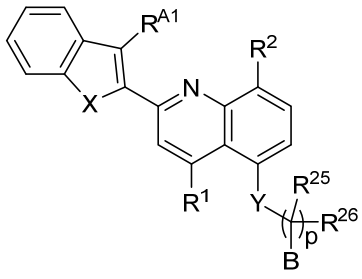
[0006a] In one aspect of the present disclosure, there is provided a compound represented by:



; or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

X is O or S;

R^{A1} is selected from the group consisting of hydrogen and C_{1-6}alkyl;

R^1 is selected from the group consisting of -C(O)OH 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 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;

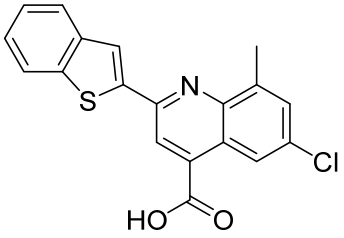
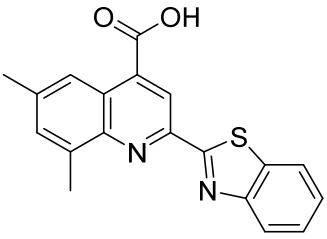
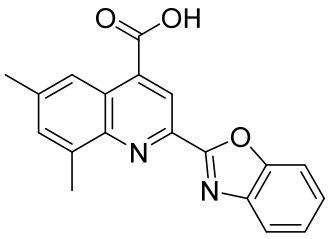
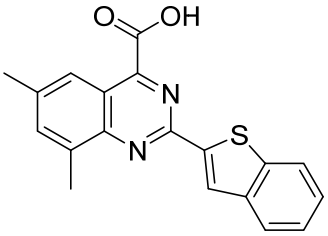
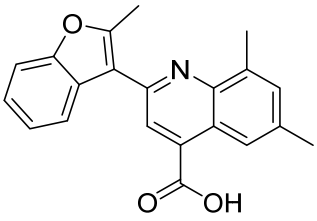
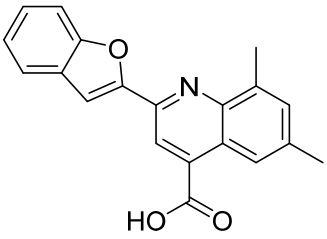
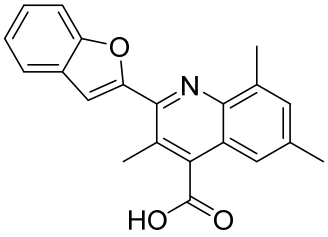
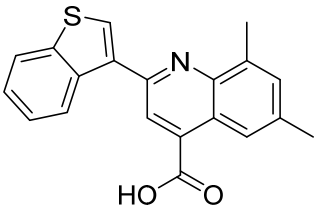
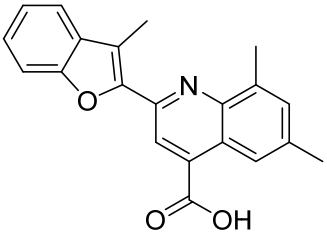
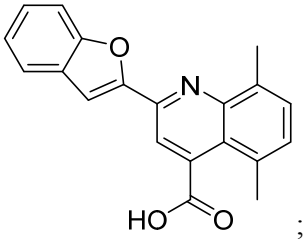
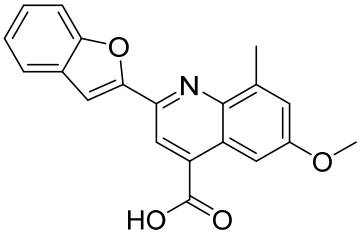
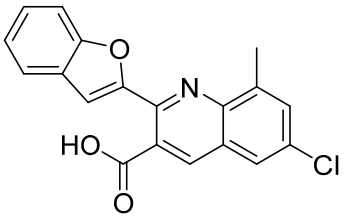
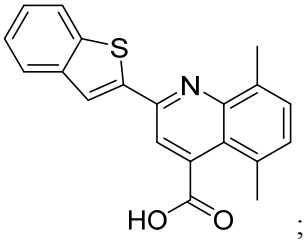
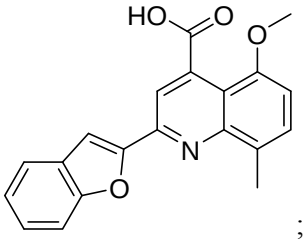
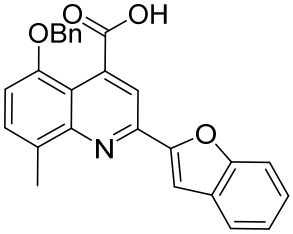
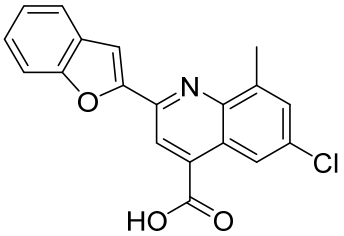
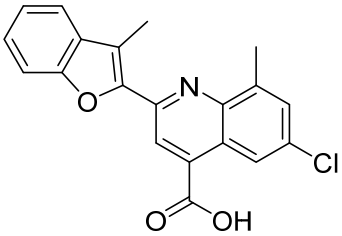
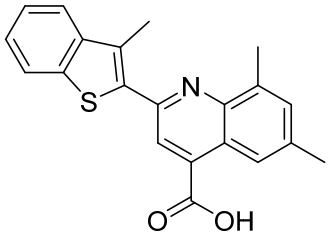
Y is O or $S(O)_w$ (where w is 0, 1 or 2);

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

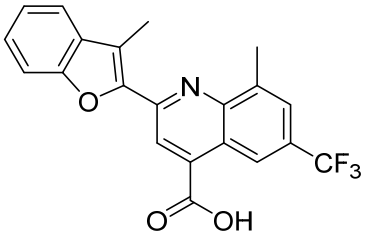
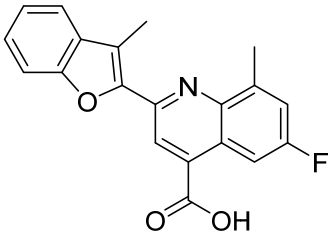
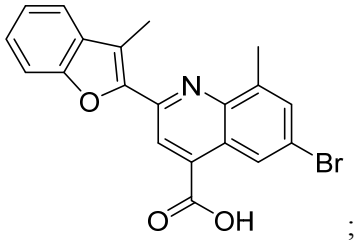
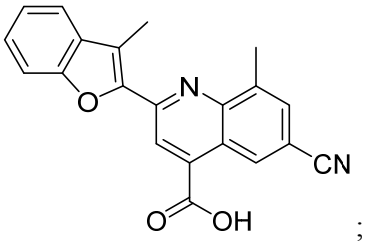
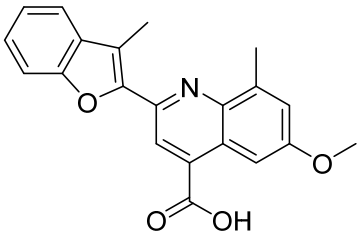
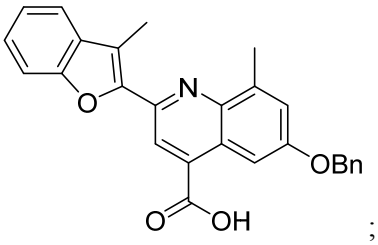
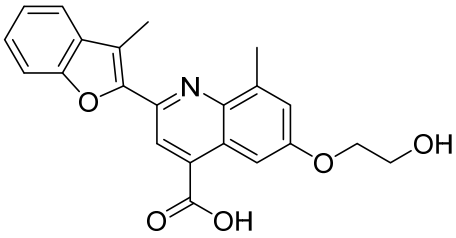
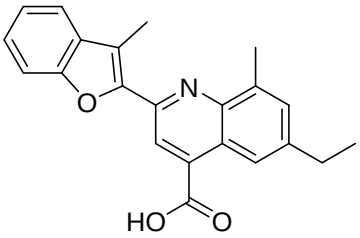
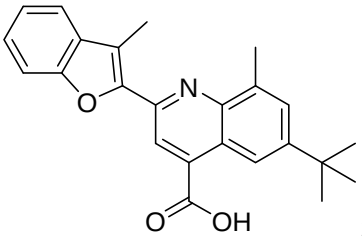
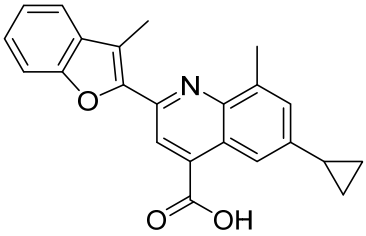
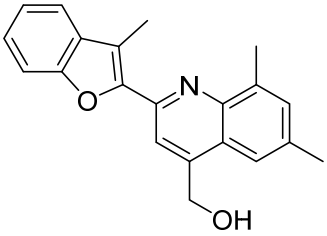
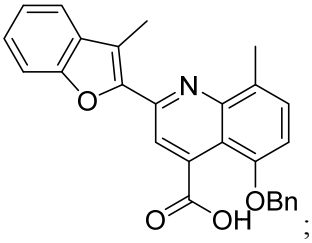
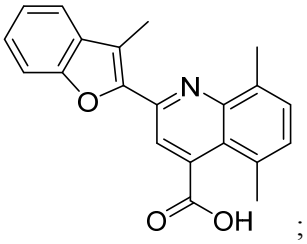
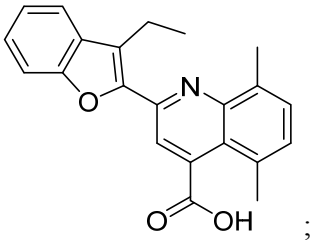
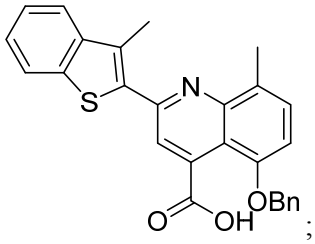
p is 0 or 1; and

B is 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 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 heterocyclic ring may optionally be substituted by one, two, three, or four substituents each independently selected from hydroxyl, C_{1-6}alkyl, C_{1-6}alkoxy, and oxo.

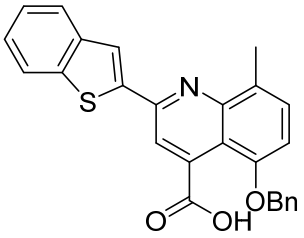
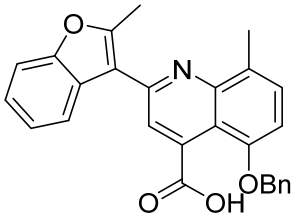
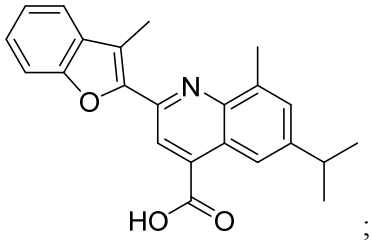
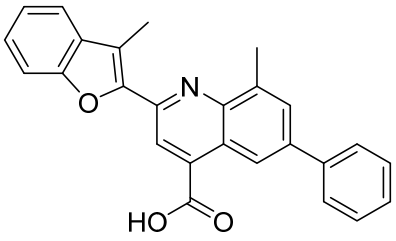
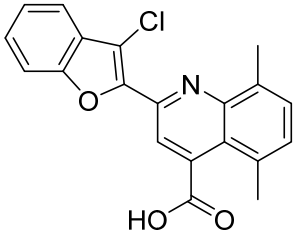
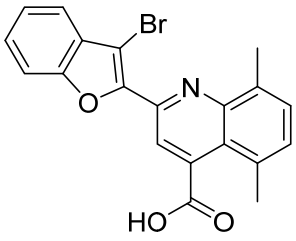
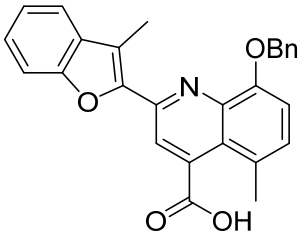
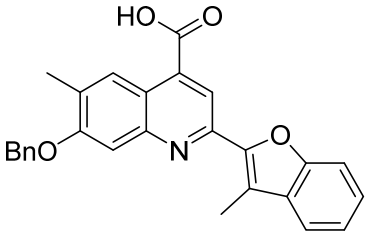
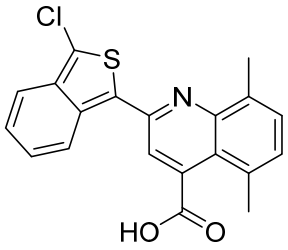
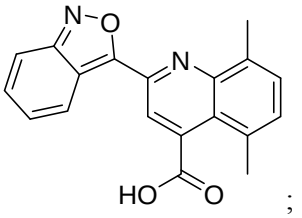
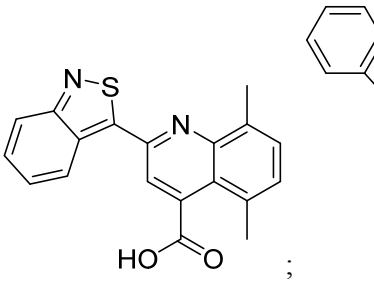
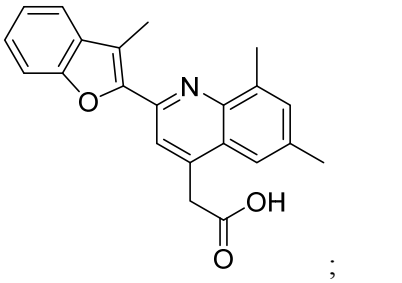
[0006b] In another aspect of the present disclosure, there is provided s compound selected from the group consisting of:

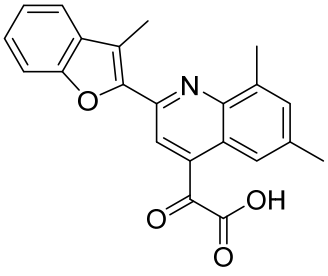
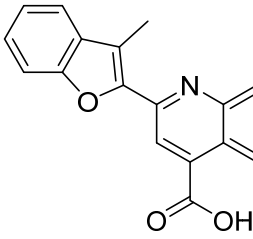
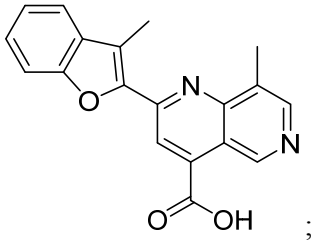

S
N
Cl
HO
O
;

O
OH
N
S
N
;

O
OH
N
O
N
;

O
OH
N
N
S
;

O
N
O
OH
;

O
N
HO
O
;

O
N
HO
O
;

S
N
HO
O
;

O
N
O
OH
;

O
N
HO
O
;

O
N
O
HO
O
;

O
N
HO
Cl
O
;

S
N
HO
O
;

HO
O
O
N
O
;

O
OH
OBn
N
O
;

O
N
Cl
HO
O
;

O
N
Cl
O
OH
;

S
N
O
OH
;

2c


N
O
CF3
O
OH
;

N
O
F
O
OH
;

N
O
Br
O
OH
;

N
O
CN
O
OH
;

N
O
O
O
OH
;

N
O
OBn
O
OH
;

N
O
O
OH
O
OH
;

N
O
HO
O
;

N
O
O
OH
;

N
O
O
OH
;

N
O
OH
;

N
O
OBn
O
OH
;

N
O
O
OH
;

N
O
O
OH
;

N
S
OBn
O
OH
;

2d


;

;

;

;

;


;

;

;

;

;

;

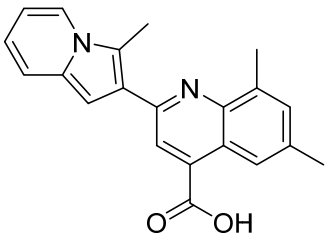
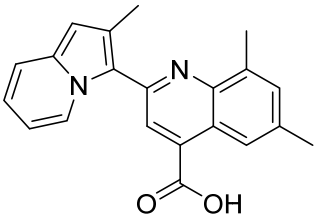
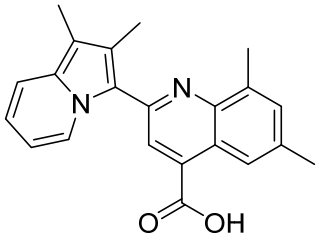
;

;

;

;

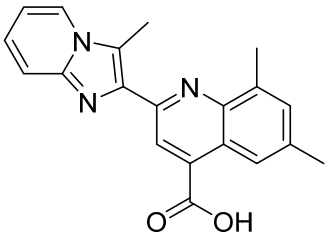
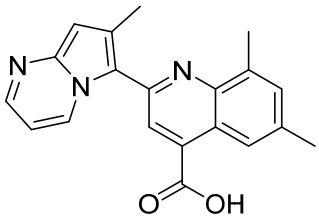
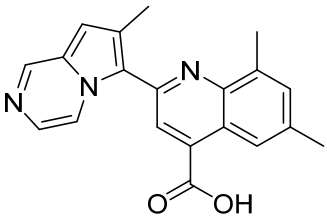
;

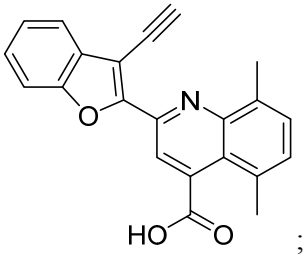
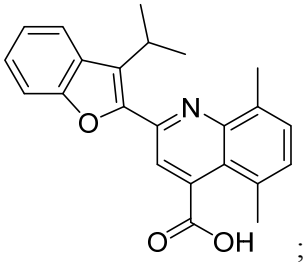
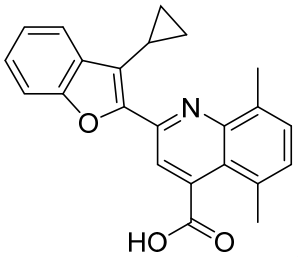
;

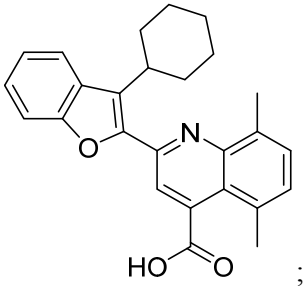
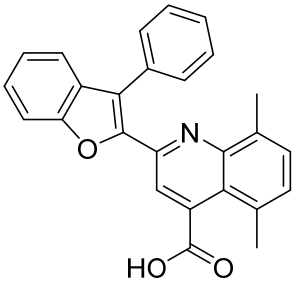
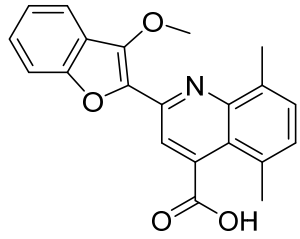
;

2e

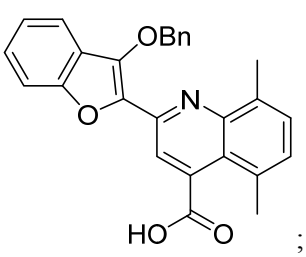
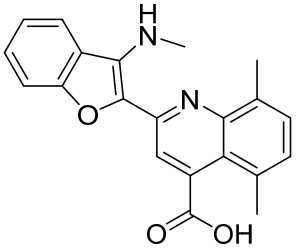
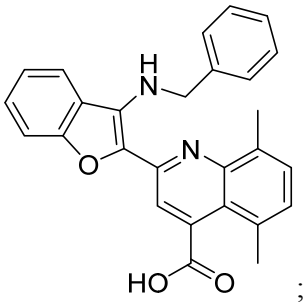
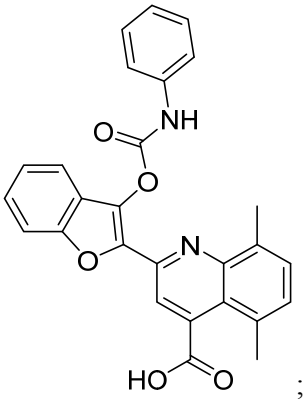
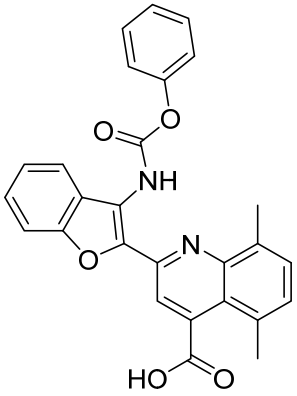
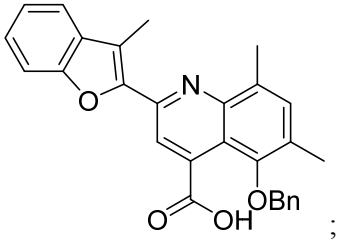
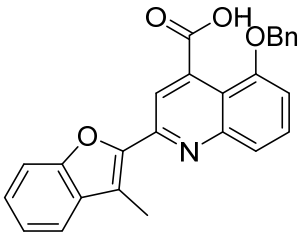
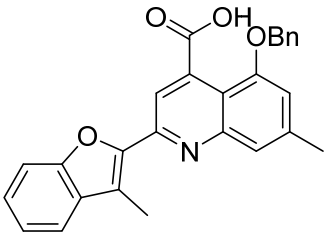
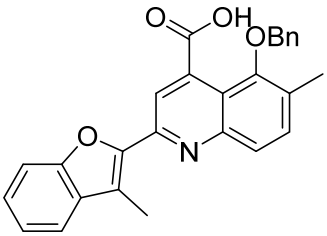

;

;

;


;

;

;

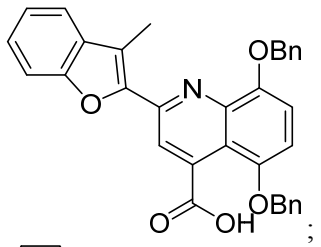
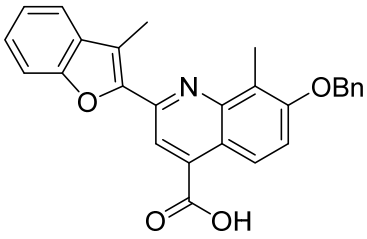
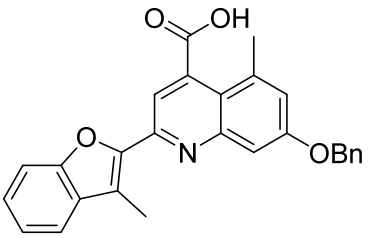
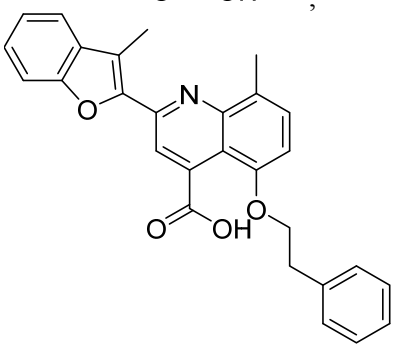
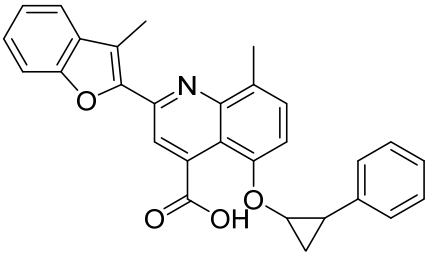
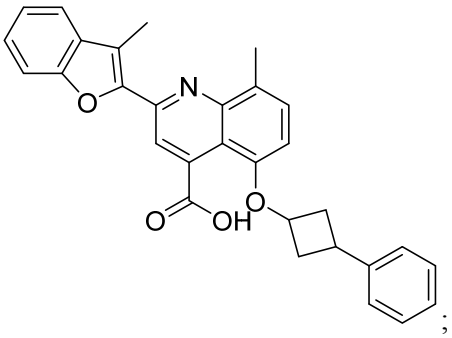
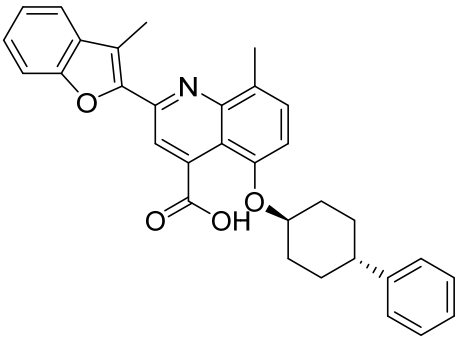
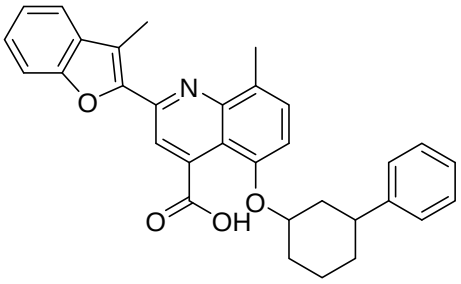
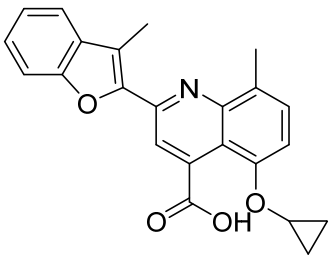
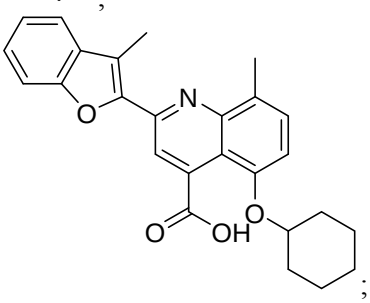
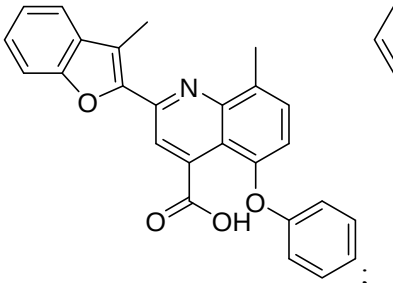
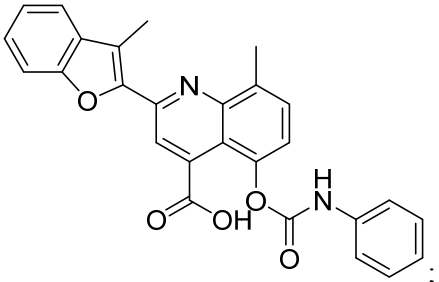

;

;

;


;

;

;

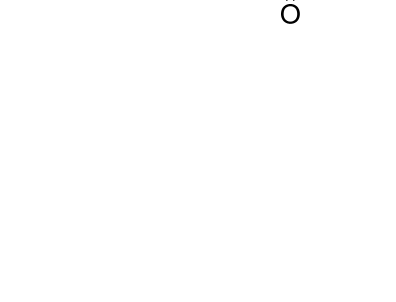
2f


OBn
N
O
HO
O
;

H
N
N
O
O
OH
;

H
N
N
O
HO
O
;

NH
O
O
N
O
HO
O
;

O
O
NH
N
O
HO
O
;

N
O
OBn
O
OH
;

O
OH
OBn
O
N
;

O
OH
OBn
O
N
;

O
OH
OBn
O
N
;

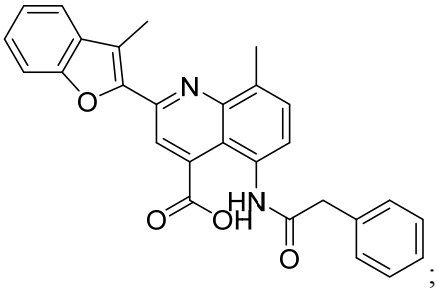
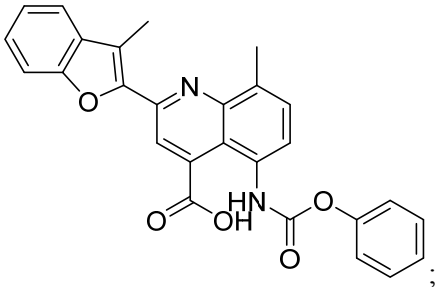
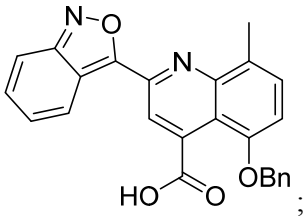
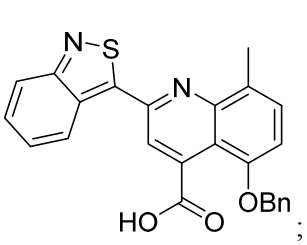
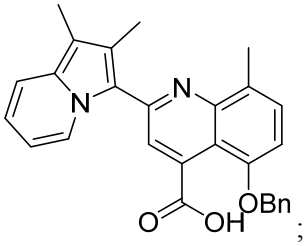
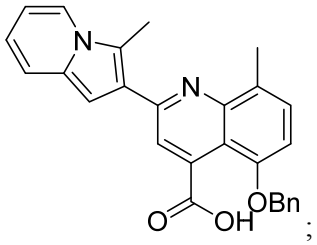
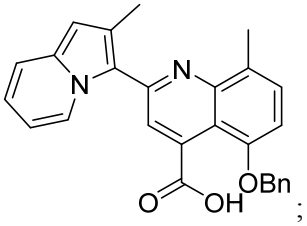
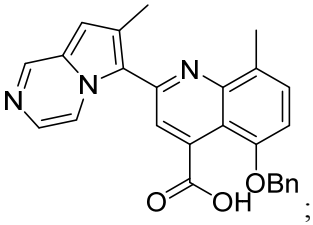
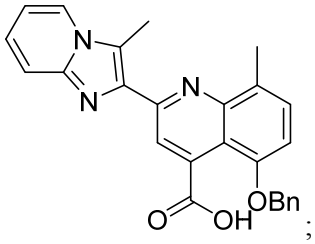
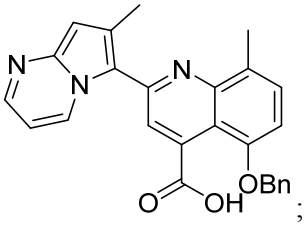
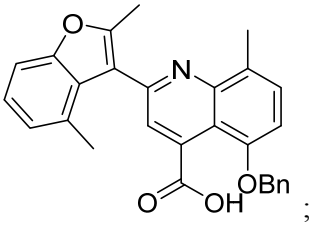
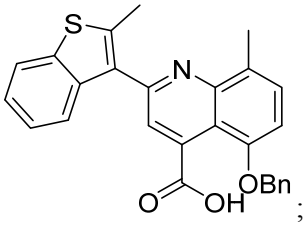
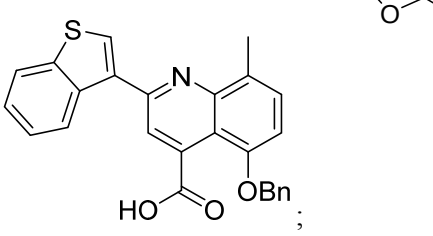
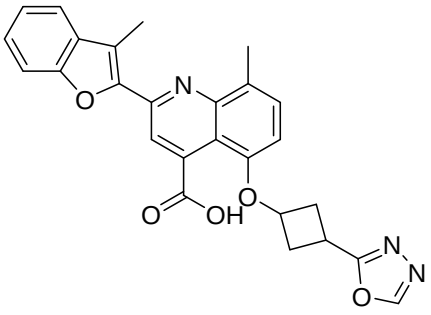
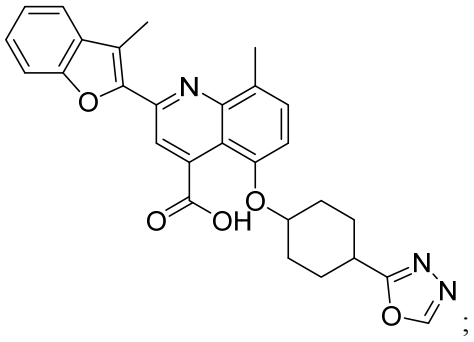
2g


OBn
N
O
OBn
O
OH
;

OBn
N
O
O
OH
;

O
OH
N
O
OBn
;

N
O
O
OH
O
;

N
O
O
OH
O
;

N
O
O
OH
O
;

N
O
O
OH
O
;

N
O
O
OH
O
;

N
O
O
OH
;

N
O
O
OH
O
;

N
O
O
OH
O
;

N
O
O
OH
O
;

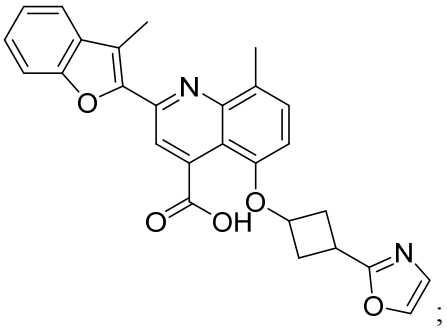
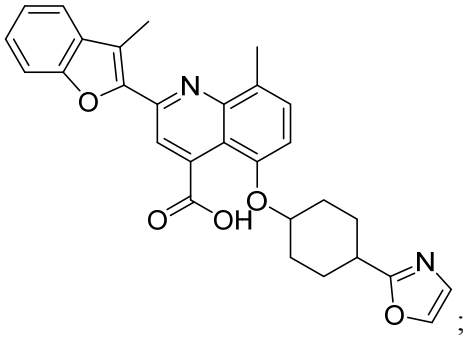
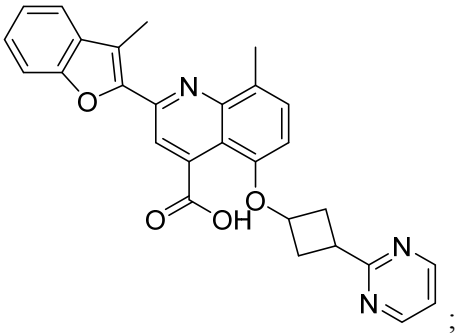
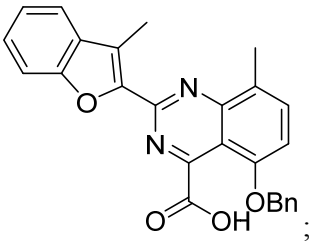
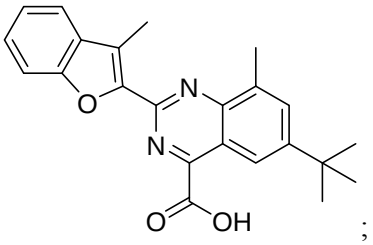
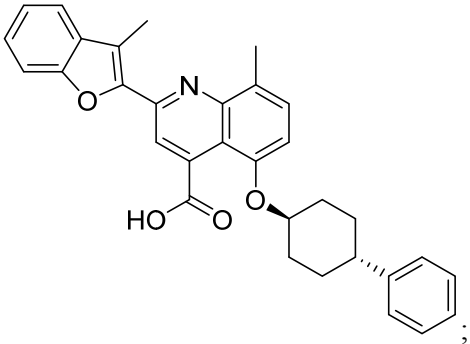
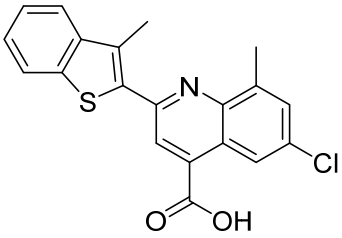
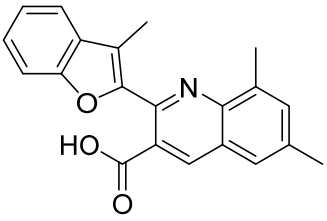
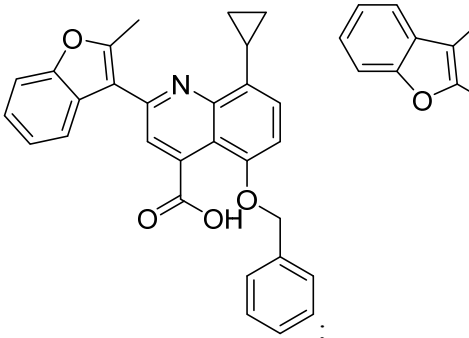
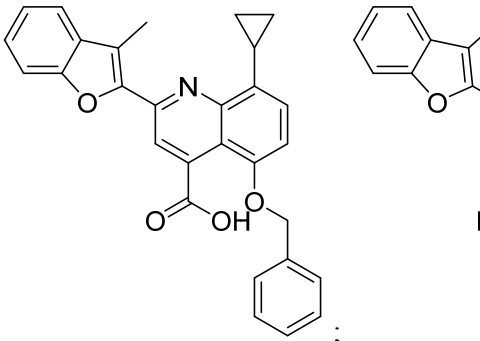
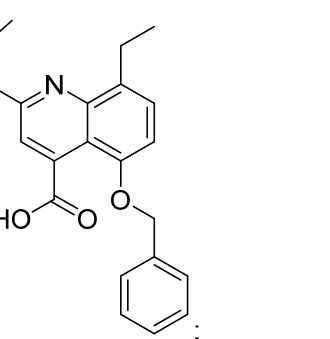
N
O
O
OH
O
;

N
O
O
OH
O
H
N
O
;

N
O
HN
OH
O
;

2h


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

2i

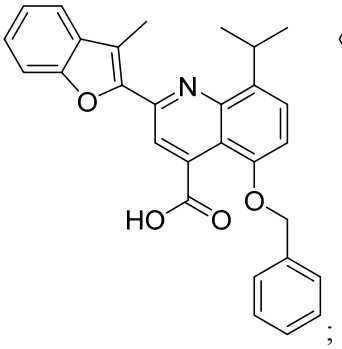
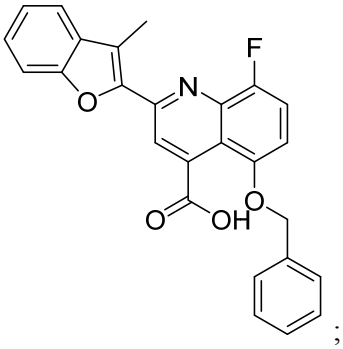
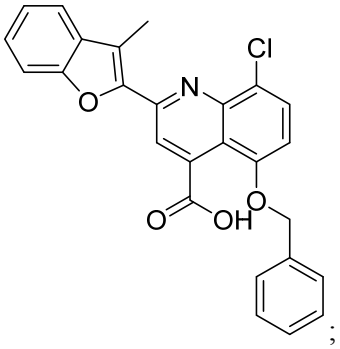
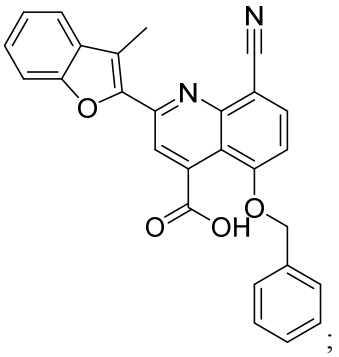
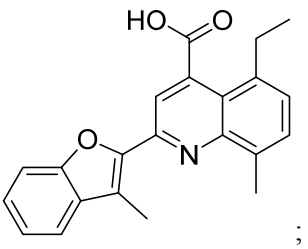
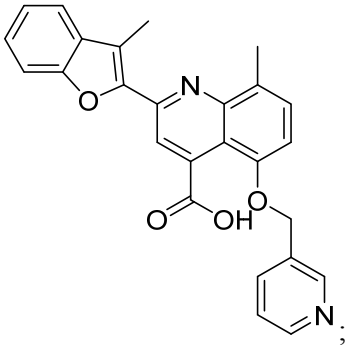
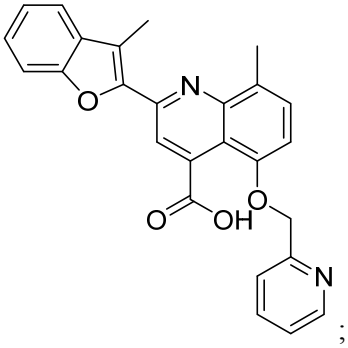
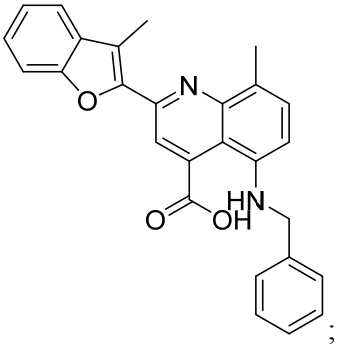
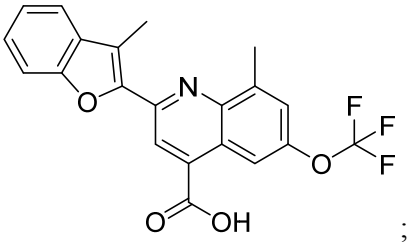
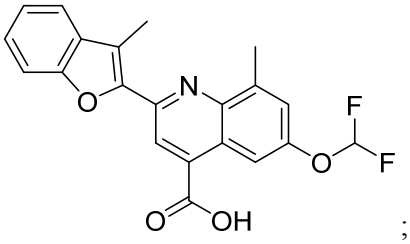
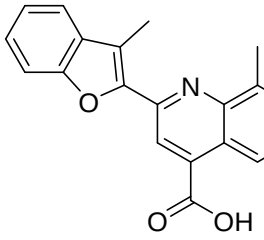
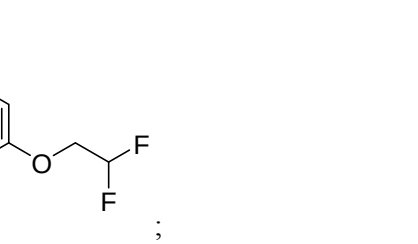

;

;

;

;

;

;

;

;

;

;

;

;

;

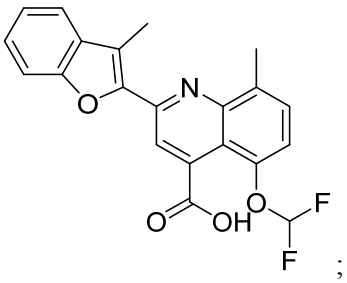
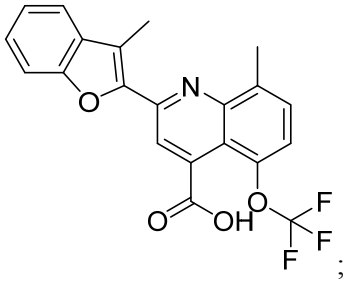
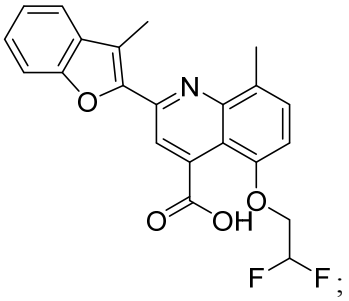
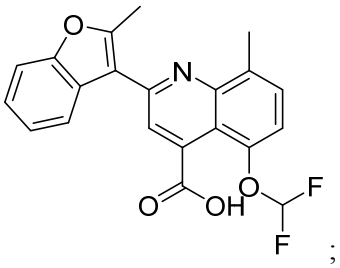
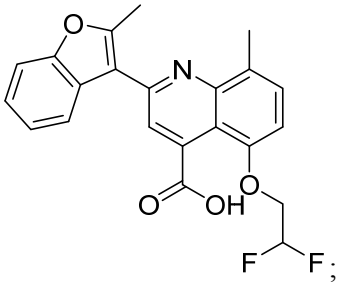
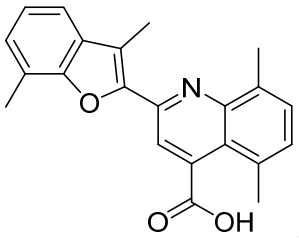
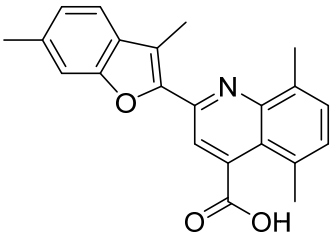
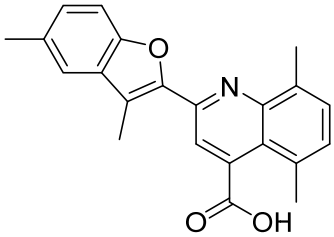
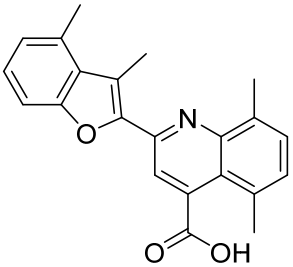
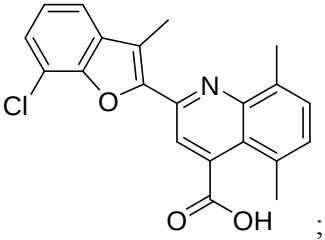
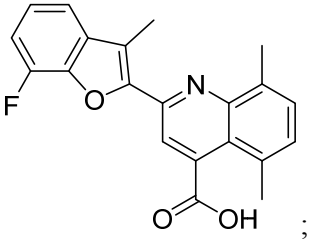
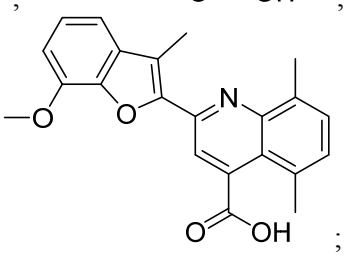
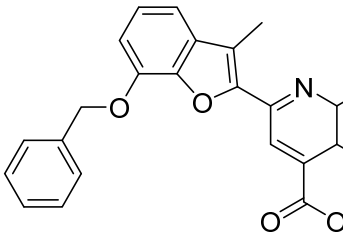
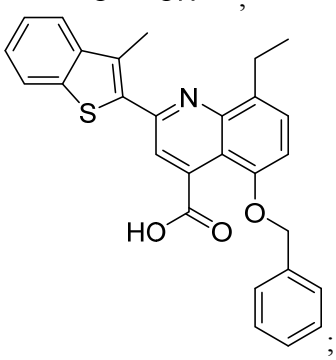
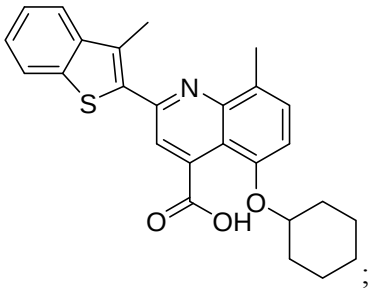
;

2j


;

;

;

;

;

;

;

;

;

;

;

;

;

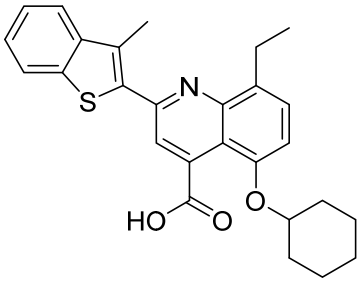
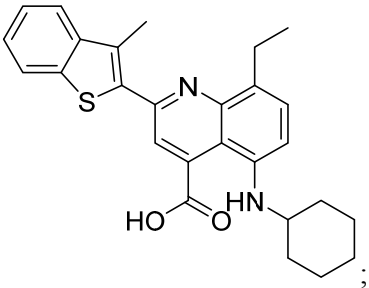
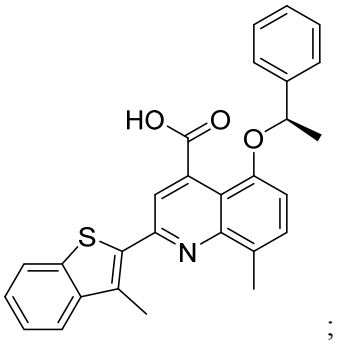
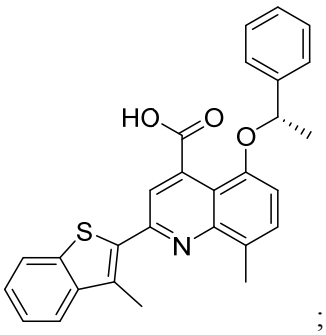
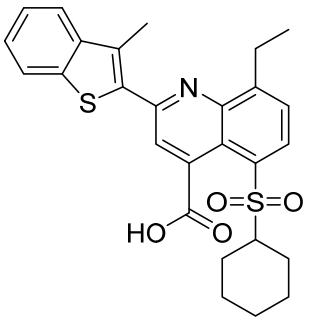
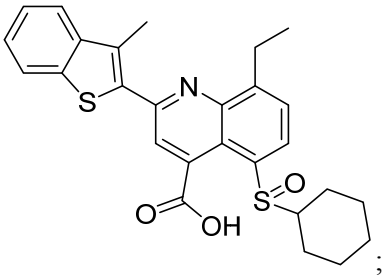
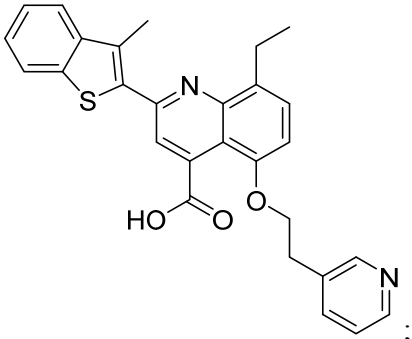
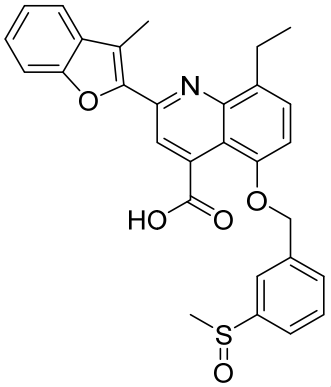
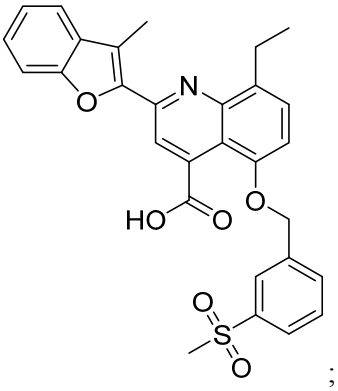
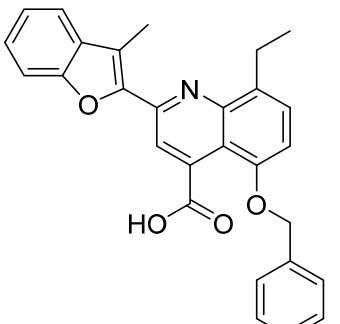
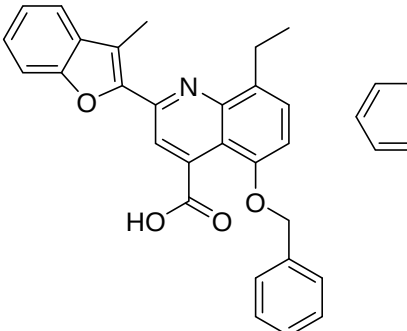
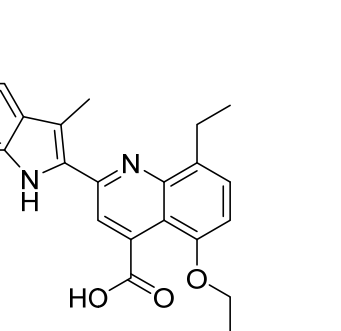
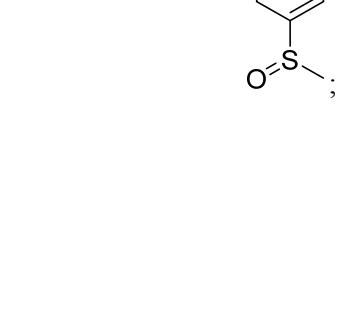
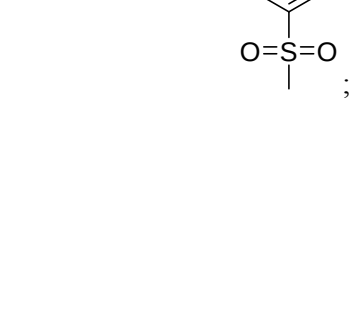
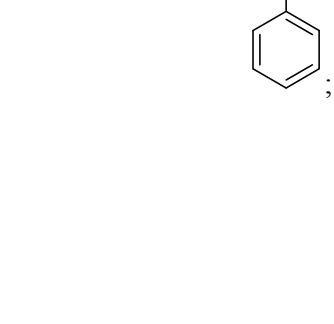
;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

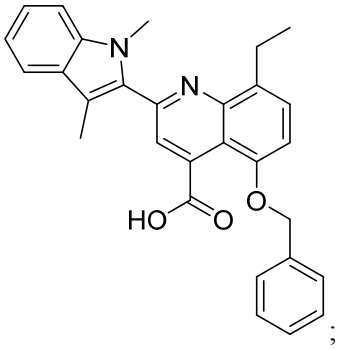
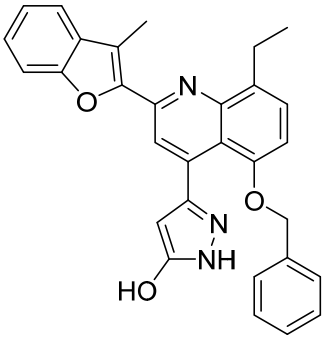
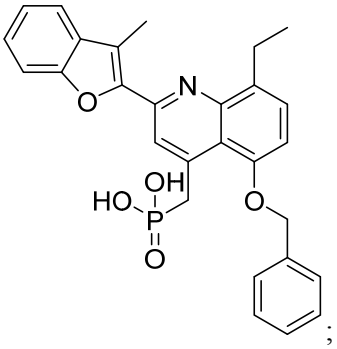
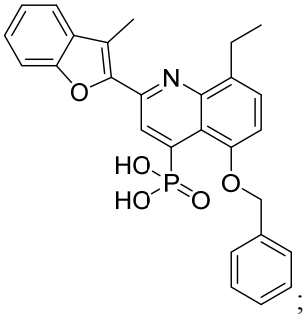
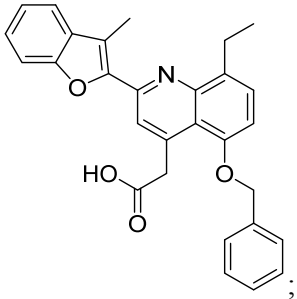
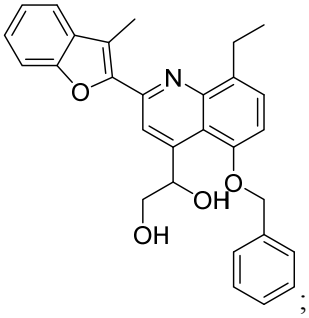
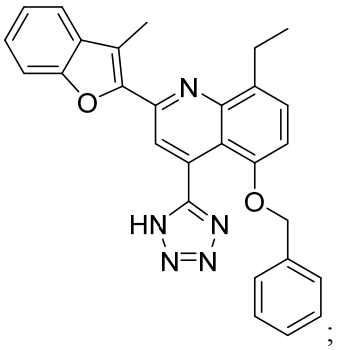
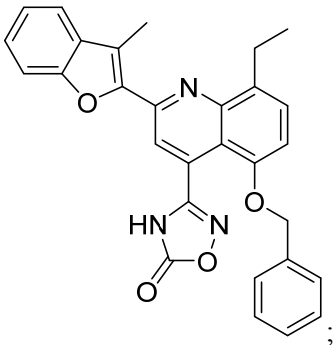
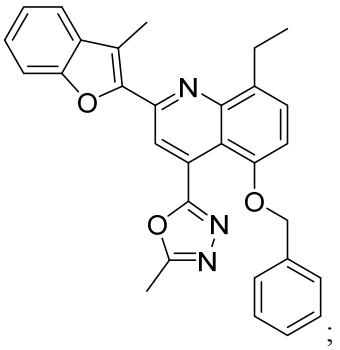
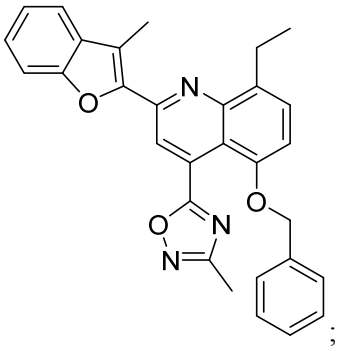
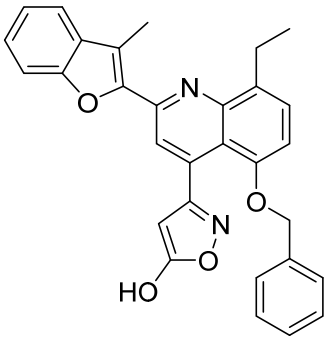
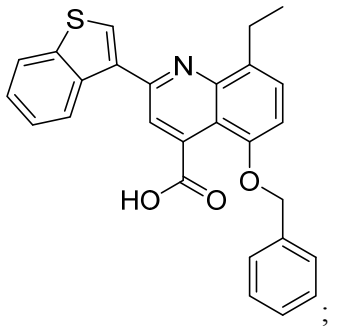
;

;

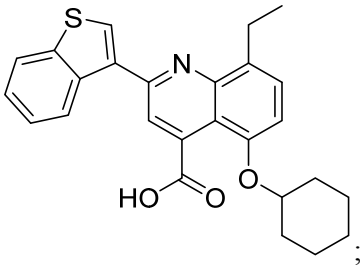
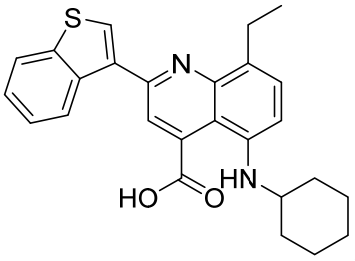
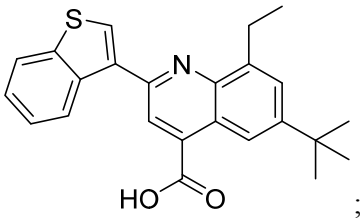
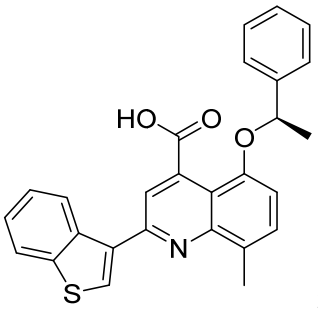
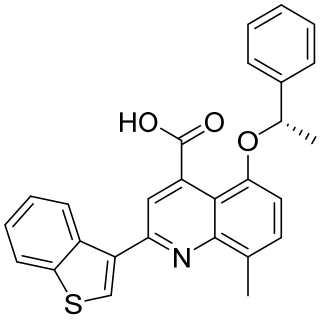
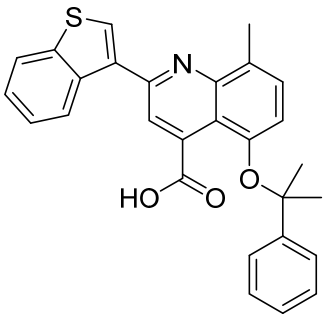
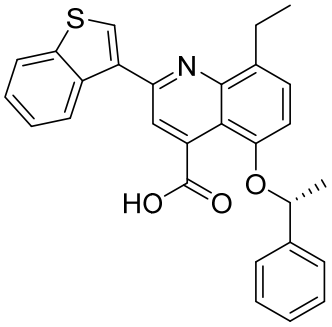
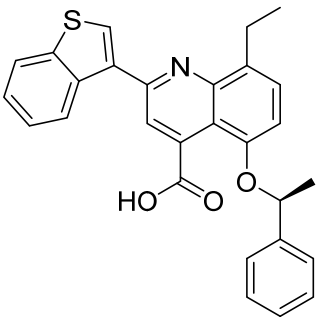
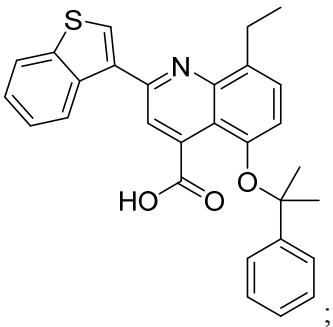
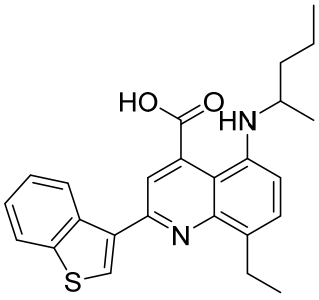
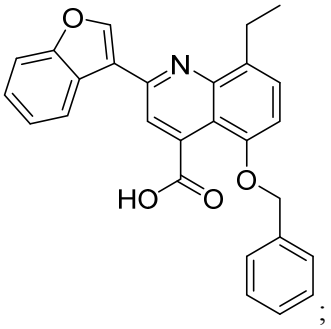
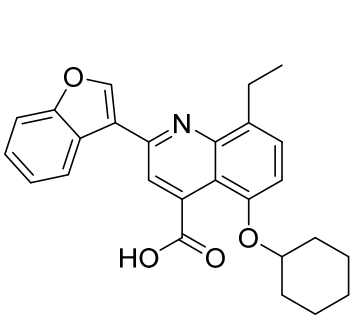
;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

2m


;

;

;

;

;

;

;

;

;

;

;

;

2n


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

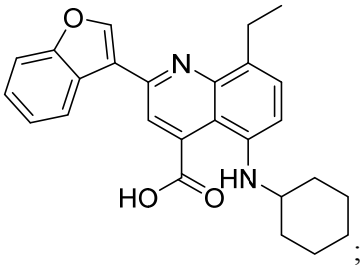
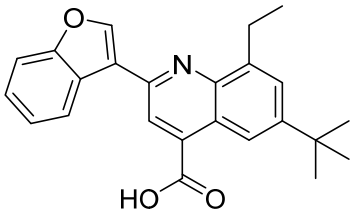
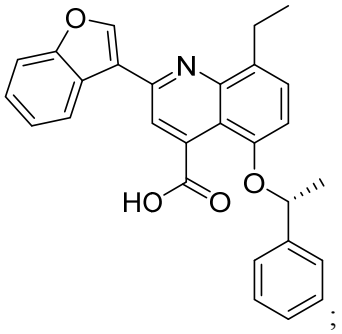
;

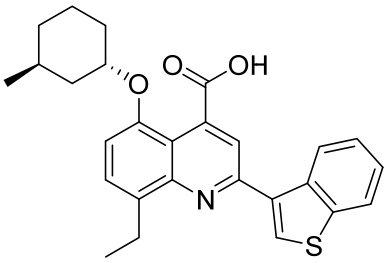
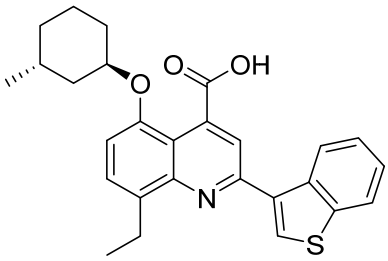
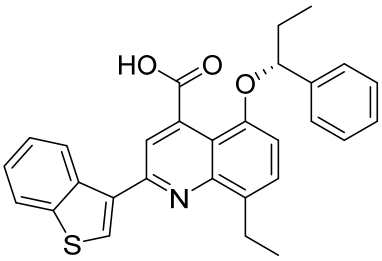
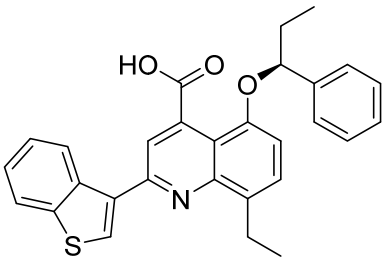
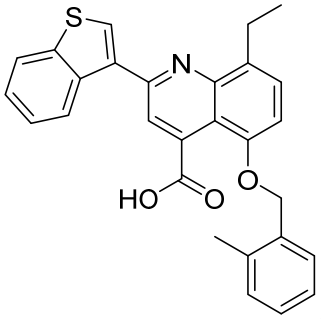
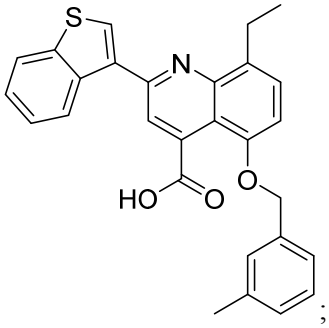
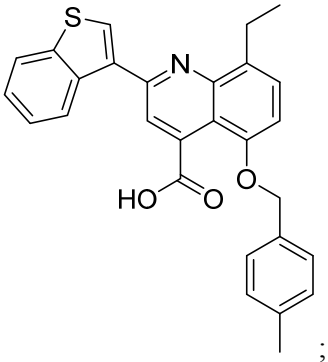
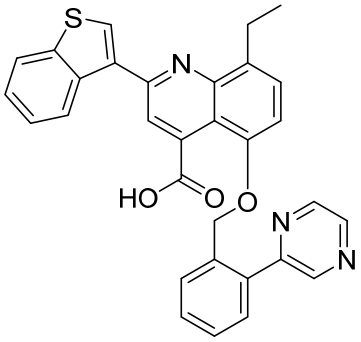
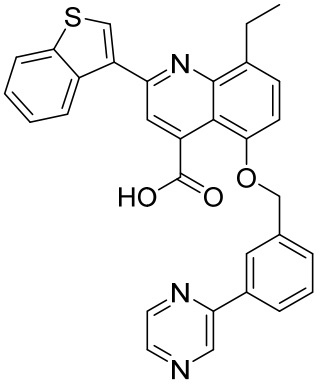
;

;

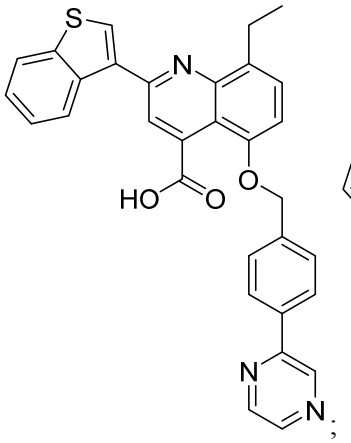
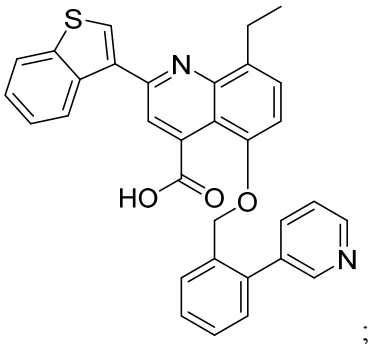
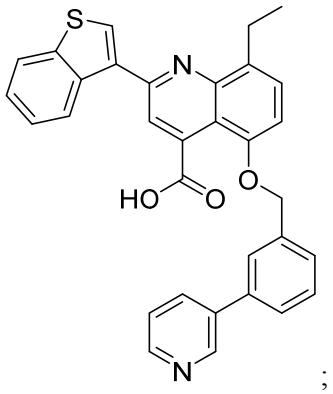
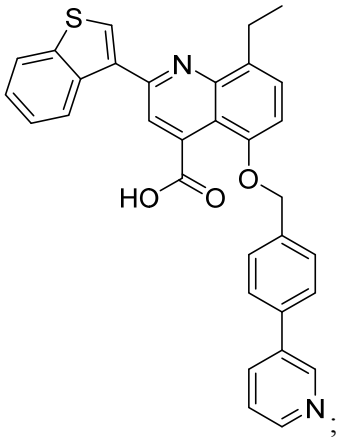
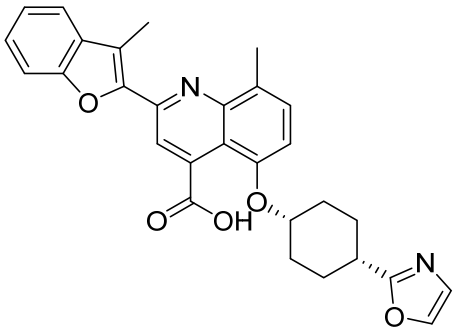
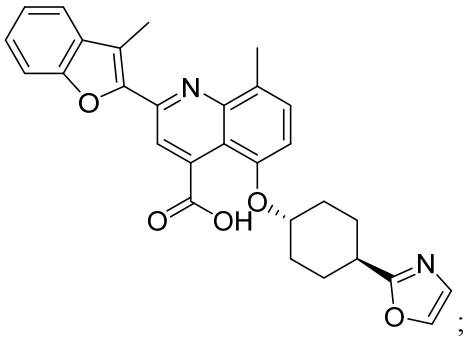
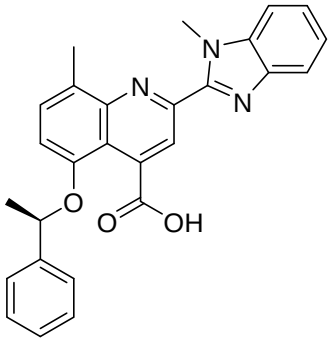
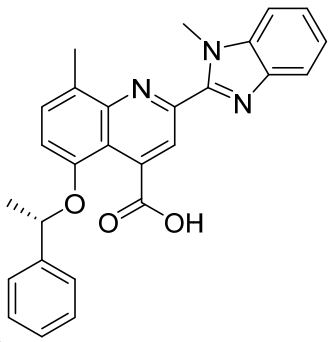
;

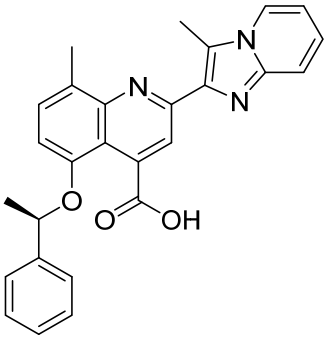
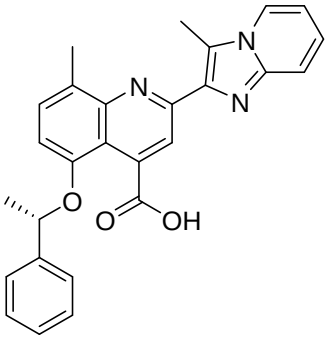
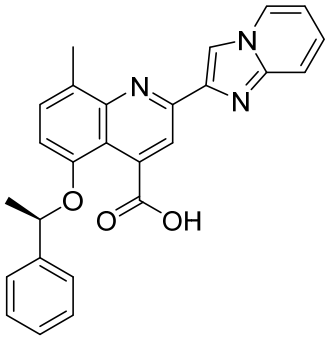
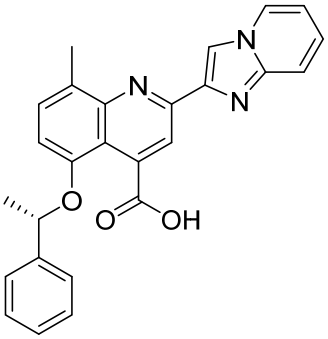
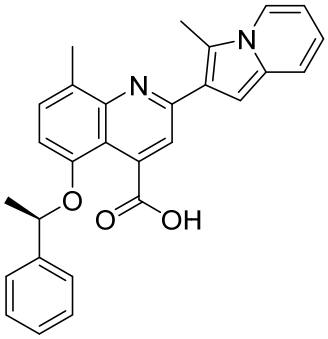
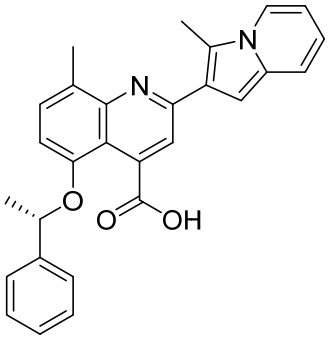
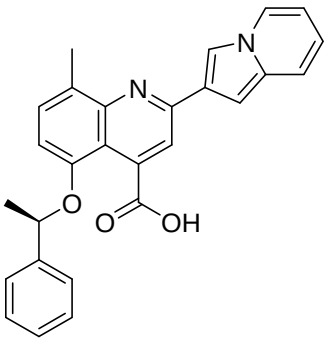
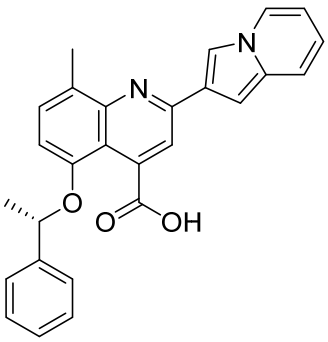
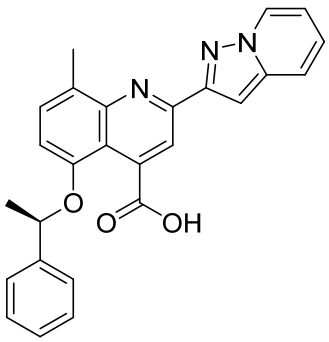
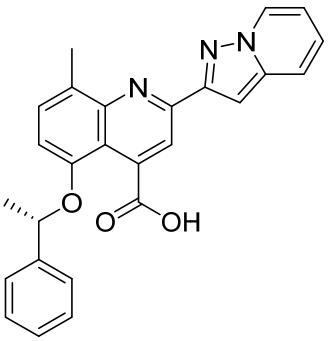
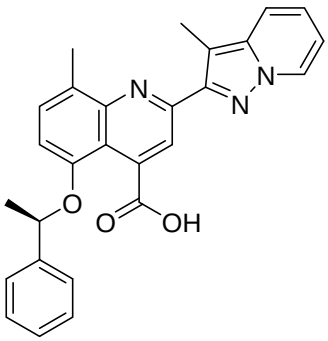
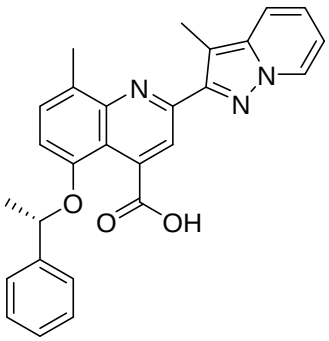
;

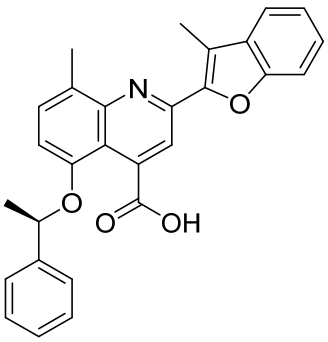
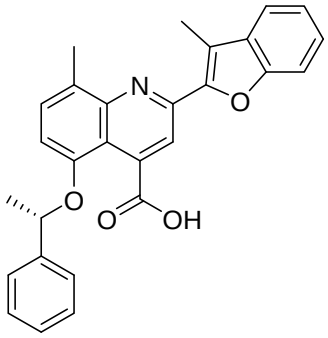
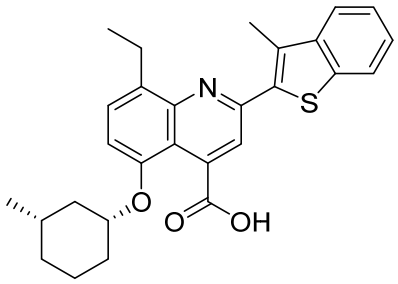
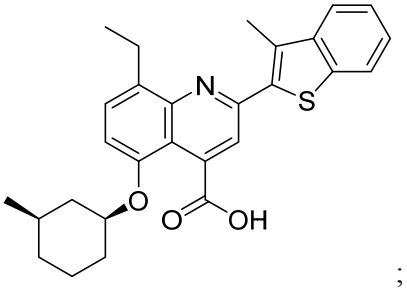
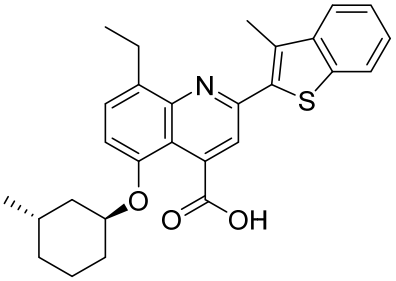
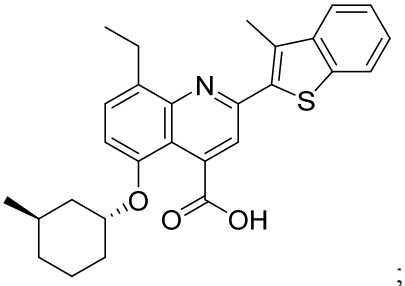
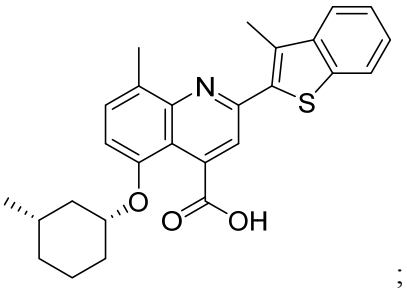
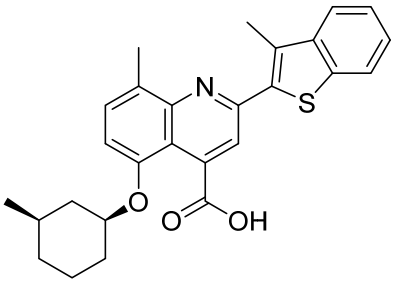
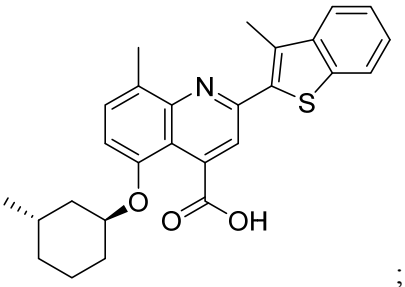
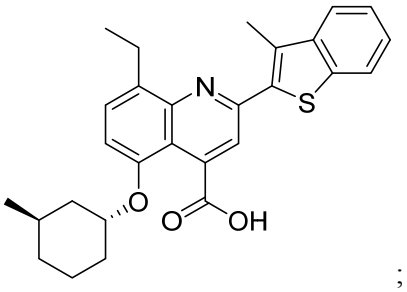
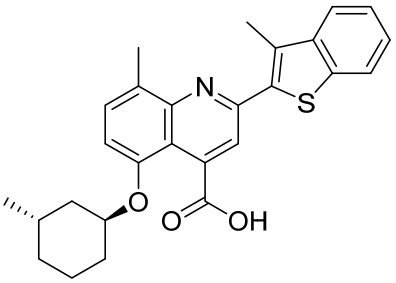
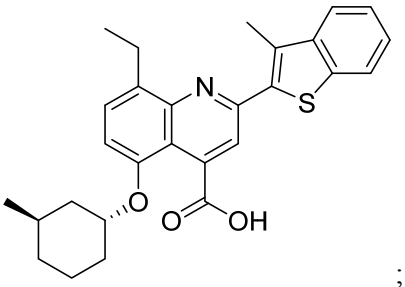

;

;

;

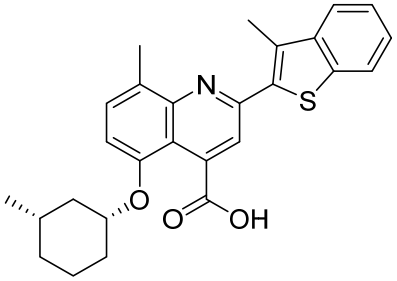
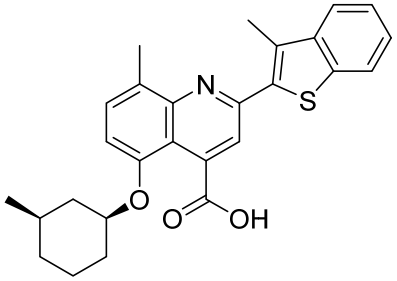
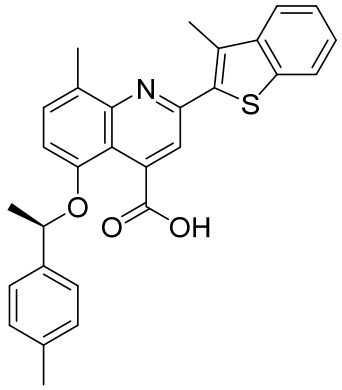
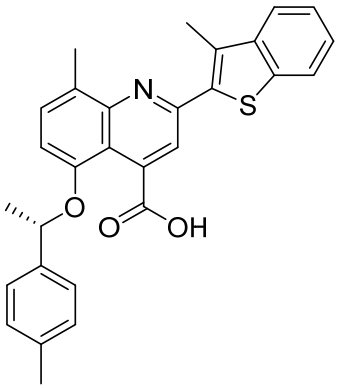
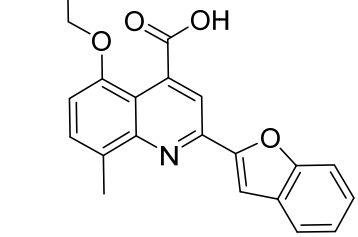
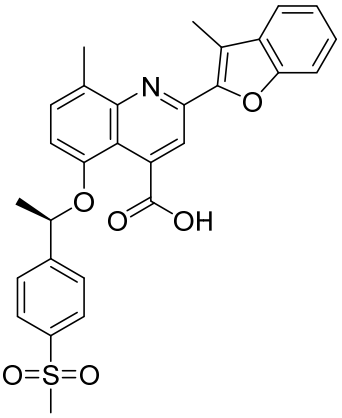
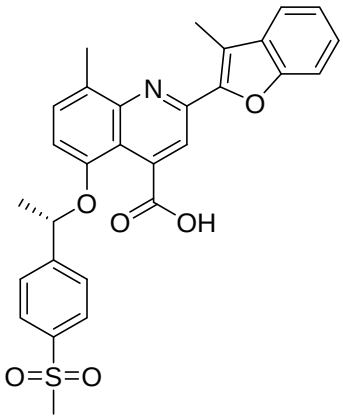
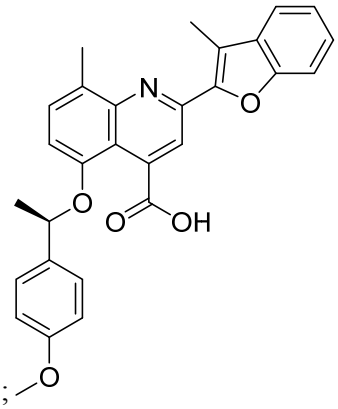
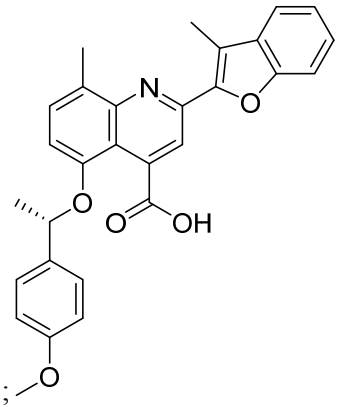

O
OH
O
N
S
;

O
OH
O
N
S
;

HO
O
O
N
S
;

HO
O
O
N
S
;

S
N
HO
O
O
;

S
N
HO
O
O
;

S
N
HO
O
O
;

S
N
HO
O
O
N
N
;

S
N
HO
O
O
N
N
;

2q

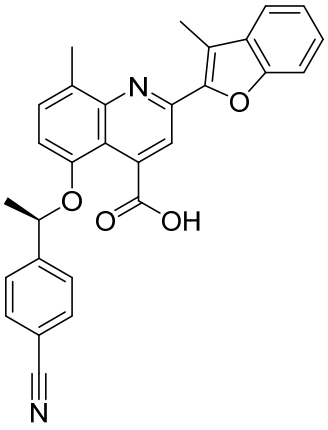
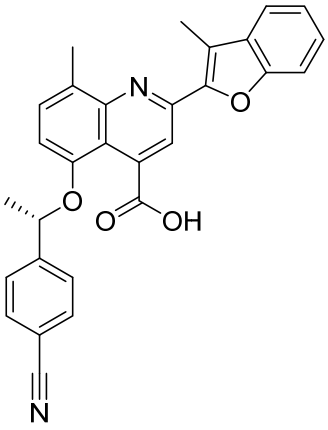
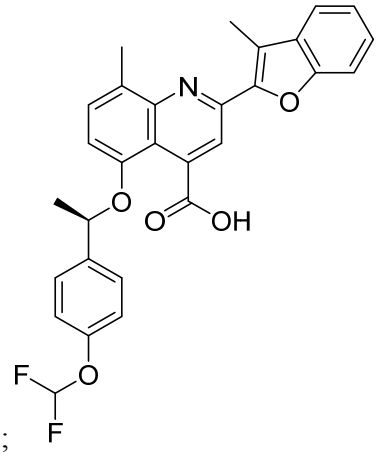
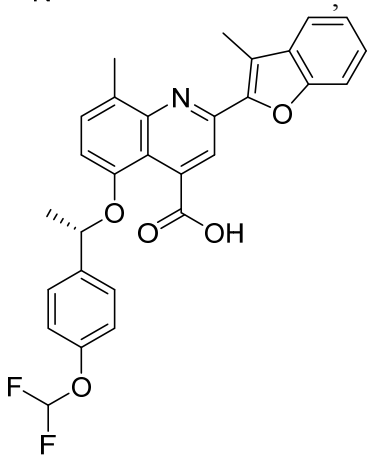
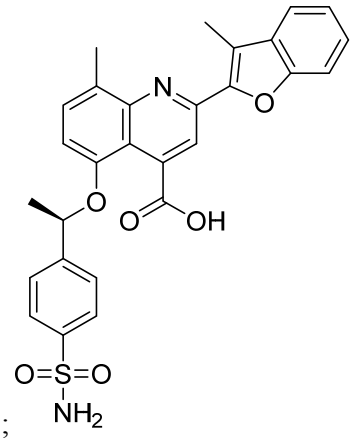
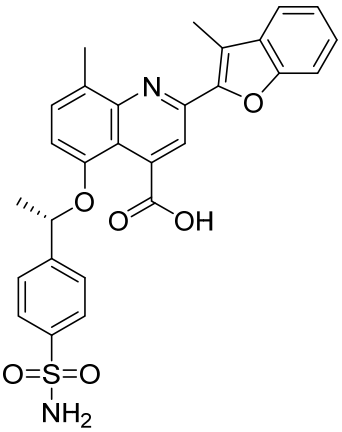
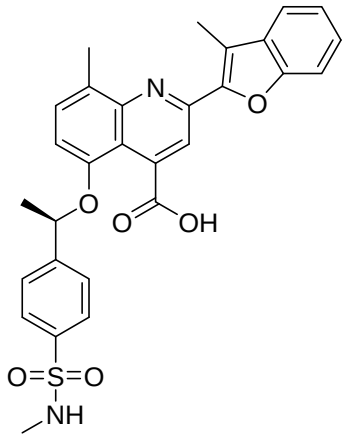
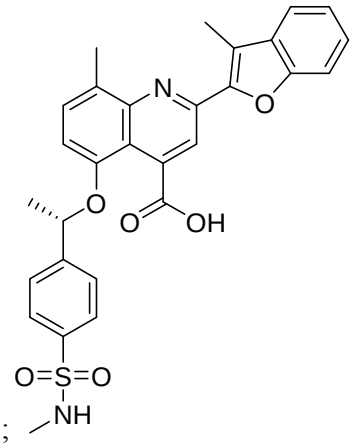
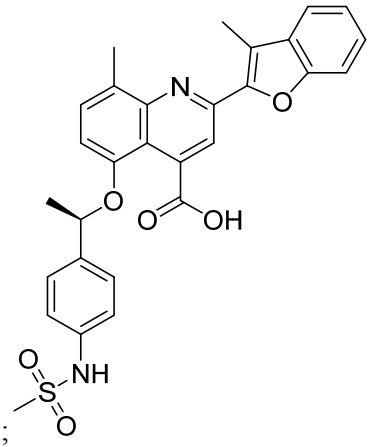

;

;

;

;

;

;

;

;

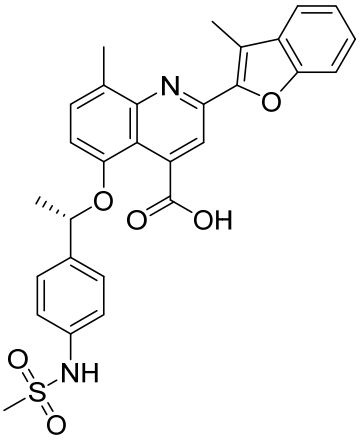
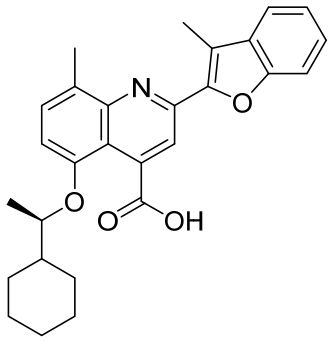
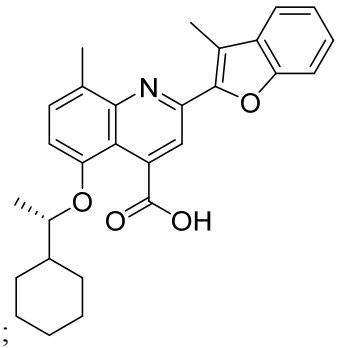
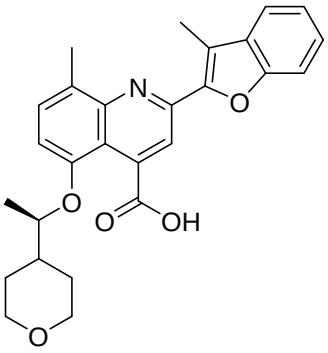
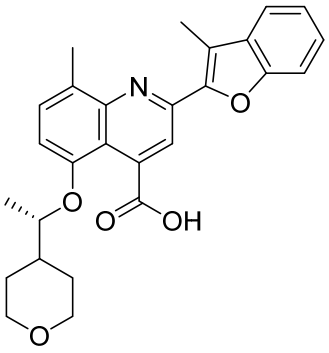
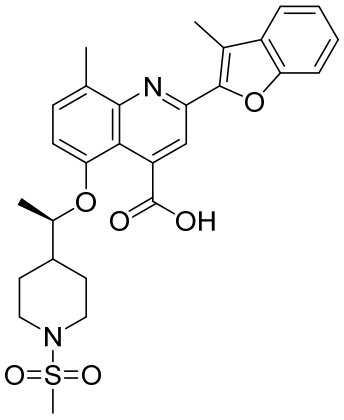
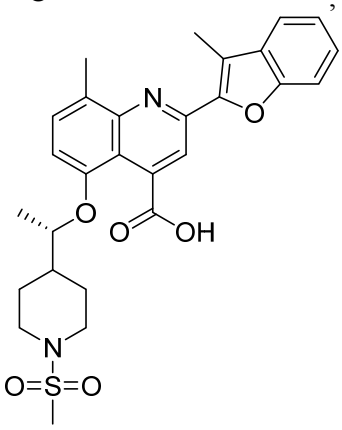
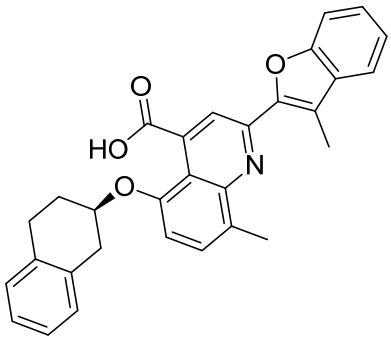
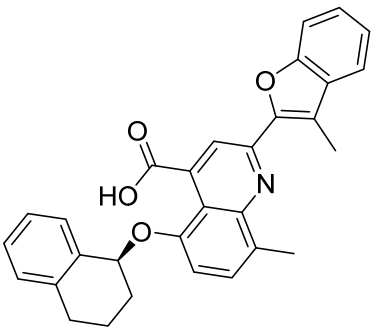

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

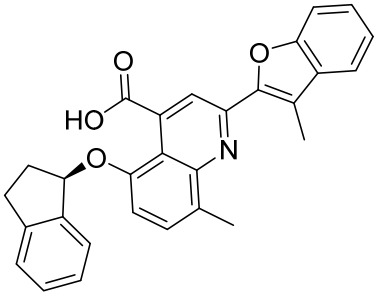
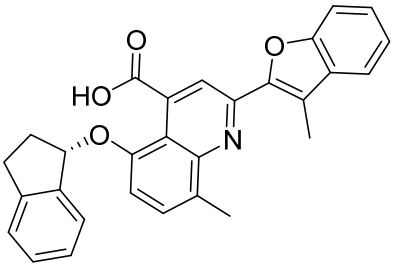
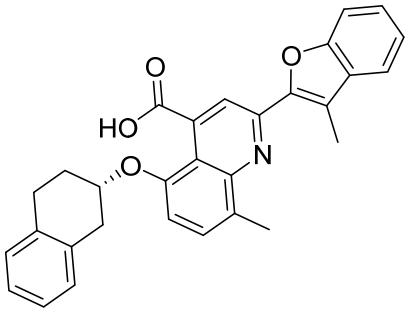
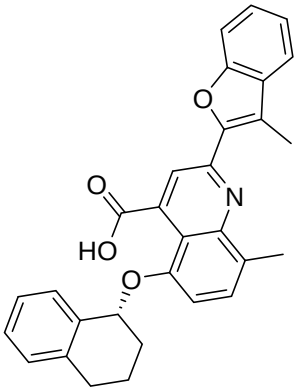
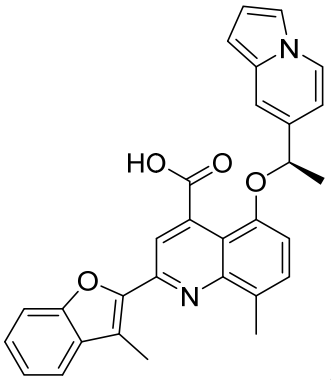
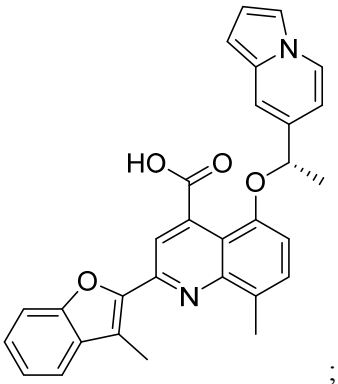
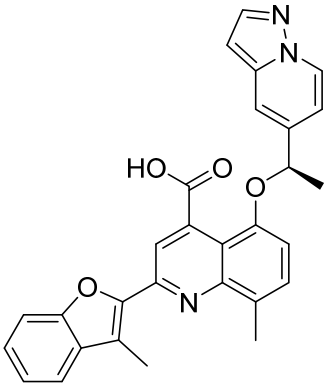
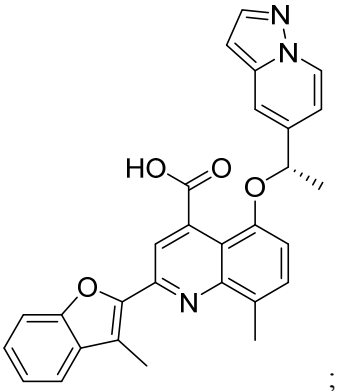
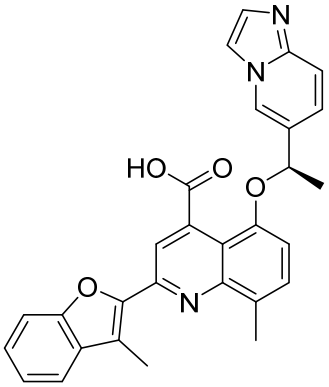

N
S
O
O
OH
;

N
S
O
O
OH
;

N
S
O
O
OH
;

N
S
O
O
OH
;

HO
O
OH
O
N
O
;

N
O
O
O
OH
O=S=O
;

N
O
O
O
OH
O=S=O
;

N
O
O
O
OH
O
;

N
O
O
O
OH
O
;

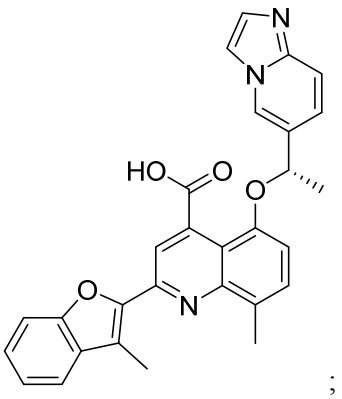
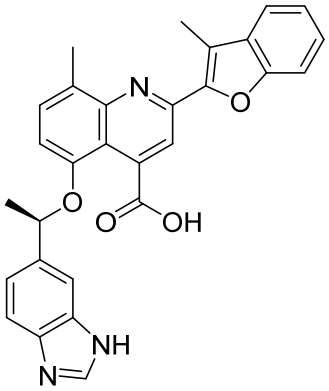
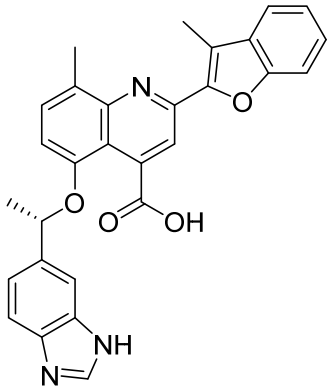
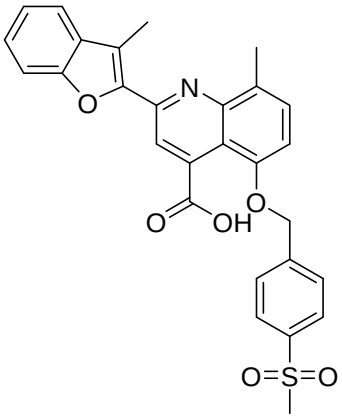
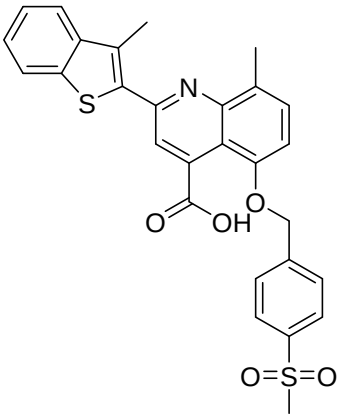
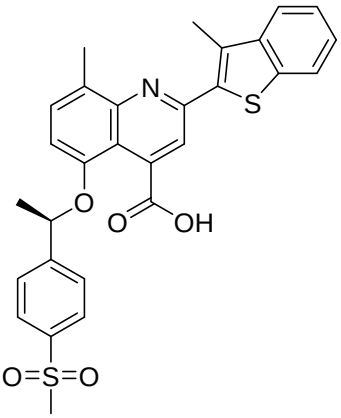
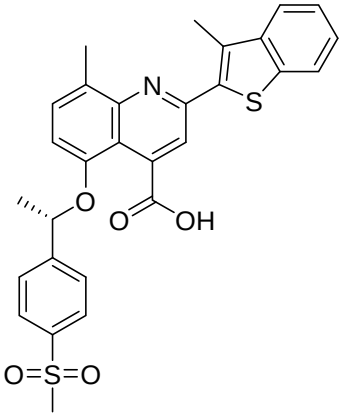
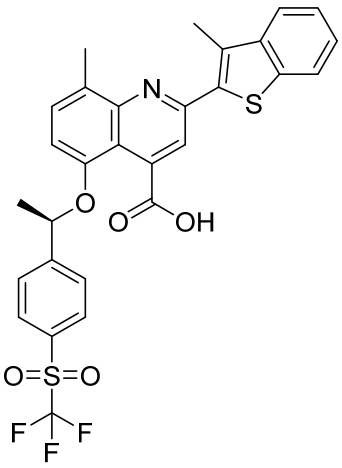
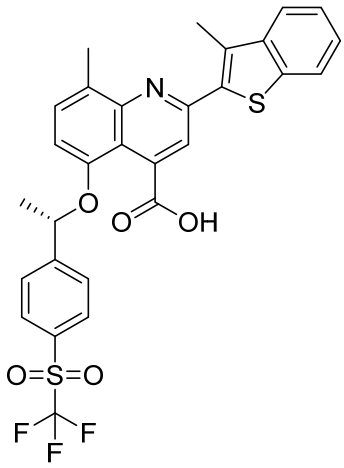
2u


;

;

;

;

;

;

;

;

;

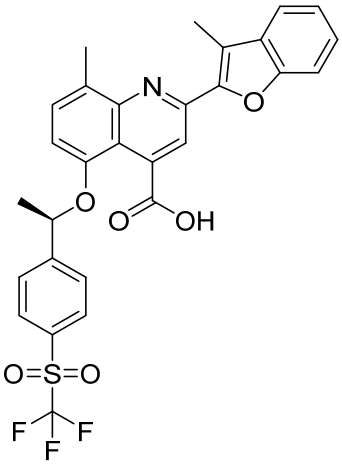
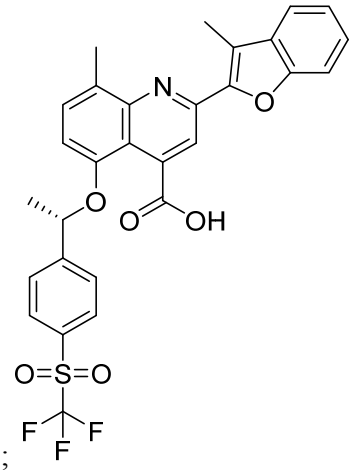
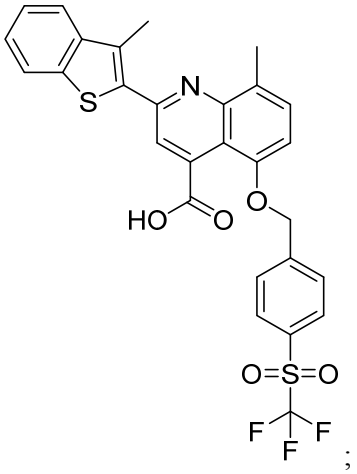
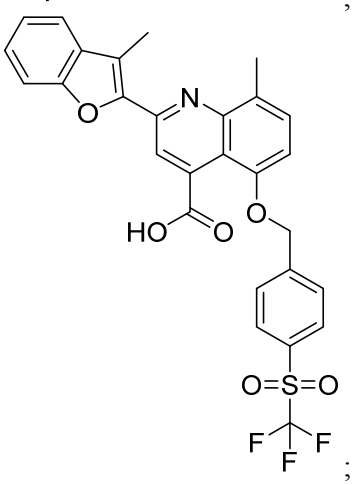
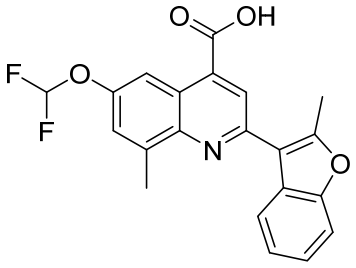
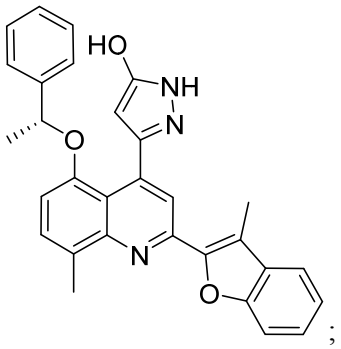
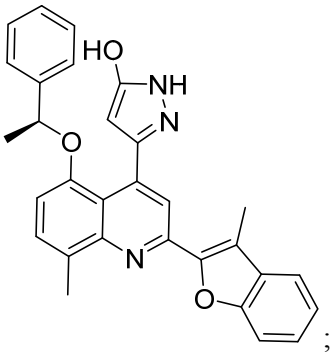
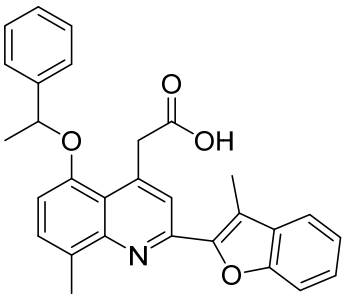
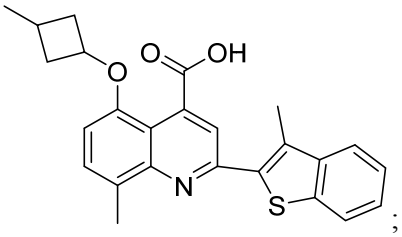

N
O
O
OH
O
NH
S
O
O
;

N
O
O
OH
O
;

N
O
O
OH
O
;

N
O
O
OH
O
O
;

N
O
O
OH
O
O
;

N
O
O
OH
O
N
O=S=O
;

N
O
O
OH
O
N
O=S=O
;

O
HO
O
N
O
;

O
HO
O
N
O
;

2w

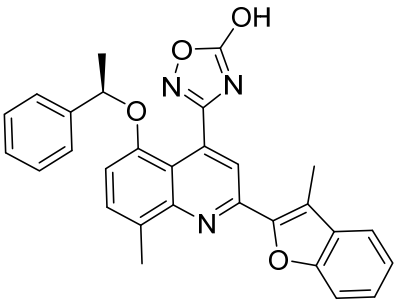
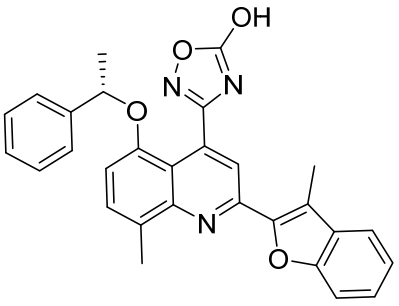
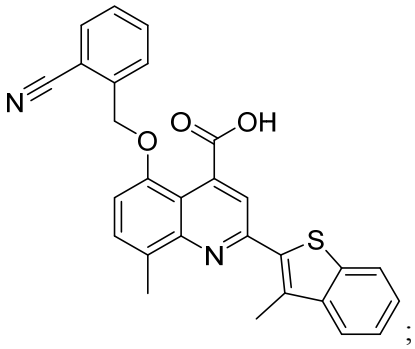
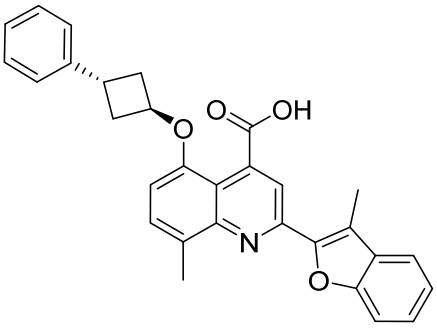
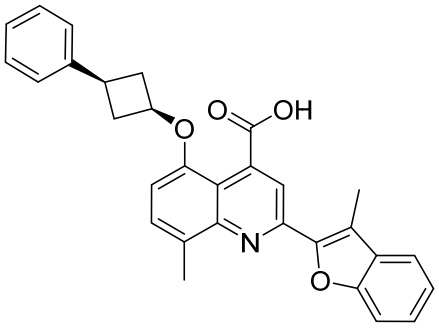
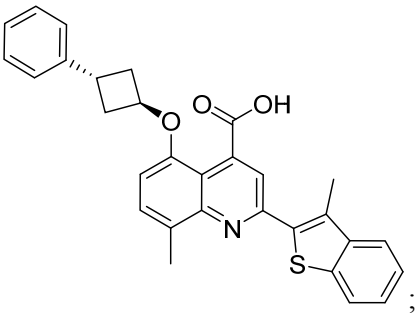
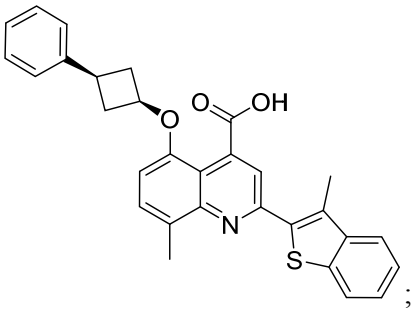
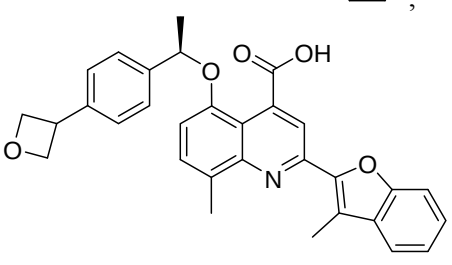
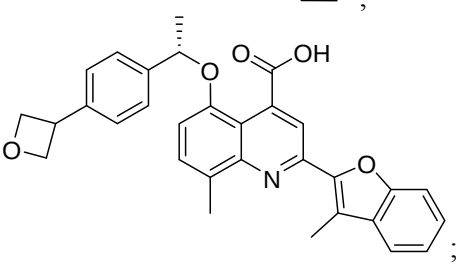

;

;

;

;

;

;

;

;

;


HO
O
O
N
N
O
N
;

N
O
O
O
OH
NH
N
;

N
O
O
O
OH
NH
N
;

O
N
O
O
OH
O
O=S=O
;

S
N
O
O
OH
O
O=S=O
;

N
S
O
O
OH
O=S=O
;

N
S
O
O
OH
O=S=O
;

N
S
O
O
OH
O=S=O
F
F
F
;

N
S
O
O
OH
O=S=O
F
F
F
;

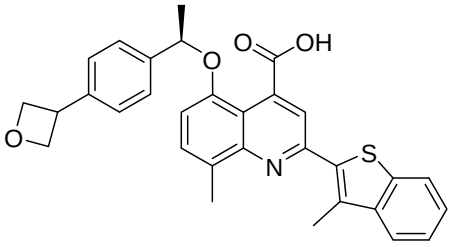
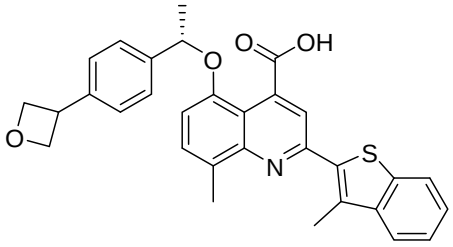
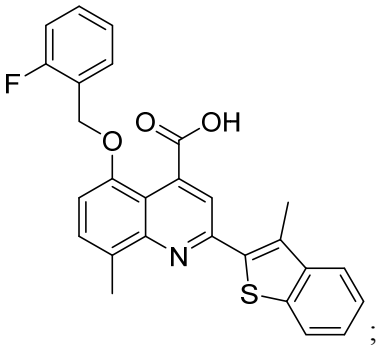
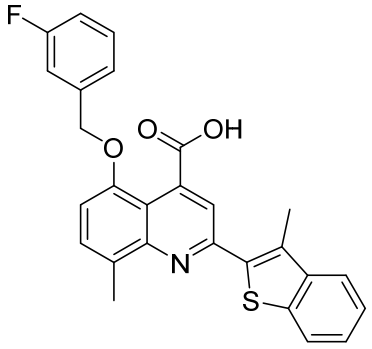
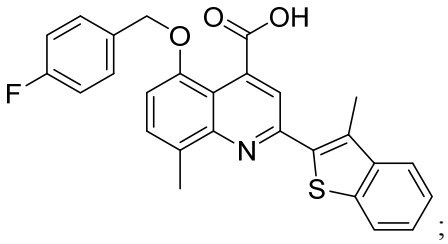
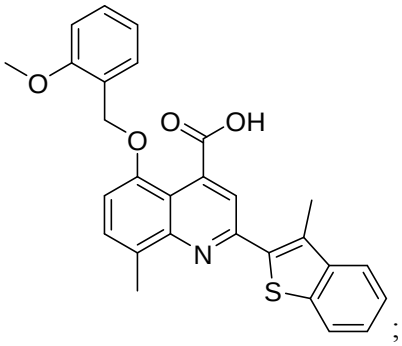
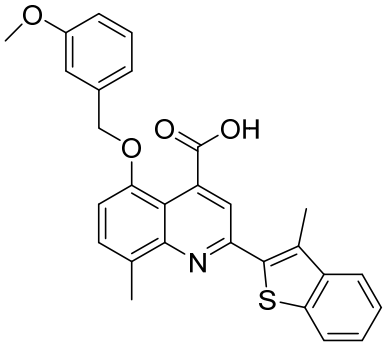
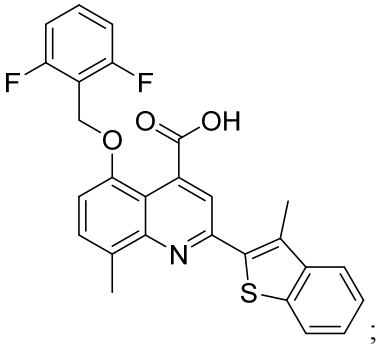
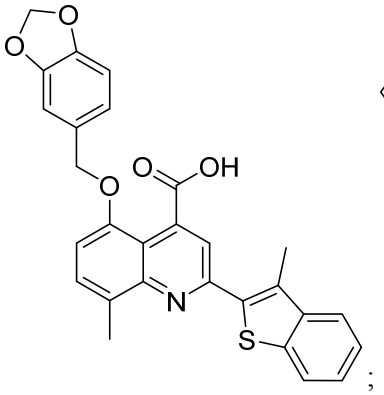
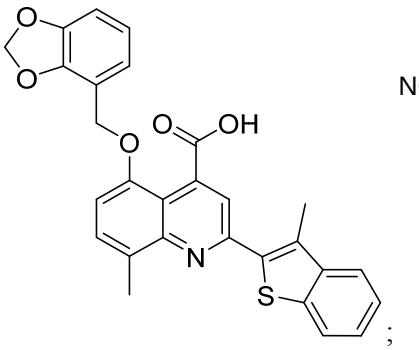
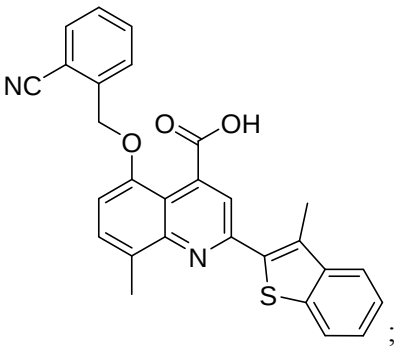
2y


;

;

;

;

;

;

;

;


2z


;

;

;

;

;

;

;

;

;

2aa

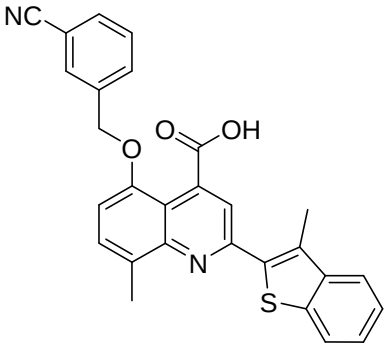

;

;

;

;

;

;

;

;

;

;

;

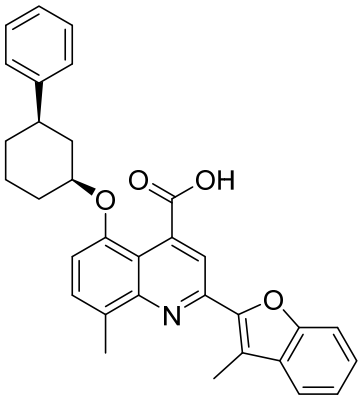
;

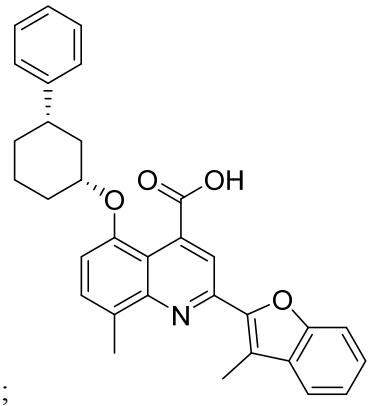
;

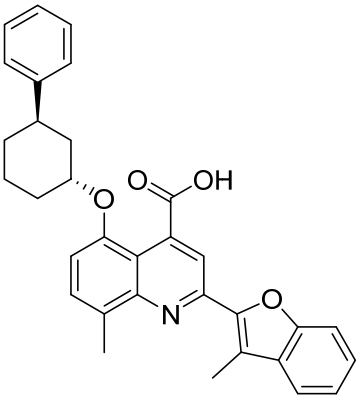
;

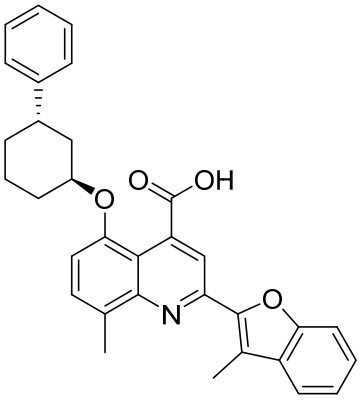
2ab

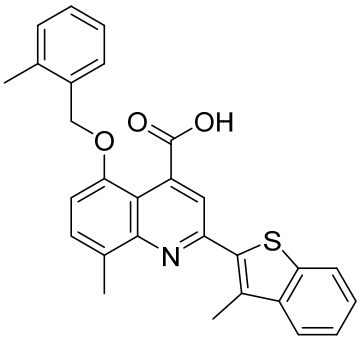

NC
O
O
OH
N
S
;

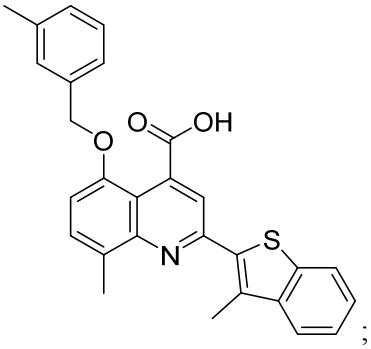

O
O
OH
N
O
;

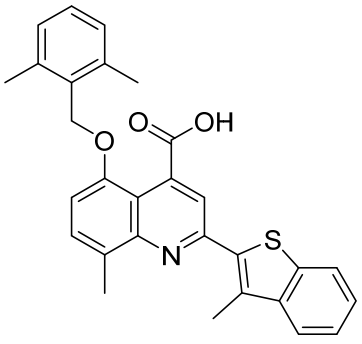

O
O
OH
N
O
;

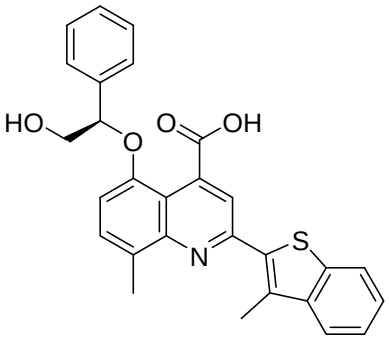

O
O
OH
N
O
;


O
O
OH
N
O
;

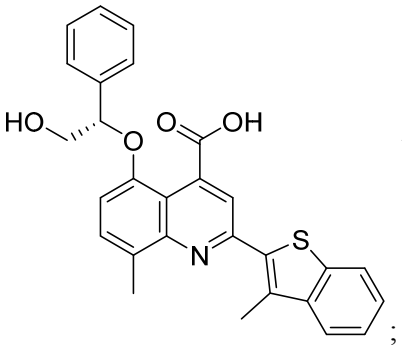
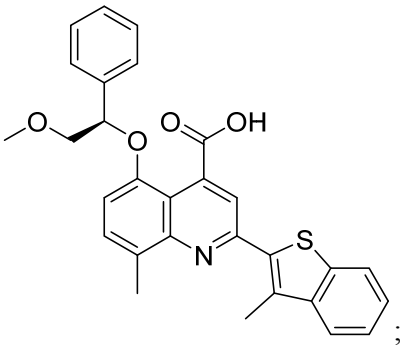
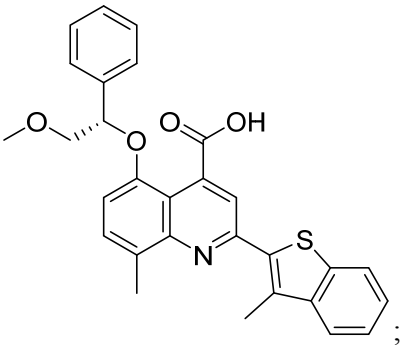
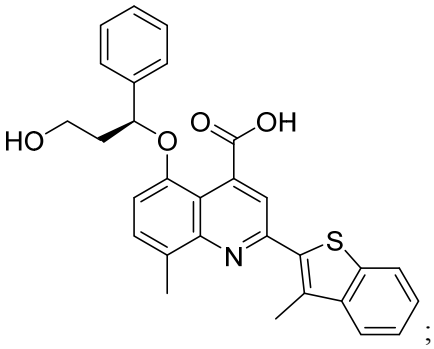
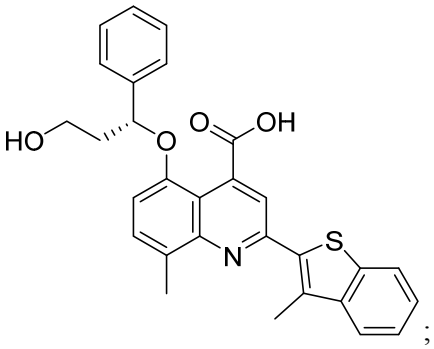
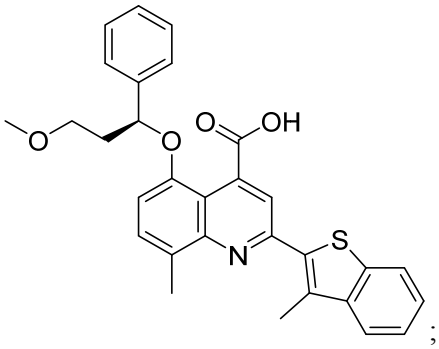
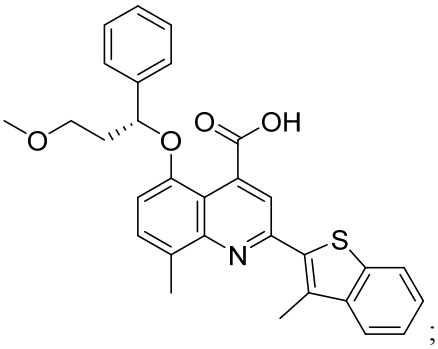
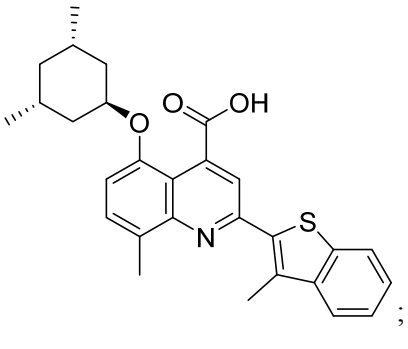
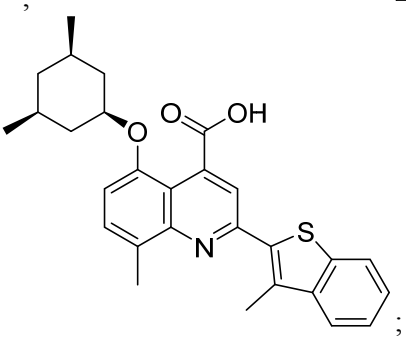
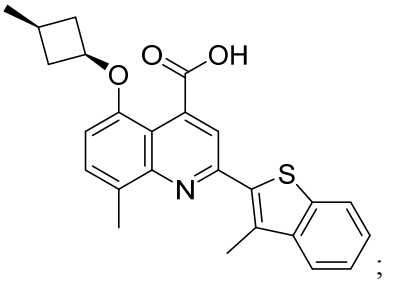

O
O
OH
N
S
;


O
O
OH
N
S
;

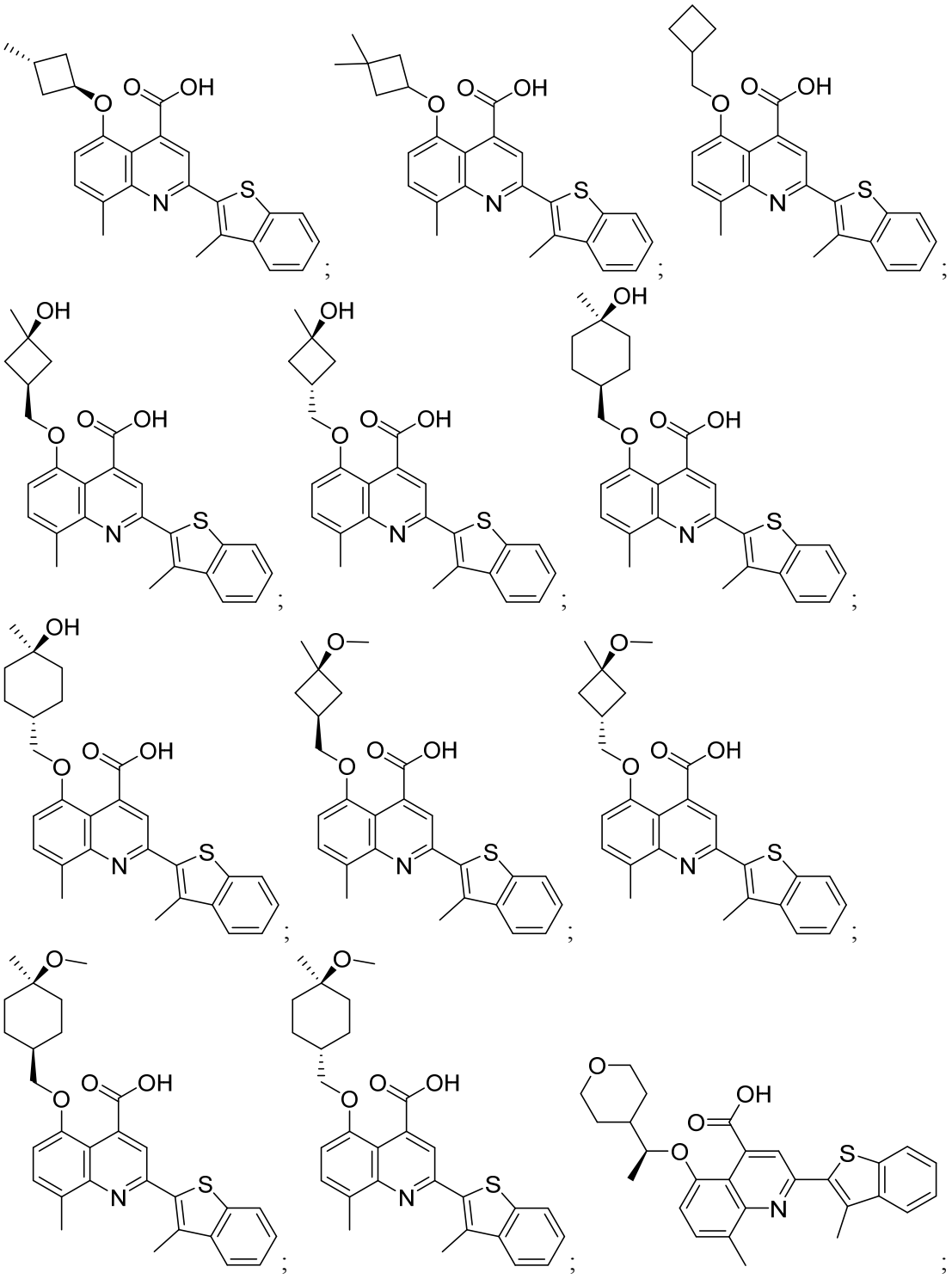

O
O
OH
N
S
;


HO
O
O
OH
N
S
;

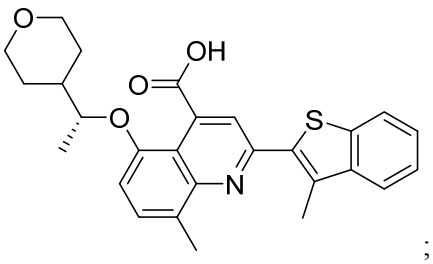
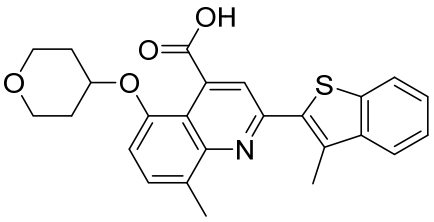
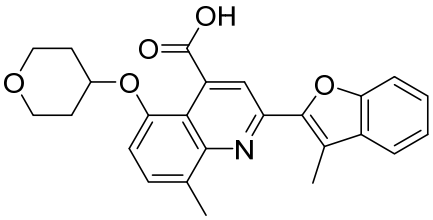
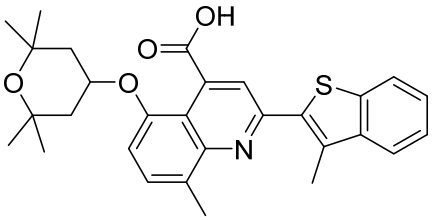
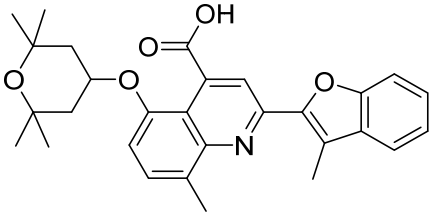
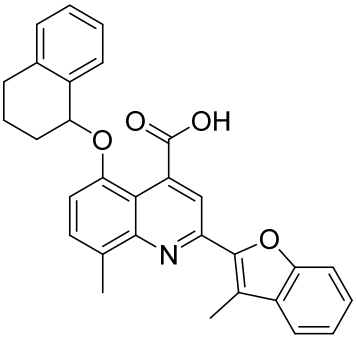
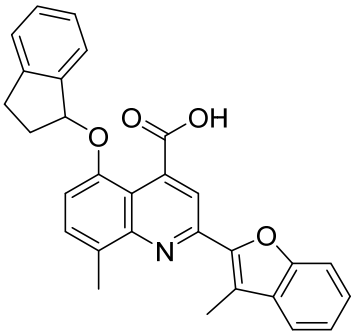
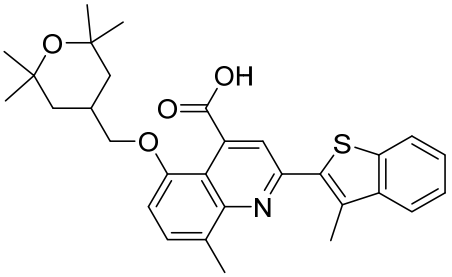
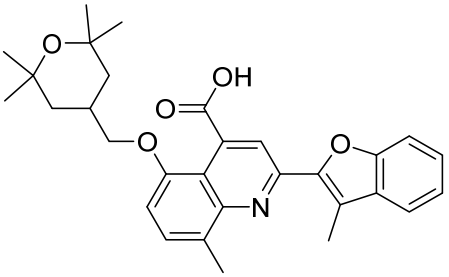
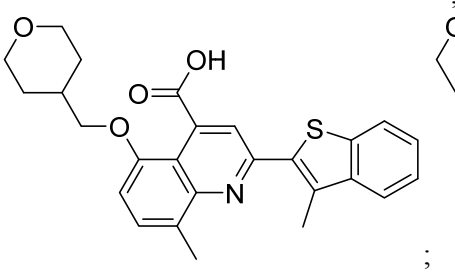
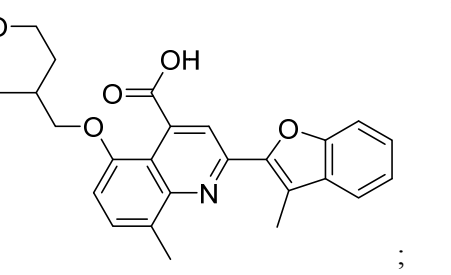
2ac


;

;

;

;

;

;

;

;

;

;

2ad



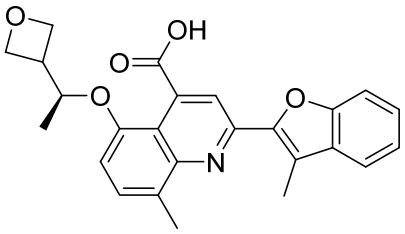
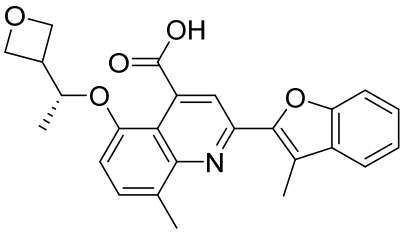
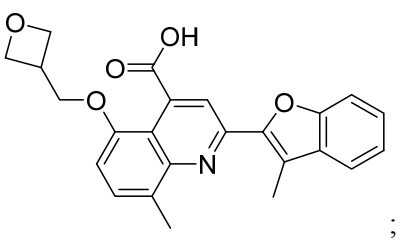
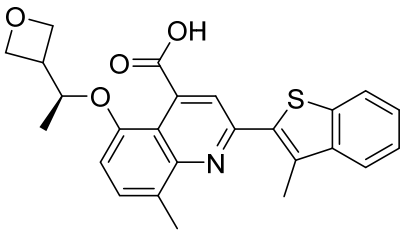
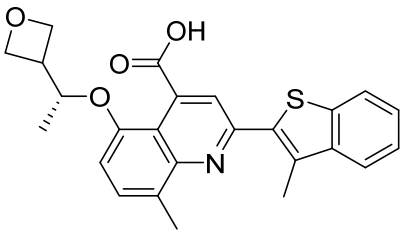
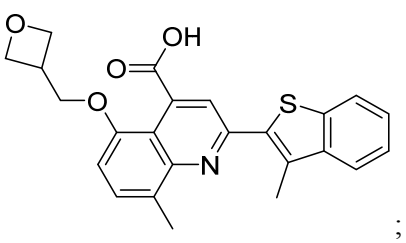
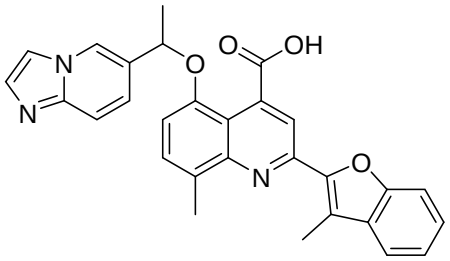
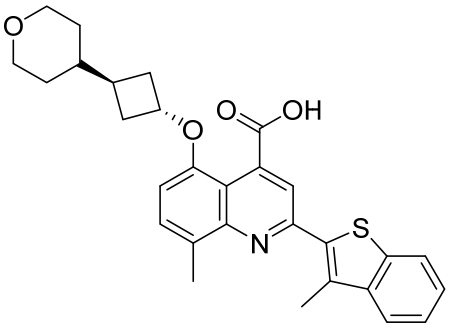
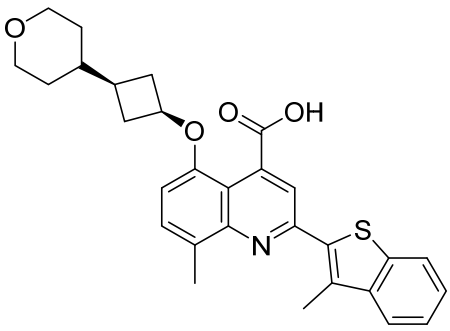
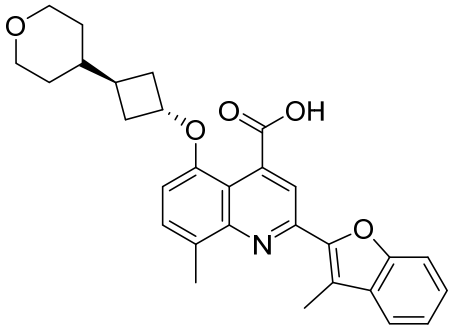
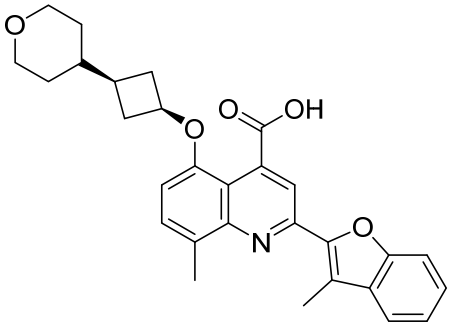
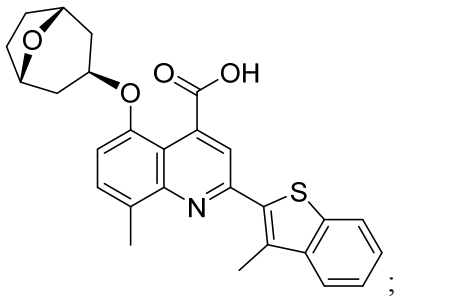
2ae


;

;

;

;

;

;

;

;

;

;

;

;

;

2af


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

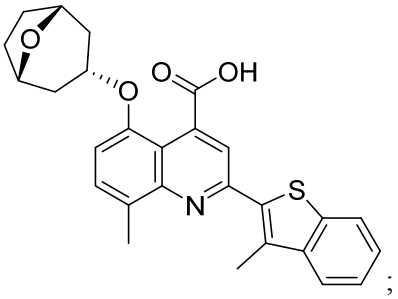
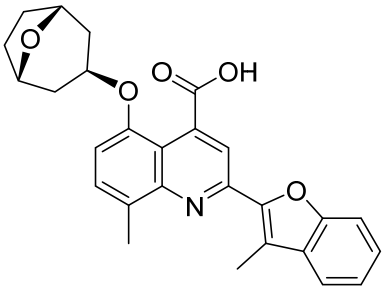
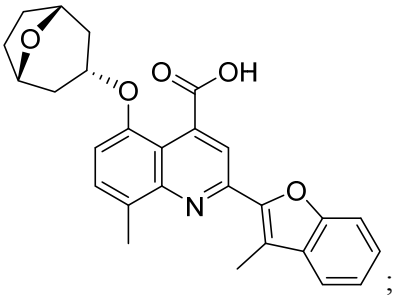
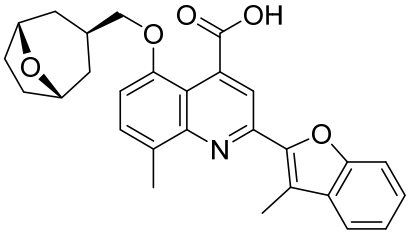
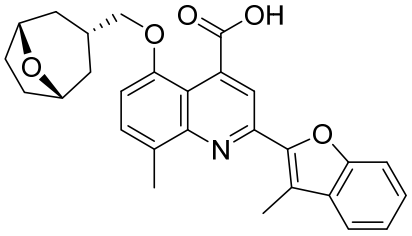
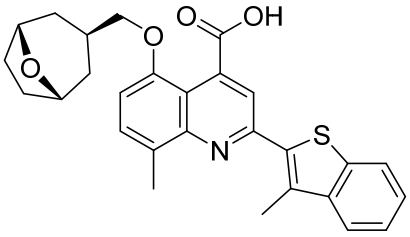
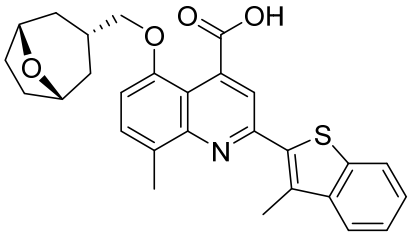
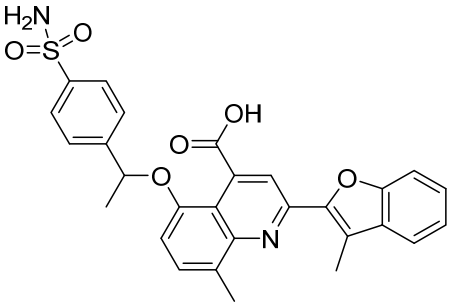
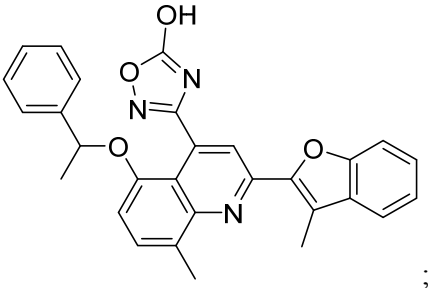
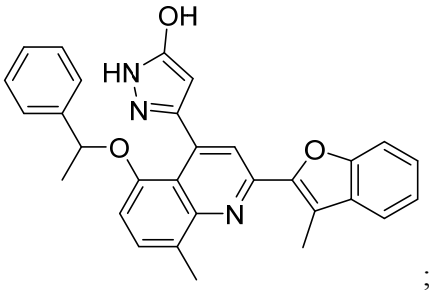
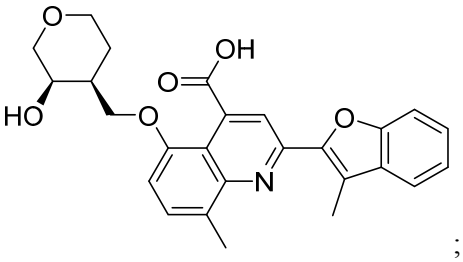
;

;

;

;

2ag


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

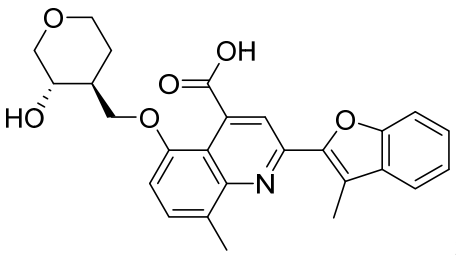
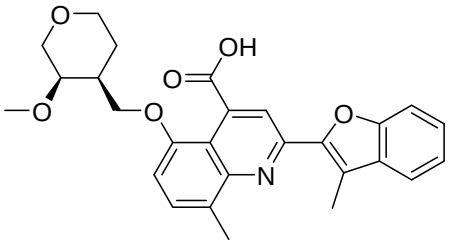
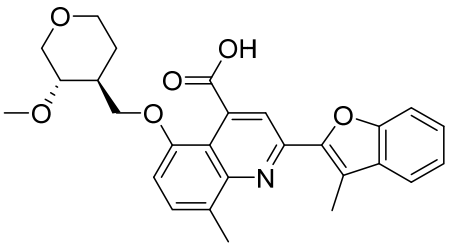
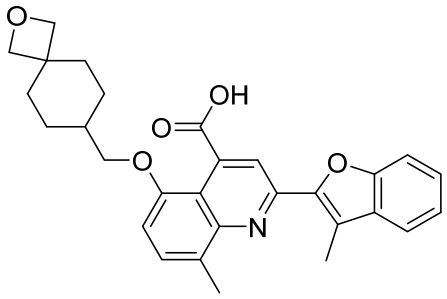
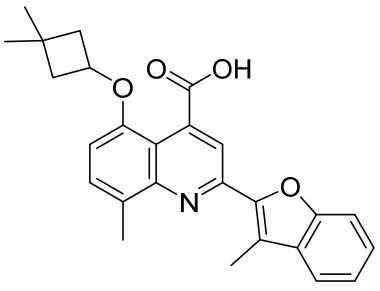
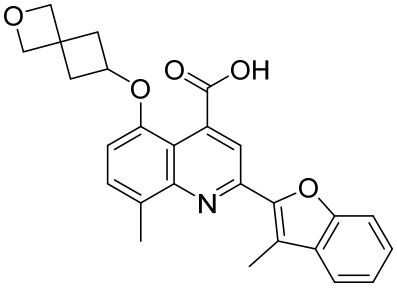
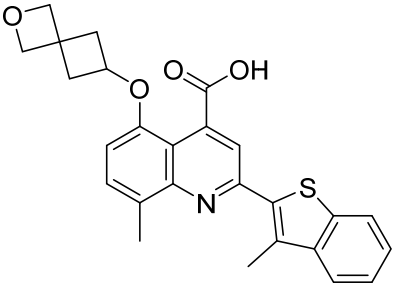
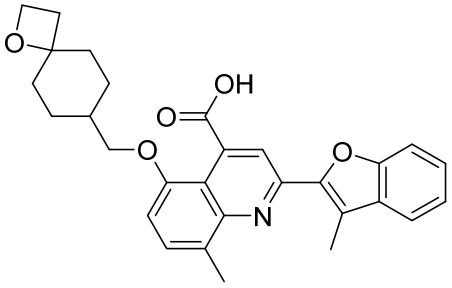
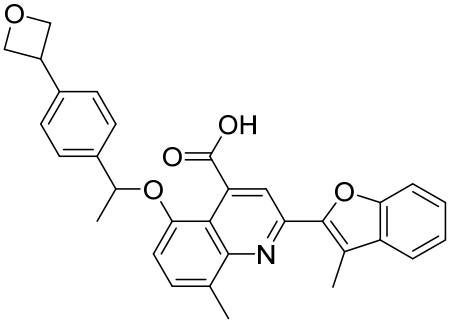
;

;

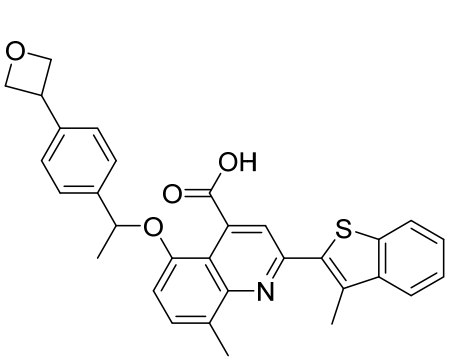
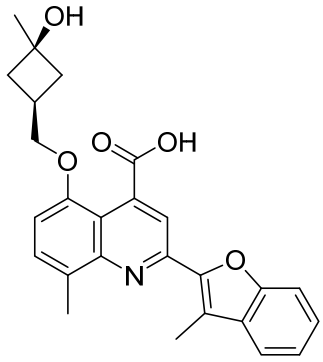
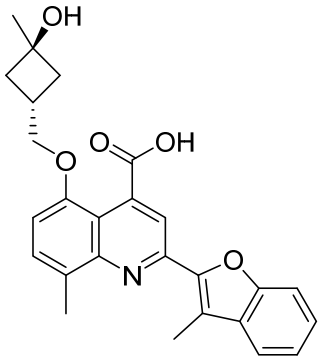
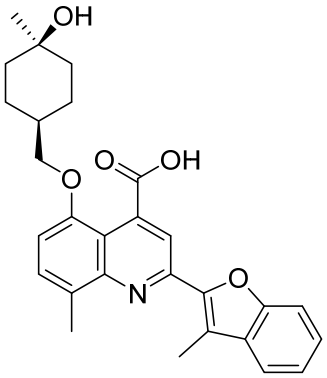
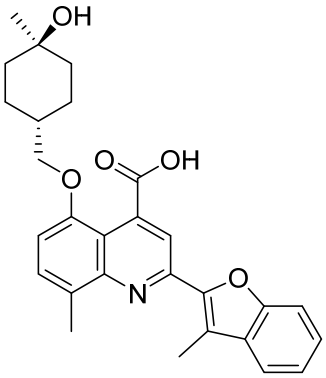
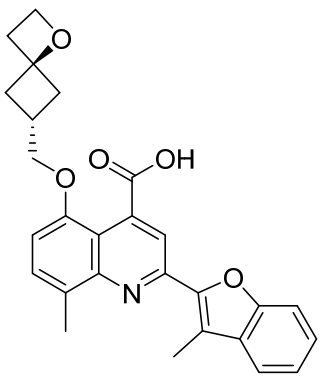
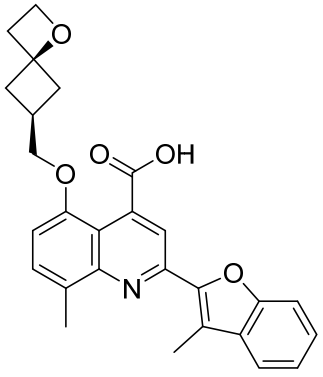
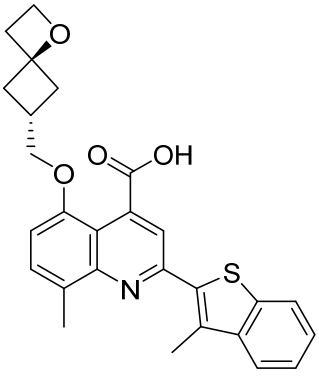
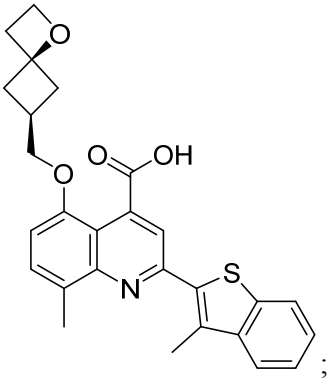
;

;

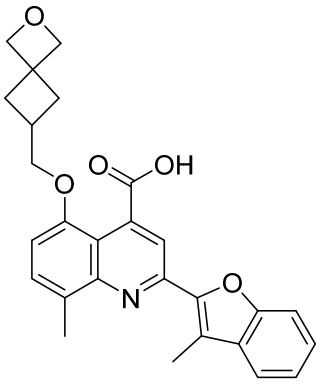
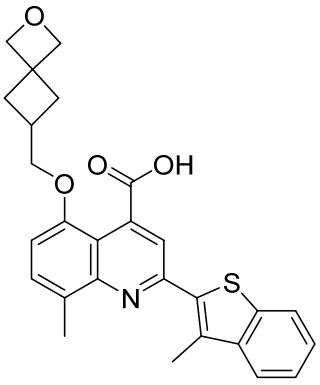
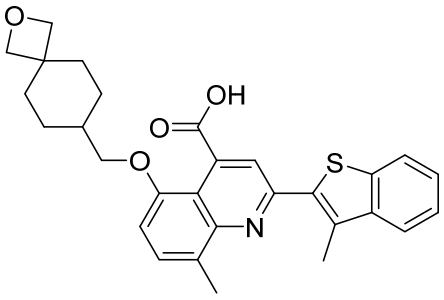
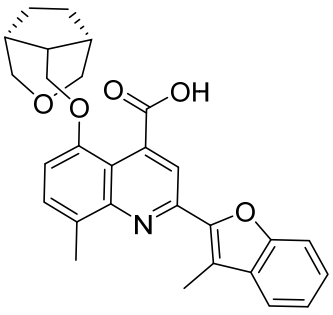
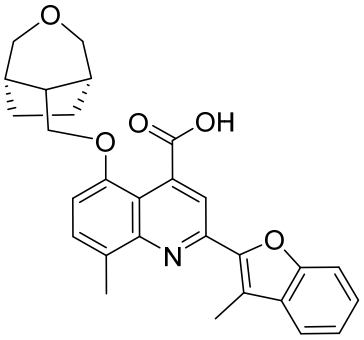
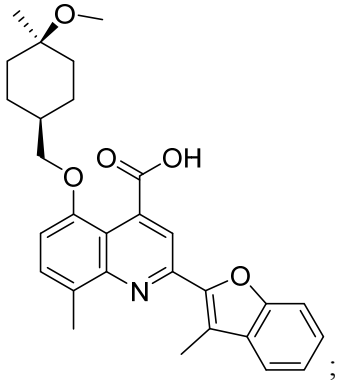
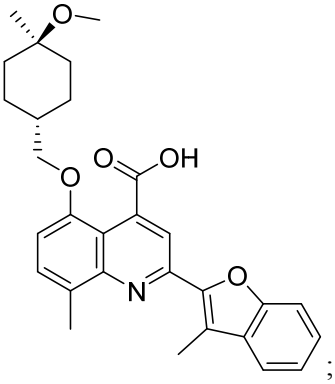
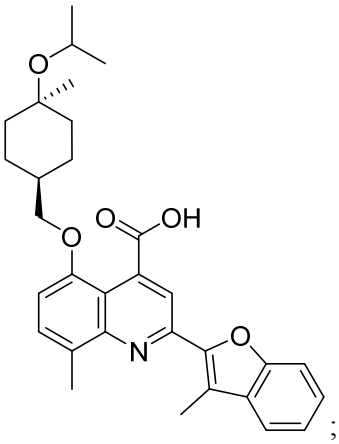
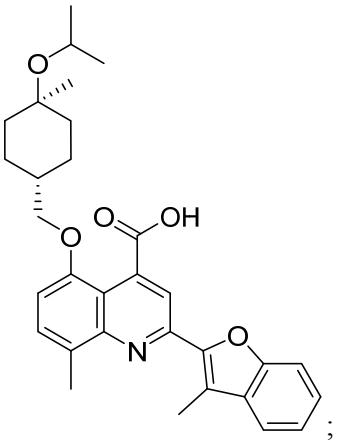
2ah


O
OH
HO
O
O
N
;

O
OH
O
O
O
N
;

O
OH
O
O
O
N
;

O
OH
O
O
O
N
;

O
OH
O
N
O
;

O
OH
O
N
O
;

O
OH
O
N
S
;

O
OH
O
O
N
;

O
OH
O
O
O
N
;

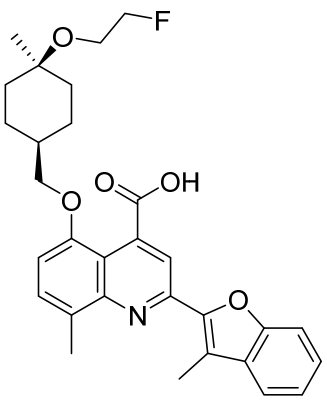
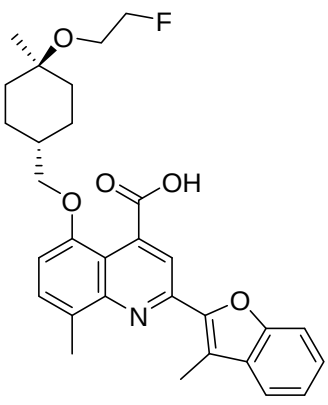
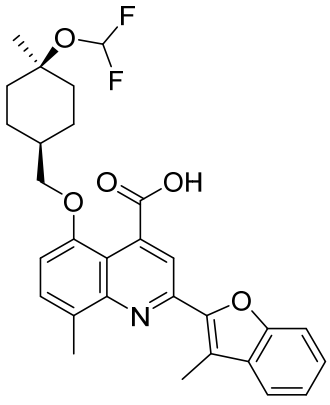
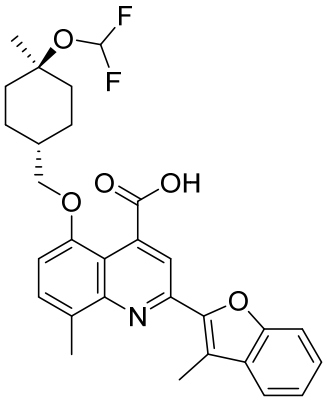
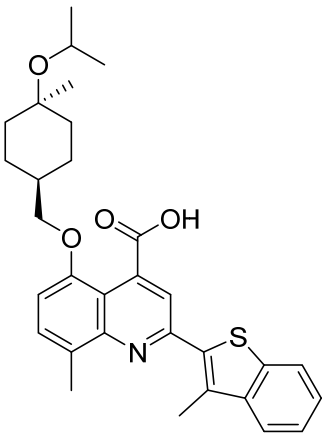
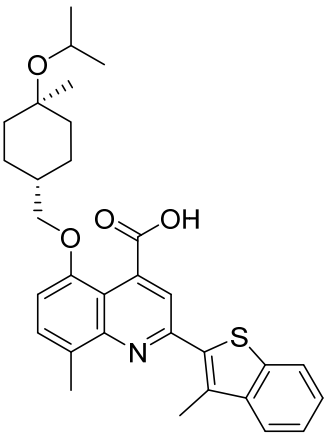
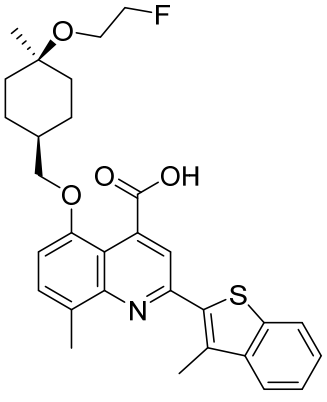
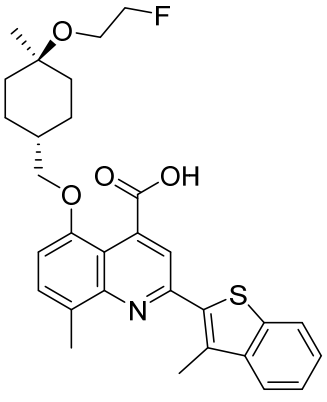
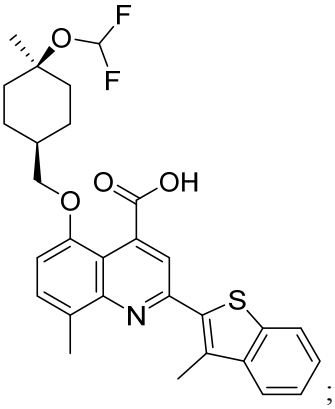
2ai

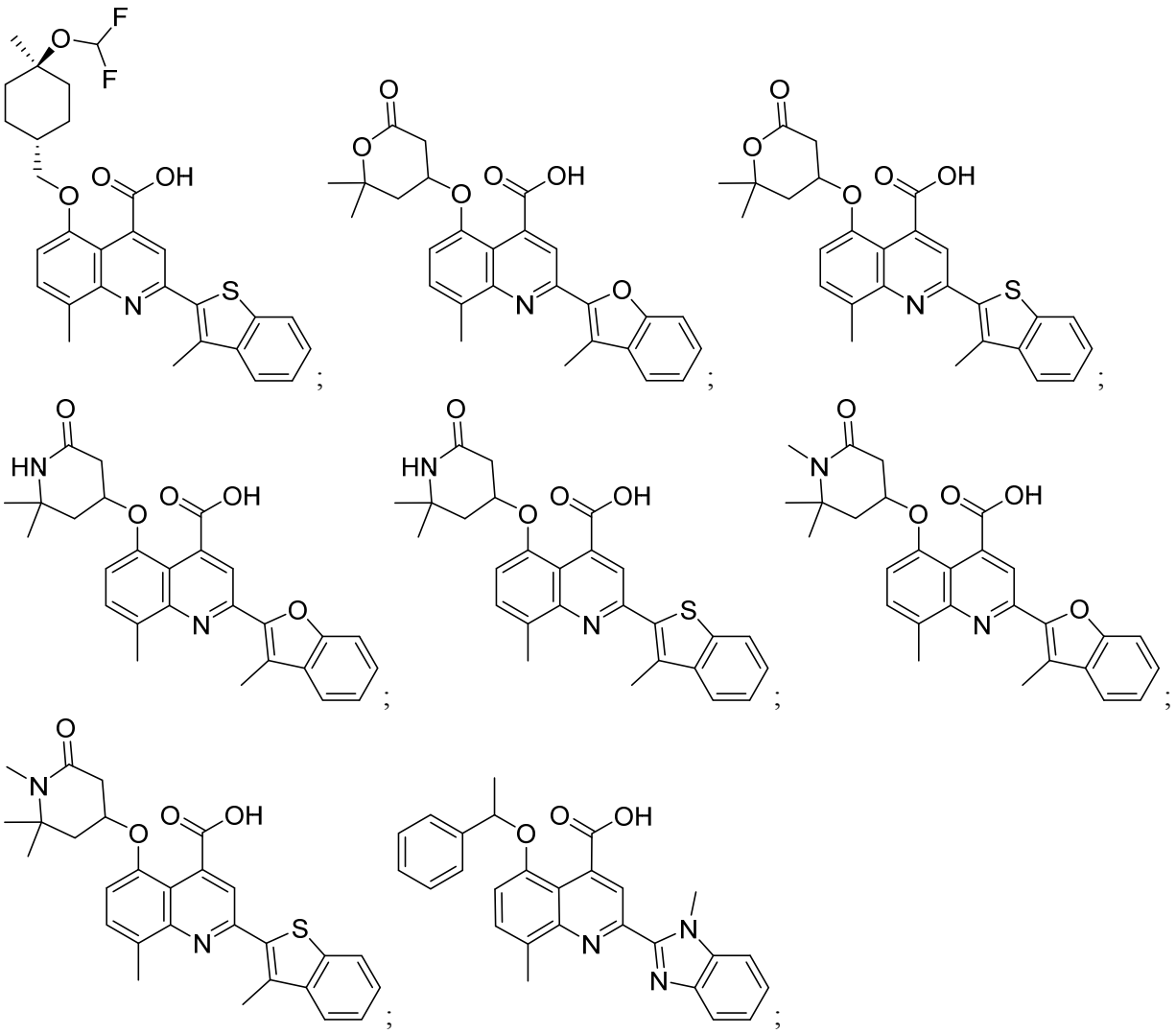

;

;

;

;

;

;

;

;

;

2aj


;

;

;

;

;

;

;

;

;

2ak


;

;

;

;

;

;

;

;

;



and a pharmaceutically acceptable salt or stereoisomer thereof.

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

[0006d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.

[0006e] In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in treating cystic fibrosis in a patient in need 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.

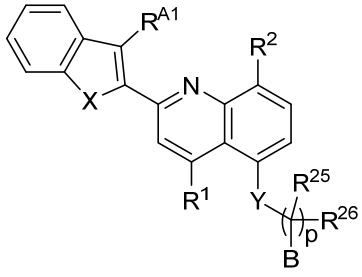
[0008] In certain embodiments, a method is provided comprising administering a disclosed compound to a subject (e.g., a human patient) suffering from a disease associated with decreased CFTR activity (e.g., cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic 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.,

What is claimed is:

1. A compound represented by:



; or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

X is O or S;

R^{A1} is selected from the group consisting of hydrogen and C_{1-6}alkyl;

R^1 is selected from the group consisting of -C(O)OH 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 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;

Y is O or $S(O)_w$ (where w is 0, 1 or 2);

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

p is 0 or 1; and

B is 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 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 heterocyclic ring may optionally be substituted by one, two, three, or four substituents each independently selected from hydroxyl, C_{1-6}alkyl, C_{1-6}alkoxy, and oxo.

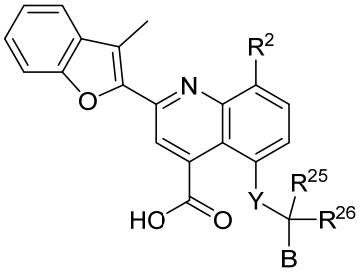
2. The compound of claim 1, wherein X is O.

3. The compound of claim 1 or 2, wherein R^{A1} is methyl.

4. The compound of any one of claims 1-3, wherein R^1 is -C(O)OH.

5. The compound of any one of claims 1-4, wherein p is 1.

6. The compound of any one of claims 1-5, represented by

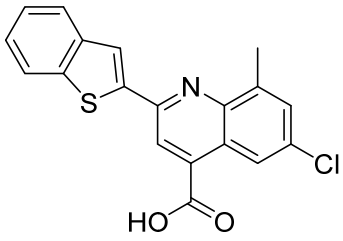
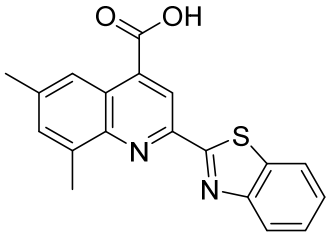
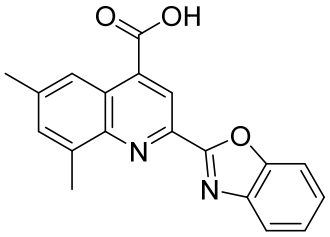
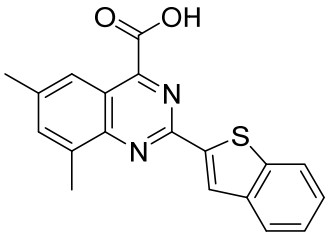
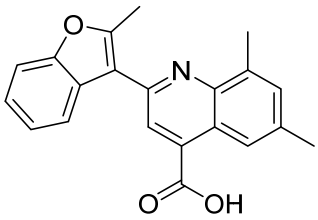
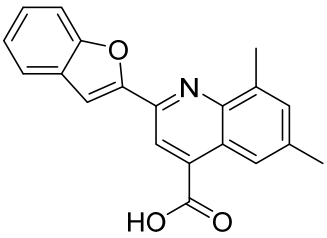
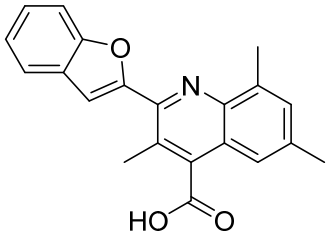
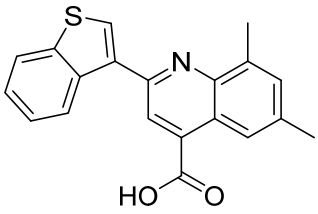
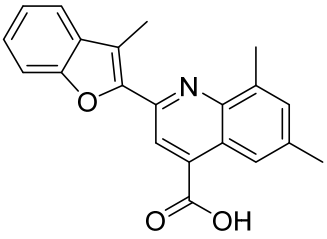
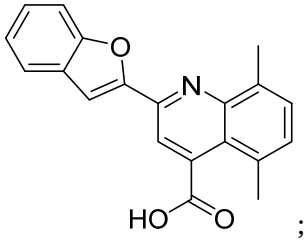
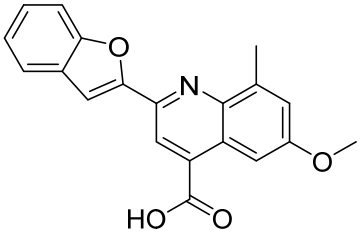
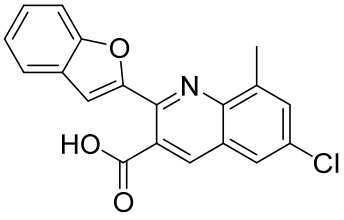
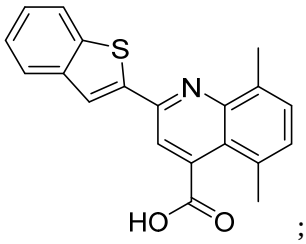
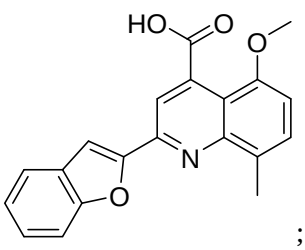
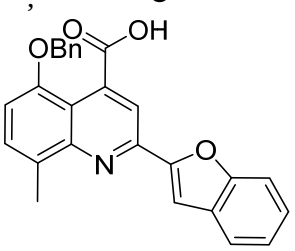


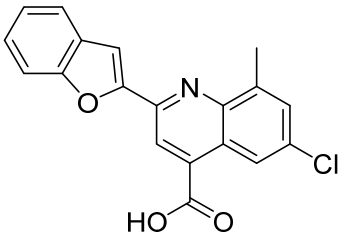
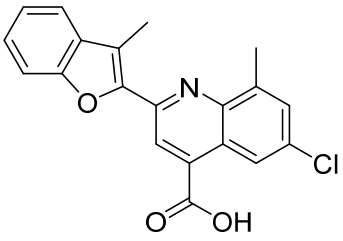
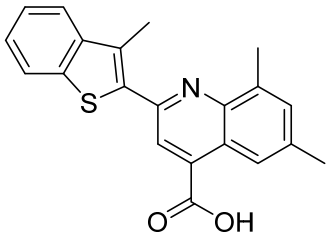
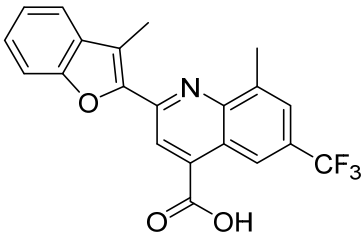
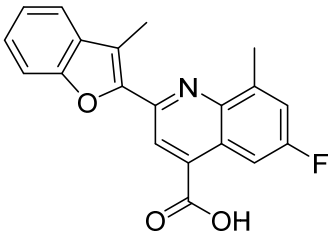
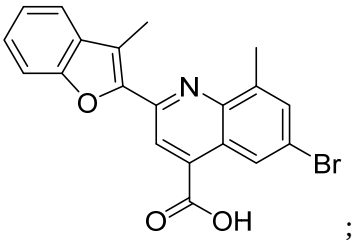
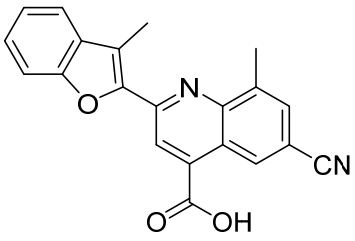
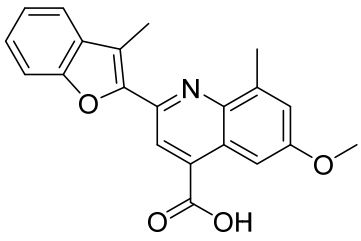
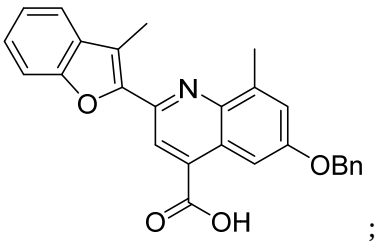
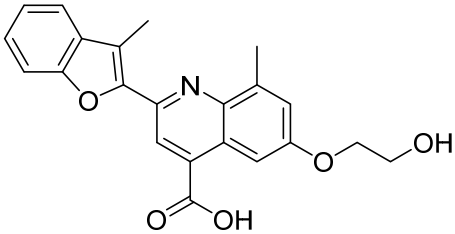
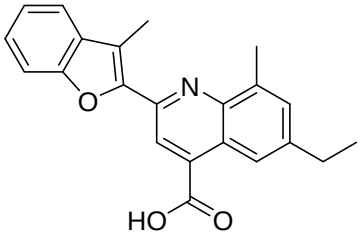
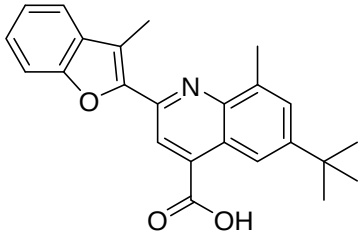
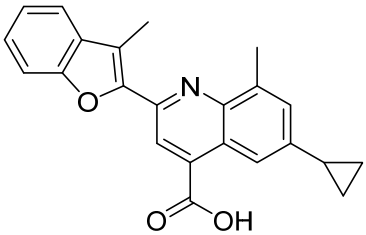
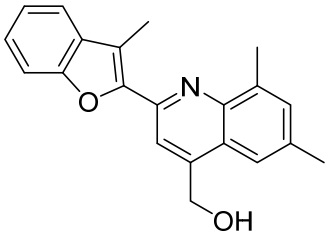
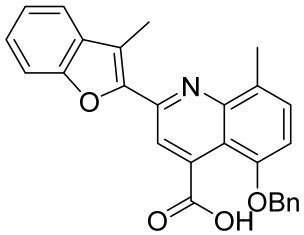
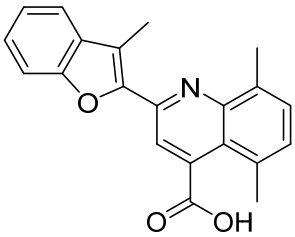
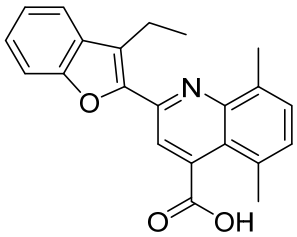
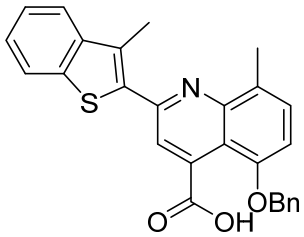
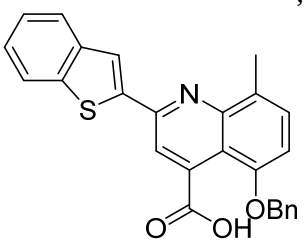
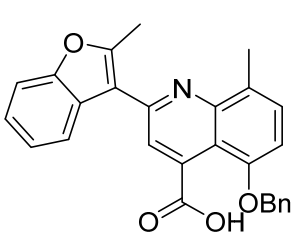
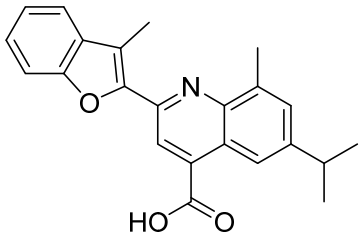
.

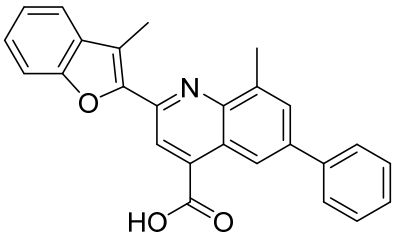
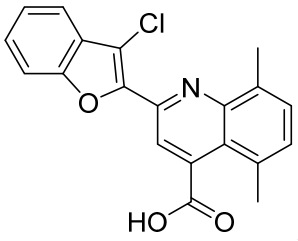
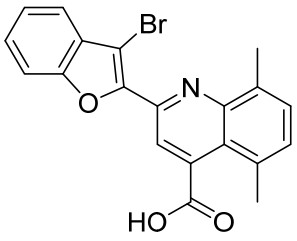
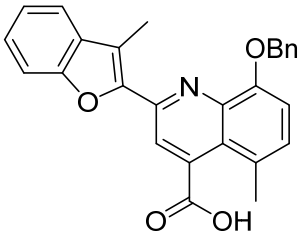
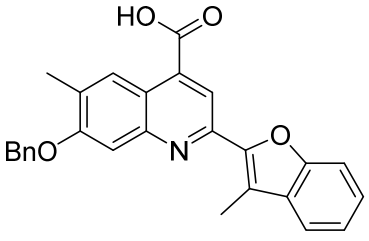
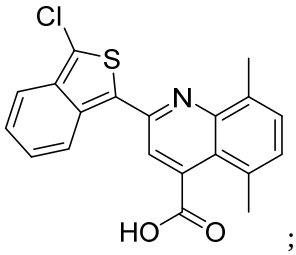
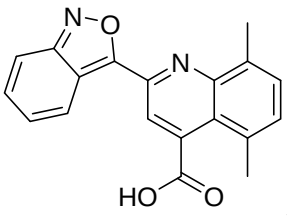
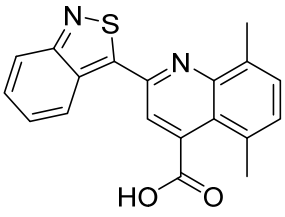
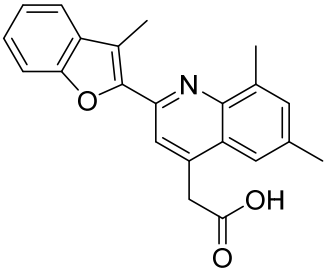
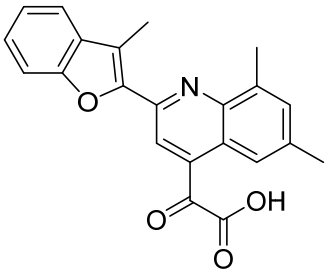
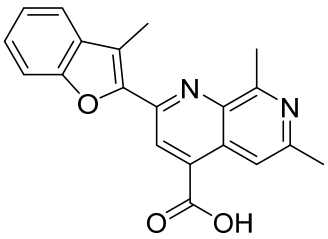
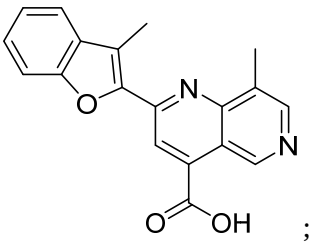
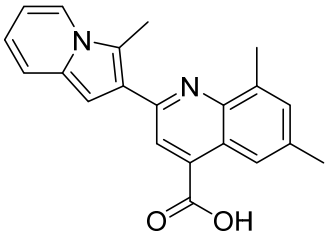
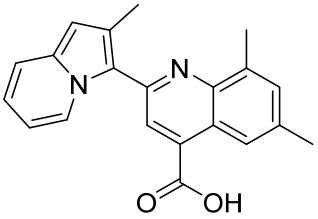
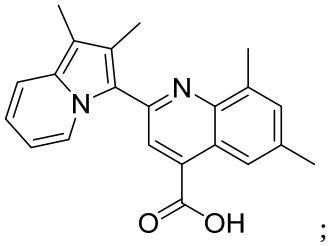
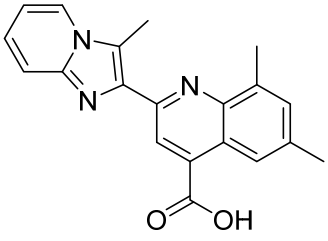
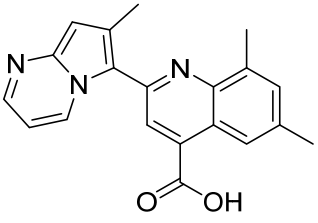
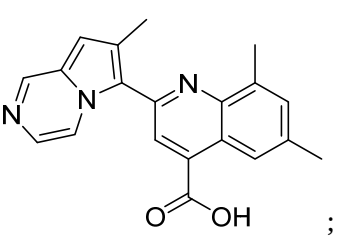
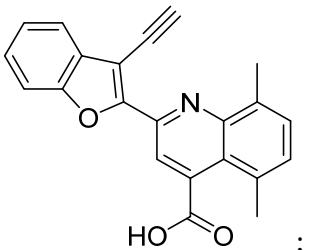
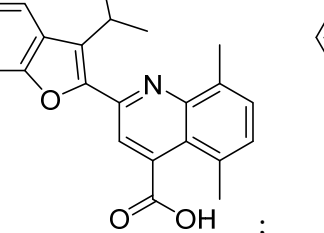
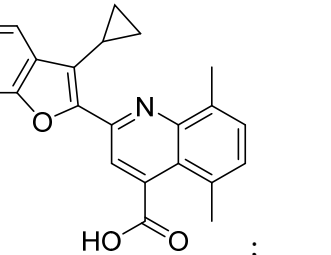
7. The compound of any one of claims 1-6, wherein Y is O.

8. The compound of any one of claims 1-7, wherein R^2 is C_{1-6}alkyl.

9. A compound selected from the group consisting of:


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

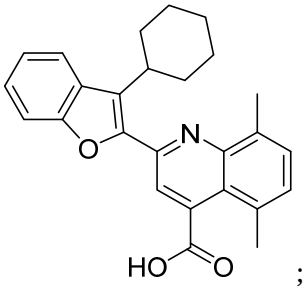
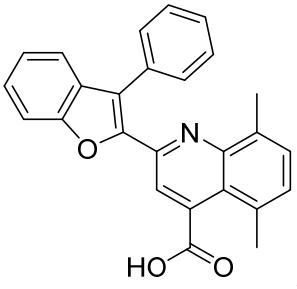
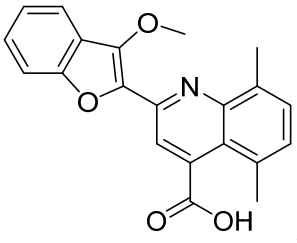
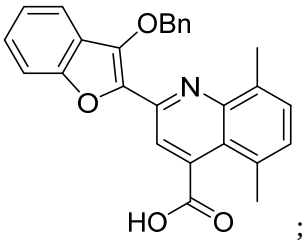
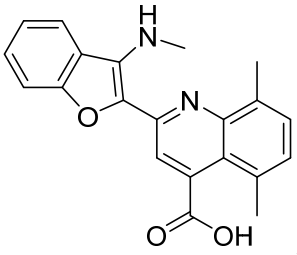
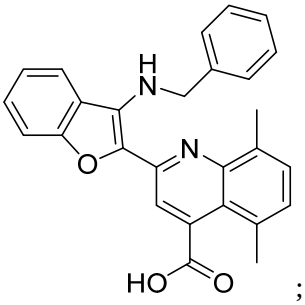
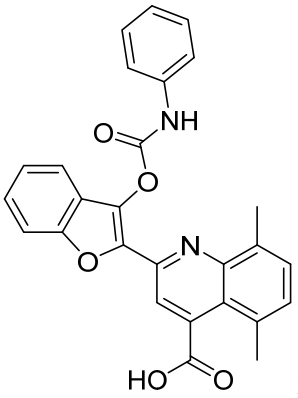
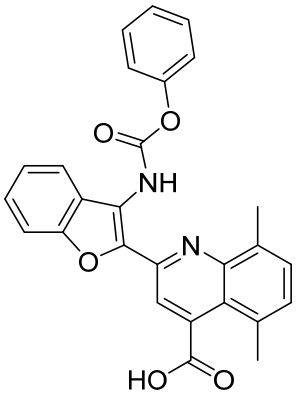
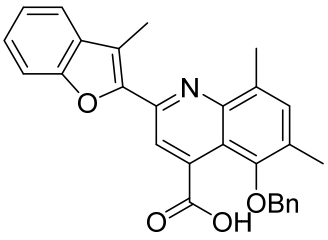
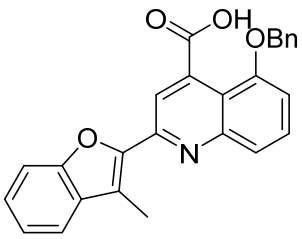
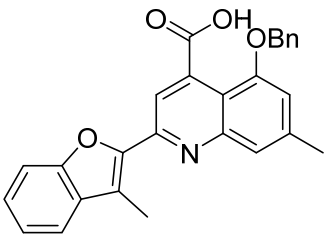
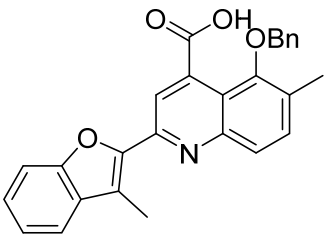
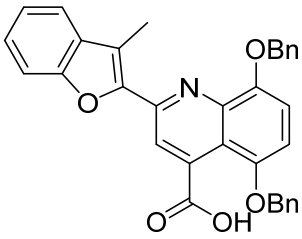
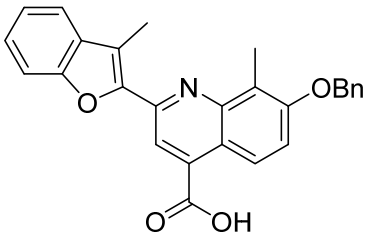
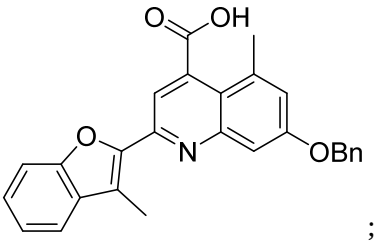
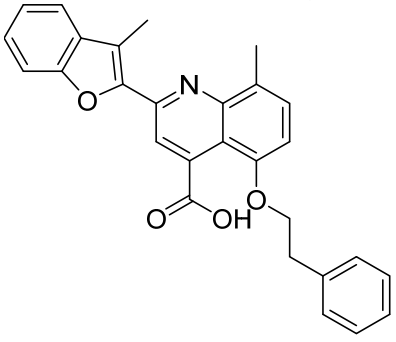
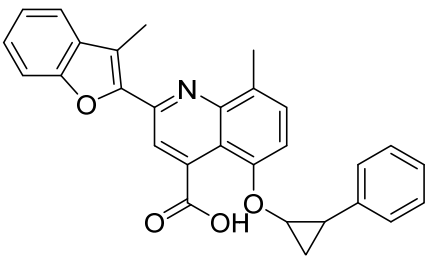

O
N
Cl
HO
O
;

O
N
Cl
O
OH
;

S
N
O
OH
;

O
N
CF3
O
OH
;

O
N
F
O
OH
;

O
N
Br
O
OH
;

O
N
CN
O
OH
;

O
N
O
O
OH
;

O
N
OBn
O
OH
;

O
N
O
OH
O
OH
;

O
N
HO
O
;

O
N
O
OH
;

O
N
O
OH
;

O
N
OH
;

O
N
OBn
O
OH
;

O
N
O
OH
;

O
N
O
OH
;

S
N
OBn
O
OH
;

S
N
OBn
O
OH
;

O
N
OBn
O
OH
;

O
N
HO
O
;

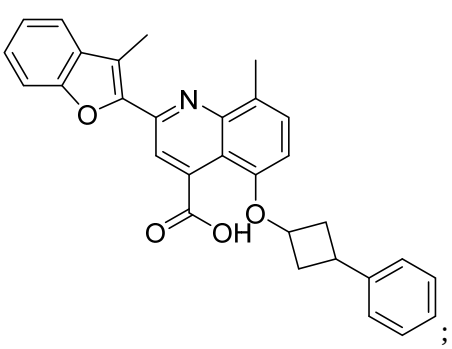
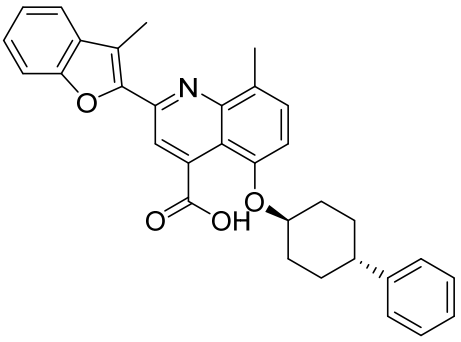
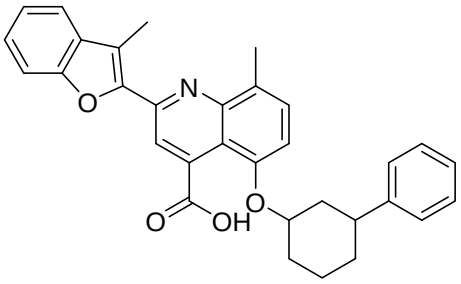
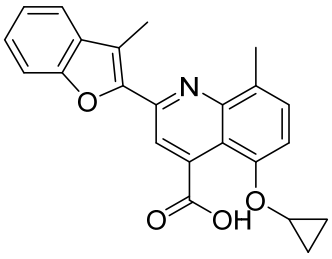
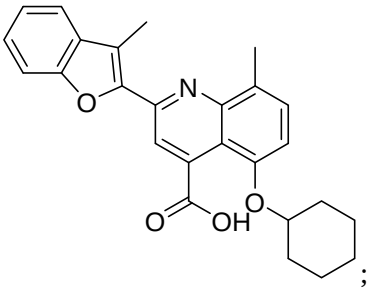
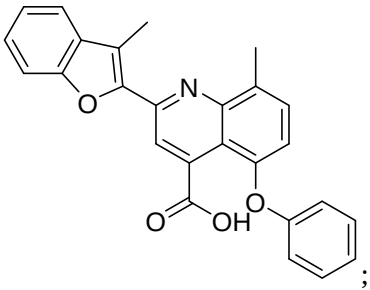
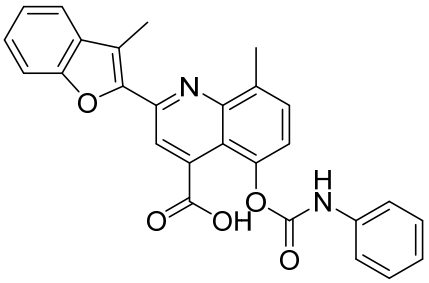
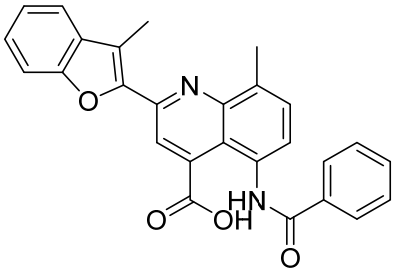
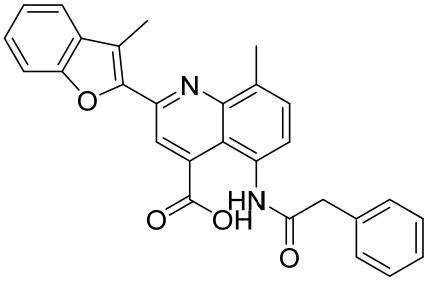
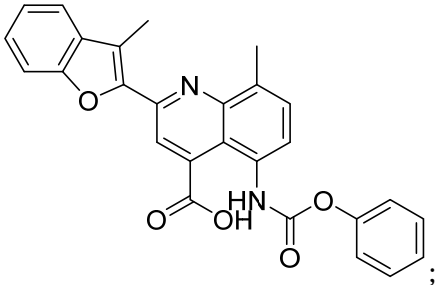
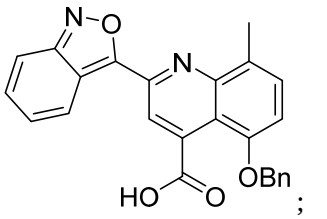
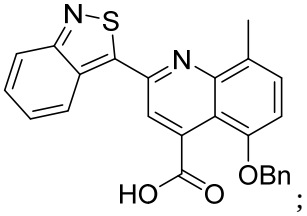
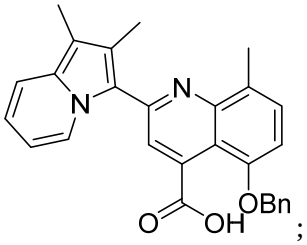
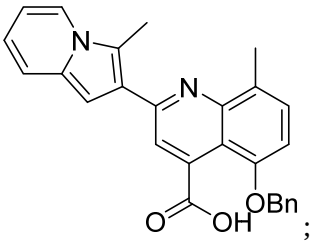
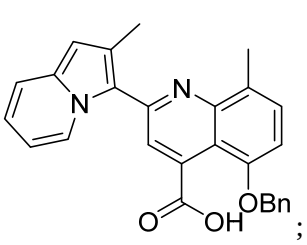
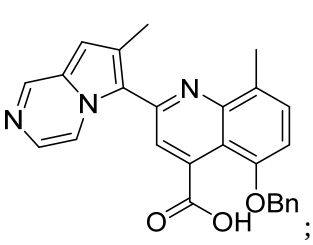
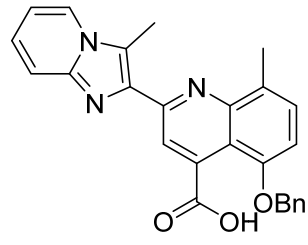

HO
O
N
O
;

Cl
HO
O
N
O
;

Br
HO
O
N
O
;

OBn
O
OH
N
O
;

HO
O
BnO
N
O
;

Cl
S
HO
O
N
;

N
O
HO
O
N
;

N
S
HO
O
N
;

OH
O
N
O
;

OH
O
O
N
O
;

N
O
N
OH
O
;

N
O
N
N
OH
O
;

N
O
N
O
OH
;

N
O
N
O
OH
;

N
O
N
N
O
OH
;

N
N
O
OH
;

N
N
O
OH
;

N
N
O
OH
;

N
N
N
O
OH
;

N
N
N
O
OH
;

N
N
N
O
OH
;

HO
O
N
O
;

O
OH
N
O
;

HO
O
N
O
;

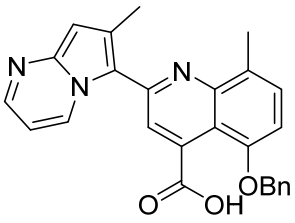
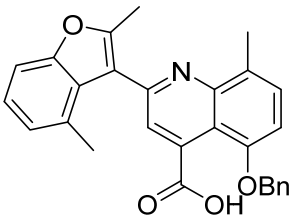
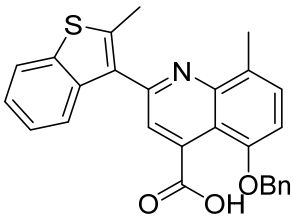
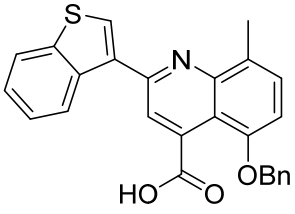
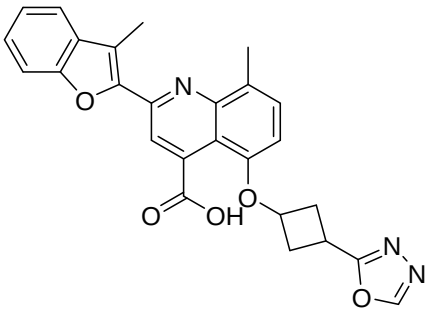
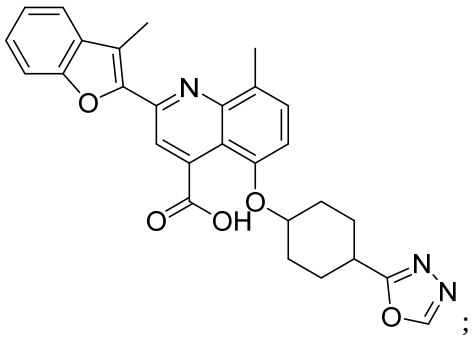
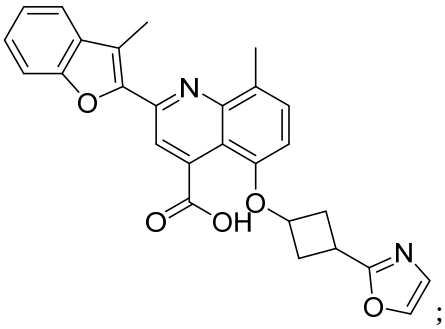
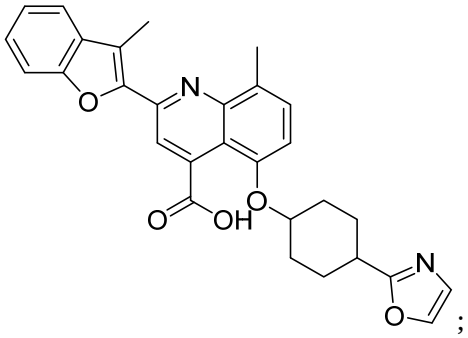
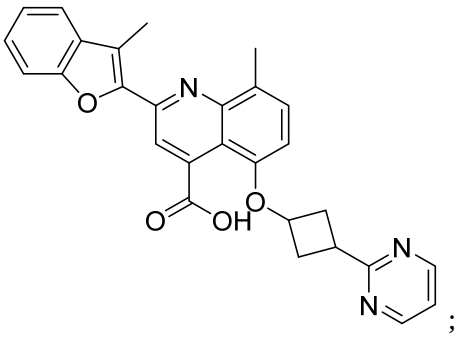
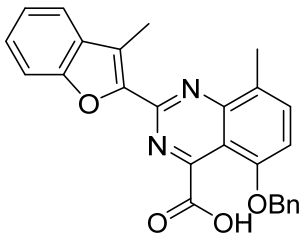
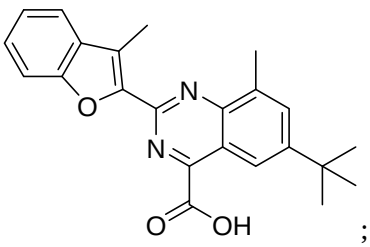
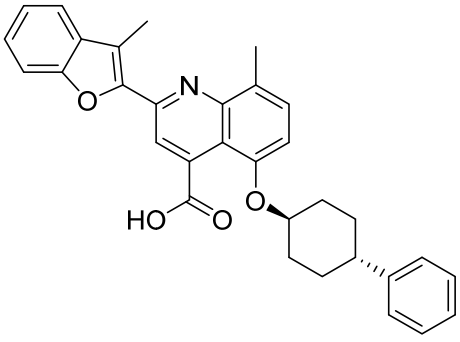
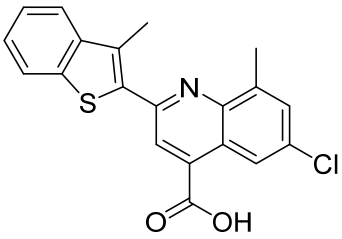
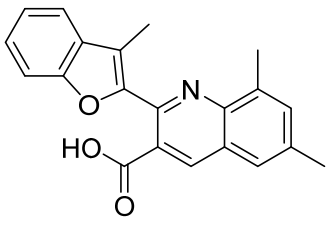

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

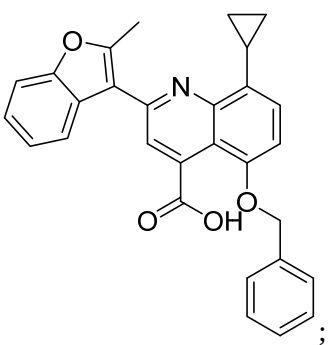
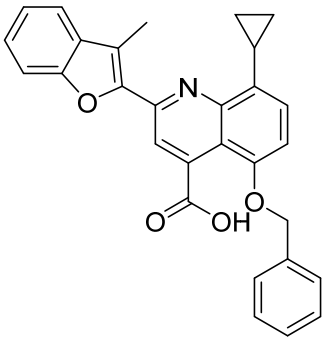
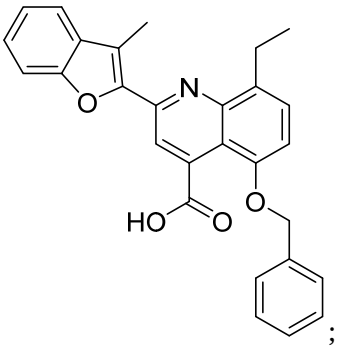
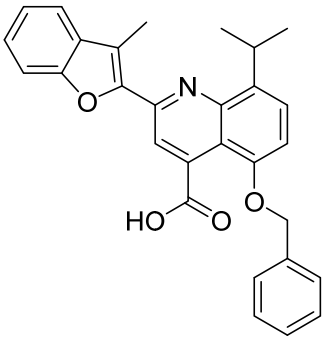
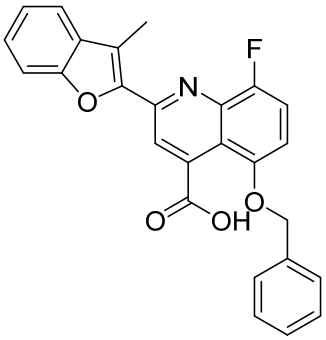
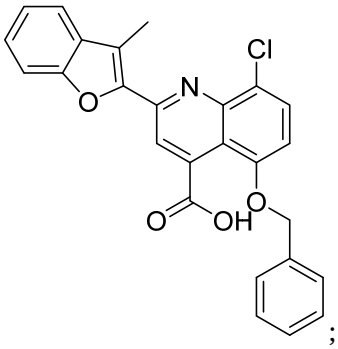
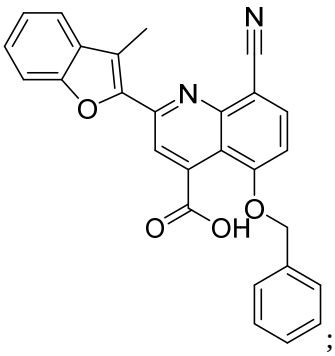
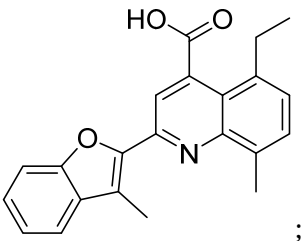
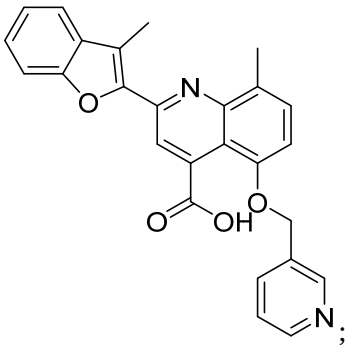
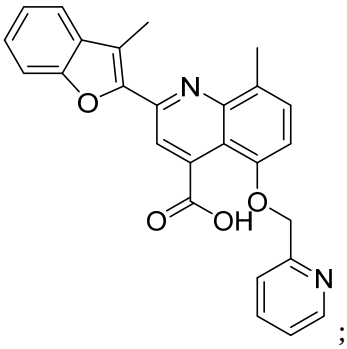
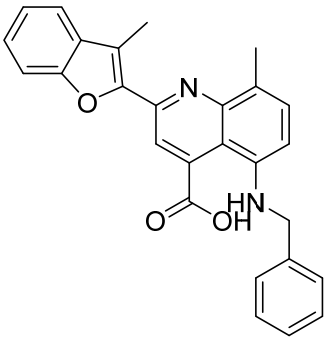
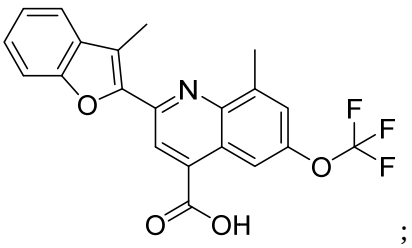
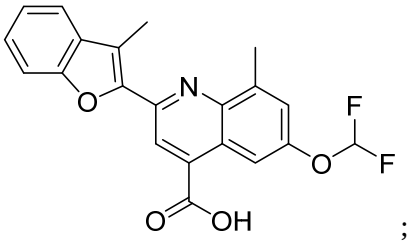
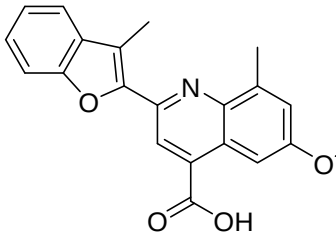

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

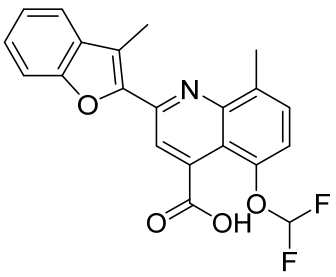
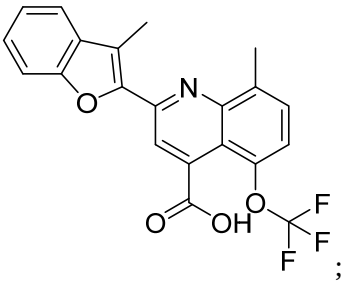
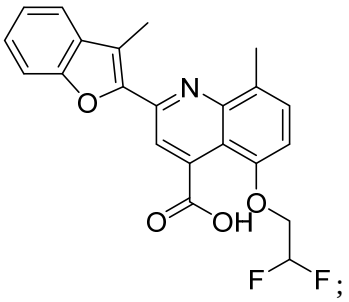
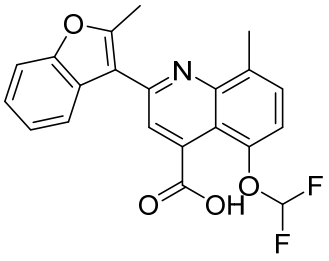
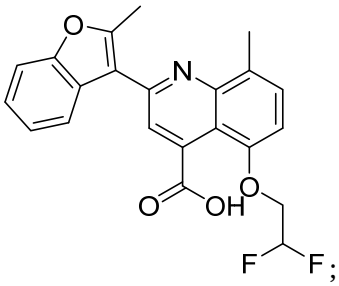
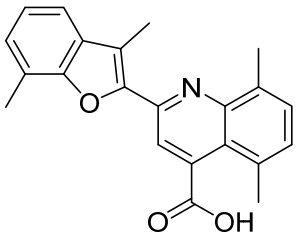
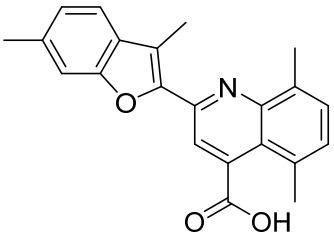
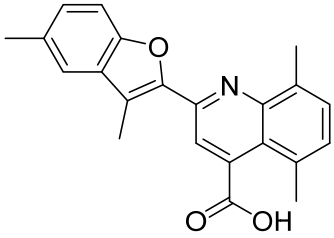
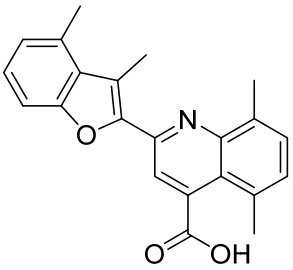
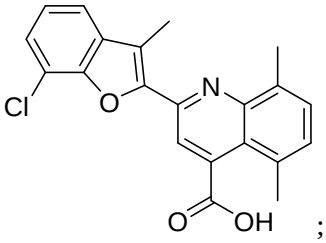
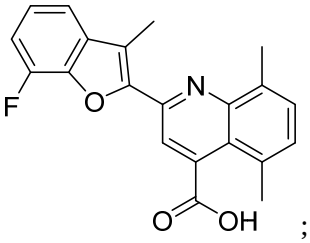
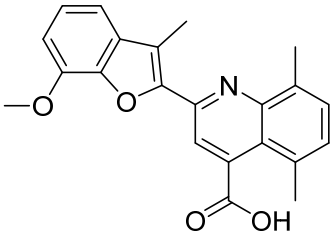
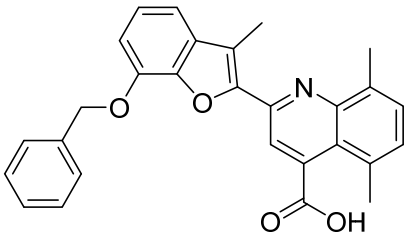
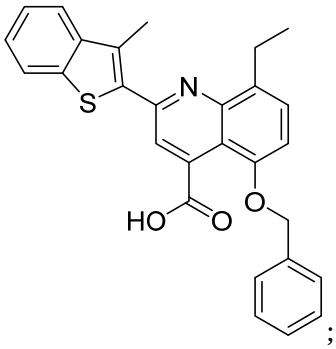
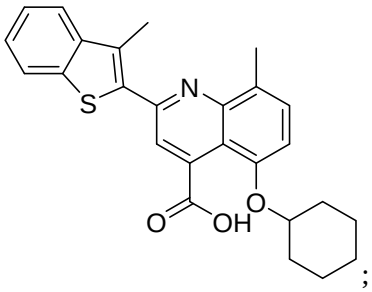
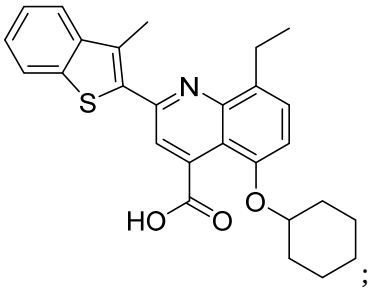
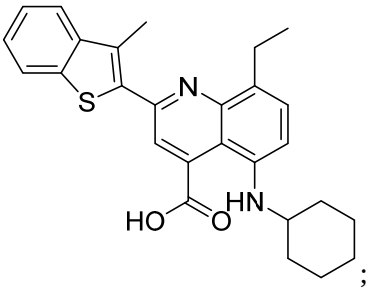
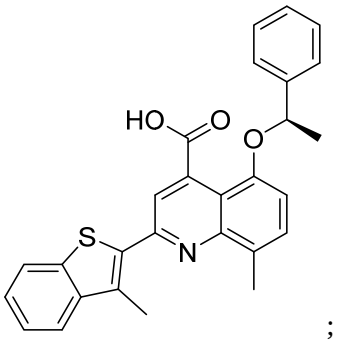
;

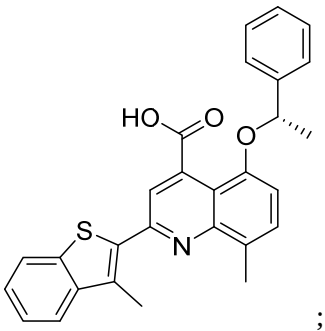
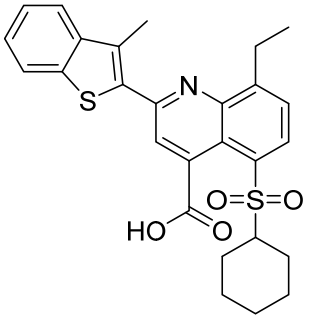
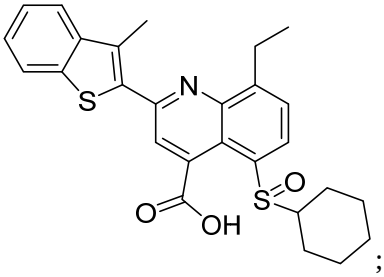
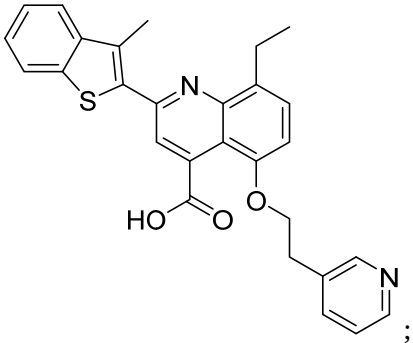
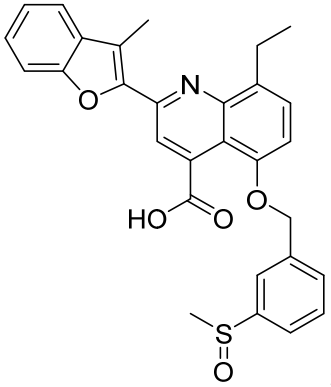
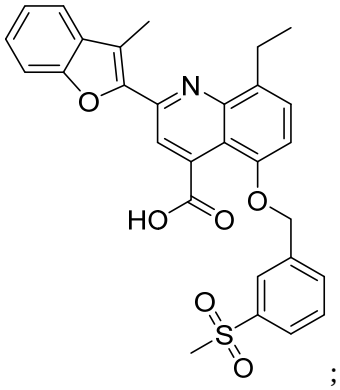
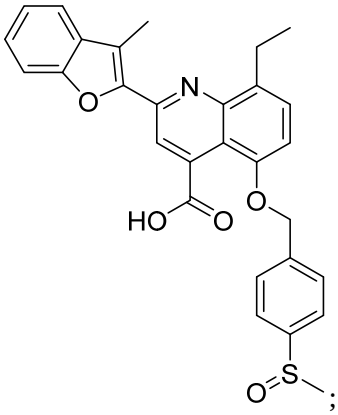
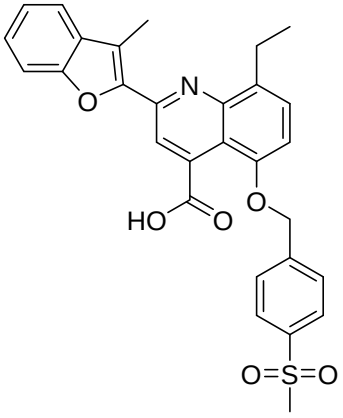
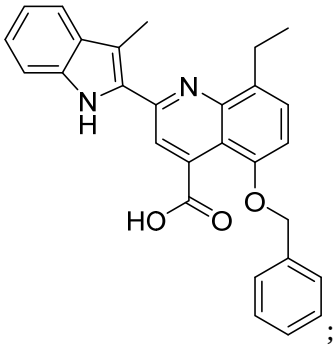
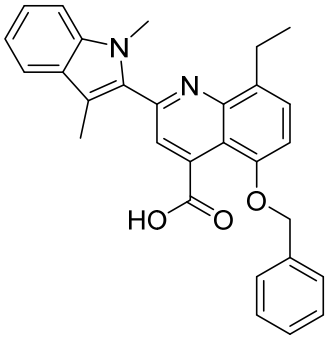
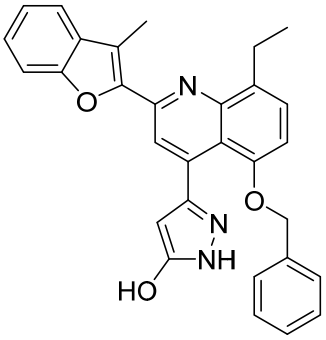
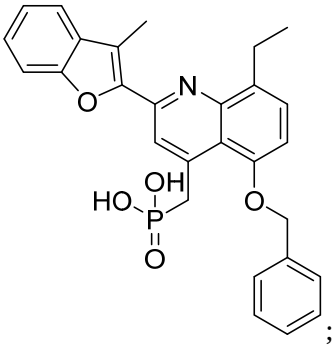
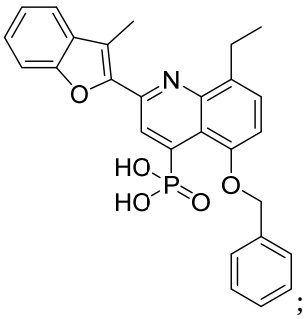
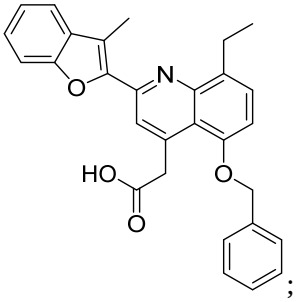
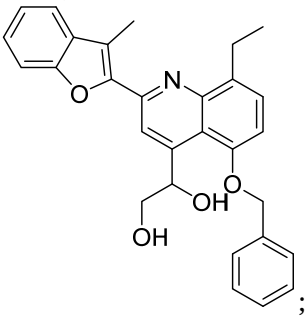
;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

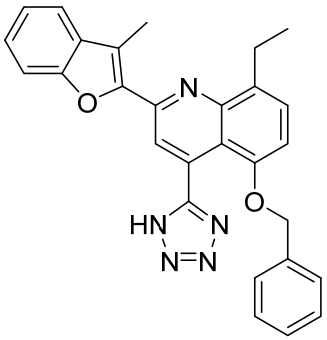
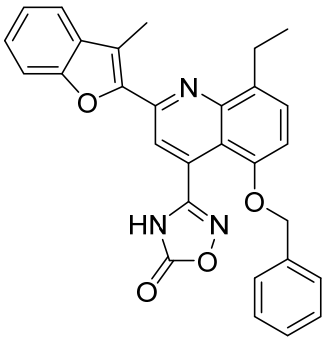
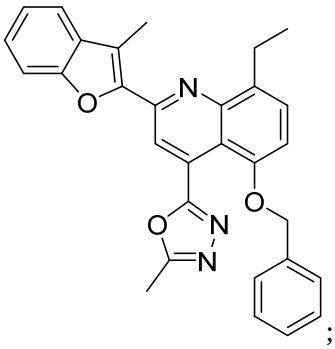
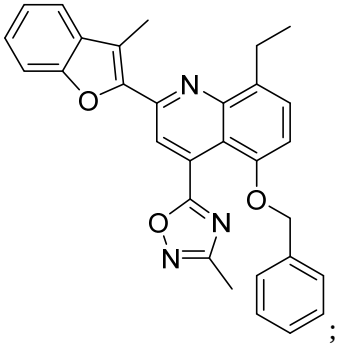
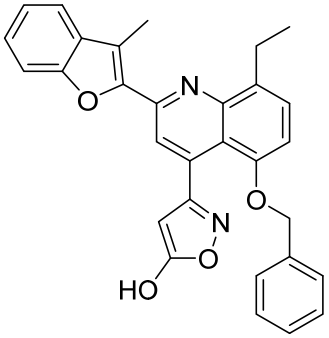
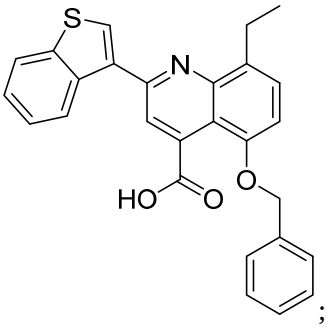
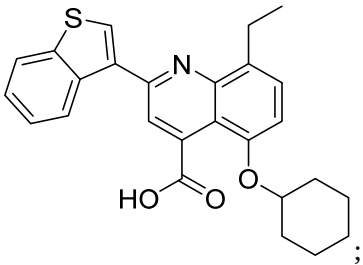
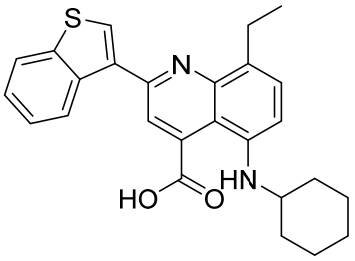
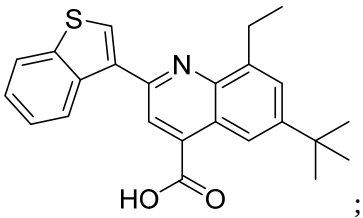
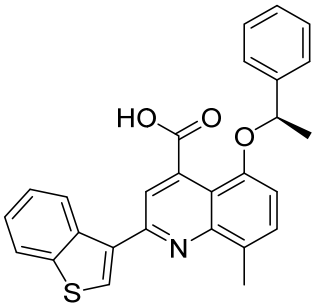
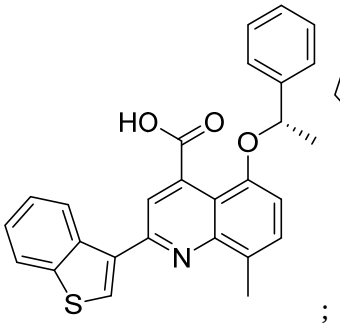
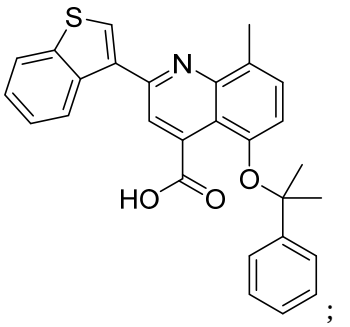
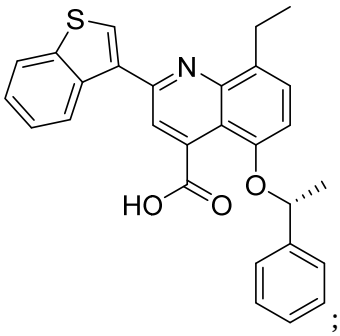
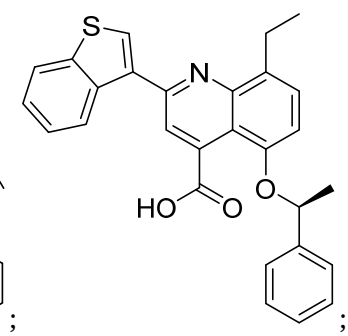
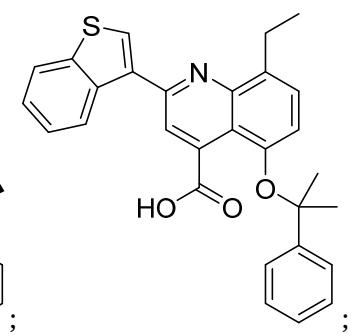

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

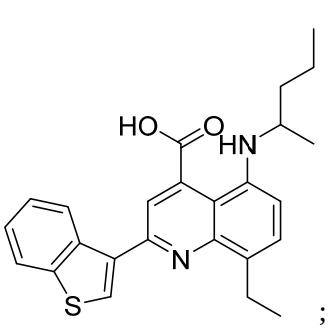
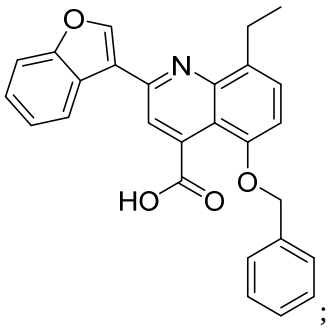
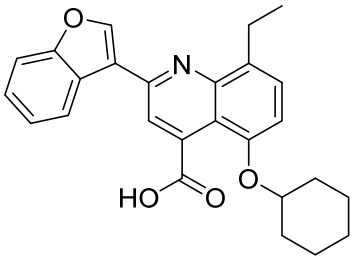
;

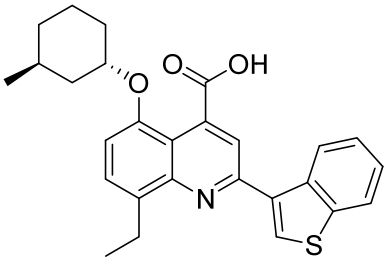
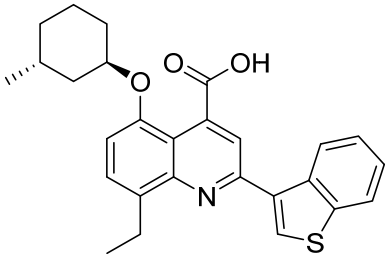
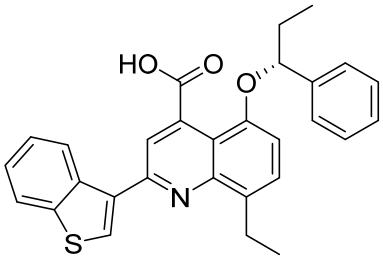
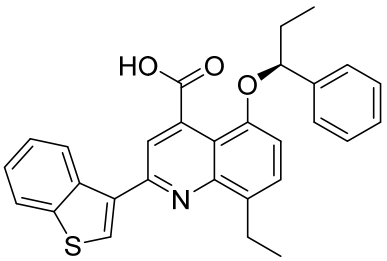
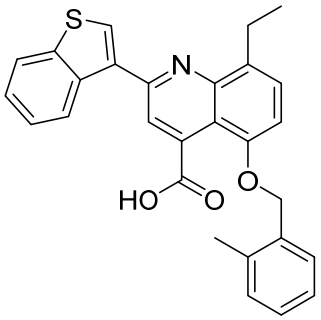
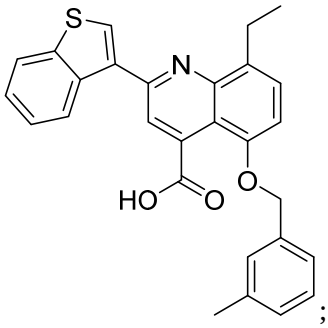
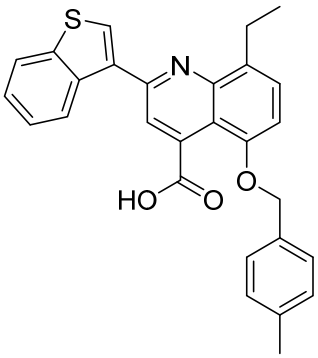
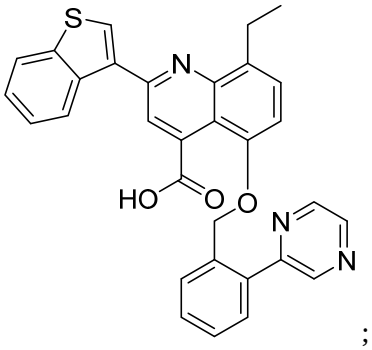
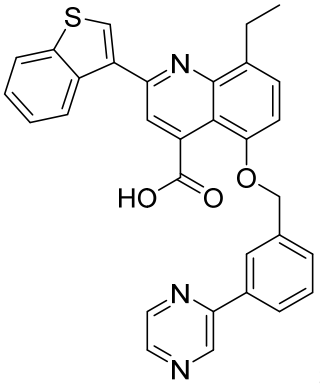
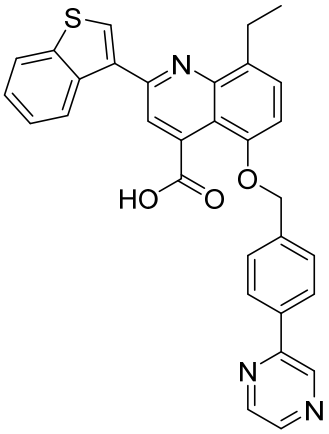
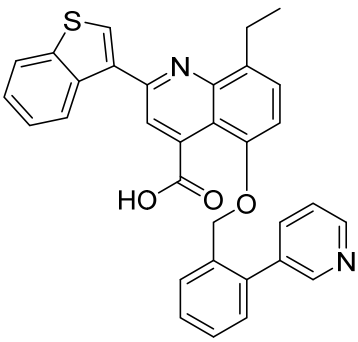
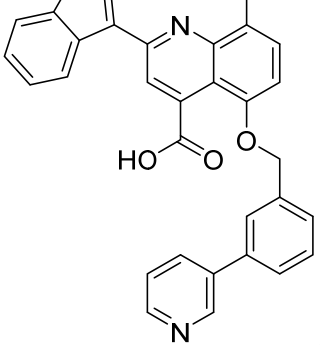

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

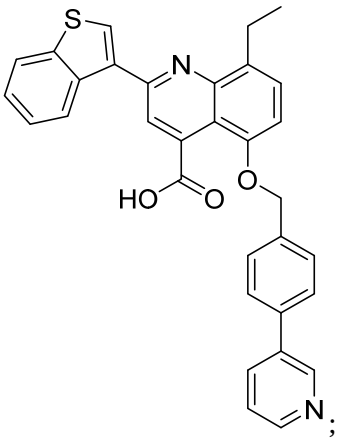
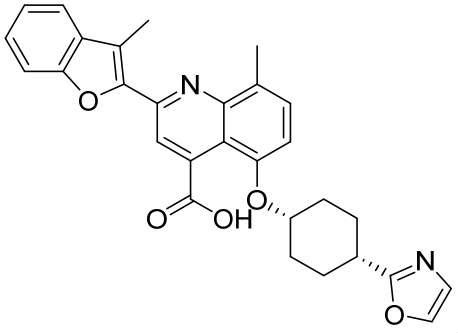
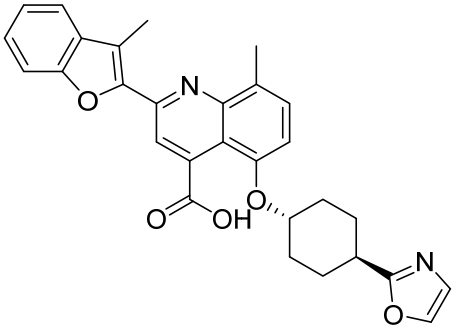
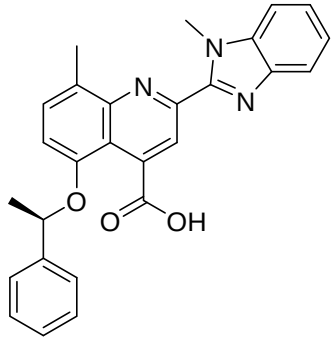
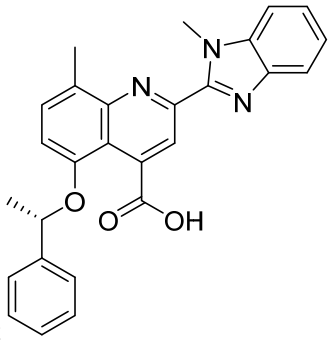
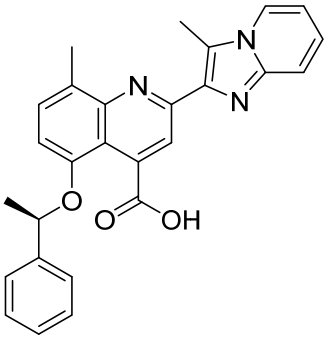
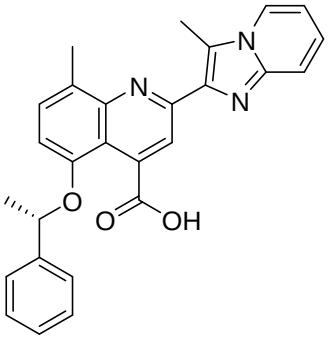
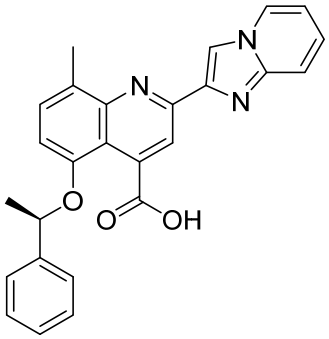
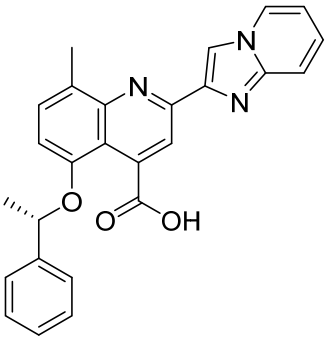
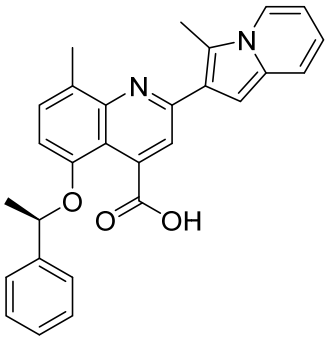
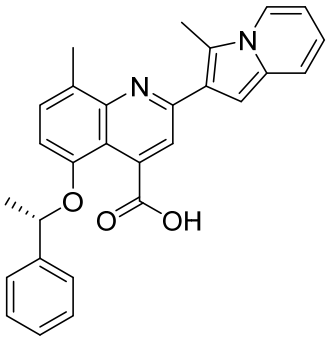
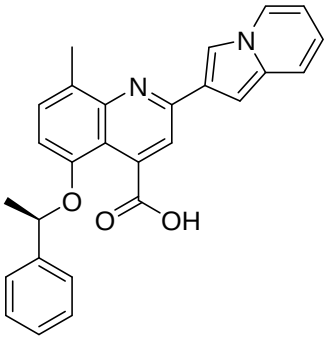
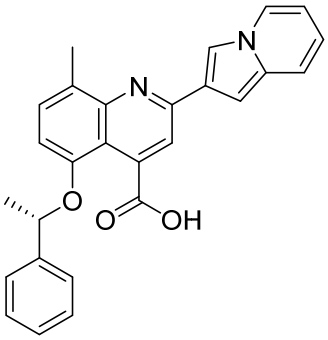
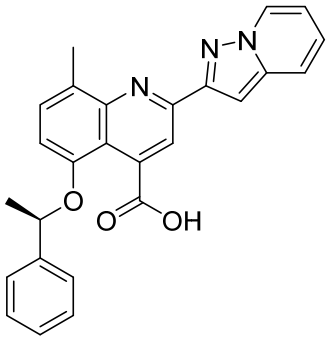




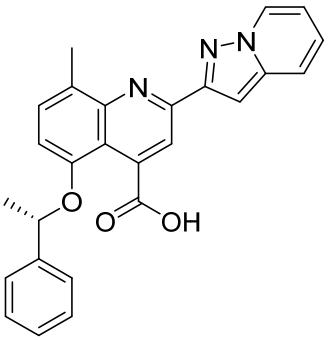
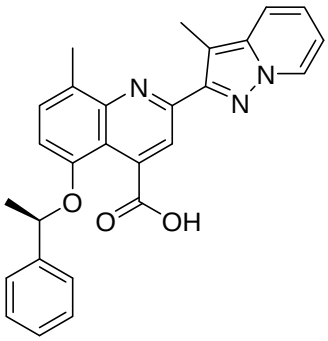
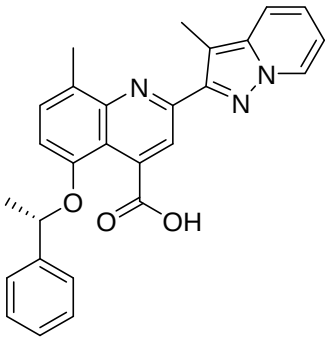
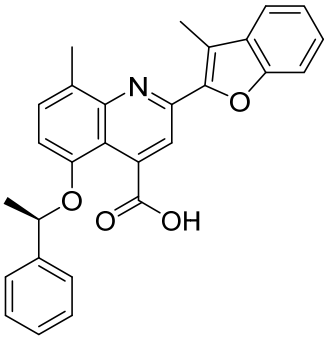
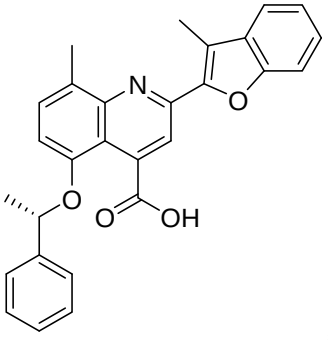
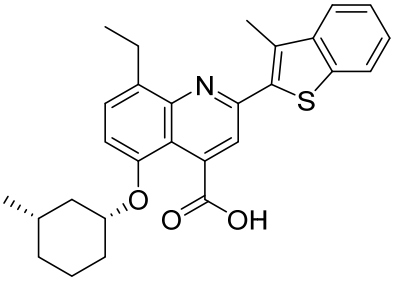
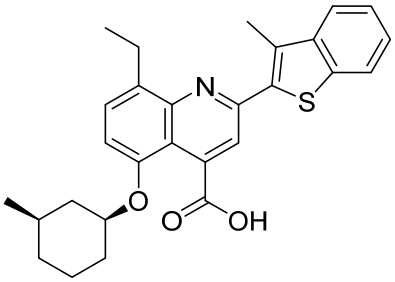
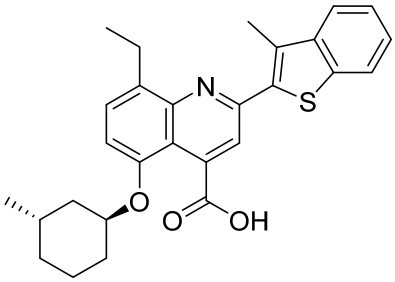
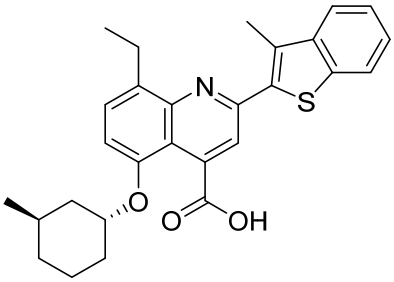
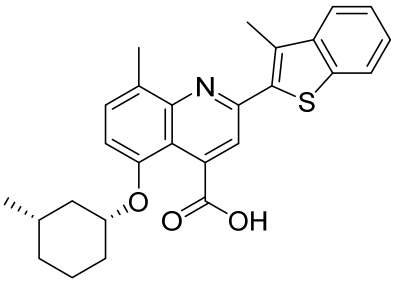
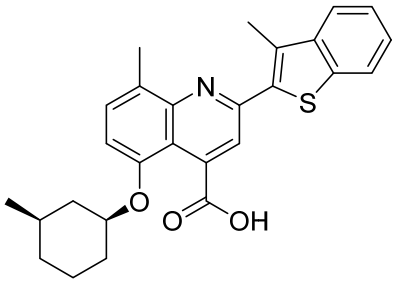
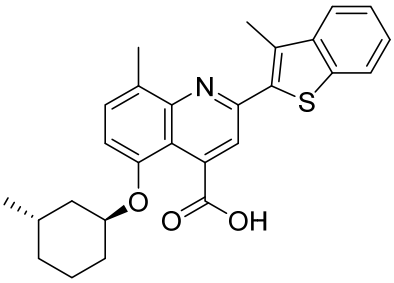
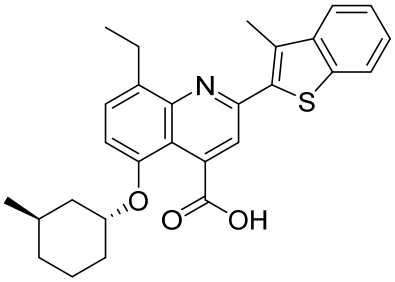
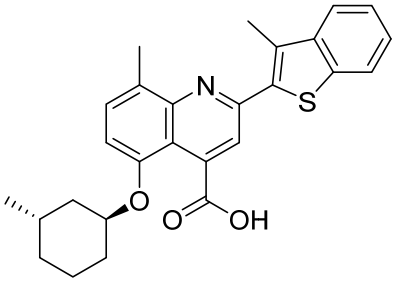
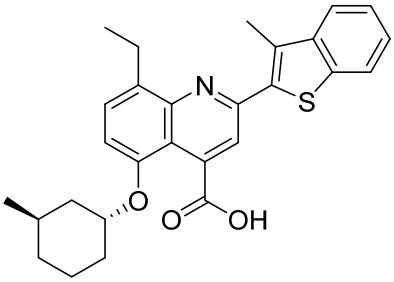

;

;

;

;

;

;

;

;

;

;

;

;

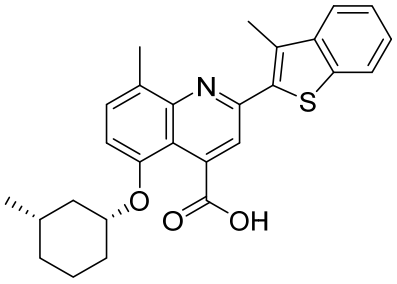
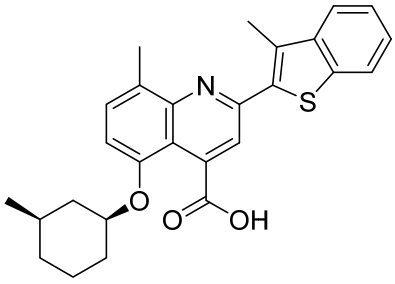
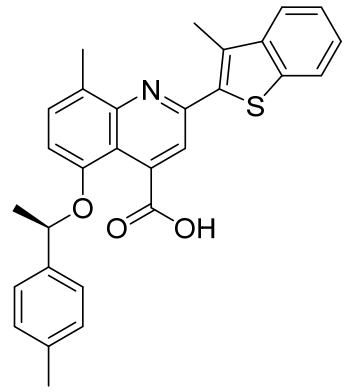
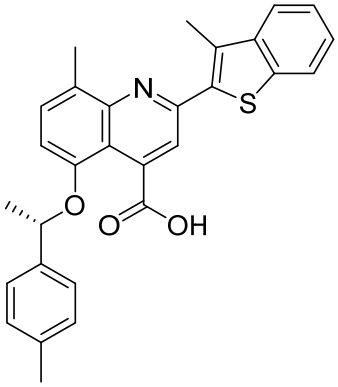
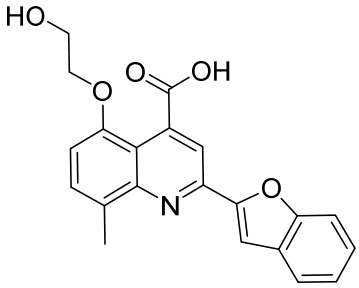
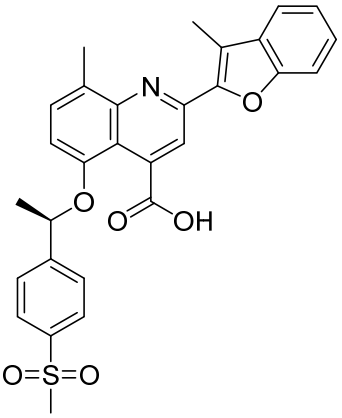
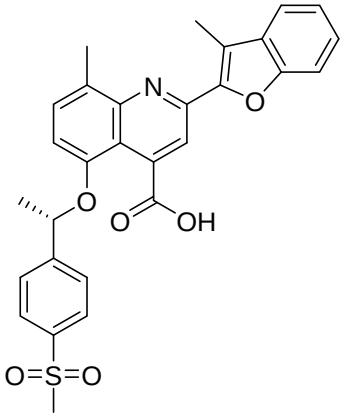
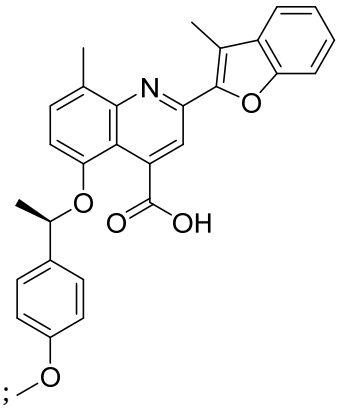
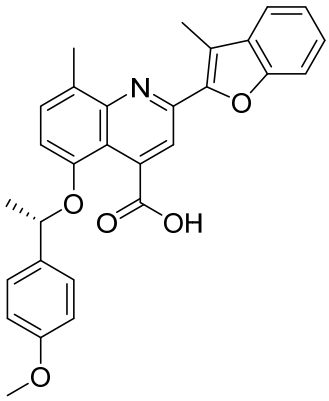
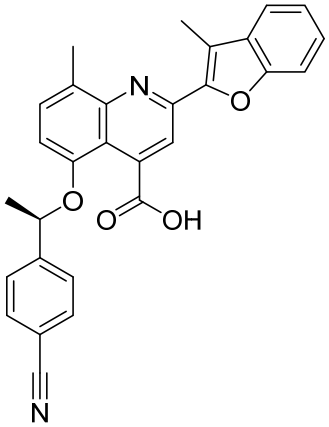
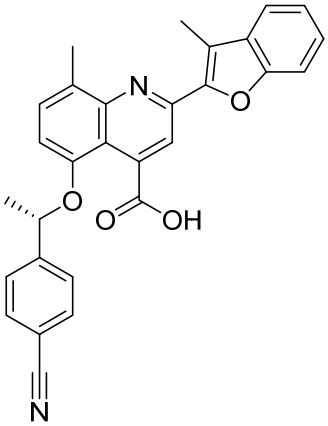
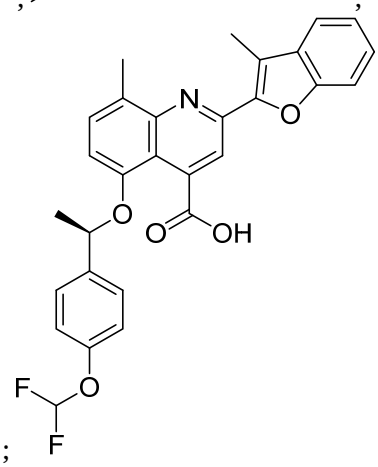
;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

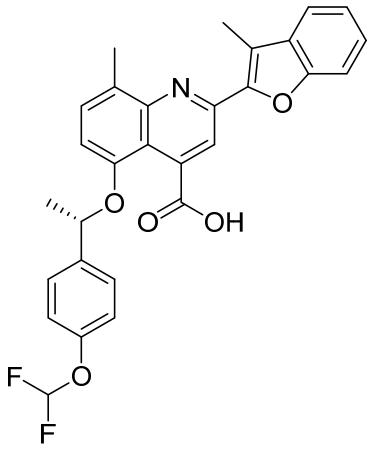
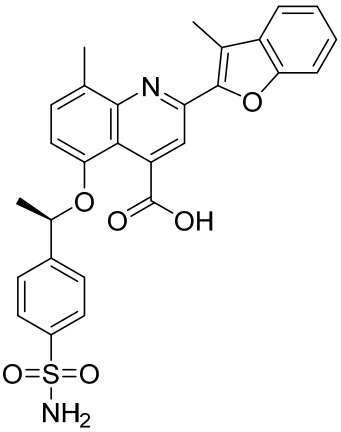
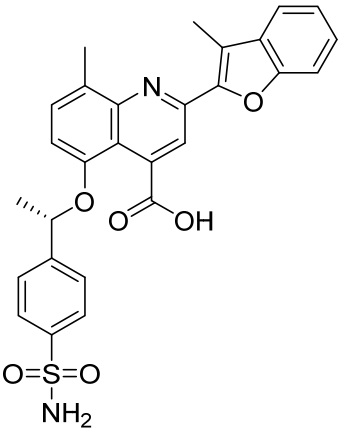
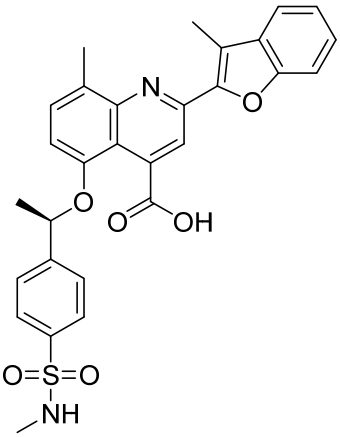
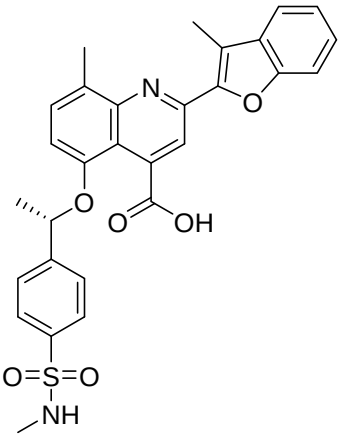
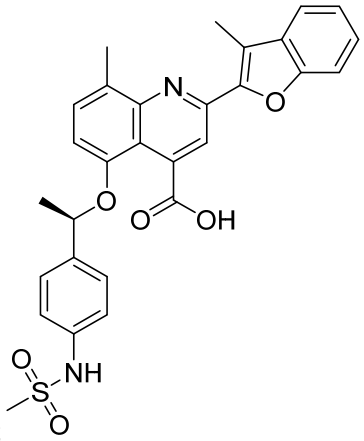
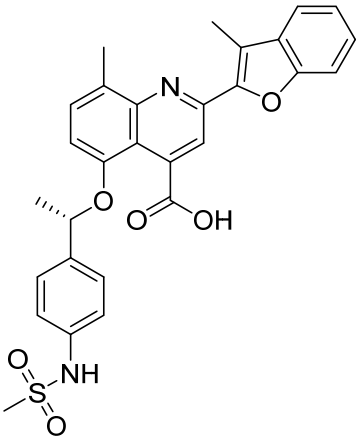
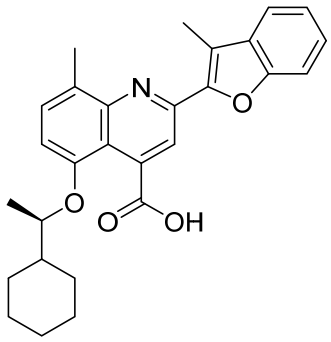
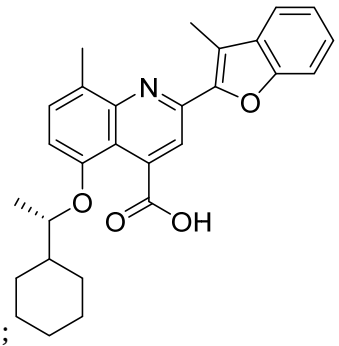
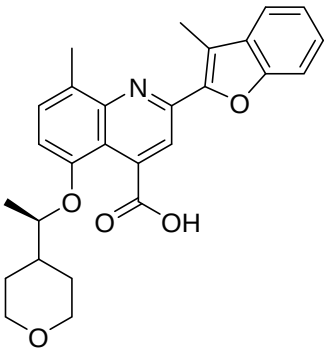
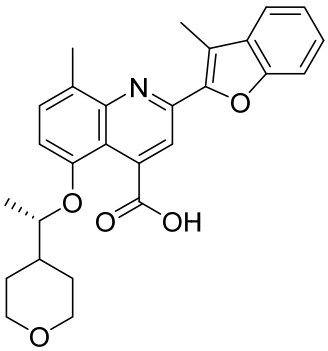
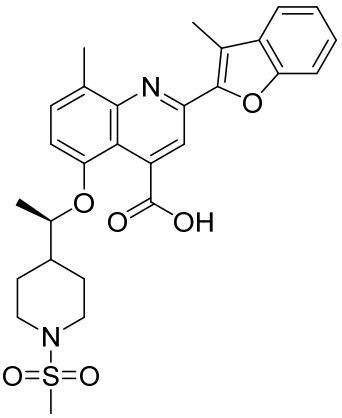

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

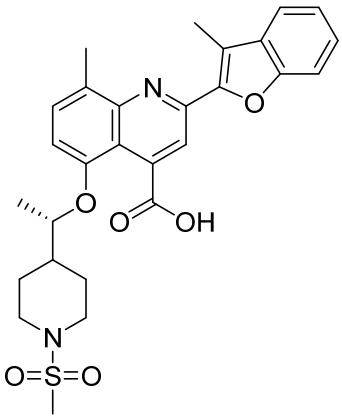
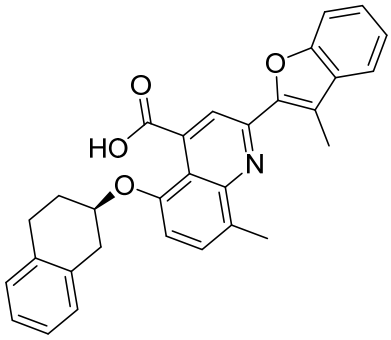
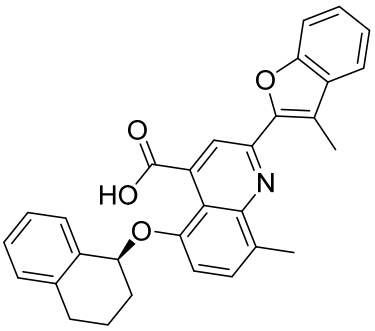
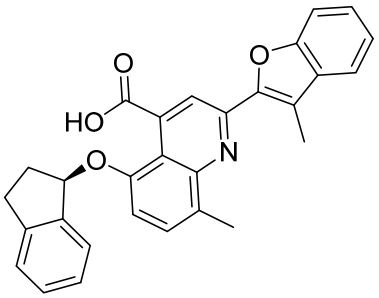
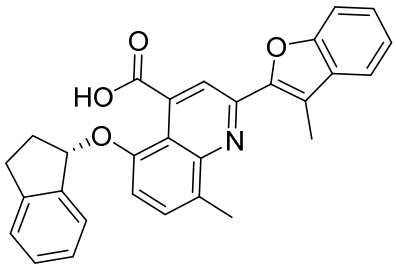
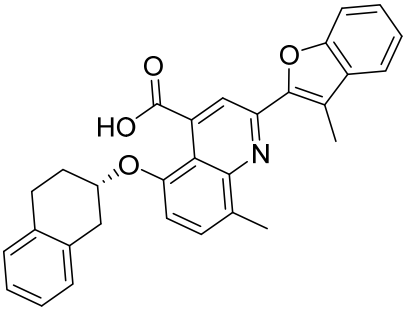
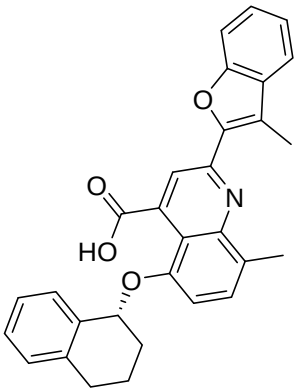
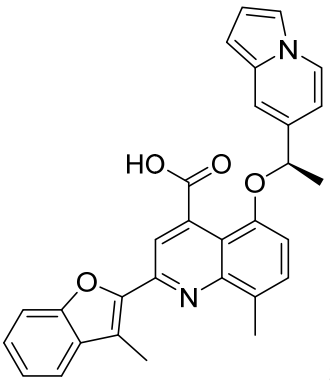
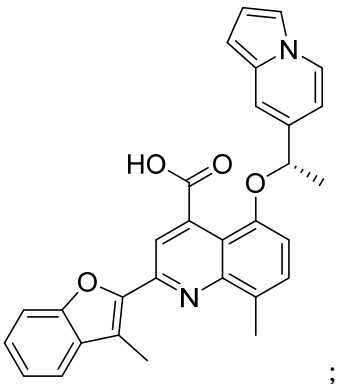
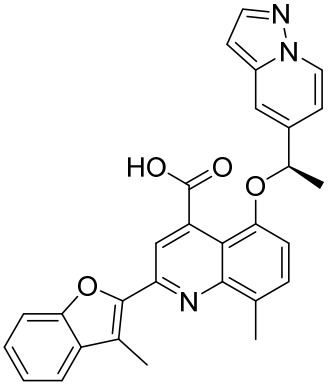
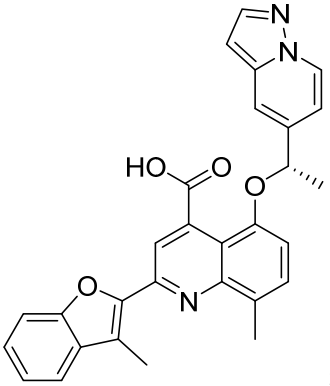
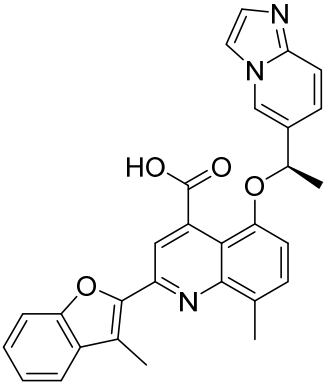

;

;

;

;

;

;

;

;

;

;

;

;

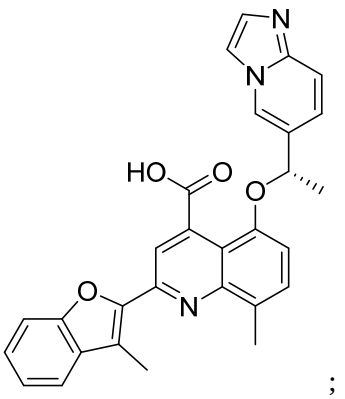
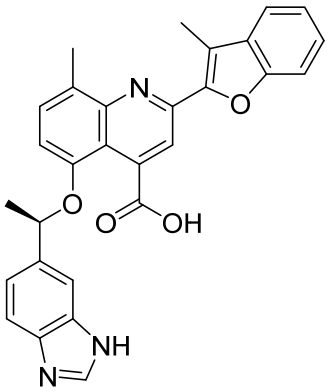
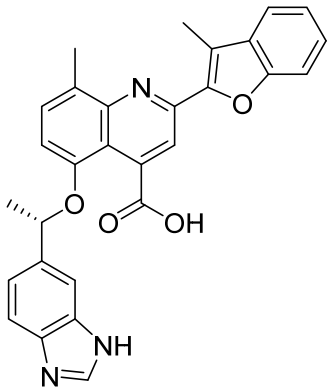
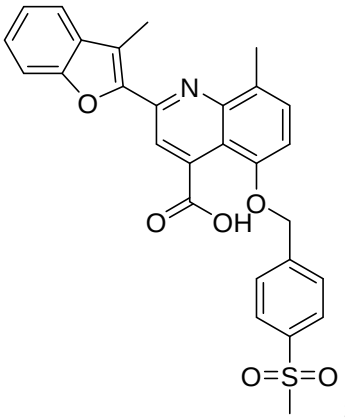
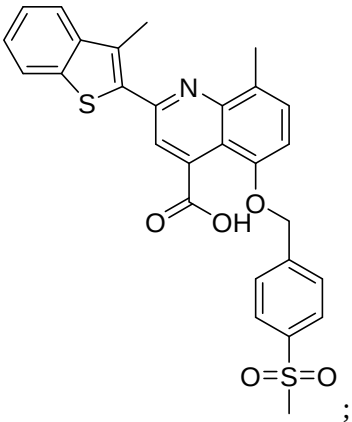
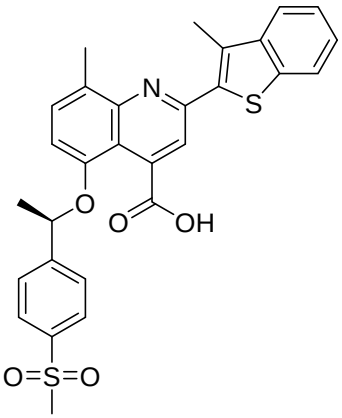
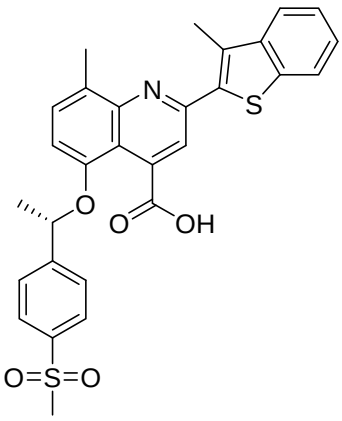
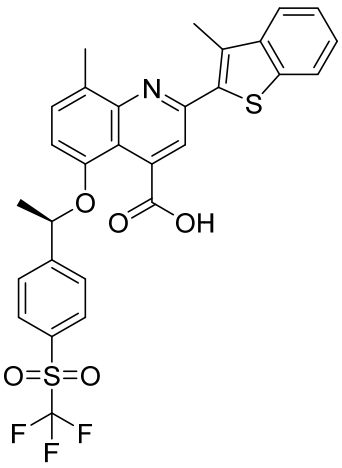
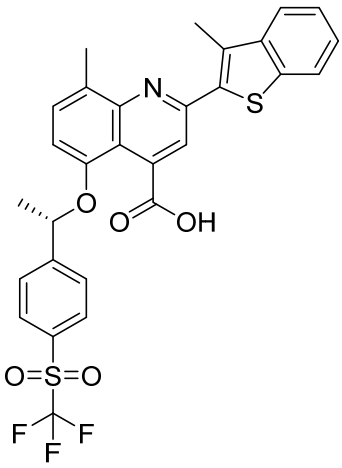
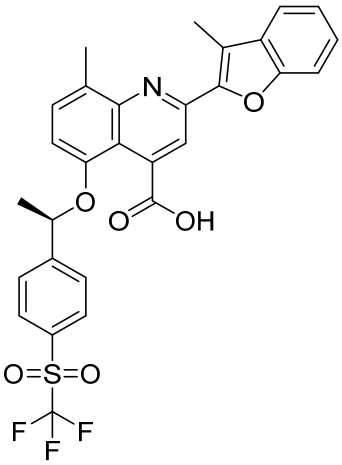
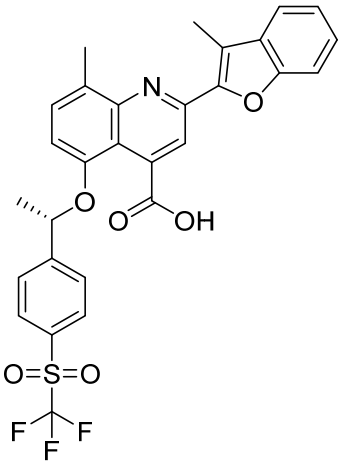
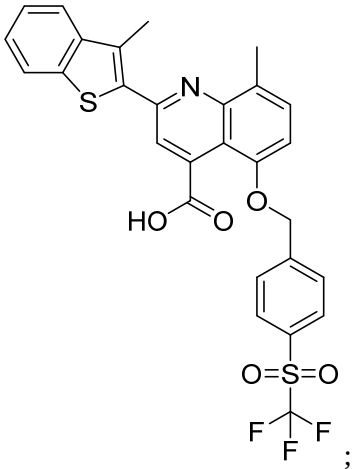
;

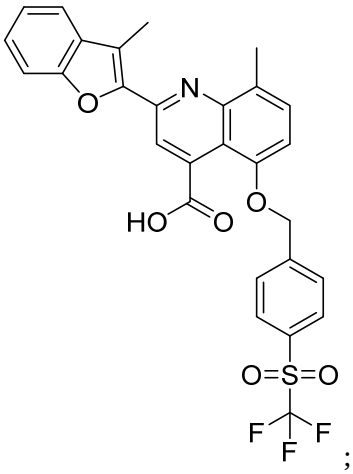
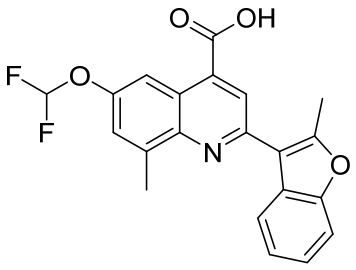
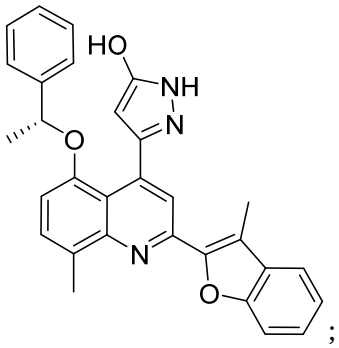
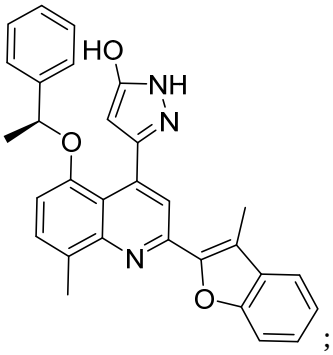
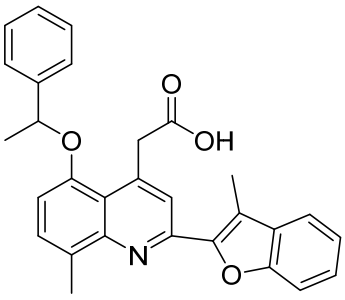
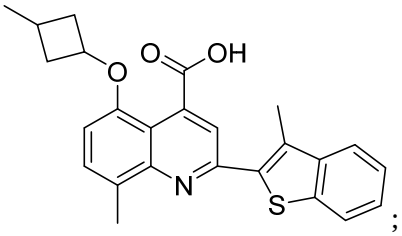
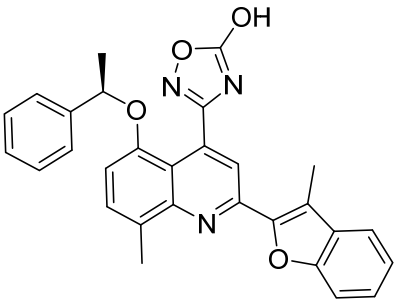
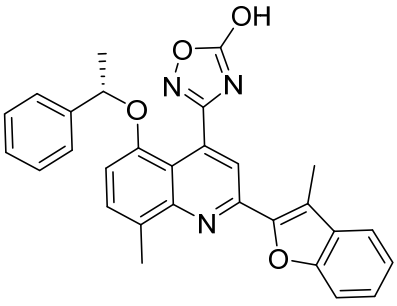
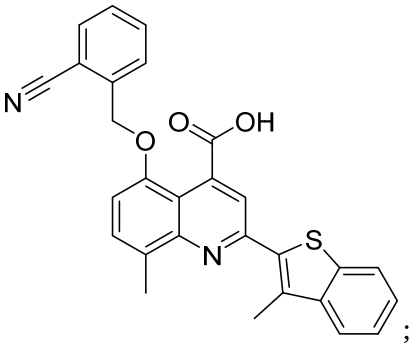
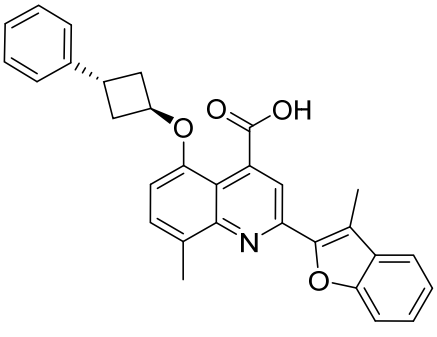
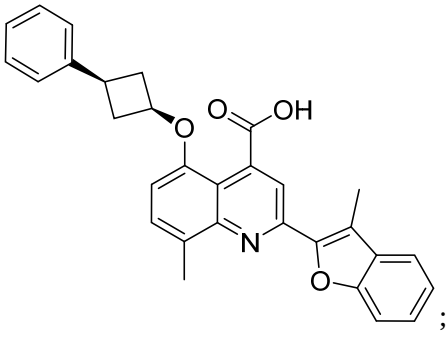
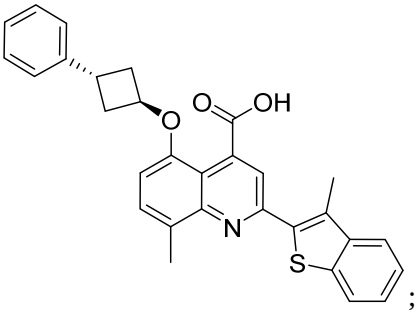
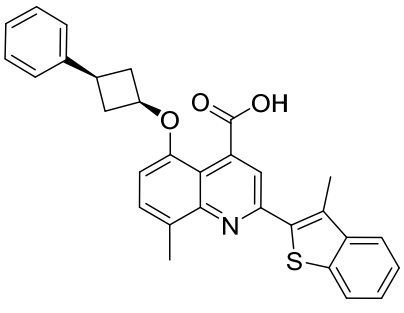
;

;


;

;

;

;

;

;

;

;

;

;

;

;

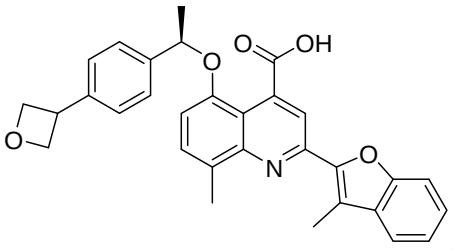
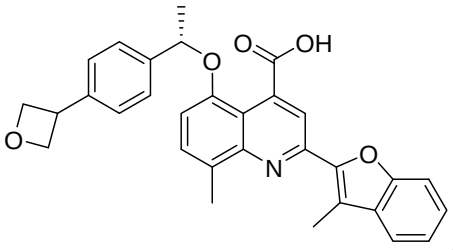
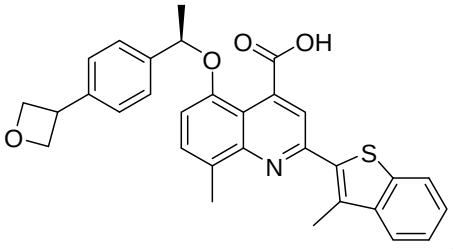
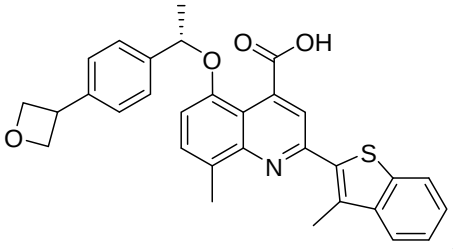
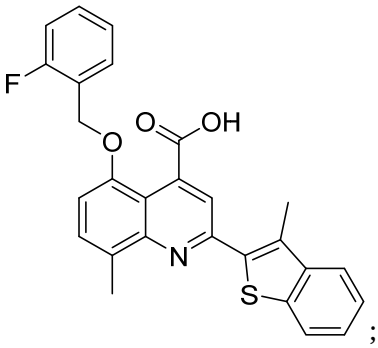
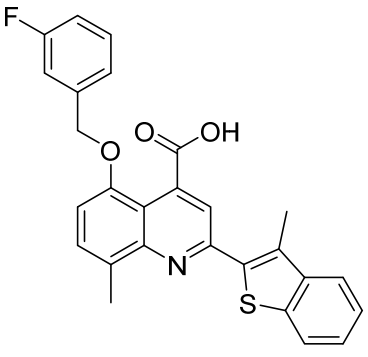
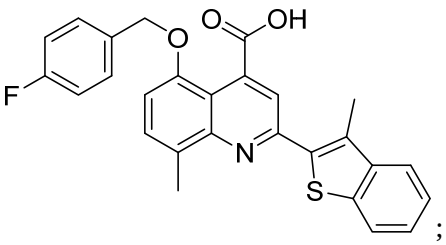
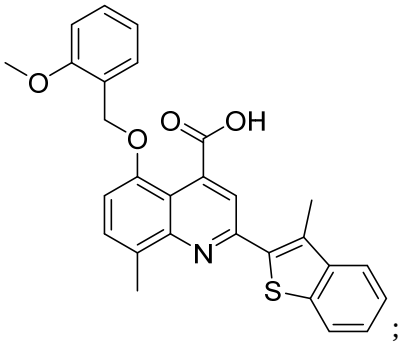
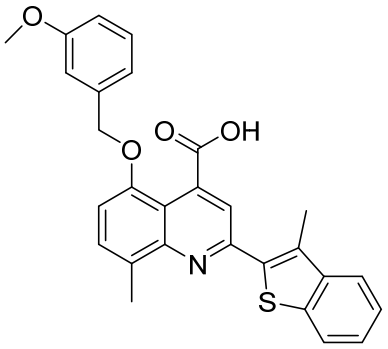
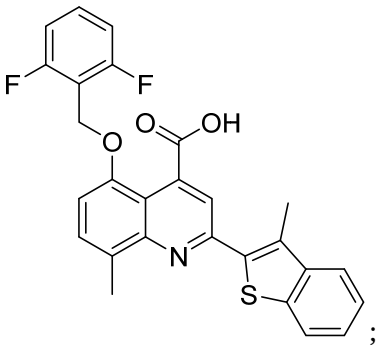
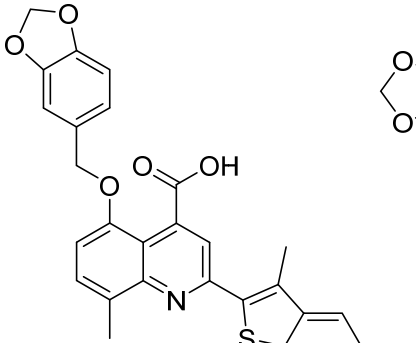
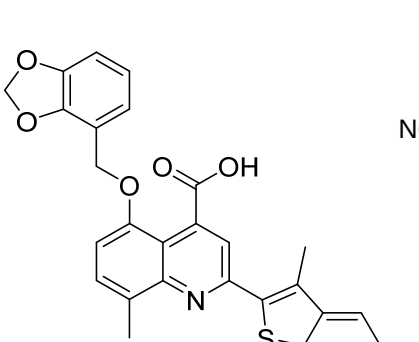
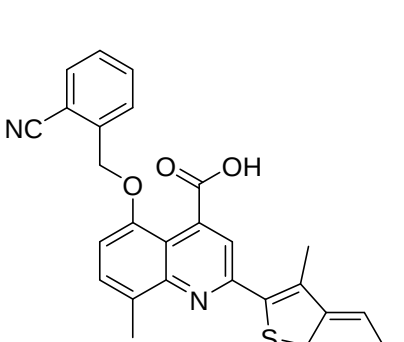
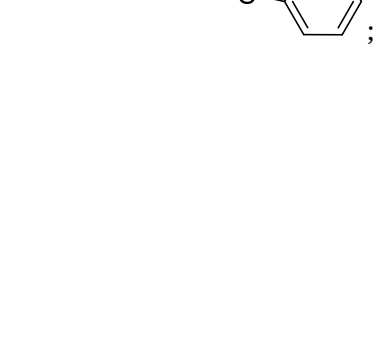
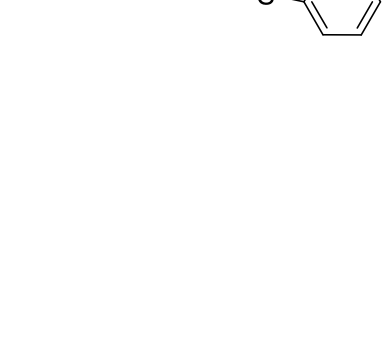
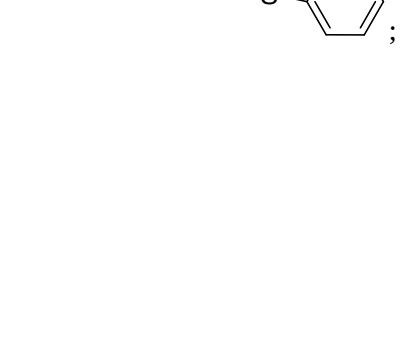













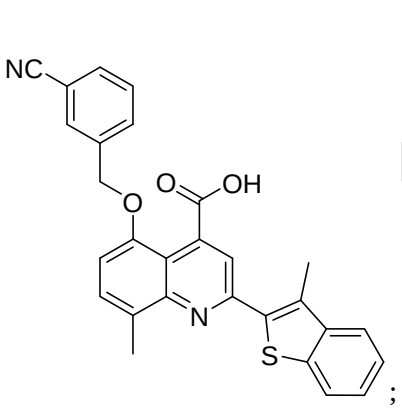

N
N
HO
O
O
O
N
;

N
O
O
O
OH
NH
N
;

N
O
O
O
OH
NH
N
;

O
N
O
OH
O
O=S=O
;

S
N
O
OH
O
O=S=O
;

N
S
O
O
OH
O=S=O
;

N
S
O
O
OH
O=S=O
;

N
S
O
O
OH
O=S=O
F
F
F
;

N
S
O
O
OH
O=S=O
F
F
F
;

N
O
O
O
OH
O=S=O
F
F
F
;

N
O
O
O
OH
O=S=O
F
F
F
;

S
N
HO
O
O
O=S=O
F
F
F
;

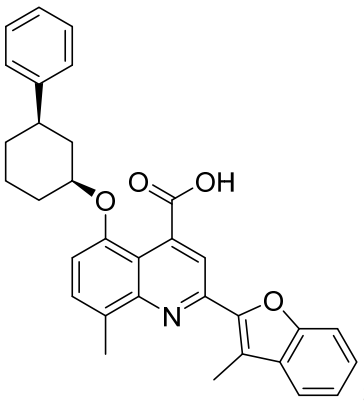

;

;

;

;

;

;

;

;

;

;

;

;

;

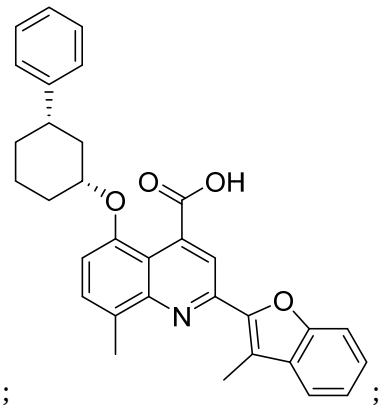
;

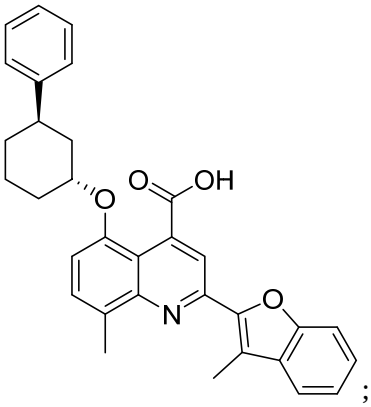
;

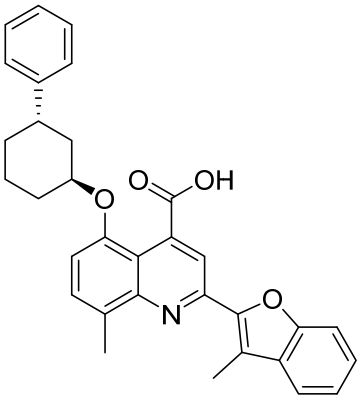

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

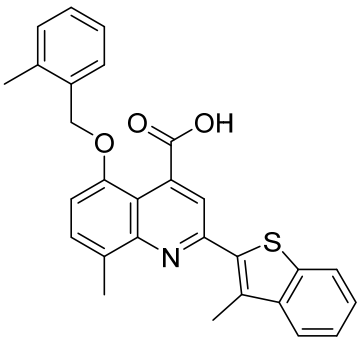

NC
O
OH
O
N
S
;

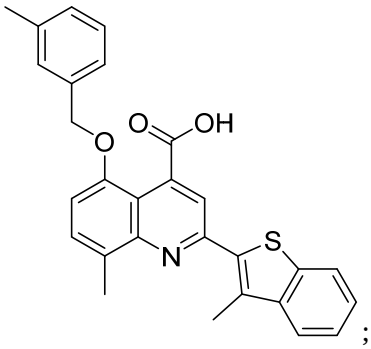

O
OH
O
N
O
;

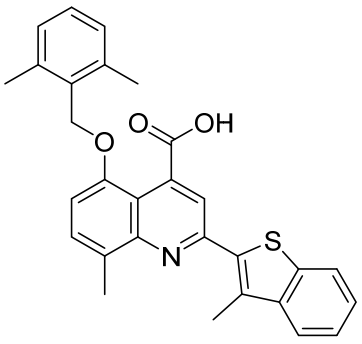

O
OH
O
N
O
;

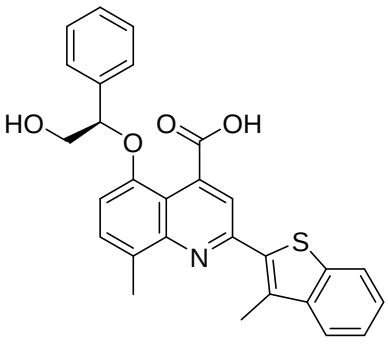

O
OH
O
N
O
;

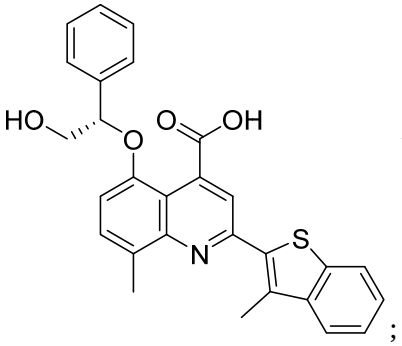

O
OH
O
N
O
;

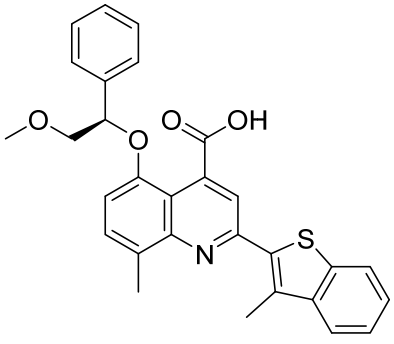

O
OH
O
N
S
;

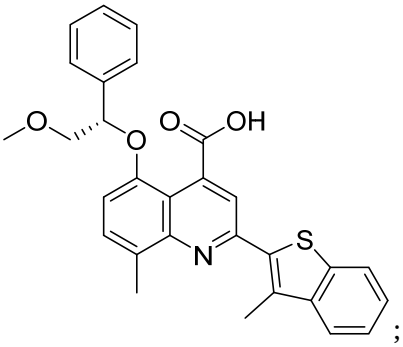

O
OH
O
N
S
;

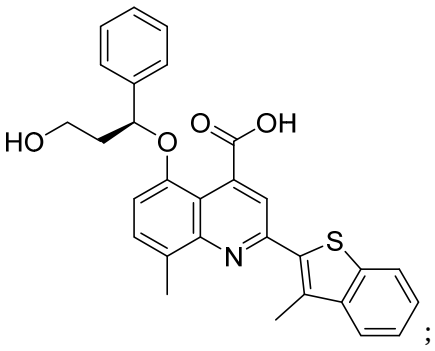

O
OH
O
N
S
;

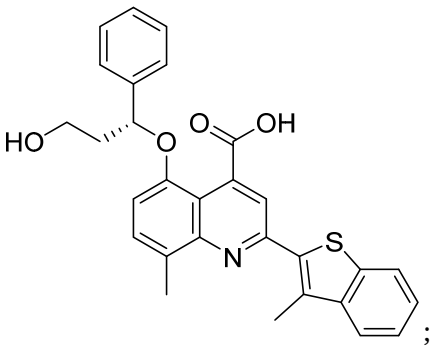

HO
O
OH
O
N
S
;

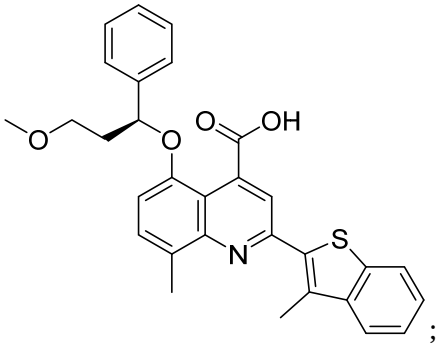

HO
O
OH
O
N
S
;

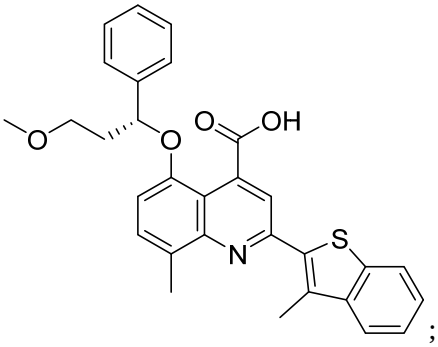

O
O
OH
O
N
S
;

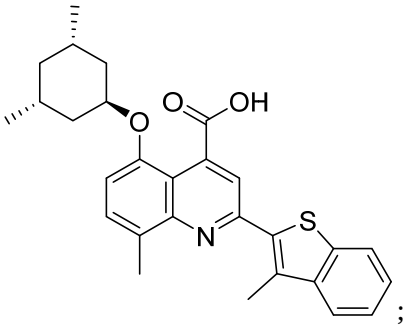

O
O
OH
O
N
S
;

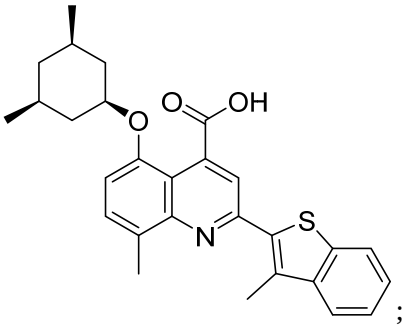

HO
O
O
OH
N
S
;

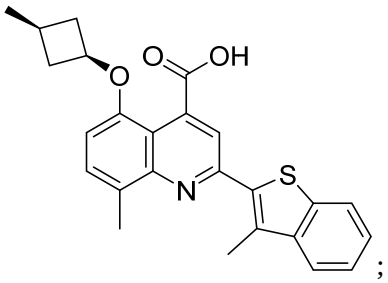

HO
O
O
OH
N
S
;

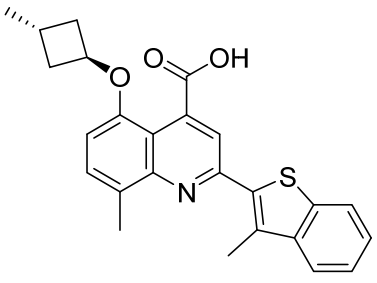

O
O
O
OH
N
S
;

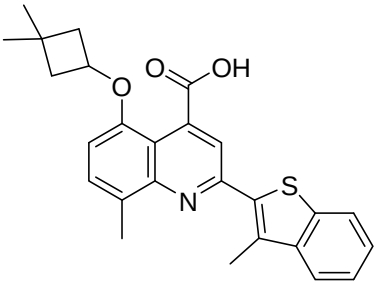

O
O
O
OH
N
S
;

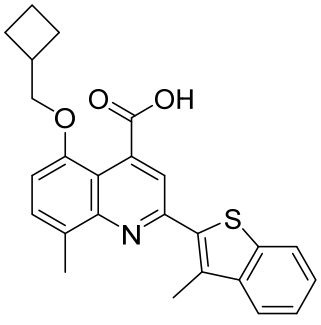

O
O
OH
N
S
;

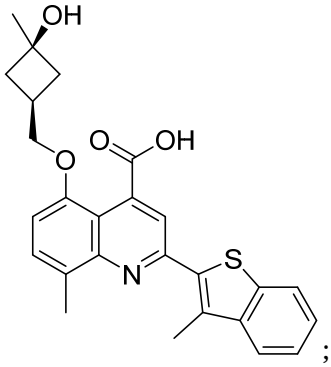

O
O
OH
N
S
;

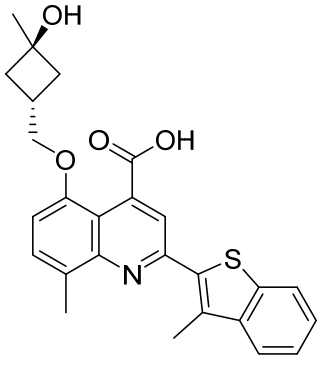

O
O
OH
N
S
;

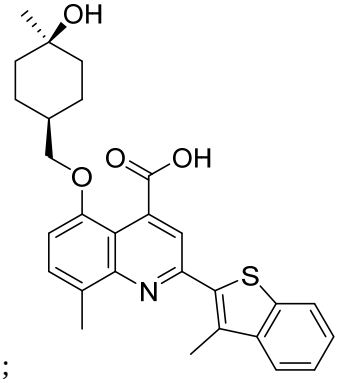

O
O
OH
N
S
;

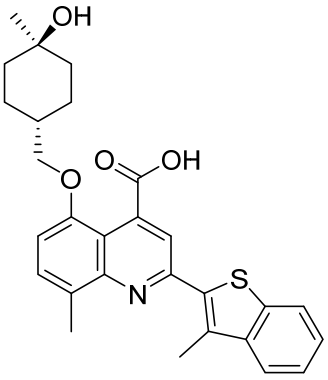
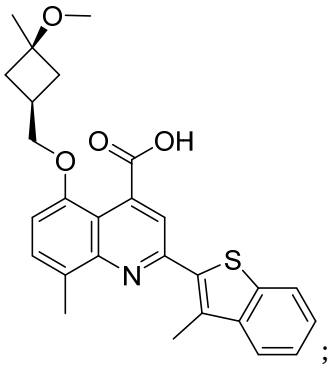
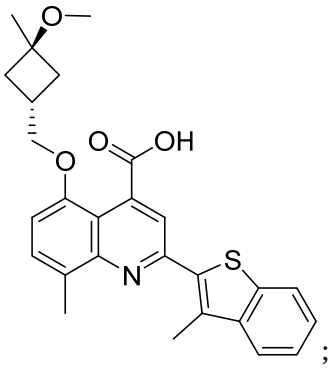
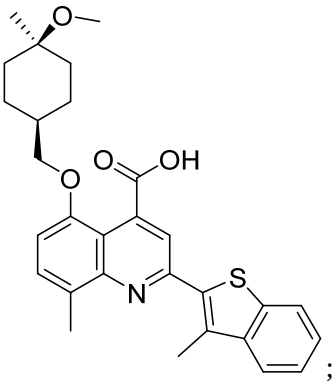
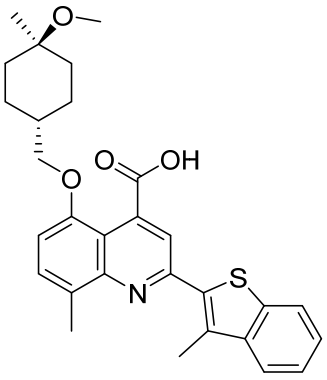
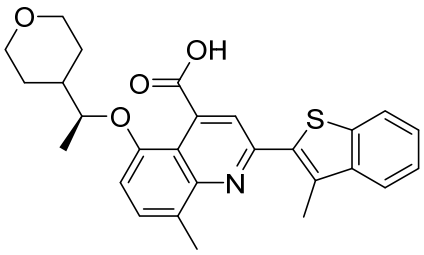
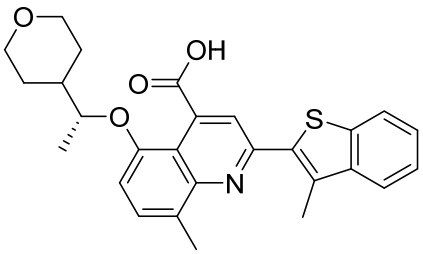
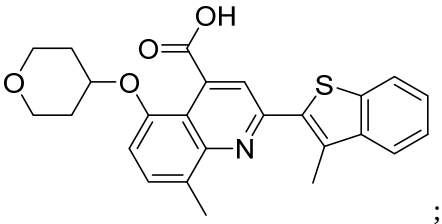
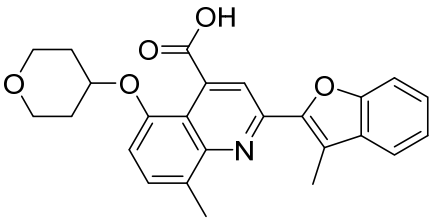
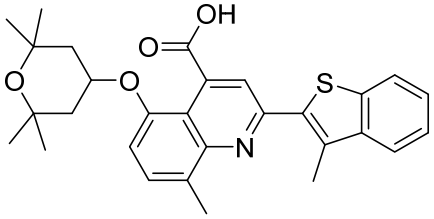
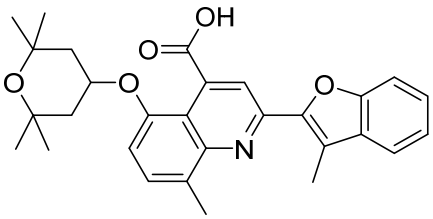
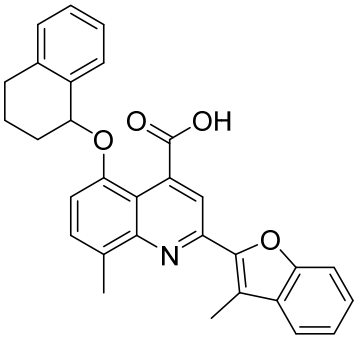
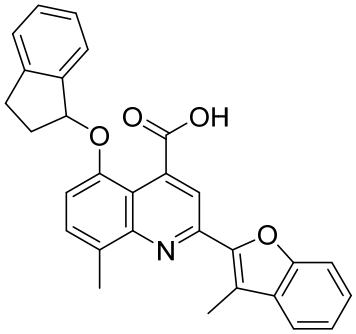

O
O
OH
N
S
;

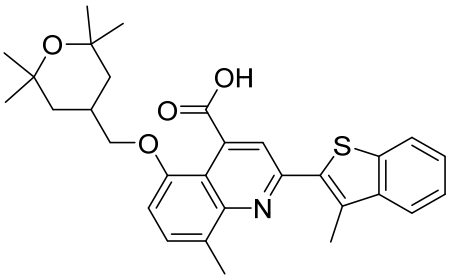
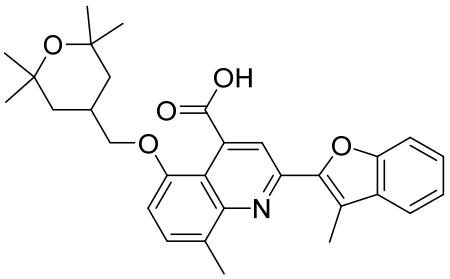
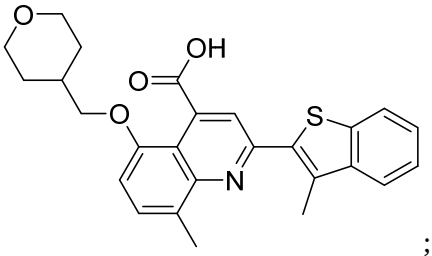
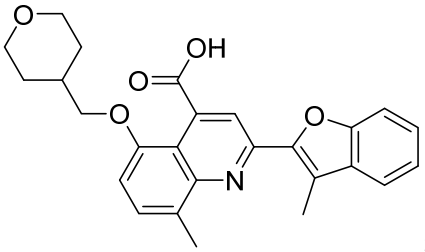
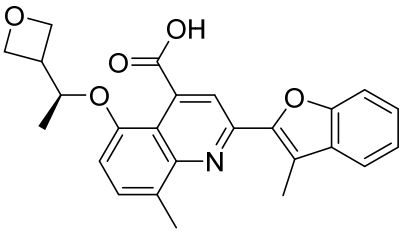
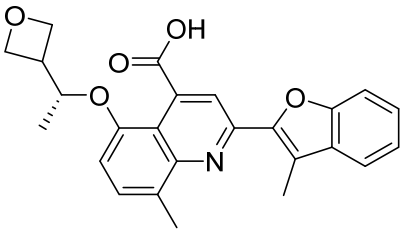
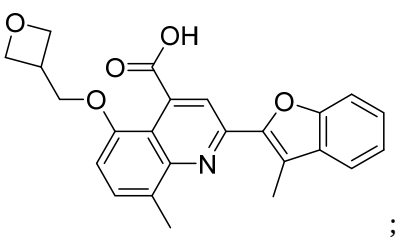
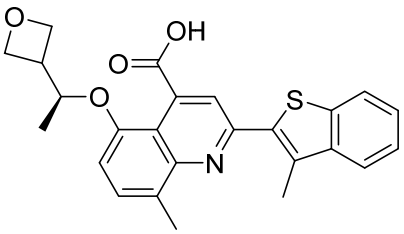
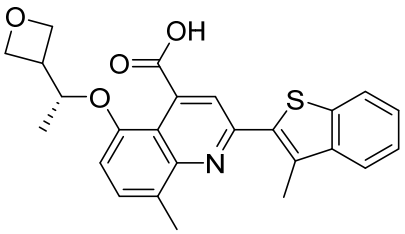
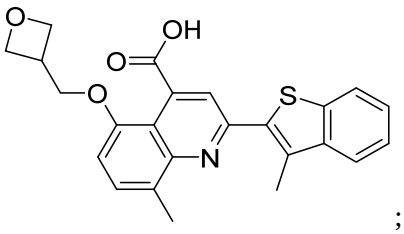
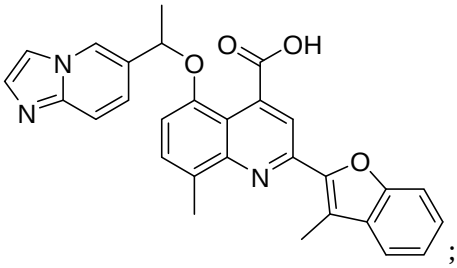
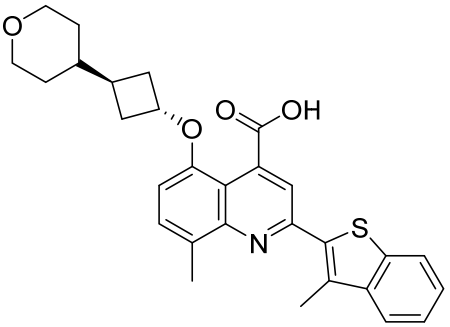
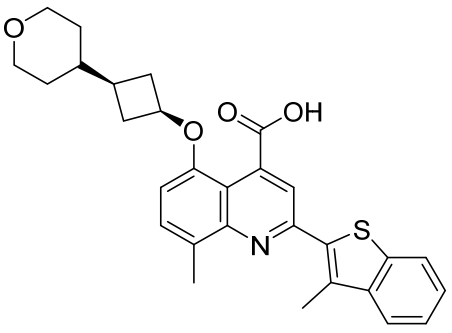
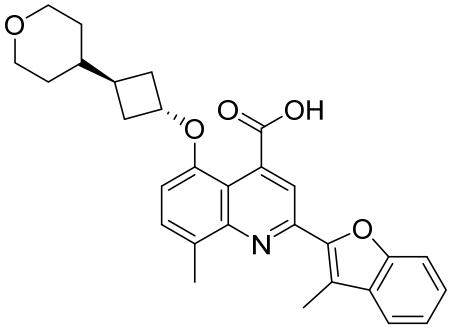

O
O
OH
N
S
;

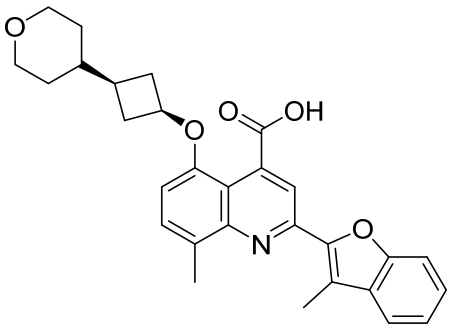
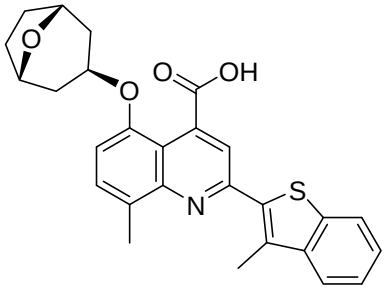
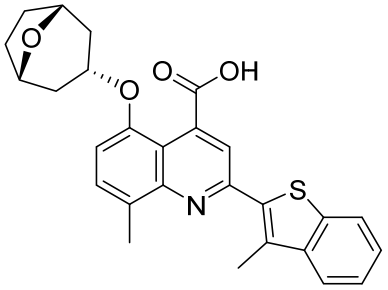
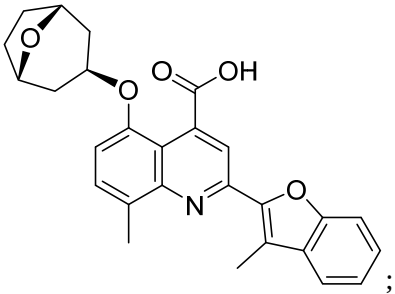
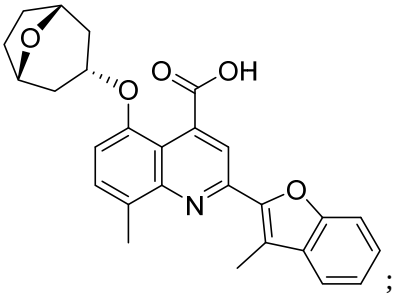
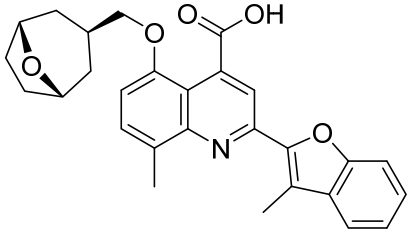
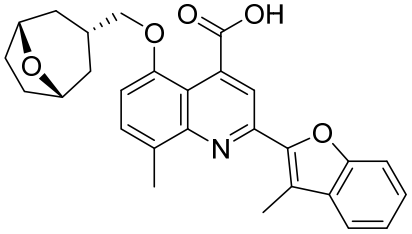
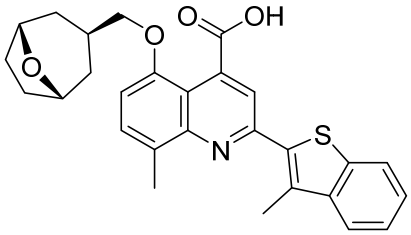
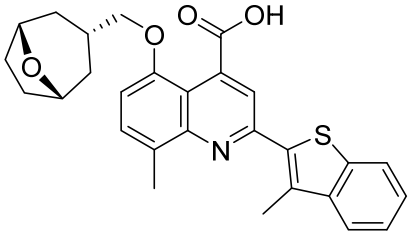
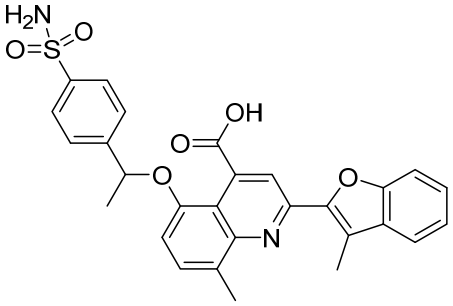
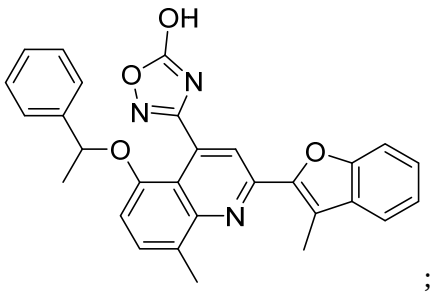
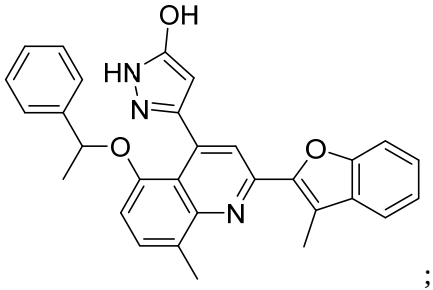
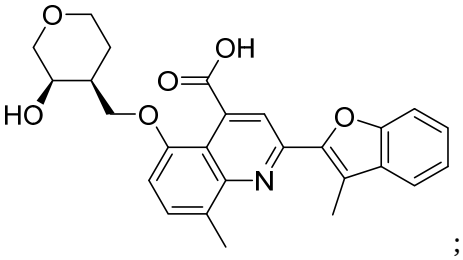

OH
O
O
OH
N
S
;

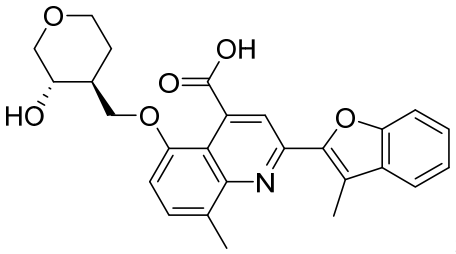
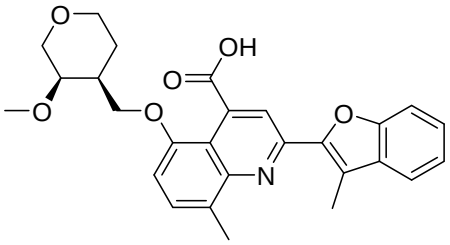
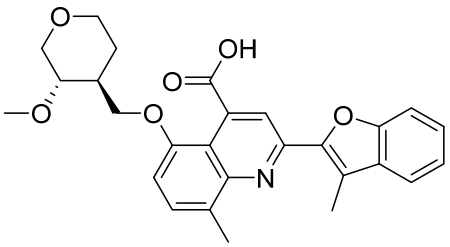
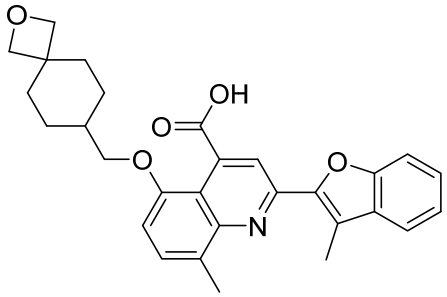
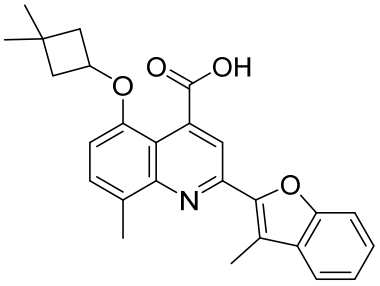
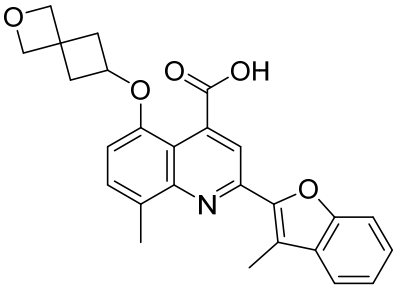
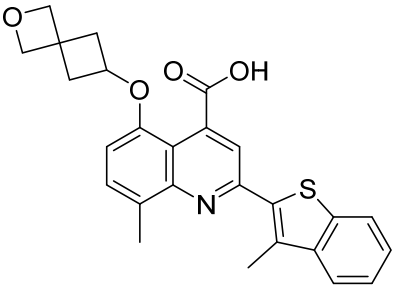
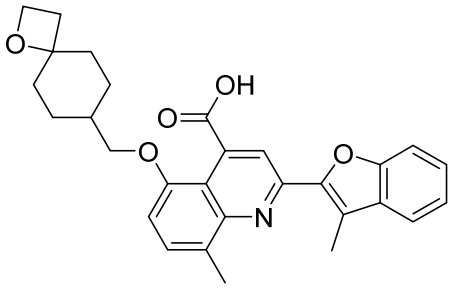
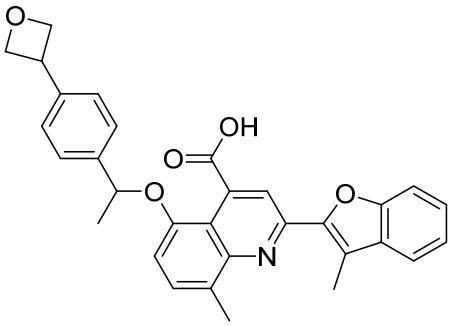
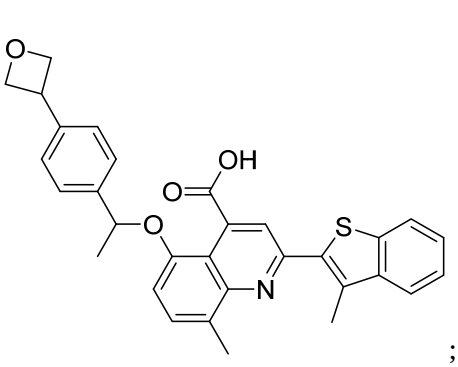
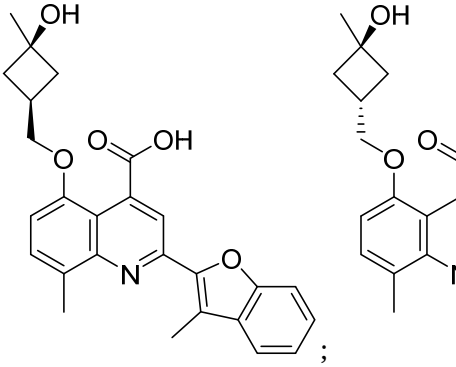

OH
O
O
OH
N
S
;


OH
O
O
OH
N
S
;

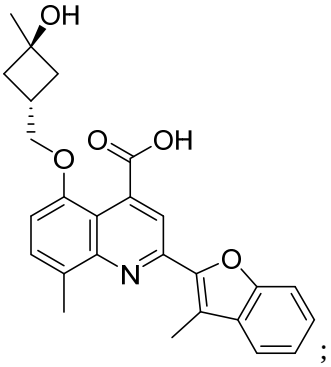

;

;

;

;

;

;

;

;

;

;

;

;

;

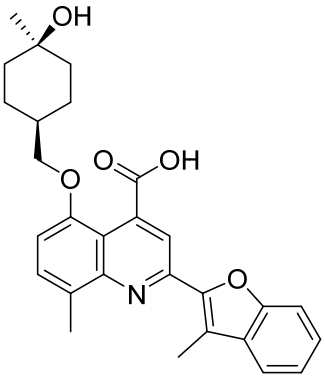
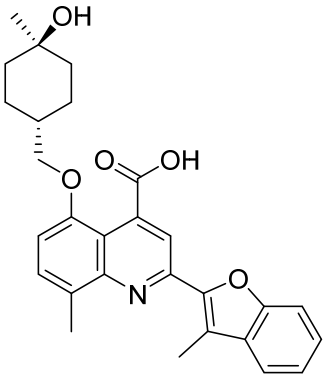
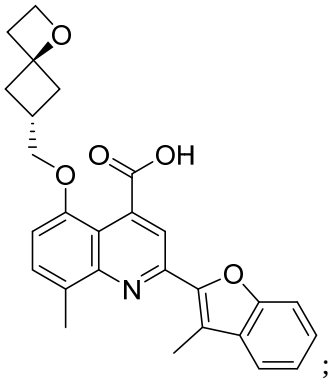
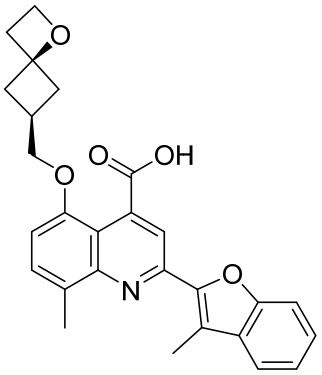
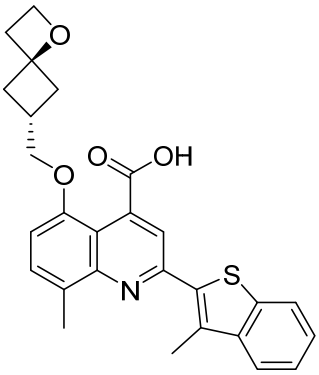
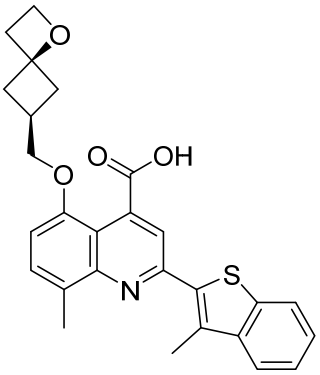
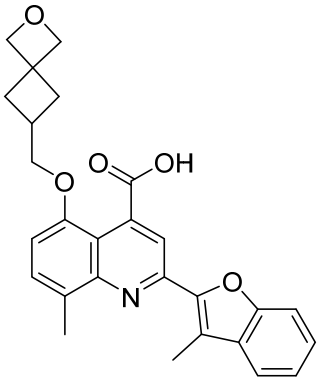
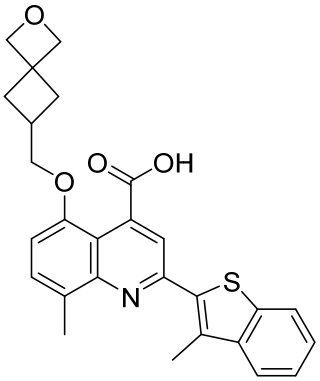
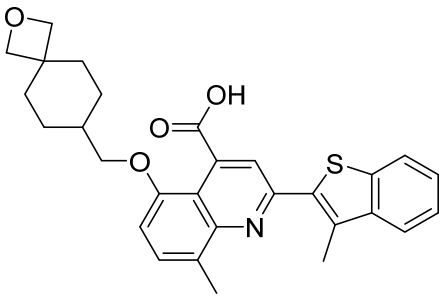
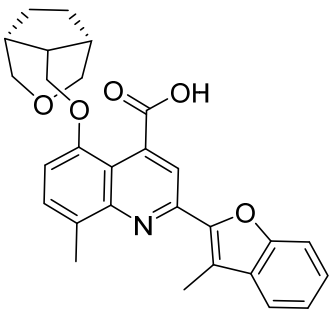
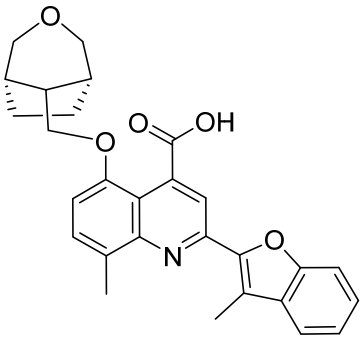
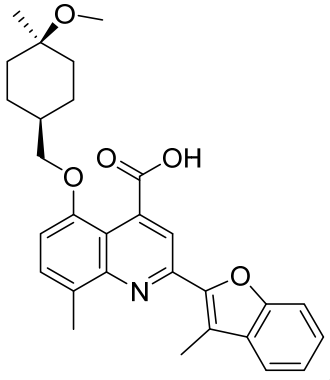

;

;

;

;

;

;

;

;

;

;

;

;

;

;

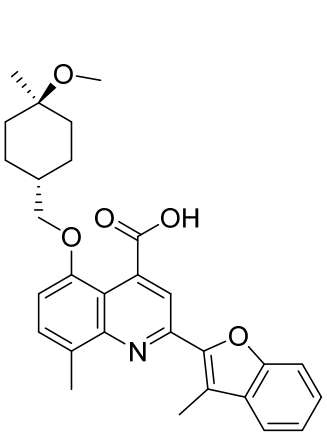
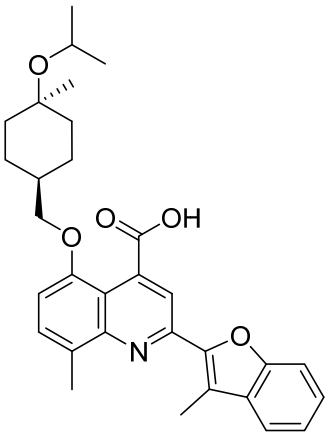
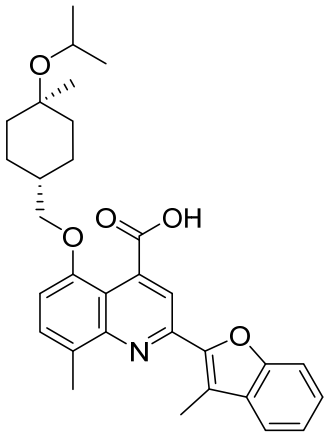
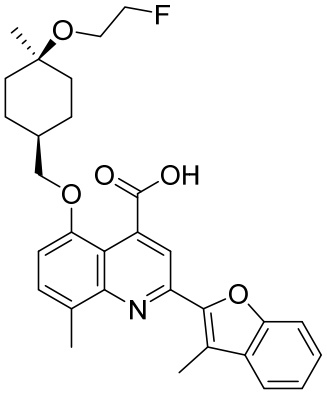
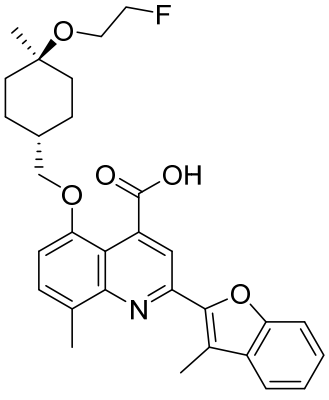
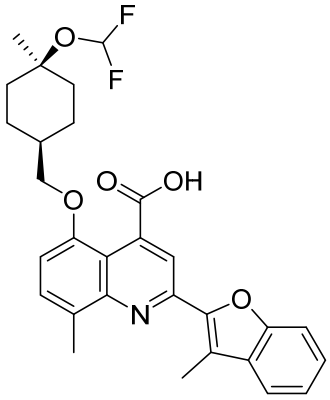
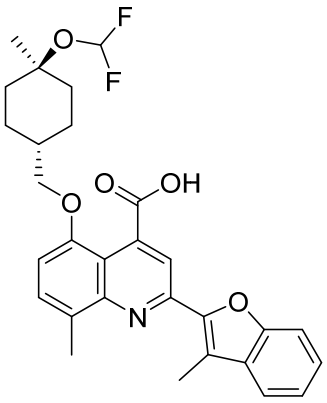
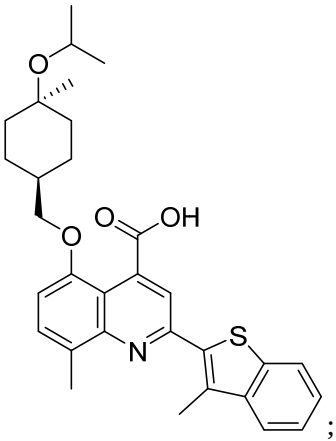
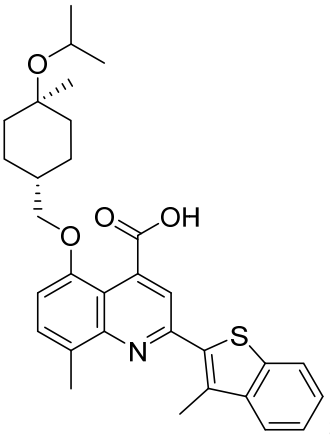
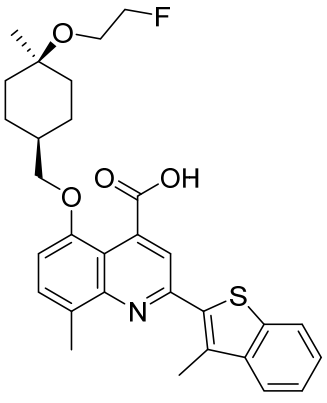
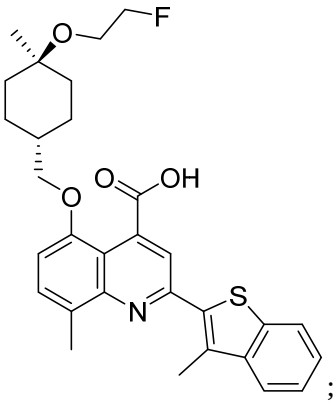
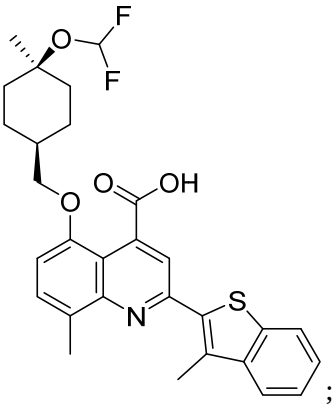

;

;

;

;

;

;

;

;

;

;

;

;

;

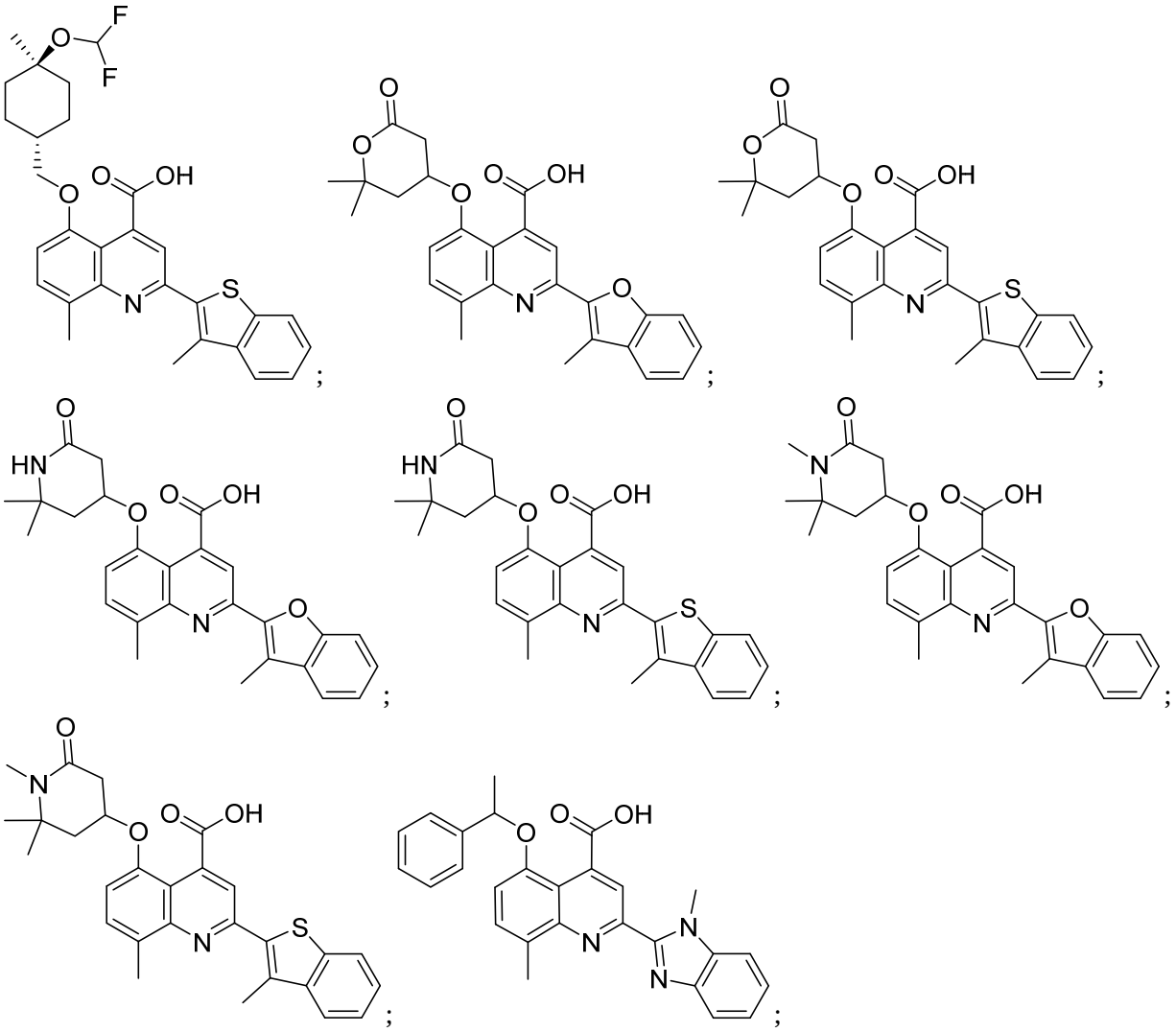

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;



and a pharmaceutically acceptable salt or stereoisomer thereof.

10. A pharmaceutical composition comprising a compound of any one of claims 1 to 9 and a pharmaceutically acceptable excipient.

11. The pharmaceutical composition of claim 10, wherein the composition further comprises at least one additional CFTR modulator.

12. The pharmaceutical composition of claim 11, wherein the composition further comprises two, three, four or more additional CFTR modulators.

13. Use of a compound of any one of claims 1-9 in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.

14. A compound of any one of claims 1-9 for use in treating cystic fibrosis in a patient in need thereof.