Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 2309–2323

BIOORGANIC & MEDICINAL CHEMISTRY

The Difluoromethylenesulfonic Acid Group as a Monoanionic Phosphate Surrogate for Obtaining PTP1B Inhibitors

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Received 6 November 2001; accepted 10 January 2002

Abstract—Three peptides, **7**–**9**, bearing sulfono(difluoromethyl)phenylalanine (F_2Smp, **2**), a nonhydrolyzable, monoanionic phosphotyrosine mimetic, were prepared and evaluated as PTP1B inhibitors. The most effective inhibitor was the nonapeptide, ELEF(F_2Smp)MDYE-NH_2, (**9**) which exhibited a K_i of 360 nM. A comparison of F_2Smp-bearing peptides **7** [DADE(F_2Smp)LNH_2, $K_i = 3.4\,\mu M$] and **8** [EEDE(F_2Smp)LNH_2, $K_i = 0.74\,\mu M$] with their phosphono(difluoromethyl)phenylalanine (F_2Pmp)-bearing analogues indicated that F_2Smp is not as effective a pTyr mimetic as F_2Pmp by 100- to 130-fold. Although F_2Smp is not as effective as F_2Pmp, a comparison of peptide **7** with analagous peptides bearing other monoanionic pTyr mimetics recently reported in the literature indicates that F_2Smp is about 65-fold more effective than any other non-hydrolyzable, monanionic pTyr mimetic reported to date. To further assess the difluoromethylenesulfonic acid (DFMS) group as a monoanionic phosphate mimetic, a series of 24 nonpeptidyl biaryl compounds bearing the DFMS group were prepared using polymer-supported methodologies and screened for PTP1B inhibition. Several of these compounds were selected for further study and their IC_{50}'s compared to their difluoromethylenephosphonic (DFMP) analogues. The differences in IC_{50}'s between the DFMS and DFMP non-peptidyl compounds was not as great as with the F_2Smp- and F_2Pmp-bearing peptides. Possible reasons for this and its implication to the design of small molecule PTP1B inhibitors is discussed.

Introduction

There are numerous signal transduction pathways that rely on protein tyrosine phosphorylation/dephosphorylation for signal transmission. The phosphorylation event is catalyzed by protein tyrosine kinases (PTKs) while the dephosporylation reaction is catalyzed by protein tyrosine phosphatases (PTPs). Due to their potential for the treatment of a variety of disease states, inhibitors of both the PTKs and PTPs have been pursued with considerable vigour over the last decade.[1,2] Among the PTPs, human protein tyrosine phosphatase 1B (PTP1B) has received the most attention. PTP1B is widely expressed in insulin-sensitive tissues and has been implicated in the attenuation of insulin signaling.[3] Recent studies with a PTP1B knock-out mouse has demonstrated that PTP1B plays a key regulatory role in modulating both insulin sensitivity and resistance to diet-induced obesity.[4] Thus, PTP1B is now recognized as a potential therapeutic target for the treatment of type 2 diabetes and obesity and numerous papers have appeared in recent years describing inhibitors of this enzyme.[2]

Since the phosphate group is crucial for PTP-substrate binding,[5] an effective non-hydrolyzable phosphate mimetic is an important aspect of PTP inhibitor design. The most effective phosphate mimetic reported to date is the difluoromethylenephosphonic acid (DFMP) group. Peptides bearing phosphono(difluoromethyl)phenylalanine (F_2Pmp, **1**) bind better than the analogous peptide substrates and can be up to three orders of magnitude more effective than their non-fluorinated analogues.[2,6a–d] The DFMP group also been found to be effective for the development of non-peptidyl PTP inhibitors.[7a–g]

Although the DFMP group has proven to be useful for obtaining inhibitors of PTP1B, its dianionic nature may compromise cell permeability.[7a] Consequently, there has been considerable interest in the development of less highly charged pTyr mimics.[8,9] A variety of other phosphate mimetics have been examined but none have proven to be as effective as the DFMP group.[8,9] Several

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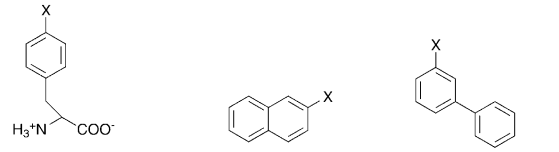
0968-0896/02/$ - see front matter
PII: S0968-0896(02)00062-7

years ago, Liotta and co-workers reported that a synthetic tri-sulfotyrosyl dodecapeptide analogue of the insulin receptor kinase domain was an inhibitor of PTP1B.[10] Later, Desmarais and co-workers performed a more detailed analysis of sulfotyrosyl peptides as PTP1B inhibitors.[11] These workers found that peptides bearing acidic residues N-terminal to the sTyr residue exhibited IC_{50}'s in the low μM region[11] which indicates that these peptides bind almost as well as the best peptide substrates.[6d] However, the hydrolytic lability of phenyl sulfates makes them unsuitable as phosphate mimetics for drug development. Since the effect of the fluorines in DFMP-bearing compounds is believed to be due to H-bonding of the fluorines with residues in the active site and not pK_a effects,[6c,7b] we reasoned that the difluoromethylsulfonic acid (DFMS) group would be an effective hydrolytically stable, monoanionic phosphate mimetic. We developed a method for constructing α-fluorosulfonic acids using electrophilic fluorination[12,13] and evaluated compounds **3** and **5** as inhibitors of PTP1B.[14] These compounds were found to be moderate inhibitors of PTP1B (**3**, $IC_{50} = 175\,\mu M$; **5**, $IC_{50} = 115\,\mu M$) and were approximately 5- to 8-fold less potent than their DFMP analogues **4** and **6** (**4**, $IC_{50} = 35\,\mu M$; **6**, $IC_{50} = 15\,\mu M$)[14,15] Since this work appeared, several other monanionic pTyr mimetics have been reported and evaluated on peptidyl scaffolds.[8,9] In order to compare the DFMS group as a phosphotyrosine mimetic to those reported by other workers,[8,9] we decided to prepare several peptides bearing the DFMS group. We recently reported an enantioselective synthesis of sulfono(difluoromethyl)phenylalanine (F_2Smp, **2**) suitably protected for peptide synthesis and its incorporation into a peptide.[16] Here we report the evaluation of three F_2Smp-containing peptides as PTP1B inhibitors and a comparison of the potency of one of these peptides with analagous peptides bearing other pTyr mimetics reported by other workers. The synthesis of 24 non-peptidyl compounds bearing the DFMS group, prepared using soluble polymer supported organic synthesis (SPSOS) methodologies, is also reported. Their evaluation as PTP1B inhibitors and a comparison of the inhibitory potency of selected DFMS compounds with their DFMP analogues is also reported.



1, X = $CF_2PO_3^{-2}$ (F_2Pmp)
2, X = $CF_2SO_3^-$ (F_2Smp)
3, X = $CF_2SO_3^-$
4, X = $CF_2PO_3^{-2}$
5, X = $CF_2SO_3^-$
6, X = $CF_2PO_3^{-2}$

Results and Discussion

Studies with F_2Smp-bearing peptides

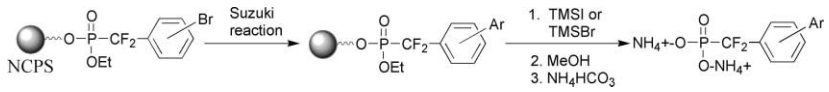
Three F_2Smp-bearing peptides, **7**–**9,** were prepared and then examined as PTP1B inhibitors (Table 1). Peptide **7** was constructed since the DADE-X-L sequence has been used extensively for examining phosphotyrosine mimetics for obtaining inhibitors of PTP1B.[9] This peptide would allow us to compare the F_2Smp moiety to other pTyr mimetics. Peptide **8** was prepared since Huyer et al. have shown that the peptide EEDE(F_2Pmp)M exhibits a K_i of 7.2 nM, making it the most potent peptide-based PTP1B inhibitor reported to date.[6d] Finally, using a reverse alanine scan to find high-affinity substrates for PTP1B, Vetter et al. discovered that AcELEFpYMDYENH$_2$ is one of the best peptide substrates, in terms of k_{cat}/K_m, for PTP1B ever reported.[17] Consequently, we anticipated that its F_2Smp analogue (**9**) would be a good PTP1B inhibitor.

Peptides **7**–**9** were constructed using the procedure described previously for peptide **7**.[16] The results from the inhibition studies with peptide **7**–**9** are shown in Table 1. All of the peptides were competitive inhibitors. The most potent of these three peptides was the non-apeptide **9** which exhibited a K_i of 360 nM which is consistent with AcELEFpYMDYENH$_2$ being an outstanding peptide substrate.[17] The K_i for peptide **9** is approximately 2 times lower than the K_i for peptide **8** and about 10-fold lower than that for peptide **7**. Comparing peptides **7** and **8** with similar F_2Pmp-bearing peptides **10** and **11** (Table 1), it can be seen that F_2Smp is not as effective a pTyr mimetic as F_2Pmp by at least 100- to 130-fold. This was somewhat surprising since Desmarais et al.'s results with sTyr-containing peptide inhibitors[11] suggested that the monoanionic SO_4^- group binds almost as well as the PO_4^{-2} group. For example, the tripeptide AcDE(sY)L (**10**) has a K_i of 5.0 μM, which is approximately the same as the K_m (3.2 μM) of the pentapeptide substrate, AcDADE(pY)LNH$_2$ (**11**).[11] Although the sTyr analogue of peptides **7**–**9** have not been reported, it is clear that substituting the labile oxygen in sTyr-bearing peptide inhibitors with a difluoromethylene group does not result in an increase in inhibitory potency. This is in contrast to F_2Pmp bearing peptides which have K_i's that are 26- to 75-fold lower than the K_m's of their substrate analogues.[6d] Our earlier inhibition studies with compounds **3** and **5** and their non-fluorinated analogues indicated that the fluorines are essential for good inhibition.[14] Sulfonates, whether bearing α-fluorines or not, are highly acidic and should be completely ionized at the pH under which these studies were performed (pH 6.5). This suggests that the enhanced effect of the fluorines with the CF_2-sulfonates is most likely a result of a direct interaction of the fluorines with residues in the enzyme active site and is not due to pK_a effects. It is possible that the

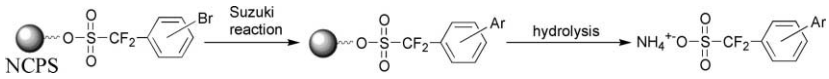
Table 1. Inhibition of PTP1B with F_2Smp- and F_2Pmp-bearing peptides

Peptide	K_i (uM)
DADE(F_2Smp)LNH$_2$ (**7**)	3.4
EEDE(F_2Smp)LNH$_2$ (**8**)	0.74
ELEF(F_2Smp)MDYENH$_2$ (**9**)	0.36
DADE(F_2Pmp)L (**10**)	0.026[a]
EEDE(F_2Pmp)L (**11**)	0.0072[a]
AcDE(sY)L (**12**)	5.0[b]
AcDADE(pY)LNH$_2$ (**13**)	$K_m = 3.2$[c]

[a]From ref 6d.
[b]From ref 11.
[c]From ref 18.

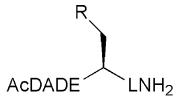


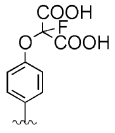
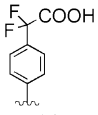
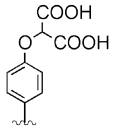
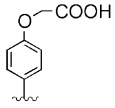
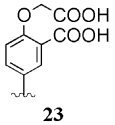
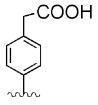
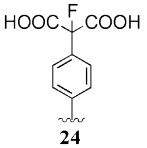
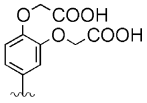
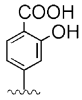
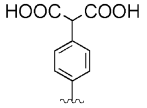
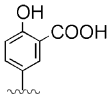
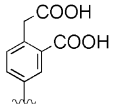
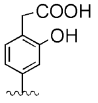
Scheme 1.



Scheme 2.

Table 2. Inhibition of PTP1B with non-phosphorus, monoanionic and dianionic phenylphosphate mimetics[a]



R (monoanionic)	IC_{50} (μM)	R (dianionic)	IC_{50} (μM)
DADE(F_2Smp)LNH_2 **7**	10	 **21**	1
 **14**	650	 **22**	10
 **15**	1200	 **23**	19
 **16**	2500	 **24**	430
 **17**	4400	 **25**	800
 **18**	4600	 **26**	1500
 **19**	5300	 **27**	3700
 **20**	13,000		

[a]All values were obtained from ref 9 with the exception of compound **7**, which was obtained from these studies.

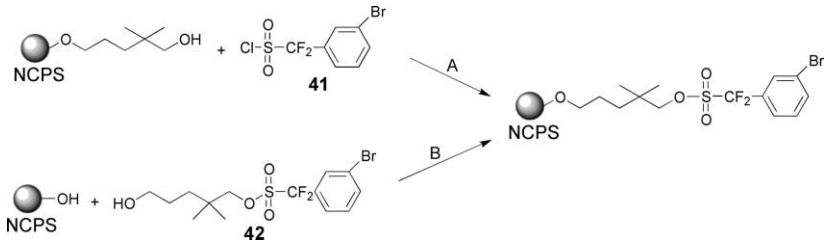
unusually strong H-bond that has been proposed to account for the high affinity of DFMP-bearing inhibitors[7b] may not be able to form in an optimal manner in the F_2Smp-bearing peptides due to overall size and/or geometric constraints. Nevertheless, whether due to pK_a effects or H-bonding, it is clear that the DFMS group is poorer phosphate mimetic than the DFMP group.

Although F_2Smp is not as effective as F_2Pmp, a comparison of F_2Smp-bearing peptide **7** with similar peptides bearing other monoanionic pTyr mimetics recently reported in the literature,[9] indicates that the DFMS group is about 65-fold more effective than *any other non-hydrolyzable, monanionic phosphate mimetic reported to date* (**14**–**20**, Table 2). F_2Smp compares very favorably even to non-phosphorus, dianionic pTyr mimics (**21**–**27**, Table 2) and only the fluoromalonyl group (**21**) is more effective.[19]

Synthesis of non-peptidyl compounds bearing the DFMS group on a soluble polymer support

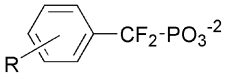
It is interesting to note that in contrast to the above peptide inhibitors, small molecule inhibitors **3** and **5** were only 5- to 8-fold less potent than their DFMP analogues **4** and **6**.[14] This prompted us to investigate non-peptidyl compounds bearing the DFMS group in more detail. We recently described a method by which non-peptidyl DFMP compounds could be prepared using non-crosslinked polystyrene (NCPS), a soluble polymer, as a support.[20] This procedure was used to prepare a small library of biaryl DFMP's (Scheme 1).[21] We wished to prepare the same or similar DFMS-bearing compounds and compare the inhibitory potency of these compounds to some of their DFMP analogues. We anticipated that our polymer-supported methodology would be a rapid approach to the synthesis of the DFMS compounds (Scheme 2). Indeed, we felt that our polymer-supported methodology would be even better suited to preparing DFMS compounds as opposed to DFMP compounds, since the DFMS compounds could be removed from the support by simple hydrolysis, rather than with the more harsh TMSBr or TMSI as was the case with the DFMP compounds.

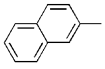
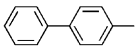
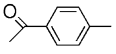
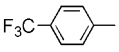
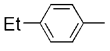
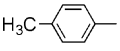
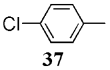
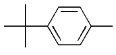
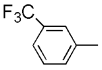
Before preparing the DFMS compounds, a rapid screen of the compounds obtained from the previously reported DFMP library[20] was performed by assaying PTP1B in the presence of 150 μM of each compound. The



Scheme 3.

Table 3. Percent inhibition of PTP1B with DFMP compounds

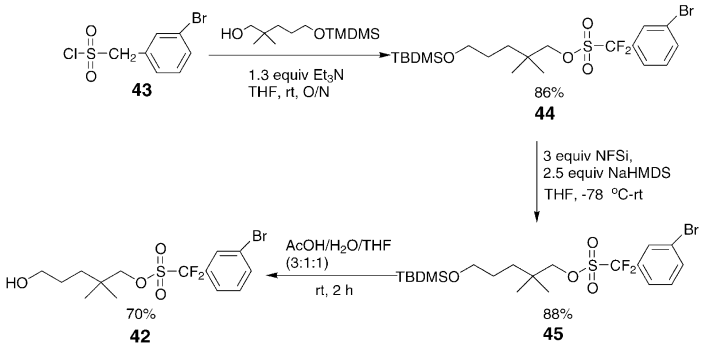


R	% Inhibition *para* series 150 μM	% Inhibition *meta* series	
		150 μM	50 μM
 **28**	80	99	89
 **29**	ND[a,b]	98	87
 **30**	50	94	80
 **31**	43	91	75
 **32**	41	90	74
 **33**	61	89	74
 **34**	38	88	74
 **35**	54	88	70
 **36**	38	87	70
 **37**	50	92	65
 **38**	41	85	59
 **39**	56	60	ND[a]
 **40**	29	24	ND[a]

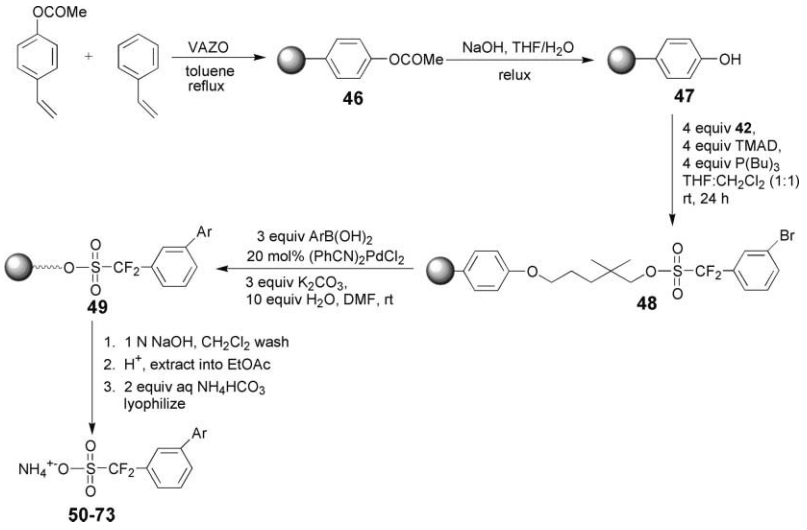
[a]ND, not determined.
[b]Not determined due to solubility problems.

results of these studies are shown in Table 3. The *meta* series of compounds were better inhibitors than the *para* series and none of the *para* series of compounds was particularly good inhibitors. This is consistent with our earlier finding that compound **6** was a 6-fold better inhibitor than its *para* isomer.[7c] A number of the *meta* compounds appeared to be promising with the exception of compounds **39** and **40**, which bore ortho substituents on the distal aryl ring. Compounds **28**–**38** of the *meta* series were rescreened using 50 μM of each compound which enable us to better differentiate between these inhibitors. The majority of the *meta* compounds showed approximately the same level of inhibition (between 70 and 80% inhibition at 50 μM) with the exception of compounds **37** and **38** (59 and 65% inhibition at 50 μM, respectively) which bore a *para*-*t*-butyl group (**37**) and a *para*-chloro group (**38**) on the distal aryl ring and compounds **28** and **29** which were substituted with the 2-naphthyl and biphenyl groups, respectively, and were the best two inhibitors. The IC_{50}'s of **28** and **29** were determined to be 21 and 8 μM, respectively. The IC_{50} of compound **30** was also determined and found to be 24 μM. Compound **29** represents an approximately 8-fold improvement in inhibitory potency compared to the parent compound **6**.

For the DFMS library, we focused on the *meta*-substituted compounds since the above studies indicated that the *para* biaryl compounds were not as effective inhibitors as the *meta* series. We chose to construct of the DFMS analogues of the above DFMP-*meta* series as well as other biaryl compounds, some bearing heterocyclic rings. It was anticipated that the polymer-bound DFMS compounds would be quite hydrolytically labile and therefore, would have to be attached to the polymer by a linker arm that would confer enough stability to enable chemistry to be performed on the aryl ring, yet still allow the compounds to be removed by mild hydrolysis. Our initial approach was to construct sulfonyl chloride **41** and then attach it to NCPS modified with a 2,3-dimethylpentanol linker arm as outlined in Scheme 3 (pathway A). It was anticipated that the two methyl groups on the linker arm would help confer some hydrolytic stability to the polymer-bound sulfonates. However, attempts to prepare **41** from the corresponding sulfonic acid or its salts using a variety of different procedures were unsuccessful. This is in contrast to its nonfluorinated analogue (**43**, Scheme 4) which was readily prepared by reaction of the corresponding sodium salt with $POCl_3$ in sulfolane/CH_3CN. Therefore, an alternative approach was investigated



Scheme 4.

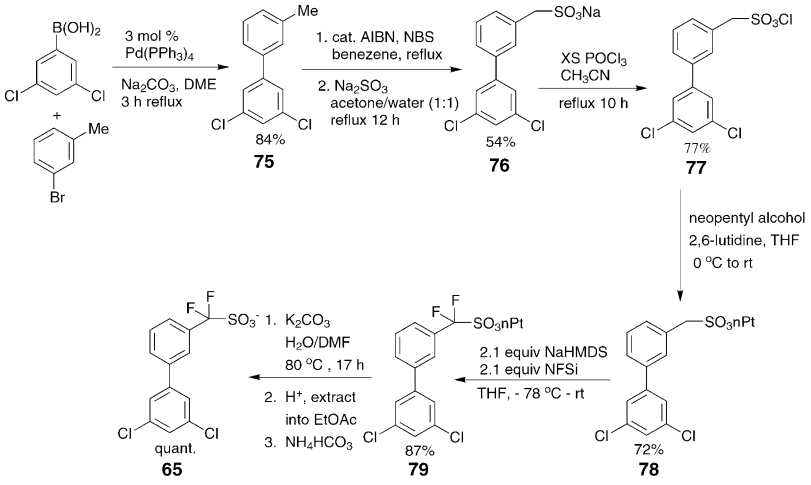


Scheme 5.

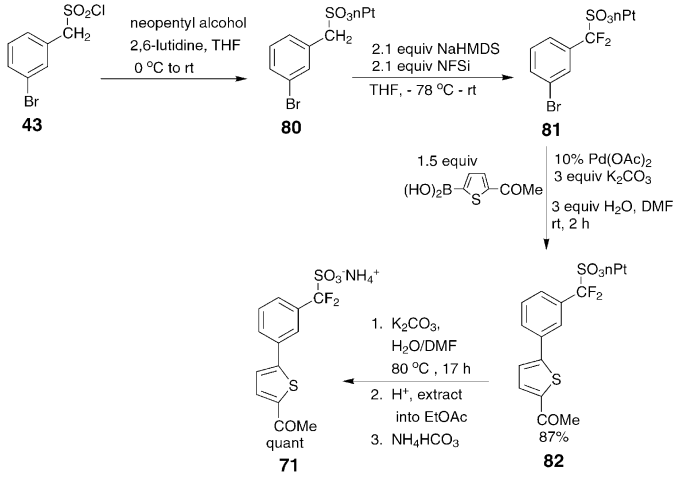
which involved attaching the linker arm to the sulfonate first to give **42** and then attaching **42** to the support (pathway B, Scheme 3). Sulfonyl chloride **43** was reacted with mono-TBDMS-protected 2,3-dimethylpentane-1,5-diol to give the sulfonate ester **44** in 86% yield. Reaction of **44** with 3 equiv *N*-fluorobenzenesulfonimide (NFSi), and 2.5 equivalents of NaHMDS in THF at −78 °C followed by warming to room temperature and stirring overnight gave the fluorinated sulfonate **45** in 88% yield. Removal of the TBDMS group was accomplished using $AcOH/H_2O/THF$ to give the free alcohol **42** in 78% yield (Scheme 4).

The sulfonate was attached to the support by a hydrolytically stable ether linkage. Styrene was copolymerized with 9 mol% of 4-acetoxystyrene in the presence of the free radical initiator 1,1′-azobis(cyclohexanecarbonitrile) (VAZO) to obtain the 4-acetoxy-functionalized NCPS, **46** (Scheme 5).[21] The polymer was then saponified by refluxing it in an aqueous solution of NaOH in THF for 24 h to give the 4-hydroxylated NCPS (**47**).[21] At each step, the polymer was purified by diluting the reaction mixture with CH_2Cl_2 and then precipitating out the polymer in MeOH. The recovery of polymer **47** was 90%. Loading of the polymer was achieved using Mitsonobu chemistry which involved reacting **47** with approximately 4 equivalents of the sulfonate **42**, 4 equivalents TMAD and 4 equivalents PBu_3 in THF/CH_2Cl_2. After 24 h, the reaction was added directly to a solution of MeOH and recovery of sulfonylated polymer **48** was 97%. The polymer loading was approximately 0.55 mmol/g as determined by NMR (see Experimental).

The polymer-bound biaryls (**49**) were prepared using the room temperature Suzuki reaction conditions we developed for the DFMP library.[20] This involved reacting the polymer-bound sulfonate **48** with 3 equivalents boronic acid in the presence of 20 mol% $(PhCN)_2PdCl_2$, 3 equivalents K_2CO_3 and 10 equivalents water in degassed DMF (Scheme 5). A total of 24 different aryl boronic acids were used. The reactions were monitored by ^{19}F NMR and within 9 h or less, almost all of the reactions had gone to completion, with the exception of 2-furanboronic acid which required 24 h, and then another 24 h with fresh reagents. After the palladium catalyst was removed by centrifugation, all polymer-bound biaryl products were purified by diluting the reaction mixture with CH_2Cl_2, precipitating out the polymer in MeOH and a few drops of brine, filtering off the polymer, and rinsing the collected polymer with MeOH. The polymer recovery ranged from 90 to 95%. The products were hydrolyzed off the polymer support with 3 equivalents of K_2CO_3, 10 equivalents of H_2O, in DMF, at 80 °C for 17 h. The crude reaction mixture was then

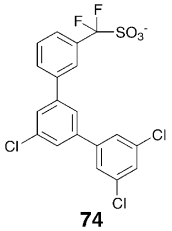


Scheme 6.



Scheme 7.

diluted with CH_2Cl_2 and added to a solution of MeOH and a few drops of brine. The precipitated polymer was filtered off, leaving the filtrate which contained the crude potassium salt of the biaryl DFMS compounds. The filtrate was concentrated, redissolved in 1 N NaOH, washed with CH_2Cl_2 to remove any residual polymer and organic impurities, and acidified to pH of approximately 0.5. The sulfonic acids were then extracted into EtOAc, concentrated, treated with an aqueous solution of NH_4HCO_3, and then lyophilized and this process was repeated until a constant weight was obtained. This gave the biaryl DFMS compounds, **50**–**73**, as their ammonium salts in yields ranging from 34 to 95% [from the polymer-bound sulfonate **48** (see Table 4)]. The variable yields were mainly a result of the extraction step. Nevertheless, sufficient amounts of each compound were obtained for inhibitor studies. The structures of all of the compounds was confirmed by low resolution and high resolution ESMS, ^1H, ^{19}F NMR. The vast majority of these 24 compounds were obtained in 95% purity or better as determined by ^{19}F NMR, analytical HPLC and ESMS and could be used directly for PTP1B screening. Although ^{19}F NMR and HPLC suggested that compound **65** was obtained in about 96–98% purity, high resolution ESMS revealed that it was contaminated with significant amounts (~9%) of compound **74,** which was most likely a result of a double Suzuki coupling on the aryl chloride product. Surprisingly, the doubly coupled products did not form to any significant extent with compounds **57**, **59**, **63** and **66** (as determined by mass spectral analysis), which were also aryl chlorides. We were unable to separate compound **74** from compound **65** and so compound **65** was resynthesized in pure form in solution using a procedure (Scheme 6) which did not yield any of the doubly coupled product. Compound **71**, which was obtained in only 77% purity (by HPLC), was also difficult to purify and therefore, was resynthesized in pure form in solution (Scheme 7).

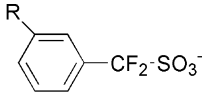


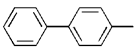
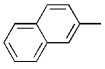
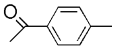
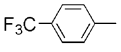
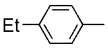
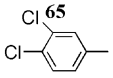
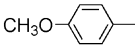
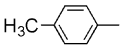
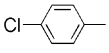
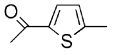
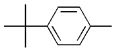
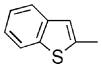
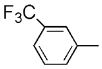
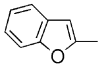
74

A rapid screen of **50**–**73** was conducted by determining the percent inhibition of PTP1B inhibition in the presence of 50 μM of each compound (Table 5). All of the DFMP compounds in Table 3 were better inhibitors than their analogous DFMS compounds (**50**–**62**, Table 5). The majority of the compounds showed little inhibitory potency. As with the DFMP compounds in Table 3, the best DFMS inhibitors were those bearing large apolar aryl moieties (**50**, **51**, **72**, and **73**). The enhanced binding of these compounds compared to the rest of the DFMS inhibitors is most likely a result of increased hydrophobic interactions.

The IC_{50}'s of the four best inhibitors (**50**, **51**, **72**, and **73**) as well as for compound **52**, were determined (Table 6). Again, the best inhibitor was the *meta*-biphenyl substituted compound **50** which displayed an IC_{50} of 26 μM. A comparison of the IC_{50}'s of DFMP compounds **28**–**30** to the analogous DFMS compounds (**50**–**52**) indicates that the DFMP compounds are approximately 3- to 8-fold better inhibitors than DFMS compounds. This difference is comparable to what we found for the difference in inhibitory potency between inhibitors **3** and **5** and inhibitors **4** and **6**.[14] Again, this is in contrast to the large difference in inhibitory potency (>100-fold) between F_2Pmp- and F_2Smp-bearing peptide inhibitors. Also, it is interesting to note that peptide **7** is only an 8-fold better inhibitor than compound **50**. This disparity between the effectiveness of certain phosphate mimetics in peptidyl scaffolds versus small

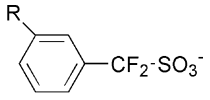
Table 4. Yields and purity of biaryl DFMS products

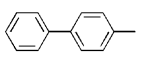
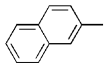
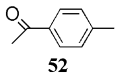
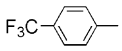
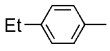
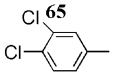
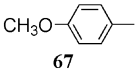
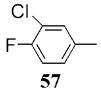
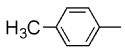
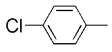
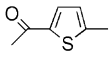
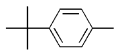
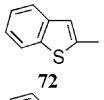
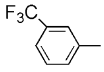
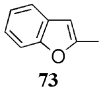


R	% Yield	% Purity		R	% Yield	% Purity	
		^{19}F NMR	HPLC			^{19}F NMR	HPLC
 **50**	34	100	99	 **62**	89	100	99
 **51**	92	100	99	 **63**	62	100	90
 **52**	54	100	100	 **64**	91	100	100
 **53**	79	100	100		95[a]	96[a]	98[a]
 **54**	71	100	98	 **66**	81	100	99
 **55**	72	100	94	 **67**	92	99	95
 **56**	67	99	95	 **68**	64	100	100
 **57**	88	100	100	 **69**	72	100	100
 **58**	63	100	100	 **70**	39	100	100
 **59**	84	100	100	 **71**	54	90	77
 **60**	85	99	100	 **72**	56	100	98
 **61**	73	100	93	 **73**	82	100	100

[a]ESMS revealed approximately 9% of compound **74** present.

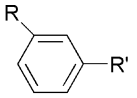
Table 5. Percent inhibition[a] of PTP1B with DFMS compounds

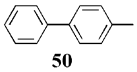
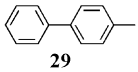
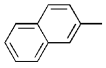
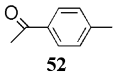
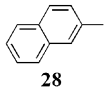
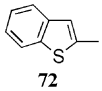
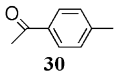
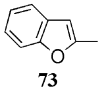


R	% inhibition[a]	R	% inhibition[a]
 **50**	77	 **62**	NI[b]
 **51**	62	 **63**	36
 **52**	8	 **64**	40
 **53**	NI	 **65**	41
 **54**	7	 **66**	44
 **55**	5	 **67**	10
 **56**	5	 **68**	NI
 **57**	5	 **69**	42
 **58**	NI	 **70**	12
 **59**	NI	 **71**	22
 **60**	43	 **72**	51
 **61**	NI	 **73**	65

[a]50 μM inhibitor.
[b]NI, no inhibition.

Table 6. IC_{50}'s of selected DFMS and DFMP compounds with PTP1B



R′ = DFMS		R′ = DFMP	
R	IC_{50} (μM)	R	IC_{50} (μM)
 **50**	26	 **29**	8
 **51**	53		
 **52**	197	 **28**	21
 **72**	56	 **30**	24
 **73**	49		

molecules has recently been noted by Burke and co-workers with other phosphate mimetics.[9] These workers suggested that the non-peptidyl compounds may have more freedom to orient the pTyr mimic in such a way that results in optimal binding and this may be what is taking place here.[9] However, when comparing mimetics within non-peptidyl platforms, it is possible that, in certain instances (such as **28** vs **50**), neither the DFMP group nor the DFMS group can form optimal interactions with the enzyme and so other factors (such as hydrophobic interactions) are also important and so less of a difference in inhibition is seen between the two classes of compounds. In any case, these results reflect the concerns of Burke and co-workers about assessing the effectiveness of pTyr mimetics using peptidyl scaffolds if the ultimate goal is the discovery of potent small molecule inhibitors.

In conclusion, this study has demonstrated that F_2Smp is the most potent non-hydrolyzable, monoanionic pTyr mimetic reported to date for obtaining PTP1B inhibitors. Although the F_2Smp-bearing peptides were at least 100-fold poorer inhibitors than F_2Pmp-bearing peptides, on small molecule scaffolds, the difference between DFMS-bearing inhibitors and their DFMP analogues was much smaller (3- to 8-fold) which suggest that the DFMS group may prove to be a very useful monoanionic phosphate mimetic for preparing small molecule inhibitors of PTP1B. We also demonstrated that the polymer supported methodologies described previously for the synthesis of DFMP compounds can also be used for the synthesis of DFMS compounds.

Experimental

General

All starting materials were obtained from commercial suppliers (Aldrich Chemical Company, Oakville, ON, Canada or Lancaster Synthesis Incorporated, Windham, NH, USA). Solvents were purchased from Caledon Laboratories (Georgetown, ON, Canada), Lancaster Synthesis Incorporated, or BDH Canada (Toronto, Canada). Tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone under argon. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under argon. Dimethylformamide (DMF) was distilled under reduced pressure from cal-

cium hydride and stored over 4 Å sieves under argon. Reactions involving moisture-sensitive reagents were executed under an inert atmosphere of dry argon or nitrogen. All glassware was pre-dried prior to use and all liquid transfers were performed using dry syringes and needles. Silica gel chromatography was performed using silica gel 60A (Silicycle, 230–400 mesh). ^{1}H, ^{19}F, ^{31}P, and ^{13}C NMR spectra were recorded on a Varian 200-Gemini, Bruker AC-200, or Bruker AC-300 NMR spectrometer. The abbreviations s, d, t, q, m, dd, dt, and br are used for singlet, doublet, triplet, quartet, multiplet, doublet of doublets, doublet of triplets, and broad, respectively. Coupling constants are reported in Hertz (Hz). Chemicals shifts (δ) for ^{1}H NMR spectra run in $CDCl_3$ are reported in ppm relative to the internal standard tetramethylsilane (TMS). Chemical shifts (δ) for ^{1}H NMR spectra run in CD_3OD are reported in ppm relative to residual solvent protons (δ 3.30). Chemical shifts (δ) for ^{1}H NMR spectra run in D_2O are reported in ppm relative to residual solvent protons (δ 4.79). For ^{13}C NMR spectra run in $CDCl_3$, chemical shifts are reported in ppm relative to the $CDCl_3$ residual carbons (δ 77.0 for central peak). For ^{13}C NMR spectra run in CD_3OD, chemical shifts are reported in ppm relative to the CD_3OD residual carbons (δ 49.0 for central peak). For ^{31}P NMR spectra, chemical shifts are reported in ppm relative to 85% phosphoric acid (external). ^{19}F NMR spectra, chemical shifts are reported in ppm relative to trifluoroacetic acid (external). Low resolution electron impact (LREIMS) and high resolution (HREIMS) electron impact mass spectra were obtained on a Micromass 70-S-250 mass spectrometer. Low resolution electrospray mass spectra (LRESMS) were obtained on a Micromass Quatro II mass spectrometer. High resolution electrospray mass spectra (HRESMS) were obtained on a Bruker Daltonics Apex II fourier transform ion cyclotron resonance spectrometer equipped with a 7.0 tesla superconducting magnet. All ESMS were run in the negative mode. All melting points were taken on a Meltemp melting point apparatus and are uncorrected. Analytical HPLC was performed on a Waters LC 4000 System using a Vydac 218TP54 analytical C-18 reverse-phase column and a Waters 86 tunable absorbance detector set at 254 nm. Buffer chemicals were obtained from Sigma Chemical Company. Enzyme assay solutions were prepared with deionized/distilled water. Fluorescein diphosphate (FDP) and human PTP1B were gifts from Merck-Frosst Canada Inc (Montreal, PQ, Canada).

Syntheses

Compounds **28**–**40** were prepared as previously described.[20]

Peptide syntheses

Peptides **8** and **9** were prepared using the procedure previously described for peptide **6**.[16] Peptide purities were assessed by ESMS and analytical reverse-phase HPLC. The mobile phase consisted of acetonitrile with 0.25% TFA (solvent A) and water with 0.025% TFA (solvent B). The following linear gradient was used: 95% A/5% B to 20% A/80% B over a period of 30 min. EEDE(F_2Smp)MNH_2 (**8**). Analytical HPLC showed only a single peak (retention time = 11.1 min). ESMS *m*/*z* calculated for $C_{34}H_{47}F_2N_7O_{17}S_2$ 926.24, found 926.07. ELEF(F_2Smp)MDYENH_2 (**9**). Analytical HPLC showed only a single peak (retention time = 15.8 min). Negative ion ESMS *m*/*z* calculated for $C_{34}H_{47}F_2N_7O_{17}S_2$ 1349.46, found 1349.14.

Synthesis of DFMS library

(3-Bromophenyl)methanesulfonyl chloride (43). To a solution of sodium (3-bromophenyl)methanesulfonate[22] (12.05 g, 44 mmol, 1 equiv) in 1:1 acetonitrile/sulfolane (44 mL) was added phosphorus oxychloride (17.3 mL, 28.46 g, 185.3 mmol, 4.2 equiv). The reaction was stirred for 3 h at 70 °C, cooled to room temperature, and then poured into cold water (300 mL) which resulted in the precipitation of the crude product. The precipitate was filtered off and then dissolved in CH_2Cl_2 (50 mL) and washed with water (3×100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give pure **43** as a white solid in 85% yield: mp 90–91 °C. ^{1}H NMR ($CDCl_3$) δ 7.62 (1H, d, J = 6.6 Hz), 7.30–7.46 (3H, m), 4.82 (2H, s); ^{13}C NMR ($CDCl_3$) δ 134.21, 133.45, 130.68, 129.98, 128.45, 123.08, 70.09. LREIMS *m*/*z* (relative intensity) 268 (9), 169 (100), 90 (45), 63 (26). HR-EIMS calcd for $C_7H_6O_2S_1Cl_1Br_1$ 267.8960, found 267.8951.

5-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-2,2-dimethylpentyl (3-bromophenyl)methanesulfonate (44). To a solution of **43** (9.00 g, 33.5 mmol, 1 equiv) and 5-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-2,2-dimethyl-1-pentanol[23] (12.40 g, 50.3 mmol, 1.5 equiv) in anhydrous THF (60 mL) at 0 °C was added a solution of triethylamine (4.43 g, 43.5 mmol, 1.3 equiv) in anhydrous THF (60 mL). The reaction was stirred at room temperature overnight then concentrated by rotary evaporation. Water (50 mL) was added and then extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Column chromatography (5:1 CH_2Cl_2/hexane) of the crude residue gave pure **44** as a white solid in 86% yield: mp 41–43 °C. ^{1}H NMR ($CDCl_3$) δ 7.25–7.60 (4H, br m), 4.31 (2H, s), 3.80 (2H, s), 3.56 (2H, t, J = 6.2 Hz), 1.15–1.55 (4H, m), 0.89 (15H, s), 0.05 (6H, s); ^{13}C NMR ($CDCl_3$) δ 133.65, 132.10, 130.47, 130.27, 129.27, 122.71, 78.12, 63.50, 56.04, 34.83, 34.06, 27.24, 25.98, 23.80, 18.31, −5.26. LREIMS *m*/*z* (relative intensity) 309 (3), 169 (28), 97 (100), 75 (21), 55 (71). HR-EIMS calcd for $C_{20}H_{36}O_4Si_1S_1Br_1$ ($M+H^+$) 479.1287, found 479.1293.

5-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-2,2-dimethylpentyl (3-bromophenyl)-difluoromethanesulfonate (45). To a solution of **44** (0.50 g, 1.05 mmol, 1 equiv) and NFSi (1.00 g, 3.15 mmol, 3 equiv) in anhyd THF (28 mL) at −78 °C was added NaHMDS (2.63 mL, 1.0 M, 2.63 mmol, 2.5 equiv) dropwise over a period of 1 h. The reaction was stirred at −78 °C for 2 h, warmed to room temperature, and stirred overnight. The reaction was then quenched with water (30 mL) and extracted with

ether (3×30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Column chromatography (1:99 EtOAc/hexane) of the crude residue yielded pure **45** as a pale-yellow oil in 88% yield. ^{1}H NMR ($CDCl_3$) δ 7.83 (1H, s), 7.71 (1H, d, J = 7.9 Hz), 7.64 (1H, d, J = 7.9 Hz), 7.38 (1H, t, J = 8.2 Hz), 4.16 (2H, s), 3.60 (9H, s), 0.06 (6H, s); ^{19}F NMR ($CDCl_3$) δ −24.28; ^{13}C NMR ($CDCl_3$) δ 135.54, 130.25, 130.06 (t, J_{CF} = 6.3 Hz), 129.95 (t, J_{CF} = 23 Hz), 125.79 (t, J_{CF} = 5.8 Hz), 122.69, 119.98 (t, J_{CF} = 285 Hz), 83.36, 63.34, 34.37, 34.33, 27.05, 25.91, 23.55, 18.28, −5.34. LREIMS m/z (relative intensity) 383 (3), 207 (100), 171 (11), 147 (23), 126 (41), 115 (14), 97 (49), 83 (63), 69 (27), 55 (70). HR-EIMS calcd for $C_{20}H_{34}O_4F_2Si_1S_1Br_1$ 515.1099, found 515.1120.

5-Hydroxy-2,2-dimethylpentyl (3-bromophenyl)difluoromethanesulfonate (42). To a solution of **45** (1.15 g, 2.24 mmol, 1 equiv) in THF (6 mL) was added a mixture of 3:1 acetic acid/water (24 mL). The reaction was stirred at room temperature for 3 h, diluted with ether (25 mL), washed with water (3×25 mL), 5% $NaHCO_3$ (3×25 mL), and brine (3×25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Column chromatography (1:3, EtOAc/hexane) of the crude residue gave pure **42** as a pale-yellow oil in 70% yield. ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, s), 7.72 (1H, d, J = 8.3 Hz), 7.63 (1H, d, J = 7.9 Hz), 7.39 (1H, t, J = 7.8 Hz), 4.16 (2H, s), 3.62 (2H, t, J = 6.4 Hz), 2.22 (1H, s), 1.49–1.59 (2H, m), 1.33–1.39 (2H, m), 0.98 (6H, s); ^{19}F NMR ($CDCl_3$) δ −24.28; ^{13}C NMR ($CDCl_3$) δ 135.58, 130.27, 130.01 (t, J_{CF} = 6.3 Hz), 129.79 (t, J_{CF} = 24 Hz), 125.77 (t, J_{CF} = 6.3 Hz), 122.67, 119.97 (t, J_{CF} = 284 Hz), 83.22, 63.01, 34.32, 34.20, 26.77, 23.50. LR-EIMS m/z (relative intensity) 205 (100), 126 (39), 115 (8), 101 (30), 83 (64), 69 (21), 55 (56). HR-EIMS calcd for $C_{14}H_{19}O_4F_2S_1Br_1$ 400.0156, found 400.0131.

4-Acetoxy non-crosslinked polystyrene polymer (46).[21] A solution of styrene (46 mL, 41.81 g, 401 mmol, 1 equiv), 4-acetoxystyrene (5.9 mL, 6.25 g, 37.02 mmol, 0.09 equiv), and VAZO (0.49 g, 2.01 mmol, 0.005 equiv) in deoxygenated and anhydrous toluene (120 mL) was heated at 95 °C for 48 h under nitrogen. The reaction was cooled to room temperature, then diluted with CH_2Cl_2 (75 mL) and then added dropwise, using an addition funnel, to a solution of MeOH (1.2 L) and brine (10 mL). Polymer **46** was collected by filtration, washed with MeOH (300 mL), and dried under high vacuum to give a white solid (44 g). ^{1}H NMR ($CDCl_3$) δ 6.30–7.60 (br d), 2.36 (br s), 1.30–2.25 (br d).

4-Hydroxylated NCPS (47).[21] To a solution of polymer **46** (5 g) in THF (40 mL) was added an aqueous solution of NaOH (5 mL, 5 M). The reaction was refluxed for 24 h, cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and then added dropwise, using an addition funnel, to a solution of MeOH (300 mL) and brine (3 mL). The polymer (**47**) was collected by filtration, washed with MeOH (100 mL), and dried under high vacuum to give a white solid (4.5 g, 90% polymer recovered): ^{1}H NMR ($CDCl_3$) δ 6.20–7.50 (br d), 4.48 (br s), 1.10–2.30 (br d).

Determination of polymer loading

Polymer loading is defined as the number of anchoring sites per gram of polymer and is expressed in units of mmol per gram (mmol/g). To determine this, 10 standards solutions in $CDCl_3$ (0.5 mL) were prepared with varying amounts of styrene and [{5-(4-ethylphenoxy)-2,2-dimethylpentyl}(3-bromophenyl)](difluoro)methanesulfonate (**83**). The total mass for each of the standards was 25 mg and the ratio of mmol of **83** to grams of styrene plus grams of **83** ranged from 0.1 to 1.0. Integration ratios of the averaged (–CH_2O–) peak area to the aromatic proton peak area were calculated and then plotted against the mmol of **83**/g of styrene and **83**. A linear relationship was obtained. Mitsonobu reactions between polymer **47** and varying quantities of compound **42**, TMAD and $P(Bu)_3$ were performed. The polymer loading was determined by calculating the integration ratio of the CH_2O(average)/Ar–H polymer protons and then using the equation of the line from the above standard curve. The polymer loading was determined to be approximately 0.50–0.55 mmol/g. A detailed description of the coupling of **42** to polymer **47** is given below.

Coupling of 42 to polymer 47 (48). To a solution of **47** (12.3 g, 6.2 mmol, 1 equiv) in an anhydrous mixture of 1:1 CH_2Cl_2/THF (50 mL) was added TMAD (4.3 g, 24.8 mmol, 4 equiv). The reaction was stirred until TMAD was completely dissolved. A solution of **42** (10.0 g, 24.8 mmol, 4 equiv) in an anhydrous mixture of 1:1 CH_2Cl_2/THF (25 mL) was then added, followed by tributylphosphine (5.0 g, 24.8 mmol, 4 equiv) added dropwise over a period of 5 min. The reaction was stirred at room temperature overnight, diluted with CH_2Cl_2 (35 mL), and then added dropwise, using an addition funnel, to a solution of MeOH (650 mL) and brine (7 mL). The resulting polymer (**48**) was stirred for 3 h, collected by filtration, washed with MeOH (250 mL), and dried under high vacuum to give a white solid (11.8 g, 96% polymer recovery). ^{1}H NMR ($CDCl_3$) δ 7.84 (br s), 7.66 (br t), 7.34 (br t), 6.20–7.22 (br d), 4.21 (br s), 3.84 (br s), 1.10–2.30 (br d), 1.02 (br s); ^{19}F NMR ($CDCl_3$) δ −24.18.

General method for Suzuki cross coupling on polymer 48 (general structure 49)

Polymer **48** (0.500 g, 0.27 mmol, 1 equiv), arylboronic acid (0.81 mmol, 3 equiv), K_2CO_3 (0.112 g, 0.81 mmol, 3 equiv), and $(PhCN)_2PdCl_2$ (0.021 g, 0.054 mmol, 0.2 equiv) were placed in a round bottom flask, flushed with nitrogen. Deoxygenated DMF (3 mL) was added followed by the addition of water (0.049 mL, 2.7 mmol, 10 equiv). The reaction mixture was stirred at room temperature and monitored by ^{19}F NMR. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and centrifuged twice to remove the palladium catalyst. The supernatants were combined and concentrated by rotary evaporation. The resulting polymer (general structure **49**) was redissolved in CH_2Cl_2 (3 mL), precipitated in a mixture of MeOH (25 mL) and a few drops of brine, collected by filtration, and washed with MeOH. Percent recovery of polymer ranged from 90–95%. Only a single polymer-bound species was evident by ^{19}F NMR.

General method for cleaving the biaryl products from the polymer

The polymer-bound biaryl derivatives (general structure **49**, 1 equiv) and K_2CO_3 (3 equiv) were placed in a 50-mL test tube, equipped with a stir bar and stopper, and dissolved in DMF (3 mL). Water (10 equiv) was then added to the reaction mixture and heated at 80 °C for 17 h. The reaction was diluted with CH_2Cl_2 (3 mL) and the polymer was precipitated out in a mixture of MeOH (25 mL) and a few drops of brine. The polymer was separated from the product by filtration, and the filtrate was concentrated by rotary evaporation. To remove trace amounts of polymer the following wash procedure was performed. The crude reaction product was dissolved in an aqueous solution of NaOH (10 mL, 1.0 N) and washed with CH_2Cl_2 (3×10 mL). The aqueous layer was acidified to pH ~0.5 with HCl (10 N). NaCl was added until a saturated solution was obtained. The sulfonic acids were then extracted with EtOAc (3×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, diluted with toluene (50 mL), and concentrated on a high vacuum rotary evaporator. The sulfonic acids were then dissolved in water (3 mL) and treated with NH_4HCO_3 (2.5 equiv). The solutions were lyophilized and this procedure was repeated until a constant weight was obtained. The biaryl sulfonates were obtained as off-white solids and analyzed by ^1H and ^{19}F NMR, LRESMS, HRESMS and analytical reverse-phase HPLC (for yields and purities, see Table 4). All HPLC analyses were performed using the following gradient (solvent A: acetonitrile; solvent B: water with 0.1% TFA): 0–30 min: 77% A, 23% B; 30–35 min: linear gradient of 77% A to 100% A; 35–45 min: 100% A.

[3 - (4′ - Biphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (50). ^1H NMR (CD_3OD) δ 7.98 (1H, s), 7.65–7.82 (8H, br m), 7.33–7.57 (4H, br m); ^{19}F NMR (D_2O) δ −24.41. LR-ESMS *m*/*z* (relative intensity) 359 (100). HR-ESMS calcd for $C_{19}H_{13}F_2S_1O_3$ 359.0554, found 359.0559. HPLC retention time = 22.1 min.

[3 - (2′ - Naphthyl)phenyl]difluoromethanesulfonic acid, ammonium salt (51). ^1H NMR (D_2O) δ 7.62–7.75 (5H, m), 7.22–7.49 (6H, br m); ^{19}F NMR (D_2O) δ −25.04. LR-ESMS *m*/*z* (relative intensity) 333 (100). HR-ESMS calcd for $C_{17}H_{11}F_2S_1O_3$ 333.0397, found 333.0402. HPLC retention time = 18.4 min.

[3-(4′-Acetylphenyl)phenyl](difluoro)methylsulfonic acid, ammonium salt (52). ^1H NMR (D_2O) δ 7.75–7.79 (3H, m), 7.64 (1H, d, *J* = 7.5 Hz), 7.57 (1H, d, *J* = 7.5), 7.44–7.49 (3H, m), 2.50 (3H, s); ^{19}F NMR (D_2O) δ −24.94. LR-ESMS *m*/*z* (relative intensity) 325 (100). HR-ESMS calcd for $C_{15}H_{11}F_2S_1O_4$ 325.0346, found 325.0352. HPLC retention time = 11.9 min.

[3 - (4′ - Trifluoromethylphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (53). ^1H NMR (D_2O) δ 7.92 (1H, s), 7.69–7.80 (6H, m), 7.58 (1H, t, *J* = 7.8 Hz); ^{19}F NMR (D_2O) δ 16.21, −25.08. LR-ESMS *m*/*z* (relative intensity) 351 (100). HR-ESMS calcd for $C_{14}H_8F_5S_1O_3$ 351.0114, found 351.0120. HPLC retention time = 16.0 min.

[3 - (4′ - Ethylphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (54). ^1H NMR (D_2O) δ 7.85 (1H, s), 7.61 (2H, d, *J* = 8.0 Hz), 7.41–7.49 (3H, m), 7.16 (2H, d, *J* = 8.2 Hz), 2.49 (2H, q, *J* = 7.67 Hz), 1.06 (3H, t, *J* = 6.7 Hz); ^{19}F NMR (D_2O) δ −24.90. LR-ESMS *m*/*z* (relative intensity) 311 (100). HR-ESMS calcd for $C_{15}H_{13}F_2S_1O_3$ 311.0554, found 311.0559. HPLC retention time = 18.2 min.

[3-(3′-Fluorophenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (55). ^1H NMR (D_2O) δ 7.82 (1H, s), 7.83 (1H, d, *J* = 7.0 Hz), 7.40–7.71 (5H, br m), 7.10–7.19 (1H, m); ^{19}F NMR (D_2O) δ −25.25, −35.23. LR-ESMS *m*/*z* (relative intensity) 301 (100). HR-ESMS calcd for $C_{13}H_8F_3S_1O_3$ 301.0146, found 301.0152. HPLC retention time = 13.7 min.

[3-(4′-Fluorophenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (56). ^1H NMR (D_2O) δ 7.88 (1H, s), 7.78 (1H, d, *J* = 7.4 Hz), 7.53–7.69 (4H, br m), 7.20 (2H, t, *J* = 8.92 Hz); ^{19}F NMR (D_2O) δ −25.18, −37.15. LR-ESMS *m*/*z* (relative intensity) 301 (100). HR-ESMS calcd for $C_{13}H_8F_3S_1O_3$ 301.0146, found 301.0152. HPLC retention time = 13.8 min.

[3 - (3′ - Chloro - 4′ - fluorophenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (57). ^1H NMR (D_2O) δ 7.79 (1H, s), 7.43–7.66 (5H, br m), 7.22 (1H, t, *J* = 8.9 Hz); ^{19}F NMR (D_2O) δ −25.15, −40.14. LR-ESMS *m*/*z* (relative intensity) 335 (100). HR-ESMS calcd for $C_{13}H_7F_3Cl_1S_1O_3$ 334.9757, found 334.9762. HPLC retention time = 16.7 min.

[3-(4′-Methylphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (58). ^1H NMR (D_2O) δ 7.91 (1H, s), 7.80 (1H, d, *J* = 7.6 Hz), 7.56–7.68 (4H, br m), 7.33 (2H, d, *J* = 7.9 Hz), 2.36 (3H, s); ^{19}F NMR (D_2O) δ −25.02. LR-ESMS *m*/*z* (relative intensity) 297 (100). HR-ESMS calcd for $C_{14}H_{11}F_2S_1O_3$ 297.0397, found 297.0402. HPLC retention time = 16.0 min.

[3 - (4α - Chlorophenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (59). ^1H NMR (D_2O) δ 7.83 (1H, s), 7.64 (2H, d, *J* = 7.0 Hz), 7.47–7.54 (3H, m), 7.36 (2H, d, *J* = 8.3 Hz); ^{19}F NMR (D_2O) δ −25.03. LR-ESMS *m*/*z* (relative intensity) 317 (100). HR-ESMS calcd for $C_{13}H_8F_2Cl_1S_1O_3$ 316.9851, found 316.9856. HPLC retention time = 16.8 min.

[3 - (4′ - *tert* - Butylphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (60). ^1H NMR (D_2O) δ 7.79 (1H, s), 7.59 (1H, d, *J* = 5.6 Hz), 7.08–7.34 (6H, br m), 0.95 (9H, s); ^{19}F NMR (D_2O) δ −24.52. LR-ESMS *m*/*z* (relative intensity) 339 (100). HR-ESMS calcd for $C_{17}H_{17}F_2S_1O_3$ 339.0867, found 339.0872. HPLC retention time = 22.3 min.

[3 - (3′ - Trifluoromethylphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (61). ^1H NMR (D_2O) δ 7.93 (2H, d, *J* = 6.4 Hz), 7.82 (2H, t, *J* = 7.5 Hz), 7.55–

7.70 (4H, br m); ^{19}F NMR (D_2O) δ 16.10, −25.20. LR-ESMS *m*/*z* (relative intensity) 351 (100). HR-ESMS calcd for $C_{14}H_8F_5S_1O_3$ 351.0114, found 351.0120. HPLC retention time = 15.5 min.

[3-(2′-Methylphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (62). ^{1}H NMR (D_2O) δ 7.53–7.71 (4H, br m), 7.29–7.39 (4H, br m), 2.23 (3H, s); ^{19}F NMR (D_2O) δ −25.08. LR-ESMS *m*/*z* (relative intensity) 297 (100). HR-ESMS calcd for $C_{14}H_{11}F_2S_1O_3$ 297.0397, found 297.0402. HPLC retention time = 15.2 min.

[3-(3′-Chlorophenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (63). ^{1}H NMR (D_2O) δ 7.89 (1H, d, *J* = 7.7 Hz), 7.68 (2H, d, *J* = 8.0 Hz), 7.55–7.62 (2H, m), 7.40–7.43 (2H, m); ^{19}F NMR (D_2O) δ −25.23. LR-ESMS *m*/*z* (relative intensity) 317 (100). HR-ESMS calcd for $C_{13}H_8F_2Cl_1S_1O_3$ 316.9851, found 316.9856. HPLC retention time = 16.7 min.

[3 - (1′ - Naphthyl)phenyl]difluoromethanesulfonic acid, ammonium salt (64). ^{1}H NMR (D_2O) δ 7.88 (1H, s), 7.62 (2H, d, *J* = 10.3 Hz), 7.18–7.54 (8H, br m); ^{19}F NMR (D_2O) δ −24.73. LR-ESMS *m*/*z* (relative intensity) 333 (100). HR-ESMS calcd for $C_{17}H_{11}F_2S_1O_3$ 333.0397, found 333.0402. HPLC retention time = 18.9 min.

[3 - (3′,5′ - Dichlorophenyl)phenyl]difluoromethanesulfonic acid (65). Although HR-ESMS, ^{19}F and ^{1}H NMR indicated that **65** was obtained, ESMS revealed that a significant quantity (∼9%) of compound **74** was also present. This compound was not evident by ^{19}F NMR and HPLC analysis which indicated that **65** was obtained in 96–98% purity. This compound was resynthesized in solution. For complete characterization data, see below description of compound **65** synthesized using solution-phase methodologies.

[3 - (3′,4′ - Dichlorophenyl)phenyl]difluoromethylsulfonic acid, ammonium (66). ^{1}H NMR (D_2O) δ 7.85 (1H, s), 7.67–7.75 (3H, m), 7.45–7.59 (3H, m); ^{19}F NMR (D_2O) δ −25.10. LR-ESMS *m*/*z* (relative intensity) 351 (100). HR-ESMS calcd for $C_{13}H_7F_2Cl_2S_1O_3$ 350.9461, found 350.9466. HPLC retention time = 21.0 min.

[3 - (4′ - Methoxyphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (67). ^{1}H NMR (D_2O) δ 7.80 (1H, s), 7.60 (2H, t, *J* = 7.0 Hz), 7.43–7.50 (3H, m), 6.93 (2H, d, *J* = 8.7 Hz), 3.75 (3H, s); ^{19}F NMR (D_2O) δ −24.98. LR-ESMS *m*/*z* (relative intensity) 313 (100). HR-ESMS calcd for $C_{14}H_{11}F_2S_1O_4$ 313.0346, found 313.0352. HPLC retention time = 13.8 min.

[3 - (2′ - Thiophene)phenyl]difluoromethanesulfonic acid, ammonium salt (68). ^{1}H NMR (D_2O) δ 7.94 (1H, s), 7.84 (1H, d, *J* = 7.0 Hz), 7.45–7.63 (4H, br m), 7.15 (1H, t, *J* = 4.4 Hz); ^{19}F NMR (D_2O) δ −25.30. LR-ESMS *m*/*z* (relative intensity) 289 (100). HR-ESMS calcd for $C_{11}H_7F_2S_2O_3$ 288.9805, found 288.9810. HPLC retention time = 13.4 min.

[3 - (3′ - Thiophene)phenyl]difluoromethanesulfonic acid, ammonium salt (69). ^{1}H NMR (D_2O) δ 7.95 (1H, s), 7.84 (1H, d, *J* = 7.84 Hz), 7.71–7.73 (1H, m), 7.50–7.63 (4H, br m); ^{19}F NMR (D_2O) δ −25.11. LR-ESMS *m*/*z* (relative intensity) 289 (100). HR-ESMS calcd for $C_{11}H_7F_2S_2O_3$ 288.9805, found 288.9810. HPLC retention time = 12.8 min.

[3 - (2′ - Furanphenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (70). ^{1}H NMR (D_2O) δ 8.02 (1H, s, Ar-H), 7.93 (1H, d, *J* = 6.6 Hz, Ar–H), 7.56–7.64 (3H, m, Ar–H), 6.93 (1H, d, *J* = 3.6 Hz, Ar–H), 6.62 (1H, s, Ar–H); ^{19}F NMR (D_2O) δ −25.38. LR-ESMS *m*/*z* (relative intensity) 273 (100). HR-ESMS calcd for $C_{11}H_7F_2S_1O_4$ 273.0033, found 273.0039. HPLC retention time = 12.1 min.

[3-(5′-Acetyl-2′-thiophene)phenyl]difluoromethanesulfonic acid, ammonium salt (71). Although HRESMS, ^{19}F and ^{1}H NMR indicated that **71** was obtained, HPLC analysis indicated that it was only 77% pure. ^{19}F NMR analysis indicated 90% purity. This compound was resynthesized in solution (see below). For complete characterization data, see below the description of compound **71** synthesized using solution-phase methodologies.

[3-(2′-Benzo[*b*]thiophene)phenyl] difluoromethanesulfonic acid, ammonium salt (72). ^{1}H NMR (D_2O) δ 7.78 (1H, s), 7.50 (1H, d, *J* = 7.3 Hz), 7.37 (1H, d, *J* = 6.9 Hz), 7.29 (2H, m), 7.17 (1H, t, *J* = 7.7 Hz), 7.08 (1H, s), 6.94–7.03 (2H, m); ^{19}F NMR (D_2O) δ −24.91. LR-ESMS *m*/*z* (relative intensity) 339 (100). HR-ESMS calcd for $C_{15}H_9F_2S_2O_3$ 338.9961, found 338.9967. HPLC retention time = 21.3 min.

[3-(2′-Benzo[*b*]furan)phenyl]difluoromethanesulfonic acid, ammonium salt (73). ^{1}H NMR (D_2O) δ 7.87 (1H, s), 7.43–7.53 (2H, m), 7.09–7.27 (3H, br m), 6.88–7.00 (2H, br m), 6.55 (1H, s); ^{19}F NMR (D_2O) δ -25.06. LR-ESMS *m*/*z* (relative intensity) 323 (100). HR-ESMS calcd for $C_{15}H_9F_2S_1O_4$ 323.0190, found 323.0195. HPLC retention time = 17.0 min.

Synthesis of 65 and 71 using solution-phase methodologies

3,5-Dichloro-3′-methyl-1,1′-biphenyl (75). To a solution of $Pd(PPh_3)_4$ (0.875 g, 0.75 mmol, 0.03 equiv) in DME (100 mL) under nitrogen was added 3-bromotoluene (3.0 mL, 25 mmol, 1 equiv) and the resulting solution was stirred for 20 min. An aqueous solution of sodium carbonate (2.78 g, 26 mmol, 1.05 equiv, 75 mL) was added followed by the addition of a solution of 3,5-dichlorobenzeneboronic acid (5.0 g, 25 mmol, 1 equiv) in DME (75 mL). The mixture was refluxed 3 h. After cooling to room temperature, the organic layer was washed with 5% sodium bicarbonate (3×350 mL) and once with brine. The organic layer was dried, filtered and concentrated. Silica gel column chromatography in 100% hexanes gave pure **75** as white solid in 84% yield: mp 43–45 °C. ^{1}H NMR ($CDCl_3$) 7.2–7.45 (7H, m), 2.41 (3H, s). LR-EIMS *m*/*z* (relative intensity) 236 (100), 292

(3). HR-EIMS calcd for $C_{10}H_{13}Cl_2$ 236.0160, found 400.0156.

3-(3,5-Dichlorophenyl)phenylmethanesulfonic acid, sodium salt (76). To a solution of AIBN (16 mg, 0.1 mmol, 0.02 equiv) and *N*-bromosuccinimide (0.98 g, 5.5 mmol, 1.1 equiv) in benzene (25 mL) was added **75** (1.19 g, 5 mmol, 1 equiv) and the solution refluxed for 1 h. The reaction was cooled to room temperature, the mixture was washed with water (3×25 mL), and the organic layer was dried ($MgSO_4$) and concentrated. Column chromatography in 100% hexanes yielded a white solid which was a mixture of mono and dibrominated product as determined by ^{1}H NMR. No attempt was made to separate these two compounds. To a solution of the crude material (1.85 g, approx 5.85 mmol) in acetone (15 mL) was added an aqueous solution of sodium sulfite (0.77 g, 6.11 mmol, 10 mL) and the mixture was refluxed for 12 h. After cooling to room temperature, the solution was concentrated in vacuo and filtered. The filter cake was washed with water (5 mL×2) and CH_2Cl_2 (20 mL×2) and dried under high vacuum overnight to give pure **76** as white solid in 66% yield. ^{1}H NMR (D_2O) δ 4.08 (s, 2H), 7.45–7.24 (m, 7H); ^{13}C NMR (D_2O) δ 56.78, 125.42, 126.46, 127.04, 128.85, 129.26, 130.35, 132.54, 134.75, 138.26, 143.13. LR-ESMS *m*/*z* 315 (100).

3-(3,5-Dichlorophenyl)phenylmethanesulfonyl chloride (77). To a suspension of **76** (1.00 g, 2.95 mmol) in acetonitrile (10 mL) under nitrogen was added freshly distilled $POCl_3$ (1.37 mL, 14.75 mmol). After refluxing for 10 h, the reaction was cooled to room temperature and diluted with ether (30 mL), and then poured into a mixture of ether (70 mL) and ice (~30 g). The ether layer was washed with cold water (2×20 mL) and brine (20 mL), and dried over $MgSO_4$ and concentrated to give **77** as an off-white solid 77% yield: mp 79–80 °C. ^{1}H NMR ($CDCl_3$) δ 4.91 (s, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.43 (d, J = 7.4 Hz, 2H), 7.45 (m, 2H), 7.62 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 70.67, 125.81, 127.17, 127.90, 129.05, 130.03, 130.09, 131.34, 135.59, 139.79, 142.89; LR-EIMS *m*/*z* (relative intensity) 334 (32), 336 (33), 235 (55), 165 (30). HR-EIMS calcd for $C_{13}H_9SO_2Cl_3$ 333.9389, found 333.9401.

Neopentyl 3-(3,5-dichlorophenyl)phenylmethanesulfonate (78). To a solution of **77** (0.70 g, 2.09 mmol) in dry THF (10 mL) under nitrogen was added neopentyl alcohol (0.37 g, 4.2 mmol). The solution was cooled to 0 °C, and 2,6-lutidine (0.5 mL, 4.2 mmol) was added. The mixture was warmed to room temperature and stirred overnight. The reaction was diluted with ether (60 mL), washed with 0.1 N HCl and water, dried ($MgSO_4$) and concentrated to give a white solid. Flash chromatography (5:1, hexane/EtOAc) of the crude mixture yield pure **78** as white solid in 72% yield: mp 69–70 °C. ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9H), 3.81 (s, 2H), 4.41 (s, 2H), 7.36 (t, J = 1.5 Hz, 1H), 7.42–7.56 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 25.94, 31.77, 56.26, 79.42, 125.61, 127.51, 127.62, 128.93, 129.32, 129.53, 130.62, 135.36, 139.19, 143.17. LR-EIMS *m*/*z* (relative intensity) 387 (5), 386 (22), 388 (17), 235 (100), 165 (37). HR-EIMS calcd for $C_{18}H_{20}SO_3Cl_2$ 386.0510, found 386.0519.

Neopentyl-[3-(3,5-dichlorophenyl)phenyl]difluoromethanesulfonate (79). To a solution of **78** (0.200 g, 0.52 mmol) and NFSi (0.487 g, 1.56 mmol) in dry THF (12 mL) at −78 °C under nitrogen was added a 1 M solution of NaHMDS in THF (1 M, 1.3 mL, 1.3 mmol) dropwise over a period of 1 h. The solution was then maintained at −78 °C for another 2 h, an then allowed to warm to room temperature. After stirring at room temperature for 1 h, the reaction was quenched with saturated NH_4Cl, extracted with ether (3×30 mL), washed with water (2×30 mL), dried ($MgSO_4$) and concentrated to give a white solid. Flash chromatography of the crude (5:1Hexane/EtOAc) gave pure **79** as white solid in 87% yield: mp 72–73 °C. ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9H), 4.15 (s, 2H), 7.37 (t, J = 2.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.72(m, 2H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.82, 32.30, 84.65, 120.58 (t, J = 284.2 Hz), 125.56 (t, J = 5.8 Hz) 127.03 (t, J = 5.8 Hz), 128.04, 128.99 (t, J = 22.0 Hz), 129.57, 131.06, 135.63, 139.36, 142.55; ^{19}F NMR ($CDCl_3$) δ −24.53. LR-EIMS *m*/*z* (relative intensity) 423 (2), 422 (5), 271 (100). HR-EIMS calcd for $C_{18}H_{18}SO_3Cl_2F_2$ 422.0322, found 422.0325.

[3 - (3,5 - Dichlorophenyl)phenyl]difluoromethanesulfonic acid, ammonium salt (65). To a solution of **79** (0.15 g, 0.355 mmol) in DMF (5 mL) was added K_2CO_3 (0.147 g, 1.06 mmol) and water (0.1 mL) and the mixture was heated to 80 °C for 17 h. The mixture was allowed to cool to room temperature and then concentrated by high vacuum rotary evaporation. The residue was dissolved in water (15 mL), acidified to pH 0.5 with 3 N HCl saturated with NaCl, extracted with ethyl acetate (5×30 mL), the organic were dried ($MgSO_4$), and then concentrated to give an off-white solid. The solid was dissolved in an aqueous solution of NH_4HCO_3 (4 mL of 0.25 N) and lyophilized. This process was repeated until a constant weight was obtained. This gave pure **65** as a white solid in 99% yield: dec. 165 °C. ^{1}H NMR (D_2O) δ 6.75 (s, 1H), 6.89 (m, 3H), 7.02 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H); ^{13}C NMR (D_2O) δ 122.55 (t, J = 277.4 Hz), 127.44 (t, J = 6.7 Hz), 127.83, 129.20 (t, J = 6.7 Hz), 129.89, 131.74, 132.17, 133.68 (t, J = 23.8 Hz),137.40, 140.56, 144.72; ^{19}F NMR (D_2O) δ −27.57. LR-ESMS *m*/*z* (relative intensity) 351 (100). HR-ESMS calcd for $C_{13}H_7F_2Cl_2S_1O_3$ 350.9461, found 350.9466. HPLC retention time = 22.1 min.

Neopentyl 3-bromophenylmethanesulfonate (80). Prepared in 70% yield from **43** using the same procedure as that used for preparing **78** from **77**. Pure product was obtained by recrystallization in hexane/EtOAc (white crystals): mp 87–88 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 9H), 3.74 (s, 2H), 4.29 (s, 2H), 7.26 (t, J = 7.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.91, 31.78, 55.76, 79.60, 122.65, 129.27, 130.07, 130.32, 132.12, 133.59. LR-EIMS *m*/*z* (relative intensity) 321 (3), 320 (18), 320 (18),169 (100), 171 (100). HR-EIMS calcd for $C_{12}H_{17}SO_3Br$, 320.0081, found 320.0095.

Neopentyl (3-bromophenyl)difluoromethanesulfonate (81). Prepared in 87% yield from **80** using the same procedure as that used for preparing **79** from **78** (colorless oil). ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9H), 4.11 (s, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.91, 32.23, 84.81, 122.83 (t, J = 283.5 Hz), 123.90, 125.93 (t, J = 6.1 Hz), 130.05 (t, J = 22.7 Hz), 130.22 (t, J = 6.7 Hz), 130.39, 135.70; ^{19}F NMR ($CDCl_3$) δ −24.74. LR-EIMS m/z (relative intensity) 357 (1), 356 (3), 358 (18), 207 (93), 205 (100). HR-EIMS calcd for $C_{12}H_{15}SO_3BrF_2$, 355.9893, found 355.9895.

Neopentyl-3-(5-acetyl-2-thienyl)methanesulfonate (82). To a solution of **81** (0.476 g, 1.33 mmol) in deoxygenated DMF (20 mL), was added 5-acetyl-2-thienylboronic acid (0.339 g, 1.99 mmol), K_2CO_3 (0.55 g, 4 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol) and H_2O (0.27 mL, 15 mmol). The reaction was stirred at room temperature under nitrogen for 2 h. The reaction was diluted with ether, washed with saturated NH_4Cl, water and brine, dried ($MgSO_4$) and concentrated to give a light-yellow solid. Flash chromatography of the crude product (5:1 hexane/EtOAc) gave pure **82** in 87% yield (white solid): mp 88–89 °C. ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9H), 2.56 (s, 3H), 4.13 (s, 2H), 7.36 (d, J = 3.9 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.65 (m, 2H), 7.82 (d, J = 7.9 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.911, 26.67, 32.22, 84.77, 120.73 (t, J = 283.9 Hz), 124.72 (t, J = 6.0 Hz), 125.11, 127.37 (t, J = 5.5 Hz), 129.16 (t, J = 22.2 Hz), 129.76, 130.14, 133.46, 134.22, 144.23, 150.32, 190.59; ^{19}F NMR ($CDCl_3$) δ −24.74. EIMS m/z 402 (30), 332 (29), 251 (100). HREIMS calcd for $C_{18}H_{20}SO_4F_2$, 402.0771, found 402.0785.

3-(5-Acetyl-2-thienyl)difluoromethanesulfonic acid, ammonium salt (71). Prepared in 98% yield from **82** using the same procedure as that used for preparing **65** from **79** (white solid): dec. at 122 °C. ^{1}H NMR (D_2O) δ 2.21 (s, 3H), 6.97 (d, J = 4.0 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.32 (m, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H); ^{13}C NMR (D_2O) δ 25.54, 119.73 (t, J = 277.2 Hz), 123.66 (t, J = 6.5 Hz), 125.36, 127.06 (t, J = 5.9 Hz), 128.55, 129.23, 131.00 (t, J = 23.3 Hz), 132.47, 136.54, 141.53, 151.86, 195.19; ^{19}F NMR (D_2O) δ −28.27. LR-ESMS m/z (relative intensity) 331 (100). HR-ESMS calcd for $C_{13}H_9F_2S_2O_4$ 330.9910, found 330.9916. HPLC retention time = 11.8 min.

[{5-(4-Ethylphenoxy)-2,2-dimethylpentyl}(3-bromophenyl)]difluoromethane-sulfonate (83). To a solution of 4-ethylphenol (0.101 g, 0.83 mmol, 1 equiv) in 1:1 anhyd THF/CH_2Cl_2 (45 mL) was added TMAD (0.287 g, 1.66 mmol, 2 equiv). Once the TMAD was completely dissolved, a solution of **42** (0.665 g, 1.66 mmol, 2 equiv) in 1:1 anhyd THF/CH_2Cl_2 (25 mL) was added. Tributylphosphine (0.427 mL, 0.35 g, 1.66 mmol, 2 equiv) was then added dropwise to the reaction mixture over a period of 5 min. The reaction was stirred at room temperature for 3 h and then concentrated by rotary evaporation. Column chromatography (1:1, CH_2Cl_2/hexane) of the crude residue yielded pure **83** as a white solid in 96% yield: mp 36–37 °C. ^{1}H NMR ($CDCl_3$) δ 7.84 (1H, s, Ar–H), 7.72 (1H, d, J = 8.0 Hz, Ar–H), 7.64 (1H, d, J = 7.3 Hz, Ar-H), 7.39 (1H, t, J = 8.1 Hz, Ar–H), 7.11 (2H, d, J = 8.0 Hz, Ar–H), 6.82 (2H, d, J = 8.8 Hz, Ar–H), 4.19 (2H, s, CH_2O), 3.93 (2H, t, J = 6.2 Hz, CH_2), 2.59 (2H, q, J = 7.6 Hz, CH_2), 1.73–1.85 (2H, m, CH_2), 1.44–1.54 (2H, m, CH_2), 1.21 (3H, t, J = 7.7 Hz, CH_3), 1.03 (6H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ −24.19; ^{13}C NMR ($CDCl_3$) δ 157.18, 136.53, 135.62 (t, J_{CF} = 1.8 Hz), 130.28, 130.21 (t, J_{CF} = 6.4 Hz), 128.70, 125.86 (t, J_{CF} = 6.0 Hz), 122.81, 120.15, 114.65, 82.99, 63.38, 34.85, 34.52, 28.00, 23.95, 23.64, 15.72. MS m/z (relative intensity) 504 (28), 205 (59), 122 (100), 107 (65), 97 (29), 83 (25), 55 (52). HRMS calcd for $C_{22}H_{27}O_4F_2S_1Br_1$ 504.0782, found 504.0774.

Kinetic studies with PTP1B

Rates of PTP1B-catalyzed dephosphorylation in the presence or absence of inhibitors were determined using fluorescein diphosphate (FDP at K_m concentration −20 μM) as substrate in assay buffer containing 50 mM Bis-Tris (pH 6.5), 2 mM EDTA, 5 mM *N*,*N*′-dimethyl-*N*,*N*′-bis(mercaptoacetyl)hydrazine (DMH) or dithiothreitol (DTT), 0.01% triton X-100 and 5% DMSO. For peptides **7**–**9** and compounds **50**–**73**, assays were carried out at 25 °C in 96-well plates with total volume of 200 μL per well. Reactions were initiated by the addition of PTP1B (final concentration 0.2 μg/mL). The phosphatase activity was followed by monitoring the production of the fluorescent product fluorescein monophosphate (FMP) continuously for 10 min using the Cytofluor II plate reader (PerSeptive Biosystems), with excitation at 440 nm (slit width 20 nm) and emission 530 nm (slit width 25 nm), or the SPECTRAmax GEMINI XS (Molecular Devices) dual-scanning microplate spectrofluorometer, with excitation at 485 nm and emission at 538 nm. For compounds **28**–**40**, assays were carried out in 1 mL cuvettes with total volumes of 700 μL. The phosphatase activity was followed by monitoring the production of FMP at 450 nm using a Varian Cary 1 spectrophotometer. IC_{50}'s were determined using at least nine different inhibitor concentrations. For K_i determinations (peptides **7**–**9**), substrate concentrations of 15, 20, 25, 35, and 50 μM were used. 1/v versus 1/[S] plots were obtained which exhibited competitive inhibition patterns for all three peptides. The slopes of these plots were determined using Microsoft Excel. These slopes were replotted against the concentration of the inhibitor using Microsoft Excel and the K_i was obtained from the x-intercept of this replot.

Acknowledgements

We thank Sunia Afzaal, Gary Kruppa and Paul Speir at BrukerDaltonics for obtaining the high-resolution FTICR-ES mass spectra.

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