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REVIEW ARTICLE **OPEN ACCESS**

Spiropiperidine Derivatives in Pharmaceutical Drugs: A Review on Synthesis and Biological Activity

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ABSTRACT
Spiropiperidineare found beneficial and are mandatory part of some drugs. Thus this review on the synthesis and biological activity is written with special emphasis on medicines with a spiropiperidine scaffold from recent years. Spiropiperidine in medicine increase the rigidity of the whole molecule and decrease the amount of rotatable free bonds, which enhances the pharmacokinetic profile and boost the effectiveness of the contact with the enzyme. Medicines created in the previous two years have the potential to treat diseases like SARS-CoV-2, leishmania, tuberculosis, and dengue etc.
Keyword: *Spiropiperidine, SARS-CoV-2, Anti-tuberculosis, Anti-DENVE, Antiproliferative, Antileishmanial*

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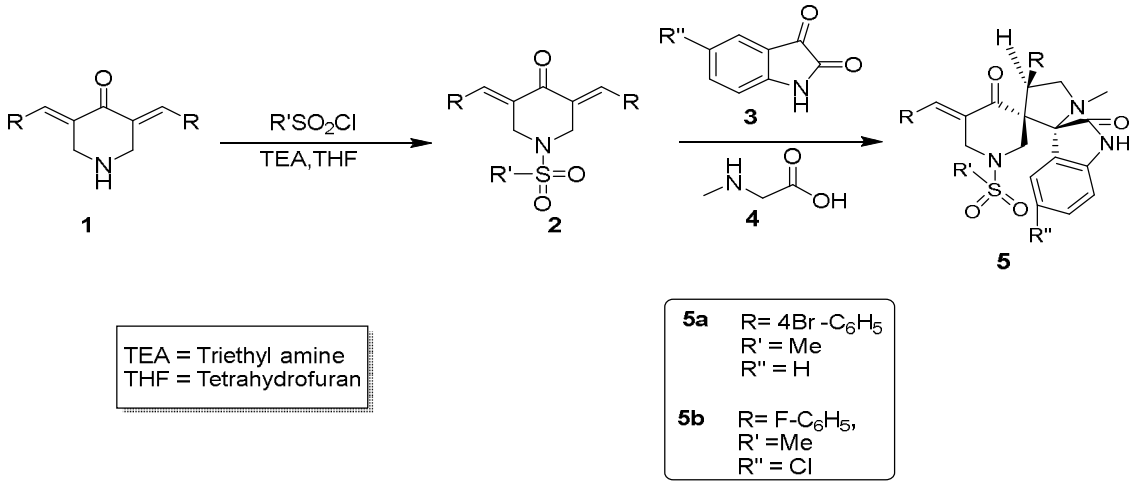
Introduction

The most frequent nitrogen heterocyclic structure found in medications that have received Food and Drug Administration (FDA) approval is the piperidine framework [1]. The importance of the spiro atom in piperidine is that it increases the rigidity of the whole molecule and decreases the amount of rotatable free bonds, which may enhance the pharmacokinetic profile and boost the effectiveness of the contact with the enzyme. FDA-approved medicines have spiropiperidine structures are less known, Drugs based on spiropiperidine have been employed as cardiovascular, CNS, anti-HIV, anti-inflammatory, and other agents [2]. It would be interesting to know that spiropiperidine exist in 2-,3-,4- spiropiperidine forms but only 3- and 4- spiropiperidine scaffold are often present in pharmaceutically important drugs [3]. A few drugs based on 2- spiropiperidine scaffold are also found but they are limited in drug scaffold. In this review, we include a summary of the research from recent years on the synthesis and biological activity of medicines having a spiropiperidine scaffold.

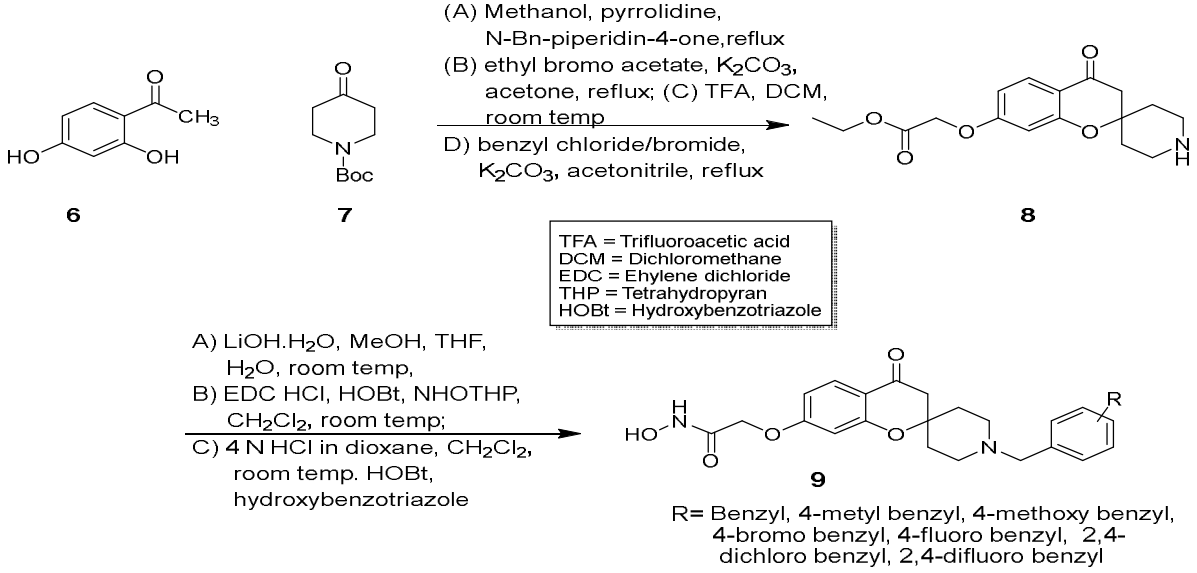
RECENTLY DEVELOPED MEDICINAL DRUGS CONTAINING SPIROPIPERIDINE SCAFFOLD

Nehmedo et al. synthesized numerous 3-spiropiperidine based compounds by the regioselective dipolar. cycloaddition. reaction [5]. The majority of synthetic derivatives that have been produced have encouraging antiproliferation properties against human Colon Cancer Cell Line-116, Michigan Cancer Foundation-7, A431, and PaCa2. Furthermore, these compounds had selectivity for cancer cells and do not affect normal cells (such as retinal pigment epithelial-1). When compared to 5-fluorouracil and sunitinib, compounds **5a** and **5b** have potent inhibitory activities against the investigated cell lines. Compound **5a** (**scheme-1**) is the active compound. The produced compound has inhibitory action on epidermal growth factor receptor (EGFR) and vascular endothelial growth factor-2 (VEGFR-2). A vero cell model of viral infection was used to show the synthesized compounds' antagonist properties for SARS CoV 2. The most promising one was compound 5b (scheme-1), which was around 3.3 and 4.8 times more potent than the reference drugs hydroxychloroquine and chloroquine, respectively. The synthesis process for **5a** and **5b** is shown in **Scheme 1.**



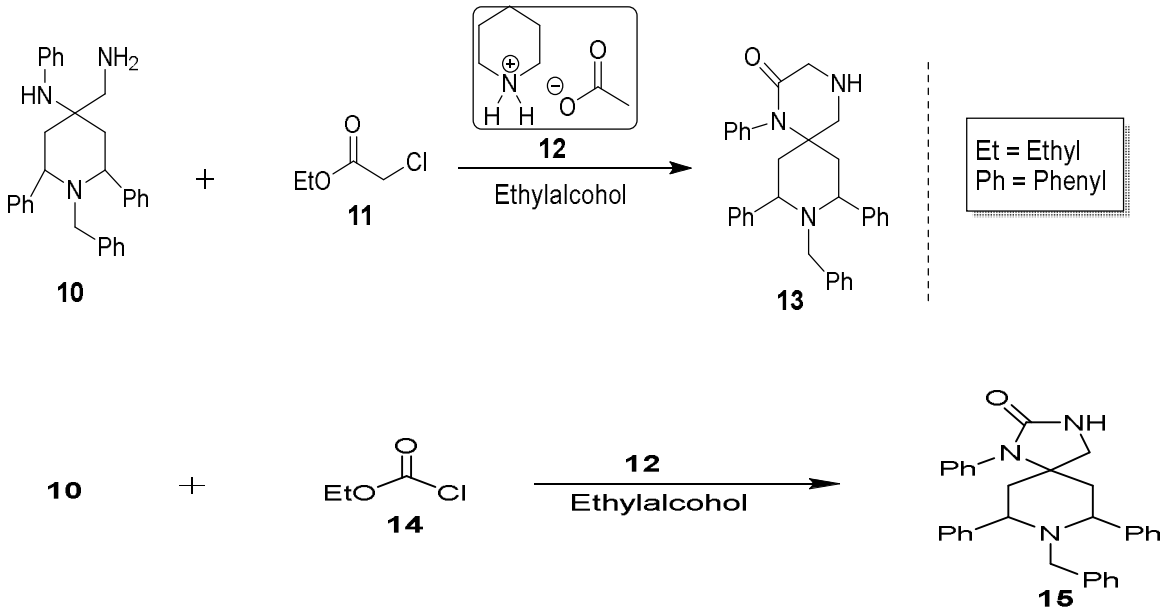
Scheme 1: Synthesis of **5a** and **5b** which have inhibitory properties towards VEGFR-2, EGFR, And SARS-CoV-2

C. Kurapati et al. [6] have designed and synthesized a series of N-benzyl spiro-piperidine hydroxamic acid-based derivatives and evaluated their HDAC inhibitory activity and drug-likeness prediction. Compound showed the highest HDAC inhibitory activity and good drug-like properties, making it a potential lead compound for further development as an HDAC inhibitor. Histone deacetylases (HDACs) are enzymes that play a vital role in the regulation of gene expression. They remove acetyl groups from histones, leading to the compaction of chromatin and inhibition of transcription. Inhibition of HDACs has emerged as a potential therapeutic strategy for the treatment of various diseases, including cancer. In this study, author reporte,d the design and synthesis of N-benzyl spiro-piperidine hydroxamic acid based derivatives and evaluates their HDAC inhibitory activity and drug-likeness prediction. These unique series of N-benzyl spiro-piperidinehydroxamic acid based compounds that have been identified as a zinc-binding moiety. It was observed that all of the synthetic substances were efficient at preventing the proliferation of the various tumor cell lines while being safe for normal cells, AD293. When comparing the molecule (containing 2, 4-dichloro or 2, 4-difluoro) with tubastatin A, in vitro fluorometric assays revealed a 101.5- and 108-fold preference for HDAC6 (Histone deacetylase 6) over HDAC8 in terms of selectivity and inhibition. Furthermore, studies on molecular docking and in vitro findings have been coincide. The newly discovered compounds reveal the relevance of chlorine and fluorine in the benzohydroxamate-based structure over class I isoforms and preferentially occupy the sub-unit of HDAC6. The synthesis method is given in **scheme 2**.



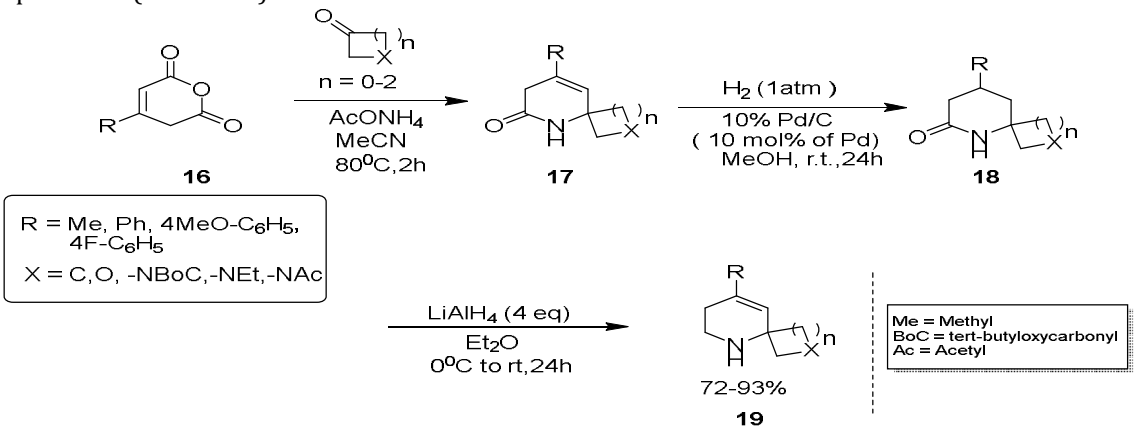
Scheme 2: Synthesis of compounds having inhibitory properties towards HDAC6

Kurapati et al. [7] synthesized new spiro-piperidine derivatives in a single pot by using green ionic liquids (**Scheme 3**). The majority of these derivatives demonstrated potential antileishmanial action, with efficacy that was superior to the reference drug miltefosine when evaluated in vitro against the amastigote and promastigote types of Leishmania major [8]. The IC_{50} values for the two highly active compounds, **13** and **15(scheme 3),** were in the sub-micromolar range, which were 0.89 M and 0.50 M, respectively, in comparison with miltefosine's IC_{50} value of 8.08 M. Furthermore, the effects of the antileishmanial action of these compounds, mitigated by folic and folinic acids, were equivalent to those of the control sample, trimethoprim. This demonstrates the fact that they start targeting PTR1 (Pteridine reductase 1) and DHFR (Dihydrofolate reductase) to activate the antifolate mechanism and exhibit antileishmanial action. These most efficient substances showed more selectivity and a safer profile against VERO cells as compared to miltefosine.



Scheme 3: Synthesis of compound **13** and **15** having antileishmanial action.

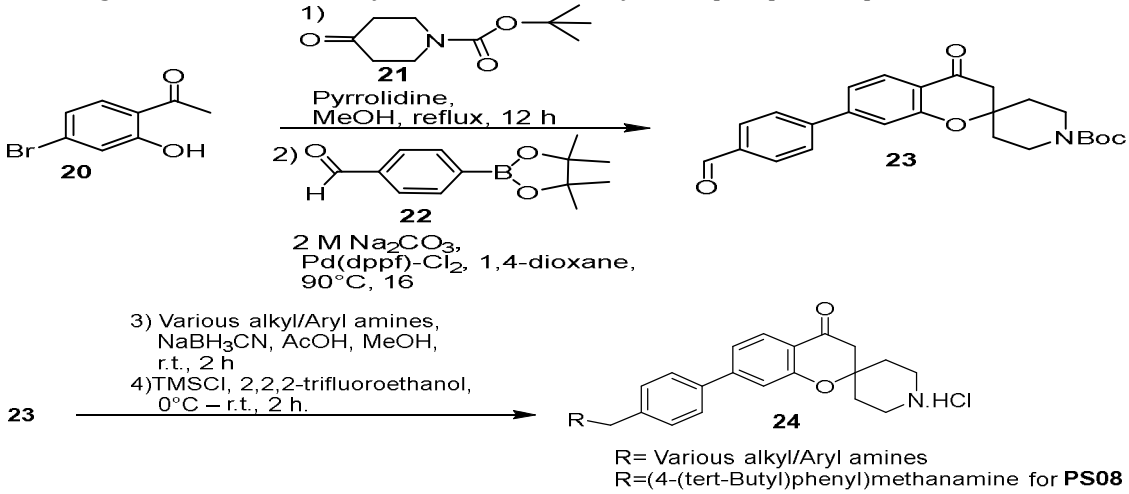
Peshkov and colleagues prepared a trace-amine-associated receptor 1 agonist, which is an appropriate target for CNS disease [4]. Castagnoli-Cushman Chemistry was used in the synthesis. Initially, **16** combined with cycloalkanone to form **17**. In the presence of Pd/C, this **17** underwent double bond hydrogenation to give rise to **18**. The carbonyl group of **18** was reduced by $LiAlH_4$ to give rise to 2-spiropiperidine base final compound **19** (**Scheme 4**).



Scheme 4: Synthesis of trace-amine-associated receptor 1 agonists.

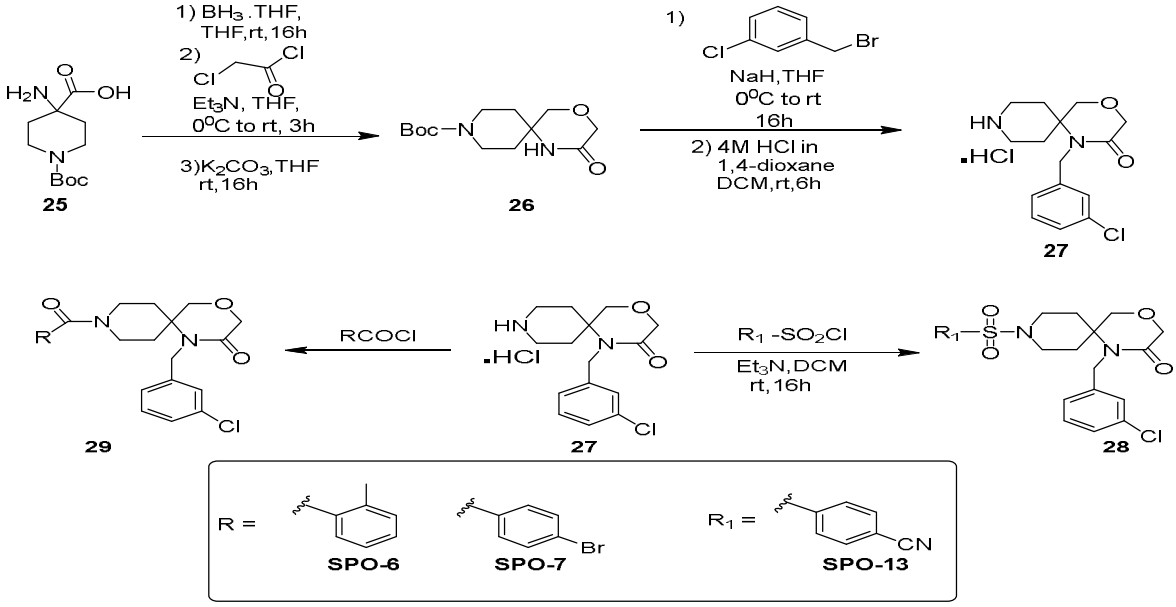
Recently, Chittiet al. [9] synthesized numerous novel spiro[chromane-2,4'-piperidin]-4 (3 H)-one compounds (**Scheme 5**). The anti-tuberculosis (anti-TB) efficacy of the synthesized derivatives against strain H37Ra of the *Mycobacterium tuberculosis* (Mtb) was investigated [10]. With a MIC value of 3.72 M, **PS08** demonstrated the greatest inhibition of all the investigated compounds when compared to the

reference drug INH (Isoniazid), which has a MIC value of 0.09 M. Furthermore, a molecular docking analysis of the highly potent compound (**PS08**) was performed in order to determine the expected binding domain of the test ligand in the active affinity of the selected Mtb tyrosine phosphatase protein.



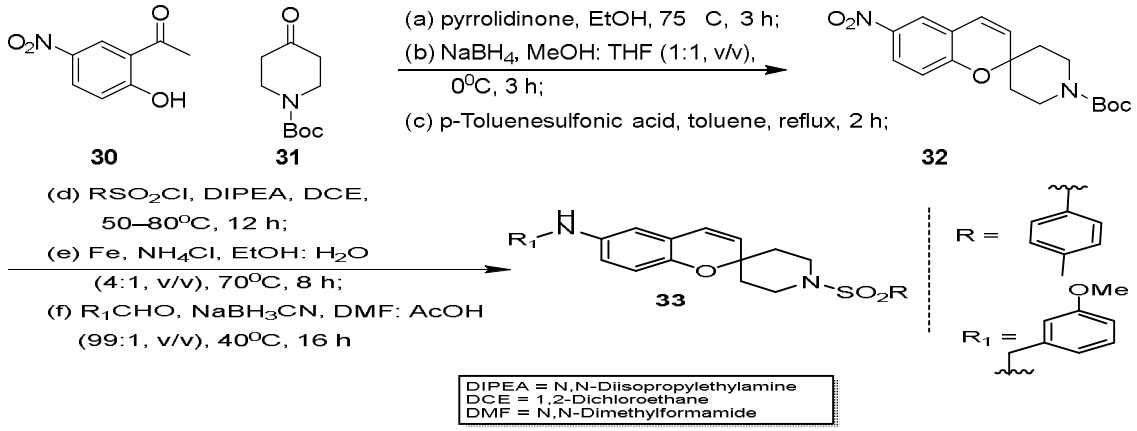
Scheme 5: Synthesis of agonist of strain H37Ra of *Mycobacterium tuberculosis*

Gangireddy et al. [11] presented a study on the synthesis of dengue virus type 2 antagonists containing 1, 9-diazaspiro [5.5] undecane structure with 3-chlorobenzyl links. In a cell-based study, compounds **SPO-6** (containing 2-methylbenzyl group), **SPO-7** (containing 4-bromobenzyl group), ands **SPO-13** (containing 4-cyanobenzyl group) were found to be antagonist towards DENV2. It's intriguing to learn that the authors have for the first time described DENV2 (Dengue virus type 2) inhibitory activity in newly separated cells. Docking calculations revealed that the NS5-methyltransferase enzyme was the most prime target for this class of chemical compounds. **Scheme 6** showed the synthesis procedures for **SPO-6**, **SPO-7**, and **SPO-13**.



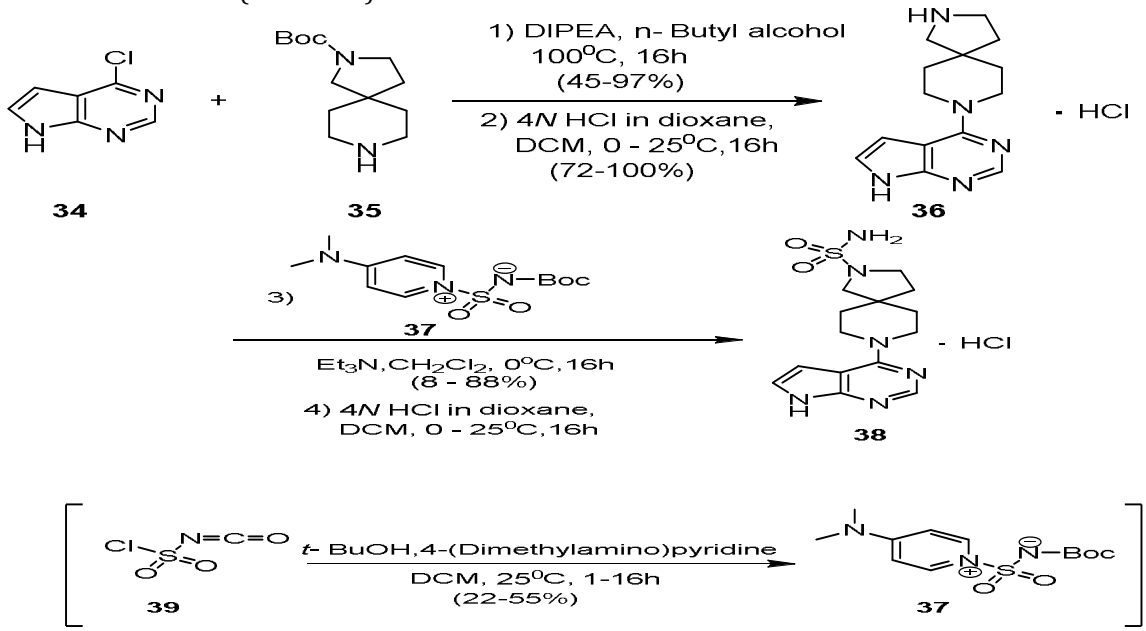
Scheme 6: Synthesis of anti- DENV2 drugs **SPO-6**, **SPO-7**, and **SPO-13**

5-Lipoxygenase (5-LO) inhibitors have the capability to treat a wide range of inflammatory conditions. Spiro [chromene-2,4′-piperidin]-6-amine-based compounds was prepared by Lee et al. [12, 13] recently, which is a novel 5-LO inhibitor (**scheme 7**). According to *in vitro* experiments with a variety of synthetic compounds, generation of leukotriene B4 was inhibited in rat basophilic leukaemia-1 cells. A mouse ear edoema model was used for an in vivo investigation of compound **33** (100 mg per kg). Oral inhalation of **33** suppressed myeloperoxidase action, leukotriene B4 production, and arachidonic acid-initiated ear edoema. The allosteric mechanism of binding between 5-LO and the generated compounds, such as **33**, was confirmed using SAR analysis and molecular docking tests.



Scheme 7: Synthesis of 5-LO inhibitor compound **33**

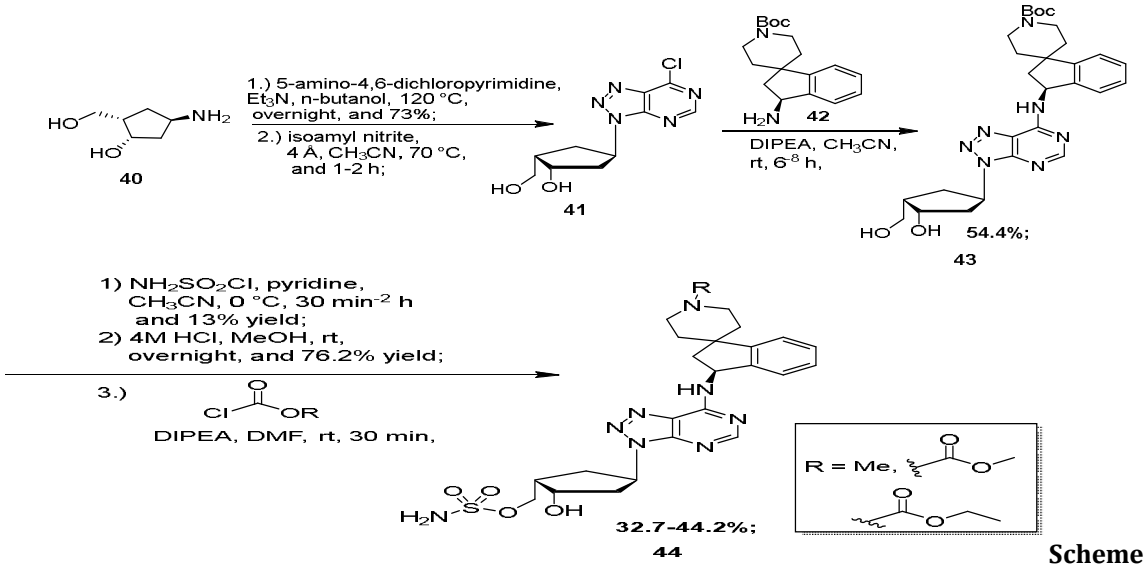
In order to activate the Stimulator of Interferon Genes (STING) pathway, Jeong et al. [14, 15] developed 4-spiropiperidine-based derivatives **38** that were non-nucleotide-derived ENPP1 (Ectonucleotide Pyrophosphatase/Phosphodiesterase 1) inhibitors [16]. At first, the yield of Boc (tert-Butyloxycarbonyl)-containing compounds obtained through the nucleophilic aromatic substitution of piperidines **35** with pyrrolopyrimidines **34** varied from 45 to 97%. Amines **36** were produced in high yields when the Boc group was removed from previously formed compound in acidic conditions. In the reaction, the Burgess-type reagent **37** and the amines **36** produced the Boc compound, which contained a sulfamide. Sulfamides **38** were synthesized by using HCl to cleave the Boc group of a previously formed Boc compound that contained sulfamide (**Scheme 8**).



Scheme 8: Synthesis of non-nucleotide-derived ENPP1 inhibitors **38**

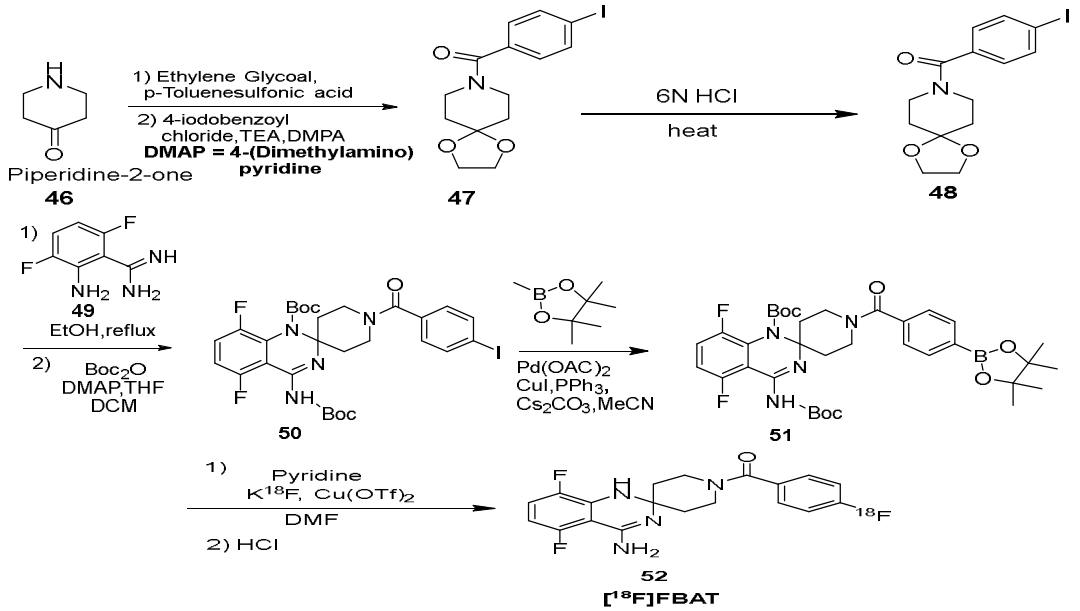
NEDD8-Activating Enzyme Inhibitors (neuronal precursor cell expressed, developmentally down-regulated 8-Activating Enzyme Inhibitors) Inhibitors were prepared by Xiong et al. [17] (**Scheme 9).** A key signaling molecule involved in cell homeostasis and operational maintenance is the protein NEDD8, which is ubiquitin-like [18]. Dysregulation of this mechanism was thought to be responsible for various human diseases, such as cancer, etc. The NAE E1 (NEDD8-activating enzyme E1), the neddylation pathway's sole activated enzyme, was thus been identified as a promising anticancer target of these drugs. The method started with **40**, which produced a free amine compound after reaction with Et_3N (Triethyl amine) and 5-amino-4,6-dichloropyrimidine in methanol at 120°C. In CH_3CN, this compound combined with isoamyl nitrite to form **41**. Now, at RT, **41** reacted with **42** in the presence of base DIPEA in acetonirile to form **43**. The compound **44** was synthesized from **43** in three steps. The first step involved a reaction with NH_2SO_2Cl,

which resulted in the incorporation of a sulfonamide group. In the second step, the Boc group was eliminated, resulting in free amine. In the third step, this free amine combined with RCO_2Cl to produce various **44**.



Scheme 9: Synthesis of NEDD8-Activating Enzyme Inhibitors.

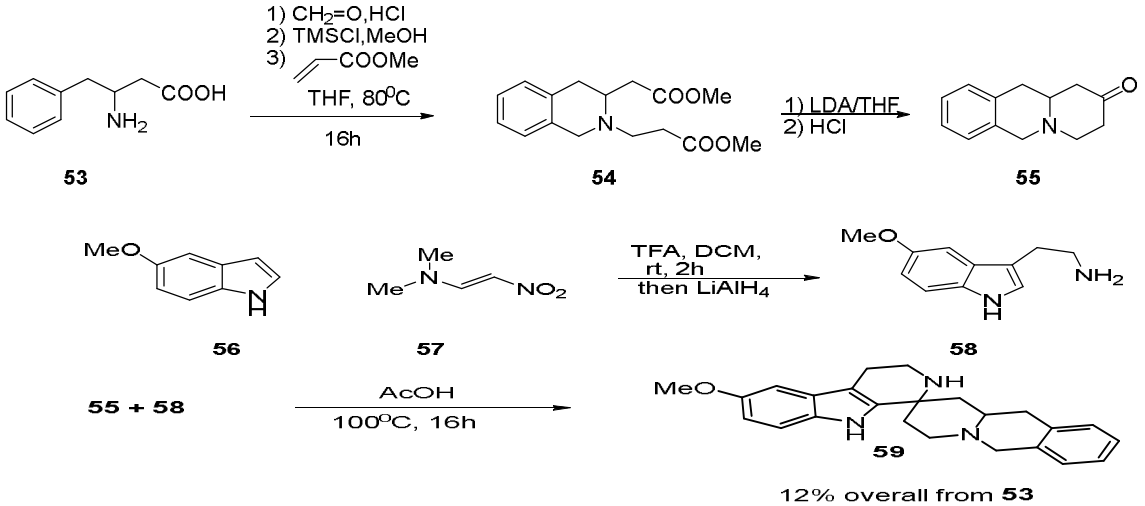
Yeh et al. [19] developed a tracer [^{18}F] FBAT for PET/MR imaging of iNOS (inducible nitric oxide synthase) in a mouse model of lipopolysaccharide (Scheme 10). It is important because iNOS action not only destroys pathogens but also had immune-regulatory functions, such as reducing T cell growth.



Scheme 10: Synthesis of tracer [^{18}F] FBAT for PET/MR imaging of iNOS.

A recent synthesis by Son et al. [20] described the synthesis and characterization of a novel series of spiro [indoline-3,4'-piperidine]-based co-potentiators for CFTR mutant. The authors also showed that this compound acted synergistically with the CFTR potentitor such as GLGP1837 or VX-770. CFTR is an ion channel that regulates the transport of chloride and bicarbonate ions across cell membranes, and its dysfunction leads to the accumulation of thick, sticky mucus in the lungs, pancreas, and other organs. While some CFTR mutations are severe and result in complete loss of function, others are less severe and result in residual CFTR activity. These minimal function CFTR mutants are potential targets for co-potentiator drugs that can increase their activity and improve CF (cystic fibrosis) symptoms. CF is a genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.In the synthetic process, the alpha amino carboxylic acid molecule **53 and** formaldehyde were combined to

produce a cyclic product. This on reaction with TMSCl (Trimethylsilyl Chloride) in MeoH changed an acid group into an ester group. At 80^0C, the methyl acrylate reacted with free amine group of cyclic product to give rise to the di-ester compound **54**. After reacting with LDA (lithium diisopropylamide) in THF (tetrahydrofuran) and HCl, **54** produced cyclic compound **55**. N, N-dimethyl-2-nitroethanamine **57** and 5-methoxy indole **56** combined to form **58** in a different vassal. Further, the reactions of **55** and **58** produced **59** (**Scheme 11**).



Scheme 11: Synthesis of co-potentiator for existing CFTR mutant.

CONCLUSION

The studies discussed in this review demonstrate the potential of spiropiperidine derivatives as anti-COVID, anti-tuberculosis, anti-DENVE, antiproliferative, antileishmanial. The innovative synthetic methods reported in year 2021 and 2022 pave the way for the development of new spiropiperidine-based drugs with improved pharmacological properties. The authors also believe that despite considerable progress in spiro compound synthetic methods, more efficient techniques must be developed to produce a pharmacologically important drug containing spiropiperidine molecules. Although 3- and 4-spiropiperidine are widely found in pharmacological scaffolds, most drugs produced during the last 2 years have been based on 4-spiropiperidine scaffolds.

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CONFLICT OF INTEREST

The authors report, there are no competing interests to declare.

AUTHOR'S CONTRIBUTION

The authors have equally contributed in carrying out the survey and writing the review.

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DATA AVAILABILITY STATEMENT:

Data are openly available in a public repository that issues datasets with DOIs.

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