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Sulfonamides as Amine Component in the Petasis-Borono Mannich Reaction: A Concise Synthesis of α-Aryl- and α-Alkenylglycine Derivatives

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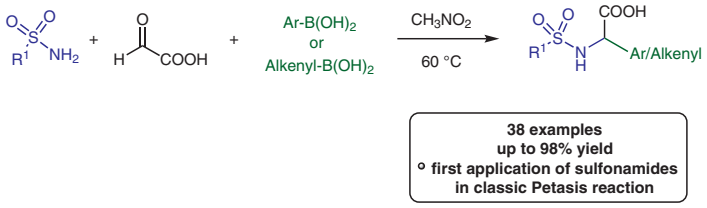


Received: 13.04.2018
Accepted after revision: 30.05.2018
Published online: 18.07.2018
DOI: 10.1055/s-0037-1610440; Art ID: ss-2018-z0255-op

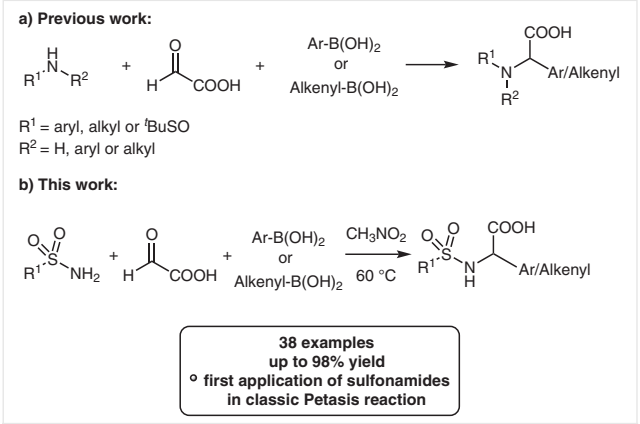
Abstract A catalyst-free three-component synthesis of α-aryl- and α-alkenylglycine derivatives starting from glyoxylic acid, sulfonamides, and aryl- or alkenylboronic acids is described. This operationally simple method tolerates a broad range of functional groups and enables the generation of a wide array of α-amino acids. Sulfonamides were utilized as amine component in the classic Petasis reaction for the first time.

Key words multicomponent reaction, Petasis-borono Mannich reaction, sulfonamides, amino acids, catalyst free

The Petasis-borono Mannich reaction, a three-component coupling of an aldehyde and an amine with an organoboron species, represents an operationally simple approach towards the synthesis of α-substituted amines.[1–5] This method provides straightforward access to important synthetic intermediates and biologically active products. Therefore, the Petasis reaction has become a powerful tool for the construction of small nitrogen-containing molecules. Of particular importance are transformations with glyoxylic acid as the aldehyde component, providing direct access to vinyl- or arylglycine analogues [Scheme 1 (a)]. Various amine components, such as primary or secondary alkylamines, hydrazines, or hydroxylamines have been utilized for the synthesis of the corresponding glycine derivatives.

In the course of our work on the palladium-catalyzed, stereoselective three-component synthesis of α-substituted amides,[6–9] we became aware of a gap in the substrate scope.

Whereas reactions with sulfinamides have been described,[10,11] there is, to the best of our knowledge, no report using sulfonamides as substrates in the classical, transition-metal-free Petasis reaction. Considering the importance of



Scheme 1 Synthesis of glycine derivatives by the Petasis reaction

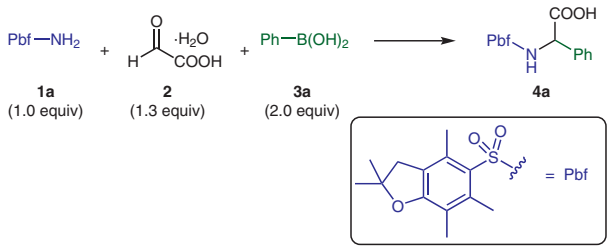
the sulfonamide group in medicinal chemistry,[12] the introduction of this functional group in a multicomponent approach would be highly useful.

Herein we wish to report the first Petasis reaction based on sulfonamides as the amine component [Scheme 1 (b)]. This method provides a versatile and operationally simple access to sulfonylated aryl- and vinylglycines.

Our investigations commenced with the reaction of glyoxylic acid (**2**), employed as the solid and easy-to-handle monohydrate, and phenylboronic acid (**3a**) with sulfonamide **1a**, which should lead to the corresponding 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonyl (Pbf)[13] protected phenylglycine **4a** (Table 1).

Surprisingly, this transformation proceeds quite efficiently in various common aprotic organic solvents, such as DCE, THF, EtOAc, or toluene (entries 1–6); the desired glycine derivative **4a** was obtained in 65–94% yield after 12 h at 60 °C. The best results were achieved with nitromethane (entry 6). Protic solvents (MeOH, EtOH, or H_2O) proved to

Table 1 Influence of the Reaction Parameters[a]



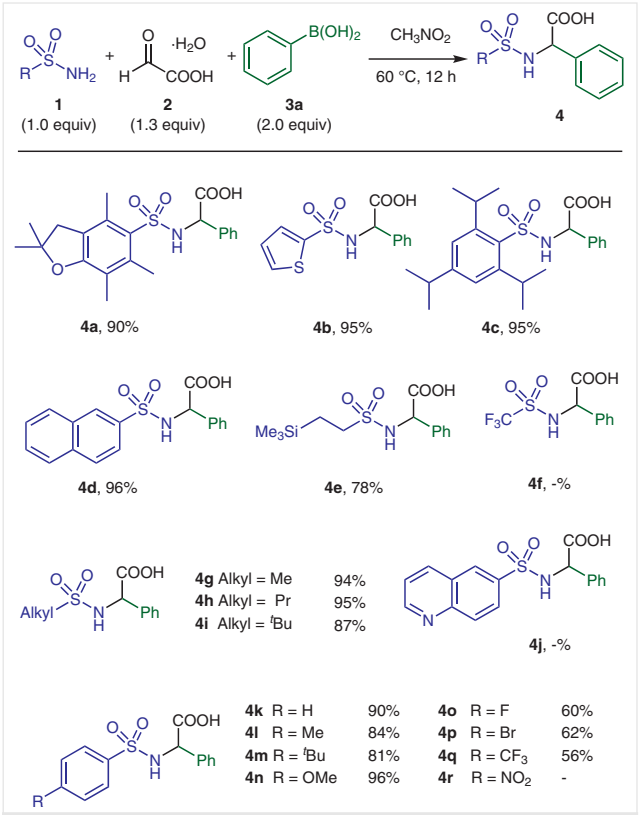
Entry	Solvent/variation	Temp (°C)	Yield[b] (%)
1	DCE	60	91
2	THF	60	87
3	toluene	60	90
4	EtOAc	60	89
5	acetone	60	65
6	CH_3NO_2	60	94
7	MeOH	60	–
8	EtOH	60	–
9	H_2O	60	–
10	CH_3NO_2	25	81
11	CH_3NO_2	40	90
12	CH_3NO_2, Ph-BF_3K	60	82
13	CH_3NO_2, Ph-Bpin	60	69
14	CH_3NO_2, Ph-MIDA	60	–

[a] Reaction conditions: Pbf-NH_2 (**1a**; 0.25 mmol), glyoxylic acid monohydrate (**2**; 1.3 equiv), $PhB(OH)_2$ (**3a**; 2 equiv), solvent (1.5 mL), temp, 12 h; reactions were carried out without exclusion of air and moisture.
[b] Yield of isolated product.

be not suitable for this transformation (entries 7–9). Performing the reaction at lower temperatures still furnished phenylglycine **4a** in high yields (entries 10 and 11). For all further studies, a reaction temperature of 60 °C was selected, since it enables a fast and reproducible product formation for almost any kind of substrate combination. Other organoboron species can be used to replace the boronic acid. The reaction of the corresponding phenyltrifluoroborate salt afforded **4a** in 82% yield (entry 12). With the pinacol ester a yield of 69% was achieved (entry 13). Only in the case of the MIDA boronate no product formation was observed (entry 14).

It has to be emphasized, that the reaction is very simple to perform. Exclusion of air or moisture is not necessary and no exogenous base, desiccant, or additive has to be added. All starting materials are commercially available and were used without further purification. With the optimized conditions in hand (Table 1, entry 6), we explored the substrate scope of this transformation.

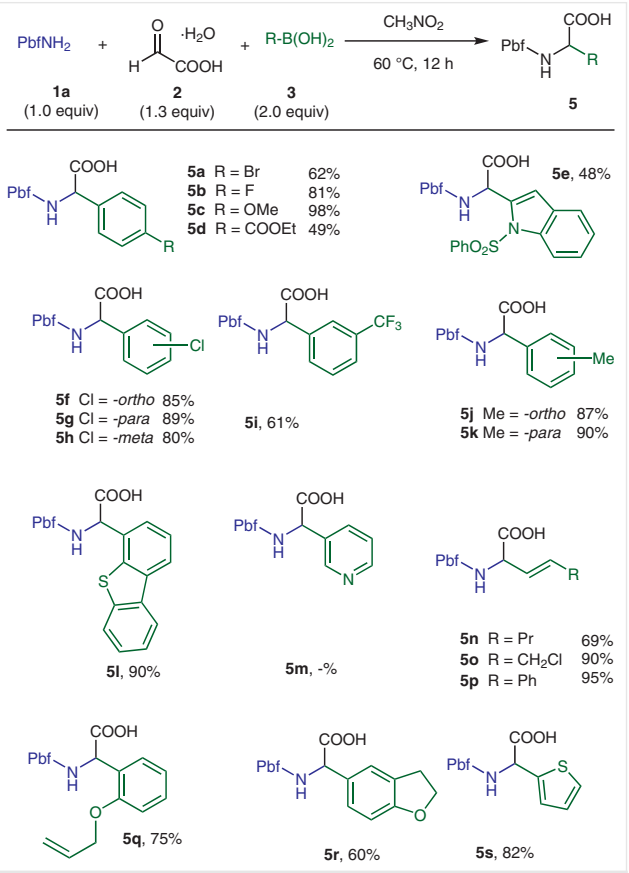
First reactions with different sulfonamides were investigated (Scheme 2). In general, good to excellent yields of the desired sulfonylated phenylglycines **4** were obtained. Aromatic, heteroaromatic, or aliphatic sulfonamides are suitable amine components for this multicomponent reaction. Only in the case of very electron-poor sulfonamides (**4f** and **4r**) or substrates containing a basic nitrogen (**4j**) was no product isolated.



Scheme 2 Variation of the sulfonamide component (all yields are given for isolated products)

This might be due to slow imine formation in the case of electron-poor, less nucleophilic sulfonamides or an interference of basic nitrogen atoms in the case of the quinolone **4j**. Full conversion of the sulfonamide was observed for all successful examples. Next reactions with different boronic acids were investigated (Scheme 3). A wide variety of different aryl- and heteroarylboronic acids are suitable starting materials and furnished the corresponding arylglycines **5a–s** in 48–98% yield. Electron-poor boronic acids, which are often problematic in the classical Petasis reaction,[1] perform satisfactorily and the ester- as well as the trifluoromethyl-substituted glycine derivatives **5d** and **5i** were obtained in 49% and 61% yield, respectively; longer reaction times proved to be beneficial in case of **5i**. Again, reactions with heteroarylboronic acids bearing basic nitrogen atoms were

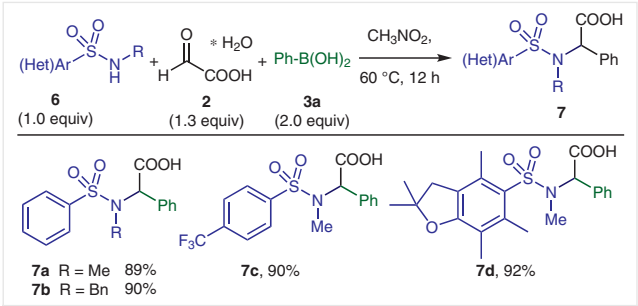
not successful (**5m**). On the other hand, alkenylboronic acids are compatible with this transformation, furnishing the corresponding vinylglycines **5n–p** in 69–95% yield.



Scheme 3 Variation of the boronic acid component (all yields are given for isolated products); [a] stirred for 64 h at 60 °C

The reaction is not limited to primary sulfonamides. Secondary sulfonamides perform equally well (Scheme 4). The desired products **7a–d** were obtained in a uniformly high 87–92% yield, even in the case of the sterically hindered substrate **6b**.

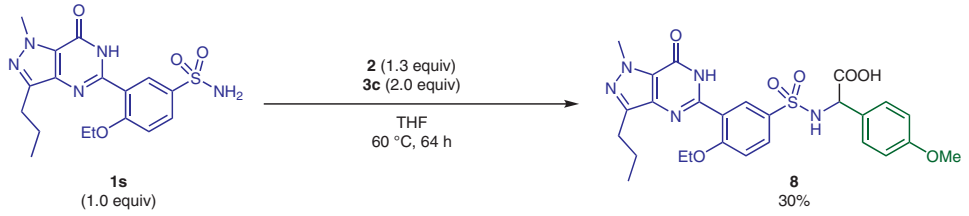
As the sulfonamide moiety can be found in many biologically active molecules and is a frequent motif in medicinal chemistry, we explored the potential application of our method in the late-stage diversification of drug-like molecules. For this purpose, we investigated the reaction of sulfonamide **1s**, a structural analogue of sildenafil,[14] with glyoxylic acid **2** and 4-methoxyphenylboronic acid (**3c**) (Scheme 5). To our delight, the desired arylglycine derivative **8** was isolated in 30% yield in THF as solvent. Although the obtained yield is rather low, this reaction showcases the potential application of this 3-component reaction as a tool for a late-stage library synthesis from complex scaffolds.



Scheme 4 Reactions with secondary sulfonamides (all yields are given for isolated products)

In summary, we have reported the first version of the Petasis reaction with sulfonamides as the amine component. This operational very simple multicomponent reaction offers a versatile approach towards sulfonylated α-aryl- and α-alkenylglycines from readily available building blocks. Various glycine derivatives, useful building blocks for the construction of biologically active molecules, were synthesized in good to excellent yields. The introduction of the sulfonamide group provides a useful handle, either as protecting group or as tool to manipulate the biological properties of the final product. The reaction displays a high functional group tolerance and can be used for the late-stage diversification of complex scaffolds. Studies towards the application of this multicomponent reaction for the construction of target-focused libraries are currently underway in our laboratory.

All reactions and manipulations were carried out in screwable glass tubes with PP-caps without avoiding ambient air or moisture. TLC was performed on precoated aluminum plates (TLC silica gel 60 F254). The resulting spots were visualized by UV light. Flash column chromatography was performed using Silica 60 (0.04–0.063 mm, 230–400 mesh). All yields refer to isolated yields. Unless stated, all



Scheme 5 Synthesis of an arylglycine analogue of sildenafil (the yield is given for the isolated product)

starting materials were purchased from different commercial sources and used without further purification. Solvents for reactions were obtained from commercial suppliers in p.a. quality and used as received. Solvents for flash column chromatography were technical standard. Methanesulfonamide, benzenesulfonamide, propane-1-sulfonamide, 2,4,6-triisopropylbenzenesulfonamide, 4-nitrobenzenesulfonamide, 4-fluorobenzenesulfonamide, 4-methoxybenzenesulfonamide, 4-bromobenzenesulfonamide, 4-*tert*-butylbenzenesulfonamide, naphthalene-2-sulfonamide, thiophene-2-sulfonamide, 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonamide, 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzenesulfonamide, *o*-tolylboronic acid, *p*-tolylboronic acid, 4-methoxyphenylboronic acid, 4-fluorophenylboronic acid, 4-bromophenylboronic acid, 4-chlorophenylboronic acid, 3-chlorophenylboronic acid, 2-chlorophenylboronic acid, and 3-trifluorophenylboronic acid were prepared according to previously reported procedures.[15,16] Melting points are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR were recorded at a frequency of 500 MHz (^{1}H), 126 MHz (^{13}C), and 471 MHz (^{19}F). Chemical shifts are reported relative to the respective solvent peak: ($CDCl_3$): δ = 7.26 (^{1}H), δ = 77.16 (^{13}C), or DMSO-d_6: δ = 2.50 (^{1}H), δ = 39.52 (^{13}C). Mass spectra were measured using ESI techniques. HRMS were measured using MALDI techniques. Infrared spectra were recorded on a FT-IR spectrometer including a diamond universal ATR sampling technique from 4000–400 cm^{-1}.

2-Alkylsulfonamido- or 2-(Hetero)arylsulfonamido-2-phenylacetic Acids 4a–r and 7a–d by Variation of the Sulfonamide; General Procedure (GP1)

A 10–mL screw cap glass tube with a PP-cap was charged with a magnetic stirring bar, sulfonamide **1** or **6** (0.25 mmol, 1.0 equiv), glyoxylic acid monohydrate (**2**; 30.0 mg, 0.33 mmol, 1.3 equiv), phenylboronic acid (**3a**; 61.0 mg, 0.5 mmol, 2.0 equiv), and nitromethane (1.5 mL, 0.17 M wrt sulfonamide) and firmly closed. The resulting mixture was stirred at 60 °C for 12 h. After cooling to r.t., the mixture was diluted with acetone and filtered through a short plug of Celite/silica gel. The plug was rinsed with additional acetone and the filtrate was concentrated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the product.

2-Alkenyl- or 2-(Hetero)aryl-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acids 5a–s by Variation of the Boronic Acid Derivative; General Procedure 2 (GP2)

A 10-mL screw-cap glass tube with PP-cap was charged with a magnetic stirring bar, 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonamide (**1a**; 68.0 mg, 0.25 mmol, 1.0 equiv), glyoxylic acid monohydrate (**2**; 30.0 mg, 0.33 mmol, 1.3 equiv), boronic acid **3** (0.5 mmol, 2.0 equiv), and nitromethane (1.5 mL, 0.17 M wrt sulfonamide) and firmly closed. The resulting mixture was stirred at 60 °C for 12 h. After cooling to r.t., the mixture was diluted with acetone and filtered through a Celite/silica gel mixture and the filtrate was concentrated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the product.

2-(2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)-2-phenylacetic Acid (4a)

Prepared from phenylboronic acid (140.2 mg, 1.15 mmol, 2.3 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2) afforded the product (180 mg, 90%) as a colorless solid.

The reaction was performed on a 2.5-mmol scale as follows: A 50-mL flask was charged with a magnetic stirring bar, 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonamide (**1a**; 680.0 mg, 2.5 mmol, 1.0 equiv), glyoxylic acid monohydrate (**2**; 300.0 mg, 3.3 mmol, 1.3 equiv), phenylboronic acid (**3a**; 610.0 mg, 5.0 mmol, 2.0 equiv), and nitromethane (0.17 M wrt sulfonamide, 15.0 mL) and closed with a rubber septum. The resulting mixture was stirred at 60 °C for 64 h. After cooling to r.t. the viridescent mixture was diluted with acetone and filtered through a Celite/silica gel mixture and the filtrate was concentrated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the product (1.6 g, 81%); mp 81–82 °C; R_f = 0.76 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 2972, 2929, 1718, 1456, 1289, 1157, 1138, 1089, 850, 782, 696, 660, 637, 614, 561, 544, 521, 505 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.12 (m, 5 H), 5.63 (d, *J* = 6.8 Hz, 1 H), 4.99 (d, *J* = 6.7 Hz, 1 H), 2.93–2.83 (m, 2 H), 2.46 (s, 3 H), 2.38 (s, 3 H), 2.02 (s, 3 H), 1.45 (s, 6 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 174.3, 160.0, 139.6, 135.0, 134.2, 128.8, 128.7, 127.9, 127.3, 125.2, 118.1, 87.0, 77.2, 59.1, 43.2, 28.7, 28.7 (partial overlap), 19.4, 17.8, 12.5.

MS (ESI): *m*/*z* calcd for $C_{21}H_{25}NO_5S$: 403.15; found: 404.15 [M + H]$^+$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{25}NO_5SNa$: 426.13456; found: 426.13409.

2-Phenyl-2-(2-thienylsulfonamido)acetic Acid (4b)

Prepared from thiophene-2-sulfonamide (41.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (71 mg, 95%) as a colorless solid; mp 150–151 °C; R_f = 0.38 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3250, 1729, 1325, 1133, 1067, 732, 678, 580, 523 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.97 (d, *J* = 9.2 Hz, 1 H), 7.83 (dd, *J* = 5.0, 1.3 Hz, 1 H), 7.49 (dd, *J* = 3.7, 1.3 Hz, 1 H), 7.33–7.25 (m, 5 H), 7.06 (dd, *J* = 4.9, 3.8 Hz, 1 H), 4.95 (d, *J* = 9.2 Hz, 1 H).

^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 170.9, 141.9, 136.4, 132.5, 131.8, 128.5, 128.1, 127.4, 127.4, 59.7.

MS (ESI): *m*/*z* calcd for $C_{12}H_{11}NO_4S_2$: 297.01; found: 295.97 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{11}NO_4S_2Na$: 320.00217; found: 320.00211.

2-Phenyl-2-(2,4,6-triisopropylphenylsulfonamido)acetic Acid (4c)

Prepared from 2,4,6-triisopropylbenzenesulfonamide (71.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (99 mg, 95%) as a colorless solid; mp 118–120 °C; R_f = 0.72 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3182, 2959, 1702, 1456, 1257, 1164, 1070, 881, 697, 662, 561 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.17 (m, 5 H), 7.07 (s, 2 H), 5.59 (d, *J* = 6.9 Hz, 1 H), 5.11 (d, *J* = 6.9 Hz, 1 H), 4.08–3.97 (m, 2 H), 2.90–2.81 (m, 1 H), 1.27–1.12 (m, 18 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 174.3, 153.3, 150.4, 135.1, 132.6, 129.0, 127.4, 123.8, 58.9, 34.3, 30.0, 24.9, 24.9, 23.7, 23.7.

MS (ESI): *m*/*z* calcd for $C_{23}H_{31}NO_4S$: 417.20; found: 416.12 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{31}NO_4SNa$: 440.18660; found: 440.18608.

2-(2-Naphthylsulfonamido)-2-phenylacetic Acid (4d)

Prepared from naphthalene-2-sulfonamide (52.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2) afforded the product (82 mg, 96%) as a colorless solid; mp 160–161 °C; R_f = 0.50 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3282, 1742, 1330, 1153, 738, 695, 630, 562, 491 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.90–8.81 (m, 1 H), 8.35 (s, 1 H), 8.07 (d, *J* = 7.9 Hz, 1 H), 8.00 (t, *J* = 9.0 Hz, 2 H), 7.80–7.75 (m, 1 H), 7.69–7.61 (m, 2 H), 7.34–7.25 (m, 2 H), 7.24–7.13 (m, 3 H), 5.01–4.95 (m, 1 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.0, 138.0, 136.6, 134.1, 131.6, 129.2, 129.0, 128.6, 128.3, 127.9, 127.7, 127.4, 127.3, 127.3, 122.5, 59.6.

MS (ESI): *m*/*z* calcd for $C_{18}H_{15}NO_4S$: 341.07; found: 340.03 $[M - H]^-$.

Analytical data are consistent with the literature.[17]

2-Phenyl-2-[2-(trimethylsilyl)ethylsulfonamido]acetic Acid (4e)

Prepared from 2-(trimethylsilyl)ethanesulfonamide (45.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (62 mg, 78%) as a colorless solid; mp 120–122 °C; R_f = 0.68 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3251, 2958, 1714, 1326, 1173, 1150, 932, 840, 740, 720, 694, 507 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.08 (d, *J* = 9.3 Hz, 1 H), 7.49–7.28 (m, 5 H), 4.98 (d, *J* = 9.2 Hz, 1 H), 2.78–2.67 (m, 2 H), 0.92–0.64 (m, 2 H), –0.09 (s, 9 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.7, 137.7, 128.5, 128.1, 127.6, 59.4, 48.8, 9.8, –2.0.

MS (ESI): *m*/*z* calcd for $C_{13}H_{21}NO_4SSi$: 315.10; found: 314.08 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{21}NO_4SSiNa$: 338.08528; found: 338.08565.

2-(Methylsulfonamido)-2-phenylacetic Acid (4g)

Prepared from methanesulfonamide (24.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2) afforded the product (54 mg, 94%) as a colorless oil; R_f = 0.40 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3247, 2930, 1724, 1313, 1147, 1096, 976, 696, 510 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.34 (m, 5 H), 5.50 (d, *J* = 6.2 Hz, 1 H), 5.28 (d, *J* = 6.4 Hz, 1 H), 2.76 (s, 3 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 173.0, 135.2, 129.3, 129.5, 127.6, 59.3, 42.4.

MS (ESI): *m*/*z* calcd for $C_9H_{11}NO_4S$: 229.04; found: 228.18 $[M - H]^-$.

Analytical data are consistent with the literature.[18]

2-Phenyl-2-(propylsulfonamido)acetic Acid (4h)

Prepared from propane-1-sulfonamide (31.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (61 mg, 95%) as a brown solid; mp 89–90 °C; R_f = 0.41 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3222, 2927, 1731, 1462, 1316, 1137, 1101, 933, 715, 562, 501 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.14 (d, *J* = 9.2 Hz, 1 H), 7.51–7.27 (m, 5 H), 4.99 (d, *J* = 9.0 Hz, 1 H), 2.92–2.76 (m, 2 H), 1.73–1.49 (m, 2 H), 0.83 (t, *J* = 7.4 Hz, 3 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.8, 137.5, 128.6, 128.1, 127.6, 59.3, 54.4, 16.7, 12.6.

MS (ESI): *m*/*z* calcd for $C_{11}H_{15}NO_4S$: 257.07; found: 256.09 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{15}NO_4SNa$: 280.06140; found: 280.06154.

2-(*tert*-Butylsulfonamido)-2-phenylacetic Acid (4i)

Prepared from 2-methylpropane-2-sulfonamide (34.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2) afforded the product (59 mg, 87%) as a colorless solid; mp 155–156 °C; R_f = 0.65 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3201, 2987, 1728, 1465, 1286, 1210, 1173, 1108, 940, 868, 702, 656, 505 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.04 (d, *J* = 9.7 Hz, 1 H), 7.45 (d, *J* = 7.7 Hz, 2 H), 7.39–7.29 (m, 3 H), 4.95 (d, *J* = 9.6 Hz, 1 H), 1.21 (s, 9 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 172.2, 138.1, 128.5, 127.9, 127.4, 60.4, 58.7, 23.7.

MS (ESI): *m*/*z* calcd for $C_{12}H_{17}NO_4S$: 271.09; found: 270.13 $[M - H]^-$.

Analytical data are consistent with the literature.[19]

2-Phenyl-2-(phenylsulfonamido)acetic Acid (4k)

Prepared from benzenesulfonamide (39.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (66 mg, 90%) as a colorless solid; mp 161–162 °C; R_f = 0.57 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3275, 2892, 1711, 1338, 1162, 1085, 789, 723, 688, 607, 576, 526 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.74 (d, *J* = 9.3 Hz, 1 H), 7.73–7.70 (m, 2 H), 7.56–7.52 (m, 1 H), 7.48–7.43 (m, 2 H), 7.28–7.21 (m, 5 H), 4.90 (d, *J* = 9.2 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 170.9, 141.0, 136.5, 132.2, 128.8, 128.4, 127.9, 127.3, 126.5, 59.6.

MS (ESI): *m*/*z* calcd for $C_{14}H_{13}NO_4S$: 291.06; found: 290.10 $[M - H]^-$.

Analytical data is consistent with the literature.[17]

2-(4-Methylphenylsulfonamido)-2-phenylacetic Acid (4l)

Prepared from 4-methylbenzenesulfonamide (43.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2) afforded the product (63 mg, 84%) as a colorless solid; mp 178–180 °C; R_f = 0.69 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3279, 2901, 1709, 1333, 1161, 1090, 918, 811, 693, 590, 528 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.63 (d, *J* = 9.2 Hz, 1 H), 7.61 (d, *J* = 8.3 Hz, 2 H), 7.29–7.23 (m, 7 H), 4.86 (d, *J* = 9.2 Hz, 1 H), 2.33 (s, 3 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.0, 142.5, 138.2, 136.6, 129.3, 128.4, 127.9, 127.3, 126.6, 59.5, 20.9.

MS (ESI): *m*/*z* calcd for $C_{15}H_{15}NO_4S$: 305.07; found: 304.02 $[M - H]^-$.

Analytical data are consistent with the literature.[20]

2-(4-*tert*-Butylphenylsulfonamido)-2-phenylacetic Acid (4m)

Prepared from 4-*tert*-butylbenzenesulfonamide (53.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (71 mg, 81%) as a colorless solid; mp 150–151 °C; R_f = 0.73 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3353, 2960, 1710, 1696, 1343, 1334, 1168, 1111, 1087, 756, 722, 696, 587, 551, 517 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.57 (m, 2 H), 7.36–7.32 (m, 2 H), 7.24–7.16 (m, 5 H), 5.79 (d, *J* = 7.3 Hz, 1 H), 5.09 (d, *J* = 7.3 Hz, 1 H), 1.28 (s, 9 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 173.6, 156.7, 136.8, 134.8, 129.0, 128.9, 127.4, 127.1, 126.0, 59.2, 35.2, 31.2.

MS (ESI): *m*/*z* calcd for $C_{18}H_{21}NO_4S$: 347.12; found: 346.08 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{21}NO_4SNa$: 370.10840; found: 370.10835.

2-(4-Methoxyphenylsulfonamido)-2-phenylacetic Acid (4n)

Prepared from 4-methoxybenzenesulfonamide (44.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 6:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (77 mg, 96%) as a colorless solid; mp 168–169 °C; R_f = 0.45 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3174, 2982, 1714, 1333, 1151, 1090, 1024, 836, 692, 670, 593, 532 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.55 (d, *J* = 9.2 Hz, 1 H), 7.70–7.62 (m, 2 H), 7.30–7.20 (m, 5 H), 7.00–6.95 (m, 2 H), 4.84 (d, *J* = 9.2 Hz, 1 H), 3.79 (s, 3 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.1, 162.0, 136.6, 132.7, 128.7, 128.4, 127.9, 127.3, 114.0, 59.5, 55.6.

MS (ESI): *m*/*z* calcd for $C_{15}H_{15}NO_5S$: 321.07; found: 319.99 $[M - H]^-$.

Analytical data are consistent with the literature.[17]

2-(4-Fluorophenylsulfonamido)-2-phenylacetic Acid (4o)

Prepared from 4-fluorobenzenesulfonamide (44.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (46 mg, 60%) as a colorless solid; mp 174–175 °C; R_f = 0.45 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3268, 1708, 1344, 1168, 1087, 840, 694, 557, 529 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.79 (d, *J* = 9.4 Hz, 1 H), 7.78–7.73 (m, 2 H), 7.31–7.22 (m, 7 H), 4.91 (d, *J* = 9.4 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 170.9, 163.9 (d, *J* = 250.4 Hz), 137.4 (d, *J* = 3.0 Hz), 136.4, 129.6 (d, *J* = 9.5 Hz), 128.4, 128.0, 127.3, 115.9 (d, *J* = 22.7 Hz), 59.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –104.81.

MS (ESI): *m*/*z* calcd for $C_{14}H_{12}FNO_4S$: 309.05; found: 308.05 $[M - H]^-$.

Analytical data are consistent with the literature.[17]

2-(4-Bromophenylsulfonamido)-2-phenylacetic Acid (4p)

Prepared from 4-bromobenzenesulfonamide (59.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (57 mg, 62%) as a colorless solid; mp 183–184 °C; R_f = 0.52 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3077, 1702, 1348, 1167, 1068, 744, 616, 527 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.86 (d, *J* = 9.4 Hz, 1 H), 7.69–7.60 (m, 4 H), 7.2–7.21 (m, 5 H), 4.91 (d, *J* = 9.4 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 170.8, 140.3, 136.3, 131.9, 128.6, 128.4, 128.0, 127.4, 126.1, 59.6.

MS (ESI): *m*/*z* calcd for $C_{14}H_{12}BrNO_4S$: 368.97; found: 367.85 $[M - H]^-$.

Analytical data are consistent with the literature.[21]

2-Phenyl-2-[4-(trifluoromethyl)phenylsulfonamido]acetic Acid (4q)

Prepared from 4-(trifluoromethyl)benzenesulfonamide (56.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (90 mg, 56%) as a colorless solid; mp 194–196 °C; R_f = 0.51 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3255, 2984, 1737, 1326, 1157, 1063, 838, 711, 598 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.02 (d, *J* = 9.4 Hz, 1 H), 7.88 (d, *J* = 8.3 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.26–7.19 (m, 5 H), 4.97 (d, *J* = 9.3 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 208.4, 182.5, 137.8, 169.5 (q, *J* = 32 Hz), 166.0, 165.6, 165.1, 165.0, 163.6 (q, 3.6 Hz), 161.1 (q, *J* = 273 Hz), 158.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –63.24.

MS (ESI): *m*/*z* calcd for $C_{15}H_{12}F_3NO_4S$: 359.04; found: 358.01 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{12}F_3NO_4SNa$: 382.03313; found: 382.03284.

2-(4-Bromophenyl)-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5a)

Prepared from 4-bromphenylboronic acid (100.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2) afforded the product (85 mg, 62%) as a colorless solid; mp 165–167 °C; R_f = 0.57 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3226, 2969, 2929, 1725, 1580, 1486, 1449, 1398, 1368, 1298, 1260, 1209, 1135, 1086, 1006, 897, 850, 816, 789, 735, 641, 613, 558, 536, 503 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.4 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 5.83 (d, *J* = 6.0 Hz, 1 H), 4.96 (d, *J* = 6.1 Hz, 1 H), 2.88 (s, 2 H), 2.44 (s, 3 H), 2.33 (s, 3 H), 2.02 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 173.7, 160.1, 139.6, 134.2, 134.1, 131.7, 129.0, 127.7, 125.3, 122.9, 118.2, 87.1, 58.6, 43.1, 28.7, 28.6 (partial overlap), 19.4, 17.8, 12.5.

MS (ESI): *m*/*z* calcd for $C_{21}H_{24}BrNO_5S$: 481.06; found: 479.81 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{24}BrNO_5SNa$: 504.04508; found: 504.04508.

2-(4-Fluorophenyl)-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5b)

Prepared from 4-fluorophenylboronic acid (70.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2) afforded the product (85 mg, 81%) as a colorless solid; mp 153–155 °C; R_f = 0.58 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 2920, 2850, 1725, 1508, 1456, 1303, 1224, 1158, 1138, 1088, 994, 896, 851, 808, 781, 731, 662, 638, 615, 559, 543, 519, 506, 487 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.11 (m, 2 H), 6.91–6.85 (m, 2 H), 5.64 (d, *J* = 6.1 Hz, 1 H), 5.00 (d, *J* = 6.1 Hz, 1 H), 2.92–2.83 (m, 2 H), 2.48 (s, 3 H), 2.36 (s, 3 H), 2.04 (s, 3 H), 1.46 (s, 6 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 173.1, 162.9 (d, *J* = 248.3 Hz), 160.0, 139.6, 134.2, 130.9 (d, *J* = 3.2 Hz), 129.2 (d, *J* = 8.4 Hz), 127.9, 125.2, 118.2, 115.6 (d, *J* = 21.9 Hz), 87.1, 58.4, 43.2, 28.7, 28.6 (partial overlap), 19.4, 17.8, 12.5.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –114.86.

MS (ESI): *m*/*z* calcd for $C_{21}H_{24}FNO_5S$: 421.14; found: 422.14 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + K]$^+$ calcd for $C_{21}H_{24}FNO_5SK$: 444.12514; found: 444.12564.

2-(4-Methoxyphenyl)-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5c)

Prepared from 4-methoxyphenylboronic acid (76.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2) afforded the product (106 mg, 98%) as a colorless solid; mp 160–162 °C; R_f = 0.58 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3266, 2971, 2932, 1721, 1609, 1576, 1511, 1453, 1410, 1371, 1302, 1249, 1177, 1156, 1136, 1086, 1030, 993, 900, 826, 782, 731, 660, 639, 614, 559, 524, 505 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.15 (d, *J* = 9.4 Hz, 1 H), 7.13–7.09 (m, 2 H), 6.79–6.75 (m, 2 H), 3.69 (s, 3 H), 2.93 (s, 2 H), 2.38 (s, 3 H), 2.36 (s, 3 H), 1.95 (s, 3 H), 1.41 (s, 3 H), 1.40 (s, 3 H).

^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 171.5, 158.8, 158.6, 138.8, 133.3, 129.3, 128.7, 128.4, 124.8, 116.7, 113.4, 86.7, 58.3, 55.1, 42.4, 28.2, 19.2, 17.5, 12.3.

MS (ESI): *m*/*z* calcd for $C_{22}H_{27}NO_6S$: 433.16; found: 431.99 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M]$^{\bullet}$ calcd for $C_{22}H_{27}NO_6S$: 433.15536; found: 433.15445.

2-[4-(Ethoxycarbonyl)phenyl]-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5d)

Prepared from 4-(ethoxycarbonyl)phenylboronic acid (97.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 7:3:0.2 → 1:1:0.2) afforded the product (58 mg, 49%) as a colorless solid; mp 184–186 °C; R_f = 0.49 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3260, 2974, 2927, 1714, 1609, 1576, 1447, 1412, 1368, 1275, 1158, 1136, 1090, 1018, 994, 897, 849, 778, 734, 706, 641, 614, 561, 539, 503 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.3 Hz, 2 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 5.85 (d, *J* = 6.2 Hz, 1 H), 5.04 (d, *J* = 6.2 Hz, 1 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 2.85 (d, *J* = 5.4 Hz, 2 H), 2.44 (s, 3 H), 2.35 (s, 3 H), 1.98 (s, 3 H), 1.43 (s, *J* = 5.2 Hz, 3 H), 1.42 (s, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 173.1, 166.2, 160.1, 140.0, 139.7, 134.2, 130.7, 129.7, 127.6, 127.4, 125.2, 118.2, 87.0, 61.3, 58.9, 43.1, 28.6, 28.6 (partial overlap), 19.4, 17.8, 14.4, 12.5.

MS (ESI): *m*/*z* calcd for $C_{24}H_{29}NO_7S$: 475.17; found: 474.03 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{29}NO_7SNa$: 498.15569; found: 498.15412.

2-(2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)-2-[1-(phenylsulfonyl)-1*H*-indol-2-yl]acetic Acid (5e)

Prepared from 1-(phenylsulfonyl)-1*H*-indol-2-ylboronic acid (151.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 7:3:0.2 → 1:1:0.2) afforded the product (70 mg, 48%) as a colorless solid; mp 123–129 °C; R_f = 0.54 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3267, 2971, 2929, 1724, 1576, 1447, 1370, 1289, 1174, 1126, 1088, 993, 725, 684, 614, 595, 577, 555, 527, 505 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88–7.81 (m, 3 H), 7.55–7.50 (m, 2 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 7.25 (s, 1 H), 7.12 (dd, *J* = 8.6, 1.4 Hz, 1 H), 6.50 (d, *J* = 3.6 Hz, 1 H), 5.81 (d, *J* = 6.7 Hz, 1 H), 5.01 (d, *J* = 6.7 Hz, 1 H), 2.78 (d, *J* = 8.5 Hz, 2 H), 2.38 (s, 3 H), 2.31 (s, 3 H), 1.89 (s, 3 H), 1.41 (d, *J* = 4.4 Hz, 6 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 174.5, 159.9, 139.5, 138.2, 134.7, 134.2, 134.17, 130.8, 130.3, 129.5, 127.8, 127.2, 126.9, 125.2, 123.9, 120.5, 118.1, 113.6, 109.1, 87.0, 59.1, 43.0, 28.6, 28.6 (partial overlap), 19.4, 17.7, 12.4.

MS (ESI): *m*/*z* calcd for $C_{29}H_{30}N_2O_7S_2$: 582.15; found: 580.99 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{30}N_2O_7S_2Na$: 605.13866; found: 605.13800.

2-(2-Chlorophenyl)-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5f)

Prepared from 2-chlorophenylboronic acid (78.2 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2 → 7:3:0.2) afforded the product (93 mg, 85%) as a colorless solid; mp 125–127 °C; R_f = 0.55 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3297, 2972, 2922, 1738, 1573, 1444, 1427, 1416, 1374, 1293, 1238, 1131, 1093, 1038, 1001, 900, 850, 786, 773, 750, 644, 609, 590, 548, 519, 510 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.41 (d, *J* = 9.4 Hz, 1 H), 7.47–7.43 (m, 1 H), 7.31–7.20 (m, 3 H), 5.20 (d, *J* = 9.4 Hz, 1 H), 2.90 (s, 2 H), 2.36 (s, 6 H), 1.90 (s, 3 H), 1.40 (s, 6 H).

^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 170.4, 158.6, 138.8, 135.1, 133.4, 132.3, 129.3, 129.0, 128.9, 128.9, 127.0, 124.8, 116.7, 86.7, 55.2, 42.4, 28.2, 28.2 (partial overlap), 19.2, 17.5, 12.2.

MS (ESI): *m*/*z* calcd for $C_{21}H_{24}ClNO_5S$: 437.11; found: 435.99 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M]$^{\bullet}$ calcd for $C_{21}H_{24}ClNO_5S$: 437.10582; found: 437.10439.

2-(4-Chlorophenyl)-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5g)

Prepared from 4-chlorophenylboronic acid (78.2 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2 → 7:3:0.2) afforded the product (97 mg, 89%) as a colorless solid; mp 167–168 °C; R_f = 0.58 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 2922, 2853, 1729, 1456, 1368, 1331, 1161, 1144, 1111, 1088, 1015, 891, 817, 783, 733, 670, 636, 619, 563, 540, 507, 457 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.5 Hz, 2 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 5.73 (d, *J* = 6.1 Hz, 1 H), 4.99 (d, *J* = 6.1 Hz, 1 H), 2.88 (s, 2 H), 2.46 (s, 3 H), 2.34 (s, 3 H), 2.03 (s, 3 H), 1.50–1.40 (m, 6 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 173.7, 159.9, 139.4, 134.7, 134.1, 133.4, 128.6, 127.7, 125.1, 118.1, 87.0, 58.4, 43.0, 29.7, 28.5, 28.5 (partial overlap), 19.3, 17.7, 12.4.

MS (ESI): *m*/*z* calcd for $C_{21}H_{24}ClNO_5S$: 437.11; found: 438.15 $[M + H]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{24}ClNO_5SNa$: 460.09559; found: 460.09404.

2-(3-Chlorophenyl)-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5h)

Prepared from 3-chlorophenylboronic acid (78.2 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2 → 7:3:0.2) afforded the product (88 mg, 80%) as a colorless solid; mp 124–126 °C; R_f = 0.55 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3223, 3211, 2980, 2923, 2365, 2152, 2015, 1968, 1726, 1581, 1439, 1374, 1299, 1253, 1199, 1142, 1088, 1037, 888, 779, 689, 642, 610, 549, 533, 506, 493 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.18–7.15 (m, 1 H), 7.12 (t, *J* = 7.7 Hz, 1 H), 7.08–7.04 (m, 2 H), 5.85 (d, *J* = 5.9 Hz, 1 H), 4.99 (d, *J* = 5.8 Hz, 1 H), 2.87 (d, *J* = 8.6 Hz, 2 H), 2.45 (s, 3 H), 2.34 (s, 3 H), 2.01 (s, 3 H), 1.45 (s, 6 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 173.4, 160.0, 139.5, 136.9, 134.5, 134.1, 129.7, 128.7, 127.7, 127.5, 125.7, 125.2, 118.3, 87.0, 58.7, 43.1, 28.7, 28.7 (partial overlap), 19.4, 17.8, 12.5.

MS (ESI): *m*/*z* calcd for $C_{21}H_{24}ClNO_5S$: 437.11; found: 436.00 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M]^•$ calcd for $C_{21}H_{24}ClNO_5S$: 437.10582; found: 437.10478.

2-(2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)-2-[3-(trifluoromethyl)phenyl]acetic Acid (5i)

Prepared from 3-(trifluromethyl)phenylboronic acid (95.0 mg, 0.50 mmol, 2.0 equiv) according to GP2 for 64 h instead of 12 h. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2 → 1:1:0.2) afforded the product (33 mg, 61%) as a colorless solid; mp 166–169 °C; R_f = 0.42 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3258, 2966, 2926, 1729, 1576, 1451, 1414, 1375, 1324, 1260, 1160, 1127, 1084, 1026, 905, 874, 852, 797, 730, 699, 656, 613, 560, 524 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.44 (d, *J* = 9.3 Hz, 1 H), 7.59–7.49 (m, 3 H), 7.43 (t, *J* = 7.7 Hz, 1 H), 4.90 (d, *J* = 9.3 Hz, 1 H), 2.87 (s, 2 H), 2.37 (s, 3 H), 2.33 (s, 3 H), 1.90 (s, 3 H), 1.38 (s, 6 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 170.6, 158.6, 138.6, 138.4, 133.1, 131.5, 129.1, 129.0, 128.70 (q, *J* = 31.5 Hz), 124.8, 124.3 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 272 Hz), 123.7 (q, *J* = 3.8 Hz), 116.7, 86.7, 58.5, 42.3, 28.2, 28.2 (partial overlap), 19.1, 17.4, 12.1.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.69.

MS (ESI): *m*/*z* calcd for $C_{22}H_{24}F_3NO_5S$: 471.13; found: 470.00 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M]^•$ calcd for $C_{22}H_{24}F_3NO_5S$: 471.13218; found: 471.13147.

2-(2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)-2-(*o*-tolyl)acetic Acid (5j)

Prepared from *o*-tolylboronic acid (68.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2) afforded the product (91 mg, 87%) as a colorless solid; mp 169–171 °C; R_f = 0.69 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3305, 3262, 2973, 2930, 1717, 1572, 1451, 1410, 1383, 1371, 1327, 1300, 1264, 1233, 1160, 1144, 1125, 1088, 1035, 971, 908, 852, 782, 755, 732, 704, 681, 641, 614, 552, 503 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.22 (d, *J* = 9.3 Hz, 1 H), 7.31–7.27 (m, 1 H), 7.17–7.04 (m, 3 H), 4.90 (d, *J* = 9.3 Hz, 1 H), 2.92 (d, *J* = 15.9 Hz, 2 H), 2.39 (s, 3 H), 2.37 (s, 3 H), 2.11 (s, 3 H), 1.95 (s, 3 H), 1.42 (s, 3 H), 1.41 (s, 3 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.6, 158.6, 138.9, 135.4, 135.4, 133.3, 130.1, 129.2, 127.8, 127.1, 125.9, 124.9, 116.7, 86.8, 54.9, 42.4, 28.2, 28.2 (partial overlap), 19.2, 18.5, 17.5, 12.3.

MS (ESI): *m*/*z* calcd for $C_{22}H_{27}NO_5S$: 417.16; found: 415.98 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M]^•$ calcd for $C_{22}H_{27}NO_5S$: 417.16045; found: 417.16005.

2-(2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)-2-(*p*-tolyl)acetic Acid (5k)

Prepared from *p*-tolylboronic acid (68.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2) afforded the product (94 mg, 90%) as a colorless solid; mp 164–165 °C; R_f = 0.61 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 2975, 1725, 1575, 1512, 1456, 1386, 1297, 1127, 1095, 1075, 894, 851, 811, 783, 725, 641, 547, 495 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.04–6.98 (m, 4 H), 5.63 (d, *J* = 6.8 Hz, 1 H), 4.93 (d, *J* = 6.8 Hz, 1 H), 2.89 (s, 2 H), 2.44 (s, 3 H), 2.39 (s, 3 H), 2.27 (s, 3 H), 2.01 (s, 3 H), 1.46 (s, 6 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 174.6, 159.9, 139.6, 138.7, 134.2, 132.1, 129.3, 128.0, 127.2, 125.1, 118.1, 86.9, 77.2, 58.9, 43.2, 28.6, 21.3, 19.4, 17.8, 12.5.

MS (ESI): *m*/*z* calcd for $C_{22}H_{27}NO_5S$: 417.16; found: 416.21 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + K]^+$ calcd for $C_{22}H_{27}NO_5SK$: 456.12215; found: 456.12275.

2-(Dibenzothiophen-4-yl)-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5l)

Prepared from dibenzothiophen-4-ylboronic acid (114 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2 → 7:3:0.2) afforded the product (115 mg, 90%) as a yellow solid; mp 198–202 °C; R_f = 0.6 (*n*-hexane/acetone 1:1 + 0.2% AcOH).

IR (ATR): 3285, 2971, 2928, 1730, 1573, 1444, 1407, 1370, 1258, 1138, 1093, 785, 609, 559, 540, 505 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.43 (d, *J* = 8.8 Hz, 1 H), 8.34–8.29 (m, 1 H), 8.23 (d, *J* = 7.7 Hz, 1 H), 8.00–7.96 (m, 1 H), 7.54–7.47 (m, 3 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 4.97 (d, *J* = 8.8 Hz, 1 H), 2.77 (d, *J* = 15.3 Hz, 1 H), 2.68 (d, *J* = 15.3 Hz, 1 H), 2.37 (s, 3 H), 2.35 (s, 3 H), 1.79 (s, 3 H), 1.29 (s, 3 H), 1.19 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.4, 158.5, 138.9, 138.1, 138.0, 135.4, 135.0, 133.3, 131.4, 128.7, 127.3, 125.5, 124.8, 124.8, 124.7, 122.7, 122.2, 121.5, 116.7, 86.6, 58.0, 42.2, 28.1, 28.0 (partial overlap), 19.3, 17.6, 12.1.

MS (ESI): *m*/*z* calcd for $C_{27}H_{27}NO_5S_2$: 509.13; found: 507.97 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M]^•$ calcd for $C_{27}H_{27}NO_5S_2$ 509.13252; found: 509.13127.

(*E*)-2-(2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)hept-3-enoic Acid (5n)

Prepared from (*E*)-pent-1-enylboronic acid (50.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 5:1:0.2) afforded the product (68 mg,

69%) as a colorless solid; mp 130 °C; R_f = 0.5 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3275, 2960, 2928, 1708, 1575, 1460, 1456, 1419, 1412, 1371, 1312, 1302, 1283, 1152, 1136, 1114, 1091, 992, 963, 900, 884, 850, 779, 663, 636, 615, 568, 562, 521, 505 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.73–5.66 (m, 1 H), 5.33–5.25 (m, 2 H), 4.42 (t, *J* = 6.7 Hz, 1 H), 2.96 (s, 2 H), 2.54 (s, 3 H), 2.47 (s, 3 H), 2.09 (s, 3 H), 1.93–1.86 (m, 2 H), 1.47 (s, 6 H), 1.31–1.24 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.3, 160.0, 139.7, 136.4, 134.3, 128.3, 125.3, 123.4, 118.2, 87.0, 57.2, 43.3, 34.3, 28.7, 21.9, 19.6, 17.9, 13.7, 12.6.

MS (ESI): *m*/*z* calcd for $C_{20}H_{29}NO_5S$: 395.18; found: 394.10 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + K]^+$ calcd for $C_{20}H_{29}NO_5SK$: 434.13980; found: 434.13884.

(*E*)-5-Chloro-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)pent-3-enoic Acid (5o)

Prepared from (*E*)-3-chloroprop-1-enylboronic acid (60.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 5:1:0.2) afforded the product (90 mg, 90%) as a colorless solid; mp 101 °C; R_f = 0.6 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3219, 2972, 2929, 1727, 1574, 1456, 1370, 1302, 1291, 1263, 1240, 1158, 1136, 1088, 994, 967, 896, 850, 782, 734, 660, 638, 614, 563, 559, 546, 506 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.80 (s, 1 H), 5.92–5.84 (m, 1 H), 5.68 (dd, *J* = 15.2, 6.0 Hz, 1 H), 5.55 (d, *J* = 7.6 Hz, 1 H), 4.51 (t, *J* = 6.5 Hz, 1 H), 3.94 (d, *J* = 6.1 Hz, 2 H), 2.97 (s, 2 H), 2.53 (s, 3 H), 2.46 (s, 3 H), 2.09 (s, 3 H), 1.47 (s, 6 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 174.2, 160.2, 139.8, 134.4, 130.7, 127.6, 127.6, 125.5, 118.4, 87.2, 56.3, 43.4, 43.2, 28.7, 19.6, 17.9, 12.6.

MS (ESI): *m*/*z* calcd for $C_{18}H_{24}ClNO_5S$: 401.10; found: 401.99 $[M + H]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{24}ClNO_5SNa$: 424.09559; found: 424.09483.

(*E*)-2-(2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)-4-phenylbut-3-enoic Acid (5p)

Prepared from (*E*)-styrylboronic acid (74.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2 → 7:3:0.2 → 1:1:0.2) afforded the product (102 mg, 95%) as a colorless solid; mp 135 °C; R_f = 0.61 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3370, 2971, 2929, 1707, 1574, 1449, 1404, 1374, 1331, 1294, 1204, 1138, 1088, 990, 972, 902, 845, 734, 694, 642, 613, 564, 544, 501 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.97 (d, *J* = 8.9 Hz, 1 H), 7.33–7.28 (m, 2 H), 7.27–7.21 (m, 3 H), 6.39 (d, *J* = 15.9 Hz, 1 H), 6.07 (dd, *J* = 15.9, 7.2 Hz, 1 H), 4.34 (t, *J* = 8.0 Hz, 1 H), 2.91 (s, 2 H), 2.46 (s, 3 H), 2.41 (s, 3 H), 1.94 (s, 3 H), 1.37 (s, 6 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.2, 158.6, 138.8, 135.7, 133.3, 132.3, 129.6, 128.7, 128.0, 126.3, 124.9, 123.9, 116.8, 86.7, 57.4, 42.4, 28.2, 28.2 (partial overlap), 19.2, 17.5, 12.3.

MS (ESI): *m*/*z* calcd for $C_{23}H_{27}NO_5S$: 429.16; found: 428.06 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd For $C_{23}H_{27}NO_5SNa$: 452.15021; found: 452.14864.

2-[2-(Allyloxy)phenyl]-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5q)

Prepared from 2-(allyloxy)phenylboronic acid (89.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 4:1:0.2 → 7:3:0.2 → 1:1:0.2) afforded the product (58 mg, 75%) as a colorless solid; mp 128–130 °C; R_f = 0.74 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3267, 2972, 2927, 1722, 1601, 1576, 1492, 1453, 1411, 1370, 1290, 1244, 1157, 1137, 1087, 1016, 993, 930, 903, 849, 781, 751, 732, 660, 640, 614, 560, 533, 504 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.17 (td, *J* = 8.1, 1.6 Hz, 1 H), 6.91 (dd, *J* = 7.4, 1.5 Hz, 1 H), 6.77–6.71 (m, 2 H), 5.93 (ddt, *J* = 17.2, 10.5, 5.2 Hz, 1 H), 5.87 (d, *J* = 7.9 Hz, 1 H), 5.35 (dd, *J* = 17.3, 1.3 Hz, 1 H), 5.25 (dd, *J* = 10.6, 1.2 Hz, 1 H), 5.04 (d, *J* = 7.9 Hz, 1 H), 4.50–4.42 (m, 2 H), 2.86 (d, *J* = 1.8 Hz, 2 H), 2.38 (s, 3 H), 2.37 (s, 3 H), 1.96 (s, 3 H), 1.45 (s, 6 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 174.1, 159.7, 155.4, 139.3, 134.0, 132.3, 130.2, 130.0, 128.3, 125.0, 124.3, 120.9, 118.4, 117.9, 111.8, 86.9, 69.3, 56.7, 43.2, 28.7, 28.7 (partial overlap), 19.3, 17.6, 12.5.

MS (ESI): *m*/*z* calcd for $C_{24}H_{29}NO_6S$: 459.17; found: 458.05 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{29}NO_6SNa$: 482.16078; found: 482.15937.

2-(2,3-Dihydrobenzofuran-5-yl)-2-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)acetic Acid (5r)

Prepared from 2,3-dihydrobenzofuran-5-ylboronic acid (82.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2 → 7:3:0.2) afforded the product (67 mg, 60%) as a yellow solid; mp 179–181 °C; R_f = 0.54 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3235, 2970, 2926, 1728, 1575, 1444, 1410, 1370, 1300, 1239, 1135, 1087, 939, 900, 641, 614, 561, 541, 503 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.03 (d, *J* = 8.9 Hz, 1 H), 6.95 (s, 1 H), 6.91 (dd, *J* = 8.3, 1.5 Hz, 1 H), 6.58 (d, *J* = 8.2 Hz, 1 H), 4.58 (d, *J* = 8.8 Hz, 1 H), 4.46 (t, *J* = 8.7 Hz, 2 H), 3.04 (t, *J* = 8.7 Hz, 2 H), 2.92 (s, 2 H), 2.37 (s, 3 H), 2.35 (s, 3 H), 1.96 (s, 3 H), 1.41 (s, 3 H), 1.40 (s, 3 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.5, 159.2, 158.5, 138.8, 133.3, 129.5, 128.6, 127.1, 127.1, 124.8, 124.0, 116.7, 108.2, 86.8, 71.0, 58.7, 42.4, 28.9, 28.2, 19.2, 17.4, 12.3.

MS (ESI): *m*/*z* calcd for $C_{23}H_{27}NO_6S$: 445.16; found: 444.05 $[M - H]^-$.

HRMS (MALDI): *m*/*z* $[M + K]^+$ calcd for $C_{23}H_{27}NO_6SK$: 484.11907; found: 484.11716.

2-(2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)-2-(2-thienyl)acetic Acid (5s)

Prepared from 2-thienylboronic acid (64.0 mg, 0.50 mmol, 2.0 equiv) according to GP2. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 4:1:0.2 → 7:3:0.2) afforded the product (84 mg, 82%) as a brown solid; mp 156–159 °C; R_f = 0.60 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3286, 2968, 2927, 1726, 1574, 1451, 1409, 1371, 1261, 1137, 1086, 782, 613, 561, 523, 504 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.46 (d, *J* = 9.6 Hz, 1 H), 7.42 (dd, *J* = 5.0, 1.2 Hz, 1 H), 6.95–6.88 (m, 2 H), 4.91 (d, *J* = 9.5 Hz, 1 H), 2.97 (s, 2 H), 2.44 (s, 3 H), 2.39 (s, 3 H), 2.00 (s, 3 H), 1.42 (s, 6 H).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 170.6, 158.7, 139.1, 138.9, 133.5, 129.0, 126.7, 126.2, 126.1, 125.0, 116.8, 86.9, 54.6, 42.4, 28.2, 19.2, 17.5, 12.3.

MS (ESI): *m*/*z* calcd for $C_{19}H_{23}NO_5S_2$: 409.10; found: 407.91 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{23}NO_5S_2Na$: 432.09099; found: 432.08928.

2-(*N*-Methylphenylsulfonamido)-2-phenylacetic Acid (7a)

Prepared from *N*-methylbenzenesulfonamide (60.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2) afforded the product (68 mg, 89%) as a colorless solid; mp 147–150 °C; R_f = 0.53 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3066, 2956, 1717, 1447, 1334, 1238, 1125, 1165, 1088, 972, 916, 820, 691, 608, 577, 545, 512, 469 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.5 Hz, 2 H), 7.63–7.48 (m, 3 H), 7.42–7.34 (m, 3 H), 7.25–7.20 (m, 2 H), 5.91 (s, 1 H), 2.74 (s, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 174.9, 139.2, 133.1, 132.9, 129.2, 129.2, 129.1, 128.9, 127.4, 62.5, 31.0.

MS (ESI): *m*/*z* calcd for $C_{15}H_{15}NO_4S$: 305.07; found: 304.01 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NO_4SNa$: 328.06140; found: 328.06137.

Analytical data are consistent with the literature.[22]

2-(*N*-Benzylphenylsulfonamido)-2-phenylacetic Acid (7b)

Prepared from *N*-benzylbenzenesulfonamide (63.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2) afforded the product (86 mg, 90%) as a colorless solid; mp 193–195 °C; R_f = 0.57 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 2971, 1710, 1436, 1335, 1308, 1165, 1151, 1091, 1033, 951, 928, 827, 730, 688, 670, 591, 574, 554, 523, 454 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77–7.71 (m, 2 H), 7.58–7.51 (m, 1 H), 7.49–7.41 (m, 2 H), 7.30–7.24 (m, 3 H), 7.22–7.15 (m, 2 H), 7.11–7.01 (m, 3 H), 6.90–6.82 (m, 2 H), 5.80 (s, 1 H), 4.63 (d, *J* = 16.1 Hz, 1 H), 4.36 (d, *J* = 16.1 Hz, 1 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 175.0, 140.0, 136.9, 133.0, 132.9, 129.7, 129.3, 129.1, 129.0, 128.2, 128.0, 127.5, 127.2, 63.4, 49.6.

MS (ESI): *m*/*z* calcd for $C_{21}H_{19}NO_4S$: 381.10; found: 380.01 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + K]$^+$ calcd for $C_{21}H_{19}NO_4SK$: 420.06664; found: 420.06630.

2-[*N*-Methyl-4-(trifluoromethyl)phenylsulfonamido]-2-phenylacetic Acid (7c)

Prepared from *N*-methyl-4-(trifluoromethyl)benzenesulfonamide (60.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2) afforded the product (84 mg, 90%) as a colorless solid; mp 167–171 °C; R_f = 0.67 (*n*-hexane/acetone/AcOH 1:1:0.2).

IR (ATR): 3040, 1720, 1364, 1327, 1168, 1158, 1135, 1062, 822, 722, 709, 698, 614, 597 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.2 Hz, 2 H), 7.78 (d, *J* = 8.3 Hz, 2 H), 7.44–7.36 (m, 3 H), 7.26–7.22 (m, 2 H), 5.94 (s, 1 H), 2.75 (s, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 174.5, 142.8, 134.6 (q, *J* = 33.1), 132.5, 129.4, 129.2, 128.9, 127.9, 126.4 (q, *J* = 3.6), 123.4 (q, *J* = 273.0), 62.7, 31.1.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –63.1.

MS (ESI): *m*/*z* calcd for $C_{16}H_{14}F_3NO_4S$: 373.06; found: 371.98 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + K]$^+$ calcd for $C_{16}H_{14}F_3NO_4SK$: 412.02272; found: 412.02261.

N,2,2,4,6,7-Hexamethyl-2,3-dihydrobenzofuran-5-ylsulfonamide (6d)

Prepared from *N*,2,2,4,6,7-hexamethyl-2,3-dihydrobenzofuran-5-sulfonyl chloride and methylamine in THF following the literature.[23] Purification by flash column chromatography (*n*-hexane/acetone/AcOH 6:1:0.2) afforded the product (1.2 g, 72%) as a colorless solid; mp 138 °C; R_f = 0.46 (*n*-hexane/EtOAc 7:3).

IR (ATR): 3316, 2970, 2929, 1571, 1313, 1299, 1281, 1160, 1144, 1119, 1094, 1059, 779, 671, 667, 663, 637, 628, 563, 535, 505, 463 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.36 (s, 1 H), 2.98 (s, 2 H), 2.60 (s, 3 H), 2.54 (s, 3 H), 2.49 (s, 3 H), 2.12 (s, 3 H), 1.48 (s, 6 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 159.9, 139.5, 134.5, 126.9, 125.3, 118.1, 86.9, 43.3, 28.9, 28.7, 19.5, 17.8, 12.7.

MS (ESI): *m*/*z* calcd for $C_{14}H_{21}NO_3S$: 283.12; found: 282.16 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{21}NO_3SNa$: 306.11344; found: 306.11334.

2-(*N*,2,2,4,6,7-Hexamethyl-2,3-dihydrobenzofuran-5-ylsulfonamido)-2-phenylacetic Acid (7d)

Prepared from *N*,2,2,4,6,7-hexamethyl-2,3-dihydrobenzofuran-5-sulfonamide (71.0 mg, 0.25 mmol, 1.0 equiv) according to GP1. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 6:1:0.2) afforded the product (96 mg, 92%) as a colorless solid; mp 147 °C; R_f = 0.53 (*n*-hexane/acetone 1:1 + 0.2% AcOH).

IR (ATR): 2972, 2928, 1722, 1575, 1323, 1134, 1085, 975, 702, 648, 616, 456, 507 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.34 (m, 3 H), 7.27–7.22 (m, 2 H), 5.71 (s, 1 H), 2.99 (s, 2 H), 2.73 (s, 3 H), 2.48 (s, 6 H), 2.12 (s, 3 H), 1.50 (s, 3 H), 1.48 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.2, 160.4, 141.1, 135.8, 133.2, 129.1, 129.0, 129.0 (overlap), 126.2, 125.4, 118.4, 87.2, 61.2, 43.3, 30.2, 28.7, 19.5, 17.7, 12.7.

MS (ESI): *m*/*z* calcd for $C_{22}H_{27}NO_5S$: 417.16; found: 416.02 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + K]$^+$ calcd for $C_{22}H_{27}NO_5SK$: 456.12415; found: 456.12338.

2-[4-Ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)phenylsulfonamido]-2-(4-methoxyphenyl)acetic Acid (8)

Prepared from 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzenesulfonamide[24] (63 mg, 0.25 mmol, 1 equiv) according to GP1 in THF instead of nitromethane. Purification by flash column chromatography (*n*-hexane/acetone/AcOH 9:1:0.2 → 6:1:0.2 → 2:1:0.2 → 1:1:0.2) afforded the product (42 mg, 30%) as a colorless solid; mp 198–202 °C.

IR (ATR): 3400, 2934, 1684, 1586, 1512, 1247, 1151, 1080, 1028, 907, 812, 654, 587 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.00 (s, 1 H), 8.47 (d, *J* = 2.3 Hz, 1 H), 7.68 (dd, *J* = 8.8, 2.3 Hz, 1 H), 7.13 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.9 Hz, 1 H), 6.67 (d, *J* = 8.6 Hz, 2 H), 6.15 (d, *J* = 7.1 Hz, 1 H), 5.11 (d, *J* = 7.5 Hz, 1 H), 4.22 (s, 3 H), 4.20–4.13 (m, 2 H), 3.67 (s, 3 H), 2.87 (t, *J* = 7.6 Hz, 2 H), 1.84–1.75 (m, 2 H), 1.46 (t, *J* = 7.0 Hz, 3 H), 0.99 (t, *J* = 7.4 Hz, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 173.2, 159.9, 159.3, 154.5, 147.1, 146.9, 138.6, 133.2, 131.4, 130.8, 128.7, 127.2, 124.2, 121.1, 114.2, 112.8, 65.9, 59.1, 55.4, 38.4, 27.7, 22.5, 14.5, 14.1.

MS (ESI): *m*/*z* calcd for $C_{26}H_{29}N_5O_7S$: 555.18; found: 554.19 [M – H]$^-$.

HRMS (MALDI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}N_5O_7S$: 556.18605; found: 556.18478.

Funding Information

This work was financially supported by the Fonds der Chemischen Industrie (Liebig Fellowship to G. M.).

Acknowledgment

We thank Prof. Michael Göbel (Goethe-University Frankfurt) for his support and Albemarle (Frankfurt) for the generous donation of chemicals.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610440.

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