Letter

Discovery of fevipiprant (NVP-QAW039), a potent and selective DP2 receptor antagonist for treatment of asthma

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Discovery of fevipiprant (NVP-QAW039), a potent and selective DP_2 receptor antagonist for treatment of asthma

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ABSTRACT: Further optimization of an initial DP_2 receptor antagonist clinical candidate NVP-QAV680 led to the discovery of a follow up molecule 2-(2-methyl-1-(4-(methylsulfonyl)-2-(trifluoromethyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid (compound **11**, NVP-QAW039, fevipiprant) which exhibits improved potency on human eosinophils and Th2 cells, together with a longer receptor residence time and is currently in clinical trials for severe asthma

Keywords: *DP_2 receptor antagonist; severe asthma; clinical candidate*

Antagonism of the action of the lipid mediator prostaglandin D_2 (PGD_2) at the DP_2 (also known as CRTh2: Chemoattractant Receptor Homologous expressed on Th2 cells) receptor represents a potential new approach for treatment of asthma and allergic rhinitis.[1] PGD_2 is produced primarily from IgE activated mast cells and promotes activation and migration of eosinophils, Th2 lymphocytes and basophils through activation of the DP_2 receptor expressed on these cell types, which are the principal drivers of the late phase allergic inflammatory response.[2] More recently, Type-2 innate lymphoid cells (ILC2) have emerged as an additional DP_2 dependent cell type important in the immune response in allergic asthma.[3] Conversely, the majority of the homeostatic functions of PGD_2 appear to be mediated by the classical prostanoid DP_1 receptor,[4] which has further increased the attractiveness of selectively targeting DP_2. Multiple drug discovery campaigns have been reported in the literature, culminating in a number of compounds (selected examples in Chart 1) which have progressed to clinical studies in allergic rhinitis, asthma, chronic obstructive pulmonary disease and eosinophilic esophagitis patients. [5]

Amongst these is NVP-QAV680 **1**, of which we have recently disclosed the discovery and characterization as a clinical candidate.[6] Following demonstration of excellent safety and tolerability in single and multiple ascending dose Phase I healthy volunteer studies, positive results in two clincial proof of concept (PoC) studies were obtained in allergic rhinitis.[7-9] However, the twice or four times daily daily dosing regime utilized was considered a limitation in respect of patient convenience and compliance and consequently a follow up compound was sought with potential for improved duration of action.

In this Letter we disclose SAR associated with the further optimization of **1**, which has culminated in discovery of 2-(2-methyl-1-(4-(methylsulfonyl)-2-(trifluoromethyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid **11** (NVP-QAW039, fevipiprant) a potent selective DP_2 receptor antagonist suitable for once daily dosing with improved potency and slower receptor dissociation compared to QAV680 and other reported DP_2 antagonists which have progressed to the clinic.[10] Fevipiprant reduces eosinophilic airway inflammation in patients with persistent asthma and raised sputum eosinophil counts. This is associated with improved lung function and asthma-related quality of life, and a favorable safety profile.[11]

During the hit-to-lead phase of the project, some variations of the core substituents of the azaindole scaffold had been investigated without leading to potency improvements. Notably substitution, truncation or extension of the C-3 acetic acid moiety, or deletion of the C-2 methyl group all suppressed DP_2 affinity, in line with subsequently disclosed SAR on related indole series.[12] However with the 4-(methylsulfonyl)benzyl moiety established as an optimal N-1 substituent in **1**, we revisited selected substitutions of the 7-azaindole scaffold, the results of which are presented in Table 1.

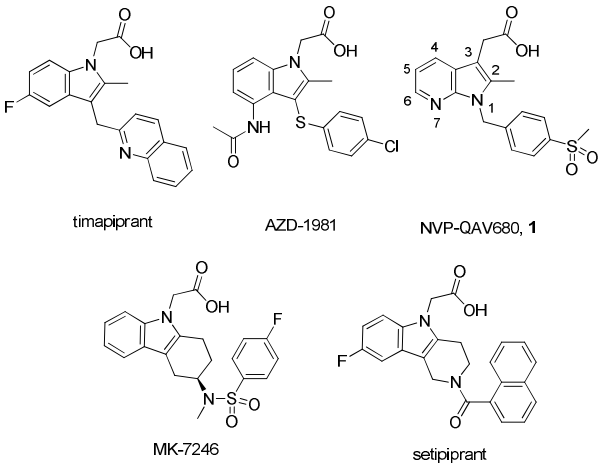
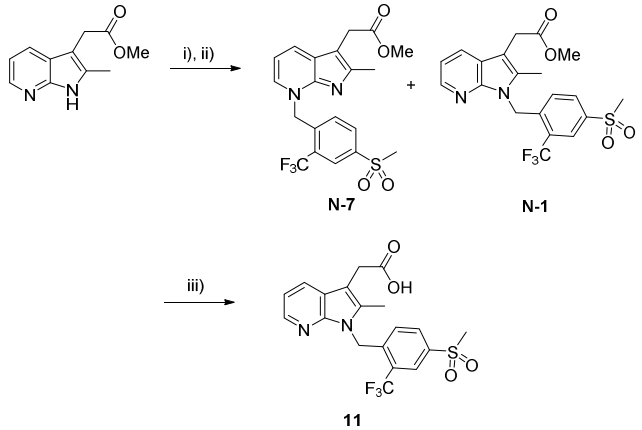


Chart 1: Selected indole and azaindole DP_2 antagonists progressed to the clinic

Compounds were prepared by alkylation of the appropriate indolyl- or 7-azaindolyl-3-acetic acid methyl ester with a benzyl bromide derivative as previously described.[6] Synthetic schemes for preparation of the substituted azaindolyl-3-acetic acid methyl esters are included in the Supplementary Information. In contrast to the synthesis of **1**, N-alkylation with the benzyl bromide precursor to **11** afforded only modest regioselectivity in favor of the desired N-1 alkyl product (Scheme 1), and the further the reaction was driven to completion, the more N-7 product was observed. However the pure compound **11** could be readily separated from the undesired N-7 isomer by crystallization after ester hydrolysis. This alkylation product ratio proved refractory to variations in base or benzyl halide selection and the development of an alternative synthetic route will be the subject of a separate publication.

Scheme 1: Synthesis of compound **11**

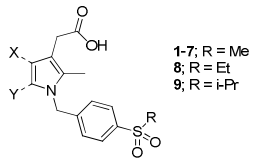


Reagents and conditions: i) Cs_2CO_3, $MgSO_4$, acetone, reflux; ii) 1-(bromomethyl)-4-(methylsulfonyl)-2-(trifluoromethyl)benzene, RT-reflux, 42%, ratio **N-7**:**N-1** 17:83; iii) aq NaOH, acetone RT, 44%

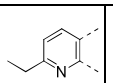
Excision of the 7-azaindole nitrogen delivered the indole **2** with similar DP_2 binding affinity, although a significant loss of potency in both the isolated and whole blood (WB) human eosinophil shape change (SC) functional assays was observed, while substitution at C-4 or C-5 (compounds **3-5**) delivered up to an order of magnitude reduction in binding affinity. C-6 was the only position where comparable activity to the prototype was retained (compounds **6-7**). Next we briefly explored the sulfone alkyl substituent, which indicated the ethyl and isopropyl sulfone analogues **8** and **9** were broadly equivalent to **1**.

At this point, in the absence of any additional potency breakthrough compared to **1**, and building on the initial binding SAR preferences for electron-deficient N-1 aromatic substituents,[6] we executed a more diverse array of polysubstituted electron-deficient N-1 benzyl analogues lacking the sulfone moiety. The key result from this exercise was the 2,4-bis(trifluoromethyl) analogue **10**, which exhibited similar binding potency to **1**, albeit with a significant drop off in WB potency. With this result in hand, a follow-up array of analogs re-incorporating the sulfone moiety together with a second aromatic ring substituent was prepared (Table 2). Several 2,4-disubstituted sulfones **11, 12**, **15** and **16** exhibited sub-10 nM binding affinity, with the 3,4-disubstitution pattern clearly less favourable as exemplified by compound **14**. However compound **11** was the stand out example in the WB assay, where sub-nM potency was attained, an approximately 40-fold improvement on **1**, although the difference in DP_2 binding affinity was somewhat lower at approximately 8-fold.

Table 1: Core modified and sulfone analogues of **1**



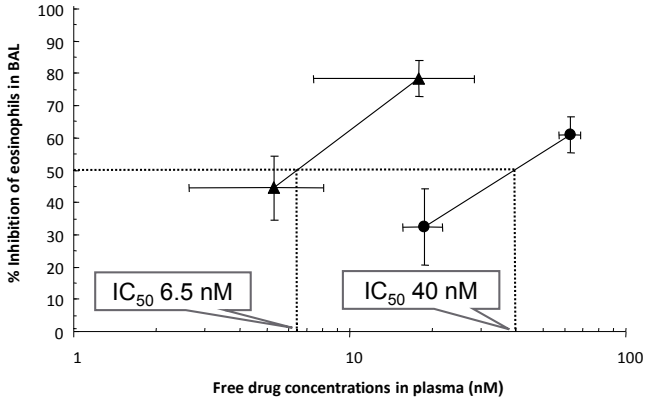
compd	X Y	DP_2 Ki (μM)[a]	Eosinophil SC IC_{50} (μM) isolated[b]	WB[c]
1		0.036	0.005	0.031
2		0.019	0.02	0.188
3		0.356	0.08	nd
4		0.735	nd	nd
5		1.335	nd	nd
6		0.072	nd	nd

7		0.047	0.006	nd
8		0.050	0.004	nd
9		0.086	nd	nd

[a] human DP_2 receptor scintillation proximity binding assay with [^{3}H]-PGD_2; [b] isolated human eosinophil shape change assay; [c] human whole blood eosinophil shape change assay; nd not determined. See reference 6 for assay descriptions. For all assays data represents the mean of at least two experiments.

Rat pharmacokinetic data generated on a selection of the potent analogues (Table 3) revealed good to excellent oral biovailability combined with generally lower clearance compared to **1**. While this pre-clinical data did not provide significant differentiation from **1** based on half life, we reasoned that a more potent compound with a similar half life could faciliate extended exposure coverage at the DP_2 receptor. Consequently, based on the human *in vitro* data, **11** was selected for a head to head comparison dosed orally with **1** in a PK-PD (pharmacokinetic-pharmacodynamic) mechanistic target engagement model of pulmonary eosinophilia induced by the DP_2 specific agonist 14,15-dihydro-15-ketoprostaglandin D_2 (DK-PGD_2) as previously described.[6] As before, we did not have access to a rat in vitro DP_2 assay, however compound **11** was approximately 6-fold more potent for inhibition of eosinophilia in broncho alveolar lavage (BAL) fluid than **1** based on free fraction derived from *in vitro* rat plasma protein binding data (Figure 1).

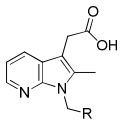
Figure 1: PK-PD comparison of **1** and **11** in a rat model of pulmonary eosinophilia

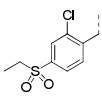
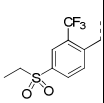


Data expressed as mean ± SEM for n = 8 animals per group. ▲ compound **11** dosed p.o. at 0.03 and 0.1 mg/kg; ● compound **1** dosed p.o. at 0.1 and 0.3 mg/kg. Y axis represents inhibition of BAL eosinophilia window between i.t. DK-PGD_2 challenged and vehicle treated animals. X-axis represents free drug concentration from unbound fractions (f_u) in rat plasma determined by equilibrium dialysis. Compound **1** rat plasma f_u 0.34; compound **11** rat plasma f_u 0.08. See reference 6 for assay descriptions

Further *in vitro* data comparing **1** with **11** for blockade of DP_2 agonist-induced IL-5 and IL-13 cytokine production in human primary CD4+ Th2 cells is shown in Table 4, where again a potency difference somewhat larger than anticipated based on binding affinity was observed. In addition, compound **11** was also a potent inhibitor of DP_2 agonist-induced IL-4 production. Blockade of the signaling of IL-4 and IL-13 using an antibody to the IL-4 receptorα (which binds both cytokines) has recently been shown to positively impact on both rates of exacerbations and lung function in persistent asthmatic patients.[13]

Table 2: Disubstituted analogues of **1**



Compd	R	DP_2 Ki (μM)[a]	Eosinophil SC IC_{50} (μM) isolated[b]	WB[c]
10		0.029	0.014	0.214
11		0.004	0.0004	0.0004
12		0.004	0.0017	0.047
13		0.031	0.004	0.032
14		0.031	0.004	0.011
15		0.006	0.0013	0.007
16		0.007	0.0008	0.004

[a] human DP_2 receptor scintillation proximity binding assay with [^{3}H]-PGD_2; [b] isolated human eosinophil shape change assay; [c] human whole blood eosinophil shape change assay. See reference 6 for assay descriptions. For all assays data represents the mean of at least two experiments.

Table 3: Rat in vivo pharmacokinetic data[a,b]

compd	Cl (ml/min/kg)	V_{ss} (L/kg)	i.v. $T_{½}$ (hr)	F_{po}
1	15.2	5.5	17.1	54%
11	1.6	1.1	13.2	43%
15	4.4	1.1	7.7	71%
16	2.9	1.2	9.2	97%

[a] Compounds dosed i.v. 0.5 mg/kg in PEG-PBS vehicle; [b] Compounds dosed p.o. 3 mg/kg suspension in 1% NaCMC vehicle. See reference 6 for experimental descriptions.

Table 4: In vitro human CD4+ Th2 cell data: inhibition of DK-PGD_2 induced cytokine production

compd	IC_{50} (μM)		
	IL-4 inhibition	IL-5 inhibition	IL-13 inhibition
1	nd	0.059	0.025
11	0.0031	0.0026	0.0014

See references 6 and 10 for assay descriptions; for all assays data represents the mean of at least two experiment; nd: not determined

While this improved human potency was critical in selection of **11** for development as a follow up to **1** with potential for improved duration of action, it also prompted further post-lead optimization exploration of the in vitro DP_2 receptor kinetics of **1** and selected analogs utilizing [^{3}H]-**11** as a radioligand.[10] (Table 5). Interestingly the effect of deleting the N-7 nitrogen (indole analog **2**) appears to confer a pronounced reduction in target residence time, while **11** clearly exhibits the most favourable kinetic profile of the four compounds. The slower off-rate of **11** from the DP_2 receptor could potentially deliver improved efficacy, as it can insurmountably block the DP_2 receptor[10] even in the face of high local concentrations of PGD_2. This may be an explanation for the increased potency of **11** in the primary human eosinophil and Th2 cell assays and may positively impact clinical efficacy. Since this work was completed, the first reports of structure-kinetic relationships for DP_2 antagonists have appeared[14-17] together with characterization of a compound LAS191859 reported to have a half life of 21 hours based on GTPγS assay data and a duration of action apparently independent of plasma levels in a guinea pig mechanistic model of systemic eosinophilia.[18] It is noteworthy that the kinetics in that work were determined at ambient temperature, whereas our studies were all undertaken at physiological temperature. This difference in experimental conditions can have a significant impact on reported receptor half life values.[19]

Table 5: DP_2 receptor kinetic data determined at 37°C[a]

compd	k_{on} ($M^{-1}min^{-1}$)	k_{off} (min^{-1})	Dissociation $T_{½}$ (min)	pK_d
1	4.80×10^7	0.66	1.29	7.82
2	2.23×10^8	4.05	0.18	7.60
11	6.27×10^7	0.061	12.04	8.99
15	1.69×10^8	0.22	3.36	8.72

[a] Determined by [^{3}H]-**11** radioligand binding. See reference 10 for assay descriptions. For all assays data represents the mean of at least two experiments.

Further profiling of **11** against related prostanoid receptor targets showed minimal affinity (IC_{50} >10 μM) for the DP_1, EP_2, EP_4, FP and TP receptors together with minimal activity as a functional agonist or antagonist (EC_{50}/IC_{50} >10 μM) at the EP_3 and IP receptors. (EP_1 activity was not determined due to non-availability of the radioligand) In broader off-target screening, compound **11** was inactive (IC_{50} >10 μM or < 50% inhibition at 10 μM) against 165 receptors, ion channels, transporters and enzymes targets in Novartis and external (MDS, now Eurofins-Panlabs) screening panels. This favorable profile was also confirmed by the absence of unexpected adverse findings in the toxicology studies performed in rats and dogs. The overall selectivity of this molecule was further underscored by the lack of activity (IC_{50} > 100 μM) against human CYP1A2, CYP2C9, CYP2D6 and CYP3A4 isoforms and in a PXR-based CYP3A4 induction assay a similar lack of activity was exhibited. Taken together, this latter data indicates a low potential for cytochrome P450 mediated drug-drug interactions involving **11** in the clinical context.

In summary, further optimization of the initial clinical candidate NVP-QAV680 **1** identified a compound **11** with improved potency across in vitro human primary cellular DP_2 assays and also in a rat pulmonary DP_2 dependent mechanistic target engagement model. Additional characterization identified a slower DP_2 receptor off rate for **11**, which may afford improved efficacy in the face of high local concentrations of PGD_2 during the allergic inflammatory response. Clinical studies in healthy volunteers confirmed safety and tolerability, combined with an improved human pharmacokinetic profile suitable for once daily dosing in comparison with **1**.[21] These data enabled a PoC study in mild-moderate uncontrolled allergic asthmatics.[22] Subsequently, in patients with persistent asthma and raised sputum eosinophil counts, a reduction of eosinophilic airway inflammation was observed, which was associated with improved lung function and asthma-related quality of life.[11] Compound **11** (NVP-QAW039, fevipiprant) is currently ongoing in Phase III clinical studies for treatment of severe asthma.[23-25]

ASSOCIATED CONTENT

Supporting Information. Synthetic schemes, experimental details and characterization data for preparation of com-

pounds **2**-**16** and associated intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors.

ABBREVIATIONS

BAL, broncho alveolar lavage; CRTh2, Chemoattractant Receptor Homologous expressed on Th2 cells; DK-PGD_2, 14,15-dihydro-15-ketoprostaglandin D_2; DP2, Prostaglandin D_2 receptor 2; fu, unbound fraction; PGD_2, prostaglandin D_2; PK-PD, pharmacokinetic-pharmacodynamic; PoC, proof of concept; SAR, structure activity relationship; SC, shape change; WB, whole blood.

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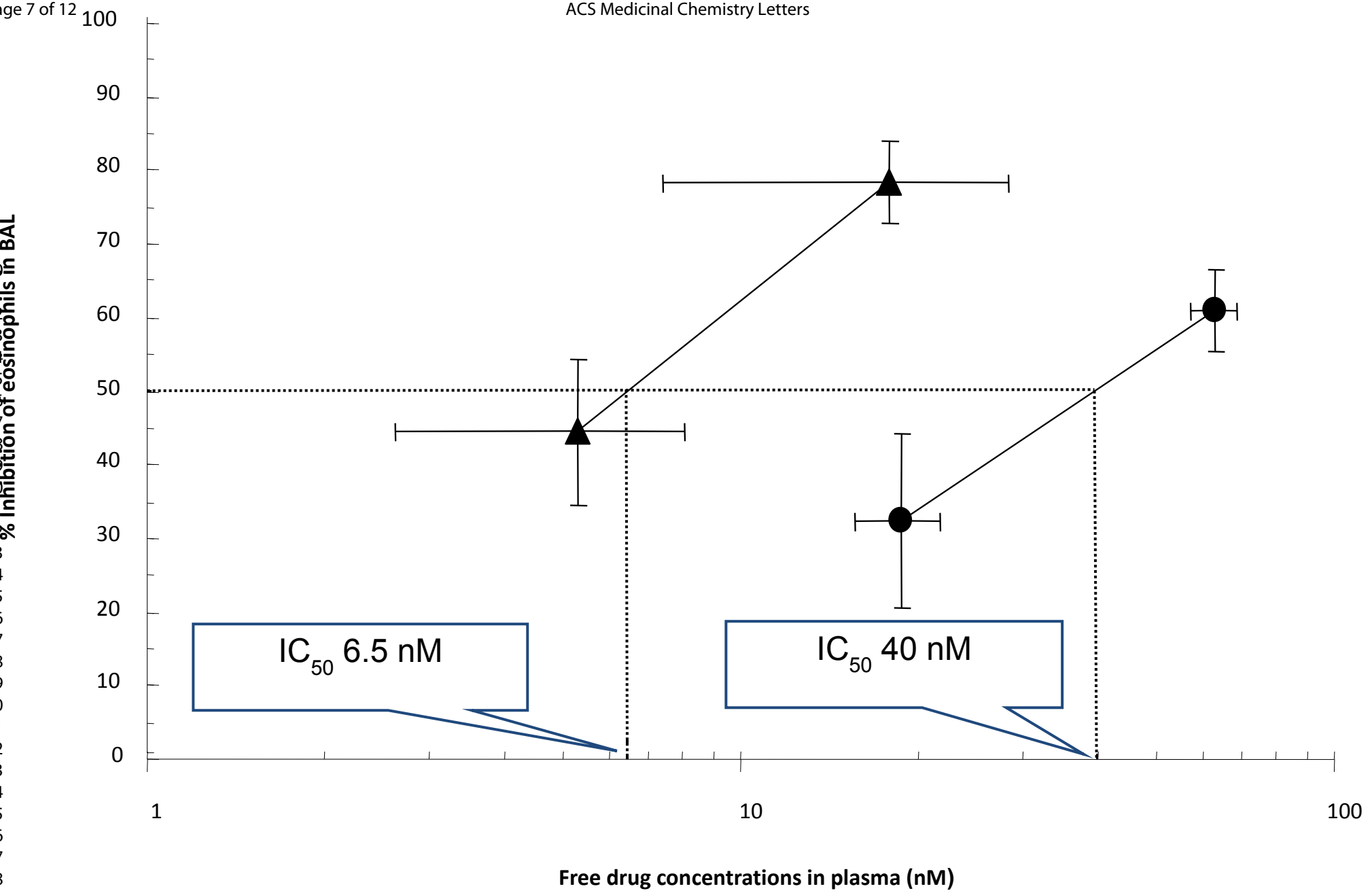
23 Clinicaltrials.gov: NCT02555683. Study of Efficacy and Safety of QAW039 in Patients With Severe Asthma Inadequately Controlled With Standard of Care Asthma Treatment (Accessed 20 April 2017) at https://clinicaltrials.gov/ct2/show/NCT02555683

24 Clinicaltrials.gov: NCT 2563067. Study of Efficacy and Safety of QAW039 in Patients With Severe Asthma Inadequately Controlled With Standard of Care Asthma Treatment (Accessed 20 April 2017) at https://clinicaltrials.gov/ct2/show/NCT02563067

25 Clinicaltrials.gov: NCT03052517. Study of Safety of QAW039 in Patients With Asthma Inadequately Controlled on Standard-of-care Asthma Treatment (Accessed 20 April 2017) at https://clinicaltrials.gov/ct2/show/NCT03052517


100
90
80
70
60
50
40
30
20
10
0
% inhibition of eosinophils in BAL
IC50 6.5 nM
IC50 40 nM
1
10
100
Free drug concentrations in plasma (nM)

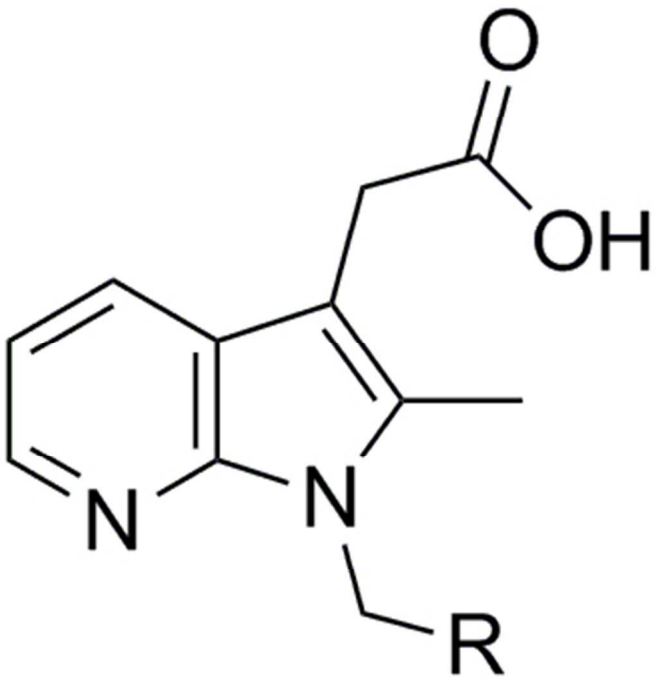


Table 2: Disubstituted analogues of 1

37x38mm (300 x 300 DPI)

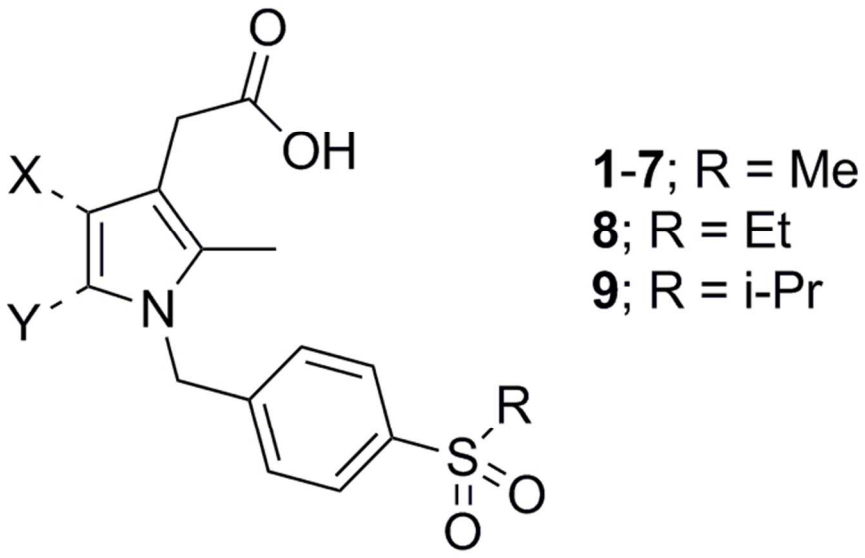
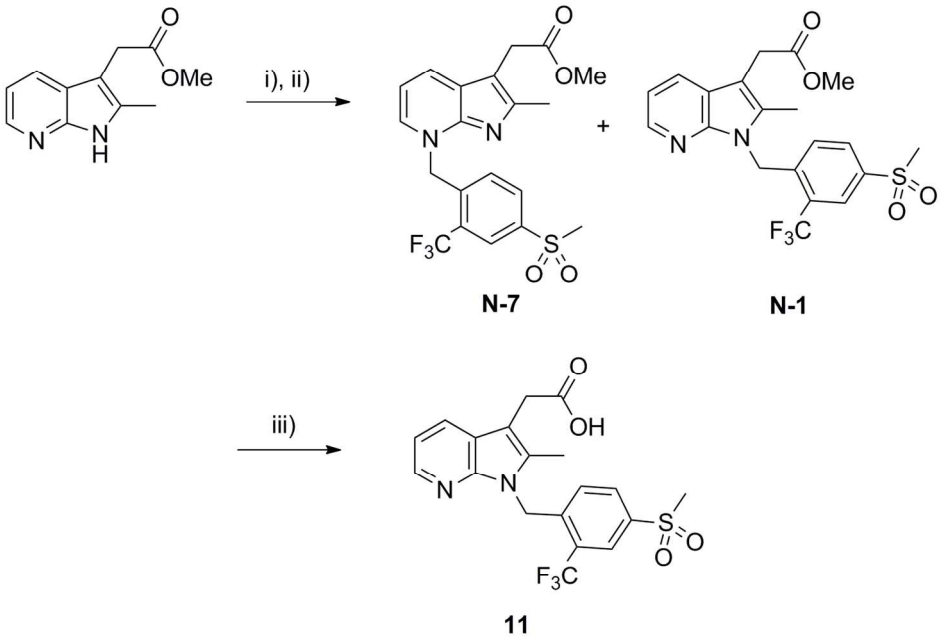


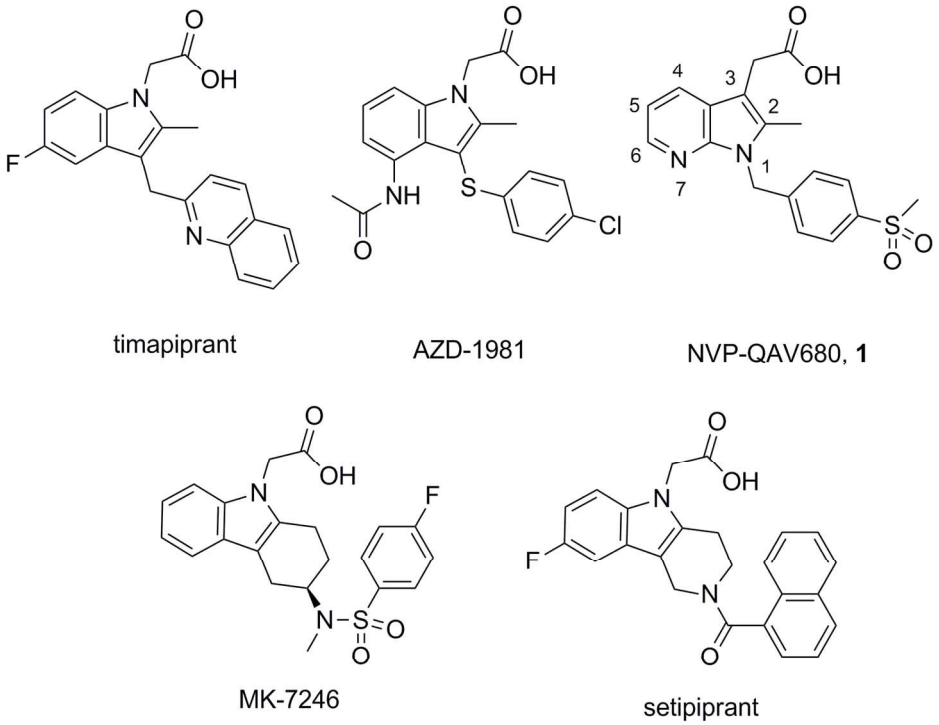
Table 1: Core modified and sulfone analogues of 1

68x47mm (300 x 300 DPI)



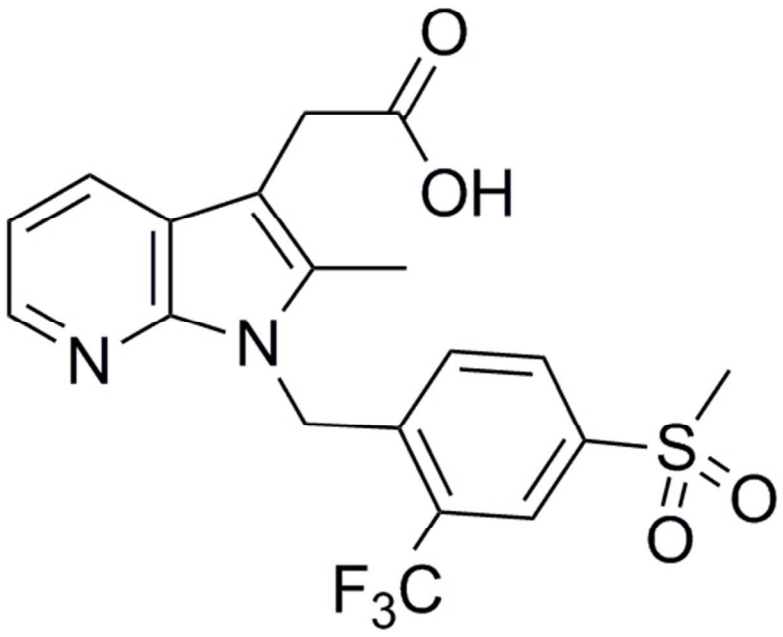
Scheme 1: Synthesis of compound 11

145x102mm (300 x 300 DPI)



Selected indole and azaindole DP2 antagonists progressed to the clinic

141x111mm (300 x 300 DPI)



11

Fevipiprant (NVP-QAW039)

Graphical abstract

54x61mm (300 x 300 DPI)