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PAPER

Efficacious *N*-protection of *O*-aryl sulfamates with 2,4-dimethoxybenzyl groups†

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Sulfamates are important functional groups in certain areas of current medicinal chemistry and drug development. Alcohols and phenols are generally converted into the corresponding primary sulfamates ($ROSO_2NH_2$ and $ArOSO_2NH_2$, respectively) by reaction with sulfamoyl chloride (H_2NSO_2Cl). The lability of the *O*-sulfamate group, especially to basic conditions, usually restricts this method to a later stage of a synthesis. To enable a more flexible approach to the synthesis of phenolic *O*-sulfamates, a protecting group strategy for sulfamates has been developed. Both sulfamate NH protons were replaced with either 4-methoxybenzyl or 2,4-dimethoxybenzyl. These *N*-protected sulfamates were stable to oxidising and reducing agents, as well as bases and nucleophiles, thus rendering such masked sulfamates suitable for multi-step synthesis. The protected sulfamates were synthesised by microwave heating of 1,1′-sulfonylbis(2-methyl-1*H*-imidazole) with a substituted phenol to give an aryl 2-methyl-1*H*-imidazole-1-sulfonate. This imidazole-sulfonate was *N*-methylated by reaction with trimethyloxonium tetrafluoroborate, which enabled subsequent displacement of 1,2-dimethylimidazole by a dibenzylamine (*e.g.* bis-2,4-dimethoxybenzylamine). The resulting *N*-diprotected, ring-substituted phenol *O*-sulfamates were further manipulated through reactions at the aryl substituent and finally deprotected with trifluoroacetic acid to afford a phenol *O*-sulfamate. The use of 2,4-dimethoxybenzyl was particularly attractive because deprotection occurred quantitatively within 2 h at room temperature with 10% trifluoroacetic acid in dichloromethane. The four key steps in the protocol described [reaction of 1,1′-sulfonylbis(2-methyl-1*H*-imidazole) with a phenol, methylation, displacement with a dibenzylamine and deprotection] all proceeded in very high yields.

Introduction

The success of the *O*-sulfamate topiramate as a treatment for epilepsy and migraine[1] and the discovery of *O*-sulfamates that inhibit steroid sulfatase[2] and carbonic anhydrase,[3] has encouraged the search for new therapeutically useful derivatives of sulfamic acid (NH_2SO_3H). The conversion of alcohols (ROH) and phenols (ArOH) into the corresponding sulfamates ($ROSO_2NH_2$ and $ArOSO_2NH_2$, respectively) is generally performed by direct reaction with sulfamoyl chloride (H_2NSO_2Cl), which is prepared from chlorosulfonyl isocyanate and formic acid.[4] This method is best implemented at a late stage of a synthesis owing to the inherent lability of *O*-sulfamates, particularly under basic conditions, which facilitates decomposition by an E1Cb mechanism. Furthermore, in common with *O*-sulfates the polarity of sulfamate groups ($-OSO_2NH_2$) can compromise their passage through several steps of a synthesis. In a drug discovery program for which phenol *O*-sulfamates were targets we needed a strategy for the protection of the amido (NH_2) group of such sulfamates. The aim was to render these sulfamates stable to bases and nucleophiles, thus able to survive a multi-step synthesis before release of the free phenol *O*-sulfamate at the final stage.

Results and discussion

The sensitivity of primary sulfamates to basic conditions was apparent when attempts to perform Suzuki cross-couplings on phenol *O*-sulfamates without protection of the amido group led to low product yields, giving predominantly a mixture of desulfamoylated product and starting material (Scheme 1). A variety of conditions was explored in which the base component was varied. The best results were obtained with weak bases such as sodium carbonate with 1,1′-bis(diphenylphosphino)ferrocene–palladium(II)dichloride [$Pd(dppf)Cl_2$] as catalyst. However, despite extensive optimisation efforts, the highest product yield was around 20%. The instability of primary phenol *O*-sulfamates

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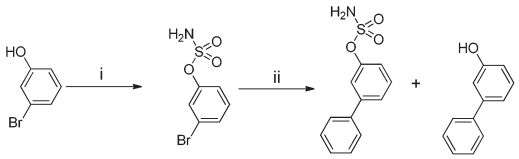
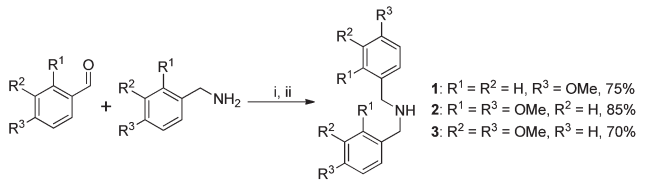


Scheme 1 Synthesis of 3-hydroxybiphenyl *O*-sulfamate [*Reagents and conditions*: i, H_2NSO_2Cl, DMA/toluene, 0 °C to room temp., 24 h, 87%; ii, $PhB(OH)_2$, 2 M aq. Na_2CO_3, $Pd(dppf)Cl_2$, DME, microwave heating (80 °C, 20 min), 22%].



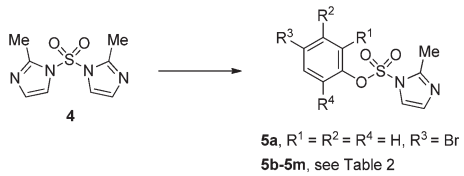
Scheme 2 Synthesis of methoxy-substituted dibenzylamines [*Reagents and conditions*: i, EtOH, heat at reflux, 4 h; ii, $NaBH_4$, room temp., 16 h].

under basic conditions is due to an E1Cb mechanism in which deprotonation of one of the sulfamate NH_2 protons precedes elimination of the phenol.[5]

Reported protecting groups for sulfamates include *N*-alkyloxycarbonyl (alkyl = *t*-butyl-,[6] benzyl-[7] or methyl-[8]) and the *N*-*t*-butyl group.[9] However, these groups all retain one proton on the sulfamate nitrogen and the sulfamate is still vulnerable to E1Cb degradation. Hence, a protecting group that masks both NH_2 protons may confer improved base stability on the sulfamate. Although the NH_2 group of sulfonamides has been protected with benzyl groups, these can be difficult to remove from nitrogen atoms.[10] The addition of electron-releasing groups to the benzyl ring enables deprotection under mild acidic conditions. Thus, benzyl (reference standard), 4-methoxybenzyl, 2,4-dimethoxybenzyl and 3,4-dimethoxybenzyl were selected for investigation as potential dual protecting groups for sulfamates. This strategy required methoxy-substituted dibenzylamines (**1**–**3**), which were readily prepared (Scheme 2).

Initially, the reaction of dibenzylamine with sulfuryl chloride in the presence of pyridine or triethylamine was investigated, but gave *N*,*N*-bis-benzylsulfamoyl chloride in poor yield. The subsequent reaction of this chloride with phenols also proceeded in disappointing yield.

1,1′-Sulfonylbis(2-methyl-1*H*-imidazole) (**4**) has been used as a sulfonyl transfer reagent for the preparation of phenyl 2-methyl-1*H*-imidazole-1-sulfonates and for the synthesis of cyclic sulfamates.[11,12] The preparation of phenyl 2-methyl-1*H*-imidazole-1-sulfonates entailed the reaction of **4** with a phenoxide in THF at room temperature. These conditions were reported to be unsuitable for poorly nucleophilic phenols such as 4-nitrophenol or 4-hydroxyacetophenone.[13] We applied this method to the preparation of 4-bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate. Thus, microwave irradiation of 4-bromophenol with 1,1′-sulfonylbis(2-methyl-1*H*-imidazole) in the presence of caesium carbonate afforded the corresponding 4-bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**5a**) in high yield (Scheme 3).

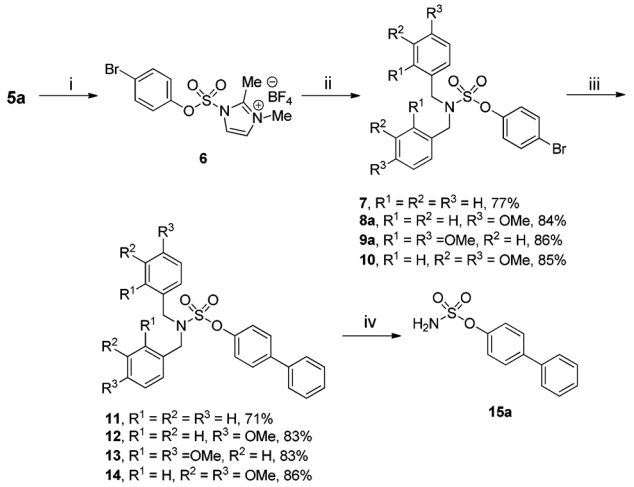


Scheme 3 Synthesis of 4-bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**5a**) [*Reagents and conditions*: substituted phenol, Cs_2CO_3, THF, microwave heating (80 °C, 30 min), 92%; for **5b**–**5m**, see Table 2].

Attempted reaction of the imidazole-sulfate **5a** with dibenzylamine under various conditions failed to displace the imidazole moiety. Activation of imidazole-sulfonates to nucleophilic attack by methylation has been utilised for the synthesis of protected sulfates of phenolic steroids (*e.g.* oestrone).[14] In the first step, an alkoxysulfonyl chloride was reacted with imidazole or 2-methylimidazole to give an alkyl imidazole-1-sulfonate. Following methylation with methyl trifluoromethanesulfonate (methyl triflate), the resulting sulfamoyl imidazolium salt acted as an electrophilic sulfonyl donor: addition of oestrone gave the corresponding protected sulfate. Owing to the extremely hazardous nature of methyl triflate, Meerwein's salt (trimethyloxonium tetrafluoroborate) was used in the present work to effect the methylation of aryl 2-methyl-1*H*-imidazole-1-sulfonates (*e.g.* **5a**) in high yield to give intermediate **6** [Scheme 4; *n.b.* attempts to methylate sulfonyl-diimidazole **4** using Meerwein's salt were unsuccessful].[15,16] Reactions of **6** with dibenzylamine or a methoxy-substituted dibenzylamine at room temperature now proceeded in high yields to give fully protected sulfamates (*e.g.* **7**, **8a**, **9a** and **10**) (Scheme 4). These compounds were subjected to Suzuki cross-coupling conditions in the presence of potassium carbonate, to afford the desired biphenyls (*e.g.* **11**, **12**, **13** and **14**), with no desulfamoylation being observed.

Deprotection of bis-benzylsulfonamides is precedented under strongly acidic conditions.[17,18] However, subjecting the bis-benzylsulfamate (**11**) to trifluoroacetic acid (48 h at room temperature) or conc. sulfuric acid (24 h at room temperature) resulted in exclusive recovery of starting material. As expected, incorporation of the methoxy functionality at the 4-, 2,4- and 3,4-positions of the benzyl groups facilitated deprotection to 4-hydroxydiphenyl *O*-sulfamate **15a** (Scheme 4, Table 1), resulting in high yields of the desired primary sulfamates under mild to moderate acidic conditions. As the conditions required for removing 3,4-dimethoxybenzyl were similar to those employed for 4-methoxybenzyl, but the reaction proceeded in much poorer yield, 3,4-dimethoxybenzyl protection was not studied further. It should be noted that 4-methoxybenzyl-protected sulfamates are stable to the acidic conditions that will remove an *N*-*t*-butyloxycarbonyl (BOC) group (see below).

To investigate the scope and limitations of this methodology, a range of phenols with diverse steric and electronic properties was progressed through the synthetic sequence. For the reaction of phenols with 1,1′-sulfonylbis(2-methyl-1*H*-imidazole), the time required for completion of the reaction for phenols with no *ortho*-substituent was found to correlate with the pK_a of the phenol: those with an electron-withdrawing substituent required extended reaction times. Sterically hindered phenols such as 2,6-dimethylphenol also required prolonged reaction times.



Scheme 4 Synthesis of 4-hydroxydiphenyl *O*-sulfamate **15a** [*Reagents and conditions*: i, $Me_3O{\cdot}BF_4$, DCM, 0 °C to room temp., 8 h, 90%; ii, Dibenzylamine (or **1**, **2** or **3**), MeCN, room temp., 16 h; iii, $PhB(OH)_2$, K_2CO_3, MeCN, microwave heating (120 °C, 20 min); iv, TFA, DCM, for time and temp. see Table 1].

Table 1 Reaction conditions for deprotection of *N*-protected 4-hydroxydiphenyl *O*-sulfamates and yields for **15a**

Compound	% TFA in DCM	*T*/°C	Time/h	Yield of **15a**/%
12	100	50	12	85
12	50	42	24	90
14	80	42	30	63
14	100	50	24	50
13	50	Room temp.	0.2	95
13	10	Room temp.	2	95
13	5	Room temp.	7	90

However, very electron poor (4-nitrophenol) and/or sterically hindered phenols (2,6-dichlorophenol), failed to yield any product.

To determine conditions of general applicability for diverse phenols, the two least reactive phenols (4-nitrophenol and 2,6-dichlorophenol) were selected for further optimisation. Four parameters were investigated: time, temperature (microwave heating), solvent and the stoichiometry of **4**. Employing THF as solvent and increasing the temperature of the reaction to 150 °C did not significantly improve conversion for these phenols. For 4-nitrophenol, the use of either DMF or acetonitrile instead of THF greatly enhanced the rate of the reaction, and after 10 min at 150 °C no starting material remained. However, a major by-product was 4,4′-oxybis(nitrobenzene), presumably resulting from S_NAr attack of the unreacted phenol on the product, with subsequent elimination of sulfamate ($NH_2SO_3^-$). The conversion was also improved for 2,6-dichlorophenol in these solvents, although unreacted 2,6-dichlorophenol was the major component after heating for 10 min.

Raising the reaction temperature to 180 °C did not improve conversion to the product. However, increasing the molar equivalents of **4** led to reduced formation of 4,4′-oxybis(nitrobenzene) and gave excellent yields of the protected phenol

Table 2 Optimised conditions for microwave heating of substituted phenols with **4**

Phenol substituent(s)	pK_a	Product	Conditions[a] (isolated yield/%)	Conditions[b] (isolated yield/%)
4-MeO	10.4	**5b**	97	n.d.
4-Br	9.7	**5a**	93	n.d.
4-Cl	9.5	**5c**	93	n.d.
3-Cl	9.3	**5d**	83	n.d.
2-Cl	7.7	**5e**	90	n.d.
2,6-Me_2	10.2	**5f**	92	n.d.
2,6-Cl_2	7.1	**5g**	0	84
4-NO_2	6.8	**5h**	0	82
3-NO_2	9.3	**5i**	72	n.d.
2-NO_2	6.9	**5j**	0	70
4-CN	7.7	**5k**	59	80
2-CN	7.0	**5l**	0	72
4-CF_3	8.5	**5m**	80	n.d.

[a] 15 min, 120 °C, 1,1′-sulfonylbis(2-methyl-1*H*-imidazole (2 equiv.). [b] 15 min, 180 °C, 1,1′-sulfonylbis(2-methyl-1*H*-imidazole (10 equiv.). n.d. = not determined.

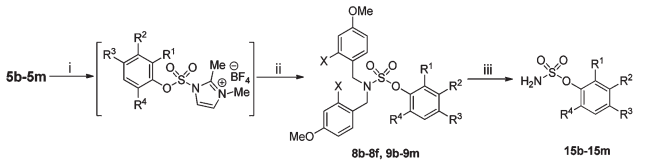
Table 3 Isolated yields for methylation/substitution with bis-4-methoxybenzylamine or bis-2,4-dimethoxybenzylamine of aryl 2-methyl-1*H*-imidazole-1-sulfamates followed by deprotection

Phenol substituent (s)	Protected phenol *O*-sulfamate (**8b–8f**, **9b–9m**)	Yield/ %	Phenol *O*-sulfamate (**15b–15m**)	Yield/ %
4-MeO	**8b** (X = H)	80	**15b**	93
4-Cl	**8c** (X = H)	81	**15c**	90
3-Cl	**8d** (X = H)	72	**15d**	86
2-Cl	**8e** (X = H)	78	**15e**	92
2,6-Me_2	**8f** (X = H)	62	**15f**	92
4-MeO	**9b** (X = OMe)	65	**15b**	90
4-Cl	**9c** (X = OMe)	63	**15c**	84
3-Cl	**9d** (X = OMe)	61	**15d**	90
2-Cl	**9e** (X = OMe)	68	**15e**	81
2,6-Me_2	**9f** (X = OMe)	61	**15f**	90
2,6-Cl_2	**9g** (X = OMe)	63	**15g**	89
4-NO_2	**9h** (X = OMe)	62	**15h**	80
3-NO_2	**9i** (X = OMe)	57	**15i**	87
2-NO_2	**9j** (X = OMe)	61	**15j**	40
4-CN	**9k** (X = OMe)	63	**15k**	92
2-CN	**9l** (X = OMe)	60	**15l**	86
4-CF_3	**9m** (X = OMe)	66	**15m**	90

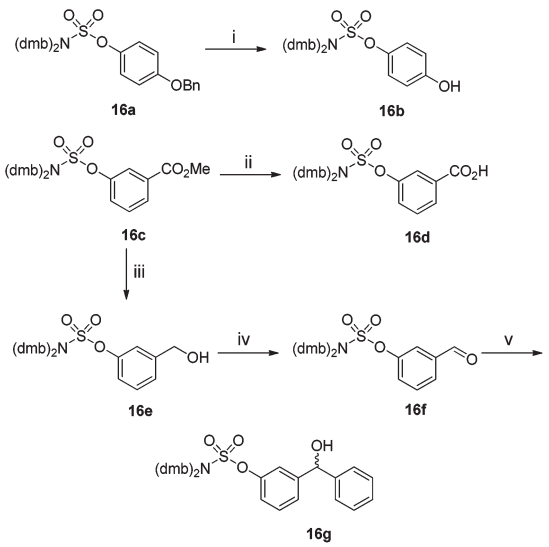
O-sulfamates. For phenols with pK_a > 7.1 and the sterically demanding phenol 2,6-dimethylphenol, high conversions could routinely be achieved under relatively mild conditions (15 min, microwave heating at 120 °C, 2 equiv. of **4**, MeCN) (Table 2).

One-pot methylation followed by substitution with **2** proceeded in similar yield for all phenols studied and deprotection was also clean and high yielding for all examples (see Table 3 and Scheme 5). The optimised conditions were also applied to the protection of a defined set of phenol *O*-sulfamates, *N*-protected by 4-methoxybenzyl. In all cases deprotection with 50% TFA in dichloromethane proceeded in high yield to the corresponding phenol *O*-sulfamate (Table 3 and Scheme 5).

To assess the broad chemical stability of 2,4-dimethoxybenzyl for *N*-protection of sulfamates, a suitable set of compounds was prepared (see ESI† for synthetic routes) to determine the robustness of *N*-2,4-dimethoxybenzyl to some common



Scheme 5 Synthesis of substituted phenol *O*-sulfamates [*Reagents and conditions*: i, $Me_3O{\cdot}BF_4$, DCM, 8 h, 0 °C to room temp.; ii, **1** or **2**, DCM/MeCN, 42 °C, 24 h; iii, TFA, DCM, (24 h, 42 °C for **8b–8f**; 2 h, room temp. for **9b–9m**); substituents for **8b–8f**, **9b–9m** and **15b–15m** correspond to those for **5b–5m**: see Scheme 3; for X see Table 3].



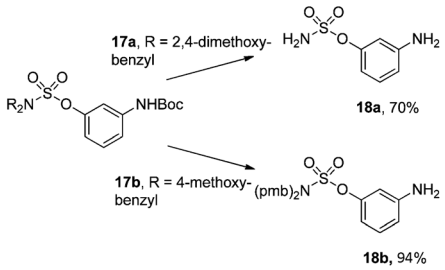
Scheme 6 Reactions demonstrating the stability of 2,4-dimethoxybenzyl-protected phenol *O*-sulfamates (**16a–16g**) towards some common reagents [*Reagents and conditions*: i, H_2, Pd/C, 60 °C, 24 h; ii, LiOH, aq. THF, 60 °C, 18 h; iii, $LiAlH_4$, THF, 0 °C, 2 h; iv, MnO_2, DCM, room temp., 16 h; v, PhMgBr, THF, 0 °C, 3 h, (all yields > 84%)].

transformations. Importantly, sulfamates bis-*N*-protected with 2,4-dimethoxybenzyl were stable to hydrogen/palladium catalyst, aqueous lithium hydroxide, lithium aluminium hydride, manganese dioxide and phenylmagnesium bromide (Scheme 6, dmb = 2,4-dimethoxybenzyl).

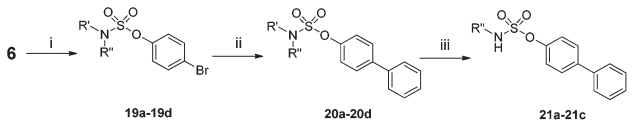
Deprotection of the *N*-*t*-butyloxycarbonyl (BOC)-aniline **17a** occurred with simultaneous removal of bis-*N*-2,4-dimethoxybenzyl from the sulfamate group to afford 3-aminophenyl *O*-sulfamate (**18a**). However, when 4-methoxybenzyl was used to protect the sulfamate (**17b**), the BOC group was removed with retention of the sulfamate protecting group (**18b**, Scheme 7). A further extension of the methodology is the synthesis of secondary sulfamates (**21a–21c**) from **6**, *via* **19a–19d** and **20a–20d** (Scheme 8 and Table 4).

Conclusions

A reliable procedure for the protection and deprotection of sulfamates derived from phenols has been presented. Especially attractive is the use of 2,4-dimethoxybenzyl as a bis-*N*-protecting group that is stable to bases, nucleophiles, and other reagents,



Scheme 7 Deprotection of BOC-anilines (R = 4-methoxybenzyl (pmb) or 2,4-dimethoxybenzyl) [*Reagents and conditions*: 10% TFA in DCM, room temp., 2 h].



Scheme 8 Synthesis of secondary sulfamates [*Reagents and conditions*: i, R′R″NH, MeCN, room temp., 16 h; ii, $Pd(PPh_3)_4$, $PhB(OH)_2$, K_2CO_3, MeCN, microwave heating (120 °C, 20 min); iii, 10% TFA/DCM, room temp., 2 h (R′ = 2,4-dimethoxybenzyl) or 50% TFA/DCM, 42 °C, 24 h (R′ = 4-methoxylbenzyl)].

Table 4 Isolated yields for steps i–iii in Scheme 8

R′	R″	i	ii	iii
4-Methoxybenzyl	Me	95%	87%	96%
2,4-Dimethoxybenzyl	Me	96%	90%	95%
2,4-Dimethoxybenzyl	Bn	89%	87%	96%
2,4-Dimethoxybenzyl	^{i}Bu	85%	85%	93%

but is readily removed by dilute trifluoroacetic acid in dichloromethane. This enables the application of a variety of reaction types (*e.g.* Suzuki coupling) to functional groups on the phenol *O*-sulfamates. Furthermore, masking of the polar sulfamate group is convenient in multistep synthesis. The strategy comprises reaction of a phenol with 1,1′-sulfonylbis(2-methyl-1*H*-imidazole) to give an aryl 2-methyl-1*H*-imidazole-1-sulfonate, which is activated by reaction with trimethyloxonium tetrafluoroborate, before further reaction with a methoxy-substituted dibenzylamine. With either 4-methoxy- or 2,4-dimethoxybenzyl, deprotection of the nitrogen and release of the phenol *O*-sulfamate could easily be accomplished by treatment with dilute trifluoroacetic acid. Each step proceeds in excellent yield (16 diverse examples of phenols). The sulfamate protecting groups are stable to common reaction conditions, providing useful orthogonality with other protecting groups. The developed mode of protection is also amenable to secondary sulfamates. It is anticipated that the methodology described will become standard for sulfamate protection.

Experimental

For details of the preparation of compounds **5b–5m**, **8c–8f**, **9b–9m**, **15b–15m**, **16a–16g**, **17a**, **17b**, **18a**, **18b**, **19a–19d**, **20a–20d**, **21a–21c** and **S1–S12** (compounds not explicitly

mentioned in the above text) and corresponding schemes see ESI.†

Materials and methods

Chemicals and solvents were obtained from reputable suppliers. Solvents were either dried by standard techniques or purchased as anhydrous. Petrol was reagent grade (bp range 40–60 °C). All reactions that required inert or dry atmosphere were carried out under dry nitrogen. Glassware was dried in an oven prior to use. Reactions needing microwave irradiation were carried out in an Initiator™ Sixty Biotage apparatus. Concerning chromatographic and spectroscopic methods see the ESI.†

General procedure A. To the appropriate amine (1 mol equiv.) in ethanol (0.5 mL $mmol^{-1}$ of benzylamine) was added the appropriate benzaldehyde (1 mol equiv.) and $MgSO_4$ (400 mg). The mixture was stirred at 78 °C for 4 h. After cooling to room temperature, sodium borohydride (1.1 mol equiv.) was carefully added to the reaction mixture. The resulting mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc (60 mL), washed with sat. aq. NH_4Cl, water and brine (30 mL each), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure B. To 1,1′-sulfonylbis(2-methyl-1*H*-imidazole) (**4**) (2 mol equiv.) and caesium carbonate (1.1 mol equiv.) in acetonitrile was added the appropriate phenol (1 mol equiv.). The mixture was heated at 120 °C for 15 min under microwave irradiation. After cooling, the mixture was concentrated *in vacuo*. The residue was dissolved in sat. aq. NH_4Cl (15 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The pooled organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure C. To 1,1′-sulfonylbis(2-methyl-1*H*-imidazole) (**4**) (10 mol equiv.) and caesium carbonate (1.1 mol equiv.) in acetonitrile was added the appropriate phenol (1 mol equiv.). The mixture was heated at 180 °C for 15 min under microwave irradiation and worked up as in General procedure B.

General procedure D. To 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**6**) (1 mol equiv.) in acetonitrile (8 mL $mmol^{-1}$ of tetrafluoroborate) was added the appropriate dibenzylamine (1 mol equiv.). The mixture was stirred for 8 h, after which the solvent was removed *in vacuo* to yield a crude product that was used in the next step without further purification.

General procedure E. A solution of the appropriate 4-bromophenyl protected sulfamate (1 mol equiv.) in acetonitrile (20 mL $mmol^{-1}$ of 4-bromophenyl sulfamate) was sparged with nitrogen for 15 min. To this solution potassium carbonate (3 mol equiv.), phenylboronic acid (1.5 mol equiv.) and tetrakis(triphenylphosphine)palladium(0) (0.1 mol equiv.) were added. The mixture was heated at 120 °C for 20 min under microwave irradiation. The solvent was removed *in vacuo* and the residue was distributed between EtOAc (20 mL) and water (20 mL). The EtOAc phase was separated and the aqueous phase was extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure F. The appropriate 2,4-dimethoxybenzyl protected sulfamate (1 mol equiv.) was solubilised in 10% TFA/DCM mixture (10 mL $mmol^{-1}$ of sulfamate). The resulting solution was stirred at room temperature for 2 h. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (20 mL), washed with 10% aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure G. The appropriate 4-methoxybenzyl protected sulfamate (1 mol equiv.) was solubilised in a 50% TFA/DCM mixture (10 mL $mmol^{-1}$ of sulfamate). The resulting solution was heated at 42 °C for 24 h. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (20 mL), washed with 10% aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure H. To the appropriate phenyl 2-methyl-1*H*-imidazole-1-sulfonate (1 mol equiv.) in DCM (10 mL $mmol^{-1}$ of sulfonate), cooled at 0 °C, was added trimethyloxonium tetrafluoroborate (1 mol equiv.). The resulting solution was stirred at 0 °C for 1 h and allowed to warm to room temperature. After 8 h, the reaction was diluted with acetonitrile (5 mL $mmol^{-1}$ of sulfonate) and the appropriate benzylamine (1 mol equiv.) was added. The resulting reaction mixture was heated at 42 °C for 24 h. Upon completion, the solvent was removed *in vacuo* to yield a crude product. The crude product was purified by column chromatography.

bis(4-Methoxybenzyl)amine, (1). Compound **1** was synthesised according to general procedure A, using the following reagents: 4-methoxybenzylamine (3.22 mL, 3.38 g, 24.6 mmol), 4-methoxybenzaldehyde (3.0 mL, 3.36 g, 24.6 mmol), sodium borohydride (1.03 g, 27.1 mmol) and ethanol (12.3 mL). The crude product was purified by column chromatography (DCM : MeOH – 1 : 0 → 94 : 6) to yield the *title compound* as an orange oil (4.81 g, 75%): R_f 0.28 (DCM : MeOH – 94 : 6); δ_H (500 MHz, $CDCl_3$) 3.73 (s, 4H, 2 × ArCH_2), 3.81 (s, 6H, 2 × OCH_3), 6.87 (d, J = 8.7 Hz, 4H, H-3, 5), 7.25 (d, J = 8.7 Hz, 4H, H-2, 6); LRMS (ESI^+) m/z 258.4 $[M + H]^+$; ^1H NMR and LRMS data were identical to literature data.[19]

bis(2,4-Dimethoxybenzyl)amine, (2). Compound **2** was synthesised according to general procedure A, using the following reagents: 2,4-dimethoxybenzylamine (2.72 mL, 3.03 g, 18.0 mmol), 2,4-dimethoxybenzaldehyde (3.0 g, 18.0 mmol), sodium borohydride (0.75 g, 19.9 mmol) and ethanol (9 mL). The crude product was purified by column chromatography (DCM : MeOH – 1 : 0 → 9 : 1) to yield the *title compound* as a pale yellow oil (4.91 g, 85%): R_f 0.34 (DCM : MeOH – 9 : 1); δ_H (500 MHz, $CDCl_3$) 3.73 (s, 4H, 2 × ArCH_2), 3.79 (s, 6H,

2 × OCH_3), 3.79 (s, 6H, 2 × OCH_3), 6.46–6.41 (m, 4H, H-3, 5), 7.17 (d, J = 8.6 Hz, 2H, H-6); LRMS (ESI$^+$) m/z 318.4 [M + H]$^+$; ^{1}H NMR data were identical to literature data.[20,21]

bis(3,4-Dimethoxybenzyl)amine, (3). Compound **3** was synthesised according to general procedure A, using the following reagents: 3,4-dimethoxybenzylamine (2.72 mL, 3.02 g, 18.0 mmol), 3,4-dimethoxybenzaldehyde (3.0 g, 18.0 mmol), sodium borohydride (0.75 g, 19.9 mmol) and ethanol (9 mL). The crude product was purified by column chromatography (DCM : MeOH – 1 : 0 → 9 : 1) to yield the *title compound* as a yellow solid (3.91 g, 68%): R_f 0.33 (DCM : MeOH – 9 : 1); mp: 68.5–70.5 °C; δ_H (500 MHz, $CDCl_3$) 3.74 (s, 4H, 2 × ArCH_2), 3.87 (s, 6H, 2 × OCH_3), 3.89 (s, 6H, 2 × OCH_3), 6.82 (d, J = 8.2 Hz, 2H, H-5), 6.86 (dd, J = 8.2, 1.8 Hz, 2H, H-6), 6.90 (d, J = 1.8 Hz, 2H, H-2); LRMS (ESI$^+$) m/z 318.4 [M + H]$^+$; ^{1}H NMR and LRMS data were identical to literature data.[22]

1,1′-Sulfonylbis(2-methyl-1*H*-imidazole), (4). To 2-methylimidazole (20.3 g, 247 mmol) in DCM (100 mL), cooled to 0 °C, was added dropwise over 30 min sulfuryl chloride (5 mL, 8.32 g, 61.7 mmol) in DCM (40 mL). The resulting solution was stirred at 0 °C for 1 h and allowed to warm up to room temperature. After 24 h, the reaction was quenched by cautious addition of water (100 mL) and extracted with DCM (2 × 50 mL). The pooled organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was purified by column chromatography (DCM : MeOH – 1 : 0 → 93 : 7) to yield the *title compound* as an off-white solid (10.2 g, 73%): R_f 0.32 (DCM : MeOH – 93 : 7); mp: 86.0–88.0 °C; λ_{max} (EtOH)/nm 220.0; δ_H (500 MHz, $CDCl_3$) 2.52 (s, 6H, CH_3), 6.95 (d, J = 1.7 Hz, 2H), 7.37 (d, J = 1.8 Hz, 2H); δ_C (126 MHz, $CDCl_3$) 15.11, 120.18, 128.64, 146.15; LRMS (ESI$^+$) m/z 227.2 [M + H]$^+$; ^{1}H NMR data were identical to literature data.[23]

4-Bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (5a). Compound **5a** was synthesised according to general procedure B, using the following reagents: 1,1′-sulfonylbis(2-methyl-1*H*-imidazole) (**4**) (262 mg, 1.16 mmol), caesium carbonate (207 mg, 0.64 mmol), 4-bromophenol (100 mg, 0.58 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (petrol : EtOAc – 1 : 0 → 8 : 2) to yield the *title compound* as a clear oil (169 mg, 93%): R_f 0.35 (petrol : EtOAc – 8 : 2); λ_{max} (EtOH)/nm 220.5; IR (film) ν_{max}/cm^{-1} 1553, 1480, 1422, 1207, 1147, 1043, 1012; δ_H (500 MHz, $CDCl_3$) 2.50 (s, 3H, CH_3), 6.81 (d, J = 8.9 Hz, 2H, H-2, 6), 6.89 (d, J = 1.7 Hz, 1H, $H_{imidazole}$), 7.12 (d, J = 1.8 Hz, 1H, $H_{imidazole}$), 7.49 (d, J = 9.0 Hz, 2H, H-3, 5); δ_C (126 MHz, $CDCl_3$) 15.09, 120.52, 122.37, 123.44, 128.25, 133.56, 146.85, 148.00; HRMS (ESI) calcd for $C_{10}H_{10}BrN_2O_3S$ [M + H]$^+$: 316.9590; found 316.9598.

2,6-Dichlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (5g). Compound **5g** was synthesised according to general procedure C, using the following reagents: 1,1′-sulfonylbis(2-methyl-1*H*-imidazole) (**4**) (3.47 g, 15.3 mmol), caesium carbonate (550 mg, 1.69 mmol), 2,6-dichlorophenol (250 mg, 1.53 mmol) and acetonitrile (20 mL). The crude yellow oil was purified by column chromatography (petrol : EtOAc – 1 : 0 → 85 : 15) to yield the *title compound* as a clear oil (396 mg, 84%): R_f 0.34 (petrol : EtOAc – 8 : 2); λ_{max} (EtOH)/nm 271.0, 278.0; IR (film) ν_{max}/cm^{-1} 1573, 1556, 1429, 1201, 1177, 1044; δ_H (500 MHz, $CDCl_3$) 2.68 (s, 3H, CH_3), 6.92 (d, J = 1.8 Hz, 1H, $H_{imidazole}$), 7.19 (d, J = 1.9 Hz, 1H, $H_{imidazole}$), 7.26–7.20 (m, 1H, H-4), 7.39 (d, J = 8.1 Hz, 2H, H-3, 5); δ_C (126 MHz, $CDCl_3$) 15.33, 120.25, 128.15, 129.19, 129.72, 129.80, 143.09, 146.81; HRMS (ESI) calcd for $C_{10}H_9Cl_2N_2O_3S$ [M + H]$^+$: 306.9705; found 306.9709.

1-((4-Bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate, (6). To 4-bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**5a**) (4.18 g, 13.2 mmol) in DCM (60 mL), cooled to 0 °C, was added trimethyloxonium tetrafluoroborate (1.96 g, 13.2 mmol). The resulting solution was stirred at 0 °C for 1 h and allowed to warm up to room temperature. After 8 h, the reaction was cooled in an ice-bath, and petrol (120 mL) was added to the mixture. The white precipitate was filtered off, washed with cold petrol (60 mL) and dried under high vacuum. The white fluffy solid (4.97 g, 90%) was used in the next step without further purification: mp: 131.0–133.0 °C; λ_{max} (EtOH)/nm 223.0; IR (film) ν_{max}/cm^{-1} 3139, 1605, 1479, 1449, 1235, 1212 1149, 1023; δ_H (500 MHz, MeOD) 2.90 (s, 3H, CH_3), 3.96 (s, 3H, NCH_3), 7.26 (d, J = 9.1 Hz, 2H, H-2, 6), 7.68 (d, J = 9.1 Hz, 2H, H-3, 5), 7.70 (d, J = 2.4 Hz, 1H, $H_{imidazole}$), 7.83 (d, J = 2.4 Hz, 1H, $H_{imidazole}$); δ_C (126 MHz, MeOD) 11.87, 36.87, 122.37, 124.16, 124.60, 125.12, 135.19, 149.62, 150.19; HRMS (ESI) calcd for $C_{11}H_{12}BrN_2O_3S$ [M – BF_4]$^+$: 330.9747; found 330.9749.

4-Bromophenyl dibenzylsulfamate, (7). Compound **7** was synthesized following two different procedures.

1st procedure: To 4-bromophenol (29 mg, 0.17 mmol) and caesium carbonate (60 mg, 0.18) in anhydrous THF was added dibenzylsulfamoyl chloride (**S1**). The resulting mixture was heated at 67 °C for 16 h. After cooling, the mixture was concentrated *in vacuo*. The resulting residue was dissolved in sat. aq. NH_4Cl (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The pooled organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 97 : 3) to yield the *title compound* as a white solid (29 mg, 40%).

2nd procedure: Compound **7** was synthesised according to general procedure D, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**6**) (400 mg, 0.96 mmol), dibenzylamine (184 μL, 189 mg, 0.96 mmol) and acetonitrile (7.7 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 97 : 3) to yield the *title compound* as a white solid (320 mg, 77%): R_f 0.34 (petrol : EtOAc – 96 : 4); mp: 86.5–88.5 °C; λ_{max} (EtOH)/nm 258.0; IR (film) ν_{max}/cm^{-1} 1481, 1452, 1369, 1154, 1061; δ_H (500 MHz, $CDCl_3$) 4.39 (s, 4H, 2 × ArCH_2), 6.99 (d, J = 8.8 Hz, 2H, H-2, 6), 7.31–7.27 (m, 4H, 4 × Ar*H*), 7.39–7.32 (m, 6H, 6 × Ar*H*), 7.44 (d, J = 8.9 Hz, 2H, H-3, 5); δ_C (126 MHz, $CDCl_3$) 51.28, 120.19, 123.78, 128.46, 128.88, 129.16, 132.92, 134.71, 149.42; HRMS (ESI) calcd for $C_{20}H_{19}BrNO_3S$ [M + H]$^+$: 432.0264; found 432.0272.

4-Bromophenyl bis(4-methoxybenzyl)sulfamate, (8a). Compound **8a** was synthesised according to general procedure D,

using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**6**) (600 mg, 1.43 mmol), bis(4-methoxybenzyl)amine (**1**) (370 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 95 : 5) to yield the *title compound* as a pale orange solid (595 mg, 84%): R_f 0.34 (petrol : EtOAc – 95 : 5); mp: 61.5–63.5 °C; λ_{max} (EtOH)/nm 274.5; IR (film) ν_{max}/cm^{-1} 1614, 1513, 1479, 1456, 1361, 1249, 1169, 1033; δ_H (500 MHz, $CDCl_3$) 3.82 (s, 6H, 2 × OCH_3), 4.30 (s, 4H, 2 × ArCH_2), 6.88 (d, J = 8.7 Hz, 4H, H-3′, 5′), 7.00 (d, J = 8.9 Hz, 2H, H-2, 6), 7.20 (d, J = 8.7 Hz, 4H, H-2′, 6′), 7.45 (d, J = 8.9 Hz, 2H, H-3, 5); δ_C (126 MHz, $CDCl_3$) 50.39, 55.47, 114.21, 120.10, 123.86, 126.77, 130.54, 132.89, 149.48, 159.74; HRMS (ESI) calcd for $C_{22}H_{26}BrN_2O_5S$ $[M + NH_4]^+$: 509.0740; found 509.0740.

4-Methoxyphenyl bis(4-methoxybenzyl)sulfamate, (8b). Compound **8b** was synthesised according to general procedure H, using the following reagents: 4-methoxyphenyl 2-methyl-1*H*-imidazole-1-sulfonate (**4**) (300 mg, 1.12 mmol), trimethyloxonium tetrafluoroborate (165 mg, 1.12 mmol), DCM (11.2 mL), acetonitrile (5.6 mL) and bis(4-methoxybenzyl)amine (**1**) (288 mg, 1.12 mmol). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 85 : 15) to yield the *title compound* as a clear oil (398 mg, 80%): R_f 0.30 (petrol : EtOAc – 85 : 15); λ_{max} (EtOH)/nm 274.5; IR (film) ν_{max}/cm^{-1} 1612, 1502, 1367, 1247, 1165, 1031; δ_H (500 MHz, $CDCl_3$) 3.80 (s, 3H, OCH_3), 3.82 (s, 6H, 2 × OCH_3), 4.29 (s, 4H, 2 × ArCH_2), 6.83 (d, J = 9.1 Hz, 2H, H-3, 5), 6.86 (d, J = 8.7 Hz, 4H, H-3′, 5′), 7.05 (d, J = 9.1 Hz, 2H, H-2, 6), 7.20 (d, J = 8.6 Hz, 4H, H-2′, 6′); δ_C (126 MHz, $CDCl_3$) 50.36, 55.43, 55.74, 114.10, 114.70, 123.16, 127.03, 130.53, 143.86, 158.12, 159.59; HRMS (ESI) calcd for $C_{25}H_{30}NO_8S$ $[M + H]^+$: 504.1687; found 504.1677.

4-Bromophenyl bis(2,4-dimethoxybenzyl)sulfamate, (9a). Compound **9a** was synthesised according to general procedure D, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**6**) (600 mg, 1.43 mmol), bis(2,4-dimethoxybenzyl)amine (**2**) (456 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 85 : 15) to yield the *title compound* as a clear oil (680 mg, 86%): R_f 0.30 (petrol : EtOAc – 85 : 15); λ_{max} (EtOH)/nm 277.0; IR (film) ν_{max}/cm^{-1} 1613, 1588, 1507, 1481, 1370, 1208, 1156, 1035; δ_H (500 MHz, $CDCl_3$) 3.73 (s, 6H, 2 × OCH_3), 3.80 (s, 6H, 2 × OCH_3), 4.44 (s, 4H, 2 × ArCH_2), 6.39 (d, J = 2.4 Hz, 2H, H-3′), 6.43 (dd, J = 8.4, 2.4 Hz, 2H, H-5′), 6.92 (d, J = 8.9 Hz, 2H, H-2, 6), 7.24 (d, J = 8.4 Hz, 2H, H-6′), 7.39 (d, J = 8.9 Hz, 2H, H-3, 5); δ_C (126 MHz, $CDCl_3$) 47.10, 55.25, 55.54, 98.33, 104.15, 116.62, 119.72, 123.85, 131.14, 132.62, 149.54, 158.62, 160.84; HRMS (ESI) calcd for $C_{24}H_{27}BrNO_7S$ $[M + H]^+$: 552.0686; found 552.0676.

4-Bromophenyl bis(3,4-dimethoxybenzyl)sulfamate, (10). Compound **10** was synthesised according to general procedure D, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**6**) (600 mg, 1.43 mmol), bis(3,4-dimethoxybenzyl)amine (**3**) (456 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 65 : 35) to yield the *title compound* as a white solid (675 mg, 85%): R_f 0.32 (petrol : EtOAc – 65 : 35); mp: 99.5–101.5 °C; λ_{max} (EtOH)/nm 278.0; IR (film) ν_{max}/cm^{-1} 1595, 1518, 1464, 1358, 1259, 1238, 1141, 1024; δ_H (500 MHz, $CDCl_3$) 3.82 (s, 6H, 2 × OCH_3), 3.89 (s, 6H, 2 × OCH_3), 4.33 (s, 4H, 2 × ArCH_2), 6.77 (dd, J = 8.1, 1.9 Hz, 1H, H-6′), 6.82 (d, J = 8.2 Hz, 2H, H-5′), 6.84 (d, J = 1.9 Hz, 2H, H-2′), 7.05 (d, J = 8.9 Hz, 2H, H-2, 6), 7.47 (d, J = 8.9 Hz, 2H, H-3, 5); δ_C (126 MHz, $CDCl_3$) 51.14, 56.04, 56.10, 111.04, 112.17, 120.21, 121.69, 123.69, 127.23, 132.99, 149.26, 149.40, 149.52; HRMS (ESI) calcd for $C_{24}H_{30}BrN_2O_7S$ $[M + NH_4]^+$: 569.0952; found 569.0947.

[1,1′-Biphenyl]-4-yl dibenzylsulfamate, (11). Compound **11** was synthesised according to general procedure E, using the following reagents: 4-bromophenyl dibenzylsulfamate (**7**) (250 mg, 0.58 mmol), potassium carbonate (240 mg, 1.73 mmol), phenyl boronic acid (106 mg, 0.87 mmol), tetrakis(triphenylphosphine) palladium(0) (67 mg, 0.06 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 97 : 3) to yield the *title compound* as a white solid (320 mg, 72%): R_f 0.42 (petrol : EtOAc – 96 : 4); mp: 131.5–133.5 °C; λ_{max} (EtOH)/nm 251.0; IR (film) ν_{max}/cm^{-1} 1483, 1455, 1363, 1187, 1149, 1051; δ_H (500 MHz, $CDCl_3$) 4.43 (s, 4H, 2 × ArCH_2), 7.21 (d, J = 8.7 Hz, 2H, H-3, 5), 7.39–7.27 (m, 11H, 11 × Ar*H*), 7.45 (t, J = 7.6 Hz, 2H, H-4′), 7.58–7.52 (m, 4H, 4 × Ar*H*); δ_C (126 MHz, $CDCl_3$) 51.30, 122.26, 127.26, 127.72, 128.37, 128.55, 128.83, 129.01, 129.20, 134.88, 140.04, 140.16, 149.85; HRMS (ESI) calcd for $C_{26}H_{24}NO_3S$ $[M + H]^+$: 430.1471; found 430.1478.

[1,1′-Biphenyl]-4-yl bis(4-methoxybenzyl)sulfamate, (12). Compound **12** was synthesised according to general procedure E, using the following reagents: 4-bromophenyl bis(4-methoxybenzyl)sulfamate (**8a**) (400 mg, 0.81 mmol), potassium carbonate (337 mg, 2.44 mmol), phenyl boronic acid (149 mg, 1.22 mmol), tetrakis(triphenylphosphine)palladium(0) (94 mg, 0.08 mmol) and acetonitrile (16 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 95 : 5) to yield the *title compound* as a pale yellow oil (330 mg, 83%): R_f 0.38 (petrol : EtOAc – 95 : 5); λ_{max} (EtOH)/nm 251.0; IR (film) ν_{max}/cm^{-1} 1610, 1511, 1484, 1379, 1248, 1178, 1153, 1052, 1031; δ_H (500 MHz, $CDCl_3$) 3.81 (s, 6H, 2 × OCH_3), 4.34 (s, 4H, 2 × ArCH_2), 6.87 (d, J = 8.7 Hz, 4H, H-3″, 5″), 7.24–7.19 (m, 6H, 6 × Ar*H*), 7.39–7.34 (m, 1H, H-4′), 7.45 (dd, J = 7.6, 7.6 Hz, 2H, H-3′, 5′), 7.58–7.52 (m, 4H, H-2, 6 & H-2′, 6′); δ_C (126 MHz, $CDCl_3$) 50.41, 55.45, 114.17, 122.32, 126.95, 127.25, 127.72, 128.51, 129.01, 130.57, 139.97, 140.17, 149.88, 159.67; HRMS (ESI) calcd for $C_{28}H_{31}N_2O_5S$ $[M + NH_4]^+$: 507.1948; found 507.1945.

[1,1′-Biphenyl]-4-yl bis(2,4-dimethoxybenzyl)sulfamate, (13). Compound **13** was synthesised according to general procedure E, using the following reagents: 4-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**9a**) (450 mg, 0.81 mmol), potassium carbonate (337 mg, 2.44 mmol), phenyl boronic acid (149 mg, 1.22 mmol), tetrakis(triphenylphosphine)palladium(0) (94 mg, 0.08 mmol) and acetonitrile (16 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0

→ 85 : 15) to yield the *title compound* as a yellow oil (375 mg, 83%): R_f 0.32 (petrol : EtOAc – 85 : 15); λ_{max} (EtOH)/nm 250.5; IR (film) ν_{max}/cm^{-1} 1612, 1590, 1507, 1469, 1369, 1206, 1154, 1042, 1034; δ_H (500 MHz, $CDCl_3$) 3.73 (s, 6H, 2 × OCH_3), 3.78 (s, 6H, 2 × OCH_3), 4.48 (s, 4H, 2 × ArCH_2), 6.39 (d, J = 2.4 Hz, 2H, H-3″), 6.43 (dd, J = 8.4, 2.4 Hz, 2H, H-5″), 7.15 (d, J = 8.7 Hz, 2H, H-3, 5), 7.27 (d, J = 8.4 Hz, 2H, H-6″), 7.38–7.33 (m, 1H, H-4′), 7.44 (dd, J = 7.6, 7.6 Hz, 2H, H-3′, 5′), 7.51 (d, J = 8.7 Hz, 2H, H-2, 6), 7.55 (dd, J = 8.3, 1.2 Hz, 2H, H-2′, 6′); δ_C (126 MHz, $CDCl_3$) 47.04, 55.25, 55.52, 98.30, 104.14, 116.80, 122.32, 127.23, 127.60, 128.29, 128.96, 131.12, 139.56, 140.31, 149.97, 158.61, 160.75; HRMS (ESI) calcd for $C_{30}H_{32}NO_7S$ $[M + H]^+$: 550.1894; found 550.1887.

[1,1′-Biphenyl]-4-yl bis(3,4-dimethoxybenzyl)sulfamate, (14). Compound **14** was synthesised according to general procedure E, using the following reagents: 4-bromophenyl bis(3,4-dimethoxybenzyl)sulfamate (**10**) (450 mg, 0.81 mmol), potassium carbonate (337 mg, 2.44 mmol), phenyl boronic acid (149 mg, 1.22 mmol), tetrakis(triphenylphosphine)palladium(0) (94 mg, 0.08 mmol) and acetonitrile (16 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 65 : 35) to yield the *title compound* as a yellow solid (385 mg, 86%): R_f 0.35 (petrol : EtOAc – 65 : 35); mp: 120.5–122.5 °C; λ_{max} (EtOH)/nm 237.5; IR (film) ν_{max}/cm^{-1} 1593, 1518, 1450, 1370, 1261, 1237, 1140, 1019; δ_H (500 MHz, $CDCl_3$) 3.82 (s, 6H, 2 × OCH_3), 3.87 (s, 6H, 2 × OCH_3), 4.36 (s, 4H, 2 × CH_2), 6.78 (dd, J = 8.2, 1.8 Hz, 2H, H-6″), 6.81 (d, J = 8.2 Hz, 2H, H-5″), 6.87 (d, J = 1.8 Hz, 2H, H-2″), 7.25 (d, J = 8.6 Hz, 2H, H-3, 5), 7.39–7.32 (m, 1H, H-4′), 7.44 (dd, J = 7.6, 7.6 Hz, 2H, H-3′, 5′), 7.59–7.51 (m, 4H, H-2, 6 & H-2′, 6′); δ_C (126 MHz, $CDCl_3$) 51.15, 56.03, 56.08, 111.01, 112.20, 121.69, 122.15, 127.22, 127.43, 127.76, 128.57, 129.01, 140.05, 149.17, 149.36, 149.90; HRMS (ESI) calcd for $C_{30}H_{35}N_2O_7S$ $[M + NH_4]^+$: 567.2159; found 567.2155.

[1,1′-Biphenyl]-4-yl sulfamate, (15a). Compound **15a** was synthesized following two different procedures.

1st procedure: Compound **15a** was synthesised according to general procedure F, using the following reagents: [1,1′-biphenyl]-4-yl bis(2,4-dimethoxybenzyl)sulfamate (**13**) (180 mg, 0.33 mmol), DCM (3.0 mL) and TFA (0.33 mL). The crude product was purified by column chromatography (petrol : EtOAc – 1 : 0 → 7 : 3) to yield the *title compound* as an off-white solid (77 mg, 95%).

2nd procedure: Compound **15a** was synthesised according to general procedure G, using the following reagents: [1,1′-biphenyl]-4-yl bis(4-methoxybenzyl)sulfamate (**12**) (100 mg, 0.20 mmol), DCM (1.0 mL) and TFA (1.0 mL). The crude product was purified by column chromatography (petrol : DCM – 1 : 0 → 0 : 1) to yield the *title compound* as an off-white solid (45 mg, 90%): R_f 0.34 (petrol : EtOAc – 7 : 3); δ_H (500 MHz, DMSO) 7.42–7.34 (m, 3H, H-3, 5 & H-4′), 7.48 (dd, J = 7.7, 7.7 Hz, 2H, H-3′, 5′), 7.66 (dd, J = 8.3, 1.1 Hz, 2H, H-2′, 6′), 7.75 (d, J = 8.7 Hz, 2H, H-2, 6), 8.04 (s, 2H, NH_2); LRMS (ESI$^-$) m/z 248.2 $[M - H]^-$; ^{1}H NMR data were identical to literature data.[24]

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