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Discovery of MK-7246, a selective CRTH2 antagonist for the treatment of respiratory diseases

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ABSTRACT

In this manuscript we wish to report the discovery of **MK-7246** (4), a potent and selective CRTH2 (DP2) antagonist. SAR studies leading to **MK-7246** along with two synthetic sequences enabling the preparation of this novel class of CRTH2 antagonist are reported. Finally, the pharmacokinetic and metabolic profile of **MK-7246** is disclosed.

In response to various extracellular stimuli, prostaglandins (PGE2, PGD2, PGF2, PGI2, and TAX2) are rapidly generated through the consecutive action of the cyclooxygenase and their respective synthases from membrane arachidonic acid and exert their action in close proximity to the site of their synthesis.[1] To date, nine prostanoid receptors have been cloned and characterized. These receptors are members of the growing class of G-protein-coupled receptors.[2] PGE2 binds preferentially on the EP1, EP2, EP3, and EP4 receptors, PGD2 to the DP1 and CRTH2 (referred occasionally as DP2) receptors, PGF2 to the FP receptor, PGI2 to the IP receptor and TAX2 to the TP receptor. Activation of the DP1 receptor by its endogenous ligand PGD2 results in vasodilatation,[3] which was shown to be reversed pharmacologically by the action of an antagonist.[4] As a result, Laropiprant®, a selective and potent DP1 antagonist,[5] was developed to reverse the facial flushing induced by Niacin.[5] Alternatively, activation of CRTH2[6] (chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells), the second prostanoid receptor targeted by PGD2, stimulates the recruitment of leukocytes, the release of Th2 cytokines and the degranulation of basophils and eosinophils. The combined pharmacological action of such biological events plays a key role in late phase allergic inflammation.[7] Additionally, high levels of PGD2 are found in the lungs of asthmatic patients[8] and genetic polymorphism leading to increased CRTH2 mRNA stability is significantly associated with asthma in two independent populations.[9] Together, these observations provide a sound biological rational for the development of selective CRTH2 antagonists for the treatment of asthma.[10] Consequently numerous pharmaceutical companies have initiated medicinal chemistry programs targeting selective CRTH2 antagonists for the treatment of respiratory diseases.[11]

The affinity and selectivity of compounds described herein for human CRTH2 and recombinant human prostanoid receptors was determined by equilibrium competition analysis using the relevant

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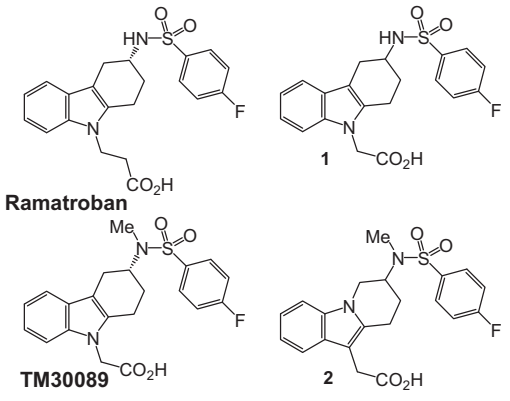
radioligands and cell membranes expressing the various receptors.[12] CRTH2 is a Gi-coupled receptor that signals through inhibition of adenylate cyclase leading to an inhibition of intracellular cAMP production.[13] As a result, a functional assay was developed to measure intracellular cAMP levels resulting from receptor activation using recombinant cells overexpressing human CRTH2 (HEK293E/CRTH2). DK-PGD2, a CRTH2-selective metabolite of PGD2, was used to activate the CRTH2 receptor leading to a decrease in intracellular cAMP. The ability of our compounds to block DK-PGD2-induced inhibition of cAMP formation was measured and is reported as cAMP IC_{50}. Finally, a physiologically relevant whole blood assay was developed to assess the potency of compounds on the CRTH2 receptor, endogenously expressed at the surface of human cells. Eosinophil activation triggers a shape change, as a consequence of cytoskeleton reorganization predisposing the leukocyte for cell movement and transmigration, which can be quantified by flow cytometry through changes in forward light scatter.[14] The ability of an antagonist to inhibit the DK-PGD2-induced shape change was measured and is reported as ESC IC_{50}.

Ramatroban[15a] (Table 1), a dual TP/CRTH2 antagonist,[15b] was reported to exhibit some degree of efficacy in allergic rhinitis and is currently commercialized in Japan. Shortening the carboxylic acid chain by one methylene unit, as exemplified by compound **1**, reverses the selectivity in favor of the CRTH2 receptor. N-Methylation of the sulfonamide moiety led the Shionogi team to the discovery of the tetrahydro-carbazole TM30089,[16] a potent and selective CRTH2 antagonist. We prepared the reverse indole of TM30089 (i.e., compound **2**) and found that the potency and selectivity for the CRTH2 receptor was maintained. This discovery constituted the starting point of SAR studies performed in our laboratories. The results are described in this manuscript.

Chiral resolution of the racemic compound **2** confirmed previously disclosed data on Ramatroban and TM30089, that the affinity and selectivity for CRTH2 is superior for the *R* enantiomer (i.e., **4**) than for the *S* (i.e., **3**) as shown in Table 2. Compound **4** behaved as a full antagonist in our functional assay and was barely shifted (threefold) in the whole blood assay. Additionally, **4** demonstrated low affinity for the six remaining prostanoid receptors (K_i > 7.5 μM). SAR studies were initiated to further improve the potency and selectivity of **4**.

Table 1
Discovery of a new class of CRTH2 ligands



Compd	K_i (nM)[a]		
	CRTH2	DP1	TP
Ramatroban	137	11,020	0.58
1	5.5	6140	53
TM30089	1.5	1115	6852
2	6.0	653	1394

[a] K_i determinations are averages of at least two experiments.

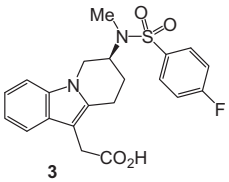
Substitution on the indole core was first examined (Table 3). In general mono- and disubstituted analogs were tolerated but in some cases, significant loss of selectivity over DP (<20-fold) was observed as exemplified by compounds **5** and **17**. Unexpectedly, full reversal of selectivity was found for the 4,6-dichloro analog **16**, favoring affinity for the DP receptor over CRTH2. Overall, three compounds demonstrated a superior profile to the lead compound **4**. The 6-fluoro (**8**), 7-fluoro (**18**), and 6,7-difluoro (**15**) analogs displayed a slight improvement in potency on the CRTH2 receptor, superior selectivity over DP and improved and whole blood activity over their unsubstituted counterpart **4**.

Next, we studied the substitution of the sulfonamide nitrogen in order to further improve potency and selectivity (Table 4). As expected, the unsubstituted analog **20** was equipotent on the CRTH2 and TP receptors. Surprisingly, the addition of one methylene unit as in the *N*-ethyl analog **21** lead to substantial lost of selectivity against DP. A similar observation was made for the trifluoroethyl compound **25**. The *N*-pentyl derivative **22** exhibited enviable selectivity but was highly shifted (67-fold) in the whole blood eosinophil shape change assay. Only the *N*-(4-fluorobenzyl) analog **24** displayed an improved profile compared to **4** especially in terms of selectivity over the DP receptor.

Finally, the substitution of the phenyl component of the sulfonamide was examined (Table 5). Unfortunately, all attempts to improve potency and selectivity failed. Briefly, repositioning the fluorine atom or replacing it with larger electron withdrawing groups led to loss of selectivity over DP. Introduction of a heterocyclic group as a phenyl ring replacement was also unsuccessful.

Following the optimization of our lead compound based on CRTH2 potency, whole blood activity and selectivity over the remaining prostanoid receptors, compounds **4**, **8**, **15**, **18**, and **24** were further characterized. Their respective Cytochrome P450, protein covalent binding, off-target activity, physicochemical, and pharmacokinetic profiles are summarized in Table 6. In general, compounds in this series of tetrahydropyrido[1,2-*a*] indoles are not competitive inhibitors of CYP2D6 and 3A4 nor do they display affinity for the hERG channel or the pregnane X receptor[17] (PXR), a nuclear receptor involved in the induction of CYP3A4. They were also found to be orally bioavailable in rats and displayed moderate to long half-life. Conversely, members of this class of compounds were found to be moderate CYP2C9 competitive inhibitors. Such a property could potentially lead to undesired drug–drug interactions if patients are under multiple therapies.[18] Of the five compounds selected for further profiling, **4**, **18**, and **24** maintained acceptable properties. Time-dependent inhibition of CYP3A4 has also the potential to perpetrate drug–drug interactions in humans. Measuring the difference (reported as% lost) between the CYP3A4 mediated degradation of testosterone (250 μM) to 6-β-hydroxytestosterone, with and without pre-incubation of the potential perpetrator (10 μM), allowed us to rapidly assess if this class of tetrahydropyrido[1,2-*a*] indoles acted as time-dependent CYP3A4 inhibitors.[19] As a result, the 7-fluoro analog **18** was found to be less susceptible to cause drug–drug interaction by this mechanism. As part as of our routine characterization of potential development candidate, the top five analogs were also submitted to various stress conditions to assess their overall stability. In one of these experiments, representatives of this class of compounds (2 mM solution in MeOH) were exposed to full UV light spectrum (1.0 KLux/m^2) for 15 min in a Q-Sun Xenon Light Test Chamber. Variable rates of photodegradation were observed. This phenomenon may represent a developmental challenge as photoinstability of a molecule that distribute to light exposed tissues (i.e., eye and skin) has the potential to induce toxicities via the formation of reactive degradation products.[20] The two most photostable analogs found were those bearing a fluorine atom at the 7 position of the indole core (i.e., **15** and **18**). Photodegradation was observed only in

Table 2
In vitro characterization of the two enantiomers of compound **2**



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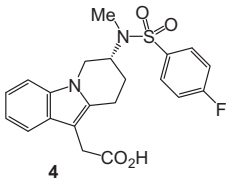
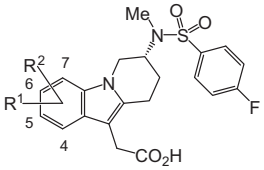


4

Compd	K_i[a] (nM)			IC_{50}[a] (nM)	
	CRTH2	DP	TP	cAMP	ESC
3	144 ± 19(3)	2391 ± 439(3)	>21,660(3)	864 ± 25(3)	325 ± 43(3)
4	2.5 ± 0.5(8)	373 ± 96(6)	3804 ± 1290(6)	3.0 ± 1.3(4)	2.2 ± 1.0(10)

[a] K_i and IC_{50} are mean ± standard deviation with *n* values in parenthesis.

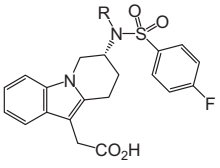
Table 3
SAR studies on the indole core substitution



Compd	R^1	R^2	K_i[a] (nM)			IC_{50}[a] (nM)	
			CRTH2	DP1	TP	cAMP	ESC
4	H	H	2.5	373	3804	3.0	2.2
5	4-F	H	11	216	888	26.5	
6	5-F	H	4.6	284	1872	3.0	11.5
7	5-SO_2Me	H	1083	>3235	>6489	>10,000	
8	6-F	H	1.1	248	727	2.6	1.4
9	6-Cl	H	1.1	104	3949	3.0	11.5
10	6-CF_3	H	1.7	395	1518	3.6	10.8
11	6-CN	H	8.8	2093	>7139	9.0	
12	6-SO_2Me	H	13	>3952	>7247	38	5.0
13	6-Ph	H	2.4	1282	2890	4.5	30.5
14	6-F	5-F	2.5	121	719	3.8	
15	6-F	7-F	1.0	541	962	2.5	1.1
16	6-Cl	4-Cl	26	5.6	1330	24	
17	6-Cl	5-F	3.7	48	1840	5.7	
18	7-F	H	1.6	1079	2152	2.5	1.8
19	7-F	5-F	4.0	711	427	9.9	14.1

[a] K_i and IC_{50} determinations are averages of at least two experiments.

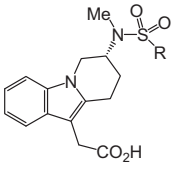
Table 4
SAR studies on the sulfonamide residue



Compd	R	K_i[a] (nM)			IC_{50} (nM)	
		CRTH2	DP	TP	cAMP	ESC
4	Me	2.7	373	3804	3.0	2.2
20	H	9.8	>4069	10.9	35.5	1.6
21	Et	1.8	14.6	2142	8.1	
22	Pentyl	1.6	1213	904	4.9	107
23	*c*-$PrCH_2$	4.9	130	1222	6.7	
24	4-F-Bn	1.4	2292	1569	5.7	4.1
25	CF_3CH_2	3.7	15.5	1357	6.9	

[a] K_i and IC_{50} determinations are averages of at least two experiments.

Table 5
SAR studies on the phenyl residue



Compd	R	K_i[a] (nM)			IC_{50}[a] (nM)
		CRTH2	DP	TP	cAMP
4	4-F-Ph	2.7	373	3804	3.0
26	2-F-Ph	17	892	>21,160	22
27	2-Tol	7.6	51	>5591	27
28	3-F-Ph	21	1075	>7054	33
29	3-Tol	8.7	250	>5591	13
30	H	4.3	537	>7054	12
31	4-Cl	5.5	47	1039	8.5
32	4-CF_3-Ph	40.8	123	2118	214
33	4-MeO-Ph	4.4	26	>7096	5.5
34	4-Et-Ph	20	16	>5591	15
35	4-F-Bn	20	799	>5745	25
36	5-Cl-thiophene-2-yl	6.3	283	2840	13
37	1-Me-pyrazole-4-yl	124	>3901	>7181	63
38	3,5-Di Me-isoxazole-4-yl	296	322	>7054	250
39	2-Pyridinyl	117	>3901	>7181	308

[a] K_i and IC_{50} determinations are averages of at least two experiments.

solution under full UV spectrum light (sunlight) but not in ambient light (laboratory light) nor in the solid form. As a consequence of these results, two analogs, **4** and **18** were further profiled by performing in vitro covalent binding studies in rat and human microsome using radiolabeled material. A significant level of covalent binding was observed for the photostable analog **18** compared to the des-fluoro analog **4**.

Based on the overall profiles of our top five optimized CRTH2 antagonists and in particular with respect to their relative CYP profiles, compound **4** was chosen for further development becoming **MK-7246**.[21]

MK-7246 was further characterized by establishing its overall metabolism profile and performing additional pharmacokinetic studies in non-rodent preclinical species (Table 7). The rank order of metabolic stability of **MK-7246** in hepatocytes was Sprague–Dawley rat > beagle dog > cynomolgus monkey > rhesus monkey ~ human. In all species, the acyl glucuronide of the parent (**40**) was the major metabolite observed (Fig. 1). Minor metabolites detected included a product of oxidative decarboxylation (**41**) and its putative acyl glucuronide (**42**). Low turnover of **MK-7246** was observed in rat, dog, monkey and human liver microsomes and the major metabolites detected were **41**, and two monohydroxylated products **43** and **44** of undetermined structure. All

Table 6
Comparative profile of optimized CRTH2 antagonists

Compd	CYP inhibition IC_{50}[a] (μM)			3A4 TDI	PXR	Photosensitivity	hERG	In vitro CB (pmol equiv/mg protein)		Rat PK[b]		
	2D6	2C9	3A4	% Lost @ 10 μM	EC_{50}[a] (μM)	% Degradation in solution	K_i[a] (μM)	Rat	Human	F (%)	Cl (mL/min/kg)	$T_{1/2}$ (h)
4	>100	9.4	34	20	>30	45	>29	154 ± 27	205 ± 23	107	2.2	5.6
8	>50	13.6	>50	17	>30	89	35			100	1.8	4.3
15	>50	6.4	>50	26	>30	1				72	0.4	13
18	>50	4.2	>50	12	>30	4	>60	455 ± 30	568 ± 42	62	0.4	16
24	>50	21.0	>50	49	>30	26	>60					

[a] K_i, IC_{50}, EC_{50}, % lost and % degradation are averages of at least two experiments
[b] Rat PK studies were conducted in Sprague–Dawley rats at 10 mg/kg po in 0.5% methocel ($n = 2$) and 5 mg/kg iv in PEG200 60% ($n = 2$).

Table 7
Pharmacokinetic profile of **MK-7246** in preclinical species

Species	F (%)	Cl (mL/min/kg)	V_{dss} (L/kg)	$T_{1/2}$ (h)	$AUC_{40}/AUC_{MK\text{-}7246}$
SD Rat	107	2.2	0.98	5.6	0.02
Beagle dog	67	15	2.3	8.4	0.06
Cynomolgus	10	4.8	0.5	11	0.5
Rhesus	57	6.9	2.6	8.1	1.7

Rat PK studies were conducted in Sprague–Dawley rats at 10 mg/kg po in 0.5% methocel ($n = 2$) and 5 mg/kg iv in PEG 200 60% ($n = 2$). Dog and monkey PK studies were conducted using the same vehicle at 1 mg/kg po and 0.5 mg/kg iv.

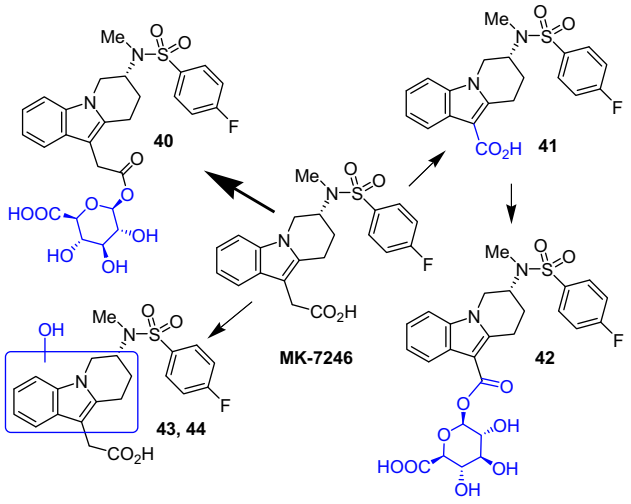


Figure 1. Structure of metabolites of **MK-7246**.

metabolites identified in human liver preparations were also detected in the corresponding incubations from preclinical species. The structure of the acyl glucuronide metabolite **40** was confirmed with a synthetic standard[22] and was found to have low affinity for the CRTH2 receptor ($K_i > 207$ nM)[23] and for the remaining eight prostanoid receptors ($K_i > 10$ μM). The decarboxylated metabolite **41** was isolated from a large-scale microsomal incubation. It was also found to display low affinity for the CRTH2 receptor ($K_i > 7.2$ μM) as well as for the others prostanoid receptors ($K_i > 2$ μM). Analysis of bile, feces and urine recovered for 48 h from permanently bile-cannulated male rats dosed iv with ^{3}H-**MK-7246** (1 mg/kg, 300 μCi/kg) showed that the major component excreted in bile was the acyl glucuronide **40** (90%), the parent **MK-7246** (2.7%), the decarboxylated metabolite **41** (2.3%) and various oxidative metabolites (5%) accounting for 77% of total radioactivity. Remaining radioactive material was found in feces (6%) and urine (1%) for a cumulative recovery of 84%.

To evaluate the level of acyl glucuronidation of **MK-7246** in preclinical species, the compound was monitored in all subsequent pharmacokinetic studies. To this end, plasma samples were quenched with CH_3CN containing 0.5% formic acid to stabilize the glucuronide **40** and allow its quantification. The results are reported in Table 7 as a ratio to the parent compound **MK-7246**. In all species, **MK-7246** exhibited a low to moderate plasma clearance (2.2–15 mL/min/kg), a moderate volume of distribution (0.5–4.8 L/kg), and a moderate plasma terminal half-life, ranging from 5.6 to 11 h. The oral bioavailability was greater than 57% in all species with the exception of cynomolgus monkey where it was only 10%. The acyl glucuronide **40** was found circulating in all species, however, its relative plasma exposure versus that of **MK-7246** revealed marked species differences and was highest in non-human primates (0.5–1.5) compared to dogs (0.06) and SD rats (0.02).

To lessen the main metabolic pathway by which **MK-7246** is eliminated, three additional analogs were prepared bearing α-substituent to the carboxylic acid, with the anticipation that steric hindrance would reduce the rate of glucuronidation. To this end, the cyclopropyl **45**[24] and the two α-methyl diastereoisomers **46** and **47**[25] were prepared (Fig. 2). Unfortunately, these modifications resulted in loss of affinity for the CRTH2 receptor (CRTH2 $K_i = 318$, 341, and 316 nM for **45**, **46**, and **47**, respectively).

The syntheses of the tetrahydropyrido[1,2-*a*] indoles described in this manuscript were prepared according to two distinct synthetic sequences. **MK-7246** and analogs bearing various substituents on the nitrogen of the sulfonamide moiety (Table 4) or the phenylsulfonyl group (Table 5) were prepared as described in Scheme 1. Briefly, condensation of phenyl hydrazine hydrochloride with diethyl 4-oxopimelate in refluxing toluene, followed by treatment of the resulting tetrahydropyridazine **48** with methanesulfonic acid in refluxing *n*-propanol afforded the diester indole **49**. This procedure is a slight modification to the classic Fisher indole

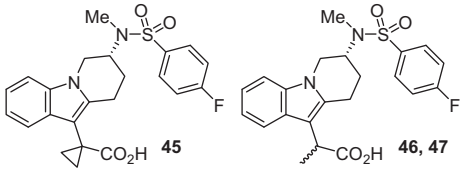
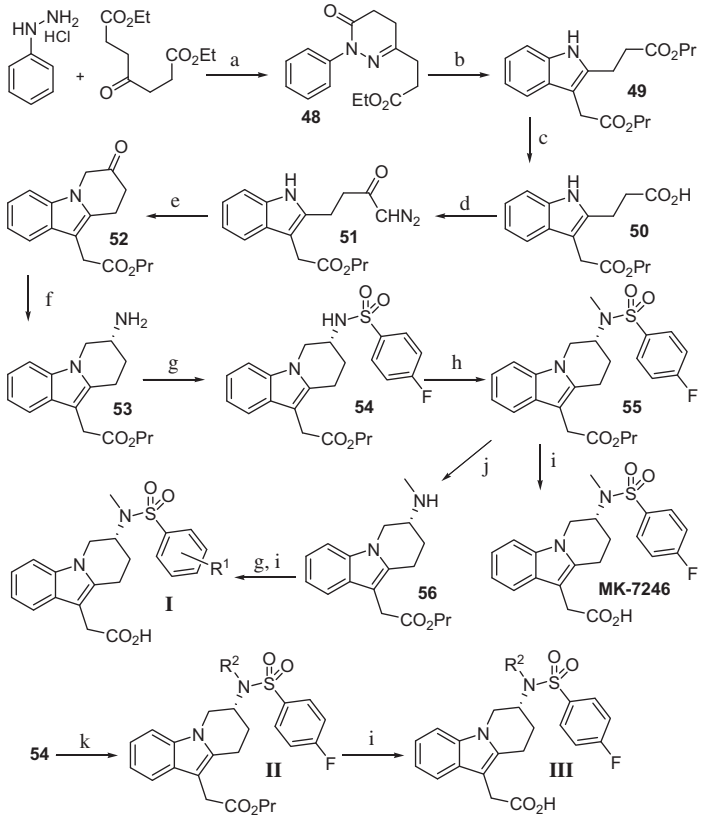
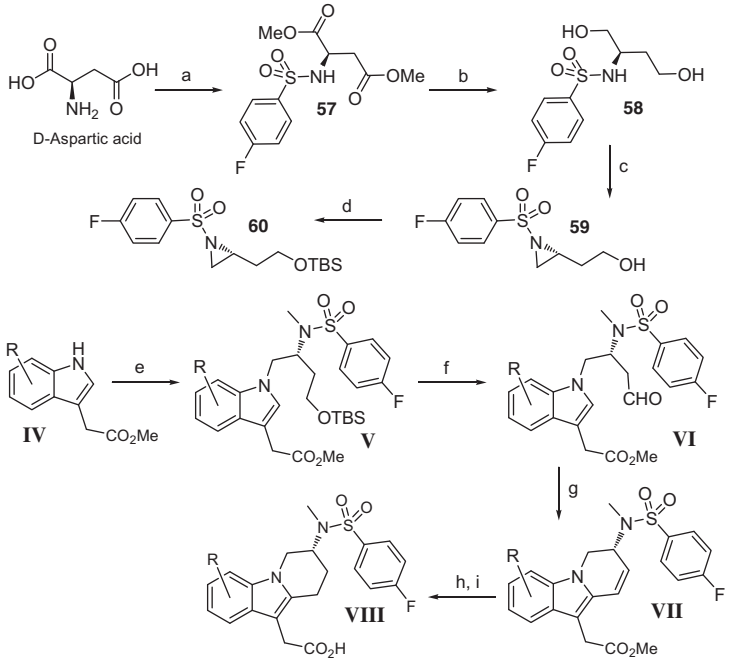


Figure 2. Structure of α-substituted analogs of **MK-7246**.



Scheme 1. Synthetic sequence A. Reagents and conditions: (a) toluene, reflux; (b) CH_3SO_3H, *n*-propanol, 80 °C; (c) KOH, *n*-propanol, 50 °C, 4 h; (d) (i) EtOCOCl, THF, 0 °C then dropwise addition of NMM; (ii) CH_2N_2, 0 °C; (e) $Rh_2(Oct)_4$ (10%), CH_2Cl_2, rt; (f) ATA enzyme, alanine, FDH system, 99% ee; (g) 4-F-phenylsulfonyl chloride, NEt_3, DMAP, CH_2Cl_2, rt; (h) NaH, DMF, 0 °C then MeI; (i) THF, *iso*-propanol, aqueous LiOH (1 M); (j) Mg, MeOH; (k) appropriately substituted aryl sulfonyl chloride, NEt_3, DMAP, CH_2Cl_2, rt.



Scheme 2. Synthetic sequence B. Reagents and conditions: (a) (i) $SOCl_2$, MeOH; (ii) NEt_3, THF; (b) $NaBH_4$, EtOH; (c) 1,1′-(azodicarbonyl)dipiperidine, PBu_3, THF; (d) TBSCl, imidazole, THF; (e) (i) NaH, DMF; (ii) **59**; (iii) MeI; (f) (i) TBAF, THF; (ii) DMSO, $(COCl)_2$, cat. DMF; (g) PPTS, toluene; (h) H_2, MeOH, cat. Pd/C 10%; (i) aqueous LiOH (1 M), THF, MeOH.

synthesis described by Sapi[26] on related compounds. On larger scale, we found that using methanesulfonic acid in *n*-propanol instead of the usual HCl gas/MeOH gave higher and more reproducible yields. Selective saponification[26] of **49** and subsequent formation of the diazomethylketone **51** enabled the rhodium catalyzed carbene insertion yielding the tricyclic ketone **52** as

described by Capretta.[27] The conversion of **52** to the corresponding chiral amine **53** was the key step in this sequence. Reductive amination via a transaminase/dehydrogenase catalytic system yielded the desired chiral amine with a 99% ee. Details on this pivotal reaction will be disclosed in a separated manuscript. Coupling of the chiral amine **53** with 4-fluorobenzenesulfonyl chloride, followed by N-methylation of the resulting sulfonamide **54** and hydrolysis of the propyl ester afforded the desired enantiomerically pure **MK-7246**. Removal of the 4-fluoro phenylsulfonyl group under mild conditions (Mg/MeOH) afforded the desired *N*-methyl analog **56**. Coupling of various arylsulfonyl chlorides with **56** and subsequent saponification afforded the desired analogs described in Table 4. Finally, alkylation of the sulfonamide **54** with different alkyl and benzyl bromides followed by hydrolysis yielded the compounds described in Table 3.

Substituted indole cores were made following the synthetic sequence B described in Scheme 2. Briefly, esterification of D-aspartic acid followed by treatment with 4-fluorophenylsulfonyl chloride and subsequent reduction afforded the diol **58**. The aziridine **60** was prepared via a Mitsunobu variation of the Wenker reaction[28] and subsequent silylation of the alcohol moiety. Opening of the aziridine **60** by the sodium salt of appropriately substituted indole ester (**IV**)[29] followed by direct methylation of the resulting sulfonamide sodium salt afforded the silyl ether **V**. Removal of the silyl ether protecting group and subsequent Swern oxidation yielded to key aldehyde precursor **VI**. Acid promoted cyclization of aldehyde **VI** in refluxing toluene afforded the alkene indole **VII**. Hydrogenation and saponification of the unsaturated ester completed the synthetic sequence. This convergent approach enabled a rapid access to compounds described in Table 5.

In summary, the results presented in this manuscript recapitulate our effort towards the identification of a potent and selective CRTH2 antagonist. **MK-7246** is the end result of this endeavor and after successfully completing preclinical safety studies in rats and rhesus monkeys, **MK-7246** entered Phase I clinical trials. The results of those studies will be disclosed in separate manuscripts.

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