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Review Article:

Coumarin-Based Derivatives: A Review of Their Synthetic Routes, Reactivity, and Biomedical Attributes

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Abstract

Background: Coumarin-based derivatives (Cou-Ds) are one of the most important types of heterocycles, with a wide range of uses in synthetic and medicinal chemistry. Cou-Ds have interested researchers due to their wide range of biomedical potential and application as valuable synthetic scaffolds, which have been instrumental in the creation of coumarin chemistry. Cou-Ds are a unique class of bioactive candidates with novel therapeutic attributes due to their bacteriostatic, antifungal, antioxidant, anticancer, antidepressant, and other pharmacological properties. In addition to their biomedical uses, the literature illustrates the uses of Cou-Ds from a material point of view, such as those in food additives, fragrances, beauty products, optical brighteners, and would disperse fluorescent and laser dyes. Numerous optical purposes using Cou-Ds have been thoroughly investigated. A wide range of natural sources and newly created Cou-Ds are being isolated or produced at a growing rate. The procedures of synthesis and therapeutic uses of Cou-Ds in the treatment of various illnesses were critically found in many published papers. **Aim**: The aim of this review article is to highlight the most up-to-date information about Cou-Ds and clarify the various natural sources, synthetic strategies, reactions, biological activity, and different pharmaceutical applications of Cou-Ds. **Conclusion**: From the collected and discussed reviewing information, the authors concluded that the Cou-Ds can open the drug development door for producing more potent, biosafe medicines.

1. Introduction

The concern of medicinal chemists has been drowned in the chemistry of oxygen-derived heterocycles due to their increased value in the creation of a variety of biomedical derivatives (1). Also, the most prevalent heteroatoms are nitrogen, oxygen, and sulfur, while heterocyclic rings with other different heteroatoms are also well-known (2). The number of heterocyclic compounds known is enormous and is growing quickly, such as coumarin-based derivatives (Cou-Ds), pyrazoles, pyrans, oxazines, oxadiazole, and thiadiazoles (3). A form of heterocyclic molecule known as benzopyrone is created when the pyrone ring and benzene nucleus fuse. There are two different varieties of benzopyrone (4). They are benzo-α-pyrone (**1**), also known as Cou-D, and benzo-γ-pyrone (**2**), also known as chromones, and the only difference between them is where the carbonyl group is located in the pyrone ring (5), as shown in **Figure 1.**

Cou-D is chemically known as 2*H*-1-benzopyran-2-one and was first specified as an oxygen-containing heterocycle in the 1820s (6). It is most well-known for its vanilla-like or newly mowed hay-like odor. It was initially segregated from the tonka bean in 1822 (7), and then from woodruff, bison grass, and sweet clover. Cou-D is a white crystalline powder of distinct, sweet, fragrant, creamy smell with specific nutty shadings. It is widely used in synthetic form as a fragrance component for perfumery as well as for soaps and detergents with fragrance (8).

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The chemical structure of Cou-Ds determines how they are categorized, such as simple Cou-Ds (e.g., umbelliferon), furano-Cou-Ds that consist of a five-member furan ring connected to the Cou-D moiety, such as linear furano-Cou-Ds (e.g., angeligin), and angular furano-Cou-Ds (e.g., xanthotoxin), as shown in **Figure 2**. Simple Cou-Ds are alkylated, alkoxylated, or hydroxylated on the benzene ring (9–11).

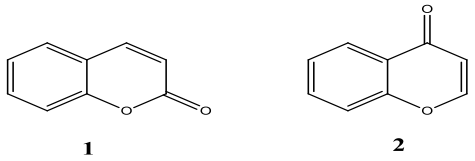

Figure 1. Types of benzopyrone according to location of carbonyl group

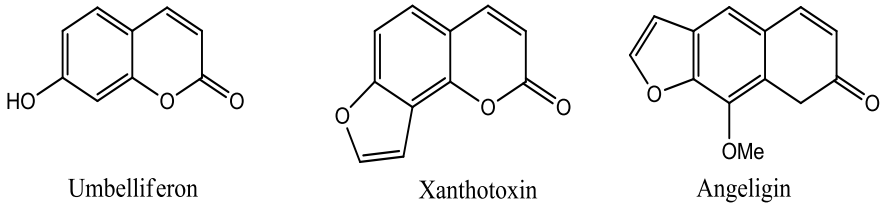

Figure 2. Chemical structures of some simple Cou-Ds and furano-Cou-Ds

Pyrano-Cou-Ds like seselin and xanthyletin, as shown in **Figure 3,** have a six-membered ring connected to the Cou-D moiety (12).

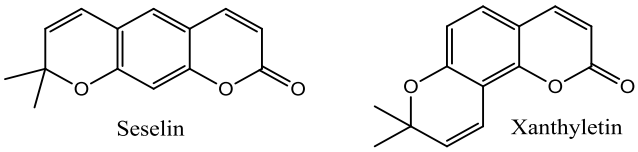

Figure 3. Chemical structures of some pyrano-Cou-Ds

Cou-Ds are one of the most potent classes of heterocycles, and a wide range of biomedical activities, including antibacterial (13,14), antifungal (15,16), anti-inflammatory (6,17), antidepressant (18,19), anti-HIV (20), and anticancer (21,22), have been demonstrated for them. Additionally, Cou-Ds have been employed as blockers of lipoxygenase and cyclooxygenase pathways of the arachidonic acid anabolism (23). In addition to their biomedical uses, the literature illustrates their applications in other life fields as in food additives, fragrances, beauty products, optical brighteners, and would disperse fluorescent and laser dyes. Numerous optical purposes using Cou-Ds, including laser dyes, nonlinear optical chromophores, fluorescent whiteners, science of polymers, and solar energy collectors, have been thoroughly investigated (24–27). Microorganism can also be found to have Cou-Ds. Aflatoxin from aspergillum microorganism and novobiocin from streptomycin microorganism are examples of Cou-Ds that have been extracted from microbial sources. They serve as an enhancing factor in aesthetics like soap, toothpaste, and alcoholic beverages and fragrances (28). Additionally, it serves as a neutralizer in rubber and plastic products as well as in sprays and paints to mask the undesirable smells (29).

2. Natural suppliers of Cou-Ds

Cou-Ds belong to special classes of compounds that occur naturally and play a specific role in nature, and attention to their chemistry continues to flourish because they are useful as bioactive agents (30). They are widespread secondary plant metabolites that show a variety of remarkable biomedical features. More than 1800 diverse naturally occurring Cou-Ds have been discovered. The majority of them are mono- or dioxygenated in the aromatic ring (31). Carrots, coriander, and garden angelica all contain 7-hydroxy-Cou-D (umbelliferone), a popular natural substance with a coumarin nucleus. It has been utilized as a dye indicator, fluorescence indicator, and sunscreen (32,33). A naturally occurring substance with the 4-hydroxy Cou-D is warfarin. It has been separated from woodruff and lavender and is employed for the prevention of blood clotting in the components of the circulating system (34).

Calophyllumdispar (Clusiaceae) fruit and stem bark were recently used to isolate six new Cou-Ds. The genus *Calophyllum*, which includes 200 different species, is spread across tropical rain forests, many of which are used in folklore medicine (35). The marine alkaloids ningalin B and

lamellarin D, which exhibit HIV-1 integrate inhibition, cytotoxicity, and immune-modulatory action, are Cou-Ds, as shown in **Figure 4** (36,37).

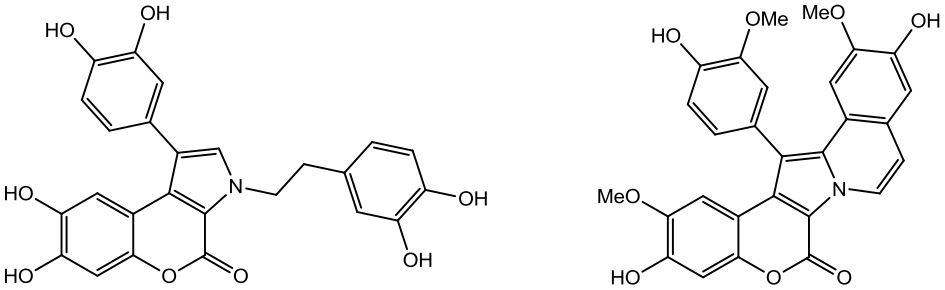

Figure 4. Chemical structures of Cou-Ds of marine alkaloids

The non-nucleoside reverse transcriptase inhibitor, (+)-calanolide A, which was isolated from *Calophyllumlanigerum* (38) and (+)-Cordatolide A, was isolated in 1985 from the leaves of *Calophyllumlanigerum cordatooblangum* (39) are tetracyclic Cou-D with significant anti-HIV-1 attribute. According to research, (+)-Inophyllum B, which was isolated from *Calophyllumlanigerum inophyllum*, as shown in **Figure 5**, has the most potent anti-HIV attribute (40).

Miglietta A and coworkers (41) isolated a new medicine that targets tubulin, which is geiparyarin from the leaves of *Geijeraparviflora*, as shown in **Figure 6**. They examined the cytotoxic and anti-microtubular attributes of newly created aryl geiparvarin-based compounds and found that these applicants can inhibit the microtubular protein assembly.

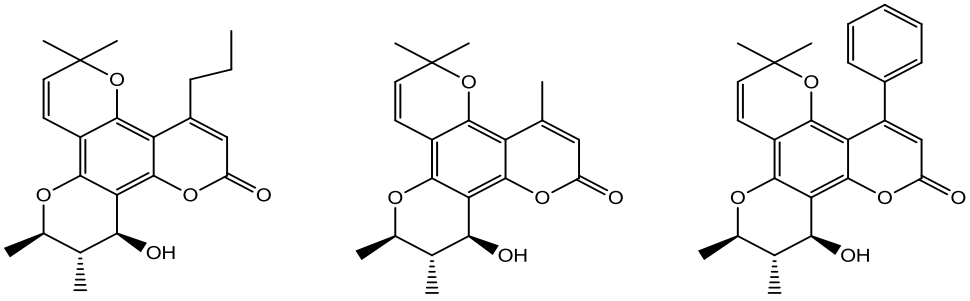

Figure 5. Chemical structures of Cou-Ds with anti-HIV attribute

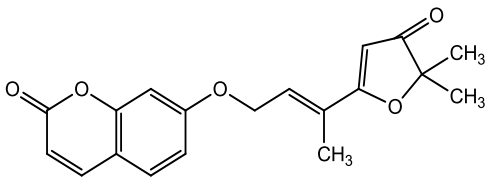

Figure 6. Chemical structure of the natural geiparyarin

3. Creation of Cou-Ds

The creation of Cou-Ds has caught the interest of organic chemists due to their numerous biomedical uses (42). For the creation of Cou-Ds, a number of methodologies have been established, including the Wittig reaction, Pechmann condensation, Perkin reaction, Knoevenagel condensation, and others (43). Pechmann and Duisberg published the first description of the Pechmann condensation reaction in 1883. It got a lot of attention and publicity because of its simple preparation and cheap building units. The synthetic route (44), comprises the reaction of phenol (Ph-OH) and β-ketoester using an acid initiator, as shown in **Figure 7**.

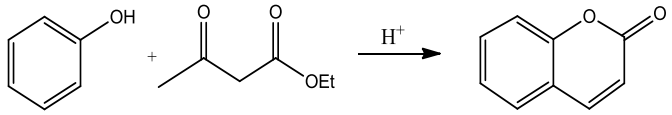

Figure 7. The general route of Pechmann condensation reaction

According to Vahid et al. (45), Cou-Ds were produced in a one-pot without the use of solvents from substituted Ph-OH congeners and diacetic ether under microwave irradiation conditions with the use of FeF_3 as a initiator, as shown in **Figure 8**. High yield, rapid reaction times, and a simple isolation approach are all features of this methodology

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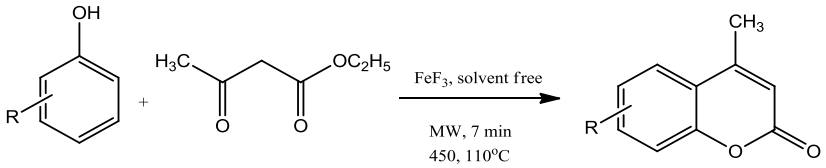

Figure 8. Solvent-free one-pot creation of Cou-D via Pechmann condensation reaction

Sun and collaborators (46), have established an alternate Pechmann condensation method by using Gallium (III) triiodide as a initiator. This deviation from the standard method offers many benefits, including gentle operating conditions, rapidly occurring reaction, ease of use and a high percentage of yield. They used Gallium (III) triiodide as an initiator in the reaction of naphthalen-1-ol and diacetic ether to produce 4-methyl-2*H*-benzo[*H*]chromen-2-ones, as shown in **Figure 9**.

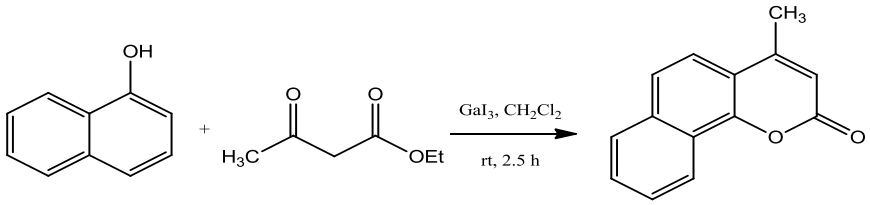

Figure 9. Alternative Gallium (III) triiodide-promoted Pechmann condensation reaction

Jalal Albadi and collaborators (47) described the synthetic process of Cou-Ds from Ph-OH congeners and diacetic ether in the foundation of the initiator named poly(4-vinylpyridine)-CuI without the use of solvent at 80 °C, as shown in **Figure 10**. The initiator was produced by refluxing poly(4-vinylpyridine) with CuI in EtOH under N_2 environment. This initiator can possibly be re-obtained by simple filtration and reused up to eight independent trials without losing its effectiveness (48).

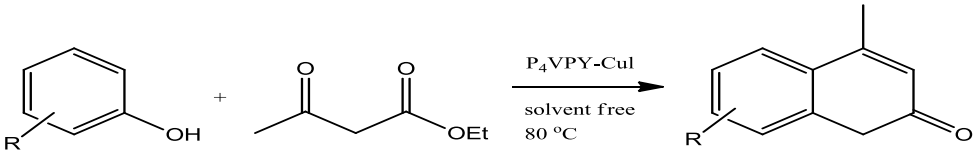

Figure 10. Creation of Cou-D from Ph-OH congeners and diacetic ether using poly(4-vinylpyridine)-CuI as initiator

Khaligh reported performing an environment friendly creation of Cou-Ds using a combination of Ph-OH congeners and β-ketoesters without using solvent at 40°C, utilizing [Msim] HSO_4 as a catalytic agent, as shown in **Figure 11**. The initiator was successfully recovered by separation through the decantation process and is reutilized five times with barely a slight decline in its catalytic effectiveness [30].

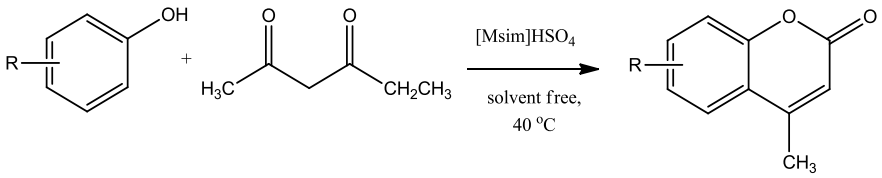

Figure 11. The green creation of Cou-Ds as reported by Khaligh

Another valuable method for the creation of Cou-Ds is the Perkin reaction. For example, Augustine et al. (49), reported using propylphosphonic anhydride (T3P) to mediate the one-pot creation of Cou-Ds from 2-formylphenol and cyanoacetic acid, as shown in **Figure 12**.

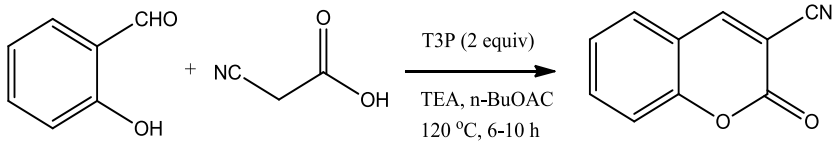

Figure 12. One-pot creation of Cou-Ds mediated by T3P

Knoevenagel reaction is another method to create Cou-Ds, which include arylaldehydes and activated methylene compounds condensation that initiated by a tertiary amine. Singh and coworkers (50), published a simple method for producing 3-alkanoyl-2*H*-chromene-2-thiones by β-oxodithioesters and 2-formylphenol condensation in the foundation of tertiary without using a solvent, as shown in **Figure 13**.

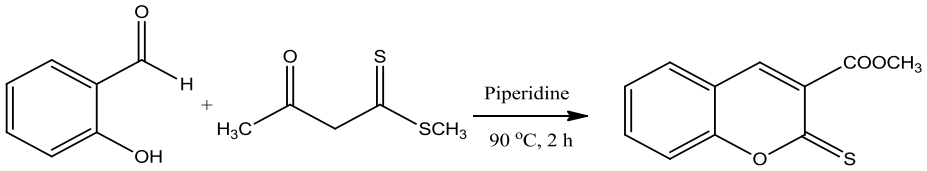

Figure 13. Creation of Cou-Ds via Knoevenagel reaction

Wittig reaction method includes an arylaldehyde or arylketone reaction with a phosphonate or phosphorous ylide. Cou-Ds were generated in good yields, for example, as shown in **Figure 14**, when 2-formylphenol-based compound and ethylchloroacetate reacted in the foundation of phosphorus triphenyl and MgONa/MeO (51).

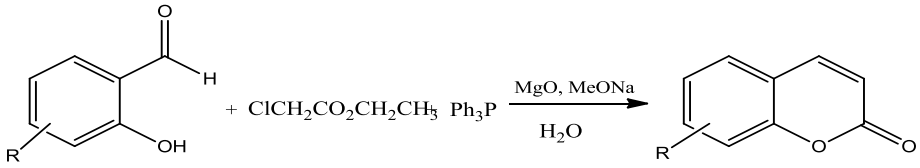

Figure 14. Creation of Cou-Ds via Wittig reaction

Yavari and coworkers (52), described the one-pot multistep reaction procedure to produce Cou-Ds from dimethylacetylenedicarboxylate 4-fluorophenol. This coupling involves the formation of the complex by condensing phosphorus triphenyl and dimethylacetylenedicarboxylate with Ph-OH congeners in order to undergo an aromatic-electrophilic substitution reaction, cyclic ester creation to produces 4-methoxycarbonyl Cou-Ds, as shown in **Figure 15**.

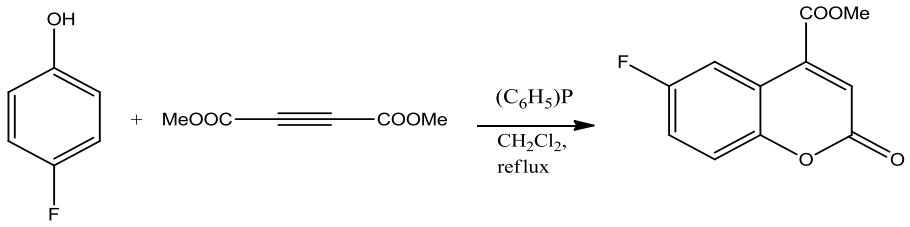

Figure 15. Creation of Cou-Ds via one-pot multistep reaction

In the Heck condensation chemical reaction promoted by Pd, includes the palladium catalyzed aryl halides and alkenes are coupled to produce conjugated alkenes in a decided way.

To produce Cou-Ds, the reaction is performed on cinnamic acid esters and 2-bromophenols (53), as shown in **Figure 16**.

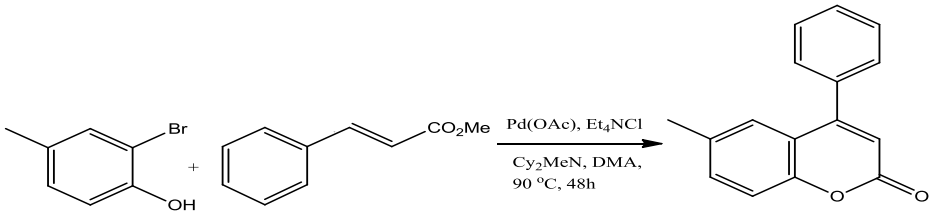

Figure 16. Creation of Cou-Ds via Heck coupling reaction

Due to their distinct biomedical characteristics, iso-Cou-Ds have attracted a great deal of attention. Rhodium was used as a initiator in the reaction between benzoic acid and alkynes to produce iso-Cou-Ds (54). To create highly substituted iso-Cou-D derivatives, phenyl acids can oxidatively integrated with alkynes through region-selective rhodium-promoted C-H linkage broken (55). This direct annulation process is significantly more step economical than the other typical multistep synthetic methods. A method for the production of Cou-Ds by palladium(II) catalyzed and trifluoroacetic acid mediated intramolecular cycloisomerization of arylated alkynoates has been established by Jia and coworkers (56), as shown in **Figure 17**.

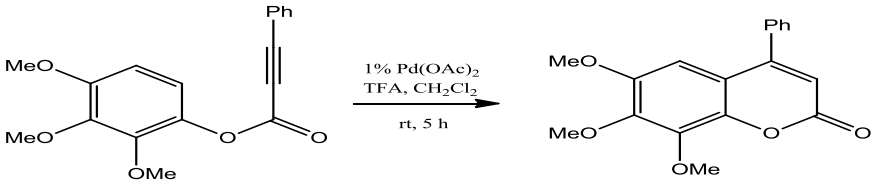

Figure 17. Preparation of Cou-Ds by palladium(II)-catalyzed and TFA

Selles et al. (57), produced significantly substituted fused Cou-Ds in two steps beginning with boronic acids and enoltriflates. Initially, the intermediate ester was formed by a coupling reaction mediated by $Pd(TPP)_4$, and then Ph-OH was easily lactonized to produce Cou-Ds by deprotecting the Ph-OH hydroxyl group with BBr_3, as shown in **Figure 18**.

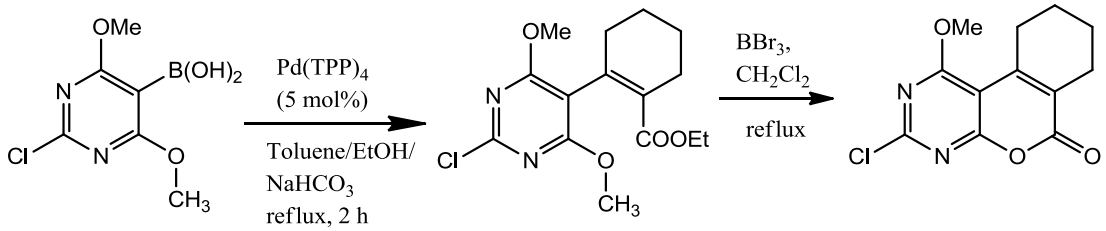

Figure 18. Creation of highly substituted fused Cou-Ds in two steps

2-Formylphenol-derived compound, Meldrum's acid, and alcohol were used as the starting components in a multicomponent reaction established by X. He et al. (58), to produce Cou-3-carboxylic esters by $FeCl_3$-catalyzed multicomponent reaction, as shown in **Figure 19**. The approach is both environmentally friendly and highly inexpensive.

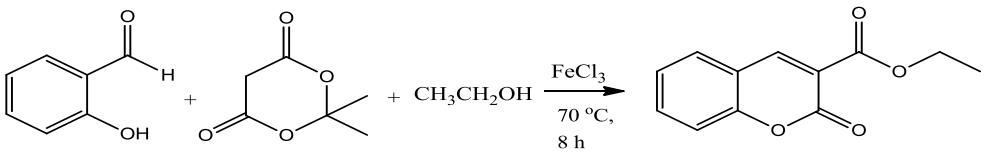

Figure19. Creation of Cou-Ds by $FeCl_3$-catalyzed multicomponent reaction

By treating the α-halocarboxylic acid ester of 2-formylphenol by Na_2Te or Li_2Te induced cyclization, 3 bromo-Cou-Ds are produced, as shown in **Figure 20**. In THF, the reaction operated under neutral circumstances. The authors indicated that the creation of Cou-D using Li_2Te was more effective than Na_2Te (59).

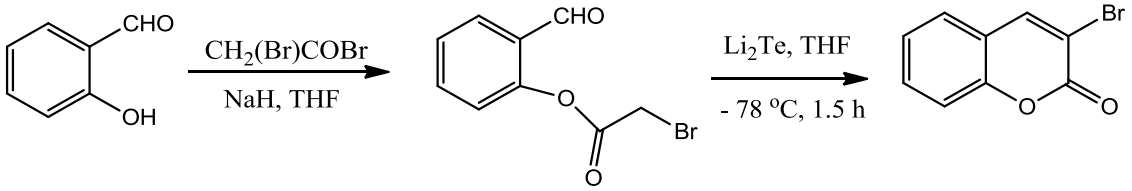

Figure 20. Creation of 3-Bromo-Cou-Ds under non-basic condition

Cou-Ds were produced by gently reacting a range of electron-rich Ph-OH congeners and electron-rich cinnamates with the existence of trifluoroacetic acid at 25 °C. The low yield of Cou-Ds produced by electron-deficient Ph-OH congeners made the procedure utilization limited (60). Through the N-hetero-cyclic carbene (NHC)-catalyzed umpolung reaction between 2-chloro-2-arylacetaldehydes and 2-formylphenol, 3-aryl-Cou-Ds are produced in excellent yields (61), as shown in **Figure 21**. The procedure is mild and straightforward experimentally.

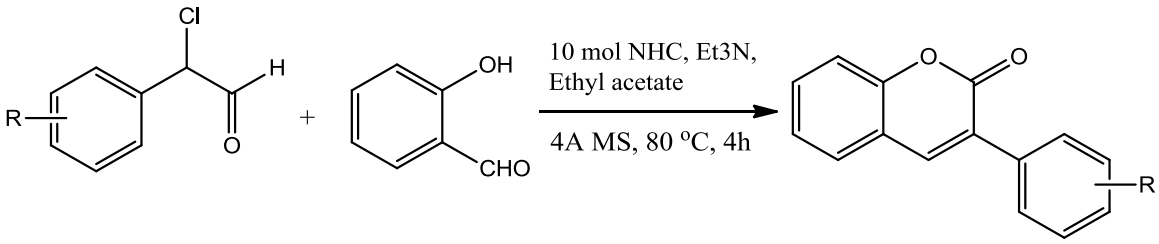

Figure 21. Creation of Cou-Ds from electron-rich Ph-OH congeners and electron-rich cinnamates

The Cou-Ds were produced using the Baylis-Hillman method by Kaye et al (30). In the foundation of DABCO acting as an initiator, 2-formylphenol interacts with t-butyl acrylate to produce Baylis-Hillman adducts. The 3-(iodomethyl)-Cou-Ds were then produced in good yields when these intermediate compounds were coupled with HI/acetic acid medium, as shown in **Figure 22**.

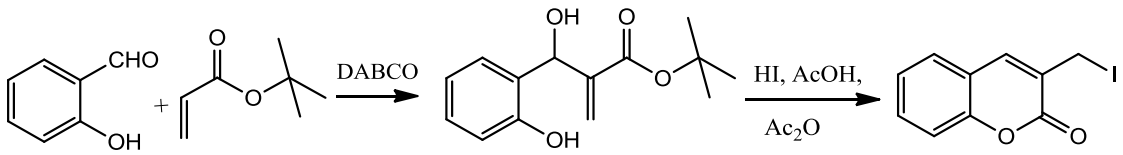

Figure 22. Creation of Cou-Ds by Baylis-Hillman method

By employing the Grubbs initiator in ring-closing metathesis, Polito and collaborators (62), demonstrated a straightforward and easy way to create Cou-Ds, as shown in **Figure 23**. It includes the formation of acrylic ester by reacting 2-hydroxy styrene with prop-2-enoyl chloride. On the ester mediated from acrylic acid ester, the alkene

metathesis reaction was carried out using an initiator in dichloromethane. The technique is an alternate for current Cou-D creation processes, which require nearly neutral conditions for ring formation (63).

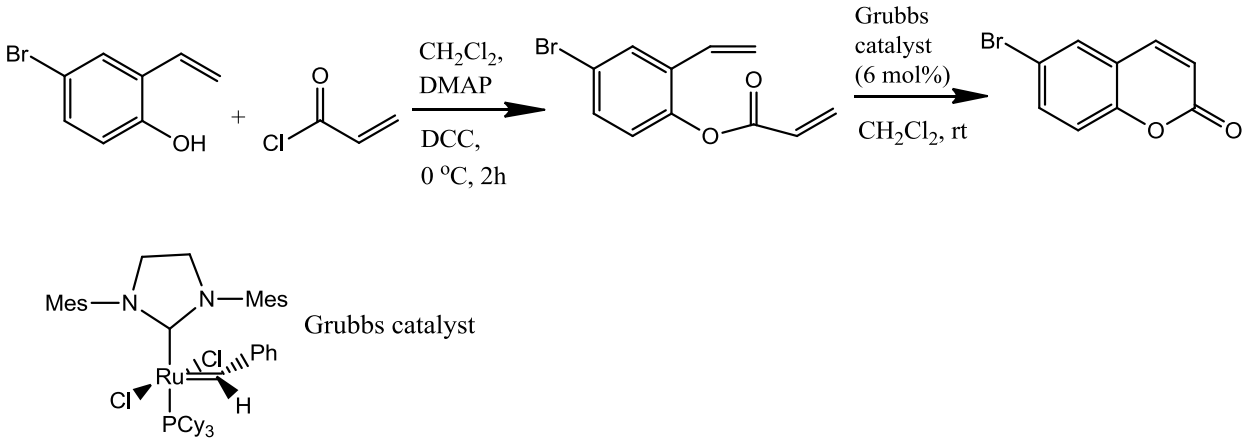

Figure 23. Creation of Cou-Ds via ring closing metathesis using Grubbs initiator

4. Reactivity of Cou-Ds

Because they contain an aliphatic component that is extremely reactive, Cou-Ds are likely to experience ring opening at the acyl center (64). Electrophilic attack on carbon-6 on the aromatic ring, can result in the production of 6-substituted derivatives by Friedel-Crafts acylation and sulphonation (65). Depending on where it is attached, a methyl functionality on the Cou-D entity may behave and communicate in a variety of ways. The Ph-OH group's location at C-7, makes it readily undergo benzoylation, acylation and Friedel-Crafts processes (66).

Cou-D-3-formyl chloride was used to produce Cou-D-based benzothiazoles. The precursor Cou-D-3-formyl chloride has been produced from Cou-D-3-carboxylic acid and $SOCl_2$ in the foundation of tertiary amine. The target chemical, as shown in **Figure 24** (67), was produced by treating these formyl chloride with *ortho*-aminobenzothiazole and N,N-diethylethanamine in CH_2Cl_2 at 25 °C.

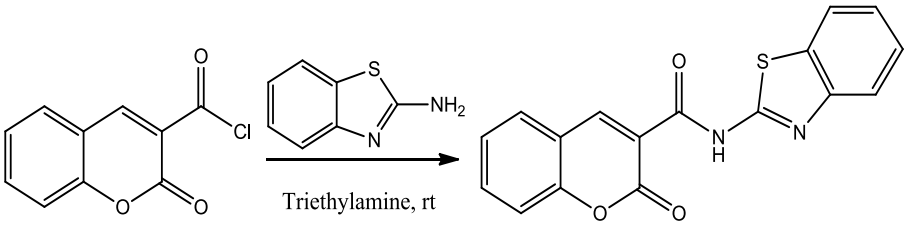

Figure 24. Creation of Cou-D-based benzothiazole derivatives

An accessible and straightforward method was used to create a number of Cou-D attached formyl-pyrazoles. The intermediate compounds are formed during the interaction of phenylhydrazine hydrochlorides with 8-acetyl-4-methyl-7-hydroxy-Cou-D, then the resultant derivative, in the foundation of $POCl_3$, reacts with DMF and produces formyl-pyrazoles with Cou-D moiety in valid yield, as shown in **Figure 25** (68). The obtained intermediate as well as the newly synthesized compounds have been evaluated *in vitro* for their antioxidant, antifungal and antibacterial properties. The chloro-substituted compounds showed hopeful antimicrobial action against the various tested species (3). Later, they successfully transformed the formyl pyrazoles into fused pyrans (69).

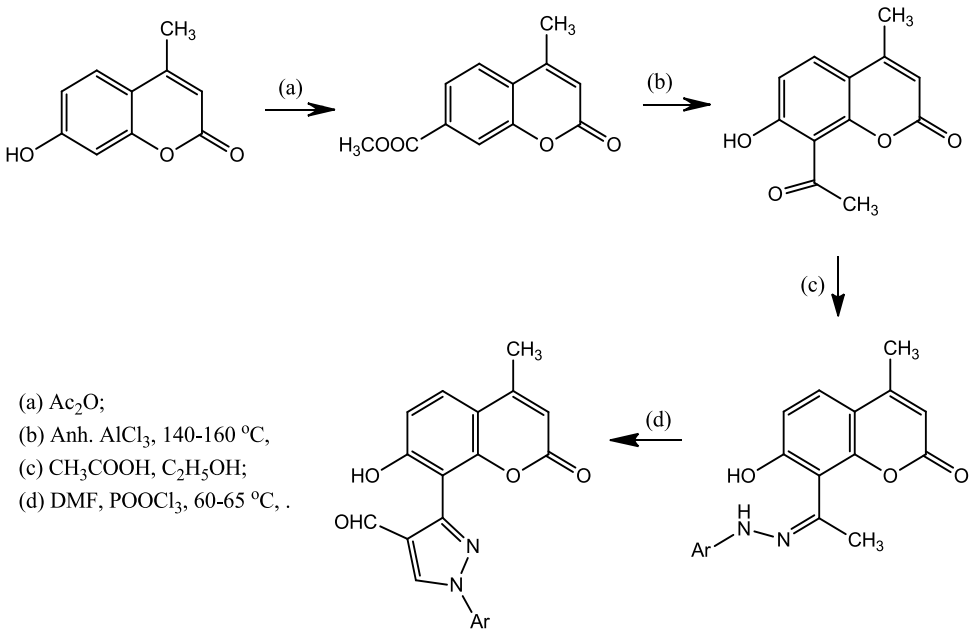

Figure 25. Creation of series of Cou-D appended formyl-pyrazole

Sahoo et al. (70), successfully converted 8-amino-7-hydroxy-4-methyl-Cou-D into several types of 7,8-coumarin-fused heterocyclic compounds depending on the reactants used, as shown in **Figure 26**.

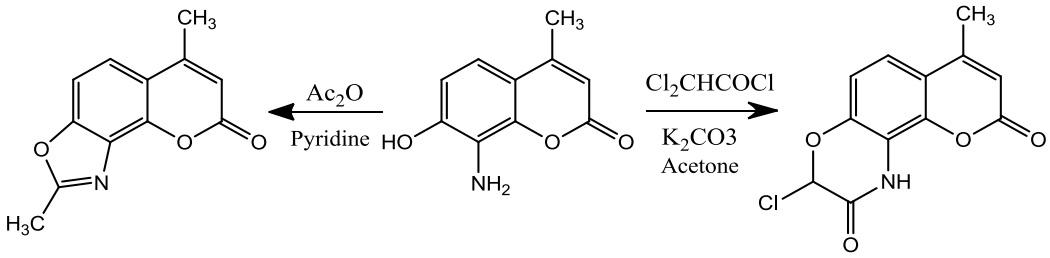

Figure 26. Creation of various 7,8-coumarin-fused heterocyclic compounds

Farahi and collaborators (71), established a straightforward process to produce novel sulphonamide-substituted-Cou-Ds by using N-sulfonylaldimines and 5,7-dihydroxy-4-methyl-Cou-D with NaOH, as shown in **Figure 27**. The 4-toluenesulfonamide and aromatic aldehydes were reacted in the foundation of $AlCl_3$ to yield the sulfonylaldimines. Additionally, in the foundation of $ZrOCl_2/SiO_2$ initiator, condensation of phloroglucinol and ethylacetate was used to yield 5,7-dihydroxy-4-methyl-Cou-D (72).

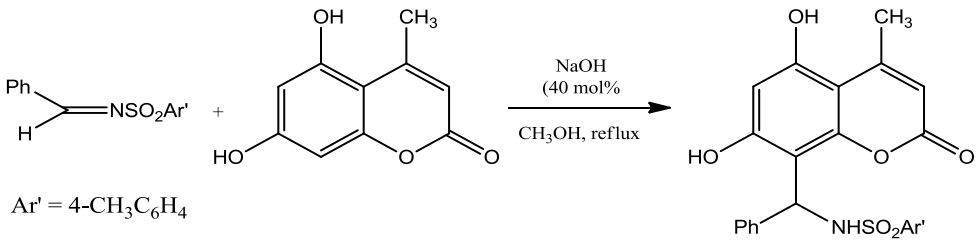

Figure 27. Creation of new sulphonamide-substituted Cou-Ds

Liang Han and collaborators (73), used the compound 7-diethylamino-3-(4-formylphenyl)-Cou-D in order to produce novel Cou-D-type dyes. Tetrakis (triphenylphosphine)palladium in THF was used to combine the 4-formylphenyl boric acid with 3-bromo-7-diethylamino-Cou-D to get the formyl-Cou-D. Satyanarayana Reddy et al. (74), established by mildly base-promoting, the reaction of 4-chloro-3-formyl-Cou-D with 3-hydroxyphenol in the foundation of N,N-diethylethanamine and EtOH at 25 °C to produce 7*H*-benzopyrano[3, 2-c]-Cou-Ds, as shown in **Figure 28**.

Under basic conditions, ethyl-10-cyano-9-hydroxy-6-oxo-7-phenyl-6*H*-benzo[c]chromen-8-caboxylate produced by treating 3-benzoyl-2*H*-chromen-2-one with ethylcyanoacetate (75). The pathway of the reaction is supposed to be carried out by the carbanion nucleophilic addition to the acetylene bridge of 3-benzoyl-2*H*-chromen-2-one, giving the predicted pyranochromen, which then interacts with another electrophile. After that, the cyclic system is opened and reclosed with the HCN elimination to produce the final product, as shown in **Figure 29** (76).

Using a convenient and applicable method, Omaima and colleagues (77), produced Cou-D-based pyrimidines, -pyridines, and -pyrazole derivatives. These key reactions include the intermediate production of chalcones (**3**). A simple method of producing these synthesized α,β-unsaturated ketones include the condensation of 3-acetyl-4-hydroxy-Cou-D with the necessary aldehydes. By reacting 4-hydroxy-Cou-D with acetyl chloride in the foundation of pyridine or piperidine, acetyl Cou-Ds were produced. 4-Aryl-2-amino-6-(4-hydroxy-Cou-D-3yl)-pyridine-3-carbonitriles were produced by cyclizing the appropriate chalcones with malononitrile and ammonium acetate (**4**). Furthermore, pyrimidin-2-thiones (**5**) were synthesized by cyclo-condensing the chemical (**3**) with thiourea in a solution of 5% ethanolic KOH. Additionally, 5-aryl-4,5-dihydro-3-4-hydroxy-2-oxo-2*H*-chromen-3-yl)-pyrazol-1-carbothioamide (**6**) were produced by refluxing a blend of compound (**3**) and thiosemicarbazide in EtOH in the foundation of glacial acetic acid" (78). The critical intermediate chalcones were refluxed with hydrazine hydrate in glacial acetic acid to produce N-acetylpyrazolines (**7**) in a similar manner, as shown in **Figure 30**.

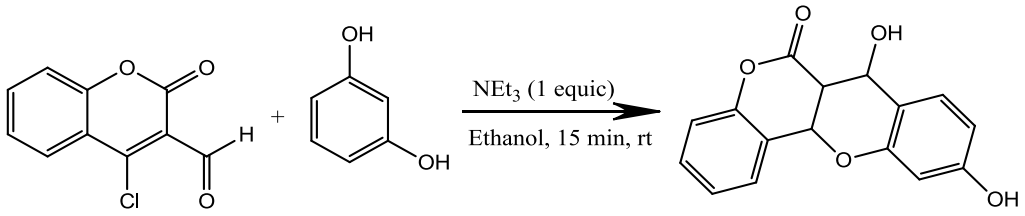

Figure 28. N,N-diethylethanamine-promoted synthesis of 3,4-coumarin fused heterocycle

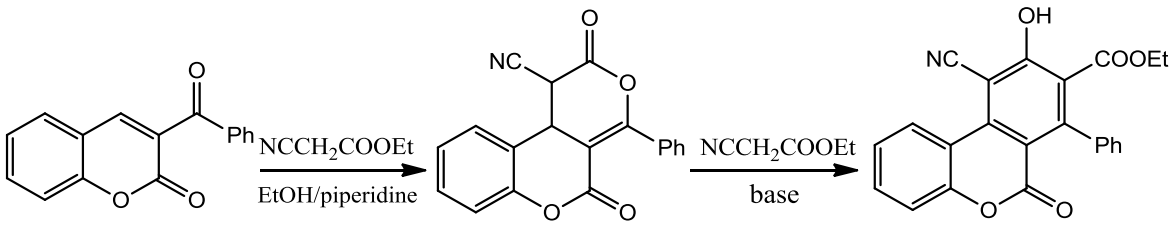

Figure 29. Creation of 3,4-coumarin-aromatic hybrid

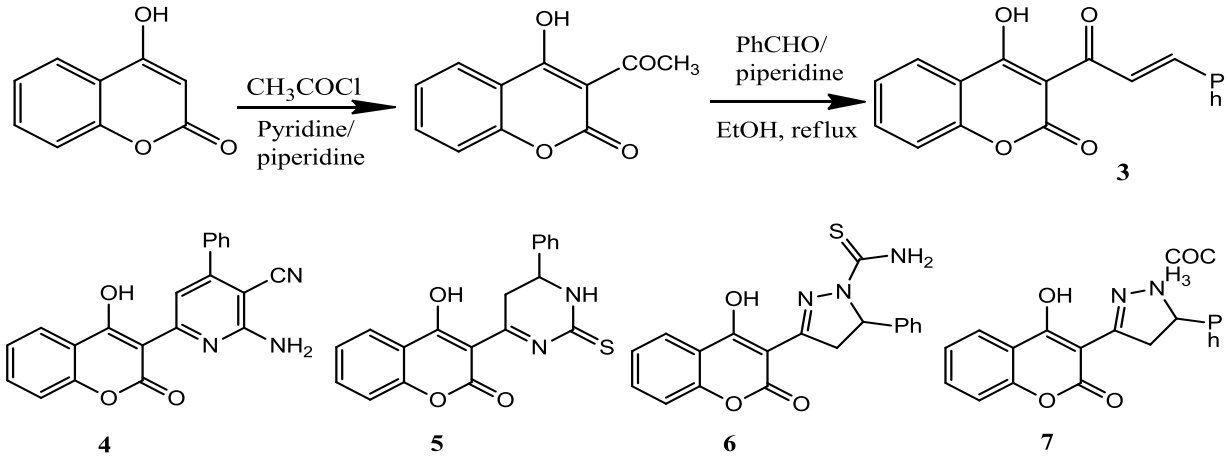

Figure 30. Formation of Cou-D based N-heterocycles

From the essential intermediate **8**, a series of Cou-D-based traizole and pyrazole derivatives are produced. Compound **8** produced **9** upon compound **8** condensation with pentane-2,4-dione, whereas with potassium isothiocyanate it produced a salt that was immediately transformed into compound **10** in a good yield by heating it in aqueous KOH and then acidifying it with HCl. An acetic acid ester and 100% hydrazine hydrate, as shown in **Figure 31**, were combined to produce the intermediate **8** (79).

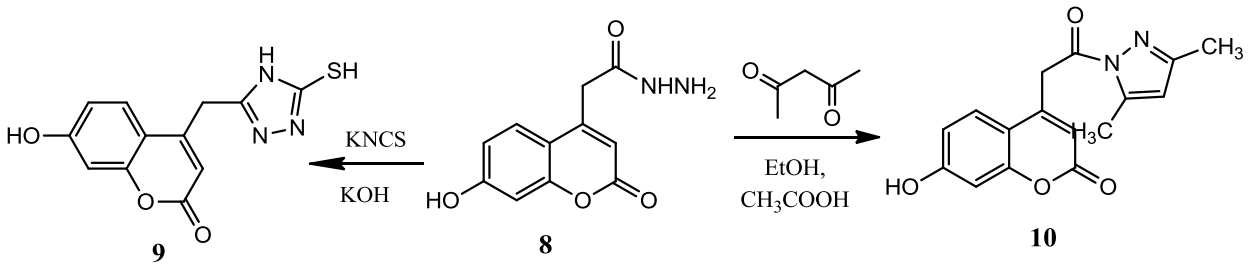

Figure 31. Creation of Cou-D based triazole and pyrazole derivatives

1-Benzopyrano[3,4-*c*]pyrrolidines are produced by 1,3-dipolar cycloaddition of *in situ* formed azomethine-ylide with *meta*-functionalized Cou-D and α-amino acids that are functionalized from the nitrogen side, as shown in **Figure 32** (80).

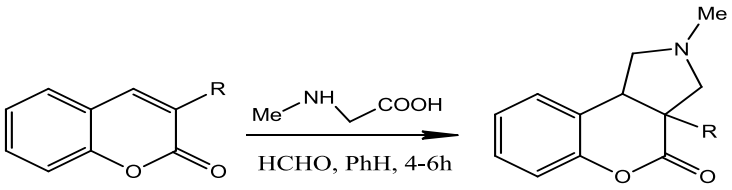

Figure 32. Creation of 1-Benzopyrano [3, 4-c]pyrrolidines

A series of Cou-D-3-yl-carbamates was produced by dissolving 3-amino-Cou-D in a cocktail of $CHCl_2$ and aromatic tertiary amine. The solution was chilled and to which, the previously prepared acetyl chloride congeners was dropped. The solvent was vaporized following the magnetic bar stirring for 3 hours at 25 °C. The crude was then purified by column chromatography to give (Cou-D-3-yl) carbamates (81). Through a one-pot Povarov reaction, functionalized pyrido[2,3-*c*]-Cou-Ds were produced by interacting aryl aldehydes, 3-amino-Cou-Ds, and aryl acetylene in the foundation of I_2 (10%) in ACN under reflux circumstances, as shown in **Figure 33** (82).

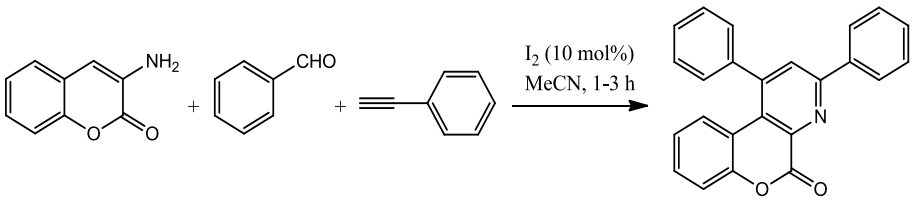

Figure 33. One-pot Povarov reaction to get substituted pyrido[2,3-*c*]-Cou-Ds

The compound **11** and 2-phenylenediamine were used to produce a novel compound numbered 1**2** in polyphosphoric acid under reflux conditions for 12 hours. In addition to which, this reaction also produced compound **13**, as shown in **Figure 34**, which was then separated using column chromatography (83).

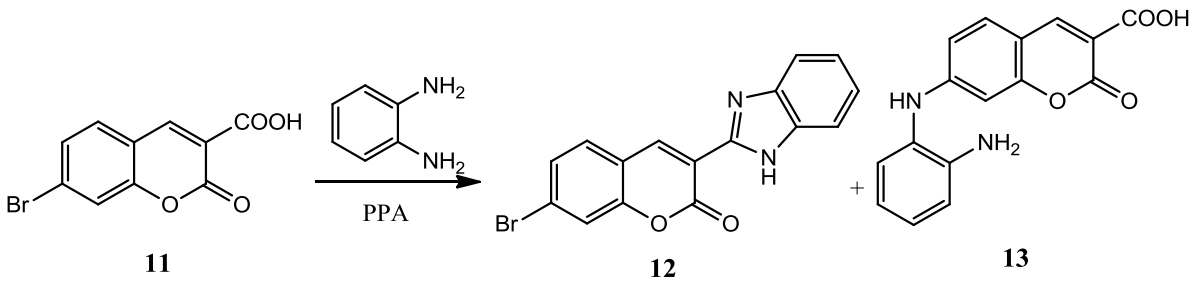

Figure 34. Creation of novel Cou-Ds **12** and **13**

5. Biomedical Incorporates of Cou-Ds

Due to their biomedical characteristics, Cou-Ds are of enormous interest. Particularly appealing for further backbone derivation and exploring for a new potential medication due to their bacteriostatic, physiological, and anti-cancer action (84). In numerous tumor cell lines, Cou-Ds have demonstrated promise to serve as cellular growth inhibitors (82). Additionally, it has been demonstrated that a gastric cancer cell line was sensitive to 4- and 7-hydroxyCou-D and inhibited cell proliferation (85).

A number of different functionalized 3-aryl-1-(3-Cou-D-yl)propan-1-ones were combined with hydrazinobenzene, in the foundation of warmed aromatic tertiary amine to produce a series of new 5-(substituted) aryl-3-(3-Cou-Dyl)-1-phenyl-2-pyrazolines (**14**), as shown in **Figure 35**. All of the synthetic substances were tested for their analgesic and anti-inflammatory properties *in vitro* (86). When compared to diclofenac as a standard medication, compounds containing 4-Cl and 2,4-Cl demonstrated considerable anti-inflammatory efficacy in a model of acute inflammation like carrageenan-induced rat paw edema. Significant analgesic efficacy was also discovered for these substances in an acetic acid-induced writhing model (87).

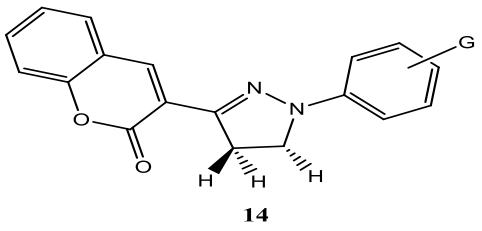

Figure 35. The chemical structure of the prototype **14**

The creation and antibacterial attribute of compound **15** and its analogues, as shown in **Figure 36**, were reported by Pradeep Kumar et al. in their study (88). They tested the produced substances against bacterial and fungal strains for antimicrobial potential. Compounds with flouro-substitution among the produced compounds have demonstrated strong antimicrobial attribute (89).

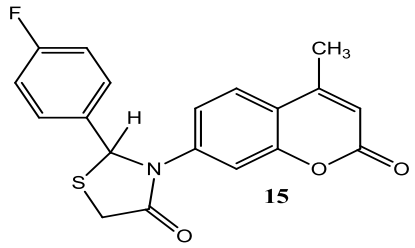

Figure 36. The chemical structure of the prototype **15**

Compounds **16** and **17**, as shown in **Figure 37**, which were extracted from the tree named scientifically *Marilapluricostata* tree, can block the HIV-1 replication in Jurkat T cells (90). Mesuol targets the nuclear factor-κB (NF-κB) pathway to inhibit TNF-α induced HIV-1-LTR transcriptional attribute. Mesuol does not block either TNFα-stimulated cells from phosphorylating and degrading the NF-κBp65 subunit or NF-κB from binding to DNA. These findings demonstrate the NF-κB nuclear component's potential as a goal for anti-HIV-1 substances like **16**, which may be utilized as lead compounds for the creation of new anti-AIDS therapies (91).

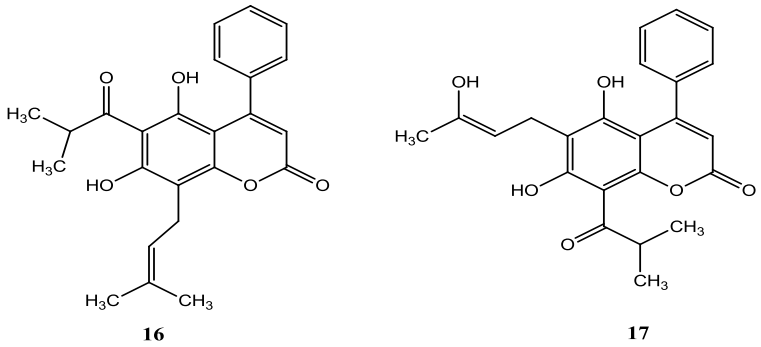

Figure 37. The chemical structure of the compounds **16** and **17**

Azide and alkyne dipolar cycloaddition were used to create a series of compound **18** analogues, as shown in **Figure 38**. The cytotoxic potential of these compounds against the cancerous cellular populations named MOLT-3, A549, HepG2, and HuCCA-1, was examined. The 2,3-dimethoxy derivatives with a triazole ring at position 3 have been found to be the best antiproliferative applicant among these triazole hybrids against MOLT-3 cell lines without harming normal cells (92).

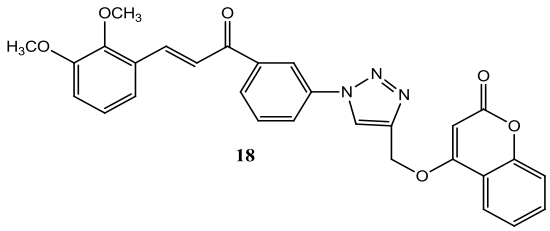

Figure 38. The chemical structure of the compound **18**

Ranjana et al. (93), produced several novel analogues for compound (**19**), as shown in **Figure 39**. All of these novel items were tested for their antimicrobial effectiveness. The macro-dilution vessel methodology was used to determine the MIC values of the produced compounds against various bacteriomers. Any one of these compounds that has Cl and F substituents was recommended to be the best agent against *P. mirabilis* and *E. coli* when the results matched those acquired from the reference drug, cefixime.

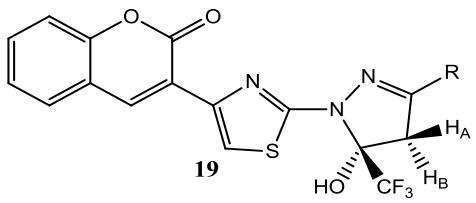

Figure 39. The chemical structure of the compound **19**

A novel class of iodinated-4-aryloxymethyl-Cou-Ds (**20**, **21**), as shown in **Figure 40**, has been produced from different types of 4-bromomethyl-Cou-Ds with various iodophenols (94). Using the MTT-based assay to calculate IC_{50} values, all of the synthesized compounds were tested for their *in vitro* anticancer attribute against the cancer cell lines A-549 human lung carcinoma and MDA-MB human adenocarcinoma mammary gland. Among these synthesized derivatives, a molecule with iodine at position 4 on the phenoxy moiety and chlorine functionalities at positions 6 and 7 on the Cou-D displayed strong anticancer attribute (95).

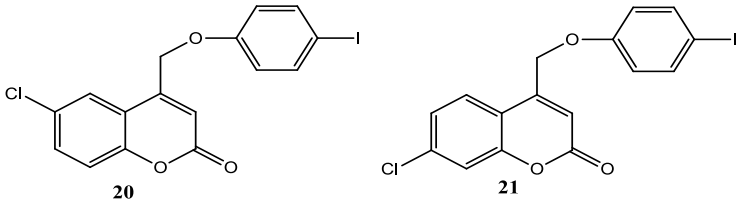

Figure 40. The chemical structures of the compounds **20** and **21**

A number of Cou-D-based aminopyran derivatives were synthesized by Koneni et al. (96) and examined on Swiss albino mice to see if they had any antidepressant properties. Compound (**22**), as depicted in Figure 41, from the entire set demonstrated notable efficacy in the compelled Bathing Check at an extremely low dose of 0.5 mg/kg and decreased the duration of motionlessness by 86.5% in comparison to the reference drug, fluoxetine, which decreased motionlessness moment by 69.8% at a dosage of 20 mg/kg (97). All of the key components were also looked at for the tail suspension test. This proved that the compounds in question didn't affect motor function negatively (97). Derivatives of Cou-D-aminopyran may therefore be useful therapeutically in the medical management of mental depression (98).

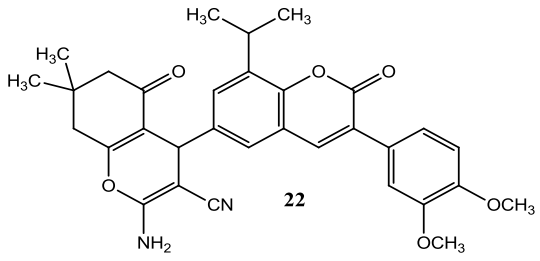

Figure 41. The chemical structure of the compound **22**

A series of new Cou-D-3-carboxamides, with the prototype numbered (**23**), were produced and examined for their *in vivo* anti-inflammatory and *in vitro* antioxidant properties (99). These carboxamide-Cou-Ds exhibited strong anti-inflammatory and antioxidant properties. According to the findings, structure-attribute relationship was established in order to determine the structural requirements for attribute (100). In the same regard, new 3,4-dimethoxyphenylethyl-1,3,5-triazinyl thiourea derivative (**24**), as shown in **Figure 42**, was produced by Patel R. B. and collaborators, as an anti-HIV and antibacterial agent (101).

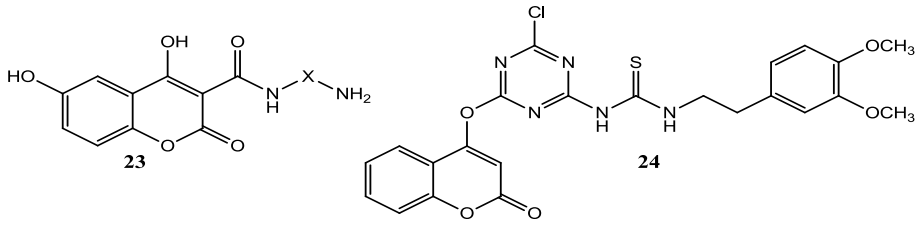

Figure 42. The chemical structures of the compounds **23** and **24**

The 4-methyl-Cou-Dyl-7-oxyacetic acid, hydrazides, and thiomalic acid were used to synthesize the compound numbered (**25**), as shown in **Figure 43**, under reflux conditions (102). The mixture was solubilized in an aqueous solution of $NaHCO_3$ (10%) after the reaction was finished and then re-precipitated by HCl and recrystallized from EtOH (103). By using a DPPH-based assay, the resulting product was assessed for antioxidant capacity. When compared to vitamin C as-is, the resultant molecule with the unsubstituted benzene group exhibited greater antioxidant functions by 95% (104).

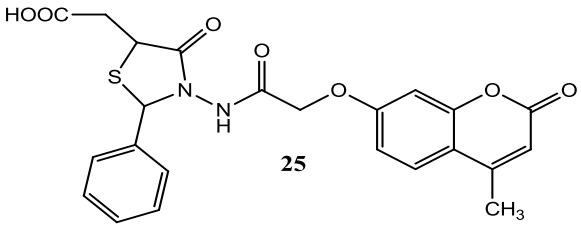

Figure 43. The chemical structure of the compound **25**

6. Conclusion

An effort has been made to clarify the source, creation methods, reactions, and biomedical incorporates of Cou-Ds in this paper. Regularly, new Cou-D analogues are being explored or synthesized from a variety of natural or lab sources. Cou-Ds are highly sought-after due to their medicinal potential and are a unique class of pharmaceuticals with novel and versatile therapeutic attributes due to their pharmacokinetic-desired, antimicrobial, antioxidant, anticancer, and other pharmacological characteristics. The manner of creation and therapeutic incorporation of the Cou-Ds in the treatment of various illnesses were critically examined. From the above-mentioned reviewing information, the authors concluded that the Cou-Ds can open the drug development door for producing more potent, biosafe medicines.

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المشتقات القائمة على الكومارين: مراجعة لطرقها التركيبية ، والتفاعلية ، وانشطتها الطبية الحيوية

الخلاصة

المقدمة: تعتبر المشتقات التي أساسها الكومارين (Cou-Ds) واحدة من أهم أنواع الدورات غير المتجانسة ، مع مجموعة واسعة من الاستخدامات في الكيمياء التركيبية والطبية. اهتمت Cou-Ds بالباحثين نظرًا لمجموعتها الواسعة من الإمكانات والتطبيقات الطبية الحيوية كسقالات تركيبية قيّمة ، والتي لعبت دورًا أساسيًا في إنشاء كيمياء الكومارين. تعتبر Cou-Ds فئة فريدة من المرشحين النشطين بيولوجيًا مع سمات علاجية جديدة نظرًا لخصائصها المضادة للجراثيم والفطريات ومضادات الأكسدة ومضادات السرطان ومضادات الاكتئاب وغيرها من الخصائص الدوائية. بالإضافة إلى الاستخدامات الطبية الحيوية ، توضح الأدبيات استخدامات Cou-D من وجهة نظر مادية ، مثل تلك الموجودة في المضافات الغذائية ، والعطور ، ومنتجات التجميل ، والمبيضات الضوئية ، وسوف تشتت الفلوريسنت وأصباغ الليزر. تم التحقيق بدقة في العديد من الأغراض البصرية باستخدام Cou-Ds. يتم عزل أو إنتاج مجموعة واسعة من المصادر الطبيعية و Cou-Ds المنشأة حديثًا بمعدل متزايد. تم العثور على إجراءات التوليف والاستخدامات العلاجية لـ Cou-Ds في علاج الأمراض المختلفة بشكل حاسم في العديد من الأوراق المنشورة. **الهدف**: الهدف من مقالة المراجعة هذه هو تسليط الضوء على أحدث المعلومات حول Cou-Ds وتوضيح المصادر الطبيعية المختلفة ، والاستراتيجيات التركيبية ، والتفاعلات ، والنشاط البيولوجي ، والتطبيقات الصيدلانية المختلفة لـ Cou-Ds. **الاستنتاج**: من معلومات المراجعة التي تم جمعها ومناقشتها ، استنتج المؤلفون أن Cou-Ds يمكن أن يفتح باب تطوير الأدوية لإنتاج أدوية أكثر فاعلية وأمانًا بيولوجيًا.

الكلمات المفتاحية: مشتق أساسه الكومارين، طرائق التصنيع، الإمكانات الطبية الحيوية، مصادر طبيعية؛ مضادات الميكروبات، مضادات السرطان، مضادات الأكسدة