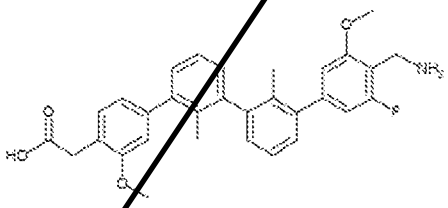
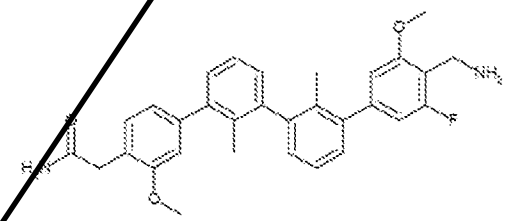
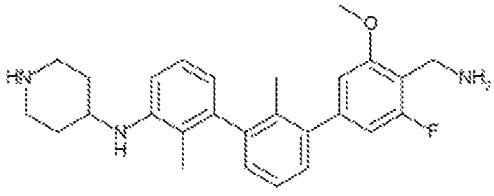
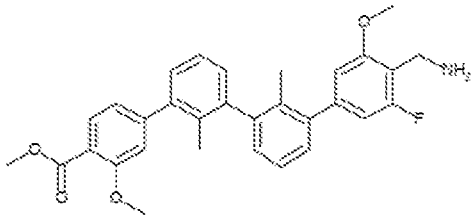
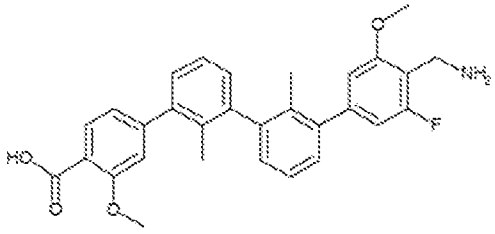
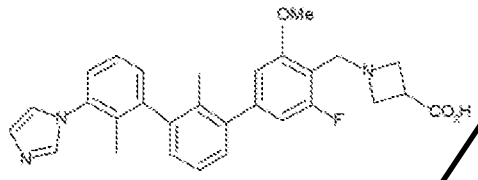
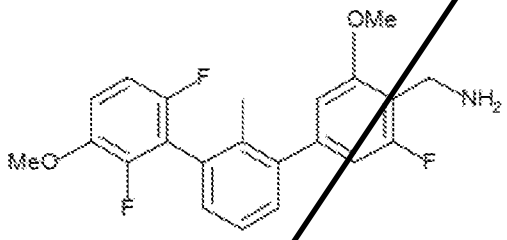
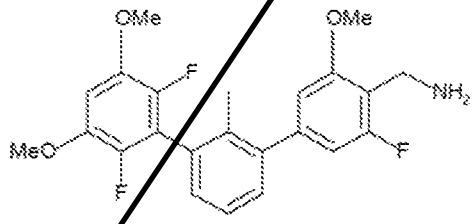
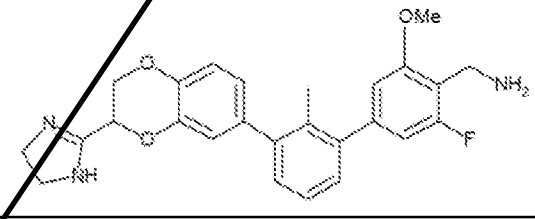
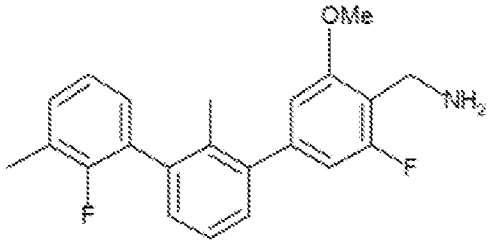
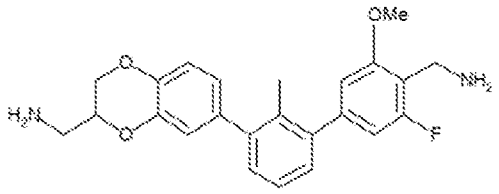
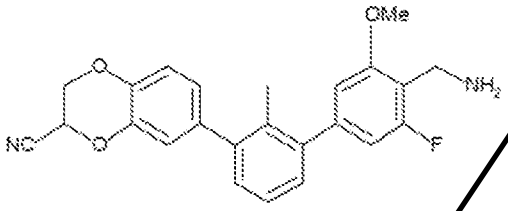
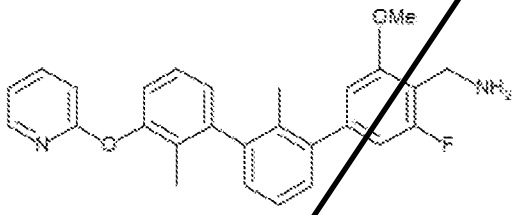
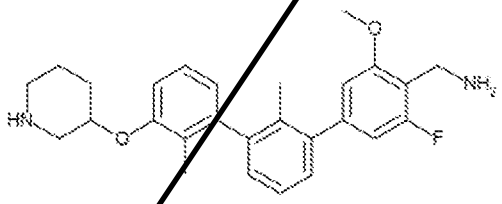
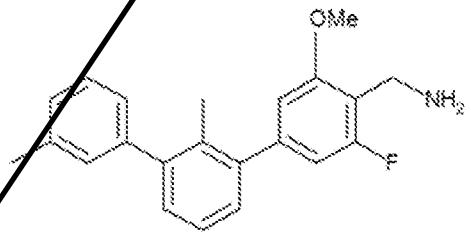
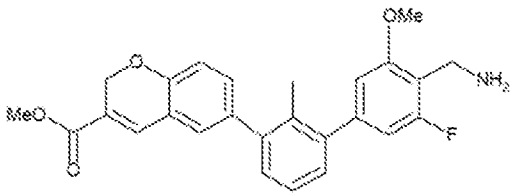
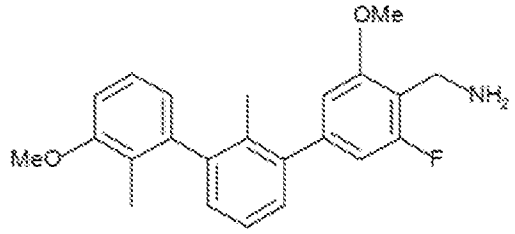
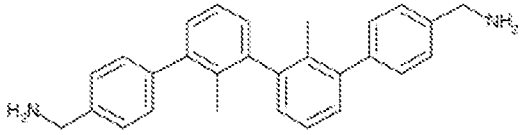
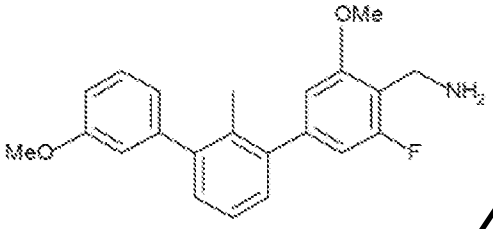
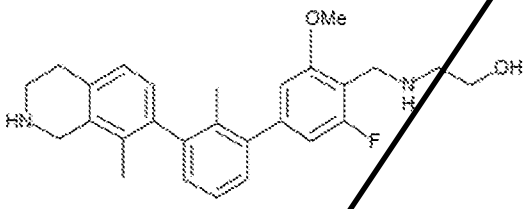
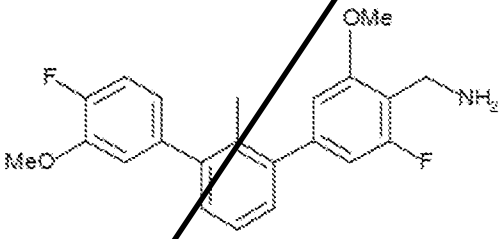
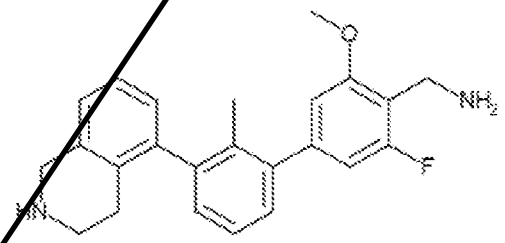
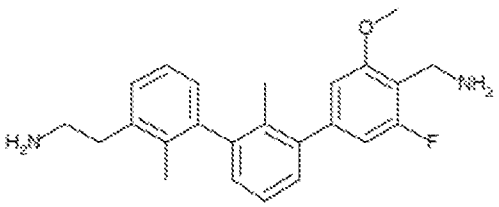
[0185] 96 Well plates were coated with 1μg/mL of human PD-L1 (obtained from R&D) in PBS overnight at 4 °C. The wells were then blocked with 2% BSA in PBS (W/V) with 0.05 % TWEEN-20 for 1 hour at 37 °C. The plates were washed 3 times with PBS/0.05% TWEEN-20 and the compounds were serial diluted (1:5) in dilution medium and added to the ELISA plates. Human PD-1 and biotin 0.3μg/mL (ACRO Biosystems) were added and incubated for 1 hour at 37 °C then washed 3 times with PBS/0.05% TWEEN-20. A second block was performed with 2% BSA in PBS (W/V)/0.05% TWEEN-20 for 10 min at 37 °C and the plates were washed 3 times with PBS/0.05% TWEEN-20. Streptavidin–HRP was added for 1 hour at 37 °C then the plates were washed 3 times with PBS/0.05% TWEEN-20. TMB substrate was added and reacted for 20 min at 37 °C. A stop solution (2 N aqueous H_2SO_4) was added. The absorbance was read at 450 nm using a micro-plate spectrophotometer. The results are shown in Table 1: IC_{50} values are provided as follows: from 1000 to 10,000 nM (+); Less than 1000 nM (++).

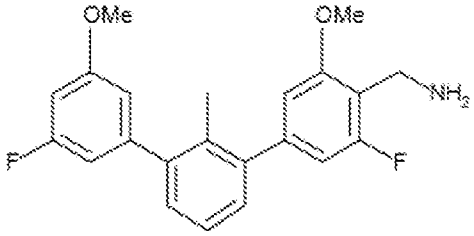
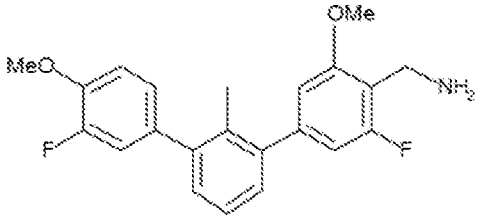
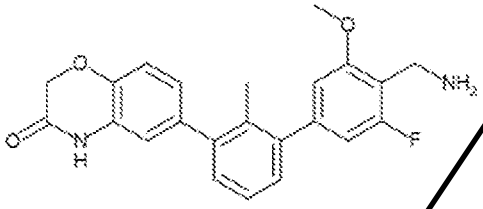
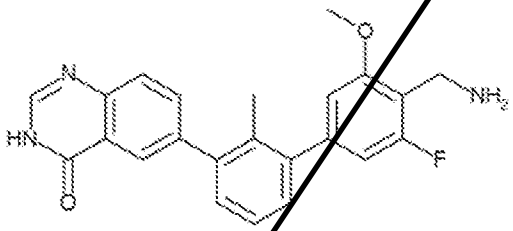
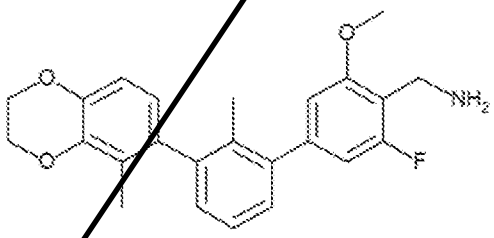
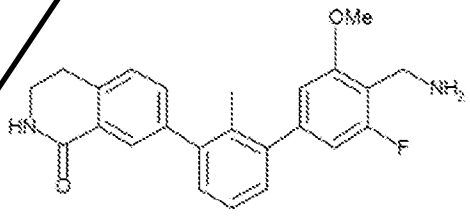
Table 1

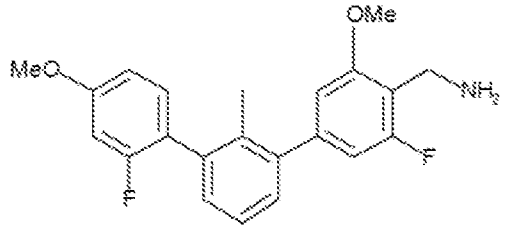
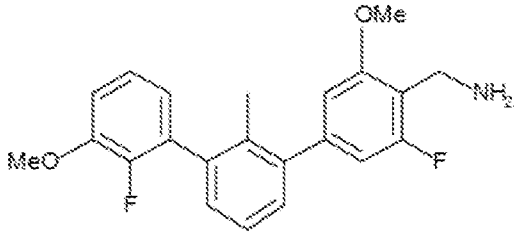
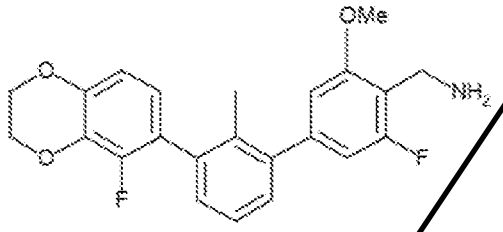
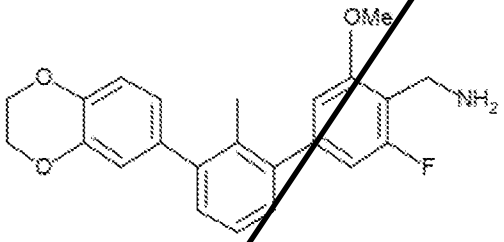
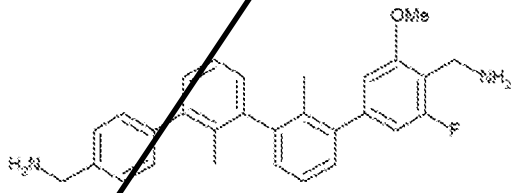
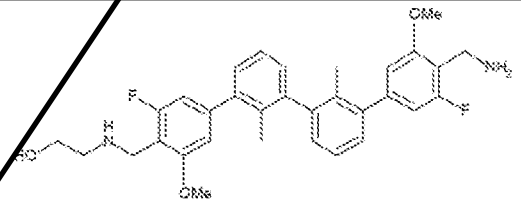
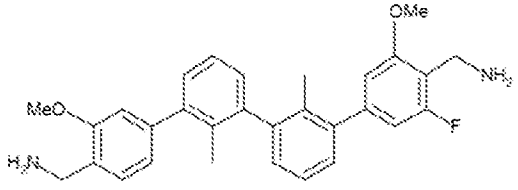
Compd ID	Structure	ELISA IC_{50} (nM)	*m/z*ES	HPLC RT (min)	HPLC Method
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1.002		++	482.2 $[M+H]^+$	2.6	A
1.003		++	434.2 $[M+H]^+$	2.1	B

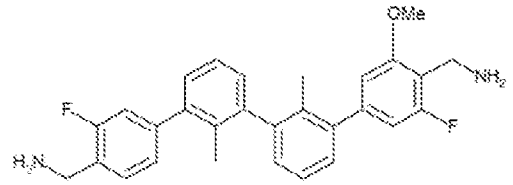
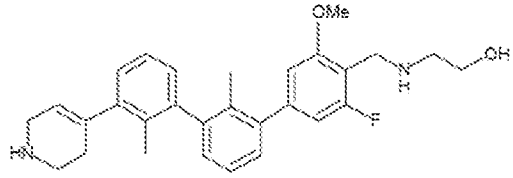
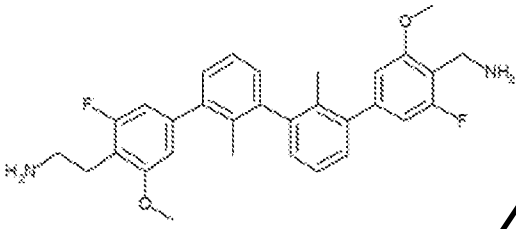
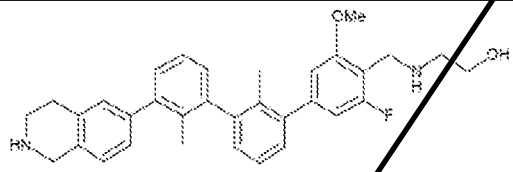
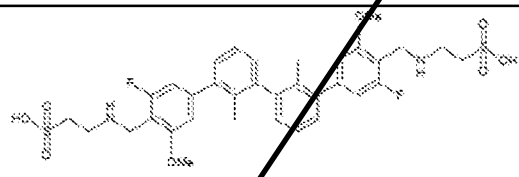
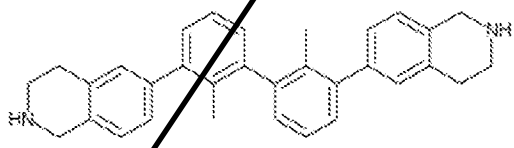
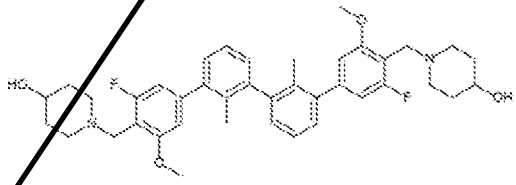
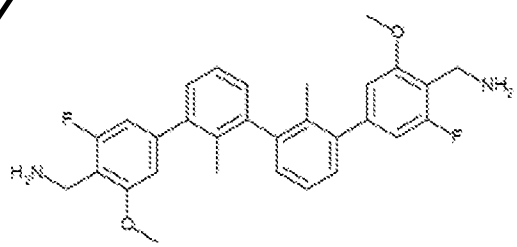
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1.005		+	486.4 $[M+H]^+$	2.5	A
1.006		+	486.2 $[M+H]^+$	2.1	B
1.007		++	371.1 $[M-NH_2]^+$	2.5	A
1.008		++	401.2 $[M-NH_2]^+$	2.4	A
1.009		+	448.1 $[M+H]^+$	2.1	B

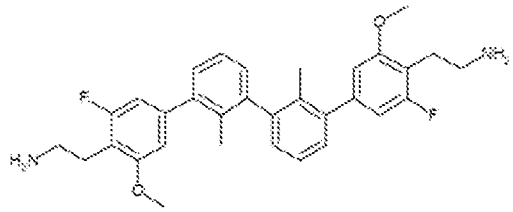
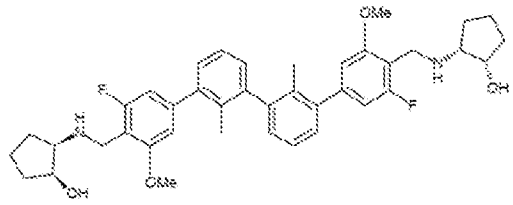
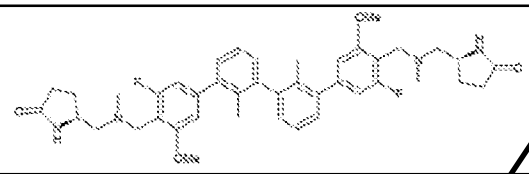
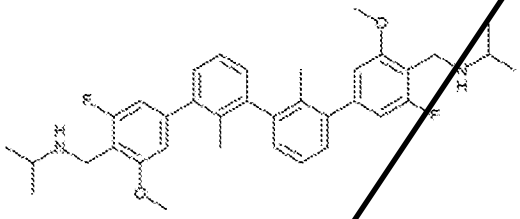
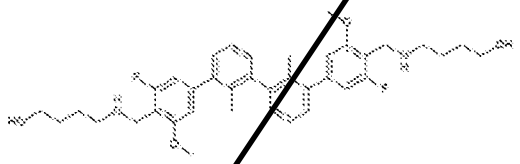
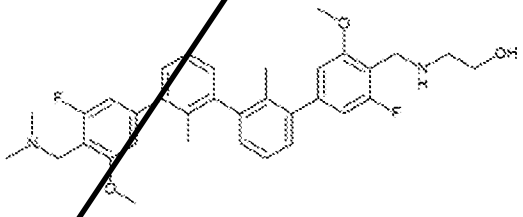
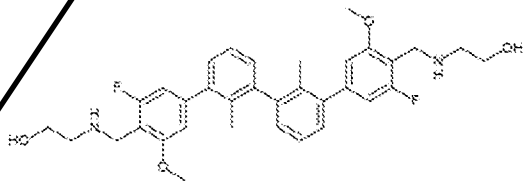
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1.011		++	392.1 [M-NH_2]$^+$	2.0	B
1.012		+	338.0 [M-NH_2]$^+$	2.1	B
1.013		+	415.0 $[M+H]^+$	2.8	B
1.014		+	435.1 $[M+H]^+$	2.1	B
1.015		++	319.1 [M-NH_2]$^+$	2.5	A
1.016		++	434.1 $[M+H]^+$	2.3	B

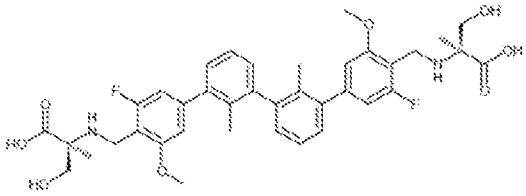
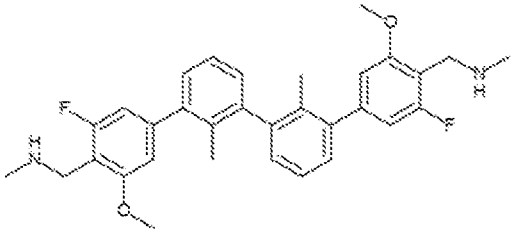
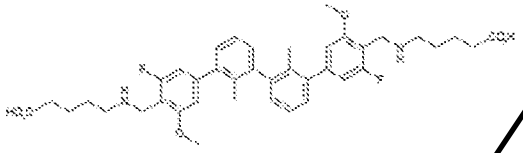
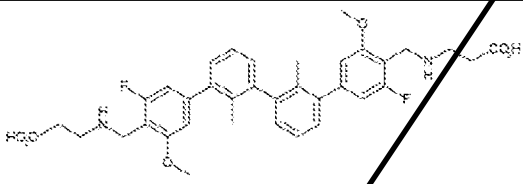
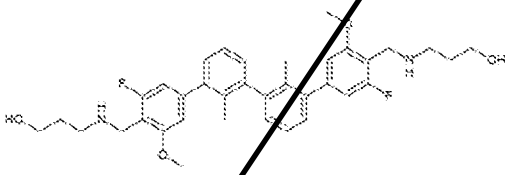
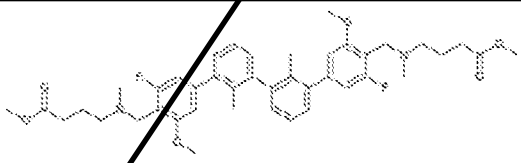
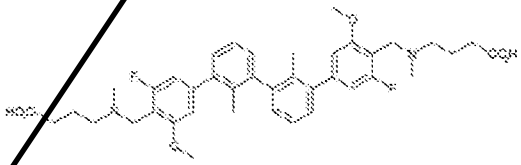
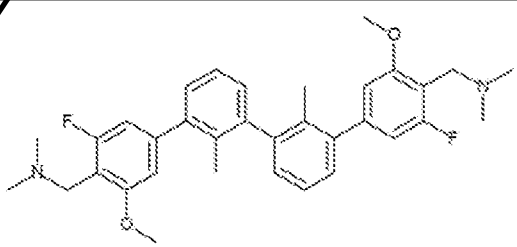
1.017		++	349.1 [M-NH_2]$^+$	2.6	A
1.018		++	376.2 [M-NH_2]$^+$	2.2	B
1.019		++	335.2 [M-NH_2]$^+$	3.0	A
1.020		+	435.1 [M+H]$^+$	2.1	B
1.021		+	353.2 [M-NH_2]$^+$	2.4	A
1.022		+	377.1 [M+H]$^+$	1.9	B
1.023		+	362.1 [M-NH_2]$^+$	2.1	B

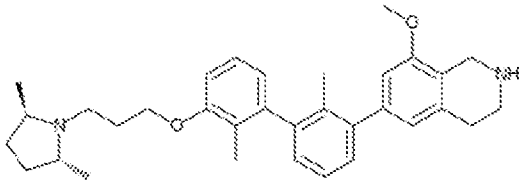
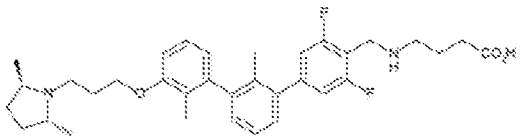
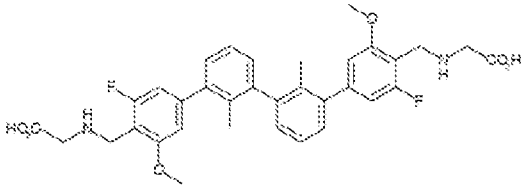
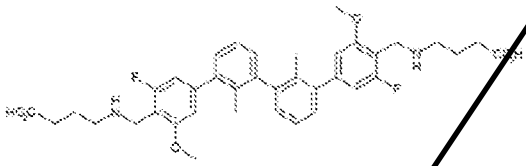
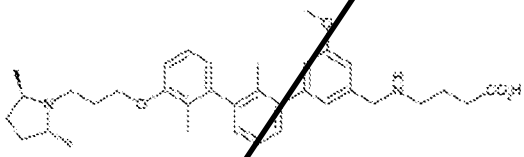
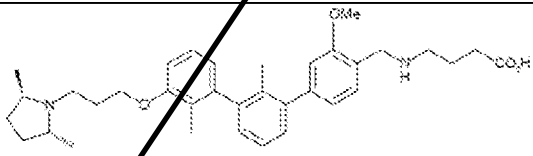
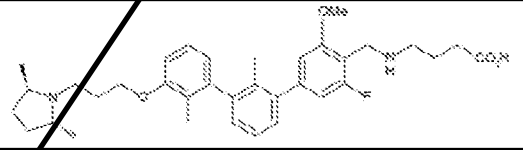
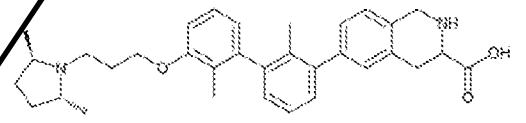
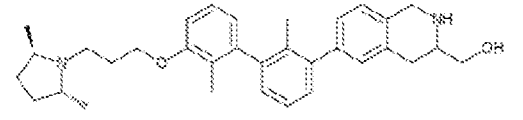
1.024		++	353.2 [M-NH_2]$^+$	2.5	A
1.025		+	353.2 [M-NH_2]$^+$	2.2	A
1.026		++	376.0 [M-NH_2]$^+$	2.4	B
1.027		++	373.1 [M-NH_2]$^+$	1.6	A
1.028		++	377.2 [M-NH_2]$^+$	3.2	B
1.029		+	391.2 $[M+H]^+$	2.3	B

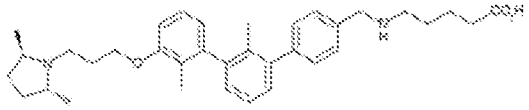
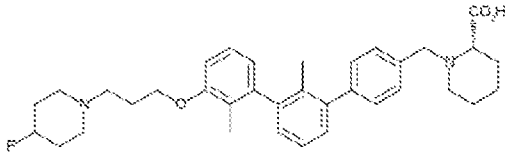
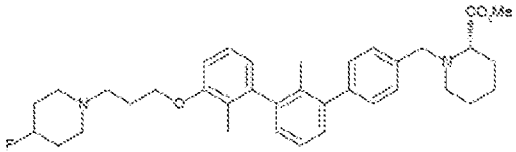
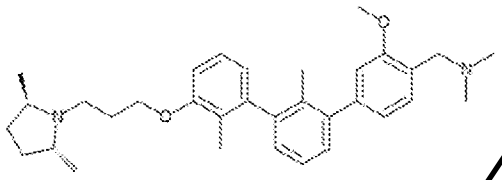
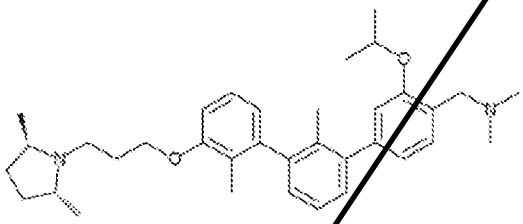
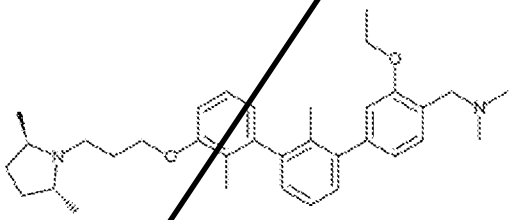
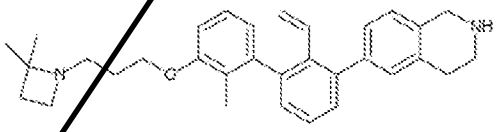
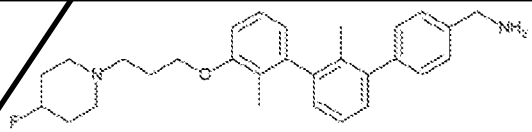
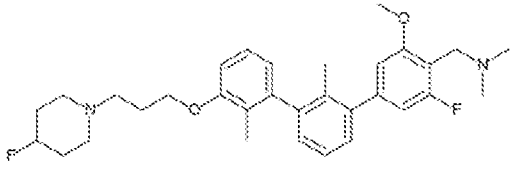
1.030		+	353.1 [M-NH_2]$^+$	2.9	A
1.031		++	353.2 [M-NH_2]$^+$	1.9	A
1.032		++	381.2 [M-NH_2]$^+$	2.4	A
1.033		++	363.2 [M-NH_2]$^+$	2.3	A
1.034		++	424.2 [M-NH_2]$^+$	1.5	A
1.035		++	533.3 $[M+H]^+$	1.7	A
1.036		++	471.3 $[M+H]^+$	1.6	A

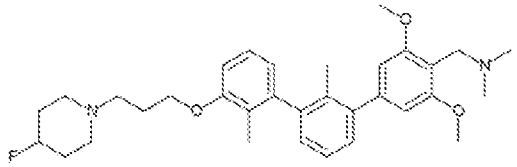
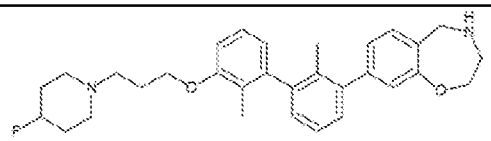
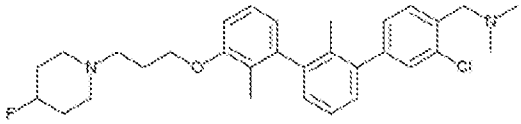
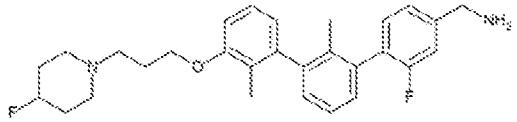
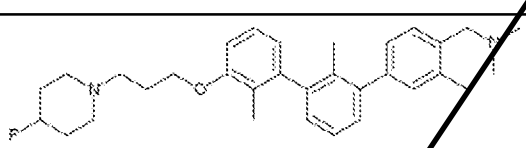
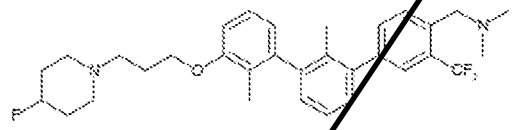
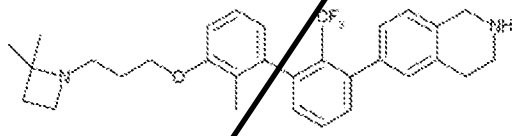
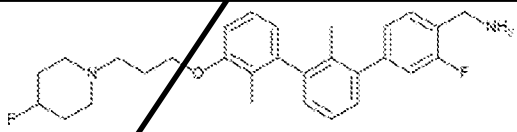
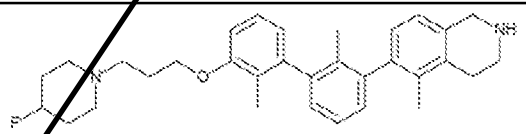
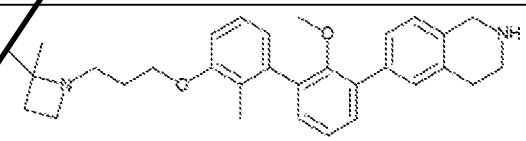
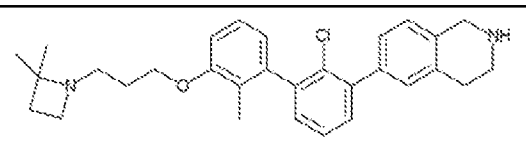
1.037		++	459.2 $[M+H]^+$	1.6	A
1.038		+	421.2 $[M+H]^+$	1.9	B
1.039		++	503.2 $[M+H]^+$	2.4	B
1.040		++	511.2 $[M+H]^+$	2.2	B
1.041		++	705.2 $[M+H]^+$	2.5	B
1.042		++	445.2 $[M+H]^+$	1.5	A
1.043		++	657.2 $[M+H]^+$	1.5	A
1.044		++	472.0 $[M-NH_2]^+$	1.6	A

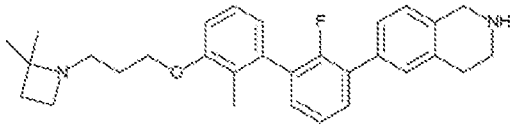
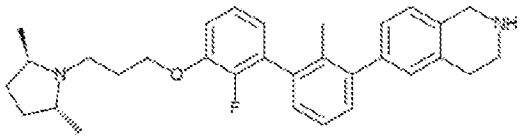
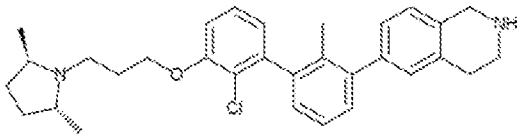
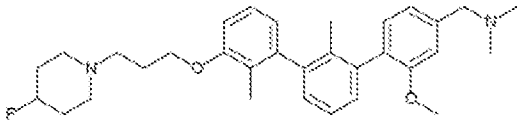
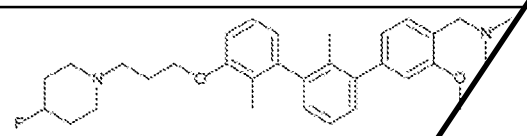
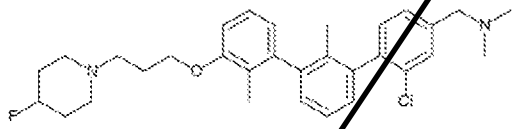
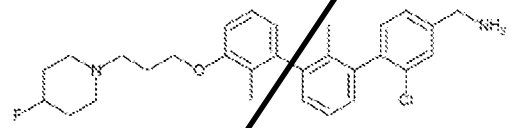
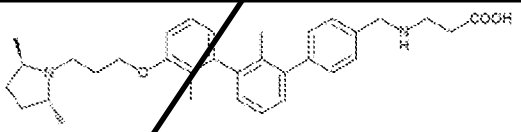
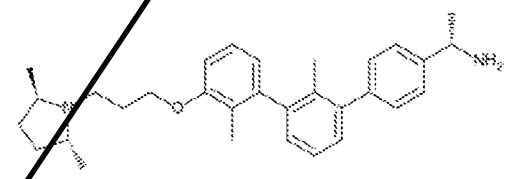
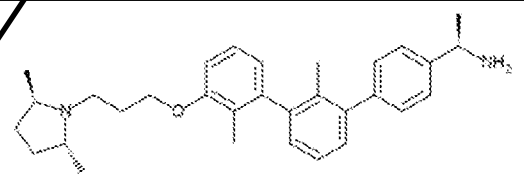
1.045		++	517.2 $[M+H]^+$	2.4	B
1.046		++	657.3 $[M+H]^+$	2.1	A
1.047		++	711.3 $[M+H]^+$	1.7	A
1.048		++	573.3 $[M+H]^+$	2.3	B
1.049		++	633.3 $[M+H]^+$	1.5	A
1.050		++	561.2 $[M+H]^+$	1.6	A
1.051		++	577.2 $[M+H]^+$	1.6	A

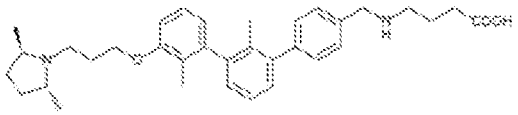
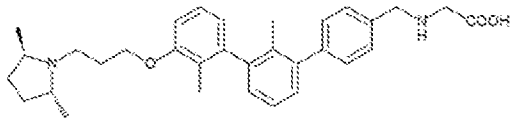
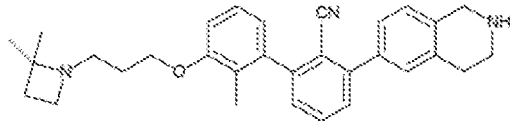
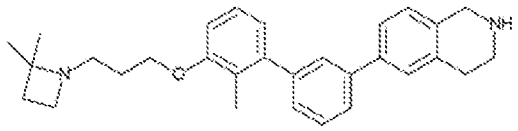
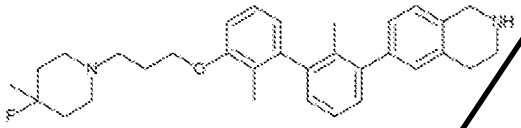
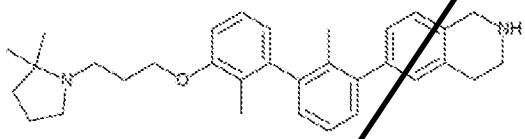
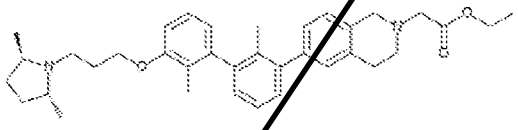
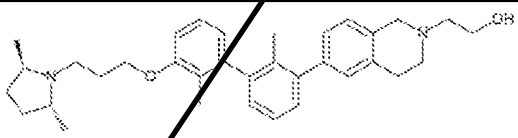
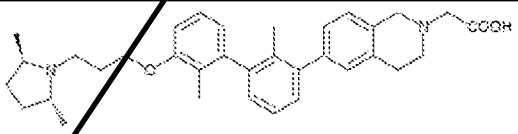
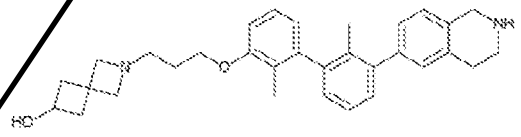
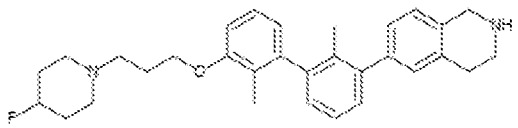
1.052		++	639.2 $[M+H]^+$	2.2	B
1.053		++	517.2 $[M+H]^+$	1.5	A
1.054		++	689.3 $[M+H]^+$	2.3	B
1.055		++	633.2 $[M+H]^+$	2.2	B
1.056		++	605.3 $[M+H]^+$	1.6	A
1.057		++	717.3 $[M+H]^+$	2.4	B
1.058		++	689.3 $[M+H]^+$	2.3	B
1.059		++	545.3 $[M+H]^+$	2.2	B

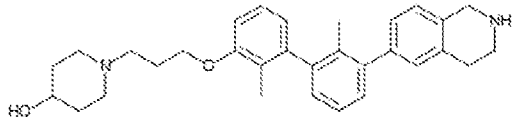
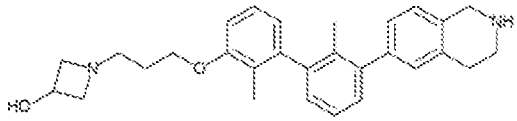
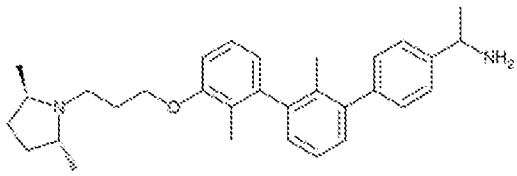
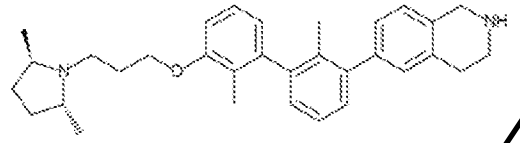
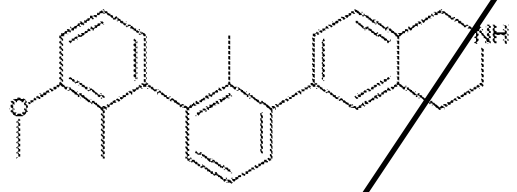
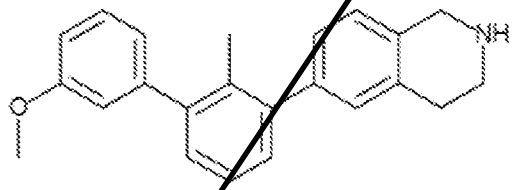
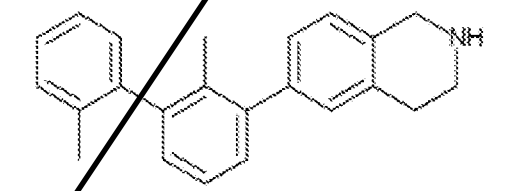
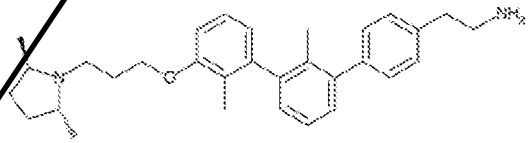
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1.061		++	565.2 $[M+H]^+$	2.0	B
1.062		++	605.2 $[M+H]^+$	2.2	B
1.063		++	661.2 $[M+H]^+$	2.2	B
1.064		+	513.3 $[M+H]^+$	2.2	B
1.065		+	559.3 $[M+H]^+$	2.2	B
1.066		++	559.3 $[M+H]^+$	2.2	B
1.067		++	577.3 $[M+H]^+$	2.1	B
1.068		++	513.3 $[M+H]^+$	2.0	B
1.069		++	499.2 $[M+H]^+$	2.1	B

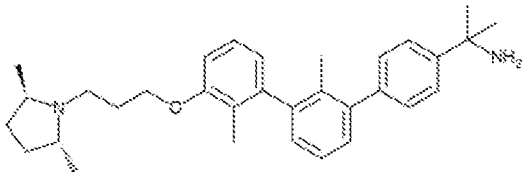
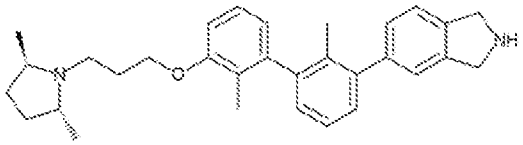
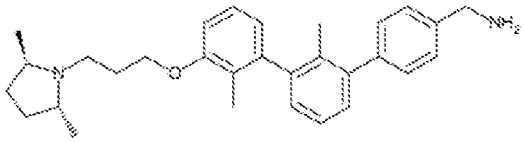
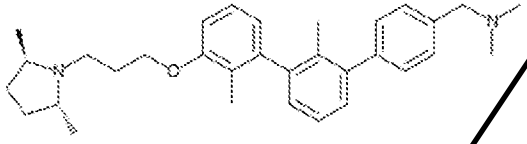
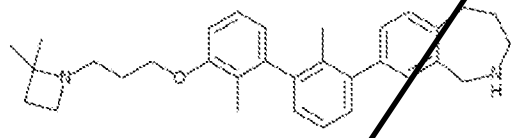
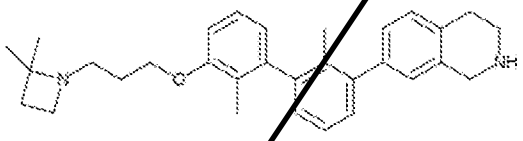
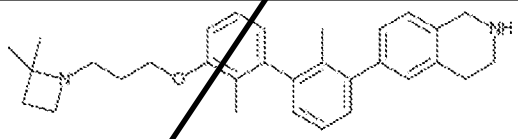
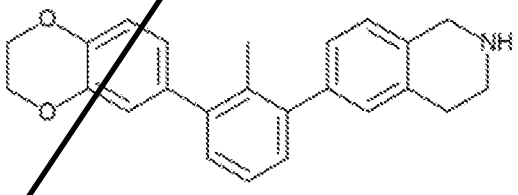
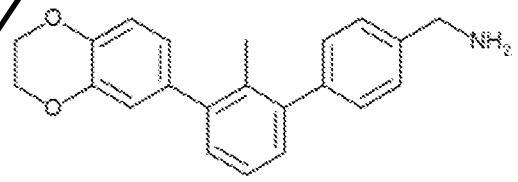
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1.071		+	559.2 $[M+H]^+$	2.0	B
1.072		+	573.3 $[M+H]^+$	2.2	B
1.073		++	501.3 $[M+H]^+$	2.2	B
1.074		++	529.3 $[M+H]^+$	2.1	B
1.075		++	515.2 $[M+H]^+$	2.1	B
1.076		++	467.3 $[M+H]^+$	2.2	B
1.077		++	447.1 $[M+H]^+$	2.0	B
1.078		++	523.2 $[M+H]^+$	1.8	B

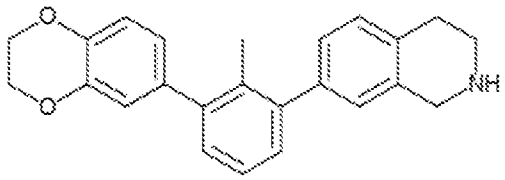
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1.081		++	509.2 $[M+H]^+$	2.0	B
1.082		++	465.1 $[M+H]^+$	2.0	B
1.083		++	489.3 $[M+H]^+$	2.1	B
1.084		+	543.2 $[M+H]^+$	2.2	B
1.085		+	509.4 $[M+H]^+$	1.6	A
1.086		++	465.1 $[M+H]^+$	2.0	B
1.087		+	487.2 $[M+H]^+$	1.8	B
1.088		++	471.4 $[M+H]^+$	2.1	B
1.089		++	475.3 $[M+H]^+$	2.1	B

1.090		++	459.4 $[M+H]^+$	2.1	B
1.091		++	473.3 $[M+H]^+$	1.7	A
1.092		++	489.1 $[M+H]^+$	1.4	A
1.093		+	505.2 $[M+H]^+$	1.9	B
1.094		++	505.2 $[M+H]^+$	1.7	B
1.095		+	509.2 $[M+H]^+$	1.9	B
1.096		+	481.2 $[M+H]^+$	2.0	B
1.097		++	515.2 $[M+H]^+$	2.0	B
1.098		++	457.2 $[M+H]^+$	2.1	B
1.099		++	457.2 $[M+H]^+$	1.9	B

1.100		++	529.3 $[M+H]^+$	2.0	B
1.101		++	501.3 $[M+H]^+$	2.1	B
1.102		++	466.4 $[M+H]^+$	1.9	B
1.103		+	441.3 $[M+H]^+$	1.9	B
1.104		++	487.2 $[M+H]^+$	2.0	B
1.105		++	469.2 $[M+H]^+$	2.0	B
1.106		+	555.3 $[M+H]^+$	1.7	A
1.107		++	513.3 $[M+H]^+$	1.9	A
1.108		++	527.2 $[M+H]^+$	1.7	A
1.109		++	483.3 $[M+H]^+$	1.7	B
1.110		++	473.3 $[M+H]^+$	2.1	B

1.111		++	471.3 $[M+H]^+$	1.9	B
1.112		++	443.2 $[M+H]^+$	2.0	B
1.113		++	457.2 $[M+H]^+$	1.4	A
1.114		++	469.2 $[M+H]^+$	1.4	A
1.115		+	344.2 $[M+H]^+$	2.0	A
1.116		+	330.1 $[M+H]^+$	1.9	A
1.117		+	314.1 $[M+H]^+$	2.0	A
1.118		++	457.0 $[M+H]^+$	1.6	A

1.119		++	471.3 $[M+H]^+$	1.4	A
1.120		++	455.3 $[M+H]^+$	1.4	A
1.121		++	443.2 $[M+H]^+$	1.6	A
1.122		++	471.3 $[M+H]^+$	1.7	A
1.123		++	469.2 $[M+H]^+$	1.6	A
1.124		++	455.3 $[M+H]^+$	1.8	A
1.125		++	455.3 $[M+H]^+$	1.7	A
1.126		++	358.2 $[M+H]^+$	2.1	A
1.127		+	315.1 $[M+H]^+$	1.9	A

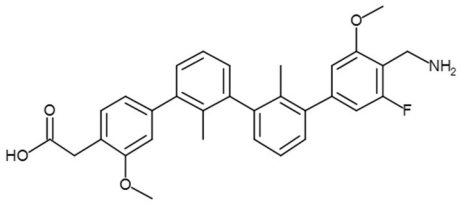
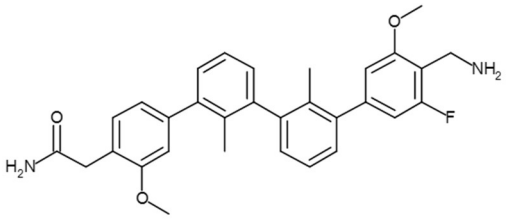
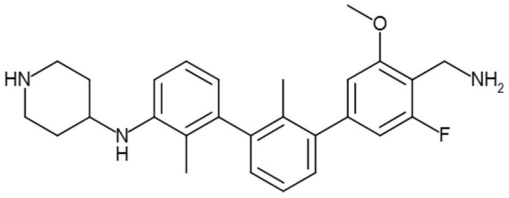
1.128		+	358.2 $[M+H]^+$	1.7	A

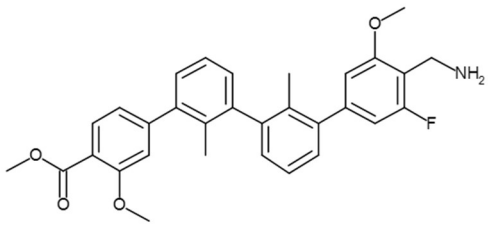
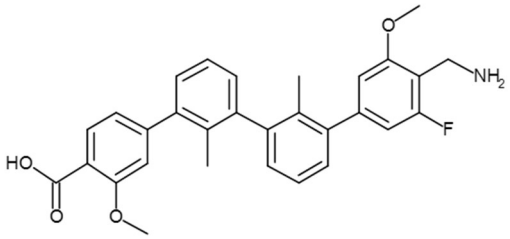
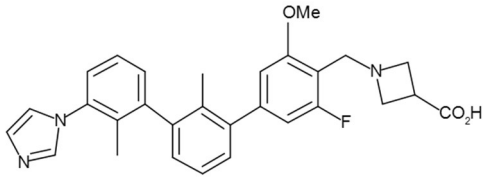
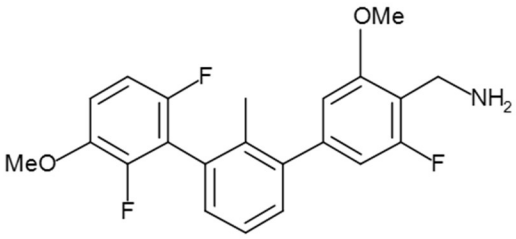
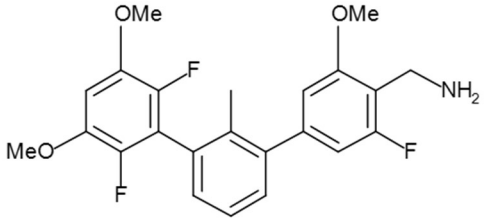
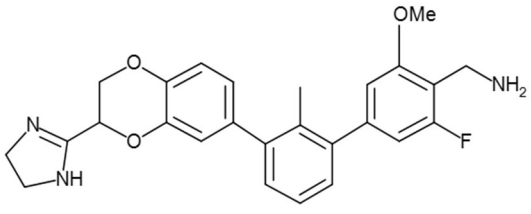
[0186] Particular embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Upon reading the foregoing, description, variations of the disclosed embodiments may become apparent to individuals working in the art, and it is expected that those skilled artisans may employ such variations as appropriate. Accordingly, it is intended that the invention be practiced otherwise than as specifically described herein, and that the invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

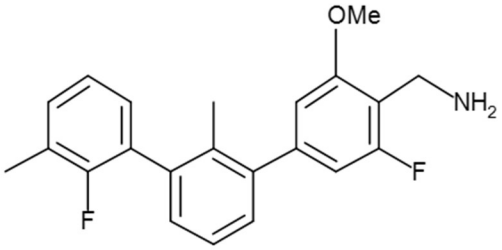
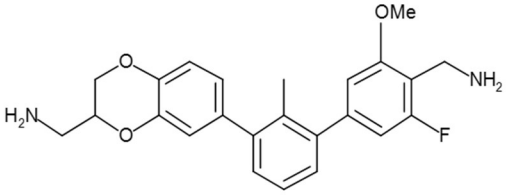
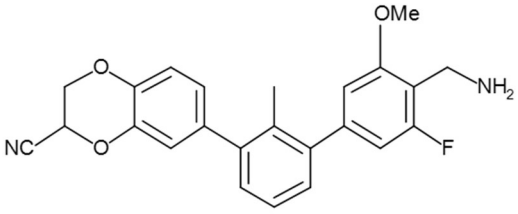
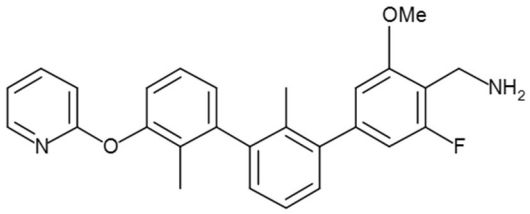
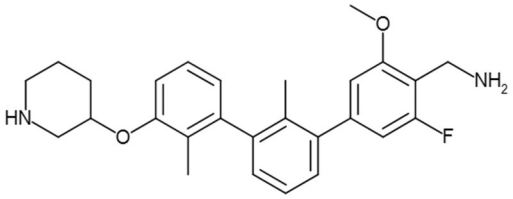
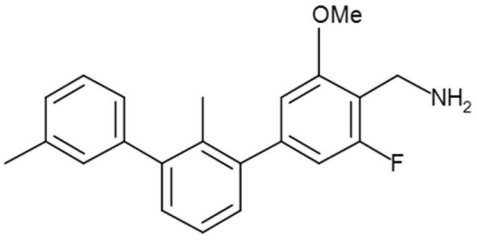
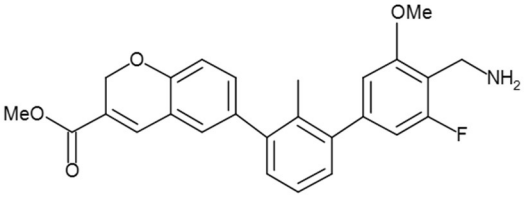
[0187] All publications, patent applications, accession numbers, and other references cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

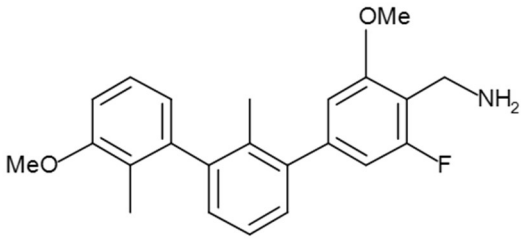
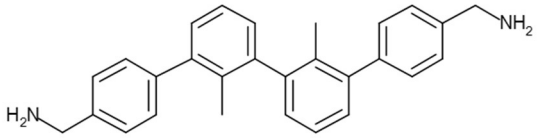
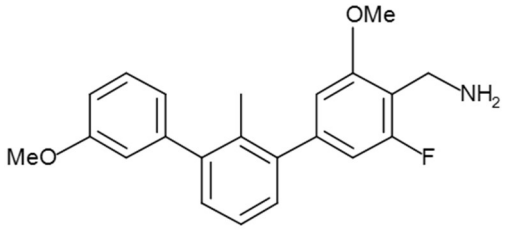
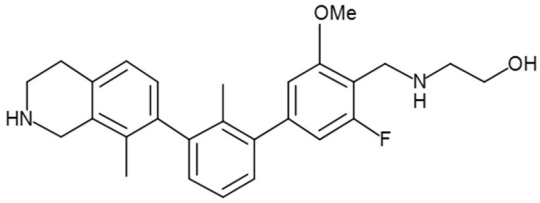
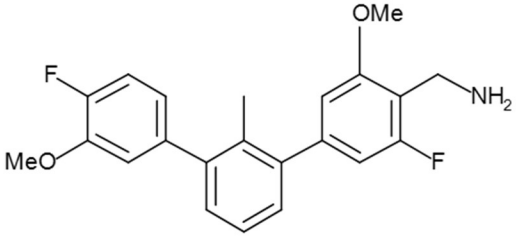
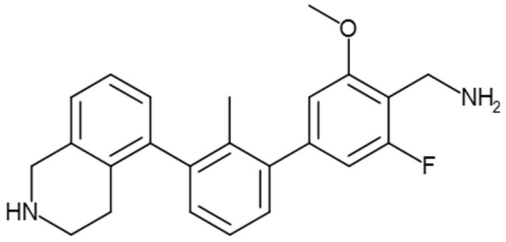
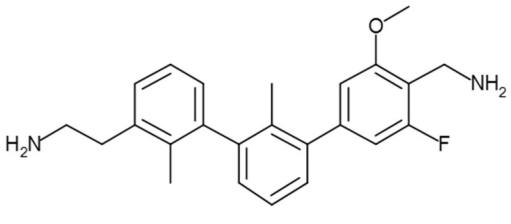
[0185] 96 Well plates were coated with 1µg/mL of human PD-L1 (obtained from R&D) in PBS overnight at 4 °C. The wells were then blocked with 2% BSA in PBS (W/V) with 0.05 % TWEEN-20 for 1 hour at 37 °C. The plates were washed 3 times with PBS/0.05% TWEEN-20 and the compounds were serial diluted (1:5) in dilution medium and added to the ELISA plates. Human PD-1 and biotin 0.3µg/mL (ACRO Biosystems) were added and incubated for 1 hour at 37 °C then washed 3 times with PBS/0.05% TWEEN-20. A second block was performed with 2% BSA in PBS (W/V)/0.05% TWEEN-20 for 10 min at 37 °C and the plates were washed 3 times with PBS/0.05% TWEEN-20. Streptavidin–HRP was added for 1 hour at 37 °C then the plates were washed 3 times with PBS/0.05% TWEEN-20. TMB substrate was added and reacted for 20 min at 37 °C. A stop solution (2 N aqueous H_2SO_4) was added. The absorbance was read at 450 nm using a micro-plate spectrophotometer. The results are shown in Table 1: IC_{50} values are provided as follows: from 1000 to 10,000 nM (+); Less than 1000 nM (++).

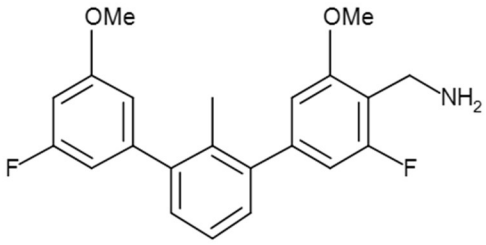
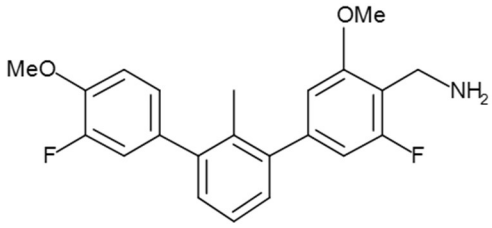
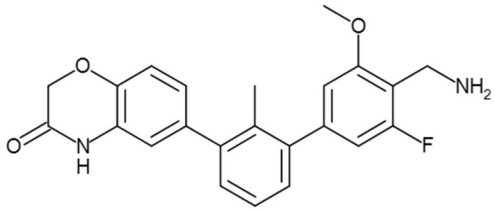
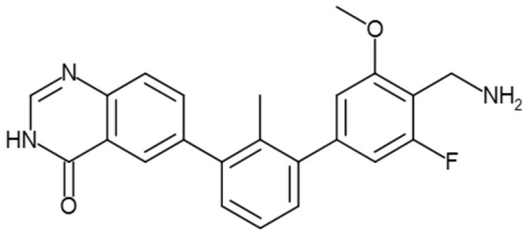
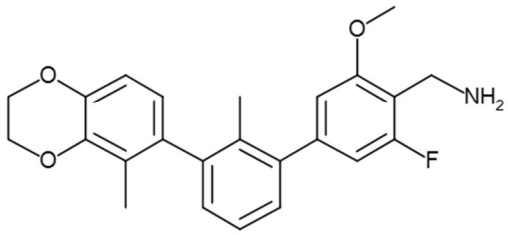
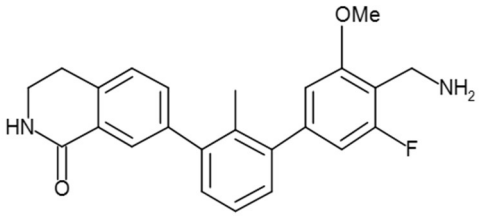
Table 1

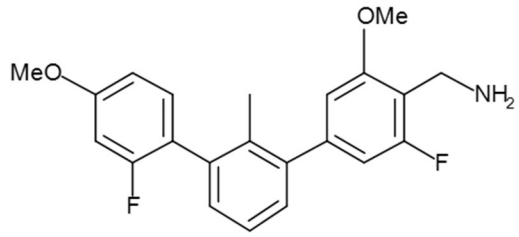
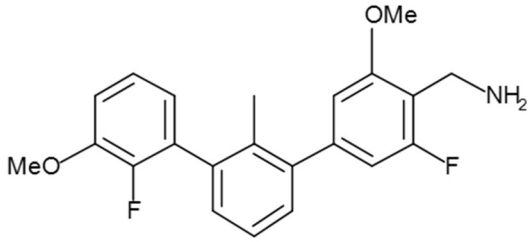
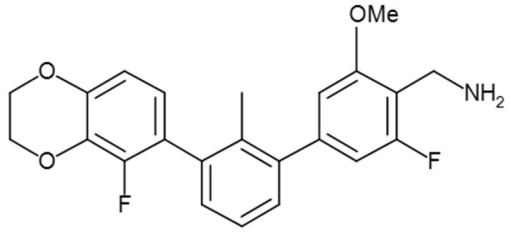
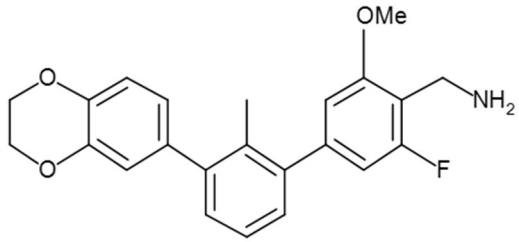
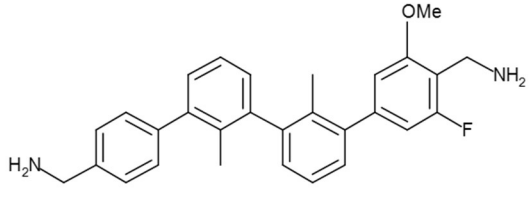
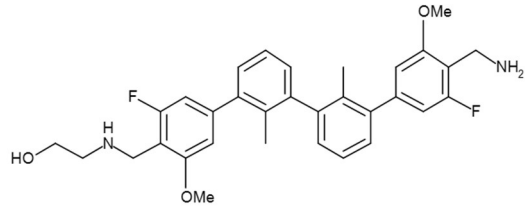
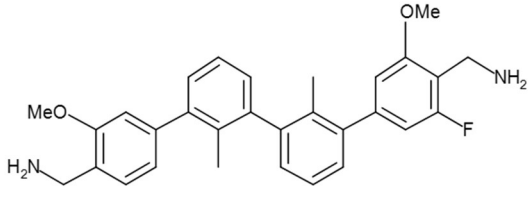
Compd ID	Structure	ELISA IC_{50} (nM)	*m/z*ES	HPLC RT (min)	HPLC Method
1.001		+	500.3 $[M+H]^+$	2.9	A
1.002		++	482.2 $[M+H]^+$	2.6	A
1.003		++	434.2 $[M+H]^+$	2.1	B

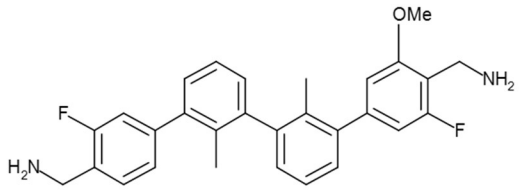
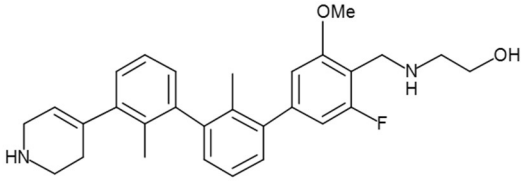
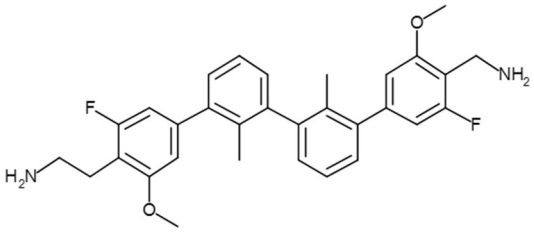
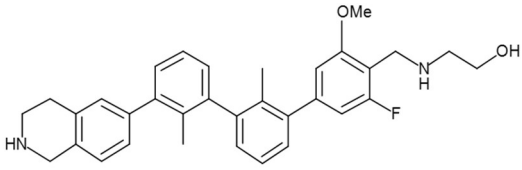
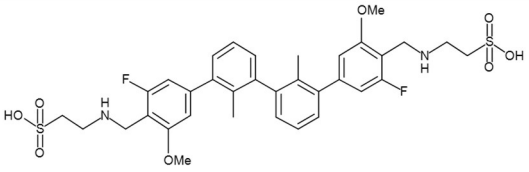
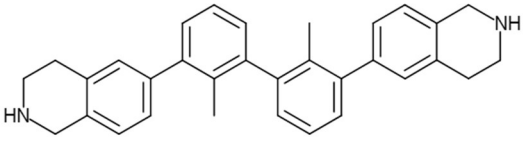
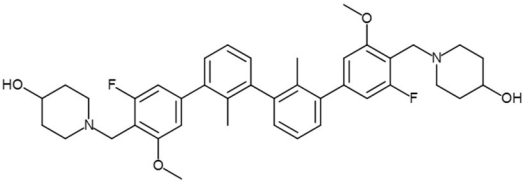
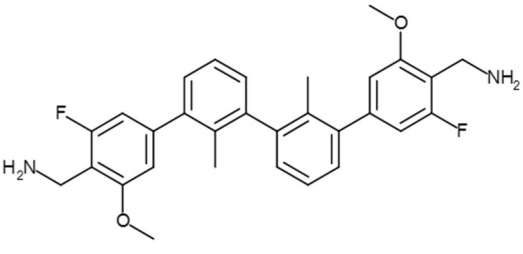
1.004		++	483.2 $[M+H]^+$	3.3	A
1.005		+	486.4 $[M+H]^+$	2.5	A
1.006		+	486.2 $[M+H]^+$	2.1	B
1.007		++	371.1 $[M-NH_2]^+$	2.5	A
1.008		++	401.2 $[M-NH_2]^+$	2.4	A
1.009		+	448.1 $[M+H]^+$	2.1	B

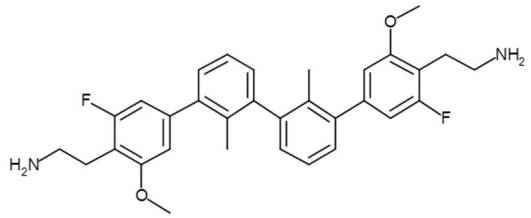
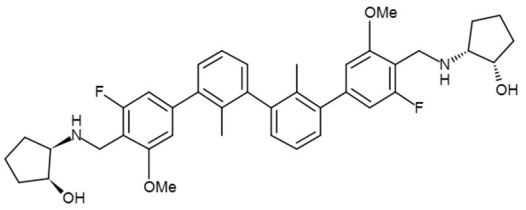
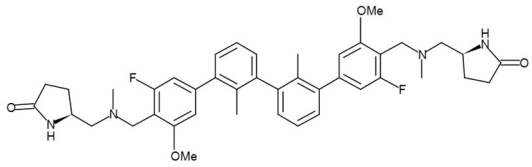
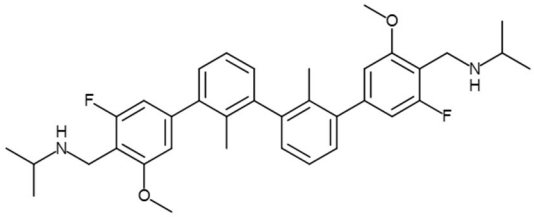
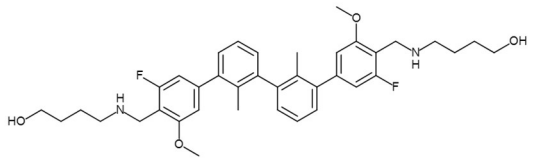
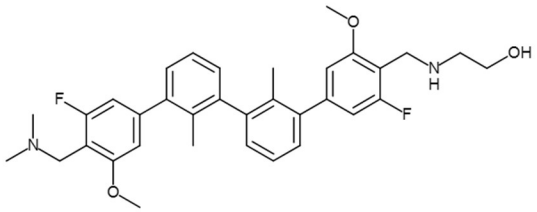
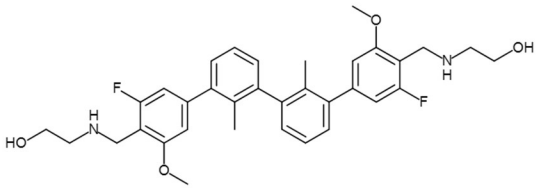
1.010		++	337.2 [M-NH_2]$^+$	2.9	A
1.011		++	392.1 [M-NH_2]$^+$	2.0	B
1.012		+	338.0 [M-NH_2]$^+$	2.1	B
1.013		+	415.0 $[M+H]^+$	2.8	B
1.014		+	435.1 $[M+H]^+$	2.1	B
1.015		++	319.1 [M-NH_2]$^+$	2.5	A
1.016		++	434.1 $[M+H]^+$	2.3	B

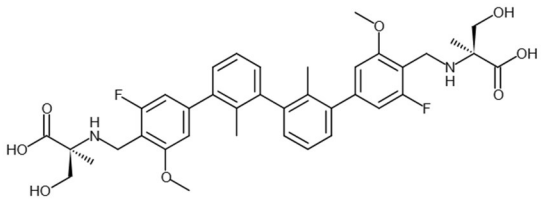
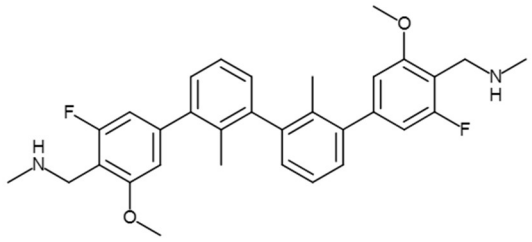
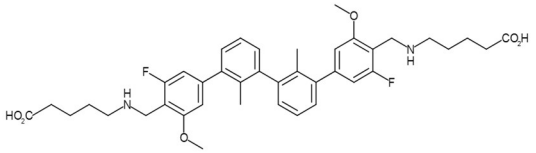
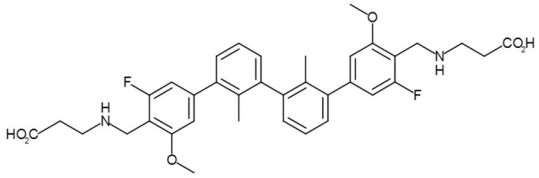
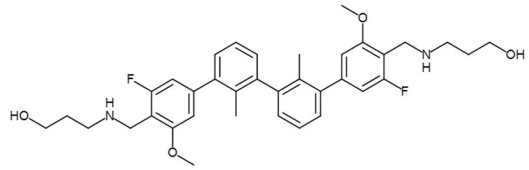
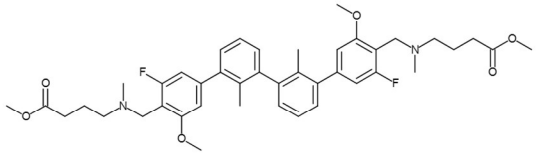
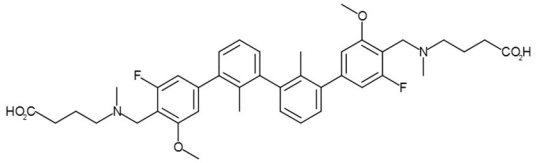
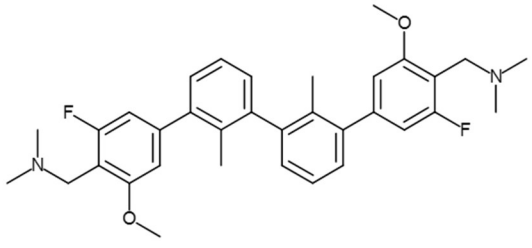
1.017		++	349.1 [M-NH_2]$^+$	2.6	A
1.018		++	376.2 [M-NH_2]$^+$	2.2	B
1.019		++	335.2 [M-NH_2]$^+$	3.0	A
1.020		+	435.1 [M+H]$^+$	2.1	B
1.021		+	353.2 [M-NH_2]$^+$	2.4	A
1.022		+	377.1 [M+H]$^+$	1.9	B
1.023		+	362.1 [M-NH_2]$^+$	2.1	B

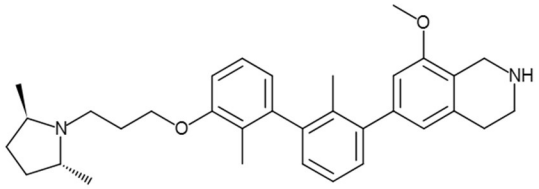
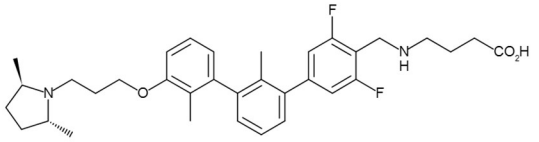
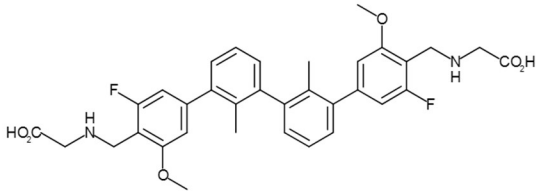
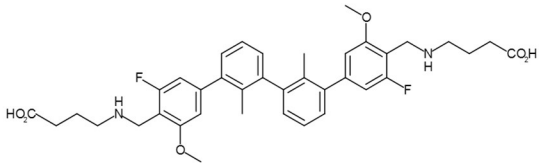
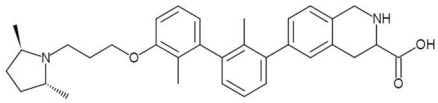
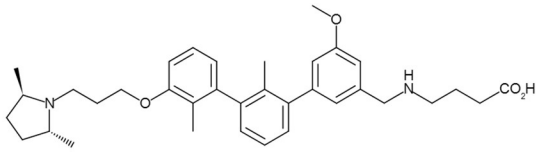
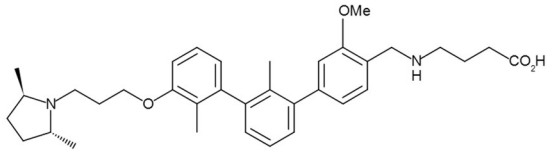
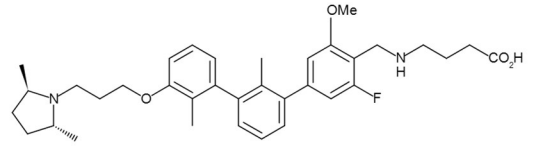
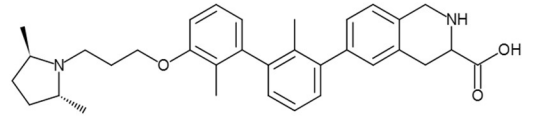
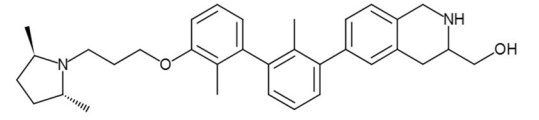
1.024		++	353.2 [M-NH_2]$^+$	2.5	A
1.025		+	353.2 [M-NH_2]$^+$	2.2	A
1.026		++	376.0 [M-NH_2]$^+$	2.4	B
1.027		++	373.1 [M-NH_2]$^+$	1.6	A
1.028		++	377.2 [M-NH_2]$^+$	3.2	B
1.029		+	391.2 [M+H]$^+$	2.3	B

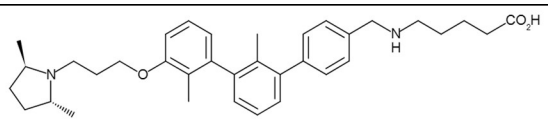
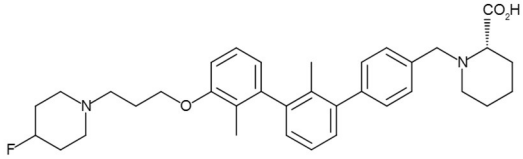
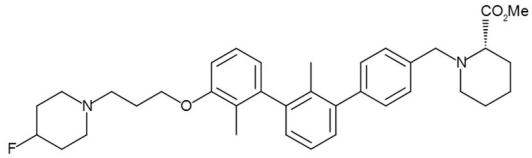
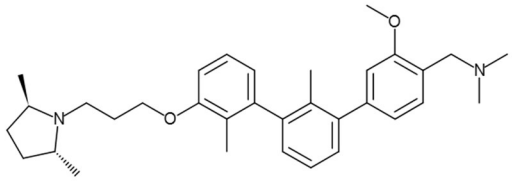
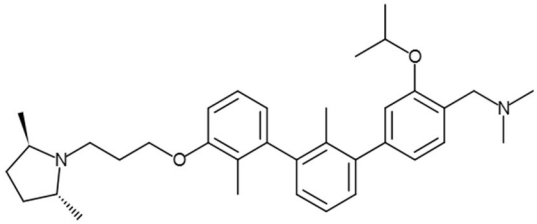
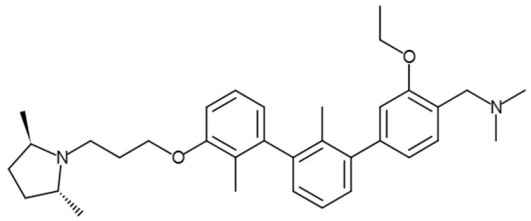
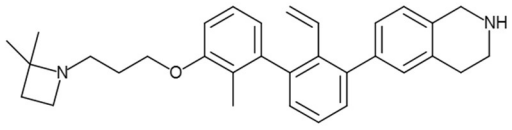
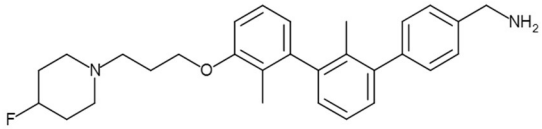
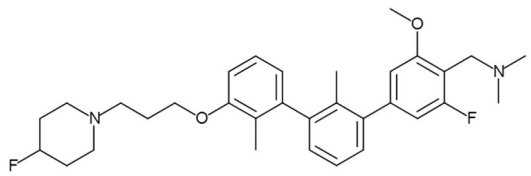
1.030		+	353.1 [M-NH_2]$^+$	2.9	A
1.031		++	353.2 [M-NH_2]$^+$	1.9	A
1.032		++	381.2 [M-NH_2]$^+$	2.4	A
1.033		++	363.2 [M-NH_2]$^+$	2.3	A
1.034		++	424.2 [M-NH_2]$^+$	1.5	A
1.035		++	533.3 [M+H]$^+$	1.7	A
1.036		++	471.3 [M+H]$^+$	1.6	A

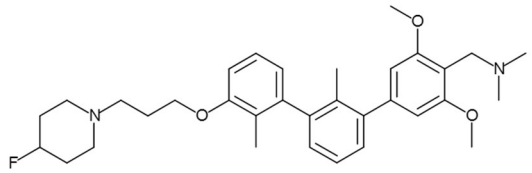
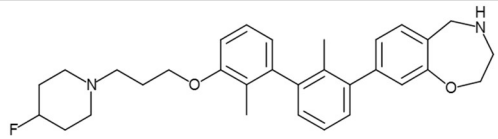
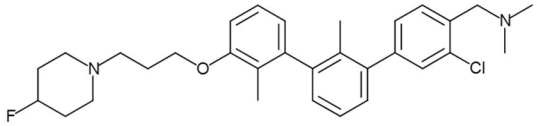
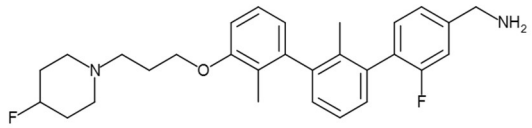
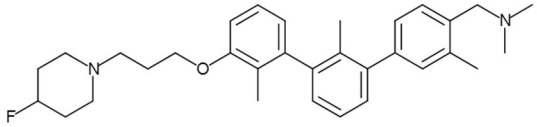
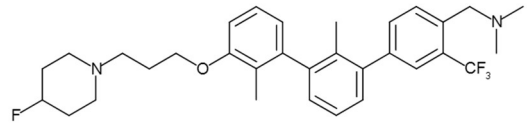
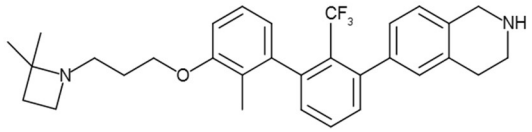
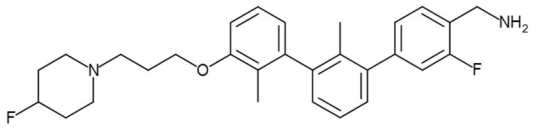
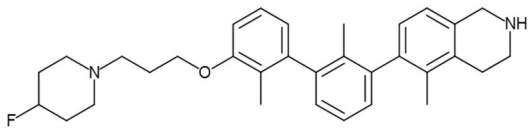
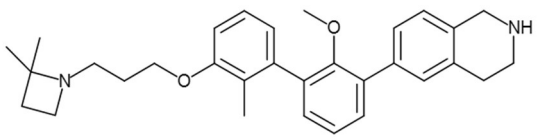
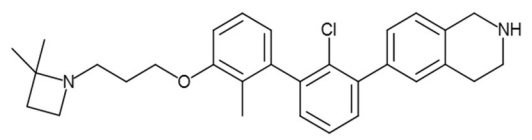
1.037		++	459.2 $[M+H]^+$	1.6	A
1.038		+	421.2 $[M+H]^+$	1.9	B
1.039		++	503.2 $[M+H]^+$	2.4	B
1.040		++	511.2 $[M+H]^+$	2.2	B
1.041		++	705.2 $[M+H]^+$	2.5	B
1.042		++	445.2 $[M+H]^+$	1.5	A
1.043		++	657.2 $[M+H]^+$	1.5	A
1.044		++	472.0 $[M-NH_2]^+$	1.6	A

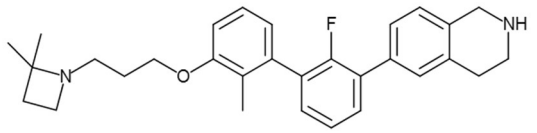
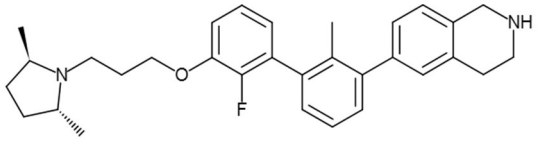
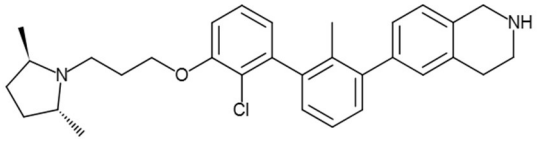
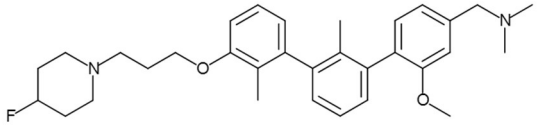
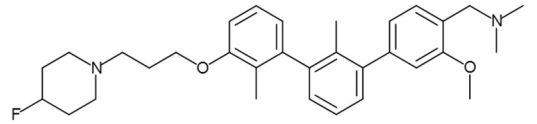
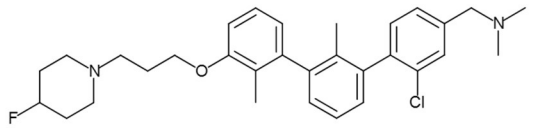
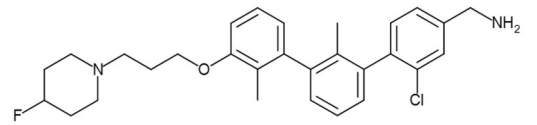
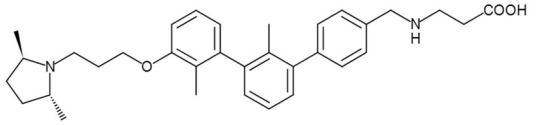
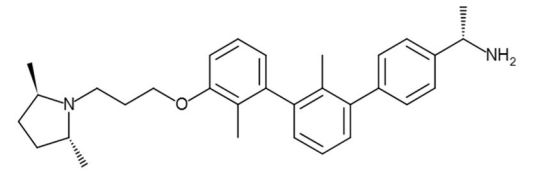
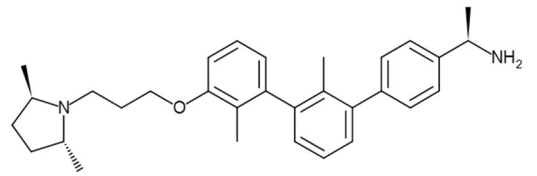
1.045		++	517.2 $[M+H]^+$	2.4	B
1.046		++	657.3 $[M+H]^+$	2.1	A
1.047		++	711.3 $[M+H]^+$	1.7	A
1.048		++	573.3 $[M+H]^+$	2.3	B
1.049		++	633.3 $[M+H]^+$	1.5	A
1.050		++	561.2 $[M+H]^+$	1.6	A
1.051		++	577.2 $[M+H]^+$	1.6	A

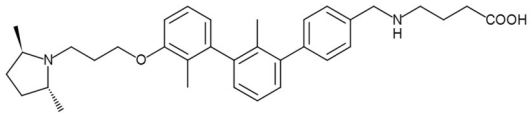
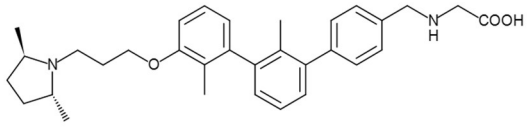
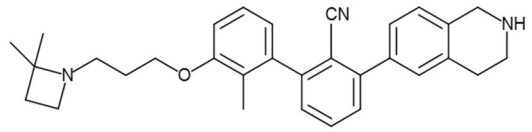
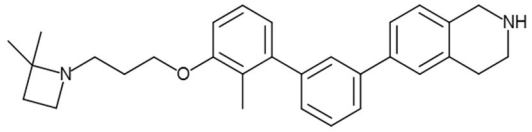
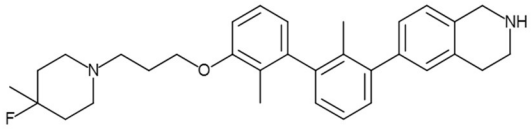
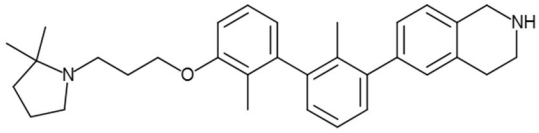
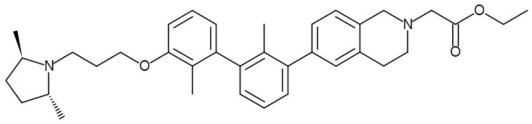
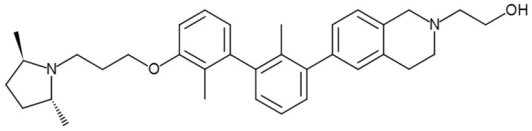
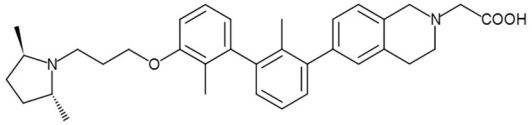
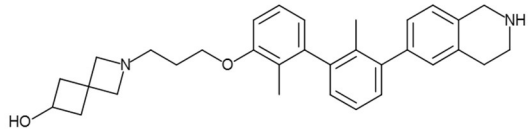
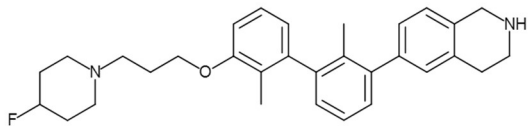
1.052		++	639.2 $[M+H]^+$	2.2	B
1.053		++	517.2 $[M+H]^+$	1.5	A
1.054		++	689.3 $[M+H]^+$	2.3	B
1.055		++	633.2 $[M+H]^+$	2.2	B
1.056		++	605.3 $[M+H]^+$	1.6	A
1.057		++	717.3 $[M+H]^+$	2.4	B
1.058		++	689.3 $[M+H]^+$	2.3	B
1.059		++	545.3 $[M+H]^+$	2.2	B

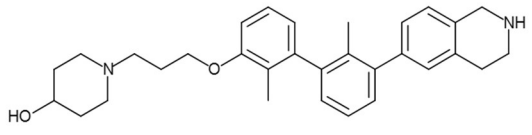
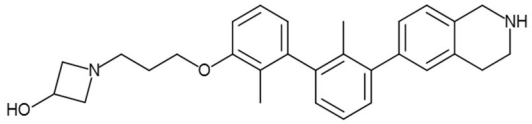
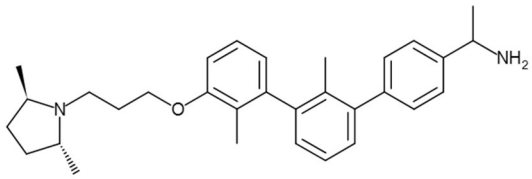
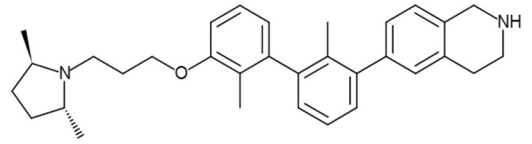
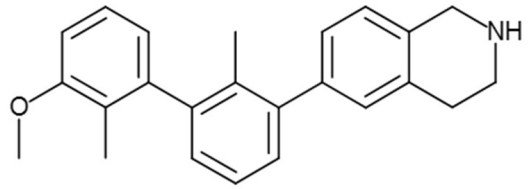
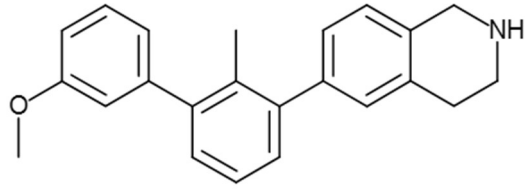
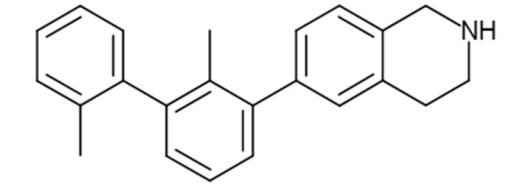
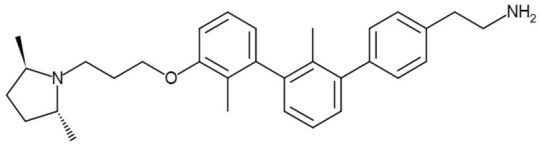
1.060		++	499.2 $[M+H]^+$	2.1	B
1.061		++	565.2 $[M+H]^+$	2.0	B
1.062		++	605.2 $[M+H]^+$	2.2	B
1.063		++	661.2 $[M+H]^+$	2.2	B
1.064		+	513.3 $[M+H]^+$	2.2	B
1.065		+	559.3 $[M+H]^+$	2.2	B
1.066		++	559.3 $[M+H]^+$	2.2	B
1.067		++	577.3 $[M+H]^+$	2.1	B
1.068		++	513.3 $[M+H]^+$	2.0	B
1.069		++	499.2 $[M+H]^+$	2.1	B

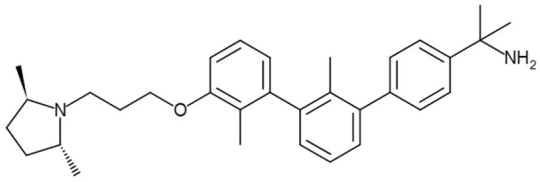
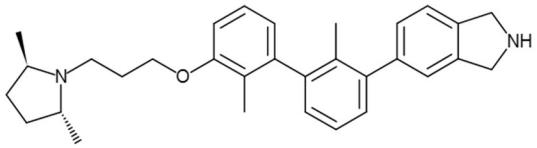
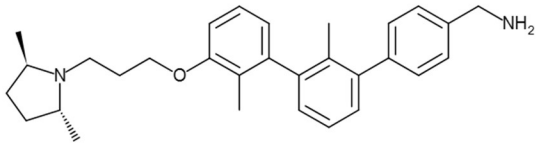
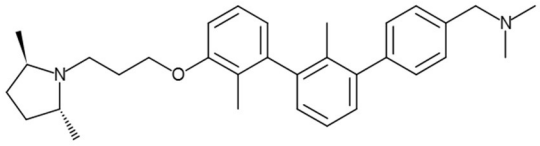
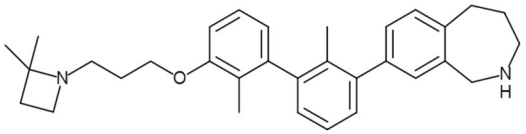
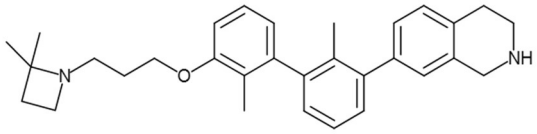
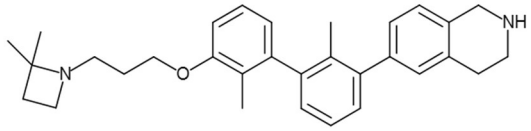
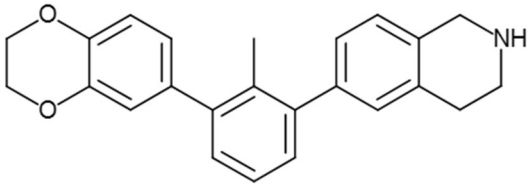
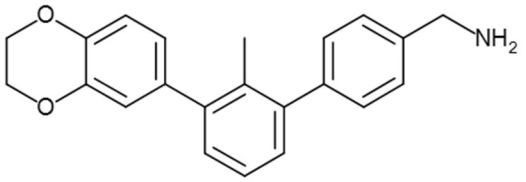
1.070		+	525.3 $[M+H]^+$	2.5	B
1.071		+	559.2 $[M+H]^+$	2.0	B
1.072		+	573.3 $[M+H]^+$	2.2	B
1.073		++	501.3 $[M+H]^+$	2.2	B
1.074		++	529.3 $[M+H]^+$	2.1	B
1.075		++	515.2 $[M+H]^+$	2.1	B
1.076		++	467.3 $[M+H]^+$	2.2	B
1.077		++	447.1 $[M+H]^+$	2.0	B
1.078		++	523.2 $[M+H]^+$	1.8	B

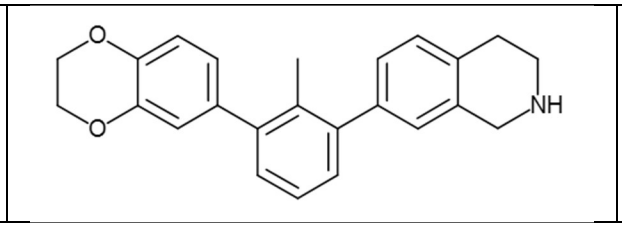
1.079		+	535.2 $[M+H]^+$	2.1	B
1.080		++	489.2 $[M+H]^+$	1.9	B
1.081		++	509.2 $[M+H]^+$	2.0	B
1.082		++	465.1 $[M+H]^+$	2.0	B
1.083		++	489.3 $[M+H]^+$	2.1	B
1.084		+	543.2 $[M+H]^+$	2.2	B
1.085		+	509.4 $[M+H]^+$	1.6	A
1.086		++	465.1 $[M+H]^+$	2.0	B
1.087		+	487.2 $[M+H]^+$	1.8	B
1.088		++	471.4 $[M+H]^+$	2.1	B
1.089		++	475.3 $[M+H]^+$	2.1	B

1.090		++	459.4 $[M+H]^+$	2.1	B
1.091		++	473.3 $[M+H]^+$	1.7	A
1.092		++	489.1 $[M+H]^+$	1.4	A
1.093		+	505.2 $[M+H]^+$	1.9	B
1.094		++	505.2 $[M+H]^+$	1.7	B
1.095		+	509.2 $[M+H]^+$	1.9	B
1.096		+	481.2 $[M+H]^+$	2.0	B
1.097		++	515.2 $[M+H]^+$	2.0	B
1.098		++	457.2 $[M+H]^+$	2.1	B
1.099		++	457.2 $[M+H]^+$	1.9	B

1.100		++	529.3 $[M+H]^+$	2.0	B
1.101		++	501.3 $[M+H]^+$	2.1	B
1.102		++	466.4 $[M+H]^+$	1.9	B
1.103		+	441.3 $[M+H]^+$	1.9	B
1.104		++	487.2 $[M+H]^+$	2.0	B
1.105		++	469.2 $[M+H]^+$	2.0	B
1.106		+	555.3 $[M+H]^+$	1.7	A
1.107		++	513.3 $[M+H]^+$	1.9	A
1.108		++	527.2 $[M+H]^+$	1.7	A
1.109		++	483.3 $[M+H]^+$	1.7	B
1.110		++	473.3 $[M+H]^+$	2.1	B

1.111		++	471.3 $[M+H]^+$	1.9	B
1.112		++	443.2 $[M+H]^+$	2.0	B
1.113		++	457.2 $[M+H]^+$	1.4	A
1.114		++	469.2 $[M+H]^+$	1.4	A
1.115		+	344.2 $[M+H]^+$	2.0	A
1.116		+	330.1 $[M+H]^+$	1.9	A
1.117		+	314.1 $[M+H]^+$	2.0	A
1.118		++	457.0 $[M+H]^+$	1.6	A

1.119		++	471.3 $[M+H]^+$	1.4	A
1.120		++	455.3 $[M+H]^+$	1.4	A
1.121		++	443.2 $[M+H]^+$	1.6	A
1.122		++	471.3 $[M+H]^+$	1.7	A
1.123		++	469.2 $[M+H]^+$	1.6	A
1.124		++	455.3 $[M+H]^+$	1.8	A
1.125		++	455.3 $[M+H]^+$	1.7	A
1.126		++	358.2 $[M+H]^+$	2.1	A
1.127		+	315.1 $[M+H]^+$	1.9	A

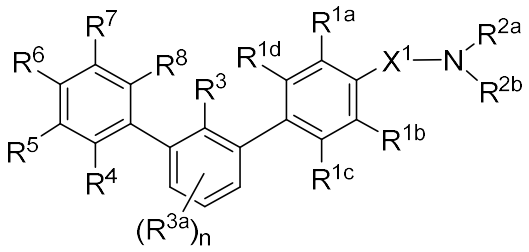
1.128		+	358.2 $[M+H]^+$	1.7	A

[0186] Particular embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Upon reading the foregoing, description, variations of the disclosed embodiments may become apparent to individuals working in the art, and it is expected that those skilled artisans may employ such variations as appropriate. Accordingly, it is intended that the invention be practiced otherwise than as specifically described herein, and that the invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0187] All publications, patent applications, accession numbers, and other references cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

CLAIMS:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof~~, or a prodrug or bioisostere thereof,~~ wherein:

R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each independently selected from the group consisting of H, F, Cl, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and CN;

X^1 is C_{1-3} alkylene, optionally substituted with one or two C_{1-2} alkyl or CO_2H;

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, -Y, $-X^2$-$C(O)_2R^a$, $-X^2$-OR^a, $-X^2$-NR^aR^b, $-X^2$-$CONR^aR^b$, $-X^2$-SO_2R^a, $-X^2$-$SO_2NR^aR^b$, $-X^2$-SO_3R^a, and $–X^2$-Y, wherein each X^2 is C_{1-6} alkylene, and and any C_{1-8} alkyl or C_{1-6} alkylene~~,~~ is optionally further substituted with one or two members independently selected from OH, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, ~~or~~ and CO_2H, and each Y is selected from the group consisting of C_{3-6} cycloalkyl, C_{4-8} heterocyclyl, and 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkoxy, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, and CO_2H;

o~~O~~r R^{2a} and R^{2b} are combined to form a 4- to 8-membered ring or spirocyclic ring, optionally having one or two additional ring vertices selected from O, N, and~~or~~ S;

or R^{1a} and R^{2a} ~~or X^1~~ are combined to form a 5- to 7-membered ring;

or R^{1b} and R^{2b} ~~or X^1~~ are combined to form a 5- to 7-membered ring;

wherein the rings formed by combining R^{2a} and R^{2b}, R^{1a} and R^{2a} ~~or X^1~~, or R^{1b} and R^{2b} ~~or X^1~~, are substituted with 0 to 4 substituents independently selected from the group consisting of oxo, C_{1-8} alkyl, C_{1-8} haloalkyl, $-X^3$-$C(O)_2R^a$, $-X^3$-OR^a, $-X^3$-NR^aR^b,

-X^3-$CONR^aR^b$, -X^3-SO_2R^a, -X^3-$SO_2NR^aR^b$, and –X^3-SO_3R^a; wherein X^3 is a bond or C_{1-6} alkylene;

R^3 is selected from the group consisting of ~~H,~~ F, Cl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{2-3} alkenyl, and CN;

the subscript n is 0~~, 1 or 2~~;

each R^{3a} is independently selected from the group consisting of F, Cl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{2-3} alkenyl, and CN;

each of R^4, R^6, R^7, and R^8 is independently selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, -Y^1, -X^4-$C(O)_2R^a$,

-X^4-OR^a, -X^4-NR^aR^b, -X^4-$CONR^aR^b$, -X^4-SO_2R^a, -X^4-$SO_2NR^aR^b$, -X^4-SO_3R^a,

–O-X^4-Y^1, and –X^4-Y^1, wherein each X^4 is a bond or C_{1-6} alkylene and is optionally further substituted with OH, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, or CO_2H, and each Y^1 is selected from the group consisting of C_{3-6} cycloalkyl, C_{4-8} heterocyclyl, and 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkoxy, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, and CO_2H;

R^5 is a member selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, -Y^2, -X^5-$C(O)_2R^a$, -X^5-OR^a, -X^5-NR^aR^b, -X^5-$CONR^aR^b$, -X^5-SO_2R^a, -X^5-$SO_2NR^aR^b$, -X^5-SO_3R^a, –X^5-Y^2, –O-X^5-Y^2, and –A-Z, wherein each X^5 is a bond or C_{1-6} alkylene and is optionally further substituted with OH, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, or CO_2H, and each Y^2 is selected from the group consisting of C_{3-6} cycloalkyl, C_{4-8} heterocyclyl, C_{7-9} spiroheterocyclyl, and 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, halogen, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkoxy, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, and CO_2H;

wherein

A is a member selected from the group consisting of a bond, -O-, and –$N(R^a)$-;

Z is selected from the group consisting of:

i) a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three R^c; and

~~ii) phenyl, optionally substituted with one to three R^e; and~~

ii~~i~~) a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted with one to three R^c;

~~and when A is -O- or -N(R^a)-, then Z is other than phenyl;~~

and two of R^4, R^5, R^6, R^7, and R^8 on adjacent carbon atoms are optionally combined to form a 5- or 6-membered non-aromatic heterocyclic ring having one or two ring vertices selected from the group consisting of O, –N(R^b)-, and =N-; wherein said non-aromatic heterocyclic ring is optionally substituted with oxo and optionally with from one to four R^c;

and at least one of R^4, R^5, R^6, R^7, and R^8 is other than H;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylene-CO_2H, C_{1-6} alkylene-COO-C_{1-8}alkyl, and C_{1-6} alkylene-SO_3H;

each R^b is independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylene-CO_2H, C_{1-6} alkylene-SO_3H, and C_{1-6} alkylene-Y^3, wherein Y^3 is C_{3-6} cycloalkyl or C_{4-8} heterocyclyl, and each R^b is optionally further substituted with one or two members independently selected from oxo, OH, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, and CO_2H;

and R^a and R^b, when attached to the same nitrogen atom, are optionally combined to form a 4- to 8-membered ring or spirocyclic ring, optionally substituted with halogen, OH, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, or CO_2H; and

each R^c is independently selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -Y^4, -X^6-$C(O)_2R^a$, -X^6-OR^a, -X^6-NR^aR^b, -X^6-$CONR^aR^b$, -X^6-SO_2R^a, -X^6-$SO_2NR^aR^b$, -X^6-SO_3R^a, and -N(R^a)-X^6-$C(O)_2R^a$, wherein each X^6 is a bond or C_{1-6} alkylene, and each Y^4 is selected from the group consisting of C_{3-6} cycloalkyl and C_{4-8} heterocyclyl; and optionally two R^c on adjacent ring vertices are combined to form a fused 5- or 6-membered heterocyclic ring.

2. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein R^5 is –A-Z.

3. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein R^5 is $–O\text{-}X^5\text{-}Y^2$.

~~**4.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof wherein R^5 is –A-Z, A is a bond, and Z is phenyl, optionally substituted with one to three R^e.~~

~~**5**~~**4.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein X^1 is $–CH_2$-.

~~**6**~~**5.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein R^{1c}, R^7, and R^8 are H, and R^3 is selected from the group consisting of F, Cl, CH_3, CF_3, and OCH_3.

~~**7**~~**6.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein a ring is formed between one pair of R^4 and R^5, R^5 and R^6, R^{1b} and R^{2b}, or R^{1a} and R^{2a}.

~~**8**~~**7.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein R^5 is –A-Z, and Z is selected from the group consisting of piperidinyl, imidazolyl, and pyridinyl.

~~**9.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof wherein n is 0.~~

~~**10**~~**8.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of F, Cl, CH_3, CF_3, and OCH_3.

~~**11**~~**9.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein ~~the group~~ R^{1a} is OCH_3 and R^{1b} is F.

~~12~~10. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each H.

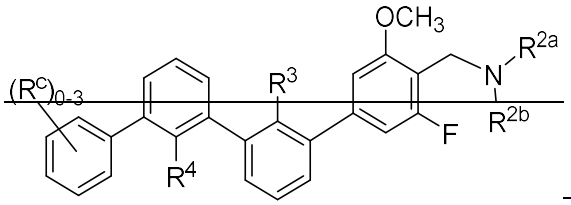
~~13~~11. The compound of any one of claims **1** to **3**, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are combined to form a 4- to 8-membered ring or spirocyclic ring, optionally having one or two additional ring vertices selected from O, N, ~~or~~ and S; wherein said ring or spirocyclic ring is substituted with 0 to 4 substituents independently selected from the group consisting of oxo, C_{1-8} alkyl, C_{1-8} haloalkyl, ~~C_{1-8} hydroxyalkyl, -X^2X^3-~~ $C(O)_2R^a$,
~~-~~X^2X^3-OR^a,
~~-~~X^2X^3-NR^aR^b, ~~-~~X^2X^3-$CONR^aR^b$, ~~-~~X^2X^3-SO_2R^a, ~~-~~X^2X^3-$SO_2NR^aR^b$, and ~~–~~X^2X^3-SO_3R^a; wherein ~~X^2~~-X^3 is a bond or C_{1-6} alkylene.

~~14~~12. The compound of any one of claims **1** to **3,** or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H or C_{1-8} alkyl; and R^{2b} is –Y or $–X^1$-Y.

~~15~~13. The compound of claim **~~14~~12,** or a pharmaceutically acceptable salt thereof, wherein Y is selected from the group consisting of C_{3-6} cycloalkyl and C_{4-8} heterocyclyl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkoxy, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, and CO_2H.

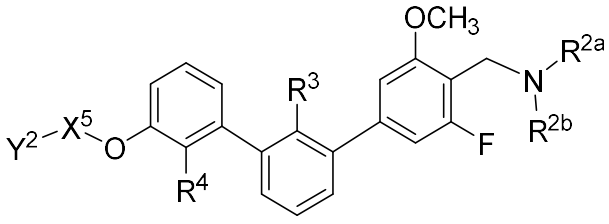
~~16~~14. The compound of claim **1,** or a pharmaceutically acceptable salt thereof, having the formula:

~~(Ia):~~



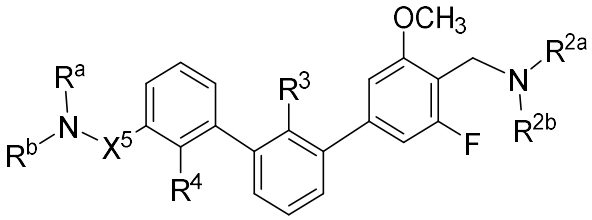
~~(Ia) ;~~

(Ib):



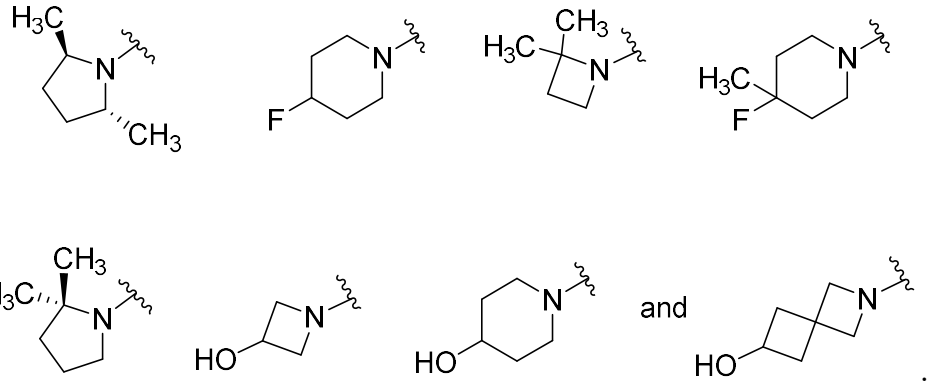
(Ib); or

(Ic):

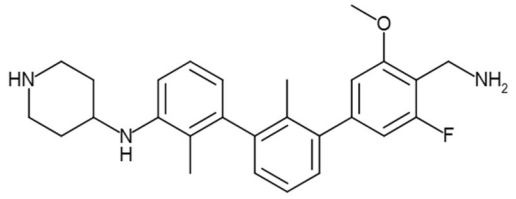
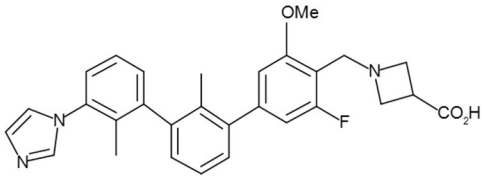
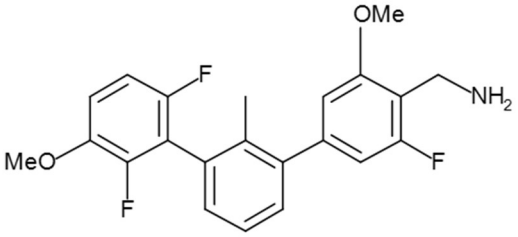
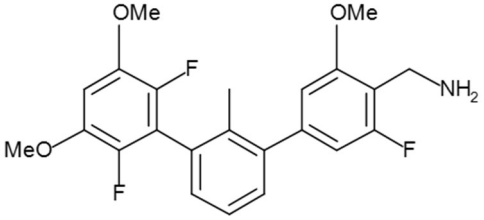
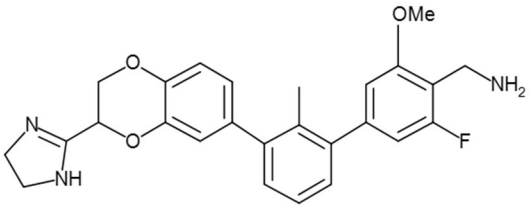
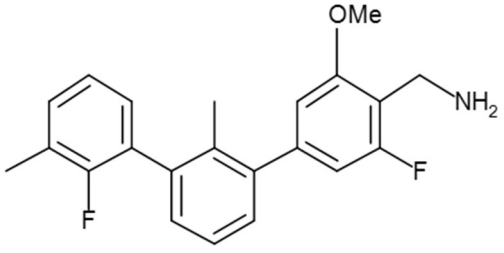


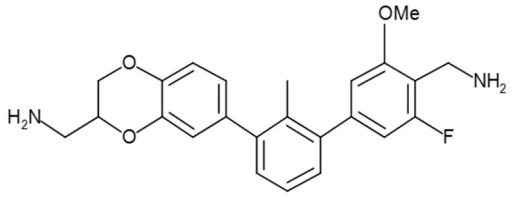
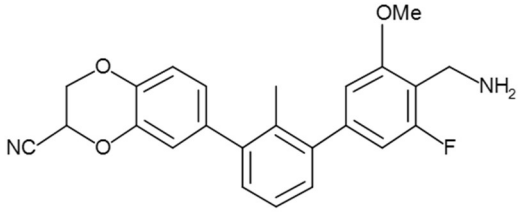
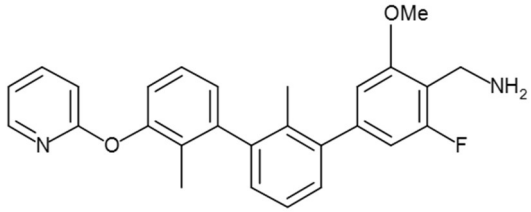
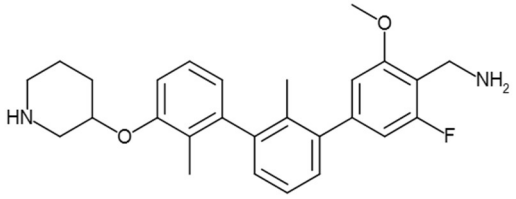
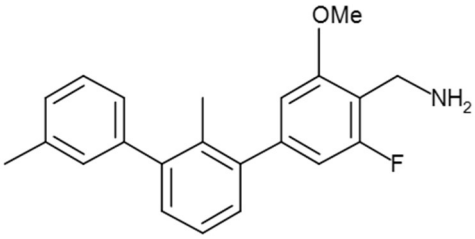
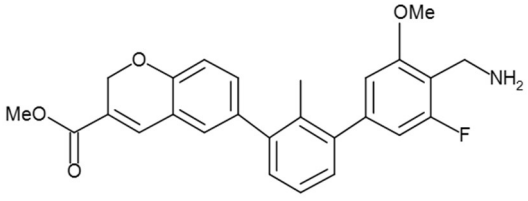
(Ic).

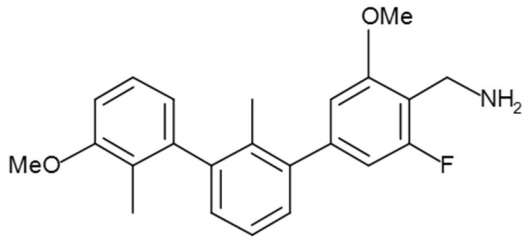
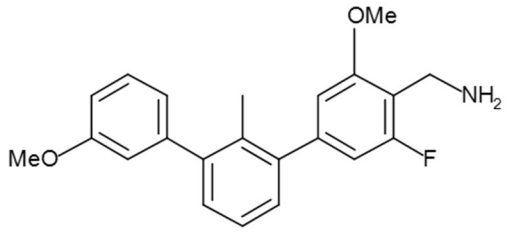
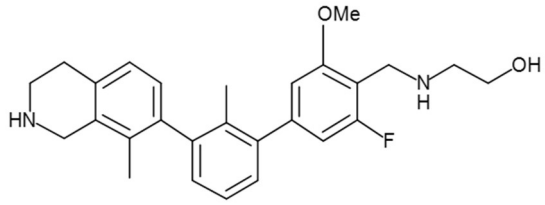
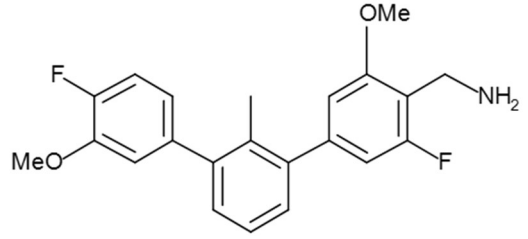
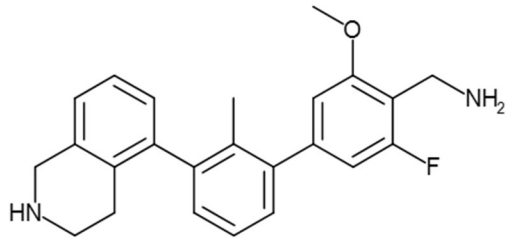
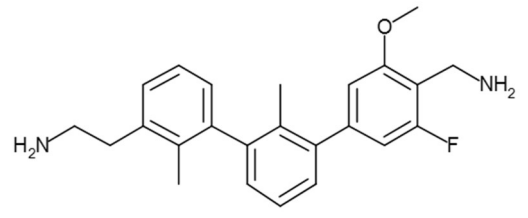
~~17~~15. The compound of claim **~~16~~14**, or a pharmaceutically acceptable salt thereof, wherein Y^2 is selected from the group consisting of:

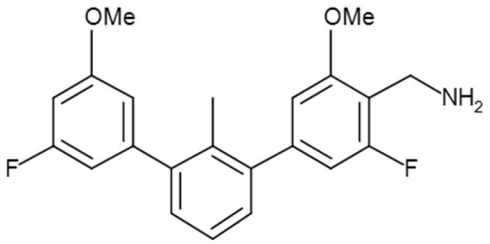
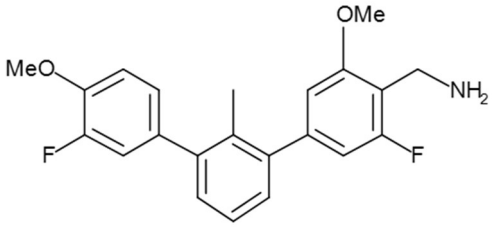
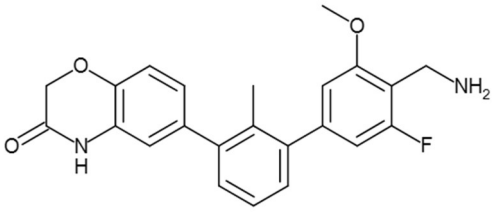
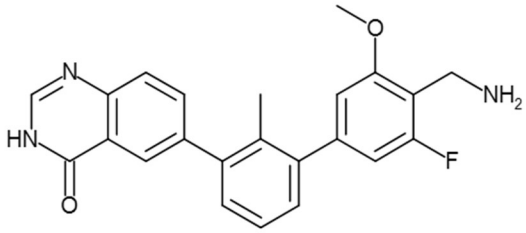
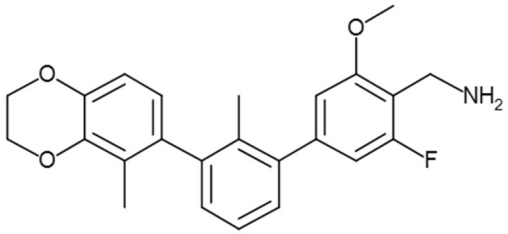
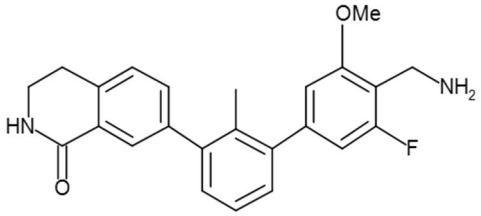


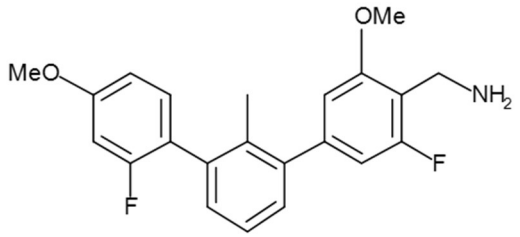
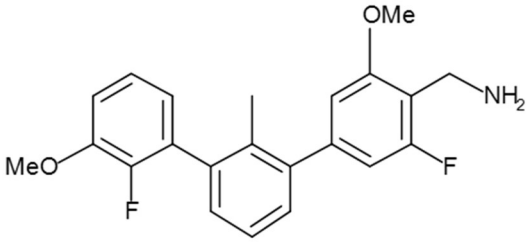
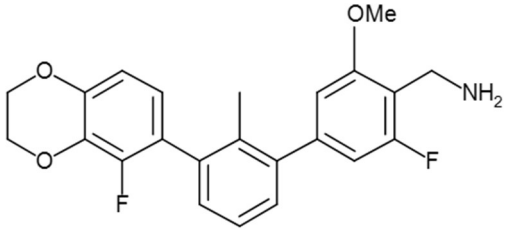
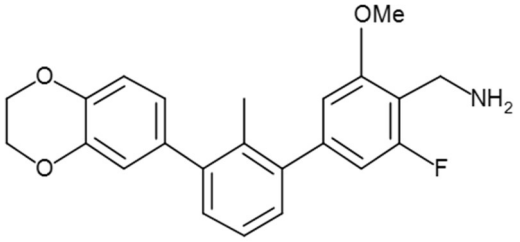
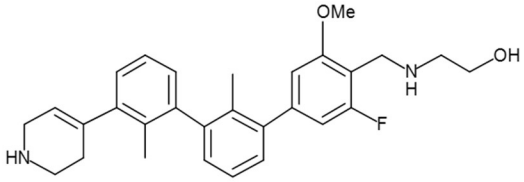
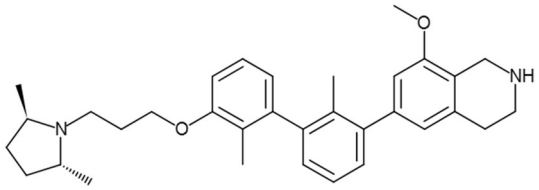
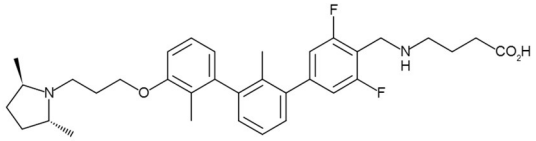
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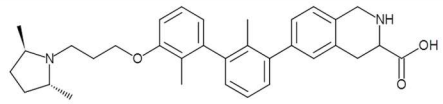
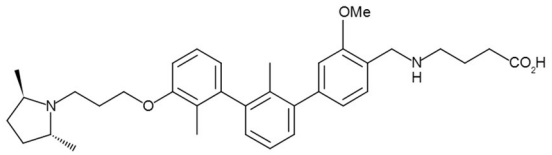
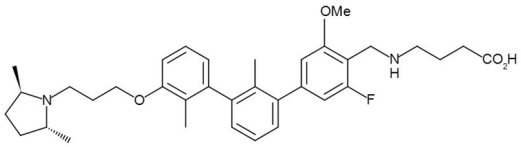
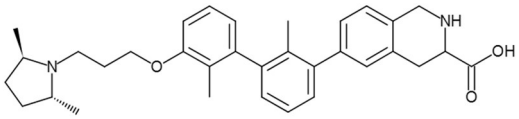
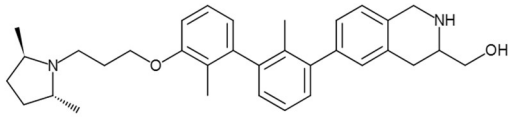
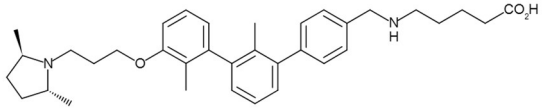
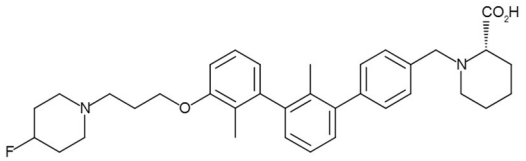
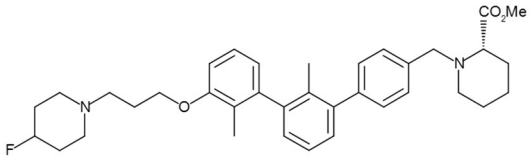
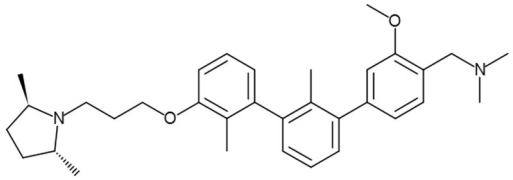
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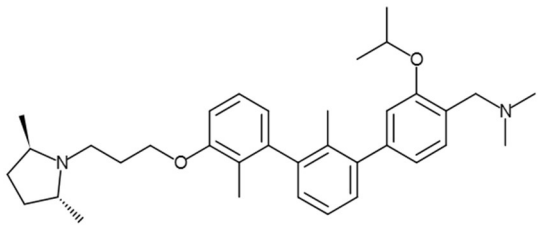
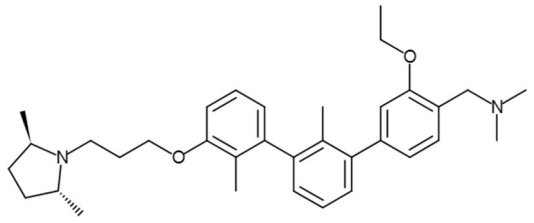
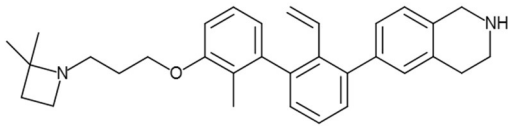
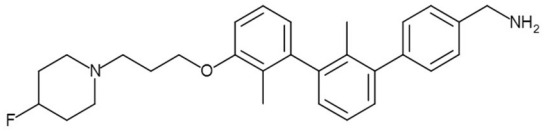
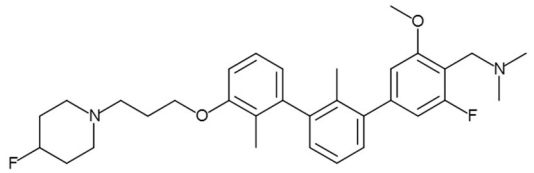
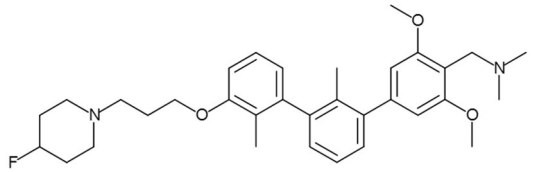
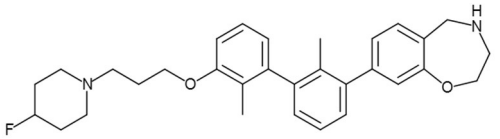
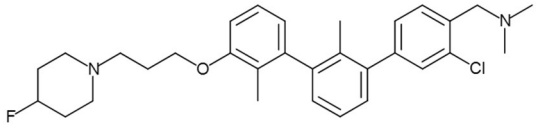
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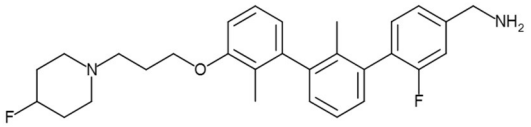
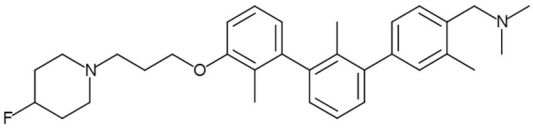
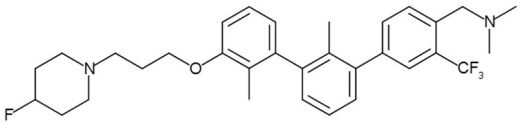
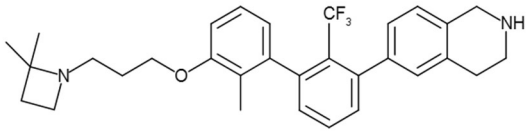
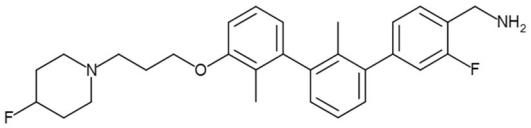
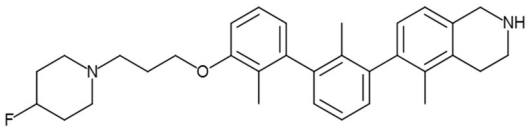
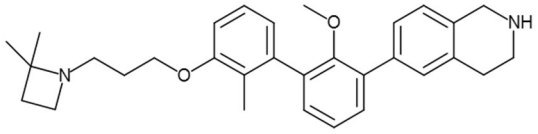
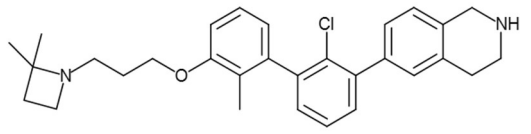
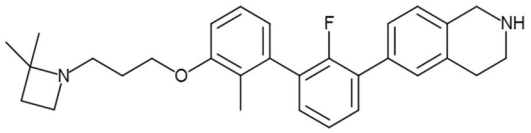
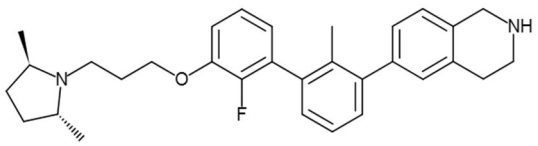
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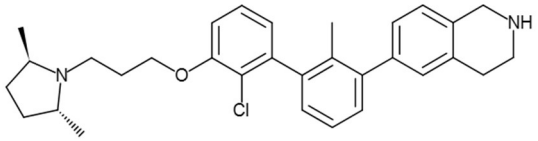
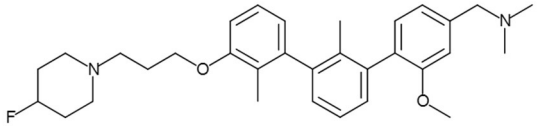
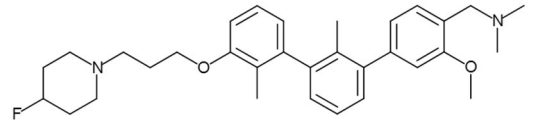
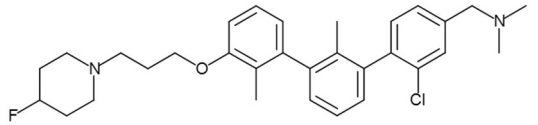
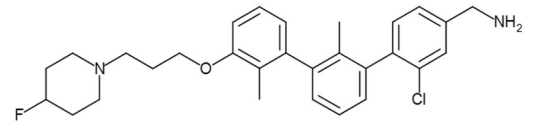
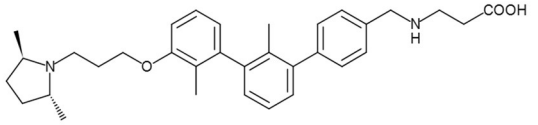
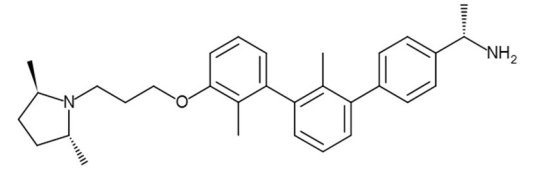
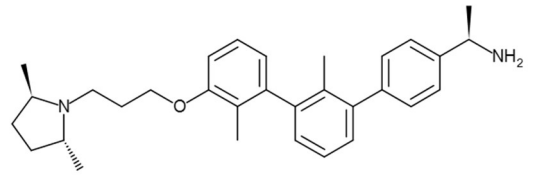
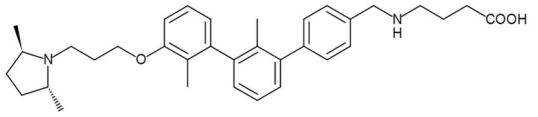
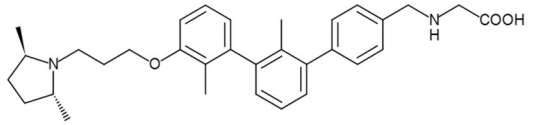
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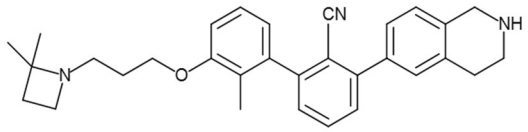
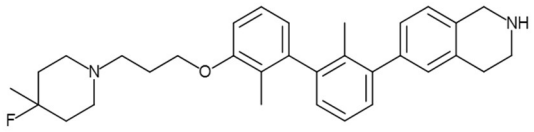
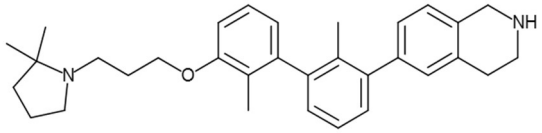
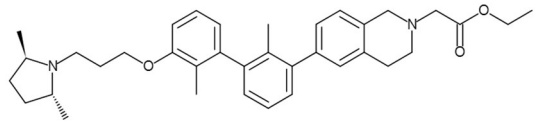
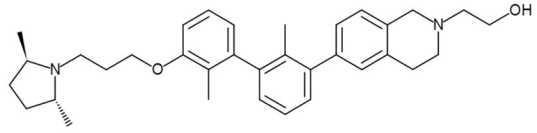
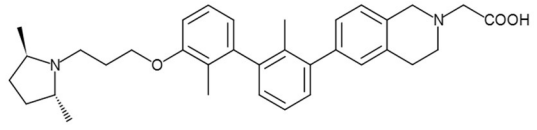
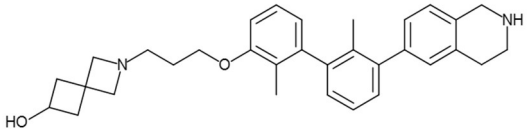
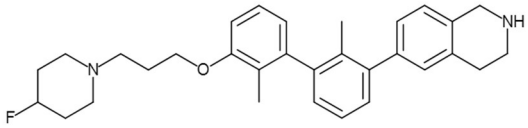
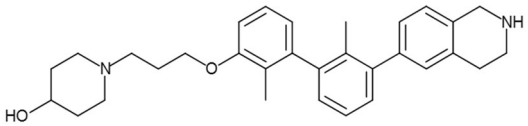
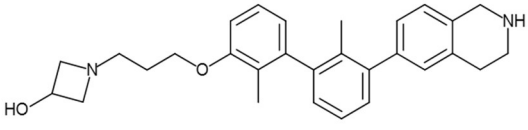
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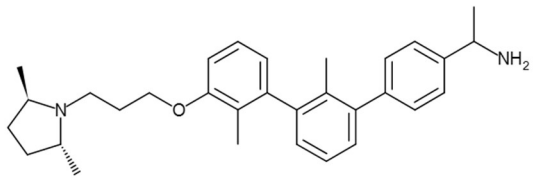
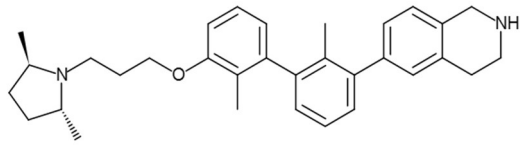
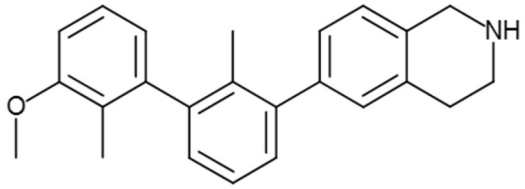
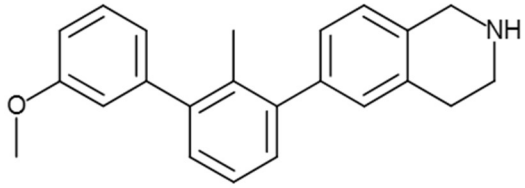
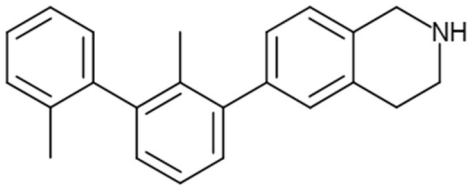
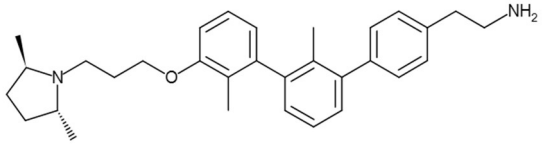
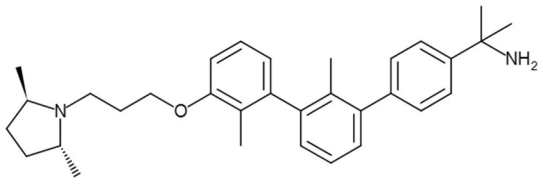
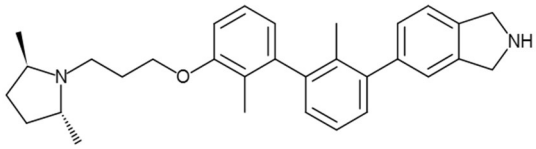
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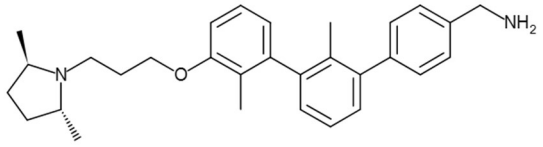
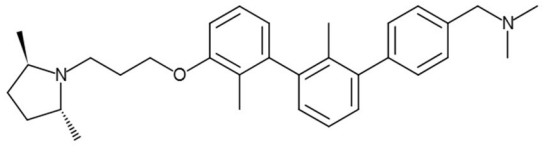
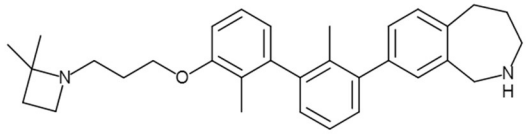
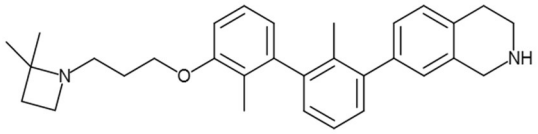
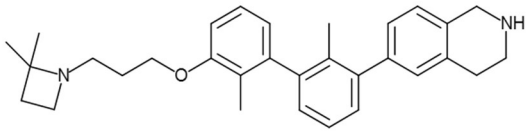
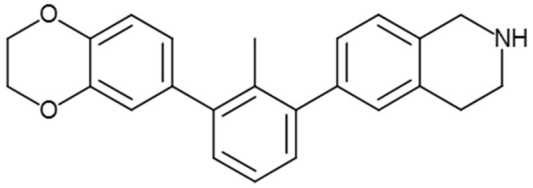
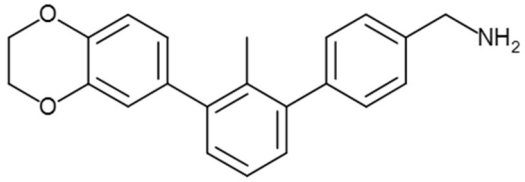
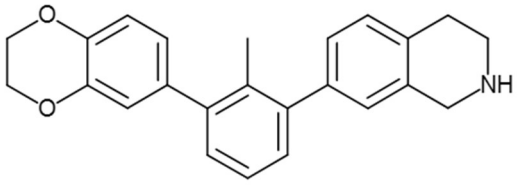
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or a pharmaceutically acceptable salt thereof~~, selected from Table 1~~.

~~19~~17. A pharmaceutical composition comprising a compound of any one of claims **1** to **~~18~~16**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

~~20~~18. Use of a compound of any one of claims **1** to **~~18~~16**, or a pharmaceutically acceptable salt thereof, or a composition of claim **~~19~~17**, in the preparation of a medicament for inhibiting growth, proliferation, or metastasis of cancer cells in a subject~~.~~.

~~21~~19. Use of a compound of any one of claims **1** to **~~18~~16**, or a pharmaceutically acceptable salt thereof, or a composition of claims ~~**19**~~**17**, in the preparation of a medicament for treating a subject suffering from or susceptible to a disease or disorder mediated by the PD-1 signaling pathway, wherein the disease or disorder is selected from the group consisting of melanoma, glioblastoma, esophagus tumor, nasopharyngeal carcinoma, uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate cancer, castration-resistant prostate cancer, chronic myelocytic leukemia, Kaposi's sarcoma fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma of soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland, liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or intraocular malignant melanoma, renal cell carcinoma, small-cell lung cancer, lung cancer, mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous NSCLC, colorectal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, pancreatic cancer, pancreatic ductal adenocarcinoma, squamous cell carcinoma of the head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, HIV, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, herpes viruses, papillomaviruses, influenza, bone cancer, skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes,

carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of the kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, epidermoid cancer, abestosis, carcinoma, adenocarcinoma, papillary carcinoma, cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, transitional cell carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms tumor, pleomorphic adenoma, liver cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma, and fibroma.

~~22~~**20.** The use of ~~any one of claims **20** to **21**~~claim **18**, wherein the subject suffers from a disease or disorder selected from the group consisting of an infectious disease, a bacterial infectious disease, a viral infectious disease, a fungal infectious disease, a solid tumor, a hematological malignancy, an immune disorder, an inflammatory disease, and cancer.

~~**23.** The method of claim **21**, wherein the disease or disorder is selected from the group consisting of melanoma, glioblastoma, esophagus tumor, nasopharyngeal carcinoma, uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate cancer, castration-resistant prostate cancer, chronic myelocytic leukemia, Kaposi's sarcoma fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, , meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma of soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland, liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or intraocular malignant melanoma, renal cell carcinoma, small-cell lung cancer, lung cancer, mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous~~

~~NSCLC, colorectal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, pancreatic cancer, Pancreatic ductal adenocarcinoma, squamous cell carcinoma of the head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, HIV, Hepatitis A, Hepatitis B, Hepatitis C, hepatitis D, herpes viruses, papillomaviruses, influenza, bone cancer, skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of the kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, epidermoid cancer, abestosis, carcinoma, adenocarcinoma, papillary carcinoma, cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, transitional cell carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, wilm's tumor, pleomorphic adenoma, liver cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma..~~