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Computational and Experimental Evaluation of α -(*N*-2-Quinolonyl)ketones: A New Class of Nonbiaryl Atropisomers

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ABSTRACT

Given the usefulness of atropisomers within both asymmetric catalysis and pharmaceuticals, a thorough computational study of substituted α -(*N*-2-quinolonyl)ketones has been conducted. This class of tertiary amides is unique, as the amide is embedded within an aromatic construct, and the nitrogen bears an aliphatic substituent. Using a computational approach, 8'-substituted quinolones were identified as potential class 2 and 3 atropisomeric targets with calculated C–N rotational barriers of greater than 20 kcal/mol. These results, along with experimental efforts towards the synthesis of these targets, are reported.

Keywords:

Quinolone; microwave-assisted synthesis; atropisomerism; gold-catalysis

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1. Introduction

Atropisomerism is a stereochemical property that arises as a result of hindered rotation around a central bond. Depending on the barrier to rotation, atropisomers can be grouped into three unique classes.¹ The most configurationally stable, denoted as class 3 isomers, possess rotational barriers that exceed 30 kcal/mol, leading to a $t_{1/2}$ for racemization on the order of years. Compounds in this class exist as chiral structures that can be isolated as single enantiomers or diastereomers, depending on the presence or absence of secondary chiral centers (e.g. BINOL).² Compounds whose rotational barriers are more moderate (20–30 kcal/mol) are known as class 2 atropisomers and exhibit rotational half-lives of hours to days. Class 1 atropisomers, with barriers less than 20 kcal/mol, can sometimes be observed by spectroscopic means (e.g. NMR or chiral HPLC) but can only be isolated as equilibrating mixtures under normal laboratory conditions.³

The presence of atropisomerism in pharmaceutical targets has become a concern in recent years.⁴ While class 3 atropisomers can be treated as other stereoisomeric leads, many compounds of interest exhibit rotational restriction but are not configurationally stable.⁵ The issues associated with the characterization and regulatory registration of such class 2 atropisomeric drug candidates are significant.

In addition, many privileged asymmetric catalyst and ligand structures rely on non- C_2 symmetric axial chirality.⁶ Within this important group of compounds, biaryl structures (e.g. BINOL, BINAP, and NOBIN) have garnered the most attention; however,

nonbiaryl species can also exist as stable pairs of atropisomers, including: amides, macrocycles, and molecules whose characteristic ring flips are restricted.⁷ Exploration and application of molecules from these classes to current problems in asymmetric catalysis remains an important synthetic goal.⁸

Scheme 1. Synthesis of α -(*N*-2-Quinolonyl)ketone **2**.

In the course of our work developing new methods for the synthesis of α -(*N*-2-pyridonyl)ketones and α -(*N*-2-quinolonyl)ketones, we noted irregularities in the ¹H NMR of quinolone **2**, indicative of slowed rotation around the central C–N bond (Scheme 1).⁹ Computational studies supported this observation, suggesting that compound **2** is a class 1 atropisomeric structure with a barrier to rotation of 14.0 kcal/mol.⁹ Further examination of quinolone **2**, suggests that additional substitution at the positions adjacent to the hindered C–N bond might slow rotation further, enabling the formation of more configurationally stable class 2 or even class 3 atropisomeric compounds, rendering them potentially useful as ligands for asymmetric catalysis or as templates suitable for elaboration into inhibitors of various biological targets.

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While the rotational barriers of tertiary amides have been well studied,^{8,10} α -(*N*-2-quinolonyl)ketones represent a new class of nonbiaryl atropisomers, in which the amide functionality is imbedded within an aromatic construct. Further, although *N*-acyl indoles,¹¹ *N*-aryl quinazolinones¹² and *N*-aryl bicyclic lactams¹³ provide some insight into the restriction to C–N bond rotation in systems related to that discussed here, the aromatic system and aliphatic nitrogen substitution present in the current study make quinolone **2** and its analogues unique. As such, a computational evaluation of substituted analogues of quinolone **2** was conducted with the goal of illuminating this gap in the literature. Herein, we report these studies as well as attempts to use our current technology to prepare the more rotationally stable analogues that were identified computationally.

2. Computational Methods

All computations were done using Gaussian 09 at the B3LYP/6-31G(d) level of theory.¹⁴ The dihedral angle under investigation was defined as the angle between the two carbonyl carbons, along the carbon-nitrogen bond of compound **3** (Figure 1). Positions A–G were defined as, and limited to, equivalent methyl groups, unless specifically stated otherwise. Substitution at each position was done sequentially and then in combinations of up to 4 methyl groups simultaneously. The dihedral angle was varied in 10° increments and energies were optimized at each point, allowing for the energy barrier for rotation around the C–N bond to be determined.

Figure 1. Computationally Studied α -(*N*-2-Quinolonyl)ketone **3**.

3. Results and Discussion

Computed C–N rotational barriers for methyl substituted analogues **3** appear in Table 1. Unlike in *N*-aryl amides, a variety of positions on both the quinolone ring and the aliphatic sidechain have the potential to increase the C–N rotational barrier. An initial scan of mono-methylated quinolones revealed that quinolone **3c**, bearing substitution at position B on the quinolone ring, has the highest rotational barrier in the set (entries 1–6). Incorporation of a methyl group elsewhere on the ring or sidechain resulted in only small increases relative to unsubstituted quinolone **3a**. Coupling substitution at position D or E of the chain with key ring position B, was shown to provide no additional hindrance over that observed for compound **3c** (entries 10 and 11). However, quinolone **3m**, bearing an isopropyl group α to the ketone and the required ring methyl substituent, did afford a small increase in the predicted rotational barrier (entry 13). Other di- and trimethylated analogues were predicted to have lower rotational barriers (entries 7–9, 12, 14–15). Among the methylated analogues, tetramethyl (quinolonyl)ketone **3q** was predicted to have the highest rotational barrier (28.4 kcal/mol, entry 17). Replacement of the methyl group at position D of **3q** with a methoxy group increased the predicted barrier to rotation to 32.0 kcal/mol, highlighting methoxy quinolone **4** as a possible class 3 atropisomeric target (entry 18).

entry		CH ₃ position	rotational barrier (calc, kcal/mol)	atropisomer class
1	3a	–	13.9	1
2	3b	A	14.1	1
3	3c	B	27.0	2
4	3d	D	19.1	1
5	3e	E	13.8	1
6	3f	F	15.2	1
7	3g	F G	22.9	1
8	3h	A D	17.2	1
9	3i	A E	15.6	1
10	3j	B D	26.1	2
11	3k	B E	26.6	2
12	3l	A F G	20.9	1
13	3m	B F G	27.8	2
14	3n	D F G	20.8	2
15	3o	E F G	20.3	2
16	3p	D E F G	18.9	1
17	3q	B D F G	28.4	2
18	4	B D ^a F G	32.0	3

^a–OMe.

Table 1. Computed C–N Rotational Barriers for Compounds **3** and **4**.¹⁴

Scheme 2. Synthesis of 2-Propargyloxyquinolines **6**.¹⁵

Having determined that substitution on the quinolone ring at position B was critical for hindering C–N bond rotation, efforts shifted to the synthesis of these targets. Access to quinolones **3** and **4** and their analogues was anticipated to be achieved via the Au(III)-catalyzed tandem amination-hydration of 2-propargyloxyquinolines **6** (Scheme 2). To facilitate the synthesis of quinolines **6**, an additional methyl group was incorporated at position 4 (quinoline numbering), allowing ready access to this class of substrates directly from 2-methyl aniline and *tert*-butylacetoacetate.¹⁵ As this additional methyl group points away from the reactive site, it was not expected to influence the C–N rotational barrier of the quinolones **7** that result after amination-hydration. Synthesis of substituted 2-chloroquinoline **5** was accomplished following literature methods

(Scheme 2).¹⁵ Coupling via nucleophilic aromatic substitution with a variety of unbranched propargyl alcohols then provided quinolines **6**, which serve as precursors to analogues of computed structure **3c**. While quinolones **7a-c** are only predicted to provide class 2 atropisomeric species (Scheme 2), compounds **6a-c** were targeted initially to see if the tandem amination-hydration would tolerate the increased steric demand of methylation at position B.

Subjecting compound **6a** to the Au(III)-catalyzed reaction led initially to only meager amounts of the desired quinolone **7a** (Scheme 3, Table 2). Under the standard reaction conditions, 5% of the methylated quinolone product **7a** was observed, while 95% of quinoline **6a** was recovered (entry 1). This stands in stark contrast to the 86% yield of quinolone **2** that was observed upon rearrangement of unsubstituted quinoline **1** (Scheme 1). Increasing the temperature incrementally to 175 °C and implementing microwave heating provided no improvement in yield (entries 1-5). A slight improvement was realized when 10% H₂O/EtOH was used as the solvent (entry 6); however, further increases to the amount of water in the solvent mixture led to no additional gains (entry 7). Altering the amount of either trimethylamine or Dowex 50WX2-200(H) resin also resulted in no change in yield (entries 8-9). Alternatively, changing from ethanol to 1-butanol allowed the temperature to be increased further, although rather than promoting the desired rearrangement, ionization to give 4,8-dimethyl-2-quinolone was observed (entries 10-13). Interestingly, however, when the reaction was conducted in ethanol and heated conventionally for 21 h at 100 °C, comparable yields to those observed previously were achieved (entry 14).

Given these results, compounds **7b** and **7c**, which have smaller computed C–N rotational barriers (19.4 kcal/mol and 20.7 kcal/mol, respectively) were targeted. Assuming that lower rotational barriers correlate to a reduced steric demand, it was anticipated that compounds **6b** and **6c** would undergo the amination-hydration process more readily than the bulkier quinoline **6a**. Gratifyingly, after 3 hours at 160 °C in the microwave reactor, butynyl quinoline **6b** underwent rearrangement to provide 22% yield of the desired quinolone **7b** (Table 3, entry 1). Modifying the amount of Dowex 50WX2-200(H) resin and NEt₃ improved the yield to 66% (entry 2). Again, heating the reaction conventionally at 100 °C for 21 hours gave similar results (entry 3). Phenyl-substituted alkyne **6c**, however, proved to be more difficult, providing only 16% of quinolone **7c** under the best conditions (entries 4-6).

Given the poor to moderate yields observed in the rearrangement of quinolines **6**, bromine-substituted derivatives **10** were prepared as an alternative for accessing these unusual atropisomers. Bromoquinolone **11a** was calculated to have a similar barrier to C–N bond rotation as quinolone **3c** (26.0 kcal/mol),¹⁴ but replacement of the methyl substituent with bromine potentially enables bromoquinolone **11a** to be used as an intermediate for further elaboration at the substituted position. Treatment of 2-bromoaniline with cinnamoyl chloride, followed by Friedel-Crafts alkylation, provided 8-bromoquinolone (**8**) (Scheme 5).¹⁶ Chlorination with POCl₃ then afforded the desired 2-chloroquinoline **9** in 77% yield. Subsequent, coupling of quinoline **9** with either 2-octyn-1-ol or 2-butyn-1-ol afforded 2-

propargyloxyquinolines **10a** and **10b** in 94% and 89% yields, respectively.

Scheme 3. Amination-Hydration of 2-Propargyloxyquinoline **6a**.

entry	H ₂ O (%)	Dowex (wt%)	NEt ₃ (equiv)	temp (°C)	time (h)	yield (%)
1	5	20	1.5	100 ^a	21	5
2	5	20	1.5	120	3	7
3	5	20	1.5	140	3	4
4	5	20	1.5	160	3	5
5	5	20	1.5	175	3	7
6	10	20	1.5	175	3	19
7	15	20	1.5	175	3	18
8	10	20	0.5	180	3	20
9	10	20	0.8	180	3	19
10	5 ^b	20	1.5	180	3	—
11	10 ^b	20	1.5	180	3	—
12	10 ^b	30	0.5	180	3	13
13	10 ^b	30	0.5	215	3	—
14	10	30	0.5	100 ^a	21	22

^aconventional heating. ^bsolvent: H₂O/1-butanol.

Table 2. Amination-Hydration of Quinoline **6a**.

Scheme 4. Amination-Hydration of 2-Propargyloxyquinolines **6b** and **6c**.

entry		Dowex (wt%)	NEt ₃ (equiv)	temp (°C)	time (h)	yield 7 (%)
1	6b	20	1.5	160	3	22
2	6b	30	0.5	160	3	66
3	6b	30	0.5	100 ^a	21	58
4	6c	20	1.5	160	3	6
5	6c	30	0.5	160	1.5	14
6	6c	30	0.5	100 ^a	21	16

^aconventional heating.

Table 3. Preparation of Quinolones **7b** and **7c**.

Scheme 5. Synthesis of Bromoquinolines **10**.¹⁶

Subjecting octynyl quinoline **10a** to the amination-hydration reaction at $160\text{ }^\circ\text{C}$, however, provided none of the desired brominated quinolone **11a** (Scheme 6). Rather, only a small amount of unalkylated quinolone **8** was observed, with the remainder of the mass being recovered starting material **10a**. The less hindered bromoquinolone **10b** gave similar results, although in this case, a small amount of debrominated (quinolonyl)ketone **11b'** was also observed.

Scheme 6. Amination-Hydration of Brominated Quinolines **10**.

These results, and those in the methylated quinolone system, make it clear that the Au(III)-catalyzed amination-hydration process has steric limitations that will need to be addressed before rotationally restricted systems, such as quinolones **4**, **7** and **11**, will be accessible. Efforts to access these and related analogues through a late stage functionalization will be reported in due course.

4. Conclusion

Although the rotational barriers of tertiary amides have been well studied, a significant gap exists with regards to amides that are, themselves, imbedded within aromatic systems. As such, a

thorough computational study of substituted α -(*N*-2-quinolonyl)ketones was conducted, leading to the identification of a number of class 2 and 3 atropisomeric targets. Synthesis of these compounds using our Au(III)-catalyzed amination-hydration methodology resulted in low to moderate yields of the desired atropisomers and revealed that access to these targets will require a modified approach. Despite this limitation, rotational barriers for a range of substituted α -(*N*-2-quinolonyl)ketones have been calculated, allowing this unique class of rotationally restricted tertiary amides to be placed within the larger context of other atropisomeric amide structures.

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