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3-Indolyl sultams as selective CRTh2 antagonists

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ABSTRACT

CRTh2 (DP_2) is a prostaglandin D_2 receptor implicated in the recruitment of eosinophils and basophils within the asthmatic lung. Here we report the discovery of a novel series of 3-indolyl sultam antagonists with low nM affinity for CRTh2. These compounds proved to be selective over the other primary prostaglandin D_2 receptor (DP1) as well as the thromboxane A_2 receptor (TP).

Prostaglandin D_2 (PGD_2) produced by mast cells is a key mediator of asthmatic and allergic inflammatory responses.[1] There are two known receptors of PGD_2: DP1 and DP2 (also known as CRTh2).[2–4] The latter receptor is expressed on the surface of eosinophils, basophils, and Th2 cells and is responsible for PGD_2-induced chemotaxis in all three cell types.[5] Moreover, CRTh2 is involved in cytokine release from Th2 cells and degranulation of eosinophils.[6,7] This has led to widespread interest in antagonists of CRTh2 as potential agents for the treatment of asthma and related allergic diseases.[8–13] Recent publication of the effect of CRTh2 antagonists in various animal models of asthma and allergic rhinitis have spurred further interest in the exploration of this target.[14–16]

Ramatroban and its acetic acid analog (**1**, Fig. 1) have been reported to be potent antagonists of CRTh2.[17,18] We previously disclosed the SAR of a series of 'reverse Ramatroban' analogs with similar potency to compound **1**.[10] In our attempts to design additional novel CRTh2 antagonists, we hypothesized that the saturated ring of compound **1** could be excised from the tetrahydrocarbazole and instead form a bicyclic sulfonamide, as shown in Figure 1. One such embodiment of this hypothesis is benzosultam **3**. This analog seemed especially fitting given that it would retain and rigidify the cisoid geometry that sulfonamides such as Ramatroban naturally adopt. The synthesis of compound **3** and related compounds is illustrated in Scheme 1. The synthesis begins with $AlCl_3$ promoted electrophilic addition of compound **2** (derived in one step from saccharin)[19] to an indole, giving intermediate **A**. The indole nitrogen of **A** is alkylated with *t*-butyl bromoacetate and the sulfonyl imine is subsequently reduced to give the benzosultam **C**. Deprotection of the *tert*-butyl group is accomplished with TFA giving compounds **3–10**.

Compound **3** proved to be only weakly active as an antagonist of CRTh2, with binding affinity (K_i) of approximately 9.2 μM (Table 1). Incorporation of various substituents at the 5-position (**4–6**) improved affinity by 2–3-fold. Incorporation of methyl at the 2-position (**7**) also increased binding by threefold. The effect of substituents at the 2- and 5-positions proved to be additive, as

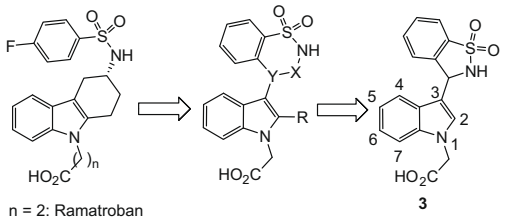

Figure 1. Stuctures of Ramatroban and lead molecule **3**.

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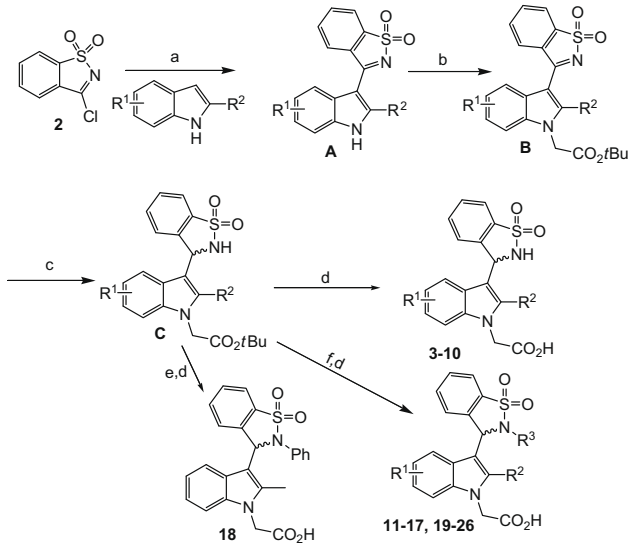
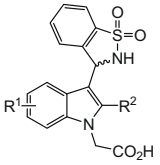


Scheme 1. Regents and conditions: (a) $AlCl_3$, DCE, 65 °C; (b) *t*-butyl bromoacetate, K_2CO_3, DMF, 80 °C; (c) $NaBH_4$, MeOH, 30 min; (d) TFA, DCM; (e) CuI (1 equiv), K_2CO_3, $MeNHCH_2CH_2NHMe$ (2 equiv), PhBr, toluene, 110 °C, 3 days; (f) alkyl halide, DMF, K_2CO_3, 80 °C, 1 h.

Table 1
SAR of unsubstituted sulfonamides



Compd[a]	R^1	R^2	K_i[b] (μM)
3	H	H	9.2
4	5-Me	H	2.9
5	5-Cl	H	2.9
6	5-CN	H	2.0
7	H	Me	2.8
8	5-Me	Me	1.5
9	5-Cl	Me	0.69
10	5-F	Me	0.43

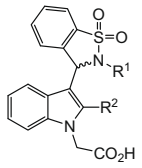
[a] All compounds were purified by preparative HPLC and were evaluated for proper identity and purity by analytical HPLC-MS and by ^{1}H NMR.
[b] Values shown are the means of at least triplicate samples from radioligand binding inhibition assays utilizing cells expressing human CRTh2.

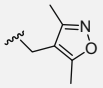
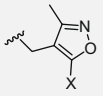
can be seen by comparing compounds **3–5** with compounds **7–9**. Combining a methyl at the 2-position with a halogen at the 5-position gave our first sub-μM compounds in this series, **9** and **10**.

We next set about to explore substitution on the sultam nitrogen. The nitrogen of intermediate **C** (Scheme 1) was alkylated by standard conditions ultimately giving compounds **11–17** and **19–26** after deprotection of the carboxylic acid. Alternatively, an Ullmann-like coupling[20] gave direct aryl substitution on nitrogen (**18**). We began our explorations with various alkylations on the unsubstituted indole scaffold (R_2 = H, Table 2). Small alkyl groups, such as methyl (**11**) and neopentyl (**12**) gave little improvement over the parent compound (**3**). However, larger groups such as 2-phenylethyl (**14**) gave more than a 10-fold improvement in affinity. To our astonishment, a dimethyl isoxazole (**15**) gave nearly a 500-fold boost in receptor-binding. This compound was greater than 10-fold more potent than any other compound in the series.

Combining a 2-methyl indole core with *N*-alkyl substituents generally improved the affinity of compounds by 2–3-fold (e.g., see **12**/**16** and **14**/**22**). Interestingly, however, the addition of a 2-methyl group to compound **15** had little effect on the potency (**19**). Rather, the presence of the isoxazole ring itself seems to drive the exceptional potency. Substitution of the isoxazole (**20**) and substitution of the indole core (**21**) had only minor effects on potency. Interestingly, the incorporation of a hydrogen bond acceptor into compound **22** resulted in compounds (**23**/**24**) with similar potency to the isoxazoles. Movement of the hydrogen bond acceptor further from the core (**25**) or replacement of the acceptor with a donor (**26**) resulted in compounds with significantly decreased potency. Taken together, these results clearly indicate that optimal potency can be obtained by incorporation of a strategically placed hydrogen bond acceptor within a few bond lengths of the sultam nitrogen.

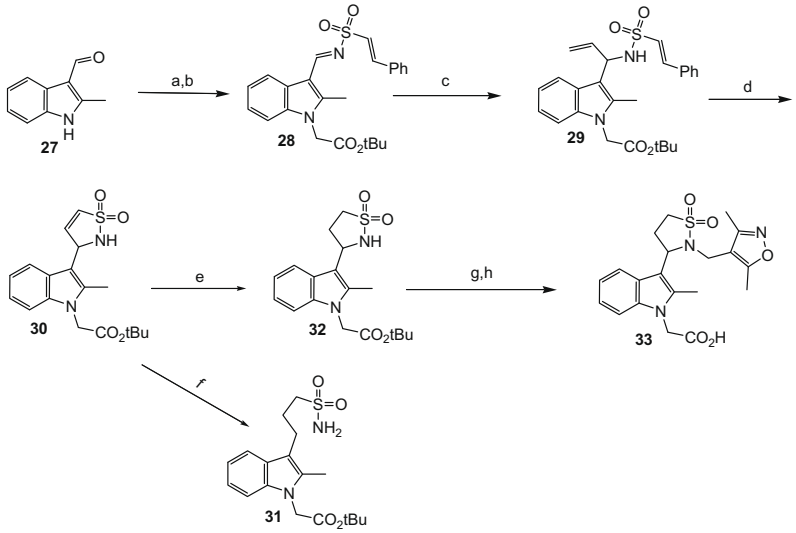
Table 2
SAR of sulfonamide substitution



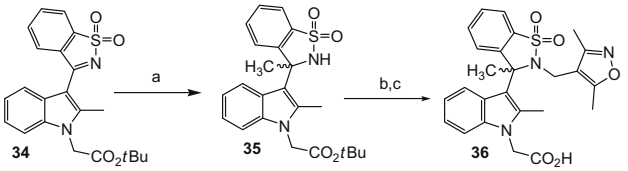
Compd[a]	R^1	R^2	K_i[b] (μM)
3	H	H	9.2
11	Me	H	8.1
12	$CH_2CH_2CH(CH_3)_2$	H	2.3
13	CH_2Ph	H	1.1
14	CH_2CH_2Ph	H	0.63
15		H	0.018
7	H	Me	2.8
16	$CH_2CH_2CH(CH_3)_2$	Me	0.56
17	$CH(CH_3)_2$	Me	0.92
18	Ph	Me	0.48
19		Me	X = Me, 0.012
20		Me	X = Ph, 0.013
21		Me	X = Me, 0.008 (5-Cl indole core)
22	CH_2CH_2Ph	Me	0.22
23	CH_2CH_2OPh	Me	0.029
24	CH_2CH_2O-(4-Cl-Ph)	Me	0.035
25	$CH_2CH_2CH_2OPh$	Me	1.4
26	CH_2CH_2OH	Me	1.4

[a] All compounds were purified by preparative HPLC and were evaluated for proper identity and purity by analytical HPLC-MS and by ^{1}H NMR.
[b] Values shown are the means of at least triplicate samples from radioligand binding inhibition assays utilizing cells expressing human CRTh2.

As previously stated, the most unexpected finding from this series of compounds was the identification of a dimethyl isoxazole side chain that gave dramatically improved binding over the parent compounds. Holding this piece of the molecule constant, a series of analogs were made to further understand the SAR of the core sultam ring. Scheme 2 shows the synthesis of a ring-deleted analog of **19**. 2-Methyl-indole-3-carbaldehyde (**27**) was alkylated and treated with (*E*)-2-phenylethenesulfonamide to give imine **28**. $AlCl_3$ mediated addition of vinyl Grignard gave compound **29**. The key step of this sequence is the ring-closing metathesis of **29** to form **30**, which occurs in good yield in refluxing DCM. Hydrogenation of **30** resulted in C–N bond cleavage giving the undesired ring-opened analog **31**. However, conjugate reduction via sodium borohydride gave the desired key intermediate **32**, which was alkylated and deprotected to give the desired product, **33**. Interestingly, acid promoted deprotection to give **32** gave a complex mixture of products and therefore a one-pot transesterification/saponification was used to remove the *tert*-butyl ester.



Scheme 2. Reagents and conditions: (a) *t*-butyl bromoacetate, K_2CO_3, DMF, 80 °C; (b) (*E*)-2-phenylethenesulfonamide, PPTS, toluene, reflux; (c) $AlMe_3$, vinyl MgBr 10 min, rt, toluene; (d) Grubb's catalyst, DCM, reflux; (e) NaBH4, *i*PrOH, 80 C; (f) H_2, Pd, EtOH (g) 4-(chloromethyl)-3,5-dimethylisoxazole, K_2CO_3, DMF, 80 °C; (h) NaOH, EtOH, 80 °C, 1 h.



Scheme 3. Reagents and conditions: (a) $AlMe_3$, MeMgBr, 10 min, 0 °C; (b) 4-(chloromethyl)-3,5-dimethylisoxazole, K_2CO_3, DMF, 80 °C; (c) TFA, DCM.

Exploration of the stereogenic carbon[21] was explored via $AlCl_3$ mediated addition of a methyl Grignard to compound **34** as outlined in Scheme 3. Addition of the dimethylisoxazole tail followed by standard deprotection of the *tert*-butyl ester gave the desired compound **36**.

As illustrated in Figure 2, addition of a methyl group to the stereogenic carbon (**36**) results in only a threefold loss of potency. Complete removal of the 'northern' aromatic ring (**33**) results in only a modest loss of affinity. This taken together with the results in Table 2, suggests that the primary driver of potency for these molecules is the combination of the 'southern' 2-methyl indole core and the strategically placed isoxazole ring. The southern carboxylate/indole moiety presumably anchors the molecule in such a way that allows the isoxazole to make one or more key hydrogen bonds with the receptor.

A few of the most active compounds were screened for selectivity against the other prostaglandin D2 receptor, DP1. Since the compounds described herein are ultimately relatives of Ramatroban, a Thromboxane-A2 (TXA2) receptor antagonist[22], we also

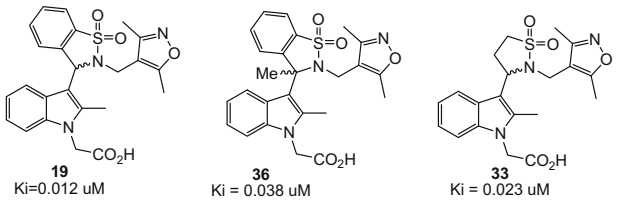


Figure 2. SAR of sultam region. (a) Values shown are the means of at least triplicate samples from radioligand binding inhibition assays utilizing cells expressing human CRTh2.

Table 3
Selectivity of the most potent compounds against the DP and TP receptors

Compd	CRTh2 K_i (μM)	DP1[a,b]	TP[a,b]
19	0.012	0% at 10 μM	0% at 10 μM
21	0.008	15% at 10 μM	0% at 10 μM
23	0.029	0% at 10 μM	K_i = 7.8 μM
24	0.035	28% at 10 μM	K_i = 3.4 μM

[a] Values shown are % inhibition of specific radioligand binding unless otherwise noted.
[b] Values shown are the means of at least triplicate samples from radioligand binding inhibition assays utilizing cells expressing human CRTh2.

screened for selectivity against the TXA2 receptor (TP). The results are shown in Table 3. As can be seen, these compounds are clearly very selective for CRTh2 over the DP1 and TP receptors. The assays described above are receptor-binding assays which do not directly measure the function (antagonism/agonism) of the compounds. To this end, compound **19** was evaluated in a FLIPR-based functional assay in order to verify that one of the most potent compounds of this series was, in fact, an antagonist of the CRTh2 receptor in a cellular context. Gratifyingly, compound **19** was shown to block the activation of the receptor by PGD_2, with a K_i of 28 nM.

In conclusion, we have identified and explored the SAR of a series of novel 3-indolyl substituted sultams that are low nanomolar antagonists of the CRTh2 receptor. The SAR indicates the importance of a hydrophobic pocket encompassing the 2-position of the indole ring along with key H-bond acceptors in the vicinity of the sulfonyl and the sultam N-substituent. The most potent compounds show essentially no activity against the other prostaglandin D2 receptor, DP1. Studies are ongoing to explore the utility of these compounds in inflammation disease models.

References and notes

1. Liu, M. C.; Bleecker, E. R.; Lichtenstein, L. M.; Kagey-Sobotka, A.; Niv, Y.; McLemore, T. L.; Permutt, S.; Proud, D.; Hubbard, W. C. *Am. Rev. Respir. Dis.* **1990**, *142*, 126.
2. Narumiya, S.; Sugimoto, Y.; Ushikubi, F. *Physiol. Rev.* **1999**, *79*, 1193.
3. Cosmi, L.; Annunziato, F.; Maggi, E.; Romagnani, S.; Manetti, R. *Int. Arch. Allergy Immunol.* **2001**, *125*, 273.
4. Nagata, K.; Hirai, H.; Tanaka, K.; Ogawa, K.; Aso, T.; Sugamura, K.; Nakamura, M.; Takano, S. *FEBS Lett.* **1999**, *459*, 195.
5. Hirai, H.; Tanaka, K.; Yoshie, O.; Ogawa, K.; Kenmotsu, K.; Takamori, Y.; Ichimasa, M.; Sugamura, K.; Nakamura, M.; Takano, S.; Nagata, K. *J. Exp. Med.* **2001**, *193*, 255.

6. Tanaka, K.; Hirai, H.; Takano, S.; Nakamura, M.; Nagata, K. *Biochem. Biophys. Res. Commun.* **2004**, *316*, 1009.
7. Gervais, F. G.; Cruz, R. P. G.; Chateauneuf, A.; Gale, S.; Sawyer, N.; Nantel, F.; Metters, K. M.; O'Neill, G. P. *J. Allergy Clin. Immunol.* **2001**, *108*, 982.
8. Ly, T. W.; Bacon, K. B. *Expert Opin. Invest. Drugs* **2005**, *14*, 769.
9. Ulven, T.; Kostenis, E. *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)* **2006**, *6*, 1427.
10. Robarge, M. J.; Bom, D. C.; Tumey, L. N.; Varga, N.; Gleason, E.; Silver, D.; Song, J.; Murphy, S. M.; Ekema, G.; Doucette, C.; Hanniford, D.; Palmer, M.; Pawlowski, G.; Danzig, J.; Loftus, M.; Hunady, K.; Sherf, B. A.; Mays, R. W.; Stricker-Krongrad, A.; Brunden, K. R.; Harrington, J. J.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1749.
11. Birkinshaw, T. N.; Teague, S. J.; Beech, C.; Bonnert, R. V.; Hill, S.; Patel, A.; Reakes, S.; Sanganee, H.; Dougall, I. G.; Phillips, T. T.; Salter, S.; Schmidt, J.; Arrowsmith, E. C.; Carrillo, J. J.; Bell, F. M.; Paine, S. W.; Weaver, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4287.
12. Sandham, D. A.; Adcock, C.; Bala, K.; Barker, L.; Brown, Z.; Dubois, G.; Budd, D.; Cox, B.; Fairhurst, R. A.; Furegati, M.; Leblanc, C.; Manini, J.; Profit, R.; Reilly, J.; Stringer, R.; Schmidt, A.; Turner, K. L.; Watson, S. J.; Willis, J.; Williams, G.; Wilson, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4794.
13. Crosignani, S.; Page, P.; Missotten, M.; Colovray, V.; Cleva, C.; Arrighi, J.-F.; Atherall, J.; Macritchie, J.; Martin, T.; Humbert, Y.; Gaudet, M.; Pupowicz, D.; Maio, M.; Pittet, P.-A.; Golzio, L.; Giachetti, C.; Rocha, C.; Bernardinelli, G.; Filinchuk, Y.; Scheer, A.; Schwarz, M. K.; Chollet, A. *J. Med. Chem.* **2008**, *51*, 2227.
14. Hoegberg, T.; Ulven, T.; Receveur, J.-M.; Grimstrup, M.; Rist, O.; Frimurer, T. M.; Gerlach, L.-O.; Mathiesen, J. M.; Kostenis, E.; Uller, L. *J. Med. Chem.* **2006**, *49*, 6638.
15. Shichijo, M.; Arimura, A.; Hirano, Y.; Yasui, K.; Suzuki, N.; Deguchi, M.; Abraham, W. M. *Clin. Exp. Allergy* **2009**, *39*, 1404.
16. Stearns, B. A.; Baccei, C.; Bain, G.; Broadhead, A.; Clark, R. C.; Coate, H.; Evans, J. F.; Fagan, P.; Hutchinson, J. H.; King, C.; Lee, C.; Lorrain, D. S.; Prasit, P.; Prodanovich, P.; Santini, A.; Scott, J. M.; Stock, N. S.; Truong, Y. P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4647.
17. Sugimoto, H.; Shichijo, M.; Iino, T.; Manabe, Y.; Watanabe, A.; Shimazaki, M.; Gantner, F.; Bacon, K. B. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 347.
18. Iwahashi, M.; Naganawa, A.; Nishiyama, T.; Nagase, T.; Kobayashi, K.; Nambu, F.; (Ono Pharmaceutical Co., Ltd., Japan), WO2004078719, 2004.
19. Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P., Jr.; Harakal, M. E.; Gosciniak, D. J. *J. Org. Chem.* **1990**, *55*, 1254.
20. Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.
21. All compound were made as racemates. Attempts to separate the two enantiomers by chiral HPLC were unsuccessful.
22. McKenniff, M. G.; Norman, P.; Cuthbert, N. J.; Gardiner, P. J. *Br. J. Pharmacol.* **1991**, *104*, 585.