Ash, Not Alchemy: Testing Bio-Waste Catalysts in Coumarin Synthesis

Pooja Sharma[1], Swarup J. Chatterjee[2]
[1]*S. N. College of Pharmacy, Babupur, Lucknow Road, Jaunpur – 222132, Uttar Pradesh, India (affiliated to Dr. A. P. J. Abdul Kalam Technical University, Lucknow)*
[2]*Professor & Principal, Department of Pharmaceutical Chemistry, S. N. College of Pharmacy, Babupur, Lucknow Road, Jaunpur – 222132, Uttar Pradesh, India.*

***Abstract*—Burn an agricultural residue, extract the ash with water, and you have a cheap alkaline material that will drive a Knoevenagel condensation to coumarins at room temperature. A large and growing literature does exactly this and describes the result as a reusable heterogeneous catalyst. Each of those three words is a separate empirical claim, and each has a standard experiment attached to it that most papers do not report. This review sets out the claims and the tests. Reusable is established by elemental analysis of the filtrate and by comparing fresh with recovered solid, not by five cycles of unchanged yield, which Sheldon and co-workers showed long ago cannot exclude leaching. Heterogeneous is established by a hot-filtration or Sheldon test conducted at reaction temperature; a water extract of ash is a solution of soluble potassium salts and is homogeneous by definition, whatever it is called. Catalytic requires a turnover number, and loadings expressed as percent weight per volume frequently correspond to turnover numbers near unity, which describes a reagent. Green requires an E-factor or process mass intensity rather than the absence of an organic solvent in the reaction step alone. The chemistry constrains the claims further: the Knoevenagel route to coumarin-3-carboxylates is base-catalysed and an alkaline ash is a plausible catalyst for it, whereas the Pechmann route from phenols requires an acid and the same ash should be inactive a control that is almost never run. Reported coumarin bioactivity is then reviewed against the same standard: the aminocoumarin antibiotics have an established target in the DNA gyrase B ATPase, while radical-scavenging activity belongs to appended phenols rather than to the lactone.**

***Index Terms*—Coumarin; Knoevenagel condensation; agro-waste catalyst; heterogeneous catalysis; hot-filtration test; turnover number; DNA gyrase B**

I. INTRODUCTION

The appeal of a bio-waste catalyst is immediate. Banana peel, papaya stem, rice husk, eggshell and pomelo rind are free, locally abundant and otherwise discarded. Dried, burned and calcined, they give an ash rich in potassium and calcium; suspended or extracted in water, that ash is alkaline enough to deprotonate an active methylene compound. Condensations that normally call for piperidine or sodium ethoxide then proceed at room temperature, and the 3-carboxycoumarins that result are obtained in high yield in a few hours [10].

The chemistry works. What is contested here is the description. A typical title promises a reusable, bio-waste-derived, heterogeneous catalyst, and those are four separate claims, each with an established experiment attached. Reusability is a statement about what remains after the reaction; heterogeneity is a statement about where the catalysis happens; catalysis is a statement about turnover; and greenness is a statement about mass. None of them is settled by a high yield, and three of them are routinely asserted on evidence that the catalysis literature has long regarded as insufficient [1,18,20,21].

This review takes those claims in turn, grounds each in the specific chemistry of the coumarin syntheses involved (Schemes 1–3), and then applies the same standard to the biological half of such projects. The argument is constructive: every test proposed here can be done in a college laboratory with the equipment already needed to run the reaction, and a series that reports them is worth considerably more than one that reports another five recycling bars.

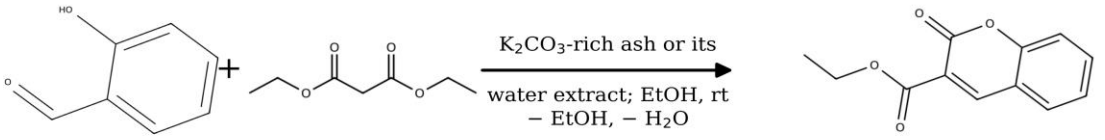
II. WHAT EACH COUMARIN SYNTHESIS DEMANDS OF A CATALYST

2.1 The Knoevenagel route needs a base

Condensation of salicylaldehyde with diethyl malonate gives ethyl coumarin-3-carboxylate (Scheme 1), and with ethyl acetoacetate gives 3-acetylcoumarin (Scheme 2) [8]. The mechanism begins with removal of a proton from the active methylene carbon, whose acidity is enhanced by two flanking carbonyls; the resulting carbanion adds to the aldehyde, water is lost, and the phenolic oxygen closes the lactone with expulsion of ethanol. Every step after the first is spontaneous once the carbanion forms, which is why a mild base is sufficient and why these reactions run at room temperature.

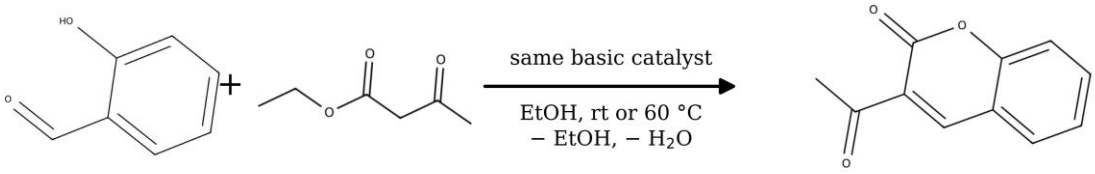
This is precisely the demand that a potassium-carbonate-rich ash can meet. The reported basicity of such materials, measured by Hammett indicator titration, is of the order of 1.6 mmol g^{-1} for the most potassium-rich examples [11], and the aqueous extracts are alkaline at around pH 9–10 [10]. A base of that strength deprotonates diethyl malonate, whose pK_a is about 13 in water, sufficiently to sustain the reaction. The match between what the reaction needs and what the material offers is the genuine result in this literature, and it is a real one. Computed atom economies for the two Knoevenagel routes are 77.3% and 74.6%, with ethanol and water as the only by-products.

One detail of Scheme 1 is worth noting because it is often mis-drawn. The ring closure is an intramolecular transesterification, not a simple dehydration: the phenolic oxygen attacks one of the two ester carbonyls and ethanol leaves. That is why diethyl malonate gives the ethyl ester rather than the free acid, why the product of the ethyl acetoacetate reaction is 3-acetylcoumarin rather than a 3-carboxylate, and why Knoevenagel coumarin syntheses are usually run in ethanol the solvent is also the leaving group, and using methanol quietly produces a mixture of esters. A paper reporting a 3-carboxylic acid directly from diethyl malonate has either hydrolysed the product in a step it did not mention or has mis-assigned it; the two differ by 28 mass units and by an unmistakable ethyl pattern in the proton spectrum.



salicylaldehyde diethyl malonate ethyl coumarin-3-carboxylate
AE = 77.3%

Scheme 1. Knoevenagel route to ethyl coumarin-3-carboxylate. The catalyst's only required function is to deprotonate the active methylene carbon; everything after that is downhill. AE = atom economy computed from the balanced equation.



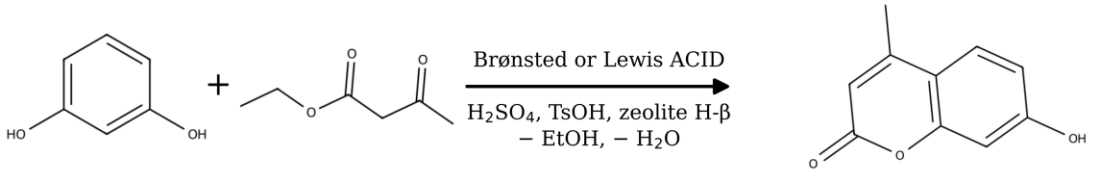
salicylaldehyde ethyl acetoacetate 3-acetylcoumarin
AE = 74.6%

Scheme 2. The same condensation with ethyl acetoacetate gives 3-acetylcoumarin, the second product commonly reported from these catalysts.

2.2 The Pechmann route needs an acid and is the missing control

The other classical coumarin synthesis condenses a phenol with a β-ketoester and requires a Brønsted or Lewis acid: resorcinol and ethyl acetoacetate give 7-hydroxy-4-methylcoumarin over sulfuric acid, p-toluenesulfonic acid or zeolite H-β (Scheme 3) [9,14]. The acid activates the ketone toward electrophilic attack by the electron-rich arene; a base cannot perform that role.

This gives the field a control experiment it has largely overlooked. If a bio-waste ash works because it is a potassium carbonate base, it should catalyse the Knoevenagel route and fail at the Pechmann route. If a paper reports the same ash driving both, either the material contains acidic sites that have not been characterised, or the attributed mechanism is wrong, or the reaction is proceeding thermally. Running the Pechmann reaction with and without the ash takes one afternoon and tests the mechanistic claim directly far more informatively than another substrate scope table.



resorcinol ethyl acetoacetate 7-hydroxy-4-methylcoumarin
AE = 73.3%

Scheme 3. The Pechmann route requires an acid catalyst and is therefore the natural negative control for an alkaline bio-waste ash: a base should not drive it.

III. WHAT A BIO-WASTE CATALYST IS MADE OF

3.1 Composition, and the units it is reported in

Characterisation of these materials by X-ray diffraction, energy dispersive X-ray analysis and X-ray photoelectron spectroscopy consistently identifies potassium as K_2CO_3, KCl and K_2O, with calcium, magnesium and sodium as minor components [11,12]. Potassium content is the variable that tracks activity: the most active of six agro-waste ashes screened for the synthesis of ethyl coumarin-3-carboxylate was the one with the highest potassium loading and the highest measured basicity, and it gave 97% yield at room temperature in four hours [11].

Figure 2b illustrates a problem that runs through the field. Three well-characterised catalysts report potassium contents of 15.98, 36.54 and 14.69 in atomic percent, in unspecified percent and in weight percent respectively [11,12]. These numbers cannot be compared with one another, and none of them is the quantity a kineticist wants, which is the density of basic sites per gram. Hammett titration or temperature-programmed desorption of carbon dioxide supplies that number directly, and reporting it would make two ashes from two laboratories comparable for the first time.

Behind this lies a deeper difficulty. Ash composition depends on the plant species, the cultivar, the soil, the part of the plant, the drying regime and above all the calcination temperature. Banana peel ash is therefore not a defined reagent in the way that potassium carbonate is, and a protocol specifying it is reproducible only to the extent that those variables are specified. The minimum is species, plant part, calcination temperature and duration, and a measured basicity for the batch actually used.

It is worth being explicit about the alternative, because the honest comparison is not with homogeneous piperidine but with the well-characterised solid bases already established for fine-chemical synthesis: calcined hydrotalcites, alkali-loaded mixed oxides, basic zeolites and supported amines, all of which have defined compositions, measured site densities and documented leaching behaviour [13,14]. An agro-waste ash competes with those on cost and on the

circular-economy argument rather than on performance, and the useful framing for a dissertation project is that it is testing whether a free, variable material can do a job that a defined one already does. Framed that way, a partial or negative result is still a result, and the characterisation work becomes the contribution rather than an obstacle to the yield table.

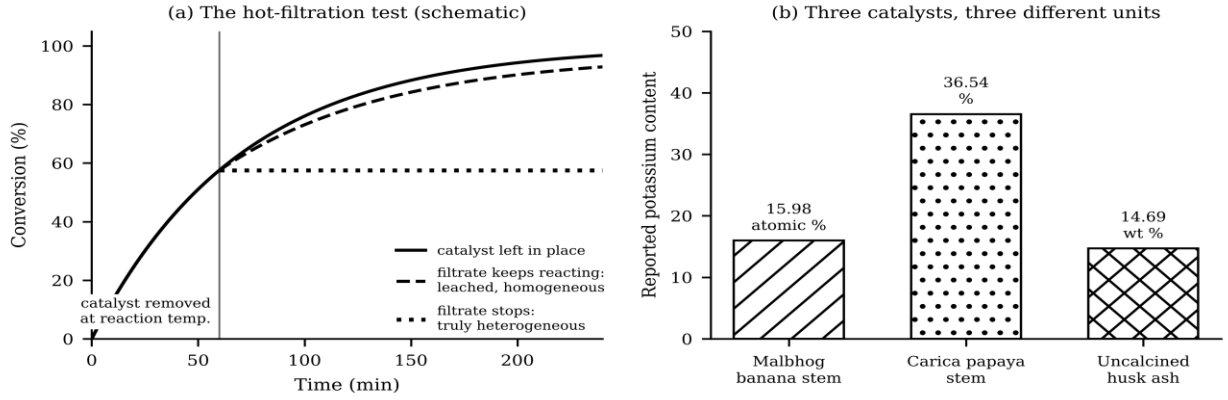


Fig. 2. (a) The hot-filtration test, drawn schematically. After the solid is removed at reaction temperature, a filtrate that keeps reacting shows that a leached, soluble species is the catalyst; a filtrate that stops shows genuine surface catalysis. (b) Reported potassium contents of three characterised agro-waste catalysts, each given in a different unit, so that the three cannot be compared [11,12].

3.2 The solid and its extract are not the same thing

Two distinct materials circulate under the same general description, and Table 1 separates them. The first is the calcined solid, used as a suspension and recovered by filtration; this is a candidate heterogeneous catalyst and the question of whether it functions as one is a real question. The second is the aqueous extract water extract of banana peel ash and its many relatives prepared by stirring the ash in water and filtering off the insoluble residue [10].

The extract is a solution of potassium carbonate, potassium chloride and related salts. It is a homogeneous medium by construction: the solid has been deliberately discarded. Describing it as a heterogeneous catalyst is not a borderline judgement but a category error, and it matters in practice, because it determines what recovery means. A solid can be filtered off and weighed; a dissolved carbonate cannot be recovered except by evaporating the solvent, at which point the energy accounting changes entirely. Several papers using such extracts are candid that the medium acts as solvent and base together, which is an accurate and defensible description that the word catalyst then undermines.

Table 1. The calcined ash and its water extract are two different materials and support different claims. Much of the confusion in this literature follows from treating them as one [10–12].

Attribute	Calcined solid ash	Aqueous extract of the ash
Physical state in the reaction	Suspended solid; two phases present	Clear solution; the insoluble residue has been filtered away
Correct classification	Candidate heterogeneous catalyst; must be tested	Homogeneous by construction; cannot be a heterogeneous catalyst
Active species	Surface basic sites, plus whatever dissolves	Dissolved K_2CO_3, KCl and related salts
Recovery after reaction	Filtration, washing, drying; mass recovered can be reported	Only by evaporating the water, which changes the energy balance
Quantification of loading	mg per mmol substrate, with basicity in mmol g^{-1}	Requires titration of the extract; % w/v alone is not interpretable
Appropriate heterogeneity test	Hot filtration at reaction temperature; Sheldon test on the filtrate	Not applicable; the question does not arise

IV. FOUR CLAIMS AND THE EXPERIMENTS THAT TEST THEM

Table 2 sets out each claim, the standard experiment, and the weaker evidence usually offered in its place.

4.1 Is it catalytic?

A catalyst is consumed in no net amount and therefore turns over. The measure is the turnover number: moles of product per mole of active site, and it is the quantity that separates a catalyst from a promoter in every standard treatment of the subject [15–17]. For a solid base of 1.6 mmol g^{-1} basicity used at 50 mg per 1 mmol of salicylaldehyde, the catalyst supplies 0.08 mmol of basic sites and a quantitative reaction corresponds to a turnover number of about 12 modest but unambiguously catalytic. Loadings quoted as 5% w/v of an aqueous extract, or as a volume of extract used as the solvent, cannot be converted into a turnover number at all unless the base concentration of that extract is measured. A simple acid–base titration of the extract supplies it.

The distinction is not pedantic. If the turnover number is near one, the material is a reagent; the reaction is still useful, the waste stream is still benign, and the paper is still publishable but as a stoichiometric promoter, not a catalyst, and the reusability question becomes moot.

4.2 Is it heterogeneous?

The hot-filtration test, illustrated schematically in Figure 2a, answers this. The reaction is run to partial conversion, the solid is removed by filtration at the reaction temperature the temperature matters, because dissolved species redeposit on cooling and the filtrate is returned to the bath and monitored. If conversion stops, catalysis required the solid. If it continues, a soluble species was doing the work [1,18,20]. The related Sheldon test compares the elemental analysis of the filtrate with that of the fresh catalyst.

The result matters here more than in most systems, because the active component of these ashes is potassium carbonate, which is soluble in water and appreciably soluble in ethanol–water mixtures. An alkaline solid base is close to the worst case for a heterogeneity claim: systematic filtration studies of base-catalysed reactions over MgO, CaO, the alkaline-earth carbonates and related solids have repeatedly found that the observed catalysis is homogeneous, carried by leached species, where it had been assumed to be surface chemistry [1,19,21]. Nothing about an agro-waste origin exempts a material from that finding. To the credit of the field, the better papers now run the test: the agro-waste study that gave 97% yield reports both a Sheldon leaching test and a recyclability study [11].

4.3 Is it reusable?

Recycling plots five bars of near-constant yield are the field's standard evidence and are the weakest of the three. Sheldon and co-workers pointed out three decades ago that failure to observe a decline in activity over several recycles does not exclude leaching, because a small quantity of a highly active leached species can sustain the reaction while the solid acts as a reservoir that replenishes it [1,20]. The point is sharpened when conversions are run to completion, since a reaction that reaches 95% with half the catalyst will also reach 95% with all of it.

Three additions convert a recycling plot into evidence. Run the recycles at deliberately low conversion, where rate differences are visible. Analyse the filtrate for potassium by atomic absorption or inductively coupled plasma spectroscopy and report milligrams per litre. And characterise the recovered solid by the same techniques used for the fresh one X-ray diffraction, infrared spectroscopy, surface area and basicity so that any loss of carbonate is visible. Weighing the recovered catalyst and reporting the mass recovered is a useful fourth.

4.4 Is it green?

Atom economy, computed from the balanced equation, is 73–77% for the three routes in Schemes 1–3 and is a property of the route rather than of the protocol [2]. The E-factor kilograms of waste per kilogram of product and process mass intensity capture what the protocol actually costs, and solvent dominates both [3,5,6]. A reaction performed in an aqueous ash extract at room temperature starts from a genuinely favourable position, and that advantage is often spent in the work-up: extraction into ethyl acetate, washing, drying and recrystallisation can contribute more mass than the reaction itself. Reporting the comparison honestly, for the new protocol and the piperidine-catalysed one it replaces, is the single most useful green chemistry measurement available to this kind of project [7]. The twelve principles this field cites in its introductions are

themselves framed around measurable quantities waste prevention, atom economy, safer solvents, energy efficiency and a protocol can satisfy two of them while quietly failing a third [4].

Table 2. The four claims in a typical title, the experiment that settles each, and the substitute commonly accepted in its place [1,2,5,16–18,20,21].

Claim	Standard experiment	What counts as a pass	Evidence usually offered instead
Catalytic	Compute turnover number from measured basic-site loading	TON clearly greater than 1; rate proportional to loading	Loading quoted as % w/v or 'a few drops', with no site count
Heterogeneous	Hot filtration at reaction temperature; monitor the filtrate	Conversion stops when the solid is removed	The catalyst was a visible solid, therefore the catalysis was heterogeneous
Reusable	Recycles at low conversion; filtrate analysed for potassium; fresh vs recovered solid characterised	Rate maintained, leaching below detection, unchanged XRD and basicity	Five bars of near-constant yield at full conversion
Green	Atom economy plus E-factor or PMI including work-up solvents	Numbers given for both the new route and the one displaced	The reaction solvent was water, or there was no solvent
Base-catalysed	Run the acid-requiring Pechmann condensation with the same material	No conversion, confirming the catalyst acts as a base	The mechanism is drawn but never tested

V. THE BIOLOGY, MEASURED TO THE SAME STANDARD

5.1 Antimicrobial activity: one established coumarin mechanism

Coumarins occupy an unusual position among the scaffolds screened in student projects, in that one subclass has a thoroughly established antibacterial mechanism. The aminocoumarins novobiocin, clorobiocin and coumermycin A_1, produced by Streptomyces species inhibit bacterial DNA gyrase by binding the ATP site of the GyrB subunit as competitive inhibitors of the ATPase reaction, and they are potent against Gram-positive organisms [22–25]. Structure–activity work by combinatorial biosynthesis showed how finely tuned the natural products are: the 8′-methyl group of novobiocin and the carbamoyl group on the noviose sugar both contribute measurably to gyrase inhibition [23]. Novobiocin has since been shown to bind a second target, the LptB ATPase that powers lipopolysaccharide transport, which is a reminder that one established mechanism does not exclude others [26].

Two consequences follow for a new series of simple coumarins. First, a docking study against DNA gyrase B has a real precedent here, which is more than most scaffolds can claim but the aminocoumarin pharmacophore is a 3-amido-4-hydroxycoumarin bearing a noviose sugar, and an ethyl coumarin-3-carboxylate shares only the bicycle. Second, the comparison sets the bar: if gyrase is the proposed target, the enzyme assay exists and is standard.

Reported activity for synthetic 3-substituted coumarins is otherwise modest and should be measured as a minimum inhibitory concentration by broth microdilution rather than as a zone of inhibition, since zone diameter depends on diffusion through agar as much as on potency [36–38]. A mammalian cytotoxicity counter-screen run alongside allows a selectivity index to be quoted, without which an MIC in the tens of micrograms per millilitre is uninterpretable.

It is also worth setting a realistic expectation before the screening plate is poured. The aminocoumarins are large, glycosylated natural products refined by selection; a simple 3-substituted coumarin of molecular weight under 250 is a fragment by comparison, and fragments rarely show single-digit micromolar antibacterial activity. The informative experiment for such a series is therefore not a broad panel but a narrow one read quantitatively: two Gram-positive strains, one Gram-negative, one yeast, MICs rather than zones, and a cytotoxicity line. That design distinguishes a weak but selective hit, which is worth following, from a moderately cytotoxic compound, which is not.

5.2 Antioxidant activity: the lactone donates nothing

The coumarin nucleus itself has no hydrogen to donate to a radical. It is a benzopyranone: an aromatic ring

fused to an unsaturated lactone, with no O–H and no readily abstractable C–H. Every coumarin that performs well in a DPPH or ABTS assay does so because of a substituent, and the pattern is the familiar phenolic one (Fig. 1). Umbelliferone carries a single 7-hydroxyl; esculetin carries a 6,7-catechol and is substantially more active, exactly as the catechol arrangement predicts for flavonoids and phenolic acids, because the ortho-hydroxyl stabilises the resulting phenoxyl radical by hydrogen bonding and lowers the O–H bond dissociation enthalpy [34,35].

The practical implication for a synthetic series is direct. If the compounds prepared are 3-carboxylates or 3-acetyl derivatives with no phenolic hydroxyl, strong DPPH activity should not be expected, and if it is observed the first hypothesis should be an impurity or an assay artefact rather than a new antioxidant pharmacophore. If antioxidant activity is the goal, the design follows from the chemistry: use a dihydroxy-substituted salicylaldehyde so that the product carries a catechol. Two mechanistically distinct assays should be reported with the solvent stated, because the apparent mechanism of DPPH quenching shifts between hydrogen-atom transfer and electron transfer with solvent and with added acid or base [31–33].

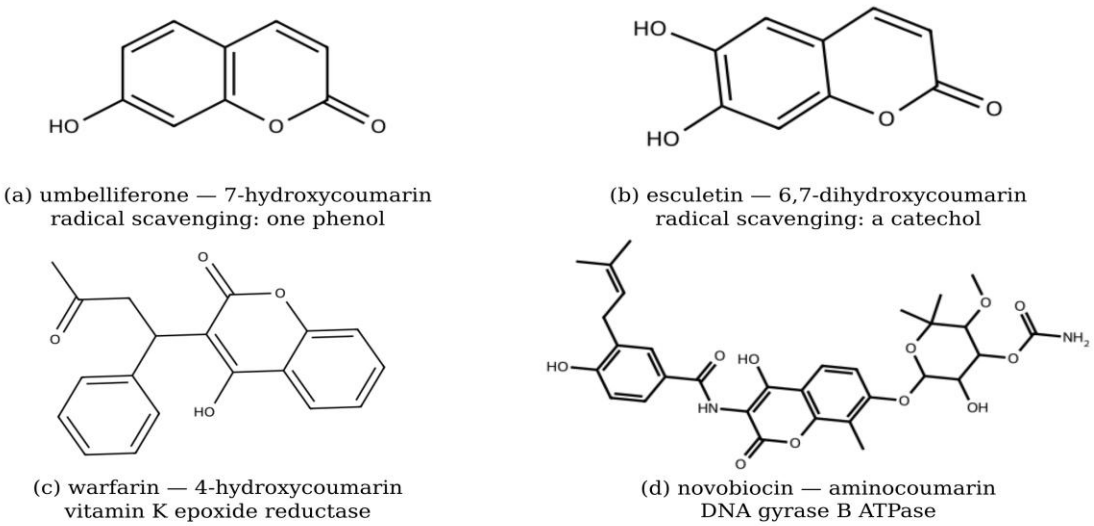


Fig. 1. Bioactive coumarins. (a) and (b) are antioxidants because of their phenolic substituents, the catechol of esculetin being the more effective arrangement; (c) and (d) act on defined protein targets. The unsubstituted coumarin lactone itself has no hydrogen to donate to a radical.

Table 3. Coumarin bioactivity for which a mechanism is actually established, and what each case implies for the design and interpretation of a new synthetic series.

Compound	Reported activity	Established mechanism	What it implies for a new series	Ref.
Novobiocin, clorobiocin, coumermycin A_1	Potent against Gram-positive bacteria	Competitive inhibition of the GyrB ATPase; co-crystal structures available	Gyrase B is a legitimate docking target for coumarins, with a positive control available	[22–25]
Novobiocin (second target)	Synergy with polymyxin	Binds and activates the LptB ATPase of lipopolysaccharide transport	One established mechanism does not exclude another	[26]
Warfarin and 4-hydroxycoumarins	Anticoagulant	Inhibition of vitamin K epoxide reductase	A 4-hydroxycoumarin series carries a real toxicological liability	[27,28]

Compound	Reported activity	Established mechanism	What it implies for a new series	Ref.
Umbelliferone (7-hydroxycoumarin)	Radical scavenging	Hydrogen-atom donation by a single phenol	Activity requires a phenol; the lactone contributes none	[29,30]
Esculetin (6,7-dihydroxycoumarin)	Stronger radical scavenging	Catechol; ortho-hydroxyl lowers the O–H bond dissociation enthalpy	If antioxidants are the goal, design the catechol in from the aldehyde	[34,35]

VI. DOCKING, AND WHAT IT IS FOR

Molecular docking is cheap, fast and almost universally included. Used properly it prioritises compounds and generates hypotheses. Used as most papers use it one favourable binding energy for the most active compound, a list of contacted residues, and a claim of mechanism it adds nothing that the activity data did not already contain. Docking programs reproduce crystallographic poses reasonably well but rank affinities poorly, and comparative assessments report modest, target-dependent correlation between score and measured potency [39,40].

Three habits make the section worth reading. Redock the co-crystallised ligand and report the root-mean-square deviation, which shows the protocol reproduces a known answer; for gyrase B, novobiocin co-crystal structures are available and make an ideal positive control. Report the correlation between docking score and measured MIC across the whole series, not for the best compound alone. And keep the predicted target a hypothesis until an enzyme assay tests it. Screening the series against published assay interference substructures before investing in it costs nothing and prevents a familiar kind of disappointment [41].

VII. A CHECKLIST FOR THIS KIND OF PROJECT

For the catalyst: state species, plant part, calcination temperature and time; measure basicity by Hammett titration or carbon dioxide temperature-programmed desorption and report it in mmol g^{-1}; distinguish explicitly between the calcined solid and its aqueous extract; compute a turnover number.

For the claims: run a hot-filtration test at reaction temperature and show the conversion–time curve; analyse the filtrate for potassium; characterise fresh and recovered solid by the same methods; run recycles at low conversion; and run the Pechmann reaction as a negative control for an alkaline catalyst.

For the green claim: report atom economy from the balanced equation, and an E-factor or process mass intensity computed from the real solvent volumes including work-up, for both the new protocol and the one it displaces.

For the biology: MICs by broth microdilution with a vehicle control and a mammalian cell line; at least two antioxidant assays with the solvent stated; and docking presented as a hypothesis, with a redocking control.

VIII. CONCLUSION

Bio-waste ashes are a sound idea with a real chemical basis. Burning a potassium-rich residue concentrates alkali carbonates, and those carbonates are exactly the kind of mild base that the Knoevenagel route to coumarins requires; the reported yields are high and the conditions are mild. The weakness of the literature is not its chemistry but its vocabulary. Reusable, heterogeneous, catalytic and green are four measurable properties that have drifted into use as adjectives, and the experiments that would settle them a hot filtration, a filtrate analysis, a turnover number, a mass balance are cheaper than the substrate scope tables that appear in their place. The same discipline applied to the biological half would put the DPPH results on the substituent where they belong and the docking results in the hypothesis column where they belong. None of this requires new equipment. It requires deciding that the claim in the title is something to be tested rather than something to be stated.

REFERENCES

[1] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, and U. Schuchardt, “Heterogeneous catalysts for liquid-phase oxidations: Philosophers' stones or Trojan horses?” *Accounts of Chemical Research*, vol. 31, no. 8, pp. 485–493, 1998.

[2] B. M. Trost, "The atom economy—A search for synthetic efficiency," *Science*, vol. 254, no. 5037, pp. 1471–1477, 1991.

[3] R. A. Sheldon, "The E factor at 30: A passion for pollution prevention," *Green Chemistry*, vol. 25, no. 5, pp. 1704–1728, 2023.

[4] P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*. Oxford, U.K.: Oxford University Press, 1998.

[5] C. Jiménez-González, C. S. Ponder, Q. B. Broxterman, and J. B. Manley, "Using the right green yardstick: Why process mass intensity is used in the pharmaceutical industry to drive more sustainable processes," *Organic Process Research & Development*, vol. 15, no. 4, pp. 912–917, 2011.

[6] D. J. C. Constable, A. D. Curzons, and V. L. Cunningham, "Metrics to 'green' chemistry—which are the best?" *Green Chemistry*, vol. 4, no. 6, pp. 521–527, 2002.

[7] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, and P. J. Dunn, "CHEM21 selection guide of classical- and less classical-solvents," *Green Chemistry*, vol. 18, no. 1, pp. 288–296, 2016.

[8] E. Knoevenagel, "Condensation von Malonsäure mit aromatischen Aldehyden durch Ammoniak und Amine," *Berichte der Deutschen Chemischen Gesellschaft*, vol. 31, no. 3, pp. 2596–2619, 1898.

[9] H. von Pechmann and C. Duisberg, "Ueber die Verbindungen der Phenole mit Acetessigäther," *Berichte der Deutschen Chemischen Gesellschaft*, vol. 16, no. 2, pp. 2119–2128, 1883.

[10] S. D. Bagul, J. D. Rajput, and R. S. Bendre, "Synthesis of 3-carboxycoumarins at room temperature in water extract of banana peels," *Environmental Chemistry Letters*, vol. 15, no. 4, pp. 725–731, 2017.

[11] "Room temperature synthesis of ethyl coumarin-3-carboxylate using agro-waste derived ash as heterogeneous catalyst," *Inorganic Chemistry Communications*, 2025.

[12] "Carica papaya stem: A source of versatile heterogeneous catalyst for biodiesel production and C–C bond formation," *Renewable Energy*, vol. 147, 2020.

[13] M. J. Climent, A. Corma, and S. Iborra, "Heterogeneous catalysts for the one-pot synthesis of chemicals and fine chemicals," *Chemical Reviews*, vol. 111, no. 2, pp. 1072–1133, 2011.

[14] Corma and H. García, "Lewis acids: From conventional homogeneous to green homogeneous and heterogeneous catalysis," *Chemical Reviews*, vol. 103, no. 11, pp. 4307–4365, 2003.

[15] J. Hagen, *Industrial Catalysis: A Practical Approach*, 3rd ed. Weinheim, Germany: Wiley-VCH, 2015.

[16] M. Boudart, "Turnover rates in heterogeneous catalysis," *Chemical Reviews*, vol. 95, no. 3, pp. 661–666, 1995.

[17] S. Kozuch and J. M. L. Martin, "'Turning over' definitions in catalytic cycles," *ACS Catalysis*, vol. 2, no. 12, pp. 2787–2794, 2012.

[18] N. T. S. Phan, M. Van Der Sluys, and C. W. Jones, "On the nature of the active species in palladium catalyzed Mizoroki–Heck and Suzuki–Miyaura couplings: Homogeneous or heterogeneous catalysis, a critical review," *Advanced Synthesis & Catalysis*, vol. 348, no. 6, pp. 609–679, 2006.

[19] J. M. Richardson and C. W. Jones, "Strong evidence of solution-phase catalysis associated with palladium leaching from immobilized thiols during Heck and Suzuki coupling of aryl iodides, bromides, and chlorides," *Journal of Catalysis*, vol. 251, no. 1, pp. 80–93, 2007.

[20] R. H. Crabtree, "Resolving heterogeneity problems and impurity artifacts in operationally homogeneous transition metal catalysts," *Chemical Reviews*, vol. 112, no. 3, pp. 1536–1554, 2012.

[21] J. A. Widegren and R. G. Finke, "A review of the problem of distinguishing true homogeneous catalysis from soluble or other metal-particle heterogeneous catalysis under reducing conditions," *Journal of Molecular Catalysis A: Chemical*, vol. 198, nos. 1–2, pp. 317–341, 2003.

[22] F. Collin, S. Karkare, and A. Maxwell, "Exploiting bacterial DNA gyrase as a drug target: Current state and perspectives," *Applied Microbiology and Biotechnology*, vol. 92, no. 3, pp. 479–497, 2011.

[23] R. H. Flatman, A. Eustáquio, S. M. Li, L. Heide, and A. Maxwell, "Structure-activity relationships of aminocoumarin-type gyrase and topoisomerase IV inhibitors obtained by combinatorial biosynthesis," *Antimicrobial Agents and Chemotherapy*, vol. 50, no. 4, pp. 1136–1142, 2006.

[24] L. Heide, "The aminocoumarins: Biosynthesis and biology," *Natural Product Reports*, vol. 26, no. 10, pp. 1241–1250, 2009.

[25] Maxwell, "DNA gyrase as a drug target," *Biochemical Society Transactions*, vol. 27, no. 2, pp. 48–53, 1999.

[26] J. M. May, T. W. Owens, M. D. Mandler, B. W. Simpson, M. B. Lazarus, D. J. Sherman, R. M. Davis, S. Okuda, W. Massefski, N. Ruiz, and D. Kahne, "The antibiotic novobiocin binds and activates the ATPase that powers lipopolysaccharide transport," *Journal of the American Chemical Society*, vol. 139, no. 48, pp. 17221–17224, 2017.

[27] M. A. Stahmann, C. F. Huebner, and K. P. Link, "Studies on the hemorrhagic sweet clover disease. V. Identification and synthesis of the hemorrhagic agent," *Journal of Biological Chemistry*, vol. 138, no. 2, pp. 513–527, 1941.

[28] D. S. Whitlon, J. A. Sadowski, and J. W. Suttie, "Mechanism of coumarin action: Significance of vitamin K epoxide reductase inhibition," *Biochemistry*, vol. 17, no. 8, pp. 1371–1377, 1978.

[29] K. N. Venugopala, V. Rashmi, and B. Odhav, "Review on natural coumarin lead compounds for their pharmacological activity," *BioMed Research International*, vol. 2013, Art. no. 963248, 2013.

[30] F. Borges, F. Roleira, N. Milhazes, L. Santana, and E. Uriarte, "Simple coumarins and analogues in medicinal chemistry: Occurrence, synthesis and biological activity," *Current Medicinal Chemistry*, vol. 12, no. 8, pp. 887–916, 2005.

[31] D. Huang, B. Ou, and R. L. Prior, "The chemistry behind antioxidant capacity assays," *Journal of Agricultural and Food Chemistry*, vol. 53, no. 6, pp. 1841–1856, 2005.

[32] R. Apak, M. Özyürek, K. Güçlü, and E. Çapanoğlu, "Antioxidant activity/capacity measurement. 1. Classification, physicochemical principles, mechanisms, and electron transfer (ET)-based assays," *Journal of Agricultural and Food Chemistry*, vol. 64, no. 5, pp. 997–1027, 2016.

[33] G. Litwinienko and K. U. Ingold, "Abnormal solvent effects on hydrogen atom abstractions. 1. The reactions of phenols with 2,2-diphenyl-1-picrylhydrazyl in alcohols," *Journal of Organic Chemistry*, vol. 68, no. 9, pp. 3433–3438, 2003.

[34] J. S. Wright, E. R. Johnson, and G. A. DiLabio, "Predicting the activity of phenolic antioxidants: Theoretical method, analysis of substituent effects, and application to major families of antioxidants," *Journal of the American Chemical Society*, vol. 123, no. 6, pp. 1173–1183, 2001.

[35] C. A. Rice-Evans, N. J. Miller, and G. Paganga, "Structure–antioxidant activity relationships of flavonoids and phenolic acids," *Free Radical Biology and Medicine*, vol. 20, no. 7, pp. 933–956, 1996.

[36] H. Dickert, K. Machka, and I. Braveny, "The uses and limitations of disc diffusion in the antibiotic sensitivity testing of bacteria," *Infection*, vol. 9, no. 1, pp. 18–24, 1981.

[37] M. Balouiri, M. Sadiki, and S. K. Ibnsouda, "Methods for in vitro evaluating antimicrobial activity: A review," *Journal of Pharmaceutical Analysis*, vol. 6, no. 2, pp. 71–79, 2016.

[38] Clinical and Laboratory Standards Institute, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*, CLSI Standard M07, 11th ed. Wayne, PA, USA: CLSI, 2018.

[39] O. Trott and A. J. Olson, "AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading," *Journal of Computational Chemistry*, vol. 31, no. 2, pp. 455–461, 2010.

[40] G. L. Warren, C. W. Andrews, A. M. Capelli, B. Clarke, J. LaLonde, M. H. Lambert, *et al*., "A critical assessment of docking programs and scoring functions," *Journal of Medicinal Chemistry*, vol. 49, no. 20, pp. 5912–5931, 2006.

[41] J. B. Baell and G. A. Holloway, "New substructure filters for removal of pan assay

interference compounds (PAINS) from screening libraries and for their exclusion in bioassays," *Journal of Medicinal Chemistry*, vol. 53, no. 7, pp. 2719–2740, 2010.