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Structure–Activity Relationship on the Human EP_3 Prostanoid Receptor by Use of Solid-Support Chemistry

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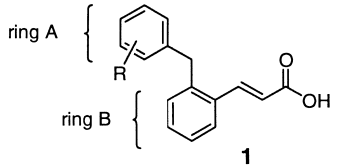
Abstract—Potent and selective EP_3 receptor ligands were found by making a library using solid-support chemistry. These compounds can be obtained by a Suzuki coupling reaction of a solid-supported benzyl bromide using various boronic acids. The yields obtained for this reaction were in the range of 24–95% of arylmethyl cinnamic acid **1** after cleavage from the Wang resin. © 2001 Published by Elsevier Science Ltd.

Recently, the eight known human prostanoid receptors have been cloned and characterized.[1] The ligand specificity for a human prostanoid receptors can now be determined and consequently, the correlation of a specific receptor with various pathologies could potentially be established. Our search for a selective EP_3 receptor ligand was initiated by screening a large number of compounds from our sample collection.[2] One particular class of compounds, namely the 2-(arylmethyl) cinnamic acid (**1**) was identified as a potential series. An effective and rapid way to explore the ring A and study SAR involved making a library using solid-phase synthesis.



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The preparation of small molecule libraries using solid-phase organic chemistry is now routinely applied in pharmaceutical research. For lead discovery and lead optimization, it has proven to be a powerful method.[3] The Suzuki coupling reaction[4] using polymer-supported aryl bromides with boronic acids to obtain biaryl adducts has been widely used over the past few years.[5] For our purpose, a benzylic bromide instead of an aryl bromide would be necessary in the Suzuki coupling reaction to achieve the biaryl methane core. Benzylic bromides have only been used rarely for Suzuki coupling reaction in solution[6a] and even more rarely on solid support.[6b] In this paper, we report the preparation of a small library using a polymer-supported benzyl bromide and various boronic acids to find a potent and selective EP_3 antagonist.

The benzyl bromide used in the Suzuki coupling reactions was first synthesized and then linked on a solid support. The synthesis is outlined in Scheme 1. Starting from 2-methylcinnamic acid, the ester **2** was obtained under standard Fischer conditions. Benzylic bromination followed by hydrolysis and conversion of the carboxylic acid to the acyl chloride gave the intermediate **3** in 43% overall yield (three steps). Addition of the Wang resin to **3** yielded **4** with a loading of 0.57 mmol/g (Scheme 1).

With the polymer **4** in hand, we were ready to affect Suzuki coupling reactions with boronic acids. Typically, the reactions were performed using 3.0 equiv of boronic acid, 6.0 equiv of CsF with 10 mol% of $Pd(PPh_3)_4$ in DME at 100 °C for 10 h. The substrate was then cleaved from the resin with either 20% TFA in CH_2Cl_2 for 10 min at room temperature or sodium hydroxide in THF/MeOH.[7] Under these conditions, 20 substituted arylmethyl cinnamic acids were rapidly obtained in 24–95% yield but most importantly in high purity. Table 1 summarizes the results of these reactions. The only major impurity was determined to be 2-methylcinnamic acid, which resulted from reduction of halide **4** and then cleavage from the resin. This compound was found to

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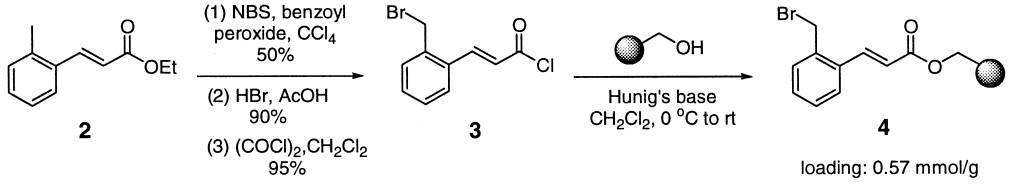
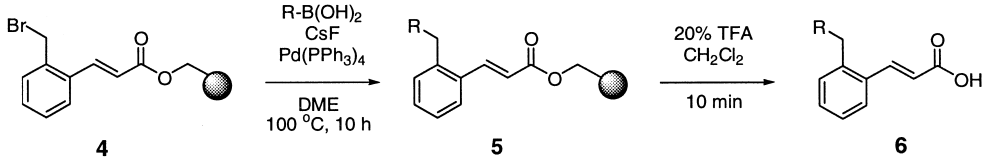


Scheme 1. Synthesis of the solid-supported benzyl bromide **4**.

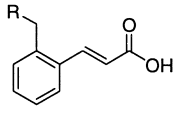
Table 1. Suzuki coupling of boronic acids and benzyl bromide on solid support.

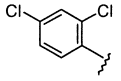
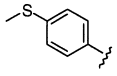
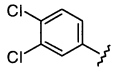
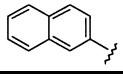


Entry	Boronic acid	Yield (%)[a]	Purity (%)[b]	Residual binding on EP_3 (%)[d]
1	1-Naphthalene boronic acid	67	96	48
2	3,4-Dichlorobenzene boronic acid	48	90	8
3	3-Chlorobenzene boronic acid	90	90 (5)[c]	55
4	2,4-Dichlorobenzene boronic acid	92	96	25
5	3-(Trifluoromethyl)benzene boronic acid	76	89 (8)[c]	54
6	2-(Trifluoromethyl)benzene boronic acid	67	83 (11)[c]	89
7	Benzo[*b*]furan-2-boronic acid	49	95	61
8	2-Methoxybenzene boronic acid	62	74 (7)[c]	93
9	2-Naphthalene boronic acid	77	88	5
10	2*H*-Benzo[*d*]1,3-dioxolene-5-boronic acid	33	72 (13)[c]	73
11	Thiophene-2-boronic acid	38	93	74
12	Thiophene-3-boronic acid	72	94	77
13	3-(Hydroxymethyl)benzene boronic acid	87	64 (30)[c]	84
14	2-[(2-Phenylethylthio)methyl]benzene boronic acid	24	59 (9)[c]	68
15	3-[(2-Phenylethylthio)methyl]benzene boronic acid	41	33 (32)[c]	52
16	2-(Methylthio)benzene boronic acid	95	95	96
17	2-Furan boronic acid	51	60 (24)[c]	91
18	4-(Methylthio)benzene boronic acid	21	89	27
19	4-{[(*tert*-Butyl)amino]sulfonyl}benzene boronic acid	94	69	100
20	3,4-Dimethoxybenzene boronic acid	57	92	84

[a]Isolated yields from the crude reaction mixture (yields based on the original loading of the resin).
[b]Purities evaluated by HPLC at 275 nm.
[c]Percentage of 2-methylcinnamic acid.
[d]The residual binding is the percentage of radiolabelled PGE_2 bound on the receptor when the drug is present (evaluated at 1 μM).

Table 2. Full profile of potent EP_3 antagonists.



		K_i (μM)[a]							
Entry	R	EP_1	EP_2	EP_3	EP_4	FP	DP	IP	TP
1		>100	4.1	0.11	>40	63	2.5	31	0.52
2		>100	43	0.080	>50	>83	4.1	>76	4.6
3		63	13	0.032	10	41	2.4	37	0.90
4		>100	12	0.020	3.1	69	0.53	>100	10

[a]Data in Table 2 are an average value from at least two separate experiments.

be inactive on the EP_3 receptor. The residual binding[8] of PGE_2 on the EP_3 receptor is also reported in Table 1. From these results, we found four compounds that showed high affinity for this receptor with less than 30% of residual binding (entries 2, 4, 9, and 18).

These compounds were then prepared by standard solution-phase chemistry, purified and fully characterized.[9] They all have activities equal to or less than 110 nM on the EP_3 receptor (Table 2). The best activity was achieved when R was 3,4-dichlorophenyl and 2-naphthyl with K_i values of 32 nM and 20 nM, respectively (entries 3 and 4). These two compounds were also selective over the EP receptors by a factor of at least 155 and by a factor of 30 over the other prostanoid receptors.

In conclusion, we have reported the preparation of an arylmethyl cinnamic acid library using a solid-supported benzyl bromide and various boronic acids in a Suzuki type reaction. The benzylcinnamic acids reported herein constitute a novel series of EP_3 selective ligands. The SAR from the library indicated that substitution with 2-naphthyl and 3,4-dichlorophenyl were the most potent and selective EP_3 antagonists with activities on EP_3 of 20 nM and 32 nM. The pharmacology studies and further optimization of these leads will be disclosed elsewhere.

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7. **Typical procedure for the Suzuki coupling reaction on solid support:** To a suspension of the resin (300 mg, 0.57 mmol/g, 0.17 mmol) in 1.5 mL of DME was added the boronic acid (0.51 mmol), cesium fluoride (156 mg, 1.03 mmol) (Na_2CO_3 aq 2 M may also be used) and $Pd(PPh_3)_4$ (20 mg, 10 mol%). The reaction mixture was stirred at 95 °C for 10 h and cooled to rt. The mixture was then filtered and successively washed with THF/H_2O (1:1) (2×), THF (2×), CH_2Cl_2 (2×) and MeOH (2×) and dried under high vacuum for 1 h. Cleavage: to the resin was added 5 mL of a solution of 20% TFA in CH_2Cl_2. The mixture was stirred 10 min at rt, filtered and evaporated to dryness.

8. The residual binding is the percentage of radiolabelled PGE_2 bound on the receptor when the drug is present.

9. All new compounds reported herein were characterized (^1H NMR, and MS) and gave satisfactory elemental analysis.