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Optimization of phenylacetic acid derivatives for CRTH2 and DP selective antagonism

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ABSTRACT

We have previously reported that optimization of a series of phenylacetic acid derivatives led to the discovery of CRTH2 and DP dual antagonists, such as AMG 009 and AMG 853. During the optimization process, we discovered that minor structural modifications also afforded potent and selective CRTH2 or DP antagonists. Here we report the structure–activity relationship that led to the discovery of selective CRTH2 antagonists such as **2** and **17**, and selective DP antagonists, such as **4** and **5**.

CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells, also known as DP_2) and DP (prostanoid D receptor, also known as DP_1) are both G-protein coupled receptors. Their endogenous ligand is prostaglandin D_2 (PGD_2), which plays a key role in mediating allergic reactions seen in allergic diseases.[1,2] Stimulation of these two GPCRs promotes a number of biological effects associated with the development and maintenance of allergic responses. Numerous studies using DP and CRTH2 antagonists, combined with genetic analysis, support the view that these receptors play a pivotal role in mediating allergic diseases.[3–5] Therefore, there has been great interest in the discovery and development of DP and CRTH2 antagonists, especially for CRTH2 antagonists for the treatment of asthma and other allergic diseases.[6–21]

We have previously reported the optimization of phenylacetic acid derivatives that led to the discovery of AMG 009 and AMG 853 (Fig. 1), two potent CRTH2 and DP dual antagonists.[22,23] Here we report that the same optimization also identified potent selective antagonists of CRTH2 and DP.

The synthesis of compounds in this publication is shown in Schemes 1–3. Compounds **1**–**4** and **8**–**11** were prepared using the same route as previously reported (Scheme 1).[22,23]

Compound **5** was prepared in a similar manner to the one in Scheme 1 with an additional fluorination step (Scheme 2). Difluorination of the α-oxophenylacetate to form the α,α-difluorophenylacetate was achieved using DAST (step iii of b, Scheme 2).[24] Compounds **6** and **7** were synthesized from AMG 009 using reported procedures.[25,26]

Compounds **14**–**19** were synthesized in five steps (Scheme 3). 2-Fluoro-5-nitrobenzoic acid was treated with 3-hydroxy-4-methoxyphenylacetic acid ethyl ester in the presence of potassium carbonate to give the bisaryl ether, whose nitro group was reduced using hydrogenation. The aniline was then converted into the corresponding propionyl amide. The benzoic acid was also converted into various amides through reaction with amines in step d. The ethyl ester was finally hydrolyzed to afford the phenylacetic acids.

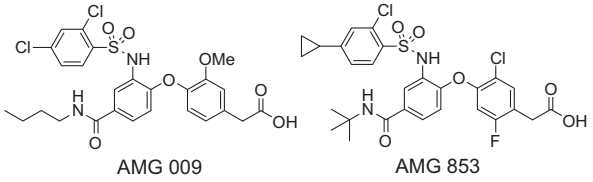

Figure 1.

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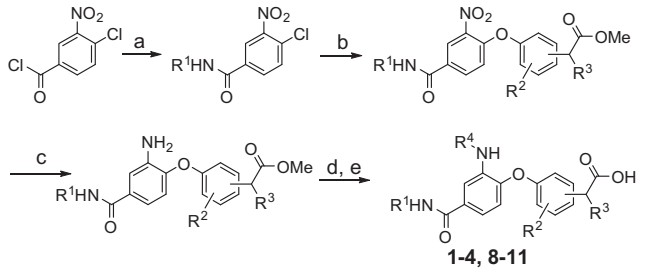
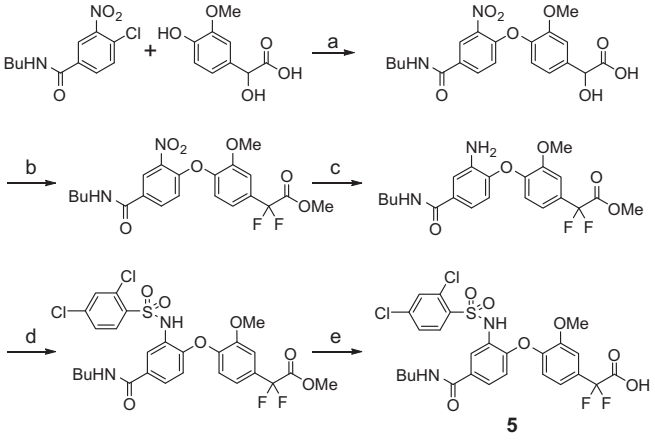
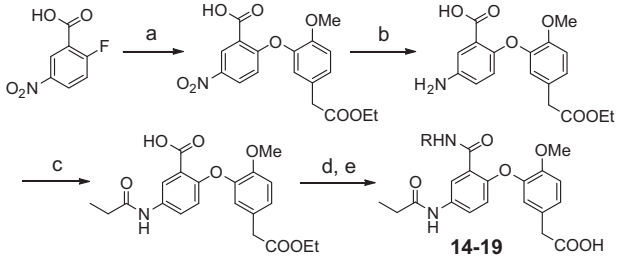


Scheme 1. Reagents and conditions: (a) Ethylamine or *n*-butylamine, triethylamine, DCM, rt, 4 h, ~90%; (b) phenylacetic acids methyl ester, cesium carbonate, DMSO, 70 °C, 6 h, ~85%; (c) H_2, Pd/C, EtOH, rt, 1 h, 100% or $SnCl_2$, EtOAc, 60 °C, 4 h, 80%; (d) For sulfonamides **1**–**4** and **8**, sulfonyl chlorides, pyridine, rt, 24 h, 70%; for amines **9** and **10**, aldehydes, $NaBH(OAc)_3$, DCE, rt, 3 h, 80%; for urea **11**, isocyanate, triethylamine, EtOAc, rt, 12 h, 80%; (e) LiOH, MeOH/THF/H_2O, 23 °C, 2 h, ~80%.



Scheme 2. Reagents and conditions: (a) Cs_2CO_3, DMSO, 60 °C, 3 days, 68%; (b) (i) $TMSCHN_2$, MeOH/benzene, 23 °C, 0.5 h; (ii) Dess–Martin periodinane, DCM, 23 °C, 14 h; (iii) DAST, DCE, 90 °C, 4 h, 55%, three steps (Ref.[23]); (c) H_2, Pd/C, EtOH/EtOAc, 23 °C, 48 h, 88%; (d) 2,4-dichlorobenzenesulfonyl chloride, 2,6-lutidine, 40 °C, 20 h, 67%; (e) LiOH, MeOH/THF/H_2O, 23 °C, 2 h, 47%.



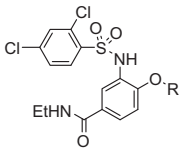
Scheme 3. Reagents and conditions: (a) 3-Hydroxy-4-methoxyphenylacetic acid ethyl ester, K_2CO_3, DMSO, 80 °C, 8 h, 70%; (b) H_2, Pd/C, EtOH, rt, 1 h, 100%; (c) propionyl chloride, triethylamine, DCM, rt, 3 h, 90%; (d) Amines, EDC, HOBt, triethylamine, DCM, rt, 1 day, 80%; (e) LiOH, MeOH/THF/H_2O, 23 °C, 2 h, ~80%.

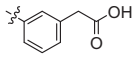
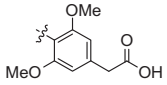
Modification of the phenylacetic acid moiety affected the selectivity toward CRTH2 and DP. As previously reported, *meta*-phenylacetic acid derivatives, such as **1**, are CRTH2 selective (Table 1) and the *para*-phenylacetic acid derivatives can either be CRTH2 and DP dual antagonist (AMG 009) or CRTH2 selective antagonist (**2**), depending on the substitutions on the phenyl ring of the phenylacetic acid.[22]

DP selective antagonists were generated through modifying the acetic acid moiety (Table 2). Dialkylation at the α-position of the acetic acid moiety provided molecules, exemplified by **3** and **4**, with increased selectivity for DP over CRTH2. The α,α-difluorophenylacetate (**5**) has improved affinity for DP and significantly reduced activity on CRTH2 compared to AMG 009. Bioisosteric replacements of the carboxylic acid also afforded DP selective antagonists. The tetrazole (**6**) and acyl sulfonamide (**7**) maintained similar activity on the DP receptor as compared to the corresponding carboxylic acid (AMG 009). However, their affinity for the CRTH2 receptor was greatly reduced.

CRTH2 selective antagonists were also obtained by modifying the sulfonamide moiety. Several replacements of the sulfonamide moiety were evaluated and a few representative compounds are listed in Tables 3 and 4. The data in these tables indicates that replacement of the sulfonamide moiety leads to loss of DP activity. With the exception of sulfone **12**, none of the compounds in Table 3

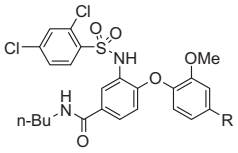
Table 1
CRTH2 selective antagonists



Compd	R	CRTH2 IC_{50}[a] in buffer (μM)	DP IC_{50}[a] in buffer (μM)
1		0.016	>10
2		0.002	16.0

[a] Displacement of ^{3}H-PGD_2 from the CRTH2 or DP receptors expressed on 293 cells. Assay run in buffer containing 0.5% BSA. See Ref. 27 for assay protocol. Values are means of three experiments, standard deviation is ± 30%.

Table 2
Modification of the acetic acid moiety



Compd	R	CRTH2 IC_{50}[a] in buffer (μM)	DP IC_{50}[a] in buffer (μM)
AMG 009		0.003	0.012
3		>10	0.91
4		>10	0.013
5		0.42	0.003
6		0.35	0.007
7		0.33	0.006

[a] Displacement of ^{3}H-PGD_2 from the CRTH2 or DP receptors expressed on 293 cells. Assay run in buffer containing 0.5% BSA. See Ref. 27 for assay protocol. Values are means of three experiments, standard deviation is ± 30%.