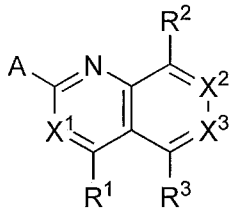
[0006a] In one aspect of the present disclosure, there is provided a compound represented by Formula I:



Formula I

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

A is a 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms each selected from the group consiting of O, N, and S; wherein the bicyclic heteroaryl may optionally be substituted by one, two or three substituents each independently selected from R^{A1};

X^1 is selected from the group consisting of N and $C(R^{X1})$;

X^2 is selected from the group consisting of N and $C(R^{X2})$;

X^3 is selected from the group consisting of N and $C(R^{X3})$;

wherein only one of X^1, X^2 or X^3 can be N;

R^1 is selected from the group consisting of hydrogen; -C(O)OH, -C(O)OC_{1-6}alkyl, -C(O)-C(O)OH, -P(O)$(OH)_2$, C_{1-6}alkyl, and a 5-6 membered monocyclic heteroaryl having one, two, three, or four heteroatoms each selected from the group consisting of O, N, and S; wherein C_{1-6} alkyl may optionally be substituted by one, two, or three substituents each selected independently from the group consisting of halogen, hydroxyl, C(O)OH, -P(O)$(OH)_2$, and -C(O)OC_{1-6}alkyl; and wherein said heteroaryl may optionally be substituted by one or two substituents each independently selected from the group consisting of halogen, hydroxyl, and C_{1-4}alkyl;

R^2 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl; wherein C_{1-6}alkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, hydroxyl, and phenyl; and wherein phenyl may optionally be substituted by one or more substituents each independently selected from R^p;

R^3 is selected from the group consisting of hydrogen, halogen, hydroxyl, C_{1-6}alkyl, C_{1-6}alkoxy, -$S(O)_w$-C_{1-6}alkyl (where w is 0, 1, or 2), -NR^a-C_{1-6}alkyl, C_{3-6}cycloalkoxy, -$S(O)_w$-C_{3-6}cycloalkyl (where w is 0, 1, or 2), -NR^a-C_{3-6}cycloalkyl, -O-phenyl, -$S(O)_w$-phenyl (where w is 0, 1, or 2), -NR^a-phenyl, C_{8-12}benzocycloalkoxy, -NR^aR^b, -OC(O)NR^a-phenyl, -NR^a-C(O)-O-phenyl, -NR^a-C(O)-C_{1-6}alkyl-phenyl, -C_{1-6}alkyl-NR^a-phenyl, -NR^a-C_{1-6}alkyl-phenyl, and a 4-10 membered monocyclic, bridged bicyclic, or spirocyclic heterocyclyloxy, heterocyclyl-NR^a-, or heterocyclyl-$S(O)_w$- moiety (where w is 0, 1, or 2) having one or two heteroatoms each independently selected from the group

consisting of O, N, and S; wherein if said heterocyclyloxy, heterocyclyl-NR^a-, or heterocyclyl-$S(O)_w$- ring contains an –NH moiety, that nitrogen may optionally be substituted by a subsituent selected from the group consisting of C_{1-6}alkyl,-C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, and -$S(O)_w$-C_{1-3}alkyl (where w is 0, 1, or 2); and wherein said heterocyclyloxy, heterocyclyl-NR^a-, and heterocyclyl-$S(O)_w$ may optionally be substituted by one, two, three, or four substituents each independently selected from R^{ff}; and wherein said phenyl moiety of -O-phenyl, -$S(O)_w$-phenyl, -NR^a-phenyl, -OC(O)NR^a-phenyl, -NR^a-C(O)-O-phenyl, -NR^a-C(O)-C_{1-6}alkyl-phenyl, -C_{1-6}alkyl-NR^a-phenyl and -NR^a-C_{1-6}alkyl-phenyl may optionally be substituted by one, two, or three substituents each independently selected from R^p; and wherein C_{1-6}alkoxy, -$S(O)_w$-C_{1-6}alkyl (where w is 0, 1, or 2), -NR^a-C_{1-6}alkyl, C_{3-6}cycloalkoxy, -$S(O)_w$-C_{3-6}cycloalkyl (where w is 0, 1, or 2), and -NR^a-C_{3-6}cycloalkyl may optionally be substituted by one, two, or three substituents each independently selected from R^{gg};

R^{ff} is independently selected for each occurrence from the group consisting of halogen, hydroxyl, -NR^aR^b, oxo, C_{1-6}alkyl and C_{1-6}alkoxy;

R^{gg} is independently selected for each occurrence from the group consisting of halogen, hydroxyl, -NR^aR^b, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl (optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-3}alkyl and C_{1-3}alkoxy (optionally substituted by one, two or three fluorine atoms)), phenyl, a 5-6 membered monocyclic or 8-10 membered bicyclic heteroaryl having one, two or three heteroatoms each independently selected from the group consisting of O, N, and S, and a 4-10 membered monocyclic, bridged bicyclic, or spirocyclic heterocyclic ring having one or two heteroatoms each independently selected from the group consisting of O, N, and S; wherein if said heterocyclic ring contains an –NH moiety, that nitrogen may optionally be substituted by a substituent selected from the group consisting of C_{1-6}alkyl,-C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, and -$S(O)_w$-C_{1-3}alkyl (where w is 0, 1, or 2); and wherein phenyl may optionally be substituted by one, two, or three substituents each independently selected from R^{hh}; and wherein said 4-10 membered monocyclic, bridged bicyclic, or spirocyclic heterocyclic ring may optionally be substituted by one, two, three, or four substituents each independently selected from R^{ii};

R^{hh} is independently selected for each occurrence from the group consisting of halogen, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, $S(O)_w$-C_{1-3}alkyl, -$S(O)_w$-NR^aR^b, -NR^a-$S(O)_w$-C_{1-3}alkyl (where w is 0, 1, or 2), a 5-6 membered monocyclic heteroaryl having one, two or three heteroatoms each independently selected from the group consisting of O, N, and S, and a 4-7 membered heterocyclic ring having one or two heteroatoms each independently selected from the group consisting of O, N, and S; wherein C_{1-6}alkoxy and $S(O)_w$-C_{1-3}alkyl may optionally be substituted by one, two, or three halogens;

R^{ii} is independently selected for each occurrence from the group consisting of halogen, hydroxyl, -NR^aR^b, oxo, C_{1-6}alkyl and C_{1-6}alkoxy;

R^{A1} is independently for each occurrence selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_3-C_6cycloalkyl, phenyl, -NR^aR^b, -O-C(O)-NR^a-phenyl, -NR^a-C(O)-phenyl, and -NR^a-C_{1-4}alkyl-phenyl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl and phenyl may optionally be substituted by one or more substituents selected from the group consisting of halogen, hydroxyl, phenyl, and -NR^aR^b;

R^{X1} is selected from the group consisting of hydrogen, -C(O)OH, and C_{1-6}alkyl; wherein C_{1-6}alkyl may optionally be substituted by one, two or three halogens;

R^{X2} is selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, and -C_{1-6}alkoxy-phenyl; wherein phenyl may optionally be substituted by one or more substituents selected from R^p;

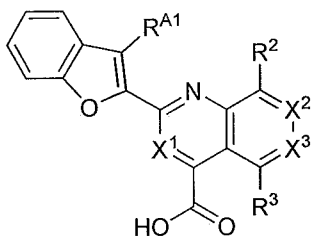
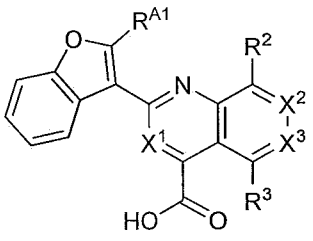
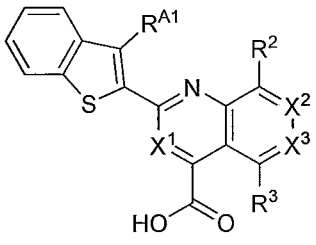
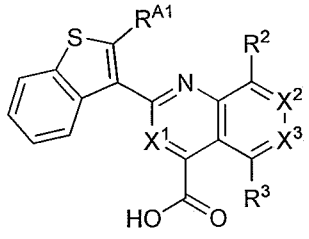
R^{X3} is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, -C_{1-6}alkoxy-phenyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkoxy, and phenyl; wherein C_{1-6}alkyl and C_{1-6}alkoxy may optionally be substituted by one, two, or three substituents selected from the group consisting of hydroxyl and halogen; and wherein phenyl may optionally be substituted by one or more substituents selected from R^p;

R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, phenyl, -C(O)-phenyl, and -C(O)-C_{1-6}alkyl; or

R^a and R^b taken together with the nitrogen to which they are attached form a heterocyclic ring; and

R^p is independently selected for each occurrence from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, phenyl, C_{3-6}cycloalkoxy, -$S(O)_w$-C_{1-3}alkyl (where w is 0, 1, or 2), -$S(O)_w$-NR^aR^b, and –NR^aR^b.

[0006b] In another aspect of the present disclosure, there is provided a compound represented by Formula II, III, IV, or V:


II,

III,

IV, or

V,

and pharmaceutically acceptable salts thereof, wherein:

X^1 is selected from the group consisting of N and $C(R^{X1})$;

X^2 is selected from the group consisting of N and $C(R^{X2})$;

X^3 is selected from the group consisting of N and $C(R^{X3})$;

wherein only one of X^1, X^2 or X^3 can be N;

R^2 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl; wherein C_{1-6}alkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, hydroxyl, and phenyl; and wherein phenyl may optionally be substituted by one or more substituents each independently selected from R^p;

R^3 is selected from the group consisting of hydrogen, halogen, hydroxyl, C_{1-6}alkyl, C_{1-6}alkoxy, $-S(O)_w-C_{1-6}$alkyl (where w is 0, 1, or 2), $-NR^a-C_{1-6}$alkyl, C_{3-6}cycloalkoxy, $-S(O)_w-C_{3-6}$cycloalkyl (where w is 0, 1, or 2), $-NR^a-C_{3-6}$cycloalkyl, -O-phenyl, $-S(O)_w$-phenyl (where w is 0, 1, or 2), $-NR^a$-phenyl, C_{8-12}benzocycloalkoxy, $-NR^aR^b$, $-OC(O)NR^a$-phenyl, $-NR^a-C(O)$-O-phenyl, $-NR^a-C(O)-C_{1-6}$alkyl-phenyl, $-C_{1-6}$alkyl-NR^a-phenyl, $-NR^a-C_{1-6}$alkyl-phenyl, and a 4-10 membered monocyclic, bridged bicyclic, or spirocyclic heterocyclyloxy, heterocyclyl-NR^a-, or heterocyclyl-$S(O)_w$- moiety (where w is 0, 1, or 2) having one or two heteroatoms each independently selected from the group consisting of O, N, and S; wherein if said heterocyclyloxy, heterocyclyl-NR^a-, or heterocyclyl-$S(O)_w$- ring contains an –NH moiety, that nitrogen may optionally be substituted by a subsituent selected from the group consisting of C_{1-6}alkyl,$-C(O)-C_{1-6}$alkyl, $-C(O)-O-C_{1-6}$alkyl, and $-S(O)_w-C_{1-3}$alkyl (where w is 0, 1, or 2); and wherein said heterocyclyloxy, heterocyclyl-NR^a-, and heterocyclyl-$S(O)_w$ may optionally be substituted by one, two, three, or four substituents each independently selected from R^{ff}; and wherein said phenyl moiety of -O-phenyl, $-S(O)_w$-phenyl, $-NR^a$-phenyl, $-OC(O)NR^a$-phenyl, $-NR^a-C(O)$-O-phenyl, $-NR^a-C(O)-C_{1-6}$alkyl-phenyl, $-C_{1-6}$alkyl-NR^a-phenyl and $-NR^a-C_{1-}$

$_{6}$alkyl-phenyl may optionally be substituted by one, two, or three substituents each independently selected from R^{p}; and wherein C_{1-6}alkoxy, -$S(O)_w$-C_{1-6}alkyl (where w is 0, 1, or 2), -NR^a-C_{1-6}alkyl, C_{3-6}cycloalkoxy, -$S(O)_w$-C_{3-6}cycloalkyl (where w is 0, 1, or 2), and -NR^a-C_{3-6}cycloalkyl may optionally be substituted by one, two, or three substituents each independently selected from R^{gg};

R^{ff} is independently selected for each occurrence from the group consisting of halogen, hydroxyl, -NR^aR^b, oxo, C_{1-6}alkyl and C_{1-6}alkoxy;

R^{gg} is independently selected for each occurrence from the group consisting of halogen, hydroxyl, -NR^aR^b, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl (optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-3}alkyl and C_{1-3}alkoxy (optionally substituted by one, two or three fluorine atoms)), phenyl, a 5-6 membered monocyclic or 8-10 membered bicyclic heteroaryl having one, two or three heteroatoms each independently selected from the group consisting of O, N, and S, and a 4-10 membered monocyclic, bridged bicyclic, or spirocyclic heterocyclic ring having one or two heteroatoms each independently selected from the group consisting of O, N, and S; wherein if said heterocyclic ring contains an –NH moiety, that nitrogen may optionally be substituted by a substituent selected from the group consisting of C_{1-6}alkyl,-C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, and -$S(O)_w$-C_{1-3}alkyl (where w is 0, 1, or 2); and wherein phenyl may optionally be substituted by one, two, or three substituents each independently selected from R^{hh}; and wherein said 4-10 membered monocyclic, bridged bicyclic, or spirocyclic heterocyclic ring may optionally be substituted by one, two, three, or four substituents each independently selected from R^{ii};

R^{hh} is independently selected for each occurrence from the group consisting of halogen, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, $S(O)_w$-C_{1-3}alkyl, -$S(O)_w$-NR^aR^b, -NR^a-$S(O)_w$-C_{1-3}alkyl (where w is 0, 1, or 2), a 5-6 membered monocyclic heteroaryl having one, two or three heteroatoms each independently selected from the group consisting of O, N, and S, and a 4-7 membered heterocyclic ring having one or two heteroatoms each independently selected from the group consisting of O, N, and S; wherein C_{1-6}alkoxy and $S(O)_w$-C_{1-3}alkyl may optionally be substituted by one, two, or three halogens;

R^{ii} is independently selected for each occurrence from the group consisting of halogen, hydroxyl, -NR^aR^b, oxo, C_{1-6}alkyl and C_{1-6}alkoxy;

R^{A1} is independently for each occurrence selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, phenyl, -NR^aR^b, -O-C(O)-NR^a-phenyl, -NR^a-C(O)-phenyl, and -NR^a-C_{1-4}alkyl- phenyl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl and phenyl may optionally be substituted by one or more substituents selected from the group consisting of halogen, hydroxyl, phenyl, and -NR^aR^b;

R^{X1} is selected from the group consisting of hydrogen, -C(O)OH, and C_{1-6}alkyl; wherein C_{1-6}alkyl may optionally be substituted by one, two or three halogens;

R^{X2} is selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, and -C_{1-6}alkox-phenyl; wherein phenyl may optionally be substituted by one or more substituents selected from R^p;

R^{X3} is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, -C_{1-6}alkoxy-phenyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkoxy, and phenyl; wherein C_{1-6}alkyl and C_{1-6}alkoxy may optionally be substituted by one, two, or three substituents selected from the group consisting of hydroxyl and halogen; and wherein phenyl may optionally be substituted by one or more substituents selected from R^p;

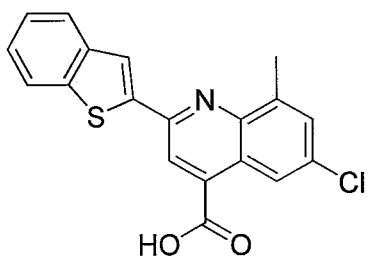
R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl, phenyl, -C(O)-phenyl, and -C(O)-C_{1-6}alkyl; or

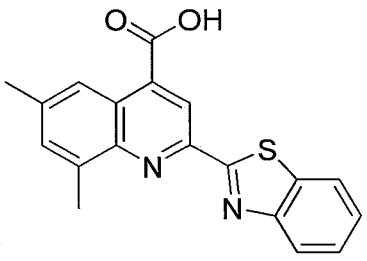
R^a and R^b taken together with the nitrogen to which they are attached form a heterocyclic ring; and

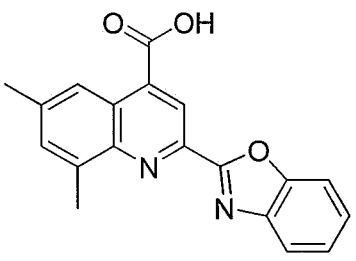
R^p is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, phenyl, C_{3-6}cycloalkoxy, -$S(O)_w$-C_{1-3}alkyl (where w is 0, 1, or 2), -$S(O)_w$-NR^aR^b, and –NR^aR^b.

[0006c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable excipient.

[0006d] In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

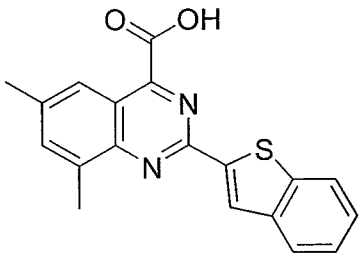
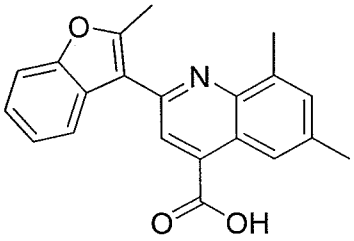
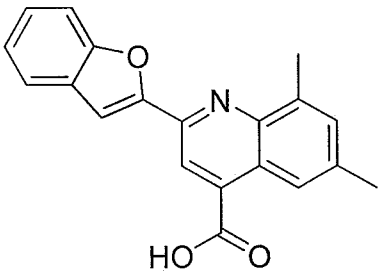
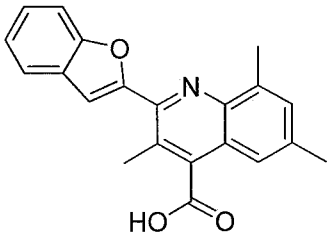
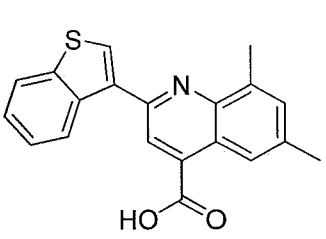
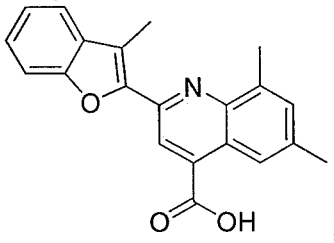
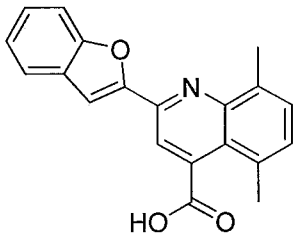
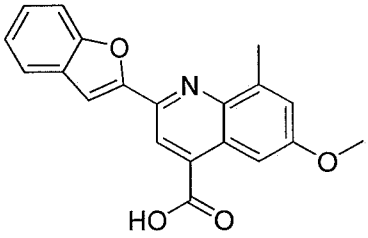
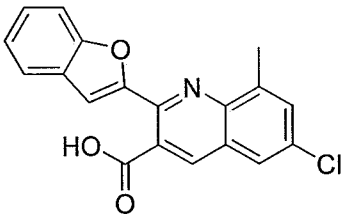
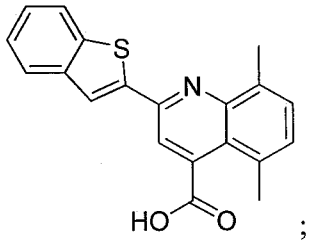
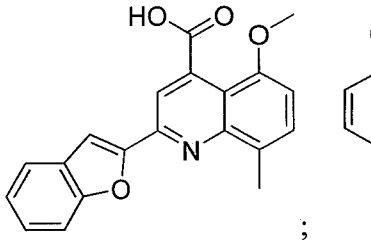
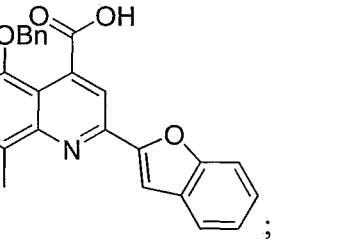


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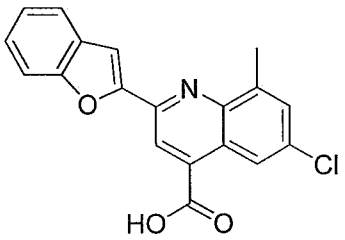
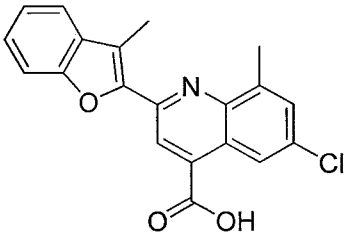
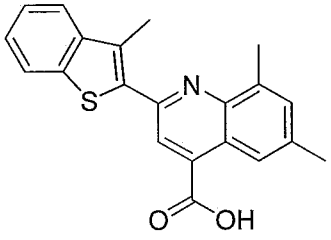
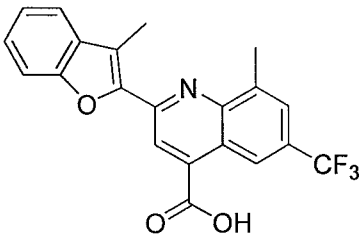
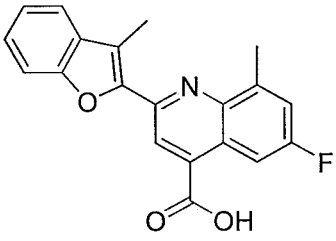
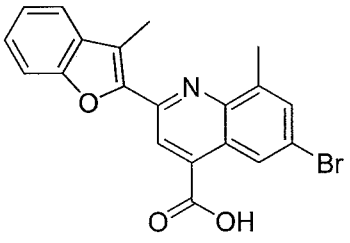
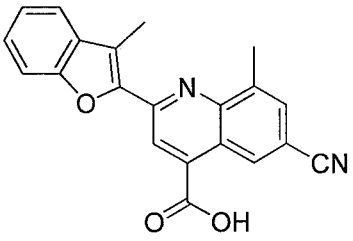
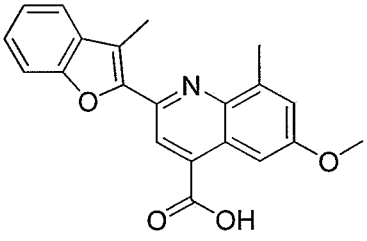
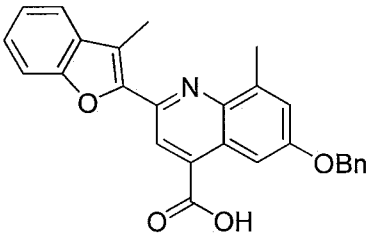
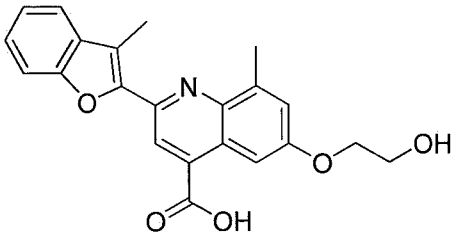
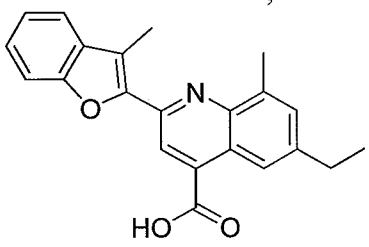
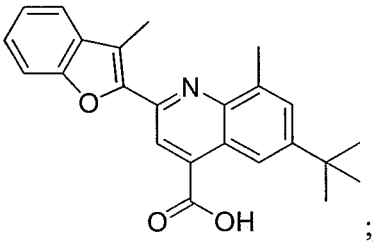
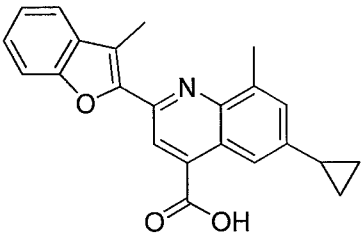
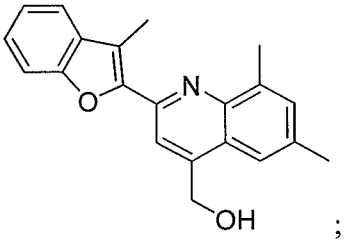
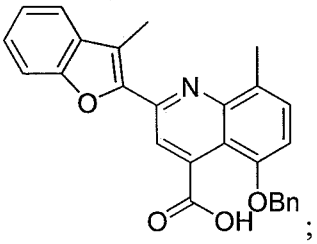
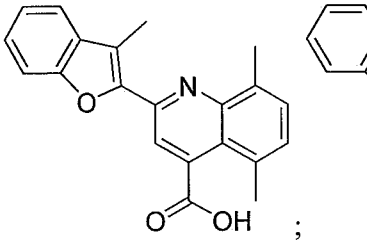
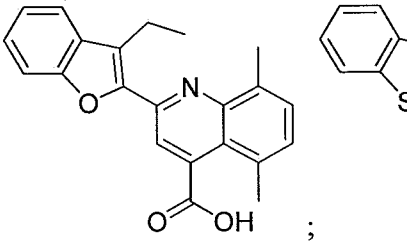
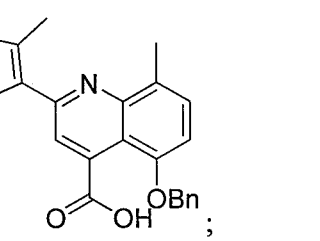
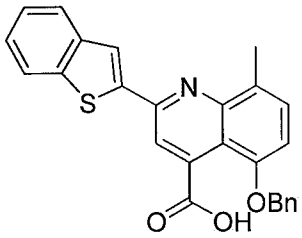
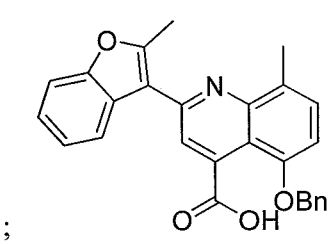
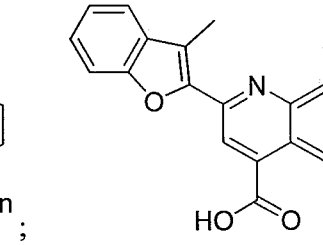
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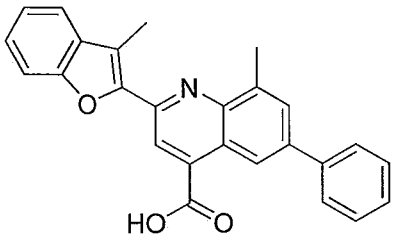
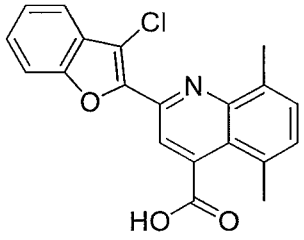
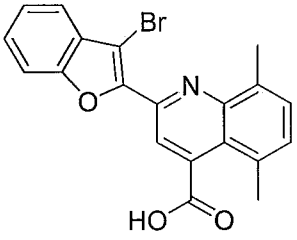
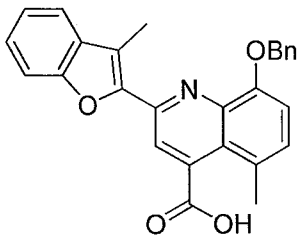
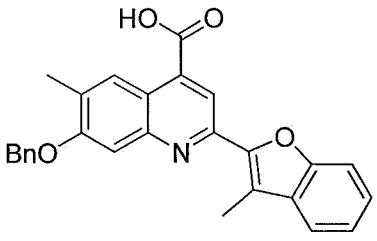
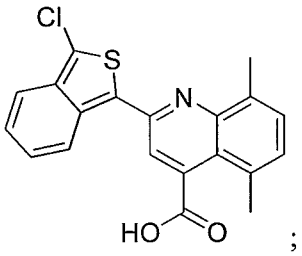
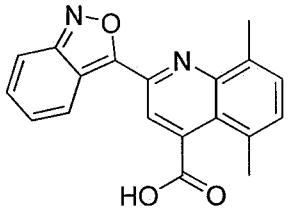
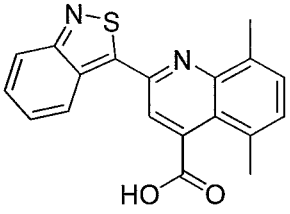
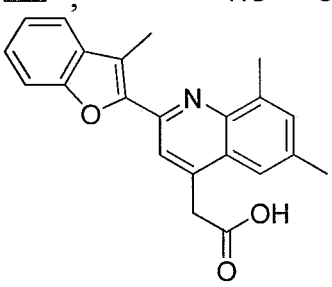
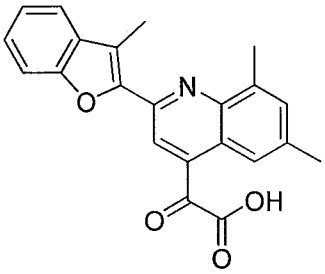
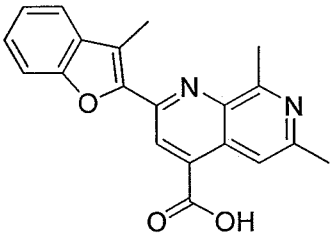
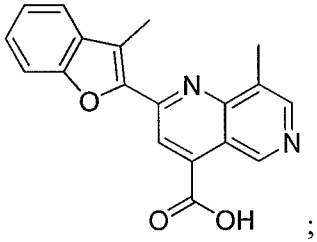
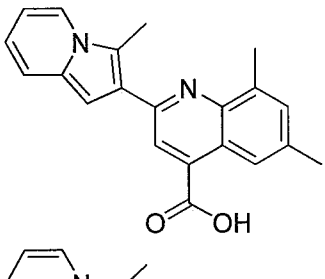
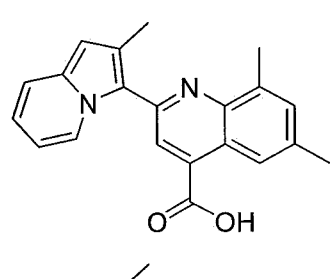
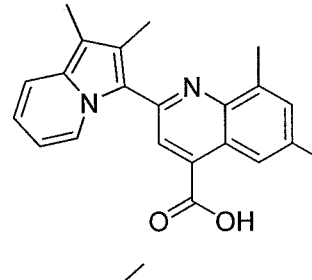
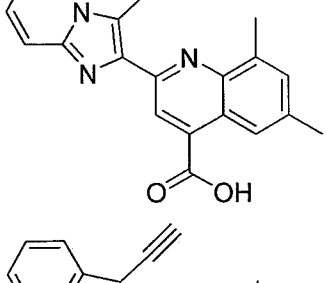
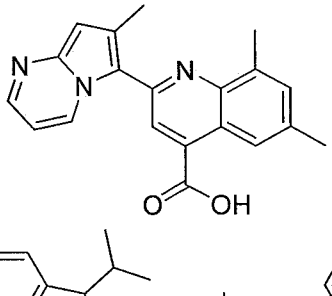
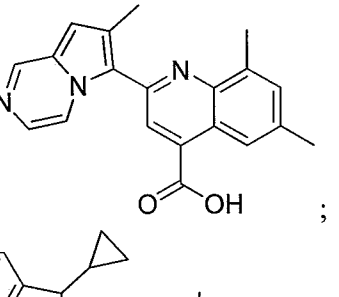
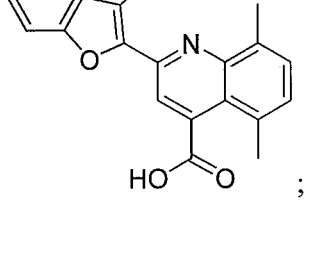
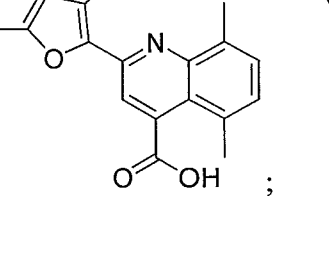
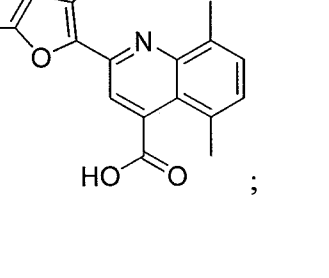
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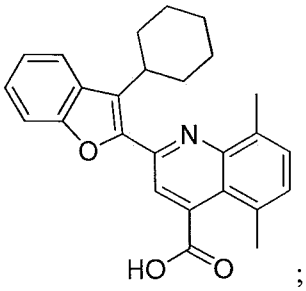
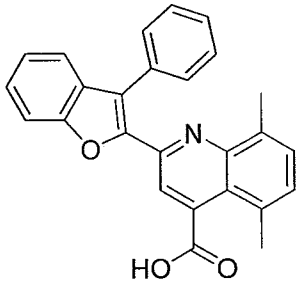
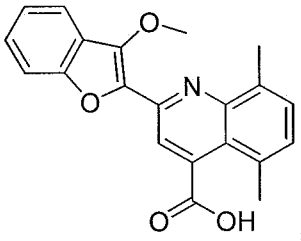
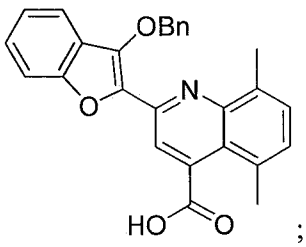
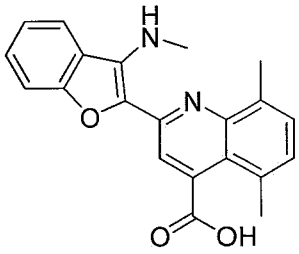
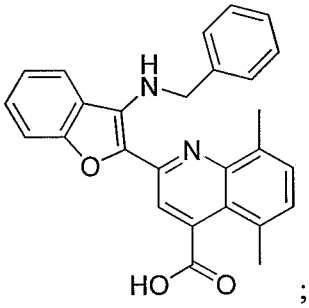
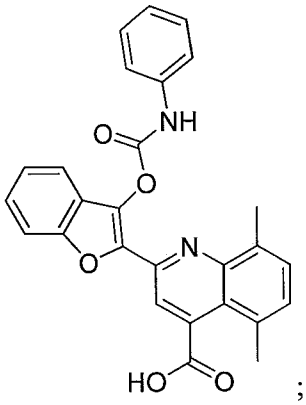
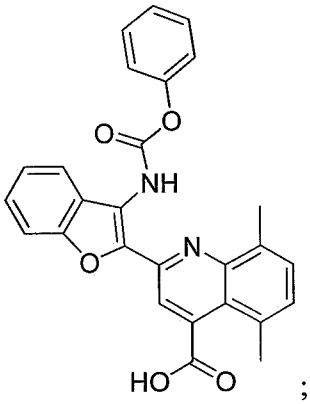
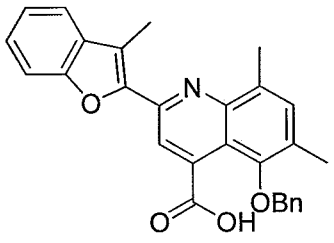
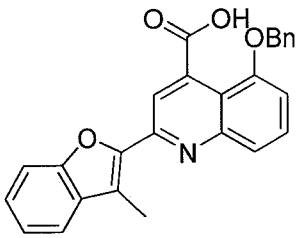
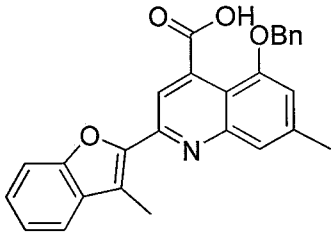
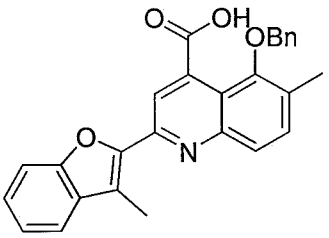
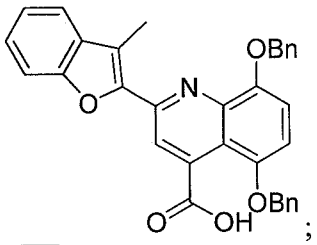
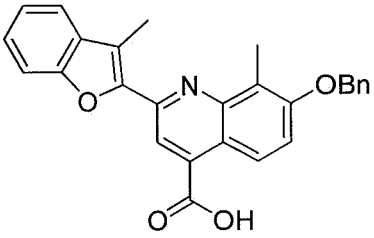
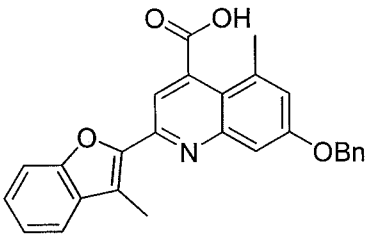
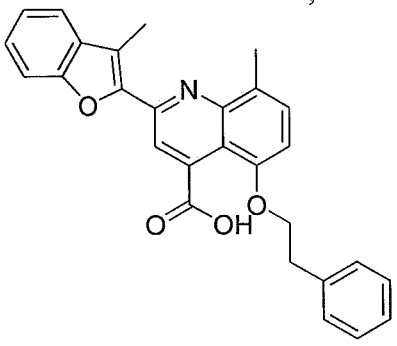
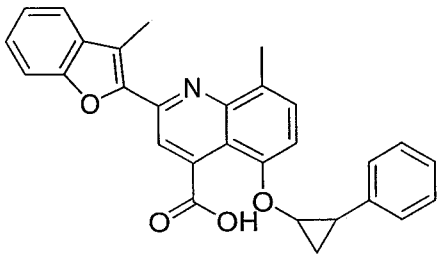
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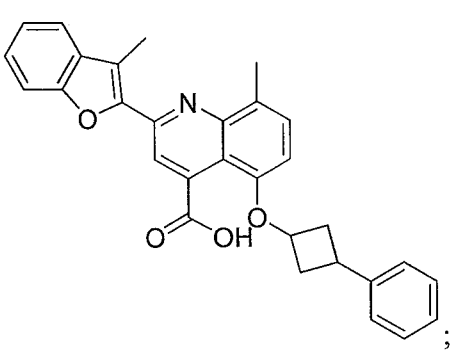
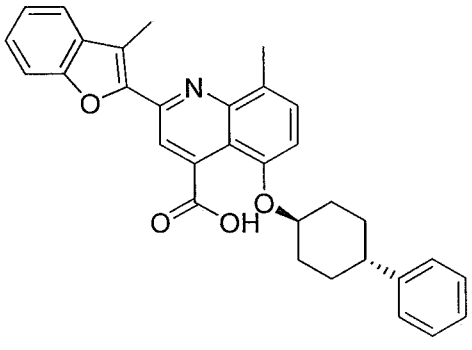
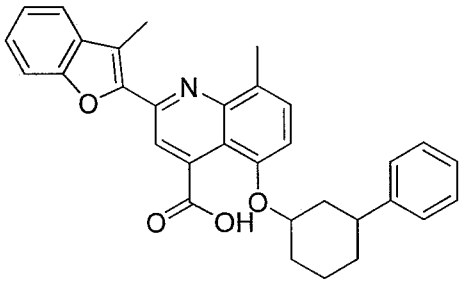
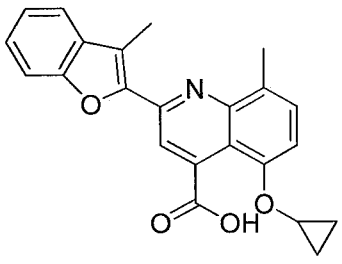
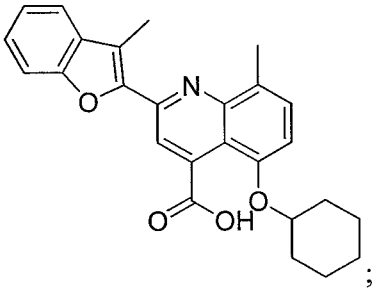
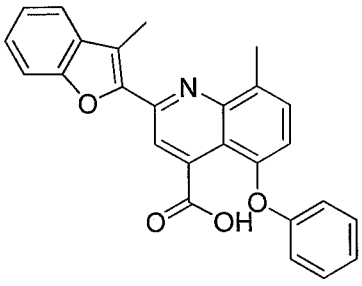
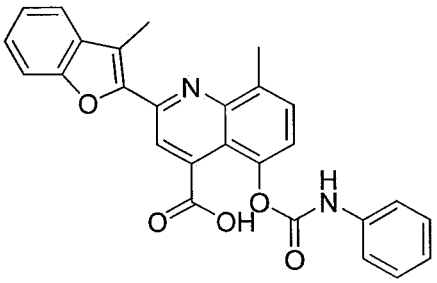
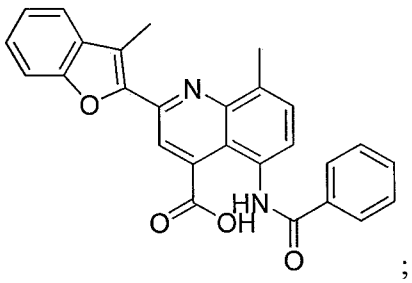
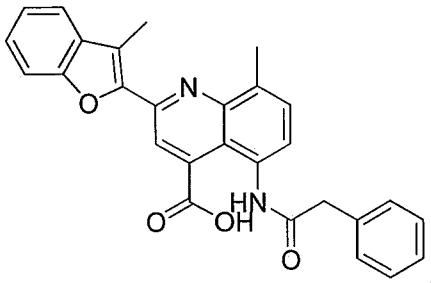
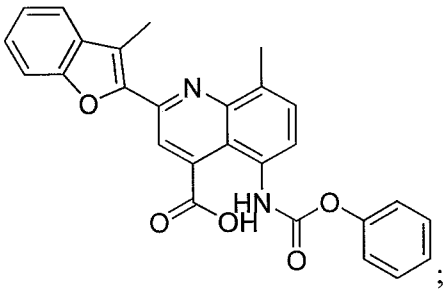
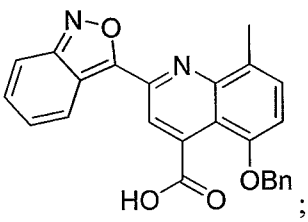
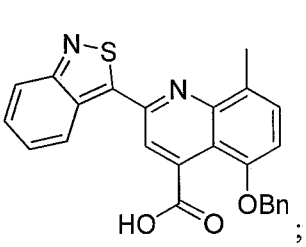
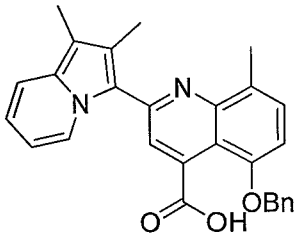
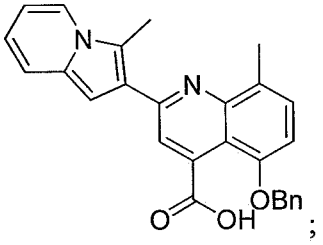
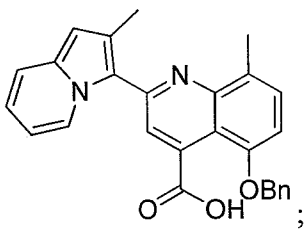
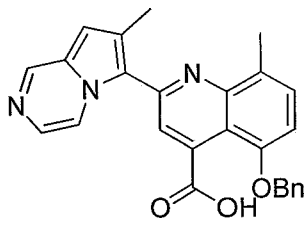
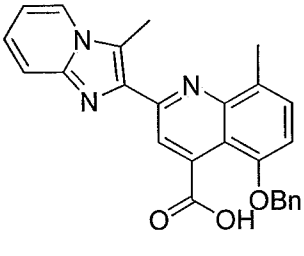

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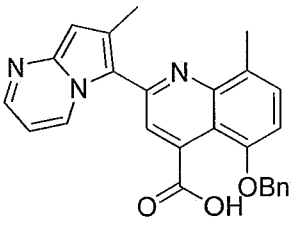
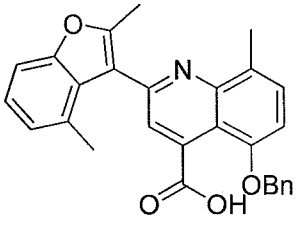
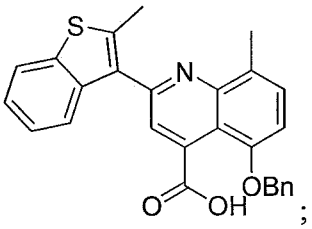
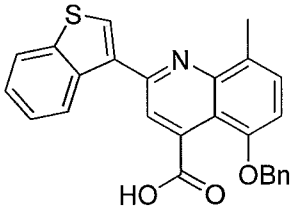
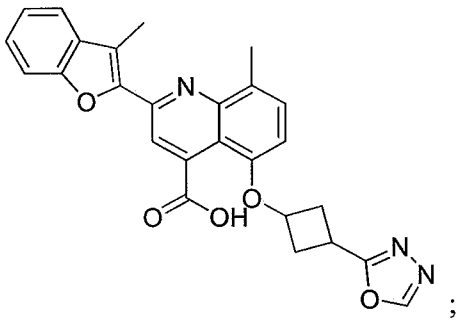
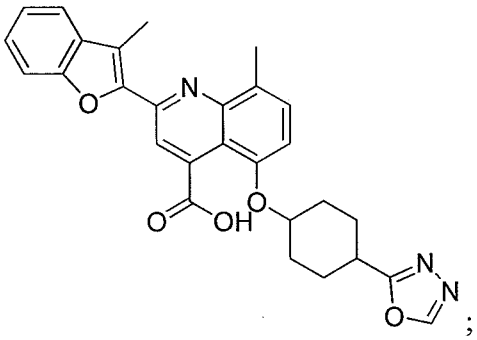
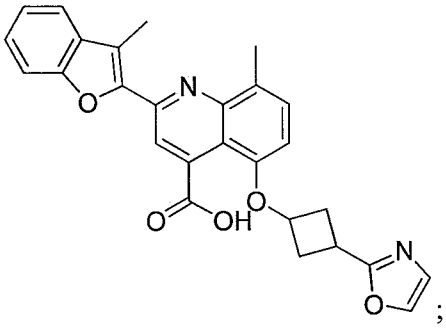
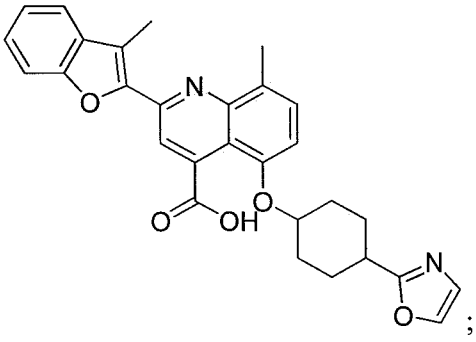
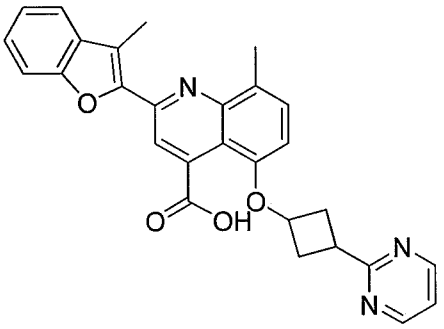
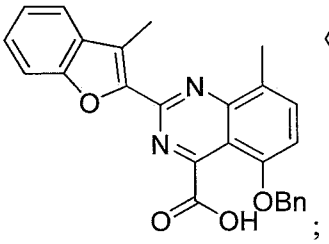
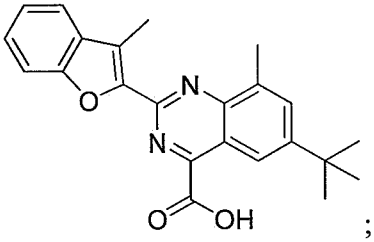
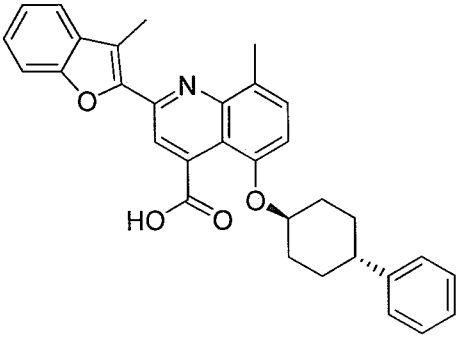
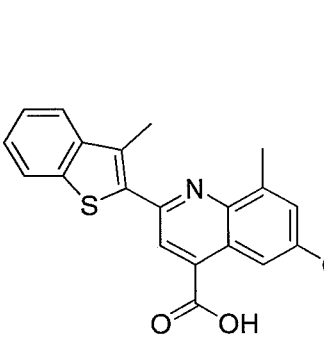

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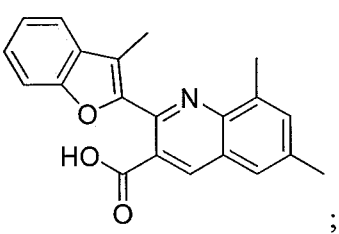

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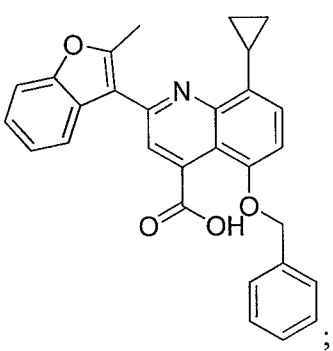
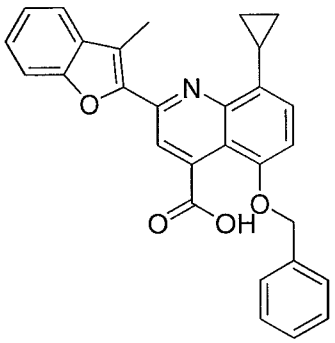
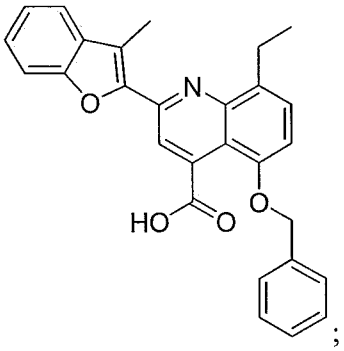
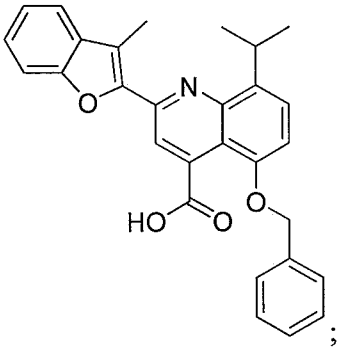
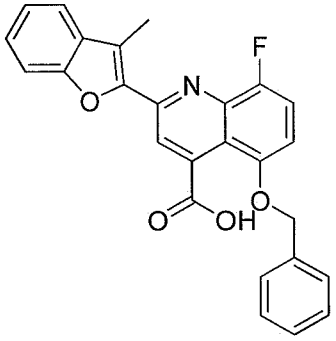
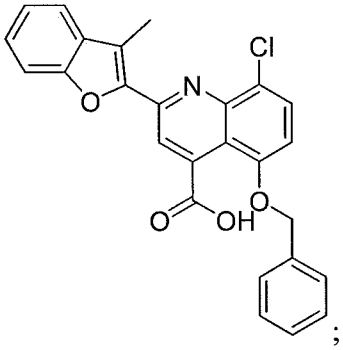
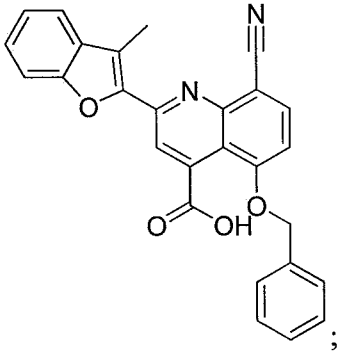
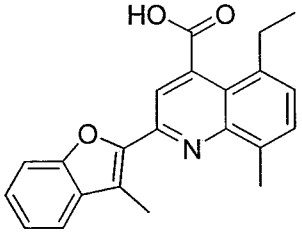
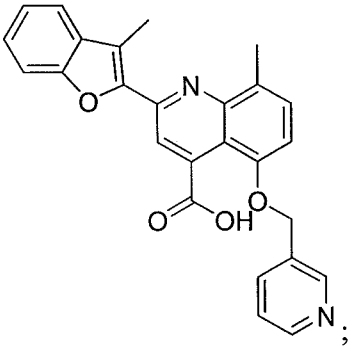
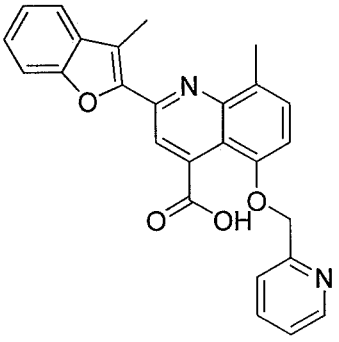
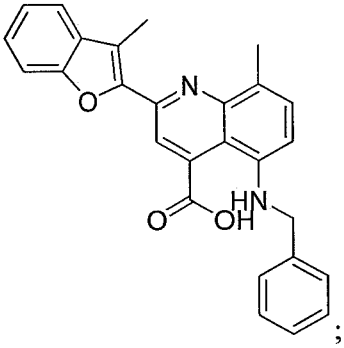
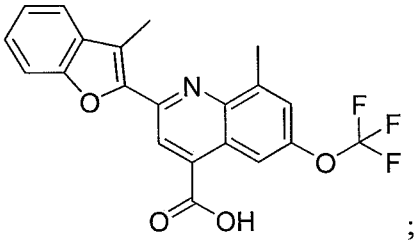
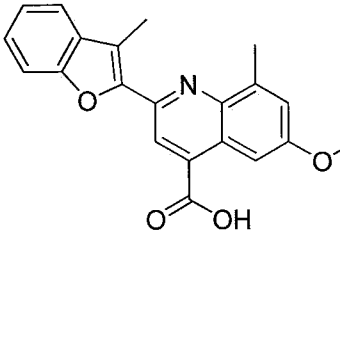
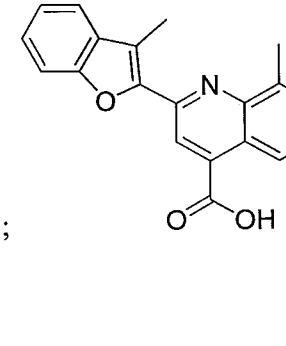
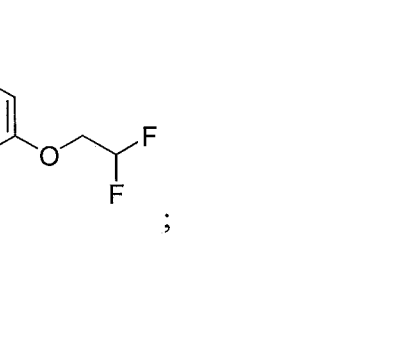

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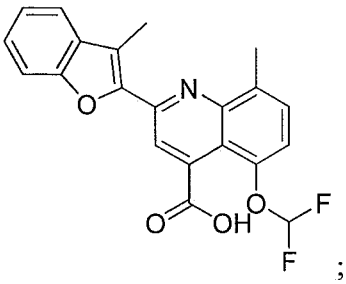
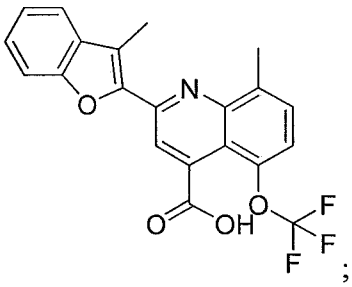
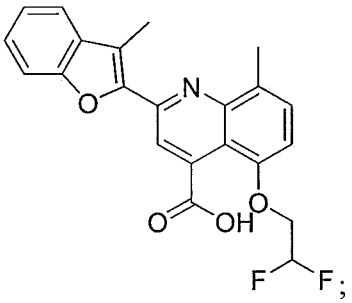
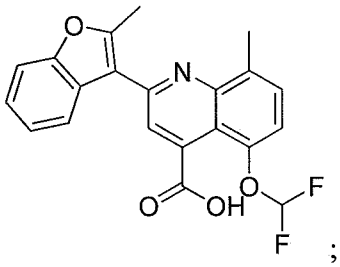
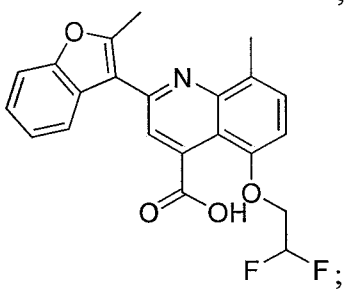
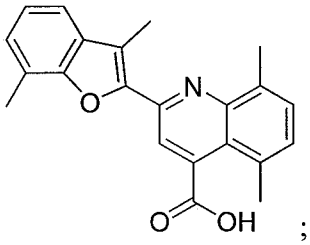
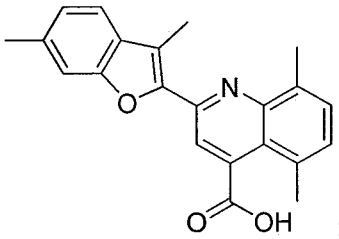
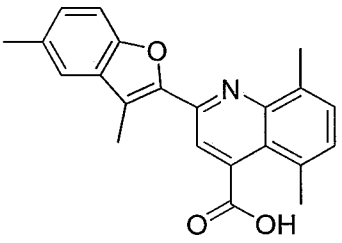
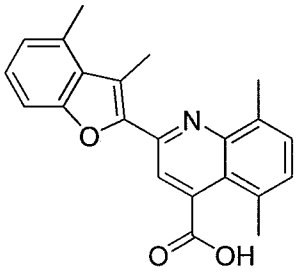
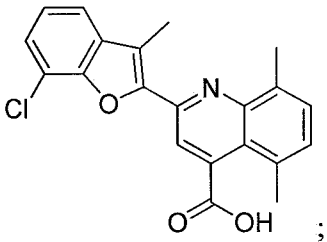
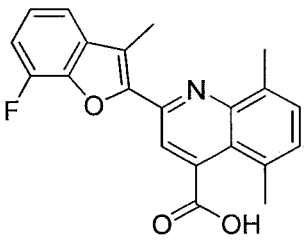
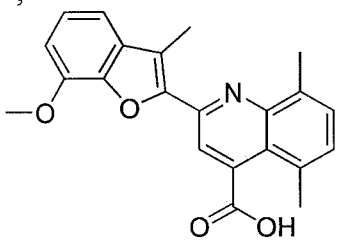
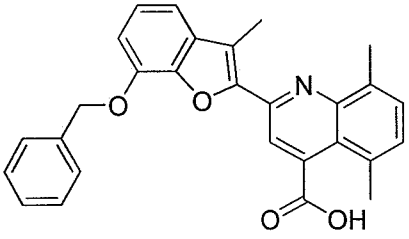
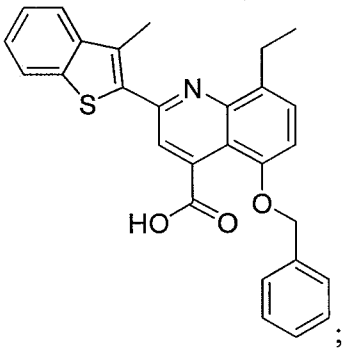
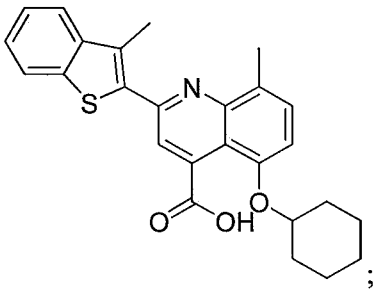
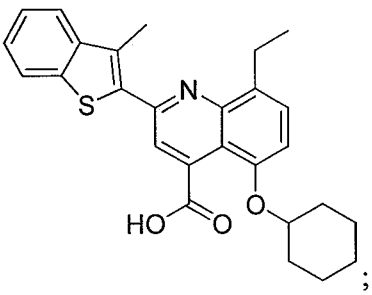
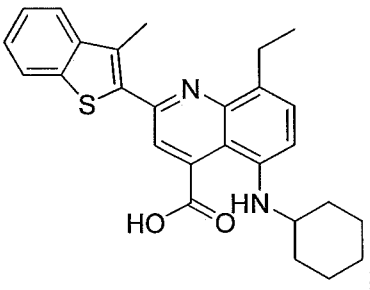
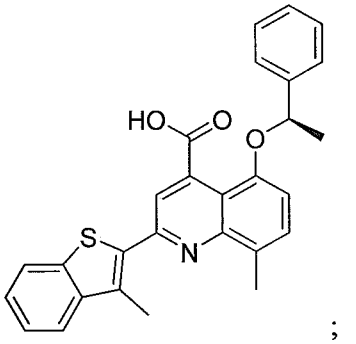
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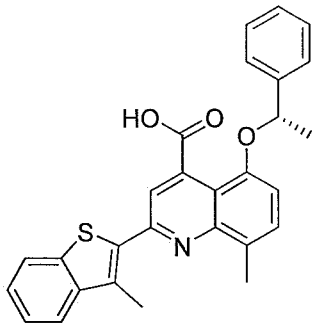
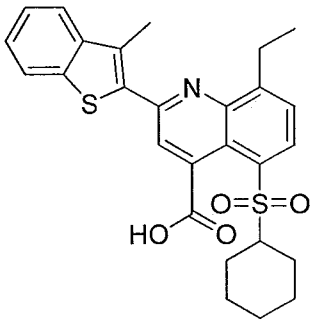
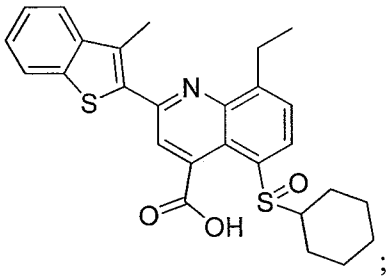
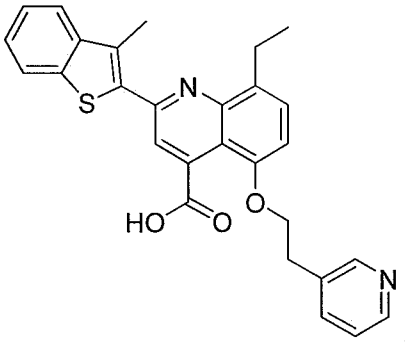
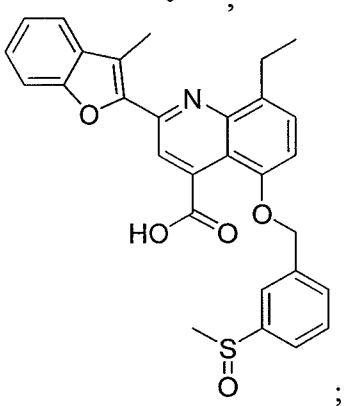
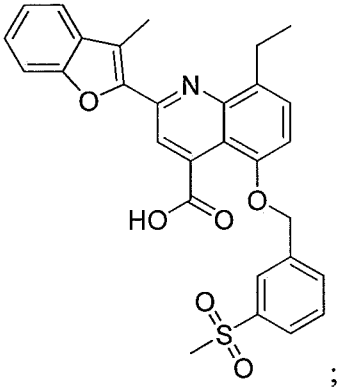
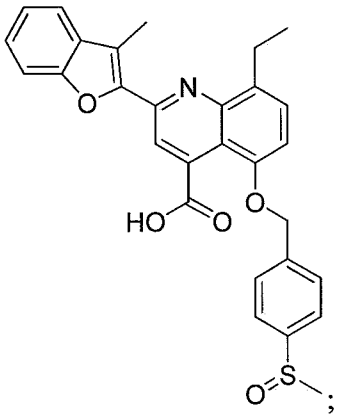
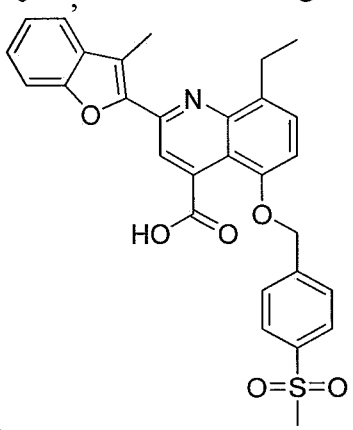
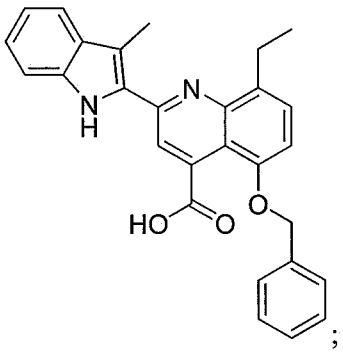
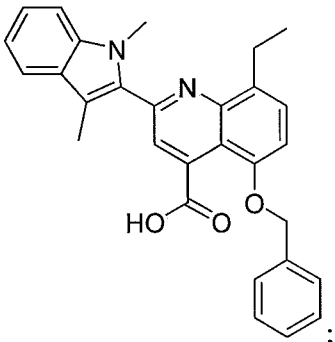
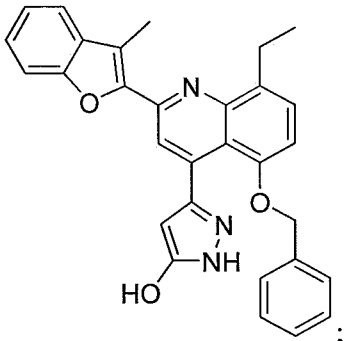
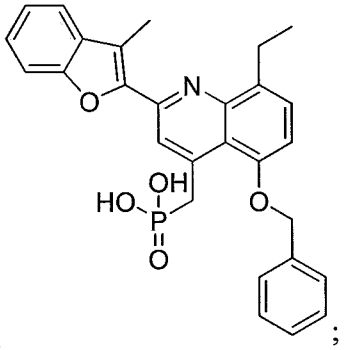
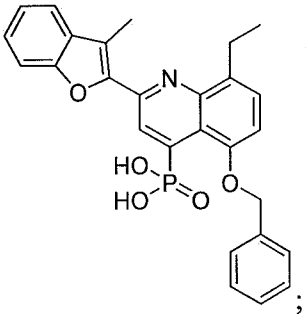
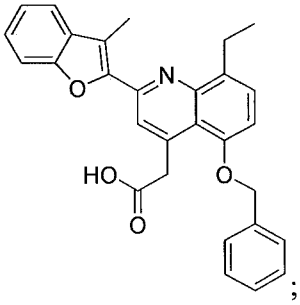
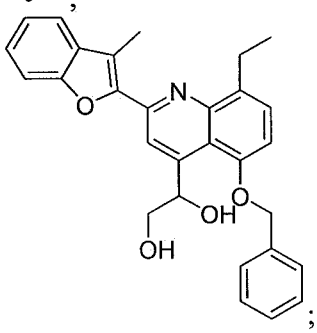
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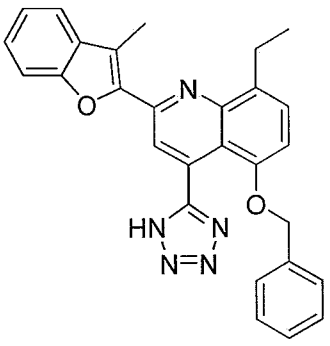
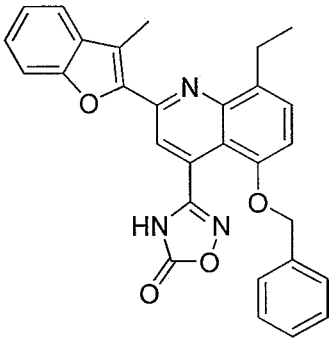
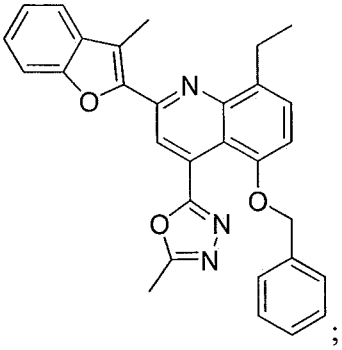
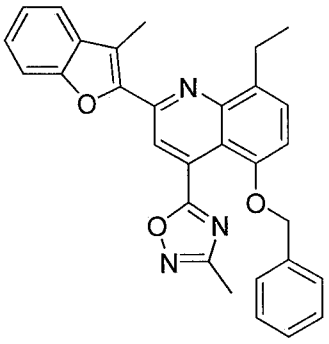
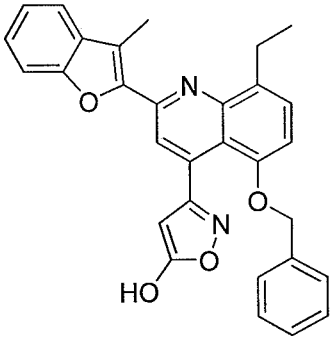
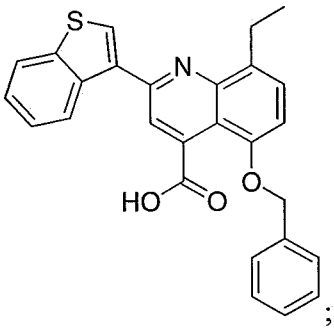
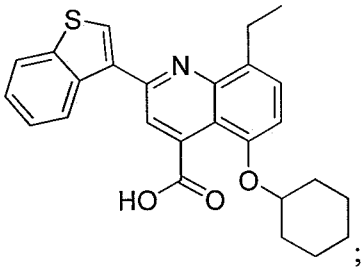
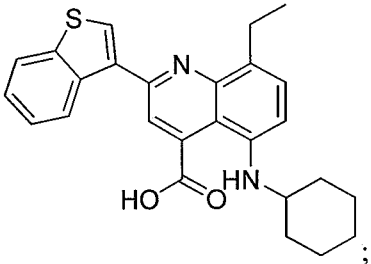
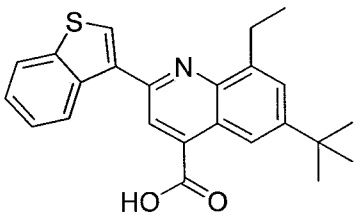
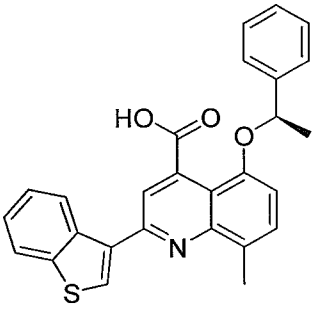
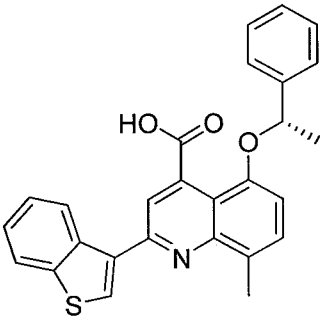
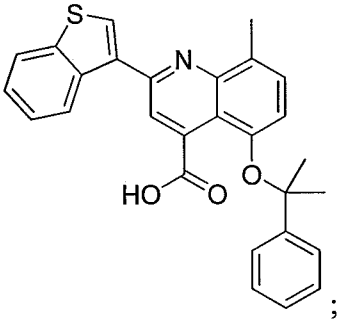
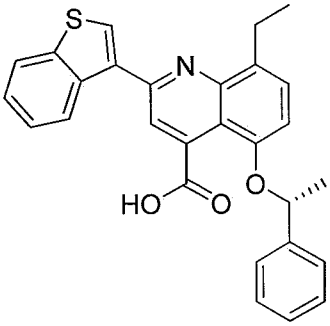
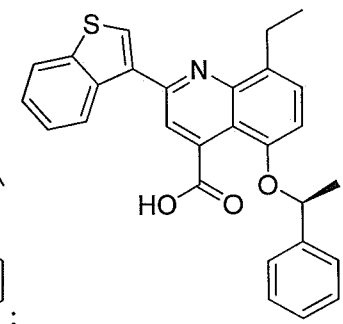
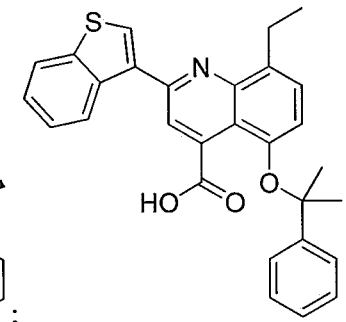

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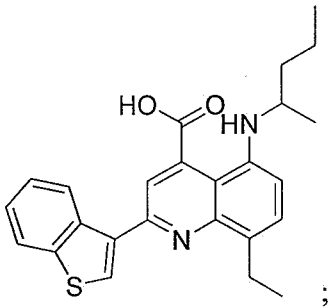
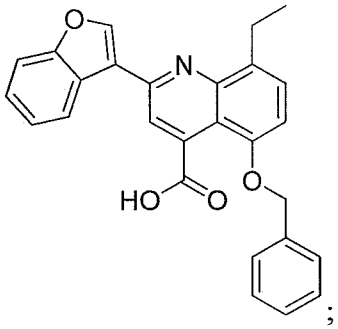
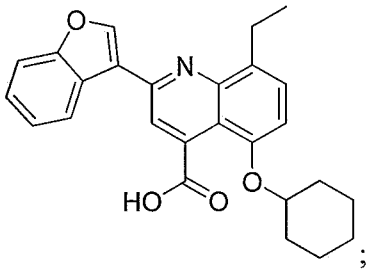
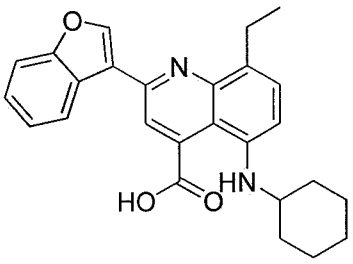
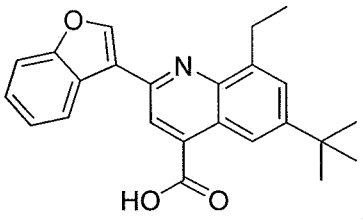
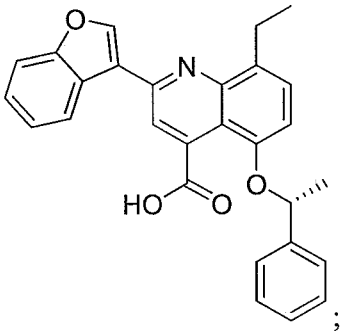
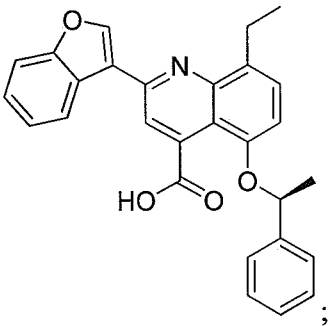
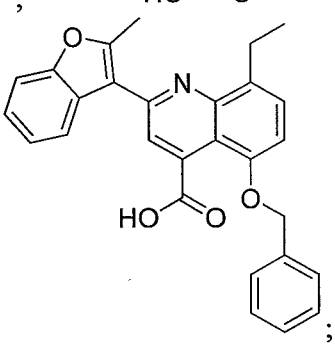
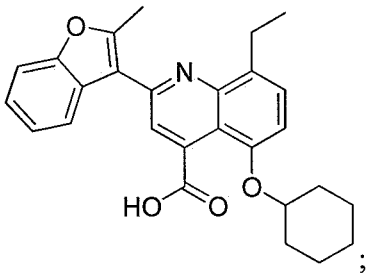
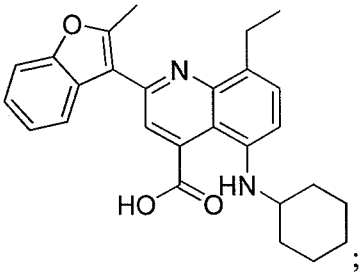
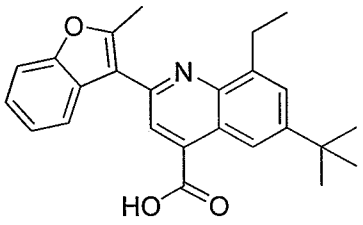
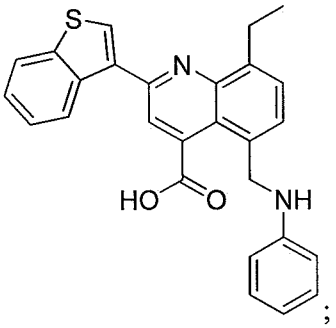
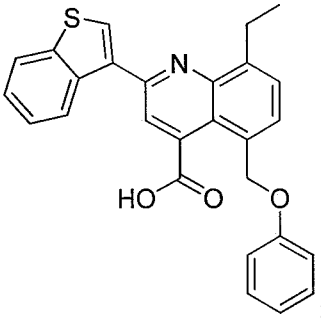
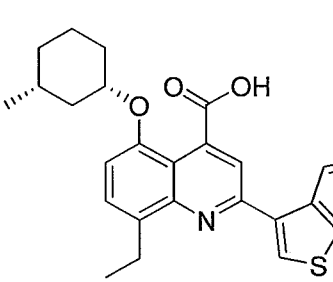
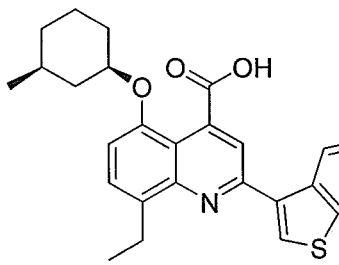

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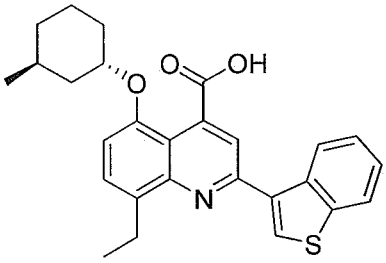
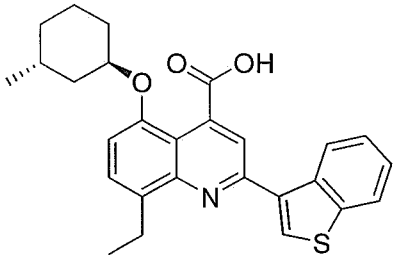
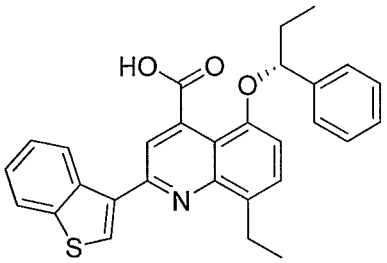
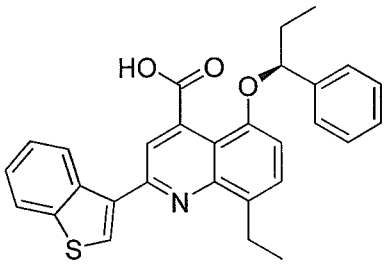
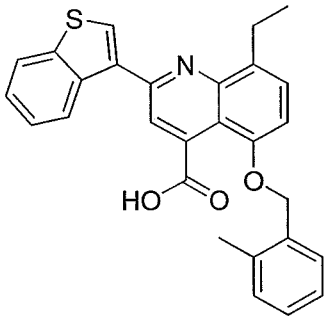
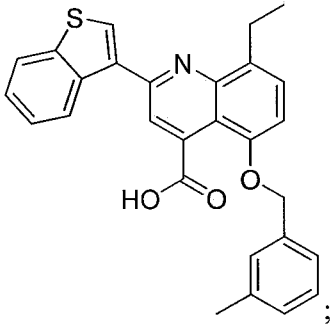
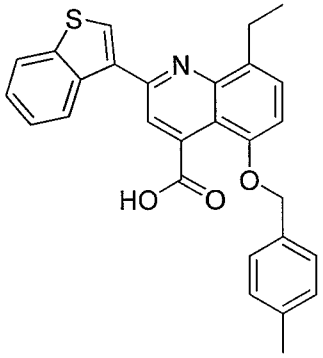
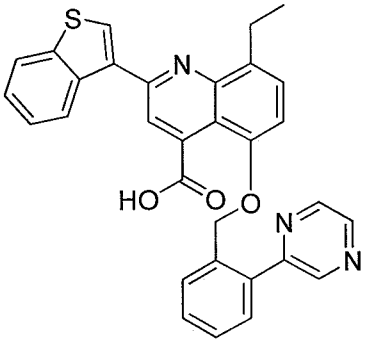
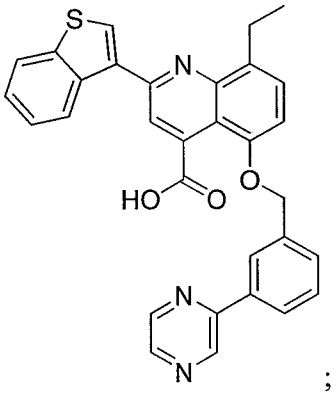
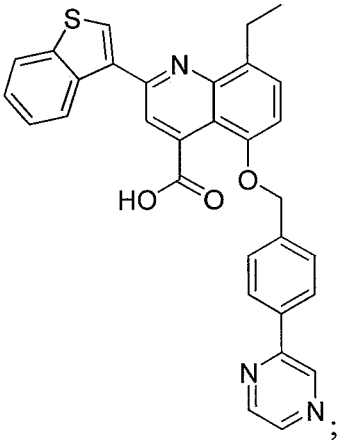
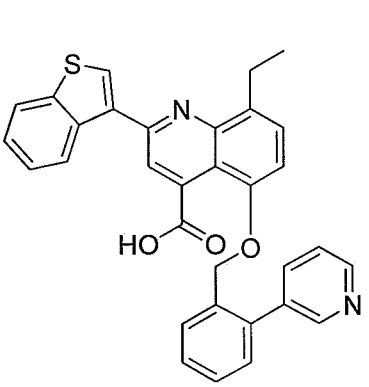
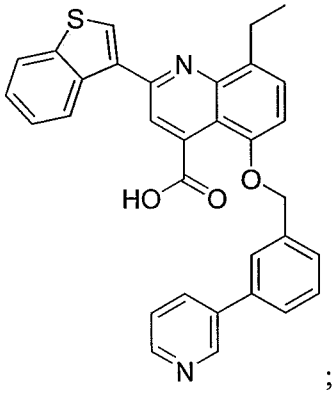

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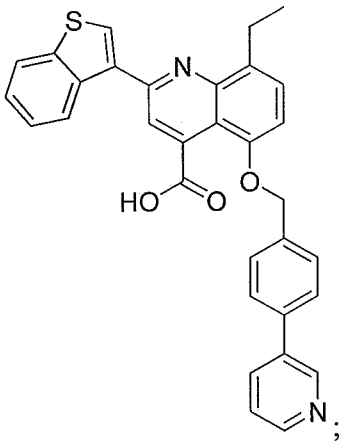
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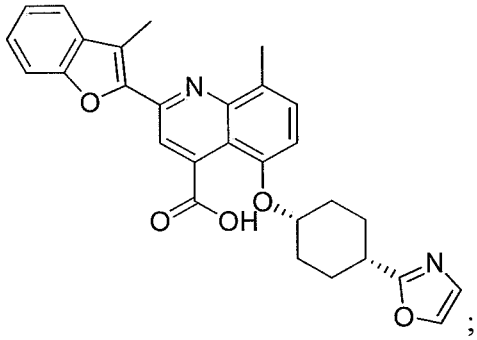
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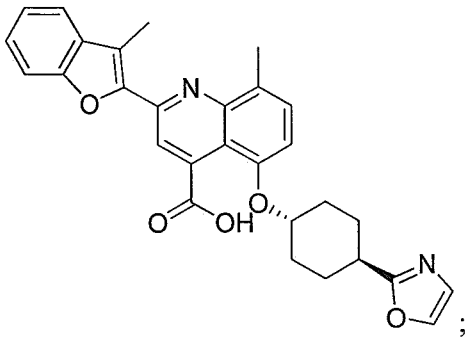
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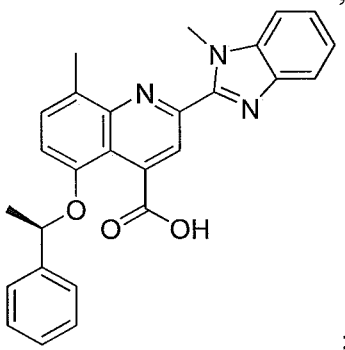
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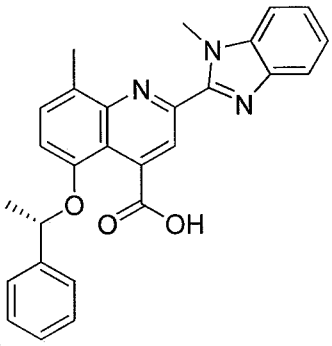

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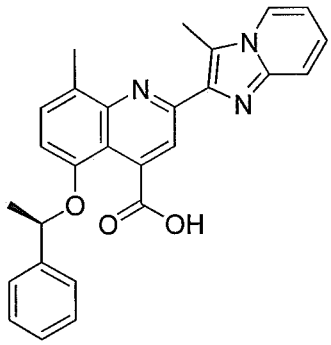

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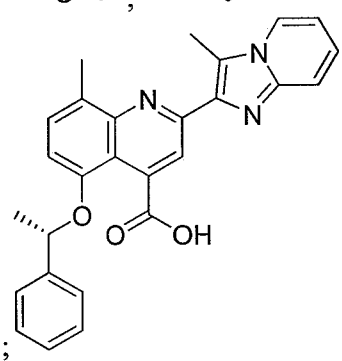

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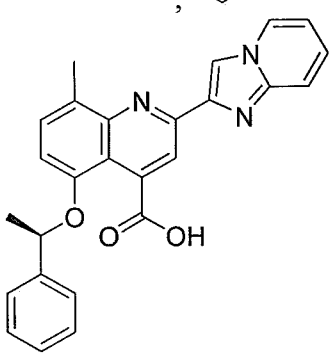

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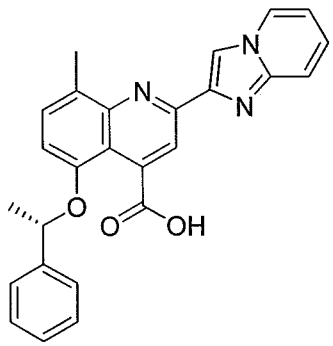

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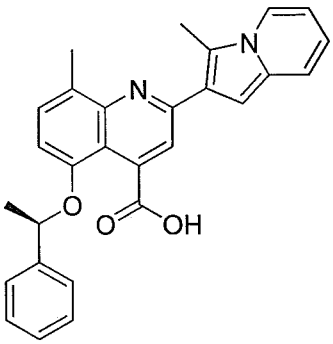

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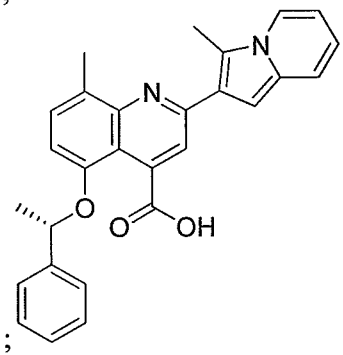

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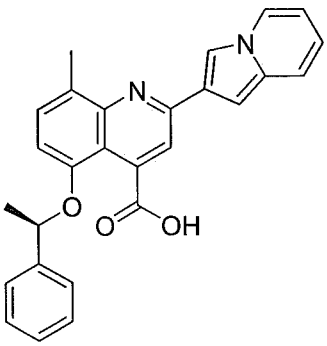

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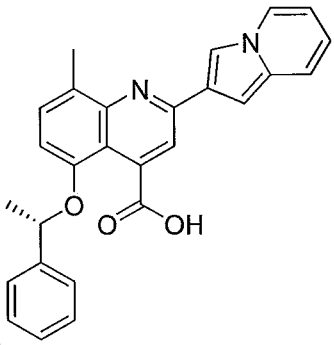

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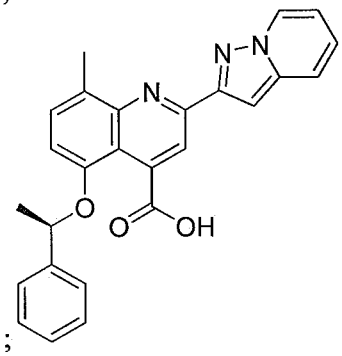

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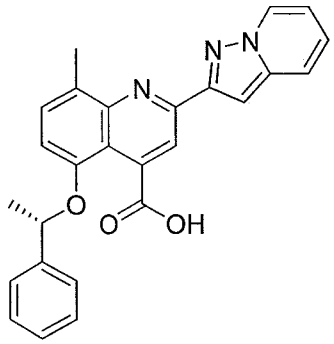
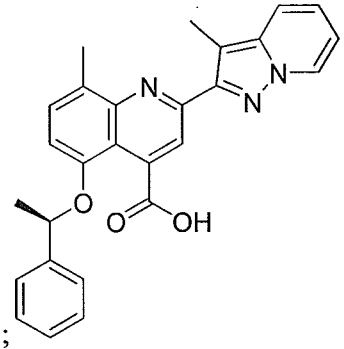
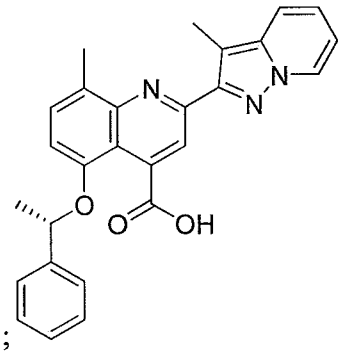
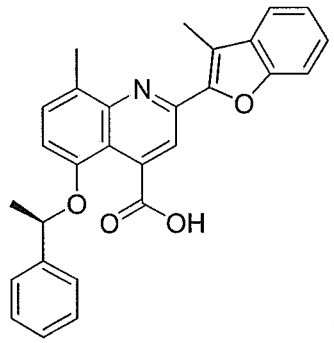
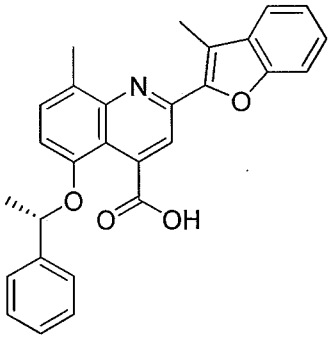
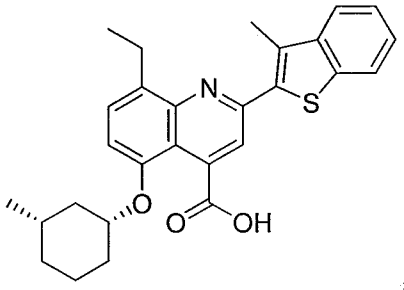
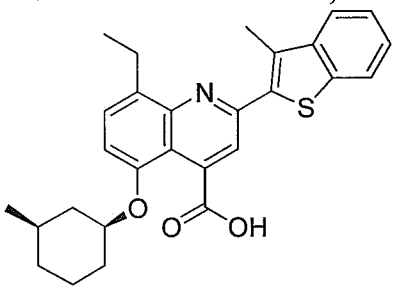
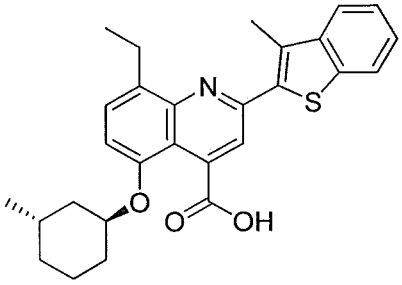
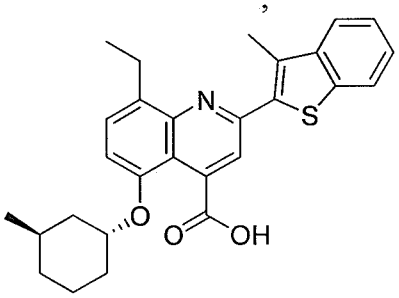
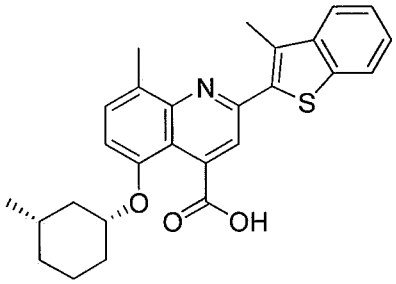
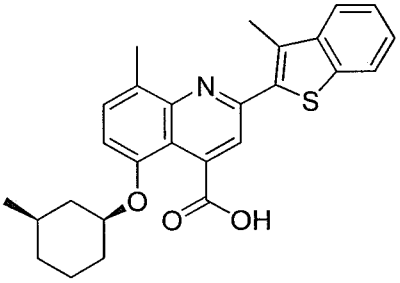
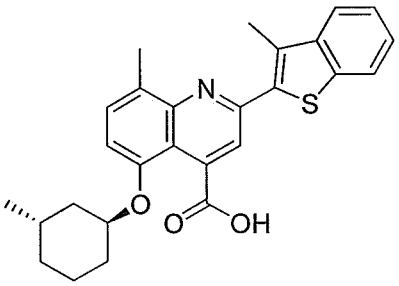
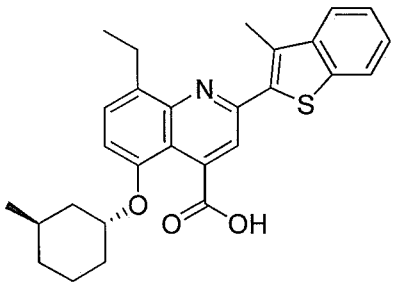
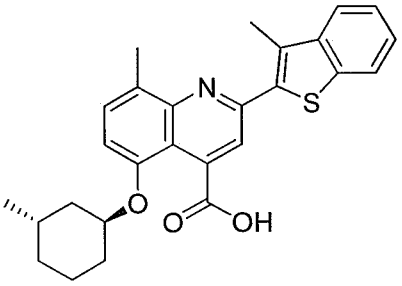
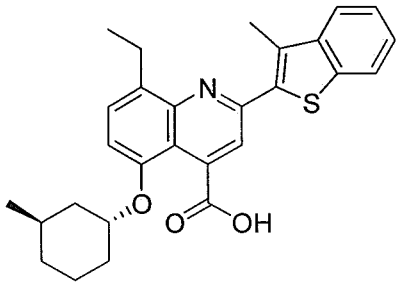

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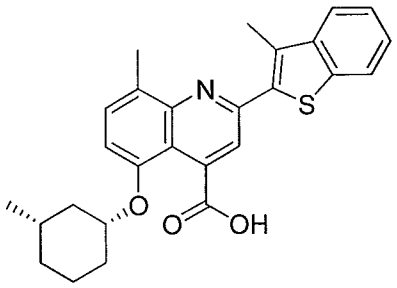
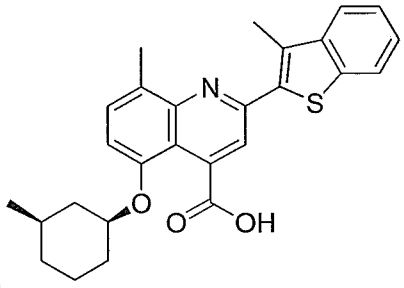
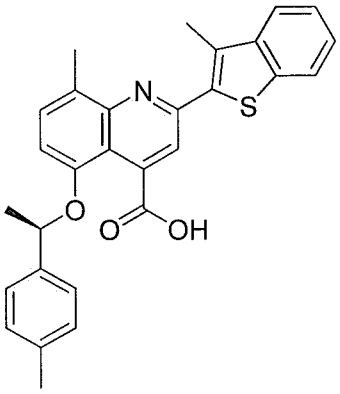
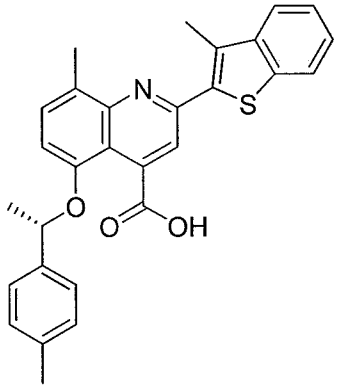
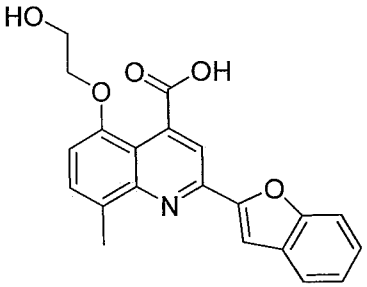
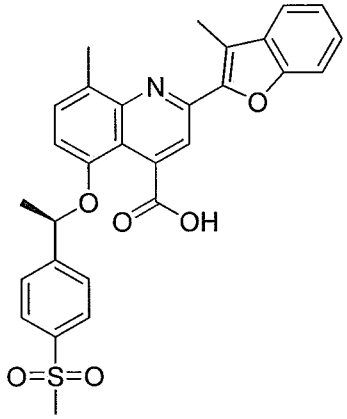
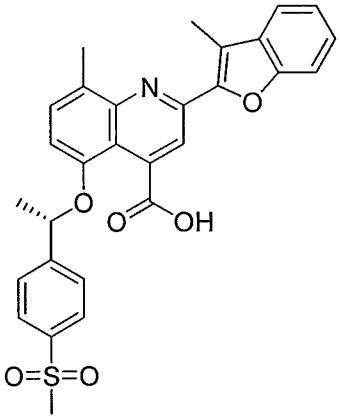
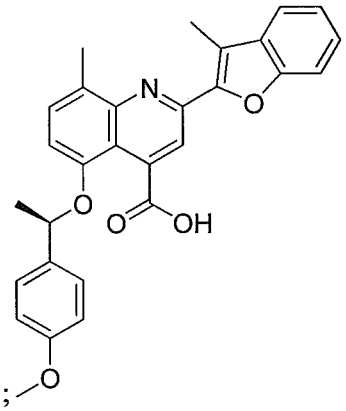
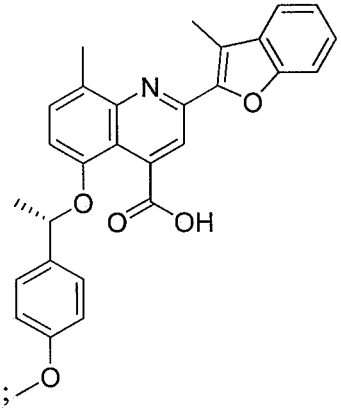
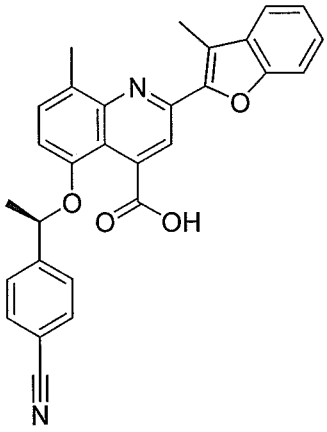
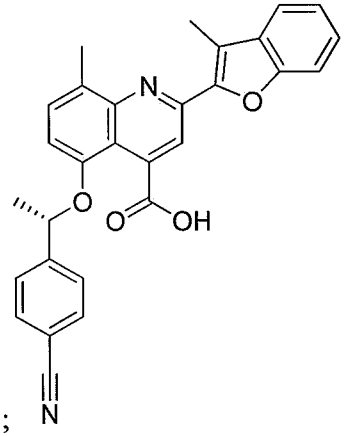
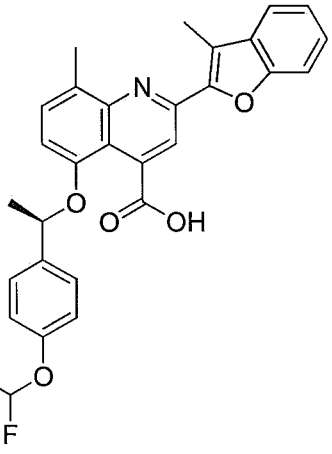

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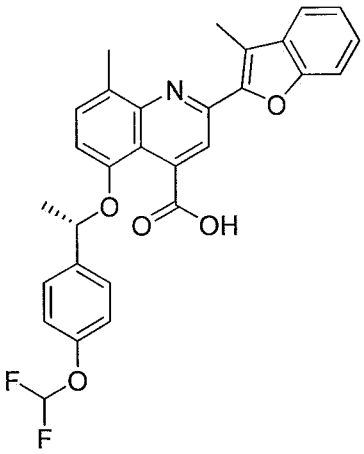
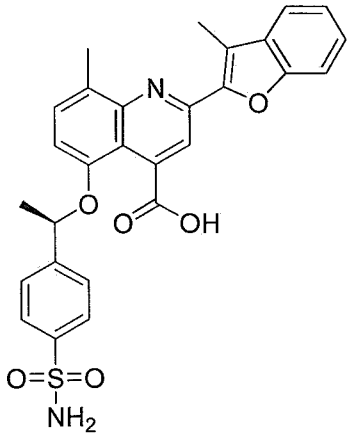
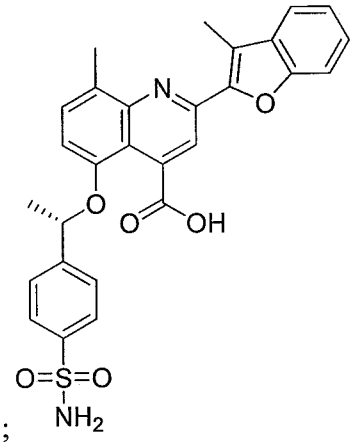
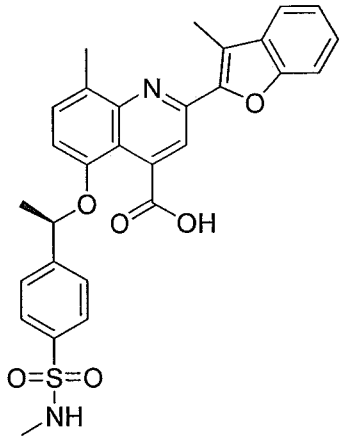
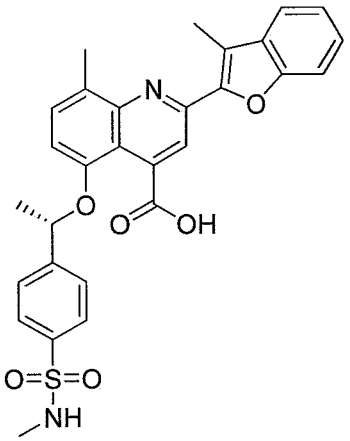
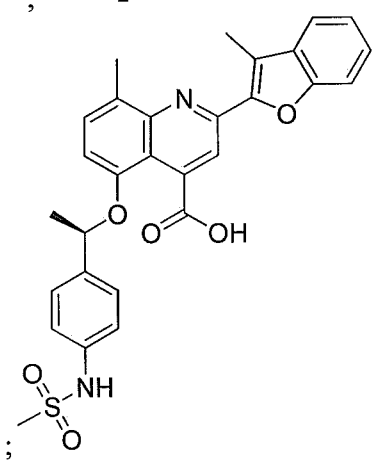
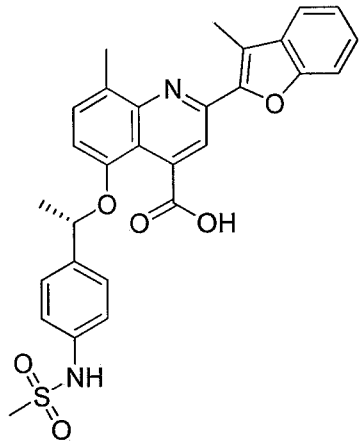
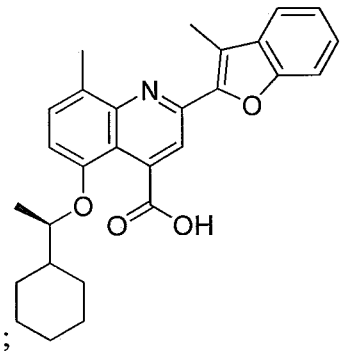
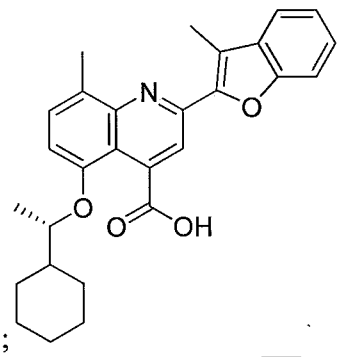
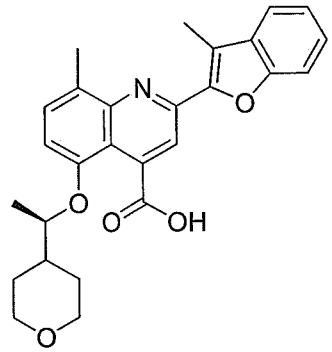
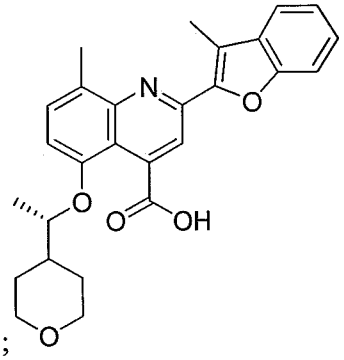
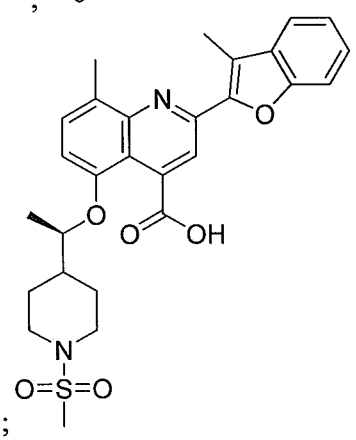

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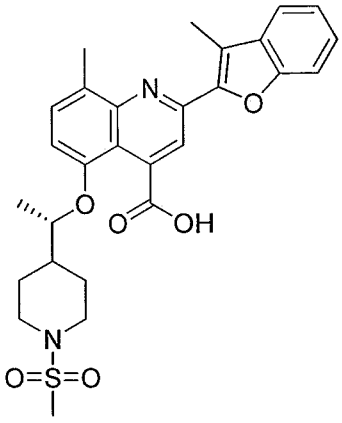
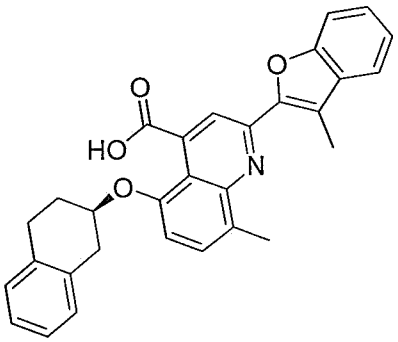
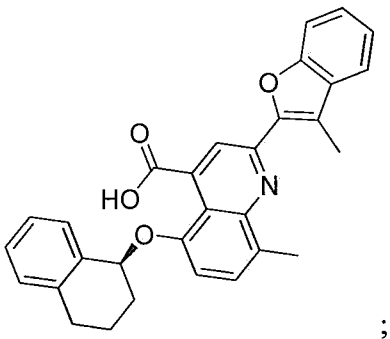
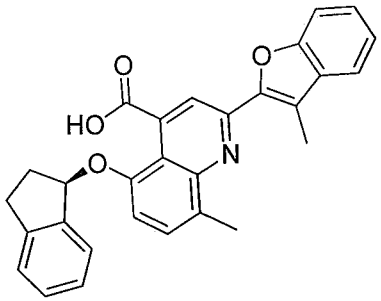
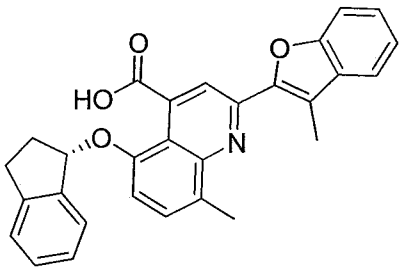
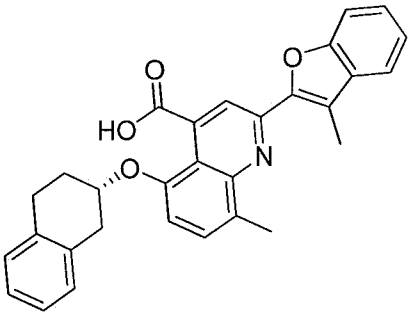
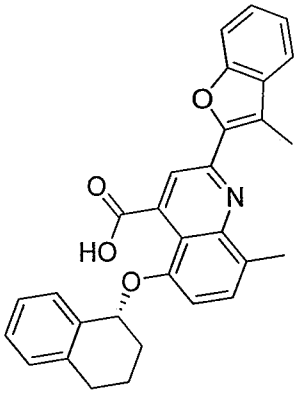
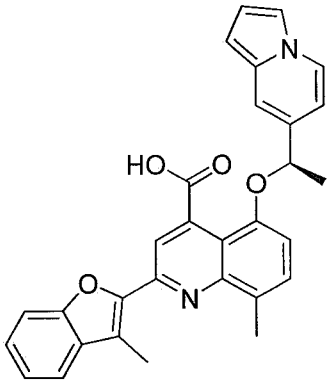
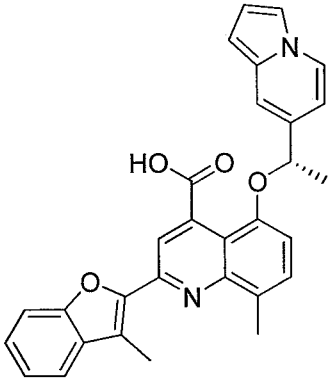
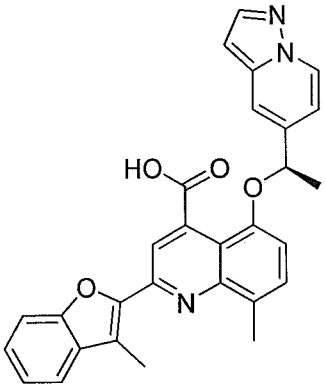
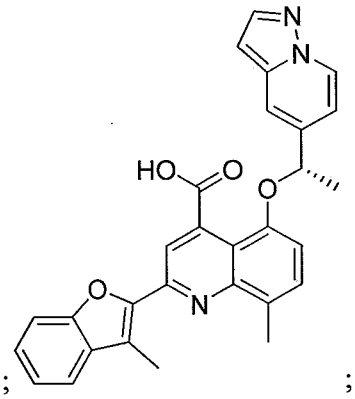
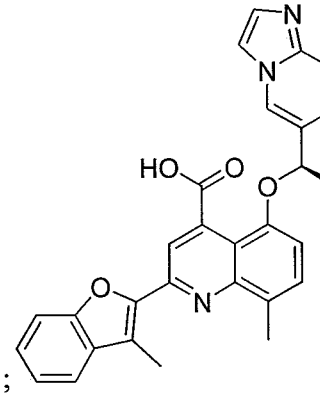

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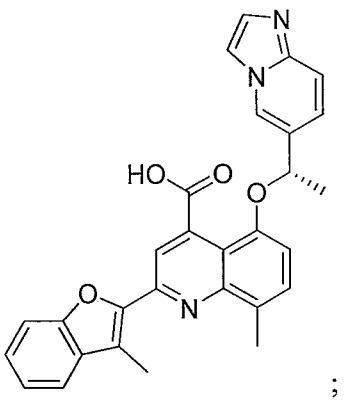
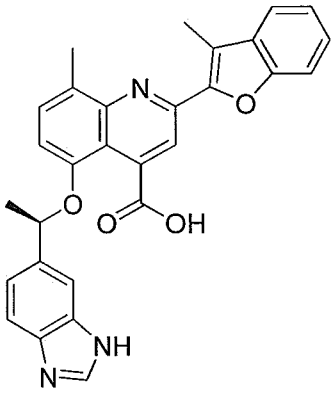
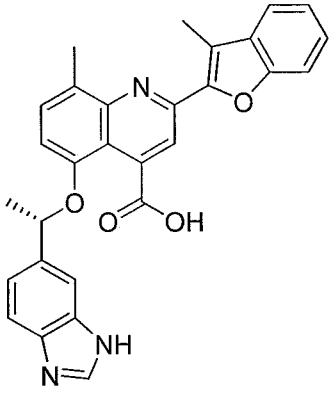
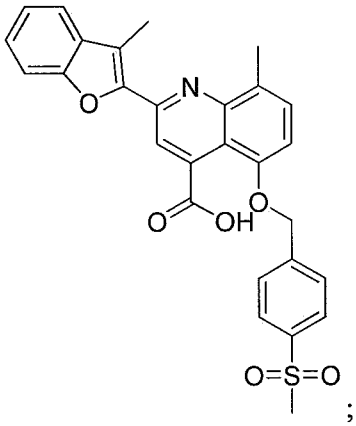
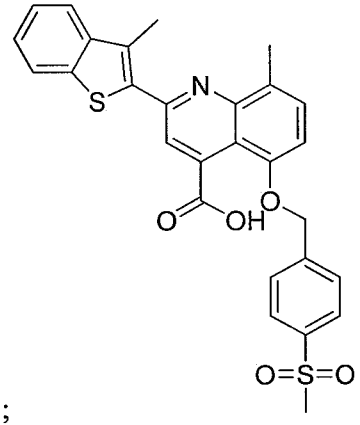
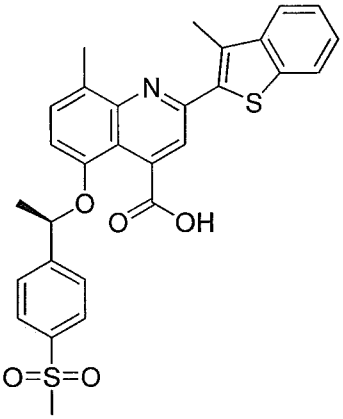
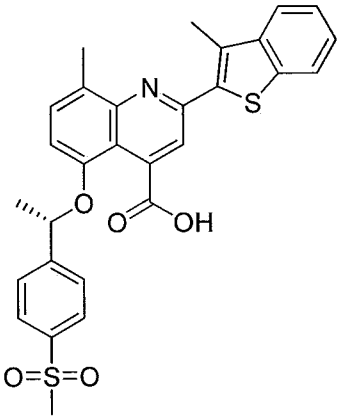
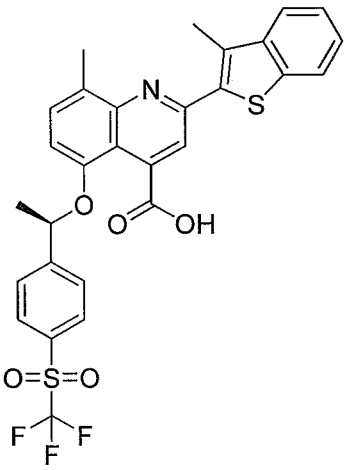
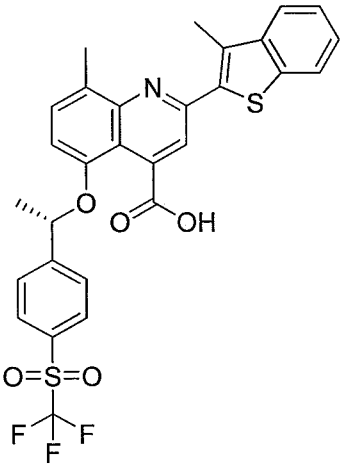
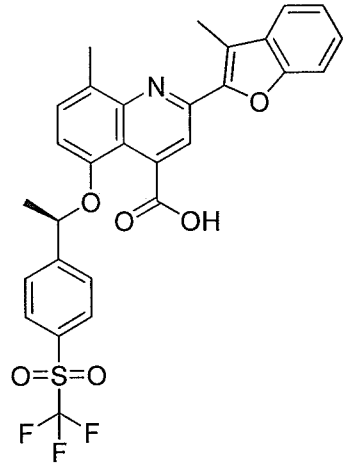
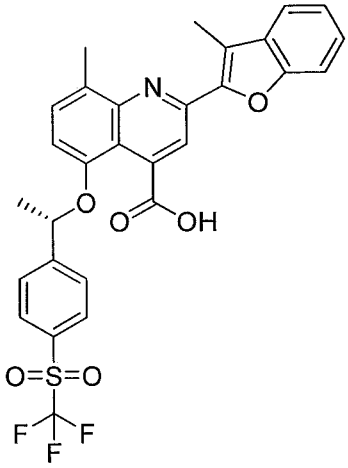
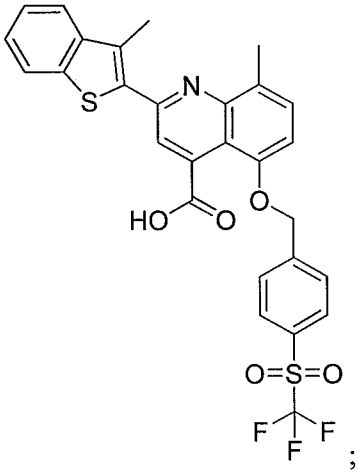

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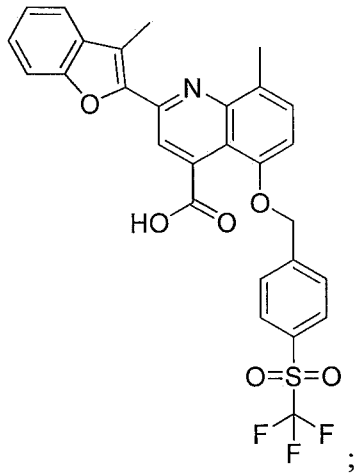
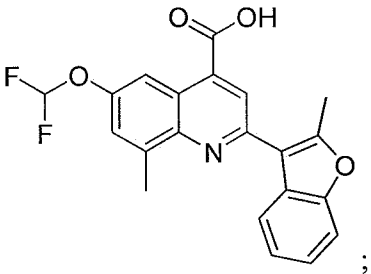
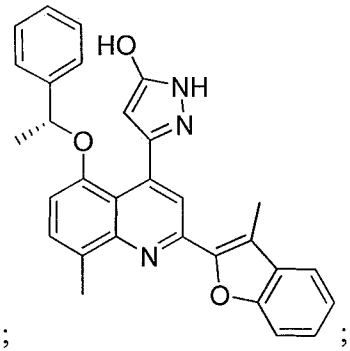
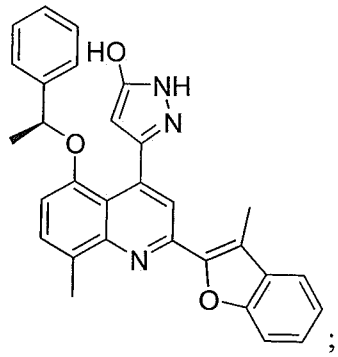
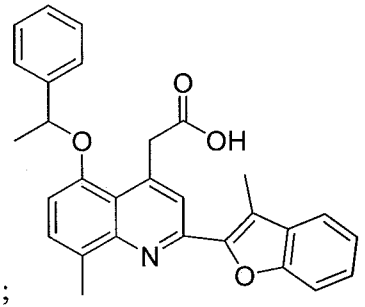
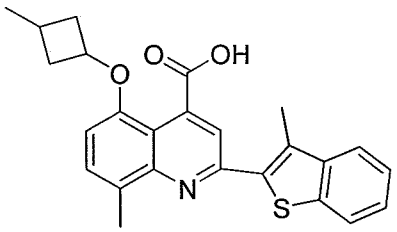
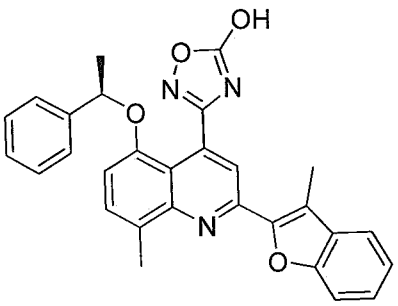
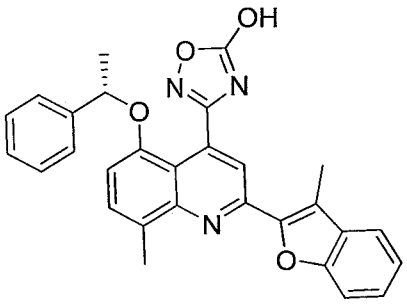
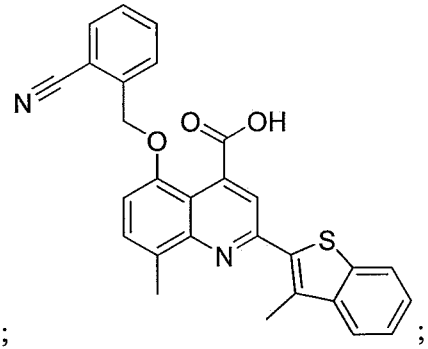
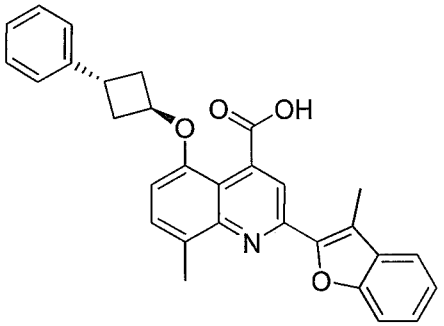
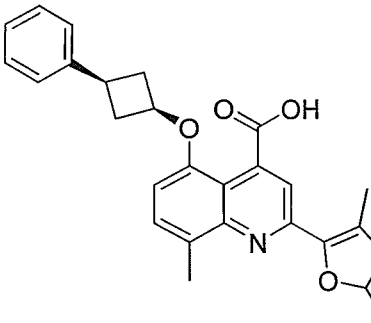
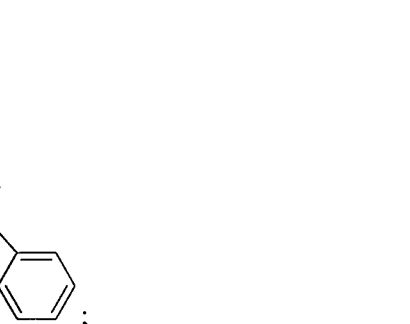
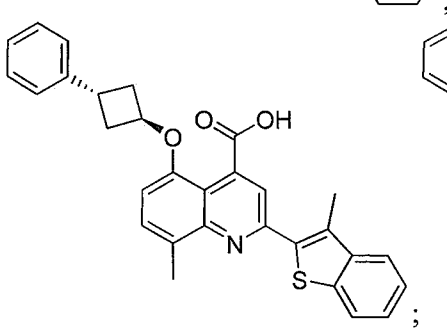
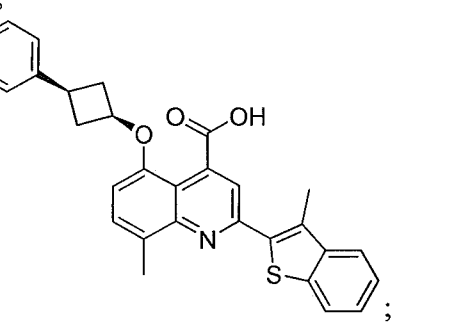

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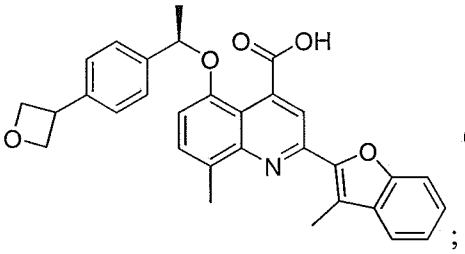













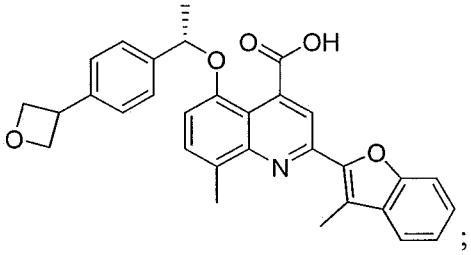













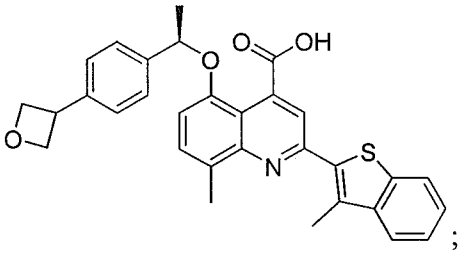

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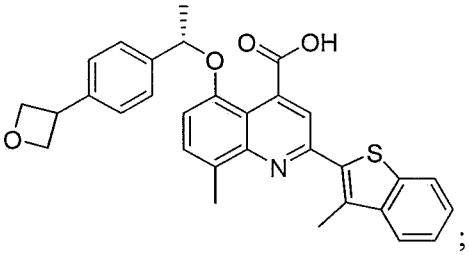
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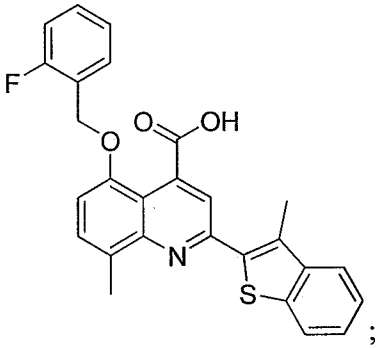
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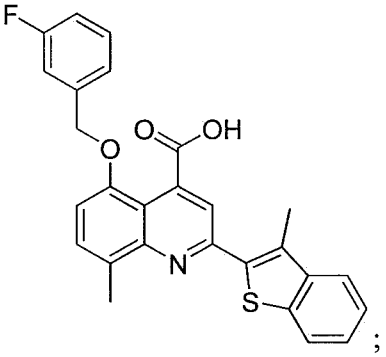

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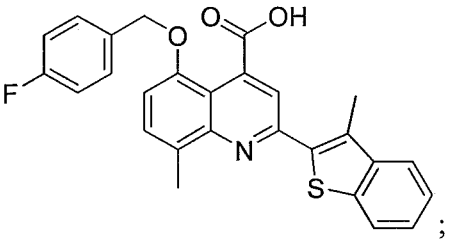

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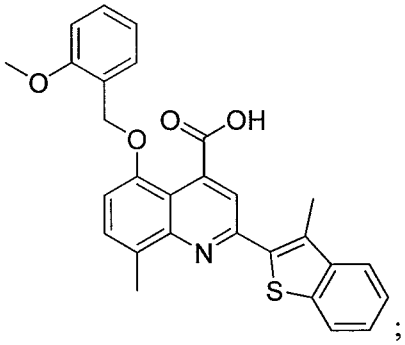

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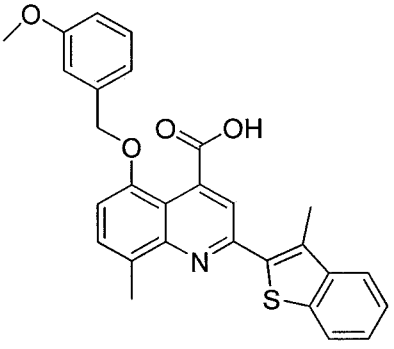

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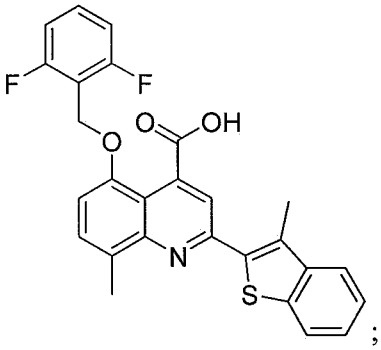

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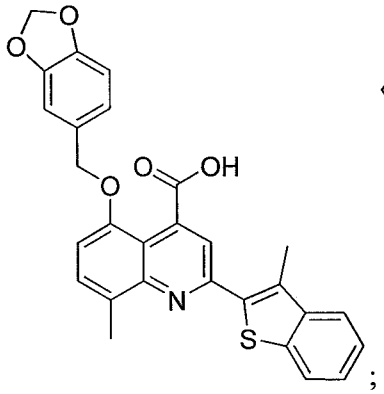

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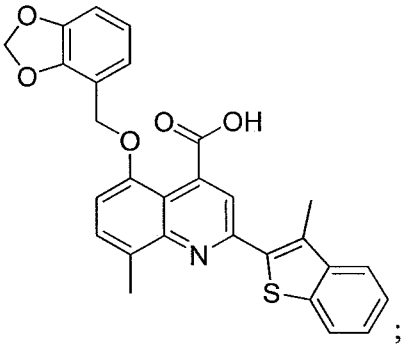

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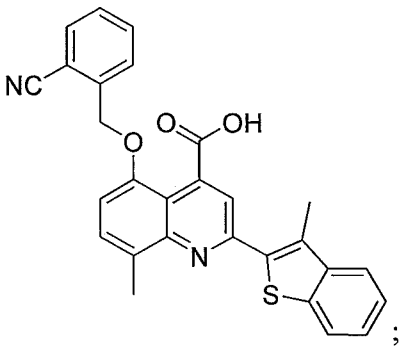

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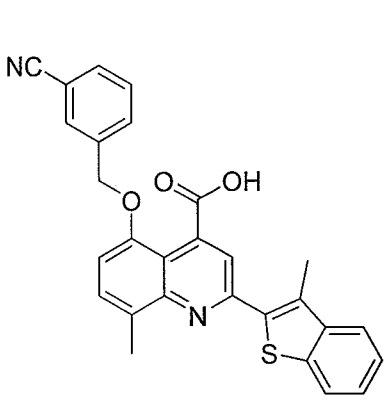

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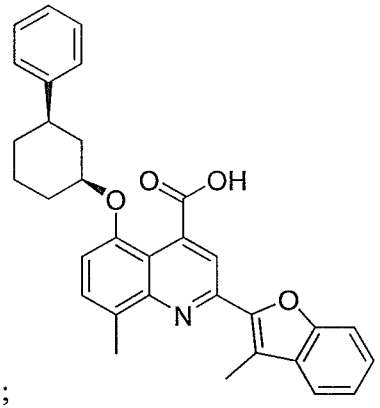

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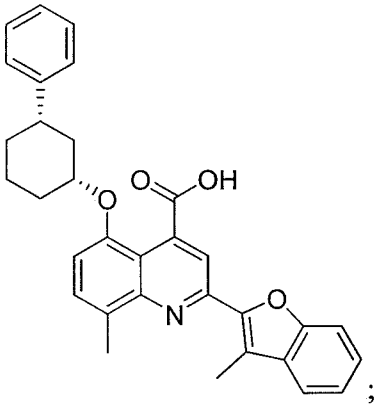

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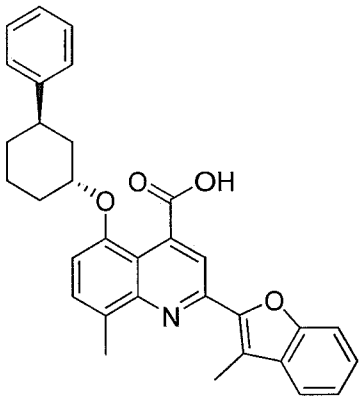

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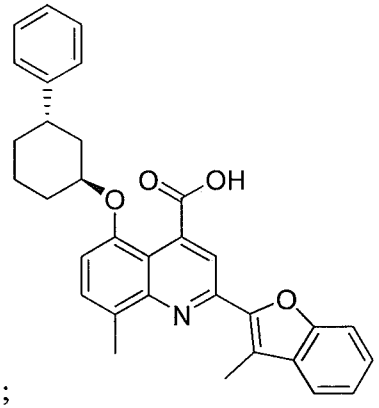
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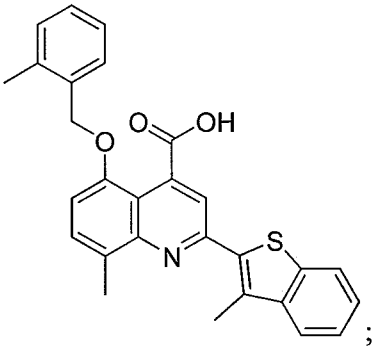

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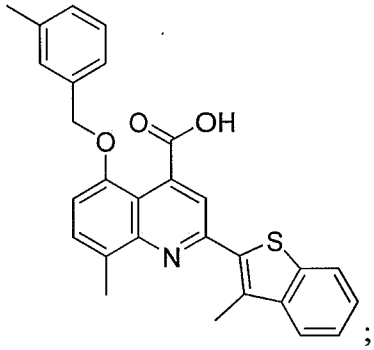

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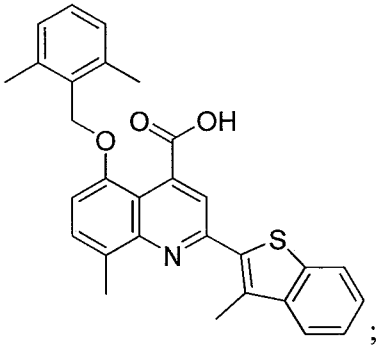

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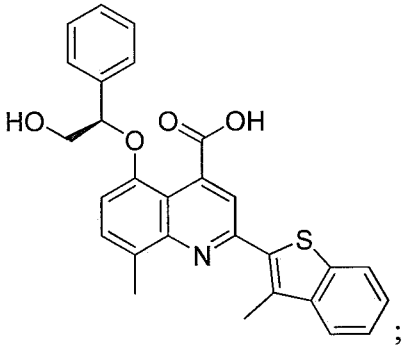

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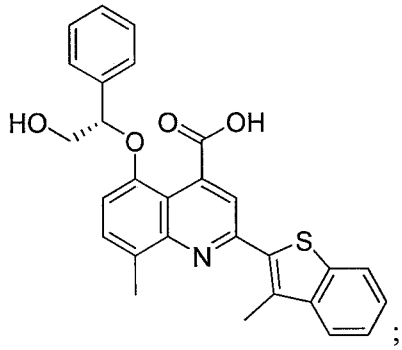

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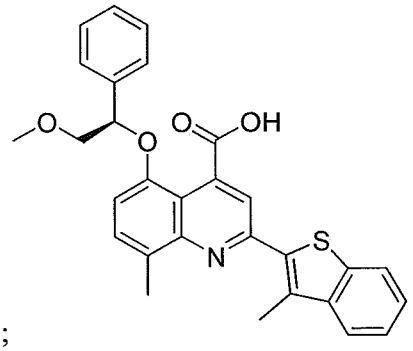

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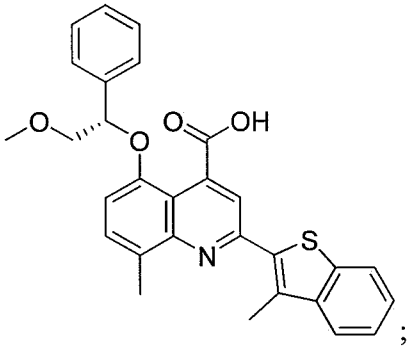

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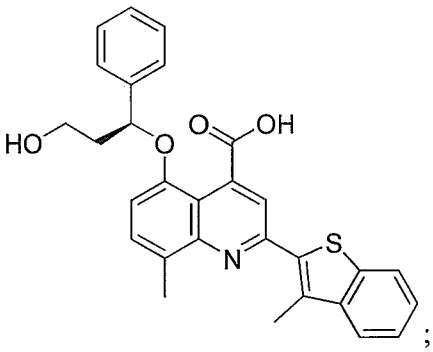
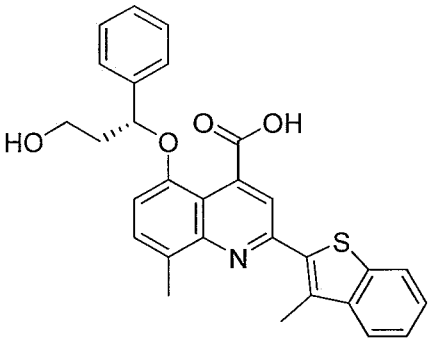
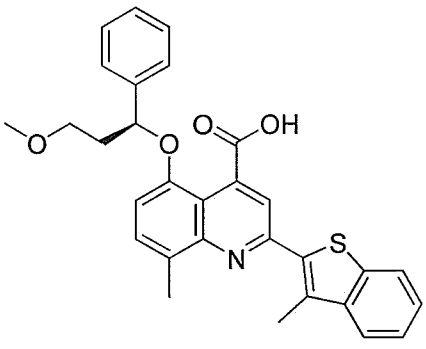
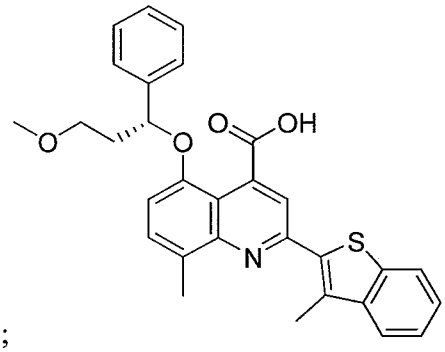
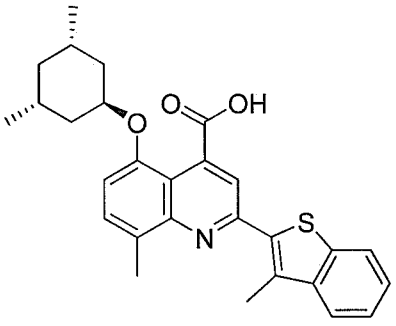
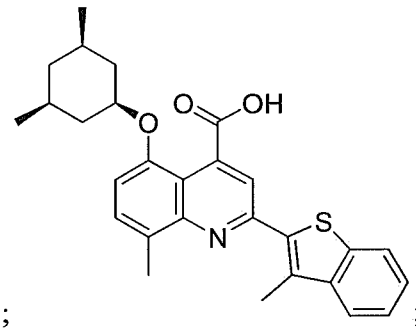
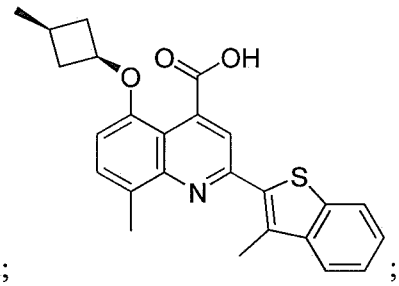
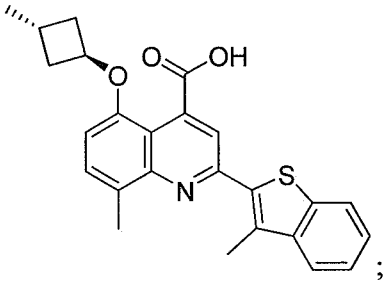
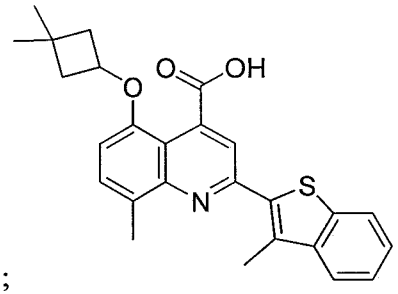
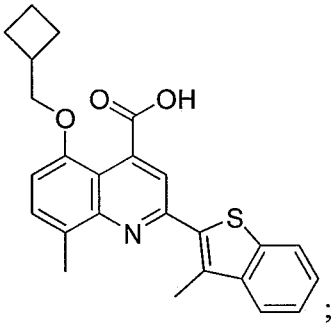
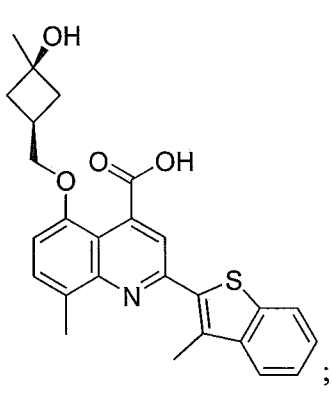
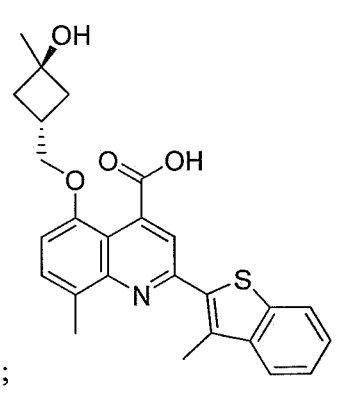
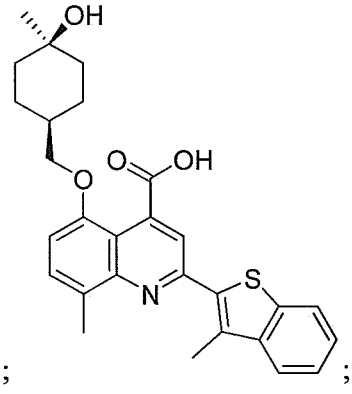

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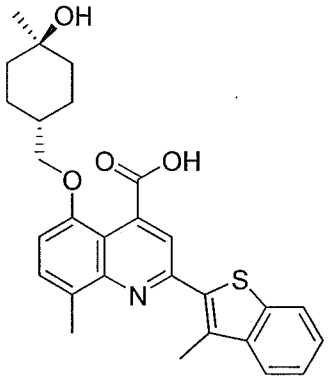
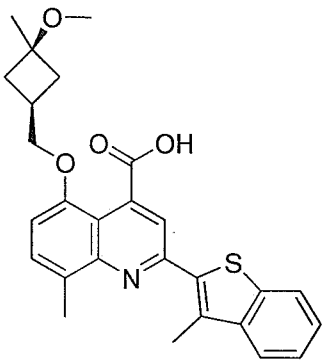
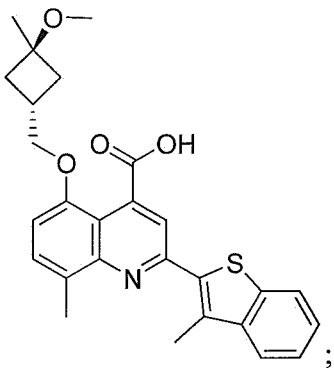
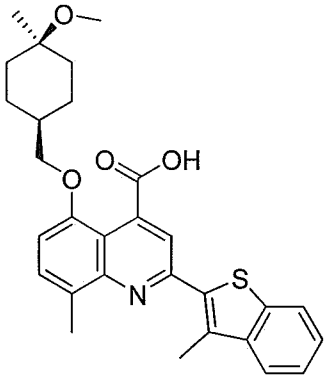
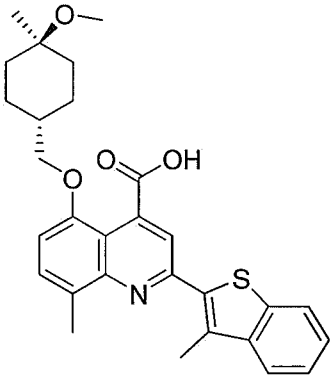
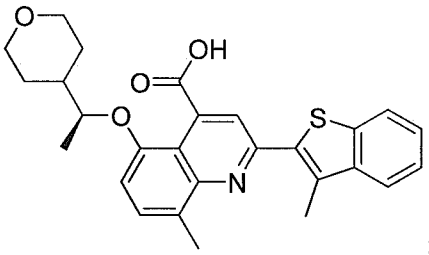
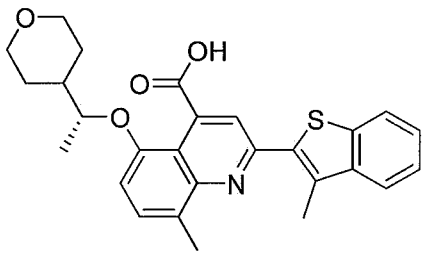
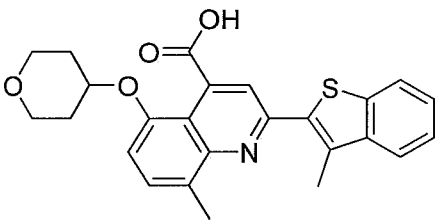
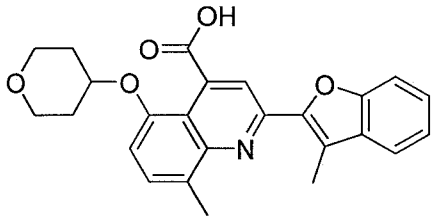
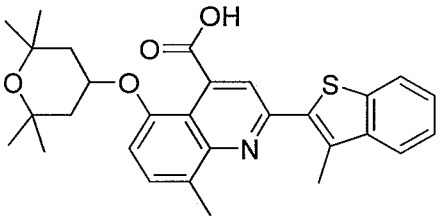
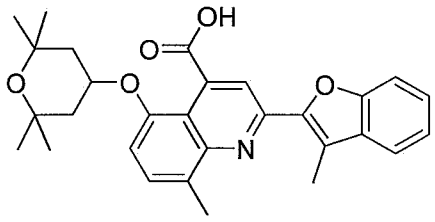
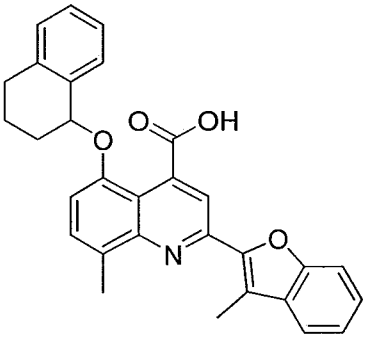
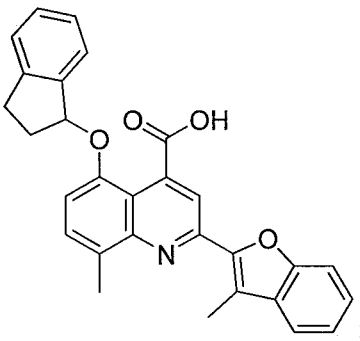

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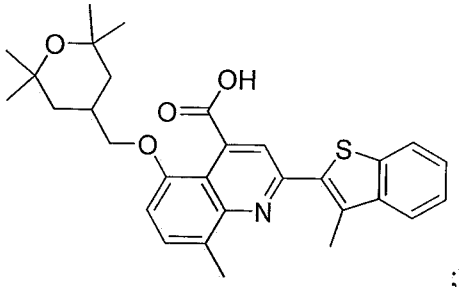
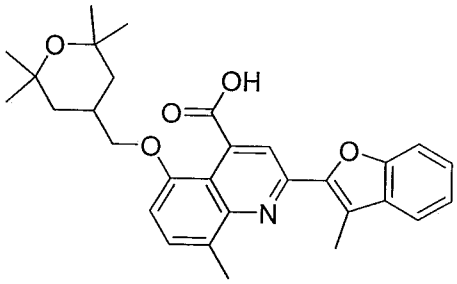
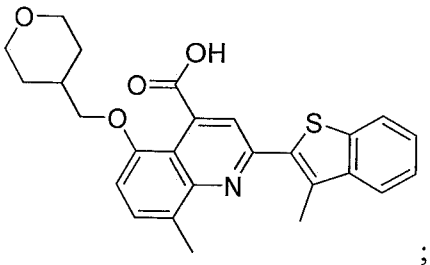
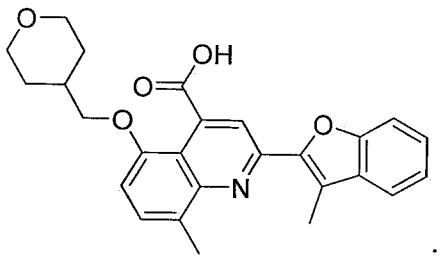
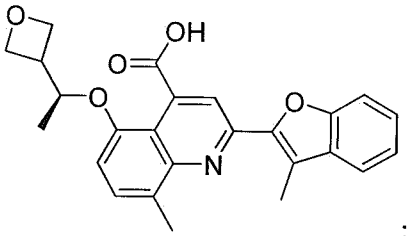
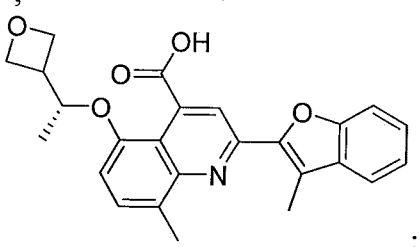
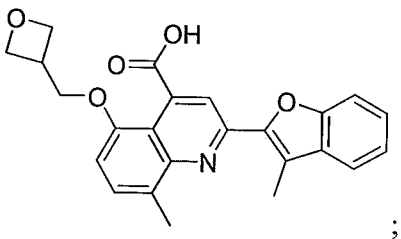
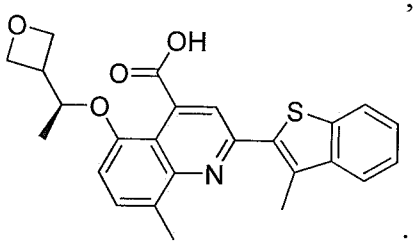
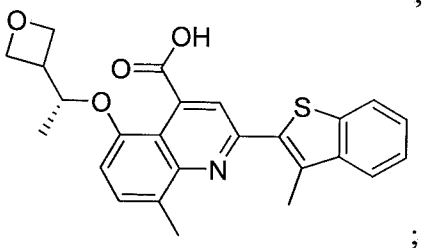
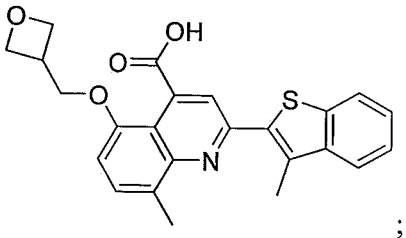
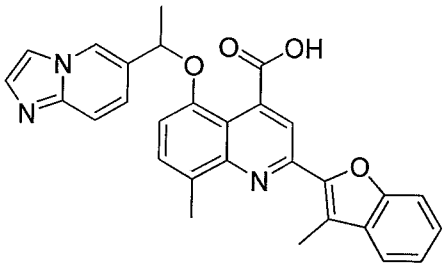
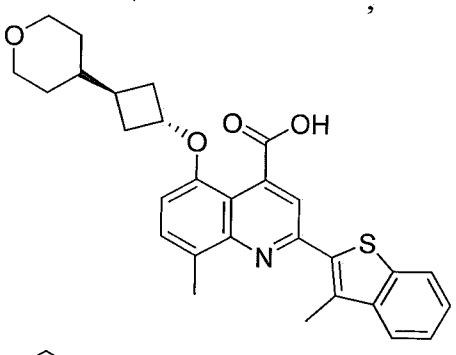
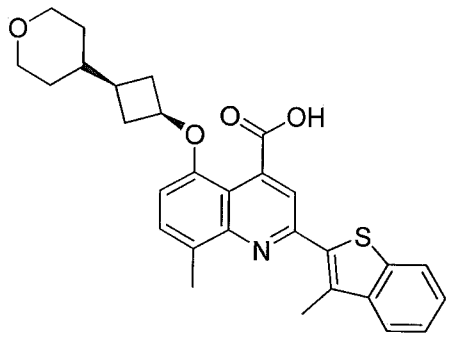
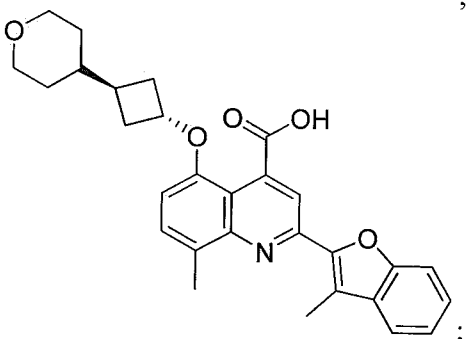

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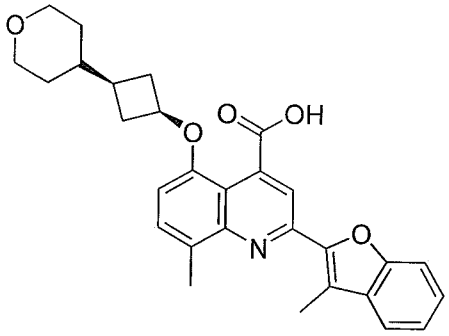
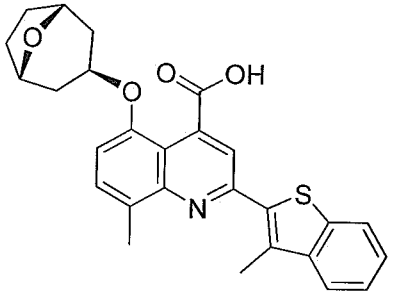
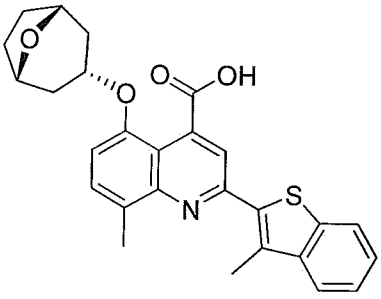
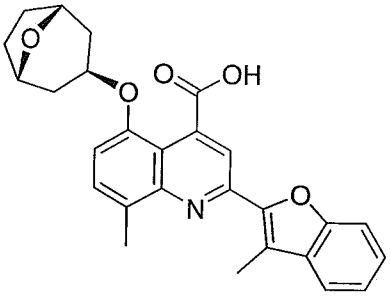
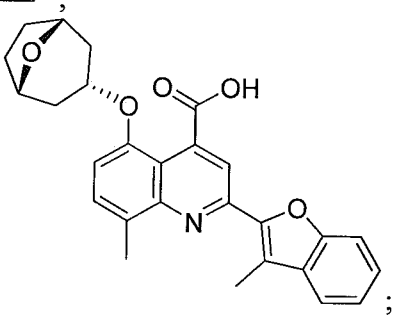
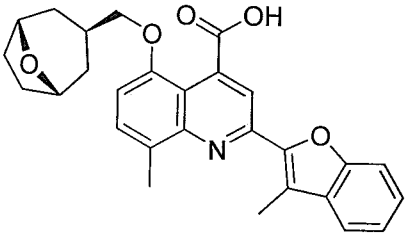
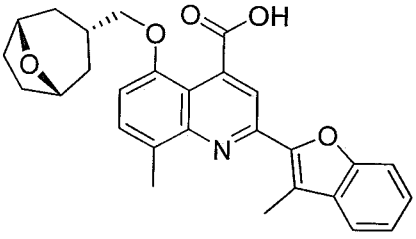
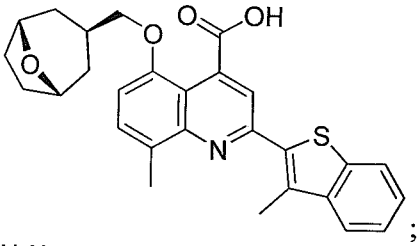
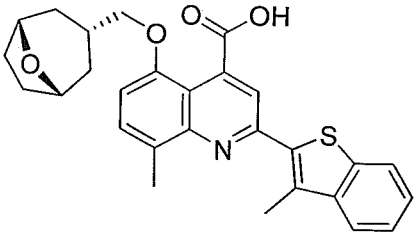
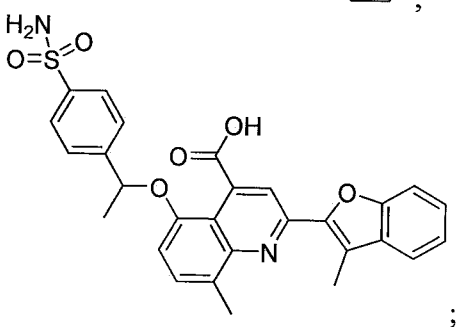
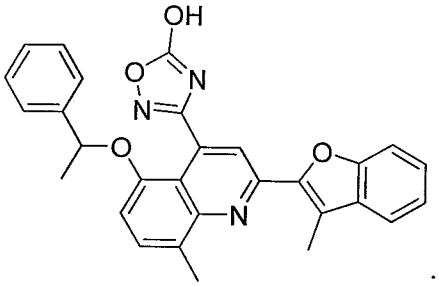
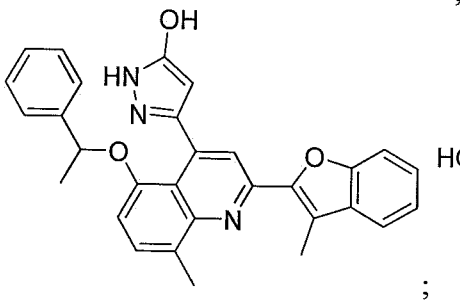
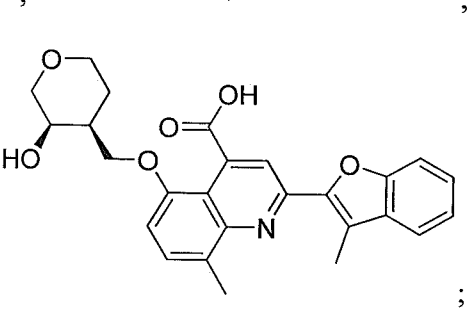
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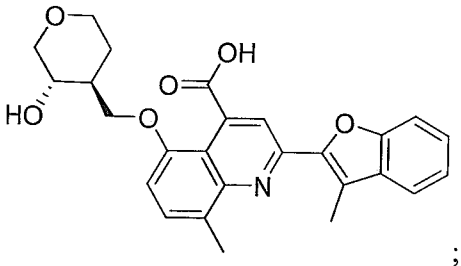
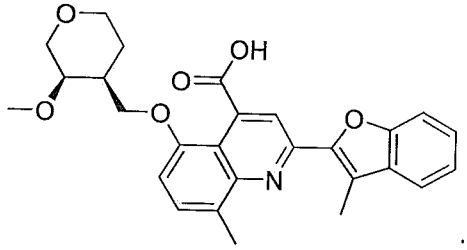
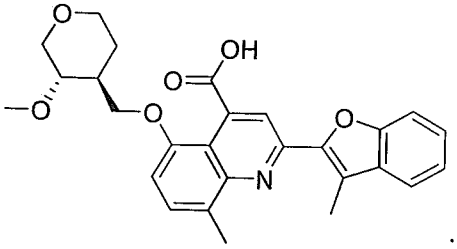
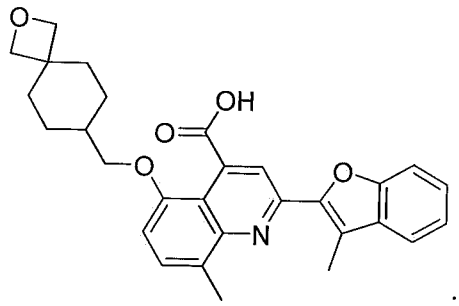
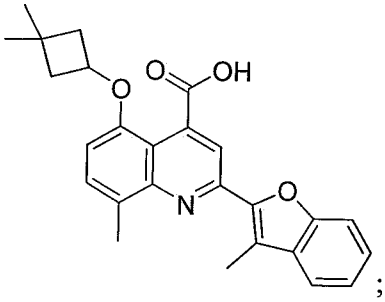
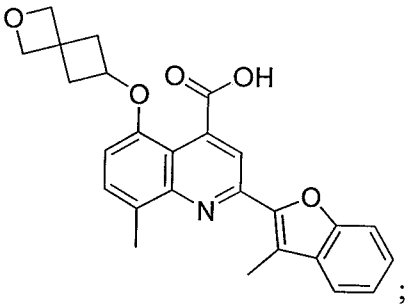
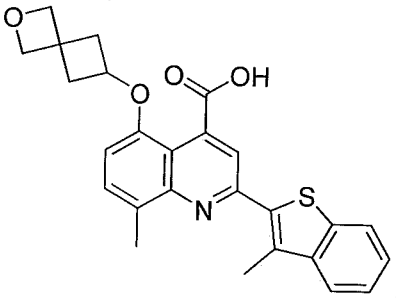
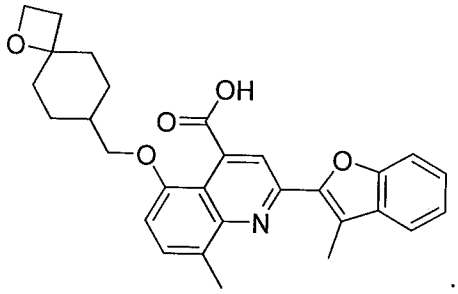
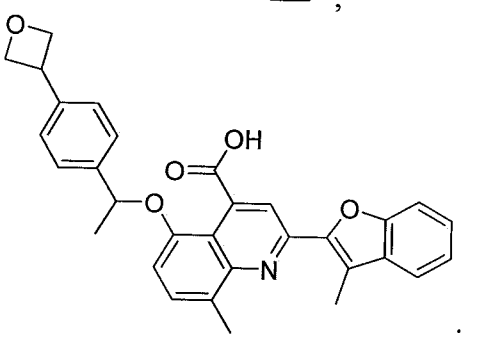
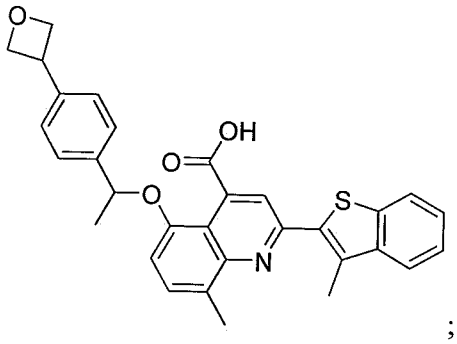
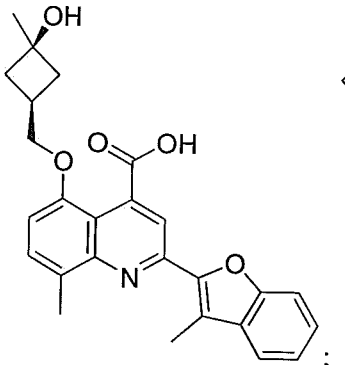
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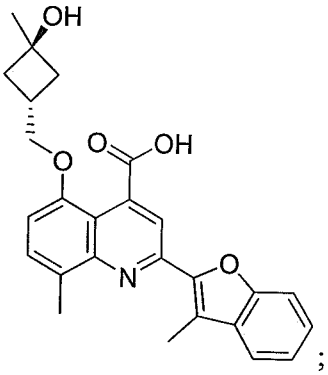

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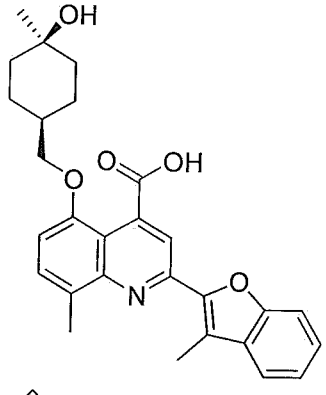
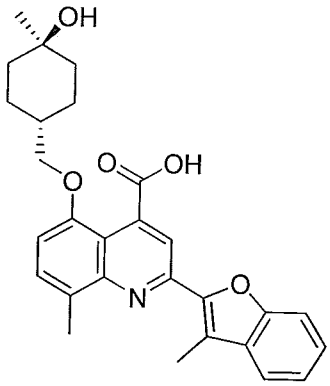
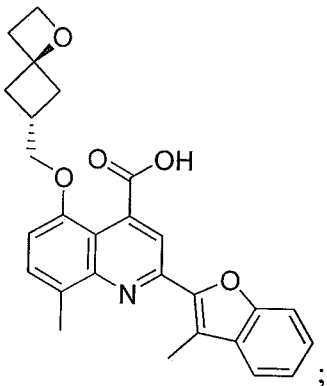
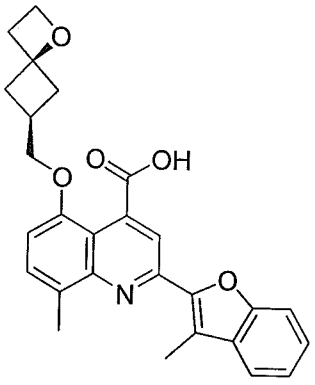
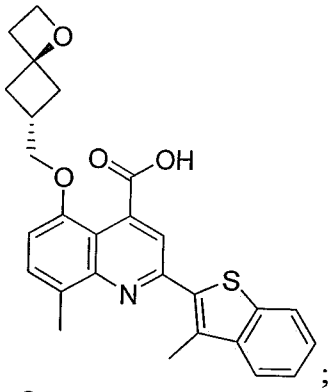
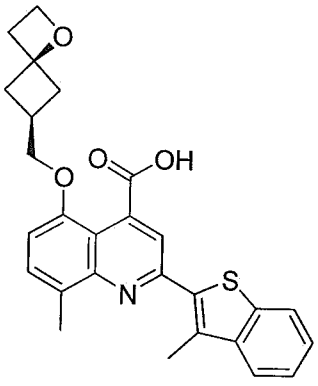
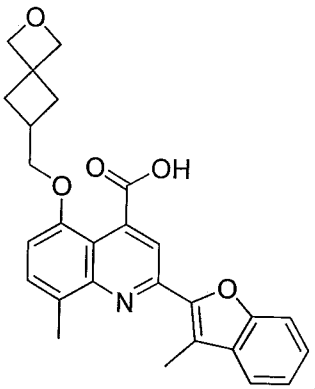
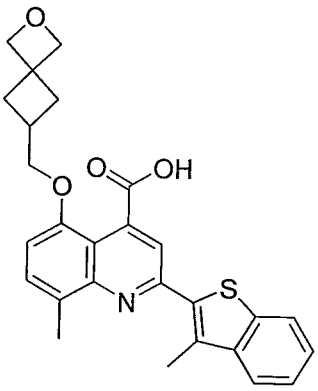
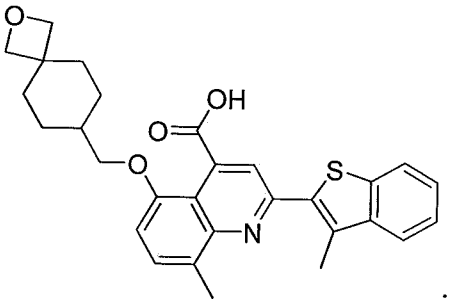
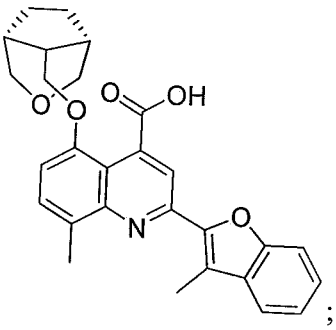
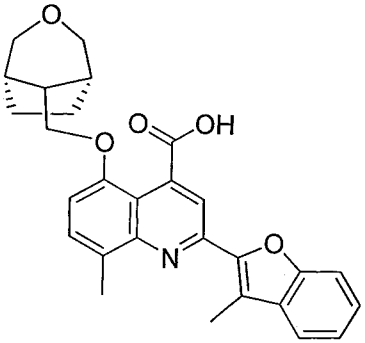
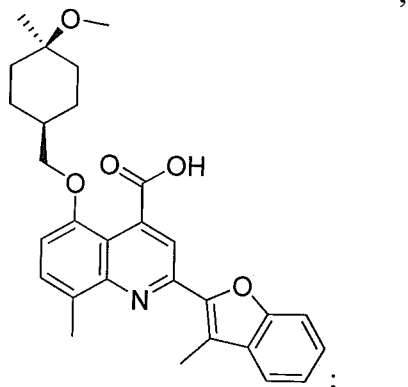
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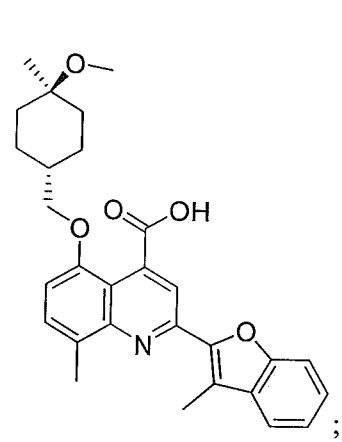
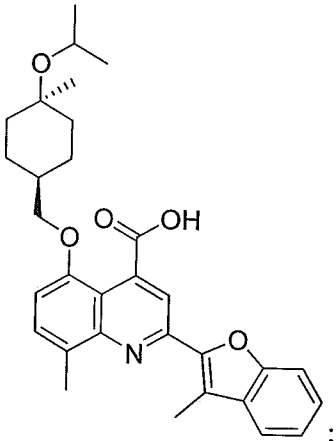
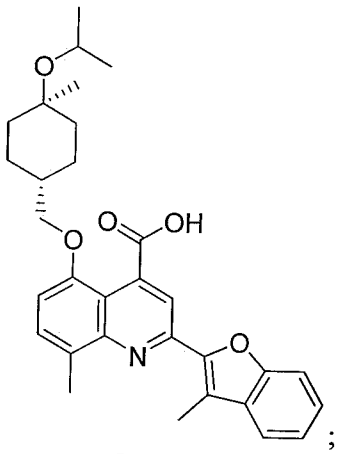
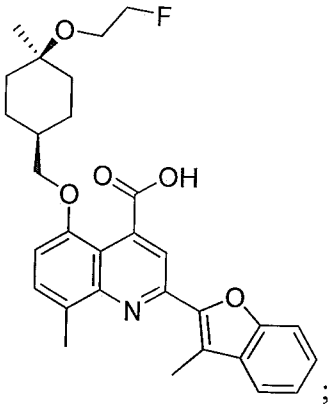
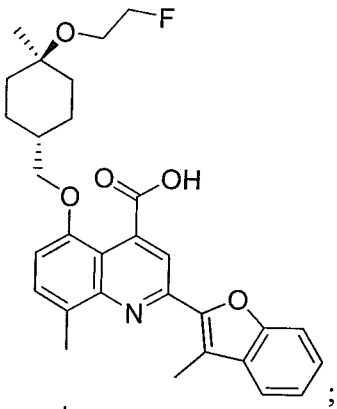
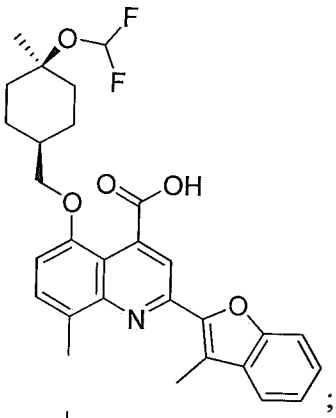
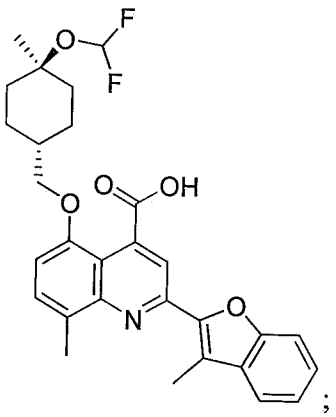
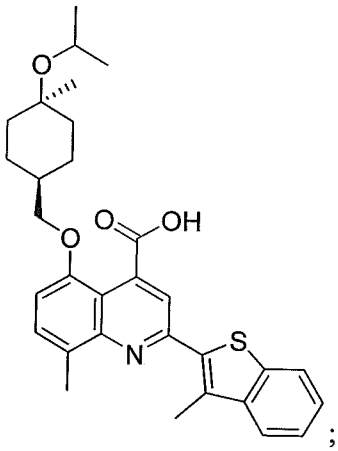
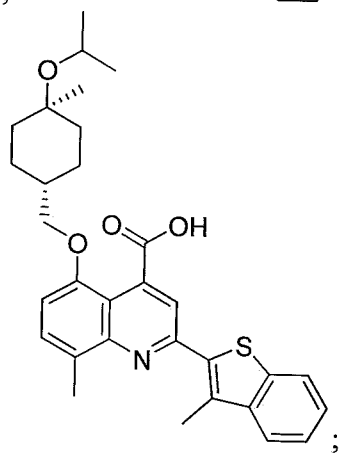
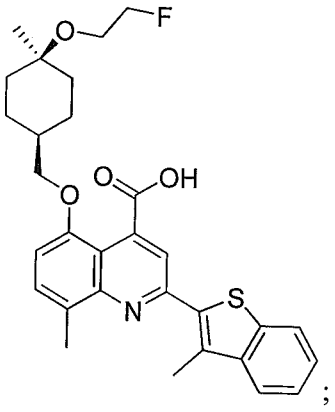
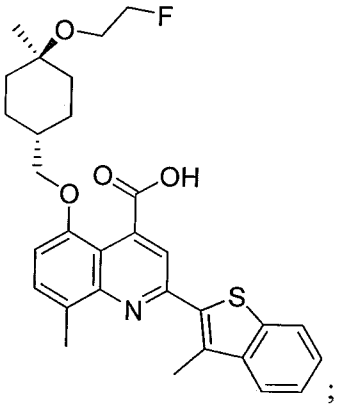
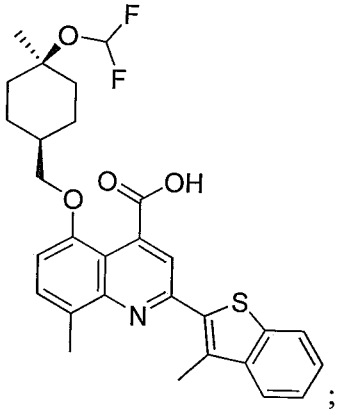

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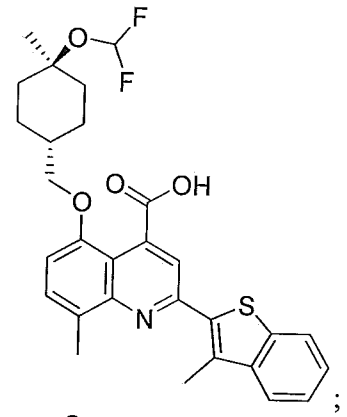
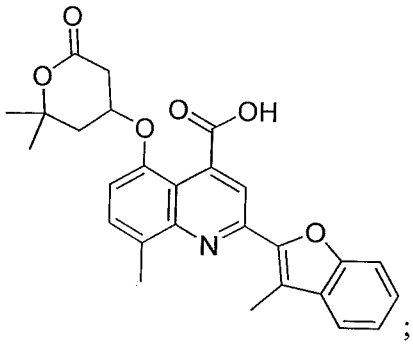
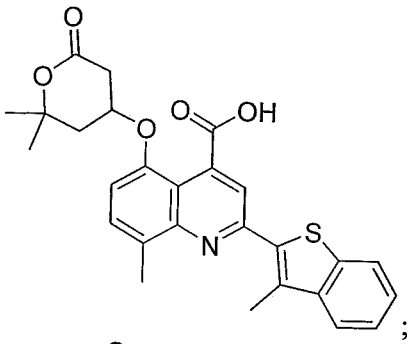
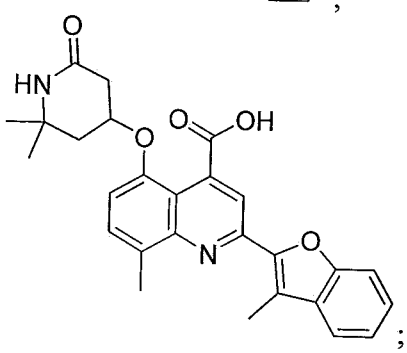
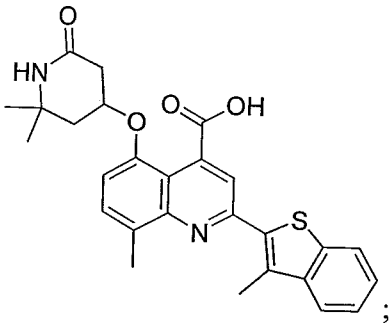
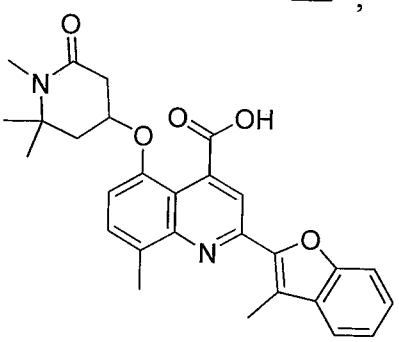
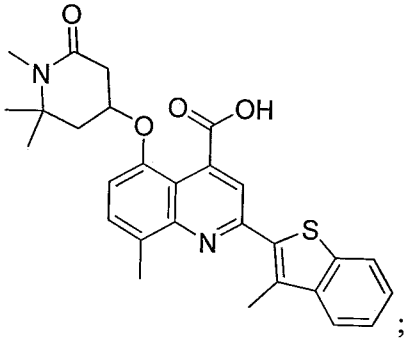
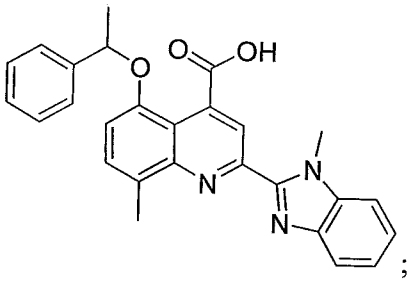
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and a pharmaceutically acceptable salt or steroisomer thereof.

[0007] Also contemplated herein are pharmaceutical compositions that include a disclosed compound such as those compounds having disclosed formulas such as Formula I and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the compositions can include at least one additional CFTR modulator, for example, may include one, two, three, four , five or more additional CFTR modulators.

[0007a] In a further aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof.

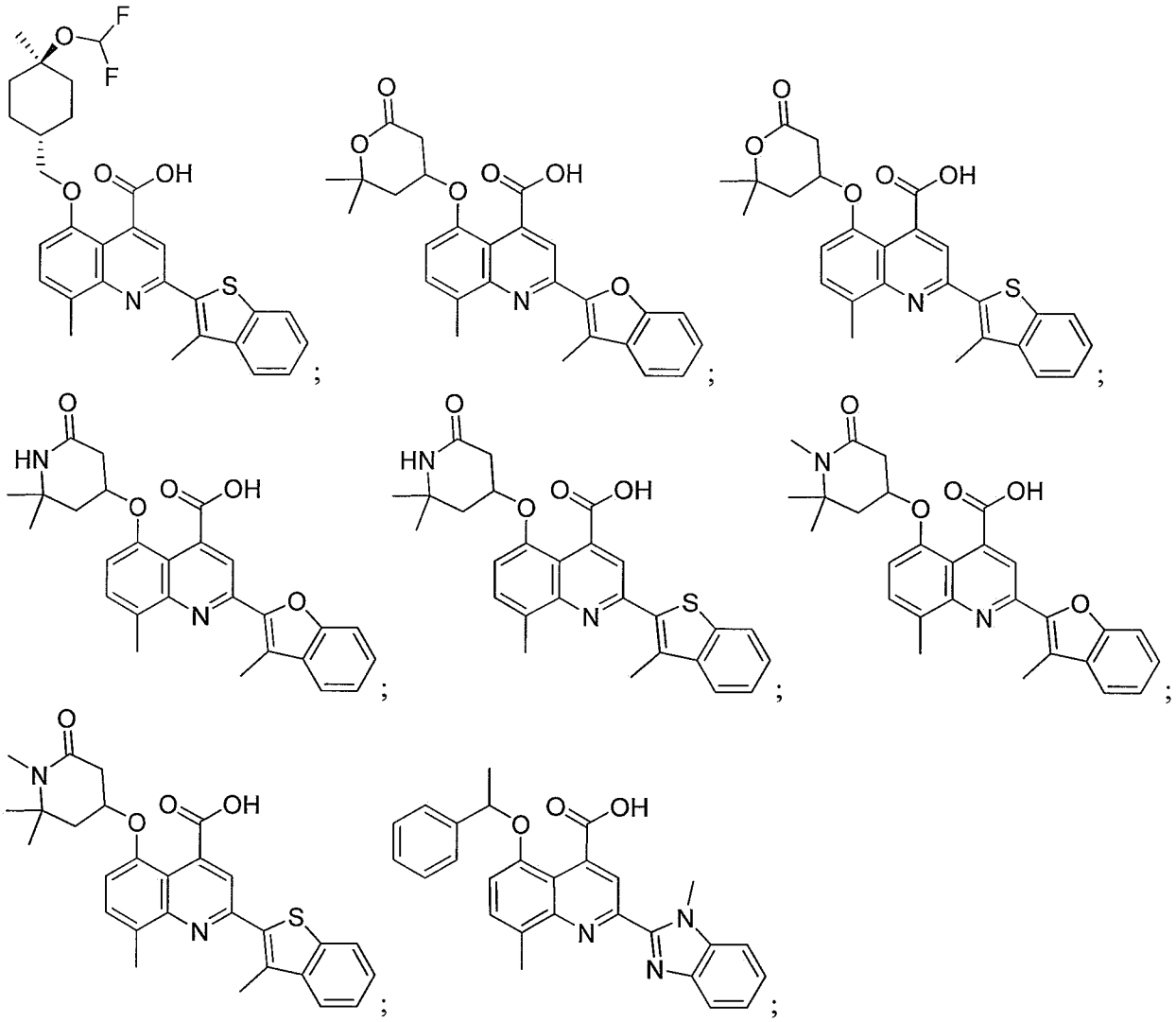
[0007b] In another aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.

[0007c] In yet another aspect of the present disclosure, there is provided a compound as defined herein for use in enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity, or for use in treating cystic fibrosis.

[0008] In certain embodiments, a method is provided comprising administering a disclosed compound to a subject (e.g., a human patient) suffering from a disease associated with decreased CFTR activity (e.g., cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, A-β-lipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolyis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, Sjogren's syndrome, familial hypercholesterolemia, I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, Huntington's disease, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidoluysian, myotonic dystrophy, hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, and Straussler-Scheinker syndrome). In certain embodiments, the disease is cystic fibrosis. For example,

contemplated herein is a method for treating a patient suffering from cystic fibrosis comprising administering to said patient an effective amount of a disclosed compound.

[0009] In some embodiments, disclosed methods described herein can further include administering at least one additional CFTR modulator e.g., administering at least two, three, four or five additional CFTR modulators. In certain embodiments, at least one additional CFTR modulator is a CFTR corrector (e.g., VX-809, VX-661 and VX-983) or potentiator (e.g.,



and a pharmaceutically acceptable salt or steroisomer thereof.

43. A pharmaceutical composition comprising a compound of any one of claims 1 to 42 and a pharmaceutically acceptable excipient.

44. The pharmaceutical composition of claim 43, wherein the composition further comprises at least one additional CFTR modulator.

45. The pharmaceutical composition of claim 44, wherein the composition further comprises two, three, four or more additional CFTR modulators.

46. Use of a compound of any one of claims 1 to 42 in the manufacture of a medicament for enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof.

47. The use of claim 46, wherein the cellular processing of a mutant CFTR is enhanced.

48. The use of claim 47, wherein the mutant CFTR is selected from the group consisting ΔF508, S549N, G542X, G551D, R117H, N1303K, W1282X, R553X, 621+1G>T, 1717-1G>A, 3849+10kbC>T, 2789+5G>A, 3120+1G>A, I507del, R1162X, 1898+1G>A, 3659delC, G85E, D1152H, R560T, R347P, 2184insA, A455E, R334W, Q493X, and 2184delA CFTR.

49. The use of claim 48, wherein ΔF508 CFTR activity is enhanced.

50. The use of any one of claims 46-49, wherein the subject is suffering from a disease associated with decreased CFTR activity.

51. The use of claim 50, wherein the disease is selected from the group consisting of cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, A-β-lipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolyis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, Sjogren's syndrome, familial hypercholesterolemia, I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, Huntington's disease, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidoluysian, myotonic dystrophy, hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, and Straussler-Scheinker syndrome.

52. The use of claim 51, wherein the disease is cystic fibrosis.

53. The use of any one of claims 46-52, wherein the subject is a human patient.

54. The use of any one of claims 46-53, wherein at least one or two additional CFTR modulators is to be further administered.

55. The use of claim 54, wherein one, two, three or four or more additional CFTR modulators are to be administered.

56. The use of any one of claims 54 or 55, wherein at least one CFTR modulator is an additional CFTR corrector or potentiator.

57. The use of claim 56, wherein at least one CFTR corrector or potentiator is independently selected from the group consisting of VX-152, VX-440, VX-770 (ivacaftor), VX-809 (lumacaftor) (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid, VX-661 ((R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropane-1-carboxamide), VX-983, QBW251, GLPG2222, GLPG2851, GLPG2665, GLPG2737, FDL169, GLPG2451, GLPG1837, and genistein.

58. The use of claim 57, wherein the CFTR corrector is selected from the group consisting of VX-809, VX-661,VX-152, VX-440, GLPG2222 and VX-983 and the CFTR potentiator is selected from the group consisting of GLPG2451, GLPG1837, ivacaftor and genistein.

59. Use of a compound of any one of claims 1-42 in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.

60. A compound of any one of claims 1-42 for use in enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity, or for use in treating cystic fibrosis.