), 155.32(C), 157.02(C), 160.81(CO of coumarin). Anal.Calcd.for$C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45%. Found: C, 77.32; H, 5.06; N, 6.37%.

7-methoxy-8-(6-(4-methoxyphenyl)-4,4'-bipyridin-2-yl)-4-methyl-coumarin (13b)

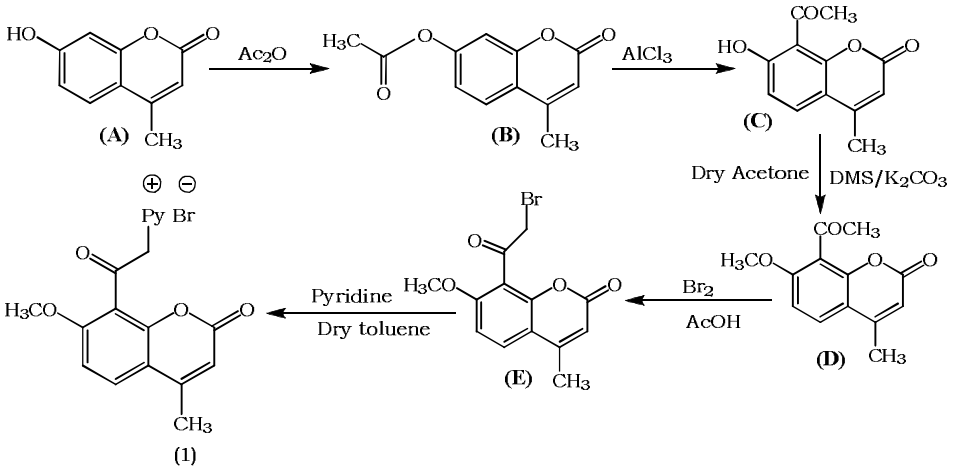
R = OCH_3, Yield = 63%, mp224-225°C, IR (cm^{-1}), ν_{max}1730 (C=O stretching of δ-lactone of coumarin), 1598 and 1384 (aromatic C=C and C=N stretchings), 817 (C-H bending vibrations of p-disubstituted benzene ring), 2925 (aliphatic C-H stretching), 3028 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (3H, singlet, CH_3), 3.86 and 3.88 (6H, two singlets, 2 × OCH_3), 6.17 (1H, singlet,proton at C_3), 6.98-7.99 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.73 (2H, ortho coupled doublet, J = 6.4 Hz, protons at C_2" and C_6"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 55.85(OCH_3), 56.13(OCH_3), 107.81(CH), 112.53(CH), 113.82(C), 114.82(CH), 118.13(C), 118.74(CH), 118.74(CH), 121.12(CH), 124.46(CH), 128.67(CH), 131.22(C), 144.43(C), 147.14(C), 149.34(C), 149.79(CH), 152.71(C), 153.76(C), 155.32(C), 157.00(C), 159.22(C), 160.82(CO of coumarin).Anal.Calcd.for$C_{28}H_{22}N_2O_4$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.57; H, 4.85; N, 6.17%.

8-(6-(4-chlorophenyl)-4,4'-bipyridin-2-yl)-7-methoxy-4-methyl-coumarin (13c)

R = Cl, Yield = 66%, mp248-249°C, IR (cm^{-1}), ν_{max}1727 (C=O stretching of δ-lactone of coumarin), 1599 and 1499 (aromatic C=C and C=N stretchings), 820 (C-H bending vibrations of p-disubstituted benzene ring), 2939 (aliphatic C-H stretching), 3034 (aromatic C-H stretching).^{1}H NMR (δ, ppm) ($CDCl_3$) 2.46 (3H, singlet, CH_3), 3.88 (3H, singlet, OCH_3), 6.17 (1H, singlet,proton at C_3), 7.03-7.99 (10H, multiplet, aromatic protons except protons at C_2" and C_6"), 8.73 (2H, ortho coupled doublet, J = 6.4 Hz, protons at C_2" and C_6"). ^{13}C NMR (δ, ppm) 19.41(CH_3), 56.12(CH_3), 107.82(CH), 112.53(CH), 113.82(C), 118.13(C), 118.73(CH), 118.73(CH), 121.15(CH), 124.45(CH), 129.01(CH), 129.31(CH), 132.92(C), 137.12(C), 144.43(C), 147.13(C), 149.32(C), 149.81(CH), 152.71(C), 153.77(C), 155.31(C), 157.00(C), 160.82(CO of coumarin).Anal.Calcd.for$C_{27}H_{19}N_2O_3Cl$: C, 71.29; H, 4.21; N, 6.16%. Found: C, 71.25; H, 4.16; N, 6.08%.

Preparation of 4-methyl-7-methoxy-8-coumarinoyl methyl pyridinium bromide salt (1).

A mixture of **(A)**4-methyl-7-hydroxy coumarin(0.16 mol) and acetic anhydride (0.56 mol) was placed in a 250 mL round bottom flask fitted with a reflux condenser. The reaction mixture was refluxed for 1.5 hours in an oil bath. It was then cooled to about 50°C and poured with vigorous stirring in to ice cold water. The solid obtained was filtered, washed with cold water and dried. It was recrystallized from ethanol**(B)** [23].



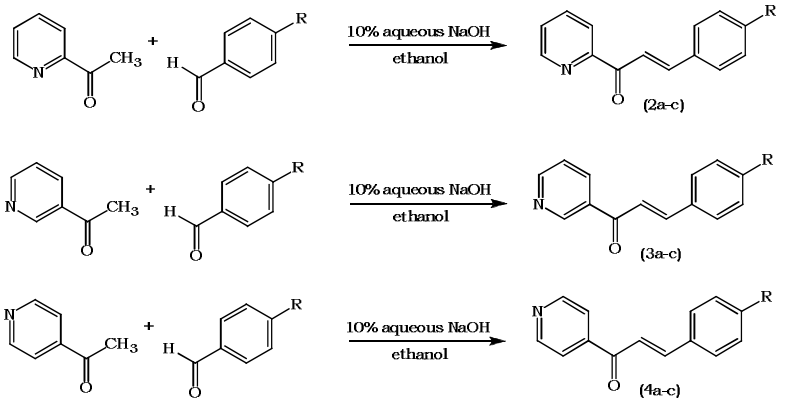
Scheme-4

A powdered**(B)**4-methyl-7-acetoxycoumarin (0.092 mol) and finely powdered anhydrous aluminum chloride (0.34 mol) were placed in a 500 mL round bottom flask. The flask was stoppered and shaken vigorously for 3 to 5 minutes in order to mix the ingredients thoroughly. The stopper was removed and the flask was attached with reflux condenser, provided with a gas-absorption tube. The flask was placed in an oil bath and the temperature was quickly raised to 125°C and then slowly to 170°C over a period of 2 hours. At the end of this, the flask was removed from the oil bath, allowed to cool and immersed in an ice bath. About 100g of crushed ice was added slowly and then 240 mL of dilute hydrochloric acid (1:7) was added over a period of about 2 hours. The reaction mixture was then heated on a steam bath for 30 minutes with vigorous stirring in order to effect complete decomposition. It was cooled and the solid was filtered out, washed with three 50 mL portions of cold water and dried. It was recrystallized from R-spirit**(C)**[23]. In a 500 mL round bottom flask, a mixture of **(C)**4-methyl-7-hydroxy-8-acetylcoumarin(0.055 mol), dimethyl sulfate(10 mL), dry acetone (300 mL) and anhydrous pottasium carbonate(60g) was refluxed for 8-hours. Acetone was removed by distillation and cold water was added to the residue to dissolve K2CO3. It was kept at room temperature for 2-3 hours. The solid was filtered out and washed with cold water. It was recrystallized from chloroform-haxane to white crystals **(D)** [24]. In a 250mL three necked round bottom flask equipped with a dropping funnel, gas absorption trap and a magnetic needle, was placed**(D)**4-methyl-7-methoxy-8-acetyl coumarin (0.043 mole) in glacial acetic acid (50mL). To this, bromine (0.048 mole) in glacial acetic acid (5mL) was added dropwise with stirring during 15 minutes at room temperature. The reaction mixture was stirred at room temperature for 3 hours. It was then poured into ice cold water and solid product obtained was filtered out. The product was washed with water, dried and recrystallized from chloroform to white needles **(E)** [24]. In 250 mL round bottom flask fitted with a reflux condenser, a solution of**(E)**4-methyl-7-methoxy-8-(bromoacetyl)coumarin(0.03 mole) in dry toluene (100mL) was taken and pyridine (0.0315 mole) was added slowly. The reaction mixture was refluxed in an oil bath for 2 hours. It was then allowed to cool to room temperature and was kept aside for 4-5 hours. The

pyridinium bromide salt separated out was then filtered and washed with hot toluene. It was dried and recrystallized from acetic acid **(1)** [24].

Preparation of 3-aryl-1-(pyridin-2-yl)-prop-2-en-1-ones (2a-c); 3-aryl-1-(pyridin-3-yl)prop-2-en-1-ones (3a-c) and 3-aryl-1-(pyridin-4-yl)prop-2-en-1-ones (4a-c) (Scheme-5)

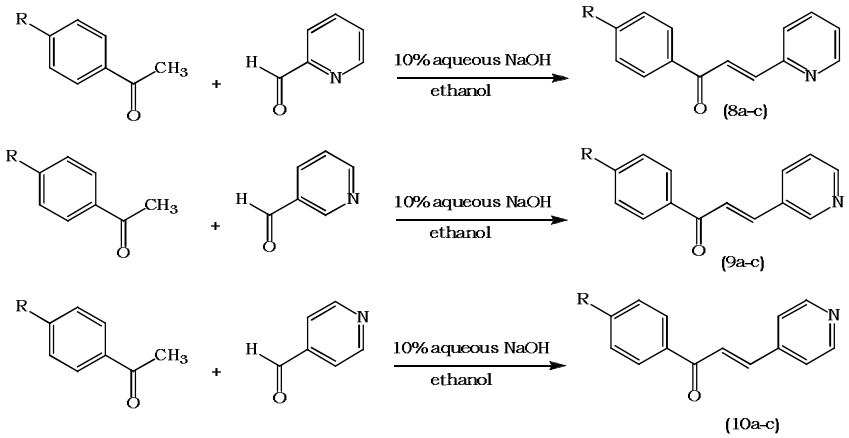
In a 100 mL three necked flask equipped with a thermometer and magnetic needle, an aqueous 10% sodium hydroxide solution (25 ml) and ethanol (20 ml) were added with stirring and the mixture was cooled to 0-10°C in an ice bath. An appropriate aromatic aldehyde (0.02 mol) was introduced in one portion. Then appropriate acetyl pyridine (0.02 mol) was added in small portions over a period of 10 minutes. The mixture was stirred for three hours at 10°C under stirring. The resulting solid was isolated by filtration and was washed with cold ethanol. The solid was then dried and recrystallized from ethanol to give yellow crystals [25-27].



Scheme-5

Preparation of 3-(pyridin-2-yl)-1-aryl–prop-2-ene-1-ones (8a-c); 3-(pyridin-3-yl)-1-aryl-prop-2-ene-1-ones (9a-c) and 3-(pyridin-4-yl)-1-aryl-prop-2-ene-1-ones (10a-c) (Scheme-6)

In a 100 mL three necked flask equipped with a thermometer and magnetic needle, an aqueous 10% sodium hydroxide solution (25 ml) and ethanol (20 ml) were added with stirring and the mixture was cooled to 0-10°C in an ice bath. An appropriate formyl pyridine (0.02 mol) was introduced in one portion. Then appropriate para- substituted acetophenone(0.02 mol) was added in small portions over a period of 10 minutes. The mixture was stirred for three hours at 10°C under stirring. The resulting solid was isolated by filtration and was washed with cold ethanol. The solid was then dried and recrystallized from ethanol to give yellow crystals[28-29].



Scheme-6

III. Results and Discussion

The newly synthesized target compounds **(5a-c)**, **(6a-c)**, **(7a-c)**,**(11a-c)**, **(12a-c)** and **(13a-c)**were evaluated for their in vitro antibacterial activity against two Gram positive bacteria Staphylococcus aureus (MTCC 96) and Bacillus subtilis(MTCC 441) and two Gram negative bacteria Escherichia coli (MTCC 443)

and Salmonella typhi(MTCC 98). They were also evaluated for their in vitro antifungal activity against Candida albicans (MTCC 227) and Aspergillusniger (MTCC 282) as fungal strains. Broth dilution method was used for the determination of the antibacterial and antifungal activity as recommended by NCCLS [30].

Ampicillin, Chloramphenicol and Norfloxacin were used as standard antibacterial drugs, whereas Griseofulvin and Nystatin were used as standard antifungal drugs. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against above mentioned known drugs. Mueller-Hinton broth was used as the nutrient medium for the test bacteria and Sabouraud Dextrose broth was used for the test fungi. Inoculum size for the test strains was adjusted to 10^8 CFU (Colony Forming Unit per milliliter) per milliliter by comparing the turbidity. Each synthesized compound was diluted with DMSO so as to have the stock solution of 2000 µg/mL concentration as a stock solution. The results were recorded in the form of primary and secondary screening. The synthesized compounds **(3a-l)** were screened for their antibacterial and antifungal activity at the concentration of 1000, 500 and 250 µg/mL for the primary screening. The synthesized compound showing activity against microbes in the primary screening were further screened in a second set of dilution at concentrations of 200, 100, 62.5, 50 and 25 µg/mL. The suspensions of 10 µL from each well were further incubated and growth was noted at 37°C after 24 hour for bacteria and 48 hour for fungi. The lowest concentration which showed no visible growth (turbidity) after spot subculture was considered as the minimum inhibitory concentration (MIC) for each compound.

Table 1 [Biological Activity of **(5a-c)**, **(6a-c)**, **(7a-c)**,**(11a-c)**, **(12a-c)** and **(13a-c)** against standard drugs]

Compound	Minimum Inhibitory Concentration (MIC, µgmL^{-1})					
	Gram +ve bacteria		Gram –ve bacteria		Fungi	
	B.s.	S.a.	E.c.	S.t.	A.n.	C.a.
5a	**250**	**250**	125	200	>1000	>1000
5b	500	500	**100**	200	1000	1000
5c	**100**	**125**	**62.5**	**100**	250	**500**
6a	**100**	**100**	**100**	250	500	1000
6b	500	500	500	500	500	**500**
6c	500	500	500	500	500	**500**
7a	**200**	**200**	250	250	500	>1000
7b	500	500	**100**	200	250	>1000
7c	**100**	**100**	**50**	125	500	**500**
11a	**250**	**250**	200	250	500	1000
11b	500	500	200	200	>1000	>1000
11c	**100**	**100**	**62.5**	**100**	500	**500**
12a	**250**	**250**	**100**	125	>1000	1000
12b	**250**	**125**	200	125	>1000	1000
12c	**200**	**125**	250	125	500	>1000
13a	**250**	**200**	250	125	1000	**500**
13b	**100**	**250**	200	200	1000	1000
13c	**100**	**100**	**50**	**100**	250	**250**
Ampicillin	250	250	100	100	-	-
Chloramphenicol	50	50	50	50	-	-
Ciprofloxacin	50	50	25	25	-	-
Norfloxacin	100	10	10	10	-	-
Gentamycin	0.5	0.25	0.05	1	-	-
Griseofulvin	-	-	-	-	100	500
Nystatin	-	-	-	-	100	100

B.s.: Bacillus subtilis, **S.a.:** Staphylococcus aureus, **E.c.:** Escherichia coli,
S.t.: Salmonella typhi, **A.n.:**Aspergillusniger, **C.a.:** Candida albicans

Upon evaluating the antimicrobial activity data, it has been observed that compounds **5c**, **6a**, **7c**, **11c**, **13b** and **13c** (MIC = 100µg/mL) showed excellent activity compared to Ampicillin (MIC = 250µg/mL) and equal activity to Norfloxacin (MIC = 100µg/mL) against gram positive bacteria Bacillus subtilis. Compounds **7a** and**12c** (MIC = 200µg/mL) were found to be more active against Bacillus subtilis as compared to Ampicillin. Compounds **5a**, **11a**, **12a, 12b** and **13a** (MIC = 250µg/mL) were found to be equipotent to Ampicillin against Bacillus subtilis.

Whereas, compounds **6a**, **7c**, **11c**, **13c**(MIC = 100µg/mL), **5c**, **12b** and **12c** (MIC = 125µg/mL) showed excellent activity against gram positive bacteria Staphylococcus aureus compared to Ampicillin (MIC = 250µg/mL). Compounds **7a** and **13a** (MIC = 200µg/mL) were found to be more active against Staphylococcus aureus compared to Ampicillin. Compounds **5a**, **11a**,**12a** and **13b** (MIC = 250µg/mL) were found to be equipotent to Ampicillin against Staphylococcus aureus.

Compounds **7c, 13c** (MIC = 50µg/mL) and **5c**, **11c** (MIC = 62.5µg/mL)displayed excellent activity against gram negative bacteria Escherichia coli compared to Ampicillin (MIC = 100µg/mL). Compounds **5b, 6a, 7b, 12a** (MIC = 100 µg/mL) were found to be equipotent to Ampicillin (MIC = 100µg/mL) against Escherichia coli.

Compounds **5c**, **11c**, and **13c** (MIC = 100µg/mL) exhibited equal inhibition against Salmonella typhi compared to Ampicillin (MIC = 100µg/mL).

Towards the Candida albicans, compound **13c** (MIC = 250µg/mL) showed good activity than Griseofulvin (MIC = 500µg/mL). Compounds **5c**, **6b**, **6c**, **7c**, **11c** and **13a** were found equipotent to Griseofulvin (MIC = 500µg/mL) against Candida albicans. While none of the tested compounds showed better activity against Aspergillusniger.

All the newly synthesized compounds **5a-c**, **6a-c**,**7a-c**, **11a-c**, **12a-c** and **13a-c** have exerted significant inhibitory activity against the employed strains. The antimicrobial activity data revealed that change in the position of nitrogen atom of the bipyridine ring in the molecule altered the antimicrobial potency appreciably of the synthesized derivatives and the following conclusion can be drawn about the SAR.

Among the compounds **5a-c**, **6a-c**,**7a-c**, **11a-c**, **12a-c** and **13a-c**, compounds **5a-c**, **7a-c**,**11a-c** and **13a-c** bearing 2",2'-bipyridinyl substituted, 4",2'-bipyridinyl substituted, 2",4'-bipyridinyl substituted and 4",4'-bipyridinyl substituted moiety were found to be more potent than other derivatives. Compounds having R=OCH_3 and R=CH_3 substituent showed moderate antibacterial activity. Interestingly, compounds having (R = Cl) dramatically enhanced the antibacterial activity e.g compounds **5c**, **7c**, **11c** and **13c**. The enhanced activity of the above compounds can be attributed due to the presence of -Clgroup.

The compounds **5c**, **7c**, **11c** and **13c** possess the highest antimicrobial effectiveness among all the tested compounds.

Acknowledgements

I am thankful to Dr.Dinkar I. Brahmbhatt, my research guide for his every inspiration and guidance during my entire work. I am also thankful to department of chemistry of SPU for providing laboratory facilities. I am also thankful toThe Principal and The SSR Memorial Trust for every needful support.

References

[1]. S Sen, V Srivastava, J. Ind. Chem. Soc., 66, 166 (1989).
[2]. A Vogel, Gilbert's ann. Phys., 64, 161 (1820).
[3]. V N Gupta, B R Sharma, R RArora, J. Sci. Ind. Res., 20B, 300 (1961).
[4]. F M Dean, Progr. Chem. Org. Nat. Prod., 9, 225 (1952).
[5]. P K Bose, J. Ind. Chem. Soc., 35, 367 (1958).
[6]. T A Gexssman, E Hineiner, Bot. Rev., 18, 77 (1952).
[7]. R Robinson, "The structural relations of natural products", Clarenden Press, Oxford (1955).
[8]. G Rappa, K Shyam, A Lorico, O Fodstad, A C Sartorelli, Oncology Res., 113 (2000).
[9]. E B Yang, Y N Zhao, K Zhang, P Mack, Biochem. Biophys. Res. Commun., 260, 682 (1999).
[10]. B Sreenivasulu, V Sundaramurthy and Rao N V Subba, Proc. Ind. Acad. Sci., A **79**, 41(1974).
[11]. R B Moffett, J. Med. Chem., **7**, 446 (1964).
[12]. R B Moffett, U.S., 3,156,697 (1964); CA, **62**, 5257f (1965).
[13]. R B Moffett, U. S., 3, 201, 406 (1965); CA, **63**, 13220f (1965).
[14]. V N Kozhevnikov, D NKozhevnikov, O V Shabunina, V L Rusinov, O N Chupakhin, Tet. Lett.,**46**, 1791 (2005).
[15]. R Ziessel, In Photosensitization and Photocatalysis Using Inorganic and Organic Compounds; Kalyanasundaram, K., Gratzel, M., Eds.; Kluwer Academic: Dordrecht, 1993, pp 217–246.
[16]. M H Keefe, K D Benkstein, J T Hupp, Coord. Chem. Rev., **205**, 201 (2000).
[17]. A K Saha, K Kross, E D Kloszewski, D A Upson, J L Toner, R A Snow, C D Black, V C Decai, J. Am. Chem. Soc., **115**, 11032 (1993)
[18]. (a) J Zyss, C Dhenaut, T Chau Van, I Ledoux, Chem. Phys. Lett., **206**, 409 (1993)
[19]. (b) O Maury, H Le Bozec, Acc. Chem. Res., **38**, 691 (2005)
[20]. (c) F W Vance, J T J Hupp, J. Am. Chem. Soc., **121**, 4047 (1999)
[21]. (d) B J Coe, J A Harris, B S Brunschwig, I Asselberghs, K Clays, J Garin, J Orduna, J. Am. Chem. Soc., **127**, 13399 (2005)
[22]. B M Kelly-Basetti, D J Cundy, S M Pereira, W H F Sasse, G P Savage, G W Simpson, Bioorg. Med. Chem. Lett., **5**, 2989 (1995)

[23]. D W Robertson, E EBeedle, J K Swartzendruber, N D Jones, T K Elzey, R F Kauffman, H Wilson, J S Hayes., J. Med. Chem., **29**, 635 (1986).
[24]. F Krohnke and W Zecher, Chem. Ber., **94**, 690 (1961).
[25]. F Krohnke, Synthesis, **1**, 1 (1976); CA, **84**, 164540m (1976).
[26]. E. Horning, Org. Synth. Coll. Vol., III, pp 283, John Wiley and Sons (NY) (1955).
[27]. B R Hirani, Ph.D Thesis, "Synthetic studies in coumarins and coumarin polymers", Sardar Patel University, V.V.Nagar (1995)
[28]. C Chamchoumis and P G. Potvin, J. Chem. Research (S), 180, (1998).
[29]. Y R Prasad, P P Kumar, P R Kumar and A S Rao, E-Journal of Chemistry, 5(1), 144(2008).
[30]. A A Patel, Ph.D Thesis, "Synthesis, characterization and antimicrobial study of some heterocyclic substituted and heterocyclic fused coumarin derivatives", Sardar Patel university, V.V.Nagar (2011).
[31]. K R Pandya, Ph.D Thesis, "Synthesis and antimicrobial activity study of some bipyridinyl/pyrazolylpyrazoline substituted and yrazolo/pyrrolo fused coumarins", Sardar Patel university, V.V. Nagar (2013).
[32]. H B Lad, Ph.D Thesis, "Synthesis, characterization and antimicrobial screening of some coumarin derivatives containing modified pyridine and pyrazoline moieties", Sardar Patel university, V.V. Nagar (2012).
[33]. U Galm, M A Dessoy, J Schmidt, L A Wessjohann, L Heide Chem. Biol., 11, 173 (2004).

Jigar Patel "Synthesis, Characterization and Antimicrobial screening of some new bipyridinyl substituted coumarin "International Journal of Engineering Science Invention (IJESI), vol. 07, no. 07, 2018, pp 12-23