

Brief Report

Duvelisib: A 2018 Novel FDA-Approved Small Molecule Inhibiting Phosphoinositide 3-Kinases

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Abstract: Duvelisib (Copiktra[®]) is a dual inhibitor of phosphoinositide 3-kinases (PI3K δ and PI3K γ). In 2018, duvelisib was first approved by the Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL)/ small lymphocytic lymphoma (SLL) after at least two prior therapies. Duvelisib has also been approved under accelerated track for relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. In this review, we provide a series of information about duvelisib, such as the development of clinical trials for LLC/SLL and FL and the steps used for its synthesis.

Keywords: approved drugs; duvelisib; Copiktra; FDA; phosphoinositide 3-kinases; cancer

1. Introduction

In 2014, Food and Drug Administration (FDA) approved the idelalisib (1), a first-in-class inhibitor of PI3K δ , for the treatment of relapsed chronic lymphocytic leukaemia (CLL), relapsed follicular B-cell non-Hodgkin lymphoma (NHL) and relapsed small lymphocytic leukaemia (SLL) [1]. Although idelalisib (1) (Figure 1) possesses an enhanced selectivity for the PI3K δ , it opened a new road ahead for the family of phosphoinositide 3-kinase (PI3K) inhibitors. In 2017, the approval of copanlisib (2) (Figure 1) for the treatment of relapsed follicular lymphoma (FL) and the ongoing trials on several hematological and solid malignancies has showed the usefulness of the pan-PI3K inhibitors in the clinics [2,3].

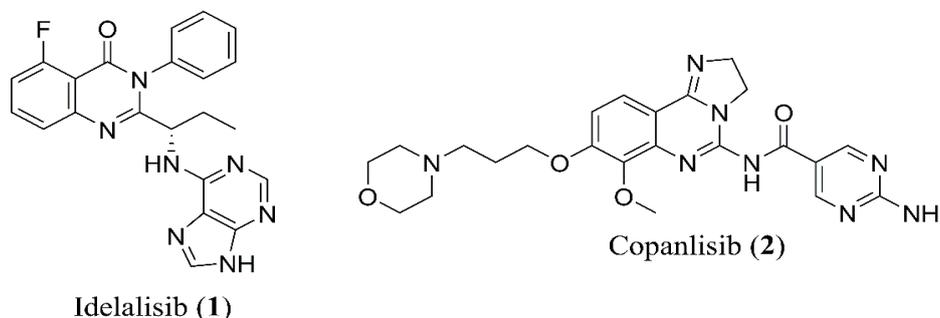


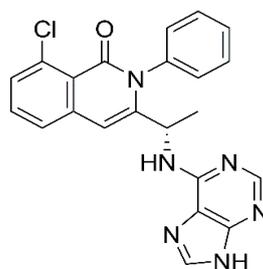
Figure 1. Chemical structure of PI3K inhibitor drugs idelalisib (1) and copanlisib (2).

The purpose of this review is to provide a series of information on the third PI3K inhibitor approved by FDA in 2018: duvelisib (IPI-145, formerly developed by Intellikine and further developed by Infinity Pharmaceuticals, which granted to Verastem Oncology in 2016 the rights of development and commercialization worldwide [4]).

2. Duvelisib

2.1. Names and Structure

Duvelisib (**3**, Figure 2) is commercialized by Verastem Oncology, under the brand name Copiktra[®]. Its IUPAC name is: (S)-3-(1-((7H-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one, CAS 1201438-56-3.



Duvelisib (**3**)

Figure 2. Chemical structure of duvelisib (**3**).

2.2. Uses

Duvelisib (**3**) was first approved on September 24, 2018, in the USA, for the treatment of adult patients with relapsed or refractory CLL/ SLL after at least two prior therapies (NCT02004522) [5,6]. Based on overall response rate (ORR) the drug has also been approved under fast track for the treatment of relapsed or refractory FL after at least two prior systemic therapies, but the continued approval depends on the clinical benefit demonstrated in the trials (NCT02204982) [7].

2.3. Targets and Selectivity

The phosphoinositide 3-kinases (PI3Ks) play an important role in various processes, such as proliferation, differentiation, motility, survival, and intracellular trafficking [8–11]. This signaling pathway is commonly activated in cancer [10]. There are three classes of PI3K, but the drug discovery process is mainly focused in the enzymes of class I, which is divided into class IA (PI3K α , PI3K β and PI3K δ) and IB (PI3K γ) [12].

Duvelisib (**3**) is a dual PI3K δ and PI3K γ inhibitor with enhanced selectivity for PI3K δ (10-fold) over PI3K γ (Table 1). The selectivity for PI3K δ over PI3K α can be attributed to the conformation that the compounds adopt in the active site, namely propeller-shaped, which opens a hydrophobic pocket that is not present in the apoenzyme [13,14]. Duvelisib (**3**) was shown to be selective for the inhibition of PI3K from class I, not being active against other protein or lipid kinases [15].

Table 1. Inhibitory profile of idelalisib (**1**), copanlisib (**2**), and duvelisib (**3**) against each PI3K isoform (IC₅₀ values in nM).

Drug	PI3K α	PI3K β	PI3K δ	PI3K γ	Reference
Idelalisib (1)	8600	4000	19	2100	[13]
Copanlisib (2)	0.5	3.7	6.4	0.7	[3]
Duvelisib (3)	1602	85	2.5	27	[15]

Although there is no crystal structure of the duvelisib (**3**) in the active site of PI3K, this drug should possess a similar interaction mode of idelalisib (**1**), given the structural similarities between these two compounds. Figure 3 presents the binding modes of idelalisib (**1**) in PI3K δ (PDB:4XE0) [13] and copanlisib (**2**) in PI3K γ (PDB:5G2N) [3].

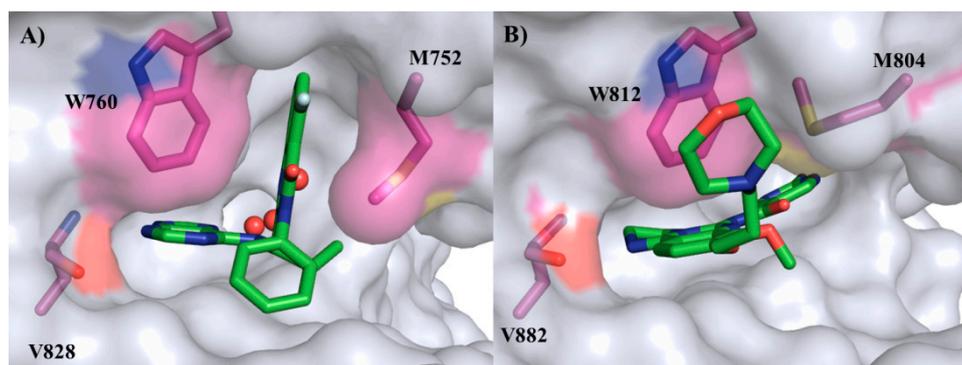


Figure 3. Binding modes of idelalisib (1) in PI3K δ (PDB:4XE0) (A) and copanlisib (2) in PI3K γ (PDB:5G2N) (B).

The duvelisib (3) binds at the ATP binding region, which is one of the most conserved throughout the PI3K family [8,16,17]. It is possible to explore the model generally used for the development of protein kinase inhibitors, incorporating features related to the inhibition of PI3K [18,19]. In general, PI3K inhibitors form hydrogen bond interactions in the region of the hinge, occupying the adenine binding site (Figure 4). The presence of the hydrophobic regions I and II in the active site of PI3K should be noted [20]. The former is also called the “affinity pocket” and it is commonly exploited by pan-PI3K inhibitors through a series of polar interactions. On the other hand, the hydrophobic region II is a region exposed to the solvent [20]. The compounds with the so-called propeller-shaped conformation open a hydrophobic pocket between the residues of tryptophan and methionine, also known as the “specificity pocket”, conferring selectivity for PI3K δ [20] (Figure 4).

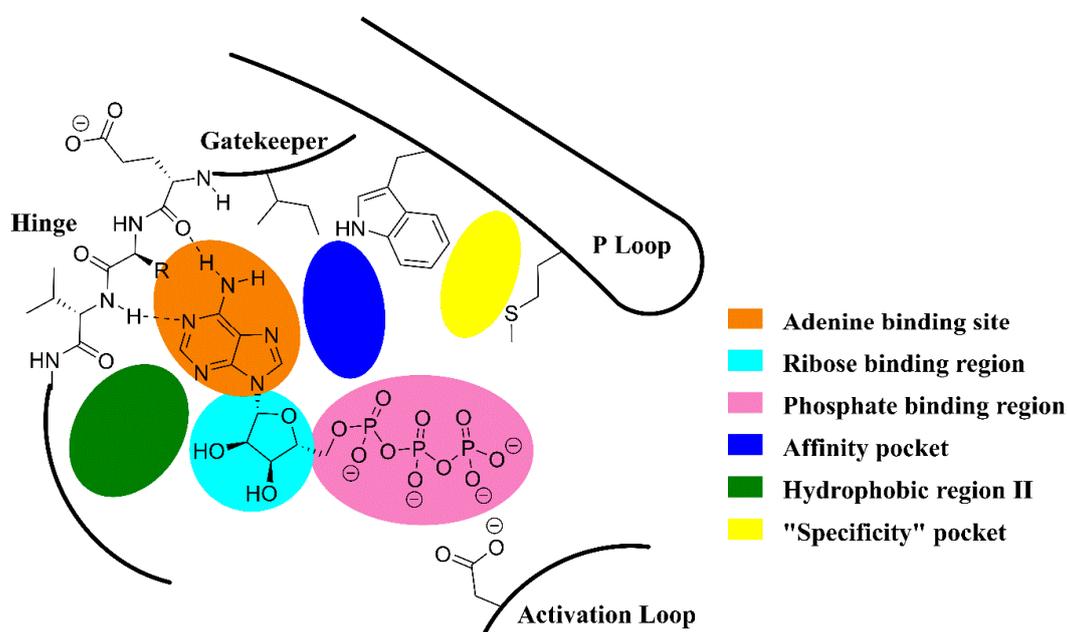


Figure 4. General model for the design of PI3K inhibitors [18,19].

Although the duvelisib (3) presents a high similarity to idelalisib (1), it possesses unique features related with to the binding affinity by PI3K. Duvelisib (3) presents a long target residence time, which may be closely associated with more durable effects [15].

2.4. Clinical Trials

The differential profile of the duvelisib (3) is based on the dual inhibition of PI3K δ and PI3K γ , which are mainly expressed in the immune system [10,21]. They present a non-overlapping cellular

function in the immune system, considering the innate and adaptive immune response [22–24]. Several clinical trials with duvelisib (3) are completed and ongoing for the treatment of cancer, inflammatory, and autoimmune diseases.

During the phase I studies, assessment of the maximum tolerated dose (MTD), after dosing range up to 100 mg twice daily, showed that the MTD was 75 mg twice daily based on dose-limiting toxicities (DLT) [25]. The pharmacodynamics evaluation by inhibition of p-AKT showed that inhibition of this mediator was not dose-dependent; it was maximal when duvelisib (3) was administered 25 mg twice daily. The use of duvelisib administered 25 mg twice daily advanced for the phase II and III studies [25]. Following administration of the duvelisib (3), the phosphorylated-AKT (p-AKT) levels were decreased. The p-AKT is a downstream marker of PI3K/AKT/mTOR pathway signaling. It is important to note that the administration of the duvelisib (3) leads to reduced levels of some chemokines, cytokines, and matrix metalloproteinases [25–27]. The reduction of several serum factors is consistent with alterations in the tumor microenvironment [25–27].

Duvelisib (3) is rapidly absorbed, with a maximum concentration after 1–3 h [25]. Following the administration of 25 mg of duvelisib (3), the absolute bioavailability in healthy volunteers is 42% [28]. Duvelisib (3) presents a volume of distribution of 28.5 L which is consistent with distribution to peripheral tissues. It is eliminated with a half-life of 4.7 h [28]. Duvelisib (3) is primarily metabolized by cytochrome P450 CYP3A4. The concomitant use with a strong inhibitor of CYP3A4 can increase the risk of toxic effects [4,28].

As expected, the most common adverse events in pretreated patients were the occurrence of opportunistic infections and cytopenias, with some cases resulting in fatal events [25–27,29]. Duvelisib (3) showed clinical efficacy and acceptable safety for the treatment of heavily pretreated patients with hematological malignancies, showing an overall response rate (ORR) higher than 50% [25–27,29].

In the phase III study for the relapsed or refractory CLL/SLL (NCT02004522) [6], the efficacy and safety of duvelisib (3) was compared with ofatumumab, an approved monoclonal antibody. Duvelisib (3) monotherapy showed a significant improvement of the ORR when compared with ofatumumab, resulting in the approval of this drug as an additional option for treatment of relapsed or refractory CLL/SLL [5].

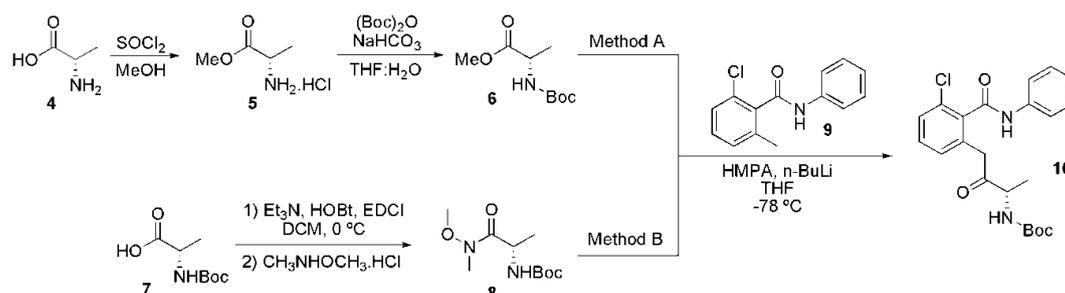
Combinations of the duvelisib (3) with other approved drugs are under clinical studies for the treatment of cancer. Duvelisib (3) is being tested in combination with romidepsin or bortezomib against relapsed/refractory T-cell lymphomas (NCT02783625) [30]. Duvelisib (3) is also being combined with venetoclax for the treatment of relapsed or refractory CLL or SLL (NCT03534323) [31].

The clinical trials for the treatment of inflammatory and autoimmune diseases were both phase II studies, where the safety and efficacy of duvelisib (3) was tested for the treatment of asthma (NCT01653756) [32] and moderate to severe rheumatoid arthritis (NCT01851707) [33], respectively.

2.5. Syntheses

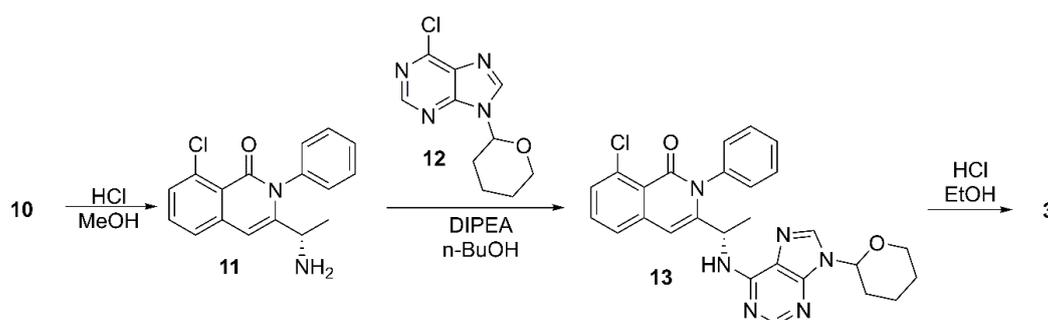
Duvelisib (3) can be obtained by two synthetic routes [34,35]. These routes differ in preparing the key intermediate, *tert*-butyl (*S*)-4-(3-chloro-2-(phenylcarbamoyl)phenyl)-3-oxobutan-2-ylcarbamate (10), from two different methods (Scheme 1).

In method A, the (*S*)-2-aminopropanoic acid (4) reacted with thionyl chloride and anhydrous methanol to form (*S*)-methyl 2-aminopropanoate hydrochloride (5). The amine group on 5 was protected by its reaction with di-*tert*-butyl dicarbonate. The protected intermediate 6 was then coupled with the carbanion derived from 2-chloro-6-methyl-*N*-phenylbenzamide (9), giving the key intermediate 10. In method B, *N,O*-dimethylhydroxylamine hydrochloride was added to a mixture of (*S*)-2-(*tert*-butoxycarbonylamino)propanoic acid 7, triethylamine, HOBT, EDCI in dichloromethane for the preparation of (*S*)-*tert*-butyl-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (8), which, after reaction with the carbanion of 9, furnished the same key intermediate 10.



Scheme 1. Methods for preparing the key intermediary, *tert*-butyl (S)-4-(3-chloro-2-(phenylcarbamoyl)phenyl)-3-oxobutan-2-ylcarbamate (**10**).

Treatment of the key intermediate **10** with hydrochloric acid in MeOH resulted in deprotection of the amine group and cyclization to form the isoquinolinone derivative **11** (Scheme 2). Next, the aromatic nucleophilic substitution reaction between **11** and 6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (**12**) was carried out, yielding 8-chloro-2-phenyl-3-((1S)-1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)isoquinolin-1(2H)-one (**13**). Finally, compound **13** was treated with hydrochloric acid in ethanol to remove the THP protecting group, resulting in the formation of the desired compound, duvelisib (**3**).



Scheme 2. Preparation of duvelisib (**3**) from *tert*-butyl (S)-4-(3-chloro-2-(phenylcarbamoyl)phenyl)-3-oxobutan-2-ylcarbamate (**10**).

3. Perspectives

The pharmacological profile of duvelisib (**3**) showed the safety and efficacy of this drug in the treatment of several hematological malignancies, indicating that it can be further approved for other uses beyond CLL, SLL, and FL. The use of duvelisib (**3**) for inflammatory and autoimmune diseases will be contested by the adverse events that occurred during the clinical trials, but the use of this drug for these applications probably will depend on the clinical benefit. The usefulness of the modulation of PI3K can be highlighted by the efforts on the discovery and development of novel PI3K δ , PI3K γ , and PI3K δ/γ for the treatment of cancer, inflammatory, and autoimmune diseases [22,23].

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