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ω-(Imidazol-4-yl)alkane-1-sulfonamides: A New Series of Potent Histamine H_3 Receptor Antagonists

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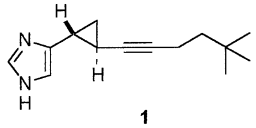
Abstract—ω-(1*H*-Imidazol-4-yl)alkane-1-sulfonamides were prepared and found to be potent histamine H_3 receptor antagonists. High receptor affinity and a low difference in the data between the bioassays were achieved with 5-(1*H*-imidazol-4-yl)pentane-1-sulfonic acid 4-chlorobenzylamide (**16**). Good in vitro profiles were also obtained for 2-hydroxysulfonamide and vinylsulfonamide analogues. This complements and completes the existing set of imidazole-based sulfonamides and sulfamides. © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

The histamine H_3 receptor was identified in 1983[1] and selective antagonists and agonists were reported four years later.[2] Much has been written during the intervening years about the physiological role of the H_3 receptor and many reports have described novel and selective agonists and antagonists.[3–6] The cloning of the human H_3 receptor,[7] and the subsequent cloning of guinea pig[8] and rat receptors,[9] may have profound consequences for research in the area and for the development of clinical agents.[10] The clinical value and role of compounds acting through the H_3 receptor has yet to be firmly established. However, the entry of Perceptin (GT-2331, **1**) into Phase II clinical trials for the reatment of attention-deficit hyperactivity disorder (ADHD) may be a defining moment for H_3 antagonists.[11]



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Current H_3 antagonists can be broadly categorized as imidazole and non-imidazole compounds.[6] The former predominate, although considerable progress with the latter has been made of late.[12] Perceptin is unusual among imidazole H_3 antagonists in that it features a relatively rigid carbon framework between the imidazole and the distal lipophilic group. In most other cases a polar group has been used as part of the intervening linker, the optimum structures for the linker and the lipophilic tail varying with each polar group. Central to our development of imidazole-based H_3 receptor antagonists has been the utilisation of sulfamide[13] and sulfonamide groups,[13,14] in compounds such as JB96132 (**2**) and **3** respectively (Fig. 1).

Not only have these compounds filled an important gap, as recognized in retrospect by others,[15] but also distinct advantages can be gained by using the sulfonamide and sulfamide groups in preference to other polar linkers. For example, the in vitro affinities of JB96132 are one to two orders of magnitude greater than its urea equivalent (G.P. Cortex pK_i 8.2; G.P. Ileum pK_B 6.6). Furthermore, we have not encountered (data not presented here) the toxicological problems that seem to have dogged the development of other sulfur-containing H_3 antagonists.[16] We would like to report herein, further observations from the sulfamide series, and the subsequent development of a new series of sulfonamides.[17]

During exploration of the sulfamide group,[13a] it was found that differential *N*-methylation of the two nitrogens had a direct bearing on affinity at the H_3 receptor (Fig. 1).[13b] The choice of assays has previously been discussed.[14] Relative to JB96132, di-*N*-methylation (**4**)

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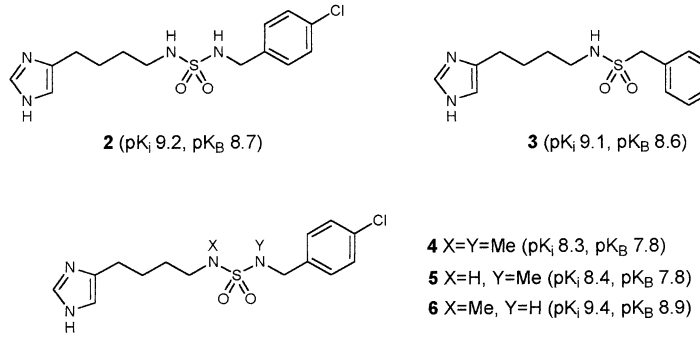


Figure 1. *N*-Methylation of JB96132 (pK_i: g.p. cortex; pK_B: g.p. ileum).

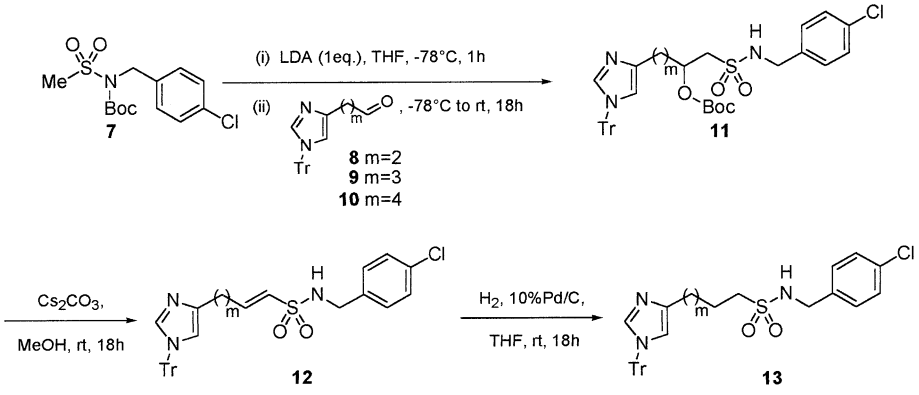
or methylation of the nitrogen adjacent to the 4-chlorobenzyl group (**5**) resulted in a loss of affinity, in the order of a log unit in both functional and radioligand binding assays. In contrast, no such loss was observed on methylation of the nitrogen nearest the imidazole (**6**). To facilitate a more extensive investigation of this position, we undertook the synthesis of a new series of sulfonamides (–SO_2NH–), the reverse of the original sulfonamides (–$NHSO_2$–). If the SAR for sulfonamides parallels the analogous amide series of H_3 antagonists, such a reversal would be expected to have a deleterious effect.[18] The synthetic route to the new reverse sulfonamides generated a more structurally diverse set of intermediates than those of previous series. With a view to broadening our understanding of the structure–activity relationships (SAR) of the new series, some of these intermediates were also examined in the in vitro assays.

Chemistry

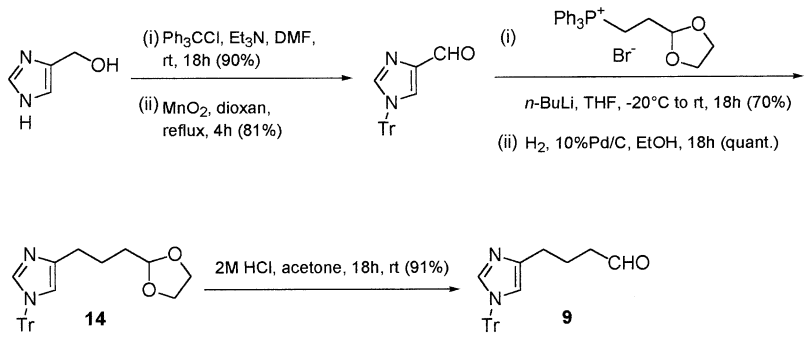
The previous sulfonamides and sulfamides were readily generated from histamine and its homologues.[13,14] However, a different approach was required for the 'reverse' sulfonamides and we turned to methodology developed within the group for this purpose.[19a] The lynchpin was, thus, the base mediated condensation of (imidazol-4-yl)alkyl aldehydes (**8**–**10**) and *N*-Boc-methanesulfonamides (such as **7**) (Scheme 1).

Aldehydes (**8**–**10**) were prepared either by oxidation of the corresponding alcohols (for **8**)[20] or by homologation of lower aldehydes using standard Wittig reactions with hydrogenation of the resulting double bond. The latter approach was used for the conversion of 1-trityl-1*H*-imidazole-4-carbaldehyde to the 4-butanal analogue **9**, via intermediate **14** using a commercially available phosphonium salt (Scheme 2). Similarly, the 6-hexanal analogue **10** was prepared from aldehyde **8**. The two-carbon homologation, based on a Wadsworth–Emmons reaction of triethylphosphonoacetate, was followed by reduction of the double bond (palladium-on-charcoal catalysed hydrogenation) and the ester (lithium aluminium hydride), and oxidation of the ensuing alcohol.

The key carbon–carbon bond forming reaction between the aldehydes and the prefabricated sulfonamide units, such as **7**, was performed according to its two-step variant,[19a] giving the isolable intermediates **11** en route to vinylsulfonamides **12**. With non-imidazole aldehydes the condensation/elimination process has been achieved through a one-pot reaction using potassium *t*-butoxide as the base,[19a] conditions which were found to be incompatible with the trityl protecting group of the imidazole. The choice of base for this reaction is critical for its success and, while potassium *t*-butoxide was optimal for the direct formation of vinylsulfonamides, we have found, through the current work, that lithium diisopropylamide (LDA) is an acceptable alternative in the initial condensation reaction. In contrast to potassium *t*-butoxide, the use of multiple equivalents of LDA did not give clean conversion to the vinylsulfonamides, self-condensation of the aldehyde being a significant side-reaction. The *trans*-vinylsulfonamides (**12**) were generated in high yields and stereoselectivities by treating compounds **11** with cesium carbonate in anhydrous methanol.



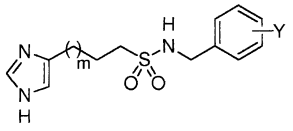
Scheme 1.



Scheme 2.

The reverse sulfonamide skeleton was completed by hydrogenation under palladium catalysis to give compounds **13**. While the ubiquitous 4-chlorobenzyl group was not sensitive to these conditions, the 4-bromo, 2-chloro and 3-chloro analogues underwent hydrogenolysis, and thus dehalogenation, to varying degrees. A rhodium-on-alumina catalyst was used to circumvent this problem. Deprotection of the imidazole to give the final targets (Table 1) was accomplished by treatment with trifluoroacetic acid at room temperature. The same procedure was used to convert the intermediate compounds **11** and **12** into 2-hydroxysulfonamides (**28**–**30**) and vinylsulfonamides (**25** and **26**), respectively, for assessment in the bioassays (Table 2). We have previously reported the stereoselective synthesis of buta-1,3-diene-1-sulfonic acid amides, such as compound **27**.[19a,b] The aldehyde precursor to compound **27** was derived from commercially available *trans*-urocainic acid using the chemistry described herein.

Table 1. In vitro data from histamine H_3 receptor bioassays for various ω-(1*H*-imidazol-4-yl)alkane-1-sulfonamides



Compd[a,b]	*m*	Y	G.P. Cortex pK_i±SEM[c]	G.P. LMMP pK_i±SEM[e]	G.P. Ileum pK_B±SEM[d]
15	2	4-Cl	8.58±0.16	8.07±0.06	8.06±0.16
16	3	4-Cl	8.58±0.09	8.73±0.25	8.46±0.09
17	4	4-Cl	8.54±0.08	—	8.29±0.15
18	3	2-Cl	7.71±0.09	—	6.61±0.20
19	3	3-Cl	7.91±0.13	—	7.23±0.16
20	3	H	8.05±0.07	—	7.23±0.18
21	3	4-Br	9.05±0.14	—	8.47±0.23
22	3	4-F	8.15±0.12	—	7.72±0.17
23	3	4-CF_3	8.82±0.11	—	8.03±0.11
24	3	4-Me	8.21±0.05	—	7.59±0.14

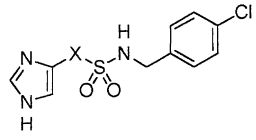
[a]Satisfactory ^{1}H NMR spectra and elemental analyses were obtained for all new compounds.
[b]All compounds were tested as maleic acid salts.
[c]pK_i±SEM values were estimated from at least three separate competition experiments in which [^{3}H]-(*R*)-α-methylhistamine was used to label histamine H_3-binding sites in guinea pig cortical homogenates.
[d]pK_B±SEM values were estimated from single shifts of (*R*)-α-methylhistamine concentration-effect curves in the guinea pig isolated, electrically-stimulated, ileum assay, in at least four separate tissues, in which the compounds behaved as surmountable antagonists.
[e]pK_i±SEM values were estimated from 3 separate competition experiments in which [^{3}H]-(*R*)-α-methylhistamine was used to label histamine H_3 binding sites in guinea pig ileum LMMP homogenates.

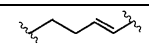
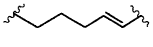
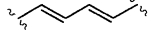
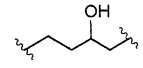
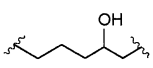
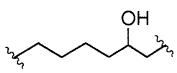
Results and Discussion

The compounds were evaluated in the guinea pig isolated ileum assay,[21a] in which histamine H_3 receptors mediate inhibition of neurogenic contractions,[21b] and in radioligand binding assays using guinea pig cerebral cortex and ileal longitudinal muscle myenteric plexus (LMMP) membranes (selected examples).[22] The choice and interpretation of the assays has been discussed previously.[14] It is sufficient to note here that optimum affinity and minimal inter-assay differences were primary objectives.

In the first instance, we concentrated on an imidazole-sulfonamide chain length of four to six methylene units and a terminal 4-chlorobenzyl group, these two features being

Table 2. In vitro data from histamine H_3 receptor bioassays for miscellaneous reverse sulfonamide analogues



Compd[a,b]	X	G.P. Cortex pK_i±SEM[c]	G.P. LMMP pK_i±SEM[e]	G.P. Ileum pK_B±SEM[d]
25		8.56±0.16	7.99±0.03	7.90±0.11
26		8.23±0.20	—	7.60±0.06
27		5.80±0.03	—	5.58±0.21
28		6.57±0.09	—	6.62±0.07
29		8.30±0.15	7.90±0.02	7.79±0.14
30		8.37±0.14	—	7.90±0.10

[a–e]See the corresponding footnotes in Table 1.

associated with the optimum in vitro profile in the previous sulfonamide and sulfamide series. The 4-chlorobenzyl compounds **15**, **16** and **17** behaved as competitive antagonists in the ileum functional assay with affinities in the nanomolar range (Table 1). The affinities for compounds **15** and **16** in the ileum radioligand binding assay mirrored their functional counterparts. The levels of affinity and the close correlation between assays were comparable with the behaviour of analogous compounds from the previous sulfonamide and sulfamide series. The five-methylene chain length was consequently chosen as the basis for an investigation into the effect of the nature and position of the aromatic substituent (**18**–**24**, Table 1). The importance of the 4-position for the chloro substituent may be judged from the loss in activity of 2- and 3-chloro substituted compounds (**18** and **19**, respectively). This may be a result either of losing an element of binding or the introduction of an unfavourable intramolecular interaction. The latter, may be invoked, at least in part, to explain the relatively low affinity of the 2-chloro-substituted compound (**18**), particularly in light of the equivalence between the unsubstituted analogue (**20**) and the 3-chloro compound (**19**). The 4-bromo compound **21** produced an affinity comparable with that of compound **16**, while the other substituents were associated with either lower affinities or greater differences between radioligand binding and functional assays. In broad terms, this is in keeping with the trends observed for both the original sulfonamide and sulfamide series.

It has been proposed, on the basis of molecular modelling studies in a non-related series of H_3 antagonists, that ligand conformation correlates with ligand behaviour.[23] A preliminary examination of the effect of conformational constraint has been possible through the vinylsulfonamides **25** and **26** and the dienylsulfonamide **27** (Table 2). While the *trans*-double bond of the vinylsulfonamides **25** and **26** may be associated with a marginal loss of affinity relative to the fully saturated systems, a much more substantial reduction was observed for the *trans,trans*-dienyl sulfonamide **27**. A bicyclic structure derived from compound **27** was similarly a very modest H_3 antagonist,[19b] thus underlining the precision required for successful conformational constraints. As indicated above, small structural changes to the sulfamide can have an adverse effect on affinity. Through the 2-hydroxysulfonamides derived from intermediate **11**, we sought to examine the feasibility of introducing an additional polar substituent in the vicinity of the sulfonamide. The 2-hydroxysulfonamides **28**–**30** behaved as antagonists in the ileum functional assay. As with the vinylsulfonamides, the affinities of compounds **29** and **30** were slightly lower than those of the corresponding saturated analogues. This is in sharp contrast with the in vitro profile of **28**. It thus seems that the hydroxyl group is more readily accommodated by the longer alkyl chains of compounds **29** and **30**. One might speculate that an unfavourable intramolecular interaction in **28** is overcome by the conformational preferences of the longer chains. It is not yet possible to determine the role of the sulfonamide group, which may interact directly with the receptor or may stabilise a favourable conformation of the ligand, by stereoelectronic predisposition or an internal hydrogen bond. Those additional functionality present in **27** and **28** clearly interferes with the properties of **15** that make it a superior ligand.

In addition to optimising affinity, we also sought to minimise the inter-assay differences. The origin and consequences of inter-assay differences, whether between species or tissue-types, have been discussed by us elsewhere.[12a,14,22c] Similar 'discrepancies' have been noted by others and viewed as evidence for the existence of receptor sub-types.[24] It has been noted that certain sets of compounds can be used to distinguish receptors in the guinea pig ileum from those in the guinea pig cortex.[22c] For the reverse sulfonamides and the previous two series[13,14] there is a consistent, if slight, difference between these two sets of data. The data from the guinea pig ileum radioligand binding assay tends to correlate better with affinities measured in the ileum functional assay than in the guinea pig cortex radioligand binding assay. This may provide additional evidence for the ongoing discussion of receptor heterogeneity and residual efficacy.[14,22c]

The reverse sulfonamides described herein represent a third highly potent series of H_3 antagonists, satisfying our primary criteria for affinities in the nanomolar range with minimal differences between the assays. Moreover, for the key compound **16**, and its unsaturated analogue **25**, selectivity for the H_3 receptor over the histamine H_1 and H_2 receptor subtypes has been found to be approximately three orders of magnitude.[25] The SAR, in general terms, paralleled the previous sulfonamides and sulfamides, although an exploration of greater structural diversity has been possible and some insight has been gained into the deleterious effects of imposing conformational constraints on the imidazole–SO_2 chain. In summation of the three series, it would seem that optimum in vitro behaviour is associated with a well defined disposition of the imidazole and SO_2 groups (a five-atom imidazole–SO_2 chain), and a 4-chlorobenzyl cap for the sulfonamide or sulfamide linker.

Experimental

All reagents and solvents were obtained from commercial suppliers and were used without further purification. Solvents were of either AR or HPLC grade. Preparative flash column chromatography was performed on Merck Kieselgel 60 (particle size 0.063–0.040) under pressure. ^{1}H NMR spectra were recorded on a Bruker DRX-300 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.26 ppm, methanol in MeOH-d_4 at 3.35 ppm, and DMSO in DMSO-d_6 at 2.49 ppm). Signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br, broad. Elemental analyses were performed at the London School of Pharmacy. All reactions were carried out under a positive pressure of argon.

***N*-(*tert*-Butoxycarbonyl)-*N*-(4-chlorobenzyl)methanesulfonamide (7). Step a:** A solution of 4-chlorobenzylamine (12.2 g, 86.2 mmol) and triethylamine (14.4 mL, 103 mmol) in dichloromethane (200 mL) was cooled in an ice bath. Methanesulfonyl chloride (7.34 mL, 94.9 mmol) was added dropwise and the solution was stirred for 10 min. The cold bath was removed and the solution stirred for a further 2 h. The reaction was diluted with an equal volume of dichloromethane and washed with 10% citric acid and brine. The solvent was evaporated and the residue recrystallised from hot ethyl acetate. *N*-(4-Chlorobenzyl)methanesulfonamide was thus obtained as a colourless crystalline solid (15.3 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.32 (4H, m), 4.75 (1H, br m), 4.30 (2H, d, $J=6.3$ Hz), 2.89 (3H, s). **Step b**: to a of solution *N*-(4-chlorobenzyl)methanesulfonamide (15.30 g, 69.6 mmol) and di-*tert*-butyl-dicarbonate (18.27 g, 83.6 mmol) in dichloromethane (150 mL) was carefully added *N,N*-4-dimethylaminopyridine (848 mg, 6.96 mmol), which was followed by an immediate and vigorous effervescence. The solution was stirred for 30 min, by which time effervescence had ceased. The solution was diluted to a total volume of 500 mL with dichloromethane and washed twice with 10% citric acid and brine. The solvent was evaporated to give a yellow solid, which was recrystallised from hot propan-2-ol (100 mL) and dried in vacuo at 50 °C to afford the product as a colourless crystalline solid (19.70 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.32(4H, s), 4.84 (2H, s), 3.20 (3H, s), 1.51 (9H, s). Found: C 48.95, H 5.40, N 4.47%; $C_{13}H_{18}ClNO_4S$ requires: C 48.82, H 5.67, N 4.38%.

4-(3-[1,3]Dioxolan-2-ylpropyl)1-trityl-1*H*-imidazole (14). Step a: A suspension of [2-(1,3-dioxolan-2-yl)ethyl]-triphenylphosphonium bromide (48.5 g, 109 mmol) in tetrahydrofuran (500 mL) was cooled to −20 °C. *n*-Butyl lithium (1.6 M, 68.3 mL, 109 mmol) was added dropwise and the solution stirred for 1 h. A solution of 1-trityl-1*H*-imidazole-4-carbaldehyde[27] (36.8 g, 109 mmol) in tetrahydrofuran (500 mL) was added slowly and the reaction mixture stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, water was added and the mixture filtered through a pad of Celite®. The filtrate was extracted with dichloromethane (2×500 mL) and the combined extracts dried over magnesium sulfate. Filtration and evaporation gave a yellow oil. From flash column chromatography (10–20% ethyl acetate/hexane) (*Z*)-4-(3-[1,3]dioxolan-2-yl-allyl)1-trityl-1*H*-imidazole was isolated as a yellow oil (19.7 g, 42%). **Step b:** a solution of the product from step a in ethanol was hydrogenated in the presence of a catalytic quantity of 10% palladium-on-charcoal at atmospheric pressure and temperature for 18 h. Compound **14** was isolated as a colourless oil in quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) 7.33 (10 H, m), 7.13 (6H, m), 6.54 (1H, s), 4.86 (1H, t, $J=4.5$ Hz), 3.93 (2H, m), 3.81 (2H, m), 2.59 (2H, m), 1.72 (4H, m).

4-[1-(Triphenylmethyl)-1*H*-imidazol-4-yl]butanal (9). A suspension of the compound **14** (19.8 g, 46.6 mmol) in a mixture of acetone (300 mL) and 2 M hydrochloric acid (50 mL) was stirred at room temperature for 20 h. The mixture was neutralised with sodium hydrogen carbonate, filtered and the filtrate extracted with dichloromethane (3×100 mL). The combined extracts were dried over magnesium sulfate, filtered and evaporated to give aldehyde **9** as a colourless oil (16.1 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) 9.72 (1H, t, $J=1.8$ Hz), 7.32 (10H, m), 7.14 (6H, m), 6.54 (1H, s), 2.59 (2H, t, $J=7.5$ Hz), 2.44 (2H, dt, $J=7.5$, 1.8 Hz), 1.97 (2H, quin., $J=7.5$ Hz).

Carbonic acid *tert*-butyl ester 1-[(4-chlorobenzylsulfamoyl)methyl]-4-(1-trityl-1*H*-imidazol-4-yl)butyl ester (11, *m*=3). A solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-chlorobenzyl)methanesulfonamide (**7**) (1.53 g, 4.80 mmol) in THF (16 mL) was cooled to −78 °C, lithium diisopropylamide (1.5 M, 3.20 mL, 4.80 mmol) was added dropwise and the solution was stirred for 1 h. A solution of the aldehyde **9** (1.83 g, 4.80 mmol) in THF (16 mL) was added by means of a cannula, the cold bath was removed and the solution was stirred for 2 h. The reaction was quenched with saturated ammonium chloride solution (20 mL) and the mixture was extracted with ethyl acetate (2×20 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and the solvent evaporated. Flash column chromatography (50% ethyl acetate/toluene) of the residue gave the product (**11**, $m=3$) as a colourless oil (1.60 g, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.33 (10H, m), 7.22 (4H, m), 7.10 (6H, m), 6.52 (2H, m), 5.11 (1H, m), 4.27 (2H, d, $J=6.0$ Hz), 3.38 (1H, dd, $J=14.4$, 6.6 Hz), 3.11 (1H, dd, $J=12.3$, 6.6 Hz), 2.55 (2H, m), 1.87 (1H, m), 1.68 (3H, m), 1.47 (9H, s).

(*E*)-5-(1-Trityl-1*H*-imidazol-4-yl)pent-1-ene-1-sulfonic acid 4-chlorobenzylamide (12, *m*=3). To a solution of compound (**11**, $m=3$) (1.60 g, 2.29 mmol) in anhydrous methanol (16 mL) was added cesium carbonate (1.49 mg, 4.58 mmol). The mixture was stirred overnight and the solvent evaporated. The residue was purified by flash column chromatography (ethyl acetate). The vinylsulfonamide product (**12**, $m=3$) was thus obtained as a white solid (1.20 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.33 (10H, m), 7.26 (4H, m), 7.14 (6H, m), 6.77 (1H, dt, $J=15.0$, 7.0 Hz), 6.53 (1H, s), 6.11 (1H, d, $J=15.0$ Hz), 4.76 (1H, t, $J=6.3$ Hz), 4.14 (2H, d, $J=6.3$ Hz), 2.56 (2H, t, $J=7.2$ Hz), 2.23 (2H, m), 1.79 (2H, quin., $J=7.2$ Hz).

5-(1-Trityl-1*H*-imidazol-4-yl)pentane-1-sulfonic acid 4-chlorobenzylamide (13, *m*=3). A mixture of the compound (**12**, $m=3$) (172 mg, 0.30 mmol), 10% palladium-on-charcoal (27 mg) and tetrahydrofuran (10 mL) was degassed in vacuo and vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated. The residue was purified by flash column chromatography (0.5:5:95 ammonia (880)/methanol/dichloromethane) and gave the product (**13**, $m=3$) as a colourless oil (148 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.33 (10H, m), 7.28 (4H, m), 7.12 (6H, m), 6.52 (1H, d, $J=0.9$ Hz), 5.45 (1H, m), 4.24 (2H, d, $J=6.3$ Hz), 2.96 (2H, t, $J=7.2$ Hz), 2.53 (2H, t, $J=7.5$ Hz), 1.81 (2H, quin., $J=7.5$

Hz), 1.63 (2H, quin., $J=7.5$ Hz), 1.46 (2H, quin., $J=7.2$ Hz).

5-(1*H*-Imidazol-4-yl)pentane-1-sulfonic acid 4-chlorobenzylamide (16). A solution of compound (**13**, $m=3$) (146 mg, 0.25 mmol) in trifluoroacetic acid (3.5 mL) was left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (1:10:90 ammonia (880)/methanol/dichloromethane) was isolated as a white solid (73 mg, 84%): ^{1}H NMR (300 MHz, MeOH-d_4) 7.59 (1H, d), 7.35 (4H, m), 6.78 (1H, s), 4.20 (2H, s), 2.93 (2H, m), 2.58 (2H, t, $J=7.5$ Hz), 1.74 (2H, quin., $J=7.8$ Hz), 1.62 (2H, quin., $J=7.8$ Hz), 1.39 (2H, quin., $J=7.8$ Hz). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.70, H 5.24, N 9.18%; $C_{19}H_{24}ClN_3O_6S$ requires: C 49.83, H 5.28, N 9.18%.

The following reverse sulfonamides were prepared in similar fashion. For the syntheses of compounds **18**, **19** and **21** the vinylsulfonamide intermediates, analogous to **12**, were hydrogenated in the presence of 5% rhodium-on-alumina.

4-(1*H*-Imidazol-4-yl)butane-1-sulfonic acid 4-chlorobenzylamide (15). ^{1}H NMR (300 MHz, MeOH-d_4) 7.57 (1H, s), 7.34 (4H, s), 6.79 (1H, s), 4.19 (2H, s), 2.97 (2H, m), 2.58 (2H, t, $J=6.9$ Hz), 1.72 (4H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 48.95, H 5.00, N 9.47%; $C_{18}H_{22}ClN_3O_6S$ requires: C 48.70, H 5.00, N 9.47%.

6-(1*H*-Imidazol-4-yl)hexane-1-sulfonic acid 4-chlorobenzylamide (17). ^{1}H NMR (300 MHz, MeOH-d_4) 7.56 (1H, d), 7.35 (4H, m), 6.76 (1H, s), 4.20 (2H, s), 2.92 (2H, m), 2.58 (2H, t, $J=7.5$ Hz), 1.72 (2H, m), 1.62 (2H, m), 1.35 (4H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 50.67, H 5.63, N 9.01%; $C_{20}H_{26}ClN_3O_6S$ requires: C 50.90, H 5.55, N 8.90%.

5-(1*H*-Imidazol-4-yl)pentane-1-sulfonic acid 2-chlorobenzylamide (18). ^{1}H NMR (300 MHz, MeOH-d_4) 7.56 (1H, s), 7.50 (1H, m), 7.39 (1H, m), 7.31 (2H, m), 6.75 (1H, s), 4.22 (2H, s), 2.92 (2H, m), 2.56 (2H, t, $J=7.5$ Hz), 1.74 (2H, quin., $J=7.5$ Hz), 1.60 (2H, quin., $J=7.5$ Hz), 1.38 (2H, quin., $J=7.5$ Hz). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.59, H 5.30, N 8.95%; $C_{19}H_{24}ClN_3O_6S$ requires: C 49.83, H 5.28, N 9.18%.

5-(1*H*-Imidazol-4-yl)pentane-1-sulfonic acid 3-chlorobenzylamide (19). ^{1}H NMR (300 MHz, MeOH-d_4) 7.56 (1H, s), 7.41 (1H, m), 7.31 (3H, m), 6.77 (1H, s), 4.22 (2H, s), 2.93 (2H, m), 2.58 (2H, t, $J=7.2$ Hz), 1.75 (2H, m), 1.62 (2H, quin., $J=7.5$ Hz), 1.39 (2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.84, H 5.26, N 9.08%; $C_{19}H_{24}ClN_3O_6S$ requires: C 49.83, H 5.28, N 9.18%.

5-(1*H*-Imidazol-4-yl)pentane-1-sulfonic acid benzylamide (20). ^{1}H NMR (300 MHz, MeOH-d_4) 7.55 (1H, s), 7.30 (5H, m), 6.75 (1H, s), 4.22 (2H, s), 2.86 (2H, m), 2.55 (2H, t, $J=7.5$ Hz), 1.68 (2H, quin., $J=7.8$ Hz), 1.56 (2H, quin., $J=7.5$ Hz), 1.34 (2H, quin., $J=7.5$ Hz). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 53.87, H 6.03, N 10.03%; $C_{19}H_{25}N_3O_6S$ requires: C 53.89, H 5.95, N 9.92%.

5-(1*H*-Imidazol-4-yl)pentane-1-sulfonic acid 4-bromobenzylamide (21). ^{1}H NMR (300 MHz, $CDCl_3$) 7.47 (3H, m), 7.24 (2H, m), 6.74 (1H, s), 4.50 (2H, br s), 4.23 (2H, s), 2.91 (2H, t, $J=7.5$ Hz), 2.58 (2H, t, $J=7.5$ Hz), 1.72 (2H, quin., $J=7.5$ Hz), 1.59 (2H, quin., $J=7.2$ Hz), 1.34 (2H, quin., $J=7.2$ Hz). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 45.51, H 4.85, N 8.28%; $C_{19}H_{24}BrN_3O_6S$ requires: C 45.42, H 4.82, N 8.36%.

5-(1*H*-Imidazol-4-yl)pentane-1-sulfonic acid 4-fluorobenzylamide (22). ^{1}H NMR (300 MHz, $CDCl_3$) 7.52 (1H, s), 7.33 (2H, m), 7.04 (2H, m), 6.76 (1H, s), 5.12 (1H, br s), 4.27 (2H, s), 2.93 (2H, t, $J=7.5$ Hz), 2.61 (2H, t, $J=7.5$ Hz), 1.80 (2H, quin., $J=7.8$ Hz), 1.65 (2H, quin., $J=7.5$ Hz), 1.45 (2H, quin., $J=7.8$ Hz). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.50, H 5.60, N 9.41%; $C_{19}H_{24}FN_3O_6S$ requires: C 51.69, H 5.48, N 9.52%.

5-(1*H*-Imidazol-4-yl)pentane-1-sulfonic acid 4-trifluoromethylbenzylamide (23). ^{1}H NMR (300 MHz, DMSO-d_6) 11.45 (1H, br s), 7.71 (2H, d, $J=8.1$ Hz), 7.65 (1H, br s), 7.56 (2H, d, $J=8.1$ Hz), 7.51 (1H, s), 6.71 (1H, s), 4.23 (2H, d, $J=6.0$ Hz), 2.95 (2H, m), 2.45 (2H, t, $J=7.5$ Hz), 1.63 (2H, m), 1.53 (2H, m), 1.34 (2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 44.07, H 5.29, N 7.61%; $C_{20}H_{24}F_3N_3O_6S.2.8H_2O$ requires: C 44.30, H 5.51, N 7.75%.

5-(1*H*-Imidazol-4-yl)pentane-1-sulfonic acid 4-methylbenzylamide (24). ^{1}H NMR (300 MHz, DMSO-d_6) 11.40 (1H, br s), 7.60 (1H, br s), 7.52 (1H, t, $J=6.3$ Hz), 7.47 (1H, s), 7.20 (2H, d, $J=8.1$ Hz), 7.12 (2H, d, $J=8.1$ Hz), 6.68 (1H, s), 4.06 (2H, d, $J=6.0$ Hz), 2.83 (2H, m), 2.43 (2H, t, $J=7.5$ Hz), 2.26 (3H, s), 1.60 (2H, quin., $J=7.8$ Hz), 1.49 (2H, quin., $J=7.5$ Hz), 1.27 (2H, quin., $J=7.5$ Hz). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.73, H 6.44, N 9.17%; $C_{19}H_{27}N_3O_6S.1.4H_2O$ requires: C 51.83, H 6.50, N 9.07%.

(*E*)-4-(1*H*-Imidazol-4-yl)but-1-ene-1-sulfonic acid 4-chlorobenzylamide (25). A solution of compound (**12**, $m=2$) (85 mg, 0.15 mmol) in trifluoroacetic acid (2 mL)

was left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (1:10:90 ammonia (880)/methanol/dichloromethane). The product was isolated as a white solid (39 mg, 80%): ^{1}H NMR (300 MHz, MeOH-d_4) 7.60 (1H, d), 7.31 (4H, m), 6.84 (1H, d), 6.65 (1H, dt, J = 15.0, 7.0 Hz), 6.23 (1H, dt, J = 15.0, 1.5 Hz), 3.99 (2H, s), 2.74 (2H, m), 2.57 (2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 48.64, H 4.74, N 9.46%; $C_{18}H_{20}ClN_3O_6S$ requires: C 48.93, H 4.56, N 9.51%.

(*E*)-4-(1*H*-Imidazol-4-yl)pent-1-ene-1-sulfonic acid 4-chlorobenzylamide (26). A solution of compound (**12**, m = 3) (100 mg, 0.17 mmol) in trifluoroacetic acid (2 mL) was left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (1:10:90 ammonia (880)/methanol/dichloromethane). The product was isolated as a colourless oil (47 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.54 (1H, s), 7.28 (4H, m), 6.76 (1H, s), 6.70 (1H, m), 6.12 (1H, d, J = 15.0 Hz), 4.15 (2H, s), 5.32 (1H, br s), 2.61 (2H, t, J = 7.2 Hz), 2.23 (2H, quin., J = 7.2 Hz), 1.78 (2H, quin., J = 7.2 Hz). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.55, H 5.32, N 9.26%; $C_{19}H_{22}ClN_3O_6S$ requires: C 51.55, H 4.86, N 9.22%.

(*E,E*)-4-(1*H*-Imidazol-4-yl)-buta-1,3-diene-1-sulfonic acid 4-chloro-benzylamide (27). Step a: a mixture of manganese dioxide (2.50 g, 28.8 mmol), 3-(1-trityl-*1*H-imidazol-4-yl)-prop-2-en-1-ol (1.06 g, 2.88 mmol)[28] and chloroform was heated at reflux for 2.5 h. The solid residues were removed by filtration and the filtrate evaporated to afford the 3-(1-trityl-1*H*-imidazol-4-yl)-propenal as a white solid (759 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) 9.60 (1H, d, J = 7.8 Hz), 7.53 (1H, s), 7.35 (10H, m), 7.15 (7H, m), 6.78 (1H, dd, J = 15.6, 8.1 Hz). **Step b**: a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-chlorobenzyl)methanesulfonamide (**7**) (658 mg, 2.06 mmol) in tetrahydrofuran (5 mL) was cooled to −78 °C, 1.5M lithium diisopropylamide (1.37 mL, 2.06 mmol) was added dropwise and the solution was stirred for 1 h. A solution of 3-(1-trityl-1*H*-imidazol-4-yl)-propenal (750 mg, 2.06 mmol) was added by means of a cannula and the solution was stirred overnight, allowing it to warm slowly to room temperature. The reaction mixture was partitioned between saturated ammonium chloride solution (20 mL) and ethyl acetate (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated. Flash column chromatography (10–50% ethyl acetate/DCM) of the residue gave (*E*,*E*)-4-(1-trityl-1*H*-imidazol-4-yl)-buta-1,3-diene-1-sulfonic acid 4-chlorobenzylamide as a pale yellow solid (132 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.45–7.12 (22H, m), 6.90 (1H, m), 6.74 (1H, d, J = 15.3 Hz), 6.23 (1H, d, J = 14.8 Hz), 4.70 (1H, t, J = 6.0 Hz), 4.16 (2H, d, J = 6.0 Hz). **Step c**: trifluoroacetic acid (2 mL) was added to the product from the previous step (100 mg, 0.15 mmol). The resultant yellow solution left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (1:10:90 ammonia (880)/methanol/dichloromethane). Thus, the title compound was isolated as a colourless oil (54 mg, 73%): ^{1}H NMR (300 MHz, MeOH-d_4) 7.74 (1H, s), 7.32 (4H, m), 7.27 (1H, s), 7.11 (1H, dd, J = 14.7, 10.5 Hz), 6.90 (1H, d, J = 15.6 Hz), 6.78 (1H, dd, J = 15.3, 10.5 Hz), 6.34 (1H, d, J = 14.7 Hz), 4.13 (2H, s). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.09, H 4.16, N 9.60%; $C_{18}H_{18}ClN_3O_6S$ requires: C 49.15, H 4.12, N 9.55%.

2-Hydroxy-4-(1*H*-imidazol-4-yl)butane-1-sulfonic acid 4-chlorobenzylamide (28). A solution of compound (**11**, m = 2) (137 mg, 0.20 mmol) in trifluoroacetic acid (3 mL) was left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (1:10:90 ammonia (880)/methanol/dichloromethane). The product was isolated as a white solid (56 mg, 70%): ^{1}H NMR (300 MHz, MeOH-d_4) 7.57 (1H, s), 7.34 (4H, s), 6.81 (1H, s), 4.22 (2H, s), 4.08 (1H, m), 3.15 (2H, m), 2.70 (2H, m), 1.85 (2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 46.85, H 5.06, N 8.86%; $C_{18}H_{22}ClN_3O_7S$ requires: C 47.01, H 4.82, N 9.14%.

The following 2-hydroxysulfonamides were prepared in analogous fashion.

2-Hydroxy-4-(1*H*-imidazol-4-yl)pentane-1-sulfonic acid 4-chlorobenzylamide (29). ^{1}H NMR (300 MHz, MeOH-d_4) 7.56 (1H, d), 7.35 (4H, m), 6.78 (1H, d), 4.22 (2H, s), 4.08 (1H, m), 3.10 (2H, m), 2.60 (2H, m), 1.75 (2H, m), 1.53 (2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 47.78, H 5.27, N 8.61%; $C_{19}H_{24}ClN_3O_7S$ requires: C 48.15, H 5.10, N 8.87%.

2-Hydroxy-4-(1*H*-imidazol-4-yl)hexane-1-sulfonic acid 4-chlorobenzylamide (30). ^{1}H NMR (300 MHz, MeOH-d_4) 7.56 (1H, s), 7.35 (4H, m), 6.77 (1H, s), 4.22 (2H, s), 4.04 (1H, m), 3.08 (2H, m), 2.60 (2H, t, J = 7.5 Hz), 1.66 (2H, m), 1.53 (2H, m), 1.37 (2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 47.52, H 5.44, N 8.36%; $C_{20}H_{26}ClN_3O_7S$ requires: C 47.65, H 5.56, N 8.33%.

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