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Conformation of *gem*-disubstituted alkylarylpiperidines and their implication in design and synthesis of a conformationally-rigidified NK_1 antagonist

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Abstract

Piperidines are ubiquitous in pharmaceuticals and bioactive natural products. Understanding the structural and functional properties of piperidines plays key role in drug design and development. This paper reported studies of conformation of a set of *gem*-disubstituted methylphenylpiperidines in the context of discovery of NK_1 antagonists. The findings led to re-design and an efficient synthesis of a potent NK_1 antagonist with excellent *in vivo* activity and rodent and monkey pharmacokinetic profiles.

Key Words

Piperidine conformation
NMR study on conformation
Piperidine synthesis
Diastereoselective synthesis
NK_1 antagonists

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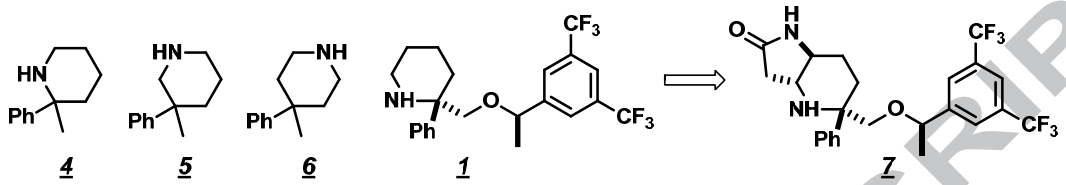
Graphic Abstract:

Conformation studies of piperidines 1 and 4-6 revealed insights that guided design and synthesis of a potent NK_1 antagonist 7 with excellent pharmacokinetic properties.



4 *5* *6* *1* *7*

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Conformation of *gem*-disubstituted alkylarylpiperidines and their implication in design and synthesis of a conformationally-rigidified NK_1 antagonist

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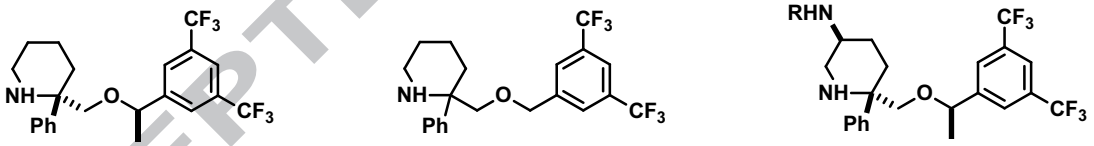
Piperidines are important motifs in pharmaceuticals and bioactive natural products.[1] Understanding the structural and functional properties of piperidines naturally plays key role in drug design and development.[2] Synthesis of piperidines also attracted much attention and several reviews[3] have been published on that subject. In this paper, we would like to report our study of conformation of a set of *gem*-disubstituted methylphenylpiperidines in the context of discovery of neurokinin 1 (NK_1) antagonists.[4] Our findings led to re-design and an efficient synthesis of a potent NK_1 antagonist with excellent *in vivo* activity and rodent and monkey pharmacokinetic profile.

Neurokinin 1 (NK_1) receptor belongs to the family of G-protein coupled receptors (GPCRs). This receptor mediates the action of substance P and other tachykinins in both the central and peripheral nervous systems. Therefore, NK_1 receptor antagonists may have therapeutic values in treating emesis, anxiety, depression, inflammation and pain.[4] In 2003, US Food and Drug Administration (FDA) approved Merck's Emend® for the treatment of chemotherapy-induced nausea and vomiting (CINV).[5] This demonstrated the clinic utility of NK_1 antagonists and further stimulated discovery research in this area. Recently we reported[5] our discovery of a non-racemic NK_1 antagonist **1** based on an earlier literature lead **2**.[6] Shortly after establishment of **1** as our program lead for in-depth medicinal study, we also accomplished two complimentary stereoselective asymmetric syntheses[7] of **1**. Armed with these chemistries, we undertook an SAR investigation of **1** to improve its overall biological profiles. Our efforts resulted in the discovery of a series potent, orally active NK_1 antagonists[8] represented by compound **3a** (Figure 1).

Figure 1. Representative NK_1 antagonists.



During the process of this investigation, particularly in efforts to address development issues of **3a** (*vide infra*), we became interested by the conformation effect of these 2, 2-disubstituted piperidines. It was reported that compound **2** existed in a single chair conformation in which the phenyl group took an axial position.[9] This result was somewhat intriguing and prompted some questions. Considering the well-established 1,1-methylphenylcyclohexane case, the phenyl showed only moderate preference of occupying axial position with a ratio of 72:28.[10] For the strong axial phenyl preference of compound **2,** did the large alkylether group play a role or if the piperidine nitrogen contributed to it? Our desire to answer these fundamentally important questions, coupled with long-standing interests in the properties of piperidines, motivated our studies of the conformational equilibriums of 2,2-methylphenylpiperidine (**4**) along with 3,3- (**5**) and 4,4-methylphenyl (**6**) piperidines. As in case of 1,1-methyl-phenylcyclohexane, conformational equilibriums of **4**-**6** are described by two chair forms with axial (A) and equatorial (B) orientations of phenyl group (Figure 2):

Figure 2. Conformational equilibriums in compounds **4**-**6**.

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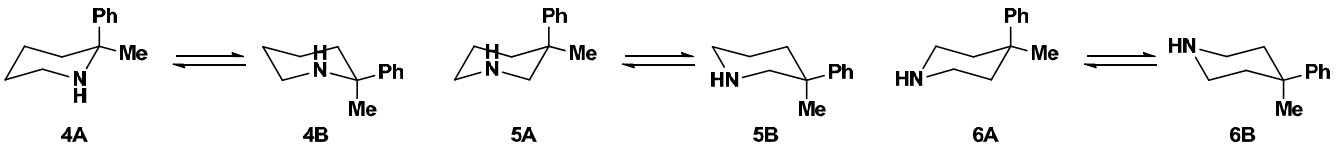


Conformational equilibriums of **4**-**6** were studied by NMR spectroscopy.[11] Conformational analysis was performed based on vicinal proton-proton *J*-couplings. At room temperature the exchange between A and B conformations is fast and therefore experimentally measured *J*-couplings are seen as average values described by the following equation (Equation 1):

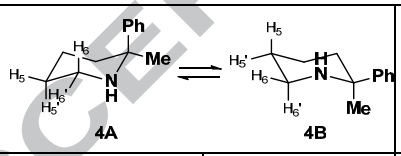
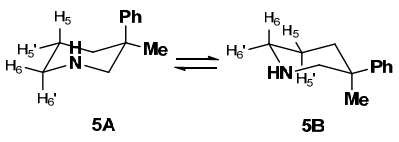
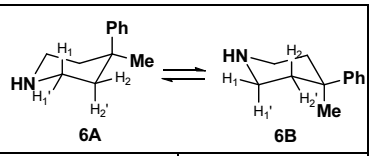
$$J^{exp} = p_A J_A + p_B J_B, \quad (1)$$

where J^{exp} is experimentally observed *J*-coupling, J_A and J_B are corresponding *J*-couplings in conformations A and B, and p_A and p_B are probabilities of conformations A and B. Since probabilities are normalized ($p_A + p_B = 1$), only one of them needs to be determine.

The J_A and J_B-couplings was calculated quantum-mechanically using density functional theory (DFT) method at the B3LYP/6-311+G(d,p) level. That method showed excellent accuracy in predicting homo- and heteronuclear J-couplings,[12] as well as NMR chemical shifts.[13]

Among different *J*-couplings that can be measured in pepridines **4**-**6**, the most relevant for conformational analysis are trans-$^3J_{HH}$. The wide range of trans-$^3J_{HH}$ from 2-3 Hz between diequatorial protons to 10-12 Hz between diaxial protons makes them a sensitive parameter to small changes in conformational equilibrium, particularly when equilibrium constants are close to unity. With J_A and J_B couplings calculated by DFT, the p_A:p_B ratio can be estimated from a single experimentally measured *J*-coupling by solving equation 1. To ensure a higher accuracy of estimated conformational probabilities we have used two trans-$^3J_{HH}$ for each of the studied piperidines. In this case a least-squares minimization approach was applied to find conformational probabilities producing the best fit of both trans-^3J-couplings (J^{calc}) to their corresponding experimental values (J^{exp}) simultaneously. Results of conformational analysis of **4**-**6** are summarized in Table 1.

Table 1. Conformational analysis of piperidines **4-6.**

						
	4A 4B		5A 5B		6A 6B	
	$J_{H5,H6'}$	$J_{H5',H6}$	$J_{H5,H6'}$	$J_{H5',H6}$	$J_{H1',H2}$	$J_{H1,H2'}$
J_A, Hz	2.4	12.6	2.4	12.5	3.4	12.7
J_B, Hz	12.8	2.6	12.5	2.4	12.7	2.7
J^{exp}, Hz	4.1	10.7	7.5	7.2	6.4	9.9
J^{calc}, Hz[a]	4.23	10.84	7.60	7.30	6.19	9.70
RMSD[b]	0.17		0.10		0.21	
p_A:p_B	82:18		48.5:51.5		70:30	

[a] J^{calc} were calculated as $p_A J_A + p_B J_B$

[b] Root-mean-square deviations (RMSD) were calculated as $(\Sigma(J^{calc}-J^{exp})^2/2)^{1/2}$.

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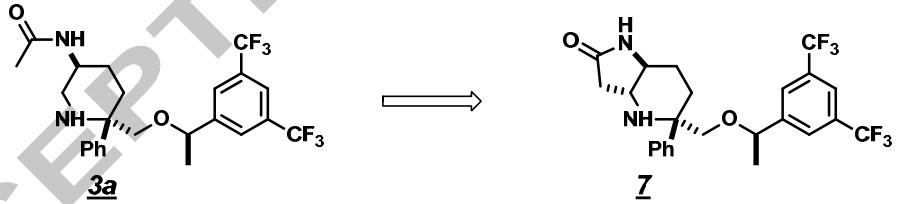
As seen by a very small root-mean-square deviations (RMSD) of *J*-coupling fittings (0.10 – 0.21 Hz), the DFT method used to predict *J*-couplings for individual conformations was well justified.

The combined experimental and calculated results were quite interesting. First of all, the conformer ratio of phenyl ax:eq for 4,4-substituted piperidine was 70:30. This ratio was in good agreement with the corresponding cyclohexane case of 72:28. As in 4,4-substituted piperidine system the nitrogen atom was not in a position that could influence the conformation of 4 position, this result was indeed highly anticipated. This also further validated our NMR-based method used in this study. Similarly, the 3,3-substitution can be viewed to have less 1,3-diaxial interaction with axial methyl group,[14] resulting in little difference between the methyl and phenyl substituents. This was reflected by near equal distribution of axial and equatorial phenyl group in a ratio of 48.5:51.5. A similar phenomenon had been observed in the 1,3-dioxane system.[14] Intriguing and relevant to NK_1 antagonists, the 2,2-piperidine pattern produced a more preferred conformation, with an ax:eq ratio of 82:18. In addition, when the NK_1 antagonist **1** was subjected to the same NMR analysis, the ax:eq ratio of 88:12 was observed. This result corroborated the fact that for 2,2-disubstituted NK_1 antagonists, the preferred conformation is the axial phenyl. It is an inherent preference of 2,2-methylphenylpiperidines, the bulky *bis*-trifluoromethylbenzyl ether side chain contributed marginally to this phenomenon.

The result of NMR study confirmed the preference of phenyl group in axial position in compound **1** and **2**, which shed a light of addressing the program issue of lead **3a**. At the time, it was found that **3a** was metabolized in vivo to yield **3b**. This diamine metabolite showed undesirable long half-life in rat brain.[8] Literature precedents indicated that dibasic amine drugs tend to attach to lipid bilayer and were likely to induce phospholipidosis.[15] To circumvent the problem, it was envisioned that the acetyl group could be cyclized to various positions on the piperidine ring to generate bicyclic lactam structures.[16] Among a number of potential targets, the fused analog **7**, which would maintain desired axial phenyl conformation, emerged as a high priority target (Figure 3).

Figure 3. Evolution of design strategy based on NMR study.



The synthesis of **7** was based on reproduction of chirality approach[17] using commercial oxazolidinone template **8.**[18] Alkylation with alkyl bromide **9** (ref. 19) afforded the desired quaternary chiral center in **10**. The ester was reduced to the corresponding hydroxyl oxazolidine **11**. Subsequent Wittig reaction provided required carbon framework of piperidine. After saturation of alkene double bond with hydrogenation, an acid-promoted cyclization on acetal **12** yielded enamide **13**. The nucleophilic enamide was treated with NO_2BF_4 to install the nitro functionality[20] and set the stage for the ensuing Michael reaction. The nitroalkene **14** reacted with lithium enolate of EtOAc to afford key nitroester **15** and **16** as a pair of diastereomer in 2:1 ratio separable with 0-80% EtOAc in hexanes (v:v) on silica gel column. Final approach towards target **7** was completed by reduction of nitro group using hydrogenation with Ni(Ra) with concomitant removal of Cbz group. The crude mixture was treated with K_2CO_3 in refluxing MeOH to afford the final product **7**. The diastereomer **17** was also obtained in the same fashion (Scheme 1).

Scheme 1. Synthesis of compound **7**.

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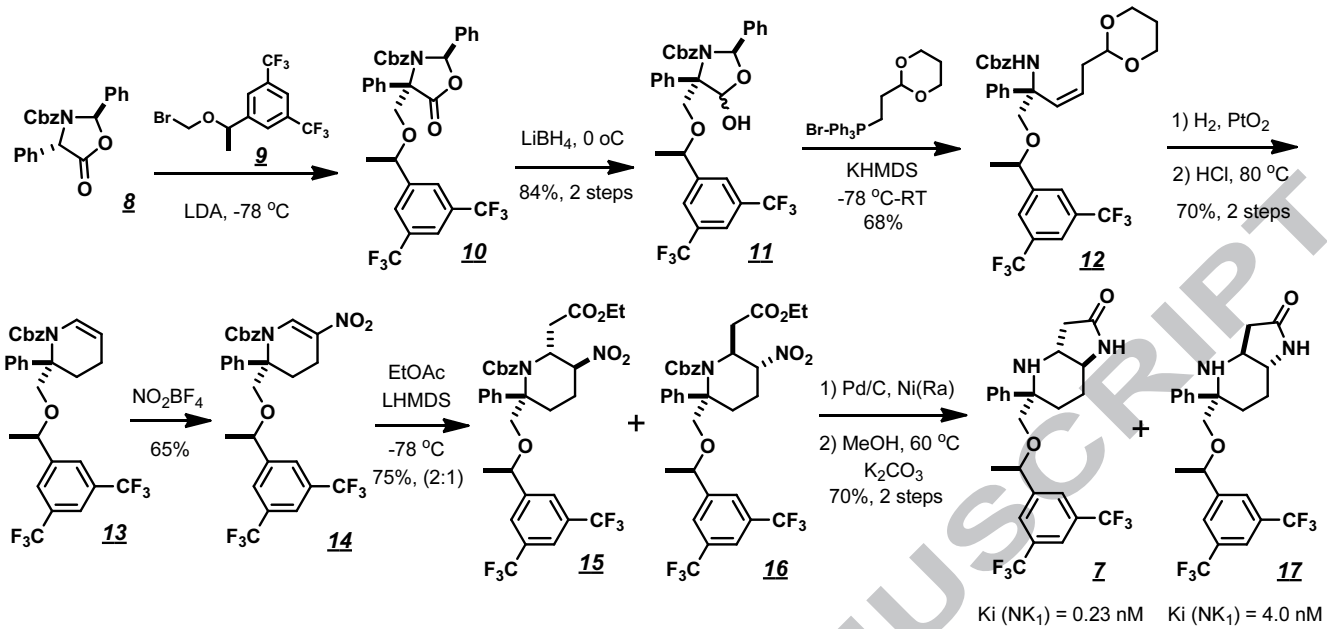

The analog **7** indeed proved to be a potent NK_1 antagonist whereas diastereomer **17** showed significant 17 fold loss of NK_1 potency based on their dissociation constants (Ki).[8] Additional data of analog **7**, also known as L-004060882, was obtained. In a pharmacodynamic model, the gerbil foot thumping (GFT) assay,[8] L-004060882 showed 100% inhibition at 4 h and 6 h with 1 mpk *per oral* dosing. It showed excellent pharmacokinetic profiles in rodents and monkeys.[21]

The attractive preliminary profiles of L-004060882 demanded a better synthesis in order to generate multi-gram quantity for additional investigations. We decided to concentrate on improving the yield and selectivity in key Michael addition step. Initially, we thought that the selectivity can be delivered by using chiral nucleophiles, therefore, several chiral enolates were screened (Scheme 2). For example, neither enantiomer of the lithium enolates of acetyloxazolidinone **20** or **21**[21] was reactive enough towards the nitroalkene **14**. The more reactive enolates of chiral cyclohexanolacetate[22] provided good yield of products. It was interesting to confirm that selectivity was indeed predominantly controlled by the chirality of enolates. The (*1S, 2R*) cyclohexnolacetate **22** afforded mostly **19**, while the (*1R, 2S*) isomer **23** provided an excellent selectivity of 14.7:1 favoring **18**, reflecting a match and mismatch case. The resulting nitroester **18**, however, could not be converted to the final product. After nitro group reduction, the lactam cyclization failed even under forcing conditions, likely due to extreme steric hindrance of cyclohexylester. We were, therefore, forced to investigate other routes. Literature search revealed that silylketeneacetal could add to nitroalkene efficiently[23] when promoted by Lewis acids, such as MAD (Figure 5).[24] This extremely hindered Lewis acid has been shown to convey excellent selectivity[25] in a number of synthetic transformations. When substrate **14** was treated with 2 eq. of MAD followed by addition of silylketeneacetal at -78 °C, a very clean reaction occurred and the desired product was obtained in greater than 20:1 selectivity and 90% yield. This excellent selectivity was a result of spatial preference of MAD-nitro adduct, which took equatorial position, forcing the nucleophilic addition from axial direction (Figure 4). With the improved Michael addition step adopted, the overall synthesis of L-004060882 was achieved in 10 steps and 16% overall yield starting from **8**. In the end, greater than ten grams of this potent NK_1 antagonist was synthesized, which greatly facilitated its characterization (Scheme 2).

Scheme 2. Optimization of the key Michael addition step.

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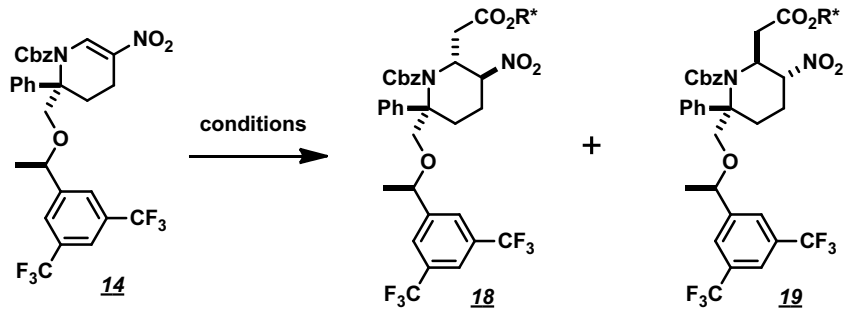
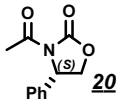
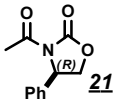
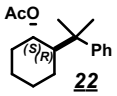
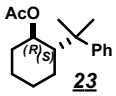
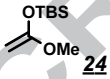
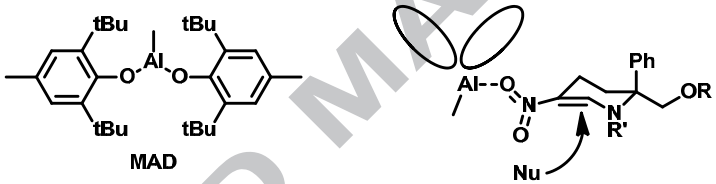


Reaction Conditions @ -78 °C	 20 LHMDS	 21 LHMDS	 22 LHMDS	 23 LHMDS	 24 MAD
yield:	NR	NR	65%	68%	90%
ratio (18:19):	ND	ND	1:5	14.7:1	>20:1

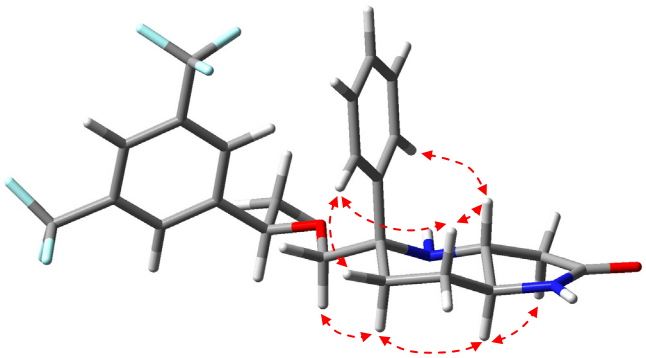
* R in ractions with 22 and 23 were corresponding chiral alcohols, while with 24 a methyl group.

Fiugure 4. MAD and postulated transition state of Michael addition reaction.



To finally confirm the proposed conformation, NMR study was conducted on compound **7**. As shown in Figure 5, in the energy optimized conformation by MMX force filed (PCModel software), which was consistent with experimental long-range NOE's, the phenyl group indeed occupied an axial position (Figure 5).

Figure 5: Energy optimized conformation and long-range NOE's (red arrows) of **7**.



To summarize our research, we investigated the conformational preference of gem-disubstituted methyl-phenyl piperidines. It was revealed that only in 2,2-methylphenylpiperidine system that the phenyl group has a strong preference in occupying axial position. This information was used to design a constrained bicyclic

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piperidine NK_1 antagonist L-004060882. A practical stereoselective synthesis was achieved to deliver the designed NK_1 antagonist, which proved to be very potent and devoid of later stage metabolic complications.

Acknowledgement: We would like to thank Dr. Ruth Duffy for NK_1 binding assay, Dr. Goeff Varty for GFT assay, Dr. Walter Korfmacher for DMPK studies and Dr. John J. Piwinski for support of this program.

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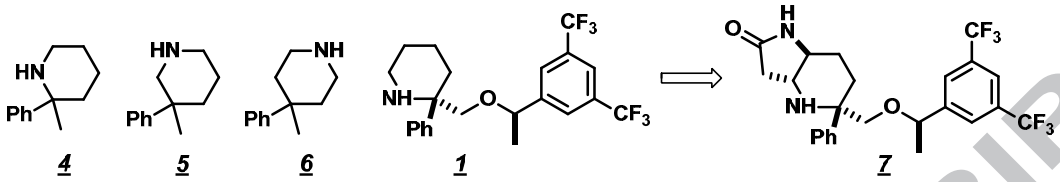
Graphic Abstract:

Conformation studies of piperidines 1 and 4-6 revealed insights that guided design and synthesis of a potent NK_1 antagonist 7 with excellent pharmacokinetic properties.



4 *5* *6* *1* *7*

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