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RECENT ADVANCES IN THE SYNTHESIS OF PHARMACOLOGICALLY BENIGN COUMARIN AND INDOLE HETERO-STRUCTURED DERIVATIVES: A REVIEW

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Keywords:

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ABSTRACT: Indole and coumarin are the most versatile and cogent heterocyclic scaffolds which are not only decisively used in the synthesis of various organic compounds but also play a consequence role in natural product synthesis, modulation of biofilm formation, virulence and stress responses. In last few decades, an individual has witnessed considerable activity towards the synthesis of indole derivatives due to the possibilities for the design of polycyclic structures by the incorporation of multiple fused heterocyclic scaffolds in an attempt to achieve promising new heterocycles with chemical and biomedical relevance. Whereas, coumarin is a 2-oxo-2*H*-1-benzopyran and, also, have a wide range of application in the pharmaceutical field. In this review, we provide an overview of the synthesis of coumarin and indoles and their pharmacological evolution. The coumarin was synthesized using phenols, salicylaldehyde, benzaldehyde, phenylacetate, styrenes, and cinnamic acid with different catalyst and photocatalyst to give the best yield. Similarly, Indoles were synthesized iodobenzoic acid, alkynes, amines, alcohols, Nitrobenzaldehyde with the different catalyst under conventional and irradiation method. The effect of various catalytic medium, solvents and operational condition are discussed for obtaining the best yield. A comparative account of various reaction pathways like one-pot synthesis (Multicomponent reaction) and the multistep reaction of coumarin and indoles are discussed.

INTRODUCTION: Coumarins belong to a large family of heterocyclic compounds with a benzo-a-pyrone moiety, of natural and synthetic origin. Coumarin is the most representative molecule are widely distributed in plants like tonka bean (Dipteryx odorata Wild). It has been extensively used in biochemical and pharmaceutical fields [1].

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Dicoumarol is a naturally occurring anticoagulant, was discovered in moldy, wet sweet-clover hay [2]. Osthole was found in Cnidium monnieri, and scoparone was found in Artemisia scoparia both have potential pharmacological properties including immune suppression and vasorelaxation [3, 4] **Fig. 1**.

Coumarins have attracted strong scientific interest over the past decades, stemming from their wide spectrum of pharmacological activities, such as antidepressants, [5] antimicrobials, [6] anti-oxidants, [7] anti-inflammatories, [8] antinociceptives, [9] anti-tumor agents, antiasthmatics, [10] antivirals (including anti-HIV) [11] and anti-coagulants [12].

Zacharski *et al*., demonstrated a beneficial effect of warfarin in cancer patients leading to prolonged survival [13]. These derivatives have also been shown to be lipid-lowering agents that possess moderate triglyceride-lowering activity [14]. Some reviews have recently summarized many important medicinal properties of coumarin and its derivatives [15]. Furthermore, coumarins are used as lipid-lowering agents with moderate triglyceride lowering activity. The hydroxycoumarins are powerful chain-breaking antioxidants and prevent free radical injury by scavenging reactive oxygen species [16]. Their capacities for inhibition of aromatase are useful in preventing the emergence of menopause-related diseases, *i.e.*, osteoporosis, increased risk of cardiovascular events/heart disease and cognitive deficiencies [16].

Coumarins also show optical properties, including an extended spectral response, high quantum yields, and superior photostability. The optical applications of these compounds also been investigated, such as safer laser dyes, nonlinear optical chromophores, fluorescent whiteners, fluorescent probes, polymers, optical recording, and solar energy collectors [17]. Moreover, these heterocyclic compounds containing coumarin moieties are widely found as additives in food, in cosmetic products, as pharmaceutical agents [18] and in luminescent materials [19].

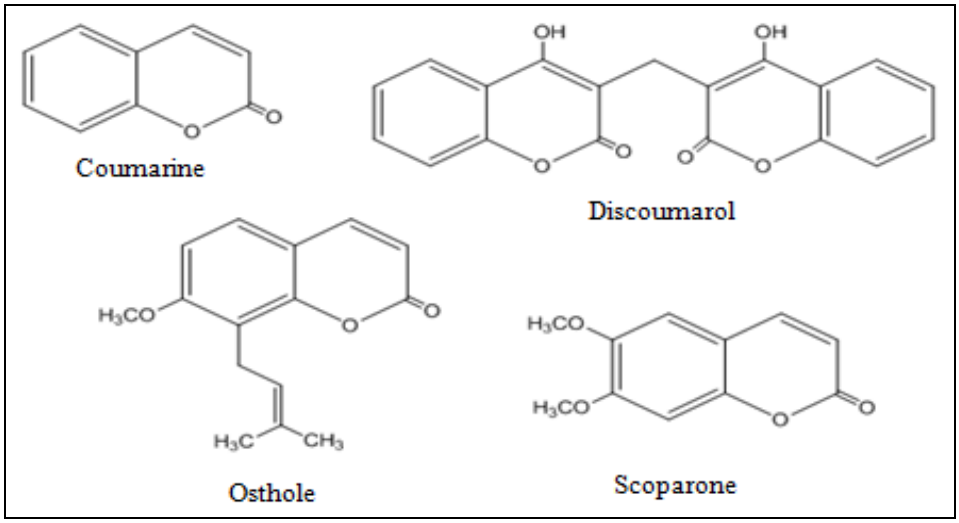


FIG. 1: EXAMPLE OF BIOLOGICALLY ACTIVE COUMARIN BEARING COMPOUNDS

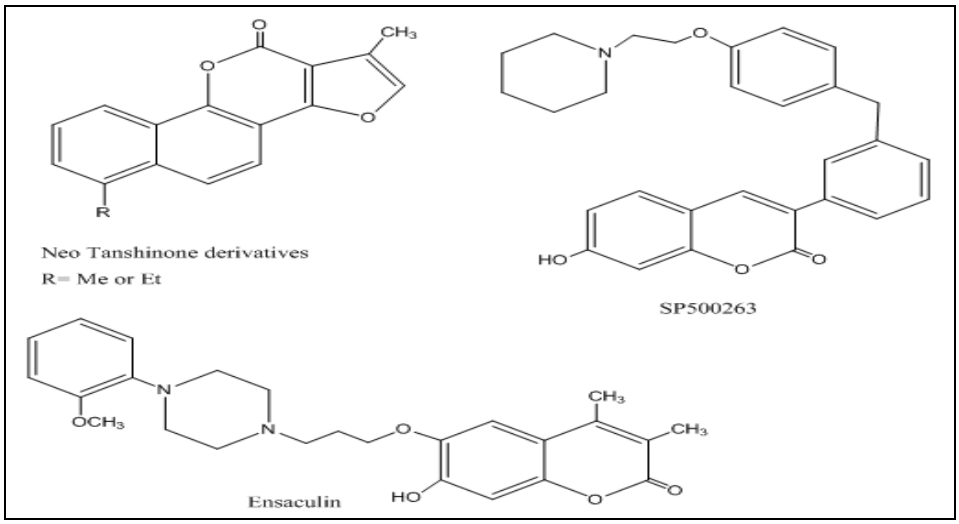


FIG. 2: EXAMPLE OF PHARMACOLOGICALLY ACTIVE COUMARIN BEARING COMPOUNDS

Compounds containing two or more heterocycles play a vital role in natural and synthetic bioactive compounds [20]. In this review, many examples of biologically active coumarins containing hetero-cycles have been cited. The incorporation of another heterocyclic moiety, either as a substituent group or as a fused component into coumarin, creates a change in the properties of the parent

material. The resulting compounds may generally demonstrate promising or even unprecedented properties.

For example, neo-anshinlactone, a component isolated from an ethanolic extract of Salviamiltiorrhiza, was 10-fold more potent and 20-fold more selective against breast cancer cells than tamoxifen [21]. SP500263, a coumarin derivative with piperidine-ethoxy-benzyl side-chain at C-4, bound with high affinity to both estrogen receptor a and b, and functions as a potent antiestrogen in *in-vitro* and *in-vivo* models of breast cancer [22]. Ensaculin, a coumarin with a piperazine moiety was identified as a unique compound profile of pharmacodynamics effects on the central nervous system and has been tagged as potential support in the treatment of dementia **Fig. 2**. [23]

The synthesis of 3-benzyl substituted 4-hydroxycoumarins got much attention in recent years, owing to their tremendous application in various research fields including biological sciences and medicinal chemistry. 3-benzyl substituted 4-hydroxycoumarin derivatives are a component of numerous natural products like warfarin, phenprocoumon, coumatetralyl, carbochromen, bromadiolone, **Fig. 3** are also shows a widespread biological activities [24].

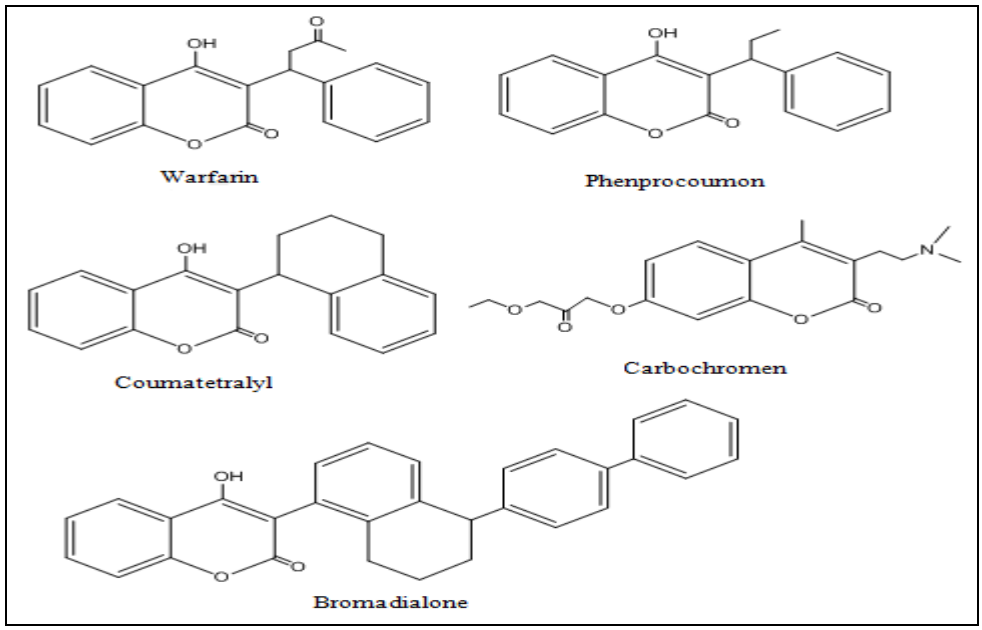


FIG. 3: BIOLOGICALLY ACTIVE 3- SUBSTITUTED COUMARINS

Methods for Synthesis of Coumarin Derivatives: A variety of methods have been developed for the construction of coumarin and indole framework in which inter or intramolecular C-O and C-C bond are formed for engagement of different group in these heterocycles.

Synthesis of Coumarin using Phenol: A mixture or Ethyl acetoacetate & bismuth chloride as catalyst and ethanol as a solvent were taken in an iodine flask and stirred for 12 h on the Magnetic stirrer. The reaction mixture was poured into crushed ice precipitate separated which is then filtered, dried and recrystallized by ethanol. The reaction was monitored by TLC, and the melting point of the recrystallized sample was determined [25].

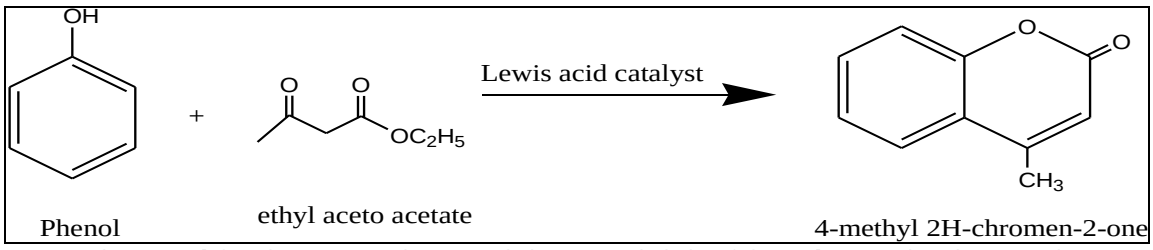
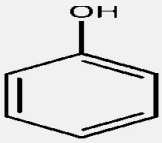
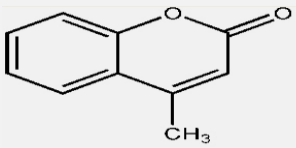
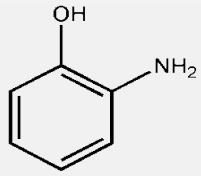
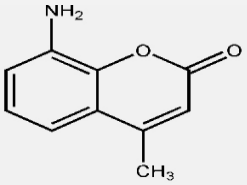


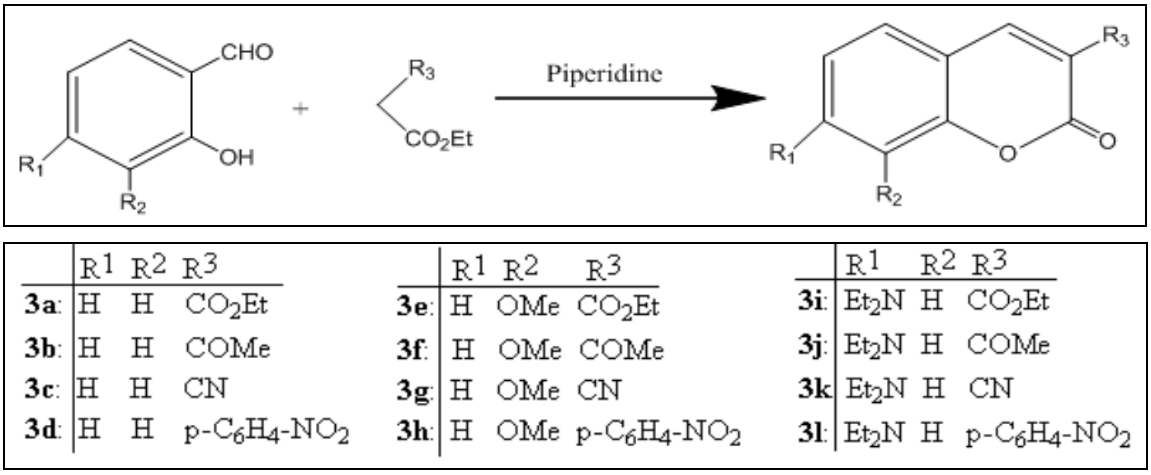
FIG. 4: REACTION REPRESENTING SYNTHESIS OF COUMARIN USING PHENOL

TABLE 1: SYNTHESIS OF COUMARIN *VIA* VON-PACHMANN CONDENSATION OF PHENOL WITH β–KETOESTERS INDUCED BY BICL3 CATALYST AND SOLVENT

S. no.	Substrate	Time (h)	[a] product	m.p.	% yield
1	 Phenol	12	 4-methyl 2H-chromem-2-one	78 ºC	86
2	 2-Amino-phenol	12	 8-Amino-4-methyl-chromen-2-one	145-149 ºC	71.57

Synthesis of Coumarin from Salicylaldehyde: The knoevenagel condensation can be successfully used for the synthesis of coumarin by a solvent free reaction under microwave irradiation.

The coumarins were synthesized by the condensation of salicylaldehyde or its derivative with various derivatives of ethyl acetate in the presence of piperidine [26, 27].



	R1	R2	R3
3a	H	H	CO_2Et
3b	H	H	COMe
3c	H	H	CN
3d	H	H	p-C_6H_4-NO_2

	R1	R2	R3
3e	H	OMe	CO_2Et
3f	H	OMe	COMe
3g	H	OMe	CN
3h	H	OMe	p-C_6H_4-NO_2

	R1	R2	R3
3i	Et_2N	H	CO_2Et
3j	Et_2N	H	COMe
3k	Et_2N	H	CN
3l	Et_2N	H	p-C_6H_4-NO_2

FIG. 5: SYNTHESIS SCHEME OF COUMARINS *VIA* CONDENSATION OF SALICYLALDEHYDE OR ITS DERIVATIVE WITH VARIOUS DERIVATIVE OF ETHYL ACETATE IN THE PRESENCE OF PIPERIDINE

TABLE 2: RESULT OF THE COUMARINS SYNTHESIS BY KNOEVENAGEL REACTION UNDER MICROWAVE IRRADIATION

Compound	Temp. (C)	Yield (%)	m.p.(°C)
3a	129	89	91-92
3b	90	94	120-122
3c	201	76	182-184
3d	220	85	274-275
3e	131	72	89-91
3f	r.t.	90	167-169
3g	r.t.	90	224-225
3h	90	78	294-296
3i	220	55	80-82

The solvent-free condition under microwave irradiation offers advantages over expensive, toxic, difficult to remove in the case of aprotic dipolar solvent with high boiling point Solvent are often environment polluting agent. The resulted compound is shown in **Table 2** produced with good yield under room temperature reaction condition. All compounds were identified by GC/MS, IR, NMR, and gave satisfactory result in comparison with authentic samples. Melting points are in good agreement with literature data.

Synthesis of Substituted Coumarins by Knoevenagel Condensation of 2-hydroxybenzaldehydes:

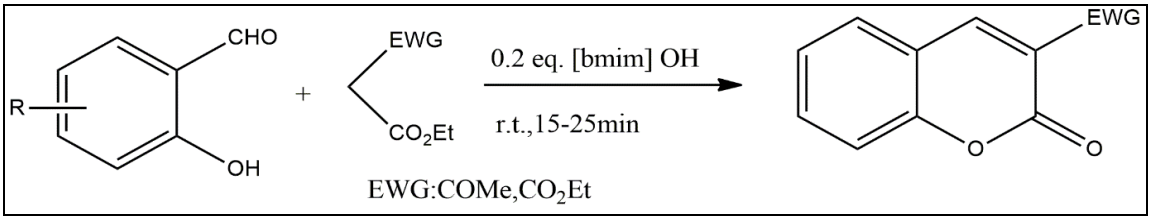


FIG. 6: SYNTHESIS SCHEME OF SUBSTITUTED COUMARINS DEVELOPED BY KNOEVENAGEL CONDENSATION OF 2-HYDROXYBENZALDEHYDES REACTS WITH KETONES OR ALDEHYDE

The basic ionic liquid 1-butyl-3-methyl-imidazolium hydroxide, [bmim]OH, efficiently catalyzes the knoevenagel condensation of different aliphatic and aromatic aldehydes and ketones with active methylenes group at room temperature without the requirement of any organic solvent in THF reflux [28].

The ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate has also been used for knoevena-gel condensation of aldehydes or ketones with active methylene compound catalyzed by ethylene-diammonium diacetate (EDDA). The catalyst and solvent can be recycled [29].

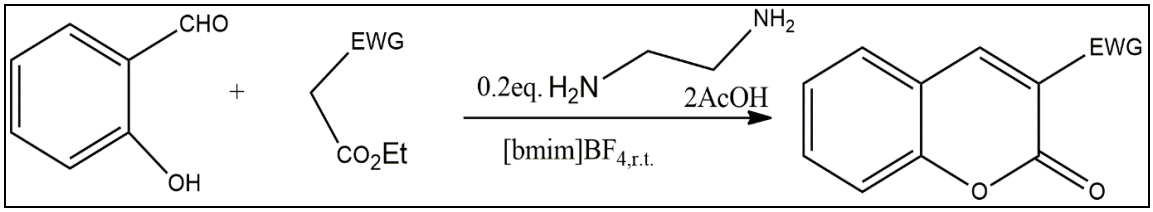


FIG. 7: SYNTHESIS SCHEME OF COUMARINS USING HYDROXYL BENZALDEHYDE AND KETONES CATALYSED BY EDDA

The synthesis of 4- carboxyalkyl- 8- formyl coumarins have also been developed with the reaction of 2-hydroxybenzaldehydes and triphenylphosphine and dialkyl acetylene dicarboxylate [30].

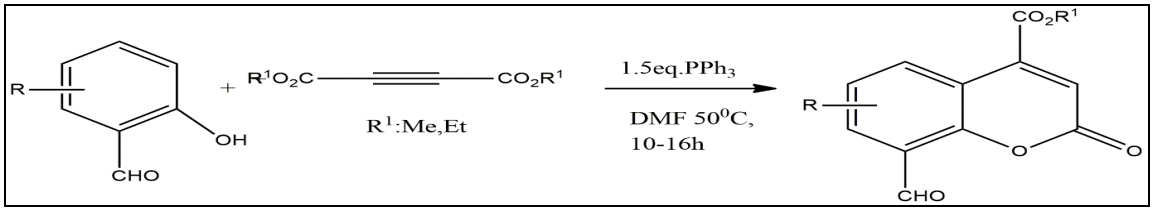


FIG. 8: SYNTHESIS SCHEME OF 4-CORBOXYALKYL-8-FORMYL COUMARINS

Synthesis of Coumarins Derivatives using Different Solvents:

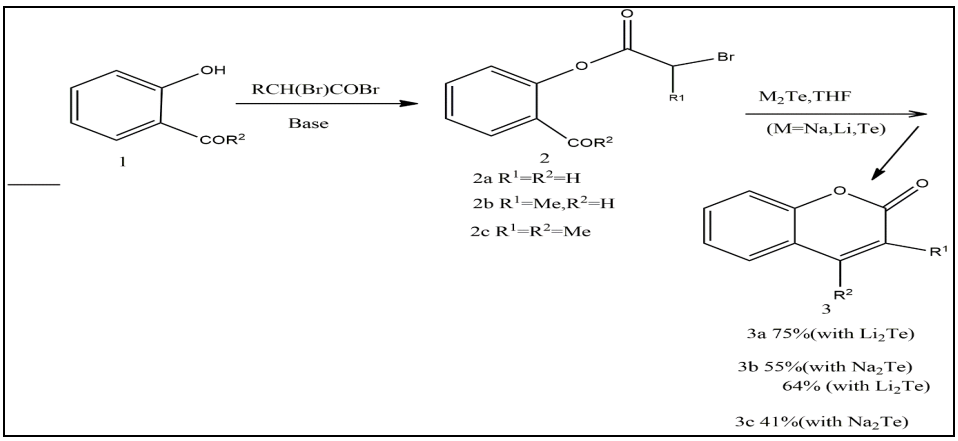


FIG. 9: SYNTHESIS SCHEME OF COUMARINS

The sodium and lithium telluride-triggered cyclization of bromoacetate of salicylaldehyde to coumarin. The change of the telluride counter ion from sodium to lithium reduced reaction times and increases the yield of coumarin to 75%. [31, 32]

TABLE 3: SOLVENT EFFECTS ON YIELD OF COUMARINS 3A (FIG. 9) *VIA* SODIUM OR LITHIUM TELLURIDE

Entry	Solvent	T (°C)	Time (hour)	Telluride	% Yield
1	DMF	-20 to rt	2	Na_2Te	trace
2	THF	-20 to rt	16	Na_2Te	11-23
3	Benzene-THF (19:1)	6 to rt	16	Na_2Te	46
4	Ether-THF (9:1)	-20 to rt	24	Na_2Te	45
5	THF	-78 to rt	1.5	Li_2Te	75

One-Pot Synthesis of Coumarin:

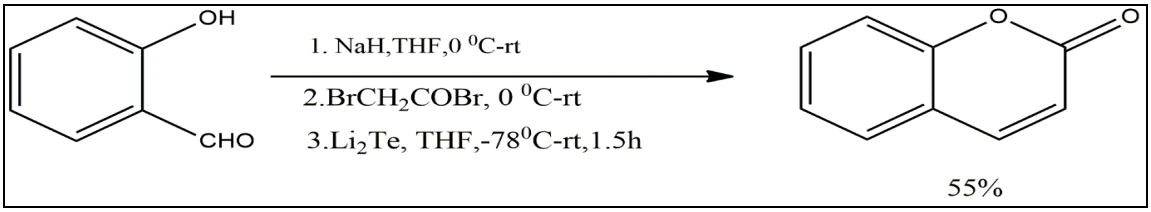


FIG. 10: REACTION SCHEME FOR ONE-POT SYNTHESIS OF COUMARIN USING BENZALDEHYDE

The use of cyanuric chloride (TCT) [2, 4, 6-trichloro-1, 3, 5-triazine] and N-methyl morpholine (NMM) enables an efficient and general protocol for rapid synthesis of substituted 3-aryl coumarins. A series of substituted phenylacetic acids have been successfully reacted with substituted 2-hydroxybenzaldehydes to give an excellent yield of 3-aryl coumarins [33].

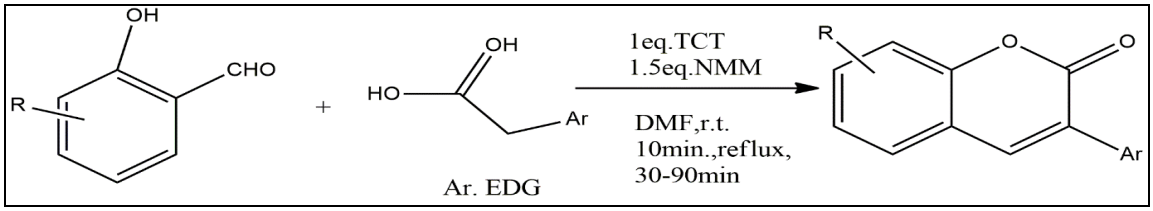


FIG. 11: SYNTHESIS SCHEME OF COUMARINS *VIA* REACTION OF PHENYLACETIC ACIDS AND SUBSTITUTED SALICYLALDEHYDE

Synthesis of 4-Hydroxycoumarins: Ring-closing metathesis and one-pot synthesis of coumarins from the corresponding o-carbonylphenols [34, 35]

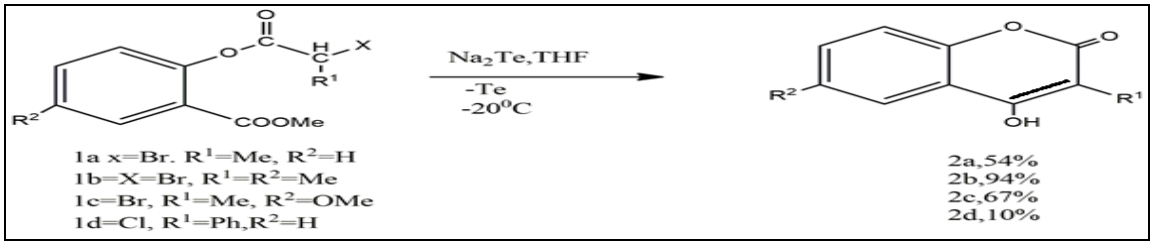


FIG. 12: REACTION SCHEME OF 4-HYDROXYCOUMARINS

Synthesis of Coumarins from Cinnamic Acid:

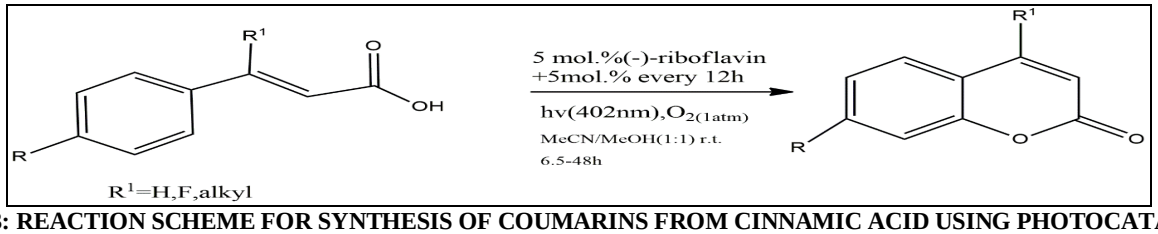
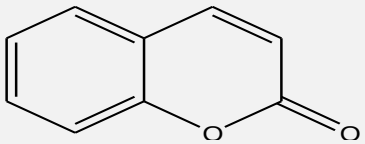
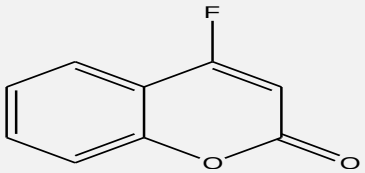
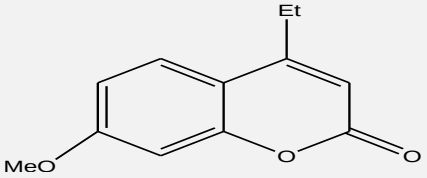
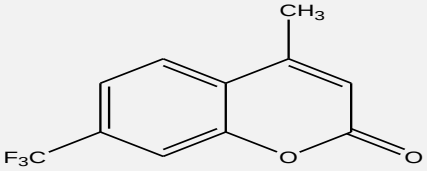
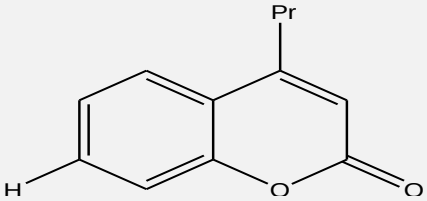


FIG. 13: REACTION SCHEME FOR SYNTHESIS OF COUMARINS FROM CINNAMIC ACID USING PHOTOCATALYST

The one-pot synthesis of coumarin using two photochemical and photocatalyst activation modes of (-) –riboflavin sequentially include isomerization and cyclization by energy transfer (ET) and single-electron transfer (SET) activation pathways in an emulation of coumarin biosynthesis pathway via a key photochemical E-Z isomerization step I this reaction the substituted propyl group and low time product will be highest [36].

TABLE 4: SUBSTITUTION, PRODUCT, AND YIELD OF COUMARINS FROM CINNAMIC ACID

R^1	R	Product	Time (h)	% Yield
H	H		13.5	79
F	H		48	77
Et	OMe		10	81
CF_3	CH_3		48	48
Pr	H		13.5	91

Synthesis of Coumarins from Phenyl Acetate: An efficient annulations of phenolic acetates with acrylates, in the presence of $[Rh_2(OAc)_4]$ as a catalyst and formic acid as reducing agent provides a high yield of coumarin derivatives *via* C-H bond activation. The yield of the product was increased by the addition of NaOAc as a base. The reaction is instantly successful for both electron-rich, and electron-deficient phenolic acetate gives coumarins with excellent regioselectivity [37].

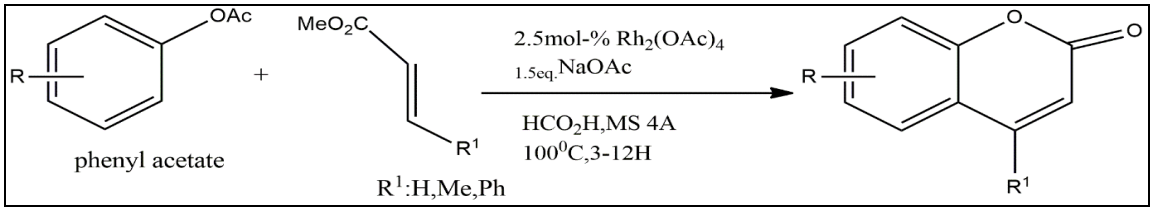


FIG. 14A: SYNTHESIS SCHEME OF COUMARIN FROM PHENOLIC ACETATES REACTION WITH ACRYLATES IN EXISTENCE OF CATALYST

Synthesis of Coumarins from 2-hydroxy-styrenes: In this one-pot synthesis reaction, a direct carboxylation of alkenyl C-H bond of 2-hydroxystyrenes in the presence of catalyst $Pd(OAc)_2$ and Cs_2Co_3 under atmospheric pressure of CO_2 gives coumarins in excellent yield. The reaction undergoes a reversible nucleophilic addition of the alkenyl palladium intermediate to CO_2. [38]

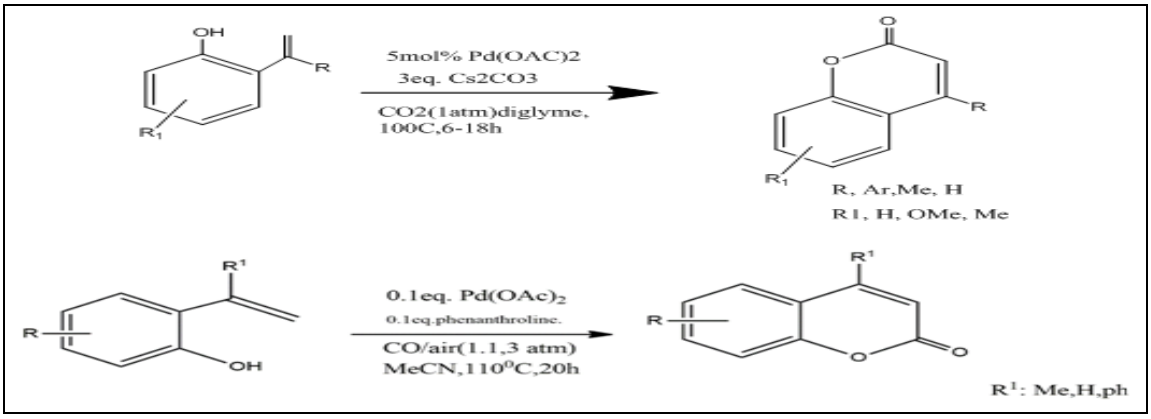


FIG. 14B: SYNTHESIS SCHEME OF COUMARINS FROM 2-HYDROXYSTYRENES TAKING Pd AS CATALYST

The direct synthesis of various coumarin derivatives *via* palladium-catalyzed oxidative cyclocabonylation of 2-vinylphenols in the presence of low pressures of CO, and air or 1, 4-benzoquinone as the oxidant gives a good yield. The reaction is environmentally benign in terms of condensations and operational simplicity [39].

Three-Components Synthesis of Coumarin Derivatives:

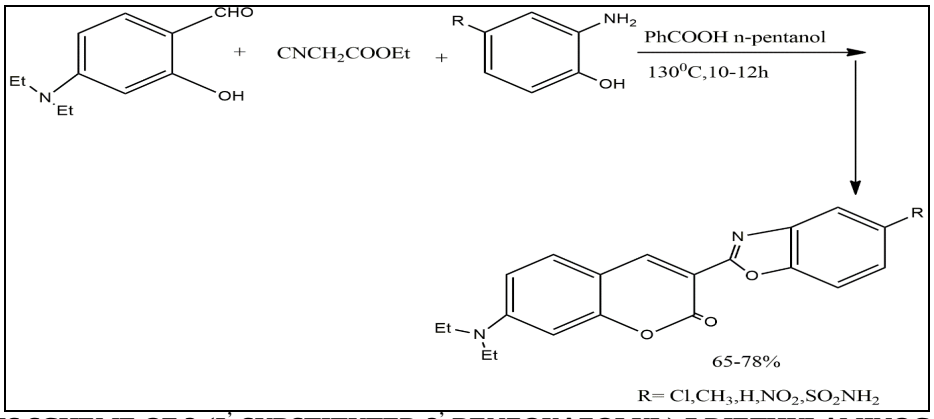


FIG. 15: SYNTHESIS SCHEME OF 3-(5'-SUBSTITUTED-2'-BENZOXAZOLYL)-7-DIETHYLAMINOCOUMARINS FROM 4-DIETHYLAMINOSALICYLALDEHYDE, ETHYL CYNOACETATE, AND 4-SUBSTITUTED-2-AMINOPHENOL WITH PENTANOL CONTAINING BENZOIC ACID, REFLUXED FOR 10-12h

These multicomponent reaction (MCR) was conducted with equimolar amounts of starting compounds taking benzoic acid as catalyst and n-pentanol as a solvent with the oil bath temperature at 138 °C for 12 h. The isolated yield is represented in **Table 5**. The purity is obtained from HPLC analysis after recrystallization. The UV-Vis spectra were observed in methanol [40].

TABLE 5: R SUBSTITUTION AND THEIR RESPECTIVE YIELD WITH λ_{max} (UV-VIS)

Entry	R	Yield	Purity (%)	λ_{max} (nm)
1	-Cl	65	99.9	451
2	$-CH_3$	78	99.23	446
3	-H	68	98.92	442
4	$-NO_2$	64	99.20	454
5	$-SO_2NH_2$	66	98.77	435

Methods for Synthesis of Indole Derivatives:

Synthesis of Indoles from 2-iodobenzoic Acid and Alkynes: These reactions are based on a multi-component process that follows the transformation of readily available one-pot curtius rearrangement palladium-catalyzed indolization process **Fig. 16**. In this reaction, the 2-iodoaniline intermediate is not isolated and produces a by-product via curtius rearrangement. The formation of 2, 3-dipropyl-1*H*-indole using a one-pot curtius-indolization process starting from 2-iodobenzoic acid. This substrate was treated under the standard Curtius reaction

conditions, which allows the direct conversion of aromatic carboxylic acids into carbamates and ureas [41]. The CBz protected aniline intermediate was not isolated, but directly reacted with the palladium-catalyzed indolization reaction condition. But a disappointing 29% low yield of the desired indole derivative was obtained when the standard reaction conditions for indolization (including one equivalent of LiCl) were used (**Table 6**, entry 1). Formerly it has been shown that an excess of a chloride salt in the reaction is detrimental for palladium-catalyzed hetero-annulations [42] After optimization conditions, three equivalents of sodium carbonate proved to be the best base and gives 84 % excellent yield (compare **Table 6**, entries 2–4 and 5-6) [43].

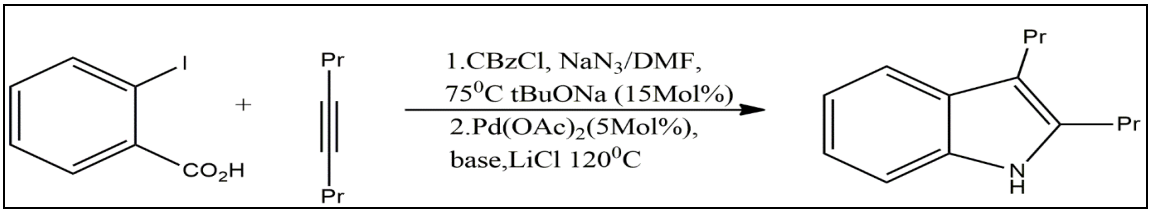


FIG. 16: ONE-POT MULTICOMPONENT SYNTHESIS SCHEME OF INDOLES FROM 2-IODOBENZOIC ACID

TABLE 6: ONE-POT CURTIUS REARRANGEMENT- PALLADIUM-CATALYZED INDOLIZATION STARTING FROM 2-IODOBENZOIC ACID AND 4-OCTYNE

Entry	LiCl	Base (equiv)	Alkyne(equiv)	Yield (%)
1	yes	K_2CO_3 (5.0)	5.0	29
2	no	Na_2CO_3 (1.5)	1.5	71
3	no	K_2CO_3 (1.5)	1.5	73
4	no	Cs_2CO_3 (1.5)	1.5	40
5	no	Na_2CO_3 (3.0)	3.0	84
6	no	K_2CO_3 (3.0)	3.0	73

One-Pot Three-Component Synthesis of Indoles:

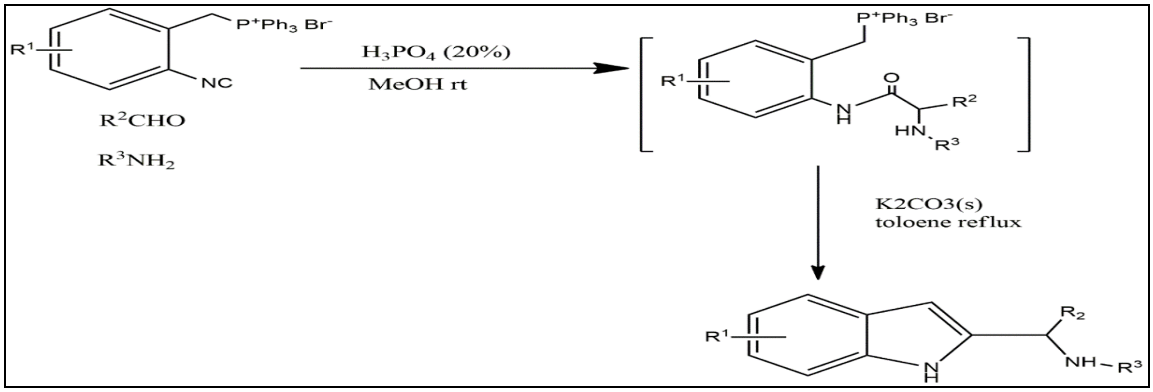
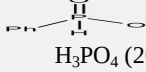


FIG. 17: ONE-POT REACTION SCHEME OF INDOLES FROM 2-ISOCYANOBENZYL TRIPHENYL-PHOSPHONIUM BROMIDES, ALDEHYDES AND AMINES

In such reactions, where p-toluene sulfonic acid was utilized, the yields of entries 6 and 7 **Table 7** was obtained low to 40-50%. When catalyst was used up to 10% resulted in a rather lower yield (44%, entry5). While for entry 4 **Table 7** the yield was increased by 72%. When an aromatic aldehyde or amine (R2 or R3=aryl) was used, a good yield of the products was obtained [44].

A green multicomponent one-pot synthesis of 2-(1H-indol-3-ylmethyl)-5, 5-dimethyl-cyclohexane-1,3-diones was conveniently carried out in an aqueous medium at room temperature over heterogeneous catalyst as mpCuO, produces excellent yields.

TABLE 7: OPTIMIZATION OF THE REACTION CONDITIONS

Entry	Catalyst (%)	Yield (%)
1	-	0
2	$FeCl_3$ (20)	0
3	 (20)	0
4	H_3PO_4 (20)	72
5	H_3PO_4 (10)	44
6	TsOH (20)	57
7	TsOH (20)	40

The highly catalytic, maximum surface area and recyclability features make mpCuO a suitable catalyst. The *in-vitro* antitubercular examination has verified that these compounds are used to generate reliable antitubercular analogs with better selectivity. The porous nano-catalyst has been recycled five times without a significant drop in product yield [45-47].

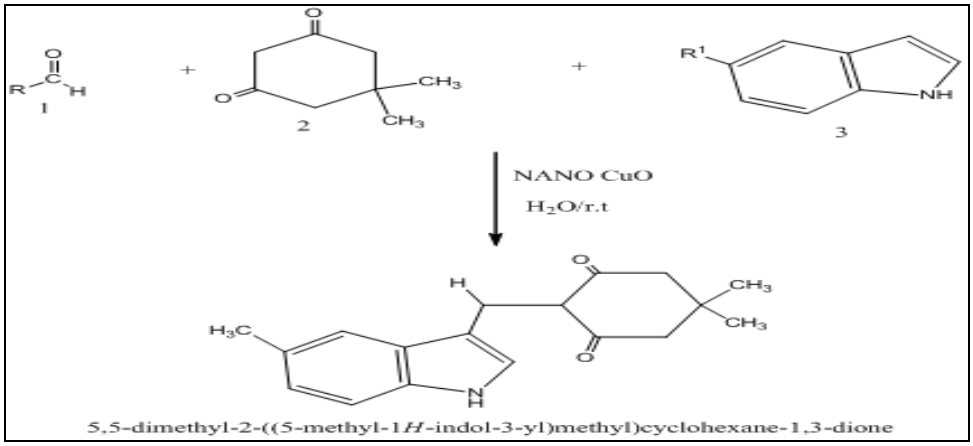


FIG. 18: ONE-POT THREE COMPONENT REACTION SCHEME OF INDOLE DERIVATIVES FROM INDOLE, ALDEHYDE AND DIMEDONE CATALYSED WITH GREEN MESOPOROUS CuO

TABLE 8: REACTION CONDITION FOR WATER MEDIATED ONE-POT SYNTHESIS OF 2-1H-(INDOLE-3-YLMETHYL)-5, 5-DIMETHYL-CYCLOHEXANE-1, 3-DIONES

Entry	R	R^1	Time(min)	Temp (°C)	(%) yield isolated	m.p.(°C)
1	p-ClC_6H_5	H	20	rt	96	133-136
2	C_6H_5	H	15	rt	91	141-144
3	m-$NO_2C_6H_5$	H	23	rt	85	139-142
4	p-$NO_2C_6H_5$	H	20	rt	89	127-130
5	p-$OMeC_6H_5$	H	22	rt	95	152-155
6	CH_3	H	17	rt	82	135-138
7	p-ClC_6H_5	Br	23	rt	90	146-149
8	C_6H_5	Br	19	rt	83	139-142
9	m-NO2C_6H_5	Br	27	rt	85	126-129
10	p-$NO_2C_6H_5$	Br	23	rt	88	162-165
11	p-$OMeC_6H_5$	Br	31	rt	91	169-172
12	CH_3	Br	20	rt	78	144-147

[rt]Room temperature

Synthesis of Substituted Indoles: These reactions were based on N-methyl indole, a substituted benzaldehyde, and N-methylaniline. The reaction conditions were optimized by monitoring a model reaction between substituted indole, 4-chloro-benzaldehyde or 4-methoxy benzaldehyde and N-methylaniline. The acetonitrile solvent was found to be more efficient reaction media and using $Yb(OTf)_3$-SiO_2 as a catalyst, gives good yield (88%) while the reaction yield investigated in other solvents and other catalyst was very poor [48].

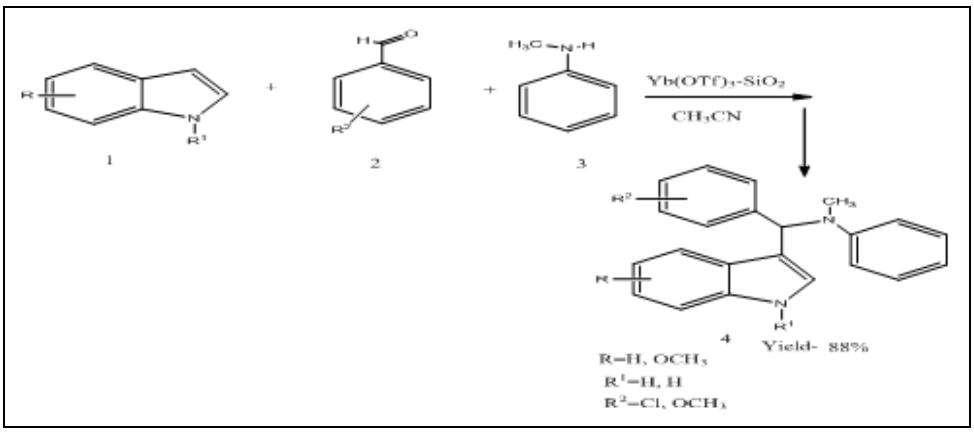


FIG. 19: ONE-POT THREE COMPONENT COUPLING REACTION SCHEME OF 3-SUBSTITUTED INDOLES

The 3-substituted indoles are structural units of many natural and biologically interesting compounds, which possess various pharmacologically activities. The indole-based derivatives have been investigated for anticancer activities [49].

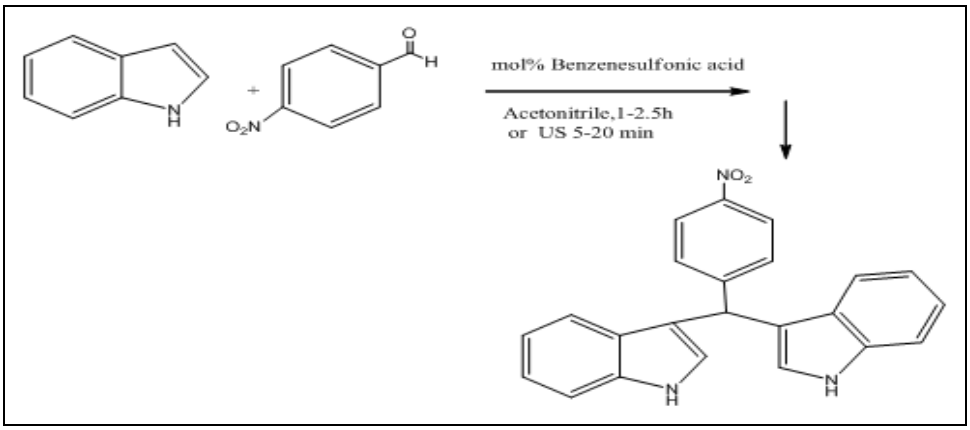


FIG 20: SYNTHESIS SCHEME OF BIS (INDOLYL) METHANE DERIVATIVES CATALYSED BY BENZENESULFONIC ACID AND ACETONITRILE UNDER CONVENTIONAL AND IRRADIATION METHOD

TABLE 9: THE REACTION OF INDOLE WITH 4-NITROBENZALDEHYDE IN THE PRESENCE OF DIFFERENT CATALYST AND EFFECT OF SOLVENTS IN THIS REACTION CATALYZED BY BENZENESULFONIC ACID

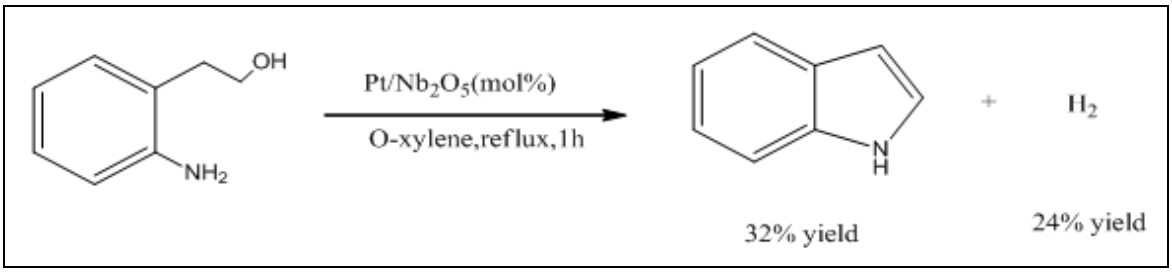
Entry	Solvents[a]	Catalyst[b]	Time(h)	Yield(%)[b]	Time(h)	Yield (%)[ac] [Solvents and $C_6H_5SO_3H$]
1	H_2O	$C_6H_5SO_3H$[c]	0.25	95	16	48
2	MeOH	$Cu(OTf)_2$	3	90	19	60
3	EtOH	$LiClO_4$	12	30	22	65
4	THF	$FeCl_3$	12	59	06	85
5	CH_3CN	$KHSO_3$	13	60	01	95
6	DCM	Sulphamic acid	10	67	18	53

The reaction of indole with the 4-Nitrobenzaldehyde compound in the presence of 5-mol% benzene-sulfonic acid in acetonitrile solvent performed to synthesize 3,3''-((4-Nitrophenyl) methylene) bis (1H-indole) compound is observed that the reaction proceeded in shorter reaction times and times and in high yield in the ultrasonic method than compare to the conventional method. Its synthesized compound was tested for antioxidant activity. Synthesized compound characterized by ^{1}H NMR, ^{13}C NMR, and Mass spectroscopy.

TABLE 10: EFFECT OF CONCENTRATION OF BENZENESULFONIC ACID ON REACTION OF INDOLE WITH 4-NITROBENZALDEHYDE

Entry	Mole % of catalyst	Time (min)	Yield (%)
1	1	45	41
2	2.5	30	69
3	5	15	95
4	10	15	95
5	15	15	95

Synthesis of Indole 2-(2-aminophenyl) Ethanol:



The using Pt/Nb_2O_5 and Pt/HBEA as two of the effective catalysts for this reaction, we carried out detailed catalytic studies. For Pt/Nb_2O_5.

The yield of indole increased with time and reached 93% after 7 h. For Pt/HBEA, the yield of indole reached 95% after 12 h. [50]

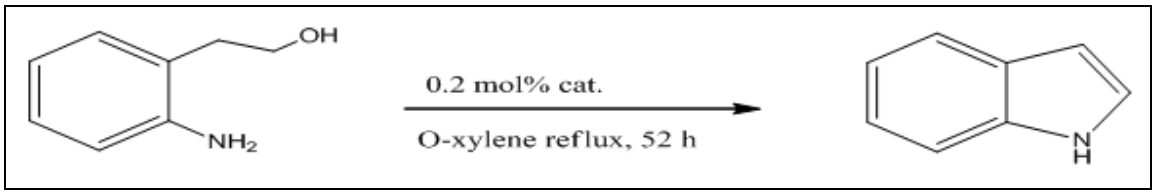


FIG. 21: SYNTHESIS SCHEME OF INDOLE FORM 2(2-AMINOPHENYL) ETHANOL

TABLE 11: HETEROGENEOUS Pt CATALYSTS, GC YIELD, AND TURNOVER NUMBER (TON)

Cat.	GC yield	TON
Pt/Nb_2O_5	76%	380
Pt/HBEA	90%	450

The reactions with 0.2 mol% of Pt/Nb_2O_5 and Pt/HBEA as two of the effective catalysts for this reaction, we carried out 52 h. A green and environmentally benign protocol for electrophilic substitution reaction of indole derivatives with various aldehydes in the water taking squaric acid catalyst provides good yield [51, 52].

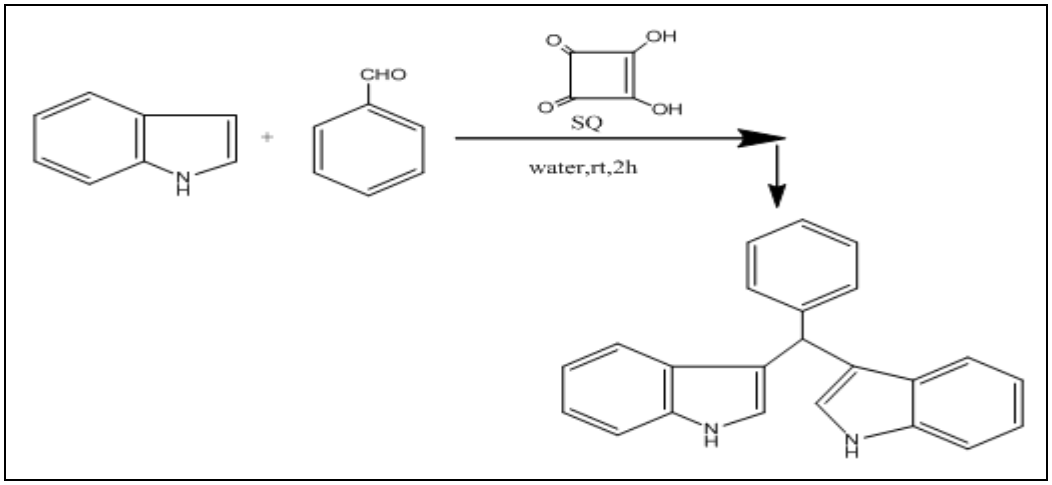


FIG. 22: SYNTHESIS SCHEME OF BIS (INDOLYL) METHANE IN WATER FOR GREEN PROCEDURE

TABLE 12: COMPARISON OF THE CATALYTIC EFFICIENCY OF VARIOUS CATALYSTS REPORTED

Entry	Catalyst	Condition	% Yield
1	$ZrOCl_2$	CH_3CN/rt	89
2	$Al(HSO_4)_3$	EtOH	92
3	$LiCl_4$	CH_3/rt	90
4	$Dy(OTf)_3$	IL	98
5	$NbCl_5$	MeOH	98
6	HBF_4-SiO_2	Neat/rt	94
7	SQ	H_2O	90

CONCLUSION: This review summarizes recent advances in the synthesis of pharmacologically important coumarin and indole heterocyclic derivatives. Over past decades, synthesis of coumarins and indoles fused or linked with different heterocycle derivatives has been gaining importance because of their medical chemical and biological applications. The present review is emphasized on the innovative synthesis scheme of substituted coumarin and indoles via green techniques and harmless chemical. Although, this review describes the interesting, green and efficient syntheses strategy of coumarin and indole derivatives to obtaining good yield in less time. But shortly new eco-compatible protocols are strongly expected.

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REFERENCES:

1. Witaicenis A, Seito LN, Chagas DSA, de Almeida LD, Luchini AC, Rodrigues-Orsi P, Cestari SH and Di Stasi LC: Antioxidant and intestinal anti-inflammatory effects of plant-derived coumarin derivatives. Phytomedicine 2014; 21(3): 240-46.
2. Fiorito S, Epifano F, Taddeo VA and Genovese S: Ytterbium triflate promoted coupling of phenols and propiolic acids: synthesis of coumarins. Tetrahedron Letters 2016; 57(29): 2939-42.
3. Yao L, Lu P, Li Y, Yang L, Feng H, Huang Y, Zhang D, Chen J and Zhu D: Osthole relaxes pulmonary arteries through endothelial phosphatidylinositol 3-kinase/Akt-eNOS-NO signaling pathway in rats. European Journal of Pharmacology 2013; 699: 23-32.
4. Chavan SS, Pavlov VA and Tracey KJ: Mechanisms and Therapeutic Relevance of Neuro-immune Communication. Immunity 2017; 46(6): 927-42.
5. Sashidhara KV, AK, Chatterjee M, Rao KB, Singh S, Verma AK and Palit G: Discovery and synthesis of novel 3-phenylcoumarin derivatives as antidepressant agents Bioorg. Med. Chem. Letters 2011; 21(7): 1937-41.
6. Sahoo J, Mekap SK and Paideswtty SK: Synthesis, spectral characterization of some new 3-heteroaryl azo 4-hydroxy coumarin derivatives and their antimicrobial evaluation. Journal of Taibah University for Science 2018; 9(2): 187-95.
7. Xi GL and Liu ZQ: Coumarin-Fused Coumarin: Antioxidant Story from N, N-Dimethylamino and Hydroxyl Groups J. Agric. Food Chemistry 2015; 63(13): 3516-23.
8. Sethi P, Bansal Y and Bansal G: Synthesis and PASS-assisted evaluation of coumarin–benzimidazole derivatives as potential anti-inflammatory and anthelmintic agents. Medicinal Chemistry Research 2018; 27(1): 61-71.
9. Cheriyan BV, Kadhirvelu P, Nadipelly J, Shanmuga-sundaram J, Sayeli VK and Subramanian V: Anti-nociceptive effect of 7-methoxy coumarin from eupatorium triplinerve. Pharmacogn Mag. 2017; 13(49): 81-84.
10. Sanchez-Recillas A, Navarrete-Vazquez G, Hidalgo-Figueroa S, Rios MY, Ibarra- Barajas M and Estrada SS: Semi synthesis, ex vivo evaluation, and SAR studies of coumarin derivatives as potential antiasthmatic drugs. Eur J Med Chemistry 2014; 77: 400-8.
11. Tang J, Jones SA, Jeffrey JL, Miranda SR, Galardi CM, Irlbeck DM, Brown KW, McDanal CB and Johns BA: Discovery of a novel and potent class of anti-HIV-1 maturation inhibitors with improved virology profile against gag polymorphisms. Bioorganic and Med Chem Letters 2017; 27(12): 2689-94.
12. Peng XM, Damu GL and Zhou C: Current Developments of Coumarin Compounds in Medicinal Chemistry. Current Pharmaceutical Design 2013; 19: 3884-30.
13. Frouws MA, van Herk-Sukel MPP, Maas HA, Van de Velde CJH, Portielje JEA, Liefers GJ and Bastiaannet E: The mortality reducing effect of aspirin in colorectal cancer patients: Interpreting the evidence. Cancer Treatment 2017; 55: 120-27.
14. Jain MR, Giri SR, Trivedi C, Bhoi B, Rath A, Vanage G, Vyas P, Ranvir R and Patel PR: Saroglitazar, a novel PPARα/γ agonist with predominant PPARα activity, shows lipid-lowering and insulin-sensitizing effects in preclinical models. British Pharmacological Society 2015; 3: 136.
15. Pereira, Thiago M, Franco, Portella D, Vitorio, Felipe, Kummerle and Eugen A: Coumarin Compounds in Medicinal Chemistry: Some Important Examples from the Last Years. Current Topics in Medicinal Chemistry 2018; 18: 124-48.
16. Peters R, J Anstey K, Booth A, Beckett N, Warwick J, Antikainen R, Rockwood K, Peters J and Bulpitt JC: Orthostatic hypotension and symptomatic subclinical orthostatic hypotension increase risk of cognitive impairment: an integrated evidence review and analysis of a large older adult hypertensive cohort. European Heart Journal 2018; 39(33): 3135-43.
17. Nian L, Zhang W, Zhu Na, Liu L, Xie Z, Wu H, Würthner F and Ma YJ: Amarican Chemical Society: Photoconductive Cathode Interlayer for Highly Efficient Inverted Polymer Solar Cells. 2015; 137(22): 6995-98.
18. Keri RS, Sasidhar BS, Nagaraj BM and Santos MA: Recent progress in the drug development of coumarin derivatives as potent antituberculosis agents. European Journal of Medicinal Chemistry 2015; 100: 257-69.
19. Wang H and Liu G: Advances in luminescent materials with aggregation-induced emission (AIE) properties for biomedical applications. Journal of Materials Chemistry B 2018; 6(24): 4029-42.
20. Stefanachi A, Leonetti F, Pisani L, Catto M and Carotti A: Coumarin: A Natural, Privileged and Versatile Scaffold for Bioactive Compounds. Molecules 2018, 23(2): 250.
21. Costa A, Kieffer Y, Scholer-Dahirel A, Pelon F, Bourachot B, Cardon M, Parrini M-C, Soumelis V, Vincent-Salomon A and Mechta-Grigoriou F: Fibroblast Heterogeneity and Immunosuppressive Environment in Human Breast Cancer. Cancer Cell 2018; 33(3): 463-79.
22. Lecomte S, Demay F, Ferrière F and Pakdel F: Phytochemicals Targeting Estrogen Receptors: Beneficial Rather Than Adverse Effects. International J Mol Science 2017; 18(7): 1381.
23. Nabavi M, Seyed, Habtemariam, Solomon, Daglia, Maria, Braidy, Nady, Loizzo R, Monica, Tundis, Rosa, Nabavi Faze and Seyed: Neuroprotective Effects of Ginkgolide B against Ischemic Stroke. Current Topics in Medicinal Chemistry 2015; 15: 2222-32.
24. Banerjee B: Recent developments on nano-ZnO catalyzed synthesis of bioactive heterocycles. Journal of Nanostructure in Chemistry 2017; 7(4): 389-13.
25. Chaudhari PS and Patil SS: Bismuth (III) chlorides environmentally begin one-pot synthesis of coumarin derivative. International Journal of Engineering Sciences and Research Technology 2016; 5(7): 2277.
26. Bogdal D: Coumarins: Fast Synthesis by Knoevenagel Condensation under Microwave Irradiation. J Chem Research 1998; 468-69.
27. Heinosuke Y and Hiroshi M: The knoevenagel reaction between hydroxybenzaldehydes and ethyl cyanoacetate. Bulletin of the Chemical Society of Japan 1966; 39(8): 1754-59.
28. Ranu BC and Jana R: Ionic liquid as catalyst and reaction medium - a simple, efficient and green procedure for kno-evenagel condensation of aliphatic and aromatic carbonyl compounds using a task-specific basic ionic liquid. Eur J Organic Chemistry 2006; 16: 3767-70.
29. Hu X, Ngwa C and Zheng Q: A simple and efficient procedure for knoevenagel reaction promoted by imidazolium-based ionic liquids cur. Organic Synthesis 2016; 13: 101-10.
30. Mujumdar KC, Ansary I, Samanta S and Roy B: Aromatic electrophilic substitution *vs*. intramolecular wittig reaction: Vinyltriphenylphosphonium Salt Mediated Synthesis of 4-Carboxyalkyl-8-formyl Coumarins. Synthetic organic Chemistry 2011; 694-98.

31. Dittmer DC, Li Q and Avilov DV: Synthesis of Coumarins, 4-Hydroxycoumarins, and 4-Hydroxy-quinolinones by Tellurium-Triggered Cyclizations. J Organic Chemistry 2005; 70: 4682-86.
32. Salem MA, Helal MH, Gouda MA Ammar YA, El-Gaby MSA and Abbas SY: An overview on synthetic strategies to coumarins. Synthetic Communication 2018; 48: 1534-50.
33. Sashidhara KV, Palnati GR, Avula SR and AK: Efficient and General Synthesis of 3-Aryl Coumarins Using Cyanuric Chloride. Science of Synthesis 2012; 23: 611-21.
34. Dittmer DC, Li Q and Avilov DV: Synthesis of Coumarins, 4-Hydroxycoumarins, and 4-Hydroxy-quinolinones by Tellurium-Triggered Cyclizations. J Org Chemistry 2005; 70(12): 4682-86.
35. Schmidt B, Krehl S, Kelling A and Schilde U: Synthesis of 8-Aryl-Substituted Coumarins Based on Ring-Closing Metathesis and Suzuki–Miyaura Coupling: Synthesis of a Furyl Coumarin Natural Product from *Galipea panamensis.* J Organic Chemistry 2012; 77(5): 2360-67.
36. Metternich JB and Gilmour R: One Photocatalyst, n Activation Modes Strategy for Cascade Catalysis: Emulating Coumarin Biosynthesis with (−)-Riboflavin. J Am. Chemical Society 2016; 138: 1040-45.
37. Gadakh SK, Dey S and Sudalai A: Rh-Catalyzed Synthesis of Coumarin Derivatives from Phenolic Acetates and Acrylates via C-H Bond Activation J Organic Chemistry 2015; 80: 11544-50.
38. Sasano K, Takaya J and Lwasawa N: Palladium (II)-Catalyzed Direct Carboxylation of Alkenyl C–H Bonds with CO_2. J Am Chemical Society 2013; 135: 10954-57.
39. Ferguson J, Zeng F and Alper H: Synthesis of Coumarins *via* Pd-Catalyzed Oxidative Cyclocarbonylation of 2-Vinylphenols Organic Letters 2012; 14: 5602-05.
40. Ye FF, Gao JR, Sheng WJ and Jia JH: One-pot synthesis of coumarin derivatives. Dyes and Pigments 2008; 77: 556-58.
41. Lebel H, Leogane O: Curtius Rearrangement of aromatic carboxylic acids to access protected anilines and aromatic ureas. Organic Letters 2006; 8: 5717-20.
42. Iida H, Yuasa Y and Kibayashi C: Intramolecular cyclization of enaminones involving arylpalladium complexes. Synthesis of carbazoles. J Organic Chemistry 1980; 45(15): 2938-42.
43. Leogane O and Lebel H: One-Pot Multicomponent Synthesis of Indoles from 2-Iodobenzoic Acid Angew. Chem. Int Ed 2008; 47: 350-52.
44. Yan YM, Rao Y and Ding MW: One-pot synthesis of indoles by a sequential ugi-3cr/wittig reaction starting from odorless isocyanide-substituted phosphonium salts. J Organic Chemistry 2017; 82: 2772-76.
45. Khan GA, War JA, and Naikoo GA, Pandit UJ and Das R: Porous CuO catalysed green synthesis of some novel 3-alkylated indoles as potent antitubercular agents. Journal of Saudi Chemical Society 2018; 22: 6-15.
46. Bose P, Harit AK and Halder KK: Tuberculosis Still a Way to go ahead for a Lead- A Review. J. Analytical & Pharmaceutical Research 2017; 5(6): 00161-67.
47. Khan GA, Naikoo GA, War JA, Sheikh IA, Pandit UJ, Khan I, Harit AK and Das R: An efficient green synthesis of some functionalized spiro chromene based scaffolds as potential antitubercular agents. J Heterocyclic Chemistry 2018; 55(3): 699-08.
48. Rao VK, Chhikara BS, Shirazi AN, Tiwari R, Parang K and Kumar A: 3-Substituted indoles: One-pot synthesis and evaluation of anticancer and Src kinase inhibitory activities. Bioorg Med Chemistry Letters 2011; 21: 3511-14.
49. Simha PR, Mangali MS, Gari DK, Venkatapuram P and Adivireddy P: Benzenesulfonic Acid: a versatile catalyst for the synthesis of bis(indolyl)methanes as Antioxidants. J Heterocyclic Chemistry 2017; 54(5): 2717-24.
50. Moromi SK, Touchy AS, Siddiki MAHS, Alia A and Shimizu KI: Synthesis of indoles *via* dehydrogenative N-heterocyclization by supported platinum catalysts RSC Advances 2015; 5: 1059-62.
51. Malkania L, Bedi P and Pramanik T: Lactic acid catalyzed and microwave-assisted green synthesis of pharmaceutically important bis(indolyl) methane analogs in an aqueous medium. Drug Invention Today 2018; 10(9): 1740-44.
52. Azizi N, Gholibeghlo E and Manocheri Z: Green procedure for the synthesis of bis(indolyl) methanes in water. Scientia Iranica C 2012; 19(3): 574-78.

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