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Regioselective assembly of fused pyrazole-azepine heterocycles: Synthesis of the 5-HT$_7$ antagonist 1-benzyl-3-(4-chlorophenyl)-1,4,5,6,7,8-hexahydropyrazolo[3,4-*d*]azepine

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ABSTRACT

The synthesis of the 5-HT$_7$ antagonist 1-benzyl-3-(4-chlorophenyl)-1,4,5,6,7,8-hexahydropyrazolo[3,4-*d*]azepine is described using a regioselective assembly of a pyrazole ring fused to an azepine ring. Two different approaches were examined for the construction of the fused pyrazole-azepine heterocyclic core. These were based on the timing and method of installation of the appended aryl ring and construction of the fused heterocycle. The team focused on a route that featured a palladium coupling reaction to introduce the aryl ring via a pyrazole triflate and a selective alkylation to set the position of benzyl moiety on the pyrazole nitrogen. This led to a scalable synthesis of **1** (JNJ-18038683) allowing the discovery team to select and advance a clinical candidate.

The 5-HT$_7$ receptor is the most recently discovered member of the serotonin family of signaling proteins. Protein expression for 5-HT$_7$ is predominantly located within the central nervous system and can be found in the cortex, thalamus, hypothalamus, septum and striatum. 5-HT$_7$ receptors are involved in the regulation of circadian rhythms and consequently their modulation may be beneficial in antidepressant drugs' pharmacology [1]. This prompted the Neuroscience discovery team at Janssen to explore the potential for selective 5-HT$_7$ modulations in the treatment of mood and related disorders (Fig. 1).

A high through-put screening campaign of the Janssen compound collection followed by initial hit optimization resulted in the identification of **1** as a selective 5-HT$_7$ antagonist. Subsequently we reported [2] the full pre-clinical assessment of **1** in animal models for 5-HT$_7$ engagement as well as the clinical evaluation of **1** (JNJ-18038683) in healthy volunteers. 5-HT$_7$ blockade demonstrated based on sleep parameters, which were utilized as surrogate biomarkers for target engagement. Further clinical studies are still needed to evaluate the full potential of 5-HT$_7$ ligands, including JNJ-18038683. This current communication describes the synthetic challenges that were encountered during the discovery of JNJ-18038683 and the chemistry that was developed to help advance the program).

The fused azepine heterocycle represents in interesting motif for exploration [3]. In evaluating the structure of **1**, two primary strategies were explored for the construction of the fused pyrazole-azepine heterocyclic core. Initially, following a method described by Winters [4] et al., *N*-Boc azepan-4-one **2** was treated with morpholine and catalytic TsOH in toluene to form isomeric enamines upon dehydration [5]. Treatment of the mixture with benzoyl chloride affords isomeric 1,3-diketones that are not isolated but used directly in the ensuing step. Reaction of the 1,3-diketone intermediates with hydrazine [6] provides the core heterocyclic framework in a three-step sequence that can be telescoped in a single vessel. However, this procedure results in the production both fused pyrazole isomers **3** and **4** in an approximately ~ 1:1 mixture likely due to enamine formation occurring at either enolizable position of the non-symmetrical azepane ketone (**2**) Scheme 1. Whilst this method was highly valuable for the generation of the initial structure activity relationship (SAR) studies for the program, it became obvious that moving forward with compound optimization and more advanced profiling that an improved and scalable synthetic route would become necessary to enable the studies required for compound progression and ultimately new development compound selection.

The issue that represented a high priority for the team was addressing the regiocontrol of the fused pyrazole onto the azepine ring which would allow for a more efficient access to the desired heterocycle **4**. The seven-membered ring ketone found in azepane **2** lacks a plane of symmetry through the carbonyl and thus both

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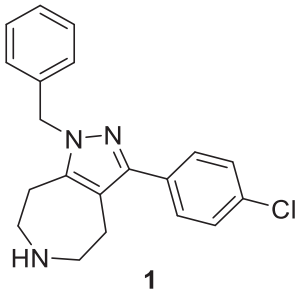
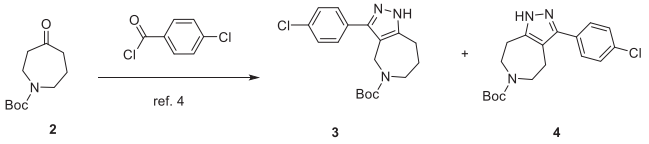


Fig. 1. JNJ-18038683.



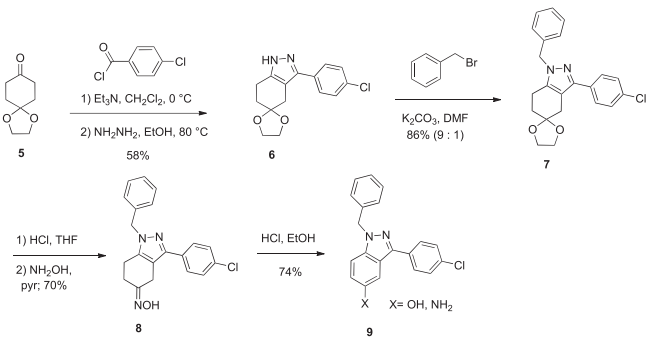
Scheme 1. Non-selective Pyrazole Synthesis.

possible enamines were being formed leading to two different fused pyrazole-azepine isomers. One potential solution would be to take advantage of a symmetrical ketone to build the pyrazole prior to a ring expansion event to afford the azepine ring. The Beckmann rearrangement of a cyclohexanone oxime to give a caprolactam would be well suited to explore a late stage ring expansion strategy. There have also been reports of a Dibal-H mediated reductive Beckmann rearrangement [7] that would allow for the direct formation of the corresponding secondary amine. To examine this in detail Scheme 2, 1,4-dioxaspiro[4.5]decan-8-one, a protected 1,4-dione, was subjected to the identical three step one-pot sequence to construct the 4-chloroaryl pyrazole in modest yield affording fused heterocycle **6**. Alkylation of **6** with benzyl bromide produced the fully elaborated fused pyrazole **7** along with traces of a benzyl regioisomer that was easily removed by flash silica gel column chromatography. The oxime **8** was then prepared by treating the ketal with aqueous HCl to remove the protecting group followed immediately by the addition of hydroxylamine hydrochloride to the resulting ketone in a solution of pyridine. The oxime **8** precipitated directly from the reaction and was thus isolated by a simple filtration.

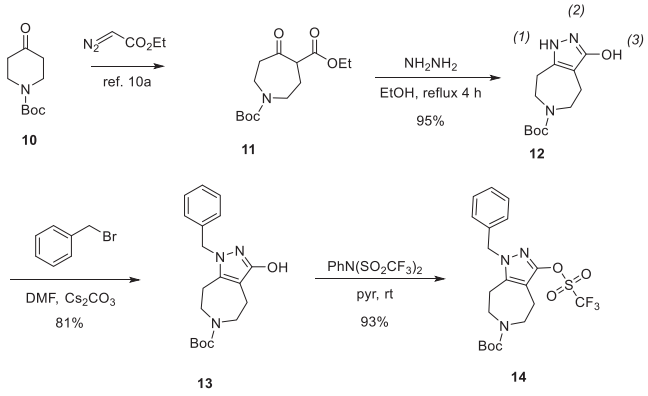
Subjecting oxime **8** to strong acids (HCl; H_2SO_4, TFA) to attempt a Beckmann rearrangement resulted in generating the corresponding fully aromatic aniline or phenol analogue of **9** via a dehydration/aromatization sequence that is known as the Semmler-Wolff reaction [8]. The oxime was poorly soluble in most organic solvents and attempts to convert the oxime hydroxyl group into a suitable leaving group, such as a tosylate, was also met with failure. A reductive Beckmann was also attempted on oxime **8** (Dibal-H at 0 °C) however this produced multiple products as was not perused.

This led us to explore synthesizing the seven-membered ring much earlier in the synthetic sequence. Diazo compounds are known to react with ketones in a Tiffeneau-Demjanov-type ring expansion reaction to give a one carbon ring expansion when the ketone substrate is cyclic [9]. The inserting carbon on the diazo moiety carries with it any substituents during the formation of the new N + 1 ring. Therefore, a diazoacetophenone would directly provide the correct 1,3-diketo intermediate required for the fused pyrazole system in question. However, this strategy would require the reaction between diazomethane and the corresponding benzoyl chloride and we wished to avoid the necessity of having to prepare diazomethane on scale. We consequently chose to examine the use of ethyl diazoacetate, which is commercially available and a more stable diazo substrate. The reaction between *N*-Boc-4-piperidone and ethyl diazoacetate proceeds smoothly to provide the corresponding β-keto ester **11** [10]**.** An examination of **11** reveals that all three carbon atoms required for the pyrazole heterocycle are contained within the β -keto ester subunit. Therefore, we sought to explore the utility of **11** as a central starting point in the construction of fused pyrazole-azepine heterocycles Scheme 3.

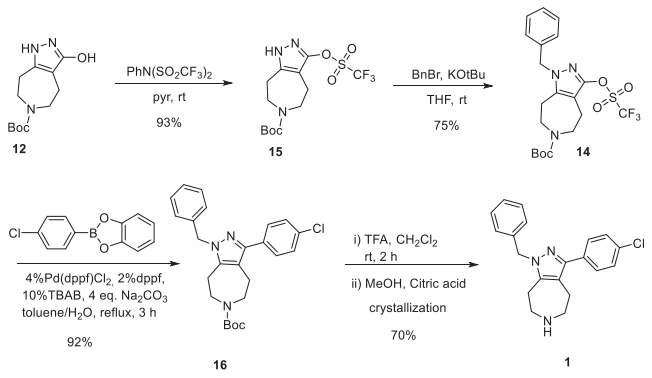
To this end, reaction of **11** with a slight excess of hydrazine in hot ethanol gave pyrazole **12** in excellent yield. Treatment of **12** with benzyl bromide provided a mixture of benzylated compounds in a ca. 81% overall yield. The mixture was a ~ 1:1 ratio of the N and O benzylated isomers that were not separable on flash silica gel chromatography. Gratifyingly, when this mixture was subjected to *N*-phenyltriflamide, the desired O-triflate **14** could be isolated cleanly away from the mixture containing the O benzyl derivative. No attempts were made to recycle this O-benzylated side product. The sequence leading to triflate **14** was ultimately improved by changing the order of triflate formation and benzylation. As shown in Scheme 4**,** pyrazole **12** was first treated with *N*-phenyltriflamide in pyridine to provide pyrazole triflate **15** in excellent yield. The resulting reagent byproduct from *N*-phenyltriflamide after the transfer of a single trifluorosulfinyl moiety was found to interfere with subsequent steps. This reagent byproduct could be removed by simply washing the mixture with a mild base, such as aqueous potassium carbonate, allowing for the isolation of the desired triflate **15** in sufficient purity to proceed on in the sequence. The alkylation of the pyrazole heterocycle had already exhibited a preference for reactivity at the N1 nitrogen and with the triflate in place, similar regiochemistry was observed as the benzyl group was selectively installed on the N1 nitrogen of **15** with benzyl bromide and potassium *tert*-butoxide to give key intermediate **14**.



Scheme 2. Synthesis of Oxime 8.



Scheme 3. Selective Synthesis of Key Pyrazole Triflate.



Scheme 4. Synthesis of JNJ-18038683.

Interestingly, when examining the possibility of bringing in the benzyl group already incorporated on the hydrazine fragment, treatment of keto ester **11** with benzyl hydrazine exclusively produced the isomeric benzyl derivative of **13**. This did provide expedient access to a series of differentially substituted heterocyclic systems whose SAR was explored separately [11].

With key pyrazole triflate **14** in hand, the Suzuki-Miyaura reaction of pyrazole triflates [12] was used, as previously described, to introduce the 4-chlorophenyl moiety onto the core heterocycle giving the fully elaborated structure **16**. Indeed, the coupling reaction to install the aryl ring proceeded as expected in good yield. A bi-phasic solvent system of toluene/water was found to be optimal and no triflate hydrolysis was observed. Traces of a second Suzuki reaction to give a bi-aryl side-product was observed and minimized by limiting the amount of boronic ester used in the coupling reaction (1.1–1.2 equiv). Removal of the BOC protecting group was accomplished by treatment of **16** with trifluoroacetic acid to give the free base of the amine after standard workup. The free base was converted into the corresponding citrate salt and salt formation was then carried out with a slurry of the free base and citric acid in methanol. A final recrystallization provided the clinical candidate **1** as a free-flowing non-hydroscopic powder (Scheme 4).

In conclusion, a concise and scalable synthesis of the 5-HT_7 antagonist JNJ-18038683 (**1**) has been developed as described above. Key issues were addressed in the regiochemistry of the pyrazole heterocycle during the formation of the fused junction with the azepine ring. The substitution pattern on the pyrazole nitrogen was established by selective alkylation between a benzyl halide and the fused pyrazole triflate. This procedure was used to prepare JNJ-18038683 in support of toleration studies to enable a FIH start in Phase 1. In addition, using benzyl hydrazine in the pyrazole formation with beta keto ester **11** provided a complimentary benzyl substitution pattern on the pyrazole heterocycle. Future exploration is on-going to examine the activity profiles of these series of differentially substituted pyrazoles.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152843.

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