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SAR of tricyclic sulfones as γ-secretase inhibitors‡

XU Ruo*, COLE David, ASBEROM Ted, BARA Tom, BENNETT Chad, BURNETT Duane A., CLADER John, DOMALSKI Martin, GREENLEE William J., HYDE Lynn, JOSIEN Hubert, LI HongMei, McBRIAR Mark, McKITTRICK Brian, PISSARNITSKI Dmitri, QIANG Li, RAJAGOPALAN Murali, SASIKUMAR Thavalakulamgara, SU Jing, TANG HaiQun, WU Wen-Lian, ZHANG LiLi & ZHAO ZhiQiang

Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033, USA

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Novel tricyclic sulfones as γ-secretase inhibitors have been reported by this laboratory for the treatment of Alzheimer's disease. Compounds in this series have comparable or better *in vitro* activities and *in vivo* efficacies than sulfonamide analogues reported previously by this laboratory. Based on the previously reported tricyclic sulfone scaffold, additional SAR studies of C ring were carried out. Various C-ring structures including cyclohexane, pyran, and piperidine were tolerated. Additionally, the 7- and 8- positions of the C-ring were identified as the best sites to introduce substituent for modulating the pharmacokinetic properties of compounds from this series.

tricyclic sulfones, γ-secretase, Alzheimer's disease, inhibitors

1 Introduction

Alzheimer's disease (AD) is a debilitating neurodegenerative disease that affects a large population world wide and is not well treated by existing drug therapies. One of the main characteristics of AD is the formation of amyloid plaques in the patient's brain, composed of mostly Aβ 40/42 amyloid β-peptides. Extensive studies of this disease in the past few decades have led to a generally accepted theory regarding the cause and progression of AD, commonly known as the amyloid hypothesis. This hypothesis states that AD is caused by the overproduction and/or reduced clearance of Aβ peptides, which in turn leads to the formation of β-amyloid plaques, and subsequent neuronal cell death [1]. Based largely on the amyloid hypothesis, lowering the Aβ concentration in the brains of patients is proposed as one potential treatment strategy to prevent, slow down, or even reverse the progression of AD [2]. Furthermore, since Aβ is generated from β-amyloid precursor peptides (APP) by a sequential proteolytic cleavage catalyzed by β- and γ-secretases, inhibitors of these secretases should reduce Aβ concentration in patients, which have thus been proposed as therapeutic targets for AD [3]. As the result, there are many ongoing secretase inhibitor programs in various research institutions which have led to numerous literature reports about the secretase inhibitors for the treatment of AD [4].

We have previously reported the design and synthesis of tricyclic sulfones as γ-secretase inhibitors. In the earlier report, A and B rings of the tircyclic core were optimized first, and the C ring was then introduced to generate tricyclic sulfones [5]. These new compounds have completely eliminated the P-450 enzyme inhibition and liver toxicity problems of our earlier sulfonamide γ-secretase inhibitors [6], and also have shown greatly reduced mechanism based side effects compared to our previous γ-secretase inhibitors. As a result, this new series became the focus of the γ-secretase inhibitor program at this laboratory and additional SAR studies were carried out. The strategy was to systematically study and optimize the size and type of the C

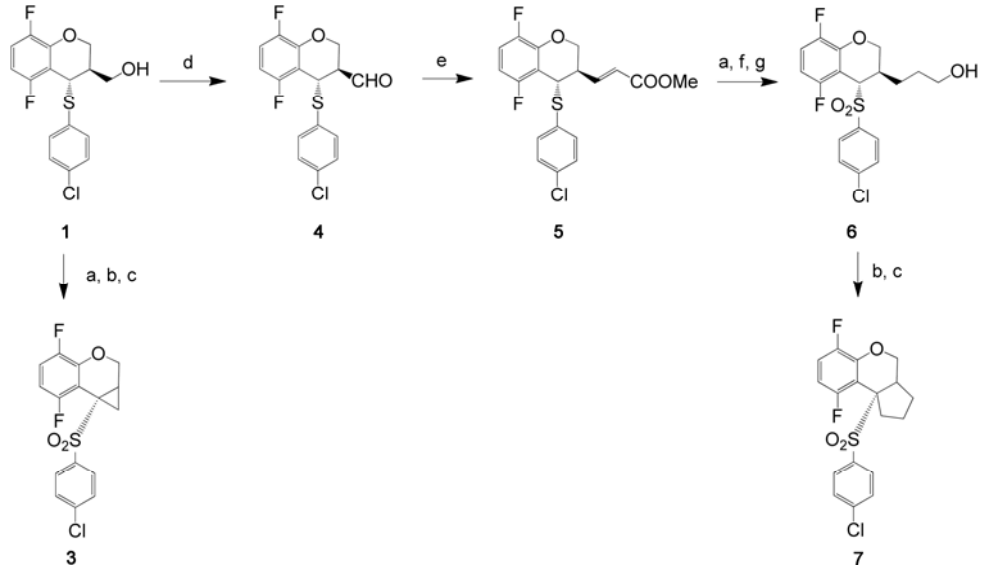
*Corresponding author (email: ruo.xu@merck.com)
‡Dedicated to Prof. Ronald Breslow on the occasion of his 80th birthday

ring first while keeping the previously optimized A and B rings constant, and then introduce various substitutions on all positions of C ring to further optimize the resulting compounds. Herein, we report the results of these studies.

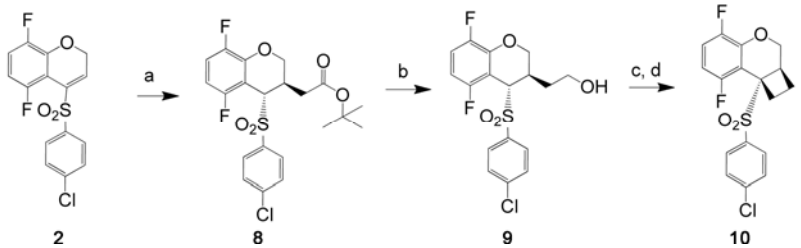
2 Chemistry

We have previously optimized the A and B rings, and developed two versatile intermediates **1** and **2** that bear all the desired functionalities of the optimized AB system [5]. Relatively straightforward and scalable synthetic routes were also developed to produce large quantities of these intermediates. As the result, all subsequent studies commenced from one of these intermediates. The first task was to synthesize compounds with various C ring sizes and the synthetic routes shown in Schemes 1–3 were developed for this purpose. Oxidation of thioether **1** to the corresponding sulfone with MCPBA, followed by mesylation of the hydroxyl group and ring closure with potassium t-butoxide gave compound **3** with cyclopropyl as the C ring. Alternatively, oxidation of the hydroxyl group of compound **1** with Dess-Martin reagent gave aldehyde **4**, which underwent Wittig reaction to form α, β-unsaturated ester **5**. At this point the thioether of **5** was oxidized to the sulfone and then the double bond and ester were reduced by catalytic hydrogenation and lithium borohydride respectively to give compound **6**. It should be noted if the thioether of **1** was oxidized to the sulfone first, oxidation of the hydroxyl group of the resulting sulfone led only to elimination of the sulfone group. Standard aforementioned ring closure reactions gave five membered C ring compound **7**. On the other hand, the synthesis of cyclobutyl C ring started from vinyl sulfone **2**. The Michael addition of the lithium salt of t-butyl acetate to **2** gave ester **8**. Reduction of the ester to hydroxyl compound **9**, followed by standard ring closure reactions gave compound **10** with cyclobutane as the C ring. The synthesis of the cyclohexane C ring analogue took only three steps from a simple sulfone **11** as shown in Scheme 3. Compound **11** was alkylated with 6-bromohexene first, then the double bond of resulting compound was oxidized with MCPBA to give epoxide **12**. This epoxide underwent non-selective ring opening and SNAr ring closure reactions sequentially in one pot to give two rather complex tricyclic compounds **13** and **14**.

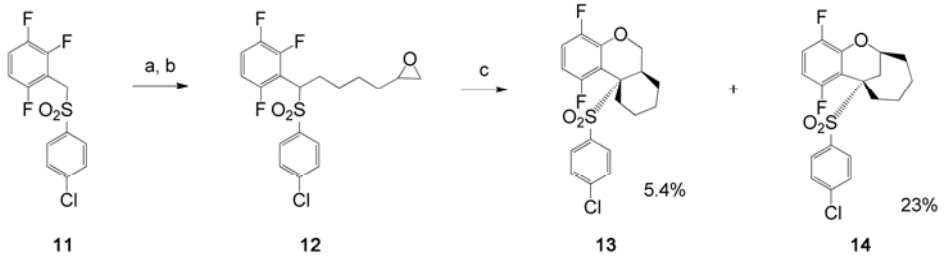
Six membered C rings with hetero atoms, such as tetrahydropyran and piperidine were also synthesized (Scheme 4) starting again from the versatile intermediates **1** and



Scheme 1 Reagents and conditions: (a) MCPBA ; (b) MsCl, NEt_3; (c) *t*-BuOK; (d) Dess Martin reagent; (e) Ph_3P=CHCOOMe; (f) PtO_2/C, H_2; (g) $LiBH_4$.



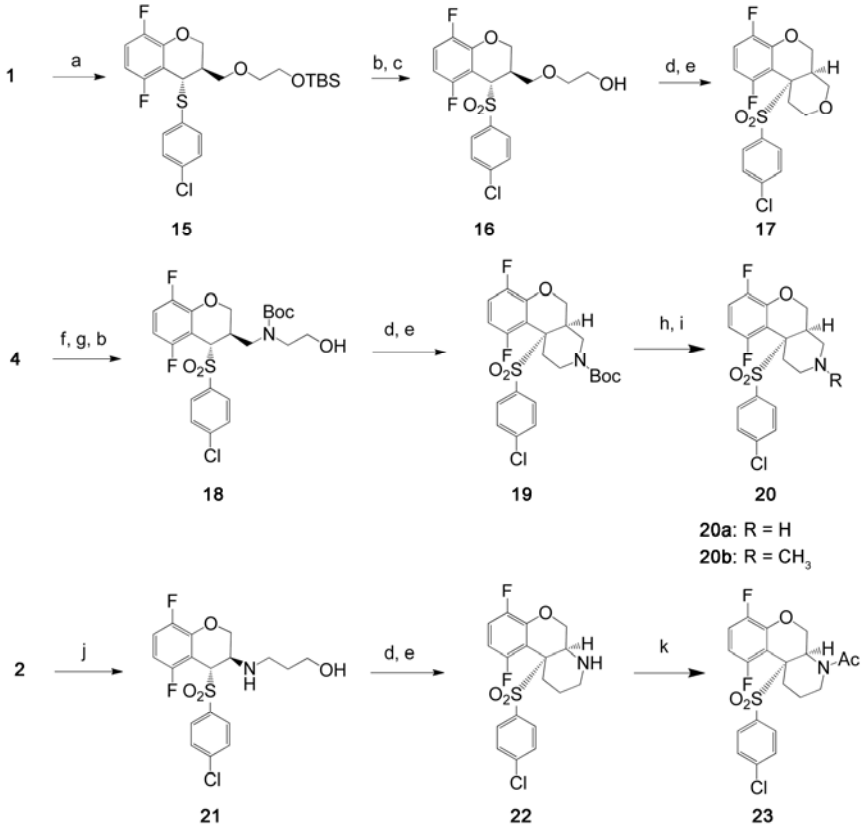
Scheme 2 Reagents and conditions: (a) $LiCH_2COOt$-Bu; (b) $LiBH_4$; (c) MsCl, NEt_3; (d) *t*-BuOK.



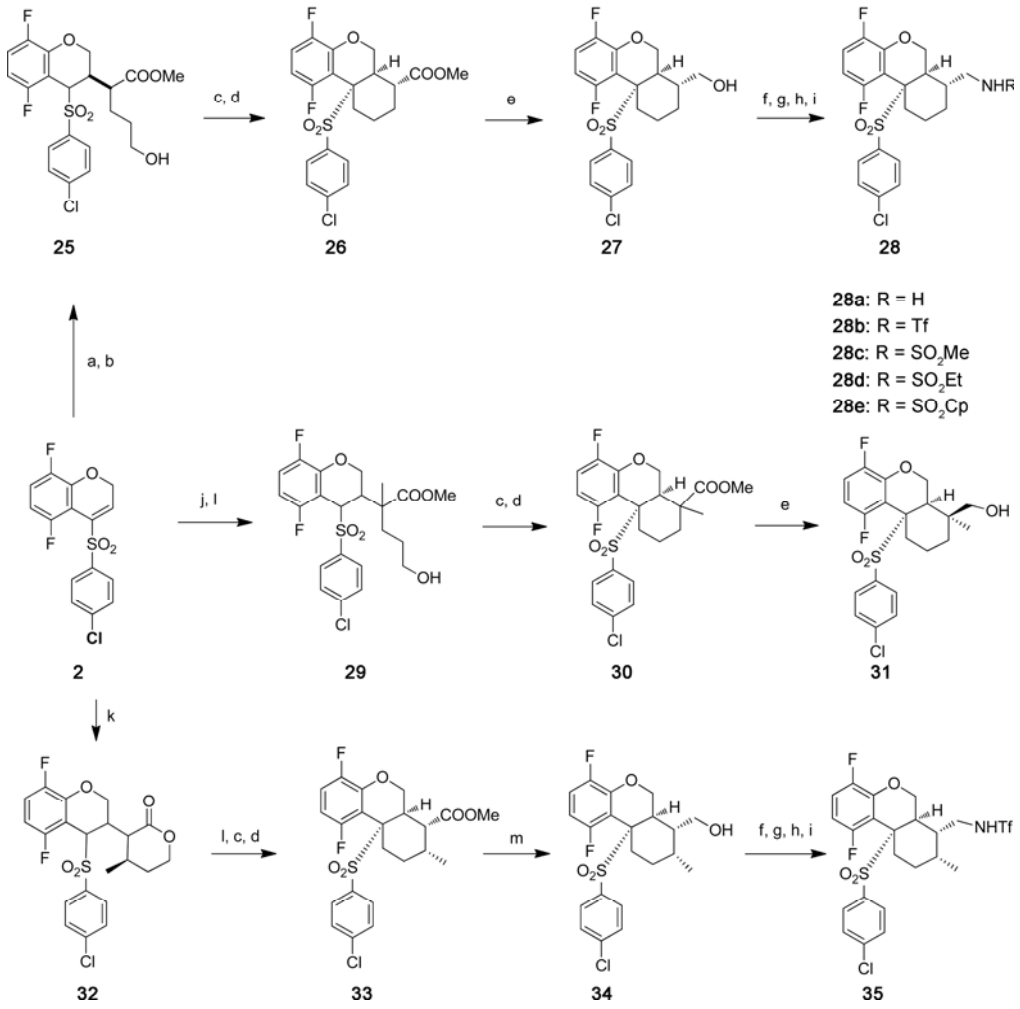
Scheme 3 Reagents and conditions: (a) 6-bromohexene, NaH; (b) MCPBA; (c) *t*-BuOK.

2. The hydroxyl group of **1** was alkylated with TBS protected bromoethanol to give compound **15**. The thioether of **15** was oxidized to sulfone with MCPBA and then the TBS protecting group was removed with TBAF to give **16**. Standard ring closure procedure gave bis-pyran **17**. Furthermore, previously mentioned compound **4** underwent reductive amination with aminoethanol, the resulting secondary amine was protected by a Boc group, and the thioether was then oxidized with MCPBA yielding compound **18**. Standard C ring closure procedure yielded 8-piperidine C ring compound **19**. The Boc group of **19** was removed, followed by standard functional group manipulation to give additional derivatives as exemplified by **20**. On the other hand, 3-amino propanol was added directly to **2**, which formed pure trans adduct **21**. Since the secondary amine at 7-position was much hindered, no protection for this amine was needed for subsequent ring closure reactions. Once the C-ring was formed, the piperidine nitrogen could be further modified, yielding compounds such as **23**.

In order to further modify the overall profile of these compounds, we systematically introduced substitutions on the C ring starting again from fore mentioned advanced intermediate **2**. The typical synthetic scheme to introduce substitutions on cyclohexane C ring is shown in Scheme 5. We have previously reported that vinyl sulfone **2** acted as the dienophile of Deals-Alder reaction en route to our early lead compound **24** which has substitution at C-8 position [5]. In order to make C-7 substituted compounds, another synthetic route was developed as shown in Scheme 5. Methyl 5-(benzyloxy)pentanoate was deprotonated by butyllithium



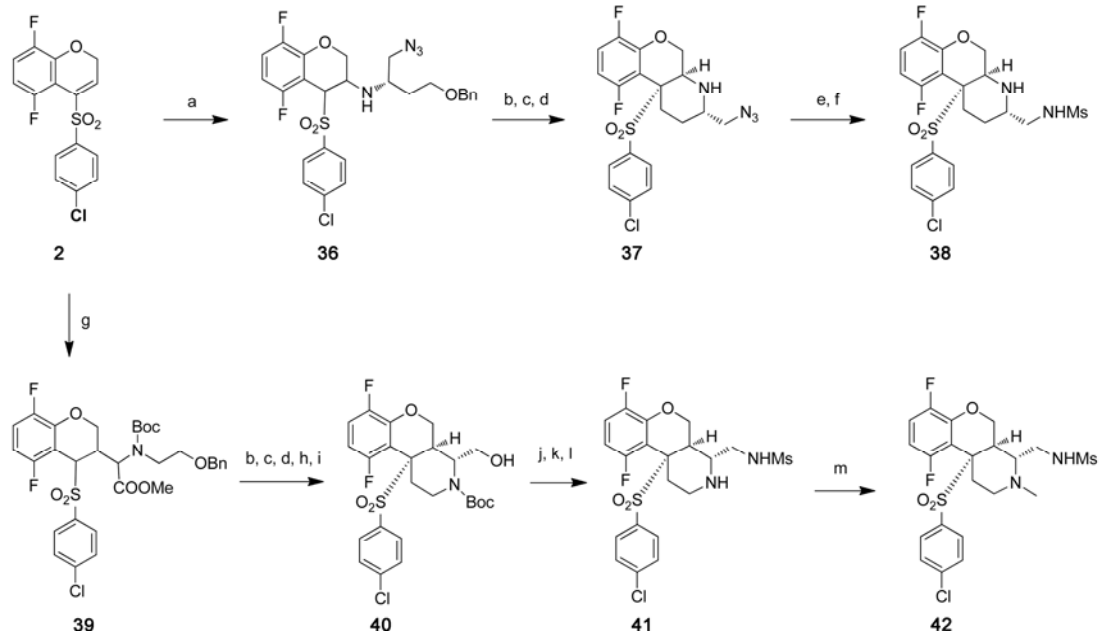
Scheme 4 Reagents and conditions: (a) $BrCH_2CH_2OTBS$, NaH; (b) MCPBA; (c) TBAF; (d) MsCl, NEt_3; (e) *t*-BuOK; (f) $NH_2CH_2CH_2OH$, $NaBH_4$; (g) Boc_2O; (h) TFA; (i) CH_2O, $NaBH_4$; (j) 3-amino propanol; (k) Ac_2O.



Scheme 5 Reagents and conditions: (a) Methyl 5-(benzyloxy)pentanoate, LDA, −78 °C to rt; (b) $Pd(OH)_2$, H_2; (c) MsCl, NEt_3; (d) *t*-BuOK; (e) $LiBH_4$; (f) mesyl chloride, NEt_3; (g) NaN_3; (h) PPh_3, H_2O; (i) Tf_2O, NEt_3; (j) 3-methyltetrahydro-2*H*-pyran-2-one, LDA, −78 °C to rt, 31%; (k) (*R*)-4-methyltetrahydro-2*H*-pyran-2-one, LDA, −78 °C to rt, 88%; (l) $Mg(OMe)_2$; (m) LAH.

first, the resulting anion was added to **2** in a Michael reaction fashion to yield **25** which was a mixture of diastereomers at this point. The benzyl protecting group was removed and resulting alcohol underwent standard ring closure reactions to yield compound **26**. We were pleasantly surprised that the product had pure *cis* configuration between sulfone and methyl ester group, which was the result of methyl ester group isomerizing to its more thermodynamically stable form upon treatment with a strong base. The ester of **26** can be transformed to a variety of groups using similar procedure as mentioned before. The direct alkylation of **25** or **26** failed to generate 7,7-disubstituted compounds probably due to the steric hindrance of this position. So the second substitution at 7-position had to be introduced prior to Michael addition reaction in order to generate 7,7-di substituted compounds. Starting with methyl 5-(benzyloxy)-2-methylpentanoate, compounds **29**, **30** and **31** were synthesized using the similar procedure as that of **28**. The difference was that the methyl ester could no longer isomerize. The desired pure *cis* compound was separated from the *cis*/*trans* mixture by column chromatography. 7,8-Disubstituted compounds were also made using a similar procedure. Pure enantiomeric starting material (*R*)-4-methyltetrahydro-2*H*-pyran-2-one was added to **2** to give compound **32**. The lactone ring of **32** was opened with magnesium methoxide, and the resulting alcohol went through standard ring closure procedure to form compound **33**. The methyl ester could again be isomerized, although not as readily as **26**, to the *cis* configuration between sulfone and methyl ester. Column chromatography could be used to separate the diastereomers of compound **34**.

Two typical routes to introduce functionalities on the piperidine C ring compounds are shown in Scheme 6 and they both started with the Michael addition of a nucleophile to vinyl sulfone **2**. (*S*)-1-Azido-4-(benzyloxy)butan-2-amine, which can be easily synthesized from corresponding amino acid, was added to **2** to give **36**. The benzyl protecting group was removed with boron trichloride and the product



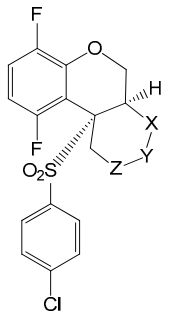
Scheme 6 Reagents and conditions: (a) (*S*)-1-azido-4-(benzyloxy)butan-2-amine, DIPEA, 57%; (b) BCl_3; (c) MsCl, NEt_3; (d) *t*-BuOK, 52% for three steps; (e) PPh_3, H_2O; (f) MsCl, NEt_3; (g) methyl 2-((2-(benzyloxy)ethyl)(*tert*-butoxycarbonyl)amino)acetate, LDA, −78 °C to rt; (h) NaOMe; (i) BH_3SMe_3; (j) Dess-Martin reagent; (k) NH_3, $Ti(O\text{-}i\text{-}Pr)_4$, $NaBH_4$; (l) MsCl, NEt_3; then HCl; (m) CH_2O, $NaBH(OAc)_3$.

underwent standard ring closure reactions to form tricyclic **37**. The azide was reduced to amine and the usual derivatives were made as before. On the other hand, methyl 2-((2-(benzyloxy)ethyl)(*tert*-butoxycarbonyl)amino) acetate could be added to **2** in Michael reaction fashion to form compound **39**. Benzyl removal, ring closure and functional group manipulation yielded compounds **40**, **41** and **42**. It should be noted that the aforementioned Michael addition, and then ring closure reaction sequence was very robust and could be used to introduce many other substituted C rings.

3 Result and discussion

We have determined previously that a tricyclic system could give rise to very potent compounds in both *in vitro* and *in vivo* assays of gamma secretase inhibition. The goal of current study was to develop the SAR of C ring and further improve the overall profile of resulting compounds. The first task was to determine the optimal size and type of the newly introduced C ring. Thus compounds with different C rings were synthesized while keeping the previously optimized A and B rings constant. The membrane $A\beta_{40}$ IC_{50} data of these compounds are listed in Table 1. The results showed unequivocally that the six-member C ring is optimal. The activity increased drastically when the size of all carbon C-ring increased from 3 (3100 nM) to 6 (20 nM). 7-Member C-ring compounds were also synthesized and they were not as active as 6 member C ring compounds [7]. Furthermore, the data also showed both cyclohexane and pyran C rings are well tolerated. A piperidine C ring was also tolerated although to a lesser extent. Bis pyran **17** was resolved to its pure enantiomers, and results showed that the activity resided mostly in (−) enantiomer as shown for pre-

Table 1 Membrane $A\beta_{40}$ IC_{50} data for various tricyclic compounds



Compounds [a]	X	Y	Z	Mem. $A\beta_{40}$ IC_{50} (nM) [b]
3	–	–	–	3100
10	–	–	CH_2	303
7	–	CH_2	CH_2	113
13	CH_2	CH_2	CH_2	22
17	CH_2	O	CH_2	22
(+) 17 [c]	CH_2	O	CH_2	10000
(–) 17 [c]	CH_2	O	CH_2	9.0
20a	CH_2	NH	CH_2	780
20b	CH_2	NCH_3	CH_2	132
22	CH_2	CH_2	NH	81
23	CH_2	CH_2	NAc	47

a) All compounds are racemic unless otherwise indicated. b) Values are means of two experiments. c) Pure enantiomer.

viously published compounds [5]. As the result, whenever it is possible, the pure enantiomers were obtained *via* chiral HPLC separation and were used for more detailed biological studies.

Compounds such as **13** and **17** were potent enough to warrant further *in vivo* studies. Unfortunately, subsequent studies revealed that they have a very poor pharmacokinetic profile, most likely due to their high log*P* values. Because of their poor PK, they also had limited efficacies in our *in vivo* CRND8 mouse studies as shown by the data in Table 2. Thus further modification of this core was needed to improve their overall profile, especially to reduce their log*P* value. Since the 6 member C ring was determined to be the optimal ring size, we concentrated our effort on 6-membered C ring compounds. We have demonstrated previously that substitutions at the C-8 position on the tricyclic system were well tolerated and the compounds with polar substitutions at 8-position had excellent *in vitro* and *in vivo* activities as represented by compound **24** [5]. A complete SAR studies around the C-ring was then carried out and the *in vitro* and *in vivo* data for representative compounds are shown in Table 2. When the substitutions were introduced to 7-position, the resulting compounds were among the most potent in this series as indicated by compound **24**–**28e**. When appropriate functional groups, such as in compounds **28c**, **28d** and **28e**, were introduced at this position and the compounds were resolved to their pure enantiomeric form, the resulting compounds have lower single digit nanomolar activities in both membrane and whole cell assays. On the other hand, the *in vivo* efficacies of the compounds depended on both the *in vitro* IC_{50}s and *in vivo* PK profiles. Among all the compounds tested, the triflamide **28b** had the best rat PK and brain penetration profile. As the result, it had the highest percentage inhibition although it did not have the lowest IC_{50}. This compound was studied in more detail in our animal studies and the results showed that it inhibited plasma and brain $A\beta_{40}$ of CRND8 mouse by 98 and 69 percent respectively when dosed orally at 30 mg/kg. Additionally, the peripheral properties of these compounds, such as CYP inhibition and PXR induction, are generally acceptable. The detailed *in vivo* studies of these compounds were carried out and will be reported in due time.

Since both 7- and 8-positions are well tolerated, we decided to make di-substituted compounds at these two positions. Large libraries of compounds with di-substitutions at 7- and/or 8-positions including amides, sulfonamides, urea, carbonamides, sulfones and heterocycles were synthesized and evaluated and a few of representative compounds are listed in Table 2. As the data for **30**–**35** show, membrane $A\beta_{40}$ IC_{50}s of 7, 8-disubstituted compounds were generally lower than mono-substituted analogs. Although 7,7-disubstituted compounds could yield very active compounds in terms of IC_{50}, further studies showed that they offered no advantage in terms of overall profile of the compounds.

Table 2 *In vitro* IC_{50} and rat *in vivo* data for various tricyclic compounds

Compounds [a]	Mem $A\beta_{40}$ IC_{50} (nM) [b]	Whole Cell $A\beta_{40}$ IC_{50} (nM) [b]	Whole Cell $A\beta_{42}$ IC_{50} (nM) [b]	Rat $AUC_{0\text{-}6h}$ (h.nM) brain/plasma	% inh. of $A\beta_{40}$ CRND8 mouse [e] plasma, brain
13	22	43	27	–	19, 32
(–) **17** [c]	9	10	8	–	20, –12
20a	780				
20b	132	81	61		
22	81	58	44	0, –	
23	47	70	47		4, –
24 [c]	27	108	46	9254, 0.3	90, 42
26	21	27	15	0, –	
27 [c]	15	21	8		
28b [c]	14	15	6	1868, 1.68	98, 69
28c	2.5	2	2	43, –	73, 34
28d	1.6	4	2	185, –	49, 3
28e	3.1	4	4	540	6, 21
30 [d]	19	78	26	0	
31	550				
33 [c]	128				
34 [c]	271				
35 [c]	172				
37 [c]	290				
38 [c]	92				
40	364				
41	80	33	18		
42	122				

a) All compounds are racemic unless otherwise indicated. b) Values are means of two experiments. c) Pure enantiomer. d) Mixture of diastereomers. e) Dosed at 30 mg/kg po.

Compounds with a piperidine C ring were also studied in detail and a few representative compounds are listed in Table 2. As the data for compounds **37**–**42** shown, these compounds are generally less active than corresponding cyclohexane compounds. Although selected compounds in di-substituted series should show improved activity via enantiomeric resolution, the majority of work was done on mono-substituted compounds, such as **24** and **28b** due to their easy synthetic accessibility.

This report concentrated on *p*-chlorophenyl at the aryl sulfone portion of the compounds since it was shown to be one of the best groups in various studies. Other groups at this position, especially the *p*-trifluorophenyl group were also studied. Since the synthesis and SAR trend of these compounds were almost the mirror image of results presented here, they are not included in this paper. Detailed biological studies were carried out to differentiate the compounds with *p*-chlorophenyl or *p*-trifluorophenyl as aryl sulfone and the results will be reported in due course.

4 Conclusion

Detailed C ring SAR studies of tricyclic sulfone γ-secretase inhibitors were carried out. Compounds in this new series have comparable or better *in vitro* activities and *in vivo* efficacies than previously reported sulfonamide compounds. The 6-membered ring was identified as the optimal size for C ring. Pyran and cyclohexane were the best while piperidine was also tolerated as C ring. Additionally, 7- and 8-positions were identified as sweet spots on the tricyclic core to introduce polar groups for the fine tuning the final compounds. The best compounds in this series had excellent *in vitro* activities and *in vivo* efficacies in addition to their clean peripheral profiles. Further studies also revealed that they have reduced mechanism based Notch side effects that plagued previous sulfonamide γ-secretase inhibitors.

5 Experimental

General

Silica gel chromatography was performed using pre packed silica gel cartridges (Biotage or Isco) on ISCO CombiFlash™ or Analogix intelliflash 280 system. NMR spectra were obtained on a Varian XL-400 spectrometer in $CDCl_3$ unless otherwise indicated and are reported as ppm downfield from Me_4Si. Purity was checked via LCMS analysis, performed on an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Alltech platinum C18, 3 micron, 33 mm × 7 mm ID; gradient flow: 0 min-10% CH_3CN, 5 min-95% CH_3CN, 7 min-95% CH_3CN, 7.5 min-10% CH_3CN, 9 min-stop. All tested compounds were more than 95% pure by this HPLC method unless otherwise noted and all compounds also showed correct M + 1 or M + Na peak by LCMS. *In vitro* and *in vivo* data given throughout the text and in Tables 1 and 2 were collected using previously described method [8].

*7b-(4-Chlorophenylsulfonyl)-4,7-difluoro-1,1a,2,7b-tetrahydrocyclopropa [c]chromene (**3**)*

1 (2 g, 5.8 mmol) was dissolved in 100 mL DCM and MCPBA (77%, 3.9 g, 17.5 mmol) was added. The reaction was stirred at room temperature for 3 h. 8 g $NaHSO_3$ in 50 mL water were added to quench excess MCPBA. The organic layer was separated, washed with 1 N NaOH solution, brine, dried over Na_2SO_4 and concentrated. The product was purified by column using EtOAc/hexane as the eluent (gradient from 0/100 to 75/25 in 40 min). Yield: 1.6 g, 75%. Part of the product (0.3 g, 0.76 mmole) was dissolved in 50 mL DCM and MsCl (0.43 g, 3.8 mmol) and NEt_3 (0.38 g, 3.8 mmol) were added. The mixture was stirred at room temperature for 2 h. KO*t*-Bu (1 M in THF, 5 mL) was added and the reaction was stirred at room temperature for 1 h. 50 mL water was added. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The product was purified by column using EtOAc/hexane as eluent (gradient from 0/100 to 25/75 in 40 min). Yield: 101 mg, 37%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 8.8 Hz, 2 H), 6.99 (m, 1 H), 6.67 (m, 1 H), 4.84 (dd, J = 11.7 and 8.1 Hz, 1 H), 3.33 (dd, J = 11.7 and 8.1 Hz, 1 H), 2.57 (m, 1 H), 2.44(dd, J = 11.7 and 8.1 Hz, 1 H), 1.34 (t, J = 5.9 Hz, 1 H).

*Trans-4-(4-chlorophenylthio)-5,8-difluorochroman-3-carbaldehyde (**4**)*

1 (2.8 g, 8.8 mmol) was dissolved in 15 mL DCM and Dess-Martin reagent (4.1 g, 9.7 mmol) was added. The reaction was stirred at room temperature for 3 h. 40 mL EtOAc and 30 mL saturated $Na_2S_2O_3$ solution were added and the organic layer was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residue (2.8 g, quant.) was used in next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1 H), 7.45 (d, J = 8.8 Hz, 2 H), 7.34 (d, J = 8.8 Hz, 2 H), 6.97 (m, 1 H), 6.62 (m, 1 H), 4.87–4.95 (m, 2 H), 4.74 (dd, J = 11.7 and 2.9 Hz, 1 H), 2.83 (m, 1 H).

*Trans-methyl (3-(4-(4-chlorophenylthio)-5,8-difluorochroman-3-yl))acrylate (**5**)*

4 (0.43 g, 1.2 mmol) was dissolved in 20 mL THF and methyl (triphenylphosphoranylidene) acetate (0.77 g, 2.3 mmol) was added. The reaction was stirred at room temperature for 3 h. 30 mL EtOAc was added. The organic layer was washed with water, dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (EtOAc/hexane from 0/100 to 25/75 in 45 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2 H), 7.34 (d, J = 8.8 Hz, 2 H), 7.00 (m, 1 H), 6.79 (m, 1H), 6.60 (m, 1 H), 5.86 (dd, J = 16.1 and 1.5 Hz, 1 H), 4.76 (dd, J = 11.0 and

2.2 Hz, 1 H), 4.37–4.43 (m, 2 H), 2.81 (m, 1 H).

*Trans-3-(-4-(4-chlorophenylsulfonyl)-5,8-difluorochroman-3-yl)propan-1-ol (**6**)*

5 (0.21 g, 0.53 mmol) was dissolved in 10 mL DCM and MCPBA (77%, 0.5 g) was added. The reaction was stirred at room temperature for 3 h. 1 g $Na_2S_2O_3$ in 50 mL water and 100 mL EtOAc were added. The organic layer was separated, washed with 1 N NaOH solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was dissolved in 20 mL EtOAc and 2 drops of acetic acid was added. PtO_2/C (0.1 g) was added and hydrogen was introduced *via* a balloon. The reaction was stirred at room temperature overnight. The catalyst was filtered and residue was dissolved in 10 mL THF and $LiAlH_4$ (1 M in THF, 0.9 mL) was added. The mixture was stirred at room temperature for 0.5 h. 50 mL EtOAc was added and the organic layer was washed with 1 N HCl solution (2 × 50 mL), dried over Na_2SO_4 and concentrated. The product was purified by column (EtOAc/hexane from 0/100 to 50/50 in 35 min). Yield: 60 mg, 29% for three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.71 (d, J = 8.8 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 2 H), 7.02 (m, 1H), 6.39 (m, 1 H), 4.96 (dd, J = 11.7 and 2.9 Hz, 1 H), 4.41–4.46 (m, 2 H), 3.52–3.67 (m, 2 H), 2.84 (m, 1H), 1.30–1.70 (m, 5 H).

*9b-(4-Chlorophenylsulfonyl)-6,9-difluoro-1,2,3,3a,4,9b-hexahydrocyclopenta[c]chromene (**7**)*

6 (48 mg, 0.12 mmol) and MsCl (16.3 mg, 0.14 mmol) were dissolved in 5 mL DCM. NEt_3 (24 mg, 0.24 mmol) was added. The mixture was stirred at room temperature for 10 min. 50 mL water and 50 mL EtOAc were added. The organic layer was washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was dissolved in 10 mL THF and KO*t*-Bu (1 M in THF, 0.3 mL) was added. The mixture was stirred at room temperature for 30 min. 50 mL water and 50 mL EtOAc were added. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The product was purified by column (EtOAc/hexane from 0/100 to 25/75 in 45 min). Yield: 30 mg, 65% for two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.51 (d, J = 8.1 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H), 6.99 (m, 1 H), 6.45 (m, 1 H), 4.58 (dd, J = 11.7 and 5.1 Hz, 1 H), 3.87 (dd, J = 11.7 and 5.8 Hz, 1 H), 3.27 (m, 1 H), 2.86 (m, 1 H), 2.41 (m, 1 H), 2.12 (m, 1 H), 1.95 (m, 1 H), 1.61 (m, 2 H).

*t-Butyl-2-((3S,4R)-4-(4-chlorophenylsulfonyl)-5,8-difluorochroman-3-yl)acetate (**8**)*

2 (0.49 g, 1.4 mmol) was dissolved in 10 mL dry THF and cooled to −78°C. (2-*tert*-Butoxy-2-oxoethyl)lithium (208 mg, 1.70 mmol) in 10 mL of THF was cooled to −78°C and added to the solution of 23 via cannula. The reaction was stirred at −78°C for 1 h. TLC showed starting material was still present so an additional 203 mg (2-*tert*-butoxy-2-oxoethyl)lithium in 10 mL THF at −78°C was added via cannula. The reaction was stirred at −78°C for 1.5 h. The reaction was quenched with 100 mL EtOAc and 100 mL of water. The organic layer was separated, washed with brine (2 × 50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (Hexane/EtOAc from 100/0 25/75 to 75/25 in 50 minutes). Yield: 330 mg, 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.1 Hz, 2H), 7.00 (m, 1H), 6.42 (m, 1 H), 4.89 (dd, J = 11.7 and 2.9 Hz, 1 H), 4.48 (s, 1 H), 4.29 (d, J = 11.7 Hz, 1 H), 3.22 (m, 1 H), 2.34 (dd, J = 16.8 and 6.6 Hz, 1 H), 2.10 (dd, J = 11.7 and 8.7 Hz, 1 H).

*8b-(4-Chlorophenylsulfonyl)-5,8-difluoro-2,2a,3,8b-tetrahydro-1H-cyclobuta[c]chromene (**10**)*

10 was synthesized from **9** using the similar procedure as that of compound **7**. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.54 (d, J = 8.1 Hz, 2 H), 7.42 (d, J = 8.7 Hz, 2 H), 7.01 (m, 1H), 6.48 (m, 1 H), 4.21 (dd, J = 11.7 and 5.1 Hz, 1 H), 4.02 (dd, J = 11.7 and 4.4 Hz, 1 H), 3.68 (m, 1H), 3.17 (m, 1 H), 2.24–2.41 (m, 2H), 1.89 (m, 1 H).

*(5-(4-Chlorophenylsulfonyl)-5-(2,3,6-trifluorophenyl)pentyl)-oxirane (**12**)*

11 (1.0 g, 3.1 mmol) and 5-bromopentene (1.5 g, 6.3 mmol) were dissolved in 20 mL THF and *t*-BuOK (1M in THF, 6.2 mL) was added. The reaction was stirred at room temperature overnight. 50 mL water and 50 mL EtOAc were added. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The product, 2-(1-(4-chlorophenylsulfonyl)hept-6-enyl)-1,3,4-trifluorobenzene, was purified by column using EtOAc/Hexane as eluent (gradient from 0/100 to 25/75 in 40 min). The purified product (0.65 g, 1.6 mmol) and MCPBA (77%, 0.71g, 3.2 mmol) were stirred in 50 DCM for 5 h. 2 g Na_2SO_3 in 100 mL water were added to quench excess MCPBA. The organic layer was separated, washed with 1 N NaOH solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. The product was purified by column using EtOAc/hexane as eluent (gradient from 0/100 to 40/60 in 40 min). (0.52 g, 77%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 8.8 and 1.5 Hz, 2 H), 7.44 (d, J = 8.1 Hz, 2 H), 7.14 (m, 1 H), 6.78 (m, 1 H), 4.60 (m, 1 H), 2.83 (m, 1H), 2.71 (m, 1H), 2.39–2.50 (m, 3 H), 1.35–1.70 (m, 6H).

*(6aR,10aS)-10a-(4-chlorophenylsulfonyl)-1,4-difluoro-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene (**13**) and 7(S)-[(4-chlorophenyl)sulfonyl]-8,11-difluoro-2,3,4,5,6,7-hexahydro-2(S),7-methano-1-benzoonin (**14**)*

12 (0.52 g, 1.24 mmol) was dissolved in 25 mL THF and *t*-BuOK (1 M in THF, 3.72 mL) was added. The reaction was heated to 50 °C for 4 h. 50 mL water and 50 mL EtOAc were added. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The product

was purified by column using EtOAc/hexane as eluent (gradient from 0/100 to 25/75 in 40 minutes). Two compounds were isolated.

Compound **13** (27 mg, 5.4%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.1 Hz, 2 H), 7.48 (d, J = 8.8 Hz, 2 H), 7.06 (m, 1 H), 6.39 (m, 1 H), 5.22 (dd, J = 11.7 and 2.9 Hz, 1 H), 4.14 (d, J = 11.7 Hz, 1 H), 2.6 (m, 2H), 0.9–1.9 (m, 7 H).

Compound **14** (112 mg, 23%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.1 Hz, 2 H), 7.39 (d, J = 8.1 Hz, 2 H), 7.01 (m, 1H), 6.60 (m, 1 H), 4.85 (m, 1 H), 3.12 (m, 1 H), 2.80 (m, 1 H), 1.1–2.4 (m, 8 H).

*tert-Butyl-{2-[trans-4-(4-chloro-phenylsulfanyl)-5,8-difluoro-chroman-3-ylmethoxy]-ethoxy}-dimethyl-silane (**15**)*

1 (0.4 g, 1.2 mmol), (2-bromoethoxy)-*tert*-butyl-dimethylsilane (0.56 g, 2.3 mmol) and NaH (60% in oil, 0.5 g) were stirred in 25 mL THF at 50 °C for 5 h. 100 mL water and 100 mL EtOAc were added. The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (EtOAc/hexane from 0/100 to 10/90 in 45 min). Yield: 85 mg, 15%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.43 (d, J = 8.8 Hz, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 6.96 (m, 1 H), 6.57 (m, 1 H), 4.60 (dd, J = 8.8 and 2.2 Hz, 1 H), 4.51 (br, 1 H), 4.38 (td, J = 11.0 and 1.5 Hz, 1 H), 3.68 (t, J = 4.4 Hz, 2 H), 3.28–3.50 (m, 4H), 2.35 (m, 1 H), 0.86 (s, 9H), 0.01 (s, 6 H).

*2-[trans-4-(4-Chloro-benzenesulfonyl)-5,8-difluoro-chroman-3-ylmethoxy]-ethanol (**16**)*

15 (85 mg, 0.17 mmol) was dissolved in 25 mL DCM and MCPBA (77%, 0.11 g, 0.51 mmol) was added. The reaction was stirred at room temperature for 3 h. 2 g $Na_2S_2O_3$ in 50 mL water and 100 mL EtOAc were added. The organic layer was washed with 1 N NaOH solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. The product (75 mg, 0.14 mmol) was dissolved in 20 mL THF and TBAF (0.2 g) was added. The reaction was stirred at room temperature for 3 h. 50 mL water and 50 mL EtOAc were added. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (EtOAc/hexane from 0/100 to 50/50 in 35 min). Yield: 50 mg, 70% for two steps. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.73 (d, J = 8.1 Hz, 2 H), 7.51 (d, J = 8.1 Hz, 2 H), 7.03 (m, 1 H), 6.41 (m, 1 H), 4.90 (dd, J = 8.8 and 2.9 Hz, 1 H), 4.57 (s, 1 H), 4.39 (td, J = 11.7 and 1.5 Hz, 1 H), 3.68(br, 2 H), 3.41–3.54 (m, 3 H), 2.30 (t, J = 9.5 Hz, 1 H), 3.15 (m, 1 H).

*Trans-10b-(4-Chloro-benzenesulfonyl)-7,10-difluoro-1,4a,5,10b-tetrahydro-2H,4H-pyrano[3,4-c]chromene (**17**)*

16 (25 mg, 0.06 mmol) and MsCl (68 mg, 0.59 mmol) were dissolved in 5 mL DCM and NEt_3 (59 mg, 59 mmol) was added. The mixture was stirred at room temperature for 2 h. 50 mL water and 50 mL EtOAc were added. The organic layer was washed with 1 N HCl solution (2 × 50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. The product (26 mg, 0.052 mmol) was dissolved in 5 mL THF and KOt-Bu (1 M in THF, 0.5 mL) was added. The mixture was stirred at room temperature overnight. 50 mL water and 50 mL EtOAc were added. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (EtOAc/hexane from 0/100 to 50/50 in 45 min). Yield: 17 mg, 81%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.62 (d, J = 8.8 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 2 H), 7.10 (m, 1 H), 6.44 (m, 1 H), 5.16 (dd, J = 8.8 and 2.9 Hz, 1 H), 4.14 (d, J = 12.4 Hz, 1 H), 3.82-3.97 (m, 2 H), 3.32 (t, J = 11.7 Hz, 1 H), 3.12 (t, J = 11.7 Hz, 1 H), 2.89 (m, 1H), 2.56 (d, J = 13.1 Hz, 1 H), 2.33 (m, 1 H).

The racemic mixture can be separated into two pure enantiomers using chiral OJ (size: 15 x 250 mm) column with pure ethanol as the solvent. The first fraction is compound 17(−), [α] = −138.4 degree (c =1.000 in DCM). The second fraction is compound 17(+), [α] = + 137.2 degree (c =1.000 in DCM).

*tert-Butyl (4-(4-chlorophenylsulfonyl)-5,8-difluorochroman-3-yl)methyl(2-hydroxyethyl)carbamate (**18**)*

4 (2.2 g, 5.9 mmol) and ethanolamine (1.1 g, 18 mmol) were dissolved in 20 mL THF. The reaction was stirred at room temperature overnight. $NaBH_4$ (2 g, 52 mmol) and MeOH (10 mL) were added and the reaction was stirred for 3 h. 100 mL water and 100 mL EtOAc were added. The organic layer was washed with water (100 mL), dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (EtOAc/hexane from 25/75 to 100/0 in 45 min). The desire product (0.40 g, 18%) was dissolved in 20 mL DCM and Boc_2O (0.24 g, 1.2 mmol) was added. The reaction was stirred at room temperature for 3 h. MCPBA (77%, 0.8 g, 3.6 mmol) was then added and the reaction was stirred at room temperature for 2 h. 2 g $Na_2S_2O_3$ in 50 mL water was added to quench the reaction and 100 mL EtOAc was added to extract the product. The organic layer was washed with 1 N NaOH solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (EtOAc/hexane from 0/100 to 50/50 in 45 min). Yield: 0.44 g, 85%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.71 (d, J = 8.1 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.02 (m, 1 H), 6.40 (m, 1 H), 4.90 (d, J = 11.7 Hz, 1 H), 4.40 (m, 1 H), 4.28 (d, J = 11.7 Hz, 1 H), 3.7 (m, 2 H), 3.10–3.40 (m, 5 H), 1.26 (s, 9 H).

*tert-Butyl-10b-(4-chlorophenylsulfonyl)-7,10-difluoro-4,4a,5,10b-tetrahydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate (**19**)*

Compound **19** is synthesized from **18** using the same

method as that of 17. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.60 (d, J = 8.1 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H), 7.09 (m, 1 H), 6.43 (m, 1 H), 5.20 (dd, J = 11.7 and 2.2 Hz, 1 H), 4.23 (d, J = 12.4 Hz, 1 H), 4.1 (m, 2 H), 2.30–2.82 (m, 4 H), 2.11 (m, 1 H), 1.44 (s, 9 H).

*(4aR,10bS)-10b-(4-Chlorophenylsulfonyl)-7,10-difluoro-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]pyridine (**20a**)*

19 (0.21 g, 0.42 mmol) was dissolved in 20 mL DCM and TFA (5 mL) was added. The mixture was stirred at room temperature for 1 h. 100 mL saturated Na_2CO_3 solution and 100 mL EtOAc were added. The organic layer was washed with saturated Na_2CO_3 solution (50 mL), dried over Na_2SO_4 and concentrated. The residue was pure product. Yield, 0.16 g, 100%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.61 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.08 (m, 1 H), 6.42 (m, 1 H), 5.18 (dd, J = 11.7 and 2.2 Hz, 1 H), 4.15 (d, J = 11.7 Hz, 1 H), 2.98–4.11 (m, 2 H), 2.58–2.73 (m, 3 H), 2.35 (td, J = 12.4 and 1.5 Hz, 1 H), 2.08 (m, 1 H).

*(4aR,10bS)-10b-(4-Chlorophenylsulfonyl)-7,10-difluoro-3-methyl-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]pyridine (**20b**)*

20a (10 mg), CH_3I and NaH (60% in oil, 10 mg) were refluxed in 5 mL DCM for 5 h. 50 mL water and 50 mL EtOAc were added. The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The product was purified by column (EtOAc/hexane from 0/100 to 100/0 in 45 min). Yield; 1.8 mg, 17%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.64 (d, J = 8.8 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H), 7.09 (m, 1H), 6.43 (m, 1 H), 5.17 (dd, J = 11.7 and 2.9 Hz, 1 H), 4.16 (d, J = 11.7 Hz, 1 H), 2.74-2.98 (m, 2H), 2.64 (m, 1 H), 2.26 (m, 2 H), 2.18 (s, 3 H), 1.97 (t, J = 13.2 Hz, 1 H), 1.67 (m, 1 H).

*3-(4-(4-Chlorophenylsulfonyl)-5, 8-difluorochroman-3-ylamino)-propan-1-ol (**21**)*

2 (0.84 g, 1.94 mmol) was dissolved in 20 mL THF and 3-aminopropanol (1.7 g, 22.6 mmol) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with 100 mL saturated Na_2CO_3 solution and 100 mL EtOAc was added. The organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated. The product was purified by column using EtOAc/hexane as the eluent (gradient from 0/100 to 25/75 in 50 min). Yield: 0.61 g, 75%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.69 (d, J = 8.8 Hz, 2 H), 7.48 (d, J = 8.1 Hz, 2 H), 6.99 (td, J = 9.5, 5.1 Hz, 1 H), 6.38 (td, J = 9.5, 3.7 HZ, 1 H), 4.80 (dd, J = 12.5, 2.9 Hz, 1 H), 4.53 (s, 1 H), 4.43 (d, J = 11.8 Hz, 1 H), 3.78 (s, 1 H), 3.61 (t, J = 5.9 Hz, 2 H), 2.86–2.71 (m, 2H), 2.25 (bs, 1 H), 1.57 (m, J = 5.9 Hz, 2 H).

*10b-(4-Chlorophenylsulfonyl)-7,10-difluoro-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-b]pyridine (**22**)*

21 (290 mg, 0.69 mmol) was dissolved in 50 mL of dichloromethane. MsCl (64 μL, 0.83 mmol) and NEt_3 (117 μL, 0.83 mmol) were added respectively and stirred at room temperature overnight. The solution was quenched with water (40 mL) and dichloromethane (40 mL). The layers were separated and the aqueous layer was washed with DCM. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The product was used without further purification. Yield: 0.28 g, 81%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.71 (d, J = 8.8 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H), 7.01 (td, J = 10.3, 5.1 Hz, 1 H), 6.41 (td, 8.8, 3.7 Hz, 1 H), 4.80 (dd, J = 11.8, 2.2 Hz, 1 H), 4.53 (s, 1H), 4.48 (d, J = 11.8 Hz, 1 H), 4.22 (t, 5.9 Hz, 2 H), 3.75 (s, 1 H), 2.93 (s, 3 H), 2.82–2.67 (m, 2 H), 1.79 (m, 2 H).

The product from above reaction (0.28 g, 0.57 mmol) was dissolved in 25 mL of THF then 1 M *t*-BuOK solution (2.4 mL, 2.4 mmol) was added. The reaction was stirred at room temperature for 3.5 h. The reaction was quenched with water (50 mL) and washed with 50 mL EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The compound was then purified by prep TLC (EtOAc/hexane = 50/50). Yield: 0.14g, 60%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.60 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.08 (td, J = 9.5, 4.4 Hz, 1H), 6.47–6.40 (m, 1H), 5.21(dd, J = 11.8, 2.2 Hz, 1 H), 4.33 (d, J = 11.8 Hz, 1 H), 3.70 (s, 1 H), 3.00 (d, J = 13.2 Hz, 1 H), 2.76 (td, J = 12.4 Hz, 2.9 Hz, 1 H), 2.68 (d, J = 13.2 Hz, 1 H), 2.17(tt, J = 13.2, 2.9 Hz 1 H), 1.66-1.44 (m, 2 H), 1.21−1.07(m, 1 H).

*1-[4a-(4-Chloro-benzenesulfonyl)-5,8-difluoro-2,3,4,4a,10,10a-hexahydro-9-oxa-1-aza-phenanthren-1-yl]-ethanone (**23**)*

The compound was made using standard amide coupling reaction. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.61 (d, J = 8.8 Hz, 2 H), 7.43 (d, J = 8.8 Hz, 2 H), 7.05 (td, J = 9.5, 4.4 Hz, 1 H), 6.60–6.51 (m, 1 H), 5.40 (bs, 1 H), 4.50 (dd, J = 11.8, 3.7 Hz, 1 H), 4.20 (dd, J = 11.8, 5.9 Hz, 1 H), 3.62 (bs, 1 H), 2.90 (bs, 1 H), 2.70–2.60 (m, 1 H), 2.50–2.40 (m, 1 H), 2.22–2.03 (m, 4 H), 1.52−1.41 (m, 1 H).

*Methyl-2-(4-(4-chlorophenylsulfonyl)-5,8-difluorochroman-3-yl)-5-hydroxypentanoate (**25**)*

Diisopropylamine (6.16 g, 61 mmol) was dissolved in 100 mL of dry THF and the reaction was cooled to 0 °C. BuLi (2.5M in THF, 24.0 mL) was added slowly and the reaction was stirred at 0 °C for 10 min then cooled to –78 °C. Methyl 5-(benzyloxy)pentanoate (11.5 g, 51.8 mmol) in 50 mL dry THF was added *via* cannula. The reaction was stirred for 55 minutes at –78 °C. **2** (6.94 g, 20.2 mmol) in 100 mL dry THF (pre-cooled to –78 °C) was added *via* cannula over 10 min. The reaction was stirred at –78 °C for 1 h. 100 mL of water was added at –78 °C to quench the reaction. The reaction was allowed to warm up to room temperature overnight. 600 mL EtOAc was added.

The organic layer was washed with brine (2 x 400 mL), dried over Na_2SO_4 and concentrated. The residue (13.5 g) was dissolved in 200 mL EtOAc. $Pd(OH)_2$ (20% on carbon, 2.5 g) was added then the system was purged with hydrogen. The reaction was stirred at room temperature for 3.5 h. The reaction solution was filtered through a celite cake and concentrated. The product was purified by column using hexane/EtOAc as the eluent (gradient from 100/0 to 40/60 in 60 min). Yield: 7.80 g, 69%, as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.71–7.80 (m, 2 H), 7.50–7.56 (m, 2 H), 7.00–7.09 (m, 1 H), 6.50 (m, 0.6 H), 6.43 (m, 0.4 H), 4.90 (m, 1 H), 4.52 (m, 1 H), 4.27 (m, 1 H), 3.54–3.66 (m, 6 H), 3.11 (m, 0.4 H), 2.95 (m, 0.6 H), 1.32–1.96 (m, 2 H).

*(6aR,7R,10aS)-methyl-10a-(4-chlorophenylsulfonyl)-1,4-difluoro-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-7-carboxylate (**26**)*

26 was synthesized using the same procedure as that for compound **17**. However, during ring closure step upon treatment with strong base, the methyl carboxlate group completely isomerized to more stable trans isomer. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.61 (d, J = 8.1 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.08 (m, 1 H), 6.63 (m, 1 H), 5.19 (dd, J = 12.4 and 2.9 Hz, 1 H), 4.20 (d, J = 11.7 Hz, 1 H), 3.73 (s, 3 H), 2.98 (M, 1 H), 2.64 (m, 1 H), 2.45 (m, 1 H), 1.93 (m, 2 H), 1.77 (m, 1 H), 1.54 (m, 1 H), 1.11 (m, 1 H).

*((6aR,7R,10aS)-10a-(4-Chlorophenylsulfonyl)-1,4-difluoro-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-7-yl)methanol (**27**)*

26 (0.88 g, 1.93 mmol) was dissolved in 25 mL dry THF and excess $NaBH_4$ (1.0 g) was added. The reaction was stirred at room temperature overnight. 1 N HCl solution (100 mL) and 50 mL EtOAc were added. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column using EtOAc/hexane as eluent (gradient from 0/100 to 50/50 in 35 min) to yield desired product (0.51 g, 62%). ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.62 (d, J = 8.4 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.05 (m, 1 H), 6.43 (m, 1 H), 5.17 (dd, J = 12.4 and 2.4 Hz, 1 H), 4.63 (d, J = 12.4 Hz, 1 H), 3.88 (m, 1 H), 3.70 (m, 1 H), 2.70 (m, 1 H), 2.52 (m, 1 H), 1.54–1.95 (m, 5 H), 1.11 (m, 1 H).

*((6aR,7R,10aS)-10a-(4-Chlorophenylsulfonyl)-1,4-difluoro-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-7-yl)methanamine (**28a**)*

28a was synthesized using same procedure as that for **24**. The compound **27** was separated using chiral OD® column and the active enantiomer was carried forward to give enantiomerically pure final compounds. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.61 (d, J = 8.8 Hz, 2 H), 7.48 (d, J = 8.8 Hz, 2 H), 7.05 (m, 1 H), 6.41 (m, 1 H), 5.15 (dd, J = 12.4 and 2.9 Hz, 1 H), 4.57 (d, J = 11.7 Hz, 1 H), 2.96 (m, 1 H), 2.80 (m, 1 H), 2.56 (m, 2 H), 1.88 (td, J = 13.2 and 2.8 Hz, 1 H), 1.75 (m, 2 H), 1.00–1.50 (m, 3 H).

*N-((10a-(4-Chlorophenylsulfonyl)-1,4-difluoro-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-7-yl)methyl)-1,1,1-trifluoromethanesulfonamide (**28b**)*

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.62 (d, J = 8.1 Hz, 2 H), 7.51 (d, J = 8.1 Hz, 2 H), 7.09 (m, 1 H), 6.46 (m, 1 H), 5.20 (d, J = 13.2 Hz, 1 H), 5.08 (bs, 1 H), 4.52 (d, J = 13.2 Hz, 1 H), 3.41–3.58 (m, 2 H), 2.57 (m, 2 H), 1.60–1.92 (m, 4 H), 1.31(m, 1 H), 1.00 (m, 1 H).

*N-((10a-(4-Chlorophenylsulfonyl)-1,4-difluoro-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-7-yl)methyl)acetamide (**28c**)*

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.59 (d, J = 8.8 Hz, 2 H), 7.47 (d, J = 8.8 Hz, 2 H), 7.05 (m, 1 H), 6.43 (m, 1 H), 5.85 (t, J = 5.9 Hz, 1 H), 5.12 (dd, J = 12.4 and 2.2 Hz, 1 H), 4.68 (d, J = 12.4 Hz, 1 H), 3.61 (m, 1 H), 3.26 (m, 1 H), 2.58 (d, J = 12.4Hz, 1 H), 2.38 (d, J = 11Hz, 1 H), 1.97 (s, 3 H), 1.82 (m, 1 H), 1.63–1.74 (m, 2 H), 1.54(m, 1 H), 1.24 (m, 1 H), 1.05 (m, 1 H).

*N-(((6aR,7R,10aS)-10a-(4-Chlorophenylsulfonyl)-1,4-difluoro-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-7-yl)-methyl)ethanesulfonamide (**28d**)*

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.61 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.05 (m, 1 H), 6.43 (m, 1 H), 5.13 (dd, J = 12.4 and 2.2 Hz, 1 H), 4.96 (t, J = 6.8 Hz, 1 H), 4.59 (d, J = 12.4 Hz, 1 H), 3.39 (m, 1 H), 3.21 (m, 1 H), 3.06 (q, J = 7.2 Hz, 2 H), 2.58 (m, 2 H), 1.86 (m, 1 H), 1.34–1.74 (m, 7 H), 1.05 (m, 1 H).

*N-(((6aR,7R,10aS)-10a-(4-Chlorophenylsulfonyl)-1,4-difluoro-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-7-yl)-methyl)cyclopropanesulfonamide (**28e**)*

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.62 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.06 (m, 1 H), 6.44 (m, 1 H), 5.15 (dd, J = 12.4 and 2.2Hz, 1 H), 4.84 (t, J = 6.8 Hz, 1 H), 4.60 (d, J = 12.4 Hz, 1 H), 3.40 (m, 1 H), 3.28 (m, 1 H), 2.58 (m, 2 H), 2.42 (m, 1 H), 1.54–1.91 (m, 4 H), 0.98-1.42 (m, 6 H).

*Methyl-5-(benzyloxy)-2-(4-(4-chlorophenylsulfonyl)-5,8-difluorochroman-3-yl)-2-methylpentanoate (**29**)*

Diisopropylamine (2.0 g, 20 mmol) was dissolved in 100 mL dry THF and the reaction was cooled to 0 °C. BuLi (2.5 M in toluene, 8.0 mL, 20 mmol) was added and the reaction was stirred at 0 °C for 10 min. The reaction was cooled to −78 °C and 3-methyltetrahydro-2*H*-pyran-2-one (2.3 g, 20 mmol) in 30 mL dry THF was added. The reaction was stirred for 1 h at −78 °C. 2 (3.4 g, 10 mmol) in 70 mL THF (pre-cooled to −78 °C) was added. The reaction was taken out of dry ice bath and stirred for 1 h. 200 mL brine and 200

mL EtOAc was added. The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The product was purified by column using EtOAc/hexane as eluent (gradient from 0/100 to 50/50 in 45 minutes). Yield: 1.4 g, 31%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.76–7.85 (m, 2 H), 7.52–7.56 (m, 2 H), 7.02–7.10 (m, 1 H), 6.48–6.59 (m, 1 H), 4.80–4.88 (m, 1 H), 4.62–4.76 (m, 1 H), 4.00–4.50 (m, 2 H), 3.28 (m, 1 H), 1.30–2.00 (m, 8 H).

The product from above step (1.4 g, 3.1 mmole) was dissolved in 100 mL MeOH and $Mg(OMe)_2$ (6%–10% in MeOH, 6.7 mL) was added. The reaction was stirred at room temperature for 2 h. The reaction was then concentrated to about 20 mL. 200 mL EtOAc and 200 mL 1N HCl solution were added. The organic layer was washed with brine (2 × 200 mL), dried over Na_2SO_4 and concentrated. The product was purified by column (EtOAc/hexane from 0/100 to 60/40 in 45 min). Yield: 1 g, 66%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.68–7.76 (m, 2 H), 7.48–7.54 (m, 2 H), 6.98–7.05 (m, 1 H), 6.38–4.49 (m, 1 H), 4.79–4.86 (m, 1 H), 4.37–4.66 (m, 2 H), 3.54–3.67 (m, 1 H), 3.53 (s, 1.5 H), 3.41 (s, 1.5 H), 3.04–3.16 (m, 1 H), 1.30–1.88 (m, 4 H), 1.03 (m, 3 H).

Starting from **29**, compounds **30** and **31** were synthesized using the same procedure as that of compounds **26** and **27**. The only difference is that the *cis* and *trans* isomers between hydroxymethyl and sulfone of **31** were separated by column chromatagraph.

*Methyl-10a-(4-chlorophenylsulfonyl)-1,4-difluoro-7-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-7-carboxylate (**30**)*

The product was a mixture of cis and trans isomer between methyl ester and sulfone. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.44–7.54 (m, 4 H), 6.99–7.10 (m, 1 H), 6.33–6.41 (m, 1 H), 5.13–5.25 (m, 1 H), 4.83 (d, J = 12.4 Hz, 0.5 H), 4.32 (d, J = 12.4 Hz, 0.5 H), 3.74 (s, 1.5 H), 3.37 (s, 1.5 H), 2.64 (m, 1 H), 1.25–2.10 (m, 6 H), 1.42 (s, 1.5 H), 1.03 (s, 1.5 H).

*((6aR,7R,10aS)-10a-(4-chlorophenylsulfonyl)-1,4-difluoro-7-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-7-yl)methanol (**31**)*

Cis and *trans* isomers were separated by column chromatography and *trans* compound is studied in more detail because it is the more active isomer. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.44–7.52 (m, 4 H), 7.07 (m, 1 H), 6.39 (m, 1 H), 5.18 (dd, J = 12.4 and 4.8 Hz, 1 H), 4.74 (d, J = 12.4 Hz, 1 H), 3.45 (d, J = 11.6 Hz, 1 H), 3.05 d, J = 11.6 hz, 1 H), 2.57-2.64 (m, 2 H), 1.88–2.02 (m, 2 H), 1.58 (m, 1 H), 1.20–1.28 (m, 2 H), 1.19 (m, 3 H).

Using the same procedures as described above and starting from optically pure (*R*)-4-methyltetrahydro-2*H*-pyran-2-one, compounds **32**–**35** were synthesized. Since the starting material was a chiral compound, the different stereo isomers of compound **33** and **34** are diastereomers thus could be separated with normal column chromatography. As the result, they were separated and only the active diastereomers are listed here.

*(4R)-3-(4-(4-Chlorophenylsulfonyl)-5,8-difluorochroman-3-yl)-4-methyltetrahydro-2H-pyran-2-one (**32**)*

This was a mixture of diatereomers. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.74 (m, 0.7 H), 7.44–7.56 (m, 3.3 H), 6.98–7.07 (m, 1 H), 6.45–6.53 (m, 1 H), 4.85–4.93 (m, 1 H), 4.24–4.56 (m, 3.3 H), 4.01 (m, 0.3 H), 3.38 (m, 0.7 H), 3.15 (m, 0.3 H), 2.70 (m, 0.7 H), 2.28 (m, 0.3 H), 1.90–2.15 (m, 2 H), 1.60–1.70 (m, 1 H), 1.15–1.28 (m, 4 H).

*(6aR,7R,8R,10aS)-Methyl-10a-(4-chlorophenylsulfonyl)-1,4-difluoro-8-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]-chromene-7-carboxylate (**33**)*

This was the desired pure diastereomer that was separated from the reaction mixture. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.63 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8Hz, 2 H), 7.07 (m, 1 H), 6.43 (m, 1 H), 5.19 (dd, J = 12.4 and 2.8 Hz, 1 H), 4.33 (d, J = 12.4 Hz, 1 H), 3.71 (s, 3 H), 3.14 (d, J = 12.4 Hz, 1 H), 2.63 (dd, J = 12 and 4.8 Hz, 1 H), 2.40 (m, 1 H), 1.34–1.60 (m, 2 H), 0.96 (d, J = 7.2 Hz, 3 H).

*((6aR,7R,8R,10aS)-10a-(4-Chlorophenylsulfonyl)-1,4-difluoro-8-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-7-yl)methanol (**34**)*

This was the desired pure diastereomer. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.63 (d, J = 8.4 Hz, 2 H), 7.49 (d, J = 8.4 Hz, 2 H), 7.06 (m, 1 H), 6.45 (m, 1 H), 5.17 (dd, J = 12.4 and 2.4 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 3.88 (dd, J = 10.8 and 4.8 Hz, 1 H), 3.74 (dd, J = 10.8 and 4.8 Hz, 1 H), 2.79 (d, J = 12.0 Hz, 1 H), 2.30 (m, 1 H), 2.19 (m, 1 H), 2.04 (m, 1 H), 1.74 (m, 1 H), 1.50 (m, 1 H), 1.34 (m, 1 H), 1.02 (d, J = 6.8 Hz, 3 H).

*N-(((6aR,7R,8R,10aS)-10a-(4-Chlorophenylsulfonyl)-1,4-difluoro-8-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]-chromen-7-yl)methyl)-1,1,1-trifluoromethanesulfonamide (**35**)*

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.62 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 2 H), 7.07 (m, 1 H), 6.46 (m, 1 H), 5.18 (d, J = 12.8 Hz, 1 H), 4.40 (d, J = 12.8 Hz, 1 H), 3.52 (dd, J = 13.2 and 4.8 Hz, 1 H), 3.22 (dd, J = 13.2 and 4.8 Hz, 1 H), 2.68 (d, J = 11.6 Hz, 1 H), 2.30 (m, 1 H), 2.16 (m, 1 H), 2.05 (m, 1 H), 1.72 (m, 1 H), 1.55 (m, 1 H), 1.29 (m, 1 H), 1.00 (d, J = 6.8 Hz, 3 H).

Using the same procedures as described above and starting from pure enantiomer (*S*)-1-azido-4-(benzyloxy) butan-2-amine, compounds **36**–**38** were synthesized. Since the starting material was a chiral compound, the resulting diastereomers **37** could be separated with normal column chromatography. As the result, they were separated and only the active diastereomers were taken forward.

*N-((S)-1-Azido-4-(benzyloxy)butan-2-yl)-4-(4-chlorophenylsulfonyl)-5,8-difluorochroman-3-amine (**36**)*

This was a mixture of diastereomers. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.74 (d, J = 8.4 Hz, 1.35 H), 7.64 (d, J = 8.4 Hz, 0.65 H), 7.50 (d, J = 7.6 Hz, 1.35 H), 7.43 (d, J = 7.6 Hz, 0.65 H), 7.19–7.37 (m, 5 H), 6.94–7.03 (m, 1 H), 6.37–6.44 (m, 1 H), 4.92 (dd, J = 12.0 and 2.8 Hz, 0.35 H), 4.79 (dd, J = 12.0 and 2.8 Hz, 0.65 H), 4.20–4.62 (m, 3 H), 3.90 (m, 1 H), 2.90–3.58 (m, 5 H), 1.44–1.76 (m, 2 H).

*(3S,4aR,10bR)-3-(Azidomethyl)-10b-(4-chlorophenylsulfonyl)-7,10-difluoro-2,3,4,4a,5,10b-hexahydro-1H-chromeno-[3,4-b]pyridine (**37**)*

This was the more potent enantiomer that was isolated from the reaction. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.59 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.07 (m, 1 H), 6.43 (m, 1 H), 5.17 (dd, J = 12.0 and 2.4 Hz, 1 H), 4.29 (d, J = 12.0 Hz, 1 H), 3.86 (bs, 1 H), 3.69 (m, 1 H), 3.26 (m, 1 H), 3.08 (m, 1 H), 3.41 (m, 2 H), 1.40–1.80 (m, 2 H).

*N-(((3S,4aR,10bR)-10b-(4-Chlorophenylsulfonyl)-7,10-difluoro-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-b]pyridin-3-yl)methyl)methanesulfonamide (**38**)*

This was a pure enantiomer. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.57 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 2 H), 7.07 (m, 1 H), 6.43 (m, 1 H), 5.15 (dd, J = 12.0 and 2.8 Hz, 1 H), 5.06 (d, J = 12.0 Hz, 1 H), 4.29 (d, J = 11.6 Hz, 1 H), 3.78 (bs, 1 H), 3.41 (m, 1 H), 3.10 (m, 1 H), 3.03 (m, 1 H), 2.99 (s, 3 H), 1.60 (m, 1 H), 1.45 (m, 1 H).

Using the same procedures as described above and starting from methyl 2-((2-(benzyloxy)ethyl)(*tert*-butoxycarbonyl)amino)acetate, compounds **39**–**42** were synthesized. The compounds were racemic mixtures of *cis* isomer between hydroxylmethyl and sulfone.

*Methyl-2-((2-(benzyloxy)ethyl)(tert-butoxycarbonyl)amino)-2-(4-(4-chlorophenylsulfonyl)-5,8-difluorochroman-3-yl)acetate (**39**)*

This was a mixture of diastereomers. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.88 (m, 1 H), 7.63 (m, 1 H), 7.51 (m, 1 H), 7.45 (m, 1 H), 7.15–7.37 (m, 5 H), 6.95–7.07 (m, 1 H), 6.47–6.52 (m, 1 H), 4.60–5.10 (m, 2 H), 4.48 (m, 2 H), 4.29–4.40 (m, 2 H), 4.00–4.15 (m, 2 H), 3.40–3.70 (m, 5 H). 1.43 (m, 9 H),1.36–1.45 (m, 2 H).

*(4R,4aR,10bS)-tert-Butyl-10b-(4-chlorophenylsulfonyl)-7,10-difluoro-4-(hydroxymethyl)-4,4a,5,10b-tetrahydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate (**40**)*

This was a racemic mixture. However, it had *cis* configuration between hydroxymethyl and sulfone groups. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.60 (d, J = 8.4 Hz, 2 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.01 (m, 1 H), 6.40 (m, 1 H), 5.03 (dd, J = 12.0 and 2.4 Hz, 1 H), 4.35 (d, J = 12.0 Hz, 1 H), 4.00 (bs, 1 H), 3.79 (m, 2 H), 3.43 (m, 1 H), 3.18 (m, 1 H), 3.00 (m, 1 H), 2.65 (m, 1 H), 2.33 (m, 1 H), 1.26 (2, 9 H).

*N-(((4R,4aR,10bS)-10b-(4-Chlorophenylsulfonyl)-7,10-difluoro-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]pyridin-4-yl)methyl)methanesulfonamide (**41**)*

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.63 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 8.4 Hz, 2 H), 7.09 (m, 1 H), 6.47 (m, 1 H), 5.15 (dd, J = 12.4 and 2.4 Hz, 1 H), 4.49 (d, J = 12.4 Hz, 1 H), 3.33-3.45 (m, 2 H), 2.99-3.06 (m, 1 H), 3.00 (s, 3 H), 2.76 (m, 1 H), 2.58–2.66 (m, 2 H), 2.40 (m, 1 H), 2.07 (m, 1 H).

*N-(((4R,4aR,10bS)-10b-(4-chlorophenylsulfonyl)-7,10-difluoro-3-methyl-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]pyridin-4-yl)methyl)methanesulfonamide (**42**)*

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.66 (d, J = 8.4 Hz, 2 H), 7.52 (d, J = 8.4 Hz, 2 H), 7.10 (m, 1 H), 6.49 (m, 1 H), 5.17 (dd, J = 13.2 and 2.8 Hz, 1 H), 4.51 (d, J = 13.2 Hz, 1 H), 3.44 (s, 2 H), 3.00 (s, 3 H), 2.78–2.84 (m, 2 H), 2.62 (m, 1 H), 2.18 (s, 3 H), 1.94–2.18 (m, 3 H).

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