Nitrogen Heterocyclic (NHC) Scaffold Contains Recently Approved Drugs and Their Synthetic Routes: A Mini-Review

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Abstract — The development of new drug molecules is one of the most important processes in maintaining a healthy human life across the world. In this regard, we successfully reviewed the most acceptable synthetic route to the development of recently approved dermatologic, immunologic, and metabolic drugs containing nitrogen heterocyclic (NHC) systems in 2020.

IndexTerms — Nitrogen heterocyclic, drugs, synthetic approaches.

I. INTRODUCTION
In the field of organic chemistry, researchers are primarily focused on ongoing research to develop innovative and sustainable synthetic methods that utilize the building of large numbers of bioactive compounds [1]. Among them, the synthesis of known and unknown active drugs is the most challenging endeavor at the forefront of synthetic organic chemistry [2]. In addition, synthetic chemists are looking to develop new drug molecules containing heterocycles due to their beneficial effects on various diseases, patient health, and success in all stages of drug discovery [3]. From this background, the scientific community has developed efficient synthetic approaches to obtain medicinally active molecules composed heteroatoms with cyclic systems [4]. Among other heterocyclic, nitrogen heterocyclic compounds (NHCs) have wide relevance in the field of drug synthesis related to medical research [5].

Dermatologic Drugs

\begin{center}
\includegraphics[width=\textwidth]{dermatologic_drugs.png}
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Immunologic/inflammation drugs

\begin{center}
\includegraphics[width=\textwidth]{immunologic_drugs.png}
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Metabolic Drug

\begin{center}
\includegraphics[width=\textwidth]{metabolic_drug.png}
\end{center}
Figure 1 Recently approved immunologic, dermatologic and metabolic drug molecules consisting NHC system.

Regarding NHC molecules, medicinal chemists accounted for the development of the numerous of nitrogen heterocyclic structures and studied their organic hobby in opposition to a chain of sicknesses which includes anti-HIV, antioxidant, antitumor, lipid lowering, antifungal, antihyperglycemic dealers and protein inhibitors, anti-allergic, and antimicrobial [6]. Therefore, in recent years, many NHC systems have been successfully synthesized and studied their pharmacological behavior [7]. Nevertheless, there has been a recent surge of interest in synthesizing NHC-related drug systems as a result of their potent activity against newly identified virus such as coronavirus (Covid-19) [8]. In this review, we have taken care to summarize efficient synthetic routes for building newly approved dermatological, immunological, and metabolic drugs, including nitrogen heterocycle (NHC) systems (Figure 1). Also, this review encouraged the pharmacological investigators and synthetic organic chemists, who are involved to discover novel drug molecules with better therapeutic activities in future.

II. SYNTHETIC APPROACHES OF NHC DRUG MOLECULES

Dermatologic drugs
A dermatological drug applied directly to the skin to treat or prevent a skin condition or for regular skin care. Abametabir (Xeglyze) is one of the topical dermatological agents used to treat pediculosis [9]. The drug was approved by the USFDA (United States Food and Drug Administration) in July 2020 and the marketing rights were acquired by Dr. Reddy’s Laboratory [10]. Jayachandra et al. described a multigram-scale synthetic methodology for the construction of the drug abametavir (Scheme 1) [11].

![Scheme 1: Synthetic approach of abametabir](image)

Kinex Pharmaceuticals has discovered a first-in-class dual inhibitor of tyrosine-protein kinase CSK is called “Tirbanibulin” [12]. Recently, Somlinski and his collaborators successfully investigated the detailed use of tirbanibulin [13]. In December, it approved this NHC-based drug system for the treatment of actinic keratosis. In 2021, Kinex researchers discovered and profited from kilogram-scale synthesis of tirbanibulin (Scheme 2) [14].

![Scheme 2: Synthetic approach of tirbanibulin](image)

Immunologic / Inflammation drugs
Berotralstat dihydrochloride is a member of the NHC drug system, called a kallikrein inhibitor, used to prevent severe swelling attacks (hereditary angioedema-HAE) in adult and pediatric patients [15]. This HAE inhibitor was approved by the USFDA in December 2020 [16]. “Orladeyo” is the other name of Berotralstat dihydrochloride. BioCryst Pharmaceuticals has discovered a patent presented as an efficient multi-kilogram synthetic approach to construct belotralstat dihydrochloride (Scheme 3) [17].

Stepwise synthetic methods of Berotralstat dihydrochloride

1. H
c
Cl
4-bromophenol
K_2CO_3, DMF,
60-65 ^\circ C
O
O
N
N
O
Br
Br
Na_2CO_3, Pd(PPh_3)_4,
DME, H_2O, 75-85 ^\circ C
1. NaHMDS, MeCN,
THF, -10 ^\circ C
2. H_2SO_4, MeOH
3. benzylamine,
anisole, 142 ^\circ C
58% Tirbanibulin

Scheme 3: Synthetic approach of tirbanibulin.
Step -1
Synthesis of Berotralstat carboxylic acid fragment (A)

\[
\begin{align*}
&\text{NH}_2 \quad \text{CN} \quad \text{CF}_3 \\
&\text{NH}_2 \quad \text{CN} \quad \text{CF}_3 \\
&\text{SnCl}_2 \cdot 2\text{H}_2\text{O} \quad \text{NaNO}_2, \text{HCl} \\
&\rightarrow \\
&\text{CN} \quad \text{CF}_3 \\
&\text{KMnO}_4 \\
&\rightarrow \\
&\text{CN} \quad \text{COOH}
\end{align*}
\]

1. NiCl₂, H₂O, NaBH₄
2. NaOH, (Boc)₂O, then

\[
\begin{align*}
&\text{H}_2\text{N} \quad \text{N} \quad \text{H} \\
&\text{NHBoc} \quad 70\% \ (A)
\end{align*}
\]

Step -2
Synthesis of Berotralstat dibenzylamine fragment (B)

\[
\begin{align*}
&\text{CN} \quad \text{CHO} \\
&\text{CN} \quad \text{CHO} \\
&\text{KHSO}_4 \quad \text{DCM, rt} \\
&\rightarrow \\
&\text{CN} \quad \text{CH}_3 \quad \text{CH}_3 \\
&\text{81}\% \\
&\text{Mg, I}_2, \text{THF/PPh}_3, -60 \text{ to } -35 \text{ °C} \\
&\text{then HCl, iPrOH} \\
&\rightarrow \\
&\text{H}_2\text{N} \quad \text{F} \\
&\text{H}_2\text{N} \quad \text{F}
\end{align*}
\]

\[
\begin{align*}
&\text{Br} \quad \text{NH}_2 \\
&\text{Br} \quad \text{NH}_2 \\
&T\text{MSOTI, TEA, DCM, rt} \\
&\rightarrow \\
&\text{Br} \quad \text{Si(CH}_3)_3 \\
&\text{Si(CH}_3)_3 \\
&\text{87}\%
\end{align*}
\]
Step -3

Synthesis of Berotralstat dihydrochloride [3]

Delgocitinib or Corectim acts good Janus kinase (JAK) inhibitor due to the presence of nitrogen heterocyclic (NHC) system such as pyrrolopyrimidine ring. It is likewise used to inhibits all 4 members [JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2)] of Janus kinase due to the structural resemblance of formerly used drug molecules, that is referred to as tofacitinib [18]. In 2020, it was approved as a treatment for atopic dermatitis for the first time in Japan [19]. The construction of highly stereo specific delgocitinib is outlined in Scheme 4 [20].
In 2020, filgiritinib (Jyseleca) was approved by the European Medicines Agency (EMA) for the treatment of rheumatoid arthritis [21]. This selective drug acts as a potent and reversible Janus kinase 1 (JAK) inhibitor [22]. In addition, the pharmaceutical use of filgiritinib has been successfully studied in many diseases such as Crohn’s disease and ulcerative colitis (UC) [21]. In recent years, numerous synthetic approaches to construct filgiritinib have been reported [23]. Underneath, we described an efficient synthetic sequence in Scheme 5.

Scheme 4: Synthetic approach of Delgocitinib [4].
Scheme 5: Synthetic approach of Filgotinib hydrochloride [5].

Metabolic drug
Osilodrostat phosphate is used to treat hypercortisolism, also known as Cushing's disease, which means it is thought to inhibit increased cortisol biosynthesis in the adrenal glands [24]. Therefore, osilodrostat phosphate is an excellent new option for providing a new treatment option for adrenocorticotropic hormone (ACTH) hypersecretion that causes excessive bioproduction of cortisol. Osilodrostat Phosphate is also known as Isturisa and in 2020 it was approved by the USFDA [25]. Scheme 6 shows an excellent synthetic route for constructing osilodrostat phosphate [26].
III. CONCLUSION

In this review, we mainly describe the synthetic routes to allowing the construction of recently approved dermatological, immunological, and metabolic drugs containing the nitrogen heterocycle (NHC) system. From our covering literature and patents encourage the young synthetic chemists and biologists to discover efficient synthetic routes helps to achieve novel drug molecules.

IV. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane (or) glyme</td>
</tr>
<tr>
<td>i-PrOH</td>
<td>isopropyl alcohol</td>
</tr>
<tr>
<td>Boc</td>
<td>di-tertiary-butyl dicarbonate</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>MTBE</td>
<td>Methyl tertiary-butyl ether</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LiAlH₄</td>
<td>lithium aluminium hydride</td>
</tr>
<tr>
<td>t-BuOH</td>
<td>tertiary butyl alcohol</td>
</tr>
<tr>
<td>BHT</td>
<td>butylated hydroxytoluene</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1'-Bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>TrCl</td>
<td>Trifluoromethyl chloride or trityl chloride</td>
</tr>
<tr>
<td>MsCl</td>
<td>methanesulfonyl chloride</td>
</tr>
<tr>
<td>BH₃</td>
<td>borane</td>
</tr>
<tr>
<td>Rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>H₃PO₄</td>
<td>phosphoric acid</td>
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