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Enantioselective Approach for Expanding the Three-Dimensional Space of Tetrahydroquinoline to Develop BET Bromodomain Inhibitors**

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[**] BET = bromodomain and extra terminal

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Abstract: The pharmaceutical industry has a pervasive need for chiral specific molecules with optimal affinity for their biological targets. However, the mass production of such compounds is currently limited by conventional chemical routes, that are costly and have an environmental impact. Here, we propose an easy access to obtain new tetrahydroquinolines, a motif found in many bioactive compounds, that is rapid and cost effective. Starting from simple raw materials, the procedure uses a proline-catalyzed Mannich reaction followed by the addition of $\text{BF}_3 \cdot \text{OEt}_2$, which generates a highly electrophilic aza-ortho-quinone methide intermediate capable of reacting with different nucleophiles to form the diversely functionalized tetrahydroquinoline. Moreover, this enantioselective one-pot process provides access for the first time to tetrahydroquinolines with a *cis*-2,3 and *trans*-3,4 configuration. As proof of concept, we demonstrate that a three-step reaction sequence, from simple and inexpensive starting compounds and catalysts, can generate a BD2-selective BET bromodomain inhibitor with anti-inflammatory effect.

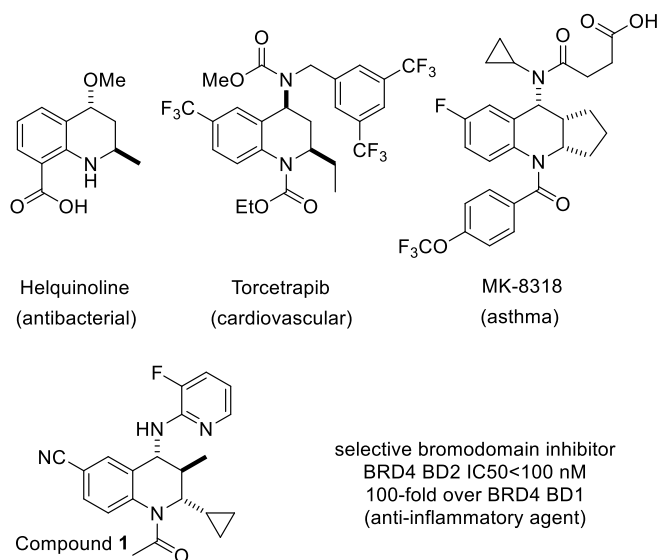


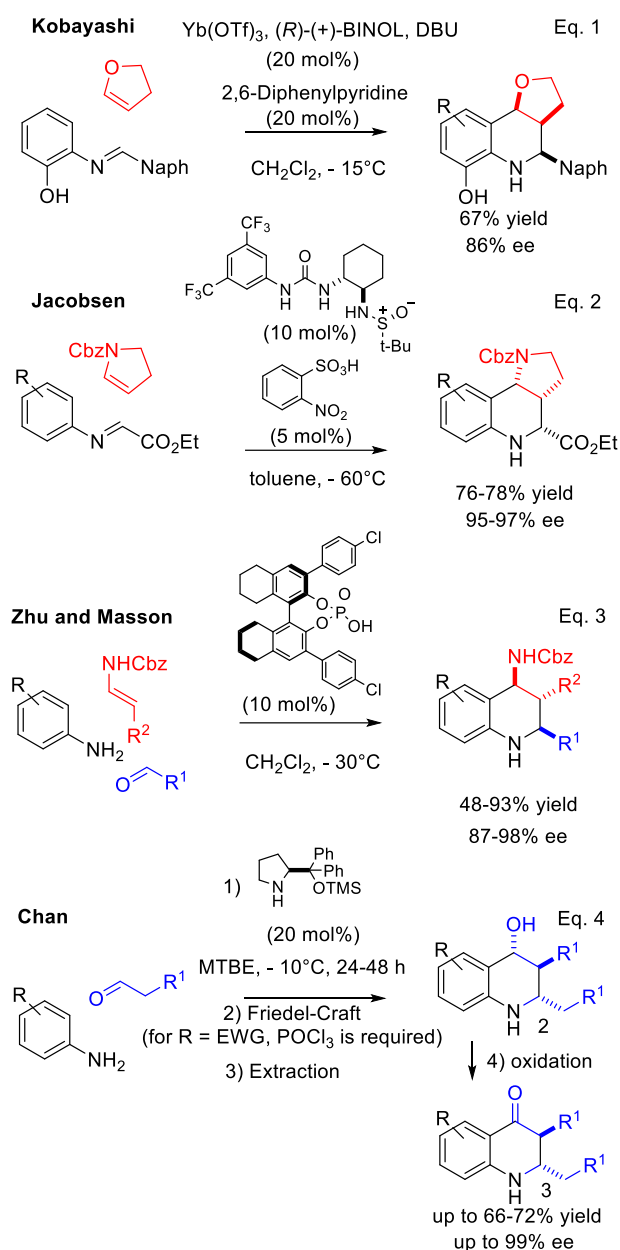
Figure 1. Various bioactive natural and synthetic 1,2,3,4-tetrahydroquinolines.

Introduction

The pharmaceutical industry is faced with the challenge of producing large quantities of active pharmaceutical ingredients, often with sophisticated structures. However, chemistry must remain simple and greener to address both production cost and environment impact by focusing on reducing synthetic steps (one-pot, multicomponent reactions), saving atoms, and using catalysis to limit resources and waste.¹ Another challenge for this industry is to selectively produce chirality, which is known to increase clinical success.²

The presence of chiral centers induces the formation of complex three-dimensional structures that give the drug specificity towards its biological target. This requires the production and purification of a single enantiomer, which can have significant impacts on the cost and environmental burden of their production.³ Furthermore, in the case of compounds with several asymmetric centers, accessibility to multiple combinations of configurations must remain trivial to simplify the optimization step and, subsequently, the production of the best diastereomer at large scale. In this prospect, we were interested in the synthesis of chiral poly-substituted 1,2,3,4-tetrahydroquinoline (THQ) scaffold which is a widespread pharmacophore group also present in natural products.^{4,5} Examples include the natural

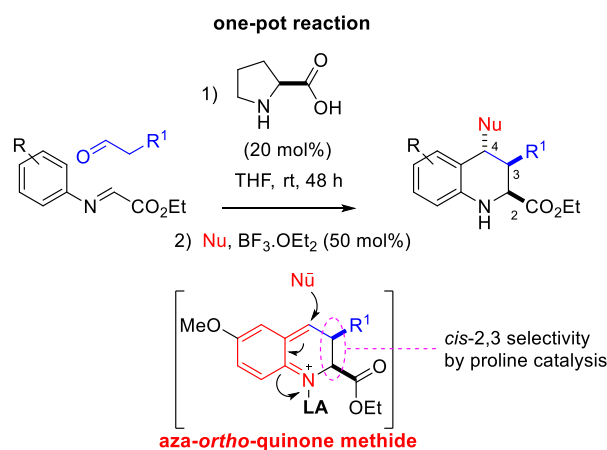
product Helquinoline,⁶ the synthetic products Torcetrapib,⁷ MK-8318⁸ and compound **1**⁹ (Figure 1). In all these bioactive products, chirality plays an important role since having the correct enantiomer is essential for bioactivity and selectivity.



Scheme 1. Enantioselective Povarov reactions to give tri-substituted tetrahydroquinoline.

There are many synthetic routes to access chiral THQ,⁵ but the simplest and most versatile to implement with a multicomponent approach remains the asymmetric Povarov reaction.^{10,11} Synthesis of highly optically pure THQs can be achieved by enantioselective Povarov reactions based on a [4+2] cycloaddition or a Mannich/Friedel-Craft sequence mechanism.⁴ The seminal work by Kobayashi and co-workers showed that tri-substituted THQ can be obtained in good enantioselectivity with a *cis*-2,3 and *cis*-3,4 configuration (Scheme 1, Eq. 1).¹² However, the method was limited to *ortho*-phenolic substituted imines. More versatile enantioselective approaches use chiral catalysts

such as Jacobsen urea (Eq. 2)¹³ and phosphoric acid involved in a multicomponent approach described by Zhu, Masson and co-workers (Eq. 3)¹⁴ that yield 2,3,4-substituted THQ with *cis*-2,3 and *cis*-2,3 configuration and *trans*-2,3 and *trans*-2,3 configuration, respectively. Recently, Chan and co-workers reported the Mannich/Friedel-Craft sequential reaction, catalyzed by the silylated proline/POCl₃ catalysts, respectively, to give after extraction, the crude transient 4-hydroxyl-THQ **2**. The latter must then be oxidized to yield a more stable *trans*-2,3-substituted 2,3-dihydroquinolinone **3** (Eq. 4).¹⁵ The role of the Lewis acid POCl₃ was only limited to catalyzing the Friedel-Craft reaction. However, an enantioselective reaction capable of accessing the *cis*-2,3 and *trans*-3,4 configuration of 2,3,4-substituted THQ has not yet been reported and will expand the three-dimensional space of THQ. Given the potential of THQ to easily generate chemical libraries,^{16,17} this would be of great interest to access this rare configuration and open the door to the exploration of new chemical spaces.



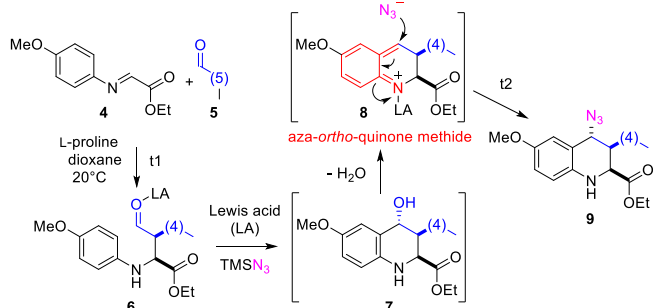
Scheme 2. One-pot multicomponent reaction including the generation of an *aza-ortho-quinone methide* species to form *cis*-2,3 *trans*-3,4 trisubstituted THQ.

To achieve this goal and keep the process simple, the development of a one-pot multicomponent reaction based on the Mannich/Friedel-Craft reaction sequence was undertaken to incorporate the additional generation of an *aza-ortho-quinone methide* species¹⁸ simultaneously (Scheme 2). Indeed, the first *cis*-2,3 configuration can be controlled by the proline catalyzed Mannich reaction.¹⁹ We identified mild conditions to achieve the Friedel-Craft reaction and the subsequent formation of the highly reactive *aza-ortho-quinone methide* intermediate. The addition of various nucleophiles is tolerated and selectively gives the *trans*-3,4 configuration. The use of proline also has the advantage of being the simplest and most environmentally benign organocatalyst.²⁰ This new configuration has proven to be essential in our program to develop new inhibitors acting on epigenetic mechanisms.

Results and Discussion

The first enantioselective Mannich reaction step used the proline-catalyzed List-Barbas reaction, starting with imine **4** and aldehydes to give the Mannich product **6** with *syn* selectivity (Scheme 3).¹⁹ At this stage, product **6** does not

spontaneously cyclize to form 4-hydroxy THQ **7** and the assistance of a Lewis acid like POCl₃¹⁵ is thus required. Interestingly, *o*-aminobenzyl alcohols are known to be a precursor able to generate *aza-ortho*-quinone methide *in situ* by means of Lewis acid catalysis.¹⁸ Indeed, Lau and co-workers described the use of BF₃·OEt₂ to catalyze this conversion.²¹ In our approach, we wondered whether BF₃·OEt₂ can both catalyze the Friedel-Craft reaction leading to **7**, as well as inducing subsequently the generation of *aza-ortho*-quinone methide species **8** in the same vessel.



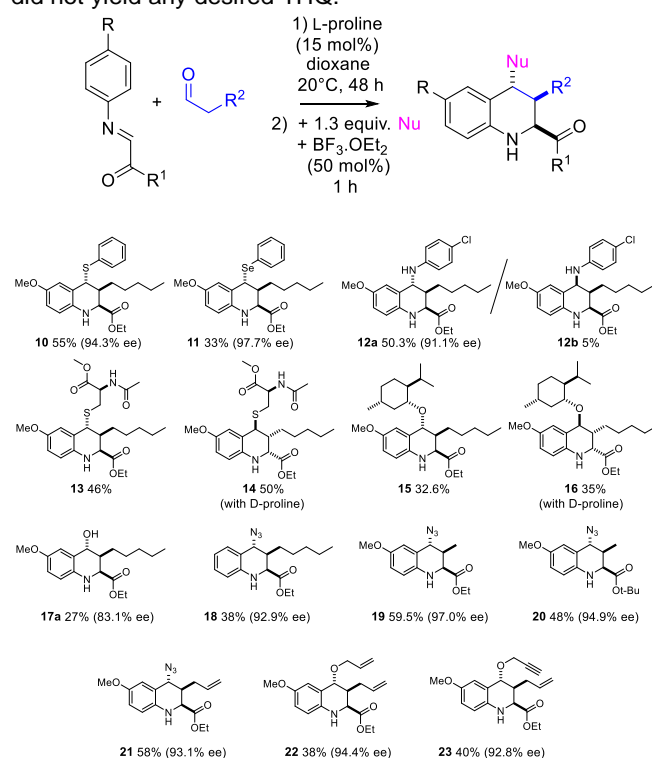
Scheme 3. One-pot multicomponent synthesis of enantio-enriched THQ **9** with *cis*-2,3 and *trans*-4,4 configuration

Table 1. Reaction conditions for the THQ **9** synthesis (in dioxane)

Entry	L-Pro (mol%)	t1 (h)	Cat. 2	Quantity Cat.2 (mol%)	t2 (h)	Yield of 9 (%)	ee
1	10	24	BF ₃ ·OEt ₂	50	1	46	88.9
2	10	48	BF ₃ ·OEt ₂	50	1	65	92.4
3	15	48	BF ₃ ·OEt ₂	50	1	66	96.4
4	20	48	BF ₃ ·OEt ₂	50	1	66	94.4
5	15	48	POCl ₃	50	1	0	-
6	15	48	POCl ₃	50	24	0	-
7	15	48	Yb(OTf) ₃	10	24	33	95.4
8	15	48	Y(OTf) ₃	10	24	12	95.4
9	15	48	Zn(OTf) ₃	10	24	24	95.3
10	15	48	InCl ₃	10	24	24	-
11	15	48	(<i>R</i>)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate	50	2	0	-

To test this hypothesis, our initial trial used the same conditions described by Barbas and co-workers, *i.e.* stirring imine **4** with heptanal **5** in the presence of L-proline (10 mol %) and in dioxane for 24 h at room temperature, to first produce the Mannich product **6** with high control of enantio- and diastereoselectivities.¹⁹ We subsequently added to this vessel TMSN₃ (1.3 equivalent) as nucleophile followed by BF₃·OEt₂ (50 mol%). As expected, the desired THQ **9** was formed in 46% yield and in 89 % ee (Table 1, entry 1). During the Mannich reaction, we noticed traces of imine **4**

remaining after 24 h. When adding BF₃·OEt₂, this residual material can react with the aldehyde **5** and TMSN₃ to directly generate racemic Povarov product **9**. By stirring the Mannich reaction over 48 h to ensure the consumption of all the imine **4**, we were able to improve both the yield and the enantiomeric excess (entry 2). Finally, the best condition was to use 15 mol% of proline for 48 h, followed by the addition of 50 mol% of BF₃·OEt₂ in the presence of the nucleophile (entry 3). Adding more BF₃·OEt₂ did not improve the yield whereas using a lower amount resulted in incomplete conversion to form the THQ. BF₃·OEt₂ was shown to be the best catalyst. In this one-pot process, POCl₃ used by Chan and co-workers¹⁵ could not yield the desired compound **9** suggesting its inability to generate the *aza-ortho*-quinone methide species **8** (entries 5 and 6). The use of other Lewis acid catalysts resulted in a slow reaction with low yields (entries 7-9). Finally, we tested whether phosphoric acid as Brønsted acid can trigger the Friedel-Craft/*aza-ortho*-quinone methide sequence by replacing BF₃·OEt₂ with (*R*)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (entry 11). Even in the presence of 50 mol%, the Mannich product **6** remained unchanged. Having the optimized condition in hand, we explored the use of different nucleophiles, aldehydes and imines (Scheme 4). The reaction exhibited good tolerance with various nucleophiles. Phenyl-heteroatom compounds like phenylthiol, phenylselenium, and aniline were nucleophilic enough to yield the corresponding THQs. In the case of aniline, a major compound **12a** was obtained along with a small amount of another minor diastereomer **12b**. The alkyl thiols and alkyl alcohols were also successfully grafted on the THQ scaffold (**13-16**, **22**, **23**). In contrast, alkyl amines did not yield any desired THQ.



Scheme 4. Enantioselective one-pot synthesis of various tri-substituted THQ; ^a water was added as nucleophile.

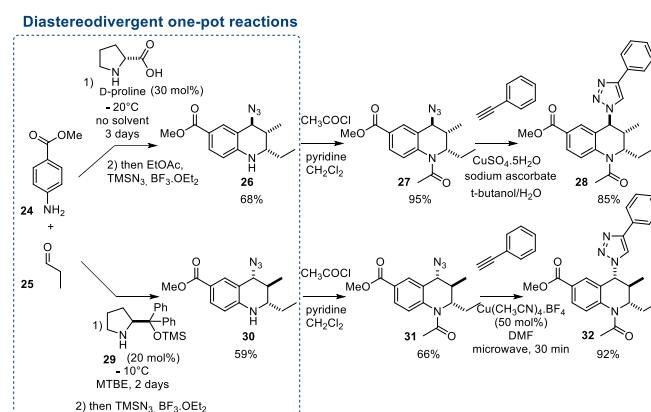
Use of other aldehydes and imines resulted in the corresponding THQ (**19–23**). Compound **21** was crystalline and its structure was solved by X-ray analysis confirming the *cis*-2,3 and *trans*-3,4 configuration (Fig. S1). The hydroxyl THQ **17** was obtained, albeit in low yield, by adding water to the media.

We chose to apply this methodology to the development of inhibitors selective for a specific subset of bromodomains (BDs).²² The BET (Bromodomain and Extra Terminal) protein family consists of four members (BRD2, BRD3, BRD4 and BRDT) and plays a key role in the regulation of gene transcription. Each member has two bromodomains, BD1 and BD2, which bind to the acetylated lysines of histones and recruit the molecular machinery required to activate transcription. Previous studies have identified numerous BET bromodomain inhibitors, starting with JQ1 and I-BET.²³ Recently, the identification of molecules that selectively inhibit BET BD2, but not BD1, has elicited great interest as they impair the activation of pro-inflammatory genes without affecting the expression of housekeeping and maintenance genes, thereby limiting their toxicity and improving the drug safety profile.²⁴ Selective BD2 inhibitors have been shown to present a more selective phenotypic fingerprint through the inhibition of key pro-inflammatory mediators.²⁴

We chose to apply our approach to obtain two diastereomeric THQ structures inspired by compound **1** (Scheme 1) and investigated whether the new accessible configuration would play an important role. Self-Mannich product can be obtained by directly reacting an aniline with two alkyl aldehydes to give the corresponding Mannich products in an enantioselective manner either with a *cis*-2,3 or a *trans*-2,3 configuration through proline¹⁹ or silylated prolinol¹⁵ catalysis, respectively. D-proline was used as the catalyst to set up the appropriate bioactive (*S*)-configuration at position 2 of the THQ.²⁵ The Mannich reaction was optimized to accommodate the weak nucleophilic aniline **24** (Scheme 5). Indeed, the reaction with aldehyde **25** proved to be slow and cooling to low temperature was essential to maintain good enantioselectivity. Co-formation of the unwanted aldol product also complicated the progress of the reaction as it tends to neutralize the proline catalyst.²⁶ Finally, performing the reaction at -22°C for 3 days with 30 mol% of D-proline under solvent-free conditions²⁶ accelerated the reaction while minimizing aldol product formation. Subsequent additions of solvent (EtOAc), followed by the addition of TMSN₃ (1.5 equivalent) and BF₃.OEt₂ (70 mol%) at 0°C afforded THQ **26** in 68% yield and in 91.8% ee. The reaction was run at larger scale (with 3 g of **24**). At this scale and to accelerate the Friedel-Craft reaction and the formation of aza-*ortho*-quinone methide, more BF₃.OEt₂ was added (1.36 equivalent). The desired product **26** was isolated in 77.5% yield and in 86.1% ee.

After recrystallization, THQ **26** was obtained in enantiopure form (>99% ee) in 40% yield from aniline **24**.

THQ **26** was next acetylated to obtain compound **27** on which a simple triazole-phenyl group was installed by Huisgen copper-catalyzed click reaction to lead to the new analogue **28**. To make the corresponding diastereomer with the *trans*-2,3 and *trans*-3,4 configuration, aniline **24** and propionaldehyde **25** were reacted with silylated prolinol **29** (20 mol%) in MTBE for 2 days at -10°C .¹⁵ Subsequently addition of TMSN₃ (1.5 equivalent) and BF₃.OEt₂ (2.1 equiv.) in the same vessel gave the product **30** with the desired configuration in 59% yield and with 96% ee. Compound **30** was acetylated to give **31**. Likely due to steric hindrance around the azido group, the conventional conditions for the copper-catalyzed Huisgen reaction gave less than 40% yield for product **32**. By performing the reaction under thermal conditions and in the presence of Cu(CH₃CN)₄.BF₄ catalyst,²⁷ compound **32** was finally obtained in good yield (92%).



Scheme 5. Diastereodivergent synthesis of bromodomain inhibitors in three steps

The bioactivities of these compounds were evaluated *in vitro* on recombinant BET Brd4 BD1 and BD2 using a homogeneous time resolved fluorescence (HTRF) assay²⁸ (Table 2 and see Fig. S2 for IC₅₀ curves). In short, this assay evaluates the ability of compounds to inhibit the interaction of a BD with its natural cognate ligand, here a peptide mimicking the N-terminal tail of histone H4, acetylated on lysine residues 5, 8, 12 and 16. JQ1, a non-selective BD1/BD2 inhibitor, and RVX-208,²⁹ a selective inhibitor for BD2 versus BD1, were used as controls. The simplest compound **27** showed a significant BET inhibition, with high selectivity (>60-fold) for BD2 versus BD1 (entry 3). The corresponding enantiomer (*ent*)-**27** showed no activity (entry 4) which is consistent with the importance of having an (*S*)-configuration at position 2 of the THQ.²⁵

Table 2. Evaluation of bromodomain inhibitors using the HTRF assay for efficacy and BD2/BD1 selectivity.

Entry	Compound	BD1 IC50 (nM)	BD2 IC50 (nM)	Selectivity BD2/BD1
1	JQ1	67.5	33.6	2
2	RVX208	30 600	254	150
3	27	95 300	1510	63
4	(<i>ent</i>)-27	> 500 000	>50 000	-
5	31	>400 000	>100 000	-
6	28	26 100	481	54
7	32	>100 000	29 900	-

The importance of having the right configuration is highlighted by the lack of or very low inhibitory activity of the compound **31** on BD1 and BD2, demonstrating that the *cis*-2,3 and *trans*-3,4 THQ configuration is critical for efficient BET bromodomain inhibition with this scaffold (entry 5). This was also evident for the phenyl

substituted analogue **28** (entry 6) compared to its nearly inactive diastereomer **32** (entry 7). Compared to product **27**, the presence of the phenyltriazole moiety at position 4 in the compound **28** improved activity approximately 3-fold without significantly altering selectivity for BD2 versus BD1 (entry 6). Compounds **27**, **28**, **31**, **32** and JQ1 and RVX-208 were next evaluated for their potency as anti-inflammatory agents and for their cytotoxicity on macrophage cells (Figure 2). These compounds led to a dose-dependent decrease of pro-inflammatory molecules such as IL-6 (Figure 2A) and TNF α (Figure 2B) upon an LPS-mediated induction of inflammation. Compounds **27** and especially **28** efficiently inhibited the secretion of both molecules, whereas their respective *trans*-2,3 and *trans*-3,4 isomers **31** and **32** had no or very weak effects. As previously reported, JQ1 showed cytotoxicity.³⁰ In contrast, all BD2-selective compounds displayed much lower cytotoxicity (Figure 2C). Strikingly, our compounds were significantly less cytotoxic compared to the BD2-selective reference molecule RVX-208. Taken together, compound **28** combines the best efficacy and cytotoxicity profile of all products tested (Figure 2D).

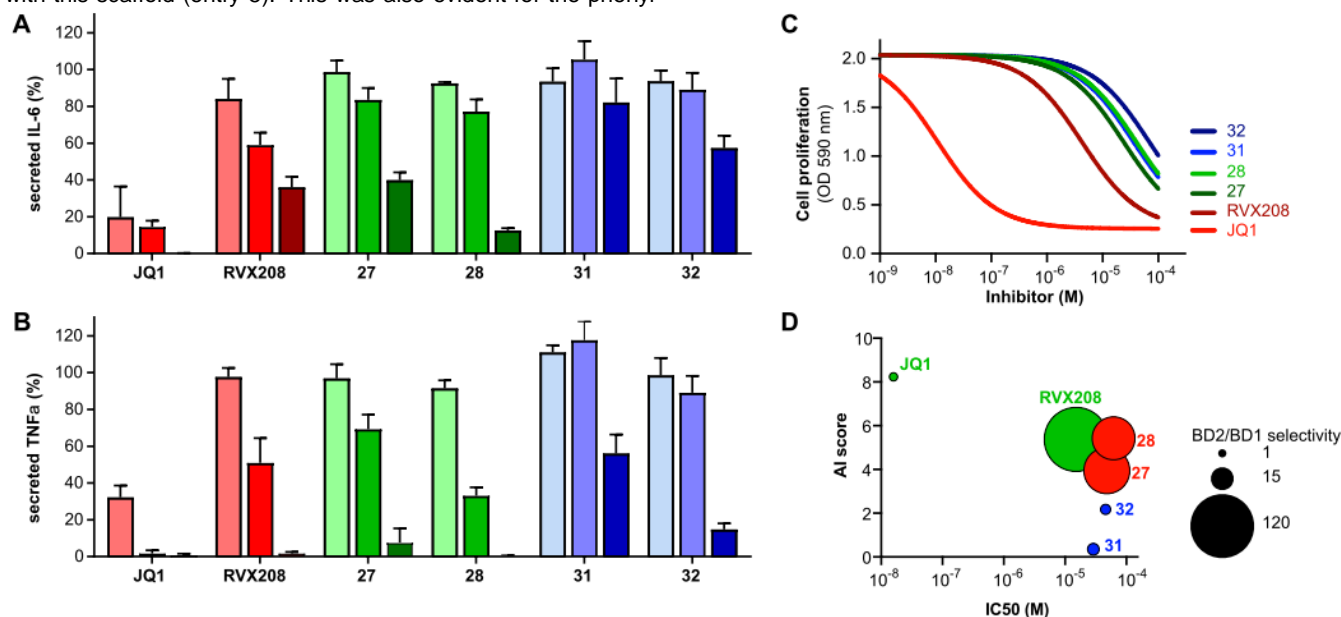


Figure 2. Evaluation of anti-inflammatory activity and cellular toxicity in J774 macrophage cells. A-B. Level of secreted IL-6 (A) and TNF- α (B) measured after treatment of J774 macrophages with LPS (inflammation inducer) and increasing doses (1-10-100 μ M) of BET inhibitor (represented by colour gradient). Data are normalised to LPS-treated conditions. C. Dose-response curves showing impact of BET inhibitor treatment on cellular toxicity evaluated through MTT assay. D. Bubble plot representing anti-inflammatory activity (AI score) versus toxicity (MTT log IC₅₀).

Conclusion

The development of enantiopure bioactive compounds is a challenge for the pharmaceutical industry considering its cost and the subsequent large-scale production. In addition, access to new homochiral configurations opens the door to the exploration of new interaction properties with biological targets. Here we report a one-pot multicomponent reaction that produces THQ via the mild formation of *aza-ortho*-quinone methide species. Coupled with a previous proline catalysis, this protocol provided access to a new

configuration allowing for intensification of the structural complexity and diversification from very simple starting materials and catalysts. In our research program on epigenetic inhibitors, the optically pure THQ **26** was easily obtained in large quantities as a building block for the development of BET bromodomain inhibitor. In only two synthetic steps from **26**, we were able to identify compound **28** as a selective inhibitor for Brd4 BD2 versus BD1, and as an anti-inflammatory agent with a favourable efficacy/toxicity profile. In this context, the new *cis*-2,3 and *trans*-3,4 THQ configuration was critically important for these properties compared to the *trans*-2,3 and *trans*-3,4 configuration obtained from previous synthetic methods.

Modulations are underway to improve the pharmacological properties of this lead compound. Given the above results, this simple and cost-effective multicomponent synthesis should open new perspectives for the use of enantiopure THQ as a versatile synthon and as an advanced active pharmaceutical ingredient to enable the production of future drugs.

Experimental Section

Synthesis of (2S,3S,4R)-Ethyl-4-azido-6-methoxy-3-pentyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (**9**)

To a solution of ethyl (*E*)-2-((4-methoxyphenyl)imino)acetate **4** (300.0 mg, 1.45 mmol) and freshly distilled heptanal (248.0 mg, 2.17 mmol) in anhydrous dioxane (10 mL) was added L-proline (26.4 mg, 0.21 mmol) at rt. The reaction mixture was stirred for 48 h at the same temperature. After the reaction was complete, TMSN₃ (216.0 mg, 1.88 mmol) and BF₃·Et₂O (90 μL, 0.73 mmol) were added and the mixture was stirred at rt for 1 h. The reaction was quenched with NaOH (2 N) until neutralization, extracted with EtOAc, dried by MgSO₄, filtered off and concentrated *in vacuo*. After flash chromatography (silica gel, 5% EtOAc/cyclohexane), the product **9** was isolated as an oil (333.0 mg, 66.4%); *R*_f = 0.27 (10% EtOAc/cyclohexane); [α]_D²⁰ +126.6 (c 1.03 in CHCl₃); IR *v*_{max} (thin film, CH₂Cl₂) 3393, 2954, 2927, 2091, 1734, 1622, 1501, 1463, 1224 cm⁻¹; UV : 208, 245, 325; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.84 (t, *J* = 6.9 Hz, 3H), 0.94-1.29 (m, 8H), 1.32 (t, *J* = 7.1 Hz, 3H), 2.24 (m, 1H), 3.76 (s, 3H), 4.19 (m, 1H), 4.26 (m, 1H), 4.29 (m, 1H), 4.40 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 14.1 (CH₃), 14.4 (CH₃), 22.6 (CH₂), 26.4 (CH₂), 27.0 (CH₂), 31.8 (CH₂), 38.6 (CH), 53.5 (CH), 56.0 (CH₃), 61.4 (CH), 61.6 (CH₂), 115.6 (CH), 115.8 (C), 116.3 (CH), 117.1 (CH), 136.8 (C), 151.9 (C), 172.5 (C); LRMS (ESI+) *m/z* (%) 347 (20) [*M*+H]⁺, 304 (100); HRMS (ESI+) *m/z* calc. for C₁₈H₂₇N₄O₃ 347.2078, found 347.2077.

Deposition Number
(<https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202202293>) 2143668 (for **21**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <http://www.ccdc.cam.ac.uk/structures>, Access Structures service.

For other experimental Procedures/Data, see Supporting Information

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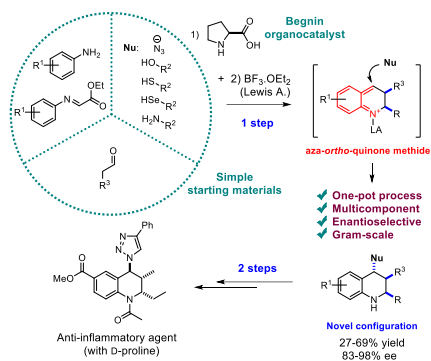
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Keywords: anti-inflammatory agent • aza-*ortho*-quinone methide • BET bromodomain inhibitor • organocatalysis • tetrahydroquinoline

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Simple and selective. Assembling simple functional groups by proline organocatalysis coupled with the addition of $\text{BF}_3 \cdot \text{OEt}_2$ in the same flask allows for the mild formation of *aza-ortho-quinone methide* species that undergo nucleophilic addition to give access to enantio-enriched tri-substituted tetrahydroquinolines with a novel configuration. This advanced three-dimensional structure, after only two additional steps, gave rise to a valuable enantiopure and selective anti-inflammatory compound.

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