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Discovery of potent and selective DP1 receptor antagonists in the azaindole series

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ABSTRACT

Azaindole based structures were evaluated as DP1 receptor antagonists. This work has lead to the discovery of potent, selective and distinct DP1 receptor antagonists.

Niacin (nicotinic acid) has been clinically demonstrated to improve the lipid profile and reduce cardiovascular events in patients with cardiovascular disease.[1] However, the clinical use of niacin for treating dyslipidemia has been limited by niacin-induced flushing (erythema, warmth, pruritis, tingling) of the face, neck and upper torso.[1] Preclinical and clinical studies have shown that blockade of the prostaglandin D_2 (PGD_2) G-protein coupled receptor termed DP1 suppresses the vasodilation and symptoms associated with niacin administration,[2–4] thus significantly improving its tolerability. It is noteworthy that PGD_2 possesses two distinct receptors; DP1 and CRTH2.[2] The niacin-induced vasodilation adverse effect is mediated by means of PGD_2 acting through the DP1 receptor, rather than the CRTH2 receptor.[2]

MK-0524 **1** (Fig. 1) an indole derivative has been identified as a potent (K_i 0.57 nM) and selective DP1 receptor antagonist.[5] Following the discovery of MK-0524, our group focused on the identification of backup compounds in distinct structural classes **2**.[6]

The azaindole group was considered as a potential surrogate for the indole core, thus providing a distinct series of DP1 receptor antagonists. Azaindoles are less electron rich as compared to indoles and may possess improved metabolic stability. Initially, we turned our attention to the synthesis of azaindole analogs **3** (Fig. 2) based on the reverse indole series **2** (Fig. 1).[6] Therefore, the development of an efficient method to prepare the azaindole core structure **4**, with substitution at C_4 in order to mimic the

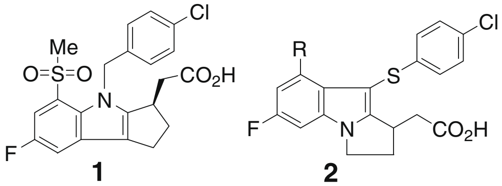

Figure 1. MK-0524 (**1**) a potent DP1 receptor antagonist (K_i = 0.57 nM) and reverse indole series (**2**).

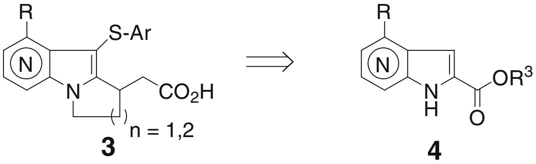

Figure 2. Core structure of azaindoles.

MK-0524 structure (**1**), became a key element for the elaboration of DP antagonists in this series.

One expedient method that allows the preparation of methyl 2-indole carboxylate in good yields, is the thermolysis of 2-azidophenyl acrylates as described by Hemetsberger et al.[7] Only a few examples were reported in the literature on the application of this thermolysis for the synthesis of azaindoles.[8] In a previous report, we demonstrated that a large variety of azaindoles can be prepared from 2-azidopyridine acrylates **5** (Fig. 3) using this approach provided that appropriate reaction temperatures are chosen.[9] Azain-

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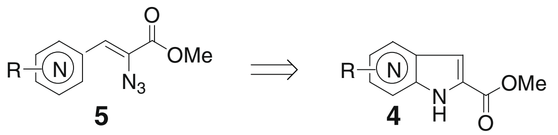
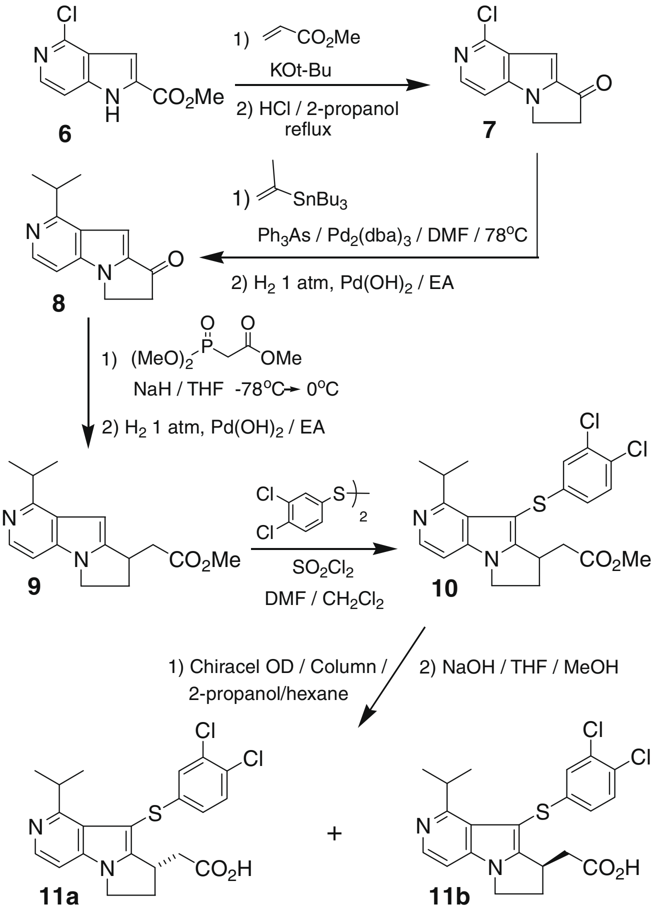


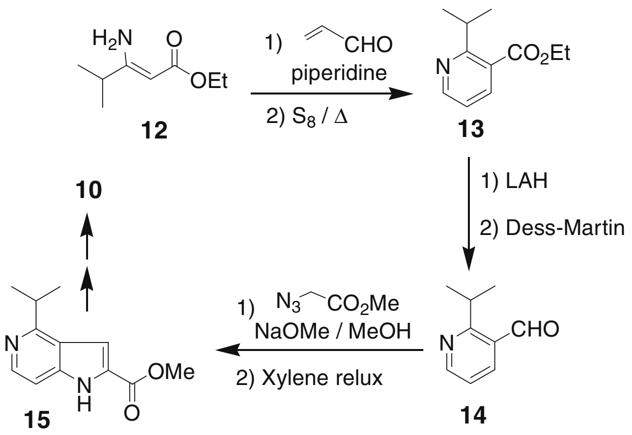
Figure 3. Preparation of azaindoles via thermolysis of 2-azidopyridine acrylates.



Scheme 1. Synthesis of azaindole DP1 antagonists.

doles **4** were then converted in a straightforward manner to the desired DP1 antagonists **3**.

For example (Scheme 1) methyl 4-chloroazaindole carboxylate **6**[10] was condensed on methyl acrylate with potassium *tert*-butoxide followed by decarboxylation with HCl/*i*PrOH at 100 °C to provide ketone **7** in 69% yield. The isopropyl moiety was introduced by stannylation using 2-methylvinyltributyltin in the presence of $Pd_2(dba)_3$ followed by hydrogenation at 1 atm with $Pd(OH)_2$ to provide almost quantitatively ketone **8**. Subsequently, the ketone was converted to the conjugated ester via the Horner–Wadsworth–Edmmons reaction followed by hydrogenation to afford ester **9**. The thioaryl substituent was then introduced by treatment of **9** with bis(3,4-dichlorophenylsulfide) and SO_2Cl_2 in DMF/CH_2Cl_2 to give compound **10** in 62% yield. The ester was then hydrolyzed under standard conditions to provide racemic acid **11**. Resolution was achieved on ester **10** by chiral HPLC using OD column (10% isopropanol in hexane) followed by hydrolysis to provide acid **11a** from more mobile ester and **11b** from less mobile ester. The absolute stereochemistry was determined by X-ray crystallographic analysis of resolved ester **10**.[11]



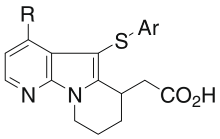
Scheme 2. Synthesis of 2-isopropyllpyridine-3-carboxaldehyde.

Alternatively, 2-isopropyl-3-pyridinecarboxaldehyde **14** can be used as starting material for the Hemetsberger–Knittel reaction (Scheme 2). The ester **13** was obtained in 50% yield from enamine **12** using an adapted protocol.[12] After reduction of ester **13** followed by oxidation, the aldehyde **14** was obtained in 70% yield. Methyl azidoacetate was then condensed on aldehyde **14** with subsequent thermolysis to afford azaindole **15** in 50% yield which in turn was subsequently converted to compound **10** as described in Scheme 1.

The above approach has been used to prepare several potent analogs in the 5- and 7-azaindole series.[13] A few 6-azaindoles were also synthesized but they showed no advantage in terms of receptor affinity or selectivity.

The DP1 receptor affinity and selectivity over the TP receptor of various racemic 7-azaindoles (**16–29)** are shown in Table 1.[14] In general, their DP1 affinities are comparable to the reverse indole series **2** but they are less selective. In the 5-azaindole series, the 4-methylsulfone analogs were initially prepared (**30–32**) and found to be potent and highly selective as described in Table 2. These 5-azaindole analogs were found to be more selective than the corresponding reverse indole compounds **2**. However, they

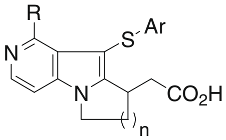
Table 1
K_i values of 7-azaindoles as PGD_2 antagonists[14]



	R	Ar	DP[a] K_i (nM)	TP[a] K_i (nM)
16	SO_2Me	4-Methylphenyl	6.0	171.6
17	SO_2Me	Naphthyl	1.6	41.5
18	SO_2Me	2,3-Dichlorophenyl	1.9	17.9
19	SO_2Me	4-Chlorophenyl	4.0	39.4
20	SO_2Me	3,4-Dichlorophenyl	1.3	23.1
21	SO_2Me	4-Bromophenyl	3.3	35.7
22	SO_2Me	4-Trifluoromethylphenyl	3.7	64.8
23	SO_2Me	2-Chloro-4-fluorophenyl	3.7	24.5
24	SO_2Me	2,4-Dichlorophenyl	1.8	3.8
25	SO_2Me	Phenyl	16.3	646.4
26	SMe	4-Chlorophenyl	12.4	78.9
27	OMe	4-Chlorophenyl	107.4	339.8
28	Isopropyl	3,4-Dichlorophenyl	2.3	13.9
29	Isopropyl	4-Chlorophenyl	0.88	7.0

[a] Radioligand competition binding assays using recombinant human prostaglandin D_2 (DP1) and recombinant human thromboxane receptor (TP).Values are means from at least three experiments.

Table 2
K_i values of 5-azaindoles as PGD_2 antagonists[14]



	n	R	Ar	DP[a] K_i (nM)	TP[a] K_i (nM)
30	2	SO_2Me	3,4-Dichlorophenyl	1.3	995
31	1	SO_2Me	3,4-Dichlorophenyl	1.4	6887
32	1	SO_2Me	4-Chlorophenyl	2.1	12183
33	1	H	3,4-Dichlorophenyl	13.6	2917
34	1	Phenyl	3,4-Dichlorophenyl	1.0	>20 μM
35	2	Ethyl	3,4-Dichlorophenyl	1.0	687
36	1	Ethyl	3,4-Dichlorophenyl	0.91	1687
37	2	Cyclopropyl	3,4-Dichlorophenyl	2.5	990
38	1	Cyclopropyl	3,4-Dichlorophenyl	0.8	415
39	2	1-Methyl-cyclopropyl	3,4-Dichlorophenyl	1.0	587
40	1	1-Methyl-cyclopropyl	3,4-Dichlorophenyl	0.74	3428
41	2	*n*-Propyl	3,4-Dichlorophenyl	1.14	626
42	1	Isopropyl	4-Chlorophenyl	0.71	2813
43	2	Isopropyl	3,4-Dichlorophenyl	0.88	468
11	1	Isopropyl	3,4-Dichlorophenyl	0.53	2081
44	1	Isopropyl	2,6-Dichlorophenyl	1.2	>20uM
45	1	Isopropyl	2,4-Dichlorophenyl	0.39	387
46	1	Isopropyl	4-Trifluoromethylphenyl	0.67	6144
47	1	Isopropyl	2,4,5-Trichlorophenyl	0.39	186

[a] Radioligand competition binding assays using recombinant human prostaglandin D_2 (DP1) and recombinant human thromboxane receptor (TP).Values are means from at least three experiments.

exhibited short half-lives and low exposure in rats. For example compound **32**, in rat, has a half-life of 2.2 h (IV 5 mg/kg) and rat bile cannulation study (IV 5 mg/kg) indicated rapid excretion in bile (56% of parent compound over 5 h, (C_{max} 2 mM, T_{max} 0.5 h). Replacement of the methylsulfone functional group by an alkyl substituent was shown to provide highly potent, selective compounds that possess favorable pharmacokinetics. The racemic isopropyl analog **11** exhibited the best overall profile. The in vitro profiles of both enantiomers **11a** and **11b** are described in Table 3. It is interesting to note that both enantiomer **11a** and **11b** are almost equipotent, whereas the enantiomer of MK-0524 is 1000-fold less active than MK-0524.

From Table 3 data it can be concluded that both enantiomers have comparable overall profile in term of DP1 binding affinity and selectivity. However, antagonist **11b** displays superior potency in the DP1 functional assay[15] where it inhibits the PGD_2 induced production of cAMP in platelet rich plasma with an IC_{50} value of 2.2 nM compared to 5.0 nM in the case of enantiomer **11a** (Table 4). Compound **11b** also demonstrates high levels of functional selectivity versus TP (IC_{50} 4040 nM) as predicted from the receptor binding assay. Excellent pharmacokinetics were observed with compound **11b** (Table 5) in rat, dog, cynomolgus monkey and squirrel monkey.

Table 3
Receptor binding profiles of enantiomers **11a** and **11b**

K_i (nM)	**11a**	**11b**
DP1	0.64 ± 0.12	0.32 ± 0.13
TP	5039 ± 1426	935 ± 220
EP1	28,500	28,500
EP2	7323 ± 3181	3975 ± 2768
EP3	710 ± 55	851 ± 320
EP4	6549 ± 5412	>11,300
FP	25,700	>25,700
IP	>25,700	>20,500
CRTH2	233 ± 59	4789 ± 2440

Table 4
Human DP1 and TP receptor functional activity of compounds **11a** and **11b**[15]

	IC_{50}[a] (nM)		
	DPWP[b]	DP PRP[c]	TP PRP[d]
11a	0.22 ± 0.10 (n = 5)	4.99 ± 1.63 (n = 5)	–
11b	0.14 ± 0.04 (n = 8)	2.15 ± 0.57 (n = 7)	4040 ± 1330 (n = 11)

[a] Values are means from at least three experiments. IC_{50} = concentration at which process is inhibited by 50%.

[b] DP WP assay involved inhibition of the accumulation of cAMP in washed platelets challenged with PGD_2.

[c] DP PRP assay involved inhibition of the accumulation of cAMP in platelet-rich plasma challenged with PGD_2.

[d] TP PRP assay involved the inhibition of U44619-induced platelet aggregation in platelet-rich plasma.

Table 5
Pharmacokinetic data of **11b**

	Rat	Beagle dog	Cyno monkey	Squirrel monkey
F (%)	53	23	4	43
Terminal $t_{1/2}$ (h)	8.3 (10)	8.6 (10)	13.8 (10)	1.4 (10)
C_{max} (μM)	28 (30)	9.0 (10)	0.06 (4)	8.5 (10)
CLp (ml/min/kg)	1.6 (10)	4.0 (2)	21 (2)	7.3 (5)
Vdss (L/kg)	0.47 (10)	1.2 (2)	1.2 (2)	0.78 (5)

Doses (mg/kg) are indicated in parenthesis.

In summary, potent and selective DP1 antagonists were identified in both the 5- and 7-azaindoles series. 5-Azaindoles in particular, possess excellent pharmacokinetics and selectivity profile for further development.

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15. The DP1 functional assays were performed on blood collected from normal human volunteers. Platelet-rich plasma (PRP) was prepared by centrifugation at 150*g* for 15 min. A portion of the PRP fraction was used to prepare the washed platelet fraction by isolating the platelets by centrifugation (10 min at 800*g*) and resuspension of the platelet cell pellet in buffer (25 mM HEPES, pH 7.4, HBSS without Ca^{2+}, Mg^{2+}). The WP and PRP assays were conducted as follows: isobutylmethylxanthine (IBMX; 2 mM final concentration) was added to prevent degradation of cAMP. Samples (100 μL) of either human WP or PRP were then preincubated (10 min at 37 °C) with increasing concentrations of test compound in DMSO. Samples were then challenged with PGD_2 (300 nM final) added in DMSO and incubated for an additional 2 min at 37 °C. The reaction was then terminated by the addition of 200 μL of ethanol to disrupt the cells and extract the cAMP. The samples were mixed thoroughly and centrifuged at 1400*g* for 10 min at 4 °C. Supernatant aliquots (100 μL) were removed and the ethanol removed by evaporation. cAMP was measured by [^{125}I] cAMP scintillation proximity assay (SPA) (RPA556), Amersham).