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Exploration of the synthesis of imidazo[1,2-a]pyridin-3-amine derivatives with heteroatom linkers as potential HIV-1 reverse transcriptase inhibitors

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Abstract

The biological activity of imidazo[1,2-*a*]pyridine compounds as antimicrobial, antineoplastic and antiviral agents has been well documented for both *in vitro* and *in vivo* studies. Of particular importance for this study was the antiviral properties of these agents against the HI virus. Previous studies in our laboratory led to the discovery of an imidazo[1,2-*a*]pyridine analogue with appreciable antiviral activity against wild-type HIV reverse transcriptase with an IC_{50} value of 0.18 μM and a selectivity index of 867. In our quest to optimize the antiviral activity of the analogue and its derivatives, a series of virtual modelling studies was performed. The studies revealed that a heteroatom linker and possibly a $-CH_2$ bridge between the imidazole ring of the imidazo[1,2-*a*]pyridine core and the phenyl group substituent at position C-2, has the potential to improve binding affinity of the analogue at the allosteric pocket of HIV-1 reverse transcriptase. Our focus was on inserting a nitrogen linker in this position. To do this, we first attempted to synthesize imidazo[1,2-*a*]pyridine analogues without an attachment at position C-2. However, unexpectedly, imidazo[1,2-*a*]pyridines with a methyl ester attached at position C-2 were obtained. This prompted us to revise our synthetic strategy given the structural diversity and possible transformations of the ester group. The new approach was to functionalize the ester group by transforming it into an amine via an amide group conversion.

Interestingly, upon scaling up the reactions to synthesise more ester compounds, we discovered that the carboxylic acid group of glyoxylic acid undergoes rapid decarboxylation during cyclization and as a result no ester derivatives could be obtained and instead imidazo[1,2-*a*]pyridine compounds without an attachment at position C-2 were exclusively obtained. To remedy this effect, the carboxylic acid of glyoxylic acid was first protected by esterifying in methanol to afford a methyl glyoxylate ester. The ester was subsequently reacted *in situ* in a multicomponent Groebke-Blackburn-Bienaymé reaction involving 2-amino pyridine derivatives and cyclohexyl isocyanide in the presence of perchloric acid to afford the desired ester compounds.

The ester intermediate compounds were reacted with 2-chloro-aniline in the presence of aluminium chloride catalyst and sodium hydride in an attempt to form an amide product which could be reduced to an amine. However, the poor yield of the reaction meant that this

was not a viable approach. The ester analogues were then subjected to a base hydrolysis reaction using aqueous NaOH in an attempt to obtain imidazo[1,2-*a*]pyridine compounds with a carboxylic acid moiety at position C-2. However, we were unable to obtain the carboxylic acid derivatives and instead compounds without an attachment at position C-2 were obtained. This served as confirmation to earlier studies by other researchers that carboxylic acid derivatives of imidazo[1,2-*a*]pyridin-3-amines are unstable and impossible to obtain as they rapidly self-decarboxylate to afford mono-substituted imidazo[1,2-*a*]pyridin-3-amines.

The next step was to reduce ester analogues to alcohols using $LiAlH_4$. This was successfully achieved in excellent yields. This was followed by tosylation of the alcohol group but surprisingly we did not isolate the tosyl product, instead an aldehyde product was isolated. This was nonetheless a positive outcome as it served as confirmation that aldehyde derivatives of these compounds were stable as compared to their carboxylic acid counterparts. Oxidation of the alcohol analogues by PCC in an attempt to synthesise the aldehydes was then undertaken. However, the desired aldehydes could not be obtained as anticipated. Single Crystal X-ray Diffraction (SCXRD) data analysis revealed that a ring-opened product was instead obtained and had a missing carbon in relation to its parent compound. On close examination, we speculated that the missing carbon could have been lost as CO_2 and that the oxidation reaction possibly proceeded via decarboxylation and subsequent ring opening. A less harsh method of oxidising the alcohol using IBX as oxidant was then employed. However, similarly a ring-opened product was obtained, albeit in lower yields than with oxidation with PCC. Using an oxidizing enzyme, laccase, from *T. versicolor* with TEMPO as a mediator afforded the same ring-opened product in the quickest time of 5 minutes in an open vessel reaction.

This prompted us to seek an alternative route for synthesizing the aldehydes. The alcohol was first brominated with molar equivalents of PBr_3. Upon isolation, it was discovered that the bromide product was highly hygroscopic, and it had the potential to hydrolyse back to the alcohol. The alkyl bromide was then reacted without further purification with DMSO in the presence of $NaHCO_3$ to furnish the desired aldehyde. Further reductive amination on the aldehyde afforded the desired novel imidazo[1,2-*a*]pyridines with a nitrogen and -CH_2 linker between the imidazopyridine scaffold and the phenyl ring.