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Structure–Activity Study of Bioisosteric Trifluoromethyl and Pentafluorosulfanyl Indole Inhibitors of the AAA ATPase p97

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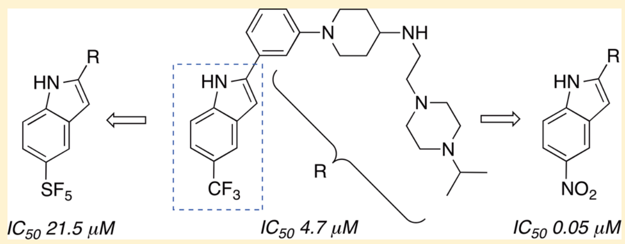
Supporting Information

ABSTRACT: Exploratory SAR studies of a new phenyl indole chemotype for p97 inhibition revealed C-5 indole substituent effects in the ADPGlo assay that did not fully correlate with either electronic or steric factors. A focused series of methoxy-, trifluoromethoxy-, methyl-, trifluoromethyl-, pentafluorosulfanyl-, and nitro-analogues was found to exhibit IC_{50}s from low nanomolar to double-digit micromolar. Surprisingly, we found that the trifluoromethoxy-analogue was biochemically a better match of the trifluoromethyl-substituted lead structure than a pentafluorosulfanyl-analogue. Moreover, in spite of their almost equivalent strongly electron-depleting effect on the indole core, pentafluorosulfanyl- and nitro-derivatives were found to exhibit a 430-fold difference in p97 inhibitory activities. Conversely, the electronically divergent C-5 methyl- and nitro-analogues both showed low nanomolar activities.



KEYWORDS: *AAA ATPase, p97 inhibitors, pentafluorosulfanyl-indole, trifluoromethyl-indole, structure–activity relationships, fluorinated substituent effects*

Among recent developments in organofluorine chemistry, the pentafluorosulfanyl (SF_5) group is notable for its greater electronegativity, lipophilicity, stability, and larger size versus the much more commonly encountered[1] trifluoromethyl (CF_3) group.[2–5] While methods for introducing SF_5-groups on aromatic, heteroaromatic, and aliphatic precursors are still in need of further development,[6] several pentafluorosulfanyl arenes are commercially available, and the syntheses of an increasing number of other SF_5-substituted building blocks, such as pyridines,[7] quinolines,[8] and indoles[9] have been reported.[3] SF_5-substituted organic molecules have proven to be metabolically very stable.[10,11] Therefore, these compounds would appear to be uniquely suited for materials research and the development of agrochemicals and pharmaceuticals, but relatively few case studies have focused on the comparative structure–activity relationship (SAR) of SF_5-substituted drug candidates.[3,5,8,10,12–16] We now report a systematic investigation of the SAR of SF_5-indole inhibitors of the AAA ATPase p97, comparing SF_5, a "super-sized" CF_3-group sterically equivalent to a *t*-butyl but electronically most closely related to a nitro functionality, to the corresponding CH_3O-, CF_3O-, CH_3-, CF_3-, and NO_2-analogues.

The ATPase Associated with various cellular Activities (AAA) p97, also known as Valosin-Containing Protein (VCP), or Cdc48p in yeast, regulates endoplasmic reticulum associated degradation, cell cycle, autophagy, transcription factors, mitochondrial associated degradation, membrane and ubiquitin fusion, and other rather diverse processes that involve protein and membrane processing.[17] Binding to ATP followed by hydrolysis to ADP initiates massive conformational changes in the hexameric p97 that can segregate a bound protein from a macromolecular ligand, including other proteins and membrane segments (Figure 1).[18]

As found for other chaperones,[20,21] various forms of cancer, including breast, lung, pancreatic, and colorectal cancer, upregulate p97 as a response to accelerated growth and deteriorating protein quality control.[22,23] This property might render cancer cells more sensitive to p97 inhibitors than normal cells. In particular, combinations with proteasome or heat shock protein inhibitors could further widen the therapeutic window, but the test of this hypothesis awaits the development of clinically efficacious p97 antagonists.

While p97 is not yet a validated clinical cancer target, several small molecule inhibitors have been identified that could enable

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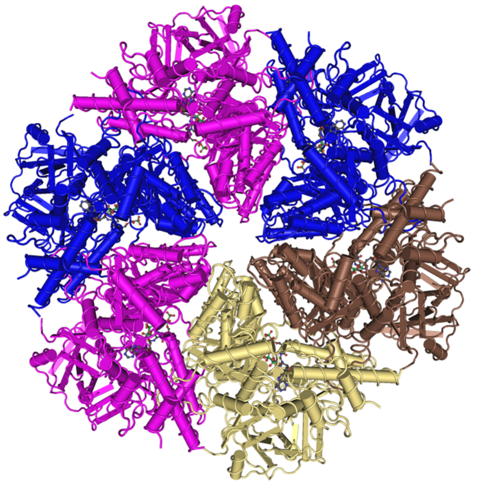


Figure 1. Crystal structure of hexameric, full-length p97 in complex with ADP (PDB ID 3CF3).[19]

proof-of-principle of therapeutic efficacy.[24] This list includes several amino-heterocycles, such as the diaminoquinazolines **1**,[25] **2**,[26] and **3**,[27] aminothiazole **4**,[28] and the irreversible inhibitor chloroacetamide **5**[29] (Figure 2). 1,2,4-Triazole **6**,[30]

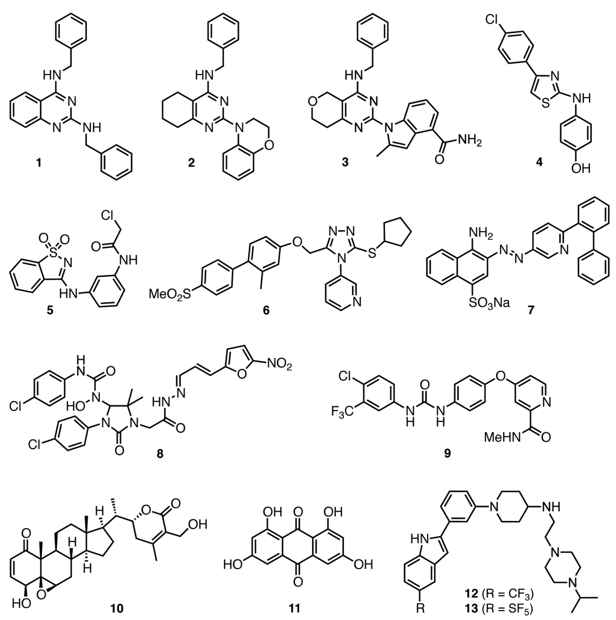


Figure 2. Structures of p97 inhibitors.

sulfonate **7**,[31] and imidazolinone **8**[32] were identified by high throughput screening campaigns, whereas the discovery of the anticancer agent **9**[33] (sorafenib) and the natural products **10**[34] (withaferin A) and **11**[35] (rheoemodin) as p97 inhibitors was based on specific mechanism of action and targeted lead identification studies.

As part of a medicinal chemistry campaign to optimize p97 inhibitors, we generated the C-5 trifluoromethylated indole **12** as a promising lead structure.[36] In the ADPGlo assay,[37] we determined a 4.7 ± 2.0 μM IC_{50} for this compound (Table 1), and we decided to probe the effect of replacing the CF_3- with an SF_5-group at the C-5 position as shown for compound **13**.

For the initial preparation of **12**, we performed a Pd(II)/Cu(I)-catalyzed indole synthesis[38] on the imine derived from

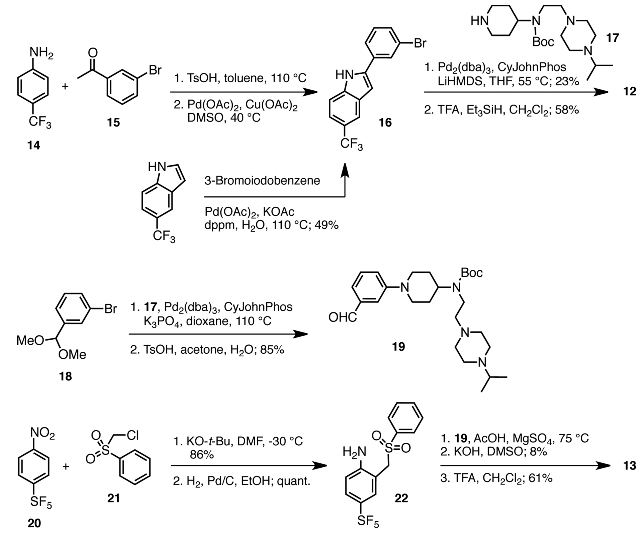
Table 1. Biochemical Activities of p97 Inhibitors[a]

entry	compound/R-group	p97-ADPGlo IC_{50} [μM]	p97-ADPGlo Std. Dev. [μM]
1	**12**/CF_3	4.7	±2.0
2	**13**/SF_5	21.5	±0.4
3	**23**/NO_2	0.05	±0.04
4	**24**/CH_3	0.24	±0.11
5	**25**/OCH_3	0.71	±0.22
6	**26**/OCF_3	3.8	±0.8

[a]Assay conditions: ADPGlo with 20 nM p97 ATPase WT in the presence of 100 μM ATP.[37] Assays were run in quadruplicate (**12**, **13**, **25**, **26**), seven times (**24**), or nine times (**23**).

condensation of amine **14** with ketone **15**, followed by a cross coupling[39,40] of aryl bromide **16** with secondary amine **17** and Boc-deprotection (Scheme 1).[41] Subsequently, a more direct

Scheme 1. Preparation of CF_3- and SF_5-Substituted p97 Inhibitors 12 and 13



synthesis of **16** was accomplished by a C,H-arylation of commercially available 5-trifluoromethylindole with 3-bromoiodobenzene, which provided indole **16** in 49% yield.[42] A different indole synthesis[43] was used for the preparation of the pentafluorosulfanyl analogue **13**. Pd(0)-catalyzed coupling of bromide acetal **18** with amine **17**[41] followed by selective acetal hydrolysis provided aldehyde building block **19**. After nucleophilic alkylation of SF_5-arene **20** with sulfone **21** and reduction of the nitro group, aniline **22** was condensed with this aldehyde and the indole was formed by cyclization and elimination, albeit in a low 8% yield from **22**. Removal of the Boc-group with TFA provided the C-5 pentafluorosulfanyl indole **13** in 61% yield.

Surprisingly, replacement of the trifluoromethyl with a pentafluorosulfanyl group reduced the p97 inhibition almost 5-fold to an IC_{50} of 21.5 ± 0.4 μM. We hypothesized that this decrease could either be due to the larger size of the SF_5 group or its stronger electron-withdrawing effect on the indole ring, and we decided to synthesize the corresponding nitro (**23**), methyl (**24**), methoxy (**25**), and trifluoromethoxy (**26**) analogues to test these parameters. Electron-density surfaces encoded with electrostatic potential maps for the indole segments of these compounds illustrate both their steric features as well as the range of their inductive effects on the

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aromatic π-system (Figure 3). Sterically, SF_5-analogue **13** and CF_3O-analogue **26** are the closest match, but their electronic effects on the indole ring and the indole nitrogen are significantly different. As expected, nitro-analogue **23** is the best electronic match of the pentafluorosulfanyl derivative. Sterically, and, in particular, electronically, CH_3O-analogue **25** is most closely related to CH_3-analogue **24**. Arguably, CF_3-analogue **12** is somewhat unique in this series, but sterically its closest match would be CH_3-analogue **24**, whereas electronically **12** is situated between SF_5-analogue **13** and CF_3O-analogue **26**. Accordingly, we expected that the methylated indole **24** would have similar activity to **12** if steric effects were dominant, whereas electronic effects would likely favor ethers **25** and **26** since the bulkier and more electron-deficient pentafluorosulfanyl had registered a significant drop in activity.

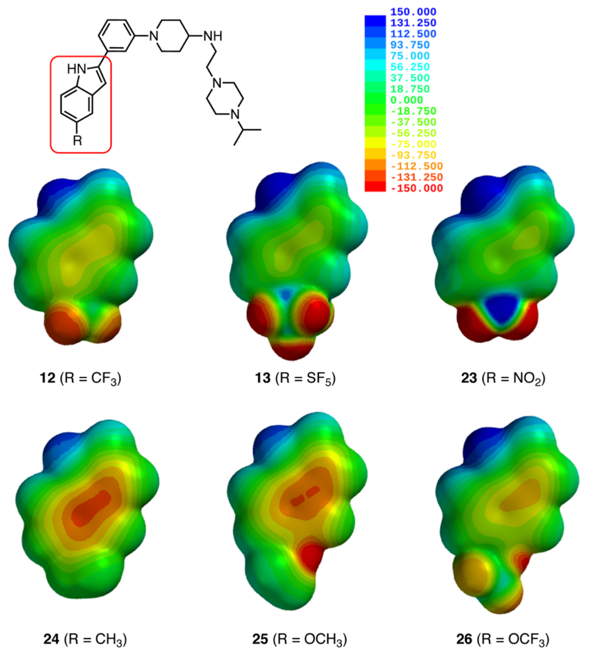
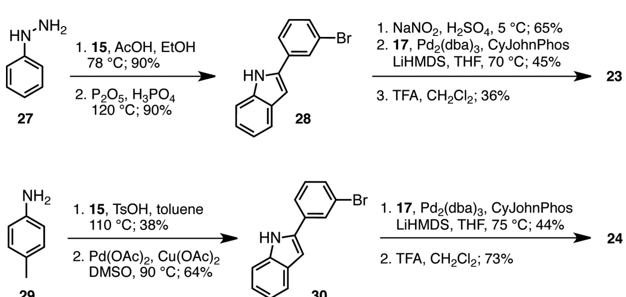


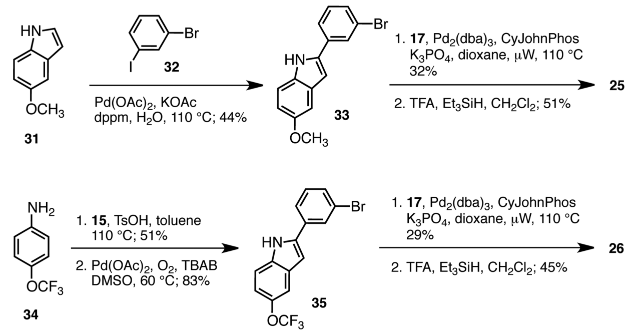
Figure 3. Structures and steric/electronic features[46] of new phenyl indole p97 inhibitors. The color coding on the electron-density surface of the indole moiety reflects the electrostatic potential experienced by a positive probe charge (red = attractive, blue = repulsive).

Syntheses of analogues **23**–**26** are summarized in Schemes 2 and 3. Acid-catalyzed condensation of phenyl hydrazine **27** with bromoacetophenone **15** provided an intermediate hydrazone that was cyclized[44] in a Fischer indole synthesis in the presence of P_2O_5 and H_3PO_4 to give indole **28**. Nitration was selective for the C-5 position of the indole[45] and was followed by Pd(0)-catalyzed cross-coupling with Boc-protected tetramine **17**. TFA-mediated removal of the Boc-group yielded nitro-indole **23**. A related sequence starting with aniline **29** and bromoacetophenone **15** led to an imine intermediate that was subjected to Pd(II)/Cu(I)-catalyzed indole synthesis conditions[38] to give **30**, and after cross-coupling with **17** and Boc-deprotection, methyl-indole **24** was obtained in 8% yield over the four steps (Scheme 2).

Scheme 2. Preparation of NO_2- and CH_3-Substituted p97 Inhibitors 23 and 24



Scheme 3. Preparation of CH_3O- and CF_3O-Substituted p97 Inhibitors 25 and 26



The C,H-bond activation[42] strategy was selected for the preparation of methoxy-indole intermediate **33** (Scheme 3). C-2 arylation of **31** with 3-bromoiodobenzene **32** led to the coupling product **33** in high selectivity but moderate yield (44%). Cross-coupling with tetramine **17** and deprotection provided the desired CH_3O-analogue **25** in 7% yield over the three steps. Starting with the commercially available aniline **34**, the corresponding CF_3O-analogue **26** was prepared in four steps and 6% overall yield using the alternative imine-cyclization[38] strategy.

Evaluation of **23**–**26** in the p97 ADPGlo assay revealed a remarkable 3 orders of magnitude range of activities between the six indoles (Table 1). Nitro-analogue **23** was found to be a ca. 50 nM inhibitor of the AAA ATPase (entry 3, IC_{50} 0.05 ± 0.04 μM). CF_3O-analogue **26** was considerably less active (entry 6, IC_{50} 3.8 ± 0.8 μM), but was slightly more potent than CF_3-analogue **12**. Methylated **24** and methoxylated **25** had intermediate but still submicromolar IC_{50}s (entries 4 and 5, IC_{50} 0.24 ± 0.11 and 0.71 ± 0.22 μM, respectively).

Most of the literature precedence on the biological activities of SF_5-containing compounds versus the corresponding CF_3-analogues report relatively minor, but predominantly improved potencies.[47] For example, an SF_5-containing bosentan analogue was shown to be slightly more active at the human endothelin receptor subtypes A and B, but was less active than the corresponding *t*-butyl, bicyclo[1.1.1]pentanyl, and cyclopropyl-trifluoromethyl derivatives.[10] In the mefloquine series, SF_5-substitution of CF_3-groups did not change potency.[8,16] In a study of cannabinoid receptor ligands, SF_5-pyrazoles generally showed slightly higher or equivalent CB_1 receptor affinity and selectivity toward the CB_2 receptor relative to both CF_3- and *t*-butyl-analogues.[14] A recent analysis of matched pairs of CF_3/SF_5-analogues from Novartis detected a mean 1.6-fold increase in *in vitro* potency.[13] In contrast, our study of trifluoromethyl and pentafluorosulfanyl indole based inhibitors of the AAA ATPase p97 shows that the bioisosteric replacement strategy with fluorinated building blocks can lead to surprising SAR results, with the possibility for both steric and electronic features contributing to the inhibitory activities. In the series of

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CH_3O-, CF_3O-, CH_3-, SF_5-, and NO_2-analogues of the CF_3-indole **12**, IC_{50}s vary >400-fold, and the SF_5-analogue is, in fact, the least active compound. The CF_3O-derivative is biochemically the closest match of the CF_3 lead structure. Steric factors alone do not account for the differences in potency in this series, as substituents with similar sizes have 20-fold different potencies (e.g., **24** vs **12**). If an electron-rich indole is preferred, it would indeed be consistent that **24** and the methyl ether **25** have nanomolar activities, whereas the pentafluorosulfanyl derivative **13** has a double-digit micromolar effect. The outlier in this analysis is, however, clearly nitro-indole **23**, which has the strongest electron-depleting effect on the π-system of the indole and yet exhibits the most potent p97 inhibition of this set with a 50 nM IC_{50}, a 5-fold increase in potency compared to the electron rich CH_3-analogue **24**, and a 430-fold increase compared to the electronically similar SF_5-derivative **13**. The relative lipophilicity in this series, as expressed by clogP values[48] for **12** (2.95), **13** (4.03), **23** (2.01), **24** (2.59), **25** (1.91), and **26** (3.50) can only provide a partial correlation to observed IC_{50} values. An intriguing alternative explanation is that the indole ring of these p97 inhibitors is involved in π-stacking interactions[49] with the protein, which might explain both the affinity for electron-rich π-systems (such as in **24** and **25**) as well as the improved activity of the flat, strongly electron-deficient π-system in **23**. Structural information on the binding of these inhibitors to p97 will be necessary to further investigate this hypothesis.

In conclusion, we report the first direct comparison of five CF_3-isosteres as part of a preliminary SAR analysis of a new series of p97 inhibitors. Four different synthetic approaches to the phenyl indole moiety were developed to provide access to the six indole substitutions. The biological activity in this focused series is highly sensitive to the nature of the C-5 indole substituent, spanning a >400-fold difference in IC_{50}s between the SF_5-analogue **13** and the NO_2-analogue **23**. Contrary to expectation and literature precedence, we found that it was not the SF_5- but the CF_3O-analogue that was biochemically the closest match to the CF_3-substituted lead structure **12** and that, in spite of the similar electron-withdrawing effect on the indole core, SF_5- and NO_2-derivatives provided the most divergent inhibitors in terms of their *in vitro* assay activities. Steric or electronic factors alone can not explain this SAR. The preparation of additional analogues that probe more diverse side-chain substituent effects, as well as structural biology studies that might shed light on π-stacking interactions are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00364.

Experimental details and spectral data for all new products (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CyJohnPhos, (1,1′-biphenyl-2-yl)dicyclohexylphosphine; dppm, 1,1-bis(diphenylphosphino)methane; TBAB, tetra-*n*-butylammonium bromide; TFA, trifluoroacetic acid

■ REFERENCES

(1) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **2015**, DOI: 10.1021/acs.jmedchem.5b00258.

(2) Sheppard, W. A. Electrical effect of the sulfur pentafluoride group. *J. Am. Chem. Soc.* **1962**, *84*, 3072−3076.

(3) Bowden, R. D.; Comina, P. J.; Greenhall, M. P.; Kariuki, B. M.; Loveday, A.; Philp, D. A new method for the synthesis of aromatic sulfurpentafluorides and studies of the stability of the sulfur pentafluoride group in common synthetic transformations. *Tetrahedron* **2000**, *56*, 3399−3408.

(4) Savoie, P. R.; Welch, J. T. Preparation and utility of organic pentafluorosulfanyl-containing compounds. *Chem. Rev.* **2015**, *115*, 1130−1190.

(5) Altomonte, S.; Zanda, M. Synthetic chemistry and biological activity of pentafluorosulphanyl (SF_5) organic molecules. *J. Fluorine Chem.* **2012**, *143*, 57−93.

(6) Umemoto, T.; Garrick, L. M.; Saito, N. Discovery of practical production processes for arylsulfur pentafluorides and their higher homologs, bis- and tris-(sulfur pentafluorides): beginning of a new era of super-trifluoromethyl arene chemistry and its industry. *Beilstein J. Org. Chem.* **2012**, *8*, 461−471.

(7) Kanishchev, O. S.; Dolbier, W. R., Jr. Synthesis and characterization of 2-pyridylsulfur pentafluorides. *Angew. Chem., Int. Ed.* **2015**, *54*, 280−284.

(8) Wipf, P.; Mo, T.; Geib, S. J.; Caridha, D.; Dow, G. S.; Gerena, L.; Roncal, N.; Milner, E. E. Synthesis and biological evaluation of the first pentafluorosulfanyl analogs of mefloquine. *Org. Biomol. Chem.* **2009**, *7*, 4163−4165.

(9) Iakobson, G.; Posta, M.; Beier, P. Synthesis of pentafluorosulfanyl-containing indoles and oxindoles. *Synlett* **2013**, *24*, 855−859.

(10) Westphal, M. V.; Wolfstaedter, B. T.; Plancher, J.-M.; Gatfield, J.; Carreira, E. M. Evaluation of *tert*-butyl isosteres: case studies of

physicochemical and pharmacokinetic properties, efficacies, and activities. *ChemMedChem* **2015**, *10*, 461−469.
(11) Micheli, F.; Andreotti, D.; Braggio, S.; Checchia, A. A specific and direct comparison of the trifluoromethyl and pentafluorosulfanyl groups on the selective dopamine D3 antagonist 3-(3-{[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-1-phenyl-3-azabicyclo[3.1.0]hexane template. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4566−4568.
(12) Karagiannidis, L. E.; Haynes, C. J. E.; Holder, K. J.; Kirby, I. L.; Moore, S. J.; Wells, N. J.; Gale, P. A. Highly effective yet simple transmembrane anion transporters based upon ortho-phenylenediamine bis-ureas. *Chem. Commun.* **2014**, *50*, 12050−12053.
(13) Barnes-Seeman, D.; Beck, J.; Springer, C. Fluorinated compounds in medicinal chemistry: recent applications, synthetic advances and matched-pair analyses. *Curr. Top. Med. Chem.* **2014**, *14*, 855−864.
(14) Altomonte, S.; Baillie, G. L.; Ross, R. A.; Riley, J.; Zanda, M. The pentafluorosulfanyl group in cannabinoid receptor ligands: synthesis and comparison with trifluoromethyl and *tert*-butyl analogues. *RSC Adv.* **2014**, *4*, 20164−20176.
(15) Chia, P. W.; Brennan, S. C.; Slawin, A. M. Z.; Riccardi, D.; O'Hagan, D. Allosteric agonists of the calcium receptor (CaR): Fluorine and SF_5 analogues of cinacalcet. *Org. Biomol. Chem.* **2012**, *10*, 7922−7927.
(16) Mo, T.; Mi, X.; Milner, E. E.; Dow, G. S.; Wipf, P. Synthesis of an 8-pentafluorosulfanyl analog of the antimalarial agent mefloquine. *Tetrahedron Lett.* **2010**, *51*, 5137−5140.
(17) Woodman, P. G. p97, a protein coping with multiple identities. *J. Cell Sci.* **2003**, *116*, 4283−4290.
(18) Li, G.; Huang, C.; Zhao, G.; Lennarz, W. J. Interprotomer motion-transmission mechanism for the hexameric AAA ATPase p97. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 3737−3741.
(19) Davies, J. M.; Brunger, A. T.; Weis, W. I. Improved structures of full-length p97, an AAA ATPase: Implications for mechanisms of nucleotide-dependent conformational change. *Structure* **2008**, *16*, 715−726.
(20) Brandvold, K. R.; Morimoto, R. I. The chemical biology of molecular chaperones-implications for modulation of proteostasis. *J. Mol. Biol.* **2015**, *427*, 2931−2947.
(21) Manos-Turvey, A.; Brodsky, J.; Wipf, P. The effect of structure and mechanism of the Hsp70 chaperone on the ability to identify chemical modulators and therapeutics. *Top. Med. Chem.* **2015**, *16*, 1−49.
(22) Deshaies, R. J. Proteotoxic crisis, the ubiquitin-proteasome system, and cancer therapy. *BMC Biol.* **2014**, *12*, 94.
(23) Haines, D. S. p97-containing complexes in proliferation control and cancer: emerging culprits or guilt by association? *Genes Cancer* **2010**, *1*, 753−763.
(24) Chapman, E.; Maksim, N.; De La Cruz, F.; La Clair, J. J. Inhibitors of the AAA+ chaperone p97. *Molecules* **2015**, *20*, 3027−3049.
(25) Chou, T.-F.; Brown, S. J.; Minond, D.; Nordin, B. E.; Li, K.; Jones, A. C.; Chase, P.; Porubsky, P. R.; Stoltz, B. M.; Schoenen, F. J.; Patricelli, M. P.; Hodder, P.; Rosen, H.; Deshaies, R. J. Reversible inhibitor of p97, DBeQ, impairs both ubiquitin-dependent and autophagic protein clearance pathways. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 4834−4839.
(26) Fang, C.-J.; Gui, L.; Zhang, X.; Moen, D. R.; Li, K.; Frankowski, K. J.; Lin, H. J.; Schoenen, F. J.; Chou, T.-F. Evaluating p97 inhibitor analogues for their domain selectivity and potency against the p97-p47 complex. *ChemMedChem* **2015**, *10*, 52−56.
(27) Zhou, H.-J.; Parlati, F.; Wustrow, D. Preparation of fused pyrimidines as inhibitors of p97 complex. Patent WO2014015291, 2014.
(28) Bursavich, M. G.; Parker, D. P.; Willardsen, J. A.; Gao, Z.-H.; Davis, T.; Ostanin, K.; Robinson, R.; Peterson, A.; Cimbora, D. M.; Zhu, J.-F.; Richards, B. 2-Anilino-4-aryl-1,3-thiazole inhibitors of valosin-containing protein (VCP or p97). *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1677−1679.
(29) Magnaghi, P.; D'alessio, R.; Valsasina, B.; Avanzi, N.; Rizzi, S.; Asa, D.; Gasparri, F.; Cozzi, L.; Cucchi, U.; Orrenius, C.; Polucci, P.; Ballinari, D.; Perrera, C.; Leone, A.; Cervi, G.; Casale, E.; Xiao, Y.; Wong, C.; Anderson, D. J.; Galvani, A.; Donati, D.; O'Brien, T.; Jackson, P. K.; Isacchi, A. Covalent and allosteric inhibitors of the ATPase VCP/p97 induce cancer cell death. *Nat. Chem. Biol.* **2013**, *9*, 548−556.
(30) Polucci, P.; Magnaghi, P.; Angiolini, M.; Asa, D.; Avanzi, N.; Badari, A.; Bertrand, J.; Casale, E.; Cauteruccio, S.; Cirla, A.; Cozzi, L.; Galvani, A.; Jackson, P. K.; Liu, Y.; Magnuson, S.; Malgesini, B.; Nuvoloni, S.; Orrenius, C.; Sirtori, F. R.; Riceputi, L.; Rizzi, S.; Trucchi, B.; O'Brien, T.; Isacchi, A.; Donati, D.; D'alessio, R. Alkylsulfanyl-1,2,4-triazoles, a new class of allosteric valosine containing protein inhibitors. Synthesis and structure-activity relationships. *J. Med. Chem.* **2013**, *56*, 437−450.
(31) Kakizuka, A.; Hori, S.; Shudo, T.; Fuchigami, T. Preparation of 2-(arylazo or heteroarylazo)-4-aminonaphthalene-1-sulfonic acid derivatives as regulators of vasolin-containing protein (VCP). PCT Int. Appl. WO 2012014994, 2012.
(32) Wang, Q.; Li, L.; Ye, Y. Inhibition of p97-dependent protein degradation by eeyarestatin I. *J. Biol. Chem.* **2008**, *283*, 7445−7454.
(33) Yi, P.; Higa, A.; Taouji, S.; Bexiga, M. G.; Marza, E.; Arma, D.; Castain, C.; Le Bail, B.; Simpson, J. C.; Rosenbaum, J.; Balabaud, C.; Bioulac-Sage, P.; Blanc, J.-F.; Chevet, E. Sorafenib-mediated targeting of the AAA+ ATPase p97/VCP leads to disruption of the secretory pathway, endoplasmic reticulum stress, and hepatocellular cancer cell death. *Mol. Cancer Ther.* **2012**, *11*, 2610−2620.
(34) Tao, S.; Tillotson, J.; Wijeratne, E. M. K.; Xu, Y.-M.; Kang, M.; Wu, T.; Lau, E. C.; Mesa, C.; Mason, D. J.; Brown, R. V.; La Clair, J. J.; Gunatilaka, A. A. L.; Zhang, D. D.; Chapman, E. Withaferin A analogs that target the AAA+ chaperone p97. *ACS Chem. Biol.* **2015**, *10*, 1916−1924.
(35) Kang, M. J.; Wu, T.; Wijeratne, E. M. K.; Lau, E. C.; Mason, D. J.; Mesa, C.; Tillotson, J.; Zhang, D. D.; Gunatilaka, A. a. L.; La Clair, J. J.; Chapman, E. Functional chromatography reveals three natural products that target the same protein with distinct mechanisms of action. *ChemBioChem* **2014**, *15*, 2125−2131.
(36) Manuscript in preparation.
(37) Chou, T.-F.; Bulfer, S. L.; Weihl, C. C.; Li, K.; Lis, L. G.; Walters, M. A.; Schoenen, F. J.; Lin, H. J.; Deshaies, R. J.; Arkin, M. R. Specific inhibition of p97/VCP ATPase and kinetic analysis demonstrate interaction between D1 and D2 ATPase domains. *J. Mol. Biol.* **2014**, *426*, 2886−2899.
(38) Wei, Y.; Deb, I.; Yoshikai, N. Palladium-catalyzed aerobic oxidative cyclization of N-aryl imines: indole synthesis from anilines and ketones. *J. Am. Chem. Soc.* **2012**, *134*, 9098−9101.
(39) Harris, M. C.; Huang, X.; Buchwald, S. L. Improved functional group compatibility in the palladium-catalyzed synthesis of aryl amines. *Org. Lett.* **2002**, *4*, 2885−2888.
(40) Kazock, J.-Y.; Thery, I.; Chezal, J.-M.; Chavignon, O.; Teulade, J.-C.; Gueiffier, A.; Enguehard-Gueiffier, C. From the particular reactivity of 8-iodoimidazo[1,2-*a*]pyridine towards copper- and palladium-catalyzed aminations. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 775−779.
(41) See Supporting Information for experimental details.
(42) Joucla, L.; Batail, N.; Djakovitch, L. "On water" direct and site-selective Pd-catalysed C-H arylation of (NH)-indoles. *Adv. Synth. Catal.* **2010**, *352*, 2929−2936.
(43) Iakobson, G.; Pošta, M.; Beier, P. Synthesis of pentafluorosulfanyl-containing indoles and oxindoles. *Synlett* **2013**, *24*, 855−859.
(44) Kuehne, M. E.; Kitagawa, T. Reactions of indoles with benzyne. *J. Org. Chem.* **1964**, *29*, 1270−1273.
(45) Noland, W. E.; Rush, K. R.; Smith, L. R. Nitration of indoles. IV. Nitration of 2-phenylindole. *J. Org. Chem.* **1966**, *31*, 65−69.
(46) Electron-density surfaces encoded with electrostatic potential maps were calculated in Spartan 10 (Wave Function, Inc., Irvine, CA) with PM3 parametrization.
(47) Hendriks, C. M. M.; Penning, T. M.; Zang, T.; Wiemuth, D.; Gründer, S.; Sanhueza, I. A.; Schoenebeck, F.; Bolm, C. Penta-

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ACS Med. Chem. Lett. 2015, 6, 1225−1230

fluorosulfanyl-containing flufenamic acid analogs: Syntheses, properties and biological activities. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4437–4440.
(48) cLogP values were calculated with Spartan 10 (Wave Function, Inc., Irvine, CA) and Instant JChem 15.7.27.0 205. ChemAxon; http://www.chemaxon.com.
(49) Hunter, C. A.; Sanders, J. K. M. The nature of π-π interactions. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534.

DOI: 10.1021/acsmedchemlett.5b00364
ACS Med. Chem. Lett. 2015, 6, 1225–1230