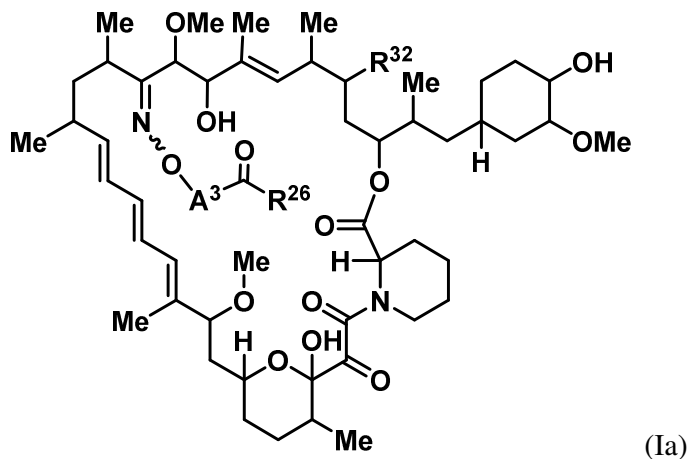


CLAIMS

1. A compound of Formula Ia:



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

R^{32} is H, =O, -OR³, or -N₃;

A³ is -[C(R³)₂]_n-, (C₆-C₁₀)arylene, cycloalkylene, heteroarylene, or heterocyclylene;

R²⁶ is -A¹-L¹-A²-B; -A¹-A²-B; -L²-A¹-L¹-A²-L³-B; ~~or -OH;~~

A¹ and A² are independently absent or are independently selected from

wherein the bond on the left side of A¹, as drawn, is bound to –C(=O)– or L²; and

wherein the bond on the right side of the A² moiety, as drawn, is bound to B or L³;

each Q is independently 1 to 3 rings selected from arylene, cycloalkylene, heteroarylene, and heterocyclylene;

each X is independently absent or 1 to 2 rings selected from arylene, cycloalkylene, heteroarylene, and heterocyclylene;

each X¹ is independently a heteroarylene or heterocyclylene ring;

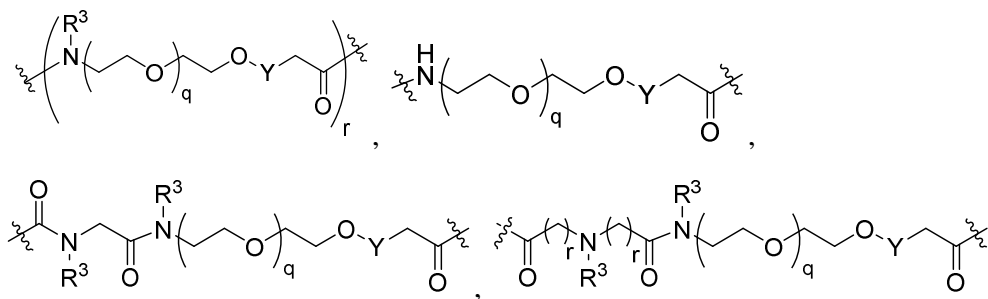
each W is independently absent or 1 to 2 rings selected from arylene, cycloalkylene, heteroarylene, and heterocyclylene;

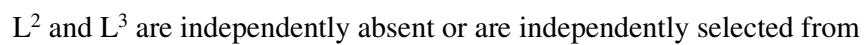
each W¹ is independently a heteroarylene or heterocyclylene ring;

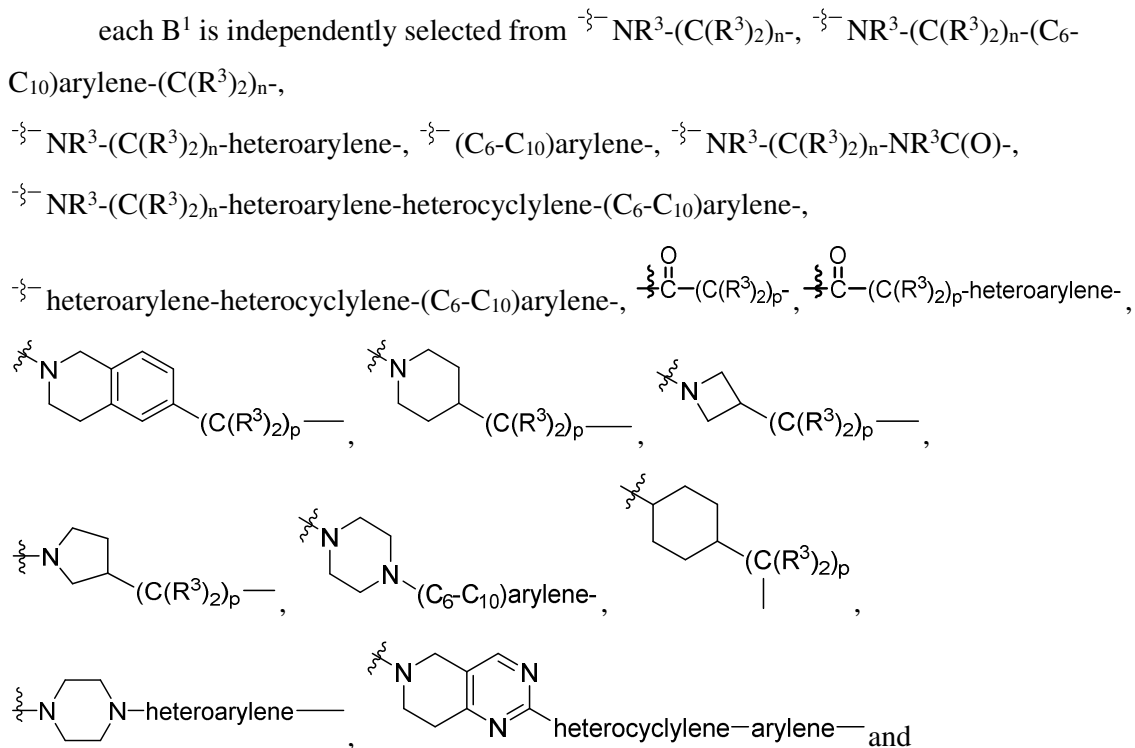
each G is independently absent or a ring selected from arylene, cycloalkylene, heteroarylene, and heterocyclylene;

each G¹ and G² are independently heteroarylene or heterocyclylene ring;

each L¹ is independently selected from







each R⁴ is independently H, (C₁-C₆)alkyl, halogen, 5-12 membered heteroaryl, 5-12 membered heterocyclyl, (C₆-C₁₀)aryl, wherein the heteroaryl, heterocyclyl, and aryl are each

independently optionally substituted with $-N(R^3)_2$, $-OR^3$, halogen, $(C_1-C_6)alkyl$, $-(C_1-C_6)alkylene-heteroaryl$, $-(C_1-C_6)alkylene-CN$, $-C(O)NR^3-heteroaryl$, or $-C(O)NR^3-heterocyclyl$;

each R^5 is independently H, $(C_1-C_6)alkyl$, $-C(O)OR^3$, or $-N(R^3)_2$, wherein the alkyl of $(C_1-C_6)alkyl$ is optionally substituted with $-N(R^3)_2$ or $-OR^3$;

each R^6 is independently H, $(C_1-C_6)alkyl$, $-C(O)OR^3$, or $-N(R^3)_2$, wherein the alkyl of $(C_1-C_6)alkyl$ is optionally substituted with $-N(R^3)_2$ or $-OR^3$;

each R^7 is independently H, $(C_1-C_6)alkyl$, $-C(O)OR^3$, or $-N(R^3)_2$, wherein the alkyl of $(C_1-C_6)alkyl$ is optionally substituted with $-N(R^3)_2$ or $-OR^3$;

each R^8 is independently H, $(C_1-C_6)alkyl$, $-C(O)OR^3$, or $-N(R^3)_2$, wherein the alkyl of $(C_1-C_6)alkyl$ is optionally substituted with $-N(R^3)_2$ or $-OR^3$;

each Y is independently $C(R^3)_2$ or a bond;

each n is independently an integer from one to 12;

each o is independently an integer from zero to 30;

each p is independently an integer from zero to 12;

each q is independently an integer from zero to 30; and

each r is independently an integer from one to 6.

2. The compound of claim 1, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{32} is $=O$.

3. The compound of claim 1, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{32} is $-OR^3$.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein A^3 is $-[C(R^3)_2]_n-$.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein A^3 is $-(C_6-C_{10})arylene-$.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{26} is $-A^1-L^1-A^2-B$, wherein A^1 and A^2 are absent.

7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{26} is $-A^1-L^1-A^2-B$, wherein A^2 is absent.

8. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{26} is $-A^1-L^1-A^2-B$, wherein A^1 is absent.

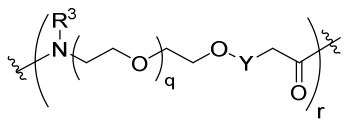
9. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{26} is $-A^1-L^1-A^2-B$.

10. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{26} is $-A^1-A^2-B$.

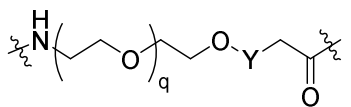
11. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{26} is $-L^2-A^1-L^1-A^2-L^3-B$.

12. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R^{26} is $-OH$.

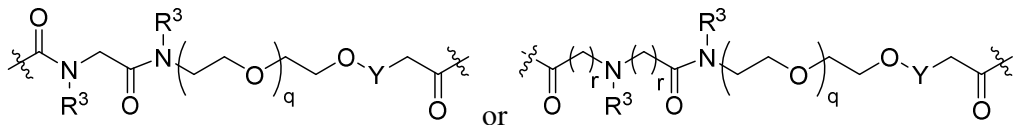
13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L^1 is



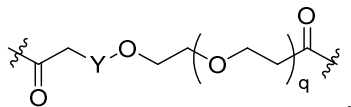
14. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L^1 is



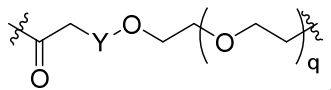
15. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L^1 is



16. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L^1 is

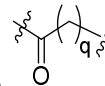


17. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L¹ is

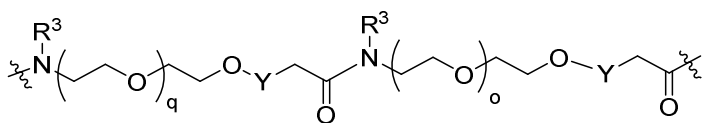


18. The compound of any one of claims 1-11, or a pharmaceutically acceptable

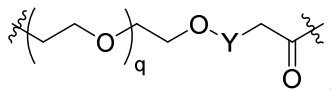
salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L¹ is



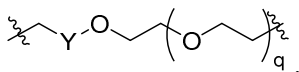
19. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L¹ is



20. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L¹ is

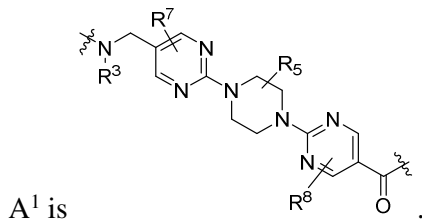


21. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein L¹ is

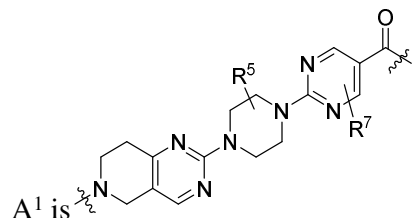


22. The compound of any one of claims 1-11 and 13-21, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein A¹ is absent.

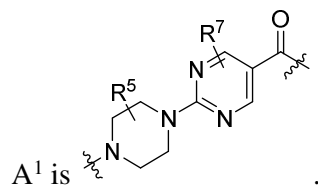
23. The compound of any one of claims 1-5, 7, 9-11 and 13-21, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



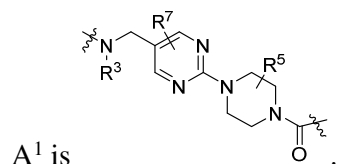
24. The compound of any one of claims 1-5, 7, 9-11 and 13-21, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



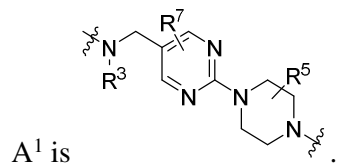
25. The compound of any one of claims 1-5, 7, 9-11 and 13-21, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



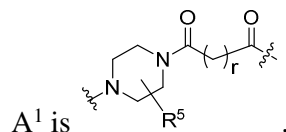
26. The compound of any one of claims 1-5, 7, 9-11 and 13-21, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



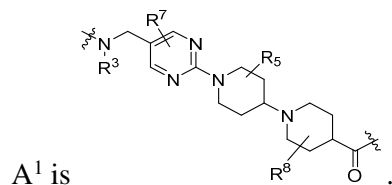
27. The compound of any one of claims 1-5, 7, 9-11 and 13-21, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



28. The compound of any one of claims 1-5, 7, 9-11 and 13-21, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein

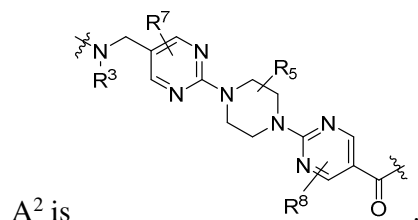


29. The compound of any one of claims 1-5, 7, 9-11 and 13-21, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein

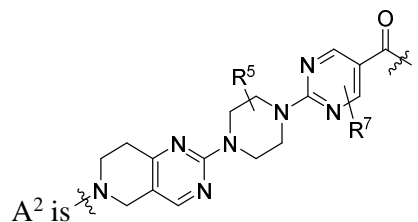


30. The compound of any one of claims 1-11 and 13-29, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein A² is absent.

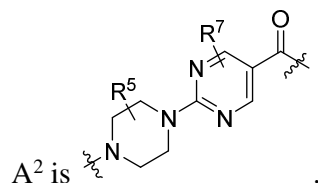
31. The compound of any one of claims 1-5, 8-11 and 13-29, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



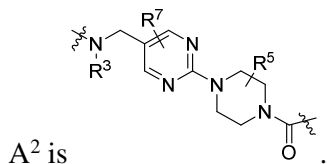
32. The compound of any one of claims 1-5, 8-11 and 13-29, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



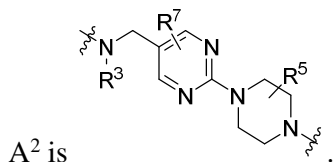
33. The compound of any one of claims 1-5, 8-11 and 13-29, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



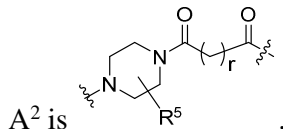
34. The compound of any one of claims 1-5, 8-11 and 13-29, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



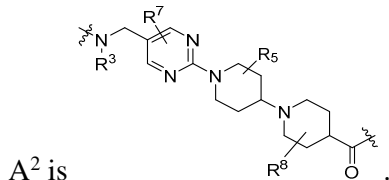
35. The compound of any one of claims 1-5, 8-11 and 13-29, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



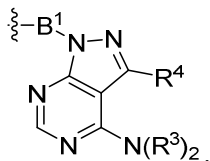
36. The compound of any one of claims 1-5, 8-11 and 13-29, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



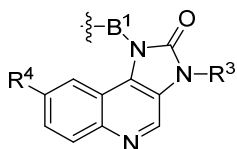
37. The compound of any one of claims 1-5, 8-11 and 13-29, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein



38. The compound of any one of claims 1-11 and 13-37, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein B is

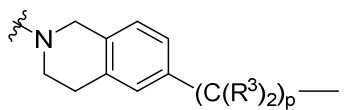


39. The compound of any one of claims 1-11 and 13-37, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein B is



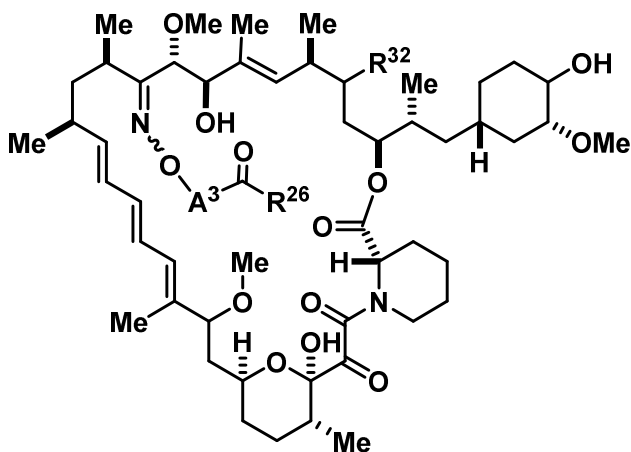
40. The compound of any one of claims 1-11 and 13-39, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein B¹ is $^{-\frac{1}{n}}\text{NR}^3\text{-(C(R}^3\text{)}_2)_n$.

41. The compound of any one of claims 1-11 and 13-39, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein B¹ is

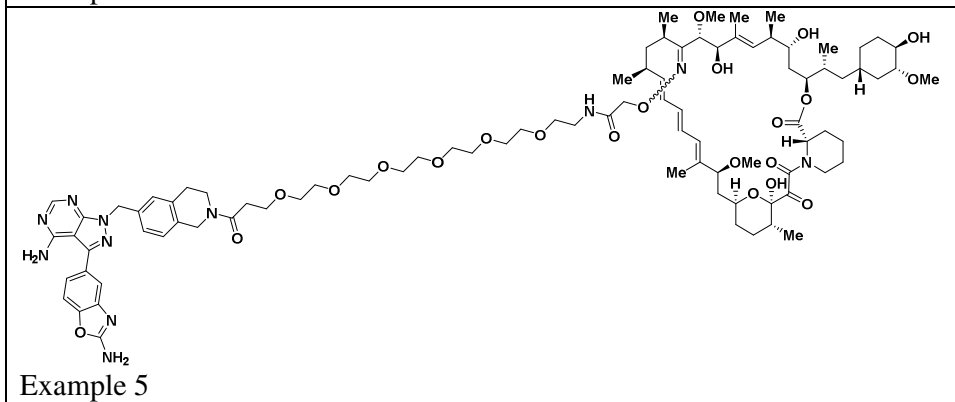
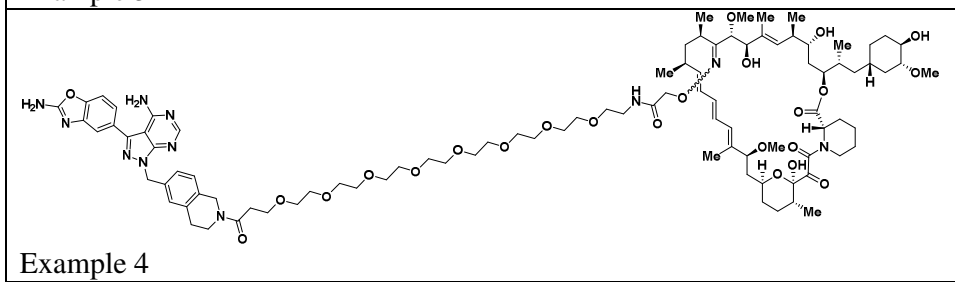
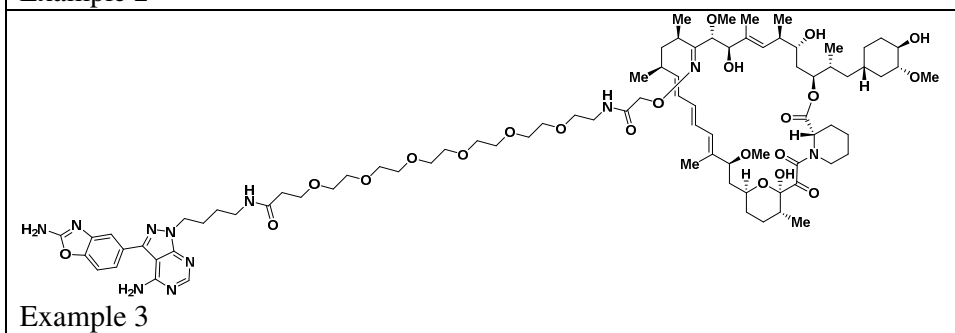
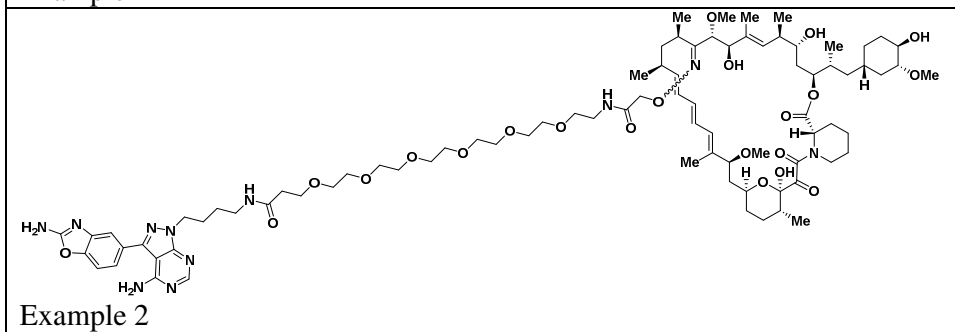
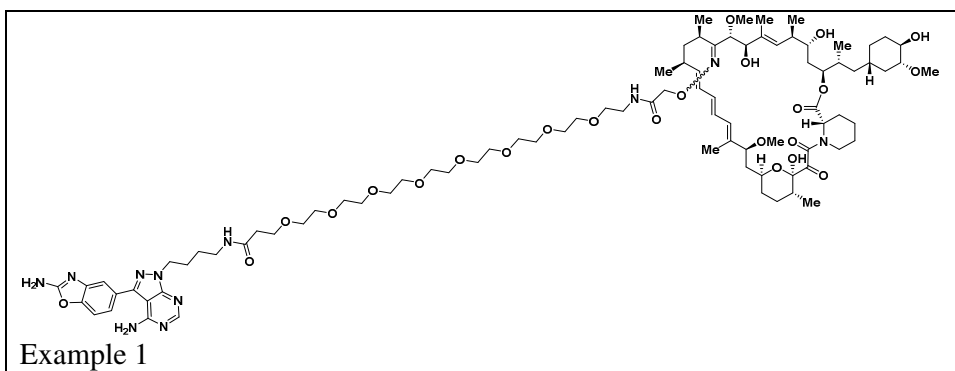


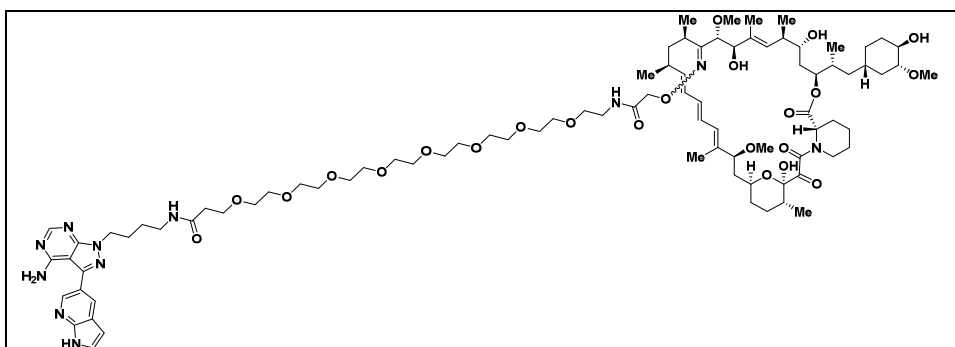
42. The compound of any one of claims 1-11 and 13-41, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein R⁴ is 5-12 membered heteroaryl, optionally substituted with $-\text{N(R}^3\text{)}_2$, $-\text{OR}^3$, halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $-(\text{C}_1\text{-C}_6)\text{alkylene-heteroaryl}$, $-(\text{C}_1\text{-C}_6)\text{alkylene-CN}$, or $-\text{C(O)NR}^3\text{-heteroaryl}$.

43. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, wherein compound has the following formula:

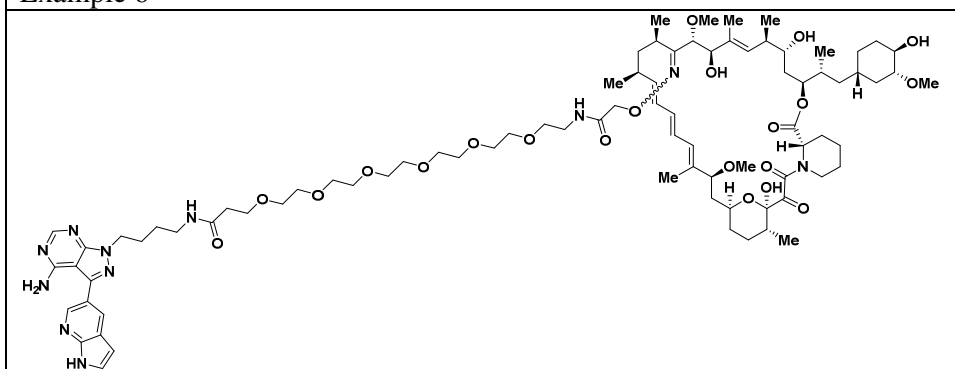


44. A compound selected from the group consisting of:

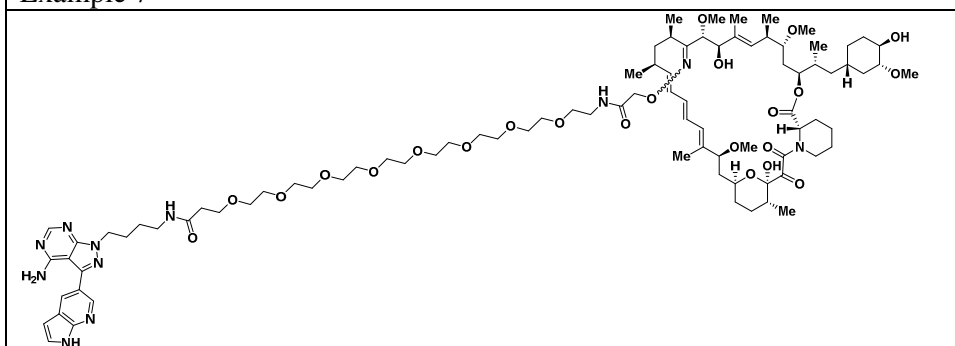




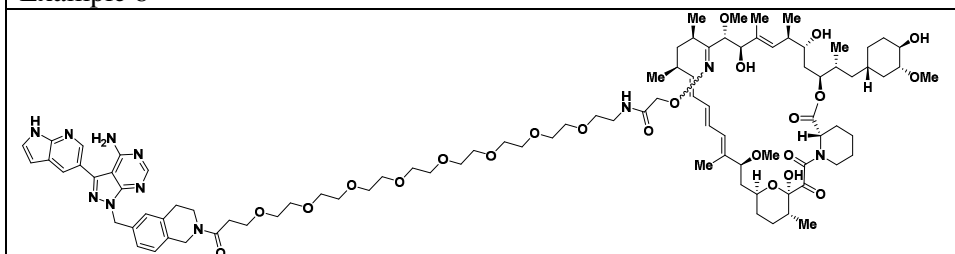
Example 6



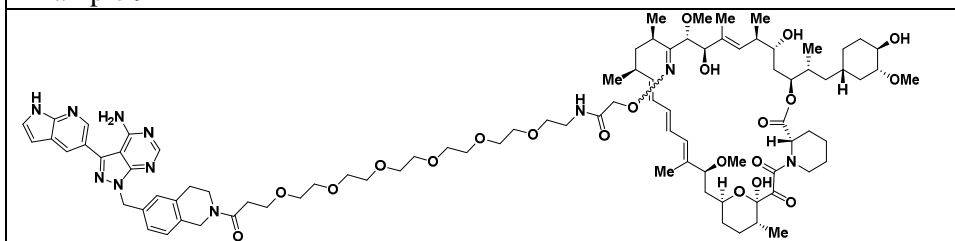
Example 7



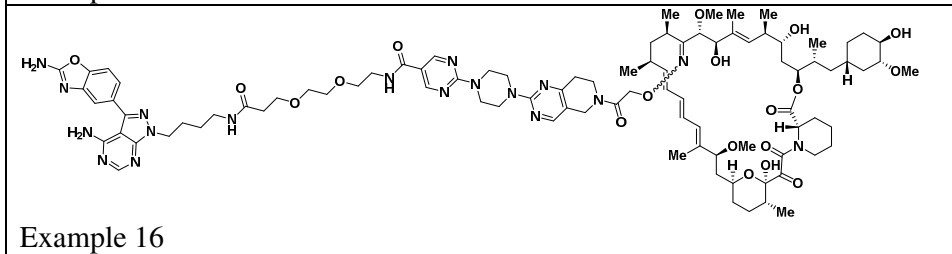
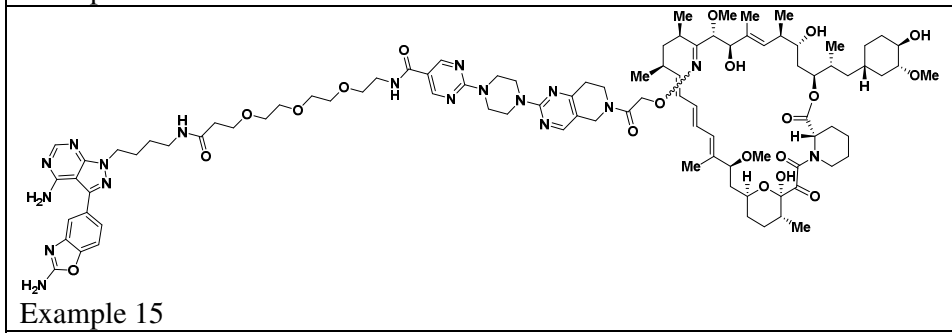
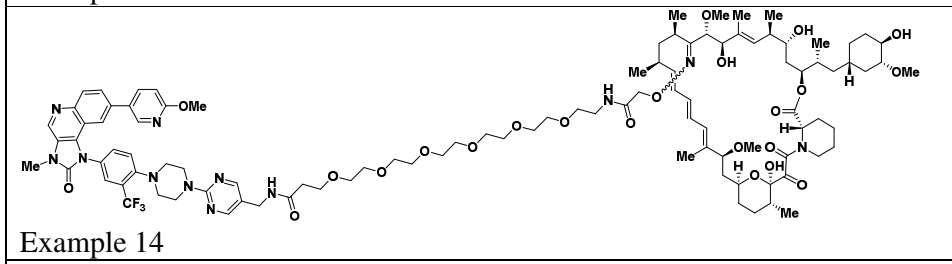
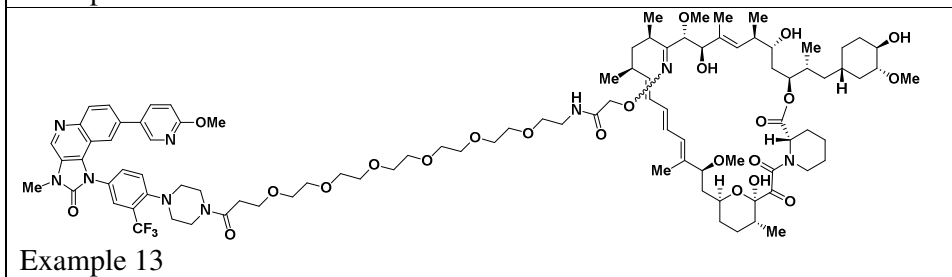
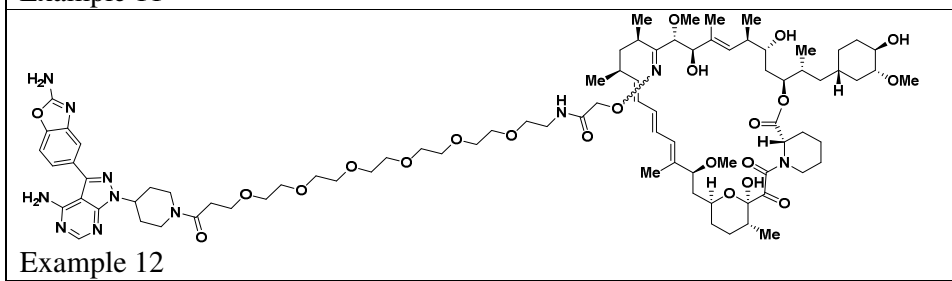
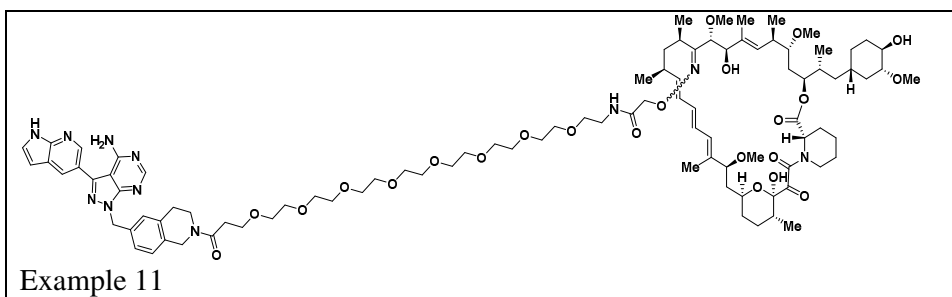
Example 8

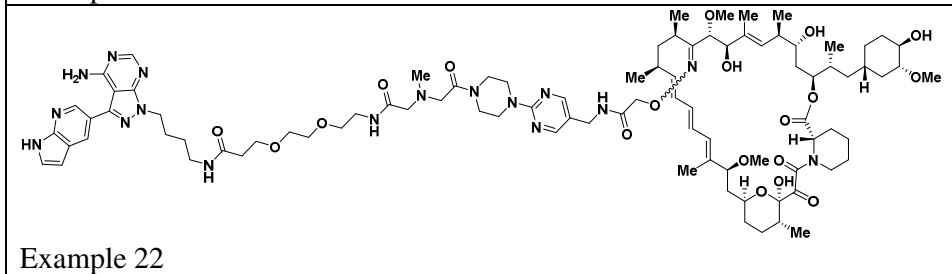
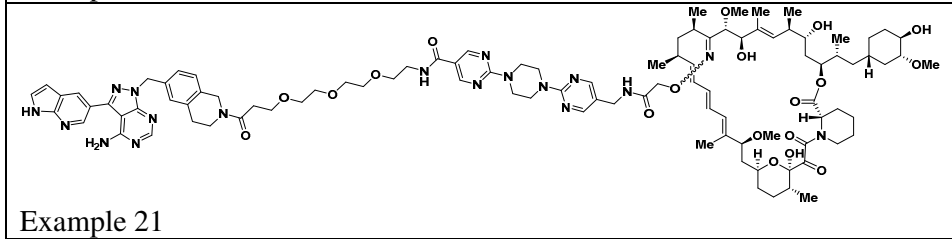
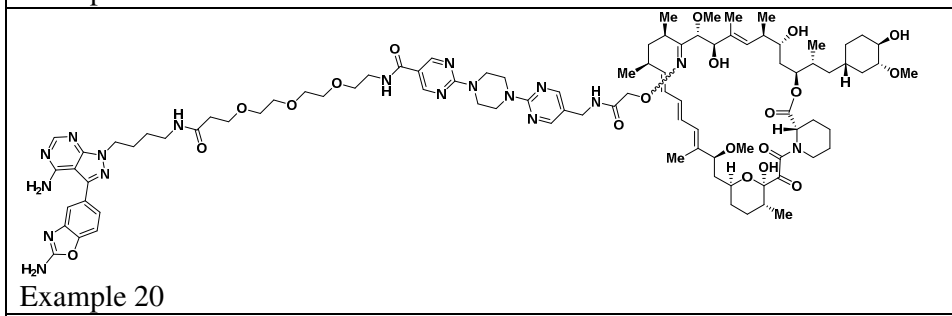
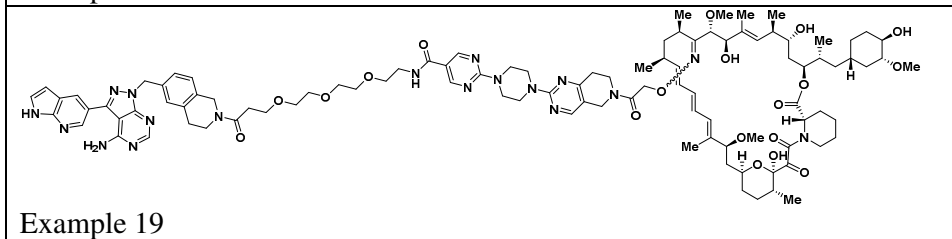
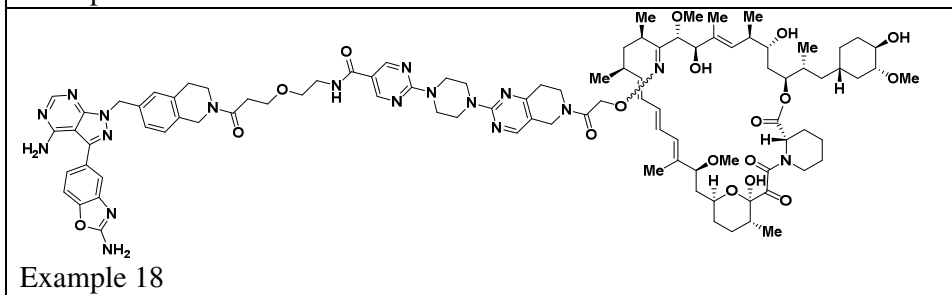
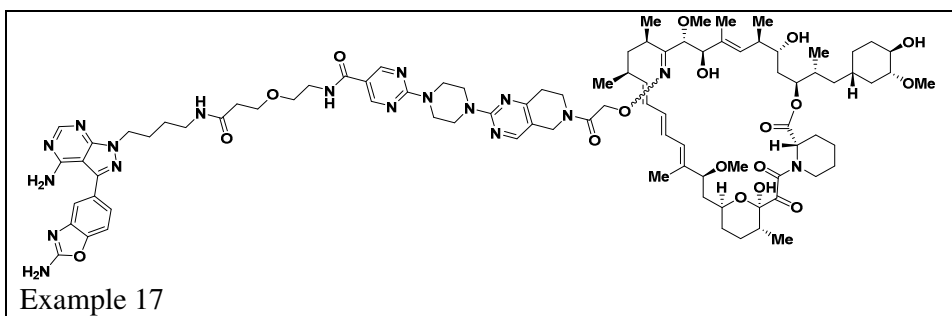


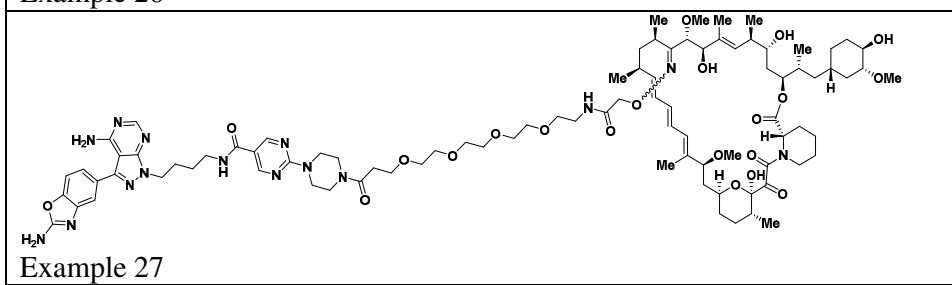
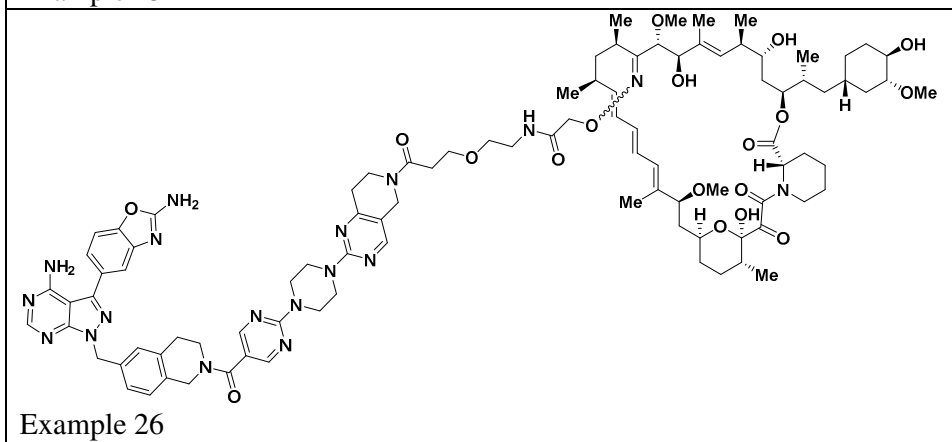
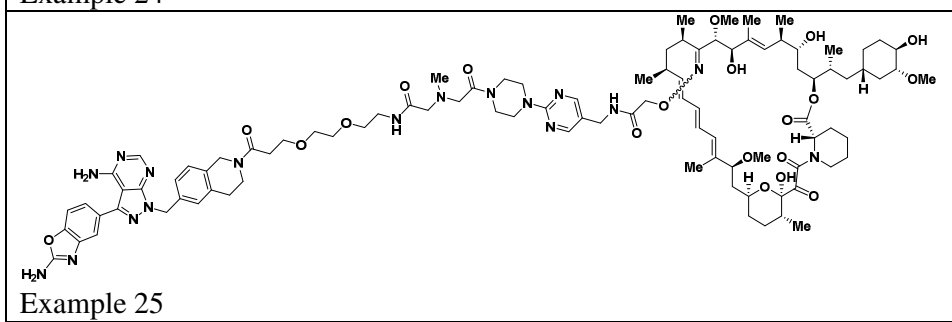
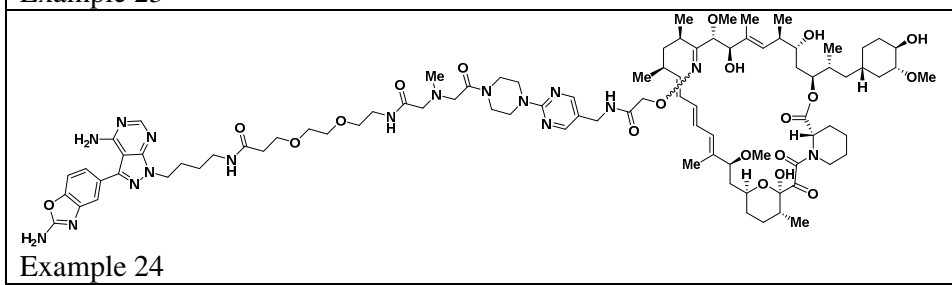
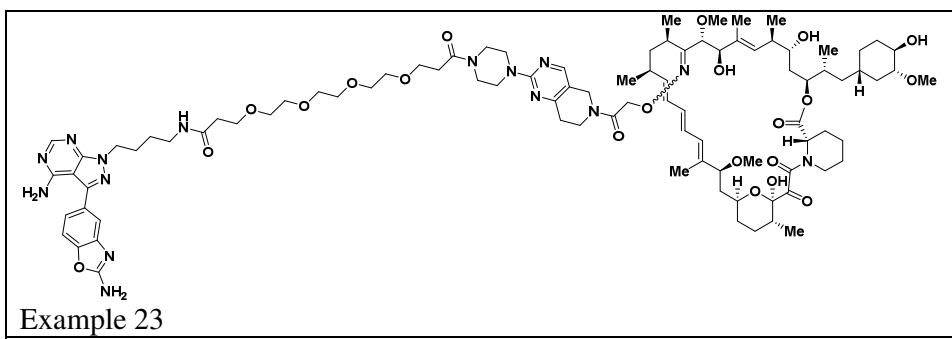
Example 9

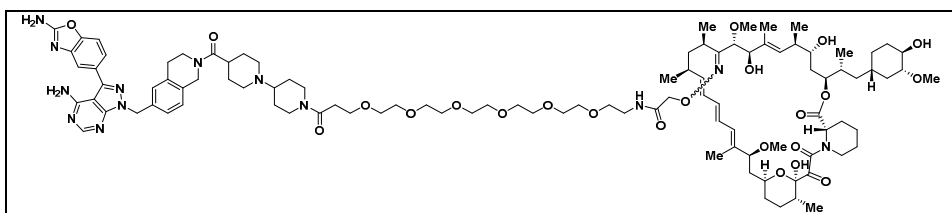


Example 10

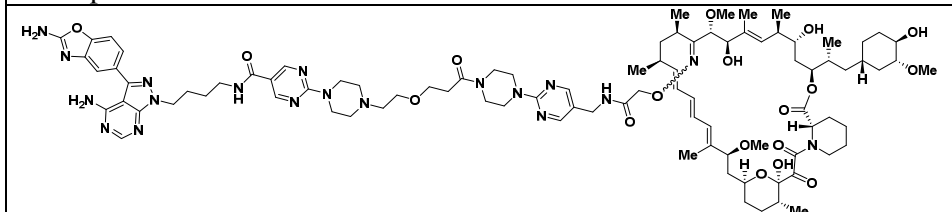




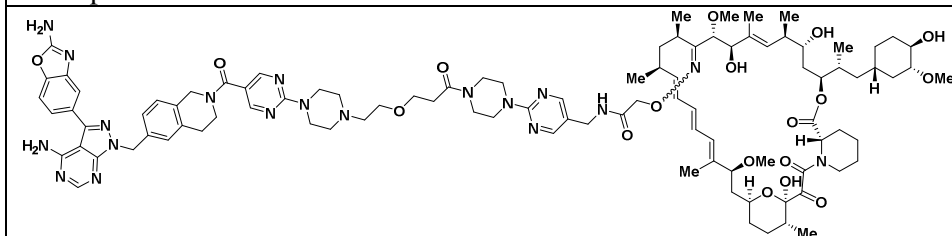




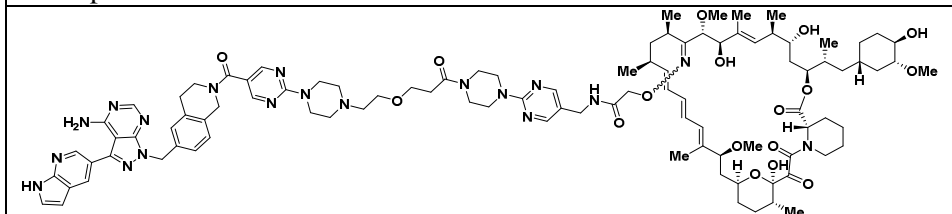
Example 28



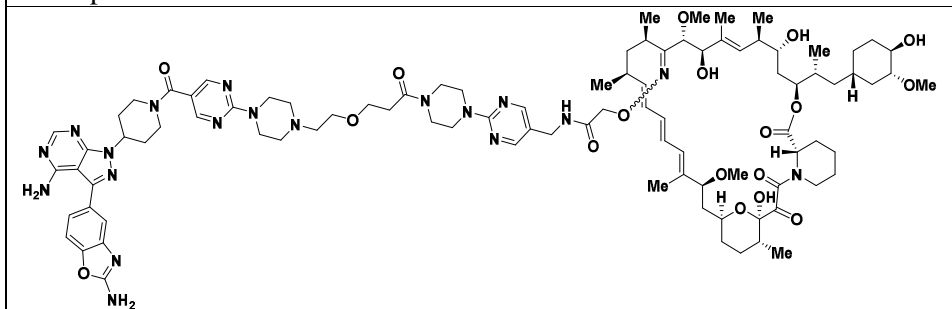
Example 29



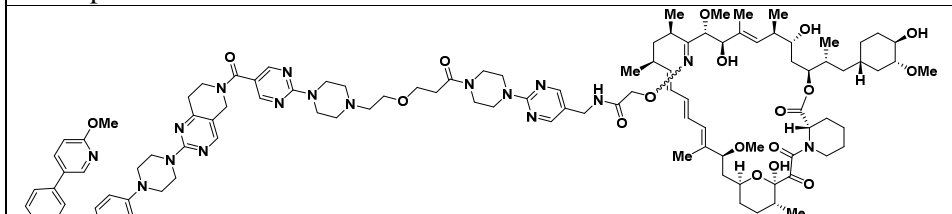
Example 30



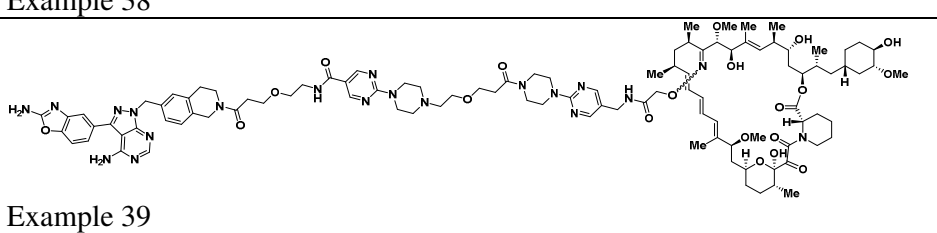
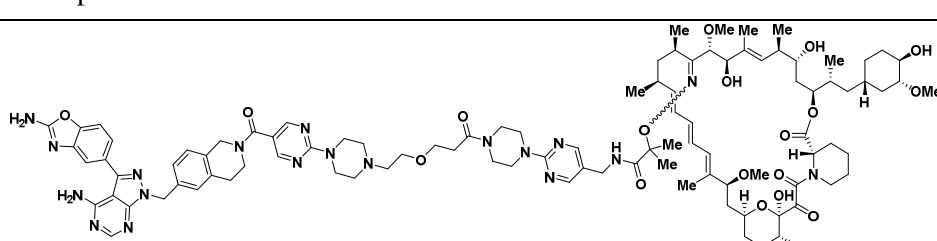
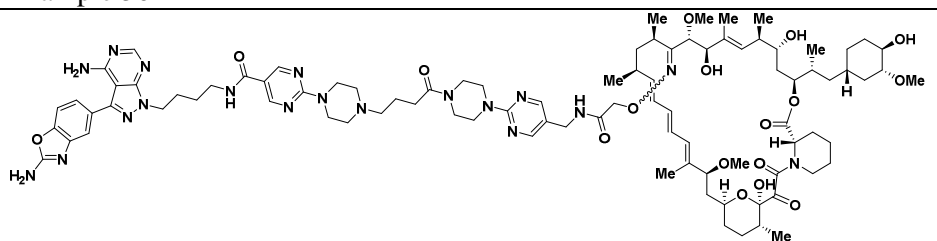
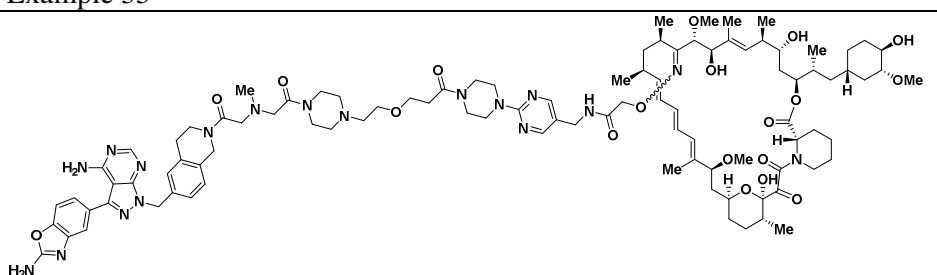
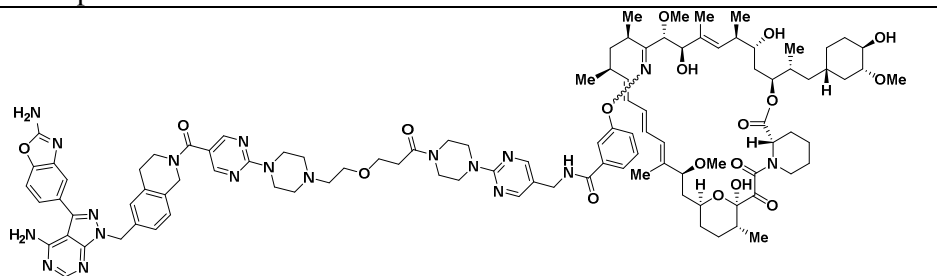
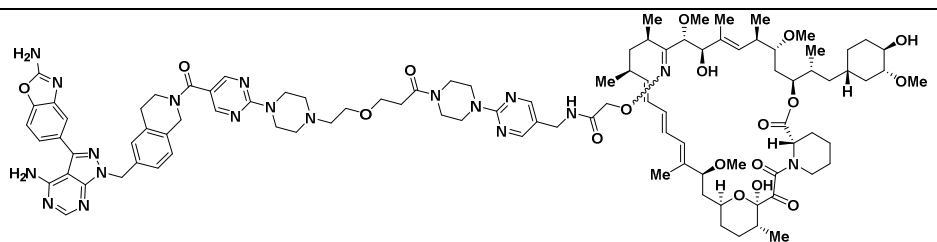
Example 31

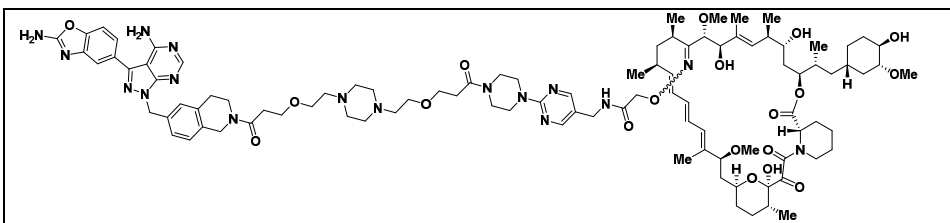


Example 32

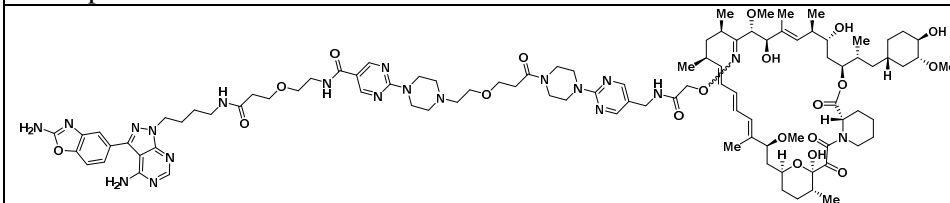


Example 33

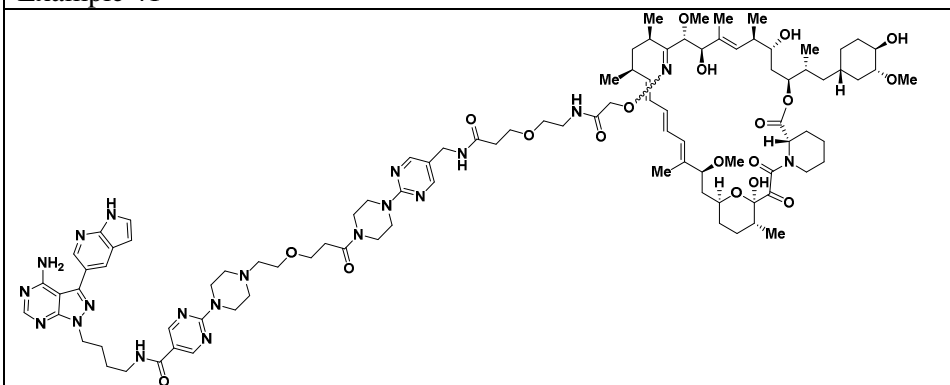




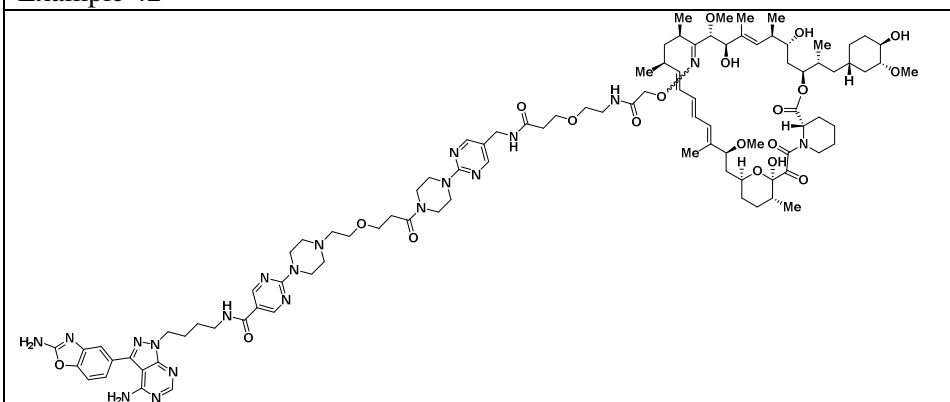
Example 40



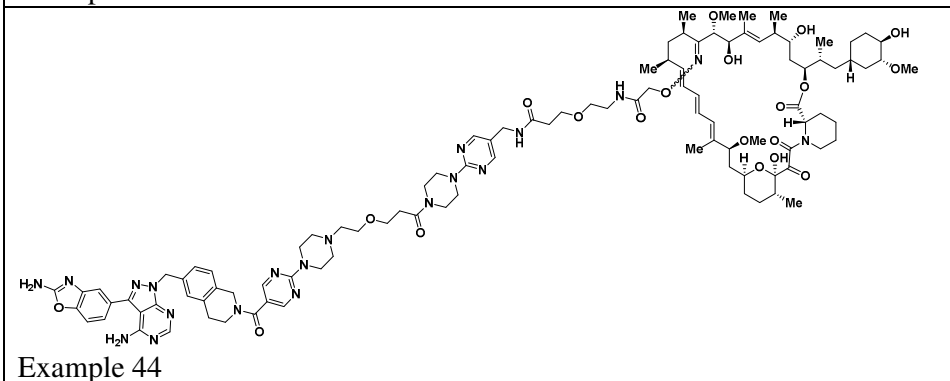
Example 41



Example 42



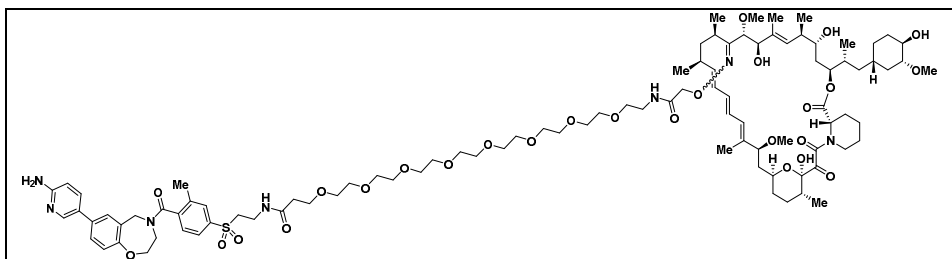
Example 43



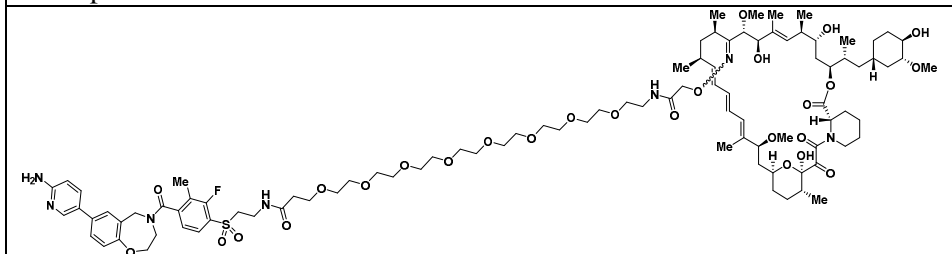
Example 44

or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof.

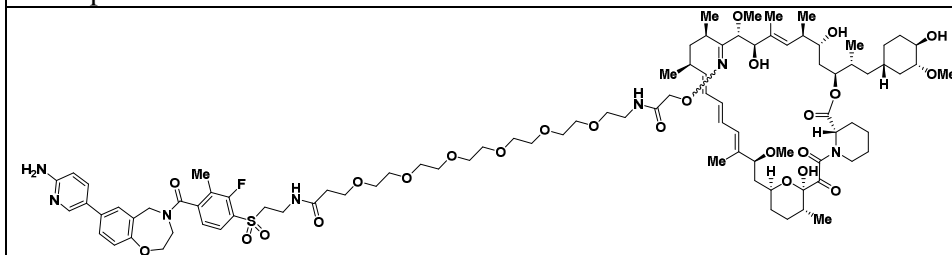
45. A compound selected from the group consisting of:



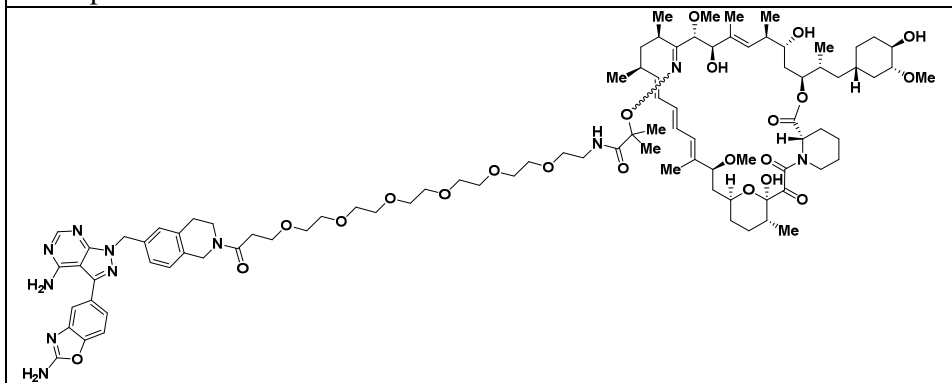
Example 45



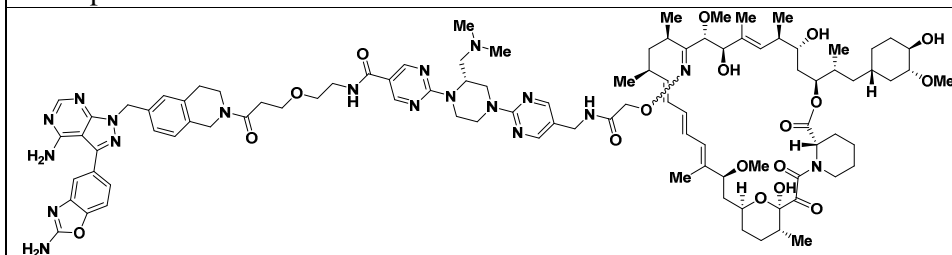
Example 46



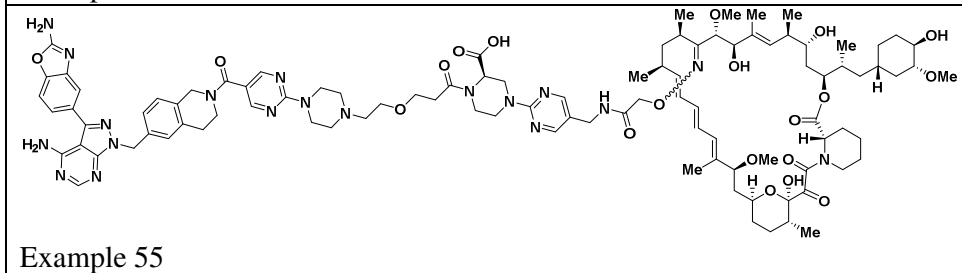
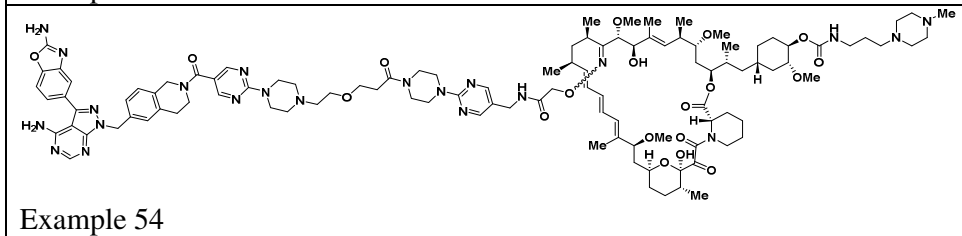
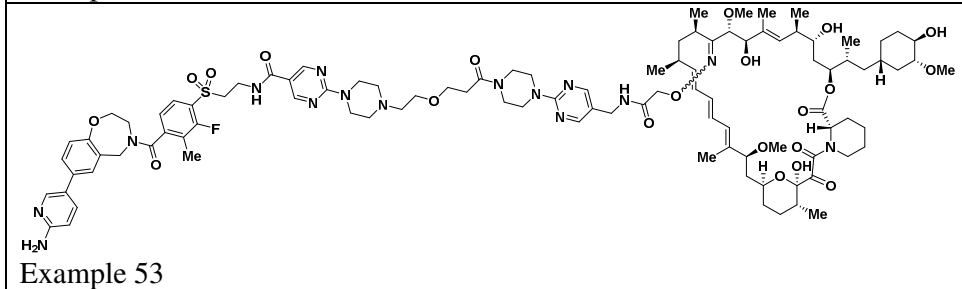
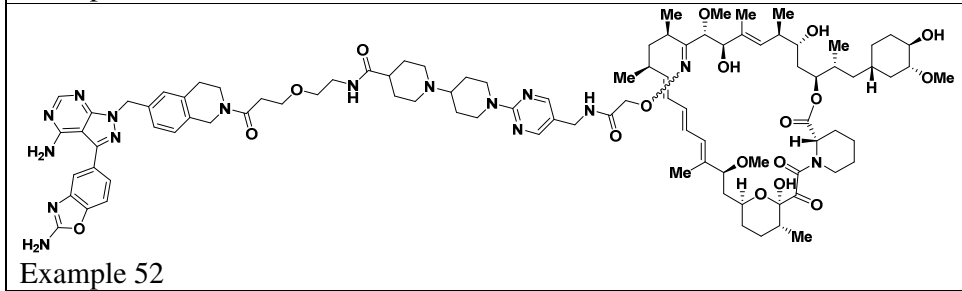
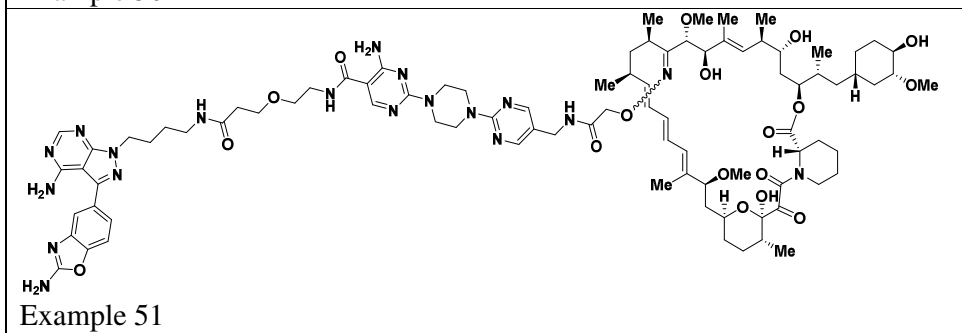
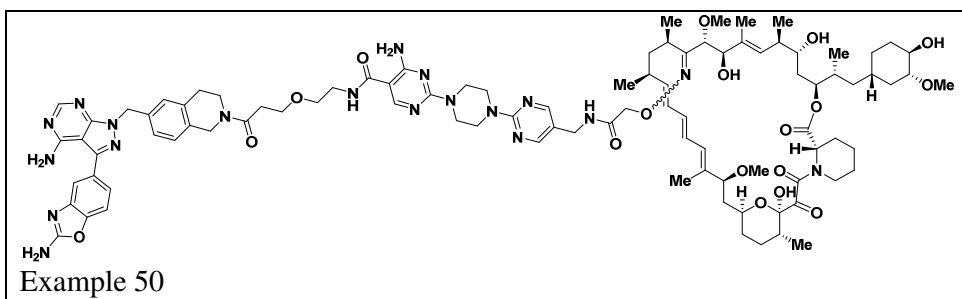
Example 47

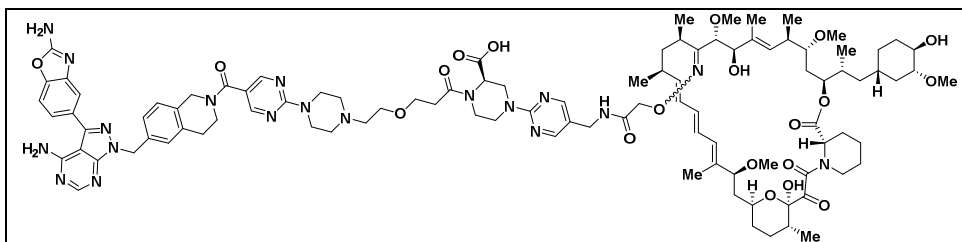


Example 48

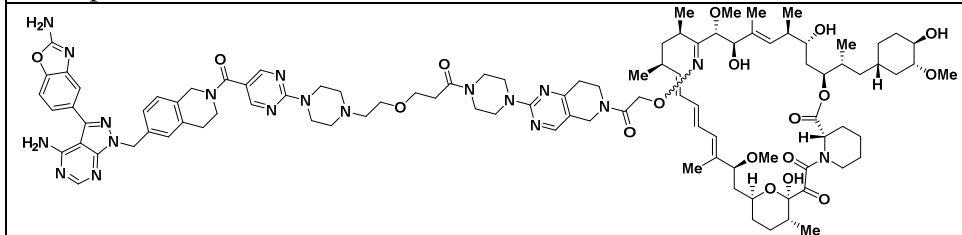


Example 49

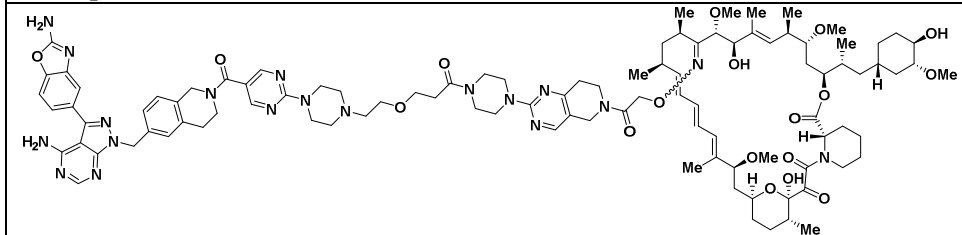




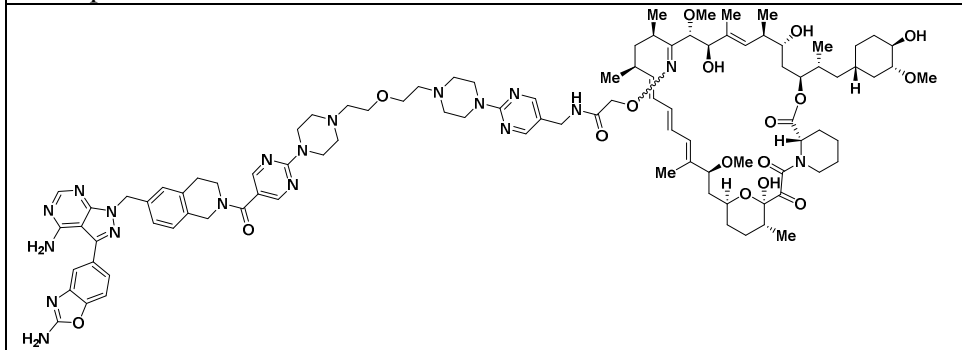
Example 56



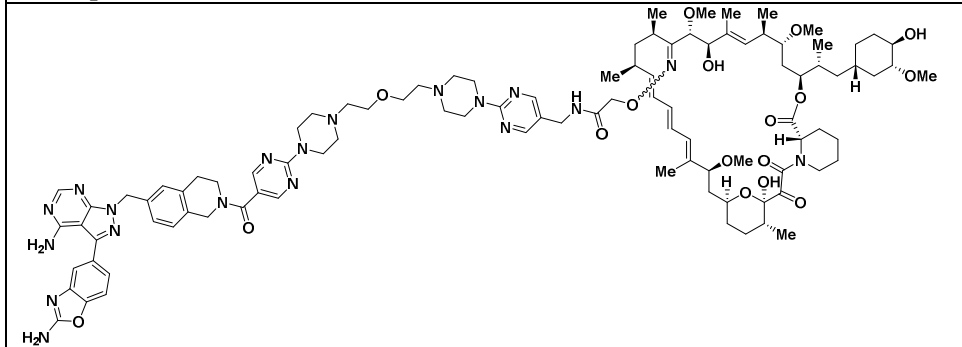
Example 57



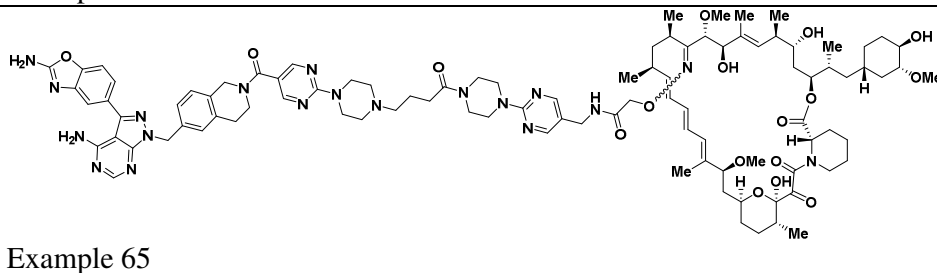
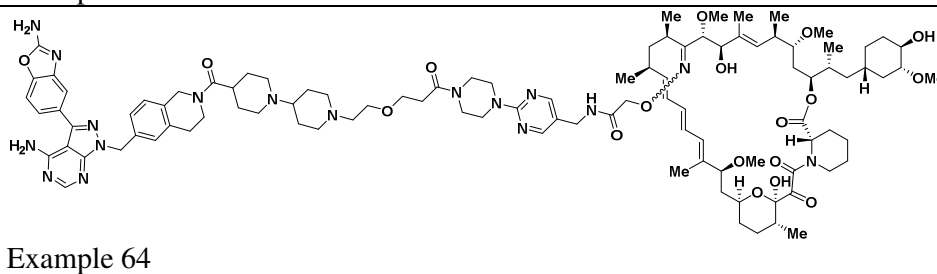
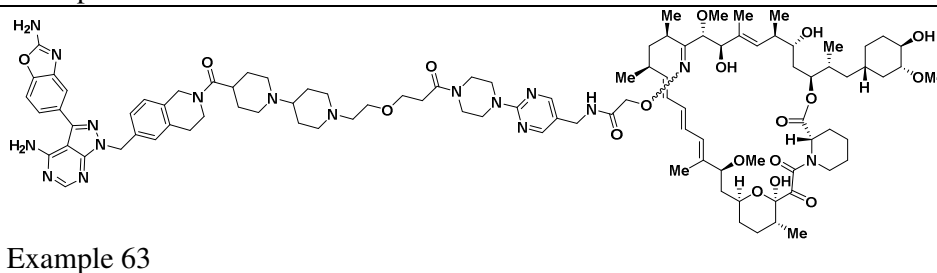
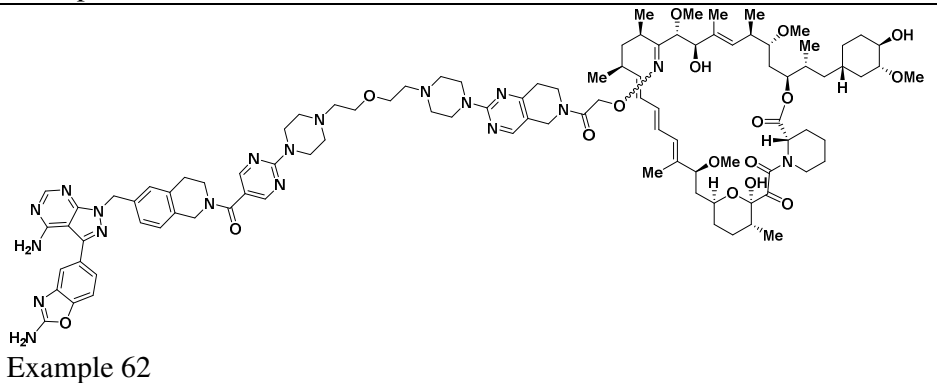
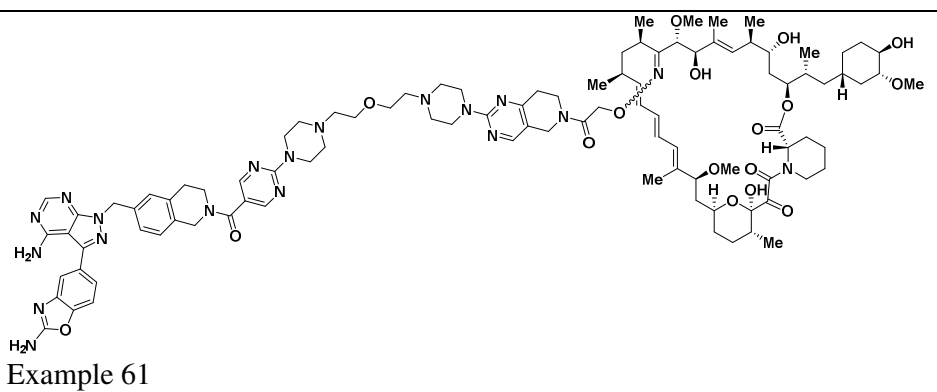
Example 58

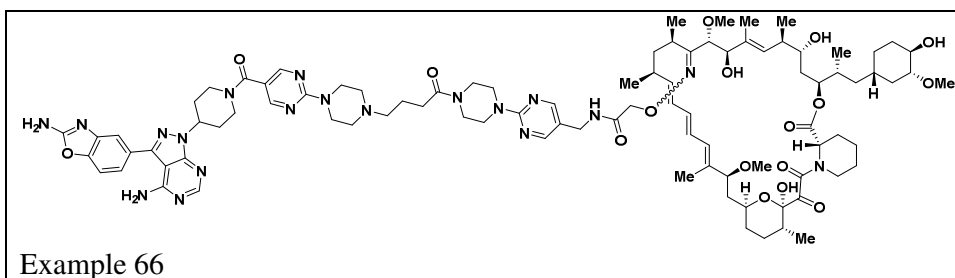


Example 59



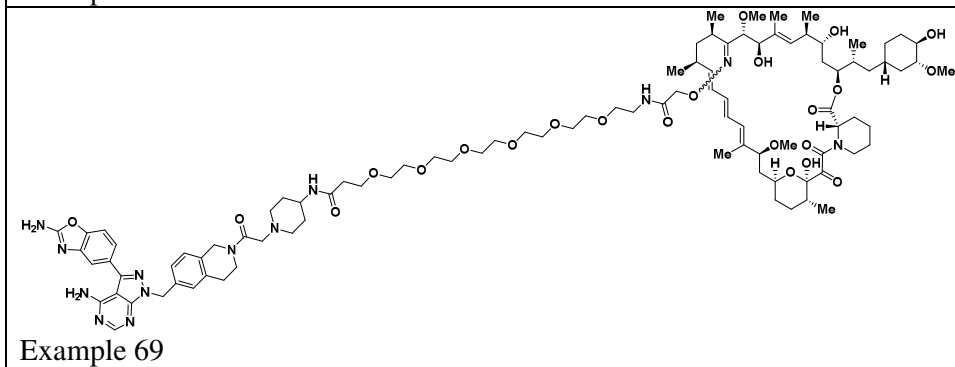
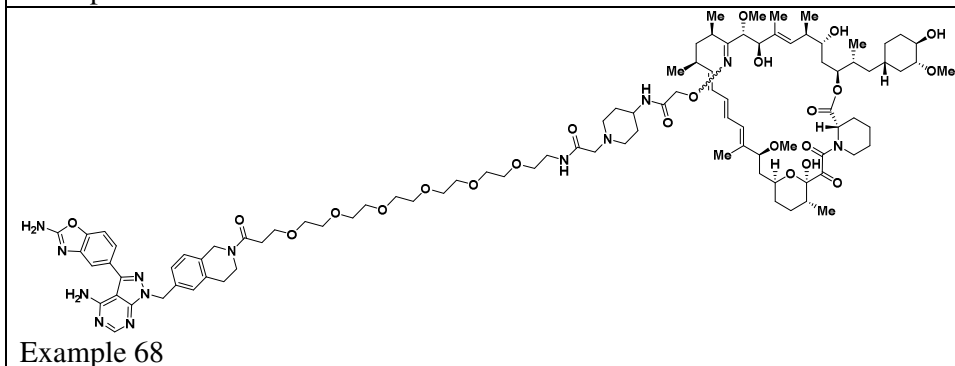
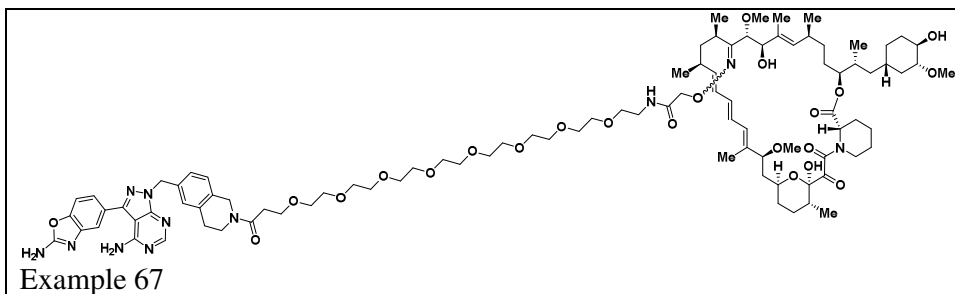
Example 60

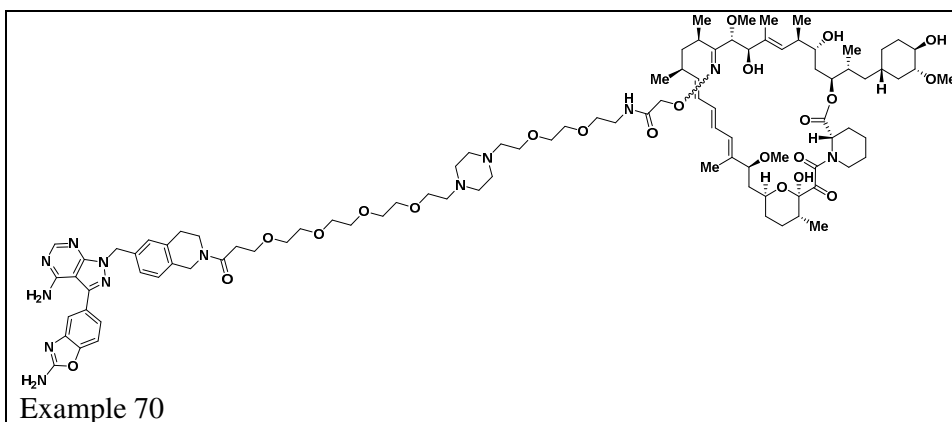




or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof.

46. A compound selected from the group consisting of:





or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof.

47. A pharmaceutical composition comprising a compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

48. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, for use in method of treating a disease or disorder selected from the group consisting of cancer, immune-mediated disease, and age related condition mediated by mTOR comprising administering to the subject suffering from or susceptible to developing a disease or disorder mediated by mTOR a therapeutically effective amount of one or more compounds of any one of claims 1-46, or a pharmaceutically acceptable salt thereof..

49. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, for use in method of preventing a disease or disorder selected from the group consisting of cancer, immune-mediated disease, and age related condition mediated by mTOR comprising administering to the subject suffering from or susceptible to developing a disease or disorder mediated by mTOR a therapeutically effective amount of one or more compounds of any one of claims 1-46, or a pharmaceutically acceptable salt thereof

50. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, for use in method of reducing the risk of a disease or disorder selected from the group consisting of cancer, immune-mediated disease, and age related condition mediated by mTOR comprising administering to the subject suffering from or susceptible to developing a disease or disorder mediated by mTOR a therapeutically effective amount of one or more compounds of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.

51. The compound for use method of any one of claims ~~47-49~~ 48-50, wherein the disease is cancer or an immune-mediated disease.

52. The compound for use method of claim 51, wherein the cancer is selected from brain and neurovascular tumors, head and neck cancers, breast cancer, lung cancer, mesothelioma, lymphoid cancer, stomach cancer, kidney cancer, renal carcinoma, liver cancer, ovarian cancer, ovary endometriosis, testicular cancer, gastrointestinal cancer, prostate cancer, glioblastoma, skin cancer, melanoma, neuro cancers, spleen cancers, pancreatic cancers, blood proliferative disorders, lymphoma, leukemia, endometrial cancer, cervical cancer, vulva cancer, prostate cancer, penile cancer, bone cancers, muscle cancers, soft tissue cancers, intestinal or rectal cancer, anal cancer, bladder cancer, bile duct cancer, ocular cancer, gastrointestinal stromal tumors, and neuro-endocrine tumors.

53. The compound for use method of claim 51, wherein the immune-mediated disease is selected from resistance by transplantation of heart, kidney, liver, medulla ossium, skin, cornea, lung, pancreas, intestinum tenue, limb, muscle, nerves, duodenum, small-bowel, or pancreatic-islet-cell; graft-versus-host diseases brought about by medulla ossium transplantation; rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, allergic encephalomyelitis, and glomerulonephritis.

54. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, for use in method of treating cancer ~~comprising administering to the subject a therapeutically effective amount of one or more compounds of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

55. The compound for use method of claim 54, wherein the cancer is selected from brain and neurovascular tumors, head and neck cancers, breast cancer, lung cancer, mesothelioma, lymphoid cancer, stomach cancer, kidney cancer, renal carcinoma, liver cancer, ovarian cancer, ovary endometriosis, testicular cancer, gastrointestinal cancer, prostate cancer, glioblastoma, skin cancer, melanoma, neuro cancers, spleen cancers, pancreatic cancers, blood proliferative disorders, lymphoma, leukemia, endometrial cancer, cervical cancer, vulva cancer, prostate cancer, penile cancer, bone cancers, muscle cancers, soft tissue cancers, intestinal or rectal cancer, anal cancer, bladder cancer, bile duct cancer, ocular cancer, gastrointestinal stromal tumors, and neuro-endocrine tumors.

56. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, for use in method of treating an immune-mediated disease ~~comprising administering to the subject a therapeutically effective amount~~

~~of one or more compounds of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

57. The compound for use method of claim 56, wherein the immune-mediated disease is selected from resistance by transplantation of heart, kidney, liver, medulla ossium, skin, cornea, lung, pancreas, intestinum tenue, limb, muscle, nerves, duodenum, small-bowel, or pancreatic-islet-cell; graft-versus-host diseases brought about by medulla ossium transplantation; rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, allergic encephalomyelitis, and glomerulonephritis.

58. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, for use in method of treating an age related condition ~~comprising administering to the subject a therapeutically effective amount of one or more compounds of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

59. The compound for use method of claim 58, wherein the age related condition is selected from sarcopenia, skin atrophy, muscle wasting, brain atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, high blood pressure, erectile dysfunction, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life expectancy, impaired kidney function, and age-related hearing loss, aging-related mobility disability (e.g., frailty), cognitive decline, age-related dementia, memory impairment, tendon stiffness, heart dysfunction such as cardiac hypertrophy and systolic and diastolic dysfunction, immunosenescence, cancer, obesity, and diabetes.

~~60. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, for use in treating, preventing, or reducing the risk of a disease or condition mediated by mTOR.~~

~~61~~60. Use of a compound of any of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating, preventing, or reducing the risk of a disease or disorder selected from the group consisting of cancer, immune-mediated disease, and age related condition ~~mediated by mTOR.~~

~~62. — A compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, for use in treating cancer.~~

~~63~~61. Use of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating cancer.

~~64. — A compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, for use in treating an immune-mediated disease.~~

~~65~~62. Use of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating an immune-mediated disease.

~~66. — A compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, for use in treating an age-related condition.~~

~~67~~63. Use of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt, oxepane isomer, stereoisomer, or tautomer thereof, in the manufacture of a medicament suitable for treating an age-related condition.