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Synthesis, SAR, and atropisomerism of imidazolopyrimidine DPP4 inhibitors

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ABSTRACT

The synthesis and SAR of aminomethyl-substituted imidazolopyrimidine DPP4 inhibitors bearing varied pendant aryl groups is described. Compound **1**, which exists as a separable mixture of non-interconvertible atropisomers was used as the starting point for investigation. The effects of substituent pattern and type as well as stereochemical effects on inhibitor potency are discussed.

The serine protease dipeptidyl peptidase IV (DPP4) is the primary enzyme responsible for the in vivo degradation of the incretin hormone glucagon-like peptide 1 (7–36) amide (GLP-1) to the inactive GLP-1 (9–36) amide.[1] The demonstrated ability of GLP-1 to promote glucose stimulated insulin secretion[2] and pancreatic β-cell preservation[3] led to considerable interest in the pharmacological inhibition of DPP4 as a method for the treatment of type 2 diabetes.[4] Several DPP4 inhibitors have reached advanced stages of development[5] where they have shown fasting plasma glucose reductions, lowering of glycosylated hemoglobin (HbA_{1c}), improved glucose tolerance, and have been well tolerated in a wide clinical population.[6] Furthermore, both sitagliptin (JANUVIA™) and saxagliptin (ONGLYZA™) are now FDA approved for the treatment of type 2 diabetes mellitus, alone or in combination with other oral antidiabetic agents.

First generation inhibitors from these laboratories, including saxagliptin, were based on a dipeptidic motif loosely resembling the DPP4 cleavage products. As part of our ongoing research program, we recently disclosed our preliminary findings in establishing alternative chemotypes as novel DPP4 inhibitor scaffolds wherein we described aminomethyl-substituted bicyclic heteroaromatics culminating with the discovery of the potent imidazolopyrimidine **1** (K_i = 15 nM, Table 2).[7] Herein we provide further elaboration of the structure–activity relationships (SAR) around this lead by modification of the lower aromatic appendage (2,4-dicholophenyl in **1**) and the existence of and biochemical impact of restricted rotation (atropisomerism)[8] in *ortho*-substituted analogs of this series.

We had originally conceptualized the synthesis of a series of analogs of **1** utilizing a late-stage coupling strategy to install various aryl replacements for the 2,4-dichlorophenyl ring. A disappointing lack of reactivity of any suitable imidazolopyrimidine coupling partners (chloride, bromide, triflate) toward conditions to introduce this biaryl bond led us to proceed with a more lengthy yet generally effective route (Schemes 1–3). A conserved component of all of the desired inhibitors, the (2-methoxyphenyl)imidazolo portion, was derived from 2-amino-4-(2-methoxyphenyl)imidazole (**3**), which was obtained by the condensation of 2-aminopyrimidine with 2-bromo-2′-methoxyacetophenone (92% yield), followed by cleavage of intermediate **2** with hydrazine hydrate in ethanol in 93% yield (Scheme 1).

With **3** in hand the synthesis of 4-chlorophenyl analog **9** began with the Knoevenagel condensation of 4-chlorobenzaldehyde and *t*-butyl acetoacetate to give enone **4** in 87% yield (Scheme 1). Combination of **4** with aminoimidazole **3** using NaOMe in MeOH/THF at 70 °C provided the dihydroimidazolopyrimidine **5**, which was oxidized to **6** with DDQ (46% over two steps). A three-step process of *t*-butyl ester cleavage with TFA, acid chloride formation using oxalyl chloride, and reduction with $NaBH_4$ gave alcohol **7** (29% over three steps). Conversion of **7** to the chloride **8** proceeded smoothly with methylsulfonyl chloride/Et_3N (90% yield), followed by subsequent reaction with 7 M ammonia in MeOH at elevated temperatures in a sealed tube to provide product **9** (75% yield). Compounds **18** and **22–24** (Table 2) were also made using this method.

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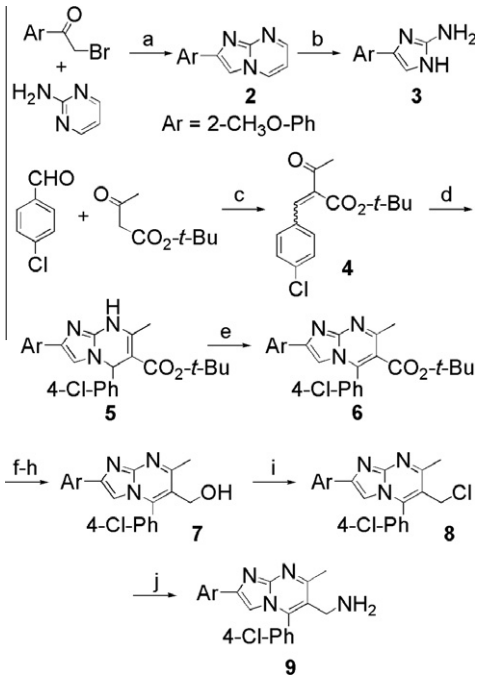
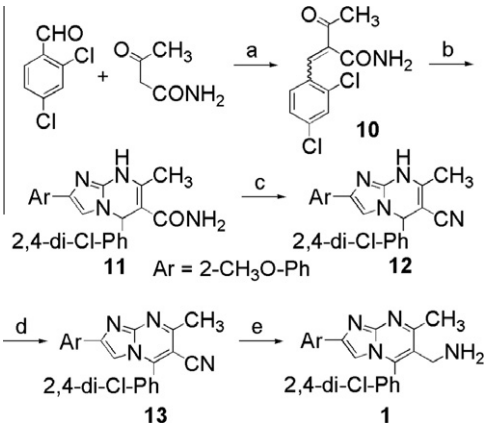
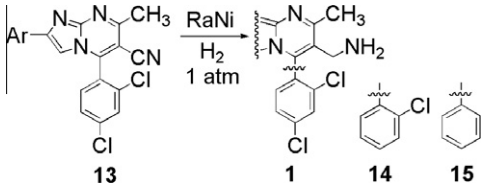


Scheme 1. Reagents and conditions: (a) EtOH, reflux (92%); (b) EtOH, hydrazine hydrate, 70 °C (93%); (c) toluene, piperidine (87%); (d) **3**, $NaOCH_3$, THF, CH_3OH, 70 °C; (e) DDQ, CH_2Cl_2 (46% over two steps); (f) TFA, CH_2Cl_2; (g) oxalyl chloride, DMF, CH_2Cl_2; (h) $NaBH_4$, THF, DMF, −78 °C (29% over three steps); (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2 (90%); (j) 2 M NH_3 in CH_3OH, 70 °C (75%).



Scheme 2. Reagents and conditions: (a) piperidine, AcOH, IPA, 70 °C (65%); (b) **3**, $(i\text{-}Pr)_2NEt$, IPA, 75 °C (34%); (c) TFAA, Et_3N, CH_2Cl_2 (91%); (d) DDQ, CH_2Cl_2 (70%); (e) RaNi, H_2 (1 atm), 1:1 CH_2Cl_2/CH_3OH (58%).



Scheme 3. Raney nickel reduction of cyano compound **13** to **1**/**14**/**15**.

A shorter route to this class of products was also devised and executed (Scheme 2). Acetoacetamide was used in the initial Knoevenagel condensation with 2,4-dichlorobenzaldehyde to give enone amide **10**, installing the requisite nitrogen of the aminomethyl component of the final products early on in the sequence. Combination of **10** with aminoimidazole **3** using Hunig's base in IPA at 75 °C gave **11** (34% yield); subsequent dehydration of the amide with trifluoroacetic anhydride produced **12** (91% yield); and finally, oxidation with DDQ afforded imidazolopyrimidine nitrile **13** (70% yield). After an extensive survey of reductive methods for adjusting the oxidation state of the nitrile down to that of a primary amine (wherein H_2 addition to the imidazolopyrimidine core and dechlorination were the major by-products), hydrogenolysis with Raney Ni emerged as the most selective set of conditions for the conversion of **13** to the desired aminomethyl analog **1** (58% yield), minimizing the amount (<10%) of dechlorinated by-products formed. Additional compounds produced using this method included **14**–**17**, **19**–**21**, and **25** and **26** (Table 2). All compounds obtained by either method were of 98% or greater purity[9] and gave appropriate ^1H and ^{13}C NMR spectra as well as positive ion MS data.[10]

During the optimization of the reduction of **13** to **1** we observed a significant solvent effect on the reaction profile. While compound **13** was very soluble in methylene chloride (>20 mg/mL), the reduction with Raney Ni and H_2 did not occur, and only starting material was recovered (Table 1, first entry). When the solvent was changed to MeOH, in which **13** had much lower solubility (<4 mg/mL), overreduction occurred with dechlorinated products **14** (loss of 4-chlorine atoms from **1**) and **15** (loss of both the 2- and 4-chlorine atoms from **1**) as the only products observed (Table 1, second entry). Significantly more favorable results were obtained through the use of the mixed solvent 1:1 CH_2Cl_2/CH_3OH, which provided the best conversion of **13** to **1** (92%) with an isolated product yield of 58%.

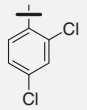
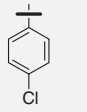
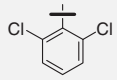
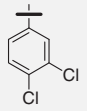
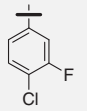
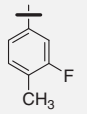
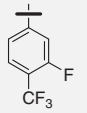
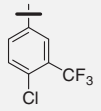
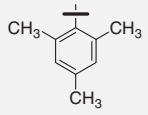
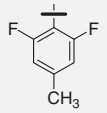
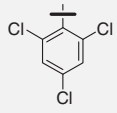
Compounds **1**, **9**, and **14–26** were evaluated for their ability to inhibit DPP4 (Table 2). All compounds were tested in vitro against purified human DPP4 using the substrate H-Gly-Pro-*p*NA, measuring production of *p*-nitroaniline at 405 nm over 15 min.[5c] In addition, the inhibition of the homologous yet physiologically undefined proteases DPP8[11] and DPP9[12] were also determined. While all of the compounds tested showed either minimal or no inhibition of DPP8/9 (all K_i's >3982 nM, with many >30,000 nM, Table 2) the level of DPP4 inhibition displayed a significant dependence on substitution pattern and type. The unsubstituted phenyl analog **15** had lost 16-fold in potency (K_i = 241 nM) relative to the initial lead **1** (K_i = 15 nM), while mono-chloro substituted compounds demonstrated the regiochemical preference of *ortho*>*para*>*meta* (**14** = 26 nM, **9** = 96 nM, **16** = 1530 nM). The 3-fluoro analog **19** (K_i = 550 nM) was slightly more active than the 3-chloro compound **16**, while combination of the 3-fluoro group with substitution at C-4 of the phenyl ring provided only modest potency enhancements as shown for **20** and **21** (K_i = 495 and 438 nM, respectively) or the loss of activity as in **22** (K_i >10,000 nM). The 2,6- and 3,4-dichlorophenyl compounds **17** (K_i = 113 nM) and **18** (K_i = 612 nM), respectively, were weaker inhibitors than either of the 2- or 4-monochloro analogs (**14** and **9**, respectively). This suggests that the greater level of inhibition observed for 2,4-dichloro compound **1** results from a more favorable space filling interaction in the DPP4

Table 1
Conditions and results for the reaction in Scheme 3

Solvent/time (concn of **13**)	**13**[a]	**1**[a]	**14**[a]	**15**[a]
CH_2Cl_2/44 h (0.050 M)	100 (100)	—	—	—
CH_3OH/21 h (0.010 M)	—	—	83 (50)	17
1:1 CH_2Cl_2/CH_3OH/21 h (0.025 M)	—	92 (58)	8	—

[a] Percent conversion by LC analysis (isolated yield, %).

Table 2
DPP4/DPP8/DPP9 inhibition for **1**, **9**, and **14**–**26**

Compound		DPP4 K_i[a] (nM)	DPP8 K_i (nM)	DPP9 K_i (nM)
1		15 ± 9	7836	>10 K[b]
9		96 ± 28	>30 K	>30 K
14		26 ± 18	>10 K	>10 K
15		241 ± 34	>30 K	>30 K
16		1530 ± 451	>30 K	>30 K
17		113 ± 7	>30 K	>30 K
18		612 ± 95	>30 K	>30 K
19		550 ± 43	>30 K	>30 K
20		495 ± 145	>30 K	>30 K
21		438 ± 52	>30 K	>30 K
22		>10 K	>30 K	>30 K
23		>10 K	>30 K	>30 K
24		113 ± 13	>30 K	>30 K
25		27 ± 7	>30 K	>30 K
26		19 ± 4	>30 K	>30 K

[a] All K_i values are the mean ± SD of at least triplicate determinations.
[b] 10 K = 10,000; 30 K = 30,000.

active site. Example **23** (K_i >10,000 nM) has a 3-CF_3 group which further demonstrates the disfavorable impact of sterics in this region of the pharmacophore. Compounds **24**–**26** were symmetrical 2,4,6-trisubstituted-phenyl analogs. Trichloro analog **26** (K_i = 19 nM) was one of the most potent compounds against DPP4. Comparison of the K_i's for 2,4-dichloro compound **1** (K_i = 15 nM) and **26** indicated that the addition of the third chlorine atom to the lower phenyl ring was tolerated without loss of potency. However, the 2,6-dichlorophenyl analog **17** (K_i = 113 nM) was fourfold less active than the 2-chlorophenyl compound **14**.

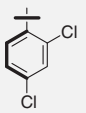
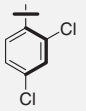
A key feature of some of these molecules, apparent from the ^{1}H NMR spectra, was the existence of restricted rotation (atropisomerism)[8] around the biaryl bond linking the lower phenyl ring to the bicyclic core. Molecules such as **1** and **14** contain unsymmetrically substituted phenyl rings with at least one *ortho*-group. This resulted in an AB-quartet in the ^{1}H NMR spectra for the $-CH_2-NH_2$ methylene protons due to their diastereotopicity. The thermal stability of the individual atropisomers was qualitatively assessed on other analogs within this and a similar series of compounds.[13] It was demonstrated that the barrier to free rotation was sufficiently large that <5% of racemization occurred in DMSO at >100 °C over several days, while no detectable racemization was observed in human and rat plasma after 3 h at 37 °C. To address the effect of atropisomerism on target potency, the separation and in vitro analysis of the individual atropisomers of **1** and **14** was carried out.

A survey of chiral columns and conditions allowed for the separation of the individual atropisomers of **1**[14] and **14**.[15] The in vitro data for these compounds are shown in Table 3. We tentatively assigned the absolute configurations for (+)-**1**, (−)-**1**, (+)-**14**, and (−)-**14** shown in Table 3 based on a correlation of measured DPP4 inhibitory potency with results of modeling of the individual enantiomers of **1** into the DPP4 active site.[16] The two views of (S_a)-**1**[17] shown in Figure 1 suggest that the 2-chloro substituent occupies a hydrophobic pocket in the enzyme, whereas the opposite enantiomer would place the chlorine in a more sterically encumbered position clashing with the aryl ring of Tyr666.

The data in Table 3 show a significant potency enhancement resulting from resolution of the individual atropisomers. The improved activities for (+)-**1** (K_i = 9 nM) and (+)-**14** (K_i = 11 nM) relative to corresponding enantiomers represent 27-fold and 74-fold enhancements in K_i, respectively. While compound (+)-**1**, the most potent member of this series represents a highly active compound with respect to biochemical potency, as reported earlier this class of molecules displayed liabilities that remained to be eliminated.[7]

We have described the synthesis and DPP4 inhibitory activity for a series of replacements for the 2,4-dichlorophenyl ring in compound **1**. All compounds were selective against DPP8 and DPP9.

Table 3
DPP4/DPP8/DPP9 inhibition for (+)-**1**, (−)-**1**, (+)-**14**, and (−)-**14**

Compound		DPP4 K_i[a] (nM)	DPP8 K_i (nM)	DPP9 K_i (nM)
(+)-**1**		9 ± 1	3982	>10 K[b]
(−)-**1**		241 ± 117	>10 K	>10 K
(+)-**14**		11 ± 9	>10 K	>10 K
(−)-**14**		814 ± 84	>10 K	>10K

[a] All K_i values are the mean ± SD of at least triplicate determinations.
[b] 10 K = 10,000.

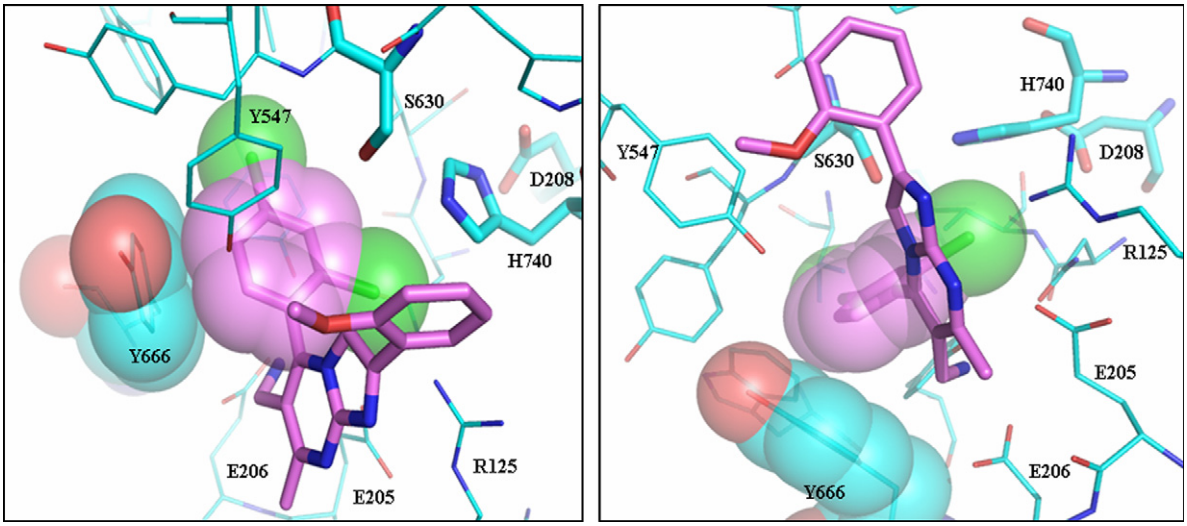


Figure 1. Model of (S_a)-**1** in DPP4 active site from two perspectives.

The existence of isolable atropisomers provided enhanced activity as illustrated for preferred isomer (+)-**1**. Modification of other regions of these molecules to enhance potency and minimize liabilities has been described in a recent disclosure from these laboratories.[13]

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8. Atropisomerism. In *Tetrahedron Symposia-In-Print*; Clayden, J., Ed.; Elsevier: Amsterdam, 2004; Vol. 60, pp 4335–4558.
9. Compound **17** was obtained in 94% purity.
10. Data for compound **1**: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.97 (d, J = 1.7 Hz), 7.85 (dd, J = 1.1, 7.7 Hz, 1H), 7.78 (dd, J = 1.7, 8.3 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.70 (s, 1H), 7.50 (t, J = 6.7 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.11 (t, J = 6.9 Hz, 1H), 4.28 (d, J = 4.9 Hz, 1H), 4.09 (d, J = 4.9 Hz, 1H), 3.90 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 159.0, 145.6, 141.0, 135.8, 133.9, 133.7, 132.6, 130.9, 130.3, 126.8, 122.7, 119.7, 113.3, 111.1, 56.6, 37.4, 24.5. MS m/z: $[M+H]^+$ 413.0.
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14. The separation of the enantiomers of racemic **1** was carried out using a Chiralpak AD-H column (20 × 250 mm) eluting with EtOH/heptane/Et_2NH 20:80:0.1 at 20 mL/min; 254 nm detection. Faster eluting isomer (+)-**1**: t_R = 11.2 min; $[\alpha]_{589}^{25.2}$ (3.51×10^{-6}, CH_3OH) = +125.93°. Slower eluting isomer (−)-**1**: t_R = 16.1 min; $[\alpha]_{589}^{25.4}$ (3.39×10^{-6}, CH_3OH) = −103.24°. The enantiomeric excesses were determined using a Chiralpak AS column (4.6 × 250 mm) eluting with IPA/heptane/Et_2NH 25:75:0.1 at 1.0 mL/min, 254 nm detection: (+)-**1** (t_R = 8.2 min), 100% ee; (−)-**1** (t_R = 11.2 min), 100% ee.
15. The separation of the enantiomers of racemic **14** was carried out using a Chiralpak AD-H column (20 × 250 mm) eluting with EtOH/heptane/Et_2NH 20:80:0.1 at 20 mL/min; 254 nm detection. Faster eluting isomer (+)-**14**: t_R = 11.5 min; $[\alpha]_{589}^{25.4}$ (7.33×10^{-6}, CH_3OH) = +117.05°. Slower eluting isomer (−)-**14**: t_R = 16.3 min; $[\alpha]_{589}^{25.9}$ (7.96×10^{-6}, CH_3OH) = −133.17°. The enantiomeric excesses were determined using a Chiralpak AD column (4.6 × 250 mm) eluting with IPA/heptane/Et_2NH 25:75:0.1 at 1.0 mL/min, 254 nm detection: (+)-**14** (t_R = 10.6 min), 100% ee; (−)-**14** (t_R = 13.1 min), 100% ee.
16. The modeling of compound **1** was based on the X-ray structure described in the following reference: Rasmussen, H. B.; Branner, S.; Wiberg, F. C.; Wagtmann, N. *Nat. Struct. Biol.* **2003**, *10*, 19.
17. The 'S_a' stereochemical designation refers to the axis of asymmetry imparted to the molecule by virtue of the restricted rotation around the biaryl bond; see also: Oki, M. *Top. Stereochem.* **1984**, *14*, 1.