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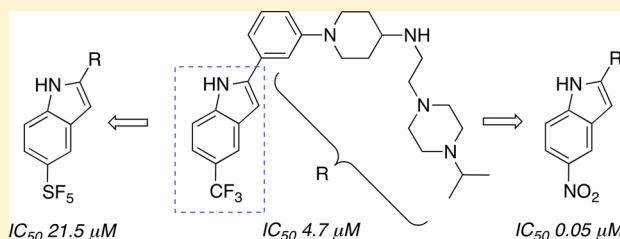
## Structure–Activity Study of Bioisosteric Trifluoromethyl and Pentafluorosulfanyl Indole Inhibitors of the AAA ATPase p97

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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<sup>1</sup> trifluoromethyl ( $CF_3$ ) group.<sup>2–5</sup> While methods for introducing  $SF_5$ -groups on aromatic, heteroaromatic, and aliphatic precursors are still in need of further development,<sup>6</sup> several pentafluorosulfanyl arenes are commercially available, and the syntheses of an increasing number of other  $SF_5$ -substituted building blocks, such as pyridines,<sup>7</sup> quinolines,<sup>8</sup> and indoles<sup>9</sup> have been reported.<sup>3</sup>  $SF_5$ -substituted organic molecules have proven to be metabolically very stable.<sup>10,11</sup> 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.<sup>3,5,8,10,12–16</sup> 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.<sup>17</sup> 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).<sup>18</sup>

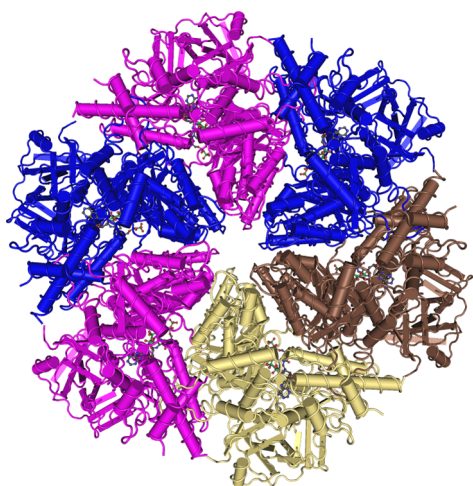
As found for other chaperones,<sup>20,21</sup> various forms of cancer, including breast, lung, pancreatic, and colorectal cancer, upregulate p97 as a response to accelerated growth and deteriorating protein quality control.<sup>22,23</sup> This property might render cancer cells more sensitive to p97 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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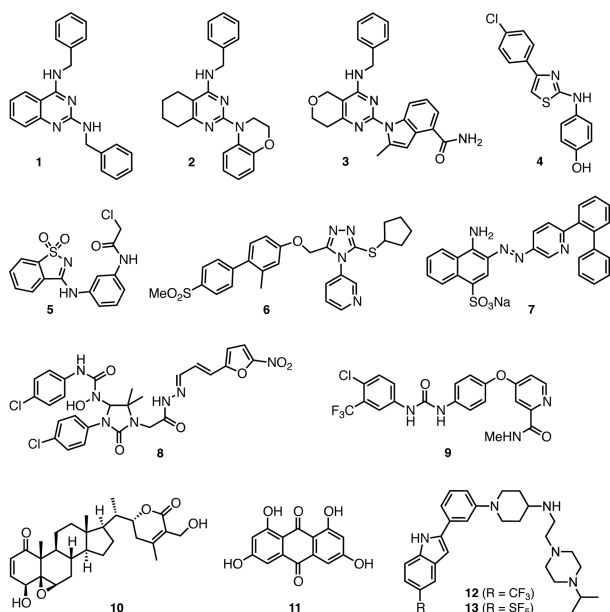
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**Figure 1.** Crystal structure of hexameric, full-length p97 in complex with ADP (PDB ID 3CF3).<sup>19</sup>

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



**Figure 2.** Structures of p97 inhibitors.

sulfonate **7**,<sup>31</sup> and imidazolinone **8**<sup>32</sup> were identified by high throughput screening campaigns, whereas the discovery of the anticancer agent **9**<sup>33</sup> (sorafenib) and the natural products **10**<sup>34</sup> (withaferin A) and **11**<sup>35</sup> (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.<sup>36</sup> In the ADPGlo assay,<sup>37</sup> we determined a  $4.7 \pm 2.0 \mu\text{M}$   $\text{IC}_{50}$  for this compound (Table 1), and we decided to probe the effect of replacing the  $\text{CF}_3$ - with an  $\text{SF}_5$ -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<sup>38</sup> on the imine derived from

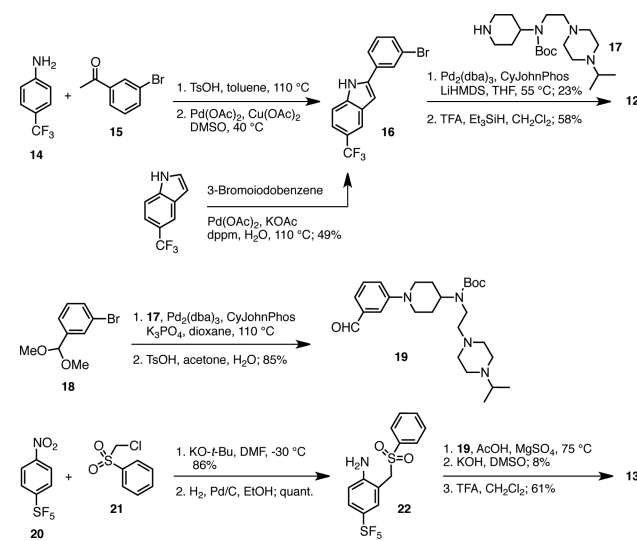
**Table 1.** Biochemical Activities of p97 Inhibitors<sup>a</sup>

entry	compound/R-group	p97-ADPGlo $\text{IC}_{50}$ [ $\mu\text{M}$ ]	p97-ADPGlo Std. Dev. [ $\mu\text{M}$ ]
1	<b>12</b> / $\text{CF}_3$	4.7	$\pm 2.0$
2	<b>13</b> / $\text{SF}_5$	21.5	$\pm 0.4$
3	<b>23</b> / $\text{NO}_2$	0.05	$\pm 0.04$
4	<b>24</b> / $\text{CH}_3$	0.24	$\pm 0.11$
5	<b>25</b> / $\text{OCH}_3$	0.71	$\pm 0.22$
6	<b>26</b> / $\text{OCF}_3$	3.8	$\pm 0.8$

<sup>a</sup> Assay conditions: ADPGlo with 20 nM p97 ATPase WT in the presence of 100  $\mu\text{M}$  ATP.<sup>37</sup> 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<sup>39,40</sup> of aryl bromide **16** with secondary amine **17** and Boc-deprotection (Scheme 1).<sup>41</sup> Subsequently, a more direct

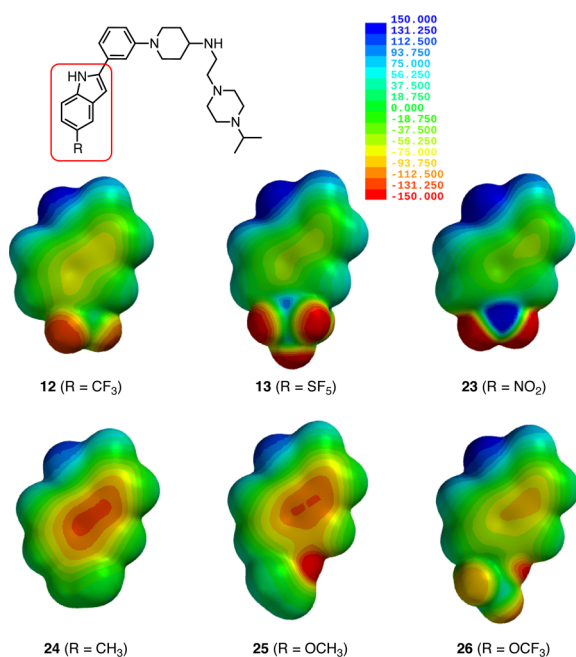
**Scheme 1.** Preparation of  $\text{CF}_3$ - and  $\text{SF}_5$ -Substituted p97 Inhibitors **12** and **13**



synthesis of **16** was accomplished by a  $\text{C}_7\text{H}$ -arylation of commercially available 5-trifluoromethylindole with 3-bromiodobenzene, which provided indole **16** in 49% yield.<sup>42</sup> A different indole synthesis<sup>43</sup> was used for the preparation of the pentafluorosulfanyl analogue **13**. Pd(0)-catalyzed coupling of bromide acetal **18** with amine **17**<sup>41</sup> followed by selective acetal hydrolysis provided aldehyde building block **19**. After nucleophilic alkylation of  $\text{SF}_5$ -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  $\text{IC}_{50}$  of  $21.5 \pm 0.4 \mu\text{M}$ . We hypothesized that this decrease could either be due to the larger size of the  $\text{SF}_5$  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

aromatic  $\pi$ -system (Figure 3). Sterically, SF<sub>5</sub>-analogue 13 and CF<sub>3</sub>O-analogue 26 are the closest match, but their electronic

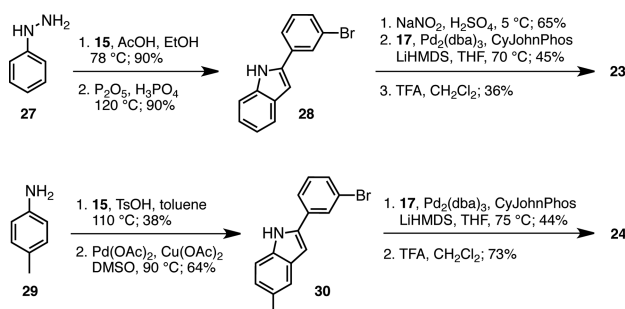


**Figure 3.** Structures and steric/electronic features<sup>46</sup> of new phenyl indole p97 inhibitors. The color coding on the electron-density surface of the indole moiety reflects the electrostatic potential experienced by a positive probe charge (red = attractive, blue = repulsive).

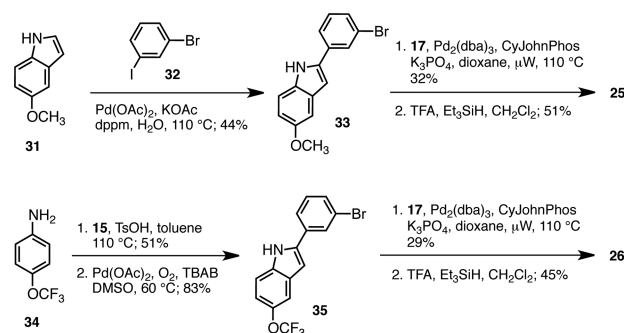
effects on the indole ring and the indole nitrogen are significantly different. As expected, nitro-analogue 23 is the best electronic match of the pentafluorosulfanyl derivative. Sterically, and, in particular, electronically, CH<sub>3</sub>O-analogue 25 is most closely related to CH<sub>3</sub>-analogue 24. Arguably, CF<sub>3</sub>-analogue 12 is somewhat unique in this series, but sterically its closest match would be CH<sub>3</sub>-analogue 24, whereas electronically 12 is situated between SF<sub>5</sub>-analogue 13 and CF<sub>3</sub>O-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.

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<sup>44</sup> in a Fischer indole synthesis in the presence of P<sub>2</sub>O<sub>5</sub> and H<sub>3</sub>PO<sub>4</sub> to give indole 28. Nitration was selective

#### Scheme 2. Preparation of NO<sub>2</sub>- and CH<sub>3</sub>-Substituted p97 Inhibitors 23 and 24



#### Scheme 3. Preparation of CH<sub>3</sub>O- and CF<sub>3</sub>O-Substituted p97 Inhibitors 25 and 26



for the C-5 position of the indole<sup>45</sup> 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<sup>38</sup> 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).

The C<sub>2</sub>H-bond activation<sup>42</sup> 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<sub>3</sub>O-analogue 25 in 7% yield over the three steps. Starting with the commercially available aniline 34, the corresponding CF<sub>3</sub>O-analogue 26 was prepared in four steps and 6% overall yield using the alternative imine-cyclization<sup>38</sup> 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<sub>50</sub> 0.05 ± 0.04  $\mu$ M). CF<sub>3</sub>O-analogue 26 was considerably less active (entry 6, IC<sub>50</sub> 3.8 ± 0.8  $\mu$ M), but was slightly more potent than CF<sub>3</sub>-analogue 12. Methylated 24 and methoxylated 25 had intermediate but still submicromolar IC<sub>50</sub>s (entries 4 and 5, IC<sub>50</sub> 0.24 ± 0.11 and 0.71 ± 0.22  $\mu$ M, respectively).

Most of the literature precedence on the biological activities of SF<sub>5</sub>-containing compounds versus the corresponding CF<sub>3</sub>-analogues report relatively minor, but predominantly improved potencies.<sup>47</sup> For example, an SF<sub>5</sub>-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.<sup>10</sup> In the mefloquine series, SF<sub>5</sub>-substitution of CF<sub>3</sub>-groups did not change potency.<sup>8,16</sup> In a study of cannabinoid receptor ligands, SF<sub>5</sub>-pyrazoles generally showed slightly higher or equivalent CB<sub>1</sub> receptor affinity and selectivity toward the CB<sub>2</sub> receptor relative to both CF<sub>3</sub>- and *t*-butyl-analogues.<sup>14</sup> A recent analysis of matched pairs of CF<sub>3</sub>/SF<sub>5</sub>-analogues from Novartis detected a mean 1.6-fold increase in *in vitro* potency.<sup>13</sup> 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

CH<sub>3</sub>O-, CF<sub>3</sub>O-, CH<sub>3</sub>-, SF<sub>5</sub>-, and NO<sub>2</sub>-analogues of the CF<sub>3</sub>-indole **12**, IC<sub>50</sub>s vary >400-fold, and the SF<sub>5</sub>-analogue is, in fact, the least active compound. The CF<sub>3</sub>O-derivative is biochemically the closest match of the CF<sub>3</sub> 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  $\pi$ -system of the indole and yet exhibits the most potent p97 inhibition of this set with a 50 nM IC<sub>50</sub>, a 5-fold increase in potency compared to the electron rich CH<sub>3</sub>-analogue **24**, and a 430-fold increase compared to the electronically similar SF<sub>5</sub>-derivative **13**. The relative lipophilicity in this series, as expressed by clogP values<sup>48</sup> 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<sub>50</sub> values. An intriguing alternative explanation is that the indole ring of these p97 inhibitors is involved in  $\pi$ -stacking interactions<sup>49</sup> with the protein, which might explain both the affinity for electron-rich  $\pi$ -systems (such as in **24** and **25**) as well as the improved activity of the flat, strongly electron-deficient  $\pi$ -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<sub>3</sub>-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<sub>50</sub>s between the SF<sub>5</sub>-analogue **13** and the NO<sub>2</sub>-analogue **23**. Contrary to expectation and literature precedence, we found that it was not the SF<sub>5</sub>- but the CF<sub>3</sub>O-analogue that was biochemically the closest match to the CF<sub>3</sub>-substituted lead structure **12** and that, in spite of the similar electron-withdrawing effect on the indole core, SF<sub>5</sub>- and NO<sub>2</sub>-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  $\pi$ -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/acsmchemlett.5b00364](https://doi.org/10.1021/acsmchemlett.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; dpmm, 1,1-bis(diphenylphosphino)methane; TBAB, tetra-*n*-butylammonium bromide; TFA, trifluoroacetic acid

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