

Synthesis of a New Lopinavir Phosphinic Analog as HIV-1 Inhibitor

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How to cite this paper: Kellow, R. and Matziari, M. (2019) Synthesis of a New Lopinavir Phosphinic Analog as HIV-1 Inhibitor. *Journal of Materials Science and Chemical Engineering*, 7, 36-41.

<https://doi.org/10.4236/msce.2019.77005>

Received: May 27, 2019

Accepted: July 7, 2019

Published: July 10, 2019

Abstract

HIV/AIDS has been one of the most devastating global diseases. HIV-1 protease proteolytic action is responsible for the manufacture of grown, infectious species, consequently HIV-1 protease has become an attractive goal in the treatment and therapy of HIV. Several HIV-1 protease inhibitors based therapeutic agents are under investigation or currently in the market. Lopinavir (ABT-378) has a great value in this research field. Therefore, different methods have appeared aiming to develop efficient analogs by the utilization of variable techniques, since Lopinavir had showed low bioavailability when being prescribed alone, and various side effects after the combination of Lopinavir with another HIV-1 inhibitors such as Ritonavir, which is available in the markets nowadays under the brand name Kaletra. Replacement of the hydroxyethylene moiety in Lopinavir structure, which is responsible for the monohydroxylated metabolites with the stable to hydrolysis phosphinic group has been considered, since that hydroxyl group in the central core is responsible for the interaction with the carboxylic acid in the catalytic aspartyl residue of HIV-1 by hydrogen bonding and consequently supports the drug affinity to the protease. The small scale processes for the synthetic strategies for the new candidate phosphinic analog of Lopinavir protease inhibitor (PL1) is presented here in along with some preliminary pharmacological data.

Keywords

HIV-1, Lopinavir, PL1

1. Introduction

Human immunodeficiency virus is considered as a group of retroviruses causing sicknesses characterized by a delay in the onset of symptoms after infection

called lentivirus. This virus has two main types, HIV-1 which is mainly responsible for this epidemic, and HIV-2, which is related to the first type but it is widespread in western Africa [1]. HIV-1 protease is classified as an aspartic acid protease which contains 99 amino acid residues that include the active site at the interface between the protein units with a homodimer function, and similar to all dimers, it is symmetrical, with two fold rotational (C_2) symmetry [2]. Lopinavir (ABT-378) (**Figure 1**) is a peptidomimetic HIV-1 protease inhibitor which is considered to interact with the active catalytic site of the protease. Therefore, it has the ability to prevent the transformation process of polyprotein precursors into the mature form, and as a result, it blocks the division and replication operation of the protease inside the virus. It was discovered in 2000 as an improved analog of Ritonavir, and was firstly prescribed to control the interactions between Val 82 active site residues of the HIV-1 protease with the inhibitor, however the residuals of the virus were considerably transformed into drug resistant strains [3].

Phosphinic peptides act as potent and selective inhibitors of metalloproteases (Matrix metalloproteinase, Angiotensin-converting enzyme, Neprilysin, etc.) that are involved in many pathophysiological conditions, such as cancer and hypertension, exhibiting high selectivity and low toxicity properties [4] [5] [6]. Phosphinic peptide inhibitors of aspartic acid proteases have also been reported for serine proteases [7] and serine kinases [8].

2. Results and Discussion

2.1. Retrosynthetic Strategy for PL1

According to the retrosynthetic analysis study, four main fragments are present in PL1, **a-d**, which come from the disconnections 1 - 3. As shown in **Figure 2**, fragment **a** corresponds to the Cbz-(*R*)-Phe- PO_2H_2 [9], fragment **b** come from an acid chloride, fragment **c** corresponds to (2-nitroallyl) benzene [10], and fragment **d** to a valine analog [11].

2.2. Synthesis of Fragment a

The synthesis of ((*R*)-1-(((benzyloxy) carbonyl) amino)-2-phenylethyl) phosphinic acid **7a** (precursor of fragment **a**, **Scheme 1**) had taken place after several

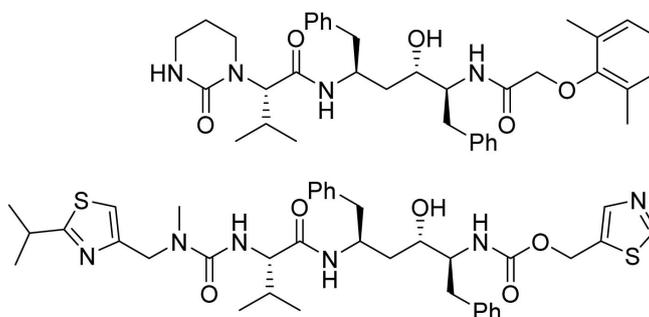


Figure 1. Lopinavir and Ritonavir structures.

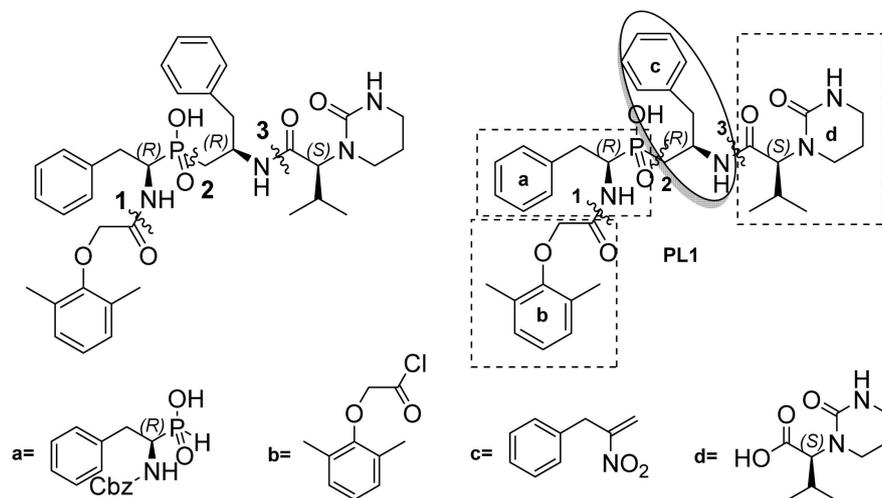
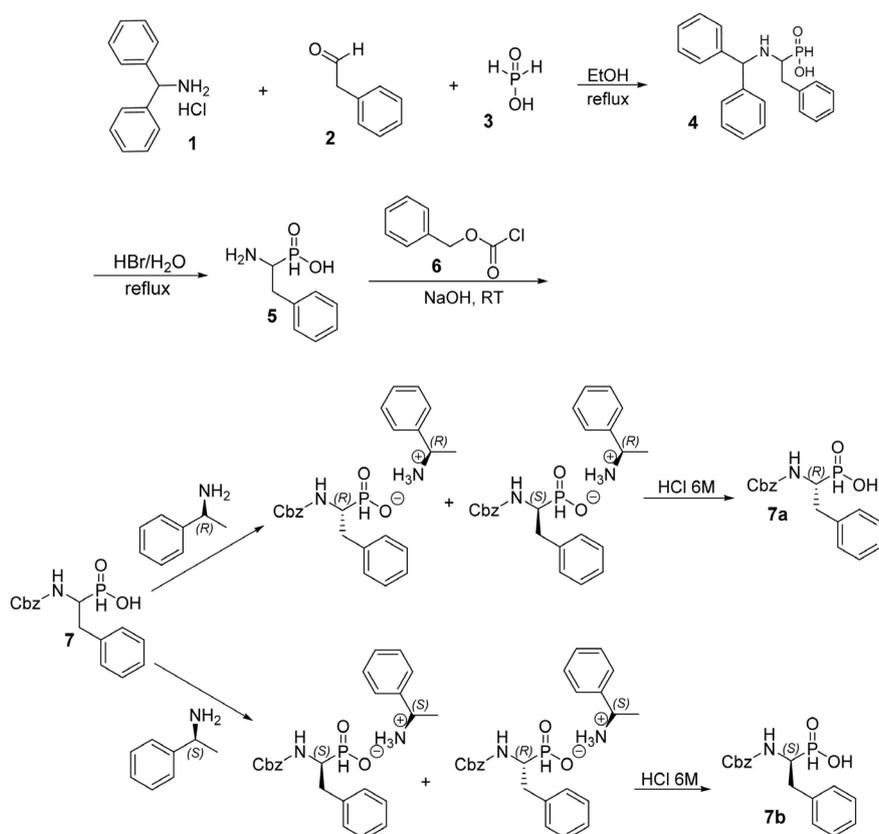


Figure 2. Main disconnections for PL1.



Scheme 1. Synthesis of fragment a.

steps, started from the addition of **3** to the *in situ* formed imine of **1** and **2** (Scheme 1). Removal of the diphenyl group by refluxing in strong acid followed by the protection of the amino group of the obtained product with benzyl carbonylchloridate **6** to produce the product **7** (precursor of fragment **a**) in the form of racemic mixture (Scheme 1). Then, the resolution through the formation of diastereomeric salts using (*R*)-phenylethyl amine led to the desired (*R*)-isomer

7a [9]. As shown in **Scheme 1**, the mixture of enantiomers of **7** was converted to salts with the chiral amine (*R*)-phenylethyl amine. The salt containing a mixture of two diastereomers, which was separated by crystallization. The procedure was repeated with (*S*)-phenylethyl amine to produce the (*S*)-isomer **7b**. The enantiomeric purity of the **7a** and **7b** was determined by optical rotation measurements.

2.3. Synthesis of the Precursor for Fragment c

The most high yielding attempt to obtain **9** was the reduction of (*E*)-(2-nitrovinyl) benzene **8** as shown in **Scheme 2**, followed by olefination to get product **10**.

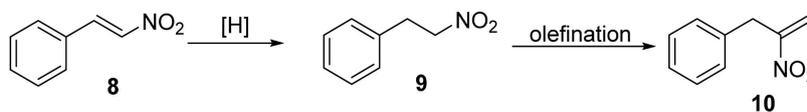
2.4. Synthesis of Fragment d

As shown in **Scheme 3**, the synthesis of **13** (fragment **d**) was accomplished in high yield through two steps beginning from the conversion of L-valine **11** to N-phenoxycarbonyl-L-valine and then transformed to the derivative **13** [11].

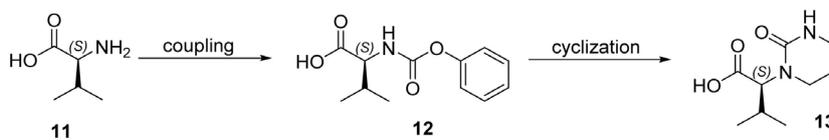
2.5. Assembly of PL1

PL1 was synthesized according to the series of reactions shown in **Scheme 4**, started from the assembly of the precursor for fragment **c** (2-nitroallyl) benzene (**10**) with fragment **a** (**7a**) through Michael addition reaction to afford **14** in a good yield. Then, the reduction reaction of **14**, which was achieved under very mild conditions leading to conversion of the nitro ($-\text{NO}_2$) group to amine ($-\text{NH}_2$) in a high yield without affecting the Cbz-protecting group to produce compound **15** as shown in **Scheme 4**. The next step was to assemble the resulted **15** with valine urea (fragment **d**) (**13**), which affording **16** in a good yield. Removal of carboxybenzyl (Cbz-) group of **16** was produced product **17** as shown in **Scheme 4**. The final step to obtain **PL1** was the coupling of **17** with fragment **b**, which was accomplished in good yield (**Scheme 4**).

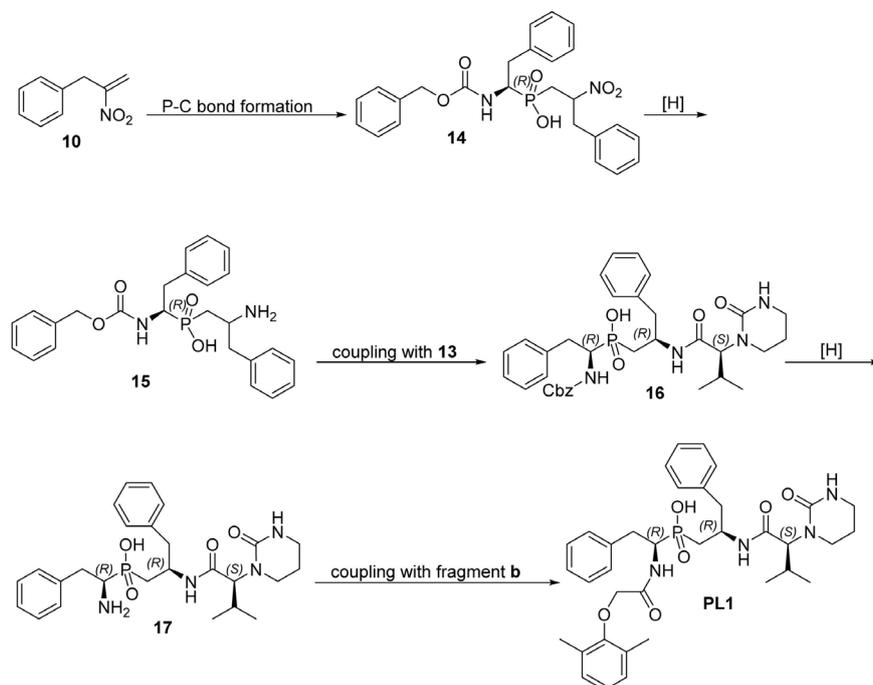
The synthesized **PL1** was tested against HIV-1 to test its potency as phosphinic inhibitor using HIV-1 Protease Inhibitor Assay Kit (Fluorometric) (ab211106) by Abcam. The result displayed that **PL1** efficiently inhibits HIV-1 with an IC_{50} in the low nanomolar range ($\text{IC}_{50} = 50 \text{ nm}$).



Scheme 2. Synthesis of the precursor for fragment **c**.



Scheme 3. Synthesis of fragment **d**.



Scheme 4. Assembly of **PL1**.

3. Conclusion

HIV/AIDS has become a devastating disease and resulted in an enormous human suffering. Lopinavir played a major role in the era of boosted protease inhibitor therapy, and in offering a good option to patients affected with this virus. Considering those findings, **PL1**, a new potent Lopinavir phosphinic analog as HIV-1 inhibitor was designed and synthesized. Its potency was assessed toward HIV-1 inhibitory and pharmacokinetic activities.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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