



- (51) **International Patent Classification:**
C07C 215/46 (2006.01) *A61K 31/133* (2006.01)
- (21) **International Application Number:**
PCT/US2016/034774
- (22) **International Filing Date:**
27 May 2016 (27.05.2016)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
62/168,540 29 May 2015 (29.05.2015) US
62/168,551 29 May 2015 (29.05.2015) US
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- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).
- Declarations under Rule 4.17:**
— *of inventorship (Rule 4.17(iv))*
- Published:**
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*
— *with information concerning incorporation by reference of missing parts and/or elements (Rule 20.6)*

(54) **Title:** TETRASUBSTITUTED ALKENE COMPOUNDS AND THEIR USE

(57) **Abstract:** Disclosed herein are compounds, or pharmaceutically acceptable salts thereof, and methods of using the compounds for treating breast cancer by administration to a subject in need thereof a therapeutically effective amount of the compounds or pharmaceutically acceptable salts thereof. The breast cancer may be an ER-positive breast cancer and/or the subject in need of treatment may express a mutant ER- α protein.



TETRASUBSTITUTED ALKENE COMPOUNDS AND THEIR USE**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims priority to United States Provisional Patent Application No. 62/168,540, filed on May 29, 2015, and United States Provisional Patent Application No. 62/168,551, filed on May 29, 2015. Both of those applications are incorporated by reference herein.

BACKGROUND

Breast cancer is the most commonly diagnosed malignancy among women today with nearly 200,000/1.7 million new cases diagnosed in the US/worldwide each year respectively. Since about 70% of breast tumors are positive for the estrogen receptor alpha (ER α)— a key oncogenic driver in this subset of tumors— several classes of therapies have been developed to antagonize ER α function, including 1) selective estrogen receptor downregulators (SERDs) of which fulvestrant is an example, 2) selective estrogen receptor modulators (SERMs) of which tamoxifen is an example and 3) aromatase inhibitors that reduce systemic levels of estrogen. These therapies have been largely effective in the clinic reducing occurrence and progression of ER α + breast tumors. However there are on-target liabilities associated with these different classes of compounds. For example, tamoxifen has been shown to activate signaling activity in the endometrium leading to an increase in risk of endometrial cancers in the clinic (Fisher et al., (1994) *J Natl Cancer Inst.* Apr 6;86(7):527-37; van Leeuwen et al., (1994) *Lancet* Feb 19;343(8895):448-52). In contrast, since fulvestrant is a pure antagonist, it can lead to loss of bone density in post-menopausal women as ER α activity is critical for bone building. In addition to on-target side effects, clinical resistance is also beginning to emerge to these classes of ER α antagonists highlighting the need to develop next-generation compounds.

Several mechanisms of resistance have been identified using *in vitro* and *in vivo* models of resistance to various endocrine therapies. These include increased ER α /HER2 “crosstalk” (Shou et al., (2004) *J Natl Cancer Inst.* Jun 16;96(12):926-35), aberrant expression of ER α coactivators/corepressors (Osborne et al., (2003) *J Natl Cancer Inst.* Mar 5;95(5):353-61) or loss of ER α altogether to allow ER-independent growth (Osborne CK, Schiff R (2011) *Annu Rev Med* 62: 233–47).

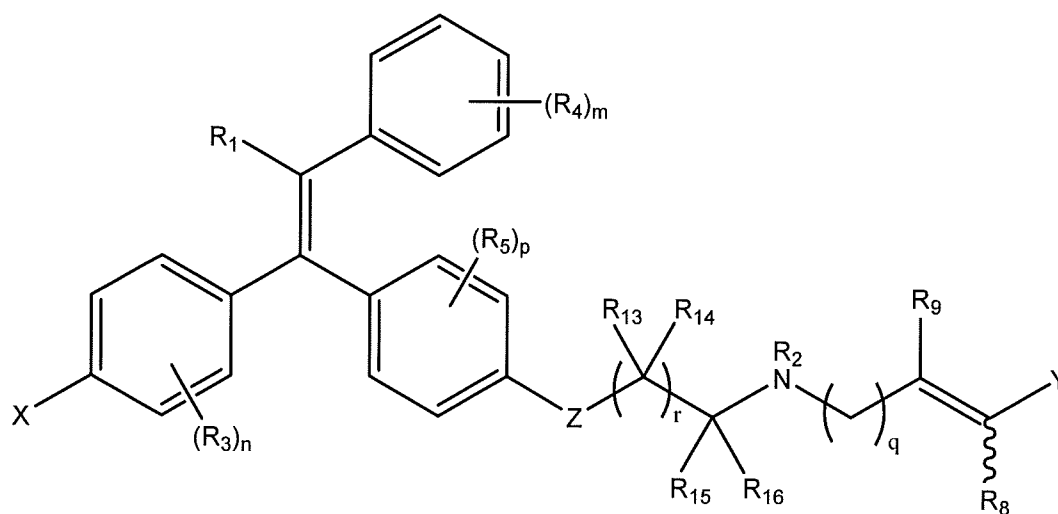
In the hopes of identifying clinically relevant mechanisms of resistance, great effort has also recently gone into deeply characterizing the genetics of endocrine-therapy resistant

metastases isolated from patients. Several independent labs have recently published the multitude of genetic lesions observed in the resistant vs the primary tumors (Li *et al.*, (2013) *Cell Rep.* Sep 26;4(6):1116-30; Robinson *et al.*, (2013) *Nat Genet.* Dec;45(12):1446-51; Toy *et al.*, (2013) *Nat Genet.* 2013 Dec;45(12):1439-45). Among these are the highly recurrent mutations in the ligand-binding domain of *ESR1* (gene which encodes ER α protein) found to be significantly enriched in about 20% of resistant tumors relative to endocrine therapy naïve tumors (Jeselson *et al.*, (2014) *Clin Cancer Res.* Apr 1;20(7):1757-67; Toy *et al.*, (2013) *Nat Genet.* 2013 Dec;45(12):1439-45; Robinson *et al.*, (2013) *Nat Genet.* Dec;45(12):1446-51; Merenbakh-Lamin *et al.*, (2013) *Cancer Res.* Dec 1;73(23):6856-64; Yu *et al.*, (2014) *Science* Jul 11;345(6193):216-20; Segal and Dowsett (2014), *Clin Cancer Res* Apr 1;20(7):1724-6), suggesting the potential for these mutations to functionally drive clinical resistance. In contrast to the enrichment in *ESR1* mutations observed in therapy-resistant tumors, mutations in other cancer-related genes failed to show such a robust enrichment strongly implying the importance of ER α mutations in promoting resistance (Jeselson *et al.*, (2014) *Clin Cancer Res.* Apr 1;20(7):1757-67).

SUMMARY

Described herein are novel compounds useful for treating cancer.

In some embodiments, compounds are described by Formula VII:

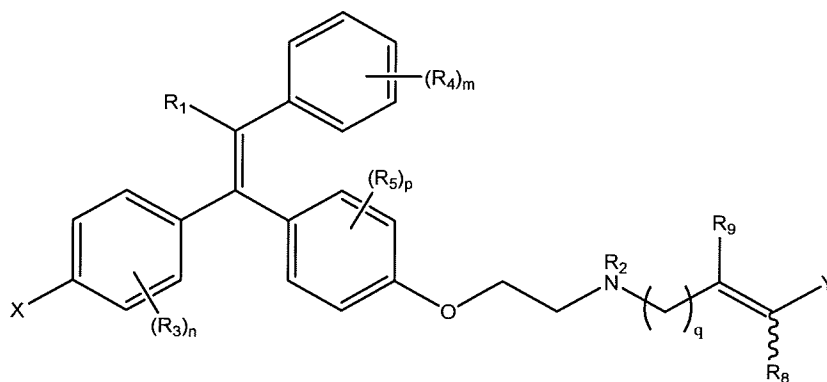


VII

wherein: R1 is selected from the group consisting of C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R2 is selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R3 are the same or different, and

are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C3 alkoxy optionally substituted with at least one halogen; n is 0-4; R₄ are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl, and OR₁₁, wherein R₁₁ is selected from the group consisting of C3-C6 cycloalkyl, C1-C6 alkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring; m is 0-5; R₅ are the same or different and are independently selected from the group consisting of H, halogen, C1-C4 alkyl, C1-C4 alkoxy, C3-C4 cycloalkyl, C3-C4 cycloalkoxy and a C4 heterocyclic ring; p is 0-4; q is 1-2; X is selected from the group consisting of H, -OH, halogen, NH₂ and NHR₁₂, wherein R₁₂ is selected from the group consisting of acyl, C1-C6 alkyl and C3-C6 cycloalkyl; R₈ and R₉ are the same or different and are independently selected from the group consisting of halogen, H and C1-C3 alkyl; Y is selected from the group consisting of -S(O)₂R₆, -S(O)₂NR₆R₇, -C(O)NR₆R₇, -C(O)R₆, -C(O)OR₆ and -CN; or wherein Y and R₈ both represent -CF₃; R₆ and R₇ are the same or different and are independently selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring, wherein said alkyl is saturated or unsaturated or wherein R₆ and R₇ form a 4-6 membered heterocyclic ring with the N to which they are attached, optionally also containing an O atom; R₁₃, R₁₄, R₁₅, and R₁₆ are independently selected from the group consisting of -H, -CH₃, -CH₂CH₃, propyl, isopropyl or butyl; r = 1-3; Z = O, S or is absent; and wherein any carbon containing moiety of R₁-R₁₂ may be optionally substituted with one or more halogen atoms, fluoromethane, difluoromethane or trifluoromethane, or -OH; or pharmaceutically acceptable salts thereof.

In embodiments, such novel compounds are described by Formula I:



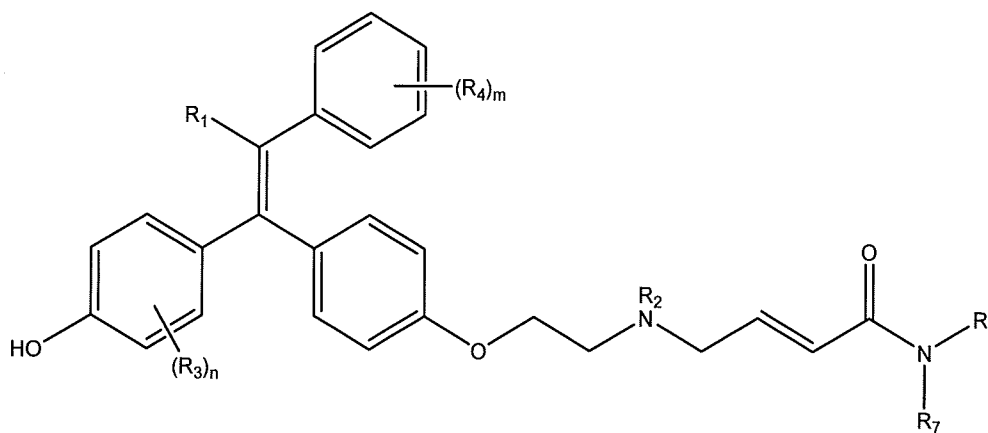
I

wherein: R1 is selected from the group consisting of C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R2 is selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R3 are the same or different, and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C3 alkoxy optionally substituted with at least one halogen; n is 0-4; R4 are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl, and OR11, wherein R11 is selected from the group consisting of C3-C6 cycloalkyl, C1-C6 alkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring; m is 0-5; R5 are the same or different and are independently selected from the group consisting of H, halogen, C1-C4 alkyl, C1-C4 alkoxy, C3-C4 cycloalkyl, C3-C4 cycloalkoxy and a C4 heterocyclic ring; p is 0-4; q is 1-2; X is selected from the group consisting of H, -OH, halogen, NH₂ and NHR12, wherein R12 is selected from the group consisting of acyl, C1-C6 alkyl and C3-C6 cycloalkyl; R8 and R9 are the same or different and are independently selected from the group consisting of halogen, H and C1-C3 alkyl; Y is selected from the group consisting of -S(O)₂R6, -S(O)₂NR6R7, -C(O)NR6R7, -C(O)R6, -C(O)OR6 and -CN; or wherein Y and R8 both represent -CF₃; R6 and R7 are the same or different and are independently selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring, wherein said alkyl is saturated or unsaturated or wherein R6 and R7 form a 4-6 membered heterocyclic ring with the N to which they are attached, optionally also containing an O atom; and wherein any carbon containing moiety of R1-R12 may be optionally substituted with one or more halogen atoms, fluoromethane, difluoromethane or trifluoromethane, or -OH; or pharmaceutically acceptable salts thereof.

In more specific embodiments, such novel compounds are described by Formula I or Formula VII, wherein: R2 is selected from the group consisting of H and CH₃; R3 are the same or different, and are independently selected from the group consisting of H, halogen, methyl and ethyl; R4 are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C6 alkoxy; R5 are the same or different and are independently selected from the group consisting of H, halogen, methyl and ethyl; X is selected from the group consisting of H, -OH, halogen and NH₂; R8 and R9 are the same or different and are independently selected from the group consisting of H and methyl; R6 and R7 are the same or different and are independently selected from the group consisting of H and C1-C6 alkyl, wherein said alkyl is saturated or unsaturated or wherein R6 and R7 form a

4-6 atom heterocyclic ring with the N to which they are attached, optionally also containing an O atom.

In some embodiments, compounds are described by Formula VIII:



VIII

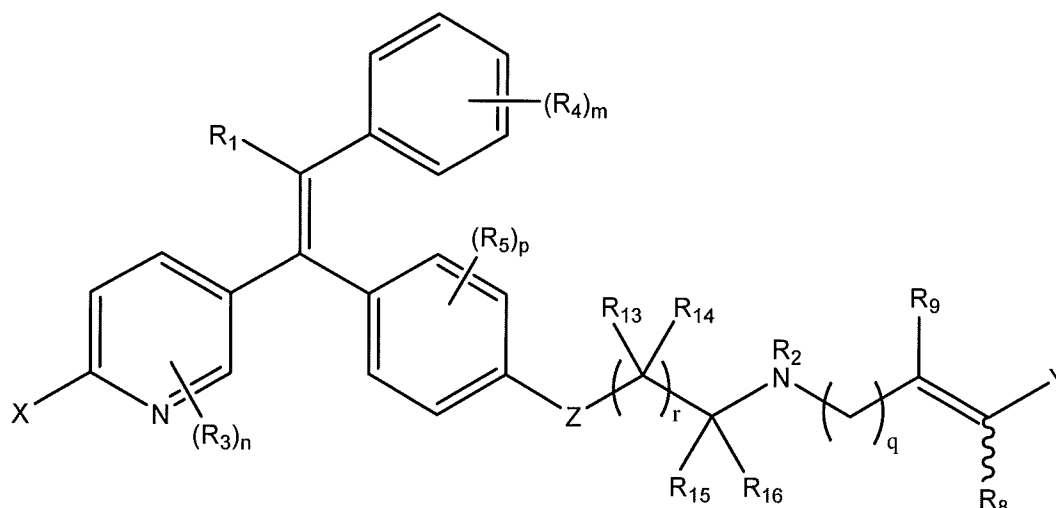
wherein: R1 is selected from the group consisting of ethyl and cyclobutyl; R2 is selected from the group consisting of H and -CH3; n is 0-1; R3 is selected from the group consisting of -CH3, -Cl, -F and -OCH3; m is 0-2; R4 is selected from the group consisting of -CF3, F, -CH(CH3)2, -CH2CH3 and -CH3; R6 and R7 are the same or different and are independently selected from the group consisting of -CH3, -CH2CH2CF2CF3, -CH2(CH2)5CH3 and -CH2(CH2)4CF2CF3; or pharmaceutically acceptable salts thereof.

Embodiments may provide a compound selected from the group consisting of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)(methyl)amino)-N-methyl-N-(6,6,7,7,7-pentafluoroheptyl) but-2- enamide; (E)-N-heptyl-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)(methyl)amino)-N-methylbut-2-enamide; (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)(methyl)amino)-N-methyl-N-(3,3,4,4,4-pentafluorobutyl)but-2-enamide; (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)(methyl)amino)-N,N-dimethylbut-2-enamide; (E)-5-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy) ethyl)amino)-N,N-dimethylpent-2-enamide; (E)-4-((2-(4-((E)-1-(6-aminopyridin-3-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((E)-1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-

yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((E)-1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((Z)-1-(4-aminophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((Z)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-N,N-dimethyl-4-((2-(4-((E)-2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl)phenoxy)ethyl) amino)but-2-enamide; (E)-4-((2-(4-((E)-1-(4-hydroxyphenyl)-2-(3-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino) -N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-isopropyl-phenyl)but-1-en-1-yl)phenoxy) ethyl)amino)-N,N-dimethylbut-2-enamide; and (2E)-4-((2-(4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)-phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; or pharmaceutically acceptable salts thereof

Embodiments may provide compound selected from the group consisting of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((Z)-2-cyclobutyl-1-(4-hydroxyphenyl)-2-phenylvinyl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((Z)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((E)-1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(o-tolyl)but-1-en-1-yl)phenoxy)ethyl) amino)-N,N-dimethylbut-2-enamide; (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(3-(trifluoromethyl) phenyl) but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide; and (E)-5-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylpent-2-enamide; or pharmaceutically acceptable salts thereof.

Embodiments may have the structure of Formula IX:

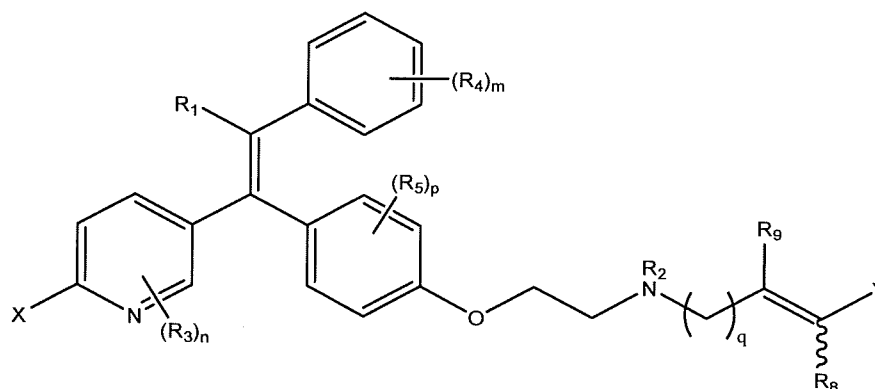


IX

wherein: R₁ is selected from the group consisting of C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R₂ is selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R₃ are the same or different, and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C3 alkoxy optionally substituted with at least one halogen; n is 0-3; R₄ are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl, and OR₁₁, wherein R₁₁ is selected from the group consisting of C3-C6 cycloalkyl, C1-C6 alkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring; m is 0-5; R₅ are the same or different and are independently selected from the group consisting of H, halogen, C1-C4 alkyl, C1-C4 alkoxy, C3-C4 cycloalkyl, C3-C4 cycloalkoxy and a C4 heterocyclic ring; p is 0-4; q is 1-2; X is selected from the group consisting of H, -OH, halogen, NH₂ and NHR₁₂, wherein R₁₂ is selected from the group consisting of acyl, C1-C6 alkyl and C3-C6 cycloalkyl; R₈ and R₉ are the same or different and are independently selected from the group consisting of halogen, H and C1-C3 alkyl; Y is selected from the group consisting of -S(O)₂R₆, -S(O)₂NR₆R₇, -C(O)NR₆R₇, -C(O)R₆, -C(O)OR₆ and -CN; or wherein Y and R₈ both represent -CF₃; R₆ and R₇ are the same or different and are independently selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring, wherein said alkyl is saturated or unsaturated or wherein R₆ and R₇ form a 4-6 membered heterocyclic ring with the N to which they are attached, optionally also containing an O atom; R₁₃, R₁₄, R₁₅, and R₁₆ are independently selected from the group consisting of -H, -CH₃, -CH₂CH₃, propyl, isopropyl or butyl; r = 1-3; Z = O, S or is absent; and wherein any carbon containing moiety of R₁-R₁₂ may be optionally substituted

with one or more halogen atoms, fluoromethane, difluoromethane or trifluoromethane, or –OH; or pharmaceutically acceptable salts thereof.

In embodiments, such novel compounds are described by Formula III:



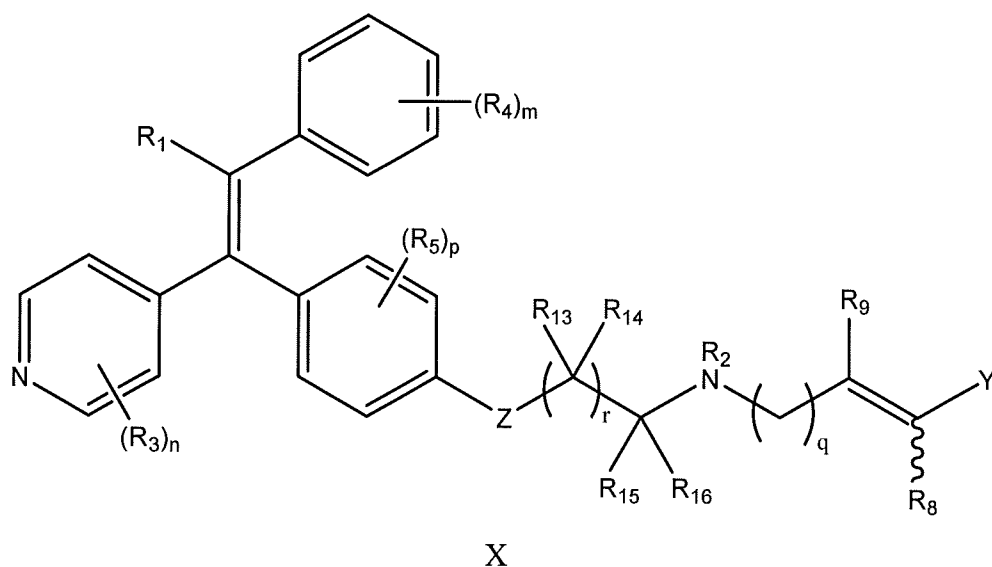
III

wherein: R1 is selected from the group consisting of C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R2 is selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R3 are the same or different, and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C3 alkoxy optionally substituted with at least one halogen; n is 0-3; R4 are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl, and OR11, wherein R11 is selected from the group consisting of C3-C6 cycloalkyl, C1-C6 alkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring; m is 0-5; R5 are the same or different and are independently selected from the group consisting of H, halogen, C1-C4 alkyl, C1-C4 alkoxy, C3-C4 cycloalkyl, C3-C6 cycloalkoxy and a C4 heterocyclic ring; p is 0-4; q is 1-2; X is selected from the group consisting of H, –OH, halogen, NH2 and NHR12, wherein R12 is selected from the group consisting of acyl, C1-C6 alkyl and C3-C6 cycloalkyl; R8 and R9 are the same or different and are independently selected from the group consisting of halogen, H and C1-C3 alkyl; Y is selected from the group consisting of –S(O)2R6, –S(O)2NR6R7, –C(O)NR6R7, –C(O)R6, –C(O)OR6 and –CN; or wherein Y and R8 both represent –CF3; R6 and R7 are the same or different and are independently selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring, wherein said alkyl is saturated or unsaturated or wherein R6 and R7 form a 4-6 membered heterocyclic ring with the N to which they are attached, optionally also containing an O atom; and wherein any carbon containing moiety of R1-R12 may be

optionally substituted with one or more halogen atoms, fluoromethane, difluoromethane or trifluoromethane, or $-OH$; or pharmaceutically acceptable salts thereof.

In more specific embodiments, such novel compounds are described by Formula III or Formula IX, wherein: R_2 is selected from the group consisting of H and CH_3 ; R_3 are the same or different, and are independently selected from the group consisting of H, halogen, methyl and ethyl; R_4 are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C6 alkoxy; R_5 are the same or different and are independently selected from the group consisting of H, halogen, methyl and ethyl; X is selected from the group consisting of H, $-OH$, halogen and NH_2 ; R_8 and R_9 are the same or different and are independently selected from the group consisting of H and methyl; R_6 and R_7 are the same or different and are independently selected from the group consisting of H and C1-C6 alkyl, wherein said alkyl is saturated or unsaturated or wherein R_6 and R_7 form a 4-6 atom heterocyclic ring with the N to which they are attached, optionally also containing an O atom.

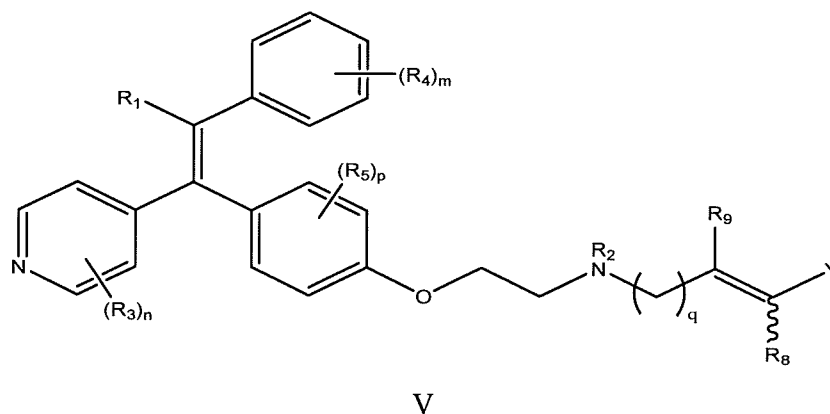
In embodiments, novel compounds may be described by Formula X:



wherein: R_1 is selected from the group consisting of C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R_2 is selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R_3 are the same or different, and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C3 alkoxy optionally substituted with at least one halogen; n is 0-4; R_4 are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl, and

OR11, wherein R11 is selected from the group consisting of C3-C6 cycloalkyl, C1-C6 alkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring; m is 0-5; R5 are the same or different and are independently selected from the group consisting of H, halogen, C1-C4 alkyl, C1-C4 alkoxy, C3-C4 cycloalkyl, C3-C4 cycloalkoxy and a C4 heterocyclic ring; p is 0-4; q is 1-2; R8 and R9 are the same or different and are independently selected from the group consisting of halogen, H and C1-C3 alkyl; Y is selected from the group consisting of $-S(O)_2R_6$, $-S(O)_2NR_6R_7$, $-C(O)NR_6R_7$, $-C(O)R_6$, $-C(O)OR_6$ and $-CN$; or wherein Y and R8 both represent $-CF_3$; R6 and R7 are the same or different and are independently selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring, wherein said alkyl is saturated or unsaturated or wherein R6 and R7 form a 4-6 membered heterocyclic ring with the N to which they are attached, optionally also containing an O atom; R₁₃, R₁₄, R₁₅, and R₁₆ are independently selected from the group consisting of $-H$, $-CH_3$, $-CH_2CH_3$, propyl, isopropyl or butyl; r = 1-3; Z = O, S or is absent; and wherein any carbon containing moiety of R1-R12 may be optionally substituted with one or more halogen atoms, fluoromethane, difluoromethane or trifluoromethane, or $-OH$; or pharmaceutically acceptable salts thereof.

In embodiments, such novel compounds are described by Formula V:

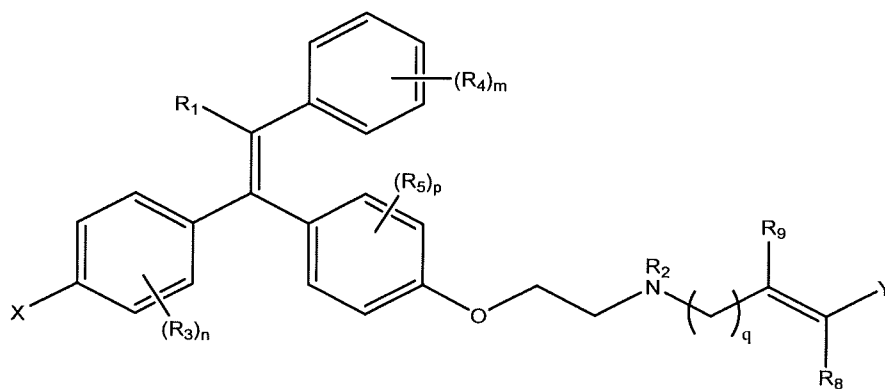


wherein: R1 is selected from the group consisting of C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R2 is selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R3 are the same or different, and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C3 alkoxy optionally substituted with at least one halogen; n is 0-4; R4 are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl, and OR11, wherein R11 is selected from the group consisting of C3-C6 cycloalkyl, C1-C6 alkyl,

aryl, heteroaryl and a 4-6 membered heterocyclic ring; m is 0-5; R₅ are the same or different and are independently selected from the group consisting of H, halogen, C1-C4 alkyl, C1-C4 alkoxy, C3-C4 cycloalkyl, C3-C6 cycloalkoxy and a C4 heterocyclic ring; p is 0-4; q is 1-2; X is selected from the group consisting of H, -OH, halogen, NH₂ and NHR₁₂, wherein R₁₂ is selected from the group consisting of acyl, C1-C6 alkyl and C3-C6 cycloalkyl; R₈ and R₉ are the same or different and are independently selected from the group consisting of halogen, H and C1-C3 alkyl; Y is selected from the group consisting of -S(O)₂R₆, -S(O)₂NR₆R₇, -C(O)NR₆R₇, -C(O)R₆, -C(O)OR₆ and -CN; or wherein Y and R₈ both represent -CF₃; R₆ and R₇ are the same or different and are independently selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring, wherein said alkyl is saturated or unsaturated or wherein R₆ and R₇ form a 4-6 membered heterocyclic ring with the N to which they are attached, optionally also containing an O atom; and wherein any carbon containing moiety of R₁-R₁₂ may be optionally substituted with one or more halogen atoms, fluoromethane, difluoromethane or trifluoromethane, or -OH; or pharmaceutically acceptable salts thereof.

In more specific embodiments, such novel compounds are described by Formula V or Formula X, wherein: R₂ is selected from the group consisting of H and CH₃; R₃ are the same or different, and are independently selected from the group consisting of H, halogen, methyl and ethyl; R₄ are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C6 alkoxy; R₅ are the same or different and are independently selected from the group consisting of H, halogen, methyl and ethyl; X is selected from the group consisting of H, -OH, halogen and NH₂; R₈ and R₉ are the same or different and are independently selected from the group consisting of H and methyl; R₆ and R₇ are the same or different and are independently selected from the group consisting of H and C1-C6 alkyl, wherein said alkyl is saturated or unsaturated or wherein R₆ and R₇ form a 4-6 atom heterocyclic ring with the N to which they are attached, optionally also containing an O atom.

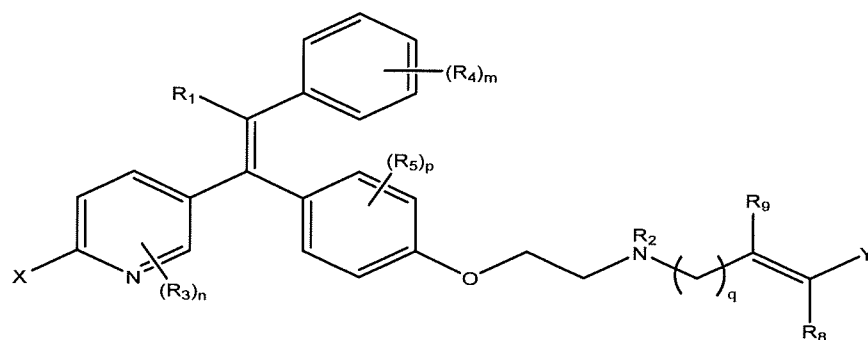
In embodiments, such novel compounds are described by Formula II:



II

wherein: R1 is selected from the group consisting of C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R2 is selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R3 are the same or different, and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C3 alkoxy optionally substituted with at least one halogen; n is 0-4; R4 are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl, and OR11, wherein R11 is selected from the group consisting of C3-C6 cycloalkyl, C1-C6 alkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring; m is 0-5; R5 are the same or different and are independently selected from the group consisting of H, halogen, C1-C4 alkyl, C1-C4 alkoxy, C3-C4 cycloalkyl, C3-C6 cycloalkoxy and a C4 heterocyclic ring; p is 0-4; q is 1-2; X is selected from the group consisting of H, -OH, halogen, NH2 and NHR12, wherein R12 is selected from the group consisting of acyl, C1-C6 alkyl and C3-C6 cycloalkyl; R8 and R9 are the same or different and are independently selected from the group consisting of halogen, H and C1-C3 alkyl; Y is selected from the group consisting of -S(O)2R6, -S(O)2NR6R7, -C(O)NR6R7, -C(O)R6, -C(O)OR6 and -CN; or wherein Y and R8 both represent -CF3; R6 and R7 are the same or different and are independently selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring, wherein said alkyl is saturated or unsaturated or wherein R6 and R7 form a 4-6 membered heterocyclic ring with the N to which they are attached, optionally also containing an O atom; and wherein any carbon containing moiety of R1-R12 may be optionally substituted with one or more halogen atoms, fluoromethane, difluoromethane or trifluoromethane, or -OH; or pharmaceutically acceptable salts thereof.

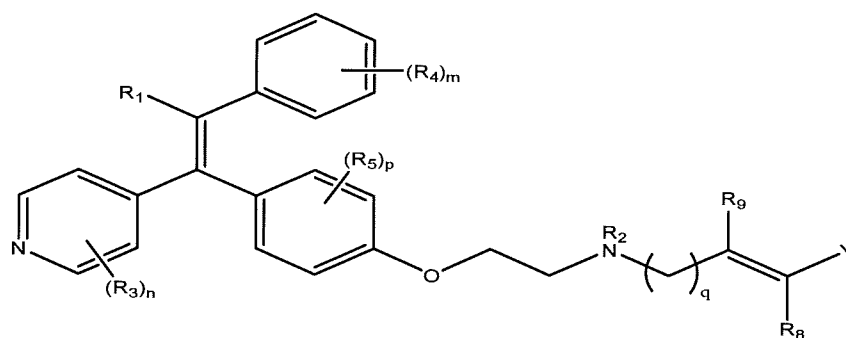
In embodiments, such novel compounds are described by Formula IV:



IV

wherein: n is 0; Y is -C(O)NR₆R₇; and R₆ and R₇ are both -CH₃.

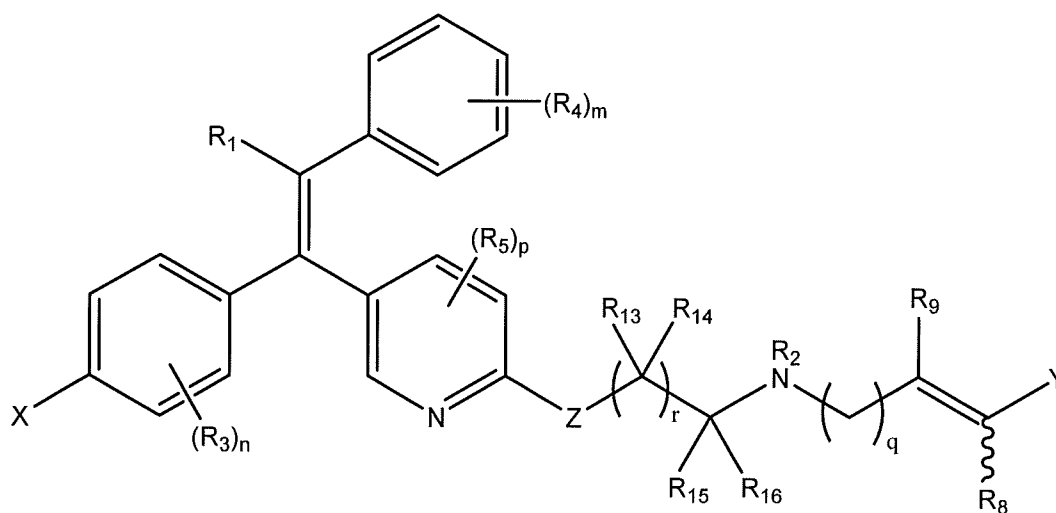
In embodiments, such novel compounds are described by Formula VI:



VI

wherein: n is 0; Y is -C(O)NR₆R₇; and R₆ and R₇ are both -CH₃.

Further embodiments may have the structure of Formula XI:



XI

wherein: R1 is selected from the group consisting of C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R2 is selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl and a 4-6 membered heterocyclic ring; R3 are the same or different, and are independently selected from the group consisting of H, halogen, C1-C6 alkyl and C1-C3 alkoxy optionally substituted with at least one halogen; n is 0-4; R4 are the same or different and are independently selected from the group consisting of H, halogen, C1-C6 alkyl, and OR11, wherein R11 is selected from the group consisting of C3-C6 cycloalkyl, C1-C6 alkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring; m is 0-5; R5 are the same or different and are independently selected from the group consisting of H, halogen, C1-C4 alkyl, C1-C4 alkoxy, C3-C4 cycloalkyl, C3-C4 cycloalkoxy and a C4 heterocyclic ring; p is 0-3; q is 1-2; X is selected from the group consisting of H, -OH, halogen, NH₂ and NHR12, wherein R12 is selected from the group consisting of acyl, C1-C6 alkyl and C3-C6 cycloalkyl; R8 and R9 are the same or different and are independently selected from the group consisting of halogen, H and C1-C3 alkyl; Y is selected from the group consisting of -S(O)₂R6, -S(O)₂NR6R7, -C(O)NR6R7, -C(O)R6, -C(O)OR6 and -CN; or wherein Y and R8 both represent -CF₃; R6 and R7 are the same or different and are independently selected from the group consisting of H, C1-C6 alkyl, C3-C6 cycloalkyl, aryl, heteroaryl and a 4-6 membered heterocyclic ring, wherein said alkyl is saturated or unsaturated or wherein R6 and R7 form a 4-6 membered heterocyclic ring with the N to which they are attached, optionally also containing an O atom; R₁₃, R₁₄, R₁₅, and R₁₆ are independently selected from the group consisting of -H, -CH₃, -CH₂CH₃, propyl, isopropyl or butyl; r = 1-3; Z = O, S or is absent; and wherein any carbon containing moiety of R1-R12 may be optionally substituted with one or more halogen atoms, fluoromethane, difluoromethane or trifluoromethane, or -OH; or pharmaceutically acceptable salts thereof.

In embodiments, the compounds of any of the above Formulas have the following permutations or combinations of permutations, when the substituent is present in the Formula: Y is -C(O)NR6R7; Y and R9 are in "cis" configuration relative to each other; R6 and R7 are methyl; R8 and R9 are both H; R1 is ethyl or cyclobutyl; R2 is H or CH₃; n is 1 and R3 is F; m is 1 and R4 is F; X is -OH; q is 1; m and n are both 0; m is 0 and n is 1; m is 1 and n is 0; R₁₃, R₁₄, R₁₅ and R₁₆ are H; r is 1; and wherein in Z is an oxygen atom.

Also disclosed herein are methods of using the novel compounds, for example, to treat breast cancer. In embodiments, such methods include administration to a subject in need thereof a

therapeutically effective amount of any of the compounds of any of the above Formulas or pharmaceutically acceptable salts thereof. In embodiments, use is made of the compounds of any of the above Formulas or pharmaceutically acceptable salts thereof for treating breast cancer. In embodiments, the breast cancer is an ER-positive breast cancer. In embodiments, the subject in need of treatment expresses a mutant ER- α protein.

In embodiments, the compounds disclosed herein are useful for inhibiting the cell culture growth of MCF7 ER-alpha (wildtype) and MCF7 ER-alpha (Y537S mutant) cells. Other compounds (e.g., tamoxifen, raloxifene and fulvestrant) known to inhibit the cell culture growth of MCF7 ER-alpha (wildtype) cells are currently used to treat breast cancer in human patients. Hence, the compounds disclosed herein are useful for treating ER-alpha expressing breast cancer in human patients, and are useful for treating Y537S mutant ER-alpha expressing breast cancer in human patients.

In embodiments, the compounds disclosed herein are useful for treating breast cancer. In embodiments, the breast cancer is ER- α +. In embodiments, the breast cancer expresses an ER- α mutation, which is L536Q (Robinson *et al.* Nat Genet. 2013 Dec;45(12)), L536R (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45), Y537S (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45; Robinson *et al.* Nat Genet. 2013 Dec;45(12); Jeselsohn *et al.* Clin Cancer Res. 2014 Apr 1;20(7):1757-67), Y537N (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45; Jeselsohn *et al.* Clin Cancer Res. 2014 Apr 1;20(7):1757-67), Y537C (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45; Jeselsohn *et al.* Clin Cancer Res. 2014 Apr 1;20(7):1757-67) and D538G (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45; Robinson *et al.* Nat Genet. 2013 Dec;45(12); Jeselsohn *et al.* Clin Cancer Res. 2014 Apr 1;20(7):1757-67; Merenbakh-Lamin *et al.* Cancer Res. 2013 Dec 1;73(23):6856-64), all of which are incorporated by reference in their entireties for their teachings of ER- α mutations.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows phenotypic resistance observed in mutant-bearing lines relative to control lines to existing clinical compounds, whereby MCF7 cells engineered to overexpress various ER α^{MUT} showed partial resistance to various endocrine therapies.

DETAILED DESCRIPTION

All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Where the text of this disclosure and the text of one or more documents incorporated by reference conflicts, this disclosure controls. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The embodiments described herein having now been described by way of written description, those of skill in the art will recognize that the embodiments described herein may be practiced in a variety of embodiments and that the description and examples provided herein are for purposes of illustration and not limitation of the claims.

As used herein, "alkyl", "C₁, C₂, C₃, C₄, C₅ or C₆ alkyl" or "C₁-C₆ alkyl" is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl is intended to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl groups. Examples of alkyl include moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl or n-hexyl.

In certain embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (e.g., C₁-C₆ for straight chain, C₃-C₆ for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

As used herein, the term "cycloalkyl" refers to a saturated or unsaturated nonaromatic hydrocarbon ring having 3 to 7 carbon atoms (e.g., C₃-C₇). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

The term "heterocycloalkyl" refers to a saturated or unsaturated nonaromatic 3-8 membered monocyclic groups, 7-10 membered fused bicyclic groups having one or more heteroatoms (such as O, N, or S), unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, oxiranyl, azetidiny, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, tetrahydrothiophene, dihydropyranyl, pyranly,

morpholinyl, 1,4-diazepanyl, 1,4-oxazepanyl, and the like.

Additional examples of heterocycloalkyl groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiaziny, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidiny, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazol5(4H)-one, oxazolidiny, oxazolyl, oxindolyl, pyrimidiny, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, piperidonyl, 4-piperidonyl, piperonyl, pteridiny, puriny, pyranly, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidiny, pyrrolidiny, pyrroliny, 2H-pyrrolyl, pyrrolyl, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofuranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

The term "optionally substituted alkyl" refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents may include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro,

trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

An "arylalkyl" or an "aralkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl(benzyl)). An "alkylaryl" moiety is an aryl substituted with an alkyl (e.g., methylphenyl).

"Alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight chain alkenyl groups (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term "C₂-C₆" includes alkenyl groups containing two to six carbon atoms. The term "C₃-C₆" includes alkenyl groups containing three to six carbon atoms.

The term "optionally substituted alkenyl" refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents may include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

"Alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, "alkynyl" includes straight chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term "C₂-C₆" includes alkynyl groups containing two to six

carbon atoms. The term "C₃-C₆" includes alkynyl groups containing three to six carbon atoms.

The term "optionally substituted alkynyl" refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents may include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidinyl and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl.

"Aryl" includes groups with aromaticity, including "conjugated," or polycyclic systems with at least one aromatic ring and do not contain any heteroatom in the ring structure. Examples include phenyl, benzyl, 1,2,3,4-tetrahydronaphthalenyl, etc.

"Heteroaryl" groups are aryl groups, as defined above, except having from one to four heteroatoms in the ring structure, and may also be referred to as "aryl heterocycles" or "heteroaromatics." As used herein, the term "heteroaryl" is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or e.g., 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR' wherein R' is H or other substituents, as defined).

The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

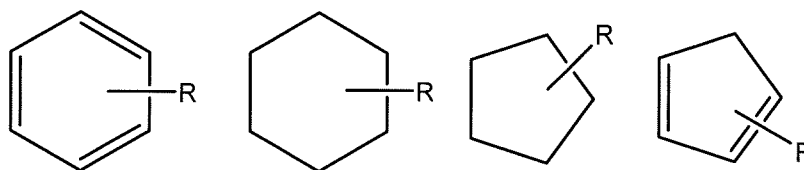
Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

Furthermore, the terms "aryl" and "heteroaryl" include multicyclic aryl and heteroaryl groups, e.g., bicyclic. Non-limiting example of such aryl groups include, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, naphthrydine, indole, benzofuran, purine, benzofuran, deazapurine, indolizine.

In the case of multicyclic aromatic rings, only one of the rings needs to be aromatic (e.g., 2,3-dihydroindole), although all of the rings may be aromatic (e.g., quinoline).

The cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring may be substituted at one or more ring positions (e.g., the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups may also be fused with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (e.g., tetralin, methylenedioxyphenyl).

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring (as shown by the examples below with substituent R), then such substituent may be bonded to any atom in the ring.



When any variable (e.g., R₁) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R₁ moieties, then the group may optionally be substituted with up to two R₁ moieties and R₁ at each occurrence is selected independently from the definition of R₁.

The term "hydroxy" or "hydroxyl" includes groups with an -OH or -O⁻.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo and iodo. The term "perhalogenated" generally refers to a moiety wherein all hydrogen atoms are replaced by halogen atoms. The term "haloalkyl" or "haloalkoxyl" refers to an alkyl or alkoxyl substituted with one or more halogen atoms.

"Alkoxyalkyl," "alkylaminoalkyl," and "thioalkoxyalkyl" include alkyl groups, as described above, wherein oxygen, nitrogen, or sulfur atoms replace one or more hydrocarbon backbone carbon atoms.

The term "alkoxy" or "alkoxyl" includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups may be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino,

diaryl amino, and alkylaryl amino), acyl amino (including alkylcarbonyl amino, arylcarbonyl amino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

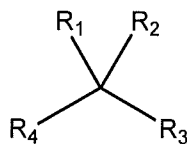
"Isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers."

Stereoisomers that are not mirror images of one another are termed "diastereoisomers," and stereoisomers that are non-superimposable mirror images of each other are termed "enantiomers" or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture."

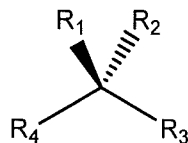
A carbon atom bonded to four nonidentical substituents is termed a "chiral center."

"Chiral isomer" means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture." When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the Sequence Rule of Cahn, Ingold and Prelog. (Cahn et al., *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn et al., *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn et al., *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

In the present specification, each incidence of a chiral center within a structural formula, such as the non-limiting example shown here:



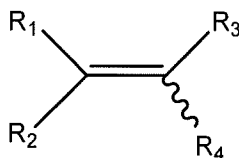
is meant to depict all possible stereoisomers. In contrast, a chiral center drawn with hatches and wedges, such as the non-limiting example shown here:



is meant to depict the stereoisomer as indicated (here in this sp^3 hybridized carbon chiral center, R₃ and R₄ are in the plane of the paper, R₁ is above the plane of paper, and R₂ is behind the plane of paper).

"Geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes *cis* and *trans*, or *Z* and *E*, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

In the present specification, each incidence within a structural formula including a wavy line adjacent to a double bond as shown:



is meant to depict both geometric isomers. In contrast, such structures drawn without a wavy line is meant to depict a compound having the geometric configuration as drawn.

"Tautomer" is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds.

Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerizations is called tautomerism.

Where the present specification depicts a compound prone to tautomerization, but only depicts one of the tautomers, it is understood that all tautomers are included as part of the meaning of the chemical depicted. It is to be understood that the compounds disclosed herein may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included, and the naming of the compounds does not exclude any tautomer form.

Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group ($--CHO$) in a sugar chain molecule reacting with one of the hydroxy groups ($--OH$) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (e.g., in nucleobases such as guanine, thymine and cytosine), imine-enamine and enamine-enamine.

Furthermore, the structures and other compounds disclosed herein include all atropic isomers thereof, it being understood that not all atropic isomers may have the same level of activity. "Atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

The term "crystal polymorphs", "polymorphs" or "crystal forms" means crystal structures in which a compound (or a salt or solvate thereof) may crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility.

Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Crystal polymorphs of the compounds may be prepared by crystallization under different conditions. It is understood that the compounds disclosed herein may exist in crystalline form, crystal form mixture, or anhydride or hydrate thereof.

The compounds disclosed herein include the compounds themselves, as well as their salts and solvates, if applicable. A salt, for example, may be formed between an anion and a positively charged group (e.g., amino) on an aryl- or heteroaryl-substituted benzene compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluoroacetate). The term "pharmaceutically acceptable anion" refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt may also be formed between a cation and a negatively charged group (e.g., carboxylate) on an aryl- or heteroaryl-substituted benzene compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The aryl- or heteroaryl-substituted benzene compounds also include those salts containing quaternary nitrogen atoms.

Additionally, the compounds disclosed herein, for example, the salts of the compounds, may exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds disclosed herein wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic,

sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, e.g., glycine, alanine, phenylalanine, arginine, etc.

Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt may be 1:1, or any ratio other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

"Solvate" means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

Chemicals as named or depicted are intended to include all naturally occurring isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of ¹H hydrogen include tritium and deuterium, and isotopes of ¹²C carbon include ¹³C and ¹⁴C.

It will be understood that some compounds, and isomers, salts, esters and solvates thereof, of the compounds disclosed herein may exhibit greater *in vivo* or *in vitro* activity than others. It

will also be appreciated that some cancers may be treated more effectively than others, and may be treated more effectively in certain species of subjects than others, using the compounds, and isomers, salts, esters and solvates thereof, of the compounds disclosed herein.

As used herein, "treating" means administering to a subject a pharmaceutical composition to ameliorate, reduce or lessen the symptoms of a disease. As used herein, "treating" or "treat" describes the management and care of a subject for the purpose of combating a disease, condition, or disorder and includes the administration of a compound disclosed herein, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" may also include treatment of a cell in vitro or an animal model.

Treating cancer may result in a reduction in size of a tumor. A reduction in size of a tumor may also be referred to as "tumor regression." Preferably, after treatment, tumor size is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor size is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Size of a tumor may be measured by any reproducible means of measurement. The size of a tumor may be measured as a diameter of the tumor.

Treating cancer may result in a reduction in tumor volume. Preferably, after treatment, tumor volume is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor volume is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Tumor volume may be measured by any reproducible means of measurement.

Treating cancer may result in a decrease in number of tumors. Preferably, after treatment, tumor number is reduced by 5% or greater relative to number prior to treatment; more preferably, tumor number is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or

greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. Number of tumors may be measured by any reproducible means of measurement. The number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

Treating cancer may result in a decrease in number of metastatic lesions in other tissues or organs distant from the primary tumor site. Preferably, after treatment, the number of metastatic lesions is reduced by 5% or greater relative to number prior to treatment; more preferably, the number of metastatic lesions is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. The number of metastatic lesions may be measured by any reproducible means of measurement. The number of metastatic lesions may be measured by counting metastatic lesions visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

As used herein, “subject” or “subjects” refers to any animal, such as mammals including rodents (e.g., mice or rats), dogs, primates, lemurs or humans.

Treating cancer may result in an increase in average survival time of a population of treated subjects in comparison to a population receiving carrier alone. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

Treating cancer may result in an increase in average survival time of a population of treated subjects in comparison to a population of untreated subjects. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more

preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

Treating cancer may result in increase in average survival time of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound disclosed herein, or a pharmaceutically acceptable salt thereof. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

Treating cancer may result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving carrier alone. Treating cancer may result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. Treating cancer may result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound disclosed herein, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the mortality rate is decreased by more than 2%; more preferably, by more than 5%; more preferably, by more than 10%; and most preferably, by more than 25%. A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means. A decrease in the mortality rate of a population may be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with an active compound. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with an active compound.

Treating cancer may result in a decrease in tumor growth rate. Preferably, after treatment, tumor growth rate is reduced by at least 5% relative to number prior to treatment; more preferably, tumor growth rate is reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Tumor growth rate may be measured by any reproducible means of measurement. Tumor growth rate may be measured according to a change in tumor diameter per unit time.

Treating cancer may result in a decrease in tumor regrowth, for example, following attempts to remove it surgically. Preferably, after treatment, tumor regrowth is less than 5%; more preferably, tumor regrowth is less than 10%; more preferably, less than 20%; more preferably, less than 30%; more preferably, less than 40%; more preferably, less than 50%; even more preferably, less than 50%; and most preferably, less than 75%. Tumor regrowth may be measured by any reproducible means of measurement. Tumor regrowth is measured, for example, by measuring an increase in the diameter of a tumor after a prior tumor shrinkage that followed treatment. A decrease in tumor regrowth is indicated by failure of tumors to reoccur after treatment has stopped.

Treating or preventing a cell proliferative disorder may result in a reduction in the rate of cellular proliferation. Preferably, after treatment, the rate of cellular proliferation is reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The rate of cellular proliferation may be measured by any reproducible means of measurement. The rate of cellular proliferation is measured, for example, by measuring the number of dividing cells in a tissue sample per unit time.

Treating or preventing a cell proliferative disorder may result in a reduction in the proportion of proliferating cells. Preferably, after treatment, the proportion of proliferating cells is reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The

proportion of proliferating cells may be measured by any reproducible means of measurement. Preferably, the proportion of proliferating cells is measured, for example, by quantifying the number of dividing cells relative to the number of nondividing cells in a tissue sample. The proportion of proliferating cells may be equivalent to the mitotic index.

Treating or preventing a cell proliferative disorder may result in a decrease in size of an area or zone of cellular proliferation. Preferably, after treatment, size of an area or zone of cellular proliferation is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Size of an area or zone of cellular proliferation may be measured by any reproducible means of measurement. The size of an area or zone of cellular proliferation may be measured as a diameter or width of an area or zone of cellular proliferation.

Treating or preventing a cell proliferative disorder may result in a decrease in the number or proportion of cells having an abnormal appearance or morphology. Preferably, after treatment, the number of cells having an abnormal morphology is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. An abnormal cellular appearance or morphology may be measured by any reproducible means of measurement. An abnormal cellular morphology may be measured by microscopy, e.g., using an inverted tissue culture microscope. An abnormal cellular morphology may take the form of nuclear pleiomorphism.

As used herein, the term "alleviate" is meant to describe a process by which the severity of a sign or symptom of a disorder is decreased. Importantly, a sign or symptom may be alleviated without being eliminated. In a preferred embodiment, the administration of pharmaceutical compositions disclosed herein leads to the elimination of a sign or symptom, however, elimination is not required. Effective dosages are expected to decrease the severity of a sign or symptom. For instance, a sign or symptom of a disorder such as cancer, which may occur in multiple locations, is alleviated if the severity of the cancer is decreased within at least one

of multiple locations.

As used herein, the term "severity" is meant to describe the potential of cancer to transform from a precancerous, or benign, state into a malignant state. Alternatively, or in addition, severity is meant to describe a cancer stage, for example, according to the TNM system (accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC)) or by other art-recognized methods. Cancer stage refers to the extent or severity of the cancer, based on factors such as the location of the primary tumor, tumor size, number of tumors, and lymph node involvement (spread of cancer into lymph nodes). Alternatively, or in addition, severity is meant to describe the tumor grade by art-recognized methods (see, National Cancer Institute, www.cancer.gov). Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The specific factors used to determine tumor grade vary with each type of cancer. Severity also describes a histologic grade, also called differentiation, which refers to how much the tumor cells resemble normal cells of the same tissue type (see, National Cancer Institute, www.cancer.gov). Furthermore, severity describes a nuclear grade, which refers to the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are dividing (see, National Cancer Institute, www.cancer.gov).

In another aspect of embodiments described herein, severity describes the degree to which a tumor has secreted growth factors, degraded the extracellular matrix, become vascularized, lost adhesion to juxtaposed tissues, or metastasized. Moreover, severity describes the number of locations to which a primary tumor has metastasized. Finally, severity includes the difficulty of treating tumors of varying types and locations. For example, inoperable tumors, those cancers which have greater access to multiple body systems (hematological and immunological tumors), and those which are the most resistant to traditional treatments are considered most severe. In these situations, prolonging the life expectancy of the subject and/or reducing pain, decreasing the proportion of cancerous cells or restricting cells to one system, and improving cancer stage/tumor grade/histological grade/nuclear grade are considered alleviating a sign or symptom of the cancer.

As used herein the term "symptom" is defined as an indication of disease, illness, injury, or

that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by non-health-care professionals.

A "pharmaceutical composition" is a formulation containing a compound disclosed herein in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (e.g., a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound disclosed herein include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

The present disclosure also provides pharmaceutical compositions comprising any compound disclosed herein in combination with at least one pharmaceutically acceptable excipient or carrier.

A pharmaceutical composition disclosed herein is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application may include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH may be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation may be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

A compound or pharmaceutical composition disclosed herein may be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, for treatment of cancers, a compound disclosed herein may be injected directly into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (e.g., cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

The term "therapeutically effective amount", as used herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect may be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation may be determined by routine experimentation that is

within the skill and judgment of the clinician. In a preferred aspect, the disease or condition to be treated is cancer. In another aspect, the disease or condition to be treated is a cell proliferative disorder.

For any compound, the therapeutically effective amount may be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information may then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it may be expressed as the ratio, LD_{50}/ED_{50} .

Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

The pharmaceutical compositions containing active compounds disclosed herein may be manufactured in a manner that is generally known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that may be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions may be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions may be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions may also be prepared

using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials may be included as part of the composition. The tablets, pills, capsules, troches and the like may contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

The active compounds may be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers may be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the compounds disclosed herein are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with embodiments described herein vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. Dosages may range from about 0.01 mg/kg per day to about 5000 mg/kg per day. In preferred aspects, dosages may range from about 1 mg/kg per day to about 1000 mg/kg per

day. In an aspect, the dose will be in the range of about 0.1 mg/day to about 50 g/day; about 0.1 mg/day to about 25 g/day; about 0.1 mg/day to about 10 g/day; about 0.1 mg to about 3 g/day; or about 0.1 mg to about 1 g/day, in single, divided, or continuous doses (which dose may be adjusted for the patient's weight in kg, body surface area in m², and age in years). An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term "dosage effective manner" refers to amount of an active compound to produce the desired biological effect in a subject or cell.

The pharmaceutical compositions may be included in a container, pack, or dispenser together with instructions for administration.

Techniques for formulation and administration of the compounds disclosed herein may be found in Remington: the Science and Practice of Pharmacy, 19th edition, Mack Publishing Co., Easton, Pa. (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, may be used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

Exemplary cancers that may be treated using one or more compounds disclosed herein include, but are not limited to, breast cancer, uterine endometrial, ovarian carcinoma, sarcoma, thyroid carcinoma, prostate, lung adenocarcinoma, and hepatocellular carcinoma.

In embodiments, the compounds disclosed herein may be useful for treating breast cancer. In embodiments, the breast cancer is ER- α +. In embodiments, the breast cancer expresses an ER- α mutation, which may be L536Q (Robinson *et al.* Nat Genet. 2013 Dec;45(12)), L536R (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45), Y537S (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45; Robinson *et al.* Nat Genet. 2013 Dec;45(12); Jeselsohn *et al.* Clin Cancer Res. 2014 Apr 1;20(7):1757-67), Y537N (Toy *et al.* Nat Genet. 2013

Dec;45(12):1439-45; Jeselsohn *et al.* Clin Cancer Res. 2014 Apr 1;20(7):1757-67), Y537C (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45; Jeselsohn *et al.* Clin Cancer Res. 2014 Apr 1;20(7):1757-67) and D538G (Toy *et al.* Nat Genet. 2013 Dec;45(12):1439-45; Robinson *et al.* Nat Genet. 2013 Dec;45(12); Jeselsohn *et al.* Clin Cancer Res. 2014 Apr 1;20(7):1757-67; Merenbakh-Lamin *et al.* Cancer Res. 2013 Dec 1;73(23):6856-64), all of which are incorporated by reference in their entireties for their teachings of ER- α mutations.

Thus, the compounds disclosed herein may be also useful for additional indications and genotypes. *ESR1* mutations (Y537C/N) were recently discovered in 4 of 373 cases of endometrial cancers (Kandoth *et al.* Nature 2013 May 2;497(7447):67-73; Robinson *et al.* Nat Genet. 2013 Dec;45(12)). Since it has been shown that *ESR1* mutations Y537C/N significantly drive resistance to currently marketed SOC therapies, the compounds disclosed herein may be useful for treating ER α ^{MUT} endometrial cancers.

Exemplary cell proliferative disorders that may be treated using one or more compounds disclosed herein include, but are not limited to breast cancer, a precancer or precancerous condition of the breast, benign growths or lesions of the breast, and malignant growths or lesions of the breast, and metastatic lesions in tissue and organs in the body other than the breast. Cell proliferative disorders of the breast may include hyperplasia, metaplasia, and dysplasia of the breast.

A breast cancer that is to be treated may arise in a male or female subject. A breast cancer that is to be treated may arise in a premenopausal female subject or a postmenopausal female subject. A breast cancer that is to be treated may arise in a subject 30 years old or older, or a subject younger than 30 years old. A breast cancer that is to be treated has arisen in a subject 50 years old or older, or a subject younger than 50 years old. A breast cancer that is to be treated may arise in a subject 70 years old or older, or a subject younger than 70 years old.

A compound disclosed herein, or a pharmaceutically acceptable salt thereof, may be used to treat or prevent a cell proliferative disorder of the breast, or to treat or prevent breast cancer, in a subject having an increased risk of developing breast cancer relative to the population at large, or used to identify suitable candidates for such purposes. A subject with an increased risk of developing breast cancer relative to the population at large is a female subject with a family history or personal history of breast cancer. A subject with an increased risk of developing breast cancer relative to the population at large is a female who is greater than 30

years old, greater than 40 years old, greater than 50 years old, greater than 60 years old, greater than 70 years old, greater than 80 years old, or greater than 90 years old.

A cancer that is to be treated may include a tumor that has been determined to be less than or equal to about 2 centimeters in diameter. A cancer that is to be treated may include a tumor that has been determined to be from about 2 to about 5 centimeters in diameter. A cancer that is to be treated may include a tumor that has been determined to be greater than or equal to about 3 centimeters in diameter. A cancer that is to be treated may include a tumor that has been determined to be greater than 5 centimeters in diameter. A cancer that is to be treated may be classified by microscopic appearance as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated. A cancer that is to be treated may be classified by microscopic appearance with respect to mitosis count (e.g., amount of cell division) or nuclear pleiomorphism (e.g., change in cells). A cancer that is to be treated may be classified by microscopic appearance as being associated with areas of necrosis (e.g., areas of dying or degenerating cells). A cancer that is to be treated may be classified as having an abnormal karyotype, having an abnormal number of chromosomes, or having one or more chromosomes that are abnormal in appearance. A cancer that is to be treated may be classified as being aneuploid, triploid, tetraploid, or as having an altered ploidy. A cancer that is to be treated may be classified as having a chromosomal translocation, or a deletion or duplication of an entire chromosome, or a region of deletion, duplication or amplification of a portion of a chromosome.

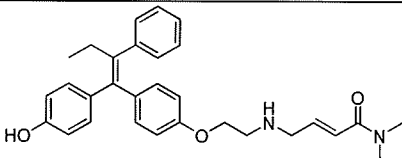
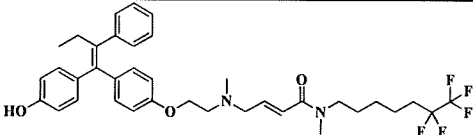
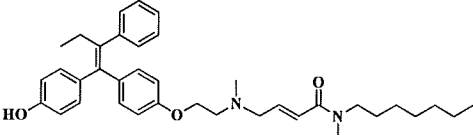
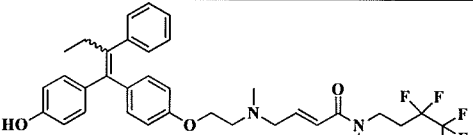
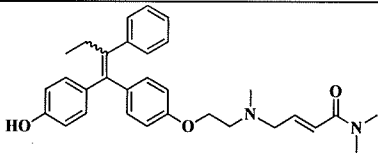
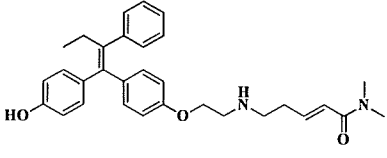
The compounds, or pharmaceutically acceptable salts thereof may be administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

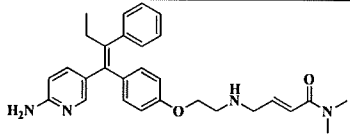
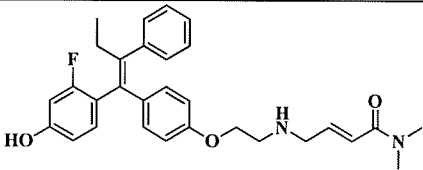
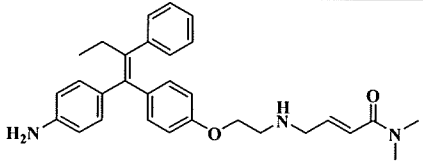
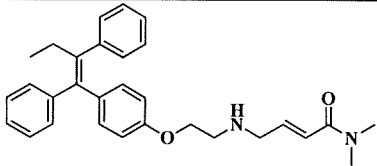
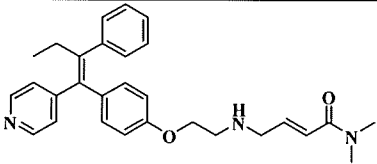
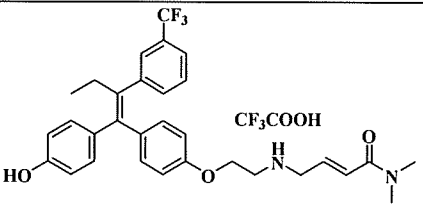
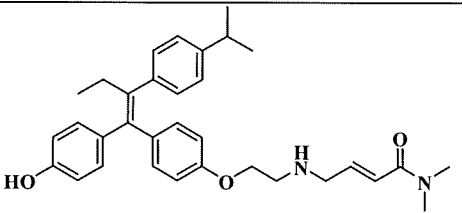
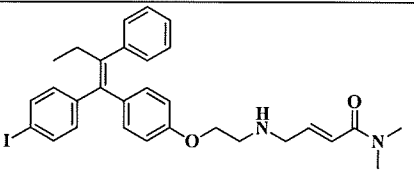
The dosage regimen utilizing the compounds may be selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian may readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

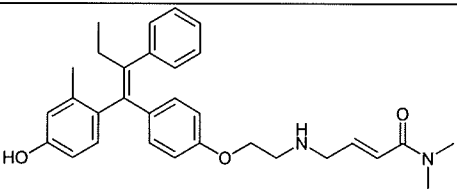
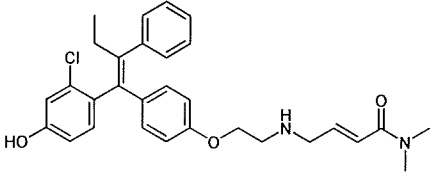
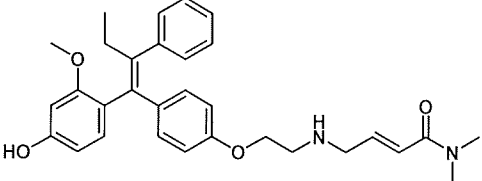
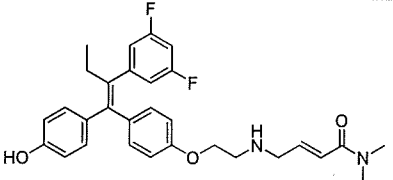
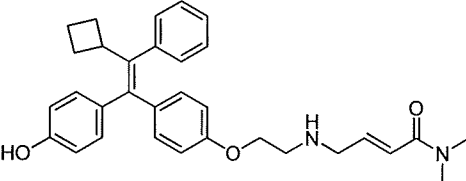
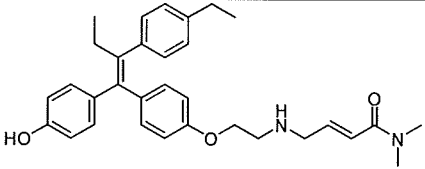
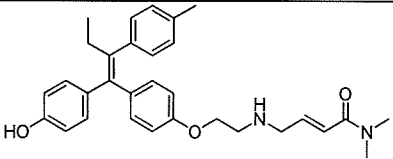
EXAMPLES

Hereby are provided non-limiting examples of embodiments of compounds disclosed herein. If there is any discrepancy between a compound's depicted chemical structure and its chemical name, the depicted chemical structure will control.

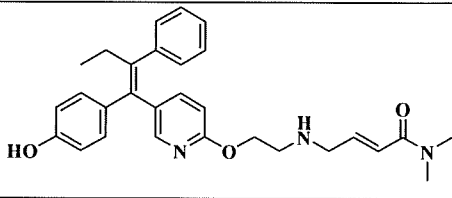
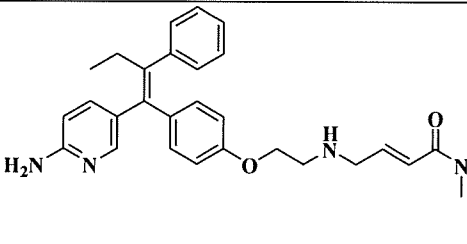
Table 1

Example #	Structure	GI50 WT (nM)	GI50 MUT (Y537S) (nM)
1		1.23 ± 0.13 (2)	10.37 ± 0.13 (2)
2		11.06	55.96
3		10.94	167.94
4		14.87 ± 2.40 (3)	176.20 ± 47.58 (3)
5		6.98 ± 1.24 (2)	320.50 ± 173.73 (3)
6		4.61	53.14

7		79.8	403.9
8		3.39 ± 3.37 (2)	16.58 ± 5.31 (2)
9		10.04 ± 2.29 (2)	121.07 ± 48.07 (2)
10		121.76	2899.63
11		24.1	297.08
12		1.2	12.3
13		8.05 ± 4.91 (2)	181.10 ± 88.28 (2)
14		4.33	247.49

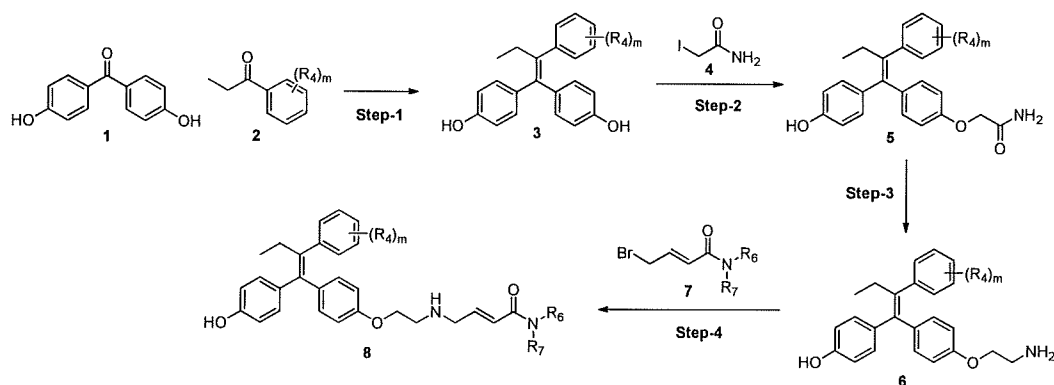
15		7.33	38.41 ± 3.26 (2)
16		2.48	25.20 ± 2.42 (2)
17		19.38 ± 2.73 (2)	234.11 ± 48.99 (2)
18		2.20 ± 2.04 (2)	35.34 ± 29.92 (2)
19		1.76 ± 2.01 (2)	29.53 ± 33.87 (2)
20		8.03 ± 4.33 (2)	180.57 ± 132.8 (2)
21		4.85 ± 4.34 (2)	39.35 ± 0.16 (2)

22		1.03	16.4
23		2.74	46.63
24		6.2	181.5
25		6.5	904.5
26		2.5	49.5
27		4.9	75.4
28		3.9	77.8
29		20.6	365.1

30		0.8	20.9
31		84.3	359

General Procedures

Scheme 1:



Step-1: To a suspension of zinc dust (36.6 g, 560 mmol) in dry THF (200 mL) at -10 °C was added TiCl₄ (50.4 g, 266 mmol) under nitrogen atmosphere. The contents were stirred there for 15 min, slowly allowed to warm to 23 °C and heated to reflux for 2 h. The resulting mixture was cooled to 0 °C and a solution of bis(4-hydroxyphenyl)methanone (**1**, 46.7 mmol) and propiophenone (**2**, 140 mmol) in dry THF (20 mL) was added and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was cooled to 23 °C and quenched with saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate (500 mL x 3), the combined organic layers were washed with water, saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified over 230-400 mesh silica gel column chromatography using (3:7) ethyl acetate in *n*-hexane to afford 4,4'-(2-phenylbut-1-en-1,1-diyl)diphenol (**3**, 40 mmol, 85%) as a brown colour solid.

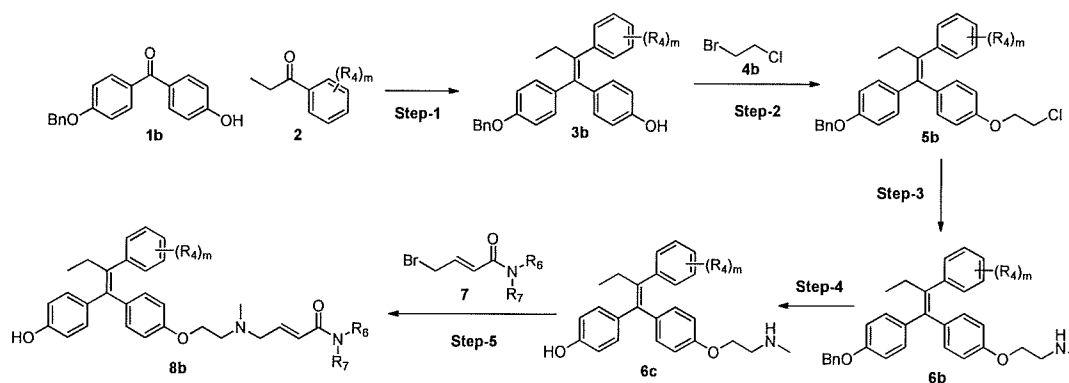
Step-2: To a stirred solution of 4,4'-(2-phenylbut-1-en-1,1-diyl)diphenol (**3**, 31.6 mmol) in acetone (100 mL) was added K₂CO₃ (13.0 g, 94.8 mmol) at 23 °C and the contents were

heated at 80 °C for 15 min. To this mixture, a solution of 2-iodoacetamide (**4**, 34.8 mmol) in 50 mL of acetone was added slowly over a period of 3 h at 80 °C and the contents were stirred for 1 h at 80 °C. The reaction mixture was diluted with cold water (100 mL), extracted with ethyl acetate, organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using (7:3) ethyl acetate in *n*-hexane as an eluent to afford 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)acetamide (**5**, 12.6 mmol, 40%) as a gummy solid.

Step-3: To a suspension of LiAlH₄ (6.18 g, 163 mmol) in dry THF (200 mL) at 0 °C was added AlCl₃ (6.27 g, 47 mmol) portion wise under nitrogen atmosphere. The contents were stirred for 15 min at room temperature, reaction mixture was re-cooled to 0 °C, and a solution of 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)acetamide (**5**, 10 mmol) in 100 mL of dry THF was added. The reaction mixture was stirred for 5 h at room temperature, after completion of reaction, reaction mixture was quenched with saturated Na₂SO₄ solution, filtered through sodium sulphate bed and washed with ethyl acetate. The combined organic layers were washed with water, saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography over 100-200 mesh silica gel using (1:9) methanol in dichloromethane as an eluent to afford 4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (**6**, 6.3 mmol, 63%) as a brown colour solid.

Step-4: To a stirred solution of **6** (1.07 mmol) in DMF (10 mL) were added at 0 °C, (*E*)-4-bromo-*N,N*-dimethylbut-2-enamide (**7**, 1.6 mmol) and DIPEA (0.18 mL, 1.28 mmol). The reaction mixture was stirred for 2 h at 23 °C, was diluted with cold water (50 mL) extracted with dichloromethane. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 3% methanol in dichloromethane to afford *E/Z* mixture, which was then separated by HPLC with a chiral column to give a pure desired isomer **8** (0.45 mmol, 28.3%).

Scheme 2:



Step-1: Zinc dust (31 g, 473 mmol) was suspended in dry THF (100 mL) and cooled this suspension to -10°C . To this TiCl_4 (44 g, 230 mmol) was added slowly under nitrogen atmosphere, stirred there for 15 min, slowly allowed it to reach room temperature and heated to reflux for 2 h. The resulting mixture was cooled to 0°C , and a solution of **1b** (59.2 mmol) and propiophenone (**2**, 176 mmol) in dry THF (80 mL) were added and the contents were refluxed for 2.5 h. The reaction mixture was cooled to room temperature and quenched with 10% aqueous K_2CO_3 solution and was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated. The crude material was purified by column chromatography over 230-400 mesh silica using (2:8) ethyl acetate in *n*-hexane to afford **3b** (49 mmol, 83 %) as a colorless solid.

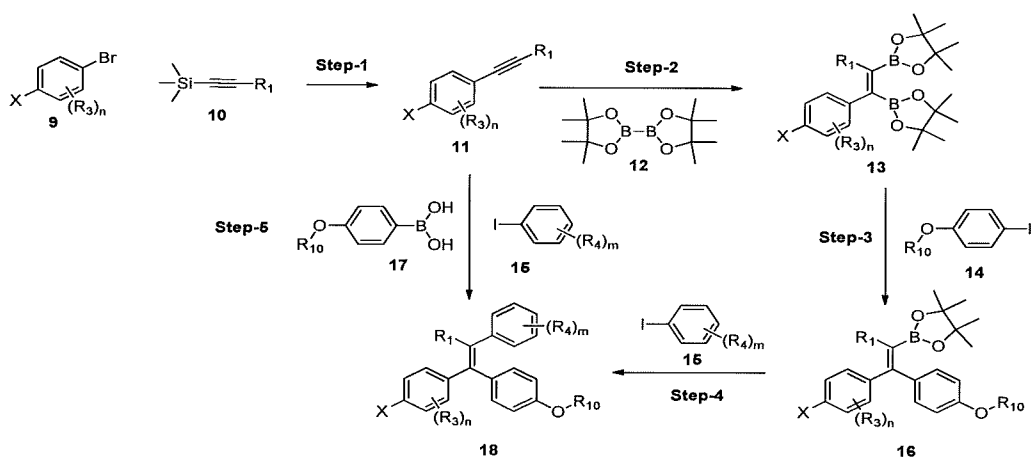
Step-2: To a solution of **3b** (17 mmol) in acetonitrile (140 mL) was added potassium carbonate (7.1 g, 51 mmol) and 1-bromo-2-chloro ethane (**4b**, 34 mmol). The reaction mixture was heated to 80°C and maintained at this temperature for 24 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate (500 mL x 2). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using (5:95) ethyl acetate in *n*-hexane to afford **5b** (8.9 mmol, 52.5%) as a colourless gum.

Step-3: To a suspension of **5b** (8 mmol) in methanol (100 mL) was added 40 % aq. methylamine (150 mL). The reaction mixture was heated at 80°C for 16 h in a sealed tube, cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate and the organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford **6b** (7.0 mmol, 87.8 %) as a pale yellow gummy mass.

Step-4: To a stirred solution of **6b** (1.29 mmol) in dichloromethane (36 mL) was added BBr₃ (1M solution in dichloromethane, 2.6 mL, 2.59 mmol) at -78 °C. The reaction mixture was stirred for 0.5 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the benzylated **6c** (1.17 mmol, 91 %) as a gummy mass.

Step-5: To a stirred solution of **6c** (1.07 mmol) in DMF (10 mL) were added at 0 °C, (*E*)-4-bromo-N,N-dimethylbut-2-enamide (**7**, 1.6 mmol) and DIPEA (0.18 mL, 1.28 mmol). The reaction mixture was stirred for 2 h at 23 °C, was diluted with cold water (50 mL) extracted with dichloromethane. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 3% methanol in dichloromethane to afford *E/Z* mixture of **8b**, which was further purified by chiral HPLC to give the desired pure isomer **8b** (0.30 mmol, 28.3%).

Scheme 3:



Step-1: To a stirred solution of **9** (10.989 mmol) in 30 mL of MeOH:DMA:H₂O (1:1:1) in a sealed tube, were added copper iodide (0.235 g, 1.098 mmol) and cesium carbonate (4.849 g, 15.3 mmol) at 23 °C. This mixture was degassed with three vacuum/N₂ cycles, and were added **10** (22 mmol) followed by Pd(PPh₃)₂Cl₂ (0.384 g, 0.5 mmol). The pressure tube was sealed and heated at 90 °C for 12 h. Upon completion by TLC, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 X 50 mL). The combined organic extracts were washed with water, brine, dried over sodium sulphate and concentrated. The crude product was purified over 230-400 mesh silica column chromatography using 5% EtOAc in *n*-hexane to afford **11** (9.67 mmol, 88%) as a white solid.

Step-2: To a stirred solution of **11** (73.9 mmol) in 2-methyl THF (136 mL), was added bis(pinacolato) diboron (22.52 g, 88.6 mmol), tetrakis(triphenylphosphine)platinum(0) (919 mg, 0.739 mmol) under nitrogen atmosphere, reaction mixture was heated at 90 °C for 5 h. After completion of reaction, reaction mixture was diluted with water and extracted with EtOAc. The Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. to afford **13** (56 mmol, 76%).

Step-3: To a stirred solution of **13** (12.74 mmol), 4-iodophenol (**14**, 10.61 mmol), bis(triphenylphosphine)palladium(II) dichloride (372 mg, 0.530 mmol), cesium carbonate (6.9 g, 21.23 mmol) and 2-methyl THF (60 mL) were added. This mixture was degassed with nitrogen and water (5 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, reaction mixture was diluted with water and extracted with EtOAc. The Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using MeOH in dichloromethane (1.6:98.4) to afford **16** (5.47 mmol, 43%).

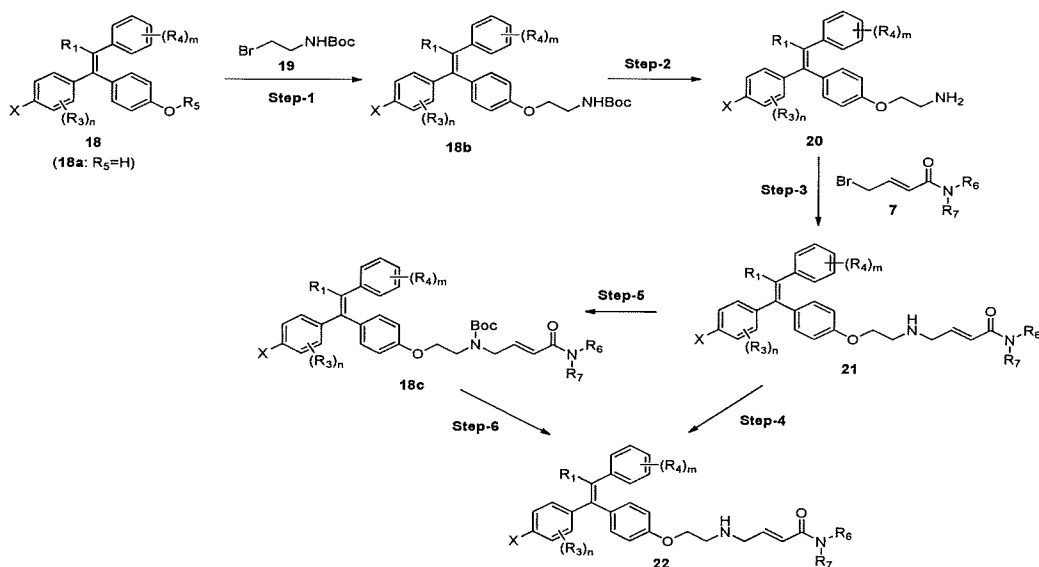
Step-4: To a stirred solution of **16** (1.8 mmol) in 2-methyl THF (30 mL), iodobenzene (**15**, 1.8 mmol), 4M aqueous KOH (5 mL) and Pd(PPh₃)₂Cl₂ (63 mg, 0.09 mmol) were added and the mixture was degassed with nitrogen for 15 min and heated at 90 °C for 8 h. Upon completion, the reaction mixture was diluted with EtOAc. Organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was purified by silica gel chromatography (2:8 EtOAc in *n*-hexane) to give a desired product (**18**, 0.74 mmol, 41%).

Combined Step-2, Step-3 and Step-4: To a stirred solution of **11** (13.78 mmol) in 2-methyl THF (30 mL), was added bis(pinacolato)diboron (**12**, 3.53 g, 13.94 mmol), tetrakis(triphenylphosphine)platinum(0) (130 mg, 0.104 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 10 h. The solution was allowed to cool to 23 °C and iodobenzene **14** (13.78 mmol), bis(triphenylphosphine)palladium (II) dichloride (483 mg, 0.68 mmol), cesium carbonate (8.9 g, 27.55 mmol) and 2-methyl THF (30 mL) were added. This mixture was degassed with nitrogen and water (10 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (10 mL) and iodobenzene **15** (19.28 mmol) were added. Reaction mixture was stirred at 80 °C for 7 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous

sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using EtOAc in *n*-hexane (2.5:7.5) to afford **18** (11.2 mmol, 81 %) as a white solid.

Step-5: To a solution of **11** (6.09 mmol), iodobenzene (**15**, 18.29 mmol), phenyl boronic acid (**17**, 18.29 mmol), in *N,N*-dimethyl formamide/water (2:1, 15 mL) was added K₂CO₃ (2.52 g, 18.29 mmol). The contents were degassed with three vacuum/N₂ cycles, and then stirred for 1 h until the solution was homogeneous. A solution of Pd(PhCN)₂Cl₂ (0.022 g, 0.0609 mmol) in *N,N*-dimethyl formamide (1 mL) was added and the resulting mixture was stirred at 45 °C for 12 h. Upon completion by TLC, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, brine, dried over sodium sulphate and concentrated. The crude material was purified over 230-400 mesh silica column chromatography using 20% ethyl acetate in *n*-hexane to afford **18** (8.6 mmol, 47%) as an off-white solid.

Scheme 4:



Step-1: To a solution of **18a** (3.4 mmol) in DMF (30 mL), at 0 °C, were added sequentially potassium carbonate (1.4 g, 10.1 mmol) and *tert*-butyl (2-bromoethyl)carbamate (**19**, 8.5 mmol). The reaction mixture was stirred at 80 °C for 16 h, was diluted with ethyl acetate, washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 15% ethyl acetate in *n*-hexane to afford the desired product (**18b**, 1.8 mmol, 53%) as a light brown colour gummy mass.

Step-2: To a stirred solution of **18b** (2.5 mmol) in ethanol (10 mL) was added at 0 °C, 2M HCl in ether (10 mL). The reaction mixture was stirred for 16 h at 23 °C. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with 10% MeOH in dichloromethane. Organic layer was concentrated under reduced pressure and the crude material was purified by column chromatography over 230-400 mesh silica gel using (4-5%) MeOH in DCM to afford the desire product (**20**, 1.25 mmol, 50%) as a brown coloured semi solid.

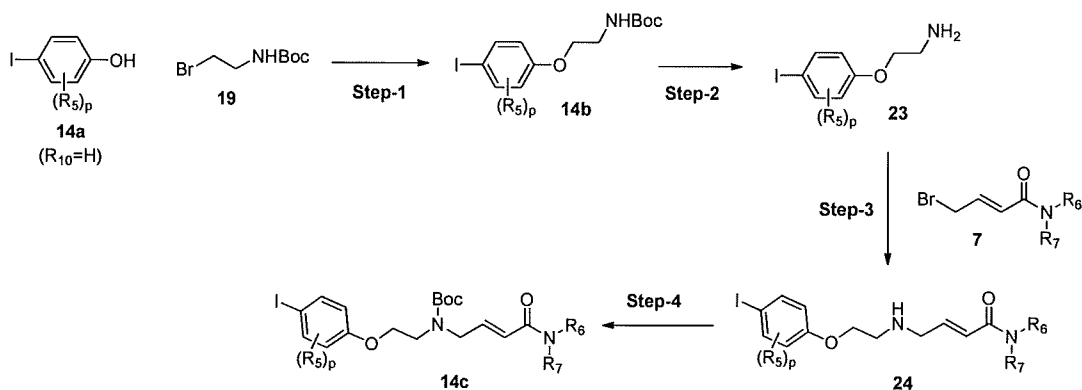
Step-3: To a stirred solution of **20** (1.24 mmol) in DMF (5 mL) was added at 0 °C, (*E*)-4-bromo-*N,N*-dimethylbut-2-enamide (**7**, 1.24 mmol) and DIPEA (0.321 g, 2.49 mmol). The reaction mixture was stirred for 48 h at 23 °C, was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a crude mixture of **21**.

Step-4: The crude material obtained from previous step was purified by preparative HPLC to afford pure isomer **22** (0.06 mmol, 5%) as a white solid. The ¹H NMR, HPLC and MS data were collected.

Step-5: To a stirred solution of **21** (1.25 mmol) in DCM (10 mL) was added di-tert-butyl dicarbonate (0.546 g, 2.5 mmol). The reaction mixture was stirred for 1 h at 23 °C, after completion of reaction, reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Crude compound was purified by column chromatography using 2% MeOH in DCM to afford **18c** (0.63 mmol, 50%) as a light brown semi-solid.

Step-6: To a stirred solution of **18c** (0.622 mmol) in MeOH (5 mL) was added at 0 °C, 2M HCl in ether (10 mL). The reaction mixture was stirred for 16 h at 23 °C. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with 10% MeOH in DCM. Organic layer was concentrated under reduced pressure to obtain crude compound (**15**, 0.07 mmol) as an off-white solid. Crude compound was purified by preparative HPLC to afford desired pure isomer (**22**, 0.03 mmol, 4.1%) as an white solid. The ¹H NMR, HPLC and MS data were collected.

Scheme 5:



Step-1: To a stirred solution of 4-iodophenol (**14a**, 227 mmol) in DMF (750 mL) was added potassium carbonate (188 g, 1.363 mol) and stirred for 30 min at 23 °C, to the above mixture tert-butyl (2-bromoethyl)carbamate (**19**, 71.27 g, 318 mmol) was added. The contents were stirred at 70 °C for 12 h. After completion of reaction, reaction mixture was poured onto ice cold water, solid separated was filtered and dried under reduced pressure to obtain desired compound tert-butyl (2-(4-iodophenoxy)ethyl)carbamate as an off-white solid (**14b**, 220 mmol, 97%).

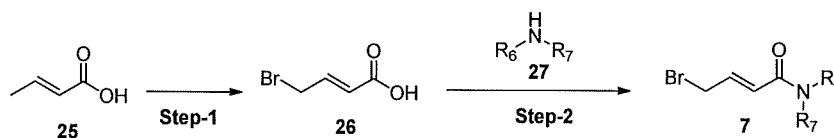
Step-2: To a stirred solution of **14b** (68.6 mmol) in ethanol (50 mL) was added at 0 °C, 2M HCl in ether (250 mL). The reaction mixture was stirred for 12 h at 23 °C. After completion of reaction, reaction mixture was basified with saturated NaHCO_3 , extracted with 10% MeOH in DCM. Organic layer was concentrated under reduced pressure and the crude material was used in next step without further purification (**23**, 60 mmol, 88%).

Step-3: To a stirred solution of **23** (60.6 mmol) in DMF (65 mL) was added at 0 °C, 4-bromo-*N,N*-dimethylbut-2-enamide (**7**, 42.4 mmol) and DIPEA (11.72 g, 90.9 mmol). The reaction mixture was stirred for 5 h at room temperature, was diluted with cold water (250 mL) and extracted with dichloromethane. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (**24**, 50 mmol, 83%, crude).

Step-4: To a stirred solution of **24** (50.26 mmol) in dry dichloromethane (150 mL) was added DIPEA (6.4g, 50.2 mmol) at 0 °C, stirred for 15 min at 0 °C. To the above reaction mixture, was added di-*tert*-butyl dicarbonate (13.1 g, 60.3 mmol), resulting mixture was stirred at 23 °C for 12 h. Upon completion by TLC, the reaction mixture was cooled to 0 °C, quenched with ice cold water (500 mL) and extracted with dichloromethane (500 mL). The combined organic extracts were washed with water, followed by brine, dried over anhydrous sodium

sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica using 3% MeOH in dichloromethane as an eluent to afford **14c** (19 mmol, 37.8%).

Scheme 6:

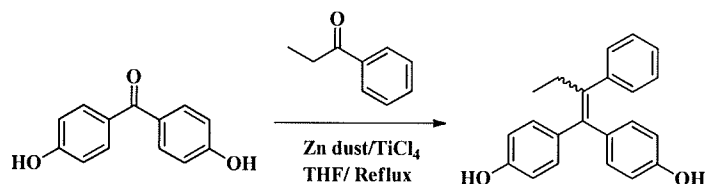


Step-1: To a stirred solution of but-2-enoic acid (**25**, 116.0 mmol) in benzene (150 mL) was added *N*-Bromo succinamide (31.4 g, 120.0 mmol) followed by Benzoyl peroxide (0.200 g, 1.4 mmol) at 23 °C. The reaction mixture was heated to reflux for 4 h, which resulted in precipitation of succinamide crystals. The crystals were filtered off and the filtrate was concentrated. The crude was recrystallized with minimum amount of hexane and washed with hexane to afford 4-bromobut-2-enoic acid (**26**, 42.5 mmol, 37 %) as a white solid.

Step-2: bromobut-2-enoic acid (**26**, 9 mmol) was taken in dichloromethane (30 mL) and cooled to 0 °C. To this solution oxalyl chloride (1.6 mL, 18 mmol), DMF (0.1 mL) were added and stirred for 0.5 h at 23 °C. The reaction mixture was concentrated under nitrogen atmosphere, residue was diluted with THF (30 mL), cooled to 0 °C and was basified with DIPEA (3.1 mL, 18 mmol). To this mixture, an amine (**27**, 9 mmol) was added slowly as a solution in dichloromethane and the contents were stirred at 23 °C for 1h. The volatiles were removed by concentration under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated. The crude material was purified by column chromatography over 230-400 mesh silica gel using 3-7% ethyl acetate in hexane to afford the desired amide (**7**, 0.85 mmol, 9.4%) as a brown colour liquid.

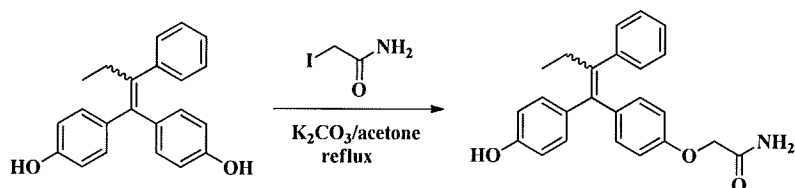
Example 1: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of 4,4'-(2-phenylbut-1-ene-1,1-diyl)diphenol



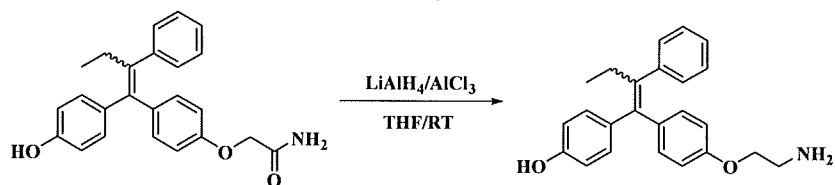
To a suspension of zinc dust (36.6 g, 560 mmol) in dry THF (200 mL) at -10 °C was added TiCl₄ (50.4 g, 266 mmol) under nitrogen atmosphere. The contents were stirred there for 15 min, slowly allowed to warm to room temperature and heated to reflux for 2 h. The resulting mixture was cooled to 0 °C and a solution of bis(4-hydroxyphenyl)methanone (10 g, 46.7 mmol) and propiophenone (18.7 g, 140 mmol) in dry THF (20 mL) was added and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was cooled to room temperature and quenched with saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate (500 mL x 3), the combined organic layers were washed with water, saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified over 230-400 mesh silica gel column chromatography using (3:7) ethyl acetate in *n*-hexane to afford 4,4'-(2-phenylbut-1-ene-1,1-diyl)diphenol (12.6 g, 85%) as a brown colour solid.

Step-2: Synthesis of 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy) acetamide



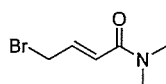
To a stirred solution of 4,4'-(2-phenylbut-1-ene-1,1-diyl)diphenol (10 g, 31.6 mmol) in acetone (100 mL) was added K₂CO₃ (13.0 g, 94.8 mmol) at room temperature and the contents were heated at 80 °C for 15 min. To this mixture, a solution of 2-iodoacetamide (6.6 g, 34.8 mmol) in 50 mL of acetone was added slowly over a period of 3 h at 80 °C and the contents were stirred for 1 h at 80 °C. The reaction mixture was diluted with cold water (100 mL), extracted with ethyl acetate, organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using (7:3) ethyl acetate in *n*-hexane an eluent to afford 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)acetamide (4.8 g, 40%) as a gummy solid.

Step-3: Synthesis of 4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol



To a suspension of LiAlH₄ (6.18 g, 163 mmol) in dry THF (200 mL) at 0 °C was added AlCl₃ (6.27 g, 47 mmol) portion wise under nitrogen atmosphere. The contents were stirred for 15 min at room temperature, reaction mixture was re-cooled to 0 °C, and a solution of 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)- acetamide (4 g, 10 mmol) in 100 mL of dry THF was added. The reaction mixture was stirred for 5 h at room temperature, after completion of reaction, reaction mixture was quenched with saturated Na₂SO₄ solution, filtered through sodium sulphate bed and washed with ethyl acetate. The combined organic layers were washed with water, saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography over 100-200 mesh silica gel using (1:9) methanol in dichloromethane as an eluent to afford 4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (2.45 g, 63%) as a brown colour solid.

Step-4: *Synthesis of (E)-4-bromo-N,N-dimethylbut-2-enamide*

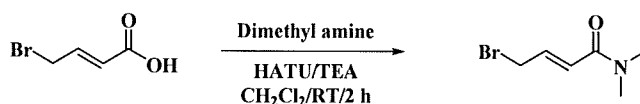


Step-4.1: *Synthesis of (E)-4-bromobut-2-enoic acid*



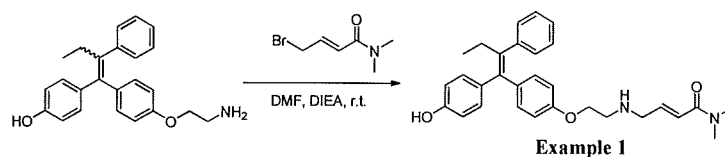
To a stirred solution of (E)-but-2-enoic acid (10.0 g, 116.0 mmol) in benzene (150 mL) was added N-Bromosuccinamide (31.4 g, 120.0 mmol) followed by Benzoyl peroxide (0.200 g, 1.4 mmol) at 23 °C. The reaction mixture was heated to reflux for 4 h, which resulted in precipitation of succinamide crystals. The crystals were filtered off and the filtrate was concentrated. The crude was recrystallized with minimum amount of hexane and washed with hexane to afford (E)-4-bromobut-2-enoic acid (6.97 g, 37 %) as a white solid.

Step-4.2: *Synthesis of (E)-4-bromo-N,N-dimethylbut-2-enamide*



(*E*)-4-bromobut-2-enoic acid (2 g, 12.2 mmol) was taken in dichloromethane (20 mL) and at 0 °C were added HATU (5.5 g, 14 mmol), triethyl amine (2.56 mL, 18.4 mmol) and stirred for 10 min at RT. To this mixture *N,N*-dimethyl amine (9.2 mL, 18 mmol) was added slowly and the contents were stirred at room temperature for 2 h. The volatiles were removed under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated. The crude material was purified by column chromatography over 100-200 silica gel using 20% ethyl acetate in *n*-hexane to afford (*E*)-4-bromo-*N,N*-dimethylbut-2-enamide (0.4 g, 17 %) as a pale green colour liquid. MS (ESI) 192 [M+H]⁺

Step-5: Synthesis of (*E*)-4-((2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (Example 1)

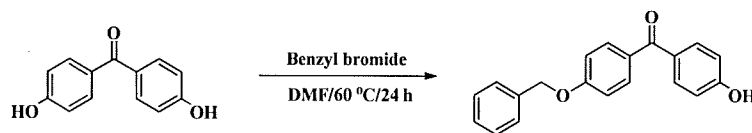


A solution of 4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (200 mg, 0.56 mmol) and 4-bromo-but-2-enoic acid dimethylamide (110 mg, 0.56 mmol) in DMF (5 mL) was added DIEA (85 mg, 0.67 mmol). The resulting mixture was stirred at room temperature for 0.5 hours. LC-MS showed that the reaction was completed. Concentration and the residue was purified by Prep-HPLC to give a mixture of cis and trans isomers (21 mg, yield: 9%). The sample was combined with last batch and further separated by SFC to afford (*E*)-4-((2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (5.1 mg)

Example 1: ¹H-NMR (400 MHz, MeOH-d₄) δ 7.16-7.01 (m, 7H), 6.80-6.64 (m, 5H), 6.61-6.58 (m, 3H), 3.99 (t, 2H), 3.50 (t, 2H), 3.11 (s, 3H), 2.99-2.94 (m, 5H), 2.50 (q, 2H), 0.92 (t, 3H); MS (ESI) 471 [M+H]⁺.

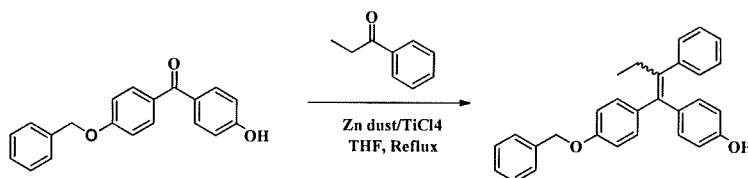
Example 2: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy) ethyl)(methyl)amino)-N-methyl-N-(6,6,7,7,7-pentafluoroheptyl) but-2-enamide

Step-1: Synthesis of 4-(Benzyloxyphenyl) (4-hydroxyphenyl) methanone



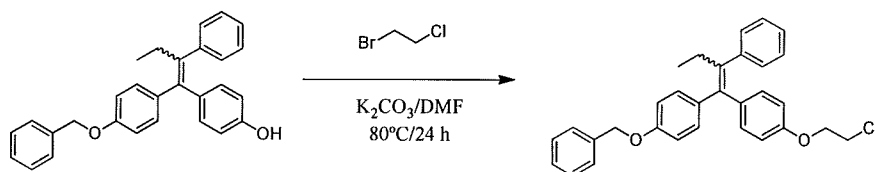
To a solution of bis (4-hydroxyphenyl)methanone (50 g, 234 mmol) in DMF (500 mL), were added potassium carbonate (35 g, 252 mmol) and benzyl bromide (43 g, 255 mmol) sequentially at 0 °C. The resulting mixture was heated at 60 °C for 24 h and the completion of the reaction monitored by TLC. The reaction mixture was cooled to room temperature, quenched by adding crushed ice (100 g) and stirred for 10 min. The precipitated solid was filtered, washed with ice cold water and dried under vacuum to afford 4-(benzyloxyphenyl)(4-hydroxyphenyl) methanone (18 g, 25 %) as an off-white solid.

Step-2: Synthesis of 4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenol



The same procedure as described in Scheme 2, Step-1, to afford 4-(1-(4-(benzyloxy) phenyl)-2-phenylbut-1-en-1-yl)phenol (20 g, 83 %) as a colorless solid.

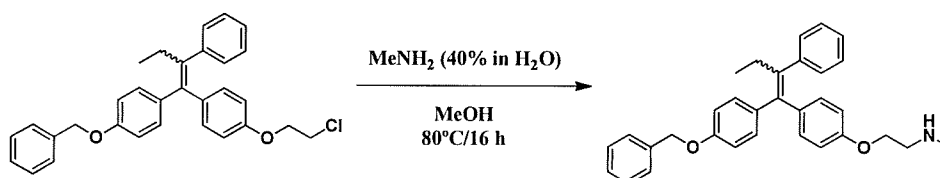
Step-3: Synthesis of 1-(Benzyloxy)-4-(1-(4-(2-chloroethoxy)phenyl)-2-phenylbut- 1-en-1-yl)benzene



To a solution of 4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (7 g, 17 mmol) in acetonitrile (140 mL) was added potassium carbonate (7.1 g, 51 mmol) and 1-bromo-2-chloroethane (2.9 mL, 34 mmol). The reaction mixture was heated to 80 °C and maintained at

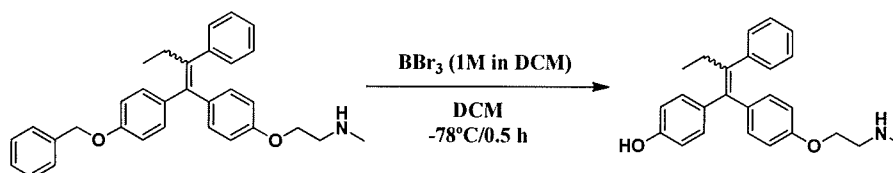
this temperature for 24 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate (500 mL x 2). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using (5:95) ethyl acetate in *n*-hexane to afford 1-(benzyloxy)-4-(1-(4-(2-chloroethoxy)phenyl)-2-phenylbut-1-en-1-yl)benzene (4.2 g, 52.5%) as a colourless gum.

Step-4: Synthesis of 2-(4-(1-(4-(benzyloxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy) -N-methylethan-1-amine



To a suspension of 1-(benzyloxy)-4-(1-(4-(2-chloroethoxyphenyl)-2-phenylbut-1-en-1-yl)benzene (4.2 g, 8 mmol) in methanol (100 mL) was added 40 % aq. methyl amine (150 mL). The reaction mixture was heated at 80 °C for 16 h in a sealed tube, cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate and the organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 2-(4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)-N-methylethan-1-amine (3.6 g, 87.8 %) as a pale yellow gummy mass.

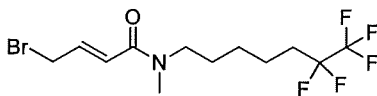
Step-5: Synthesis of 4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol



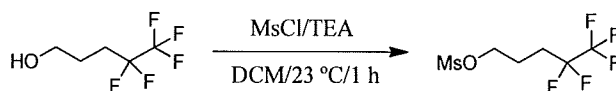
To a stirred solution of 2-(4-(1-(4-(benzyloxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy) -N-methylethan-1-amine (0.6 g, 1.29 mmol) in dichloromethane (36 mL) was added BBr₃ (1M solution in DCM, 2.6 mL, 2.59 mmol) at -78 °C. The reaction mixture was stirred for 0.5 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced

pressure to afford 4-(1-(4-(2-(methylamino) ethyl) phenyl)-2-phenylbut-1-en-1-yl)phenol (0.44 g, 91 %) as a gummy mass.

Step-6: Synthesis of (E)-4-bromo-N-methyl-N-(6,6,7,7,7-pentafluoroheptyl)but-2-enamide

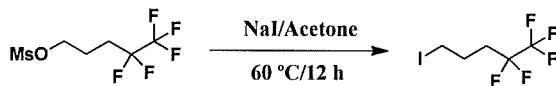


Step-6.1: Synthesis of 4,4,5,5,5-pentafluoropentyl methanesulfonate



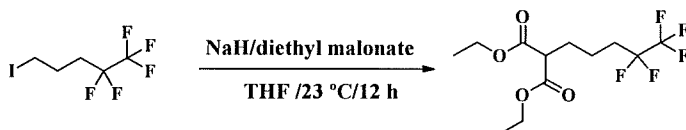
To a stirred solution of 4,4,5,5,5-pentafluoropentanol (7.5 g, 42.13 mmol) in dichloromethane (100 mL) at 0 °C was added triethylamine (7.1 mL, 50.56 mmol) and methane sulfonyl chloride (3.53 mL, 46.34 mmol). The reaction mixture was stirred for 1 h at RT and diluted with dichloromethane. The organic layer was washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 4,4,5,5,5-pentafluoropentyl methanesulfonate (6.0 g, 56%) as a brown colour liquid.

Step-6.2: Synthesis of 1,1,1,2,2-pentafluoro-5-iodopentane



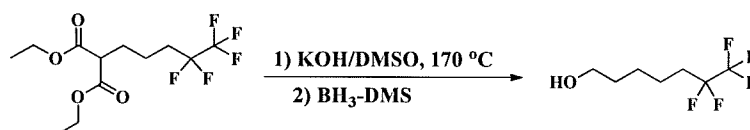
Sodiumiodide (9.7 g, 64.45 mmol) was added to a solution of 4,4,5,5,5-pentafluoropentyl methanesulfonate (6.0 g, 23.43 mmol) in acetone (100 mL) and the contents were heated under reflux for 12 h. After completion of reaction, the reaction mixture was filtered and was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and was washed with water, brine solution and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give 1,1,1,2,2-pentafluoro-5-iodopentane (4.8 g, 71.6%).

Step-6.3: Synthesis of diethyl 2-(4,4,5,5,5-pentafluoropentyl)malonate

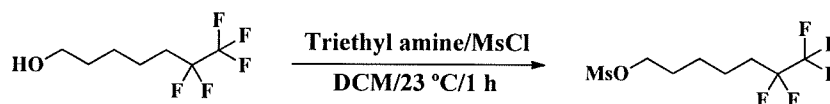


Sodium hydride (1.07 g, 29.9 mmol) was taken in anhydrous THF (50 mL) and at 0 °C, diethylmalonate (4.8 mL, 33.3 mmol) was added dropwise and the contents were stirred for 1 h at room temperature. 1,1,1,2,2-pentafluoro-5-iodopentane (4.8 g, 16.6 mmol) dissolved in anhydrous THF was then added drop wise to this reaction mixture and the reaction was continued for 12 h at room temperature. Water was added to the reaction mixture and extracted twice with ethyl acetate. The combined organic layer was washed with saturated sodium chloride solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by 230-400 mesh silica gel column chromatography and elution with ethyl acetate/*n*-hexane, 1:40 gave the desired Diethyl 2-(4,4,5,5,5-pentafluoropentyl) malonate (5.0 g, 90 %).

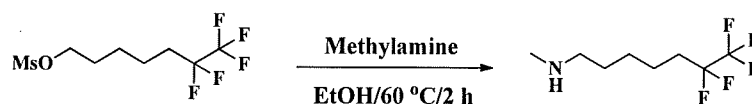
Step-6.4: Synthesis of 6,6,7,7,7-pentafluoroheptan-1-ol



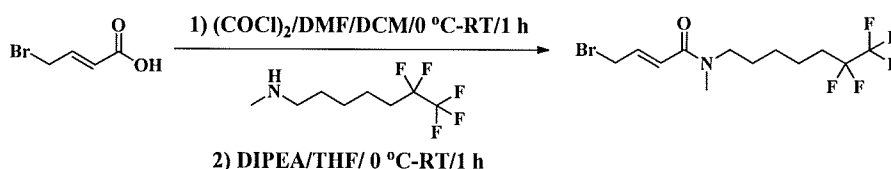
A solution of potassium hydroxide (18.2 g, 325.0 mmol), in water (25 mL) was added to a solution of diethyl 2-(4,4,5,5,5-pentafluoropentyl)malonate (5.0 g, 16.25 mmol) and the contents were stirred at 60 °C for 16 h. The reaction mixture was adjusted to pH 5 by slowly adding 1N HCl drop wise, and then extracted with ethyl acetate. The combined organics were washed with brine solution, dried over sodium sulphate and concentrated under reduced pressure. The residue was dissolved in dimethylsulphoxide (20 mL), and stirred at 170 °C for 18 h. Water was added to the reaction mixture and was then extracted three times with ethyl acetate. The combined organic layers were washed with water followed by brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (20 mL), cooled to -30 °C and borane-methyl sulphide complex (0.96 g, 9.69 mmol) was added drop wise and the contents were stirred for 3 h at room temperature. The reaction was quenched with methanol, water was added to the reaction mixture and was extracted twice with ethyl acetate. The combined organic layers were washed with water followed by brine solution and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue was purified over 230-400 mesh silica gel column chromatography. Elution of the column with (1:20) ethyl acetate/*n*-hexane as an eluent afforded 6,6,7,7,7-pentafluoroheptan-1-ol (1.1 g, 78% over 2 steps).

Step-6.5: Synthesis of 6,6,7,7,7-pentafluoroheptylmethanesulfonate

To a stirred solution of 6,6,7,7,7-pentafluoroheptan-1-ol (1.1 g, 5.04 mmol) in dichloromethane (20 mL) at 0 °C was added triethylamine (1.06 mL, 7.50 mmol) and methanesulfonyl chloride (0.53 mL, 5.54 mmol). The reaction mixture was stirred for 1 h at RT and diluted with dichloromethane. The organic layer was washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated to afford 6,6,7,7,7-pentafluoroheptylmethanesulfonate (1.2 g, 83.9%) as a brown colour liquid.

Step-6.6: Synthesis of 6,6,7,7,7-pentafluoro-N-methylheptan-1-amine

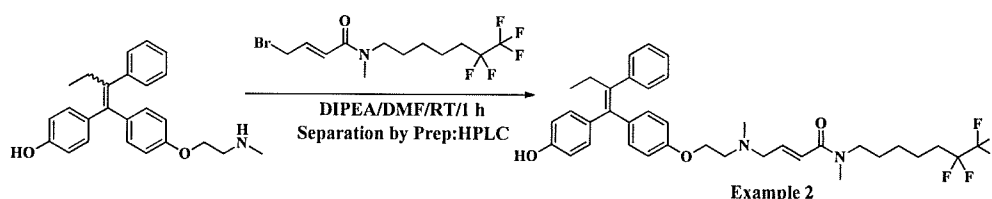
A solution of 6,6,7,7,7-pentafluoroheptylmethanesulfonate (0.23 g, 0.80 mmol) in ethanol (10 mL) was added aqueous 40% methylamine (5 mL). The contents were heated at 60 °C under nitrogen for 2 h. After completion of reaction, reaction mixture was cooled to room temperature, the volatiles removed under vacuum and extracted with dichloromethane (30 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulphate to give 6,6,7,7,7-pentafluoro-N-methylheptan-1-amine, organic layer was directly used for next step.

Step-6.7: Synthesis of (E)-4-bromo-N-methyl-N-(6,6,7,7,7-pentafluoroheptyl)but-2-enamide

To a solution of (E)-4-bromobut-2-enoic acid (0.180 g, 1.08 mmol, **Example 1**, Step-4.1) in dichloromethane (10 mL) at 0 °C were added oxalyl chloride (0.188 mL, 2.18 mmol) and DMF (0.1 mL) and the contents were stirred for 0.5 h at RT. The reaction mixture was concentrated under nitrogen atmosphere, residue was diluted with dichloromethane (10 mL)

and was added to a mixture of 6,6,7,7,7-Pentafluoro- *N*-methylheptan-1-amine (0.17 g, 0.776 mmol) and DIPEA (0.74 mL, 2.18 mmol) in dichloromethane. The reaction mixture was stirred at 0 °C, for 30 min and was diluted with water and extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified over 230-400 mesh silica gel column chromatography using ethyl acetate/*n*-hexane (1:20) to give (*E*)-4-bromo-*N*-methyl-*N*-(6,6,7,7,7-pentafluoroheptyl)but-2-enamide (0.14 g, 52 %).

Step-7: Synthesis of (*E*)-4-((2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) (methyl)amino)-*N*-methyl-*N*-(6,6,7,7,7-pentafluoroheptyl)but-2-enamide (Example 2).

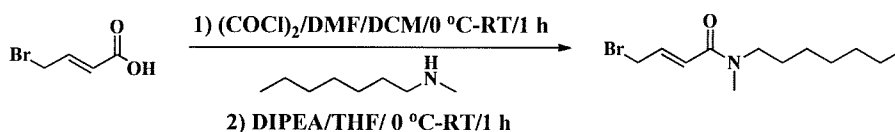


To a stirred solution of 4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (0.240 g, 0.6434 mmol) in DMF (5 mL) at room temperature were added (*E*)-4-bromo-*N*-methyl-*N*-(6,6,7,7,7-pentafluoroheptyl)but-2-enamide (0.235 g, 0.6438 mmol) and DIPEA (0.332 mL, 1.930 mmol) at RT. The reaction mixture was stirred for 1 h at room temperature and was diluted with dichloromethane (50 mL), washed with water, brine, dried over anhydrous sodium sulphate and concentrated. The crude was purified by column chromatography over 230-400 mesh silica gel, using (2:98) methanol in DCM to afford *E/Z* mixture of products, which was further purified by chiral HPLC to give pure isomer (*E*)-4-((2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)(methyl)amino)-*N*-methyl-*N*-(6,6,7,7,7-pentafluoroheptyl)but-2-enamide (0.200 g, 42%) as a gummy solid.

Example 2: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.42 (s, 1H), 7.18-7.06 (m, 5H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.74-6.68 (m, 4H), 6.57-6.52 (m, 4H), 3.90 (t, *J* = 4.8 Hz, 2H), 3.30 (s, 2H), 3.15 (d, *J* = 4.8 Hz, 2H), 2.96 (s, 1H), 2.82 (s, 2H), 2.66-2.61 (m, 2H), 2.39 (q, *J* = 7.3 Hz, 2H), 2.19 (s, 5H), 1.51-1.47 (m, 4H), 1.31-1.22 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). ES (MS) 659.3 [M+H]⁺.

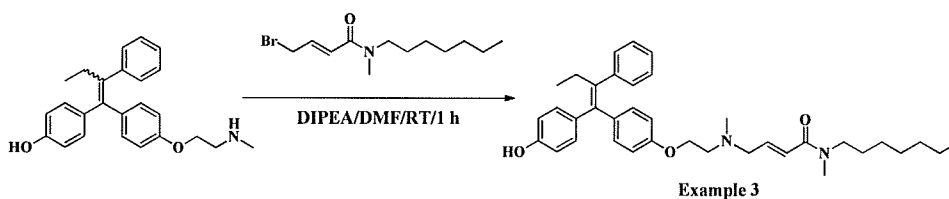
Example 3: Synthesis of (E)-N-heptyl-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy) ethyl)(methyl)amino)-N-methylbut-2-enamide

Step-1: Synthesis of (E)-4-bromo-N-heptyl-N-methylbut-2-enamide



The reaction was carried out according to Scheme 6, Step-2, using (E)-4-bromobut-2-enoic acid (**Example 1**, Step-4.1) and N-methylheptan-1-amine, to give (E)-4-bromo-N-heptyl-N-methylbut-2-enamide (0.55 g, 43%).

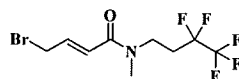
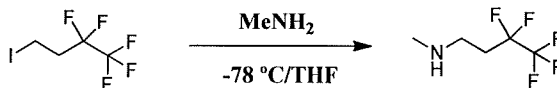
Step-2: Synthesis of (E)-N-heptyl-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)(methyl)amino)-N-methylbut-2-enamide (Example 3).



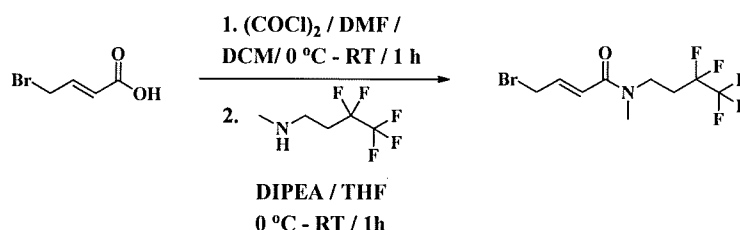
The reaction was carried out according to Scheme 2, Step-5, using (E)-4-bromobut-2-enoic acid (**Example 1**, Step-4.1), to give a crude product, which was purified by preparative HPLC to afford E/Z mixture, which was then purified by chiral HPLC to give a pure isomer of (E)-N-heptyl-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)(methyl)amino)-N-methylbut-2-enamide (0.09 g, 30 %) as a light brown colour sticky solid.

Example 3: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.40 (s, 1H), 7.18-7.07 (m, 5H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.58-6.53 (m, 4H), 3.90 (t, *J* = 5.0 Hz, 2H), 3.16 (d, *J* = 4.8 Hz, 2H), 2.95 (s, 1H), 2.90 (d, *J* = 7.2 Hz, 1H), 2.82 (s, 2H), 2.67-2.62 (m, 1H), 2.43-2.39 (m, 2H), 2.20 (s, 3H), 1.45-1.43 (m, 2H), 1.23-1.13 (m, 10H), 0.86-0.80 (m, 6H). ES (MS) 568.4 [M+H]⁺.

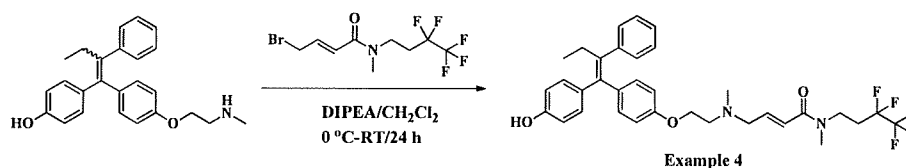
Example 4: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy) ethyl) (methyl)amino)-N-methyl-N-(3,3,4,4,4-pentafluorobutyl)but-2-enamide

Step-1: Synthesis of (E)-4-bromo-N-methyl-N-(3,3,4,4,4-pentafluorobutyl)but-2-enamide**Step-1.1: Synthesis of 3,3,4,4,4-pentafluoro-N-methylbutan-1-amine**

To a stirred solution of 1,1,1,2,2-pentafluoro-4-iodobutane (5 g, 18 mmol) in THF (25 mL) at -78 °C was added methyl amine (2M in THF, 18 mL, 36 mmol). The reaction mixture was slowly allowed to attain room temperature and stirred for 16 h at RT. The reaction mixture was diluted with dichloromethane (70 mL), washed with water (50 mL X 3) and dried over sodium sulphate and filtered. The resulting solution was directly used for next reaction (Note: Here the DCM solution of compound should be stored below 8 °C).

Step-1.2: Synthesis of 4-bromo-N-methyl-N-(3,3,4,4,4-pentafluorobutyl)but-2-enamide

The reaction was carried out according Scheme 6, Step-2, using (E)-4-bromobut-2-enoic acid (**Example 1**, Step-4.1) to afford 4-bromo-N-methyl-N-(3,3,4,4,4-pentafluorobutyl)but-2-enamide (0.26 g, 9.4%) as a brown colour liquid.

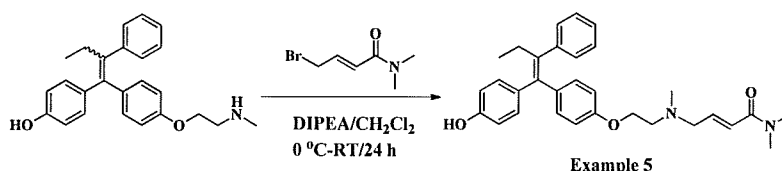
Step-2: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) (methylamino)-N-methyl-N-(3,3,4,4,4-pentafluorobutyl)but-2-enamide (Example 4)

The same procedure as described in Scheme 2, Step-5, using 4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (**Example 2**, Step-5), to give a

mixture, which was separated by chiral HPLC to give a pure isomer (0.13 g, 26.3%) as a light brown colour sticky solid.

Example 4: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.39 (s, 1H), 9.14 (s, 1H), 7.16 (d, $J = 6.8$ Hz, 4H), 7.08 (d, $J = 8.8$ Hz, 8H), 6.98-6.91 (m, 4H), 6.75-6.63 (m, 4H), 6.60-6.55 (m, 8H), 6.39 (d, $J = 8.4$ Hz, 2H), 4.07 (s, 2H), 3.91 (s, 2H), 3.70-3.56 (m, 4H), 3.24 (d, $J = 5.2$ Hz, 2H), 3.17 (d, $J = 5.2$ Hz, 2H), 3.05 (d, $J = 9.2$ Hz, 4H), 2.97 (d, $J = 5.6$ Hz, 2H), 2.74 (s, 2H), 2.65 (d, $J = 8.8$ Hz, 4H), 2.43-2.33 (m, 6H), 2.27-2.20 (s, 6H), 0.84 (t, $J = 7.2$ Hz, 6H). ES (MS) 617 $[\text{M}+\text{H}]^+$.

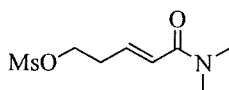
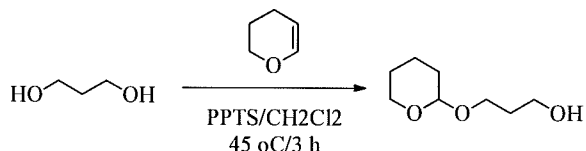
Example 5: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) (methyl)amino)-N,N-dimethylbut-2-enamide



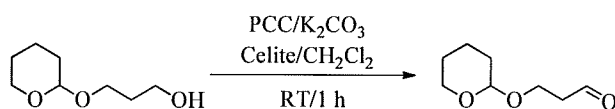
The same procedure as described in Scheme 2, Step-5, using 4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (**Example 2**, Step-5) and (E)-4-bromo-N,N-dimethylbut-2-enamide (**Example 1**, Step-4.2), to give (2E)-4-((2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)-ethyl)(methyl)- amino)-N,N-dimethylbut-2-enamide (0.15 g, 28.3 %).

Example 5: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.40 (s, 1H), 9.14 (s, 1H), 7.19-7.07 (m, 12H), 6.98-6.91 (m, 4H), 6.69-6.60 (m, 4H), 6.59-6.55 (m, 8H), 6.39 (d, $J = 8.0$ Hz, 2H), 4.07 (t, $J = 5.6$ Hz, 2H), 3.91 (t, $J = 5.6$ Hz, 2H), 3.23-3.15 (m, 4H), 3.02 (s, 3H), 2.99 (s, 3H), 2.86-2.81 (m, 6H), 2.73 (t, $J = 5.6$ Hz, 2H), 2.63 (t, $J = 5.6$ Hz, 2H), 2.43-2.36 (m, 4H), 2.27-2.20 (bs, 6H), 0.84 (t, $J = 7.2$ Hz, 6H). ES (MS) 485 $[\text{M}+\text{H}]^+$.

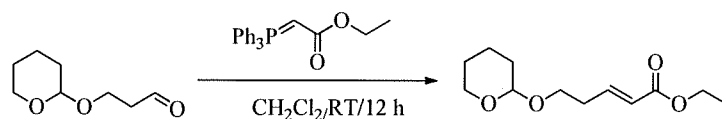
Example 6: Synthesis of (E)-5-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) amino)-N,N-dimethylpent-2-enamide

Step-1: Synthesis of (E)-5-(dimethylamino)-5-oxopent-3-en-1-yl**Step-1.1: Synthesis of 3-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol**

To a stirred solution of 1,3-propanediol (88 g, 1190 mmol) and dihydropyran (20 g, 238 mmol) in dichloromethane (200 mL) was added PPTS (100 mg) at 0 °C, mixture was stirred at room temperature for 3 h. After completion of reaction, reaction mixture was diluted with cold water (250 mL) and extracted with dichloromethane (500 mL), organic layer was washed with water, saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was used in next step without further purification (20 g, crude).

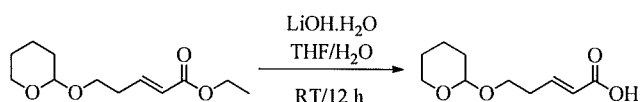
Step-1.2: Synthesis of 3-((tetrahydro-2H-pyran-2-yl)oxy)propanal

To a stirred solution of 3-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (20 g, 125 mmol) in dichloromethane (200 mL), PCC (40 g, 187.5 mmol), K₂CO₃ (8.6 g, 62.5 mmol) and celite (10 g) were added at 0 °C, mixture was stirred at room temperature for 1 h. After completion of reaction, reaction mixture was filtered through celite, filtrate was diluted with cold water (250 mL) and extracted with dichloromethane (500 mL), organic layer was washed with saturated NaCl solution and dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The crude material was used in next step without further purification (9 g, crude).

Step-1.3: Synthesis of ethyl (E)-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-enoate

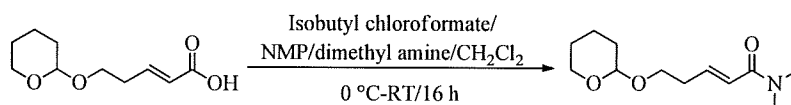
To a stirred solution of 3-((tetrahydro-2H-pyran-2-yl)oxy)propanal (4.5 g, 28.6 mmol) in dichloromethane (100 mL), ethyl-2-(triphenyl-15-phosphanylidene)acetate (9.9 g, 28.6 mmol) was added. Reaction mixture was stirred at room temperature for 12 h. After completion of reaction, reaction mixture was concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica using (5:95) ethyl acetate in *n*-hexane as an eluent to afford title compound (4.6 g, 70%).

Step-1.4: Synthesis of (E)-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-enoic acid



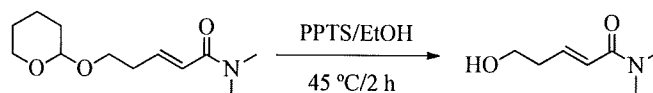
To a solution of ethyl (E)-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-enoate (4.6 g, 20.8 mmol) in THF/H₂O (75:25) (45 mL) at 0 °C, was added LiOH·H₂O (4.2 g, 100 mmol). The reaction mixture was stirred for 12 h at room temperature. After completion of reaction, reaction mixture was concentrated under reduced pressure. Crude compound was diluted with water, acidified with acetic acid then extracted with ethyl acetate. Organic layer was washed with saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford desired compound, which was used in next step without further purification (4 g crude).

Step-1.5: Synthesis of (E)-N,N-dimethyl-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-enamide



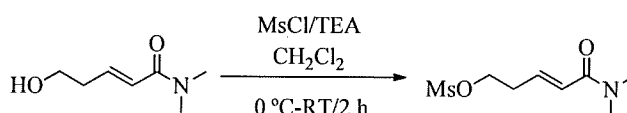
To a solution of (E)-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-enoic acid (4 g, 20 mmol) in dichloromethane (50 mL) at 0 °C were added NMP (2.4 mL, 22 mmol) followed by isobutyl chloroformate (2.86 mL, 22 mmol) and the contents were stirred for 1 h at 0 °C. To the above mixture dimethyl amine (25 mL, 50 mmol) was added at 0 °C, reaction mixture was stirred at RT for 16 h. After completion of reaction, diluted with water and extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified over 230-400 mesh silica gel column chromatography using ethyl acetate in *n*-hexane (1:1) to give title compound (1.7 g, 37 %).

Step-1.6: Synthesis of (E)-5-hydroxy-N,N-dimethylpent-2-enamide



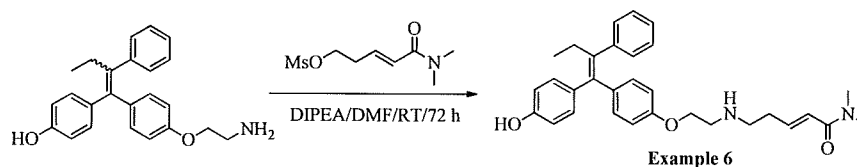
To a stirred solution of (*E*)-*N,N*-dimethyl-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-enamide (1.7 g, 7.48 mmol) in ethanol (50 mL) was added at 0 °C, PPTS (281 mg, 1.123 mmol). The reaction mixture was stirred for 2 h at RT. After completion of reaction, diluted with water and extracted with EtOAc (50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was used in next step without further purification (0.9 g, 84%).

Step-1.7: Synthesis of (*E*)-5-(dimethylamino)-5-oxopent-3-en-1-yl methanesulfonate



To a stirred solution of (*E*)-5-hydroxy-*N,N*-dimethylpent-2-enamide (0.9 g, 6.29 mmol) in dichloromethane (20 mL) at 0 °C was added triethylamine (1.06 mL, 7.54 mmol) and methanesulfonyl chloride (0.53 mL, 6.99 mmol). The reaction mixture was stirred for 1 h at room temperature and diluted with dichloromethane. The organic layer was washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford (*E*)-5-(dimethylamino)-5-oxopent-3-en-1-yl methanesulfonate (0.9 g, 79%).

Step-2: Synthesis of (*E*)-5-((2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylpent-2-enamide (Example 6)



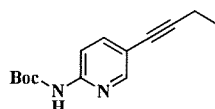
A solution of (*E*)-5-(dimethylamino)-5-oxopent-3-en-1-yl methanesulfonate (0.9 g, 4.07 mmol) in DMF (15 mL) was added DIPEA (1.45 mL). To the above mixture 4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (1.46 g, 4.07 mmol, **Example 1**, Step-3) was added. The contents were stirred at 23 °C under nitrogen for 72 h. After completion of reaction, reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulphate to give crude (*E*)-5-((2-(4-((*Z*)-1-(4-

hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylpent-2-enamide, which was purified by preparative HPLC (12 mg, 0.6%).

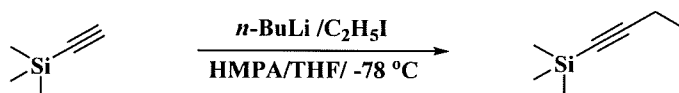
Example 6: ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.40 (s, 1H), 7.20-6.97 (m, 7H), 6.76-6.56 (m, 7H), 6.40 (d, $J = 8.0$ Hz, 1H), 3.85 (t, $J = 5.6$ Hz, 2H), 3.02 (s, 3H), 2.99 (s, 3H), 2.79 (t, $J = 5.6$ Hz, 2H), 2.65 (t, $J = 5.6$ Hz, 2H), 2.40 (t, $J = 5.6$ Hz, 2H), 2.33 (t, $J = 5.6$ Hz, 2H), 0.84 (t, $J = 7.2$ Hz, 3H). ES (MS): 485 $[\text{M}+\text{H}]^+$.

Example-7: Synthesis of (*E*)-4-((2-(4-((*E*)-1-(6-aminopyridin-3-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) amino)-*N,N*-dimethylbut-2-enamide

Step-1: Synthesis of tert-butyl (5-(but-1-yn-1-yl)pyridin-2-yl)carbamate

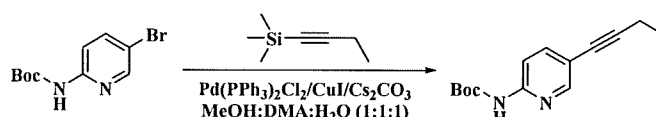


Step-1.1: Synthesis of but-1-yn-1-yltrimethylsilane:



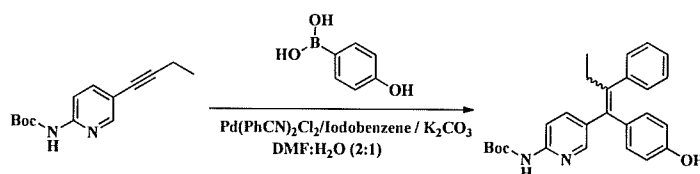
To a stirred solution of (trimethylsilyl)acetylene (116 g, 1.19 mol) in dry THF (400 mL) was added *n*-BuLi (2.5M in THF, 500 mL) at -78°C over 2 h. The resulting mixture was warmed to 0°C for 10 min. The reaction mixture was again cooled to -78°C , HMPA (234 g, 1.13 mol) was added to the above mixture and stirred at -78°C for 30 min. To the above reaction mixture iodoethane (200 g, 1.28 mol) was added and the resulting mixture was stirred at room temperature for 16 h. After completion of reaction, the reaction mixture was quenched with water, extracted with ethyl acetate (1000 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The product but-1-yn-1-yltrimethylsilane was distilled between $125-135^\circ\text{C}$ to afford the desired product (91 g, 61 %) as a colourless liquid.

Step-1.2: Synthesis of tert-butyl (5-(but-1-yn-1-yl)pyridin-2-yl)carbamate



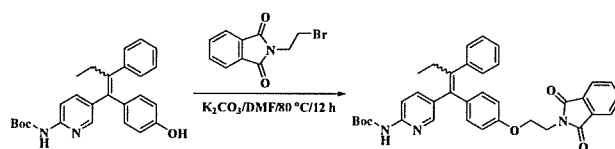
To a stirred solution of tert-butyl (5-bromopyridin-2-yl)carbamate (3 g, 10.989 mmol) in 30 mL of MeOH:DMA:H₂O (1:1:1) in a sealed tube, were added copper iodide (0.235 g, 1.098 mmol) and cesium carbonate (4.849 g, 15.3 mmol) at room temperature. This mixture was degassed with three vacuum/N₂ cycles, and were added but-1-yn-1-yltrimethylsilane (2.76 g, 22 mmol) followed by Pd(PPh₃)₂Cl₂ (0.384 g, 0.5 mmol). The pressure tube was sealed and heated at 90 °C for 12 h. Upon completion by TLC, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 X 50 mL). The combined organic extracts were washed with water, brine, dried over sodium sulphate and concentrated. The crude product was purified over 230-400 mesh silica column chromatography using 5% EtOAc in *n*-hexane to afford tert-butyl (5-(but-1-yn-1-yl)pyridin-2-yl)carbamate (2.5 g, 88%) as a white solid.

Step-2: *Synthesis of tert-butyl (E)-(5-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate*



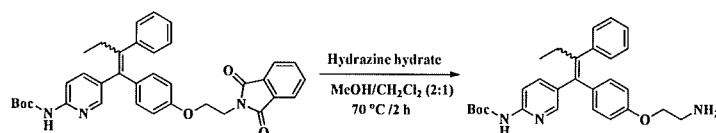
To a solution of tert-butyl (5-(but-1-yn-1-yl)pyridin-2-yl)carbamate (1.5 g, 6.09 mmol), iodobenzene (3.73 g, 18.29 mmol), 4-hydroxyphenyl boronic acid (2.52 g, 18.29 mmol), in *N,N*-dimethyl formamide/water (2:1, 15 mL) was added K₂CO₃ (2.52 g, 18.29 mmol). The contents were degassed with three vacuum/N₂ cycles, and then stirred for 1 h until the solution was homogeneous. A solution of Pd(PhCN)₂Cl₂ (0.022 g, 0.0609 mmol) in *N,N*-dimethyl formamide (1 mL) was added and the resulting mixture was stirred at 45 °C for 12 h. Upon completion by TLC, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, brine, dried over sodium sulphate and concentrated. The crude material was purified over 230-400 mesh silica column chromatography using 20% ethyl acetate in *n*-hexane to afford tert-butyl (E)-(5-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (1.2 g, 47%) as an off-white solid.

Step-3: *Synthesis of tert-butyl (E)-(5-(1-(4-(2-(1,3-dioxoisindolin-2-yl)ethoxy)-phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate*



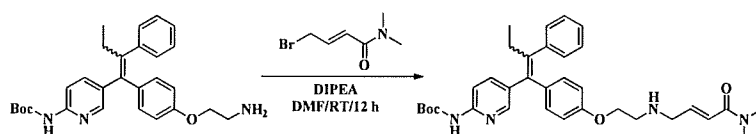
To a solution of *(E)*-(5-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.5 g, 1.2 mmol) in DMF (12 mL), at 0 °C, were added sequentially potassium carbonate (0.663 g, 4.8 mmol) and 2-(2-bromoethyl)isoindoline-1,3-dione (1.52 g, 6 mmol). The reaction mixture was stirred at 80 °C for 12 h, was diluted with ethyl acetate, washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 20% ethyl acetate in *n*-hexane to afford tert-butyl *(E)*-(5-(1-(4-(2-(1,3-dioxoisindolin-2-yl)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)-pyridin-2-yl)carbamate (0.35 g, 50%) as a light brown colour gummy mass.

Step-4: Synthesis of tert-butyl *(E)*-(5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate



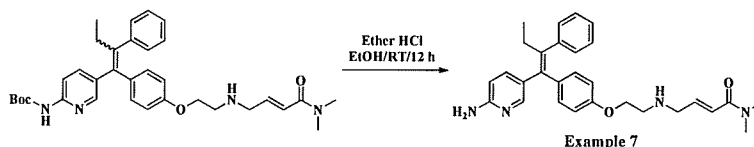
To a solution of *(E)*-(5-(1-(4-(2-(1,3-dioxoisindolin-2-yl)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.5 g, 0.8488 mmol) in MeOH/DCM (2:1, 15 mL) was added hydrazine hydrate (10 mL) at room temperature. The reaction mixture was stirred at 70 °C for 2 h, quenched with NH₄OH and extracted with dichloromethane. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 100-200 mesh silica gel using 10% methanol in DCM to afford tert-butyl *(E)*-(5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.12 g, 30%) as an off-white solid.

Step-5: Synthesis of tert-butyl (5-((*E*)-1-(4-(2-(((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)amino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate



To a stirred solution of tert-butyl (*E*)-(5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.120 g, 0.261 mmol) in DMF (10 mL) was added at 0 °C, (*E*)-4-bromo-*N,N*-dimethylbut-2-enamide (0.05 g, 0.261 mmol, **Example 1**, Step-4.2) and DIPEA (0.068 g, 0.522 mmol). The reaction mixture was stirred for 12 h at 23 °C, after completion of reaction, reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 100-200 mesh silica gel using 5% methanol in DCM to afford tert-butyl (5-((*E*)-1-(4-(2-(((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)amino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.05 g, 33%) as an off-white solid.

Step-6: Synthesis of (*E*)-4-((2-(4-((*E*)-1-(6-aminopyridin-3-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) amino)-*N,N*-dimethylbut-2-enamide (**Example 7**)

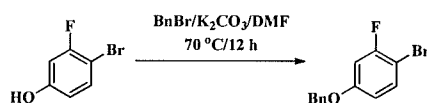


To a stirred solution of tert-butyl (5-(1-(4-(2-(((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)amino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.1 g, 0.176 mmol) in ethanol (5 mL) was added at 0 °C, 2M HCl in ether (10 mL). The reaction mixture was stirred for 12 h at room temperature. After completion of reaction, reaction mixture was basified with sat. NaHCO₃, extracted with 10% MeOH in DCM. Organic layer was concentrated under reduced pressure and the crude material was purified by preparative HPLC to afford (*E*)-4-((2-(4-((*E*)-1-(6-aminopyridin-3-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) amino)-*N,N*-dimethylbut-2-enamide (37 mg, 45%) as a white solid.

Example 7: ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.78 (d, *J* = 2 Hz, 1H), 7.19-7.15 (m, 2H), 7.11-7.07 (m, 4H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.57-6.51 (m, 2H), 6.43 (d, *J* = 8.4 Hz, 1H), 5.95 (s, 2H), 3.89 (d, *J* = 5.6 Hz, 2H), 3.36 (d, *J* = 4.8 Hz, 2H), 3.0 (s, 3H), 2.85 (s, 3H), 2.82-2.81 (m, 2H), 2.46-2.42 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H). ES (MS): 471.2 [M+H]⁺.

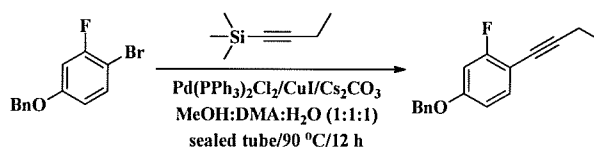
Example-8: Synthesis of (E)-4-((2-(4-((E)-1-(2-fluoro-4-hydroxyphenyl)-2-phenyl but-1-en-1-yl)phenoxy) ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of 4-(benzyloxy)-1-bromo-2-fluorobenzene



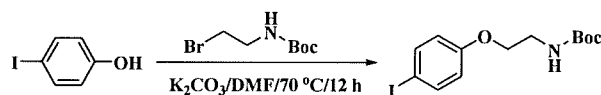
To a solution of 4-bromo-3-fluorophenol (3 g, 15.7 mmol) in DMF (15 mL), were added potassium carbonate (4.3 g, 31.41 mmol) and benzyl bromide (3.2 g, 18.8 mmol) sequentially at room temperature. The resulting mixture was heated at 70 °C for 12 h, completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure. The crude compound was purified over 230-400 mesh silica gel column chromatography using 10% EtOAc in *n*-hexane to afford 4-(benzyloxy)-1-bromo-2-fluorobenzene (4 g, 90%) as brown colour oil.

Step-2: Synthesis of 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-fluorobenzene



The reaction was carried out according to Scheme 3, Step-1, using but-1-yn-1-yltrimethylsilane (**Example 7**, Step-1.1) to afford 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-fluorobenzene (6.5 g, 94%) as brown oil.

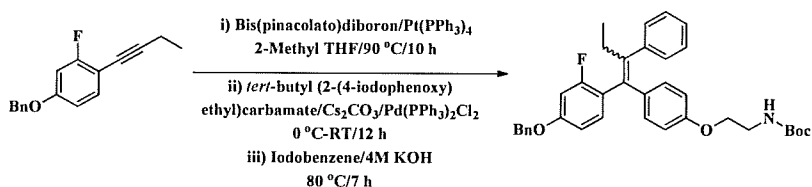
Step-3: Synthesis of tert-butyl (2-(4-iodophenoxy)ethyl)carbamate



To a stirred solution of 4-iodophenol (50 g, 0.227 mol) in DMF (750 mL) was added potassium carbonate (188 g, 1.363 mol) and stirred for 30 min at room temperature, to the above mixture tert-butyl (2-bromoethyl)carbamate (71.27 g, 0.318 mol) was added. The contents were stirred at 70 °C for 12 h. After completion of reaction, reaction mixture was poured onto ice cold water, solid separated was filtered and dried under reduced pressure to

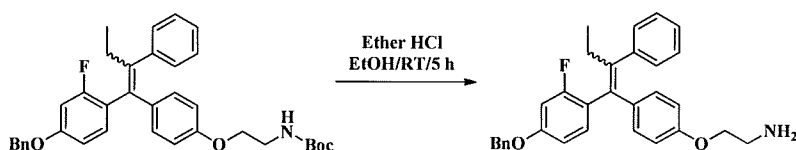
obtain desired compound tert-butyl (2-(4-iodophenoxy)ethyl)carbamate as an off-white solid (80 g, 97%).

Step-4: Synthesis of tert-butyl (2-(4-(1-(4-(benzyloxy)-2-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-fluorobenzene (3.5 g, 13.78 mmol) in 2-methyl THF (30 mL), was added bis(pinacolato)diboron (3.53 g, 13.94 mmol), tetrakis(triphenylphosphine)platinum(0) (130 mg, 0.104 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 10 h. The solution was allowed to cool to room temperature and *tert*-butyl (2-(4-iodophenoxy)ethyl)carbamate (5 g, 13.78 mmol), bis(triphenylphosphine)palladium (II) dichloride (483 mg, 0.68 mmol), cesium carbonate (8.9 g, 27.55 mmol) and 2-methyl THF (30 mL) were added. This mixture was degassed with nitrogen and water (10 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (10 mL) and iodobenzene (3.9 g, 19.28 mmol) were added. Reaction mixture was stirred at 80 °C for 7 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using EtOAc in *n*-hexane (2.5:7.5) to afford *tert*-butyl (2-(4-(1-(4-(benzyloxy)-2-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (6.1 g, 81 %) as a white solid.

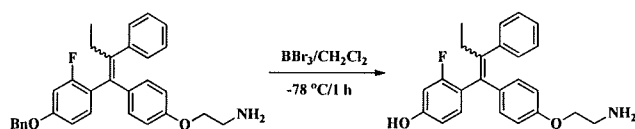
Step-5: Synthesis of 2-(4-(1-(4-(benzyloxy)-2-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine



To a stirred solution of *tert*-butyl (2-(4-(1-(4-(benzyloxy)-2-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (11.5 g, 20.2 mmol) in ethanol (40 mL) was added at 0 °C, 2M

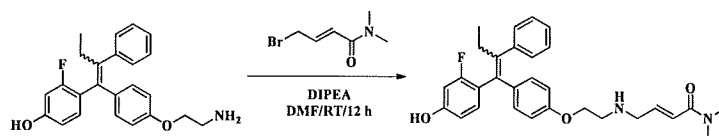
HCl in ether (120 mL). The reaction mixture was stirred for 5 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO_3 , extracted with 10% MeOH in dichloromethane. Organic layer was concentrated under reduced pressure and the crude material was purified by column chromatography over 230-400 mesh silica gel using (1:9) MeOH in dichloromethane to afford 2-(4-(1-(4-(benzyloxy)-2-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (9 g, 95%) as a brown colour oil.

Step-6: Synthesis of 4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-fluorophenol



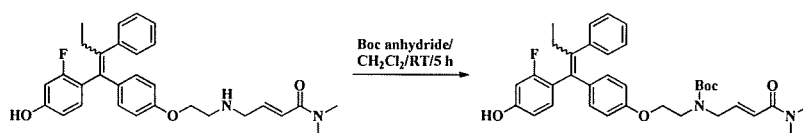
To a stirred solution of 2-(4-(1-(4-(benzyloxy)-2-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (4.5 g, 9.6 mmol) in dichloromethane (45 mL) was added BBr_3 (1M solution in dichloromethane, 48 mL, 48 mmol) at -78°C . The reaction mixture was stirred for 0.5 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-fluorophenol (2.2 g, 61%) as a light brown solid.

Step-7: Synthesis of (2E)-4-((2-(4-(1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy) ethyl)amino)-N,N-dimethylbut-2-enamide



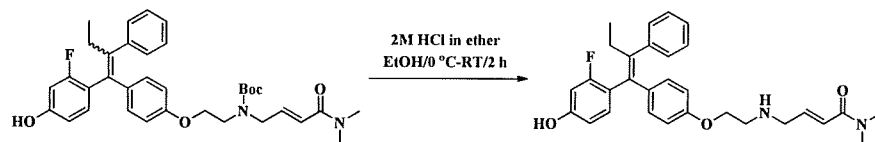
The reaction was carried out according to Scheme 4, Step-3, using (E)-4-bromo-N,N-dimethylbut-2-enamide (**Example 1**, Step-4.2) to give a crude product, which was used in next step without further purification (4.5 g, crude).

Step-8: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-(1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (2*E*)-4-((2-(4-(1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (4.5 g, 9.2 mmol) in dichloromethane (50 mL) was added boc anhydride (2.4 g, 11 mmol). The reaction mixture was stirred for 5 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by column chromatography over 230-400 mesh silica gel using (1:9) MeOH in dichloromethane to obtain tert-butyl ((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-(1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.21 g, 3.8%) as a light brown fluffy solid.

Step-9: Synthesis of (*E*)-4-((2-(4-((*E*)-1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (Example 8)

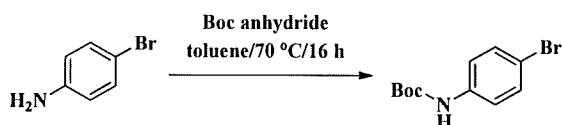


To a stirred solution of tert-butyl ((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-(1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.21 g, 3.5 mmol) in EtOH (1 mL) was added at 0 °C, 2M HCl in diethyl ether (4 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative TLC to afford desired compound (*E*)-4-((2-(4-((*E*)-1-(2-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (40 mg, 22.9%) as an off-white solid.

Example 8: ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.86 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.14-7.04 (m, 4H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.65-6.55 (m, 5H), 6.5 (d, *J* = 15.2 Hz, 1H), 3.87 (t, *J* = 5.6 Hz, 2H), 2.99 (s, 3H), 2.85 (s, 3H), 2.77 (t, *J* = 5.6, 2H), 2.5 (m, 2H), 2.3-2.28 (m, 2H), 0.79 (t, *J* = 7.6 Hz, 3H). LCMS: 489.3 [M+H]⁺.

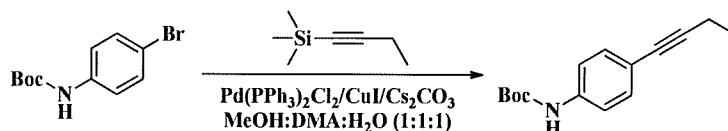
Example-9: Synthesis of (E)-4-((2-(4-((Z)-1-(4-aminophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl) amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of tert-butyl (4-bromophenyl)carbamate



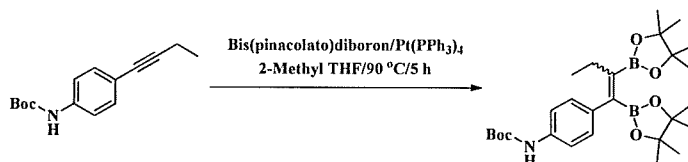
To a stirred solution of 4-bromoaniline (10 g, 58 mmol) in toluene (200 mL) was added boc anhydride (12.6 g, 58 mmol). The reaction mixture was stirred for 16 h at 70 °C, after completion of reaction (monitored by TLC), excess of toluene was removed under reduced pressure. Residue was diluted with water (250 mL) solid obtained was filtered and dried under reduced pressure to obtain desired compound (10.2 g, 64%).

Step-2: Synthesis of tert-butyl (4-(but-1-yn-1-yl)phenyl)carbamate



The same procedure as described in Scheme 3, Step-1, using but-1-yn-1-yltrimethylsilane (**Example 7**, Step-1.1) to afford tert-butyl (4-(but-1-yn-1-yl)phenyl)carbamate (3.5 g, 77%).

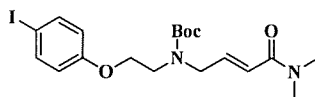
Step-3: Synthesis of tert-butyl (4-(1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenyl)carbamate



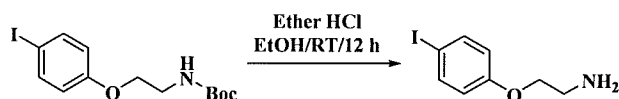
To a stirred solution of tert-butyl (4-(but-1-yn-1-yl)phenyl)carbamate (3 g, 12 mmol) in 2-methyl THF (30 mL), was added bis(pinacolato)diboron (3.1 g, 12 mmol), tetrakis(triphenylphosphine)platinum(0) (152 mg, 0.01 mmol) under nitrogen atmosphere, reaction mixture was heated at 90 °C for 5 h. After completion of reaction, reaction mixture was diluted with water and extracted with EtOAc. The Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 15% EtOAc in *n*-

hexane to afford tert-butyl (4-(1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenyl)carbamate (3.5 g, 57%).

Step-4: Synthesis of tert-butyl (E)-(4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-iodophenoxy) ethyl)carbamate

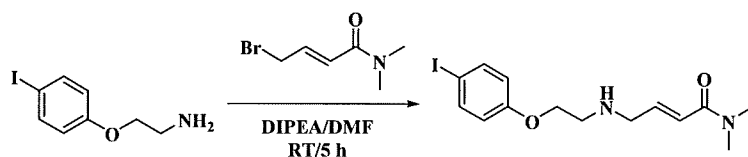


Step-4.1: Synthesis of 2-(4-iodophenoxy)ethan-1-amine



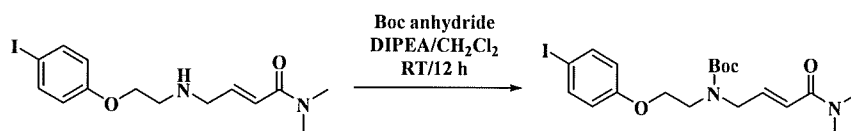
To a stirred solution of tert-butyl (2-(4-iodophenoxy)ethyl)carbamate (25 g, 68.6 mmol, **Example 8**, Step-3) in ethanol (50 mL) was added at 0 °C, 2M HCl in ether (250 mL). The reaction mixture was stirred for 12 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with 10% MeOH in DCM. Organic layer was concentrated under reduced pressure and the crude material was used in next step without further purification (16 g, 88%).

Step-4.2: Synthesis of (E)-4-((2-(4-iodophenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



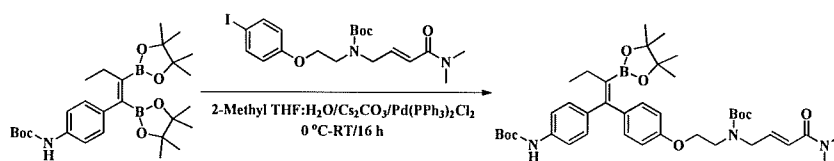
To a stirred solution of 2-(4-iodophenoxy)ethan-1-amine (16 g, 60.6 mmol) in DMF (65 mL) was added at 0 °C, (E)-4-bromo-N,N-dimethylbut-2-enamide (8.1 g, 42.4 mmol, **Example-1**, Step-4.2) and DIPEA (11.72 g, 90.9 mmol). The reaction mixture was stirred for 5 h at room temperature, was diluted with cold water (250 mL) and extracted with dichloromethane. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (18.8 g, crude).

Step-4.3: Synthesis of tert-butyl (E)-(4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-iodophenoxy) ethyl)carbamate



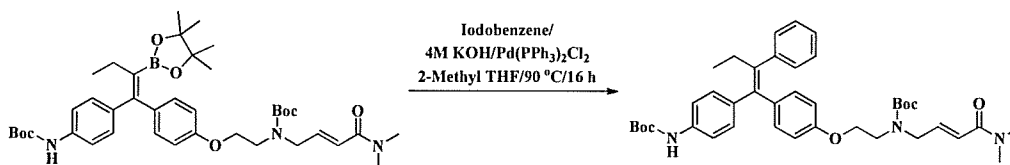
To a stirred solution of (*E*)-4-((2-(4-iodophenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (18.8 g, 50.26 mmol) in dry dichloromethane (150 mL) was added DIPEA (6.4g, 50.2 mmol) at 0 °C, stirred for 15 min at 0 °C. To the above reaction mixture, was added boc anhydride (13.1 g, 60.3 mmol), resulting mixture was stirred at room temperature for 12 h. Upon completion by TLC, the reaction mixture was cooled to 0 °C, quenched with ice cold water (500 mL) and extracted with dichloromethane (500 mL). The combined organic extracts were washed with water, followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica using 3% MeOH in dichloromethane as an eluent to afford tert-butyl (*E*)-(4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-iodophenoxy)ethyl)carbamate (9 g, 37.8%).

Step-5: *Synthesis of tert-butyl (2-(4-(1-(4-((tert-butoxycarbonyl)amino)phenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl) carbamate*



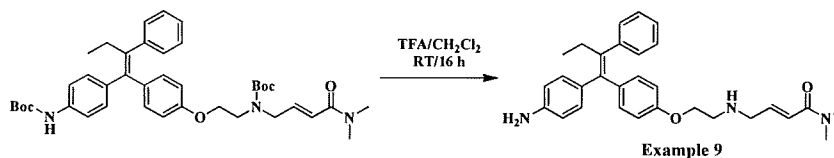
To a stirred solution tert-butyl (4-(1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenyl)carbamate (2 g, 4 mmol), tert-butyl (*E*)-(4-(dimethyl amino)-4-oxobut-2-en-1-yl)(2-(4-iodophenoxy)ethyl)carbamate (1.89 g, 4 mmol), bis(triphenylphosphine)palladium(II) dichloride (140 mg, 0.2 mmol), cesium carbonate (2.6 g, 8 mmol) and 2-methyl THF (20 mL) were added, degassed with nitrogen and water (0.2 mL) was added. The reaction mixture was stirred at room temperature for 16 h. After completion of reaction, reaction mixture was diluted with water and extracted with EtOAc. The Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (2.8 g, crude).

Step-6: *Synthesis of tert-butyl (2-(4-(1-(4-((tert-butoxycarbonyl)amino)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate*



To a stirred solution of tert-butyl (2-(4-(1-(4-((tert-butoxycarbonyl)amino)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (2.8 g, 3 mmol) in 2-methyl THF (20 mL), iodobenzene (794 mg, 3 mmol), 4M aqueous KOH (2 mL) and Pd(PPh₃)₂Cl₂ (136 mg, 0.1 mmol) were added and the mixture was degassed with nitrogen for 15 min and heated at 90 °C for 16 h. Upon completion, the reaction mixture was diluted with EtOAc. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (2:8 EtOAc in *n*-hexane) to give title compound (0.55 g, 21%).

Step-7: Synthesis of (E)-4-((2-(4-((Z)-1-(4-aminophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (Example 9)

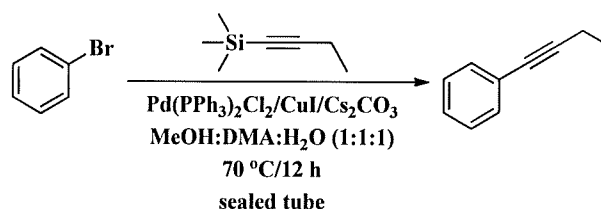


To a stirred solution of tert-butyl (2-(4-(1-(4-((tert-butoxycarbonyl)amino)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.55 g, 0.82 mmol) in dichloromethane (10 mL) was added at 0 °C, trifluoroacetic acid (2 mL). The reaction mixture was stirred for 16 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired (E)-4-((2-(4-((Z)-1-(4-aminophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.024 g, 3%) as an off-white solid.

Example 9: ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.18-7.06 (m, 5H), 6.82 (d, *J* = 7.6 Hz, 2H), 6.7 (d, *J* = 8.8 Hz, 2H), 6.63-6.49 (m, 6H), 5.07 (bs, 2H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.0 (s, 3H), 2.85 (s, 3H), 2.8 (t, *J* = 5.2 Hz, 3H), 2.47-2.42 (m, 3H), 0.85 (t, *J* = 7.2 Hz, 3H). LCMS: 470.3 [M+H]⁺.

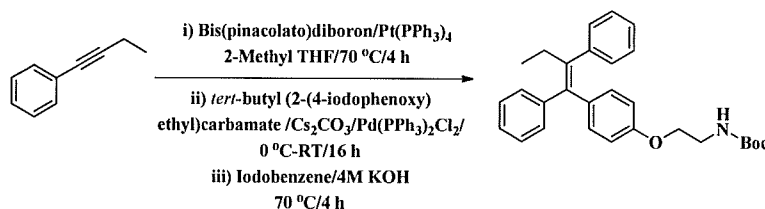
Example-10: Synthesis of (E)-4-((2-(4-((Z)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of but-1-yn-1-ylbenzene



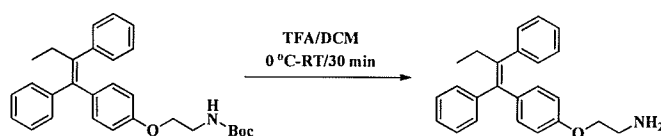
The reaction was carried out according to Scheme 3, Step-1, using but-1-yn-1-yltrimethylsilane (**Example 7**, Step-1.1) to afford but-1-yn-1-ylbenzene (2 g, 83%).

Step-2: Synthesis of tert-butyl (Z)-(2-(4-(1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



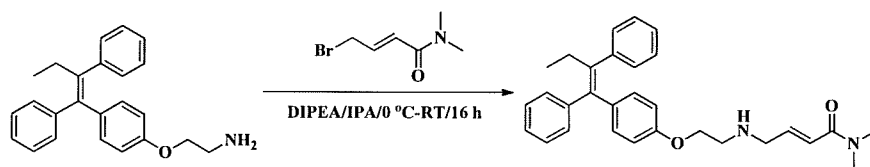
The same procedures as described in **Example 7**, Step-2, using tert-butyl (2-(4-iodophenoxy)ethyl) carbamate (**Example 8**, Step-3) and iodobenzene, to afford tert-butyl (Z)-(2-(4-(1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl) carbamate (2 g, 30%).

Step-3: Synthesis of (Z)-2-(4-(1,2-diphenylbut-1-en-1-yl)phenoxy)ethan-1-amine



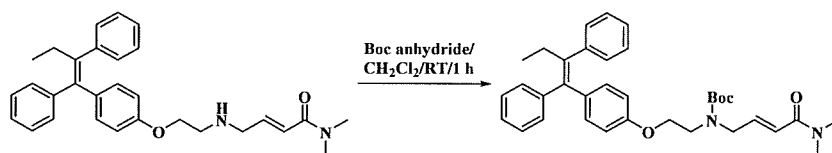
The reaction was carried out according to Scheme 4, Step-2, to give a crude compound, which was used in next step without further purification (1.3 g, crude).

Step-4: Synthesis of (E)-4-((2-(4-((Z)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



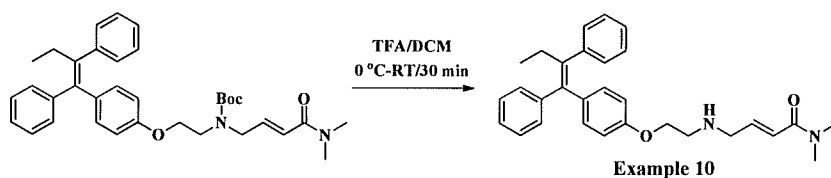
The reaction was carried out according to Scheme 4, Step-3, using (*E*)-4-bromo-*N,N*-dimethylbut-2-enamide (**Example 1**, Step-4.2) to give a crude product, which was used in next step without further purification (2 g, crude).

Step-5: *Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl)carbamate*



The reaction was carried out according to Scheme 4, Step-5, to give a crude compound, which was purified by column chromatography over 230-400 mesh silica-gel by eluting with 2% MeOH in dichloromethane as an eluent to afford tert-butyl ((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((*Z*)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.4 g, 16%).

Step-6: *Synthesis of (E)-4-((2-(4-((Z)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl) amino)-N,N-dimethylbut-2-enamide (Example 10)*

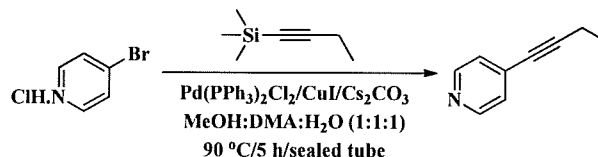


The reaction was carried out according to Scheme 4, Step-6, to give a crude product, which was purified by preparative HPLC to afford desired compound (*E*)-4-((2-(4-((*Z*)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (20 mg, 16%) as a brown colour semi solid.

Exxample 10: ^1H NMR (400 MHz, DMSO- d_6): δ 7.39-7.36 (m, 2H), 7.30-7.27 (m, 1H), 7.22-7.18 (m, 4H), 7.13-7.11 (m, 3H), 6.73 (d, J = 8.8 Hz, 2H), 6.63-6.57 (m, 3H), 6.51 (d, J = 14.1 Hz, 1H), 3.88 (t, J = 5.8 Hz, 2H), 3.33-3.31 (m, 3H), 2.99 (s, 3H), 2.85 (s, 3H), 2.79 (t, J = 5.4 Hz, 2H), 2.37 (q, J = 7.6 Hz, 2H), 0.84 (t, J = 7.6 Hz, 3H). LCMS: 455.3[M+H] $^+$.

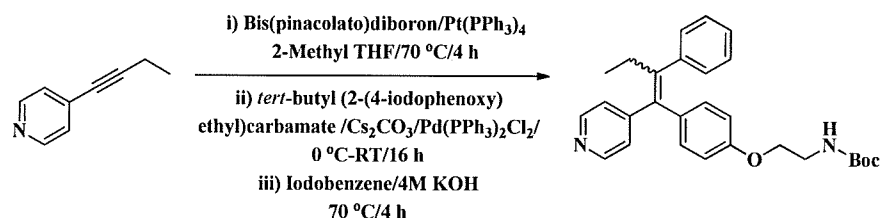
Example-11: Synthesis of (E)-N,N-dimethyl-4-((2-(4-((E)-2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl) phenoxy)ethyl)amino)but-2-enamide

Step-1: Synthesis of 4-(but-1-yn-1-yl)pyridine



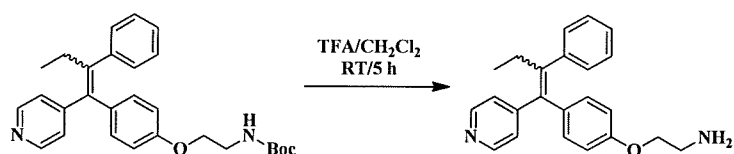
The reaction was carried out according to Scheme 3, Step-1, using but-1-yn-1-yltrimethylsilane (**Example 7**, Step-1.1), to give a crude product, which was purified by combiflash eluting with 5-10% EtOAc in *n*-hexane to afford 4-(but-1-yn-1-yl)pyridine (1.55 g, 65%) as light brown liquid.

Step-2: Synthesis of tert-butyl (2-(4-(2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl)phenoxy)ethyl)carbamate



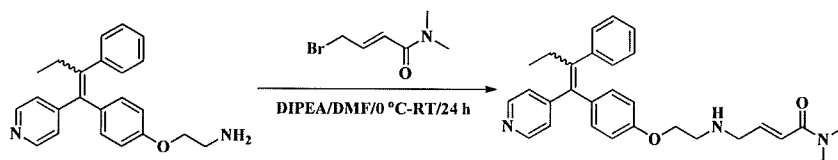
The same procedures as described in **Example 7**, Step-2, using tert-butyl (2-(4-iodophenoxy)ethyl) carbamate (**Example 8**, Step-3) and iodobenzene, to give a crude product, which was purified by combi-flash using 20-23% ethyl acetate in *n*-hexane to afford tert-butyl (2-(4-(2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl)phenoxy) ethyl)carbamate (0.36 g, 7.2%).

Step-3: Synthesis of 2-(4-(2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl)phenoxy)ethan-1-amine



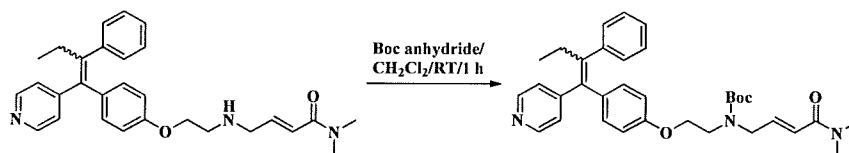
The reaction was carried out according to Scheme 4, Step-2, to give a crude compound, which was used in next step without further purification (0.225 g, 81.2%) as a light brown solid.

Step-4: Synthesis of (2E)-N,N-dimethyl-4-((2-(4-(2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl)phenoxy) ethyl)amino)but-2-enamide



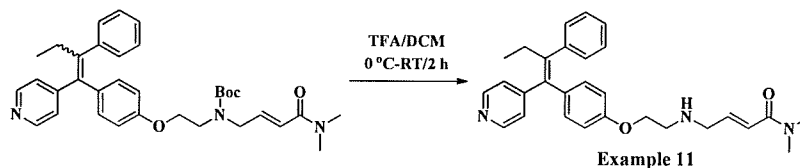
The reaction was carried out according to Scheme 4, Step-3, using (E)-4-bromo-N,N-dimethylbut-2-enamide (**Example 1**, Step-4.2) to give a crude product, which was used in next step without further purification (0.14 g, crude).

Step-5: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-(2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl)phenoxy)ethyl)carbamate



The reaction was carried out according to Scheme 4, Step-5, to give a crude product, which was purified by combiflash eluting with 2-2.5% MeOH in ethyl acetate to afford tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-(2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.045 g, 26.5%) as a light brown semi solid.

Step-6: Synthesis of (E)-4-((2-(4-((Z)-1,2-diphenylbut-1-en-1-yl)phenoxy)ethyl) amino)-N,N-dimethylbut-2-enamide (**Example 11**)

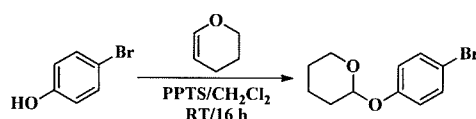


The reaction was carried out according to Scheme 4, Step-6, to give a crude compound, which was purified by preparative HPLC to afford desired (E)-N,N-dimethyl-4-((2-(4-((E)-2-phenyl-1-(pyridin-4-yl)but-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (0.012 g, 33.3%).

Example 11: ^1H NMR (400 MHz, DMSO- d_6): δ 8.58-8.56 (m, 2H), 7.23-7.12 (m, 8H), 6.74 (d, J = 8.8 Hz, 2H), 6.64-6.49 (m, 4H), 3.88 (t, J = 5.6 Hz, 2H), 2.99 (s, 3H), 2.85 (s, 3H), 2.78 (t, J = 5.2 Hz, 2H), 2.39-2.34 (m, 3H), 0.87 (t, J = 7.2 Hz, 3H) LCMS: 456.3 $[\text{M}+\text{H}]^+$.

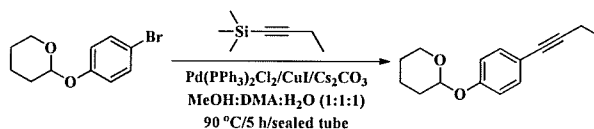
Example-12: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(3-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide 2,2,2-trifluoroacetate

Step-1: Synthesis of 2-(4-bromophenoxy)tetrahydro-2H-pyran



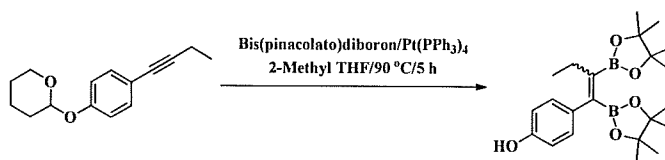
To a stirred solution of 4-bromophenol (15 g, 86 mmol) in dry dichloromethane (150 mL) at room temperature was added dihydro pyran (17.58 g, 173 mmol) followed by addition of pyridinium *p*-toluene sulfonate (50 mg). The resulting mixture was stirred at reflux temperature for 2 h. Upon completion by TLC, the reaction mixture was quenched with water (500 mL) and extracted with dichloromethane (2 x 500 mL). The combined organic extracts were washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica using 6% ethyl acetate in *n*-hexane to afford 2-(4-bromophenoxy)tetrahydro-2H-pyran (20 g, 90%).

Step-2: Synthesis of 2-(4-(but-1-yn-1-yl)phenoxy)tetrahydro-2H-pyran



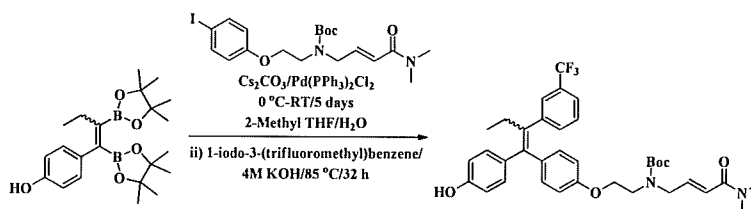
The reaction was carried out according to Scheme 3, Step-1, using but-1-yn-1-yltrimethylsilane (**Example 7**, Step-1.1) to give a crude product, which was purified by column chromatography over 230-400 mesh silica gel by eluting with 3% EtOAc in *n*-hexane to afford 2-(4-(but-1-yn-1-yl)phenoxy)tetrahydro-2H-pyran (17 g).

Step-3: Synthesis of 4-(1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenol



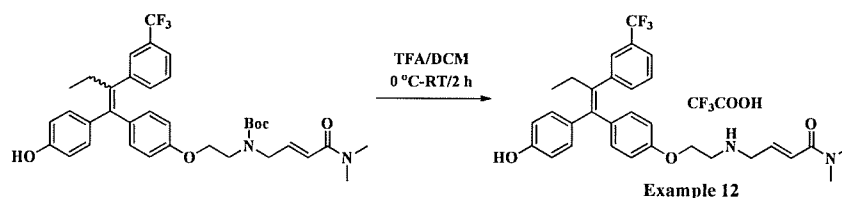
The reaction was carried out according to Scheme 3, Step-2, to afford 4-(1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenol (21.5 g, 76%).

Step-4: *Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-(1-(4-hydroxyphenyl)-2-(3-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)- carbamate*



To a stirred solution of 4-(1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenol (1.5 g, 3.9 mmol) in 2-methyl THF (10 mL), was added tert-butyl (E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-iodophenoxy)ethyl)carbamate (0.864 g, 1.8 mmol, **Example 9**, Step-4), bis(triphenylphosphine)palladium(II) dichloride (91 mg, 0.13 mmol), cesium carbonate (1.69 g, 5.2 mmol) and 2-methyl THF (10 mL) were added. This mixture was degassed with nitrogen and water (2 mL) was added. Reaction mixture was stirred at room temperature for 5 days. After completion of reaction (monitored by TLC), 1-iodo-3-(trifluoromethyl)benzene (738 mg, 2.71 mmol) and 4M aqueous KOH (4 mL) were added and the mixture was degassed with nitrogen and heated at 85 °C for 32 h. Upon completion (monitored by TLC), the reaction mixture was filtered through a celite/silicagel pad and washed with EtOAc. The filtrate was washed with water, saturated NaCl solution and dried over anhydrous sodium sulphate. The organic layer was filtered and concentrated under reduced pressure. The crude product was purified by column chromatography over 230-400 mesh silica gel by eluting with 2% MeOH in dichloromethane to afford desired compound along with the starting material, which was used in next step (500 mg, crude).

Step-5: *Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(3-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide 2,2,2-trifluoroacetate (Example 12)*

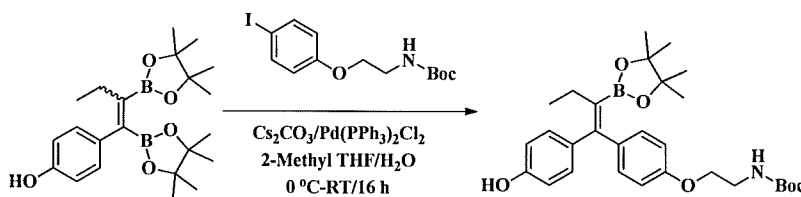


To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-(1-(4-hydroxyphenyl)-2-(3-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)-carbamate (0.5 g, 0.78 mmol) in EtOH (2 mL) was added at 0 °C, 2M HCl in diethyl ether (15 mL). The reaction mixture was stirred for 5 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with dichloromethane. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC using to afford desired (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(3-(trifluoromethyl)phenyl)but-1-en-1-yl)-phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide 2,2,2-trifluoroacetate (0.016 g).

Example 12: ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.5 (s, 1H), 8.9 (bs, 1H), 7.45-7.41 (m, 3H), 7.37 (s, 1H), 7.0 (d, *J* = 8.8 Hz, 2H), 6.82-6.7 (m, 5H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.6-6.53 (m, 1H), 4.08 (t, *J* = 4.8 Hz, 2H), 3.8 (d, *J* = 4.8 Hz, 2H), 3.28 (bs, 2H), 3.04 (s, 3H), 2.88 (s, 3H), 2.45-2.4 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 2H). LCMS: 539.3[M+H]⁺.

Example-13: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

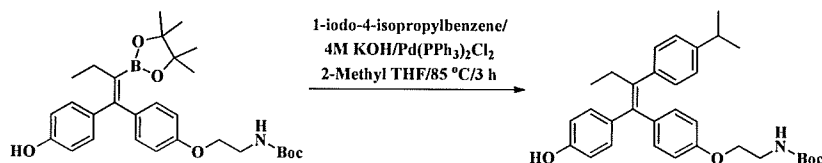
Step-1: Synthesis of tert-butyl (E)-(2-(4-(1-(4-hydroxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenoxy)ethyl)carbamate



The reaction was carried out according to Scheme 3, Step-3, using tert-butyl (2-(4-iodophenoxy)ethyl)carbamate (**Example 8**, Step-3) to give a crude product, which was purified by column chromatography over 230-400 mesh silica gel by eluting with 20%

acetone in *n*-hexane to 5% MeOH in dichloromethane to afford desired compound (2 g, boronate ester, 1 g boronic acid).

Step-2: Synthesis of tert-butyl (E)-2-(4-(2-cyclobutyl-2-phenyl-1-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)phenoxy)ethyl)carbamate



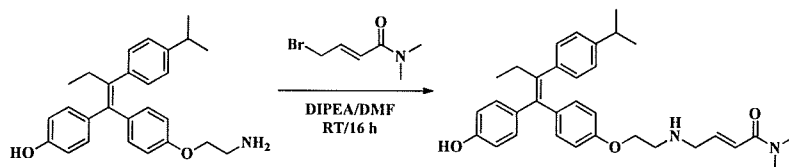
The reaction was carried out according to Scheme 3, Step-4, using 1-iodobenzene, to give a crude product, which was purified by silica gel chromatography (2:8 EtOAc in *n*-hexane) to give title compound (0.52 g, 41%).

Step-3: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenol



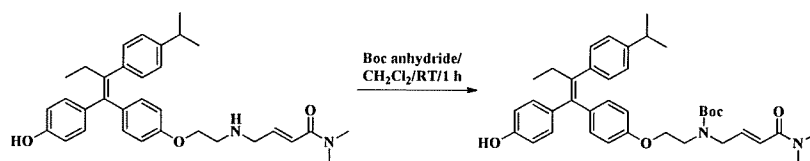
The reaction was carried out according to Scheme 4, Step-2 to give a crude material, which was purified by column chromatography over 230-400 mesh silica gel using (2:98%) MeOH in dichloromethane to afford (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenol (0.44 g).

Step-4: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



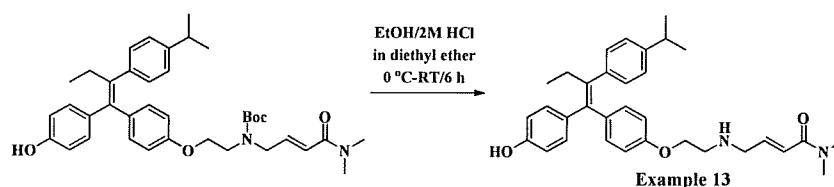
The reaction was carried out according to Scheme 4, Step-3, using (E)-4-bromo-N,N-dimethylbut-2-enamide (**Example 1**, Step-4.2) to afford (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.5 g crude).

Step-5: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



The reaction was carried out according to Scheme 4, Step-5 to give a crude compound, which was purified by column chromatography eluting with 3% MeOH in dichloromethane to afford tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.16 g, 27%).

Step-6: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (Example 13)

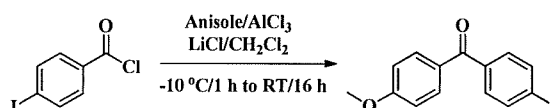


The reaction was carried out according to Scheme 4, Step-6 to give a crude compound, which was purified by preparative HPLC to afford desired (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-isopropylphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.01 g, 7%).

Example 13: ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.38 (s, 1H), 7.05-6.99 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.63-6.59 (m, 3H), 6.50 (d, *J* = 15.2 Hz, 1H), 3.87 (t, *J* = 5.2 Hz, 2H), 2.99 (s, 3H), 2.85 (s, 3H), 2.78 (t, *J* = 5.6 Hz, 2H), 2.40-2.35 (m, 3H), 1.15 (d, *J* = 6.8 Hz, 6H), 0.83 (t, *J* = 7.4 Hz, 3H). LCMS: 513.3[M+H]⁺.

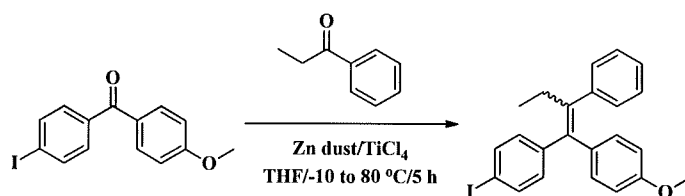
Example-14: Synthesis of (2E)-4-((2-(4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)-phenoxy)ethyl) amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of (4-iodophenyl)(4-methoxyphenyl)methanone



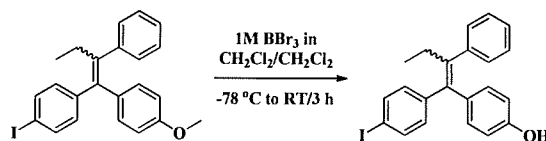
To a stirred solution of 4-iodobenzoyl chloride (2.1 g, 7.8 mmol) and anisole (1.12 mL, 10.2 mmol) in dry dichloromethane (25 mL) at -10 °C was added AlCl₃ (1.5 g, 11 mmol). The resulting mixture was stirred at room temperature for 16 h. Upon completion by TLC, the reaction mixture was quenched with ice cold water (50 mL) and 1N HCl (200 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extracts were washed with water, brine and dried over anhydrous sodium sulphate and concentrated at 40 °C without reduced pressure to give a yellow colour liquid (2.4 g, 92%).

Step-2: Synthesis of 1-iodo-4-(1-(4-methoxyphenyl)-2-phenylbut-1-en-1-yl)benzene



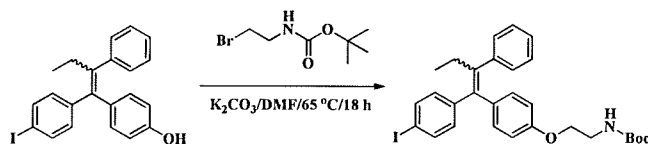
The reaction was carried out according to Scheme 2, Step-1, using propiophenone, to give a crude material, which was purified by column chromatography over 230-400 mesh silica gel by eluting with 5% EtOAc in *n*-hexane to afford 1-iodo-4-(1-(4-methoxyphenyl)-2-phenylbut-1-en-1-yl)benzene (4 g, 50%) as a yellow colour sticky solid.

Step-3: Synthesis of 4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenol



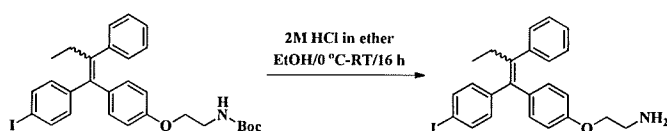
To a solution of 1-iodo-4-(1-(4-methoxyphenyl)-2-phenylbut-1-en-1-yl)benzene (5 g, 11.36 mmol) in dichloromethane (50 mL) was added at -78 °C, BBr₃ (1M solution in dichloromethane, 68 mL, 68.16 mmol). The reaction mixture was stirred for 3 h at room temperature and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature, water was added (50 mL) and the layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude compound, crude material was purified by preparative HPLC to 4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenol as yellow colour semi solid (2.1 g, 43%).

Step-4: Synthesis of tert-butyl (2-(4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



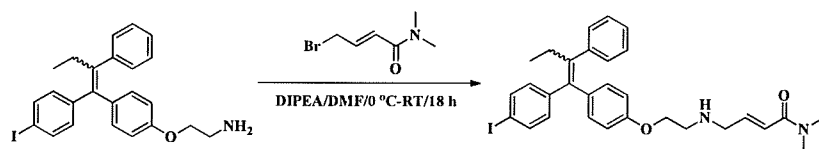
The reaction was carried out according to Scheme 4, Step-1, using tert-butyl (2-bromoethyl)carbamate, to give a crude material, which was purified by combi-flash to afford tert-butyl (2-(4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (1.7 g, 60%) as an off-white sticky solid.

Step-5: Synthesis of 2-(4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenoxy) ethan-1-amine



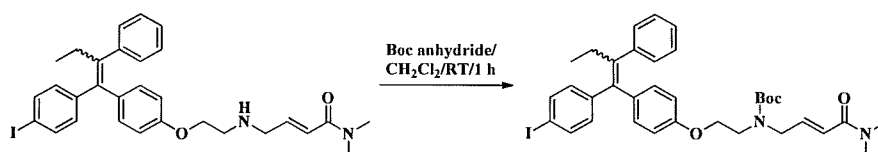
The reaction was carried out according to Scheme 4, Step-2 to give a crude compound, which was used in next step without further purification (1.2 g, 85%).

Step-6: *Synthesis of (2E)-4-((2-(4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethylamino)-N,N-dimethylbut-2-enamide*



The reaction was carried out according to Scheme 4, Step-3, using (*E*)-4- bromo-*N,N*-dimethylbut-2-enamide (**Example 1**, Step-4.2) to give a crude product was used in next step without further purification (0.88 g, crude).

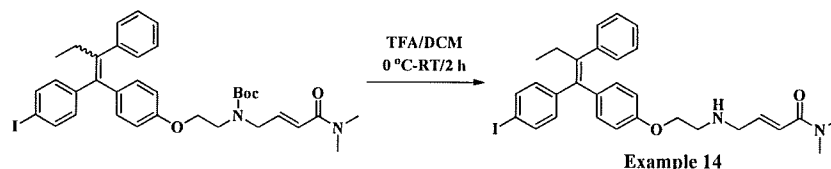
Step-7: *Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate*



The reaction was carried out according to Scheme 4, Step-5 to give a compound, which was purified by combiflash to afford tert-butyl ((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-

(1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)-phenoxy)ethyl)- carbamate (0.48 g) as a yellow colour sticky solid.

Step-8: Synthesis of (E)-4-((2-(4-((E)-1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (Example 14)

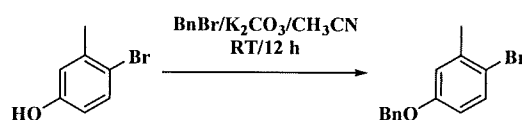


The same procedure as described in Scheme 4, Step-6 to give the desired compound, (E)-4-((2-(4-((E)-1-(4-iodophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.12 g, 25%).

Example 14: ^1H NMR (400 MHz, DMSO- d_6): δ 7.73 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.22-7.20 (m, 4H), 7.19-7.09 (m, 9H), 7.11 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 9.2 Hz, 2H), 6.63-6.52 (m, 7H), 4.04 (t, J = 5.6 Hz, 2H), 3.87 (t, J = 5.2 Hz, 2H), 3.80 (d, J = 4.0 Hz, 2H), 3.02 (s, 3H), 2.99 (s, 3H), 2.89-2.85 (m, 8H), 2.78 (t, J = 5.4 Hz, 2H), 2.46-2.32 (m, 4H), 0.87-.083 (m, 6H). LCMS: 581.2 $[\text{M}+\text{H}]^+$.

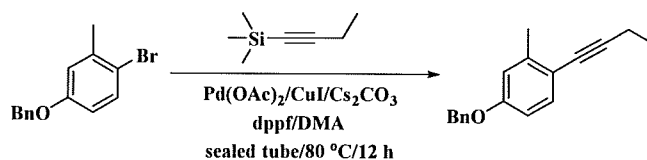
Example 15: Synthesis of (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of 4-(benzyloxy)-1-bromo-2-methylbenzene



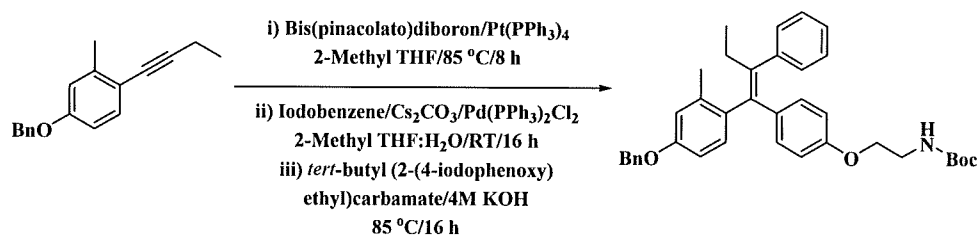
To a solution of 4-bromo-3-methylphenol (10 g, 53.4 mmol) in acetonitrile (200 mL), were added potassium carbonate (22.13 g, 160 mmol) and benzyl bromide (11.89 g, 69.5 mmol) sequentially at room temperature. The resulting mixture was stirred at room temperature for 12 h, completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to afford desired compound (13 g, 87%) as brown colour oil.

Step-2: Synthesis of 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-methylbenzene



To a stirred solution of 4-(benzyloxy)-1-bromo-2-methylbenzene (5 g, 18 mmol) in 50 mL of DMA in a sealed tube, were added copper iodide (0.344 g, 1.8 mmol) and cesium carbonate (8.79 g, 27 mmol) at room temperature. This mixture was degassed with three vacuum/ N_2 cycles, and were added but-1-yn-1-yltrimethylsilane (6.9 g, 27.40 mmol, Example-16, Step-2) followed by $\text{Pd}(\text{OAc})_2$ (0.540 g, 2.3 mmol). The pressure tube was sealed and heated at 80°C for 12 h. Upon completion by TLC, the reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified over 230-400 mesh silica gel column chromatography using 10% EtOAc in *n*-hexane to afford 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-methylbenzene (4.52 g, 88%).

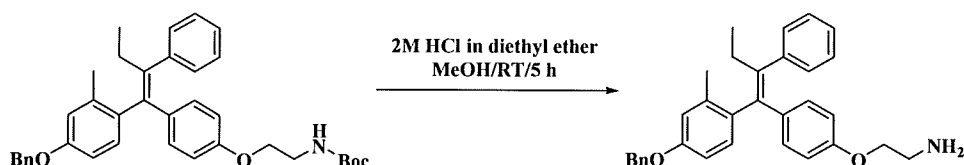
Step-3: Synthesis of *tert*-butyl (*E*)-(2-(4-(1-(4-(benzyloxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-methylbenzene (7.1 g, 29.55 mmol) in 2-methyl THF (72 mL), was added bis(pinacolato)diboron (7.58 g, 29.85 mmol), tetrakis(triphenylphosphine)platinum (0) (0.294 g, 0.236 mmol) under nitrogen atmosphere, reaction mixture was stirred at 85°C for 8 h. After completion of reaction (monitored by TLC), solution was allowed to cool to room temperature, bis(triphenylphosphine)palladium (II) dichloride (0.483 g, 0.68 mmol), cesium carbonate (8.9 g, 27.55 mmol) and iodobenzene (3.9 g, 19.28 mmol) were added, reaction mixture was degassed with nitrogen and water (20 mL) was added, reaction mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (18 mL) and *tert*-butyl (2-(4-iodophenoxy)ethyl)carbamate (4.3 g, 11.88 mmol, Example-17, Step-2), and 2-methyl THF (30 mL) were added. Reaction mixture was stirred at 85°C for 16 h. After completion of

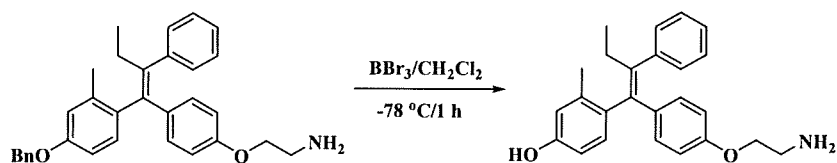
reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 5-10% EtOAc in *n*-hexane to afford tert-butyl (E)-2-(4-(1-(4-(benzyloxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (3.2 g, 43 %).

Step-4: Synthesis of (E)-2-(4-(1-(4-(benzyloxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine



To a stirred solution of tert-butyl (E)-2-(4-(1-(4-(benzyloxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (3.8 g, 6.74 mmol) in methanol (20 mL) was added at 0 °C, 2M HCl in diethyl ether (40 mL). The reaction mixture was stirred for 5 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO_3 , extracted with 10% MeOH in dichloromethane. Organic layer was concentrated under reduced pressure and the crude material was purified by column chromatography over 230-400 mesh silica gel using (4-5%) MeOH in dichloromethane to afford (E)-2-(4-(1-(4-(benzyloxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (2.4 g, 77%).

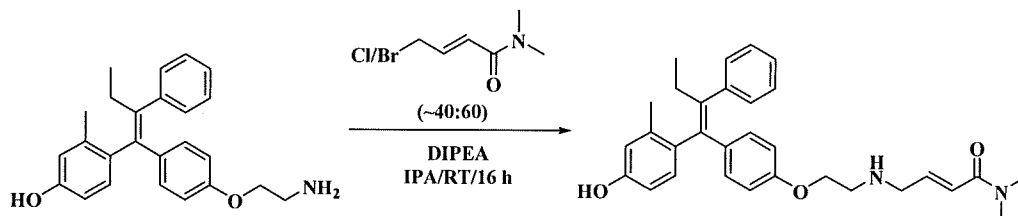
Step-5: Synthesis of (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenol



To a stirred solution of (E)-2-(4-(1-(4-(benzyloxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (2.4 g, 5.1 mmol) in dichloromethane (24 mL) was added BBr_3 (1M solution in dichloromethane, 26 mL, 25 mmol) at -78 °C. The reaction mixture was stirred for 0.5 h and quenched with MeOH (5 mL). The resulting mixture was cooled to 0 °C, basified with saturated NaHCO_3 solution, slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to

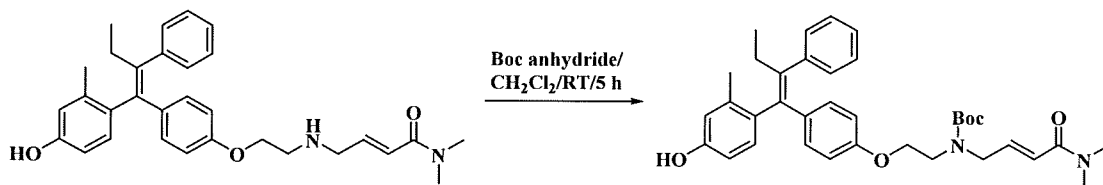
afford (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenol (0.9 g, 47%).

Step-6: Synthesis of (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenol (0.9 g, 2.4 mmol) in IPA (10 mL) was added DIPEA (0.62 g, 4.8 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.368 g, 1.9 mmol, Example-101, Step-7) in IPA (5 mL) was added drop wise, reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (1.29 g, crude).

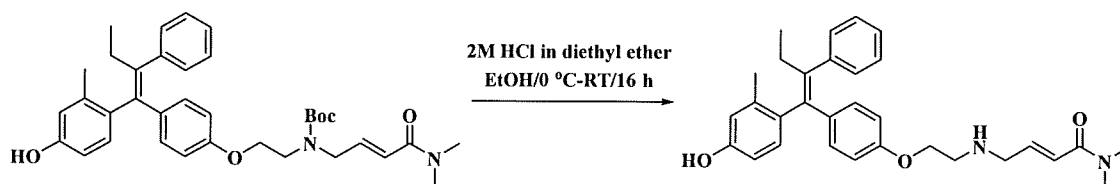
Step-7: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (1.29 g, 2.6 mmol) in dichloromethane (25 mL) was added boc anhydride (0.87 g, 4.01 mmol). The reaction mixture was stirred for 2 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by

column chromatography over 230-400 mesh silica gel using 2% MeOH in dichloromethane to obtain tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.26 g, 16.8%).

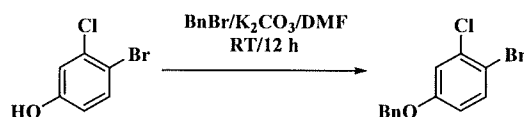
Step-8: Synthesis of (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.26 g, 0.44 mmol) in EtOH (2 mL) was added at 0 °C, 2M HCl in diethyl ether (4 mL). The reaction mixture was stirred for 16 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.15 g, 69.7%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.22 (s, 1H), 7.22-7.14 (m, 2H), 7.13-7.11 (m, 3H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.72-6.64 (m, 2H), 6.61-6.47 (m, 6H), 3.86 (t, *J* = 5.6 Hz, 2H), 2.98 (s, 3H), 2.84 (s, 3H), 2.77 (t, *J* = 5.6 Hz, 2H), 2.32-2.15 (m, 2H), 2.01 (s, 3H), 0.74 (t, *J* = 7.4 Hz, 3H). LCMS: 485.4 [M+H]⁺

Example 16: Synthesis of (E)-4-((2-(4-((E)-1-(2-chloro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

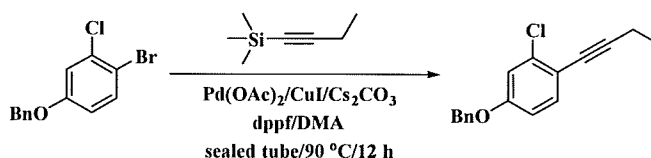
Step-1: Synthesis of 4-(benzyloxy)-1-bromo-2-chlorobenzene



To a solution of 4-bromo-3-chlorophenol (10 g, 48.3 mmol) in DMF (200 mL), were added potassium carbonate (19.99 g, 144 mmol) and benzyl bromide (6.93 mL, 57.97 mmol) sequentially at room temperature. The resulting mixture was stirred at room temperature for

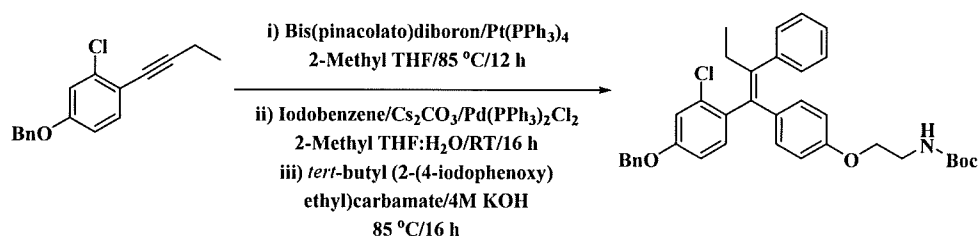
12 h, completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to afford desired compound (13 g, 91%).

Step-2: Synthesis of 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-chlorobenzene



To a stirred solution of 4-(benzyloxy)-1-bromo-2-chlorobenzene (13 g, 43.91 mmol) in 130 mL of DMA in a sealed tube, were added copper iodide (0.833 g, 4.39 mmol) and cesium carbonate (28.63 g, 87.83 mmol) at room temperature. This mixture was degassed with three vacuum/ N_2 cycles, and were added but-1-yn-1-yltrimethylsilane (11 g, 87.83 mmol, Example-16, Step-2) followed by Pd(OAc)_2 (1.079 g, 4.39 mmol) and dppf (2.4 g, 4.39 mmol). The pressure tube was sealed and heated at 90 °C for 12 h. Upon completion by TLC, the reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified over 230-400 mesh silica gel column chromatography using 3% EtOAc in *n*-hexane to afford 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-chlorobenzene (9.4 g, 80%).

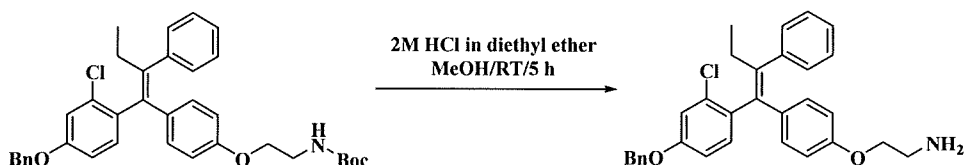
Step-3: Synthesis of tert-butyl (E)-(2-(4-(1-(4-(benzyloxy)-2-chlorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-chlorobenzene (4 g, 14.81 mmol) in 2-methyl THF (32 mL), was added bis(pinacolato)diboron (4.54 g, 17.87 mmol), tetrakis(triphenylphosphine)palladium (0) (0.185 g, 0.148 mmol) under nitrogen atmosphere, reaction mixture was stirred at 85 °C for 12 h. After completion of reaction (monitored by TLC), solution was allowed to cool to room temperature, bis(triphenylphosphine)palladium

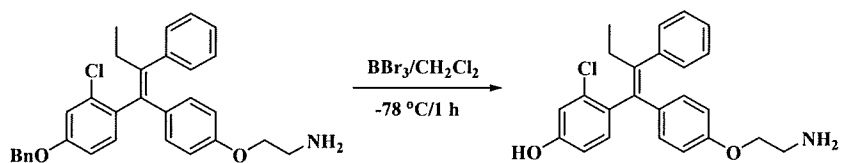
(II) dichloride (0.488 g, 0.66 mmol), cesium carbonate (8.51 g, 26.21 mmol) and iodobenzene (2.72 g, 13.35 mmol) were added, reaction mixture was degassed with nitrogen and water (1 mL) was added, reaction mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (3 g) and *tert*-butyl (2-(4-iodophenoxy)ethyl)carbamate (3.23 g, 8.9 mmol, Example-17, Step-2), and 2-methyl THF (50 mL) were added. Reaction mixture was stirred at reflux temperature for 12 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 25% EtOAc in *n*-hexane to afford *tert*-butyl (E)-2-(4-(1-(4-(benzyloxy)-2-chlorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (3.3 g, 46%).

Step-4: Synthesis of (E)-2-(4-(1-(4-(benzyloxy)-2-chlorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine



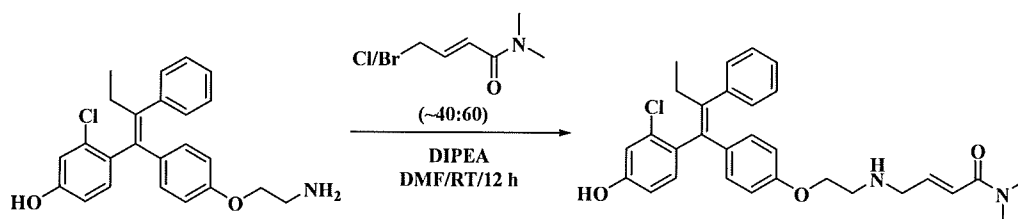
To a stirred solution of *tert*-butyl (E)-2-(4-(1-(4-(benzyloxy)-2-chlorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (3.34 g, 5.71 mmol) in ethanol (10 mL) was added at 0 °C, 2M HCl in diethyl ether (40 mL). The reaction mixture was stirred for 12 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with 10% MeOH in dichloromethane. Organic layer was concentrated under reduced pressure and the crude material was purified by column chromatography over 230-400 mesh silica gel using (4-5%) MeOH in dichloromethane to afford (E)-2-(4-(1-(4-(benzyloxy)-2-chlorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (2.7 g).

Step-5: Synthesis (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-chlorophenol



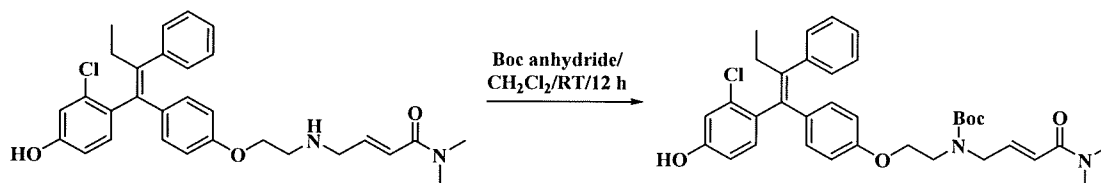
To a stirred solution of (E)-2-(4-(1-(4-(benzyloxy)-2-chlorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (2.7 g, 5.57 mmol) in dichloromethane (30 mL) was added BBr₃ (1M solution in dichloromethane, 27.8 mL, 27.8 mmol) at -78 °C. The reaction mixture was stirred for 1.5 h and quenched with MeOH (5 mL). The resulting mixture was cooled to 0 °C, basified with saturated NaHCO₃ solution, slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-chlorophenol (0.78 g, 35%).

Step-6: Synthesis of (E)-4-((2-(4-((E)-1-(2-chloro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



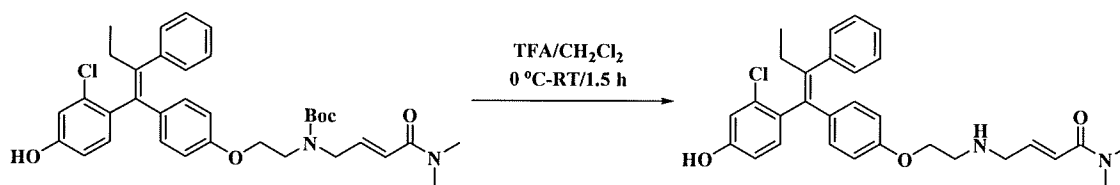
To a stirred solution of (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-chlorophenol (0.78 g, 1.98 mmol) in DMF (16 mL) was added DIPEA (0.693 g, 3.97 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.379 g, 1.98 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (1.0 g, crude).

Step-7: Synthesis of tert-butyl (2-(4-((E)-1-(2-chloro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate



To a stirred solution of (E)-4-((2-(4-((E)-1-(2-chloro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (1.0 g, 1.98 mmol) in dichloromethane (15 mL) was added boc anhydride (0.648 g, 2.97 mmol). The reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by column chromatography over 230-400 mesh silica gel using 2% MeOH in dichloromethane to obtain tert-butyl (2-(4-((E)-1-(2-chloro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.465 g, 39%).

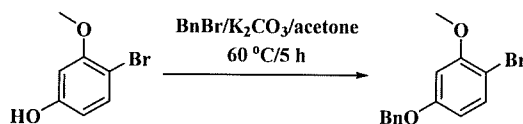
Step-8: Synthesis of (E)-4-((2-(4-((E)-1-(2-chloro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl (2-(4-((E)-1-(2-chloro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.44 g, 0.728 mmol) in dichloromethane (9 mL) was added at 0 °C, TFA (1 mL). The reaction mixture was stirred for 1.5 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (0.195 g, 53%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.85 (s, 1H), 7.23-7.11 (m, 6H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.79 (dd, *J*₁ = 8.2 Hz, *J*₂ = 1.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.62 (t, *J* = 5.2 Hz, 1H), 6.59-6.47 (m, 3H), 3.86 (t, *J* = 5.6 Hz, 2H), 3.25-3.31 (m, 2H), 2.98 (s, 3H), 2.84 (s, 3H), 2.77 (t, *J* = 5.6 Hz, 2H), 2.29-2.21 (m, 2H), 2.19-2.05 (m, 1H), 0.77 (t, *J* = 7.4 Hz, 3H). LCMS: 505.3 [M+H]⁺

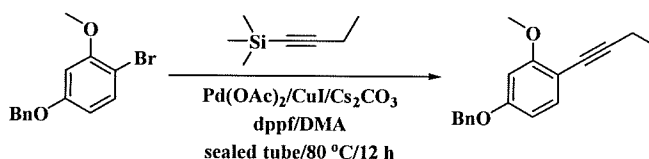
Example 17: Synthesis of (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of 4-(benzyloxy)-1-bromo-2-methoxybenzene



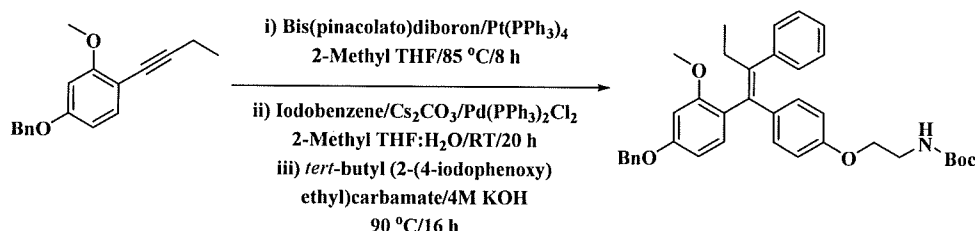
To a solution of 4-bromo-3-methoxyphenol (10 g, 49.2 mmol) in acetone (100 mL), were added potassium carbonate (20.4 g, 147.7 mmol) and benzyl bromide (6.42 mL, 54.18 mmol) sequentially at room temperature. The resulting mixture was stirred at 60 °C for 5 h, completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to afford desired compound (14 g, 95%).

Step-2: Synthesis of 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-methoxybenzene



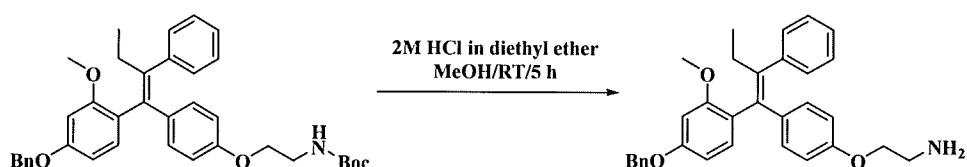
To a stirred solution of 4-(benzyloxy)-1-bromo-2-methoxybenzene (7 g, 23.89 mmol) in 70 mL of DMA in a sealed tube, were added copper iodide (0.45 g, 2.38 mmol) and cesium carbonate (11.64 g, 35.83 mmol) at room temperature. This mixture was degassed with three vacuum/ N_2 cycles and were added but-1-yn-1-yltrimethylsilane (4.2 g, 33.44 mmol, Example-16, Step-2) followed by $\text{Pd}(\text{OAc})_2$ (0.54 g, 2.38 mmol) and dppf (1.34 g, 2.38 mmol). The pressure tube was sealed and heated at 80 °C for 12 h. Upon completion by TLC, the reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified over 230-400 mesh silica gel column chromatography using 25% EtOAc in *n*-hexane to afford 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-methoxybenzene (5 g, 78%).

Step-3: Synthesis of tert-butyl (E)-(2-(4-(1-(4-(benzyloxy)-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 4-(benzyloxy)-1-(but-1-yn-1-yl)-2-methoxybenzene (5 g, 18.77 mmol) in 2-methyl THF (50 mL), was added bis(pinacolato)diboron (4.8 g, 18.96 mmol), tetrakis(triphenylphosphine)platinum (0) (0.186 g, 0.150 mmol) under nitrogen atmosphere, reaction mixture was stirred at 85 °C for 8 h. After completion of reaction (monitored by TLC), solution was allowed to cool to room temperature, bis(triphenylphosphine)palladium (II) dichloride (0.98 g, 1.39 mmol), cesium carbonate (18.16 g, 55.88 mmol) and iodobenzene (5.13 g, 25.14 mmol) were added, reaction mixture was degassed with nitrogen and water (20 mL) was added, reaction mixture was stirred at room temperature for 20 h. After completion of reaction, to the above reaction mixture 4M KOH (50 mL) and *tert*-butyl (2-(4-iodophenoxy)ethyl)carbamate (10.13 g, 27.90 mmol, Example-17, Step-2), and 2-methyl THF (50 mL) were added. Reaction mixture was stirred at 90 °C for 16 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 5-10% EtOAc in *n*-hexane to afford *tert*-butyl (E)-2-(4-(1-(4-(benzyloxy)-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl carbamate (3.4 g, 31%).

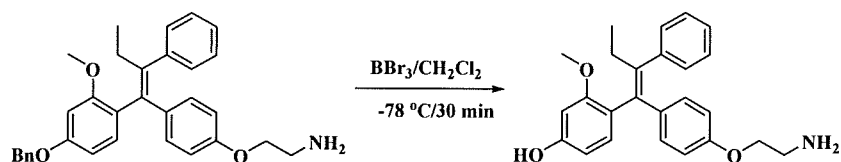
Step-4: Synthesis of (E)-2-(4-(1-(4-(benzyloxy)-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine



To a stirred solution of *tert*-butyl (E)-2-(4-(1-(4-(benzyloxy)-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl carbamate (3.4 g, 19.94 mmol) in methanol (15 mL) was added at 0 °C, 2M HCl in diethyl ether (35 mL). The reaction mixture was stirred for 5 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO_3 , extracted with 10% MeOH in dichloromethane. Organic layer was concentrated

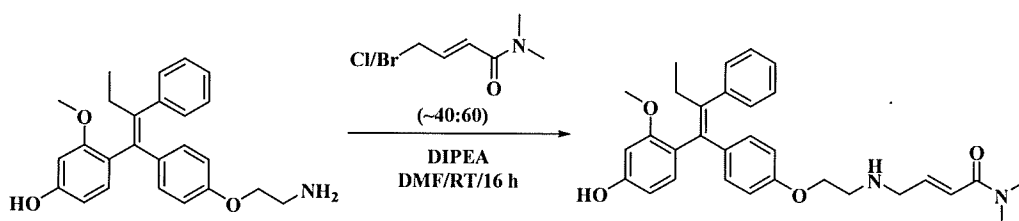
under reduced pressure and the crude material was purified by column chromatography over 230-400 mesh silica gel using (4-5%) MeOH in dichloromethane to afford (E)-2-(4-(1-(4-(benzyloxy)-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (2.4 g).

Step-5: Synthesis (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methoxyphenol



To a stirred solution of (E)-2-(4-(1-(4-(benzyloxy)-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (2.4 g, 5.01 mmol) in dichloromethane (15 mL) was added BBr_3 (1M solution in dichloromethane, 28 mL, 25 mmol) at -78°C . The reaction mixture was stirred for 30 min and quenched with MeOH (5 mL). The resulting mixture was cooled to 0°C , basified with saturated NaHCO_3 solution, slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methoxyphenol (1.02 g, 51%).

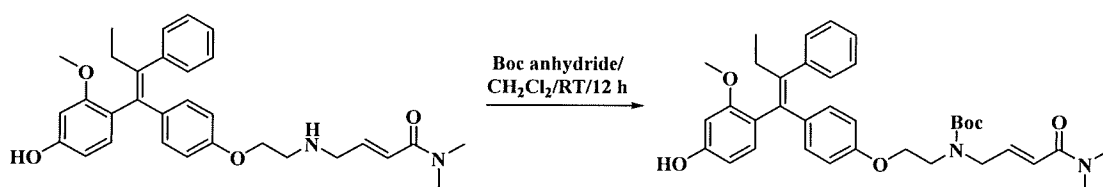
Step-6: Synthesis of (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methoxyphenol (1 g, 2.5 mmol) in DMF (10 mL) was added DIPEA (0.66 g, 5.14 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.39 g, 2.05 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 16 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane.

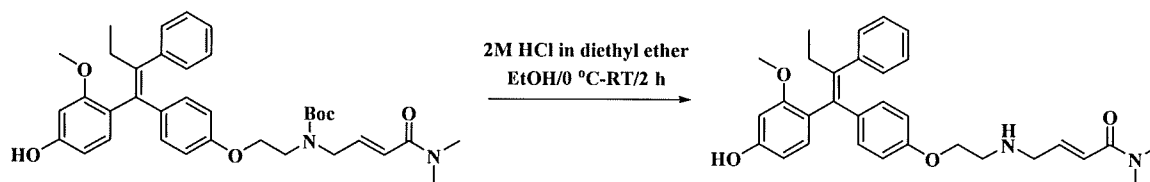
The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (2.3 g, crude).

Step-7: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(4-hydroxy-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (2.3 g, 4.5 mmol) in dichloromethane (30 mL) was added boc anhydride (1.2 g, 5.5 mmol). The reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by column chromatography over 230-400 mesh silica gel using 2-3% MeOH in dichloromethane to obtain tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(4-hydroxy-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.43 g).

Step-8: Synthesis of (E)-4-((2-(4-((E)-1-(4-hydroxy-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

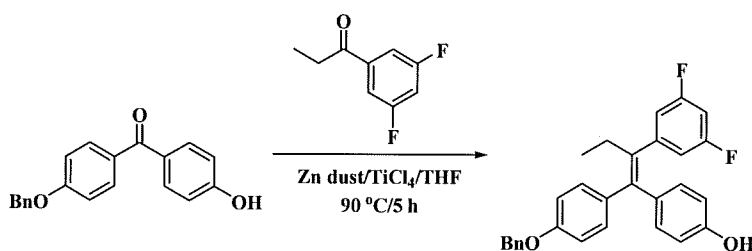


To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(4-hydroxy-2-methoxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.43 g, 0.728 mmol) in ethanol (3 mL) was added at 0 °C, 2M HCl in diethyl ether (5 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain

crude compound. Crude compound was purified by preparative HPLC to afford desired compound (0.075 g, 13.9%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.38 (s, 1H), 7.24-7.07 (m, 5H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 2H), 6.62 (t, $J = 5.0$ Hz, 1H), 6.58 (t, $J = 5.4$ Hz, 1H), 6.55-6.52 (m, 2H), 6.48-6.35 (m, 2H), 3.85 (t, $J = 5.6$ Hz, 2H), 3.61 (s, 3H), 2.99 (s, 3H), 2.84 (s, 3H), 2.77 (t, $J = 5.6$ Hz, 2H), 2.24 (dd, $J_1 = 14.4$ Hz, $J_2 = 7.2$ Hz, 2H), 0.74 (t, $J = 7.2$ Hz, 3H). LCMS: 501.3 $[\text{M}+\text{H}]^+$

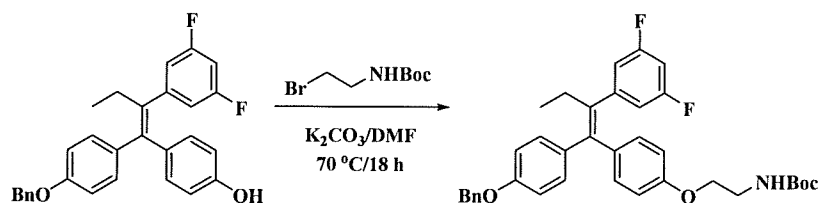
Example 18: Synthesis of (E)-4-((2-(4-((Z)-2-(3,5-difluorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of (E)-4-(1-(4-(benzyloxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenol



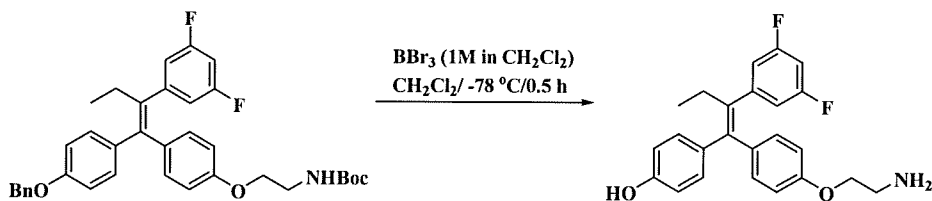
Zinc dust (5.2 g, 78.6 mmol) was suspended in dry THF (50 mL) and cooled this suspension to -10 °C. To this TiCl_4 (4.4 mL, 39.3 mmol) was added slowly under nitrogen atmosphere, stirred there for 15 min, slowly allowed it to reach room temperature and heated to reflux for 2 h. The resulting mixture was cooled to 0 °C, and a solution of 4-(benzyloxy) phenyl(4-hydroxyphenyl) methanone (4 g, 13.1 mmol) and 1-(3,5-difluorophenyl)propan-1-one (2.35 g, 13.8 mmol) in dry THF (80 mL) were added and the contents were refluxed for 5 h. The reaction mixture was cooled to room temperature and quenched with 10% aqueous K_2CO_3 solution and was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated. The crude material was purified by column chromatography over 230-400 mesh silica using (2:8) ethyl acetate in *n*-hexane to afford (E)-4-(1-(4-(benzyloxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenol (4.05 g, 69.8 %).

Step-2: Synthesis of tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



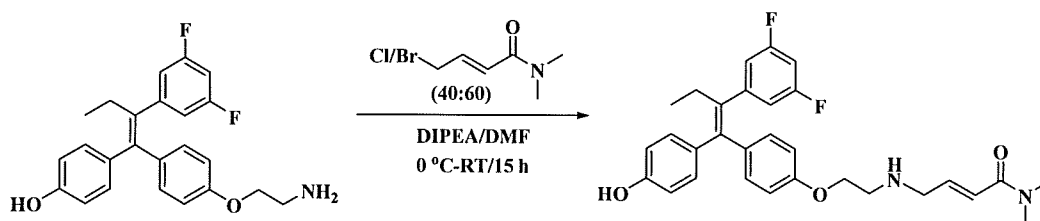
To a solution of (E)-4-(1-(4-(benzyloxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenol (4 g, 9.04 mmol) in DMF (40 mL) was added potassium carbonate (12.5 g, 90.4 mmol) and tert-butyl (2-bromoethoxy)ethyl carbamate (3.05 g, 13.5 mmol). The reaction mixture was heated to 70°C and maintained at this temperature for 18 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate (250 mL x 2). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 15% ethyl acetate in *n*-hexane to afford tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (4.5 g, 85%).

Step-3: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenol



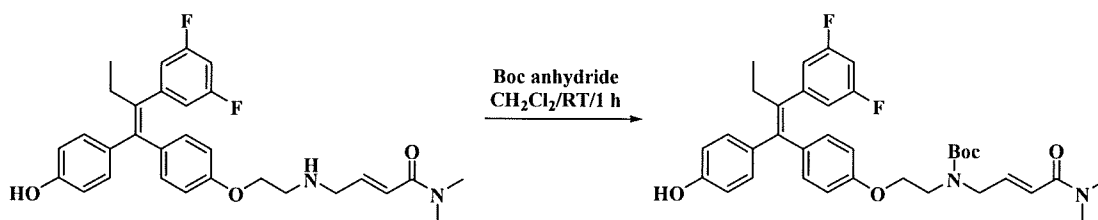
To a stirred solution of tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (4 g, 6.8 mmol) in dichloromethane (80 mL) was added BBr_3 (1M solution in dichloromethane, 34.2 mL, 34.2 mmol) at -78°C . The reaction mixture was stirred for 0.5 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (100 mL) and layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude compound. The crude material was purified by column chromatography over 230-400 mesh silica gel using 10% MeOH in dichloromethane to afford desired compound (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenol (1.35 g, 50 %).

Step-4: Synthesis of (E)-4-((2-(4-((Z)-2-(3,5-difluorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(3,5-difluorophenyl)but-1-en-1-yl)phenol (1.5 g, 3.79 mmol) in DMF (15 mL) was added DIPEA (0.98 mL, 5.6 mmol) stirred for 15 min at room temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.51 g, 2.65 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 15 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (1.8 g, crude).

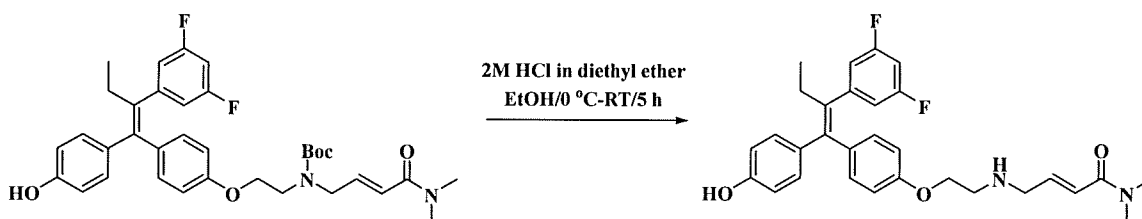
Step-5: Synthesis of tert-butyl (2-(4-((Z)-2-(3,5-difluorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate



To a stirred solution of (E)-4-((2-(4-((Z)-2-(3,5-difluorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (1.8 g, 3.55 mmol) in dichloromethane (20 mL) was added boc anhydride (1.16 g, 5.33 mmol). The reaction mixture was stirred for 1 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by combi-flash eluting with 100% EtOAc to obtain tert-butyl (2-(4-

((Z)-2-(3,5-difluorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.47 g, 21.9%).

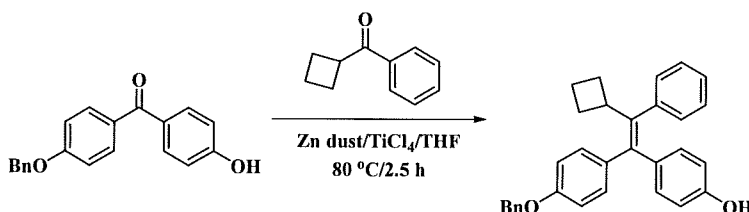
Step-6: Synthesis of (E)-4-((2-(4-((Z)-2-(3,5-difluorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl (2-(4-((Z)-2-(3,5-difluorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.47 g, 0.775 mmol) in ethanol (5 mL) was added at 0 °C, 2M HCl in diethyl ether (15 mL). The reaction mixture was stirred for 5 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (0.042 g, 10.7%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.46 (s, 1H), 6.98-6.93 (m, 3H), 6.80-6.74 (m, 6H), 6.68-6.61 (m, 3H), 6.60-6.40 (m, 1H), 3.91 (t, *J* = 5.4 Hz, 2H), 3.32-3.20 (m, 2H), 3.00 (s, 3H), 2.85-2.80 (m, 5H), 2.40 (q, *J* = 7.6 Hz, 2H), 0.87 (t, *J* = 7.2 Hz, 3H). LCMS: 507.3 [M+H]⁺

Example 19: Example-107: Synthesis of (E)-4-((2-(4-((Z)-2-cyclobutyl-1-(4-hydroxyphenyl)-2-phenylvinyl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

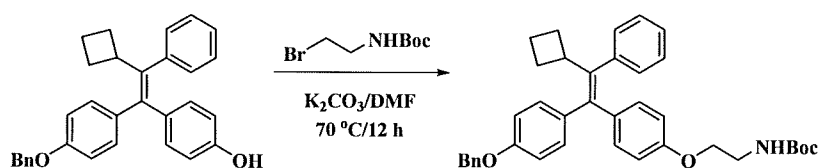
Step-1: Synthesis of (E)-4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenol



Zinc dust (5.16 g, 65.39 mmol) was suspended in dry THF (50 mL) and cooled this suspension to -10 °C. To this TiCl₄ (4.34 mL, 39.45 mmol) was added slowly under nitrogen atmosphere, stirred there for 15 min, slowly allowed it to reach room temperature and heated to reflux for 2 h. The resulting mixture was cooled to 0 °C, and a solution of 4-(benzyloxy)

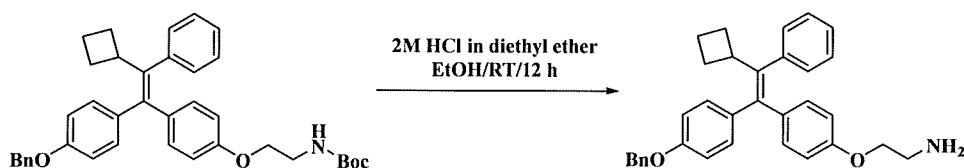
phenyl)(4-hydroxyphenyl) methanone (4 g, 13.15 mmol) and cyclobutyl(phenyl)methanone (5.71 g, 35.62 mmol) in dry THF (30 mL) were added and the contents were refluxed for 2.5 h. The reaction mixture was cooled to room temperature and quenched with 10% aqueous K_2CO_3 solution and was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated. The crude material was purified by column chromatography over 230-400 mesh silica using 10% ethyl acetate in *n*-hexane to afford (E)-4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenol (4.91 g, 86 %).

Step-2: Synthesis of tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenoxy)ethyl)carbamate



To a solution of (E)-4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenol (4.9 g, 11.34 mmol) in DMF (50 mL) was added potassium carbonate (4.6 g, 34.02 mmol) and tert-butyl (2-bromoethyl)carbamate (3.81 g, 17.01 mmol). The reaction mixture was heated to 70 °C and maintained at this temperature for 12 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate (250 mL x 2). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 15% ethyl acetate in *n*-hexane to afford tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenoxy)ethyl)carbamate (5.6 g, 86%).

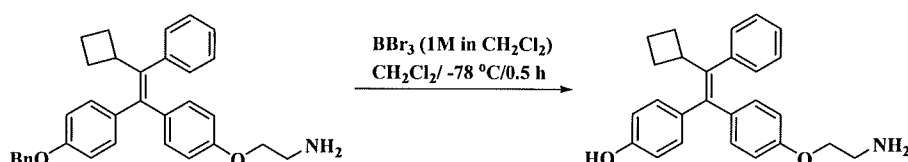
Step-3: Synthesis of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenoxy)ethan-1-amine



To a stirred solution of tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenoxy)ethyl)carbamate (4.35 g, 7.56 mmol) in ethanol (15 mL) was added at 0

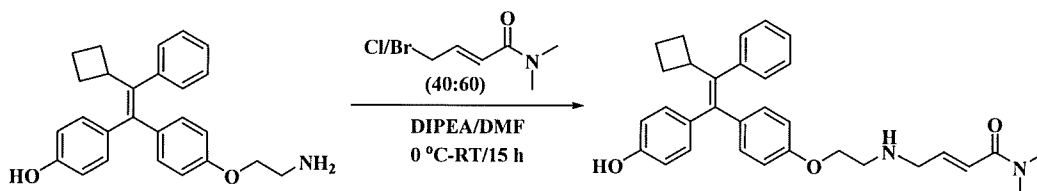
°C, 2M HCl in diethyl ether (50 mL). The reaction mixture was stirred for 12 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO_3 , extracted with 10% MeOH in dichloromethane. Organic layer was concentrated under reduced pressure and the crude material was purified by column chromatography over 230-400 mesh silica gel using (4-5%) MeOH in dichloromethane to afford (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenoxy)ethan-1-amine (2.87 g, 79.9%).

Step-4: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenol



To a stirred solution of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenoxy)ethan-1-amine (2.87 g, 6.04 mmol) in dichloromethane (30 mL) was added BBr_3 (1M solution in dichloromethane, 30.2 mL, 30.2 mmol) at -78°C . The reaction mixture was stirred for 0.5 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (100 mL) and layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude compound. The crude material was purified by column chromatography over 230-400 mesh silica gel using 10% MeOH in dichloromethane to afford desired compound (0.725 g, 31%).

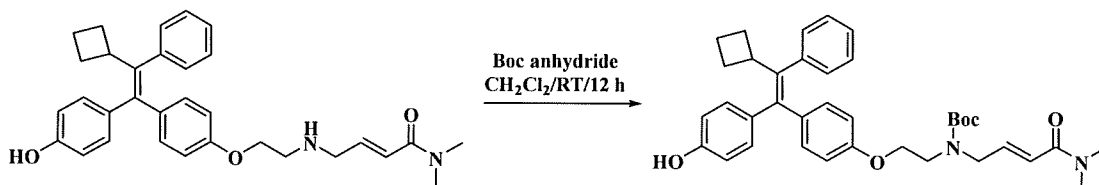
Step-5: Synthesis of (E)-4-((2-(4-((Z)-2-cyclobutyl-1-(4-hydroxyphenyl)-2-phenylvinyl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-cyclobutyl-2-phenylvinyl)phenol (0.725 g, 1.88 mmol) in DMF (10 mL) was added DIPEA (0.492 mL, 2.52 mmol) stirred for 15 min at room temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.269 g, 1.41 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 15 h at room temperature, after completion of reaction (monitored by TLC),

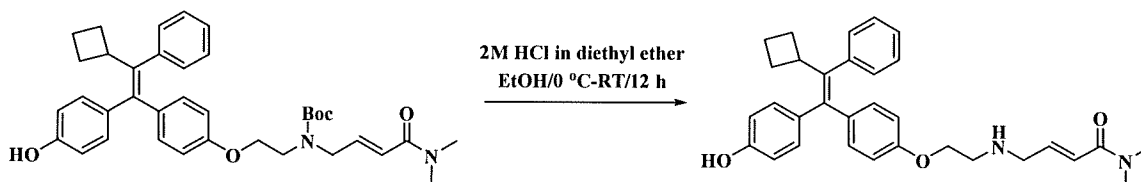
reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (0.908 g, crude).

Step-6: Synthesis of tert-butyl (2-(4-((Z)-2-cyclobutyl-1-(4-hydroxyphenyl)-2-phenylvinyl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate



To a stirred solution of (E)-4-((2-(4-((Z)-2-cyclobutyl-1-(4-hydroxyphenyl)-2-phenylvinyl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.908 g, 1.83 mmol) in dichloromethane (15 mL) was added boc anhydride (0.598 g, 2.74 mmol). The reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 2% MeOH in dichloromethane to afford desired compound (0.332 g, 30%).

Step-7: Synthesis of (E)-4-((2-(4-((Z)-2-cyclobutyl-1-(4-hydroxyphenyl)-2-phenylvinyl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

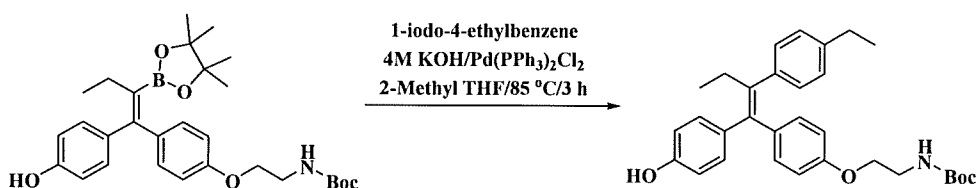


To a stirred solution of tert-butyl (2-(4-((Z)-2-cyclobutyl-1-(4-hydroxyphenyl)-2-phenylvinyl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.332 g, 0.55 mmol) in ethanol (5 mL) was added at 0 °C, 2M HCl in diethyl ether (10 mL). The reaction mixture was stirred for 12 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to

obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (0.032 g, 11.59%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.40 (s, 1H), 7.24-7.20 (m, 2H), 7.15-7.13 (m, 1H), 7.02 (d, $J = 6.8$ Hz, 2H), 6.96 (d, $J = 7.6$ Hz, 2H), 6.76-6.71 (m, 4H), 6.62-6.57 (m, 1H), 6.55-6.48 (m, 3H), 3.83 (t, $J = 5.6$ Hz, 2H), 3.42-3.90 (m, 1H), 3.31-3.30 (m, 2H), 2.98 (s, 3H), 2.84 (s, 3H), 2.76 (t, $J = 5.6$ Hz, 2H), 1.81-1.75 (m, 4H), 1.75-1.59 (m, 1H), 1.38-1.28 (m, 1H). LCMS: 497.3 $[\text{M}+\text{H}]^+$

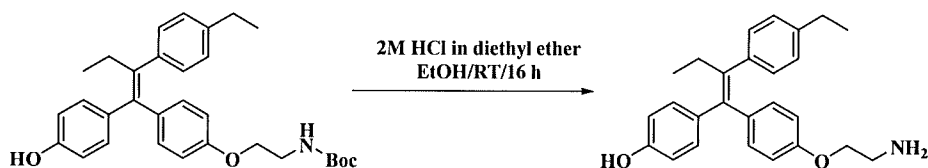
Example 20: Synthesis of (E)-4-((2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of tert-butyl (Z)-2-(4-(2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of tert-butyl (E)-2-(4-(1-(4-hydroxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)phenoxy)ethyl)carbamate (1.3 g, 2.55 mmol, Example-46, Step-1) in 2-methyl THF (15 mL), 1-iodo-4-ethylbenzene (0.651 mg, 2.8 mmol), 4M aqueous KOH (2 mL) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (89 mg, 0.127 mmol) were added and the mixture was degassed with nitrogen for 15 min and heated at 85 °C for 3 h. Upon completion, the reaction mixture was diluted with EtOAc. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (2:8 EtOAc in *n*-hexane) to give title compound (0.5 g, 40%).

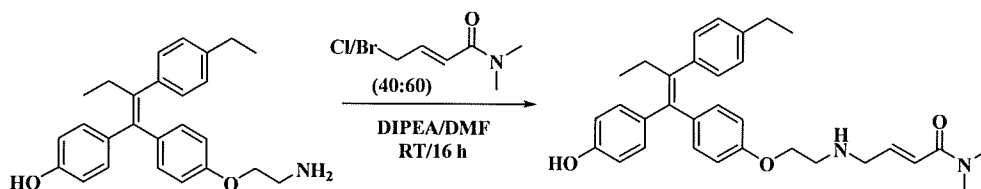
Step-2: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(4-ethylphenyl)but-1-en-1-yl)phenol



To a stirred solution of tert-butyl (Z)-2-(4-(2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.5 g, 1.03 mmol) in ethanol (2 mL) was added at 0 °C, 2M

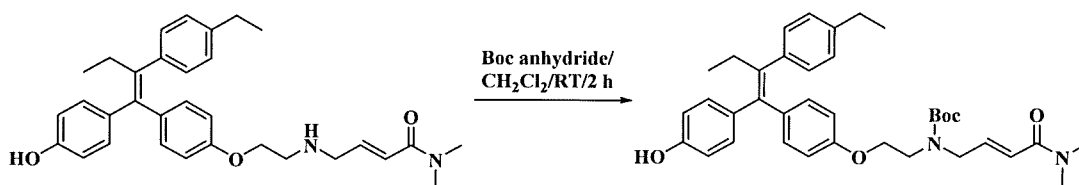
HCl in diethyl ether (40 mL). The reaction mixture was stirred for 16 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃ solution, extracted with 10% MeOH in dichloromethane. The organic layer was concentrated under reduced pressure and the crude material was purified by column chromatography over 230-400 mesh silica gel using (2:98%) MeOH in dichloromethane to afford (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(4-ethylphenyl)but-1-en-1-yl)phenol (0.39 g).

Step-3: Synthesis of (E)-4-((2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(4-ethylphenyl)but-1-en-1-yl)phenol (0.39 g, 1 mmol) in DMF (2 mL) was added at 0 °C, DIPEA (0.27 mL, 1.5 mmol) and (E)-4-bromo-N,N-dimethylbut-2-enamide (0.144 g, 0.75 mmol, Example-101, Step-7). The reaction mixture was stirred for 16 h at room temperature, after completion of reaction, reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford (E)-4-((2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.15 g).

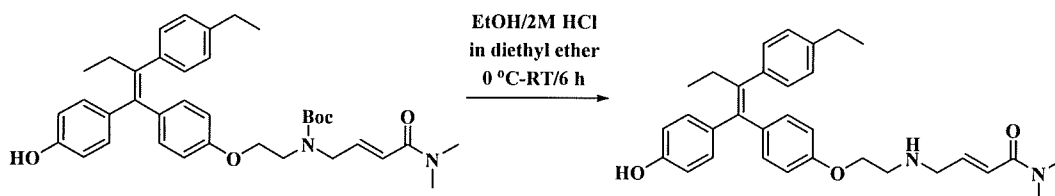
Step-4: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.15 g, 0.3 mmol) in dichloromethane (5 mL) was added boc anhydride (0.065 mg, 0.3 mmol). The reaction mixture was stirred for 2 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture

was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude compound was purified by column chromatography eluting with 3% MeOH in dichloromethane to afford tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.13 g, 72%).

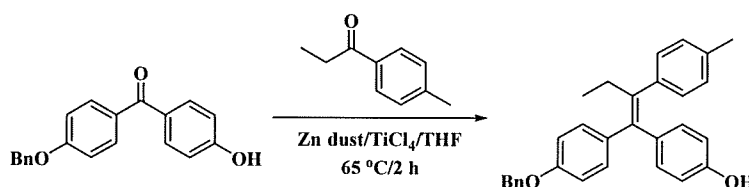
Step-5: Synthesis of ((E)-4-((2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.13 g, 0.261 mmol) in EtOH (2 mL) was added at 0 °C, 2M HCl in diethyl ether (10 mL). The reaction mixture was stirred for 6 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with dichloromethane. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((Z)-2-(4-ethylphenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.075 g, 5%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.38 (s, 1H), 7.00-6.95 (m, 6H), 6.75-6.45 (m, 8H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.40-3.39 (m, 2H), 2.99 (s, 3H), 2.85 (s, 3H), 2.78 (t, *J* = 5.2 Hz, 2H), 2.40-2.32 (m, 4H), 1.13 (t, *J* = 7.6 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H). LCMS: 499.3 [M+H]⁺

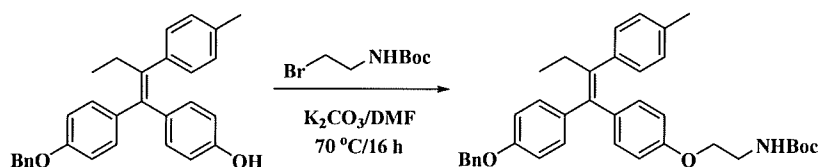
Example 21: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(*p*-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of (E)-4-(1-(4-(benzyloxy)phenyl)-2-(*p*-tolyl)but-1-en-1-yl)phenol



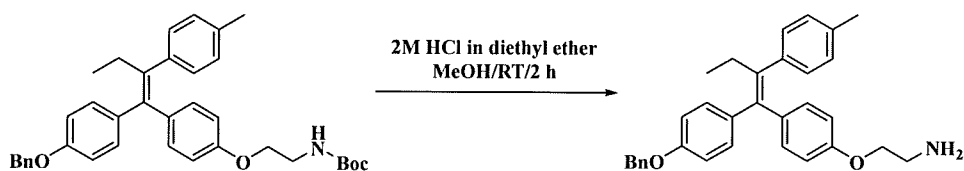
Zinc dust (6.4 g, 98.57 mmol) was suspended in dry THF (100 mL) and cooled this suspension to -10 °C. To this TiCl₄ (5.4 mL, 49.28 mmol) was added slowly under nitrogen atmosphere, stirred there for 15 min, slowly allowed it to reach room temperature and heated to reflux for 2 h. The resulting mixture was cooled to 0 °C, and a solution of 4-(benzyloxy)phenyl(4-hydroxyphenyl) methanone (5 g, 16.42 mmol) and 1-(p-tolyl)propan-1-one (2.35 g, 13.8 mmol) in dry THF (100 mL) were added and the contents were refluxed for 2 h. The reaction mixture was cooled to room temperature and quenched with 10% aqueous K₂CO₃ solution and was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated. The crude material was purified by column chromatography over 230-400 mesh silica using 10% ethyl acetate in *n*-hexane to afford (E)-4-(1-(4-(benzyloxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenol (4.5 g, 65.2 %).

Step-2: Synthesis of tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



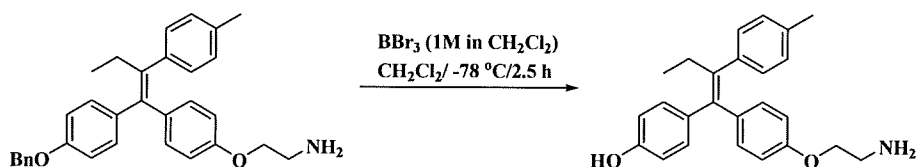
To a solution of (E)-4-(1-(4-(benzyloxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenol (4.5 g, 10.71 mmol) in DMF (50 mL) was added potassium carbonate (14.8 g, 107 mmol) and tert-butyl (2-bromoethyl)carbamate (3.6 g, 16.07 mmol). The reaction mixture was heated to 70 °C and maintained at this temperature for 16 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate (250 mL x 2). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 5-20% ethyl acetate in *n*-hexane to afford tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (3.3 g).

Step-3: Synthesis of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethan-1-amine



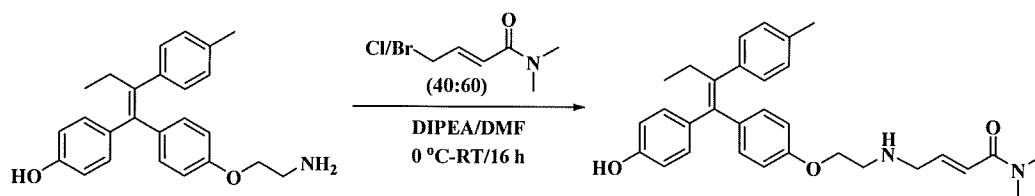
To a stirred solution of tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethylcarbamate (3 g, 5.32 mmol) in methanol (15 mL) was added at 0 °C, 2M HCl in diethyl ether (60 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with 10% MeOH in dichloromethane. Organic layer was concentrated under reduced pressure and the crude material was purified by column chromatography over 230-400 mesh silica gel using (4-5%) MeOH in dichloromethane to afford (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethan-1-amine (2.3 g, 93.5%).

Step-4: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenol



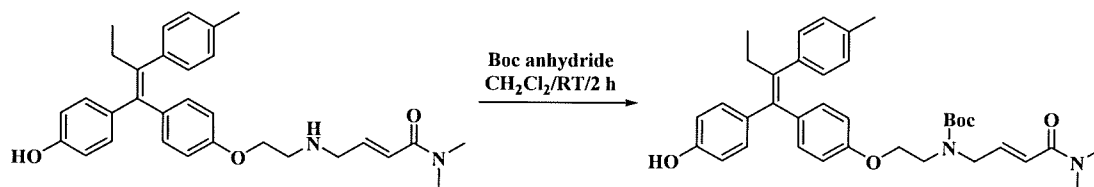
To a stirred solution of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethan-1-amine (2.3 g, 4.9 mmol) in dichloromethane (23 mL) was added BBr₃ (1M solution in dichloromethane, 6.2 g, 24.84 mmol) at -78 °C. The reaction mixture was stirred for 2.5 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (100 mL) and layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude compound. The crude material was purified by column chromatography over 230-400 mesh silica gel using 10% MeOH in dichloromethane to afford desired compound (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenol (0.92 g, 40.8 %).

Step-5: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



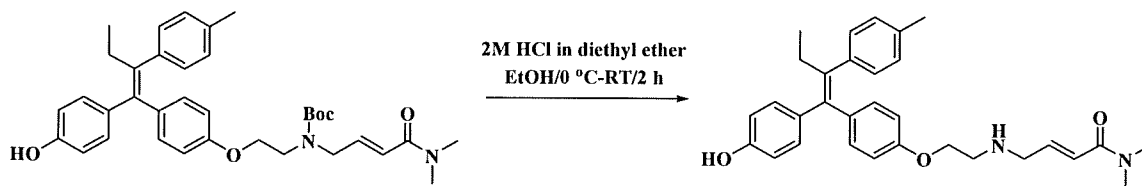
To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(p-tolyl)but-1-en-1-yl)phenol (0.92 g, 2.02 mmol) in DMF (5 mL) was added DIPEA (0.52 g, 4.04 mmol) stirred for 15 min at room temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.29 g, 1.51 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 16 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (1 g, crude).

Step-6: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (1 g, 2.06 mmol) in dichloromethane (20 mL) was added boc anhydride (0.54 g, 2.47 mmol). The reaction mixture was stirred for 2 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 2-3% MeOH in dichloromethane to afford desired compound tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.27 g).

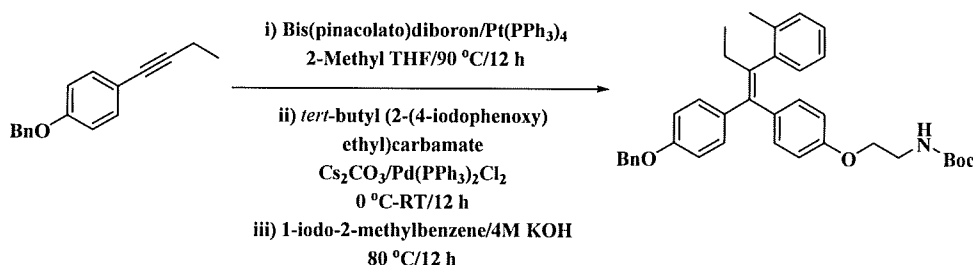
Step-7: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(p-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.27 g, 0.557 mmol) in ethanol (1.5 mL) was added at 0 °C, 2M HCl in diethyl ether (10 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (0.025 g, 11.2%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.40 (s, 1H), 6.97-6.91 (m, 4H), 6.74-6.72 (m, 4H), 6.69-6.41 (m, 6H), 3.88 (t, *J* = 5.4 Hz, 2H), 3.00 (s, 3H), 2.85 (s, 3H), 2.81-2.67 (m, 2H), 2.55-2.50 (m, 2H), 2.45-2.35 (m, 2H), 2.21 (s, 3H), 0.83 (t, *J* = 7.2 Hz, 3H). LCMS: 485.3 [M+H]⁺

Example 22: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(o-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

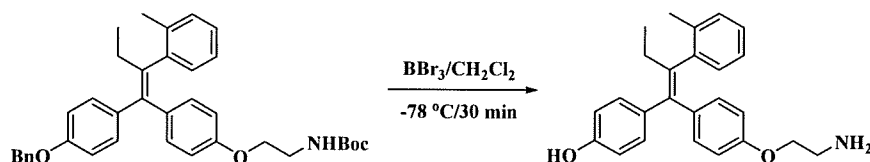
Step-1: Synthesis of tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-(o-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 1-(benzyloxy)-4-(but-1-yn-1-yl)benzene (3 g, 12.7 mmol, Example-125, Step-4) in 2-methyl THF (30 mL), was added bis(pinacolato)diboron (3.22 g, 12.7 mmol), tetrakis(triphenylphosphine)platinum (0) (0.13 g, 0.104 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 12 h. The solution was allowed to cool to room temperature and tert-butyl (2-(4-iodophenoxy)ethyl)carbamate (4.29 g, 11.8 mmol),

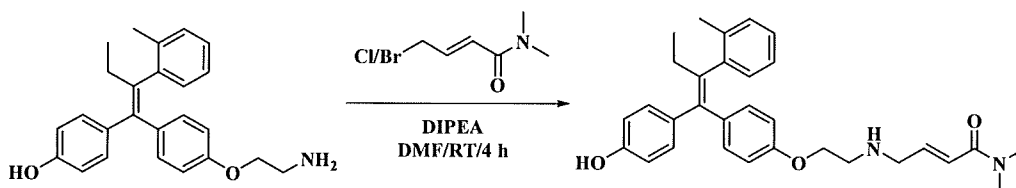
bis(triphenylphosphine)palladium (II) dichloride (0.415 g, 0.59 mmol), cesium carbonate (7.71 g, 23.6 mmol) and 2-methyl THF (60 mL) were added. This mixture was degassed with nitrogen and water (1 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (2.31 g, 56 mmol) and 1-iodo-2-methylbenzene (3.57 g, 15 mmol) were added. Reaction mixture was stirred at 80 °C for 12 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 5% EtOAc in *n*-hexane to afford tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (1.7 g, 40%).

Step-2: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenol



To a stirred solution of tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (1 g, 2.07 mmol) in dichloromethane (10 mL) was added BBr₃ (1M solution in dichloromethane, 10.35 mL, 10.35 mmol) at -78 °C. The reaction mixture was stirred for 30 min and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenol (0.5 g, 64%).

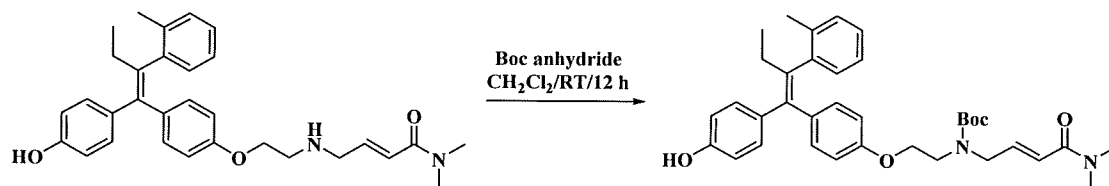
Step-3: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide



To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenol (0.35 g, 0.938 mmol) in DMF (2.5 mL) was added DIPEA (0.242 g, 1.87 mmol) at room

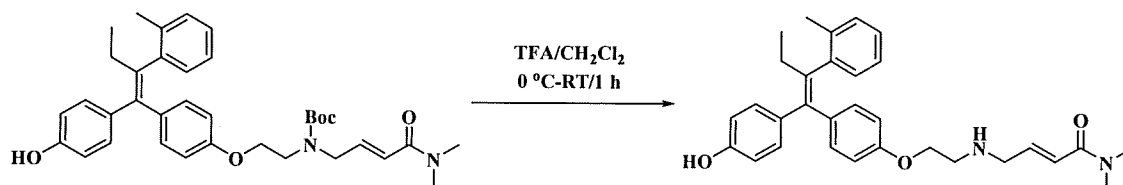
temperature, stirred for 15 min at same temperature. A solution of (*E*)-4-bromo-*N,N*-dimethylbut-2-enamide and (*E*)-4-chloro-*N,N*-dimethylbut-2-enamide mixture (0.143 g, 0.75 mmol, Example-101, Step-7) in DMF (2.5 mL) was added drop wise, reaction mixture was stirred for 5 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (0.8 g, crude).

Step-4: Synthesis of tert-butyl ((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (*E*)-4-((2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (0.8 g, 1.65 mmol) in dichloromethane (10 mL) was added boc anhydride (0.72 g, 3.30 mmol). The reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by column chromatography over 230-400 mesh silica gel using 2% MeOH in dichloromethane to obtain tert-butyl ((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.22 g, 22%).

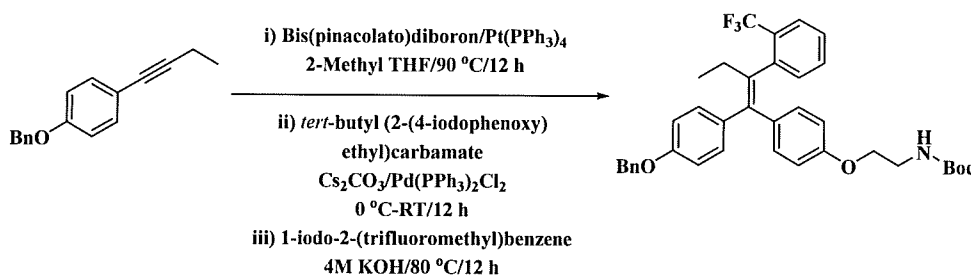
Step-5: Synthesis of (*E*)-4-((2-(4-((*Z*)-1-(4-hydroxyphenyl)-2-(*o*-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(o-tolyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.2 g, 0.342 mmol) in dichloromethane (10 mL) was added at 0 °C, TFA (1.5 mL). The reaction mixture was stirred for 1 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(o-tolyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.030 g) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.39 (s, 1H), 7.19-7.11 (m, 1H), 7.07 (dd, *J*₁ = 10.6 Hz, *J*₂ = 1.4 Hz, 1H), 7.04 (d, *J* = 1.6 Hz, 2H), 7.03-7.00 (m, 2H), 6.77-6.68 (m, 4H), 6.62 (t, *J* = 5 Hz, 1H), 6.59-6.47 (m, 3H), 3.84 (t, *J* = 5.2 Hz, 2H), 3.31-3.30 (m, 2H), 2.98 (s, 3H), 2.84 (s, 3H), 2.76 (t, *J* = 5.8 Hz, 2H), 2.31 (q, *J* = 7.4 Hz, 2H), 2.04 (s, 3H), 0.83 (t, *J* = 7.6 Hz, 3H). LCMS: 485.3 [M+H]⁺

Example 23: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

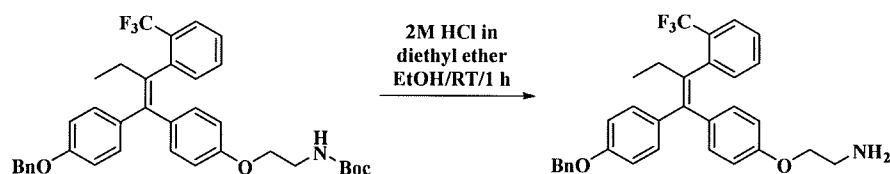
Step-1: Synthesis of tert-butyl (Z)-((2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 1-(benzyloxy)-4-(but-1-yn-1-yl)benzene (2 g, 8.47 mmol, Example-125, Step-4) in 2-methyl THF (20 mL), was added bis(pinacolato)diboron (2.15 g, 8.47 mmol), tetrakis(triphenylphosphine)platinum (0) (0.13 g, 0.104 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 12 h. The solution was allowed to cool to room temperature and tert-butyl (2-(4-iodophenoxy)ethyl)carbamate (2 g, 5.51 mmol), bis(triphenylphosphine)palladium (II) dichloride (0.276 g, 0.393 mmol), cesium carbonate (5.1 g, 15.74 mmol) and 2-methyl THF (20 mL) were added. This mixture was degassed with nitrogen and water (0.2 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (11 mL, 4.48 mmol)

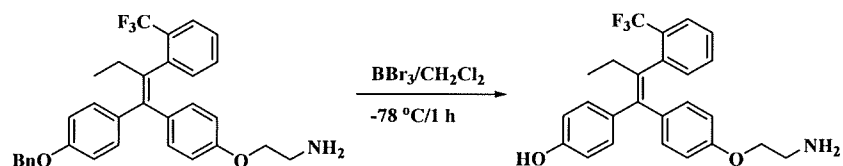
and 1-iodo-2-(trifluoromethyl)benzene (3.2 g, 12.2 mmol) were added. Reaction mixture was stirred at 80 °C for 12 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 5% EtOAc in *n*-hexane to afford tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (2 g, 36%).

Step-2: Synthesis of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethan-1-amine



To a stirred solution of tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (2 g, 3.24 mmol) in EtOH (2 mL) was added at 0 °C, 2M HCl in ether (30 mL). The reaction mixture was stirred for 1 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with EtOAc. Organic layer was concentrated under reduced pressure to afford (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethan-1-amine (1.5 g).

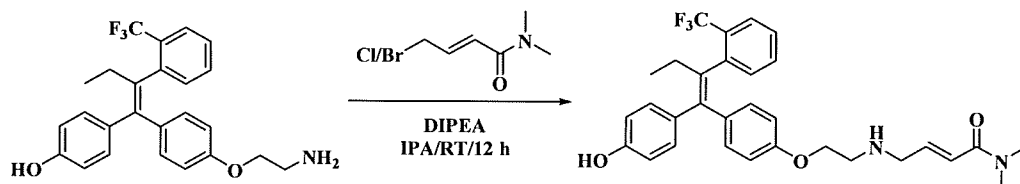
Step-3: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenol



To a stirred solution of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethan-1-amine (1.5 g, 2.9 mmol) in dichloromethane (20 mL) was added BBr₃ (1M solution in dichloromethane, 14.5 mL, 14.5 mmol) at -78 °C. The reaction mixture was stirred for 1 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium

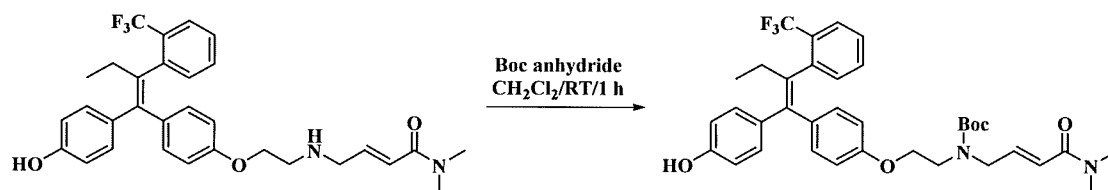
sulphate and concentrated under reduced pressure to obtain (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenol (0.8 g, 62%).

Step-4: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenol (0.8 g, 1.87 mmol) in IPA (10 mL) was added DIPEA (0.67 mL, 3.74 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.322 g, 1.87 mmol, Example-101, Step-7) in IPA (10 mL) was added drop wise, reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (0.9 g, crude).

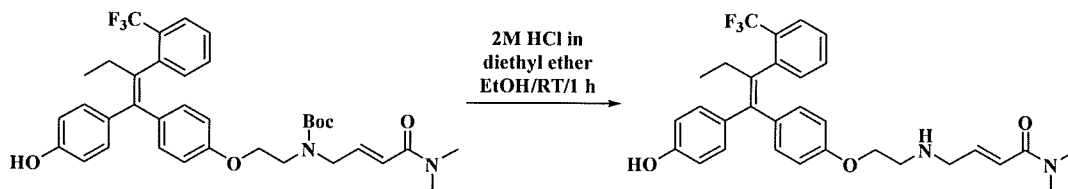
Step-5: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.9 g, 1.67 mmol) in dichloromethane (20 mL) was added boc anhydride (0.54 mL, 2.5 mmol). The reaction mixture was stirred for 1 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under

reduced pressure. Crude material was purified by combi-flash using 2% MeOH in dichloromethane to obtain tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.2 g, 20%).

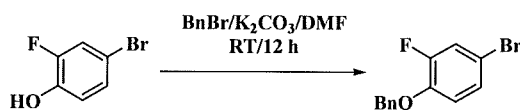
Step-6: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.2 g, 0.313 mmol) in EtOH (1 mL) was added at 0 °C, 2M HCl in diethyl ether (10 mL). The reaction mixture was stirred for 1 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.12 g) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.41 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.54-7.50 (m, 1H), 7.39-7.34 (m, 2H), 7.01-6.99 (m, 2H), 6.78-6.72 (m, 4H), 6.62-6.47 (m, 4H), 3.84 (t, *J* = 5.6 Hz, 2H), 3.31-3.25 (m, 2H), 2.98 (s, 3H), 2.84 (s, 3H), 2.76 (t, *J* = 5.6 Hz, 2H), 2.33-2.17 (m, 2H), 0.82 (t, *J* = 7.6 Hz, 3H). LCMS: 539.3 [M+H]⁺

Example 24: Synthesis of (E)-4-((2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

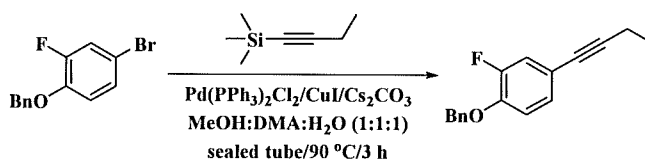
Step-1: Synthesis of 1-(benzyloxy)-4-bromo-2-fluorobenzene



To a solution of 4-bromo-2-fluorophenol (10 g, 52.3 mmol) in DMF (70 mL), were added potassium carbonate (8.7 g, 62.8 mmol) and benzyl bromide (9.85 g, 57.5 mmol) sequentially

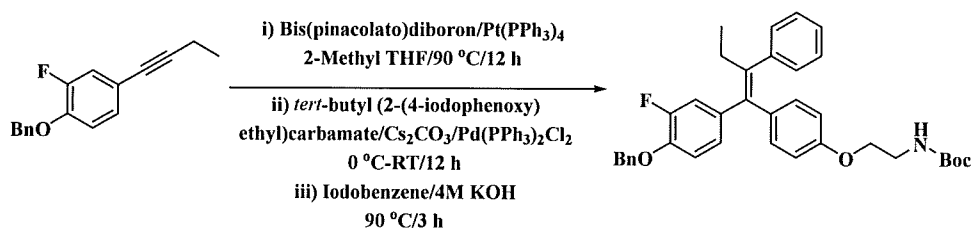
at room temperature. The resulting mixture was stirred at room temperature for 12 h, completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure. The crude compound was purified over 230-400 mesh silica gel column chromatography using 8% EtOAc in *n*-hexane to afford 1-(benzyloxy)-4-bromo-2-fluorobenzene (12.7 g, 86.6%).

Step-2: Synthesis of 1-(benzyloxy)-4-(but-1-yn-1-yl)-2-fluorobenzene



To a stirred solution of 1-(benzyloxy)-4-bromo-2-fluorobenzene (6 g, 21.4 mmol) in 60 mL of MeOH:DMA:H₂O (1:1:1) in a sealed tube, were added copper iodide (0.41 g, 2.14 mmol) and cesium carbonate (12.57 g, 38.5 mmol) at room temperature. This mixture was degassed with three vacuum/N₂ cycles, and were added but-1-yn-1-yltrimethylsilane (10.8 g, 85.7 mmol, Example-16, Step-2) followed by Pd(PPh₃)₂Cl₂ (0.752 g, 1.07 mmol). The pressure tube was sealed and heated at 90 °C for 3 h. Upon completion by TLC, the reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by combo-flash using 0.2% EtOAc in *n*-hexane to afford 1-(benzyloxy)-4-(but-1-yn-1-yl)-2-fluorobenzene (2.88 g, 51.8%).

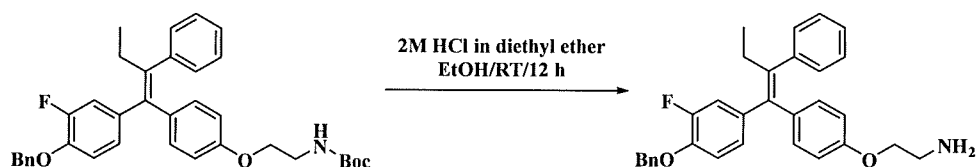
Step-3: Synthesis of tert-butyl (E)-(2-(4-(1-(4-(benzyloxy)-3-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 1-(benzyloxy)-4-(but-1-yn-1-yl)-2-fluorobenzene (2.85 g, 11.2 mmol) in 2-methyl THF (30 mL), was added bis(pinacolato)diboron (2.85 g, 11.2 mmol), tetrakis(triphenylphosphine)platinum (0) (0.106 g, 0.0852 mmol) under nitrogen atmosphere,

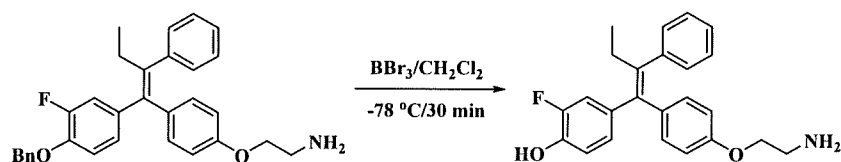
reaction mixture was stirred at 90 °C for 12 h. The solution was allowed to cool to room temperature and *tert*-butyl (2-(4-iodophenoxy)ethyl)carbamate (2.85 g, 7.85 mmol, Example-17, Step-2), bis(triphenylphosphine)palladium (II) dichloride (0.393 g, 0.56 mmol), cesium carbonate (7.315 g, 22.4 mmol) and 2-methyl THF (30 mL) were added. This mixture was degassed with nitrogen and water (10 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (15.4 mL, 61.6 mmol) and iodobenzene (1.38 mL, 12.3 mmol) were added. Reaction mixture was stirred at 90 °C for 3 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 12.5% EtOAc in *n*-hexane to afford *tert*-butyl (E)-2-(4-(1-(4-(benzyloxy)-3-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (3.8 g, 59.7 %).

Step-4: Synthesis of (E)-2-(4-(1-(4-(benzyloxy)-3-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine



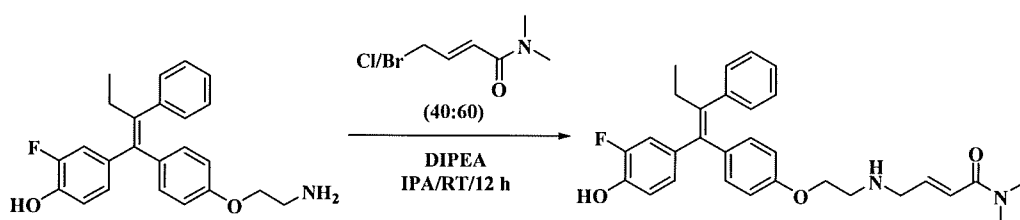
To a stirred solution of *tert*-butyl (E)-2-(4-(1-(4-(benzyloxy)-3-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (3.8 g, 6.7 mmol) in ethanol (10 mL) was added at 0 °C, 2M HCl in diethyl ether (30 mL). The reaction mixture was stirred for 12 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Organic layer was concentrated under reduced pressure to afford crude (E)-2-(4-(1-(4-(benzyloxy)-3-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (3.1 g crude).

Step-5: Synthesis of (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-fluorophenol



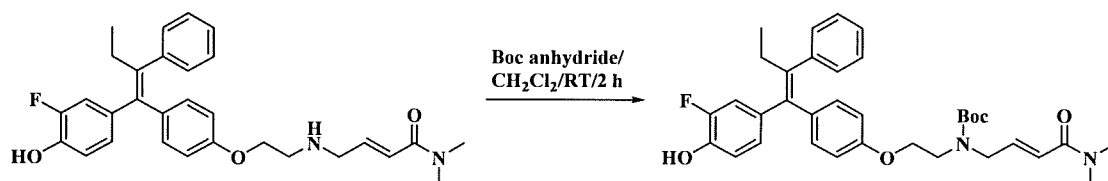
To a stirred solution of (E)-2-(4-(1-(4-(benzyloxy)-3-fluorophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (3.1 g, 6.6 mmol) in dichloromethane (75 mL) was added BBr₃ (1M solution in dichloromethane, 33.2 mL, 33.19 mmol) at -78 °C. The reaction mixture was stirred for 0.5 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-fluorophenol (1.4 g, crude).

Step-6: Synthesis of (E)-4-((2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



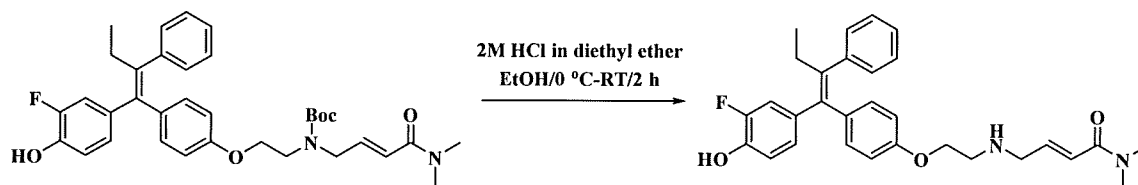
To a stirred solution of (E)-4-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-fluorophenol (1.4 g, 3.7 mmol) in IPA (15 mL) was added DIPEA (1.28 mL, 7.4 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.512 g, 2.9 mmol, Example-101, Step-7) in IPA (5 mL) was added drop wise, reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (0.42 g, crude).

Step-7: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



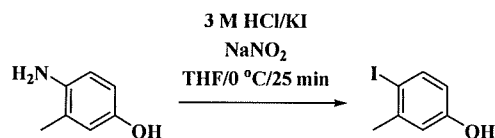
To a stirred solution of (E)-4-((2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.42 g, 0.86 mmol) in dichloromethane (10 mL) was added boc anhydride (0.375 g, 1.7 mmol). The reaction mixture was stirred for 2 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by column chromatography over 230-400 mesh silica gel using (30%) acetone in dichloromethane to obtain tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.15 g, crude).

Step-8: Synthesis of (E)-4-((2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

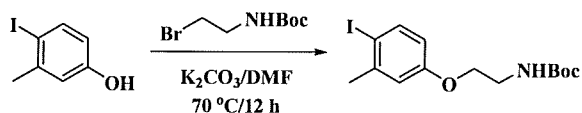


To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.15 g, 0.25 mmol) in EtOH (0.2 mL) was added at 0 °C, 2M HCl in diethyl ether (2.5 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative TLC to afford desired compound (E)-4-((2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.006 g, 4.8%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.87 (s, 1H), 7.20-7.08 (m, 5H), 6.95 (t, *J* = 8.8 Hz, 1H), 6.88-6.81 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.63-6.61 (m, 4H), 3.95-3.85 (m, 2H), 3.59-3.41 (m, 2H), 3.01 (s, 3H), 2.96-2.88 (m, 2H), 2.85 (s, 3H), 2.40 (q, *J* = 7 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). LCMS: 489.3 [M+H]⁺

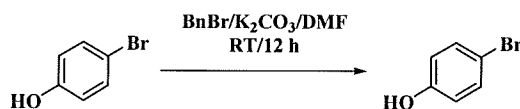
Example 25: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of 4-iodo-3-methylphenol

To a solution of 4-amino-3-methylphenol (10 g, 81 mmol) in THF (45 mL) was added 3M HCl (35 mL) at 0 °C over a period of 10 min followed by NaNO₂ (6.1 g, 89 mmol). To the above reaction mixture, potassium iodide (53.89 g, 166 mmol) in water (140 mL) was added dropwise and stirred at 0 °C for 15 min. After completion of reaction, reaction mixture was extracted with EtOAc. Organic layer was washed water followed by brine, concentrated under reduced pressure to obtain the crude compound. Crude material was purified by column chromatography over 230-400 mesh silica gel using 10% EtOAc in *n*-hexane to give the title compound (9 g, 47%).

Step-2: Synthesis of tert-butyl (2-(4-iodo-3-methylphenoxy)ethyl)carbamate

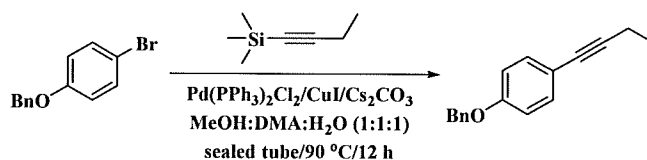
To a solution of 4-iodo-3-methylphenol (8 g, 34.3 mmol) in DMF (80 mL) was added potassium carbonate (28.4 g, 206 mmol) and tert-butyl (2-bromoethyl)carbamate (15.38 g, 68.6 mmol). The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched with water and extracted with ethyl acetate (250 mL x 2). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford tert-butyl (2-(4-iodo-3-methylphenoxy)ethyl)carbamate (3.4 g, 28%).

Step-3: Synthesis of 1-(benzyloxy)-4-bromobenzene

To a solution of 4-bromophenol (5 g, 28.9 mmol) in DMF (50 mL), were added potassium carbonate (11.9 g, 86.7 mmol) and benzyl bromide (5.9 g, 34.6 mmol) sequentially at room temperature. The resulting mixture was stirred at room temperature for 12 h, completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature,

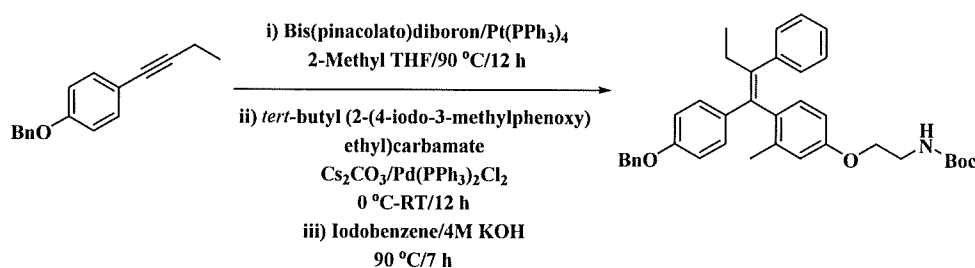
diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure. The crude compound was purified over 230-400 mesh silica gel column chromatography using 8% EtOAc in *n*-hexane to afford 1-(benzyloxy)-4-bromobenzene (6 g, 79%).

Step-4: Synthesis of 1-(benzyloxy)-4-(but-1-yn-1-yl)benzene



To a stirred solution of 1-(benzyloxy)-4-bromobenzene (2.5 g, 9.54 mmol) in 30 mL of MeOH:DMA:H₂O (1:1:1) in a sealed tube, were added copper iodide (0.181 g, 0.95 mmol) and cesium carbonate (4.3 g, 13.3 mmol) at room temperature. This mixture was degassed with three vacuum/N₂ cycles, and were added but-1-yn-1-yltrimethylsilane (2.4 g, 19 mmol, Example-16, Step-2) followed by Pd(PPh₃)₂Cl₂ (0.334 g, 0.479 mmol). The pressure tube was sealed and heated at 90 °C for 12 h. Upon completion by TLC, the reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography using 1% EtOAc in *n*-hexane to afford 1-(benzyloxy)-4-(but-1-yn-1-yl)benzene (1.6 g, 72%).

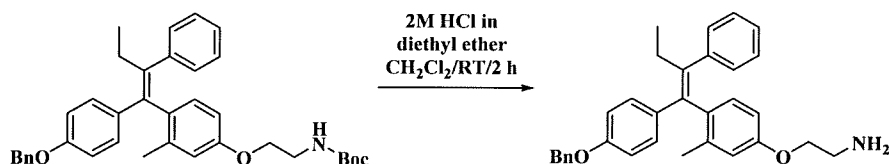
Step-3: Synthesis of tert-butyl (Z)-(2-(4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)carbamate



To a stirred solution of 1-(benzyloxy)-4-(but-1-yn-1-yl)benzene (3 g, 12.7 mmol) in 2-methyl THF (30 mL), was added bis(pinacolato)diboron (3.22 g, 12.7 mmol), tetrakis(triphenylphosphine)platinum (0) (0.13 g, 0.104 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 12 h. The solution was allowed to cool to room

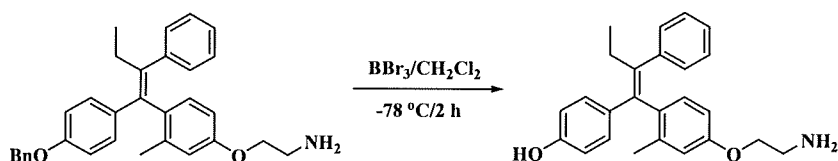
temperature and tert-butyl (2-(4-iodo-3-methylphenoxy)ethyl)carbamate (3.4 g, 8.99 mmol), bis(triphenylphosphine)palladium (II) dichloride (0.315 g, 0.44 mmol), cesium carbonate (5.86 g, 17.9 mmol) and 2-methyl THF (30 mL) were added. This mixture was degassed with nitrogen and water (0.5 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (2.51 g, 44.8 mmol) and iodobenzene (1.66 g, 8.15 mmol) were added. Reaction mixture was stirred at 90 °C for 7 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 25% EtOAc in *n*-hexane to afford tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)carbamate (1.8 g, 40 %).

Step-4: Synthesis of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethan-1-amine



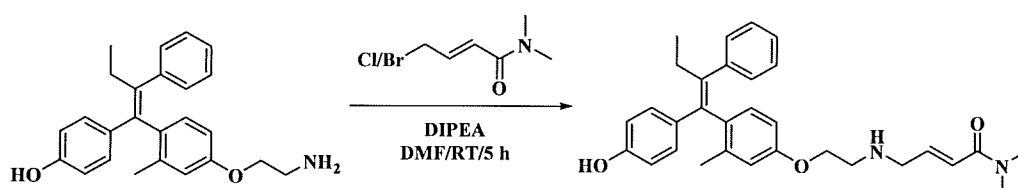
To a stirred solution of tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)carbamate (1.8 g, 3.19 mmol) in dichloromethane (10 mL) was added at 0 °C, 2M HCl in ether (20 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with 10% MeOH in dichloromethane. Organic layer was concentrated under reduced pressure to afford (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethan-1-amine (1.5 g).

Step-5: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenol



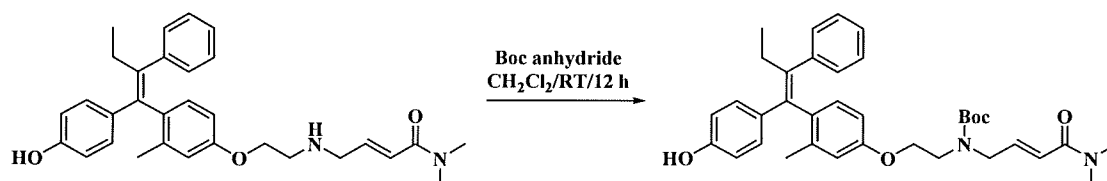
To a stirred solution of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethan-1-amine (1.5 g, 3.2 mmol) in dichloromethane (15 mL) was added BBr₃ (1M solution in dichloromethane, 16 mL, 16 mmol) at -78 °C. The reaction mixture was stirred for 2 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain (Z)-4-(1-(4-(2-aminoethoxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenol (0.8 g, 66%).

Step-6: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



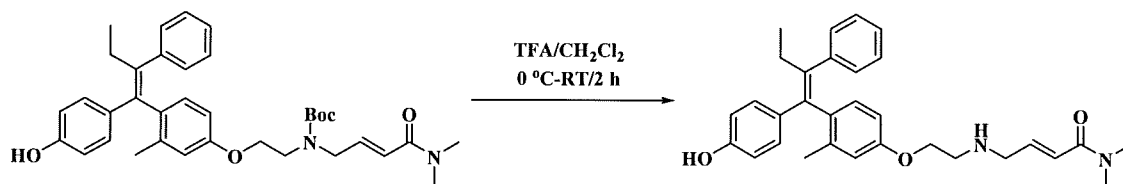
To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)-2-methylphenyl)-2-phenylbut-1-en-1-yl)phenol (0.8 g, 2.14 mmol) in DMF (6 mL) was added DIPEA (0.55 g, 4.2 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.4 g, 2.14 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 5 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (1.5 g, crude).

Step-7: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (1.5 g, 3 mmol) in dichloromethane (20 mL) was added boc anhydride (1.35 g, 6.1 mmol). The reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by column chromatography over 230-400 mesh silica gel using 2% MeOH in dichloromethane to obtain tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)carbamate (0.35 g, 19%).

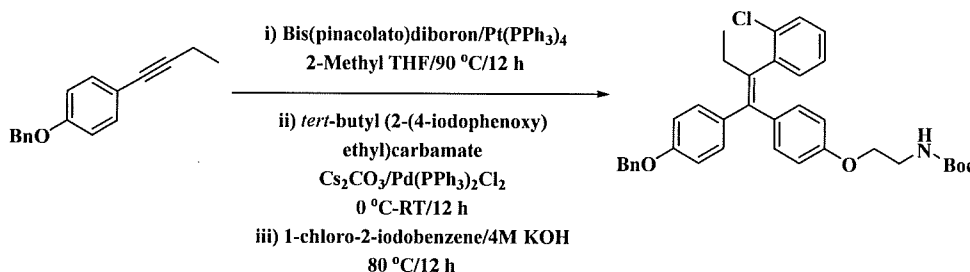
Step-8: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)carbamate (0.35 g, 0.599 mmol) in dichloromethane (5 mL) was added at 0 °C, TFA (1 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)-3-methylphenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (4.2 mg) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.37 (s, 1H), 7.13-7.09 (m, 2H), 7.05-7.01 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.63-6.52 (m, 1H), 6.51-6.46 (m, 3H), 3.86 (t, *J* = 6.0 Hz, 2H), 3.33-3.31 (m, 2H), 2.99 (s, 3H), 2.85 (s, 3H), 2.78 (t, *J* = 5.6 Hz, 2H), 2.50-2.49 (m, 2H), 1.95 (s, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). LCMS: 485.3 [M+H]⁺

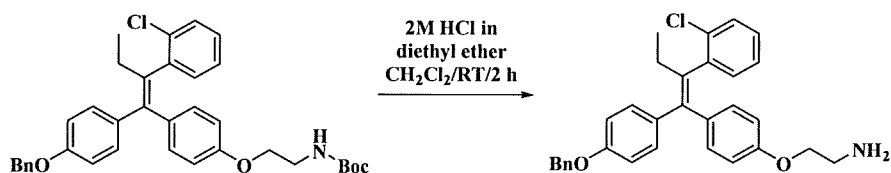
Example-26: Synthesis of (E)-4-((2-(4-((Z)-2-(2-chlorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



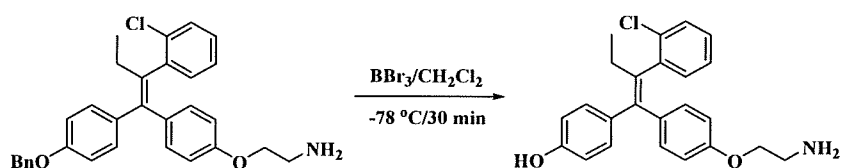
To a stirred solution of 1-(benzyloxy)-4-(but-1-yn-1-yl)benzene (3 g, 12.7 mmol, Example-125, Step-4) in 2-methyl THF (30 mL), was added bis(pinacolato)diboron (3.22 g, 12.7 mmol), tetrakis(triphenylphosphine)platinum (0) (0.13 g, 0.104 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 12 h. The solution was allowed to cool to room temperature and *tert*-butyl (2-(4-iodophenoxy)ethyl)carbamate (4.29 g, 11.8 mmol), bis(triphenylphosphine)palladium (II) dichloride (0.415 g, 0.59 mmol), cesium carbonate (7.71 g, 23.6 mmol) and 2-methyl THF (60 mL) were added. This mixture was degassed with nitrogen and water (1 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (3.59 g, 64.2 mmol) and 1-chloro-2-iodobenzene (5.56 g, 23.3 mmol) were added. Reaction mixture was stirred at 80 °C for 12 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 5% EtOAc in *n*-hexane to afford *tert*-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (3 g, 44%).

Step-2: Synthesis of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenoxy)ethan-1-amine



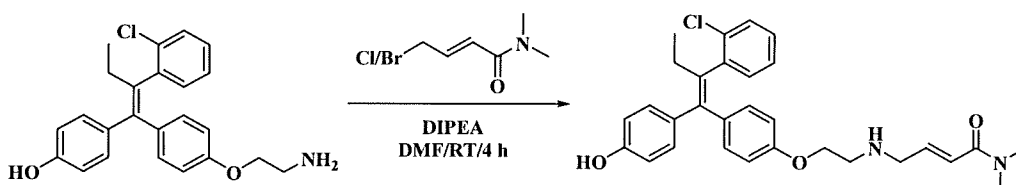
To a stirred solution of tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (3 g, 5.1 mmol) in dichloromethane (30 mL) was added at 0 °C, 2M HCl in ether (30 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with 10% MeOH in dichloromethane. Organic layer was concentrated under reduced pressure to afford (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenoxy)ethan-1-amine (2.5 g).

Step-3: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenol



To a stirred solution of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenoxy)ethan-1-amine (2.5 g, 5.1 mmol) in dichloromethane (30 mL) was added BBr₃ (1M solution in dichloromethane, 25.8 mL, 25.8 mmol) at -78 °C. The reaction mixture was stirred for 30 min and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenol (1 g, 50%).

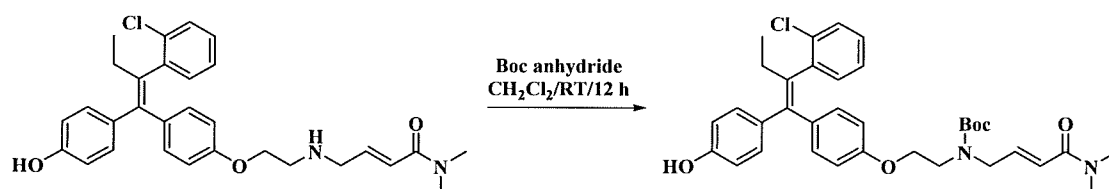
Step-4: Synthesis of (E)-4-((2-(4-((Z)-2-(2-chlorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(2-chlorophenyl)but-1-en-1-yl)phenol (1 g, 2.5 mmol) in DMF (5 mL) was added DIPEA (0.9 mL, 5 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.437 g, 2.29 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was

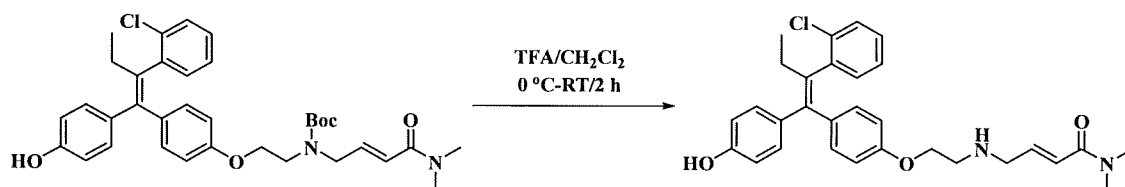
stirred for 5 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (1.5 g, crude).

Step-5: Synthesis of tert-butyl (2-(4-((Z)-2-(2-chlorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate



To a stirred solution of (E)-4-((2-(4-((Z)-2-(2-chlorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (1.5 g, 2.97 mmol) in dichloromethane (20 mL) was added boc anhydride (1.29 g, 5.95 mmol). The reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by column chromatography over 230-400 mesh silica gel using 2% MeOH in dichloromethane to obtain tert-butyl (2-(4-((Z)-2-(2-chlorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.35 g, 23%).

Step-6: Synthesis of (E)-4-((2-(4-((Z)-2-(2-chlorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

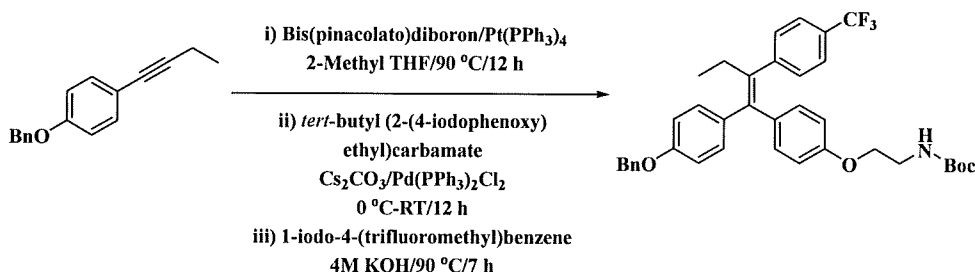


To a stirred solution of tert-butyl (2-(4-((Z)-2-(2-chlorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.35 g, 0.604 mmol) in dichloromethane (15 mL) was added at 0 °C, TFA (0.2 mL, 2.89 mmol). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction,

reaction mixture was basified with saturated NaHCO_3 , extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((Z)-2-(2-chlorophenyl)-1-(4-hydroxyphenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.045 g) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.42 (s, 1H), 7.31 (d, $J = 7.6$ Hz, 1H), 7.19-7.13 (m, 3H), 7.02 (d, $J = 8.4$ Hz, 2H), 7.78-7.75 (m, 4H), 6.67-6.57 (m, 3H), 6.50 (d, $J = 15.2$ Hz, 1H), 3.86 (t, $J = 5.6$ Hz, 2H), 2.99 (s, 3H), 2.85 (s, 3H), 2.36 (q, $J = 7.6$ Hz, 2H), 0.86 (t, $J = 7.6$ Hz, 3H). LCMS: 505.3 $[\text{M}+\text{H}]^+$

Example 27: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

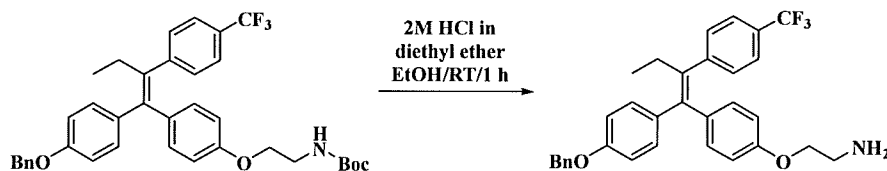
Step-1: Synthesis of tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 1-(benzyloxy)-4-(but-1-yn-1-yl)benzene (2 g, 8.47 mmol, Example-125, Step-4) in 2-methyl THF (20 mL), was added bis(pinacolato)diboron (2.15 g, 8.47 mmol), tetrakis(triphenylphosphine)platinum (0) (0.13 g, 0.104 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 12 h. The solution was allowed to cool to room temperature and tert-butyl (2-(4-iodophenoxy)ethyl)carbamate (2.67 g, 7.3 mmol), bis(triphenylphosphine)palladium (II) dichloride (0.286 g, 0.41 mmol), cesium carbonate (5.32 g, 16.3 mmol) and 2-methyl THF (20 mL) were added. This mixture was degassed with nitrogen and water (0.5 mL) was added. This mixture was stirred at room temperature for 12 h. After completion of reaction, to the above reaction mixture 4M KOH (11 mL, 4.48 mmol) and 1-iodo-4-(trifluoromethyl)benzene (3.2 g, 12.2 mmol) were added. Reaction mixture was stirred at 90 °C for 7 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was

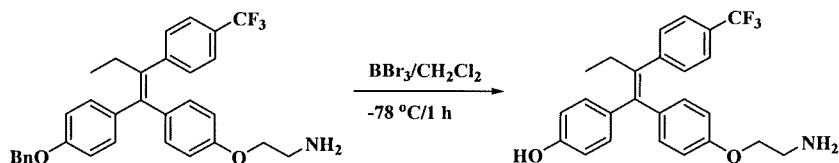
purified by column chromatography over 230-400 mesh silica gel using 20% EtOAc in *n*-hexane to afford tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (3.2 g, 64%).

Step-2: Synthesis of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethan-1-amine



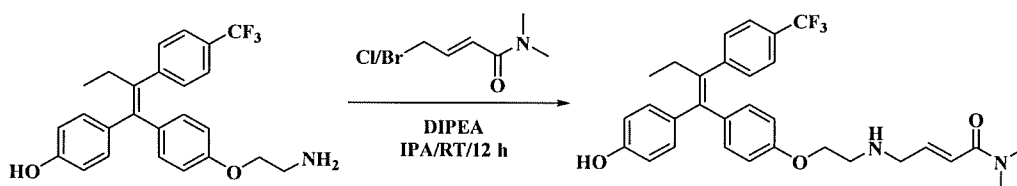
To a stirred solution of tert-butyl (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (3.2 g, 5 mmol) in EtOH (15 mL) was added at 0 °C, 2M HCl in ether (30 mL). The reaction mixture was stirred for 1 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with EtOAc. Organic layer was concentrated under reduced pressure to afford (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethan-1-amine (2.5 g, 93%).

Step-3: Synthesis of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenol



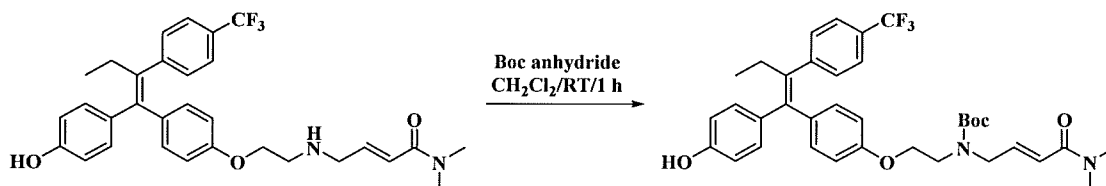
To a stirred solution of (Z)-2-(4-(1-(4-(benzyloxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethan-1-amine (2.5 g, 4.8 mmol) in dichloromethane (50 mL) was added BBr₃ (1M solution in dichloromethane, 24.1 mL, 24.1 mmol) at -78 °C. The reaction mixture was stirred for 1 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenol (0.785 g, 38%).

Step-4: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (Z)-4-(1-(4-(2-aminoethoxy)phenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenol (0.78 g, 1.82 mmol) in IPA (5 mL) was added DIPEA (0.63 mL, 3.65 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.314 g, 1.82 mmol, Example-101, Step-7) in IPA (5 mL) was added drop wise, reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (1.15 g, crude).

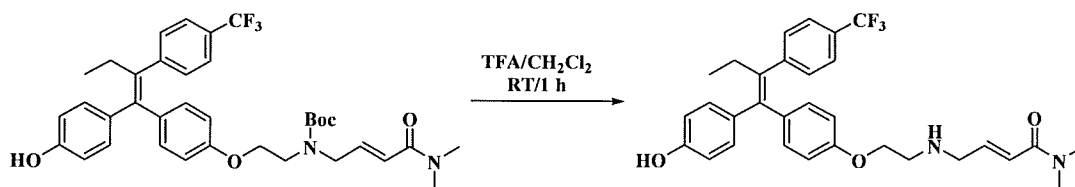
Step-5: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (1.12 g, 2 mmol) in dichloromethane (10 mL) was added boc anhydride (0.9 g, 4 mmol). The reaction mixture was stirred for 1 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by combi-flash using 3.5% MeOH in dichloromethane to obtain tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-

hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.07 g, 7.1%).

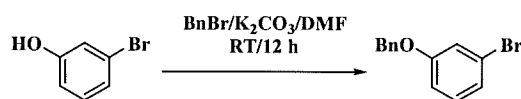
Step-6: Synthesis of (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)carbamate (0.36 g, 0.564 mmol) in dichloromethane (10 mL) was added at 0 °C, TFA (2 mL). The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((Z)-1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.055 g, 18%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.45 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 2.0 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 3.0 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.64-6.57 (m, 3H), 6.49, (d, *J* = 15.2 Hz, 1H), 3.87 (t, *J* = 5.4 Hz, 2H), 2.99 (s, 3H), 2.84 (s, 3H), 2.78 (t, *J* = 5.4 Hz, 2H), 2.50-2.44 (m, 2H), 2.06 (bs, 1H), 0.84 (t, *J* = 7.4 Hz, 3H). LCMS: 539.3 [M+H]⁺

Example 28: Synthesis of (E)-4-((2-(4-((E)-1-(3-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

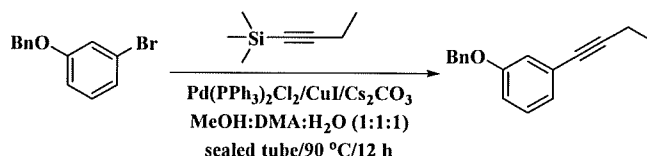
Step-1: Synthesis of 1-(benzyloxy)-3-bromobenzene



To a solution of 3-bromophenol (5 g, 28.9 mmol) in DMF (50 mL), were added potassium carbonate (11.9 g, 86.7 mmol) and benzyl bromide (5.9 g, 34.6 mmol) sequentially at room temperature. The resulting mixture was stirred at room temperature for 12 h, completion of

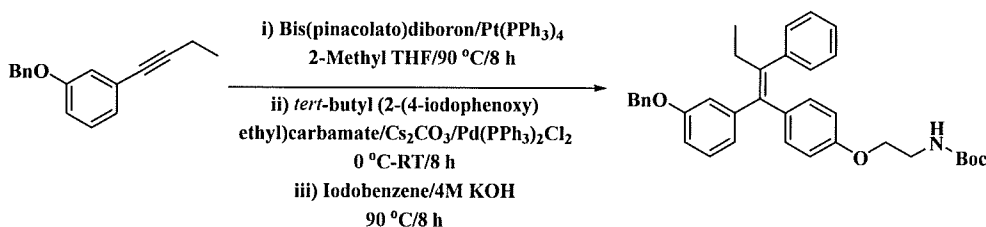
the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure. The crude compound was purified over 230-400 mesh silica gel column chromatography using 8% EtOAc in *n*-hexane to afford 1-(benzyloxy)-3-bromobenzene (6 g, 79%).

Step-2: Synthesis of 1-(benzyloxy)-3-(but-1-yn-1-yl)benzene



To a stirred solution of 1-(benzyloxy)-3-bromobenzene (2.5 g, 9.54 mmol) in 30 mL of MeOH:DMA:H₂O (1:1:1) in a sealed tube, were added copper iodide (0.181 g, 0.95 mmol) and cesium carbonate (4.3 g, 13.3 mmol) at room temperature. This mixture was degassed with three vacuum/N₂ cycles, and were added but-1-yn-1-yltrimethylsilane (2.4 g, 19 mmol, Example-16, Step-2) followed by Pd(PPh₃)₂Cl₂ (0.334 g, 0.479 mmol). The pressure tube was sealed and heated at 90 °C for 12 h. Upon completion by TLC, the reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography using 1% EtOAc in *n*-hexane to afford 1-(benzyloxy)-3-(but-1-yn-1-yl)benzene (1.6 g, 72%).

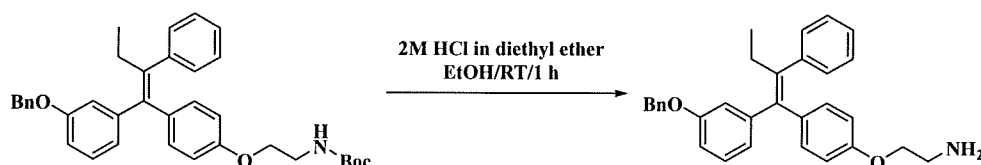
Step-3: Synthesis of tert-butyl (E)-(2-(4-(1-(3-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 1-(benzyloxy)-3-(but-1-yn-1-yl)benzene (3.2 g, 13.55 mmol) in 2-methyl THF (30 mL), was added bis(pinacolato)diboron (3.4 g, 13.55 mmol), tetrakis(triphenylphosphine)platinum (0) (0.118 g, 0.094 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 8 h. The solution was allowed to cool to room

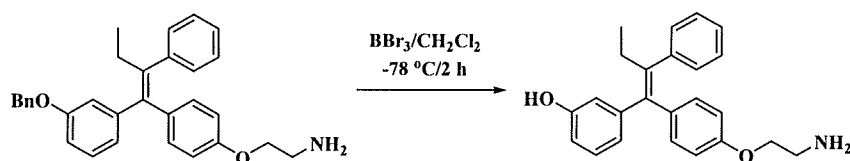
temperature and *tert*-butyl (2-(4-iodophenoxy)ethyl)carbamate (4.2 g, 11.63 mmol, Example-17, Step-2), bis(triphenylphosphine)palladium (II) dichloride (0.408 g, 0.58 mmol), cesium carbonate (7.5 g, 23.26 mmol) and 2-methyl THF (50 mL) were added. This mixture was degassed with nitrogen and water (1 mL) was added. This mixture was stirred at room temperature for 8 h. After completion of reaction, to the above reaction mixture 4M KOH (16 mL, 64.24 mmol) and iodobenzene (2.3 g, 11.68 mmol) were added. Reaction mixture was stirred at 90 °C for 8 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 2% MeOH in dichloromethane to afford *tert*-butyl (E)-2-(4-(1-(3-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (8 g, crude).

Step-4: Synthesis of (E)-2-(4-(1-(3-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine



To a stirred solution of *tert*-butyl (E)-2-(4-(1-(3-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (8 g, 14.56 mmol) in ethanol (10 mL) was added at 0 °C, 2M HCl in diethyl ether (70 mL). The reaction mixture was stirred for 1 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Organic layer was concentrated under reduced pressure to afford crude (E)-2-(4-(1-(3-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (2.5 g).

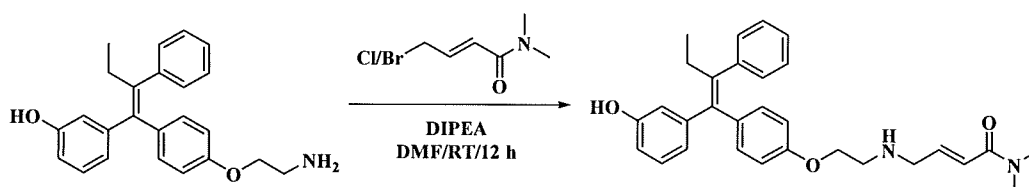
Step-5: Synthesis of (E)-3-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol



To a stirred solution of (E)-2-(4-(1-(3-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethan-1-amine (2.5 g, 5.56 mmol) in dichloromethane (50 mL) was added BBr₃ (1M solution in dichloromethane, 27.8 mL, 27.8 mmol) at -78 °C. The reaction mixture was

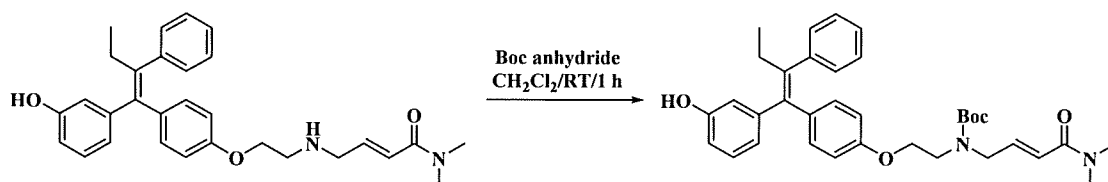
stirred for 2 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude (E)-3-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (1.1 g, crude).

Step-6: Synthesis of (E)-4-((2-(4-((E)-1-(3-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (E)-3-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (1.1 g, 3.06 mmol) in DMF (20 mL) was added DIPEA (1.1 mL, 6.12 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.42 g, 2.45 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 12 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (1.4 g, crude).

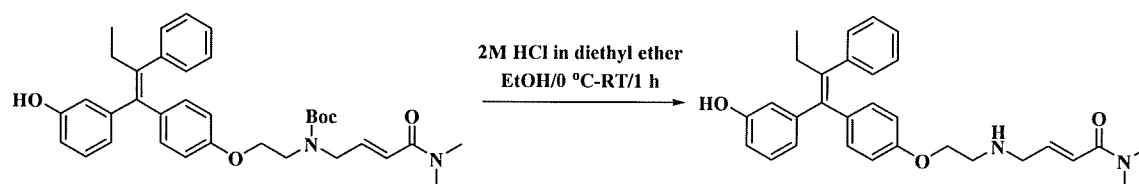
Step-7: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(3-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-(4-((E)-1-(3-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (1.4 g, 2.97 mmol) in dichloromethane (20 mL) was added boc anhydride (0.97 g, 4.46 mmol). The reaction mixture was stirred for 1 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture

was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by combi-flash to obtain tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(3-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.6 g).

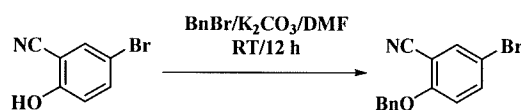
Step-8: Synthesis of (E)-4-((2-(4-((E)-1-(3-fluoro-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-1-(3-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (0.6 g, 1.05 mmol) in EtOH (3 mL) was added at 0 °C, 2M HCl in diethyl ether (15 mL). The reaction mixture was stirred for 1 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((E)-1-(3-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.16 g). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.34 (s, 1H), 7.20-7.09 (m, 6H), 6.73-6.67 (m, 2H), 6.66-6.48 (m, 7H), 3.87 (t, *J* = 5.8 Hz, 2H), 3.32-3.31 (m, 2H), 2.99 (s, 3H), 2.84 (s, 3H), 2.78 (t, *J* = 5.4 Hz, 2H), 2.39 (q, *J* = 7.4 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). LC MS: 471.3 [M+H]⁺

Example 29: Synthesis of (E)-4-((2-(4-((E)-1-(3-cyano-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

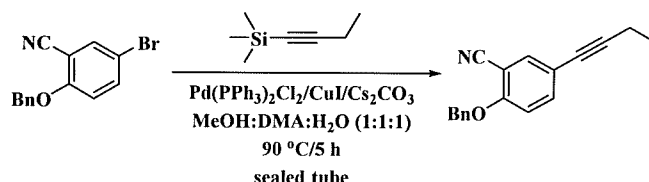
Step-1: Synthesis of 2-(benzyloxy)-5-bromobenzonitrile



To a solution of 5-bromo-2-hydroxybenzonitrile (10 g, 50.5 mmol) in acetonitrile (100 mL), were added potassium carbonate (62.7 g, 454 mmol) and benzyl bromide (6.5 mL, 55 mmol)

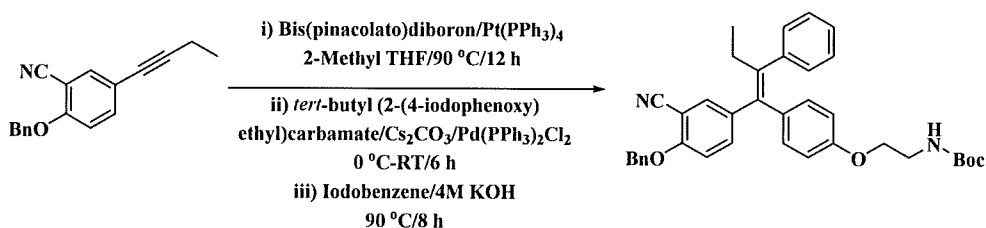
sequentially at room temperature. The resulting mixture was stirred at room temperature for 12 h, completion of the reaction was monitored by TLC. The reaction mixture was diluted with water, extracted with ethyl acetate and washed with sodium bicarbonate solution. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to afford 2-(benzyloxy)-5-bromobenzonitrile (13.8 g, 81%).

Step-2: Synthesis of 2-(benzyloxy)-5-(but-1-yn-1-yl)benzonitrile



To a stirred solution of 2-(benzyloxy)-5-bromobenzonitrile (10 g, 29.8 mmol) in 90 mL of MeOH:DMA:H₂O (1:1:1) in a sealed tube, were added copper iodide (0.570 g, 2.98 mmol) and cesium carbonate (17.51 g, 53.7 mmol) at room temperature. This mixture was degassed with three vacuum/N₂ cycles, and were added but-1-yn-1-yltrimethylsilane (7.52 g, 59 mmol, Example-16, Step-2) followed by Pd(PPh₃)₂Cl₂ (1 g, 1.49 mmol). The pressure tube was sealed and heated at 90 °C for 5 h. Upon completion by TLC, the reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography using 3% EtOAc in *n*-hexane to afford 2-(benzyloxy)-5-(but-1-yn-1-yl)benzonitrile (6.8 g, 88%).

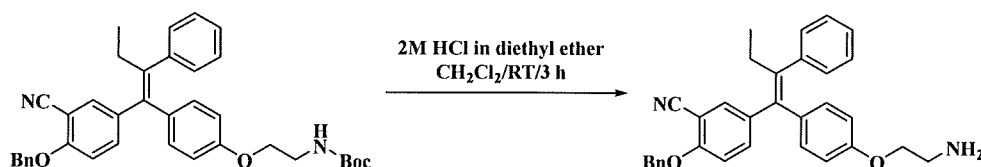
Step-3: Synthesis of tert-butyl (E)-(2-(4-(1-(4-(benzyloxy)-3-cyanophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate



To a stirred solution of 2-(benzyloxy)-5-(but-1-yn-1-yl)benzonitrile (6.8 g, 26 mmol) in 2-methyl THF (60 mL), was added bis(pinacolato)diboron (6.61 g, 26 mmol), tetrakis(triphenylphosphine)platinum (0) (0.324 g, 0.26 mmol) under nitrogen atmosphere, reaction mixture was stirred at 90 °C for 12 h. The solution was allowed to cool to room

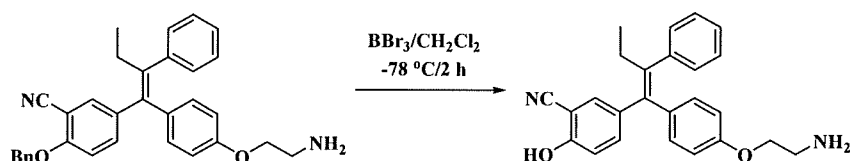
temperature and *tert*-butyl (2-(4-iodophenoxy)ethyl)carbamate (9.44 g, 26 mmol, Example-17, Step-2), bis(triphenylphosphine)palladium (II) dichloride (0.913 g, 1.3 mmol), cesium carbonate (16.96 g, 52 mmol) and 2-methyl THF (30 mL) were added. This mixture was degassed with nitrogen and water (2 mL) was added. This mixture was stirred at room temperature for 6 h. After completion of reaction, to the above reaction mixture 4M KOH (7.99 g, 142.7 mmol) and iodobenzene (7.41 g, 36.3 mmol) were added. Reaction mixture was stirred at 80 °C for 12 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 5-6% EtOAc in *n*-hexane to afford *tert*-butyl (E)-(2-(4-(1-(4-(benzyloxy)-3-cyanophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (6.3 g, 43%).

Step-4: Synthesis of (E)-5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-(benzyloxy)benzonitrile



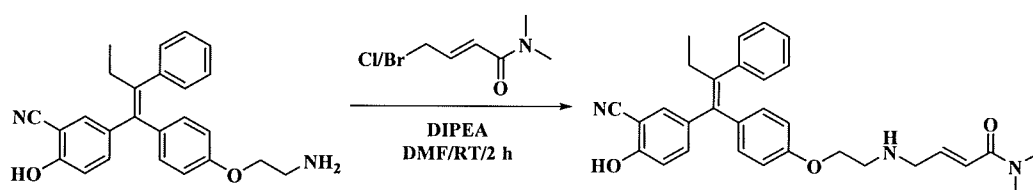
To a stirred solution of *tert*-butyl (E)-(2-(4-(1-(4-(benzyloxy)-3-cyanophenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (6.3 g, 10.9 mmol) in dichloromethane (60 mL) was added at 0 °C, 2M HCl in diethyl ether (30 mL). The reaction mixture was stirred for 3 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Organic layer was concentrated under reduced pressure to afford (E)-5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-(benzyloxy)benzonitrile (4.6 g, 92%).

Step-5: Synthesis of (E)-5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-hydroxybenzonitrile



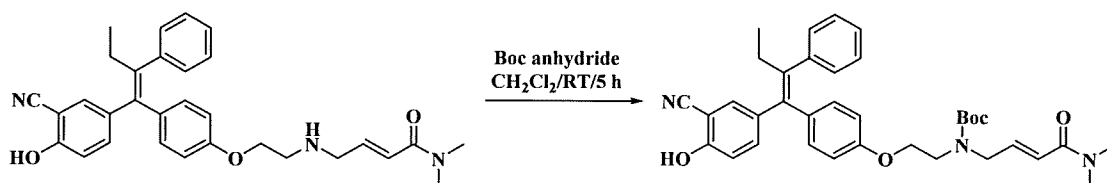
To a stirred solution of (E)-5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-(benzyloxy)benzonitrile (1 g, 2.1 mmol) in dichloromethane (10 mL) was added BBr₃ (1M solution in dichloromethane, 10.5 mL, 10.5 mmol) at -78 °C. The reaction mixture was stirred for 2 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude (E)-5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-hydroxybenzonitrile (0.38 g, 47%).

Step-6: Synthesis of (E)-4-((2-(4-((E)-1-(3-cyano-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



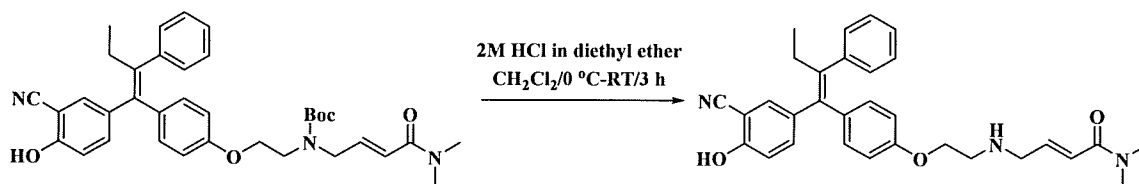
To a stirred solution of (E)-5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)-2-hydroxybenzonitrile (0.38 g, 0.989 mmol) in DMF (8 mL) was added DIPEA (0.255 g, 1.979 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.188 g, 0.989 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 2 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (0.5 g, crude).

Step-7: Synthesis of tert-butyl (2-(4-((E)-1-(3-cyano-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate



To a stirred solution of (E)-4-((2-(4-((E)-1-(3-cyano-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.5 g, 1.01 mmol) in dichloromethane (5 mL) was added boc anhydride (0.33 g, 1.5 mmol). The reaction mixture was stirred for 2 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude material was purified by combi-flash to obtain tert-butyl (2-(4-((E)-1-(3-cyano-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.08 g, 13.3%).

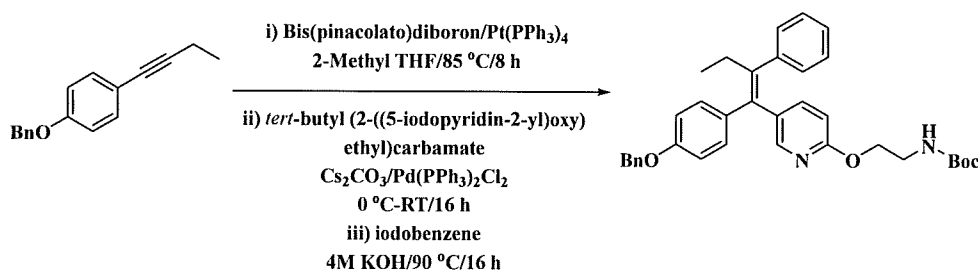
Step-8: Synthesis of (E)-4-((2-(4-((E)-1-(3-cyano-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl (2-(4-((E)-1-(3-cyano-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (0.26 g, 0.436 mmol) in dichloromethane (10 mL) was added at 0 °C, 2M HCl in diethyl ether (5 mL). The reaction mixture was stirred for 3 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO₃, extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-(4-((E)-1-(3-cyano-4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.025 g). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.35 (d, *J* = 2.0 Hz, 1H), 7.29 (dd, *J*₁ = 8.6 Hz, *J*₂ = 2.2 Hz, 1H), 7.20-7.17 (m, 2H), 7.12-7.09 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.64-6.48 (m, 4H), 3.87 (t, *J* = 5.6 Hz, 2H), 3.32-3.16 (m, 2H), 2.99 (s, 3H), 2.84 (s, 3H), 2.78 (t, *J* = 5.8 Hz, 2H), 3.70 (q, *J* = 7.4 Hz, 2H), 0.85 (t, *J* = 7.6 Hz, 3H). LCMS: 496.3 [M+H]⁺

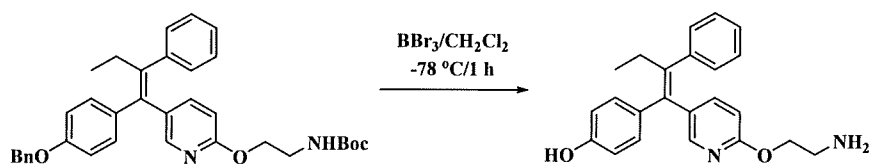
Example 30: Synthesis of (E)-4-((2-((5-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)-N,N-dimethylbut-2-enamide

Step-1: Synthesis of tert-butyl (Z)-2-((5-((1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)carbamate



To a stirred solution of 1-(benzyloxy)-4-(but-1-yn-1-yl)benzene (6.2 g, 26.2 mmol, Example-125, Step-4) in 2-methyl THF (62 mL), was added bis(pinacolato)diboron (6.7 g, 26.5 mmol), tetrakis(triphenylphosphine)platinum (0) (0.32 g, 0.26 mmol) under nitrogen atmosphere, reaction mixture was stirred at 85 °C for 8 h. The solution was allowed to cool to room temperature and *tert*-butyl (2-((5-iodopyridin-2-yl)oxy)ethyl)carbamate (9.5 g, 26.5 mmol, Example-62, Step-1), bis(triphenylphosphine)palladium (II) dichloride (0.93 g, 1.3 mmol), cesium carbonate (17.06 g, 52.5 mmol) and 2-methyl THF (60 mL) were added. This mixture was degassed with nitrogen and water (2 mL) was added. This mixture was stirred at room temperature for 16 h. After completion of reaction, to the above reaction mixture 4M KOH (36 mL, 144 mmol) and iodobenzene (7.49 g, 36.7 mmol) were added. Reaction mixture was stirred at 90 °C for 16 h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 10-15% EtOAc in *n*-hexane to afford *tert*-butyl (Z)-2-((5-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)carbamate (12.1 g, 78%).

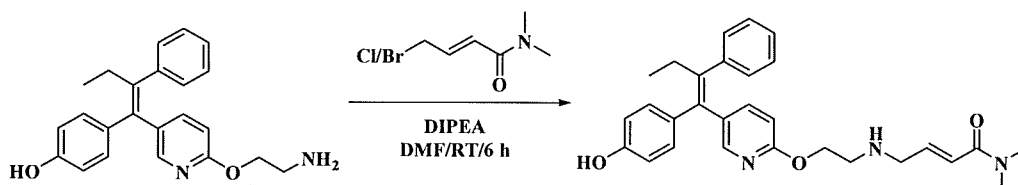
Step-2: Synthesis of (Z)-4-(1-(6-(2-aminoethoxy)pyridin-3-yl)-2-phenylbut-1-en-1-yl)phenol



To a stirred solution of *tert*-butyl (Z)-2-((5-(1-(4-(benzyloxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)carbamate (7 g, 12.7 mmol) in dichloromethane (70 mL) was added BBr_3 (1M solution in dichloromethane, 63.6 mL, 63.6 mmol) at -78 °C. The reaction mixture was stirred for 1 h and quenched with MeOH (5 mL). The resulting mixture was slowly warmed to room temperature; water was added (50 mL) and layers were separated. The

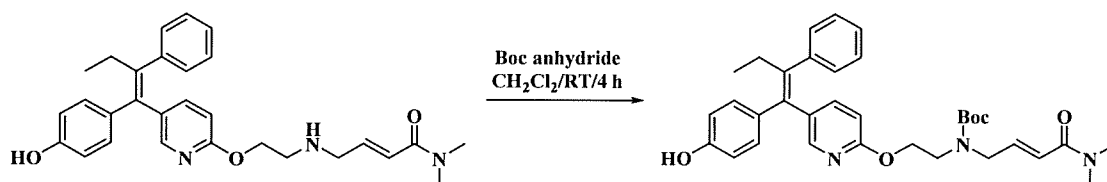
organic layer was washed with saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain (Z)-4-(1-(6-(2-aminoethoxy)pyridin-3-yl)-2-phenylbut-1-en-1-yl)phenol (3.5 g, 76%).

Step-3: Synthesis of (E)-4-((2-((5-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of (Z)-4-(1-(6-(2-aminoethoxy)pyridin-3-yl)-2-phenylbut-1-en-1-yl)phenol (2 g, 5.55 mmol) in DMF (15 mL) was added DIPEA (1.43 g, 11 mmol) at room temperature, stirred for 15 min at same temperature. A solution of (E)-4-bromo-N,N-dimethylbut-2-enamide and (E)-4-chloro-N,N-dimethylbut-2-enamide mixture (0.94 g, 5.55 mmol, Example-101, Step-7) in DMF (5 mL) was added drop wise, reaction mixture was stirred for 6 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by saturated NaCl solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was used in next step without further purification (3.2 g, crude).

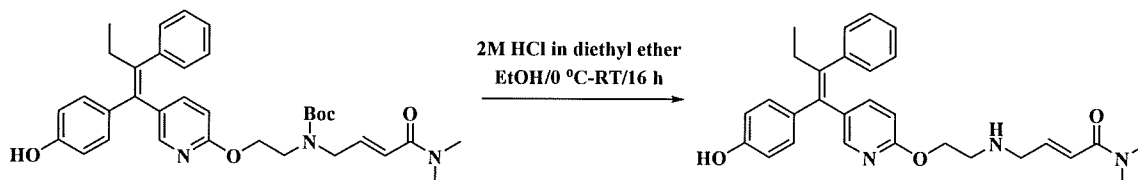
Step-4: Synthesis of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-((5-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)carbamate



To a stirred solution of (E)-4-((2-((5-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)-N,N-dimethylbut-2-enamide (3.2 g, 6.78 mmol) in dichloromethane (32 mL) was added boc anhydride (2.2 g, 10 mmol). The reaction mixture was stirred for 4 h at room temperature, after completion of reaction (monitored by TLC), reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water followed by saturated NaCl solution,

dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified by combi-flash using 2-3% MeOH in dichloromethane to obtain tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-((5-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)carbamate (0.76 g).

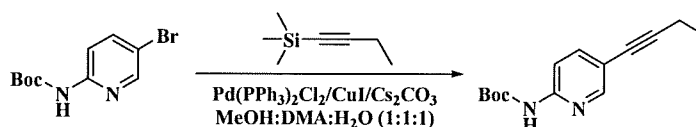
Step-5: Synthesis of (E)-4-((2-((5-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)-N,N-dimethylbut-2-enamide



To a stirred solution of tert-butyl ((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)(2-((5-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)carbamate (0.75 g, 0.564 mmol) in EtOH (3.5 mL) was added at 0 °C, 2M HCl in diethyl ether (3.5 mL). The reaction mixture was stirred for 16 h at room temperature. After completion of reaction, reaction mixture was basified with saturated NaHCO_3 , extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. Crude compound was purified by preparative HPLC to afford desired compound (E)-4-((2-((5-((Z)-1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)-N,N-dimethylbut-2-enamide (0.045 g, 7.3%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.45 (s, 1H), 7.53 (s, 1H), 7.23-7.19 (m, 2H), 7.17-7.07 (m, 4H), 7.02-7.00 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 6.63-6.59 (m, 1H), 6.50-6.47 (m, 2H), 4.12 (t, J = 5.6 Hz, 2H), 3.31-3.33 (m, 2H), 2.99 (s, 3H), 2.84 (s, 3H), 2.77 (t, J = 5.6 Hz, 2H), 2.40 (q, J = 7.7 Hz, 2H), 0.84 (t, J = 7.7 Hz, 3H). LCMS: 472.3 $[\text{M}+\text{H}]^+$

Example 31: Synthesis of (E)-4-((2-((E)-1-(6-aminopyridin-3-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-N,N-dimethylbut-2-enamide

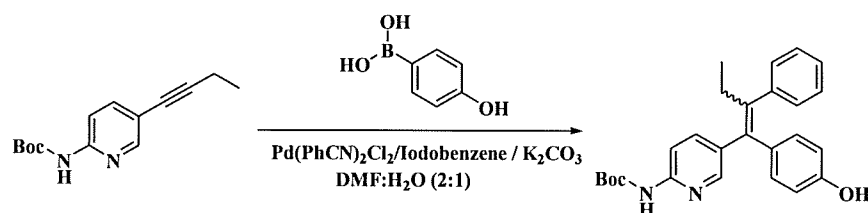
Step-1: Synthesis of tert-butyl (5-(but-1-yn-1-yl)pyridin-2-yl)carbamate



To a stirred solution of tert-butyl (5-bromopyridin-2-yl)carbamate (3 g, 10.989 mmol) in 30 mL of MeOH:DMA:H₂O (1:1:1) in a sealed tube, were added copper iodide (0.235 g, 1.098

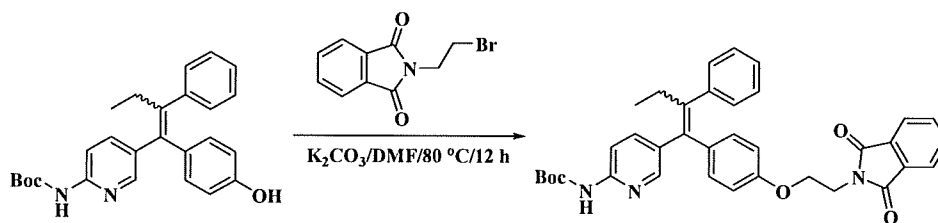
mmol) and cesium carbonate (4.849 g, 15.3 mmol) at room temperature. This mixture was degassed with three vacuum/N₂ cycles, and were added but-1-yn-1-yltrimethylsilane (2.76 g, 22 mmol, Example-16, Step-2) followed by Pd(PPh₃)₂Cl₂ (0.384 g, 0.5 mmol). The pressure tube was sealed and heated at 90 °C for 12 h. Upon completion by TLC, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 X 50 mL). The combined organic extracts were washed with water, brine, dried over sodium sulphate and concentrated. The crude product was purified over 230-400 mesh silica column chromatography using 5% EtOAc in *n*-hexane to afford tert-butyl (5-(but-1-yn-1-yl)pyridin-2-yl)carbamate (2.5 g, 88%) as a white solid.

Step-2: Synthesis of tert-butyl (E)-(5-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate.



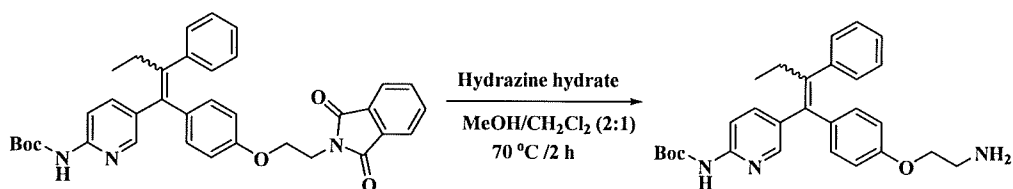
To a solution of tert-butyl (5-(but-1-yn-1-yl)pyridin-2-yl)carbamate (1.5 g, 6.09 mmol), iodobenzene (3.73 g, 18.29 mmol), 4-hydroxy phenyl boronic acid (2.52 g, 18.29 mmol), in N,N-dimethyl formamide/water (2:1, 15 mL) was added K₂CO₃ (2.52 g, 18.29 mmol). The contents were degassed with three vacuum/N₂ cycles, and then stirred for 1 h until the solution was homogeneous. A solution of Pd(PhCN)₂Cl₂ (0.022 g, 0.0609 mmol) in N,N-dimethyl formamide (1 mL) was added and the resulting mixture was stirred at 45 °C for 12 h. Upon completion by TLC, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, brine, dried over sodium sulphate and concentrated. The crude material was purified over 230-400 mesh silica column chromatography using 20% ethyl acetate in *n*-hexane to afford tert-butyl (E)-(5-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (1.2 g, 47%) as an off-white solid.

Step-3: Synthesis of tert-butyl (E)-(5-(1-(4-(2-(1,3-dioxoisindolin-2-yl)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate



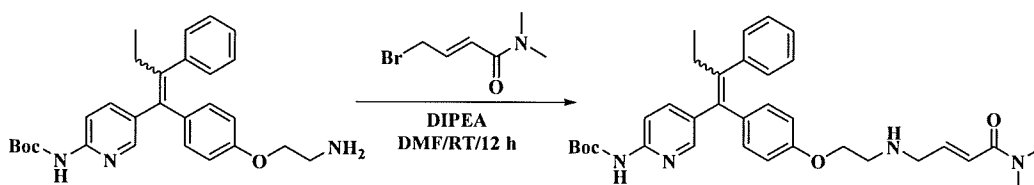
To a solution of (E)-(5-(1-(4-hydroxyphenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.5 g, 1.2 mmol) in DMF (12 mL), at 0 °C, were added sequentially potassium carbonate (0.663 g, 4.8 mmol) and 2-(2-bromoethyl)isoindoline-1,3-dione (1.52 g, 6 mmol). The reaction mixture was stirred at 80 °C for 12 h, was diluted with ethyl acetate, washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 230-400 mesh silica gel using 20% ethyl acetate in n-hexane to afford tert-butyl (E)-(5-(1-(4-(2-(1,3-dioxoisindolin-2-yl)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.35 g, 50%) as a light brown colour gummy mass.

Step-4: Synthesis of tert-butyl (E)-(5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate



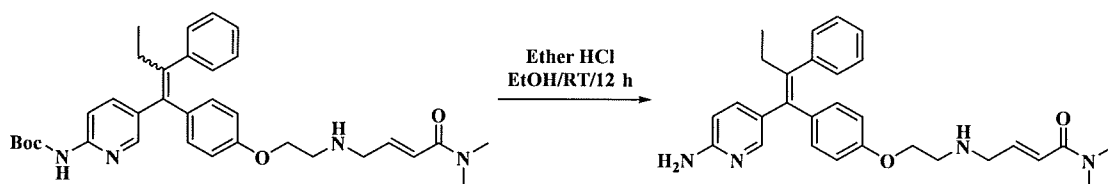
To a solution of (E)-(5-(1-(4-(2-(1,3-dioxoisindolin-2-yl)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.5 g, 0.8488 mmol) in MeOH/DCM (2:1, 15 mL) was added hydrazine hydrate (10 mL) at room temperature. The reaction mixture was stirred at 70 °C for 2 h, quenched with NH₄OH and extracted with dichloromethane. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 100-200 mesh silica gel using 10% methanol in DCM to afford tert-butyl (E)-(5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.12 g, 30%) as an off-white solid.

Step-5: Synthesis of tert-butyl (5-((E)-1-(4-(2-(((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)amino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate



To a stirred solution of *tert*-butyl (5-(1-(4-(2-aminoethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.120 g, 0.261 mmol) in DMF (10 mL) was added at 0 °C, (*E*)-4-bromo-*N,N*-dimethylbut-2-enamide (0.05 g, 0.261 mmol) and DIPEA (0.068 g, 0.522 mmol). The reaction mixture was stirred for 12 h at room temperature, after completion of reaction, reaction mixture was diluted with cold water (50 mL) and extracted with dichloromethane. The organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography over 100-200 mesh silica gel using 5% methanol in DCM to afford *tert*-butyl (5-((*E*)-1-(4-(2-(((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)amino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.05 g, 33%) as an off-white solid.

Step-6: Synthesis of (*E*)-4-((2-(4-((*E*)-1-(6-aminopyridin-3-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide



To a stirred solution of *tert*-butyl (5-((*E*)-1-(4-(2-(((*E*)-4-(dimethylamino)-4-oxobut-2-en-1-yl)amino)ethoxy)phenyl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)carbamate (0.1 g, 0.176 mmol) in ethanol (5 mL) was added at 0 °C, 2M HCl in ether (10 mL). The reaction mixture was stirred for 12 h at room temperature. After completion of reaction, reaction mixture was basified with sat. NaHCO₃, extracted with 10% MeOH in DCM. Organic layer was concentrated under reduced pressure and the crude material was purified by preparative HPLC to afford (*E*)-4-((2-(4-((*E*)-1-(6-aminopyridin-3-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide (37 mg, 45%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.78 (d, *J* = 2 Hz, 1H), 7.19-7.15 (m, 2H), 7.11-7.07 (m, 4H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.57-6.51 (m, 2H), 6.43 (d, *J* = 8.4 Hz,

1H), 5.95 (s, 2H), 3.89 (d, $J = 5.6$ Hz, 2H), 3.36 (d, $J = 4.8$ Hz, 2H), 3.0 (s, 3H), 2.85 (s, 3H), 2.82-2.81 (m, 2H), 2.46-2.42 (m, 2H), 0.86 (t, $J = 7.2$ Hz, 3H). ES (MS): 471.2 [M+H]⁺

Example 32: Compounds That Inhibit ER α ^{WT/MUT} activity in vitro

Cell culture

MCF7 BUS cells (Coser, *et al.*, (2003) *PNAS* 100(24): 13994-13999) were maintained in Dulbecco's Modified Eagle Medium supplemented with 10% FBS, 4 mM L-glutamine and 1x non-essential amino acids. Lenti-X 293T cells (Clontech, Cat # 632180) were routinely cultured in Dulbecco's Modified Eagle Medium supplemented with 10% FBS.

Site-direct mutagenesis and cell line engineering

The QuikChange II XL Site-Directed Mutagenesis Kit (Agilent Technologies, Cat #200523) was used to generate Y537S, Y537C, Y537N and D538G mutations within the ER α exon 8. Wild-type *ESR1* cDNA (GeneCopoeia Inc., Cat# GC-A0322, accession no. NM 000125) was used as a template with the following mutagenesis primers (where the underlined nucleotides represent site mutations); Y537S: F-AAG AAC GTG GTG CCC CTC TCT GAC CTG CTG CTG GAG ATG (SEQ ID NO: 1), R-CAT CTC CAG CAG CAG GTC AGA GAG GGG CAC CAC GTT CTT (SEQ ID NO: 2); Y537N: F-AAG AAC GTG GTG CCC CTC AAT GAC CTG CTG CTG GAG ATG (SEQ ID NO: 3), R-CAT CTC CAG CAG CAG GTC ATT GAG GGG CAC CAC GTT CTT (SEQ ID NO: 4); Y537C: F-AAG AAC GTG GTG CCC CTC TGT GAC CTG CTG CTG GAG ATG (SEQ ID NO: 5), R-CAT CTC CAG CAG CAG GTC ACA GAG GGG CAC CAC GTT CTT (SEQ ID NO: 6); D538G: F-AAC GTG GTG CCC CTC TAT GGC CTG CTG CTG GAG ATG CTG (SEQ ID NO: 7), R-CAG CAT CTC CAG CAG CAG GCC ATA GAG GGG CAC CAC GTT (SEQ ID NO: 8). WT and mutant *ESR1* cDNAs were cloned into the designation lentiviral vector pLenti6.3/V5-Dest (Invitrogen, Cat #V533-06). To make lentivirus, DNAs (WT and mutant *ESR1*) were co-transfected with packaging plasmids into Lenti-X 293T cells using TransIT (Mirus, Cat #MIR 2700). 48h post-transfection, virus containing media was filtered and added to MCF7 cells in the presence of 8 μ g/ml polybrene overnight. Two days following infection, cells were placed under selection with 10 μ g/ml blasticidin for 2 weeks for stable expression.

In vitro proliferation assays

MCF7-WT and -Y537S cells were seeded at 1500 cells/well in black-walled 96-well plates (assay plates, Costar, Cat #3904). In parallel, cells were also seeded in a separate 96-well plate (8 wells/cell line, control plate) for which a CTG (CellTiter-Glo® Luminescent Viability Assay, Promega, Cat #G7572) was measured the following day (day 0 reading). The day 0 reading was used for the GI₅₀ calculation at the termination of the experiment. The day following seeding, compounds were added to assay plates. Briefly, a 1:4 serial dilution was prepared in DMSO at 200x final concentration for a total of 10 concentrations (9 dilutions containing compound and one is DMSO only). Serially diluted compounds were pipetted into medium to prepare a compound-medium mix at 10x final concentration. 10 µl of compound-medium mix was added to MCF7-WT and -Y537S cells at 3 wells/concentration (triplicate for each concentration). On day 3, media/compound was removed and replaced with fresh media/compound as described above. On day 6, CTG was measured and compared to day 0 readings from control plate to assess GI₅₀.

Results

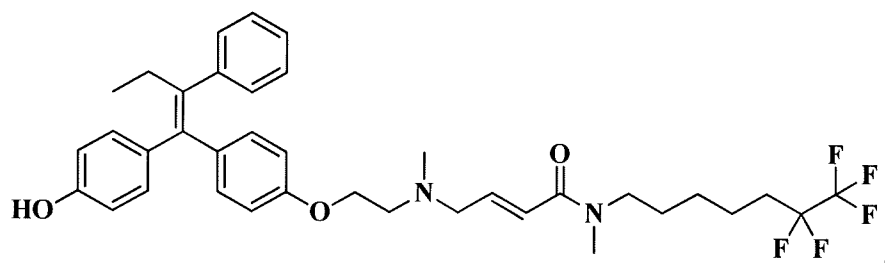
FIG. 1 shows that ectopic expression of ERα^{Y537S/N/C, D538G} in MCF7 cells conferred phenotypic resistance to currently marketed therapies tamoxifen (SERM), raloxifene (SERM) and fulvestrant (SERD). Similar observations were also recently published by several independent labs (Jeselsehn et al., (2014) *Clin Cancer Res.* Apr 1;20(7):1757-67; Toy et al., (2013) *Nat Genet.* 2013 Dec;45(12):1439-45; Robinson et al., (2013) *Nat Genet.* Dec;45(12):1446-51; Merenbakh-Lamin et al., (2013) *Cancer Res.* Dec 1;73(23):6856-64; Yu et al., (2014) *Science* Jul 11;345(6193):216-20). Having confirmed that ERα^{MUT} drive resistance to current endocrine therapies, identification of novel compounds that would reduce proliferation of the ERα^{MUT}-bearing MCF7 cells more efficaciously than the corresponding clinical compound 4-hydroxytamoxifen was sought. Using the WT and mutant viability assay as a screening tool, compounds were identified that were more potent towards the Y537S-bearing MCF7 line relative to 4-hydroxytamoxifen. The results of the viability assay screen are shown in Table 1 above.

It will now be apparent that new, improved, and nonobvious compositions have been described in this specification with sufficient particularity as to be understood by one of ordinary skill in the art. Moreover, it will be apparent to those skilled in the art that modifications, variations, substitutions, and equivalents exist for features of the compositions which do not materially depart from the spirit and scope of the embodiments disclosed

herein. Accordingly, it is expressly intended that all such modifications, variations, substitutions, and equivalents which fall within the spirit and scope of the invention as defined by the appended claims shall be embraced by the appended claims.

WHAT IS CLAIMED IS:

1. A compound given by the following formula:



or a pharmaceutically acceptable salt thereof.

1/1

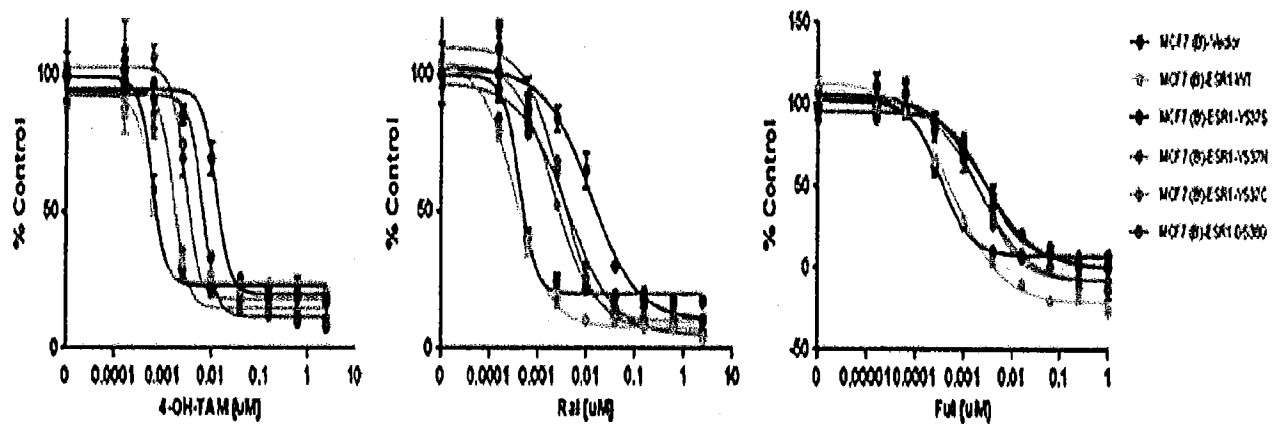


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/34774

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07C 215/46, A61K 31/133 (2016.01)

CPC - C07C 317/28, 323/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): C07C 215/46, A61K 31/133 (2016.01)

CPC: C07C 317/28, 323/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Scifinder; Google/Google Scholar; breast, cancer, ER, positive, mutant, alpha, endoxifen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 8,063,249 D1 (KUSI INC., P et al.) 22 November 2011; column 2, lines 53-67, column 3, lines 1-55	1
A	WO 2009/120999 A2 (OLEMA PHARMACEUTICALS, INC.) 01 October 2009; entire document	1
A	WO 2011/129837 A1 (OLEMA PHARMACEUTICALS, INC.) 20 October 2011; entire document	1

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

03 August 2016 (03.08.2016)

Date of mailing of the international search report

07 SEP 2016

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