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Applications of the Ritter reaction in the synthesis of biologically active compounds: A review

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REVIEW ARTICLE



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ABSTRACT

Nitrogen-containing compounds play a fundamental role in biological systems. Proteins, the essential macromolecules responsible for virtually all cellular functions, are composed of amino acids linked through amide (peptide) bonds, highlighting the critical importance of nitrogen-containing functionalities in life processes. Ritter reaction methodologies have provided access to novel amide-containing scaffolds, which are valuable in medicinal chemistry and the creation of drug libraries. Ritter reactions are widely used in the synthesis of highly functionalized heterocycles, fused heterocycles and linear amides. These classes of compounds exhibit notable biological activities, including antibacterial, antiviral, antiproliferative, and anticancer activities. This review aims to compile recent advancements and applications of the Ritter reaction and mainly focuses on synthetic strategies for the synthesis of different classes of bioactive compounds. The evaluation of potential therapeutic applications of the most promising molecules synthesized using Ritter reaction is also covered in the present review.

KEYWORDS

 Nitriles
 Alcohol
 Amines
 Amides
 Inhibitors
 Ritter reaction

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1. Introduction

Nitrogen-containing compounds play a central role in medicinal chemistry, since many pharmaceuticals and biologically active natural products incorporate nitrogen atoms within their molecular frameworks. Both amide and amine derivatives are common structural motifs found in numerous therapeutic agents due to their stability, hydrogen bonding capability, and favorable pharmacological properties. Amides are present in >25% of drugs, including antihistamines, local anesthetics, and CNS drugs [1]. The Ritter reaction emerged as a potential method for generating functionalized amides [2] and for the synthesis of several biologically active molecules, including antiallergic, antibiotic, antitumor, antibacterial, antiinfluenza, antiproliferative, and antimicrobial drugs.

Among the synthetic approaches for related nitrogen-containing molecules, the Ritter reaction has emerged as a valuable and versatile transformation. First reported by John J. Ritter in 1948, this reaction involves the acid-mediated conversion of tertiary alcohols, alkenes, or carbocations with nitriles to generate amide products [3,4]. The process typically proceeds through the formation of a carbocation intermediate that reacts with a nitrile to produce a nitrilium ion that

subsequently undergoes hydrolysis to yield the corresponding amide.

In recent decades, the Ritter reaction has been widely applied in the synthesis of a variety of biologically active compounds, including pharmaceuticals, agrochemicals, and natural product derivatives. The reaction is particularly valuable in medicinal chemistry for the preparation of nitrogen-containing heterocycles and functionalized amides that exhibit diverse biological activities, such as antimicrobial, antiviral, anticancer, and anti-inflammatory effects. For example, the Ritter reaction has been used in the synthesis of Crixivan (1) as an anti-human immunodeficiency virus (HIV) drug [5], Aristotelone (2) alkaloid receptor ligands and dopamine receptors [6] and amantadine (3) as an antiviral and anti-Parkinsonian drug [7] (Figure 1).

Recent advances have expanded the scope of the Ritter reaction because of the development of mild catalysts, the optimization of reaction conditions, and innovative synthetic strategies, thus making this reaction more pertinent and applicable for modern drug discovery. This review focuses on applications of Ritter reactions for the synthesis of drug molecules, lead compounds, and other biologically relevant scaffolds.

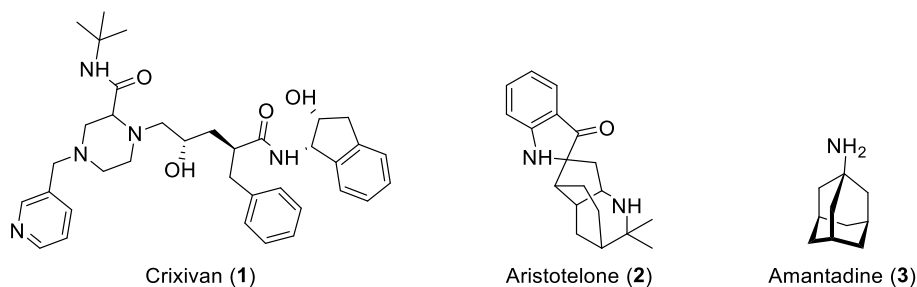
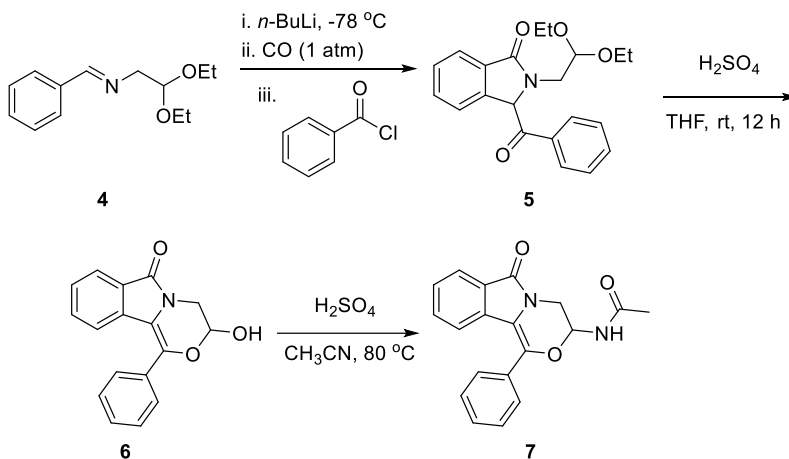
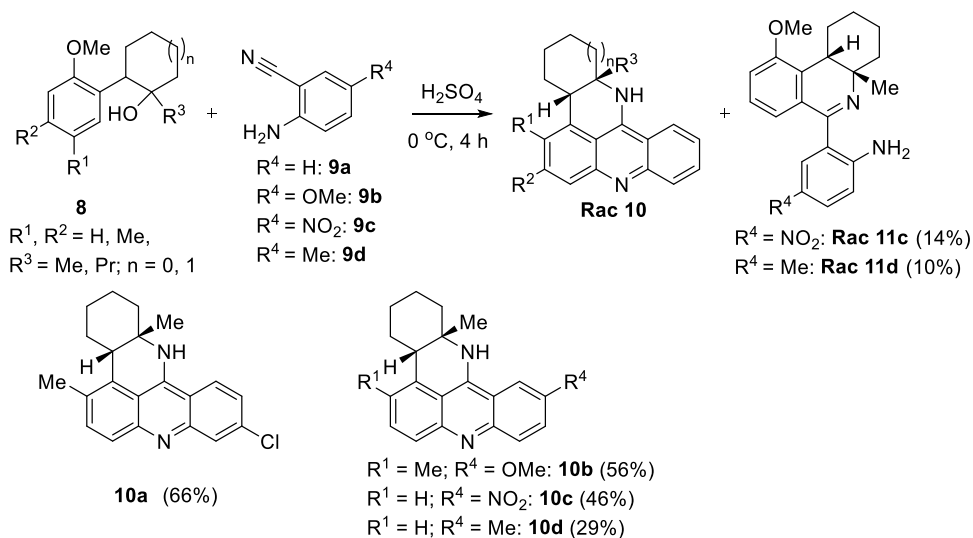


Figure 1. Structures of crixivan (1), aristotelone (2), and amantadine (3) synthesized by the Ritter reaction.



Scheme 1. Synthesis of amide (7) from secondary alcohol (6).



Scheme 2. Synthesis of new quinolino[4,3,2-kl]acridines (10a-f).

The biological activity of these compounds is also covered in the current review. this reaction for the synthesis of pharmacologically important compounds.

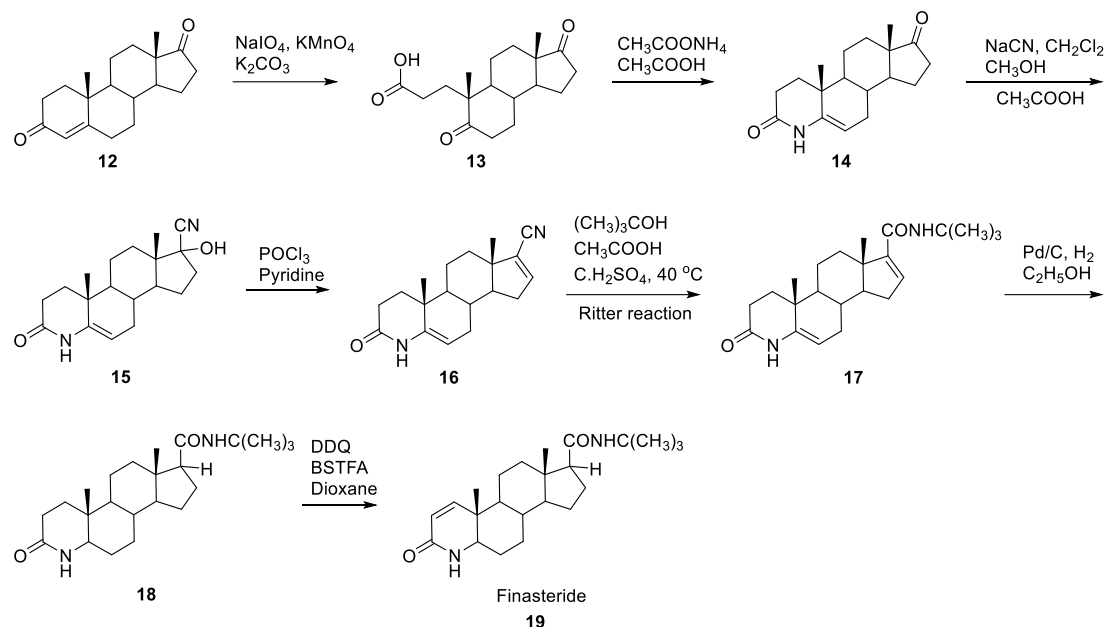
2. Applications of the Ritter reaction for the synthesis of biologically active compounds

2.1. Ritter reactions using sulfuric acid

Fan Z. and co-workers reported acid-catalyzed intramolecular cyclization of isoindolinone derivatives [8]. Cyclic

alcohol (6) was obtained from compound (5) by a series of cyclization reactions and acid-catalyzed intramolecular rearrangements. H₂SO₄-mediated Ritter reaction in acetonitrile provided amide (7) (Scheme 1). A series of compounds were synthesized as a novel pesticide showing good fungicidal or systemically acquired resistance activities.

Rozhkova Y. S. and co-workers developed a domino sequence that involves an initial dearomative electrophilic orthospirocyclization through the Ritter reaction, followed by intramolecular nucleophilic trapping of the spiro-σ-intermediate by the amino group and subsequent aromatization



Scheme 3. Synthesis of finasteride (**19**) from 4-androstene-3,17-dione.

through [1,2]-alkyl shift acridines that shows high antibacterial activity against *S. epidermidis* ATCC 29887 and *M. smegmatis* mc2 155 [9]. Briefly, the reaction of alcohols (**8**) with 2-aminobenzonitriles (**9a** and **9b**) resulted in the diastereoselective formation of new quinolino [4,3,2-kl] acridines (**10a** and **10b**), respectively, in good yields (Scheme 2). Reactions of 2-amino-5-nitro or 2-amino-5-methylbenzonitriles (**9c** and **9d**) with alcohol (**8**) containing an unsubstituted ortho-methoxyphenyl unit ($R_1 = R_2 = H$) furnished compounds **10c** and **10d** in yields of 46 and 29 %, respectively, along with side products phenanthridines (**11c**) and (**10d**) in low yields.

Zhong-Xing Jiang and co-workers reported an efficient seven-step synthesis of finasteride (3-oxo-4-aza-5-androst-1-ene-17-(*N*-*tert*-butylcarboxamide)) starting from 4-androstene-3,17-dione (AD) (**12**). The overall yield of the reported synthesis is 18.6% (Scheme 3) [10]. A key synthetic step in this synthesis was the Ritter reaction, which was employed to introduce the essential 17-(*N*-*tert*-butylcarboxamide) group, a critical pharmacophore of finasteride (**19**). The reaction involved the concentrated sulfuric acid-catalyzed conversion of a nitrile intermediate (**16**) using *tert*-butanol in acetic acid.

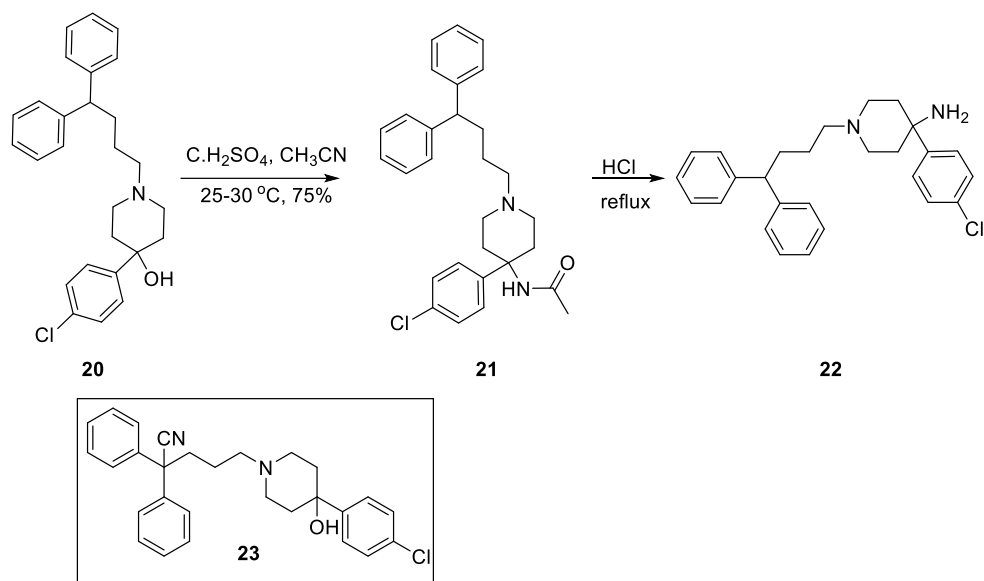
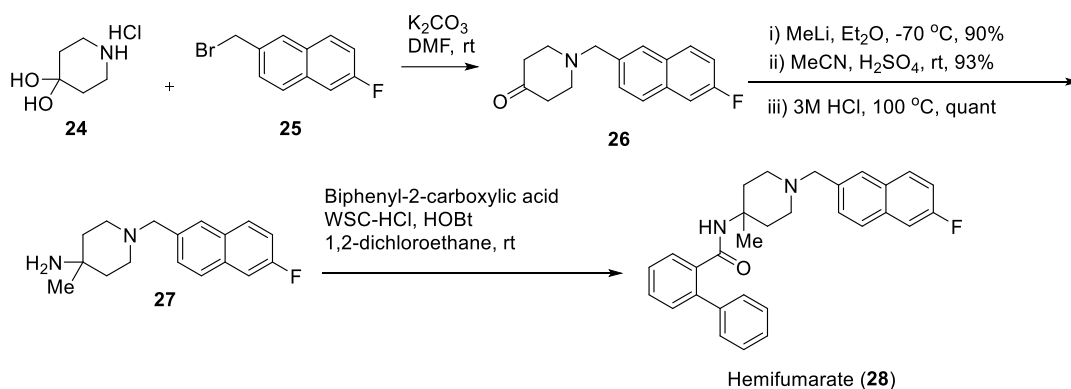
This Ritter reaction-based approach provided a convenient and higher-yielding method compared to previous routes. The final product, finasteride (**19**), is a biologically active azasteroidal compound widely used for the treatment of benign prostatic hyperplasia (BPH) [11–13], androgenic alopecia (hair loss) [14,15] and to reduce the risk of prostate cancer [16]. The successful introduction of the amide group *via* the Ritter reaction was essential to achieve the desired biological activity, as this functional group plays a key role in enzyme inhibition and therapeutic efficacy.

Viral G-protein-coupled receptors (GPCRs) constitute a highly under investigated group of potential therapeutic targets [17]. Janneke W. Hulshof *et al.* reported the synthesis and pharmacological evaluation of the first series of inverse agonists directed toward the human cytomegalovirus (HCMV) encoded receptor US28 [18]. Compound **20** was subjected to the Ritter reaction using conc. H_2SO_4 and acetonitrile at room temperature to obtain compound **21** (Scheme 4). Structural modification of the lead compound **23**, including substitution at the *N*-acetyl position to produce compound **21** and amino functionality to produce compound **22** resulted in

approximately 2- and 3.5-fold increases in receptor binding affinity, respectively. These newly synthesized inverse agonists serve as valuable tools for investigating the role of constitutive receptor activity in viral disease progression and may offer promising starting points for the development of new antiviral therapeutics. Alkyl polyglycosides (APG) [19,20] and *N*-acyl-*N*-methylglucamides [21–24] are non-ionic carbohydrate-based surfactants (NICBS). NICBS exhibit advantageous characteristics such as low toxicity, biodegradability, and biocompatibility, highlighting their potential for sustainable and green chemistry applications.

Ippei Sato and co-workers designed and synthesized a novel class of potent CCR3 receptor antagonists, starting from *N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide as a key intermediate [25]. Compound **28** hemifumarate was prepared from intermediate (**24**) through a five-step synthetic sequence (Scheme 5). A key step in the synthesis was a Ritter reaction employing acetonitrile and sulfuric acid, which introduced the acetamide functionality to afford compound **27** which was subsequently hydrolyzed under acidic conditions, followed by condensation with biphenyl-2-carboxylic acid, and finally, crystallization to afford the target compound **28** as its hemifumarate salt. These compounds demonstrated potent CCR3 receptor antagonistic activity, highlighting their potential therapeutic application in the treatment of allergic and inflammatory diseases.

John T. Randolph and co-workers reported a series of thiadiazine compounds that exhibit low nanomolar potency as inhibitors of the NS5B polymerase of genotype 1 HCV [26,27]. A new series of neohexyl-substituted analogues of B-ring aminothiadiazine inhibitors was designed using molecular modeling [28]. This synthetic strategy allowed access to a structurally diverse set of compounds that exhibited different functional groups suitable for biological investigation. In the reported pathway, compound **29** was initially converted into tertiary alcohol intermediate (**30**), which was subsequently transformed into thiadiazine derivative **32** through a two-step sequence (Scheme 6). The intermediate (**32**) was then subjected to a Ritter reaction in acetonitrile to generate compound **33**. Further transformation involving acidic hydrolysis, removal of the acetyl protecting group, and reductive alkylation with various aldehydes produced second-

Scheme 4. Synthetic pathway for the synthesis of compounds **21** and **22**.Scheme 5. Synthesis of hemifumarate **28**.

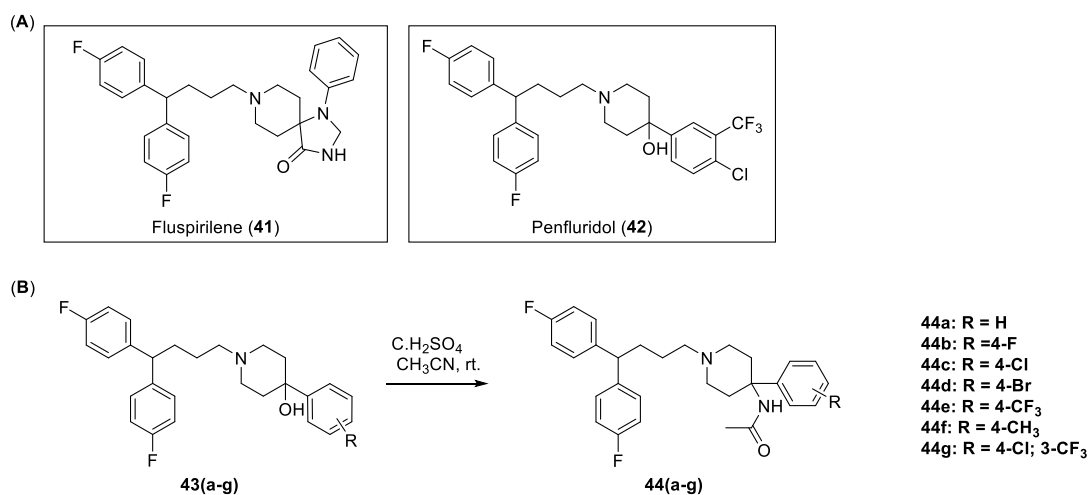
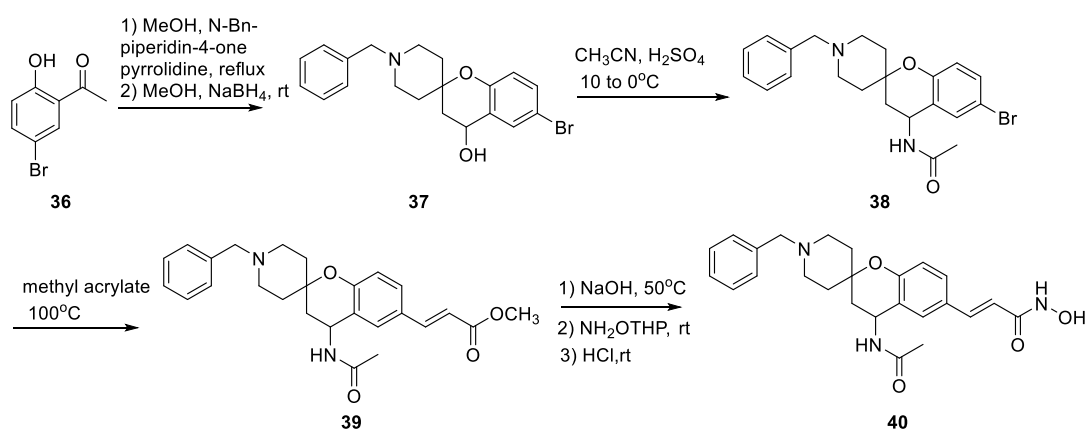
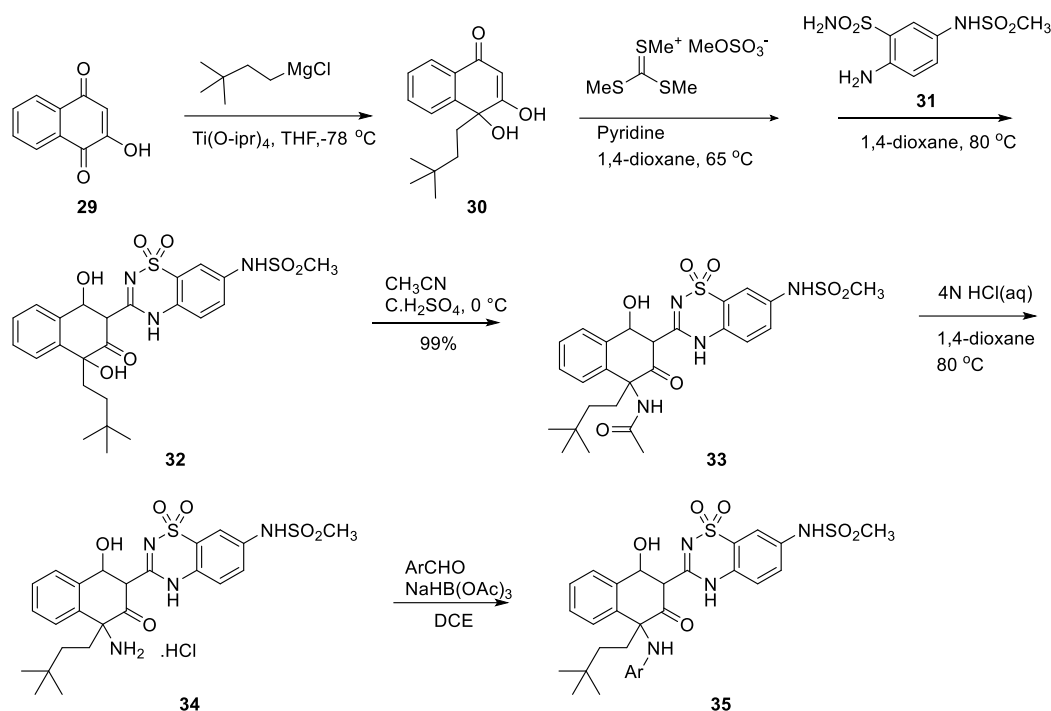
dary amine (**35**), yielding the desired B-ring amino analogues. These synthesized compounds demonstrated favorable characteristics and were identified as promising candidates for further development as therapeutic agents against HCV infection (IC_{50} ranging from 5-151 nM). represent common structural elements in many pharmacologically active molecules [29,30].

SAHA [31,32]. (also known as vorinostat) and the cyclic depsipeptide romidepsin or FK228 [33] are FDA approved hydroxamic acid derivatives which are HDAC inhibitors that have been used for the treatment of cutaneous T-cell lymphoma (CTCL). A benzylspiro-piperidine derivative (**40**) was prepared from 1-(5-bromo-2-hydroxyphenyl)ethenone as the starting material (**36**) (Scheme 7) [34]. Subsequently, alcohol (**37**) was converted into the acetylaminospir-piperidine derivative (**38**) through a Ritter reaction using acetonitrile in the presence of sulfuric acid. Further modification of this amide (**38**) through a two-step transformation provided the target *N*-hydroxy-acrylamide compound (**40**). The synthesized compounds were then examined for their ability to inhibit histone deacetylases (HDACs) in nuclear extracts and were also assessed for their antiproliferative activity against various cancer cell lines in vitro. The results indicated that these molecules have promising potential as anticancer agents (IC_{50} for **40** in HDCs was found to be 5.15 μ M).

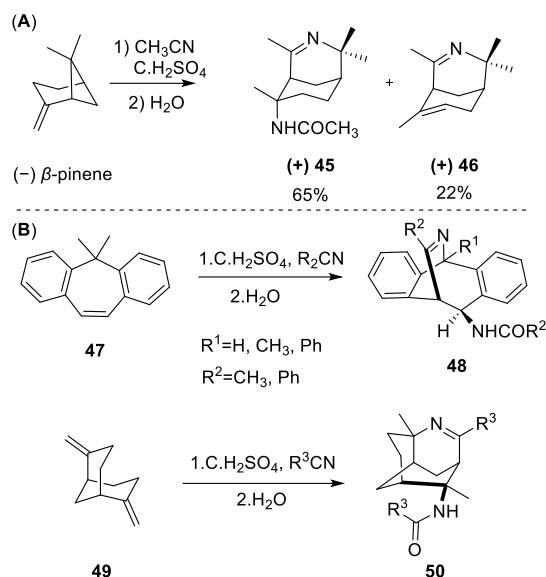
Diphenylbutylpiperidine (DPBP), a class of compounds that were initially developed as dopamine D2 receptor antagonists, is currently used clinically in the treatment of various psychotic disorders [35]. Furthermore, recent studies indicate that DPBPs can also function as potent calcium channel antagonists [36-41]. In addition, penfluridol, another well-known member of the DPBP family that was not included in the screened compound library, was also found to act as an effective inducer of autophagy with an EC_{50} value of 3.2 μ M.

Gang Chen, Chengye Yuan, and colleagues reported the development of a new class of DPBP derivatives as autophagy inducers [42]. Detailed structure-activity relationship (SAR) investigations identified several derivatives that exhibited approximately 10-fold higher activity compared to the original lead compounds fluspirilene (**41**) [EC_{50} = 2.4 μ M] and penfluridol (**42**) (Scheme 8A). Compounds (**43a-g**) were subjected to Ritter reaction using Concentrated H_2SO_4 in acetonitrile at room temperature to produce the corresponding derivatives (**44a-g**) (Scheme 8B).

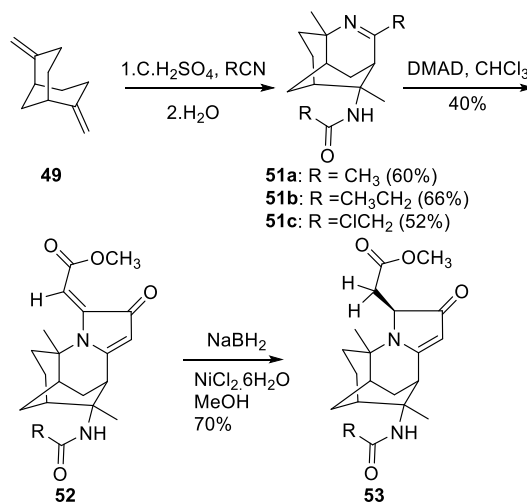
The 3-azabicyclo [3.3.1] non-ane framework represents a key structural motif present in several biologically active alkaloids. The distinctive biological properties of these cyclic compounds are largely attributed to their close structural resemblance to the relatively less explored Aristotelia alkaloids [43-45].



Scheme 8. (A) Structures of the original lead compounds fluspirilene (41) and penfluridol (42) and (B) synthesis of the compounds (44a-g).



Scheme 9. Synthesis of the 3-azabicyclo[3.3.1]non-3-ene skeleton containing compounds **45**, **46**, **48** and **50** via the bridged-Ritter reaction.



Scheme 10. Synthesis of tricyclic imines and their derivatisation.

Alison T. Ung and coworkers reported the stereoselective synthesis of alkaloid-like compounds featuring the 3-azabicyclo[3.3.1]non-3-ene framework through a bridged-Ritter reaction strategy [46]. In this approach, optically active 6-alkyl(aryl)amido-4-alkyl(aryl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-3-enes (imino amides) and 4-alkyl(aryl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-dienes (imino alkenes) were synthesized in a single step from (-)- β -pinene and the corresponding nitriles under strongly acidic conditions [47].

Specifically, treatment of (-) β -pinene with acetonitrile in the presence of concentrated sulfuric acid afforded the optically active imino amide (**45**) and imino alkene (**46**) products in a ratio of 2.78:1 (Scheme 9A). Imino amide was isolated in 64% yield under these conditions. Treatment of compound **47** and **49** under similar reaction conditions was offered in (**48**) and (**50**), respectively (Scheme 9B).

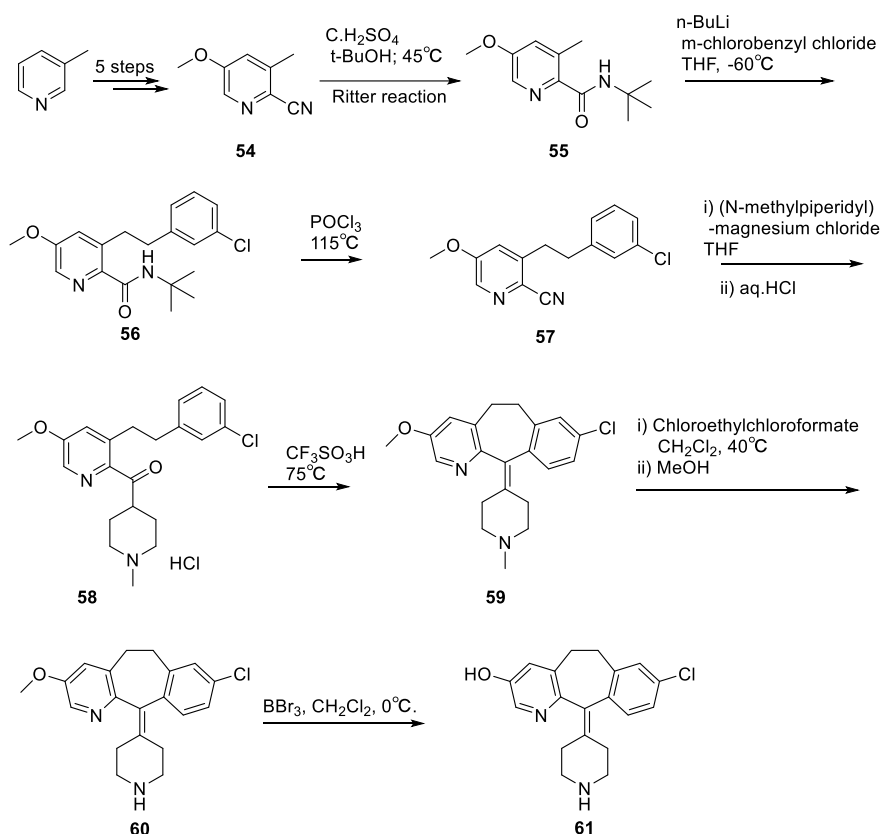
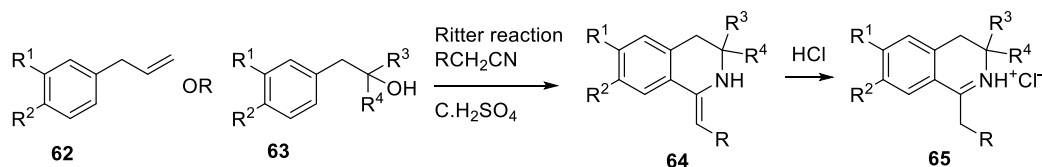
This one-step methodology provides access to optically active imino amides and imino alkenes, offering a rapid and efficient route to architecturally sophisticated heterocycles of potential relevance in synthetic and medicinal chemistry.

To explore their ongoing research on alkaloid-like compounds as anticancer agents [46], Alison T. Ung and coworkers synthesized a library of structurally diverse tricyclic

compounds employing the Bridged Ritter reaction as the central synthetic transformation [48]. The reactions (-)- β -pinene and a variety of nitriles in benzene under strongly acidic conditions (concentrated sulfuric acid), provided compounds (**51a-c**) (Scheme 10). Reaction with various nitrile compounds allowed modulation of the imine functionality and enabled further scaffold diversification. Subsequent synthetic transformations involve reduction, reductive alkylation, and cyclo-addition with dimethyl acetylenedicarboxylate (DMAD) to expand the chemical space of the resulting frameworks [49].

Biological evaluation demonstrated that compound **52** exhibited broad-spectrum anticancer activity, with selectivity toward certain type of leukemia, colon, melanoma, and breast cancer cell lines. Compound **53c** also showed selective cytotoxicity against the aggressive triple negative breast cancer cell line (MDA-MB-231), while no significant antiproliferative effect against MCF-7 cells was observed at concentrations up to 50 μ M.

3-Hydroxy desloratadine is a major active metabolite in Loratadine and desloratadine [50-53]. Lei Tian and co-workers reported the synthesis of 3-hydroxydesloratadine through a multistep synthetic route (Scheme 11) [54].

Scheme 11. Synthesis of 3-hydroxydesloratadine (**61**).

Scheme 12. General scheme for the synthesis of substituted 3,4-dihydroisoquinoline derivatives.

The key nitrile intermediate (**54**) was prepared from 3-methylpyridine in five steps. This intermediate (**54**) was subjected to a Ritter reaction using *tert*-butyl alcohol and sulfuric acid, converting nitrile into the corresponding *tert*-butylamide (**55**) as a protective transformation [55]. The resulting amide (**55**) was then subjected to a series of chemical transformations-alkylation, dehydration, cyclodehydration and methanolysis, to obtain 3-methoxydesloratadine (**60**). Finally, demethylation of (**60**) with boron tribromide (BBr_3) provided 3-hydroxydesloratadine (**61**).

Mikhailovskii and coworkers used a Ritter reaction strategy involving alcohols (**62**) [56] or olefins (**63**) [57] and various nitriles to generate the corresponding amide intermediates (**64**) (Scheme 12). These amides on treatment with hydrochloric acid were subsequently converted into their corresponding hydrochloride salts (**65**). The resulting compounds demonstrated pronounced biological activities, including antiarrhythmic, anticonvulsant, and analgesic effects.

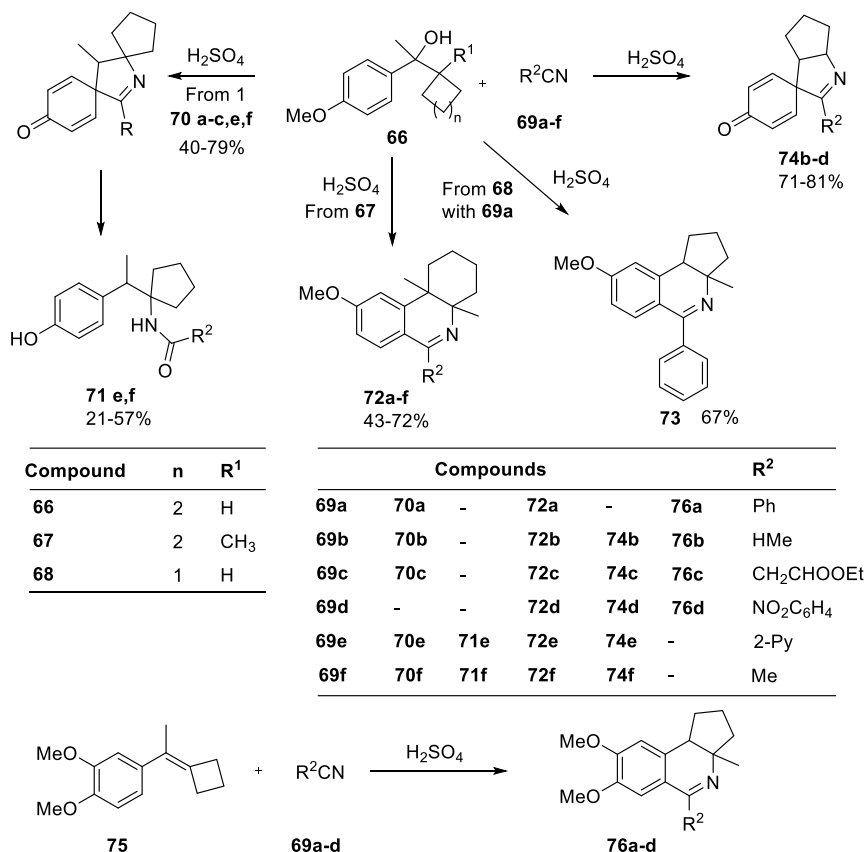
In addition to its traditional use in the formation of amides, the Ritter reaction has been employed in the synthesis of various heterocyclic structures, including 3,4-dihydroisoquinoline and 2-azaspiro [4.5] decane (spiropyrraline) derivatives [58,59]. Anna N. Perevoshchikova and colleagues reported the synthesis of novel 3,4-dihydroisoquinoline and 2-azaspiro [4,5] decane derivatives with promising biological

potential [60]. The synthetic approach relied on the in situ generation of carbocation intermediates from tertiary, benzylic, and cycloalkyl carbinols under strongly acidic conditions (92–94% sulfuric acid) (Scheme 13). Subsequently, these reactive carbocations were involved with various nitriles, proceeding through Ritter-type mechanisms that were often accompanied by Wagner–Meerwein rearrangements [61–63].

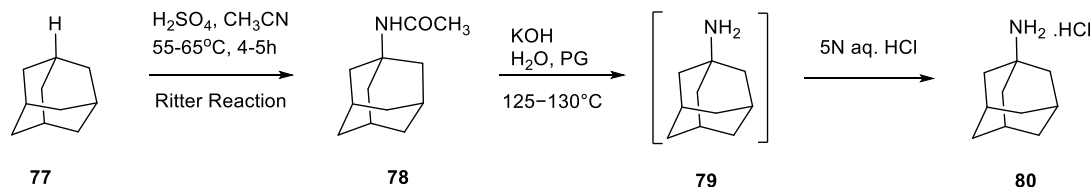
Biological and computational investigations suggested that several of the synthesized compounds have a high likelihood of inhibiting ubiquinol-cytochrome c reductase (bc_1 complex), a key enzyme in the mitochondrial respiratory chain, and an established target for antifungal [64] and antimalarial activities [65].

Amantadine hydrochloride is widely recognized as an antiviral agent for the treatment of influenza A infections and has also been used in the treatment of symptoms and dyskinesia of early stage Parkinson's disease [66,67]. The reported method therefore represents a safer and more practical approach to the preparation of this clinically important compound.

Chau Dinh Phan and coworkers described a convenient two-step synthesis of amantadine hydrochloride (**80**) starting from Adamantane (**77**) through a Ritter reaction pathway (Scheme 14) [68].



Scheme 13. Synthesis of 3,4-dihydroisoquinolines and 2-azaspiro[4.5]dec-anes (spiropyrrrolines).



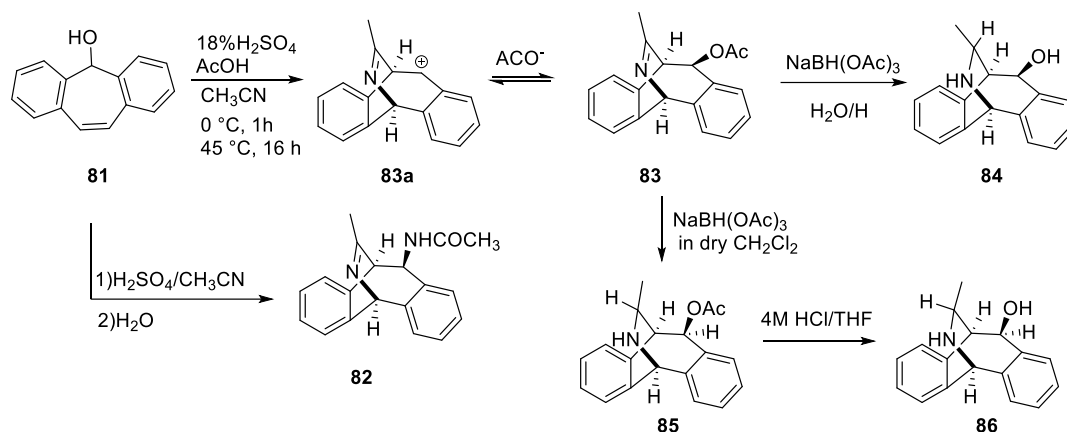
Scheme 14. Two-step synthesis of amantadine hydrochloride (**80**) from adamantane (**77**).

The key transformation involved acetamidation under strongly acidic conditions using concentrated sulfuric acid and acetonitrile. In this step, the nitrile group ($-C\equiv N$) was added to the adamantyl carbocation intermediate, affording the corresponding acetamide intermediate. Subsequent hydrolysis of the acetamide intermediate (**78**) using potassium hydroxide in propylene glycol to obtain amantadine (**79**), followed by acidic workup, provided amantadine hydrochloride in an overall yield of 67%. This strategy eliminated the need for hazardous reagents, such as liquid bromine or fuming nitric acid, thereby reducing the toxicity and improving the safety profile of the synthetic process.

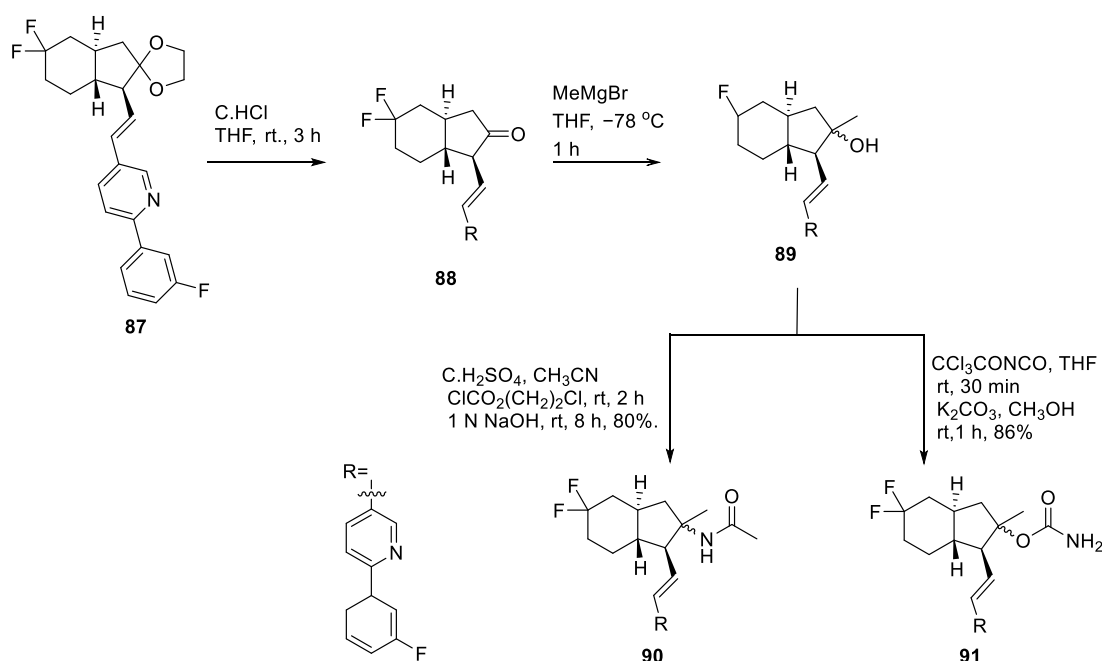
Alison T. Ung and coworkers reported the synthesis of benzo[c]azepine derivatives incorporating either amide or hydroxyl functionalities through a bridged-Ritter reaction strategy [69]. The synthesis of compound **82** was achieved by subjecting 5*H*-dibenzo[*a,d*]cycloheptanol (**81**) to a bridged Ritter reaction with acetonitrile under mildly acidic and polar conditions (Scheme 15). For the synthesis of compound **83**, the reaction was carried out using acetonitrile in a mixture of 18% sulfuric acid and glacial acetic acid. The use of a polar solvent such as acetic acid was found to stabilize the intermediate carbocation (**83a**), thus facilitating the reaction.

Interestingly, the study revealed that acetate ions could compete with nitriles as nucleophiles, attacking the carbocation at the C-11 position to provide compound **83**. These results demonstrated that acetic acid not only stabilizes the carbocation intermediate (**82**) but also enables the selective incorporation of acetate as a weaker nucleophile from the upper face of the bicyclic scaffold. This synthetic strategy provided access to diastereomeric compounds **84** and **86** which are stereoisomers of a previously reported acetylcholinesterase (AChE) inhibitor. Furthermore, compound **84** exhibited strong inhibitory activity of AChE, with a minimum inhibitory requirement (MIR) of 10 ng (0.04 nmol), which underlines its potential applications in neuropharmacological research.

Biological evaluation revealed that the synthesized natural products and their analogues exhibited antimicrobial activity against both Gram-positive and Gram-negative bacteria. Furthermore, the formulation of these compounds into solid lipid nanoparticles (SLNs) further enhanced their antimicrobial efficacy. Antagonists of protease-activated receptor 1 (PAR1) are considered relatively safe antiplatelet agents and are associated with a lower risk of bleeding compared with other antithrombotic therapies [70-73].



Scheme 15. Synthesis of benzo[c]azepine derivatives via the bridging Ritter reactions.



Scheme 16. Synthesis of 2-methyl-2-acetamide analogues.

Sunkyoung Lee *et al.* reported the preparation of a 2-methyl-2-acetamide analogue (**90**) using a Ritter reaction protocol [74]. The synthesis began with a known ketal precursor (**87**), which was converted into the corresponding 2-methyl-2-alcohol intermediate (**89**) (Scheme 16). This intermediate was then subjected to Ritter conditions using concentrated sulfuric acid and acetonitrile at room temperature, in the presence of 2-chloroethyl chloroformate [ClCO₂(CH₂)₂Cl], to furnish compound **90**.

Biological evaluation demonstrated that compound (**90**) exhibited inhibitory activity against protease-activated receptor (PAR1), along with good metabolic stability and moderate antithrombotic effects.

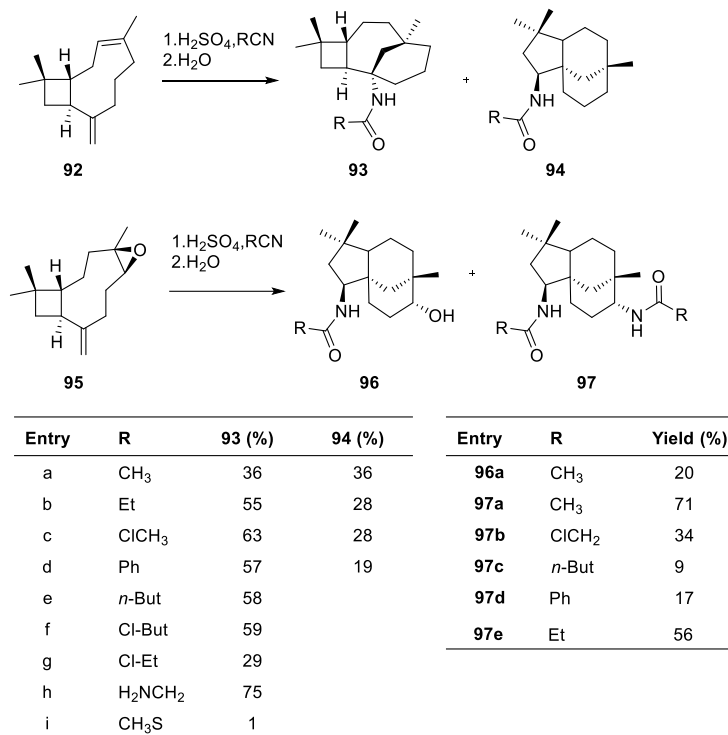
β -Caryophyllene is a naturally occurring sesquiterpene present in clove (*Eugenia caryophyllata*) and is well known for its diverse biological activities, including anti-inflammatory, antimicrobial, antioxidant, and anticancer effects.

Alison T. Ung and co-workers described the preparation of a new class of tricyclic amide derivatives as potential anticancer agents through a Ritter reaction strategy involving β -caryophyllene and its monoepoxide analogue [75]. Under

strongly acidic conditions, various nitriles were reacted with β -caryophyllene for a stereoselective Ritter reaction to obtain optically active tricyclic amides. Reactions of β -caryophyllene (**92**) with various nitriles furnished two distinct structural types of tricyclic amides: compounds (**93a-l**) with a caryolane-type framework and compounds (**94a-d**) possessing a clovane-type skeleton (Scheme 17). The nitriles were selected on the basis of their reactivity and introduction of structural diversity through varied substituents.

The synthesized compounds were subjected to antiproliferative activity against the aggressive MDA-MB-231 breast cancer cell line. Several derivatives demonstrated promising activity, highlighting the potential application of Ritter reactions for the synthesis of modified terpene scaffolds with anticancer properties.

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease defined by persistent limitation of expiratory airflow and chronic airway inflammation, and it constitutes a major cause of global morbidity and mortality [76-78].



Scheme 17. General synthesis of caryophyllene derivatives and monoepoxide derivatives *via* the Ritter reaction.

Maosheng Cheng and co-workers reported the design and synthesis of a new series of β_2 -adrenoceptor (β_2 -AR) agonists having (2-amino-1-hydroxyethyl)-6-hydroxy-1,4-benzoxazine-3(4H)-one core structure [79]. The biological activity of these compounds was evaluated using cell-based assays to evaluate their stimulatory effects on human β_2 and β_1 adrenoceptors.

Among the synthesized series of compounds, several potent β_2 -AR agonists were identified. In particular, compound ((*R*) **102**) exhibited exceptionally high β_2 -AR agonistic potency, with an EC₅₀ value of 24 pM (Scheme 18A). In isolated guinea pig trachea, ((*R*) **102**) demonstrated a strong bronchodilatory effect, characterized by rapid onset of action (3.5 min) and prolonged duration exceeding 12 hours.

From a synthetic perspective, a variety of 'tail' fragments (**106a-h**) were constructed (Scheme 18B). A ketone precursors (**103a-l**) were subjected to a sequence of chemical transformations involving alkene reduction, Grignard addition, a Ritter reaction, and subsequent deacetylation to furnish the tail fragments (**106a-h**). The "head" moiety was synthesized separately and then reacted with the tail fragments. Acetophenone (**98**) was first oxidized to provide intermediate (**103**), which was then reacted with the primary amines (**110a-h**). The final deprotection of the benzyl group produced the target β_2 -AR agonists (**102a-h**).

Acaricides are widely used in agriculture to control phytophagous mites, which can cause significant damage to crops and fruit yields. Therefore, the development of efficient and scalable synthetic routes to such agents is of considerable practical importance [80-83].

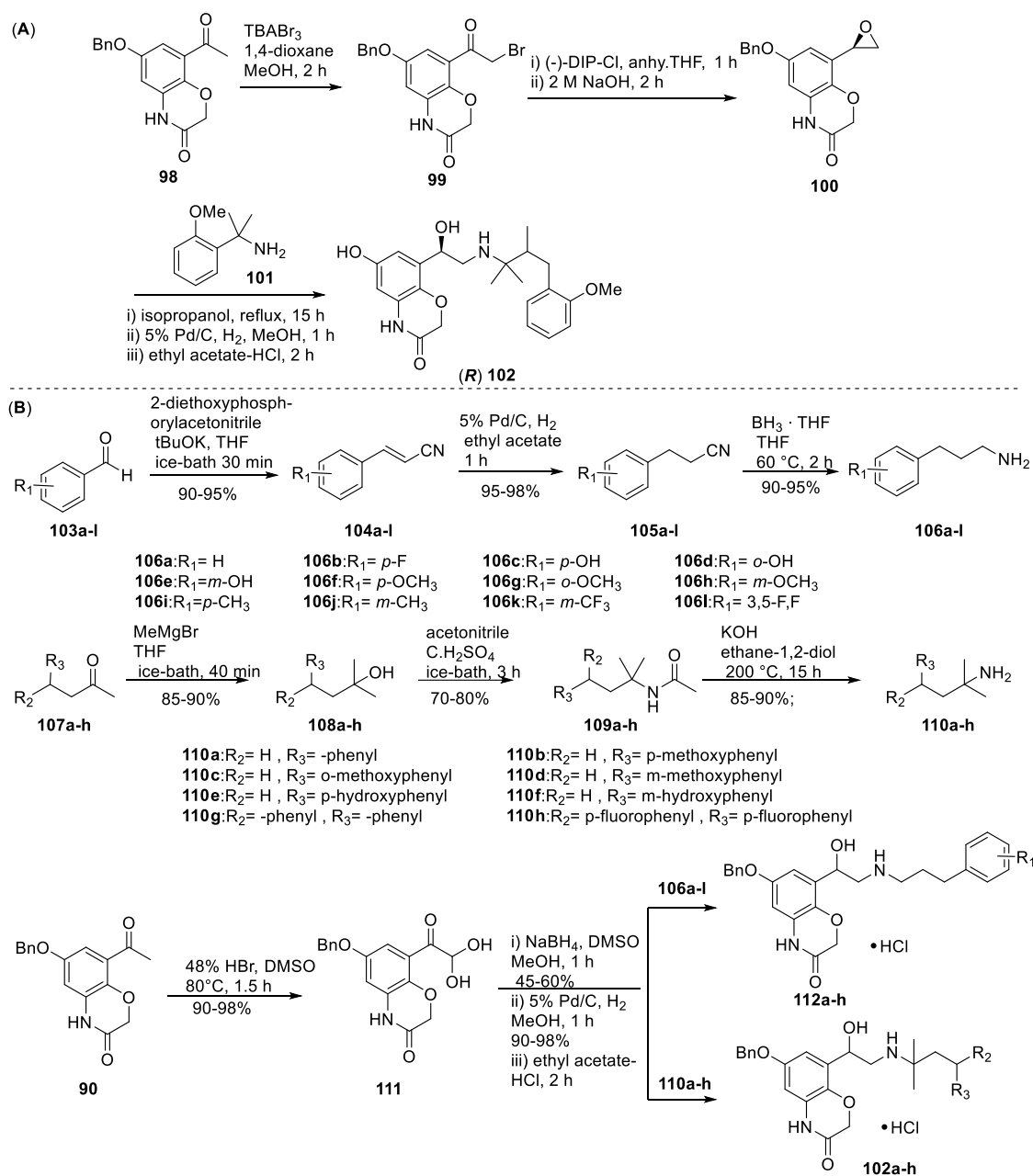
Maosheng Cheng and co-workers designed and synthesized a series of 8-hydroxyquinolin-2(1*H*)-one derivatives and evaluated their β_2 -adrenoceptor (β_2 -AR) agonistic activity using a cellular cAMP assay [84]. Synthetic routes to the required primary amine intermediates originated from commercially available substituted benzaldehydes and are described through multistep sequences that involve classical carbon-carbon bond formation and functional group transformation reactions (Scheme 19).

Ritter reaction of *tert*-alcohol intermediates (**113**) with acetonitrile in the presence of conc. H₂SO₄ furnished acetamide intermediates (**114a-j**). Based on these synthetic efforts, the team developed a focused library of 5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2 (1*H*)-one analogs as β_2 -AR agonists. Studies of the structure-activity relationship indicated that α -dimethyl or α -methyl substitution on the amino side chain slightly enhanced receptor activity. Among the tested, compound **116h** exhibited an exceptional potency (EC₅₀ < 20 pM) along with good β_2 -selectivity. In non-overexpressed HEK293 cells, compound **116h** behaved as partial β_2 -agonists. In addition, rapid onset and prolonged bronchodilatory effects are demonstrated in isolated preparations of guinea pig tracheal smooth muscle.

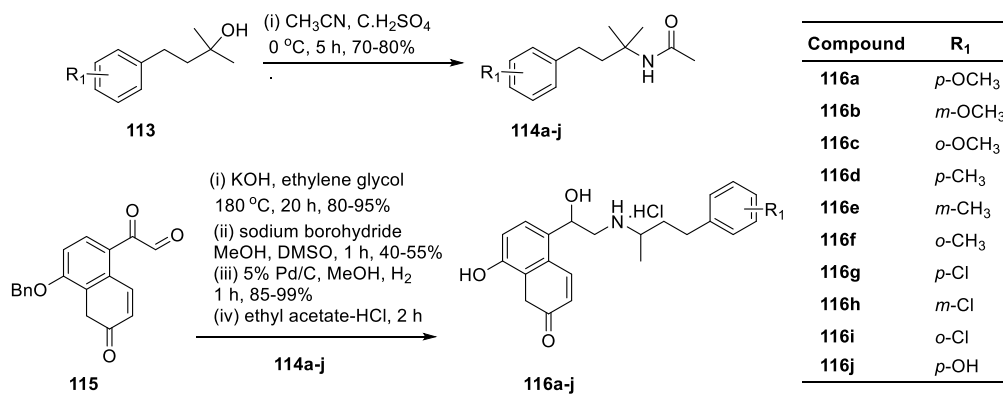
N-Acetylcolchicinol is a known tubulin polymerisation inhibitor that has toxic side effects. Andrei V. Malkov *et al.* described a more sustainable and step-efficient synthetic route to ($\pm$)-*N*-acetylcolchicinol [85]. (Scheme 20).

Ritter reaction of alcohol (**117**) with acetonitrile and H₂SO₄, providing acetamide (**118**). The final conversion to the target compound, ($\pm$)-*N*-acetylcolchicinol (**119**), was achieved using a non-divided electrochemical cell equipped with carbon electrodes. The optimized conditions are 10 mol% tetrabutylammonium tetrafluoroborate (*n*Bu₄NBF₄) in acetonitrile, along with an equivalent of trifluoroacetic anhydride (TFAA) and an equivalent of trifluoroacetic acid (TFA).

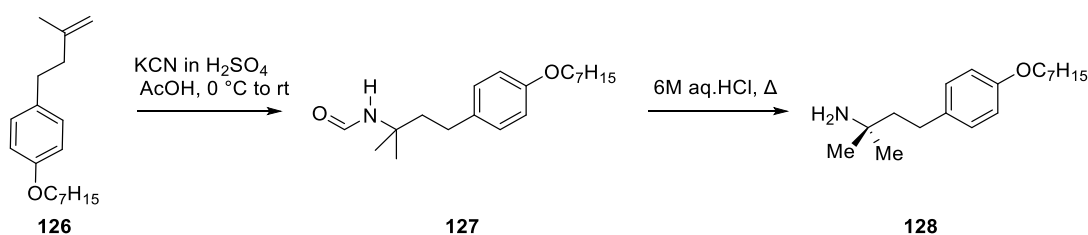
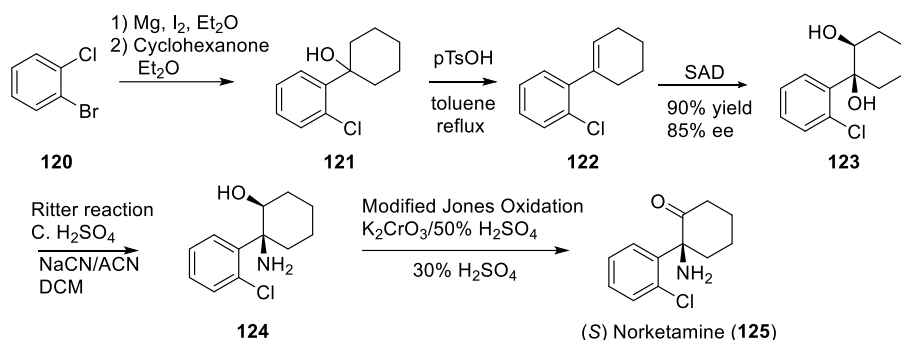
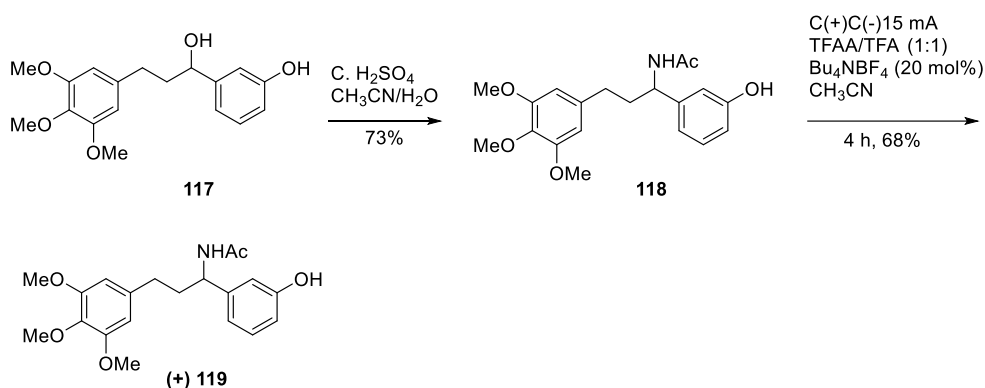
Ketamine is widely known as a dissociative anesthetic [86]; however, its metabolite norketamine retains analgesic properties while exhibiting a reduced incidence of adverse effects [87]. Consequently, norketamine is considered a potentially safer alternative to ketamine. Moreover, emerging studies suggest that norketamine and its derivatives may possess promising antidepressant activity [88], highlighting the therapeutic importance of efficient asymmetric synthetic routes to these compounds.



Scheme 18. (A) Synthesis of ((R) 102) and (B) synthesis of compounds (105 a-h) and (112 a-h).



Scheme 19. Synthesis of compound (116a-j).



Peter A. Crooks and co-workers reported an asymmetric synthesis of (*S*)-norketamine and (*R*)-norketamine in which the Ritter reaction played a central role [89].

The synthetic sequence began with the preparation of 1-(2-chlorophenyl)-1-cyclohexene (**122**) from 2-chlorobromobenzene (**120**) in two steps [Scheme 21] [90]. This intermediate (**122**) was subjected to Sharpless asymmetric dihydroxylation to provide the corresponding enantioenriched diol (**123**) which subsequently underwent a stereo controlled Ritter amination. In this transformation, concentrated sulfuric acid was used instead of the more corrosive and expensive triflic acid (TfOH) to generate the carbocation intermediate, which subsequently reacted with sodium cyanide to produce amine (**124**) with 99% enantiomeric excess after a single recrystallization. The amine intermediate (**124**) was further oxidized using a modified Jones reagent, where acetone was replaced with 30% sulfuric acid, to furnish (*S*) norketamine (**125**) in 87% isolated yield.

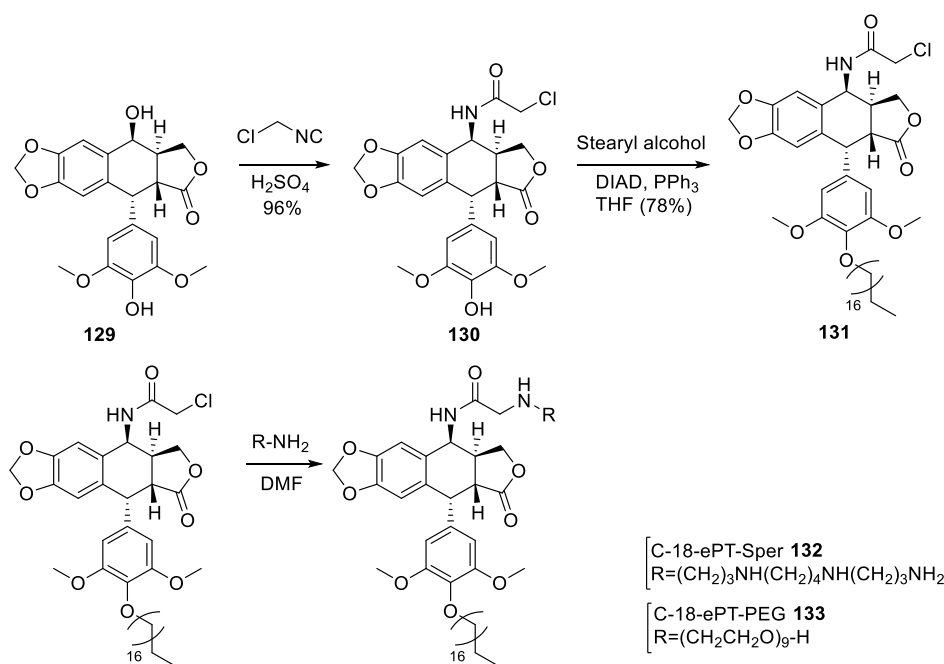
The chiral deoxy derivative AAL(*S*), related to the FDA-approved drug FTY720, has demonstrated the ability to inhibit proliferation and promote apoptosis in various cancer cell lines, possibly through activation of protein phosphatase 2A (PP2A). Jonathan C. Morris and co-workers reported the preparation of novel cytotoxic derivatives of the AAL(*S*)₁ des-hydroxy analog

(**126**), an achiral amine, using a Ritter reaction-based strategy [91].

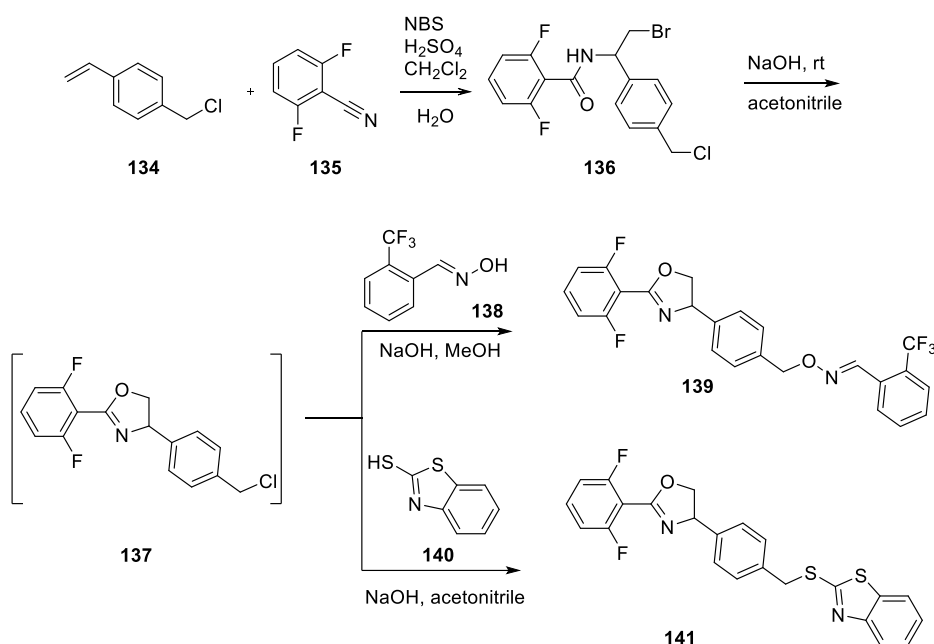
The synthetic approach involved the treatment of a readily accessible alkene (**126**) with potassium cyanide in a mixture of sulfuric acid and acetic acid at 0 °C [Scheme 22]. Subsequent acidic hydrolysis of (**127**) using 6 M aqueous hydrochloric acid furnished compound (**128**).

Biological studies demonstrated that analogue (**128**) displayed significantly enhanced cytotoxic activity in an acute myeloid leukemia model, primarily through activation of protein phosphatase 2A (PP2A). Furthermore, this compound exhibited significant antiproliferative and pro-apoptotic activity in multiple cancer cell lines, highlighting its therapeutic potential as an anticancer agent.

Gravel, Doris, and co-workers developed an efficient synthetic approach to generate amphiphilic drug conjugates with micelle formation capacity based on the biologically active 4'-demethylepipodophyllotoxin scaffold [92]. From this starting material (**129**), two amphiphilic derivatives-C18-ePT-Sper (**132**) and C18-ePT-PEG (**133**) were synthesized [Scheme 23]. A crucial transformation in the synthetic sequence was a Ritter reaction at the C-4 position of 4'-demethylepipodophyllotoxin (**129**).



Scheme 23. Synthesis of C-18-ePT-Sper3 (**132**) and C-18-ePT-PEG 4 (**133**) amphiphiles.



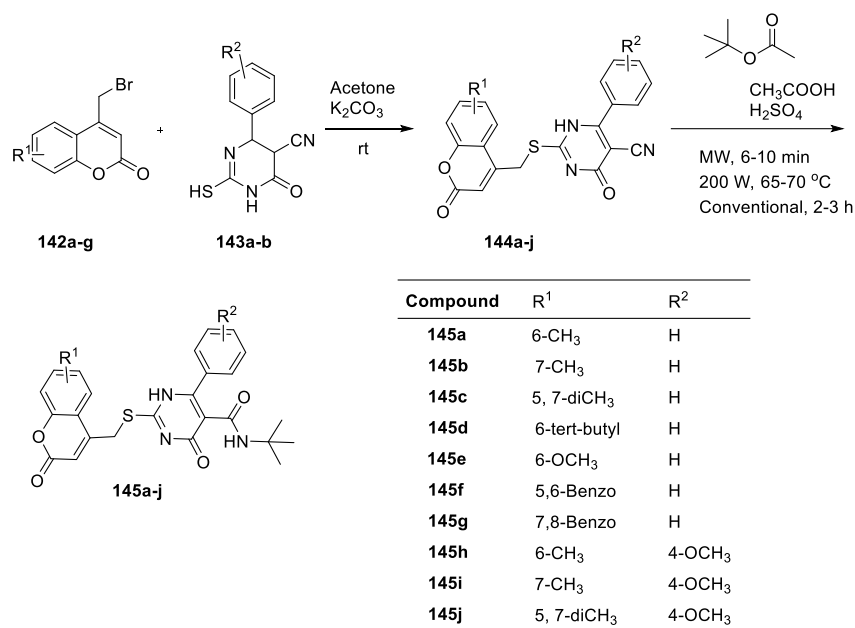
Scheme 24. Synthesis of compounds **139** and **141**.

Reaction with chloroacetonitrile in the presence of substoichiometric sulfuric acid provided the corresponding chloroacetamide intermediate (**130**). The chloroacetamide derivative (**130**) was then subjected to a Mitsunobu reaction with stearyl alcohol (C18), introducing a hydrophobic alkyl chain to produce the compound (**131**). Subsequent nucleophilic substitution of the chlorine atom with spermine provided the amphiphilic conjugate C18-ePT-Sper (**132**). In an analogous manner, the reaction of the chlorinated precursor (**131**) with PEG400-NH₂ produced the PEGylated amphiphile C18-ePT-PEG (**133**).

Biological studies demonstrated that spermine-containing epipodophyllotoxin micelles showed improved cellular internalization in PTS (+) cells and enhanced cytotoxic effects

relative to control micellar systems. These findings underscore the strategic value of the Ritter reaction for site-selective functionalization of complex natural product frameworks and for the development of self-assembling amphiphilic drug conjugates with superior biological activity.

Qingmin Wang and co-workers developed an abbreviated and more efficient synthetic pathway to the acaricidal candidates FET-II-L (**139**) and NK-12 (**141**) [93]. Their strategy employed an aminohalogenation approach based on a Ritter-type transformation, enabling conversion of intermediates (**134**) and (**135**) to target compounds in only two steps (Scheme 24). Compared with previously reported methods, this protocol eliminates the need for isolation of intermediates, involves fewer synthetic steps, and simplifies operational



Scheme 25. Synthetic route to synthesize the title compounds (145a-j).

procedures, which resulted in substantially enhanced overall yields. Further optimizations in reaction conditions resulted in overall yields of 71% and 69% for compounds **139** and **141**, respectively, with high HPLC purities of 96% and 98%. These streamlined reaction conditions possess strong potential for large-scale production. β_2 -agonists, muscarinic acetylcholine receptor (mAChR) antagonists, phosphodiesterase-4 (PDE4) inhibitors, and inhaled corticosteroids (ICS) represent the principal classes of drugs used in the pharmacological management of asthma and chronic obstructive pulmonary disease [94,95].

Joshi and coworkers described the microwave-assisted synthesis of a new series of *N*-tert-butyl-4-(4-substituted phenyl)-2-((substituted-2-oxo-2H-chromen-4-yl)methylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxamide derivatives (**145a-j**) [96]. These novel coumarin-pyrimidine amide hybrids were prepared *via* a Ritter reaction protocol and subsequently evaluated for their *in vitro* antibacterial and anti-inflammatory activities.

The synthetic route involved reacting coumarin-dihydropyrimidine carbonitriles (**144a-j**) with *tert*-butyl acetate in the presence of sulfuric acid and acetic acid at room temperature, affording the corresponding *tert*-butyl amide derivatives (**144a-j**) (Scheme 25). *Tert*-Butyl acetate was selected as the *tert*-butyl cation source instead of tertiary alcohols or olefins, as its combination with acetic acid provides an internal buffering system for isobutylene formation, thereby minimizing uncontrolled gas evolution and improving reaction safety. Biological screening revealed promising pharmacological properties. Compound **145f** demonstrated notable antibacterial activity against the Gram-positive strain *Staphylococcus aureus*, exhibiting a minimum inhibitory concentration (MIC) of 2.5 $\mu\text{g/mL}$, which was superior to the reference drug ciprofloxacin (MIC = 10 $\mu\text{g/mL}$). Furthermore, compound **145c** shows significant anti-inflammatory activity as it inhibited heat-induced protein denaturation by 75.42% at a concentration of 31.25 $\mu\text{g/mL}$, which is markedly higher activity compared to that of a standard drug aceclofenac.

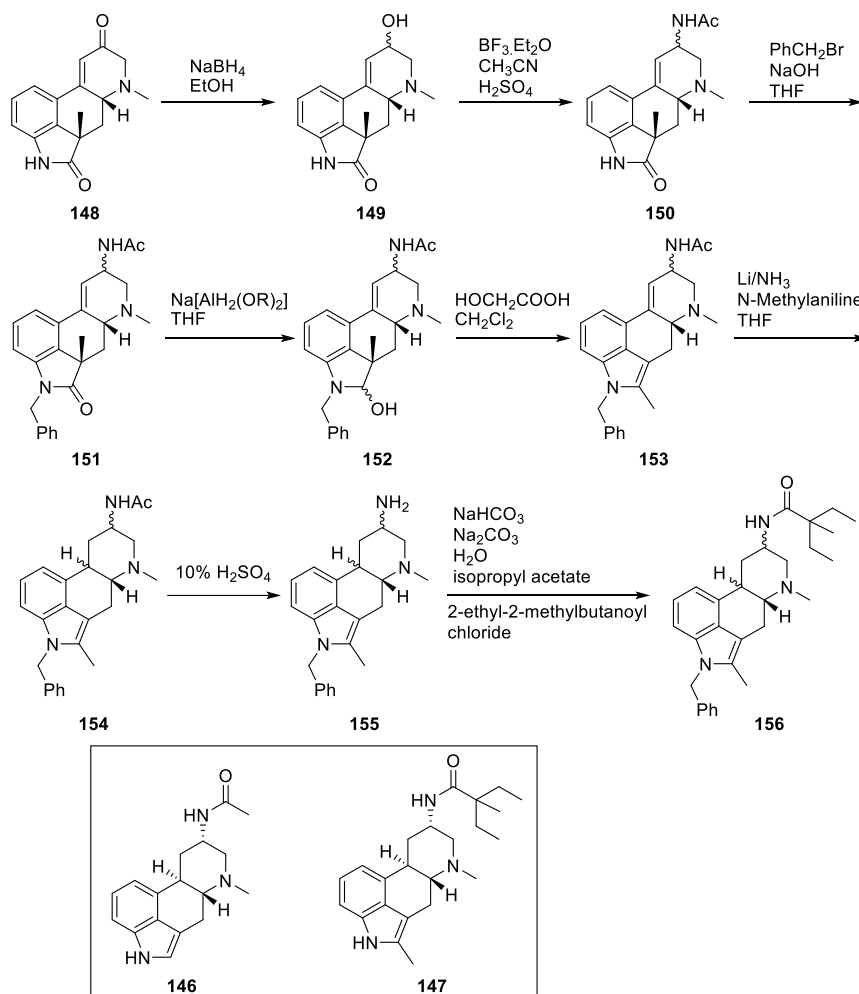
2.2. Ritter reactions using Boron trifluoride etherate (BF₃·Et₂O)

An industrial method for the stereoselective total synthesis of racemic 2,6-dimethylergolin-8a-amine derivative (**147**), originally obtained by semi-synthetic modification of lysergic acid, has previously been described [97].

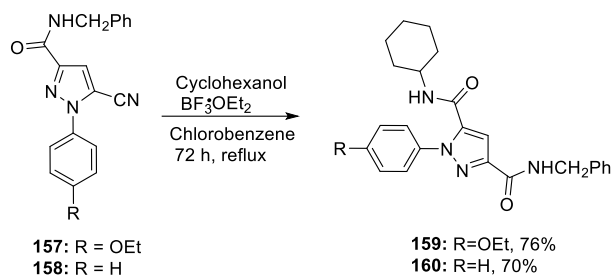
A stereoselective total synthesis of the racemic 2,6-dimethylergolin-8a-amine derivative (**153**) was developed by Waldvogel E. and co-workers [98]. Reduction of enone (**148**) with NaBH₄ produced a mixture of epimeric allylic alcohols (**149**) (8 β /8 α) in the ratio 7:3 (Scheme 26). Conversion of this mixture through a Ritter reaction using H₂SO₄ and BF₃·Et₂O in acetonitrile yielded stereoselective 8a-amide (**150**) in high yield. Subsequent benzylation, reduction, rearrangement and Birch reduction gave the transfused ergoline derivative (**154**), which upon hydrolysis gave amine (**155**). The final acylation with 2-ethyl-2-methylbutanoyl chloride produced the racemic target compound **153**. This approach could also be applied to the total synthesis of the biologically active (5R, 8S,10R)-enantiomer (**147**).

Fung Fuh Wong and colleagues reported a convenient and efficient synthetic route to pyrazole-based dihydroorotate dehydrogenase (DHODase) inhibitors starting from 3-aryl-4-cyanosynone (**159**) and (**160**) (Scheme 27) [99]. The Ritter reaction was tried by treating compounds **157** and **158** with cyclohexanol in refluxing formic acid; however, the resultant reaction mixture was complex and only provided a small amount of the expected *N*-alkylation products. Therefore, the Ritter reaction was modified by using boron trifluoride as an acid catalyst and cyclohexanol as an aprotic and nonaqueous solvent.

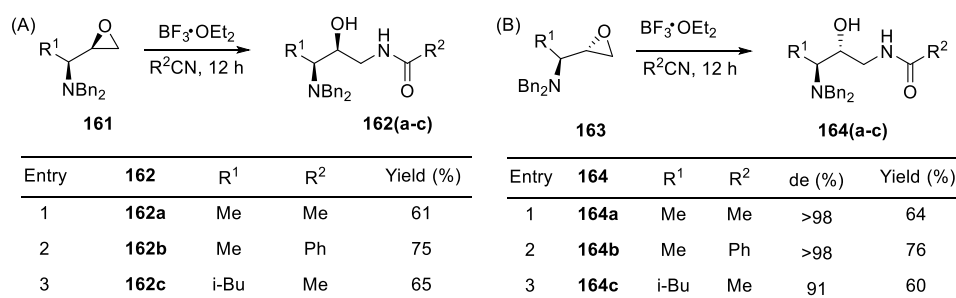
The (2R,3S)-1,3-diaminoalkan-2-ol framework is present in several peptidomimetic inhibitors of HIV-1 protease used for the treatment of AIDS [100-104]. Moreover, acylated amine groups workers showed that 1,3-diaminoalkan-2-ols could be efficiently prepared *via* Ritter-type ring opening of amino epoxides with nitriles [105]. In this study, Concellón and coauthors established a straightforward and efficient method to synthesize trifluoromethyl-containing diamino alcohols (**165a-c**) and (**167a-c**) through the Ritter reaction of trifluoromethyl substituted amino epoxide (**161**) and (**163**) with nitriles using BF₃·Et₂O and trifluoroethanol (Scheme 28).



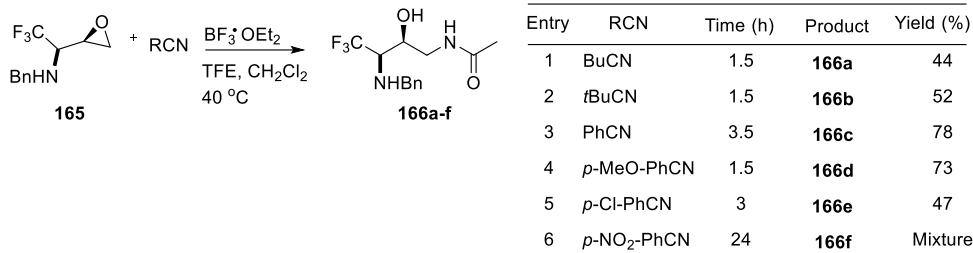
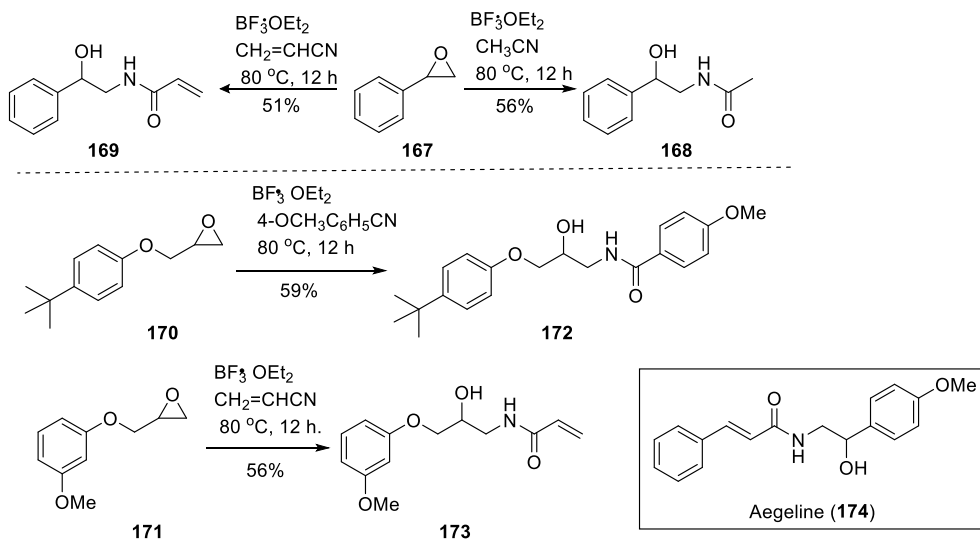
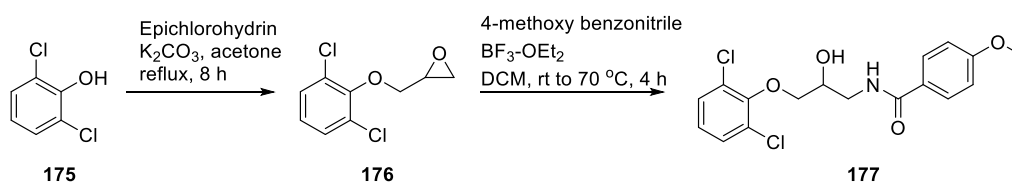
Scheme 26. A stereoselective total synthesis of the racemic 2,6-dimethylergolin-8a-amine derivative (**153**).



Scheme 27. Synthesis of pyrazole-based DHODase inhibitors **159** and **160**.



Scheme 28. Synthesis of (2*R*,3*S*)-1,3-diaminoalkan-2-ols (**162**) and (2*S*,3*S*)-1,3-diaminoalkan-2-ols (**164**).

Scheme 29. Synthesis of (2*R*,3*S*)-1,3-diaminoalkan-2-ols (**166a-f**).Scheme 30. Synthesis of *N*-acylated-1-amino-3-aryloxy-2-propanols (**168**), (**172**), (**173**) and structure of aegeline (**174**).Scheme 31. Synthesis of *N*-(2-hydroxy-3-phenoxypropyl)benzamide derivative (**177**).

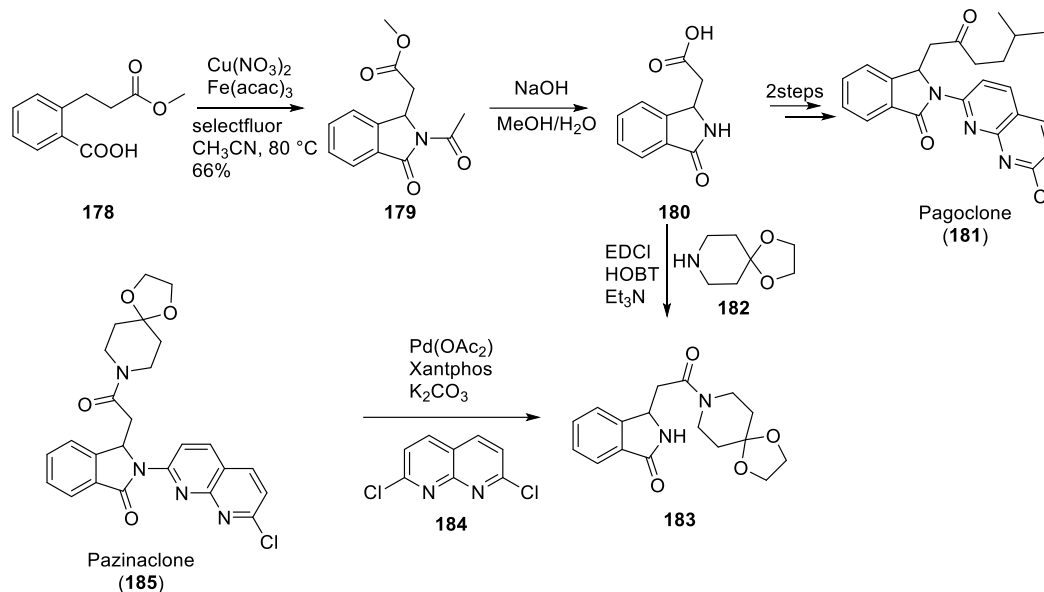
Benoit Crousse and coworkers investigated the effect of fluorinated alcohols on BF₃·Et₂O-mediated Ritter-type reactions (Scheme 29) [106]. Trifluoroethanol/BF₃·Et₂O system effectively promoted the ring opening of fluorinated epoxide (**165**) in the presence of various nitriles, providing access to (2*R*,3*S*)-1,3-diaminoalkan-2-ols (**166a-f**) commonly found in protease inhibitors. Hydroxylethylamine units, which are important pharmacophores in many biologically active molecules, can be readily synthesized through epoxide ring-opening reactions, allowing the generation of structurally diverse compounds.

Aegeline (**174**), a naturally occurring *N*-acyl-1-amino-2-alcohol, served as structural inspiration for this study. Previous work by the same research group had shown that aegeline analogs possessed promising antidyslipidemic and antioxidant activities in the Triton-induced hyperlipidemia model [107,108].

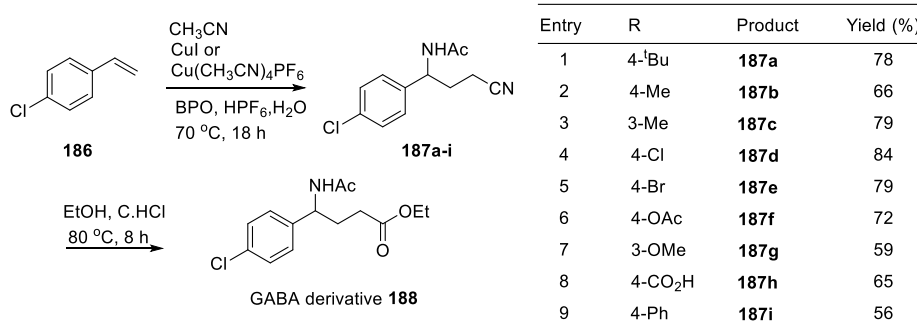
Based on these findings, Satinath Sarkar *et al.* reported the synthesis of a new series of *N*-acyl-1-amino-2-alcohol derivatives through a Ritter reaction strategy and systematically evaluated their lipid lowering potential, effects on lipoprotein triglyceride levels, lipoprotein lipase (LPL) activity, antioxidant capacity, and LDL oxidation [109]. Synthesized compounds

included *N*-acylated-1-amino-2-phenylethanol (**168**) and (**169**) and *N*-acylated-1-amino-3-aryloxypropanol derivatives (**172**) and (**173**) (Scheme 30). These molecules were evaluated for their *in vivo* antihyperlipidemic activity using a Triton-induced hyperlipidemia model, as well as for their ability to inhibit LDL oxidation and exhibit antioxidant properties. Among the synthesized compounds, derivatives (**169**, **172** and **173**) demonstrated significant lipid-lowering effects along with notable antioxidant and LDL oxidation inhibitory activity, showing comparable efficacy to a marketed antidyslipidemic drug.

Anil N. Gaikwad and co-workers reported the synthesis of aegeline-inspired derivatives that incorporate relevant pharmacophoric features [110]. The target *N*-acylated 1-amino-3-aryloxy-2-propanols were prepared using a Ritter reaction strategy. Initially, the substituted phenol (**175**) reacted with epichlorohydrin in acetone under basic conditions to generate the corresponding oxirane intermediate (**176**) (Scheme 31). Subsequently, these epoxides were subjected to ring-opening reactions with various benzonitriles in the presence of boron trifluoride etherate (BF₃·OEt₂), affording *N*-(2-hydroxy-3-phenoxypropyl)benzamide derivative (**177**) in good yields.



Scheme 32. Synthesis of the anxiolytic drugs pagoclone (**181**) and pazinaclone (**183**).



Scheme 33. Copper-catalyzed carboamination of terminal vinylarenes to afford the corresponding products (**187a-i**) and the synthesis of the GABA derivative (**188**).

Among the synthesized compounds, the derivative (**177**) demonstrated promising biological activity. The results supported the potential therapeutic relevance of β_3 -adrenergic receptor ($\beta_3\text{AR}$) agonists in the management of insulin resistance and type 2 diabetes, highlighting the value of the Ritter reaction in the construction of biologically active aegeline analogs. Integrating two pharmacologically significant scaffolds, coumarins and pyrimidines, within a single molecular framework may lead to enhanced or synergistic biological activity.

2.3. Copper-catalyzed Ritter reactions

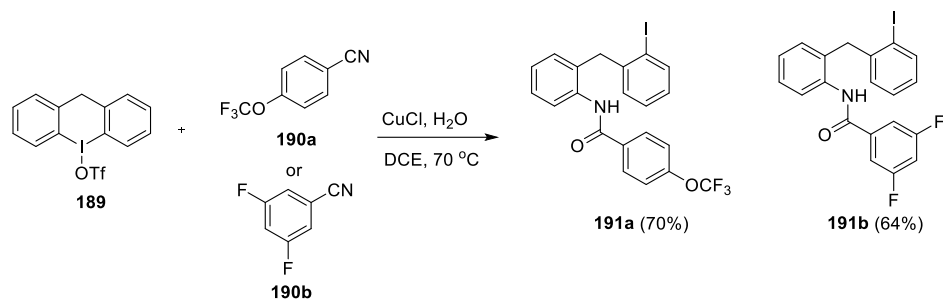
Ritter reactions proceed *via* formation of a carbocation intermediate, which is subsequently captured by a nitrile. An intramolecular Ritter reaction approach was employed for oxidative C–H amination [111]. Wei He and coworkers developed a copper/iron co-catalyzed Ritter-type C–H activation and amination protocol that enables efficient and selective intermolecular functionalization of benzylic C–H bonds [112]. Compound **179** was synthesized by using Cu/Fe salts as the co-catalyst and Selectfluor as the oxidant *via* Ritter-type reaction (Scheme 32). This methodology operates under straightforward reaction conditions, utilizes readily accessible reagents, and exhibits broad substrate compatibility. One pot ester hydrolysis and *N*-acetyl deprotection offered intermediate (**180**), which provides a practical route to structurally

diverse nitrogen-containing heterocycles including two anxiolytic drugs Pagoclone (**181**) and Pazinaclone (**185**).

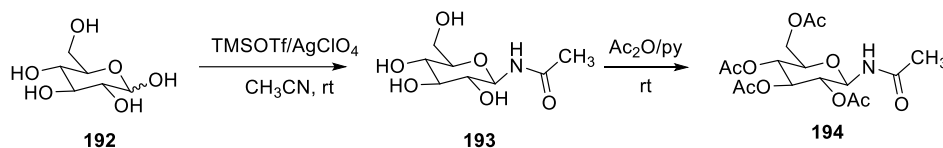
γ -Aminobutyric acid (GABA) serves as the main inhibitory neurotransmitter in the mammalian central nervous system [113–115]. A variety of structurally related GABA analogs have been developed for clinical use, particularly in the treatment and treatment of neurodegenerative and neurological disorders [116,117]. A copper-catalyzed carboamination strategy for alkenes was introduced, providing an efficient approach to assemble the core framework of γ -aminobutyric acid (GABA) derivatives directly from simple alkene substrates (Scheme 33) [118]. In this transformation, nitriles function as dual carbon and nitrogen sources, enabling simultaneous difunctionalization of the alkene.

Jianjun Chan and co-workers developed Ritter reaction conditions for the synthesis of diarylmethane amide derivatives through the copper-catalyzed reaction of cyclic diaryliodonium salts with nitriles [119]. Copper chloride (CuCl) catalyzed reaction conditions allowed the efficient acylation of diaryliodonium intermediates with a variety of commercially available and relatively unreactive nitriles, providing a practical route to iodo-functionalized diarylmethane amides (Scheme 34).

The reaction exhibited a broad substrate scope. Benzodioxine carbonitrile and heterocyclic nitriles such as 3-cyanothiophene, 2-furonitrile, and pyrrolenitrile provided the desired amide products in good yields (typically 67–70%).



Scheme 34. Copper-catalyzed selective arylation of nitriles.

Scheme 35. Preparation of *N*-acyl-1-deoxy-β-D-glucopyranosyl-amines and their derivatives.

On the contrary, the cyanopyridine derivatives failed to undergo the transformation, likely because of their electron-deficient nature. Both aliphatic nitriles (*eg.* acetonitrile and butyronitrile) and aryl substituted nitriles (such as 2-phenylacetonitrile and related homologues) were compatible, delivering the corresponding amides in moderate to good yields (52 to 69%). Notably, increasing the alkyl spacer length between the phenyl group and the nitrile functionality resulted in lower yields. Alicyclic nitriles also performed well, providing the desired products in satisfactory yields (60–67%). Biological studies of the selected derivatives show promising neuroprotective activity. Compound **191a** demonstrated strong neuroprotective effects against glutamate-induced cytotoxicity in HT-22 cells, while compound **191b** showed moderate to significant antiproliferative activity across multiple cancer cell lines. Overall, this copper-catalyzed Ritter reaction protocol offers convenient access to structurally novel diarylmethane amides with potential neuroprotective and anticancer properties.

2.4. Ritter reactions with miscellaneous reagents

Zerong Daniel Wang and co-workers reported the application of the Ritter reaction for the synthesis of *N*-glycosidic bond-linked, nonionic carbohydrate-based surfactants (**194**) using carbohydrates and nitriles in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and silver perchlorate (AgClO₄) under high-speed mechanical shaking conditions (Scheme 35) [120]. This study introduced a novel class of non-ionic carbohydrate-derived surfactants that possess structurally attractive features and environmentally favorable properties. These surfactants can be efficiently synthesized through a mechanochemically assisted Ritter reaction between unprotected carbohydrates and long-chain nitriles, eliminating the need for prior protection or activation of functional groups.

Thorsten Bach and Philipp Rubenbauer reported an acid-catalyzed Ritter reaction of secondary chiral benzylic alcohols, providing a diastereoselective method for the synthesis of chiral amides [121]. These chiral amides are valuable intermediates for the preparation of important compounds such as chiral 1,2-diamines and β-amino acids. A stereoselective approach was developed to convert chiral benzylic alcohols into the corresponding benzylic amines through an S_N1-type substitution mechanism. In this process, the stereogenic center

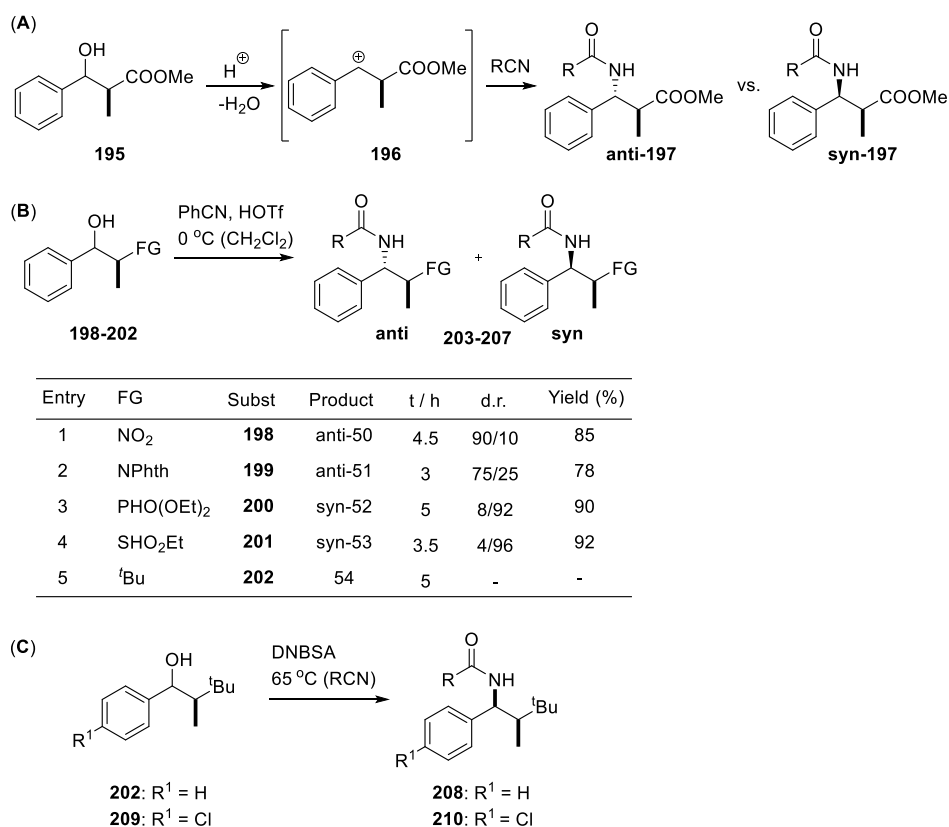
located adjacent to the carbocation intermediate plays a key role in controlling the stereochemical outcome of the reaction.

Preliminary investigations were carried out using the β-hydroxy ester (**195**) [122,123], which was expected to undergo reaction through intermediate carbocation (**196**), which ultimately led to the formation of the corresponding amides (**197**) (Scheme 36A). Systematic experimentation revealed that trifluoromethanesulfonic acid (HOTf) in dichloromethane efficiently catalyzes transformation, leading to the formation of target amides (**203–207**) in high yields (Scheme 36B). However, the tert-butyl-substituted alcohol (**202**) did not undergo reaction with benzonitrile under the established conditions (Scheme 36B, entry 5). Instead, a significant decomposition was observed, likely due to the presence of the strong Brønsted acid. To address this issue, milder reaction conditions were investigated. It was subsequently found that dinitrobenzenesulfonic acid (DNBSA), as previously reported by Sanz *et al.* [124], acts as an effective catalyst for tert-butyl-containing substrates (Scheme 36C).

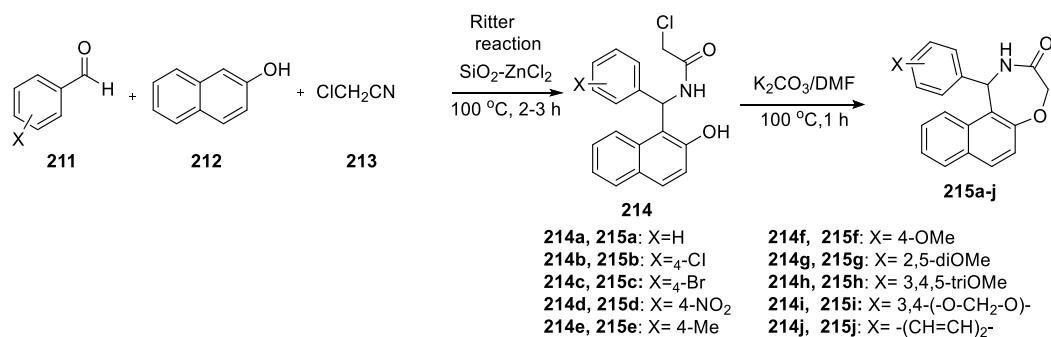
Soliman *et al.* reported one-pot, three-component condensation reaction involving various aldehydes, chloroacetonitrile (**213**), and β-naphthol (**212**) under solvent-free conditions [125].

Silica-supported zinc chloride (SiO₂-ZnCl₂, “silzic”) was used as a reusable heterogeneous catalyst and the reaction proceeds *via* a Ritter-type mechanism to afford a library of amidochloroalkynaphthol derivatives (Scheme 37). Subsequent cyclization of intermediates (**214**) using potassium carbonate in DMF at 100 °C afforded 1-aryl-1,2-dihydro-naphtho[1,2-*f*]oxazepin-3(4*H*)-one derivatives (naphthoxazepinones) (**215a–j**). These heterocyclic compounds were evaluated for their anticancer activity. In particular, compounds **215c** and **215i** exhibited significant cytotoxicity compared to that of doxorubicin as the reference drug. Compound **215c** showed IC₅₀ values of 76.9 and 56.1 μM against liver and colon cancer cell lines, respectively, while compound **215i** showed IC₅₀ values of 77.2 μM (liver) and 52.3 μM (colon). Other compounds in the series exhibited comparatively lower anticancer activity.

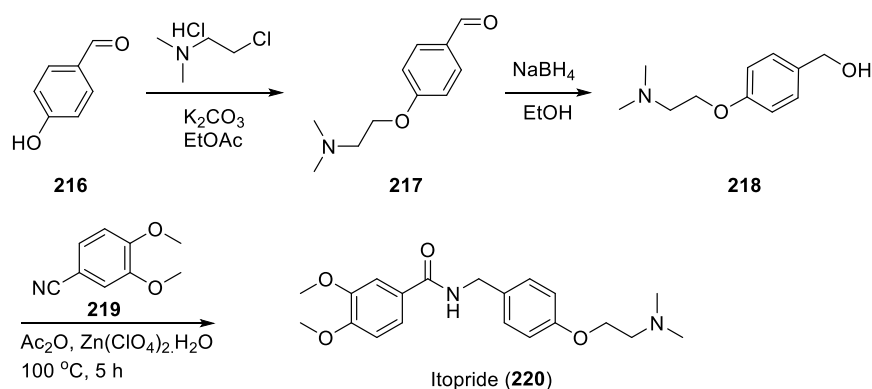
Ji and co-workers reported a novel Zn(ClO₄)₂·H₂O catalyzed one-pot Ritter-type protocol for the synthesis of a series of amide derivatives [126]. This methodology provides a straightforward and efficient route for synthesis of structurally diverse amides under relatively mild reaction conditions.



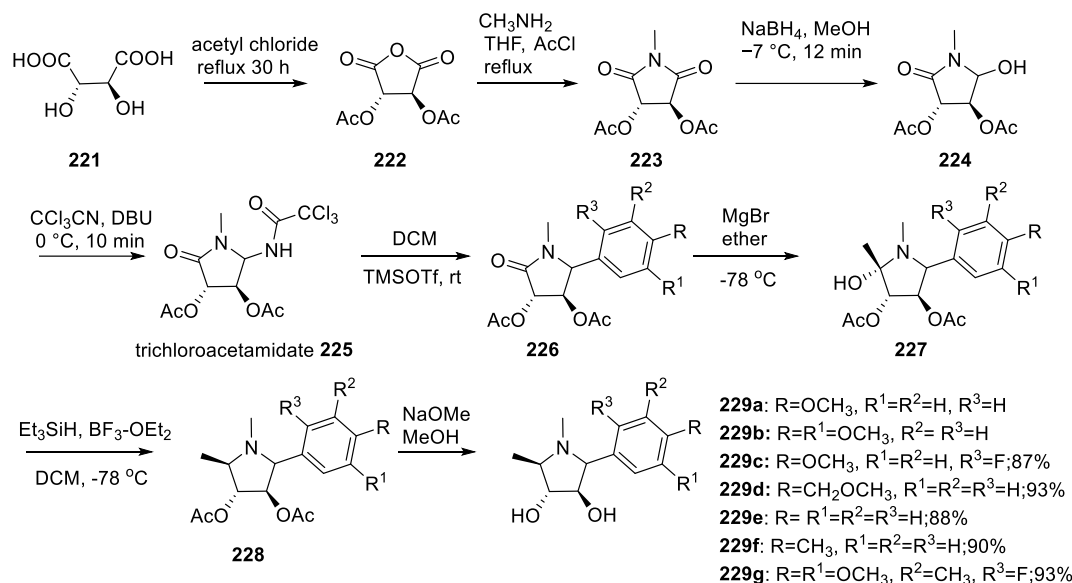
Scheme 36. (A) Acid-catalysed diastereoselective reaction of β -hydroxyester **195** with various nitriles to give amides **197**, (B) Ritter reaction of alcohols **198–202** with benzonitrile promoted by HOTf, (C) Dinitrobenzenesulfonic acid (DNBSA) catalysed Ritter reaction of alcohol **203** and **209**.



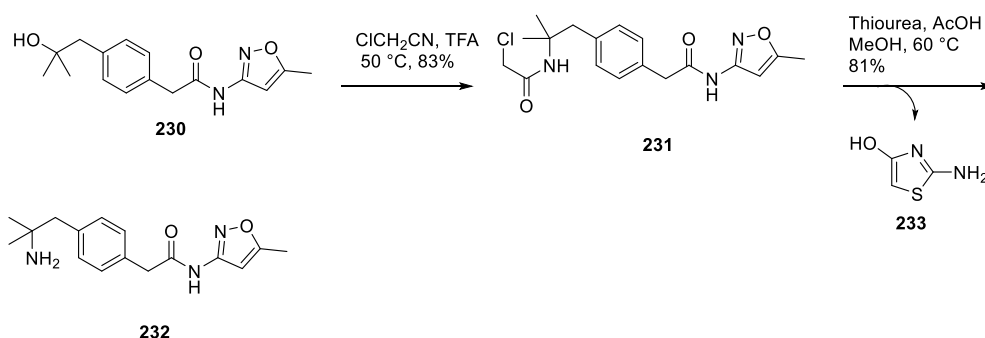
Scheme 37. Synthesis of 1-aryl-1,2-dihydronaphtho[1,2-f][1,4]oxazepin-3(4H)-one derivatives (naphthoxazepinones) (**214a–j**).



Scheme 38. Synthesis of itopride (**220**).



Scheme 39. Synthesis of (-)-codonopsinine (229a), (-)-codonopsine (229b), and a series of codonopsinine analogues (229c-g).



Scheme 40. Preparation of the key amine intermediate 232.

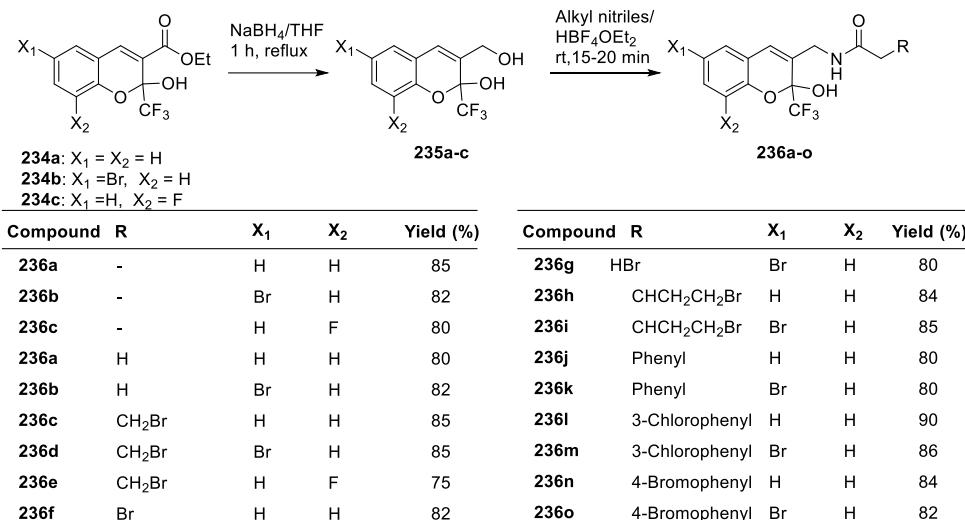
The practical applicability of this synthetic protocol was demonstrated in the synthesis of itopride (220) (Scheme 38). Alcohol (218) was reacted with acetic anhydride and aryl nitrile (219) under optimized catalytic reaction conditions to obtain Itopride (220). This example highlights the potential of the developed Ritter reaction conditions in the synthesis of pharmaceutically relevant compounds.

Over the past few decades, five-member heterocyclic alkaloids, particularly polyhydroxylated pyrrolidines known as iminosugars and their derivatives, have emerged as important bioactive compounds due to their wide range of pharmacological effects, including antimicrobial, antiviral, antidiabetic, and α -glucosidase inhibitory activities [127-130]. Ahmed O. H. El-Nezhawy and co-workers described a straightforward and efficient synthetic route to (-)-codonopsinine (229a), (-)-codonopsine (229b), and a series of codonopsinine analogues (229c-g) [131]. Synthesis started from *D*-tartaric acid and involved the preparation of a crucial trichloroacetamidate intermediate (225), which was subsequently reacted with electron-rich carbon nucleophiles to construct the target molecules (Scheme 39). The key intermediate (225) was generated *via* a Ritter-type transformation. Specifically, treatment of the 5-hydroxypyrrolidinone derivative (224) with trichloroacetonitrile in the presence of the catalytic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded (3*R*,4*R*)-1-methyl-2-oxo-5-(2,2,2-trichloroacetamido)pyrrolidine-3,4-diyl diacetate (225).

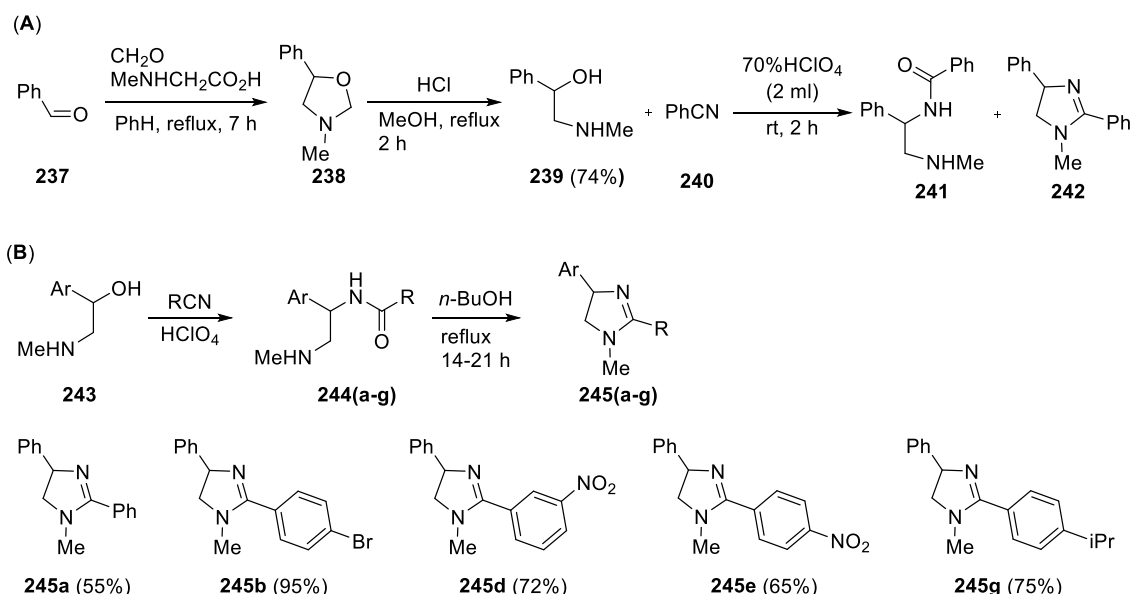
Pharmaceutical companies have progressed numerous β -3 agents into development for obesity and Type 2 diabetes [132-134], as well as for urinary incontinence [135,136].

Paul A. Bradley, Robert J. Carroll, and colleagues described the synthesis of two highly potent β -3-adrenergic receptor agonists. To support detailed pharmacological studies, these compounds needed to be prepared on a large scale, which was achieved through a shared key amine intermediate (232) [137]. The formation of the intermediate (232) involved a Ritter reaction as a critical step in the synthetic pathway (Scheme 40). Specifically, Ritter transformation was performed using a 2:1 mixture of trifluoroacetic acid (TFA) and chloroacetonitrile, applied in (233) and 12 molar equivalents, respectively, which efficiently produced intermediate (231) with excellent yield. The development of β -3-adrenergic receptor agonists has attracted considerable interest due to their therapeutic potential in the treatment of metabolic and related disorders, and the incorporation of the Ritter reaction provided an effective and scalable approach to accessing these biologically important compounds.

B. Narsaiah and coworkers reported the synthesis of a new series of amide-functionalized 2*H*-chromene derivatives [138]. The synthetic route began with ethyl-2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylate (234) [139], which was reduced using sodium borohydride in tetrahydrofuran at room temperature for 10 minutes, followed by reflux for one hour, to afford 3-(hydroxymethyl)-2-(trifluoromethyl)-2*H*-chromen-2-ol (235) (Scheme 41).



Scheme 41. Amide functionalized 2H-chromene derivatives.

Scheme 42. (A) Reaction of halostachnine (**239**) with benzonitrile (**240**) to obtain (**241**) and (**242**); (B) Cyclization to imidazoles and structures of 2,4-diarylimidazoles (**245a-g**).

The resulting alcohol (**235**) was subsequently subjected to a Ritter amidation reaction with various substituted acetonitriles in the presence of $\text{HBF}_4 \cdot \text{OEt}_2$ under solvent-free conditions. This protocol was further employed in the synthesis of a series of amide-functionalized 2H-chromene derivatives (**236a-o**) in excellent yields. Mechanistically, selective protonation of the primary hydroxyl group of (**235a-c**) by HBF_4 facilitated nucleophilic attack by the nitrile at the primary carbon, resulting in the formation of the series of corresponding amide products. Biological evaluation of the synthesized compounds revealed promising antimicrobial properties. Among the series compounds (**236g**) exhibited the most potent antimicrobial activities, minimum bactericidal concentration (MBC) and antibiofilm activities. Structure-activity relationship (SAR) analysis indicated that the presence of two bromine substituents at the sixth and *R* positions significantly increased biological activity.

Imidazoles and imidazolines form an important five membered nitrogen-containing heterocyclic skeleton widely found in natural products [140-142], medicinal plants, and

pharmaceutical compounds [143-149]. Smorodina A. A. and coworkers reported a three-step synthetic strategy to construct imidazole cores starting from aryloethanolamines [150]. A key transformation in this synthetic sequence is a perchloric acid-promoted Ritter reaction of halostachnine (**239**), which gives mixture of 2-amino-ethyl-1-benzamide (**241**) and 2,4-diphenylimidazoline (**242**) in 96:4 ratio (Scheme 42A). Subsequently, these intermediates were converted into 4-arylimidazolines via thermal cyclization by heating in *n*-butanol, affording the corresponding products. The practicality of the developed method was further demonstrated through a one-pot synthesis of 2,4-diarylimidazoles (**245a-g**) from readily available precursors, including aromatic aldehydes, sarcosine, paraformaldehyde and benzonitriles, affording the desired heterocycles in overall yields of 42-49% (Scheme 42B). The reported approach provides an efficient and versatile route for the synthesis of biologically significant scaffolds.

Table 1. Summary of Ritter reactions.

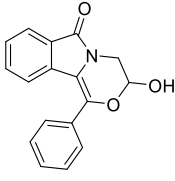
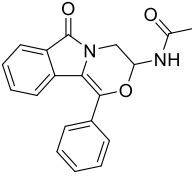
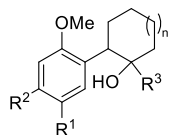
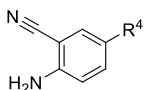
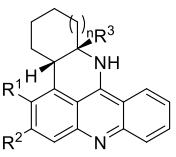
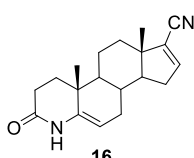
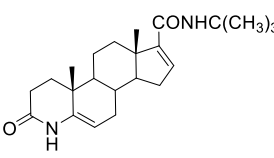
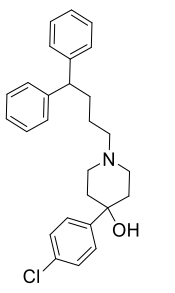
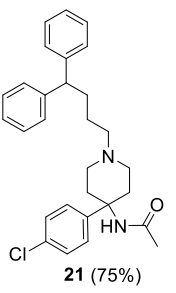
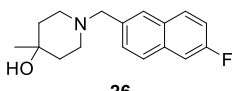
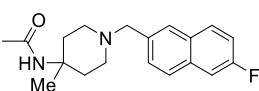
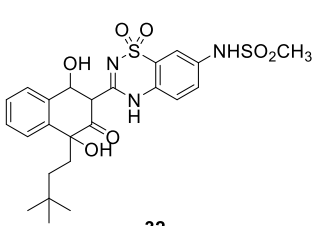
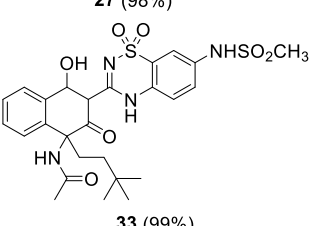
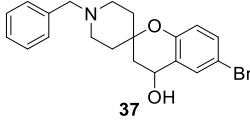
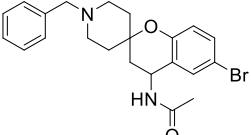
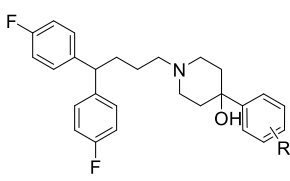
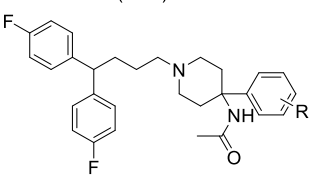
Scheme no	Reactant	Alkyne	Product (yield %)	Reference
Ritter reactions using sulphuric acid				
1	 6	ACN	 7 (68%)	[8]
2	 8 R¹, R² = H, Me, R³ = Me, Pr; n = 0, 1	 R⁴ = H: 9a R⁴ = OMe: 9b R⁴ = NO₂: 9c R⁴ = Me: 9d	 Rac 10 (29-56%)	[9]
3	<i>tert</i> Butanol	 16	 17 (80%)	[10]
4	 20	ACN	 21 (75%)	[18]
5	 26	ACN	 27 (98%)	[25]
6	 32	ACN	 33 (99%)	[28]
7	 37	ACN	 38 (98%)	[34]
8	 43 (a-g)	ACN	 44 (a-g)	[42]

Table 1. Continued.

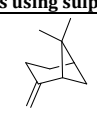
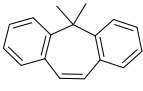
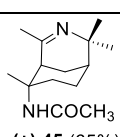
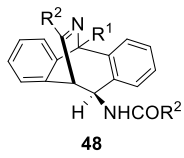
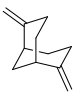
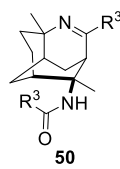
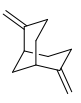
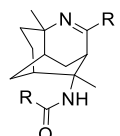
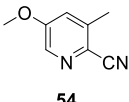
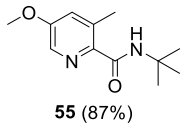
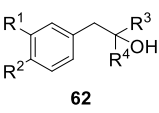
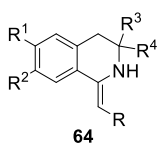
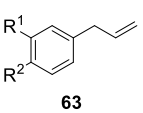
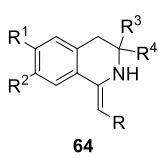
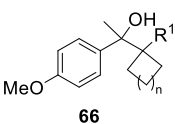
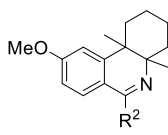
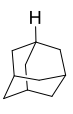
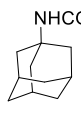
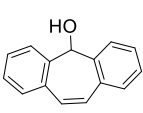
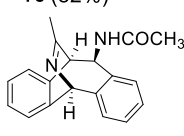
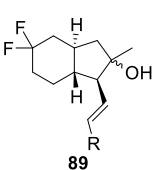
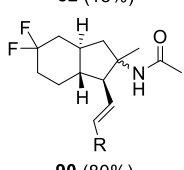
Scheme no	Reactant	Alkyne	Product (yield %)	Reference
Ritter reactions using sulphuric acid				
9	 (-) β -pinene  47	ACN	 NHCOCH ₃ (+) 45 (65%)	[46]
		R ² CN	 48	
	 49	R ³ CN	 50	
10	 49	ACN EtCN ClCH ₂ CN	 51a: R = CH ₃ (60%) 51b: R = CH ₃ CH ₂ (66%) 51c: R = ClCH ₂ (52%)	[48]
11	tert Butanol	 54	 55 (87%)	[54]
12	 62	RCH ₂ CN	 64	[56]
	 63	RCH ₂ CN	 64	[57]
13	 66	R ² CN	 72(a-f) (43-47%)	[60]
14	 77	ACN	 78 (82%)	[68]
15	 81	ACN	 82 (18%)	[69]
16	 89	ACN	 90 (80%)	[74]

Table 1. Continued.

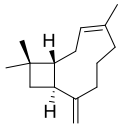
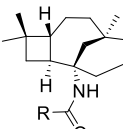
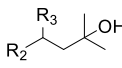
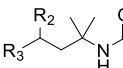
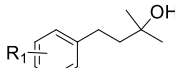
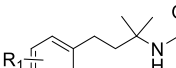
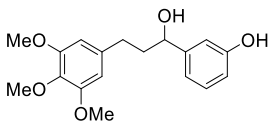
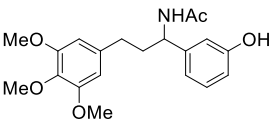
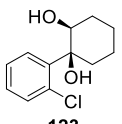
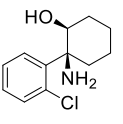
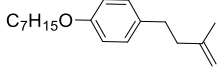
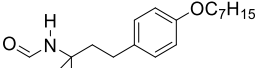
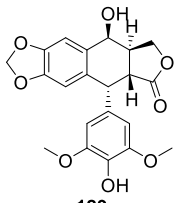
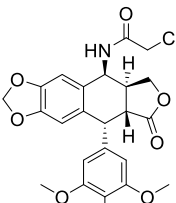
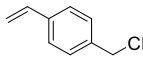
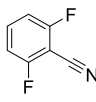
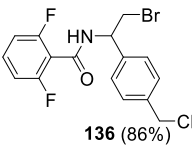
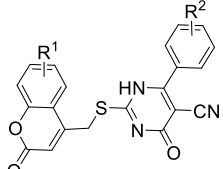
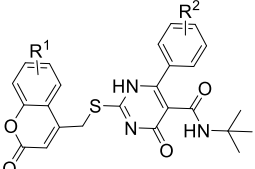
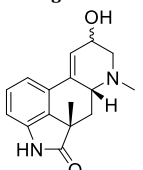
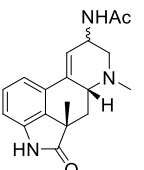
Scheme no	Reactant	Alkyne	Product (yield %)	Reference
Ritter reactions using sulphuric acid				
17	 92	RCN	 93 (1-63%)	[75]
18	 108a-h	ACN	 109(a-h) (70-80%)	[79]
19	 113	ACN	 114a-j (70-80%)	[84]
20	 117	ACN	 118 (73%)	[85]
21	 123	NaCN/ACN	 124 (47%)	[90]
22	 126	KCN	 127 (97%)	[91]
23	 129	ClCH ₂ CN	 130 (96%)	[92]
24	 134	 135	 136 (86%)	[93]
25	<i>tert</i> Butyl acetate	 144a-j	 145(a-j) (55-71%)	[96]
Ritter reactions using Boron trifluoride-etherate (BF₃·Et₂O)				
26	 149	ACN	 150 (84%)	[98]

Table 1. Continued.

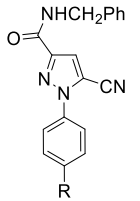
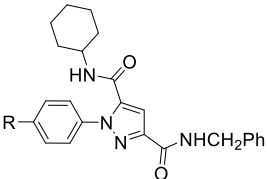
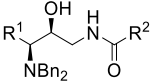
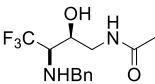
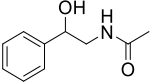
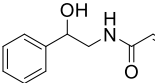
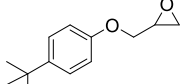
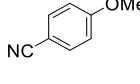
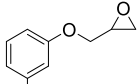
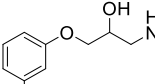
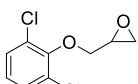
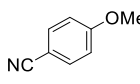
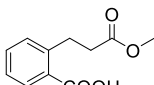
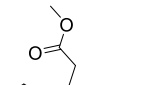
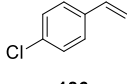
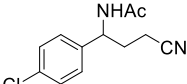
Scheme no	Reactant	Alkyne	Product (yield %)	Reference
Ritter reactions using Boron trifluoride-etherate (BF₃·Et₂O)				
27	Cyclohexanol	 157: R = OEt 158: R = H	 159: R = OEt (76%) 160: R = H (70%)	[99]
28	 161	R ² CN	 162(a-c) (61-75%)	[105]
29			 166(a-f) (44-78%)	[106]
30	 167	ACN	 168 (56%)	[109]
		CH ₂ =CHCN	 169 (51%)	
	 170	 172 (59%)		
	 171	CH ₂ =CHCN	 173 (56%)	
31	 176	 177		[110]
Copper catalyzed Ritter reactions				
32	 178	CH ₃ CN Cu(NO ₃) ₂ Fe(acac) ₃ Selectfluor	 179 (66%)	[112]
33	 186	CH ₃ CN CuI or Cu(CH ₃ CN) ₄ PF ₆ BPO, HPF ₆ , H ₂ O	 187(a-i) (56-84%)	[118]

Table 1. Continued.

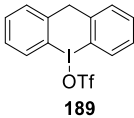
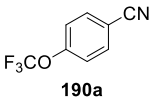
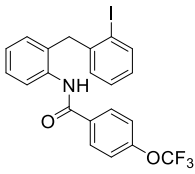
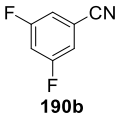
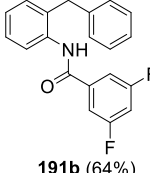
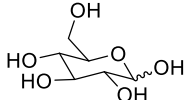
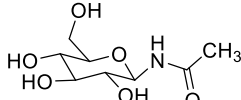
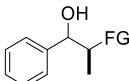
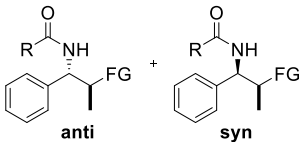
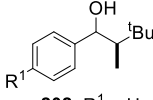
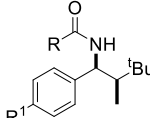
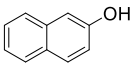
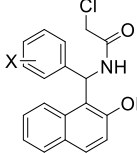
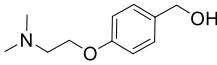
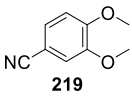
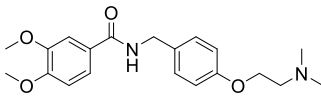
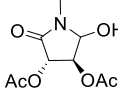
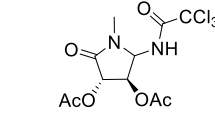
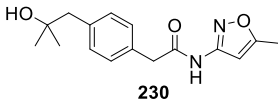
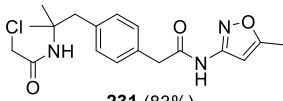
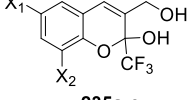
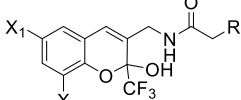
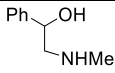
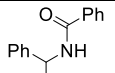
Scheme no	Reactant	Alkyne	Product (yield %)	Reference
Copper catalyzed Ritter reactions				
34	 189	 190a CuCl	 191a (70%)	[119]
		 190b CuCl	 191b (64%)	
Ritter reactions with miscellaneous reagents				
35	 192	CH ₃ CN TMSOTf AgClO ₄	 193 (86%)	[120]
36	 198-202	PhCN, HOTf	 203-207 (78-92%)	[121]
	 202 : R ¹ = H 208 : R ¹ = Cl	RCN DNBSA	 207 : R ¹ = H (69%) 209 : R ¹ = Cl (84%)	
37	 211 +  212	ClCH ₂ CN SiO ₂ -ZnCl ₂	 214(a-j) (65-83%)	[125]
38	 218	 219 Ac ₂ O Zn(ClO ₄) ₂ ·H ₂ O	 Itopride (220)	[126]
39	 224	CCl ₃ CN DBU	 trichloroacetamide 225 (72%)	[131]
40	 230	ClCH ₂ CN TFA	 231 (83%)	[137]
41	 235a-c	Alkyl nitriles HBF ₄ ·OEt ₂	 236(a-o) (80-90%)	[138]

Table 1. Continued.

Scheme no	Reactant	Alkyne	Product (yield %)	Reference
Ritter reactions with miscellaneous reagents				
42	 239	PhCN 70% HClO ₄	 241 (81%)	[150]

3. Summary of Ritter reaction conditions

Ritter reactions covered in this review are summarized below (Table 1). Based on acids and other catalysis used in Ritter reactions, these are broadly classified into (i) sulfuric acid-mediated, (ii) boron trifluoride-mediated, (iii) Cu catalysed and (iv) miscellaneous Ritter reactions in which trifluoroacetic acid (TFA), triflic acid (TfOH), etc. are used.

4. Conclusions

Recent advances in the Ritter reaction conditions have been covered in this review. Applications of these modified Ritter reactions for the synthesis of different classes of biologically active molecules including heterocyclic compounds, cyclic molecules, steroids, fused cyclic rings, etc. are described. A key role of the Ritter reaction in multistep synthesis has been highlighted. The biological activity of synthesized compounds is also covered. We strongly believe that the Ritter reaction has significant unexplored potential for the synthesis of novel and structurally complex molecules across diverse classes of organic compounds. Further advancements in Ritter reaction conditions could lead to broader applications of this method.

Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered to.

CRediT authorship contribution statement

Conceptualization: Reshma Bhanudas Shevale; Writing - Original Draft: Reshma Bhanudas Shevale; Writing, Review and Editing: Reshma Bhanudas Shevale and Smita Ravindra Waghmare; Supervision: Smita Ravindra Waghmare.

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