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Trifluoromethyl Oxetanes: Synthesis and Evaluation as a *tert*-Butyl Isostere

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Abstract

The synthesis of a new trifluoromethyl oxetane was developed utilizing a Corey-Chaykovsky epoxidation/ring-expansion reaction of trifluoromethyl ketones. The reaction was shown to proceed under mild conditions and displays a broad substrate scope. The trifluoromethyl oxetane was also evaluated as a *tert*-butyl isostere in the context of the γ-secretase modulator (GSM) program. We demonstrate that the trifluoromethyl oxetane-containing GSM has reduced lipophilicity, improved lipophilic efficiency (LipE) and metabolic stability relative to the corresponding *tert*-butyl GSM analog, thus highlighting several benefits of trifluoromethyl oxetane as a more polar *tert*-butyl isostere.

Body

Oxetanes are an increasingly prevalent structural motif in drug discovery and have been used as surrogates for carbonyl groups, *geminal*-dimethyl and *tert*-butyl groups.[1] Furthermore, oxetanes have also been used to increase the polarity of drug molecules and to improve metabolic stability. Several new synthetic approaches have recently been developed to facilitate access to a number of useful oxetanes.[2] Herein, we describe a general synthesis of the trifluoromethyl oxetane substituent and evaluate the trifluoromethyl oxetane as an isostere for the *tert*-butyl group in the context of the γ-secretase modulator (GSM) program (Figure 1).
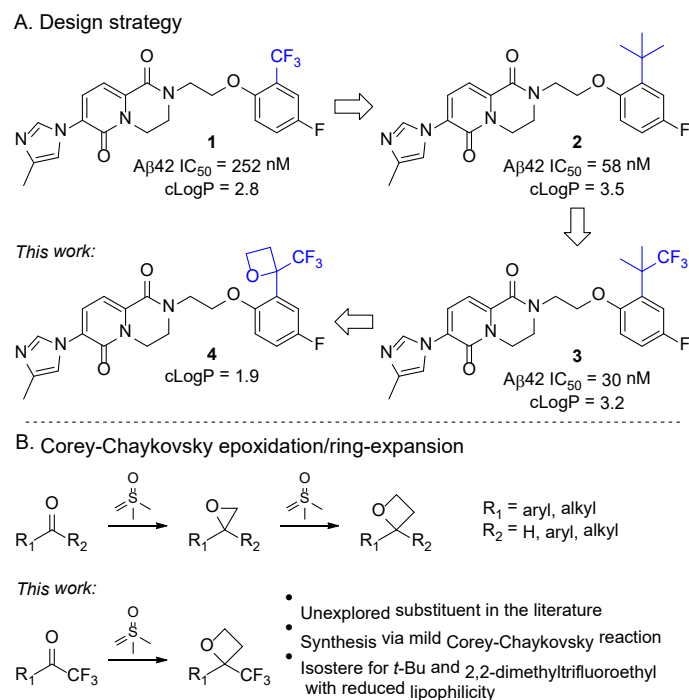
A. Design strategy

B. Corey-Chaykovsky epoxidation/ring-expansion

This work:

- Unexplored substituent in the literature
- Synthesis via mild Corey-Chaykovsky reaction
- Isostere for *t*-Bu and 2,2-dimethyltrifluoroethyl with reduced lipophilicity

Figure 1. A) Design of the trifluoromethyl oxetane GSM **4**. B) Synthesis strategy to access the novel trifluoromethyl oxetanes via a Corey-Chaykovsky epoxidation/ring expansion.

γ-Secretase modulators have gained considerable interest as a potential therapeutic approach for the treatment of Alzheimer's disease.[3] We have previously reported on the design of a novel series of GSMs that incorporate a pyridopyrazine-1,6-dione heterocyclic core.[4] This chemotype provided a significantly improved alignment of potency, physicochemical properties and absorption, distribution, metabolism and excretion (ADME) profile. One of the initial leads (**1**) exhibited moderate in vitro Aβ42 lowering activity (Aβ42[4] IC_{50} = 252 nM), and a favorable physicochemical profile (cLogP[5] = 2.8 and CNS MPO[6] = 5.35, Figure 1A). Furthermore, compound **1** had excellent passive permeability (RRCK[7] $P_{app,A \rightarrow B}$ = 17.7×10^{-6} cm/s) and low potential for P-glycoprotein (P-gp) mediated efflux (MDR[8] Er = 1.5), as well as good microsomal stability (HLM[9] $CL_{int,app}$ = 8.8 mL/min/kg). However, further gain in potency was required to achieve an acceptable human dose projection. Introduction of heteroaryl rings in place of the 2-CF$_3$ substituent on GSM **1** resulted in excellent potency, but at the expense of reduced permeability and poor brain penetration.[10] We therefore turned
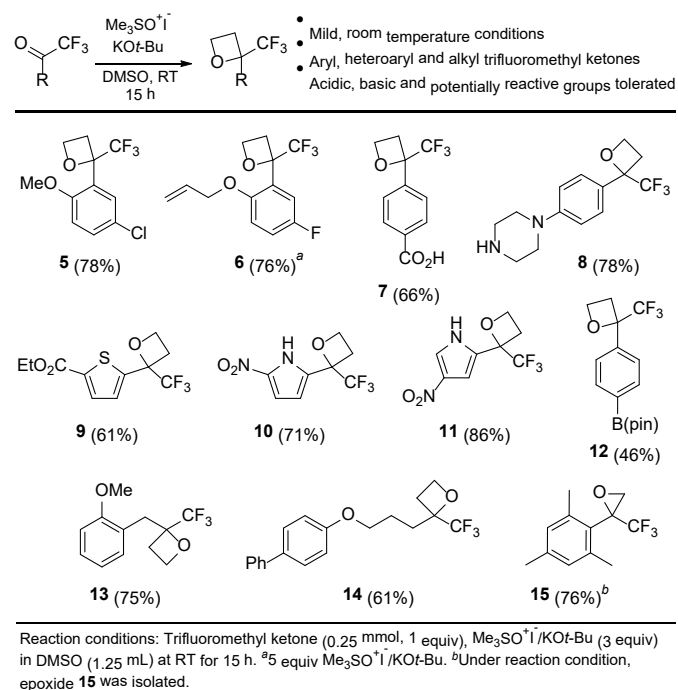
our attention to alkyl substituents to increase sp^3 character.[11] Towards this end, compound **2** was synthesized, which had improved potency (Aβ42 IC$_{50}$ of 58 nM);[12] however, the metabolically labile *tert*-butyl group resulted in poor microsomal stability (HLM $CL_{int,app}$ = 70.1 mL/min/kg) along with increased lipophilicity (cLogP = 3.5). The 2,2-dimethyltrifluoroethyl group has previously been described as a *tert*-butyl isostere with improved metabolic stability.[13] Analogue **3** did indeed have greater microsomal stability (HLM $CL_{int,app}$ = 24.3 mL/min/kg), as well as improved Aβ42 lowering activity (IC$_{50}$ = 30 nM) relative to GSM **2**; however, lipophilicity remained high (cLogP = 3.2).[10] Alternatively, the trifluoromethyl oxetane moiety was envisioned as a more polar replacement for the *tert*-butyl and 2,2-dimethyltrifluoroethyl substituents (Figure 1A). Therefore, we set out to develop an efficient synthesis of trifluoromethyl oxetane GSM **4** and assess the impact of the trifluoromethyl oxetane group on potency, physiochemical properties and ADME in a pairwise analysis with GSMs **1-3**.

General synthetic routes to oxetanes include the intramolecular Williamson ether synthesis or a Paterno-Büchi [2+2] cycloaddition between a substituted olefin and a carbonyl group.[2] Alternatively, 2,2-disubstituted oxetanes can be prepared via a Corey-Chaykovsky epoxidation[14] of an aldehyde or ketone followed by a ring-expansion (Figure 1B).[15] However, to the best of our knowledge, unsubstituted 2-aryl and 2-alkyl-2-trifluoromethyl oxetanes have not been previously described in the literature.[16] We envisioned that a Corey-Chaykovsky epoxidation/ring-expansion of a trifluoromethyl ketone would provide direct access to the desired trifluoromethyl oxetane moiety (Figure 1B).[17]

The synthesis of oxetanes from ketones via the intermediacy of epoxides has previously been reported to require elevated temperatures and prolonged reaction times.[15] However, with an electron deficient trifluoromethyl ketone, the reaction was found to proceed under fairly mild conditions. For example, treatment of 1-(5-chloro-2-methoxyphenyl)-2,2,2-trifluoroethanone with two equivalents of trimethylsulfoxonium iodide and potassium *tert*-butoxide at room temperature resulted in rapid formation of the corresponding epoxide, albeit with an incomplete conversion to the oxetane **5** after 72 hours (see Supporting Information). Further examination of the reaction conditions

revealed that 2.2 equivalents of the dimethylsulfoxonium methylide was sufficient to achieve complete conversion to oxetane **5** (by GCMS) after 15 hours at room temperature. Upon further optimization, the use of three equivalents of dimethylsulfoxonium methylide was deemed to be a more general protocol. These conditions were therefore used to explore the scope of the reaction (Table 1).

Table 1. Synthesis of trifluoromethyl oxetanes

Reaction conditions: Trifluoromethyl ketone (0.25 mmol, 1 equiv), Me$_3$SO$^+$I$^-$/KO*t*-Bu (3 equiv) in DMSO (1.25 mL) at RT for 15 h. ^{a}5 equiv Me$_3$SO$^+$I$^-$/KO*t*-Bu. ^{b}Under reaction condition, epoxide **15** was isolated.

We first examined trifluoromethyl ketone substrates bearing an *ortho*-protected phenol because of the structural similarity to the trifluoromethyl oxetane in GSM **4**. Towards this end, subjecting the *ortho*-methyl and allyl ether substrates to the optimized reaction conditions, generated the corresponding oxetanes **5** and **6** in good yield (Table 1).[18] To further assess the scope and limitations of the reaction, we explored trifluoromethyl ketone substrates incorporating acidic, basic and sensitive functional groups. We observed that a free carboxylic acid was tolerated, as demonstrated by the synthesis of oxetane **7** in 66% yield. Crystallization of carboxylic acid **7** from ethyl acetate/heptane yielded single crystals suited for X-ray analysis (Figure 2). This confirmed the structure of the trifluoromethyl oxetane group and showcases the orientation of the oxetane in relation to the aryl ring. Likewise, a basic amine did not

hinder the reaction, as exemplified by the isolation of piperazine **8** in 78% yield. The reaction was also compatible with heterocyclic trifluoromethyl ketone substrates, as well as with ester, nitro and boronate functional groups (oxetanes **9-12**). Expanding the scope beyond aryl trifluroromethyl ketones, we found that both benzyl and alkyl trifluoromethyl ketones could be converted to the respective oxetanes in moderate to good yield (**13** and **14**). A limitation to the epoxidation/ring-expansion was observed when attempting to use a more sterically encumbered aryl trifluoromethyl ketone substrate. Intermediate epoxide **15** was isolated as opposed to the desired oxetane even after prolonged reaction times and heating (50 → 100 °C over 24 h).
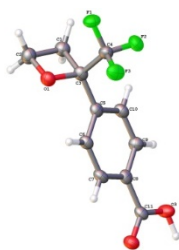

Figure 2. Crystal structure of trifluoromethyl oxetane **7**.

We next sought to apply the epoxidation/ring-expansion reaction to synthesize GSM **4**. Given the broad functional group tolerance, we pursued a route in which the oxetane was installed in the last step in the sequence (Scheme 1). Alkylation of the chloroethyl pyridone **16**[4] with 5-fluoro-2-hydroxybenzaldehyde proceeded in 21% yield to give aldehyde **17**, with chloride elimination as the major side product. Installation of the requisite trifluoromethyl ketone was accomplished by a Ruppert–Prakash trifluoromethylation[19] followed by oxidation with Dess-Martin periodinane.[20] However, subjecting trifluoromethyl ketone **19** to the optimized reaction protocol described above (see Table 1) resulted in isolation of the desired oxetane product **4** in only 24% yield. Analysis of the reaction mixture indicated hydrolysis of the trifluoromethyl ketone to a carboxylic acid. This problem was solved through a minor modification to the reaction procedure: by preforming the methylide and then slowly adding it to a solution of ketone **19**, the desired trifluoromethyl oxetane GSM **4** was isolated in 59% yield. The ability to carry out the Corey-Chaykovsky epoxidation/ring-expansion reaction to form the

trifluoromethyl oxetane on the fully elaborated GSM template further highlights the broad substrate scope of this transformation.
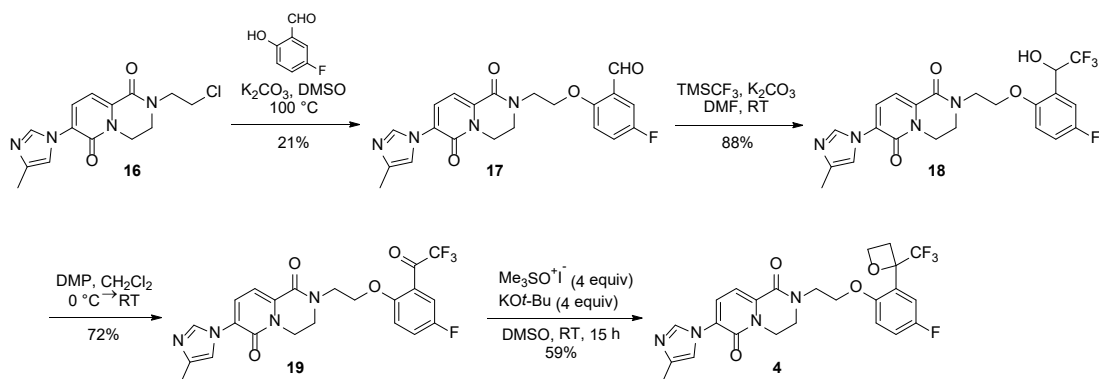
Scheme 1. Synthesis of trifluoromethyl oxetane GSM **4**.

We were pleased to observe that the trifluoromethyl oxetane GSM **4** retained favorable in vitro Aβ-lowering activity as the racemate (IC_{50} = 74 nM, Table 2). As predicted, GSM **4** is less lipophilic ($ELogD^{[21]}$ = 3.6) as compared to both the *tert*-butyl analog **2** (ELogD = 4.6) and 2,2-dimethyltrifluoroethyl GSM **3** (ELogD = 4.3). As a result, the lipophilic efficiency (LipE)[22] of the trifluoromethyl oxetane **4** was increased (LipE = 3.5) relative to analogs **2** and **3** (LipE = 2.6 and 3.2, respectively) despite a slight reduction in the overall potency. Along with the reduced lipophilicity, the metabolic stability of oxetane **4** was improved compared to the *tert*-butyl compound **2** (HLM $CL_{int,app}$ 39.2 vs 74.1 mL/min/kg), although slightly less stable than the corresponding 2,2-dimethyltrifluoroethyl **3** (HLM $CL_{int,app}$ 25.7 mL/min/kg). The trifluoromethyl oxetane GSM **4** also maintained good passive permeability and MDR efflux ratio (RRCK $P_{app,A \rightarrow B}$ = 16.3 × 10^{-6} cm/s; MDR ER = 1.6). Furthermore, trifluoromethyl oxetane **4** was shown to be stable in aqueous acid, neutral and basic solutions (pH 1.2, 7.4, and 10, respectively) over 24 hours at 37 °C (see Supporting Information for details).

Table 2. Comparison of γ-secretase modulators **1-4**.

Compound	Aβ42 IC$_{50}$ [nM][a]	cLogP/ELogD[b]	LipE[c]	HLM $CL_{int,app}$ [ml/min/kg][d]	MDR ER[e]	RRCK $P_{app,A \rightarrow B}$ [cm/s][f]
1	252	2.8/3.6	3.0	<8.8	1.5	17.7×10^{-6}
2	58	3.5/4.6	2.6	70.0	2.0	12.6×10^{-6}
3	30	3.2/4.3	3.2	24.3	1.8	9.3×10^{-6}
4	74	1.9/3.6	3.5	37.1	1.6	16.3×10^{-6}

[a]Aβ42 IC$_{50}$ values were obtained using CHO APP$_{wt}$ cells. Aβ42 IC$_{50}$ values are the geometric mean of at least three experiments.[4] [b]Experimental LogD.[21] [c]Lipophilic efficiency.[22] [d]Human liver microsome-derived scaled intrinsic clearance.[9] [e]MDR efflux ratio using a MDR1/MDCK assay utilizing MDCK cells transfected with the gene that encodes human P-glycoprotein.[8] [f]RRCK cell apparent permeability in the apical to basolateral (A→B) direction.[7]

In summary, we have developed a mild, one-pot synthesis of trifluoromethyl oxetanes from trifluoromethyl ketones utilizing Corey-Chaykovsky epoxidation/ring expansion chemistry. The reaction sequence tolerates a variety of functional groups and can be applied to both aryl and alkyl trifluoromethyl ketones. Additionally, the trifluoromethyl oxetane moiety was evaluated in the context of the γ-secretase modulator program as a novel isostere for *tert*-butyl and 2,2-dimethyltrifluoroethyl substituents. We observed that the trifluoromethyl oxetane GSM **4** maintained similar potency while reducing lipophilicity as compared to the *tert*-butyl and 2,2-dimethyltrifluoroethyl GSMs (compounds **2** and **3**). This, in turn, resulted in an overall improvement in LipE and metabolic stability of trifluoromethyl oxetane **4** relative to *tert*-butyl analog **2**, demonstrating the utility of the trifluoromethyl oxetane as a *tert*-butyl isostere. We hope this report will encourage others to explore the value of this oxetane.

Experimental Section

General Procedure for the Synthesis of Trifluoromethyl Oxetanes. To a 2-dram vial containing potassium *tert*-butoxide (170 mg, 0.75 mmol) in DMSO (1 mL) was added trimethylsulfoxonium iodide (84 mg, 0.75 mmol) and the reaction was stirred at room temperature for 10 minutes. A solution of the trifluoromethyl ketone (0.25 mmol) in DMSO (0.25 mL) was added dropwise to the reaction, and the resulting solution was stirred at room temperature overnight (15 hours). The crude reaction was partitioned between diethyl ether and brine. The organic layer was separated, washed once more with brine, dried over anhydrous sodium sulfate, and concentrated under reduced

pressure. The crude product was purified by silica gel flash chromatography (heptane/ethyl acetate) to afford the corresponding trifluoromethyl oxetane.

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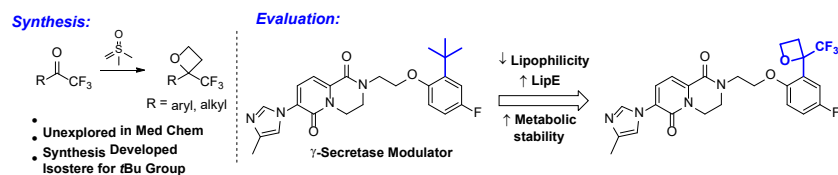
An epoxidation/ring-expansion approach was utilized to synthesize the trifluoromethyl oxetane moiety. Analysis of the trifluoromethyl oxetane as a *tert*-butyl isostere in the gamma secretase modulator program revealed the oxetane to be a LipE winner with improved properties.