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Kabbe condensation: a comprehensive review of spirochromanone synthesis and medicinal applications

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The Kabbe reaction is an organic condensation reaction that specifically involves an enamine and 2-hydroxy acetophenone reacting to form a spirochromanone skeleton. This review covers various methods and advancements, highlighting a range of Kabbe products, particularly spirochromanones, which are heterocycles exhibiting significant biological activities. The Kabbe method incorporates ring-closing metathesis (RCM), the synthesis of annulated chalcone conjugates, natural product synthesis, base-catalyzed reactions, organo-catalysis, Mukaiyama–Kabbe adaptations, organocatalytic variants, redox-mediated processes, and dual or sequential condensations. Consequently, researchers in this domain will find this overview valuable and beneficial towards the synthesis of various Kabbe products in the synthesis of spirochromanones, spirochromanone–chalcone hybrids, carbamide molecular hybrids, and spirochromanone–flavanone hybrids. This review provides a comprehensive overview of spirochromanones and their derivatives, covering literature from their inception up to 2025.

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1 Introduction

Benzene-annulated six-membered oxygen heterocycles, commonly known as benzopyrans, constitute an important class of natural and synthetic compounds with significant relevance in chemical biology and drug discovery. These oxygen heterocycles, particularly flavanones, chroman-4-ones, and coumarins are widely distributed in the plant kingdom and are associated with diverse biological properties.[1–3] Flavanones (2-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-ones) are broadly classified as phytoalexins and exhibit extensive biological activity.[4–6] Chroman-4-one derivatives also display a wide spectrum of pharmacological properties, including anti-HIV,[7] anticancer,[8] antimicrobial,[9,10] antitumor,[11] antiviral,[12] anti-inflammatory,[13] and antioxidant effects.[14] Spirocyclic heterocycles, particularly those incorporating heteroatoms, are comparatively rare in nature but often exhibit exceptional biological activities.[15–17] Natural products such as robustidial A (**1A.1**), isolated from eucalyptus leaves, have exhibited anticancer properties, with EC_{50} values of 17 μM against MCF cancer cells, and also have been used in traditional Chinese medicine.[18] Other spiro-heterocycles, including (**1A.2**), have demonstrated *in vitro* anti-arrhythmic activity with an EC_{50} of 0.013 μM,[19] while **1A.3–1A.6** compounds were tested using a DPPH radical assay and exhibited promising antioxidant properties in the percentage range of 14–66 at a concentration of 200 μM.[20–23] Additionally, spirochromanone dehydrolupinifolinol (**1A.7**), eriosemaone A (**1A.8**), and (+)-calanolide A (**1A.9**) (Scheme 1) have shown notable antitubercular activity with MIC values of 25, 12.5 and 3.13 μg mL^{-1} respectively against the H37Rv strain of *M. tuberculosis*.[24–27] Although spirochromanones are rarely found in nature, they exhibit a rigid and conformationally restricted three-dimensional structure. Their fixed shape allows them to navigate through space effectively, enabling spirochromanones to align more suitably with particular biological targets, which can enhance the biological properties of these compounds. In contrast to their more flexible counterparts, these twisted formations fit seamlessly into narrow enzyme cavities, an aspect that contemporary drug design is increasingly focused on. Despite their scarcity in biological systems, the synthesis of such ring structures typically requires extensive laboratory procedures, executed meticulously step by step.[28] In 1978, Kabbe introduced a method that quietly changed how certain structures are built. This process skips unnecessary steps, fitting together different building blocks without fuss. It works well across many starting materials, consistently forming a key spiral-shaped core such as spirochromanones. It can be readily

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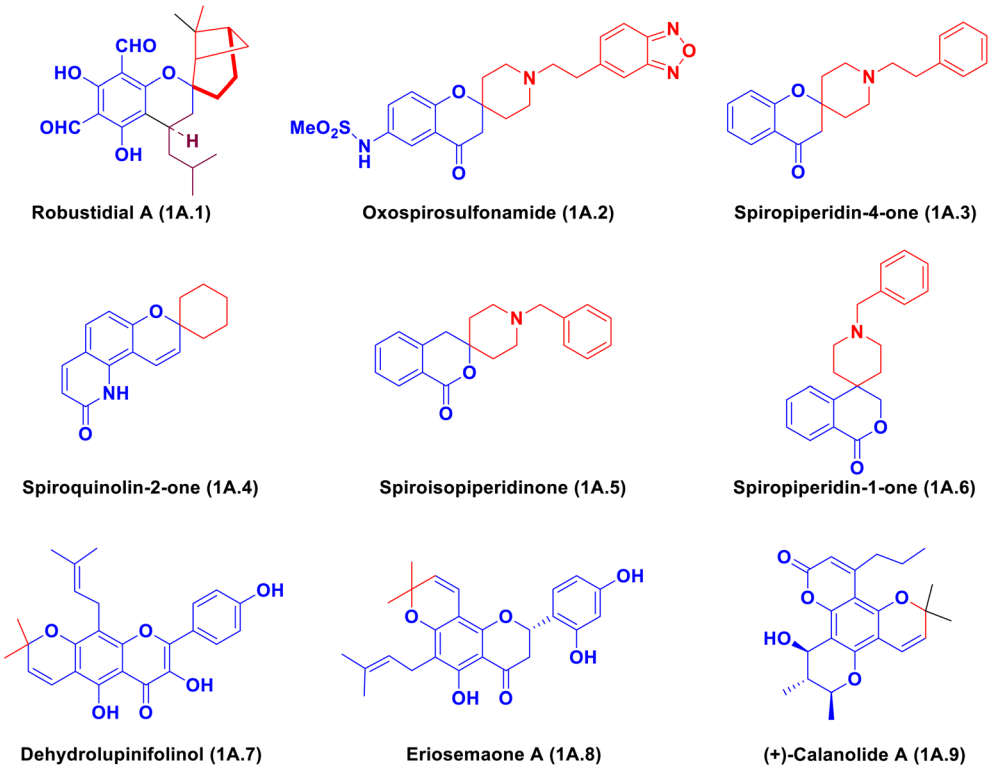


Scheme 1 Notable natural products and pharmaceutical drug candidates of spirochromanones (1A–9).

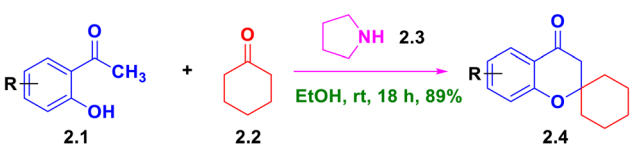
synthesized in a one-pot manner by employing the simple base pyrrolidine without the use of a metal catalyst.[29] Because it's so handy, chemists now rely on it often when making ring-containing compounds. Even though plenty has been written about chromanones and what they do biologically, nobody has pulled together all the cases where spiro versions were made using this specific reaction.[30] Moreover, with recent advances such as natural product synthesis, cascade reactions, spirobindane generation, metal-free Kabbe variants, and applications in antitubercular drug discovery (2020–2025) a modern critical evaluation is both timely and necessary. Given the increasing biological relevance and synthetic accessibility of these molecules, the following review provides a consolidated and systematic discussion of the Kabbe condensation, covering mechanistic aspects, synthetic applications such as Mukaiyama–Kabbe modification, organocatalytic and asymmetric approaches, spirochromanone–piperidine hybrids, chromanone containing natural products, spirochromanone–chalcone hybrids, carbamide molecular hybrids, spirochromanone–flavanone hybrids and their biological activity profiles.

2 Kabbe condensation reaction

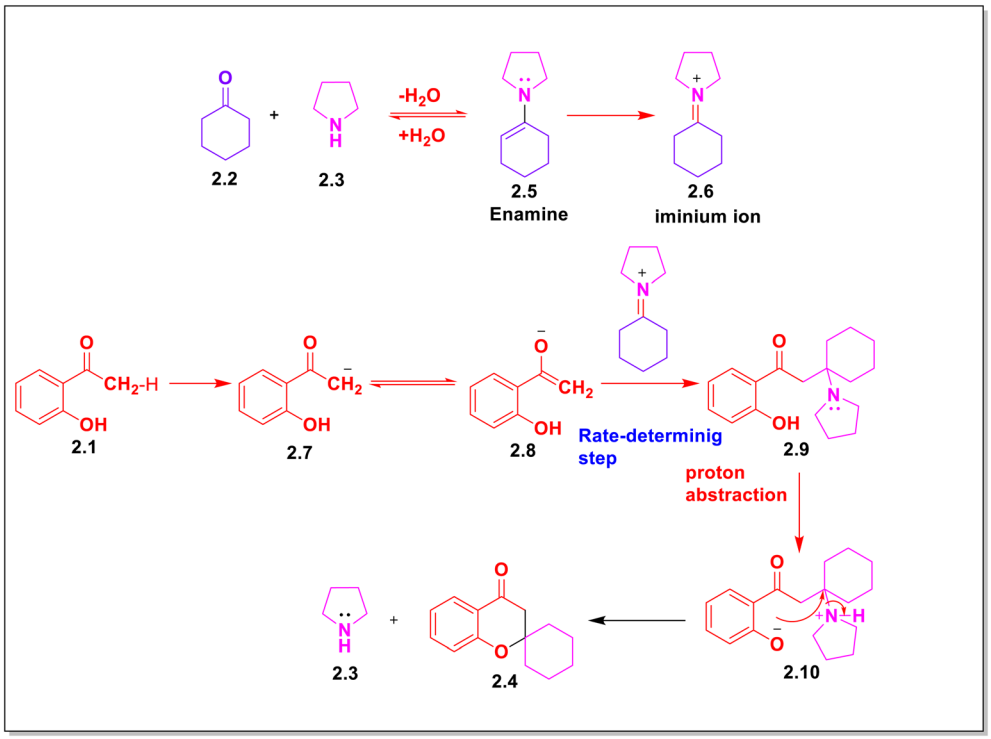
The Kabbe condensation is one of the most efficient and widely used carbon–carbon bond-forming reactions for constructing spirochromanones and related heterocycles. It was first reported by Kabbe in 1978, where the authors demonstrated that 2-hydroxyacetophenone derivatives condense smoothly with aldehydes or ketones in the presence of secondary amines such as pyrrolidine.[28] This transformation rapidly generates chromanone or spirochromanone frameworks through a one-pot intramolecular cyclisation pathway, making it an attractive method for assembling architecturally complex molecules. In the classical Kabbe protocol, 2-hydroxyacetophenone (**2.1**) reacts with aliphatic or aromatic ketones **2.2** in the presence of pyrrolidine **2.3**, yielding spirochromanone derivatives **2.4** in moderate to excellent yields (Scheme 2). The reaction generally proceeds smoothly under reflux conditions, and in cases where carboxyl-substituted substrates are employed, higher catalyst loading may be required to achieve good conversion. Several of the resulting spirochromanones have demonstrated notable biological activity, including antitubercular effects.[31–33] This has significantly increased interest in the Kabbe condensation as a tool for medicinal chemistry and drug discovery.

2.1 Mechanism of Kabbe conversions

The Kabbe reaction presents a fascinating mechanism, as it entails the sequential formation of multiple bonds, leading to visually appealing and architecturally novel spirocyclic products. In the first step, the aldehyde or ketone reacts with



Scheme 2 Synthesis of spirochroman-4-one **2.4** *via* Kabbe reaction.



Scheme 3 Mechanism for the formation of spirochroman-4-one **2.4** *via* the Kabbe reaction.

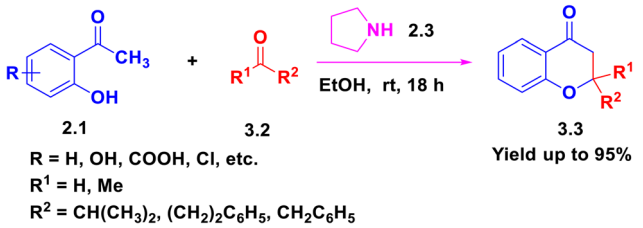
pyrrolidine to form the corresponding enamine **2.5**. This enamine, which has sufficient basicity ($pK_a \approx 8.84$), deprotonates the *ortho*-hydroxyacetophenone **2.1** to generate the enolate **2.8** along with the complementary iminium species **2.6.** The enolate then attacks the iminium carbon, producing the pyrrolidine-substituted intermediate **2.10**. After this step, proton transfer from the phenolic OH occurs, enabling the phenolate to undergo an intramolecular nucleophilic attack that displaces pyrrolidine and furnishes the final spirochromanone **2.4** (Scheme 3). The efficiency of the Kabbe transformation largely stems from the simultaneous *in situ* generation of a nucleophilic enolate and an electrophilic iminium ion, which drives rapid C–C bond formation (rate-determining step). However, the reaction outcome is sensitive to substrate architecture; highly substituted or conformationally rigid ketones may not cyclize efficiently and can instead give open-chain chalcones, as observed by Gabbutt *et al.*[34] This mechanistic insight has provided the foundation for several modern adaptations, including Mukaiyama–Kabbe reactions, asymmetric organocatalytic variants, and double Kabbe condensations, which have broadened the utility of the method toward bis-spirochromanones, spirobenzopyrans, and other structurally complex systems.

3 Synthetic approaches for spirochromanones

Over the years, the Kabbe condensation has developed into a remarkably flexible reaction for assembling chromanone, benzopyran, and spirochromanone frameworks. The earliest Kabbe condensations relied primarily on pyrrolidine as the organocatalyst. Since then, several modified protocols have been developed, including metal free variants, Mukaiyama type approaches, and strategies involving redox mediated steps. These methodological advances have expanded substrate scope and improved reaction consistency and efficiency. The original reaction conditions are summarized in the section that follows, along with later changes that have gradually improved the transformation's usefulness and adaptability.

3.1 Classical Kabbe condensation

In 1982, Kabbe and Widdig reported a protocol that has since become one of the most widely used methods for the synthesis of spirochromanones. Their strategy involves the condensation of 2-hydroxyacetophenones **2.1** with either acyclic or cyclic ketones **3.2** in the presence of pyrrolidine **2.3**, affording the corresponding spirochromanones **3.3** in generally good to excellent yields (60–95%) (Scheme 4).[28] The method is operationally simple, proceeds under mild conditions, and shows broad functional group tolerance. Electron-rich substrates, such as 4-methoxy-substituted acetophenones, typically react more rapidly due to facile enolate formation. In contrast, sterically demanding or conformationally rigid ketones tend to slow enamine generation, often requiring extended reaction times. Removal of water is commonly achieved using a Dean Stark apparatus, which shifts the equilibrium toward product formation and frequently improves isolated yields. When carboxylated acetophenones are employed, higher loadings of



Scheme 4 Synthesis of chromanone **3.3** *via* Kabbe reaction.

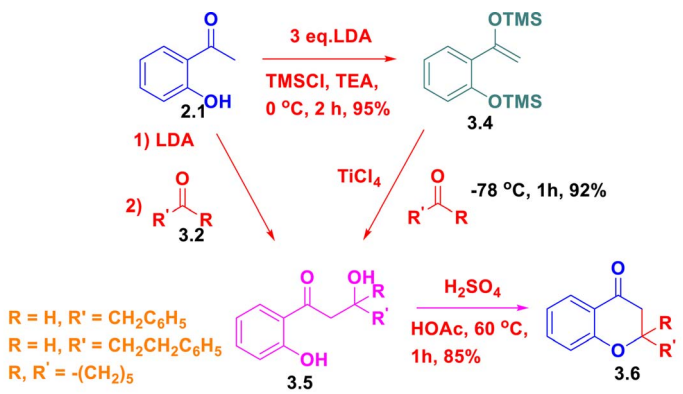
pyrrolidine are generally required because of increased substrate acidity. Overall, the classical Kabbe condensation is particularly effective for the construction of five, six, and seven-membered spirocyclic systems, consistently delivering well-defined, conformationally rigid three-dimensional architectures. The classical Kabbe reaction remains the benchmark because it tolerates a wide range of carbonyl substrates and yields highly functionalized spirocyclic products with better yields up to 95%. Its efficiency arises from *in situ* formation of both the nucleophile (enolate) and electrophile (iminium), minimizing side reactions and ensuring high step economy. This reaction is appropriate for the synthesis of a diverse array of substituted derivatives, because the mild conditions allow for the reaction of substrates that contain labile groups. Furthermore, due to its straightforward nature, the synthesis can be performed on a larger scale with ease. Consequently, it paves the way for the desired production of new chromans, and often offers a valuable or superior alternative method for synthesizing established benzopyrans.

3.2 Mukaiyama–Kabbe modification

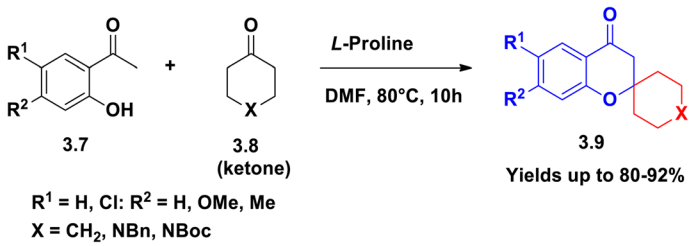
Kelly and Vanderplas (1991) developed a robust Mukaiyama-type alternative to the classical Kabbe condensation for synthesising substituted chromanones, particularly in cases involving base-sensitive aldehydes or ketones. Instead of relying on traditional enamine catalysis, they employed a Mukaiyama aldol strategy in which the bis-silyl enol ether **3.4**, derived from 2-hydroxyacetophenone **2.1**, was reacted with aldehydes or ketones **3.2**, in the presence of $TiCl_4$ to produce β-hydroxy ketones **3.5** in excellent yields (81–92%). These intermediates were then subjected directly to acid-catalysed cyclisation using H_2SO_4 in acetic acid to afford chromanone derivatives **3.6** in 85–91% yield (Scheme 5).[35] This method obviates the need for enamine formation, thereby avoiding decomposition of amine–aldehyde intermediates and enabling the use of aldehydes unstable under basic conditions, including α-halo aldehydes. $TiCl_4$ also provides strong stereochemical control during the aldol step, and the reaction tolerates a broad range of substituents, including arylmethyl, arylethyl, and spiro-cyclohexyl groups, with good selectivity and scalability. TiCl4 maintains stereochemical control by forming a rigid, cyclic chelated transition state that enforces axial or equatorial preferences and minimizes steric repulsion, leading to diastereoselective product formation. Overall, this two-step Mukaiyama variant significantly broadened the scope of the Kabbe reaction, expanding chromanone synthesis to more complex and base-sensitive carbonyl substrates. The Mukaiyama aldol reaction, succeeded by the acidic ring closure of the *P*-hydroxy ketone intermediate, has demonstrated itself to be a widely applicable and high-yielding technique for the synthesis of sensitive chromanones that are not easily obtainable through base-catalyzed methods.

3.3 Organocatalytic and asymmetric approaches

Chandrasekhar and co-workers (2005) demonstrated that L-proline serves as an effective organocatalyst in the Kabbe protocol for synthesizing substituted flavanones and spiro-chromanone–flavanone hybrids **3.9** (Scheme 6).[36] Using a variety of substrates, including 2-hydroxyacetophenones **3.7** and *N*-substituted cyclic ketones **3.8**, they observed that ketones furnished spirocyclic flavanones exclusively, whereas aldehydes yielded mixtures of flavanones, chalcones, and spiro-chromanones due to competing Knoevenagel or Claisen–Schmidt-type condensations. The transformation proceeds through a chiral enamine intermediate generated by L-proline, offering only modest asymmetric induction. Aldehydes that are substituted with electron-withdrawing groups, such as nitro and chloro, along with electro-donating groups like methyl (Me), methoxy (OMe), and hydroxyl (OH) in ketones, enhance the yields of Kabbe spiro-chromanone products up to 80–92%.



Scheme 5 Synthesis of substituted spiro-chromonone **3.6** *via* Kabbe reaction.



Scheme 6 Synthesis of substituted spirochromonone 3.9 *via* Kabbe Reaction.

Selectivity further decreases with bulkier or electron-withdrawing substrates due to the presence of competing pathways. Despite the moderate stereocontrol, this work laid the groundwork for asymmetric Kabbe reactions and indicates that future advancements employing improved chiral amines, dual thiourea–enamine catalysts, or chiral phase-transfer systems could substantially enhance enantioselectivity.

3.4 Spirochromanones from indanone substrates

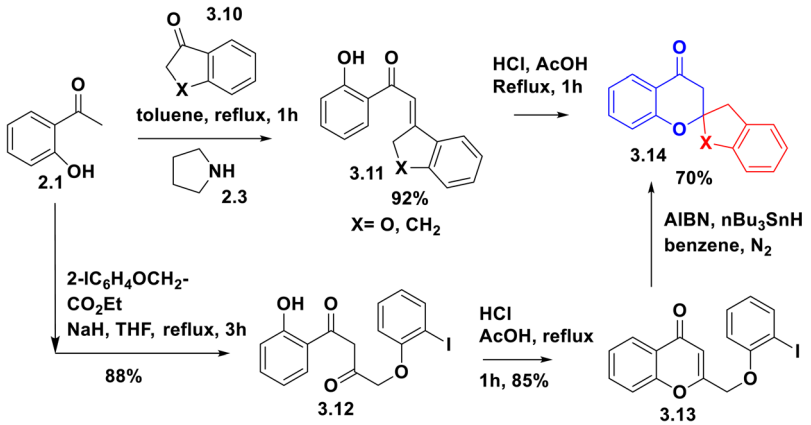
Gabbutt *et al.* (1998) studied the Kabbe reaction between 2-hydroxyacetophenone **2.1** and indanone **3.10** and, instead of obtaining the expected spirocyclic product, they unexpectedly isolated chalcone **3.11** (X = CH_2) in moderate yield, a result attributed to the rigid fused bicyclic structure of indanone, which imposes steric and conformational constraints on the enolate and iminium intermediates and disfavors intramolecular spirocyclization; nevertheless, acidic cyclization of **3.11** through refluxing in acetic acid with HCl successfully produced spirochromanone **3.14** (Scheme 7).[34] This transformation likely proceeds through protonation of the chalcone carbonyl followed by intramolecular phenolate attack, and overall, the study highlights how carbonyl geometry and substrate architecture critically govern the outcome of the Kabbe reaction, with deviations such as chalcone formation offering alternative synthetic routes to spirochromanones.

3.5 Spirobenzopyran and quinone derivatives

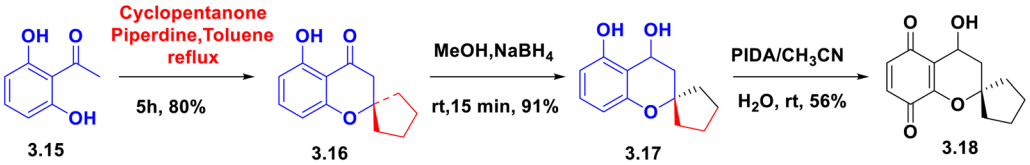
In 2006, Tapia *et al.* reported an efficient Kabbe condensation in which 2,6-dihydroxyacetophenone **3.15** was refluxed with cyclopentanone and piperidine in toluene for 12 hours to afford 2-spirobenzopyran **3.16** in 80% yield. This regioselective ring closure is promoted by the 2,6-dihydroxy substitution pattern.[37] Subsequent $NaBH_4$ reduction of **3.16** in methanol produced 4-hydroxyspirochromanone **3.17** in 91% yield, and oxidation of the resulting phenol using phenyliodine(III) diacetate (PIDA) in a 2 : 1 acetonitrile/water mixture at room temperature furnished 2-spirobenzopyranoquinone **3.18** in 59% yield, a transformation consistent with Diels–Alder type oxidative cyclizations (Scheme 8).[38,39] Together, these steps demonstrate that Kabbe intermediates are highly versatile redox scaffolds capable of undergoing reduction and oxidative functionalization to generate quinone frameworks with natural product-like structural features and enhanced biological and redox potential.

3.6 Semicarbazone and thiosemicarbazone derivatives

Abdelatef *et al.* (2018) reported a comprehensive and facile strategy for synthesising spirobenzo[*h*]chromenes and spirochromanes, beginning with the preparation of methyl hydrazinecarbodithioate **3.21** from hydrazine hydrate, carbon disulfide, and KOH in isopropanol/water below 10 °C, followed by methylation with iodomethane to afford a crystalline thioamide. Condensation of this reagent with spiro[benzo[*h*]chromen-4-one] **3.20** itself obtained *via* Kabbe condensation of cyclohexanone with 10-hydroxy-2′-acetonaphthone and pyrrolidine yielded methyl 2-(spiro[benzo[*h*]chromene-2,10-cyclohexan]-4(3*H*)-ylidene)hydrazinecarbodithioate 3.22 (Scheme 9).[40] From **3.22**, thiosemicarbazide derivatives **3.23a–f** were generated through *S*-methyl displacement with amines such as piperidine, piperazine, morpholine, and various alkylamines

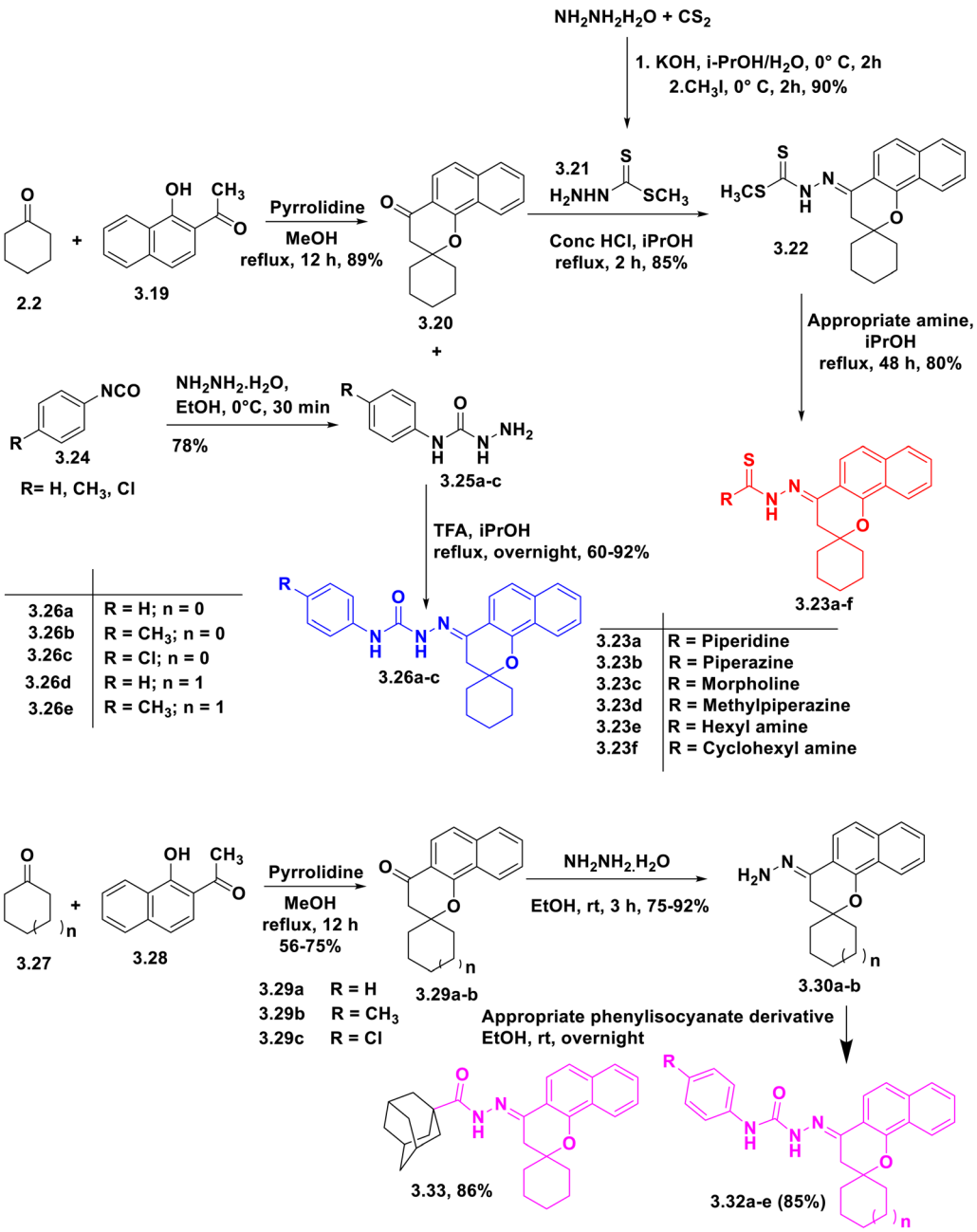


Scheme 7 Synthesis of substituted spirochromonone 3.14 *via* Kabbe Reaction.



Scheme 8 Synthesis of substituted spirochromonone **3.16** *via* Kabbe reaction.

under reflux until methyl mercaptan ceased evolving. Parallel synthesis of phenylsemicarbazides **3.25a–c** was achieved by reacting phenyl isocyanates with hydrazine hydrate in cold ethanol, enabling subsequent coupling with spiro[benzo[*h*]chromen-4-one] **3.20** to furnish spirobenzo[*h*]chromene semicarbazides **3.26a–c**. Similarly, spirochromane semicarbazides **3.31a–e** were synthesised from Kabbe-derived spirochromane intermediates **3.29a** (cyclohexyl) and **3.29b** (cycloheptyl), which were first converted to hydrazones **3.30a–b** using hydrazine hydrate and then directly coupled with



Scheme 9 Synthesis of spirobenzo[*h*]chromenes **3.31** and **3.32** *via* Kabbe reaction.

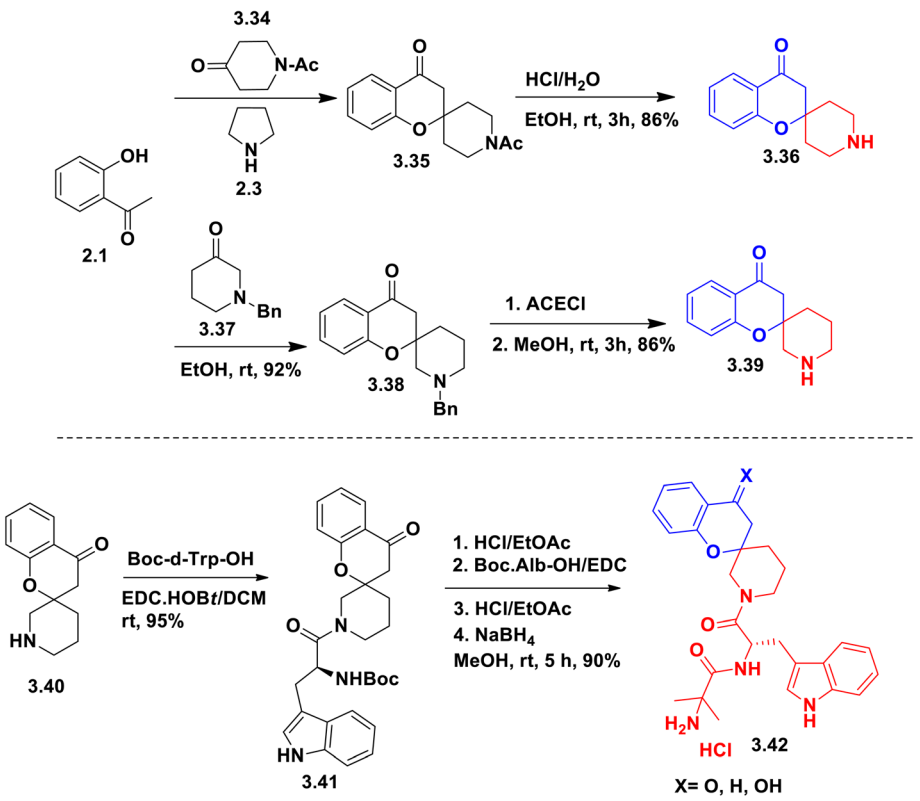
phenyl isocyanates to give the final derivatives. Together with their earlier demonstration that spirochromanone **3.24** smoothly undergoes condensation with hydrazines to form semicarbazones and thiosemicarbazones **3.26a–c**, **3.31a–e**, **3.32** exhibiting potent anticancer activity compared to sorafenib, the multi-kinase inhibitor, which has IC_{50} values ranging from 1.78 to 5.47 mM, or erlotinib, which has IC_{50} values exceeding 20 mM. Among these, compound **3.32** exhibited the highest potency as an EGFR inhibitor with an IC_{50} of 1.2 mM. This study showcases the reactive carbonyl of Kabbe products as an ideal handle for generating structurally diverse hydrazone-based scaffolds, where thiosemicarbazones often show enhanced lipophilicity and bioavailability and substituent electronics strongly influence biological potency highlighting a simple yet powerful diversification strategy for producing bioactive derivatives.

3.7 Piperidine and azaspiro fused chromanones (spirochromanone–piperidine hybrids)

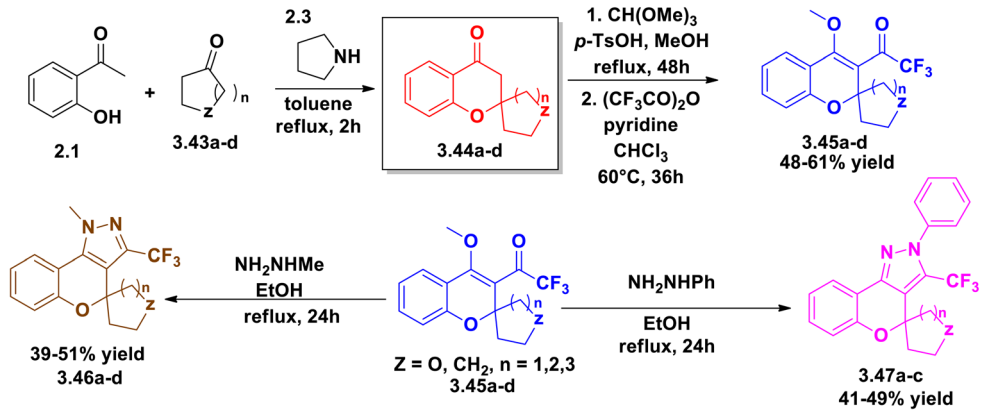
In 1998, Yang *et al.* carried out a pyrrolidine-catalyzed Kabbe reaction between 2-hydroxyacetophenone **2.1** and *N*-acetyl-4-piperidinone **3.34**, affording the *N*-acetyl spirochromanone **3.35**, from which acidic hydrolysis under reflux in HCl produced the corresponding piperidine spirochromanone **3.36** in good yield. Using standard peptide-coupling methods with Boc protection, these piperidine intermediates were further elaborated into growth hormone secretagogues, including spiro(3*H*-1-benzopyran-2,3′-piperidine) **3.41**, Boc-D-Trp-OH, and Boc-Aib-OH derivatives **3.42** (Scheme 10).[41] Complementing this work, they also prepared *N*-acetyl spirochromanones **3.35**, **3.38–3.42**, demonstrating that the *N*-acetyl group stabilises intermediates during cyclisation, while subsequent deprotection exposes free amines capable of effectively engaging with GHS receptors; moreover, the rigid spirochromanone framework enhances receptor-binding affinity. Their structure–activity relationship studies confirmed enhanced growth hormone secretagogue activity across these azaspiro derivatives, collectively highlighting the Kabbe reaction as a powerful entry point to biologically active spirochromanone-based scaffolds.

3.8 Fluorinated spirochromanones

Bonacorso *et al.* (2014) developed a regioselective route to highly functionalized fluorinated spiro heterocycles by first assembling Kabbe-type chromanone adducts **3.44a–d** from cycloalkanones **3.43a–d**, 2-hydroxyacetophenone, and pyrrolidine, which were then smoothly trifluoroacetylated *via in situ*-generated enol ethers and dimethyl acetals using TFAA/pyridine to afford key intermediates **3.45a–d** in 48–61% yields (Scheme 11).[42] Subsequent hydrazine-mediated cyclocondensation with phenyl- or methylhydrazine in refluxing ethanol furnished spiro-fused chromen[4,3-*c*]pyrazoles **3.46a–c** and **3.47a–d**, with regioselective formation of 2,3-disubstituted pyrazoles in the *N*-phenyl series and 1,3-disubstituted analogs in the *N*-methyl series. Structural confirmation through ^{1}H, ^{13}C, ^{19}F NMR, HMBC, MS, and X-ray crystallography revealed an unusual five-bond ^{13}C–^{19}F coupling ($^{5}JCF \approx 1$ Hz) in **3.47a–c**, strongly



Scheme 10 Synthesis of substituted spirochromonone 3.39–3.40 & 3.42 *via* Kabbe reaction.



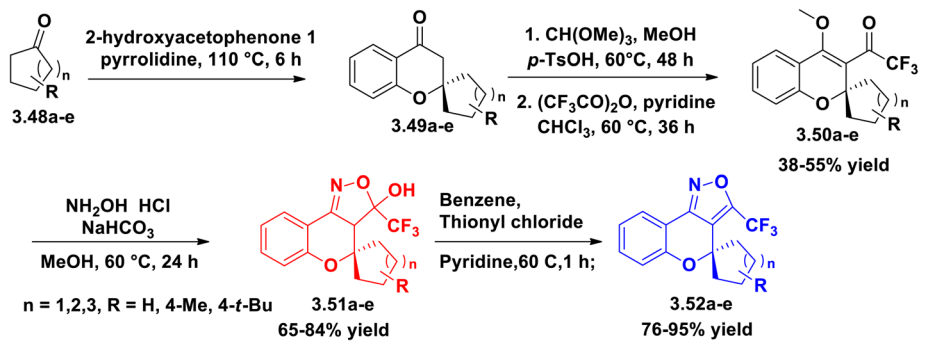
Scheme 11 Synthesis of Kabbe-type chromanone adducts **3.44a–d** and the formation of spiro-fused chromen[4,3-*c*]pyrazoles **3.47a–c**.

supporting the regioisomeric assignment. The incorporation of CF_3 groups not only enabled this efficient functionalization but also enhanced metabolic stability, lipophilicity, and membrane permeability, while the pyrazole/triazole motifs contributed favorable hydrogen-bonding and binding characteristics features that collectively position these fluorinated spirochromanone derivatives as promising antimicrobial and anticancer lead structures. This work underscores fluorinated spirochromanones as an expanding and highly relevant frontier in medicinal chemistry.

Integrating well with their earlier fluorinated spiroheterocycle strategy, Bonacorso *et al.* in 2017 extended the utility of Kabbe-derived scaffolds by developing a novel synthesis of 3-(trifluoromethyl)-3,3a-dihydrospiro[chromeno[4,3-*c*]isoxazolines] **3.51a–e** and their aromatized isoxazole analogs **3.52a–e**, complex tetracyclic systems incorporating multiple pharmacophoric units including chromenes, isoxazolines, isoxazoles, spirocycles, and CF_3 groups with strong potential for biological activity.[43] The synthetic route begins with a Kabbe condensation between cycloalkanones **3.48a–e**, 2-hydroxyacetophenone, and pyrrolidine to afford spiro[chroman-2,10-cycloalkan]-4-ones **3.49a–e**, which are subsequently transformed into trifluoroacetylated intermediates **3.50a–e** *via* trimethyl orthoformate-mediated enol ether formation followed by treatment with trifluoroacetic anhydride and pyridine. Cyclisation of these CF_3-activated substrates with hydroxylamine hydrochloride and sodium bicarbonate in refluxing methanol (60 °C, 24 h) furnishes the desired spiro-fused isoxazolines **3.51a–e** (Scheme 12), which undergo smooth aromatisation to isoxazoles **3.52a–e** upon dehydration with thionyl chloride and pyridine in benzene at 60 °C for 1 h. The trifluoromethyl group proved pivotal in modulating reactivity, electronic distribution, and NMR characteristics. Structural analyses revealed high regioselectivity and clear stereochemical preferences, particularly in cyclohexyl derivatives bearing bulky *tert*-butyl substituents, which favoured equatorial orientations.[44] The findings show that the synthetic utility and physicochemical properties of Kabbe-derived scaffolds can be greatly expanded by adding CF_3 substituents. The presence of these strong electron-withdrawing groups enables the construction of highly functionalized spiro-heterocycles that exhibit improved stability, adjustable electronic properties, and promise in medicinal chemistry. As a result, fluorinated Kabbe intermediates emerge as a valuable foundation for designing advanced, drug-oriented molecular architectures.

3.9 Cyclopropane-fused spirochromanones

Prathima and co-workers (2018) reported a flexible synthetic route that starts from 2,4-dihydroxyacetophenone. The substrate is first allylated, then transformed through a Claisen

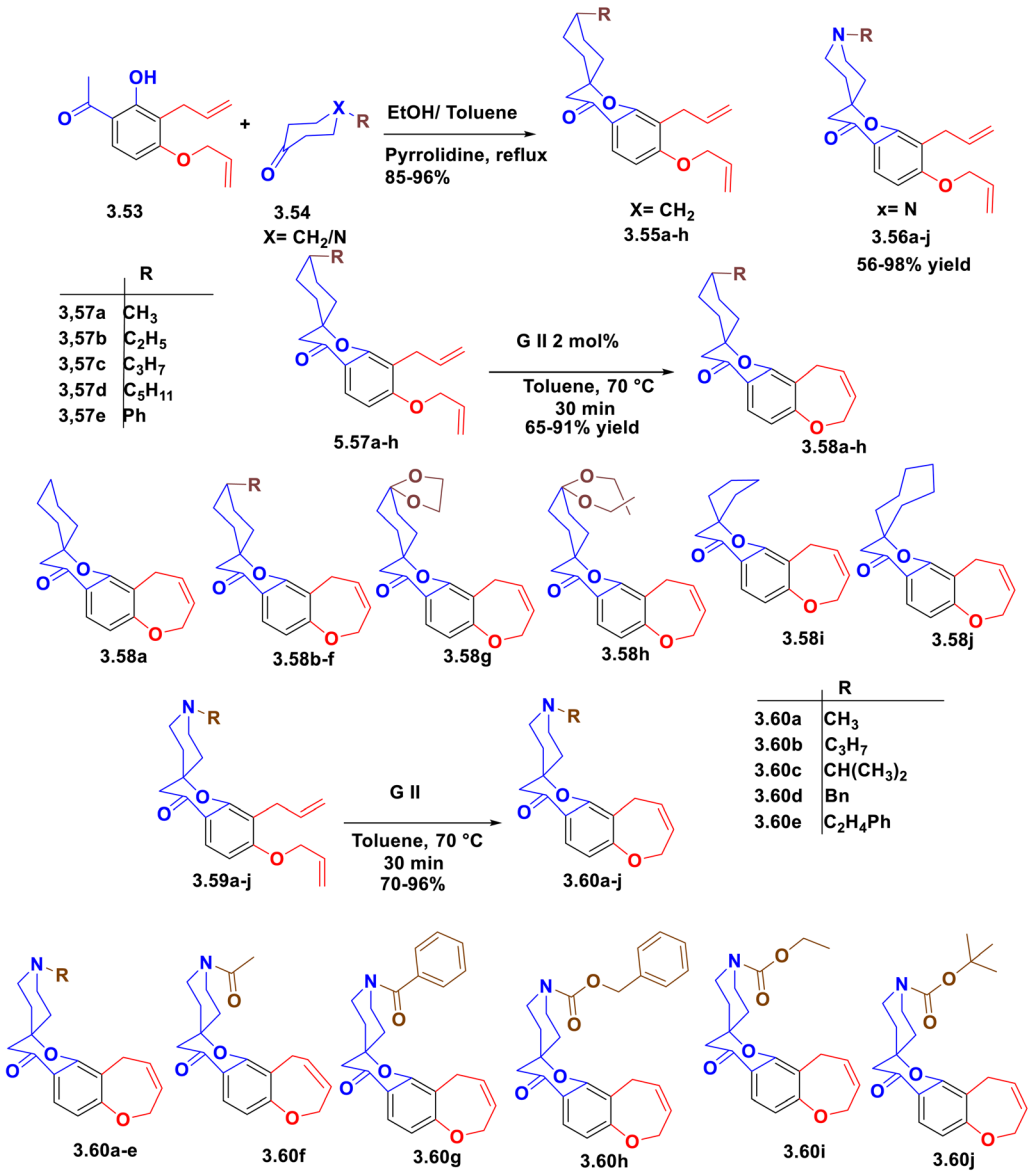


Scheme 12 Synthesis of 3-(trifluoromethyl)-3,3a-dihydrospiro[chromeno[4,3-*c*]isoxazolines] (**3.51a–e**) and their corresponding aromatized isoxazole derivatives (**3.52a–e**).

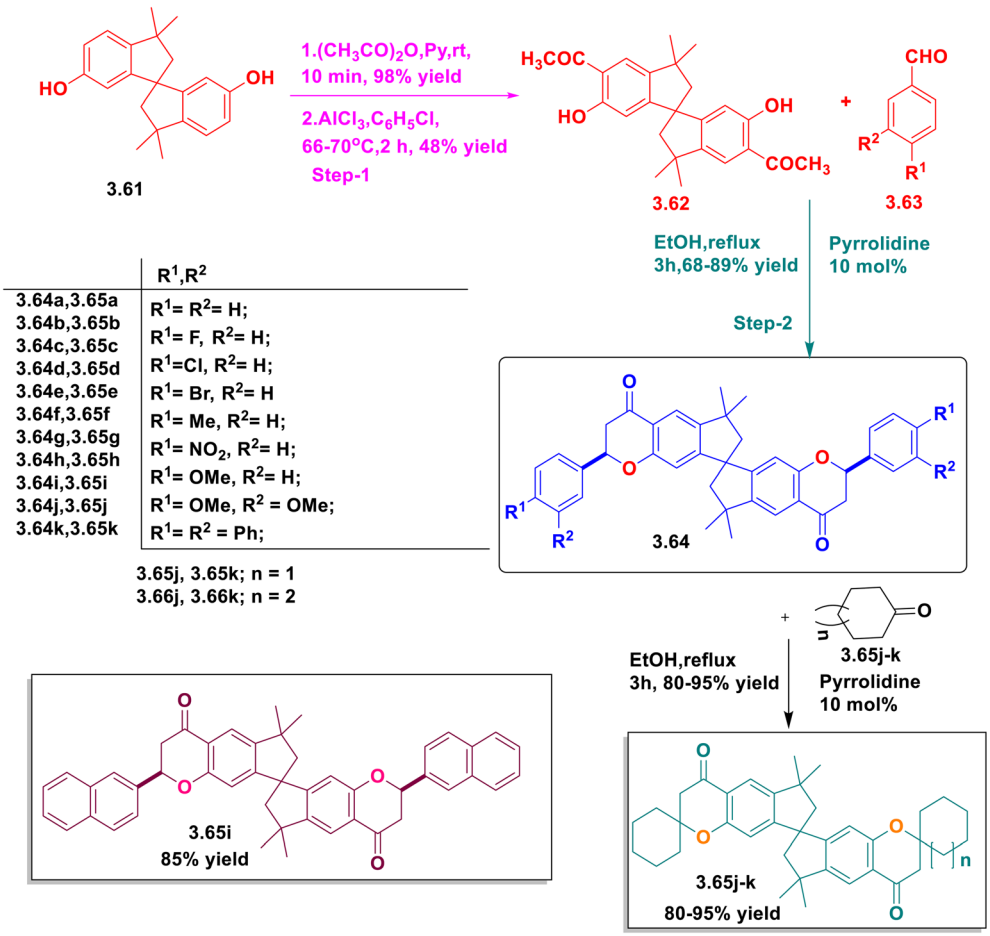
rearrangement, followed by a second allylation step to furnish the corresponding bis-allylic diene intermediate.**3.53**. This intermediate underwent Kabbe condensation with various cyclic ketones or *N*-substituted piperidones in the presence of pyrrolidine (EtOH/ACN/toluene, 80 °C) to yield spiro diene derivatives **3.55a–h** and aza-spiro precursors **3.56a–j**. The diene series **3.55a–h** was subsequently transformed *via* ring-closing metathesis (RCM) using 2 mol% Grubbs II catalyst in dry toluene at 70 °C, furnishing benzannulated oxepine spirochromanones **3.58a–h** in excellent yields (65–91%). In contrast, the aza-spiro analogues **3.56a–j** required modified conditions including higher catalyst loading, increased temperatures, and strategic *N*-protection or electron-withdrawing substituents to counteract catalyst deactivation by the basic nitrogen, ultimately affording the corresponding RCM products **3.60a–j** in good yields (Scheme 13).[45] This work showcases the compatibility of Kabbe scaffolds with advanced ring-forming strategies, highlights the value of strained sp^3-rich motifs for enhancing drug-like properties, and reinforces the growing medicinal relevance of highly functionalized, three-dimensional spirochromanone architectures.[46,47]

3.10 Bis-spirochomanones (double Kabbe reaction)

The successful execution of double Kabbe condensations to access complex bis-spirochromanone architectures further demonstrates the robustness of this transformation. The suitability of Kabbe condensation for advanced medicinal chemistry and lead-optimization campaigns is demonstrated by its capacity to construct polyspiro frameworks in good yields. In 2013, Rao and Tangeti developed an efficient Kabbe condensation strategy to construct spirobiindane-derived bisflavanones and bis-chroman-4-ones from racemic spirobiindane bisphenol **3.61** (Scheme 14).[48] The two-step



Scheme 13 Synthesis of benzannulated oxepine-spirochromanones 3.60a–j.

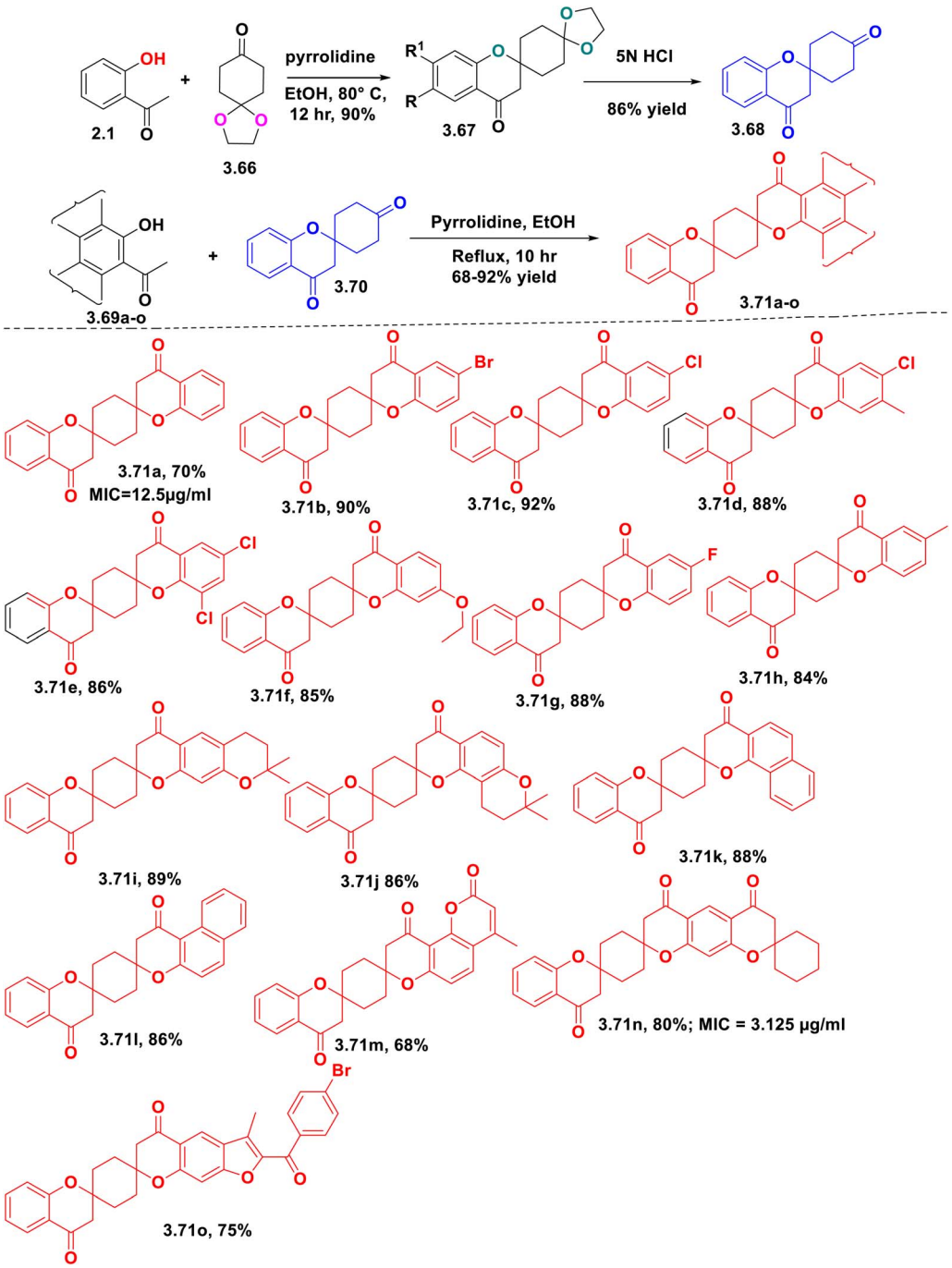


Scheme 14 Synthesis of bis-flavanone **3.65a–i** and trispirochromanones **3.65j–k**.

transformation of **3.61** to bis-acetophenone **3.62** enabled its condensation with substituted benzaldehydes **3.63a–h** using pyrrolidine in ethanol, affording the corresponding bis-flavanones **3.64a–h** as single diastereomers in excellent 68–89% yields, with C_2-symmetry and *cis*-aryl orientation confirmed by diagnostic $^1H/^{13}C$ NMR signals. Extending this methodology, treatment of **3.62** with cyclic ketones such as cyclohexanone and cycloheptanone (**3.63j–k**) furnished poly-spirocyclic bis-chroman-4-ones **3.65j–k** in 80–95% yields, with the presence of three quaternary carbon resonances evidencing the fully spirofused architecture. This work highlights the strategic power of spirobiindane as a rigid, C_2-symmetric template for enforcing diastereocontrol in multicyclic systems, demonstrating that Kabbe condensation can be leveraged not only for simple chromanones but also for assembling complex polyspirocyclic frameworks. The high yields, stereochemical precision, and structural modularity underscore the value of this platform for developing architecturally sophisticated molecules with potential in biological properties.

Dongamanti *et al.* (2017) achieved a landmark advancement in spirocycle construction through a double Kabbe condensation that generated a diverse library of bis-spirochromanones **3.71a–o**, beginning with the assembly of the central diketone scaffold **3.68** *via* condensation of 2-hydroxyacetophenone **2.1** and 1,4-dioxaspiro[4.5]decan-8-one **3.66**, followed by acetal deprotection of intermediate **3.67** (Scheme 15).[49] A second Kabbe condensation between this key intermediate and various substituted 2-hydroxyacetophenones **3.69a–o** furnished the final bis-spiro products **3.71a–o** in moderate to good yields. This "double Kabbe" strategy creates molecules bearing two spiro centres, markedly increasing conformational rigidity and enhancing the dual-chromanone framework's ability to interact with FtsZ, a validated antitubercular target. Several derivatives notably **3.71h**, **3.71n**, and **3.71o** exhibited excellent potency (MIC = 3.125 μg mL^{-1}) with low cytotoxicity in HEK cells, underscoring their promise as lead candidates. Overall, the dual-spiro construction achieved through the double Kabbe condensation stands as one of the most innovative developments in modern spirocycle synthesis, offering structurally rich, biologically potent polyspiro scaffolds for future drug discovery.

Muthukrishnan *et al.* (2009) developed a simple and safe method for synthesizing bis-spirochromanones (**3.75**) from 4,6-diacetylresorcinol (**3.72**) using a Kabbe condensation carried out in the ionic liquid [bbim]Br (**3.74**) at room temperature (Scheme 16).[50] This protocol exploits the dual role of the ionic liquid as solvent and promoter: its high solvating power and intrinsic Brønsted/Lewis acidity facilitate enamine formation, activate the carbonyl groups, and promote efficient cyclization

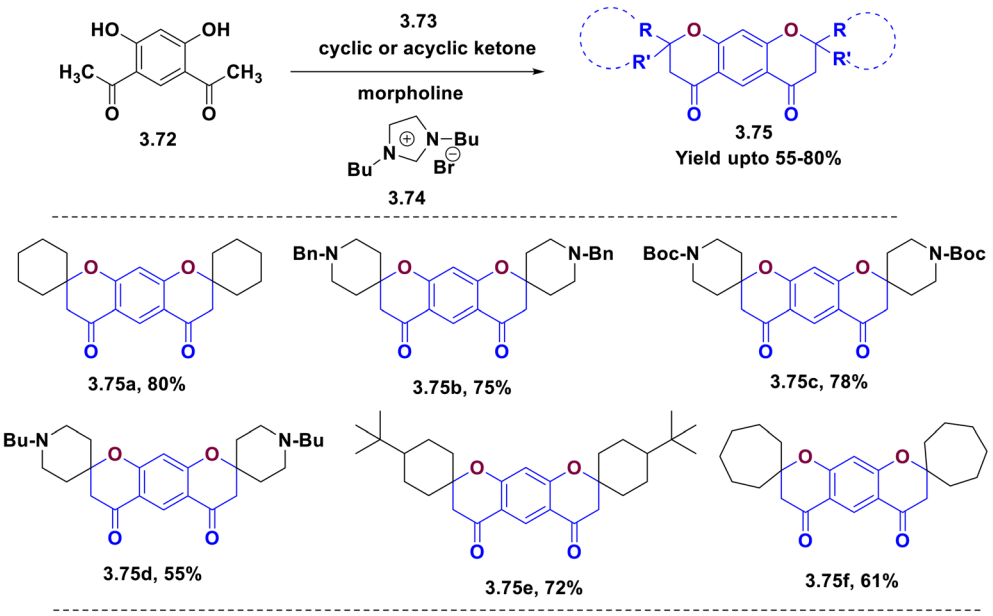


Scheme 15 Synthesis of bis-spirochromanones derivatives 3.71a–o.

to form the dual spiro centers.[51,52] Using only a catalytic amount of inexpensive morpholine as the base, the reaction proceeds cleanly to give a diverse library of bis-spirochromanones in moderate to good yields, with straightforward workup and excellent reusability of the ionic liquid. The reaction occurs through a homogeneous catalytic system. This study demonstrates that ionic-liquid-mediated Kabbe condensation provides a practical and eco-friendly platform for constructing bis-spirochromanone architectures, significantly broadening the accessible structural diversity for downstream biological screening. By combining solvent reusability with clean reaction profiles, the use of recyclable ionic liquids in Kabbe condensation offers an environmentally friendly and process-friendly platform. Scalable synthesis and industrial translation greatly benefit from such features.

3.11 Green and biomass-derived approaches

Dihydrolevoglucosenone and other biomass-derived solvents enhance Kabbe condensation's sustainability profile. The relevance of Kabbe chemistry for contemporary process



Scheme 16 Synthesis of substituted bis-spirochromanones **3.75** *via* Kabbe reaction.

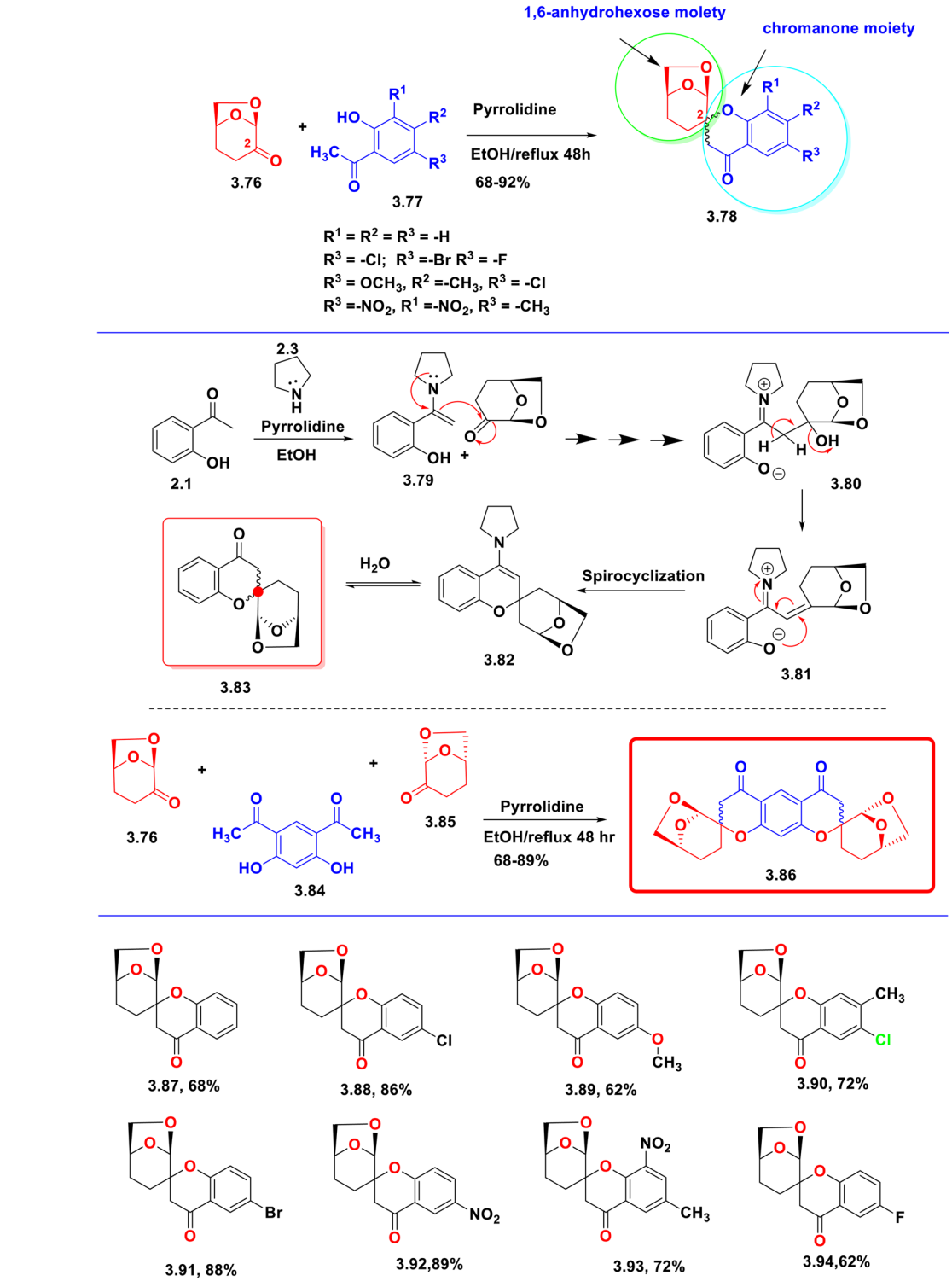
development is further supported by these green protocols, which show that highly efficient reaction conditions can be combined with environmental responsibility. Jankowski *et al.* (2025) developed an efficient and sustainable synthesis of C-2 spiro-substituted chromanones **3.78** using the biomass-derived solvent dihydrolevoglucosenone (DHL, **3.77**) and *o*-hydroxyacetophenones **3.77** in anhydrous alcohol with pyrrolidine as the base (Scheme 17).[53] In this process, 2′-hydroxyacetophenone first forms an enamine **3.79** with pyrrolidine, after which the nucleophilic enamine carbon attacks the C2 carbonyl of DHL **3.76**, leading to water elimination and intramolecular cyclization to generate the six-membered spiro ring **3.82**. The release of pyrrolidine yields the spirochromanone product **3.78** with excellent stereochemical purity under mild conditions, often at room temperature. Encouraged by these results, the authors extended the method to the symmetric diketone 1,1′-(4,6-dihydroxy-1,3-phenyl)bis(ethan-1-one) **3.84**, reacting it with DHL **3.76** under identical conditions to yield the doubly functionalized spirochromanone **3.86** in greater than 90% yield and high purity. Together with related derivatives **3.81** and **3.85–3.86**, this work demonstrates that DHL is an eco-friendly, renewable solvent that enables mild, stereochemically clean Kabbe-type spirocyclizations-marking a significant step forward toward sustainable and green Kabbe chemistry.

3.12 Castro's modified Kabbe condensation

Castro *et al.* (2020) developed a multistep synthetic strategy to access substituted chromone derivatives (**3.95–3.99**) beginning from 4-hydroxybenzonitrile through sequential acetylation, $AlCl_3$-mediated cyclization, Claisen condensation, reduction/Boc protection, and final Jones oxidation to furnish the chromone-4-one **3.99c** (Scheme 18).[54] Biological evaluation revealed that **3.99c**, a secondary amine derivative, exhibited the most promising antileishmanial activity, with IC_{50} values lower than those of the related quinolinones. Incorporation of a nitrogenated quinolinone ring did not enhance potency, and most analogues showed low macrophage toxicity, while only the styryl derivative displayed notable promastigote inhibition. These findings indicate that the chromone/chromanone core is superior to quinolinone scaffolds for anti-leishmanial efficacy, and that amine substitution and conjugated side chains play key roles in modulating activity providing essential early SAR direction for next-generation analogue design.[55–59]

4.1 Halogenated spirochromanones

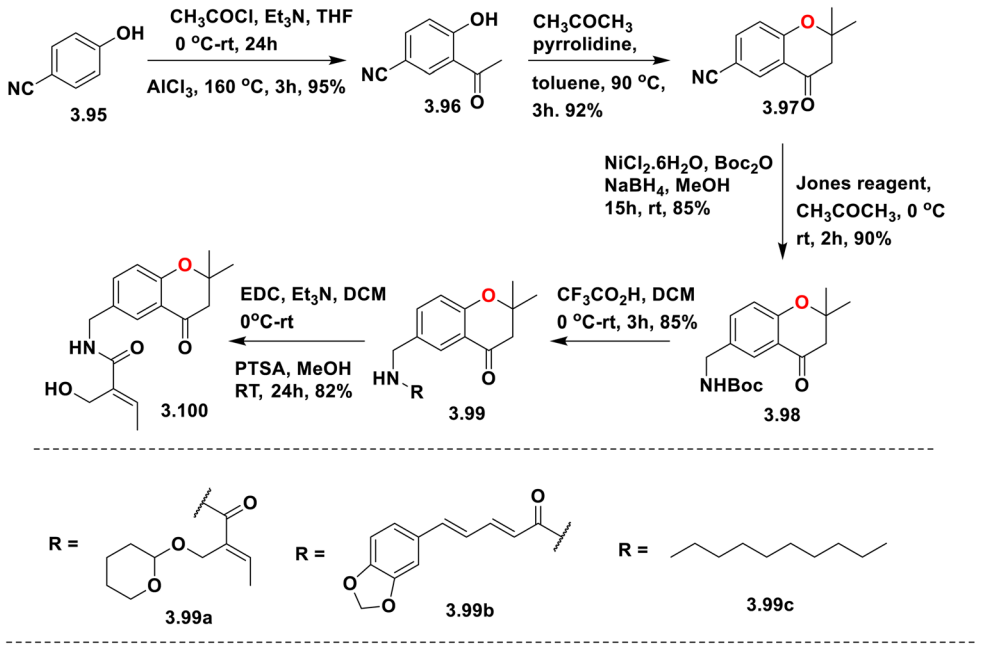
Desoky *et al.* in 1997 performed a Kabbe condensation using a range of cyclic ketones **4.1** with visnaginone (R = H) and khellinone (R = OMe) **4.2**, producing spirofurochromanone derivatives **4.3** (Scheme 19) where piperidine acted as the base facilitating spirocyclization.[60] These spirofurochromanones **4.3** were subsequently demethylated using pyridinium chloride to yield halogenated spirochromanones **4.4** in moderate yields, establishing the first halogenated members of this structural class. Halogenation markedly increases electrophilicity, improving suitability for cross-coupling reactions such as Suzuki, Heck, and Buchwald–Hartwig, while brominated analogues show particularly enhanced reactivity and can undergo acid-promoted intramolecular cyclizations due to the excellent leaving-group ability of bromide. These halogenated spirochromanones serve as privileged intermediates in medicinal chemistry, as halogens modulate lipophilicity, membrane interactions, and metabolic stability. Their compatibility with downstream heterocycle formation and late-stage functionalization makes them ideal precursors for generating diverse, drug-like spiro frameworks.



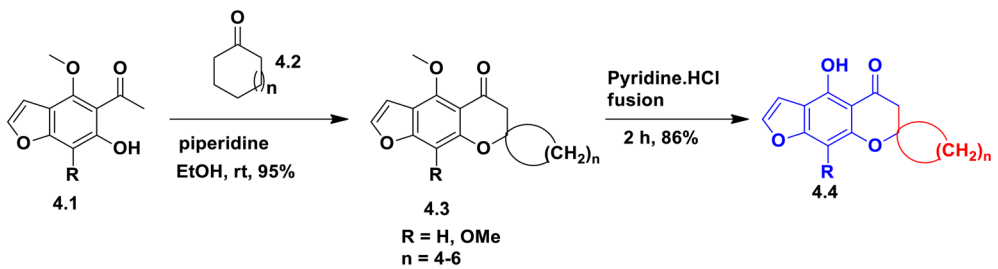
Scheme 17 Synthesis of C-2 spiro carbon with chromanone moiety 3.78 and bis spiro-chromanone 3.86.

4.2 Substituted chromanones and quinones

4.2.1 Substituted chromanones. Kabbe-derived spiro-chromanone scaffolds are widely used in medicinal chemistry programs, including growth hormone secretagogues, ACC inhibitors, antitubercular agents, and anticancer leads, The Kabbe condensation's synthetic dependability and translational relevance are highlighted by its frequent application in various therapeutic fields. Villarroel-Vicente *et al.* in 2024 developed a modular Kabbe-based route to 2-prenylated benzopyrans, starting from the condensation of 2,5-dihydroxyacetophenone



Scheme 18 Synthesis of chromanones 3.99 and 3.100 *via* Kabbe condensation.

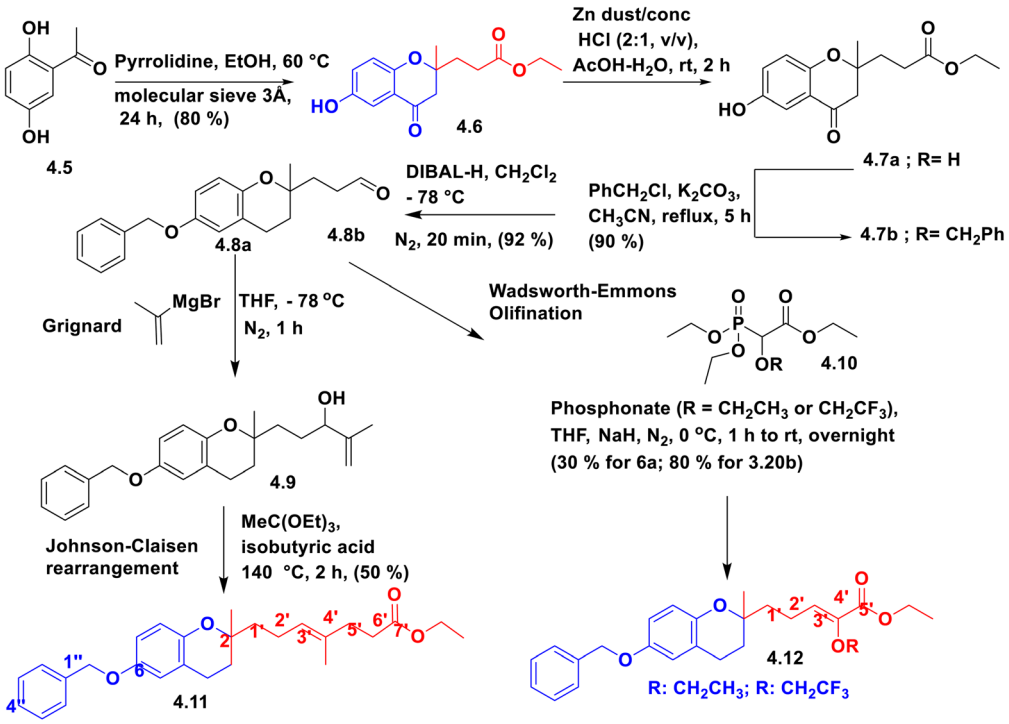


Scheme 19 Synthesis of substituted spirochromonone 4.4 *via* Kabbe reaction.

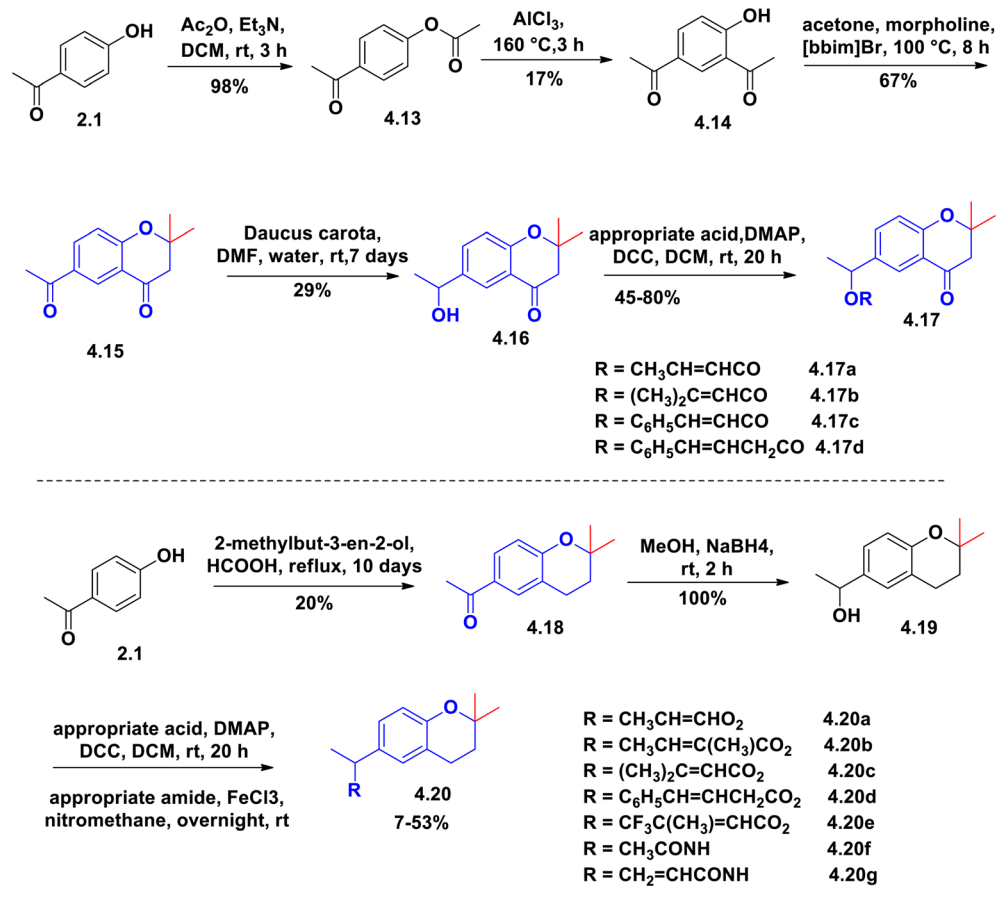
(**4.5**) with ethyl levulinate to furnish chroman-4-one **4.6**, which was reduced to **4.7a**, benzyl-protected to **4.7b**, and converted *via* DIBAL-H reduction to aldehyde **4.8**. Prenylation through a Grignard reaction followed by a Johnson–Claisen rearrangement yielded the γ,δ-unsaturated ester **4.11**, while a complementary Horner–Wadsworth–Emmons olefination of **4.8** provided the *O*-alkoxylated analogue **4.12a** (Scheme 20).[61] Both **4.11** and **4.12** displayed potent pan-PPAR activity, acting as full PPAR-α agonists with variable PPAR-γ/βδ activation; notably, the quinoline analogue showed complete hPPAR-α activation twice that of WY-14,643 and suppressed LPS-induced MCP-1 and IL-6 expression. Overall, the study highlights the Kabbe condensation as a key strategy for rapidly assembling benzopyran frameworks tailored for metabolic syndrome therapeutics, with the γ,δ-unsaturated ester motif critical for pan-PPAR modulation.

4.2.2 Benzopyran-containing chromanone derivatives. Cardoso *et al.* in 2024 reported the synthesis of chromanones belonging to the benzopyran class, specifically derivatives **4.17a–d** and **4.20a–g**, and evaluated their anti-leishmanial activities. The chromanone series **4.18** was obtained by initiating the cyclization of 2-methylbut-3-en-2-ol in formic acid, generating diketone **4.15** in 20% yield; subsequent quantitative reduction of **4.15** using sodium borohydride in methanol afforded the secondary alcohol **4.16**, which upon esterification or amidation delivered derivatives **4.20a–g** (Scheme 21).[62] In a parallel route, **4.15** was directly reduced to **4.16** and esterified analogously to furnish the same **4.20a–g** series in 7–34% yields. All synthesized derivatives were evaluated for their *in vitro* anti-leishmanial properties, and among them, **4.17d**, structurally related to the natural product uniflorol, emerged as the most potent candidate demonstrating strong potency (IC_{50} 7.29 μM), and shows low cytotoxicity (SI > 10.99). Notably, this 4-chromanone bearing an α,β-unsaturated ketone side chain exhibited strong anti-leishmanial activity, highlighting the importance of conjugation and lipophilic extension in enhancing biological potency within this benzopyran-derived chromanone scaffold.

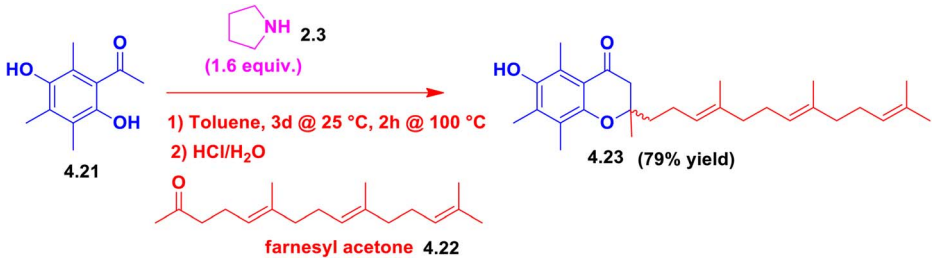
4.2.3 Substituted chromanone natural product. Kabbe and Heitzer in 1978 reported a concise Kabbe–Heitzer protocol for synthesizing the chromanone-type natural product 4-oxo-tocotrienol **4.23** through the condensation of 2-acetyl-3,5,6-



Scheme 20 Synthesis of spirochromanone derivatives 4.11 and 4.12.



Scheme 21 Synthesis of benzopyran containing chromanones (4.17a–d) and (4.20a–g).



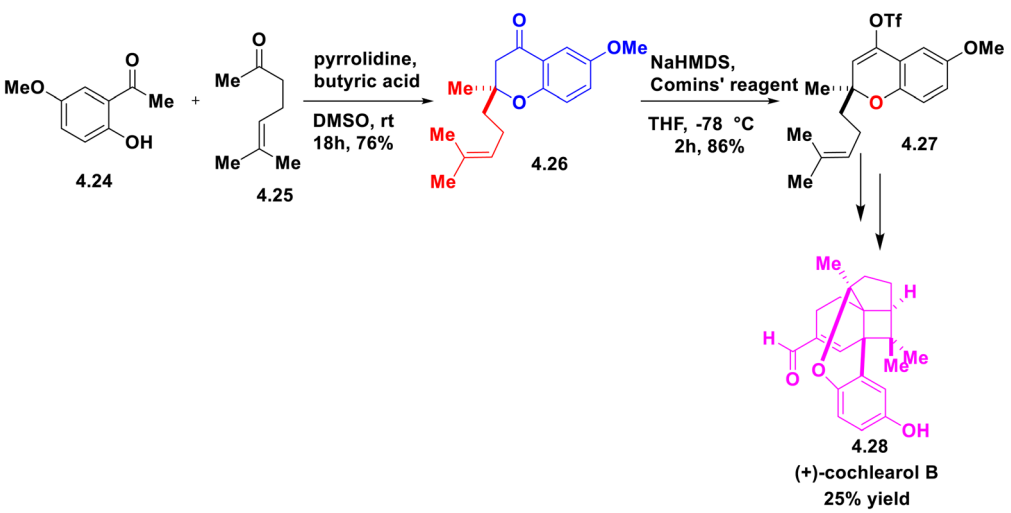
Scheme 22 The Kabbe–Heitzer protocol to 4-oxo-tocotrienol **4.23** using Kabbe condensation.

trimethylhydroquinone **4.21** with farnesyl acetone (**4.22**) using pyrrolidine as a non-chiral organocatalyst (Scheme 22).[28] This enamine-mediated cyclization efficiently constructed the substituted chromanone framework, demonstrating the utility of the Kabbe condensation in assembling meroterpenoid natural products. The method highlights how simple catalytic conditions can merge a quinonoid aromatic core with a prenyl-derived side chain to generate **4.23**, a tocotrienol analogue possessing a biologically relevant chromanone scaffold.[63]

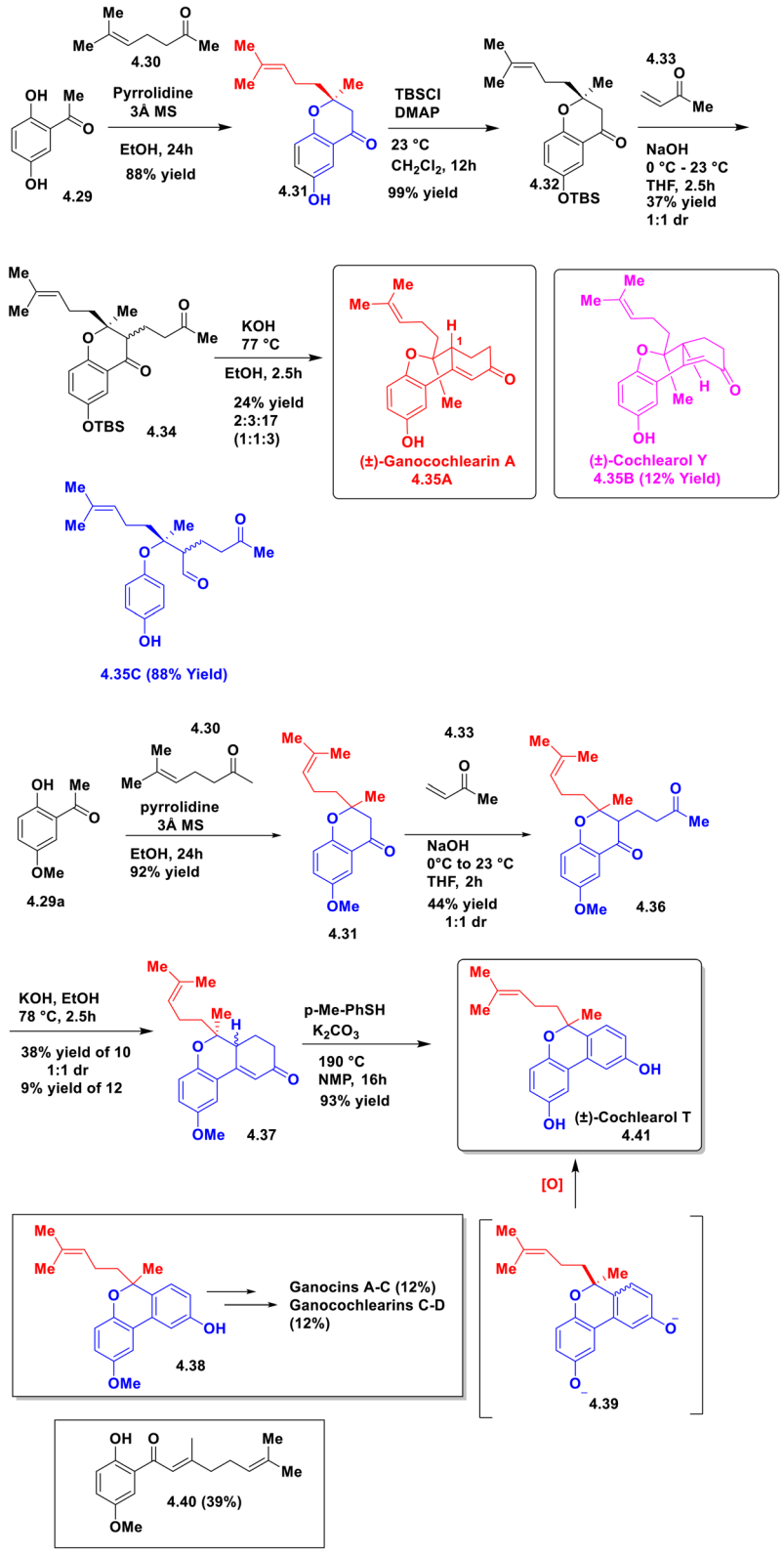
4.2.4 Spirochromenes (contains chromanone intermediate). Richardson *et al.* in 2022 established a Kabbe-based strategy for constructing spirochromenes, where the key chromanone intermediate **4.26** was generated *via* a Kabbe condensation between phenol **4.24** and sulcatone **4.25** using pyrrolidine as the catalyst (Scheme 23).[64] This enamine-mediated annulation efficiently built the chromanone nucleus essential for meroterpenoid synthesis, and the resulting racemic **4.26** was resolved with (R)-*tert*-butanesulfinamide to obtain an enantioenriched intermediate. Subsequent triflation delivered the vinyl triflate **4.27**, which enabled a Catellani reaction followed by a visible-light-mediated [2 + 2] cycloaddition en route to the highly complex natural product (+)-cochlearol B **4.28**. The strategic use of a Kabbe-derived chromanone scaffold highlights the reaction's power in complex meroterpenoid synthesis, where its rigid framework and synthetically flexible functional handles allow precise downstream diversification, making **4.26** an exceptional platform for constructing densely substituted spirocyclic natural products.

4.2.5 Chromanone contains natural products synthesis. Kakde *et al.* in 2024 established a concise unified route to the meroterpenoids (±)-ganocochlearin A (**4.35A**), (±)-cochlearol Y (**4.35B**), and (**4.35C**) beginning with a Kabbe condensation between 2,5-dihydroxyacetophenone **4.29** and sulcatone **4.30** to form chromanone **4.31**, which was TBS-protected to give **4.32**. Michael addition with methyl vinyl ketone **4.33** yielded diketone **4.34**, and subsequent intramolecular aldol condensation produced tricyclic products **4.35A–C**. A parallel pathway from **4.29a** and **4.30** furnished chromanone **4.35**, whose TBS-protected derivative **4.40** underwent Michael addition and Robinson annulation to deliver (±)-cochlearol T (**4.41**) after demethylation. Additionally, α-bromination of **4.35** generated **4.38**, enabling further enolate-based diversification toward ganocin and ganocochlearin analogs (Scheme 24).[65] These transformations highlight the Kabbe-derived chromanone core as a powerful branching scaffold capable of driving cascade reactions and C–C bond formations, enabling rapid access to structurally complex meroterpenoids that exhibit potent anti-fibrotic activity.

4.2.6 Benzannulated oxepine-spirochromanones. Kapuriya *et al.* in 2020 developed a mild and efficient organocatalyzed Kabbe condensation using a pyrrolidine–butanoic acid system in DMSO at ambient temperature to synthesise 2,2-dialkyl

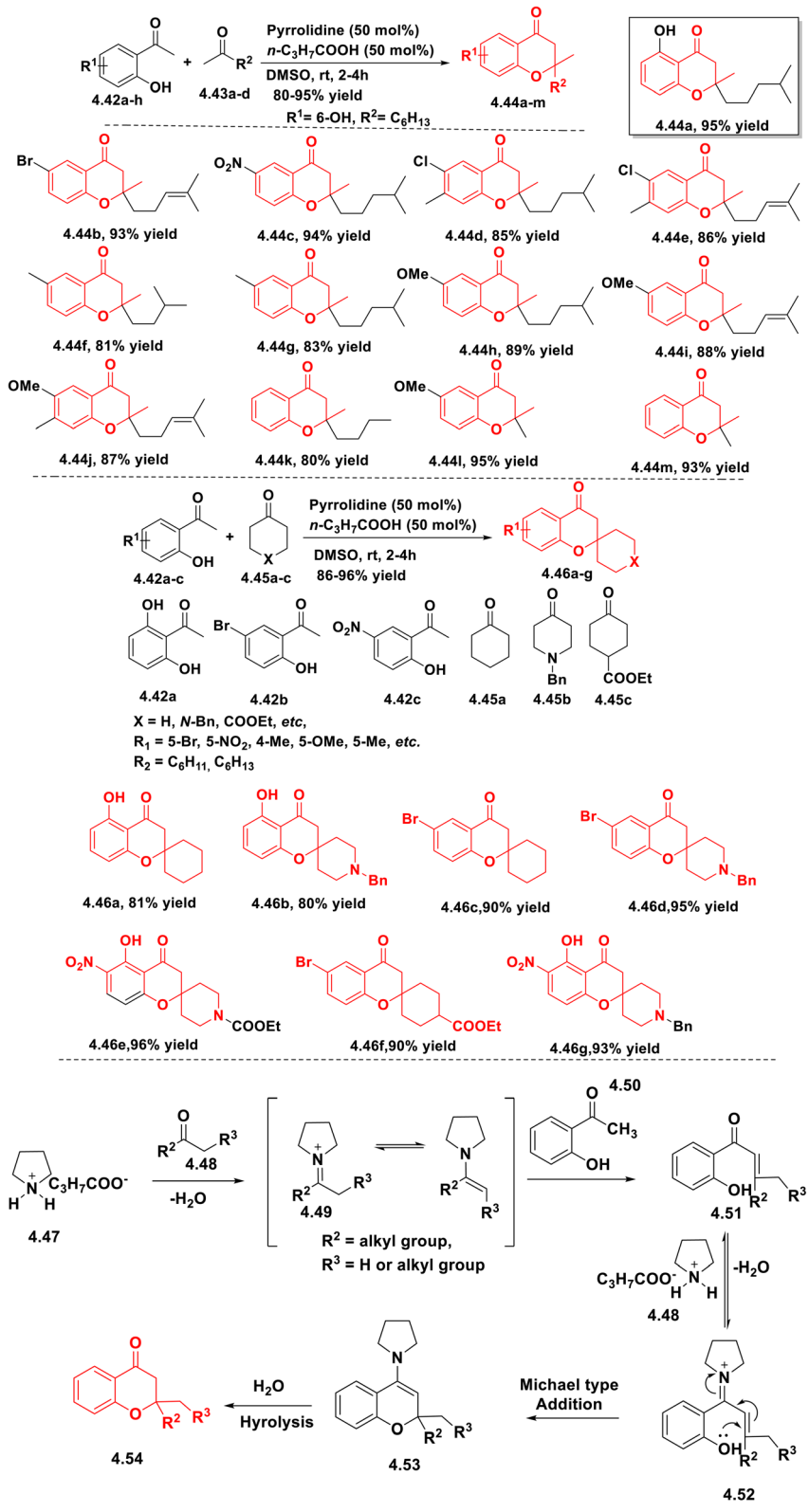


Scheme 23 Synthesis of spirochromenes **4.28** *via* Kabbe condensation.



Scheme 24 Synthesis of (±)-ganocochlearin A (**4.14A**), (±)-cochlearol Y (**4.14B**), and desilylated phenol (**4.40C**) and (±)-cochlearol T (**4.41**).

chroman-4-ones (**4.44a–m**) and 2-spiro-chroman-4-ones (**4.46a–g**) (Scheme 25). Reaction of 2,6-dihydroxyacetophenones (**4.42a–h**) with acyclic ketones such as **4.43a–d** afforded highly substituted chromanones **4.44** in up to 95% yield, while their reaction with cyclic ketones **4.45a–c** delivered spiro-chromanones **4.46** in excellent yields (80–96%) within 1.5–3



Scheme 25 The synthesis of both 2,2-dialkyl chroman-4-ones **4.44a–m** and 2-spiro-chroman-4-ones **4.46a–g**.

hours.[66] The transformation proceeds through a bifunctional mechanism in which pyrrolidine forms a nucleophilic enamine from the ketone, while butanoic acid stabilizes the iminium and transition states *via* hydrogen bonding, enabling rapid Michael addition, intramolecular oxo-Michael cyclization, and regeneration of the catalyst. This cooperative organocatalytic

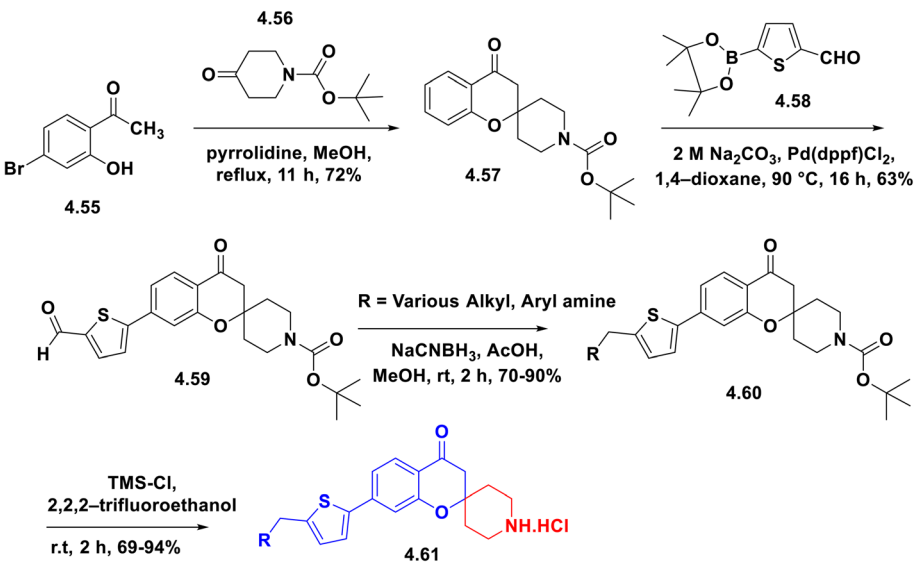
system significantly broadens the scope of Kabbe condensation, allowing the construction of sterically congested quaternary centers under metal-free, green conditions. The high efficiency, mildness, and scalability make the pyrrolidine–butanoic acid protocol a powerful platform for accessing densely substituted chromanones and spirocyclic scaffolds pivotal in modern medicinal chemistry.

4.2.7 Substituted spirochromanone analogues. Chitti *et al.* (2021) reported Kabbe-derived spirochromanone–piperidine hybrids **4.61** derived from bromo containing 2-hydroxy acetophenone **4.55** with *tert*-butyl 4-oxopiperidine-1-carboxylate **4.56** the presence of pyrrolidine at 70 °C to afford tertiary butyl-7-bromo-4-oxospiro-[chroman–2,4′–piperidine]-1′-carboxylate **4.57**. The compound **4.57** was undergoes palladium-catalyzed Suzuki coupling with thiophene boronate ester **4.58**, resulting in the formation of intermediate **4.59**, Subsequently, intermediate **4.59** was subjected to reductive amination with a variety of amines (alkyl and aryl) to provide amine analogues **4.60**. In the final step, these amine conjugates **4.60** were treated with mild acidic conditions for the deprotection of the Boc group, utilizing 2,2,2-trifluoroethanol and trimethylsilylchloride, affords spirochromanone–piperidine hybrids **4.61** of HCl salt. The collection of thirty-one analogues **4.61** highlights the minimal structural alterations around the amine side chain can substantially affect anticancer efficacy and selectivity (Scheme 26).[67] The rigid spiro-fused chromanone core offers a specific 3D orientation that improves target interaction and reduces off-target effects, while the attached amine substituents influence lipophilicity, cellular permeability, and apoptotic signaling. Importantly, derivatives containing simple alkyl or aromatic amines especially the methylamine, benzylamine, and thiophen-2-ylmethyl analogue **4.61** exhibited significant cytotoxicity (IC_{50} = 5–10 μM) against MCF-7 and B16F10 cancer cells, with diminished toxicity towards normal HEK-293 cells.[68] SAR investigations have underscored the advantages of minimal, electron-neutral substituents, indicating that steric simplicity and a balanced polarity promote mitochondrial apoptosis and G2/M phase arrest.

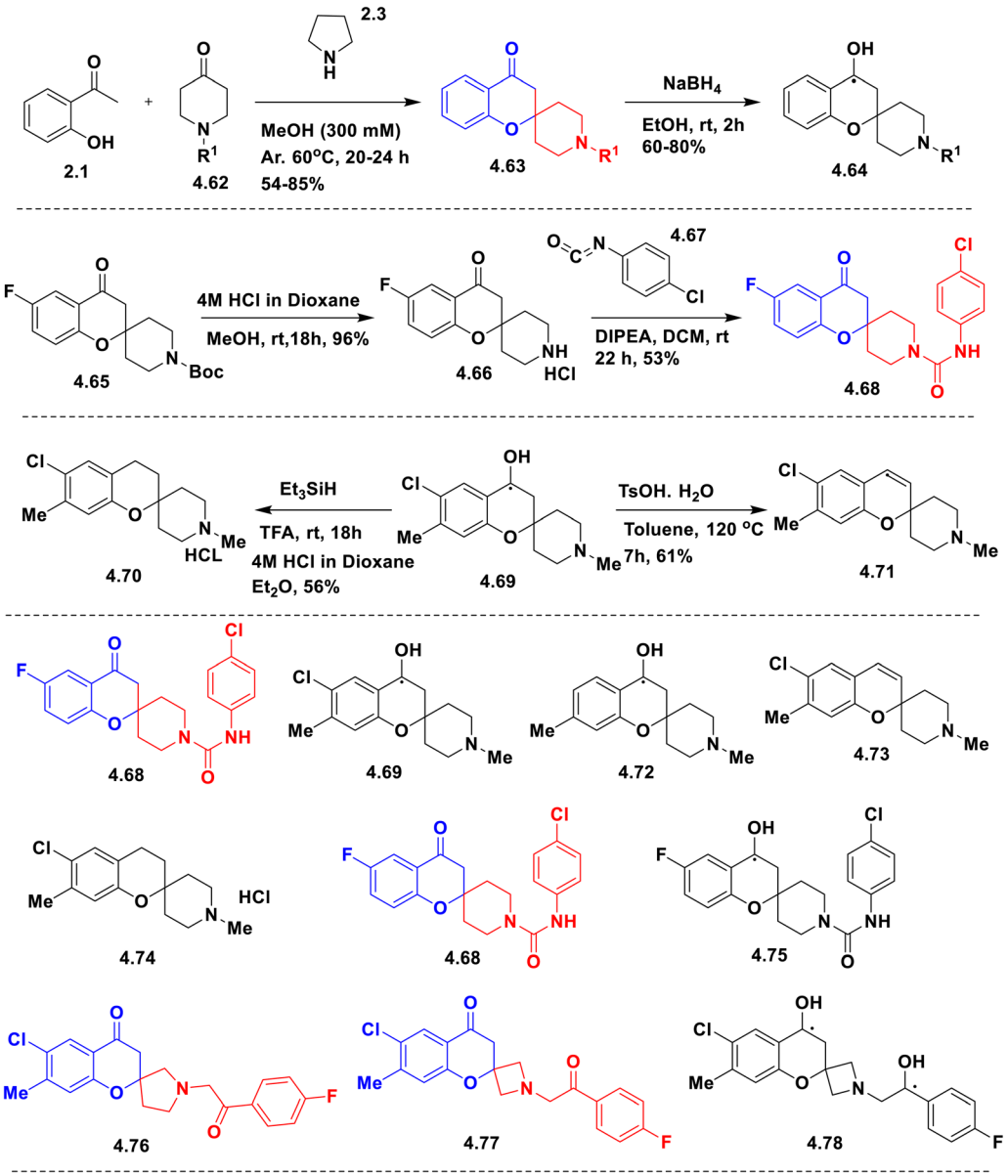
4.2.8 Amine-substituted spirochromanone derivatives. Bonesconto *et al.* in 2024 reported a practical Kabbe-condensation route to access a library of amine-substituted spirochromanone derivatives **4.63** for Chagas disease programs (Scheme 27).[69] The acetophenone derivative **2.1** was condensed with piperidone **4.62** using pyrrolidine **2.3** in refluxing methanol to furnish the spirochromanone scaffold **4.63** in 54–85% yield on a multigram scale, with only minor by-product formation. Subsequent $NaBH_4$ reduction of **4.63** generated the corresponding secondary alcohols in 60–86% yield as racemic mixtures, which served as primary bioactive candidates. Further derivatization involved Boc-deprotection of **4.65** to the hydrochloride salt (96% yield), followed by condensation with aryl isocyanate **4.67** using DIPEA to afford the urea-linked analogue **4.68** in 53% yield, expanding the SAR profile against *T. cruzi*. The amine-substituted spirochromanone scaffold provides a rigid, conformationally locked framework that is ideal for targeting narrow parasitic enzyme pockets. Meanwhile, modular *N*-functionalization enables the fine-tuning of polarity, permeability, and antiparasitic selectivity. The ease of synthesizing **4.63** and its derivatives through Kabbe condensation followed by simple *N*-modifications positions these spirochromanones as robust, rapidly accessible starting points for next-generation Chagas disease therapeutics.

4.3 Spirochromanone–piperidine hybrids

4.3.1 Synthesis of substituted spirochromanone. Elliott *et al.* in 1992 reported the efficient synthesis of class III antiarrhythmic agents based on the 4-oxospiro[benzopyran-2,4′-piperidine] scaffold **4.84**. The sequence began with the conversion of *p*-anisidine **4.79** to 5-acetamido-2-hydroxyacetophenone **4.80**, which after hydrolysis and



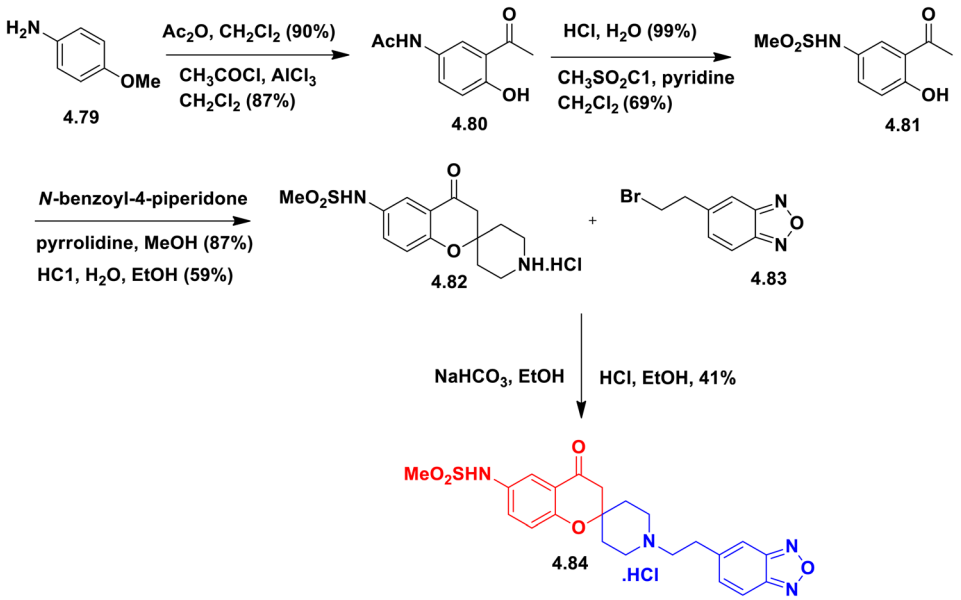
Scheme 26 Synthesis of aminomethyl-thiophen-spiro-[chroman–2,4′-piperidin]-4-one hydrochloride **4.61** *via* Kabbe condensation.



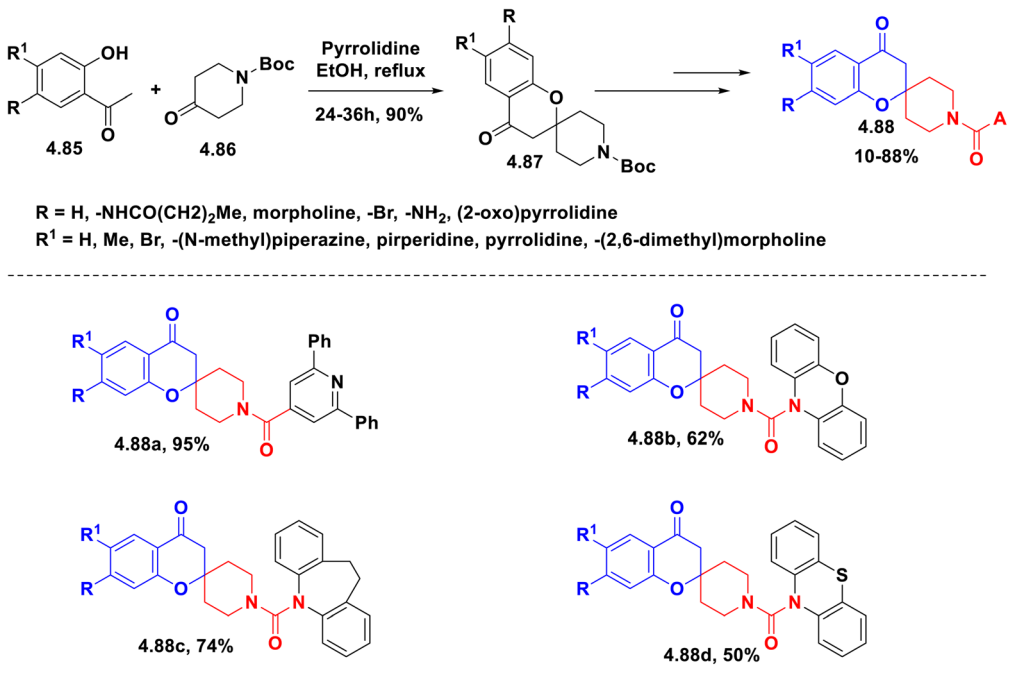
Scheme 27 Amine substituted spirochromane derivatives 4.68.

mesylation yielded 5-methanesulfonamido-2-hydroxyacetophenone **4.81**. Kabbe-type spirocyclization of **4.81** with *N*-benzoyl-4-piperidone under pyrrolidine catalysis produced the spirocyclic amine **4.82**, and subsequent alkylation with benzofurazan ethyl bromide **4.83** furnished the target molecules **4.84** in moderate yield (Scheme 28).[70] Most members of the **4.84** series displayed strong *in vivo* antiarrhythmic efficacy, good absorption, and prolonged duration of action, with several candidates advancing into human studies. The rigid spiro-fusion between the benzopyranone and piperidine rings imparts a well-defined 3D architecture that enhances ion-channel selectivity and metabolic stability, while the 6-methanesulfonamide group improves polarity and pharmacokinetic behavior. This work demonstrates how Kabbe-derived spiro scaffolds serve as powerful, drug-like frameworks for cardiovascular therapeutics.

4.3.2 Synthesis of substituted spiro-chroman-piperidin-one. In 2009, Shinde *et al.* synthesized a series of spirochromanones linked to hydrophobic cores *via* amidic linkages (**4.88**) using the Kabbe reaction and evaluated them for *in vitro* acetyl-CoA carboxylase (ACC) inhibitory activity (Scheme 29).[71] Among these, the diphenylisonicotinoyl-conjugated spiro [chroman-2,4′-piperidin]-4-one **4.88a** exhibited exceptional potency, achieving over 90% ACC inhibition at 10 μM with low-nanomolar efficacy. SAR analysis revealed that modification of the C–N bond at the C-6 position of the aromatic ring is critical for activity, and further substitution at the C-6/C-7 positions could enhance metabolic stability and *in vivo* effectiveness. The spirochromanone–piperidinone core in **4.88** offers a rigid, conformationally locked framework ideal for engaging ACC's deep hydrophobic pocket, with the perpendicular orientation enforced by the spiro junction improving binding selectivity



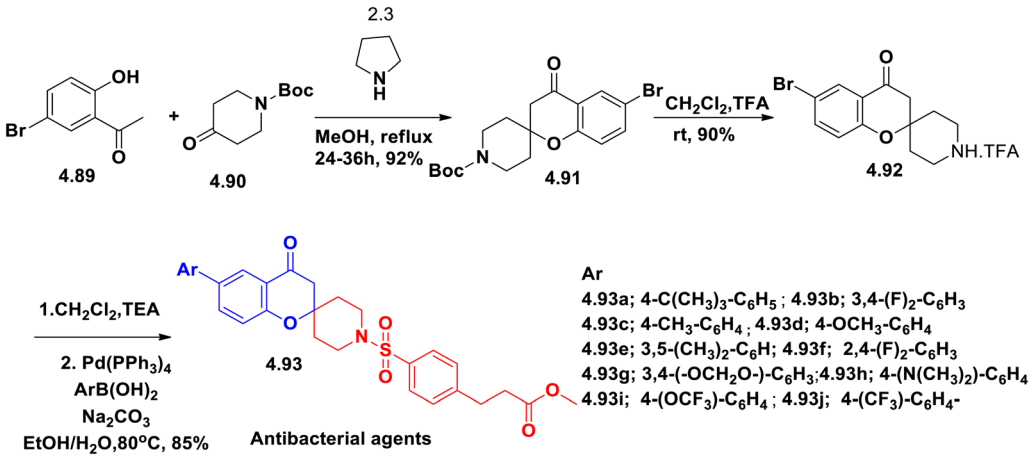
Scheme 28 Synthesis of substituted spirochromonone 4.84 *via* Kabbe reaction.



Scheme 29 Synthesis of substituted spiro-chromanpiperidinone 4.88 *via* Kabbe reaction.

and minimizing off-target lipophilicity. The strong performance of **4.88a** underscores how strategic aryl or heteroaryl substitutions can fine-tune potency, highlighting Kabbe-derived spirochromanones as privileged scaffolds for next-generation metabolic disease therapeutics, including obesity, NAFLD, and diabetes-associated disorders.

4.3.3 Synthesis of 2-spiropiperidinechroman-4-one derivatives. In 2012, Patel *et al.* reported a Kabbe condensation between hydroxy acetophenone **4.89** and *N*-Boc piperidone **4.90** using pyrrolidine, furnishing spirochromanone **4.91**, which after TFA-mediated deprotection gave **4.92**. This intermediate underwent Pd-catalyzed Suzuki coupling with various phenyl boronic acids to afford a library of aryl-substituted spiropiperidinechromanones **4.93a–j** in good yields (Scheme 30).[72] The derivatives were evaluated against *E. coli*, *S. aureus*, *P. aeruginosa*, *B. subtilis*, and *Candida albicans*, revealing that *ortho* and *meta*-substituted analogues exhibited superior antimicrobial activity compared to *para*-substituted ones. Moderately



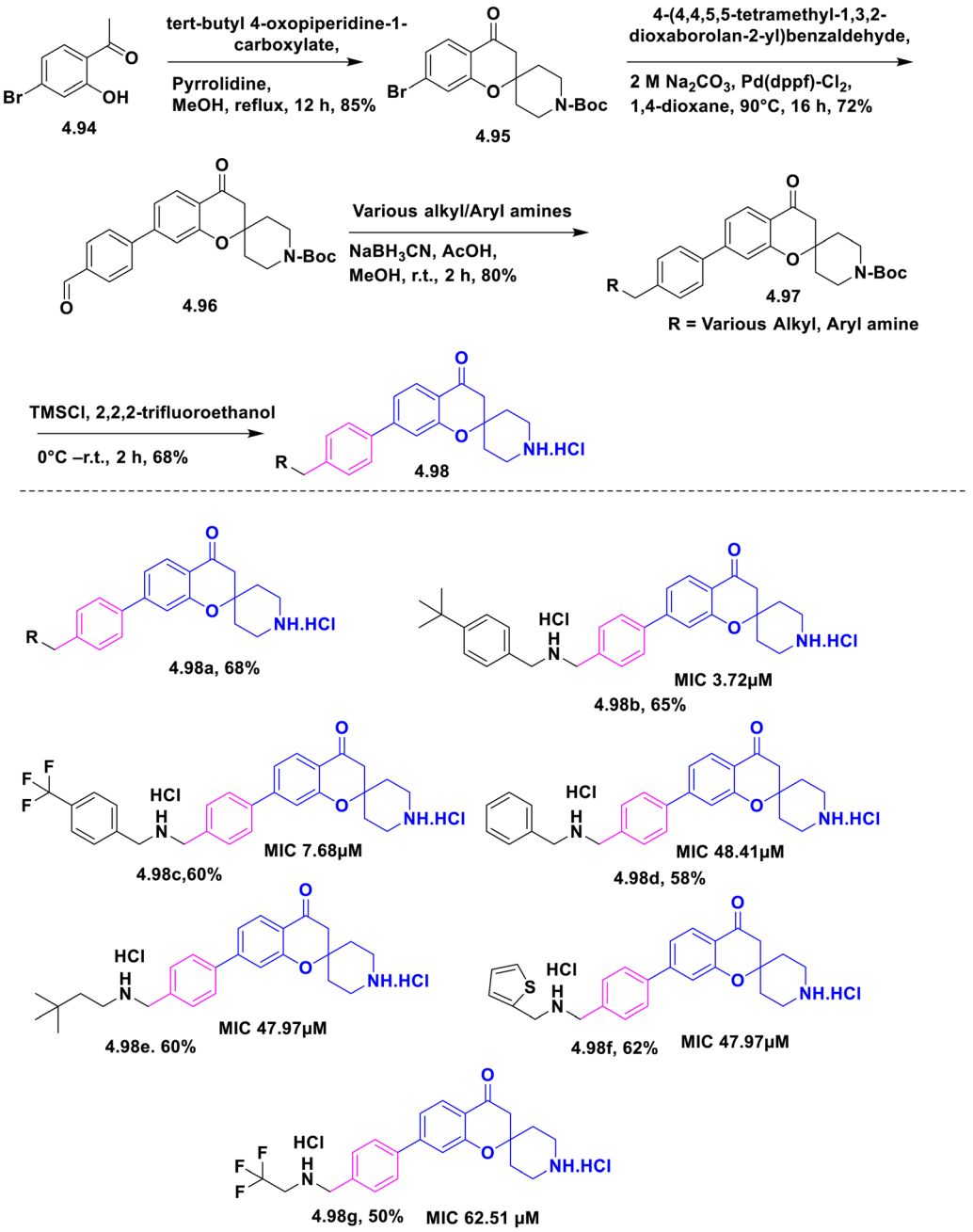
Scheme 30 Synthesis of 2-spiropiperidinechroman-4-one derivatives **4.93**.

active examples included **4.93a**, **4.93c**, **4.93d**, **4.93h**, **4.93i**, and **4.93j**, while the disubstituted 3,5-dimethyl analogue **4.93e** was the most potent member of the series. The rigid spiro-fused chromanone–piperidine core provides a privileged 3D scaffold for antimicrobial activity, with the sulfonyl-linked aryl substituents enabling optimal hydrophobic and π-stacking interactions. Enhanced potency in *ortho*/*meta* and disubstituted analogues highlights the importance of steric bulk and electronic tuning for efficient microbial target engagement, confirming Kabbe-derived spirochromanones **4.93** as promising antimicrobial leads.

4.3.4 Synthesis of novel spiro-[chroman-2,4′-piperidin]-4-one. In 2025, Chitti *et al.* synthesized a series of spiro-[chroman-2,4′-piperidin]-4-one derivatives **4.98** using optimised Kabbe reaction conditions (Scheme 31).[73] All compounds were fully characterized and screened for antitubercular activity, displaying MIC values ranging from 3.72 to 230.42 μM against *Mycobacterium tuberculosis*. Among them, **4.98b**, bearing an electron-releasing *tert*-butyl group at the *para*-position of the benzylamine moiety, showed the strongest activity (MIC 3.72 μM). The electron-withdrawing *para*-CF_3 analogue **4.98c** also demonstrated good potency (MIC 7.68 μM), whereas the unsubstituted benzylamine derivative **4.98d** exhibited considerably weaker activity (MIC 48.41 μM). The strong performance of **4.98b** and **4.98c** highlights the importance of fine electronic modulation on the benzylamine substituent for enhancing antimycobacterial potency. Electron-donating and electron-withdrawing groups both improve binding efficiency compared to the unsubstituted analogue, suggesting that the rigid spirochromanone piperidinone core tolerates diverse electronic environments while benefiting from optimized ligand target complementarity. These results position **6.100** derivatives as promising Kabbe-derived scaffolds for next-generation anti-TB agents.

4.3.5 Synthesis of amino methyl-phenyl spiro-chromane-piperidin-4-one hydrochloride. In 2024, Chaitanya *et al.* synthesized a series of spirochromanone–piperidinone derivatives **4.104** *via* a Kabbe condensation between compound **4.94** and 1-Boc-piperidone (**4.99**) in methanol using pyrrolidine at 70 °C, affording the *tert*-butyl-protected spiro intermediate 4.100 (Scheme 32).[74] Subsequent Suzuki coupling of **4.100** with phenyl boronate ester **4.101** generated the biaryl intermediate **4.102**, which then underwent reductive amination with various alkyl and aryl amines to yield the corresponding amine derivatives **4.103**, ultimately providing the target analogues **4.104**. These compounds were evaluated for anti-quorum-sensing activity against *Chromobacterium violaceum* ATCC 12472, where most derivatives showed significant inhibition of QS-regulated violacein production. Notably, the three most active molecules contained aromatic substituents in the tail region, which enhanced receptor engagement, as supported by a docking score of −7.99 kcal mol^{-1} for **4.104**, while aliphatic analogues showed comparatively weaker activity. The rigid spiro-fused chromanone-piperidinone core in **4.104** provides a well-defined 3D orientation that mimics native autoinducer conformations, enabling effective disruption of bacterial communication without bactericidal pressure. The presence of aromatic groups enhances π-stacking and hydrophobic interactions within the QS receptor pocket, improving binding stability and selectivity. Together, these results position Kabbe-derived spirochromanones as promising anti-virulence scaffolds for next-generation quorum-sensing inhibitors.

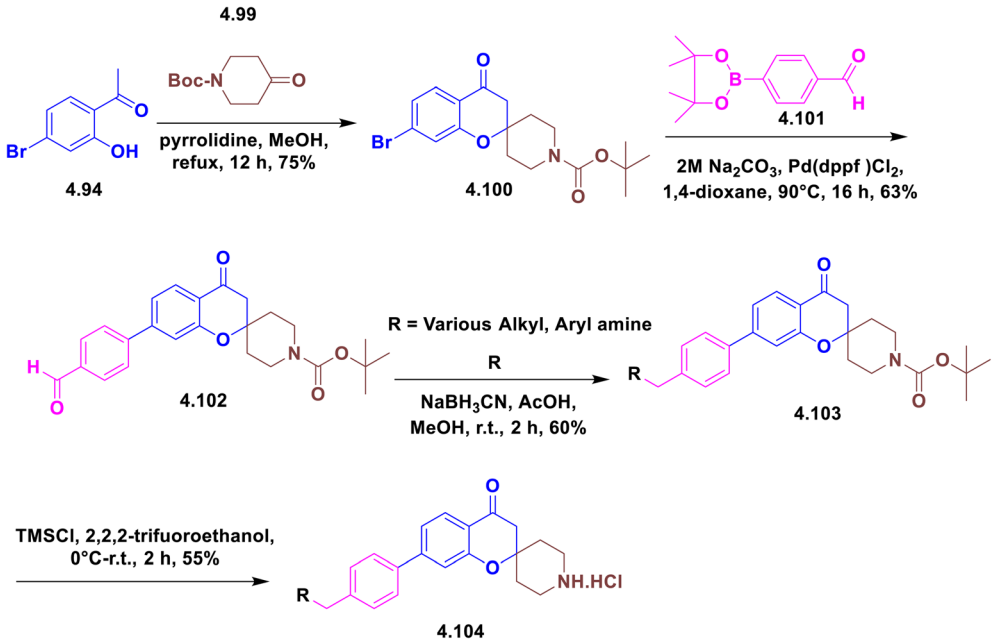
4.3.6 Synthesis of spiro-chromane piperidine derivatives. Muthukrishnan *et al.* (2011) developed a Kabbe condensation-inspired multistep route to access novel 1,2,3-triazole-fused spirochromone conjugates (**4.110** and **4.111**) with potent antimycobacterial properties. The sequence begins with a Kabbe condensation between 2,4-dihydroxyacetophenone (**4.105**) and either cyclohexanone or *N*-Boc-piperidone, using pyrrolidine as a base in acetonitrile at 50 °C, affording the spirochromanone intermediates **4.107a** (X = CH_2) and **4.107b** (X = *N*-Boc) in 72% and 75% yields, respectively. *O*-alkylation with epichlorohydrin produced epoxides **4.107**, which underwent azidation to generate **4.108**. Subsequent Cu(I)-catalysed azide–alkyne cycloaddition furnished the final triazole-linked spirochromones **4.110** (X = CH_2) and **4.111** (X = *N*-Boc) in 65–90% yields (Scheme 33).[75] Among these, **4.110e** displayed exceptional antimycobacterial potency with an MIC of 0.78 μg mL^{-1} against



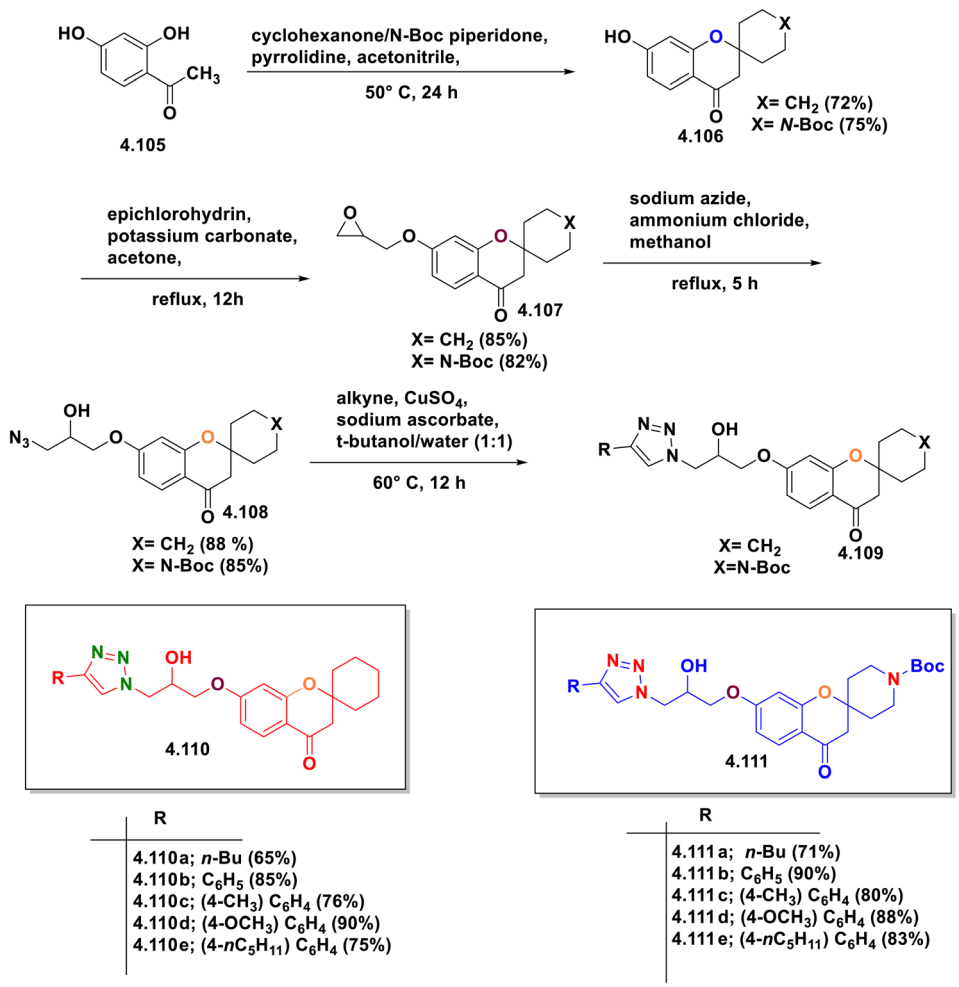
Scheme 31 Synthesis of novel spiro-[chroman-2,4′-piperidin]-4-one **4.98a–g**.

Mycobacterium tuberculosis H37Rv, outperforming ethambutol (MIC = 1.56 μg mL^{-1}). This work demonstrates that Kabbe-derived spirochromanones serve as privileged, modular scaffolds for constructing complex nitrogen-rich heterocycles, and that triazole fusion dramatically enhances antimycobacterial potency, positioning these hybrids as promising leads for next-generation TB therapeutics.

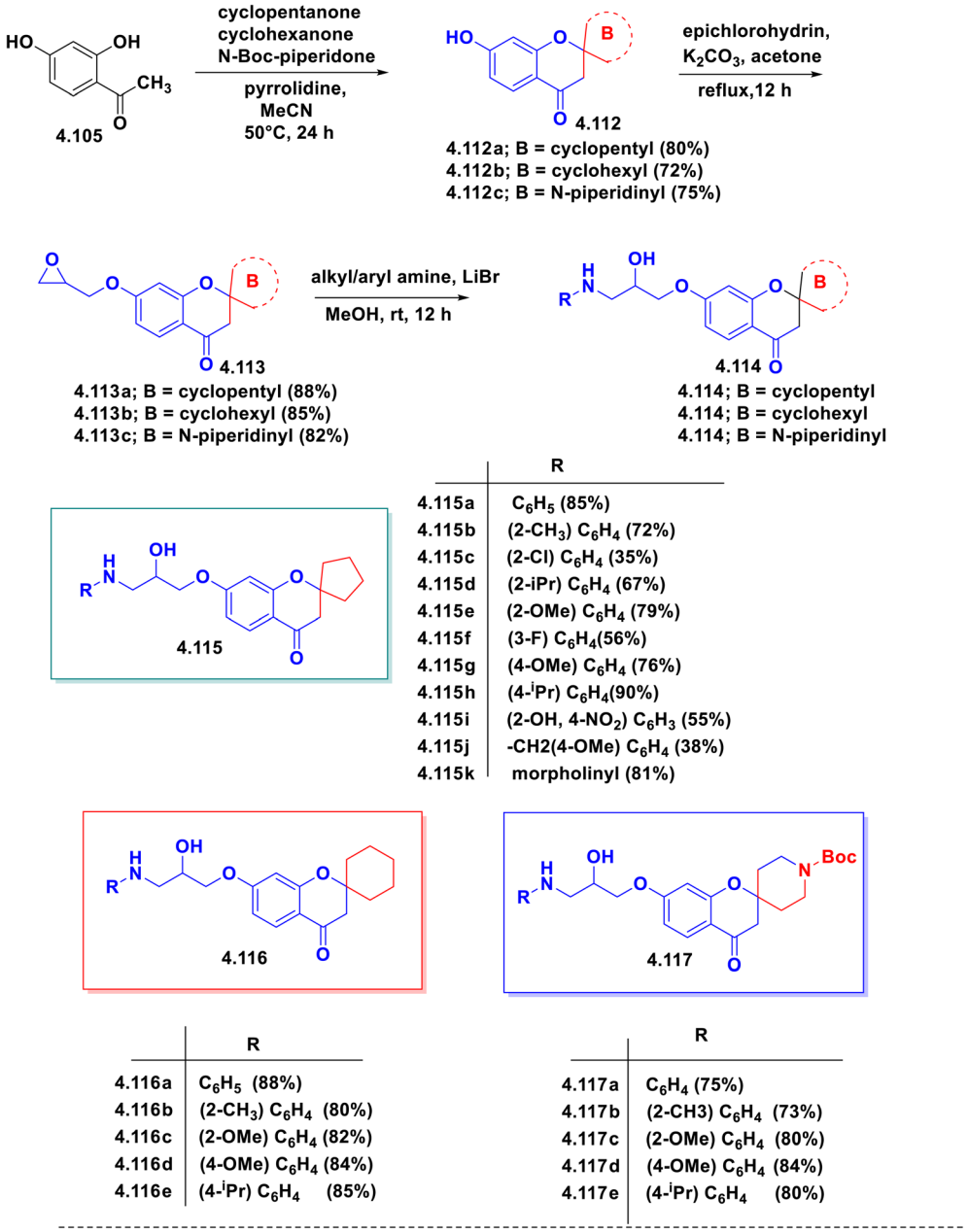
4.3.7 Synthesis of amino alcohol-fused spirochromanones. Muthukrishnan *et al.* (2009) reported the first synthesis of amino alcohol fused spirochromone conjugates (**4.115**, **4.116**, **4.117**) using an efficient Kabbe condensation-based strategy. The sequence began with the formation of spirochromanone intermediates **4.112a–c** *via* Kabbe condensation of 2,4-dihydroxyacetophenone (**2.58**) with various cycloalkanones using pyrrolidine as the base. These intermediates were then *O*-alkylated with epichlorohydrin under reflux to afford the corresponding epoxides (**4.112a–c**, 82–88%), which underwent nucleophilic ring opening with a range of aromatic and aliphatic amines to yield amino alcohol–fused spirochromone conjugates **4.114a–c** in moderate to good yields (Scheme 34).[76] Biological evaluation revealed that most analogues exhibited moderate to good antimycobacterial activity, with **4.115f**



Scheme 32 Synthesis of amino methyl-phenyl spiro chromanepiperidin-4-one hydrochloride 4.104.



Scheme 33 Synthesis of substituted 1,2,3-triazole fused spirochromone conjugates 4.110 & 4.111.

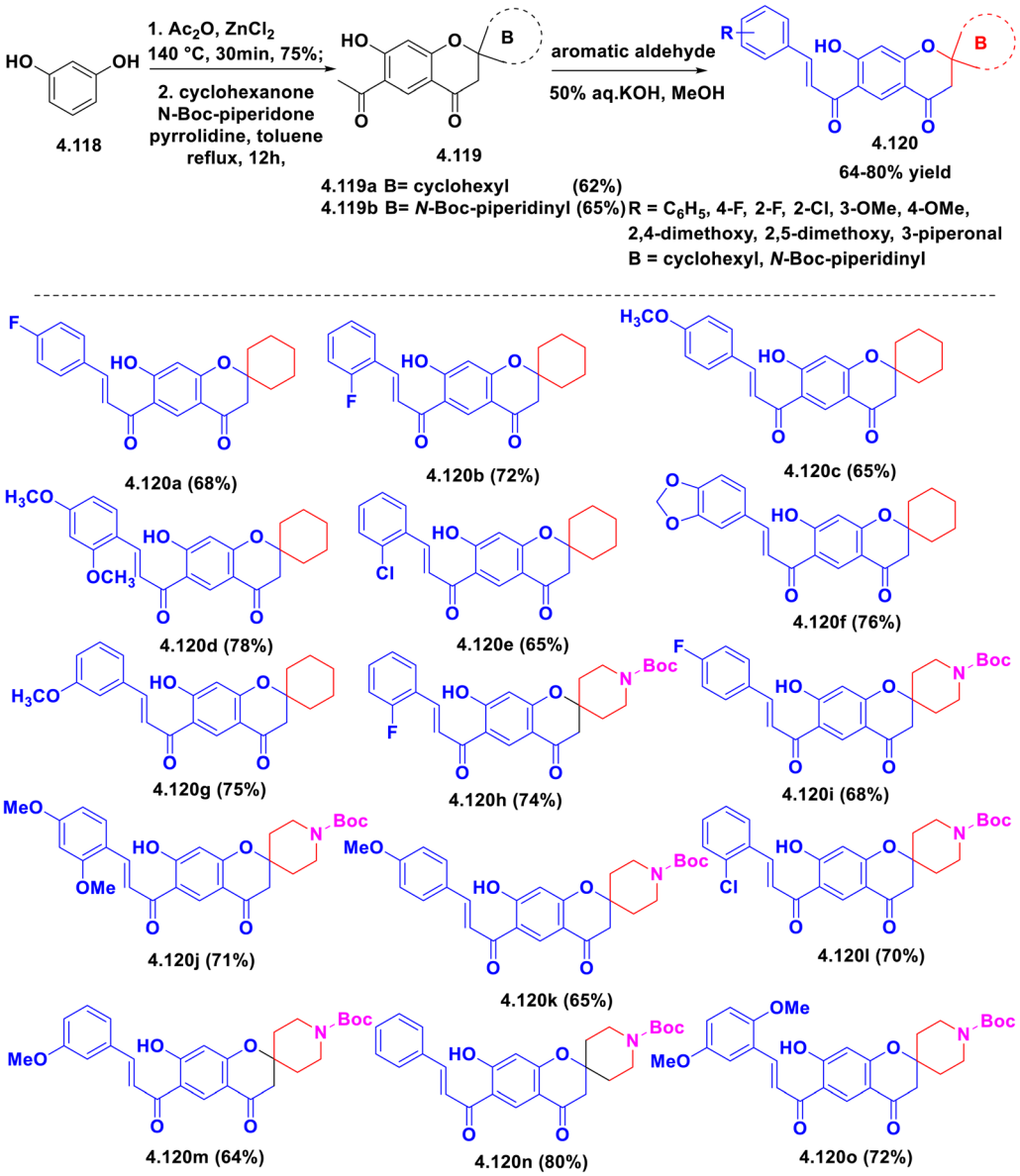


Scheme 34 Synthesis of amino alcohol annulated spirochromone conjugates 4.16–4.117.

emerging as the most potent (MIC = 3.13 μg mL^{-1} against *Mycobacterium tuberculosis* H37Rv). The combination of a rigid spirochromanone core with flexible amino alcohol substituents creates a privileged hybrid scaffold capable of engaging diverse biological targets, underscoring these conjugates as promising leads for antimycobacterial drug development.

4.3.8 Synthesis of spirochromanone–chalcone hybrids. Mujahid *et al.* (2015) synthesized a new class of spirochromanone–chalcone hybrids by annulating chalcone motifs onto Kabbe-derived spirochromanone cores (**4.119a**, **4.119b**) prepared from 4,6-diacetylresorcinol and either cyclohexanone or *N*-Boc-piperidone (Scheme 35).[77] Subsequent Claisen–Schmidt condensations produced the final conjugates (**4.120a–g**, **4.120h–o**), among which five compounds (**4.120a**, **4.120b**, **4.120i**, **4.120h**, **4.120l**) showed notable antimycobacterial activity, with **4.120h** exhibiting the strongest potency (MIC = 3.13 μg mL^{-1}). Docking studies identified MtbPtpB as a likely target, and QSAR/DFT analyses correlated activity with low LUMO energies and key substituents such as halogens and piperidinyl groups on the spiro core. ADME/Tox profiling further confirmed favorable drug-like features including BBB permeability, high HIA, and low toxicity. These results demonstrate that spirochromanone–chalcone hybrids effectively merge two privileged pharmacophores into a single scaffold, producing potent anti-TB leads such as **4.120h**, with strong biochemical activity and excellent drug-development potential.

4.3.9 Synthesis of indolin-2-one-annulated spirochromanone hybrids. Ashok *et al.* (2015) developed an efficient

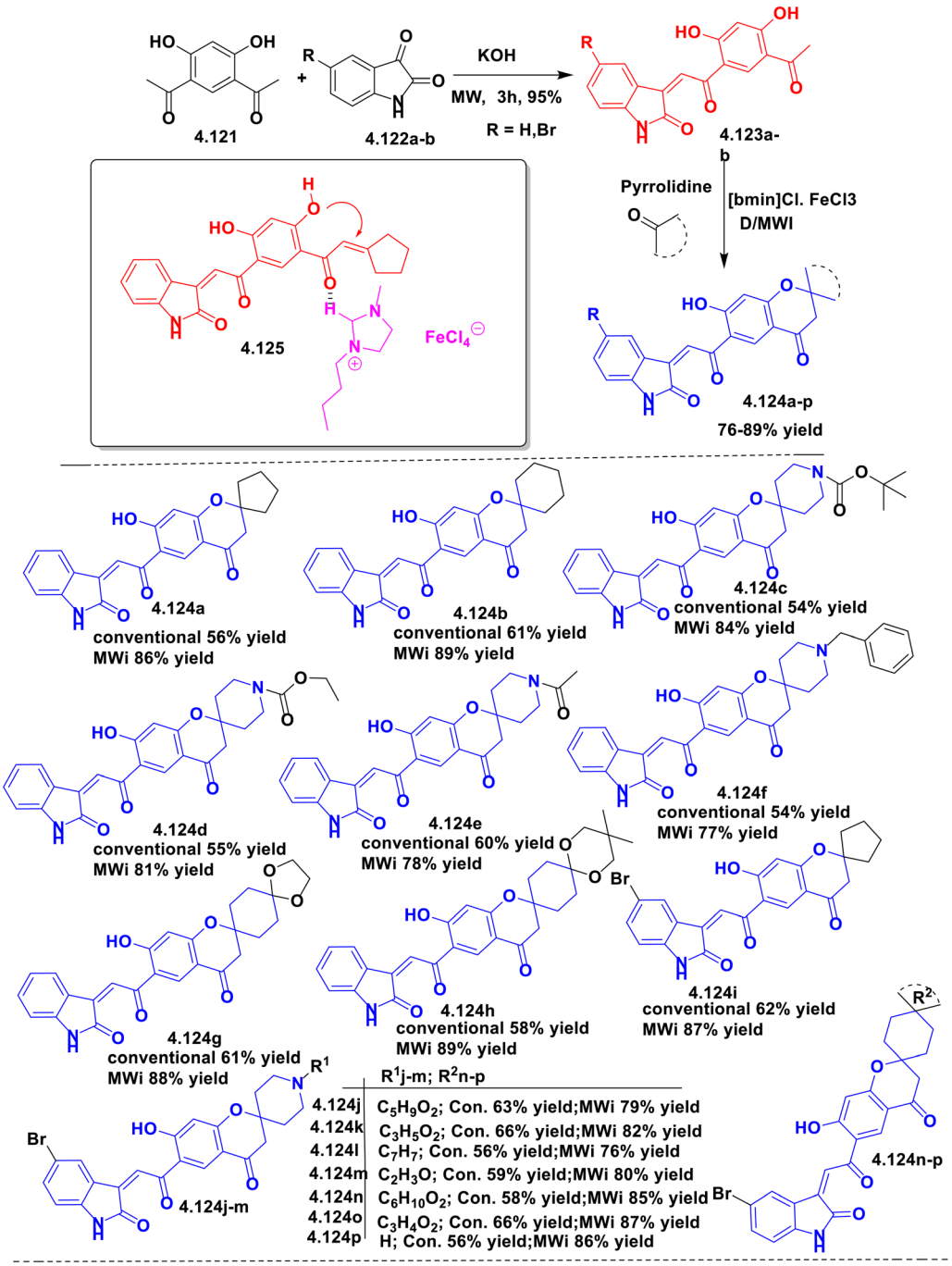


Scheme 35 Synthesis of spirochromone annulated chalcone conjugates **4.120**.

Kabbe condensation protocol for the synthesis of indolin-2-one-annulated spirochromanone hybrids (**4.124a–p**) using substituted indolin-2-one **4.123a** and various cycloalkanones under pyrrolidine catalysis in a [bmim]Cl·$FeCl_3$ ionic liquid. Microwave irradiation (100 W, 5–6 min) enabled rapid, high-yielding formation of the fused spiro frameworks, giving **4.124a–p** in 76–89% yields (Scheme 36).[78] Biological evaluation revealed that **4.124b** and **4.124d** displayed exceptional antioxidant activity with IC_{50} values of 1.25 and 1.74 μM, surpassing ascorbic acid. These spirochromanone–indolinone hybrids demonstrate how Kabbe condensation can be paired with microwave and ionic-liquid technologies to rapidly generate complex fused heterocycles with superior antioxidant potency.

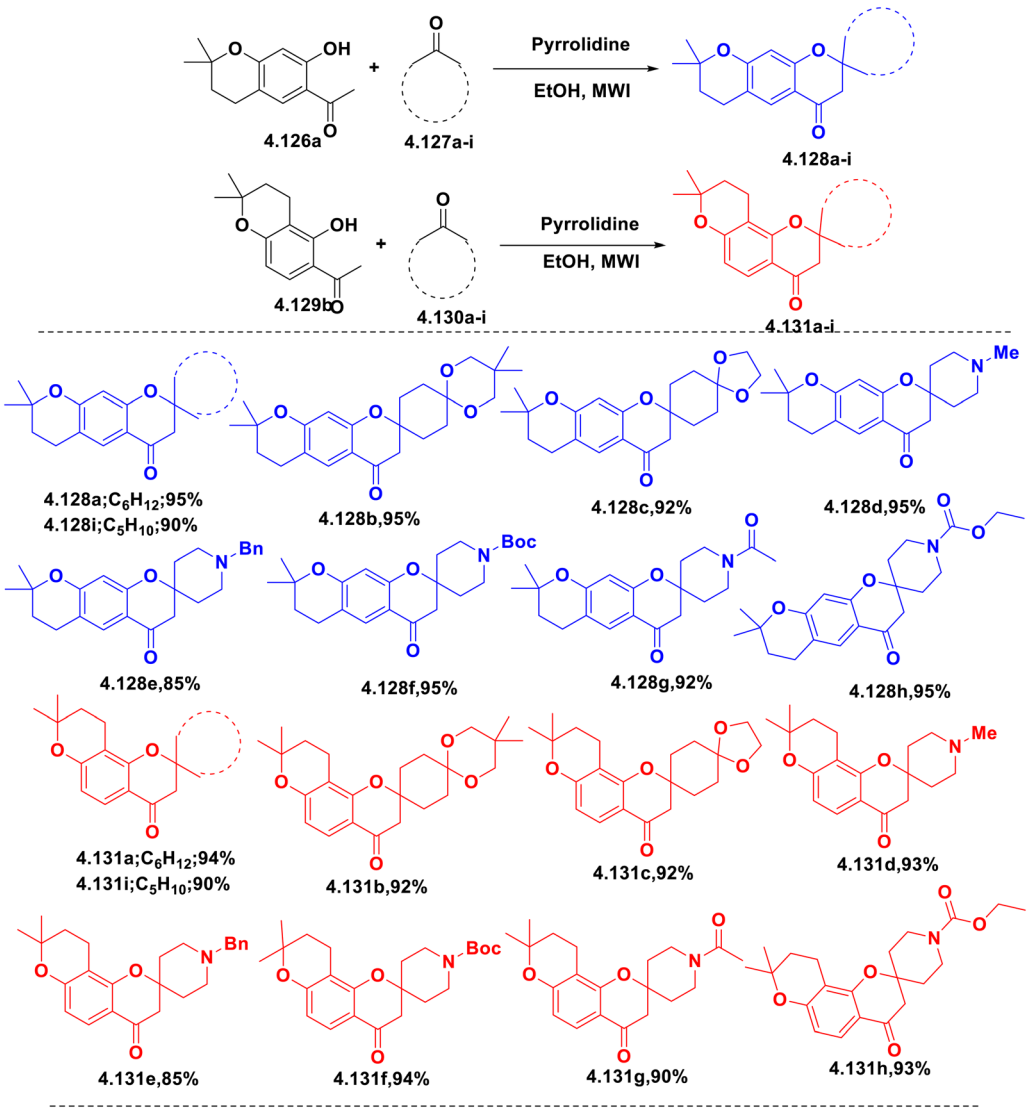
Building on this, Ashok *et al.* (2016) applied a similar microwave-assisted Kabbe strategy to synthesize a broader library of nonhybrid spirochromanone derivatives (**4.128a–i** and **4.131a–i**) using 2-hydroxyacetophenone derivatives (**4.26a**, **4.129b**) and cyclic ketones (**4.127a–i**) under rapid conditions (100 W, 3 min), achieving up to 95% yield (Scheme 37).[79] Several analogues demonstrated potent antioxidant activity particularly **4.131a** (IC_{50} = 1.17 μM) and **4.131b** (IC_{50} = 0.50 μM) as well as strong anti-inflammatory effects, with **4.128a–d** outperforming diclofenac sodium. Whereas the 2015 study produced true spirochromanone–indolinone hybrids, the 2016 work shows that even non-hybrid spirochromanones generated *via* microwave Kabbe condensation can achieve excellent biological profiles, underscoring the versatility and pharmacological value of the core spirochromanone scaffold.

Following their earlier developments on spirochromanone chemistry, Ashok *et al.* (2017) further extended this platform by synthesising a new series of non-hybrid spirochromanone derivatives (**4.135a–i**) *via* microwave-assisted Kabbe



Scheme 36 Synthesis of indolin-2-one fused spirochromanone conjugates **4.124**.

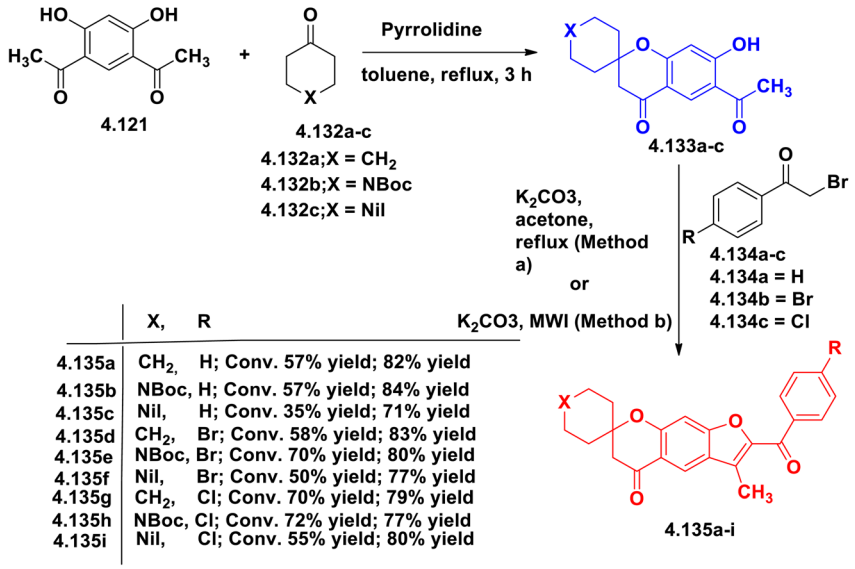
condensation of 2-hydroxyacetophenones with cyclic ketones (Scheme 38).[80] Unlike their 2015 indolinone-fused hybrids (**4.124a–p**) and their 2016 expanded simple spirochromanone library (**4.128a–i**, **4.131a–i**), this 2017 work continued the trend of using microwave irradiation to generate diverse spirochromanone frameworks rapidly and in high yield. Biological evaluation revealed potent antioxidant activity for **4.135b**, **4.135d**, **4.135f**, and **4.135g**, with **4.135f** achieving 90.4% DPPH inhibition, comparable to ascorbic acid. Compounds **4.135d**, **4.135e**, and **4.135f** also demonstrated strong anti-inflammatory effects, with **4.135f** reaching 85.7% inhibition near that of diclofenac. Molecular docking with COX-2 (PDB: 1CX2) showed strong hydrophobic and hydrogen-bonding interactions for **4.135**, **4.135d**, and **4.135g**, correlating with their bioactivity. Together with the 2015 hybrid series and the 2016 expanded non-hybrid library, the **4.135** series reinforces the versatility of microwave-accelerated Kabbe condensation, demonstrating that even non-hybrid spirochromanones can achieve excellent antioxidant and anti-inflammatory profiles, with **4.135f** emerging as a particularly promising lead.



Scheme 37 Synthesis of spirochromanone derivatives 4.128 and 4.131.

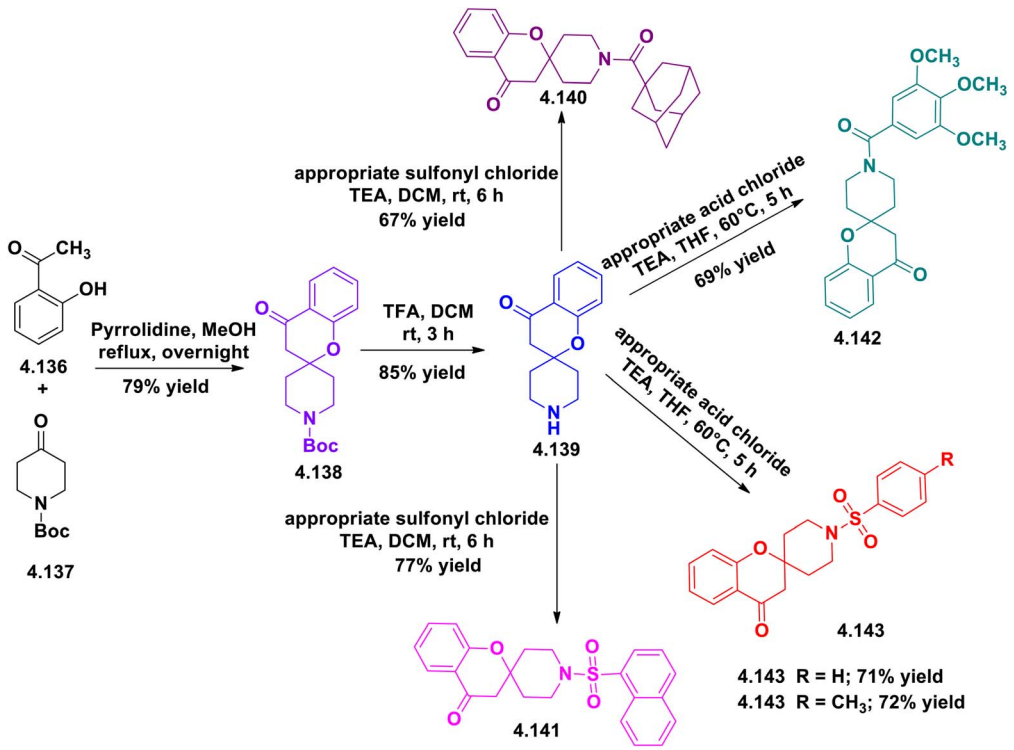
4.3.10 Synthesized of series of spiro[chroman-2,4′-piperidine] derivatives. Abdelatef *et al.* (2018) expanded the spirochromanone–piperidine hybrid family by synthesizing a new series of spiro[chroman-2,4′-piperidine] derivatives (**4.138–4.141**) *via* a Kabbe condensation between 2-hydroxyacetophenone and *N*-Boc piperidone in methanol using pyrrolidine under reflux, yielding **4.138** in 79% (Scheme 39).[81] Subsequent Boc deprotection produced the free spirocarbonyl intermediate **4.139** (85%), which was diversified through two routes: (A) acylation to give carbonyl-linked analogues **4.140** and **4.142** (67–69% yield), and (B) sulfonylation to afford sulfonyl-linked hybrids **4.143**, **4.143**, and **4.141** (71–77% yield). Cytotoxicity screening revealed that sulfonyl derivatives were markedly more potent than their carbonyl counterparts, with **4.143** showing exceptional activity across MCF-7, A2780, and HT-29 cancer cell lines (IC_{50} = 5.62, 0.31, and 0.47 μM), whereas **4.142** was significantly less active (18.8–47.1 μM). Mechanistic studies confirmed that **4.143** induces dose-dependent apoptosis and causes G2/M arrest, reinforcing its anticancer potential. These results highlight that spirochromanone–piperidine hybrids, especially sulfonyl-linked derivatives such as **4.143**, exhibit strong structure-dependent cytotoxicity and represent highly promising scaffolds for anticancer lead development.

4.3.11 Synthesized of series of spirochromane derivatives 4.145a–i by Kabbe condensation. Chamness and colleagues (2025) introduced a practical and scalable Kabbe condensation method for the synthesis of chromanone **4.145**, demonstrating that the transformation can be carried out efficiently on a gram scale using low-cost, readily available reagents (Scheme 40).[82] In their study, a 2 g preparation employing catalytic butyric acid together with an excess of pyrrolidine delivered compound **4.145** in high yield and with excellent purity, emphasising the simplicity and reliability of the protocol. This work highlights the strong translational value of the Kabbe condensation, demonstrating that chromanone scaffolds, including those of interest in medicinal chemistry, can be generated on a preparative scale without specialised equipment, thereby making these frameworks more accessible for subsequent



	X,	R	
4.135a	CH_2,	H;	Conv. 57% yield; 82% yield
4.135b	NBoc,	H;	Conv. 57% yield; 84% yield
4.135c	Nil,	H;	Conv. 35% yield; 71% yield
4.135d	CH_2,	Br;	Conv. 58% yield; 83% yield
4.135e	NBoc,	Br;	Conv. 70% yield; 80% yield
4.135f	Nil,	Br;	Conv. 50% yield; 77% yield
4.135g	CH_2,	Cl;	Conv. 70% yield; 79% yield
4.135h	NBoc,	Cl;	Conv. 72% yield; 77% yield
4.135i	Nil,	Cl;	Conv. 55% yield; 80% yield

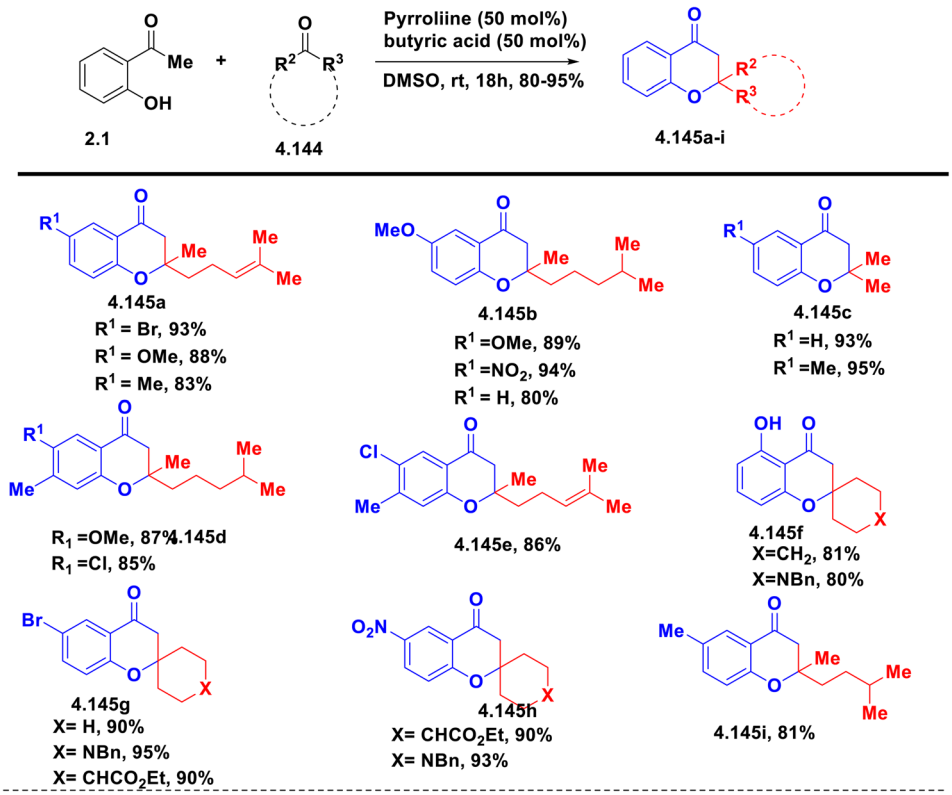
Scheme 38 Synthesis of spirochromanone compounds 4.135a–i.



Scheme 39 Synthesis of spiro[chroman-2,4′-piperidine] derivatives 4.143–4.141.

diversification and drug development efforts. Notably, they have reported gram-scale Kabbe protocols confirm that this reaction can be reliably performed on preparative scale using low-cost reagents and simple experimental setups, directly addressing process scalability and reproducibility considerations.

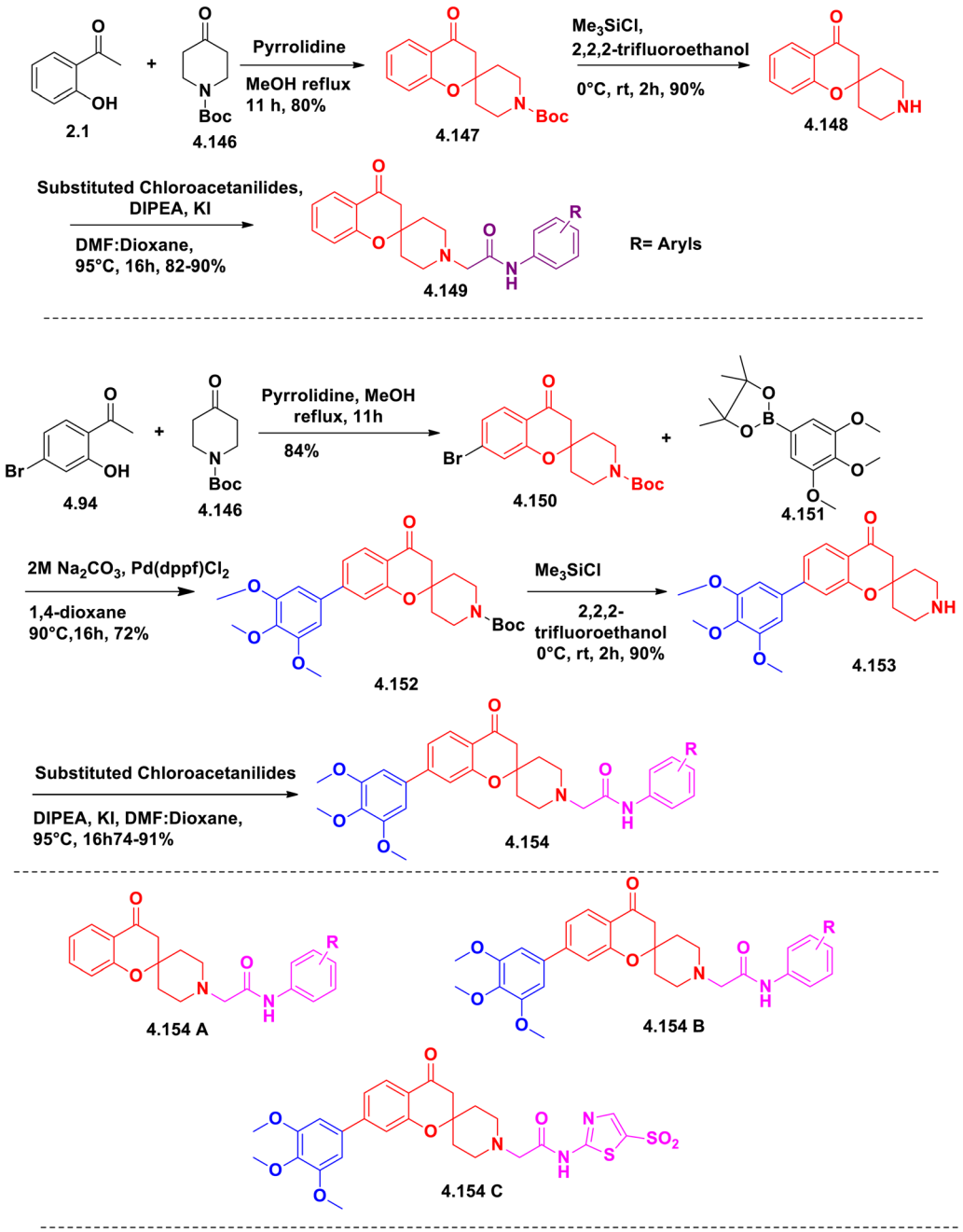
4.3.12 Synthesized of series of spiro[chromane-2,4′-piperidin]-4-ones. Nakka and co-workers (2025) prepared a series of twenty-three spiro[chromane-2,4′-piperidin]-4-one derivatives (**4.154**) through a Kabbe condensation approach (Scheme 41) and assessed their cytotoxic effects against the MCF-7, U87-MG, and SCC-25 cancer cell lines.[83] At began, 4-oxospirochromane-carboxylate **4.147** was prepared by reaction of **2.1** and **4.146** in the presence of pyrrolidine as base and followed by *N*-Boc de-protection of **4.147** under acidic conditions to give intermediate **4.148.** The compound **4.148** was then reacted with various chloro-acetanilides in the presence of diisopropylethylamine and potassium iodide at a temperature of 95 °C for 16 hours, resulting in formation of spiro-chromananonepiperidinones



Scheme 40 Spirochromane derivatives 4.145a–i by Kabbe condensation.

4.149. By using the same Kabbe strategy, author synthesized *tert*-butyl-7-bromo-4-oxospiro[chromane-2,4′-piperidine]-1′-carboxylate **4.150** and then undergoes Suzuki coupling reaction with compound **4.151**, leading to the formation of intermediate **4.152**. In the last step, the *N*-Boc deprotection of compound **4.152** was performed under mildly acidic conditions, yielding compound **4.153**. The free nitrogen atom in compound **4.153** reacted with various chloro-acetanilides in the presence of di-isopropylethylamine and potassium iodide to provide spiro [chromane-2,4′-piperidin]-4-one derivatives (**4.154**). Among the libraries, compounds **4.154A**, **4.154B**, and **4.154C** proved to be the most active, exhibiting IC_{50} values ranging from 3.5 to 18.5 μM. Mechanistic studies revealed that these three molecules triggered pronounced apoptotic responses in MCF-7 cells, producing approximately 70-, 83-, and 93-fold increases in apoptotic populations, respectively. Clonogenic assays further confirmed their ability to inhibit long-term cancer cell proliferation. Computational ADME analysis indicated that the compounds possess favourable drug-like characteristics, while molecular docking studies showed stable and reproducible binding interactions with EGFR. Key residues, including Lys745, Glu749, and Glu758, were consistently involved in hydrogen bonding and hydrophobic contacts across all docked complexes. Collectively, these results demonstrate that the spirochromanone piperidine hybrids, particularly **4.154A–C**, exhibit promising anticancer activity through a combination of apoptosis induction, EGFR engagement, and favourable ADME properties. These attributes position them as strong lead candidates for further refinement in oncology-focused drug discovery.[84–86]

4.3.13 Synthesis of spirochromanone and carbamide molecular hybrids. In 2025, Mudda *et al.* described an efficient method for the synthesis of hybrid molecules based on carbamide–spirochromanone derivatives by the reaction of *O*-hydroxyacetophenones **2.1** and *N*-Boc-cycloketones **4.155** were treated with pyrrolidine to yield spiro compound **4.156** *via* Kabbe condensation. This compound was subsequently treated with TFA to produce spiro compound **4.157** which then reacted with CBZ-Cl to form the target molecule spirochromanone and carbamide molecular hybrids **4.158–4.160** with good yields (Scheme 42).[87] All the synthesized derivatives underwent screening for their cytotoxic activity through *in vitro* methods against both cancerous and non-cancerous cell lines, including A549, HCT116, U2OS, Jurkat, CCRF-CEM, MOLT-4, RAMOS, K562, MRC-5, and BJ. Among all, **4.160B** demonstrated superior potency against MOLT-4, achieving an inhibition value of 45.57 ± 7.56 μM. Furthermore, the **4.160** series displayed significant cytotoxicity against Jurkat and CCRF-CEM cell lines, with inhibition values ranging from 23.18 ± 4.20 to 41.43 ± 7.18 μM. Of the twelve compounds assessed, C-**4.159B** and **4.160B** recorded the highest docking scores of −9.3 and −8.8 kcal mol^{-1}, respectively, against ITK. The **4.160** series also achieved a docking score exceeding −10 kcal mol^{-1} against BTK. Notably, the cytotoxicity against RAMOS cells was observed across multiple series, with a decrease in activity from the **4.158** to the **4.160** series. All six series of compounds, including **4.158C** and

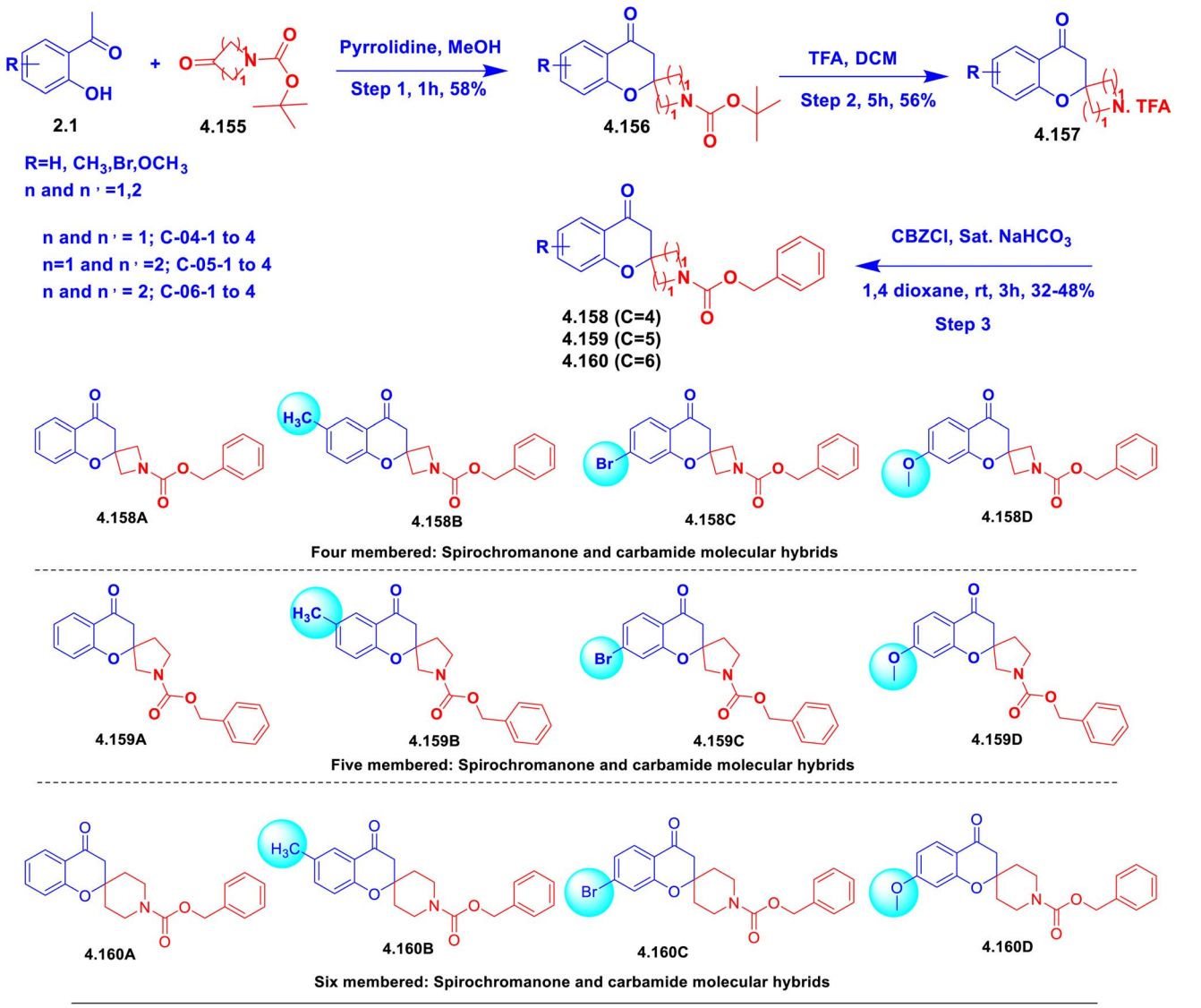


Scheme 41 Spiro[chromane-2,4′-piperidin]-4-one derivatives **4.154** by Kabbe condensation.

4.159B, demonstrated significant cytotoxic effects against the RAMOS cell line (BTK).

5 Synthesis of spirochromanone–flavanone hybrids

Kishore *et al.* (2017) reported an efficient one-pot synthesis of spirochromanone–flavonol hybrids (**5.4a–g**) using a modified Algar–Flynn–Oyamada reaction (Scheme 43). The key intermediate **5.1a** was first prepared *via* Kabbe condensation between 1,1′-(4,6-dihydroxy-1,3-phenylene)diethanone (**4.121**) and cyclohexanone **2.2** under microwave irradiation.[88] Subsequent reaction of **5.1a** with aromatic aldehydes in alkaline ethanol, followed by oxidative cyclization using H_2O_2/NaOH, yielded the hybrid flavonol derivatives **5.4a–g** without isolating chalcone intermediates. Antimicrobial evaluation revealed that **5.4a**, **5.4c**, and **5.4d** exhibited strong antibacterial activity against *Bacillus subtilis* and *Pseudomonas aeruginosa*, achieving inhibition zones of ≥21 mm, comparable to streptomycin. However, antifungal activity was modest. These spirochromanone–flavonol hybrids demonstrate how merging two bioactive frameworks *via* Kabbe condensation and oxidative cyclization creates potent

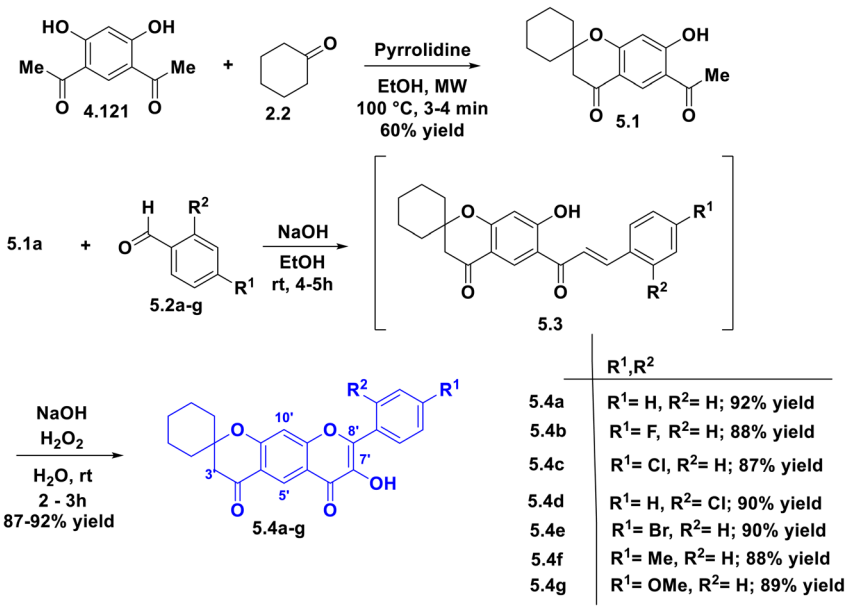


Scheme 42 Synthesis of spirochromanone and carbamide hybrids (1.158–1.160).

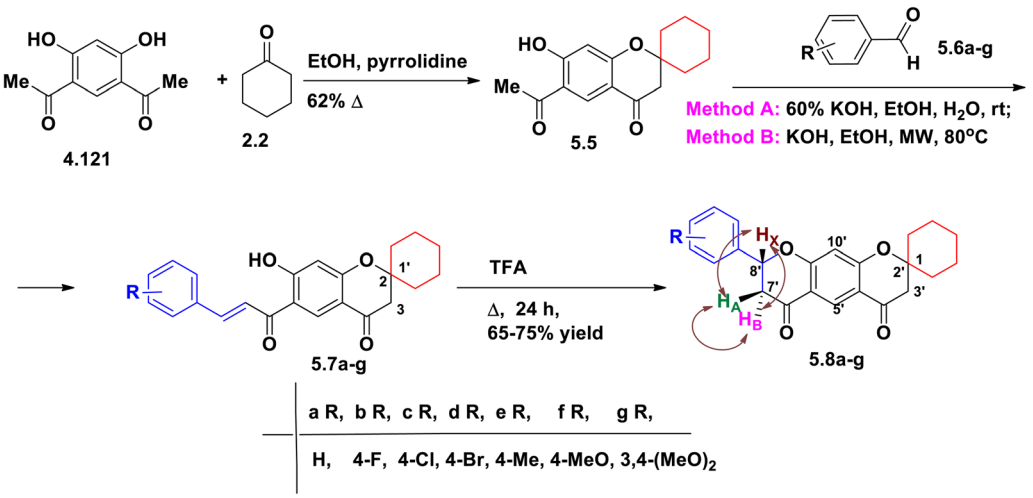
antibacterial scaffolds, particularly when electron-donating substituents enhance conjugation and biological response.

They also developed a rapid and efficient method for synthesising spirochromanone flavanone hybrids *via* a microwave-assisted Kabbe condensation followed by Claisen–Schmidt condensation and TFA-promoted cyclisation (Scheme 44).[89] Beginning with 4,6-diacetylresorcinol (**4.121**) and cyclohexanone **2.2**, the Kabbe reaction furnished the spirochromanone intermediate **5.5**, which was subsequently condensed with aryl aldehydes **5.6a–g** under microwave conditions to afford spiropyran-annulated chalcones **5.7a–g** with excellent yields (91–95%) and short reaction times. Cyclisation of these chalcones in TFA produced the flavanone derivatives **5.8a–g** efficiently. Antimicrobial evaluation revealed that halogenated derivatives, particularly **5.7b–d** and **5.8b–d**, exhibited strong antibacterial and antifungal activities, in several cases surpassing those of standard drugs such as ampicillin and griseofulvin (*e.g.*, **5.7b**, inhibition zone 28 mm *vs. B. subtilis*; **5.8c**, 18–20 mm *vs. Fusarium oxysporum*). By merging a Kabbe-derived spirochromanone with a flavanone pharmacophore, these spirochromanone–flavanone hybrids exemplify how stepwise annulation dramatically enhances antimicrobial potency, demonstrating the value of microwave-assisted green protocols for constructing complex bioactive heterocycles.

Krasylov *et al.* (2023) developed an efficient Kabbe condensation strategy for synthesizing (spiro)pyranocoumarins (**5.10**) by reacting *o*-hydroxyacetyl coumarins **5.8** with a range of cyclic ketones **5.9** in acetonitrile at 50 °C using pyrrolidine as a base, affording sixteen derivatives (twelve novels) in 52–88% yields (Scheme 45).[90] These spirochromanone–pyranocoumarin hybrids were further diversified *via* selective oximation of the exocyclic chromanone carbonyl, producing oximes **5.11** in excellent yields (up to 98%). The structural series incorporated diverse substituents-including dimethyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornanyl, 4,4-difluorocyclohexyl, and 1,4-dioxaspiro[4.5]decane groups demonstrating the broad



Scheme 43 Synthesis of spirochromanone-based flavonols 5.4a–g.



Scheme 44 Synthesis of spirochromanone–flavanone hybrid compounds 5.8a–g.

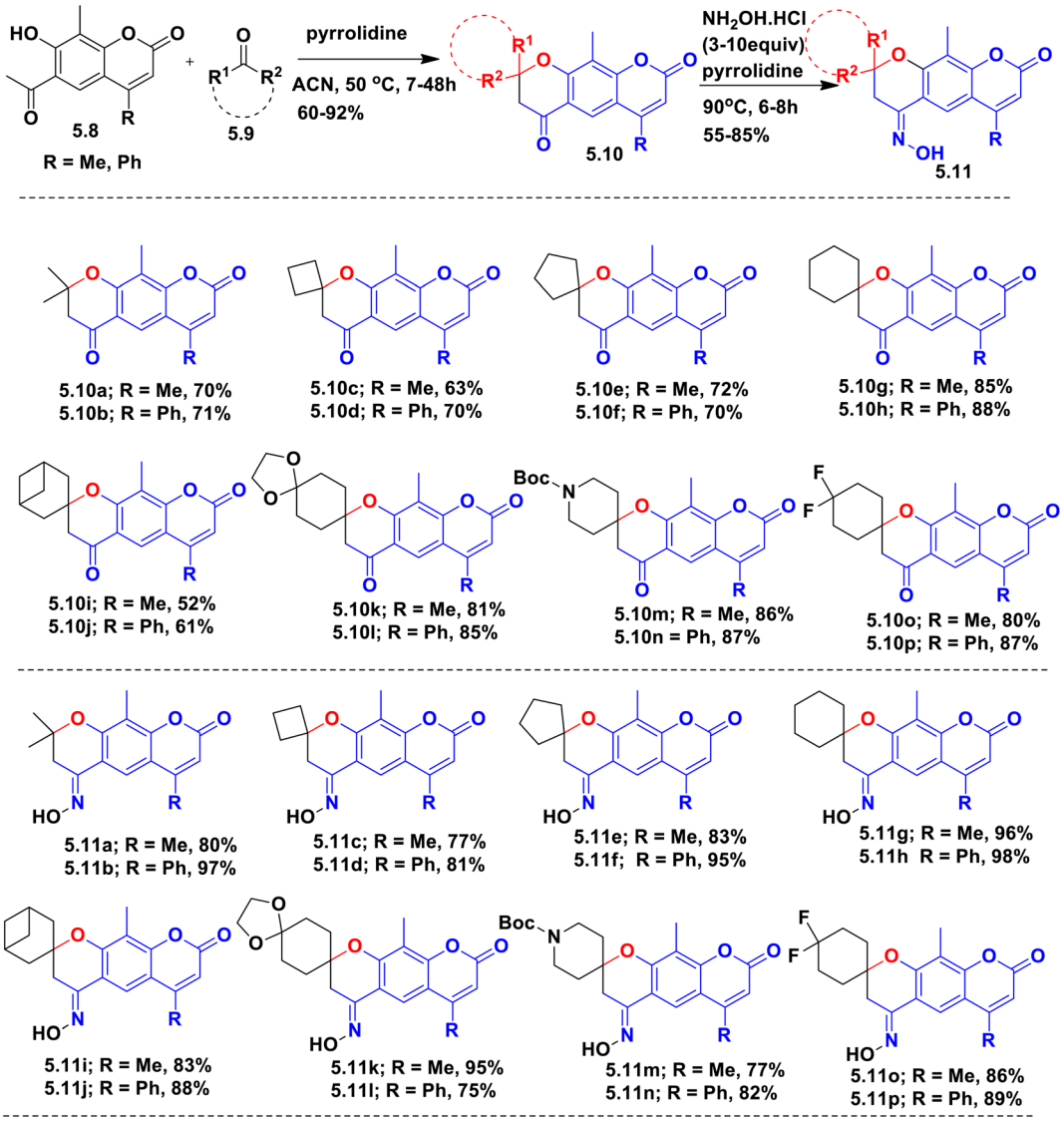
compatibility of the Kabbe platform. Selective oxidation confirmed predictable reactivity at the chroman-4-one site, emphasizing the synthetic flexibility of these fused heterocycles. This work highlights the utility of Kabbe condensation in generating spirochromanone–pyranocoumarin hybrids with accessible late-stage modification points, offering promising scaffolds for antimicrobial, anticancer, and neuroprotective drug discovery based on coumarin-chromanone synergy.

6 Future perspectives

Even though the Kabbe condensation was first used more than 40 years ago, its operational flexibility, modular design, and effectiveness in assembling spirocyclic chromanone frameworks continue to draw a lot of attention. Kabbe-derived scaffolds are now widely used in early-stage drug discovery, medicinal chemistry, and natural product synthesis. However, there is still much space to extend the reaction's reach, enhance mechanistic understanding, and fortify the link between transformation and translational medical applications. A number of promising avenues for further investigation are highlighted in the section that follows.

6.1 Development of asymmetric Kabbe reactions

Even though the enantioselectivity of L-proline and related organocatalysts is only moderate,[36] the asymmetric Kabbe condensation has not received much attention, despite the fact that it presents a substantial opportunity for the production of chiral scaffolds in medicinal chemistry. Various catalytic



Scheme 45 Synthesis of target (spiro)pyranocoumarins 5.10 and their oxime derivatives 5.11.

methods offer promising opportunities to promote asymmetry. Such as metal ligand complexes utilizing Cu, Zn, or Sc, bifunctional thiourea amine systems, chiral phase transfer catalysts, and chiral secondary amines like MacMillan type iminium/enamine catalysts. The availability of enantioenriched spiro-chromanones would greatly increase their use in pharmaceutical research, especially in fields where molecular chirality significantly affects potency, selectivity, and pharmacokinetic behavior, such as kinases, GPCRs, and antitubercular enzymes.

6.2 Flow chemistry and continuous synthesis

The reaction is well-suited for intensification utilizing flow chemistry platforms because the Kabbe condensation occurs through an exothermic enamine-formation stage followed by intramolecular cyclization. There are several advantages to implementing this transformation in continuous flow, such as safer reactive intermediate management, increased repeatability, quicker reaction kinetics, and better heat dissipation when compared to conventional batch processing. Additionally, flow reactors make it simple to scale up, allowing for the effective synthesis of structurally complex spirocyclic frameworks. The industrialization of the synthesis of spirochromanone intermediates and APIs might thus be greatly aided by the integration of flow technology into Kabbe chemistry, which would offer a stable, scalable, and dependable pathway to these pharmacologically relevant molecules.

6.3 Expansion to green and renewable solvents

Dihydrolevoglucosenone (DHL) has already demonstrated considerable potential as a biomass-derived solvent for Kabbe condensations,[53] and future advances could extend this environmentally friendly approach through the use of cyrene (a closely related analogue of DHL), deep eutectic solvents (DES), aqueous micellar systems, or even solvent-free and mechanochemical techniques. These greener strategies offer

opportunities to minimise waste, enhance safety, and improve overall energy efficiency while still delivering strong reaction performance. Progress in sustainable Kabbe chemistry would not only support global environmental objectives but also provide scalable, eco-conscious routes to bioactive spirochromanones, helping reinforce the sustainability profile of contemporary medicinal chemistry.

6.4 Diversification *via* late-stage functionalization

Late-stage diversification (LSD) offers a powerful means of rapidly expanding the structural diversity of spirochromanones without modifying the underlying Kabbe condensation step. Several promising LSD strategies can be applied to these scaffolds, including C–H activation near the spiro centre, halogenation followed by cross-coupling reactions such as Suzuki or Buchwald Hartwig, trifluoromethylation to enhance ADMET characteristics, radical-based spirocycloadditions, and a variety of photoredox-mediated transformations. These approaches highlight the exceptional robustness of the spirochromanone core, which can accommodate extensive downstream functionalization while retaining its rigid, pharmacologically important architecture. This resilience makes spirochromanones ideal platforms for LSD-driven discovery initiatives, enabling rapid SAR development and streamlined lead optimization.

6.5 Applications in chemical biology and target identification

Although numerous spirochromanones exhibit strong biological activity, their exact molecular targets and mechanisms of action are still unclear in many cases. Future studies should therefore emphasize target-deconvolution approaches such as CETSA, DARTS, and chemoproteomics, supported by molecular docking and molecular dynamics simulations to help define key binding interactions. Particular focus should be directed toward pathways involving FtsZ, growth hormone secretagogue (GHS) receptors, kinases, and quinone-interacting proteins, as these systems have already shown sensitivity to Kabbe derived scaffolds. Developing activity-based probes inspired by spirochromanone structures would further aid in identifying targets and validating engagement within complex cellular environments. A clearer picture of these molecular interactions will greatly accelerate rational design and SAR refinement, ultimately making spirochromanones more predictable and clinically promising lead candidates.

6.6 Exploration of polyspiro frameworks

The recent finding disclosed that bis spirochromanones **3.71a–o** act as potent antitubercular agents[49] underscores the largely unexplored promise of polyspiro architectures in medicinal chemistry. Building on this momentum, future work could investigate tris-spiro frameworks, more extensively fused polycyclic spiro systems, and mixed heteroatom junctions incorporating O–N, O–S, or N–S linkages. Expanding into these structural domains would greatly enlarge the accessible chemical space and provide scaffolds with distinctive three-dimensional shapes and new binding orientations. Such polyspiro motifs hold significant potential for achieving unique selectivity profiles against challenging biological targets, positioning them as exciting prospects for next-generation antimicrobial, anticancer, and CNS-active therapeutics.

6.7 Computational design and machine learning (AI-assisted Kabbe chemistry)

As computational capabilities continue to expand, AI offers powerful opportunities to accelerate the design and optimization of Kabbe derived scaffolds. Potential applications range from predicting suitable Kabbe substrates and estimating biological activity to generating spirochromanone libraries, modelling toxicity and ADMET properties, and even performing automated retrosynthetic planning in which the Kabbe condensation serves as a central strategic step. By rapidly pinpointing promising analogues, simplifying synthetic route selection, and reducing the need for extensive experimental screening, AI-guided approaches could greatly enhance the efficiency of lead-optimization efforts. In this way, AI has the potential to transform the development of spirochromanone based therapeutics and significantly speed up the drug-discovery process.

6.8 Kabbe condensation in natural product synthesis

Because many natural products such as calanolide analogues feature spirochromanone motifs, the Kabbe condensation can be deliberately integrated into total syntheses, biomimetic strategies, and semi-synthetic modifications of these structures. Its capacity to forge essential C–C bonds while simultaneously establishing the spirocyclic chromanone core makes it a highly versatile tool for assembling complex molecular frameworks. As a result, Kabbe chemistry offers an efficient and strategically useful approach for constructing natural product-like architectures, thereby broadening synthetic access to bioactive spirochromanone systems, which are particularly significant in medicinal chemistry.

7 Biological activities of spirochromanones

Spirochromanones constitute a structurally privileged class of heterocycles exhibiting a diverse range of biological activities. The rigid spiro-fused framework enhances three-dimensionality, metabolic stability, and selectivity toward biological targets. Kabbe-derived chromanone and spirochromanone scaffolds have been widely evaluated in medicinal chemistry programs, showing promising anticancer, antimicrobial, antiviral, antitubercular, antioxidant, and enzyme-inhibitory activities. This section summarizes the biological relevance of these scaffolds as reported in the literature.

7.1 Antimicrobial and antibacterial activity

Several Kabbe-derived spirochromanones demonstrate significant antimicrobial and antibacterial activity across different

structural subclasses. Shinde *et al.*[71] (Scheme 6.4) reported the preparation of spiro[chroman-2,4′-piperidin]-4-one derivatives that exhibited notable inhibition of ACC, an enzyme central to bacterial fatty-acid biosynthesis. This mechanistic link accounts for their promising antimicrobial activity. The incorporation of halogens, such as chlorine, bromine, and fluorine, increased the compounds' lipophilicity and improved their ability to cross microbial membranes. At the same time, the rigid spirocyclic framework contributed to greater metabolic stability and enforced a fixed three-dimensional shape, which together enhanced specificity toward the biological target. Direct antimicrobial evaluation was reported by Patel *et al.*[72] (Scheme 30), where a series of aryl-substituted 2-spiropiperidinechroman-4-one derivatives (**4.93a–j**) were screened against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Candida albicans*. Derivatives bearing *ortho* and *meta*-substituted aryl groups showed improved activity, and the 3,5-dimethyl analogue **4.93e** emerged as the most potent among the synthesised molecules. These findings establish Kabbe-derived spirochromanones as promising scaffolds for antibacterial drug discovery, with both enzyme-targeted and direct antimicrobial pathways contributing to their pharmacological potential.

7.2 Anticancer activity

Abdelatef *et al.* reported that several Kabbe-derived spirochromanones particularly semicarbazone and thiosemicarbazone functionalized scaffolds exhibited strong anticancer properties. (Scheme 9)[40] describes compounds **3.31a–e** and **3.32**, many of which showed cytotoxicity superior to sorafenib and erlotinib. (Scheme 39)[81] presents piperidine-spirochromanone derivatives **4.143** that further demonstrated potent inhibition of EGFR and B-RAF kinases, accompanied by apoptosis induction. The spirocyclic coupling of C-2/C-3 substituents and sp^2–sp^3 hybridization enhances binding at kinase and tubulin sites, positioning these motifs as strong anticancer leads.

7.3 Antitubercular activity (anti-TB)

Kabbe-derived spirochromanones display broad antitubercular activity across several structural subclasses (Schemes 15, 26 and 33–35). Triazole-linked derivatives (Scheme 33)[75] and amino alcohol conjugates (Scheme 34)[76] showed moderate to potent activity, while spirochromanone–chalcone hybrids (Scheme 35)[77] revealed several hits with MIC values down to 3.13 μg mL^{-1}. Chitti's spirochromanone–piperidine analogues (Scheme 26)[67] further yielded potent molecules with MIC values ranging from 3.72 to 7.68 μM. Among all, bis-spirochromanones **3.71h**, **3.71n**, and **3.71o** (Scheme 15)[49] demonstrated the strongest anti-TB effect (MIC 3.125 μg mL^{-1}) with excellent FtsZ binding. These results collectively position Kabbe-derived spirocycles as highly promising scaffolds for anti-TB agents.

7.4 Growth hormone secretagogue activity (GHS)

Yang and colleagues synthesized a diverse series of piperidine-containing, *N*-acetyl, and deacetylated spirochromanones, illustrated in (Scheme 10)[41] for piperidine-substituted spirochromanones and spiro-piperidine analogues all of which demonstrated strong growth hormone secretagogue (GHS) activity. Early findings confirmed that the spiro-piperidine motif is the essential pharmacophore driving receptor affinity, while Yang *et al.* further showed that free-amine derivatives exhibit markedly enhanced potency compared to their *N*-acetylated counterparts. The chromanone carbonyl simultaneously acts as a key hydrogen-bonding anchor within the GHS receptor pocket. Together, these Kabbe-derived spirochromanone frameworks establish a potent, non-peptidic, and structurally tunable class of GHS modulators.

7.5 Antioxidant and free radical scavenging activity

Antioxidant activity is prominently showcased across (Schemes 36–38) where structurally diverse spirochromanone derivatives demonstrated potent DPPH radical-scavenging and anti-inflammatory properties. (Scheme 36)[78] features indolin-2-one fused spirochromanones (**4.12a–p**), among which compounds **4.124b** and **4.124d** displayed impressive IC_{50} values of 1.25 and 1.74 μM, respectively. (Scheme 37)[79] presents microwave-assisted spirochromanones such as **4.131a** and **4.131b**, which exhibit strong DPPH and anti-inflammatory activity, highlighting the efficiency of rapid, solvent-assisted Kabbe cyclisation strategies. (Scheme 38)[80] introduces a broader spirochromanone library (**4.135a–i**), with compound **4.135f** achieving nearly 90% inhibition, surpassing the standard antioxidants. In these compound series, the presence of phenolic hydroxyl groups, together with conjugated carbonyl functionalities, facilitates electron delocalisation and supports the efficient stabilisation of radical intermediates. The spirocyclic framework further contributes by locking the molecular geometry in an arrangement that favours reactive oxygen species (ROS) scavenging. Taken together, these Kabbe-derived architectures offer promising antioxidant potential and represent valuable structural platforms for developing agents that modulate free-radical processes.

7.6 Antiallergic activity

Compound **1A.6** (Fig. 1.0), a naturally occurring spirobenzopyran, shows notable anti-allergic properties,[22,23] largely by suppressing mast-cell degranulation pathways. This example highlights the broad pharmacological potential of spirochromanone and spirobenzopyran frameworks, demonstrating that their utility extends well beyond anticancer and antimicrobial areas to include immunomodulatory and anti-allergic applications as well.

7.7 Antiviral activity

(+)-Calanolide A (**1A.9**) (Fig. 1.0) and several related spirochromanones exhibit potent antiviral activity, particularly against HIV and dengue viruses,[24–27] acting through inhibition of viral reverse transcriptase and disruption of key replication pathways. Their unique three-dimensional spiro-architecture and favourable physicochemical properties make these scaffolds especially attractive for antiviral drug discovery, reinforcing the continued relevance of spirochromanones in the search for novel therapeutics.

7.8 Quorum sensing inhibition (QSI)

Chaitanya and co-workers reported the synthesis of spirochromanone derivatives **4.104**, which displayed strong quorum-sensing inhibitory (QSI) effects in *Chromobacterium violaceum* violacein assays (Scheme 32).[74] This type of activity is of growing importance in the fight against antimicrobial resistance, as these molecules interfere with bacterial communication systems rather than exerting direct bactericidal pressure, thereby lowering the likelihood of resistance development. The aromatic substituents present in these compounds appear to enhance both their stability and their ability to engage the quorum-sensing receptor, consistent with the docking score of -7.99 kcal mol^{-1} observed for derivative **4.104**. These compounds also showed meaningful biological activity against *Chromobacterium violaceum* ATCC 12472. Together, the results suggest that this series of spirochromanone derivatives constitutes a promising class of new quorum-sensing inhibitors.

7.9 Multi-target activity profiles

Kabbe-derived spirochromanones often exhibit broad polypharmacological profiles, as demonstrated in Schemes 29 and 36–38.[71,78–80] Across these studies, the scaffolds act on multiple biological targets, including ACC inhibition (Scheme 29), COX modulation combined with antioxidant activity (Scheme 36), parallel COX and antioxidant pathways (Scheme 37), and dual COX-2/ROS regulation (Scheme 38). Their rigid three-dimensional shape, enforced by the orthogonal arrangement at the spiro centre, allows these molecules to interact simultaneously with more than one binding pocket. This structural orientation supports productive engagement with ACC enzymes, COX isoforms, kinases, and tubulin, while also contributing to favorable ADMET behavior. Taken together, these features make Kabbe-based spirochromanones compelling platforms for developing multitarget therapeutic agents.

8 Conclusion of future perspectives

Although the Kabbe condensation is fundamentally straightforward, it remains an exceptionally powerful method for assembling complex spirocyclic architectures. Ongoing developments in asymmetric catalysis, sustainable reaction media, continuous-flow processing, late-stage functionalization, and AI-assisted molecular design are poised to greatly expand the reach of this transformation. Together, these advancements will help ensure that the Kabbe condensation continues to play a central role in the synthesis of pharmacologically relevant spirochromanone derivatives for years to come.

9 Conclusion

The Kabbe condensation has matured from a straightforward enamine-driven cyclization into a highly adaptable synthetic platform capable of delivering structurally diverse spirochromanone frameworks. Its ease of execution, tolerance for a wide range of substrates, and remarkable efficiency in constructing rigid spirocyclic motifs ensure its continued significance in heterocyclic chemistry. We have conducted a thorough systematic analysis of Kabbe condensation and its medicinal uses. Previously published reviews did not adequately address recent research on spirochomanones, the synthesis of natural products that include chromanone, benzannulated oxepine–spirochromanones, spirochromanone–chalcone hybrids, carbamide molecular hybrids, and spirochromanone–flavanone hybrids. Spirochromanones produced through Kabbe and Kabbe-inspired strategies have demonstrated an impressive diversity of biological activities. These include anticancer, antimicrobial, antiviral, antitubercular, antioxidant, anti-inflammatory, quorum-sensing inhibitory, and enzyme-modulatory effects. Notably, several bis-spirochromanones have shown strong potency against *Mycobacterium tuberculosis*, underscoring their relevance for neglected tropical diseases and drug-resistant infections. Nitrogen-containing azaspirochromanones and halogenated derivatives have also emerged as promising growth-hormone secretagogues and ACC inhibitors, respectively, highlighting the broad therapeutic potential of these scaffolds. From a synthetic standpoint, Kabbe-derived intermediates offer a rich platform for extensive downstream diversification, enabling access to fused heterocycles, fluorinated analogues, pyrazoles, triazoles, quinones, and more complex polyspiro systems. These transformations significantly expand the available chemical space and facilitate rapid SAR exploration. The introduction of greener solvents such as dihydrolevoglucosenone (DHL) further enhances the sustainability and environmental compatibility of Kabbe chemistry. Looking ahead, continued development of asymmetric Kabbe methodologies, integration of flow-assisted synthesis, strategic late-stage diversification, and AI-based molecular design will undoubtedly elevate the impact of this transformation. As mechanistic understanding deepens and new biologically active derivatives continue to emerge, the Kabbe condensation remains an indispensable reaction for both synthetic organic chemists and medicinal chemists. In conclusion, the Kabbe condensation stands as a robust and versatile transformation one that continues to serve as a gateway to pharmaceutically valuable spirochromanone architectures. Ongoing advancements, combined with expanding biological relevance and modern sustainable practices, ensure that this reaction will maintain its central role in heterocycle synthesis and drug discovery for many years to come.

Author contributions

Rashinikumar. S: writing – review & editing for manuscript. Boopathi Komarasamy: writing – review of the manuscript. Prasanth. M: writing – review & editing for manuscript; Prabhakara. J: writing – review & editing for the manuscript. Manohar: writing – review for manuscript. Abdul. F. writing – review & editing for the manuscript. Parthiban. A: supervision – conceptualization.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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References

1 J. Hepworth, *Comprehensive Heterocyclic Chemistry I*, ed. A. R. Katritzky and C. Rees, Pergamon, Oxford, UK, 1984, vol. 3, pp. 737–883.
2 G. R. Geen, J. M. Evans and A. K. Vong, in. *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. Scriven, Pergamon, Oxford, UK, 2005, vol. 5, pp.469–500.
3 J. Santamaría and C. Valdés, in. *Modern Heterocyclic Chemistry*, ed. B. J. Alvarez, J. J. Vaquero and K. Barluenga, J. Wiley-VCH, Weinheim, 2011, vol. 3, pp.1631–1682.
4 E. Grotewold, *The Science of Flavonoids*, Springer, New York, 2006, pp. 36–37.
5 B. A. Bohm, *Introduction to Flavonoids*, Harwood Academic Press, Amsterdam, 1998, pp. 351–353.
6 I. M. Lockhart, *Chromenes, Chromanones and Chromones*, ed. Ellis G. P., John Wiley & Sons, London, 1977, pp. 207–428.
7 Y. Kashiwada, K. Yamazaki, Y. Ikeshiro, T. Yamagishi, T. Fujioka, K. Mihashi, K. Mizuki, L. M. Cosentino, K. Fowke and S. L. Morris-Natschke Lee, *Tetrahedron*, 2001, **57**, 1559–1563.
8 D. J. Chang, H. An, K. S. Kim, H. H. Kim, J. Jung, J. M. Lee, N. J. Kim, Y. T. Han, H. Yun, S. Lee and G. Lee, *J. Med. Chem.*, 2012, **55**, 10863–10884.
9 C. W. Brown, S. Liu, J. Klucik, K. D. Berlin, P. J. Brennan, D. Kaur and D. M. Benbrook, *J. Med. Chem.*, 2004, **47**, 1008–1017.
10 S. Thareja, A. Verma, A. Kalra, S. Gosain, P. V. Rewatkar and G. R. Kokil, *Acta Pol. Pharm.*, 2010, **67**, 423–427.
11 S. J. Mohr, M. A. Chirigos, F. S. Fuhrman and J. W. Pryor, *Cancer Res.*, 1975, **35**, 3750–3754.
12 Q. F. Hu, B. Zhou, J. M. Huang, X. M. Gao, L. D. Shu, G. Y. Yang and C. T. Che, *J. Nat. Prod.*, 2013, **76**, 292–296.
13 S. Y. Cheng, K. J. Huang, S. K. Wang, Z. H. Wen, P. W. Chen and C. Y. Duh, *J. Nat. Prod.*, 2010, **73**, 771–775.
14 W. Gregor, G. Grabner, C. Adelwöhrer, T. Rosenau and L. Gille, *J. Org. Chem.*, 2005, **70**, 3472–3483.
15 H. Hidayat, H. Javid, A. H. Ahmed and K. Karsten, *Tetrahedron*, 2012, **68**, 2553–2578.
16 K. Acosta-Quiroga, C. Rojas-Peña, L. S. Nerio, M. Gutiérrez and E. Polo-Cuadrado, *RSC Adv.*, 2021, **11**, 21926–21954.
17 Y. Zhang, X.-Z. He, H. Yang, H.-Y. Liu and L.-K. An, *Phytother Res.*, 2021, **35**, 5282–5289.
18 J. M. Elliott, H. G. Selnick, D. A. Claremon, J. J. Baldwin, S. A. Buhrow, J. W. Butcher, C. N. Habecker, S. W. King, J. J. Lynch, B. T. Philips, G. S. Ponticello, E. M. Radzilowski, D. C. Remy, R. B. Stein, J. I. White and M. B. Young, *J. Med. Chem.*, 1992, **35**, 3973–3976.
19 N. G. Ghatpande, J. S. Jadhav, R. V. Kaproormath, M. E. Soliman and M. M. Shaikh, *Bioorg. Med. Chem.*, 2020, **28**, 115813.
20 V. Panteleon, P. Marakos, N. Pouli, E. Mikros and I. Andreadou, *Chem. Pharm. Bull.*, 2003, **51**, 522–529.
21 K. M. Ejner and K. P. Jens, Japanese Patent JP 55143980, 1980, PCT Int. Appl.
22 Y. Masatoshi, H. Kuniko, T. Akira and D. Kenji, *Chem. Pharm. Bull.*, 1981, **29**, 3494–3497.
23 S. Sutthivaiyakit, O. Thongnak, T. Lhinhatrakool, O. Yodchun, R. Srimark, P. Dowtaisong and M. Chuankamnerdkarn, *J. Nat. Prod.*, 2009, **72**, 1092–1096.
24 P. C. Pan, M. J. Cheng, C. F. Peng, H. Y. Huang, J. J. Chen and I. S. Chen, *J. Nat. Prod.*, 2010, **73**, 890–896.
25 Z. Q. Xu, W. W. Barrow, W. J. Suling, L. Westbrook, E. Barrow, Y. M. Lin and M. T. Flavin, *Bioorg. Med. Chem.*, 2004, **12**, 1199–1207.
26 A. Termentzi, I. Khouri, T. Gaslonde, S. Prado, B. Saint-Joani, F. Bardou Amanatiadou, I. S. Vizirianakis, J. Kordulakova, M. Jackson, R. Brosch, Y. L. Janin, M. Daffé Tillequin and F. S. Michel, *Eur. J. Med. Chem.*, 2010, **45**, 5833–5847.
27 F. H. Elghareeb, E. M. Kandil, M. Abou-Elzahab, M. Abdelmoteleb and M. A. Abozeid, *RSC Adv.*, 2021, **11**, 21301–21314.
28 H. J. Kabbe and H. Heitzer, *Synthesis*, 1978, 886–889.
29 N. Verma, S. Arora, A. K. Singh and A. Kumar, *Targets*, 2025, **3**, 32.
30 H. J. Kabbe and A. Widdig, *Angew. Chem., Int. Ed.*, 1982, **21**, 247–256.
31 P. Kumar, A. Singampalli, R. Bandela, B. Srimounika, S. I. Rajyalakshmi, A. Devi, S. Nanduri and Y. V. Madhavi, *Future Med. Chem.*, 2025, **17**, 819–837.
32 P. Kumar, A. Singampalli, R. Bandela, S. M. Bellapukonda, S. Nanduri and V. M. Yaddanapudi, *RSC Med. Chem.*, 2025, 5925–5952.
33 S. Chakroborty, P. Panda, S. C. Ramirez-Lopez, E. M. A. Garcia, E. C. Yañez, L. Strekowski and M. V. B. Unnamatlad, *Heterocycl*, 2022, **104**, 27–68.
34 C. D. Gabbutt, J. D. Hepworth, B. M. Heron and J. L. Thomas, *Tetrahedron Lett.*, 1998, **39**, 881.
35 S. E. Kelly and B. C. Vanderplas, *J. Org. Chem.*, 1991, **56**, 1325–1327.
36 S. Chandrasekhar, K. Vijeender and K. V. Reddy, *Tetrahedron Lett.*, 2005, **46**, 6991.
37 R. A. Tapia, A. Bau and C. Salas, *Synth. Commun.*, 2006, **36**, 771.
38 J. Liang, K. Xu, S. Arora, J. E. Laaser and S. K. Fullerton-Shirey, *Materials*, 2020, **13**, 1089.
39 S. Arora, J. Liang, S. K. Fullerton-Shirey and J. E. Laaser, *ACS Mater. Lett.*, 2020, **2**(4), 331–335.

40 S. A. Abdelatef, M. T. El-Saadi, N. H. Amin, A. H. Abdelazeem, H. A. Omar and K. R. A. Abdellatif, *Eur. J. Med. Chem.*, 2018, **150**, 567–578.
41 L. Yang, G. Morriello, K. Prendergast, K. Cheng, T. Jacks, W. W. S. Chan, K. D. Schleim, R. G. Smith and A. A. Patchett, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 107.
42 H. G. Bonacorso, F. D. Garcia, C. R. Belo, A. Z. Tier, C. P. Frizzo, M. A. P. Martins and N. Zanatta, *J. Fluorine Chem.*, 2014, **166**, 44.
43 H. G. Bonacorso, A. Ketzer, F. D. Garcia, W. C. Rosa, T. P. Calheiro, S. C. Feitosa, G. M. Dal Forno, N. Zanatta, M. A. P. Martins and C. P. Frizzo, *J. Fluorine Chem.*, 2017, **197**, 6.
44 N. Verma, S. Arora, A. K. Singh and J. Ahmed, *RSC Pharm.*, 2025, **2**, 1201–1226.
45 K. Prathima, D. Ashok, M. Sarasija, P. Sripadi, M. Vemula, V. S. Komarraju, B. Gorai and S. Prakash, *RSC Adv.*, 2018, **67**, 38673–38680.
46 N. Verma and S. Arora, *Pharmaceutics*, 2025, **17**, 990.
47 S. Arora and N. Verma, *RSC Appl. Polym.*, 2024, **2**, 317–355.
48 H. S. P Rao and T. V. Swamy, *Lett. Org. Chem.*, 2013, **4**, 307–310.
49 A. Dongamanti, V. K. Aamate, M. G. Devulapally, S. Gundu, S. Balabadra, V. Manga, P. Yogeeswari, D. Sriram and S. Balasubramanian, *Mol. Divers.*, 2017, **21**, 999–1010.
50 M. Muthukrishnan, U. M. V. Basavanag and V. G. Puranik, *Tetrahedron Lett.*, 2009, **50**, 2643.
51 S. Arora, J. Rozon and J. E. Laaser, *Macromolecules*, 2021, **54**, 6466–6476.
52 S. Arora and N. Verma, *ChemistrySelect*, 2026, **11**, e02016.
53 N. Jankowski, C. Hager, H. Arcure, J. Lopez, A. M. B. Gomez, Z. J. Witczak, R. Bielski and D. E. Mencer, *Carbohydr. Res.*, 2025, **552**, 109466.
54 H. Castro, T. Cruz, P. A. Amaral, P. S. Cardoso, A. Alsaffar, P. Farrell, A. M. Tomás and J. W. Barlow, *Heliyon*, 2020, **6**, e03614.
55 A. Parthiban and P. Makam, *Bioorg. Chem.*, 2020, **105**, 104379.
56 P. Jayaraj, R. Krishnamoorthy, P. Adhikari, M. Singh, S. Rajamanickam, D. Dhillon, J. Muthukumaran and P. Anaikutti, *ChemistrySelect*, 2025, **10**, e202500106.
57 R. Krishnamoorthy, M. Singh, P. Anaikutti, L. Edwin Paul, S. Dhanasekaran and T. Sathiah, *Bioorg. Chem.*, 2023, **134**, 106434.
58 R. Krishnamoorthy and P. Anaikutti, *RSC Adv.*, 2023, **13**, 36439–36454.
59 A. Parthiban, R. Sivasankar, B. Rajdev, R. N. Asha, T. C. Jeyakumar, R. Periakaruppan and V. G. M. Naidu, *J. Mol. Struct.*, 2022, **1270**, 133885.
60 S. I. Desoky, M. A. Hammad, N. Grant, E. M. El-Telbany and A. H. Abdel-Rahman, *Tetrahedron*, 1997, **53**, 15799.
61 C. Villarroel-Vicente, A. García, K. Zibar, M. A. Schiel, J. Ferri, N. Hennuyer, R. D. Enriz, B. Staels, D. Cortes and N. Cabedo, *Bioorg. Med. Chem. Lett.*, 2024, **106**, 129770.
62 P. da Silva Cardoso, L. B. Niero, T. E. A. Frizon, S. DalBo, A. C. L. Lamer, N. Gouault, P. de. A. Amaral and J. W. barlow, *Med. Chem. Res.*, 2024, **33**, 1657–1670.
63 H. J. Kabbe and H. Heitzer, *Liebigs Ann. Chem.*, 1976, 511–518.
64 A. D. Richardson, T. R. Vogel, E. F. Traficante, K. J. Glover and C. S. Schindler, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201213.
65 B. N. Kakde, S. W. An, Y. S. Jebaraj, S. Neelam, M. T. F. Wolf and U. K. Tambar, *ACS Med. Chem. Lett.*, 2024, **15**(12), 2220–2224.
66 N. P. Kapuriya, J. J. Bhalodia, M. A. Ambasana, R. B. Patel and A. H. Bapodra, *J. Heterocycl. Chem.*, 2020, **57**, 3369.
67 S. Chitti, S. Pulya, A. Nandikolla, T. K. Patel, B. K. Kumar, S. Murugesan, B. Ghosh and K. V. G. C. Sekhar, *Bioorg. Chem.*, 2021, **112**, 104865.
68 S. Arora and C. Mao, *Nucleosides, Nucleotides Nucleic Acids*, 2024, **43**, 316–339.
69 J. P. N. Bonesconto, L. R. Cruz and L. C. Dias, *et al. XXXII Congresso de Iniciação Científica da UNICAMP*, 2024.
70 J. M. Elliott, H. G. Selnick, D. A. Claremon, J. J. Baldwin, S. A. Buhrow, J. W. Butcher, C. N. Habecker, S. W. King, J. J. Lynch and B. T. Phillips, *J. Med. Chem.*, 1992, **35**(21), 3973–3976.
71 P. Shinde, S. K. Srivastava, R. Odedara, D. Tuli, S. Munshi, J. Patel, S. P. Zambad, R. Sonawane, R. C. Gupta, V. Chauthaiwale and C. Dutt, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 949.
72 M. C. Patel and N. N. Gajera, *Chem. Sin.*, 2012, **3**, 80–90.
73 S. Chitti, A. Nandikolla, Y. M. Khetmalis, K. Van Calster, B. V. S. Kumar, B. K. Kumar, S. Murugesan, D. Cappoen and K. V. G. C. Sekhar, *Chem. Biodiversity*, 2055, **19**, e202200304.
74 K. S. Chaitanya, P. Gupta, S. Chitti, Y. M. Khetmalis, A. Chandu, S. Murugesan, M. Pasupuleti and K. V. Sekhar, *J. Chem.*, 2024, **2024**, 8227205.
75 M. Muthukrishnan, M. Mujahid, P. Yogeeswari and D. Sriram, *Tetrahedron Lett.*, 2011, **52**, 2387–2389.
76 M. Muthukrishnan, U. M. V. Basavanag and V. G. Puranik, *Tetrahedron Lett.*, 2009, **50**, 2643.
77 M. Mujahid, P. Yogeeswari, D. Sriram, U. M. V. Basavanag, E. Díaz-Cervantes, L. Córdoba-Bahena, J. Robles, R. G. Gonnade, M. Karthikeyan, R. Vyas and M. Muthukrishnan, *RSC Adv.*, 2015, **5**, 106448–106460.
78 D. Ashok, S. Gundu, V. K. Aamate, M. G. Devulapally and M. S. Reddy, *Russ. J. Gen. Chem.*, 2015, **85**, 708.
79 D. Ashok, D. M. Gandhi, A. V. Kumar, G. Srinivas, M. S. Reddy, S. S. Kanth and M. Vijjulatha, *Med. Chem. Res.*, 2016, **25**, 2882.
80 D. Ashok, E. V. L. Madhuri, M. Sarasija, S. Sree Kanth, M. Vijjulatha, M. D. Alaparthi and S. R. Sagurthi, *RSC Adv.*, 2017, **7**, 25710–25724.
81 S. A. Abdelatef, M. T. Saadi, N. H. Amin, A. H. Abdelazeem Khaled and R. A. Abdellatif, *J. Appl. Pharm. Sci.*, 2018, **8**, 9.
82 S. A. Chamness, E. F. Traficante, T. R. Vogel and C. S. Schindler, *Org. Synth.*, 2025, **102**, 335–349.
83 S. Nakka, S. Sengar, K. Sai Chaitanya, Swati, A. Chandu, M. Sankaranarayanan, V. Sharma, N. Devunuri and K. V. Gowri Chandra Sekhar, *Asian J. Org. Chem.*, 2025, **14**, e202400604.

84 S. R. Natarajan, R. Krishnamoorthy, M. A. Alshuniaber, T. S. Alsulami, M. K. Gatasheh, P. Rajagopal, C. P. Palanisamy, R. Govindan, V. P. Veeraraghavan and S. Jayaraman, *Sci. Rep.*, 2025, **15**, 24674.
85 A. Eswaran, S. R. Natarajan, S. Jayaraman, J. M. Khan, S. Jasmine and V. P. Veeraraghavan, *Chem. Heterocycl. Compd.*, 2026, **40**, 57.
86 S. Jayaraman, M. Prasad, S. R. Natarajan, R. Krishnamoorthy, M. A. Alshuniaber, M. K. Gatasheh, V. P. Veeraraghavan, P. Rajagopal and C. P. Palanisamy, *Chem. Biol. Interact.*, 2025, **411**, 111443.
87 R. R. Mudda, V. Basava, R. Gundla, R. Chennuru, S. Gurská, V. Das, N. K. Katari and J. Indian, *Chem. Soc.*, 2025, **102**, 102177.
88 N. R. Kishore, D. Ashok, M. Sarasija and N. Y. S. Murthy, *Chem. Heterocycl. Compd.*, 2017, **53**, 1187.
89 N. R. Kishore, D. Ashok, B. A. Rao, M. Sarasija and N. Y. S. Murthy, *Chem. Heterocycl. Compd.*, 2017, **53**, 511–517.
90 I. V. Krasylov, V. S. Moskvina and V. P. Khilya, *Ukr. Bioorg. Acta*, 2023, **18**(1), 42–50.