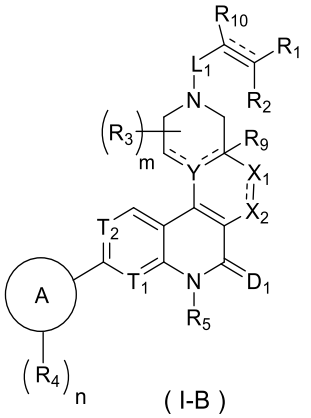
13. The most common codon variation accounted for about 39% of the mutant NSCLCs of KRAS, which is the KRAS-G12C mutation.

[0007] In lung adenocarcinoma, the positive probability of KRAS gene accounts for 1/5-1/4, which is second only to the positive mutation probability of EGFR. The lack of targeted inhibitors makes it very difficult for patients with KRAS-positive non-small cell lung cancer both in terms of treatment and prognosis. The NCCN Clinical Practice Guide for Non-small Cell Lung Cancer in 2013 clearly pointed out that before receiving EGFR-TKI treatment, patients with lung cancer must be tested for KRAS gene, and whether to use EGFR-TKI targeted drugs as a clinical treatment measure should be decided according to the test results. If the KRAS gene is mutated, the patient is not recommended for molecularly targeted therapy with EGFR-TKI.

[0008] According to the Thomson Reuters Competitive Intelligence Drug Database (Cortellis For CI), the current number of various drugs directly related to RAS genes/proteins is 162 (data accessed on August 18, 2016), wherein, there are 18 KRAS small molecule drugs, including 10 KRAS GTPase inhibitors, 4 KRAS gene inhibitors, 2 KRAS GTPase modulators and 2 KRAS gene modulators; there is 1 such drug currently under clinical research. In addition, Antroquinonol, the first KRAS inhibitor developed by a Taiwanese company, has entered the Phase II clinical trial of the US FDA, and Selumetinib, an inhibitor developed by AstraZeneca targeting the MEK downstream pathway of KRAS, is also undergoing Phase II clinical trials. KRAS mutation is the most important tumor driver gene. This part of mutation cases accounted for a certain proportion in pancreatic cancer, lung cancer and rectal gastric cancer. At present, there is no specific targeting drug acting on this target. Therefore, the project has important medical research value and clinical application value, and has greater medical value for nation. The molecular mechanism for developing KRAS-G12C small molecule drug has been basically clarified; the molecular structure and pharmacodynamics of the drug have been verified under the existing experimental conditions, and it has the characteristics of high activity and the possibility of becoming a drug.

Summary

[0008a] In a first aspect, the present disclosure refers to a compound represented by formula (I-B), an optical isomer thereof and a pharmaceutically acceptable salt thereof,



(I-B)

wherein,

R_1, R_2 are independently selected from H, halogen and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted by 1, 2 or 3 R;

R_3 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- and C_{3-6} cycloalkyl-O-, the C_{1-6} alkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- or C_{3-6} cycloalkyl-O- is optionally substituted by 1, 2 or 3 R;

R_4 is independently selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

R_5 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, 3-8 membered heterocycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, 3-8 membered heterocycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

L_1 is selected from -C(=O)-, -S(=O)- and -$S(=O)_2$-;

R_6 is selected from H, CN, C_{1-6} alkyl, C_{1-6} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-6} alkyl-3-6 membered heterocycloalkyl and C_{3-6} cycloalkyl-C(=O)-, the C_{1-6} alkyl, C_{1-6} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-6} alkyl-3-6 membered heterocycloalkyl or C_{3-6} cycloalkyl-C(=O)- is optionally substituted by 1, 2 or 3 R;

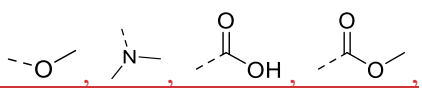
R_7 is independently selected from H, halogen, OH, NH_2, CN, -C(=O)-OH, C_{1-6} alkyl-O-C(=O)-, -C(=O)-NH_2, C_{1-6} alkyl, C_{1-6} heteroalkyl and -C_{1-6} alkyl-3-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} alkyl-O-C(=O)- or -C_{1-6} alkyl-3-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

T_1, T_2 are independently selected from N and -$C(R_8)$-;

R_8 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl or 3-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

R_9 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl and C_{1-6} heteroalkyl, the C_{1-6} alkyl or C_{1-6} heteroalkyl is optionally substituted by 1, 2 or 3 R;

R_{10} is selected from H, halogen, CN, C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylamino, the C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylamino is optionally substituted by 1, 2 or 3 R;

R is independently selected from H, halogen, OH, NH_2, CN, ,

, C_{1-6} alkyl, C_{1-6} heterocycloalkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- and 5-6 membered heterocycloalkyl-O-, the C_{1-6} alkyl, C_{1-6} heterocycloalkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- or 5-6 membered heterocycloalkyl-O- is optionally substituted by 1, 2 or 3 R';

R' is selected from F, Cl, Br, I, OH, NH_2 and CH_3;

ring A is independently selected from C_{6-10} aryl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl;

n is selected from 0, 1, 2, 3 or 4;

m is selected from 0, 1, 2, 3 or 4;

D_1 is selected from O;

Y is selected from N, CH or C;

 is  or , and when  is , R_2, R_{10} are not existed;

 is  or ;

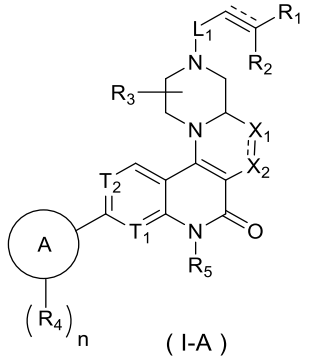
when in ,  is , X_1, X_2 are independently selected from -N=, -C(R_7)= and -C(R_7)$_2$-C(R_7)=;

when in ,  is , X_1, X_2 are independently selected from single bond, -O-, -S-, S(=O), S(=O)$_2$, -N(R_6)-, -C(=O)-, -C(R_7)$_2$- and -C(R_7)$_2$-C(R_7)$_2$-;

and, Y cannot be connected to two  at the same time, when the bond between Y and R_9 is , R_9 is not existed;

the above 3-6 membered heterocycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, 5-10 membered heteroaryl or C_{1-6} heterocycloalkyl comprises 1, 2, or 3 heteroatoms or heteroatomic groups independently selected from -O-, -NH-, -S-, -C(=O)-, -C(=O)O-, -S(=O)-, -S(=O)$_2$- and N.

[0008b] In another aspect, the present disclosure refers to a compound represented by formula (I-A), an optical isomer thereof and a pharmaceutically acceptable salt thereof,



(I-A)

wherein,

R_1, R_2 are independently selected from H, halogen and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted by 1, 2 or 3 R;

R_3 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- and C_{3-6} cycloalkyl-O-, the C_{1-6} alkyl,

C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- or C_{3-6} cycloalkyl-O- is optionally substituted by 1, 2 or 3 R;

R_4 is independently selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

R_5 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, 3-8 membered heterocycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, 3-8 membered heterocycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

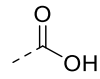
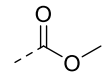
L_1 is selected from -C(=O)-, -S(=O)- and -$S(=O)_2$-;

R_6 is selected from H, CN, C_{1-6} alkyl, C_{1-6} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-6} alkyl-3-6 membered heterocycloalkyl and C_{3-6} cycloalkyl-C(=O)-, the C_{1-6} alkyl, C_{1-6} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-6} alkyl-3-6 membered heterocycloalkyl or C_{3-6} cycloalkyl-C(=O)- is optionally substituted by 1, 2 or 3 R;

R_7 is independently selected from H, halogen, OH, NH_2, CN, -C(=O)OH, C_{1-6} alkyl-O-C(=O)-, -C(=O)-NH_2, C_{1-6} alkyl, C_{1-6} heteroalkyl and -C_{1-6} alkyl-3-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} alkyl-O-C(=O)- or -C_{1-6} alkyl-3-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

T_1, T_2 are independently selected from N and -$C(R_8)$ -;

R_8 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl or 3-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

R is independently selected from H, halogen, OH, NH_2, CN, , , , , C_{1-6} alkyl, C_{1-6} heterocycloalkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- and 5-6 membered heterocycloalkyl-O-, the C_{1-6} alkyl, C_{1-6} heterocycloalkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- or 5-6 membered heterocycloalkyl-O- is optionally substituted by 1, 2 or 3 R';

R' is selected from F, Cl, Br, I, OH, NH_2 and CH_3;

ring A is independently selected from C_{6-10} aryl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl;

n is selected from 0, 1, 2, 3 or 4;

 is  or , and when  is , R_2 is not existed;

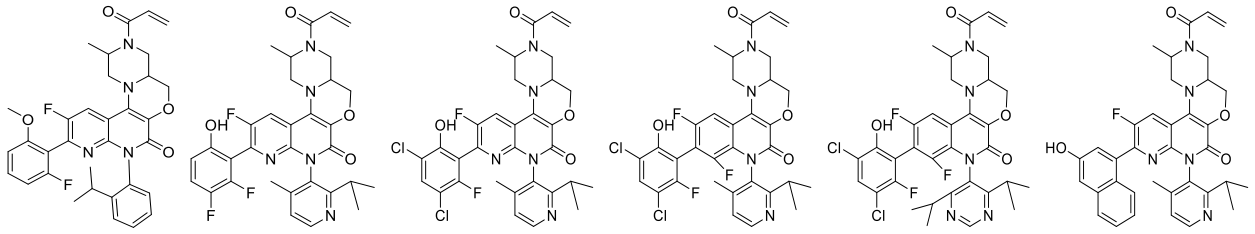
 is  or ;

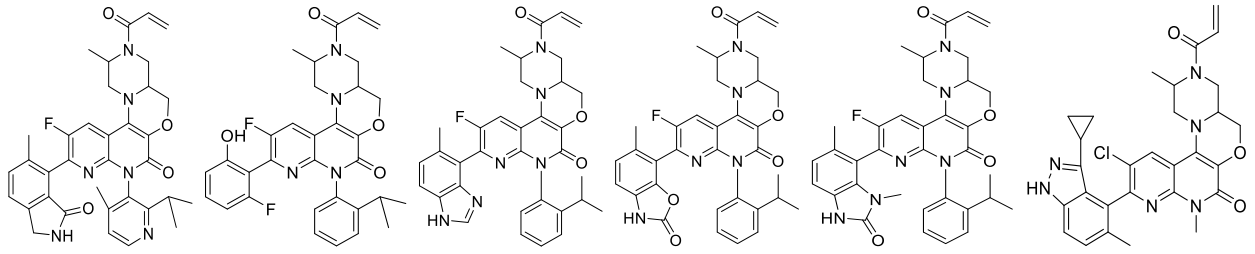
when in ,  is , X_1, X_2 are independently selected from -N=, -C(R_7)= and -C(R_7)$_2$-C(R_7)=;

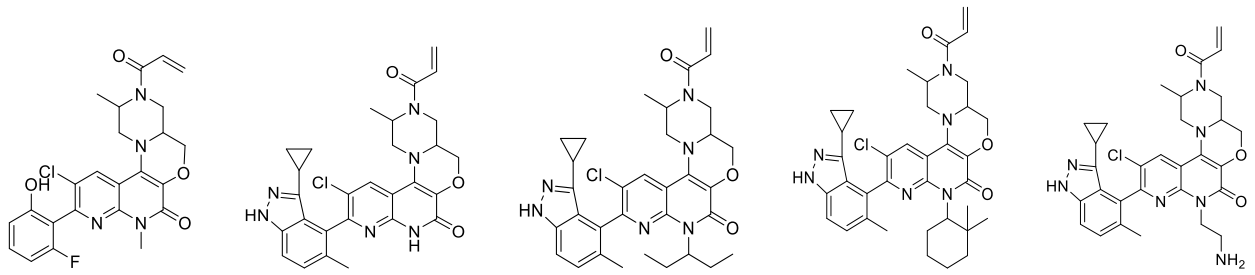
when in ,  is , X_1, X_2 are independently selected from single bond, -O-, -S-, S(=O), S(=O)$_2$, -N(R_6)-, -C(=O)-, -C(R_7)$_2$- and -C(R_7)$_2$-C(R_7)$_2$-;

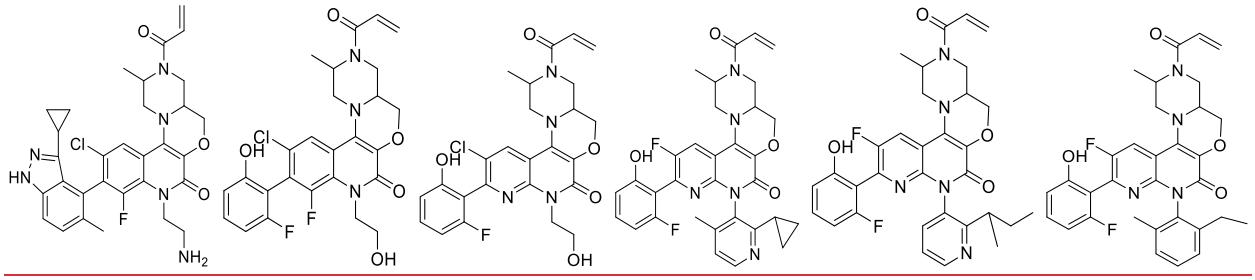
the above 3-6 membered heterocycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, 5-10 membered heteroaryl or C_{1-6} heterocycloalkyl comprises 1, 2, or 3 heteroatoms or heteroatomic groups independently selected from -O-, -NH-, -S-, -C(=O)-, -C(=O)O-, -S(=O)-, -S(=O)$_2$- and N.

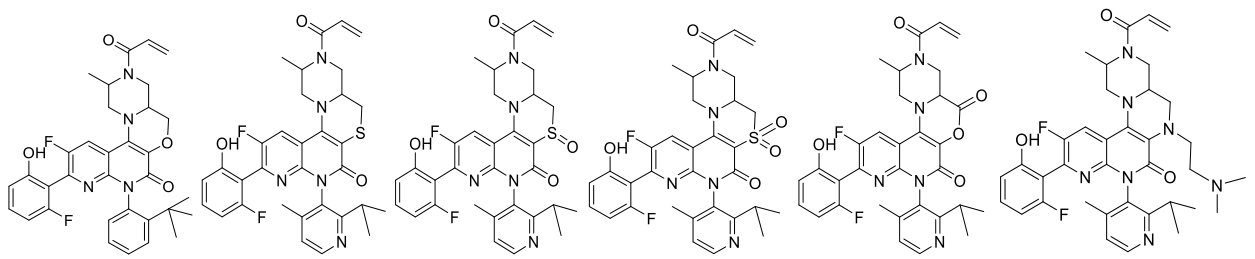
[0008c] In yet another aspect, the present disclosure refers to compounds of the following formula, optical isomers thereof and pharmaceutically acceptable salts thereof,

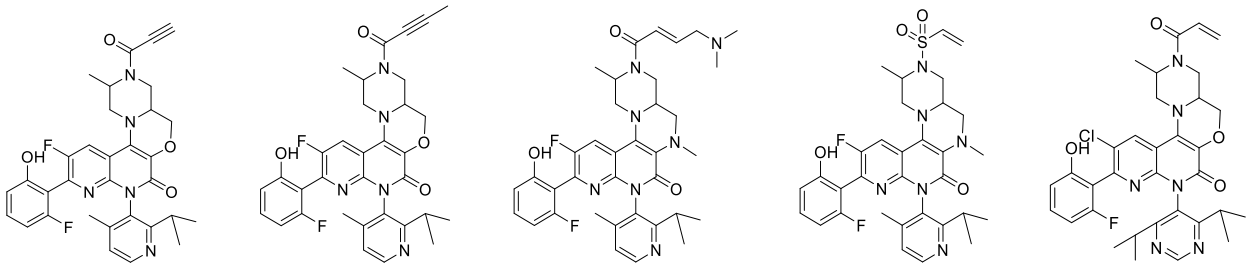


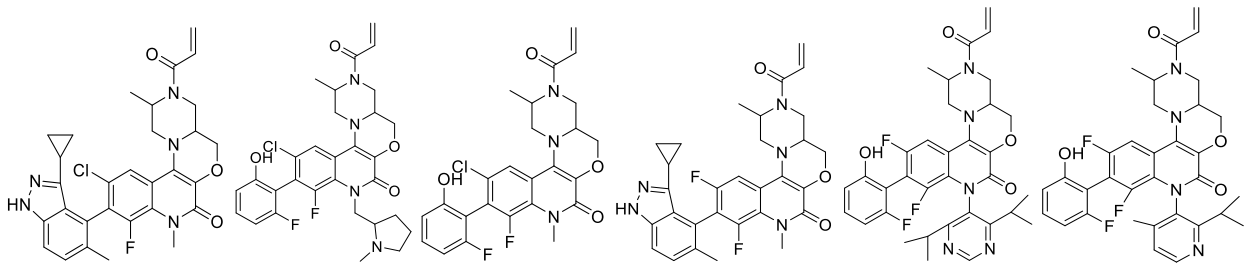


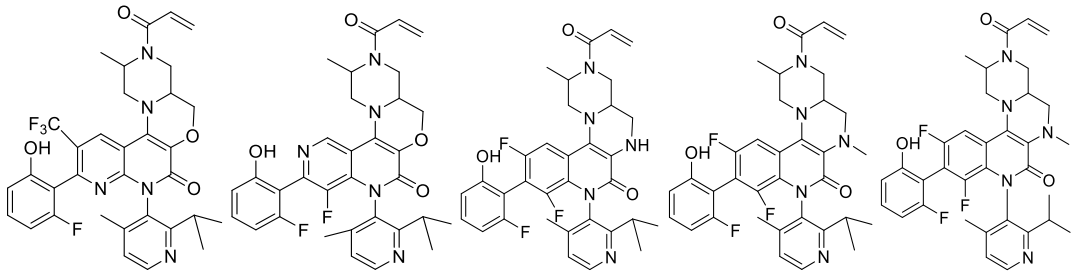


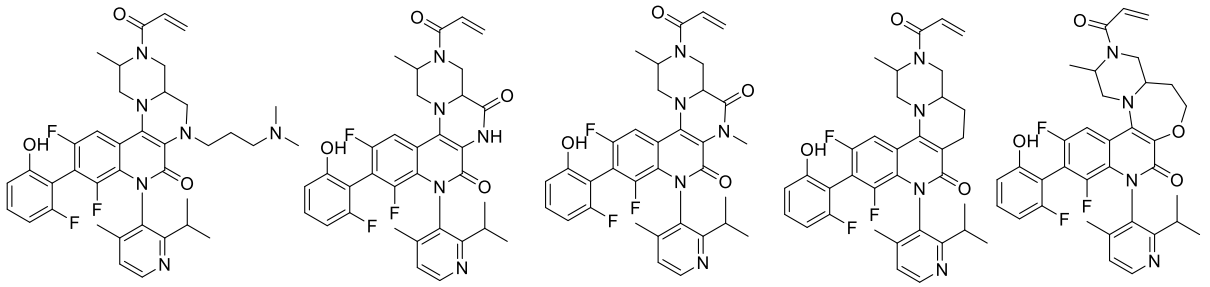


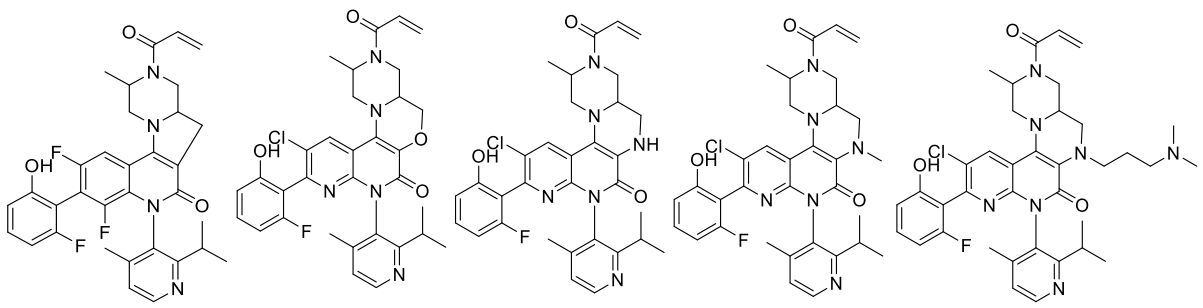


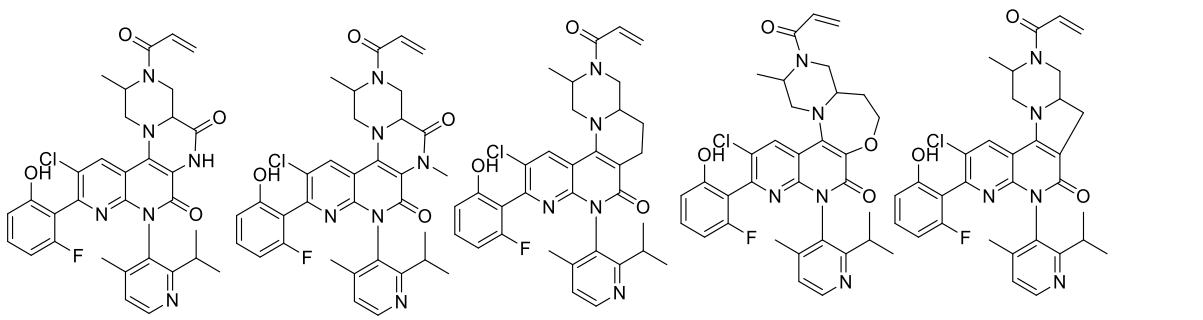


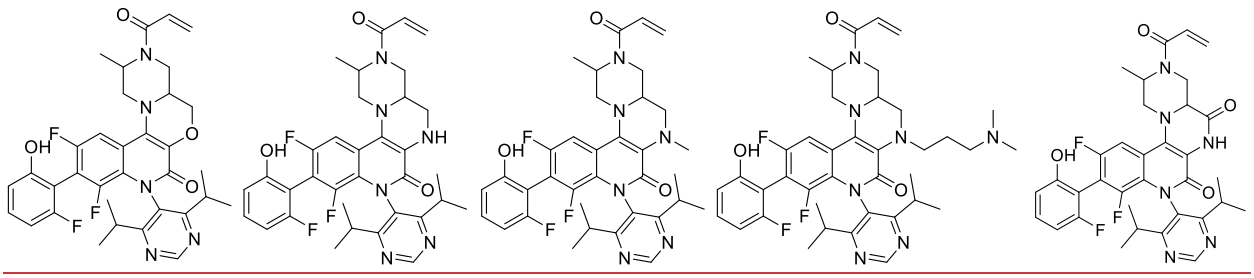


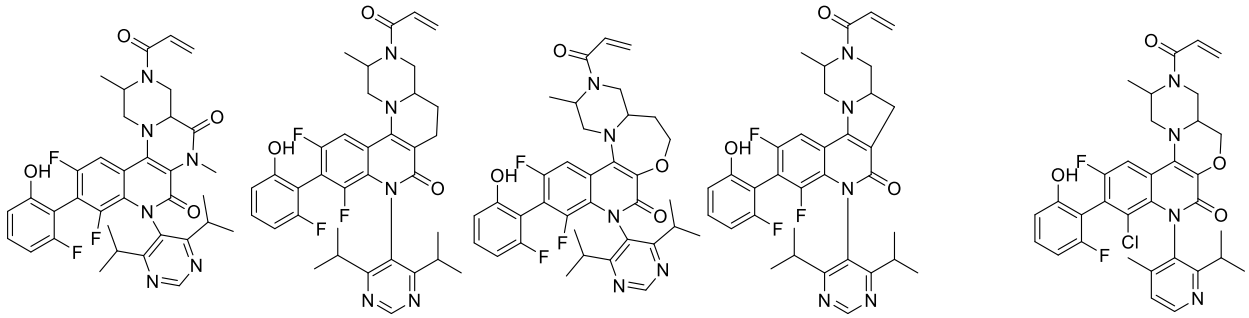


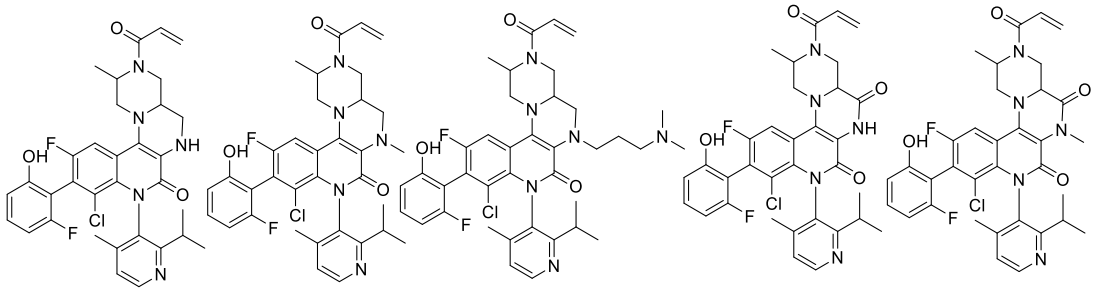


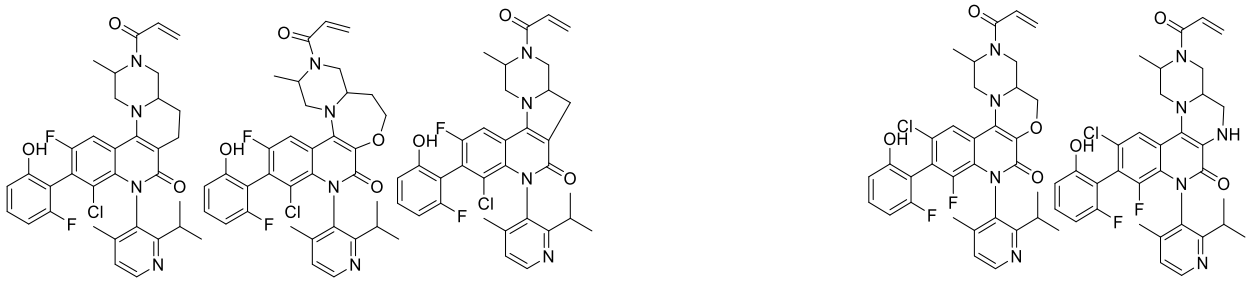


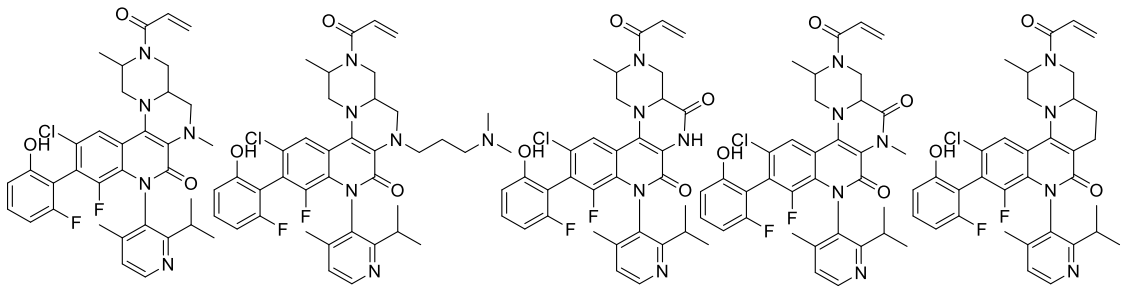


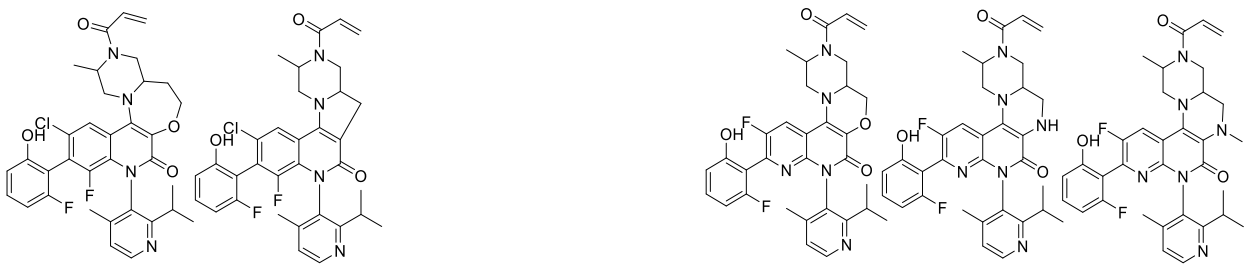


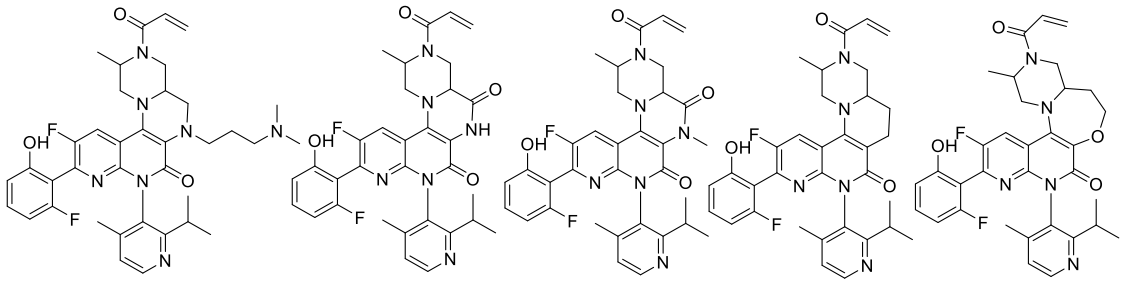


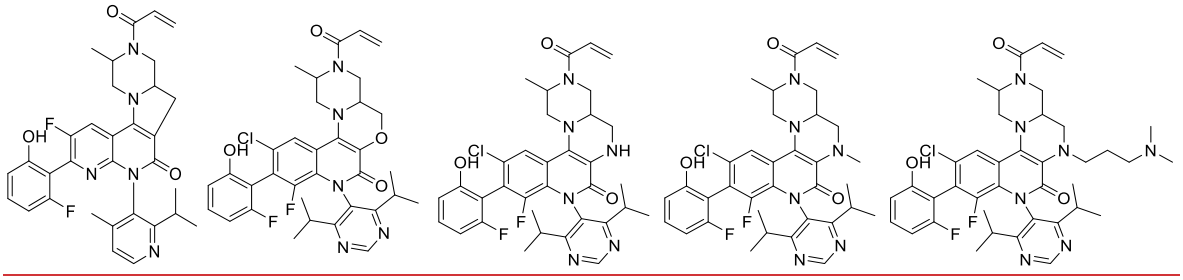


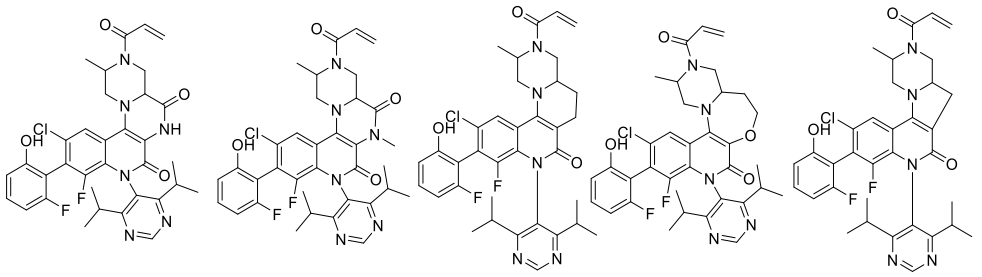


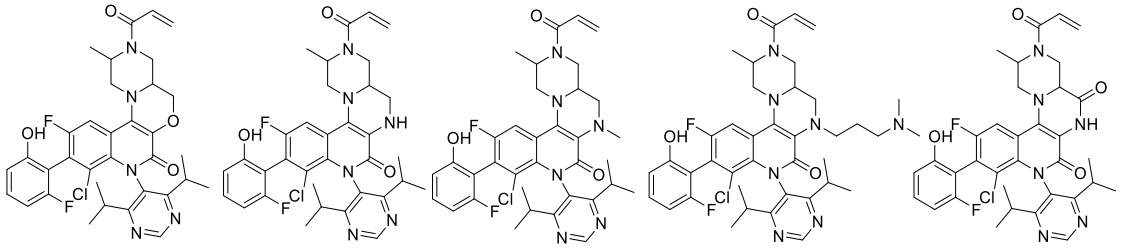


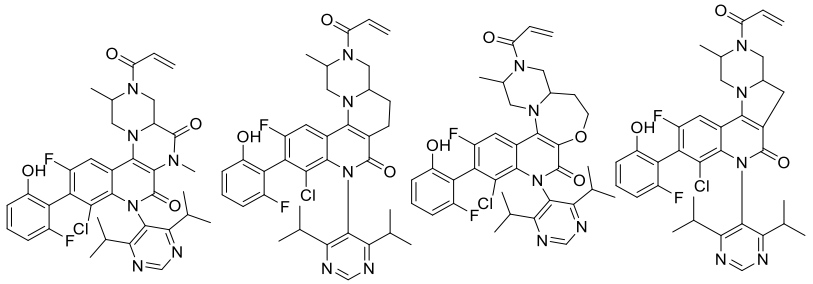


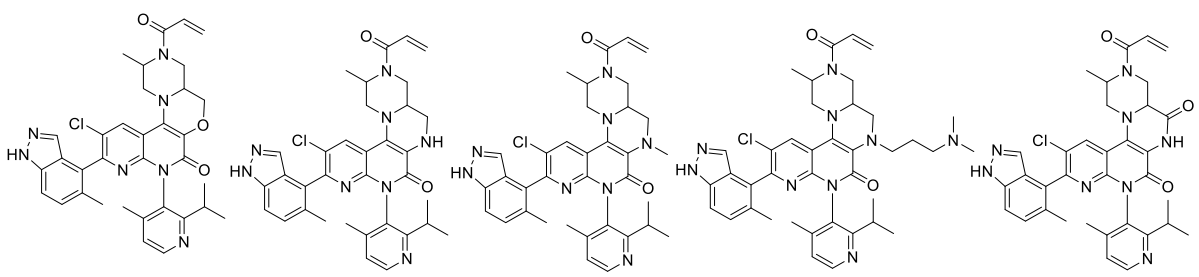




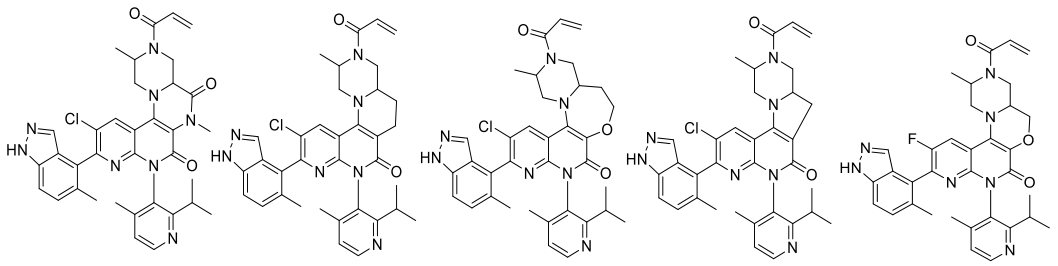


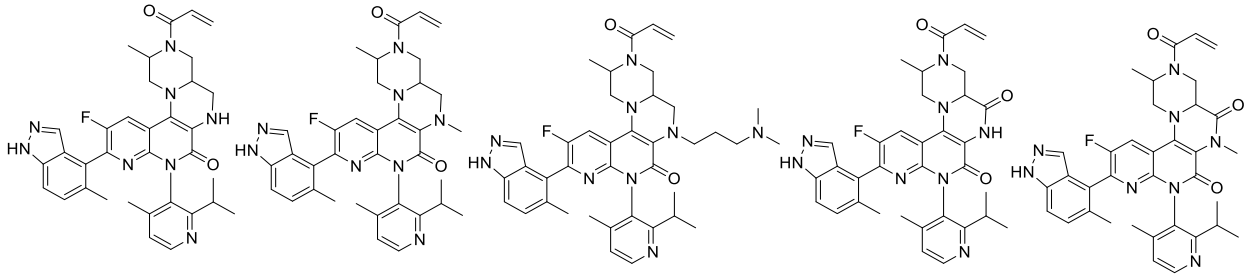


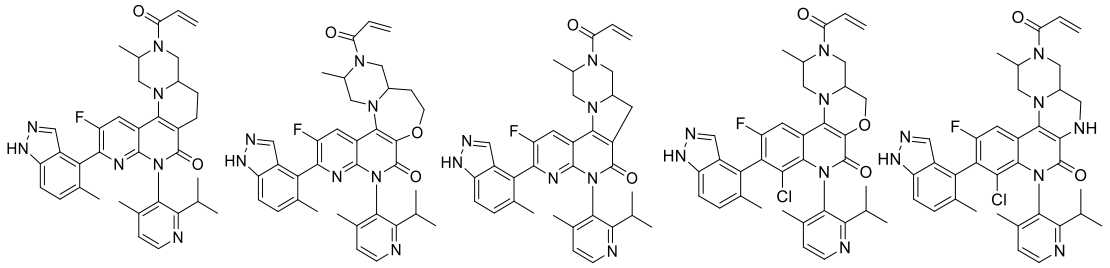


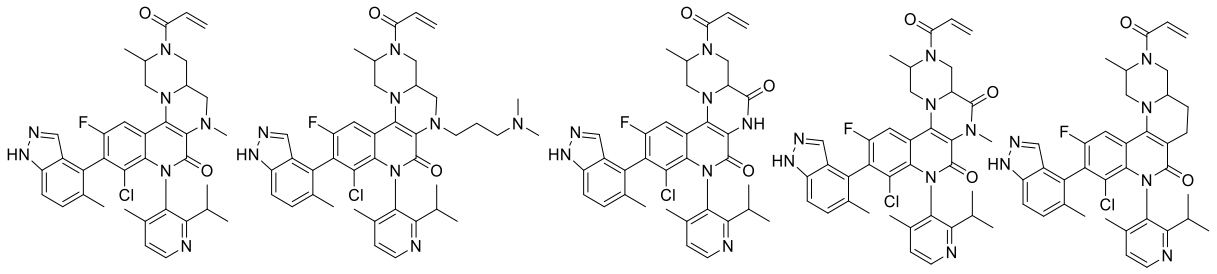


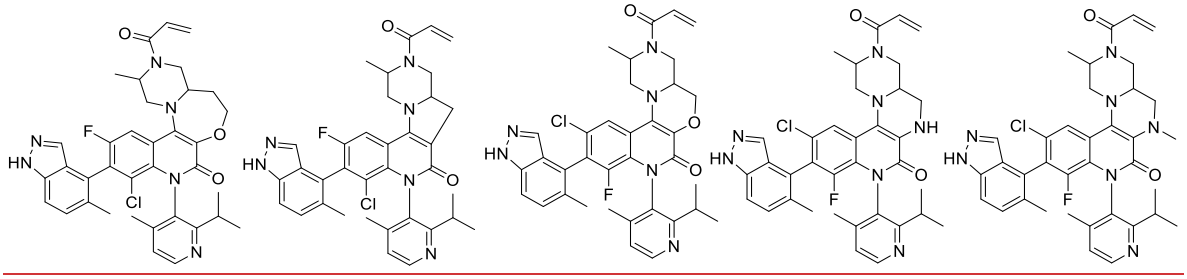
2h

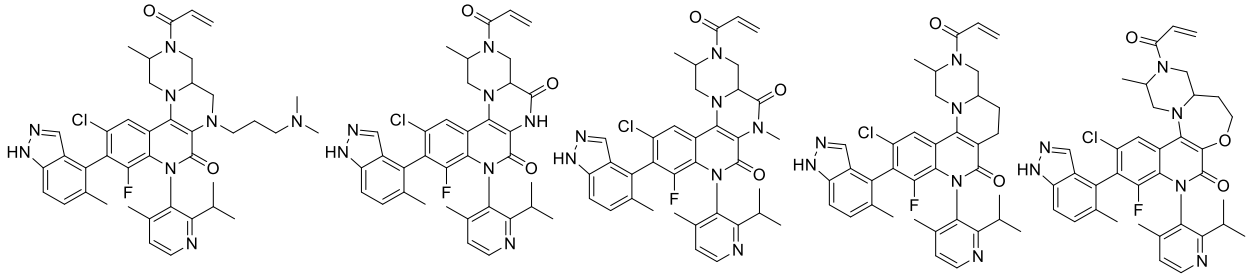


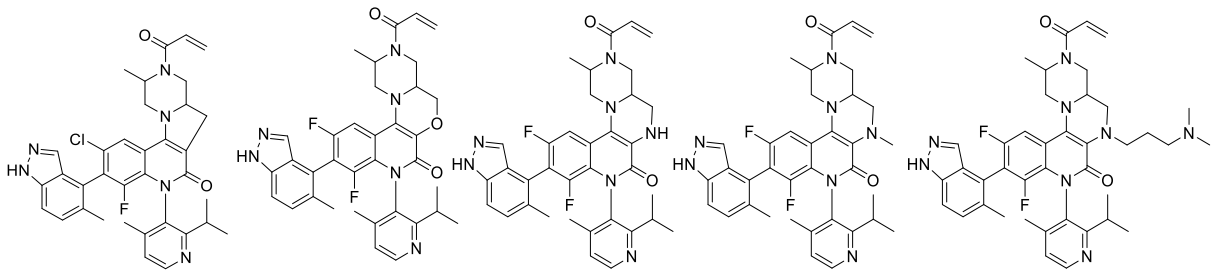


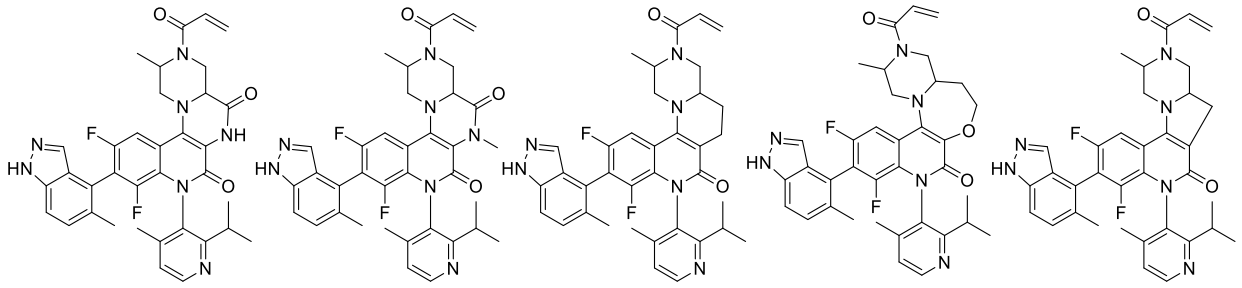


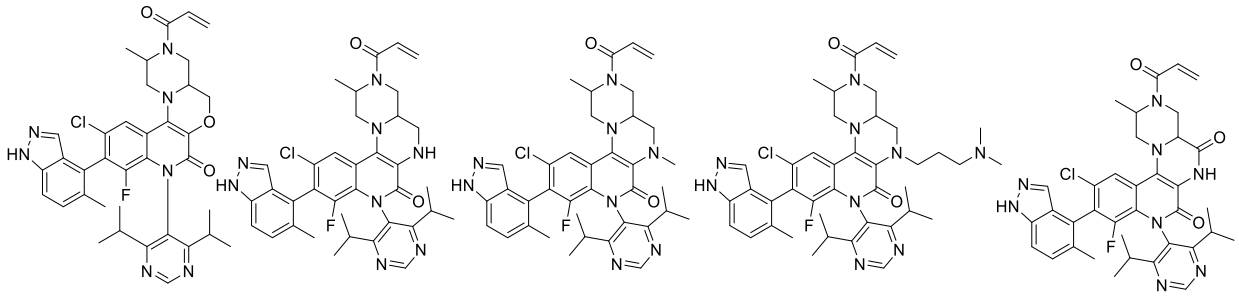


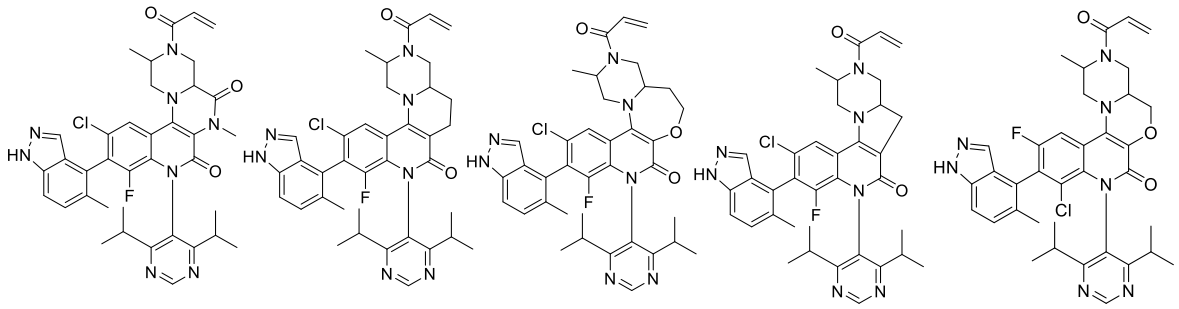


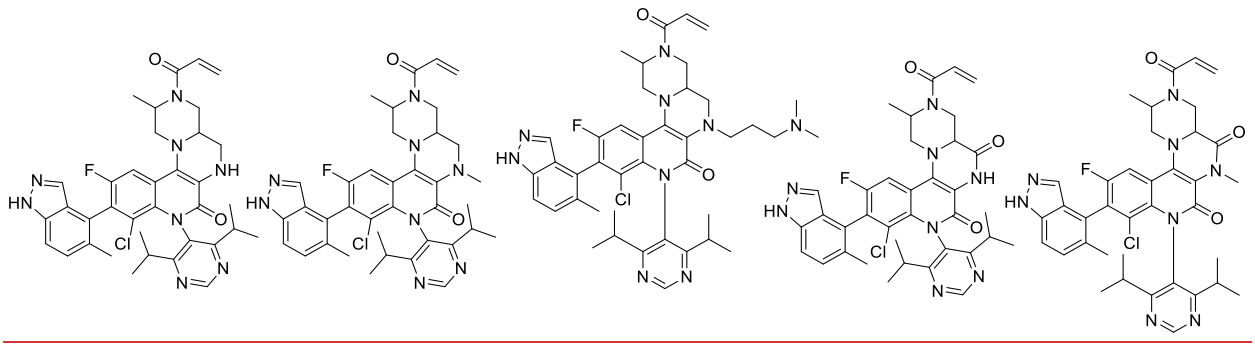


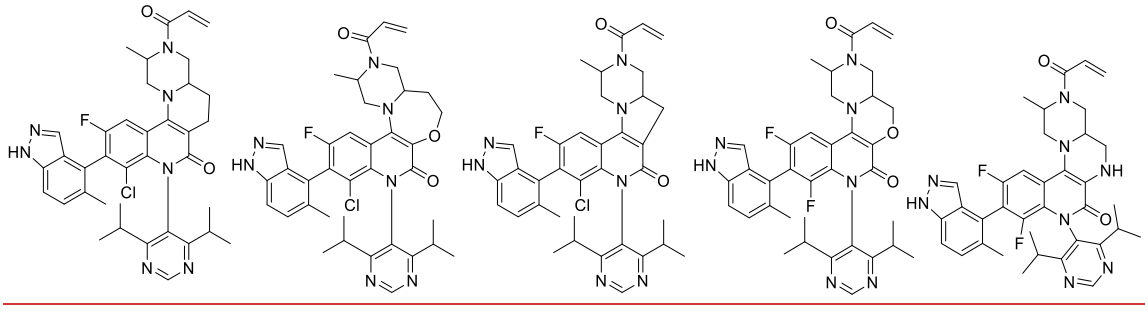


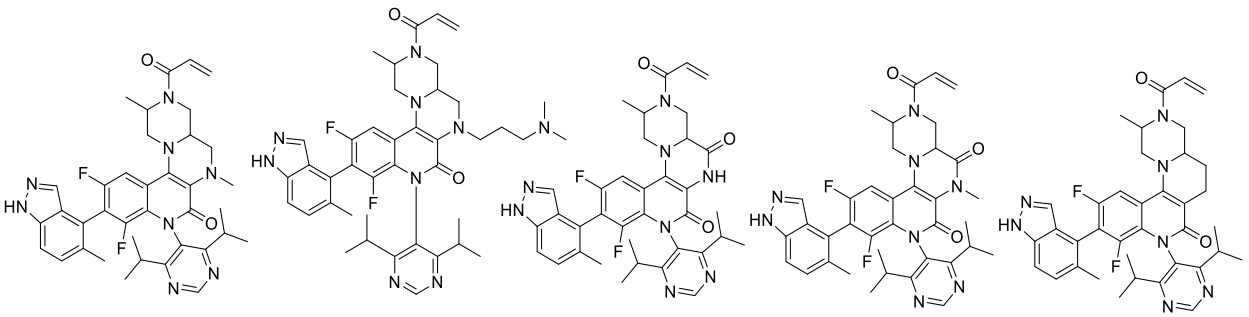


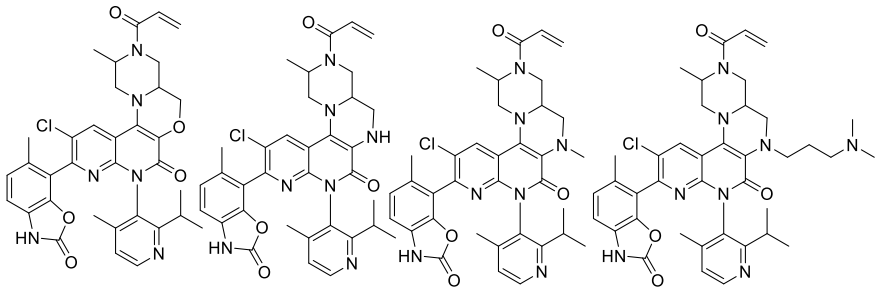


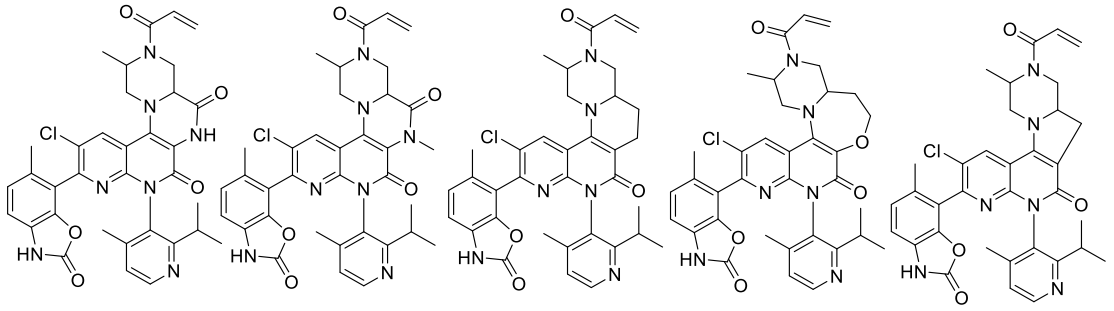


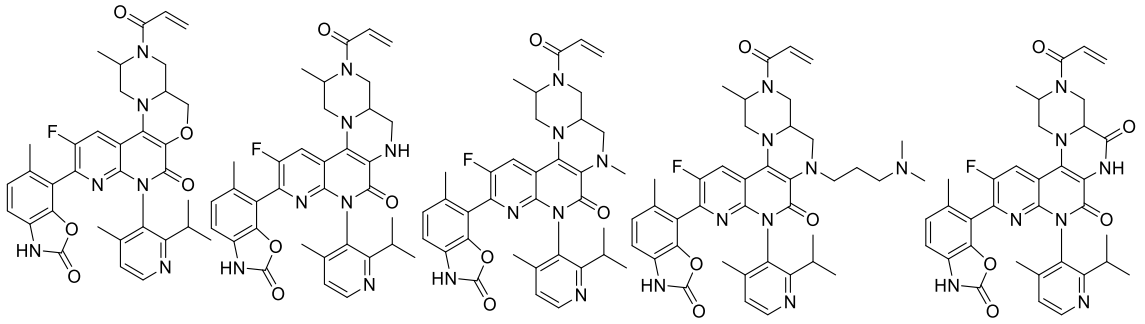


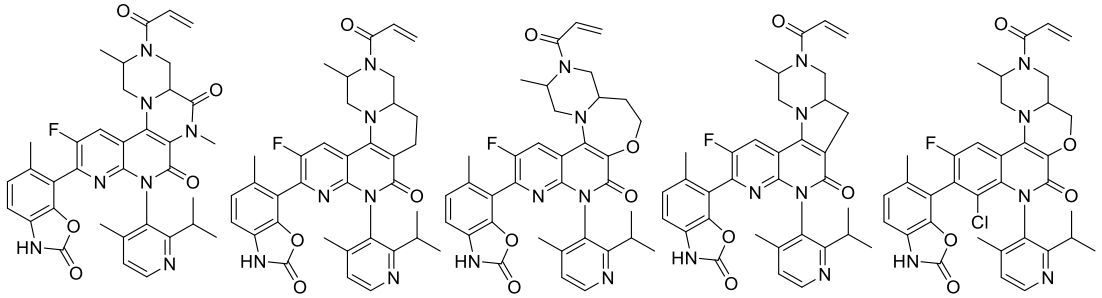


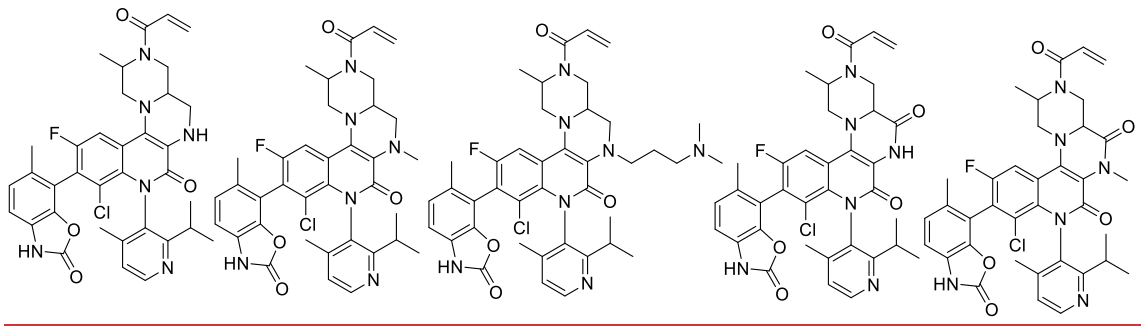


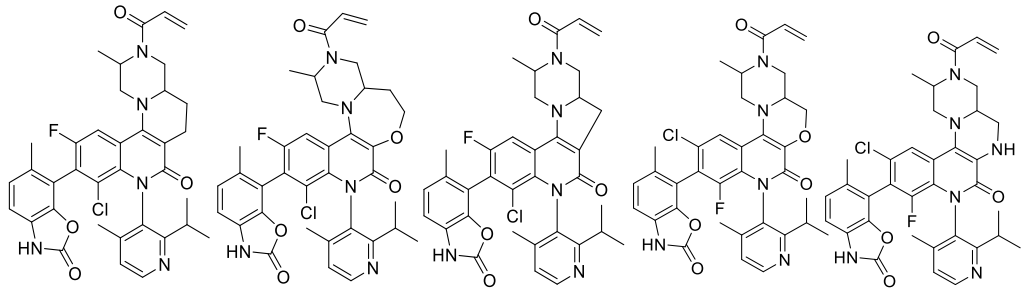


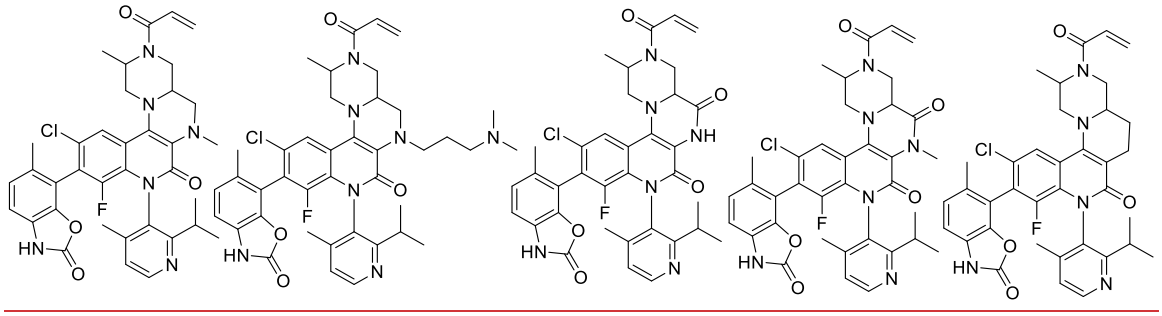


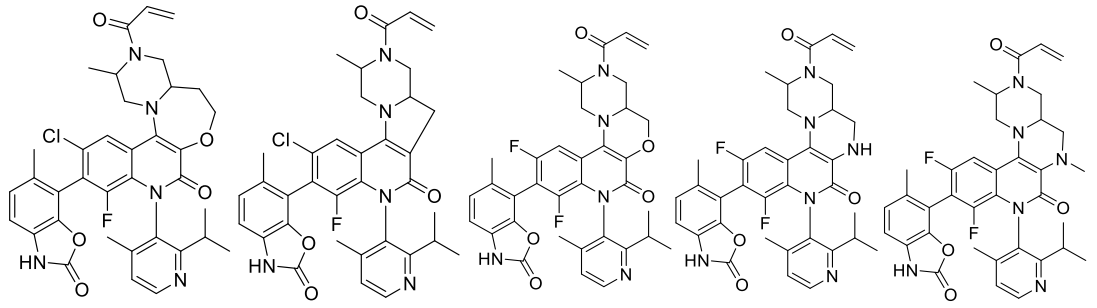


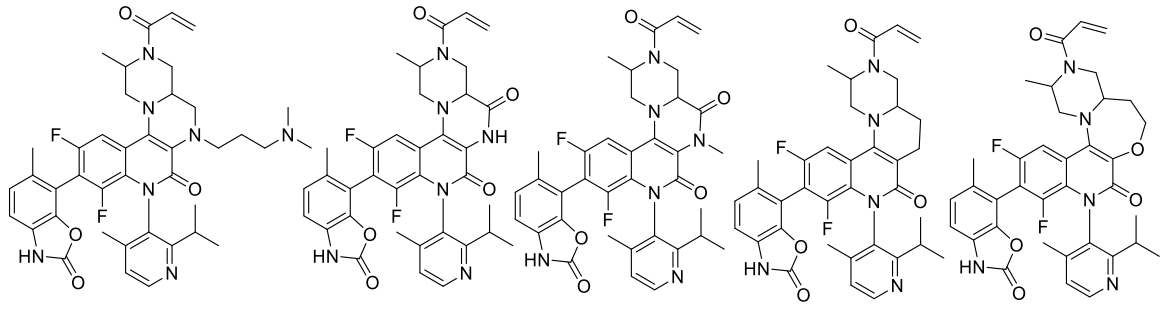


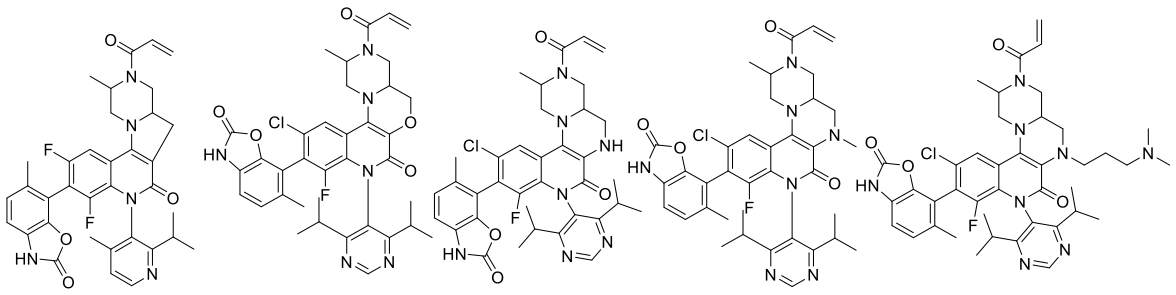


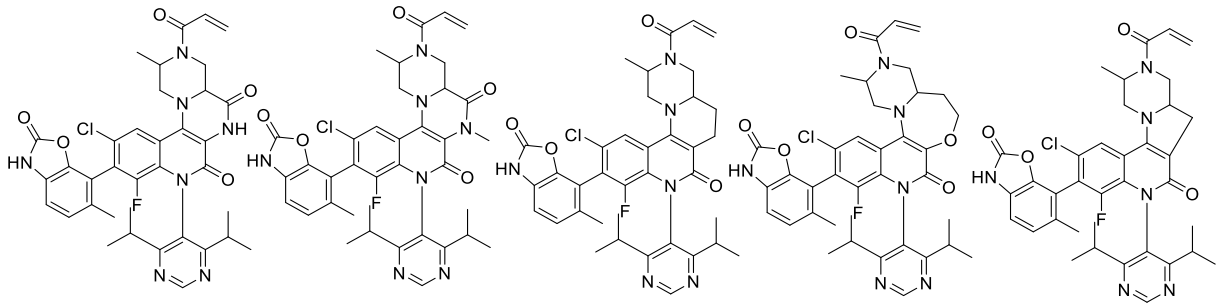


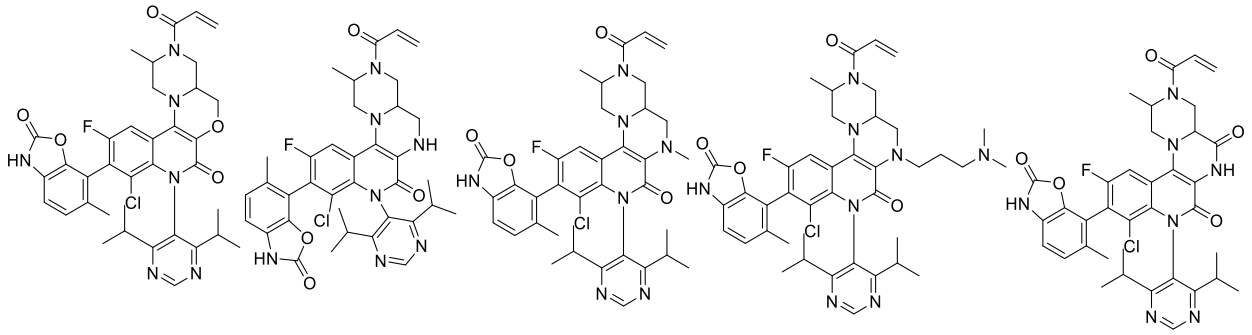


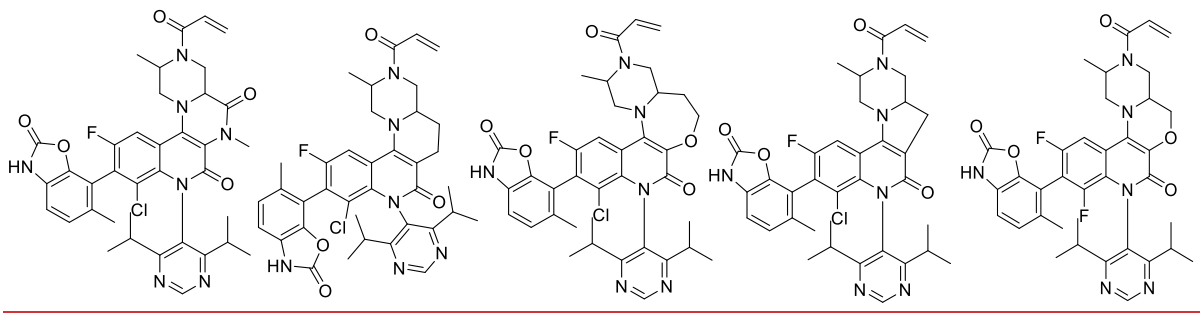


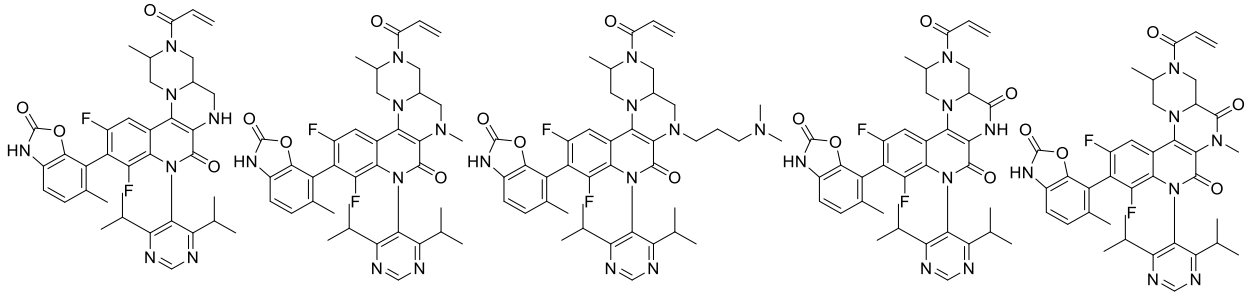




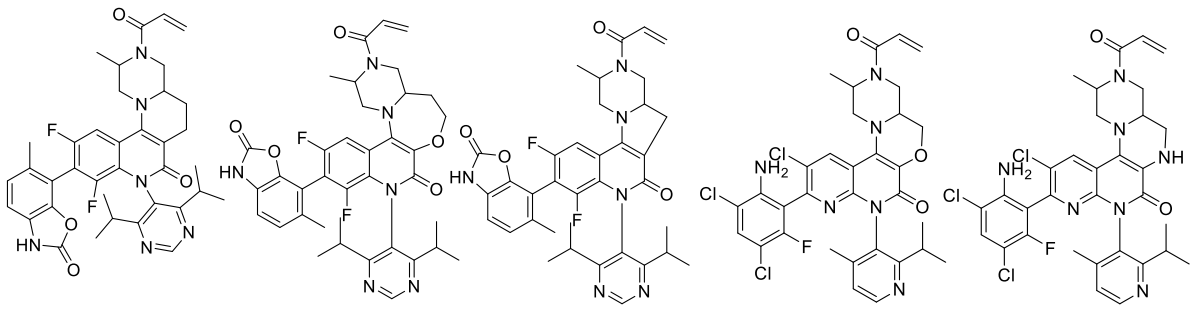


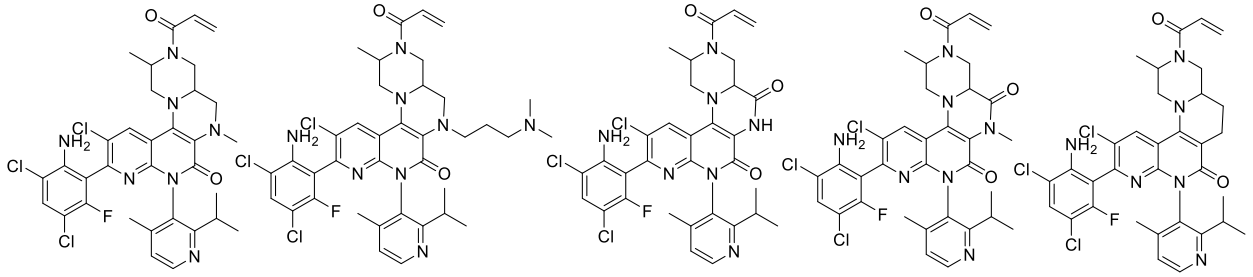


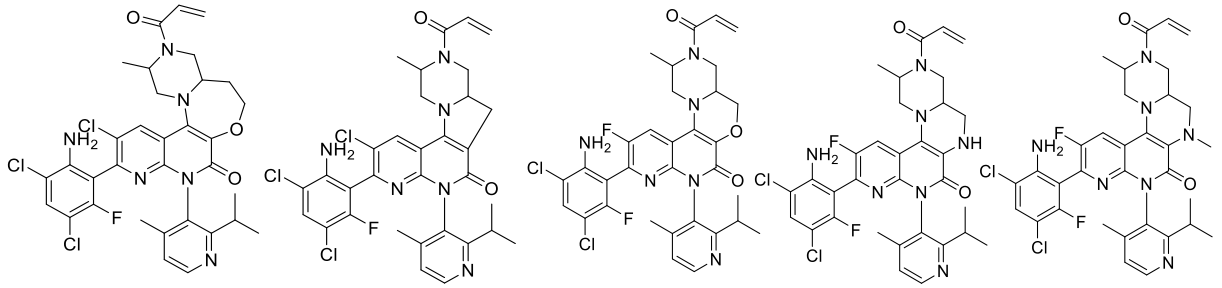


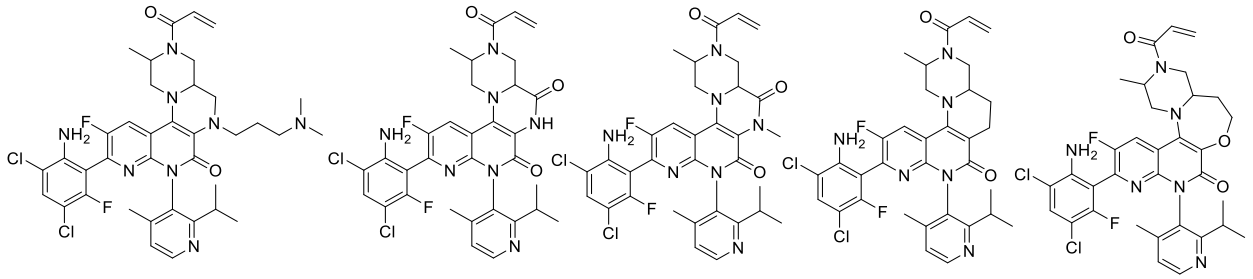


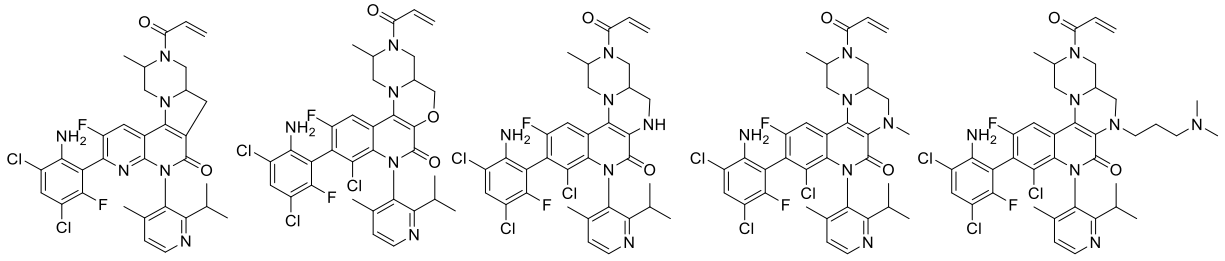
2m

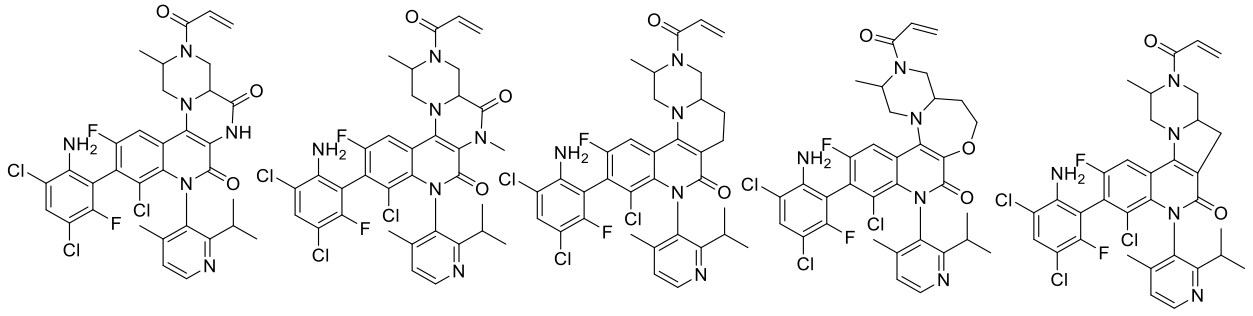


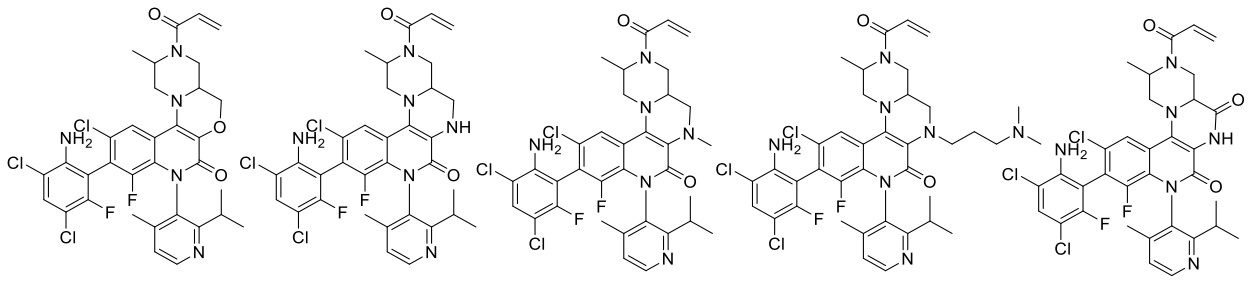


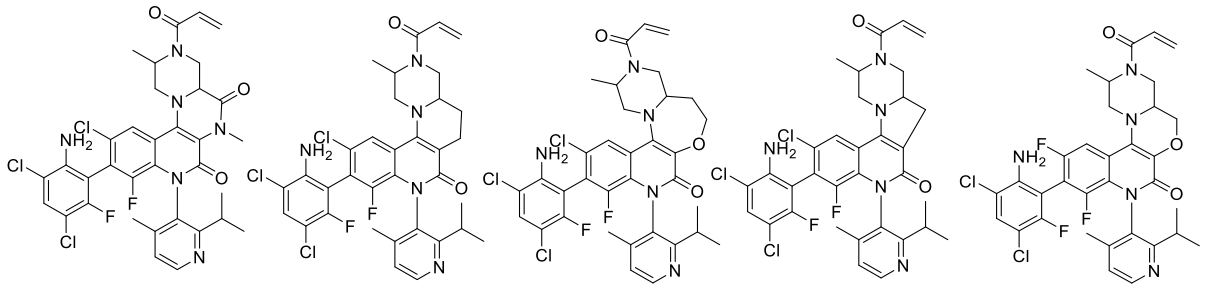


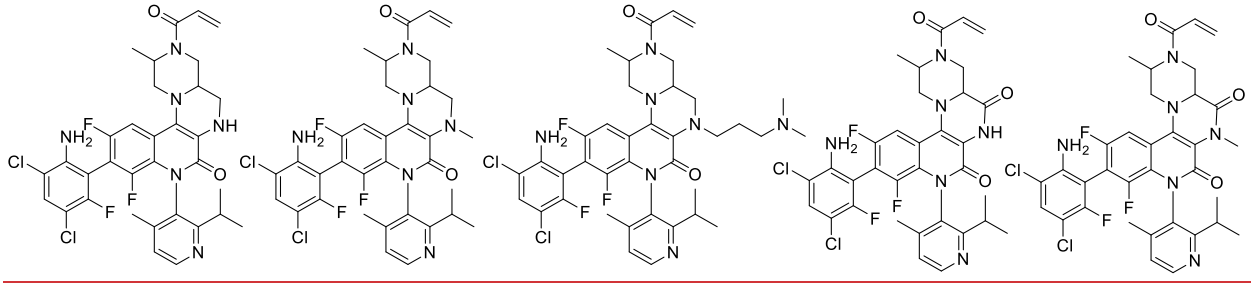


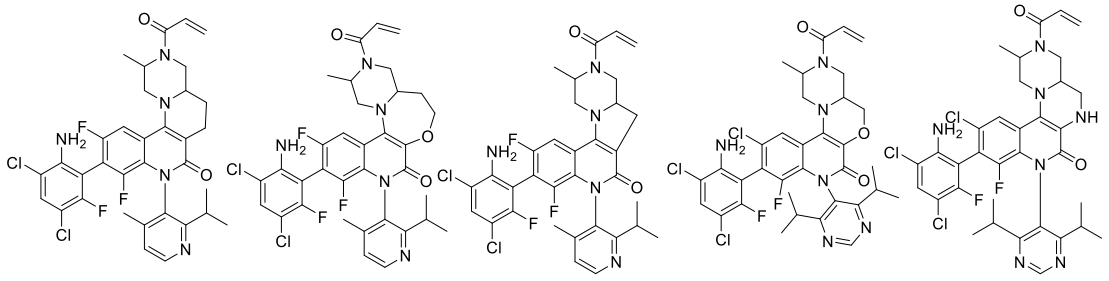


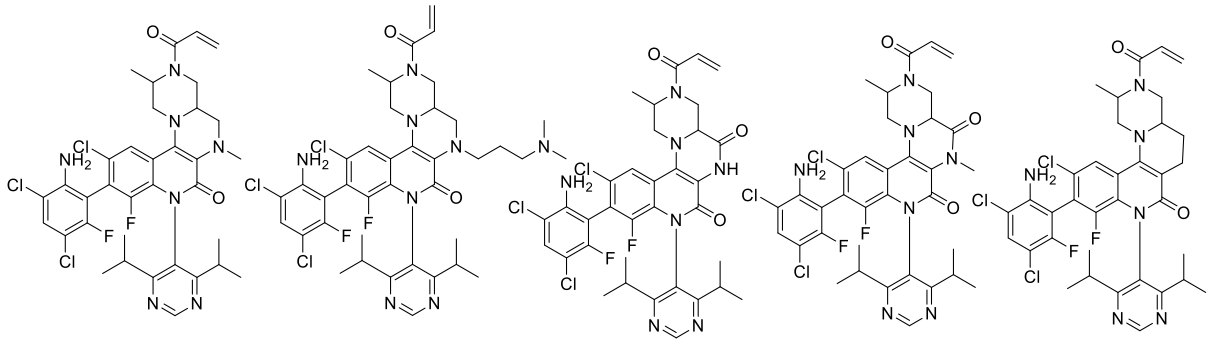


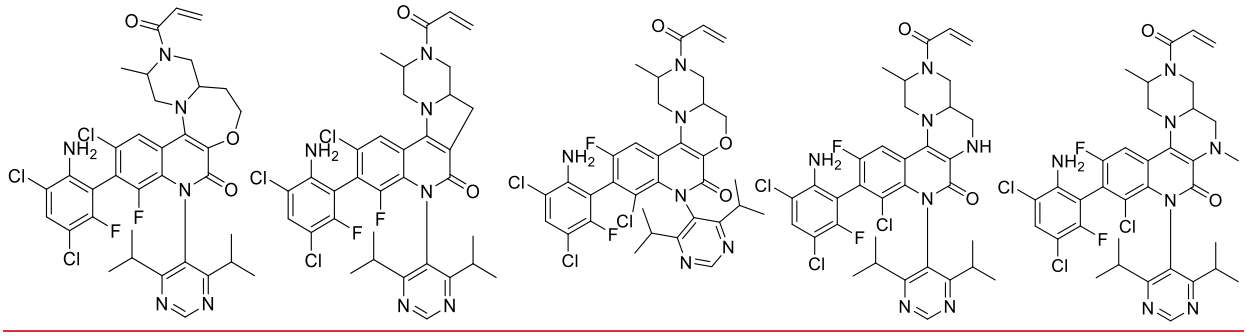


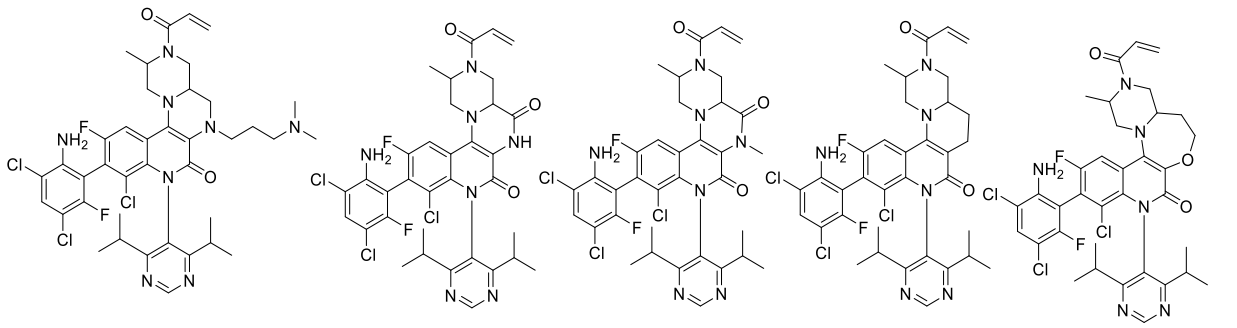


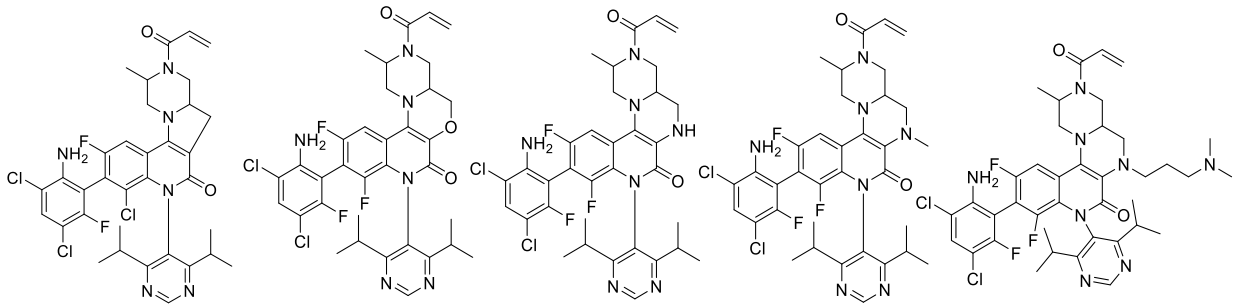


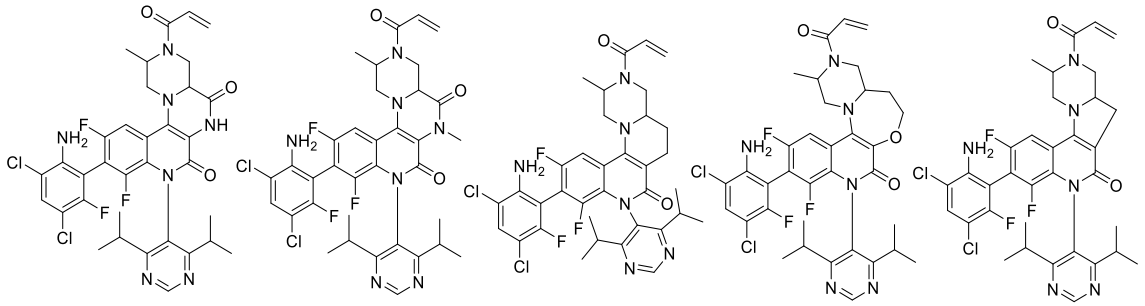


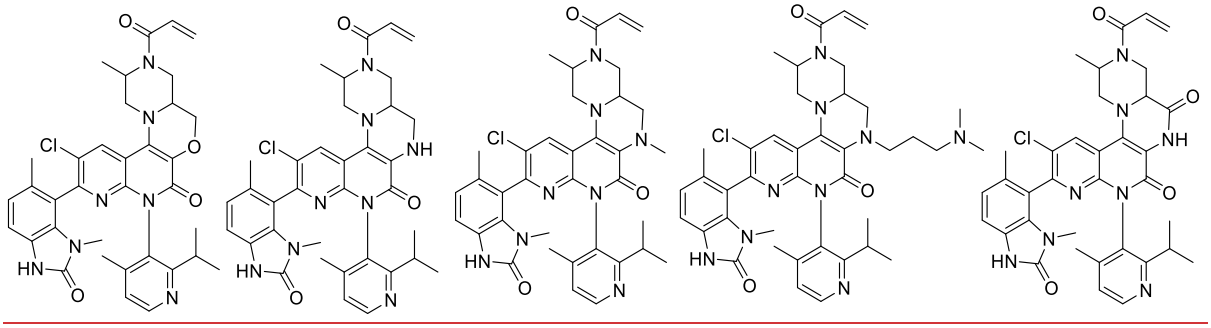


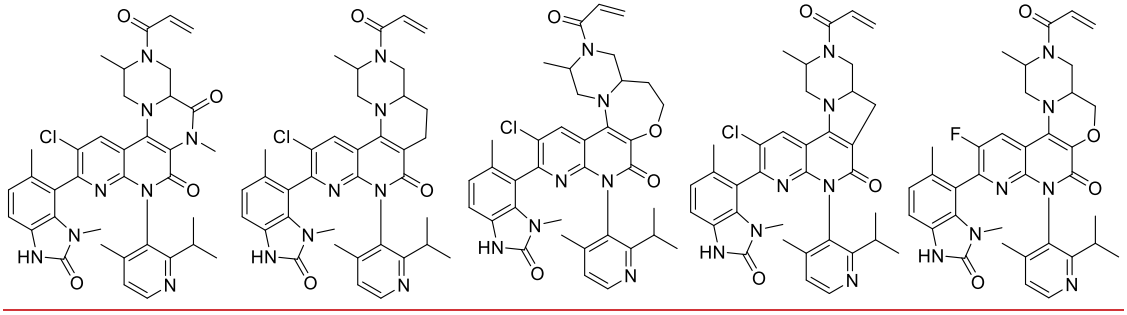


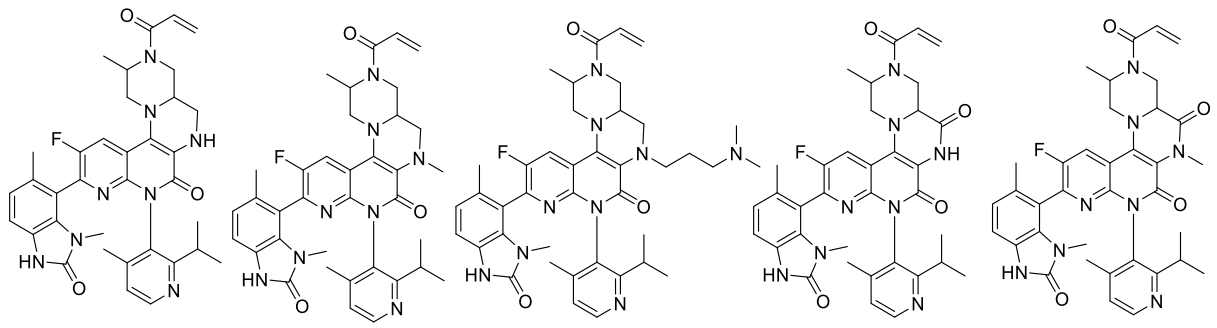


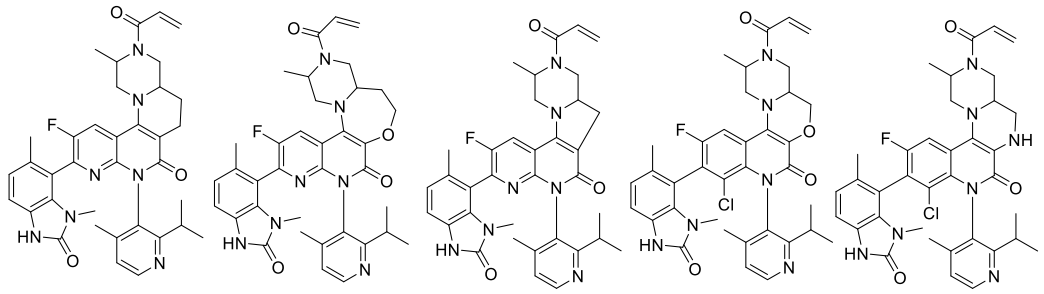


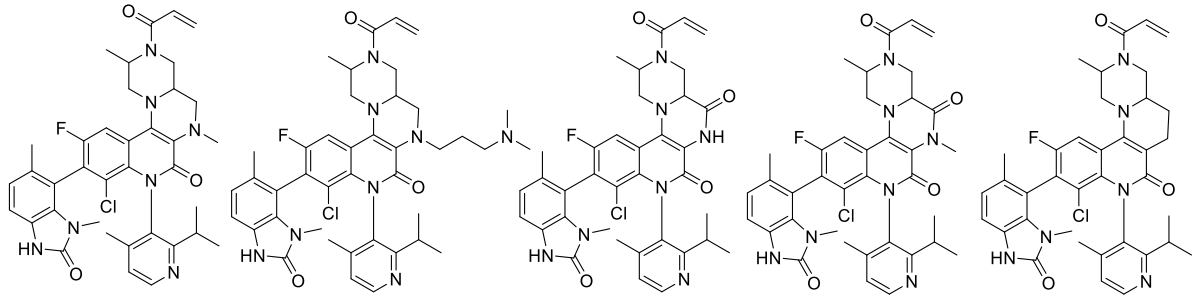


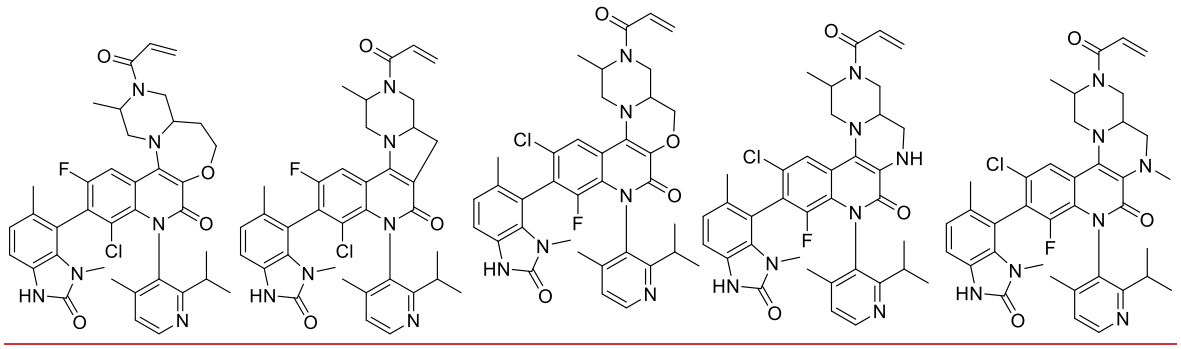


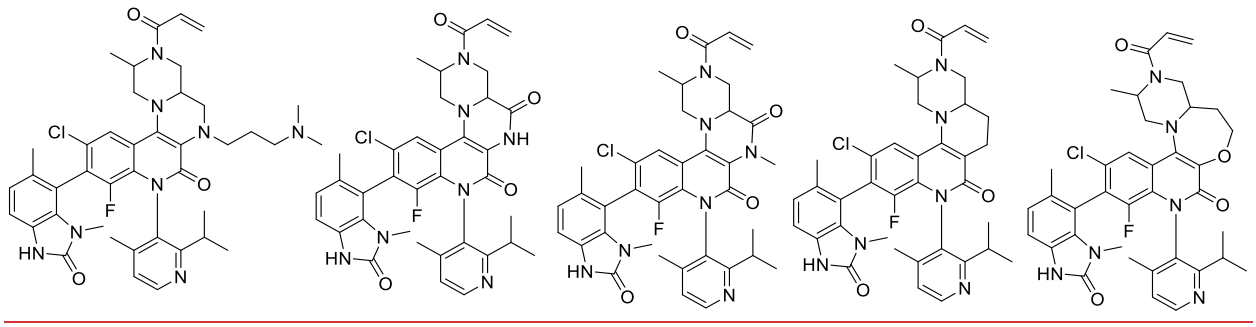


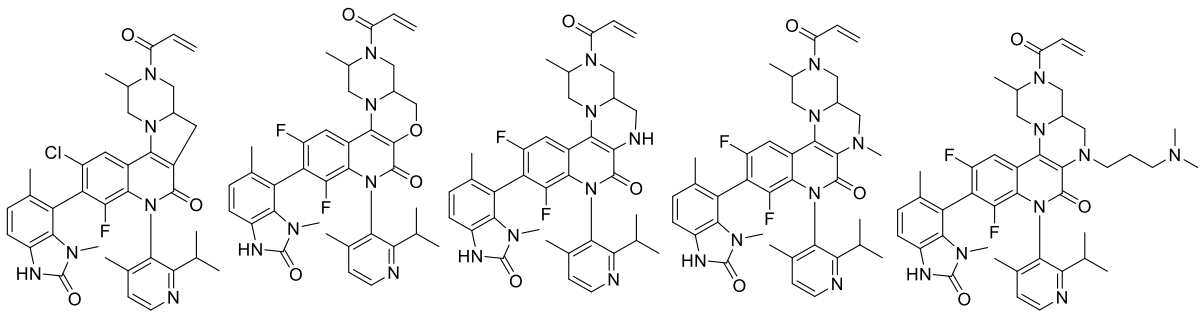


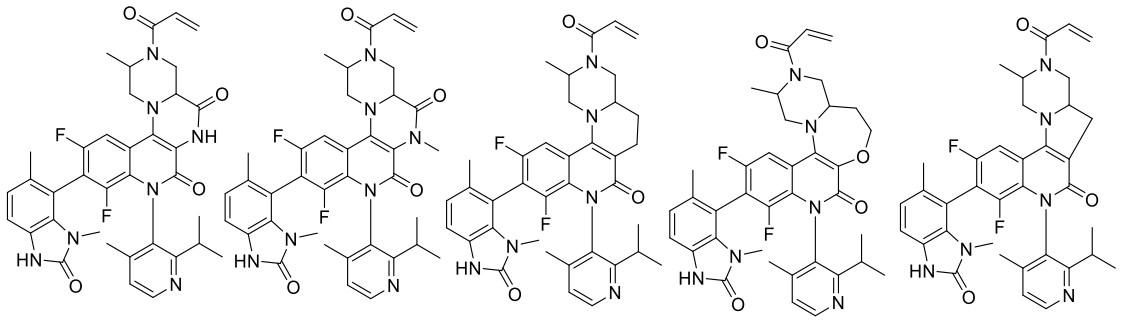


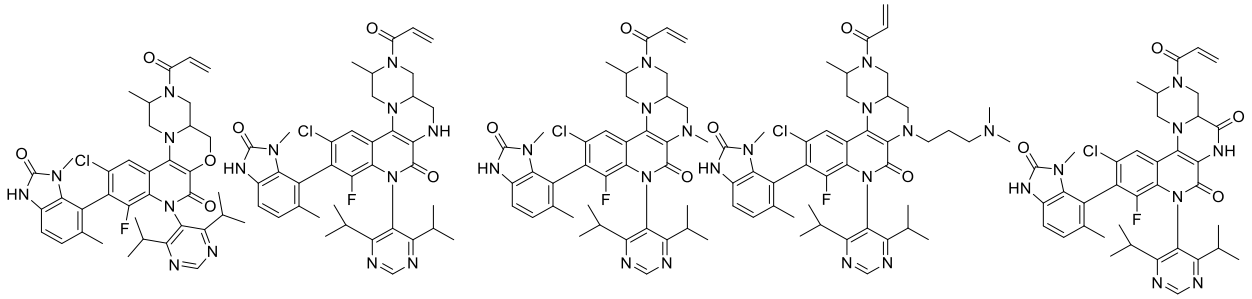


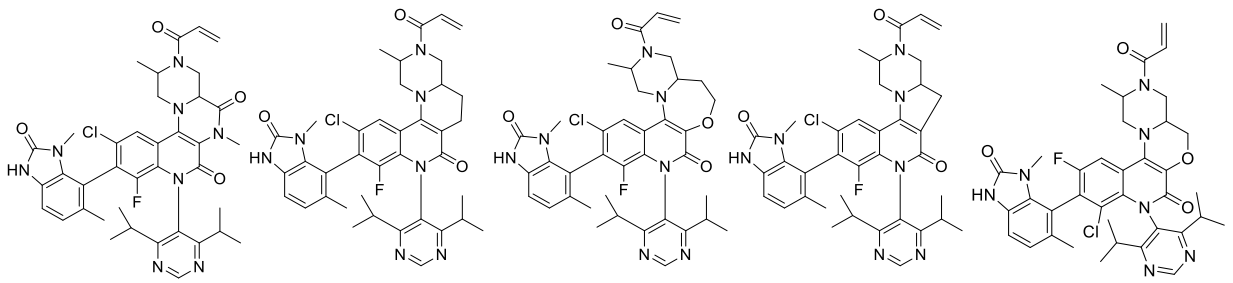


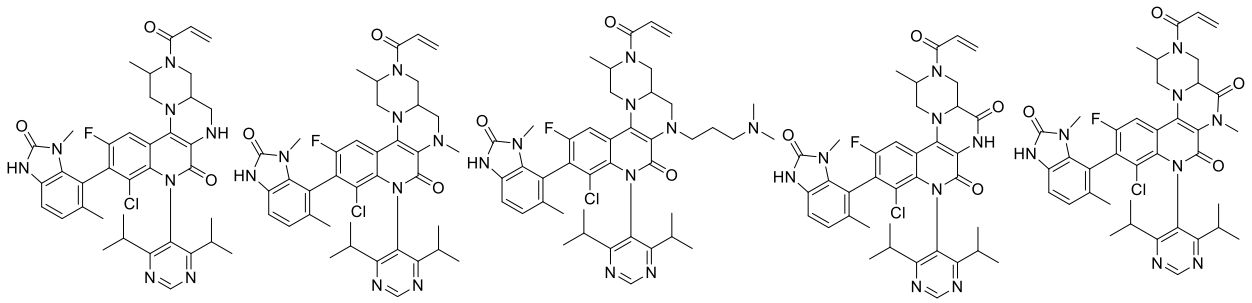


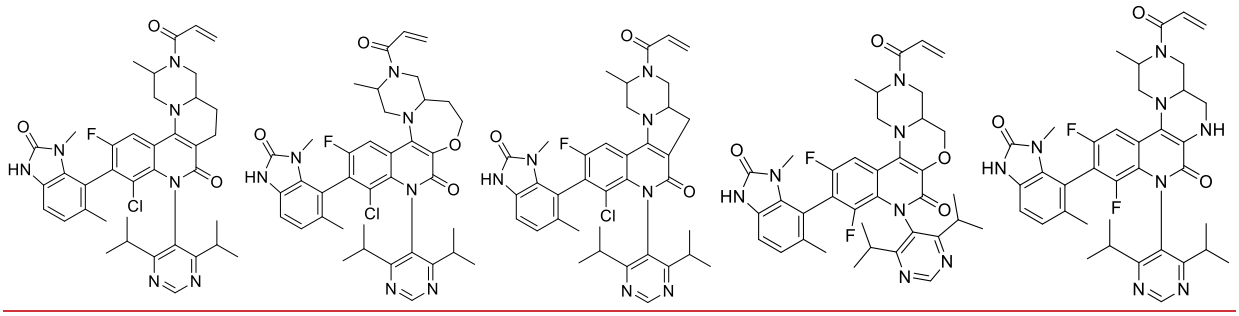


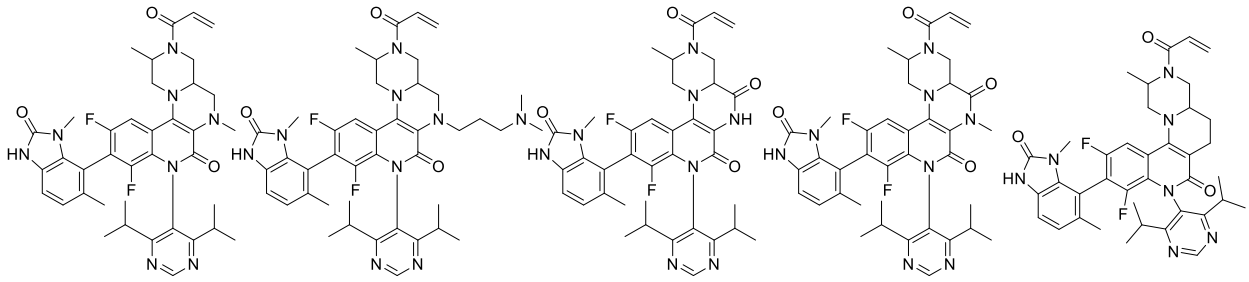


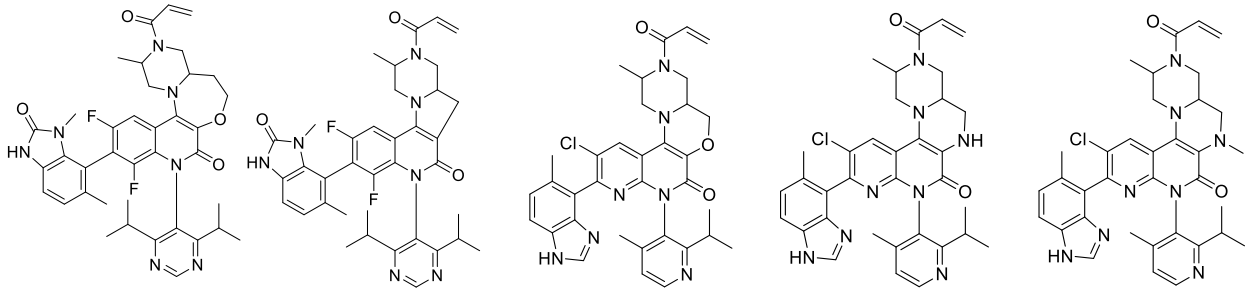


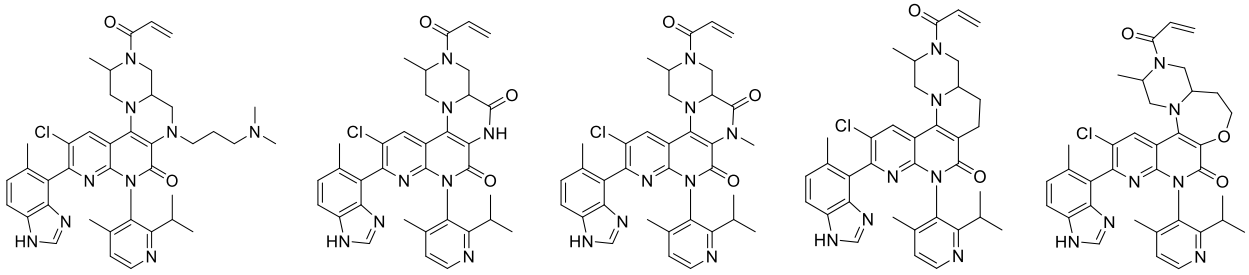


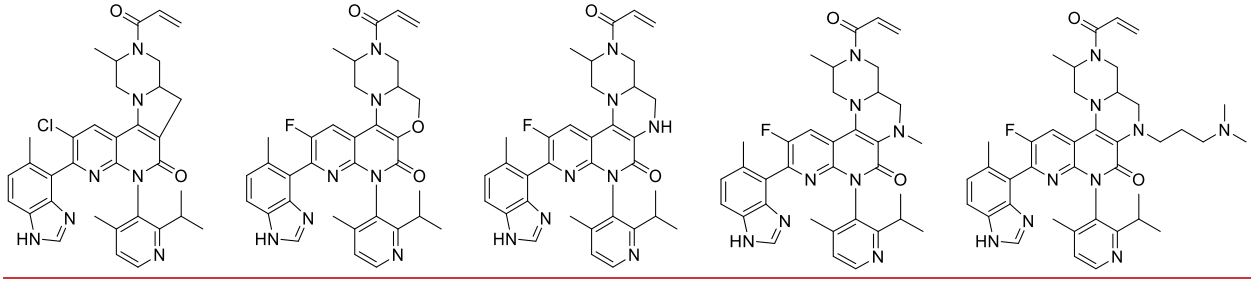


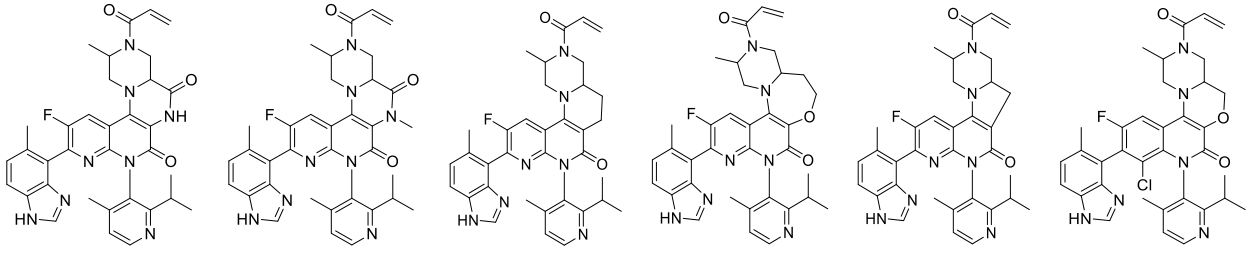


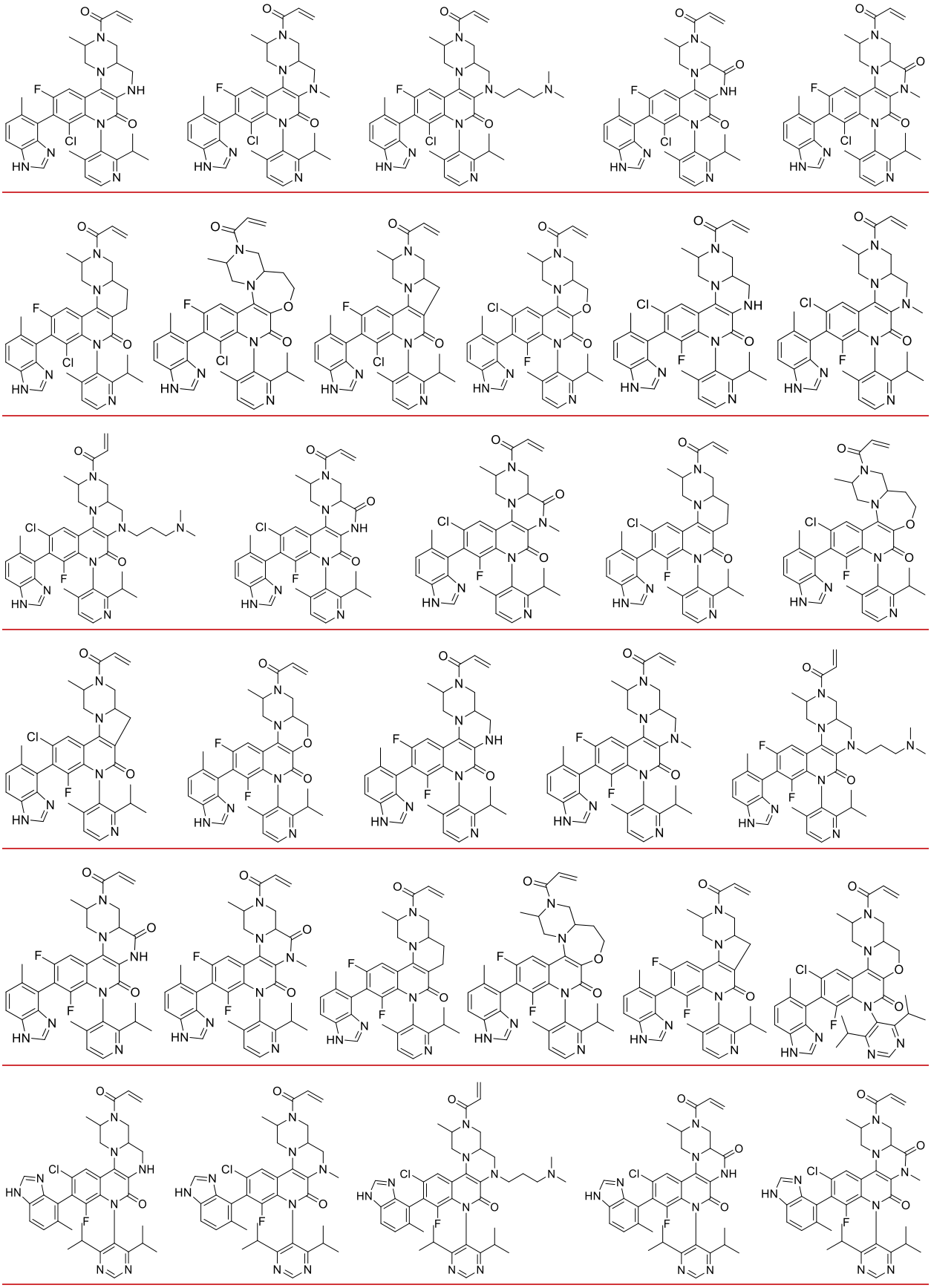


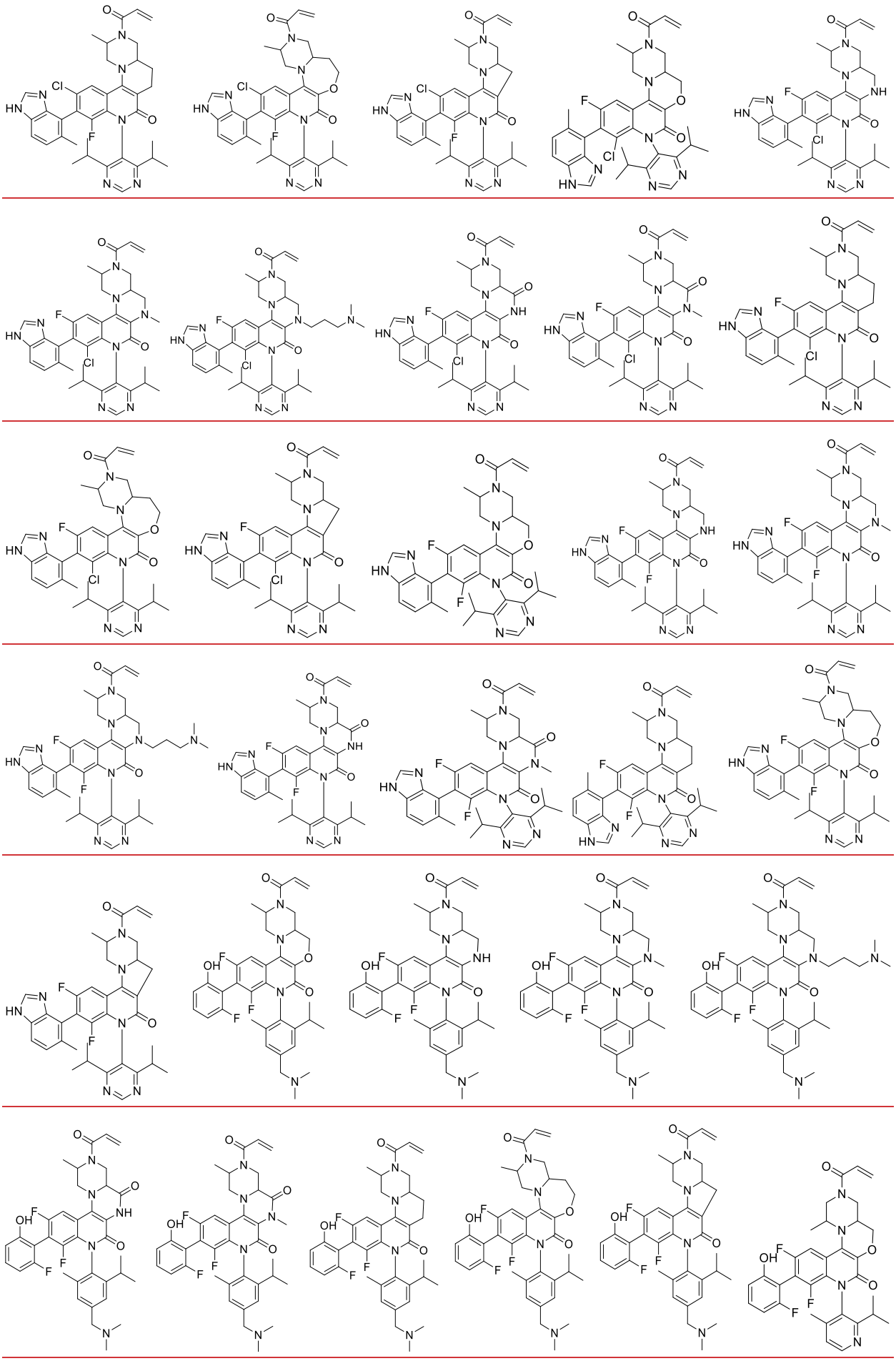




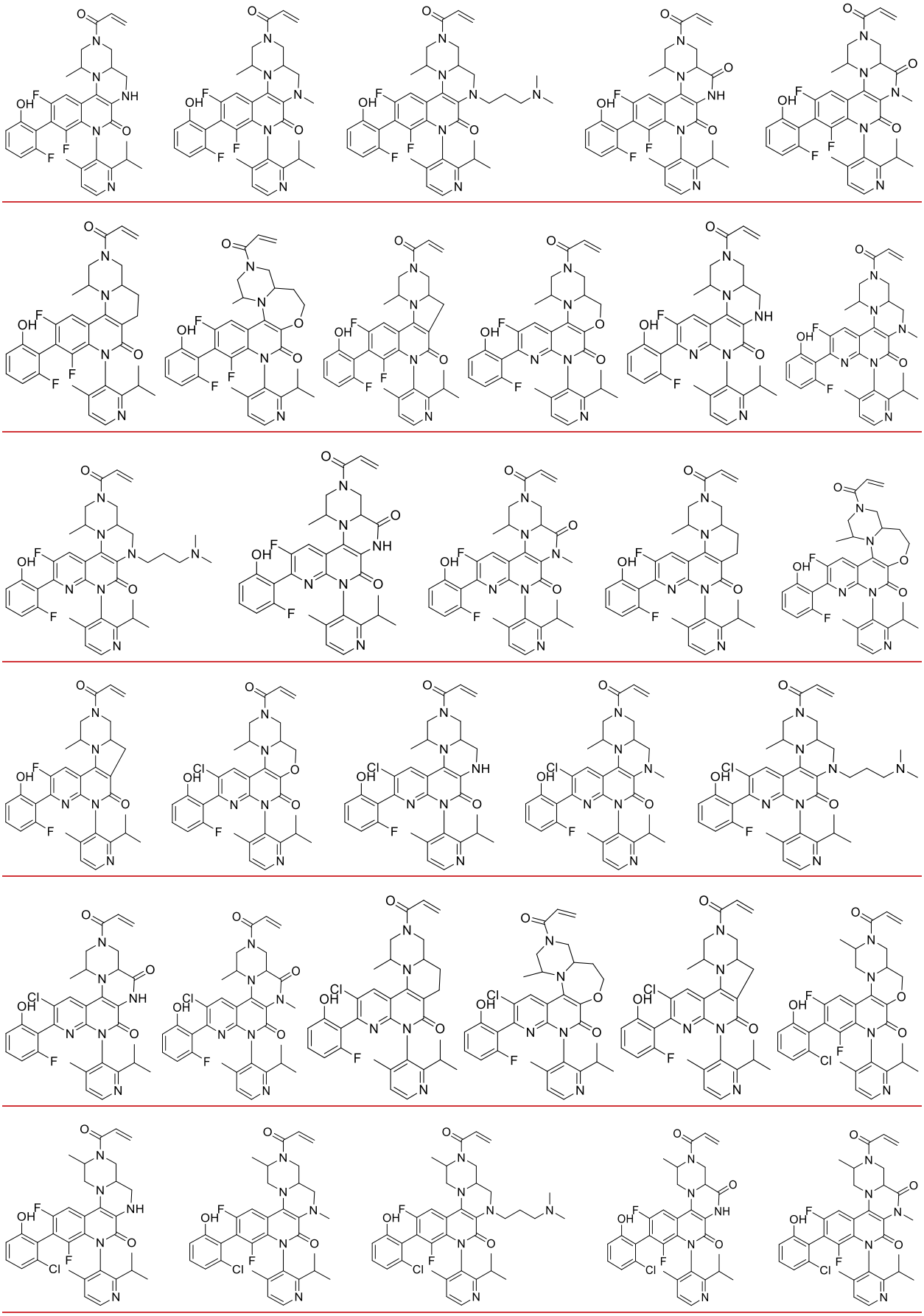


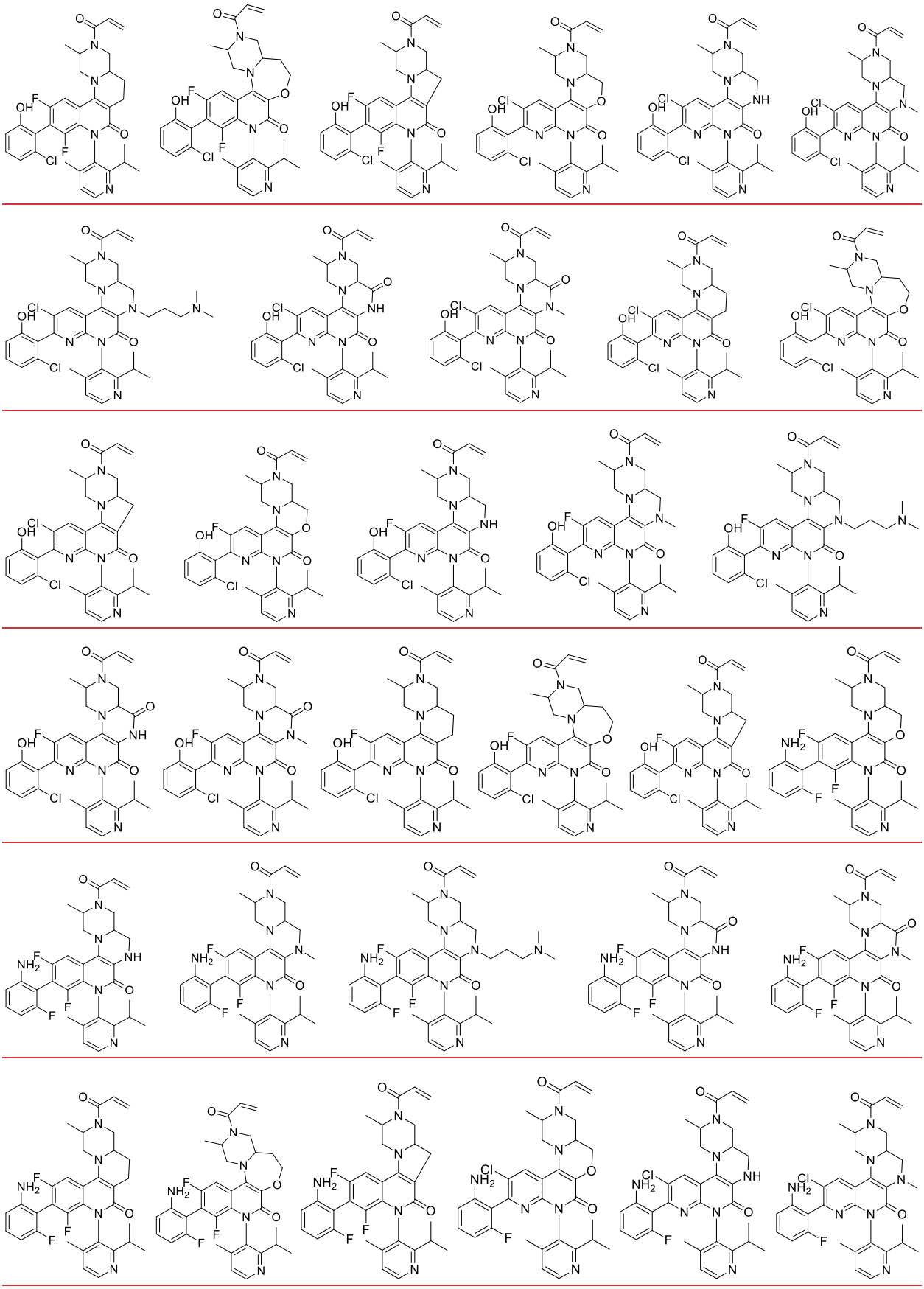


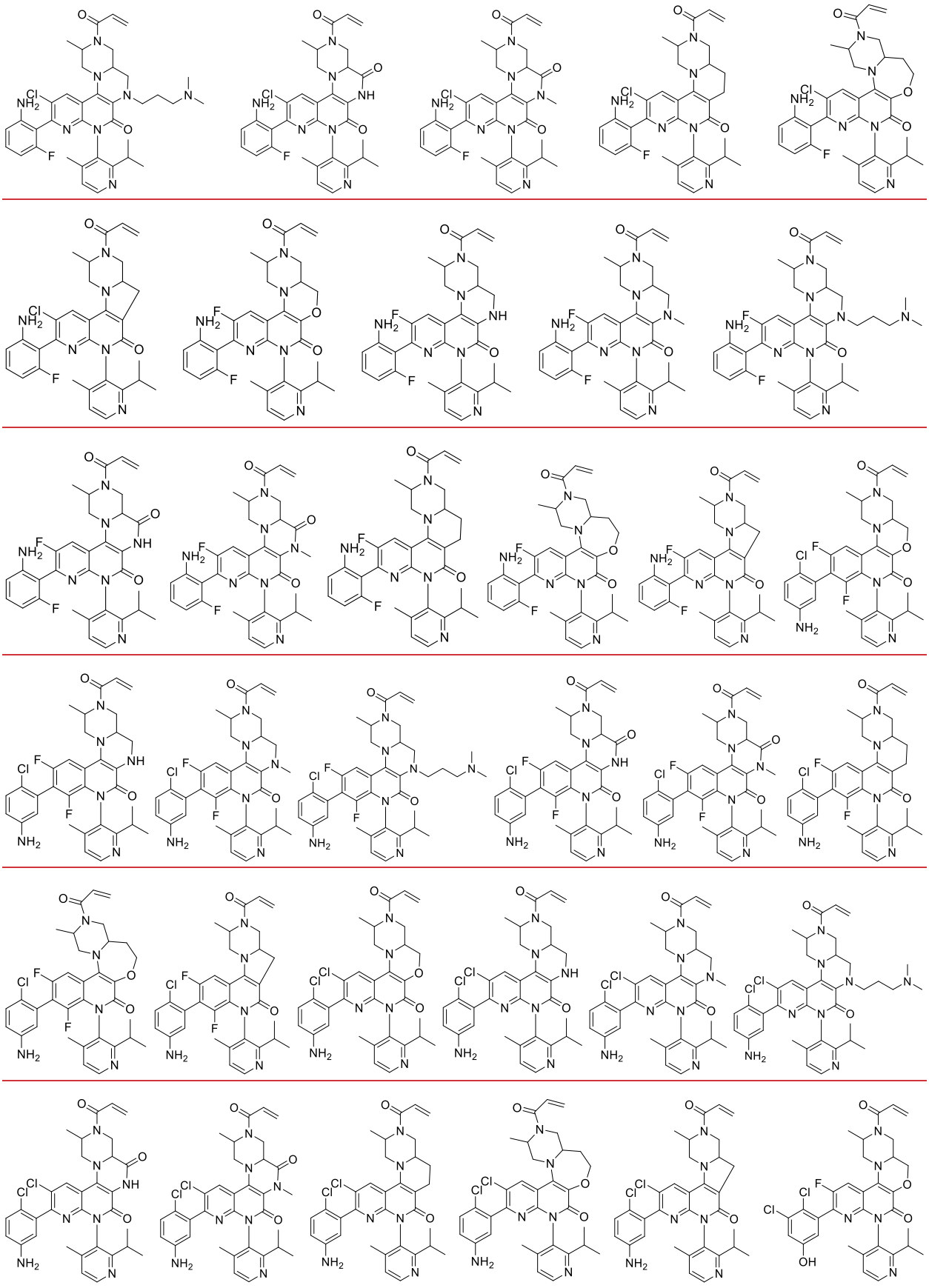




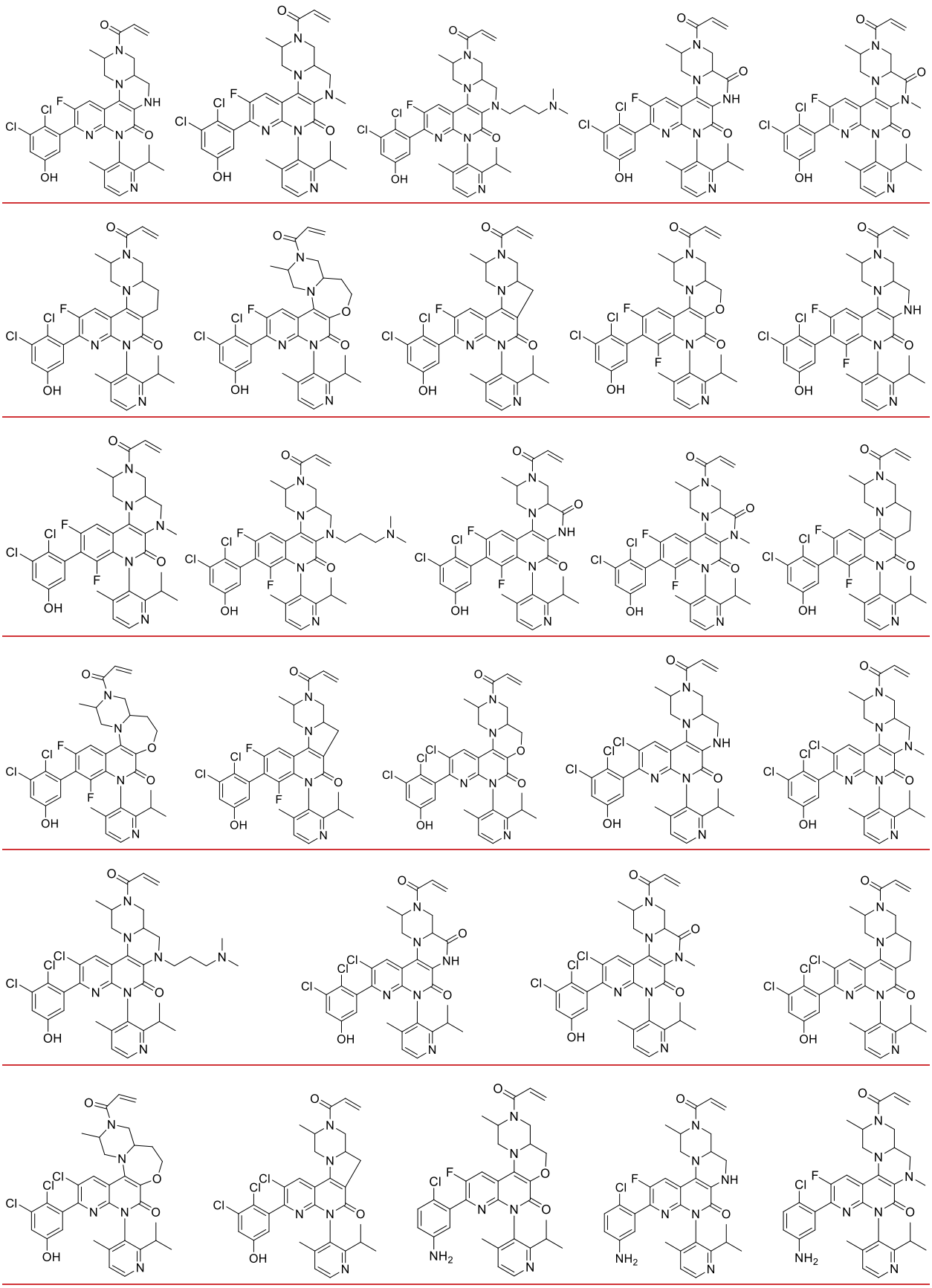
2u



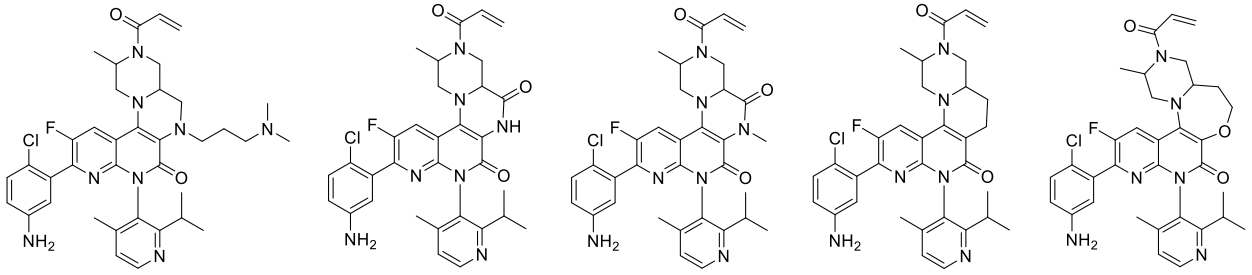


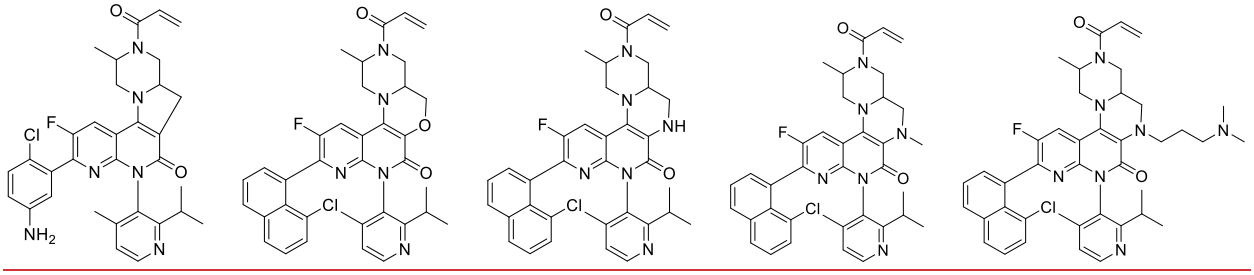


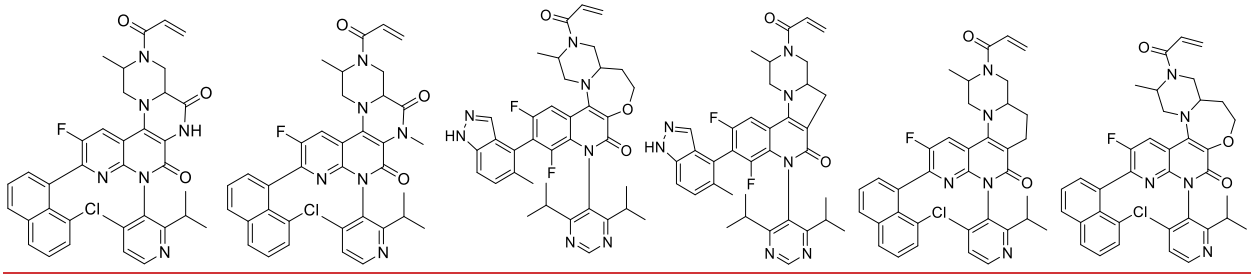
2x

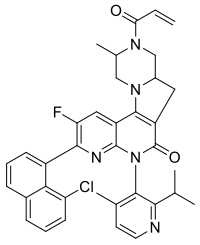


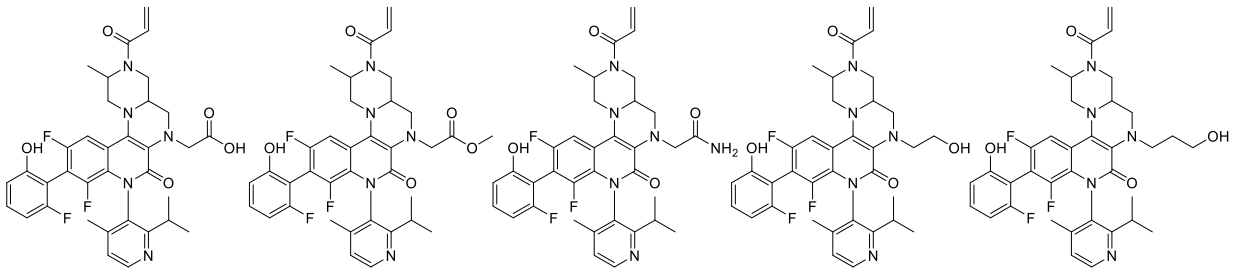
2y

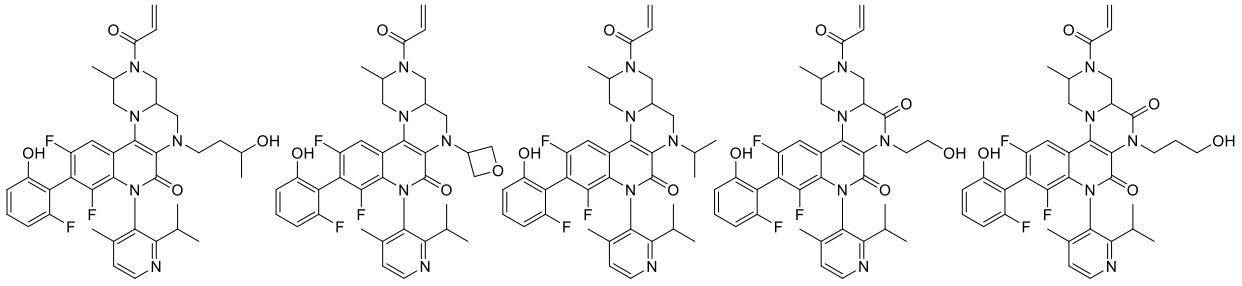


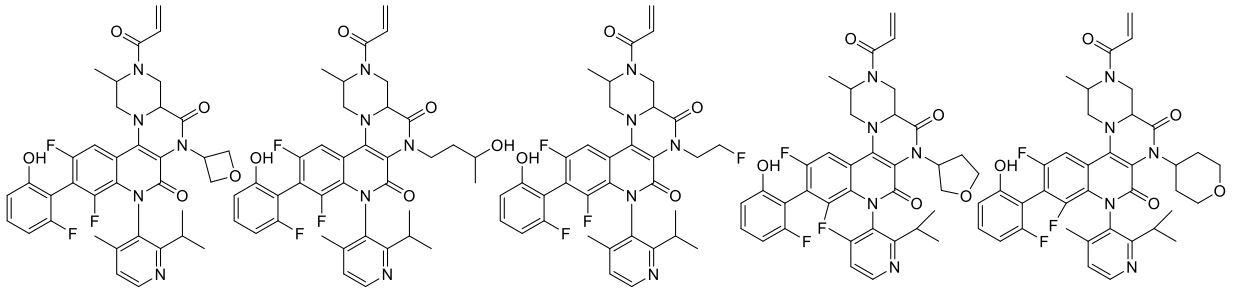


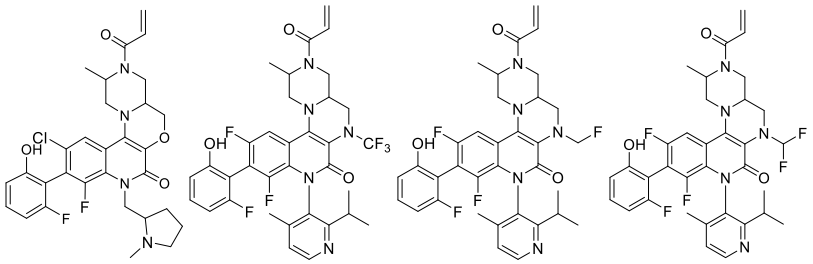


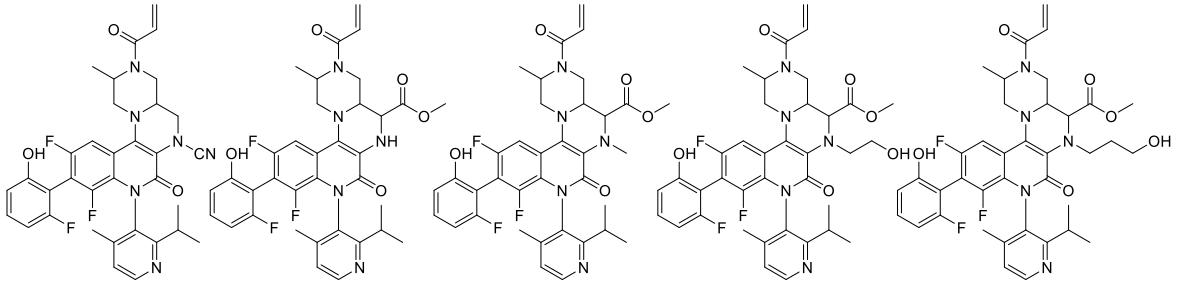


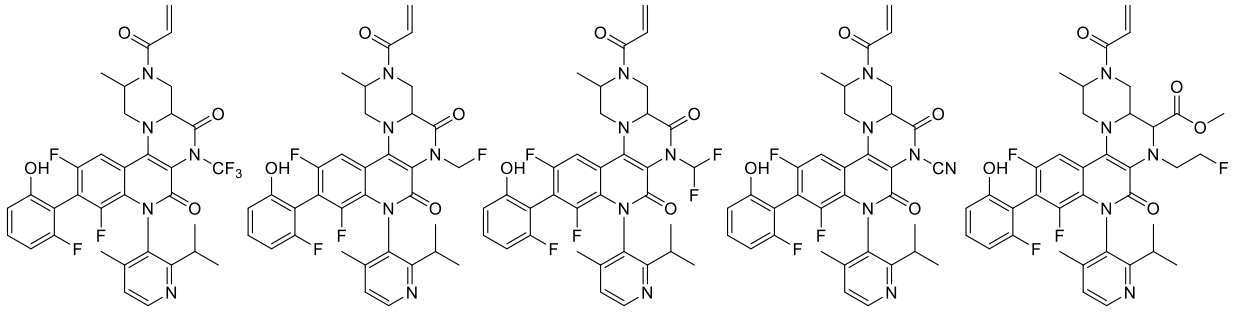


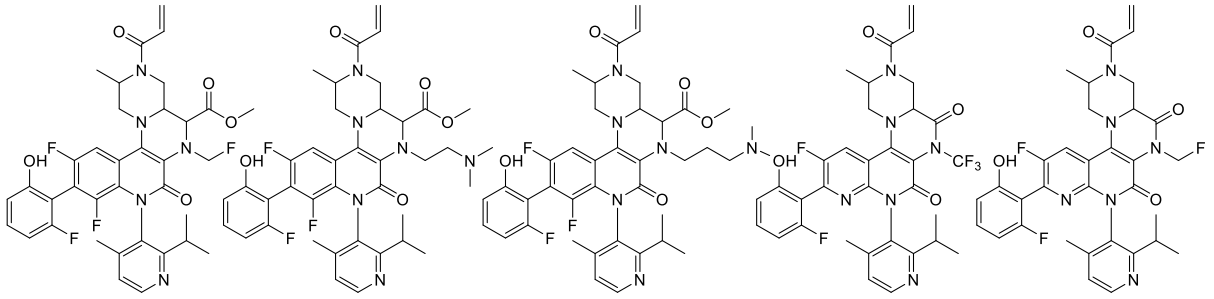


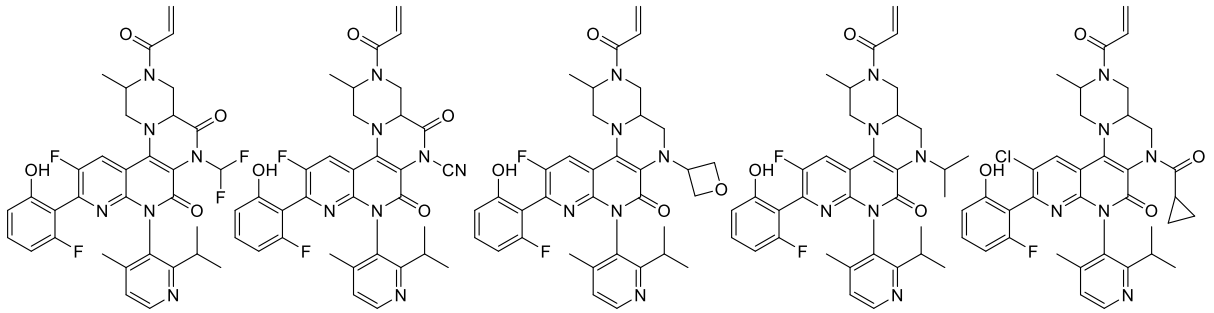




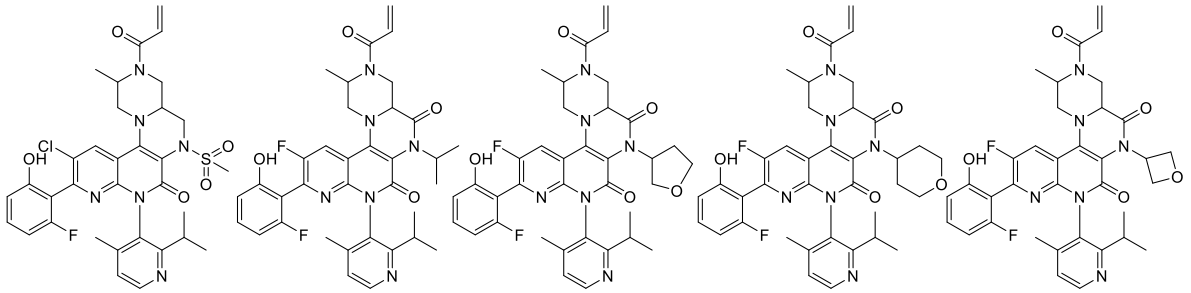


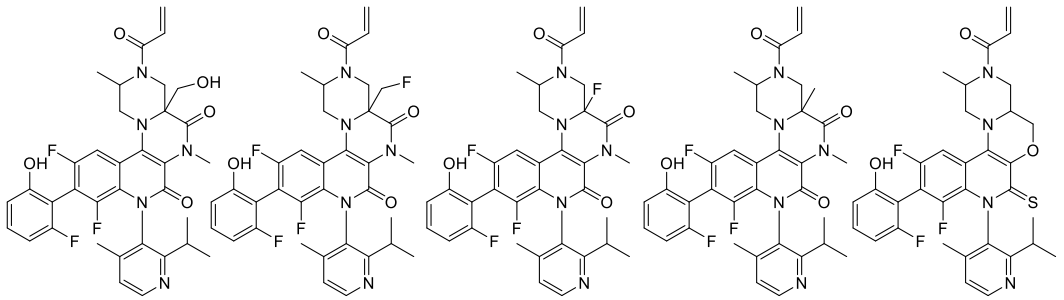


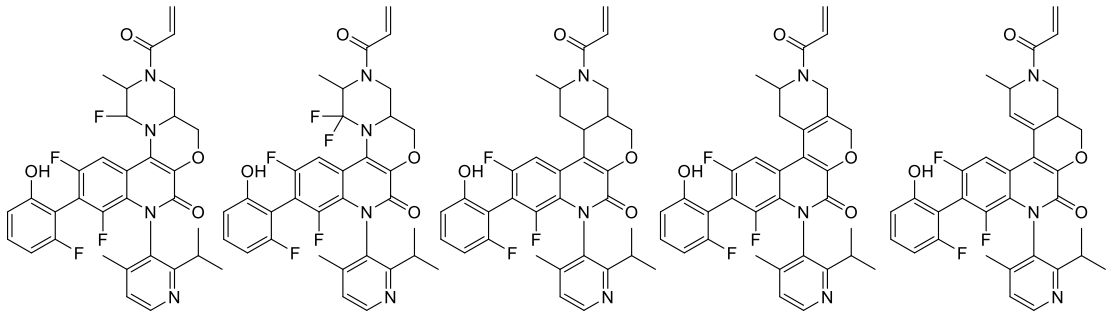


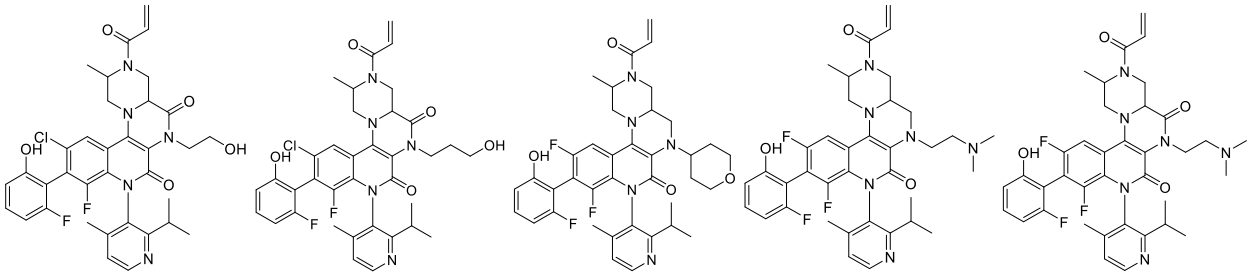


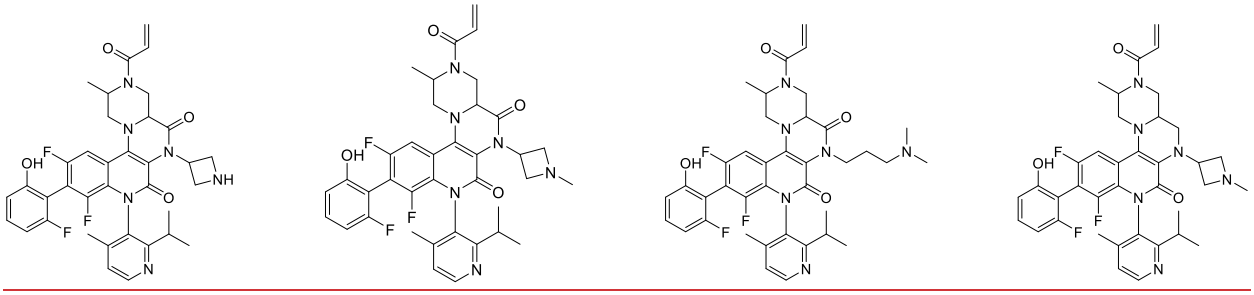
2aa

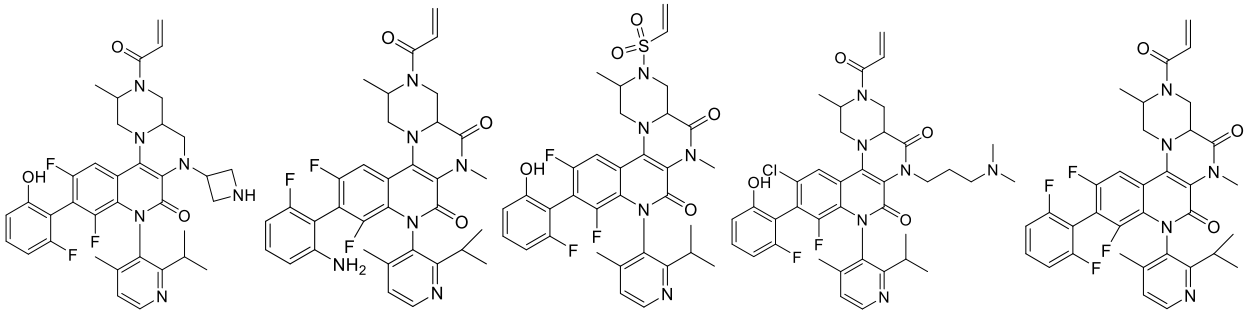




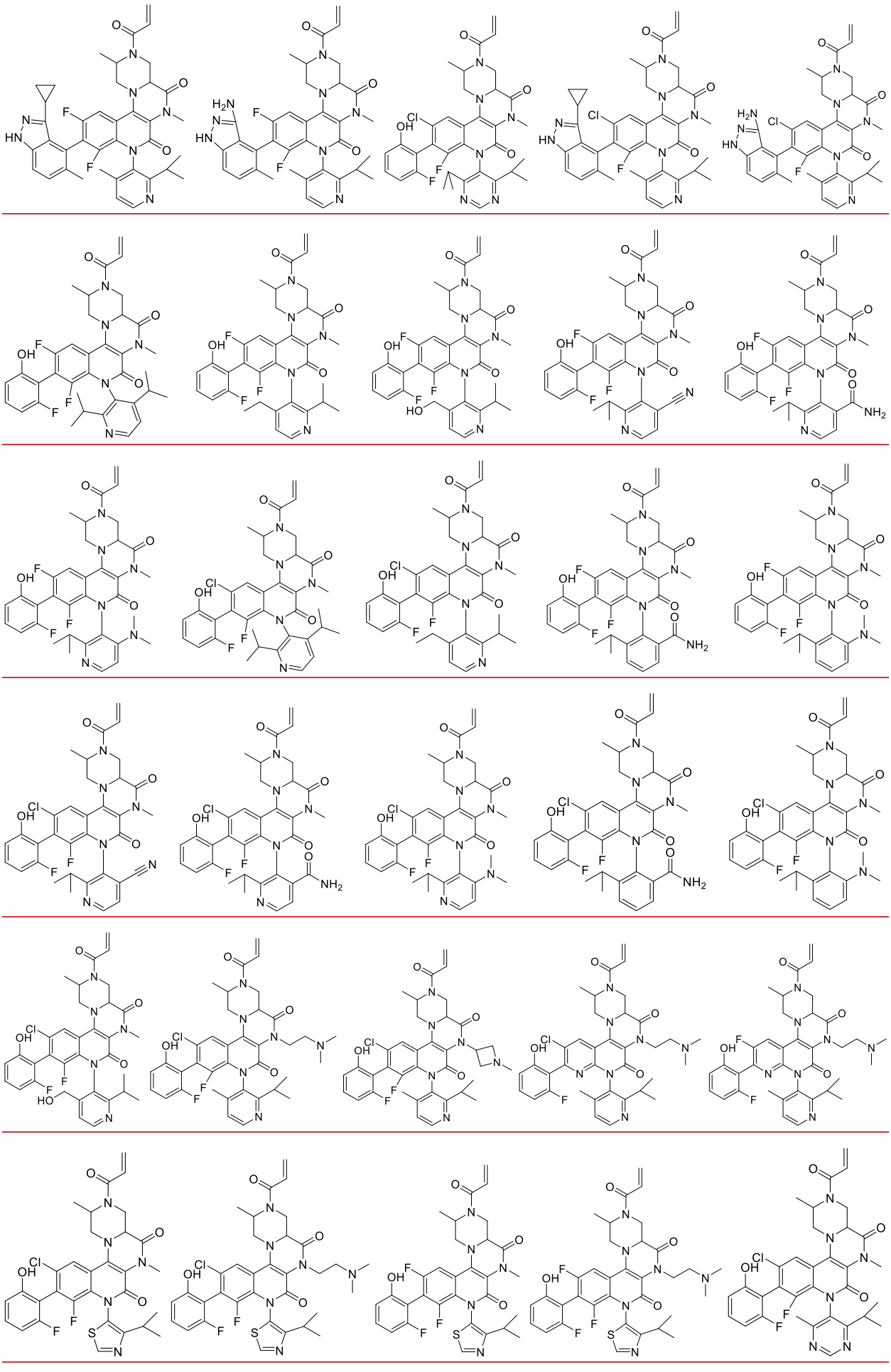




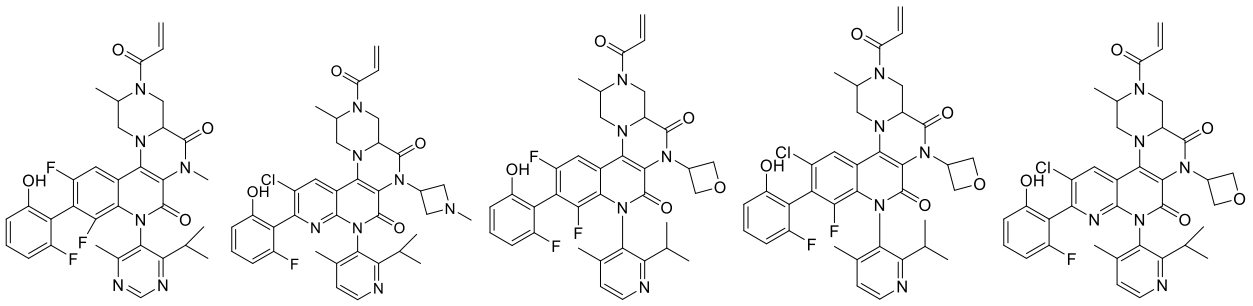


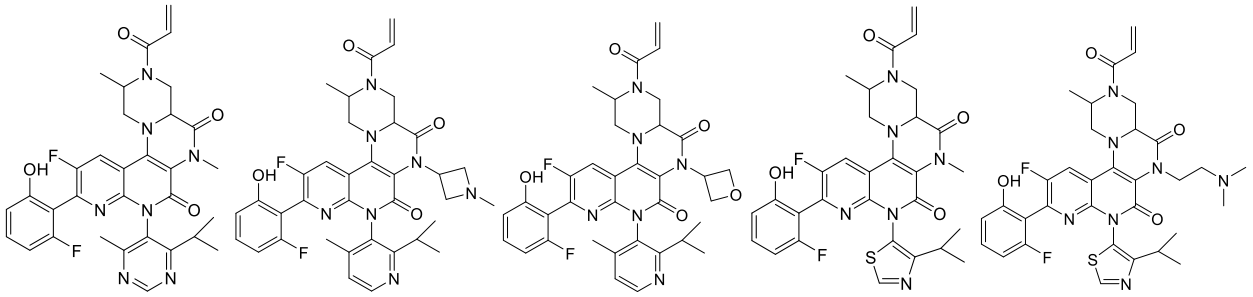


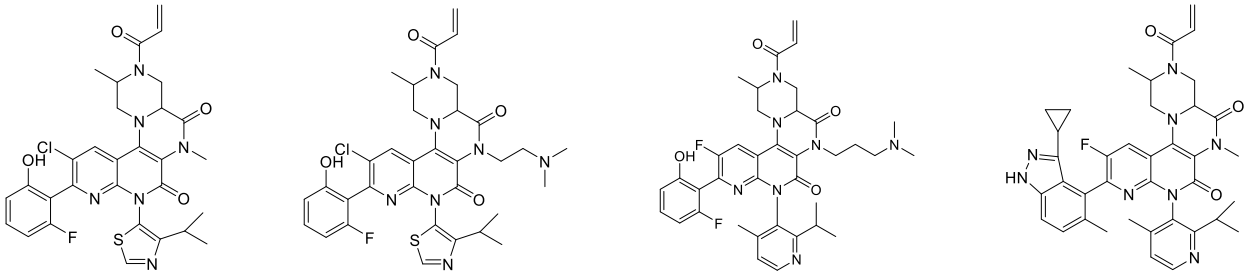
2bb

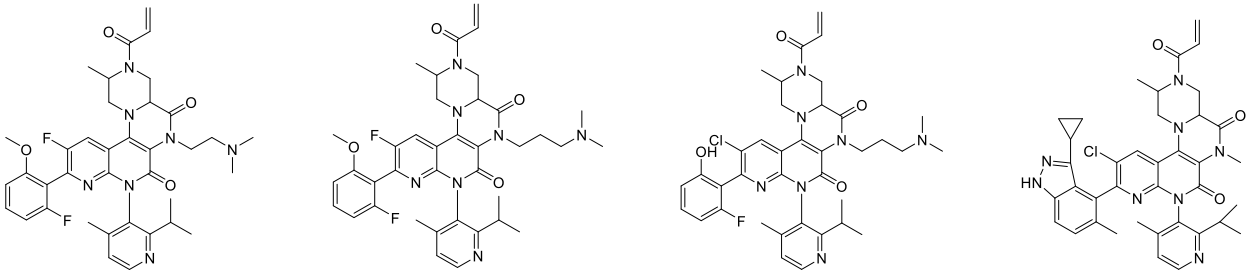


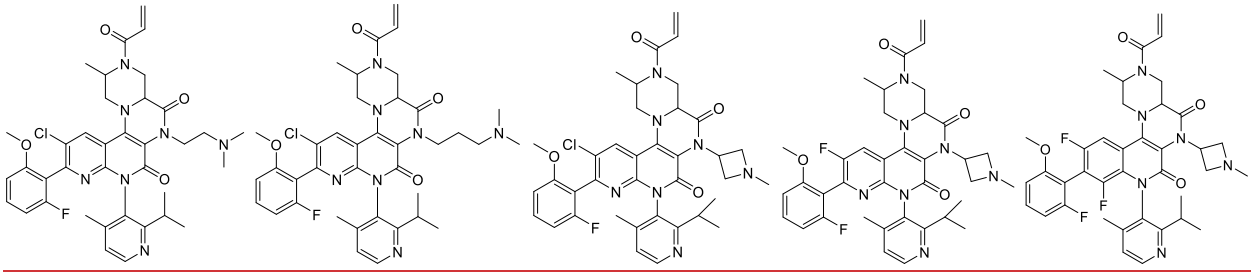
2cc

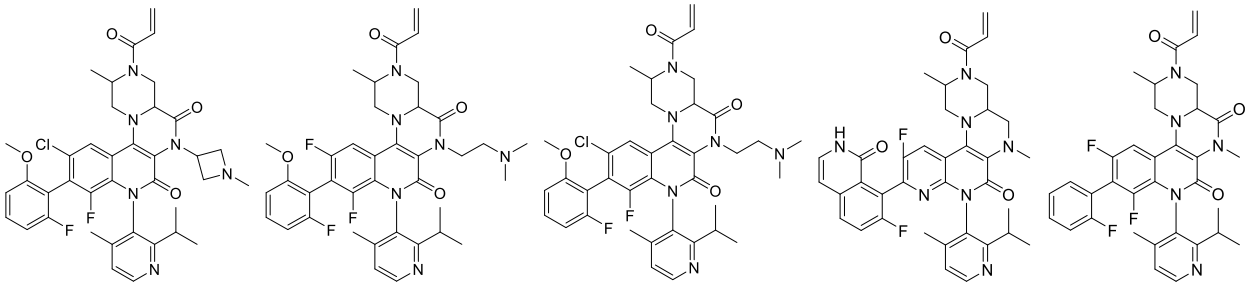


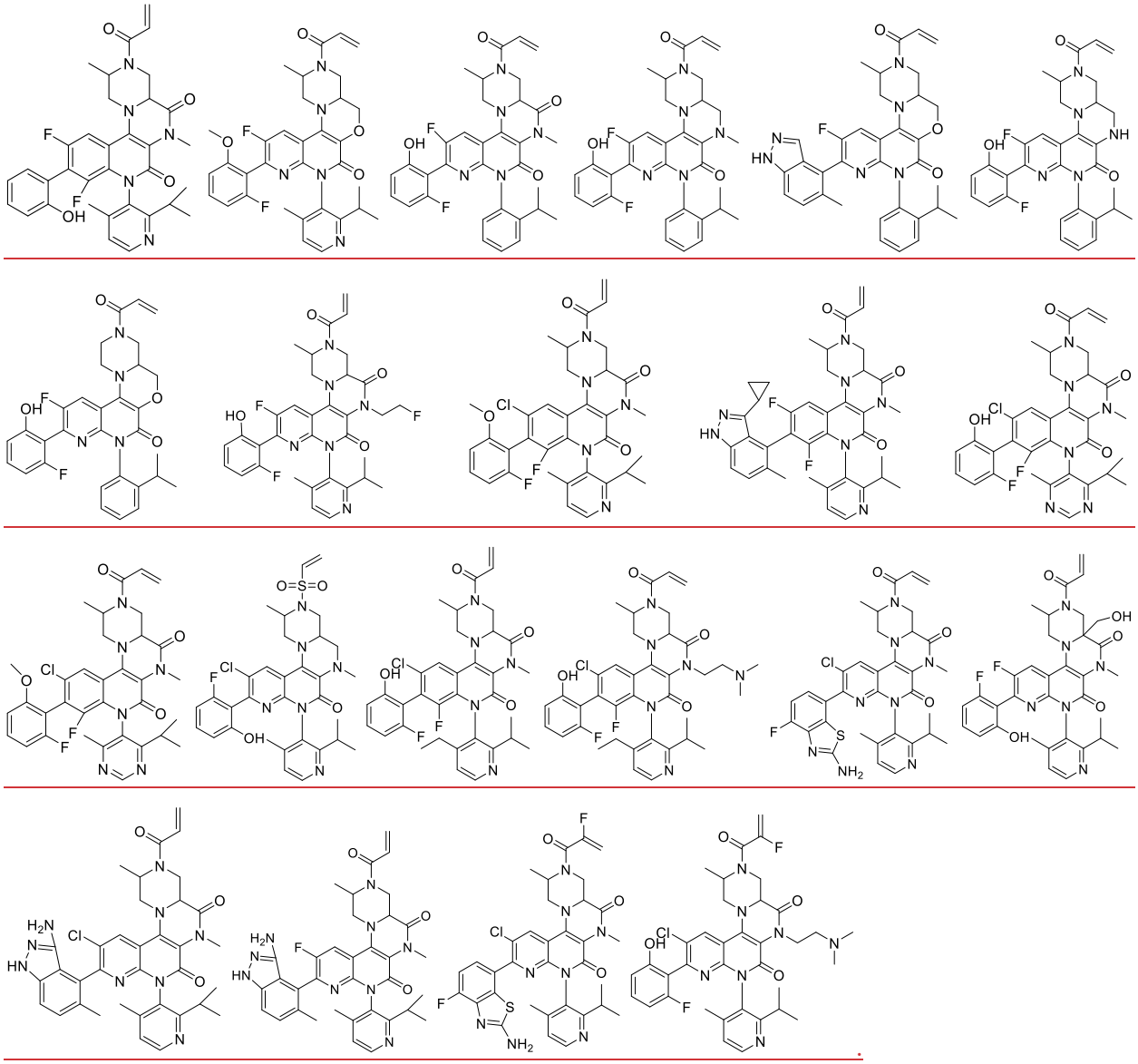












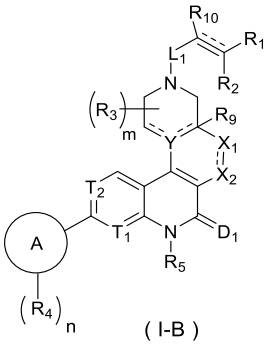
[0008d] In a further aspect, the present disclosure refers to a pharmaceutical composition, comprising the compound, the optical isomer and the pharmaceutically acceptable salt thereof as disclosed herein, and one or more pharmaceutically acceptable carriers, diluents or excipients.

[0008e] In another aspect, the present disclosure refers to a use of the compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof as disclosed herein or the pharmaceutical composition as disclosed herein in preparing a medicament for preventing and/or treating diseases related to KRAS-G12C.

[0008f] In yet another aspect, the present disclosure refers to the compound, the optical isomer thereof, and the pharmaceutically acceptable salt thereof as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in preventing and/or treating diseases related to KRAS-G12C.

Content of the invention

[0009] In the first aspect of the present disclosure, the present disclosure provides a compound represented by formula (I-B), an optical isomer thereof and a pharmaceutically acceptable salt thereof,



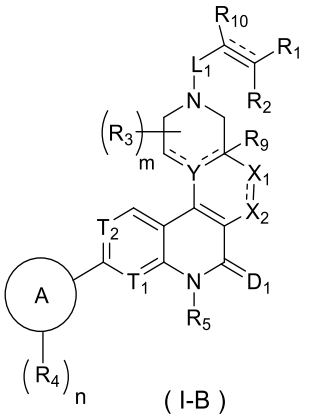
(I-B)

[0010] wherein,

[0011] R_1, R_2 are independently selected from H, halogen and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted by 1, 2 or 3 R;

What is claimed is:

1. A compound represented by formula (I-B), an optical isomer thereof and a pharmaceutically acceptable salt thereof,



(I-B)

wherein,

R_1, R_2 are independently selected from H, halogen and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted by 1, 2 or 3 R;

R_3 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- and C_{3-6} cycloalkyl-O-, the C_{1-6} alkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- or C_{3-6} cycloalkyl-O- is optionally substituted by 1, 2 or 3 R;

R_4 is independently selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

R_5 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, 3-8 membered heterocycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, 3-8 membered heterocycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

L_1 is selected from -C(=O)-, -S(=O)- and -$S(=O)_2$-;

R_6 is selected from H, CN, C_{1-6} alkyl, C_{1-6} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-6} alkyl-3-6 membered heterocycloalkyl and C_{3-6} cycloalkyl-C(=O)-, the C_{1-6} alkyl, C_{1-6} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-6} alkyl-3-6 membered heterocycloalkyl or C_{3-6} cycloalkyl-C(=O)- is optionally substituted by 1, 2 or 3 R;

R_7 is independently selected from H, halogen, OH, NH_2, CN, -C(=O)-OH, C_{1-6} alkyl-O-C(=O)-, -C(=O)-NH_2, C_{1-6} alkyl, C_{1-6} heteroalkyl and -C_{1-6} alkyl-3-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} alkyl-O-C(=O)- or -C_{1-6} alkyl-3-6 membered heterocycloalkyl is optionally substituted by

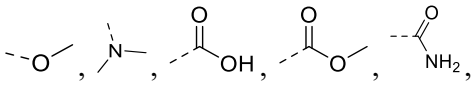
1, 2 or 3 R;

T_1, T_2 are independently selected from N and -C(R_8)-;

R_8 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl or 3-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

R_9 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl and C_{1-6} heteroalkyl, the C_{1-6} alkyl or C_{1-6} heteroalkyl is optionally substituted by 1, 2 or 3 R;

R_{10} is selected from H, halogen, CN, C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylamino, the C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylamino is optionally substituted by 1, 2 or 3 R;

R is independently selected from H, halogen, OH, NH_2, CN, , C_{1-6} alkyl, C_{1-6} heterocycloalkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- and 5-6 membered heterocycloalkyl-O-, the C_{1-6} alkyl, C_{1-6} heterocycloalkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- or 5-6 membered heterocycloalkyl-O- is optionally substituted by 1, 2 or 3 R';

R' is selected from F, Cl, Br, I, OH, NH_2 and CH_3;

ring A is independently selected from C_{6-10} aryl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl;

n is selected from 0, 1, 2, 3 or 4;

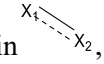
m is selected from 0, 1, 2, 3 or 4;

D_1 is selected from O;

Y is selected from N, CH or C;

 is  or , and when is , R_2, R_{10} are not existed;

 is  or ;

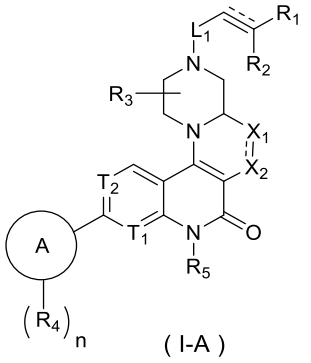
when in , is , X_1, X_2 are independently selected from -N=, -C(R_7)= and -C(R_7)$_2$-C(R_7)=;

when in , is , X_1, X_2 are independently selected from single bond, -O-, -S-, S(=O), S(=O)$_2$, -N(R_6)-, -C(=O)-, -C(R_7)$_2$- and -C(R_7)$_2$-C(R_7)$_2$-;

and, Y cannot be connected to two at the same time, when the bond between Y and R_9 is , R_9 is not existed;

the above 3-6 membered heterocycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, 5-10 membered heteroaryl or C_{1-6} heterocycloalkyl comprises 1, 2, or 3 heteroatoms or heteroatomic groups independently selected from -O-, -NH-, -S-, -C(=O)-, -C(=O)O-, -S(=O)-, -S(=O)$_2$- and N.

2. A compound represented by formula (I-A), an optical isomer thereof and a pharmaceutically acceptable salt thereof,



(I-A)

wherein,

R_1, R_2 are independently selected from H, halogen and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted by 1, 2 or 3 R;

R_3 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- and C_{3-6} cycloalkyl-O-, the C_{1-6} alkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- or C_{3-6} cycloalkyl-O- is optionally substituted by 1, 2 or 3 R;

R_4 is independently selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

R_5 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, 3-8 membered heterocycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, 3-8 membered heterocycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

L_1 is selected from -C(=O)-, -S(=O)- and -$S(=O)_2$-;

R_6 is selected from H, CN, C_{1-6} alkyl, C_{1-6} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-6} alkyl-3-6 membered heterocycloalkyl and C_{3-6} cycloalkyl-C(=O)-, the C_{1-6} alkyl, C_{1-6} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-6} alkyl-3-6 membered heterocycloalkyl or C_{3-6} cycloalkyl-C(=O)- is optionally substituted by 1, 2 or 3 R;

R_7 is independently selected from H, halogen, OH, NH_2, CN, -C(=O)OH, C_{1-6} alkyl-O-C(=O)-, -C(=O)-NH_2, C_{1-6} alkyl, C_{1-6} heteroalkyl and -C_{1-6} alkyl-3-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} alkyl-O-C(=O)- or -C_{1-6} alkyl-3-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

T_1, T_2 are independently selected from N and -C(R_8) -;

R_8 is selected from H, halogen, OH, NH_2, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl or 3-6 membered

heterocycloalkyl is optionally substituted by 1, 2 or 3 R;

R is independently selected from H, halogen, OH, NH_2, CN, , , , , C_{1-6} alkyl, C_{1-6} heterocycloalkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- and 5-6 membered heterocycloalkyl-O-, the C_{1-6} alkyl, C_{1-6} heterocycloalkyl, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- or 5-6 membered heterocycloalkyl-O- is optionally substituted by 1, 2 or 3 R';

R' is selected from F, Cl, Br, I, OH, NH_2 and CH_3;

ring A is independently selected from C_{6-10} aryl, 5-10 membered heteroaryl, benzo 5-6 membered heterocycloalkyl and 5-6 membered heteroaryl-fused 5-6 membered heterocycloalkyl;

n is selected from 0, 1, 2, 3 or 4;

 is  or , and when is , R_2 is not existed;

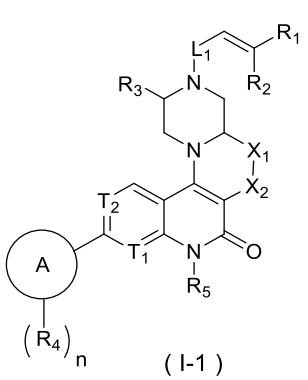
 is  or ;

when in ,  is , X_1, X_2 are independently selected from -N=, -C(R_7)= and -C(R_7)$_2$-C(R_7)=;

when in ,  is , X_1, X_2 are independently selected from single bond, -O-, -S-, S(=O), S(=O)$_2$, -N(R_6)-, -C(=O)-, -C(R_7)$_2$- and -C(R_7)$_2$-C(R_7)$_2$-;

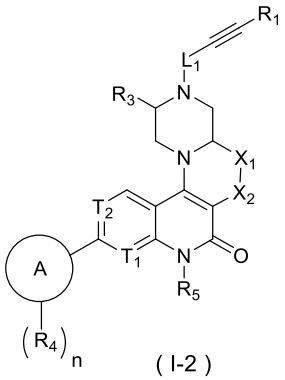
the above 3-6 membered heterocycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, 5-10 membered heteroaryl or C_{1-6} heterocycloalkyl comprises 1, 2, or 3 heteroatoms or heteroatomic groups independently selected from -O-, -NH-, -S-, -C(=O)-, -C(=O)O-, -S(=O)-, -S(=O)$_2$- and N.

3. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, selecting from



(I-1)

,



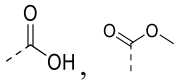
(I-2)

wherein,

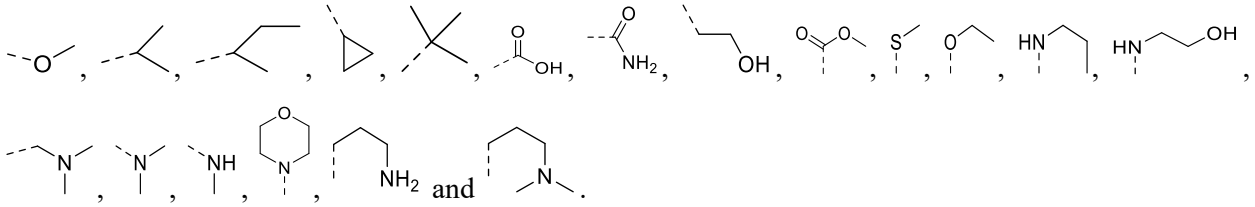
X_1, X_2 are independently selected from single bond, -O-, -S-, S(=O), S(=O)$_2$, -N(R_6)-, -C(=O)-, -C(R_7)$_2$- and -C(R_7)$_2$-C(R_7)$_2$-,

R_1, R_2, R_3, R_4, R_5, L_1, R_6, R_7, T_1, T_2, ring A and n are as defined in claim 1 or 2.

4. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 3, wherein, R is independently selected from H, halogen, OH, NH_2, CN, , ,

, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylamino, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- and -5-6 membered heterocycloalkyl-O-, the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylamino, C_{3-6} cycloalkyl, 5-6 membered heterocycloalkyl, C_{3-6} cycloalkyl-O- or 5-6 membered heterocycloalkyl-O- is optionally substituted by 1, 2 or 3 R'.

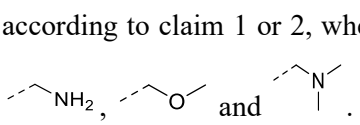
5. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 4, wherein, R is independently selected from H, F, Cl, Br, I, OH, NH_2, CN, Me, CH_2CH_3,



and

.

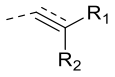
6. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein, R_1, R_2 are independently selected from H, F, Me, CF_3,



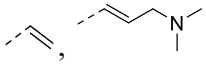
and

.

7. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 6, wherein, the structural moiety



is selected from

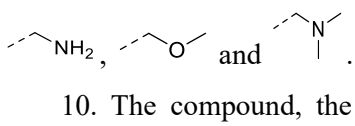


and

.

8. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein, R_3 is selected from H, halogen, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylthio, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- and C_{3-6} cycloalkyl-O-, the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylthio, 3-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl-O- or C_{3-6} cycloalkyl-O- is optionally substituted by 1, 2 or 3 R.

9. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 8, wherein, R_3 is selected from H, F, Cl, Br, I, OH, NH_2, CN, Me, CF_3,



and

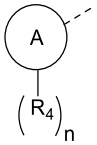
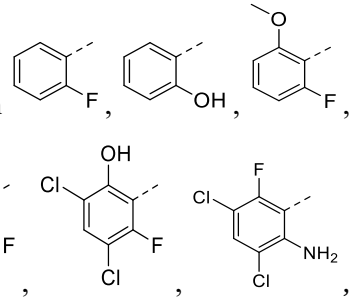
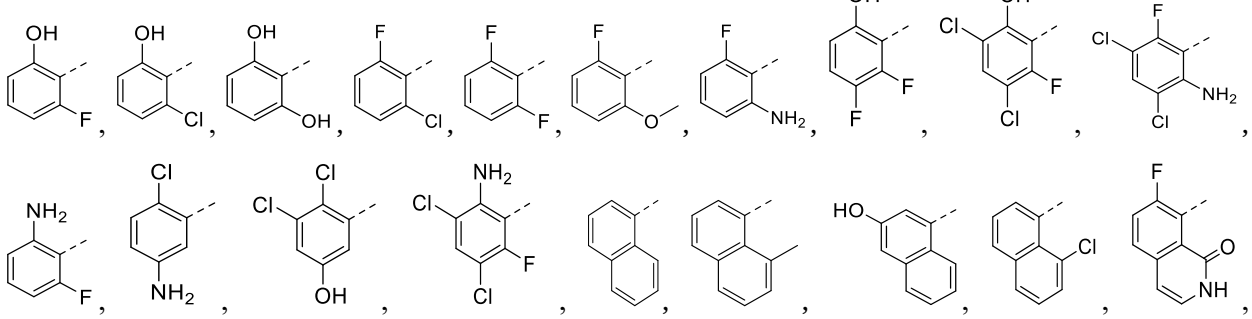
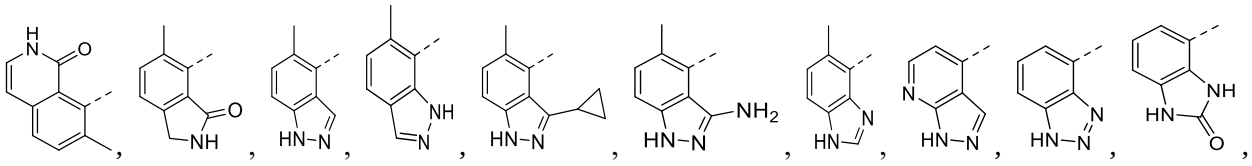
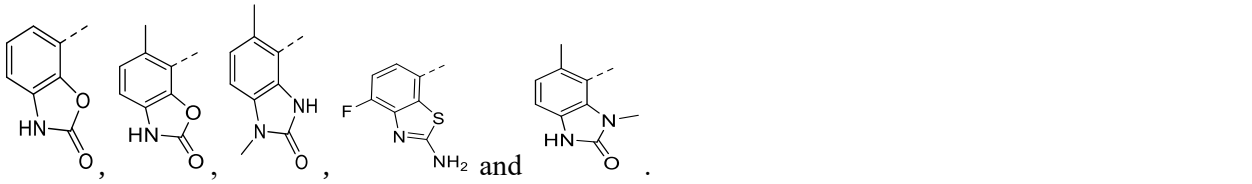
.

10. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein, R_4 is independently selected from H, halogen, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, pyridinyl, pyrimidinyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzofuranyl, benzothienyl and indolyl, the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, phenyl, pyridinyl, pyrimidinyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzofuranyl, benzothienyl or indolyl is optionally substituted by 1, 2 or 3 R.

11. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof

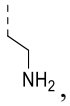
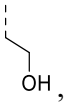
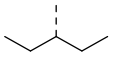
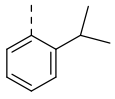
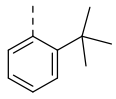
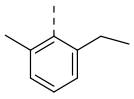
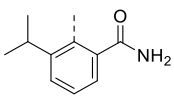
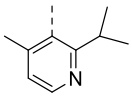
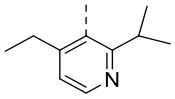
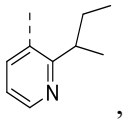
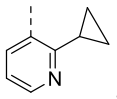
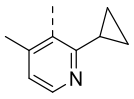
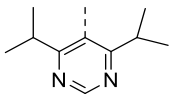
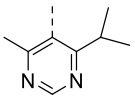
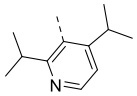
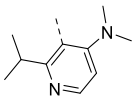
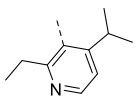
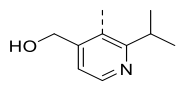
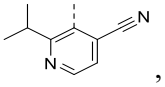
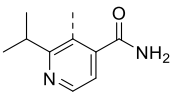
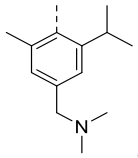
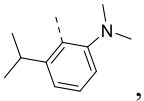
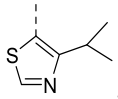
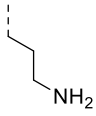
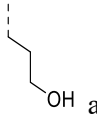
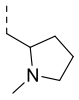
according to claim 10, wherein, R_4 is selected from H, F, Cl, Br, I, OH, NH_2, CN, Me, CF_3, ,  and .

12. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein, ring A is selected from phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzofuranyl, benzothienyl, indolyl, indazolyl, benzoimidazolyl, 1H-benzo[d]imidazolyl, benzopyrazolyl, purinyl, quinolinyl, isoquinolinyl, isoquinolin-1(2H)-one, isoindolin-1-one, benzo[d]oxazol-2(H)-one, benzo[d]oxazol-2(3H)-one, H-benzo[d] [1,2,3]triazolyl, 1H-pyrazolo[3,4-b]pyridinyl, benzo[d]thiazolyl and 1,3-dihydro-2H-benzo[d]imidazolyl-2-one, the phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzofuranyl, benzothienyl, indolyl, indazolyl, benzoimidazolyl, 1H-benzo[d]imidazolyl, benzopyrazolyl, purinyl, quinolinyl, isoquinolinyl, isoquinolin-1(2H)-one, isoindolin-1-one, benzo[d]oxazol-2(H)-one, benzo[d]oxazol-2(3H)-one, H-benzo[d] [1,2,3]triazolyl, 1H-pyrazolo[3,4-b]pyridinyl, benzo[d]thiazolyl or 1,3-dihydro-2H-benzo[d]imidazolyl-2-one is optionally substituted by 1, 2 or 3 R.

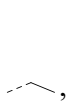
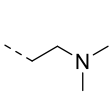
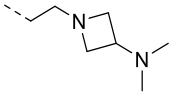
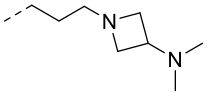
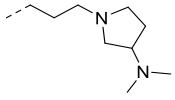
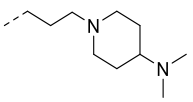
13. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 12, wherein, the structural moiety  is selected from , , ,  and .

14. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein, R_5 is selected from H, C_{1-3} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydro-2H-pyranyl, piperidinyl, piperazinyl, 5-6 membered

heterocycloalkyl-C_{1-3} alkyl-, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzofuranyl, benzothienyl, indolyl, benzoimidazolyl, benzopyrazolyl, purinyl, quinolinyl, isoquinolinyl, isoquinolin-1(2H)-one, isoindolin-1-one, benzo[d]oxazol-2(H)-one and 1,3-dihydro-2H-benzo[d]imidazolyl-2-one, the C_{1-3} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydro-2H-pyranyl, piperidinyl, piperazinyl, 5-6 membered heterocycloalkyl-C_{1-3} alkyl-, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzofuranyl, benzothienyl, indolyl, benzoimidazolyl, benzopyrazolyl, purinyl, quinolinyl, isoquinolinyl, isoquinolin-1(2H)-one, isoindolin-1-one, benzo[d]oxazol-2(H)-one or 1,3-dihydro-2H-benzo[d]imidazolyl-2-one is optionally substituted by 1, 2 or 3 R.

15. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 14, wherein, R_5 is selected from H, Me, , , , , , , , , , , , , , , , , , , , , , , , , ,  and .

16. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein, R_7 is independently selected from H, halogen, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkyl-O-C(=O)-, -C(=O)-NH_2, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylthio and -C_{1-3} alkyl-3-6 membered heterocycloalkyl, the C_{1-3} alkyl, C_{1-3} alkyl-O-C(=O)-, -C(=O)-NH_2, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylthio or -C_{1-3} alkyl-3-6 membered heterocycloalkyl is optionally substituted by 1, 2 or 3 R.

17. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 16, wherein, R_7 is independently selected from H, F, Cl, Br, I, OH, NH_2, CN, Me, CF_3, , , , , , , , , ,  and .

18. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein, R_6 is independently selected from H, CN, C_{1-3} alkyl, C_{1-3} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-3} alkyl-3-6 membered heterocycloalkyl and C_{3-6} cycloalkyl-C(=O)-,

the C_{1-3} alkyl, C_{1-3} alkyl-$S(=O)_2$-, 3-6 membered heterocycloalkyl, -C_{1-3} alkyl3-6 membered heterocycloalkyl or C_{3-6} cycloalkyl-C(=O)- is optionally substituted by 1, 2 or 3 R.

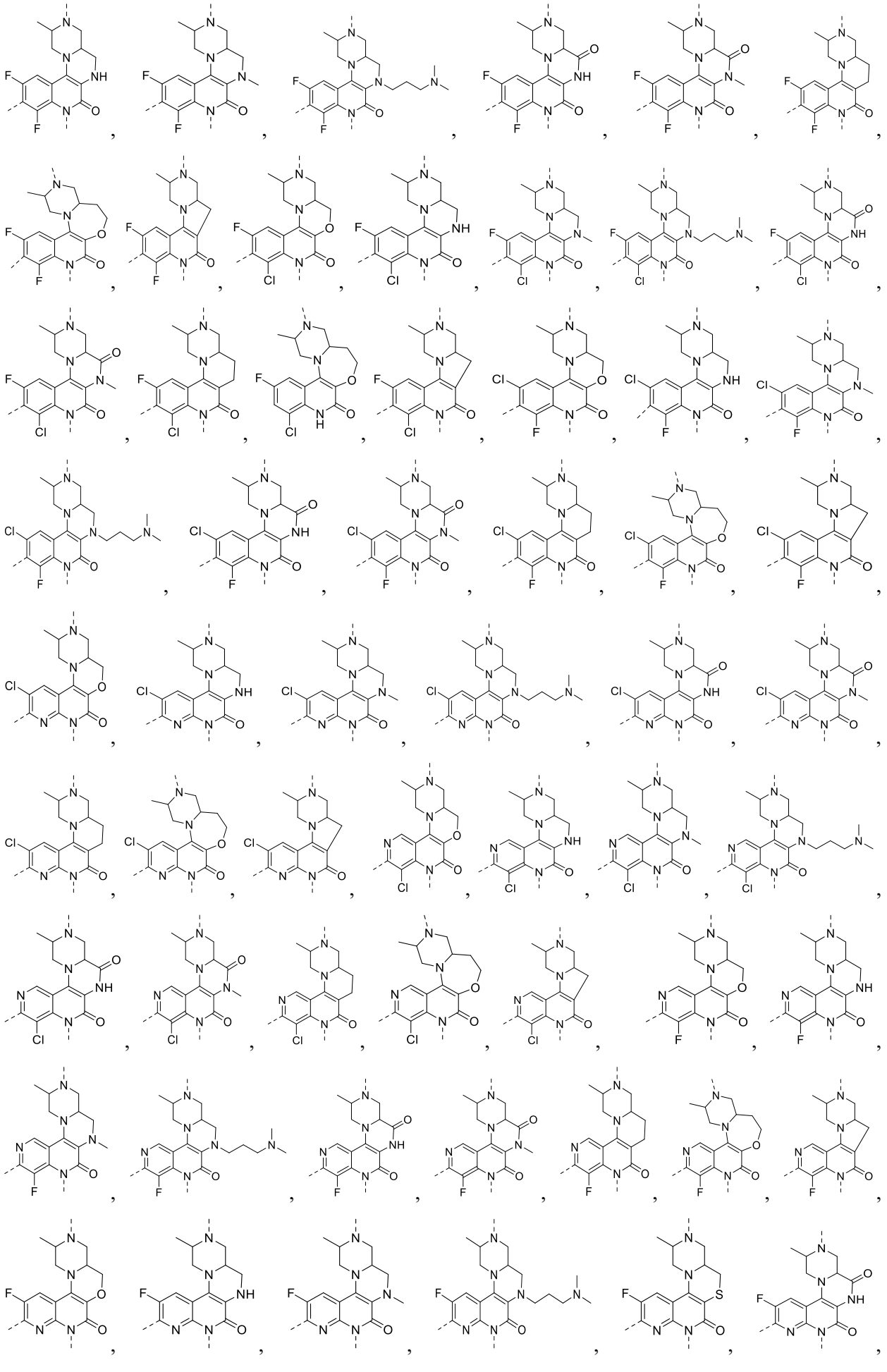
19. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 18, wherein, R_6 is independently selected from H, CN, Me, CF_3, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and .

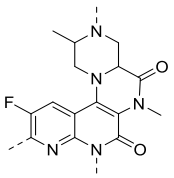
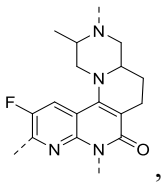
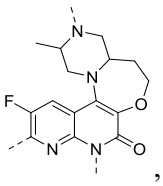
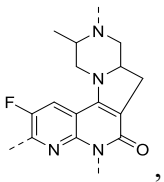
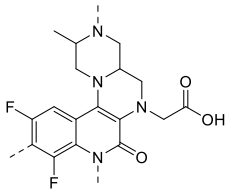
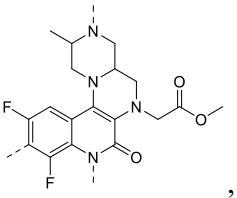
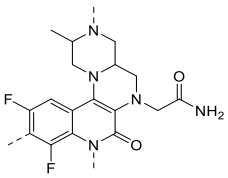
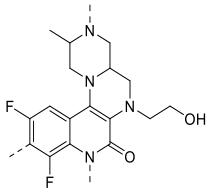
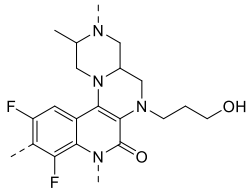
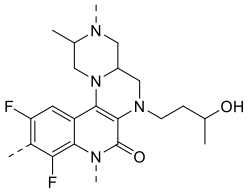
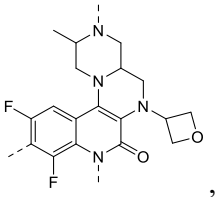
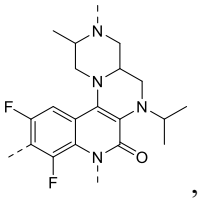
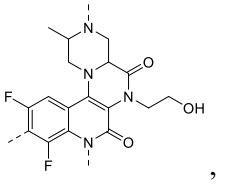
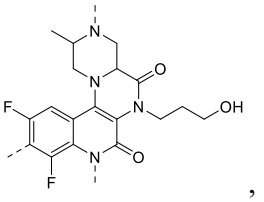
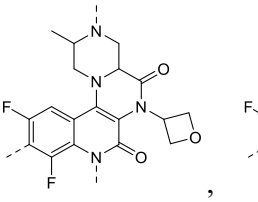
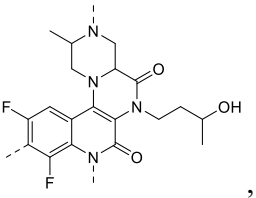
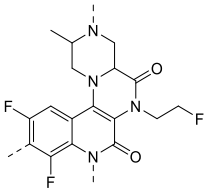
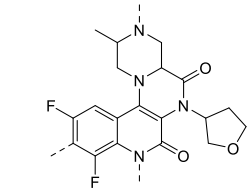
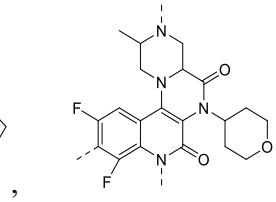
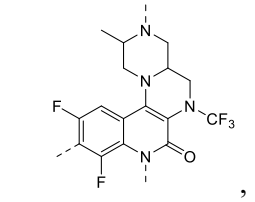
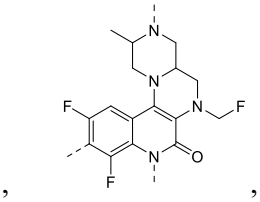
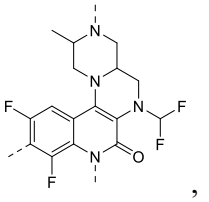
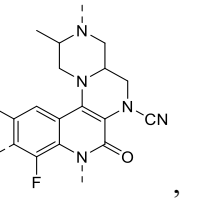
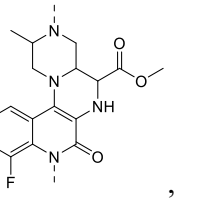
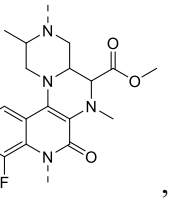
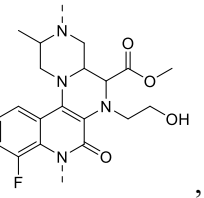
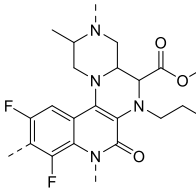
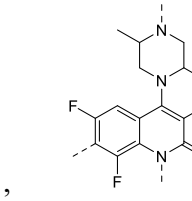
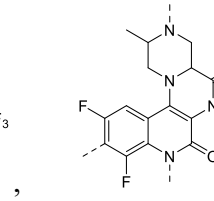
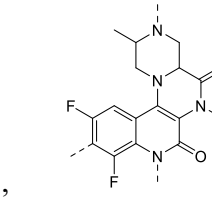
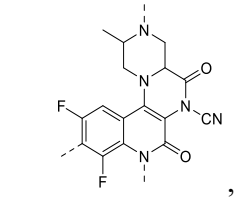
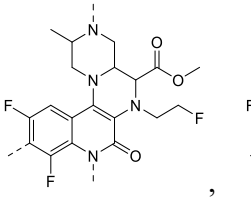
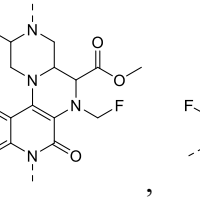
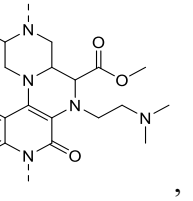
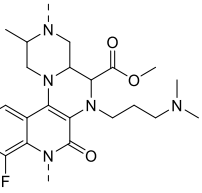
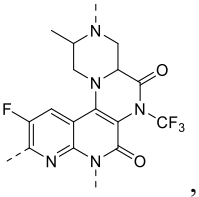
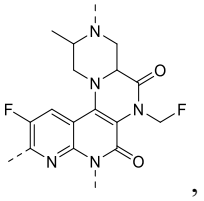
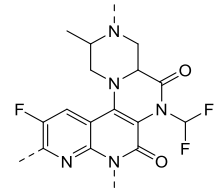
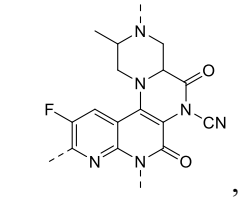
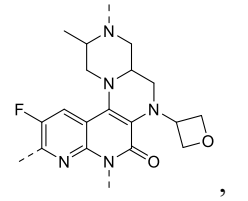
20. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 18, wherein, X_1, X_2 are independently selected from single bond, CH_2, CH_2CH_2, C(=O), O, S, NH, $N(CH_3)$, S(=O), $S(=O)_2$, and .

21. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein, R_8 is selected from H, halogen, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino and C_{1-3} alkylthio, the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino or C_{1-3} alkylthio is optionally substituted by 1, 2 or 3 R.

22. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 21, wherein, R_8 is selected from H, F, Cl, Br, I, OH, NH_2, CN, Me, CF_3, , , , , and .

23. The compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof according to claim 1, wherein, the structural moiety is selected from ,




,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

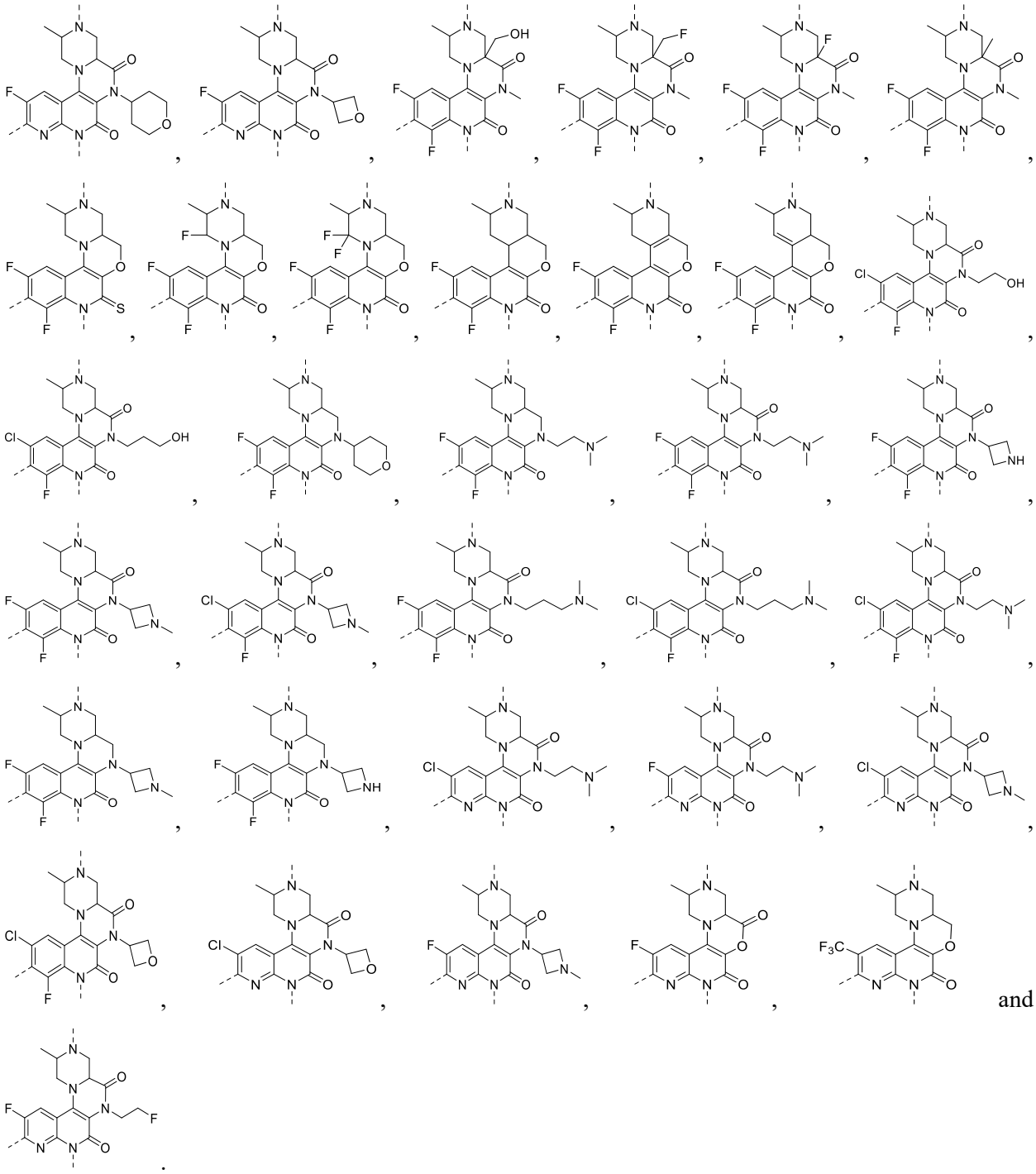
,

,

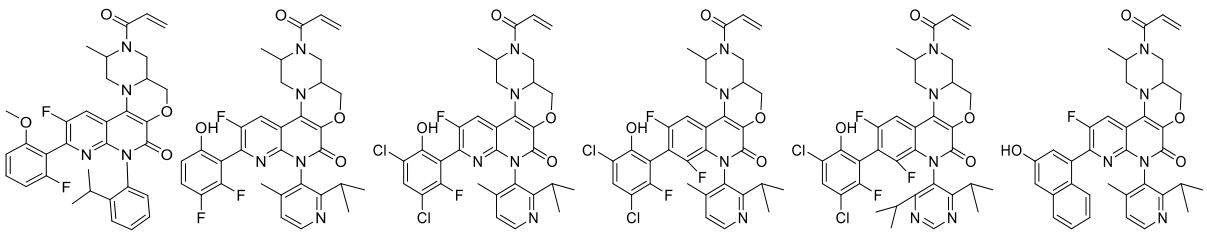
,

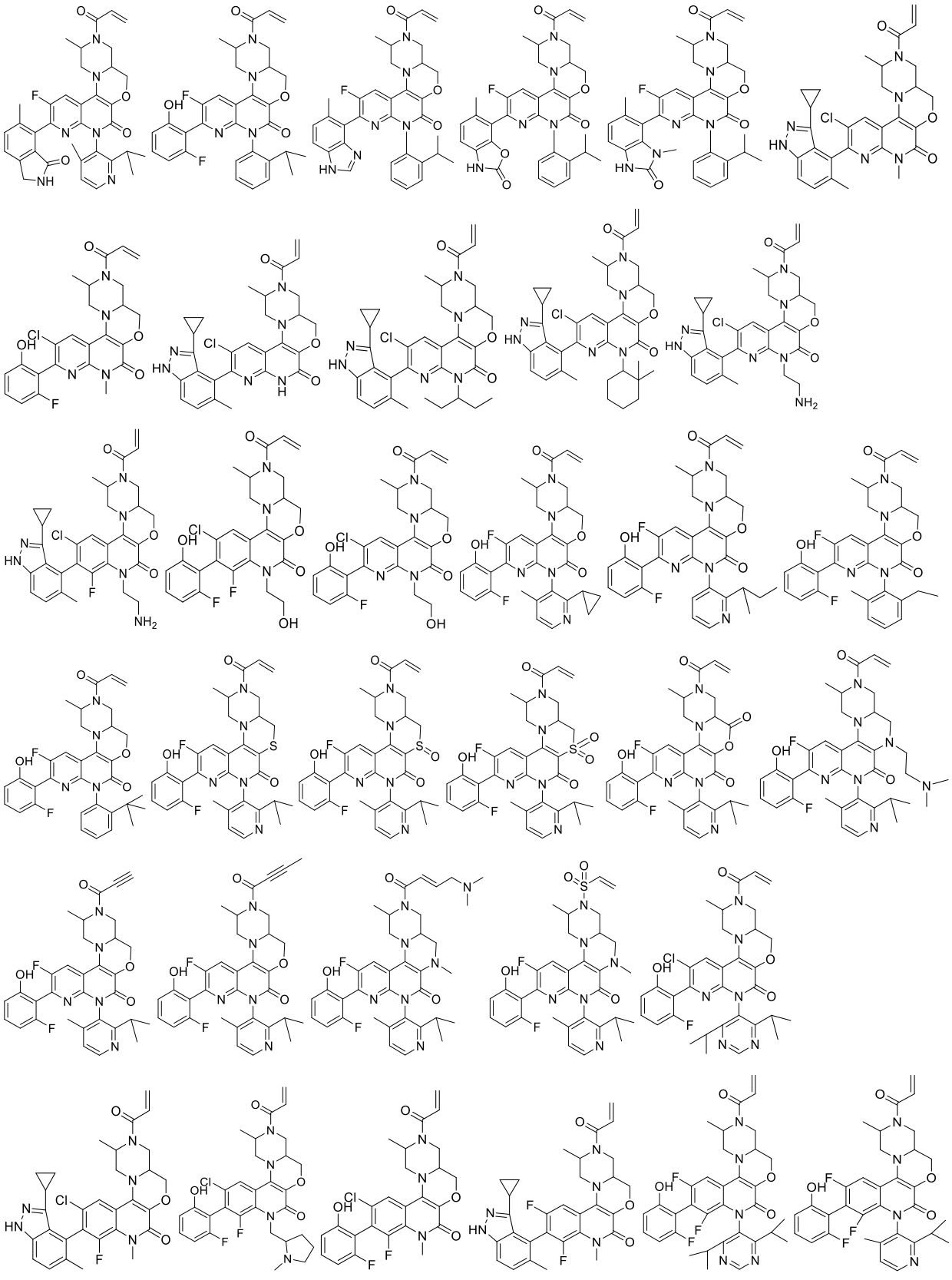
,

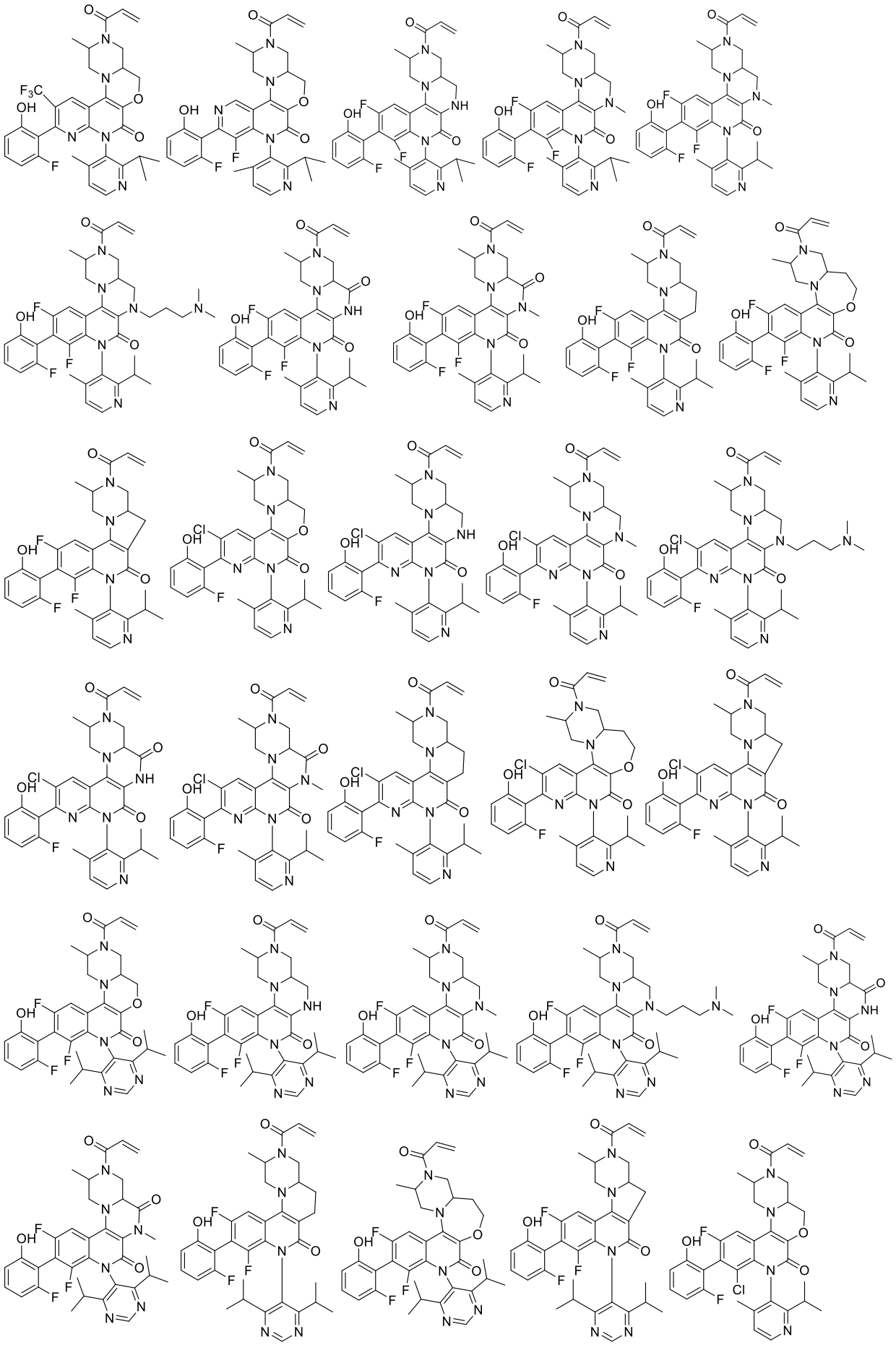
,

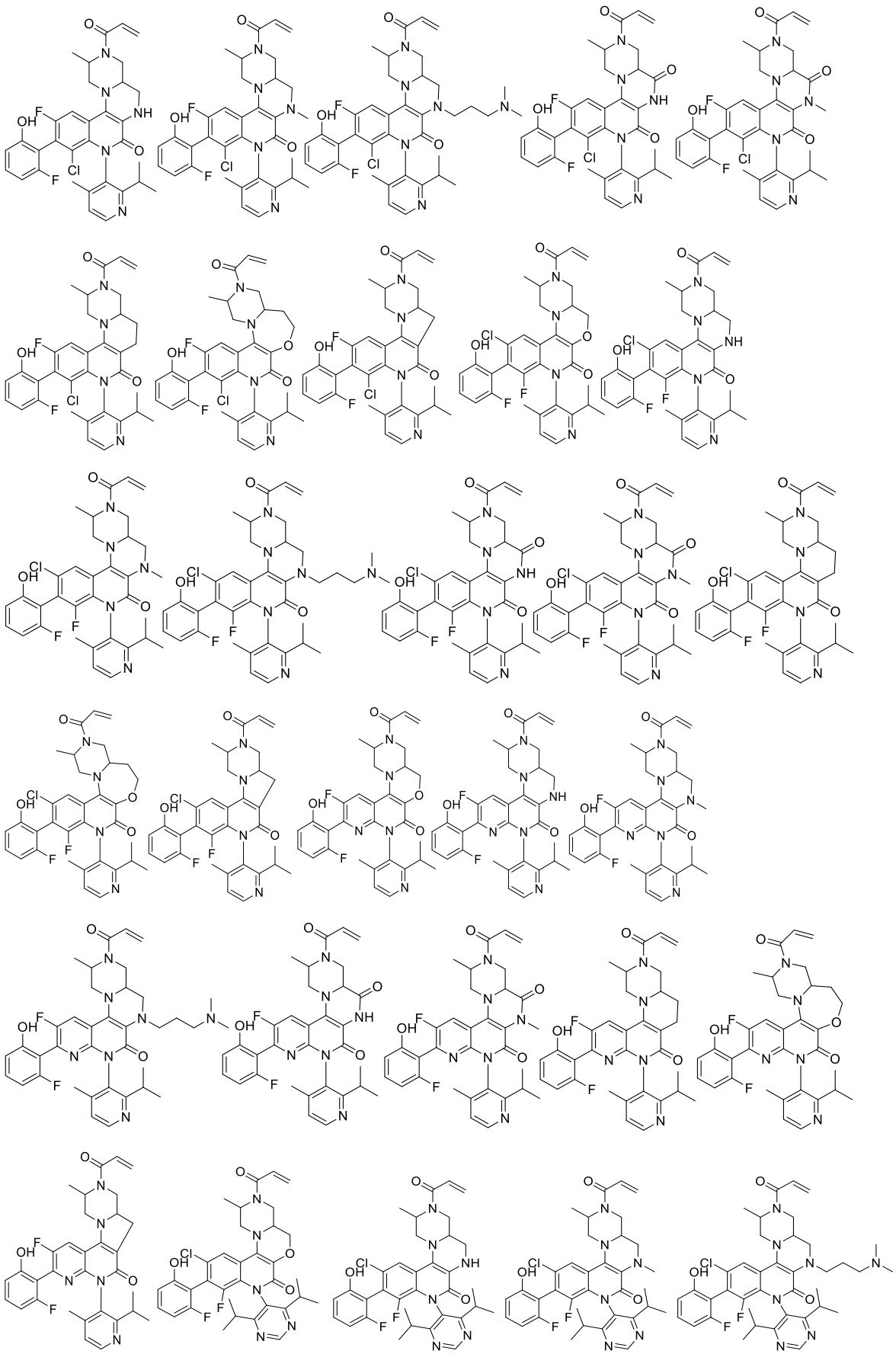


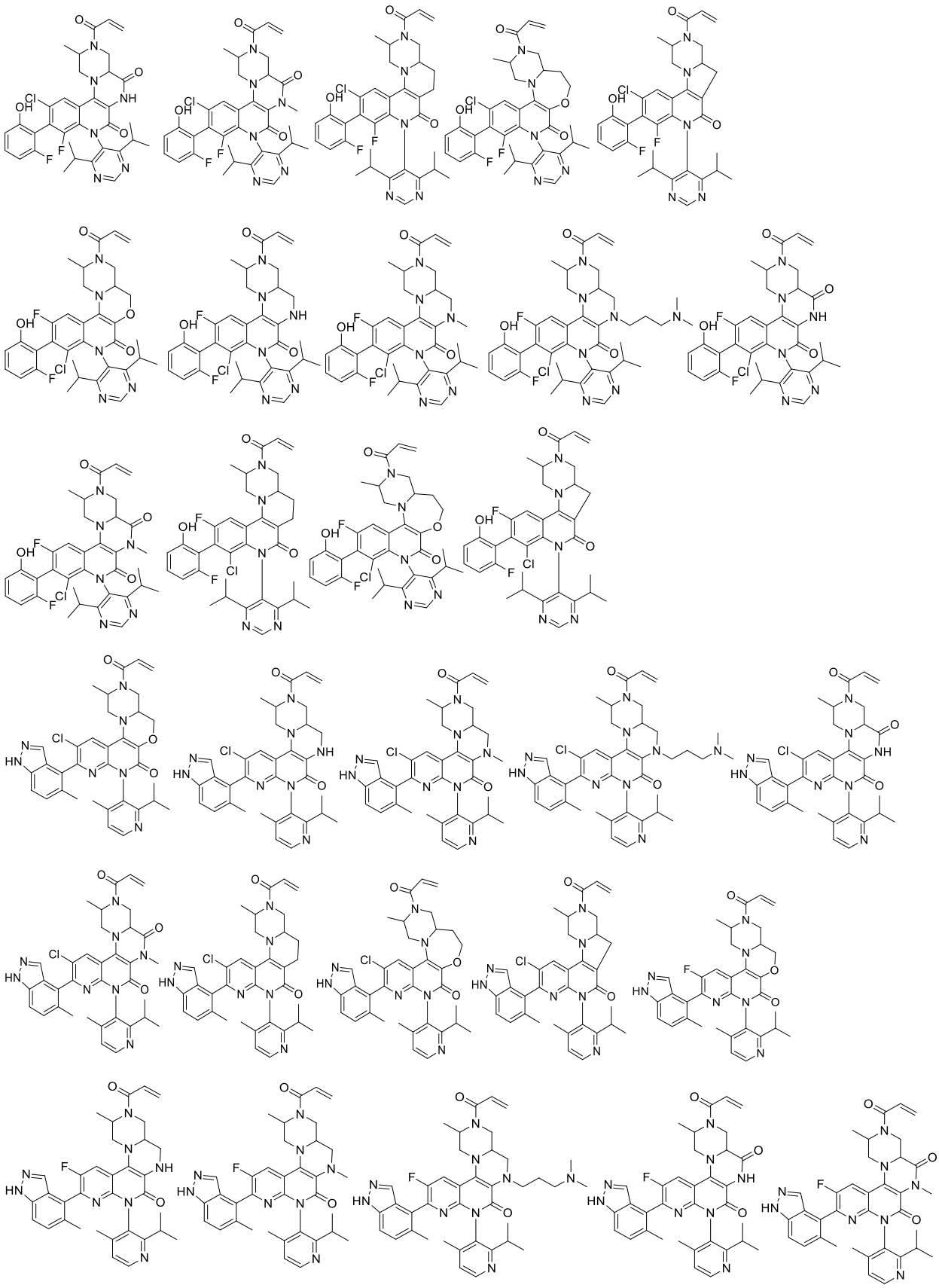
24. Compounds of the following formula, optical isomers thereof and pharmaceutically acceptable salts thereof,

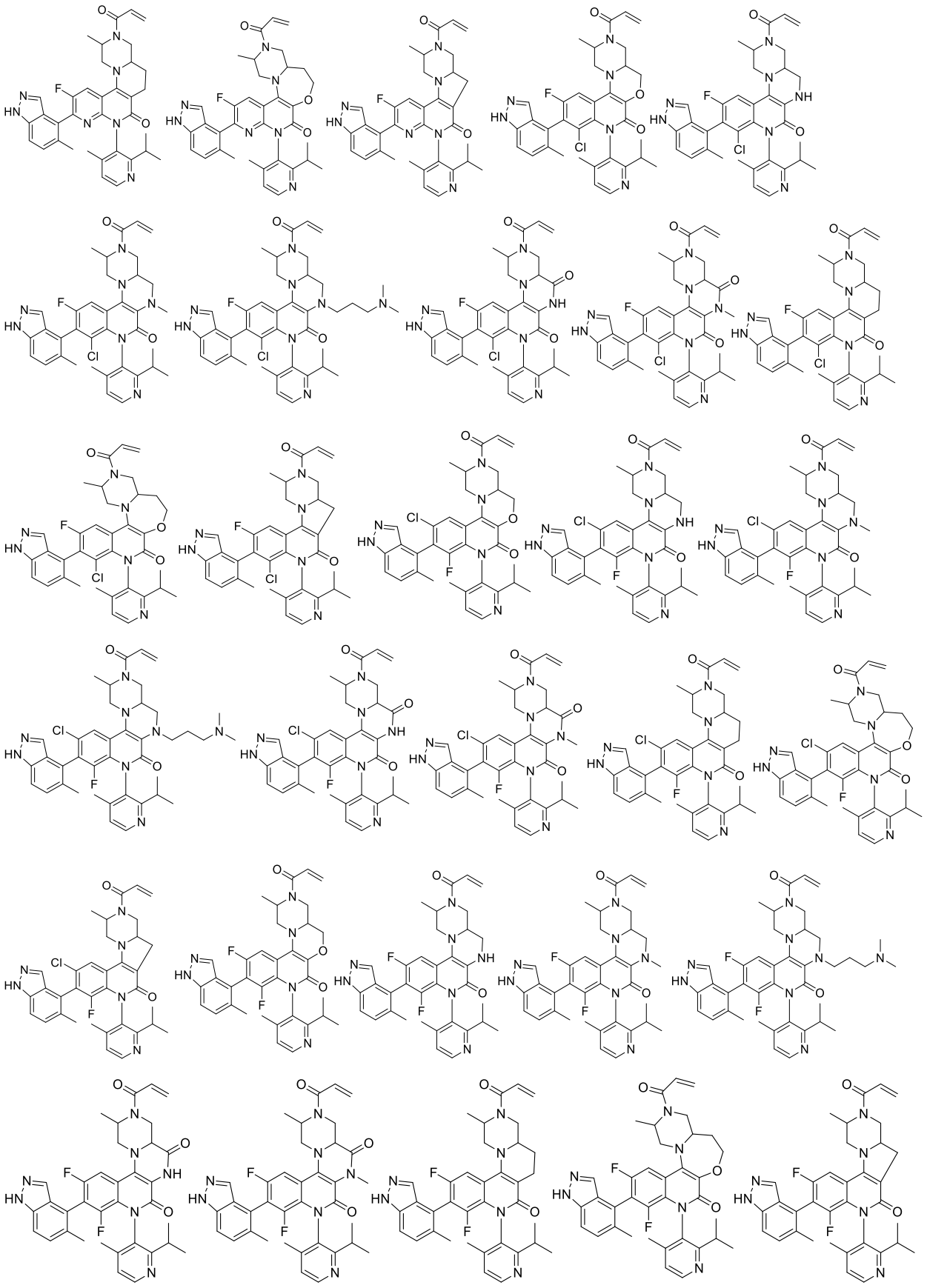


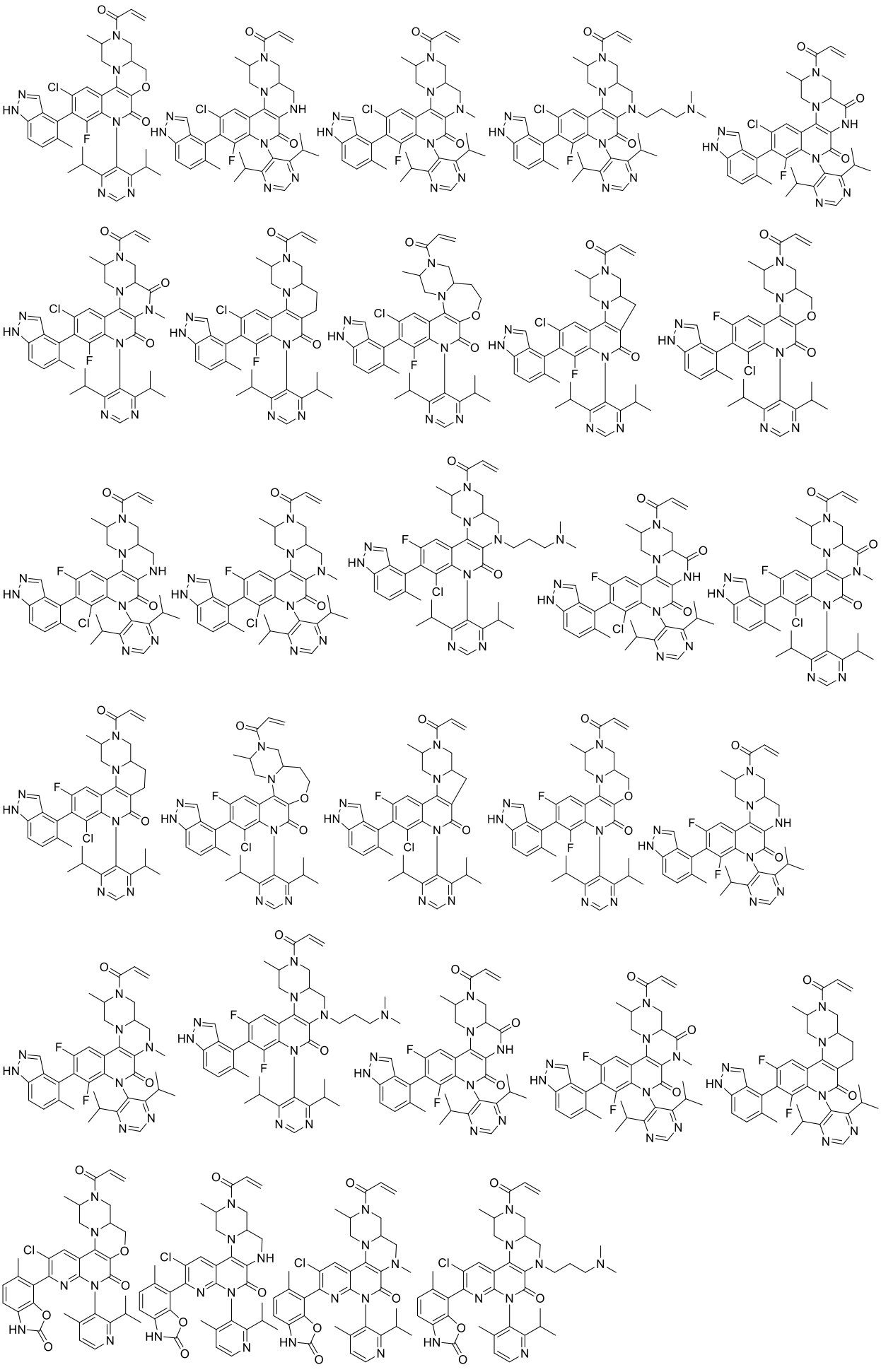


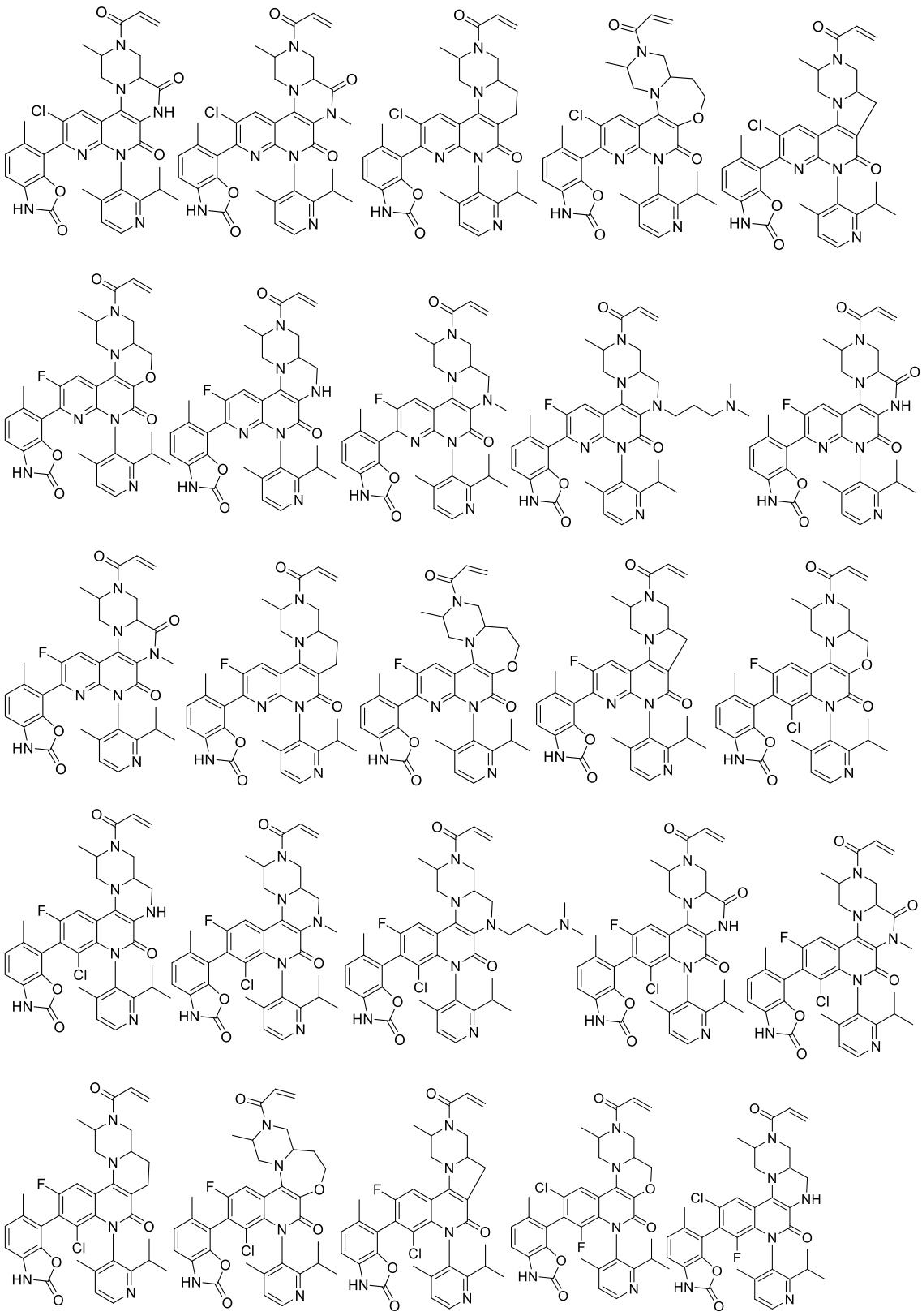


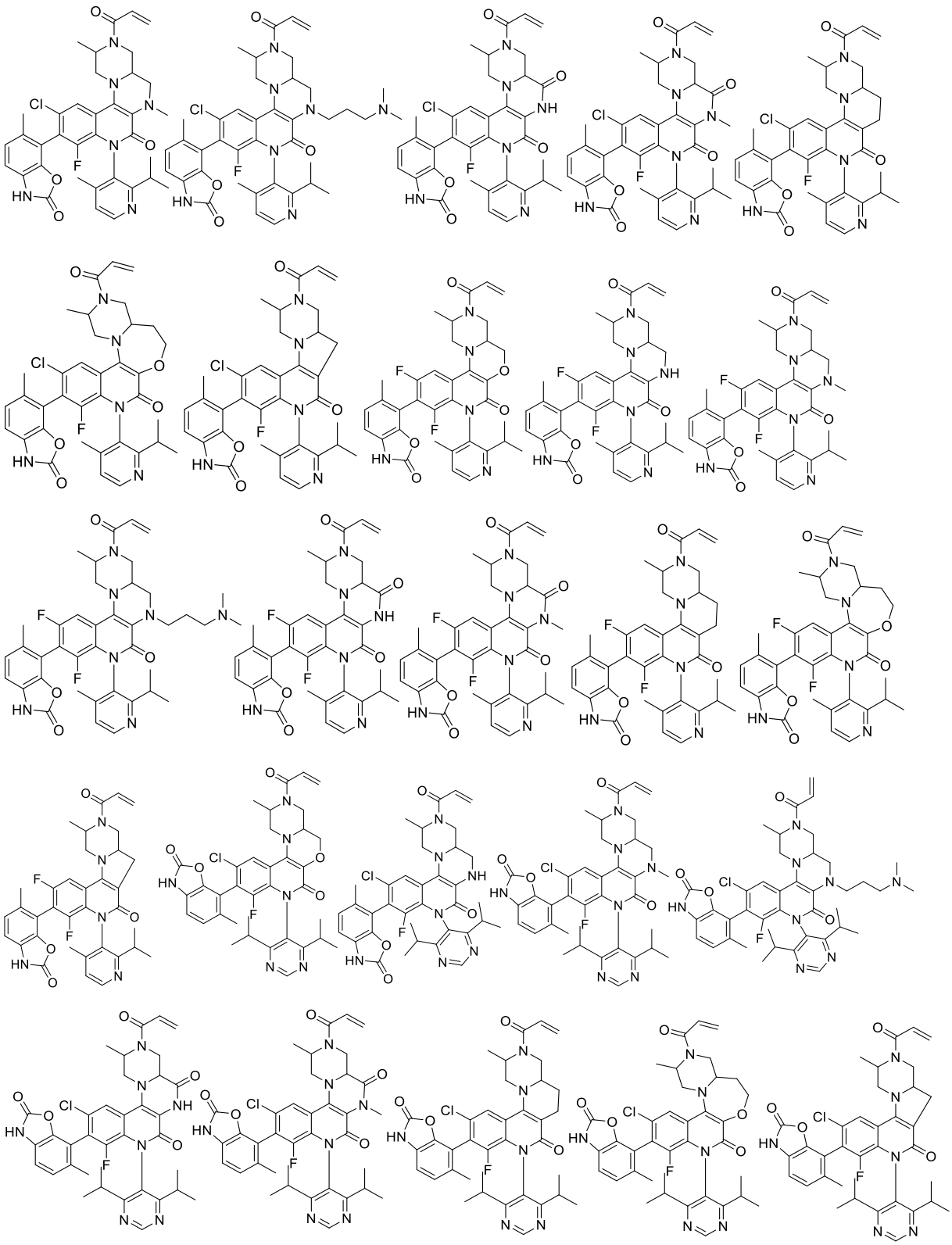


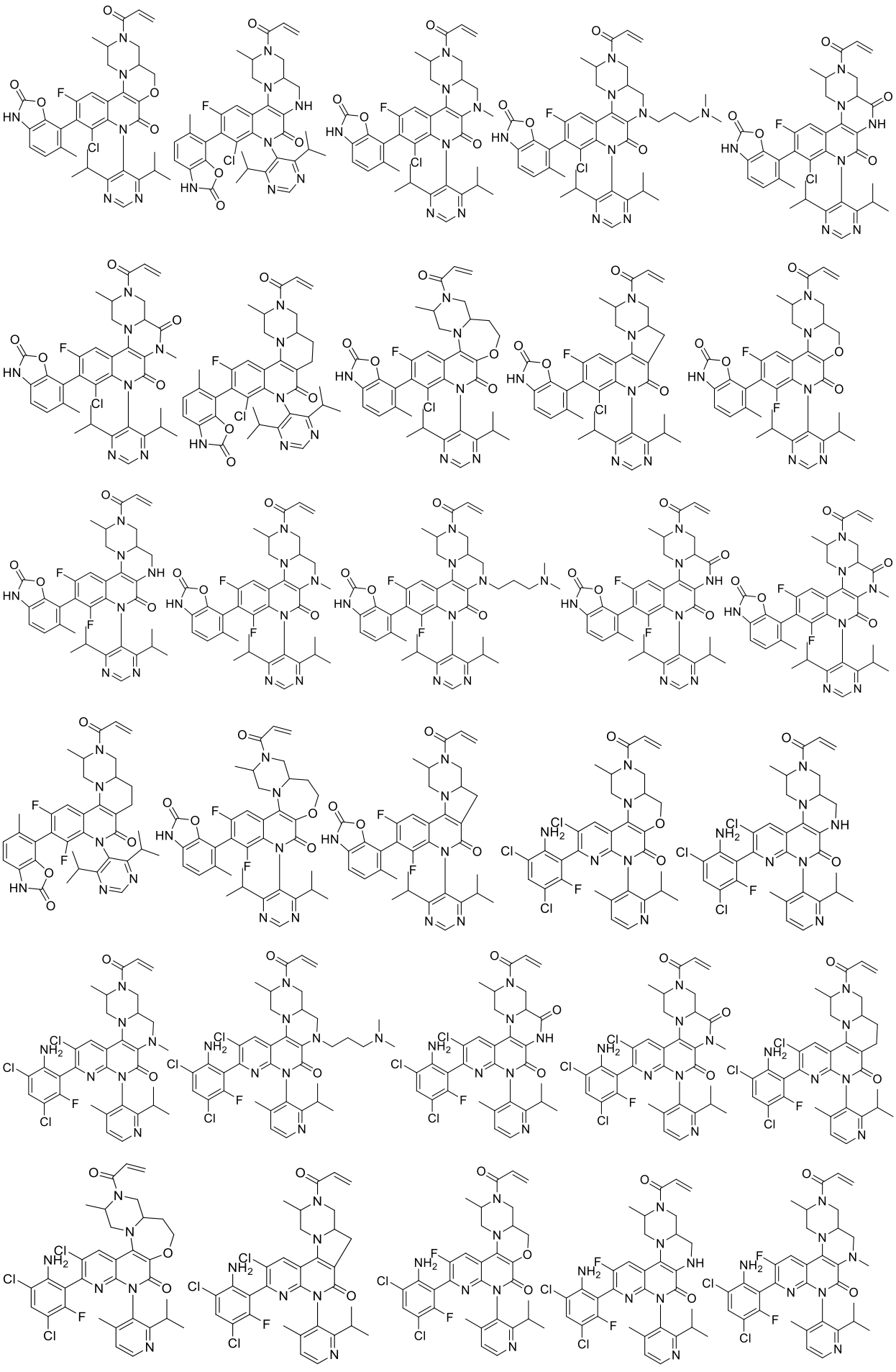


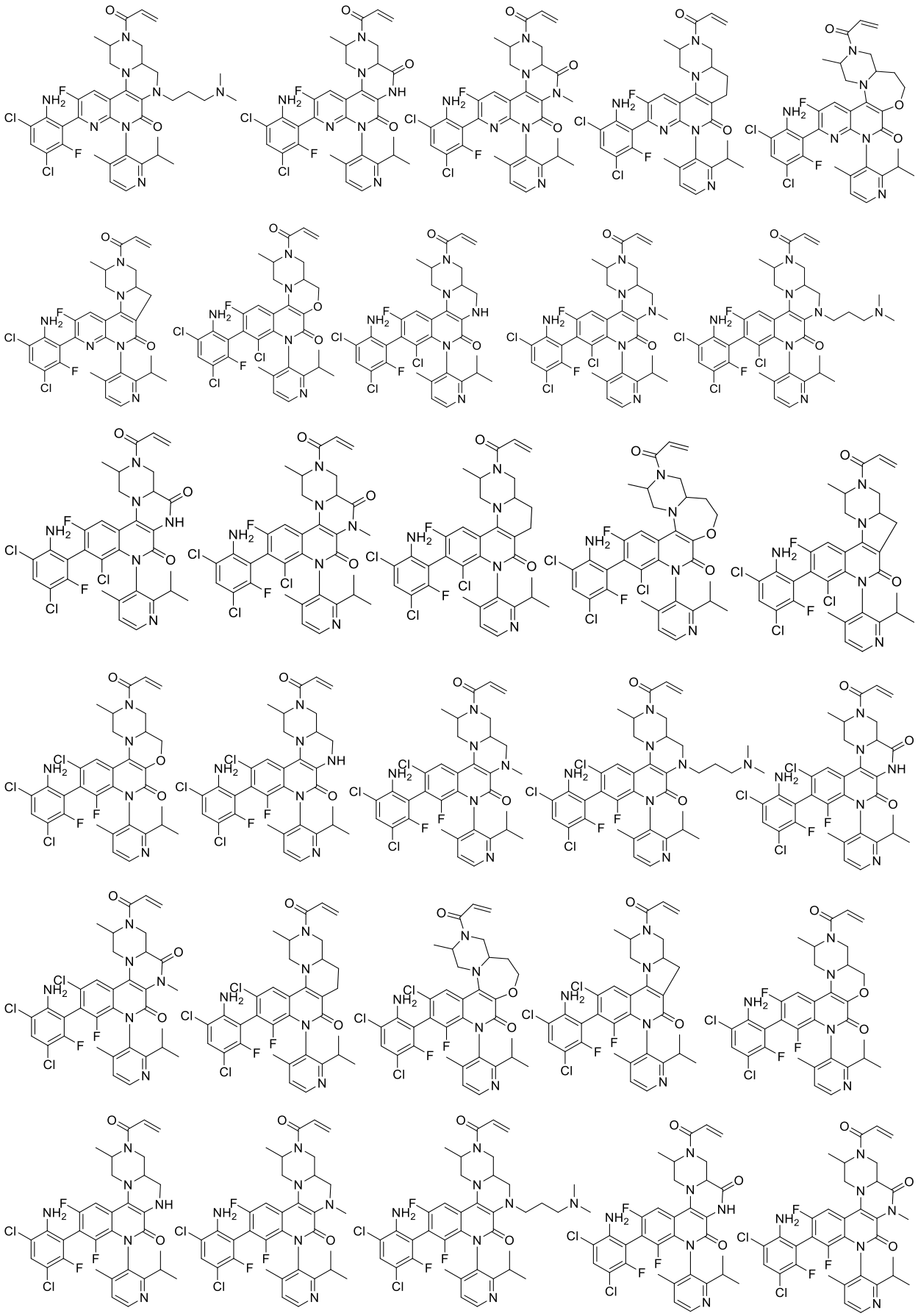


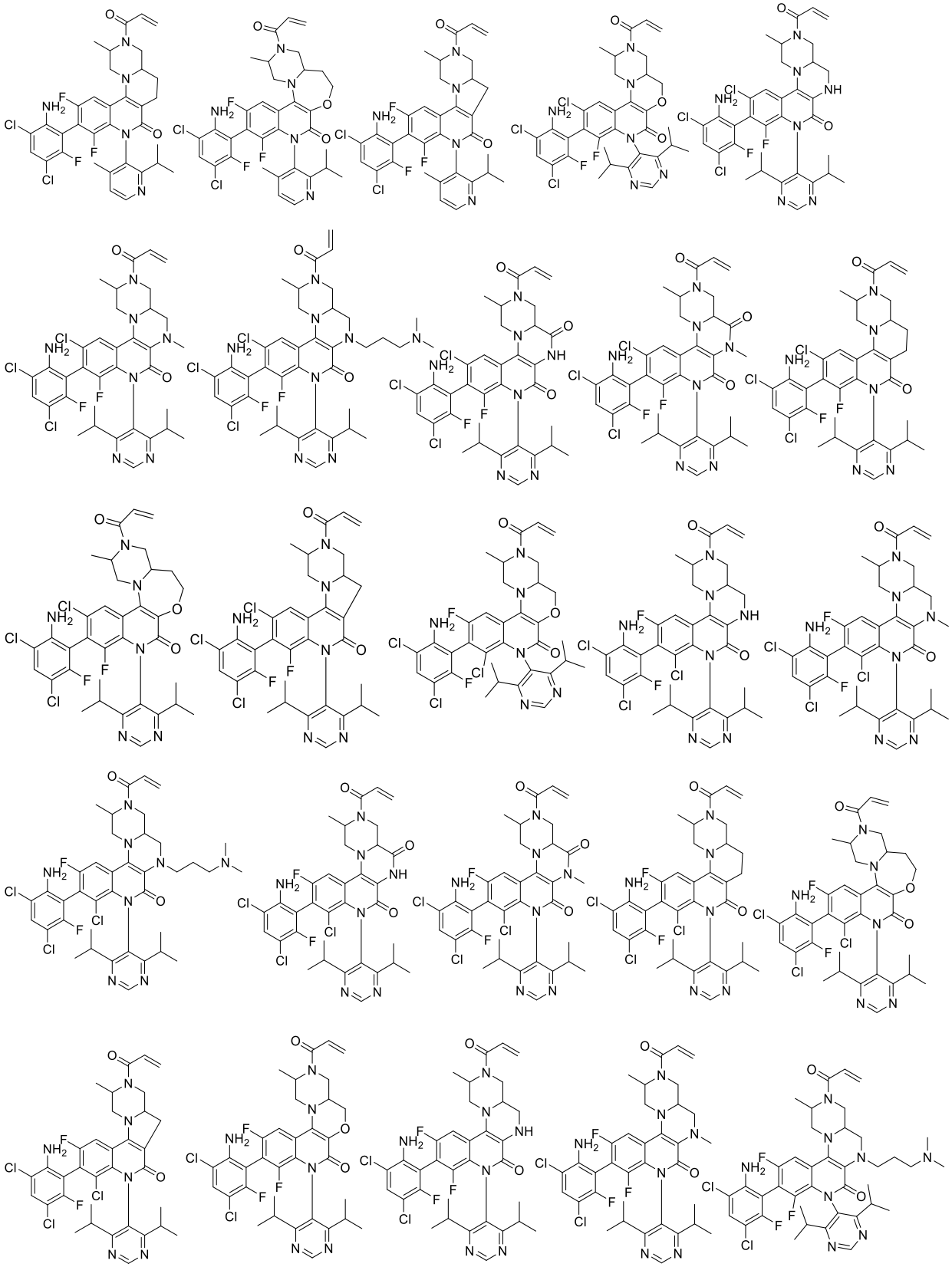


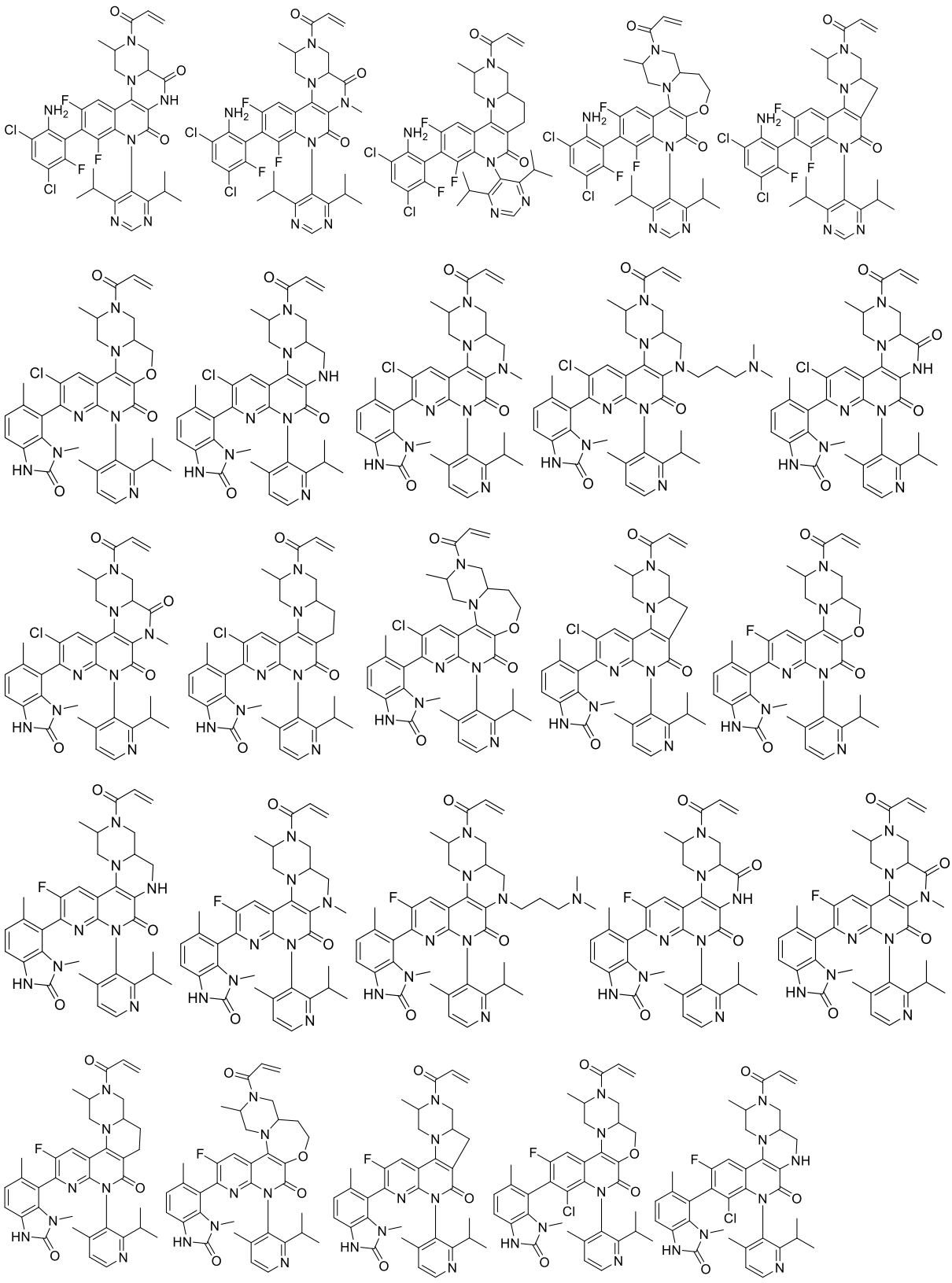


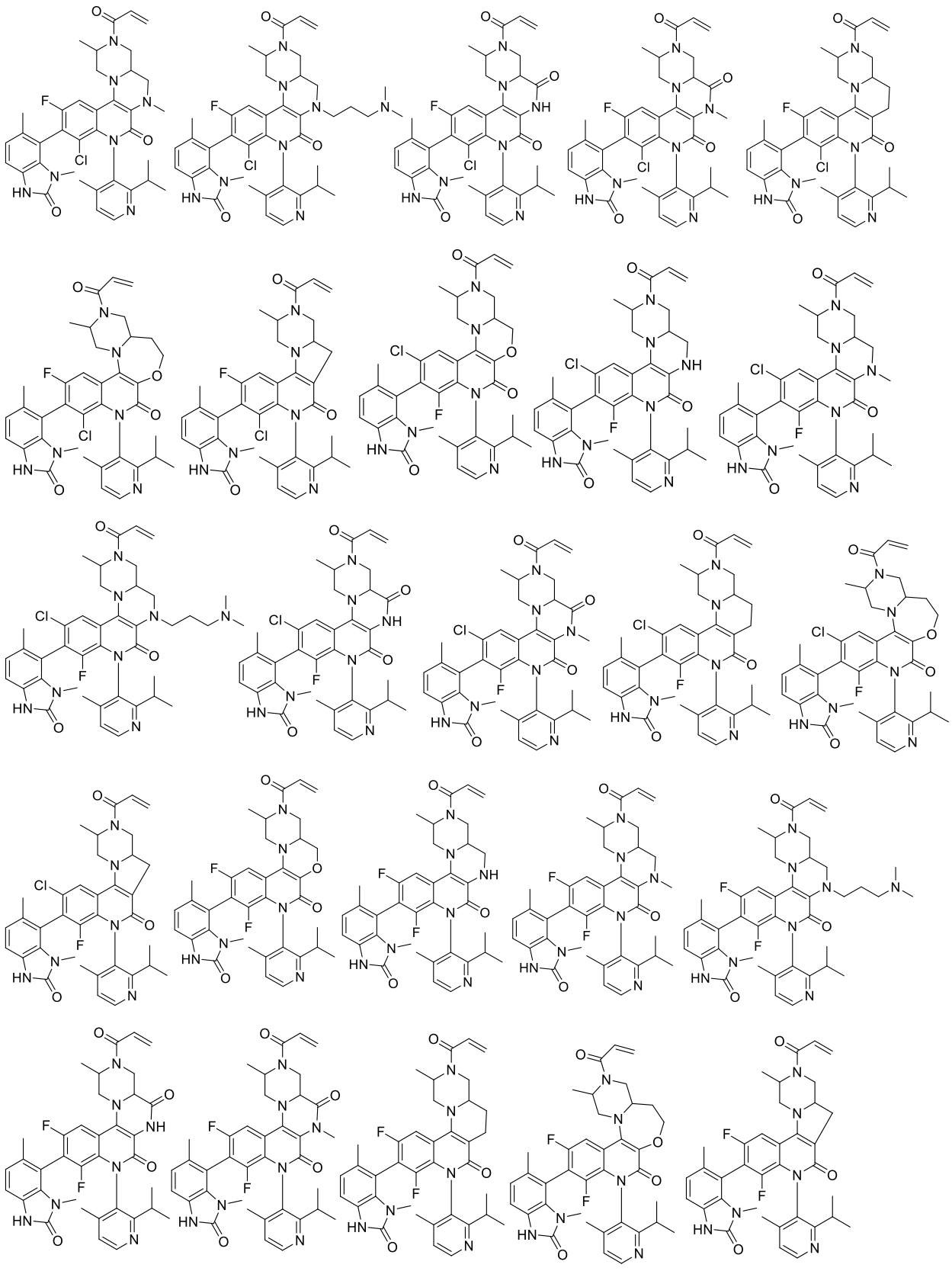


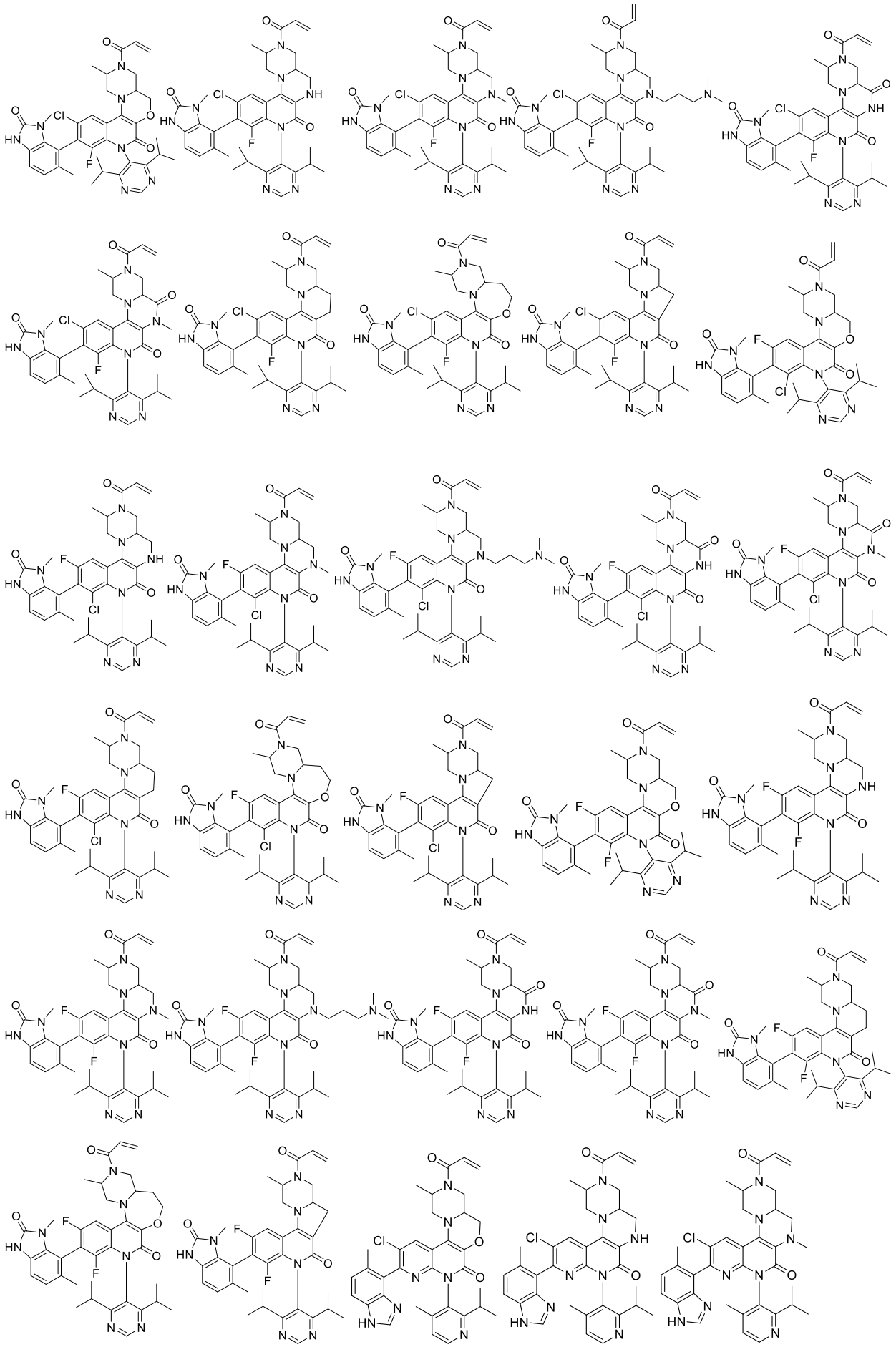


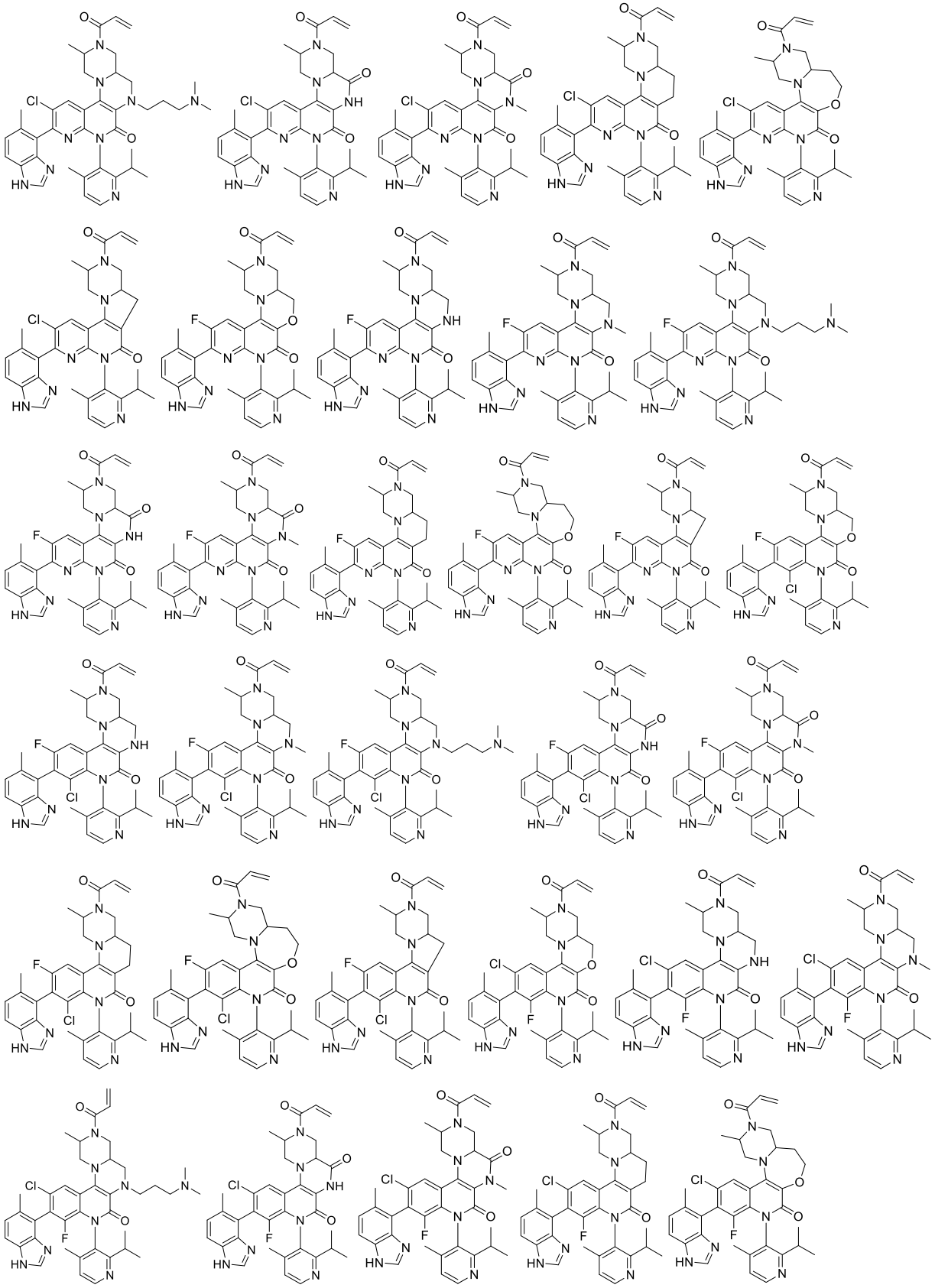


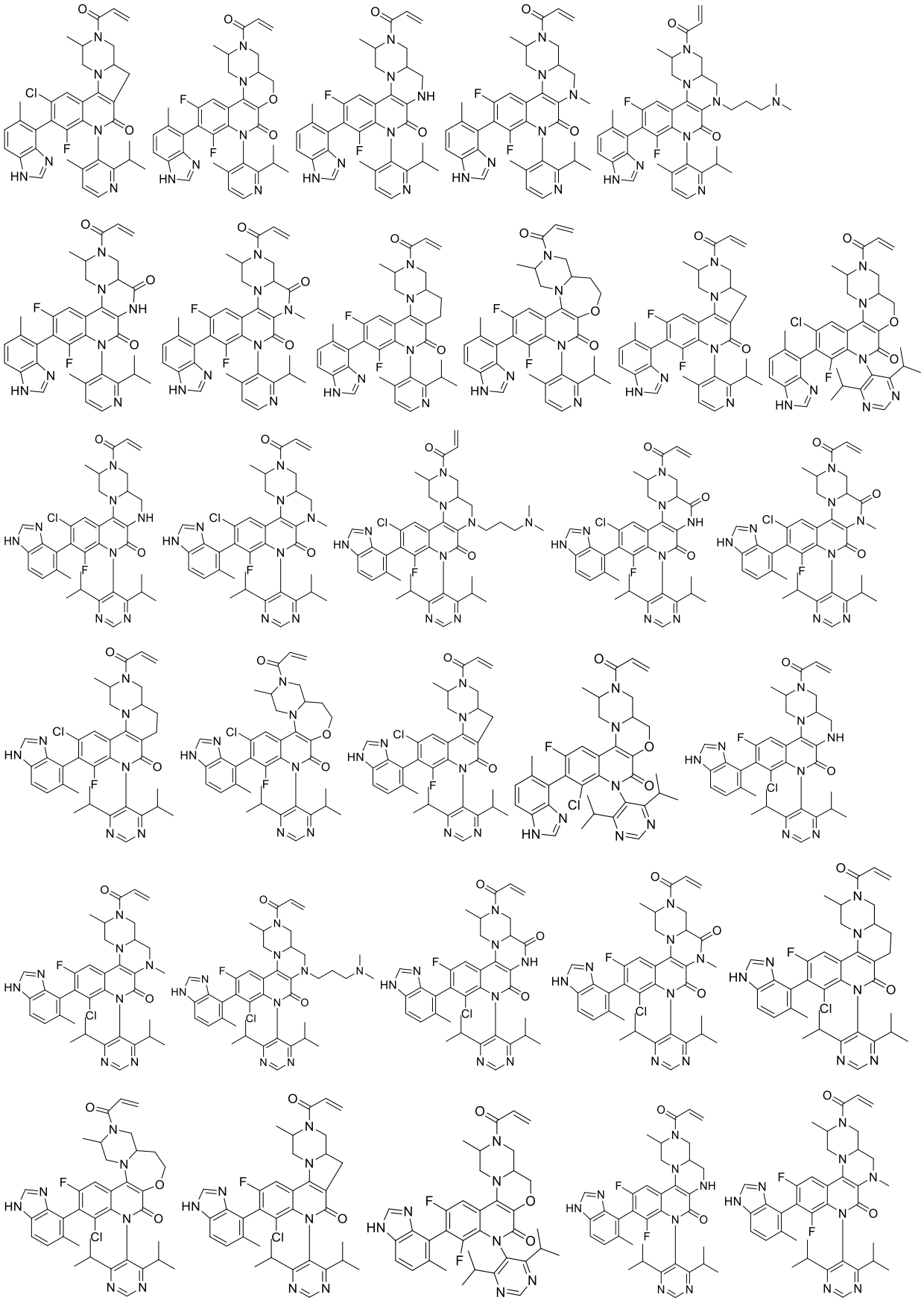


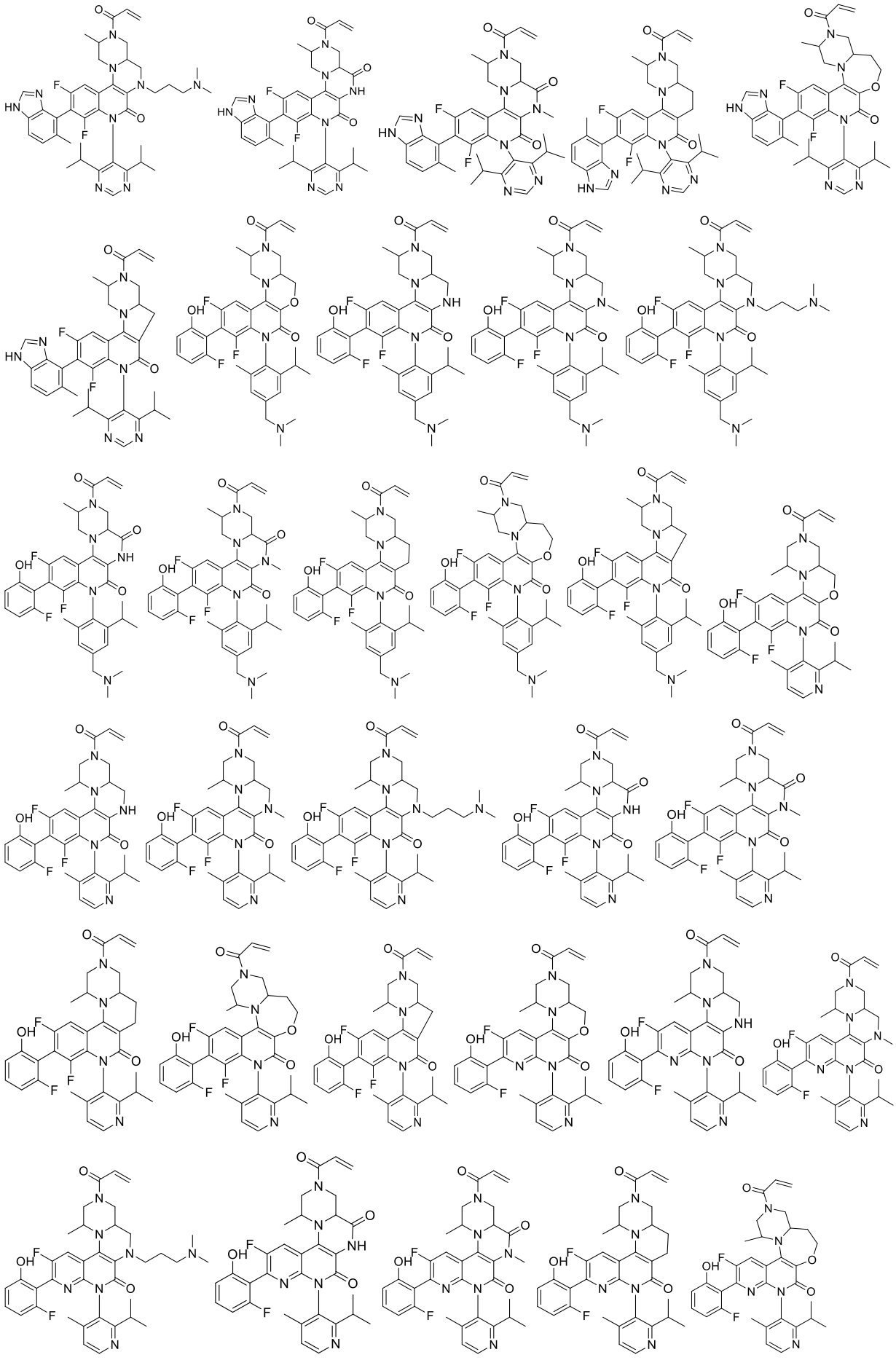


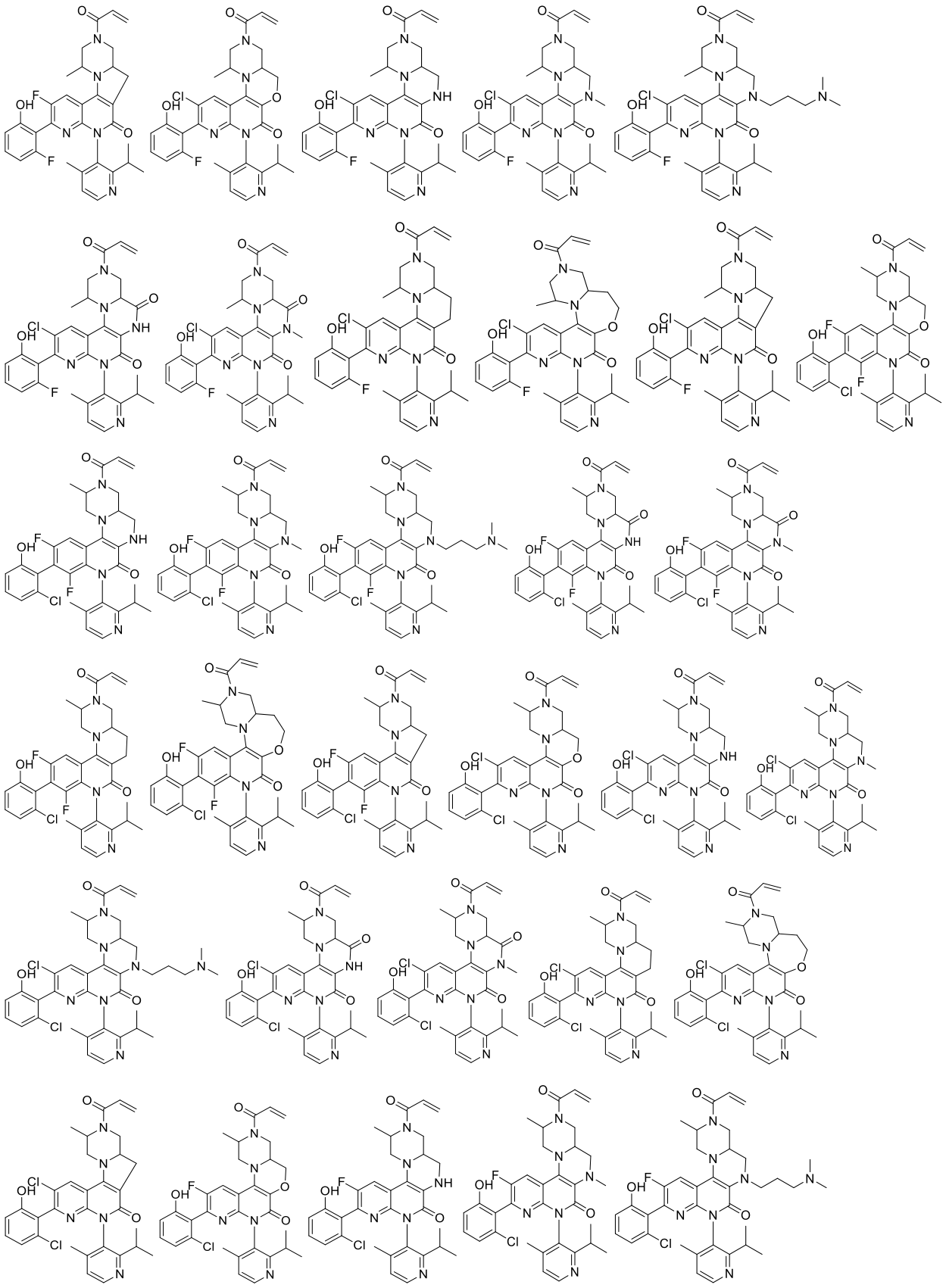


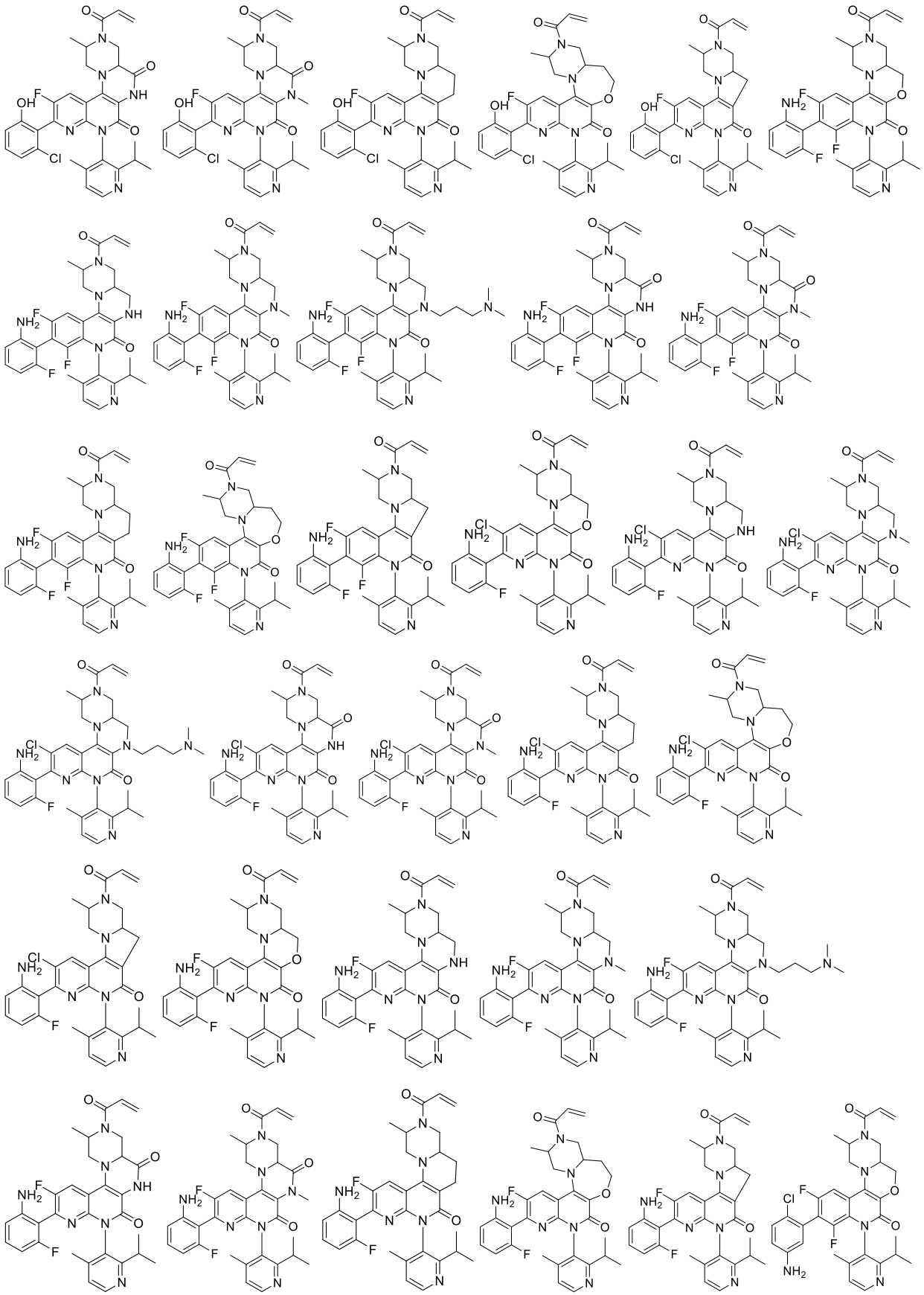


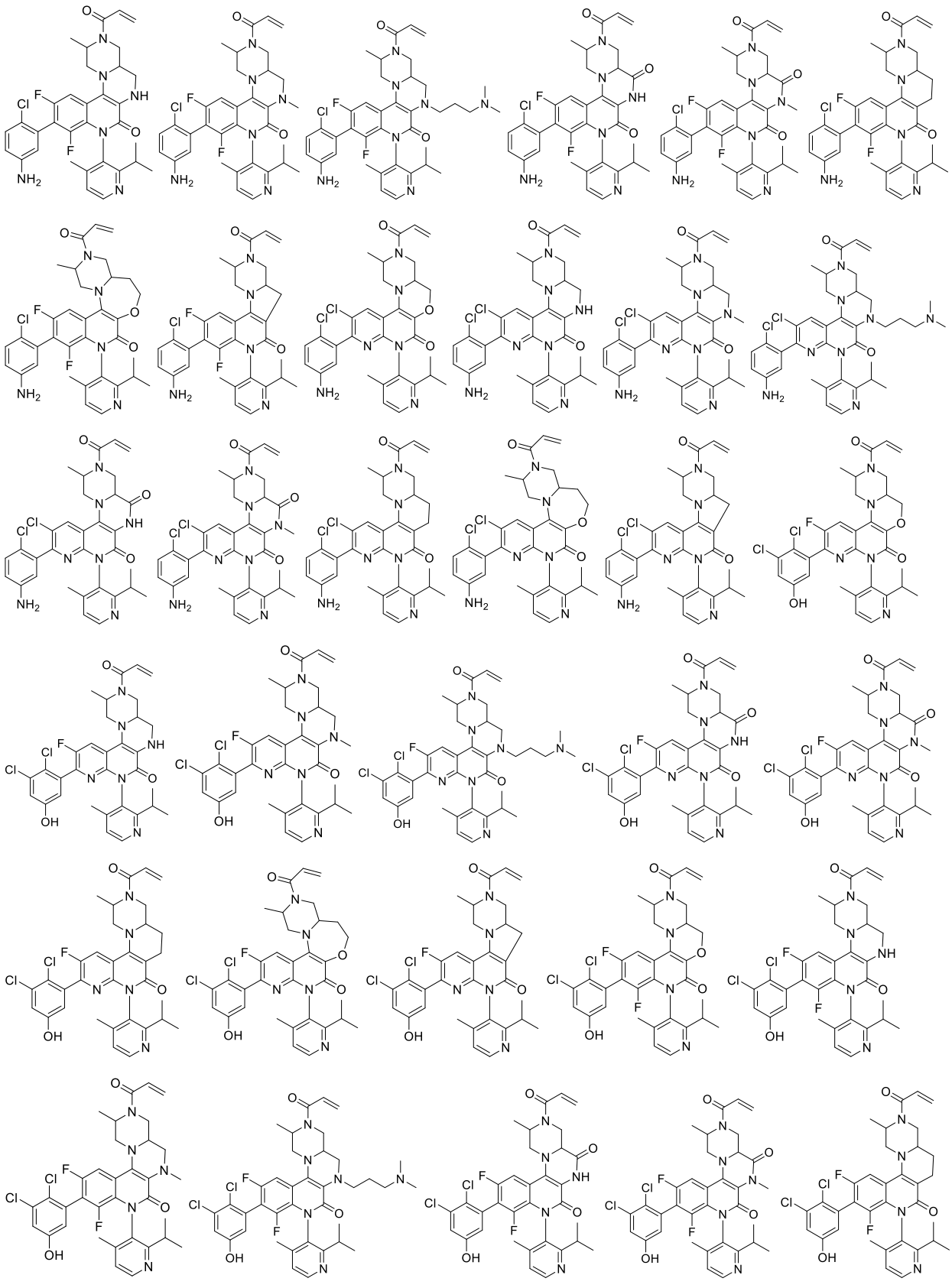


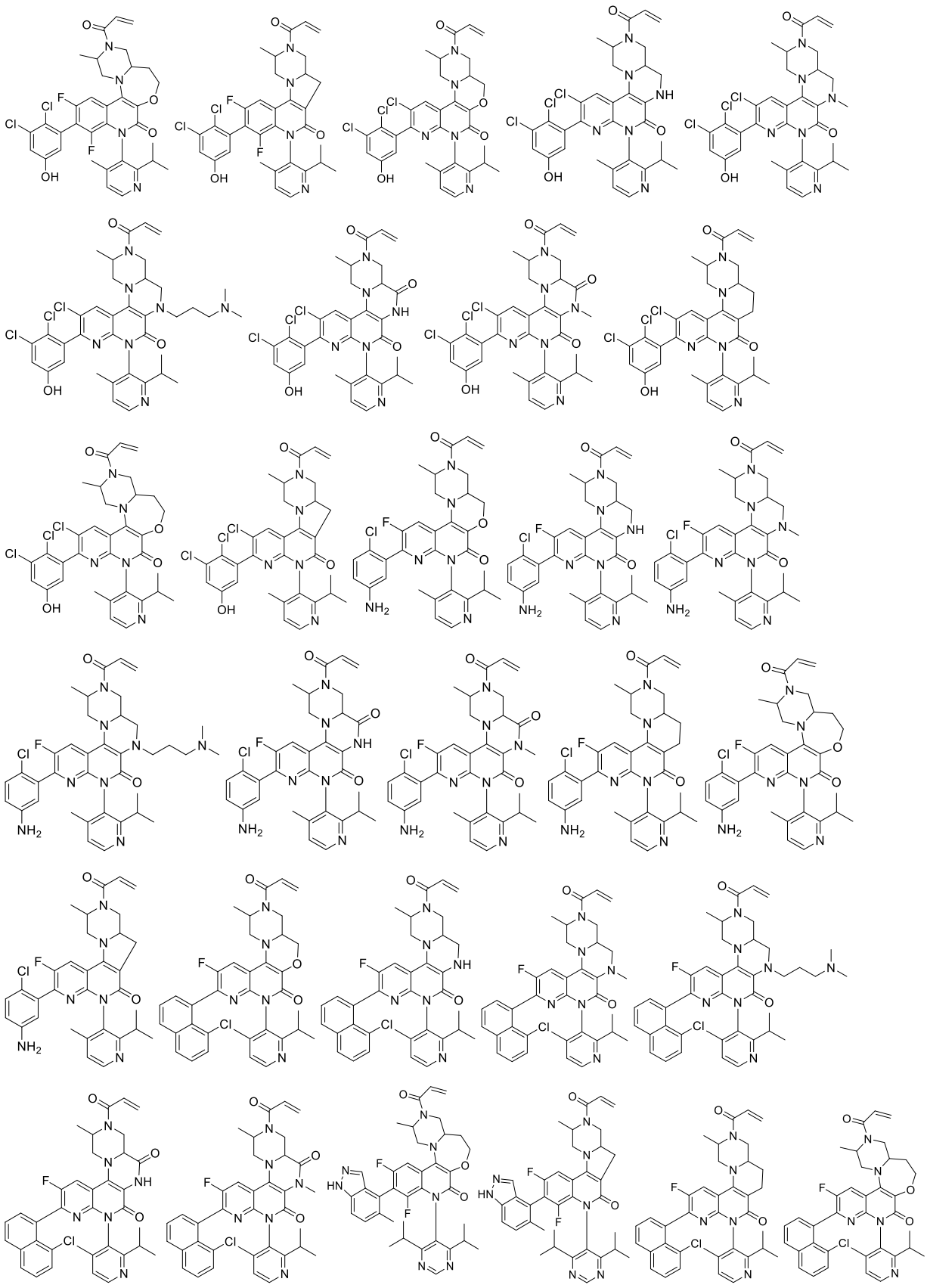


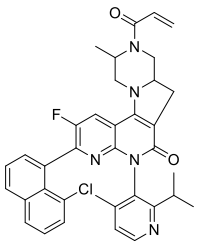


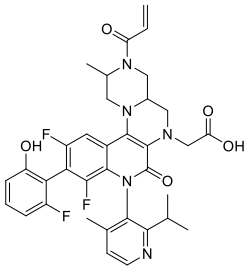


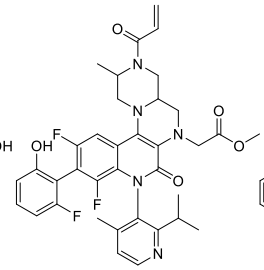


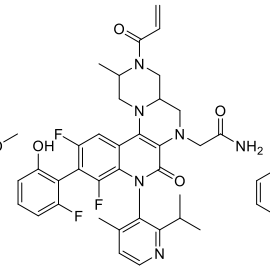


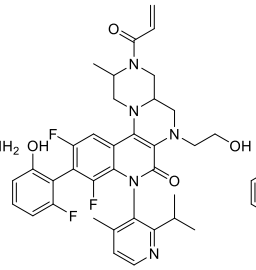


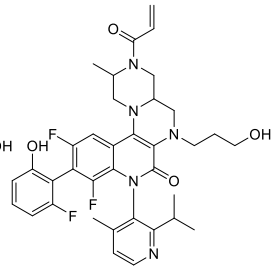


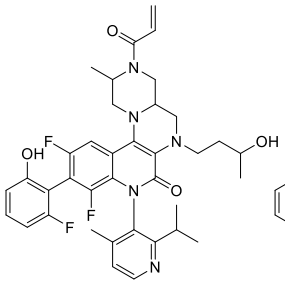


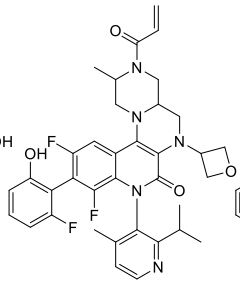


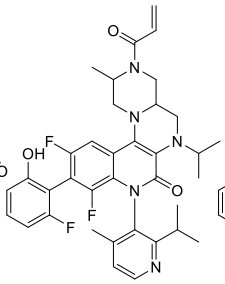


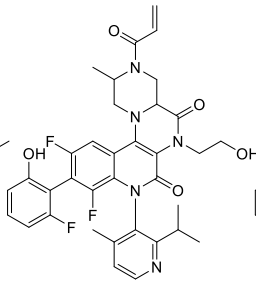


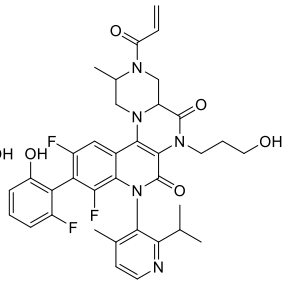


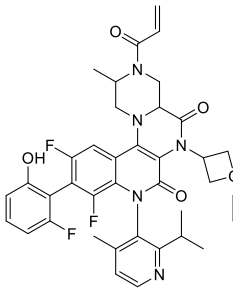


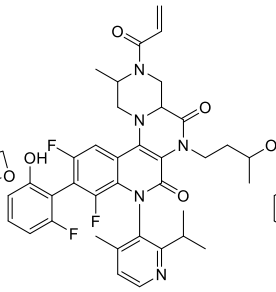


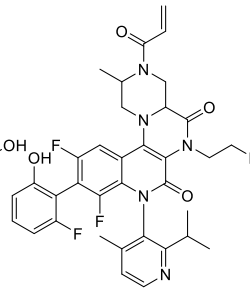


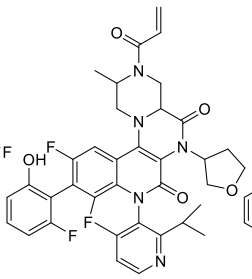


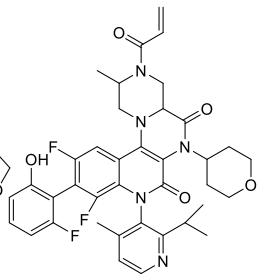


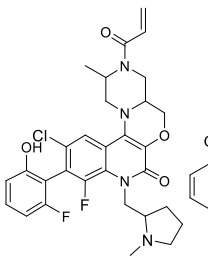


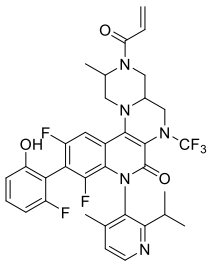


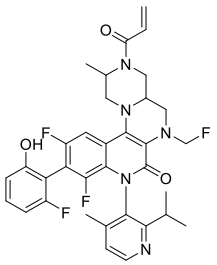


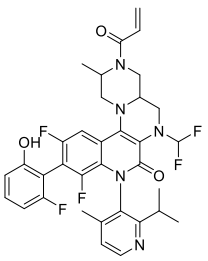


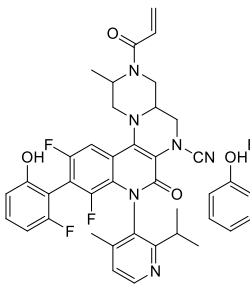


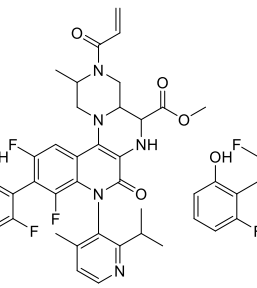


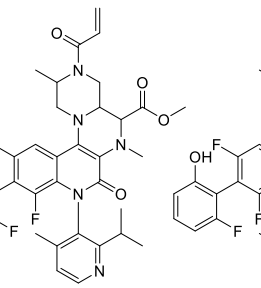


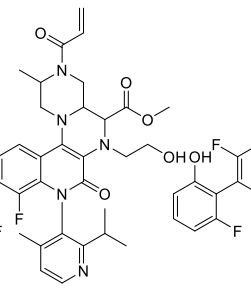


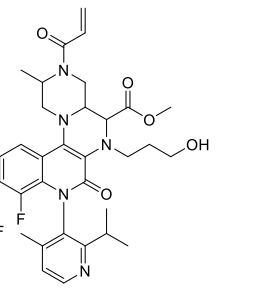


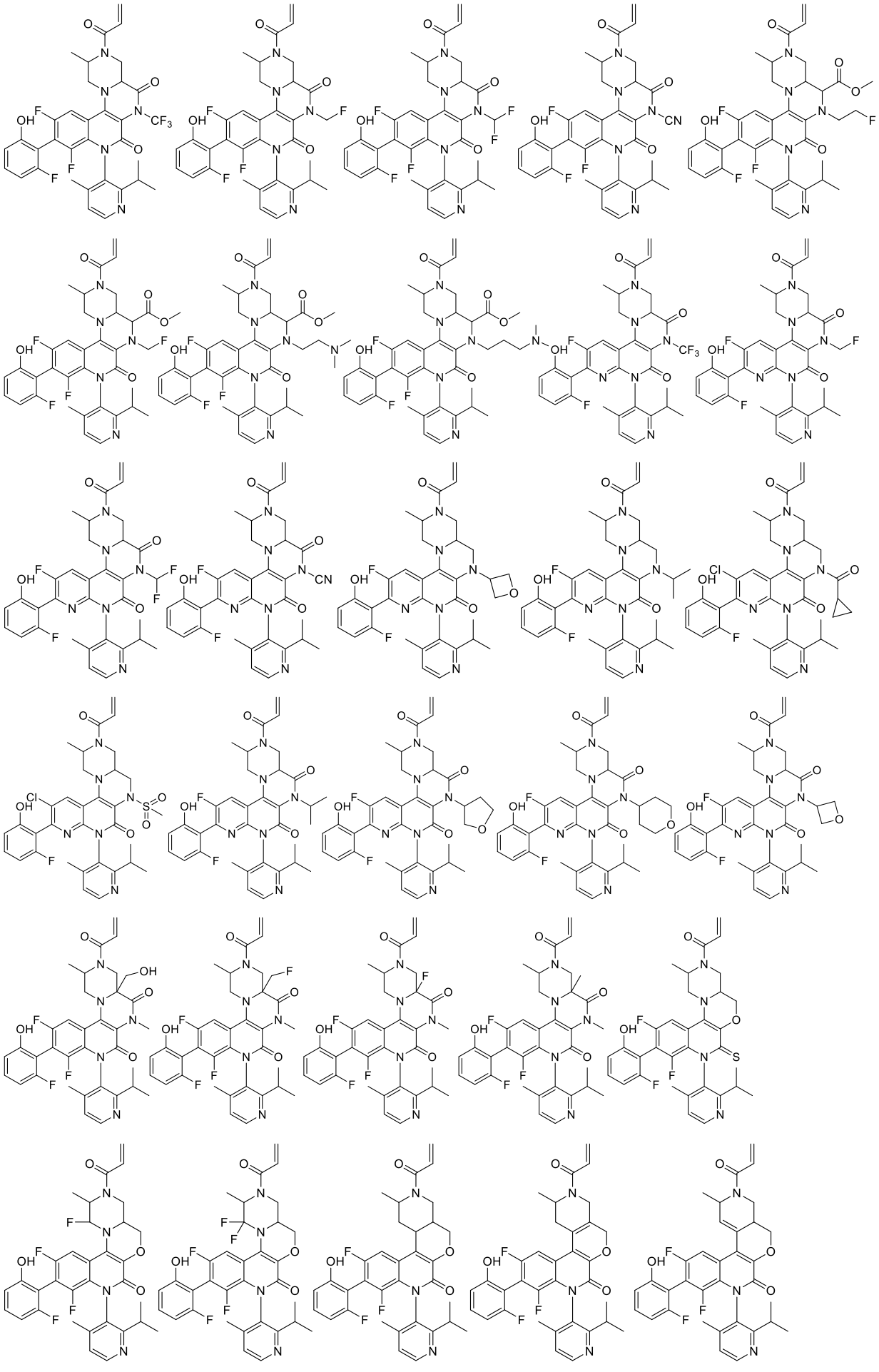


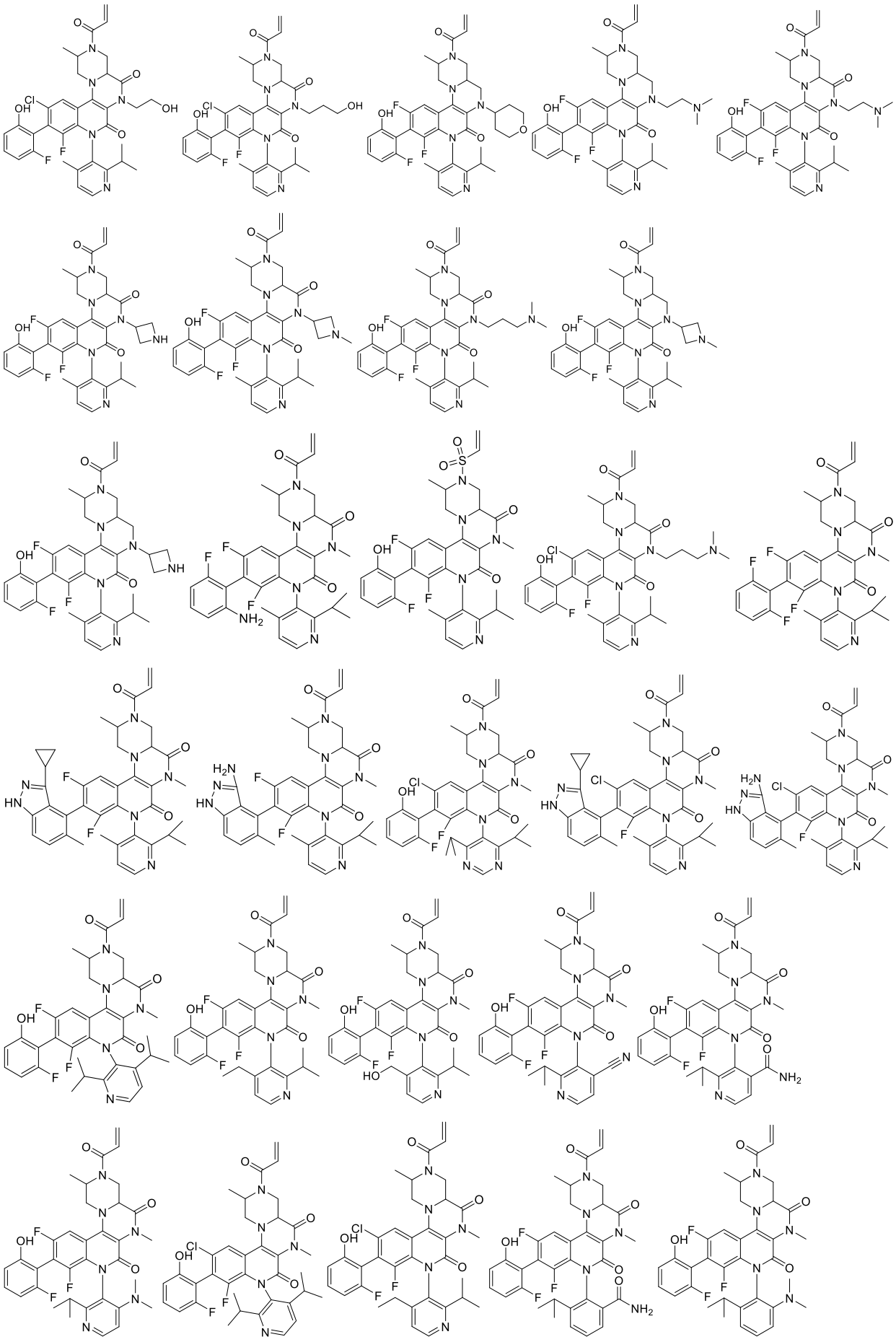


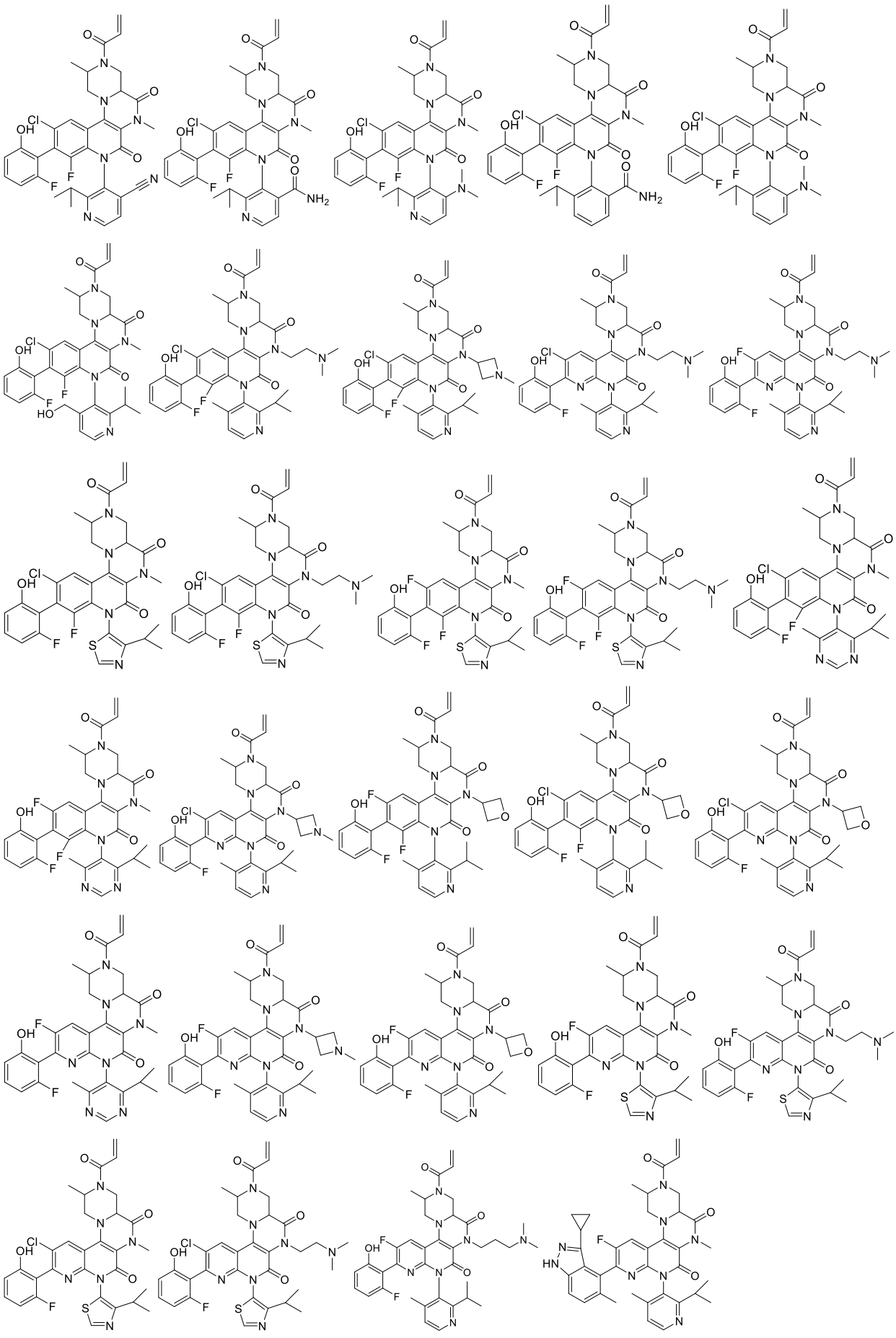


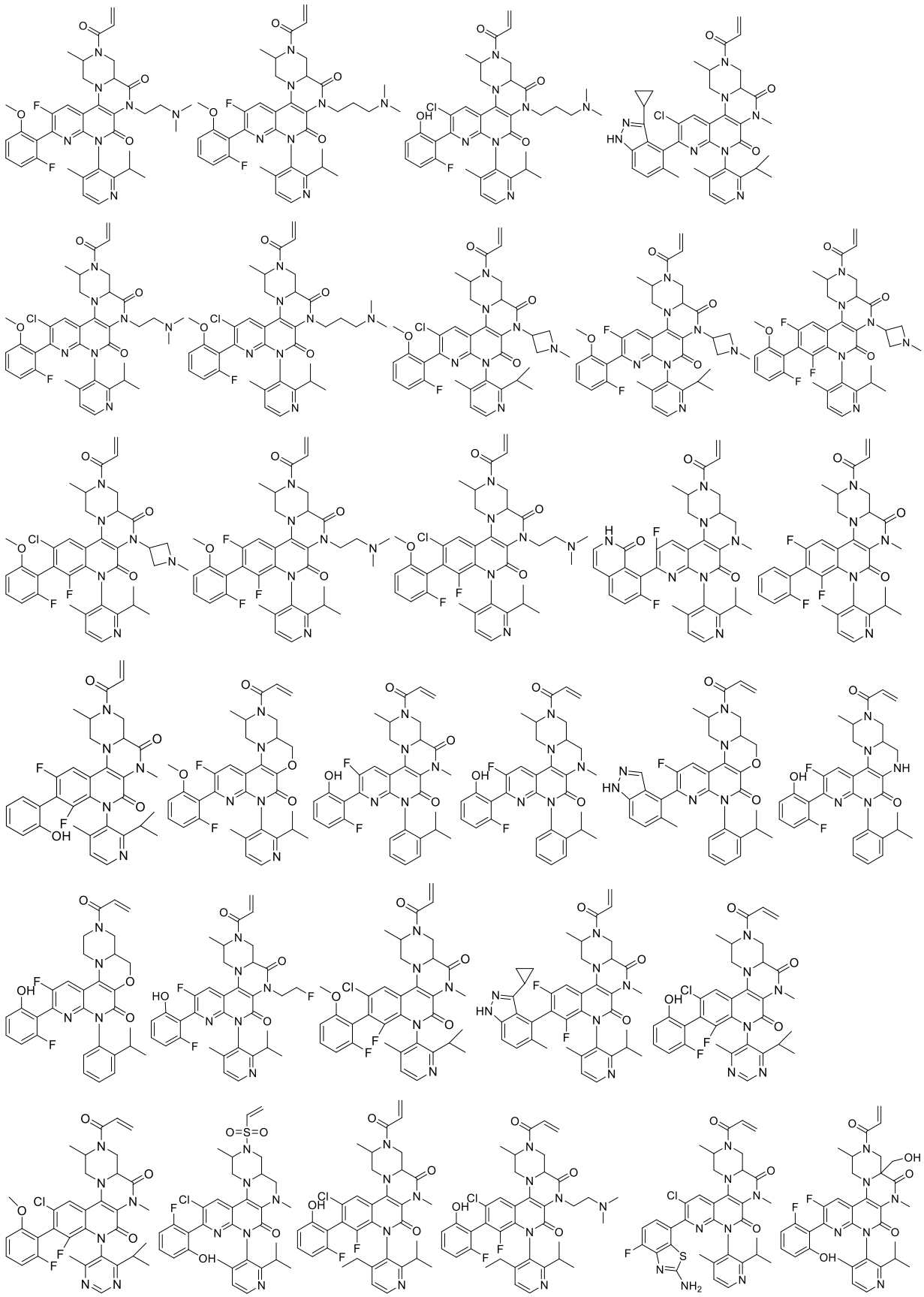


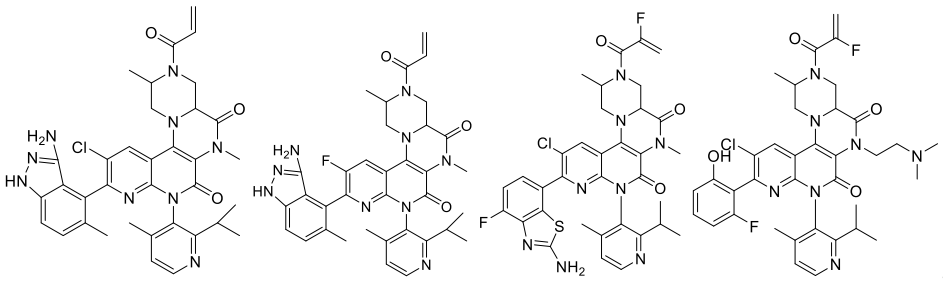












25. A pharmaceutical composition, comprising the compound, the optical isomer and the pharmaceutically acceptable salt thereof as defined in any one of claims 1-24, and one or more pharmaceutically acceptable carriers, diluents or excipients.

26. ~~A u~~Use of the compound, the optical isomer thereof and the pharmaceutically acceptable salt thereof as defined in any one of claims 1-24 or the pharmaceutical composition as defined in claim 25 in preparing a medicament for preventing and/or treating diseases related to KRAS-G12C.

27. The use according to claim 26, wherein the diseases related to KRAS-G12C are selected from non-small cell lung cancer, colon cancer and pancreatic cancer.

28. The compound, the optical isomer thereof, and the pharmaceutically acceptable salt thereof as defined in any one of claims 1-24, or the pharmaceutical composition as defined in claim 25, for use in preventing and/or treating diseases related to KRAS-G12C.