# SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW COMPOUNDS OF FIVE AND SIX MEMBERED RINGS INCORPORATING TO COUMARIN DERIVATIVES

**Mohaned Mohammed Sahb[a], Zeina Mohammed Kadam[a]***

**Article History:** **Received**: 30.05.2022 **Revised**: 29.06.2022 **Accepted**: 16.07.2022

**Abstract:** Reaction and condensation between 2-chloroquinoline-3-carbaldehyde and substituted coumarone to Produced chalcone, the derivative (3) was adopted as chalcone to react with different compound such as ethyl cyanoacetate, ammonia, urea, thiourea, phenylthiosemicarbazide, and hydroxyl amine hydrochloride to produced new ring of pyranone, pyridine, pyrimidine, pyrazole and isoxazole compounds (4,5,6,7,8,9) respectively, were identified their structure by infrared spectroscopy, Nuclear magnetic and elemental analysis. Pharmaceutical applications have been studied for the prepared compound and achievement with different drugs.

**Keywords:** Polycyclic chloroquinolines, pyrimidines, coumarin, pyranone, isoxazoles

[a]. Department of Chemistry, College of sciences, University of Al-Qadisiyah, Iraq

***Corresponding Author**

**E-mail:** dr.zeinakadam@gmail.com, zeina.m.kadam@qu.edu.iq

**DOI: 10.31838/ecb/2022.11.04.013**

## INTRODUCTION

Coumarin is a natural volatile active compound found in many plants [1]. At ambient temperatures, it is a white crystal with a melting point of 341–344K [2]. For example, coumarin was first isolated from D. odorata and is present in Cinnamomum aromatic. Coumarin has been reported to exhibit antioxidant, analgesic, anti-inflammatory, and antimutagenic properties [3]. According to [4], the main source of coumarin in the diet is cinnamon. Prior to the first toxicologic concerns about coumarin, synthetic coumarin was widely used to add flavor to alcohol [5]. Pure coumarin (*cis*-o-coumarinic acid lactone, 1, 2-benzopyrone) is a crystalline white solid. The structure of coumarin is shown in Figure. It is a representative of the lactones, in which a lactone is an ester group integrated into a carbon ring system. According to [6]. adverse effects in humans resulting from coumarin administration are rare, it is generally recognized that it is a rat liver toxicant [6-7]. At levels that exceeded the maximum tolerated dose (5000 ppm), chronic consumption of coumarin by rats increased the incidence of parenchymal liver cell tumors [8]. This has been linked to the toxic effects of coumarin. Difference literatures is indicating with progressive findings with the synthesis and pharmacological and biological activities of pyranone, pyridine, pyrimidine, pyrazole and isoxazole derivatives [9-10]. Pyrazoles have been found to used perfect as antimicrobial, antitubercular, anti-inflammatory, anti-tumor and antiviral activities. In humans, coumarin metabolism mainly occurs through 7-hydroxylation, a high-affinity reaction catalyzed by CYP2A6 [9] (Bogdal *et al*). 7-Hydroxycoumarin and its glucuronide and sulfate conjugates are not toxic [10] reported that the**y** constituted 40-97% of human urinary metabolites following an oral dose. On the other hand, rats displayed limited hepatic 7-hydroxylase activity, and the 3,4-epoxidation pathway is favored Figure 13.6 [11]. The kinetics of **c**oumarin metabolism has been detailed elsewhere [12].

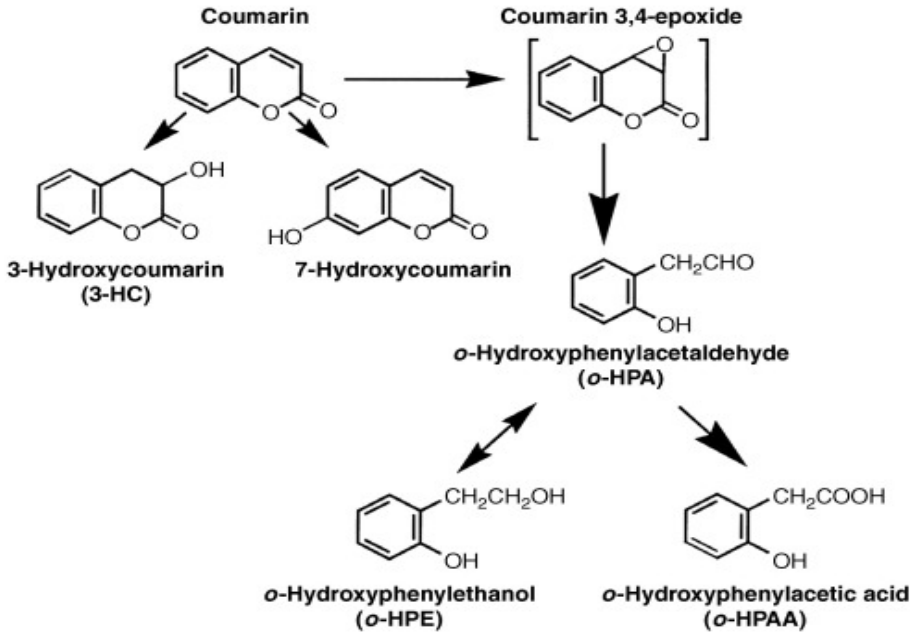


**Figure 1. Kinetic of coumarin metabolism**

## MATERIALS AND SYNTHETIC METHODS

All materials (chemicals and solvent) that used in research from Fluke, BDH, and Sigma-Aldrich. The Synthesis of carbaldehyde and modification of starting materials according to replacement of chlorine atom to produced 2-Flouroquinoline according to [13].

**3-(2-Chloroquinolin-3--yl)-1-(BPN Coumarin)-2-propenone (3)**

To the stirring mixture of 2-Flouroquinoline-3-carbaldehyde (156 mg, 1 mmol), 20 $cm^3$ Absolute $C_2H_5OH$ and coumarin 334 (283 mg, 1 mmol) at room temperature. Sodium hydroxide (60 %) was added drop wise and the reaction mixture was stirred for 10 hr. The reaction mixtures were neutralization with hydrochloric acid and filtration to recrystallization the precipitate washed with ethanol to give compound (3) in 82 % mp (152-153°); FT-IR (in KBr): C-Cl (1110), C-$H_{aroma}$ (3025 $cm^{-1}$), carbonyl conjugated (1632) $1HNMR_{DMSO\text{-}d6}$ (500 MHz) (7.11-7.23 δ, m, Aromatic-H), (8.44-8.48 δ, 5H, Quinoline protons), (7.58-7.82 δ, d,1H, J= 11.75 $H_z$ for protons of α, β-unsaturated ketone) Analytical calculation for compound (3) $C_{27}H_{21}N_2O_3Cl$ calculated, C (76.96), H (4.99), N (6.65); finding, C (76.86), H (4.63), N (6.63)

**4-(2-Chloroquinolin -3-yl)-6-( BPN Coumarin)-2-oxo-pyran-2H-3-carbonitrile (4)**

Compound (3) (842 mg, 2 mmol) was dissolved in absolute $C_2H_5OH$ (30 $cm^3$), ethyl cyanoacetate (200 mg, 2 mmol) in ethanol, and ($C_2H_5ONa/C_2H_5OH$ solution) that prepared currently was added to the mixture was refluxed for 24 hr. The resulting product was cooled, filtration, and recrystallization to give (4) as solid crystal in 78% mp (142-143°); FT-IR (in KBr): O-C=O (1698 cyclic ester), C- $H_{aromatic}$ (3020 $cm^{-1}$), cyanide (2223 $cm^{-1}$), $1HNMR_{DMSO\text{-}d6}$ (500 MHz); (7.13-7.28 δ, m, Aromatic-H), (8.45-8.78δ, 5H, Quinoline protons). Analytical calculation for compound (4) MF=$C_{30}H_{20}N_3O_4Cl$, calculated. C 76.12, H 3.89, N 8.18; finding, C 76.32, H 3.93, N 8.62

**1,2-Dihydro-4-(2-Chloroquinolin -3-yl)-6-( BPN Coumarin)-2-oxo-pyridine-3-carbonitrile (5)**

Compound (4) (514 mg, 1 mmol) in absolute $C_2H_5OH$ (10 $cm^3$), dry $NH_3$ was used. The solution was refluxed for 12 hr. The resulting product was collected and cooling, then filtration, and recrystallization in ethanol to give compound (5) as solid crystals in 75% mp (162-163°); FT-IR (in KBr): N-H (3225 $cm^{-1}$) C-Cl (1211), C- $H_{aromatic}$ (3025), N-Carbonyl (1685 $cm^{-1}$) cyanide (2222 $cm^{-1}$), $^1HNMR_{DMSO\text{-}d6}$ (400 MHz); (7.37-7.39δ, m, Aromatic-H), (8.11-8.23δ, 5H, Quinoline protons). Analytical calculation for compound (5) MF= $C_{30}H_{21}N_4O_3Cl$ calculated. C 69.16, H 4.034, N 10.76; finding, C 68.85, H 4.03, N 10.56

**1-(4,5-dihydro-5-(2-Chloroquinolin -3--yl)-3-( BPN Coumarin pyrimidin-2(1H)-one) (6)**

Compound (3) (421 mg, 1 mmol) was added to ($C_2H_5ONa/C_2H_5OH$ solution) that prepared from Na Metal (24 mg, 1 mmol) in absolute $C_2H_5OH$ (20 $cm^3$) and then added urea (60 mg, 1 mmol). The solution mixture was refluxed for overnight. The result product was isolated as a sold and collected, cooled, and recrystallization after filtration with DMF/$C_2H_5OH$ and cooled, then filtration, and recrystallization in ethanol to give compound (5) as solid crystal in 75 % to give (6) as solid crystal in 75 % mp (154-155°) ;FT-IR (in KBr): N-H (3252 $cm^{-1}$) , C-Cl (1368),C- $H_{aromatic}$( 3028) , HN-carbonyl (1682 $cm^{-1}$) imine ( 1625 $cm^{-1}$), $^1HNMR_{DMSO\text{-}d6}$ (400 MHz); (7.38-7.55 δ, m , Aromatic-H), (8.22-8.29δ, 5H, Quinoline protons). Analytical calculation for compound (6) MF= $C_{28}H_{21}N_4O_3Cl$ calculated C 67.67, H 4.23, N 11.28; finding, C 67.66, H 4.72, N 11.51

**1-(4,5-dihydro-5-(2-Chloroquinolin-3--yl)-3--(BPN Coumarin) pyrazol-1-ylpyrimidine-2(1H)-thionic) (7)**

Compound (3) (421 mg, 1 mmol) was added to ($C_2H_5ONa/C_2H_5OH$ solution) that prepared from Na Metal (24 mg, 1 mmol) in absolute $C_2H_5OH$ (30 $cm^3$) and then added thiourea (76 mg ,1 mmol). The solution mixture was refluxed

for 24 hr. The resulting-colored product was cooled, filtration, and recrystallization with mix $C_2H_5OH$/DMF to give (6) as solid crystals in 75% mp (166-167°) FT-IR (in KBr): N-$H_{aromatic}$ (3244 $cm^{-1}$) chlorine (1223 $cm^{-1}$), C- $H_{aromatic}$ (3025 $cm^{-1}$), HN-C=S (1388) imine (1625), $^1HNMR_{DMSO-d6}$ (400 MHz); (7.35-7.39δ, m, Aromatic-H), (8.22-8.28 δ, 5H, Quinoline protons). Analytical calculation for compound (7) MF= $C_{28}H_{21}N_4O_2SCl$ calculated C 65.56, H 4.098, N 10.93; finding, C 64.95, H 3.95, N 10.85

**4,5-dihydro-5-(2-Chloroquinolin -3--yl)-3--(BPN Coumarin) pyrazole-1-phenylthioamide (8)**

(40 mg, 1 mmol) from NaOH and (165 mg from 1 mmol) phenyl thiosemicarbazone added to Compound (3) (421 mg, 1 mmol) in absolute $C_2H_5OH$ (20 $cm^3$). The solution mixture was refluxed for 24 hr. The resulting products was cooled, filtration, and recrystallization with ethanol to give (8) as colure crystal in 75% mp (208-209°) FT-IR (in KBr): N-H (3355 $cm^{-1}$) chlorine (1351 $cm^{-1}$), C-$H_{aromatic}$ (3034 $cm^{-1}$), N-C=S (1397 $cm^{-1}$) C=N (1645 $cm^{-1}$), $^1HNMR_{DMSO-d6}$ (400 MHz); (7.22-7.26 δ, m, phenyl protons), (7.35-7.40 δ, m, pyrazole protons), (8.41-8.65 δ, 5H, Quinoline protons). Analytical calculation for compound (8) MF= $C_{34}H_{28}N_5O_2SCl$ calculated, C 72.40, H 4.97, N 12.42; finding, C 72.42, H 4.94, N 12.75

**3-(4,5-dihydro-3-( BPN Coumarin) isoxazol-5-yl)-2-Chloroquinolin (9)**

(70 mg, 1 mmol) from hydroxyl amine hydrochloride and (140 mg from 1 mmol) potassium carbonate that anhydrous added to Compound (3) (421, 1 mmol) in absolute $C_2H_5OH$ (20 $cm^3$). The solution mixture was refluxed for 24 hr. The resulting product was cooled in water, filtration, and recrystallization with ethanol to give (9) as sold crystals in 75% mp (142-144°). FT-IR (in KBr): $C_{aromatic}$-Cl (1345), C- $H_{aromatic}$ (3055 $cm^{-1}$), imine (1642 $cm^{-1}$), 1$HNMR_{DMSO-d6}$ (400 MHz); (7.18-7.55 δ, m, Aromatic-H), (8.30-8.60 δ, 5H, Quinoline protons). Analytical calculation for compound (9) MF= $C_{27}H_{22}N_3O_3Cl$ calculated. C 68.72, H 4.67, N 8.91; finding, C 68.76, H 4.61, N 8.82.

## RESULTS AND DISCUSSION

The reaction between 3-(2-Chloroquinolin-3--yl)-1-( BPN Coumarin)-2-propenone (3) as chalcones with ethyl cyanoacetate in solution sodium ethoxide $C_2H_5ONa$ to produced pyranone as compound (4) under refluxed for 42 hr. (scheme 1). The Spectro data that identify its structure; FT-IR (in KBr): conjugated cyclic O-C=O (1695 $cm^{-1}$), $C_{armatic}$-F (1365 $cm^{-1}$), C-$H_{aromatic}$ (3030 $cm^{-1}$), weak band of C≡N (2210 $cm^{-1}$), 1$HNMR_{DMSO-d6}$ (7.13-7.28 δ, m, Aromatic-H), (8.45-8.78 δ, 5H, as signals of Quinoline protons. Pyranone compound (4) led to produced corresponding's pyridinone (5) by condensation with $NH_3$ The Spectro data that identify its structure FT-IR (in KBr): N-H (3223 $cm^{-1}$) refer the replacement of ammonia, C-$H_{aromatic}$ (3035 $cm^{-1}$), conjugated N-carbonyl (1688 $cm^{-1}$) weak band of cyanide (2257 $cm^{-1}$), (7.32-7.35 δ, m, Aromatic-H), (8.11-8.23 δ, 5H, as signals of Quinoline protons). Reaction of compound (3) with urea or use thiourea in the presence of $C_2H_5ONa/C_2H_5OH$ to produce the pyrimidine derivative (6,7) respectively for compound (6) The Spectro data that identify its structure. FT-IR (in KBr ): N-$H_{aromatic}$ (3250), $HN_{pyrimidine}$-Carbonyl (1685) imine C=N(1620 $cm^{-1}$), $^1HNMR_{DMSO-d6}$; (7.34-7.37 δ, m , Aromatic-H) , (8.17-8.22 δ, 5H , Quinoline protons) and for compound (7) Spectro data of Spectro data IR (in KBr ) : HN-C=S (1385 $cm^{-1}$) C=$N_{cyclic}$(1622 $cm^{-1}$), N-$H_{aromatic}$ (3265 $cm^{-1}$), $^1HNMR_{DMSO-d6}$; (7.30-7.36δ, m, Aromatic-H), Reaction of compound (3) with phenylthiosemicarbazide and sodium hydroxide in $C_2H_5OH$ to produced pyrazole (8) Spectro data of Spectro data of compound (8) FT-IR (in KBr ): N-$H_{aromatic}$ (3360 $cm^{-1}$) N-C=S (1392 $cm^{-1}$) C=N(1642 $cm^{-1}$), $^1HNMR_{DMSO-d6}$; (7.16-7.28δ, m, phenyl protons), (7.31-7.33 δ, m, pyrazole protons), (8.45-8.67δ, 5H, Quinoline protons). Refluxing compound (3) with $NH_2OH.HCl$ in $C_2H_5OH$ to produced Oxazolone (9) Spectro data of Spectro data of compound (9) FT-IR (in KBr): $C_{aromatic}$-F (1348 $cm^{-1}$), C-$H_{aromatic}$ (3048 $cm^{-1}$), C=$N_{oxazo}$ (1649 $cm^{-1}$), 1$HNMR_{DMSO-d6}$ (400 MHz); (7.15-7.46 δ, m, Aromatic-H), (8.33-8.52 δ, 5H, Quinoline protons).

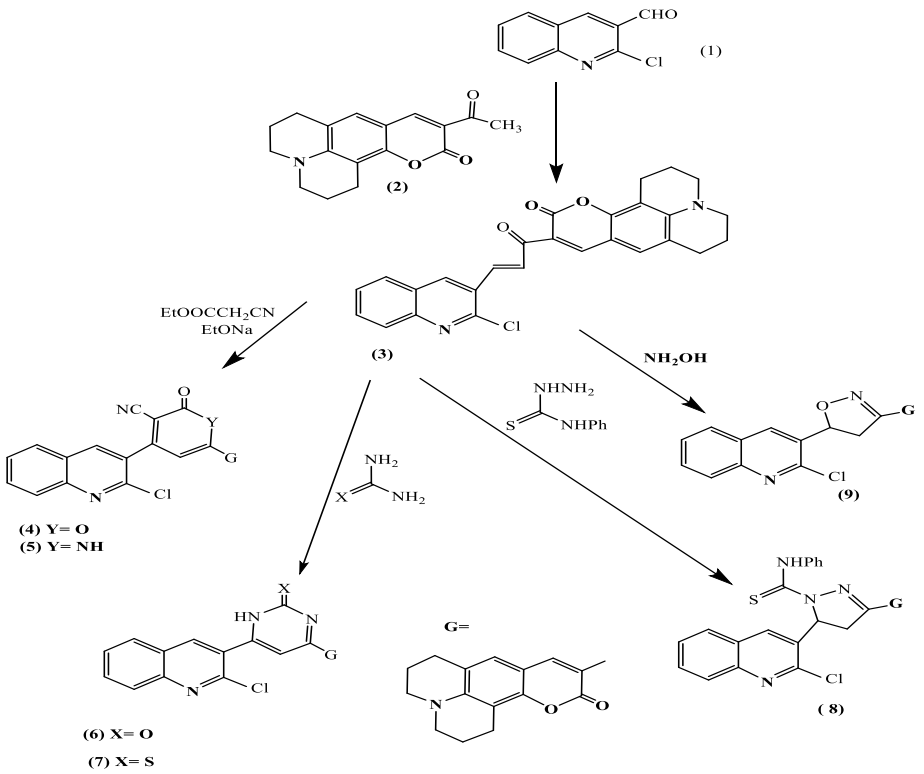


**Figure 2. Preparation the Heterocyclic compounds (4-9)**

**Biological activity of synthetic compound**

different membered (Five and six) heterocyclic synthetic derivatives that show different kinds against bacteria activities [14-15] and a Fung activity among them coumarin derivatives Moieties which are associated with same condition's diverse of biological activity such as antimicrobial [16-19]. In the present work, six newly synthetic heterocyclic compounds were tested against bacteria (-ve) Shigella, Escherichia coli, Enterobacter and Streptococcus, Bacillus, and Clostridium as (+ve) for concentration (10,20,30) µg/cm$^3$ as shown in table (1) and also fungi Aspergillus flavus and Penicillium at the same concentrations as in table (2)

**Table 1:** Pharmaceutical activity of new synthesis compounds

| Comp. No. | Conc. g/mlµ | Gram negative bacteria | | | Gram positive bacteria | | |
|---|---|---|---|---|---|---|---|
| | | E. coli | Enterobacter | Shigella | Streptococcus | Bacillus | Clostridium |
| 4 | 30 | 12 | 6 | 9 | - | - | 4 |
| | 20 | 10 | 9 | 8 | 11 | 7 | 13 |
| | 10 | - | 3 | 5 | 1 | 2 | 4 |
| 5 | 30 | 6 | 16 | - | - | - | 11 |
| | 20 | 3 | 9 | 7 | 5 | 3 | 9 |
| | 10 | - | - | - | - | - | - |
| 6 | 30 | 9 | 7 | 10 | 13 | 8 | 9 |
| | 20 | 8 | 5 | 4 | 9 | 7 | 3 |
| | 10 | 2 | 4 | 2 | 6 | 5 | - |
| 7 | 30 | 11 | 8 | 14 | 9 | 15 | 5 |
| | 20 | 7 | 9 | 4 | 5 | 6 | 10 |
| | 10 | - | 3 | 6 | 2 | - | 7 |
| 8 | 30 | 12 | 9 | 10 | 13 | 9 | 15 |
| | 20 | 11 | 8 | 7 | 10 | 8 | 9 |
| | 10 | 1 | 3 | - | - | - | 5 |
| 9 | 30 | 15 | 10 | 14 | 9 | 12 | 10 |
| | 20 | 10 | 9 | 12 | 8 | 11 | 13 |
| | 10 | - | 3 | - | 2 | - | - |
| Ciprofloxacin | | 10 | 5 | 10 | 9 | 10 | 12 |

**Table 2:** Antifungal activity of new synthesized compounds

| Comp. No. | Conc. g/mlμ | Aspergillus flavus | Penicillium |
|---|---|---|---|
| 4 | 30 | 9 | 11 |
| | 20 | 8 | 10 |
| | 10 | - | 1 |
| 5 | 30 | 10 | 7 |
| | 20 | 5 | 4 |
| | 10 | 2 | - |
| 6 | 30 | 10 | 12 |
| | 20 | 7 | 9 |
| | 10 | 5 | 3 |
| 7 | 30 | 13 | 7 |
| | 20 | 9 | 10 |
| | 10 | 6 | - |
| 8 | 30 | 15 | 8 |
| | 20 | 12 | 9 |
| | - | - | 5 |
| 9 | 30 | 13 | 9 |
| | 20 | - | 6 |
| | 10 | - | - |
| Clotrimazole | | 10 | 8 |

## CONCLUSION

New synthesized compounds of coumarin derivatives were testing on Gram negative and positive bacteria, as well as fungi, in this study conclude that these compounds are effective and can be developed in the future as a treatment for such microbes as they were compared with Ciprofloxacin and Clotrimazole that used to treat these microorganisms and the percentage of the prepared compounds was higher as an effective treatment.

**Ethical approval:** This study was approved by the ethics committee of the Al-Qadisiyah University/2021.

**Funding details:** N/A

**Conflict of interest:** N/A

**Informed Consent:** N/A

## REFERENCES


i. Mead JA, Smith JN, Williams RT (1958) Studies in detoxication. 72. The metabolism of coumarin and of o-coumaric acid. *The Biochemical Journal*. 68(1): 67-74.

ii. Spino C, Dodier M, Sotheeswaran S (1998) Anti-HIV coumarins from calophyllum seed oil. *Bioorganic and Medicinal Chemistry Letters*. 8(24): 3475-3478.

iii. Rosselli S, Maggio AM, Faraone N (2009) The cytotoxic properties of natural coumarins isolated from roots of Ferulago campestris (Apiaceae) and of synthetic ester derivatives of Angelino. *Natural Product Communications*. 4(12): 1701-1706.

iv. Rahman A, Shabbir M, Sultani ZS, Jabbar A (1997) Choudhary MI. Cinnamates and coumarins from the leaves of Murraya paniculate. *Phytochemistry*. 44(4): 683-685.

v. Cohen AJ (1079) Critical review of the toxicology of coumarin with special reference to interspecies differences in metabolism and hepatotoxic response and their significance to man. *Food and Cosmetics Toxicology*. 17(3): 277-289.

vi. Fuller RW, Bokesch HR, Gustafson KR (1994) HIV-Inhibitory coumarins from latex of the tropical rainforest tree Calophyllum teysmannii var. inophylloide. *Bioorganic and Medicinal Chemistry Letters*. 4(16): 1961-1964.

vii. Choi J, Lee KT, Ka H, Jung WT, Jung HJ, Park HJ (2001) Constituents of the essential oil of the Cinnamomum cassia stem bark and the biological properties. *Archives of Pharmacal Research*. 24(5): 418-423.

viii. Bourgaud F, Hehn A, Larbat R (2006) Biosynthesis of coumarins in plants: a major pathway still to be unraveled for cytochrome P450 enzymes. *Phytochemistry Reviews*. 5(2-3): 293-308.

ix. Bogdal D (1998) Coumarins: fast synthesis by Knoevenagel condensation under microwave irradiation. *Journal of Chemical Research, Synopses*. 8: 468-469.

x. Lake BG (1999) Coumarin metabolism, toxicity and carcinogenicity: relevance for human risk assessment. *Food and Chemical Toxicology*. 37(4): 423-453.

xi. Egan D, O'Kennedy R, Moran E, Cox D, Prosser E, Thornes RD (1990) The pharmacology, metabolism, analysis, and applications of coumarin and coumarin-related compounds. *Drug Metabolism Reviews.* 22(5): 503-529.

xii. Born SL, Hu JK, Lehman-McKeeman LD (2000a) o-hydroxy phenylacetaldehyde is a hepatotoxic metabolite of coumarin. *Drug Metab Dispos*. 28: 218-223.

xiii. Abdel-Wahab BF, Khidre RE (2013) 2-Chloroquinoline-3-carbaldehyde II: Synthesis, Reactions, and Applications. *Journal of Chemistry*. 13.

xiv. Rouveix B (2006) Clinically significant toxicity and tolerance of the main antibiotics used in lower respiratory tract infections. *Medicine et Maladies Infectiousness*. 36 (11-12): 697-705.

xv. Alwan NA Kadam ZM (2021) Preparing and diagnosing the biological activity of some metallic complexes with ligand 4-Benzophenol, Azopyrogallol (4) IOP Conference Series: *Earth and Environmental Science*. 790.

xvi. Basu HS, Mahlum A, Mehraein-Ghomi F, Kegel SJ, Guo S, Peters NR, Wilding G (2011) Pre-treatment with anti-oxidants sensitizes oxidatively stressed human cancer cells to growth inhibitory effect of superpolyamide hydroxamic acid (SAHA). Cancer Chemother. *Pharmacol*. 67, 705-715.

xvii. Abid Alradaa ZA, Kadam ZM (2021) Preparation, Characterization and Prevention Biological pollution of 4 (4-Benzophenylazo) Pyrogallol and their Metal Complexes, published under licensee by IOP Publishing Ltd. IOP Conference Series: *Earth and Environmental Science*. 790.

xviii. Ali AH, Jwad K, Kadam ZM (2019) Preparation and characterization of a novel ligand (5-MeTAQ) with some metal complexes Cd (II), Zn (II), Hg (II), IOP Conf. Series: *Journal of Physics: Conf. Series*. 1294 052039.

xix. Kadam ZM, Jeber RA, Alaa HA (2021) Azo Dyes on the ligand(5-MeTAQ) Thin Films for Dye Sensitized Solar Cells Applications Published under licensee by IOP Publishing Ltd. *Journal of Physics: Conference Series* 2021.