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Article

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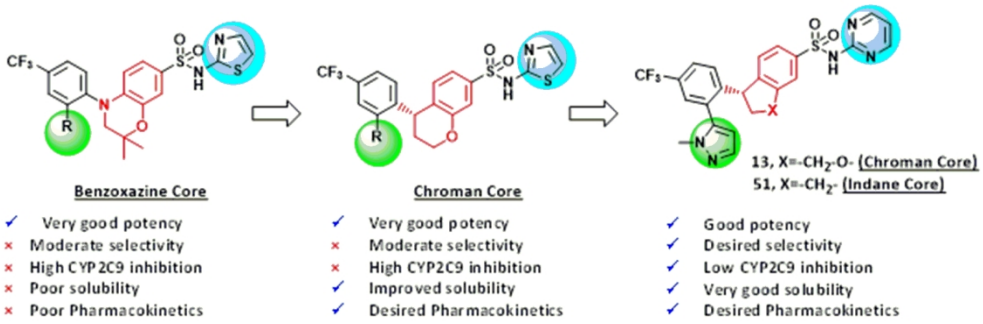

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Discovery of Potent, Selective and State-Dependent $Na_V1.7$ Inhibitors with Robust Oral Efficacy in Pain Models: Structure-Activity Relationship and Optimization of Chroman and Indane Aryl Sulfonamides

Vidya Ramdas,* Rashmi Talwar, Vijay Kanoje, Rajesh M. Loriya, Moloy Banerjee, Pradeep Patil, Advait Arun Joshi, Laxmikant Datrange, Amit Kumar Das, Deepak Sahebrao Walke, Vaibhav Kalhapure, Talha Khan, Ganesh Gote, Usha Dhayagude, Shreyas Deshpande, Javed Shaikh, Ganesh Chaure, Ravindra R. Pal, Santosh Parkale, Sachin Suravase, Smita Bhoskar, Rajesh V. Gupta, Anil Kalia, Rajesh Yeshodharan, Mahammad Azhar, Jagadeesh Daler, Vinod Mali, Geetika Sharma, Amitesh Kishore, Rupali Vyawahare, Gautam Agarwal, Himani Pareek, Sagar Budhe, Arun Nayak,† Dnyaneshwar Warude, Praveen Kumar Gupta, Parag Joshi, Sneha Joshi, Sagar Darekar, Dilip Pandey, Akshaya Wagh, Prashant B. Nigade, Maneesh Mehta, Vinod Patil, Dipak Modi, Shashikant Pawar, Mahip Verma, Minakshi Singh, Sudipto Das, Jayasagar Gundu, Kumar Nemmani, Mark Bock, Sharad Sharma, Dhananjay Bakhle, Rajender Kumar Kamboj, Venkata P. Palle

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ABSTRACT

Voltage gated sodium channel $Na_V1.7$ is a genetically validated target for pain. Identification of $Na_V1.7$ inhibitors with all the desired properties to develop as an oral therapeutic for pain has been a major challenge. Herein, we report systematic SAR studies carried out to identify novel sulfonamide derivatives as potent, selective and state-dependent $Na_V1.7$ inhibitors for pain. Scaffold hopping from benzoxazine to chroman and indane bicyclic system followed by thiazole replacement on sulfonamide led to identification of lead molecules with significant improvement in solubility, selectivity over $Na_V1.5$ and CYP2C9 inhibition. The lead molecules **13**, **29**, **32**, **43** and **51** have shown favorable PK profile across

different species and robust efficacy in veratridine and formalin induced inflammatory pain models in mice. Compound **51** has also shown significant effect in CCI induced neuropathic pain model. Profile of **51** has indicated that it has the potential for further evaluation as a therapeutic for pain.

INTRODUCTION

Pain is a major health problem, greatly reduces quality of life and imparts huge health costs and economic loss to society. One fourth of the world's population suffers from chronic pain. Pain sensations originate in peripheral neurons such as nociceptors. Increased pain sensations can result from altered electrical excitability of neurons in both peripheral and central neurons. As a therapeutic class, sodium channel blockers such as lidocaine, amitriptyline, and lamotrigine have been widely used to treat disorders where the chosen therapeutic approach is designed to decrease neuronal excitability. Such disorders involving hyper-excitability or increased neuronal sensitivity to stimulation include pain as well.[1]

Voltage-gated sodium channels (VGSCs) are key elements of excitable cells responsible for the generation and transmission of electrical activity in central and peripheral nervous system.[2] VGSCs consist of a pore-forming alpha subunit and a stabilizing beta subunit. Nine isoforms of the alpha subunit have been identified till date ($Na_V1.1$ to $Na_V1.9$) and are encoded by SCN genes.[3] All these nine members of the VGSC family have high homology of amino acid sequence in the extracellular and transmembrane domain. The sodium channels have also been further classified based on their sensitivity to the puffer fish toxin (tetrodotoxin, TTX). Channels $Na_V1.8$, $Na_V1.9$ and $Na_V1.5$ are TTX resistant (TTX-R) whereas the remaining channels are sensitive to TTX and classified as TTX sensitive (TTX-S). VGSCs mediate the influx of sodium ions into the cell in response to membrane depolarization leading to generation of the action potential to relay information of stimuli from periphery to the central nervous system. Thus, voltage-gated ion channels play a major role in determining excitability of neurons.[2,3]

$Na_V1.7$ is one of the highly expressed TTX-sensitive sodium channels in dorsal root ganglion cells and is believed to be an important contributor to signaling in both nociceptive and non-nociceptive neurons. There is a strong genetic evidence linking $Na_V1.7$ and the pain processing pathway and the evidence comes mostly in the form of mutations in human SCN9A, the gene encoding $Na_V1.7$. The gain-of-function mutations in human $Na_V1.7$ causes spontaneous pain syndromes such as inherited erythromelalgia,[4] paroxysmal extreme pain disorder,[5] and small fiber neuropathy.[6] In contrast, the loss-of-function mutations in human $Na_V1.7$ lead to a rare condition known as congenital insensitivity to pain (CIP), which manifests in the form of inability of individuals to sense pain while not significantly impacting motor or cognitive function.[7] Patients with CIP experience no pain following a wide variety of stimuli.[8]

Similarly, deletion of $Na_V1.7$ in sensory and sympathetic neurons of mice leads to a pain-free congenital insensitivity to pain (CIP) phenotype similar to that described in humans. Human and mouse $Na_V1.7$-null mutants are apparently normal, suggesting that this channel is an excellent analgesic drug target for acute, inflammatory and neuropathic pain.[9] Non-selective Na_V blockers such as mexiletine and carbamazepine have long been used clinically for the treatment of neuropathic pain. Limitations with these therapies are marginal response and adverse effects seen in patients and these are due to marginal potency and non-selectivity against other sodium channels or resting state blockade of channels.[10] The ion channel moves from closed state to open through concerted movements and then to an inactivated state where the channel stops to conduct ions. Disease states are characterized by activated state of high frequency firing channels, however the normal somatosensory system is characterized by low frequency firing channels. Hence identification of $Na_V1.7$ inhibitors that exhibit a different affinity for each of these states and show increased affinity for a slow-inactivated channel state vs. fast-inactivated may lead to functional selectivity and exhibit a better safety window. Thus, a potent, selective and state-dependent $Na_V1.7$ blocker rationalize as an effective and safe therapeutic option for treatment of chronic pain in humans.[11] One of the primary challenges associated with these efforts has been the identification of isoform-selective

inhibitors, in particular those that demonstrate suitable levels of selectivity over $Na_V1.5$, which is expressed in cardiac myocytes and plays a key role in cardiovascular function.[12]

Many aryl and acyl sulfonamide derivatives have been reported as potent and selective $Na_V1.7$ inhibitors.[13] They have been shown to bind to voltage sensing domain4 of $Na_V1.7$ and block the channel by locking it into the inactivated state.[14] However, identification of a selective $Na_V1.7$ inhibitor which shows robust efficacy in rodent pain models without any metabolic liability to develop as an oral therapeutic for pain has been a major challenge for long time since the SAR on sulfonamide derivatives were found to be non-additive for multi parameter optimization.[15] Most of the initial lead molecules reported by Pfizer,[16] Amgen,[17] Merck,[18] Xenon[19] and BMS[20] were containing either 1,2,4-thiadiazole or thiazole substituted arylsulfonamide analogs, A-F, Fig. 1. Most of these compounds suffer from high CYP3A4 and/or CYP2C9 inhibition.[16-21] In addition, many of these sulfonamide derivatives lack good pharmacokinetic profile across rodent and non-rodent species suitable for development as an oral therapeutic for pain.[13,15] From our own internal SAR studies and also from the literature reports which appeared while we were working on the project, it was clear that the CYP3A4 inhibition could overcome by replacement of 1,2,4-thiadiazole with other heteroaryl substitution on sulfonamide, compounds A, F, & G-I, Fig. 1.[16b,17d,19a,b,20b] However, CYP2C9 inhibition was still a challenge and in addition heteroaryl modification on sulfonamide led to new challenges such as decrease in potency and selectivity although the extent of compromise on potency and selectivity was dependent on the overall scaffold.[17,18b,19a,b] Herein, we report systematic SAR studies carried out to identify potent, selective and orally bioavailable chroman and indane sulfonamide derivatives as state-dependent $Na_V1.7$ blockers without any significant CYP liabilities, Fig. 2. In addition, we report complete characterization of lead molecules **13**, **29**, **32**, **43** and **51** including detailed pharmacokinetic properties across the species and in-vivo efficacy of selected lead molecules in mouse models of veratridine induced pain, formalin induced inflammatory pain and CCI induced neuropathic pain.

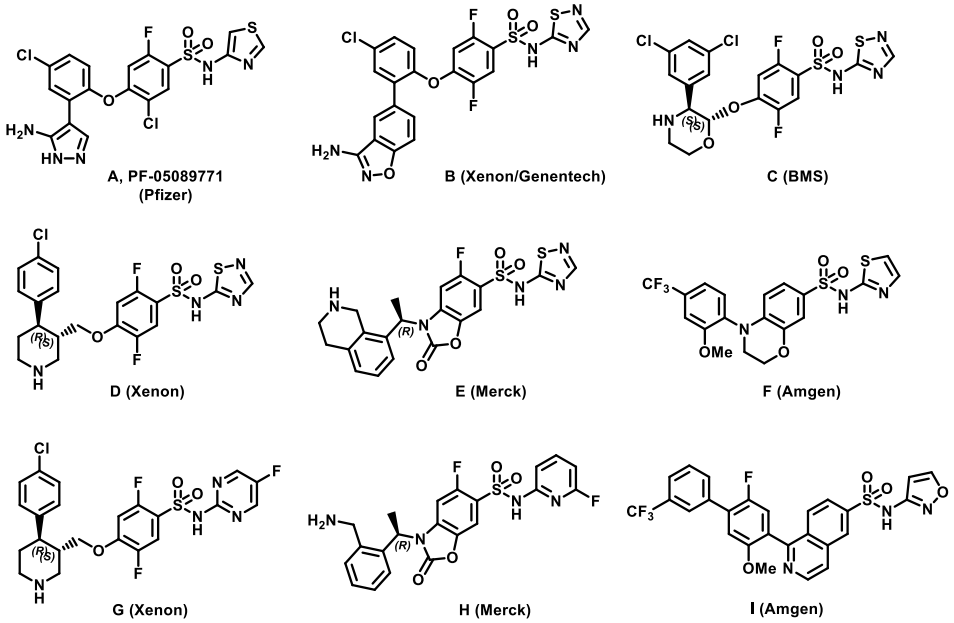


Figure 1. Structures of Selected Aryl Sulfonamide $Na_V1.7$ Inhibitors

RESULTS AND DISCUSSION

The objective was to identify a potent, selective and state dependent $Na_V1.7$ blocker which will serve as a safe oral therapeutic for chronic pain. To meet this objective we have set out a target product profile with the criteria as $Na_V1.7$ potency: $IC_{50} \leq 10$ nM; $Na_V1.5$ selectivity: $IC_{50} > 10$ μM; No significant CYP inhibition (<50% at 10μM); No significant hERG inhibition; State dependent block of target; Acceptable oral bioavailability; Significant efficacy in veratridine, formalin induced nociception and/or CCI induced pain model; and ED_{50} that allows a good therapeutic window. Initially SAR study was carried out on benzoxazine core substituted with thiazole sulfonamide. Various analogs were prepared with different aryl, heteroaryl and heterocyclyl groups as pendant substitution on terminal phenyl ring, Fig. 2. Most of these compounds have shown very good potency (1-10 nM) and moderate selectivity over $Na_V1.5$. However, these compounds suffer from high CYP2C9 inhibition, poor solubility and poor pharmacokinetic profile in spite

of their good microsomal stability. Replacement of the thiazole group with different 5-6 membered heteroaryl substitution on sulfonamide was not tolerated on this core.[17e]

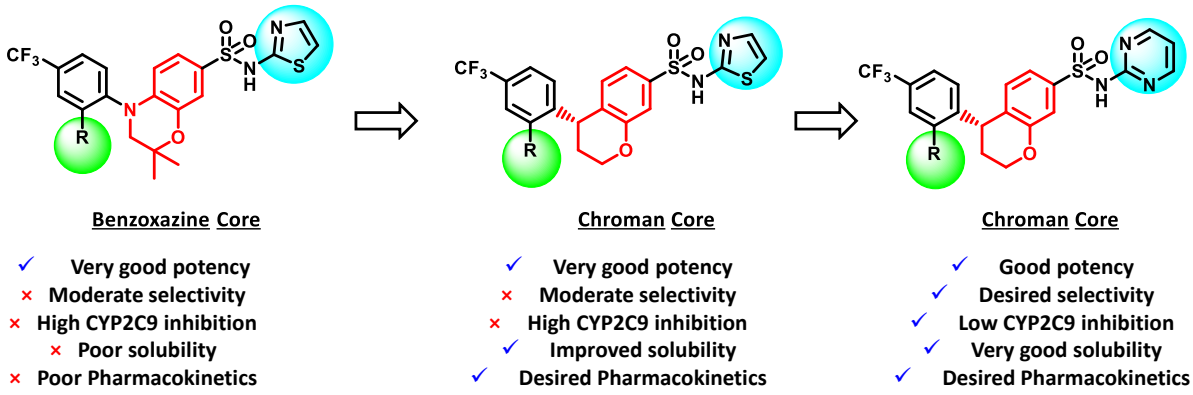


Figure 2. Central Bicyclic Core Switch from Benzoxazine to Chroman for Multi-parameter Optimization

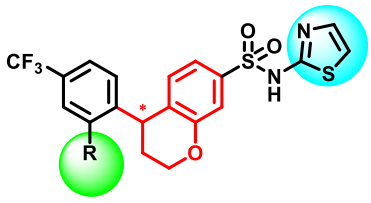
Hence, it was decided to alter the central bicyclic core. By considering multi-parameter optimization such as physchem and ADME properties, it was decided to explore other bicyclic systems such as chroman as central bicyclic core, since substituted chroman analogs are expected to possess an altered conformation compared to the corresponding substituted benzoxazine analogs. We were interested to explore the role of additional sp^3 carbon on solubility and other ADME properties, the effect of conformational change on potency and selectivity and CYP inhibition profile. Herein, we report the outcome of a systematic and elaborate SAR study on multi parameter optimization of this series.

First to check the translation of potency and selectivity, a series of chroman compounds were prepared by keeping the thiazole substitution constant on sulfonamide. A range of heteroaryl, heterocyclyl, aryl and substituted alkyl groups were tried as pendant R group substitution on the terminal phenyl ring. Absence of pendant R group or substitution such as –Cl, alkyl, or branched alkyl as pendant group led to very less potent compounds. Alkoxy alkyl and fluoro alkyl of different chain length were found to be very potent for $Na_V1.7$, however less selective over $Na_V1.5$ (data not shown). Various compounds **(1-12)** having heteroaryl, heterocyclyl or substituted aryl as pendant R group were prepared and tested for their activity

against $Na_V1.7$ and $Na_V1.5$. Since most of these compounds were prepared as racemic and then the isomers were separated by chiral column chromatography at the final stage, the potency of both the enantiomers were tested for many compounds with different R groups, and it was consistently found to be one of the isomers was significantly more potent than the other isomer. As a representation, for some of the R groups, activities of both the isomers were shown in Table 1. The absolute stereochemistry of the compounds **1a** and **1b** were determined to be '*S*' and '*R*' configuration, respectively, by using vibrational circular dichroism (VCD). Determination of absolute configuration of few additional pairs of isomers using VCD has shown that the more potent isomer consistently possess alpha orientation (below plane in drawn structures) of terminal phenyl group with respect to the bicyclic central core (chroman). This finding was further confirmed without any ambiguity through a single crystal X-ray of sulfonamide intermediate and its conversion to the lead compounds (refer supporting information for the structure and scheme).

Most of the compounds have shown very good potency (IC_{50} <10nM) for $Na_V1.7$, however, the selectivity over $Na_V1.5$ was not in the expected lines (IC_{50} >10μM), Table 1. Only a few compounds with R groups such as triazole (**4b**), morpholinone **8** and oxazolinone **9** have shown very good selectivity over $Na_V1.5$. Also, for the less active isomer, similar right ward shift of activity for $Na_V1.5$ subtype was observed.

Table 1. Profile of Chroman Compounds Substituted with Thiazole Sulfonamide



Compd (isomer)	R	$Na_V1.7$ IC_{50} nM[a]	$Na_V1.5$ IC_{50} nM[a,#,*]	LogD	Solubility (μM)	CYP3A4 (% Inhibition)		CYP2C9 (% Inhibition)	
						@1μM	@10μM	@1μM	@10μM
1a (*S*)		67.8	Inactive	2.2	65	11	26	51	92
1b (*R*)		0.4	812	2.2	83	2	28	46	93
2a (*S*)		60.5	61%	3.3	7	NT	NT	NT	NT
2b (*R*)		1.6	67%	3.3	15	6	64	88	99
3a (*S*)		850	79%	2.9	130	0	42	54	91
3b (*R*)		2.3	629	2.9	61	7	38	45	88
4a (*S*)		139	Inactive	2.3	154	NT	NT	NT	NT
4b (*R*)		0.5	Inactive	2.3	171	5	19	42	87
5a (*S*)		15.4	63%	NT	NT	10	37	70	97
5b (*R*)		0.4	154	3.2	21	6	19	48	90
6 (*R*)		4.5	362	3.5	7	15	33	38	86
7a (*S*)		222.6	69%	4.5	147	-3	17	68	94
7b (*R*)		0.5	124	4.5	39	5	35	62	94
8 (*R*)		7.8	Inactive	1.8	695	0	0	1	32
9 (*R*)		35.5	Inactive	2.1	295	6	12	19	60
10 (*R*)		6.2	50%	2.5	99	-17	1	4	68
11 (*R*)		0.8	4089	1.4	288	1	2	33	83
12 (*R*)		2.9	983	2.1	176	7	33	10	52

[a] FLIPR membrane potential assay; [#] Inactive refers to <10% inhibition at 10 μM; * % Inhibition at 10 μM; NT – Not Tested

Very good potency and the preference of one stereoisomer over the other for activity encouraged us to explore this scaffold in depth for optimization of other properties. When we tested the solubility of these compounds, as expected these compounds with chiral sp^3 carbon have shown improved solubility over the corresponding benzoxazine analogs. Then, we tested these compounds for inhibition profile of two important CYP enzymes (3A4 and 2C9). Again, most of these thiazole compounds in spite of central core modification with a wide range of R group variants have shown high CYP2C9 inhibition while CYP3A4 inhibition was not significant at 10μM (except for compound **2b**), Table 1. To our disappointment both the isomers have shown similar CYP inhibition profile. The conformational difference between the isomers did not lead to any difference in CYP inhibition profile. These trends were consistent throughout

this series of compounds, where one of the isomers was found to be several fold more potent than the other isomer, but both the isomers had similar CYP inhibition profile. Next we were interested in looking at the pharmacokinetic profile of chroman based analogs as it was one of the challenges observed in earlier benzoxazine series. A few best compounds were tested for their pharmacokinetic profile and to our delight remarkable improvement in overall PK profile was observed for chroman analogs, Table 2. Compound **4b** has shown low $t_{1/2}$ due to high clearance, however all the three compounds **1b**, **4b** and **5b** have shown very good exposures and oral bioavailability. Modification of the central bicyclic core from benzoxazine to chroman helped in improving the solubility and pharmacokinetic profile. The SAR outcome has clearly indicated that still we have two major challenges in hand, which are selectivity over $Na_V1.5$ and CYP2C9 inhibition. For optimizing these two liabilities, we have decided to modify the substitution on sulfonamide. First, we have kept the pendant R group, N-methyl pyrazole as constant and tried various substituted or unsubstituted five and six membered heteroaryls as we have attempted in the case of benzoxazine core. The data for six membered heteroaryl sulfonamide derivatives, **13-20** is shown in Table 3. To our fortune, compounds **13-15** & **18** having 2-aminopyrimidine, 4-F-2-aminopyrimidine, 4-aminopyrimidine and 6-F-2-aminopyridine, respectively have shown good potency and very good selectivity over $Na_V1.5$. In addition, compounds **13** and **14** showed low levels of CYP2C9 inhibition at 10μM (<40%), Table 3. The potency for $Na_V1.7$ was on the lower side for pyridazine **(16)** and pyrazine **(17)** compounds. Compounds **18-20** having F-pyridines as substitution on sulfonamide have shown better selectivity over compound **1b**, however, they

Table 2. Metabolic Rate and Pharmacokinetic Profile of Chroman Compounds in Male BALB/c Mice

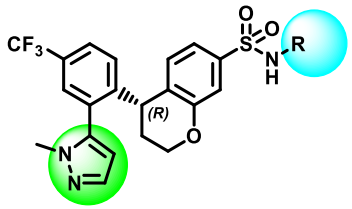
Compd	Metabolic Rate (nmol/min/mg)			PK IV (1 mpk)					PK PO (10 mpk)		
	MLM	RLM	HLM	Cmax (μM)	AUC_{last} (h*μM)	$T_{1/2}$ (h)	CL (ml/min/kg)	V_{ss} (l/kg)	Cmax (μM)	AUC_{last} (h*μM)	%F

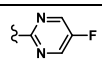
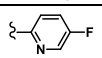
1b	0.1	0.04	0.05	1.3	2.2	2.0	14	2.2	6	15	68
4b	0.02	0.02	0.02	2.2	0.9	0.4	37	1.0	3.0	7.1	79
5b	0.04	0.05	0.03	0.8	2.0	2.8	14	2.9	4.2	19	95

Vehicle: IV: DMA (10%): PEG 300 (20%): 20% Captisol in NS (QS); PO: Tween 80 (1%): 0.5% CMC solution (QS)

did not show improvement in CYP2C9 inhibition. Overall, this SAR outcome delineated a way forward to overcome both selectivity and CYP2C9 inhibition challenges while retaining the potency for $Na_V1.7$ through modification of substitution on aryl sulfonamide of chroman scaffold. Hence, it was decided to prepare a focused library of compounds with the best pendant R groups and four different heteroaryl substitution on sulfonamide. The substitutions were chosen based on $Na_V1.7$ potency, selectivity and low CYP inhibition profile. The resultant matrix of compounds **21-50** have shown that

Table 3. Profile of Chroman Compounds Substituted with Different Heteroaryl Sulfonamide

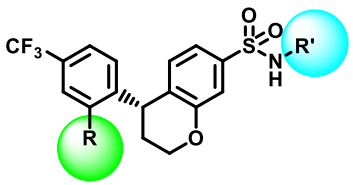


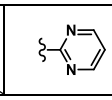
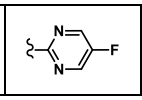
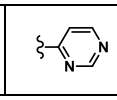
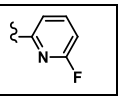
Compd	R	$Na_V1.7$ IC_{50} nM[a]	$Na_V1.5$ IC_{50} nM[a,#,*]	LogD	Solubility (μM)	CYP3A4 (% Inhibition)		CYP2C9 (% Inhibition)	
						@1μM	@10μM	@1μM	@10μM
1b		0.4	812	2.2	83	2	28	46	93
13		17.8	Inactive	3.7	532	6	15	7	36
14		24.4	Inactive	2.5	463	3	0	13	28
15		4.3	Inactive	1.8	1180	0	37	10	69
16		40.2	34%	2.2	915	3	8	19	56
17		86.3	Inactive	1.8	1174	19	68	32	74
18		0.6	Inactive	3.6	27	5	21	33	86
19		20	46%	3.8	29	13	54	31	87
20		6.5	60%	3.2	46	4	23	33	81

[a] FLIPR membrane potential assay; [#] Inactive refers to <10% inhibition at 10 μM; *34% inhibition at 10μM

the SAR is not additive. The tolerability of sulfonamide substitution varies with respect to the pendant R group. In the entire matrix, most of the compounds having heteroaryl group as pendant group were found to be potent and selective except for compounds **21** (2-methyl oxazole is pendant R group) and **25-27** (triazole is pendant R group) with a strikingly low potency for $Na_V1.7$, Table 4. Compounds with p-F phenyl **39-42** have shown significant decrease in potency. Except for morpholine, compounds **43-46**, many saturated heterocyclic groups such as morpholinone (data not shown), oxazolinone (data not shown) and thiamorpholine (**47-50**) were not tolerated as pendant R groups for modification of thiazole on sulfonamide, significant decrease in potency was observed like triazole compounds. Selected potent compounds were tested for their solubility and CYP inhibition profile. All the compounds except for 6-fluoropyridyl sulfonamide derivatives have shown very good solubility, Table 5. Most of the compounds with 6-fluoropyridyl and 4-aminopyrimidinyl substitution on the sulfonamide have shown high CYP2C9 inhibition at least at 10μM, Table 5. Poor solubility and high CYP inhibition of most of the 6-fluoropyridyl sulfonamide compounds indicates that 6-fluorpyridyl behaves the same way as thiazole on sulfonamide. Compounds with 4-F-2-aminopyrimidine substitution on the sulfonamide have shown moderate to high CYP2C9 inhibition at 10μM depending on the pendant R group. However, 2-aminopyrimidinyl sulfonamide compounds have not shown significant CYP2C9 inhibition even at 10μM, except for compound **43**, where it was found to be moderate, 54% inhibition at 10μM, Table 5.

Table 4. Potency & Selectivity of Focused Library of Chroman Sulfonamide Compounds

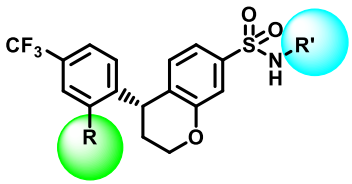


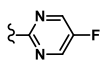
Parameter	R' / R				

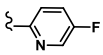
Compd		**13**	**14**	**15**	**18**
Na_V 1.7 IC_{50} nM		17.8	24.4	4.3	0.6
Na_V 1.5 IC_{50} nM#,*		Inactive	Inactive	Inactive	Inactive
Compd		**21**	**22**	**23**	**24**
Na_V 1.7 IC_{50} nM		47.3	25.9	1.8	1.6
Na_V 1.5 IC_{50} nM#,*		Inactive	Inactive	1168	44%
Compd		**25**	**26**	**27**	**28**
Na_V 1.7 IC_{50} nM		698	601	54	1.1
Na_V 1.5 IC_{50} nM#,*		Inactive	Inactive	Inactive	Inactive
Compd		**29**	**30**	**31**	
Na_V 1.7 IC_{50} nM		21	2.8	0.11	
Na_V 1.5 IC_{50} nM#,*		58%	Inactive	Inactive	
Compd		**32**	**33**	**34**	**35**
Na_V 1.7 IC_{50} nM		1.4	8.3	8.7	6.6
Na_V 1.5 IC_{50} nM#,*		Inactive	Inactive	1103	1312
Compd		**36**	**37**	**38**	
Na_V 1.7 IC_{50} nM		2.7	2.1	12	
Na_V 1.5 IC_{50} nM#,*		56%	Inactive	2516	
Compd		**39**	**40**	**41**	**42**
Na_V 1.7 IC_{50} nM		30.4	162	808	77
Na_V 1.5 IC_{50} nM#,*		1069	Inactive	50%	64%
Compd		**43**	**44**	**45**	**46**
Na_V 1.7 IC_{50} nM		7.2	11.5	3	2.3
Na_V 1.5 IC_{50} nM#,*		34%	Inactive	248	188
Compd		**47**	**48**	**49**	**50**
Na_V 1.7 IC_{50} nM		164	83	14.5	173
Na_V 1.5 IC_{50} nM#,*		Inactive	Inactive	Inactive	Inactive

Inactive refers to <10% inhibition at 10 μM; *% Inhibition at 10 μM

Table 5. Solubility & CYP Profile of Focused Library of Chroman Sulfonamide Compounds

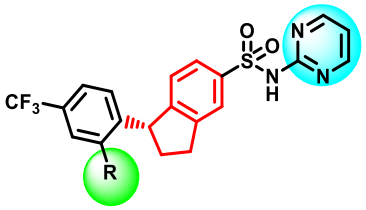


Parameter	R' / R				
Compd		**13**	**14**	**15**	**18**
LogD		3.7	2.5	1.8	3.6
Solubility (μM)		532	463	1180	27

% CYP3A4 inhbn @ 1/ 10 μM		6/15	3/-1	-2/37	5/21
% CYP2C9 inhbn @ 1/ 10 μM		7/36	13/28	10/69	33/86
Compd		**21**	**22**	**23**	**24**
LogD		2.8	2.8	NT	4
Solubility (μM)		245	281	NT	13
% CYP3A4 inhbn @ 1/ 10 μM		-3/12	-5/3	43/86	1/44
% CYP2C9 inhbn @ 1/ 10 μM		2/24	4/41	86/98	27/88
Compd		**29**	**30**	**31**	
LogD		2.8	2.9	2.3	
Solubility (μM)		408	198	742	
% CYP3A4 inhbn @ 1/ 10 μM		11/14	3/48	24/67	
% CYP2C9 inhbn @ 1/ 10 μM		0/18	8/38	90/99	
Compd		**32**	**33**	**34**	**35**
LogD		2.3	2.5	3	3.7
Solubility (μM)		280	225	181	7
% CYP3A4 inhbn @ 1/ 10 μM		0/8	-3/7	47/87	10/13
% CYP2C9 inhbn @ 1/ 10 μM		-1/28	2/68	90/99	22/85
Compd		**36**	**37**	**38**	
LogD		2.9	3	3	
Solubility (μM)		225	233	181	
% CYP3A4 inhbn @ 1/ 10 μM		-2/29	-1/28	-4/11	
% CYP2C9 inhbn @ 1/ 10 μM		4/33	6/49	0/44	
Compd		**43**	**44**	**45**	**46**
LogD		2.7	2.8	2	4.1
Solubility (μM)		91	184	1174	31
% CYP3A4 inhbn @ 1/ 10 μM		11/19	3/32	13/64	3/27
% CYP2C9 inhbn @ 1/ 10 μM		13/54	83/98	74/97	58/95

While gaining the knowledge from SAR studies on chroman series, the best combination of pendant groups and heteroaryl sulfonamide were also tried simultaneously on indane core to understand the effect of terminal phenyl ring trajectory on $Na_V1.7$ inhibition. Out of which, selected examples are shown in Table 6. We have observed good translation of SAR from chroman series to indane, except for compound **54** wherein morpholine was a pendant R group.

Table 6. Profile of Indane Compounds Substituted with Pyrimidine Sulfonamide



Compd	R	$Na_V1.7$ IC_{50} nM[a]	$Na_V1.5$ IC_{50} nM[a,#,*]	LogD	Solubility (μM)	CYP3A4 (% Inhibition)		CYP2C9 (% Inhibition)	
						@1μM	@10μM	@1μM	@10μM
51		10.3	60%	2.4	316	5	11	3	-8
52		6.9	75%	3.2	40	6	11	5	41
53		35.6	Inactive	2.8	47	1	11	8	47
54		105	2792	2.9	12	1	3	7	43

[a] FLIPR membrane potential assay; [#] Inactive refers to <10% inhibition at 10 μM; * % Inhibition at 10 μM

The best compounds with respect to potency for $Na_V1.7$, selectivity over $Na_V1.5$, good solubility and no significant CYP inhibition at 10μM were chosen for assessing the state dependent blockage of $Na_V1.7$, $Na_V1.5$ and detailed in-vitro ADMET profile. Data shown for selected compounds in Table 7 & 8. In manual patch-clamp electrophysiology assay, all the tested compounds have shown state-dependent inhibition of $Na_V1.7$, however they did not show any use-dependent effect, which is true with known sulfonamide derivatives.[17a] Compound **29** has shown resting state block with IC_{50} of 2.3 μM and compound **43** has shown moderate resting state block of 57% inhibition at 10 μM. The other three lead molecules **13, 32** & **51** did not show significant resting state inhibition, Table 7. These lead molecules exhibited low potency for fast inactivated state of $hNa_V1.5$ with an inhibition of <50% for 1st pulse and these values were shifted up to 80% for 10th pulse at 10μM, Table 7. All the five lead molecules have shown very good metabolic stability in liver microsomes across the species except for compound **43** in mice liver microsomes, Table 8. The chroman and indane compounds have shown good permeability in Caco-2 assay and moderate to

high plasma protein binding across the species, Table 8. All these compounds did not show any cytotoxicity or hERG inhibition (no to very low (<10%) inhibition) at 10 μM (data not shown).

Table 7. State Dependent Properties of Lead Compounds

Compd	**Nav1.7** IC_{50} (nM)[a]			**Nav1.7**[a]	**Nav1.5** (% Inhibition@10μM)[a]	
	Slow Inactivation	Fast Inactivation (1p)	Use Dependent Inhibition (25p)	Resting IC_{50} (μM) or % Inhibition@10μM	Fast Inactivation (1p)	Fast Inactivation (10p)
13	15.9±0.9	45.3±1.3	29.8±1.23	9.5±0.43μM	34±2%	64±2%
29	15.9 ± 1.2	44.4 ± 2.2	34.3 ± 1.5	2.28±0.28μM	46±2%	80±1%
32	39.6 ± 3.9	134 ± 8.4	108 ± 4.6	38±2% @10μM	29±2%	57±2%
43	35.1±1.3	67.4±3.2	52.1±2.8	57±2%@10μM	19±1%	71±2%
51	33±2.4	99.7±5.8	71±4.9	~8.1±0.58μM	40±1%	65±1%

[a] Manual patch clamp EP assay; IC_{50} values are at $V_{1/2}$ of slow inactivation and fast inactivation.

Table 8. Metabolic Stability, Permeability and Plasma Protein Binding of Lead Molecules

Compd	**Metabolic Rate (nmol/min/mg)**					**Permeability Caco-2 Papp (nm/sec)**			**% PPB**		
	MLM	RLM	DLM	MoLM	HLM	A-B	B-A	ER	Mice	Rat	Human
13	0	0.01	0.01	0.02	0	280	268	1	88.5	91	95.4
29	0	0	0.03	0.01	0	418	334	0.9	95.4	93.4	97.1
32	0.04	0.02	0.02	0.02	0	395	368	0.9	98	99.2	98.3
43	0.16	0.02	0.02	0.03	0.02	376	254	0.7	94.1	92.8	97.6
51	0.03	0.04	0.02	0.03	0.03	315	367	1.2	92.9	99.3	99.7

These five lead compounds were also subjected to detailed in-vivo pharmacokinetic profiling in rodent and non-rodent species. All the compounds have shown very good oral bioavailability with low clearance and good $t_{1/2}$ in mice, rats and dogs, Table 9. These compounds have shown emesis in dogs post iv and/or po dosing. This could be a species specific phenomenon. To ensure, pharmacokinetic profile of compound **51** was determined following oral gavage to cynomolgus monkeys at a higher dose of 150 mg/kg to a group of 6 animals (3 male and 3 female). No emesis was observed. The mean T_{max} was found to be 2.0h and 1.5h in male and female, respectively. The mean C_{max} and AUC_{last} were found to be similar in male (66±8µM and 684±122h*µM) and female (69±5µM and 601±12h*µM) suggesting no gender difference.

Table 9. Pharmacokinetic Profile of Lead Molecules

Compd	Species	IV (1 mpk)					PO (10 mpk)		
		Cmax (µM)	AUC_{last} (h*µM)	$T_{1/2}$ (h)	CL (ml/min/kg)	V_{ss} (l/kg)	Cmax (µM)	AUC_{last} (h*µM)	%F
13	Mice	2	12	4.2	2.7	0.9	15	107	89
	Rat	2.2±0.2	11±3	4.2±1	3±0.8	0.9±0.1	13±6	114±45	100
	Dog*	6.9±1	59±20	7.8±3.8	0.5±0.3	0.3±0	10±1.7	117±41	40±4
29	Mice	2	12	3.2	2.6	0.8	17	171	>100
	Rat	1.7±0.5	15±2	9.8±5	2±0	1.2±0.4	6.6±1.8	111±29	74
	Dog*	5.7±0.7	70±13	24±4	0.3±0.1	0.5±0	14±2	218±87	78±22
32	Mice	3	7.6	1.5	3.9	0.6	18	63	83
	Rat	2.6±0.2	5.5±0.8	1.9±0.3	5.5±0.9	0.8±0.1	19±6	112±11	>100
	Dog*	6.5±1	19±10	2.5±0.6	2±1	0.4±0.1	8.5±3	50±30	51±16
43	Mice	2	12	4.3	2.5	0.81	9.6	62	50
	Rat	2.1±0.2	5.9±0.6	2.8±0.2	5.1±0.4	1.2±0.1	2.1±0.5	19±3	31
	Dog	4.9 ± 1	48 ± 1	11 ± 2	0.5 ± 0	0.5 ± 0	nd	nd	nd
51	Mice	2	8.5	2.8	3.3	0.8	18	84	99
	Rat	2.5±0.5	7.9±5	2.7±0.3	4.9±2.6	1.0±0.3	10.9±0.7	46±7	58

Vehicle (Mouse, Rat & Dog)**:** IV: DMA (10%): PEG300 (20%): 20%Captisol in NS (q.s.); PO: Tween80 (1%): 0.5%CMC solution (QS)
*PO at 5 mpk & emesis observed in all cases; nd - not done

Taken together, systematic SAR studies on chroman series for parallel optimization of several parameters (as summarized in Fig. 3.) led to identification of many novel, potent and selective $Na_V1.7$ inhibitors with good solubility and good pharmacokinetic profile in rodent and non-rodent species devoid of any

significant CYP inhibition, which is a major liability seen with many known $Na_V1.7$ inhibitors. Based on the overall profile of lead molecules, all the lead molecules **13**, **29**, **32**, **43** and **51** were tested for efficacy at 30 mpk p.o. dose to understand the translation of in-vitro potency to in-vivo efficacy in different pain models of mice. We have used in-house developed veratridine induced pain model in mice as a primary model to assess the target engagement of $Na_V1.7$. Veratridine acts as a neurotoxin and binds to voltage-gated sodium channels leading to persistent activation and inhibits transitioning into the inactivated state, thus stimulating a pain response.[9a] Compounds were administered orally 30 min prior to sub-planter injection of veratridine. All of these compounds demonstrated statistically significant reduction in time spent in nociceptive behavior (time spent in licking and/or flinching) compared to vehicle post veratridine injection at 30 mpk po dose. Secondly, formalin induced inflammatory pain model was used as an efficacy model. In this model, formalin generates a biphasic pain response, an acute phase (or Phase I) reflective of direct activation of nociceptors and a tonic phase (or Phase II) related to inflammatory responses.[22] Lead compounds were administered orally at 30 mpk dose 30 minutes prior to formalin challenge, the total time spent in nociceptive behavior at 0 – 5 min (phase I) and 10 - 40 min interval (phase II) for each mouse was measured and it was found that all the tested compounds have shown profound effect on decrease in nociceptive behavior in phase II. The brain exposures of the compounds **13**, **29**, **32** and **43** were measured from PK-PD study at 30mpk dose (at 75 min post dose of compounds) and found to be minimal (<1μM) with 0.5%, 1.8%, 0.7%, and 4.5%, respectively, of the plasma exposure, whereas for compound **51**, the brain exposure was estimated to be 2.1μM, which is 7% of plasma exposure. When these lead molecules were assessed at 30 mpk oral dose in CCI induced neuropathic pain model in mice,[23] to our puzzle, only compounds **29** and **51** have shown effect on paw-withdrawal threshold (mechanical allodynia) using von Frey filaments (data not shown). However, compounds **29**, **32** and **43** were not chosen for further profiling due to resting state block of compound **29** and **43** and relatively inferior PK (low $t_{1/2}$ in both rodent and non-rodent) profile of compound **32**. The best two compounds **13** and **51** based on

overall profile were chosen for dose response studies. Compound **13** has shown flat dose response in veratridine induced pain model at 3, 10 and 30 mpk p.o. dose. However, in formalin induced inflammatory pain model, compound **13** demonstrated a very good dose-dependent reversal of nociceptive effects in the acute phase of the experiment (phase I) and the tonic phase of the experiment (phase II) at 3, 10 and 30 mpk p.o. dose, compared to vehicle treated animals, with statistically significant reversal of nociceptive pain at all the doses in the tonic phase, Fig. 4. Plasma concentration were measured at the end of the study and the unbound drug concentration was determined to be 0.728μM at 3 mpk dose which is 22 fold higher than the mNa$_V$1.7 IC$_{50}$ (32.6 ± 1.6 nM). Compound **13** did not show any effect even at 100 mpk dose in CCI induced neuropathic pain model. However, compound **51** demonstrated a dose dependent reduction in nociceptive effects in both veratridine induced pain model and in formalin induced inflammatory pain model at 3, 10 and 30 mpk, p.o. dose, compared to vehicle treated animals, Fig. 5. Plasma concentration were measured at the end of formalin study and the unbound drug concentration was determined to be 0.343μM at 3 mpk dose which is 10 fold above the mNa$_V$1.7 IC$_{50}$ (33 ± 1.8 nM). Compound **51** has also shown significant effect in CCI induced neuropathic pain model at 100 mpk p.o. dose, Fig. 5.

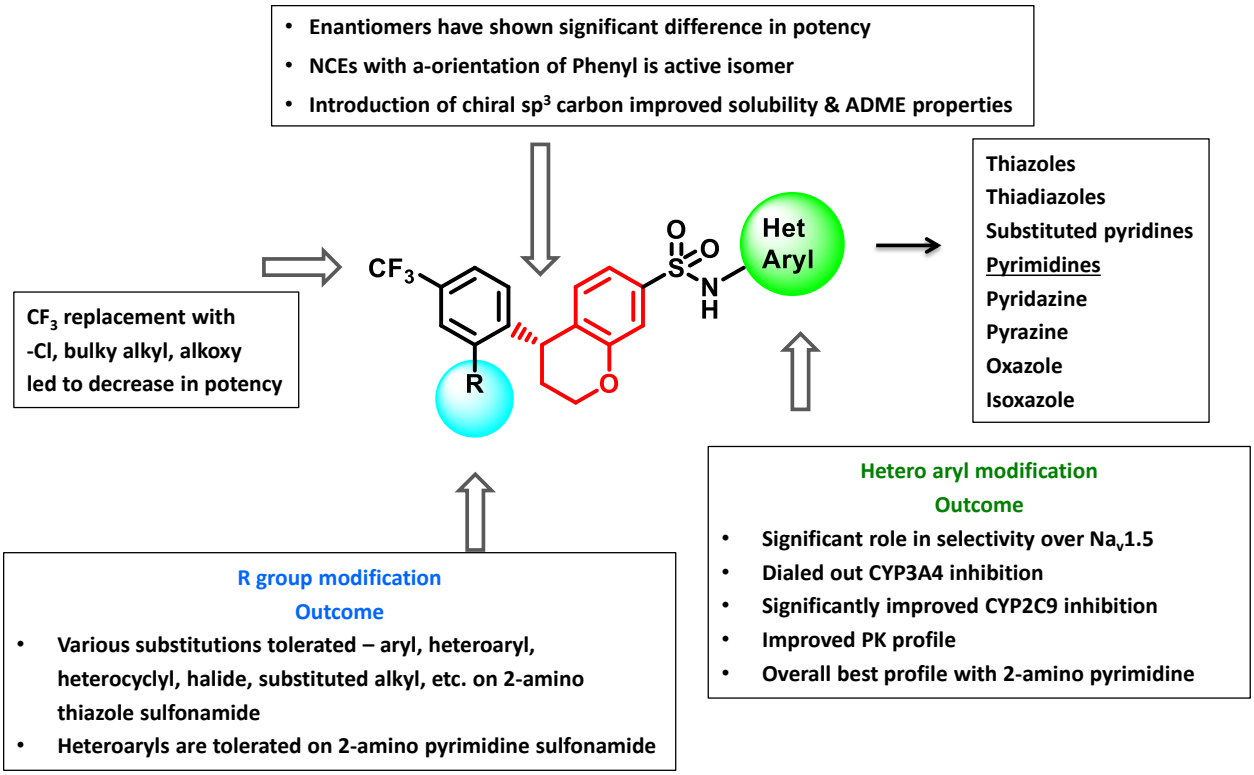


Figure 3. Overall SAR Summary of Chroman Series

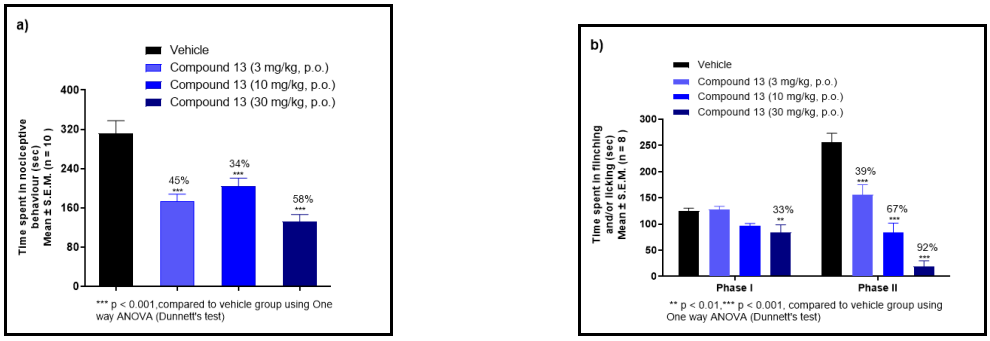


Figure 4. Effect of Compound **13** in Different Pain Models in Mice; a) Dose response effect at 3, 10, 30 mpk, p.o. on veratridine induced nociceptive behaviors; b) Dose response effect at 3, 10, 30 mpk, p.o. on phase I and II of formalin induced nociceptive behaviors; Results are presented as the mean ± SEM response (n = 8–10/group) and were analyzed by One way ANOVA followed by Dunnett's post-hoc tests; **P < 0.01, ***P < 0.001, compared to respective vehicle group.

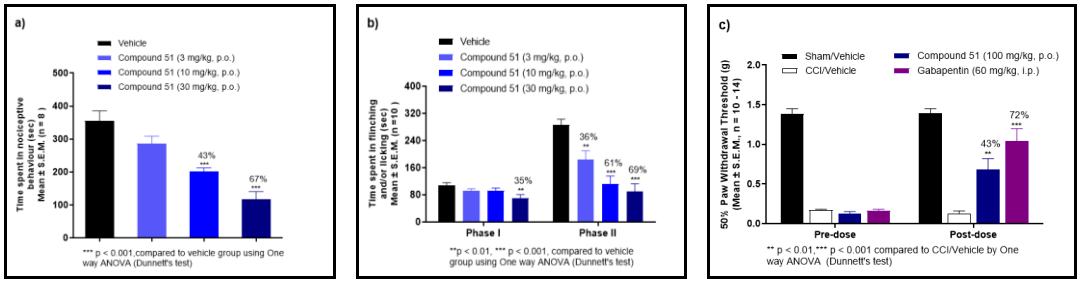


Figure 5. Effect of Compound **51** in Different Pain Models in Mice; a) Dose response effect at 3, 10, 30 mpk, p.o. on veratridine induced nociceptive behaviors; b) Dose response effect at 3, 10, 30 mpk, p.o. on phase I and II of formalin induced nociceptive behaviors; c) Response of compound **51** at 100 mpk, p.o. in CCI induced allodynia. Gabapentine (60 mpk, ip) was used as the positive control. Results are presented as the mean ± SEM response (n = 10–13/group) and were analyzed by One way ANOVA followed by Dunnett's post-hoc tests; **P < 0.01, ***P < 0.001, compared to respective vehicle group.

Table 10. State-dependent block of Compound 51 across species for $Na_V1.7$

State	IC_{50} (nM)/% Inhibition*		
	Human	Monkey	Mouse
Slow Inactivation	33 ± 2.4	60 ± 1.3	33 ± 1.8
Fast Inactivation (1P)	99.7 ± 5.8	195 ± 11	118 ± 12
Use Dependence (25P)	71 ± 4.9	145 ± 13	89 ± 4.5
Resting	~8.1 ± 0.58 µM	31 ± 3% @10 µM	36 ± 1 % @10 µM

* Manual patch clamp EP assay; IC_{50} values are at $V_{1/2}$ of slow inactivation and fast inactivation.

Table 11. Selectivity of Compound 51 over Other Na_V Isoforms

Parameter	% Inhibition at 10 µM*							
	$hNa_V1.1$	$hNa_V1.2$	$hNa_V1.3$	$hNa_V1.4$	$hNa_V1.5$	$hNa_V1.6$	$hNa_V1.8$	$hNa_V1.9$
Resting State (1st Pulse)	8 ± 2	13 ± 2	6 ± 1	7.7 ± 1	10 ± 1	32 ± 1	3 ± 1	6 ± 1
Inactivated State (2nd Pulse)	72	7.1 ± 1.1 µM (IC_{50})	51 ± 2	8.1 ± 0.6	40 ± 1	59 ± 2	27 ± 2	Not done

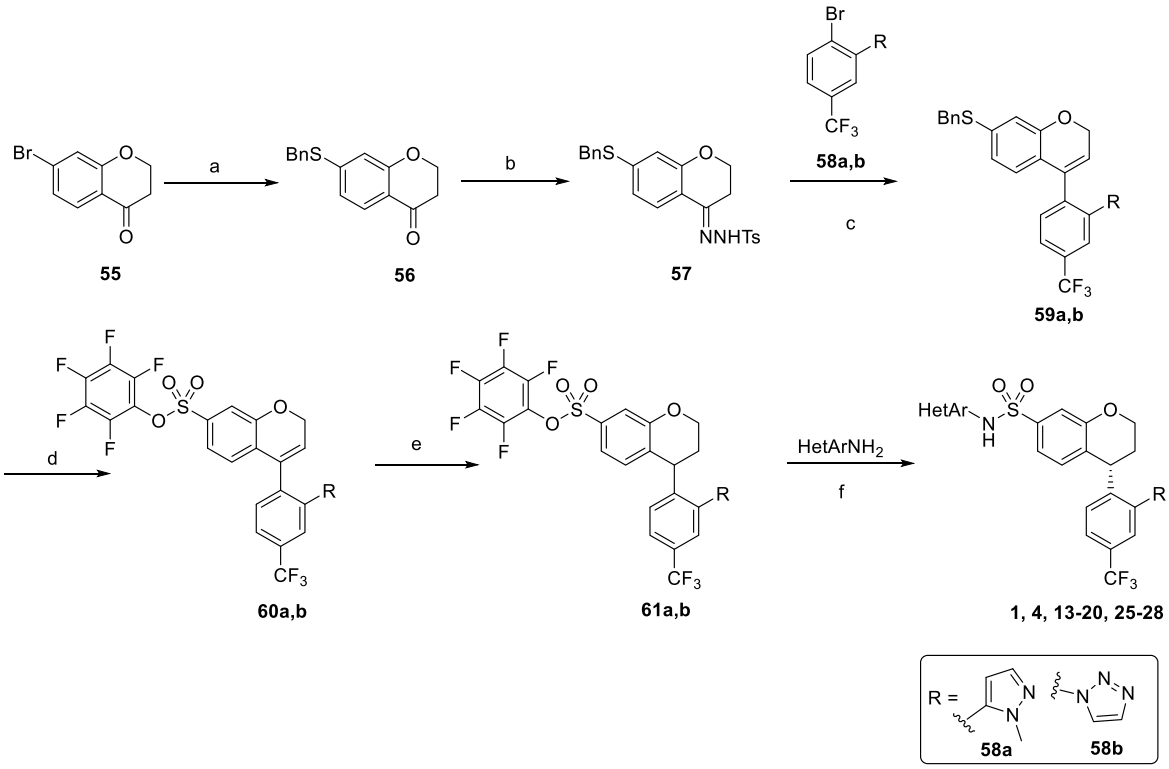
* Manual patch clamp EP assay; 2nd pulse at $V_{1/2}$ of inactivation

Having identified compound **51** as a highly desirable lead compound over compound **13** due to its efficacy in both inflammatory and neuropathic pain models, compound **51** was chosen for testing potency across rodent and non-rodent species and for extensive selectivity profiling across human Na_V channel subtypes. In manual patch clamp electro physiology assay, compound **51** exhibited state-dependent block of human, monkey and mouse $Na_V1.7$ with a similar potency range, Table 10. Pleasingly, it has also shown good selectivity against other Na_V isoforms and minimal inhibition at 10 μM for resting state across different Na_V isoforms, Table 11. Further, no significant inhibition observed at 10 μM in Eurofins CEREP ExpresS panel of 55 targets including GPCRs, other ion channels and transporters.

CHEMISTRY

Synthesis of chroman sulfonamide derivatives started with 7-bromochroman-4-one **55**. A palladium catalyzed thiolation[24] converted **55** to 7-(benzylthio)chroman-4-one **56**. The palladium catalyzed Barluenga reaction[25] was used for the elaboration of chroman ring at the 4-position with various substituted phenyl groups, Scheme 1. To convert the 7-(benzylthio)chroman-4-one **56** to a suitable substrate for the Barluenga reaction,[25] tosylhydrazide **57** was prepared from **56** and then coupled with 2-substituted 1-bromo-4-(trifluoromethyl)benzene **58a, b** to get 7-(benzylthio)-4-substituted-2H-chromene **59a, b**. The thiobenzyl group was then oxidized in situ to the sulfonyl chloride using sulfuryl chloride and then converted to the stable 2*H*-chromene-7-sulfonates **60a, b**.[26]

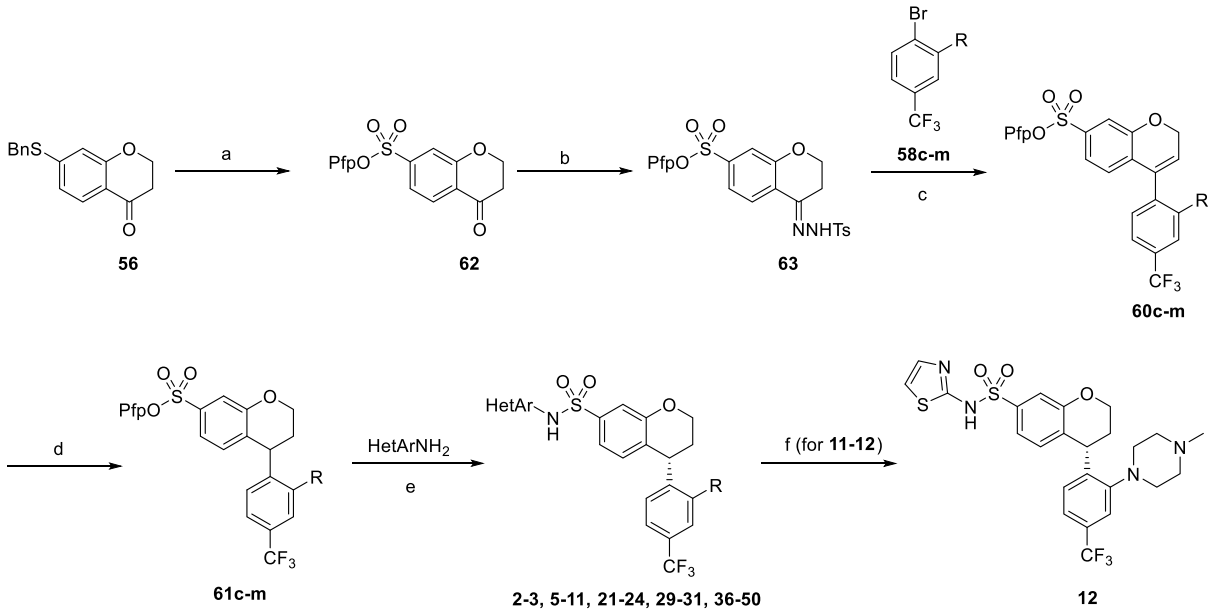
Scheme 1: Synthesis of Compounds 1, 4, 13-20 & 25-28



Reagents and conditions: (a) BnSH, $Pd_2(dba)_3$, $(^iPr)_2NEt$, 80 ^oC, 1 h, 60%; (b) Tosylhydrazide, MeOH, 80 ^oC, 16 h, 94%; (c) Na_2CO_3, $PdCl_2(dppf).DCM$, Dioxane-H_2O (85:15), 100 ^oC, 5-8 h 47-76%; (d) (i) SO_2Cl_2, AcOH, cat. H_2O, DCM, -5 ^oC , 1 h; (ii) Pentafluorophenol, Et_3N, DCM, 0 ^oC, 1 h, 60-71%; (e) H_2 (3 atm), 10% Pd-C, EtOAc, 4-6 h, rt, 83-94%; (f) (i) $HetArNH_2$, LiHMDS (1M in THF), 0 ^oC to rt, 1-2 h; (ii) Chiral separation, 9-44%.

The double bond was then reduced to generate the chiral center of the 4-substituted chroman ring **61a, b** by using hydrogen in presence of 10% Pd-C. The racemic compounds **61a, b** was then reacted with various heteroaryl amines in the presence of LiHMDS to give the final sulfonamide derivatives. At this stage, the enantiomers of the individual compounds were separated by preparative chiral HPLC to obtain chirally pure active isomers of chroman compounds **1, 4, 13-20, & 25-28**.

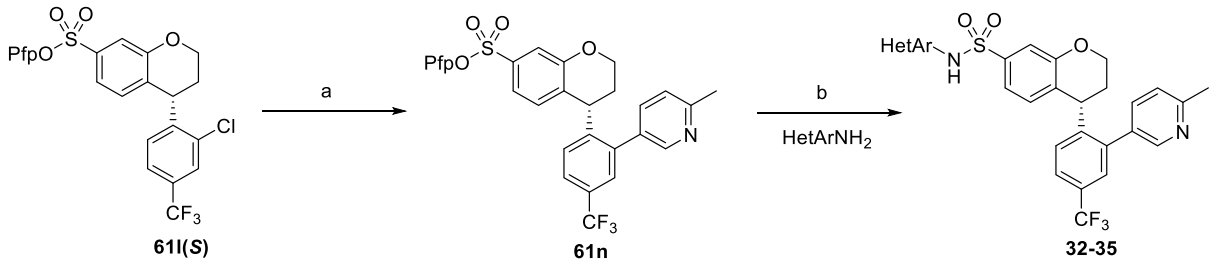
Scheme 2: Synthesis of Compounds 2-3, 5-12, 21-24, 29-31, 36-50



Reagents and conditions: (a) (i) NCS, AcOH-H_2O (4:1), 0 °C to rt, 45 min; (ii) Pentafluorophenol, Et_3N, DCM, 0 °C, 45 min, 65%; (b) Tosylhydrazide, MeOH, 80 °C, 16 h, 94%; (c) Na_2CO_3, $PdCl_2$(dppf).DCM, Dioxane-H_2O (85:15), 100 °C, 1-2 h, 38-61%; (d) H_2 (3 atm), 10% Pd-C, EtOAc, 4-6 h, rt, 50-90%; (e) (i) $HetArNH_2$, LiHMDS (1M in THF), 0 °C to rt, 1-2 h, 9-69%; (ii) chiral separation; (f) HCHO, AcOH cat., $NaBH(OAc)_3$, 16 h, 79%.

Alternatively, intermediate **56** was first oxidized in situ to the corresponding sulfonyl chloride with N-chlorosuccinimide and then converted to the stable pentafluoroester **62**, Scheme 2. This ester was converted to the tosylhydrazide **63** and then coupled with various 2-substituted 1-bromo-4-(trifluoromethyl)benzene **58c-m** to give the 2H-chromene-7-sulfonates **60c-m**. The double bond was reduced to get the racemic 4-substituted chroman compounds **61c-m** by using hydrogen in presence of 10% Pd-C, Scheme 2. The enantiomers were either separated at this step and the purified enantiomers were separately reacted with various heteroaryl amines in the presence of LiHMDS to give the final sulfonamide compounds or the amine addition reactions were done on the racemic **61c-m** and then the enantiomers of the final compounds were separated by preparative chiral HPLC.

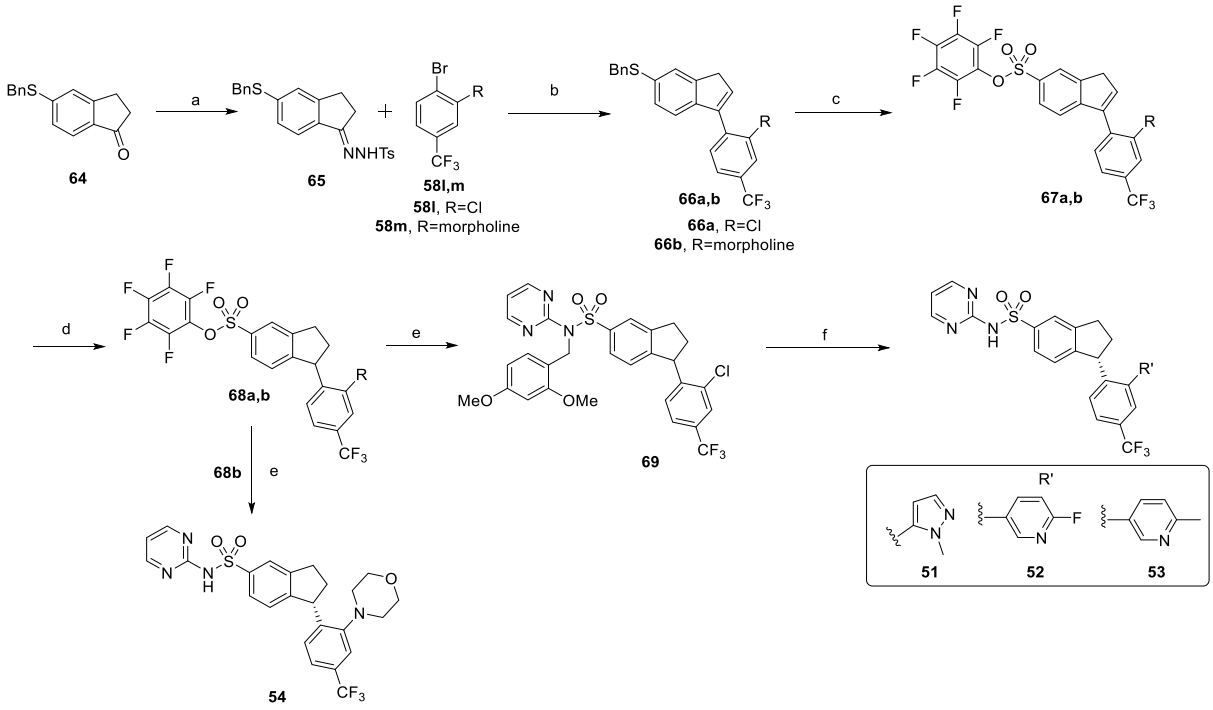
Scheme 3: Preparation of Compounds 32-35



Reagents and conditions: (a) $[(t\text{-}Bu)_3PH]BF_4$, $PdCl_2(dppf).DCM$, 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, Dioxane, 100 ^oC, 2 h, 91%; (b) $HetArNH_2$, LiHMDS (1M in THF), 0 ^oC to rt, 1-2 h, 9-78%.

Compounds **32-35** were synthesized from (*S*)-enantiomer of **61l** (obtained by separation of the enantiomers of racemic **61l** using chiral column) by following the reaction sequence as shown in Scheme 3. Suzuki coupling of **61l**(*S*) with 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine gave the pentafluoro intermediate **61n**, which was then converted to the final sulfonamide compounds **32-35** using different heteroaryl amines as described in earlier scheme.

Scheme 4: Preparation of Compounds 51-54



Reagents and conditions: (a) Tosylhydrazide, MeOH, 80 °C, 16 h, 90%; (b) Na_2CO_3, $PdCl_2$(dppf).DCM, Dioxane-H_2O (85:15), 100 °C, 4-6 h, 51-58%; (c) (i) NCS, AcOH-H_2O (4:1), 0 °C to rt, 45 min; (ii) Pentafluorophenol, Et_3N, DCM, 0 °C, 45 min, 53-55%; (d) H_2 (1 atm), 10% Pd-C, EtOAc, rt, 16 h, 87-91%; (e) N-(2,4-dimethoxybenzyl)pyrimidin-2-amine (for **68a**) or pyrimidin-2-amine (for **68b**) LiHMDS (1M in THF), 0 °C to rt, 1-2 h, 35-55%; Chiral Separation for **54**; (f) (i) $[(t\text{-}Bu)_3PH]BF_4$, $PdCl_2$(dppf).DCM, heteroarylboronic acid, Dioxane, 100 °C, 1-2 h; (ii) TFA, DCM, rt; (iii) Chiral Separation, 23-39%.

Scheme 4 depicts the reaction sequence for the synthesis of the indane sulfonamide derivatives and the transformations were carried out by following the same chemistry already described for the chroman sulfonamide compounds in Scheme 1. The starting material in this case was 5-(benzylthio)-2,3-dihydro-1H-inden-1-one **64**. The keto compound was first converted to the tosyl hydrazide **65** followed by coupling with either 1-bromo-2-chloro-4-(trifluoromethyl)benzene **58l** or 4-(2-bromo-5-(trifluoromethyl)phenyl) morpholine **58m** to give the substituted 1*H*-indene compounds **66a** and **66b**, respectively. The thiobenzyl group of **66a,b** was then oxidized in situ to the sulfonyl chloride with *N*-chlorosuccinimide and then

converted to the stable 1*H*-indene pentafluoroester **67a,b** which on reduction provided the racemic indane derivatives **68a,b**. The pentafluoroester derivative **68a** was then reacted with *N*-(2,4-dimethoxybenzyl)pyrimidin-2-amine in the presence of LiHMDS to give the sulfonamide derivative **69**. The racemic compound **69** was converted to the final compounds **51-53** by Suzuki coupling with the respective boronic acids or esters, followed by de-protection of the dimethoxybenzyl group on the sulfonamide and separation of the racemic compounds into required enantiomers by preparative chiral HPLC. Compound **54** with the morpholine side chain was obtained from **68b** by base mediated reaction with pyrimidin-2-amine and subsequent separation of the (*S*)-enantiomer by preparative chiral HPLC.

CONCLUSION

Chroman based sulfonamide derivatives have been identified as potent, selective and state-dependent $Na_V1.7$ inhibitors with very good PK and low CYP inhibition profile through systematic SAR studies and parallel optimization approach. Switching from benzoxazine scaffold to chroman bicyclic system with a sp^3 chiral carbon led to significant improvement in solubility and overall pharmacokinetic profile. Replacement of thiazole with other heteroaryl substitution on sulfonamide was tolerated on chroman core with many pendant groups and also resulted in significant improvement in selectivity over $Na_V1.5$ and lowered CYP2C9 inhibition. It is important to note that the modification of heteroaryl substitution on sulfonamide led to steep decrease in activity on many other scaffolds.[17b,e,18b,19a,b] Two major challenges were addressed with this one modification on sulfonamide, however extensive SAR studies with synthesis of a large number of NCEs in a library fashion were conducted to identify lead molecules with defined target product profile since the SAR was not additive. Also, good translation of SAR was observed on similar bicyclic system such as indane core. More importantly, the lead molecules **13**, **29**, **32**, **43** and **51** have shown favorable PK profile in both rodent and non-rodent species and robust efficacy translation in veratridine induced pain and formalin induced inflammatory pain models in mice. However, to our puzzle,

only selected leads have shown efficacy in CCI induced neuropathic pain model in mice. Finally, the detailed characterization of compound **51** has indicated that it has the desired properties for further evaluation as a therapeutic agent for pain.

EXPERIMENTAL SECTION

Chemistry. All reagents were purchased from commercial suppliers and used without purification unless otherwise noted. All anhydrous reactions were performed under a nitrogen atmosphere using dry solvents. Silica gel column chromatography was carried out on ISCO CombiFlash Companion with prepacked columns. Nuclear magnetic resonance (^{1}H & ^{13}C NMR) spectra were recorded on a Bruker AvanceV-III 400 MHz spectrometer. All spectra were determined in the solvents indicated, and chemical shifts are reported in δ units downfield from the internal standard tetramethylsilane (TMS) with inter proton coupling constants reported in hertz (Hz). All NMR spectra were analyzed using the MestReNova 10.0 program software. Liquid chromatography-mass spectrometry (LC-MS) analyses were performed either on an Agilent 1200 Series LC instrument coupled to an Agilent Iontrap MS instrument or a Thermo Scientific Accela LC instrument coupled to a Thermo Scientific MSQ Plus instrument. Preparative HPLC were performed on a Gilson GX 281 series using a YMC ODS-A column or YMC Triat column (50 mm X 250 mm, 10 µm) using either acid (0.1 % formic acid) or base (0.1% NH_4OH) modified MeCN-H_2O gradients. Most of the final compounds were prepared as racemic mixture and separated using preparative chiral HPLC at the final or pre-final stage. Preparative chiral separations and enatiomeric purity determination were carried out using Knauer Azura 2.1L purification system with different columns and mobile phase. Methods and conditions for chiral separation of all the relevant compounds are provided in the supporting information. Compound purity was determined by reverse phase HPLC performed on an Agilent 1290 Infinity equipped with either a Zorbax Eclipse Plus C18, 50 X 2.1 mm, 1.8 µm or an Acquity Beh C18, 50 X 2.1 mm, 1.7 µm column using either acid (0.1 % formic acid) or base (0.1% NH_4OH) modified MeCN-H_2O gradients. Purity of the final compounds were determined by HPLC and were greater than 95% for all the compounds except for compounds **23** (94%), **42** (94%) and **45** (93%). The synthetic procedures and the analytical data for the intermediates **58a-m** are provided in the supporting information.

(*S* & *R*)-4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide (1a & 1b). Thiazol-2-amine (25.5 g, 255 mmol) was dissolved in 2L THF and the solution was cooled to 0 °C and a 1M solution of LiHMDS (242 mL, 242 mmol) was added to it slowly. After the addition,

the solution was stirred for 20 min after which a solution of perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chroman-7-sulfonate (77 g, 127 mmol) **(61a)** in THF was added and the reaction mixture was allowed to stir for 1.5 h, after which it was quenched by the addition of 2N HCl solution and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated and the crude was purified on a 800 g Sepaflash column to obtain the racemic product (46g, 70%). The racemic product was purified on chiral prep HPLC to obtain the *R* and *S* enantiomers (19 g each, 29%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.22 – 7.15 (m, 2H), 6.92 – 6.78 (m, 2H), 6.47 (d, J = 1.9 Hz, 1H), 4.28 – 4.19 (m, 1H), 4.19 – 4.06 (m, 2H), 3.70 (s, 3H), 2.19 – 2.05 (m, 1H), 2.05 – 1.89 (m, 1H). LCMS (ESI): *m/z* 520.88 $(M+H)^+$

(*S* & *R*)-N-(thiazol-2-yl)-4-(2-(thiazol-2-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonamide (2a & 2b). Synthesized from perfluorophenyl 4-(2-(thiazol-2-yl)-4-(trifluoromethyl)phenyl)chroman-7-sulfonate **(61d)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomers (yield = 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 8.10 – 7.93 (m, 3H), 7.80 (d, J = 8.3 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.23 – 7.16 (m, 2H), 6.93 – 6.80 (m, 2H), 5.05 (t, J = 7.1 Hz, 1H), 4.31 – 4.11 (m, 2H), 2.29– 2.21 (m, 1H), 2.15 – 2.04 (m, 1H). LCMS (ESI): *m/z* 523.95 $(M+H)^+$

(*S* & *R*)-4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide (3a & 3b). Synthesized from perfluorophenyl 4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61c)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomers (yield = 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 8.44 (s, 1H), 8.00 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 8.2, 2.1 Hz, 1H), 7.33 – 7.23 (m, 1H), 7.23 – 7.18 (m, 2H), 7.15 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 6.7 Hz, 2H), 4.88 (t, J = 6.7 Hz, 1H), 4.30 – 4.10 (m, 2H), 2.52 (s, 3H), 2.40 – 2.24 (m, 1H), 2.09 – 1.94 (m, 1H). LCMS (ESI): *m/z* 521.82 $(M+H)^+$

(*S* & *R*)-4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide (4a & 4b). Synthesized from perfluorophenyl 4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61b)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomers (yield = 24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 8.68 (s, 1H), 8.03 (s, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 4.7 Hz, 1H), 7.23 – 7.15 (m, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 4.6 Hz, 1H), 4.29 – 4.17 (m, 1H), 4.18 – 4.07 (m, 1H), 3.99 (t, J = 7.1 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.09 – 1.97 (m, 1H). LCMS (ESI): *m/z* 508.06 $(M+H)^+$

(*S* & *R*)-4-(2-(6-fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide (5a & 5b). Synthesized from perfluorophenyl 4-(2-(6-fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61e)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomers (yield = 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 8.38 (d, J = 2.5 Hz, 1H), 8.15 (td, J = 8.2, 2.5 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.68 (s, 1H), 7.32 (dd, J = 8.5, 2.7 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.22 – 7.14 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 4.6 Hz, 1H), 4.29 – 4.16 (m, 2H), 4.11 (t, J = 9.9 Hz, 1H), 2.18 – 2.08 (m, 1H), 2.05 – 1.95 (m, 1H). LCMS (ESI): *m/z* 536.01 $(M+H)^+$

(*R*)-4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide (6). Synthesized from perfluorophenyl 4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61f)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 8.70 (d, J = 2.9 Hz, 1H), 7.97 – 7.85 (m, 1H), 7.84 – 7.63 (m, 3H), 7.30 – 7.23 (m, 2H), 7.22 – 7.14 (m, 2H), 6.91 – 6.77 (m, 2H), 4.63 – 4.48 (m, 1H), 4.33 – 4.18 (m, 1H), 4.16 – 4.03 (m, 1H), 2.22 – 2.10 (m, 1H), 2.08 – 1.94 (m, 1H). LCMS (ESI): *m/z* 536.07 $(M+H)^+$

(*S* & *R*)-4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-N-(thiazol-2-yl)chromane-7-sulfonamide (7a & 7b). Synthesized from perfluorophenyl 4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)chromane-7-sulfonate **(61g)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomers (yield = 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.58 – 7.49 (m, 3H), 7.32 (t, J = 8.7 Hz, 2H), 7.26 – 7.13 (m, 4H), 6.85 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 4.5 Hz, 1H), 4.35 – 4.13 (m, 2H), 4.07 (t, J = 10.8 Hz, 1H), 2.14 – 2.05 (m, 1H), 2.05 – 1.94 (m, 1H). LCMS (ESI): *m/z* 534.94 $(M+H)^+$

(*R*)-4-(2-(3-oxomorpholino)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chroman-7-sulfonamide (8). Synthesized from perfluorophenyl (R)-4-(2-(3-oxomorpholino)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61h)** by following an analogous procedure described for **1a** & **1b** (yield = 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.87 (s, 1H), 7.66 (t, J = 7.0 Hz, 1H), 7.27 (d, J = 4.5 Hz, 1H), 7.19 (dt, J = 16.3, 8.9 Hz, 3H), 6.97 – 6.75 (m, 2H), 4.43 – 4.21 (m, 5H), 4.04 (q, J = 4.7, 3.7 Hz, 2H), 3.89 (d, J = 9.1 Hz, 1H), 3.58 (dd, J = 27.7, 11.7 Hz, 1H), 2.30 – 2.16 (m, 1H), 2.06 – 1.96 (m, 1H). LCMS (ESI): *m/z* 624.21 $(M+H)^+$

(*R*)-4-(2-(2-oxooxazolidin-3-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide (9). Synthesized from perfluorophenyl 4-(2-(2-oxooxazolidin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-

sulfonate **(61i)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 23%).^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.99 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.34 – 7.10 (m, 4H), 6.84 (t, *J* = 5.9 Hz, 2H), 4.66 – 4.42 (m, 3H), 4.27 (t, *J* = 4.9 Hz, 2H), 4.13 – 3.87 (m, 2H), 2.26 (d, *J* = 13.8 Hz, 1H), 2.02 (d, *J* = 7.2 Hz, 1H). LCMS (ESI): *m/z* 526.07 $(M+H)^+$

(*R*)-4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chroman-7-sulfonamide (10). Synthesized from perfluorophenyl 4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61j)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 7.71 (s, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.27 (d, J = 4.6 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.11 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 4.6 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.83 (t, 1H), 4.33 (t, J = 9.9 Hz, 1H), 4.29 – 4.18 (m, 1H), 3.53 – 3.40 (m, 2H), 3.34 – 3.19 (m, 6H), 2.31 – 2.21 (m, 1H), 2.11 – 1.99 (m, 1H). LCMS (ESI): *m/z* 573.82 $(M+H)^+$

(*R*)-4-(2-(piperazin-1-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide hydrochloride salt (11). Synthesized from tert-butyl 4-(2-(7-((perfluorophenoxy)sulfonyl)chroman-4-yl)-5-(trifluoromethyl)phenyl)piperazine-1-carboxylate **(61k)** by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomers. The enantiomer obtained from the later eluting peak in chiral HPLC was de-protected by 4N Dioxane in HCl whereby the Boc group is de-protected and the compound was converted to its hydrochloride salt (yield = 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 8.85 (s, 2H), 7.52 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 4.6 Hz, 1H), 7.23 – 7.11 (m, 3H), 6.84 (d, J = 4.6 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 4.77 (t, J = 7.4 Hz, 1H), 4.37 – 4.19 (m, 2H), 3.32 – 3.13 (m, 6H), 3.14 – 3.01 (m, 2H), 2.28 – 2.17 (m, 1H), 2.07 (t, J = 10.6 Hz, 1H). LCMS (ESI): *m/z* 525.03 $(M+H)^+$

(*R*)-4-(2-(4-methylpiperazin-1-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide hydrochloride salt (12). To a stirred solution of (R)-4-(2-(piperazin-1-yl)-4-(trifluoromethyl)phenyl)-N-(thiazol-2-yl)chromane-7-sulfonamide hydrochloride salt **(11)** (0.22 g, 0.40 mmol) in 10 mL DCE was added 37% solution of formaldehyde (0.30 ml, 4.0 mmol) followed by acetic acid (0.11 mL, 2.0 mmol) and the reaction mixture was stirred for 1 h. Sodium triacetoxyborohydride (0.424 g, 2.0 mmol) was added and the reaction mixture was stirred for overnight at room temperature. The reaction mixture was quenched by the addition of a saturated solution of $NaHCO_3$, and extracted with 10% MeOH in DCM. The organic layer was dried over Na_2SO_4 and conc. to obtain the product which was converted to its hydrochloride salt by stirring with 2N ethereal HCl and then filtered. (0.17 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (brs, 1H), 10.94 (brs, 1H), 7.54 (d, J = 1.9 Hz, 1H), 7.48 (dd, J = 8.1, 1.9 Hz, 1H), 7.27 (d, J = 4.6 Hz, 1H), 7.22 –

7.12 (m, 3H), 6.85 (d, J = 4.6 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 4.77 (dd, J = 8.8, 5.9 Hz, 1H), 4.34 – 4.22 (m, 2H), 3.47 (d, J = 9.2 Hz, 3H), 3.32 – 3.15 (m, 5H), 2.81 (s, 3H), 2.25 (d, J = 13.3 Hz, 1H), 2.14 – 2.02 (m, 1H). LCMS (ESI): *m/z* 539.45 $(M+H)^+$

(*R*)-4-(2-(1-Methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl) chromane-7-sulfonamide (13). Synthesized from perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61a)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.53 (d, J = 4.8 Hz, 2H), 7.85 – 7.72 (m, 2H), 7.52 (s, 1H), 7.45 – 7.34 (m, 2H), 7.28 (d, J = 8.2 Hz, 1H), 7.08 (t, J = 5.0 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.44 (s, 1H), 4.30 – 4.19 (m, 1H), 4.19 – 4.03 (m, 2H), 3.70 (s, 3H), 2.18 – 2.07 (m, 1H), 2.03 – 1.91 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.84, 157.38, 155.11, 149.09, 140.55, 139.44, 138.54, 131.99, 131.09, 130.62, 130.08, 128.13 (q, J_{C-F} = 32 Hz), 127.88 (q, J_{C-F} = 4 Hz), 126.85 (q, J_{C-F} = 4 Hz), 124.32 (q, J_{C-F} = 273 Hz), 119.43, 116.29, 116.13, 107.82, 65.00, 37.85, 37.26, 30.01. HRMS m/z calculated for $C_{24}H_{20}F_3N_5O_3S$ $[M+H]^+$: 516.1312, observed: 516.1311; $[\alpha]_D$: -88.98° (*c* 1.01, $CHCl_3$).

(*R*)-*N*-(5-Fluoropyrimidin-2-yl)-4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl) phenyl) chroman-7-sulfonamide (14). Synthesized from perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61a)** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.66 (s, 2H), 7.83 – 7.73 (m, 2H), 7.53 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 7.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.45 (s, 1H), 4.29 – 4.20 (m, 1H), 4.20 – 4.10 (m, 2H), 3.70 (s, 3H), 2.20 – 2.07 (m, 1H), 2.07 – 1.91 (m, 1H). LCMS (ESI): *m/z* 534.07 $(M+H)^+$

(*R*)-4-(2-(1-Methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-4-yl) chroman-7-sulfonamide (15). Synthesized from perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61a)** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.36 (s, 1H), 7.82 – 7.74 (m, 2H), 7.53 (d, J = 1.9 Hz, 1H), 7.36 – 7.24 (m, 3H), 7.05 (d, J = 6.2 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.45 (s, 1H), 4.27 – 4.20 (m, 1H), 4.18 – 4.09 (m, 2H), 3.70 (s, 3H), 2.18 – 2.08 (m, 1H), 2.03 – 1.93 (m, 1H). LCMS (ESI): *m/z* 516.06 $(M+H)^+$

(*R*)-4-(2-(1-Methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-N-(pyridazin-3-yl) chromane-7-sulfonamide (16). Synthesized from perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-

(trifluoromethyl)phenyl)chromane-7-sulfonate **(61a)** and pyridazin-3-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.83 – 7.70 (m, 3H), 7.66 – 7.58 (m, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.23 (t, J = 3.6 Hz, 2H), 6.83 (d, J = 8.3 Hz, 1H), 6.46 (s, 1H), 4.22 (s, 1H), 4.11 (q, J = 10.8, 9.1 Hz, 2H), 3.70 (s, 3H), 2.19 – 2.06 (m, 1H), 1.99 – 1.91 (m, 1H). LCMS: *m/z* 516.19 $(M+H)^+$

(*R*)-4-(2-(1-Methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-N-(pyrazin-2-yl) chromane-7-sulfonamide (17). Synthesized from perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61a)** and pyrazin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 12%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.33 (s, 1H), 8.22 (q, J = 2.8 Hz, 2H), 7.81 – 7.73 (m, 2H), 7.52 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.27 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.43 (s, 1H), 4.23 (dt, J = 9.6, 4.2 Hz, 1H), 4.18 – 4.11 (m, 2H), 3.69 (s, 3H), 2.17 – 2.08 (m, 1H), 2.00 – 1.92 (m, 1H). LCMS: *m/z* 516.04 $(M+H)^+$

(*R*)-*N*-(6-Fluoropyridin-2-yl)-4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl) phenyl) chroman-7-sulfonamide (18). Synthesized from perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61a)** and 6-fluoropyridin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 7.87 (q, J = 8.5 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.52 (s, 1H), 7.40 – 7.31 (m, 2H), 7.27 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.42 (s, 1H), 4.29 – 4.20 (m, 1H), 4.20 – 4.08 (m, 2H), 3.69 (s, 3H), 2.20 – 2.07 (m, 1H), 2.04 – 1.91 (m, 1H). LCMS (ESI): *m/z* 533.07 $(M+H)^+$

(*R*)-*N*-(5-Fluoropyridin-2-yl)-4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl) chroman-7-sulfonamide (19). Synthesized from perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61a)** and 5-fluoropyridin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 8.21 (d, J = 3.0 Hz, 1H), 7.82 – 7.73 (m, 2H), 7.68 (dt, J = 8.6, 5.1 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.32 – 7.23 (m, 3H), 7.13 (dd, J = 9.2, 3.8 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.42 (s, 1H), 4.30 – 4.19 (m, 1H), 4.19 – 4.09 (m, 2H), 3.69 (s, 3H), 2.19 – 2.07 (m, 1H), 2.03 – 1.91 (m, 1H). LCMS (ESI): *m/z* 533.06 $(M+H)^+$

(*R*)-*N*-(4-Fluoropyridin-2-yl)-4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl) chroman-7-sulfonamide (20). Synthesized from perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61a)** and 4-fluoropyridin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (dd, J = 8.8, 6.3 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.53 (d, J = 1.8 Hz, 1H), 7.30 – 7.22 (m, 3H), 6.86 – 6.77 (m, 2H), 6.74 (s, 1H), 6.44 (s, 1H), 4.25 – 4.18 (m, 1H), 4.16 – 4.08 (m, 2H), 3.69 (s, 3H), 2.11 (dd, J = 12.6, 6.4 Hz, 1H), 1.98 – 1.90 (m, 1H). LCMS (ESI): *m/z* 533.07 $(M+H)^+$

(*R*)-4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)chroman-7-sulfonamide (21). Synthesized from perfluorophenyl 4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61c)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 10%). ^{1}H NMR (400 MHz, DMSO-d_6) 8.54 (d, J = 4.9 Hz, 2H), 8.43 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 8.3, 2.1 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.38 (dd, J = 8.1, 2.0 Hz, 1H), 7.14 (s, 1H), 7.12 – 7.04 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 4.91 (t, J = 6.6 Hz, 1H), 4.31 – 4.14 (m, 2H), 2.49 (s, 3H), 2.37 – 2.27 (m, 1H), 2.05 – 1.94 (m, 1H). LCMS (ESI): *m/z* 517.04 $(M+H)^+$

(*R*)-*N*-(5-Fluoropyrimidin-2-yl)-4-(2-(2-methyloxazol-4-yl)-4-(trifluoro methyl) phenyl) chroman-7-sulfonamide (22). Synthesized from perfluorophenyl 4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61c)** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.66 (s, 2H), 8.43 (s, 1H), 8.01 (s, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 1.9 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.14 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 4.91 (t, J = 6.7 Hz, 1H), 4.30 – 4.15 (m, 2H), 2.33 – 2.24 (m, 1H), 2.03 – 1.98 (m, 1H). LCMS (ESI): *m/z* 534.82 $(M+H)^+$

(*R*)-4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-4-yl)chroman-7-sulfonamide (23). Synthesized from perfluorophenyl 4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61c)** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.44 (s, 1H), 8.37 (s, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.35 (s, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.06 (s, 1H), 6.88 (d, J = 8.1 Hz, 1H), 4.90 (t, J = 6.8 Hz, 1H), 4.28 – 4.10 (m, 2H), 2.32 – 2.25 (m, 1H), 2.06 – 1.94 (m, 1H). LCMS (ESI): *m/z* 516.82 $(M+H)^+$

(*R*)-*N*-(6-Fluoropyridin-2-yl)-4-(2-(2-methyloxazol-4-yl)-4-(trifluoro methyl)phenyl) chroman-7-sulfonamide (24). Synthesized from perfluorophenyl 4-(2-(2-methyloxazol-4-yl)-4-

(trifluoromethyl)phenyl)chromane-7-sulfonate **(61c)** and 6-fluoropyridin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 11%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, J = 7.4 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.61 – 7.49 (m, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.31 (s, 2H), 7.05 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.64 (dd, J = 8.1, 2.3 Hz, 1H), 4.89 (t, J = 6.9 Hz, 1H), 4.33 – 4.19 (m, 2H), 2.55 (s, 3H), 2.38 – 2.27 (m, 1H), 2.14 – 2.05 (m, 1H). LCMS (ESI): *m/z* 534.07 $(M+H)^+$

(*R*)-4-(2-(1*H*-1,2,3-Triazol-1-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)chromane-7-sulfonamide (25). Synthesized from perfluorophenyl 4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61b)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.34 (s, 1H), 8.02 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.95 – 7.84 (m, 2H), 7.70 (dd, J = 9.6, 4.1 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 7.9 Hz, 1H), 4.26 – 4.17 (m, 1H), 4.11 (ddd, J = 11.4, 8.8, 2.7 Hz, 1H), 4.00 (t, J = 7.1 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.09 – 1.98 (m, 1H). LCMS: *m/z* 502.98 $(M+H)^+$

(*R*)-4-(2-(1*H*-1,2,3-Triazol-1-yl)-4-(trifluoromethyl)phenyl)-*N*-(5-fluoro pyrimidin-2-yl) chromane-7-sulfonamide (26). Synthesized from perfluorophenyl 4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61b)** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 21%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.67 (d, J = 5.8 Hz, 3H), 8.00 (d, J = 7.4 Hz, 2H), 7.91 (d, J = 8.3 Hz, 1H), 7.50 – 7.32 (m, 3H), 6.96 (d, J = 8.4 Hz, 1H), 4.30 – 4.20 (m, 1H), 4.13 (t, J = 10.2 Hz, 1H), 4.02 (t, J = 7.3 Hz, 1H), 2.25 – 2.14 (m, 1H), 2.13 – 1.99 (m, 1H). LCMS: *m/z* 520.98 $(M+H)^+$

(*R*)-4-(2-(1*H*-1,2,3-Triazol-1-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin -4-yl)chromane-7-sulfonamide (27). Synthesized from perfluorophenyl 4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61b)** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 11%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 – 8.58 (m, 2H), 8.30 (s, 1H), 7.97 (d, *J* = 11.7 Hz, 2H), 7.91 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.01 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.27 – 4.19 (m, 1H), 4.10 (t, *J* = 9.9 Hz, 1H), 3.99 (t, *J* = 7.4 Hz, 1H), 2.18 – 2.14 (m, 1H), 2.10 – 1.96 (m, 1H). LCMS: *m/z* 502.94 $(M+H)^+$

(*R*)-4-(2-(1*H*-1,2,3-Triazol-1-yl)-4-(trifluoromethyl)phenyl)-N-(6-fluoropyridin-2-yl) chromane-7-sulfonamide (28). Synthesized from perfluorophenyl 4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61b)** and 6-fluoropyridin-2-amine by following an

analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 17%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 8.66 (s, 1H), 7.99 (d, J = 4.2 Hz, 2H), 7.96 – 7.83 (m, 2H), 7.40 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 7.1 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H), 6.77 (dd, J = 8.1, 2.4 Hz, 1H), 4.32 – 4.20 (m, 1H), 4.13 (t, J = 10.0 Hz, 1H), 4.02 (t, J = 7.3 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.13 – 2.02 (m, 1H). LCMS: *m/z* 520.02 $(M+H)^+$

(*R*)-4-(2-(6-Fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)-*N*-(pyrimidin-2-yl)chromane-7-sulfonamide (29). Synthesized from perfluorophenyl 4-(2-(6-fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61e)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 8.52 (d, J = 4.9 Hz, 2H), 8.38 (d, J = 2.4 Hz, 1H), 8.23– 8.08 (m, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.69 (s, 1H), 7.41 – 7.29 (m, 3H), 7.24 (d, J = 8.3 Hz, 1H), 7.07 (t, J = 4.9 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 4.29 – 4.18 (m, 2H), 4.19 – 4.07 (m, 1H), 2.20 – 2.08 (m, 1H), 2.07 – 1.91 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.31, 161.96, 158.83, 157.42, 155.14, 147.76 (d, J_{C-F} = 15 Hz), 147.64, 143.23 (d, J_{C-F} = 8 Hz), 139.63 d, J_{C-F} = 179 Hz), 133.70 (d, J_{C-F} = 4 Hz), 131.26, 130.42 (d, J_{C-F} = 4 Hz), 127.93 (q, J_{C-F} = 31 Hz), 127.45 (q, J_{C-F} = 4 Hz), 125.96 (q, J_{C-F} = 4 Hz), 124.44 (q, J_{C-F} = 272 Hz), 119.34, 116.27, 116.04, 109.88 (d, J_{C-F} = 40 Hz), 65.02, 37.30, 30.06. HRMS m/z calculated for $C_{25}H_{18}F_4N_4O_3S$ $[M+H]^+$: 531.1109, observed: 531.1108; $[\alpha]_D$: -97.88° (*c* 1.04, MeOH).

(*R*)-4-(2-(6-Fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)-*N*-(5-fluoropyrimidin-2-yl) chromane-7-sulfonamide (30). Synthesized from perfluorophenyl 4-(2-(6-fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61e)** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.65 (s, 2H), 8.38 (d, J = 2.4 Hz, 1H), 8.15 (td, J = 8.2, 2.5 Hz, 1H), 7.74 (dd, J = 8.3, 2.1 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.37 – 7.29 (m, 3H), 7.24 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 4.29 – 4.19 (m, 2H), 4.17 – 4.09 (m, 1H), 2.19 – 2.10 (m, 1H), 2.02 – 1.98 (m, 1H). LCMS: *m/z* 549.08 $(M+H)^+$

(*R*)-4-(2-(6-Fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-4-yl)chromane-7-sulfonamide (31). Synthesized from perfluorophenyl 4-(2-(6-fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61e)** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 17%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.38 (d, J = 2.5 Hz, 2H), 8.15 (td, J = 8.3, 2.6 Hz, 1H), 7.73 (dd, J = 8.3, 2.1 Hz, 1H), 7.69 (s, 1H), 7.40 – 7.21 (m,

4H), 7.08 (brs, 1H), 6.96 (d, J = 8.3 Hz, 1H), 4.23 (q, J = 6.6, 5.8 Hz, 2H), 4.13 (t, J = 10.0 Hz, 1H), 2.18 – 2.08 (m, 1H), 2.04 – 1.90 (m, 1H). LCMS: *m/z* 530.82 $(M+H)^+$

(*R*)-4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)chromane-7-sulfonamide (32). Synthesized from perfluorophenyl (R)-4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61n)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** (yield = 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.59 – 8.46 (m, 3H), 7.82 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.62 (s, 1H), 7.36 (d, J = 6.6 Hz, 3H), 7.23 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 4.7 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 4.32 – 4.18 (m, 2H), 4.11 (t, J = 10.4 Hz, 1H), 2.22 – 2.08 (m, 1H), 2.08 – 1.95 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.84, 157.86, 157.38, 155.11, 148.66, 147.44, 140.47, 139.93, 137.51, 132.53, 131.20, 130.51, 130.40, 127.94 (q, J_{C-F} = 32 Hz), 127.26 (q, J_{C-F} = 4 Hz), 125.66 (q, J_{C-F} = 4 Hz), 124.46 (q, J_{C-F} = 274 Hz), 123.40, 119.39, 116.30, 116.05, 65.09, 37.33, 30.12, 24.13. HRMS m/z calculated for $C_{26}H_{21}F_3N_4O_3S$ $[M+H]^+$: 527.1359, observed: 527.1356; $[\alpha]_D$: -89.90° (*c* 0.51, MeOH).

(*R*)-N-(5-fluoropyrimidin-2-yl)-4-(2-(6-methylpyridin-3-yl)-4-(trifluoro methyl)phenyl)chroman-7-sulfonamide (33). Synthesized from perfluorophenyl (R)-4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61n)** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** (yield = 26%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.65 (s, 2H), 8.58 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 6.3 Hz, 2H), 7.24 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H), 4.31 – 4.21 (m, 2H), 4.12 (t, J = 10.2 Hz, 1H), 2.55 (s, 3H), 2.21 – 2.10 (m, 1H), 2.07 – 1.98 (m, 1H). LCMS (ESI): *m/z* 545.09 $(M+H)^+$

(*R*)-4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-4-yl)chroman-7-sulfonamide (34). Synthesized from perfluorophenyl (R)-4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61n)** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** (yield = 9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.56 (s, 1H), 8.40 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.30 (s, 2H), 7.24 (d, J = 8.5 Hz, 1H), 7.18 – 7.03 (m, 1H), 7.00 – 6.87 (m, 1H), 4.34 – 4.17 (m, 2H), 4.18 – 4.06 (m, 1H), 2.21 – 2.08 (m, 1H), 2.08 – 1.95 (m, 1H). LCMS (ESI): *m/z* 527.04 $(M+H)^+$

(*R*)-N-(6-fluoropyridin-2-yl)-4-(2-(6-methylpyridin-3-yl)-4-trifluoromethyl)phenyl)chroman-7-sulfonamide (35). Synthesized from perfluorophenyl (R)-4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61n)** and 6-fluoropyridin-2-amine by following an

analogous procedure described for **1a** & **1b** (yield = 22%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.55 (d, J = 2.3 Hz, 1H), 7.90 – 7.77 (m, 2H), 7.70 (dd, J = 8.4, 1.9 Hz, 1H), 7.62 (s, 1H), 7.40 – 7.27 (m, 3H), 7.22 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.1 Hz, 1H), 4.32 – 4.19 (m, 2H), 4.12 (t, J = 10.2 Hz, 1H), 2.16 – 2.10 (m, 1H), 2.05 – 1.99 (m, 1H). LCMS (ESI): *m/z* 544.03 $(M+H)^+$

(*R*)-4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)chroman-7-sulfonamide (36). Synthesized from perfluorophenyl 4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61f)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 31%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 8.69 (d, J = 2.9 Hz, 1H), 8.53 (d, J = 4.9 Hz, 2H), 7.89 (td, J = 8.7, 3.0 Hz, 1H), 7.79 (dd, J = 8.7, 4.5 Hz, 1H), 7.73 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 7.0 Hz, 2H), 7.24 (d, J = 8.1 Hz, 1H), 7.07 (t, J = 4.9 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 4.57 (dd, J = 8.8, 6.1 Hz, 1H), 4.25 (dt, J = 11.4, 4.1 Hz, 1H), 4.16 – 4.09 (m, 1H), 2.21 – 2.15 (m, 1H), 2.11 – 2.03 (m, 1H). LCMS (ESI): *m/z* 531.02 $(M+H)^+$

(*R*)-4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)-N-(5-fluoropyrimidin-2-yl)chroman-7-sulfonamide (37). Synthesized from perfluorophenyl 4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61f)** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.69 (d, J = 2.8 Hz, 1H), 8.61 (s, 2H), 7.89 (dd, J = 10.2, 7.4 Hz, 1H), 7.85 – 7.70 (m, 3H), 7.33 (d, J = 7.4 Hz, 2H), 7.24 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 4.56 (t, J = 7.6 Hz, 1H), 4.32 – 4.21 (m, 1H), 4.11 (t, J = 10.1 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.13 – 1.99 (m, 1H). LCMS (ESI): *m/z* 548.70 $(M+H)^+$

(*R*)-4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-4-yl)chroman-7-sulfonamide (38). Synthesized from perfluorophenyl 4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61f)** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 14%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.52 (s, 1H), 8.70 (d, J = 2.9 Hz, 1H), 8.30 (s, 1H), 7.97 – 7.86 (m, 2H), 7.79 (dd, J = 8.7, 4.5 Hz, 1H), 7.77 – 7.66 (m, 3H), 7.34 – 7.19 (m, 3H), 6.87 (d, J = 7.9 Hz, 1H), 4.59 – 4.53 (m, 1H), 4.27 – 4.21 (m, 1H), 4.10 (t, J = 10.3 Hz, 1H), 2.23 – 2.14 (m, 1H), 2.08 – 2.02 (m, 1H). LCMS (ESI): *m/z* = 531.22 $(M+H)^+$

(*R*)-4-(4'-Fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-N-(pyrimidin-2-yl)chromane-7-sulfonamide (39). Synthesized from perfluorophenyl 4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)chromane-7-sulfonate **(61g)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b**

followed by separation of the enantiomer (yield = 40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.53 (d, J = 4.9 Hz, 2H), 7.68 (dd, J = 8.3, 2.1 Hz, 1H), 7.61 – 7.49 (m, 3H), 7.41 – 7.29 (m, 4H), 7.21 (d, J = 8.2 Hz, 1H), 7.08 (t, J = 5.0 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 4.34 – 4.19 (m, 2H), 4.16 – 4.06 (m, 1H), 2.15 – 2.08 (m, 1H), 2.05 – 1.98 (m, 1H). LCMS: *m/z* 530.19 $(M+H)^+$

(*R*)-4-(4'-Fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-N-(5-fluoropyrimidin-2-yl) chromane-7-sulfonamide (40). Synthesized from perfluorophenyl 4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)chromane-7-sulfonate **(61g)** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.65 (s, 2H), 7.69 (d, J = 8.3 Hz, 1H), 7.61 – 7.47 (m, 3H), 7.43 – 7.28 (m, 4H), 7.21 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 4.35 – 4.21 (m, 2H), 4.10 (t, J = 9.9 Hz, 1H), 2.13 – 2.06 (m, 1H), 2.06 – 1.97 (m, 1H). LCMS: *m/z* 547.99 $(M+H)^+$

(*R*)-4-(4'-Fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-N-(pyrimidin-4-yl)chromane-7-sulfonamide (41). Synthesized from perfluorophenyl 4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)chromane-7-sulfonate **(61g)** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 21%). ^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (s, 1H), 8.37 (s, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.62 – 7.48 (m, 3H), 7.43 – 7.26 (m, 4H), 7.22 (d, J = 8.3 Hz, 1H), 7.05 (s, 1H), 6.92 (d, J = 8.3 Hz, 1H), 4.35 – 4.17 (m, 2H), 4.11 (d, J = 9.6 Hz, 1H), 2.13 – 2.06 (m, 1H), 2.08 – 1.94 (m, 1H). LCMS: *m/z* 529.97 $(M+H)^+$

(*R*)-4-(4'-Fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-N-(6-fluoropyridin-2-yl) chromane-7-sulfonamide (42). Synthesized from perfluorophenyl 4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)chromane-7-sulfonate **(61g)** and 6-fluoropyridin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 15%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.38 (s, 1H), 7.87 (q, J = 8.2 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 7.53 (dd, J = 8.3, 5.3 Hz, 2H), 7.32 (d, J = 8.6 Hz, 4H), 7.20 (d, J = 8.2 Hz, 1H), 7.02 – 6.92 (m, 2H), 6.76 (dd, J = 8.1, 2.4 Hz, 1H), 4.35 – 4.19 (m, 2H), 4.10 (t, J = 10.1 Hz, 1H), 2.15 – 2.07 (m, 1H), 2.07 – 1.96 (m, 1H). LCMS: *m/z* 547.00 $(M+H)^+$

(*R*)-4-(2-morpholino-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)chroman-7-sulfonamide (43) Synthesized from perfluorophenyl 4-(2-morpholino-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61m)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.54 (d, J = 4.9 Hz, 2H), 7.58 (d, J = 1.9 Hz, 1H), 7.43 (dd, J = 8.2, 1.9 Hz, 1H), 7.40 (d, J = 1.9 Hz, 1H), 7.36 (dd, J = 8.1, 2.0

Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 7.08 (t, J = 4.9 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 4.79 (t, J = 7.6 Hz, 1H), 4.39 – 4.10 (m, 2H), 3.78 – 3.48 (m, 4H), 3.04 – 2.89 (m, 2H), 2.89 – 2.71 (m, 2H), 2.30 – 2.17 (m, 1H), 2.17 – 2.05 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.85, 157.40, 155.25, 152.65, 145.75, 140.07, 131.27, 131.19, 130.82, 128.94 (q, J_{C-F} = 31 Hz), 124.52 (q, J_{C-F} = 273 Hz), 122.05 (q, J_{C-F} = 4 Hz), 119.39, 118.96 (q, J_{C-F} = 4 Hz), 116.32, 115.99, 66.97, 65.57, 53.58, 35.68, 29.90. HRMS m/z calculated for $C_{24}H_{23}F_3N_4O_4S$ $[M+H]^+$: 521.1465, observed: 521.1464; $[\alpha]_D$: -46.27° (*c* 1.01, $CHCl_3$).

(*R*)-N-(5-fluoropyrimidin-2-yl)-4-(2-morpholino-4-(trifluoromethyl)phenyl) chroman-7-sulfonamide (44). Synthesized from perfluorophenyl (*R*)-4-(2-morpholino-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **[61m(*R*)]** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** (yield = 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.66 (s, 2H), 7.58 (s, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.80 (d, J = 7.7 Hz, 1H), 4.28 (t, J = 5.0 Hz, 2H), 3.75 – 3.54 (m, 4H), 3.05 – 2.91 (m, 2H), 2.91 – 2.73 (m, 2H), 2.30 – 2.17 (m, 1H), 2.17 – 2.05 (m, 1H). LCMS (ESI): *m/z* 539.07$(M+H)^+$

(*R*)-4-(2-morpholino-4-(trifluoromethyl)phenyl)-N-(pyrimidin-4-yl) chroman-7-sulfonamide (45). Synthesized from perfluorophenyl (*R*)-4-(2-morpholino-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **[61m(*R*)]** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** (yield = 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.37 (s, 1H), 7.58 (d, J = 1.8 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.09 – 7.02 (m, 1H), 6.79 (d, J = 8.1 Hz, 1H), 4.79 (t, J = 7.5 Hz, 1H), 4.28 (t, J = 5.2 Hz, 2H), 3.75 – 3.56 (m, 4H), 3.02 – 2.91 (m, 2H), 2.89 – 2.75 (m, 2H), 2.27 – 2.18 (m, 1H), 2.16 – 2.05 (m, 1H). LCMS (ESI): *m/z* 521.06 $(M+H)^+$

(*R*)-N-(6-fluoropyridin-2-yl)-4-(2-morpholino-4-(trifluoromethyl)phenyl) chroman-7-sulfonamide (46). Synthesized from perfluorophenyl (*R*)-4-(2-morpholino-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **[61m(*R*)]** and 6-fluoropyridin-2-amine by following an analogous procedure described for **1a** & **1b** (yield = 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), 7.87 (q, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 1.9 Hz, 1H), 7.31 (dd, J = 8.2, 2.0 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 6.98 (dd, J = 7.9, 2.1 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.77 (dd, J = 8.0, 2.4 Hz, 1H), 4.78 (t, J = 7.4 Hz, 1H), 4.41 – 4.20 (m, 2H), 3.80 – 3.50 (m, 4H), 3.02 – 2.88 (m, 2H), 2.88 – 2.73 (m, 2H), 2.28 – 2.18 (m, 1H), 2.18 – 2.07 (m, 1H). LCMS (ESI): *m/z* 538.06 $(M+H)^+$

(*R*)-4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)chroman-7-sulfonamide (47). Synthesized from perfluorophenyl 4-(2-(1,1-dioxidothiomorpholino)-4-

(trifluoromethyl)phenyl)chromane-7-sulfonate **(61j)** and pyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** followed by separation of the enantiomer (yield = 38%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.54 (d, J = 4.9 Hz, 2H), 7.71 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 1.9 Hz, 1H), 7.35 (dd, J = 8.1, 2.0 Hz, 1H), 7.13 – 7.04 (m, 2H), 6.85 (d, J = 8.2 Hz, 1H), 4.89 – 4.78 (m, 1H), 4.34 (t, J = 10.1 Hz, 1H), 4.30 – 4.20 (m, 1H), 3.44 – 3.37 (m, 4H), 3.35 – 3.22 (m, 4H), 2.33 – 2.23 (m, 1H), 2.11 – 2.01 (m, 1H). LCMS (ESI): *m/z* 569.07 $(M+H)^+$

(*R*)-4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)-N-(5-fluoropyrimidin-2-yl)chroman-7-sulfonamide (48). Synthesized from perfluorophenyl (*R*)-4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **[61j(*R*)]** and 5-fluoropyrimidin-2-amine by following an analogous procedure described for **1a** & **1b** (yield = 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.66 (s, 2H), 7.72 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 1.9 Hz, 1H), 7.34 (dd, J = 8.1, 2.0 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.90 – 4.79 (m, 1H), 4.34 (t, J = 9.9 Hz, 1H), 4.31 – 4.22 (m, 1H), 3.51 – 3.35 (m, 4H), 3.33 – 3.17 (m, 4H), 2.32 – 2.21 (m, 1H), 2.09 – 2.00 (m, 1H). LCMS (ESI): *m/z* 586.83 $(M+H)^+$

(*R*)-4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-4-yl)chromane-7-sulfonamide (49). Synthesized from perfluorophenyl (*R*)-4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **[61j(*R*)]** and pyrimidin-4-amine by following an analogous procedure described for **1a** & **1b** (yield = 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.41 (s, 1H), 7.72 (s, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.41 – 7.25 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.1 Hz, 1H), 4.90 – 4.78 (m, 1H), 4.34 (t, J = 9.5 Hz, 1H), 4.29 – 4.19 (m, 1H), 3.54 – 3.35 (m, 4H), 3.32 – 3.17 (m, 4H), 2.32 – 2.19 (m, 1H), 2.14 – 2.01 (m, 1H). LCMS (ESI): *m/z* 568.95 $(M+H)^+$

(*R*)-4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)-N-(6-fluoropyridin-2-yl)chroman-7-sulfonamide (50). Synthesized from perfluorophenyl (*R*)-4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **[61j(*R*)]** and 6-fluoropyridin-2-amine by following an analogous procedure described for **1a** & **1b** (yield = 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 7.87 (q, J = 8.2 Hz, 1H), 7.71 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 8.2, 2.0 Hz, 1H), 7.08 (s, 1H), 6.98 (dd, J = 8.0, 2.1 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.77 (dd, J = 8.0, 2.4 Hz, 1H), 4.90 – 4.79 (m, 1H), 4.39 – 4.21 (m, 2H), 3.50 – 3.21 (m, 8H), 2.33 – 2.21 (m, 1H), 2.11 – 2.00 (m, 1H). LCMS (ESI): *m/z* 585.95 $(M+H)^+$

(*S*)-1-(2-(1-Methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide (51).

***Step* 1: (*R* and *S*)-N-(2,4-dimethoxybenzyl)-1-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide:** To a nitrogen purged solution of the 1-(2-chloro-4-(trifluoromethyl)phenyl)-N-(2,4-dimethoxybenzyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide **(69)** (0.25 g, 0.41 mmol) in 10 mL 1,4-dioxane was added 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.086 g, 0.41 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.084 g, 0.10 mmol), $K_3PO_4.3H_2O$ (0.345 g, 1.24 mmol) and tritertbutylphosphin tetrafluoroborate (0.012 g, 0.1 mmol). The reaction mixture was heated at 120ºC for 2 h after which it was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, evaporated and purified by column chromatography to obtain the product as a colorless mass (Yield = 204 mg, 76 %). LCMS (ESI): *m/z* 650.37$(M+H)^+$

Step 2: (*S*)-1-(2-(1-Methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide: To a stirred solution of the product from Step-1 (0.19 g, 0.29 mmol) in DCM (5 ml) at 0-10 °C was added TFA (0.45 ml, 5.85 mmol) and stirred at 10 ºC for 30 min. The contents were evaporated completely and diluted with MeOH (2 ml). This was evaporated again up to dryness under reduced pressure. The pink colored residue was taken up in MeOH and filtered through a membrane filter to get a sticky mass. This was dissolved in EtOAc and pentane was added to get an off white solid precipitate followed by separation of the enantiomer. (Yield = 75 mg, 52 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 8.51 (d, J = 4.9 Hz, 2H), 7.89 (d, J = 1.8 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.73 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 1.9 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.09 – 7.00 (m, 2H), 6.43 (d, J = 1.9 Hz, 1H), 4.24 (t, J = 8.6 Hz, 1H), 3.67 (s, 3H), 3.13 – 3.02 (m, 1H), 3.02 – 2.86 (m, 1H), 2.49 – 2.43 (m, 1H), 2.09 – 1.96 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.81, 157.42, 151.54, 149.25, 149.24, 145.41, 139.81, 138.51, 131.84, 129.69, 127.89 (q, J_{C-F} = 32 Hz), 127.51 (q, J_{C-F} = 4 Hz), 127.00 (q, J_{C-F} = 4 Hz), 126.95, 125.08, 124.37 (q, J_{C-F} = 274 Hz), 123.92, 116.26, 107.93, 47.74, 37.18, 36.22, 31.53. HRMS m/z calculated for $C_{24}H_{20}F_3N_5O_2S$ $[M+H]^+$: 500.1363, observed: 500.1360; $[\alpha]_D$: -69.20^o (*c* 0.97, DCM).

(*S*)-1-(2-(6-Fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide (52). The title compound was prepared by following similar procedure as described for **51** (Step-1 & 2) using 1-(2-chloro-4-(trifluoromethyl)phenyl)-N-(2,4-dimethoxybenzyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide **(69)** and 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine followed by separation of the enantiomer (yield = 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72

(brs, 1H), 8.51 (d, J = 4.8 Hz, 2H), 8.34 (d, J = 2.5 Hz, 1H), 8.11 (td, J = 8.1, 2.5 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.75 (ddd, J = 12.9, 8.1, 1.9 Hz, 2H), 7.68 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 8.4, 2.7 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.13 – 7.02 (m, 2H), 4.35 (t, J = 8.7 Hz, 1H), 3.16 – 3.02 (m, 1H), 2.99 – 2.85 (m, 1H), 2.49 – 2.42 (m, 1H), 2.06 (dq, J = 12.6, 9.2 Hz, 1H). LCMS (ESI): *m/z* 514.99 $(M+H)^+$

(*S*)-1-(2-(6-Methylpyridin-3-yl)-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide (53). The title compound was prepared by following similar procedure as described for **51** (Step-1 & 2) using 1-(2-chloro-4-(trifluoromethyl)phenyl)-N-(2,4-dimethoxybenzyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide **(69)** and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine followed by separation of the enantiomer (yield = 27%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 8.53 (s, 1H), 8.49 (d, J = 4.7 Hz, 2H), 7.87 (s, 1H), 7.82 – 7.66 (m, 3H), 7.63 (s, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 7.5 Hz, 2H), 4.37 (t, J = 8.7 Hz, 1H), 3.15 – 3.03 (m, 1H), 2.99 – 2.86 (m, 1H), 2.15 – 2.00 (m, 1H). LCMS (ESI): *m/z* 511.25 $(M+H)^+$

(*S*)-1-(2-Morpholino-4-(trifluoromethyl)phenyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide (54). The title compound was prepared by following similar procedure as described for **1a** & **1b** using perfluorophenyl 1-(2-morpholino-4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-indene-5-sulfonate **(68b)** and pyrimidin-2-amine followed by separation of the enantiomer (yield = 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.52 (d, J = 4.9 Hz, 2H), 7.91 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.07 (t, J = 4.9 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 4.96 (t, J = 8.7 Hz, 1H), 3.77 – 3.57 (m, 4H), 3.20 – 3.11 (m, 1H), 3.06 (q, J = 8.2 Hz, 1H), 2.97 – 2.86 (m, 4H), 2.71 – 2.57 (m, 1H), 2.11 – 1.95 (m, 1H). LCMS (ESI): *m/z* 505.00 $(M+H)^+$

7-(Benzylthio)chroman-4-one (56). 7-bromochroman-4-one **(55)** (390 g, 1.72 mol) was dissolved in 1, 4-dioxane (4.5 L) and the solution was purged with nitrogen and $Pd_2(dba)_3$ (39.3 g, 0.043 mol), Hunig's Base (600 mL, 3.44 mol) and benzyl mercaptan (193 mL, 1.63 mol) was added. The reaction mixture was heated to 80 °C for 1 h. After completion of the reaction as indicated by TLC, the compound was extracted with ethyl acetate and washed with water. The ethyl acetate layer was then dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography to obtain the title compound as a pale yellow solid (279 g, 60%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.3 Hz, 1H), 7.49 – 7.23 (m, 5H), 6.90 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.85 – 6.75 (m, 1H), 4.52 (m, 2H), 4.20 (s, 2H), 2.78 (m, 2H).

***N*'-(7-(Benzylthio)chroman-4-ylidene)-4-methylbenzenesulfonohydrazide (57).** 7-(Benzylthio)chroman-4-one **(56)** (100 g, 0.37 mol) and 4-methylbenzenesulfonohydrazide (76 g, 0.41 mol) was added into 2.5L

MeOH and the mixture was heated at 70 °C for overnight. The reaction mixture was then cooled in an ice salt bath for 1 h and the precipitated pale yellow solid was filtered and washed with ethanol. The solid product was then triturated with hexane and dried under vacuum to obtain the title compound (153g, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.29 (m, 7H), 6.86 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 4.25 – 4.18 (m, 2H), 4.16 (s, 2H), 2.75 (t, *J* = 6.1 Hz, 2H), 2.44 (s, 3H). LCMS (ESI): *m/z* 439.09 $(M+H)^+$

Perfluorophenyl 4-oxochroman-7-sulfonate (62). To a suspension of 7-(benzylthio) chroman-4-one **(56)** (37 g, 137 mmol) in 200 mL acetic acid and 50 mL water was added *N*-chlorosuccinimide (54.8 g, 411 mmol) in two portions and stirred for 45 min. The reaction mixture was diluted with a mixture of ether and water and extracted with ether. The combined organic layer was washed with water followed by brine and dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The sulfonyl chloride intermediate was dissolved in DCM and slowly added into a stirred solution of 2,3,4,5,6-pentafluorophenol (35.3 g, 192 mmol) and triethylamine (114 ml, 821 mmol) in 200 mL DCM at 0 °C. After the completion of addition, the reaction mixture was stirred for 45 min and then quenched with water and extracted with DCM. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography to obtain the pentafluoroester as an off-white solid (35g, 65 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.65 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.70 (t, *J* = 6.5 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H).

Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate (63). Synthesized from Perfluorophenyl 4-oxochroman-7-sulfonate **(62)** by following an analogous procedure described for **57** (yield = 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.85 (d, 2H), 7.55 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 4.32 (t, *J* = 6.2 Hz, 2H), 2.82 (t, *J* = 6.2 Hz, 2H), 2.39 (s, 3H).

5-(2-(7-(Benzylthio)-2H-chromen-4-yl)-5-(trifluoromethyl)phenyl)-1-methyl-1H-pyrazole (59a). A mixture of 2.4 L 1,4-dioxane and 400 mL water was degassed for 30 min with N_2 after which 5-(2-bromo-5-(trifluoromethyl)phenyl)-1-methyl-1H-pyrazole **(58a)** (84 g, 0.275 mol), N'-(7-(Benzylthio)chroman-4-ylidene)-4-methylbenzenesulfonohydrazide **(57)** (121 g, 0.27 mol), sodium carbonate (73 g, 0.69 mol) and $PdCl_2$(dppf)-DCM adduct (22.48 g, 0.028 mol) were added and the reaction mixture was refluxed for 5 h. After completion of the reaction as indicated by TLC, the compound was extracted with ethyl acetate and washed with water. The ethyl acetate layer was then dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography to obtain title compound as an off white solid (100 g, 76%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 1.9 Hz,

1H), 7.36 – 7.30 (m, 4H), 7.28 (s, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.70 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 5.50 (t, *J* = 3.9 Hz, 1H), 4.71 (d, *J* = 3.9 Hz, 2H), 4.13 (s, 2H), 3.65 (s, 3H). LCMS (ESI): *m/z* 479.09 $(M+H)^+$

1-(2-(7-(benzylthio)-2H-chromen-4-yl)-5-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (59b). Synthesized from N'-(7-(Benzylthio)chroman-4-ylidene)-4-methylbenzenesulfonohydrazide **(57)** and 1-(2-Iodo-5-(trifluoromethyl)phenyl)-1H-1,2,3-triazole **(58b)** by following an analogous procedure described for **59a** (yield = 47%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (d, J = 1.8 Hz, 1H), 7.83 (dd, J = 8.1, 1.8 Hz, 1H), 7.70 (d, J = 1.1 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.34 (d, J = 4.3 Hz, 5H), 6.77 (d, J = 1.8 Hz, 1H), 6.64 (dd, J = 8.0, 1.9 Hz, 1H), 6.43 (d, J = 8.0 Hz, 1H), 5.72 (t, J = 3.9 Hz, 1H), 4.82 – 4.72 (m, 2H), 4.11 (s, 2H). LCMS (ESI): *m/z* 466.17 $(M+H)^+$

Perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60a). 5-(2-(7-(benzylthio)-2H-chromen-4-yl)-5-(trifluoromethyl)phenyl)-1-methyl-1H-pyrazole **(59a)** (100 g, 199 mmol) was dissolved in 1500 mL DCM and 45.5 mL acetic acid followed by 14.31 mL water and the solution was cooled to -5 °C and sulfuryl chloride (48.4 mL, 0.60 mol) was added drop wise. After the addition, the reaction was stirred for 1 h TLC showed formation of sulfonyl chloride. The reaction mixture was washed with water and the DCM layer was dried over Na_2SO_4 and concentrated. The crude sulfonyl chloride product was diluted with 500 mL of DCM and added slowly to a stirred solution of 2, 3, 4, 5, 6-pentafluorophenol (54.8 g, 0.30 mol) and triethylamine (138 ml, 0.99 mol) in DCM at -5 °C. The reaction mixture was stirred for 1 h after which it was washed with water and the DCM layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography to obtain title compound as a pale yellow solid (85g, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.31 (m, 3H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.13 (d, *J* = 1.9 Hz, 1H), 5.84 (t, *J* = 3.8 Hz, 1H), 4.92 (d, *J* = 3.8 Hz, 2H), 3.70 (s, 3H). LCMS (ESI): *m/z* 603.03 $(M+H)^+$

Perfluorophenyl 4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60b). Synthesized from 1-(2-(7-(benzylthio)-2H-chromen-4-yl)-5-(trifluoromethyl)phenyl)-1H-1,2,3-triazole **(59b)** by following an analogous procedure described for **60a** (yield = 60%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (d, J = 1.8 Hz, 1H), 7.91 (dd, J = 8.7, 1.7 Hz, 1H), 7.72 (d, J = 1.1 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.38 (d, J = 1.9 Hz, 1H), 7.31 (d, J = 1.9 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.05 (t, J = 3.8 Hz, 1H), 4.97 (d, J = 3.8 Hz, 2H). LCMS (ESI): *m/z* 589.83 $(M+H)^+$

Perfluorophenyl 4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60c). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 4-(2-Bromo-5-(trifluoromethyl)phenyl)-2-methyloxazole **(58c)** by following an analogous procedure described for **59a** (yield = 38%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.36 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.52 – 7.41 (m, 2H), 7.25 (dd, J = 8.1, 2.0 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.10 (t, J = 3.7 Hz, 1H), 5.10 (dd, J = 6.3, 3.7 Hz, 2H). LCMS (ESI): *m/z* 603.88 $(M+H)^+$

Perfluorophenyl 4-(2-(thiazol-2-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60d). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 2-(2-bromo-5-(trifluoromethyl)phenyl)thiazole **(58d)** by following an analogous procedure described for **59a** (yield = 44%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, J = 1.9 Hz, 1H), 7.84 (d, J = 3.2 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 3.2 Hz, 1H), 7.21 (dd, J = 8.1, 1.9 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.14 (t, J = 3.7 Hz, 1H), 5.12 (t, J = 4.1 Hz, 2H). LCMS (ESI): *m/z* 606.03 $(M+H)^+$

Perfluorophenyl 4-(2-(6-fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60e). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 5-(2-Bromo-5-(trifluoromethyl)phenyl)-2-fluoropyridine **(58e)** by following an analogous procedure described for **59a** (yield = 52%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 2.5 Hz, 1H), 7.80 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.76 – 7.66 (m, 2H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.32 (dd, *J* = 13.2, 1.9 Hz, 2H), 6.89 (dd, *J* = 8.5, 2.9 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 5.95 (t, *J* = 3.7 Hz, 1H), 4.98 – 4.92 (m, 2H). LCMS: *m/z* 618.03 $(M+H)^+$

5-fluoro-2-(2-(7-((perfluorophenoxy)sulfonyl)-2H-chromen-4-yl)-5-(trifluoromethyl)phenyl)pyridine 1-oxide (60f). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 2-(2-bromo-5-(trifluoromethyl)phenyl)-5-fluoropyridine 1-oxide **(58f)** by following an analogous procedure described for **59a** (yield = 59%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (s, 1H), 7.83 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 7.9 Hz, 1H), 7.44 – 7.33 (m, 3H), 7.04 (dd, J = 12.2, 4.8 Hz, 2H), 5.97 (s, 1H), 5.02 – 4.77 (m, 2H). LCMS: *m/z* 634.01 $(M+H)^+$

Perfluorophenyl 4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2H-chromene-7-sulfonate (60g). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 4'-Fluoro-2-iodo-5-(trifluoromethyl)-1,1'-biphenyl **(58g)** by following an analogous procedure described for **59a** (yield = 52%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, J = 9.7 Hz, 2H), 7.49 (d, J = 7.9 Hz, 1H), 7.38 – 7.21 (m, 4H), 7.00 (t, J = 8.4 Hz, 2H), 6.77 (d, J = 8.1 Hz, 1H), 5.92 (t, J = 3.8 Hz, 1H), 4.92 (brs, 2H).

Perfluorophenyl 4-(2-(3-oxomorpholino)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60h). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 4-(2-Bromo-5-(trifluoromethyl)phenyl)morpholin-3-one **(58h)** by following an analogous procedure described for **59a** (yield = 42%). LCMS: *m/z* 621.71 $(M+H)^+$

Perfluorophenyl 4-(2-(2-oxooxazolidin-3-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60i). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 3-(2-iodo-5-(trifluoromethyl)phenyl)oxazolidin-2-one **(58i)** by following an analogous procedure described for **59a** (yield = 41%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.42 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.16 (t, J = 3.8 Hz, 1H), 5.17 – 4.98 (m, 2H), 4.34 – 4.16 (m, 2H), 3.98 – 3.85 (m, 1H), 3.78 – 3.61 (m, 1H). LCMS (ESI): *m/z* 630.01 $(M+Na)^+$

Perfluorophenyl 4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60j). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 4-(2-bromo-5-(trifluoromethyl)phenyl)thiomorpholine 1,1-dioxide **(58j)** by following an analogous procedure described for **59a** (yield = 32%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.49 (m, 2H), 7.50 – 7.38 (m, 3H), 6.81 (d, J = 8.2 Hz, 1H), 6.15 (t, J = 3.7 Hz, 1H), 5.12 – 4.92 (m, 2H), 3.96 – 3.85 (m, 1H), 3.67 – 3.56 (m, 2H), 3.44 – 3.29 (m, 2H), 3.22 – 3.12 (m, 1H), 2.88 – 2.72 (m, 2H). LCMS (ESI): *m/z* 656.05 $(M+H)^+$

tert-butyl 4-(2-(7-((perfluorophenoxy)sulfonyl)-2H-chromen-4-yl)-5-(trifluoromethyl)phenyl)piperazine-1-carboxylate (60k). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and tert-butyl 4-(2-bromo-5-(trifluoromethyl)phenyl)piperazine-1-carboxylate **(58k)** by following an analogous procedure described for **59a** (yield = 43%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (d, J = 1.9 Hz, 1H), 7.45 – 7.36 (m, 3H), 7.28 – 7.27 (m, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.15 (t, J = 3.8 Hz, 1H), 5.01 (dd, J = 15.6, 3.8 Hz, 2H), 3.25 – 3.03 (m, 6H), 2.84 – 2.62 (m, 2H), 1.44 (s, 9H). LCMS (ESI): *m/z* 729.20 $(M+Na)^+$

Perfluorophenyl 4-(2-chloro-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60l). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 1-bromo-2-chloro-4-(trifluoromethyl)benzene **(58l)** by following an analogous procedure described for **59a** (yield = 61%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.76 (bs, 1H), 7.66 (dd, J = 7.9, 1.8 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.38 (dd, J = 8.1, 1.9 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.02 (t, J = 3.7 Hz, 1H), 5.12 (dd, J = 13.6, 3.7 Hz, 2H), 1.34 – 1.19 (m, 1H).

Perfluorophenyl 4-(2-morpholino-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate (60m). Synthesized from Perfluorophenyl 4-(2-tosylhydrazono)chroman-7-sulfonate **(63)** and 4-(2-bromo-5-(trifluoromethyl)phenyl)morpholine **(58m)** by following an analogous procedure described for **59a** (yield = 44%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, J = 1.9 Hz, 1H), 7.45 – 7.36 (m, 3H), 6.88 (d, J = 8.2 Hz,1H), 6.16 (t, J = 3.8 Hz, 1H), 5.00 (m, 2H), 3.40 (m, 4H), 3.17 (bs, 2H), 2.79 (bs, 2H). LCMS(ESI): *m/z* 607.99 $(M+H)^+$

Perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61a). perfluorophenyl 4-(2-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60a)** (85g, 0.141mol) was dissolved in 1 L degassed ethyl acetate. The solution was put in a Parr shaker and 10% Pd-C (67.6 g, 0.0635 mol) was added and the mixture was hydrogenated at 50 psi for 4 h. After completion of reaction, the mixture was filtered through a pad of celite and the pad was washed with ethyl acetate. The filtrate was concentrated and the crude was purified by column chromatography to obtain the product as a pale yellow solid (80 g, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.63 (dd, *J* = 5.1, 1.9 Hz, 2H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.96 – 6.88 (m, 1H), 6.36 (d, *J* = 1.9 Hz, 1H), 4.39 – 4.30 (m, 1H), 4.27 (t, *J* = 7.5 Hz, 1H), 4.21 – 4.16 (m, 1H), 3.81 (s, 3H), 2.24 – 2.14 (m, 1H), 2.07 – 1.98 (m, 1H). LCMS (ESI): *m/z* 604.08 $(M+H)^+$

Perfluorophenyl 4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl) phenyl) chromane-7-sulfonate (61b). Synthesized from perfluorophenyl 4-(2-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60b)** by following an analogous procedure described for **61a** (yield = 83%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 15.9 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.68 (s, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 4.40 – 4.25 (m, 2H), 4.25 – 4.17 (m, 1H), 2.50 – 2.37 (m, 1H), 2.23 – 2.09 (m, 1H). LCMS: *m/z* 592.20 $(M+H)^+$

Perfluorophenyl 4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61c). Synthesized from Perfluorophenyl 4-(2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60c)** by following an analogous procedure described for **61a** (yield = 76%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (s, 1H), 7.77 (s, 1H), 7.55 (dd, J = 8.3, 2.0 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.36 (dd, J = 8.2, 2.0 Hz, 1H), 7.09 – 7.00 (m, 2H), 5.02 (t, J = 6.8 Hz, 1H), 4.37 – 4.22 (m, 2H), 2.57 (s, 3H), 2.47 – 2.37 (m, 1H), 2.22 – 2.09 (m, 1H). LCMS (ESI): *m/z* 605.91 $(M+H)^+$

Perfluorophenyl 4-(2-(thiazol-2-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61d). Synthesized from 4-(2-(thiazol-2-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60d)** by following an

analogous procedure described for **61a** (yield = 52%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, J = 3.3 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.63 (dd, J = 8.3, 1.9 Hz, 1H), 7.55 (d, J = 3.3 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 5.39 – 5.24 (m, 1H), 4.39 – 4.31 (m, 1H), 4.33 – 4.22 (m, 1H), 2.57 – 2.42 (m, 1H), 2.27 – 2.11 (m, 1H). LCMS (ESI): *m/z* 608.00 $(M+H)^+$

Perfluorophenyl 4-(2-(6-fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61e). Synthesized from perfluorophenyl 4-(2-(6-fluoropyridin-3-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60e)** by following an analogous procedure described for **61a** (yield = 74%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 2.5 Hz, 1H), 7.85 (td, *J* = 7.9, 2.5 Hz, 1H), 7.66 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.18 – 7.09 (m, 2H), 6.94 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.42 – 4.28 (m, 2H), 4.20 – 4.10 (m, 1H), 2.25 – 2.07 (m, 2H). LCMS (ESI): *m/z* 620.02 $(M+H)^+$

Perfluorophenyl 4-(2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61f). Synthesized from 5-fluoro-2-(2-(7-((perfluorophenoxy)sulfonyl)-2H-chromen-4-yl)-5-(trifluoromethyl)phenyl)pyridine 1-oxide **(60f)** by following an analogous procedure described for **61a** (yield = 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 2.5 Hz, 1H), 7.85 (td, *J* = 7.9, 2.5 Hz, 1H), 7.66 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.18 – 7.09 (m, 2H), 6.94 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.42 – 4.28 (m, 2H), 4.20 – 4.10 (m, 1H), 2.25 – 2.07 (m, 2H). LCMS: *m/z* 620.10 $(M+H)^+$

Perfluorophenyl 4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)chromane-7-sulfonate (61g). Synthesized from perfluorophenyl 4-(4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2H-chromene-7-sulfonate **(60g)** by following an analogous procedure described for **61a** (yield = 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.55 (m, 2H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.39 – 7.34 (m, 3H), 7.21 (t, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 4.45 – 4.40 (m, 1H), 4.39 – 4.31 (m, 1H), 4.18 – 4.14 (m, 1H), 2.20 – 2.07 (m, 2H).

Perfluorophenyl (R)-4-(2-(3-oxomorpholino)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61h). Synthesized from perfluorophenyl perfluorophenyl 4-(2-(3-oxomorpholino)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60h)** by following an analogous procedure described for **61a** (yield = 85%). LCMS (ESI): *m/z* 624.06$(M+H)^+$. The required enantiomer was separated by chiral preparative HPLC.

Perfluorophenyl 4-(2-(2-oxooxazolidin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61i). Synthesized from perfluorophenyl 4-(2-(2-oxooxazolidin-3-yl)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60i)** by following an analogous procedure described for **61a** (yield = 75%). ^{1}H NMR (400 MHz,

DMSO-d_6) δ 8.04 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 4.75 (t, J = 7.4 Hz, 1H), 4.54 (t, J = 8.2 Hz, 2H), 4.34 (t, J = 5.2 Hz, 2H), 4.14 (q, J = 7.9 Hz, 1H), 4.03 (p, J = 7.7, 6.5 Hz, 1H), 2.38 – 2.29 (m, 1H), 2.13 – 2.02 (m, 1H). LCMS (ESI): *m/z* 610.10$(M+H)^+$

Perfluorophenyl 4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61j). Synthesized from perfluorophenyl 4-(2-(1,1-dioxidothiomorpholino)-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60j)** by following an analogous procedure described for **61a** (yield = 84%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 (s, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.37 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.77 (d, *J* = 7.6 Hz, 1H), 4.46 – 4.26 (m, 2H), 3.65 – 3.34 (m, 4H), 3.31 – 3.08 (m, 4H), 2.41 – 2.12 (m, 2H). LCMS (ESI): *m/z* 657.84 $(M+H)^+$. The *R* enantiomer **[61j(R)]** was separated from the racemic compound by chiral preparative HPLC.

Tert-butyl 4-(2-(7-((perfluorophenoxy)sulfonyl)chroman-4-yl)-5-(trifluoromethyl)phenyl)piperazine-1-carboxylate (61k). Synthesized from tert-butyl 4-(2-(7-((perfluorophenoxy)sulfonyl)-2H-chromen-4-yl)-5-(trifluoromethyl)phenyl)piperazine-1-carboxylate **(60k)** by following an analogous procedure described for **61a** (yield = 81%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, J = 9.5 Hz, 2H), 7.37 (dd, J = 14.3, 8.1 Hz, 2H), 7.01 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 4.91 (s, 1H), 4.33 (dd, J = 20.5, 11.2 Hz, 2H), 3.87 – 3.37 (m, 4H), 3.14 – 2.96 (m, 2H), 2.96 – 2.80 (m, 2H), 2.42 – 2.29 (m, 1H), 2.29 – 2.11 (m, 1H), 1.51 (s, 9H). LCMS (ESI): *m/z* 709.23 $(M+H)^+$.

Perfluorophenyl (S)-4-(2-chloro-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61l). Synthesized from perfluorophenyl 4-(2-chloro-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60l)** by following an analogous procedure described for **61a** (yield = 50%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.74 (m, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.48 (dt, *J* = 8.1, 1.2 Hz, 1H), 7.42 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.06 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 4.82 (t, *J* = 6.1 Hz, 1H), 4.37 – 4.20 (m, 2H), 2.49 – 2.38 (m, 1H), 2.25 – 2.14 (m, 1H). LCMS (ESI): *m/z* 580.95 $(M+Na)^+$. The enantiomers were separated using chiral preparative HPLC.

Perfluorophenyl 4-(2-morpholino-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61m). Synthesized from perfluorophenyl 4-(2-morpholino-4-(trifluoromethyl)phenyl)-2H-chromene-7-sulfonate **(60m)** by following an analogous procedure described for **61a** (yield = 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (t, J = 2.2 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 8.2, 2.0 Hz, 1H), 7.01(d, J = 8.2 Hz, 1H), 6.88 (dd, J = 8.2, 1.0 Hz, 1H), 4.91 (t, J = 7.3 Hz, 1H), 4.43 – 4.27 (m, 2H), 3.90 (q, J = 7.2, 6.5 Hz, 4H), 3.14 – 3.01

(m, 2H), 2.92 (s, 2H), 2.34 (m, 1H), 2.19 (m, 1H). LCMS (ESI): *m/z* 610.0(M+H)$^+$. The *R* enantiomer [61m(R)] was separated from the racemic compound by chiral preparative HPLC.

Perfluorophenyl (R)-4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)phenyl)chromane-7-sulfonate (61n). A stirred suspension of Perfluorophenyl (S)-4-(2-chloro-4-(trifluoromethyl)phenyl)chromane-7-sulfonate **(61l)** (0.70 g, 1.16 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.64 g, 2.90 mmol) and Na_2CO_3 (0.25 g, 2.32 mmol) in a solvent mixture of 10 mL 1,4-dioxane and 1.0 mL water was degassed for 15 min using nitrogen then $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.095 g, 0.12 mmol) was added and heated at 100°C for 2 h. After completion of reaction as indicated by TLC, the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layer was washed with water, followed by brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography to obtain the title compound (0.65 g, 91%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (d, J = 2.3 Hz, 1H), 7.63 (m, 2H), 7.58 (d, J = 1.9 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.12 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 8.2Hz, 1H), 4.44 – 4.29 (m, 2H), 4.19 – 4.14 (m, 1H), 2.68 (s, 3H), 2.25 – 2.08 (m, 2H). LCMS (ESI): *m/z* 516.11 (M+H)$^+$

N'-(5-(benzylthio)-2,3-dihydro-1H-inden-1-ylidene)-4-methylbenzene sulfonohydrazide (65). Synthesized from 5-(benzylthio)-2,3-dihydro-1H-inden-1-one **(64)** [synthesized as described in Howbert et al., *Synth Commun*, 1990, 20 (20), 3193 – 3200] by following an analogous procedure described for **57** (yield = 90%). ^{1}H-NMR (400 MHz, DMSO-d_6), δ 10.31 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 2H), 7.43 – 7.34 (m, 5H), 7.33 – 7.27 (m, 3H), 7.26 – 7.19 (m, 2H), 4.28 (s, 2H), 2.99 – 2.92 (m, 2H), 2.76 – 2.67 (m, 2H), 2.37 (s, 3H). LCMS (ESI): *m/z* 423.01 (M+H)$^+$.

Benzyl(3-(2-chloro-4-(trifluoromethyl)phenyl)-1H-inden-6-yl)sulfane (66a). Synthesized from N'-(5-(benzylthio)-2,3-dihydro-1H-inden-1-ylidene)-4-methylbenzene sulfonohydrazide **(65)** and 1-bromo-2-chloro-4-(trifluoromethyl)benzene **(58l)** by following an analogous procedure described for **59a** (yield = 51%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (s, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.54 (s, 2H), 7.38 – 7.28 (m, 6H), 7.15 – 7.04 (m, 1H), 6.65 (d, J = 3.0 Hz, 1H), 4.17 (s, 2H), 3.58 (s, 2H). LCMS (ESI): m/z 417.18 (M+H)$^+$.

4-(2-(6-(Benzylthio)-1H-inden-3-yl)-5-(trifluoromethyl)phenyl)morpholine (66b). Synthesized from N'-(5-(benzylthio)-2,3-dihydro-1H-inden-1-ylidene)-4-methylbenzene sulfonohydrazide **(65)** and 4-(2-bromo-5-(trifluoromethyl)phenyl)morpholine **(58m)** by following an analogous procedure described for **59a** (yield = 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.1 Hz,

1H), 7.34 – 7.28 (m, 4H), 7.27 – 7.19 (m, 4H), 6.74 (d, *J* = 2.2 Hz, 1H), 4.23 (s, 2H), 3.34 (s, 2H), 3.29 (d, *J* = 5.2 Hz, 4H), 2.90 (t, *J* = 4.3 Hz, 4H). LCMS (ESI): *m/z* 468.03 $(M+H)^+$.

Perfluorophenyl 1-(2-chloro-4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-indene-5-sulfonate (67a). To a cold suspension (5 ºC) of Benzyl(3-(2-chloro-4-(trifluoromethyl)phenyl)-1H-inden-6-yl)sulfane **(66a)** (1 g, 1.9 mmol) in acetic acid (10 mL) and water (1 mL) was added NCS (0.73 g, 5.4 mmol) in two portions. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with DCM. The organic layer was washed with water, followed by brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness under vacuum. This crude sulfonyl chloride was taken in DCM (10 mL) and added into a stirred solution of 2,3,4,5,6-pentafluorophenol (0.54 g, 2.9 mmol) and triethylamine (1.9 mL, 13.6 mmol) in 10 mL DCM at 0 ºC. The reaction mixture was gradually warmed to room temperature and stirred for 45 min. The reaction mixture was quenched with water, followed by extraction with DCM. The organic layer was washed with brine, dried over Na_2SO_4 and purified by column chromatography to obtain a brown sticky mass (Yield = 700 mg, 55%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.10 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.23 (s, 1H), 3.96 – 3.83 (m, 2H). LCMS (ESI) : *m/z* 562.95 $(M+Na)^+$

Perfluorophenyl 3-(2-morpholino-4-(trifluoromethyl)phenyl)-1H-indene-6-sulfonate (67b). Synthesized from 4-(2-(6-(Benzylthio)-1H-inden-3-yl)-5-(trifluoromethyl)phenyl)morpholine **(66b)** by following an analogous procedure described for **67a** (yield = 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.18 (s, 1H), 3.81 (s, 2H), 3.26 (br s, 4H), 2.91 (br s, 4H). LCMS (ESI): *m/z* 592.03 $(M+H)^+$.

Perfluorophenyl 1-(2-chloro-4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-indene-5-sulfonate (68a). Synthesized from perfluorophenyl 1-(2-chloro-4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-indene-5-sulfonate **(67a)** by following an analogous procedure described for **61a** (yield = 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.96 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 5.02 (t, *J* = 8.3 Hz, 1H), 3.23 – 3.07 (m, 2H), 2.77 – 2.69 (m, 1H), 2.17 – 2.08 (m, 1H).

Perfluorophenyl 1-(2-morpholino-4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-indene-5-sulfonate (68b). Synthesized from perfluorophenyl 3-(2-morpholino-4-(trifluoromethyl)phenyl)-1H-indene-6-sulfonate **(67b)** by following an analogous procedure described for **61a** (yield = 87%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 7.5 Hz,

2H), 5.15 (t, *J* = 8.9 Hz, 1H), 3.90 (d, *J* = 5.0 Hz, 4H), 3.30 – 3.20 (m, 1H), 3.20 – 2.96 (m, 5H), 2.79 – 2.72 (m, 1H), 2.19 – 2.05 (m, 1H). LCMS (ESI): *m/z* 594.00 $(M+H)^+$.

1-(2-chloro-4-(trifluoromethyl)phenyl)-N-(2,4-dimethoxybenzyl)-N-(pyrimidin-2-yl)-2,3-dihydro-1H-indene-5-sulfonamide (69). Synthesized from perfluorophenyl 1-(2-chloro-4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-indene-5-sulfonate **(68a)** and N-(2,4-dimethoxybenzyl)pyrimidin-2-amine (synthesized as described in Sun et al., *Bioorg. Med. Chem. Lett*., 2014, 24(18), 4397 – 4401) by following an analogous procedure described for **1a** & **1b** (yield = 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, *J* = 4.8 Hz, 2H), 7.94 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.73 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.12 (m, 2H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 2.3 Hz, 1H), 6.48 – 6.42 (m, 1H), 5.31 (s, 2H), 4.90 (t, *J* = 8.2 Hz, 1H), 3.73 (s, 3H), 3.59 (s, 3H), 3.12 – 2.91 (m, 2H), 2.69 – 2.60 (m, 1H), 2.09 – 1.99 (m, 1H). LCMS (ESI): *m/z* 604.12 $(M+H)^+$.

Sodium Channel Inhibition Using FLIPR Membrane Potential Assay.

HEK-293 cells overexpressing the channel of interest were seeded in a 96-well plate at a density of 30000 cells/well and incubated at 37°C / 5% CO_2 for 48 hr. The assay was carried out using the Red Membrane Potential Dye (Molecular Devices) following the manufacturer's instructions. Briefly, the cells were incubated with 1X red membrane potential dye for 1.5 hour. The cells were then treated with various concentrations of the test compounds for 15-20 min followed by depolarization with 10-30 µM Veratridine. The fluorescence was read following excitation at 510-545 nm and emission at 565-625 nm in FLIPR. The "max-min" fluorescence values were used to calculate the % inhibition. IC_{50} values were calculated by plotting % inhibition against concentration and curve fitting into a sigmoidal dose response.

Manual Patch Clamp Electrophysiology Assay.

HEK-293 Cells stably expressed with hNa_V1.7 or hNa_V1.5 ion channel were held at -120mV. Inhibition of sodium current due to test article was measured using voltage step protocol. Cells were cultured in DMEM/F-12 media containing 10% FBS with 400µg/ml G418. The cells plated (20000-30000 cells/ml) on PDL coated coverslips were placed in the recording chamber on the stage of an inverted microscope, and continuously perfused (~1–2 ml/min) with bath solution at room temperature. When filled with the pipette solution, patch electrodes had a tip resistance of approximately 1–3 Mohm. After a tight gigaseal had been achieved between the patch electrode and a cell, the membrane across the electrode tip was ruptured to establish the whole-cell patch-clamp configuration. Once a stable patch status was achieved, the recordings in the voltage clamp mode, with a holding voltage of -120 mV were noted. After control

currents were recorded, solutions with set concentrations of (1, 10, 100, 1000, 2500 and 10000nM for $Na_V1.7$ & 1000 and 10000nM for $Na_V1.5$) test article were perfused through the bath. Sodium current changes in the presence of test article at each concentration was recorded till a stable point had reached. The sodium current amplitudes were measured at pretreatment control and steady state blockade for desired concentration. Each recording ended with a final application of reference standard (Propafenone, 100µM) to assess contribution of endogenous currents. Remaining uninhibited current was subtracted to determine the potency of test article for Sodium current inhibition.

Holding potential was kept at -120mV. Resting, fast and slow inactivation voltage protocols were used to study the effect of test article on $hNa_V1.7$ and $hNa_V1.5$ currents. Single pulse voltage was used from holding potential to peak for individual cell in resting state protocol.

10Hz 25pulse protocol was used for fast inactivation and use dependent phenomenon of $hNa_V1.7$. Prepulse of 500ms was given and cells were held at $V_{1/2}$ of inactivation (approx.40-50%) with repeated pulse (25 pulses) given at 10Hz. Slow inactivation protocol was given as a single pulse protocol with prepulse of 10s at $V_{1/2}$ of inactivation. Single pulse was repeated every 15s.

3Hz 10pulse protocol was used for fast inactivation and use dependent phenomenon of $hNa_V1.5$. Prepulse of 500ms was given and cells were held at $V_{1/2}$ of inactivation (approx. 40-50%) with repeated pulse (10pulses) were given at 3Hz. Single pulse was repeated every 20sec and 15sec for fast inactivated and resting state protocol for $Na_V1.5$.

Pharmacokinetic Assessment. The studies were conducted at DMPK Laboratory of Lupin Limited, Pune, India, and approved by Institutional Animal Care and Use Committee. Male BALB/c mice supplied by Research Animal Facility, Lupin Ltd (Pune, India) were randomly assigned to two treatment groups (n = 9 per group). On dosing day, mice received a single intravenous (IV) dose (1 mg/kg) or oral (PO) dose (10 mg/kg) of compound. The dosing volume was 5mL/kg for IV and 10 mL/kg, for oral administration, respectively. The blood samples were collected at 0.083 (only for IV), 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after dosing in micro-centrifuge tubes containing K_2EDTA as anticoagulant. Blood samples were collected from a set of three mice per time-point alternating between three sets. Plasma samples were harvested by centrifugation of whole blood at 7000 rpm and 4±2˚C for 5 min. All the samples were stored below -20ºC until analysis. All samples were processed for analysis by precipitation method using internal standard and analyzed with fit-for purpose LC-MS/MS method (LLOQ was 0.01 µM). The plasma concentration-time data was subjected to Non-Compartmental Analysis using Phoenix WinNonlin® (Version: 8.0) to

assess the pharmacokinetic parameters. For PK assessment in rats, male Sprague Dawley rats were randomly assigned to two treatment groups (n = 4 per group). On dosing day, rats received a single intravenous (IV) dose (1 mg/kg) or oral (PO) dose (10 mg/kg) of test compound, and ~200 µL blood samples were collected under light isoflurane anesthesia (Surgivet®) at 0.083 (only for IV), 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after dosing. Blood samples were collected from each rats per time-point. For dog PK, three male beagle dogs were used in two period crossover study design. In first period, dogs received a single intravenous 15 min infusion dose (1 mg/kg) and after washout in second period, dogs were administered orally (5 mg/kg) of test compound. Blood samples were collected at 0.083 (only for IV), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 h after dosing. Blood samples were collected from cephalic vein of each dog per time-point.

In-vitro Metabolic Stability Assay. Stock solutions of test compounds were spiked at 1 µM concentration into 0.25 mg/mL liver microsomes (rat and human) and pre-incubated for 5 min at 37 °C. The reaction was initiated by adding NADPH in potassium phosphate buffer (50 mM, pH 7.4). The reaction was quenched with 100 µL of quenching solvent at 0, 10, 20 and 30 min. A positive control reaction was performed similarly with Nicardipine (1 µM) at 0.25 mg/mL microsomal protein concentration. An NADPH negative-control was performed in a similar manner, except that in this case NADPH was withheld from the incubation mixture and the samples were collected at 0 and 30 minutes. All the samples were analyzed by LC-MS/MS. % parent remaining at 10, 20 and 30 min was quantified. Log transformed % parent remaining was plotted as a function of time and slope of the regression line was used to calculate Metabolic Rate.

CYP Inhibition Assay. The inhibitory potencies of test compounds on CYP3A4 and CYP2C9 were evaluated by incubating in pooled human liver microsomes containing isozyme specific substrates, co-factors and by monitoring the production of selective metabolites using UPLC-MS/MS. The incubation mixtures were prepared by taking pooled human liver microsomes (0.15 mg/mL) and 2 mM NADPH was diluting the mixture with 50 mM pH 7.4 potassium phosphate buffer to a final volume of 1 mL. Test compounds (1 and 10 µM) or positive inhibitors like ketoconazole and sulfaphenazole at IC_{50} concentrations (0.017, 0.685 µM) for CYP3A4 and 2C9 were taken. The CYP3A4 and 2C9 substrates were used at concentrations approximating their respective K_m values, i.e. 58 µM testosterone and 11 µM diclofenac sodium. After a 5-min pre-incubation at 37 °C, the reactions were initiated by addition of NADPH (80 µL/mL) and incubation proceeded for 10 min at 37 °C in a shaking bath. The reaction was stopped by placing the tubes on ice and adding 75 µL of ice-cold methanol containing internal standards. For each isozyme, the mean

area ratio in samples from control incubations containing no inhibitor was set to 100% and area or ratios for all other samples were expressed as % inhibition.

% Inhibition = 100 - (Area or ratio of metabolite at each concentration/ Mean area ratio of no-inhibitor controls) x 100

All the procedures conducted on animals were in accordance to the provisions of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and approval by the Institutional Animal Ethics Committee (IAEC) of Lupin Research Park.

Veratridine pain model[9a] was induced by sub-planter injection of veratridine (20 uL, 50 uM in 0.1% V/V DMSO in PBS) in C57BL6 male mice. The animals were observed for nociceptive behavior (time spent in licking and/or flinching and/or guarding) for 20 min post veratridine injection. All studied compounds were administered orally 30 min prior to veratridine injection.

In formalin pain model,[22] formalin was injected into planter region (20 uL, 1% v/v formaldehyde in normal saline) of C57BL6 male mice. The nociceptive behavior of each mouse (time spent in licking, and/or flinching of the injected paw) was recorded for consecutive 5 min intervals and for total 40 min duration. Total time spent in nociceptive behavior at 0 – 5 and 10 - 40 min interval was classified as phase I and II for each mouse, respectively. All studied compounds were administered orally 30 min prior to formalin injection.

Chronic Constriction Injury (CCI) induced neuropathic pain model[23] was developed in male ICR-CD1 mice by placing 3 loose loops of 6-0 chromic catgut around sciatic nerve keeping ~1 mm distance between them. The pain behavior was assessed by measuring paw withdrawal response (measure of mechanical allodynia) by presenting series of von-Fray filaments. All studied compounds were administered orally 30 min whereas gabapentin was administered 45 minutes prior to assessment of pain behavior.

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ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS publications website at DOI:

Synthesis of intermediates **58a-m** and analytical data (PDF)

SMILES strings for the compounds that are the subject of this publication (CSV)

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ABBREVIATIONS USED

ADME, absorption, distribution, metabolism, and excretion; AUC_{last}, area under the curve from time zero to the last measurable concentration; Cmax, maximum plasma concentration; CCI, Chronic constriction injury; Compd, Compound; CL, systemic clearance; CYP, cytochrome P450; DCE, 1,2-dichloroethane; dppf, 1,1'-Bis(diphenylphosphino)ferrocene; EP, electrophysiology; %F, oral bioavailability; IV, intravenous delivery; HEK, Human embryonic kidney 293 cells; hERG, human ether-a-go-go related gene; HPLC, high performance liquid chromatography; LiHMDS, Lithium bis(trimethylsilyl)amide; MLM, mice liver microsomes; MoLM, monkey liver microsomes; mpk, milligram per kilogram; $Na_V1.5$, voltage-gated sodium channel 1.5; $Na_V1.7$, voltage-gated sodium channel 1.7; NCS, N-Chlorosuccinimide; nd, not done; NT, not tested; nM, nanomolar; Pfp, Pentafluorophenyl; PK, pharmacokinetics; PO, per oral delivery; PPB, plasma protein binding; SAR, structure-activity relationship; Vss, volume of distribution

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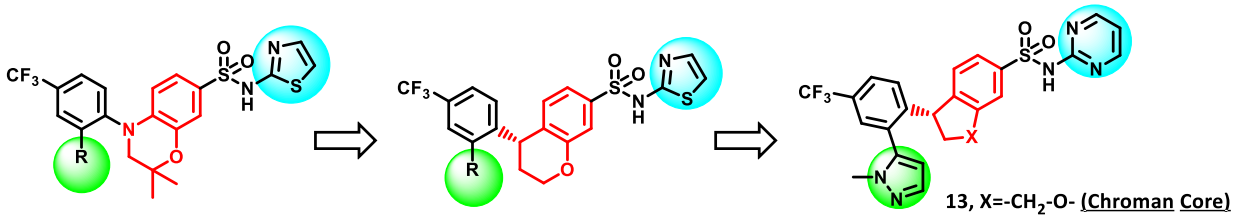
Table of Contents graphic



Benzoxazine Core	Chroman Core	13, X=-CH_2-O- (Chroman Core) 51, X=-CH_2- (Indane Core)
✓ Very good potency	✓ Very good potency	✓ Good potency
× Moderate selectivity	× Moderate selectivity	✓ Desired selectivity
× High CYP2C9 inhibition	× High CYP2C9 inhibition	✓ Low CYP2C9 inhibition
× Poor solubility	✓ Improved solubility	✓ Very good solubility
× Poor Pharmacokinetics	✓ Desired Pharmacokinetics	✓ Desired Pharmacokinetics