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Short Review Paper

Anti-covid repurposed drug Remedesivir: Zhang's catalytic chiral approach

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Abstract

Herein, author has given glimpses of possible treatment agents for the SARS-COV2 infections and discussed the case study of the synthetic utility of Remedesivir in the present scenario by highlighting Zhang's catalytic asymmetric synthetic approach. It is shown that the chiral bicyclic imidazole catalyst plays vital role for the better stereoselectivity with excellent reactivity via dynamic kinetic asymmetric transformation (DyKAT).

Keywords: *n*-COVID-19, Remedesivir antiviral drug, dynamic kinetic asymmetric transformation, chiral base, *SP*-phosphoramidate.

Introduction

Savi and Hughes *et al*. have recently reviewed the advancement of several drug candidates in clinical trials as shown in Figure-1, for treating Covid-19[1]. Author has also given a glimpse on the importance of medical diagnosis in treating Covid-19, and currently on the way to repurpose small drug molecules such as Remdesivir and Favipiravir[2].

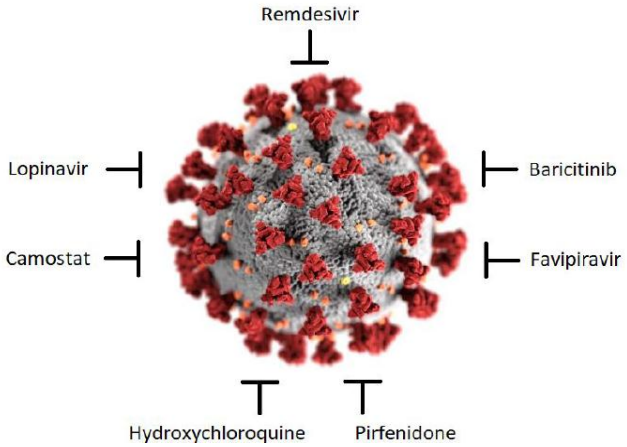
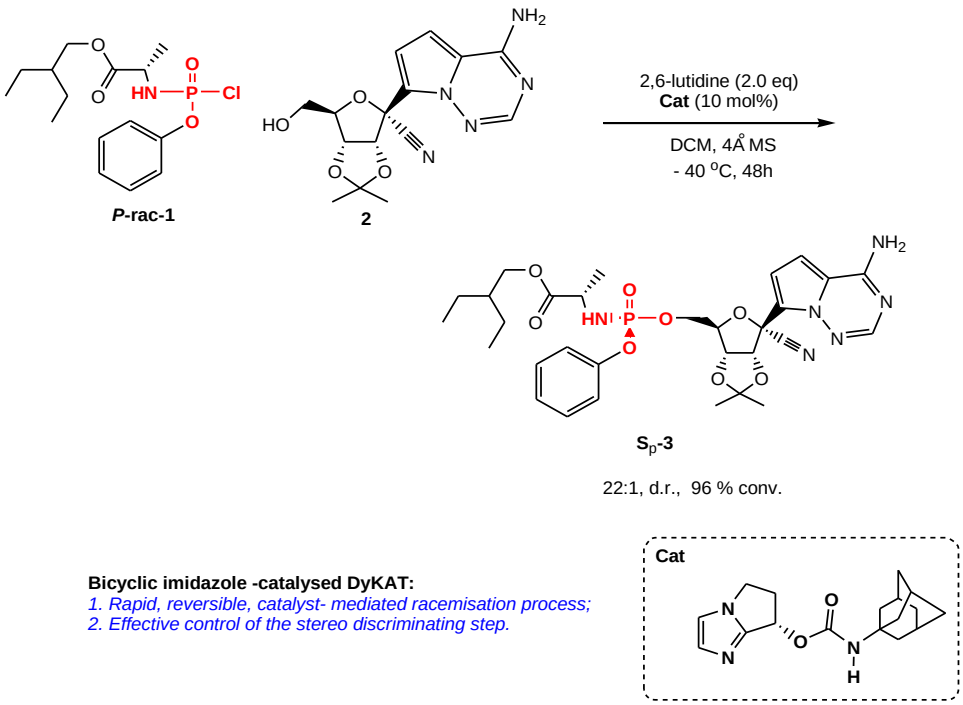


Figure-1: Repurposing small molecule drugs-Covid 19 cure.

The outbreak of novel corona virus (2019-nCov) was first observed in the Wuhan city of Central China around 12th December 2019[3] which has become pandemic, confirming 54 million cases including 1.31 million deaths across the globe as of 16th November 2020. As on today, there is no specific drug or vaccine to effectively treat COVID-19. In this regard, this pandemic has created worldwide urge to repurpose the present acceptable drugs. Based on the recent update by Jean and others,[4] various treatments are being administered to covid patients. At present, around 60 Covid-19 drug vaccine candidates are being explored as we all know that development of a vaccine takes longer duration with enormous cost[5]. Hill *et. al.* have very recently compared the cost effectiveness of various repurposed drug candidated for combatting Covid-19[6]. *In this case report, author has focused on critical evaluation of use of Remedesivir as potential drug candidate in the present scenario and its limitations.* Remdesivir (GS-5734/Veklury), a broad spectrum antiviral agent, was synthesized by Gilead Sciences[7] seems to be a viable treatment for Covid-19[8,9]. Due to it's role in inhibiting RNA polymerases, US FDA gave approval for Covid-19 emergency treatment on 1st May 2020[10]. Although, the pharma company is determined to deliver about 2 million doses by this end of 2020, the quantity does not meet up the current medical needs. Henceforth, there is current need of hour to formulate a cost-effective and viable synthetic strategy to remedesivir in order to meet up the needs of patients across the world. In this regard, very recently, Zhang and co have reported an efficient first catalytic asymmetric synthesis of Remdesivir in an effective atom-economy and viable synthetic point of view[11].

It is shown that the chiral bicyclic imidazole catalyst plays vital role for the better stereoselectivity (96% conv., 22:1 *SP*:*RP*) with excellent reactivity via first-order dynamic kinetic asymmetric transformation (DyKAT). Scaling up the reaction to 10g batch with almost similar outcomes, proved to be definitely an industry viable application. Generation of the phosphorus-based stereogenic center is a key and challenging task in the preparation of remdesivir[12].

Siegel and co.[13] reported first generation synthesis of enantiopure *SP*-phosphoramidate using chiral preparative HPLC. Later, Warren et al[14]. required additional synthetic steps and chiral resolution that lead to low synthetic efficiency. In both the approaches, *there was no selectivity of P-chirality* involving second order kinetics.



Scheme-1: Catalytic asymmetric synthesis of Remdesivir.

The significant findings of Zhang's methodology[11] (Scheme-1) are as follows: i. It is evident from the experimental results that catalyst with more nucleophilicity is responsible for highly reactive phosphorylation, ii. both the precursors have almost no role in stereochemical induction of the *P*-stereocenter, iii. presence of 2,6-lutidine in the stereodiscriminating step. iv. catalyst loading did not effect the d.r value, v. first-order dependence on catalyst concentration, vi. chiral catalyst was effectively employed for the dynamic kinetic asymmetric transformation.

The successful synthetic strategy by Zhang et al.[11] will undoubtedly open up new ways to develop catalyst/base for a large scale, stereoselective and cost-effective synthesis of Remedesivir.

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