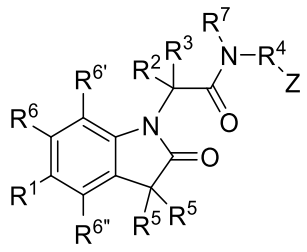
CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein:

R^1 is halo, –CN, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, C_1–C_6 alkoxy, or C_3–C_{12} cycloalkyl;

each R^2 and R^3 independently is H, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, C_1–C_6 alkoxy, C_3–C_{12} cycloalkyl, 3– to 12–membered heterocyclyl, C_6–C_{10} aryl, or 5– to 10–membered heteroaryl, where the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, –CN, –OH, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy, or R^2 and R^3 cyclize, together with the atom to which they are attached, to form a C_3–C_{12} cycloalkyl or 3– to 12–membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more halo, –CN, –OH, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

R^4 is –C_1–C_6 alkyl–, –$(L_1)_p$–(C_3–C_{12} cycloalkyl)–, –$(L_1)_p$–(3– to 12–membered heterocyclyl)–, –$(L_1)_p$–(C_6–C_{10} aryl)–, or –$(L_1)_p$–(5– to 10–membered heteroaryl)–, wherein each instance of L_1 is independently –$(C(R^{L1})_2)$–, further wherein each instance of R^{L1} is independently H, halo or C_1–C_3 alkyl, or two R^{L1} groups, together with the atom to which they are attached, form a $C_{3\text{-}4}$ cycloalkyl; and wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, –CN, –OH, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, C_1–C_6 alkoxy, or C_3 cycloalkyl;

Z is a –$(L_2)_n$–(carboxylic acid) or –$(L_2)_n$–tetrazole, wherein each instance of L_2 is independently –$(C(R^{L2})_2)$–, further wherein each instance of R^{L2} is independently H, halo or C_1–C_3 alkyl, or two R^{L2} groups, together with the atom to which they are attached, to form a $C_{3\text{-}4}$ cycloalkyl; and wherein the alkyl or cycloalkyl is optionally substituted with one or more halo, –CN, –OH, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, C_1–C_6 alkoxy, or C_3 cycloalkyl;

each R^5 is independently halo or C_1–C_6 alkyl, wherein the alkyl is optionally substituted with one or more halo, –CN, –OH, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy, or both R^5 cyclize, together with the atom to which they are attached, to form a C_3–C_{12} cycloalkyl

optionally substituted with one or more halo, –CN, –OH, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

R^6 is H, halo, –OH, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

$R^{6'}$ is H, halo, –OH, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

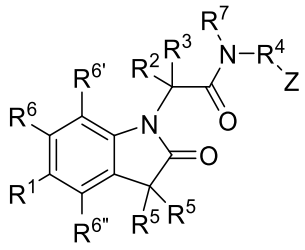
$R^{6''}$ is H, halo, –OH, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

R^7 is independently H or C_1–C_4 alkyl;

n is an integer from 0, 1, 2, or 3; and

p is an integer from 0, 1, or 2.

2. A compound of claim 1 of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

R^1 is halo, nitrile, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, C_1–C_6 alkoxy, or C_3–C_{12} cycloalkyl;

each R^2 and R^3 independently is H, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, C_1–C_6 alkoxy, C_3–C_{12} cycloalkyl, 3– to 12–membered heterocyclyl, C_6–C_{10} aryl, or 5– to 10–membered heteroaryl, where the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy, or

R^2 and R^3 cyclize, together with the atom to which they are attached, to form a C_3–C_{12} cycloalkyl or 3– to 12–membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

R^4 is C_1–C_6 alkyl, –$(CH_2)_p$–(C_3–C_{12} cycloalkyl), –$(CH_2)_p$–(3– to 12–membered heterocyclyl), C_6–C_{10} aryl, or –$(CH_2)_p$–(5– to 10–membered heteroaryl), wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6

alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

Z is a –$(CH_2)_n$–(carboxylic acid) or –$(CH_2)_n$–tetrazole;

each R^5 is independently C_1–C_6 alkyl, wherein the alkyl is optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy, or

both R^5 cyclize, together with the atom to which they are attached, to form a C_3–C_{12} cycloalkyl optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

R^6 is H, halogen, –OH, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

$R^{6'}$ is H, halogen, –OH, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

$R^{6''}$ is H, halogen, –OH, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

R^7 is independently H or C_1–C_4 alkyl;

n is an integer from 0–3; and

p is an integer from 0–2.

3. A compound of any one of the preceding claims, wherein:

R^1 is bromo, chloro, nitrile, C_1–C_6 alkyl, C_1–C_6 haloalkyl, or C_3–C_{12} cycloalkyl;

each R^2 and R^3 independently is H, C_1–C_6 alkyl, C_1–C_6 haloalkyl, C_3–C_{12} cycloalkyl, 3– to 12–membered heterocyclyl, C_6–C_{10} aryl, or 5– to 10–membered heteroaryl, where the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy, or

R^2 and R^3 cyclize together to form a C_3–C_{12} cycloalkyl or 3– to 12–membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

R^4 is an n–propyl, –$(CH_2)_p$–(C_3–C_{12} cycloalkyl), –$(CH_2)_p$–(3– to 12–membered heterocyclyl), C_6–C_{10} aryl, or –$(CH_2)_p$–(5– to 10–membered heteroaryl), wherein the n–propyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

Z is a –$(CH_2)_n$–(carboxylic acid) or –$(CH_2)_n$–tetrazole;

each R^5 is C_1–C_6 alkyl optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–

C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy, or

both R^5 cyclize, together with the atom to which they are attached, to form a C_3–C_{12} cycloalkyl optionally substituted with one or more halo, cyano, hydroxy, amino, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_1–C_6 haloalkyl, or C_1–C_6 alkoxy;

R^6 is H, halogen, –OH, C_1–C_6 alkyl, or C_1–C_6 alkoxy;

$R^{6'}$ is H, halogen, –OH, C_1–C_6 alkyl, or C_1–C_6 alkoxy;

$R^{6''}$ is H, halogen, –OH, C_1–C_6 alkyl, or C_1–C_6 alkoxy;

R^7 is independently H or C_1–C_4 alkyl;

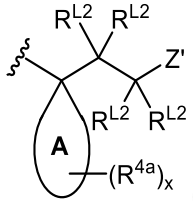
n is an integer from 0–3; and

p is integer from 0–2.

4. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein each instance of R^2 and R^3 is H.

5. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein –R^4–Z is a group of

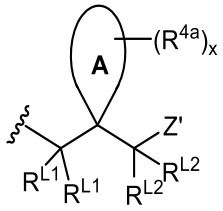
- formula (i):



(i),

wherein Z' is tetrazole or carboxylic acid; Ring A is C_3–C_5 cycloalkyl or 4– to 5–membered heterocyclyl; each R^{4a} is independently halo, C_1–C_3 alkyl, C_1–C_3 haloalkyl, or C_3 cycloalkyl; and x is 0, 1, 2, or 3; or

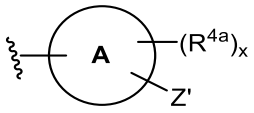
- formula (ii):



(ii),

wherein Z' is tetrazole or carboxylic acid; Ring A is C_3–C_5 cycloalkyl or 4– to 5–membered heterocyclyl; each R^{4a} is independently halo, C_1–C_3 alkyl, C_1–C_3 haloalkyl, or C_3 cycloalkyl; and x is 0, 1, 2, or 3; or

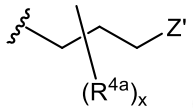
- formula (iii):



(iii),

wherein Z' is tetrazole or carboxylic acid; Ring A is C_3–C_5 cycloalkyl or 4– to 5–membered heterocyclyl; each R^{4a} is independently halo, C_1–C_3 alkyl, C_1–C_3 haloalkyl, or C_3 cycloalkyl; and x is 0, 1, 2, or 3; or

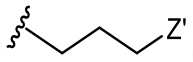
- formula (iv):

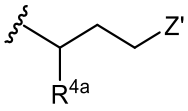


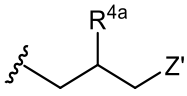
(iv),

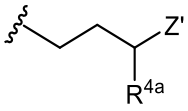
wherein Z' is tetrazole or carboxylic acid; each R^{4a} is independently halo, C_1–C_3 alkyl, C_1–C_3 haloalkyl, or C_3 cycloalkyl; and x is 0, 1, 2, or 3.

6. The compound of claim 5, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein the group of formula (iv) is:

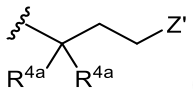


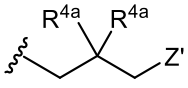
(iv–a),


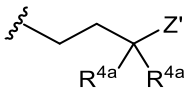
(iv–b),


(iv–c),


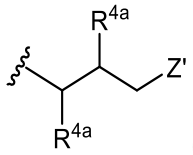
(iv–d),

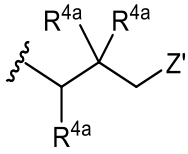


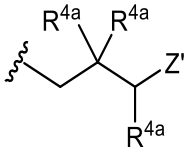
(iv–e),


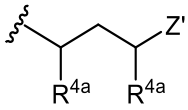
(iv–f),


(iv–g),



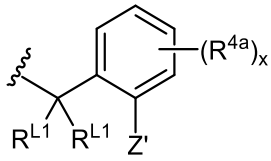
(iv–h),


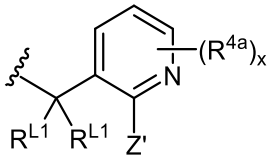
(iv–i),


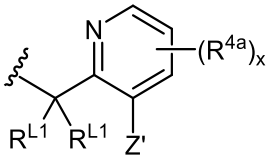
(iv–j), or


(iv–k).

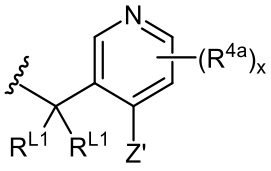
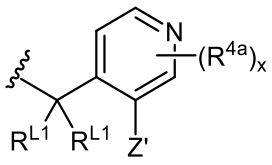
7. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein –R^4–Z group of formula:



(v–a),


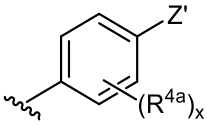
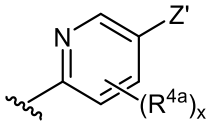
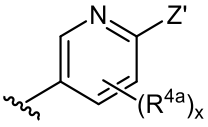
(v–b),


(v–c),

 (v–d), or  (v–e),

wherein Z' is tetrazole or carboxylic acid; each R^{4a} is independently halo, C_1–C_3 alkyl, C_1–C_3 haloalkyl; and x is 0, 1, 2, or 3.

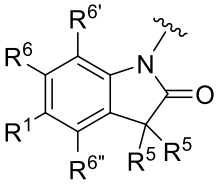
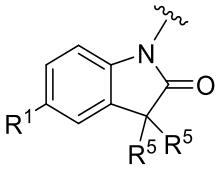
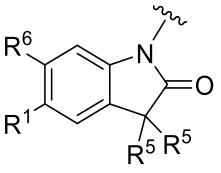
8. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein –R^4–Z is a group of formula:

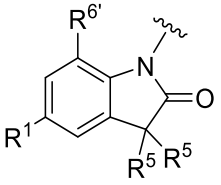
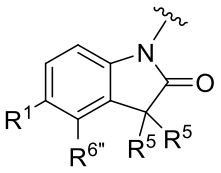
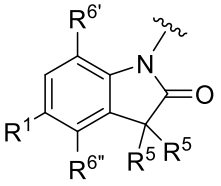
 (vii–a),  (vii–b), or  (vii–c),

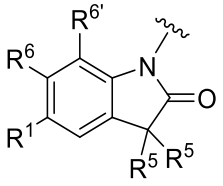
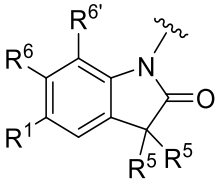
wherein Z' is tetrazole or carboxylic acid; and each R^{4a} is independently halo, C_1–C_3 alkyl, C_1–C_3 haloalkyl, and x is 0, 1, 2, or 3.

9. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein each instance of R^5 is selected from the group consisting of fluoro and C_1–C_6 alkyl, or both R^5 cyclize, together with the atom to which they are attached, to form a C_3 cycloalkyl.

10. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein the 6,5–bicyclic core of formula (viii):

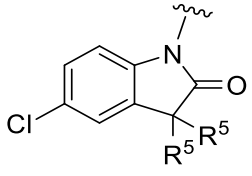
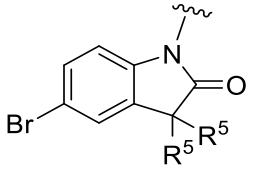
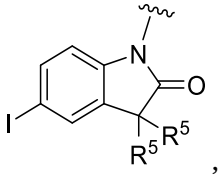
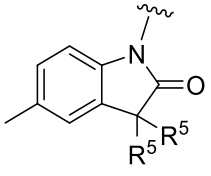
 (viii) is of formula:  (viii–a),  (viii–b),

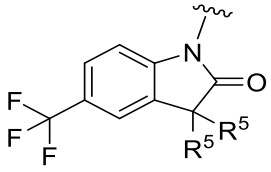
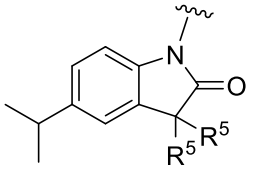
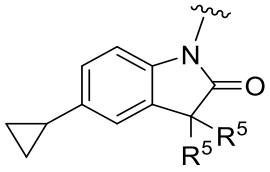
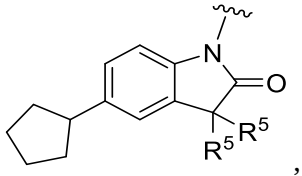
 (viii–c),  (viii–d),  (viii–e),

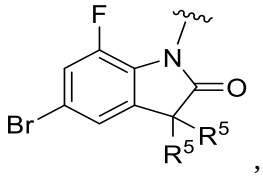
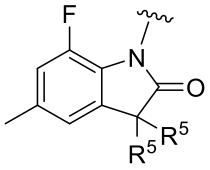
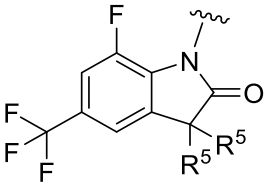
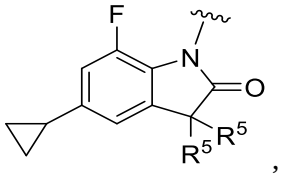
 (viii–f), or  (viii–g),

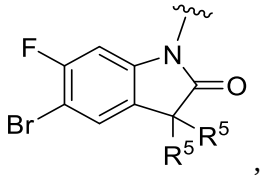
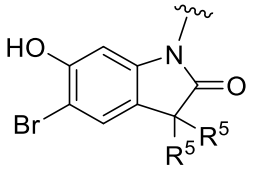
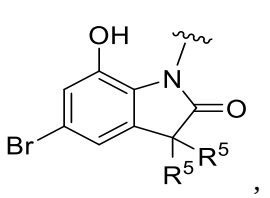
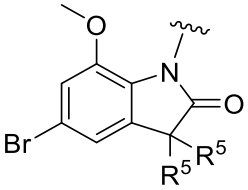
wherein at least one of R^6, $R^{6'}$ and $R^{6''}$ is not H.

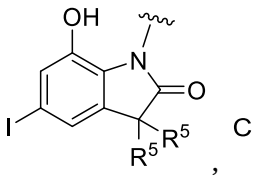
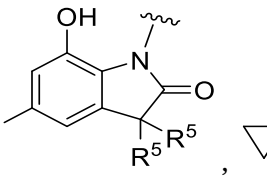
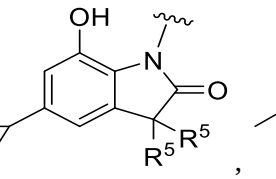
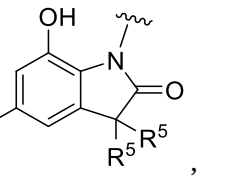
11. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein the 6,5–bicyclic core is of formula:

, , , ,

, , , ,

, , , ,

, , , ,

, , , ,

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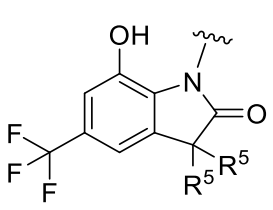
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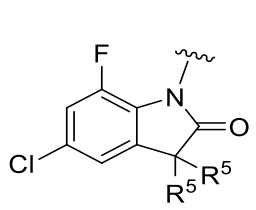
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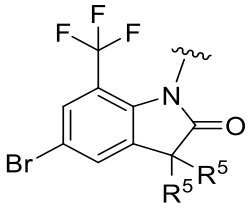
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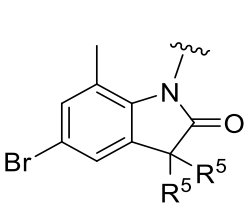
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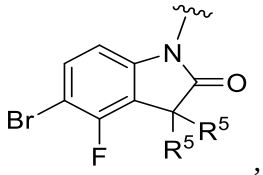
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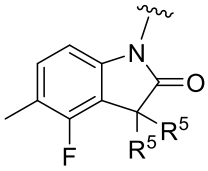
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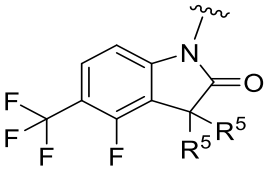
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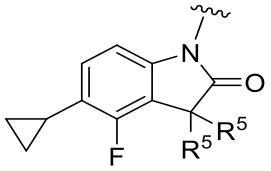
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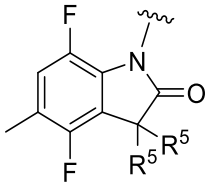
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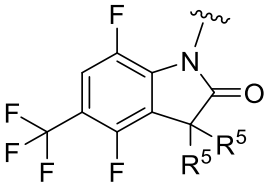
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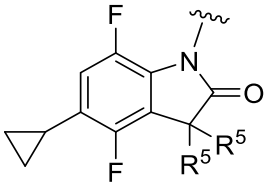
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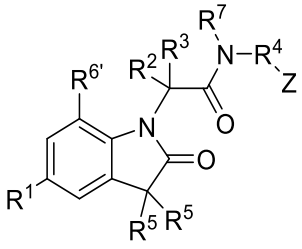
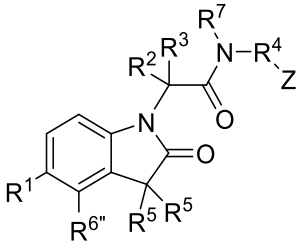
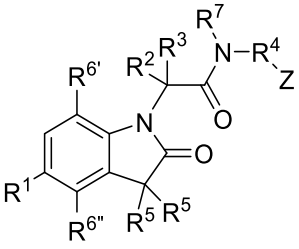
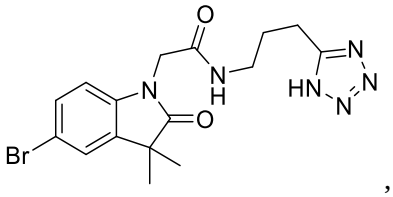
12. The compound of any one of the preceding claims, wherein the compound of Formula (I) is of Formula:


(I-E),

(I-F), or

(I-G),

or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, wherein at least one of R^6, $R^{6'}$ and $R^{6''}$ is not H.

13. The compound of claim 1 or 2, selected from the group consisting of: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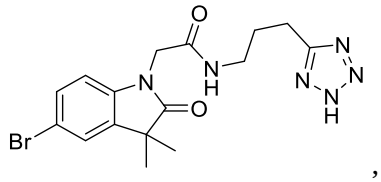
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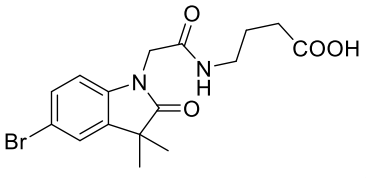
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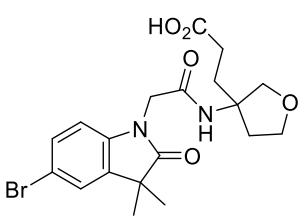
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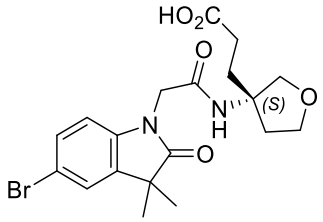
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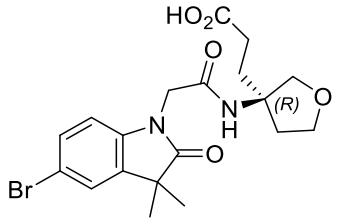
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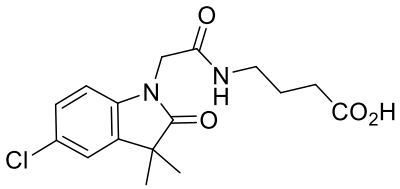
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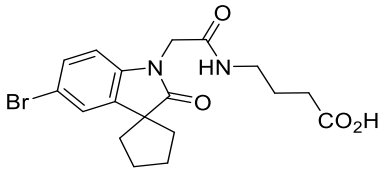
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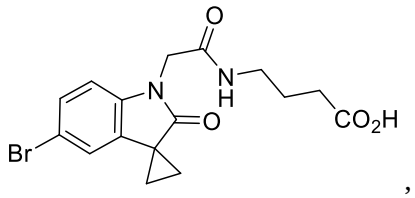
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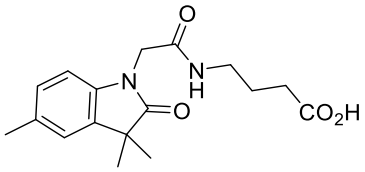
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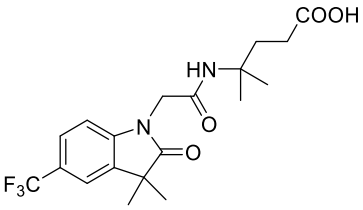
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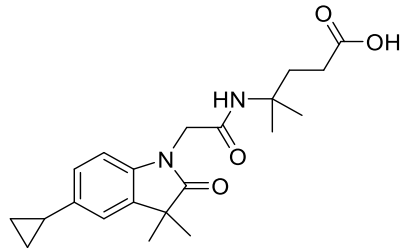
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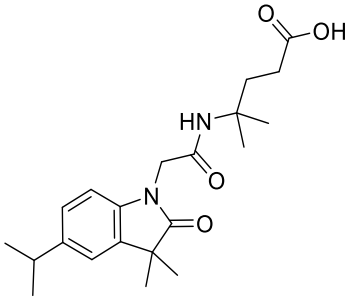
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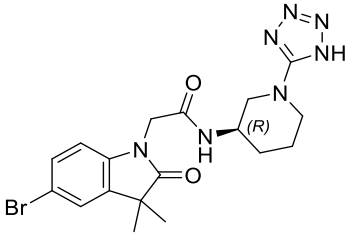
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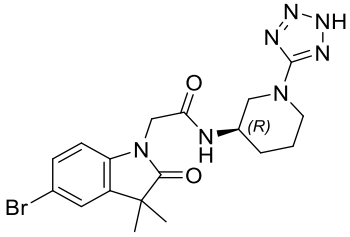
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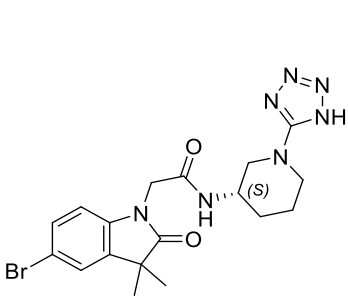
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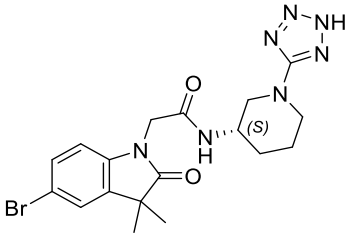
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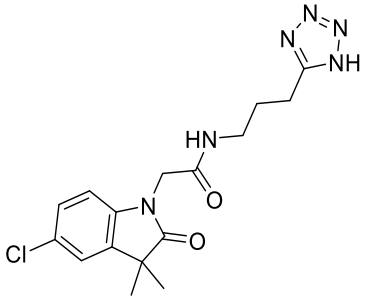
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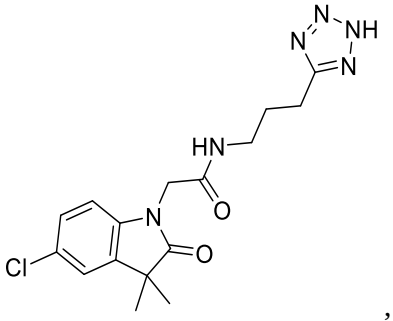
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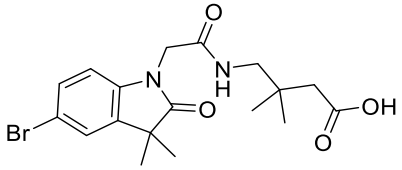
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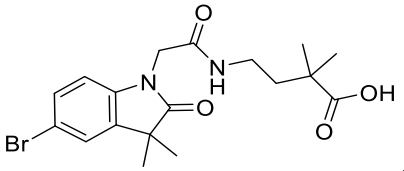
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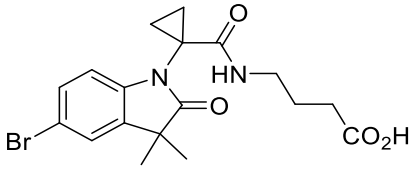
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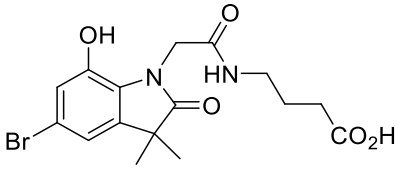
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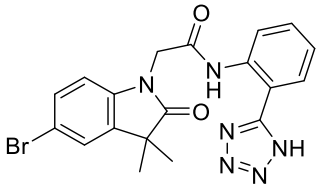
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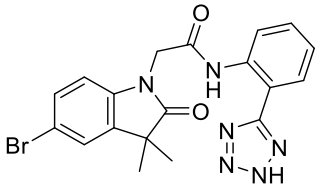
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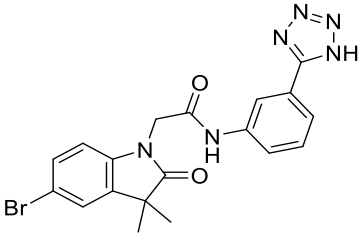
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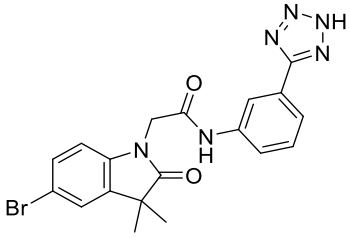
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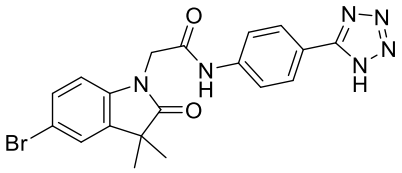
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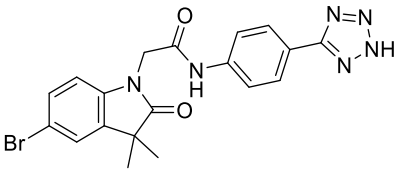
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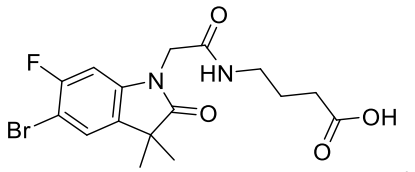
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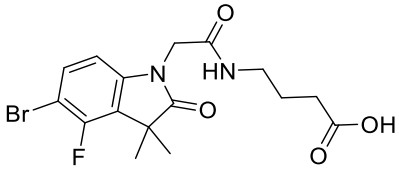
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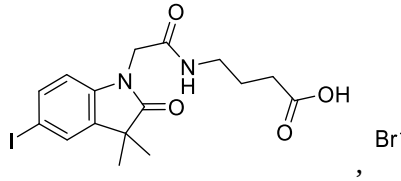
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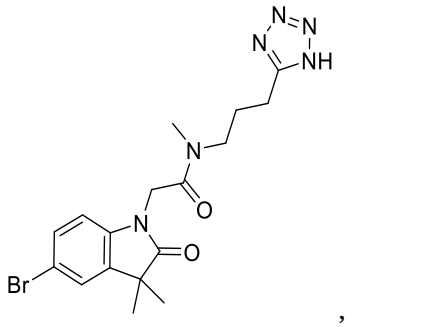
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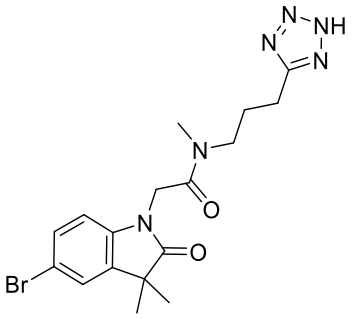
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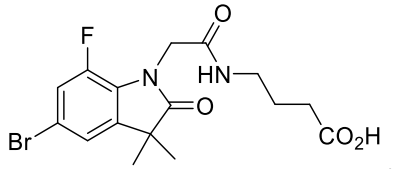
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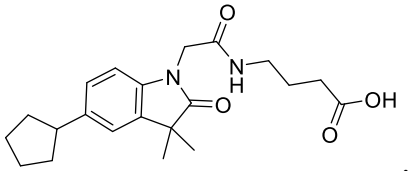
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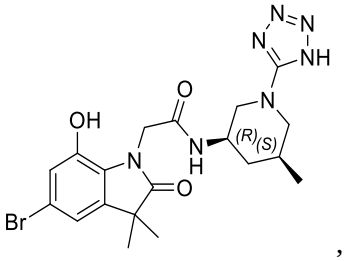
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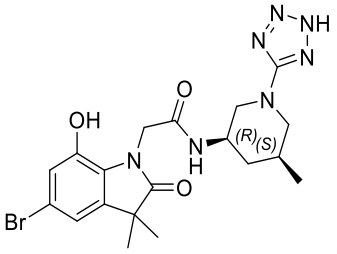
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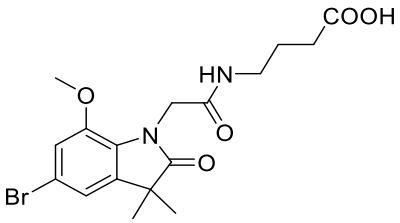
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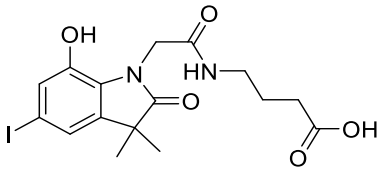
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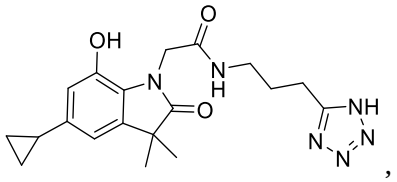
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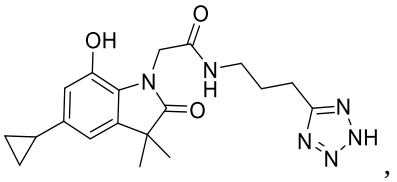
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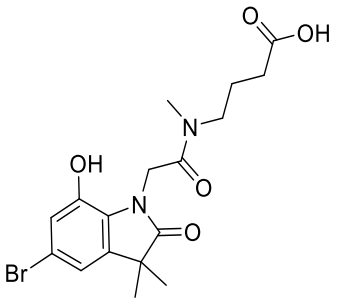
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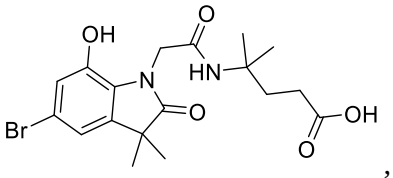
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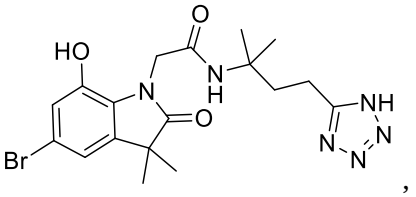
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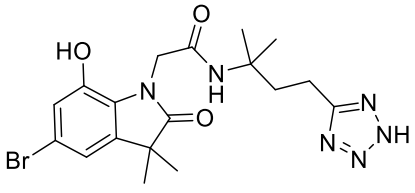
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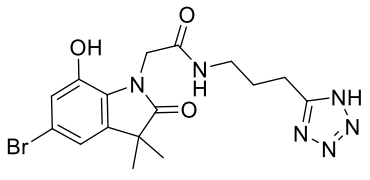
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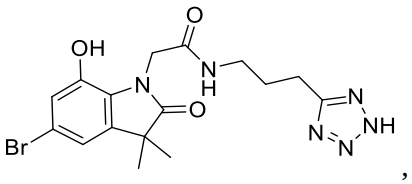
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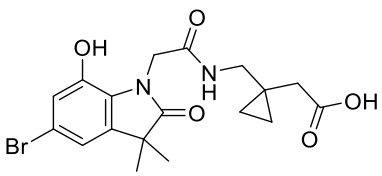
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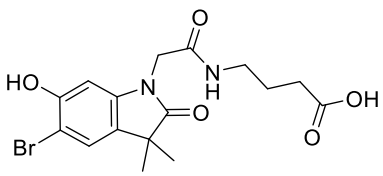
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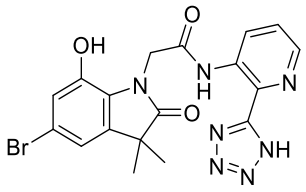
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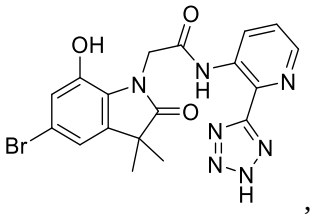
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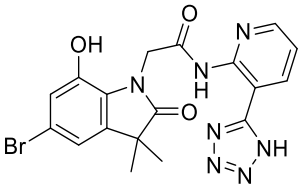
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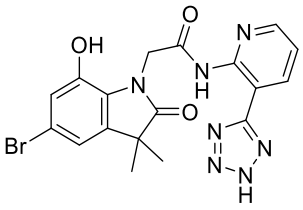
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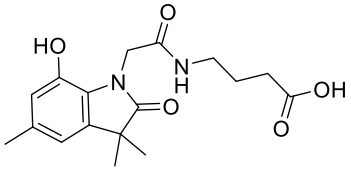
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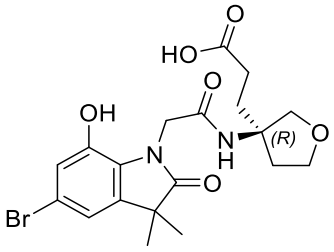
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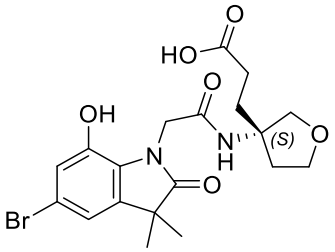
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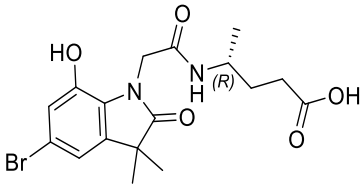
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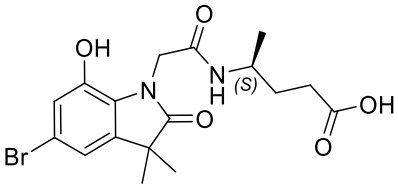
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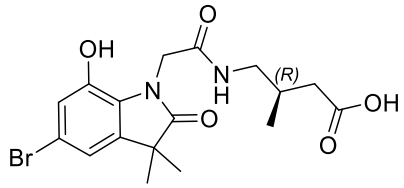
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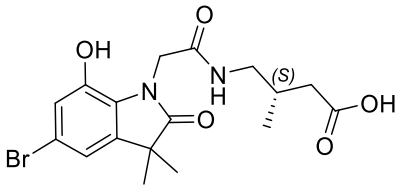
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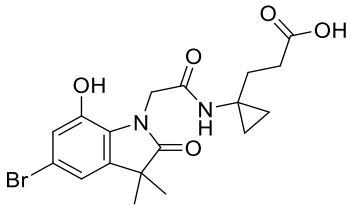
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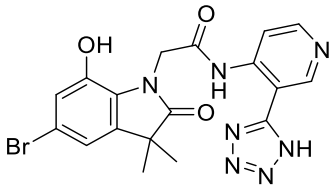
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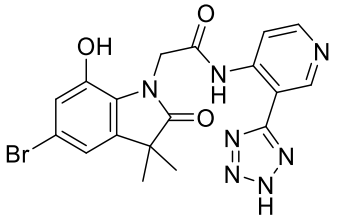
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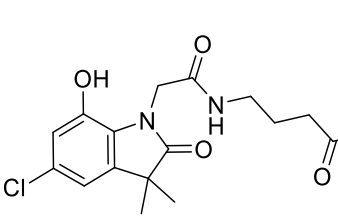
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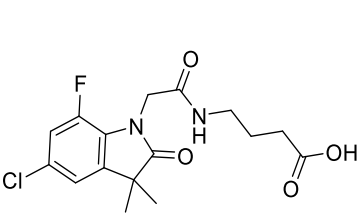
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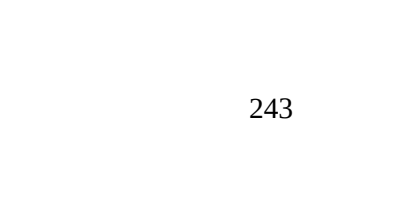
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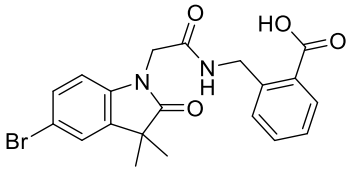
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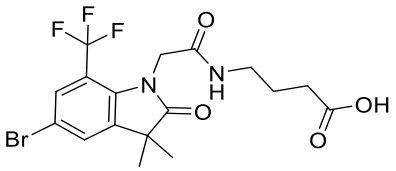
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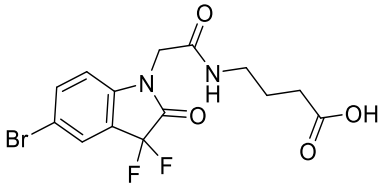
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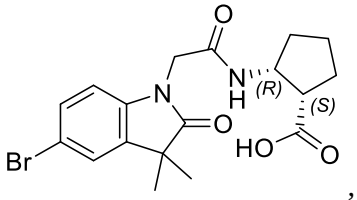
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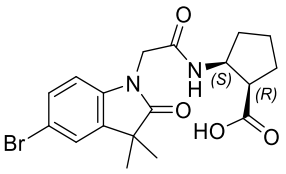
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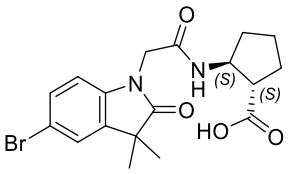
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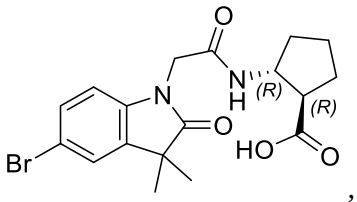
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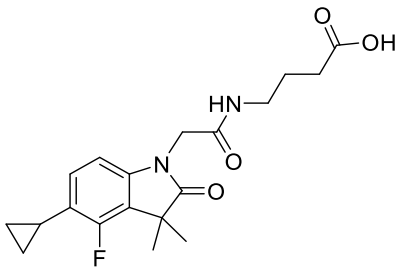
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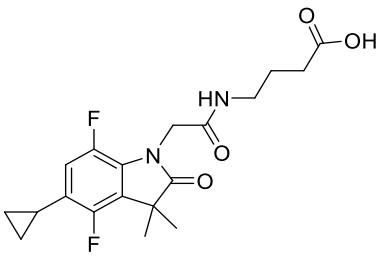
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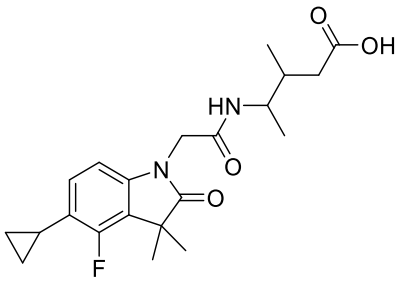
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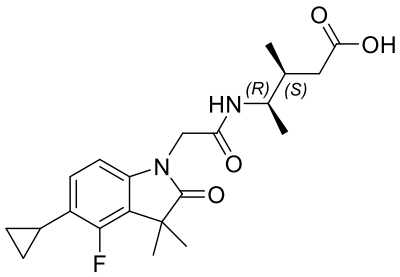
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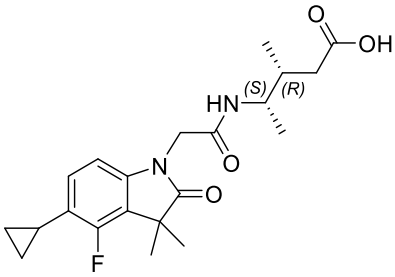
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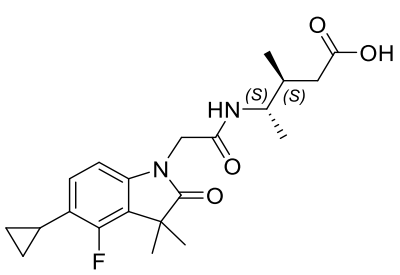
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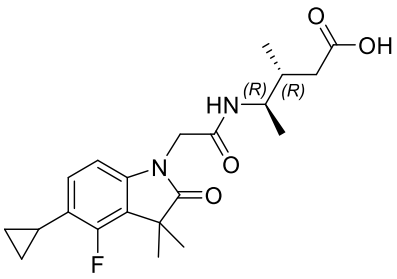
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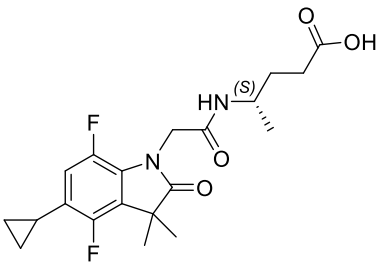
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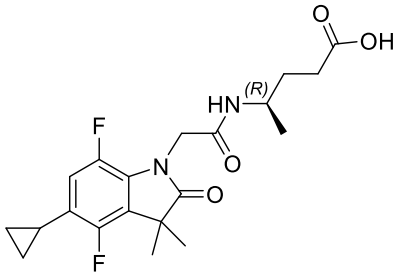
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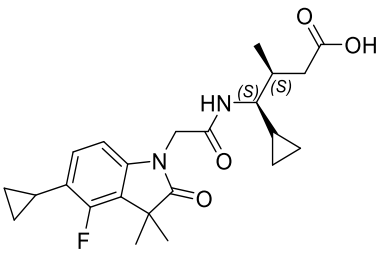
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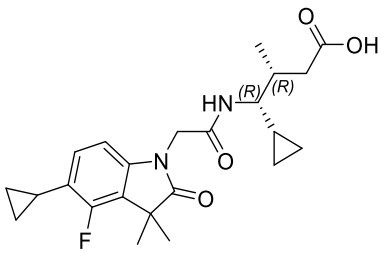
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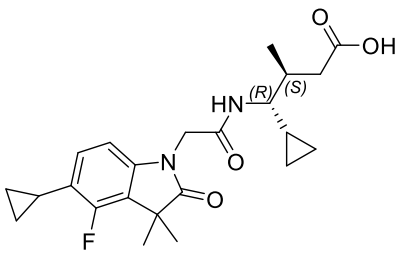
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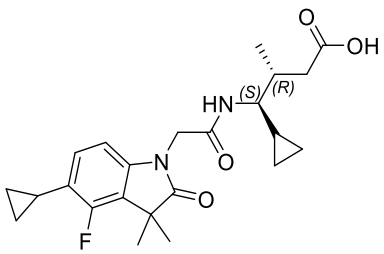
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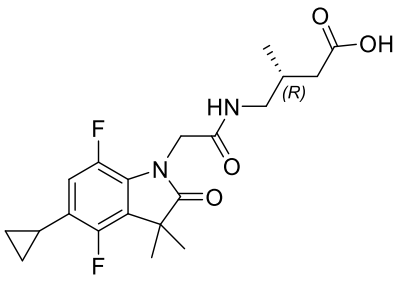
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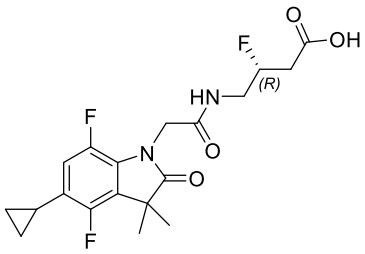
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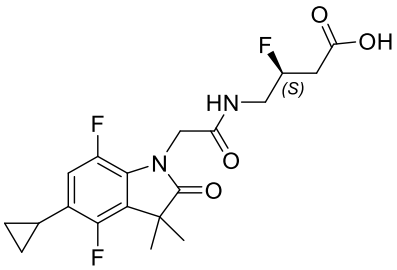
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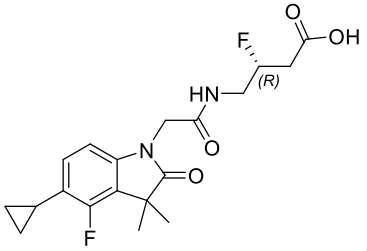
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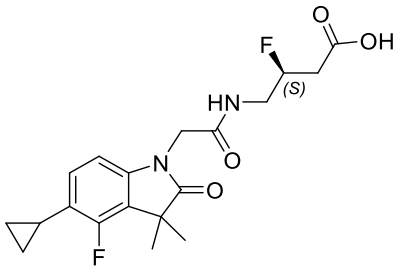
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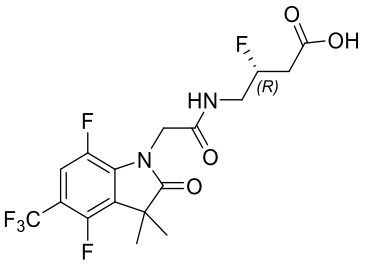
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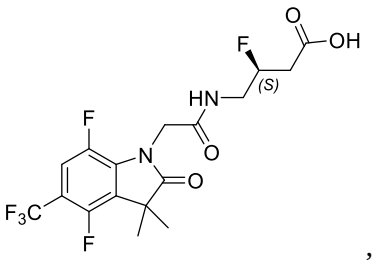
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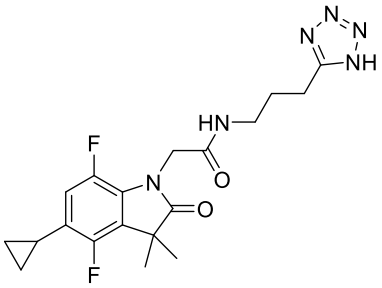
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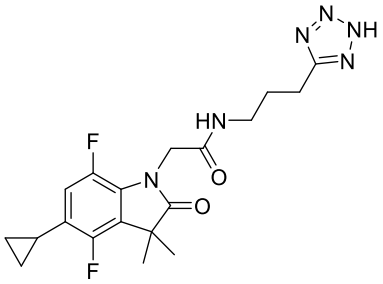
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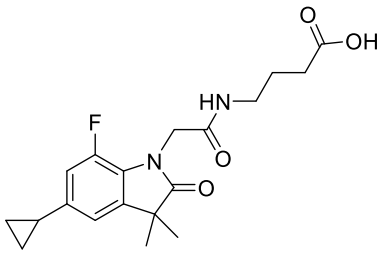
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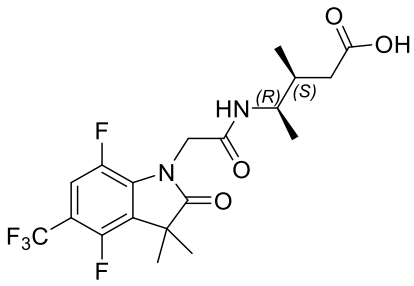
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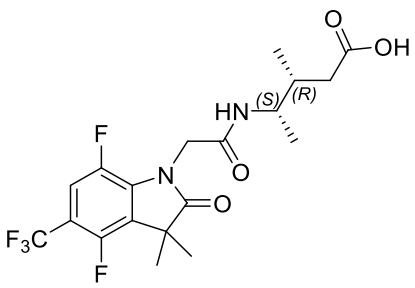
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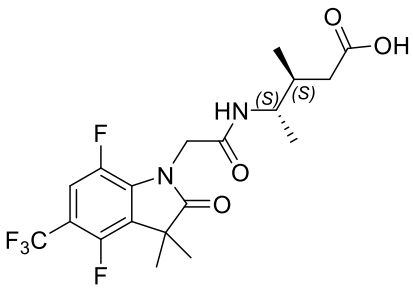
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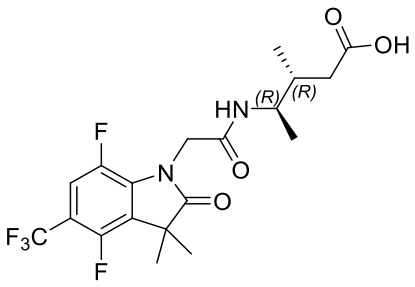
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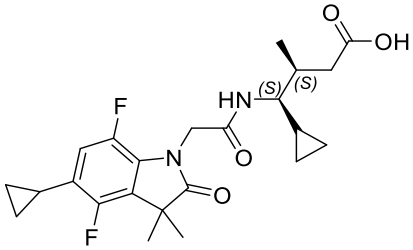
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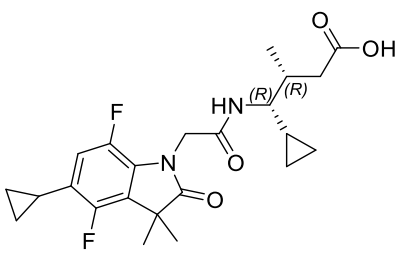
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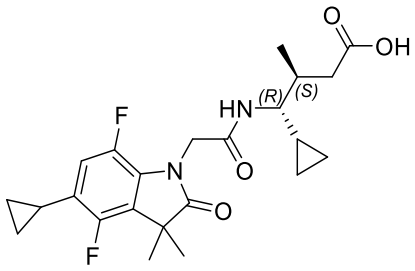
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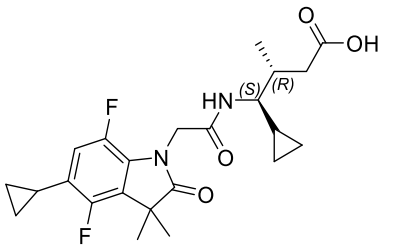
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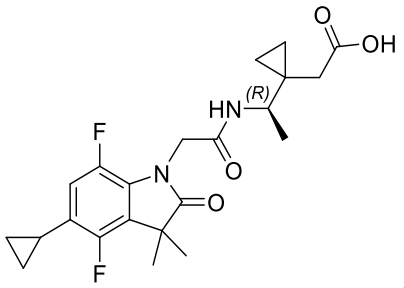
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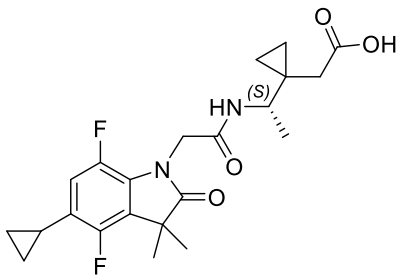
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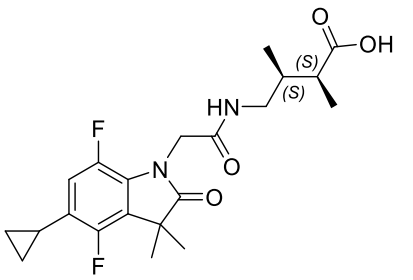
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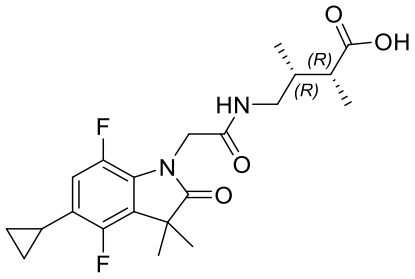
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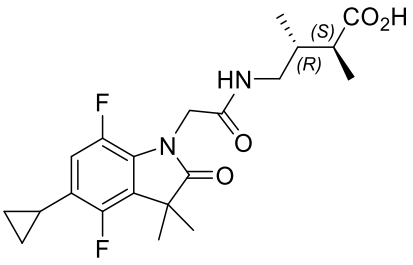
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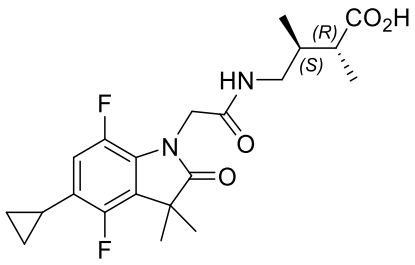
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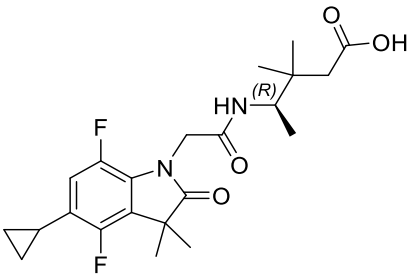
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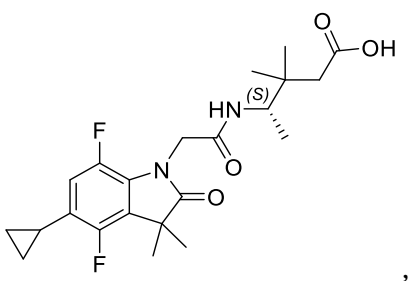
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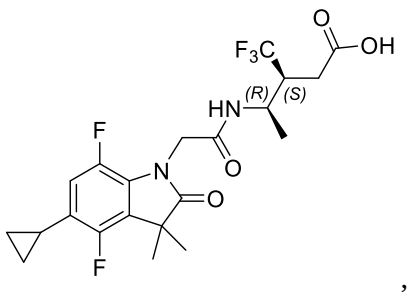
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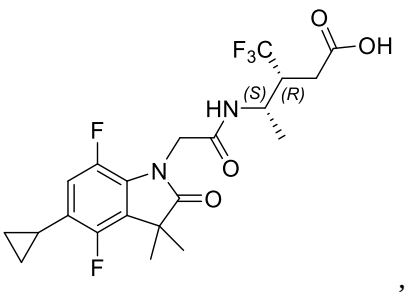
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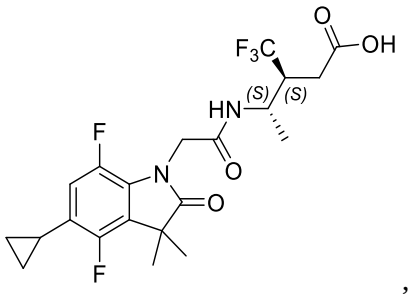
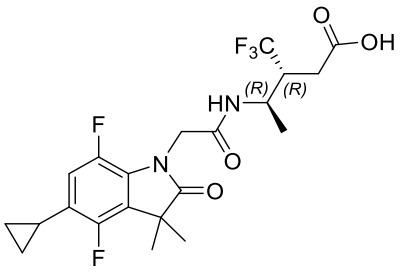


, and 

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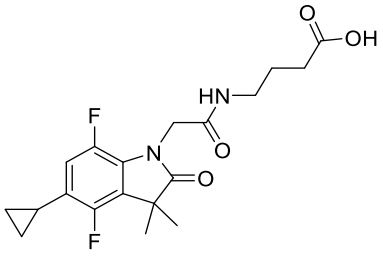
or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative of any of the foregoing.

14. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof, and one or more pharmaceutically acceptable excipients.

15. Use of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, or isotopic derivative thereof in the manufacture of a medicament for the treatment of a disease or disorder in a subject.

16. A compound of formula:



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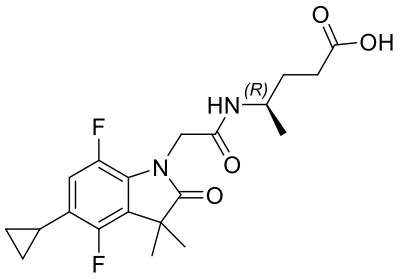
or a pharmaceutically acceptable salt thereof.

17. A compound of formula:



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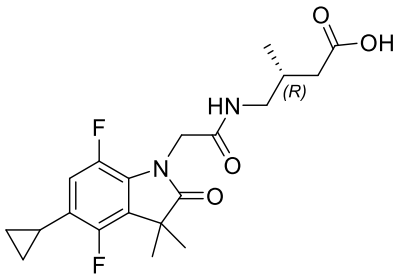
or a pharmaceutically acceptable salt thereof.

18. A compound of formula:



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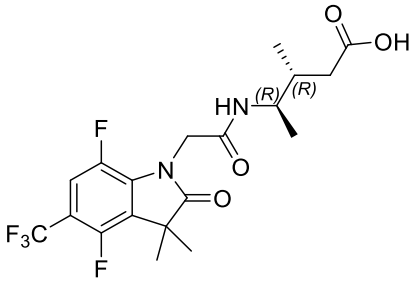
or a pharmaceutically acceptable salt thereof.

19. A compound of formula:



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or a pharmaceutically acceptable salt thereof.