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Graphical Abstract

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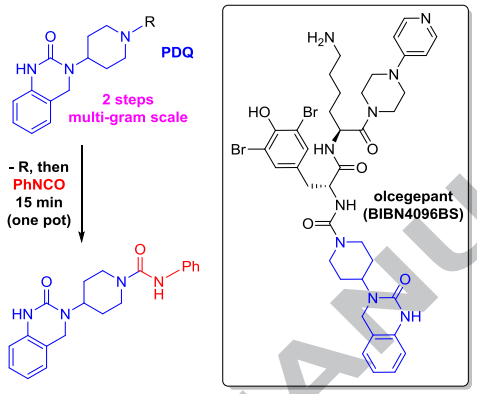

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An Efficient Synthesis of the Piperidinyl Dihydroquinazolinone (PDQ) Fragment of Olcegepant

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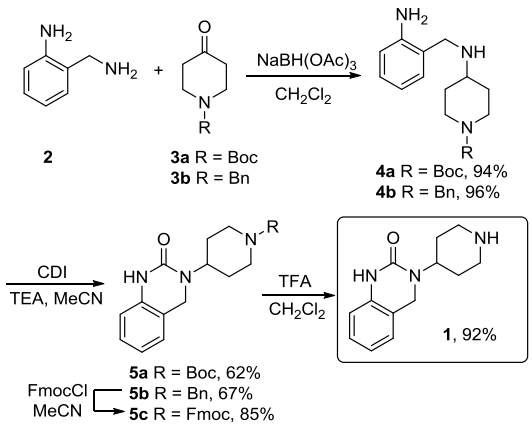
ABSTRACT

Olcegepant is one of the most potent and selective small molecule CGRP antagonists for the treatment of migraine headaches. Herein, we describe a new and efficient synthesis of the key piperidinyl dihydroquinazolinone (PDQ) fragment of olcegepant. PDQ plays a key role in the activity of CGRP antagonists. Primary improvements over existing methods include a high-yielding reductive amination step, greater overall yield, and operational simplicity. Coupling of PDQ to a D-tyrosine derivative effectively produced over one half of the total molecular structure of olcegepant. A unique tandem deprotection-nucleophilic addition sequence was also applied to the coupling of Fmoc-PDQ with phenyl isocyanate.

Olcegepant (BIBN4096BS) is a potent and highly selective calcitonin gene-related peptide (CGRP) receptor antagonist that was shown to be an effective treatment for migraines in clinical trials.[1] Additionally, olcegepant is used widely in the laboratory as a chemical tool to block vasodilation.[2] Within the chemical structure of olcegepant lies a key 3-(piperidin-4-yl)-3,4-dihydroquinazolin-2[1*H*]-one (PDQ) fragment **1** (Scheme 1) that is central to the activity of the drug.[3] The PDQ substructure is also present in a number of other CGRP antagonists such as thiazolidinones,[4] tyrosine surrogates,[5] aspartates and succinates,[6] caprolactams,[7] benzodiazepines,[8] carbamates,[9] oxadiazoles,[10] and imidazoles.[11] In addition, PDQ is an important heterocycle found in constrained aminobenzazepinone peptidomimetics,[12] inhibitors of the Na^+/Ca^{2+} exchanger,[13] and muscarinic acetylcholine receptor agonists.[14]

Given the importance of PDQ to the development of therapies for migraine and other medical conditions, efficient methods of synthesis are critical to advancing research in these areas. Herein, we report a short, flexible, and scalable synthesis of PDQ and its coupling to 3,5-dibromo-D-tyrosine methyl ester, to effectively yield over one half of the olcegepant structure. Additionally, we report a one-pot deprotection-coupling of *N*-Fmoc-protected PDQ to phenyl isocyanate.

In our attempts to prepare PDQ through existing methods we recognized that the process could be improved with respect to the number of steps, overall yield, and operational simplicity by pursuing an alternate pathway. PDQ was originally prepared by Takai and co-workers in four steps (5% overall yield) through a reductive amination strategy carried out between 2-nitrobenzaldehyde and *N*-benzyl-4-aminopiperidine.[15] More recently, PDQ has been prepared through a four-step sequence involving nucleophilic substitution by an aminopiperidine on 2-nitrobenzyl bromide.[16] A similar strategy was accomplished on solid support.[17] One common requirement of each of these pathways is the need to reduce a nitrobenzene moiety to an aniline, which increases the number of steps.

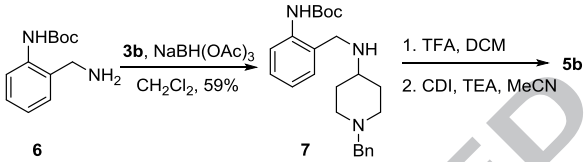


Scheme 1. Our approach to the synthesis of PDQ, highlighting improved yields and protecting group diversity.

Our approach to the synthesis of PDQ (Scheme 1) proceeds through a unique reductive amination between the more nucleophilic benzyl amine of 2-aminobenzylamine **2** and an *N*-protected 4-piperidone **3a-b** in excellent yield. Subsequent cyclo-condensation with 1,1'-carbonyldiimidazole (CDI) forms the 3,4-dihydroquinazolin-2[1*H*]-one heterocycle **5a-b**. At this point, the Boc-protecting group can be removed from **5a** by treatment with trifluoroacetic acid to yield the final PDQ **1**.[18] This three-step synthesis avoids the need to reduce a nitro group and represents an efficient and operationally simple pathway to gram-scale quantities of PDQ. The synthesis results in a 54% overall yield of **1** and requires only one chromatographic purification. The synthetic route can also be accomplished with a *N*-benzyl protecting group, which can be removed in the final step *via* hydrogenolysis. We were also delighted to find that the benzyl

protecting group could be easily exchanged by treatment with Fmoc chloride in acetonitrile to yield **5c**. We originally developed this distinctive protecting group exchange to circumvent decomposition during removal of a *N*-benzyl group *via* hydrogenolysis on a different compound.[19] Presumably, the exchange proceeds through an intermediate quaternary ammonium ion, followed by ejection of benzyl chloride *via* nucleophilic substitution. The reaction is high yielding and operationally simple due to precipitation of the product caused by the relative insolubility of the Fmoc group in acetonitrile. The diversity of protecting groups in our synthesis of PDQ adds versatility, which is particularly important during the coupling of PDQ to other chemical fragments in the development of CGRP antagonists.

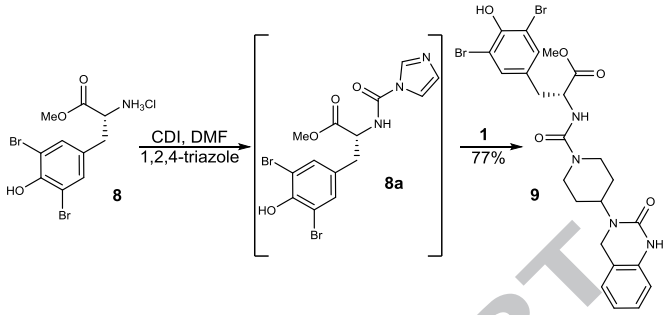
During the reductive amination step, if the aryl amine of **2** were to react with the ketone, rather than the benzyl amine, a constitutional isomer of **1** would result. Aniline is known to react with *N*-Boc-4-piperidone in reductive amination reactions.[20] However, no isomer was observed under our reaction conditions. To verify that the more nucleophilic benzyl amine of **2** engaged with the ketone of **3** preferentially during reductive amination, we conducted the reaction with an aryl-*N*-Boc protected **6**[21] (Scheme 2). Compound **7** was obtained in 59% yield. The yield is lower than that observed in Scheme 1, presumably due to steric hindrance on the nucleophilic benzyl amine from the adjacent *N*-Boc group. After Boc removal and cyclo-condensation of **7**, we obtained the expected **5b**. The NMR spectra matched that of **5b** prepared through the sequence described in Scheme 1.



Scheme 2. Alternate synthesis of **5b** used to verify that only the benzyl amine participates in the reductive amination step.

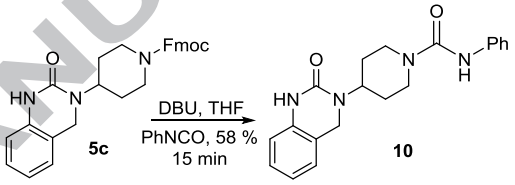
With PDQ **1** in hand, we next wanted to demonstrate its coupling to 3,5-dibromo-D-tyrosine methyl ester **8** (Scheme 3) through a connecting urea spacer. The product **9**, constitutes over one half of the olcegepant total structure. Tyrosine derivative **8** is prepared in two steps from D-tyrosine[22] and may be used in the coupling step directly as the hydrochloride salt. In our protocol adapted from the olcegepant production patent,[23] compound **8** was treated with CDI in the presence of 1,2,4-triazole, producing intermediate **8a**. PDQ **1** was added at room temperature and then heated at 55 °C for 1.5 h to initiate nucleophilic acyl substitution of the imidazolyl group of **8a** with **1**. The reaction was cooled to room temperature and water added. Product **9** precipitated and was then collected and purified by column chromatography. This simplified procedure allows for an efficient and scalable preparation of advanced intermediates in the synthesis of olcegepant and its derivatives.

Previously, we developed a rapid, one-pot tandem deprotection-coupling of an Fmoc-protected amine to isocyanates.[19] This strategy was used in the synthesis of SHA 68, a potent and selective antagonist of the neuropeptide S receptor (NPSR). The strategy proved useful in the development and screening of a library of SHA 68-based NPSR antagonist derivatives. We were curious if this tandem reaction would work on Fmoc-protected PDQ **5c**. If so, the procedure may prove useful in the development of future PDQ-based libraries of potential CGRP antagonists.



Scheme 3. Synthesis of over half of the olcegepant molecular structure.

We were delighted to find that when **5c** was suspended in THF with phenyl isocyanate and treated with DBU, the desired product **10** was produced in good yield (Scheme 4). The reaction was judged complete at 15 minutes (by TLC). The product precipitated upon addition of water to the reaction medium. Presumably, DBU quickly deprotonates the Fmoc group, leading to decomposition of the carbamate. The resultant soluble amine then attacks phenyl isocyanate to produce urea **10**.



Scheme 4. Rapid Fmoc deprotection and nucleophilic addition of the resultant amine to phenyl isocyanate.

It should be noted that compounds containing the PDQ moiety are prone to benzylic oxidation in solution over time.[9] In fact, olcegepant itself has been observed to undergo such oxidation, and yet still retains good activity.[24] We did not observe any oxidation by-products during the course of our study. However, any future development of PDQ-based libraries of CGRP antagonists should be aware of the potential oxidation.

In summary, we report an efficient and operationally simple three-step synthesis of PDQ **1** that is amenable to use of multiple *N*-protecting groups. We demonstrated coupling of PDQ **1** to tyrosine derivative **8**, which is useful in the preparation of the CGRP antagonist olcegepant. Finally, we successfully applied our previously reported tandem deprotection-coupling strategy to the reaction of Fmoc-PDQ **5c** with phenyl isocyanate.

Acknowledgments

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Conflicts of Interest

We declare no conflict of interest.

Supplementary Data

Supplementary Information is provided.

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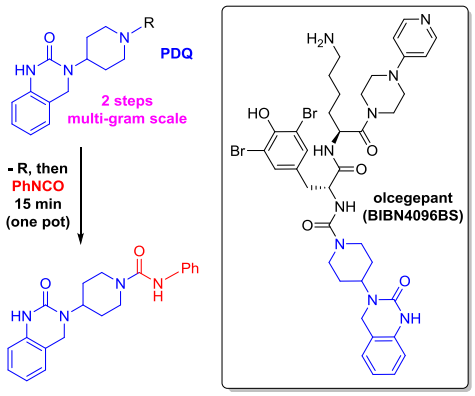

Highlights

- Highly efficient synthesis of a piperidinyl dihydroquinazolinone (PDQ) heterocycle
- High-yielding reductive amination step improves the overall yield of PDQ
- Unique one-pot *N*-benzyl-to-Fmoc protecting group exchange was demonstrated
- Applied a tandem deprotection-isocyanate coupling strategy to Fmoc-PDQ