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Synthesis and Biological Implication of Metal complexes of Chalcone-Coumarin Hybrid

Sulaima Sabrin[1], Akeel Ahamd[2], Shailendra[3]

[1]Department of Chemistry, P.G Department of Chemistry, Patna University, Patna, Bihar-India

[2]Department Of Chemistry, Mirza Ghalib College, Gaya, Bihar- India
Corresponding Author Email: *akeelchemist[at]gmail.com*

[3]Department of Chemistry, P.G Department of Chemistry, Patna University, Patna, Bihar-India

Abstract: ***The present study focuses on the synthesis, characterization, and biological evaluation of Ni(II) complexes derived from a chalcone–coumarin hybrid ligand. The hybrid ligand was designed by integrating the pharmacologically significant chalcone and coumarin scaffolds, which are well known for their diverse biological activities [1-2]. In this synthesis Resorcinol and Beta keto ester refluxed overnight in acidic medium (with Conc. Sulphuric acid H_2SO_4) to form 4-methyl-7-hydroxy coumarin. This 4-methyl-7-hydroxy coumarin further reacts with acetyl chloride (CH_3COCl) in the presence of pyridine (a basic medium) to form 4-methyl-7-acetoxy coumarin. This 4-methyl-7-acetoxy coumarin further undergoes re-arrangement in the presence of Anhyd. $AlCl_3$ (Fries Re-arrangement) to form 8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one. The structures of the newly synthesized compounds were confirmed by IR, 1H NMR, 13 C NMR spectral data and elemental analysis. All these compounds were screened for their antibacterial and antifungal activities. The results were compared with standard drugs tested under similar conditions. Some of these compounds showed promising antimicrobial activities.***

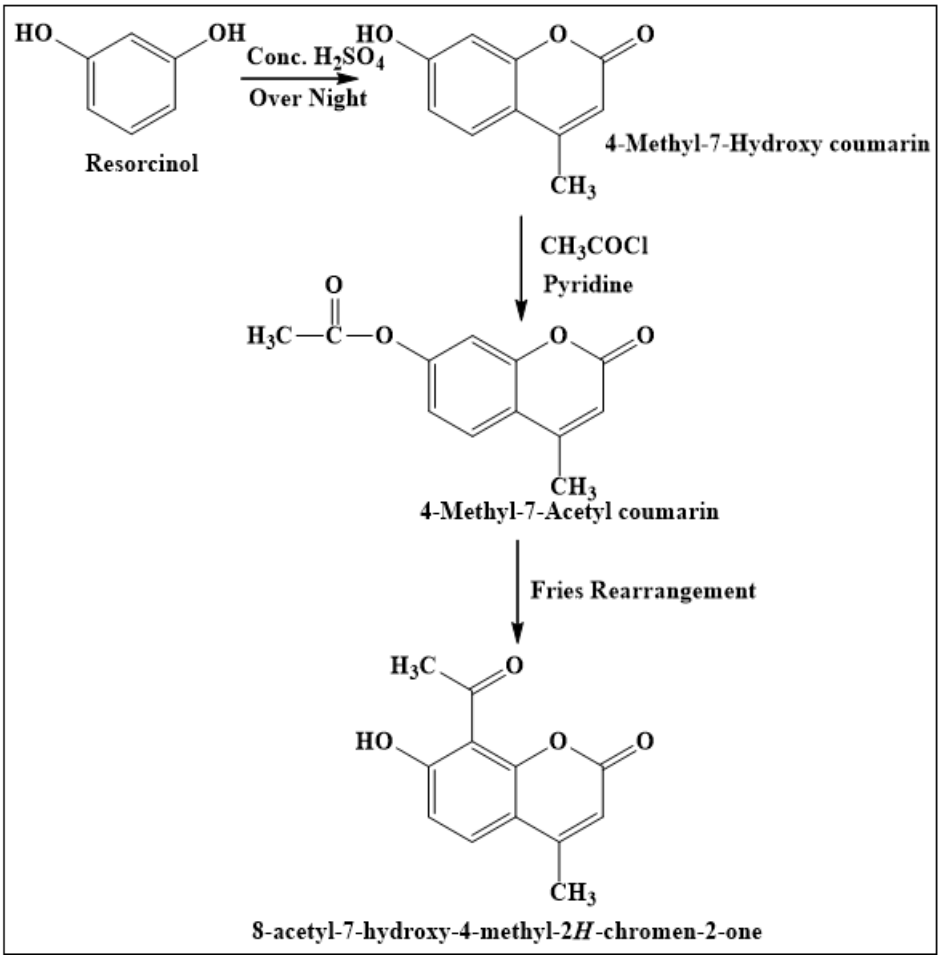
Keywords: Chalcone, Coumarin, Fries Rearrangement, IR, 1HNMR, 13CNMR, Antibacterial activity, Antifungal activity

1. Introduction

Chalcone and coumarin are two important classes of oxygen-containing heterocyclic and alpha-beta unsaturated compounds that have attracted considerable attention because of their diverse pharmacological properties [3-6]. Chalcones characterized by the presence of an open-chain flavonoid like enone system, exhibit a broad spectrum of biological activities, including antibacterial [7], antifungal [8], anti-inflammatory [9], antioxidant [10], antitumor [11], and antimalarial [12-13] effects. Similarly, coumarin and its derivatives possess significant biological potential and have been investigated for their antimicrobial [14], antioxidant [15], anticoagulant, anti-inflammatory [16], anticancer, and enzyme-inhibitory properties.

The combination of these two pharmacophores into a single molecular framework can provide a chalcone-coumarin hybrid, potentially producing enhanced or complementary biological effects. The incorporation of metal ions into biologically active organic ligands is an established strategy in coordination chemistry and medicinal chemistry. Metal complexation can modify the electronic structure, lipophilicity, solubility, stability, and overall biological behavior of a ligand. The synthesis of metal complexes of chalcone-coumarin hybrids generally involves the preparation of the hybrid ligands followed by its reaction with selected metal salts under appropriate conditions. Functional groups such as carbonyl, phenolic hydroxyl, or other donor atoms present in the hybrid ligands can participate in coordination with metal ions, resulting in mononuclear complexes with different geometries and coordination environments. The synthesized complexes can be characterized using spectroscopic and analytical techniques such as FT-IR, UV-Visible spectroscopy, NMR spectroscopy, Mass spectroscopy, elemental analysis and single crystal X-Ray diffraction.

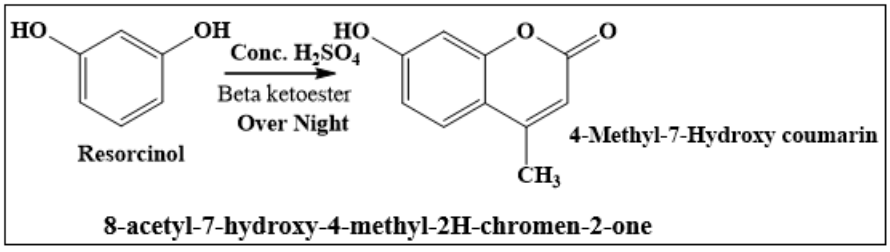
2. Methods



Scheme-1

Step. 1. Synthesis of 2-Acetyl-7-hydroxy-4-methyl coumarin

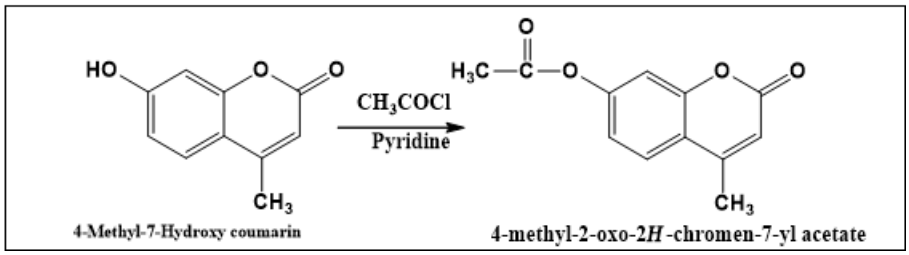
In this synthesis Resorcinol refluxed with Beta ketoester overnight in acidic medium (with Conc. Sulphuric acid H_2SO_4) to form 4-methyl-7-hydroxy coumarin. This 4-methyl-7-hydroxy coumarin further reacts with acetyl chloride (CH_3COCl) in the presence of pyridine (a basic medium) 4-methyl-7-acetoxy coumarin. This 4-methyl-7-acetoxy coumarin further undergoes re-arrangement in the presence of Anhyd. $AlCl_3$ (**Fries Re-arrangement**) to form 8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one.



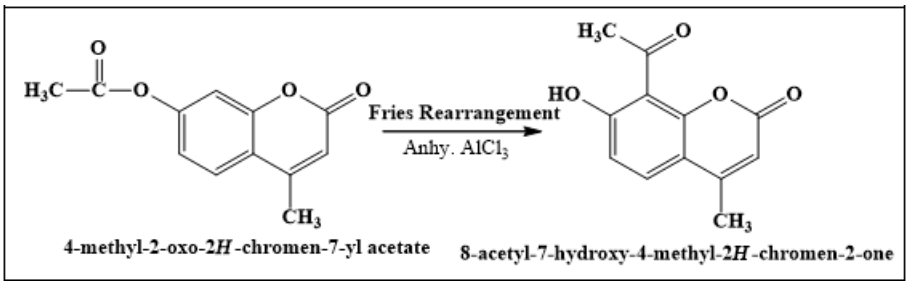
8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one

Chemical Formula: $C_{10}H_8O_3$
Exact Mass: 176.05
Molecular Weight: 176.17
m/z: 176.05 (100.0%), 177.05 (11.0%), 178.05 (1.2%)

Elemental Analysis: C, 68.18; H, 4.58; O, 27.25



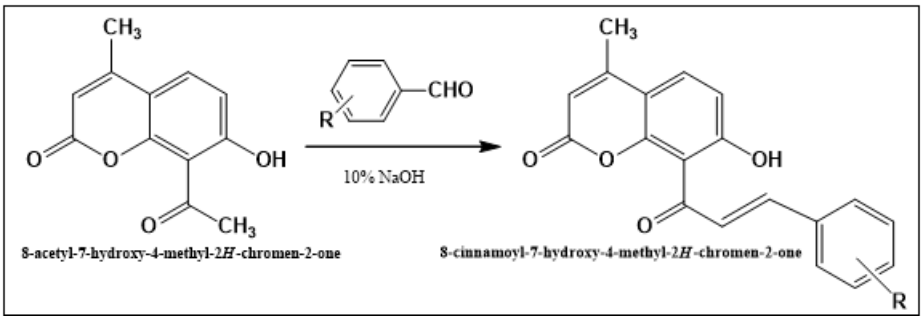
Chemical Formula: $C_{12}H_{10}O_4$
Exact Mass: 218.06
Molecular Weight: 218.21
m/z: 218.06 (100.0%), 219.06 (13.2%), 220.06 (1.6%)
Elemental Analysis: C, 66.05; H, 4.62; O, 29.33



Chemical Formula: $C_{12}H_{10}O_4$
Exact Mass: 218.06
Molecular Weight: 218.21
m/z: 218.06 (100.0%), 219.06 (13.2%), 220.06 (1.6%)
Elemental Analysis: C, 66.05; H, 4.62; O, 29.33

Step 2: Synthesis of Mono chalcones

The mono chalcones were synthesized when 8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one is subjected to Aldol Condensation with substituted benzaldehyde. This reaction is carried out in the presence of basic medium (10% NaOH solution).



Chemical Formula: $C_{19}H_{14}O_4$
Exact Mass: 306.09
Molecular Weight: 306.31
m/z: 306.09 (100.0%), 307.09 (20.7%), 308.10 (2.1%)
Elemental Analysis: C, 74.50; H, 4.61; O, 20.89

Step 3: Synthesis of metal complexes of Chalcone with metals

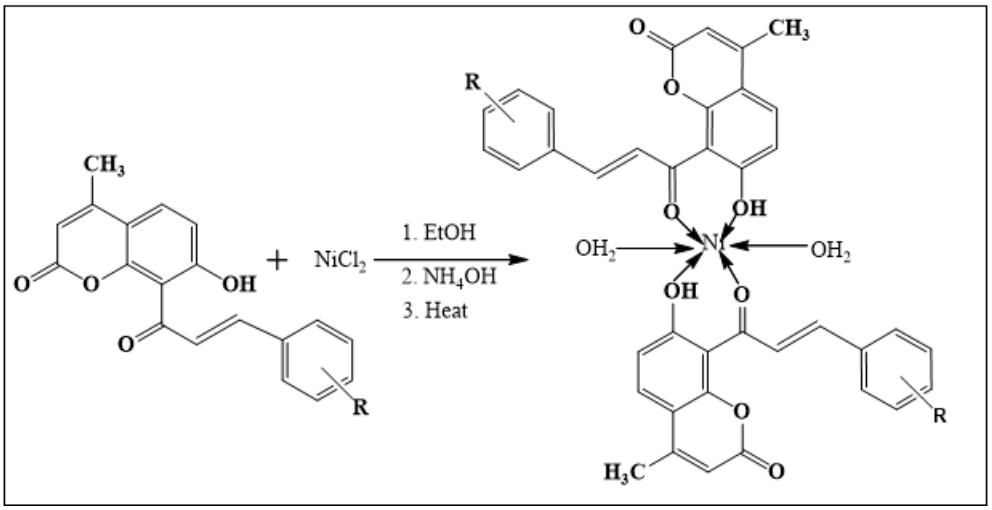


Table 1

S. No	R	mp(^{0}C)
1	H	87-89
2	2-CH_3	112-114
3	4-CH_3	105-106
4	2-OCH_3	124-125
5	4-OCH_3	119-120
6	2-Cl	140-141
7	4-Cl	136-137
8	2,4-Cl_2	148-150
9	3-NO_2	165-170
10	4-NO_2	150-152

3. Results and Discussion

Bis(E) 8-cinnamoyl-7-hydroxy-4-methyl-2H-chromen-2-one Nickel

Yellow solid; IR: 3400 (O-H Stretching), 3010 (C-H arom), 2980 (C-H aliph), 1690 (C=O), 1410 (C=C), 495 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 11.0 (s, 1H –OH proton), 7.99-6.49 (m, 6H, aromatic proton), 7.40 (d, 1 H Ethylene proton), 5.25-5.98 (dd, 2H, methylene proton), 2.53 (s, 3H, methyl proton); ^{13}C NMR (δ ppm): δ 19.0, 112.3, 112.9, 115.8, 117.2, 127.5, 127.9, 128.4, 128.8, 132.5, 135.0, 145.9, 150.8, 152.3, 158.5, 160.6, 193.9. Chemical Formula: $C_{38}H_{32}NiO_{10}$ Exact Mass: 706.13, Molecular Weight: 707.35 m/z: 706.13 (100.0%), 707.14 (41.8%), 708.13 (38.5%), 709.13 (17.7%), 708.14 (10.6%), 710.13 (6.8%), 710.14 (3.3%), 711.13 (2.3%), 709.14 (2.1%), 712.13 (1.9%), Elemental Analysis: C, 64.52; H, 4.56; Ni, 8.30; O, 22.62

Bis(E)-7-hydroxy-4-methyl-8-(3-ortho-tolylacryloyl)-2H-chromen-2-one Nickel

Blue solid; IR: 3410 (O-H Stretching), 3045(C-H arom), 2985 (C-H aliph), 1675 (C=O), 1450 (C=C), 495 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.2 (s, 1H –OH proton), 7.91-6.53 (m, 6H, aromatic proton), 5.23-5.90 (dd, 2H, methylene proton), 2.54 (s, 9H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 112.0, 112.8, 115.6, 117.5, 127.1, 127.8, 128.2, 128.7, 132.2, 135.5, 145.8, 150.4, 152.6, 158.3, 160.5, 193.6. Chemical Formula: $C_{40}H_{36}NiO_{10}$, Exact Mass: 734.17, Molecular Weight: 735.40 m/z: 734.17 (100.0%), 735.17 (44.1%), 736.16 (38.5%), 737.16 (18.3%), 736.17 (11.3%), 738.16 (5.3%), 738.17 (5.2%), 739.16 (2.3%), 740.16 (1.5%), 737.18 (1.3%), 737.17 (1.2%), 739.17 (1.1%), Elemental Analysis: C, 65.33; H, 4.93; Ni, 7.98; O, 21.76

Bis(E)-7-hydroxy-4-methyl-8-(3-para-tolylacryloyl)-2H-chromen-2-one Nickel

Dark Blue solid; IR: 3410 (O-H Stretching), 3045(C-H arom), 2985 (C-H aliph), 1675 (C=O), 1450 (C=C), 495 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.2 (s, 1H –OH proton), 7.86-6.40 (m, 6H, aromatic proton), 5.21-5.88 (dd, 2H, methylene proton), 2.54 (s, 9H, methyl proton); ^{13}C NMR (δ ppm): δ 19.0, 112.3, 112.9, 115.8, 117.2, 127.5, 127.9, 128.4, 128.8, 132.5, 135.0, 145.9, 150.8, 152.3, 158.5, 160.6, 193.9. Chemical Formula: $C_{40}H_{36}NiO_{10}$, Exact Mass: 734.17, Molecular Weight: 735.40 m/z: 734.17 (100.0%), 735.17 (44.1%), 736.16 (38.5%), 737.16 (18.3%), 736.17 (11.3%), 738.16 (5.3%), 738.17 (5.2%), 739.16 (2.3%), 740.16 (1.5%), 737.18 (1.3%), 737.17 (1.2%), 739.17 (1.1%), Elemental Analysis: C, 65.33; H, 4.93; Ni, 7.98; O, 21.76

Bis(E)-7-hydroxy-4-methyl-8-(3-ortho-methoxyphenylacryloyl)-2H-chromen-2-one Nickel

Blue solid; IR: 3442 (O-H Stretching), 3018(C-H arom), 2952 (C-H aliph), 1689 (C=O), 1420 (C=C), 490 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.2 (s, 1H –OH proton), 7.90-6.52 (m, 6H, aromatic proton), 5.23-5.90 (dd, 2H, methylene proton), 3.45 (s, 6H, methoxy proton) 2.54 (s, 3H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 112.0, 112.8, 115.6, 117.5, 127.1, 127.8, 128.2, 128.7, 132.2, 135.5, 145.8, 150.4, 152.6, 158.3, 160.5, 193.6. Chemical Formula: $C_{40}H_{36}NiO_{12}$, Exact Mass: 766.16, Molecular Weight: 767.40, m/z: 766.16 (100.0%), 767.16 (44.1%), 768.15 (38.5%), 769.15 (18.3%), 768.16 (11.8%), 770.16 (5.4%), 770.15 (5.3%), 771.15 (2.3%), 772.15 (1.5%), 769.16 (1.4%), 769.17 (1.3%), 771.16 (1.2%), Elemental Analysis: C, 62.60; H, 4.73; Ni, 7.65; O, 25.02

Bis(E)-7-hydroxy-4-methyl-8-(3-para-methoxyphenylacryloyl)-2H-chromen-2-one Nickel

Blue solid; IR: 3440 (O-H Stretching), 3020 (C-H arom), 2951 (C-H aliph), 1697 (C=O), 1421 (C=C), 491 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.1 (s, 1H –OH proton), 7.93-6.52 (m, 6H, aromatic proton), 5.23-5.90 (dd, 2H, methylene proton), 3.45 (s, 6H, methoxy proton) 2.54 (s, 3H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 54.3, 112.1, 112.9, 115.3, 117.1, 127.0, 127.6, 128.5, 128.8, 132.2,

135.5, 145.8, 150.4, 152.6, 158.3, 160.5, 193.6. Chemical Formula: $C_{40}H_{36}NiO_{12}$, Exact Mass: 766.16, Molecular Weight: 767.40, m/z: 766.16 (100.0%), 767.16 (44.1%), 768.15 (38.5%), 769.15 (18.3%), 768.16 (11.8%), 770.16 (5.4%), 770.15 (5.3%), 771.15 (2.3%), 772.15 (1.5%), 769.16 (1.4%), 769.17 (1.3%), 771.16 (1.2%), Elemental Analysis: C, 62.60; H, 4.73; Ni, 7.65; O, 25.02

Bis(E)-7-hydroxy-4-methyl-8-(3-ortho-chlorophenylacryloyl)-2H-chromen-2-one Nickel

Light green solid; IR: 3400 (O-H Stretching), 3025(C-H arom), 2963 (C-H aliph), 1700 (C=O), 1421 (C=C), 495 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.5 (s, 1H –OH proton), 8.03-6.75 (m, 6H, aromatic proton), 5.21-5.92 (dd, 2H, methylene proton), 2.53 (s, 3H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 113.1, 114.9, 115.8, 117.9, 127.1, 127.6, 128.5, 128.8, 133.2, 135.8, 145.3, 150.9, 152.8, 158.8, 161.5, 193.0. Chemical Formula: $C_{38}H_{30}Cl_2NiO_{10}$, Exact Mass: 774.06, Molecular Weight: 776.24, m/z: 776.05 (100.0%), 774.06 (97.6%), 777.06 (42.7%), 775.06 (40.8%), 778.05 (39.2%), 779.05 (17.3%), 778.06 (11.3%), 776.06 (10.2%), 780.05 (9.5%), 780.06 (3.8%), 781.05 (3.7%), 779.06 (2.3%), 782.05 (1.7%), 777.05 (1.6%), 777.07 (1.1%), Elemental Analysis: C, 58.80; H, 3.90; Cl, 9.13; Ni, 7.56; O, 20.61

Bis(E)-7-hydroxy-4-methyl-8-(3-para-chlorophenylacryloyl)-2H-chromen-2-one Nickel

Light green solid; IR: 3405 (O-H Stretching), 3029(C-H arom), 2966(C-H aliph), 1705 (C=O), 1430 (C=C), 495 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.2 (s, 1H –OH proton), 8.00-6.73 (m, 6H, aromatic proton), 5.15-5.72 (dd, 2H, methylene proton), 2.50 (s, 3H, methyl proton); ^{13}C NMR (δ ppm): δ 19.4, 115.1, 115.9, 116.8, 117.9, 128.1, 128.6, 129.5, 130.8, 133.2, 135.5, 145.1, 150.5, 152.0, 158.6, 161.3, 193.8. Chemical Formula: $C_{38}H_{30}Cl_2NiO_{10}$, Exact Mass: 774.06, Molecular Weight: 776.24, m5/z: 776.05 (100.0%), 774.06 (97.6%), 777.06 (42.7%), 775.06 (40.8%), 778.05 (39.2%), 779.0 (17.3%), 778.06 (11.3%), 776.06 (10.2%), 780.05 (9.5%), 780.06 (3.8%), 781.05 (3.7%), 779.06 (2.3%), 782.05 (1.7%), 777.05 (1.6%), 777.07 (1.1%), Elemental Analysis: C, 58.80; H, 3.90; Cl, 9.13; Ni, 7.56; O, 20.61

Bis(E)-7-hydroxy-4-methyl-8-(3-(2,4-dichloro)-phenylacryloyl)-2H-chromen-2-one Nickel

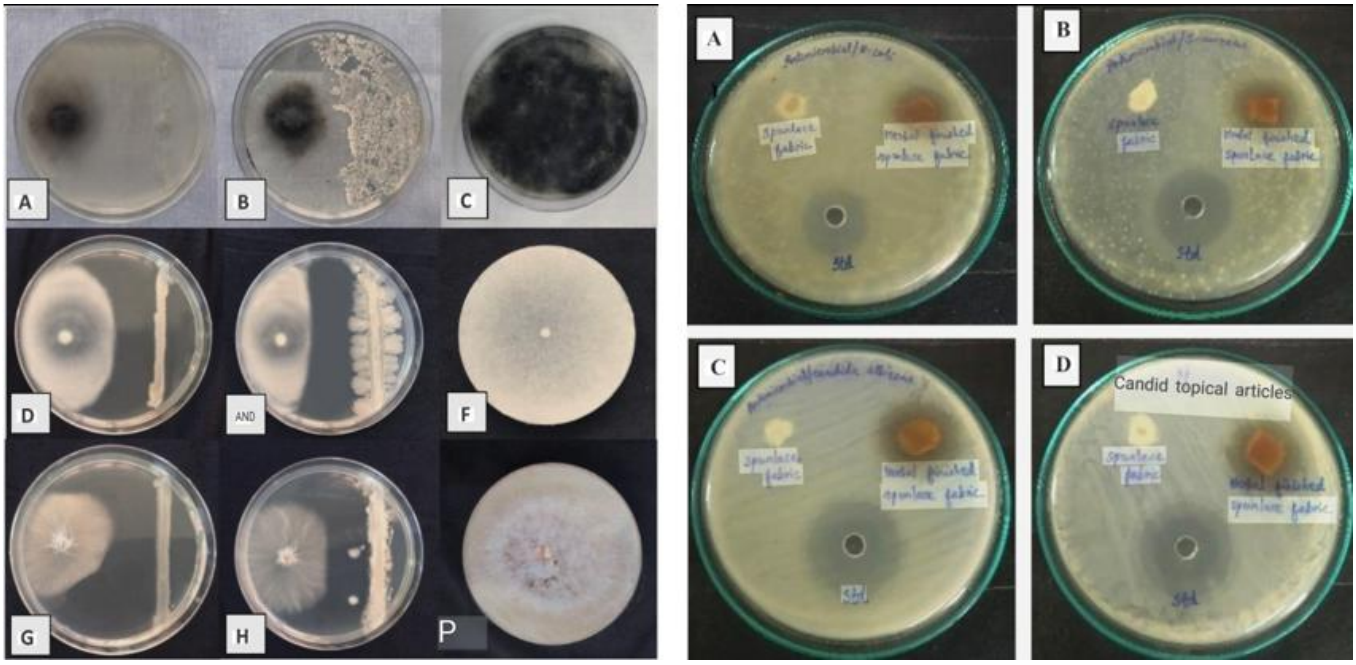
Green solid; IR: 3460 (O-H Stretching), 3015(C-H arom), 2955(C-H aliph), 1730 (C=O), 1425 (C=C), 490 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.9 (s, 1H –OH proton), 7.85-6.46 (m, 5H, aromatic proton), 5.15-5.72 (dd, 2H, methylene proton), 2.50 (s, 3H, methyl proton); ^{13}C NMR (δ ppm): δ 19.4, 114.5, 115.6, 116.5, 117.3, 128.0, 128.8, 129.9, 131.2, 133.7, 135.6, 145.6, 150.8, 152.3, 159.9, 161.2, 193.8. Chemical Formula: $C_{38}H_{28}Cl_4NiO_{10}$, Exact Mass: 841.98, Molecular Weight: 845.13, m/z: 843.98 (100.0%), 845.97 (89.2%), 841.98 (77.0%), 844.98 (53.5%), 847.97 (34.5%), 842.98 (31.9%), 843.97 (29.7%), 846.98 (23.3%), 846.97 (17.2%), 848.97 (15.2%), 845.98 (13.9%), 847.98 (10.2%), 849.97 (9.5%), 843.99 (6.6%), 850.97 (3.8%), 849.98 (3.2%), 848.98 (2.0%), 844.99 (1.5%), 851.97 (1.5%), 844.97 (1.3%), 846.99 (1.2%), Elemental Analysis: C, 54.00; H, 3.34; Cl, 16.78; Ni, 6.94; O, 18.93

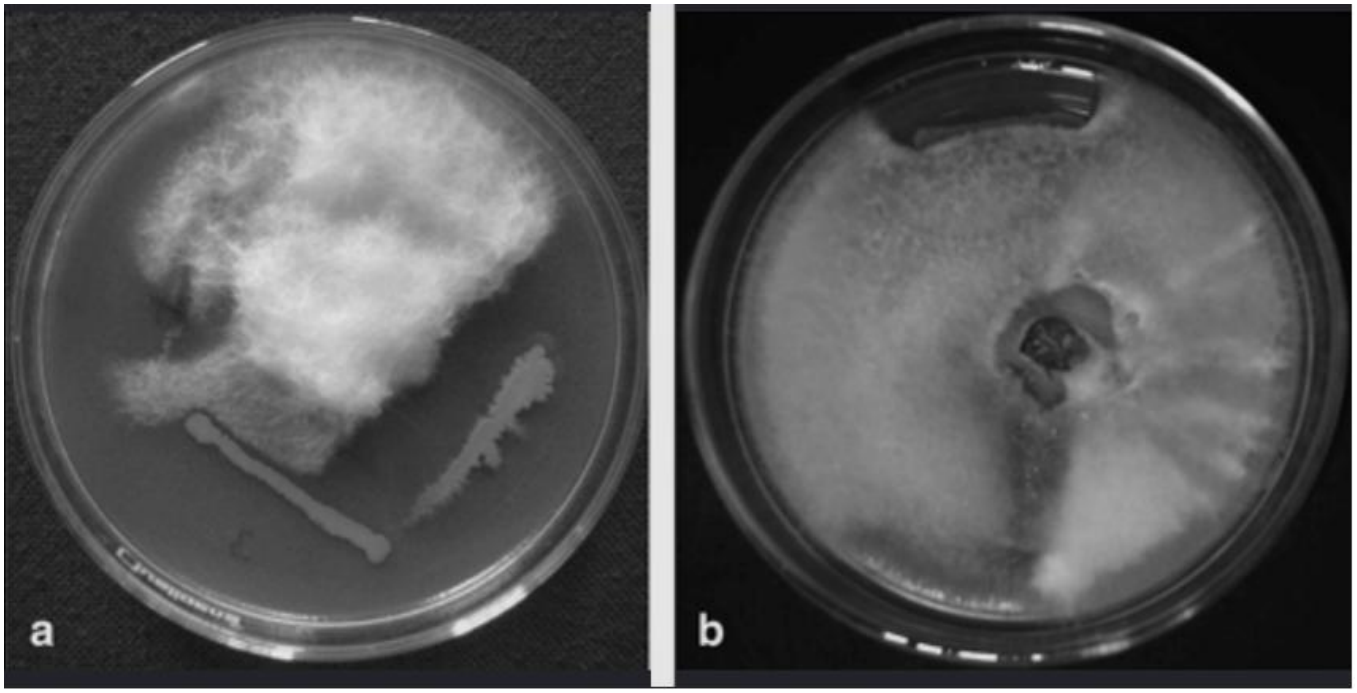
Bis(E)-7-hydroxy-4-methyl-8-(3-meta-nitrophenylacryloyl)-2H-chromen-2-one Nickel

Yellowish Green solid; IR: 3445 (O-H Stretching), 3005(C-H arom), 2950(C-H aliph), 1725 (C=O), 1420 (C=C), 492 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.5 (s, 1H –OH proton), 7.80-6.45 (m, 5H, aromatic proton), 5.10-5.70 (dd, 2H, methylene proton), 2.53 (s, 3H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 114.2, 115.8, 116.3, 117.5, 128.5, 128.9, 130.9, 131.8, 133.3, 135.7, 146.6, 151.8, 152.9, 160.9, 161.2, 192.2. Chemical Formula: $C_{38}H_{30}N_2NiO_{14}$, Exact Mass: 796.11, Molecular Weight: 797.34, m/z: 796.11 (100.0%), 797.11 (42.0%), 798.10 (38.5%), 799.10 (18.0%), 798.11 (11.8%), 800.10 (7.3%), 800.11 (3.4%), 801.10 (2.3%), 802.10 (2.0%), 799.11 (1.4%), 799.12 (1.2%), 801.11 (1.1%), Elemental Analysis: C, 57.24; H, 3.79; N, 3.51; Ni, 7.36; O, 28.09

Bis(E)-7-hydroxy-4-methyl-8-(3-para-nitrophenylacryloyl)-2H-chromen-2-one Nickel

Yellowish Green solid; IR: 3448 (O-H Stretching), 3005(C-H arom), 2925(C-H aliph), 1710 (C=O), 1415 (C=C), 490 (Ni-O starching) cm-^{1}; ^{1}H NMR (DMSO-d6): δ 10.5 (s, 1H –OH proton), 7.80-6.42 (m, 5H, aromatic proton), 5.13-5.75 (dd, 2H, methylene proton), 2.55 (s, 3H, methyl proton); ^{13}C NMR (δ ppm): δ 19.4, 114.5, 115.6, 116.5, 117.3, 128.0, 128.8, 129.9, 131.2, 133.7, 135.6, 145.6, 150.8, 152.3, 159.9, 161.2, 193.8. Chemical Formula: $C_{38}H_{30}N_2NiO_{14}$, Exact Mass: 796.11, Molecular Weight: 797.34, m/z: 796.11 (100.0%), 797.11 (42.0%), 798.10 (38.5%), 799.10 (18.0%), 798.11 (11.8%), 800.10 (7.3%), 800.11 (3.4%), 801.10 (2.3%), 802.10 (2.0%), 799.11 (1.4%), 799.12 (1.2%), 801.11 (1.1%), Elemental Analysis: C, 57.24; H, 3.79; N, 3.51; Ni, 7.36; O, 28.0





Images of Antifungal activities of this series of compounds

Bis(E) 8-cinnamoyl-7-hydroxy-4-methyl-2H-chromen-2-one Nickel

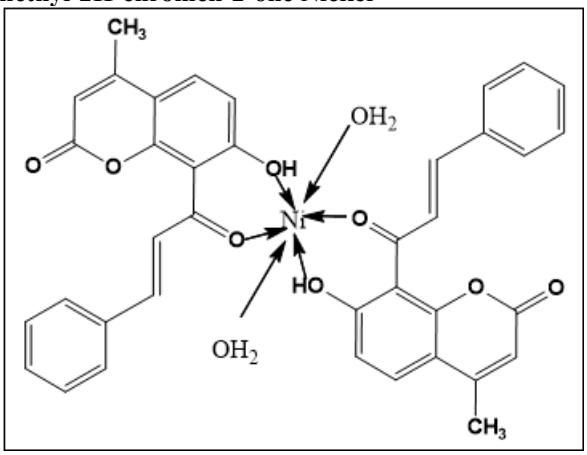
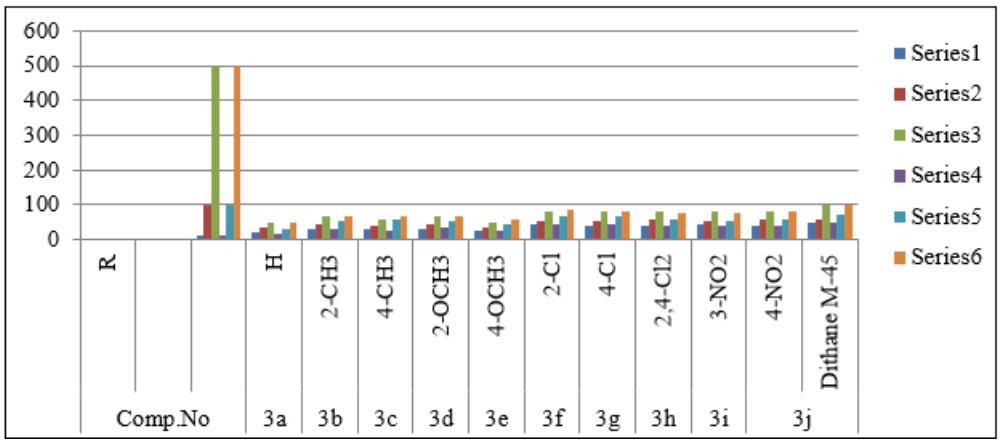


Table 2

Comp. No	R	Percent Mycelial Inhibition Aspergilus Flavus			Compound dose (ppm) Candida Albicans		
		10	100	500	10	100	500
3a	H	20	35	51	18	31	48
3b	2-CH_3	30	45	67	31	54	69
3c	4-CH_3	29	42	60	27	56	66
3d	2-OCH_3	32	46	67	34	55	68
3e	4-OCH3	24	37	50	25	43	58
3f	2-Cl	46	55	83	45	69	84
3g	4-Cl	41	53	79	44	66	80
3h	2,4-Cl_2	40	56	80	41	58	78
3i	3-NO_2	43	55	79	40	55	75
3j	4-NO_2	41	59	81	42	58	79
	Dithane M-45	50	60	100	50	72	100



4. Conclusion

The synthesis of metal complexes based on chalcone-coumarin hybrid ligands represents a promising approach for the development of biologically active coordination compounds. The molecular hybridization of chalcone and coumarin combines two pharmacologically important scaffolds and may provide enhanced biological properties through synergistic effects. Both chalcone coumarin hybrids and their metal complexes have been associated with important activities such as antimicrobial, antioxidant, anticancer, antimalerial and enzyme inhibitory effects. The 2-Cl, 2,4-Cl_2 and methyl, methoxy substituted ligands shows promising antibacterial and antifungal activities against different bacteria and fungi at different concentrations.

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Author Profile

Miss Sulaima Sabrin is currently working as a Research student in the P.G Department of Chemistry under the supervision of Prof. Shailendra. Mrs. Sabrin have completed U.G in 2018 from Patna Science College, Patna and P.G from P.G Department of Chemistry from Patna University in 2020. Mrs. Sabrin has published several papers in International reputed journals.

Dr. Shailendra is currently working as a Professor in the P.G Department of Chemistry, Patna University, Patna, Bihar. He has more than 25 years of teaching experience in both undergraduate as well as postgraduate students. Dr. Shailendra have published more than 50 papers in international as well as in National Journals as well. Dr. shailendra has supervised 15 students who have successfully completed their Ph.D. and is currently supervising 6 Ph.D. scholars. Presently He hold the post of Director in Incubation Hub in University of Patna. His area of specialization is synthetic Organic Chemistry. Dr. Shailendra was former expert in Chemistry, in Bihar University Service Commission, Patna, Bihar.

Dr. Akeel Ahamd is currently working as an Assistant Professor in the Department of Chemistry, Mirza Ghalib College, Gaya, Bihar. He has more than 13 years of teaching experience in both undergraduate as well as postgraduate students. Dr. Ahmad have published nearly 25 papers in international as well as in National Journals as well. His area of specialization is synthetic Organic Chemistry (Including Heterocyclic Chemistry, pericyclic Reaction, Name reactions, Reagents etc). Dr. Ahmad has presented papers in several International conferences including Indian Science Congress, Kathmandu Symposia, Kathmandu Nepal.