Synthesis of a New Class of Highly Functionalised Benzamides by Threefold Sequential Nucleophilic Substitution at a Resin-Bound Polyelectrophile

Marie Grimstrup[a] and Florencio Zaragoza*[a]

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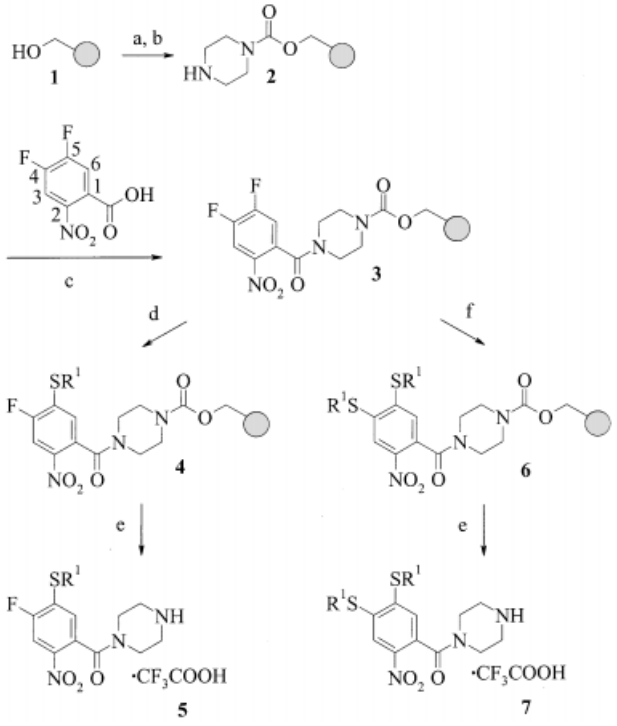
We have developed a solid-phase synthesis of a new class of highly substituted and functionalised benzamides. This synthesis is based on the sequential introduction of three different nucleophiles at a resin-bound 4,5-difluoro-2-nitrobenzamide. After displacement of one fluorine atom by a thiol and oxidation to a sulfone, the remaining fluorine atom and the nitro group could be substituted sequentially by two different, aliphatic amines. In each of the three nucleophilic substitutions it was possible to use unprotected functionalised nucleophiles, giving fast and easy access to libraries of small organic molecules featuring polar functional groups such as hydroxy, amino, and ester groups and various heterocycles.

Introduction

Since the development of high-throughput screening, the limiting factor in drug discovery has been the speed at which new organic compounds could be synthesised. A big challenge today is therefore to develop new multistep syntheses suitable for automation, which permit the production of large libraries of compounds screenable without further purification.[1,2,3] Many combinatorial libraries described in the literature consist of rather lipophilic compounds.[4] Leads from such libraries are often difficult to optimise, because the lipophilicity is likely to increase further during optimisation, and the compounds are thus taken beyond the limits for bioavailability.[4] Many leads have also resulted from screening libraries of peptides or peptidomimetics.[5] Although these compounds are more polar, they are not easy to convert into orally available drugs either, because of their large size. We therefore consider the development of new multistep syntheses enabling the production of large libraries of small organic compounds of high polarity to be of great importance for the drug discovery process, and believe that the optimisation of hits resulting from such libraries should be easier.

Sequential solid-phase nucleophilic substitution[2] would be a good strategy for such a multistep synthesis. Solid-phase reactions are generally suitable for automation,[2,3] and nucleophilic reagents such as thiols, amines, and alcohols are commercially available in large numbers, which is essential if large libraries are to be synthesised in a few steps.[2,3] Furthermore, for the synthesis of libraries in which each compound features a variable set of functional groups, the use of functionalised reagents is necessary. Since there are not many purchasable partially protected polyfunctional nucleophiles, it is also important that the multistep synthesis allows for unprotected, functionalised nucleophiles to be used. This is only possible if the use of elec-



Scheme 1. Attachment of 4,5-difluoro-2-nitrobenzoic acid to Wang resin and the first nucleophilic aromatic substitution: a) 4-nitrophenyl chloroformate (6 equiv.), pyridine (15 equiv.), DCM, 22 °C, 3 h; b) piperazine (12 equiv.), NMP, 22 °C, 12 h; c) 4,5-difluoro-2-nitrobenzoic acid (2.5 equiv.), HOBt (2.5 equiv.), DIC (2.5 equiv.), DIPEA (1 equiv.), DCM, NMP, 22 °C, 2.5 h; d) R^1 = aryl: R^1SH (13 equiv.), AcOH (13 equiv.), NMP, 22 °C, 3 h, R^1 = alkyl: R^1SH (13 equiv.), NMP, 22 °C, 3 h, or R^1 = heteroaryl: R^1SH (7 equiv.), potassium *tert*-pentoxide (2 equiv.), NMP, 22 °C, 3 h; e) TFA, DCM (1:1), 22 °C, 30 min; f) R^1 = aryl: R^1SH (13 equiv.), potassium *tert*-pentoxide (0.5 equiv.), NMP, 22 °C, 2 h; DCM = dichloromethane, NMP = *N*-methyl-2-pyrrolidinone, HOBt = 1-hydroxybenzotriazole, DIC = *N*,*N*′-diisopropylcarbodiimide, DIPEA = diisopropylethylamine, AcOH = acetic acid, TFA = trifluoroacetic acid

[a] Novo Nordisk A/S,
Novo Nordisk Park, 2760 Maaloev, Denmark
Fax: (internat.) + 45/4466-3450
E-mail: flo@novonordisk.com

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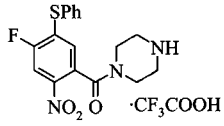
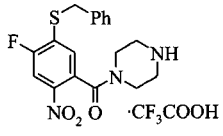
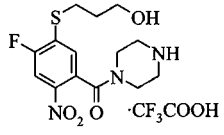
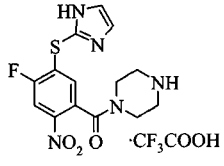
trophilic reagents such as acylating reagents is avoided, as is the case in sequential nucleophilic substitutions.

Previous work has identified electrophilic resin-bound substrates that allow for sequential introduction of two variable nucleophiles.[6] In order to increase the range of compounds available by this elegant methodology further, we searched for a resin-bound polyelectrophile that would allow sequential introduction of up to *three* variable nucleophiles. We considered several commercially available polyelectrophiles,[7] and finally decided to investigate the reactivity of a resin-bound 4,5-difluoro-2-nitrobenzamide, hoping that sequential nucleophilic aromatic substitution of both fluorine atoms and the nitro group would be possible. As far as we know, threefold sequential nucleophilic substitution at a dihalonitrobenzene has never been reported.[8] On the other hand, it is well known that twofold sequential nucleophilic substitution at various isomeric dichloronitrobenzenes is a complex matter, in which the preferred centre of reaction is highly dependent on the pattern of the electrophilic groups and on the nucleophilic reagent employed.[9] Achievement of a third nucleophilic aromatic substitution requires displacement of the nitro group, which is normally only seen when the nitro group is activated by another nitro group in the *ortho* or the *para* position.[10] It has also been reported that a nitro group activated by a sulfonyl group in the *para* position was displaced by piperidine at 200 °C.[11] The search for a way to achieve threefold sequential nucleophilic substitution at a resin-bound 4,5-difluoro-2-nitrobenzamide is therefore a matter of controlling the regiochemistry and achieving displacement of the nitro group without employing too harsh conditions.

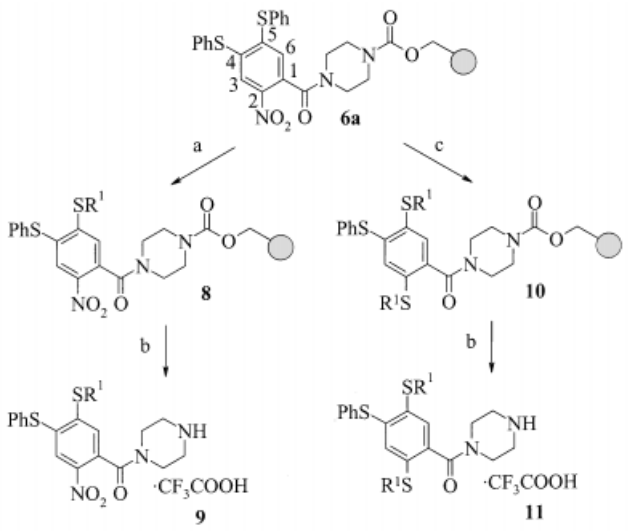
Results and Discussion

Thiols are generally more nucleophilic than amines and alcohols, and so tolerate the greatest number of additional unprotected nucleophilic functionalities (mercapto, amino, and hydroxy groups). Hence, libraries of maximum diversity would become accessible if all three sequential nucleophilic substitutions could be carried out with a range of thiols. In our investigation of the first displacement of a fluorine atom in resin-bound 4,5-difluoro-2-nitrobenzamide **3**[12] with various thiols, we found that treatment of **3** with thiophenols under neutral reaction conditions produced a mixture of the products **5** and **7** (Scheme 1), in which one or two fluorine atoms, respectively, had been substituted. Clean monosubstitution could, however, be attained under slightly acidic conditions, whereas clean disubstitution was achieved under basic conditions. Aliphatic thiols, on the other hand, gave clean monosubstitution under neutral reaction conditions. Finally, heteroaromatic thiols such as 2-mercaptoimidazole displayed remarkably low nucleophilicities and only underwent *S*-arylation in the presence of a strong base. In addition to 2-mercaptoimidazole, other unprotected, functionalised thiols such as 3-mercaptopropanol

Table 1. Yields and purities of compounds **5a−d**

Entry	Compound	LC-MS $[M+H]^+$	HPLC-purity[a] (214 nm/ 254 nm)	Overall yield[b]
5a		362	89%/ 97%	83%
5b		376	92%/ 100%	86%
5c		344	86%/ 100%	81%
5d		352	74%/ 100%	73%

[a] Purity measured by HPLC at 214 nm and 254 nm. − [b] Overall yield determined by ^{1}H NMR using [D_5]DMSO as internal standard and based on the initial loading of Wang resin at 1.07 mmol·g^{-1}



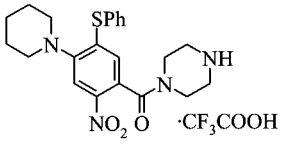
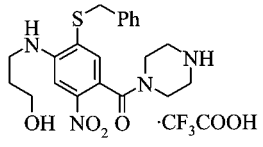
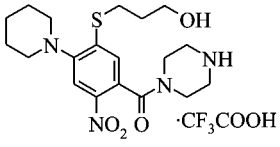
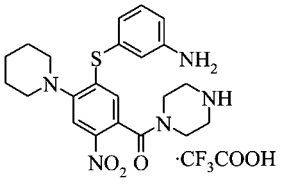
Scheme 2. Investigation of the reactivity of the nitro group: a) R^1 = alkyl: R^1SH (7 equiv.), NMP, 22 °C, 16 h; b) TFA, DCM (1:1), 22 °C, 30 min; c) R^1 = alkyl: R^1SH (7 equiv.), potassium *tert*-pentoxide (2 equiv.), NMP, 22 °C, 16 h

and 3-mercaptoaniline could be used as nucleophiles. After cleavage with TFA, the resulting sulfanylbenzamides **5** were obtained in high yields (Table 1). We also found that the resin-bound 4-fluoro-5-sulfanylbenzamides **4** (Scheme 1) were much more prone to further nucleophilic displacement than the corresponding intermediates obtained by treatment of **3** with amines or alcohols in place of thiols. This was yet another reason for choosing **4** as the substrate for the second nucleophilic substitution.

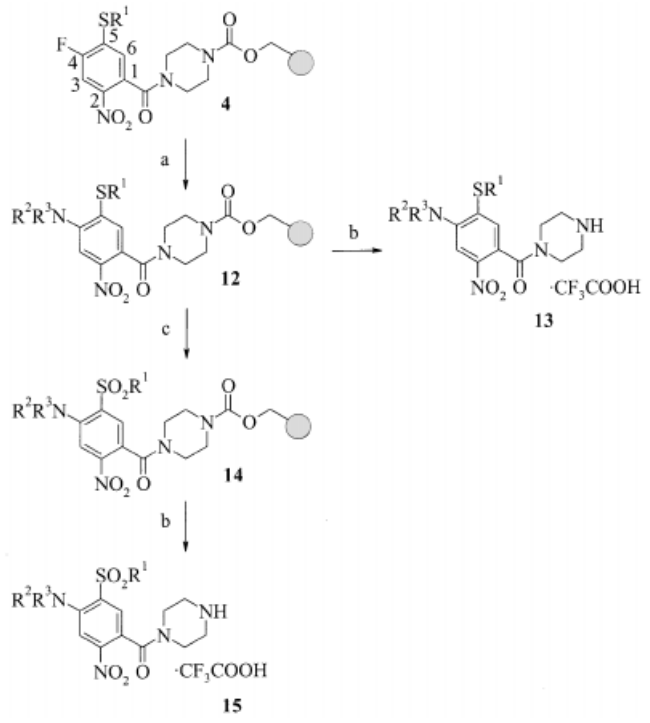
One of the most critical issues in the development of this synthesis was the achievement of a third nucleophilic substitution by displacement of the nitro group. In order to examine the reactivity of the nitro group, we treated resin-bound 2-nitro-4,5-bis(phenylsulfanyl)benzamide **6a** with various aliphatic thiols. Unfortunately, we observed that the sulfanyl group in the 5-position was displaced by the incoming thiol *before* the nitro group was displaced (Scheme 2). These observations indicated that it would probably be difficult to find reaction conditions for the sequential introduction of *three different* thiols and so this goal was abandoned.

Nucleophilic substitution of the fluorine atom in resin-bound 4-fluoro-5-sulfanylbenzamides **4** was achieved by treatment with primary or secondary aliphatic amines in NMP at 100 °C (Scheme 3, Route I). Amines should tolerate the presence of additional nucleophilic functionalities such as amino and hydroxy groups. The resulting resin-bound 4-amino-5-sulfanylbenzamides **12** were treated with TFA to yield aminosulfanylbenzamides **13** in high yields (Table 2).

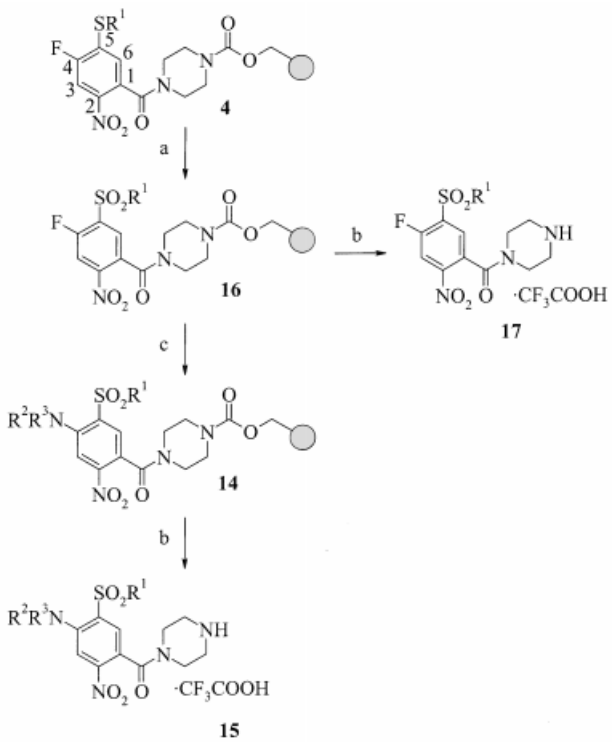
Table 2. Yields and purities of compounds **13a–d**

Entry	Compound	LC-MS $[M+H]^+$	HPLC-purity[a] (214 nm/ 254 nm)	Overall yield[b]
13a		427	91%/ 91%	77%
13b		431	77%/ 84%	76%
13c		409	86%/ 94%	73%
13d		442	86%/ 90%	77%

[a] Purity measured by HPLC at 214 nm and 254 nm. – [b] Overall yield determined by ^1H NMR using [D_5]DMSO as internal standard and based on the initial loading of Wang resin at 1.07 mmol·g^{-1}

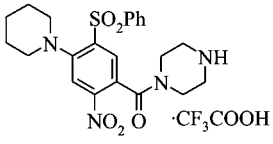
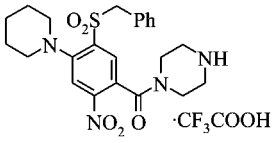


Scheme 3. Route I for a second nucleophilic aromatic substitution: a) R^2R^3NH (2 mol L^{-1}), NMP, 100 °C, 2 × 3 h; b) TFA, DCM (1:1), 22 °C, 30 min; c) *m*-CPBA (0.5 mol L^{-1}), DCM, 22 °C, 2 h; *m*-CPBA = *m*-chloroperoxybenzoic acid



Scheme 4. Route II for a second nucleophilic aromatic substitution: a) *m*-CPBA (0.5 mol L^{-1}), DCM, 22 °C, 2 × 2 h; b) TFA, DCM (1:1), 22 °C; c) R^2R^3NH (0.5 mol L^{-1}), NMP, 22 °C, 2 × 2 h

Table 3. Yields and purities of compounds **15a** and **15b** as obtained by Route I

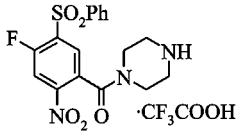
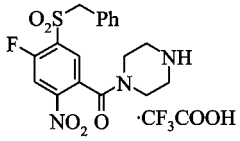
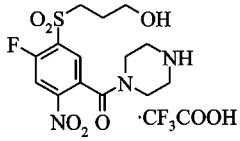
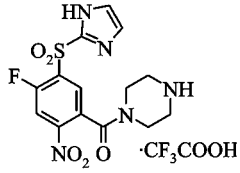
Entry	Compound	LC-MS $[M+H]^+$	HPLC-purity[a] (214 nm/ 254 nm)	Overall yield[b]
15a		459	43%/ 58%	39%
15b		473	49%/ 75%	48%

[a] Purity measured by HPLC at 214 nm and 254 nm. – [b] Overall yield determined by ^1H NMR using $[D_5]$DMSO as internal standard and based on the initial loading of Wang resin at 1.07 mmol·g^{-1}

At this point we tried to displace the nitro group in resin-bound 4-amino-2-nitro-5-sulfanylbenzamides **12** by treatment with various thiolates, amines, or alkoxides in NMP at 120 °C. However, only when aliphatic amines were used could the nitro group be partially substituted. We therefore decided to oxidise the sulfanyl group in **12** to a sulfonyl group (Scheme 3) in order to enhance the reactivity of the nitro group. Oxidation of the sulfanyl group in **12** by treatment with *m*-CPBA unfortunately only gave low yields of the aminosulfonylbenzamides **15** (Table 3). These low yields were probably caused by simultaneous oxidation of the tertiary amine during treatment with *m*-CPBA. We therefore decided to try an alternative route to obtain intermediates **15**.

In the alternative route (Scheme 4. Route II), oxidation of the sulfanyl group in resin-bound 4-fluoro-5-sulfanylbenzamides **4** was carried out by treatment with *m*-CPBA (*before* substitution of the fluorine atom) to yield, after cleavage from the resin, sulfonylbenzamides **17** (Table 4). The oxidations of **4a** to **16a** and of **4b** to **16b** proceeded in

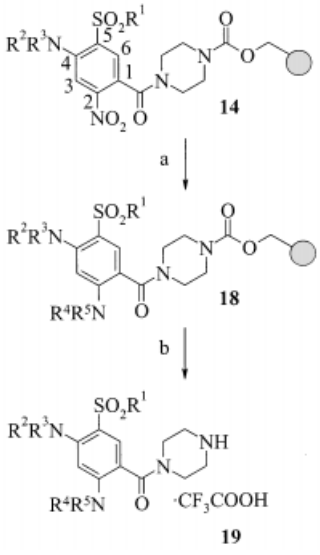
Table 4. Yields and purities of compounds **17a–d**

Entry	Compound	LC-MS $[M+H]^+$	HPLC-purity[a] (214 nm/ 254 nm)	Overall yield[b]
17a		394	97%/ 100%	76%
17b		408	98%/ 100%	72%
17c		376	90%/ 99%	72%
17d		384	88%/ 100%	73%

[a] Purity measured by HPLC at 214 nm and 254 nm. – [b] Overall yield determined by ^{1}H NMR using [D_5]DMSO as internal standard and based on the initial loading of Wang resin at 1.07 mmol·g^{-1}

92% and 84% yields, which were higher than the yields of the oxidations in Route I (51% and 64% yield). Oxidation of the sulfanyl group to a sulfonyl group caused an enhanced reactivity of the fluorine atom in **16** compared to that in **4**, and it could now be displaced by primary or secondary aliphatic amines even at room temperature (Scheme 4). The enhanced reactivity also made it possible to use less reactive amines, such as 4-aminomethylpyridine and glycine methyl ester. Fortunately, no displacement of the sulfonyl group was observed. Route II gave significantly higher yields of the aminosulfonylbenzamides **15** (Table 5) than Route I, and so was preferred for the synthesis of intermediates **15**.

As indicated earlier, we anticipated that treatment of resin-bound 4-amino-2-nitro-5-sulfonylbenzamides **14** with various amines should result in substitution of the nitro group. We were, however, aware that it might be difficult to predict whether the nitro group or the sulfonyl group would be displaced,[9] and also that it might be a problem to obtain complete conversion without using very high temperatures.[11] To our delight, however, treatment of **14** with a 2 M solution of primary or secondary aliphatic amines in NMP at 100 °C resulted in clean substitution of the nitro



Scheme 5. Third nucleophilic aromatic substitution: a) R^4R^5NH (2 mol L^{-1}), NMP, 100 °C, 2 × 3 h; b) TFA, DCM (1:1), 22 °C, 30 min

group, and complete conversion could be obtained by repeating the treatment twice (Scheme 5). The use of unprotected functionalised amines such as 3-aminopropanol and ethylenediamine was also possible in this case. In all cases, after cleavage with TFA, the final diaminosulfonylbenzamides **19** were obtained in high yields and purities (Table 6). To illustrate the high purities of the crude final products, ^{1}H NMR spectra and ^{13}C NMR spectra of both *crude* **19a** and *purified* **19a** are shown in Figure 1.

Conclusion

We have developed a multistep synthesis for a new class of highly substituted and functionalised benzamides[13] by threefold sequential nucleophilic substitution at a resin-bound 4,5-difluoro-2-nitrobenzamide. Suitable reaction conditions for each of the three sequential nucleophilic substitutions were attained through a thorough investigation of

Table 5. Yields and purities of compounds **15a−m** as obtained by Route II

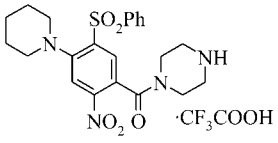
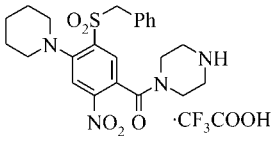
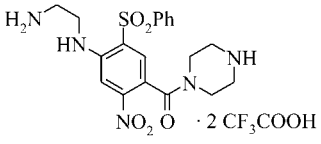
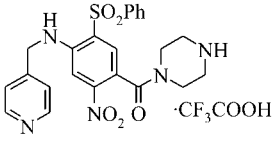
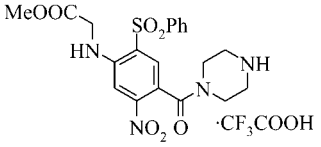
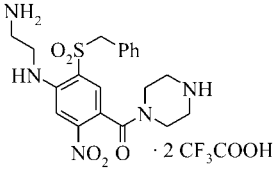
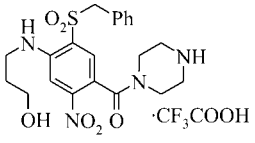
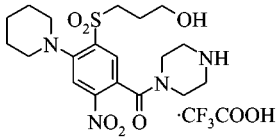
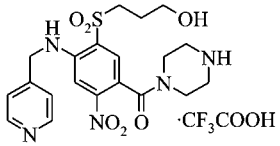
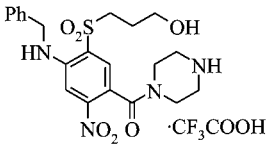
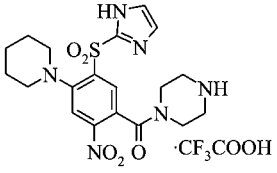
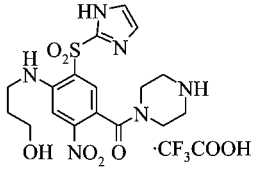
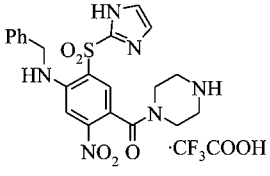
Entry	Compound	LC-MS $[M-H]^+$	HPLC-purity[a] (214 nm/ 254 nm)	Overall yield[b]
15a		459	91%/ 98%	67%
15b		473	92%/ 97%	72%
15c		434	85%/ 91%	67%
15d		482	85%/ 97%	76%
15e		463	84%/ 96%	72%
15f		448	86%/ 84%	63%
15g		463	94%/ 98%	71%

Table 5 *(Continued)*

Entry	Compound	LC-MS $[M-H]^+$	HPLC-purity[a] (214 nm/ 254 nm)	Overall yield[b]
15h		441	83%/ 87%	67%
15i		464	52%/ 55%	70%
15j		463	86%/ 96%	69%
15k		449	98%/ 99%	66%
15l		439	91%/ 94%	71%
15m		471	85%/ 89%	55%

[a] Purity measured by HPLC at 214 nm and 254 nm. – [b] Overall yield determined by ^{1}H NMR using [D_5]DMSO as internal standard and based on the initial loading of Wang resin at 1.07 mmol·g^{-1}

the reactivity of the resin-bound 4,5-difluoro-2-nitrobenzamide. All three nucleophilic substitutions proceeded with high regioselectivity, even when a great excess of the nucleophilic reagent was used. Furthermore displacement of the nitro group was achieved even at 100 °C, and finally, unprotected, functionalised nucleophiles could be used in all three substitutions. The use of unprotected, functionalised nucleophiles allowed fast and easy access to highly diverse molecules featuring structural groups important for protein binding such as hydroxy, amino, and ester groups, and various heterocycles. Since the final products were obtained in high yields and purities, they are ready for screening without further purification.

Our in-house stock of reagents for library production contains 46 thiols and 410 amines that we consider suitable for this synthesis. This means that, in theory, 7.7 million (46

$\times$ 410 $\times$ 410) substituted benzamides are accessible by this methodology, which compares favourably with other reported solid-phase syntheses of small organic molecules.[3,14] According to Teague et al., molecules with clogP[15] < 3 should be more suitable for lead optimisation than more lipophilic compounds.[4] Of compounds **19a** to **19l**, 83% have clogP < 3, and we can therefore conclude that this multistep synthesis should give access to several interesting libraries of small, highly polar molecules, which will hopefully yield more easily optimizable hits for drug discovery.

As a result of our investigations, a new method for the solid-phase synthesis of substituted 2-nitrobenzamides has also been developed. Resin-bound 2-nitrobenzamides such as **12** or **14** might be valuable intermediates in the solid-phase synthesis of various heterocycles, such as 1,4-benzodiazepine-2,5-diones[16] or quinazolin-4-ones,[17] which could be a subject for further investigation.

Table 6. Yields and purities of compounds **19a−l**

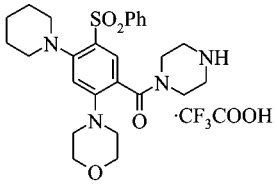
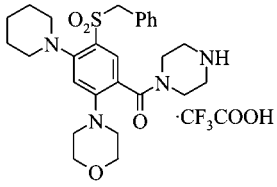
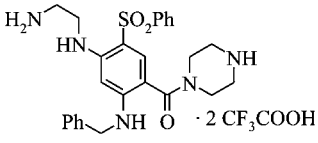
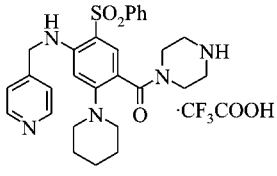
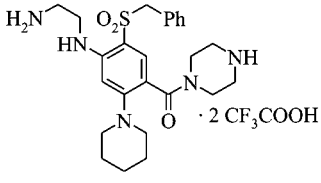
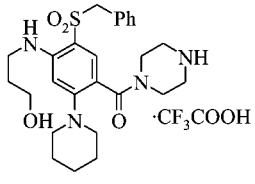
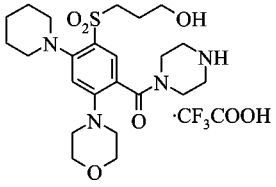
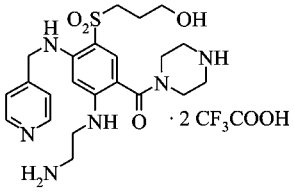
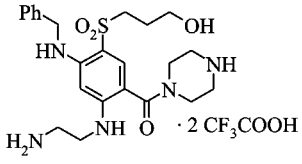
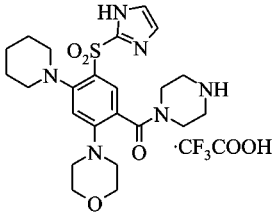
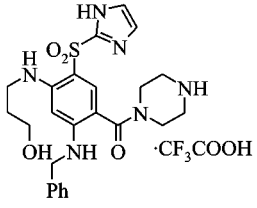
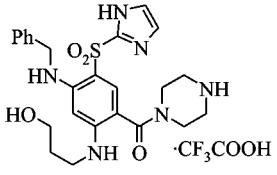
Entry	Compound	LC-MS $[M+H]^+$	HPLC-purity[a] (214 nm/ 254 nm)	Overall yield[b]
19a		499	79%/81%	66%
19b		513	84%/87%	65%
19c		494	64%/62%	46%
19d		520	82%/93%	73%
19e		486	63%/63%	47%
19f		501	82%/86%	65%

Table 6 *(Continued)*

Entry	Compound	LC-MS	[M+H]$^+$	HPLC-purity[a] (214 nm/ 254 nm)	Overall yield[b]
19g			481	79%/85%	65%
19h			477	57%/67%	68%
19i			476	93%/90%	57%
19j			489	84%/88%	61%
19k			499	79%/78%	69%
19l			499	81%/85%	46%

[a] Purity measured by HPLC at 214 nm and 254 nm. – [b] Overall yield determined by ^{1}H NMR using [D$_5$]DMSO as internal standard and based on the initial loading of Wang resin at 1.07 mmol·g^{-1}

Experimental Section

General Remarks: All reagents were used as purchased. *p*-Benzyloxybenzyl alcohol polystyrene resin (Wang resin), 200−400 mesh, loading 1.07 mmol·g^{-1} was obtained from Bachem. – ^{1}H and ^{13}C NMR spectra were recorded with a 300 MHz instrument. Chemical shifts (δ) are reported in ppm relative to residual [D$_5$]DMSO (δ = 2.49 in ^{1}H NMR spectra and δ = 39.50 in ^{13}C NMR spectra) in solvent [D$_6$]DMSO. – At least *one compound* from each class of products (**5**, **13**, **15**, **17**, and **19**) was isolated by recrystallisation and characterised by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, HSQC, LC-MS, HPLC, m.p. and elemental analysis. All other products were characterised by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, HSQC, LC-MS, and HPLC. Since the final products were intended for screening without further purification, we considered the overall yields in the crude products to be highly important. These overall yields were determined by ^{1}H NMR spectroscopy of the crude

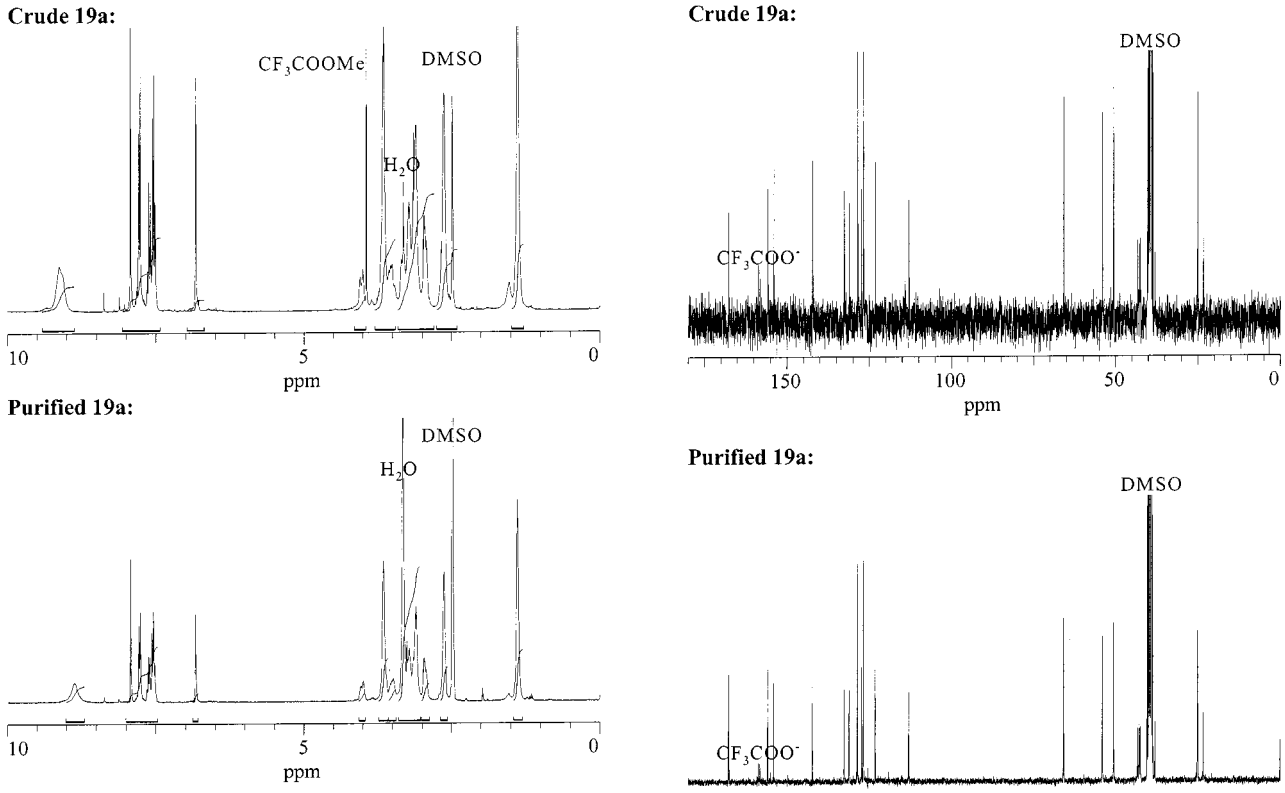


Figure 1. ^{1}H (left) and ^{13}C (right) NMR spectra for crude **19a** and for purified **19a**; the crude products were generally very clean, and the only impurities seen were peaks from H_2O, MeOH, or CF_3COOMe (formed during stripping with MeOH); in the ^{13}C NMR spectra one should expect the two carbon atoms in the trifluoroacetate ion (CF_3COO^-) to give rise to two quartets at $\delta = 159$ ($J = 32.0$ Hz) and $\delta = 117$ ($J = 297$ Hz), but these signals were often very weak, and in many cases it was only possible to recognise two signals at $\delta \approx 159$

products using [D_5]DMSO as internal standard, and based on the theoretical loading of the resin from which the product was cleaved. The theoretical loading of intermediate resins were calculated on the basis of the initial loading of Wang resin at 1.07 mmol·g^{-1}, and assuming complete conversion in the preceding steps. ^{1}H NMR chemical shifts are reported in the Exp. Sect. without assignments. Full listing of both ^{1}H NMR and ^{13}C NMR chemical shifts with subjective assignments, are included as Supporting Information, as are copies of the ^{1}H and ^{13}C NMR spectra. The structure of compound **5b** (Figure 2) was determined by ^{1}H NMR, ^{13}C NMR, HSQC, HMBC, and NOESY: Long-range coupling between C-7 and 6-H was used to determine 6-H. The ^{1}H NMR spectra showed that 6-H was the proton with the smallest coupling to the fluorine atom, which indicated that the fluorine atom was located in the 4-position. The NOE between 2 × 9-H and 6-H finally determined that the sulfanyl group was located in the 5-position. All reactions were performed in 60-mL fritted Teflon reactors mounted on a shaker. In several cases a reaction had to be repeated once to obtain complete conversion; in these cases the resin was washed with the solvent before a new portion of reagent was added. After the final treatment with reagent, the resin was washed with DCM (20 mL), MeOH (20 mL), 10% AcOH in DCM (20 mL), 2-propanol (20 mL), and DCM (2 × 20 mL). The products were cleaved from the resin by treatment with a solution of TFA and DCM (1:1) for 30 min. After cleavage, the filtrate was concentrated, stripped with MeOH, reconcentrated, and dried under reduced pressure.

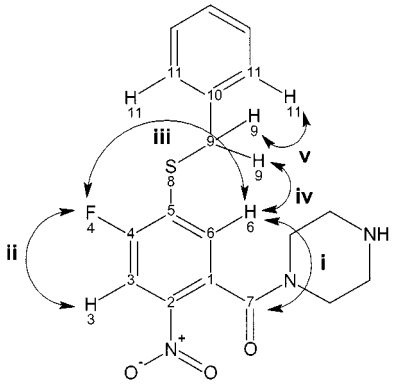


Figure 2. Structure of compound **5b**, determined by NMR: i) the HMBC spectrum showed long-range C−H coupling between C-7 and 6-H; ii) the ^{1}H NMR spectrum showed J(3-H,F) = 9.8 Hz; iii) the ^{1}H NMR spectrum showed J(6-H,F) = 7.2 Hz; iv) the NOESY spectrum showed NOE between 2 × 9-H and 2 × 11-H; v) the NOESY spectrum showed NOE between 2 × 9-H and 6-H

Resin 3: DIC (2.5 mL, 16 mmol) was added to a solution of 4,5-difluoro-2-nitrobenzoic acid (3.3 g, 16 mmol) and HOBt (2.5 g, 16 mmol) in a mixture of DCM (25 mL) and NMP (25 mL), and the mixture was added to resin **2**[12b] (5.9 g, loading 0.96 mmol·g^{-1}, 6.4 mmol). DIPEA (1.1 mL, 6.4 mmol) was added, and the mixture was shaken at 22 °C for 2.5 h.

Resin 4a: Resin **3** (2.0 g, 0.81 mmol·g^{-1}, 1.6 mmol) was treated with a solution of thiophenol (2.0 mL, 20 mmol) and AcOH (1.1 mL, 20 mmol) in NMP (20 mL) for 3 h at 22 °C.

Resins 4b−4c: Resin **3** (2.0 g, 0.81 mmol·g^{-1}, 1.6 mmol) was treated with a solution of aliphatic thiol (20 mmol) in NMP (20 mL) for 3 h at 22 °C.

Resin 4d: Resin **3** (2.0 g, 0.81 mmol·g^{-1}, 1.6 mmol) was treated with a solution of 2-mercaptoimidazole (2.0 g, 10 mmol) and potassium *tert*-pentoxide (1.8 mL of a 1.7 M solution in toluene, 3 mmol) in NMP (20 mL) for 3 h at 22 °C.

4-(4-Fluoro-2-nitro-5-phenylsulfanylbenzoyl)piperazin-1-ium Trifluoroacetate (5a): Cleavage from resin **4a** (501 mg, 0.76 mmol·g^{-1}, 0.38 mmol) followed by precipitation from 2-propanol yielded **5a** (113 mg, 63%) as a yellow solid. − M.p. 212−213 °C. − LC-MS: *m*/*z* = 362 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.93 (br. s, 2 H), 3.14 (br. s, 2 H), 3.37 (br. s, 2 H), 3.74 (br. s, 2 H), 7.15 [d, *J*(H,F) = 7.2 Hz, 1 H, 6-H], 7.43−7.62 (m, 5 H), 8.28 [d, *J*(H,F) = 9.8 Hz, 1 H, 3-H], 9.06 (br. s, 2 H). − $C_{17}H_{16}FN_3O_3S{\cdot}C_2HF_3O_2$ (475.4): calcd. C 48.00, H 3.60, N 8.84; found C 47.68, H 3.75, N 8.81.

4-(5-Benzylsulfanyl-4-fluoro-2-nitrobenzoyl)piperazin-1-ium Trifluoroacetate (5b): Cleavage from resin **4b** (493 mg, 0.75 mmol·g^{-1}, 0.37 mmol) followed by precipitation from hot 2-propanol yielded **5b** (117 mg, 64%) as a yellow solid. − M.p. 203−204 °C. − LC-MS: *m*/*z* = 376 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.87−3.45 (m, 6 H), 3.84 (br. s, 2 H), 4.49 (s, 2 H), 7.23−7.48 (m, 5 H), 7.65 [d, *J*(H,F) = 7.2 Hz, 1 H, 6-H], 8.17 [d, *J*(H,F) = 9.8 Hz, 1 H, 3-H], 9.06 (br. s, 2 H). − $C_{18}H_{18}FN_3O_3S{\cdot}C_2HF_3O_2{\cdot}0.25\ H_2O$ ($C_{20}H_{19.5}F_4N_3O_{5.25}S$, 493.9): calcd. C 48.63, H 3.98, N 8.51; found C 48.66, H 4.09, N 8.65.

4-[4-Fluoro-5-(3-hydroxypropylsulfanyl)-2-nitrobenzoyl]piperazin-1-ium Trifluoroacetate (5c): Cleavage from resin **4c** (89 mg, 0.77 mmol·g^{-1}, 0.068 mmol) yielded **5c** [0.055 mmol (^{1}H NMR), 81%]. − LC-MS: *m*/*z* = 344 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.77 (q, ^4J = 6.5 Hz, 2 H), 2.88−3.57 (m, 10 H), 3.84 (t, ^2J = 4.9 Hz, 2 H), 4.71 (br. s, 1 H), 7.57 [d, *J*(H,F) = 7.2 Hz, 1 H, 6-H], 8.15 [d, *J*(H,F) = 9.8 Hz, 1 H, 3-H], 9.26 (br. s, 2 H).

4-[4-Fluoro-5-(1*H*-imidazol-2-ylsulfanyl)-2-nitrobenzoyl]piperazin-1-ium Trifluoroacetate (5d): Cleavage from resin **4d** (98 mg, 0.76 mmol·g^{-1}, 0.075 mmol) yielded **5d** [0.055 mmol (^{1}H NMR), 73%]. − LC-MS: *m*/*z* = 352 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.00 (br. s, 2 H), 3.17 (br. s, 2 H), 3.41 (br. s, 2 H), 3.80 (br. s, 2 H), 7.24 [d, *J*(H,F) = 7.2 Hz, 1 H, 6-H], 7.49 (s, 2 H), 8.30 [d, *J*(H,F) = 9.4 Hz, 1 H, 3-H], 9.32 (br. s, 2 H).

Resin 12a−12c: Resin **4a−4c** (0.5 g, 0.76 mmol·g^{-1}, 0.38 mmol) was treated twice with a solution of amine (40 mmol) in NMP (20 mL) for 3 h at 100 °C.

Resin 12d: Resin **3** (0.5 g, 0.81 mmol·g^{-1}, 0.41 mmol) was treated with a solution of 3-mercaptoaniline (2.2 mL, 20 mmol) and AcOH (2.2 mL, 40 mmol) in NMP (20 mL) for 3 h, washed according to the standard procedure, and finally treated twice with a solution of piperidine (4.0 mL, 40 mmol) in NMP (20 mL) for 3 h at 100 °C.

4-(2-Nitro-5-phenylsulfanyl-4-piperidin-1-ylbenzoyl)piperazin-1-ium Trifluoroacetate (13a): Cleavage from resin **12a** (394 mg, 0.72 mmol·g^{-1}, 0.28 mmol) followed by crystallisation from hot MeOH yielded **13a** (99 mg, 64%) as yellow crystals. − M.p. 213 °C. − LC-MS: *m*/*z* = 427 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.50−1.75 (m, 6 H), 2.87 (br. s, 2 H), 2.97−3.12 (m, 6 H), 3.33 (br. s, 2 H), 3.69 (br. s, 2 H), 6.59 (s, 1 H, 6-H), 7.48−7.60 (m, 5 H), 7.80 (s, 1 H, 3-H), 8.91 (br. s, 2 H). − $C_{22}H_{26}N_4O_3S{\cdot}C_2HF_3O_2$ (540.6): calcd. C 53.33, H 5.03, N 10.36; found C 53.65, H 5.13, N 10.39.

4-[4-(3-Hydroxypropylamino)-2-nitro-5-phenylsulfanylbenzoyl]-piperazin-1-ium Trifluoroacetate (13b): Cleavage from resin **12b** (164 mg, 0.72 mmol·g^{-1}, 0.118 mmol) yielded **13b** [0.090 mmol (^{1}H NMR), 76%]. − LC-MS: *m*/*z* = 431 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.73 (q, ^4J = 6.2 Hz, 2 H), 2.91−3.57 (m, 10 H), 3.76 (br. s, 2 H), 4.22 (s, 2 H), 4.70 (br. s, 1 H), 6.09 (t, ^2J = 5.5 Hz, 1 H), 7.16−7.32 (m, 7 H), 9.25 (br. s, 2 H).

4-[5-(3-Hydroxypropylsulfanyl)-2-nitro-4-piperidin-1-ylbenzoyl]-piperazin-1-ium Trifluoroacetate (13c): Cleavage from resin **12c** (129 mg, 0.73 mmol·g^{-1}, 0.094 mmol) and washing of the precipitate with EtOAc yielded **13c** (36 mg, 72%) as a yellow solid. − M.p. 208−209 °C. − LC-MS: *m*/*z* = 409 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.47−1.70 (m, 6 H), 1.77 (q, ^4J = 6.7 Hz, 2 H), 2.86−3.57 (m, 14 H), 3.82 (br. s, 2 H), 4.69 (br. s, 1 H), 7.28 (s, 1 H, 6-H), 7.72 (s, 1 H, 3-H), 8.96 (br. s, 2 H). − $C_{19}H_{28}N_4O_4S{\cdot}C_2HF_3O_2{\cdot}0.5\ H_2O$ ($C_{21}H_{30}F_3N_4O_{6.5}S$, 531.5): calcd. C 47.45, H 5.69, N 10.54; found C 47.51, H 5.57, N 10.32.

4-[5-(3-Aminophenylsulfanyl)-2-nitro-4-piperidin-1-yl-benzoyl]-piperazin-1-ium Trifluoroacetate (13d): Cleavage from resin **12d** (270 mg, 0.71 mmol·g^{-1}, 0.19 mmol) followed by precipitation from a mixture of heptane and EtOAc yielded **13d** (58 mg, 54%) as a yellow solid. − M.p. 202−203 °C. − LC-MS: *m*/*z* = 442 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.56 (br. s, 2 H), 1.68 (br. s, 4 H), 2.77−3.45 (m, 10 H), 3.71 (br. s, 2 H), 5.40 (br. s, 2 H), 6.59−6.75 (m, 4 H), 7.11 (t, ^2J = 7.9 Hz, 1 H), 7.77 (s, 1 H, 3-H), 8.94 (br. s, 2 H). − $C_{22}H_{27}N_5O_3S{\cdot}C_2HF_3O_2$ (555.6): calcd. C 51.89, H 5.08, N 12.61; found C 51.69, H 5.11, N 12.39.

Resin 16a−16d: Resin **4a−4d** (1.5 g, 0.76 mmol·g^{-1}, 1.14 mmol) was treated twice with a solution of *m*-CPBA (2.5 g, 70%, 10 mmol) in DCM (20 mL) for 2 h at 22 °C.

4-(5-Benzenesulfonyl-4-fluoro-2-nitrobenzoyl)piperazin-1-ium Trifluoroacetate (17a): Cleavage from resin **16a** (179 mg, 0.71 mmol·g^{-1}, 0.13 mmol) followed by precipitation from MeOH yielded **17a** (35 mg, 52%) as an off-white solid. − M.p. 224−225 °C. − LC-MS: *m*/*z* = 394 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.07 (br. s, 2 H), 3.26 (br. s, 2 H), 3.49 (br. s, 2 H), 3.85 (t, ^2J = 5.1 Hz, 2 H), 7.66−7.86 (m, 3 H), 8.01 (d, *J* = 8.3 Hz, 2 H), 8.40 [d, *J*(H,F) = 2.3 Hz, 1 H, 3-H], 8.42 (s, 1 H, 6-H), 9.25 (br. s, 2 H). − $C_{17}H_{16}FN_3O_5S{\cdot}C_2HF_3O_2$ (507.4): calcd. C 44.97, H 3.38, N 8.28; found C 45.05, H 3.50, N 8.32.

4-(4-Fluoro-2-nitro-5-phenylmethanesulfonylbenzoyl)piperazin-1-ium Trifluoroacetate (17b): Cleavage from resin **16b** (196 mg, 0.73 mmol·g^{-1}, 0.14 mmol) followed by precipitation from MeOH yielded **17b** (54 mg, 71%) as a light brown solid. − M.p. 205−207 °C. − LC-MS: *m*/*z* = 408 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.98 (br. s, 2 H), 3.24 (br. s, 4 H), 3.77 (br. s, 2 H), 4.91 (s, 2 H), 7.12−7.42 (m, 5 H), 7.87 [d, *J*(H,F) = 6.8 Hz, 1 H, 6-H], 8.53 [d, *J*(H,F) = 9.4 Hz, 1 H, 3-H], 9.22 (br. s, 2 H). − $C_{18}H_{18}FN_3O_5S{\cdot}C_2HF_3O_2{\cdot}0.5\ H_2O$ ($C_{20}H_{20}F_4N_3O_{7.5}S$, 530.4): calcd. C 45.29, H 3.80, N 7.92; found C 45.25, H 3.93, N 8.00.

4-[4-Fluoro-5-(3-hydroxypropane-1-sulfonyl)-2-nitrobenzoyl]-piperazin-1-ium Trifluoroacetate (17c): Cleavage from resin **16c** (116 mg, 0.75 mmol·g^{-1}, 0.087 mmol) yielded **17c** [0.063 mmol (^{1}H NMR), 72%]. − LC-MS: *m*/*z* = 376 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.76 (q, ^4J = 6.8 Hz, 2 H), 3.06 (br. s, 2 H), 3.24

(br. s, 2 H), 3.39−3.60 (m, 6 H), 3.83 (br. s, 2 H), 4.45 (br. s, 1 H), 8.17 [d, *J*(H,F) = 6.4 Hz, 1 H, 6-H], 8.53 [d, *J*(H,F) = 9.4 Hz, 1 H, 3-H], 9.21 (br. s, 2 H).

4-[4-Fluoro-5-(1*H*-imidazol-2-sulfonyl)-2-nitrobenzoyl]piperazin-1-ium Trifluoroacetate (17d): Cleavage from resin **16d** (108 mg, 0.74 mmol·g^{-1}, 0.080 mmol) yielded **17d** [0.058 mmol (^{1}H NMR), 73%]. − LC-MS: *m*/*z* = 384 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.07 (br. s, 2 H), 3.26 (br. s, 2 H), 3.47 (br. s, 2 H), 3.84 (br. s, 2 H), 7.43 (br. s, 2 H), 8.38 [d, *J*(H,F) = 6.8 Hz, 1 H, 6-H], 8.44 [d, *J*(H,F) = 9.8 Hz, 1 H, 3-H], 9.19 (br. s, 2 H).

Resin 14a−14m: Resin **16a−16d** (1.0 g, 0.74 mmol·g^{-1}, 0.74 mmol) was treated twice with a solution of amine (10 mmol) in NMP (20 mL) for 2 h at 22 °C.

4-(5-Benzenesulfonyl-2-nitro-4-piperidin-1-yl-benzoyl)piperazin-1-ium Trifluoroacetate (15a): Cleavage from resin **14a** (145 mg, 0.71 mmol·g^{-1}, 0.102 mmol) yielded **15a** [0.069 mmol (^{1}H NMR), 67%]. − LC-MS: *m*/*z* = 459 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.40 (br. s, 6 H), 2.68 (br. s, 4 H), 3.11 (br. s, 2 H), 3.26 (br. s, 2 H), 3.55 (br. s, 2 H), 3.86 (br. s, 2 H), 7.56−7.87 (m, 5 H), 8.12 (s, 1 H, 3-H), 8.38 (s, 1 H, 6-H), 9.22 (br. s, 2 H).

4-(2-Nitro-5-phenylmethanesulfonyl-4-piperidin-1-ylbenzoyl)-piperazin-1-ium Trifluoroacetate (15b): Cleavage from resin **14b** (203 mg, 0.70 mmol·g^{-1}, 0.14 mmol) followed by precipitation from MeOH yielded **15b** (50 mg, 58%) as a light yellow solid. − M.p. 137−138 °C. − LC-MS: *m*/*z* = 473 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.61 (br. s, 2 H), 1.78 (br. s, 4 H), 2.95 (br. s, 2 H), 3.05−3.27 (m, 8 H), 3.76 (br. s, 2 H), 4.98 (s, 2 H), 7.07−7.15 (m, 2 H), 7.24−7.34 (m, 3 H), 7.79 (s, 1 H, 3-H), 8.21 (s, 1 H, 6-H), 9.15 (br. s, 2 H). − $C_{23}H_{28}N_4O_5S{\cdot}C_2HF_3O_2{\cdot}H_2O$ (604.6): calcd. C 49.67, H 5.17, N 9.27; found C 49.61, H 5.20, N 8.87.

4-[4-(2-Ammonioethylamino)-5-benzenesulfonyl-2-nitrobenzoyl]-piperazin-1-ium Bis(trifluoroacetate) (15c): Cleavage from resin **14c** (136 mg, 0.72 mmol·g^{-1}, 0.098 mmol) yielded **15c** [0.066 mmol (^{1}H NMR), 67%]. − LC-MS: *m*/*z* = 434 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.91 (br. s, 2 H), 3.02−3.27 (m, 4 H), 3.43−3.66 (m, 4 H), 3.80 (br. s, 2 H), 7.19 (t, ^2J = 6.2 Hz, 1 H, NH), 7.50 (s, 1 H, 3-H), 7.58−7.79 (m, 3 H), 8.03 (br. s, 3 H), 8.07 (s, 1 H, 6-H), 8.06−8.14 (m, 2 H), 9.34 (br. s, 2 H).

4-(5-Benzenesulfonyl-2-nitro-4-(pyridin-4-ylmethyl)aminobenzoyl)-piperazin-1-ium Trifluoroacetate (15d): Cleavage from resin **14d** (141 mg, 0.68 mmol·g^{-1}, 0.096 mmol) yielded **15d** [0.073 mmol (^{1}H NMR), 76%]. − LC-MS: *m*/*z* = 434 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.00−3.26 (m, 4 H), 3.52 (br. s, 2 H), 3.79 (br. s, 2 H), 4.86 (d, *J* = 6.0 Hz, 2 H), 7.27 (s, 1 H, 3-H), 7.47 (d, *J* = 6.4 Hz, 2 H), 7.59−7.84 (m, 4 H), 8.13 (s, 1 H, 6-H), 8.15 (d, *J* = 7.5 Hz, 2 H), 8.68 (d, H, H) = 6.4 Hz, 2 H), 9.26 (br. s, 2 H).

4-[5-Benzenesulfonyl-4-(methoxycarbonylmethylamino)-2-nitrobenzoyl]piperazin-1-ium Trifluoroacetate (15e): Cleavage from resin **14e** (153 mg, 0.70 mmol·g^{-1}, 0.108 mmol) yielded **15e** [0.078 mmol (^{1}H NMR), 72%]. − LC-MS: *m*/*z* = 463 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.10 (br. s, 2 H), 3.20 (br. s, 2 H), 3.53 (br. s, 2 H), 3.67 (s, 3 H), 3.80 (br. s, 2 H), 4.28 (d, *J* = 5.7 Hz, 2 H), 7.33 (t, ^2J = 5.7 Hz, 1 H), 7.39 (s, 1 H, 3-H), 7.63 (t, ^2J = 8.1 Hz, 2 H), 7.75 (t, ^2J = 7.3 Hz, 1 H), 8.07 (d, *J* = 7.5 Hz, 2 H), 8.08 (s, 1 H, 6-H), 9.22 (br. s, 2 H).

4-[4-(2-Ammonioethylamino)-2-nitro-5-phenylmethanesulfonyl-benzoyl]piperazin-1-ium Bis(trifluoroacetate) (15f): Cleavage from resin **14f** (157 mg, 0.71 mmol·g^{-1}, 0.112 mmol) yielded **15f** (0.071 mmol (^{1}H NMR), 63%). − LC-MS: *m*/*z* = 448 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.90−3.26 (m, 8 H), 3.61 (d, *J* = 6.0 Hz, 2 H), 3.72 (br. s, 2 H), 4.77 (s, 2 H), 7.00 (t, ^2J = 6.0 Hz, 1 H), 7.14−7.20 (m, 2 H), 7.24−7.34 (m, 3 H), 7.37 (s, 1 H, 3-H), 7.57 (s, 1 H, 6-H), 8.09 (br. s, 3 H), 9.32 (br. s, 2 H).

4-[4-(3-Hydroxypropylamino)-2-nitro-5-phenylmethanesulfonyl-benzoyl]piperazin-1-ium Trifluoroacetate (15g): Cleavage from resin **14g** (123 mg, 0.70 mmol·g^{-1}, 0.086 mmol) yielded **15g** (0.062 mmol (^{1}H NMR), 71%). − LC-MS: *m*/*z* = 463 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.74 (q, ^4J = 6.2 Hz, 2 H), 2.91−3.28 (m, 6 H), 3.34 (q, ^3J = 5.8 Hz, 2 H), 3.52 (t, ^2J = 6.2 Hz, 2 H), 3.71 (br. s, 2 H), 4.73 (s, 2 H), 6.88 (t, ^2J = 5.3 Hz, 1 H), 7.11−7.20 (m, 2 H), 7.25−7.34 (m, 3 H), 7.37 (s, 1 H, 3-H), 7.46 (s, 1 H, 6-H), 9.17 (br. s, 2 H).

4-[5-(3-Hydroxypropane-1-sulfonyl)-2-nitro-4-piperidin-1-yl-benzoyl]piperazin-1-ium Trifluoroacetate (15h): Cleavage from resin **14h** (148 mg, 0.71 mmol·g^{-1}, 0.106 mmol) yielded **15h** [0.070 mmol (^{1}H NMR), 67%]. − LC-MS: *m*/*z* = 441 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.48−1.62 (m, 4 H), 1.68 (br. s, 4 H), 2.92−3.13 (m, 6 H), 3.25 (br. s, 2 H), 3.41 (t, ^2J = 6.0 Hz, 2 H), 3.48 (br. s, 2 H), 3.72−3.87 (m, 4 H), 4.97 (br. s, 1 H), 8.07 (s, 1 H, 6-H), 8.21 (s, 1 H, 3-H), 9.20 (br. s, 2 H).

4-[5-(3-Hydroxypropane-1-sulfonyl)-2-nitro-4-(pyridin-4-ylmethyl)-aminobenzoyl]piperazin-1-ium Trifluoroacetate (15i): Cleavage from resin **14i** (159 mg, 0.70 mmol·g^{-1}, 0.112 mmol) yielded **15i** [0.079 mmol (^{1}H NMR), 70%]. − LC-MS: *m*/*z* = 464 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.73 (q, ^4J = 6.8 Hz, 2 H), 2.96−3.30 (m, 4 H), 3.39−3.62 (m, 6 H), 3.77 (br. s, 2 H), 4.86 (d, *J* = 5.3 Hz, 2 H), 7.32 (s, 1 H, 3-H), 7.61 (t, ^2J = 6.0 Hz, 1 H), 7.73 (d, *J* = 5.7 Hz, 2 H), 7.83 (s, 1 H, 6-H), 8.74 (d, *J* = 5.7 Hz, 2 H), 9.26 (br. s, 2 H).

4-[4-Benzylamino-5-(3-hydroxypropane-1-sulfonyl)-2-nitrobenzoyl]-piperazin-1-ium Trifluoroacetate (15j): Cleavage from resin **14j** (131 mg, 0.70 mmol·g^{-1}, 0.092 mmol) yielded **15j** [0.064 mmol (^{1}H NMR), 69%]. − LC-MS: *m*/*z* = 463 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.65−1.77 (m, 2 H), 2.98−3.27 (m, 4 H), 3.36−3.60 (m, 6 H), 3.76 (br. s, 2 H), 4.61 (d, *J* = 5.7 Hz, 2 H), 7.23−7.31 (m, 1 H), 7.31−7.42 (m, 5 H), 7.47 (t, ^2J = 5.8 Hz, 1 H), 7.79 (s, 1 H, 6-H), 9.17 (br. s, 2 H).

4-[5-(1*H*-Imidazole-2-sulfonyl)-2-nitro-4-piperidin-1-ylbenzoyl]-piperazin-1-ium Trifluoroacetate (15k): Cleavage from resin **14k** (151 mg, 0.71 mmol·g^{-1}, 0.107 mmol) yielded **15k** [0.071 mmol (^{1}H NMR), 66%]. − LC-MS: *m*/*z* = 449 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.37 (br. s, 6 H), 2.68 (br. s, 4 H), 3.11 (br. s, 2 H), 3.25 (br. s, 2 H), 3.52 (br. s, 2 H), 3.85 (br. s, 2 H), 7.29 (br. s, 2 H), 8.13 (s, 1 H, 3-H), 8.32 (s, 1 H, 6-H), 9.18 (br. s, 2 H).

4-[4-(3-Hydroxypropylamino)-5-(1H-imidazole-2-sulfonyl)-2-nitrobenzoyl]piperazin-1-ium Trifluoroacetate (15l): Cleavage from resin **14l** (159 mg, 0.72 mmol·g^{-1}, 0.114 mmol) yielded **15l** [0.081 mmol (^{1}H NMR), 71%]. − LC-MS: *m*/*z* = 439 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.71 (q, ^4J = 6.4 Hz, 2 H), 2.97−3.26 (m, 4 H), 3.36 (q, ^3J = 6.4 Hz, 2 H), 3.47 (t, ^2J = 6.0 Hz, 2 H), 3.79 (br. s, 4 H), 6.92 (t, ^2J = 5.5 Hz, 1 H), 7.40 (br. s, 2 H), 7.45 (s, 1 H, 3-H), 7.89 (s, 1 H, 6-H), 9.19 (br. s, 2 H).

4-[4-Benzylamino-5-(1H-imidazole-2-sulfonyl)-2-nitrobenzoyl]-piperazin-1-ium Trifluoroacetate (15m): Cleavage from resin **14m** (115 mg, 0.70 mmol·g^{-1}, 0.080 mmol) yielded **15m** [0.044 mmol (^{1}H NMR), 55%]. − LC-MS: *m*/*z* = 471 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.06 (br. s, 2 H), 3.18 (br. s, 2 H), 3.52 (br. s, 2 H), 3.78 (br. s, 2 H), 4.62 (d, *J* = 5.7 Hz, 2 H), 7.20−7.35 (m, 5

H), 7.37 (s, 1 H, 3-H), 7.41−7.50 (m, 3 H), 7.93 (s, 1 H, 6-H), 9.11 (br. s, 2 H).

Resin 18a−18l: Resin **14a−14m** (0.5 g, ca. 0.35 mmol) was treated twice with a solution of amine (40 mmol) in NMP (20 mL) for 3 h at 100 °C.

4-(5-Benzenesulfonyl-2-morpholin-4-yl-4-piperidin-1-ylbenzoyl)-piperazinium-1-ium Trifluoroacetate (19a): Cleavage from resin **18a** (230 mg, 0.69 mmol·g^{-1}, 0.16 mmol) followed by precipitation from a mixture of heptane and EtOAc yielded **19a** (60 mg, 61%) as an off-white solid. − M.p. 202−203 °C. − LC-MS: *m*/*z* = 499 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.39 (br. s, 6 H), 2.63 (br. s, 4 H), 2.96 (br. s, 2 H), 3.03−3.40 (m, 7 H), 3.52 (br. s, 1 H), 3.66 (br. s, 5 H), 4.03 (br. s, 1 H), 6.84 (s, 1 H, 3-H), 7.50−7.67 (m, 3 H), 7.78 (d, *J* = 7.2 Hz, 2 H), 7.93 (s, 1 H, 6-H), 8.87 (br. s, 2 H). − $C_{26}H_{34}N_4O_4S{\cdot}C_2HF_3O_2{\cdot}0.5\ H_2O$ ($C_{28}H_{36}F_3N_4O_{6.5}S$, 621.7): calcd. C 54.10, H 5.84, N 9.01; found C 54.15, H 5.56, N 9.04.

4-(2-Morpholin-4-yl-5-phenylmethanesulfonyl-4-piperidin-1-yl-benzoyl)piperazin-1-ium Trifluoroacetate (19b): Cleavage from resin **18b** (160 mg, 0.68 mmol·g^{-1}, 0.109 mmol) yielded **19b** [0.071 mmol (^{1}H NMR), 65%]. − LC-MS: *m*/*z* = 513 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.59 (br. s, 2 H), 1.74 (br. s, 4 H), 2.82 (br. s, 1 H), 2.89−3.23 (m, 12 H), 3.35 (br. s, 1 H), 3.55 (br. s, 1 H), 3.68 (br. s, 4 H), 3.98 (br. s, 1 H), 4.68 (d, *J* = 13.2 Hz, 1 H), 4.96 (d, *J* = 13.2 Hz, 1 H), 6.94 (s, 1 H, 3-H), 7.01−7.10 (m, 2 H), 7.18−7.28 (m, 3 H), 7.34 (s, 1 H, 6-H), 9.08 (br. s, 2 H).

4-[4-(2-Ammonioethylamino)-5-benzenesulfonyl-2-benzylamino-benzoyl]piperazin-1-ium Bis(trifluoroacetate) (19c): Cleavage from resin **18c** (165 mg, 0.69 mmol·g^{-1}, 0.113 mmol) yielded **19c** [0.052 mmol (^{1}H NMR), 46%]. − LC-MS: *m*/*z* = 494 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.71 (br. s, 2 H), 3.19 (br. s, 4 H), 3.34−3.42 (m, 2 H), 3.64 (br. s, 4 H), 4.39 (s, 2 H), 5.69 (s, 1 H, 3-H), 6.63 (t, *J* = 5.8 Hz, 1 H), 6.92 (br. s, 1 H), 7.18−7.38 (m, 5 H), 7.50−7.66 (m, 4 H), 7.90 (d, *J* = 6.8 Hz, 2 H), 8.03 (br. s, 3 H), 9.31 (br. s, 2 H).

4-[5-Benzenesulfonyl-2-piperidin-1-yl-4-(pyridin-4-ylmethyl)-aminobenzoyl]piperazin-1-ium Trifluoroacetate (19d): Cleavage from resin **18d** (164 mg, 0.68 mmol·g^{-1}, 0.111 mmol) yielded **19d** [0.081 mmol (^{1}H NMR), 73%]. − LC-MS: *m*/*z* = 520 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.45 (br. s, 6 H), 2.74 (br. s, 2 H), 2.87 (br. s, 2 H), 3.02 (br. s, 2 H), 3.18 (br. s, 3 H), 3.46 (br. s, 2 H), 4.10 (br. s, 1 H), 4.74 (d, *J* = 5.7 Hz, 2 H), 5.84 (s, 1 H, 3-H), 7.19 (t, ^2J = 6.0 Hz, 1 H), 7.54 (d, *J* = 6.4 Hz, 2 H), 7.58−7.76 (m, 4 H, 6-H), 8.02 (d, *J* = 7.2 Hz, 2 H), 8.70 (d, *J* = 6.4 Hz, 2 H), 9.21 (br. s, 2 H).

4-[4-(2-Ammonioethylamino)-5-phenylmethanesulfonyl-2-piperidin-1-yl-benzoyl]piperazin-1-ium Bis(trifluoroacetate) (19e): Cleavage from resin **18e** (154 mg, 0.69 mmol·g^{-1}, 0.107 mmol) yielded **19e** [0.050 mmol (^{1}H NMR), 47%]. − LC-MS: *m*/*z* = 486 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.54 (br. s, 6 H), 2.73−3.62 (m, 15 H), 4.01 (br. s, 1 H), 4.54 (m, 2 H), 6.16 (s, 1 H, 3-H), 6.43 (t, ^2J = 5.7 Hz, 1 H), 7.06 (s, 1 H, 6-H), 7.08−7.19 (m, 2 H), 7.20−7.35 (m, 3 H), 8.11 (br. s, 3 H), 9.24 (br. s, 2 H).

4-[4-(3-Hydroxypropylamino)-5-phenylmethanesulfonyl-2-piperidin-1-ylbenzoyl]piperazin-1-ium Trifluoroacetate (19f): Cleavage from resin **18f** (170 mg, 0.68 mmol·g^{-1}, 0.116 mmol) yielded **19f** [0.076 mmol (^{1}H NMR), 65%]. − LC-MS: *m*/*z* = 501 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.54 (br. s, 6 H), 1.69 (q, ^4J = 6.2 Hz, 2 H), 2.77−3.27 (m, 10 H), 3.28−3.57 (m, 5 H), 4.02 (br. s, 1 H), 4.49 (s, 2 H), 4.71 (br. s, 1 H), 6.13 (s, 1 H, 3-H), 6.30 (t, ^2J = 5.1 Hz, 1 H), 7.07 (s, 1 H, 6-H), 7.08−7.15 (m, 2 H), 7.21−7.32 (m, 3 H), 9.14 (br. s, 2 H).

4-[5-(3-Hydroxypropane-1-sulfonyl)-2-morpholin-4-yl-4-piperidin-1-ylbenzoyl]piperazin-1-ium Trifluoroacetate (19g): Cleavage from resin **18g** (143 mg, 0.69 mmol·g^{-1}, 0.099 mmol) yielded **19g** [0.065 mmol (^{1}H NMR), 65%]. − LC-MS: *m*/*z* = 481 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.53 (br. m, 4 H), 1.64 (br. s, 4 H), 2.85−3.33 (br. m, 13 H), 3.37 (t, ^2J = 6.0 Hz, 2 H), 3.45−3.78 (br. m, 8 H), 4.01 (br. d, *J* = 14.3 Hz, 1 H), 5.00 (br. s, 1 H), 6.94 (s, 1 H, 3-H), 7.65 (s, 1 H, 6-H), 9.11 (br. s, 2 H).

4-[2-(2-Ammonioethylamino)-5-(3-hydroxypropane-1-sulfonyl)-4-(pyridin-4-ylmethylamino)benzoyl]piperazin-1-ium Bis(trifluoroacetate) (19h): Cleavage from resin **18h** (130 mg, 0.70 mmol·g^{-1}, 0.091 mmol) yielded **19h** [0.062 mmol (^{1}H NMR), 68%]. − LC-MS: *m*/*z* = 477 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.67 (q, ^4J = 6.9 Hz, 2 H), 2.76 (br. s, 2 H), 3.14 (br. s, 4 H), 3.22−3.36 (m, 4 H), 3.43 (t, ^2J = 6.0 Hz, 2 H), 3.60 (br. s, 4 H), 4.75 (d, *J* = 5.7 Hz, 2 H), 5.68 (s, 1 H, 3-H), 6.16 (br. s, 1 H), 6.36 (br. s, 1 H), 7.10 (t, ^2J = 6.0 Hz, 1 H), 7.35 (s, 1 H, 6-H), 7.75 (d, *J* = 6.0 Hz, 2 H), 8.00 (br. s, 3 H), 8.73 (d, *J* = 6.0 Hz, 2 H), 9.25 (br. s, 2 H).

4-[2-(2-Ammonioethylamino)-4-benzylamino-5-(3-hydroxypropane-1-sulfonyl)benzoyl]piperazin-1-ium Bis(trifluoroacetate) (19i): Cleavage from resin **18i** (154 mg, 0.70 mmol·g^{-1}, 0.108 mmol) yielded **19i** [0.062 mmol (^{1}H NMR), 57%]. − LC-MS: *m*/*z* = 476 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.68 (m, 2 H), 2.80 (t, ^2J = 6.4 Hz, 2 H), 3.13 (br. s, 4 H), 3.17−3.22 (m, 2 H), 3.31−3.45 (m, 4 H), 3.61 (br. s, 4 H), 4.47 (d, *J* = 5.3 Hz, 2 H), 4.69 (br. s, 1 H), 5.82 (s, 1 H, 3-H), 6.38 (t, ^2J = 5.8 Hz, 1 H), 6.87 (t, ^2J = 5.7 Hz, 1 H), 7.21−7.45 (m, 6 H), 8.42 (br. s, 5 H).

4-[5-(1*H*-Imidazole-2-sulfonyl)-2-morpholin-4-yl-4-piperidin-1-yl-benzoyl]piperazin-1-ium Trifluoroacetate (19j): Cleavage from resin **18j** (146 mg, 0.69 mmol·g^{-1}, 0.101 mmol) yielded **19j** [0.062 mmol (^{1}H NMR), 61%]. − LC-MS: *m*/*z* = 489 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.34 (br. s, 6 H), 2.53−2.73 (br. m, 4 H), 2.90−3.01 (br. m, 2 H), 3.04−3.27 (br. m, 6 H), 3.33−3.41 (br. m, 1 H), 3.49−3.76 (br. m, 6 H), 3.96−4.09 (br. m, 1 H), 6.89 (s, 1 H, 3-H), 7.20 (br. s, 2 H), 7.86 (s, 1 H, 6-H), 9.08 (br. s, 2 H).

4-[2-Benzylamino-4-(3-hydroxypropylamino)-5-(1*H*-imidazole-2-sulfonyl)benzoyl]piperazin-1-ium Trifluoroacetate (19k): Cleavage from resin **18k** (159 mg, 0.69 mmol·g^{-1}, 0.109 mmol) yielded **19k** [0.076 mmol (^{1}H NMR), 69%]. − LC-MS: *m*/*z* = 499 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.48 (q, ^4J = 6.2 Hz, 2 H), 3.02 (t, ^2J = 6.2 Hz, 2 H), 3.17 (br. s, 4 H), 3.37 (t, ^2J = 6.0 Hz, 2 H), 3.67 (br. s, 4 H), 4.38 (s, 2 H), 5.62 (s, 1 H, 3-H), 6.36 (br. s, 1 H), 6.98 (br. s, 1 H), 7.19−7.35 (m, 7 H), 7.50 (s, 1 H, 6-H), 9.17 (br. s, 2 H).

4-[4-Benzylamino-2-(3-hydroxypropylamino)-5-(1*H*-imidazole-2-sulfonyl)benzoyl]piperazin-1-ium Trifluoroacetate (19l): Cleavage from resin **18l** (169 mg, 0.69 mmol·g^{-1}, 0.116 mmol) yielded **19l** [0.053 mmol (^{1}H NMR), 46%]. − LC-MS: *m*/*z* = 499 [M + H$^+$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.45 (q, ^4J = 6.2 Hz, 2 H), 2.97−3.06 (m, 2 H), 3.13 (br. s, 4 H), 3.37 (t, ^2J = 5.5 Hz, 2 H), 3.60 (br. s, 4 H), 4.45 (d, *J* = 5.3 Hz, 2 H), 4.60 (br. s, 1 H), 5.85 (s, 1 H, 3-H), 6.39 (d, *J* = 5.5 Hz, 1 H), 7.00 (t, ^2J = 5.8 Hz, 1 H), 7.17−7.35 (m, 7 H), 7.50 (s, 1 H, 6-H), 9.13 (br. s, 2 H).

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