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# Parallel synthesis of structurally diverse aminobenzimidazole tethered sultams and benzothiazepinones

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ABSTRACT

A solid-phase methodology to construct aminobenzimidazole tethered sultams and benzothiazepinones from commercial amino acids, amines, carboxylic acids, and sulfonyl chlorides is described. Coupling of Fmoc-Cys(Trt)-OH to resin-bound aminobenzimidazole scaffold provided an essential precursor for the construction of a variety of seven membered benzofused cyclic sulfonamides and thiazepinones via palladium catalyzed Buchwald–Hartwig type intramolecular cyclization.



## Introduction

Solid phase organic synthesis (SPOS) is a valuable tool for the expedited parallel synthesis of structurally diverse compounds of drug discovery interest.[1–7] Continuing with our long standing interest in the development of heterocyclic libraries utilizing resin-bound peptidyl-,[5–7] and heterocyclic scaffolds[7–9] as starting materials, we describe an efficient methodology for the parallel synthesis of structurally diverse aminobenzimidazole tethered sultams and benzothiazepinones. Sultams or cyclic sulfonamides are useful structural motifs in heterocyclic synthesis,[4] applied as chiral auxiliaries in asymmetric synthesis,[10] and are actively sought in the areas of antimalarial,[11] antiviral,[12] anticancer,[13] antimicrobial,[14] and antileukemic research.[15,16] Likewise, aminobenzimidazole is a recurring template in the design and for the development of combinatorial libraries of drugs and drug-like molecules.[17,18]

We previously reported the application of resin-bound aminobenzimidazoles as a template for the synthesis of a variety of fused and/or tethered heterocyclic compounds such as tetracyclic benzimidazoles,[8b] triazino-benzimidazoles,[8c] branched thiohydantoin benzimidazolinethiones,[9] and aminobenzimidazole tethered hydantoins, thiohydantoins,[19] and thiazoles.[20] In this Letter, we extend the application of this practical methodology toward the synthesis of aminobenzimidazole tethered sultams and benzothiazepinones.

Our retrosynthetic rationale for the synthesis of aminobenzimidazole derived cyclic sulfonamides is illustrated in Scheme 1. We envisioned the construction of benzofused cyclic sulfonamides **1** from the resin-bound free amine **2** via palladium catalyzed cyclization.[21]

The parallel synthesis of the desired sulfonamides was pursued using the tea-bag approach, wherein the resin is packed within sealed polypropylene mesh packets.[22] The synthesis of diversified resin-bound aminobenzimidazoles **3** via nucleophilic substitution of 4-fluoro-3-nitrobenzoic acid was carried out according to the literature precendents.[8b,c,9,19,20] The resin-bound aminobenzimidazole was later coupled to Fmoc-Cys(Trt)-OH **4** in the presence of PyBOP. Following Fmoc deprotection, the generated free amine **2**[19,20] was treated with 2-bromoarylsulfonyl chlorides to furnish the intermediate sulfonamides which, upon trityl group deprotection generated a thiol **5**. The treatment of resin-bound sulfonamides in the presence of $Cs_2CO_3$ and palladium led the following intramolecular cyclization in a Buchwald–Hartwig fashion to the resin-bound sultams **6**.[7,23,24] Additional third position of diversity ($R_3$) was introduced by the treatment of sultams with several aryl and alkyl halides **7** (Scheme 2). Following cleavage of the resin with anhydrous HF, the desired cyclic sultams **1**[25] were isolated in reasonable yields (Table 1).

On the basis of this result, we decided to extend the application of this protocol toward the synthesis of benzothiazepinones (Scheme 3) **8**. The reaction of the cysteine coupled to resin-bound aminobenzimidazole **2** with substituted 2-chlorobenzoic acids in the presence of DIC/HOBT, followed by cleavage of the trityl group

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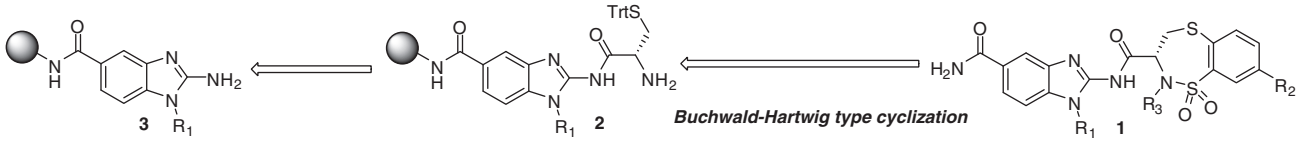
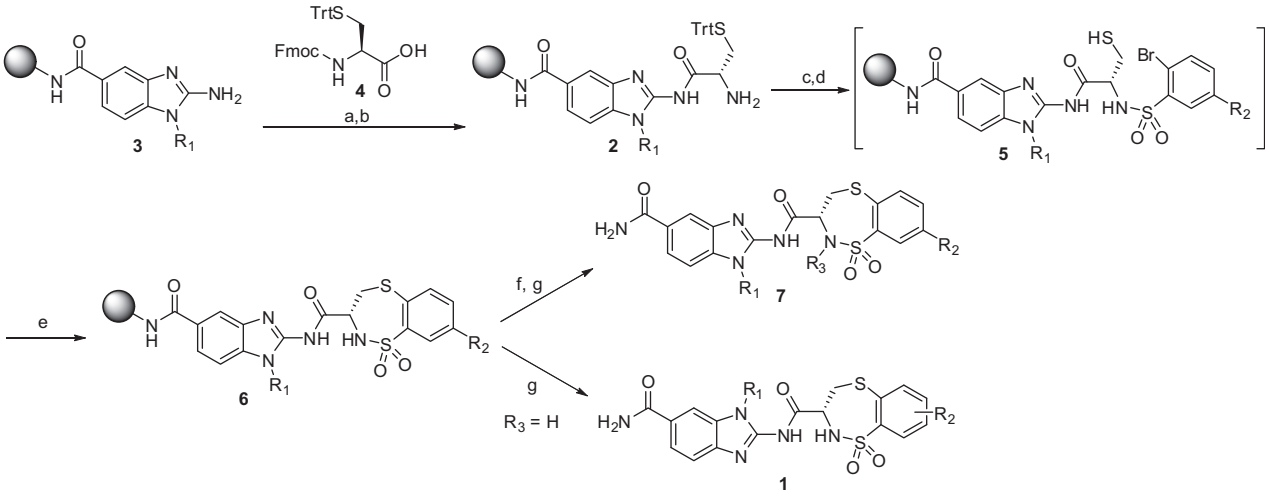
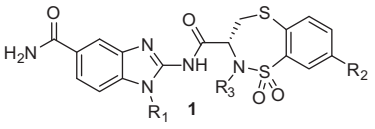



**Scheme 1.** Retrosynthetic illustration of aminobenzimidazole tethered sultams.




**Scheme 2.** (a) PyBOP (8 equiv, 0.5 M anhyd. DMF), HOBt (8 equiv), DIEA (8 equiv), 12 h, rt; (b) 20% piperidine/DMF, 15 min (2×), rt; (c) DIEA (10 equiv), $R_2SO_2Cl$ (10 equiv) 12 h, rt; (d) 6% TFA/DCM (1% TIPS), 15 min (2×); (e) $Cs_2CO_3$ (10 equiv), $Pd(PPh_3)_4$ (0.2 equiv), (±)-BINAP (0.4 equiv), anhydrous DMF, 100 °C, 16 h; (f) $R_3I$, DIEA (8 equiv, in 0.2 M DMF); (g) HF, anisole (99:5), 0 °C, 90 min.

**Table 1**



| Entry | Ri | $R_2$ | $R_3$ | Mass calcd./found | Yield[a] (%) |
|---|---|---|---|---|---|
| 1a | Cyclopentyl | H | H | 485.6/486.4 ($MH^+$) | 44 |
| 1b | *n*-Butyl | H | H | 473.5/474.3 ($MH^+$) | 47 |
| 1c | *i*-Butyl | H | H | 473.5/474.4 ($MH^+$) | 53 |
| 1d | Cyclohexanemethyl | H | H | 513.6/514.5 ($MH^+$) | 42 |
| 1e | 3-(trifluoromethyl)benzyl | H | H | 575.6/576.5 ($MH^+$) | 56 |
| 1f | Cyclopentyl | $CF_3$ | H | 553.6/554.5 ($MH^+$) | 22 |
| 19 | *n*-Butyl | $CF_3$ | H | 541.5/542.4 ($MH^+$) | 24 |
| 1h | *i*-Butyl | $CF_3$ | H | 541.5/542.4 ($MH^+$) | 18 |
| 1i | Cyclohexanemethyl | $CF_3$ | H | 581.6/582.4 ($MH^+$) | 25 |
| 1j | 3-(trifluoromethyl)benzyl | $CF_3$ | H | 643.6/644.4 ($MH^+$) | 15 |
| 1k | *i*-Butyl | H | 4-OMe-Bn | 593.7/594.5 ($MH^+$) | 16 |
| 11 | *i*-Butyl | $CF_3$ | 4-OMe-Bn | 661.7/662.5 ($MH^+$) | 18 |
| 1m | *n*-Butyl | H | Bn | 563.7/564.6 ($MH^+$) | 32 |
| 1n | *n*-Butyl | $CF_3$ | Bn | 631.7/632.5 ($MH^+$) | 36 |
| 1o | 3-(trifluoromethyl)benzyl | H | Et | 603.6/604.5 ($MH^+$) | 23 |
| 1p | 3-(trifluoromethyl)benzyl | $CF_3$ | Et | 671.6/672.5 ($MH^+$) | 12 |

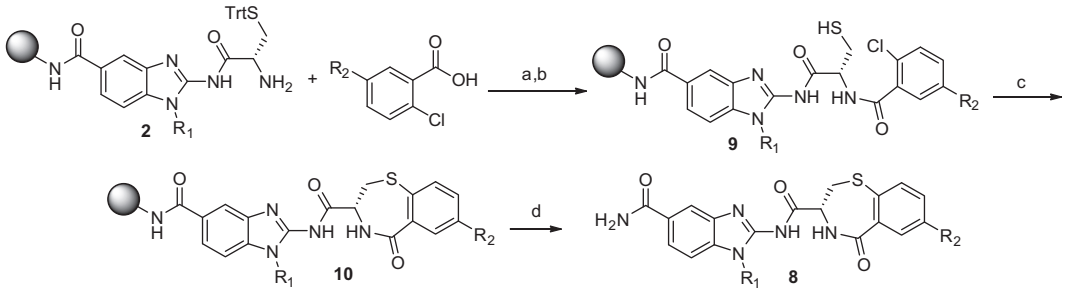
Isolated yields of aminobenzimidazole tethered sultams: The products were run on a Vydac column, gradients 5–95% formic acid in ACN in 7 min.

[a] The yields are based on the weight of purified products and are relative to the initial loading of the resin.

generated the intermediate thiol which under Buchwald–Hartwig type conditions proceeded smoothly to yield the resin-bound thiazepinones **10**. Finally, the desired benzothiazepinones **8** were obtained in moderate yields after cleavage of the resin using anhydrous HF (Scheme 3).[26] The results are summarized in Table 2. All these above synthesized products were confirmed by LC-MS and NMR spectroscopy. The incorporated heterocyclic core in the final products, is a useful pharmacophore prevalent in many bioactive compounds endowed with an array of pharmacological properties.[27,28]

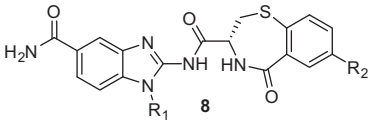
## Conclusions

In conclusion, we have developed a multistep solid-phase strategy for the parallel synthesis of aminobenzimidazole tethered sultams and benzothiazepinones via palladium-catalyzed




**Scheme 3.** Reagents and conditions: (a) DIC (8 equiv, 0.5 M anhyd. DMF), HOBt (8 equiv), 8 h, rt; (b) 6% TFA/DCM (1% TIPS), 15 min (2×); (c) $Cs_2CO_3$ (10 equiv), $Pd(PPh_3)_4$ (0.2 equiv), (±)-BINAP (0.4 equiv), anhydrous DMF, 100 °C, 16 h; (d) HF, anisole (99:5), 0 °C, 90 min.

**Table 2**



8

| Entry | | $R_2$ | Mass Calcd./Found | Yield[a] (%) |
|---|---|---|---|---|
| 8a | Cyclopentyl | H | 449.6/452.0 ($MH^+$) | 32 |
| 8b | *n*-Butyl | H | 437.5/440.0 ($MH^+$) | 43 |
| 8c | *i*-Butyl | H | 437.6/440.1 ($MH^+$) | 60 |
| 8d | Cyclohexanemethyl | H | 477.6/480.0 ($MH^+$) | 51 |
| 8e | 3-(trifluoromethyl)benzyl | H | 539.6/542.0 ($MH^+$) | 53 |
| 8f | Cyclopentyl | Cl | 484.2/486.0 ($MH^+$) | 16 |
| 8g | *n*-Butyl | Cl | 472.1/474.0 ($MH^+$) | 38 |
| 8h | *i*-Butyl | Cl | 472.2/474.0 ($MH^+$) | 11 |
| 8i | Cyclohexanemethyl | Cl | 512.1/514.0 ($MH^+$) | 18 |
| 8j | 3-(trifluoromethyl)benzyl | Cl | 574.2/576.0 ($MH^+$) | 34 |

Isolated yields of aminobenzimidazole tethered thiazepinones. The products were run on a Vydac column, gradients 5 to 95% formic acid in ACN in 7 min.

[a] The yields are based on the weight of purified products and are relative to the initial loading of the resin.

Buchwald–Hartwig type coupling/cyclization.[25,26] This methodology provided a convenient pathway for the assembly of two useful seven-membered heterocyclic units and also the construction of C–S bond formation reactions.

## Acknowledgments

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## Reference and notes

1. Ziegert, R. E.; Torang, J.; Knepper, K.; Brase, S. *J. Comb. Chem.* **2005**, *7*, 147.
2. (a) Kundu, B. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 815; (b) Feliu, L.; Vera-Luque, P.; Albericio, F.; Alvarez, M. *J. Comb. Chem.* **2009**, *11*, 175.
3. (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449; (b) Park, K.-H.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 3520.
4. (a) Levy, L. *Drugs Future* **1992**, *17*, 451; (b) Chen, W.; Li, Z.; Ou, L.; Giulianotti, M. A.; Houghten, R. A.; Yu, Y. *Tetrahedron Lett.* **2011**, *52*, 1456.
5. Nefzi, A.; Marcello, G.; Truong, L.; Rattan, S.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2002**, *4*, 175.
6. Nefzi, A.; Ostresh, J. M.; Yu, J.; Houghten, R. A. *J. Org. Chem.* **2004**, *69*, 3603.
7. Nefzi, A.; Arutyunyan, S.; Fenwick, J. E. *J. Org. Chem.* **2010**, *75*, 7939.
8. (a) Derbel, S.; Ghedira, K.; Nefzi, A. *Tetrahedron Lett.* **2010**, *51*, 3607; (b) Hoesl, C. E.; Nefzi, A.; Houghten, R. A. *J. Comb. Chem.* **2004**, *6*, 220; (c) Hoesl, C. E.; Nefzi, A.; Houghten, R. A. *Tetrahedron Lett.* **2003**, *44*, 3705.
9. Nefzi, A.; Giulianotti, M.; Houghten, R. A. *Tetrahedron Lett.* **2000**, *41*, 2283.
10. (a) Kim, B. H.; Curran, D. P. *Tetrahedron* **2011**, *49*, 293; (b) Zajac, M.; Peters, R. *Org. Lett.* **2007**, *2007*, 9; (c) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210.
11. Valente, C.; Guedes, R. C.; Moreira, R.; Iley, J.; Gut, J.; Rosenthal, P. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4115.
12. Di Santo, R.; Costi, R.; Artico, M.; Massa, S.; Marongiu, M. E.; Loi, A. G.; De Montis, A.; La Colla, P. *Antiviral Chem. Chemother.* **1998**, *9*, 127.
13. Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925.
14. Zia-ur-Rehman, M.; Choudary, J. A.; Ahmad, S.; Siddiqui, H. L. *Chem. Pharm. Bull.* **2006**, *54*, 1175.
15. Silvestri, R.; Marfe, G.; Artico, M.; La Regina, G.; Lavecchia, A.; Novellino, E.; Morgante, M.; Di Stefano, C.; Catalano, G.; Filomeni, G.; Abruzzese, E.; Ciriolo, M. R.; Russo, M. A.; Amadori, S.; Cirilli, R.; LaTorre, F.; Sinibaldi Salimei, P. *J. Med. Chem.* **2006**, *49*, 5840.
16. Lebegue, N.; Gallet, S.; Flouquet, N.; Carato, P.; Pfeiffer, B.; Renard, P.; Leonce, S.; Pierre, A.; Chavatte, P.; Berthelot, P. *J. Med. Chem.* **2005**, *48*, 7363.
17. (a) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195; (b) Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, 102.
18. (a) Yu, Y.; Nefzi, A.; Ostresh, M. J.; Houghten, R. A. In *Innnovations and Perspectives in Solid Phase Synthesis and Combinatorial Libraries*; Epton, R., Ed.; Mayflower Worldwide Ltd: London UK, 2004; (b) Nefzi, A.; Ostresh, J. M.; Yu, Y.; Houghten, R. A. *J. Org. Chem.* **2004**, *69*, 3603; (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449.
19. Dadiboyena, S.; Nefzi, A. *Tetrahedron Lett.* **2011**, *52*, 7030.
20. Dadiboyena, S.; Nefzi, A. *Synthesis* **2012**, *44*, 215.
21. (a) Reddy, C. V.; Kingston, J. V.; Verkade, J. G. *J. Org. Chem.* **2008**, *73*, 3047; (b) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973; (c) Hill, L. L.; Moore, L. R.; Huang, R.; Craciun, R.; Vincent, A. J.; Dixon, D. A.; Chou, J.; Woltermann, C. J.; Shaughnessy, K. H. *J. Org. Chem.* **2006**, *71*, 5117.
22. Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131.
23. Liu, L.; Stelmach, J. E.; Natarajan, S. R.; Chen, M.-H.; Singh, S. B.; Schwartz, C. D.; Fitzgerald, C. E.; O'Keefe, S. J.; Zaller, D. M.; Schmatz, D. M.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3979.
24. Kaldor, S. W.; Kalish, V. J.; Davies, J. F., II; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.
25. *General Procedure for the Solid-Phase Synthesis of Aminobenzimidazole tethered Sultams*: *p*-Methylbenzhydrylamine (MBHA) resin (100 mg, 1.10 meq/g, 100–200 mesh) was sealed inside a polypropylene mesh packet. Polypropylene bottles were used for all the reactions. Fmoc-Amino acid (Fmoc-Cys(Trt)-OH) coupled resin bound aminobenzimidazoles were synthesized according to a previous literature. [20,21] Following Fmoc deprotection with a solution of 20% piperidine in DMF and washings, the dried resin-bound free amine **2** was treated with corresponding benzenesulfonyl chlorides (10 equiv, 0.2 M in anhydrous DCM) and DIEA (10 equiv). The resulting resin was stirred at room temperature (8 h), and the resin was washed with DMF (2×), MeOH (2×), and DCM (2×). Deprotection of the Trityl group with 6% TFA/DCM (1% TIPS) for 15 min (3×), the resin **5** was washed with DCM (2×). The palladium-catalyzed cyclization was performed under anhydrous conditions. The resin-bound sulfonamides were treated with $Cs_2CO_3$ (10 equiv, 0.2 M in anhyd. DMF), $Pd(PPh_3)_4$ (0.2 equiv), and (±)-BINAP (0.4 equiv), and the whole reaction mixture was heated at 100 °C for 14 h. The resin was then washed with DMF (2×), DCM (2×), and methanol (2×). Diverse alkyl halides were tethered to the resin-bound sultams in the presence of DIEA in DMF at room temperature for 36 h and the resulting resin was washed with DMF (3×) and DCM (3×). The resin was cleaved with HF/anisole for 90 min at 0 °C, and the final sultams **1** were obtained following extraction with 95% AcOH in $H_2O$ and lyophilization as a white powder. The aminobenzimidazole tethered sultams **1** were purified by preparative reverse-phase HPLC and the products were characterized by LC–MS (ESI) conditions. *NMR data for entry* ***1b***: $^1$H NMR (DMSO-$d_6$): 0.91 (t, *J* = 8 Hz, 3H), 1.25–1.35 (m, 2H), 1.69–1.77 (m, 2H), 3.02–3.06 (m, 1H), 3.56–3.61 (m, 1H), 4.21 (t, *J* = 8 Hz, 1H), 4.48 (dt, *J* = 8 Hz, 12 Hz, 1H), 7.51–7.58 (m, 4H), 7.60–7.65 (m, 3H), 7.67–7.70 (m, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.94–7.97 (m, 2H), 8.01 (m, 1H); LC–MS *m/z* data Calcd. for $C_{21}H_{23}N_5O_4S_2(MH^+)$: 473.57. Found: 474.3; *NMR data for entry* ***1g***: $^1$H NMR (DMSO-$d_6$): 0.84 (t, *J* = 8 Hz, 2H), 0.93 (t, *J* = 8 Hz, 2H), 1.17–1.24 (m, 1H), 1.31–1.36 (m, 1H), 1.58–1.63 (m, 2H), 3.92–4.01 (m, 1H), 4.08–4.12 (m, 1H), 6.51 (s, 2H), 7.28 (d, *J* = 8 Hz, 1H), 7.46 (d, *J* = 8 Hz, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.68 (d, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.99 (d, *J* = 16 Hz, 2H), 8.13–8.14 (m, 2H); LC–MS *m/z* data Calcd. for $C_{22}H_{22}F_3N_5O_4S_2(MH^+)$: 541.57. Found: 542.4; *NMR data for entry* ***1l***: $^1$H NMR (DMSO-$d_6$): 0.87 (d, *J* = 8 Hz, 3H), 0.83 (d, *J* = 8 Hz, 4H), 0.92–0.96 (m, 1H), 2.03 (s, 4H), 2.51 (m, 5H), 3.88 (dd, *J* = 8 Hz, 12 Hz, 1H), 3.96 (dd, *J* = 8 Hz,

16 Hz, 1H), 6.51 (s, 1H), 7.33 (br s, 1H), 7.59 (d, $J$ = 8 Hz, 1H), 7.70 (d, $J$ = 8 Hz, 1H), 7.81 (d, $J$ = 8 Hz, 1H), 7.00 (d, $J$ = 8 Hz, 1H), 7.97–8.01 (m, 2H), 8.15 (br s, 2H); LC–MS $m/z$ data Calcd. for $C_{30}H_{30}FN_5O_2S_2(MH^+)$: 661.71. Found: 662.5; *NMR data for entry* ***1m***: $^1$H NMR (DMSO-$d_6$): 0.88 (d, $J$ = 8 Hz, 3H), 1.25–1.30 (m, 2H), 1.67–1.72 (m, 2H), 2.97–3.03 (m, 1H), 3.50 (d, $J$ = 8 Hz, 1H), 4.19 (t, $J$ = 8 Hz, 1H), 4.42 (t, $J$ = 8 Hz, 1H), 5.42 (d, $J$ = 4 Hz, 1H), 7.26–7.35 (m, 8H), 7.46–7.54 (m, 3H), 7.63–7.71 (m, 3H), 7.86–7.96 (m, 1H), 7.99–8.03 (m, 2H); LC–MS $m/z$ data Calcd. for $C_{28}H_{29}N_5O_4S_2(MH^+)$: 563.70. Found: 564.6.

26. *General Procedure for the Synthesis of Aminobenzimidazole tethered benzothiazepinones*: The resin-bound free amine **2** was coupled with substituted 2-chlorobenzoic acids using DIC (8 equiv, 0.2M in DMF) and HOBt (8 equiv) conditions for 8 h, and the resulting resin bound amides were washed with DMF (2x) and DCM (2×). The trityl group was cleaved with 6% TFA/DCM (1% TIPS) for 15 min (3×), and the resin **9** was washed with DCM (2×) and dried overnight. The palladium-catalyzed cyclization was performed under anhydrous conditions. The resin-bound intermediate amides **9** were treated with $Cs_2CO_3$ (10 equiv, 0.2 M in anhyd. DMF), $Pd(PPh_3)_4$ (0.2 equiv), and (±)-BINAP (0.4 equiv), and the whole reaction mixture was heated at 100 °C for 10 h. The resin was then washed with DMF (2×), DCM (2×), and methanol (2×). The resin was cleaved with HF/anisole for 90 min at 0 °C, and the desired benzothiazepinones **8** were obtained following extraction with 95% AcOH in $H_2O$ and lyophilization as a white powder. The aminobenzimidazole tethered benzothiazepinones **8** were purified by preparative reverse-phase HPLC and the products were characterized by LC–MS under ESI conditions. *NMR data for entry* ***8b***: $^1$H NMR (DMSO-$d_6$): 0.81 (t, $J$ = 8Hz, 3H), 1.21–1.28 (m, 2H), 1.64–1.72 (m, 2H), 4.17 (t, $J$ = 8Hz, 2H), 6.05 (br s, 1H), 6.41 (br s, 1H), 6.59 (br s, 1H), 7.31 (m, 1H), 7.49–7.62 (m, 6H), 7.72 (d, $J$ = 8Hz, 1H), 7.81 (d, $J$ = 8Hz, 1H), 8.00-8.02 (m, 2H); LC–MS $m/z$ data Calcd. for $C_{22}H_{23}N_5O_3S(MH^+)$: 437.51. Found: 440.0; *NMR data for entry* ***8i***: $^1$H NMR (DMSO-$d_6$): 0.90–1.05 (m, 6H), 1.45 (d, $J$ = 12Hz, 2H), 1.55–1.56 (m, 4H), 1.79–1.84 (m, 1H), 2,03 (s, 1H), 3.98 (d, $J$ = 8Hz, 2H), 6.00 (s, 1H), 6.36 (s, 1H), 7.30 (br s, 1H), 7.54–7.60 (m, 2H), 7.73–7.81 (m, 3H), 7.95 (br s, 1H), 8.02 (s, 1H); LC-MS $m/z$ data Calcd. for $C_{25}H_{26}ClN_5O_3S(MH^+)$: 512.02. Found: 514.0.

27. (a) Levai, A.; Kiss-Szikszai, A. *ARKIVOC* **2008**, *1*, 65; (b) Sainsbury, M. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 1036; (c) Ferrari, R. *Eur. Heart J.* **1997**, *18*, A56; (d) Salimbeni, A.; Caliari, S.; Fici, F.; Manghisi, E. U.S. Patent 5,571,807, 1996; *Chem Abstr.* **1992**, *116*, 255647x.; (e) Narita, H.; Gaino, M.; Suzuki, T.; Kurosawa, H.; Inoue, H.; Nagao, T. *Chem. Pharm. Bull.* **1990**, *38*, 407; (f) Hamanaka, E. S.; Hayward, C. M.; Hawkins, J. M. U.S. Patent 5,770,594, 1998; *Chem Abstr.* **1996**, *125*, 168038s.; (g) Lerch, U.; Henning, R. U.S. Patent 4,831,028, 1989; *Chem Abstr.* **1988**, *108*, 37851c.

28. Henning, R.; Lerch, U.; Kaiser, J. U.S. Patent 4,595,685, 1986; *Chem Abstr.* **1986**, *104*, 88571m.; (b) Rampe, D.; Triggle, D. J. *Prog. Drug. Res.* **1993**, *40*, 191; (c) Chaffman, M.; Brogden, R. N. *Drugs* **1985**, *29*, 387; (d) Katritzsky, A. R.; Odens, H. H.; Zhang, S. *J. Org. Chem.* **2001**, *66*, 6792; (e) Levai, A. *J. Heterocycl. Chem.* **2000**, *37*, 199.