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Perspective

Targeting the Estrogen Receptor for the Treatment of Breast Cancer: Recent Advances and Challenges

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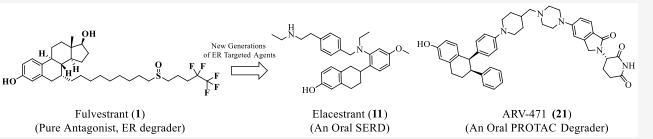
ABSTRACT: Estrogen receptor alpha (ERα) is a well-established therapeutic target for the treatment of ER-positive (ER+) breast cancers. Despite the tremendous successes achieved with tamoxifen, a selective ER modulator, and aromatase inhibitors (AIs), resistance to these therapies is a major clinical problem. Therefore, induced protein degradation and covalent inhibition have been pursued as new therapeutic approaches to target ERα. This Perspective summarizes recent progress in the discovery and development of oral selective ER degraders (SERDs), complete estrogen receptor antagonists (CERANs), selective estrogen receptor covalent antagonists (SERCAs), and proteolysis targeting chimera (PROTAC) ER degraders. We focus on those compounds which have been advanced into clinical development.



INTRODUCTION

Breast cancer (BC) remains the most common cancer among women, accounting for approximately 25% of new cases and 16% of cancer mortality worldwide.[1] Despite tremendous advances in the treatment of human breast cancers and dramatic improvements in survival rates, over half a million women died from BC worldwide in 2020, and BC is still the second leading cause of cancer mortality among women worldwide.[2,3] In the United States alone, over 250,000 women are diagnosed with BC each year.[4] Therefore, there is still an urgent need for the development of more effective and safer therapies for the treatment of human BC.

Breast cancer is a heterogeneous disease with multiple subtypes, and our understanding of these subtypes has evolved over the years. The most common and widely accepted classification of BC is from an immunohistochemical perspective, based on the expression of estrogen receptor (ER) and progesterone receptor (PR), two steroid hormone receptors (HRs), and the human epidermal growth factor receptor 2 (HER2). Using transcriptome profiling, the most commonly accepted BC subtypes are (1) Luminal A, (2) Luminal B, (3) Basal-like/triple negative (ER−/PR−/HER2−), and (4) HER2-enriched. Most of Luminal A and Luminal B subtypes are ER-positive (ER+). In fact, approximately 70% of all newly diagnosed breast cancers are ER+.

Since the discovery of the ER pathway followed the isolation of estrone, a weak estrogen, almost a century ago, there has been tremendous efforts in the development of agents to target ER or the ER pathway for the treatment of ER+ BC. Currently approved approaches that directly target ERα signaling can be grouped into three classes:[5]

(1) Selective estrogen receptor modulators (SERMs), such as tamoxifen, which antagonize the receptor by blocking the binding of estrogens and prevent ER signaling. While SERMs are highly effective at blocking the activation function AF2 domain, they leave the AF1 domain of ERα open, and this can lead to agonism in certain tissues (e.g., uterine), which has the potential to cause tumor growth.[6−8] For example, long-term treatment with tamoxifen is known to promote endometrial cancer and thromboembolic disease.[9,10]

(2) Third-generation aromatase inhibitors (AIs), such as anastrozole, letrozole, and exemestane, which prevent ER signaling by inhibiting estradiol biosynthesis. While AIs bring significant therapeutic benefits, breast cancers can become resistant due to mutations in the *ESR1* gene, which encodes ERα, that arise after prolonged treatment, resulting in constitutive activation of ERα signaling.[11,12]

(3) Pure and selective estrogen receptor antagonists and degraders (SERDs), of which fulvestrant and elacestrant are the currently approved drugs.[13−16]

Breast cancer relapse and resistance are observed in 30−50% of patients, which presents a significant challenge for advanced metastatic breast cancer (MBC) patients.[17] Multiple molecular mechanisms are known to contribute to therapeutic resistance,

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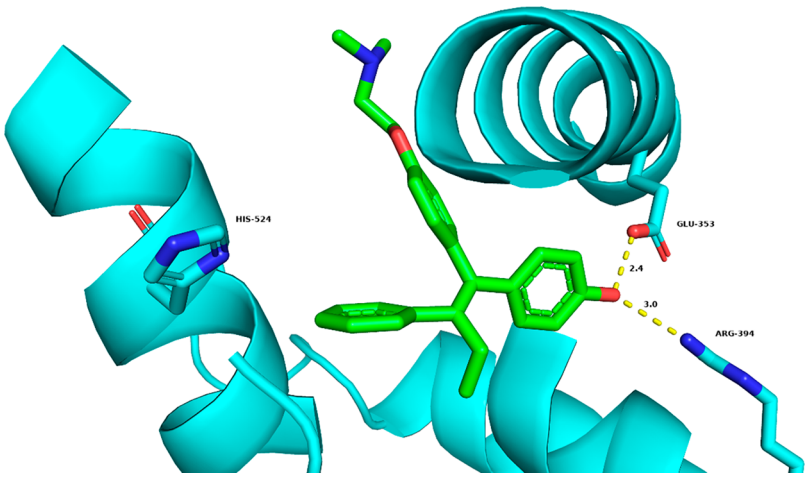

Figure 1. Crystal structure of tamoxifen bound to the ERα ligand-binding domain (PDB code 3ERT). Tamoxifen through its phenol group interacts with Glu-353 and Arg-394 of ERα through hydrogen bonding. The basic tertiary amine side chain in tamoxifen displaces H12, disrupting coactivator binding.

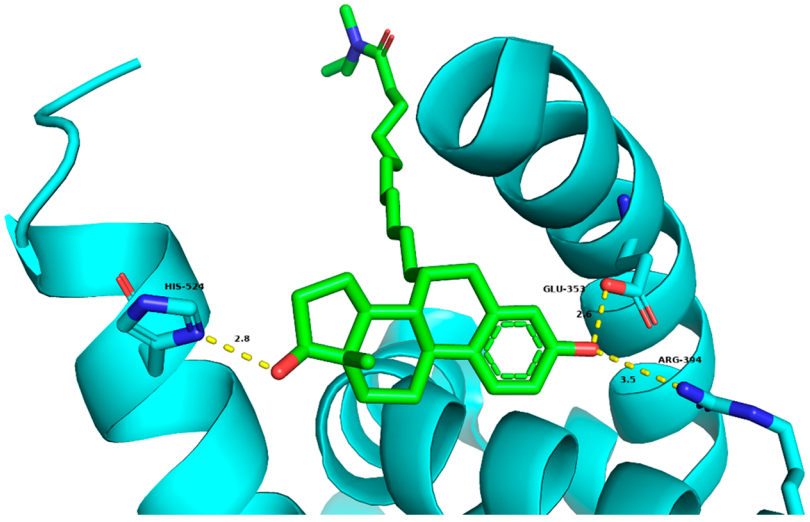

Figure 2. Structure of fulvestrant analog Desmethyl ICI164,384 with ERα (PDB code 7R62).

including ligand-independent activation via the PI3K/AKT/mTor[18−20] and RAS/RAF/MEK/ERK pathways[21] and gain-of-function mutations (e.g., Y537S and D538G) in *ESR1*.[22,23] In addition, endocrine resistance can occur via altered ER interactions with coactivators/corepressors, or via compensatory crosstalk by oncogenic signaling pathways between ER and growth factor receptors.[24] Point mutations in *ESR1* are frequent drivers of resistance in ER+ MBC.[25] The most common ligand-binding domain (LBD) point mutations in *ESR1* are D538G and Y537S, which promote estrogen-independent ER transcriptional activity, which leads to decreased sensitivity to AIs, SERMs, and SERDs.[26] Structurally, these mutations stabilize helix 12 (H12) of ER in the active conformation, similar to wild-type (WT) ER when bound to estrogen. The stabilization of H12 allows the ligand-independent binding of coactivators and decreases the affinity for estrogen and tamoxifen (Figure 1).[27]

In addition to ER point mutations, the *ESR1* gene can form a variety of fusion proteins, which retain the N-terminal DNA-binding domain of the ER but without the LBD. These *ESR1* fusion proteins drive cell proliferation and motility and upregulate the expression of epithelial-to-mesenchymal transition (EMT)-related genes to support metastatic growth.[28] In the development of ER-targeted therapies, in addition to traditional SERM molecules, fulvestrant (faslodex) and RAD1901 (elacestrant) represent important additions as pure ERα antagonists. A crystal structure of an analog of fulvestrant denoted Desmethyl ICI164,384 is shown in Figure 2 to demonstrate its interactions with the ERα LBD.

The alkyl side chain of fulvestrant extends out of the ligand binding pocket, displacing H12, thereby blocking coactivator binding. The core contains a phenol which participates in hydrogen-bonding interactions with Glu-353 and Arg-394, whereas the alcohol moiety forms a hydrogen bond with His-524. Despite its limitations of poor solubility and lack of oral bioavailability, fulvestrant was found to be as safe and effective as first-line or second-line endocrine therapy.[29] Fulvestrant was also approved to treat ER+/HER2− advanced or metastatic breast cancer in combination with palbociclib, a CDK4/CDK6 inhibitor, in women with disease progression after first-line endocrine therapy. The clinical success of fulvestrant has inspired the discovery and development of a second generation of oral SERD molecules for the treatment of ER+ BC.[30,31] A number of oral SERD molecules have been advanced into clinical development, such as SAR439839 (**13**, Sanofi, Phase 3),

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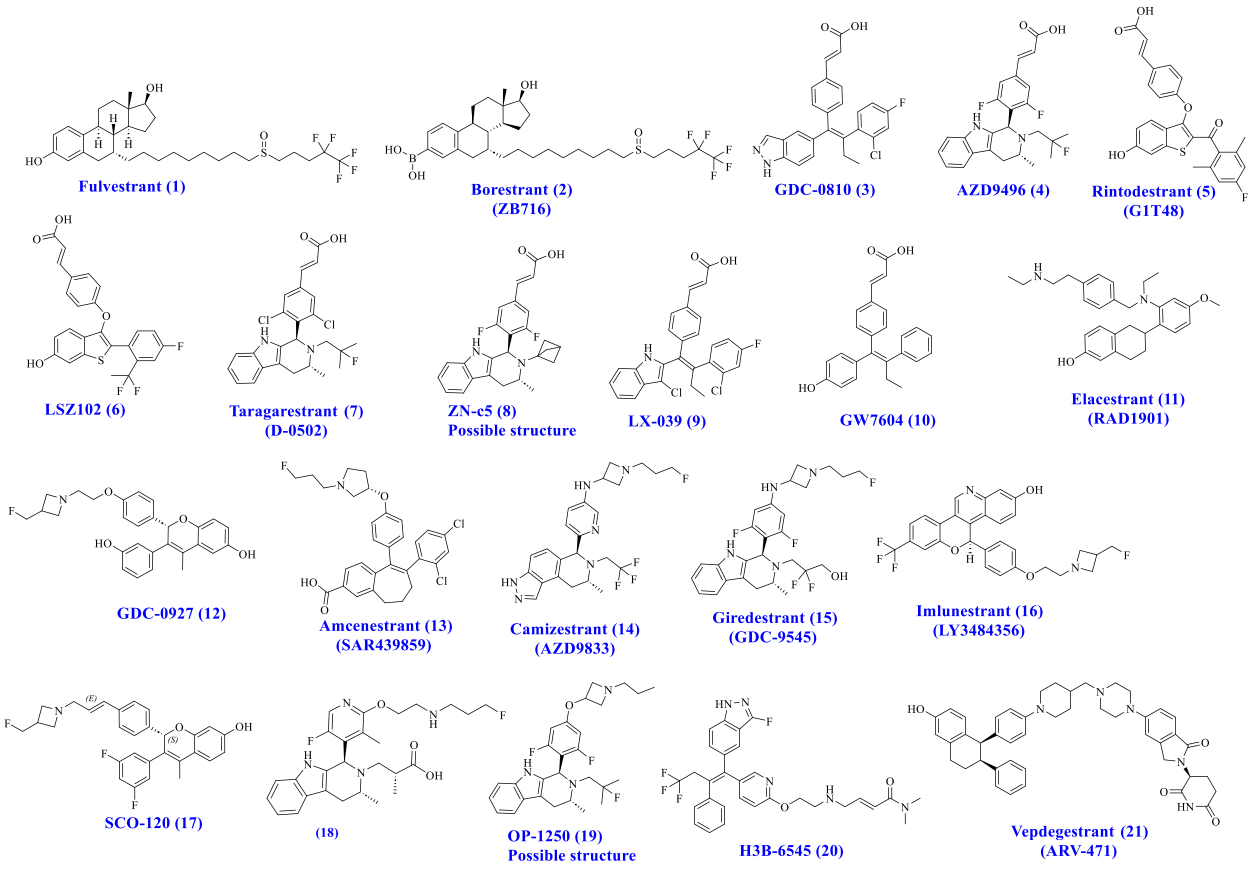

Figure 3. Structures of SERDs, SERCA, CERANs, and PROTACs.

AZD9833 (**14**, AstraZeneca, Phase 3), GDC-9545 (**15**, Roche/Genentech, Phase 3), G1T48 (**5**, University of Illinois/G1 Therapeutics, Phase 1/2), LSZ102 (**6**, Novartis, Phase 1/2), LY3484356 (**16**, Eli Lilly, Phase 2/3), ZN-c5 (**8**, Zentalis, Phase 1), OP-1250 (**19**, Olema, Phase 2), SCO-120 (**17**, Sun Pharma, Phase 1), SCR-6852 (Jiangsu Simcere, Phase 1), AND019 (Kind Pharma, Phase 1), LX-039 (**9**, Shandong Luoxin, Phase 1), and SHR9549 (Jiangsu Hengrui, Phase 1).[32−35] More recently, heterobifunctional degraders of ER have gained significant attention, and two such compounds, ARV-471 (**21**, Arvinas, Phase 2)[36,37] and AC682 (Accutar Biotech, Phase 1),[38] are now in clinical development (Figure 3).

Inspired by the clinical success of covalent inhibitors for other therapeutic targets such as EGFR,[39−43] BTK,[44−46] and KRAS G12C[47−51] for the treatment of human cancers, selective ER covalent antagonists (SERCAs) have been discovered, and one such compound, H3B-6545 (**20**, H3 Biosciences), has been advanced into Phase 1/2 clinical development.

We review herein the recent discovery and development of oral SERDs, complete estrogen receptor antagonists (CERANs), selective estrogen receptor covalent antagonists (SERCAs), and ER proteolysis targeting chimera (PROTAC) molecules. We will first discuss the scientific rationale for the development of these new generations of ER-targeted agents. We will then review their design strategy, followed by a brief structure−activity relationship (SAR) analysis and discussion of the chemical synthesis of clinical SERDs, CERAN, SERCAs, and PROTACs. We will discuss their current clinical data, development status, and future directions and challenges of these new generations of ER-targeted agents for the treatment of ER+ BC.

SCIENTIFIC RATIONALE FOR THE DEVELOPMENT OF NEW GENERATIONS OF ER-TARGETED AGENTS

The two significant isoforms of estrogen receptors are ERα and ERβ, which have different roles in human breast tumors and normal tissues.[52] ER isoforms can either homodimerize or heterodimerize and then translocate to the nucleus and bind coactivators to form a transcriptionally active complex that promotes the proliferation and survival of BC cells (Figure 4). The current standard of care (SOC), fulvestrant is a pure ER antagonist and is used for patients whose condition has reached a metastatic state. It antagonizes ERα in nearly all ER-expressing tissues and is the only clinically approved agent that can partially eradicate mutant ERα activity to basal levels. Fulvestrant competitively binds to the ligand-binding pocket and induces the degradation of ERα by disrupting H12, as shown by its analog Desmethyl ICI164,384 (Figure 2). By competing with estrogens for receptor binding, it can also antagonize ERα activity when ERα is not degraded, so the antitumor efficacy stems from the combined effect of ERα antagonization and ERα degradation.[53] Fulvestrant can be administered as a monotherapy, or with a CDK4/CDK6 inhibitor, or with a PI3K inhibitor in tumors with PIK3CA-activating mutations.[54−60] Despite its clinical success, fulvestrant has certain limitations because of its pharmacokinetic (PK) liabilities, which include poor solubility and lack of oral bioavailability. In the clinic, 500 mg of fulvestrant is administered intramuscularly into the buttocks on days 1, 15, and 29 and once monthly thereafter. Its

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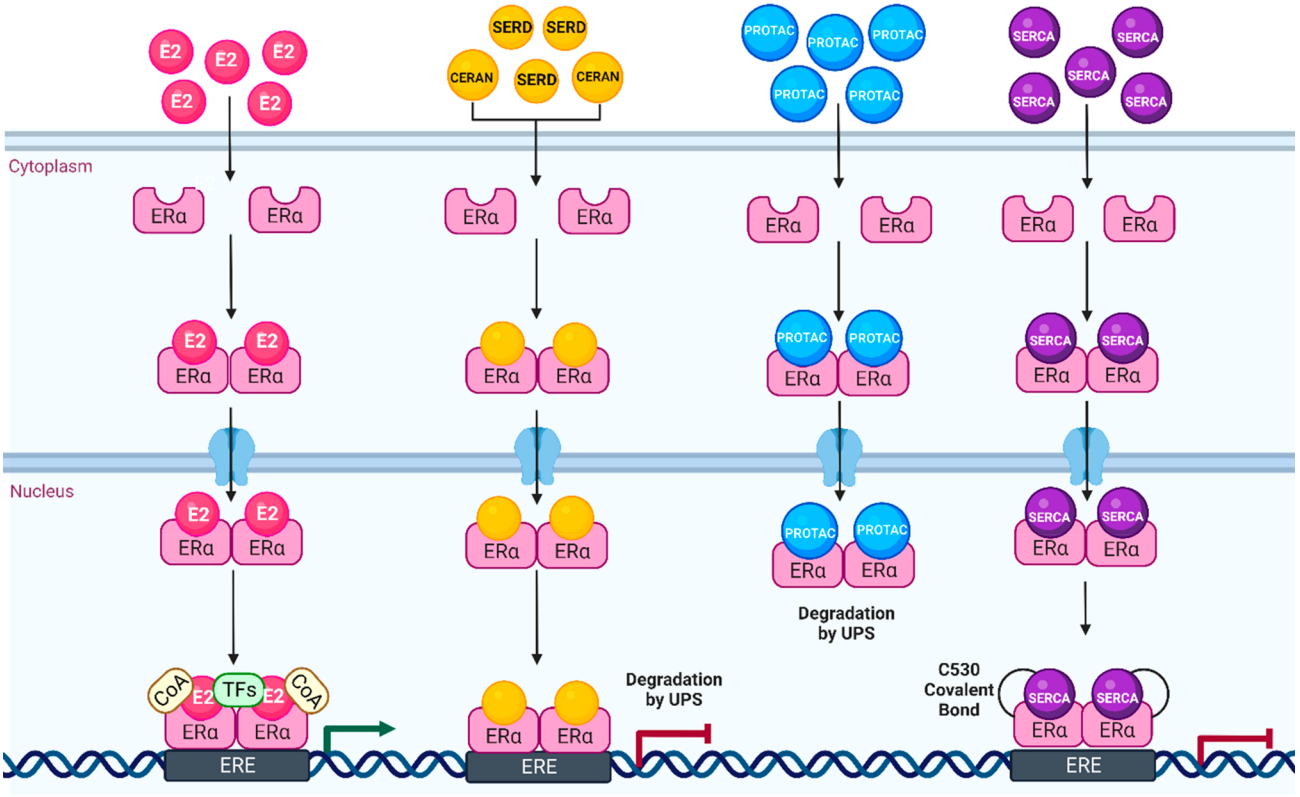

Figure 4. Mechanism of ERα signaling pathway using estradiol (E2), SERDs, CERAN, PROTACs, and SERCAs. CoA corresponds to coactivators, ERE denotes an estrogen response element, TF denotes transcription factors, and UPS denotes the ubiquitin−proteasome system. This diagram was created with BioRender.

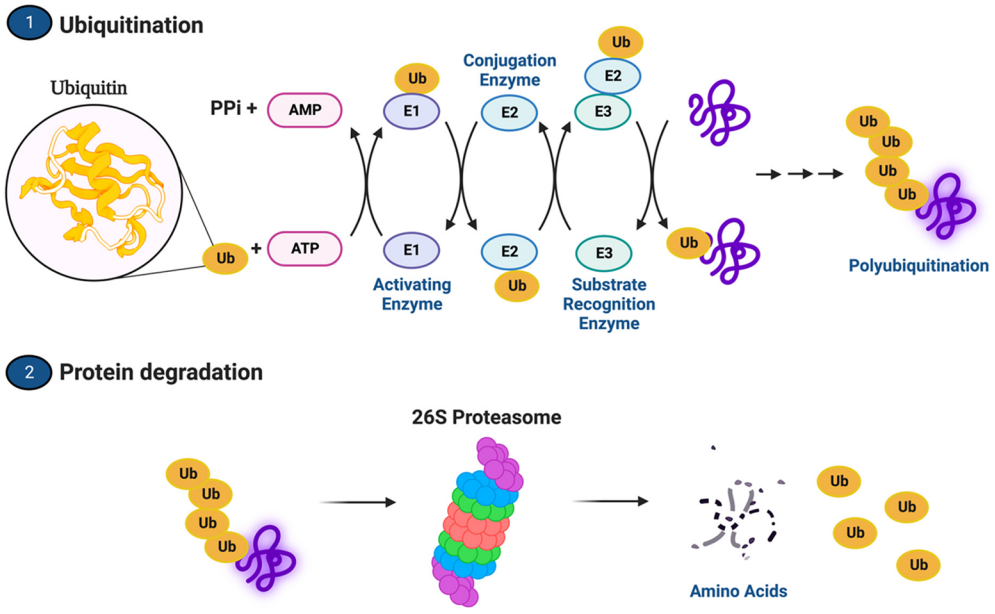

Figure 5. Mechanism of the ubiquitin−proteasome pathway. PPI corresponds to inorganic pyrophosphate, AMP corresponds to adenosine monophosphate, ATP denotes adenosine triphosphate, and Ub denotes ubiquitin. E1 corresponds to the activating enzyme, E2 corresponds to the conjugation enzyme, and E3 is the substrate recognition enzyme. This diagram was created with BioRender.

infrequent administration and short half-life (<24 h) limit its engagement with ERα and induced ER degradation.[61] To address these important limitations, orally bioavailable SERDs have been discovered and developed, which permit an oral route of administration and more frequent dosing schedules with the objective to achieve more complete ER depletion.

More recently, heterobifunctional small-molecule degraders based upon the PROTAC technology have been developed to target ER. A PROTAC degrader utilizes and recruits endogenous cellular quality control machinery to induce the degradation of target proteins.[62−65] Both SERD and PROTAC modalities take advantage of the ubiquitin−proteasome system

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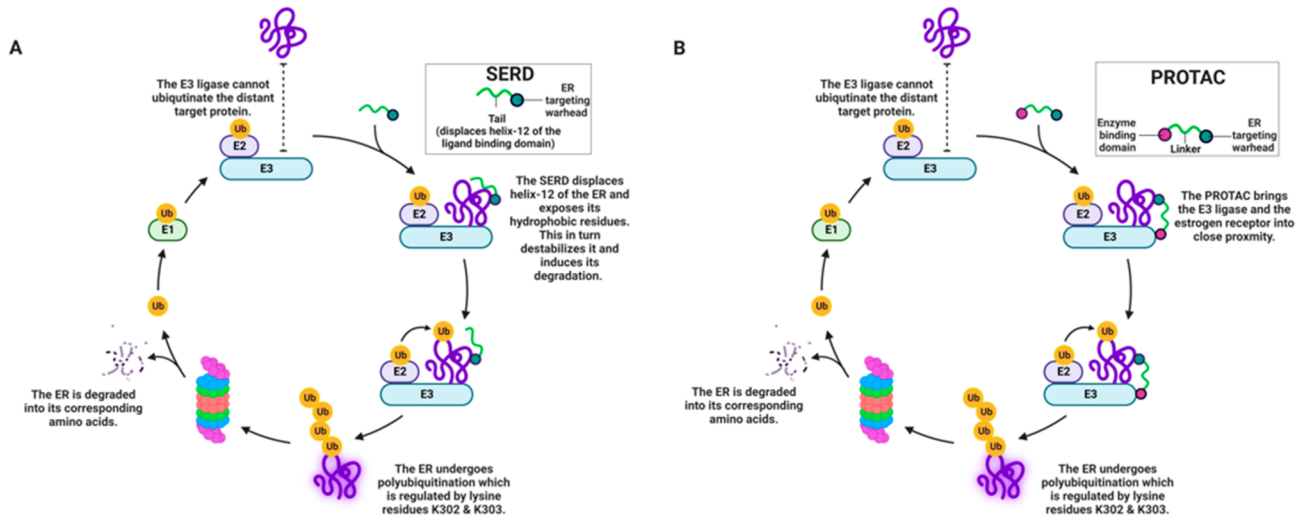

Figure 6. Mechanism of SERDs (A) and PROTACs (B). E1 corresponds to the activating enzyme, E2 corresponds to the conjugation enzyme, E3 is the substrate recognition enzyme, and UPS denotes the ubiquitin−proteasome system. This diagram was created with BioRender.

(UPS), which comprises protein degradation machinery. One or more lysine residues on the target protein of interest first undergo monoubiquitination, followed by polyubiquitination, which then directs the target protein to the 26S proteasome to undergo degradation (Figures 5 and 6). In the case of the ER, lysine residues K302 and K303 are ubiquitinated in the presence of a degrader molecule that directs the ubiquitinated ER protein to the 26S proteasome for ATP-dependent proteolysis.[66,67]

CERANs function by blocking all agonist signaling mediated by ERα by completely inactivating ER by inhibiting both activation functions of ER transcription (AF-1 and AF-2). Therefore, CERANs completely antagonize ER, block transcriptional activity, and induce ER degradation.[68]

SERCAs contain a Michael acceptor to attach covalently to a cysteine residue (C530) of ER and thereby function as covalent inhibitors of ER transcription.[69]

Below, we discuss the discovery and development for each class of these new ER-targeted agents.

SELECTIVE ESTROGEN RECEPTOR DEGRADERS

With the exception of Borestrant (**2**), oral selective estrogen receptor degraders (SERDs) can be subdivided into two main subgroups, namely nonsteroidal agents with an acrylic acid side chain and nonsteroidal analogs with a basic amine side chain.[31,70] Structurally, SERDs with acidic tails can be further classified based upon their ER ligand core used, including fulvestrant-like, indazole, tetrahydrocarboline, benzothiophene, tetrahydroisoquinoline (THIQ), and tricyclic indazole.

SERDs with an acrylic acid side chain, including GDC-0810 (**3**), AZD9496 (**4**), G1T48 (**5**), and LSZ102 (**6**), are potent antiestrogen agents which have no cross-resistance to tamoxifen. Crystallographic analysis of the complex of ERα and GW7604 (**10**), a SERD molecule, showed that the interaction of the carboxylic acid of GW7604 (**10**) with the peptide backbone of ER caused a conformational change in the ER that exposes a hydrophobic surface of the receptor, which targets ER for proteolytic degradation.[71] As a monotherapy, agents like GW7604 (**10**) have antitumor activity in endocrine-sensitive and -resistant preclinical models and *ESR1*-mutated tumors.[72−76] Further preclinical studies demonstrated that, when combined with CDK4/CDK6 inhibitors, they achieve much greater antitumor activity. For example, G1T48 (**5**) in combination with the CDK4/CDK6 inhibitor lerociclib has more significant tumor growth inhibition (TGI) than either agent used as a monotherapy.[77]

Some of the early-phase clinical trials of oral SERDs with acrylic acid side chains showed less promising efficacy and tolerability data, so the majority of these compounds have not been progressed further. For instance, the clinical trial (NCT02569801) of GDC-0810 (**3**) was terminated early when GDC-0810 was found to be inferior to fulvestrant in a Phase II study. Similarly, the Phase 1 clinical trial of LSZ102 (**6**, NCT02734615) was terminated as the interim single-agent results of LSZ102 in heavily pretreated ER+ MBC patients (endocrine therapy and chemotherapy) showed an overall response rate (ORR) of only 1.3%. LSZ102 monotherapy is associated with high rates of gastrointestinal (GI) toxicity, mainly nausea (61%) and diarrhea (55%). In combination with ribociclib, a CDK4/CDK6 inhibitor, or alpelisib, a PI3K inhibitor, the ORR improved to 17% or 7%, respectively.[78] It is worth mentioning that the toxicity profile did not substantially differ in the combination arms and the dose-limiting toxicity (DLT) was not the reason for its clinical progression.[78]

SERDs containing a basic amine side chain were developed to maximize ER degradation, and several such compounds, including RAD1901 (**11**), SAR439859 (**13**), AZD9833 (**14**), and GDC-9545 (**15**), have been progressed into late-stage clinical development (Figure 3). These agents have demonstrated good oral bioavailability and significant antitumor activity in treatment-naive and endocrine-resistant preclinical models, including *ESR1* mutations and those resistant to CDK4/CDK6 inhibition. Notably, elacestrant (RAD1901, **11**) has been recently approved by the FDA for the treatment of ER +/HER2−, *ESR1*-mutated advanced or metastatic breast cancer, marking a major milestone for the development of oral SERD molecules.[79]

Although all SERD molecules induce ER degradation, there are critical differences in their mechanisms of action based upon a study by Guan et al., who demonstrated that SERD molecules exhibit a spectrum of transcriptional activities and antiproliferative potential in ER+ models.[80] Specifically, they showed that fulvestrant-like antagonists, including fulvestrant (**1**) itself and GDC-0927 (**12**), a SERD molecule containing a basic amine group, suppress ER transcriptional activity not by ER

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Table 1. Comparison of *In Vitro* Properties of Fulvestrant (1) and ZB716 (2)

	Proliferation of Breast Cancer Cells, IC_{50} (nM)				ERα Degradation, DC_{50} (nM)		
Compound	MCF-7	T47D	MCF-7/TamR	T47D/PKCα	T47D ERα	T47D/PKCα	Binding to ERα (nM)
Fulvestrant (1)	1.5	1.2	44	42	9.3	8.5	3.0
ZB716 (2)	3.2	6.1	69	37	7.8	12.7	4.1

elimination but by markedly slowing the intranuclear mobility of ER. In contrast, SERD molecules containing an acidic group, such as GDC-0810 (**3**) and AZD9496 (**4**), have limited capability in slowing the intranuclear mobility of ER. Consequently, fulvestrant (**1**) and GDC-0927 (**12**) achieve greater suppression of ER transcriptional activity, which leads to stronger antiproliferative activity than those of GDC-0810 (**3**) and AZD9496 (**4**) in certain ER+ cell lines *in vitro*. Consistently, GDC-0927 also achieves greater antitumor activity *in vivo* compared to GDC-0810 (**3**) in two ER+ patient-derived xenograft (PDX) models. This study highlights the critical differences among different classes of SERD molecules in suppression of transcriptional activity and provides a potential explanation for the observed differences in clinical activities for different ER degraders.

On the other hand, recent work from Mader and co-workers showed that suppression of ER transcription activity by fulvestrant likely involves SUMOylation of ER.[81] They concluded that the post-transcriptional process of SUMOylation can achieve a more robust transcriptional shut-down of estrogen target genes by pure antiestrogens vs SERMs in BC cells. Collectively, these studies highlight several fascinating aspects of the roles of degradation and antagonism in SERD-mediated antitumor action.

Borestrant (ZB716, 2). Borestrant (**2**), also known as fulvestrant-3-boronic acid, was developed based upon fulvestrant (**1**) by converting the phenolic hydroxyl in fulvestrant to a boronic acid (Figure 7) to improve the level of exposure of the orally administered (PO) drug and its clinical efficacy.[82,83]

ZB716 has a similar *in vitro* profile to fulvestrant. ZB716 binds to ERα with a half-maximal inhibitory concentration (IC_{50}) of 4.1 nM compared to fulvestrant (3.0 nM) and effectively downregulates ERα in tamoxifen-sensitive and tamoxifen-resistant BC cells (Table 1). ZB716 inhibited MCF-7 and T47D cell growth with IC_{50} values of 3.2 and 6.1 nM, respectively, in cell proliferation assays. It also exhibited excellent ERα degradation activity, with half-maximal degradation concentration (DC_{50}) values of 7.8 nM in T47D vs fulvestrant (9.3 nM) and 12.7 nM in T47D PKCα cells (tamoxifen-resistant BC cells) vs fulvestrant (8.5 nM).[82]

ZB716 afforded a maximum concentration (C_{max}) >10 times higher and an area under the curve (AUC) 15 times higher in plasma after a single-dose oral gavage in comparison to fulvestrant administered subcutaneously (SC) at the same dose in mice, suggesting its clinical utility as an oral SERD (Table 2).[82] Like fulvestrant, ZB716 also has a very high plasma protein binding (PPB) (>99.9%) and a moderate cell-permeability [Caco-2 P_{app} (efflux ratio) = 0.77 (0.93)]. It has high clearance (CL) in hepatocytes of all species evaluated and is primarily metabolized by CYP2D6 and CYP3A. In human liver microsomes, ZB716 demonstrated moderate stability (Table 3).[82]

Table 2. Comparison of Pharmacokinetic Parameters of Fulvestrant (1) and ZB716 (2) in Mice

PK parameters (plasma exposure)	Fulvestrant (1)	ZB716 (2)
$t_{1/2}$ (h)	14	23
C_{max} (ng/mL)	15	170
AUC_{last} (ng·h/mL)	158	2547

Compared to fulvestrant, ZB716 demonstrated significantly improved tumor tissue exposure to the drug, consistent with enhanced drug levels in systemic circulation.[83,84] It also showed superior efficacy compared to fulvestrant in an MCF-7 xenograft model and a PDX tumor model (Table 3). The first-in-human Phase 1/2 clinical trial of ZB716 (NCT04669587, Table 4) is currently in progress.

Synthesis of ZB716 (2). ZB716 (**2**) was prepared through a four-step synthetic route starting from 17-acetyl S-deoxo fulvestrant (**2.1**, Scheme 1). Esterification of **2.1** with triflic anhydride provided the corresponding triflate (**2.2**), which was reacted with bis(pinacolato)diboron in the presence of palladium(II) acetate and tricyclohexylphosphine to afford 3-pinacolyl boronate ester (**2.3**). Removal of the 17-acetyl group under basic conditions yielded intermediate **2.4**, and subsequent oxidation of compound **2.4** using *m*-chloroperoxybenzoic acid (mCPBA) afforded the final product ZB716 (**2**) as colorless crystals (Scheme 1).[82,85]

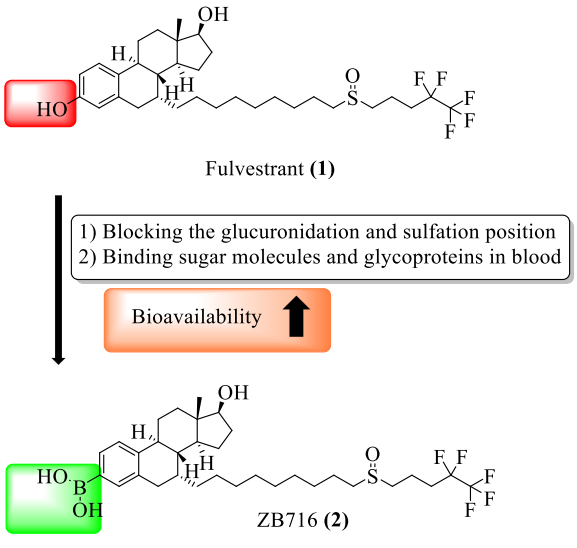

Figure 7. Design strategy of ZB716 (**2**).

■ ORAL SERDs WITH AN ACRYLIC ACID SIDE CHAIN

Brilanestrant (GDC-0810, 3). GDC-0810 (**3**) is a non-steroidal acrylic acid SERD developed based upon the structure of GW5638 (**3a**), an early SERD molecule. In 2015, Smith et al. at Seragon explored the scaffold of compound **3a** by applying a phenol-mimic strategy to improve its drug metabolism and pharmacokinetic (DMPK) properties.[86,87] In preclinical studies, GDC-0810 (**3**) displayed robust activity in antagonism (ERα transcription IC_{50} = 2 nM vs 0.6 nM by fulvestrant), degradation (ERα degradation DC_{50} = 0.7 nM vs 0.4 nM by fulvestrant), and

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Table 3. DMPK Parameters of ZB716 (2)

Compound	CYP inhibition, IC_{50} (μM)	Liver microsomal stability, CL_{int} (μL/min/10^6 cells)	PPB conc (10 μM)	MCF7 xenograft model	PDX tumor model
ZB716	1A2 > 15, 2B6 > 15, 2C8 = 6.2, 2C9 = 4.7, 2C19 = 2.2, 2D6 = 12.5, 3A4-M > 15, 3A4-T = 11.2	human = 39.7, monkey = 50.3, dog = 51.9, rat = 48.7, mouse = 40.3	human/monkey/ dog/rat/ mouse > 99.9	ZB716 was more efficacious at both oral treatment doses of 10 mg/kg and 30 mg/kg than fulvestrant at 200 mg/kg weekly injection	5 mg/kg of ZB716 demonstrated similar *in vivo* efficacy in blocking PDX tumor growth compared to a 200 mg/kg weekly injection of the fulvestrant dosing

Table 4. Clinical Trial Data for ZB716 (2)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
ZB716 (SERD)	ZB716, Palbociclib	ER+/HER2− Locally Advanced or Metastatic Breast Cancer (ENZENO Study)	ER+/HER2− locally advanced breast cancer, metastatic breast cancer	NCT04669587 (Phase I/II, recruiting)

Scheme 1. Synthesis of ZB716 (2)

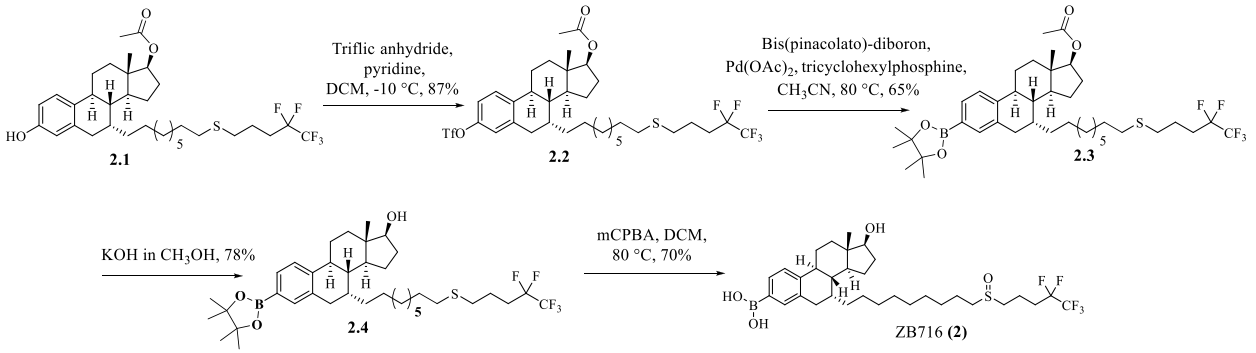

Table 5. Comparison of *In Vitro* Properties of Fulvestrant (1) and GDC-0810 (3)

	Binding IC_{50} (nM)		Transcription Antagonism	ERα Degradation		MCF-7 Viability	
Compound	ERα	ERβ	IC_{50} (nM)	DC_{50} (nM)	Efficacy (%)	IC_{50} (nM)	Efficacy (%)
GDC-0810	6.1	8.8	2.0	0.7	91	2.5	99
Fulvestrant	24	21	0.6	0.4	94	0.6	100

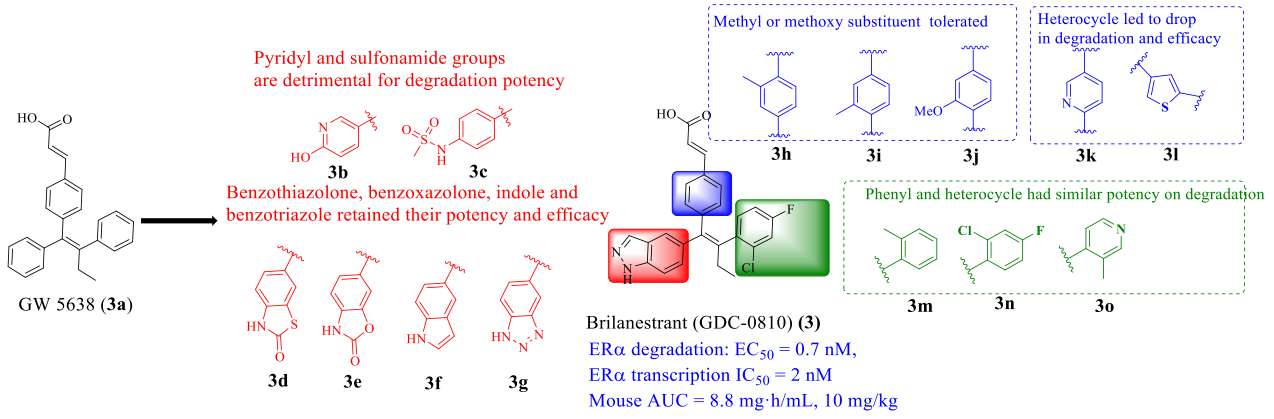

Figure 8. Design strategy and SAR analysis of GDC-0810 (3).

cell viability (MCF-7 antiproliferation IC_{50} = 2.5 nM vs 0.6 nM by fulvestrant) assays (Table 5). However, it behaved as a mixed SERM/SERD and showed partial agonism in uterine models *in vitro* and *in vivo*.[86]

Analysis of the SAR data (Figure 8) indicated that the inclusion of pyridyl (**3b**) and sulfonamide (**3c**) groups on the phenol-mimic segment was detrimental to the degradation potency and efficacy. On the other hand, groups like benzothiazolone (**3d**), benzoxazolone (**3e**), indole (**3f**), and benzotriazole (**3g**) retained the potency and efficacy (Figure 8). The introduction of a methyl or methoxy substituent (**3h**−**3j**) to the core was tolerated and yielded equipotent compounds. Replacement of the phenyl ring with a heterocycle such as pyridine (**3k**) or thiophene (**3l**) led to a substantial decrease in

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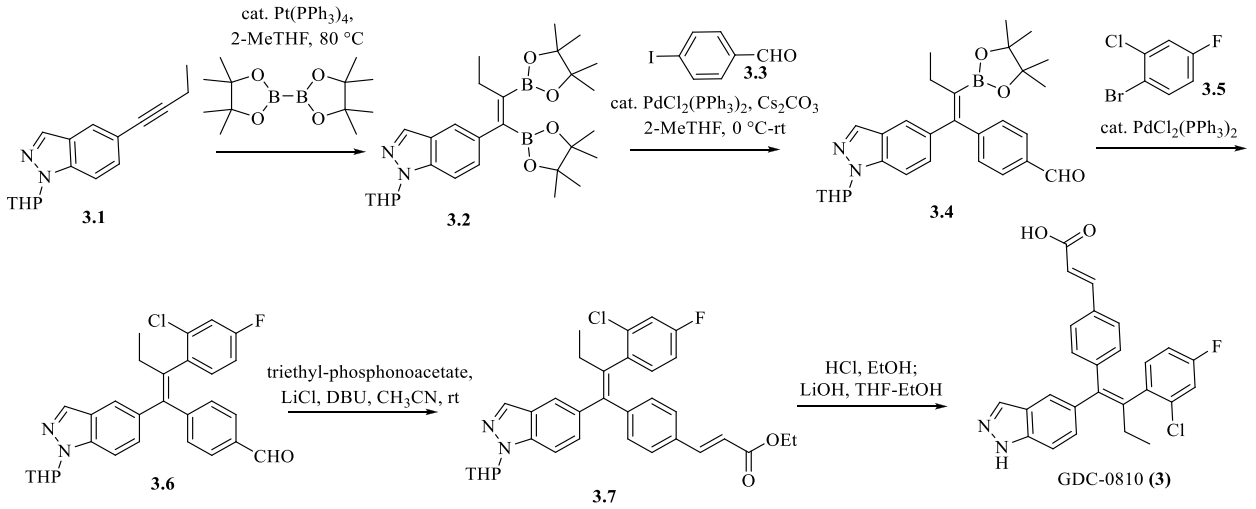
Table 6. Cross-Species Pharmacokinetics of GDC-0810 (3)

Species	V_{ss} (L/kg)	CL (mL/min/kg)	$t_{1/2}$ (IV) (h)	C_{max} (PO) (μg/mL)	AUC (PO) (μg·h/mL)	F (%)
Mouse	1.2	11	4.2	4.4	8.8	61
Rat	1.9	14	3.9	1.8	5.8	49
Dog	0.2	1.6	11	20	69	61
Monkey	0.5	7.0	13	6.1	10	42

Table 7. Clinical Trial Data for GDC-0810 (3)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
GDC-0810 (SERD)	Fulvestrant, GDC-0810	A Study of GDC-0810 versus Fulvestrant in Postmenopausal Women with Advanced or Metastatic Breast Cancer Resistant to Aromatase Inhibitor (AI) Therapy	breast cancer	NCT02569801 (terminated)
	GDC-0810, LHRH agonist, Palbociclib	A Study of GDC-0810 Single Agent or in Combination with Palbociclib and/or a Luteinizing Hormone-Releasing Hormone (LHRH) Agonist in Women with Locally Advanced or Metastatic Estrogen Receptor Positive Breast Cancer	breast cancer	NCT01823835 (terminated)

Scheme 2. Synthesis of GDC-0810 (3)



the potency, indicating that these heterocyclic rings are not well tolerated in this region. Regarding the pendant aryl ring (marked in green in Figure 8), simultaneous substitution at the *ortho* or *para* positions with halogens (**3m**–**3o**) provided the most potent analogs.[86,87]

GDC-0810 (**3**) also displayed antitumor activity in multiple ER+ cell lines, including *ESR1* mutation (Y537S and D538G) cell lines. In a cell viability assay in the absence of estradiol, GDC-0810 displayed a marked reduction in potency (22-fold reduction on DC_{50}) in ER Y537S vs ER WT cells. In the presence of a low concentration of estradiol (0.1 nM), this potency reduction is only 4-fold.[86]

The PK profile of GDC-0810 (Table 6) shows that it has a low clearance and good bioavailability (F = 40–60%) across species. GDC-0810 (**3**) is highly bound to plasma proteins, at >99.5% across species, and has a low to moderate volume of distribution of V_{ss} = 0.2–2.0 L/kg across species.[86] CYP profiling of GDC-0810 indicated that it has little to no inhibitory activity against CYP1A2, CYP2D6, or CYP3A4 (IC_{50} > 20 μM), displays modest inhibitory effects on CYP2C9 and CYP2C19 (IC_{50} = 2.2 and 3.3 μM, respectively), but shows potent inhibition of CYP2C8 (IC_{50} < 0.1 μM). However, inhibition of CYP2C8 was not considered to be a major liability, as few therapeutic agents are metabolized exclusively by CYP2C8, suggesting that drug–drug interaction potential with GDC-0810 is minimal.[88]

In Vivo Activity and Clinical Development. GDC-0810 (**3**) showed robust activity in a tamoxifen-sensitive MCF-7 xenograft model, with a 3 mg/kg/day PO dose leading to substantial TGI. At 100 mg/kg/day, the highest dose assessed, all test animals treated with GDC-0810 showed >50% tumor regression. In comparison, fulvestrant, which was used as a positive control in the *in vivo* study, caused only tumor stasis when dosed at 200 mg/kg SC weekly for 3 weeks.[86] When tested in a tamoxifen-resistant BC xenograft model, GDC-0810 led to tumor stasis at 30 mg/kg and induced tumor regression at 100 mg/kg, and fulvestrant showed only 50% TGI.[86,89]

Even though GDC-0810 is capable of degrading ERα by 91%, it lacks a full antagonist profile. In fact, GDC-0810 weakly activates ER transcription,[80] which may compromise its *in vivo* efficacy. Phase II clinical trials of GDC-0810 for the treatment of advanced BC patients who became resistant to AIs failed to demonstrate its comparable or superior efficacy compared to fulvestrant (Table 7). Therefore, the clinical development of GDC-0810 has been suspended, and a newer generation of drug candidates is currently being pursued.

Synthesis of GDC-0810 (3). The synthesis initiated with the commercially available alkyne **3.1** (Scheme 2), which was then

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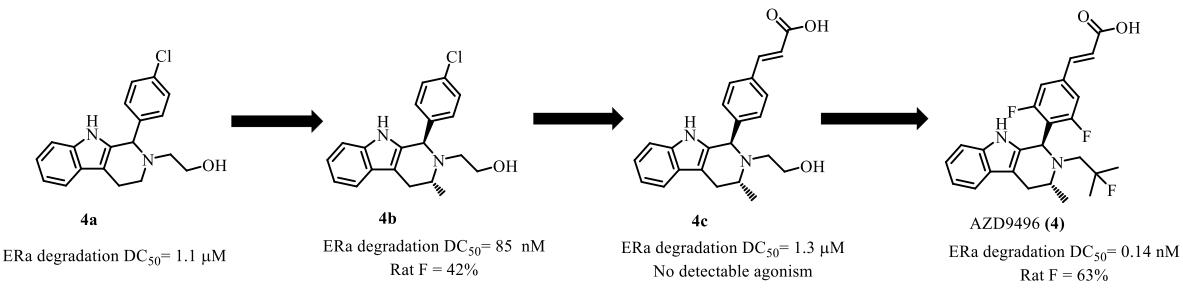

Figure 9. Design strategy and SAR analysis of AZD9496 (**4**).

converted to the bis(pinacolato)diboryl-alkene intermediate **3.2** using a platinum-catalyzed diboration reaction.[90,91] Intermediate **3.2** was then reacted with 4-iodobenzaldehyde (**3.3**) to form aldehyde **3.4**. Compound **3.4** was then coupled with 1-bromo-2-chloro-4-fluorobenzene (**3.5**) under Suzuki reaction conditions to deliver intermediate **3.6**, which was then homologated using a Horner−Wadsworth−Emmons (HWE) reaction to provide the ester **3.7**. Lastly, ester hydrolysis and tetrahydropyranyl (THP) deprotection of intermediate **3.7** afforded the targeted final product GDC-0810 (**3**).[86]

AZD9496 (4). AstraZeneca used a structure-based design strategy to develop AZD9496 from a novel but weak ER degrader (**4a**).[92,93] The identified indole derivative **4a** is a novel and moderately potent ERα degrader (ERα degradation DC_{50} = 1.1 μM, Figure 9) but with desirable physicochemical properties [MW = 317, log *D* (distribution coefficient) = 3.7]. The introduction of a methyl substituent to the ring nitrogen boosted the ERα degradation potency by exploiting a lipophilic cavity in ERα. Among the four possible stereoisomers, the best activity was from the *trans*-1*R*,3*R* enantiomer, which led to compound **4b** with a 12-fold improvement in its ERα downregulation potency (DC_{50} = 85 nM) and a promising oral bioavailability in rats (F = 42%). Unfortunately, at high concentrations, compound **4b** showed agonist activity. Installation of an acrylic acid motif in **4b** resulted in compound **4c**, which had a modest ER degradation potency (DC_{50} = 1.3 μM) but with no detectable agonism. To improve its degradation potency, an isopropyl fluoro substituent and *ortho* disubstitution on the pendant aryl ring were introduced in compound **4c**, which yielded compound **4** (AZD9496). AZD9496 achieved sub-nanomolar degradation potency (DC_{50} = 0.14 nM) and excellent rat oral bioavailability (F = 63%). AZD9496 showed high oral bioavailability (F = 60−128%) with a moderate volume of distribution across species and slow clearance in rat and dog but high clearance in mice (Table 9).[92,93]

In vitro binding studies using WT ERα and D538G and Y537S mutants showed that AZD9496 and fulvestrant bind to the mutant LBD with low nanomolar potency, a 2−3-fold reduction compared to WT (Table 8). AZD9496 displayed high selectivity over other nuclear hormone receptors, such as the androgen receptor [AR, IC_{50} = 30 μM (>30,000-fold)], the glucocorticoid receptor [GR, IC_{50} = 9.2 μM (>10,000-fold)], and the progesterone receptor [PR, IC_{50} = 0.54 μM (~650-fold)], when compared to ERα (IC_{50} = 0.8 nM).[92,93]

Table 8. Comparison of *In Vitro* Data of AZD9496 (4) and Fulvestrant (1)

	ERα LBD Binding, IC_{50} (nM)	
	AZD9496	Fulvestrant
WT	0.2	1.6
D538G	0.5	3.3
Y537S	0.6	3.8

Table 9. Cross-Species Pharmacokinetics of AZD9496 (4)

Species	V_{ss} (L/kg)	CL (mL/min/kg)	F (%)
Rat	0.43	1.0	63
Mouse	2.2	43	128
Dog	0.40	0.28	79

AZD9496 lacks a phenolic moiety and achieves its potency through different interactions with the ER protein based upon cocrystal structure with ER (Figure 10). The indole NH forms a hydrogen bond with the carbonyl of Leu-346 of the protein, with additional lipophilic interactions involving both the chiral methyl substituent, adjacent to the ring nitrogen, and the *N*-substituted isopropyl fluoro side chain occupying a "lipophilic hole" in the ER protein. The acrylic acid side chain is unusually acid−acid colocalized with Asp-351 in the helix-12 region of the ER that is thought to be crucial for a downregulator−antagonist profile.[92,93]

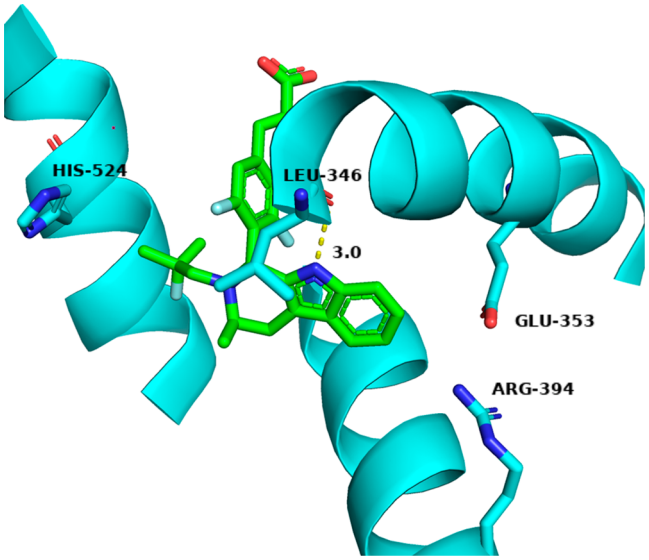

Figure 10. X-ray cocrystal structure of AZD9496 (**4**) (PDB code 5ACC) bound to ERα.

AZD9496 significantly inhibited tumor growth in the estrogen-dependent MCF-7 xenograft model. AZD9496 also caused tumor regression and downregulated ERα expression in the HCC1428 cell long-term estrogen-deprived BC model of resistance to AI treatment.[94,95]

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Scheme 3. Synthesis of AZD9496 (4)

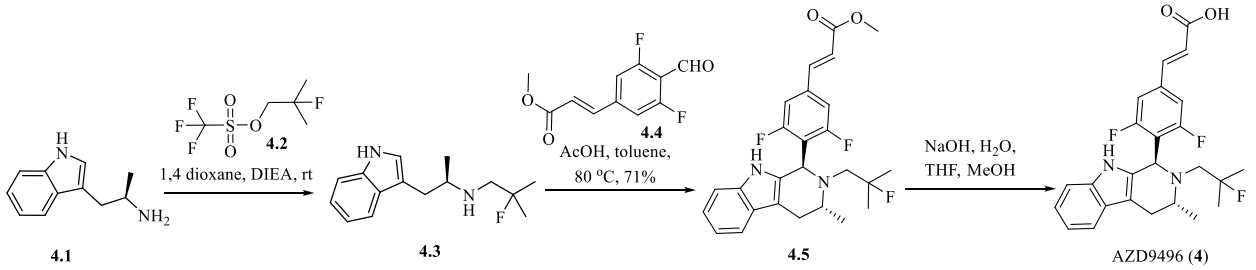

Table 10. Clinical Trial Data for AZD9496 (4)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
AZD9496 (SERD)	Standard arm: Fulvestrant, AZD9496	Study to Compare the Effects of AZD9496 vs Fulvestrant in Breast Cancer	postmenopausal women with ER+/HER2− primary breast cancer	NCT03236974 (completed)

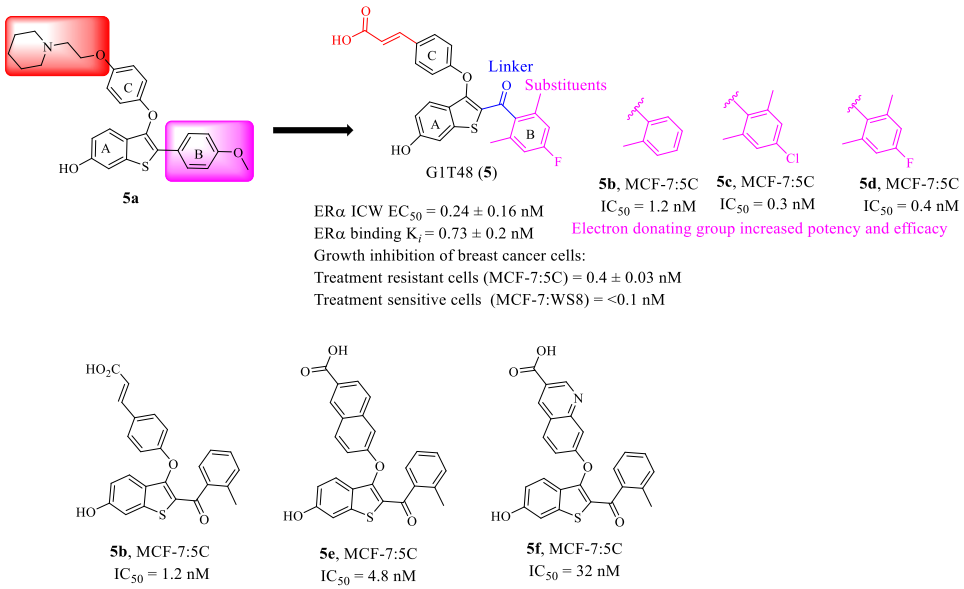

Figure 11. Design strategy and SAR analysis of G1T48 (**5**).

Synthesis of AZD9496 (4). The synthesis initiated with commercially available (*R*)-1-(1*H*-indol-3-yl) propan-2-amine (**4.1**, Scheme 3). *N*-Alkylation of intermediate **4.1** with triflate **4.2** led to intermediate **4.3**. A diastereoselective Pictet−Spengler reaction of intermediate **4.3** with methyl (*E*)-3-(3,5-difluoro-4-formylphenyl) acrylate (**4.4**) yielded the desired tetracycle **4.5**, which upon ester hydrolysis generated the final compound AZD9496 (**4**).[92,93]

Clinical Development of AZD9496 (4). In clinical trials, AZD9496 showed low response rates and an unfavorable toxicity profile (Table 10). Approximately 90% of patients experienced drug-related adverse events (AEs), including 40% with diarrhea of any grade or other GI toxicity.[94,95] The most common AEs were diarrhea (35.6%), fatigue (31.1%), and nausea (22.2%), and some patients had grade III AEs. Because of an unfavorable toxicity profile and modest clinical benefit, AZD9496's development was halted in February 2021 in favor of its more potent and better tolerated successor AZD9833, which is currently under investigation in Phase II and Phase III clinical trials, as discussed below.

Rintodestrant (G1T48, 5). Xiong et al. from the Thatcher group utilized the benzothiophene scaffold (**5a**) to design a series of ERα partial agonists (ShERPAs) for the treatment of tamoxifen-resistant BC.[96] ShERPAs are benzothiophene derivatives that mimic 17β-estradiol. They bind ER in the nucleus, causing ER translocation to extra-nuclear sites. The nuclear export of ER causes ER+ tumor cell growth inhibition. Further modification of this scaffold yielded a series of ER ligands, **5b**−**5f**, that were prepared by replacing the basic amine side chain with an acrylate-containing side chain and varying the substituents and the positions of linkers and then evaluated for oral SERD bioactivity.[96,97] Among these benzothiophene analogs, G1T48 (**5**) demonstrated low nM activity on ERα degradation and antagonism (Figure 11).[96]

The SAR study showed that the electron-donating group (in ring B) enhanced antiproliferative potency and efficacy in both drug-sensitive and drug-resistant cell lines (**5b**−**5d**). The inclusion of a naphthalene linker (**5e**) in the side chain retained the antiproliferative efficacy (MCF-7:5C IC_{50} = 4.8 nM vs 1.3 nM of **5d**), while its quinoline bioisostere (**5f**) exhibited reduced antiproliferative efficacy (MCF-7:5C IC_{50} = 32 nM).[96]

Synthesis of G1T48 (5). The synthetic strategy utilized a key starting material, 3-chloro-6-methoxybenzo[*b*]thiophene-2-carbonyl chloride (**5.1**), which allows modification of the 2 and 3

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Scheme 4. Synthesis of G1T48 (5)

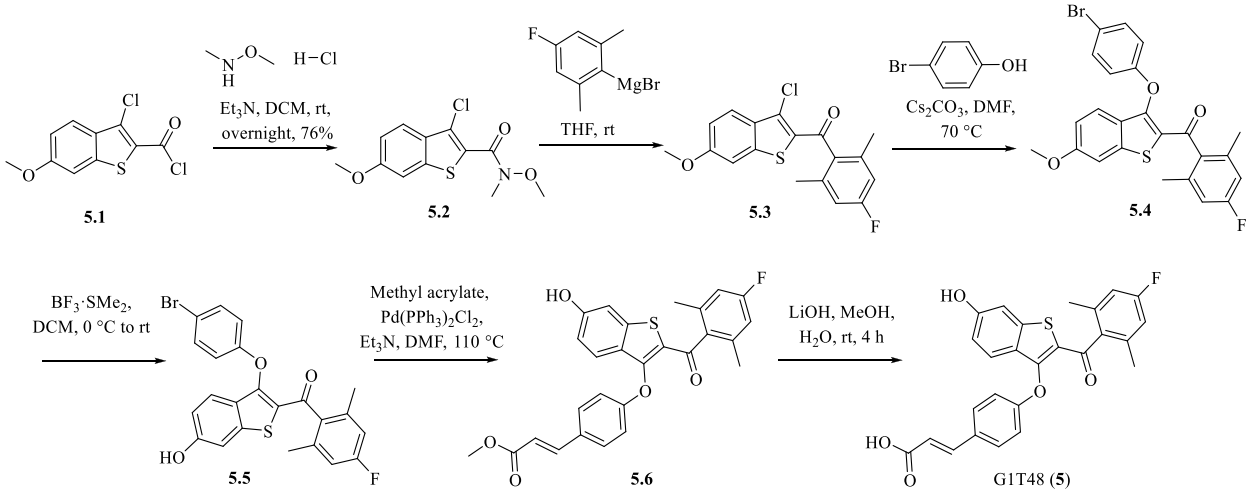

Table 11. Clinical Trial Data for G1T48 (5)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
G1T48 (SERD)	G1T48, Palbociclib	G1T48, an Oral SERD, Alone and in Combination with Palbociclib in ER-Positive, HER2-Negative Advanced Breast Cancer	carcinoma, ductal breast cancer, metastatic breast cancer, advanced breast cancer, stage IV breast cancer	NCT03455270 (Phase I, completed)

Table 12. Potency and Pharmacokinetic Parameters of LSZ102 (6) Analogs

	ERα Transcription	ERα Degradation	Mouse		
Compound	IC_{50} (μM)	DC_{50} (nM) (% ERα remaining)	CL (mL/min/kg)	C_{max} (PO) (nM)	*F* (%)
6a	0.75	31 (41)		nd	
6b	0.65	nd (18)		nd	
6c	1.8	nd (26)	22	505	19
6d	0.08	4 (19)	33	925	34
6	0.006	0.2 (17)	28	492	12

positions of the benzothiophene scaffold (Scheme 4). The acyl chloride of **5.1** was converted to a Weinreb amide (**5.2**), followed by a Grignard reaction that yielded intermediate **5.3**. The 2-keto group in compound **5.3** activates the 3-position and directly forms the oxygen linkage with the corresponding substituted phenols through nucleophilic aromatic substitution. Compound **5.4**, upon the treatment with $BF_3{\cdot}SMe_2$, achieved selective deprotection of the methyl ether over the diaryl ether. Using a palladium catalyst, the acrylate group was installed by a standard Heck coupling between the aryl bromide (**5.5**) and the methyl acrylate. A base-catalyzed ester hydrolysis of compound **5.6** yielded the final compound, G1T48 (**5**).[96]

Preclinical and Clinical Data of G1T48 (5). G1T48 demonstrated significant preclinical activity in multiple endocrine therapy resistance models, including ER-dependent BC (MCF-7), and significantly inhibited the growth of tamoxifen-resistant (TamR), long-term estrogen-deprived (LTED), and PDX tumors. An increased response was observed with the combination of G1T48 and the CDK4/CDK6 inhibitor, lerociclib.[97] According to a 2020 SABCS abstract, a Phase I study was conducted with G1T48 as a monotherapy and in combination with palbociclib. The median number of prior lines in the advanced setting was 2 (range 0−9), including fulvestrant (64%), a CDK4/CDK6 inhibitor (69%), an mTOR inhibitor (22%), and/or chemotherapy (46%). The most common treatment-related adverse effects (TRAE) in at least 10% of patients included hot flushes (24%), fatigue (21%), nausea (19%), diarrhea (18%), and vomiting (10%), mostly G1/2. The clinical benefit rate (CBR), i.e., the rate of confirmed complete or partial response or stable disease at ≥24 weeks, was 28%, similar to those from *ESR1* mutant and WT patients.[98,99] Next, G1T48 was combined with palbociclib in a less pretreated population. The median number of prior lines was 1 (0−2), including chemotherapy (48%), fulvestrant (15%), and AI (50%). TRAEs related to G1T48 were reported in 8% of patients (all G1/2) and included nausea (3%), vomiting (3%), and neutropenia (3%). The most common TRAEs, primarily attributable to palbociclib, were neutropenia (88%), leukopenia (45%), anemia (10%), and thrombocytopenia (10%). The median treatment duration was 3 months, with a CBR of 73%, including cases with *ESR1* variants.[98−100] No further clinical development of G1T48 is currently planned (Table 11).

LSZ102 (6). LSZ102 (**6**) is another novel acrylic acid oral SERD discovered by scientists from Novartis based on the benzothiophene scaffold.[78,101] Compound **6a** (ERα transcription IC_{50} = 0.75 μM) was used as a starting point for optimization of the ERα degradation efficacy. Initial optimization yielded the methoxy derivative **6b**, which showed a marginal improvement of the degradation activity (ERα transcription IC_{50} = 0.65 μM, 18% ERα remaining) compared to **6a**. Changing the methoxy to a *para*-fluoro substituent (**6c**) led to a marked improvement in bioavailability (19%) and clearance

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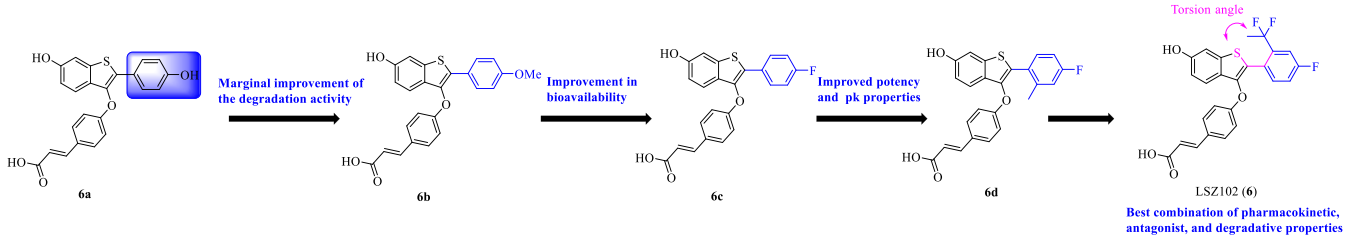

Figure 12. Design strategy and SAR analysis of LSZ102 (**6**).

(CL = 22 mL/min/kg) in mice, although it adversely affected the antagonistic potency (ERα transcription IC_{50} = 1.8 μM). The so-called "*ortho* effect" provided a further boost in the potency (Table 12). The substituents at the *ortho* position of the phenyl ring torsionally constrain these compounds, causing the 2-aryl ring to be orthogonal to the plane of the benzothiophene core (Figures 12 and 13). Such a spatial arrangement increases

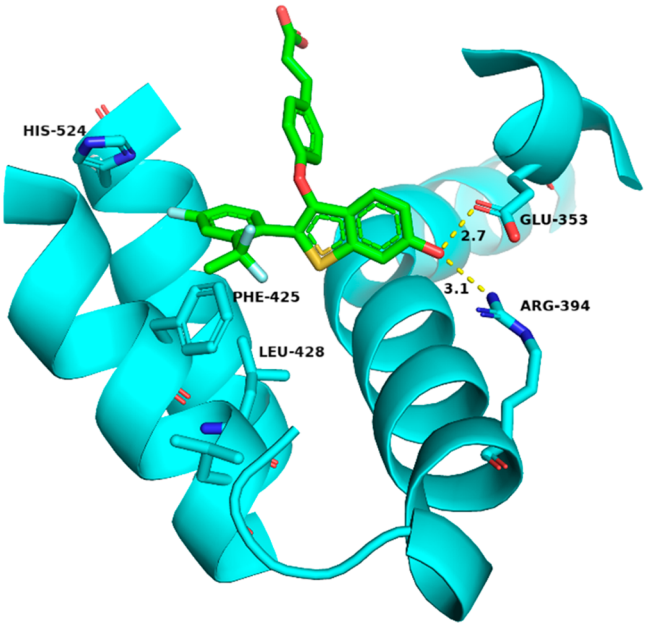

Figure 13. X-ray crystal structure of LSZ102 (**6**) (PDB code 6B0F) bound to ERα.

the hydrophobic interactions by occupying a lipophilic cavity near Leu428:Phe425 (Figure 13) and beneficially prevents glucuronidation of the 6-hydroxyl group. The resulting compound (**6d**) had better potency and improved PK properties compared to compound **6a**. Finally, a difluoroethyl group at the *ortho* and a fluorine at the *para* position yielded compound **6**, which had the best PK, antagonist, and degradative properties.[101]

*Synthesis of LSZ102 (**6**).* The key dibromo intermediate **6.3** was made by the oxidation of 6-methoxybenzo[*b*]thiophene (**6.1**) using mCPBA followed by bromination of intermediate **6.2**.[102] The critical ether linkage formed by adding 4-bromophenol to intermediate **6.3** in the presence of Cs_2CO_3 afforded **6.4** with a 98% yield. The pendant thiophene bromide reduction of **6.4** was achieved by adding $NaBH_4$ (97% yield), followed by DIBAL-H reduction of the dioxide functionality to afford the critical benzothiophene intermediate **6.5** (84% yield). The acrylate group was installed by a standard Heck coupling of the aryl bromide (**6.5**) with methyl acrylate, which gave compound **6.6** with a 61% yield. Rebromination of intermediate **6.6** by treatment with NBS afforded brominated intermediate **6.7** with a 90% yield. The methoxy group was then deprotected using BBr_3 to obtain the intermediate **6.8** with a 45% yield. Compound **6.8**, under Suzuki reaction conditions, produced the corresponding ester-protected intermediate, which upon base-catalyzed ester hydrolysis yielded the final compound LSZ102 (**6**, Scheme 5).[101]

An efficient streamlined large-scale manufacturing route for the synthesis of LSZ-102 is also known in the literature (Scheme 6).[102] 4-Bromocinnamic acid (**6.9**) was subjected to Higa cyclization with $SOCl_2$ (3.2 equiv) in the presence of pyridine. Product **6.10** was isolated with a 55% yield. Intermediate **6.10** was then reacted with ethyl (*E*)-4-hydroxycinnamate in the presence of K_2CO_3 in acetonitrile, forming the critical ether linkage yielding the biaryl ether **6.11**. The ester-containing compound **6.11** was then directly hydrolyzed, and the desired product **6.12** could be isolated with a 57% overall yield. Decarboxylation of the 2-carboxy group in intermediate **6.12** to intermediate **6.13** was achieved under thermal conditions in DMSO in the presence of K_2CO_3 at 110−120 °C with a 62% yield. A catalyst screening was performed for the critical transformation of the 6-bromo compound **6.13** to the hydroxy analog **6.14**. It was found that 0.3 mol% of palladium allyl chloride dimer as Pd source and 1 mol% *t*-BuXPhos proved to be the best catalytic system, as described by Buchwald.[103,104] The manufacture of **6.16** could be achieved from **6.14** through a Pd-catalyzed C−H activation step with a yield of 85%.[105,106] The crystalline LSZ102 (**6**) could be made in an acetic acid (AcOH)/H_2O system, providing a high-purity crystalline product on a kg scale with a 76% yield.

*Clinical Data of LSZ102 (**6**).* The Phase I clinical trial of LSZ102 (Table 13) was terminated by the trial sponsor, Novartis, but before the discontinuation, interim single-agent results of LSZ102 in heavily pretreated ER+ MBC patients showed an ORR of 1.3%, a CBR of 9.1%, and a median progression-free survival (PFS) of 1.8 months.[78] Common TRAEs were mostly mild or moderate, and among them, GI events (nausea, diarrhea, vomiting) were the most frequent. Other common AEs of combination treatment, including those with a higher proportion of grade 3 severity, were consistent with the safety profiles of ribociclib (leukopenia, neutropenia, aspartate aminotransferase increase) or alpelisib (skin rash, hyperglycemia, decreased appetite).[78,107]

Taragarestrant (D-0502, 7). D-0502 (7) was developed by InventisBio.[108] It is an orally bioavailable SERD with potent activity in various ER+ BC cell lines and xenograft models. A combination of D-0502 and palbociclib in the MCF-7 xenograft model and the *ESR1*-mutated (Y537S) PDX model resulted in robust TGI or regression. As reported in an 2018 AACR abstract, D-0502 shows superior a PK profile and better potent antitumor activity in the MCF-7 xenograft model compared to

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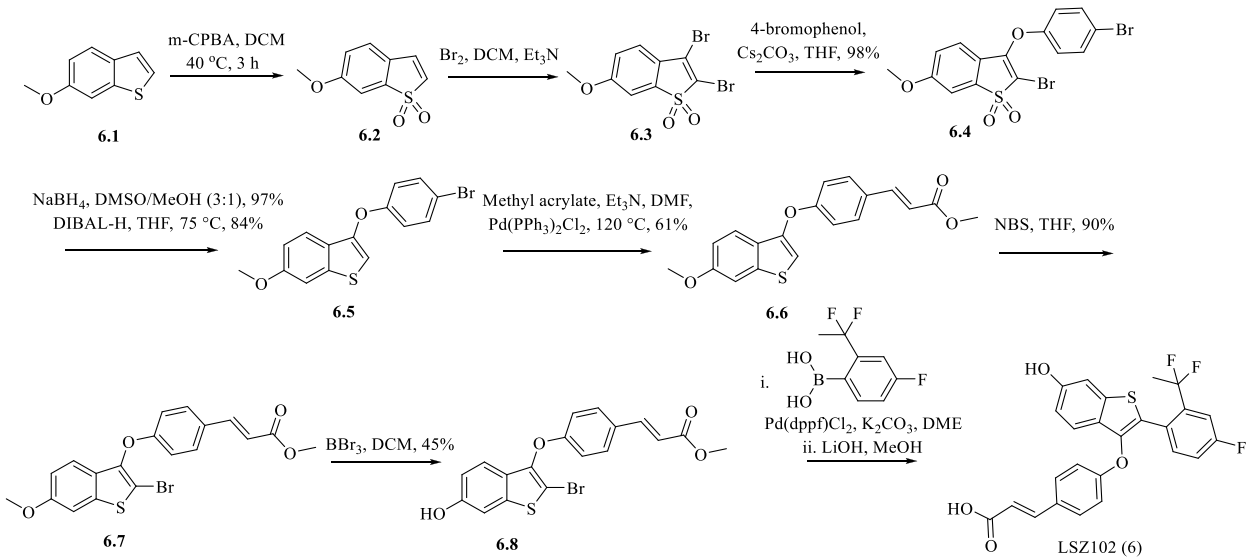
Scheme 5. Synthesis of LSZ102 (6)



Scheme 6. Efficient Manufacturing Process for LSZ102 (6)

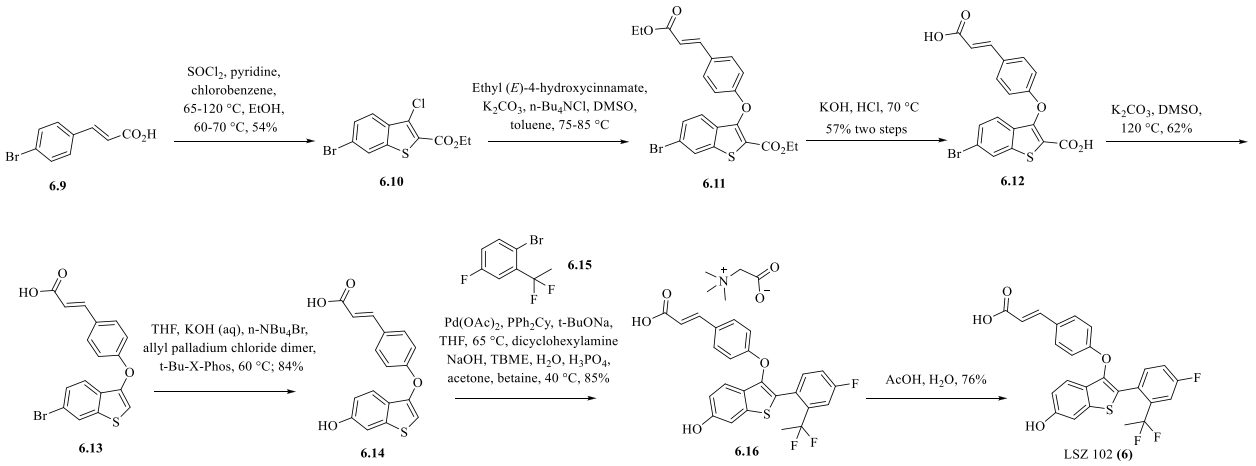


Table 13. Clinical Trial Data for LSZ102 (6)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
LSZ102 (SERD)	LSZ102, LEE011, BYL719	Phase I/Ib Trial of LSZ102 Single Agent or LSZ102 + LEE011 or LSZ102 + BYL719 in ER+ Breast Cancers	advanced or metastatic ER+ breast cancer	NCT02734615 (terminated)

Table 14. Clinical Trial Data for D-0502 (7)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
D-0502 (SERD)	D-0502, Palbociclib	A First-in-Human Study of D-0502 Alone and in Combination with Palbociclib in Women with Advanced or Metastatic ER-Positive and HER2-Negative Breast Cancer	breast cancer	NCT03471663 (Phase I, active, not recruiting)

GDC-0810, AZD9496, and fulvestrant.[108] A Phase 1a dose escalation trial has been completed, the maximum tolerable dose has been identified, and no DLTs were observed (Table 14). D-0502 (7) as a single agent or in combination is well tolerated, and a radiological tumor response and a CBR were observed.[109] It is noted that D-0502 and AZD9496 have very similar chemical structures.

Synthesis of D-0502 (7). D-0502 was made following a procedure similar to that used to synthesize AZD9496 (Scheme 7). The major difference is the use of methyl (*E*)-3-(3,5-dichloro-4-formylphenyl)acrylate (**7.1**) as a substrate in the diastereoselective Pictet−Spengler reaction.[110,111]

ZN-c5 (8). ZN-c5, a novel SERD, was developed by Zentalis and is currently in Phase I/II trials. Based on the scale of synthesis indicated in the patent, the structure of ZN-c5 is most likely compound **8**. ZN-c5 showed potent antagonist and degradative properties against ER both *in vitro* and *in vivo*. It also showed a high oral bioavailability[112] across several preclinical

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Scheme 7. Synthesis of D-0502 (7)

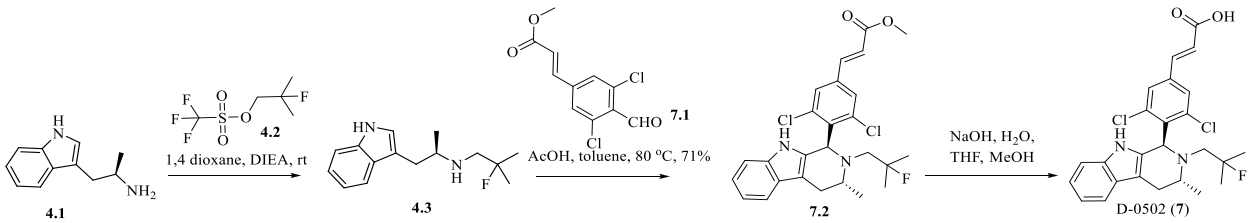
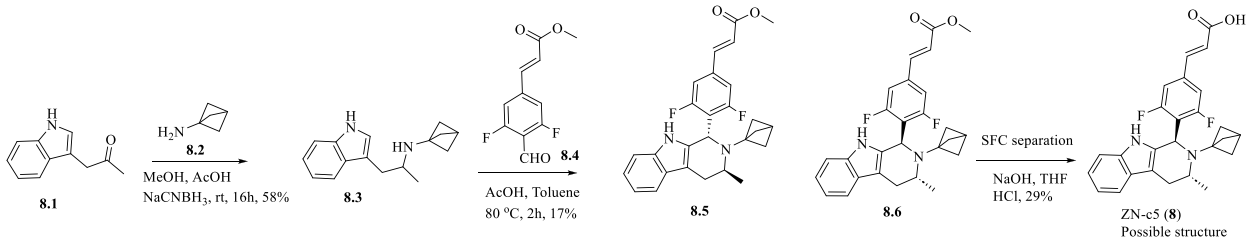


Table 15. Clinical Trial Data for ZN-c5 (8)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
ZN-c5 (SERD)	Abemaciclib	A Study of ZN-c5 and Abemaciclib in Participants with Breast Cancer	breast cancer	NCT04514159 (Phase I, active, not recruiting)
	Palbociclib	A Study of ZN-c5 in Subjects with Breast Cancer	breast cancer	NCT03560531 (Phase I, active, not recruiting)

Scheme 8. Synthesis of ZN-c5 (8)



species compared to other SERDs, as was reported in the recent AACR abstract.[113] It also showed antitumor activity in the MCF-7 orthotopic tumor xenograft model. Treatment with ZN-c5 orally at 5 mg/kg and 10 mg/kg resulted in 89% and 102% TGI, respectively. A combination of ZN-c5 with cell cycle inhibitors such as CDK4/CDK6 inhibitors or PI3K inhibitors resulted in enhanced antitumor activity. In addition to the MCF-7 model, ZN-c5 was also evaluated in ER mutant models, including WHIM20, a Y537S *ESR1* PDX model. Treatment with ZN-c5 at 40 mg/kg induced 64% TGI, while fulvestrant at 200 mg/kg resulted in 13% TGI. This data indicates that ZN-c5 has improved antitumor activity over fulvestrant in human tumor xenograft models. ZN-c5 is currently in clinical trials as a single agent and in combination studies (Table 15). The PK profile of ZN-c5 in BC patients indicates that ZN-c5 has exposure >5-fold greater than that of fulvestrant. The high exposure of ZN-c5, its good potency, and its degradative properties unfortunately did not translate into a therapeutic benefit, and its development was therefore discontinued.[113−117]

*Synthesis of ZN-c5 (**8**).* The synthesis initiated with commercially available 1-(1*H*-indol-3-yl)propan-2-one (**8.1**, Scheme 8). Reductive amination between **8.1** with amine **8.2** led to intermediate **8.3** in 58% yield. A diastereoselective Pictet−Spengler reaction of intermediate **8.3** with methyl (*E*)-3-(3,5-difluoro-4-formylphenyl) acrylate (**8.4**) yielded the desired tetracycles **8.5** and **8.6** as a racemic mixture. The desired isomer **8.6** was separated using chiral supercritical fluid chromatography (SFC), which upon ester hydrolysis generated the final compound ZN-c5 (**8**) in 29% yield as a pale-yellow solid.

LX-039 (9). Ding et al. recently reported a novel indole-based oral SERD LX-039 from a novel ER-binding motif **9a**.[118] LX-039 (**9**, Figure 14), with an indole C-3 chlorine atom, improved

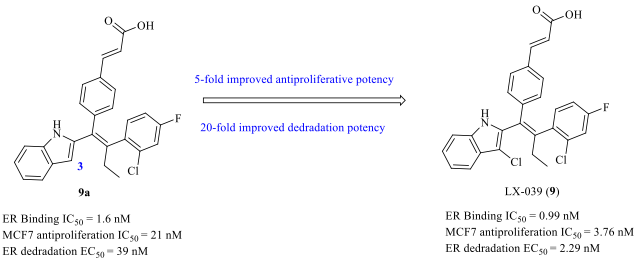


Figure 14. Design strategy and SAR analysis of LX-039 (**9**).

more than 5-fold the antiproliferative potency against the MCF-7 cell line and almost 20-fold the ER degradation potency (EC_{50}) compared to compound **9a** in MCF-7 cells. It showed excellent ER binding affinity (IC_{50} = 0.99 nM) with good degradation potency (EC_{50} = 2.29 nM) in the MCF-7 cell line. LX-039 is currently in a clinical trial (NCT04097756, Table 17) for the treatment of advanced breast cancer.

In rodents, LX-039 shows low to moderate clearance (CL = 1.4 and 7.7 mL/min/kg in mouse and rat, respectively), while clearance in the higher species was low, at CL = 0.84 mL/min/kg in dog. In all species evaluated, bioavailability ranged from *F* = 55% to 60% (Table 16). Taken together, LX-039 exhibited excellent PK, low CL, high C_{max}, and oral exposure supporting its progression into clinical trials.[118]

In a mouse MCF-7 xenograft model study, LX-039 inhibited tumor growth in a dose-dependent manner. At the maximum dose of 60 mg/kg, it induced tumor shrinkage with a TGI of 113%. The body weight changes among drug-dosed groups tracked well with vehicle control animals. In a mouse tamoxifen-resistant MCF-7 xenograft model study, LX-039 significantly

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Table 16. Cross-Species Pharmacokinetics of LX-039 (9)

Species	CL (mL/min/kg)	V_{dss} (L/kg)	C_{max} (PO) (nM)	AUC_{0-24} (PO) (nM)	F (%)
Mouse	1.4	0.5	1873 @2.5 mg/kg	15329 @2.5 mg/kg	60
Rat	7.7	2.0	381 @1.0 mg/kg	4820 @1.0 mg/kg	56
Dog	0.84	0.42	2550 @1.0 mg/kg	43800 @1.0 mg/kg	55

suppressed tumor growth from 30 to 200 mg/kg dose, with TGI at 200 mg/kg reaching 91%.[118]

*Synthesis of Compound LX-039 (**9**).* LX-039 was synthesized from commercially available compound **9.1** in three steps (Scheme 9; clinical trial data are in Table 17). Compound **9.1** was coupled with 2-chloro-4-fluoro-1-iodobenzene under Suzuki conditions followed by ester hydrolysis to give the corresponding acid **9.3**. Compound **9.3** underwent chlorination at the indole C-3 position to provide the desired compound LX-039.[118]

■ ORAL SERDs WITH A BASIC AMINE SIDE CHAIN

SERDs containing a basic amine side chain were optimized to deliver maximal ERα degradation across multiple ER+ cell lines, a property possessed by fulvestrant. New SERDs discovered in this way have better oral bioavailability while maintaining their high-affinity binding to ERα and achieving both potency and efficacy comparable to those of fulvestrant in ER-resistant or *ESR1*-mutated cell lines.[119] Currently, a number of oral SERDs with a basic amine side chain, including elacestrant (RAD1901), giredestrant (GDC-9545), imlunestrant (LY3484356), amcenestrant (SAR439859), and camizestrant (AZD9833), are in advanced clinical development, and elacestrant has been recently approved by the FDA.[14]

Elacestrant (RAD1901, 11). On January 27, 2023, the FDA approved elacestrant (RAD1901) for postmenopausal women or adult men with ER+/HER2−, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.[14] RAD1901 (**11**) has a pharmacological profile showing both SERD and SERM characteristics with a basic amine side chain. RAD1901 shows a comparable binding affinity toward the LBDs of WT ERα and various ER mutants, including D538G and Y537S mutations (Table 18). It displayed a dose-dependent inhibition of proliferation in MCF-7, T47D, and HCC1428 cell lines.[120,121]

*In Vivo Efficacy of RAD1901 (**11**) in MCF-7 Xenograft Models.* RAD1901 as a single agent or in combination with palbociclib or everolimus resulted in substantial TGI in MCF-7 tumor xenografts.[122,123] Significant TGI responses were seen at doses of 30 and 60 mg/kg of RAD1901, with TGIs of 66% and 88%, respectively. The data was comparable to the TGIs observed for tamoxifen and fulvestrant, which were 86% and 88%, respectively. RAD1901 was well tolerated, with no adverse effect on body weight. Higher doses of RAD1901 induced a more pronounced effect in this model, with a TGI of 94% in the 60 mg/kg group, 97% in the 90 mg/kg group, and 96% in the 120 mg/kg group. RAD1901 inhibited tumor growth in CDK4/CDK6 inhibitor-resistant cell lines with both *ESR1* WT and mutant backgrounds (Y537S and D538G). In addition, RAD1901 demonstrated potent antitumor activity in multiple PDX models, including those derived from heavily pretreated patients expressing WT or mutant ERα-Y537S and ERα-D538G or CDK4/CDK6 inhibitor-resistant PDX models.[122]

Treatment with RAD1901 also protected against bone loss in ovariectomized rats and prevented the uterotrophic effects of E2, suggesting that it acts as an agonist in bone but as an antagonist in breast and uterine tissues. In an intracranial MCF-7 model, RAD1901-treated animals had significantly prolonged survival in comparison to those treated with fulvestrant, suggesting the potential benefit of RAD1901 in the treatment of ER+ BC that has metastasized to the brain.[124]

*Synthesis of RAD1901 (**11**).* The synthesis of RAD1901 started with a benzyl-protected dihydronapthalene compound **11.1**. Compound **11.1**, upon palladium-catalyzed borylation followed by Suzuki coupling with the bromo compound **11.3**, provided compound **11.4**. Compound **11.4** was then reduced with $Pd(OH)_2/H_2$, which simultaneously reduced the double bond and debenzylated the phenol to produce compound **11.5**, which was subsequently deacetylated in the presence of a base, giving compound **11.6** with a yield >90%. Compound **11.6** is typically a 50:50 racemic mixture, and the desired compound has the (*R*)-stereochemistry at the 6-position. The racemic mixture was then treated with (+)-2,3-dibenzoyl-D-tartaric acid [(+)-DBTA, 0.5 equiv], and the desired salt crystallized out with >90% ee (enantiomeric excess) and >90% of the theoretical yield of the desired enantiomer. The next step was the reductive animation of compound **11.7** with benzaldehyde **11.8** to yield the crude product, which upon further reductive amination with acetaldehyde afforded the desired compound **11.9** with a 90% yield. The product **11.9** was then reduced with $NaBH_4/I_2$, which generated BH_3 *in situ*, followed by a reductive workup with $Na_2S_2O_3$ that gave the desired compound RAD1901 (**11**) with a 50% yield (Scheme 10).[125]

*Clinical Data of RAD1901 (**11**).* In a Phase I study, RAD1901 showed single-agent activity in a heavily pretreated population of postmenopausal women with three median prior lines of therapy and a 50% rate of baseline *ESR1* mutation.[31,126] These encouraging results led to the multicenter Phase III EMERALD (NCT03778931) trial which evaluated RAD1901 vs standard of care (SOC) (fulvestrant or AI) in ER+ MBC following

Scheme 9. Synthesis of LX-039 (9)

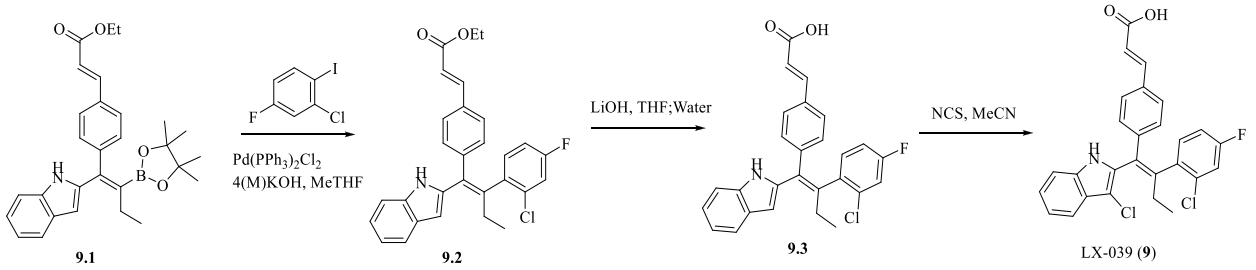

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Table 17. Clinical Trial Data for LX-039 (9)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
LX-039 (SERD)	LX-039	A Phase I Study of LX-039 Tablets in Postmenopausal Patients With ER+, HER2− Advanced Breast Cancer After Failure of Endocrine Therapy	advanced breast cancer	NCT04097756 (Phase I, enrolling by invitation)

Table 18. Determination of RAD1901 (11) Binding Affinity toward Wild-Type ERα and ERα Expressing Five Different Mutations Using a Fluorescence Polarization Method

ERα LBD	IC_{50} (nM)
WT	42
D538G	56
Y537C	30
Y537N	41
Y537S	61
S463P	53

progression on 1−2 prior lines of endocrine therapy and prior exposure to a CDK4/CDK6 inhibitor.[31,126] Eligible patients could have received up to one prior line of chemotherapy in the advanced or metastatic setting. Patients were randomized (1:1) to receive elacestrant 345 mg orally once daily (n = 239) or the investigator's choice of endocrine therapy (n = 239), which included fulvestrant (n = 166) or an AI (n = 73; exemestane, anastrozole, or letrozole). Of 477 patients enrolled in this study, 228 harbored a baseline *ESR1* mutation (47.8%). RAD1901 prolonged PFS in patients with both WT and mutant *ESR1* (hazard ratio = 0.70) and in patients with *ESR1*-mutation tumors (hazard ratio = 0.55), which were the primary end points of the study. Improved 12-month PFS and median PFS were seen in the overall population (22.3% vs 9.4%; 2.8 vs 1.9 months) and *ESR1*-mutation cohort (26.8% vs 8.2%; 3.8 vs 1.9 months). Overall, a trend toward an overall survival (OS) improvement was observed.[31,126] Most patients had visceral disease (71%), 62% had received one line of endocrine therapy, and 39% had received two lines of endocrine therapy in the advanced or metastatic setting. All patients had received prior treatment with a CDK4/CDK6 inhibitor, 24% had received prior fulvestrant, and 25% had received prior chemotherapy in the advanced or metastatic setting.[14] Analysis of PFS in the 250 (52%) patients without *ESR1* mutations (hazard ratio = 0.86) indicated that the improvement in the ITT population was primarily attributed to the results seen in the *ESR1*-mutated population. The most common TRAEs were nausea (25.3%), vomiting (11%), and fatigue (11%), primarily grades 1−2.[31,126] This study represents the first positive Phase III trial of an oral SERD. Additional data on the efficacy of elacestrant will be obtained from the ongoing Phase Ib/II trials evaluating elacestrant in combination with the CDK4/CDK6 inhibitor abemaciclib in patients with progressing brain metastases (NCT04791384, Table 19).

GDC-0927 (12). In 2018, scientists from Seragon Pharmaceuticals reported the discovery of GDC-0927 (SRN-927, **12**, Figure 15), a benzopyran-based SERD which was designed to further improve the potency over GDC-0810 (**3**).[127] The identification of GDC-0927 was based on the optimization of the ERα degradation of a series of ER modulators through side-chain substitution and the addition of a fluoromethyl azetidine group. By shifting away from the acrylic acid moiety in GDC-0810 (**3**), GDC-0927 (**12**) achieved improved potency and more consistent and complete suppression of ER signaling.[128]

Scheme 10. Synthesis of RAD1901 (11)

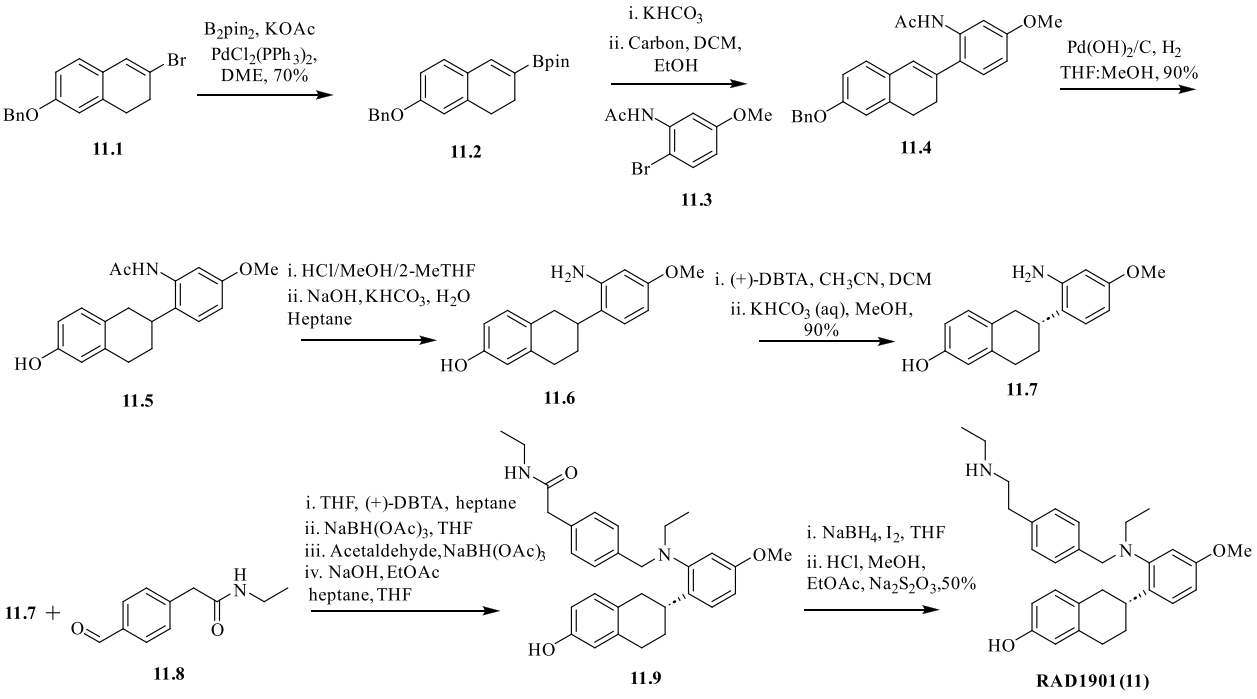

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Table 19. Clinical Trial Data for RAD1901 (11)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
Elacestrant (RAD1901) (SERD)	Abemaciclib + Elacestrant	Phase Ib/II Trial of Abemaciclib and Elacestrant in Patients with Brain Metastasis due to HR+/HER2− Breast Cancer	breast cancer	NCT04791384 (Phase II, recruiting)
	Elacestrant vs SOC	Phase 3 Trial of Elacestrant vs Standard of Care for the Treatment of Patients with ER+/HER2− Advanced Breast Cancer	breast cancer	NCT03778931 (completed)
	Elacestrant	Elacestrant in Preoperative Setting, a Window of Opportunity Study	breast cancer, HR+ breast carcinoma	NCT04797728 (completed)
	Elacestrant	ELACESTRANT in Women and Men with CDK4/CDK6 Inhibitor-Naive Estrogen Receptor-Positive, HER-2-Negative Metastatic Breast Cancer Study	metastatic breast cancer	NCT05596409 (Phase II)
	Abemaciclib + Elacestrant	Study of Abemaciclib and Elacestrant in Patients with Brain Metastasis due to HR+/Her2− Breast Cancer	breast neoplasms, brain neoplasms, neoplasms by site, breast diseases, central nervous system neoplasms, central nervous system diseases	NCT05386108 (Phase II, recruiting)

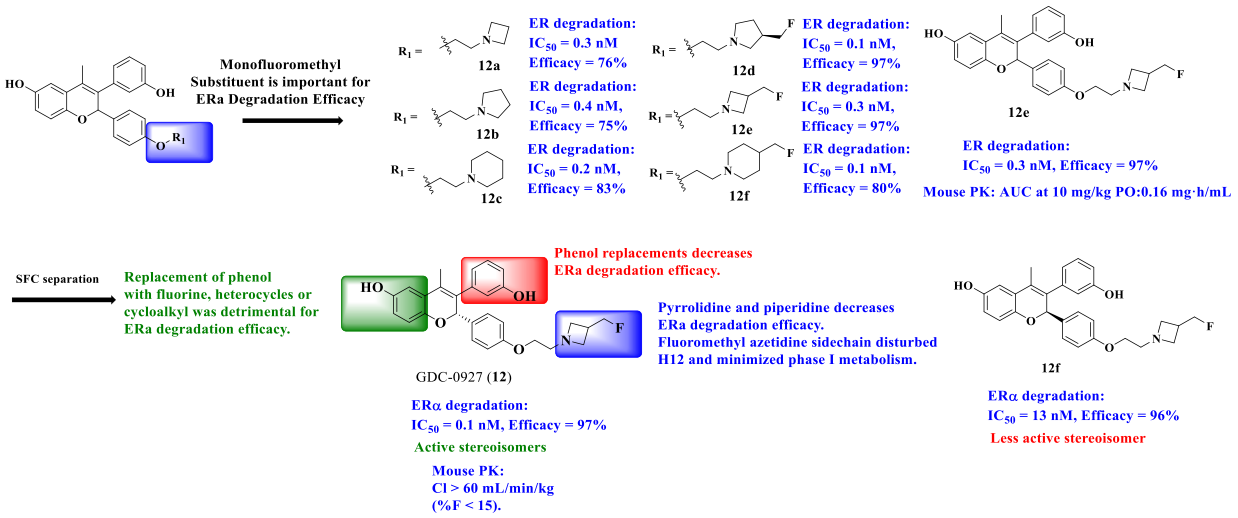

Figure 15. Design strategy and SAR analysis of GDC-0927 (**12**).

GDC-0927 exhibited high potency (IC_{50} = 0.1 nM) and degradation efficiency (97%) in *in vitro* ERα degradation assays in the MCF-7 cell line. It also showed an *in vitro* profile comparable to that of fulvestrant in other cell lines such as T-47D, HCC1500, and CAMA-1. SAR studies showed that replacing phenols with other substituents reduced the degradation efficacy (Figure 12). Attempts to replace the 3′-OH with fluorine, heterocycles, cycloalkyl, or alkyl moieties failed to improve the metabolic stability and resulted in reduced potency. A fluoromethyl azetidine side chain (**12e**) as a basic amine side chain significantly improved the ERα degradation efficacy and gave the most efficient ERα degrader. Substituents such as pyrrolidine (**12b**) and piperidine (**12c**) led to a significant reduction in degradation efficacy. Fluoromethyl substitution to either pyrrolidine (**12d**) or piperidine (**12e**) side chains led to an improvement in ERα degradation efficacy. Compound **12e** containing the fluoromethyl azetidine side chain was prioritized due to its superior PK properties and fewer stereocenters. SFC separation of compound **12e** yielded the active isomer compound GDC-0927 (**12**) with a low nanomolar potency (ERα degradation DC_{50} = 0.1 nM). However, similar to other ER ligands that also contain two phenol groups, the mouse PK of GDC-0927 are characterized by high clearance (CL > 60 mL/min/kg) and low bioavailability (F < 15%).[127,129] Nevertheless, GDC-0927 was selected for clinical development in part due to the fact that the ER-α conformations induced by GDC-0927 are distinct from those with fulvestrant and 4-hydroxytamoxifen and did not show appreciable interaction with αIII of ER.[127]

*In Vitro and In Vivo DMPK Data for GDC-0927 (**12**).* Cytochrome P450 (CYP) inhibition profiling of GDC-0927 (**12**) indicated little to no inhibitory activity against CYP1A2, CYP2C19, CYP2D6, or CYP3A4 (IC_{50} > 10 μM) and only a modest inhibitory effect on CYP2C8 and CYP2C9 (IC_{50} = 3.0 and 3.2 μM, respectively). GDC-0927 was found to have moderate hERG activity (IC_{50} = 4.6 μM).[151] The bioavailability of GDC-0927 in mice was low (<15%) and the clearance was high (CL > 60 mL/min/kg), resulting in low oral exposure, probably due to glucuronidation of the molecule's phenol groups.[151] Poor bioavailability and low oral exposure resulted in a high pill burden in the clinical setting, which ultimately limited dose escalation and clinical development, despite GDC-0927 exhibiting improved potency compared with GDC-0810.[127,128]

Antitumor Effects. The *in vivo* antitumor activity of GDC-0810 (**3**) and GDC-0927 (**12**) was compared in MCF-7 xenografts and in two endocrine-sensitive PDX models, HCI-

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Scheme 11. Synthesis of GDC-0927 (12)

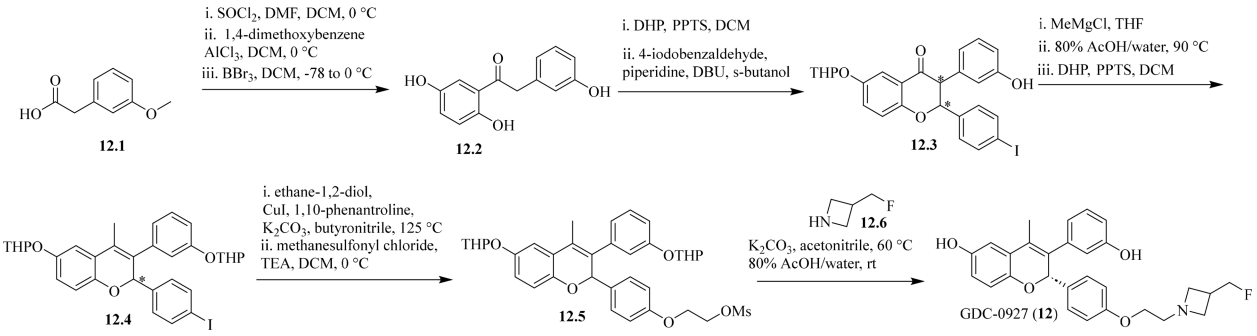

Table 20. Clinical Trial Data for GDC-0927 (12)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
GDC-0927 (SERD)	GDC-0927	A Study of GDC-0927 in Postmenopausal Women with Locally Advanced or Metastatic Estrogen Receptor Positive Breast Cancer	breast cancer	NCT02316509 (completed)

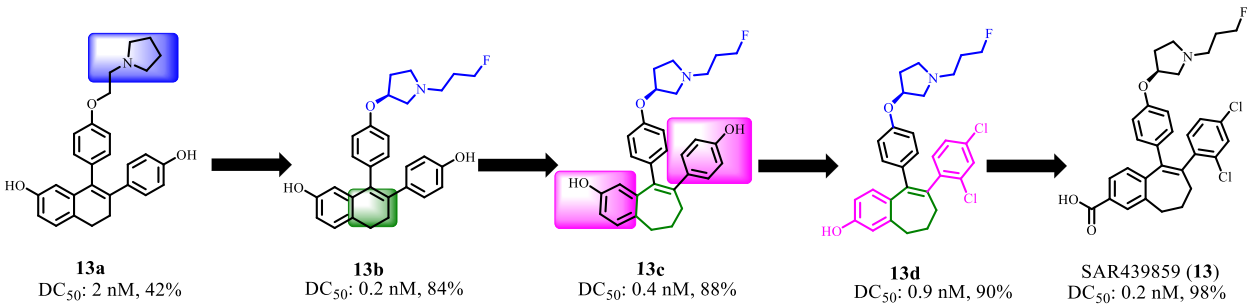

Figure 16. Design strategy and SAR analysis of SAR439859 (**13**).

013 (ER. Y537S) and HCI-011 (ER. WT). In MCF-7 xenografts, GDC-0927 and GDC-0810 showed indistinguishable efficacy, both driving tumor regressions at 100 mg/kg QD. This *in vivo* result is consistent with *in vitro* observations in the MCF-7 cell line, where GDC-0810 (**3**) and GDC-0927 (**12**) exhibited similar antiproliferative capacity. In contrast, in the HCI-013 PDX model, which expresses the ERα-Y537S mutant, GDC-0927 (**12**) demonstrated greater antiproliferative capacity when compared to GDC-0810 (**3**). In the HCI-013 PDX model, GDC-0810 (**3**) had a much weaker response (80% TGI at 100 mg/kg, QD) when compared to GDC-0927 (**12**, ~100% TGI at 30 mg/kg QD; 124% TGI at 100 mg/kg QD, respectively). This PDX model may reflect the greater antiproliferative capacity of GDC-0927 over that of GDC-0810 observed *in vitro* in non-MCF7 cell lines such as HCC1500 and CAMA-1.[80,127] GDC-0927 also showed greater efficacy than GDC-0810 in the HCI-011 PDX model, which expresses exclusively WT ER. This suggested that the greater effectiveness of GDC-0927 is not limited to ER mutant contexts. Unlike GDC-0810 and tamoxifen, GDC-0927 displayed no agonist activity in rat uterine assays.

Synthesis of GDC-0927 (12). The synthesis began with the commercially available acid **12.1**, which upon Friedel−Crafts acylation followed by demethylation produced compound **12.2** (Scheme 11). Acid-mediated THP protection followed by cyclization of compound **12.2** provided the diastereomeric mixture of compound **12.3**. Compound **12.3**, upon methyl Grignard addition followed by dehydration and THP protection, yielded an enantiomeric mixture of compound **12.4**.[154] Intermediate **12.5** was prepared from **12.4** via Ullmann coupling with ethylene glycol followed by mesylation to afford **12.5** with a 51% overall yield. The final compound GDC-0927 (**12**) was prepared by SN_2 displacement of mesylate **12.5** with the cyclic secondary amine **12.6** followed by acid-mediated THP deprotection.[127]

Clinical Data of GDC-0927 (12). In a Phase 1 dose escalation study, GDC-0927 was assessed at three dose levels (600 mg QD, 1000 mg QD, and 1400 mg QD) in 42 postmenopausal patients with ER+/HER2− MBC. GDC-0927 exhibited linear PK in humans, and exposure was dose-proportional with a $t_{1/2}$ of approximately 20 h, supporting QD dosing. FESPET (Female EStrogen recePtor in Endometrial cancer Treatment) showed a nearly complete (>90%) suppression of FES uptake to background levels, including in patients with *ESR1* mutations. Evidence of reduced ER levels and Ki67 staining (a nuclear protein and biomarker for tumor proliferation) was observed in treatment biopsies. 1400 mg QD was selected as the recommended Phase 2 dose.[155] TRAEs were all grade 1 or 2. The most common TRAEs were nausea (54%, $n = 7$), diarrhea (46%, $n = 6$), elevated aspartate aminotransferase (39%, $n = 5$), and anemia and constipation (each 31%, $n = 4$).[130,131] Although exhibiting desirable mechanistic features, GDC-0927, like fulvestrant, suffers from suboptimal drug-like properties, and consequently, the clinical development of this compound was halted in 2018 (Table 20). A newer generation of drug candidate GDC-9545 is currently being pursued.[128]

Amcenestrant (SAR439859, 13). In a recent study, Schio et al. performed a medium-throughput screening (MTS) that identified **13a** (Figure 16, ERα degradation efficacy = 42%) as an attractive starting point for optimization of the ERα degradation

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efficacy.[132] Initial optimization efforts around the pyrrolidine side chain made by varying the nature and the position of the basic residue resulted in compound **13b** which had improved degradation activity (Figure 16). Expansion of the cyclohexene ring in compound **13b** to a cycloheptene ring in compound **13c** led to a slight increase in degradation activity, probably due to the conformational constraints. Metabolic stability was significantly improved when this aryl modification was combined with the conversion of the 3-hydroxyphenyl isomer to the 2-hydroxyphenyl isomer (**13d**). Finally, the distal 2-hydroxyphenyl moiety was replaced by a carboxylic acid to lower the log *D* while maintaining a suitable metabolic profile. Among the different carboxylic acid derivatives, SAR439859 (**13**) demonstrated remarkable metabolic stability combined with high degradation efficacy and potency (DC_{50} = 0.2 nM, ERα degradation efficacy = 98%). It also had potent antagonist and degradative properties against ER both *in vitro* and *in vivo* and binds with high affinity to human WT or mutant ERα (ERα-Y537S and ERα-D538G). In cell viability assays, SAR439859 had a better potency in ER WT MCF-7 cells than in ER-mutated MCF-7 (EC_{50} = 20 nM [WT], 331 nM [ERα-Y537S mutant], 595 nM [ERα-D538G mutant]).[133] Furthermore, like fulvestrant, SAR439859 was able to downregulate both WT and HA-tagged Y537S and D538G mutant ERα protein levels (Tables 21 and 22).

Table 21. *In Vitro* Properties of SAR439859 (13)

	Transcription Luciferase, IC_{50} (nmol/L)		MCF7 ERα Degradation		MCF7 Cell Viability, EC_{50} (nM)		
Compound	ERα	ERβ	DC_{50} (nmol/L)	D_{max} (%)	WT	Y537S	D538G
Fulvestrant	0.5	0.9	0.2	98	21	262	265
SAR439859	1.8	8.4	0.4	98	20	331	595

Table 22. Potency and Pharmacokinetics Parameters of SAR439859 (13) and Analogs

	ERα Degradation		Metabolic Liability	
Compound	DC_{50} (nM)	Efficacy (%)	Total metabolism (%), human/mouse/rat	log *D*, pH 7.4
13a	2	42	–	–
13b	0.2	84	–	–
13c	0.4	88	49/55/58	–
13d	0.9	90	30/18/17	5.27
SAR439859	0.2	98	12/13/4	3.25

SAR439859 showed an excellent PK profile in rodents and nonrodent species and displayed a low clearance and good oral bioavailability (Table 23).

The X-ray crystal structure of the ERα LBD with SAR439859 (Figure 17) was analyzed at 1.48 Å resolution. In this orientation, the carboxylic group interacts with Glu353 (from which it is separated by 2.5 Å) and Arg394 (3.0 Å), while the dichlorophenyl moiety faces His524. The fluoropropyl chain is oriented toward the outside of the protein, and the basic nitrogen atom of the *N*-propylpyrrolidine moiety interacts with Asp351 (from which it is separated by 3.0 Å).

Table 23. Cross-Species Pharmacokinetics of SAR439859 (13)

Species	V_{dss} (L/kg)	CL (L/h/kg)	*F* (%)	$t_{1/2}$ (h)
Rat	0.83	0.19	76	4.13
Mouse	6.10	1.92	62	1.98
Dog	0.50	0.03	54	9.80

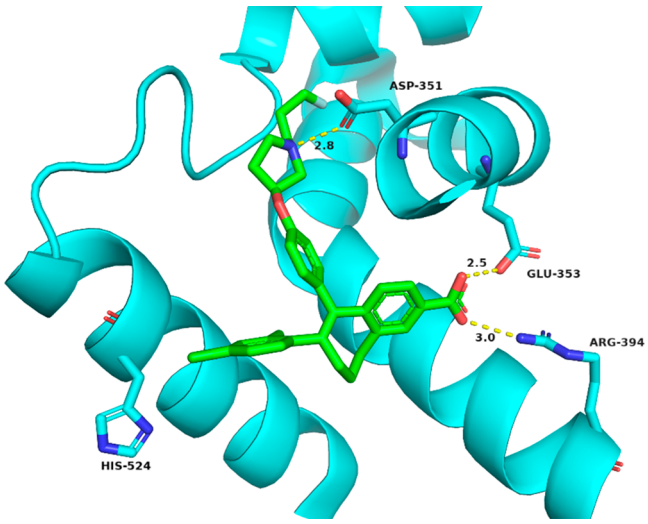

Figure 17. Cocrystal structures of SAR439859 (PDB code 6SBO) bound to ERα.

In vivo treatment with SAR439859 demonstrated significant tumor regression in ER+ BC models, including MCF-7 *ESR1* WT and mutant-Y537S mouse tumors and HCI013, a patient-derived tamoxifen-resistant xenograft tumor (Table 24). In a tamoxifen-sensitive MCF-7 xenograft tumor model, at 2.5, 5, and 12.5 mg/kg BID oral doses, SAR439859 exhibited substantial TGI, whereas at a dose of 25 mg/kg BID, it displayed tumor regression of $\Delta T/\Delta C$ = −28%.[132] SAR439859 also induced dose-dependent TGI in the ERα-Y537S model and in the HCI013 PDX model at 2.5 and 5 mg/kg BID, with tumor regression achieved at doses of 12.5 and 25 mg/kg, respectively.[132,133]

Table 24. Inhibition of Tumor Growth by SAR439859 (13)

	Efficacy, $\Delta T/\Delta C$ (%)		
Dose (BID) (mg/kg)	MCF-7 xenograft model	MCF-7 Y537S ER mutant	HCI013 patient xenograft, hormone therapy resistant
2.5	52	27	28
5.0	34	19	2
12.5	−5	−9	−31
25.0	−28	−34	−46

Synthesis of SAR439859 (13). The commercially available phenol **13.1** was protected with a pivaloyl group to generate the intermediate **13.2**, which was converted into the corresponding enol triflate intermediate **13.3**, with triflic anhydride in the presence of pyridine at room temperature. The side chain was inserted via a Suzuki coupling reaction between the triflate **13.3** and the boronate **13.8**, affording compound **13.9** with a 100% yield.[134] The compound **13.6** was synthesized via a Mitsunobu reaction[135] between the commercially available boronic ester **13.4** and (*R*)-1-*N*-Boc-3-hydroxypyrrolidine **13.5** in quantitative yield. The Boc group in compound **13.6** was then removed using 4 N HCl in dioxane to yield compound **13.7**, which was then alkylated with 1-iodo-3-fluoropropane in acetonitrile in the

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Scheme 12. Synthesis of SAR439859 (13)

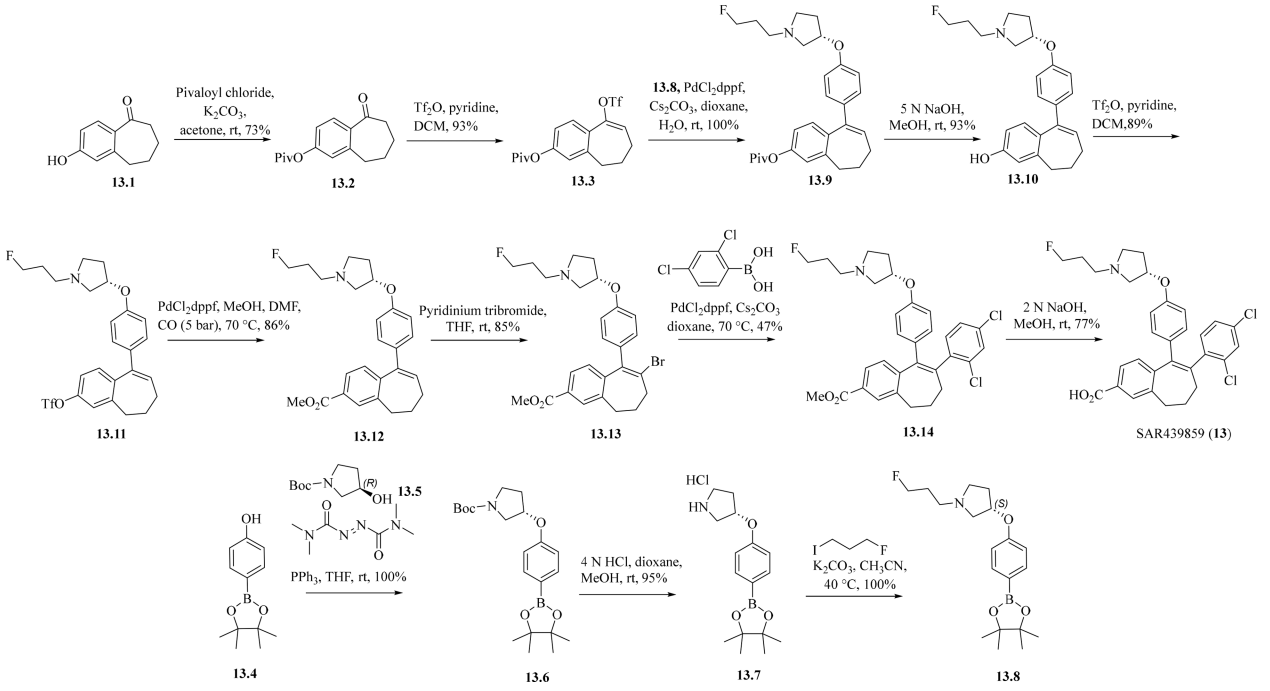

Table 25. Clinical Trial Data for SAR439859 (13)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
Amcenestrant (SAR439859) (SERD)	SAR439859, Palbociclib, Letrozole, Goserelin, Letrozole-matching placebo	A Randomized, Multicenter, Double-blind Phase 3 Study of Amcenestrant (SAR439859) plus Palbociclib versus Letrozole plus Palbociclib for the Treatment of Patients with ER (+), HER2 (−) Breast Cancer who have Not Received prior Systemic Anti-Cancer Treatment for Advanced Disease	breast cancer	NCT04478266 (Phase III, active, not recruiting)
	Amcenestrant, Fulvestrant, Anastrozole, Letrozole, Exemestane, Tamoxifen	An Open Label Randomized Phase 2 Trial of Amcenestrant (SAR439859), versus Endocrine Monotherapy as per Physician's Choice in Patients with Estrogen Receptor-positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer with prior Exposure to Hormonal Therapies	metastatic breast cancer	NCT04059484 (Phase II, active, not recruiting)
	Amcenestrant, Tamoxifen, Amcenestrant--matching placebo, Tamoxifen-matching placebo	A Randomized, Multicenter, Double-blind, Phase 3 Study of Amcenestrant (SAR439859) Versus Tamoxifen for the Treatment of Patients with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-negative or Positive, Stage IIB-III Breast Cancer who have Discontinued Adjuvant Aromatase Inhibitor Therapy Due to Treatment-related Toxicity	breast cancer	NCT05128773 (Phase III, terminated)
	Amcenestrant, Palbociclib, Alpelisib, Everolimus, Abemaciclib	A Phase 1/2 Study for the Safety, Efficacy, Pharmacokinetic and Pharmacodynamics Evaluation of Amcenestrant (SAR439859), Administered Orally as Monotherapy, then in Combination with Other Anticancer Therapies in Postmenopausal Women with Estrogen Receptor-Positive Advanced Breast Cancer	breast cancer	NCT03284957 (Phase I/II, active, not recruiting)

presence of potassium carbonate to afford compound **13.8** (Scheme 12). The carboxylic ester derivative **13.12** was then obtained by the carbonylation of the corresponding triflate **13.11** in methanol, which was made by treating the phenol **13.10** with triflic anhydride. The ester derivative **13.12** was then brominated with pyridinium tribromide[136] to obtain compound **13.13** with an 85% yield, which was next used in the Suzuki coupling reaction to afford compound **13.14** with a 47% yield. Compound **13.14**, upon saponification, gave the final compound SAR439859 (**13**) with a 77% yield.[132]

Clinical Data of SAR439859 (13). Based upon its promising preclinical results in *ESR1* WT and mutant models, SAR439859 (amcenestrant) was studied in a Phase I/II trial (NCT03284957) in pretreated metastatic patients[131] (Table 25). The optimal dose selected for monotherapy administration was 400 mg daily. An ORR of 8.5% and a CBR of 33.9% were observed. The main AEs were hot flashes (16.1%), constipation (9.7%), arthralgia (9.7%), decreased appetite (8.1%), vomiting (8.1%), diarrhea (8.1%), nausea (8.1%), and fatigue (6.5%), mostly grades 1−2. The study also consisted of a combination part with palbociclib. Recent results showed an ORR of 32.4%, a CBR of 73.5%, and a median PFS of 14.7 months.[137] The most frequent TRAEs were nausea (17.9%), fatigue (15.4%), arthralgia (10.3%), asthenia (10.3%), dry skin (10.3%), and

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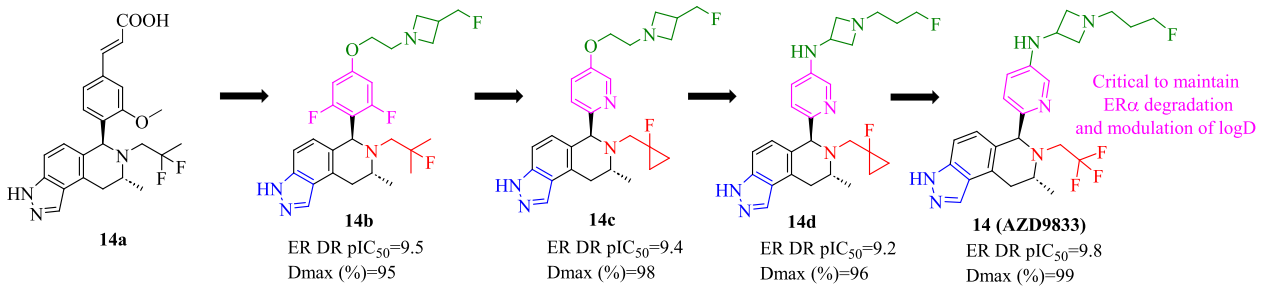

Figure 18. Design strategy and SAR analysis of AZD9833 (**14**).

Table 26. *In Vitro* Properties of AZD9833 (14) and Its Analogs

Compound	ER DR pIC_{50} (D_{max}, %)	log $D_{7.4}$	Human, % free	Rat/human hepatocyte CL_{int} (μL/min/10^6 cells)	% Deg vs Fulvestrant MCF-7/CAMA1
14b	9.9 (95)	4.4	0.8	88/8	84/66
14c	9.4 (98)	2.6	34	38/8	75/87
14d	9.2 (96)	2.5	26	24/5	90/102
14 (AZD9833)	9.8 (99)	2.9	23	23/6	94/98

Table 27. *In Vitro* and *In Vivo* DMPK Data for AZD9833 (14)

ER bind pIC_{50}	ER DR pIC_{50} (D_{max}, %)	% Deg vs fulvestrant MCF-7/CAMA1	Intrinsic Caco2 P_{app} (efflux ratio)	Mice/rat/dog/human, % free	Rat/human hepatocyte CL_{int} (μL/min/10^6 cells)	IC_{50}, CYP2D6/3A4 (μM)	IC_{50}, hERG (μM)
8.6	9.8 (99)	94/98	13 (4)	23/26/15/23	23/6	4.3/2.2	22

Table 28. Summary of Pharmacokinetic Parameters of AZD9833 (14) in Mice and Rats

Species	Dose (IV/PO) (mg/kg)	CL (mL/min/kg)	V_{dss} (L/kg)	$t_{1/2}$ (h)	F (%)	Fraction absorbed (%)
Mouse	2/5	59	9.2	5.1	16	50
Rat	0.5/1	73	13	3.0	19	>95

hot flashes (10.3%). Neutropenia was observed in 95% of patients, with at least G3 events occurring at 56.4%, but this was probably due to palbociclib rather than SAR439859. No bradycardia or eye disorders were observed. Unfortunately, SAR439859 monotherapy did not meet the primary end point of PFS (Table 25).[138−140] In August 2022, Sanofi announced the termination of global clinical development of SAR439859 based upon an interim analysis of the AMEERA-5 study, which is a randomized, double-blind study that assessed the safety and efficacy of amcenestrant and palbociclib in the first line.[141] A total of 1068 patients were randomized 1:1 to receive oral amcenestrant and palbociclib or oral letrozole and palbociclib. This study's primary end point was PFS, and secondary end points included OS, ORR, duration of response, and CBR. An independent data monitoring committee recommended stopping the trial after learning that the amcenestrant and palbociclib combination did not meet the prespecified boundary for continuation compared with the control arm. Investigators observed no new safety signals.

Camizestrant (AZD9833, 14). The tricyclic indazole AZD9833 (**14**) was reported in 2020 by Scott et al.[142] as a full ERα antagonist and is currently under investigation in Phase II and III clinical trials, whose results are shown below in Table 29.

The design of AZD9833 started from compound **14a**, a SERD molecule discovered from internal efforts by AstraZeneca.[142] Replacement of the acrylic acid chain with an ethoxyl-3-(fluoromethyl)azetidine and modifications of the phenyl group and 2,2-difluoropropyl led to compound **14b** (Figure 18), which is a potent and efficacious ER degrader (Table 26). Changing the pendant difluoro aromatic ring (**14a**) to a heteroaromatic pyridyl ring (**14b**) reduced the lipophilicity while maintaining the degradation potency (ER DR pIC_{50} = 9.4 and D_{max} = 98%). Compound **14b** had a much lower log D of 2.6 (−1.8 units) than **14a**, with a 42-fold improved percentage of free drug in humans. Reconstructing an azetidine ring proximal to the aryl ring and linking it with an amine instead of an ether resulted in compound **14c**, which had improved degradation potency in the CAMA1 and MCF-7 cell lines. This modification also decreased the lipophilicity by 0.3 unit, leading to lower human and rat hepatic clearance (CL_{hep}). Finally, the fluorocyclopropyl side chain was replaced by a trifluoromethyl side chain, delivering compound **14**, thus improving the potency in both MCF-7 and CAMA1 cell lines without altering other parameters such as PPB and CL_{hep} (Table 26).[142,143]

AZD9833 is a potent degrader and antagonist of the ERα receptor (EC_{50} < 1 nM in MCF-7 cells). It delivers maximal ERα degradation, equivalent to that of fulvestrant and greater than that of AZD9496, in all ER+ cell lines tested, including MCF-7, CAMA1, T-47D, and BT-474.[142,144]

AZD9833 is highly soluble in aqueous media (833 μM) and has good intrinsic cellular permeability (P_{app} = 13 × 10^{-6} cm/s) as measured in a Caco-2 assay. Due to its low lipophilic nature, it also showed a consistently high fraction of unbound levels in PPB assays across species (>10% free drug). In terms of CYP liability, AZD9833 showed no inhibition (IC_{50} > 30 μM) against three isoforms (CYP1A2, CYP2C19, CYP2C9) and moderate inhibition against CYP2D6 (IC_{50} = 4.3 μM) and CYP3A4 (IC_{50} = 2.2 μM) (Table 27). The compound had only weak inhibition against hERG (IC_{50} = 22 μM).

The volume of distribution was high in both mice and rats and was consistent with the compound's high free fraction and basic properties. *In vivo* clearance in both mice and rats was high,

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consistent with its modest oral bioavailability in mice (F = 16%) and rats (F = 19%) (Table 28).

The tricyclic [5.6.6] indazole core of AZD9833 is bound to the deep pocket that is lined with mostly hydrophobic residues (Figure 19). The nitrogen atoms of the tricyclic indazole interact

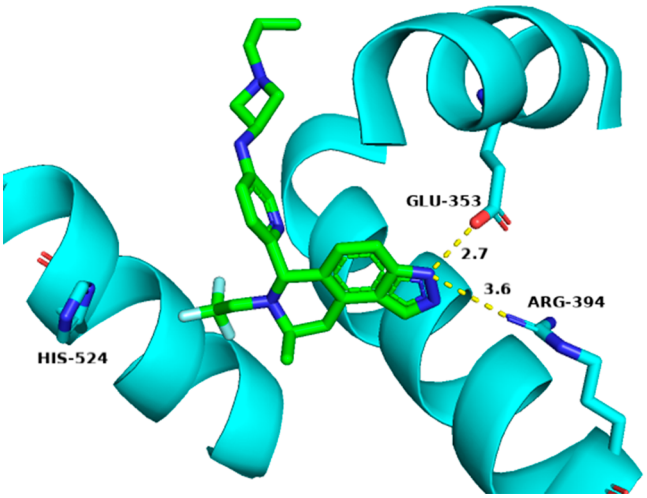

Figure 19. Cocrystal structure of AZD9833 (**14**) (PDB code 6ZOR) bound to ERα.

with a conserved water and form short hydrogen-bonding contacts with Glu353, which itself enjoys a water-mediated salt bridge to Arg394. However, the distance of the carbonyl oxygen from the protein backbone to the central ring of the tricyclic indazole is short (3.6 Å), which is a favorable contact.[142]

*Synthesis of AZD9833 (**14**).* Synthesis of AZD9833 initiated with the commercially available 4-bromo-1*H*-indazole (**14.1**, Scheme 13). Installation of the first stereogenic center was accomplished via alkylation of lithiated indazole **14.2** with *tert*-butyl (*R*)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (**14.3**), which generated compound **14.4** in a 57% yield. Boc deprotection followed by *N*-alkylation with triflate **14.6** led to compound **14.7** with a 93% yield. The key step in the synthesis of AZD9833 (**13**) is the substrate-controlled, diastereoselective Pictet–Spengler reaction[145] that delivered tetrahydroisoquinoline **14.9** followed by incorporation of 1-(3-fluoropropyl)azetidin-3-amine (**14.10**) via a Buchwald–Hartwig C–N coupling reaction.[142,143,146]

*In Vivo Pharmacology of AZD9833 (**14**).* Treatment of AZD9833 resulted in a dose-dependent decrease in tumor volume and no tolerance issues. A dose of 2 mg/kg of AZD9833 caused 73% TGI, while doses of 10 mg/kg and 50 mg/kg caused 15% and 53% tumor regression, respectively. Both 10 mg/kg and 50 mg/kg doses of AZD9833 had superior antitumor efficacy and pharmacodynamic effects than 5 mg of fulvestrant dosed three times a week.[167] Furthermore, in an *ESR1* WT and an *ESR1* D538G PDX model, AZD9833 demonstrated combinatorial benefit with palbociclib. Based on this preclinical data, AZD9833 progressed into a multistage monotherapy and palbociclib combination clinical trial, SERENA-1 (NCT03616587).[144]

*Clinical Data from AZD9833 (**14**).* In the Phase I SERENA-1 study (NCT03616587), AZD9833 was studied as a monotherapy[147] or in combination with CDK4/CDK6 inhibitors, palbociclib or abemaciclib, everolimus (an mTOR inhibitor), or capivasertib (an AKT inhibitor).[148,149] Preliminary results from 98 patients treated with AZD9833 as a monotherapy showed that, in those previously treated with fulvestrant (53%) and CDK4/CDK6 inhibitors (50%), the ORR and CBR were 10% and 35%, respectively, with a median PFS of 5.4 months. In the CDK4/CDK6 inhibitor-naive cohort which included 25 patients receiving AZD9833 plus palbociclib, the ORR and CBR were 5.9% and 28%, respectively. Of the patients treated with AZD9833 as a monotherapy, 46% had baseline *ESR1* mutations, of whom 50% achieved partial remission or stable disease at 24 weeks and 85% had reductions or loss of mutant *ESR1* with treatment. Toxicities of any grade reported in >15% of patients were visual disturbances (53%), bradycardia (45%), and nausea (18%). The SERENA-2 study (NCT04214288), evaluating AZD9833 vs fulvestrant, and the SERENA-4 and SERENA-6 studies (NCT04711252 and NCT04214288), evaluating AZD9833 plus a CDK4/CDK6 inhibitor in the first-line metastatic setting, are shown below in Table 29.[131,150] In the Phase II SERENA-2 study, AZD9833 significantly reduced the risk of disease progression or death by 42% at a 75 mg dose (hazard ratio = 0.58; median PFS of 7.2 versus 3.7 months) and 33% at a 150 mg dose (hazard ratio = 0.67; median PFS of 7.7 versus 3.7 months) compared to fulvestrant, the current SERD SOC. Among patients with *ESR1* mutations

Scheme 13. Synthesis of AZD9833 (14)

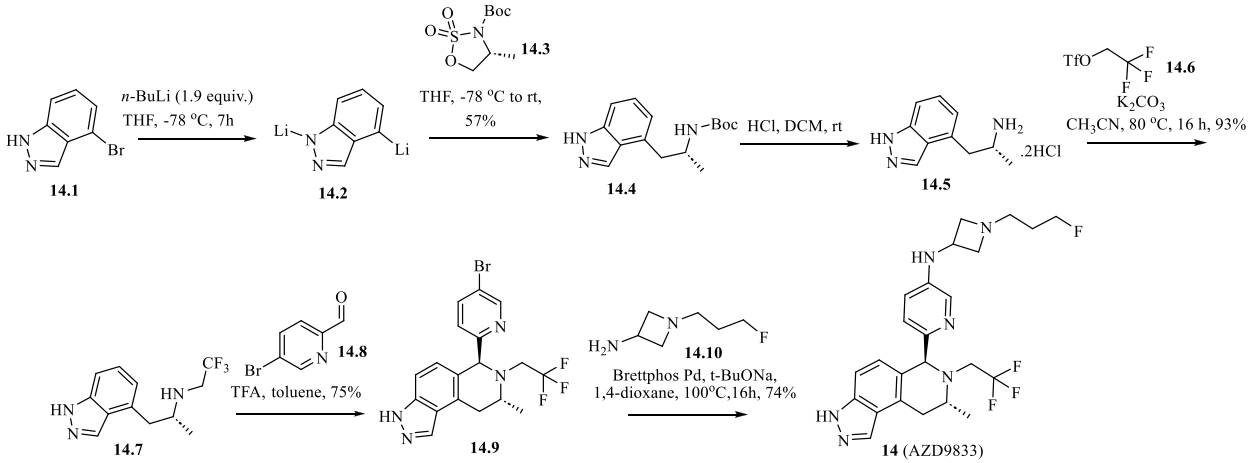

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Table 29. Clinical Trial Data for AZD9833 (14)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
AZD9833 (SERD)	Itraconazole	A Study to Assess the Pharmacokinetics of Camizestrant (AZD9833) when Administered Alone and in Combination with Itraconazole	healthy subjects	NCT05551897 (Phase I, not recruiting)
	Anastrozole, Letrozole, Palbociclib, Abemaciclib, LHRH	Phase III Study to Assess AZD9833+ CDK4/CDK6 Inhibitor in HR+/HER2-MBC with Detectable ESR1m Before Progression (SERENA-6)	ER+/HER2− breast cancer	NCT04964934 (Phase III, recruiting)
	Anastrozole, Palbociclib, LHRH	A Comparative Study of AZD9833 plus Palbociclib versus Anastrozole plus Palbociclib in Patients with ER-positive HER2 negative Breast Cancer who have Not Received any Systemic Treatment for Advanced Disease	ER+/HER2− breast cancer	NCT04711252 (Phase III, recruiting)
	Fulvestrant	A Comparative Study of AZD9833 versus Fulvestrant in Women with Advanced ER-Positive HER2-Negative Breast Cancer (SERENA-2)	advanced ER+/HER2− breast cancer	NCT04214288 (Phase II, active, not recruiting)
	Palbociclib, Everolimus, Abemaciclib, Capivasertib	Study of AZD9833 Alone or in Combination in Women with Advanced Breast Cancer	advanced ER+/HER2− breast cancer	NCT03616587 (Phase I, recruiting)

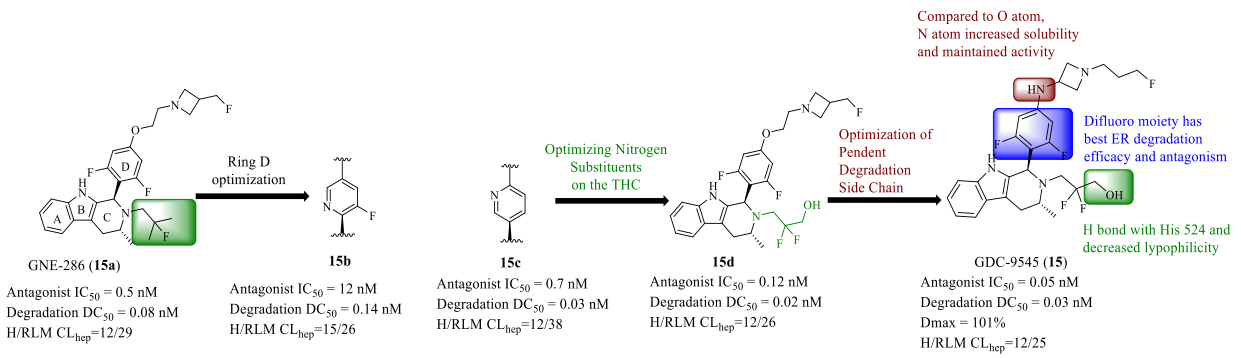

Figure 20. Design strategy and SAR analysis of GDC-9545 (**15**).

(36.7% of the trial population), AZD9833 showed a 67% reduction in the risk of disease progression or death at a 75 mg dose (hazard ratio = 0.33; median PFS of 6.3 versus 2.2 months) and a 45% reduction at a 150 mg dose (hazard ratio = 0.55, 90% CI 0.33−0.89; median PFS of 9.2 versus 2.2 months) compared to fulvestrant. Efficacy was also seen in patients without a detectable *ESR1* mutation, with a 22% and 24% reduction in the risk of disease progression or death (hazard ratio = 0.78 and 0.76) respectively for the 75 mg and 150 mg dose levels.

Giredestrant (GDC-9545, 15). To address those limitations observed for early SERD molecules GDC-0810 (**3**) and GDC-0927 (**12**), including improving the potency of the former and the oral bioavailability of the latter, scientists from Genentech carried out an extensive medicinal chemistry campaign, culminating in the discovery of GDC-9545 (**15**).[128,151]

GNE-286 (**15a**) was an attractive starting point for optimizing ERα degradation efficacy for GDC-9545 (Figure 19). Replacing one of the C−F moieties in the D-ring of GNE-286 with a pyridyl nitrogen resulted in analog **15b** and drastically eroded the antagonist activity and antiproliferation potencies. Adding a pyridyl nitrogen while removing the two fluorine atoms in the D-ring of GNE-286 resulted in analog **15c** with comparable potencies but slightly reduced liver microsomal stability. Based on a cocrystal structure of GNE-286 with ERα, a primary alcohol was installed into GNE-286 to interact with the residue His524. The resulting optimized compound **15d** had improved (2- to 5-fold) potencies in all three assays, improved degradation efficiency, and improved solubility. Therefore, the difluoropropyl alcohol side chain was identified as the optimal substituent on the tetrahydropiperidine nitrogen. Next, the side chain appended to the 4-position of the 2,6-difluorophenyl ring was optimized for maximum degradation efficiency. Changing the linker from an oxygen to an amine and reconstructing a four-membered azetidine ring with a terminal fluorine atom yielded compound GDC-9545 (**15**), which was 3-fold more potent as an antagonist than **15d** and was the most potent compound in the antagonist assay (Figures 20 and 21).[128]

The tetrahydropiperidine core in GDC-9545 offers a better foundation for metabolic stability than the SERDs with a phenol moiety, such as fulvestrant, GDC-0927, and RAD1901. A polar difluoropropyl alcohol in GDC-9545 (cLogP = 5.9) significantly mitigates the lipophilicity when compared with other SERDs, such as SAR439859 (cLogP = 6.4), RAD1901 (cLogP = 6.9), and G1T48 (cLogP = 7.4), and trends toward more drug-like properties. Exchanging the oxygen atom with a nitrogen atom on the basic amine side chain was critical for optimal antagonism, antiproliferative activity, and solubility. The low lipophilicity, high solubility, and high permeability render GDC-9545 a good candidate for oral administration.[128]

In preclinical studies, GDC-9545 was a highly potent ER antagonist (IC_{50} = 0.05 nM) and displayed potent degradation efficiency (DC_{50} = 0.03 nM, S_{inf} = 101%) in ERα degradation

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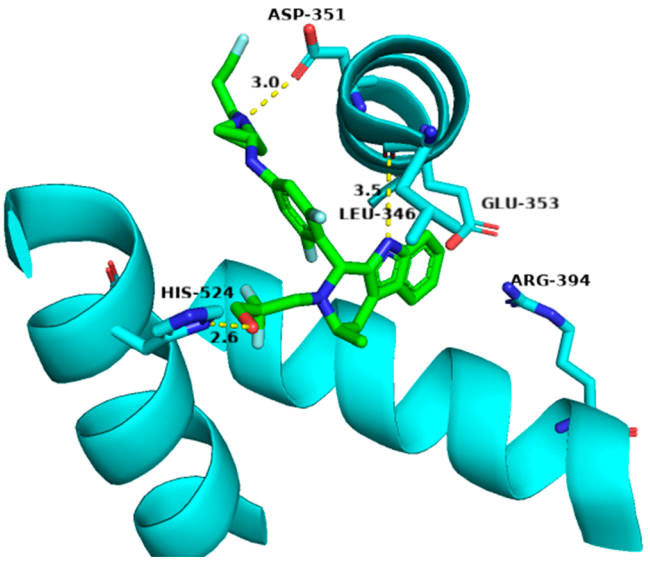

Figure 21. Cocrystal structure of GDC-9545 (**15**) bound to ERα (PDB code 7MSA).

assays in different MCF-7 cell lines.[128] Degradation efficiency and antiproliferation potencies of GDC-9545 were superior to those of fulvestrant in both WT (DC_{50} [nM]/S_{inf} = 0.06/107% vs 0.44/103%) and ERα-Y537S mutant (DC_{50} [nM]/S_{inf} = 0.17/113% vs 0.66/109%) MCF-7 cells (Table 30). GDC-9545 also showed efficient degradation compared to fulvestrant and GDC-0927 in different ER+ cell lines in Western blot assays and cellular viability assays.[128]

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile of GDC-9545 is summarized in Table 31. Predicted hepatic clearance in liver microsomes (LM) and hepatocytes (Hep) was mostly moderate across four preclinical species and humans, except for a low Hep CL_{hep} in dogs and a high Hep CL_{hep} in monkeys. The *in vivo* clearance was moderate in rats and monkeys and low in dogs. The oral bioavailability was moderate (F = 41−55%) in rats and dogs and low (17%) in monkeys. Improved oral bioavailability was observed in rats and monkeys using a crystalline tartrate salt. The PPB was high (98−99%) in all species.[128] GDC-9545 exhibited low to moderate reversible inhibition of CYP 3A4M (IC_{50} = 6.5 μM) and the other CYP enzyme isoforms, including 3A4T, 2C9, 2C19, and 2D6 (IC_{50} > 10 μM), and had moderate activity in the hERG ion channel (IC_{50} = 6.1 μM).[128]

At 1 mg/kg, GDC-9545 achieved strong efficacy (tumor regression), identical to that of GDC-0927 (100 mg/kg) in the HCI-013 PDX model. GDC-9545 also exhibited a full antagonist profile with a reduction in the uterine wet weight and had no effect on the epithelium height of the endometrium in rat uterine assays.[128] GDC-9545 demonstrated favorable nonclinical (*in vitro* and *in vivo*) safety profiles with a high safety margin (>190-fold higher than the projected human efficacious exposure) based on the HCI-013 ESR1Y537S PDX tumor model. With a highly favorable *in vitro* and *in vivo* safety profile, GDC-9545 was advanced into clinical development.[128]

*Synthesis of GDC-9545 (**15**).* Synthesis of GDC-9545 started with commercially available 2,2-difluoropropane-1,3-diol (**15.1**, Scheme 14). Monoprotection of the alcohol with TBDPSCl formed intermediate **15.2**, which was converted to the triflate **15.3** upon treatment with triflic anhydride. *N*-Alkylation of (2*R*)-1-(1*H*-indol-3-yl) propan-2-amine with triflate **15.3** led to compound **15.4** with an 87% yield. Removal of the silyl protecting group in **15.4**, followed by a Pictet−Spengler reaction[152] of **15.5** with 4-bromo-2,6-difluorobenzaldehyde, provided intermediate **15.6** with a 71% yield. Compound **15.6** was then coupled with a Boc-protected azetidine through a palladium-mediated Buchwald−Hartwig C−N coupling,[153] which yielded compound **15.7**. Upon removal of the Boc group, which was followed by *N*-alkylation with 1-fluoro-3-iodopropane, the final compound GDC-9545 (**15**) was achieved with an overall yield of 15%.[128]

The efficient manufacturing process for GDC-9545 begins with D-alanine (**15.9**), which upon coupling with tetrafluoro ester **15.10** furnished compound **15.11** with a 96% yield using NaOMe as the base (Scheme 15). Conversion of **15.11** to the acid chloride and subsequent $AlMe_3$-mediated Friedel−Crafts acylation[154] with the indole gave the desired product **15.12** with a 63% yield. $NaAl(OMe)_2H_2$ (5 equiv), prepared *in situ* from sodium aluminum hydride and methanol, was employed to efficiently reduce the ketone, amide, and methoxy moieties and remove the difluoro atoms in substrate **15.12** in a single step. Overall, the four-step sequence produced the tryptamine intermediate **15.13** with a 42% yield with >99 ee as determined by chiral HPLC analysis. A Pictet−Spengler reaction[155] of **15.13** with substituted aldehyde **15.14** produced **15.15**, which upon Buchwald−Hartwig amination[156] and tartaric salt formation with tartaric acid produced the tartaric salt of GDC-9545 with a HPLC purity of 99.0% and >99:1 dr.[157,158]

Clinical Data of GDC-9545. A Phase I/II study of GDC-9545 as a monotherapy showed an ORR of 13% and a median PFS of 7.8 months. The ORR was improved to 33% in combination with palbociclib, with a median PFS of 9.3 months. Overall, the drug was well tolerated, with TRAEs mostly grades 1−2. These mainly consisted of fatigue, arthralgia, nausea, bradycardia, and in some cases visual impairment.[159] The acelERA randomized Phase II trial (NCT04576455) comparing GDC-9545 to a physician-selected endocrine therapy failed to show a significant PFS benefit in a similar population when compared to the EMERALD and AMEERA-3 clinical trials.[160] The ongoing metastatic Phase III first-line trial persevERA (NCT04546009) and the second-line trial evERA (NCT05306340) in CDK4/CDK6 inhibitor-pretreated patients are expected to elucidate the efficacy of GDC-9545 in combination with palbociclib and everolimus, when compared to palbociclib plus letrozole and everolimus plus exemestane, respectively (Table 32). The coopERA Phase II window-of opportunity trial

Table 30. *In Vitro* Properties of GDC-9545 (15)

Compound	Antagonist IC_{50} (nM)	Degradation MCF-7 ERα, DC_{50} (nM)/S_{inf} (%)	Proliferation MCF-7, EC_{50} (nM)	Degradation MCF-7, DC_{50} (nM)/S_{inf} (%)		Proliferation MCF-7, EC_{50} (nM)	
				CRISPER WT	CRISPER Y537S	CRISPER WT	CRISPER Y537S
GDC-9545	0.05	0.03/101	0.36	0.06/107	0.17/113	0.04	0.3
Fulvestrant	0.25	0.12/103	2.4	0.44/103	0.66/109	0.1	1.3

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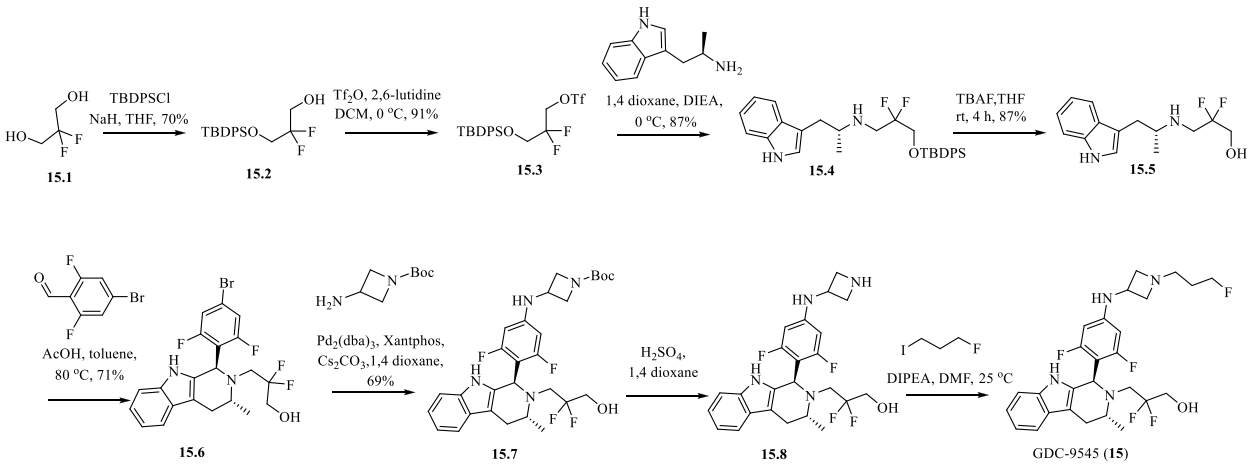
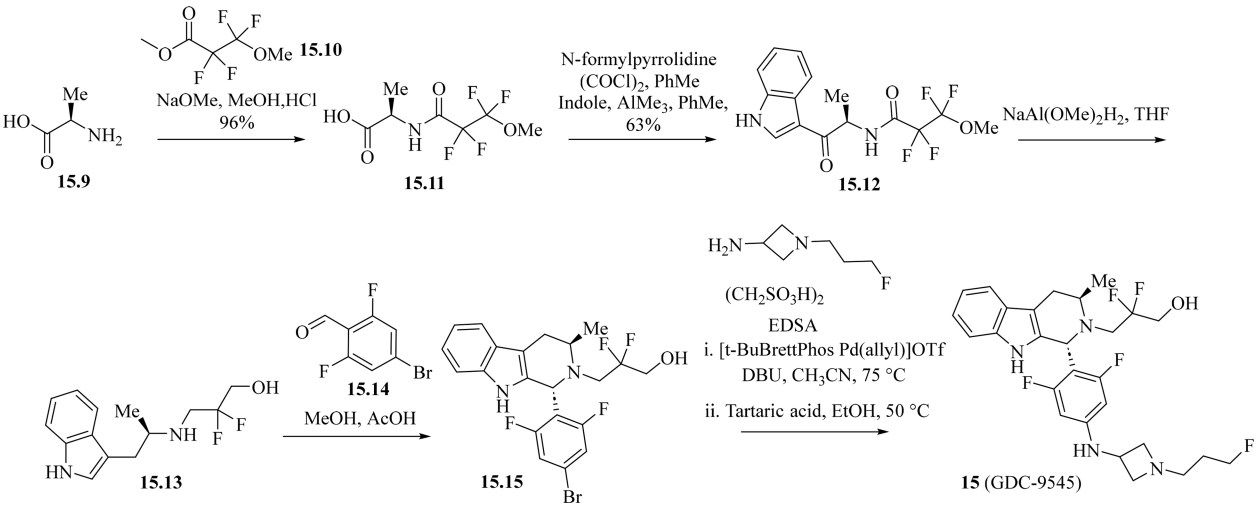
Table 31. Summary of Pharmacokinetic Parameters of GDC-9545 (15)

	In Vitro CL_{hep} (mL/min/kg)			Oral Bioavailability (%*F*)			
Species	LM	Hep	CL (mL/min/kg)	Amorphous free base (1 mg/kg)	Crystalline tartrate salt (100 mg/kg)	V_{ss} (L/kg)	$t_{1/2}$ (IV) (h)
Mouse	52	33	–		–	–	–
Rat	19	23	21	41	65	15	8
Dog	13	<7.8	3	55	–	5.1	24
Monkey	22	31	19	17	29	9.4	7.3
Human	11	12	–		–	–	–

Scheme 14. Synthesis of GDC-9545 (15)



Scheme 15. Efficient Manufacturing Process for GDC-9545 (15)



(NCT03916744) compared 2 weeks of treatment with GDC-9545 vs anastrozole followed by 16 weeks of GDC-9545 with palbociclib vs anastrozole with palbociclib before surgery in postmenopausal women with ER+/HER2− early-stage breast cancer.[161] Interim analysis results (83/202 patients) showed a more significant relative reduction of Ki67 at 2 weeks (80% vs 67%) and tumors achieving a complete cell cycle arrest (25% vs 5.1%) with GDC-9545 vs anastrozole.[162] These results point toward a potential efficacy of GDC-9545 in early-stage disease, with an antiproliferative effect superior to that of an AI and a consistent safety profile.[162] The ongoing Phase III lidERA trial is examining adjuvant giredestrant vs AI or tamoxifen for stage I–III ER+ BC (NCT04961996).

Imlunestrant (LY3484356, 16). LY3484356 was developed by the Eli Lilly Corp. Based on the structure disclosed in the WHO drug information document, compound **16** is the drug candidate.[163,164] As reported in the latest AACR abstract,[165] LY3484356 has potent activity against the WT and mutant ER. LY3484356 has K_i values of 0.64 nM and 2.8 nM against WT ERα and Y537S mutant ERα proteins, respectively. It is also a potent and highly efficient degrader of WT ERα and Y537N mutant ERα proteins in cells, with IC_{50} values of 3.0 nM and 9.6 nM. LY3484356 also is a potent inhibitor of ERα-mediated transcription *in vitro* and *in vivo*. It inhibits cell proliferation in WT ERα and *ESR1* Y537N mutant BC cell lines, with average IC_{50} values of 3 nM and 17 nM. LY3484356 has demonstrated sustained and prolonged target inhibition (>75%

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Table 32. Clinical Trial Data for GDC-9545 (15)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
GDC-9545 Giredestrant (SERD)	Palbociclib	A Study of GDC-9545 Alone or in Combination with Palbociclib and/or Luteinizing Hormone-Releasing Hormone (LHRH) Agonist in Locally Advanced or Metastatic Estrogen Receptor-Positive Breast Cancer	breast cancer	NCT03332797 (Phase I, active, not recruiting)
	Fulvestrant or an AI (physician's choice)	A Study Evaluating the Efficacy and Safety of Giredestrant Compared with Physician's Choice of Endocrine Monotherapy in Participants with Previously Treated Estrogen Receptor-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer (acelERA Breast Cancer)	ER+/HER2− locally advanced or metastatic breast cancer	NCT04576455 (Phase II, active, not recruiting)
	Letrozole, Palbociclib, LHRH agonist	A Study Evaluating the Efficacy and Safety of Giredestrant Combined with Palbociclib Compared with Letrozole Combined with Palbociclib in Participants with Estrogen Receptor-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer (persevERA Breast Cancer)	ER+/HER2− locally advanced or metastatic breast cancer	NCT04546009 (Phase III, recruiting)
	Exemestane, Everolimus, LHRH agonist	A Study Evaluating the Efficacy and Safety of Giredestrant Plus Everolimus Compared with Exemestane Plus Everolimus in Participants with Estrogen Receptor-Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer (evERA Breast Cancer)	ER+/HER2− locally advanced or metastatic breast cancer	NCT05306340 (Phase III, recruiting)
	Drug: Anastrozole, Drug: Palbociclib, Procedure: surgery	A Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Giredestrant Plus Palbociclib Compared with Anastrozole Plus Palbociclib for Postmenopausal Women with Estrogen Receptor-Positive and HER2-Negative Untreated Early Breast Cancer (coopERA Breast Cancer)	early breast cancer	NCT03916744 (completed)
	Endocrine therapy of physician's choice	A Study Evaluating the Efficacy and Safety of Adjuvant Giredestrant Compared with Physician's Choice of Adjuvant Endocrine Monotherapy in Participants with Estrogen Receptor-Positive, HER2-Negative Early Breast Cancer (lidERA Breast Cancer)	early breast cancer	NCT04961996 (Phase III, recruiting)

Scheme 16. Synthesis of LY3484356 (16)

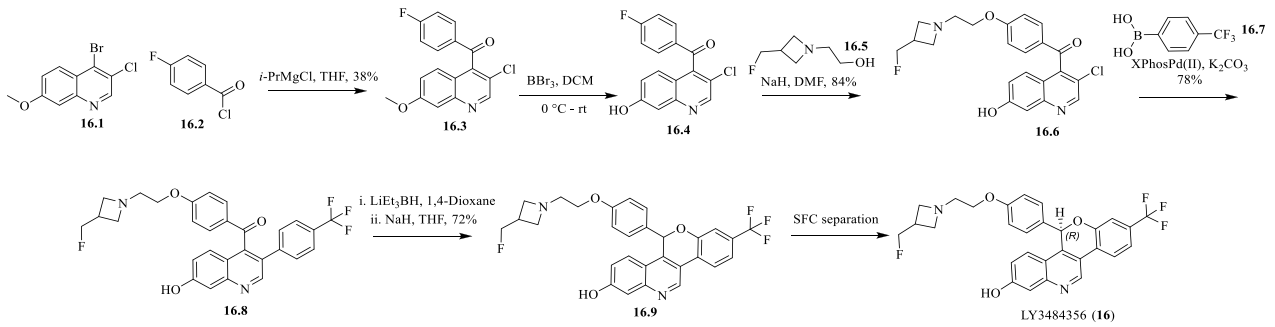

Table 33. Clinical Trial Data for LY3484356 (16)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
LY3484356 (SERD)	Exemestane, Fulvestrant, Abemaciclib	A Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant Plus Abemaciclib in Participants with ER+/HER2− Advanced Breast Cancer	breast neoplasms, neoplasm metastasis	NCT04975308 (Phase III, recruiting)
	Tamoxifen, Anastrozole, Letrozole, Exemestane	A Study of Imlunestrant versus Standard Endocrine Therapy in Participants with Early Breast Cancer	breast neoplasms	NCT05514054 (Phase III, not recruiting)
	LY3484356	A Study of LY3484356 in Women with Breast Cancer Before Having Surgery	breast cancer	NCT04647487 (Phase I, recruiting)
	Abemaciclib, Everolimus, Alpelisib, Trastuzumab, AI, Pertuzumab	A Study of LY3484356 in Participants with Advanced or Metastatic Breast Cancer or Endometrial Cancer	breast cancer, advanced breast cancer, metastatic breast cancer, endometrial cancer	NCT04188548 (Phase I, recruiting)

inhibition of PGR transcription up to 96 h after the last dose) in *ESR1* WT (MCF-7) and *ESR1* Y537S mutant (ST941/C) xenograft tumors. Consistent with its profile as a pure antagonist, immature rat studies demonstrated no significant effect on the uterine wet weight. LY3484356 showed significant TGI and tumor regressions in WT *ESR1* BC xenograft models such as MCF-7, T47D, and ZR-75-1, as well as *ESR1* mutant BC PDX models. LY3484356 has shown synergy or additivity in combination with the CDK4/CDK6 inhibitor abemaciclib, the mTOR inhibitor everolimus, and the PIK3CA inhibitor alpelisib

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Scheme 17. Synthesis of SCO-120 (17)

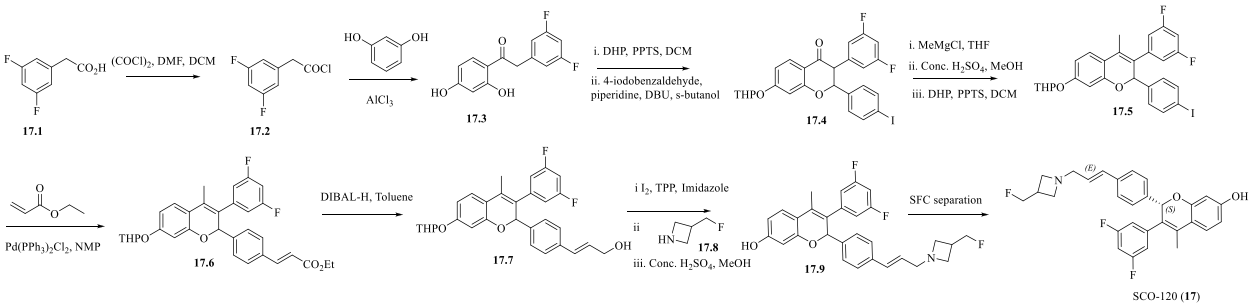

Table 34. Clinical Trial Data for SCO-120 (17)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
SCO-120 (SERD)	Single agent	A Phase 1 Study to Determine Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of SCO-120 in Hormone Receptor Positive, HER-2 Negative Advanced Breast Cancer Patients	HER2− breast cancer, advanced breast cancer, HR+ breast cancer	NCT04942054 (Phase I/II, recruiting)

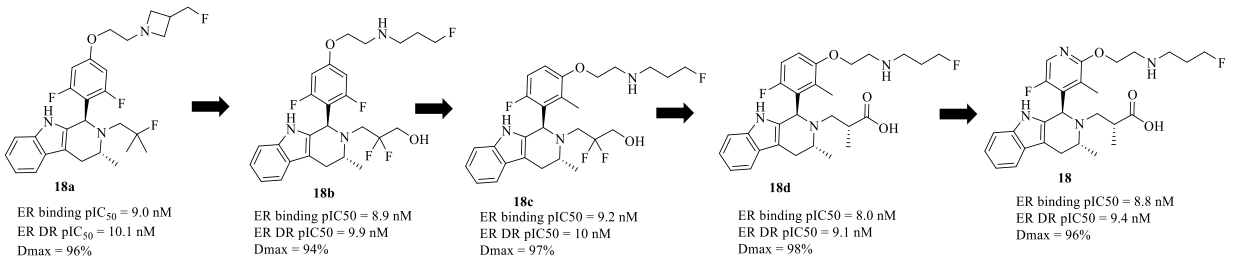

Figure 22. Design strategy and SAR analysis of compound **18**.

in inhibition of cell proliferation in ER+ BC cell lines *in vitro*, and TGI in relevant xenograft or PDX models *in vivo*.[165] The first-in-human Phase 1/2 clinical trial of LY3484356 (EMBER, NCT04188548) is currently ongoing.

*Synthesis of LY3484356 (**16**).* The synthesis of LY3484356 started with bromoquinoline **16.1**, which upon treatment with isopropyl magnesium chloride followed by dropwise addition of fluorobenzoyl chloride **16.2** afforded compound **16.3** with a 38% yield (Scheme 16). Demethylation of **16.3** using boron tribromide furnished **16.4** in quantitative yield as a light brown solid. An aromatic substitution reaction between the intermediate **16.4** and azetidine alcohol **16.5** in the presence of the base NaH produced compound **16.6** with an 84% yield. The Suzuki coupling between **16.6** with boronic acid **16.7** gave **16.8** with a 78% yield, which upon keto reduction followed by intramolecular annulation provided racemic cyclic ether **16.9** with a 72% yield. Chiral separation of compound **16.9** produced the enantiopure final compound LY3484356 (**16**) in >99% ee.[166]

*Clinical Data of LY3484356 (**16**).* The active Phase I EMBER trial (NCT04188548) is characterizing LY3484356 alone or in combination with abemaciclib, everolimus, alpelisib, trastuzumab, or AI for ER+ MBC. LY3484356 monotherapy data from the EMBER trial show efficacy in a cohort of pretreated ER+ MBC patients.[167,168] In the Phase III setting, LY3484356 with or without abemaciclib is being compared against fulvestrant or exemestane for the management of hormone-sensitive advanced breast cancer after progression on AI (EMBER-3, NCT04975308).[169] In addition, the ongoing window-of-opportunity Phase I EMBER-2 trial is evaluating the pharmacodynamic effect of LY3484356 in the neoadjuvant setting (NCT04647487) (Table 33).

Bexirestrant (SCO-120, 17). SCO-120 is a novel, orally active SERD reported by Sun Pharma in their recent patent application, and the structure was confirmed by the WHO drug information list.[170,171] The recent filing described a structurally related cluster of seven compounds, with Example 1a (**17**), with defined stereochemistry, being a key focus. SCO-120 has a chromen moiety and an azetidine ring side chain in the structure. It was found that the *S*-stereoisomer of the isomeric positioning of the core was significantly more potent and exhibited better PK properties than the *R*-isomer. It was shown to be a potent degrader of the WT ER (IC_{50} 0.3 nM) and mutant forms of ER (Y537S and D538G) and had *in vivo* efficacy in a Y537S MCF-7 xenograft model at a dose of 50 mg/kg.

*Synthesis of SCO-120 (**17**).* The synthesis began with the commercially available 3,5-difluorophenylacetic acid (**17.1**), which upon Friedel−Crafts acylation produced compound **17.3** (Scheme 17). Acid-mediated THP protection followed by cyclization of compound **17.3** provided the diastereomeric mixture of compound **17.4**. Compound **17.4**, upon methyl Grignard addition followed by dehydration and THP protection, yielded an enantiomeric mixture of compound **17.5**. Intermediate **17.6** was prepared from **17.5** via Heck coupling reaction. The ester group was reduced to alcohol using DIBAL-H then transformed into the corresponding iodo intermediate through an Appel reaction. The final compound SCO-120 (**17**) was prepared by SN_2 displacement of iodo with the cyclic secondary amine **17.8**, followed by acid-mediated THP deprotection.[171] A Phase 1 study to determine the safety, tolerability, pharmacokinetics, pharmacodynamics, and prelimi-

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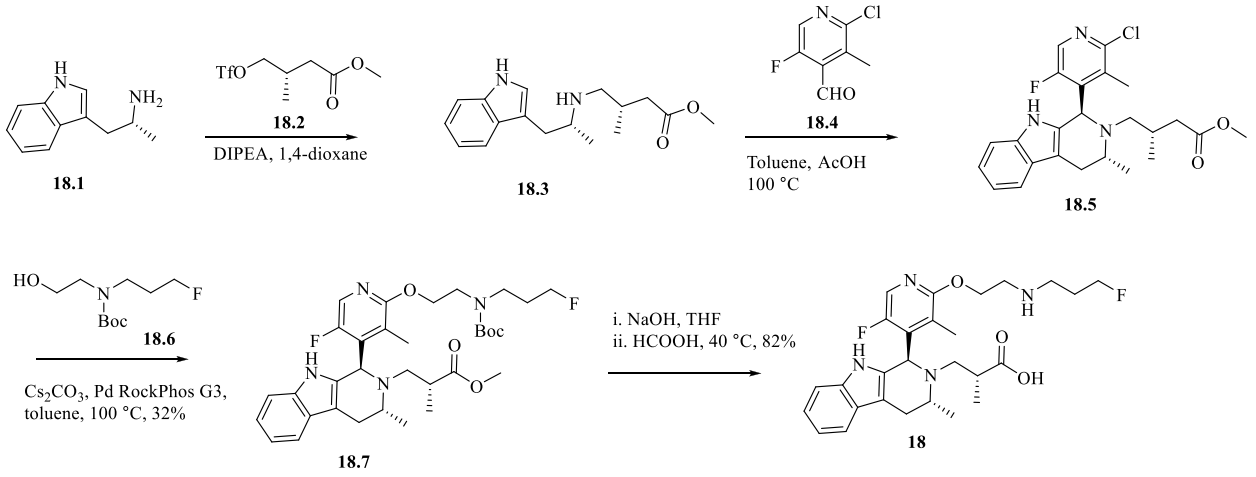
Table 35. Summary of Pharmacokinetic Parameters of GDC-9545 (18)

Species	Dose (IV/PO) (mg/mg)	CL_{int} (μM/min/10^6 cell	PPB (% free)	CL (mL/min/kg)	V_{dss} (L/kg)	$t_{1/2}$ (h)	F (%)
Mouse	0.5/1		26	30	3.9	3	45
Rat	1/3	21	37	58	2.1	0.8	19
Dog	2/5	2	20	4.0	1.1	6.3	80
Monkey	2/5	2.4	44	1.1	1.1	1.2	30

Scheme 18. Synthesis of Compound 18



nary efficacy of SCO-120 in HR+/HER2− advanced BC patients is currently undergoing (NCT04942054) (Table 34).

■ ZWITTERIONIC SERIES OF SERDS

Recently, Scott et al. reported a series of zwitterion-containing SERD antagonists for the treatment of ER+ BC.[172] Among them, compound **18** was shown to be a highly potent SERD capable of effectively degrading ERα in both MCF-7 and CAMA-1 cell lines (Figure 22). Due to its low lipophilicity and zwitterionic nature, it showed good physicochemical properties, which resulted in a clean secondary pharmacology profile and no hERG activity, good oral bioavailability in preclinical species, and potent *in vivo* activity in a mouse xenograft model. Compound **18** showed excellent ER binding affinity (pIC_{50} = 8.8 nM) with good degradation potency (ER DR pIC_{50} = 9.4 nM) and degradation efficiency (D_{max} = 96%) in the MCF-7 cell line.

SAR studies started with the previously identified tricyclic indole **18a** (Figure 22).[173] Opening of the azetidine ring to an open-chain basic nitrogen reduced the lipophilicity by a few units, and converting the piperidine tail to a difluoro hydroxymethyl group further reduced the lipophilicity by a few units. These changes maintained the potency, and compounds **18a** and **18b** are equipotent. Moving the O-linked basic nitrogen substitution from the para to meta position leads to a slight improvement in degradation efficiency. To address the hERG liability and reduce the lipophilicity, the hydroxymethyl group was changed to an acid group that further improves the degradation potency. Finally, a pyridyl group replaced the phenyl substitution, which maintains potency with an improvement on log *D*.

***In Vitro* and *In Vivo* DMPK Data for Compound 18.** The physicochemical properties of compound **18** showed modest intrinsic permeability (P_{app} = 2.0 × 10^{-6} cm/s) as measured in a Caco-2 assay with efflux inhibitors, but **18** was a substrate for active transport (P_{app} = 0.76 × 10^{-6} cm/s; ER 48) in the uninhibited form of the assay. Due to the presence of an acid moiety, compound **18** also has a very low PPB, which resulted in a high fraction unbound in PPB assays across species (>10% free). The CYP450 profile of this compound showed no significant inhibition, with IC_{50} > 30 μM in all five isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4).[172]

Pharmacokinetic Properties of Compound 18. In rodents, compound **18** shows moderate to high clearance (CL = 30 and 58 mL/min/kg in mouse and rat, respectively), while clearance in the higher species was low, at 4.0 and 1.1 in dog and monkey, respectively. In all species evaluated, bioavailability ranged from 19 to 80%. The volume of distribution was moderate, from 1.1 to 3.9 L/kg across all species evaluated, and is consistent with the zwitterionic character of the molecule and the second basic center (Tables 34 and 35). Taken together, it had suitable PK properties for progression into clinical trials.[172]

Antitumor Effects of 18. Treatment with **18** caused a dose-dependent decrease in tumor volume with no tolerance issues. It shows 46% and 96% TGI for 15 mg/kg and 50 mg/kg dose, respectively.[172]

Synthesis of Compound 18. The synthesis of compound **18** started with commercially available (*R*)-1-(1*H*-indol-3-yl)-propan-2-amine (**18.1**), which on base-mediated substitution reaction with triflate **18.2** yielded intermediate **18.3**. A diastereoselective Pictet−Spengler reaction of intermediate **18.3** with substituted benzaldehyde **18.4** in the presence of AcOH in toluene produced the desired tetracycle **18.5**. Buchwald−Hartwig cross-coupling reaction between the alcohol **18.6** and the chloride **18.5** furnished Boc-protected amine compound **18.7**. Finally, based-catalyzed saponification followed by formic acid-mediated Boc deprotection of intermediate **18.7** gave compound **18** in 82% yield (Scheme 18).[172]

OP-1250 (19, Olema Pharmaceuticals). OP-1250 is an orally bioavailable small-molecule complete estrogen receptor antagonist (CERAN) that completely antagonizes ER, blocks

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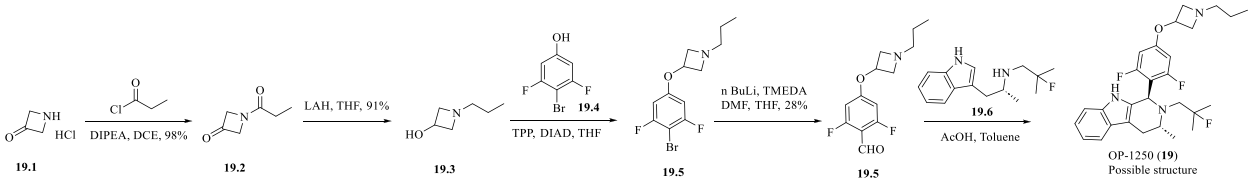
Table 36. Clinical Trial Data for OP-1250 (19)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
OP-1250 (CERAN)	Single agent	A Dose Escalation/Expansion Study of Oral OP-1250 in Subjects with Advanced and/or Metastatic HR+, HER2− Breast Cancer	HR+ breast carcinoma, HER2− breast cancer	NCT04505826 (Phase I/II, recruiting)
	Ribociclib, Alpelisib	A Phase 1b Open-Label Multicenter Study of OP-1250 in Combination With the CDK4/6 Inhibitor Ribociclib or With the PI3K Inhibitor Alpelisib in Adult Subjects With Advanced and/or Metastatic HR Positive, HER2 Negative Breast Cancer	metastatic breast cancer, advanced breast cancer, HR+ breast cancer, HER2− breast cancer	NCT05508906 (Phase I, recruiting)
	Palbociclib	A Phase 1 Dose Escalation and Expansion Open-label, Multicenter, Study of OP-1250 in Combination With the CDK4/6 Inhibitor Palbociclib in Adult Subjects With Advanced or Metastatic HR-positive, HER2-negative Breast Cancer	breast cancer	NCT05266105 (Phase I, recruiting)

Scheme 19. Synthesis of OP-1250 (19)



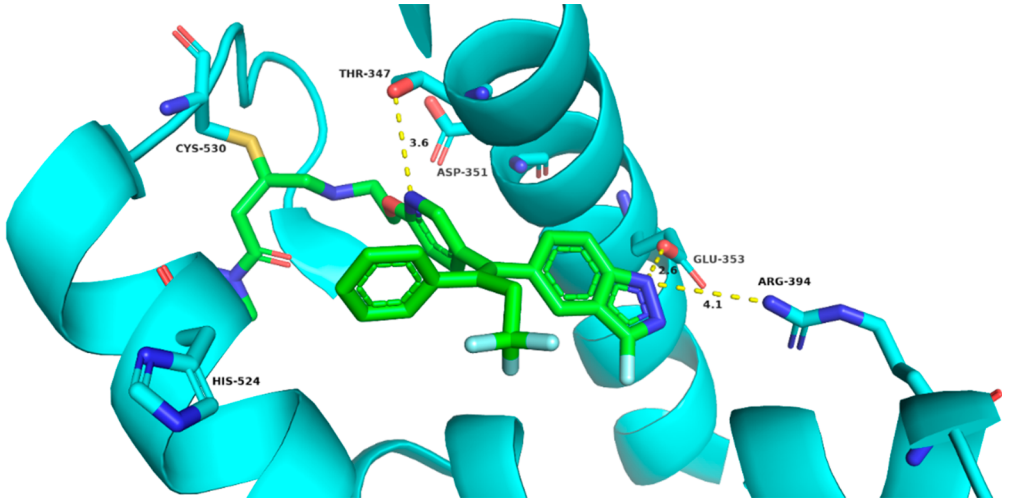


Figure 23. Cocrystal structure of H3B-6545 (**20**) (PDB code 6OWC) covalently bound to mutant ERα Y537S.

transcriptional activity, and induces ER degradation. OP-1250 is hypothesized to convey superior efficacy as it completely inactivates ER by blocking both activation functions of ER transcription (AF-1 and AF-2).[68] Based on the 2020 SABCS abstract, OP-1250 demonstrates anticancer activity in preclinical models, including activity expressing WT and Y537S mutant ER.[174,175] These findings have prompted an active Phase I−II clinical trial that is examining the activity of OP-1250 in ER+ MBC after progression on endocrine therapy (NCT04505826). Reported Phase I data showed a benefit in heavily pretreated patients, with an ORR 17% and CBR of 46% at dose levels within the recommended Phase II dose range (Table 36).[31] The structure has not been formally disclosed at the time of writing, based on disclosed patent application compounds **19** is undoubtedly a compound of significant interest.[176]

*Synthesis of OP-1250 (**19**).* Synthesis of OP-1250 initiated with the commercially available azetidin-3-one hydrochloride (**19.1**, Scheme 19) which upon treatment with propionyl chloride followed by dropwise addition of propionyl chloride gave compound **19.3** with a 91% yield. The compound **19.5** was synthesized via a Mitsunobu reaction between compounds **19.3** and **19.4**. Installation of the aldehyde functionality was accomplished via alkylation of **19.4** in the presence of BuLi and TMEDA, which generated compound **19.5** in a 28% yield. Finally, the substrate-controlled, diastereoselective Pictet−Spengler reaction between **19.5** and **19.6** afforded the target compound OP-1250 (**19**).[176]

H3B-6545 (20). H3B-6545 is a SERCA which covalently attaches to the ER via its electrophilic warhead, which interacts with a cysteine (C530), causing antagonism but not degradation of ER, as shown in Figure 23.[177,178] The indazole core has hydrogen-bonding interactions with the hydrophilic residues Glu353 and Arg394, while the pyridine nitrogen forms a short hydrogen bond with Thr347. It shows potent antagonism (GI_{50} = 0.3 nM) and demonstrates efficacy in MCF-7 xenografts (3−30 mg/kg) as well as in PDX models containing the Y537S mutation. The combination between H3B-6545 and the CDK4/CDK6 inhibitor palbociclib in the Y537S mutation model demonstrated the enhancement of its antitumor efficacy.[69,179]

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Table 37. Cross-Species PK of H3B-6545 (20) in Female Rats and Cynomolgus Monkeys

Species	Dose (IV/PO) (mg/kg)	V_{ss} (L/kg)	CL (mL/min/kg)	$t_{1/2}$ (IV) (h)	C_{max} (PO) (μg/mL)	AUC (PO) (μg·h/mL)	F (%)
Rat	5/10	1.2	7.3	2.3	1.2	14.2	62
Monkey	5/10	3.0	18.2	4.0	0.42	2.5	26

Scheme 20. Synthesis of H3B-4565 (20)

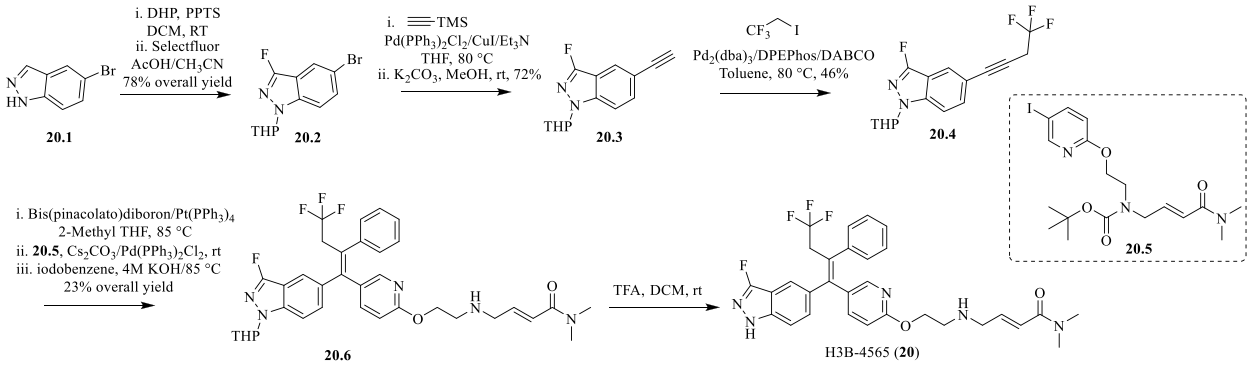

Table 38. Clinical Trial Data for H3B-6545 (20)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
H3B-6545 (SERCA)	Palbociclib	A Study of H3B-6545 in Combination with Palbociclib in Women with Advanced or Metastatic Estrogen Receptor-Positive Human Epidermal Growth Factor Receptor-2 (HER2)-Negative Breast Cancer	metastatic ER+/HER2− breast cancer	NCT04288089 (Phase I, active, not recruiting)
	Single agent	Trial of H3B-6545, in Women with Locally Advanced or Metastatic Estrogen Receptor-Positive, HER2 Negative Breast Cancer	metastatic ER+/HER2− breast cancer	NCT03250676 (Phase I, active, not recruiting)

Table 39. Clinical Trial Data for SCR-6852, AND019 and SHR9549

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
SCR-6852 (SERD)	Palbociclib	A Multicenter, Open-label, Phase I Clinical Study to Evaluate the Safety, Pharmacokinetics, and Antitumor Efficacy of SCR-6852 Alone or in Combination in Subjects With ER-positive, HER-2 Negative Locally Advanced or Metastatic Breast Cancer	breast cancer	NCT05293964 (Phase I, recruiting)
AND019 (SERD)	AND019	A Phase I Dose Escalation and Dose Expansion Study of AND019 in Patients With Estrogen Receptor Positive Human Epidermal Growth Factor Receptor 2 Negative Advanced or Metastatic Breast Cancer	advanced or metastatic breast cancer	NCT05187832 (Phase I, recruiting)
SHR9549 (SERD)	SHR9549	Phase I, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Ascending Doses of SHR9549 in Women With ER Positive HER2 Negative Advanced Breast Cancer	ER+/HER2− advanced breast cancer	NCT03596658 (terminated) (sponsor: R&D Strategy Adjustment)

In vitro clearance of H3B-6545 at concentrations of 1.0 μM was moderate to high in rats (72 μL/min/10^6 cells), monkeys (178 μL/min/10^6 cells), and human (74 μL/min/10^6 cells). Plasma protein binding was similar across the different species, at 99.5−99.8%. Preclinical studies in rats and monkeys showed that H3B-6545 had a high volume of distribution with a terminal elimination half-life of 2.3 h in rats and 4.0 h in monkeys. The bioavailability of H3B-6545 was good in mice (62%) but moderate in monkeys (26%) (Table 37).[69,179]

Synthesis of H3B-4565 (20). The synthesis of H3B-4565 (**20**) started with the commercially available bromo indazole **20.1**, which upon THP protection followed by fluorination with Selectfluor reagent furnished **20.2** with a 78% yield. Sonogashira cross-coupling of **20.2** with TMS-acetylene followed by TMS deprotection furnished terminal alkyne **20.3** with a 72% yield. Palladium-catalyzed coupling between alkyne **20.3** with 1,1,1-trifluoro-2-iodoethane afforded compound **20.4** with a 46% yield. Platinum-mediated diborylation of compound **20.4** ,followed by sequential Suzuki cross coupling with two different aromatic iodides, produced compound **20.5** with a 23% overall yield. Acid-mediated THP deprotection of compound **20.6** furnished the final product H3B-4565 (**20**, Scheme 20).[180]

Clinical Data of H3B-6545 (20). H3B-6545 demonstrated single agent antitumor activity in heavily pretreated patients with ER+ MBC. Based on a *JCO* 2001 abstract, 61% of patients harbored baseline *ESR1* mutations detected by circulating tumor DNA (ctDNA).[181,182] Among patients with *ESR1* Y537S mutations (n = 10), an ORR of 40% and a median PFS of 7.3 months were observed. AEs included asymptomatic sinus bradycardia and QTc (corrected for heart rate) prolongation. Ongoing clinical evaluation in Phase I and II settings includes H3B-6545 as a monotherapy (NCT03250676) and in combination with palbociclib (NCT04288089) for ER+ MBC progressed on prior ET (Table 38).[181,182]

A few other SERDs, for example, SCR-6852 developed by Jiangsu Simcere, AND019 by Kind Pharma, and SHR9549

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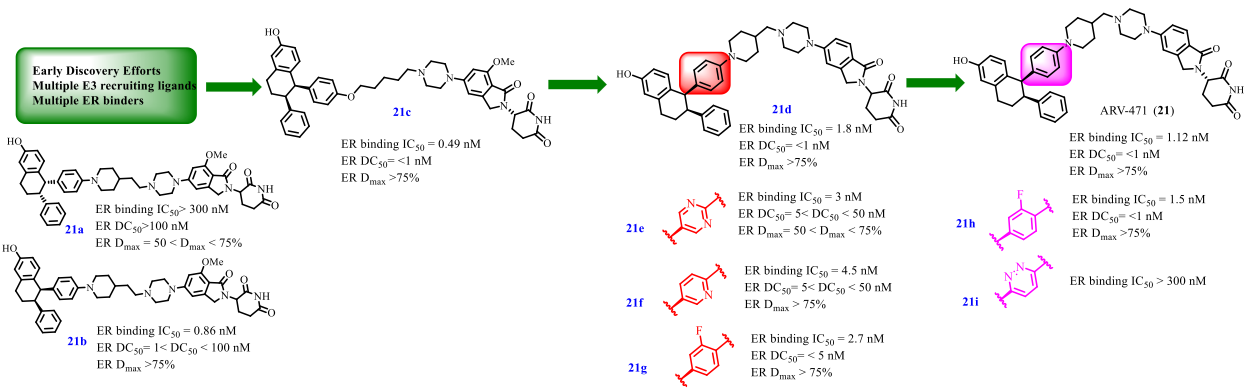

Figure 24. Design strategy and SAR analysis of ARV-471 (**21**).

Table 40. *In Vivo* Efficacy in ARV-471 (21) in MCF-7 and *ESR1* (Y537S) PDX Models

In Vivo Efficacy in MCF-7 Models					*In Vivo* Efficacy in *ESR1* (Y537S) PDX Models		
	Mean concn of drug						
Dose (PO, QD)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	TGI (%) in MCF-7 xenograft model	% ER reduction in PD (18 h post last dose)	Dose (PO, QD)	TGI (%) in *ESR1* (Y537S) PDX xenograft model	% ER reduction in PD (18 h post last dose)
3 mg/kg ARV-471	658	84	85	95	10 mg/kg ARV-471	99	79
10 mg/kg ARV-471	2538	312	98	97	30 mg/kg ARV-471	106	88
30 mg/kg ARV-471	5717	962	124	94	200 mg/kg fulvestrant[a]	62	63

[a]Fulvestrant dosed weekly via SC; ARV-471 dosed daily via PO.

(Jiangsu Hengrui), are undergoing Phase I clinical trials (Table 39).

PROTAC ER DEGRADERS

In a parallel development of SERD molecules, PROTAC ER degrader molecules have emerged as an effective strategy to target breast cancers with both WT and mutant ER.

The concept of PROTACs was first introduced by Deshaies from Caltech and Crews from Yale University in 2001.[183] In recent years, induction of targeted protein degradation by PROTAC has gained momentum with the advancement of potent and druglike small-molecule ligands for several E3 ligase systems.

Early PROTAC molecules have limited *in vitro* and *in vivo* activities due to their poor cell permeability and their large size.[184−186] A significant breakthrough in the advancement of PROTACs came during 2012 with the discovery of more druglike peptidomimetics for VHL-1 from the groups of Crews at Yale University and Ciulli at the University of Dundee.[187,188] In 2010, the landmark discovery that cereblon (CRBN)/Cullin 4A is the cellular target for thalidomide and its analogs had provided the opportunity to design PROTAC degraders using druglike small-molecule ligands. The Bradner laboratory was the first to demonstrate that thalidomide and its analogs can be successfully used for the design of potent and efficacious PROTAC degraders in 2015.[189]

In this review, we summarized the data for two ER PROTAC degraders, ARV-471 (**21**) and AC682, which have been advanced into clinical development for the treatment of endocrine-resistant BC.

Vepdegestrant (ARV-471, 21). ARV-471, developed by Arvinas, is the first ER PROTAC that progressed into clinical development for the treatment of patients with locally, advanced, or metastatic ER+ BC. ARV-471 degrades ERα across multiple ER+ cell lines with a DC_{50} of ∼1 nM. It also degrades clinically relevant *ESR1* variants (Y537S and D538G) and inhibits the growth of cell lines expressing those variants. Based on a 2021 AACR abstract, in an immature rat uterotrophic model, ARV-471 degrades rat uterine ER and demonstrates no agonist activity. PROTAC-mediated ER degradation decreases the expression of those classically regulated ER-target genes and inhibits cell proliferation of ER-dependent MCF-7 or T47D cell lines.[190,191]

Arvinas has disclosed multiple patent applications on ER PROTACs and has employed lasofoxifene, a selective estrogen receptor modulator (SERM), in those patent applications.[192−194] Some of the most potent ER PROTAC degrader molecules exhibit low nM DC_{50} values in the MCF-7 cell line (Figure 18). The SAR data for compounds **21a** and **21b** demonstrate that the degradation efficiency depends on the actual stereochemistry of the protein-targeting ligand. The SAR data for compounds **21g** and **21h** show that the (*S*)-configuration of the CRBN moiety yields a more potent PROTAC molecule than the (*R*)-configuration (Figure 24).

Preclinical animal studies show that oral administration of ARV-471 at 3, 10, or 30 mg/kg QD leads to significant antitumor activity in xenograft models. In addition, the resultant tumor ER protein reductions were >90% at study termination. At doses of 3, 10, or 30 mg/kg of ARV-471, TGIs of 85%, 98%, and 124% were observed compared to a control group in the WT ER MCF-7 xenograft model (Table 40).[192,193]

ARV-471 also showed a TGI superior to that of fulvestrant in a Y537S PDX model (Table 40). A daily oral dose of ARV-471 inhibited tumor growth by 99% at 10 mg/kg and 106% at 30 mg/kg in an *ESR1* mutant PDX model. Quantitative Western blotting shows ER protein reductions of 79% and 88% in the 10 and 30 mg/kg arms, respectively, vs 63% for fulvestrant.[192,193]

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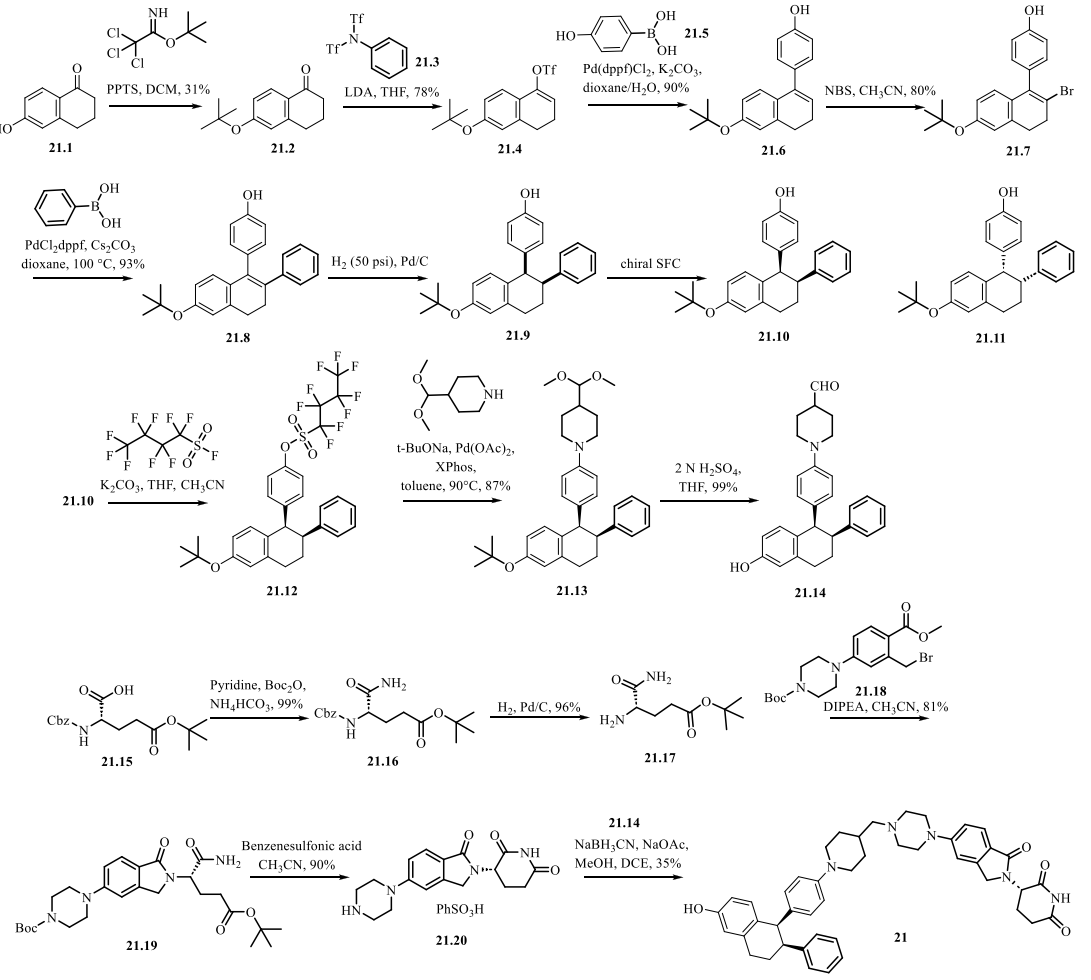
Table 41. *In Vivo* Efficacy with ARV-471 (21) in Combination with Palbociclib in MCF-7 and Tamoxifen-Resistant MCF-7 Xenografts Models

	In Vivo Efficacy with ARV-471 in Combination with Palbociclib				*In Vivo* Efficacy with ARV-471 in Tamoxifen-Resistant MCF7 Xenografts		
	Fulvestrant, 200 mg/kg	ARV-471, 30 mg/kg	Fulvestrant, 200 mg/kg[a] + Palbociclib, 60 mg/kg	ARV-471, 30 mg/kg + Palbociclib, 60 mg/kg	ARV-471, 30 mg/kg	Palbociclib, 60 mg/kg	ARV-471, 30 mg/kg + Palbociclib, 60 mg/kg
TGI (% vehicle)	46	105	108	131	65	91	113

[a]ARV-471 and palbociclib: oral (gavage), once a day for 28 days (QD×28); fulvestrant: subcutaneous (SC), twice a week for 2 weeks (BIW×2), followed by once a week for 2 weeks (QW×2).

Scheme 21. Synthesis of ARV-471 (21)



A combination of ARV-471 and the CDK4/CDK6 inhibitor palbociclib resulted in significant tumor regression and superior antitumor activity in an MCF-7 xenograft model as compared to single agents. Daily oral doses of ARV-471 (30 mg/kg) and the CDK4/CDK6 inhibitor palbociclib (60 mg/kg) were administered for 28 days. Single-agent ARV-471 activity showed 105% TGI in this model, whereas the combination of ARV-471 and palbociclib provided significant tumor regressions (TGI = 131%). In contrast, fulvestrant as a single agent produced only a modest TGI (46%), while the combination of fulvestrant and palbociclib resulted in an improved TGI (108%) (Table 41).[192]

The antitumor activity of ARV-471 as a single agent and in combination with palbociclib was evaluated in a tamoxifen-resistant ER+ BC orthotopic xenograft model (Table 41). As a single agent, ARV-471 achieved 65% TGI after once-daily oral administration of 30 mg/kg for 28 days. When combined with palbociclib (60 mg/kg/day), the combination regimen gave a superior TGI (113%) when compared to the single-agent arm data of palbociclib (91% TGI). Taken together, the preclinical data of ARV-471 support its development as a first-in-class oral ER PROTAC protein degrader.[192,193]

Synthesis of ARV-471 (21). ARV-471 was prepared according to Scheme 21. The commercially available 6-hydroxy-1-tetralone (**21.1**) was protected with a *tert*-butyl group to give the intermediate **21.2**, which was then converted into the corresponding enol triflate intermediate **21.3** with phenyl triflimide in the presence of LDA at low temperature. A Suzuki coupling reaction between the triflate **21.4** and boronic acid **21.5** produced compound **21.6** with a 90% yield. The double bond was then brominated with NBS to give the bromo

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derivative **21.7** with an 80% yield, which upon a second Suzuki coupling reaction with phenylboronic acid afforded intermediate **21.8** with a 93% yield. The double bond was then hydrogenated using Pd/C, and the desired isomer **21.10** was isolated using SFC separation. Compound **21.10** was then converted to intermediate **21.12** using nonafluoro-1-butanesulfonyl fluoride, which upon a Buchwald−Hartwig C−N coupling reaction formed intermediate **21.13** giving an 87% yield. Both the *tert*-butyl and the acetal group on intermediate **21.13** were deprotected using 2 N H_2SO_4 and gave the desired aldehyde **21.14** with a 99% yield. The synthesis of the CRBN ligand started with the commercially available acid **21.15**, which upon amination followed by hydrogenation yielded the intermediate **21.17**. The nucleophilic substitution reaction between compound **21.17** and the bromo intermediate **21.18** yielded the intermediate **21.19**, which upon a one-pot amination and Boc deprotection formed the final ligand **21.20**. The secondary amine **21.20**, upon reductive amination with the aldehyde **21.14**, afforded ARV-471 in a 35% yield and >95% optical purity.[192,193]

*Clinical Data of ARV-471 (**21**).* The initial clinical PK results are shown in Table 42, which provides exposure data for ARV-471 over 24 h post-dosing on both days 1 and 15 in patients. Once-daily oral administration of 30 mg of ARV-471 achieved the preclinical efficacious concentration associated with TGI. Drug accumulation was observed for ARV-471 (~2.5-fold higher in AUC_{tau} and ~2-fold higher in C_{max} on day 15 than those on day 1).

Table 42. Initial Clinical Pharmacokinetic Results of ARV-471 (21)

	Mean Day 1		Mean Day 15	
Dose (PO, QD) (mg)	AUC_{tau} (ng·h/mL)	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{max} (ng/mL)
30	1690	109	4100	224

In the Phase 1 dose escalation portion (Part A) of the first-in-human Phase 1/2 study, ARV-471 monotherapy was well tolerated and showed antitumor activity in patients with ER+/HER2− locally advanced or metastatic breast cancer who had previously received endocrine therapy and a CDK4/CDK6 inhibitor.

The CBR was 40% in 47 evaluable patients' data as presented at SABCS 2021.[195] Preliminary analysis of 14 paired biopsies from patients treated at 30−500 mg daily demonstrated that ARV-471 could significantly reduce the ER expression level in tumor tissues, with a median of 67%, a mean of 64%, and a maximum of 90%.[195] The degradation exceeds the reported data for fulvestrant, which was ~40−50%, from Robertson et al.[196] The Phase 2 VERITAC expansion cohort (Part B) is to evaluate ARV-471 as a monotherapy in this patient population. Palbociclib with fulvestrant is a standard treatment option for patients with ER+/HER2− BC who have had disease progression on endocrine therapy. Supported by the preclinical data, Part C of the Phase 1/2 study is to evaluate the safety and clinical activity of ARV-471 plus palbociclib in patients with BC who have previously received endocrine therapy.[196]

*Toxicity Profile of ARV-471 (**21**).* It was reported at the 2021 SABCS that ARV-471 was well tolerated at all tested dose levels and DLT was not reached.[195] Sixty patients were treated in the monotherapy escalation at total daily doses of 30 mg (n = 3), 60 mg (n = 3), 120 mg (n = 7), 180/200 mg (n = 11), 360 mg (n = 15), 500 mg (n = 17), and 700 mg (n = 4). The most common TRAEs, grade 1−2, were nausea (24%), arthralgia (19%), fatigue (19%), and decreased appetite (14%). Four patients experienced grade 3 events potentially related to ARV-471 (headache lasting 1 day, single occurrence of asymptomatic increased amylase and lipase, nausea and asymptomatic QTc prolongation, and venous embolism after a minor procedure). Advanced breast cancer is highly associated with venous embolisms. The event was determined to be potentially treatment related, so treatment with ARV-471 was ended (Table 43). Overall, only one patient out of the 60 patients required dose reduction, and one other of the 60 patients discontinued due to an AE.

AC682. AC682 is an oral PROTAC ER degrader developed by Accutar Biotech using Artificial Intelligence-empowered drug discovery. Its structure is undisclosed. As reported at the 2020 SABCS,[38] AC682 induced potent ER degradation with a subnanomolar DC_{50} in multiple ER+ BC cell lines, including tamoxifen-resistant cell lines and cell lines expressing clinically relevant *ESR1* variants (Y537S and D538G). In preclinical studies, AC682 also demonstrated potent and selective ERα protein degradation with favorable pharmacological properties and promising antitumor activity in ER+ animal tumor models.[38]

In estradiol-dependent MCF-7 xenograft tumors, daily oral dosing of AC682 led to dose-dependent TGI/regression and concomitant 90% tumor ER protein reduction at the end of the study. The combination of AC682 with CDK4/CDK6 inhibitor palbociclib showed superior activity in the estradiol-dependent MCF-7 model and a tamoxifen-resistant MCF-7 model as compared to single agents. In an *ESR1* Y537S mutation PDX model, AC682 demonstrated superior efficacy compared to fulvestrant. In summary, AC682 demonstrated robust ER degradation and antitumor efficacy in preclinical models as an

Table 43. Clinical Trial Data for ARV-471 (21)

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
ARV-471 (PROTAC)	Everolimus	ARV-471 in Combination with Everolimus for the Treatment of Advanced or Metastatic ER+, HER2− Breast Cancer	breast cancer	NCT05501769 (Phase I, recruiting)
	Palbociclib	A Phase 1/2 Trial of ARV-471 Alone and in Combination with Palbociclib in Patients with ER+/HER2- Locally Advanced or Metastatic Breast Cancer	breast cancer	NCT04072952 (Phase I/II, recruiting)
	Drug: Anastrozole	A Trial Using ARV-471 or Anastrozole in Post-Menopausal Women with Breast Cancer Prior to Surgery	breast cancer	NCT05549505 (Phase II, not recruiting)

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Table 44. Clinical Trial Data for AC682

Drug (endocrine therapy class)	Combination	Title	Conditions	Clinical Trial number (status)
AC682 (PROTAC)	Single agent	A Study of AC682 in Chinese Patients with ER+/HER2− Locally Advanced or Metastatic Breast Cancer	breast cancer	NCT05489679 (Phase I, not recruiting)
	Single agent	A Study of AC682 for the Treatment of Locally Advanced or Metastatic ER + Breast Cancer	breast cancer	NCT05080842 (Phase I, recruiting)

oral agent, which supported its clinical investigation (Table 44).[38]

SUMMARY

Tremendous efforts have been made in the discovery and development of new generations of ER-targeted agents. Inspired by the clinical activities of fulvestrant, extensive efforts have been made in the development of oral SERDs in the past decade. Oral SERDs such as AZD9496, GDC-0810, and LSZ102, which all contain a cinnamic acid, are not well tolerated and show modest clinical activity in human clinical trials, and their clinical development has been halted. In comparison, oral SERDs such as elacestrant (RAD1901), amcenestrant (SAR439859), camizestrant (AZD9833), and giredestrant (GDC-9545), which employ a basic amine group to replace the acid group, are generally better tolerated and have fewer side effects than those oral SERD molecules containing a cinnamic acid. Recently, the FDA has approved elacestrant for postmenopausal women or adult men with ER+/HER2−, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.[14] However, there were also some major setbacks for oral SERDs employing a basic amine group. For example, the clinical development of amcenestrant has recently been discontinued by Sanofi based upon the interim analysis of the Phase 3 AMEERA-5 trial (NCT04478266) evaluating amcenestrant in combination with palbociclib vs letrozole combined with palbociclib in patients with ER+/HER2− advanced breast cancer. In addition, in the acelERA trial comparing giredestrant to physician's choice of endocrine therapy for previously treated HR+/HER2− BC, giredestrant failed to meet its primary end point of improving PFS. However, Roche noted that the efficacy data for giredestrant were encouraging, with a more pronounced benefit in patients with higher dependence on ER activity. Accordingly, Roche is currently evaluating giredestrant in a large (4100 patients) Phase 3, randomized, open-label trial (NCT04961996) assessing the efficacy and safety of adjuvant giredestrant compared with physician's choice of adjuvant endocrine monotherapy in patients with ER+/HER2− early BC. In the EMERALD trial, which evaluated elacestrant in HR +/HER2− BC, a 30% reduction in PFS was observed, with most of the benefits coming from a subgroup of *ESR1*-positive patients. Therefore, biomarker-driven clinical trials focusing on *ESR1*-positive patients for oral SERD molecules are warranted.

In addition to oral SERD molecules, two oral PROTAC ER degraders have been advanced into clinical development to date. The initial clinical data for the first-in-class ARV-471 demonstrated its antitumor activity in 100% CDK4/CDK6 inhibitor-pretreated patients and a favorable tolerability profile. Based upon the VERITAC trial data presented in the 2022 SABCS, ARV-471 administered at 200 mg (n = 35) and 500 mg (n = 36) demonstrated a CBR of 38% (total n = 71) in all patients and 51.2% in patients with mutant *ESR1* tumors (n = 41). Preliminary median PFS was 3.7 months in all evaluable patients and 5.7 months in patients with mutant *ESR1* tumors (n = 41), and most of the TRAEs were grade 1 or 2. Based upon these initial encouraging data, Pfizer, the development partner of Arvinas for ARV-471, plans to initiate two Phase 3 pivotal trials. Most recently, AC682, another oral PROTAC ER degrader from Accutar, has entered Phase I human clinical trials. With the encouraging clinical efficacy and safety data for ARV-471, it is expected that additional PROTAC ER degraders may enter human clinical trials in the near future.

The clinical success of covalent inhibitors such as covalent EGFR, BTK, and KRAS G12C inhibitors for the treatment of human cancers has inspired the discovery and development of covalent drugs for other therapeutic targets. To this end, scientists from H3 Biomedicine have discovered and developed H3B-6545 as a SERCA. H3B-6545 has a manageable safety profile and demonstrated single-agent antitumor activity in heavily pretreated ER+/HER2− MBC patients in initial Phase I/II clinical trial, which suggested that H3B-6545 warrants further clinical development.

In summary, with the discovery and development of oral SERDs, oral CERANs, oral PROTAC ER degraders, and oral SERCA molecules, new, more effective, and safer estrogen receptor-targeted therapies could become treatment options for patients with both early- and late-stage ER+ human breast cancers.

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Author Contributions

[#]Rohan Kalyan Rej and Junius Eugene Thomas II contributed equally.

Notes

The authors declare the following competing financial interest(s): The University of Michigan has filed patent applications on a number of classes of ER PROTAC degraders, which have been licensed to Oncopia Therapeutics, Inc./Proteovant Therapeutics Inc. S. Wang, R. K. Rej, and R. K. Acharyya are co-inventors on these patent applications. S. Wang and the University of Michigan also owned equity in Oncopia, which was acquired by Roivant Sciences. S. Wang is a paid consultant to Roivant Sciences and Proteovant Therapeutics and owns equity in Roivant Sciences. The University of Michigan has a research contract with Oncopia Therapeutics/Proteovant Therapeutics, Inc for which S. Wang serves as the principal investigator.

Biographies

Rohan Kalyan Rej received his Ph.D. from the Indian Institute of Technology Kharagpur in the total synthesis of natural products in 2015. After spending one year as a Postdoctoral Research Fellow at Purdue University, USA, he joined Dr. Shaomeng Wang's laboratory in 2016 and is currently a research investigator. His research interests mainly focus on the design and synthesis of novel small-molecule cancer therapeutics along with PROTAC degraders against different proteins.

Junius Eugene Thomas II received his M.S. in cancer chemical biology and Ph.D. in chemical biology from the University of Michigan. He joined Dr. Shaomeng Wang's laboratory in 2019 focusing on the design, synthesis, and pharmacological evaluation of novel PROTAC degraders against CBP/p300 proteins and other targets that are relevant in cancer.

Ranjan Kumar Acharyya received his Ph.D. in asymmetric total synthesis from the Indian Institute of Technology Kharagpur in 2019. After completing his Ph.D., Dr. Acharyya moved to South Korea for his first postdoctoral study and joined Dr. Shaomeng Wang's laboratory at the University of Michigan in 2021 as a postdoctoral researcher. Dr. Acharyya's current research interest has been the discovery and development of PROTAC degraders against different proteins for the past couple of years.

James Michael Rae received his Ph.D. in pharmacology from Georgetown University, Washington, DC, in 2001. Dr. Rae is currently an associate professor with tenure in the Department of Internal Medicine with a joint appointment in the Department of Pharmacology, University of Michigan Medical School. Dr. Rae's principal expertise is in breast cancer and multiple aspects of cancer pharmacology including drug metabolism, pharmacokinetics, pharmacodynamics, pharmacogenomics, and biomarker identification and characterization, particularly as these may apply to the prediction of treatment responses.

Shaomeng Wang received his B.S. degree in chemistry from Peking University in 1986 and his Ph.D. in chemistry from Case Western Reserve University in 1993, followed by a postdoctoral fellowship at the National Institutes of Health, USA. Dr. Wang was an assistant and then associate professor between 1996 and 2001 at Georgetown University Medical Center. Dr. Wang joined the University of Michigan in 2001 and is currently the Warner-Lambert/Parke-Davis Professor in Medicine and Professor of Internal Medicine, Pharmacology and Medicinal Chemistry. Dr. Wang has served as the Co-Editor-in-Chief for *Journal of Medicinal Chemistry* between 2002 and 2020. Dr. Wang has published more than 330 peer-reviewed papers, is an inventor of 71 granted U.S. patents, and has advanced 10 compounds into Phase 1−3 clinical development.

■ ABBREVIATIONS USED

AACR, American Association for Cancer Research; AcOH, acetic acid; AE, adverse event; ADME, absorption, distribution, metabolism, elimination; AI, aromatase inhibitor; AKT, protein kinase B; $AlCl_3$, aluminum chloride; AR, androgen receptor; AUC, area under the curve; BBr_3, boron tribromide; BC, breast cancer; BH_3, borane; BRD4, bromodomain-containing protein 4; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CH_3CN, acetonitrile; CH_3OH, methanol; CO, carbon monoxide; CoA, co-activator; CL, clearance; C_{max}, maximum concentration; CRBN, cereblon; Cs_2CO_3, cesium carbonate; ctDNA, circulating tumor deoxyribonucleic acid; CuI, copper(I) iodide; CYP, cytochrome P450; DABCO, 1,4-diazabicyclo-[2.2.2]octane; DBTA, dibenzoyltartaric acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCAF15, DDB1 and CUL4 associated factor 15; DCM, dichloromethane; DC_{50}, half-maximal degradation; DHP, 3,4-dihydropyran; DIBAL-H, diisobutylaluminum hydride; DIEA, diisopropylethylamine; DLT, dose-limiting toxicity; D_{max}, maximum degradation; DME, 1,2-dimethoxyethane; DMF, *N,N*-dimethylformamide; DMPK, drug metabolism and pharmacokinetics; DMSO, dimethyl sulfoxide; DPEphos, bis[(2-diphenylphosphino)phenyl] ether; EC_{50}, half-maximal effective concentration; EFS, event-free survival; EMT, epithelial-to-mesenchymal transition; ER, estrogen receptor; ERE, estrogen response element; ERK, extracellular signal-regulated kinase; ET, endocrine therapy; EtOAc, ethyl acetate; EtOH, ethanol; Et_3N, triethylamine; E1, ubiquitin activating enzyme; E2 (in Fig. 2), estradiol; E2 (in Figs. 3 and 4), conjugation enzyme; E3, substrate recognition enzyme; FDA, U.S. Food and Drug Administration; FESPET, female estrogen receptor in endometrial cancer treatment; %*F*, oral bioavailability; GI, gastrointestinal; GR, glucocorticoid receptor; HCl, hydrochloric acid; H/D/R/M, human/dog/rat/mouse; hERG, human ether-à-go-go-related gene; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; H12, helix 12; HWE, Horner−Wadsworth−Emmons; H_2O, water; H_2SO_4, sulfuric acid; H_3PO_4, phosphoric acid; IAP, inhibitor of apoptosis proteins; IC_{50}, half-maximal inhibitory concentration; IKZF, ikaros zinc finger; i-PrMgCl, isopropylmagnesium chloride; I_2, iodine; $KHCO_3$, potassium bicarbonate; Ki-67, marker of cell proliferation; KOH, potassium hydroxide; K_2CO_3, potassium hydroxide; LBD, ligand-binding domain; LDA, lithium diisopropylamide; LHRH, luteinizing hormone-releasing hormone; LiCl, lithium chloride; $LiEt_3BH$, lithium triethylborohydride; LTED, long-term estrogen-deprived; MBC, metastatic breast cancer; mCPBA, *m*-chloroperoxybenzoic acid; MDM2, murine double minute 2; MEK, mitogen-activated ERK kinase; MeMgCl, methylmagnesium chloride; MeOH, methanol; mTOR, mammalian target of rapamycin; MTS, medium-throughput screening; MW, molecular weight; $NaBH_3CN$, sodium cyanoborohydride; $NaBH_4$, sodium borohydride; $NaBH(OAc)_3$, sodium triacetoxyborohydride; NaOH, sodium hydroxide; $Na_2S_2O_3$, sodium thiosulfate; NBS, *N*-bromosuccinimide; n-BuLi, *n*-butyllithium; ORR, objective response rate; OS, overall survival; P_{app}, apparent permeability; $PdCl_2(PPh_3)_2$, bis(triphenylphosphine)-palladium(II) dichloride; $Pd(OAc)_2$, palladium(II) acetate; PDX, patient-derived xenograft; PFS, progression-free survival; PI_3K, phosphatidylinositol-3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PK, pharmacokinetics; pK_a, negative log of acid dissociation constant; POI, protein of interest; PPB, plasma protein binding;

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PPh_2Cy, [(2-biphenyl)dicyclohexylphosphine]; PPi, inorganic pyrophosphate; PPTS, pyridinium *p*-toluenesulfonate; PROTAC, proteolysis targeting chimera; PR, progesterone receptor; QD, once a day; QTc, corrected for heart rate; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; rt, room temperature; SABCS, San Antonio Breast Cancer Symposium; SAR, structure−activity relationship; S_{inf}, saturation infinity; SERCA, selective estrogen receptor covalent antagonist; SERM, selective estrogen receptor modulator; SFC, supercritical fluid chromatography; SOC, standard of care; $SOCl_2$, thionyl chloride; ShERPA, selective human estrogen receptor partial agonist; TamR, tamoxifen-resistant; TBDPSCl, *tert*-butylchlorodiphenylsilane; TBME, *tert*-butyl methyl ether; TF, transcription factor; Tf_2O, trifluoromethanesulfonic anhydride; TGI, tumor growth inhibition; THF, tetrahydrofuran; THP, tetrahydropyranyl; $t_{1/2}$, terminal half-life; t-BuONa, sodium *tert*-butoxide; UPS, ubiquitin−proteasome system; VHL, Von Hippel−Lindau; V_{dss}, steady-state volume of distribution; V_{ss}, volume of distribution; WT, wild-type

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