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Letters

Minor Structural Modifications Convert the Dual TP/CRTH2 Antagonist Ramatroban into a Highly Selective and Potent CRTH2 Antagonist

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Abstract: Ramatroban, a thromboxane A_2 receptor (TP) antagonist with clinical efficacy in asthma and allergic rhinitis, was recently shown to also antagonize the prostaglandin D_2 receptor CRTH2. Here we report that minor structural changes to ramatroban result in a compound (**13**) with complete lack of activity on TP but sub-nanomolar potency toward CRTH2. This is the first selective CRTH2 antagonist described to date, and should prove highly valuable in further elucidating the biological significance of CRTH2.

Prostaglandin D_2 (PGD_2) is the principal prostanoid released by IgE-activated mast cells during asthmatic and allergic reactions.[1] It has long been associated with various inflammatory conditions and is considered an important mediator in asthma and allergic diseases.[2] Abrogating the effects of PGD_2, either by selectively inhibiting PGD_2 biosynthesis or by blocking PGD_2 receptors, thus represents a novel and highly attractive approach to treat a broad array of inflammatory diseases. The first receptor for PGD_2 to be characterized was the G protein-coupled seven transmembrane (7TM) receptor DP.[3] The observation that DP-deficient mice show decreased asthmatic response compared to wild type mice upon challenge in an ovalbumin-induced asthma model clearly suggests that DP-antagonists may have antiasthmatic potential,[4] and DP-antagonists displaying efficacy in in vivo models of allergy and asthma have indeed been developed.[5] However, emerging evidence suggests a more complicated picture in which PGD_2 may also exert antiinflammatory effects via the same receptor.[6,7]

Recently, chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) was identified as the second high-affinity 7TM receptor for PGD_2.[8] Later it was shown that the stable thromboxane A_2 (TXA_2) metabolite 11-dehydrothromboxane B_2, originally thought to be biologically inactive, also acts as a full CRTH2 agonist.[9] This observation is intriguing since it raises the possibility that both PGD_2 and TXA_2 metabolites contribute to allergic inflammation by activating CRTH2. CRTH2 is selectively expressed on Th2 cells, eosinophils, and basophils, all of which are implicated in asthma and allergic reactions.[8] Th2 cells are known as prime mediators of allergic asthma, driving IgE response and eosinophilia.[10] Eosinophil-deficient mice sensitized with ovalbumin were recently reported to exhibit alleviation of characteristic asthmatic symptoms compared to wild-type mice.[11,12] Basophils are also implicated in allergy and asthma,[13] and evidence suggests that CRTH2 is primarily responsible for the proinflammatory effect of PGD_2 on human basophils.[14] Notable in this relation is that PGD_2-induced chemotaxis in Th2 cells, eosinophils, and basophils is mediated by CRTH2 but not DP.[8] Furthermore, CRTH2-polymorphisms are associated with severe asthma.[15] Together, these observations convincingly suggest that CRTH2 antagonists may provide a new promising therapeutic strategy for asthma as well as other allergic diseases such as rhinitis and atopic dermatitis. However, a significant obstacle to further investigation of the biological role of CRTH2 has until now been the lack of selective antagonists for the receptor.

Ramatroban (**1**, Figure 1) is an orally available compound with established efficacy against allergic rhinitis and which is currently in phase III clinical trials for treatment of asthma.[16,17] The compound was originally developed as a TP antagonist against thrombosis and coronary artery disease[18] and was later shown to inhibit both TXA_2- and PGD_2-induced bronchoconstriction.[19] Recent studies revealed that ramatroban is also a potent CRTH2 antagonist,[20] capable of blocking eosi-

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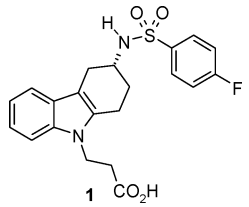
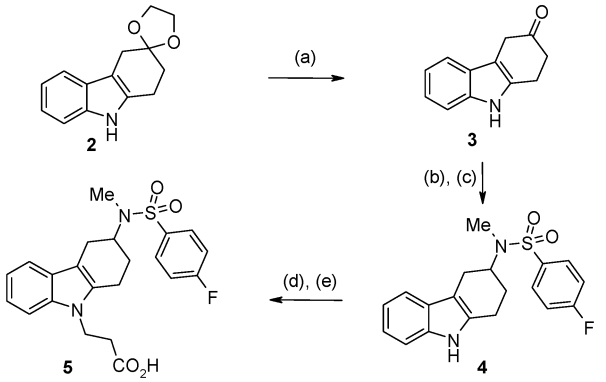


Figure 1. Structure of ramatroban.

Scheme 1[a]



[a] Reagents and conditions: (a) 15% aq. HCl, THF; (b) $MeNH_2$, $NaBH_3CN$, AcOH, MeOH; (c) 4-$FC_6H_4SO_2Cl$, Et_3N, CH_2Cl_2; (d) NaH, $Br(CH_2)_2CO_2Et$, DMF; (e) LiOH, H_2O, THF.

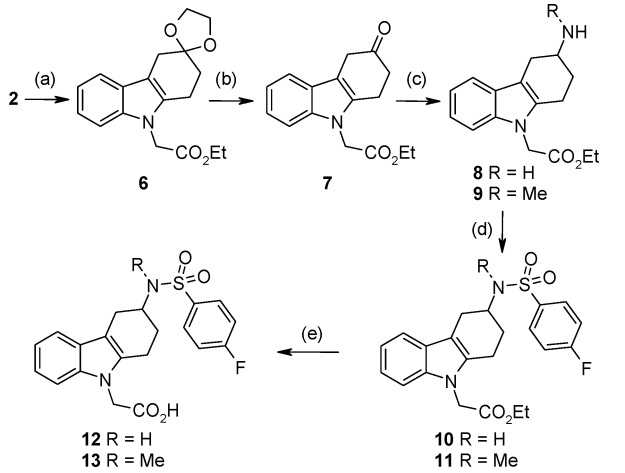
nophil migration induced by the CRTH2-selective agonist 13,14-dihydro-15-ketoprostaglandin D_2 (DK-PGD_2).[21] Ramatroban has also proven effective in alleviating PGD_2-induced airway inflammation.[22] Although several lines of evidence support a role of TP in asthmatic and allergic reactions,[23] it is tempting to suggest that the efficacy of ramatroban is at least in part mediated through CRTH2.

At present, ramatroban is the only CRTH2 antagonist described in the literature. Herein we report that minor modifications of ramatroban lead to complete loss of affinity to TP and further enhance its affinity to CRTH2, thus yielding a highly selective sub-nanomolar CRTH2 antagonist. We believe that this compound (**13**) will be of high value as a tool in the further biological characterization of CRTH2.

The ramatroban analogues[24] were synthesized via the common tetrahydrocarbazole intermediate **2**, which was obtained by a known method.[25] The racemic N-methylated ramatroban analogue **5** was synthesized from ketone **3** by reductive amination, coupling with 4-fluorophenylsulfonyl chloride, alkylation with ethyl 3-bromopropionate, and hydrolysis, as outlined in Scheme 1.

Compounds **12** and **13** were prepared as outlined in Scheme 2, by N-alkylation of **2** with ethyl bromoacetate

Scheme 2[a]



[a] Reagents and conditions: (a) NaH, $BrCH_2CO_2Et$, DMF; (b) i. 15% aq HCl, THF; ii. EDC, EtOH, CH_2Cl_2; (c) RNH_2, $NaBH_3CN$, AcOH, MeOH; (d) 4-$FC_6H_4SO_2Cl$, Et_3N, CH_2Cl_2; (e) LiOH, H_2O, THF.

to give **6** and hydrolysis of the ketal to give ketone **7**. Reductive amination with ammonia or methylamine yielded **8** and **9**, respectively, which upon reaction with 4-fluorophenylsulfonyl chloride followed by ester hydrolysis afforded compounds **12** and **13**.

Compound **13** could also efficiently be obtained by the route outlined in Scheme 1 by substituting ethyl 3-bromopropionate with ethyl bromoacetate.

The affinities of ramatroban and the three analogues to the receptors CRTH2, TP, and DP were evaluated in equilibrium competition binding assays and are given as K_i values in Table 1. Antagonistic potencies on CRTH2 and TP of the compounds were obtained in two sets of functional assays: (i) inhibition of agonist-mediated second messenger production (inositol phosphate, cAMP), and (ii) inhibition of agonist-mediated β-arrestin translocation in a *b*ioluminescence *r*esonance *e*nergy *t*ransfer (BRET) assay, and are given as IC_{50} values in Table 1. We confirmed potent antagonistic activity of ramatroban on both TP and CRTH2, whereas the affinity of ramatroban to CRTH2 was somewhat higher (Table 1) than that determined by others.[21,26] Also in accordance with previous literature, we found ramatroban to be devoid of any appreciable affinity to DP.[27]

The N-methylated analogue **5** was equipotent with ramatroban on CRTH2 in binding and functional assays. However, there was a significant drop in affinity by a factor of 2000 and in functional activity by 200 on TP. Shortening the acidic chain of ramatroban by one

Table 1. Binding and Functional Data of Ramatroban and Analogues on CRTH2, TP, and DP

	hCRTH2			hTP			hDP	
	binding[a] K_i (nM)	IP_1[c] IC_{50} (nM)	BRET[e] IC_{50} (nM)	binding[b] K_i (nM)	IP_1[d] IC_{50} (nM)	BRET[e] IC_{50} (nM)	binding[a] K_i (nM)	cAMP[c] IC_{50} (nM)
1	4.3 ± 1.3	29 ± 14	28 ± 2	4.5 ± 0.4	9.6 ± 2.2	8.4 ± 0.4	>10000	>10000
5	1.9 ± 0.2	26 ± 4	15 ± 3	3000 ± 1400	4600 ± 1200	n.d.[f]	6100 ± 2100	>10000
12	0.51 ± 0.09	3.8 ± 0.9	3.8 ± 0.6	540 ± 240	1700 ± 200	n.d.[f]	5300 ± 1100	>10000
13	0.60 ± 0.16	1.2 ± 0.3	3.0 ± 0.6	>10000	>10000	>10000	1200 ± 300	>10000

[a] [^{3}H]PGD_2 equilibrium competition binding. [b] [^{3}H]SQ29548 equilibrium competition binding. [c] Inhibition of PGD_2-induced inositol phosphate or cAMP formation. [d] Inhibition of U46619-induced inositol phosphate accumulation. [e] Antagonistic activity as inhibition of β-arrestin translocation measured in a bioluminescence resonance energy transfer (BRET) assay. [f] Not determined. All values are mean ± SEM of at least three independent determinations.

carbon atom in **12** also increased affinity and antagonistic potency on CRTH2 over TP, by 1000 and 400 times, respectively. Furthermore, this structural change resulted in about 8-fold increased affinity and potency on CRTH2 as compared with ramatroban.

Thus, both modifications yielded compounds efficiently discriminating between CRTH2 and TP activity. The combination of these two modifications in compound **13** indeed proved the effects to be additive, preserving the sub-nanomolar affinity of the acid chain shortened **12** on CRTH2 while completely abolishing affinity for and functional activity on TP, resulting in a selectivity of >10 000 in binding and both functional assays.

Notably, none of the compounds displayed significant activity on DP, exhibiting selectivity in excess of several thousand times in favor of CRTH2 (Table 1) which further underscores their usefulness as tools for exploring CRTH2. Moreover **13** retained its pharmacological profile when tested for binding to the mouse and rat orthologs of CRTH2 (data not shown).

It is noteworthy that compounds **5**, **12**, and **13** were tested as racemic mixtures, implicating that none of the enantiomers of these compounds act on TP or DP to any significant degree. Although information on the more active enantiomer would be interesting from a structural perspective, it is dispensable for exploring the utility of the compounds as biological tools and in fact significantly simplifies synthesis, as enantiomeric purity is not an issue. Of note, ramatroban utilized in our study has (3*R*)-configuration, known to be 10−100 times more potent than its enantiomer on TP.[18]

In conclusion, by N-methylating the sulfonamide of ramatroban and shortening the acidic chain by one methylene group, a highly potent CRTH2 antagonist with complete selectivity over TP was obtained. In addition, the compound also displays remarkable selectivity over the second high-affinity PGD2 receptor DP. This is the first selective CRTH2 antagonist hitherto reported. Since ramatroban is an orally available compound with favorable overall pharmacokinetic properties,[28] it is tempting to assume that these close analogues will exhibit similar properties[29] and thereby serve as valuable tools for both in vitro and in vivo studies not only for classifying PGD_2-mediated CRTH2-dependent responses but also for unraveling the biological role of CRTH2 in health and disease.

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Supporting Information Available: Synthetic procedures and compound characterization data, procedures for receptor cloning and transfection, binding assay, IP-assay, cAMP-assay, and BRET assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) One conceivable metabolic process that could result in a lowered half-life of **13** relative to ramatroban is N-demethylation at the sulfonamide. It is notable that the predicted metabolite from this process would be **12**, which is an equally potent CRTH2 antagonist and which also shows appreciable selectivity over TP and DP (Table 1).

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