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Review

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Synthesis of analgesics and antipyretics by both metal and metal free methodologies; a review of the last decade

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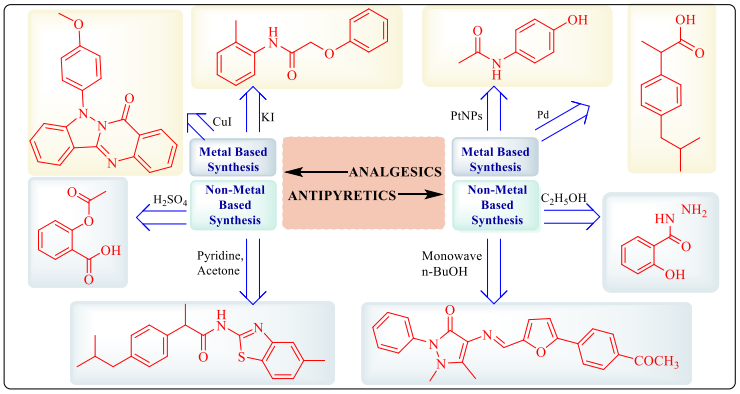
Received 03-11-2026 **Accepted** 06-08-2026 **Published on line** 06-10-2026

Abstract

Analgesics and antipyretics are among the most used pharmaceuticals worldwide so there is a constant demand to develop new efficient, sustainable and sustainable synthetic methods. This review analyzes the advancement in their synthesis over the past decade covering both metal-catalyzed and metal-free approaches. Metals catalysts like Pd, Cu, and Fe are used in pivotal reactions such as reductive carbonylation and Cu-catalyzed click cycloaddition providing high selectivity and have high functional group tolerance. Meanwhile metal-free approaches such as organocatalysis, biocatalysis offer simplicity and have low environmental impact. By evaluating important catalytic systems, existing methodologies, and the future developments in this area, this review highlights the importance of sustainability and the operational efficiency and industrial relevance in modern drug synthesis.



Keywords: Synthesis, metallic synthesis, metal free synthesis, bioactive molecules, analgesic, antipyretic

Cite as *Arkivoc* **2026** (1) 202612573

DOI: https://doi.org/10.24820/ark.5550190.p012.573

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1. Introduction

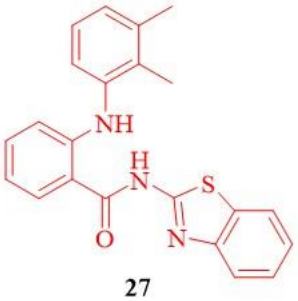
Antipyretics and analgesics are two of the most commonly used types of medications in the world. They are important for clinical use in the wide range of activities that include treatment of simple fever to relief of chronic pain involving multiple conditions and various age groups.[1] Analgesics are used to relieve pain while maintaining a significant degree of patient's consciousness and perception. Conversely, body temperatures caused by infection or inflammation can be brought down with the use of antipyretics. Among the agents that can be classified in this category are paracetamol (acetaminophen), aspirin (acetylsalicylic acid), ibuprofen, diclofenac and naproxen.[2,3] These medicines are used so frequently that there is a growing demand for the creation of new, more efficient, cost-effective, and eco-friendly synthetic methods.[4] The increasing global consumption of these medications and the need for refined techniques of synthesis to increase yield, purity and sustainability are creating a focus on research.

The synthesis of analgesics and antipyretics began with basic methods like nitration and acylation. An example is synthesis of acetylsalicylic acid, or aspirin, from salicylic acid. This method is recognized as a baseline example of industrial productivity.[3] The same is true for the production of acetaminophen from para-aminophenol, which has been adapted to incorporate some principles of green chemistry.[5]However, while the traditional methods have worked, they create harmful by-products and require harsh conditions making them too extreme to fit within the modern context of what the field has to offer.

Defining new sustainable technologies is possible due to advancements made in the last few years in areas such as synthetic organic chemistry, catalysis, and process engineering. These new sustainable methods have made it possible to develop metal catalyzed synthesis to form bonds and to do so more selectively and under milder conditions. Along with other important processes such as C-C coupling, Cu-catalyzed click cycloaddition (CuAAC) and oxidative aromatization etc, catalysts like palladium, copper and iron have helped develop more complex pharmaceuticals structures.[6,7] For example, the Suzuki-Miyaura cross-coupling reaction is a process in metal catalysis that is used to synthesize non-steroidal anti-inflammatory drugs (NSAIDs). This reaction is particularly useful in synthesis of the biaryl motifs found in many analgesics. Although the use of metal catalysis provides clear synthetic advantages, concerns regarding cost, toxicity, and presence of residual metals in the end products have drawn some regulatory and industry scrutiny.[8]

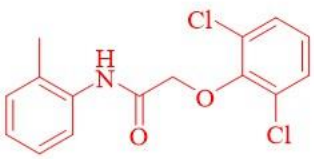
At the same time, approaches that are truly metal free have emerged that are more sustainable and even advantageous from the environmental perspective. Organocatalysis and biocatalysis offer metal-free pathways to important intermediates and final products. Organocatalysts, which are usually small organic molecules such as proline, imidazoles, and phosphines, have been shown to be quite effective in asymmetric synthesis, aldol reactions, and Michael additions that are important for the synthesis of analgesic compounds.[9] Biocatalysis, which uses enzymes such as lipases and oxidases, has been shown to be effective in achieving regio- and enantioselective synthesis in mild or even aqueous environments. Moreover, increasing applications of photoredox and electrochemical methods are contributing to the increasing novelty of sustainable synthesis in the pharmaceutical industry, especially for the activation of C–H bonds and for redox-neutral transformations.

Activities of compounds synthesised via metal based methodologies



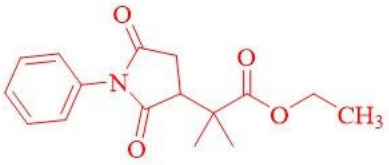
27

Inhibition of abdominal writhing : **70.89%**



31a

IC_{50} for COX-2 : **39.26 µM**
Yield : **74.19%**



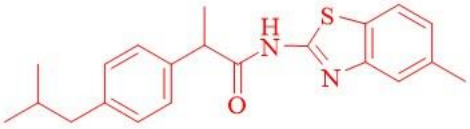
12

IC_{50} for COX-2 = **130 µg/ML**
IC_{50} for COX-1 = **314 µg/ML**

45a

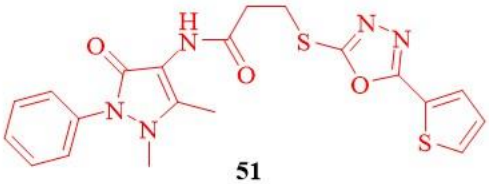
IC_{50} for COX-2 : **10 µM**

Activities of compounds synthesised via metal free methodologies



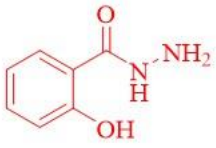
150a

Analgesic activity in tail immersion test: **17.61 ± 0.51s**
Anti-inflammatory effect in paw edema assay: **0.193 ± 0.04%**



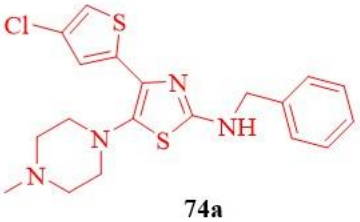
51

Inhibition of abdominal writhing: **69%**



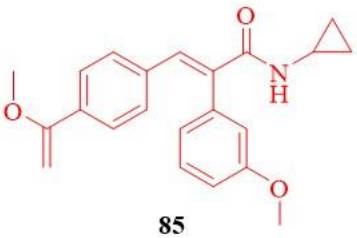
69

Inhibition of carrageenan-induced paw edema: **61.13 ± 4.82%**



74a

IC_{50} for COX-2: **0.83 ± 0.03 µM**



85

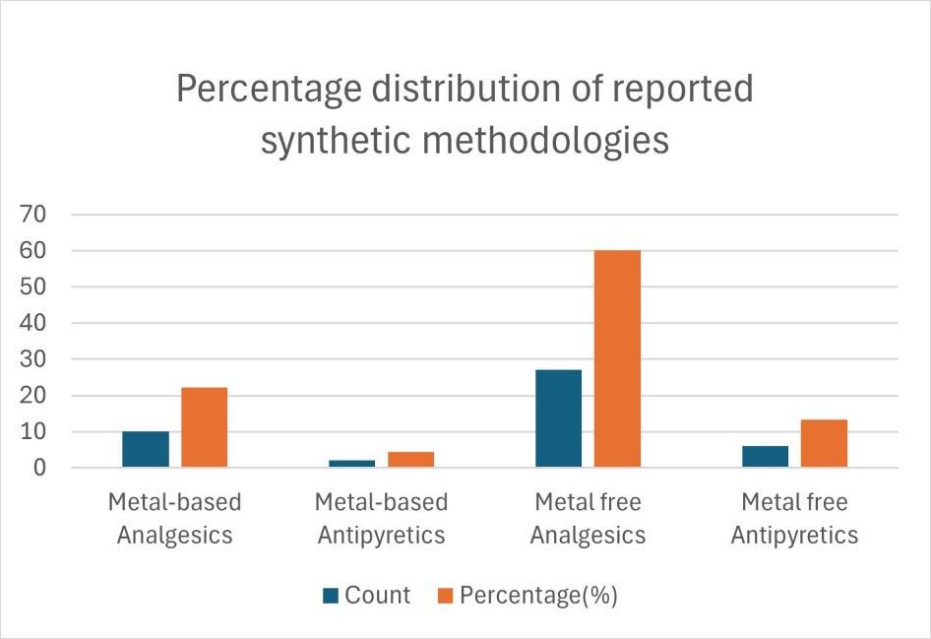
Analgesic activity: **30.07%**

Figure 1. Analgesic or anti-inflammatory activities of molecules synthesized by metal based and metal free methodologies**.**

Compounds synthesized from metal-based methodologies have shown significant biological activity (see Figure 1). A derivative of mefenamic acid with aminobenzothiazole **27** showed 70.89% inhibition in the acetic acid-induced abdominal constriction (writhing) test, indicating potent analgesic activity.[10] An N-phenylacetamide phenoxy derivative (an acetanilide analogue) **31a** showed an IC_{50} of 39.26 µM for COX-2 (in vitro) and 74.19% yield.[11] An N-succinimide N-pivalate derivative **12** showed IC_{50} of 130 µg/mL (COX-2) and 314 µg/mL (COX-1) (in vitro).[12] Additionally, a nitrophenyl urea based pyrazoline derivative **45a** demonstrated a COX-2 IC_{50} of 10 µM.[13]

Compounds synthesized via metal free synthetic approaches also showed potential bioactivities (see Figure 1). A hybrid derivative of ibuprofen and benzothiazole **150a** showed 17.61 ± 0.51s analgesic activity in the tail immersion test and anti-inflammatory activity of 0.193 ± 0.04 % in paw edema assay.[14] An oxadiazole-antipyrine hybrid **51** showed 69% inhibition in analgesic activity (acetic acid-induced writhing test),[15] while chlorothiophenyl-thiazole, a derivative of thiazole exhibited strong COX-2 selective inhibition with IC_{50} values of 93.41 ± 0.06 µM against COX-1 and 0.83 ± 0.03 µM against COX-2 (in vitro enzyme assay).[16] A salicylhydrazide derivative (2-hydroxybenzohydrazide) **69** at the dose of 60 mg/ kg produced 61.13 ± 4.82% inhibition of carrageenan-induced paw edema in mice at 3 hours which is almost equal to standard drug diclofenac sodium at 50 mg/kg.[17] These representative examples are summarized in Figure 1.

Table 1. Percentage distribution of metal catalyzed versus metal free synthetic methodologies for the analgesics and antipyretics covered in this review (data compiled from Sections 2 and 3)



Using principles of green chemistry is one of the most notable recent developments in synthetic methods. Along with other positive advancements in the field, the synthesis of analgesics and antipyretics has incorporated elements of green chemistry such as atom economy, reduced production of waste, the recycling of solvents, and the use of less harmful reagents. For example, in the synthesis of paracetamol, the environmental impact of traditional reduction methods is lessened by using catalytic reduction of p-nitrophenol in the presence of a reusable Pd/C catalyst under aqueous conditions.[4] The methods of solvent-free and microwave-assisted reactions also show improvements in energy conservation and enhancing reaction efficiency. The incorporation of more sustainable methods is of particular interest as adopting the newest

methods of metal catalysis, combined with the sustainable and consumer-driven approaches (i.e., strategies aligned with evolving consumer demands for safer, greener, and more ethically produced pharmaceuticals), combined with regulatory requirements, should prove to be the lowest-cost option in the long term.

Though it continues to improve, certain challenges still exist. In terms of metal-catalyzed processes, the scarcity and high price of certain noble metals, especially palladium and rhodium, present both an economic and geopolitical problem.[18] Additionally, the presence of residual metals in the end products have drawn increasingly stringent regulatory scrutiny from bodies such as the FDA and EMA. In contrast, non-metal-catalyzed approaches, while demonstrating the potential for greater sustainability, tend to suffer from longer reaction times, limited substrate scope, and difficulties with industrial scale-up. The search for more versatile organocatalysts or even enzymes that exhibit the same degree of reactivity and functional group tolerance as the most versatile cross-coupling metal catalysts is ongoing.

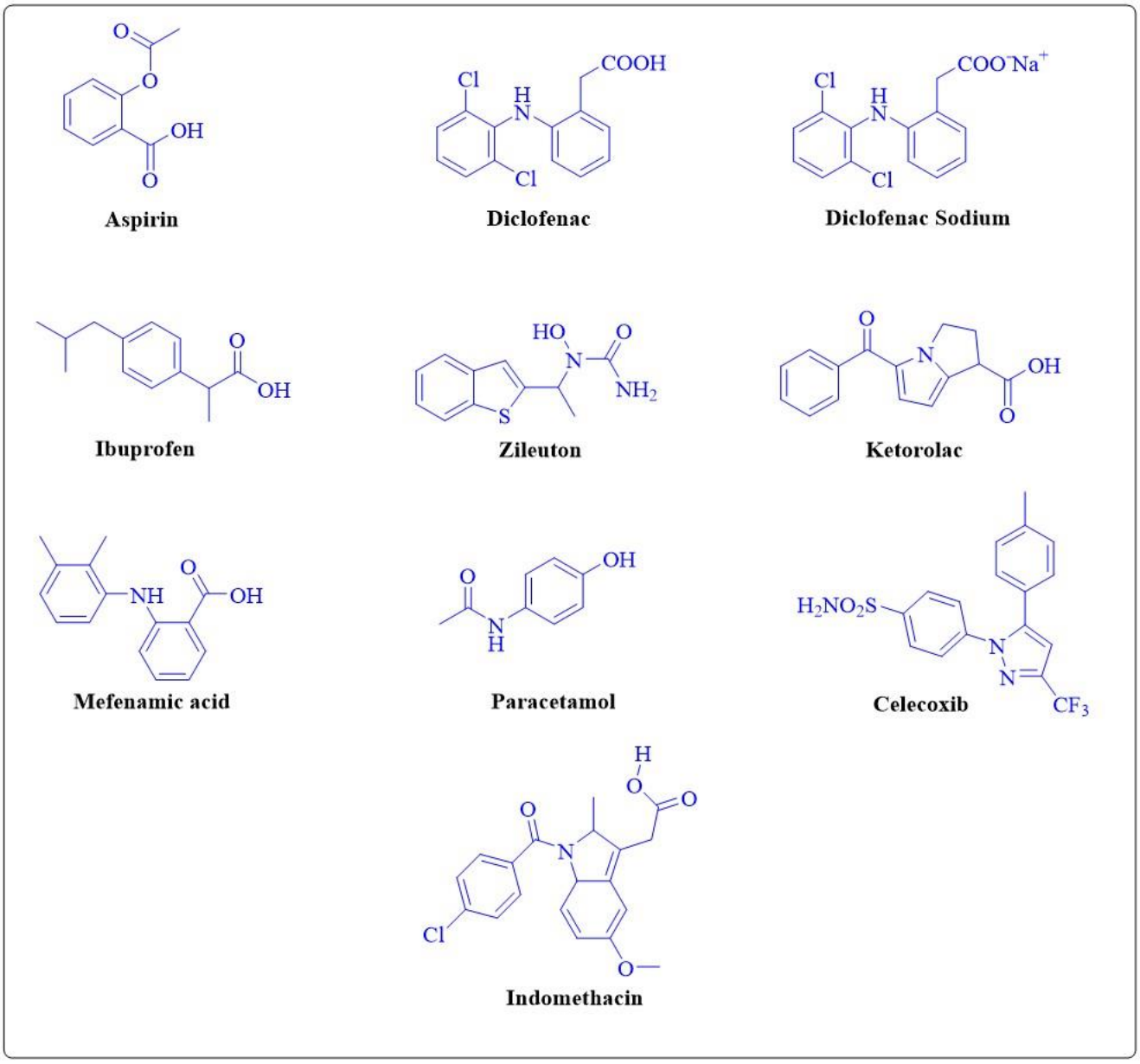


Figure 2. Structures of standard and reference drugs employed in biological evaluations of synthesized compounds throughout this review.

In the future, the synthesis of analgesics and antipyretics will involve the application of innovative techniques, such as machine learning for reaction pathways, continuous-flow synthesis, and hybrid catalysis using a combination of catalytic systems (metal and non-metal). For instance, AI is being used to forecast retrosynthetic pathways, which streamlines the development of alternative pathways to target molecules.[19] Similarly, the use of flow chemistry is becoming more popular for the continuous and safe production of high-demand drugs, which decreases the batch-to-batch variation and improves control over the reaction process. The combination of metal catalysis and organo-catalysis, or photo-catalysis, called dual or synergistic catalysis, is an example of innovative thinking that may provide new strategies for the construction of highly intricate molecules.[20]

In this review, we focus on the synthesis of analgesics and antipyretics using both metal and non-metal catalysis approaches. By analyzing the pivotal reactions, catalytic systems, and advancements in processes, we intend to provide an insightful review of the existing and anticipated advancements in this area of research while considering the importance of sustainability, operational efficiency, and the industrial relevance of contemporary drug synthesis.

2. Synthesis of Analgesics and Antipyretics by Metal-Catalyzed Methodologies

In recent years, transition metal catalysis has emerged as a powerful tool in the synthesis of analgesics and antipyretics. Metals can be used as catalysts to speed up the synthesis, as well as active components in metal-based drug composites.

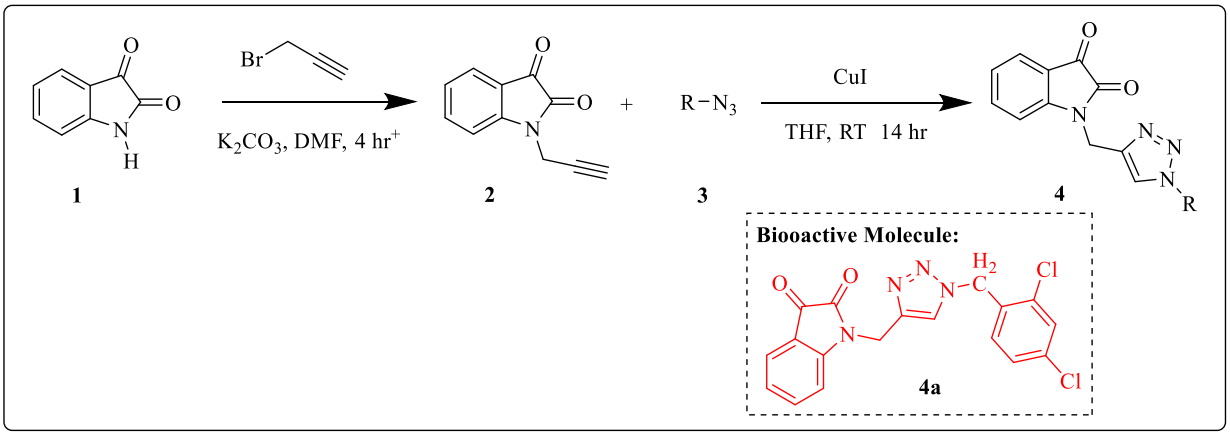
Palladium, copper, iron, and ruthenium, the most common transition metal catalysts, are used in various chemical reactions such as cross-coupling, oxidative aromatization, catalytic hydrogenation, Cu-catalyzed click cycloaddition and intramolecular cyclization.[7,21] These reactions are important in the synthesis of drugs. For example, metal-catalyzed methods have optimized the synthesis of analgesic and antipyretic drugs, paracetamol (acetaminophen), ibuprofen, and aspirin, and other drugs that are important in the synthesis of essential aromatic and heterocyclic compounds.[6]

Unlike methods that involve the formation of metal complexes as therapeutic agents, metal catalysis, in this case, functions as a temporary participant in the reaction mechanisms and as such is not incorporated into the final product. This distinction affords greater versatility in the design of syntheses and broad substrate applicability, while also observing the principles of green chemistry.[4] This report analyzes metal catalyzed reactions in the synthesis of analgesics and antipyretics, highlighting certain catalytic pathways and their mechanistic advantages in comparison to traditional synthetic pathways.

2.1. Synthesis of isatin-1,2,3-triazole hybrid analogue

Isatin (1*H*-indole-2,3-dione) and its analogs show a range of biological activities, especially in terms of anticancer and antidiabetic effects. In this research, Kumar et al.,[22] synthesized and assessed nine isatin-1,2,3-triazole conjugates **4** (scheme 1) for their in vitro anti-inflammatory properties. Isatin **1** underwent *N*-propargylation using propargyl bromide and anhydrous K_2CO_3 in DMF at 25 ^oC for four hours, yielding *N*-propargyl-isatin (**2**), which then reacted with phenyl and benzyl azides **3** through 1,3-dipolar cycloaddition, utilizing CuI as the catalyst in THF at ambient temperature for 12 to 14 hours. This resulted in new substituted 11-(1-benzyl-1*H*-1,2,3-triazol-4-yl) methyl) indoline-2,3-dione **4**. Compound **4a** exhibited notable anti-inflammatory activity by significantly reducing pro-inflammatory cytokines as it diminished TNF-α secretion by 6.65 fold and 1.50 fold, IL-6 by 1.03 fold and 1.41 fold, and MCP-1 by 3.32 fold and 1.75 fold, at concentrations of 4 mM and 8 mM,

respectively, compared to the uninduced control.[22] These results indicate that compound **4a** has strong anti-inflammatory potential, effectively downregulating key inflammatory mediators.

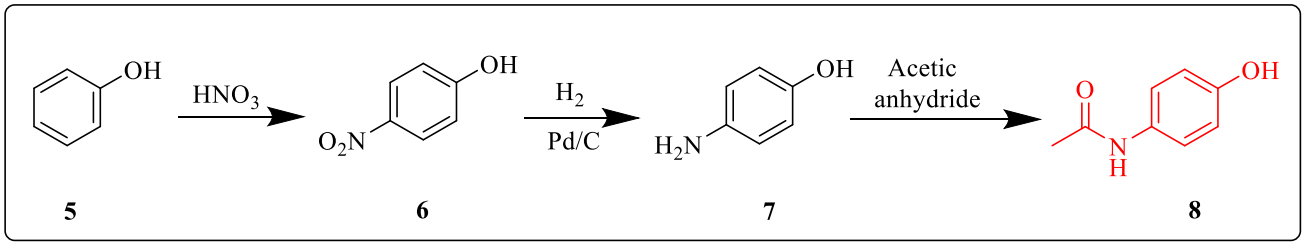


Scheme 1. Synthesis of isatin-1,2,3-triazol derivatives.

2.2. Palladium-based route to synthesis of paracetamol

New production methods for paracetamol **8** should start with renewable feedstock and work to reduce harsh chemistry that might not be able to satisfy the strict environmental standards of many nations. Due to its availability, renewability, and carbon neutrality, lignin is a viable renewable source of aromatics that might be utilized for API synthesis.[23,24] It is appealing to start with phenol **5** as the feedstock (a potential byproduct of lignin depolymerization).[25] Park et al.,[26] chose a phenol derivative 4-nitro phenol **6** for the synthesis of APAP (acetyl-para-aminophenol) **8** (scheme 2). The process involves nitration of phenol **5** to 4-nitrophenol **6,** followed by Pd/C catalyzed hydrogenation and subsequent acetylation to to synthesize paracetamo**l 8.**

In every category, the 4-NP route shows excellent green chemistry metrics. With only three stages from phenol to APAP, the process has low complexity and yields a product with quick reaction rates, near-quantitative selectivity when the proper conditions are met, and ambient reaction pressures and temperatures. With a relative process greenness score of 696%, it is rated as "Excellent".[26]

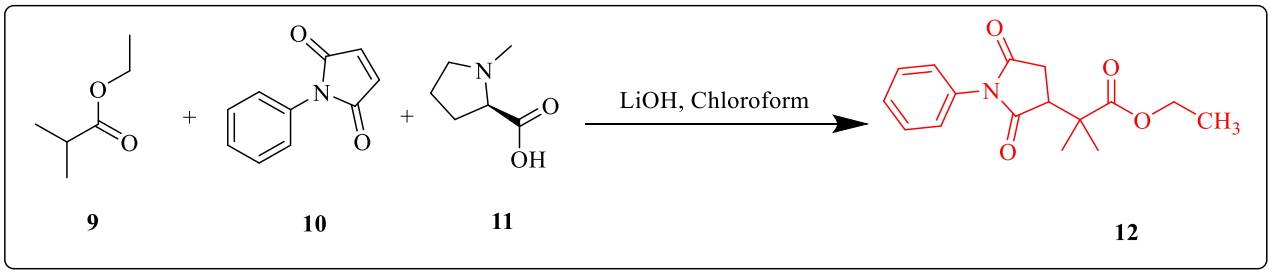


Scheme 2. Palladium based synthesis of paracetamol from phenol.

2.3. Synthesis of succinimide derivatives

Succinimide derivatives exhibit potential in treating inflammation, Alzheimer's, hypertension, oxidative stress, and diabetes due to their structural diversity. Sadiq et al.,[12] prepared ethyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanoate **12** (scheme 3) through an efficient synthetic technique that consists of a one-step reaction between ethyl isobutyrate **9** and *N*-phenylmaleimide **10** using *N*-methyl-L-proline **11** as an organocatalyst and lithium hydroxide in chloroform. Compound **12** displayed moderate anti-inflammatory

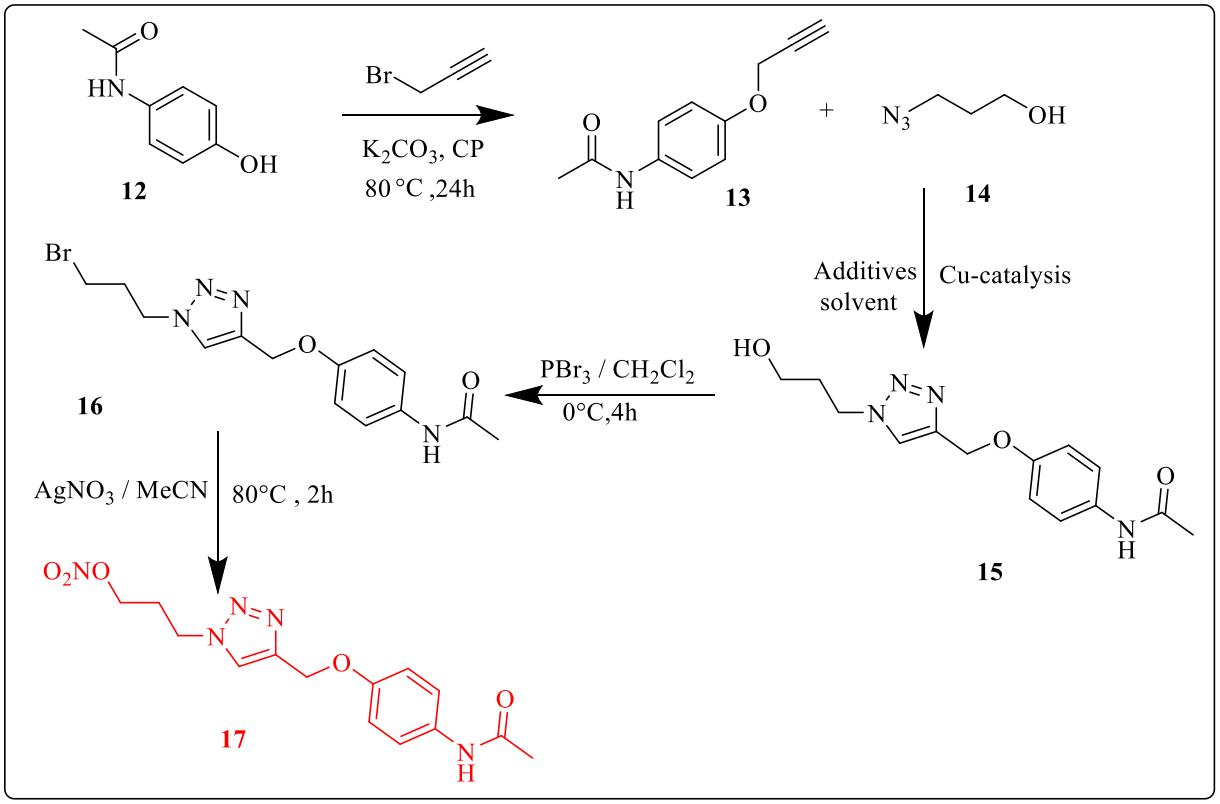
activity with IC_{50} values of 130 µg/mL against COX-2 and 314 µg/mL against COX-1 in an in vitro enzyme inhibition assay. The higher IC_{50} for COX-1 suggests some degree of COX-2 selectivtiy.[12]



Scheme 3. Synthesis of ethyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanoate.

2.4. Synthesis of 1,2,3-triazole-based acetaminophen

One important field of drug development is the study of novel APAP compounds.[27,28] Research indicates that a structural alteration of the N-acetyl p-aminophenol skeleton might enhance, decrease, or even alter a drug's enzymatic activities and, consequently, its pharmacological characteristics, such as cytotoxicity. Kouznetsov et al.,[29] designed two synthetic stages for the synthesis of the intended 1,2,3-TA-based APAP derivatives using click chemistry and green chemistry concepts (scheme 4). The synthesis began with extracting the active ingredient from expired commercial acetaminophen with a 97% extraction yield. This was followed by an O-alkylation reaction with propargyl bromide to produce O-propargyl-APAP **13**. This intermediate then underwent CuAAC (copper-catalyzed azide-alkyne cycloaddition) with 3-azidopropan-1-ol 14, followed by further transformations to yield the final nitric oxide-releasing N-propylnitrate-triazole-APAP hybrid 17 in good overall yield (61%).[29]

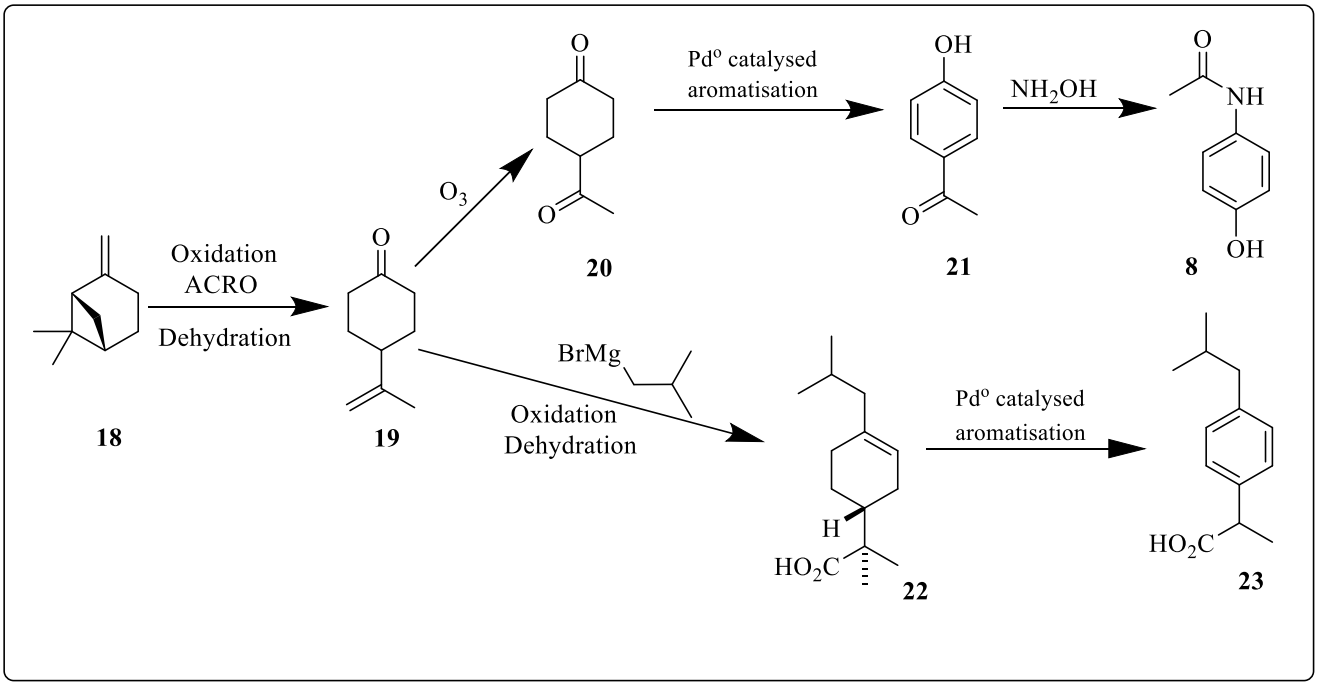


Scheme 4. Synthesis of 1,2,3-triazole-based acetaminophen through click chemistry.

2.5. Sustainable synthesis of paracetamol and ibuprofen from biorenewable β-pinene

Many frequently prescribed aromatic medications feature benzenoid rings, yet only a limited number have been produced using sustainable feedstocks. Consequently, the objective was to create synthetic pathways that transform β-pinene into the commonly utilized analgesic paracetamol. Tibbetts et al.,[30] identified methods to transform β-pinene **18** into 4-isopropenylcyclohexanone **19**, which is then used for the diverse synthesis of eco-friendly versions of ibuprofen and paracetamol. The benzenoid ring structures of both drugs result from aromatizing the cyclohexenyl rings of key intermediates through Pd-catalyzed reactions in each synthesis route.

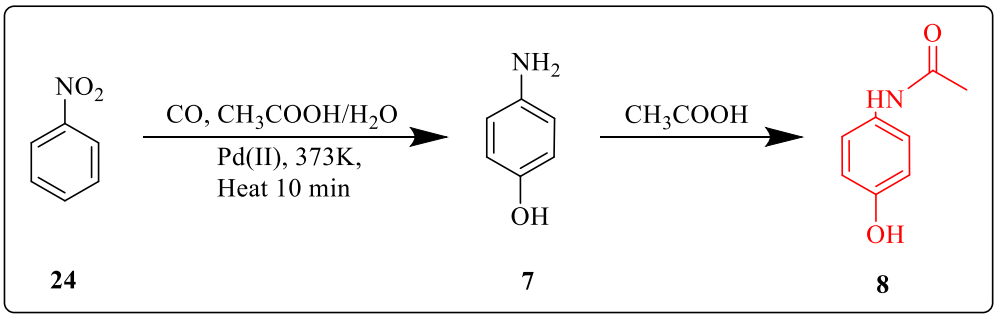
Initially, a method for oxidative ring-opening-dehydration was developed to convert compound **18** into **21**, a monocyclic compound. Subsequently, this vital intermediate serves as a bioderived feedstock for the unique synthesis of (rac)-ibuprofen **23** and paracetamol **8** (scheme 5)**.** The cyclohexyl ring structures of key intermediates 4-ACH **20** and cyclohexene acid **22** were transformed into the benzenoid rings of each analgesic using essential late-stage Pd^0-catalysed oxidative aromatization processes.



Scheme 5. Syntheses of paracetamol and (rac)-ibuprofen.

2.6. Synthesis of *N*-(4-hydroxyphenyl) acetamide selectively in one pot

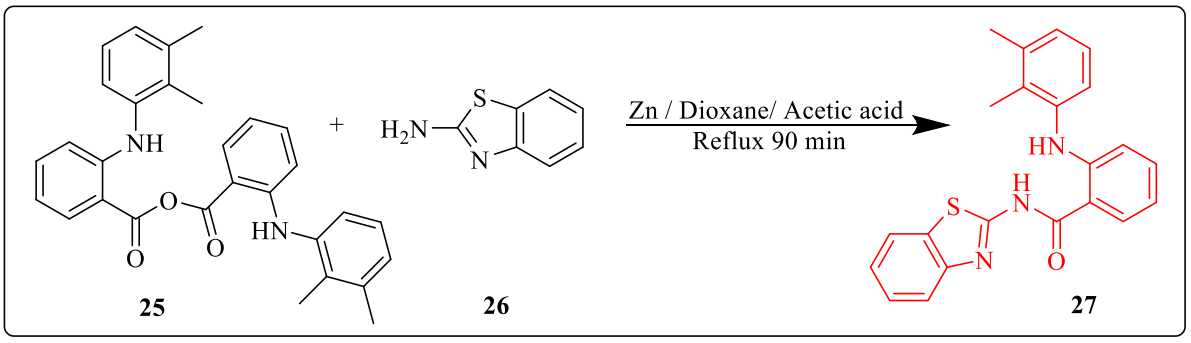
Although various strategies have been adopted to improve sustainability in industrial processes, developing more efficient and eco-friendly methods for producing acetaminophen continues to be a significant goal for numerous academic and industrial entities' researchers. Vavasori et al.,[31] synthesized *N*-(4-hydroxyphenyl)acetamide **8** in a one-pot reaction via palladium catalyzed reductive carbonylation of nitrobenzene **24** (scheme 6). The synthesis was carried out in a batch reactor using a Pd(II) complex (e.g., $[PdCl_2(dppb)]$) as a catalyst and H_2O-AcOH solvent under CO pressure at 373 K. This process affords conversion of compound **24** to acetaminophen **8** in a single pot through reduction and acetylation steps and offers good selectivity towards the desired p-hydroxy product.[31]



Scheme 6. Carbonylation of Nitrobenzene to form *N*-(4-hydroxyphenyl) acetamide.

2.7. Aminobenzothiazole derivatives of mefenamic acid

Among various heterocycles, aminobenzothiazole stands out due to its unique characteristics, including common therapeutic effects such as antibacterial, analgesic, and anti-inflammatory properties. By transforming the carboxylic acid functional group of mefenamic acid into a carboxamide group through the incorporation of aminobenzothiazole, these conjugates are regarded as isosteric functional groups that exhibit significant selectivity for COX-2. Baghernejad synthesized aminobenzothiazole analogs of mefenamic acid (scheme 7) with potential anti-inflammatory and analgesic characteristics.[10] A solution of compound **25** was refluxed with 2-aminobenzothiazole **26** in the presence of zinc powder, acetic acid, and dioxane for about 90 minutes. Ultimately, the target molecule **27** was obtained after workup and recrystallization from ethyl acetate. Analgesic activity was evaluated in vivo using the acetic acid–induced abdominal constriction (writhing) test in mice. Activity was quantified as the % inhibition of writhing relative to the control group. Compound **27** produced a constriction count of 20.31 ± 4.59 (mean ± SEM) at the dose of 31 µmol/kg, compared with 70.17 ± 2.93 in the control group. This corresponds to a 70.89% inhibition of abdominal constrictions, indicating a strong analgesic effect.[10]

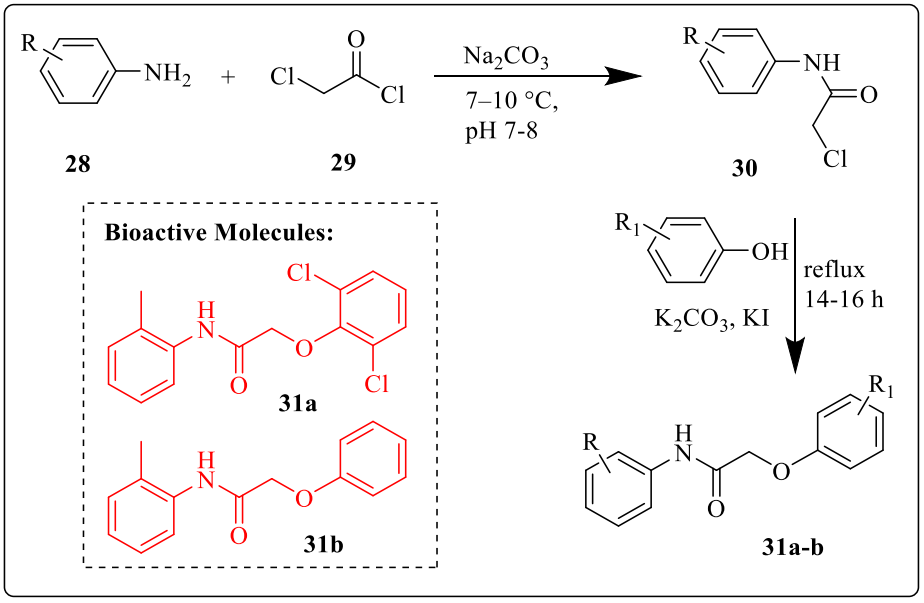


Scheme 1. Synthesis of aminobenzothiazole derivatives of mefenamic acid.

2.8. Synthesis of acetanilide derivatives

To reduce the inflammatory conditions, the primary targets include LOX, COX-1/2, and thromboxane. Some effective phenoxyacetanilide derivatives used to treat different inflammatory diseases comprise acetaminophen, indomethacin, phenacetin and phenylbutazone procainamide. Singh et al.,[11] set out to develop acetanilide derivatives **31a,b** (scheme 8) demonstrating pain-relieving and inflammation-reducing effects in laboratory animals, especially rats. These compounds were synthesized by refluxing 2-chloro-*N*-phenylacetamides **30** with phenolic compounds in anhydrous acetone using potassium carbonate, and potassium iodide under reflux conditions. Compound **31a** exhibited a COX-2 IC_{50} value of 39.26 µM (in vitro enzyme assay) and showed 80.12% reduction in carrageenan-induced paw edema in rats while **31b** exhibited

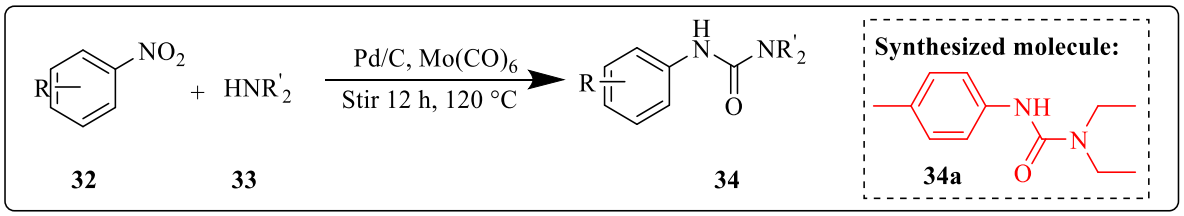
the high analgesic activity with a paw licking response of 4.9 seconds at 2 hours in the formalin-induced paw licking test in mice, indicating significant central and peripheral analgesic potential. The yield for **31a** was 74.19%.[11]



Scheme 8. Synthesis of substituted 2-phenoxy *N*-phenylacetamide**.**

2.9. Synthesis of Unsymmetrical Ureas

Ureas occupy a very important place in organic chemistry due to the many applications in the biological, pharmaceutical, agrochemical, and materials industries, as well as their use as organocatalysts. To synthesize urea derivatives, the older methods are based on very hazardous and toxic phosgene, isocyanates, and other carbamates and carbonates that are sensitive to moisture, resulting in serious environmental and health issues. There are alternative methods that use CO and CO_2 as the carbonyl source, but these methods work under extreme conditions (high pressure and temperature) and require the handling of toxic CO. Li et al.,[32] reported a Pd/C-catalyzed reductive carbonylation of cost effective and "green" nitroarenes **32** to unsymmetrical ureas **34** (scheme 9) with moderate to good yields.The synthesis of urea occurred by reacting **32** with diethylamine **33** in the presence of Pd/C and $Mo(CO)_6$ as a carbonyl source in 1,4-dioxane at 120 °C .The desired urea product **34a** was obtained with 79% yield. This method provides a safer and more eco-friendly alternative to traditional methods by avoiding the direct use of CO gas and toxic reagents.

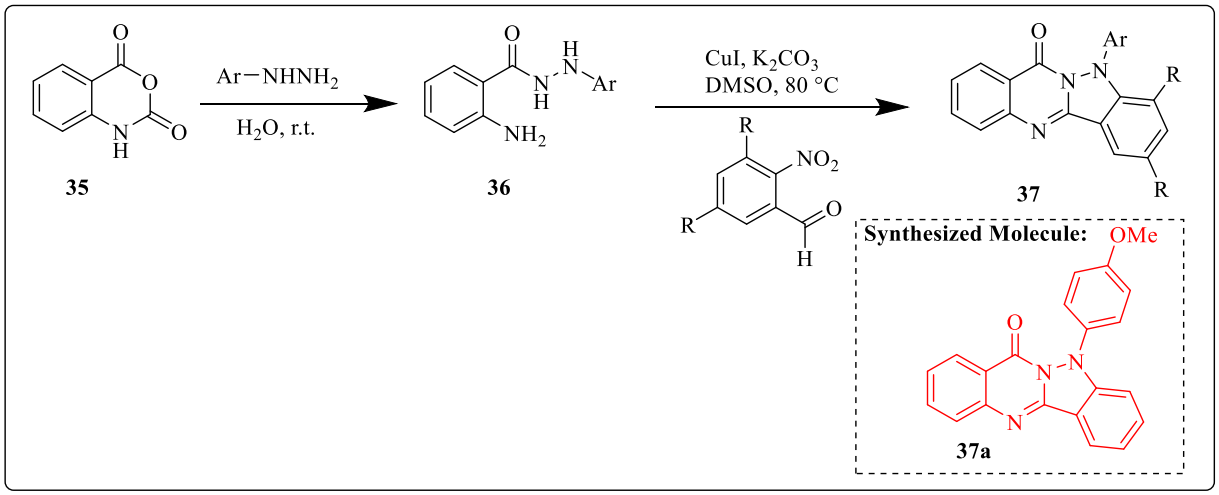


Scheme 9. Synthesis of nitroarenes from unsymmetrical ureas.

2.10. Synthesis of 5-arylindazolo [3,2-b] quinazolin-7(5*H*)-ones

Considering the varied properties of *N*-containing quinazolinone and indazole heterocycles, one can reasonably expect that fused quinazolinone-indazole derivatives, such as indazolo [3,2-b] quinazolinones, display significant

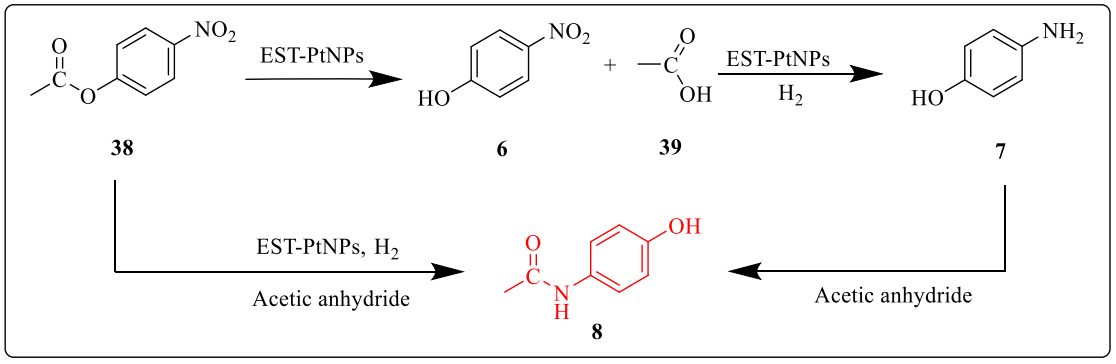
biological activity. Fard et al.,[33] developed 5-arylindazolo [3,2-b]quinazolin-7(5*H*)-ones (scheme 10) utilizing an innovative copper-catalyzed approach. The reaction between isatoic anhydride **35** and arylhydrazine readily yields 2-amino-*N*'-*N*'-arylbenzohydrazide **36**. Subsequently, the target compounds **37** are synthesized in good yields through a condensation and intramolecular cyclisation process involving 2-nitrobenzaldehydes in the presence of CuI and K_2CO_3 in DMSO at 80 °C for 8 hours. Compound **37a** was synthesized in 88% yield under ligand-free CuI-catalyzed conditions. The key benefits of this approach are the excellent yield of the products, ligand-free metal catalysis, and the simplicity of the starting ingredients.



Scheme 10. Synthesis of 5-arylindazolo [3,2-b]quinazolin-7(5*H*)-ones.

2.11. Acetaminophen synthesis via the synergistic catalytic action of EST–PtNPs

Metal nanoparticles composed of highly active metals such as platinum and palladium have undergone substantial study for use in numerous areas, including chemical synthesis and biomedicine. The combination of an enzyme and a metallic nanoparticle with complementary activities can substantially improve the catalytic efficiency, stability and functionality of both elements in biological processing. San et al.,[34] combined octameric esterase (EST) from *M. smegmatis* and platinum nanoparticle (PtNP) to create a bioinorganic nanohybrid catalyst. Compared to each catalyst alone, the combination of the two catalysts increased PtNPs' hydrogenation, esterase hydrolysis, and catalytic activity. Acetaminophen **8** was successfully synthesized (scheme 11) in multiple steps using this hybrid catalyst in a single-pot process. Using 4-nitrophenyl acetate **38**, 4-nitrophenol **6**



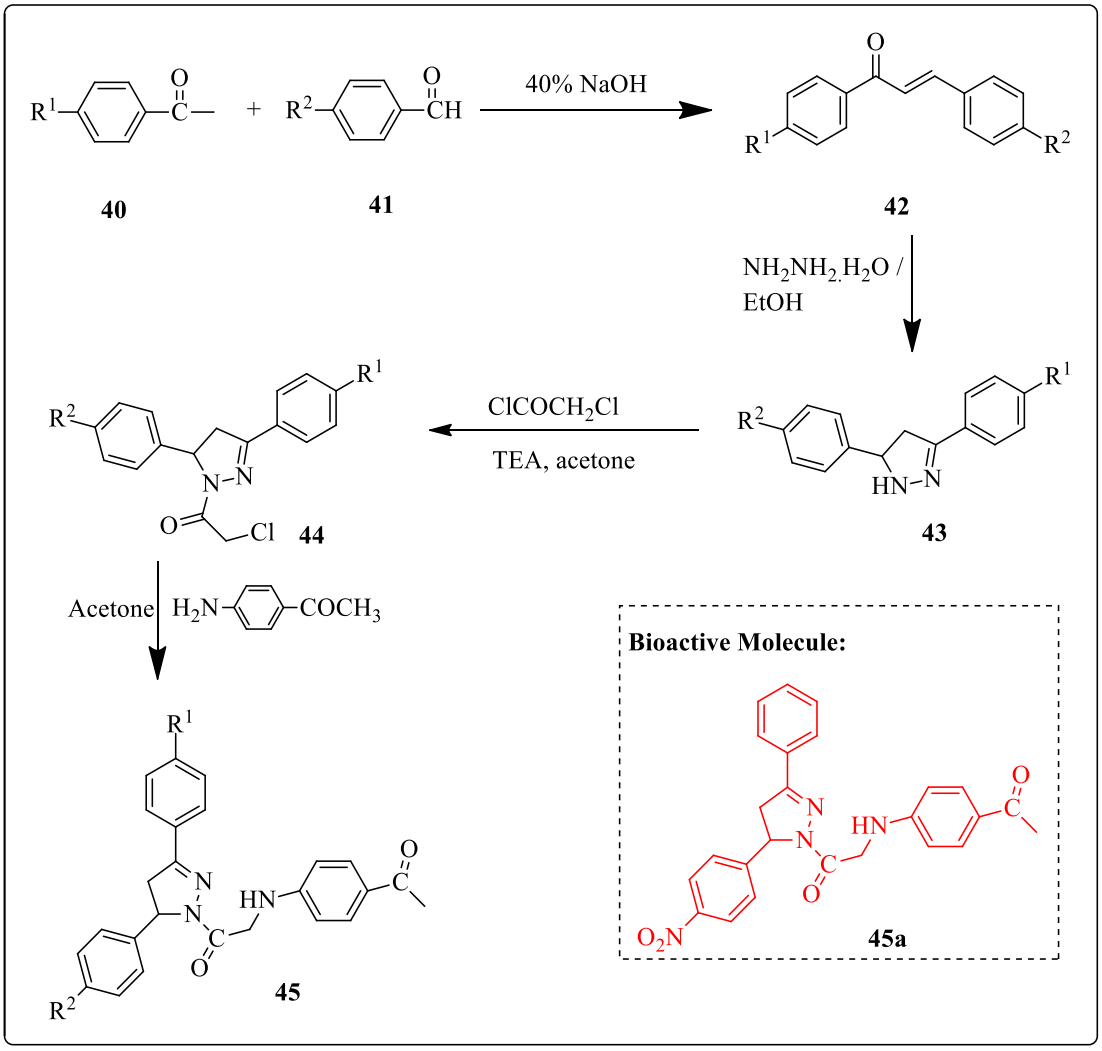
Scheme 11. Synthesis of acetaminophen from 4-nitrophenol acetate using EST–PtNPs and acetic acid anhydride.

was generated through EST-mediated hydrolysis and turned yellow. The hydrogenation of **6** was confirmed due to the disappearance of yellow color in reducing conditions using acetic acid **39**, demonstrating that a single

bioinorganic nanohybrid catalyst facilitated this two-step reaction. The final product, N-(4-hydroxyphenyl) acetamide **8**, was obtained by further reaction of the hydrogenated product **7** with acetic anhydride. The reaction of EST-PtNPs with **38**, $NaBH_4$, and acetic anhydride resulted in the formation of acetaminophen as the final product.

2.12. Synthesis of pyrazoline derivatives

Pyrazolines present a wide range of biological activities. The Claisen-Schmidt condensation of various substituted acetophenones **40** with aromatic aldehydes **41** in an aqueous solution of ethanolic sodium hydroxide produced the corresponding chalcones **42.** The cyclisation of **42** was achieved by reacting with hydrazine monohydrate in ethanol, resulting in the formation of cyclic derivatives **43**. **43** reacted with chloroacetyl chloride in acetone, using triethylamine (TEA) as a catalyst, resulting in compounds **44**. The title compounds **45** were prepared by the reaction of **44** with p-aminoacetophenone in acetone in the presence of anhydrous K_2CO_3 (scheme 12). To determine their median effective doses (ED_{50}), compound **45a** and the reference drug celecoxib (Figure 2) were evaluated for *in vivo* anti-inflammatory and analgesic activities using a carrageenan-induced rat paw edema model and a mouse hot-plate test, respectively. Compound **45a**, which has a nitrophenyl group, was recognized as the strong anti-inflammatory and analgesic compound in the study, showing ED_{50} values of 59.4±3.3 and 38.6±1.3 mg/kg, respectively. IC_{50} value for COX-2 is 10 µM. [13]

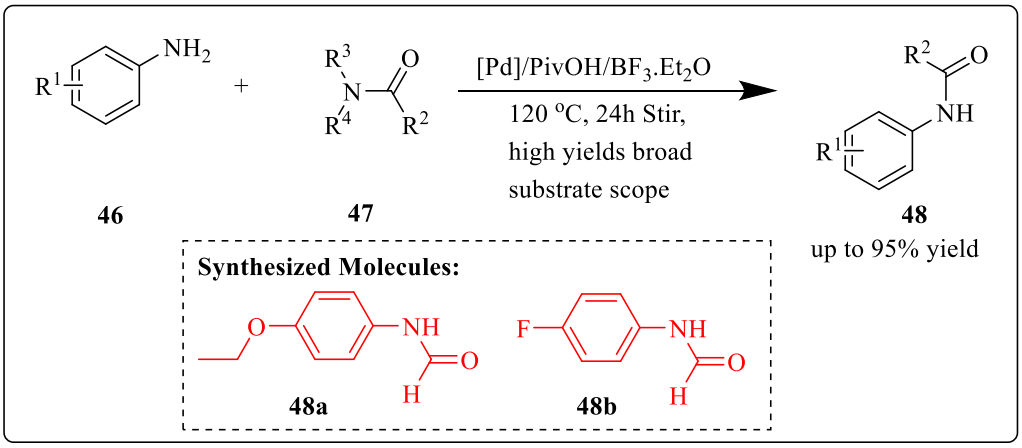


Scheme 2. Synthesis of *N*-acetylphenylaminoacetyl protected pyrazolines.

2.13. Synthesis of *N*-aryl carboxamides

The diverse uses of amides in various industries makes them an important class of compounds. Traditional methods for the formation of N-arylcarboxamides are often associated with the use of toxic and hazardous chemicals. Gu et al.,[35] reported reported a palladium-catalyzed direct transamidation of dimethylformamide (DMF) with weakly nucleophilic anilines as an efficient alternative (scheme 13).

IN this process DMF **47** reacted with anilines **46** in the presence of PivOH, and $BF_3{\cdot}Et_2O$ in toluene at 120 °C for 24 hours. This method affords the synthesis of N-aryl carboxamides **48** in upto 95% yield which shows broad substrate scope.



Scheme 13. Transamidation of DMF with anilines to synthesize *N*-arylcarboxamides.

2.14. Approved Analgesic and Antipyretic Drugs in metal based synthetic methodologies:

The metal-catalyzed synthesis of approved analgesics and antipyretics primarily features the use of transition metals, especially Palladium (Pd), to construct the core structure of the drugs. The key approved drugs synthesized via these detailed schemes are paracetamol (acetaminophen) and ibuprofen. For Paracetamol, metal catalysis has been shown in these distinct routes: a unique one-pot process using an Esterase-Platinum Nanoparticle (EST–PtNP) hybrid catalyst, Pd(II)-catalyzed reductive carbonylation and Pd/C hydrogenation route. Similarly, the synthesis of Ibuprofen is detailed via a Pd-catalyzed oxidative aromatization reaction to efficiently form its benzenoid ring from a common precursor, illustrating how modern metal-based chemistry improves the synthesis of these established drugs.

3. Synthesis of analgesics and antipyretics by metal free methodologies

Many of the analgesics and antipyretics that are widely used today are created through established organic processes that do not involve metal elements. Examples of these include paracetamol, aspirin, and ibuprofen, which are synthesized through relatively simple chemical reactions such as nitration, reduction, acetylation, and esterification. For example, paracetamol is generally produced by acetylating p-aminophenol with acetic anhydride, resulting in a stable and effective pain and fever reducer.[36] Aspirin is manufactured using what is known as an esterification reaction. In this reaction, salicylic acid is combined with an acetic anhydride molecule, and this technique has been used for over hundred years because of its simplicity.[37]

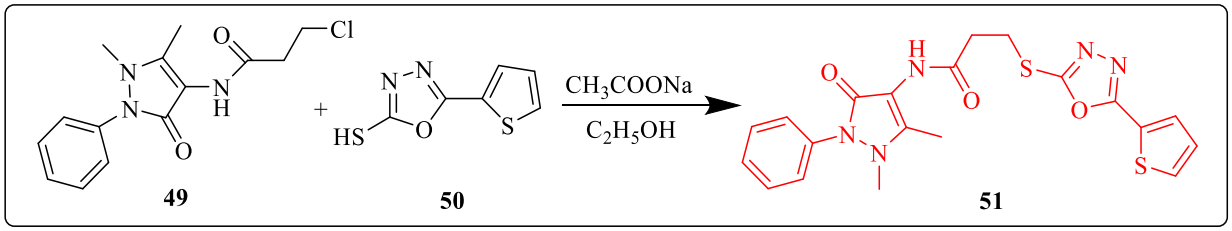
These drugs most often perform their function by blocking the actions of cyclooxygenase (COX) enzymes which play crucial role in the synthesis of prostaglandins, the important mediators of pain and fever. Non-metal-

based NSAIDs are COX-1 and COX-2 inhibitors. By blocking the actions of these COX enzymes, the drugs reduce the pain and fever and also provide an anti-inflammatory effect.[38]

In addition, the drugs are preferred because they are inexpensive to manufacture and have a very high margin of safety, if they are taken according to the prescription. They are fully developed and have a documented safety profile with respect to their absorption, metabolism, and excretion.[39] Therefore, the non-metal based analgesics and antipyretics are very important to the pharmaceutical industry as they are the first choice for over the counter treatment for headaches, muscle pain, fever, and mild arthritis.[40]

3.1. Synthesis of Novel 4-Aminoantipyrine Derivatives

The anti-inflammatory and pain-relieving potentials of 4-aminoantipyrine and its derivatives have gathered substantial interest. This encompasses the synthesis and assessment of various enaminonitrile analogs of antipyrine, regarded as promising candidates for anti-inflammatory and pain-relief purposes. Findings reveal that these compounds indeed exhibit analgesic effects. Mohammed et al.,[15] synthesized and evaluated the analgesic effects of a new amino antipyrine derivative **51** (scheme 14)**,** created by linking amino antipyrine **49** with oxadiazole and triazole structures. The final compounds were produced by a nucleophilic substitution involving the ionized sulfur (-S-) atom in oxadiazole **50** or triazole thiols attacking the methylene group (-CH_2-Cl) of the amino antipyrine derivatives **49**. The byproducts generated were acetic acid and sodium chloride. This reaction mechanism followed the SN_2 pathway.[41] Compound **51** demonstrated 69% inhibition of acetic acid-induced writhing in albino mice when evaluated at a dose of 50–100 mg/kg outperforming the standard drug paracetamol (Figure 2) in analgesic potency under the same experimental conditions.

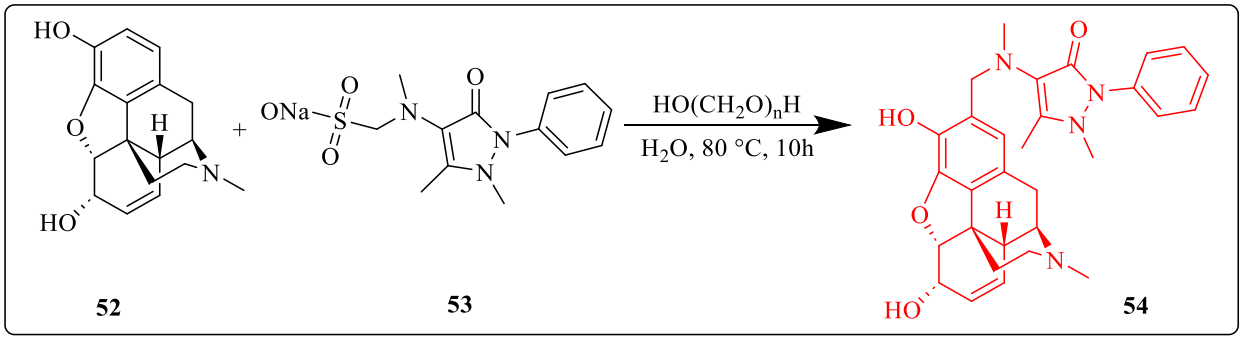


Scheme 14. Synthesis of *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-((5-(thiophene-2-yl) 1,3,4-oxadiazol-2-yl)thio)propenamide.

3.2. Synthesis of metamorphine: a morphine–metamizole adduct

Combining PCA pumps opioids, such as morphine, with other analgesics, such as metamizole **53**, is believed to alleviate the negative effects associated with the use of monotherapy PCA pumps and improve pain relief.[42] A key limitation of morphine-metamizole PCA pumps is the drug mixture's stability. Additionally, metamizole sodium functions as a prodrug, gradually decomposing in H_2O or methanol at pH 7, while it decomposes more quickly in acidic environments to produce 4-methylaminoantipyrine (4 MAA). This unforeseen reduction of both medications results from a drug interaction that causes the in situ creation of a new compound known as metamorphine **54,** through a Mannich condensation process.[42]

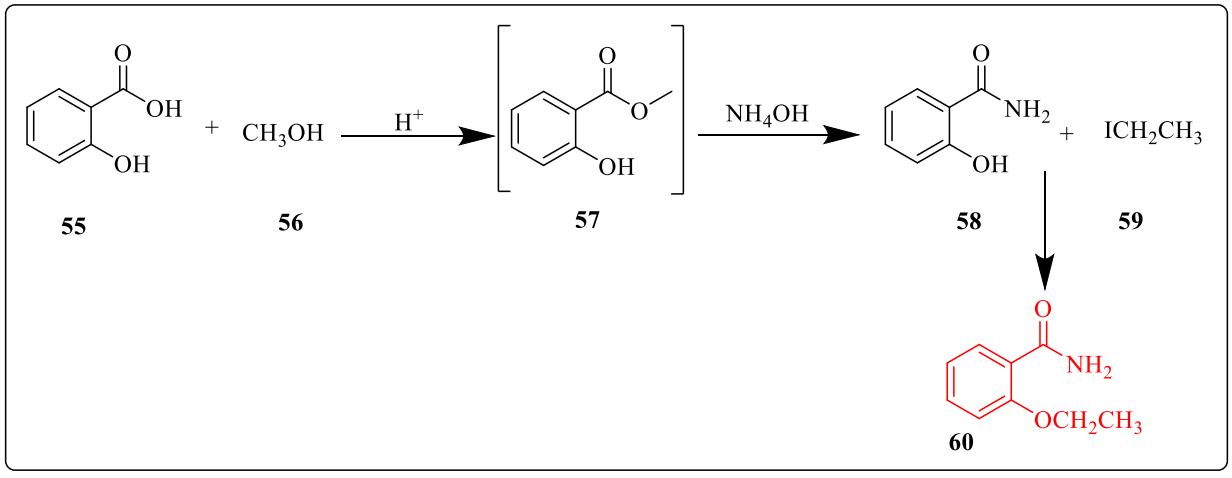
Abotaleb *et al*.,[42] described a morphine-metamizole adduct having a phenazone group located at the C2 position of the morphinan core. This compound **54** was initially discovered as a byproduct of the interaction between morphine and metamizole in PCA pumps for severe pain management. In this study, morphine hydrochloride trihydrate was reacted with compound **53** and paraformaldehyde in water at 80 °C for 10 hours to promote the formation of compound **54** (scheme 15). Experiments under various conditions indicated that a mass ratio of 5:1 of **53** to **52** yielded the quickest reaction time, achieving full conversion to **54**.



Scheme 15. Synthesis of metamorphine.

3.3. O-Alkylation of salicylamide to synthesize ethenzamide

Ethenzamide **60** is a derivative of salicylamide **58** that has analgesic and anti-inflammatory effects and can relieve skeletal muscular tension.[43,44] It is commonly used in combination with paracetamol or acetylsalicylic acid and caffeine to treat colds, headaches, toothaches, menstrual cramps, and fever. Through the O-alkylation process of **58**, Niedziejko-Cwiertnia et al.,[45] established an efficient and ecologically acceptable method for manufacturing ethenzamide **60** (scheme 16). The process begins with the synthesis of salicylamide **58** from salicylic acid **55** via esterification followed by aminolysis. The reactions were carried out under conventional circumstances in a solvent-free system using different solvents and phase transfer catalysts (PTC) under ultrasonic or microwave radiation conditions. The TBAB-catalyzed reaction (with K_2CO_3) under solvent-free conditions produced the maximum yield (92%) in 90 seconds, providing a very high yield when using a direct microwave-assisted method. [45]

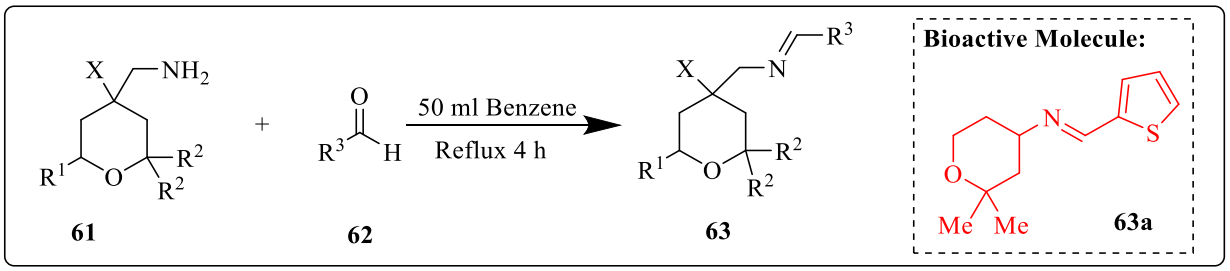


Scheme 16. Synthesis of ethenzamide via O-alkylation of salicylamide.

3.4. Synthesis of azomethine derivatives from the tetrahydropyran series

The synthesis of Schiff bases from the tetrahydropyran series involved the reaction between 2-(tetrahydropyran-4-yl)ethanamines and tetrahydropyran-4-amine with various aromatic aldehydes, such as 4-Cl, 4-F, and 4-(dimethylamino) benzaldehydes, as well as thiophene-2-carbaldehyde. To synthesize Schiff base compound **63** (scheme 17)**,** an equimolar mixture of amines **61** and the chosen aromatic aldehyde **62** was refluxed in a flask for four hours. Afterward, the solvent was evaporated. When given at a dosage of 25 mg/kg, compound **63a** showed weak to moderate effectiveness, showing 31% inhibition in the acute exudative

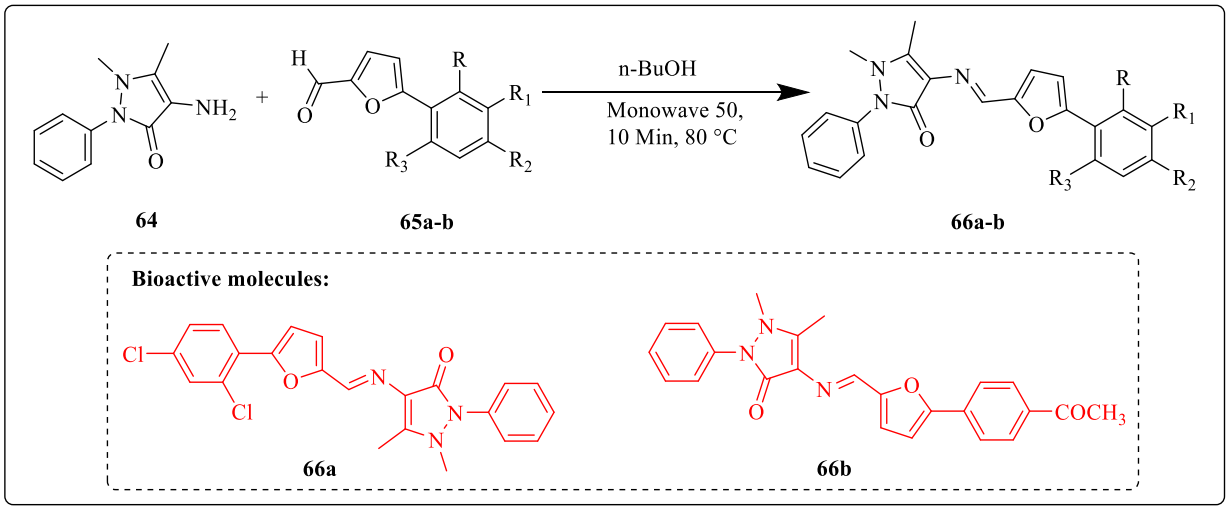
inflammation model (carrageenan-induced paw edema in rats). Synthesized compound displayed reduced anti-inflammatory, pain-relieving, and fever-reducing effects compared to the reference drugs diclofenac and indomethacin (Figure 2).[46]



Scheme 17. Synthesis of Schiff bases of tetrahydropyran.

3.5. Synthesis of Schiff bases containing arylfuran and pyrazole moieties

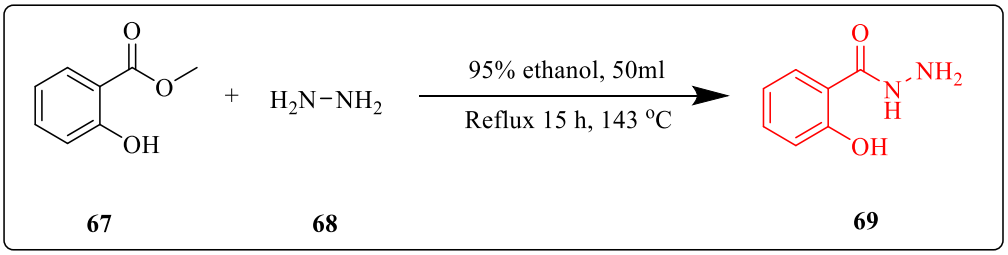
4-Aminoantipyrine **64** acts as a key intermediary in the development of bioactive molecules and prospective pharmaceuticals. Of the analogs of 4-aminoantipyrine, Schiff bases stand out due to their notable biomedical properties. Moreover, arylfurans, which demonstrate a wide range of biological activities, have been studied as candidate therapeutics. Kosylo et al.,[47] reported the synthesis of a new series of azomethines containing pyrazole and aryl furan units, in particular, the compound 4-[amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one **66a-b** (scheme 18) which was synthesized by condensing **64** with 5-arylfurfural **65a-b** in a monowave 50 synthesis reactor in 4-butanol at 80 °C for 10 minutes. The yields of Schiff bases varied between 62% and 90%. According to the results of PASS software modeling, compound **66b** is likely to have combined effects, including anti-inflammatory, insulin-suppressing, and antipyretic properties with the Ra values of 0.886, 0.909 and 0.886 respectively. Ra value is the probability of biological activity as predicted by PASS online software, with values ranging from 0 to 1, where a value closer to 1 indicates a higher probability of that activity being experimentally confirmed. Ra value = 0.815 indicates that compound **66a** possesses the highest analgesic activity among all.



Scheme 18. Synthesis of 4-(((5-Arylfuran-2-yl)methylene)amino)-1,2-dihydro-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one.

3.6. Synthesis of 2-Hydroxybenzohydrazide

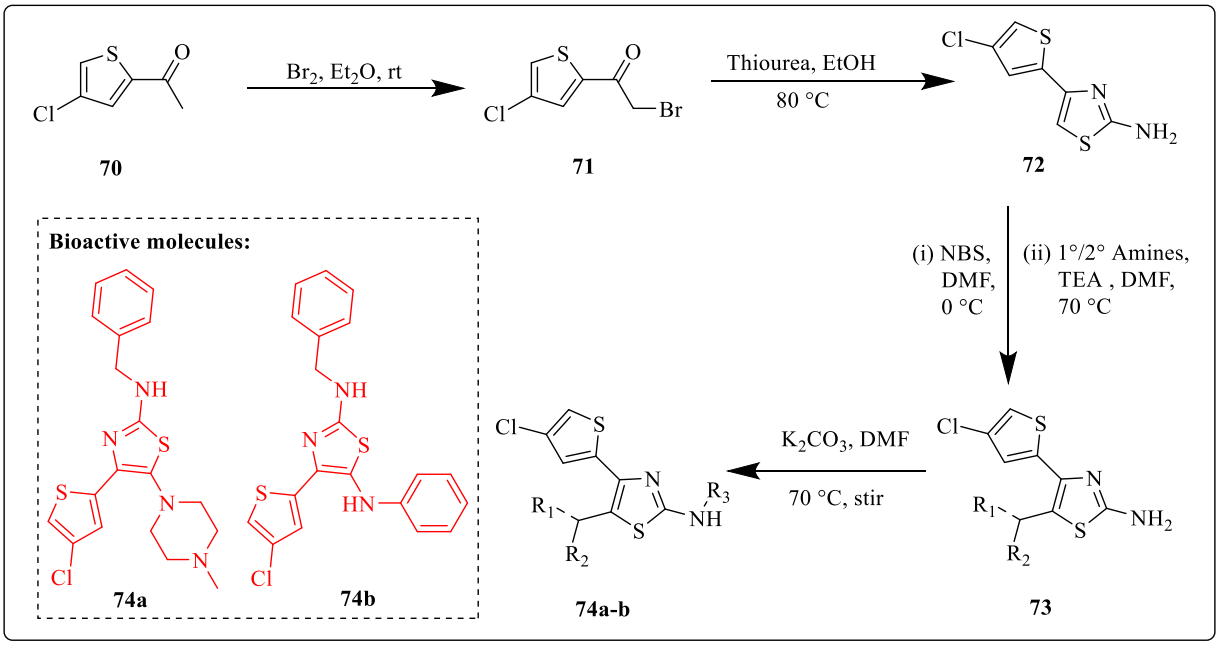
Acid hydrazides exhibit various types of pharmacological activities such antibacterial, anticancer, antitumor, and antinociceptive.[48] Ali et al.,[17] studied the effects of 2-hydroxybenzohydrazide (HBH) **69** as a potential drug for fever, inflammation, and pain. For the synthesis of compound **69** (scheme 19) , hydrazine hydrate **68** and methyl salicylate **67** were mixed and they were refluxed for 15 hours in ethanol. The mixture was then concentrated and added to crushed ice. The resultant solid was separated, obtaining the yield of 75%. Compound **69** demonstrated significant analgesic and anti-inflammatory activity. At a dose of 60 mg/kg, it produced 61.13±4.82% inhibition of carrageenan-induced paw edema at 3 hours, which was comparable to the effects of the standard drug diclofenac sodium (50 mg/kg) (Figure 2).



Scheme 19. Synthesis of 2-hydroxybenzohydrazide.

3.7. Alteration of 4-chlorothiophen-2-yl) thiazol-2-amine derivatives

The thiazole nucleus is considered a promising bioactive scaffold across multiple biological systems. In studies, any thiazole-based compounds have shown potential against cancer, bacteria, HIV, blood clotting, inflammation, and even oxidative stress. One of these compounds is the thiazole core containing anti-inflammatory drug meloxicam. Mahnashi et al.,[16] analyzed thiazole scaffolds with pharmacological potential for developing a new anti-inflammatory drug. They synthesized derivatives of 4-(4-chlorothiophen-2-yl)thiazol-2-amine **74a-b** (Scheme 20) through a multi-step synthetic approach.

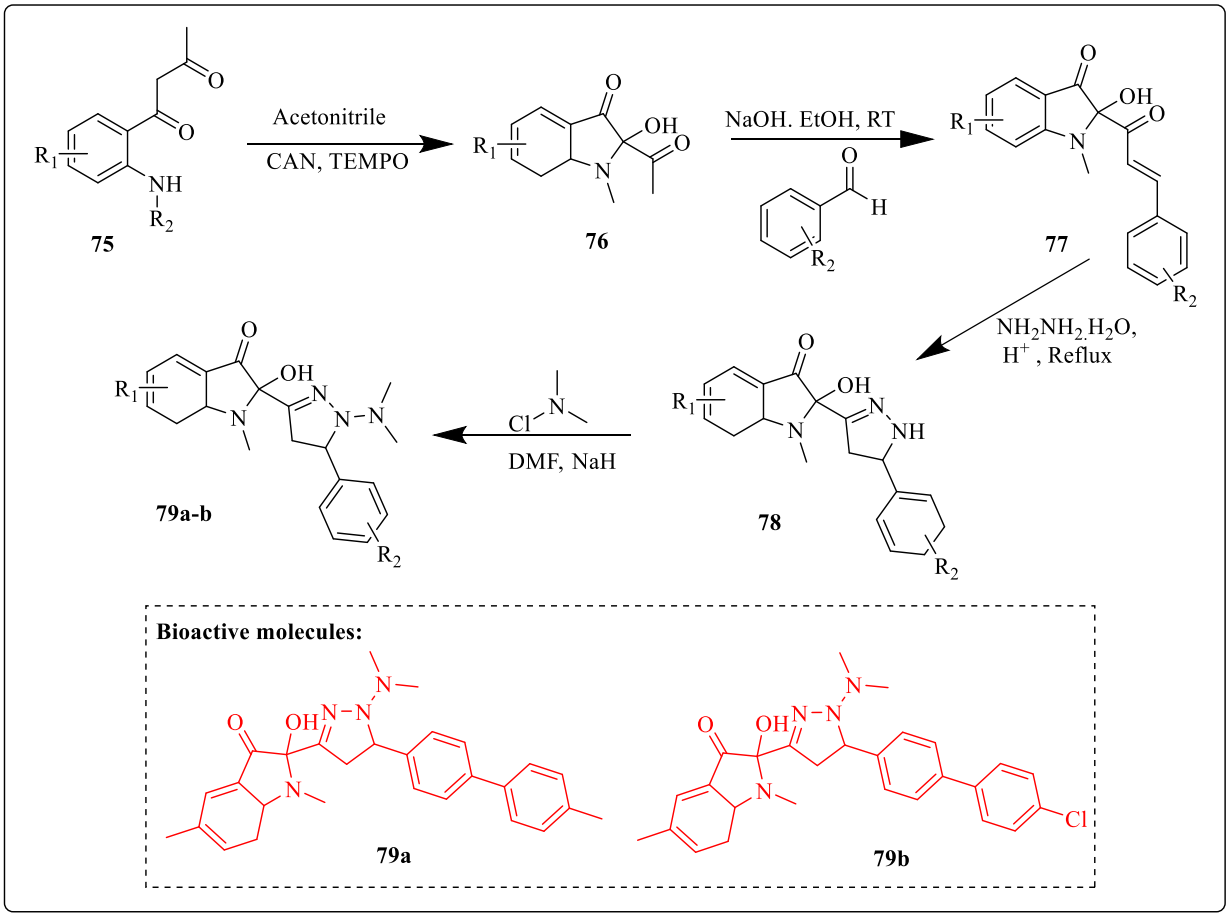


Scheme 20. 4-(4-chlorothiophen-2-yl) thiazol-2-amine derivatives.

The synthesis started with the bromination of 1-(4-chlorothiophen-2-yl) ethan-1-one **70** in diethyl ether at room temperature. The resulting brominated product **71** was then reacted with thiourea at 80 °C to yield compound 4-(4-chlorothiophen-2-yl)thiazol-2-amine **72.** Subsequent treatment with NBS, followed by incorporation of primary or secondary amines acquired the intermediate **73** which underwent treatment with potassium carbonate in dimethylformamide at 70 °C to yield the final compounds **74a-b.** In comparison to the standard medications, zileuton, aspirin, and celecoxib for 5-LOX, COX-1, and COX-2, respectively, **74a** and **74b** exhibited strong anti-COX and anti-LOX activity. In in vitro enzyme assays, against COX-1, **74a** showed an IC_{50} of 93.41±0.06 µM, and 0.83+-0.03 µM against COX-2 which shows excellent COX-2 selectivity.

3.8. Synthesis of novel pyrazolyl indoline-3-one hybrids

Indole analogs display different potentials, including antioxidant, anticancer, antidepressant, anticonvulsant, anti-inflammatory, antifungal, antiviral, anti-rheumatic, and anti-HIV properties. Various pyrazole drugs, such as sildenafil, which inhibits PDE, and celecoxib, known for its action on cannabinoid receptors and COX-2 inhibition, also exhibit anti-inflammatory effects. Swathi et al.,[49] developed a new pyrazolyl indoline-3-one hybrid **79** (Scheme21), by combining these two distinct heterocycles. The anti-inflammatory, analgesic, and



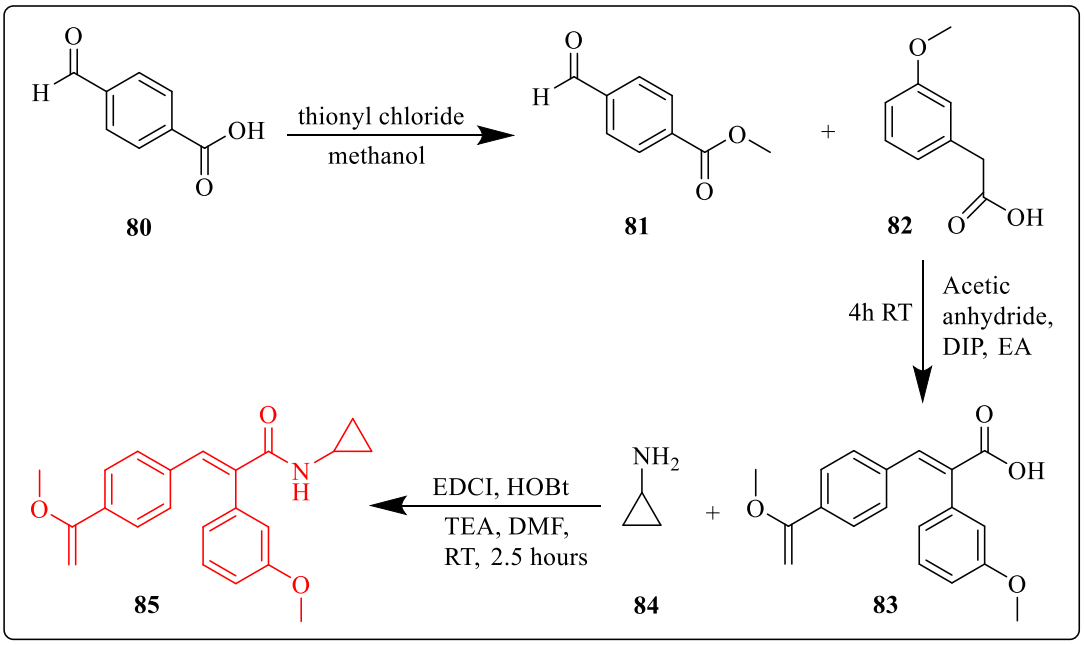
Scheme 21. Synthesis of pyrazolyl indoline-3-one hybrids.

antipyretic effects of each final product were evaluated using a dosage of 10 mg. To synthesize substituted 2-acetyl-2-hydroxy-1-methylindolin-3-one **76**, substituted 1-(2-aminophenyl)butane-1,3-dione **75**, TEMPO, and CAN were solubilized in acetonitrile under oxygen atmosphere. Compound **77** was generated via the Claisen-Schmidt condensation of compound **76** and benzaldehyde, which then reacted with hydrazine hydrate in acetic

acid to form compound **78**, which was later reduced with chloramine in DMF and sodium hydride to produce the final product **79.** Compound **79a** exhibited the highest antipyretic activity of 36.02±0.04% reduction in brewer's yeast-induced pyrexia in rats at 3 hours (10 mg/kg dose). Compound **79b** showed 50.7% inhibition of abdominal writhing in the acetic acid-induced writhing test in mice, which shows good pain-relieving potential.

3.9. Synthesis of methyl 4-[(1E)-3-(cyclopropylamino)-2-(3-methoxyphenyl)-3-oxoprop-1-eny] benzoate

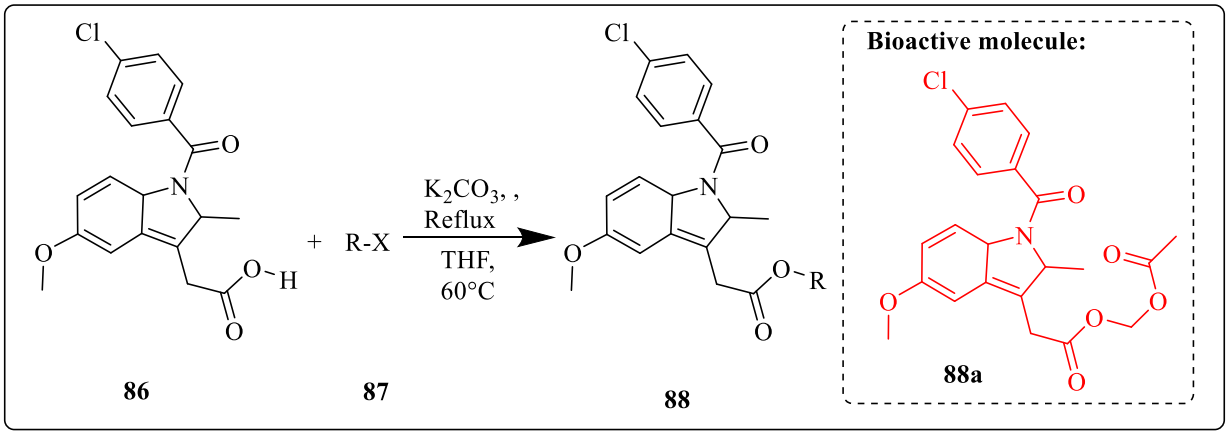
Deivanayagam et al.,[50] synthesized the chalcone-derived compound **85** as a potential bioactive molecule (scheme 22). Initially, substituted benzoic acid **80** reacts with thionyl chloride and CH_3OH to produce 4-formyl benzoate **81**. This intermediate then reacts with the acetic acid derivative **82**, yielding **83**. The next step involves treating this product with cyclopropyl amine **84** to afford the final product **85**. Compound **85** showed 52.52% rise in CNS stimulant potential compared to control and exhibited 30.07% analgesic activity in experimental models. These findings suggest that compound **85** possesses moderate analgesic properties along with some CNS stimulating effects.



Scheme 22. Synthesis of (2*E*)-3-[4-(methoxycarbonyl) phenyl]-2-(3-methoxyphenyl)prop-2-enoic acid.

3.10. Synthesis of Indomethacin Analogues

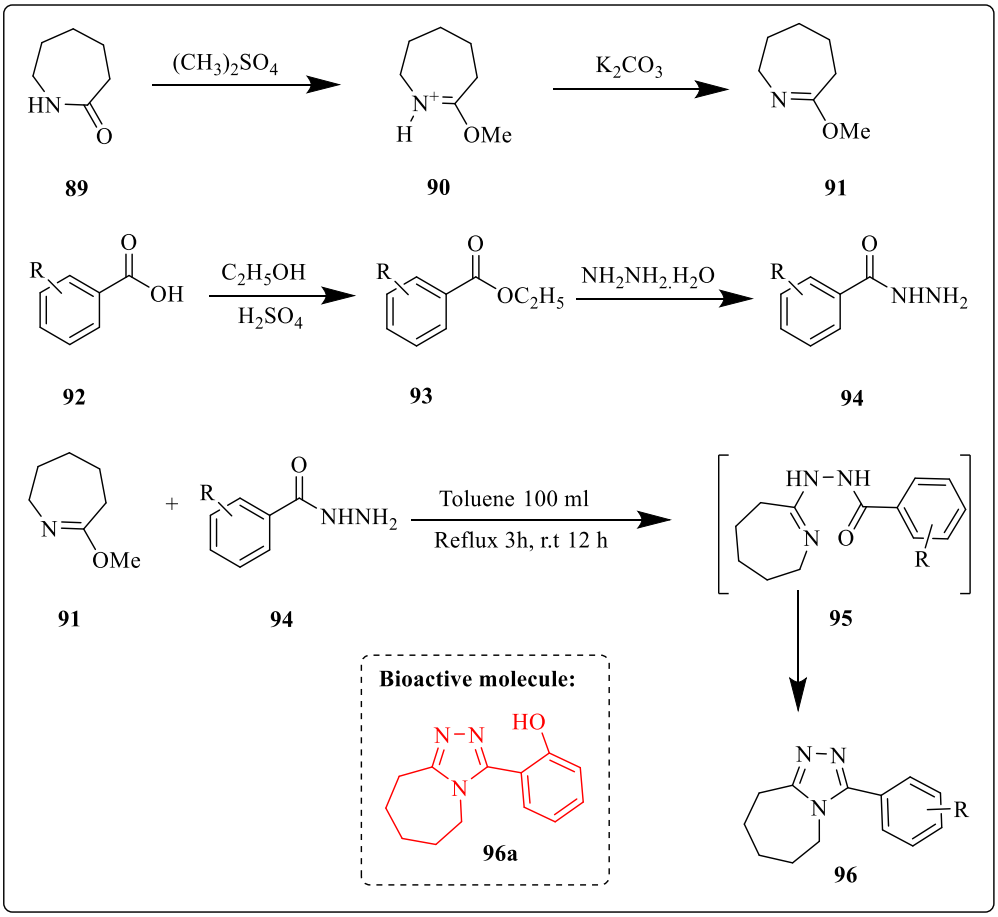
Indomethacin, a traditional NSAID from the indole acetic acid drug class, effectively alleviates pain associated with migraines and headaches. It blocks both COX enzyme isoforms involved in prostaglandin production and influences a broader spectrum of receptors and enzymes. There have been attempts to create indomethacin analogues that offer enhanced potency, efficacy, and reduced toxicity. Ahmad et al.,[51] developed a derivative **88** (scheme 23) of the lead compound, indomethacin **86**, through a reflux condensation process focused on the hydroxyl group. **86** reacted with many alkyl halides **87**, using K_2CO_3 as a base and tetrahydrofuran (THF). This resulted in the production of ester derivative **88** in high yield. Compound **88a** exhibited significant analgesic activity in the acetic acid-induced writhing test in mice, showing 61.7%, 67.5%, and 86.2% inhibition at doses of 10, 20, and 30 mg/kg, respectively which shows its analgesic potential is comparable to or better than parent drug indomethacin depending on dose.



Scheme 23. Synthesis of indomethacin analogue.

3.11. Synthesis of Fused Triazole-Azepine Hybrids

Heterocyclic compounds containing triazole and azepine rings stand out as promising targets for the development of potential new NSAIDs. Demchinko et al.,[52] researched on 3-aryl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3a]azepines **96** (Scheme 24), exploring their activity as nonsteroidal anti-inflammatory substances. First, 7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine **91** was synthesized from azepan-2-one **89**.

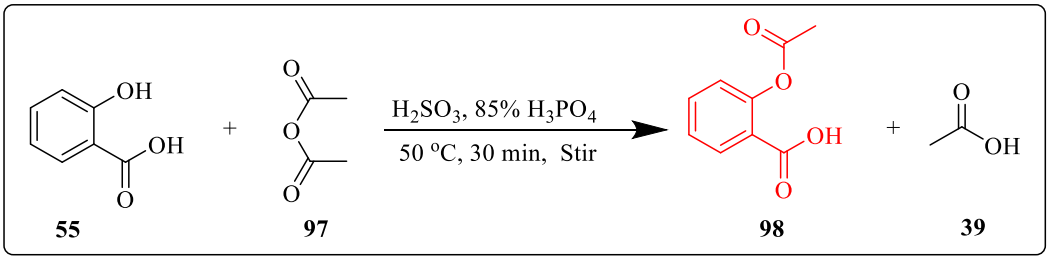


Scheme 24. Synthesis of ftriazole-azepine hybrids.

Substituted benzoic acid **92** was mixed with ethanol in the presence of sulphuric acid to produce substituted ethyl benzoate **93**, which was further mixed with hydrous hydrazine to get substituted benzohydrazide **94**.
For the synthesis of compound **96**, compound **94** was refluxed with **91** in toluene for 3 hours. In similar experimental conditions, compound **96a** proved to be more effective than ketorolac, demonstrating 95.5% inhibition of acetic acid-induced writhing in mice, whereas ketorolac (Figure 2) showed an inhibition value of 85.9%.

3.12. Synthesis of acetylsalicylic acid

Green chemistry is one of the most significant approaches to pharmaceutical sustainability. Golemac et al.,[53] conducted the syntheses of acetylsalicylic acid **98** (Scheme 25) using both the traditional method and the green chemistry method. In the process of ASA(acetylsalicylic acid**) 98** synthesis via conventional methods, salicylic acid **55** is reacted with acetic anhydride **97** in the presence of conc.H_2SO_4 at 50 °C.[54] For the **98** synthesis using green chemistry methods, the same procedure was applied, except phosphoric acid was used in place of conc.H_2SO_4 to reach the desired pH of 6.0.[55] Both methods synthesized the same product **98** but the green protocol provides benefits because of reduced environmental impact and safer handling while producing good quality product.

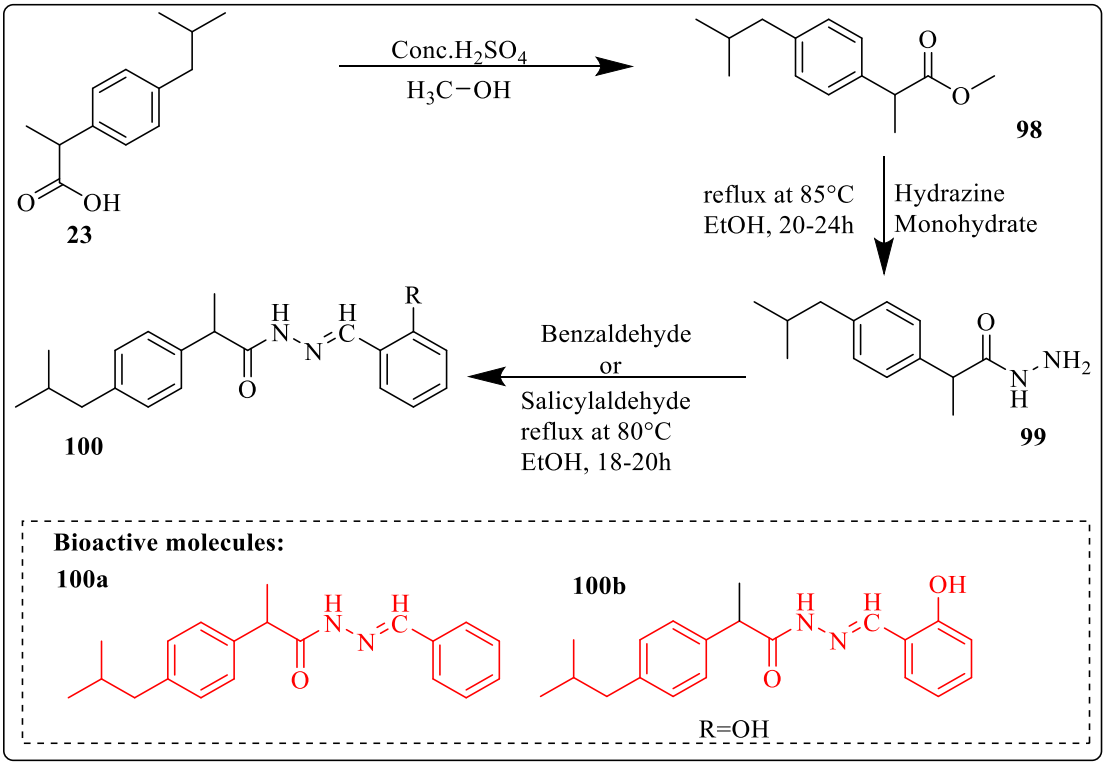


Scheme 25. Synthesis of Acetylsalicylic Acid.

3.13. Bio-oriented synthesis of ibuprofen derivatives

Postoperative pain has a negative impact on the patient's physical and mental health. The main objective of postoperative pain management is to reduce and eliminate pain and suffering using drugs that have minimal adverse effects.[56] This can be accomplished by employing a variety of pain management strategies, such as different drugs that have both anti-inflammatory and antinociceptive properties, therefore affecting several sites in pain components.[57,58] Shah et al.,[59] designed and synthesized several ibuprofen derivatives (scheme 26) by altering the carboxyl group of ibuprofen by three-step reactions.

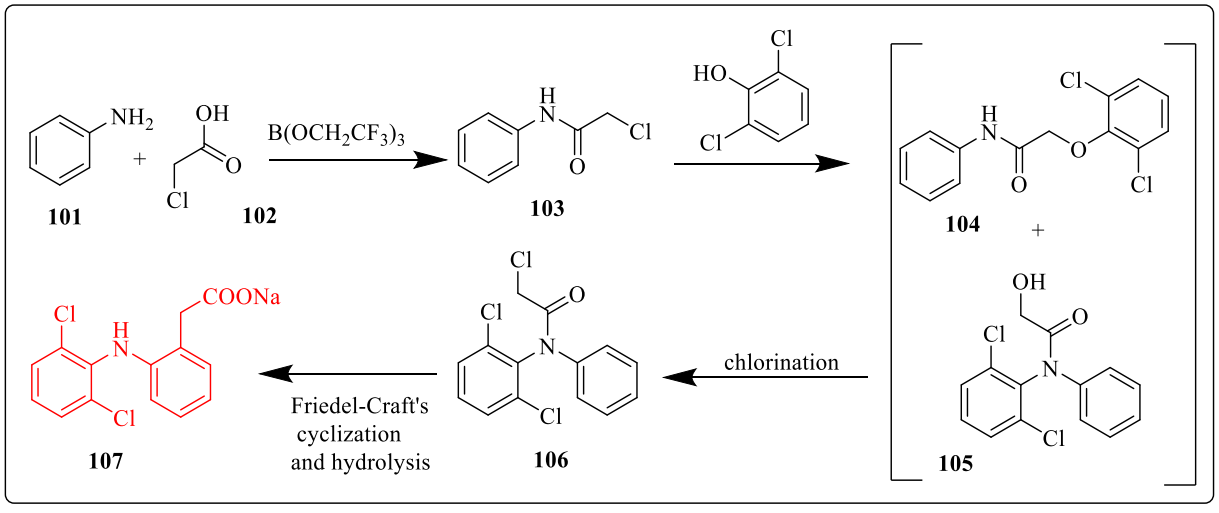
First, ibuprofen's **23** free acid group is esterified using methanol and concentrated H_2SO_4 under microwave irradiation for 10 minutes, yielding a considerable amount of ibuprofen esterified compound **98** (84% yield). Esterified ibuprofen molecule underwent hydrazide production and interacted with hydrazine monohydrate in ethanol to get the matching ibuprofen hydrazide compound **99**. Finally, Schiff's base reaction produced the desired products, ibuprofen imine with benzaldehyde (88%) and ibuprofen imine with salicylaldehyde **100** (93%) in high yields, when the resultant compound **99** reacted with benzaldehyde and salicylaldehyde in a reflux condenser using ethanol. Among the substances examined, compound **100a** and compound **100b** were determined to be the most effective derivatives showing analgesic and anti-inflammatory potential in experimental animal models.[59]



Scheme 26. Bio-oriented synthesis of ibuprofen derivatives.

3.14. Flow Synthesis of Diclofenac Sodium

The most often recommended NSAID for the treatment of inflammatory and painful rheumatism as well as several non-rheumatism disorders is diclofenac sodium.[60] With a total residence time of less than 3.5 hours, Wang et al.,[61] have created an integrated six-step continuous flow method for the synthesis of diclofenac sodium **107** (Scheme 27), beginning with aniline **101** and chloroacetic acid **102**. The synthesis technique highlights the new cascade etherification/Smiles rearrangement to hydroxyacetyldiphenylamine **105** without the production of 2,6-dichloro-*N*-diphenylaniline in the flow setting. The etherification product from the cascade reaction was smoothly transformed into the necessary compound **105** using a cartridge loaded with anhydrous K_2CO_3 three times.



Scheme 27. Six-Step Continuous Flow Synthesis of Diclofenac Sodium.

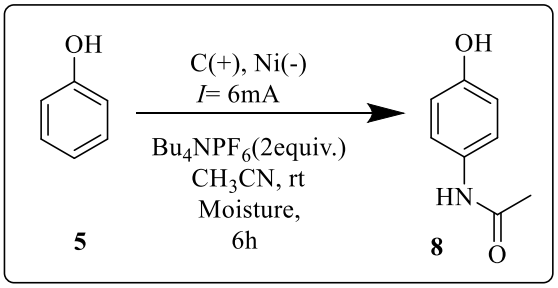
This flow method's primary benefits over traditional batch synthesis of compound **107** are its high efficiency, rapid response time, user-friendliness, and increased potential for industrial manufacturing.[61]

3.15. Synthesis of Paracetamol via Ritter-type C–H Amination of Phenol

In order to produce paracetamol in an environmentally safe and straightforward manner, Taily et al.,[62] developed a regioselective electrochemical Ritter-type reaction at the C(sp_2)–H of unprotected phenol **5** (Scheme 28).

The process uses acetonitrile, as nitrogen source, and works at room temperature to produce **8** from phenol in a single step. An undivided cell with carbon electrodes was used to electrolyze a solution of **5** in acetonitrile at room temperature with a constant current of 6 mA while Bu_4NPF_6 served as the supporting electrolyte. A reasonable yield of the required product **8** with para-selectivity was produced. Nevertheless, the initial material was not entirely converted, and the potential grew over time. Nickel was used in place of the carbon cathode to solve the issues of resistance and partial conversion. The best yield under these conditions was achieved with a 6 mA current and a full conversion of the starting material utilizing two equivalents of the supporting electrolyte.

This method produces compound **8** from **5** in a single step, is environmentally benign, straightforward to operate, and reliable. It also eliminates the need for external stoichiometric chemical oxidants. Additionally, technology may be effectively applied to different phenols and tolerates sensitive functional groups. Additionally, it is simple to recover the supporting electrolyte from the reaction mixture and reuse it in the subsequent catalytic cycle.[62]



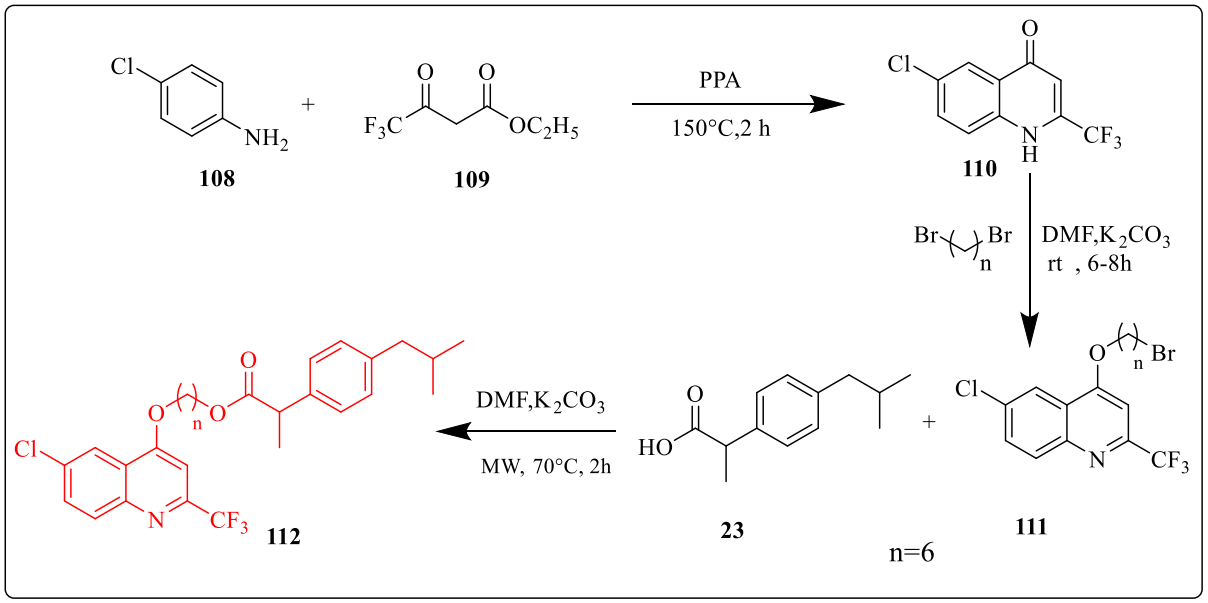
Scheme 28. Ritter-type C–H amination of phenol to synthesize Paracetamol

3.16. Synthesis of Ibuprofen-quinoline conjugates

Quinoline moieties are commonly conjugated with NSAIDs such as ibuprofen to improve pharmacological properties, including enhanced anti-inflammatory and analgesic potency, and potentially reduced gastrointestinal side effects associated with the free carboxylic acid group of ibuprofen.[63] Ghanim et al.,[63] used an optimized reaction procedure in a molecular hybridization approach to synthesize a new set of ibuprofen-quinoline conjugates consisting of quinolinyl heterocycle and ibuprofen moieties connected by an alkyl chain in good yields (scheme 29).

First, Conrad-Limpach cyclocondensation was used to synthesize 6-substituted-2-(trifluoromethyl)quinoline-4(1H)-one **110**.[64] In the presence of K_2CO_3, dibromohexane was used to alkylate the quinolones that were produced.[65,66] The primary O-alkylated quinolines **111** were produced. The target ibuprofen-quinoline combination **112** was obtained by O-alkylating the free carboxylic acid moiety in compound **23** using compound **110** with the use of microwave. Compound **112** has the highest potency and is the most

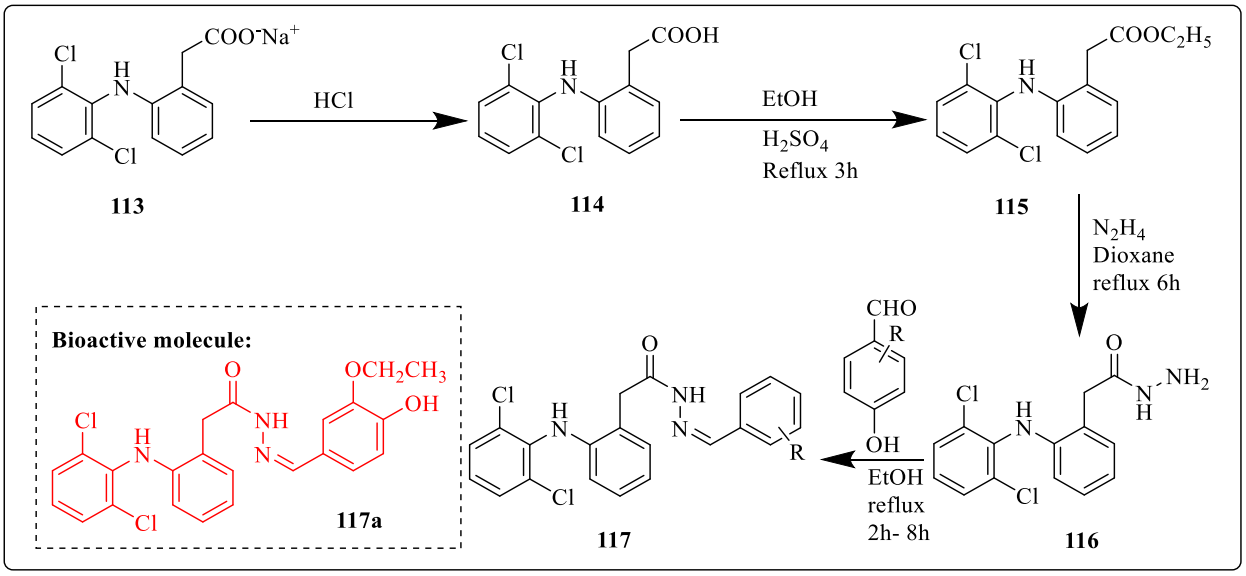
effective drug in terms of peripheral analgesic qualities when compared to indomethacin (Figure 2) at 10 mg/kg (% potency = 138.6%) in acetic acid induced abdominal writhing test in mice.[63]



Scheme 29. Synthesis of Ibuprofen-quinoline conjugates

3.17. Synthesis of Diclofenac derivative with hydrazone structure

Non-steroidal anti-inflammatory drugs such as diclofenac are employed to manage inflammation in a variety of conditions, particularly in arthritic disorders, acute musculoskeletal pains, and trauma-related pains. However, such treatments may also lead to harmful effects such as; gastrointestinal bleeding and ulceration. Regarded as possessing diverse pharmacological activities, hydrazone analogs form an interesting class of chemical compounds. Diclofenac hydrazide **116** was produced by reaction of compound **115** in dioxane with hydrazine at reflux for 6 hours (Scheme 30).



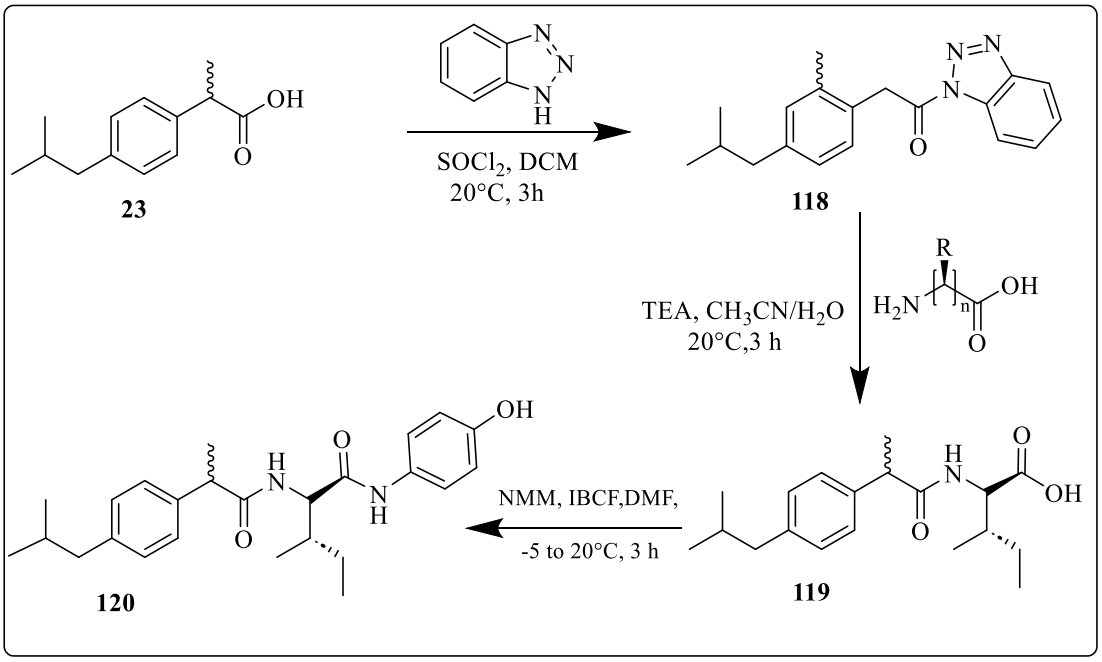
Scheme 30. Synthesis of diclofenac derivative with hydrazone structure.

Derivative **117a**, derived from the reactions of diclofenac hydrazide **116** with 3-ethoxy-4-hydroxy-benzaldehyde, showed the most pronounced in vitro anti-inflammatory activity in the bovine serum albumin denaturation assay. It displayed 95.36 ± 0.43% inhibition of protein denaturation, which was significantly higher than the standard drug diclofenac (85.67 ± 0.44% inhibition) (Figure 2) under the same conditions.[67]

3.18. Synthesis of Ibuprofen hybrid conjugates

Panda et al.,[68] used the carboxylic acid group of Ibuprofen to create hybrid compound, with 4-aminophenol using an amino acid as a linker to create safer therapeutic medicines for inflammatory diseases (Scheme 31).[69,70] It has been discovered that these novel hybrid conjugates have strong analgesic and anti-inflammatory properties while significantly lowering their ulcerogenic impact.

Triethylamine was added to an acetonitrile:water combination containing amino acids to treat the benzotriazolide of ibuprofen **23** for three hours at room temperature. The conjugate **119** was obtained by drying the ethyl acetate over anhydrous Na_2SO_4. Using 4-aminophenol in dimethylformamide (DMF) with N-methylmorpholine and isobutyl chloroformate (IBCF), ibuprofen–amino acid conjugates **119** were treated for 6 hours at -5–20°C to acquire the required product **120** in pure form. In terms of central analgesic activity, in the standard in vivo hot plate test, **120** exhibited potent analgesic effects with a potency of 2.9 fold compared to indomethacin (the reference standard) (Figure 2).[70]

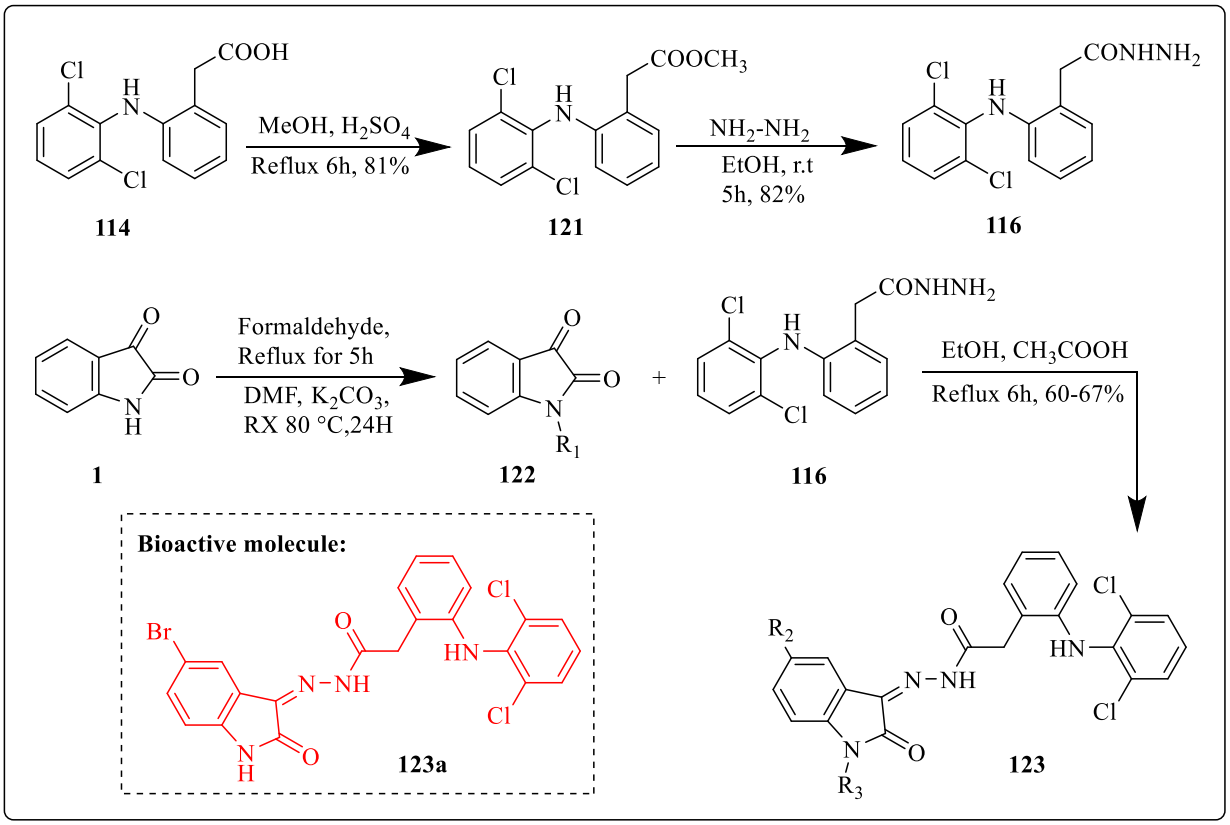


Scheme 31. Synthesis of ibuprofen hybrid conjugates

3.19. Synthesis of novel Diclofenac and isatin conjugates

New diclofenac Schiff's base **123** was synthesized through a Schiff's condensation reaction (scheme 32), and its anti-inflammatory properties were assessed. To synthesize compound **116**, compound **121**, was dissolved in absolute ethanol and 80% hydrazine hydrate and this was refluxed for 5 hours. Compound **122** was synthesized based on N-modification of isatin **1** by means of either the hydroxymethylation reaction or the N-alkylation reaction. For the synthesis of the target compound **123**, an equimolar quantity of compound **122** and **116** was dissolved in ethyl alcohol and refluxed for several hours in the presence of glacial acetic acid. Both compounds were evaluated for anti-inflammatory activity (in vivo and in silico). Compound **123a** showed the significant anti-

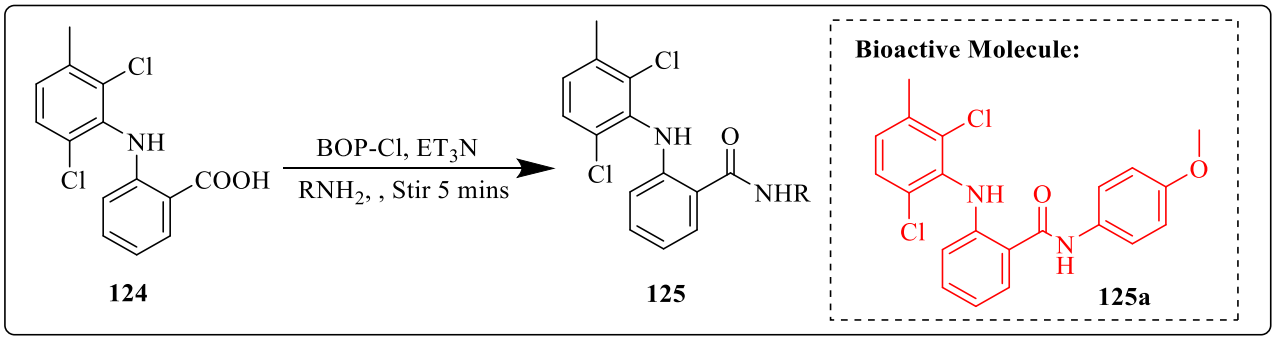
inflammatory potential in in vivo Carrageenan-induced paw edema model in rats as it showed 61.32% inhibition at 4 hours compared to diclofenac (Figure 2) 51.36% at the dose of 20mg/Kg.[71]



Scheme 32. Synthesis of Diclofenac Schiff's bases.

3.20. Synthesis of amide analogs of meclofenamic acid

Narsinghani et al.,[72] synthesized amide analogs of meclofenamic acid **125** (Scheme 33), via a one-pot technique using BOP-Cl. In anhydrous dichloromethane, a reaction mixture with **124** and BOP-Cl was treated with anhydrous triethylamine at 25 °C. This was then combined with the appropriate amine and stirred at ambient temperature. The newly synthesized compounds were tested for inflammatory activity using the carrageenan rat paw edema assay. In vivo evaluation results exhibited that compound **125a** with the N-(4-methoxybenzyl) group exhibited favorable anti-inflammatory activity.[72]

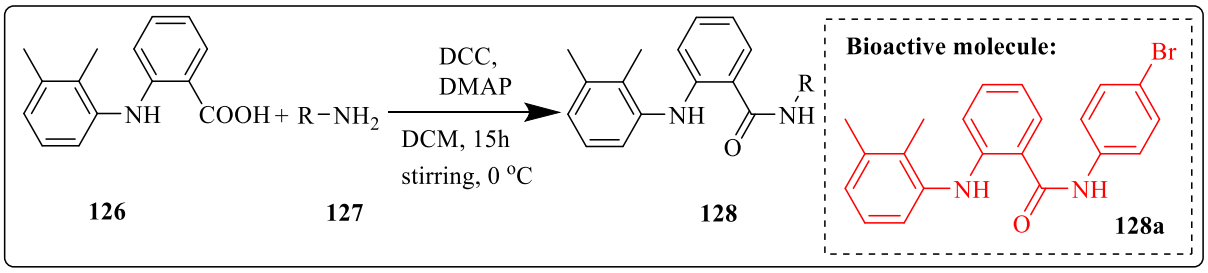


Scheme 33. Synthesis of amide derivatives of meclofenamic acid.

3.21. Synthesis of mefenamic acid derivatives

Savjani et al.,[73] focused on the synthesis of mefenamic acid derivatives **128** with the hope of increasing anti-inflammatory and decreasing adverse effects.

For the synthesis of **128** (Scheme 34), a mixture of 2-(2,3-dimethylphenylamino) benzoic acid **126** and aniline **127** was subjected to stirring in DCM in the presence of DMAP and DCC. Once the reaction was completed, the pale-yellow product was extracted with DCM. The results of the in vitro screening revealed that celecoxib (Figure 2) demonstrated a very weak inhibition of the COX-1 enzyme (4.76%) compared to **128a** (42.86%). The synthesized compound **128a** showed a COX-1 inhibitory activity of 42.86%.

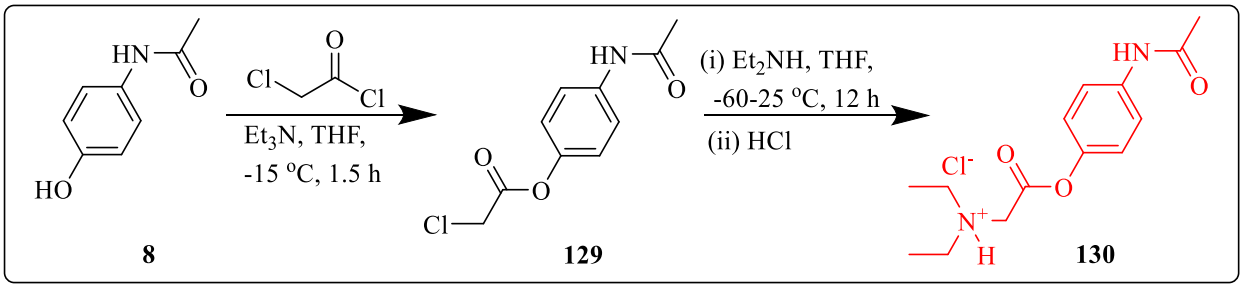


Scheme 34. Synthesis of mefenamic acid derivatives.

3.22. Synthesis of acetaminophen prodrug

Propacetamol is an intravenous prodrug of acetaminophen, aimed at managing fever and pain during the perioperative phase as part of multimodal analgesia. Murie et al.,[74] present an enhanced method for synthesizing propacetamol hydrochloride, enabling the extraction of the active pharmaceutical ingredient in high purity and output.

Conventional synthesis: To produce 4-acetamidophenyl 2-chloroacetate **129**, chloroacetyl chloride was reacted with acetaminophen **8**, THF, and triethylamine at –15 °C. At –60 °C, triethylamine and diethylamine were introduced into a flask containing compound **129**. After 12 hours, the formed precipitate was removed by filtration to obtain compound **130**, with a yield of 50% (scheme 35).[74]

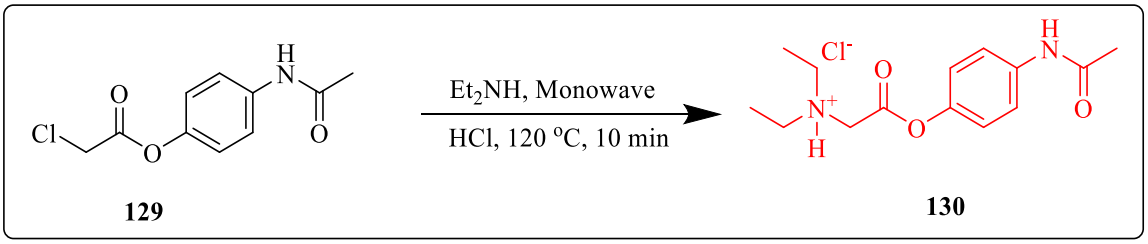


Scheme 35. Synthesis of propacetamol hydrochloride.

Microwave assisted synthesis: Microwave-assisted reactions were carried out using a single-mode microwave reactor with a maximum continuous microwave power of 850W. Diethylamine was added to a vial containing **129** and THF. The reactor was set to a temperature of 120 °C for 10 minutes. At the end of the reaction, the precipitate was filtered out. The resulting yellow oil was then dissolved in acetone and reacted with HCl (35-37%), yielding compound **130** (scheme 36)**.** A pharmacological investigation validated the fever-reducing effect of this active medication. In rat liver microsomes, ion trap tandem mass spectrometry showed

that acetaminophen is the only metabolite formed from the in vitro metabolism of propacetamol and its hydrophobic analog, acetaminophenacetate.[74]

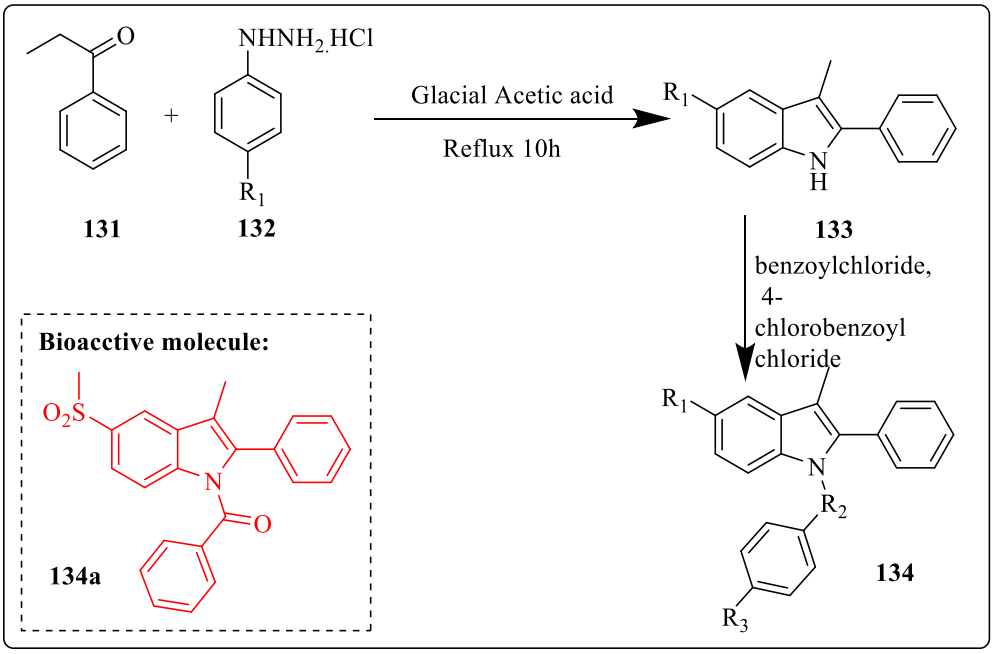
Comparison and evaluation: The microwave-assisted method offers significant advantages over the conventional approach. It reduces the reaction time from 12 hours to 10 minutes while maintaining comparable or superior yields and purity. This substantial acceleration improves energy efficiency, minimizes decomposition of sensitive intermediates, and enhances overall process scalability. Both methods successfully deliver propacetamol, which is rapidly converted *in vivo* to acetaminophen, but the microwave protocol aligns better with green chemistry principles by reducing energy consumption and processing time.[74]



Scheme 36. Synthesis of propacetamol hydrochloride by microwave-assisted reaction.

3.23. Synthesis of indoline derivatives

A novel series of 3-methyl-2-phenyl-1-substituted indole derivatives **134** has been synthesized via Fischer indole synthesis, which involved the reaction of **131** with **132** (Scheme 37). Following this, appropriate benzyl or benzoyl fragments were introduced. The target compounds **134** were obtained when **131** reacted with 132 in ethanol under Fischer indole synthesis conditions, resulting in the corresponding 2-phenyl-3-methylindole derivative **133**. Subsequently, the Cl atom in benzoyl chloride, 4-chlorobenzoyl chloride, or benzyl chloride was replaced with the indole derivatives **133** in DMF under a basic environment, yielding the target compounds **134** with moderate yields of 42–58%. Product **134a** showed the significant anti-inflammatory and analgesic effects. In acetic acid-induced writhing test in mice, the degree of inhibition of writhing was 49.1% while in carrageen-induced rat paw edema test, it showed anti-inflammatory activity of 80.1% at 3 hours interval which was comparable to that of indomethacin (Figure 2) .[75]

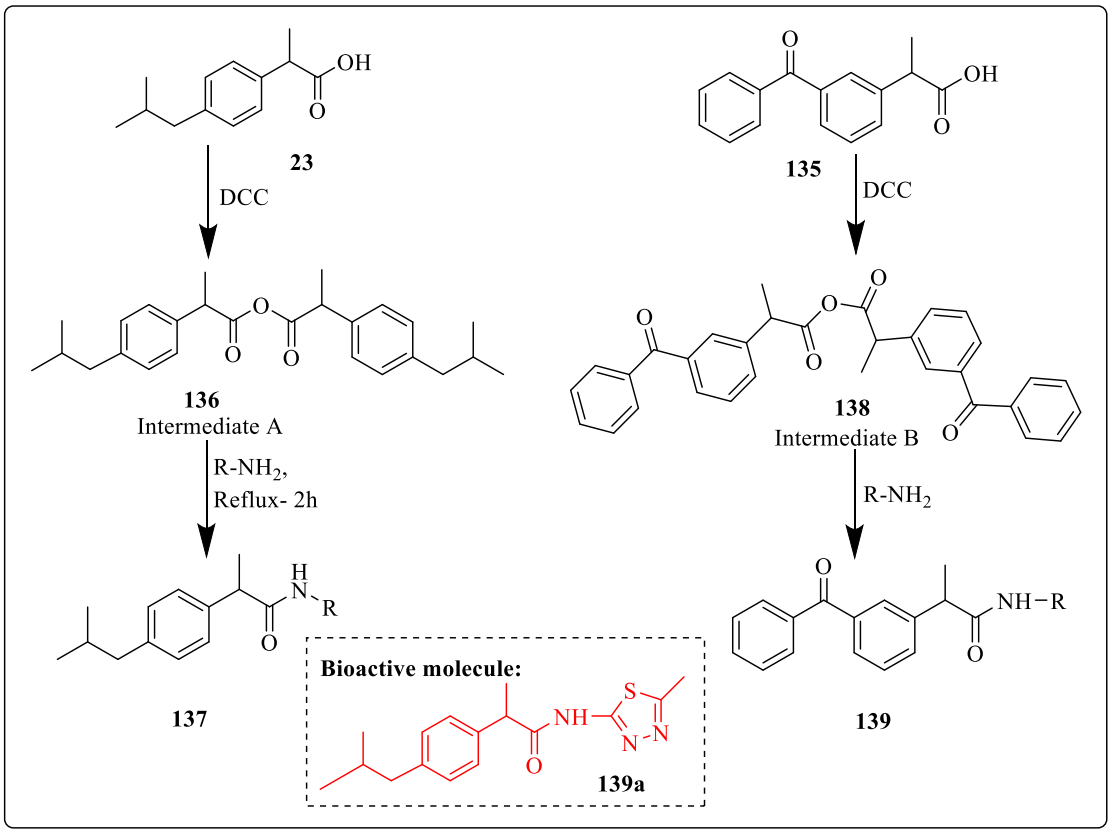


Scheme 37. Synthesis of 3-methyl-2-phenyl-1-substituted indole derivatives.

3.24. Synthesis of 3-methyl-2-phenyl-1-substituted-indole derivatives as indomethacin analogs

Al Mekhlaf et al.,[76] indicated that modifying existing traditional NSAIDs could enhance their selectivity for the COX–2 enzyme. Modified analogs were synthesized from Ibuprofen **23** and Ketoprofen **135** by linking them with intermediates **136** and **138**, respectively, using DCC as the coupling agent.

The compounds **23** and **135** were dissolved in dichloromethane and dicyclohexylcarbodiimide (DCC) was added. The intermediate compounds with 2-amino-5-methyl-1,3,4-thiadiazole, zinc dust, glacial acetic acid, and dioxane were added in separate flasks and refluxed for two hours. this reaction further proceeds and the white crystals of compounds **137** and **139** were obtained (Scheme 38). Compared to the reference agent, indomethacin (Figure 2), which had an inhibition percentage of 31.459%, compound **137a** was most notable, showing a promising 39.189% anti-inflammatory activity in carrageenan paw edema test in guinea pigs.

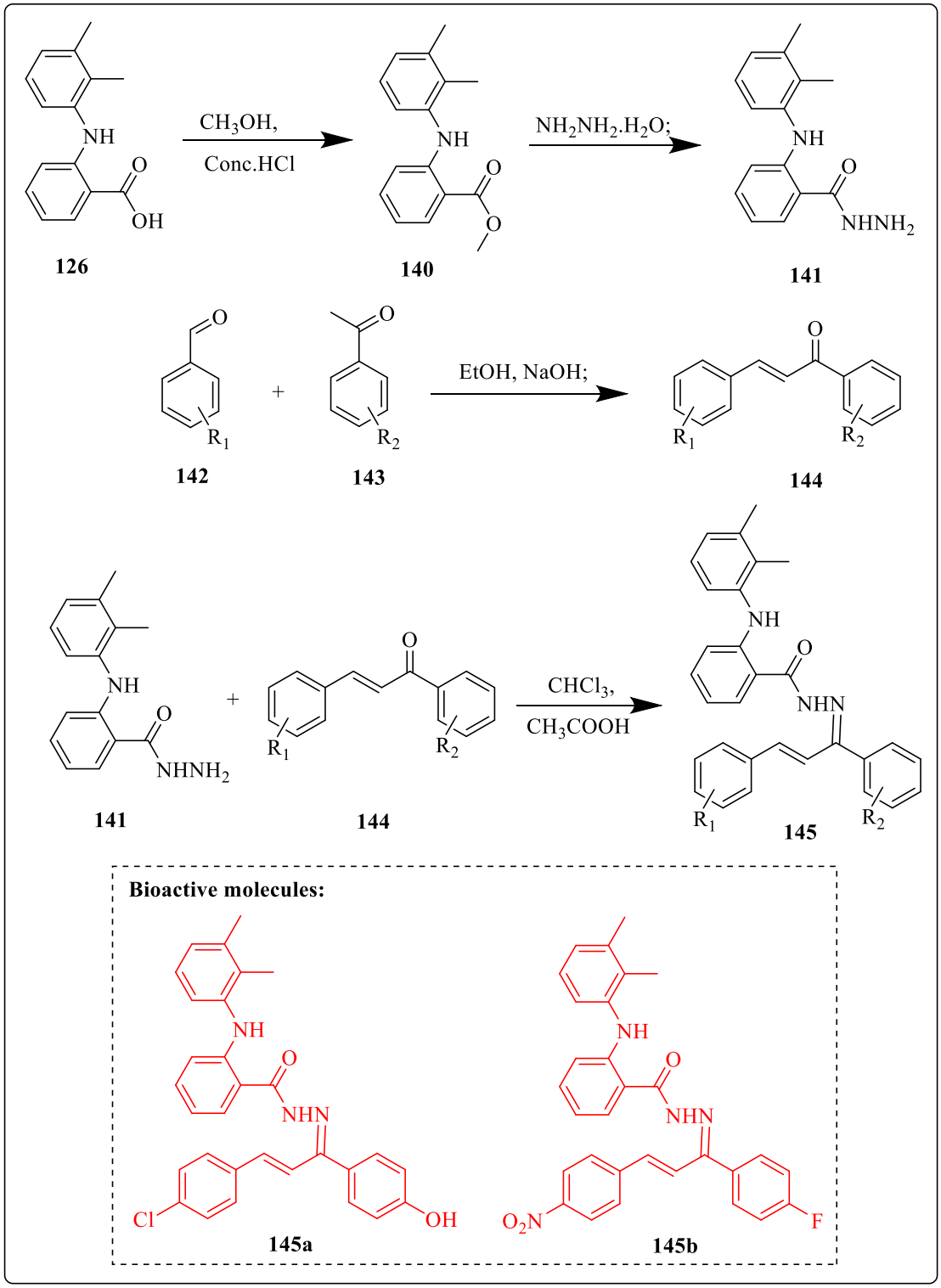


Scheme 38. Synthesis of derivatives of Ketoprofen and Ibuprofen.

3.25. Synthesis of chalconyl-incorporated hydrazone derivatives

A hydrazone compound of mefenamic acid, integrated with chalconyl, was prepared to create new compounds that may offer pain-reducing and anti-inflammatory benefits while reducing adverse effects.

The starting compound **140** was synthesized following the method described in previous studies concerning compound **126** [77]. Kumar et al.,[78] synthesized 2-(2,3-dimethylphenylamino)benzohydrazide **141** by esterifying **126** and then reacting it with NH_2NH_2 H_2O in absolute ethanol. Acetophenones **142** were treated with aromatic aldehydes **143** to create chalcones **144**. Finally, **144** was treated with **141**, yielding chalconyl-based hydrazine analogs of mefenamic acid **145** (Scheme 39)**.** Compound **145a** exhibited notable anti-inflammatory activity as it showed 92.45% inhibition compared to the standard mefenamic acid (Figure 2) which showed 90.56% in carrageenan-induced rat paw edema model in rats. Compound **145b** showed 86.99% relative analgesic activity comparable to that of standard mefenamic acid (Figure 2) in in vivo abdominal constriction test induced by tail-flick method in rats.

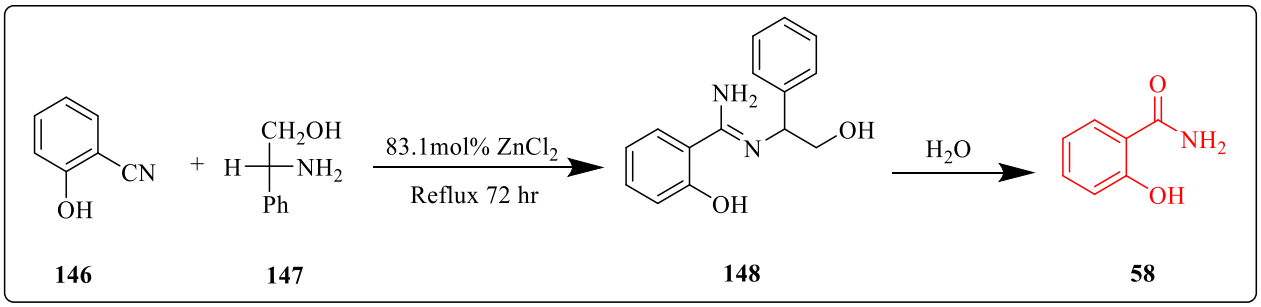


Scheme 39. Chalconyl-incorporated hydrazone derivatives of mefenamic acid.

3.26. Synthesis of salicylamide

Salicylamide **58** serves as an effective antipyretic analgesic for alleviating fever, headaches, neuralgia, joint pain, and rheumatic symptoms. It also commonly functions as an intermediate in the production of pharmaceuticals, pesticides, and fine chemicals. Mei et al.,[79] describe a new, straightforward method for synthesizing **58** via a one-step reaction (Scheme 40). In a dry Schlenk flask under anhydrous, oxygen-free conditions, dry $ZnCl_2$, 2-hydroxybenzonitrile **146,** and D-phenylalaninol **147** were mixed. These components were dissolved in dry

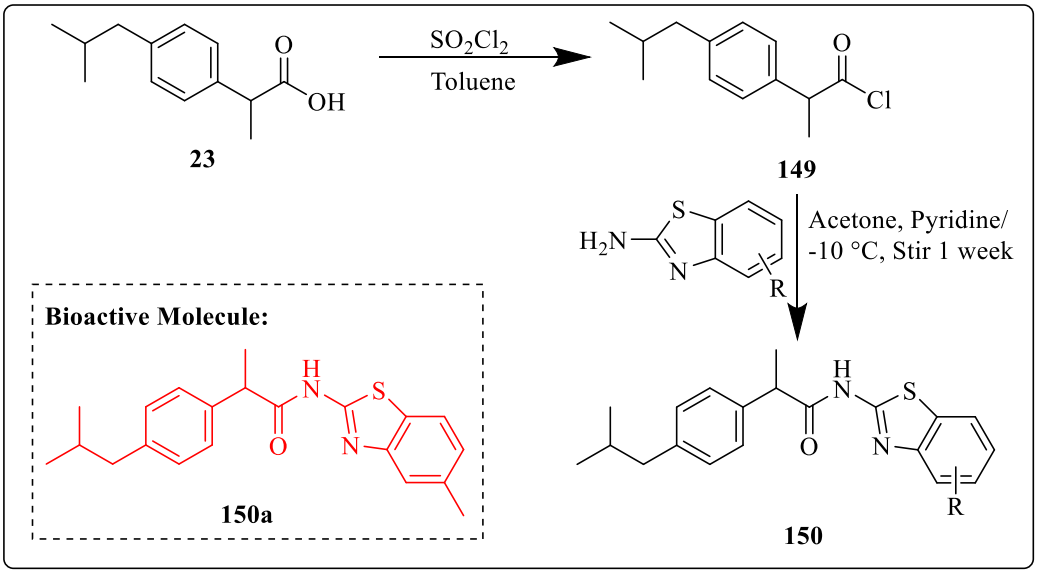
chlorobenzene and refluxed for 72 hours. Subsequently, the solvent was evaporated under low pressure to get (Z)-2-hydroxy-*N*'-(2-hydroxy-1-phenylethyl) benzimidamide **148**. Further, the residue was mixed with water and extracted using dichloromethane. The solvent was then removed under vacuum, yielding a crude red oil and ultimately the final product **58** formed.



Scheme 40. Synthesis of salicylamide.

3.27. Synthesis of novel Ibuprofen analogues

NSAIDs, including Ibuprofen, do have several therapeutic benefits, but the potential for adverse reactions, including gastrointestinal (GI) bleeding, ulcers, and possible renal toxicity, limits their clinical use. Ahmadi et al.,[14] described the development of several hybrid compounds that integrate the essential pharmacophore of ibuprofen with substituted benzothiazoles. Each synthesized compound displayed notable analgesic and anti-inflammatory properties. First, 2-(4-isobutylphenyl) propanoyl chloride **149** was prepared from ibuprofen **23** and thionyl chloride in dry toluene at 80 °C. Then, a mixture of substituted 2-aminobenzothiazole and pyridine in acetone at –10 °C was gradually incorporated into a solution of compound **149** in acetone at 40 °C, the reaction proceeds and substituted benzothiazoles **150** were obtained (scheme 41). Compound **150a** showed a more pronounced anti-inflammatory effect (0.193 ± 0.04%) in comparison to the control (0.53 ± 0.06%) and ibuprofen (0.516 ± 0.07%) in paw edema assay in mice and it also showed significant analgesic activity (17.61 ± 0.51s) exceeding that in control (5.47 ± 0.27s) and ibuprofen (9.14 ± 0.25s) (Figure 2) in the tail immersion test in mice.



Scheme 41. Synthesis of new substituted benzothiazoles.

3.28. Approved analgesic and antipyretic drugs in metal free synthetic methodologies

Metal free processes use conventional organic transformations that require no transition metals often providing simple and scalable pathways. The most notable approved drugs for which the synthetic processes are described are paracetamol, ibuprofen, salicylamide, propacetamol hydrochloride, aspirin (acetylsalicylic acid) , diclofenac sodium, indomethacin, ethenzamide.

4. Conclusions

The reviewed studies have analyzed a wide range of synthetic strategies aimed at synthesizing analgesic and antipyretic compounds, including metal and metal free approaches. In terms of metal approaches, the use of palladium and copper catalysts has proven useful in the construction of a wide range of complex molecular frameworks via methods such as reductive carbonylation, oxidative aromatization and azide-alkyne cycloaddition etc. The use of new catalyst systems, such as nanohybrid catalysts, as well as strategies such as one-pot, multi-step reactions have also contributed to increasing the efficiency and selectivity of these synthetic protocols. The use of renewable reagents such as bio-based terpenes as the starting material also demonstrates an increased focus on sustainability in the metal- catalyzed synthetic routes. These advances have, however, not solved all problems. The metal catalyzed processes are very efficient but the presence of residual metal contaminants in the final products is a matter of concern. These residues are under increasingly stringent regulatory scrutiny by agencies such as the FDA and EMA because of potential toxicity and long-term safety concerns. Therefore, it remains key to developing robust purification protocols and metal free or low metal loading alternatives.

Equally important is the use of metal free methodologies, which tend to be more flexible and user-friendly for the synthesis of analgesic and antipyretic compounds. Conventional reactions such as acetylation, Claisen–Schmidt condensation, Schiff base condensation, and organocatalytic addition have been shown to produce a wide variety of chemical structures. These techniques are preferable in situations where the synthesis must be done under metal-free conditions. In addition, these methodologies are often aligned with green chemistry approaches by employing no solvent systems, microwave synthesis, and the use of economically favorable and non-toxic materials.

In general, metal-catalyzed and metal free synthetic methodologies play complementary roles in the advancement of modern analgesic and antipyretic agents. While metal-based methods afford high synthetic efficiencies and greater structural complexity and diversity, metal free methods are characterized by simplicity, low cost, and better environmental sustainability. The synergistic use of these methodologies promotes the development of sustainable and flexible synthetic methods for the synthesis of new analgesic and antipyretic drugs.

Acknowledgements

The authors gratefully acknowledge the Organic Synthesis and Biomaterials Research Laboratory, Government College University Faisalabad, for providing the necessary academic support and research environment for this review work.

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