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New Class of Selective Estrogen Receptor Degraders (SERDs): Expanding the Toolbox of PROTAC Degrons

Lucia Wang,[†,§] Valeria S. Guillen,[‡,§] Naina Sharma,[‡] Kevin Flessa,[†] Jian Min,[‡] Kathryn E. Carlson,[‡] Weiyi Toy,[∥] Sara Braqi,[†] Benita S. Katzenellenbogen,[‡] John A. Katzenellenbogen,[‡] Sarat Chandarlapaty,[∥] and Abhishek Sharma*[,†]

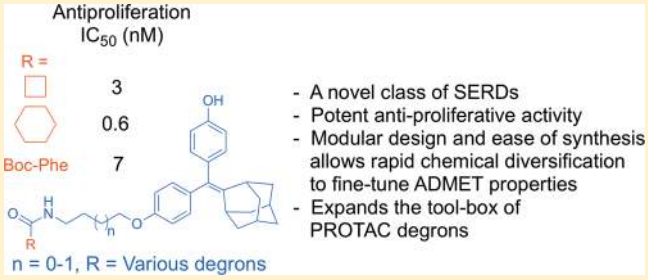
[†]Department of Chemistry and Chemical Biology, Stevens Institute of Technology, Hoboken, New Jersey 07601 United States

[‡]Department of Chemistry, Department of Molecular and Integrative Physiology, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801 United States

[∥]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, New York 10065, United States

Supporting Information

ABSTRACT: An effective endocrine therapy for breast cancer is to selectively and effectively degrade the estrogen receptor (ER). Up until now, there have been largely only two molecular scaffolds capable of doing this. In this study, we have developed new classes of scaffolds that possess selective estrogen receptor degrader (SERD) and ER antagonistic properties. These novel SERDs potently inhibit MCF-7 breast cancer cell proliferation and the expression of ER target genes, and their efficacy is comparable to Fulvestrant. Unlike Fulvestrant, the modular protein-targeted chimera (PROTAC)-type design of these novel SERDs should allow easy diversification into a library of analogs to further fine-tune their pharmacokinetic properties including oral availability. This work also expands the pool of currently available PROTAC-type scaffolds that could be beneficial for targeted degradation of various other therapeutically important proteins.



KEYWORDS: *Targeted protein degradation, estrogen receptor, antiproliferation, breast cancer, antagonist*

Estrogen receptor-alpha (ERα) is the target of endocrine therapies for treatment of the more than 70% of breast cancers that are ER-positive.[1] Among these therapies, small-molecule-induced, targeted degradation of ERs is the last line of treatment, especially in metastatic breast cancer patients who have become resistant to therapies that inhibit the function of ER.[2] This targeted destruction of ER is induced by molecules (selective estrogen receptor degraders, SERDs) that possess distinct structural elements for binding to the ligand-binding pocket (LBP) of ER and recruitment of the cellular protein degradation machinery. Despite the immense therapeutic importance of SERDs, the repertoire of molecular scaffolds known to induce ER degradation (degrons) has been rather limited, and their degron properties were discovered serendipitously. Currently, there is only one clinically approved SERD, Fulvestrant[3] (Figure 1a), and some related analogs[4] that possess a core for binding in the LBP and a long alkyl side chain (degron) that induces ER degradation.[3] The clinical utility of Fulvestrant is hampered due to its poor oral bioavailability, so that it has to be administered as a large painful intramuscular injection.[5] Moreover, the bulky and steroidal structure of Fulvestrant also limits further chemical diversification to improve its bioactivity. A second structurally distinct small molecule scaffold/degron known to confer SERD properties is an acrylic acid based side chain, which was first developed in 1994 (GW5638, Figure 1b),[6] as well as more recent versions having diversified ligand core elements but the same side chain; this class of SERDs is still awaiting full clinical evaluation.[7−10]

In view of the extremely limited pool of currently available SERDs,[11] there is an urgent need for development of structurally novel classes of small molecules that are not only capable of inducing ER degradation in breast cancer and blocking cancer cell proliferation, but also ideally would allow easy chemical diversification to fine-tune their physicochemical and biological properties.

Recently, there has been an increased interest in developing targeted protein degradation strategies for the treatment of various types of cancers and other diseases.[12−16] These proteolysis targeting chimeras (PROTACs) possess a targeting ligand attached to a recognition motif ("degron") that binds to E3 ubiquitin ligases or other proteins that ultimately promote ubiquitination-dependent proteasomal degradation of the target protein. In this context, several interesting and useful "degron motifs" have been developed for the targeted destruction of

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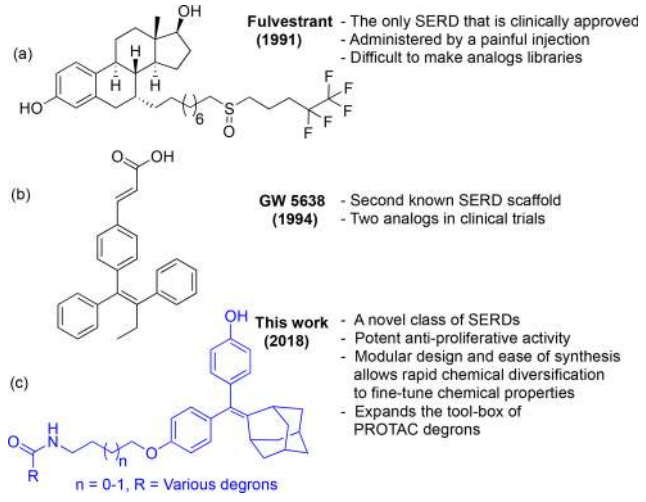


Figure 1. (a,b) Previously known SERD scaffolds and (c) the newly developed class of SERDs. The number in parentheses represents the year of discovery of each SERD. The big time gap between the last discovered SERD (b) and the latest (c) illustrates the challenges in discovering new SERD scaffolds.

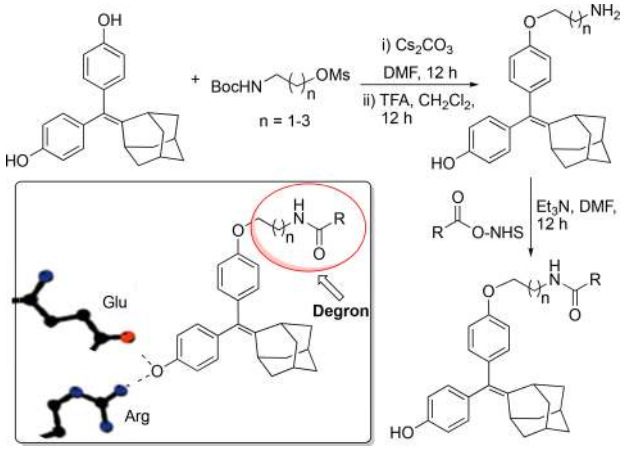
clinically relevant proteins.[12,13,17] The previous PROTACs for ER comprised peptidic[17] or bestatin ester-based degrons,[18,19] which limited their drug-like properties or imparted off-target effects and low potency, besides requiring specific E3 ligases for ubiquitin-mediated degradation.[17,20] In order to realize the full potential of PROTACs as a therapeutic option for breast cancer and other diseases, it would be beneficial to develop novel and simpler degrons that allow the characterization and optimization of functional contributions made by distinct regions of a degron to ultimately aid its clinical application.

Nature devised the ubiquitin-dependent degradation pathway for removing unwanted or damaged cellular proteins. An important component of this protein quality control machinery is the N-end rule pathway, wherein the N-terminus of target proteins is conjugated with a destabilizing amino acid (degron) that is recognized by the ubiquitin proteasome system.[21] In the course of our efforts to develop novel ER antagonists/SERDs,[22,23] we became interested in exploring the selective degradation of ERs using ligands that carry a destabilizing N-end rule amino acid or other degrons. Herein, we report on a novel class of PROTACs (Figure 1c) that (i) effectively induce ER degradation and show potent antiproliferative activity; (ii) can be easily diversified to fine-tune their biological/ADMET properties, and (iii) significantly expand the repertoire of currently known PROTAC scaffolds.

Our molecular design for SERDs involved a bisphenolic-adamantyl system (Scheme 1) as the "core" to anchor our ligand inside the LBP of ER. We had earlier developed these cyclic cores as very high affinity ligands (ca. 2−3 times higher affinity than estradiol) for ER.[24] Our molecular modeling studies (Figure S2 and S3) suggested that one of the phenols of these ligands forms the canonical H-bonds with Glu353 and Arg394 in ERα, while a side chain attached on the other phenol is expected to be projected outside the surface of ER through an exit channel in the antagonist conformation of the ligand-binding domain. Thus, we used this second phenol to attach an alkyl linker possessing an amine terminus for coupling with various degron candidates.

We initially selected Leu, Phe, and Trp from the pool of amino acids that are known to participate in the N-end rule pathway.[21]

Scheme 1. Divergent Route for Synthesis of Novel SERDs; (inset) Our Model for Design of ER Targeting PROTACs



This selection was based on the assumption that mild to strong hydrophobicity might also contribute to their degron action on ER, as is the case with other SERDs. In view of the easy availability of Boc-amino acids and the hydrophobic character of Boc group,[25] these N-protected (L) amino acids were chosen as degron-type elements along with their unprotected versions for comparison. These amino acids were converted into their NHS esters and then coupled to the amine side chain of ER ligands to give compounds **2**−**4** (Scheme 1, Table 1).

Binding assays showed that installation of these three degron side chains on this ligand core did not preclude them from binding directly to ER (Table 1), although their relative binding affinities (RBAs) decreased somewhat from that of the parent bisphenolic core.[24] Assessing cellular levels of ERα by in-cell Western (ICW) assays (Figure 2A, Table 1) showed that only the Boc-Trp analog (**4**) had high, subnanomolar potency, although it was less efficacious than Fulvestrant; removal of the Boc group in **4** completely abolished its SERD activity (not shown). All three of the Boc-amino acid PROTACs were efficacious, low nanomolar inhibitors of MCF-7 cell proliferation (Table 1, Figure 3A), with the Boc-Phe and Boc-Trp analogs (**3** and **4**) being the most potent. Thus, the Boc group as well as the amino acid side chain make distinct contributions to the ERα degradation and antiproliferative activities.

Encouraged by the initial success of our new PROTAC model for ER, we sought to systematically investigate whether the ER degrading/antiproliferative capability depends on increased structural complexity/hydrophobicity of degron motifs in PROTACs. Thus, we prepared a series of bridged bicyclic and tricyclic analogs (**5**−**10**) and a variety of monocyclic analogs (**11**−**15**); with the adamantyl[26] candidate degron, and the length of the linker chain was also varied (**5**−**7**). The RBA values of most of these compounds were comparable to those of the previous series (**1**−**4**), with one (**11**) exceeding that of fulvestrant (**1**).

All members of the bi- and tricyclic group (**5**−**10**) were low nanomolar antiproliferative agents (Table 1, Figure 3B), with overall the three compounds having an adamantane degron (**5**−**7**) giving more complete suppression than those with other degron candidates (**8**−**10**). The length of the linker in compounds **5**−**7** had only a modest effect on antiproliferative potency and efficacy. Although the potencies of these compounds in degrading ERα were good, the extent of degradation varied (Table 1, Figure 2B), with compounds **6**

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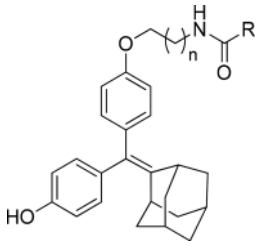
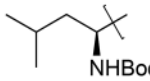
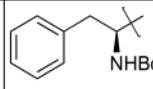
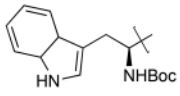
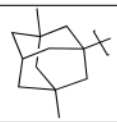
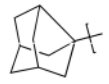
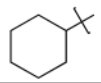
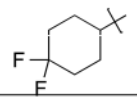
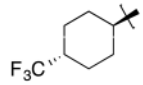
Table 1. Structure−Activity Data of Novel SERDs: Summary of ERα Binding Affinity, Potency, and Efficacy in Antiproliferation and ERα Downregulation Assays[a]



Entry	Structure (R)	RBA (estradiol = 100)	Antiproliferation IC_{50} (nM) [% of vehicle][b]	ERα Downregulation IC_{50} (nM) [% of vehicle][b]
1	Fulvestrant	61 ± 1	<0.1 [0]	<0.1 [9]
	Lipophilic amino acids as Degrons			
2		14 ± 1	36 [20]	636 [56]
3		14 ± 4	7 [25]	307 [71]
4		20 ± 6	16 [16]	0.5 [45]
	Tricyclic and Bicyclic Degrons			
5	 (C2 linker, n=1)	21 ± 6	17 [16]	ND[c] [76]
6	 (C3 linker, n=2)	26 ± 6	9 [13]	3 [42]
7		11 ± 3	13 [13]	6 [51]
8		6.0 ± 0.1	5 [57]	10 [42]

Entry	Structure (R)	RBA (estradiol = 100)	Antiproliferation IC_{50} (nM) [% of vehicle][b]	ERα Downregulation IC_{50} (nM) [% of vehicle][b]
	Tricyclic and Bicyclic Degrons			
9		17 ± 2	12 [42]	2 [71]
10		37 ± 0.3	9 [42]	0.5 [53]
	Monocyclic Degrons			
11		70 ± 1	3 [15]	ND[c] [69]
12		28 ± 6	0.6 [13]	0.4 [35]
13		30 ± 5	5 [15]	ND[c] [76]
14		30 ± 0.1	4 [20]	ND[c] [67]
15		10 ± 0.4	0.5 [13]	2 [31]

[a] n = 3, unless otherwise noted. [b] Efficacy values are expressed as % of ERα level (Figure 2) or relative proliferation rate (Figure 3) at the highest compound dose relative to vehicle control. Proliferation with Fulvestrant is considered zero. [c] IC_{50} values could not be determined accurately due to limited ERα degradation.

and **8** being more complete than the others, and **5** being the least potent and efficacious.

As a group, the monocyclic compounds (**11**−**15**) proved to be more potent and complete as antiproliferative agents than the bridged polycyclic group (Table 1, Figure 3C), with compounds **12** and **15** having subnanomolar IC_{50} values. This group was also more uniformly and fully efficacious, and all were as good as the best of the Boc-amino acids and bridged bi- and tricyclic series. Again, as ERα degraders (Table 1, Figure 2C), there were wider variations, with **12** and **15** again having the most complete reduction of ERα levels. The turnover of ER was inhibited by proteasome inhibitor (MG132) (see Figure S1). Because the extent of degradation by compounds **11**, **13**, and **14** (as well as **5** from the bridged cyclic group) was modest, accurate IC_{50} values could not be determined for these compounds.

It is notable that the above dose−response studies also suggest that the inhibitory activity of these PROTACs is not reduced at higher concentrations. The absence of this "hook effect" is an

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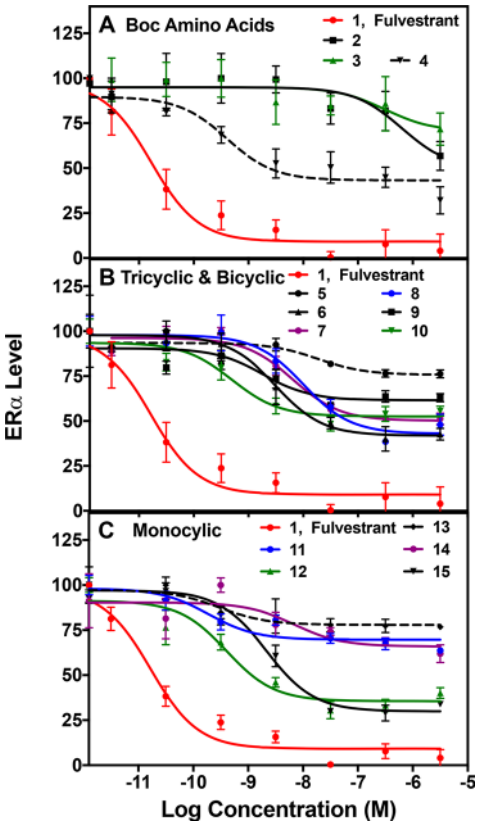

Figure 2. Dose−response of ERα level in MCF-7 cells. MCF-7 cells in stripped medium were treated with indicated concentrations of Fulvestrant (**1**) or compounds **2**−**15** for 24 h, and ERα levels were determined by in-cell Western analysis. Values represent average ± SEM of four measurements. 100% represents ERα levels in vehicle treated samples (for representative Western blots, see SI, Figure S1).

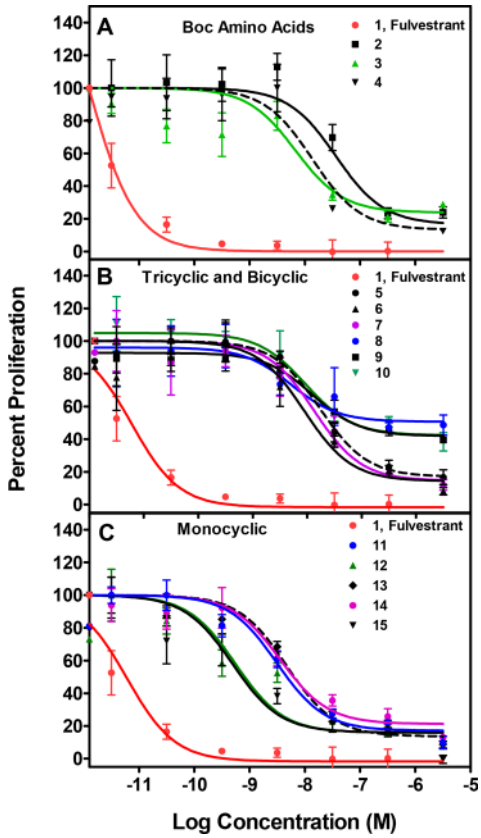

Figure 3. Dose−response of MCF-7 cell proliferation. MCF-7 cells in complete medium were treated with indicated concentrations of Fulvestrant (**1**) or compounds **2**−**15** for 6 days, and cell densities were determined by MTT assays. Values represent average ± SEM of four measurements. 100% represents proliferation in vehicle treated samples.

important benefit of these novel PROTACs as compared to many of the current PROTACs that show reduced potency at higher concentrations.[15] Overall, the compounds possessing degrons from N-end rule pathway (**2**−**4**) were less effective ERα degraders and antiproliferative agents as compared to those possessing bicyclic and monocyclic degrons (**5**−**15**). Further, the comparatively better potency of Fulvestrant could be due to its higher affinity (RBA = 61) toward the estrogen receptor compared to all of the new ligands but compound **11**.

We selected for further characterization one compound of interest from each category, based on the structural novelty of the degron and a combination of their potency and efficacy in antiproliferative and ERα degradation assays: these were the Boc-Trp (**4**), the C3-linked adamantane (**6**), and particularly the trifluoromethyl cyclohexane (**15**). We assayed their activity as antagonists on three estrogen-regulated genes, progesterone receptor (PgR), pS2, and GREB1 (Figure 4). All of the compounds reduced the low control vehicle level of agonist activity (gray bars), and they all functioned as effective antagonists of ERα transcriptional regulation of these genes in the presence of E2 (stippled dark bars).

We have previously shown that the bisphenolic-adamantyl cores are high affinity ligands and partial agonists on ERα.[24] Therefore, the ERα degradation and antiproliferative and antagonist activities of our novel PROTACs are likely mediated mainly by the side chains (presumed to be degrons). Our data suggests that hydrophobicity of the degron, alone, is not a major driver of SERD or antiproliferative action of this new class of SERDs. In fact, the degrons in the most potent compounds (**4**, **11**, **12**, and **15**) had lower cLogP values (SI, Table S1) as compared to other degrons. The mechanism of action of our mono-Boc-protected amino acid degrons (**2**−**4**) also appears to be distinct from a recently described Boc_3Arg degron that requires all three Boc groups to be present on an arginine motif to retain its activity.[27] Crews et al. have done pioneering investigations of the adamantyl motif as a degron for androgen receptor and some other proteins.[13,26] These studies suggest involvement of Heat Shock Proteins (Hsp 70 and 90) in the degradation pathway. Because Hsp 90 is also known to regulate folding/unfolding of ER,[28] this pathway might be playing a role in observed SERD behavior of some of our compounds (**5**−**8**). In addition, other factors such as enhanced cell permeability and/or inducement of distinct destabilizing conformations of ER could also contribute to the increased potency of our compounds. In fact, the observation that some of our most potent antiproliferative agents (e.g., **12** and **15**, possessing cyclohexyl degrons) were not complete ERα degraders (Table 1) suggests that these compounds could also be operating by inducing an antagonist conformation of ERα, a scenario previously shown in the case of Fulvestrant.[29] Although the precise mechanism of action of Fulvestrant is still unclear, previous studies suggest that the long alkyl chain of Fulvestrant interacts with a hydrophobic groove on ER that otherwise recruits ER coactivator proteins.[3] Subsequently, two distinct

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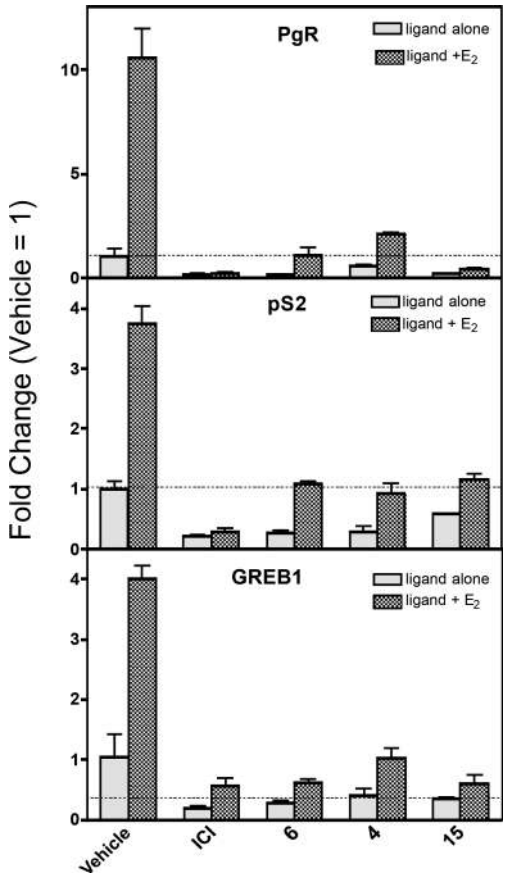

Figure 4. Assessment of selected compounds as antagonists of the expression of ER-regulated genes. MCF-7 cells were treated with 3 μM of the indicated compounds or Fulvestrant, either alone or in the presence of 1 nM estradiol (E2) for 24 h. Gene expression level was determined by qRT-PCR.

pathways operate: exposure of hydrophobic residues on ER and recruitment of corepressors to the hydrophobic groove.[3,30]

Docking studies of our novel SERDs into ERα (SI, Figures S-2 and S-3) reveal that unlike Fulvestrant, the degrons of our compounds are unable to fully occupy the coactivator groove due to the shorter linker lengths. After passing through an exit channel, the Boc-amino acid degrons project in a direction opposite to that of tricyclic and monocyclic degrons (Figure S-3C). Interestingly, the tricyclic/monocyclic degrons are likely projected toward the loop connecting the helix-11 and -12 (Figures S-2 and S-3A,B). Collectively, the above results indicate likely involvement of novel and decoupled mechanisms for ER degradation and antagonism for our SERDs. Studies to elucidate more precisely the mechanism of action of these structurally distinct degrons are currently underway.

In conclusion, this work represents a new addition to the very limited pool of distinct molecular scaffolds (Fulvestrant and GW type compounds) that are known to induce selective degradation of ERα and also antagonize ERα. Our molecular design strategy involved a PROTAC-based model, wherein a synthetically tractable ligand core was attached to various novel degron-type side chains in a highly modular fashion. Through these studies, we found members of three distinct degron classes (lipophilic amino acids, bridged cyclic systems, and simpler monocyclic systems) that had low nanomolar potencies as ERα degraders and antiproliferative agents that also inhibited ER target gene expression. The modular design, ease of synthesis and ready availability of ligand cores and degrons of this class of SERDs lay the foundation for rapid chemical diversification to optimize the ADMET properties, an area that has been a major bottleneck in clinical utility of SERDs. Beyond SERDs, this study also significantly expands the currently available toolbox for PROTACs, and these novel degrons could be useful for the development of new PROTACs for targeted degradation of various other therapeutically relevant proteins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00106.

Detailed experimental procedures for synthesis of compounds, characterization data for all compounds, cLogP data of degrons, biological assay protocols, and molecular modeling data/method (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: abhishek.sharma@stevens.edu.

ORCID

John A. Katzenellenbogen: 0000-0003-0914-0010

Abhishek Sharma: 0000-0001-6070-4403

Author Contributions

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

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ADMET, absorption, distribution, metabolism, excretion, toxicity; E2, estradiol; ER, estrogen receptor; GREB1, growth regulation by estrogen in breast cancer 1; Hsp, heat shock protein; ICW, in-cell Western assay; LBP, ligand binding pocket; NHS, *N*-hydroxysuccinimide; PgR, progesterone receptor; PROTAC, proteolysis targeting chimera; RBA, relative binding affinity; SERD, selective estrogen receptor degrader

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