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Novel methylene-linked heterocyclic EP_1 receptor antagonists

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Abstract—We describe the SAR, in terms of heterocyclic replacements, for a series of pyrazole EP_1 receptor antagonists. This study led to the identification of several aromatic heterocyclic replacements for the pyrazole in the original compound. Investigation of replacements for the methylene linker uncovered disparate SAR in the thiazole and pyridine series.

Pain is symptomatic of many diseases. In particular, inflammatory pain is associated with chronic disease states such as rheumatoid arthritis (RA) and osteoarthritis (OA).[1] Non-steroidal anti-inflammatory drugs (NSAIDs) and more recently inhibitors of (COX-2) have demonstrated efficacy in the treatment of chronic inflammatory pain,[2] however, both medicaments have been found to elicit undesirable side effects which hinder chronic dosing and therefore hamper their use for the treatment of chronic inflammatory pain.[3] Thus, there exists an opportunity for novel pain treatments devoid of side effects. The identification of selective EP_1 receptor antagonists, which block the action of the proinflammatory mediator PGE_2 at one of its four receptor subtypes, is therefore of interest for the treatment of inflammatory pain[4] as they have shown efficacy in preclinical models of inflammatory pain.[5–7]

We have described the cyclopentene (**1**)[8] and pyrrole analogues (**2** and **3**)[5a] (Fig. 1). Optimisation of the cyclopentene derivative (**1**) led to the identification of GW848687X (**4**).[6] In addition, we have recently described a further novel series of pyrazole derivatives exemplified by **5**[7] (Fig. 1).

We were intrigued by the methylene-linked pyrazole series, such as **5**, due to its considerably lower lipophilicity than compounds from our previous biaryl series, as demonstrated by the measured log D[9] values of compounds **1**–**4** all ($\log D \geqslant 2.5$) compared to compound **5** ($\log D$ 1.2) (Fig. 1).

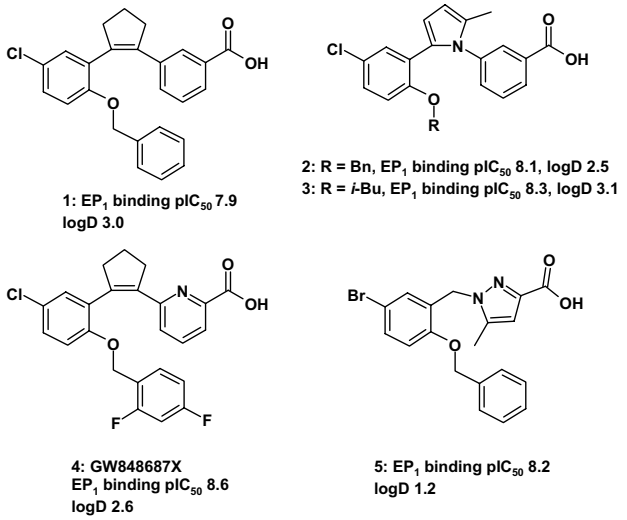

Figure 1. A selection of GSK EP_1 receptor antagonists.

Keywords: EP_1 antagonist; Pyrazole; Isostere; Heterocycle.
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In this paper, we detail our investigation into aromatic heterocyclic replacements for the pyrazole moiety in the methylene-linked series and the effect this had on lipophilicity. We present data that show that the methylene-linked series has intrinsically lower lipophilicity than the cyclopentene or pyrrole series and that the replacement of the central biaryl ring by a methylene linker was not accountable alone for the decreased lipophilicity.

We also investigated whether the SAR in the methylene-linked series was similar to the biaryl series in terms of SAR of the aromatic carboxylic acid moiety. Finally, we probed the feasibility of replacing the methylene linker with isosteric groups.

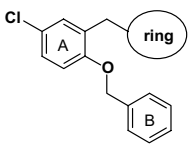
Initial analogues were prepared with the benzyloxy motif on the A-ring (Table 1). Compounds were tested in [^{3}H]-PGE_2 binding assay, and most were also profiled in a functional assay (FLIPR, data shown for key compounds).[10]

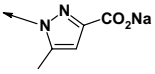
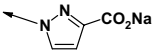
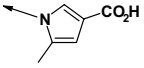
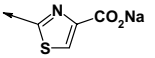
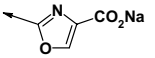
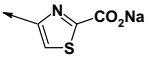
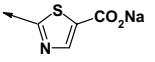
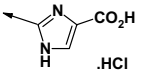
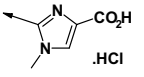
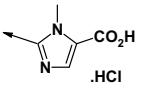
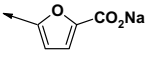
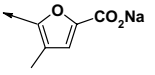
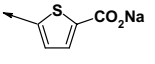
Replacement of the Br-atom (ring A) in compound **5** by a Cl-atom (**6a**) had little effect on affinity (Table 1). However, deletion of the methyl group from the 5-position of pyrazole **6a**, to give **6b**, led to a 10-fold decrease in affinity and a moderate decrease in lipophilicity. Replacement of the pyrazole N-atom in the *ortho*-position to the carboxylic acid of **6a** by CH to give the corresponding pyrrole **6c** also resulted in a marked, ~16-fold, decrease in affinity, implying that a heteroatom in the *ortho*-position to the carboxylic acid may be important for activity. This result is in line with initial SAR in this series.[7] It is noteworthy that the pyrrole **6c** is 100-fold more lipophilic than the corresponding pyrazole **6a**, log *D* 3.0 versus log *D* 1.0, respectively.[9]

Further investigation of heterocycles with the N-atom at the *ortho*-position to the carboxylic acid led to the identification of several high affinity derivatives such as thiazole **6d**, oxazole **6e** (FLIPR pK_i 8.8) and regioisomeric thiazole **6f**. Interestingly, the other regioisomeric thiazole (**6g**) displayed considerably lower affinity (30- to 100-fold) than its analogues. It was also found that not all heterocycles with a N-atom in the *ortho*-position to the carboxylic acid were active, and that more basic compounds such as the imidazoles (**6h–j**) displayed much weaker activity. It is not clear whether this marked decrease in activity was due to the increased basicity of the imidazole, relative to the pyrazole, thiazole and oxazole ring systems, or whether it is due to electronic factors.

Replacement of the N-atom by other heteroatoms was also investigated. Furan **6k** (FLIPR pK_i 8.7) displayed 10-fold higher affinity than the pyrazole **6b** but addition of a methyl group to give **6l** (FLIPR pK_i 8.7) had no effect on affinity or functional activity. Thus furan **6l** is essentially equipotent with the methyl pyrazole analogue derivative **6a**. It is not clear why the methyl group is so important in the pyrazole case but has no effect in the case of the furan. The thiophenes **6m** (FLIPR pK_i 7.8) and **6n** were also found to have activity, albeit **6m** dis-

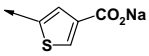
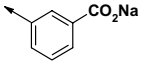
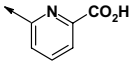
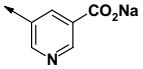
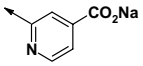
Table 1. SAR for compounds **1**, **2**, **4**, **5** and new analogues **6a–r**



Compound	Ring	Binding pIC_{50}[a]	log *D*[b]
1	n/a	7.9 ± 0.4	3.0
2	n/a	8.1 ± 0.4	2.5
4	n/a	8.6 ± 0.1	2.6
5	n/a	8.2 ± 0.0	1.2
6a		8.0 ± 0.2	1.0
6b		7.1 ± 0.0	0.7
6c		6.8 ± 0.1	3.0
6d		8.2 ± 0.1	1.2
6e		7.7 ± 0.1	0.5
6f		7.6 ± 0.1	1.1
6g		6.2 ± 0.3	0.9
6h		<6	0.6
6i		6.5 ± 0.1	0.7
6j		<6	0.7
6k		8.2 ± 0.1	1.5
6l		8.0 ± 0.1	1.8
6m		7.3 ± 0.0	2.3

(*continued on next page*)

Table 1 (*continued*)

Compound	Ring	Binding pIC_{50}[a]	log *D*[b]
6n		7.4 ± 0.1	2.8
6o		6.5 ± 0.1	3.0
6p		6.8 ± 0.2	2.2
6q		6.2 ± 0.3	1.4
6r		<6	1.1

[a] See note 10.
[b] See note 9.

played approximately 10-fold weaker affinity than the analogous furan **6k**. Surprisingly, the isomeric thiophene (**6n**) was active, despite not having a heteroatom in the *ortho*-position to the carboxylic acid (Table 1).

Despite the activity of the thiophenes **6m** and **6n**, the phenyl derivative **6o** was considerably weaker in terms of binding affinity. This result is surprising considering the activity of the phenyl derivatives in related biaryl series, for example, compounds **1**–**3**[5,8] and shows a disparity in SAR between the two series.

Adding a N-atom in the *ortho*-position to the carboxylic acid of compound **6o** to give the picolinic acid derivative **6p** improved affinity only slightly. Nicotinic acid derivative **6q** had considerably weaker binding affinity and isonicotinic acid derivative **6r** was devoid of activity (Table 1).

The fact that a benzoic acid (compound **6o**) was not well-tolerated in the methylene-linked series can be partially rationalized by molecular overlays (Figs. 2 and 3).[11] The methylene linker is considerably shorter than the cyclopentene and pyrrole linkers and results in a suboptimal overlay of the benzoic acid moieties in compounds **1** and **6o** (Fig. 2).

Five-membered heterocyclic acids such as **6a** correct for this change in geometry and location caused by the methylene linker (Fig. 3). However, the fact that not all five-membered aromatic heterocycles demonstrate activity must be accounted for by electronic factors in addition to the potential HBA interactions of the additional heteroatoms, although the latter are not possible for all of the ring systems.

Results in Table 1 show that some relatively hydrophilic ring systems can be incorporated in the methylene-linked series which is in contrast to the biaryl series we reported previously, where lipophilic rings such as benzene and pyrrole were preferred. For example, the measured log *D* values for compounds **2** and **4** are 2.5 and 2.6, respectively, whereas data from the current series show that it is possible to achieve high affinity with much less lipophilic compounds such as **6a** (log *D* 1.0), **6d** (log *D* 1.2), **6e** (log *D* 0.5) and **6f** (log *D* 1.1). There is no correlation between binding affinity and lipophilicity (Fig. 4).

Investigation of the alkoxy group on the A-ring showed that the benzyloxy group could be replaced by an isobutoxy group (Table 2) as found in the pyrrole series.[5a] The isobutoxy derivatives generally displayed affinity similar to their benzyl analogues, with the exception of picolinic acid derivative **7d** which showed markedly higher affinity. Compounds **7a**, **7c** and **7d** demonstrated antagonism in a functional assay, **7a** FLIPR pK_i 9.1, **7c** FLIPR pK_i 9.5, and **7d** FLIPR pK_i 6.8.

Next we sought to investigate alternatives to the methylene linker (Table 3). Thiazole **6d** was used for this exercise as it represented a good starting point in terms of in vitro affinity and because it allowed the methylene group to be replaced by an amino group. Thus, replace-

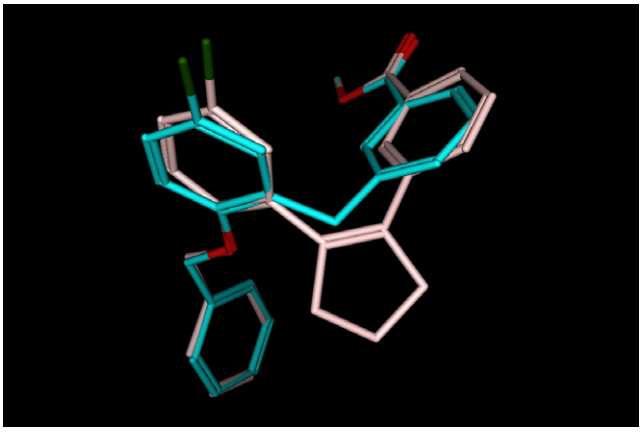


Figure 2. Molecular overlay (flexible alignment) of cyclopentene derivative **1** (pink) with methylene-linked benzoic acid derivative **6o** (turquoise).

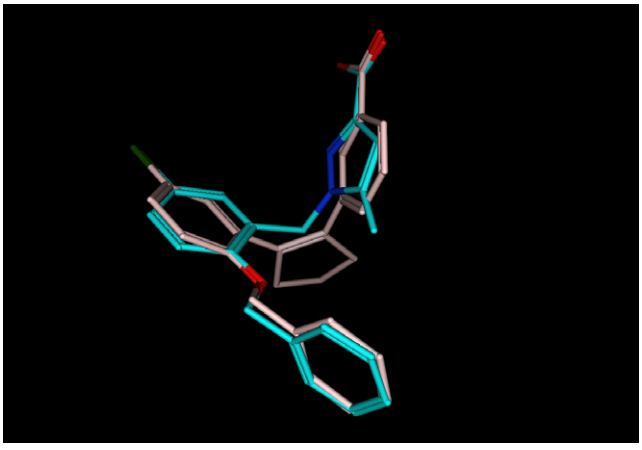


Figure 3. Molecular overlay (flexible alignment) of cyclopentene derivative **1** (pink) with methylene-linked pyrazole acid derivative **6a** (turquoise).

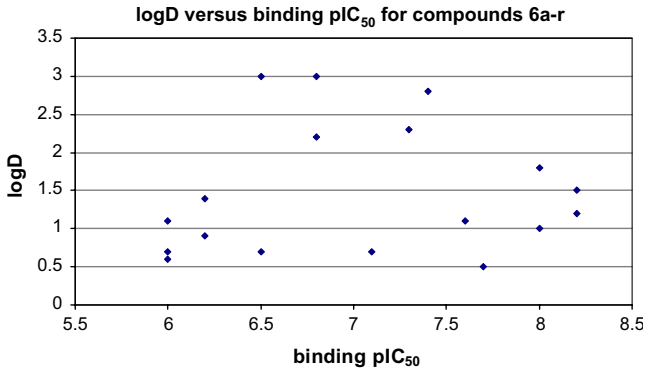
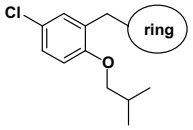
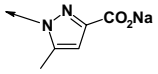
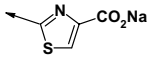
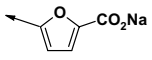
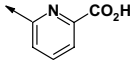


Figure 4. Plot of measured log *D* (*Y*-axis) versus binding pIC_{50} (*X*-axis) for compounds **6a**–**r**.

Table 2. SAR for isobutoxy analogues **7a**–**d**



Compound	Ring	Binding pIC_{50}[a]
3	n/a	8.3 ± 0.1
7a		8.0 ± 0.0
7b		8.1 ± 0.0
7c		8.5 ± 0.1
7d		7.4 ± 0.1

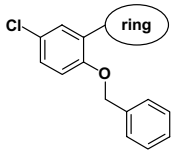
[a] See note 10.

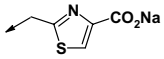
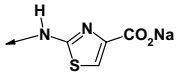
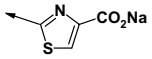
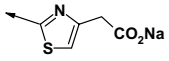
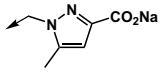
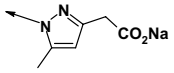
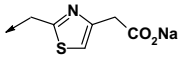
ment of the methylene group of compound **6d** with an amino linker to give **8a** (FLIPR pK_i 8.4) was well-tolerated (~3-fold decrease in affinity). Removal of this linker (**8b**) led to a marked decrease in activity. However, reinsertion of the methylene group to give the thiazole acetic acid derivative (**8c**) restored affinity to some degree. A similar modification in the pyrazole series (compare **6a** with **8d**) was not tolerated, highlighting a surprising divergence in SAR between the thiazole and pyrazole series (Table 3). Retaining the original methylene linker and but converting these compounds to acetic acid derivatives (**8e**) was again found to be detrimental (Table 3).

Finally, investigation of alternative linkers in the picolinic acid series proved much less fruitful (Table 4). Replacement of the methylene group by either an amino linker (**9a**) or an oxygen linker (**9b**) was not beneficial.

Thus, these investigations show that the methylene linker is optimal.

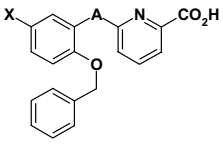
Table 3. SAR for compounds **8a**–**e**



Compound	Ring	Binding pIC_{50}[a]
3	n/a	8.3 ± 0.1
6d		8.2 ± 0.1
8a		7.6 ± 0.1
8b		6.2 ± 0.2
8c		7.3 ± 0.1
6a		8.0 ± 0.2
8d		<6
8e		<6

[a] See note 10.

Table 4. SAR for compounds **9a** and **b**



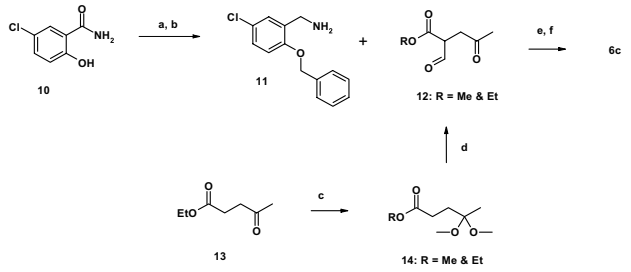
Compound	A	X	Binding pIC_{50}[a]
6p	CH_2	Cl	6.8 ± 0.2
9a	NH	H	<6
9b	O	Cl	6.1 ± 0.4

[a] See note 10.

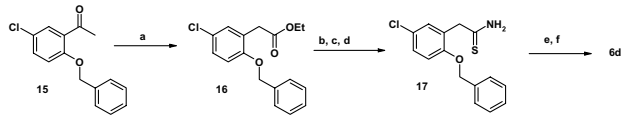
Compounds were synthesized according to literature procedures or as outlined in Schemes 1–9. Full experimental details and characterizing data for key compounds have been described.[12–15]

Pyrazole derivatives **6a** and **6b** were prepared by alkylation with the requisite benzyl bromide as described previously.[7,12]

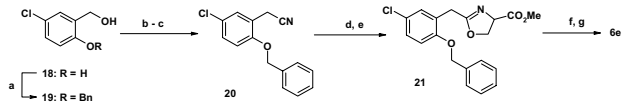
Pyrrole derivative **6c** was prepared from 5-chlorosalicylamide **10** (Scheme 1) by alkylation of the phenolic group followed by amide reduction to give **11**. Ethyl 4-oxopentanoate (**13**) was converted to the corresponding dimethyl acetal (**14**) which underwent aldol



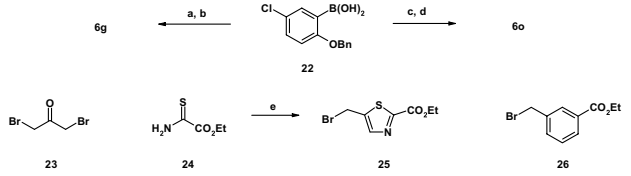
Scheme 1. Reagents and conditions: (a) BnBr, acetone, K_2CO_3, reflux; (b) $LiAlH_4$, THF 0 °C then reflux 1 h; (c) $HC(OEt)_3$, *p*-TSA·H_2O, MeOH, reflux; (d) NaH, THF, HCO_2Et 10 °C to rt, then aqueous HCl; (e) AcOH, rt, 2 h; (f) 4 equiv NaOH, EtOH–H_2O (3:1), reflux.



Scheme 2. Reagents and conditions: (a) $AgNO_3$, I_2, $HC(OEt)_3$, EtOH, reflux, 16 h; (b) 4 equiv NaOH, EtOH–H_2O (3:1), reflux; (c) EDAC, *N*-methylmorpholine, HOBt–NH_4, DCM; (d) DME, Lawesson's reagent, rt; (e) $KHCO_3$, DME then ethyl bromopyruvate, TFAA, pyridine, 0 °C to rt; (f) 4 equiv NaOH, EtOH–H_2O (3:1), 60 °C.



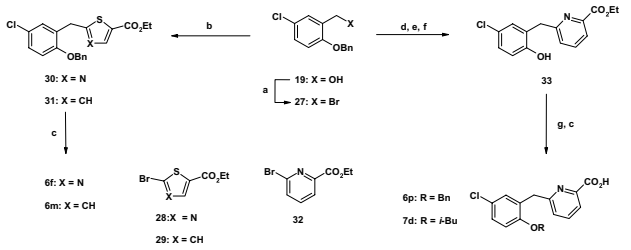
Scheme 3. Reagents and conditions: (a) benzyl bromide, K_2CO_3, Me_2CO, reflux, 2 h; (b) $SOCl_2$, DCM, rt; (c) NaCN, DMSO, 60 °C; (d) MeOH, HCl (g) 0 °C to rt; (e) (DL)-serine methyl ester, diisopropylethylamine, rt, overnight; (f) DBU, $CuBr_2$, hexamethyltetraamine, DCM 0 °C to rt; (g) 2 M NaOH, EtOH, heat.



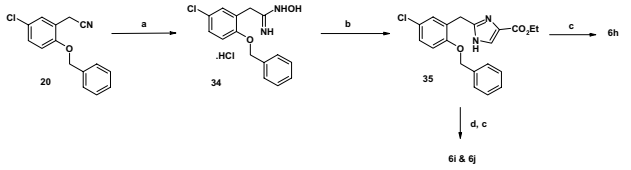
Scheme 4. Reagents and conditions: (a) **25**, $Pd(PPh_3)_4$, K_2CO_3, PhMe–EtOH, 90 °C; (b) NaOH, EtOH H_2O, 60 °C, 2 h; (c) **26**, $Pd(PPh_3)_4$, Na_2CO_3, H_2O, DME–EtOH, 90 °C; (d) 2 M NaOH, EtOH, reflux; (e) EtOH, reflux, 15 h.

reaction with ethyl formate and subsequent ketal hydrolysis to give **12**. Paal–Knorr condensation of keto-aldehyde **12** with benzylic amine **11** followed by ester hydrolysis gave compound **6c** (Scheme 1).

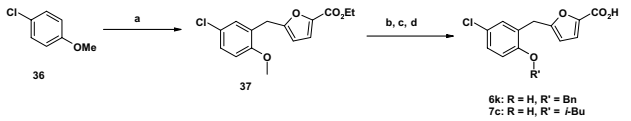
Acetophenone derivative **15** was transformed to the homologated ethyl ester **16**[16] which was then hydrolyzed, converted to the amide and subsequently the thioamide **17**. Reaction of the thioamide **17** with ethylbromo pyruvate and subsequent hydrolysis delivered compound **6d** (Scheme 2)



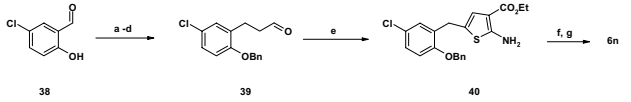
Scheme 5. Reagents and conditions: (a) PBr_3, DCM, 0 °C to rt; (b) i—THF, Zn, 1,2-dibromoethane, TMSCl; ii—**28** or **29**, $Pd(PPh_3)_4$, THF, rt, overnight; (c) 2 M NaOH, EtOH, heat; (d) i—THF, Zn, 1,2-dibromoethane, TMSCl; ii—**32**, $Pd(PPh_3)_4$, THF, rt, overnight; (e) NaSMe, DMF, 100 °C; (f) EtOH, concd H_2SO_4, reflux; (g) RBr, DMF, 60–80 °C.



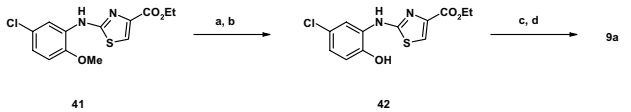
Scheme 6. Reagents and conditions: (a) MeOH, NH_2OH·HCl, $NaHCO_3$, reflux, 20 h; (b) ethyl propiolate, Ph_2O, EtOH, 190 °C, 2 h; (c) 2 M NaOH, EtOH, heat then HCl; (d) MeI, K_2CO_3, DMF, rt, separation of isomers.



Scheme 7. Reagents and conditions: (a) $AlCl_3$, $MeNO_2$, ethyl 5-(chloromethyl)-2-furancarboxylate, rt, 24 h; (b) BBr_3, DCM, −78 °C to rt; (c) R′Br, DMF, 80 °C; (d) 2 M NaOH, EtOH, heat; (e) EtI, K_2CO_3, DMF, 70 °C, 2 h; (f) benzotriazole, $SOCl_2$, DCM.



Scheme 8. Reagents and conditions: (a) DCM, rt (carbethoxymethylene)triphenylphosphorane; (b) BnBr, K_2CO_3, Me_2CO, 55 °C; (c) $LiAlH_4$, THF, rt; (d) CrO_3, pyridine, DCM, rt; (e) ethyl cyanacetate, DMF, TEA, 55 °C, 2 h; (e) sulfur, DMF, TEA, 55 °C, 2 h; (f) isoamyl nitrate, THF, reflux, 3 h; (g) 2 M NaOH, EtOH, 65 °C.



Scheme 9. Reagents and conditions: (a) NaSMe, DMF, 100 °C, 24 h; (b) EtOH, concd H_2SO_4, reflux, 3 h; (c) BnBr, K_2CO_3, Me_2CO, reflux, 7 h; (d) NaOH, H_2O, EtOH, 60 °C, 1 h.

The synthesis of oxazole **6e** is described in Scheme 3. Selective benzylation of **18** gave **19**, which was converted to **20**. The nitrile group was then transformed to the intermediate imino ether which underwent

reaction with serine methyl ester to give **21**. Oxidation furnished oxazole **6e** upon ester hydrolysis (Scheme 3)

Previously described boronic acid **22**[5a] was reacted with thiazole derivative **25** under Suzuki conditions, to give **6g** upon ester hydrolysis (Scheme 4). Thiazole **25** was prepared by condensation of 1,3-dibromoacetone and ethyl thiooxamate as shown (Scheme 4). Phenyl derivative **6o** was prepared by reaction of **22** with **26** (Scheme 4).

Benzylic alcohol **19** was converted to bromide **27** which underwent in situ reaction with zinc and subsequent Negishi coupling with thiazole **28** or thiophene **29** to give **6f** and **6m**, respectively, upon ester hydrolysis (Scheme 5). Picolinate **6p** and pyridyl isomers **6q** and **6r** were prepared in a similar manner.[15]

Imidazole **6h** was prepared from nitrile derivative **20**, via amidoxime **34** (Scheme 6). The methyl imidazoles were prepared via alkylation of **35** followed by ester hydrolysis (Scheme 6).

Furan **6k** was prepared by Friedel–Crafts alkylation of 4-chloro anisole (**36**) (Scheme 7). Selective demethylation of the phenolic ether **37** followed by alkylation and ester hydrolysis delivered the final acids. Furan **6l** was prepared in an analogous fashion.

Wittig reaction with 5-chlorosalicyaldehyde (**38**) followed by benzylation of the phenolic hydroxyl, double bond and ester reduction then oxidation of the alcohol gave aldehyde **39** (Scheme 8). Gewald reaction[17] with ethyl cyanoacetate and sulfur in the presence of triethylamine gave aminothiophene **40** which underwent deamination and ester hydrolysis to give thiophene **6n** (Scheme 8).

Commercially available amino thiazole **41** underwent deprotection and re-esterification to give phenol **42** which was alkylated with benzyl bromide (Scheme 9). Ester hydrolysis delivered aminothiazole **9a** (Scheme 9)

In summary, we have explored several aromatic heterocycles as replacements for the original pyrazole lead (**6a**). The SAR generated has shown that the pyrazole, thiazole and furan derivatives demonstrated the highest EP_1 affinity and therefore merit further investigation.

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