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SYNTHESIS AND EVALUATION OF NOVEL HETEROCYCLIC CHROMENE DERIVATIVES AS ANTIMICROBIAL AND ANTIOXIDANT AGENTS

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ABSTRACT

A series of novel derivatives of coumarin (**C1-C8**) were synthesized by treating 7-hydroxy-4-methyl-coumarin with dichloromethane to get 7-(chloromethoxy)-4-methyl-2*H*-chromen-2-one (IM) which was further treated with various heterocycles to give final compounds. IR, mass and ^{1}HNMR spectral data confirmed the structure of the synthesized compounds. The synthesized compounds were investigated for their antimicrobial and antioxidant potential. Compounds **C4** and **C6** showed significant activities.

KEY WORDS: Coumarin, Heterocycles, Anti-microbial, antioxidant activity.

1. INTRODUCTION

Compounds containing heterocyclic ring are not only essential to life but also show a wide variety of pharmacological activities. Heterocyclic compounds are those cyclic compounds whose ring contains besides carbon, one or more atom of other elements (heteroatom). The most common hetero atoms are nitrogen, sulphur and oxygen. The SAR of such molecules frequently demonstrates that the heterocyclic ring can be replaced by some other moiety with comparable electron distribution and lipophilicity without loss of biological activity.

Coumarins are a group of compounds which are naturally found in some plants, they can be synthetically produced. Because of their diverse structural variations, origin and properties most of them can be used for medicinal purposes. For example, they can be used against fungal diseases or in studying structure and biological properties of antifungal agents to discover new compounds with the similar activity (Soltani, 2009). Coumarins are nowadays used as anti-inflammatory (Timonen, 2011), antidiabetic (Tegginamath, 2011), antitumor (Chen, 2012), antimicrobial (Jani, 2009), antioxidant (Melagraki, 2009), antibacterial (Vukovic, 2010), antifungal (Al-Amiery, 2012) agents.

Reactive oxygen species are produced by all aerobic cells as byproducts of normal metabolism but their overproduction may damage biological macromolecules leading to cytotoxicity. One of the reactive oxygen species, the hydroxyl radical (˙OH), is a strong oxidizing agent and is primarily responsible for the cytotoxic effect of oxygen in plants, animals and microorganisms. The involvement of ˙OH in normal as well as pathological cell processes stimulates considerable interest in this radical. One type of process where ˙OH is believed to play an important role is in the wood-degradation by white-rot and brown-rot fungi. Wood-decaying fungi that are able either to degrade lignin (white-rot fungi) or modify it (brown-rot fungi) may affect coumarin derivatives, which may cause an under estimation of the ˙OH formation (Iakovlev, 2003). As coumarin is one of the oldest and potent compounds having antifungal, anti-inflammatory, antioxidant, antidepressant, analgesic, anticonvulsant activities, it was planned to synthesise compounds containing coumarin fused with different heterocyclic groups and evaluate them for their antimicrobial and antioxidant potential.

2. EXPERIMENTAL

The synthetic route to title compounds is shown in scheme 1. The chemicals required were obtained from Hi-media Chem. Ltd, SD-Fine Ltd. and Sigma Aldrich Pvt. Ltd and were used as such. Melting points were determined using open capillary tube melting point apparatus and are uncorrected. Reaction progress was monitored by performing thin layer chromatography on silica gel G plates, using iodine vapors and UV chamber as visualizing agents. After physical characterization, the compounds were subjected to spectral analysis. Proton nuclear magnetic resonance spectra were recorded on Bruker WM-300 (at 300 MHz) spectrometer and chemical shifts are reported in parts per million (δ value) from TMS (δ 0 ppm for ^{1}H NMR) as an internal standard. Coupling constants are given in Hertz. Mass spectra were recorded on a JEOL-SX-102 instrument using ESI. Infrared spectra were taken on Perkin-Elmer AX-1 spectrometer and values are expressed in cm^{-1}.

Synthesis of 7-hydroxy-4-methyl -2*H*-chromen-2-one: The method of Pechmann and Duisberg was followed for the preparation of 7-hydroxy- methylchromen-2-one. A solution of resorcinol (0.09 mol) and ethyl acetoacetate (0.103 mol) was added slowly to 100 ml ice cold conc. sulfuric acid with continuous stirring over a period of 2 h. maintaining the temperature below 10°C throughout the addition. The reaction mixture was kept at room temperature for 18 h after which it was poured with vigorous stirring into the mixture of 200 g of crushed ice and 300 ml of distilled water. The precipitate was collected by vacuum filtration and washed with cold water. The solid thus obtained was dissolved in 150 ml of 5% sodium hydroxide and 2 M sulphuric acid was added to it with vigorous stirring until the solution was

acidic. The crude product was collected by filtration at the pump, washed with cold water and dried. The product was recrystallized from ethanol. Progress of the reaction was monitored by using TLC (benzene:ethylacetate 4:1) (Laufer, 2003).

Synthesis of 7-(chloromethoxy) -4-methyl-2*H*-chromen-2-one: 7-Hydroxy-4-methyl-2H-chromen-2-one (0.01 mol) was dissolved in 45 ml of acetonitrile. To this solution, dichloromethane (0.01mol) and anhydrous potassium carbonate (0.02 mol) were added. The resulting reaction mixture was refluxed for 12 h. Acetonitrile was distilled off at the end of the reflux period. The reaction mixture was cooled and poured in 60 ml of iced water and immediately the 7-(chloromethoxy)-4-methyl-2*H*-chromen-2-one was precipitated as solid crystals. The crude product was filtered, washed with water, dried and recrystallized using methanol (Laufer, 2003).

Synthesis of 1-((4-methyl-2-oxo-2H-chromene-7-ylloxy) substitutedmethyl derivatives: 7-(Chloromethoxy)-4-methyl-2*H*-chromen-2-one (0.01 mol) was dissolved in 45 ml of acetonitrile. To this solution, different heterocyclic compounds (0.01 mol) and anhydrous potassium carbonate (0.02 mol) were added. The resulting reaction mixture was refluxed for 32 h. Acetonitrile was distilled off at the end of the reflux period; the reaction mixture was cooled and poured in 60 ml of iced water. 1-(4-methyl-2-oxo-2*H*-chromene-7-ylloxy) substituted methyl derivatives precipitated as solid crystals. The compounds were filtered, washed with water, dried and recrystallized from methanol (Laufer, 2003).

1-((4-methyl-2-oxo-2H-chromene-7-ylloxy) methyl) pyridinium chloride (C_1): Light Yellow, Solid, R_f =0.73, (Benzene: Ethylacetate 4:1) Yield 73.9%, Mp 160-163°C, IR (KBr) ν (cm^{-1}): Ar C-H stre 3042.1, phenyl alkyl ether 1249.7, lactone ring 1726.1, CH_2 stre 2885.4, MS (ESI) 269.9 $(M+1)^+$, ^{1}H-NMR (δ/$CDCl_3$): δ 2.104 (s, 3H, CH_3), 3.208 (s,1H,CH) , 5.094(s, 2H, CH_2), 5.65-5.64 (d, 1H, CH, *J*=4.8 Hz), 5.926 (s, 1H, CH) , 6.20 (s, 2H, Ar-H), 6.49 (s, 1H, CH), 7.05-7.03 (d, 2H, Ar- H, *J*= 4.8 Hz), 7.76-7.74 (d, 1H, Ar-H, *J*= 4.8 Hz).

4-methyl-7- (piperidin-1-ylmethoxy) -2*H*-chromen-2-one (C_2): Yellow, Solid, R_f =0.84, (Toluene : Ethylacetate 3:2) Yield 78.9%, Mp 190-192°C, IR (KBr) ν (cm^{-1}): Ar C-H str 3042.1, phenyl alkyl ether 1249.7, Lactone ring 1726.1, CH_2 stre 2885.4, MS (ESI) 273.2 $(M+1)^+$, ^{1}H-NMR (δ/$CDCl_3$): δ δ1.37-1.21 (m, 6H, Alp-H), 2.46-2.16 (m, 7H, Alp-H), 5.08 (s, 2H, CH_2), 6.18 (s, 1H, Ar-H), 6.88-6.87 (d, 2H, Ar-H, *J*=1.8 Hz), δ7.70-7.68 (d, 1H, Ar-H, *J*=6 Hz).

4- methyl-7-(pyrrol-1-ylmethoxy)-2*H*- chromen-2- one (C_3): Yellow, Solid, R_f =0 .69, (Hexane: Ethylacetate 7:3) Yield 71.5%, Mp 218-220°C, IR (KBr) ν (cm^{-1}): Ar C-H str 3020.1, phenyl alkyl ether 1236.6, Lactone ring 1727.8, -CH_2 stre 2874.8, MS (ESI) 255.3 $(M+1)^+$, ^{1}H-NMR (δ/$CDCl_3$): δ 2.31 (s,3H,CH_3), δ6.28-5.93 (m, 3H, Ar -H), δ 6.76 (s, 2H, CH_2), δ 7.136-7.122 (d, 2H, Ar- H , *J*= 4.2 Hz), δ 7.49-7.28 (m, 2H, Ar-H), δ 7.80-7.79 (d, 1H, Ar- H, *J*=3.6 Hz).

Synthesis of 4-methyl-7-(piperazin-1-ylmethoxy)-2*H*-chromen-2-one (C_4): Yellow, Solid, R_f =0.84, Benzene: Ethylacetate (4:1) Yield 83.8%, Mp 162-165°C, IR (KBr) ν (cm^{-1}): Ar C-H str 3060.8, phenyl alkyl ether 1249.9, Lactone ring 1724.8, CH_2 str 2878.4, MS (ESI) 274.3 $(M+1)^+$, ^{1}H-NMR (δ/$CDCl_3$): δ 2.056 (s, 1H, NH), 2.59-2.00 (m, 7H, Alp-H), 3.24-2.85 (m, 4H, Alp-H), 5.10 (s, 2H, CH_2), 6.24 (s, 1H, Ar-H), 7.02-6.99 (d, 2H, Ar-H, *J*=7.8 Hz), 7.85-7.85 (d, 1H, Ar-H, *J*= 1.8 Hz).

Synthesis of 1-((4-methyl-2-oxo-2*H*-chromen-7-yloxy)methyl)-1*H*-indole-3-carboxaldehyde (C_5): Yellow, Solid, R_f =0.61, Hexane: Ethylacetate (7:3) Yield 65.5%, Mp 182-185°C, IR (KBr) ν (cm^{-1}): Ar C-H stre 3060.8, phenyl alkyl ether 1249.9, Lactone ring 1724.8, CH_2 str 2878.4, MS (ESI) 333.3 $(M+1)^+$, ^{1}H-NMR (δ/$CDCl_3$): δ 2.46 (s, 3H, CH), δ 6.19 (s, 1H, Ar-H), δ 6.68 (s, 2H, CH_2), δ 7.06-7.05 (d, 2H, Ar-H, *J*=4.8 Hz), δ7.43-7.33 (m, 2H, Ar-H), δ7.93-7.90 (d, 2H, Ar-H, *J*=7.2 Hz), δ8.29 (s, 1H, CH), δ8.50-8.49 (d, 1H, Ar-H, *J*=2.4 Hz), δ9.74 (s, 1H, CHO).

Synthesis of 7-((1*H*-benzo[d]imidazol-1-yl) methoxy)-4-methyl- 2*H*- chromen-2-one (C_6): Yellow, Solid, R_f=0.70, Hexane: Ethylacetate (7:3) Yield 77.3%, Mp 167-170°C, IR (KBr) ν (cm^{-1}): Ar C-H str 3023.8, phenyl alkyl ether 1226.6, Lactone ring 1728.3, MS (ESI) 306.2 $(M+1)^+$, ^{1}H-NMR (δ/$CDCl_3$): 2.452 (s, 3H, CH_3), 6.18 (s, 1H, Ar-H), 6.60 (s, 2H, CH_2), 7.03- 7.02 (d, 2H, Ar-H, J=2.4 Hz), 7.33 -7.25 (m, 2H, Ar-H), 7.58-7.49 (m, 2H, Ar-H), 7.83-7.80 (d, 1H, Ar-H, *J*=7.2 Hz), δ 8.16 (s, 1H, CH).

Synthesis of 4- methyl-7-(morpholinomethoxy) - 2*H*-chromen-2-one (C_7): Yellow, Solid, R_f = .73, (Hexane: Ethylacetate 7:3), Yield 68.4%, Mp 202-205°C, IR (KBr) ν (cm^{-1}): Ar C-H str 3013.8, Phenyl alkyl ether 1250.6, Lactone ring 1726.4; MS (ESI) 306.2 $(M+1)^+$, ^{1}H-NMR (δ/$CDCl_3$): 2.63-2.10 (m, 7H, Alp-H), 3.53-3.22 (m, 4H, Alp-H), 5.08 (s, 2H, CH_2), 6.26 (s, 1H, Ar-H), 7.06-6.05 (d, 2H, Ar-H , *J*=2.4 Hz), 7.86-7.84 (d, 1H, Ar-H ,*J*= 4.2 Hz).

Synthesis of 3-((4-methyl-2-oxo-2*H*-chromen-yloxy) methyl) thiazolidine-2, 4 dione(C_8): Yellow, Solid, R_f = 0.61, (Hexane: Ethylacetate 7:3), Yield 74.8%, Mp 185-188°C; IR (KBr) ν (cm^{-1}): Ar C-H stre 3043.8 cm^{-1}, Phenyl alkyl ether 1228.6, Lactone ring 1727.4, C=O 1707.4; MS (ESI) 305.3 $(M+1)^+$, ^{1}H-NMR (δ/$CDCl_3$): 2.31 (s, 3H, CH_3), 4.19

(s, 2H, CH_2), 6.11 (s, 2H, CH_2), 6.26 (s, 1H, Ar-H), 6.95-6.94 (d, 2H, Ar-H, *J*=2.4 Hz), 7.82-7.80 (d, 1H, Ar-H , *J*=3.6 Hz).

Antimicrobial activity: Antimicrobial activity was determined by cup- plate method. This method solely depends upon the diffusion of the test substance from a vertical cylinder or a cavity through the solidified agar layer of a petri-dish or plate, to an extent such that the growth of the added microorganism is prevented entirely in a circular area or 'zone' around the cylinder or cavity containing a solution of the drug. A zone of inhibition around the well indicates that the microorganisms were inhibited by the tested compound which diffused into the agar media through disc or well (Indian Pharmacopoeia, 2010; Maesaki, 2000).

The compounds **(C1-C8)** were screened for antifungal activity against *Aspergillus niger* and antibacterial activity against *Pseudomonas aeruginosa* at concentrations of 50, 100, 200, 400, 800 and 1000 µg/ml. Ketoconazole and ciprofloxacin at 50 µg/ml and 100 µg/ml were used as the reference standard and 10% v/v DMSO as the vehicle. 10% v/v DMSO was used as blank and it did not show any zone of inhibition against microbial strains (Table 1 and Table 2).

Antioxidant activity by DPPH assay procedure: Different concentrations (25, 50, 75, 100 µg/ml) of test and standard (ascorbic acid) compounds were prepared in methanol and added (3.0 ml) to the DPPH solution (1.0 ml, 0.1 mM) and allowed to stand for 30 minutes in dark. The free radical scavenging activity was determined by measuring the decrease in absorption at 517 nm in a UV-visible spectrophotometer. 0.1 mM, DPPH solution was used as control (Wanasundara and Shahidi, 2005).

Statistical analysis: The absorbance of the final reaction mixture of three parallel experiments was taken and is expressed as mean ± standard deviation. The activities were also determined as a function of their percent inhibition which was calculated using the formula;

Percent Inhibition = (Ac-As/Ac) x 100

Where, Ac = absorbance of control, As = absorbance of sample.

There was a concentration dependent increase in antioxidant activity of synthesized compounds (Table 3).

All the synthesized compounds were found active against the used fungal and bacterial strains at different concentrations**.** Compounds **C4** and **C6** were found to be highly active against *Aspergillus niger* and *Pseudomonas aeruginosa* at minimum concentration of 50 µg/ml. Compounds **C1** and **C5** also showed moderate to high activity against *Aspergillus niger* and *Pseudomonas aeruginosa*. Most of the compounds showed moderate antioxidant activity. The compound **C4** emerged as most potent anti oxidant agent when compared with standard (Ascorbic acid). **C8** and **C2** also showed good antioxidant activity.

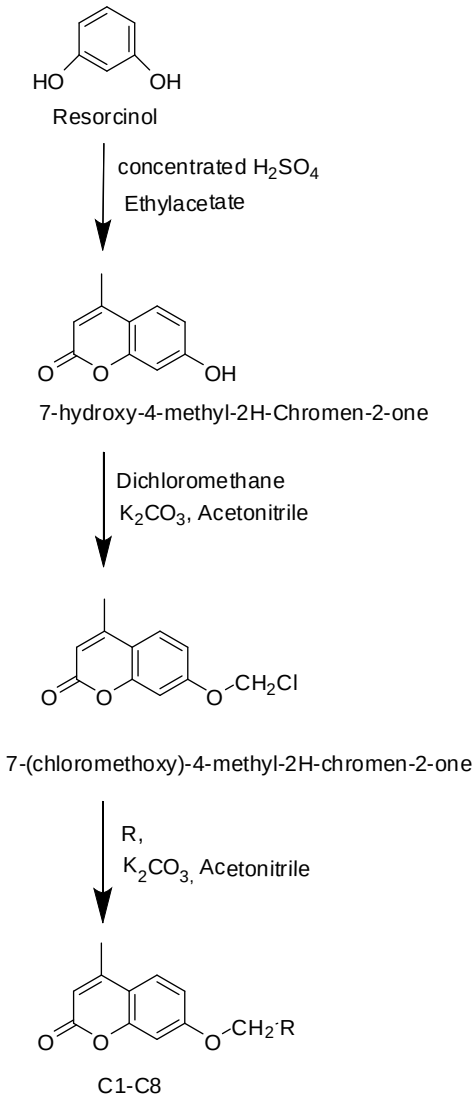
3. RESULTS AND DISCUSSION

Final derivatives were prepared by treating 7-(chloromethoxy)-4-methyl-2*H*-chromen-2-one with different heterocyclic compounds (C1-C8). 7-Hydroxy-4-methylchromen-2-one (1.76 g, 0.01 mol) was dissolved in 45 ml of acetonitrile. To this solution, dichloromethane and anhydrous potassium carbonate (2.76 g, 0.02 mol) were added. The resulting reaction mixture was refluxed for 12 h. Acetonitrile was distilled off at the end of the reflux period. The reaction mixture was cooled and poured in 60 ml of iced water and immediately the final compounds were precipitated as solid crystals. They were filtered, washed with water, dried to afford crude product and recrystallized using methanol. 7-(3-chloromethoxy)-4-methyl-2*H*-chromen- 2-one (1.87 g, 0.01 mol) was dissolved in 45 ml of acetonitrile. To this solution, different heterocyclic compounds (R) (0.68 g, 0.01 mol) and anhydrous potassium carbonate (2.76 g, 0.02 mol) were added. The resulting reaction mixture was refluxed for 32 h. Acetonitrile was distilled off at the end of the reflux period; the reaction mixture was cooled and poured in 60 ml of iced water. 1-((4-methyl-2-oxo-2*H*-chromene-7-ylloxy) methyl) pyridinium chloride precipitated as solid crystals. The compound was filtered, washed with water, dried and recrystallized from methanol.

The synthesized compounds were screened for their antimicrobial and antioxidant activities. The compounds were found to exhibit significant antimicrobial and antioxidant activities.

4. CONCLUSION

Drug discovery for infectious diseases, particularly with antibacterial, antibiotic and antifungal drugs is in a process of continuing evolution because the number of cases of multidrug-resistant infections is increasing at an alarming rate. Various heterocyclic compounds have been proved to be significant antimicrobial agents. It was found that the compounds showed higher antifungal activity than antibacterial activity. The compounds have emerged as good antimicrobial agents and at the same time they have shown the potential to scavenge free radicals.



R= Piperazine, Pyridine, Piperidine, Pyrrole, Indole-3-caboxaldehyde, Benzimidazole, Morpholine, Thiazolidinedione.

Scheme1: Synthetic route of title compounds

Table.1. Zone of inhibition of compounds against *Aspergillus niger*

Compound code	Diameter of zone of inhibition (mm)					
	50 µg/ml	100 µg/ml	200 µg/ml	400 µg/ml	800 µg/ml	1000 µg/ml
Ketoconazole	16.3±0.1	26.0±0.2	NA	NA	NA	NA
C1	-	8.0±0.1	11.0±0.1	14.3±0.1	19.6±0.1	22.3±0.2
C2	-	-	-	8.3±0.1	10.3±0.1	11.0±0.1
C3	-	-	-	10.3±0.1	11.6±0.1	13.3±0.1
C4	11.0±0.1	14.0±0.2	17.3±0.1	20.3±0.2	23.6±0.2	26.0±0.2
C5		8.3±0.1	10.6±0.1	14.3±0.2	17.3±0.2	19.6±0.1
C6	10.3±0.1	13.0±0.1	16.3±0.2	18.6±0.1	21.6±0.1	25.6±0.2
C7			10.3±0.2	11.3±0.1	15.6±0.1	18.3±0.1
C8					8.3±0.1	10.0±0.1
Blank	-	-	-	-	-	-

NA: Not applicable; - : no activity

Table 2: Zone of inhibition of compounds against *Pseudomonas aeruginosa*

Compound code	Diameter of zone of inhibition (mm)					
	50µg/ml	100µg/ml	200µg/ml	400µg/ml	800µg/ml	1000µg/ml
Ciprofloxacin	16.6±0.1	29.0±0.1	NA	NA	NA	NA
C1	-	8.0±0.1	9.0±0.2	11.3±0.2	13.3±0.2	14.6±0.2
C2	-	-	8.3±0.1	9.0±0.2	11.3±0.1	13.3±0.1
C3	-	-	8.3±0.1	10.3±0.2	12.3±0.1	14.6±0.1
C4	8.0±0.2	11.2±0.2	13.6±0.1	15.6±0.2	17.6±0.2	19.3±0.1
C5	-	-	9.6 ±0.1	11.3±0.1	13.6±0.2	16.0±0.1
C6	8.0±0.2	9.3±0.1	11.3±0.2	14.6±0.1	16.3±0.1	19.3±0.1
C7	-	-	-	8.0±0.1	10.3±0.1	11.3±0.1
C8	-	-	9.3±0.2	12.6±0.1	14.3±0.2	17.0±0.2
Blank	-	-	-	-	-	-

NA: Not applicable; - : no activity

Table 3. Antioxidant activity of the synthesized compounds.

Compound code	Concentration (µg/ml)	Absorbance	Radical scavenging activity (%)
C1	25	0.534±0.003	36.73
	50	0.495±0.009	41.35
	75	0.385±0.017	54.38
	100	0.302±0.012	64.21
C2	25	0.564±0.002	33.17
	50	0.467±0.003	44.66
	75	0.392±0.005	53.55
	100	0.299±0.007	64.57
C3	25	0.556±0.004	34.12
	50	0.501±0.004	40.63
	75	0.425±0.005	49.64
	100	0.392±0.008	53.55
C4	25	0.438±0.001	48.10
	50	0.364±0.003	56.87
	75	0.301±0.005	64.33
	100	0.219±0.006	74.05
C5	25	0.539±0.008	36.13
	50	0.491±0.002	41.82
	75	0.398±0.012	52.84
	100	0.354±0.011	58.05
C6	25	0.524±0.008	37.91
	50	0.495±0.006	41.35
	75	0.418±0.016	50.47
	100	0.356±0.003	57.82
C7	25	0.574±0.006	31.99
	50	0.498±0.001	40.99
	75	0.414±0.004	50.94
	100	0.394±0.012	53.31
C8	25	0.515±0.003	38.98
	50	0.462±0.004	45.26
	75	0.351±0.005	58.41
	100	0.296±0.007	64.92
Std	25	0.460±0.008	45.49
	50	0.310±0.004	63.27
	75	0.212±0.001	74.88
	100	0.113±0.002	86.61

Values are expressed as mean ± standard deviation (n = 3), Absorbance of control = 0.844 ± 0.002.

REFERENCES

Al-Amiery AA, Kadhum AAH, Mohamad AB, Antifungal Activities of New Coumarins, Molecules, 17, 2012, 5713-5723.

Chen Y, Liu H.R, Liu H.S, Cheng M, Xia P, Qian K, Wu PC, Lai C.Y, Xia Y, Yang Z, Morris-Natschke, SL, Lee, KH, Antitumor agents 292. Design, synthesis and pharmacological study of *S*- and *O*-substituted 7-mercapto- or hydroxy-coumarins and chromones as potent cytotoxic agents, Eur J Med Chem, 49, 2012, 74-85.

Iakovlev A, Broberg A, Stenlid J, Fungal modification of the hydroxyl radical detector coumarin-3-carboxylic acid, FEMS Microbiology Ecology, 46, 2003, ,197-202.

Indian Pharmacopoeia, Cup plate method. Govt. of India, New Delhi, 1, 2010, 54.

Jani GR, Vyas KB, Franco Z, Preparation and Antimicrobial Activity of s-Triazine Hydrazones of 7-Hydroxy Coumarin and Their Metal Complexes, E-Journal of Chemistry 6, 2009, 1228-1232.

Laufer MC, Hausmann H, Hlderich WF, Synthesis of 7-hydroxycoumarins by Pechmann reaction using Nafion resin/silica nanocomposites as catalysts, J Catalysis, 218, 2003, 315–320.

Maesaki S, Iwakawa J, Higashiyama Y, Miyazaki Y, Yanagihara K, Tomono K, Kohno S, Antifungal activity of a new triazole, voriconazole (UK-109496), against clinical isolates of *Aspergillus* spp, J Infect Chemother, 6, 2000, 101-103.

Melagraki G, Afantitis A, Igglessi-Markopoulou O, Detsi A, Koufaki M, Kontogiorgis C, Hadjipavlou-Litina D, Synthesis and evaluation of the antioxidant and anti-inflammatory activity of novel coumarin-3-aminoamides and their alpha-lipoic acid adducts, Eur J Med Chem, 44, 2009, 3020–3026.

Soltani S, Dianat S, Sardari S, Forward Modeling of the Coumarin Antifungals;SPR/SAR Based Perspective, Avicenna J Med Biotech, 1, 2009, 95-103.

Tegginamath G, Kamble RR, Kattimani PP, Margankop SB, Synthesis of 3-aryl-4-({2-[4-(6-substituted-coumarin-3-yl)-1,3-thiazol-2-yl]hydrazinylidene}methyl/ethyl)-sydnones using silica sulfuric acid and their antidiabetic, DNA cleavage activity Arabian Journal of Chemistry, 2011, http://dx.doi.org/10.1016/j.arabjc.2011.04.006.

Thareja S, Verma A, Kalra A, Gosain S, Rewatkar PV, Kokil GR, Novel chromeneimidazole derivatives as antifungal compounds: Synthesis and in vitro evaluation, Acta Poloniae Pharmaceutica Drug Research, 67, 2010, 423-427.

Timonen JM, Nieminen RM, Sareila O, Goulas A, Moilanen LJ, Haukka M, Vainiotalo P, Moilanen E, Aulaskari PH, Synthesis and anti-inflammatory effects of a series of novel 7-hydroxycoumarin derivatives, Eur J Med Chem, 46, 2011, 3845-3850

Vukovic N, Sukdolak S, Solujic S, Niciforovic N, Substituted imino and amino derivatives of 4-hydroxycoumarins as novel antioxidant, antibacterial and antifungal agents: Synthesis and *in vitro* assessments, Food Chem, 120, 2010, 1011–1018.

Wanasundara PKJPD and Shahidi F, 2005. Antioxidants: Science, Technology and Applications, John Wiley and Sons, Inc., Chapter 11, 2005, 431-442.