

HALOGEN-CONTAINING COMPOUND FOR CAPPING 5' END OF NUCLEIC ACID AND USE OF SAME

Technical Field

The present invention relates to the fields of biotechnology and synthetic chemistry, in particular to a class of nucleoside compounds, and in particular to a halogen-containing compound for capping 5' end of a nucleic acid (RNA) and a use of the halogen-containing compound.

Background Art

In recent years, as the global COVID-19 situation has changed, messenger RNA (mRNA) technology and vaccine drugs thereof have achieved breakthroughs from laboratory to clinical application. With the unprecedented success of the COVID-19 vaccine, market expectations for mRNA technology have risen sharply. The application scenarios of mRNA technology have great development potential not only in the field of infectious diseases such as COVID-19, but also in preventive vaccines, therapeutic drugs, and even cell programming and regenerative therapies.

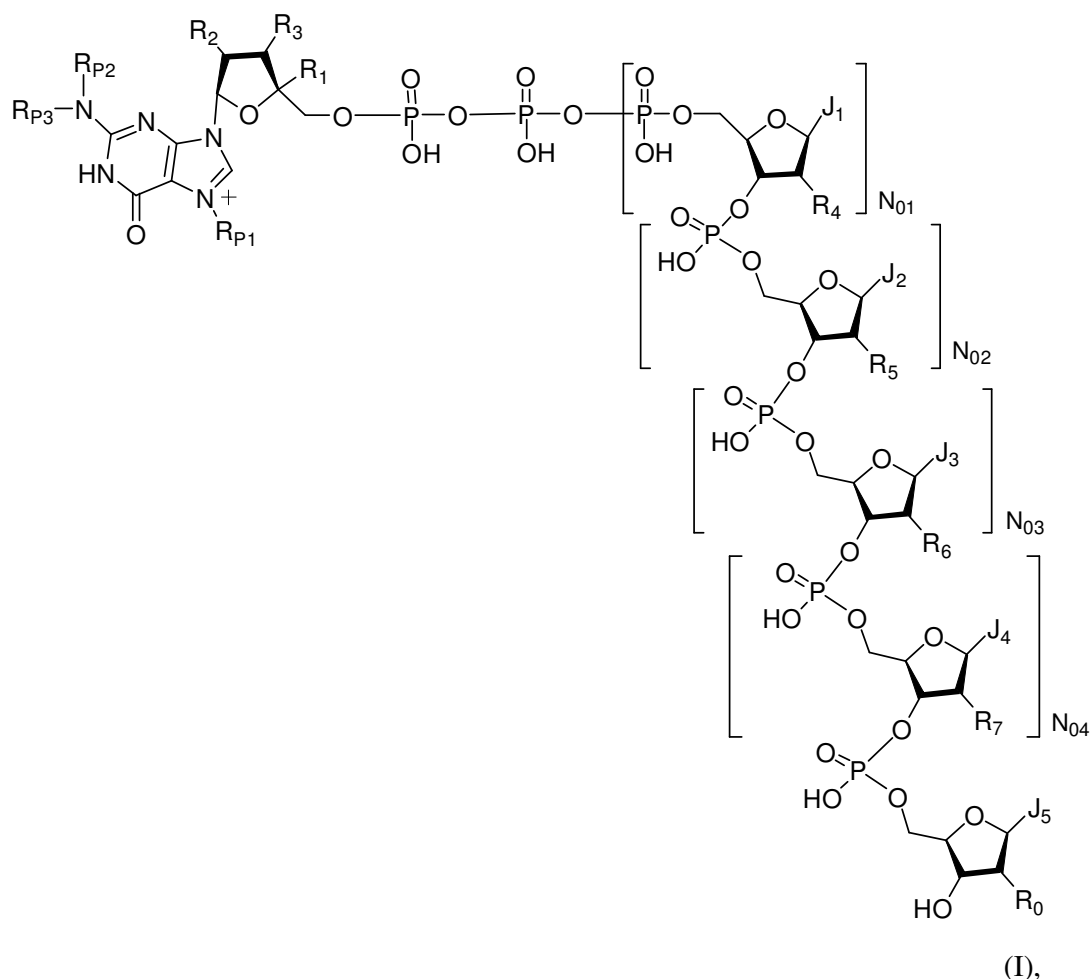
The cap structure is a RNA modification widely present in cells, which plays a key role in maintaining the stability of mRNA and regulating protein translation. Currently, many studies are devoted to further chemically modifying the cap structure to further enhance the translation efficiency of mRNA while reducing immunogenicity thereof.

Summary of the Invention

The present invention provides a halogen-containing compound for capping 5' end of a nucleic acid (RNA), a pharmaceutically acceptable, solvate, and stereoisomer thereof, and a use thereof. This compound has various modified or unmodified 7-methylguanine bases on the nucleoside at one end and a halogen substituent at the 2' position of the nucleoside at the other end. The use of this compound in a reaction to cap 5' end of mRNA has a high capping rate and good *in vitro* transcription efficiency. At the same time, it has a high translation expression efficiency at the cellular level and *in vivo*, such as in mice.

The present invention provides a halogen-containing compound for capping 5' end of a nucleic

acid, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound has a structure of Formula (I):



in which

R_0 is any one selected from the group consisting of F, Cl, Br and I,

R_1 is a group selected from the group consisting of -H, -OH, C_{1-4} alkyl and C_{1-4} alkoxy,

R_2 is any one selected from the group consisting of -H, -OH, C_{1-6} alkyl and C_{1-6} alkoxy,

optionally, R_1 and R_2 are connected to form a ring by a chemical bond, and $-R_1-R_2-$ is any one of $-(CH_2)_q-O-$, $-O-(CH_2)_q-$ and $-(CH_2)_m-O-(CH_2)_n-$, wherein q , m , n are each independently 1, 2 or 3,

R_3 is any one of H, -OH, -SH, $-N_3$, $-NH_2$, halogen, -CN, C_{1-6} alkoxy, $-O(CH_2)_sCN$, $-SR_{3a}$, $-O(CH_2)_pR_{3b}$, $OCOR_{3c}$, $O(CH_2)_pCOR_{3c}$, $-O(CH_2)_tSH$, $-O(CH_2)_pOH$, $-O(CH_2)_pN_3$, and $-O(CH_2)_pNH_2$, wherein t , p and s are each independently any integer from 1 to 6, R_{3a} is C_{1-6} alkyl, R_{3b} is C_{6-12} aryl optionally substituted with one or more R_{3d} or C_{5-12} heteroaryl optionally substituted with one or more

R_{3d}, R_{3c} is C₁₋₁₀ alkyl optionally substituted with one or more R_{3d}, C₁₋₁₀ alkenyl optionally substituted with one or more R_{3d}, C₅₋₁₂ cycloalkyl optionally substituted with one or more R_{3d}, or C₅₋₁₂ cycloalkenyl optionally substituted with one or more R_{3d}, wherein R₃ is optionally substituted with one or more R_{3e}, and R_{3d} and R_{3e} are selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, cyano, amino, nitro, -OH, and -SH,

R₄, R₅, R₆, and R₇ are each independently any one selected from the group consisting of -H, -OH, -OCH₃, halogen, -CN, and -SH,

N₀₁, N₀₂, N₀₃, and N₀₄ are each independently selected from 0 or 1,

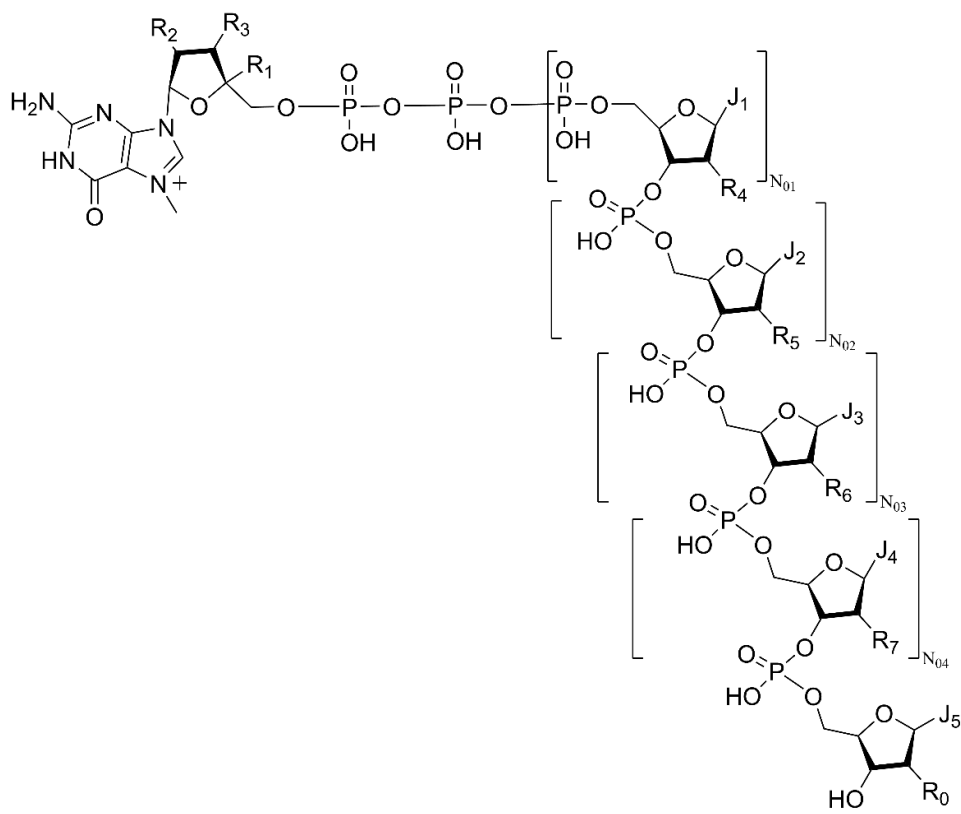
J₁, J₂, J₃, J₄, and J₅ are each independently selected from natural or modified pyrimidine nucleotide bases, or natural or modified purine nucleotide bases,

R_{P1} is C₁ to C₆ alkyl, preferably C₁ to C₃ alkyl, which is optionally substituted with -SH, -N₃, C₂ to C₆ alkenyl or C₂ to C₆ alkynyl,

R_{P2} and R_{P3} are each independently selected from the group consisting of H, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, PEG, COR_{P4}, and SO₂R_{P4}, wherein these groups are each optionally substituted with -CN, -N₃, -SH, or alkynyl, R_{P4} is selected from the group consisting of H and C₁ to C₆ alkyl, and R_{P2} and R_{P3} are optionally connected to form a ring, and

with the proviso that when N₀₁, N₀₂, N₀₃, and N₀₄ are all 0, J₅ is a guanine base, and when R₂ is -OH, R₃ is not a methoxy group.

In a preferred embodiment, the compound of the present invention has a structure of Formula (I'):



each group in Formula (I') has the same meaning as that described above with respect to Formula (I).

In a preferred embodiment, at least one of J₁, J₂, J₃, J₄, and J₅ is a modified nucleotide base, preferably a modified purine nucleotide base, more preferably a methyl-modified purine nucleotide base, and still more preferably 6-N-methyladenine.

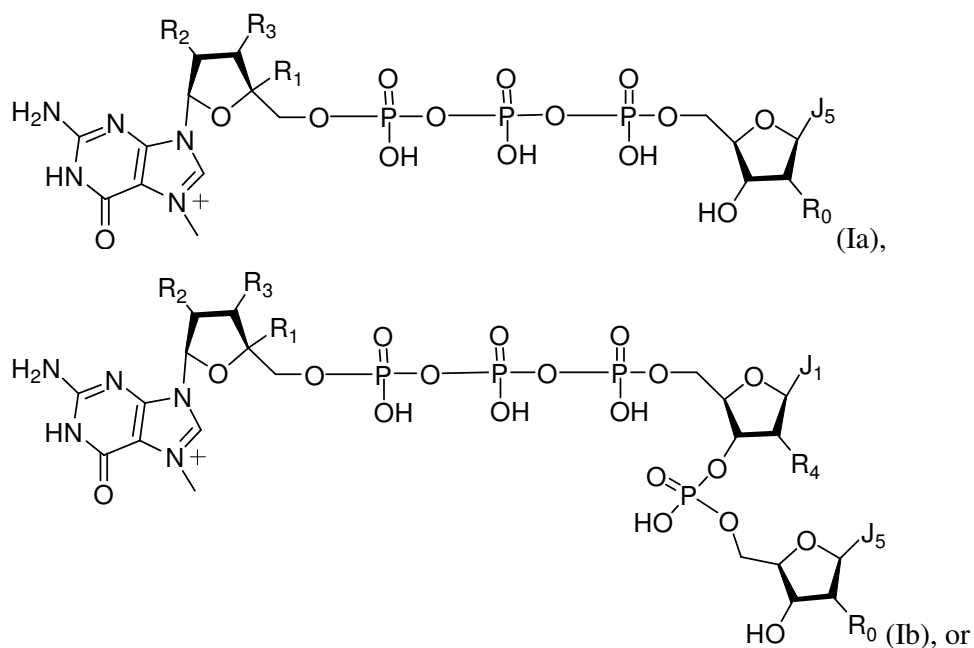
In a preferred embodiment, R₃ is any one of -H, -OH, -SH, -N₃, -NH₂, halogen, -CN, C₁₋₆ alkoxy, -O(CH₂)_pCN, -SR_{3a}, -O(CH₂)_pR_{3b}, OCOR_{3c}, O(CH₂)_pCOR_{3c}, -O(CH₂)_pSH, -O(CH₂)_pOH, -O(CH₂)_pN₃, and -O(CH₂)_pNH₂, wherein t, p and s are each independently any integer from 1 to 6, preferably 1 to 4, R_{3a} is C₁₋₄ alkyl, R_{3b} is C₆₋₁₀ aryl optionally substituted with one or more R_{3d}, or C₅₋₁₀ heteroaryl optionally substituted with one or more R_{3d}, R_{3c} is C₅₋₁₀ cycloalkyl optionally substituted with one or more R_{3d}, or C₅₋₁₀ cycloalkenyl optionally substituted with one or more R_{3d}, wherein R₃ is optionally substituted with one or more R_{3e}, and R_{3d} and R_{3e} are selected from the group consisting of C₁₋₄ alkyl, C₂₋₄ alkenyl, C₁₋₄ alkoxy, halogen, cyano, amino, nitro, -OH, and -SH.

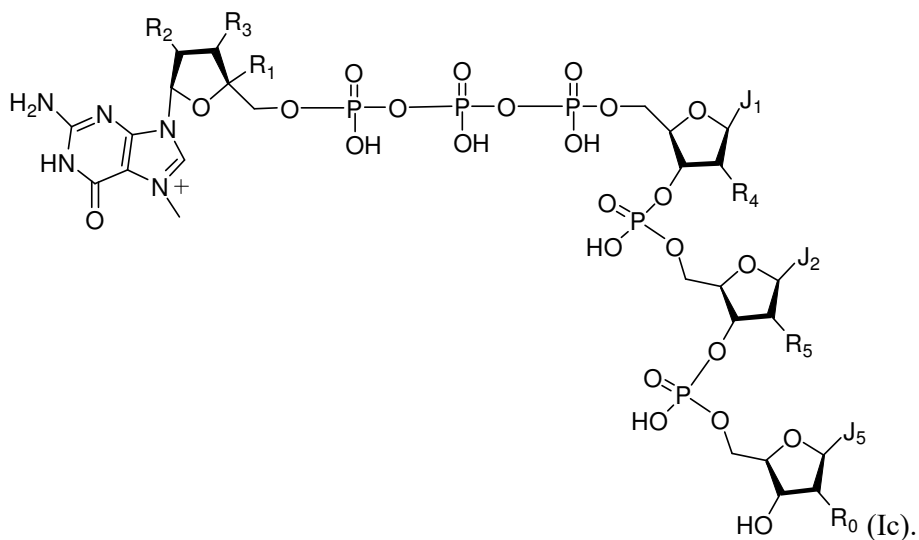
In another preferred embodiment, R and R₃ are any one of -H, -OH, -SH, -N₃, -NH₂, halogen, -CN, C₁₋₃ alkoxy, -O(CH₂)_pCN, -SR_{3a}, -O(CH₂)_pR_{3b}, OCOR_{3c}, O(CH₂)_pCOR_{3c}, -O(CH₂)_pSH, -

$\text{O}(\text{CH}_2)_p\text{OH}$, $-\text{O}(\text{CH}_2)_p\text{N}_3$, and $-\text{O}(\text{CH}_2)_p\text{NH}_2$, wherein p and s are each independently any integer from 1 to 3, t is any integer from 1 to 4, R_{3a} is methyl or ethyl, R_{3b} is C_{5-10} heteroaryl optionally substituted with one or two R_{3d} , R_{3c} is C_{5-10} cycloalkyl optionally substituted with one or two R_{3d} , or C_{5-10} cycloalkenyl optionally substituted with one or two R_{3d} , wherein R_3 is optionally substituted with one or more R_{3e} , and R_{3d} and R_{3e} are selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, halogen, cyano, amino, nitro, $-\text{OH}$, and $-\text{SH}$.

In another preferred embodiment, R_{3b} is C_5 or C_6 heteroaryl optionally substituted with C_{1-4} alkyl, for example, tetrazinyl optionally substituted with C_{1-4} alkyl, and R_{3c} is C_{5-10} cycloalkenyl optionally substituted with C_{1-4} alkyl, halogen, cyano, amino, or nitro, for example, norbornenyl or cyclooctenyl optionally substituted with C_{1-4} alkyl, halogen, cyano, amino, or nitro, and for example, unsubstituted norbornenyl or cyclooctenyl.

In a preferred embodiment, the compound has a structure of Formula (Ia), Formula (Ib) or Formula (Ic):

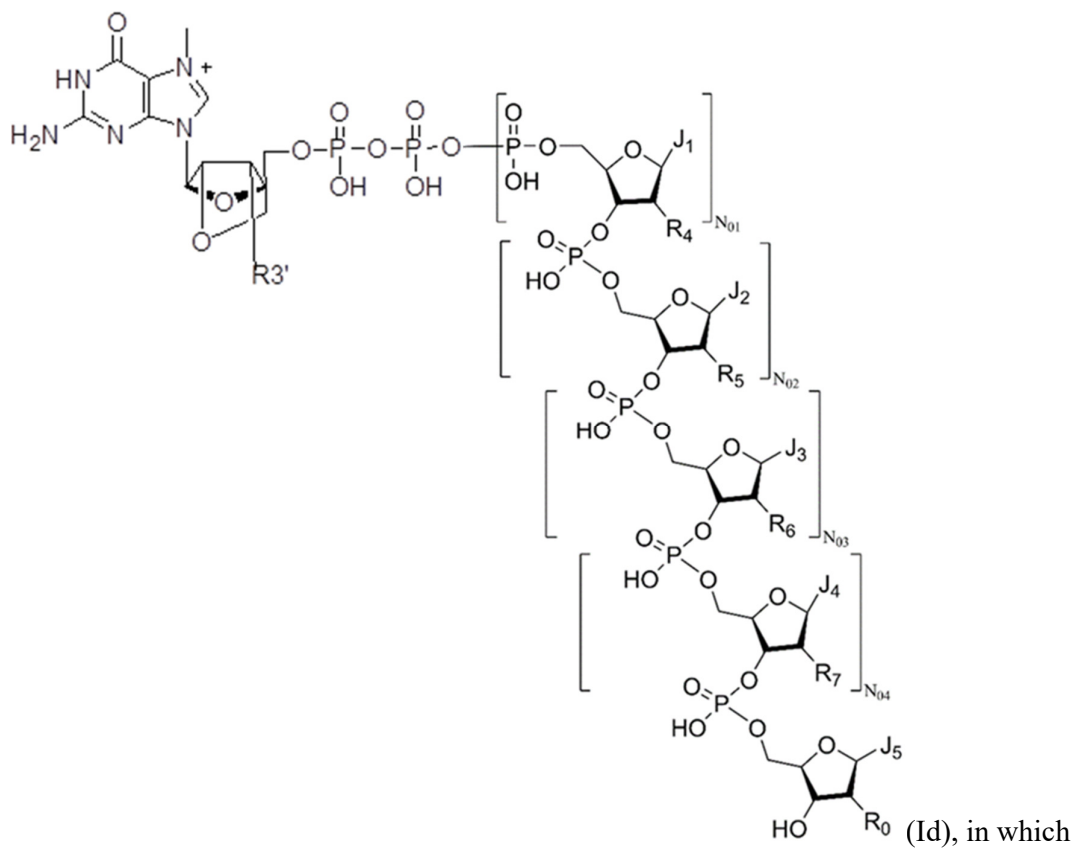




In a preferred embodiment, R₀ is -F or -Cl, and/or

R₄ and R₅ are each independently any one selected from the group consisting of H, OH, OCH₃, F, Cl, -CN, and -SH, and preferably any one selected from the group consisting of H, OH, OCH₃, and F.

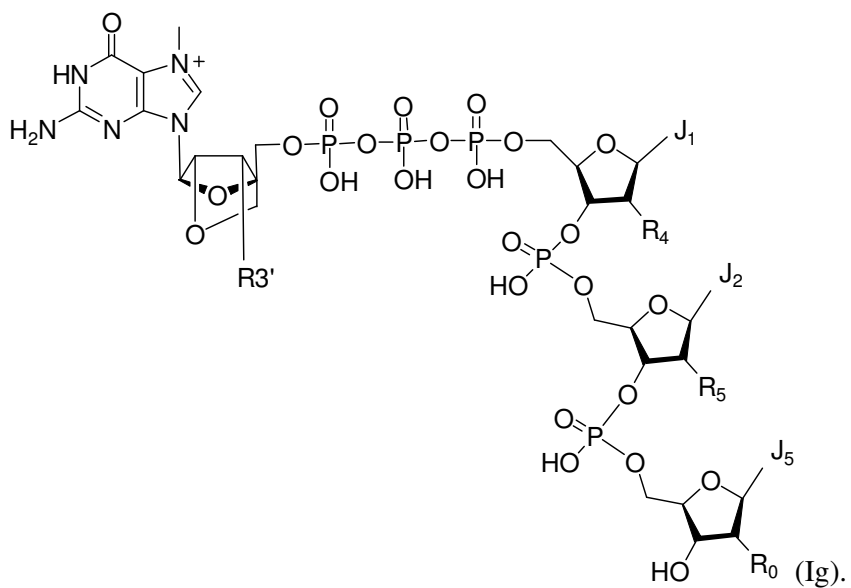
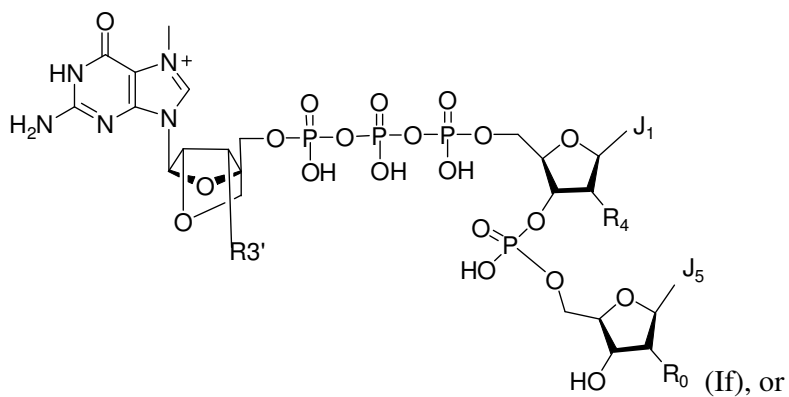
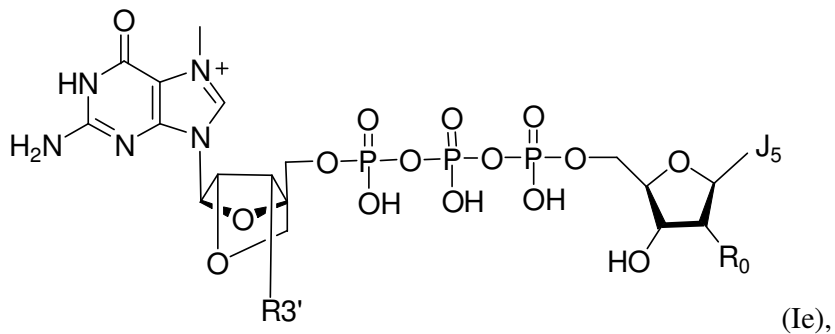
In another preferred embodiment, the compound has a structure of Formula (Id):



R₃' has a meaning the same as that defined above with respect to R₃, and

the remaining groups have the meanings same as those defined above.

In a preferred embodiment, the compound has a structure of Formula (Ie), Formula (If) or Formula (Ig):



In a preferred embodiment, R₀ is -F or -Cl, and/or

R₄ and R₅ are each independently any one selected from the group consisting of H, OH, OCH₃, F, Cl, -CN, and -SH, and preferably any one selected from the group consisting of H, OH, OCH₃, and

F.

In a most preferred embodiment, the compound has one of the structures shown in Table 1.

In a preferred embodiment, the compound of the present invention is present in the form of a pharmaceutically acceptable salt, and preferably in the form of a triethylamine salt, a sodium salt, a potassium salt, an ammonium salt, or tris(hydroxymethyl)aminomethane hydrochloride.

Another aspect of the present invention relates to a use of the compound as described above as an *in vitro* co-transcriptional RNA capping reagent.

Yet another aspect of the present invention relates to an RNA molecule including the compound as described above as a cap structure or a cap structure fragment.

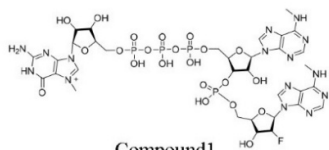
Still another aspect of the present invention relates to a pharmaceutical composition including the RNA molecule as described above, and a pharmaceutically acceptable carrier.

The present invention also relates to a method for synthesizing an RNA molecule, which includes incubating the compound as described above with a polynucleotide template in order to perform a template-based transcription.

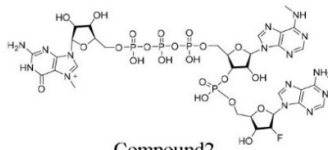
The present invention further relates to a transcriptional RNA-capping reaction system which includes a polynucleotide template, the compound as described above, NTPs, and a RNA polymerase.

According to some embodiments of the present invention, the compound (or cap analog) has one of the structures shown in Table 1 below:

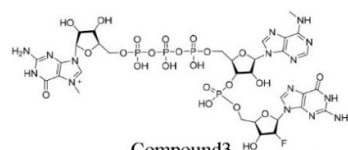
Table 1:



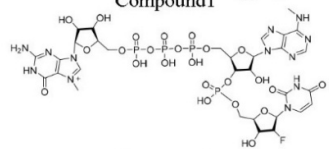
Compound1



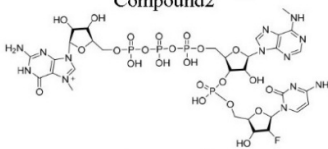
Compound2



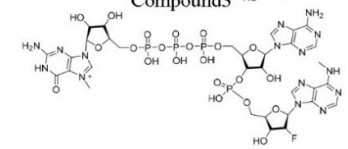
Compound3



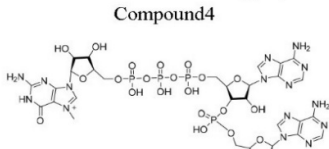
Compound4



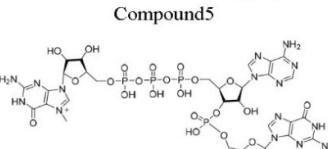
Compound5



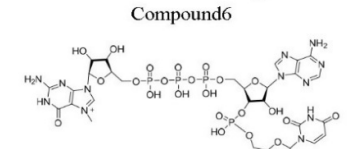
Compound6



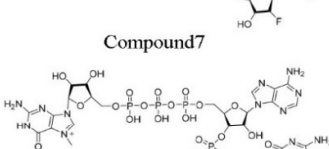
Compound7



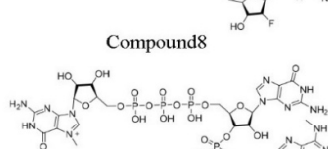
Compound8



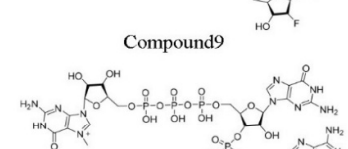
Compound9



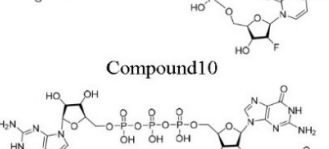
Compound10



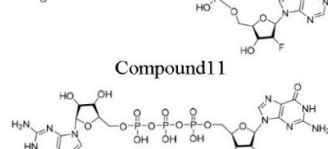
Compound11



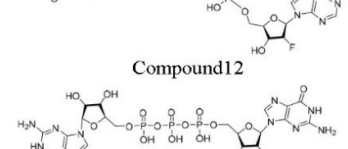
Compound12



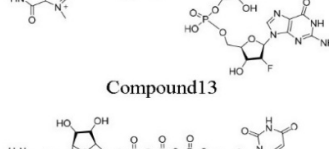
Compound13



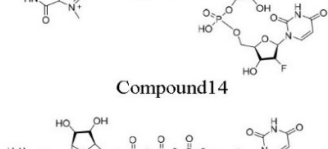
Compound14



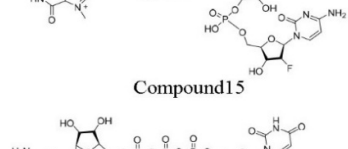
Compound15



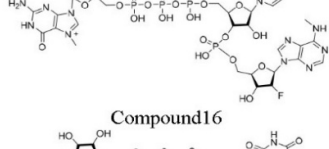
Compound16



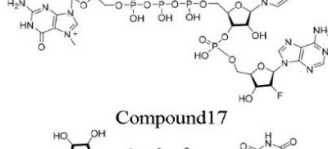
Compound17



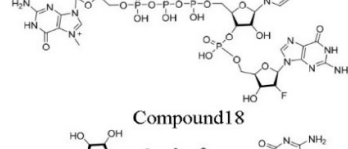
Compound18



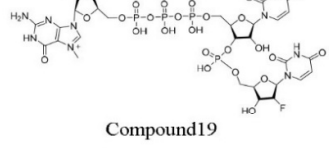
Compound19



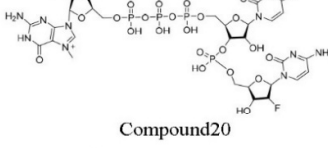
Compound20



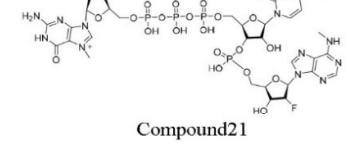
Compound21



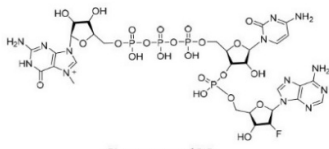
Compound22



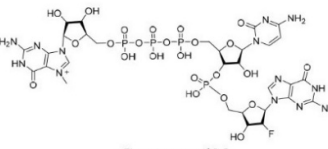
Compound23



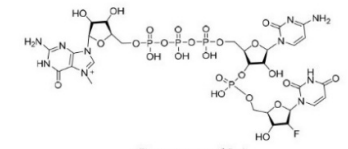
Compound24



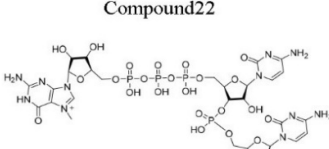
Compound25



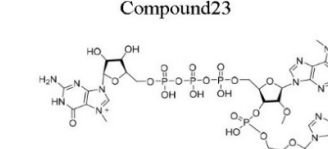
Compound26



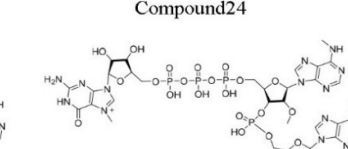
Compound27



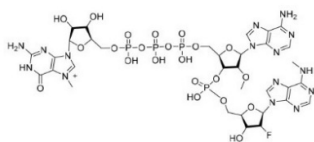
Compound28



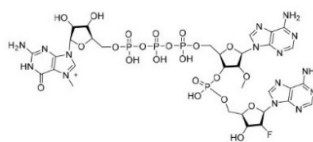
Compound29



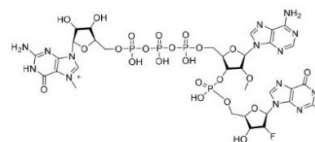
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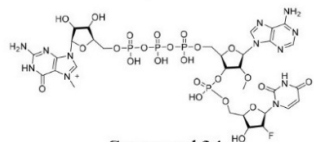
Compound 31



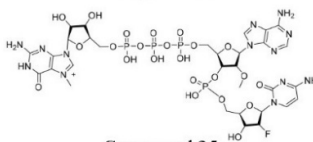
Compound 32



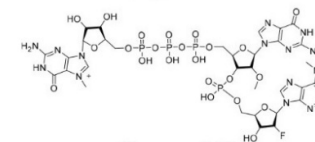
Compound 33



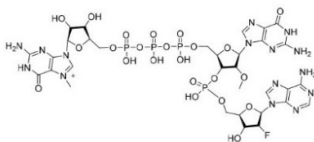
Compound 34



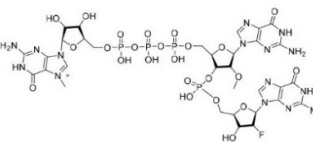
Compound 35



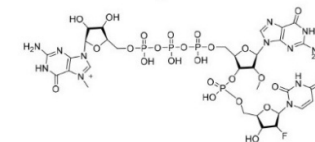
Compound 36



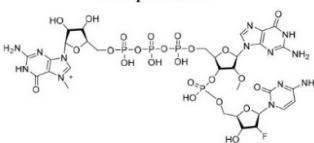
Compound 37



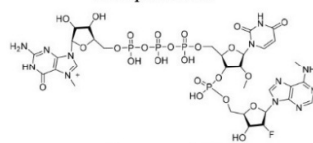
Compound 38



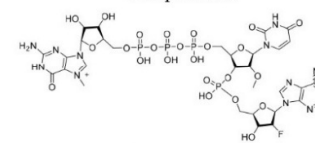
Compound 39



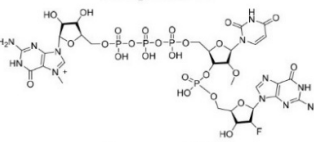
Compound 40



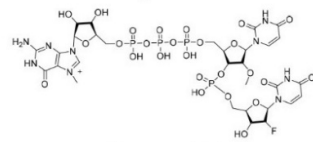
Compound 41



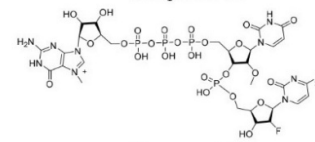
Compound 42



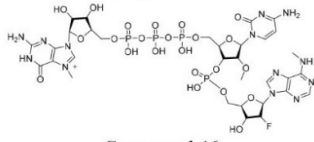
Compound 43



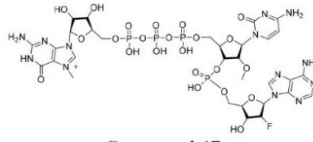
Compound 44



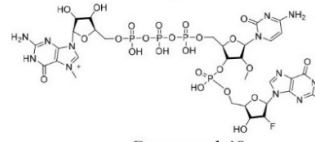
Compound 45



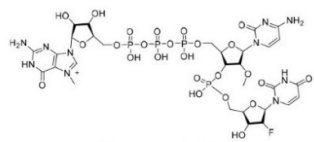
Compound 46



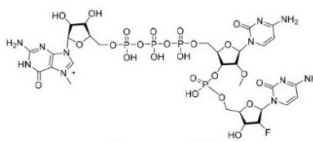
Compound 47



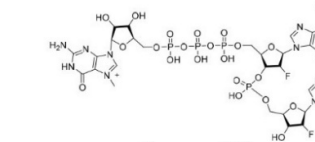
Compound 48



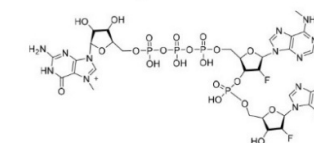
Compound 49



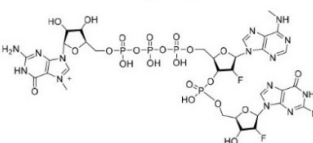
Compound 50



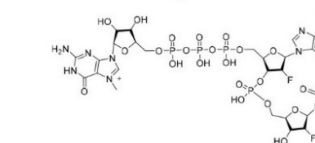
Compound 51



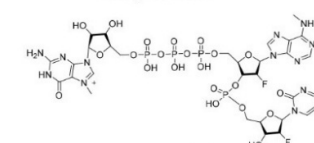
Compound 52



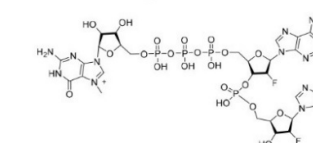
Compound 53



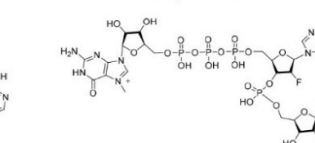
Compound 54



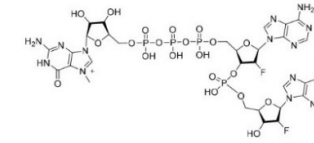
Compound 55



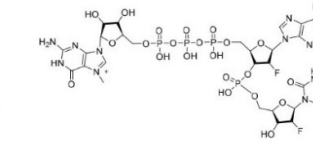
Compound 56



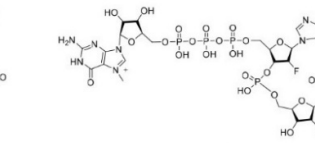
Compound 57



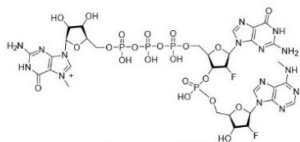
Compound 58



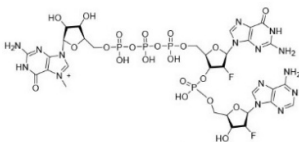
Compound 59



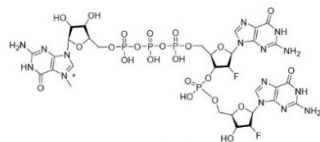
Compound 60



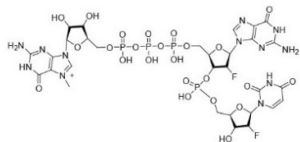
Compound 61



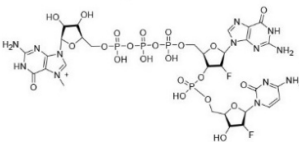
Compound 62



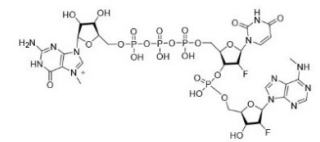
Compound 63



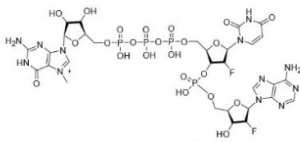
Compound 64



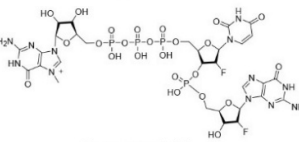
Compound 65



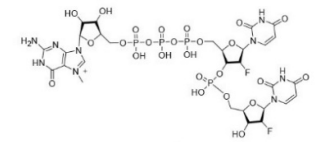
Compound 66



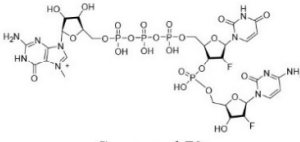
Compound 67



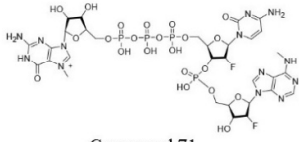
Compound 68



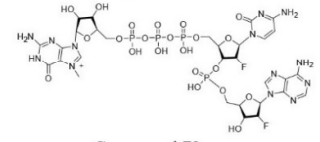
Compound 69



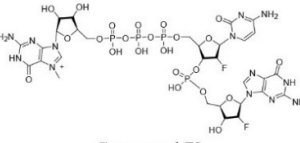
Compound 70



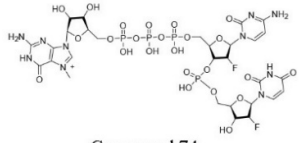
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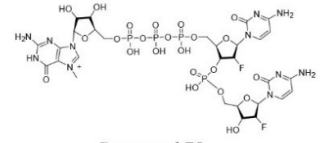
Compound 72



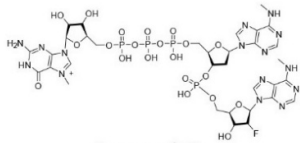
Compound 73



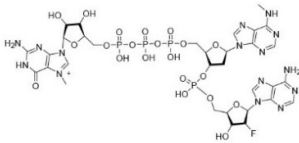
Compound 74



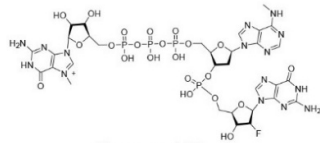
Compound 75



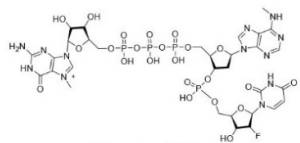
Compound 76



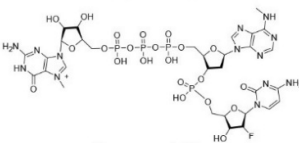
Compound 77



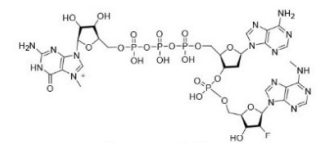
Compound 78



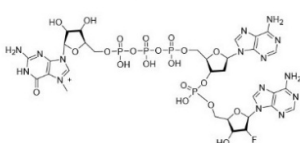
Compound 79



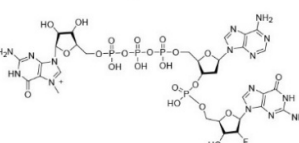
Compound 80



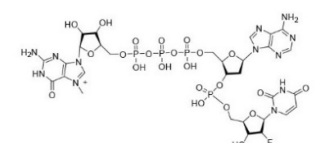
Compound 81



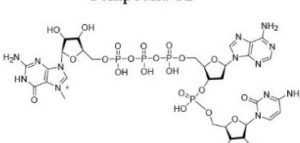
Compound 82



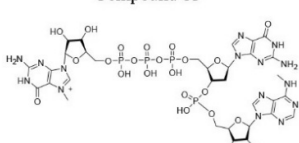
Compound 83



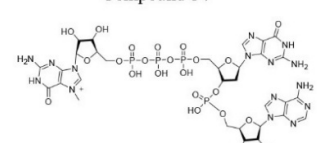
Compound 84



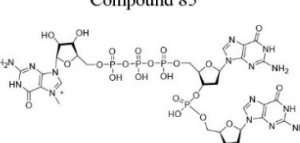
Compound 85



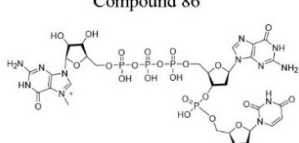
Compound 86



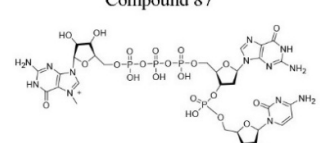
Compound 87



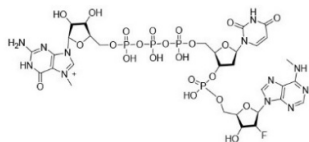
Compound 88



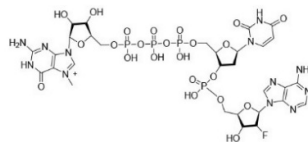
Compound 89



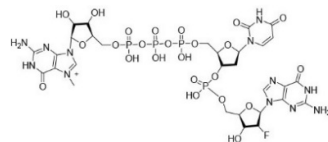
Compound 90



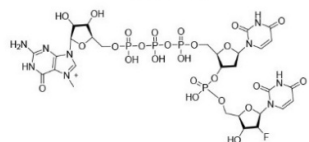
Compound 91



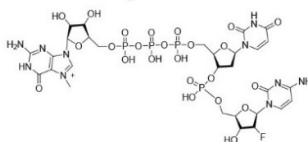
Compound 92



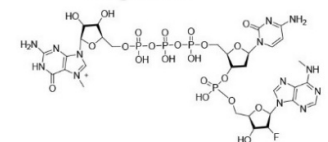
Compound 93



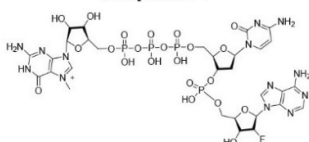
Compound 94



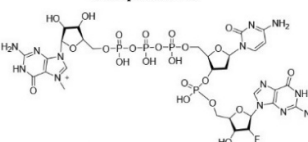
Compound 95



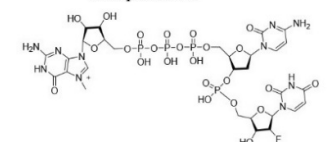
Compound 96



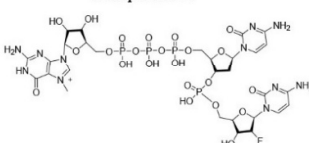
Compound 97



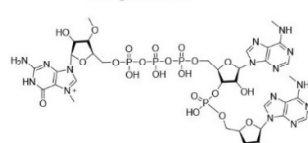
Compound 98



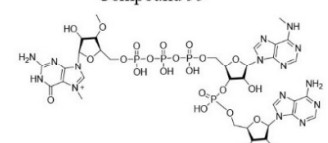
Compound 99



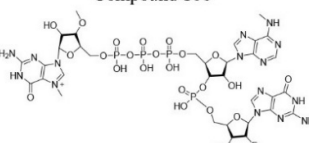
Compound 100



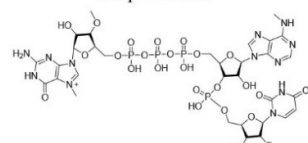
Compound 101



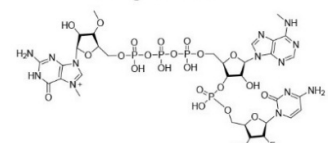
Compound 102



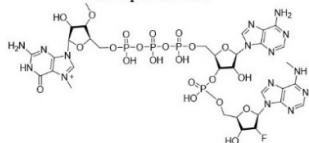
Compound 103



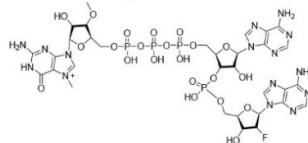
Compound 104



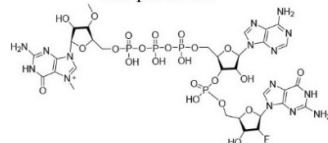
Compound 105



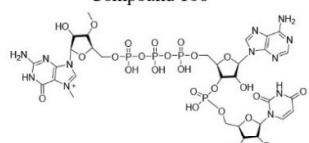
Compound 106



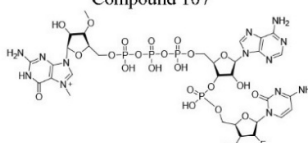
Compound 107



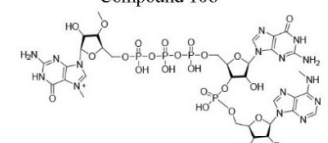
Compound 108



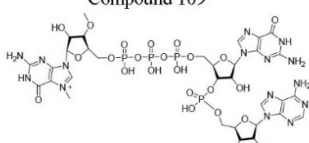
Compound 109



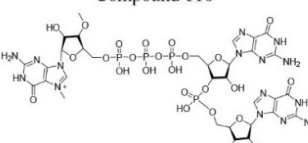
Compound 110



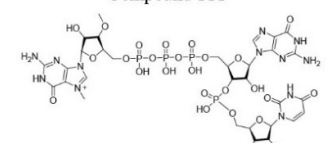
Compound 111



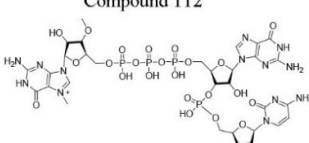
Compound 112



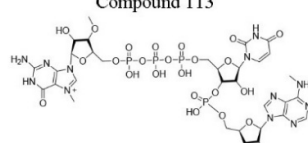
Compound 113



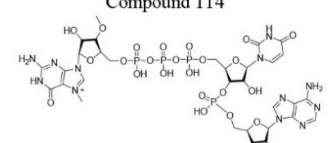
Compound 114



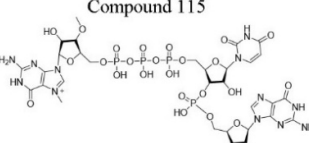
Compound 115



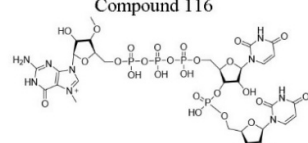
Compound 116



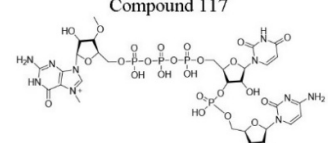
Compound 117



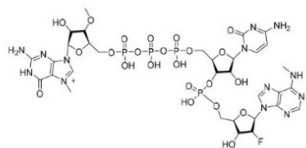
Compound 118



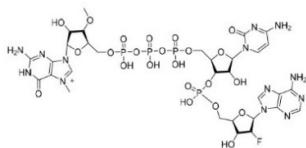
Compound 119



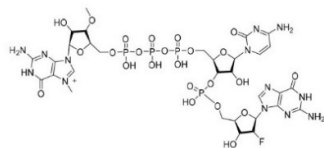
Compound 120



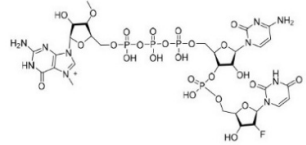
Compound 121



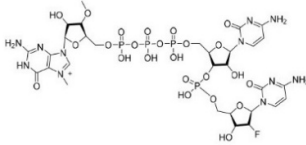
Compound 122



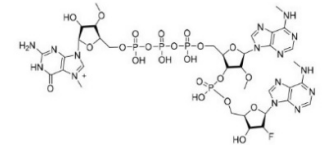
Compound 123



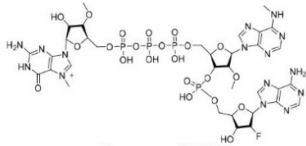
Compound 124



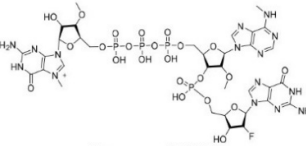
Compound 125



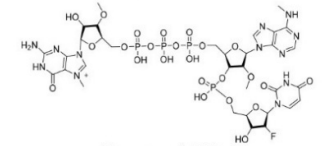
Compound 126



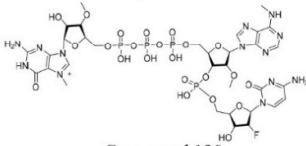
Compound 127



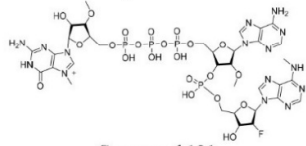
Compound 128



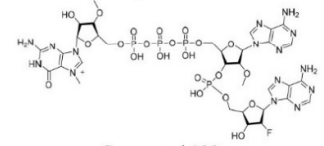
Compound 129



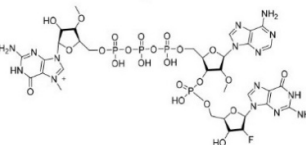
Compound 130



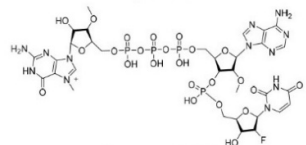
Compound 131



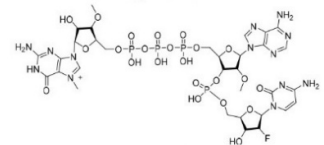
Compound 132



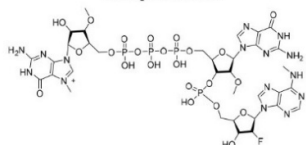
Compound 133



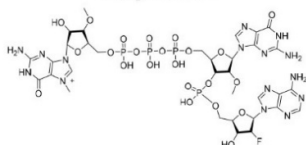
Compound 134



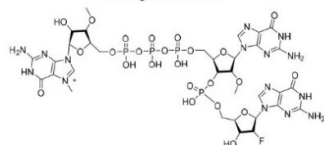
Compound 135



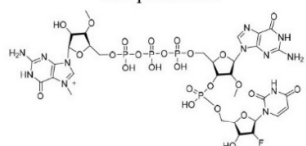
Compound 136



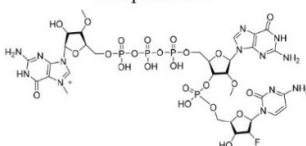
Compound 137



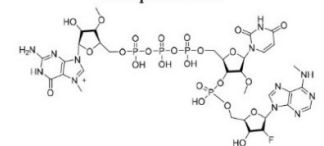
Compound 138



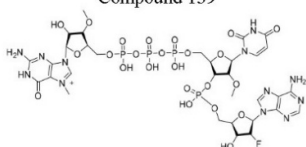
Compound 139



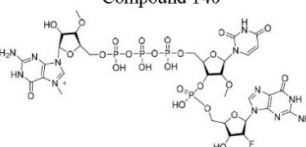
Compound 140



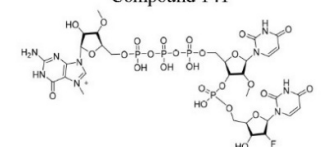
Compound 141



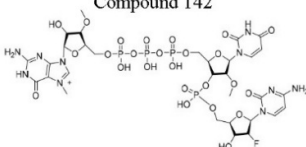
Compound 142



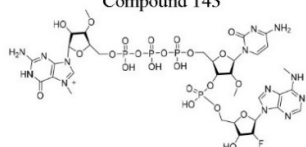
Compound 143



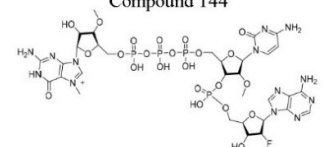
Compound 144



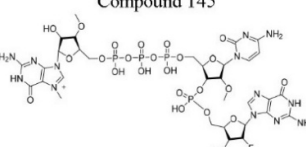
Compound 145



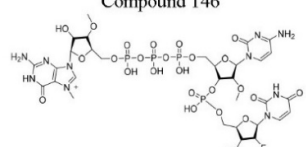
Compound 146



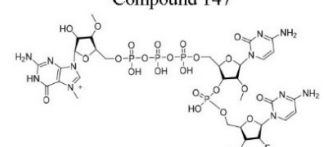
Compound 147



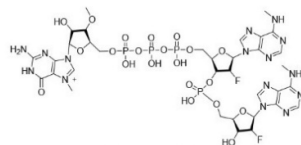
Compound 148



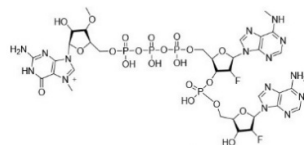
Compound 149



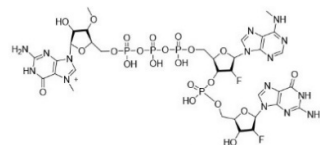
Compound 150



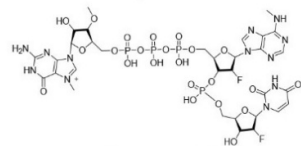
Compound 151



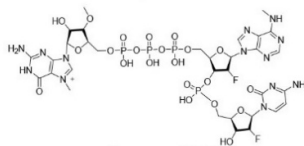
Compound 152



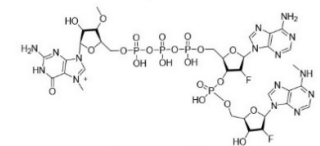
Compound 153



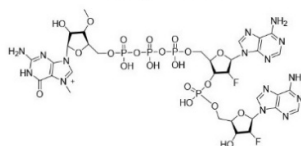
Compound 154



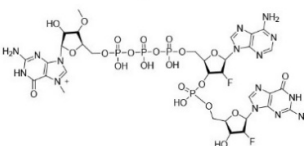
Compound 155



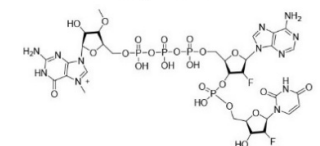
Compound 156



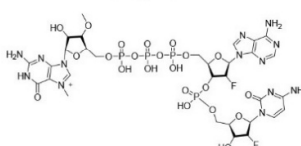
Compound 157



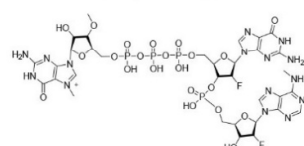
Compound 158



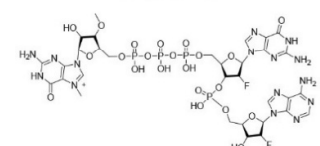
Compound 159



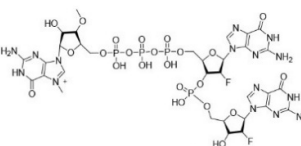
Compound 160



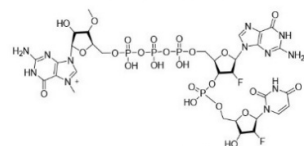
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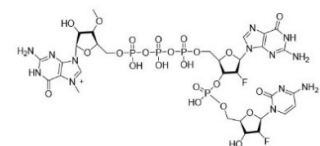
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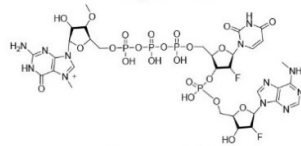
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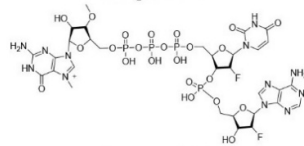
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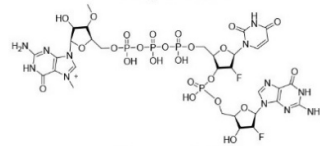
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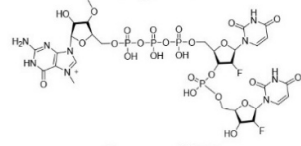
Compound 166



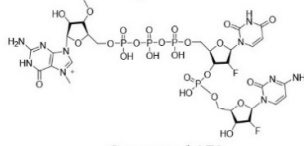
Compound 167



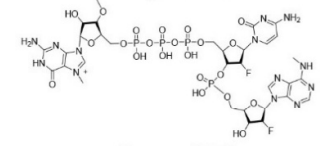
Compound 168



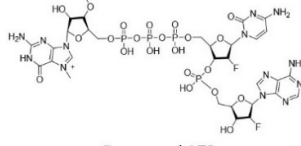
Compound 169



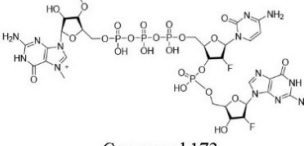
Compound 170



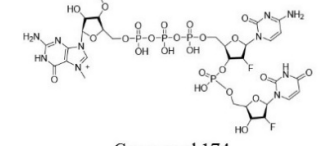
Compound 171



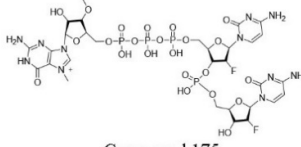
Compound 172



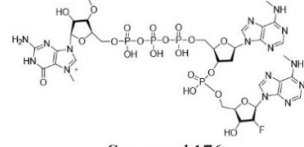
Compound 173



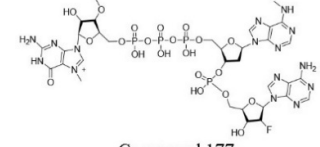
Compound 174



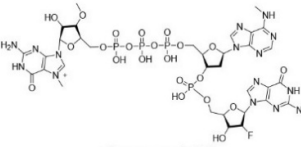
Compound 175



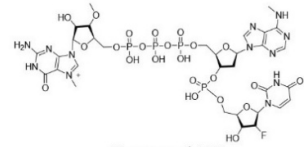
Compound 176



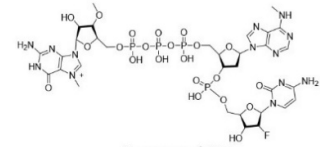
Compound 177



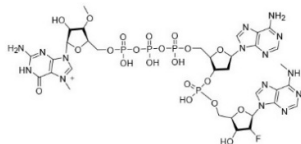
Compound 178



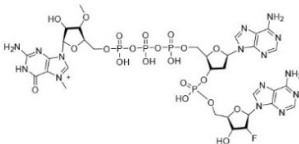
Compound 179



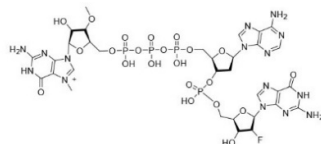
Compound 180



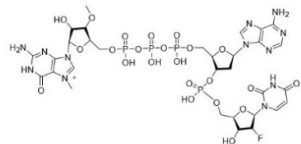
Compound 181



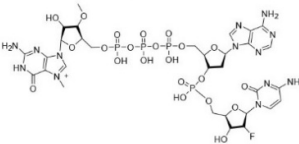
Compound 182



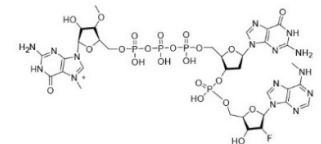
Compound 183



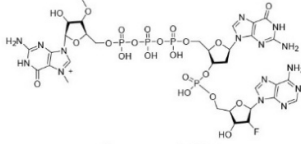
Compound 184



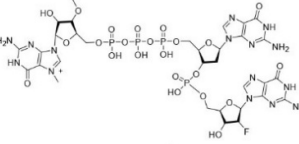
Compound 185



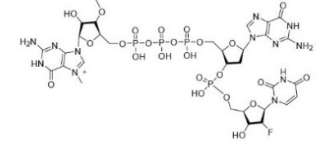
Compound 186



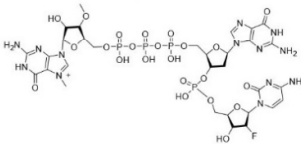
Compound 187



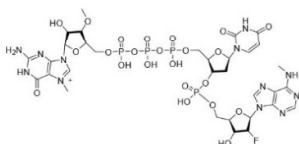
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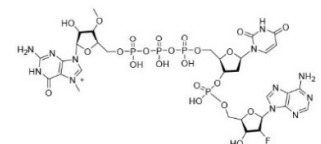
Compound 189



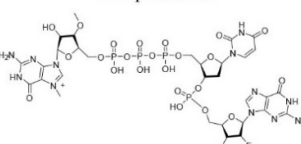
Compound 190



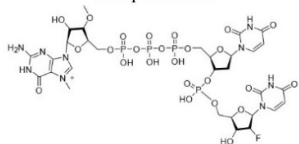
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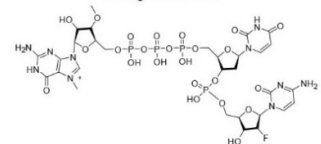
Compound 192



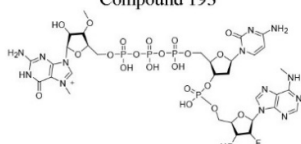
Compound 193



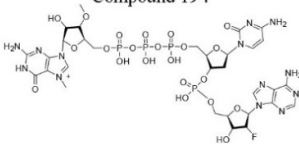
Compound 194



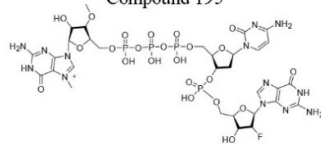
Compound 195



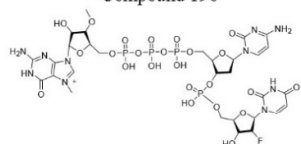
Compound 196



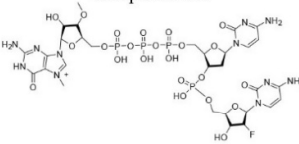
Compound 197



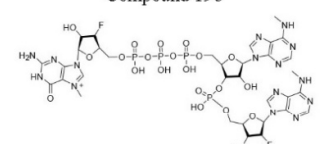
Compound 198



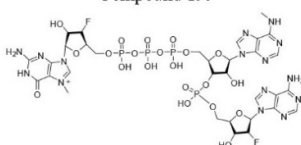
Compound 199



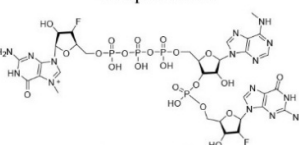
Compound 200



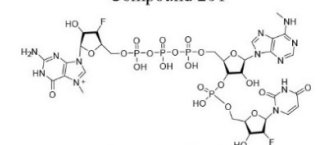
Compound 201



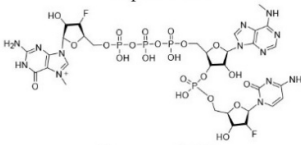
Compound 202



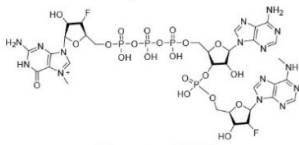
Compound 203



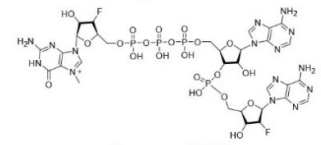
Compound 204



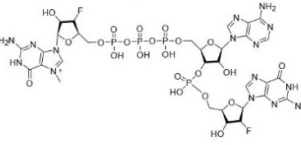
Compound 205



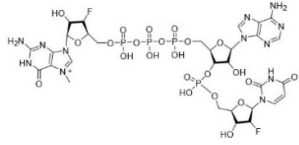
Compound 206



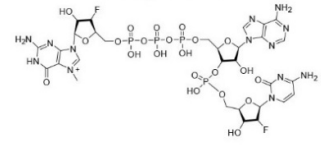
Compound 207



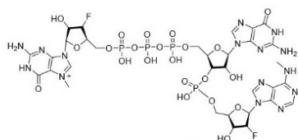
Compound 208



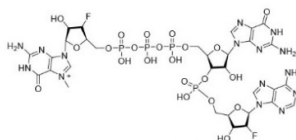
Compound 209



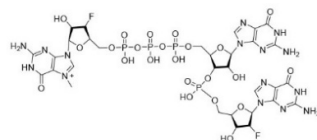
Compound 210



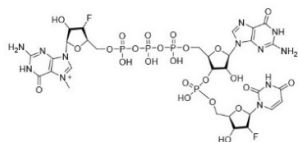
Compound 211



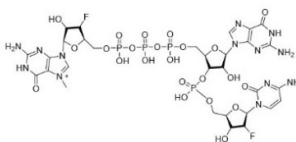
Compound 212



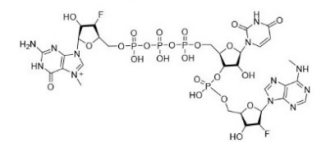
Compound 213



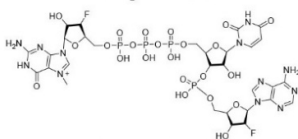
Compound 214



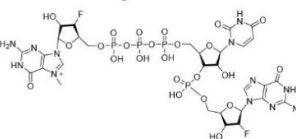
Compound 215



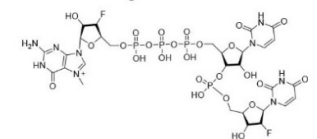
Compound 216



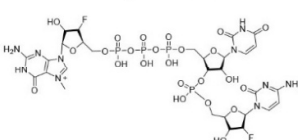
Compound 217



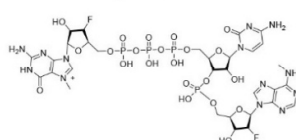
Compound 218



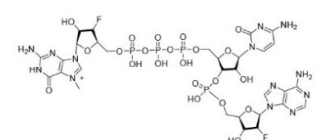
Compound 219



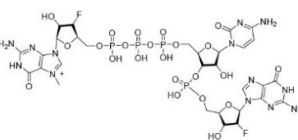
Compound 220



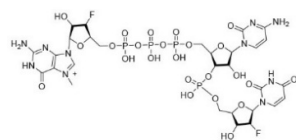
Compound 221



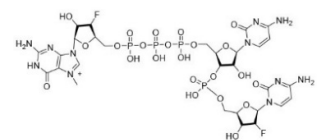
Compound 222



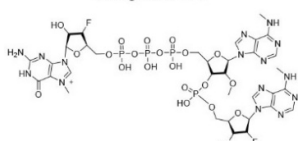
Compound 223



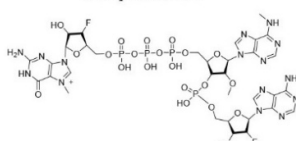
Compound 224



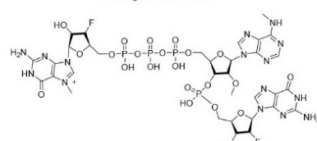
Compound 225



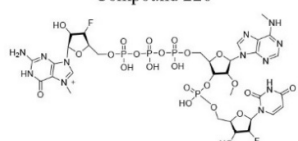
Compound 226



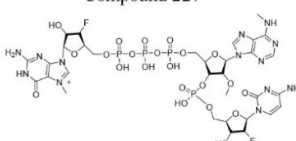
Compound 227



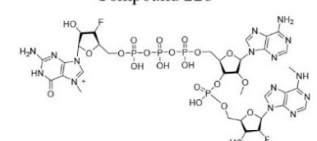
Compound 228



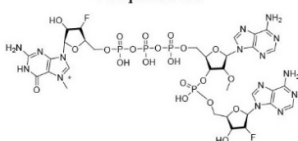
Compound 229



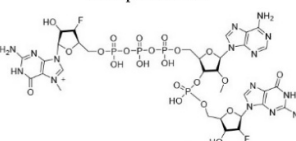
Compound 230



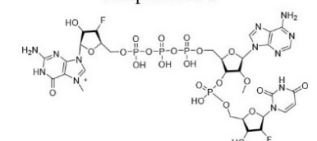
Compound 231



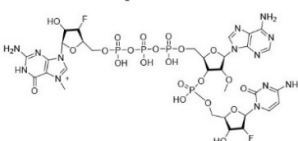
Compound 232



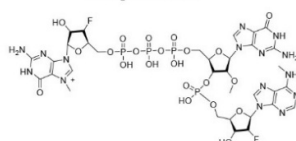
Compound 233



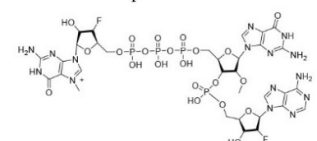
Compound 234



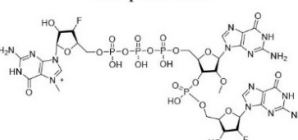
Compound 235



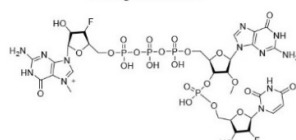
Compound 236



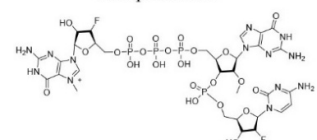
Compound 237



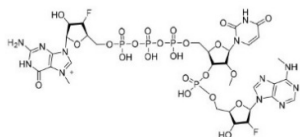
Compound 238



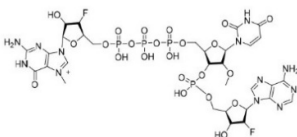
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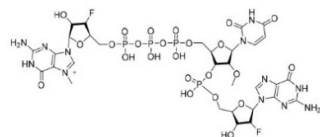
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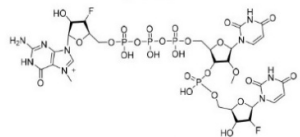
Compound 241



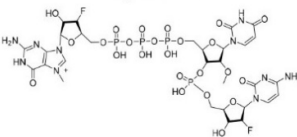
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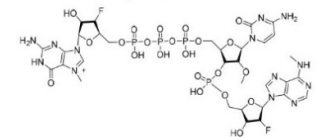
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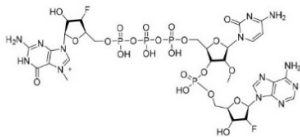
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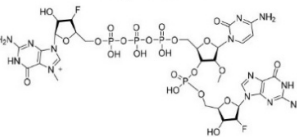
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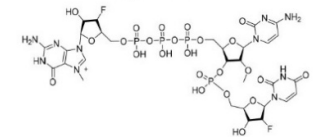
Compound 246



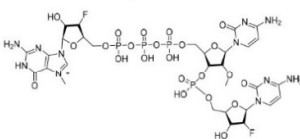
Compound 247



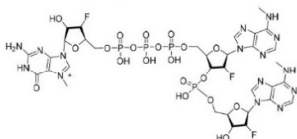
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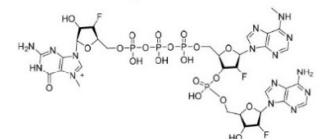
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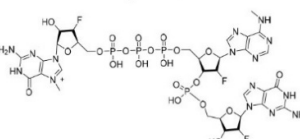
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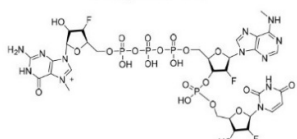
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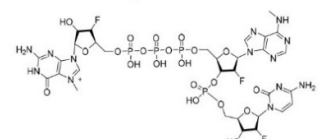
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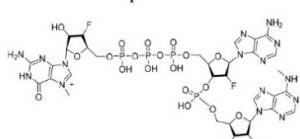
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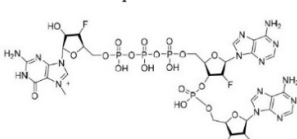
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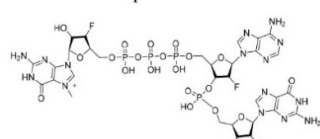
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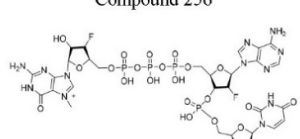
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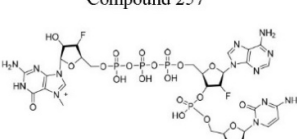
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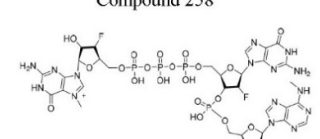
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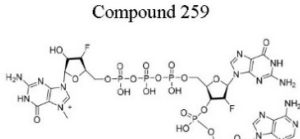
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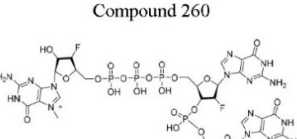
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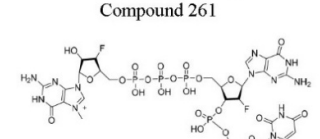
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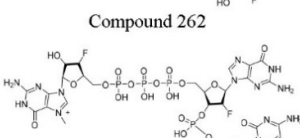
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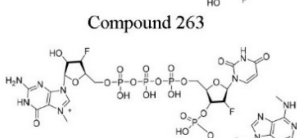
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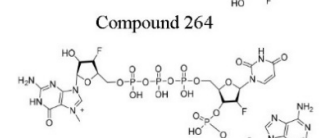
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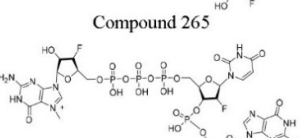
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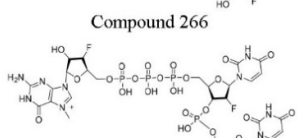
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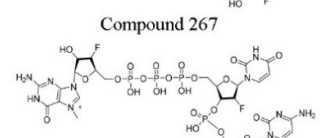
Compound 267



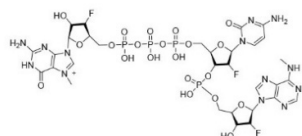
Compound 268



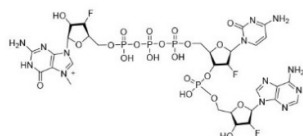
Compound 269



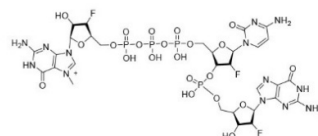
Compound 270



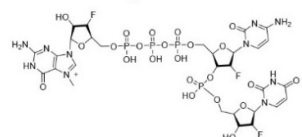
Compound 271



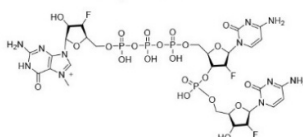
Compound 272



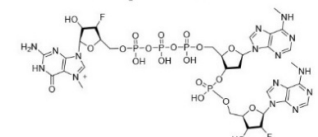
Compound 273



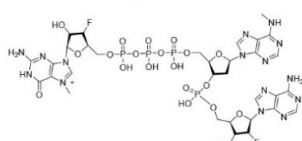
Compound 274



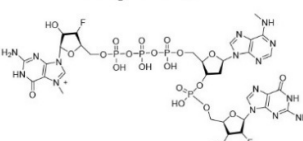
Compound 275



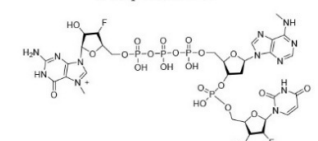
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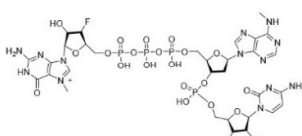
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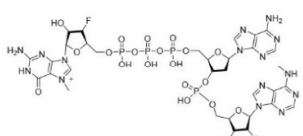
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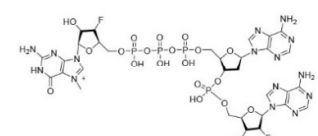
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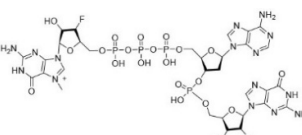
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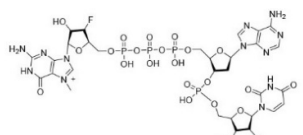
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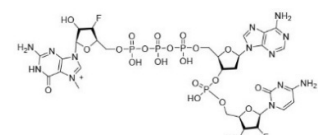
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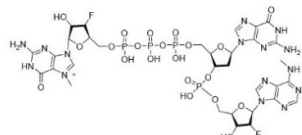
Compound 283



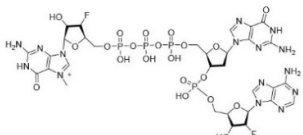
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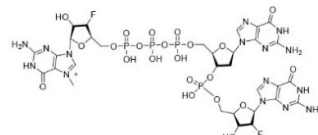
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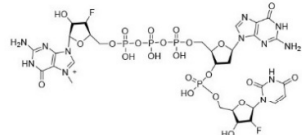
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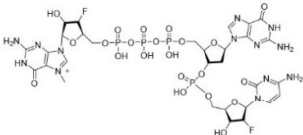
Compound 287



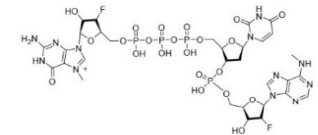
Compound 288



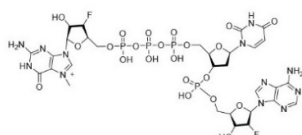
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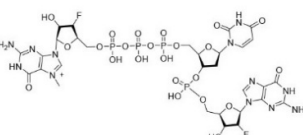
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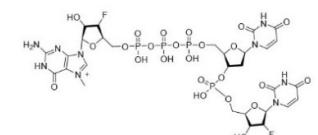
Compound 291



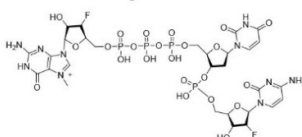
Compound 292



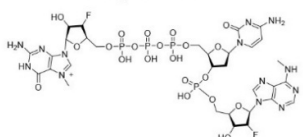
Compound 293



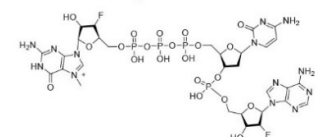
Compound 294



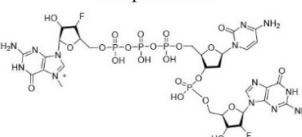
Compound 295



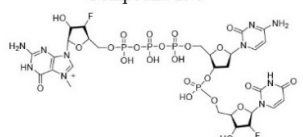
Compound 296



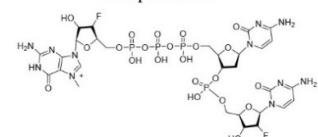
Compound 297



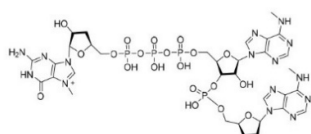
Compound 298



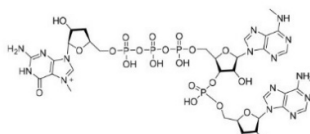
Compound 299



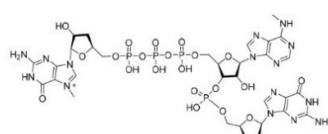
Compound 300



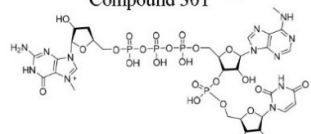
Compound 301



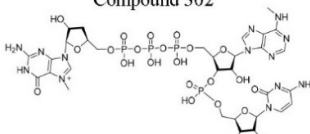
Compound 302



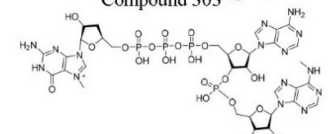
Compound 303



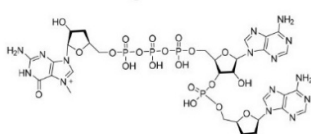
Compound 304



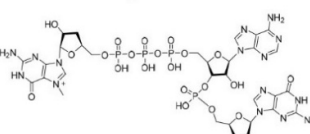
Compound 305



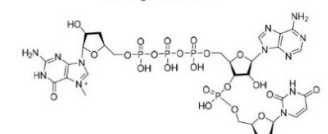
Compound 306



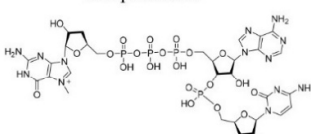
Compound 307



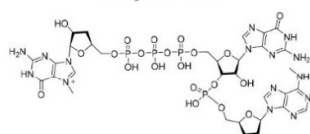
Compound 308



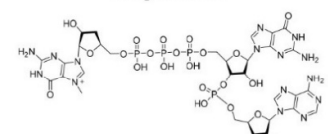
Compound 309



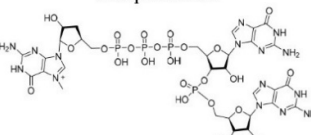
Compound 310



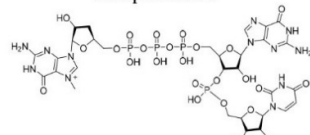
Compound 311



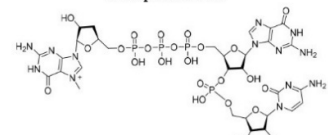
Compound 312



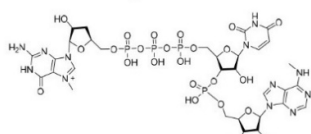
Compound 313



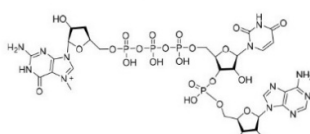
Compound 314



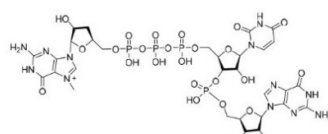
Compound 315



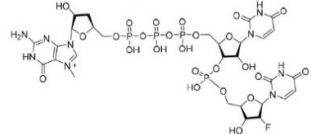
Compound 316



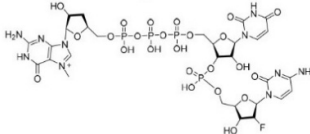
Compound 317



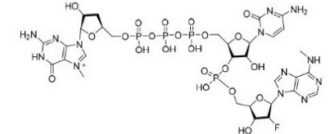
Compound 318



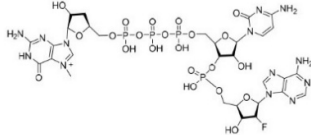
Compound 319



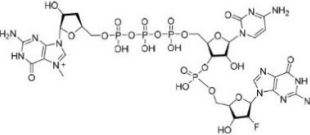
Compound 320



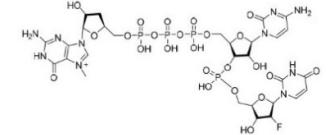
Compound 321



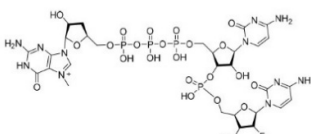
Compound 322



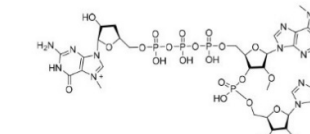
Compound 323



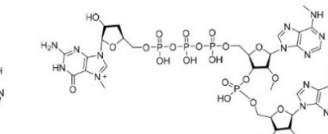
Compound 324



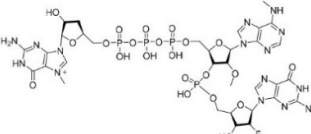
Compound 325



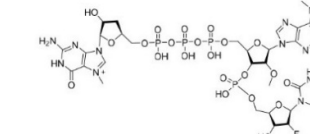
Compound 326



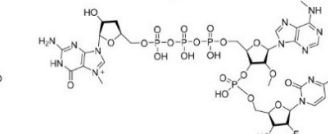
Compound 327



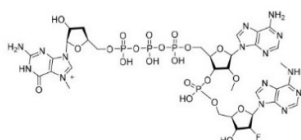
Compound 328



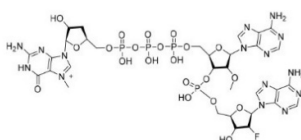
Compound 329



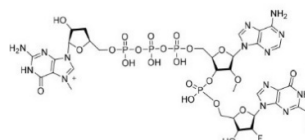
Compound 330



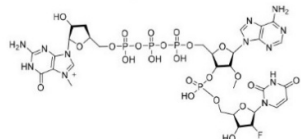
Compound 331



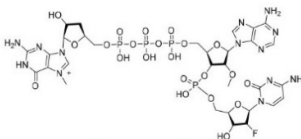
Compound 332



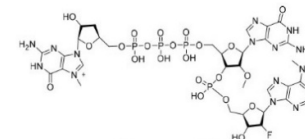
Compound 333



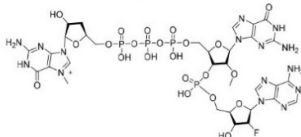
Compound 334



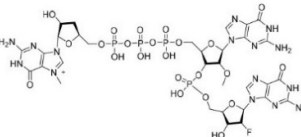
Compound 335



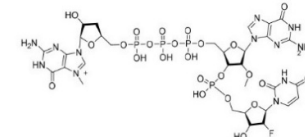
Compound 336



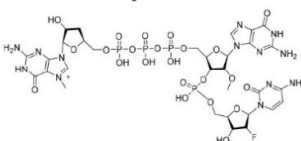
Compound 337



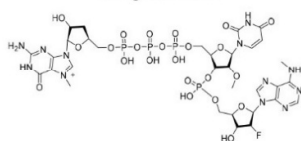
Compound 338



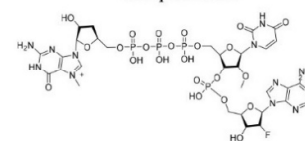
Compound 339



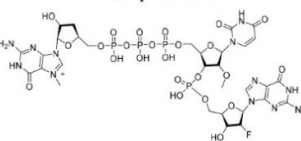
Compound 340



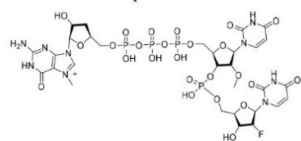
Compound 341



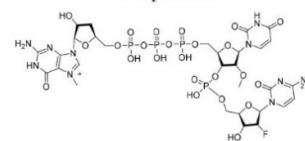
Compound 342



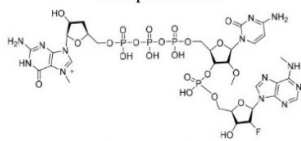
Compound 343



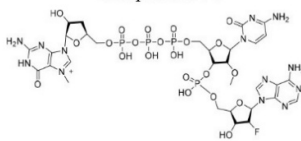
Compound 344



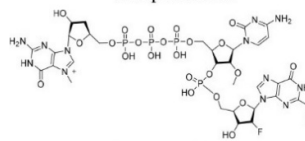
Compound 345



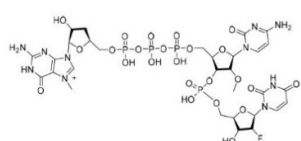
Compound 346



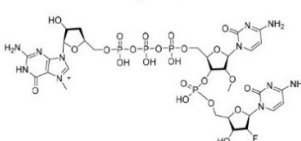
Compound 347



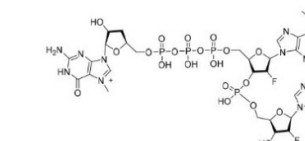
Compound 348



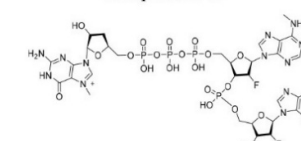
Compound 349



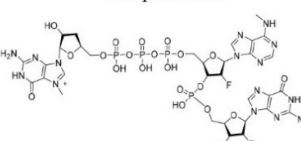
Compound 350



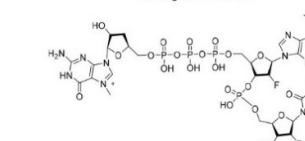
Compound 351



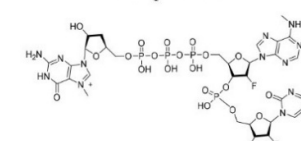
Compound 352



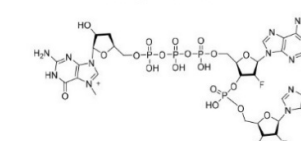
Compound 353



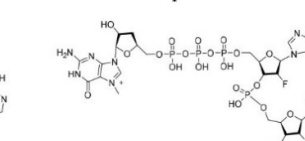
Compound 354



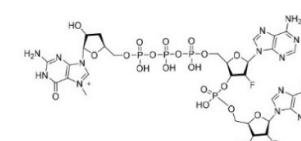
Compound 355



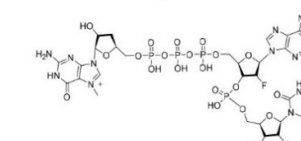
Compound 356



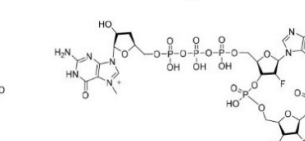
Compound 357



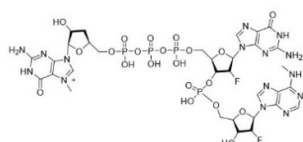
Compound 358



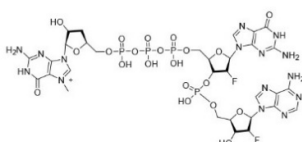
Compound 359



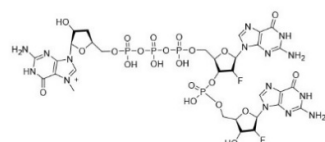
Compound 360



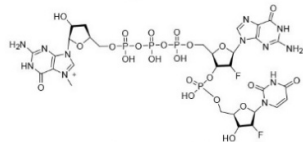
Compound 361



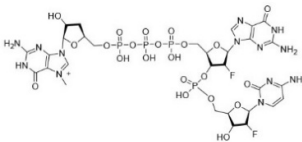
Compound 362



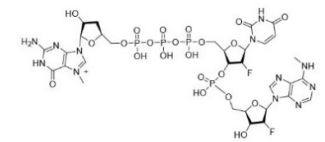
Compound 363



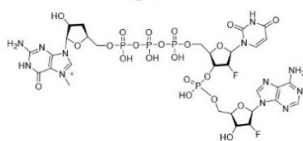
Compound 364



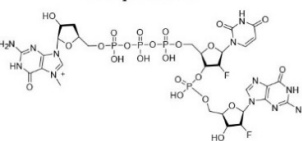
Compound 365



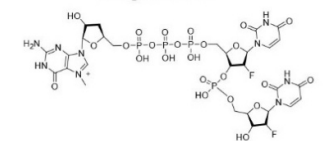
Compound 366



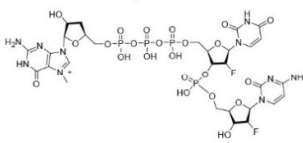
Compound 367



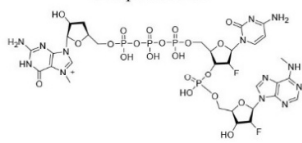
Compound 368



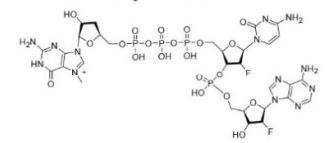
Compound 369



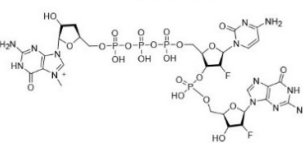
Compound 370



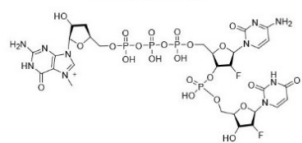
Compound 371



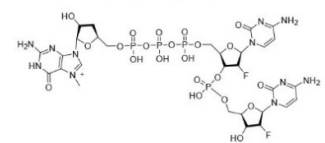
Compound 372



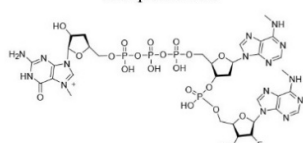
Compound 373



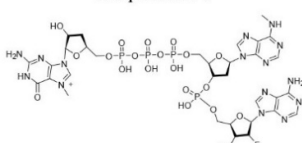
Compound 374



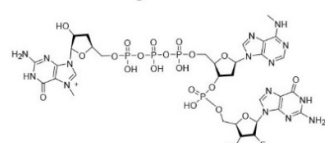
Compound 375



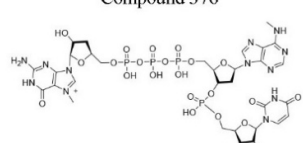
Compound 376



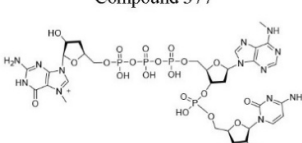
Compound 377



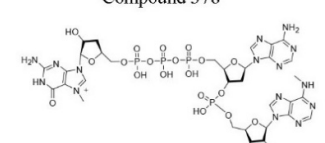
Compound 378



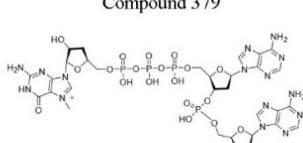
Compound 379



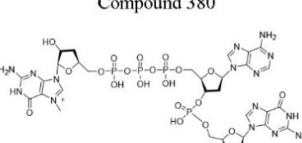
Compound 380



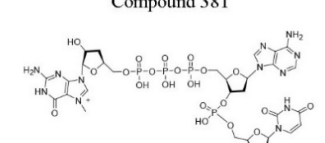
Compound 381



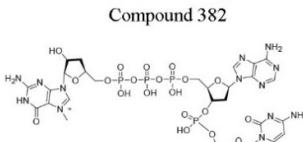
Compound 382



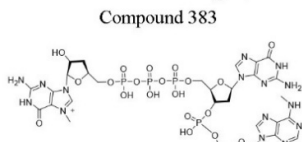
Compound 383



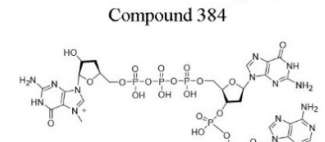
Compound 384



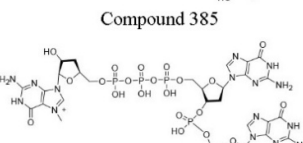
Compound 385



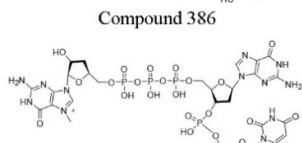
Compound 386



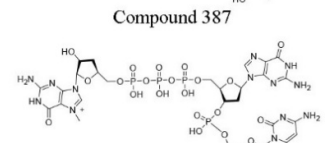
Compound 387



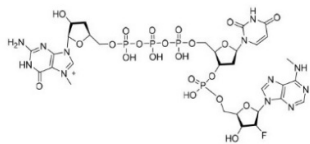
Compound 388



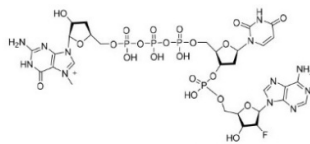
Compound 389



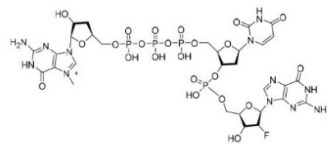
Compound 390



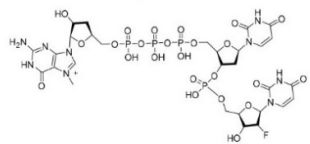
Compound 391



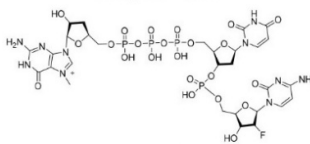
Compound 392



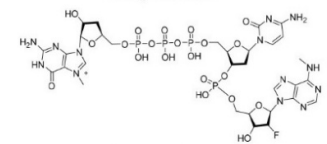
Compound 393



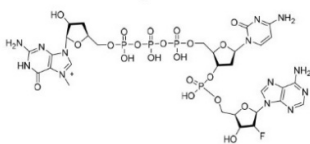
Compound 394



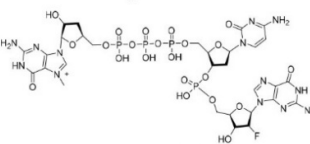
Compound 395



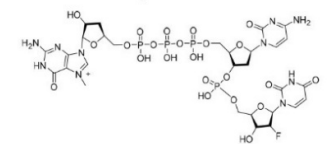
Compound 396



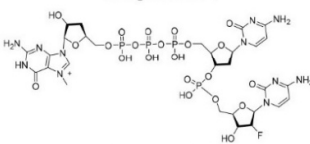
Compound 397



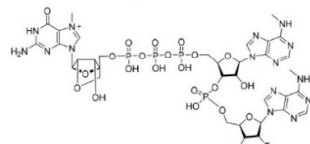
Compound 398



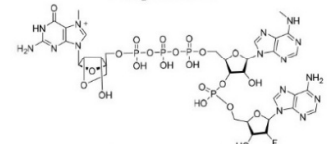
Compound 399



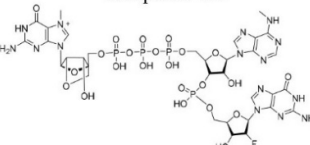
Compound 400



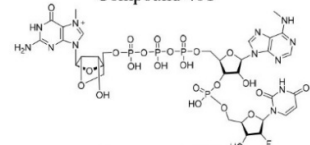
Compound 401



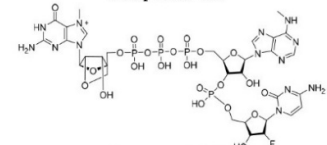
Compound 402



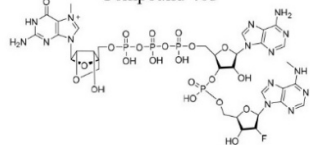
Compound 403



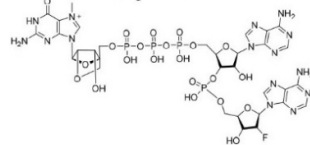
Compound 404



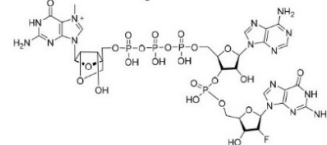
Compound 405



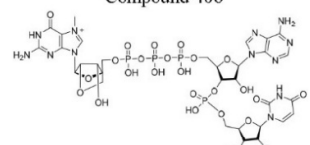
Compound 406



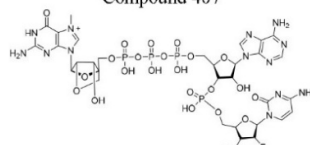
Compound 407



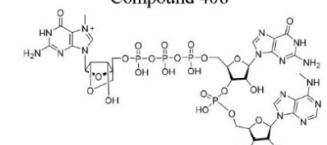
Compound 408



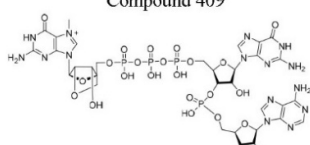
Compound 409



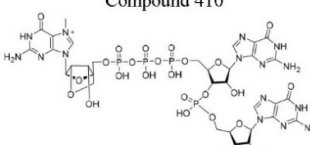
Compound 410



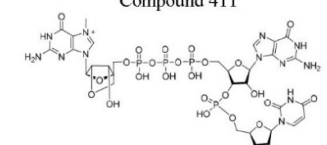
Compound 411



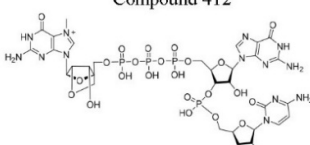
Compound 412



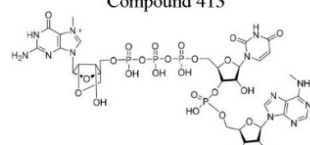
Compound 413



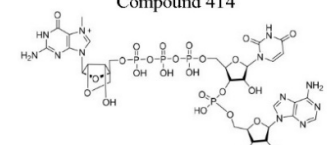
Compound 414



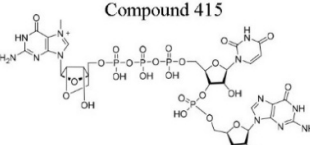
Compound 415



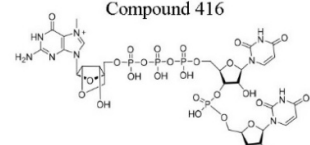
Compound 416



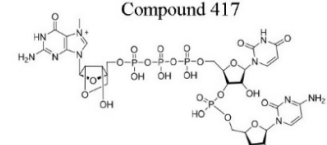
Compound 417



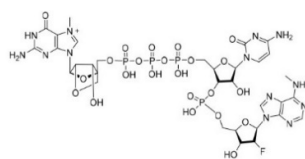
Compound 418



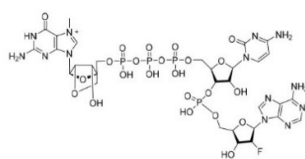
Compound 419



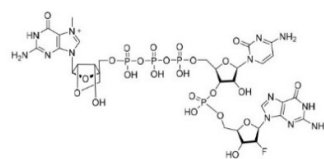
Compound 420



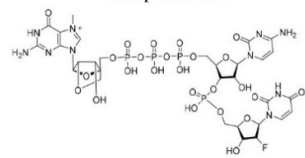
Compound 421



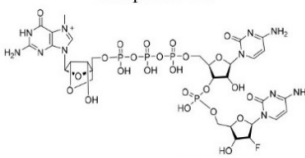
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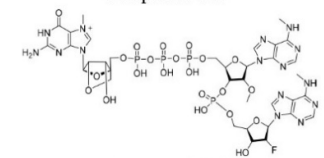
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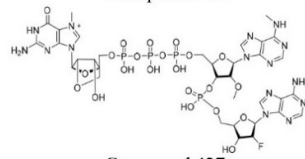
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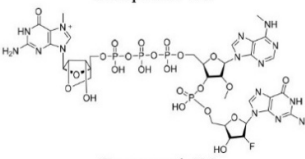
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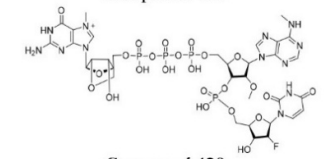
Compound 426



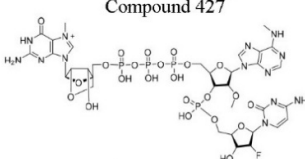
Compound 427



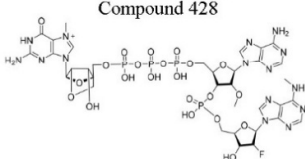
Compound 428



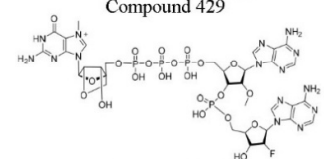
Compound 429



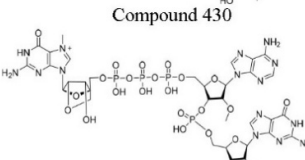
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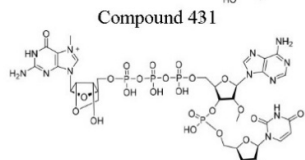
Compound 431



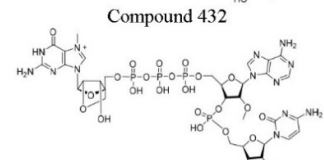
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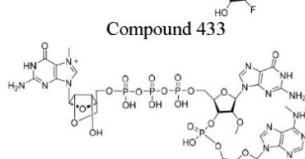
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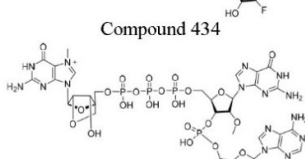
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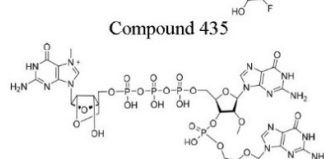
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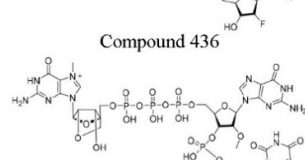
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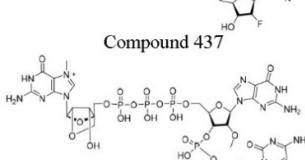
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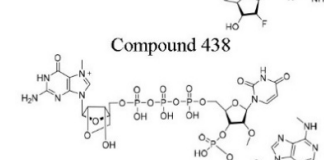
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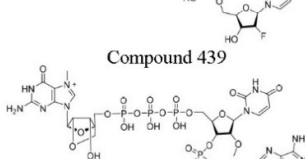
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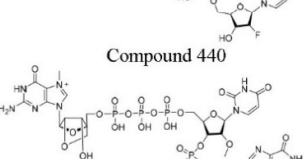
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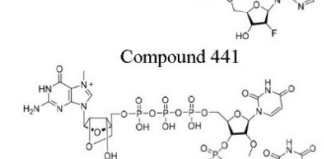
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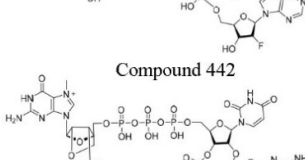
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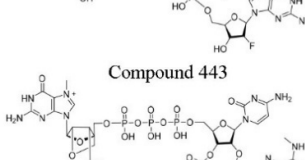
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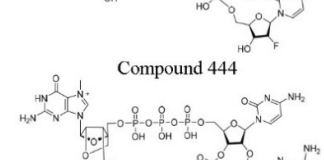
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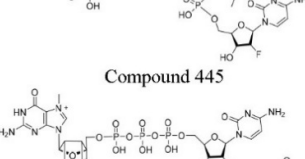
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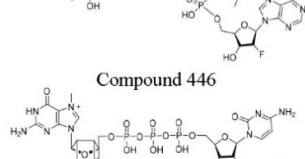
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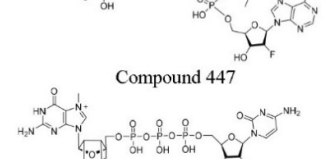
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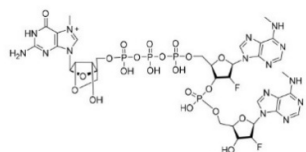
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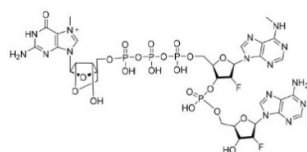
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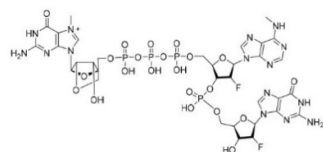
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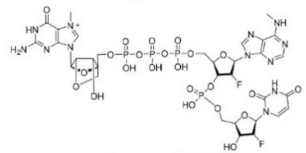
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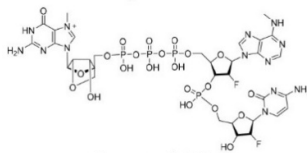
Compound 452



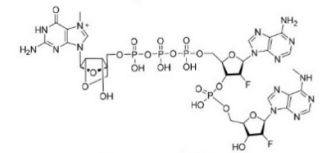
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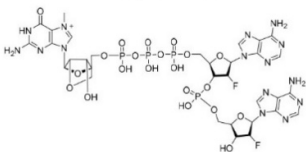
Compound 454



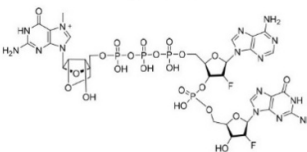
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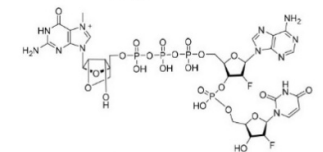
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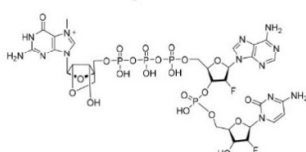
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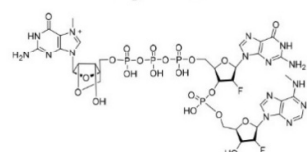
Compound 458



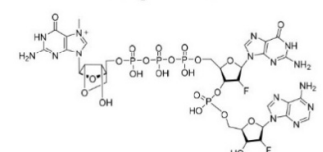
Compound 459



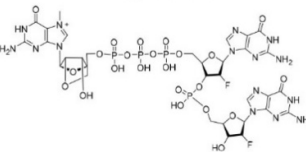
Compound 460



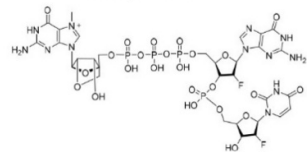
Compound 461



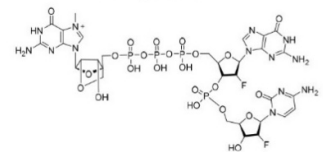
Compound 462



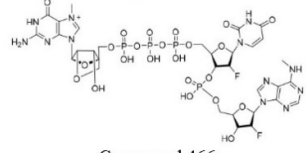
Compound 463



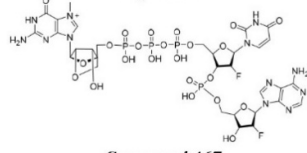
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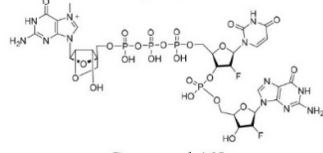
Compound 465



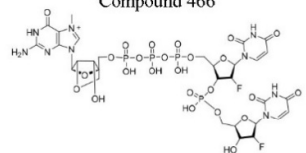
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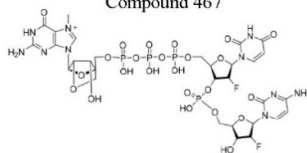
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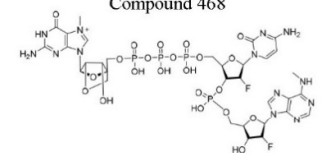
Compound 468



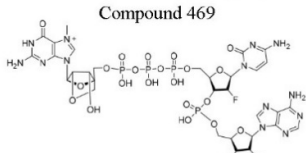
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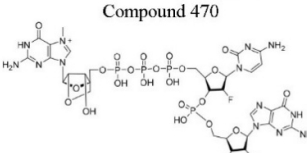
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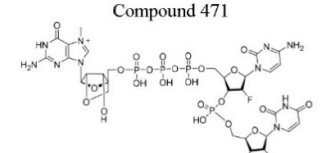
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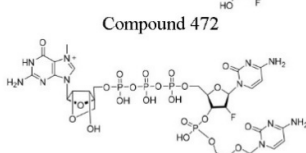
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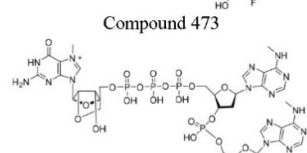
Compound 473



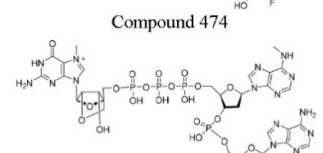
Compound 474



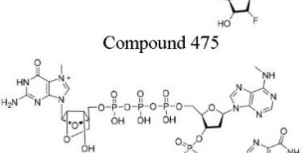
Compound 475



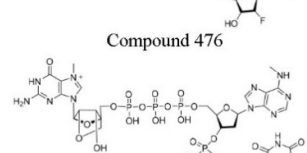
Compound 476



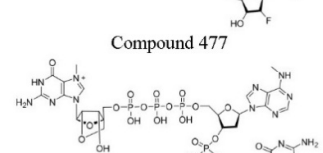
Compound 477



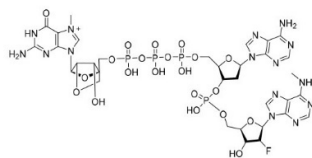
Compound 478



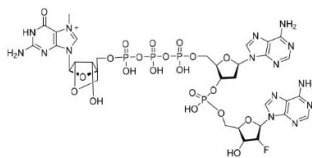
Compound 479



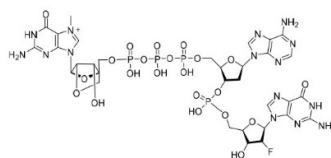
Compound 480



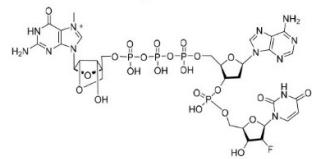
Compound 481



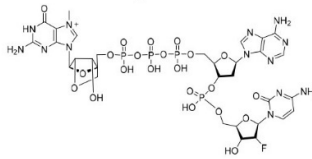
Compound 482



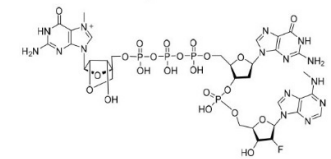
Compound 483



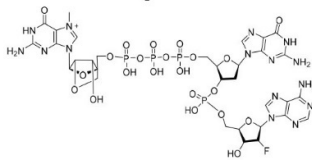
Compound 484



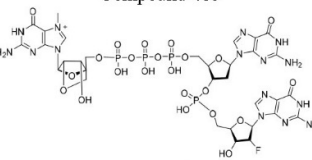
Compound 485



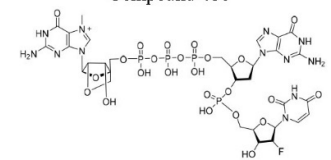
Compound 486



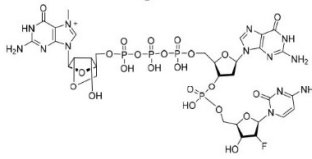
Compound 487



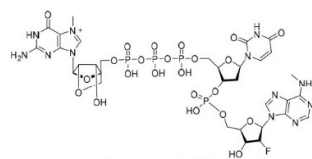
Compound 488



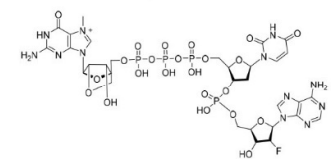
Compound 489



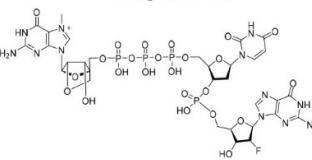
Compound 490



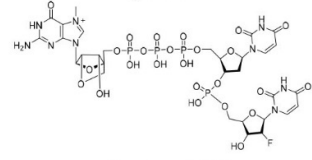
Compound 491



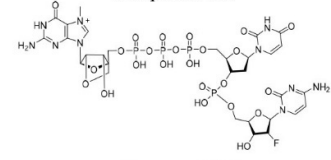
Compound 492



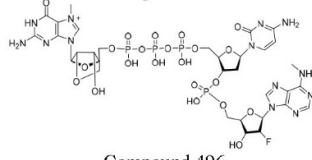
Compound 493



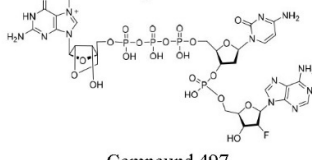
Compound 494



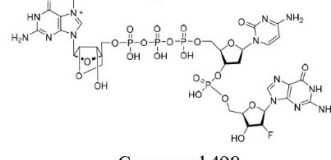
Compound 495



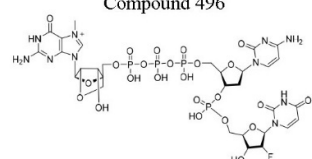
Compound 496



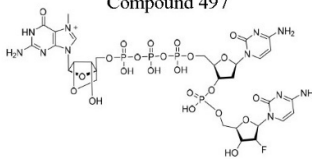
Compound 497



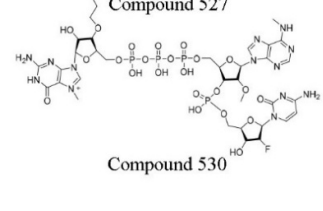
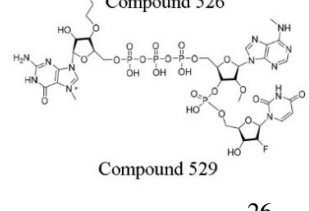
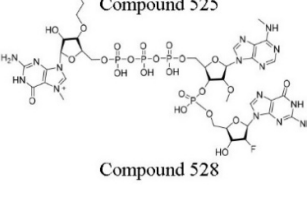
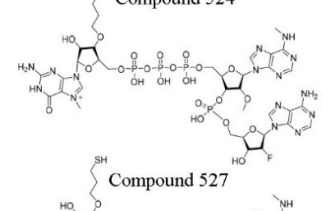
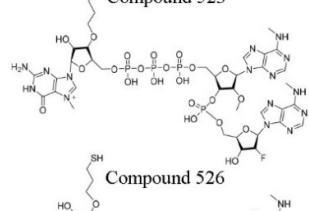
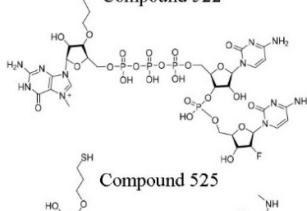
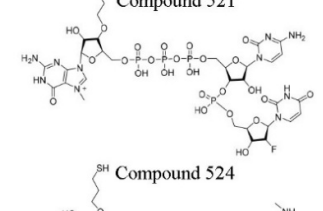
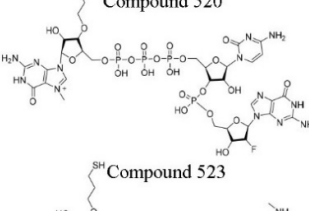
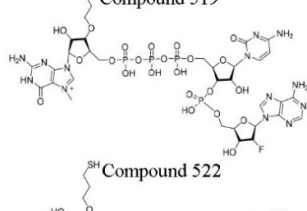
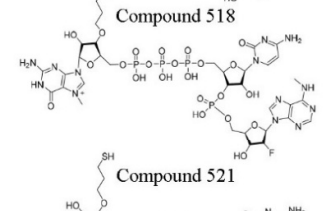
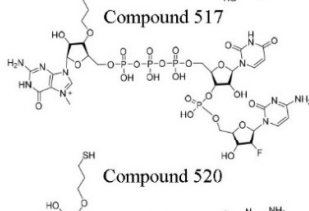
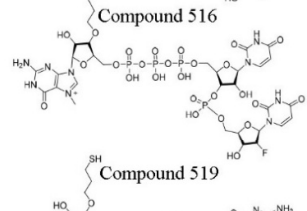
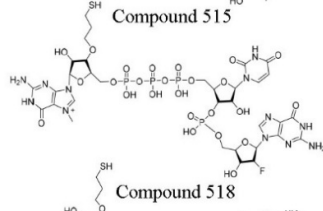
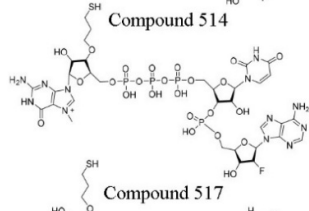
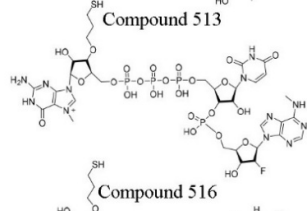
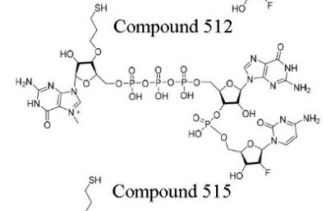
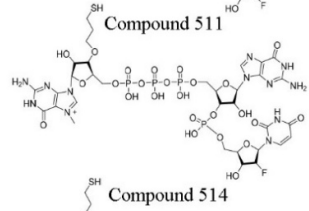
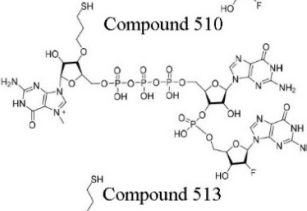
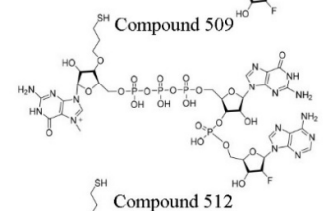
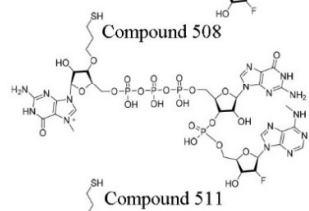
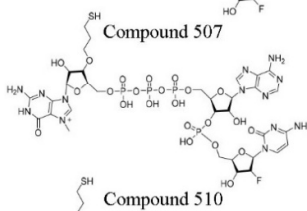
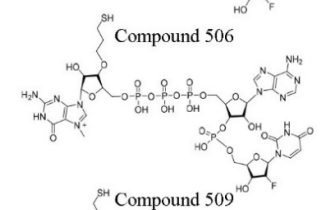
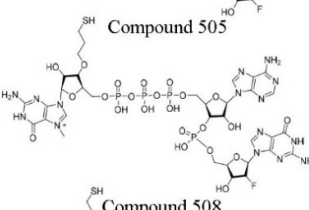
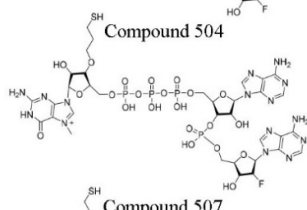
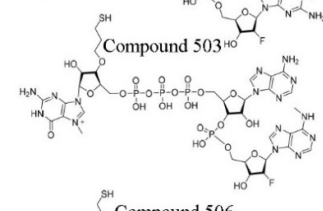
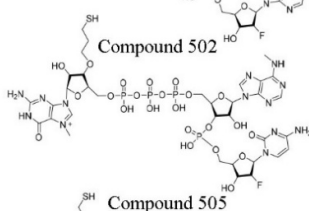
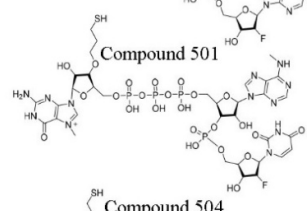
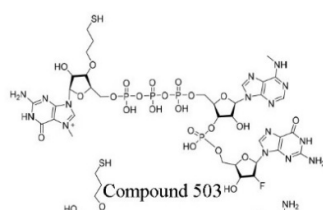
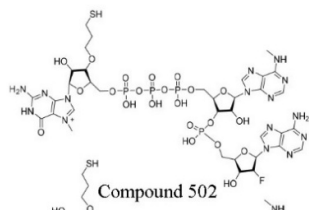
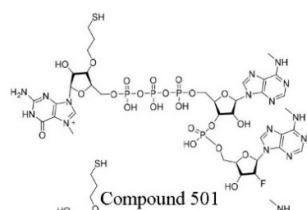
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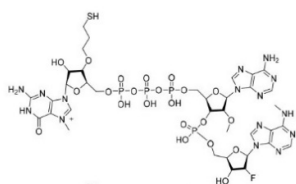


Compound 499

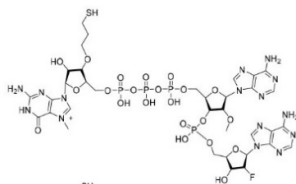


Compound 500

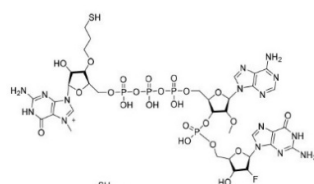




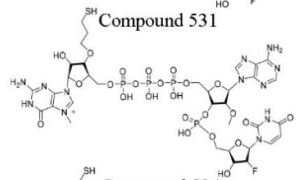
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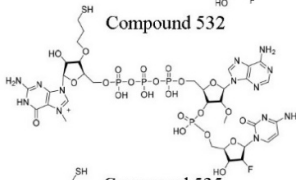
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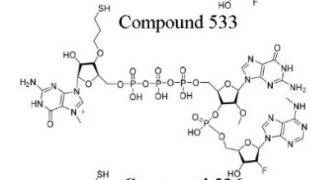
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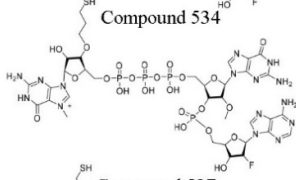
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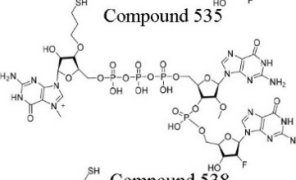
Compound 535



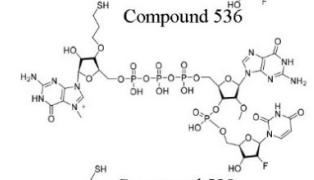
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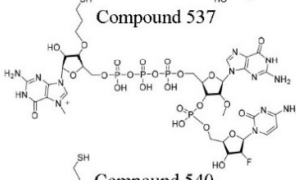
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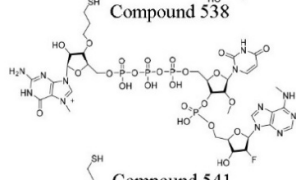
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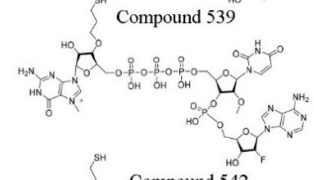
Compound 539



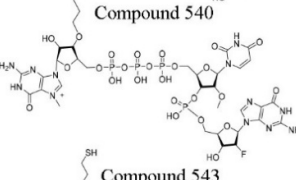
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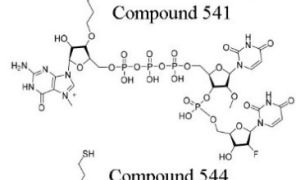
Compound 541



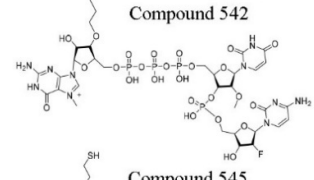
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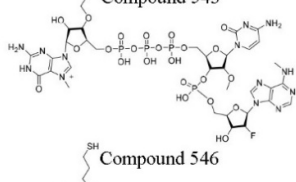
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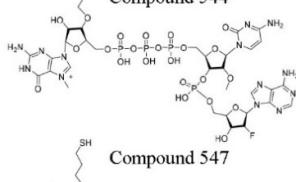
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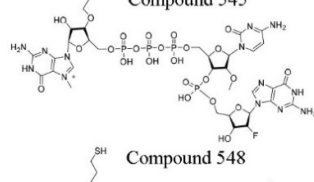
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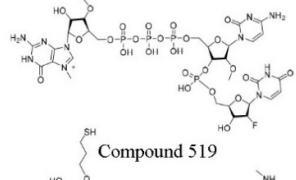
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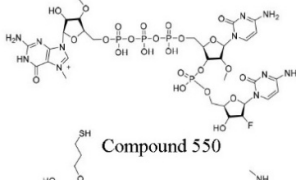
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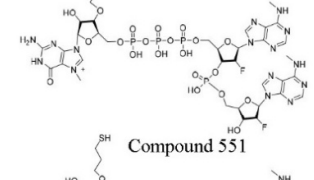
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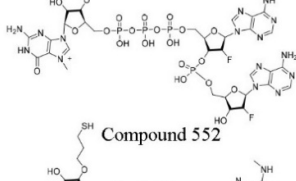
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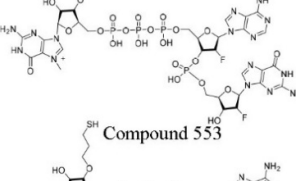
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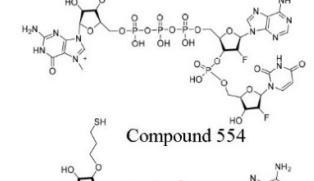
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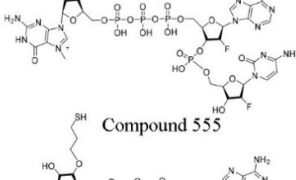
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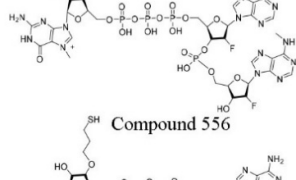
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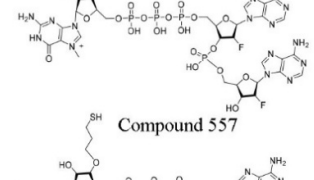
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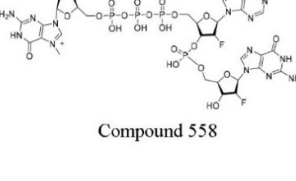
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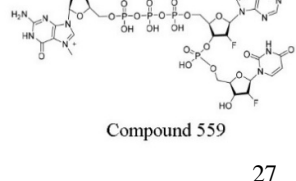
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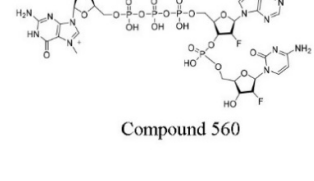
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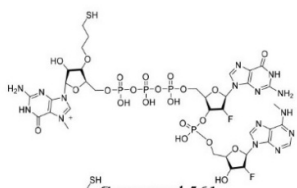
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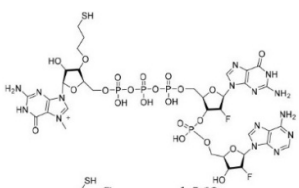
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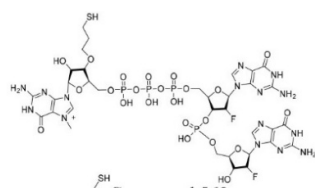
Compound 560



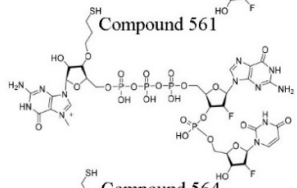
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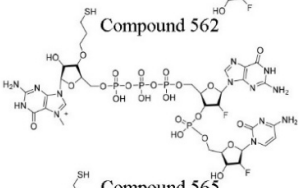
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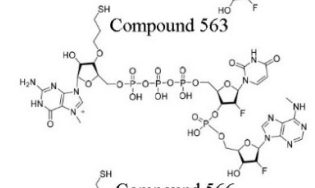
Compound 563



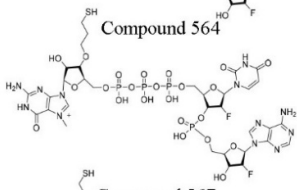
Compound 564



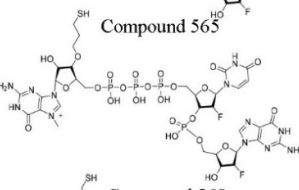
Compound 565



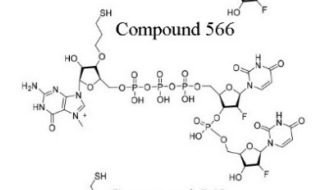
Compound 566



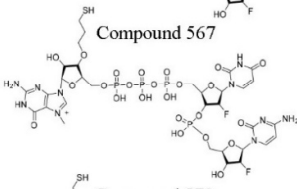
Compound 567



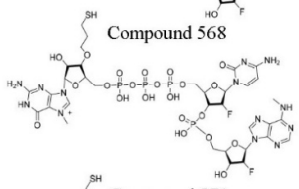
Compound 568



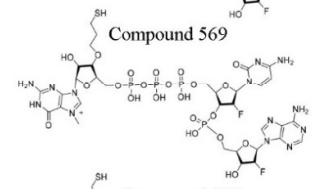
Compound 569



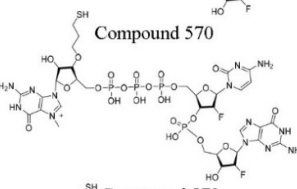
Compound 570



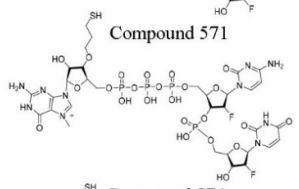
Compound 571



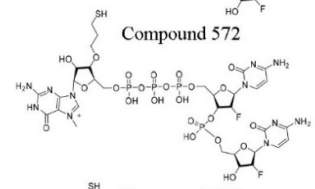
Compound 572



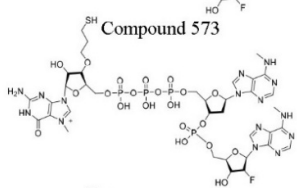
Compound 573



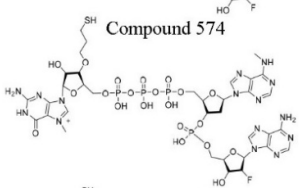
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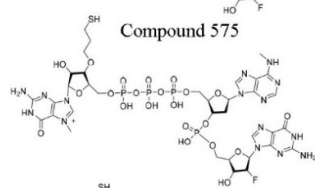
Compound 575



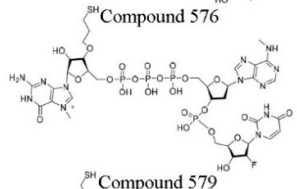
Compound 576



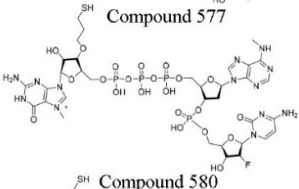
Compound 577



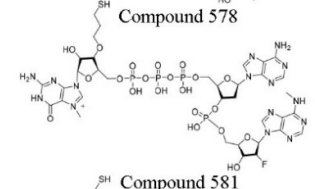
Compound 578



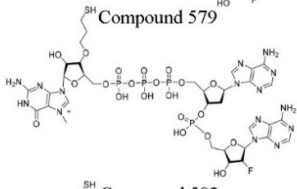
Compound 579



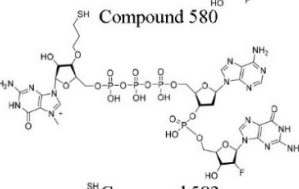
Compound 580



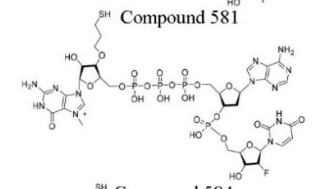
Compound 581



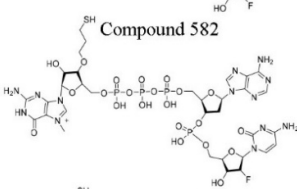
Compound 582



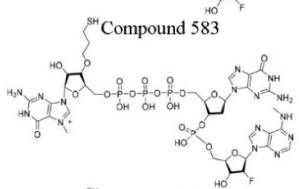
Compound 583



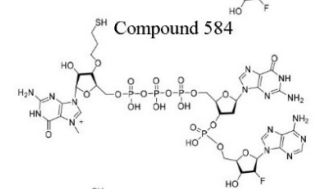
Compound 584



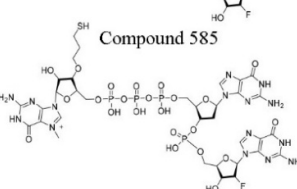
Compound 585



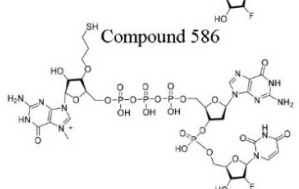
Compound 586



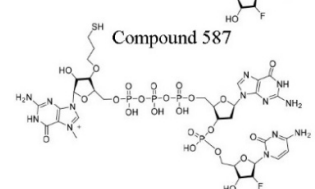
Compound 587



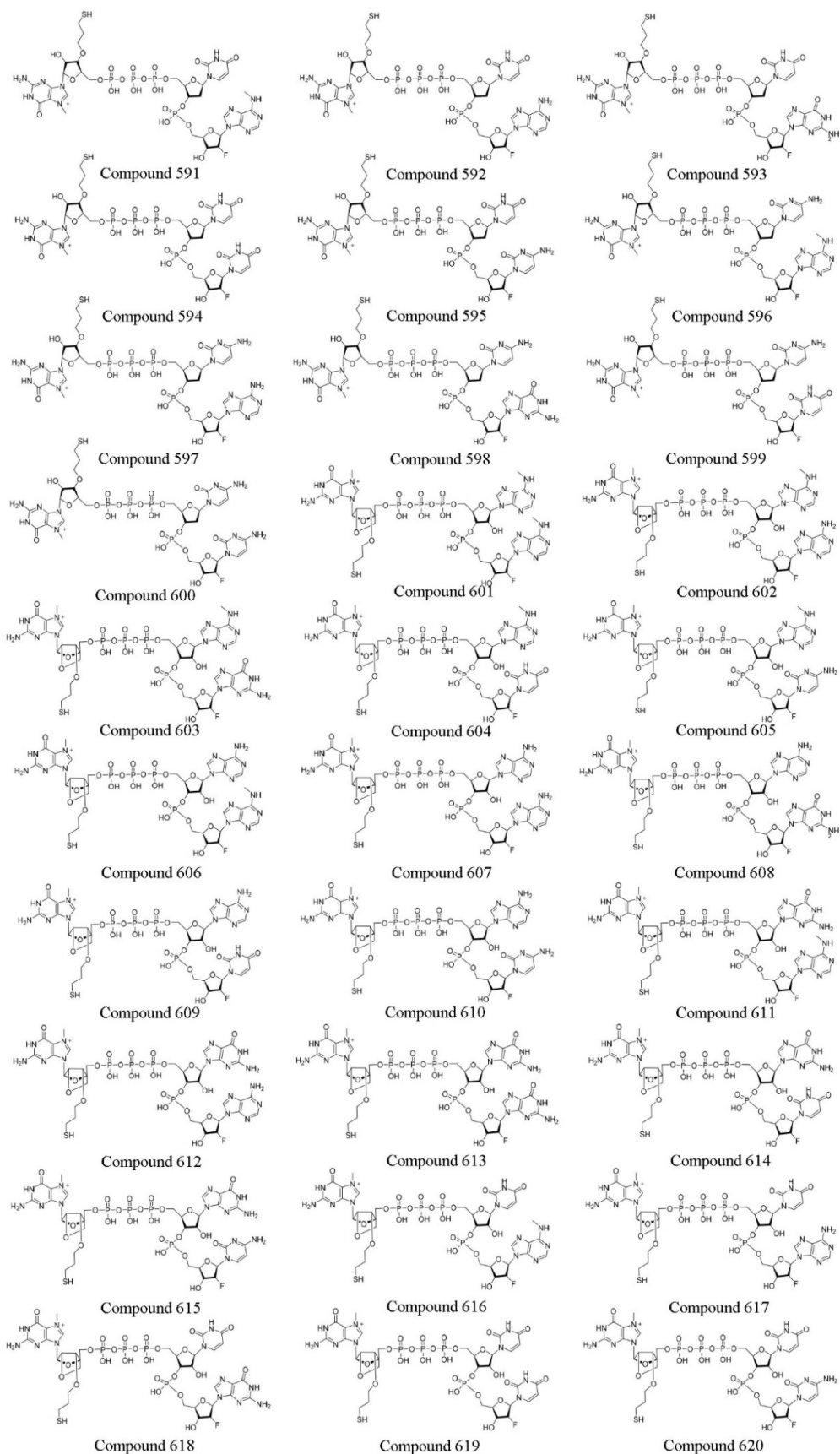
Compound 588

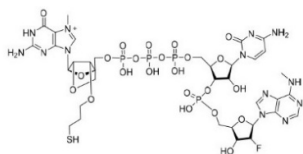


Compound 589

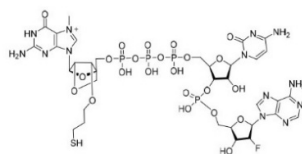


Compound 590

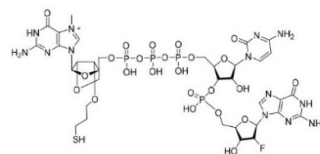




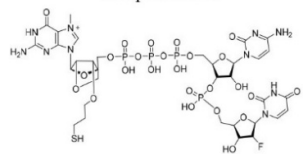
Compound 621



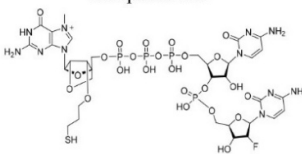
Compound 622



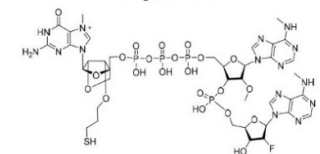
Compound 623



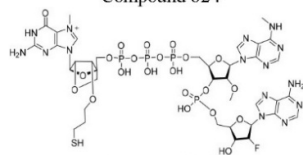
Compound 624



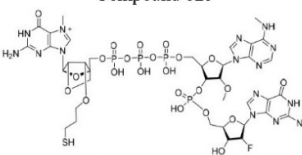
Compound 625



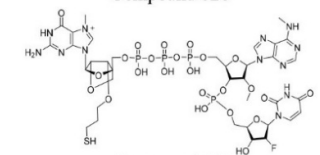
Compound 626



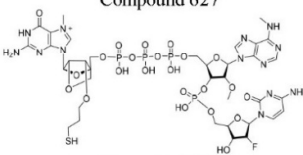
Compound 627



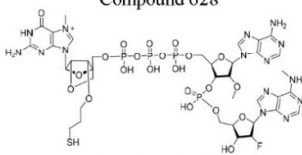
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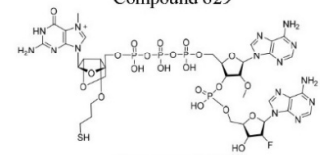
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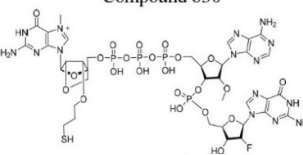
Compound 630



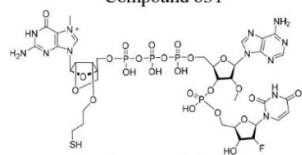
Compound 631



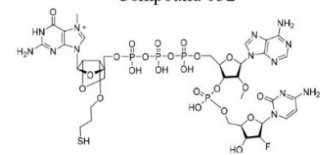
Compound 632



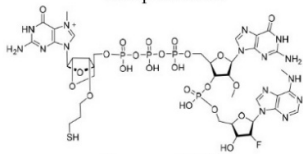
Compound 633



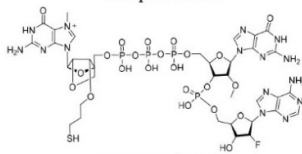
Compound 634



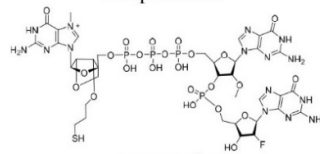
Compound 635



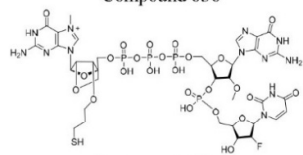
Compound 636



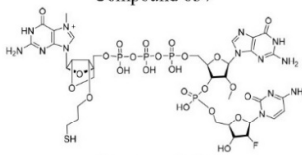
Compound 637



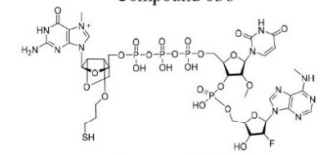
Compound 638



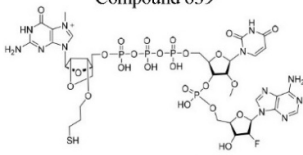
Compound 639



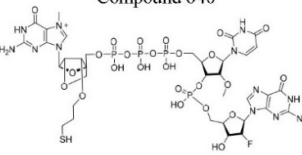
Compound 640



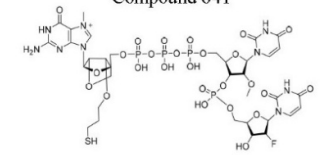
Compound 641



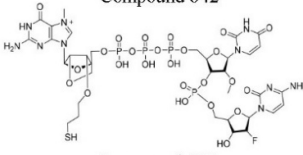
Compound 642



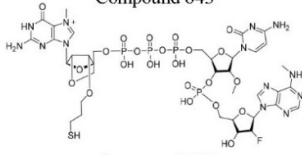
Compound 643



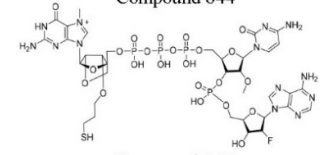
Compound 644



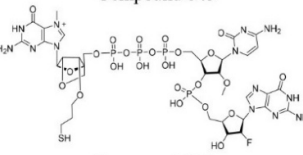
Compound 645



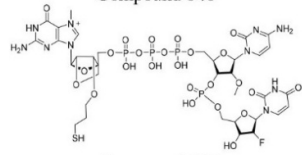
Compound 646



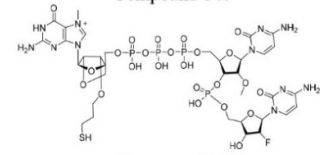
Compound 647



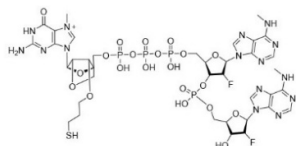
Compound 648



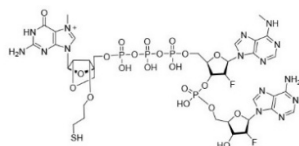
Compound 649



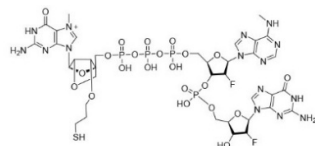
Compound 650



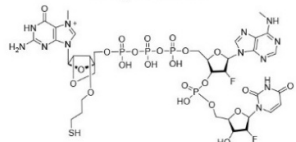
Compound 651



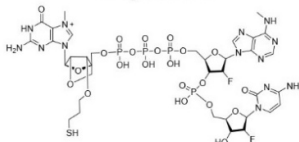
Compound 652



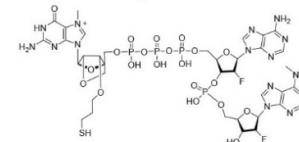
Compound 653



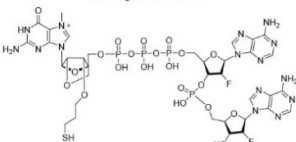
Compound 654



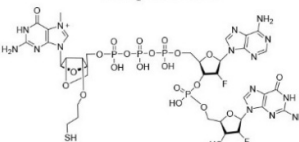
Compound 655



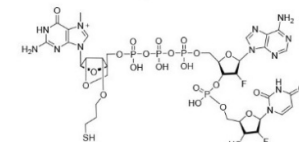
Compound 656



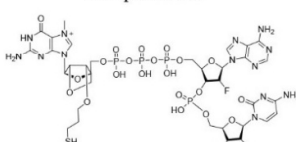
Compound 657



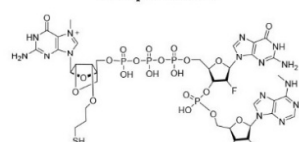
Compound 658



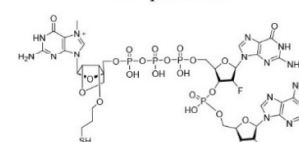
Compound 659



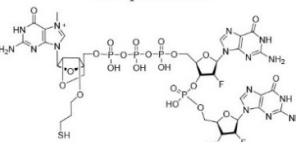
Compound 660



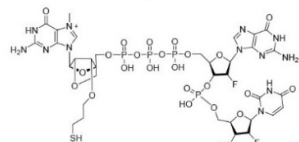
Compound 661



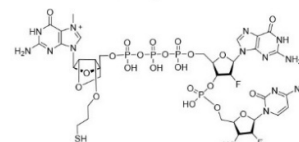
Compound 662



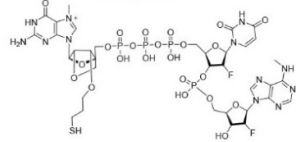
Compound 663



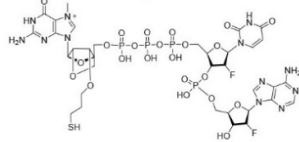
Compound 664



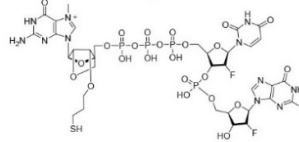
Compound 665



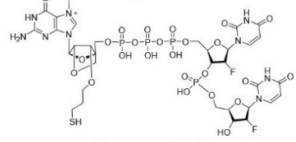
Compound 666



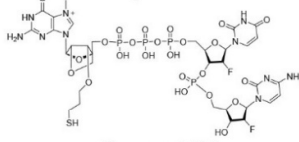
Compound 667



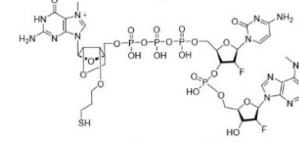
Compound 668



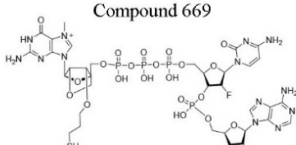
Compound 669



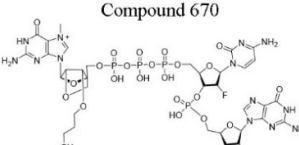
Compound 670



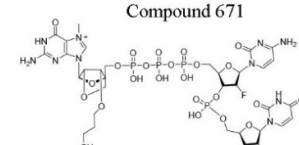
Compound 671



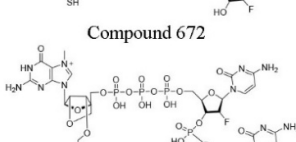
Compound 672



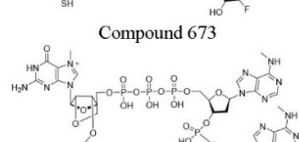
Compound 673



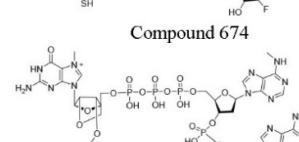
Compound 674



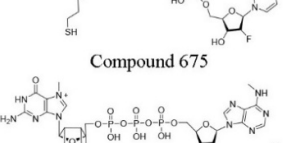
Compound 675



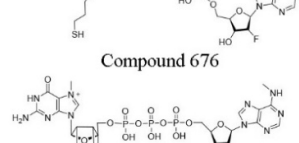
Compound 676



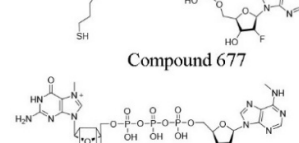
Compound 677



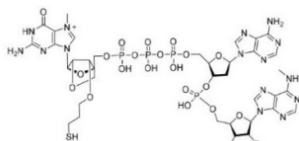
Compound 678



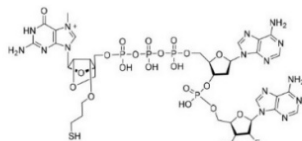
Compound 679



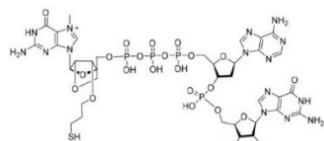
Compound 680



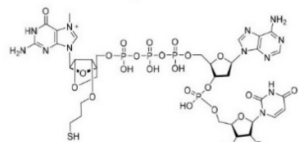
Compound 681



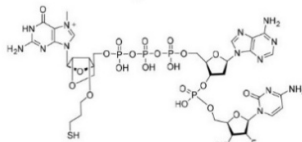
Compound 682



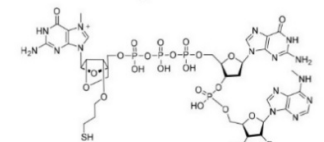
Compound 683



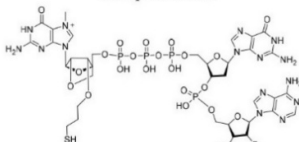
Compound 684



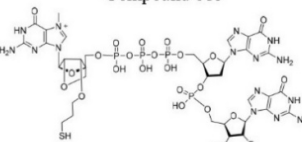
Compound 685



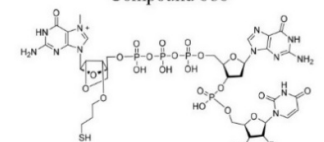
Compound 686



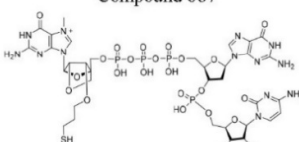
Compound 687



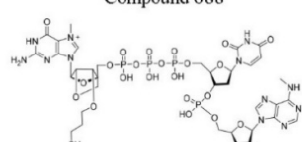
Compound 688



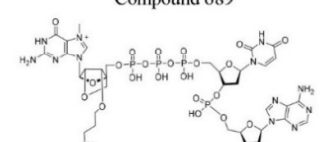
Compound 689



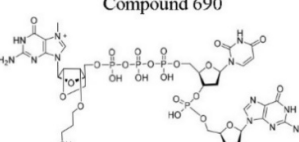
Compound 690



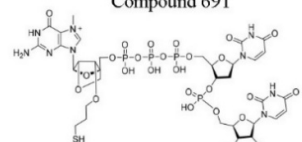
Compound 691



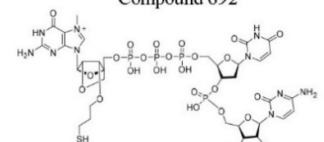
Compound 692



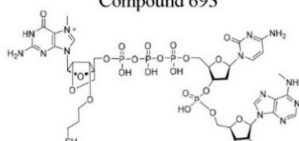
Compound 693



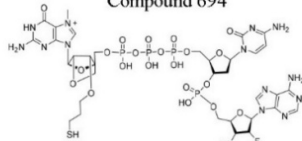
Compound 694



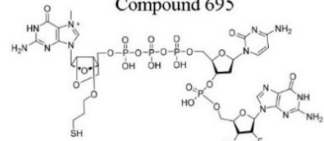
Compound 695



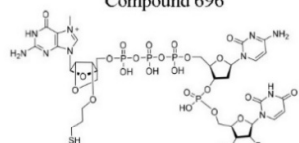
Compound 696



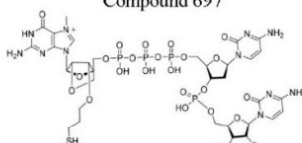
Compound 697



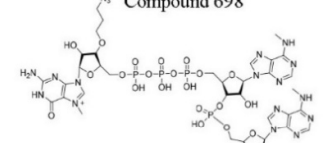
Compound 698



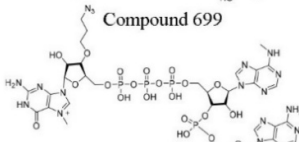
Compound 699



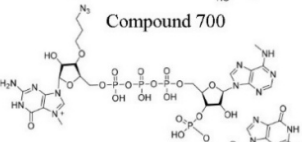
Compound 700



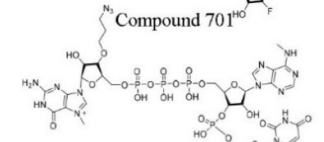
Compound 701



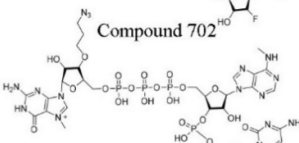
Compound 702



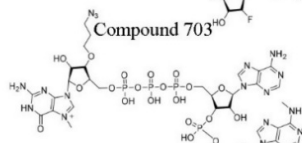
Compound 703



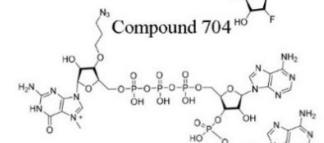
Compound 704



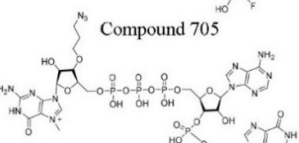
Compound 705



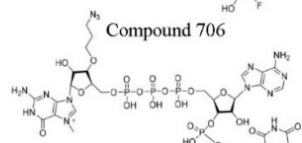
Compound 706



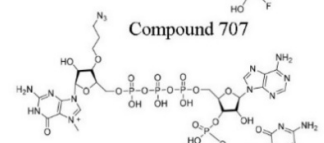
Compound 707



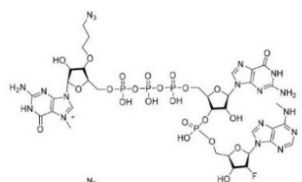
Compound 708



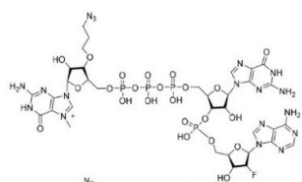
Compound 709



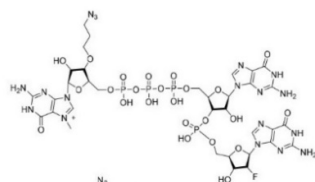
Compound 710



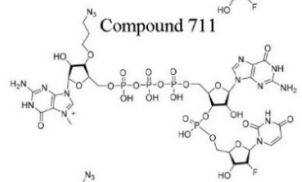
Compound 711



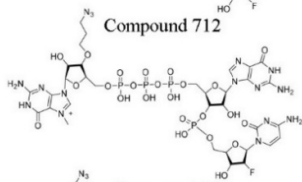
Compound 712



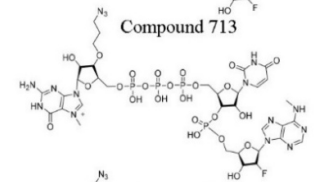
Compound 713



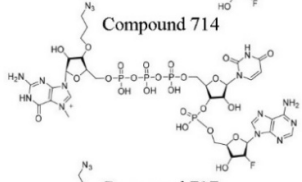
Compound 714



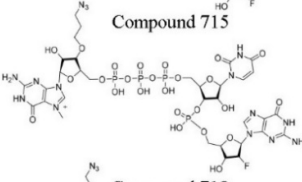
Compound 715



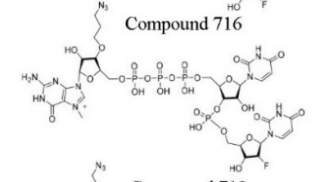
Compound 716



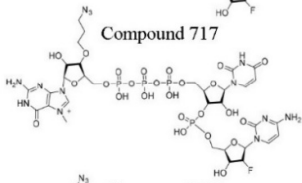
Compound 717



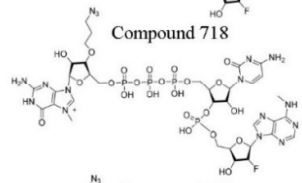
Compound 718



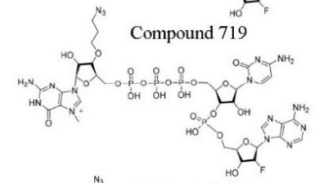
Compound 719



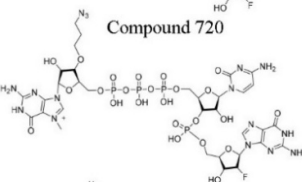
Compound 720



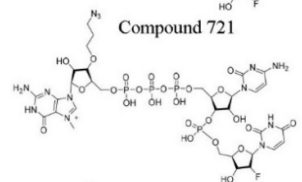
Compound 721



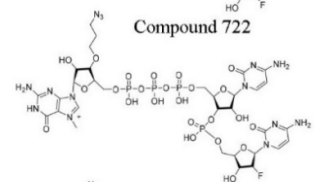
Compound 722



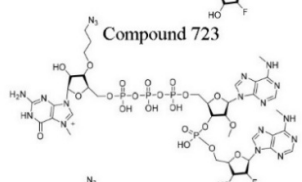
Compound 723



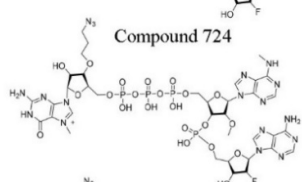
Compound 724



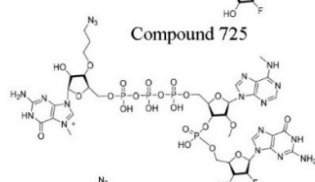
Compound 725



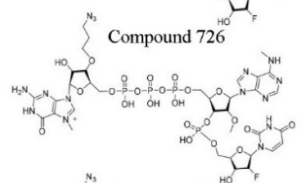
Compound 726



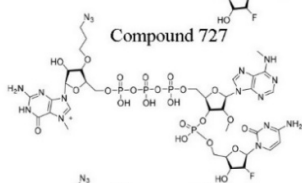
Compound 727



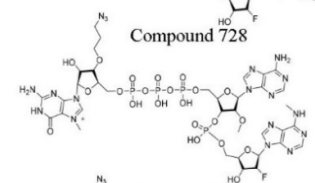
Compound 728



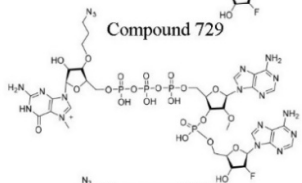
Compound 729



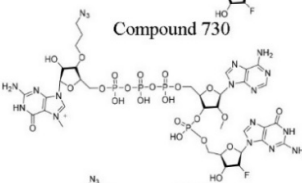
Compound 730



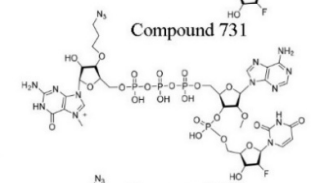
Compound 731



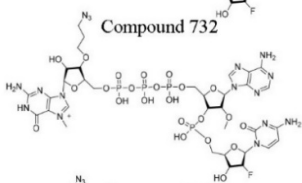
Compound 732



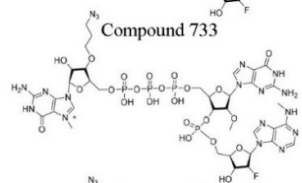
Compound 733



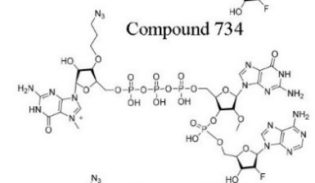
Compound 734



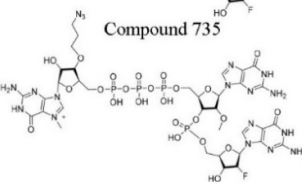
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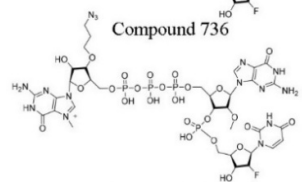
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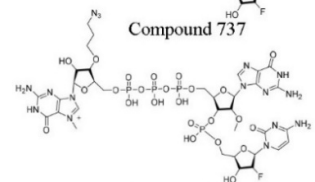
Compound 737



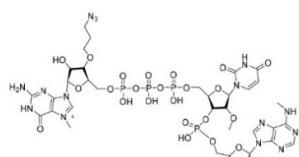
Compound 738



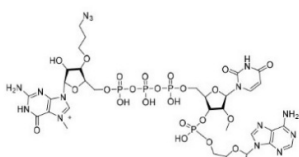
Compound 739



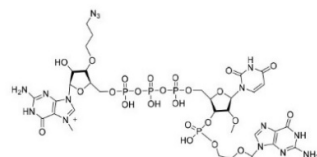
Compound 740



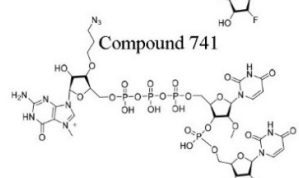
Compound 741



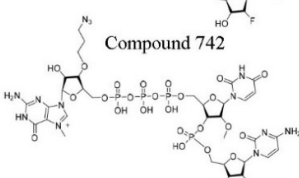
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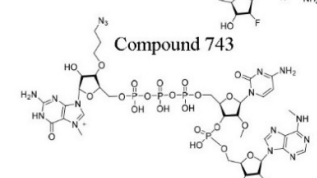
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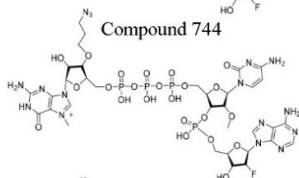
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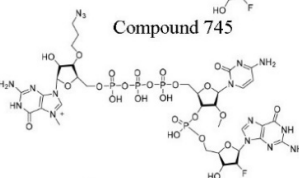
Compound 745



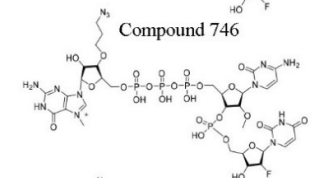
Compound 746



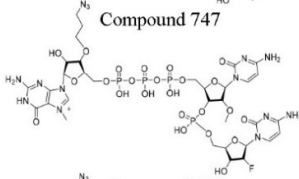
Compound 747



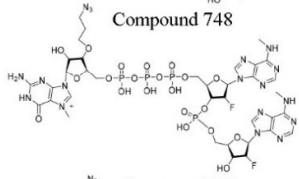
Compound 748



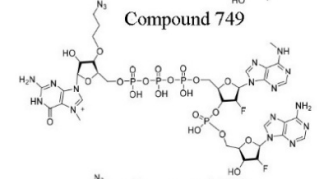
Compound 749



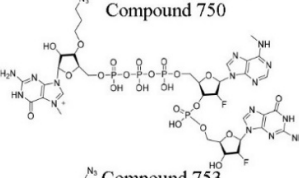
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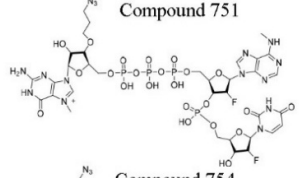
Compound 751



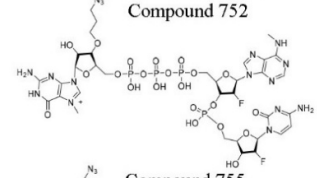
Compound 752



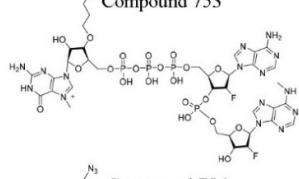
Compound 753



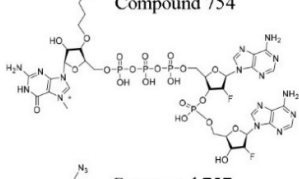
Compound 754



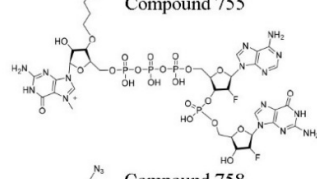
Compound 755



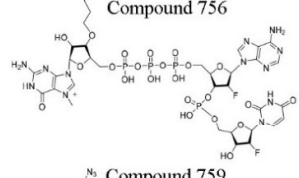
Compound 756



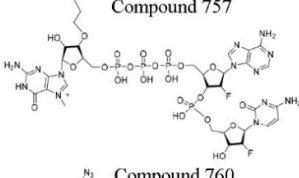
Compound 757



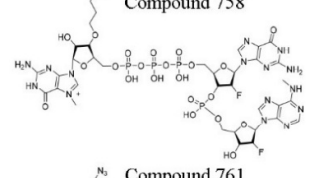
Compound 758



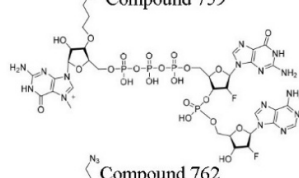
Compound 759



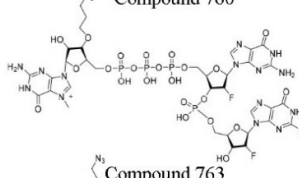
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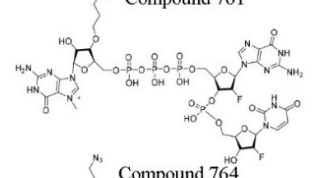
Compound 761



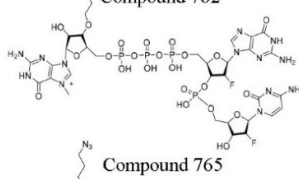
Compound 762



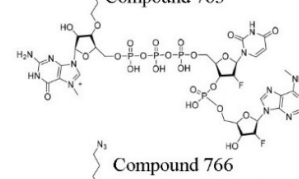
Compound 763



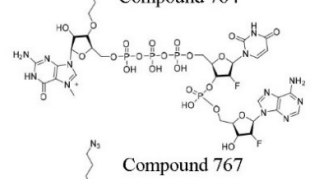
Compound 764



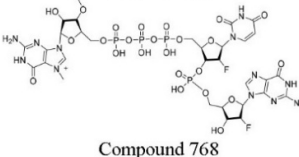
Compound 765



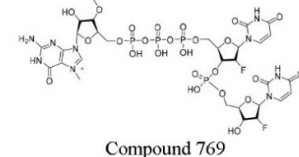
Compound 766



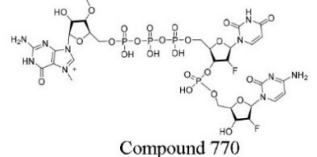
Compound 767



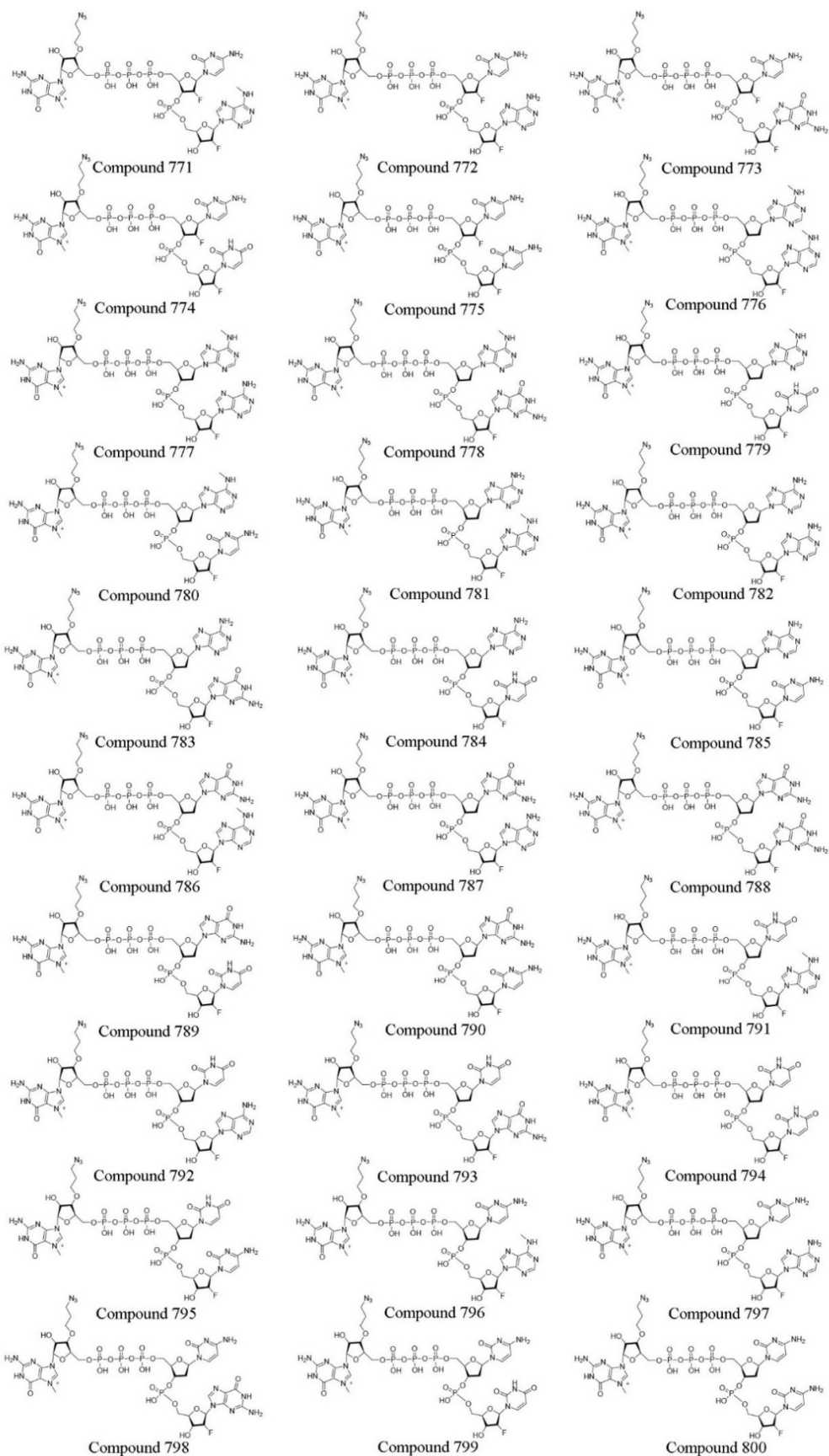
Compound 768

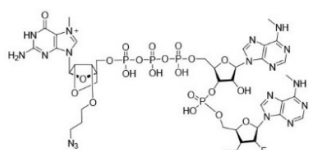


Compound 769

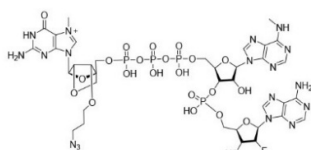


Compound 770

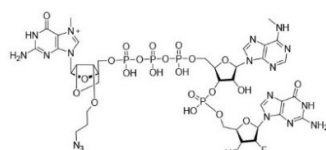




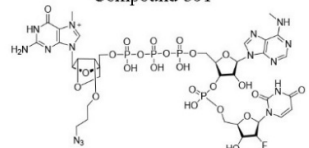
Compound 801



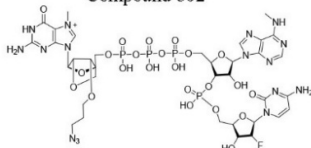
Compound 802



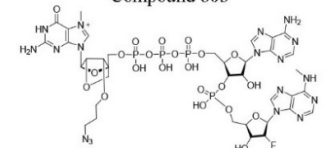
Compound 803



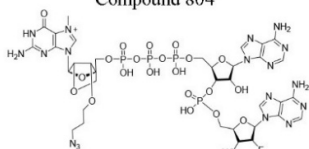
Compound 804



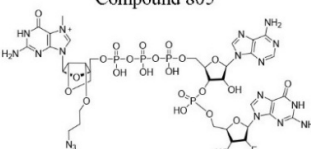
Compound 805



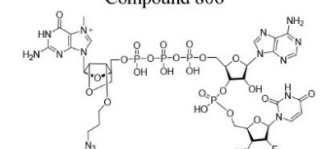
Compound 806



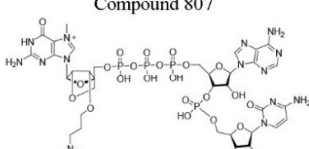
Compound 807



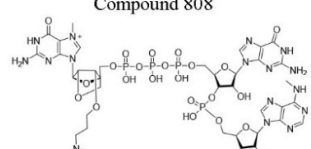
Compound 808



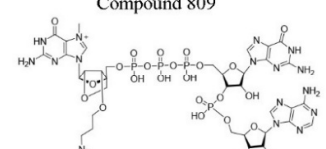
Compound 809



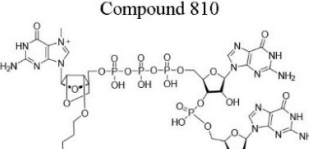
Compound 810



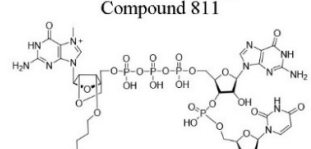
Compound 811



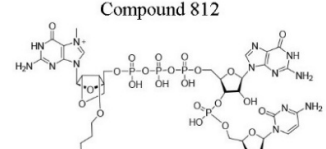
Compound 812



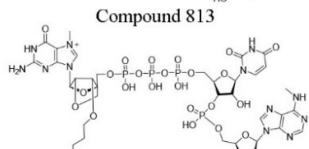
Compound 813



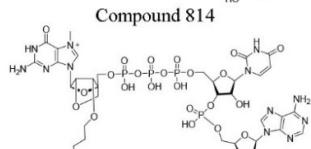
Compound 814



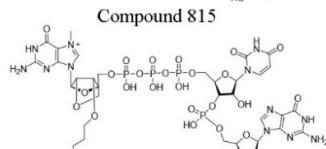
Compound 815



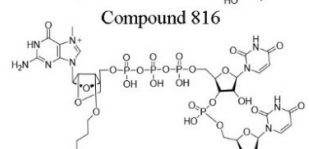
Compound 816



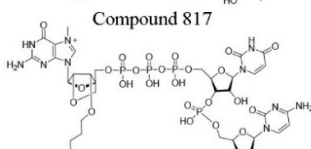
Compound 817



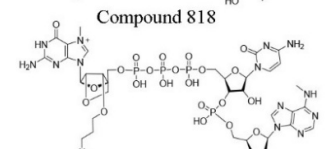
Compound 818



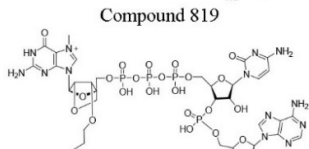
Compound 819



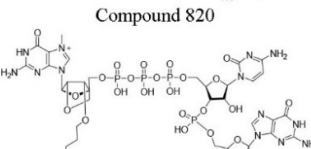
Compound 820



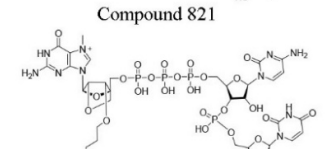
Compound 821



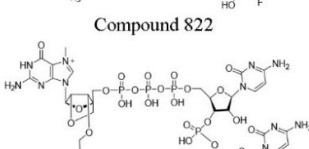
Compound 822



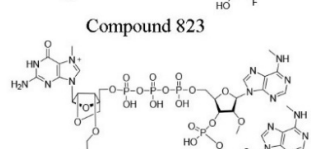
Compound 823



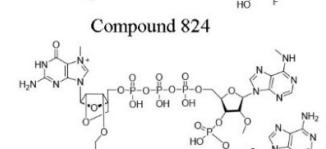
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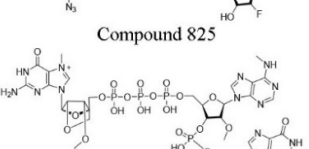
Compound 825



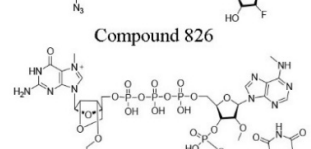
Compound 826



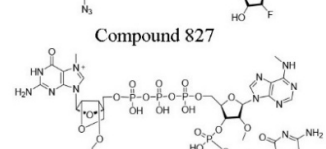
Compound 827



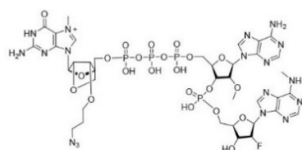
Compound 828



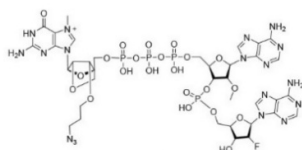
Compound 829



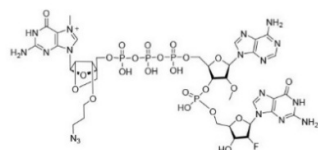
Compound 830



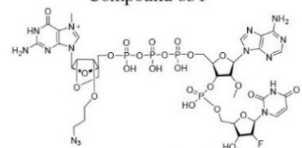
Compound 831



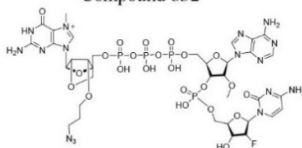
Compound 832



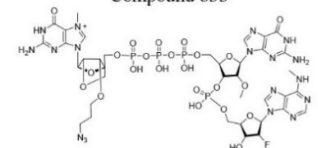
Compound 833



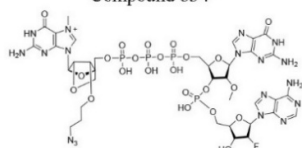
Compound 834



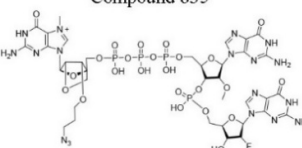
Compound 835



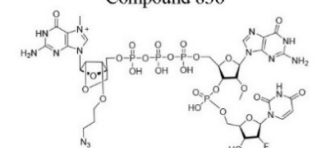
Compound 836



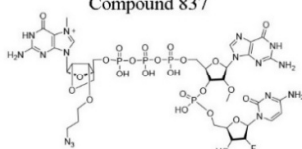
Compound 837



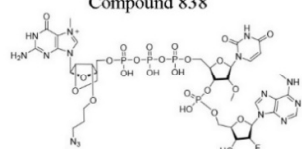
Compound 838



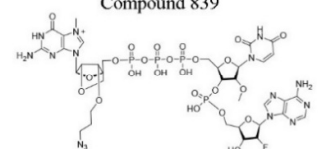
Compound 839



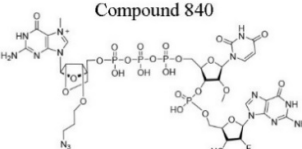
Compound 840



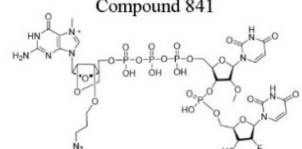
Compound 841



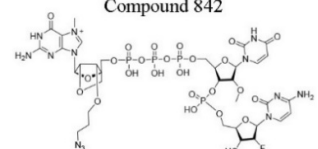
Compound 842



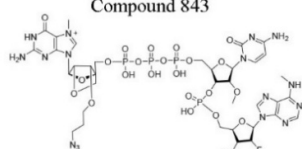
Compound 843



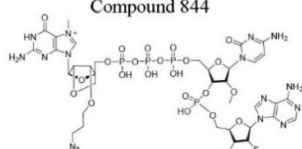
Compound 844



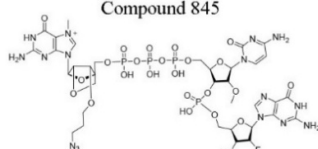
Compound 845



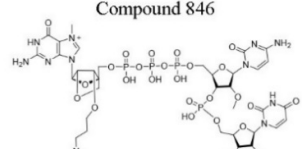
Compound 846



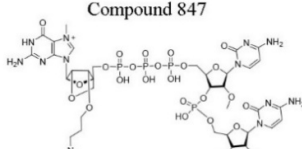
Compound 847



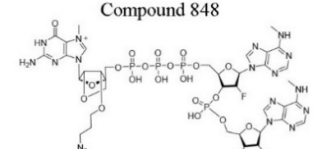
Compound 848



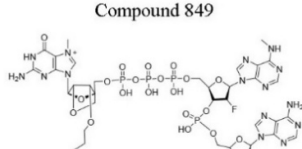
Compound 849



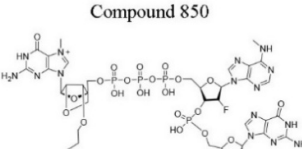
Compound 850



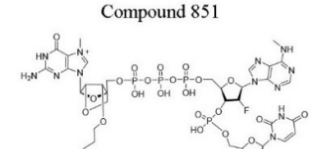
Compound 851



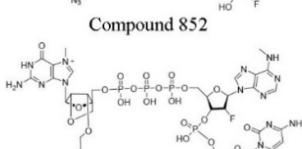
Compound 852



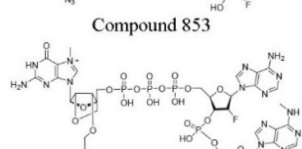
Compound 853



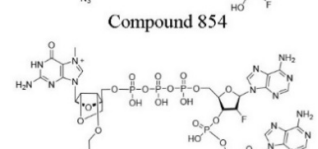
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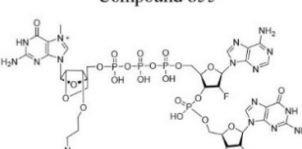
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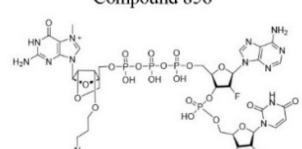
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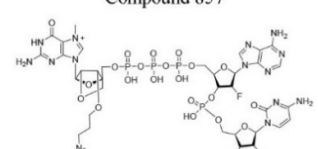
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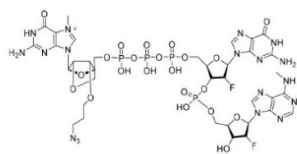
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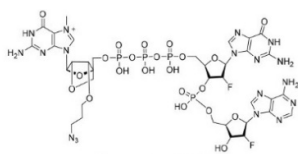
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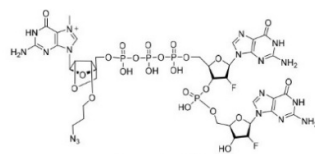
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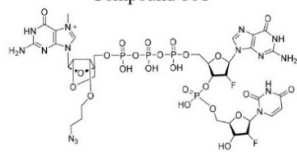
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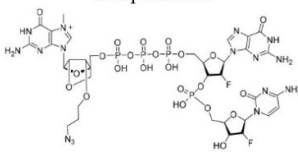
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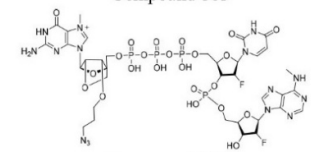
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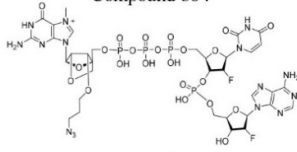
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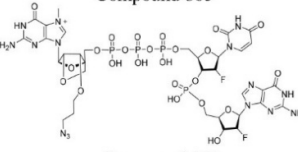
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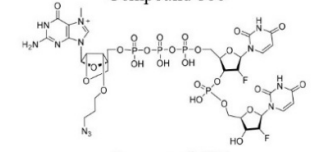
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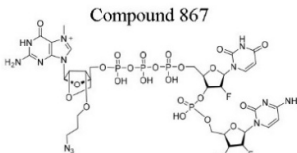
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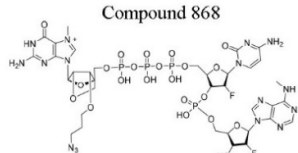
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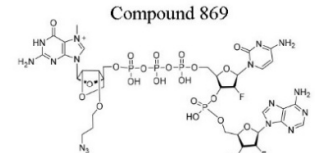
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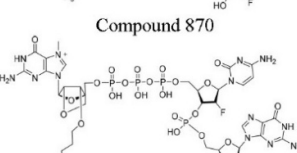
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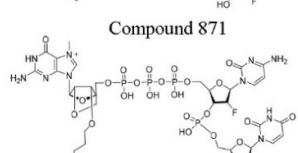
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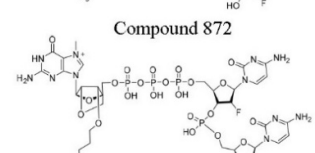
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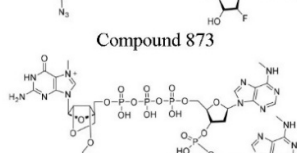
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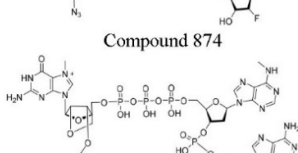
Compound 874



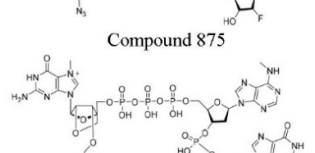
Compound 875



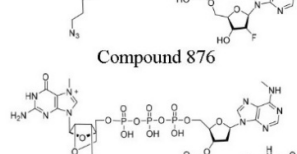
Compound 876



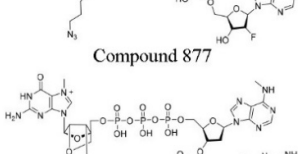
Compound 877



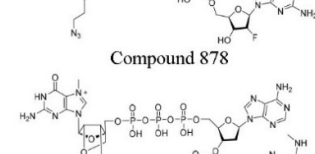
Compound 878



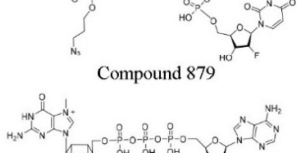
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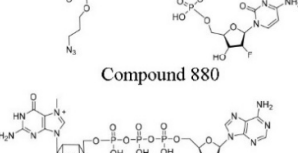
Compound 880



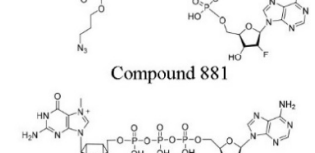
Compound 881



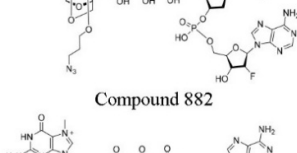
Compound 882



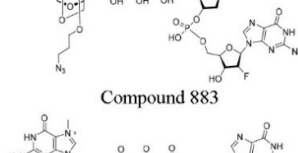
Compound 883



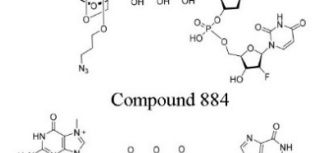
Compound 884



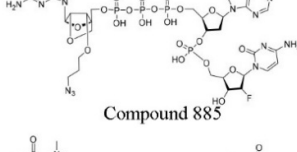
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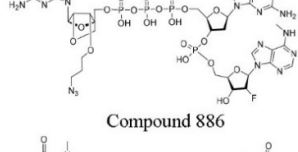
Compound 886



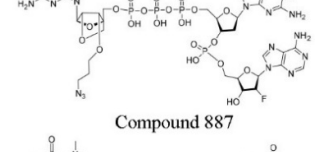
Compound 887



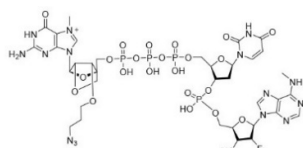
Compound 888



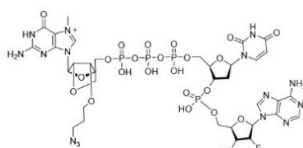
Compound 889



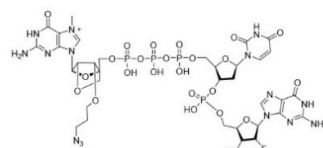
Compound 890



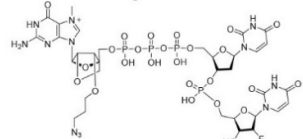
Compound 891



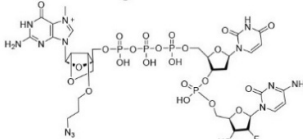
Compound 892



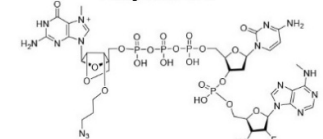
Compound 893



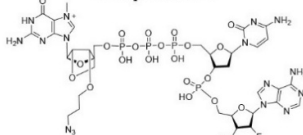
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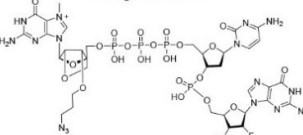
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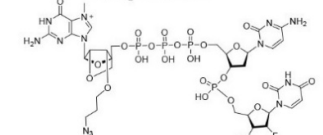
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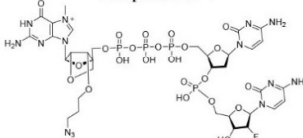
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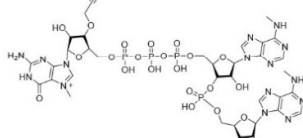
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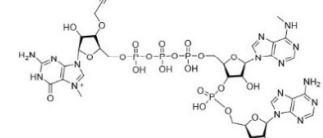
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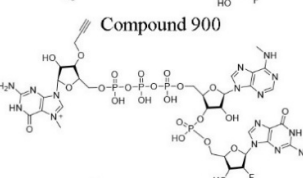
Compound 900



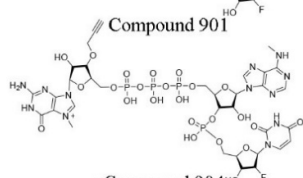
Compound 901



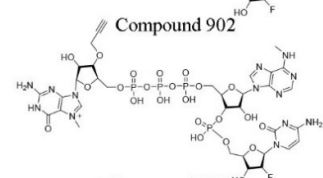
Compound 902



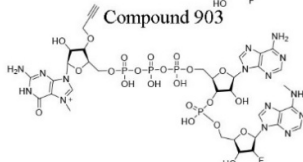
Compound 903



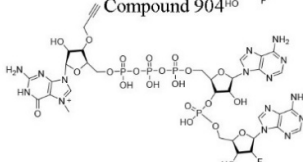
Compound 904



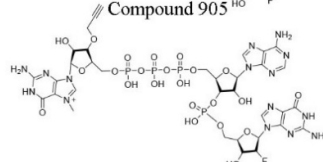
Compound 905



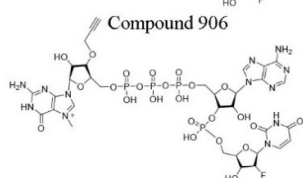
Compound 906



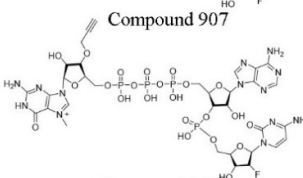
Compound 907



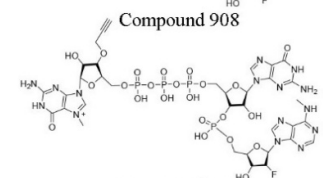
Compound 908



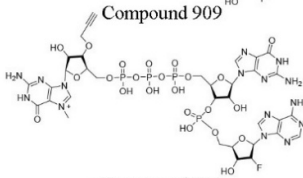
Compound 909



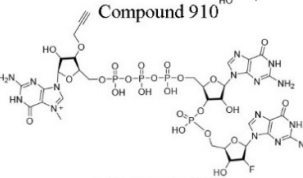
Compound 910



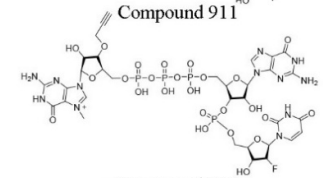
Compound 911



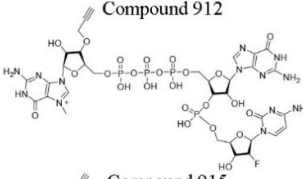
Compound 912



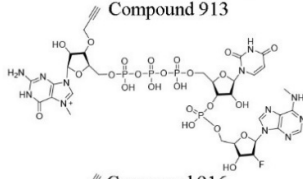
Compound 913



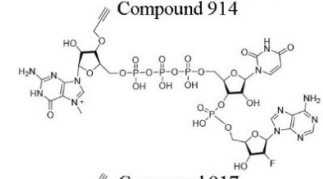
Compound 914



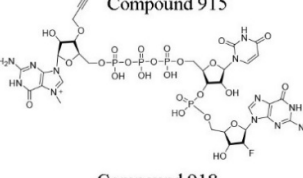
Compound 915



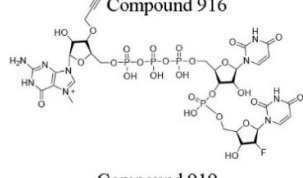
Compound 916



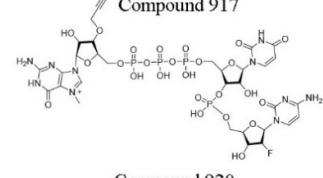
Compound 917



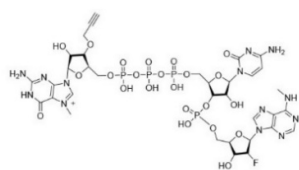
Compound 918



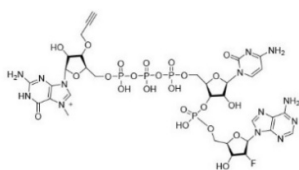
Compound 919



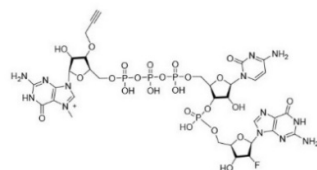
Compound 920



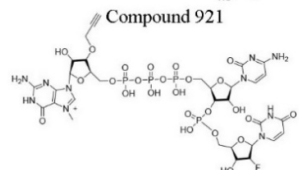
Compound 921



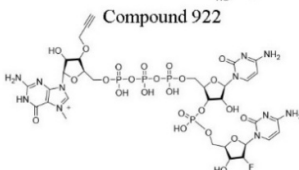
Compound 922



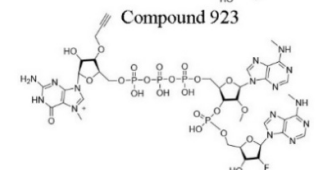
Compound 923



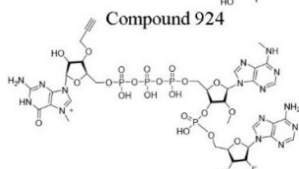
Compound 924



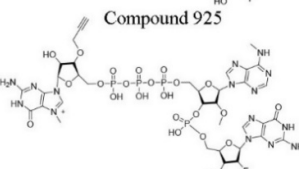
Compound 925



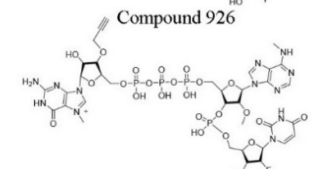
Compound 926



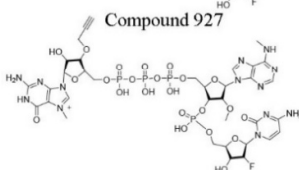
Compound 927



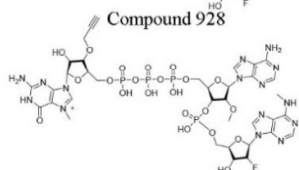
Compound 928



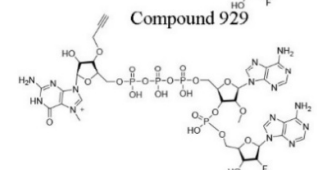
Compound 929



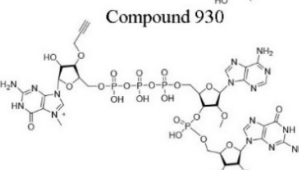
Compound 930



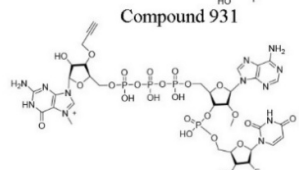
Compound 931



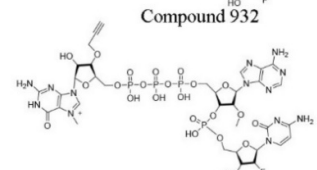
Compound 932



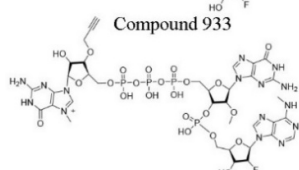
Compound 933



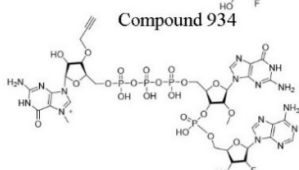
Compound 934



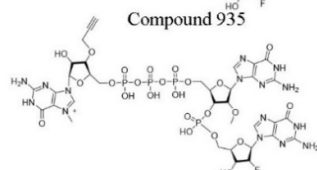
Compound 935



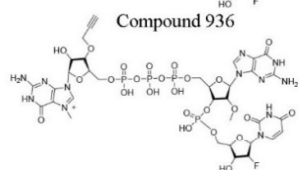
Compound 936



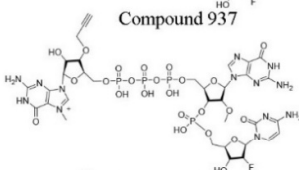
Compound 937



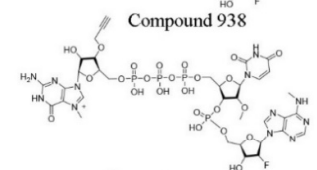
Compound 938



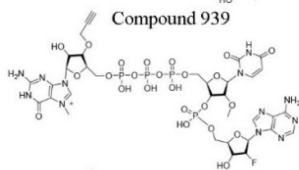
Compound 939



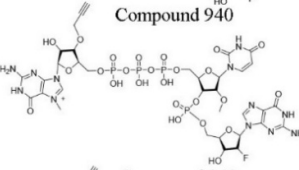
Compound 940



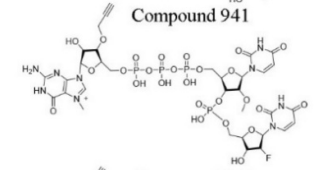
Compound 941



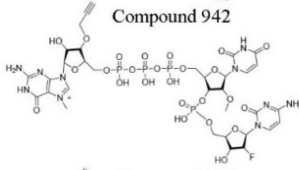
Compound 942



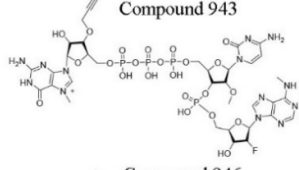
Compound 943



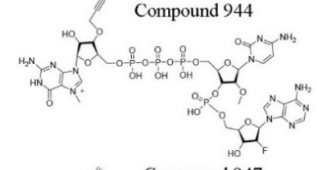
Compound 944



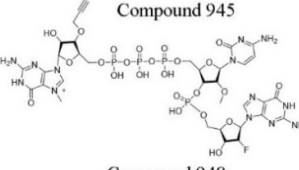
Compound 945



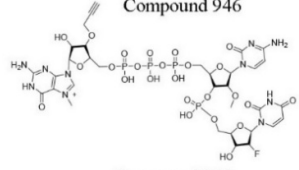
Compound 946



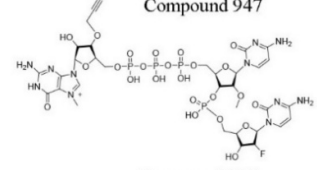
Compound 947



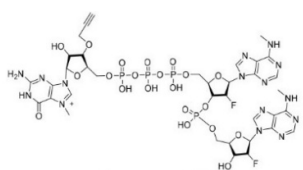
Compound 948



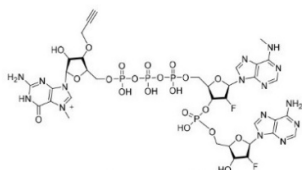
Compound 949



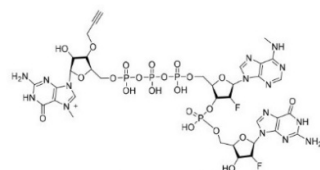
Compound 950



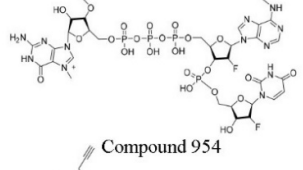
Compound 951



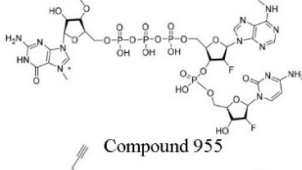
Compound 952



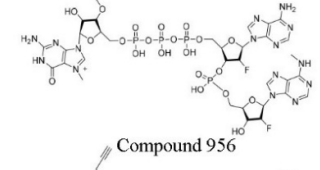
Compound 953



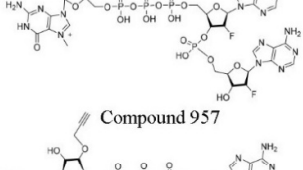
Compound 954



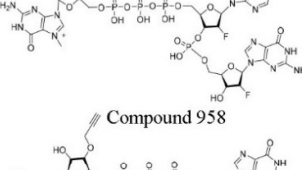
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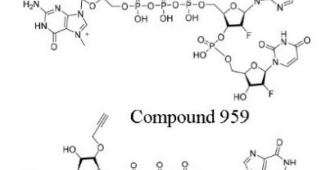
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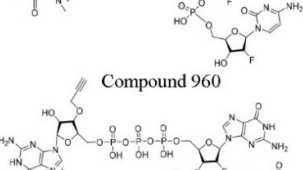
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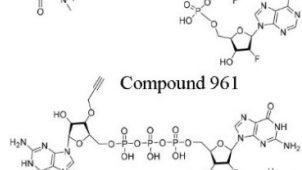
Compound 958



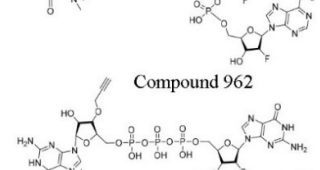
Compound 959



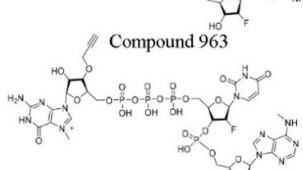
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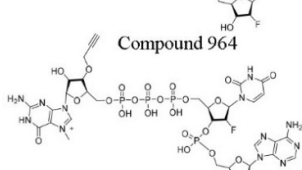
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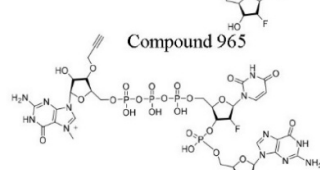
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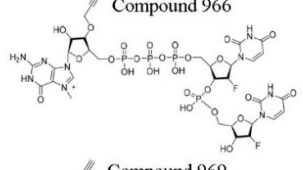
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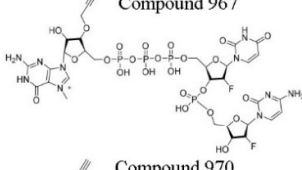
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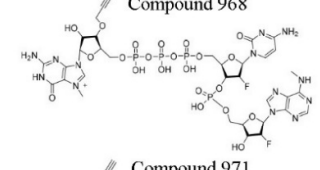
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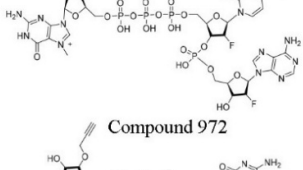
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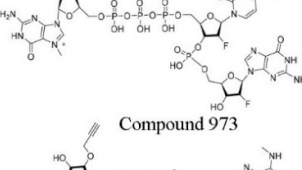
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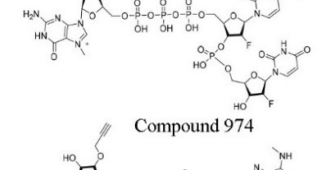
Compound 968



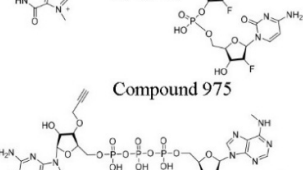
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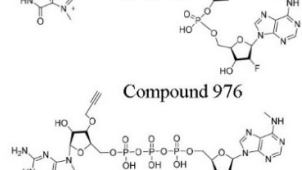
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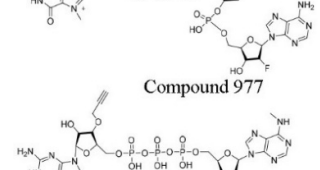
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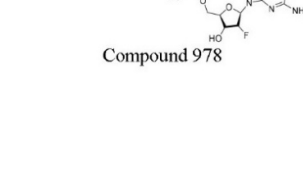
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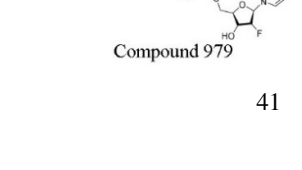
Compound 973



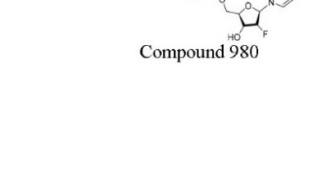
Compound 974



Compound 975



Compound 976

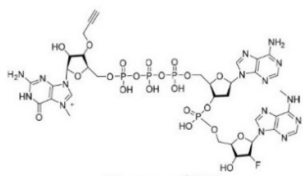


Compound 977

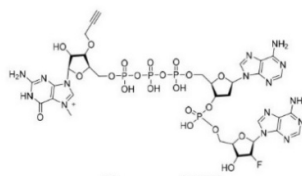
Compound 978

Compound 979

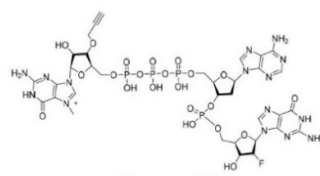
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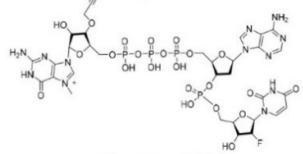
Compound 981



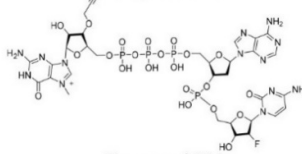
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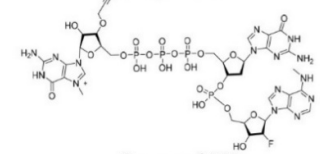
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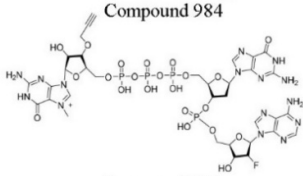
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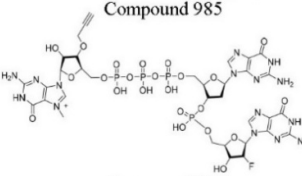
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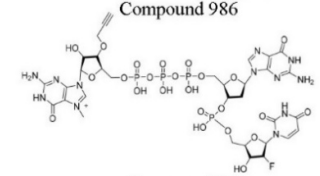
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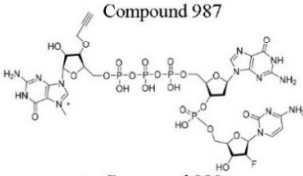
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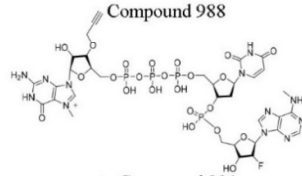
Compound 988



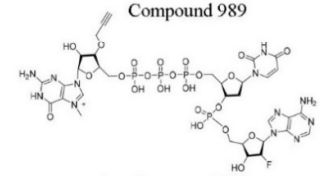
Compound 989



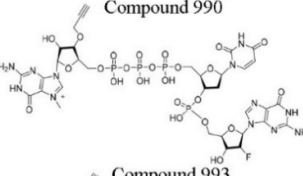
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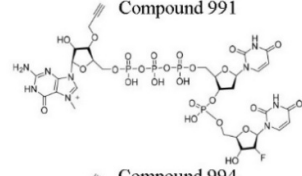
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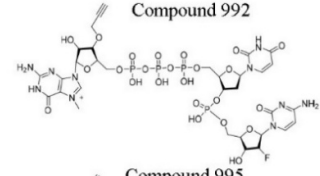
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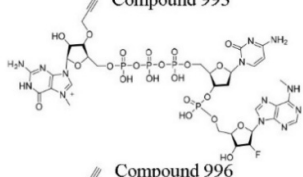
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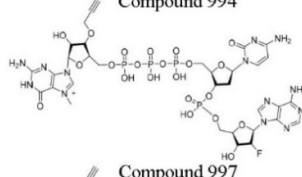
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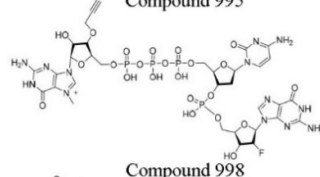
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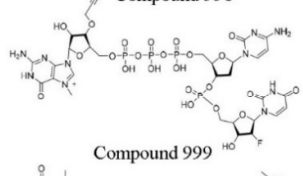
Compound 996



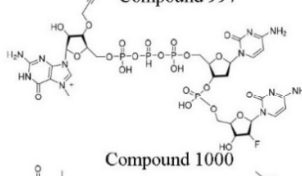
Compound 997



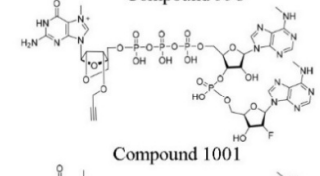
Compound 998



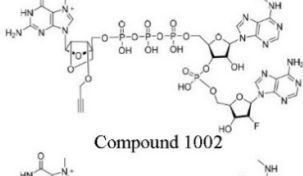
Compound 999



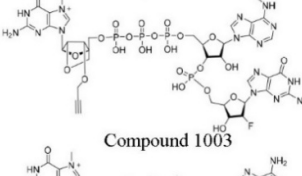
Compound 1000



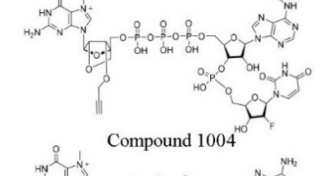
Compound 1001



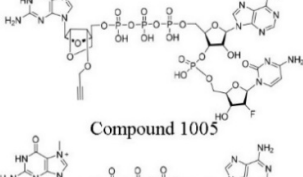
Compound 1002



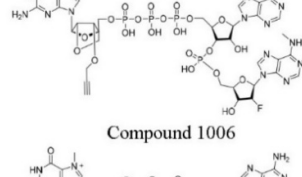
Compound 1003



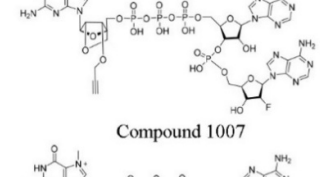
Compound 1004



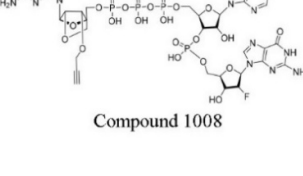
Compound 1005



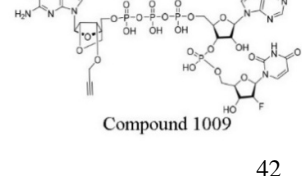
Compound 1006



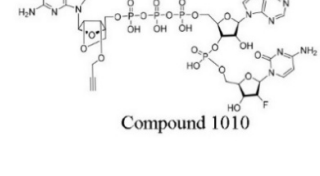
Compound 1007



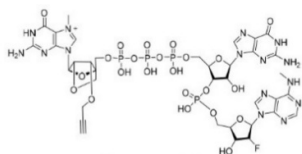
Compound 1008



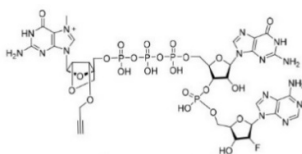
Compound 1009



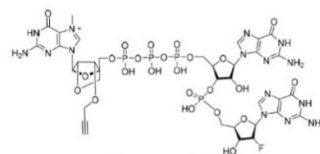
Compound 1010



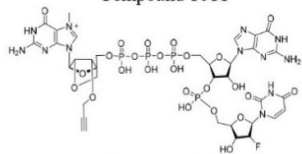
Compound 1011



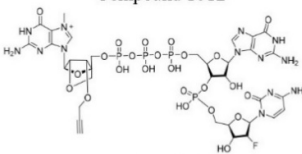
Compound 1012



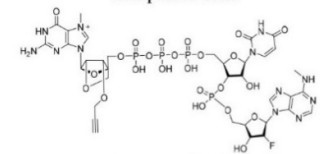
Compound 1013



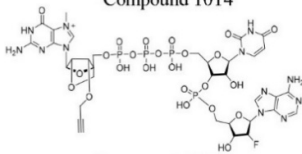
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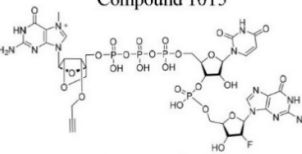
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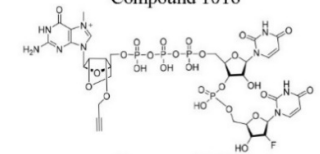
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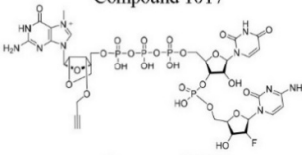
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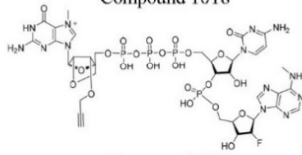
Compound 1018



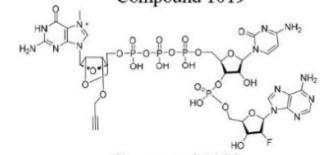
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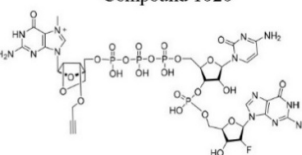
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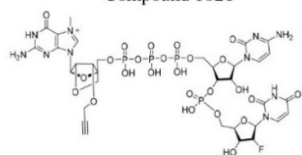
Compound 1021



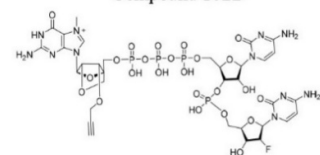
Compound 1022



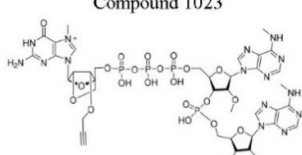
Compound 1023



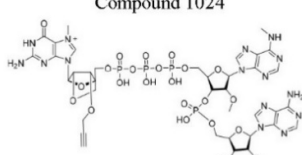
Compound 1024



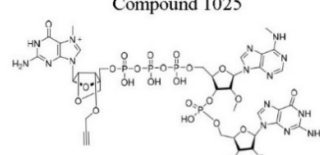
Compound 1025



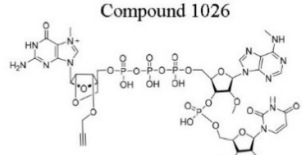
Compound 1026



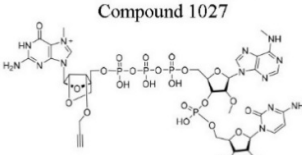
Compound 1027



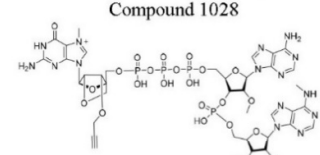
Compound 1028



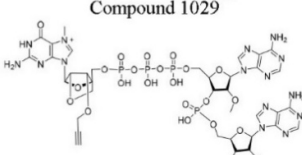
Compound 1029



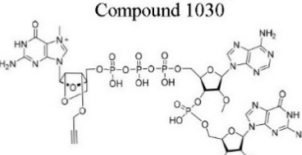
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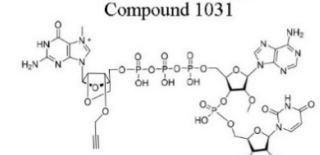
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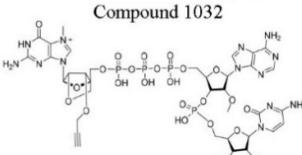
Compound 1032



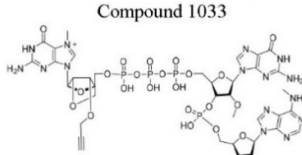
Compound 1033



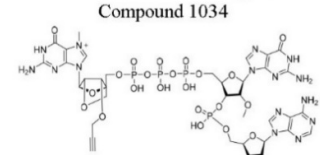
Compound 1034



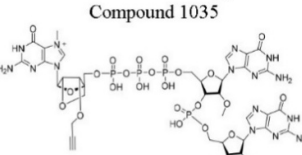
Compound 1035



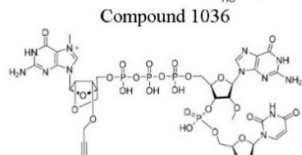
Compound 1036



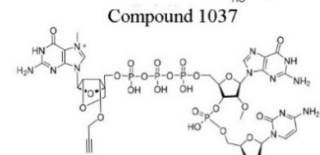
Compound 1037



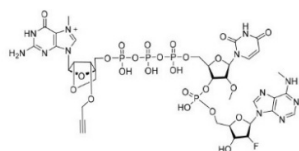
Compound 1038



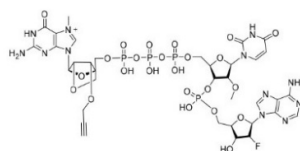
Compound 1039



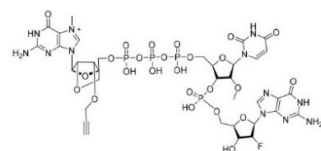
Compound 1040



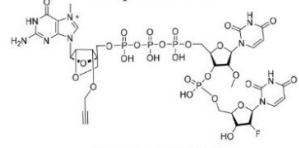
Compound 1041



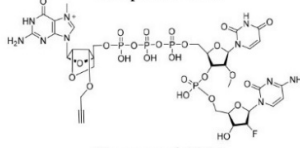
Compound 1042



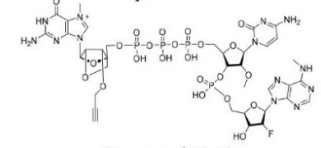
Compound 1043



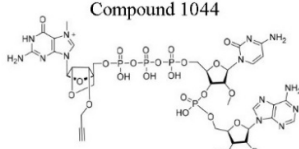
Compound 1044



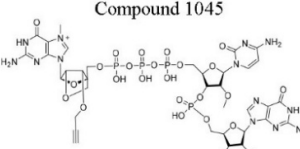
Compound 1045



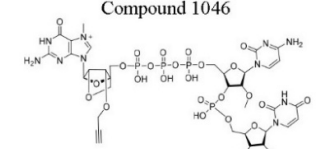
Compound 1046



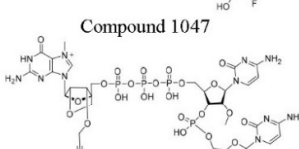
Compound 1047



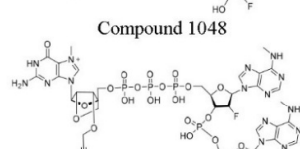
Compound 1048



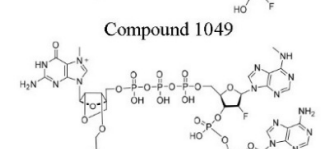
Compound 1049



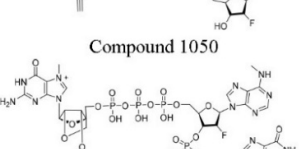
Compound 1050



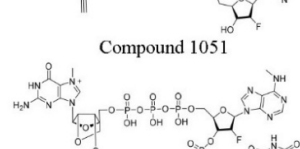
Compound 1051



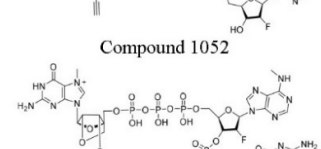
Compound 1052



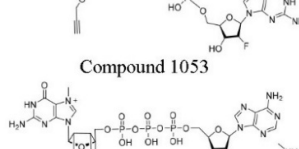
Compound 1053



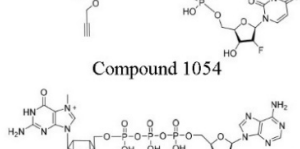
Compound 1054



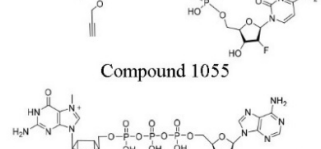
Compound 1055



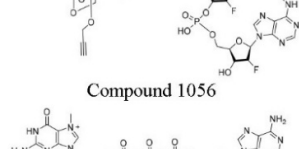
Compound 1056



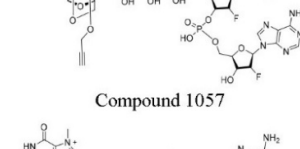
Compound 1057



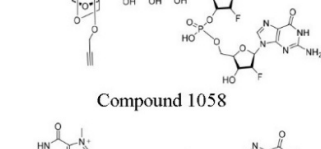
Compound 1058



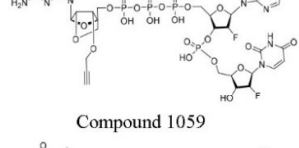
Compound 1059



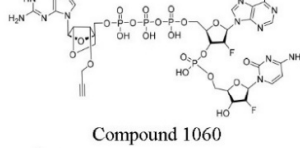
Compound 1060



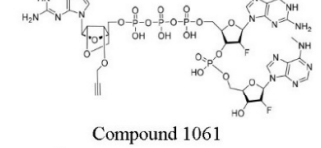
Compound 1061



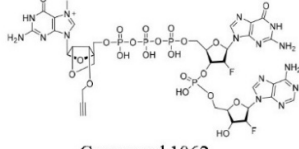
Compound 1062



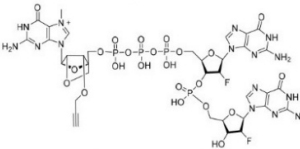
Compound 1063



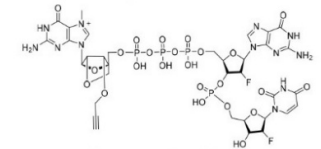
Compound 1064



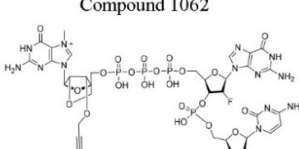
Compound 1065



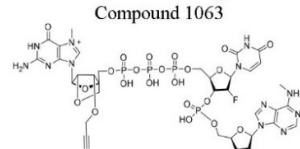
Compound 1066



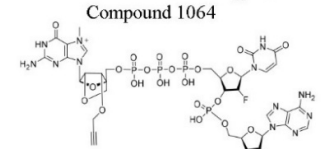
Compound 1067



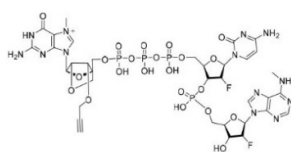
Compound 1068



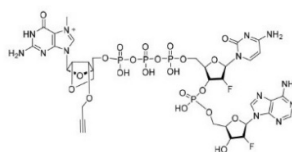
Compound 1069



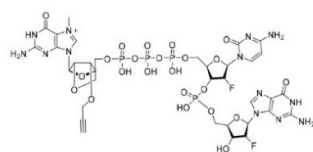
Compound 1070



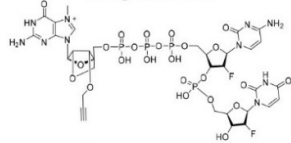
Compound 1071



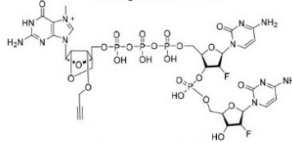
Compound 1072



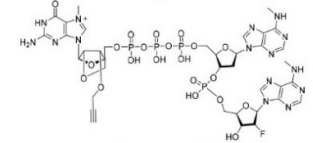
Compound 1073



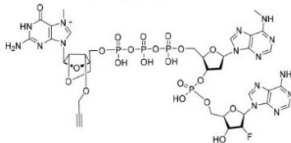
Compound 1074



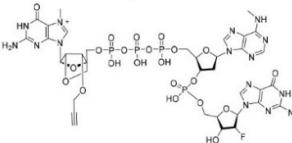
Compound 1075



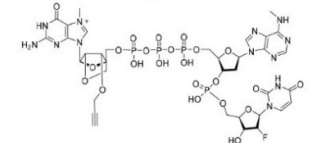
Compound 1076



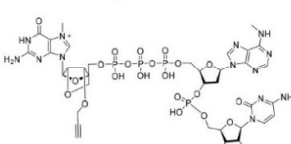
Compound 1077



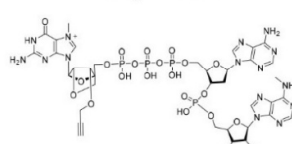
Compound 1078



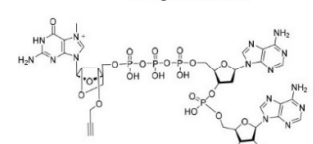
Compound 1079



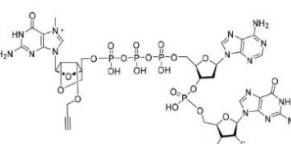
Compound 1080



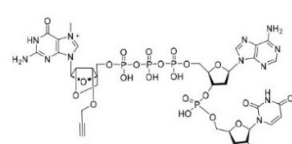
Compound 1081



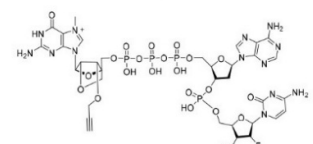
Compound 1082



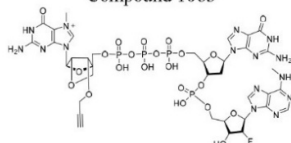
Compound 1083



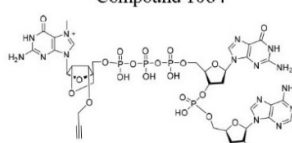
Compound 1084



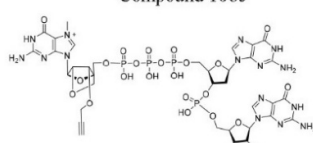
Compound 1085



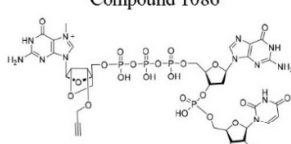
Compound 1086



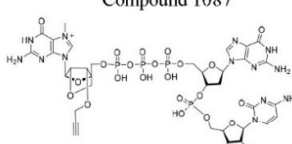
Compound 1087



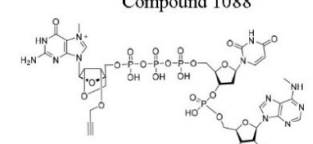
Compound 1088



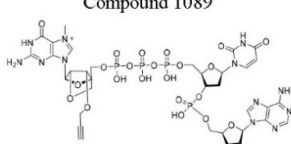
Compound 1089



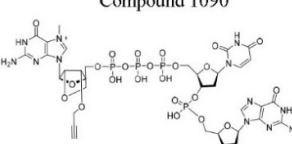
Compound 1090



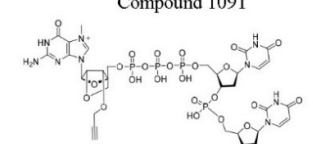
Compound 1091



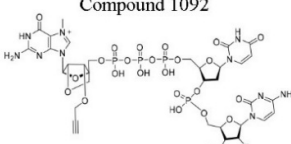
Compound 1092



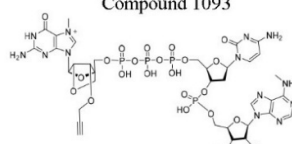
Compound 1093



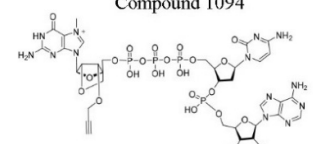
Compound 1094



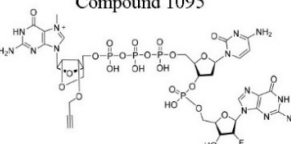
Compound 1095



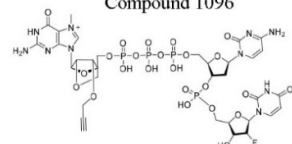
Compound 1096



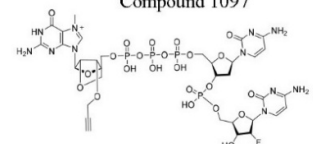
Compound 1097



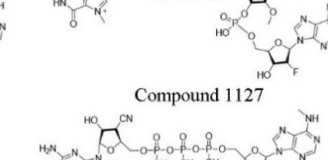
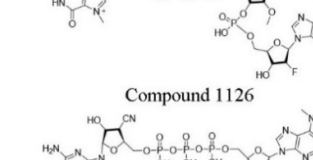
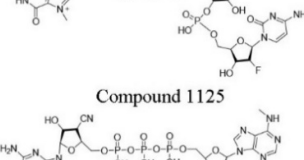
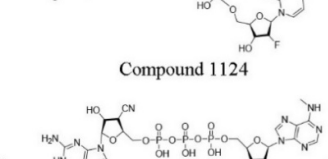
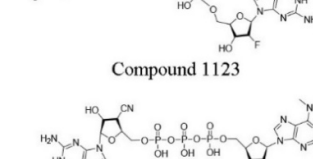
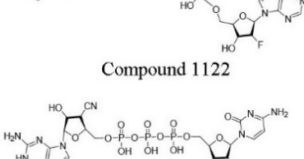
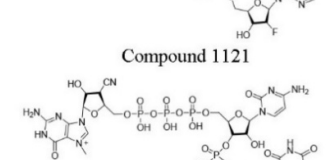
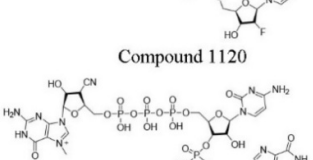
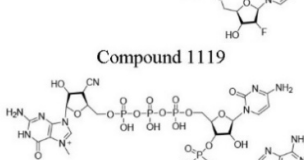
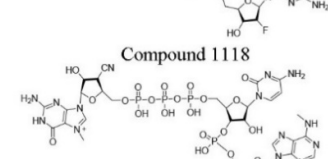
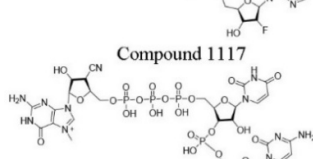
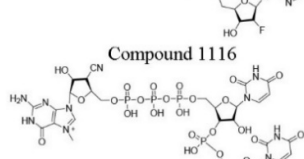
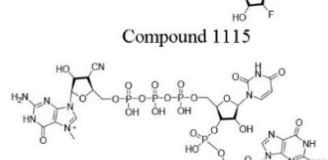
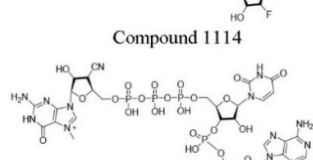
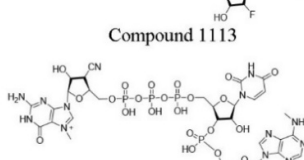
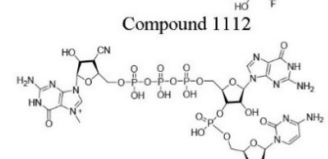
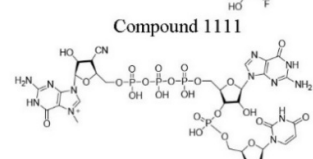
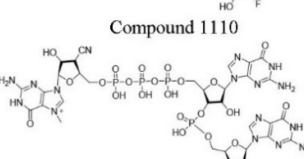
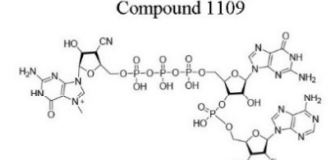
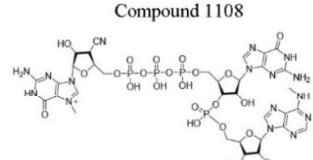
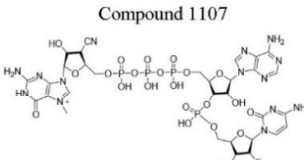
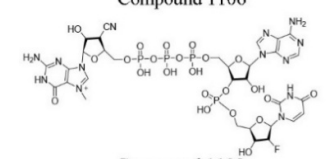
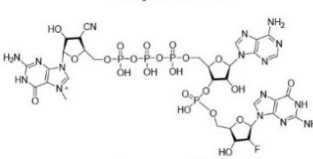
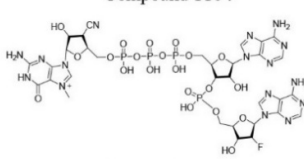
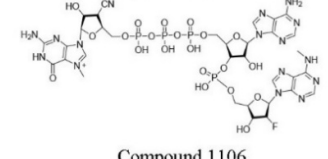
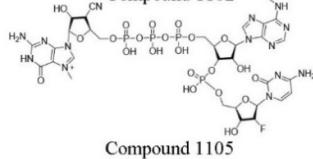
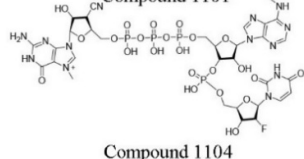
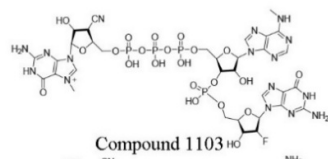
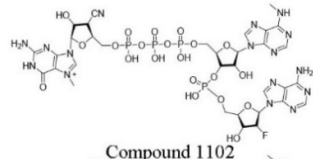
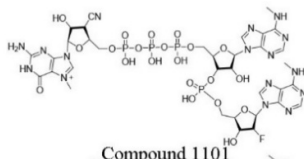
Compound 1098

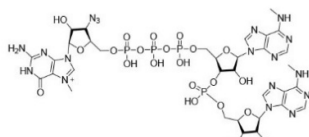


Compound 1099

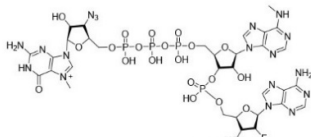


Compound 1100

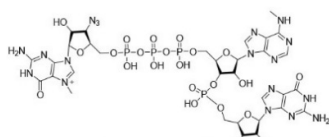




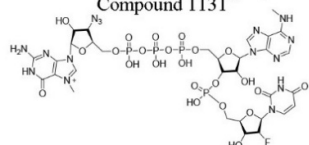
Compound 1131



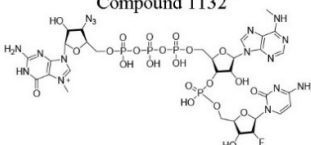
Compound 1132



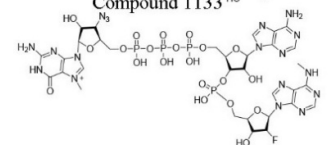
Compound 1133



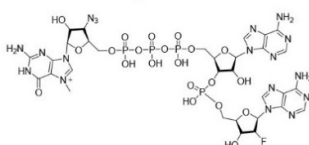
Compound 1134



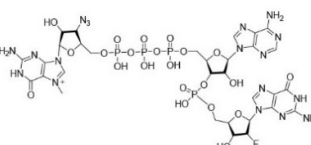
Compound 1135



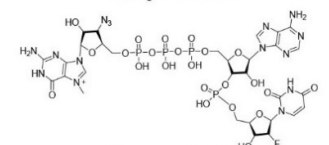
Compound 1136



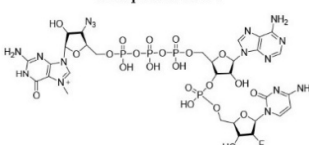
Compound 1137



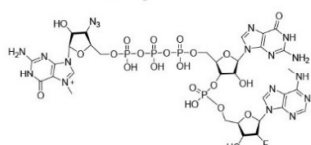
Compound 1138



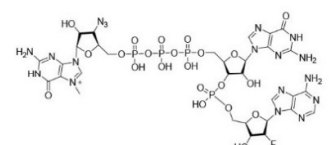
Compound 1139



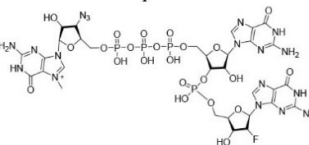
Compound 1140



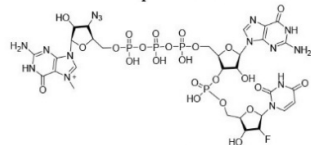
Compound 1141



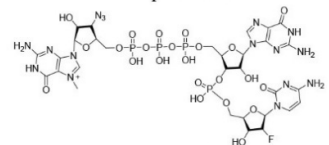
Compound 1142



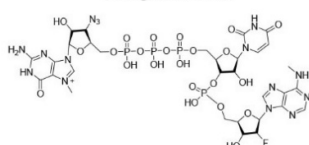
Compound 1143



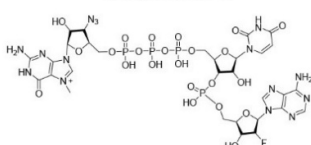
Compound 1144



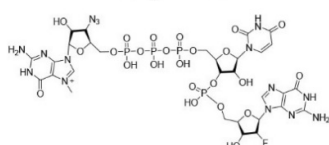
Compound 1145



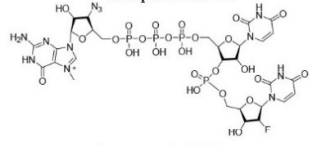
Compound 1146



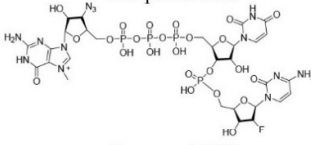
Compound 1147



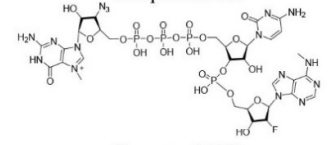
Compound 1148



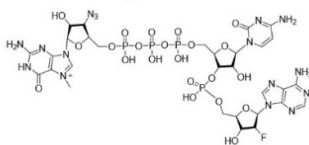
Compound 1149



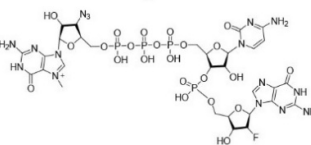
Compound 1150



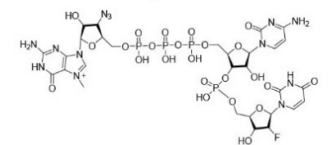
Compound 1151



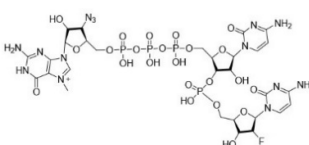
Compound 1152



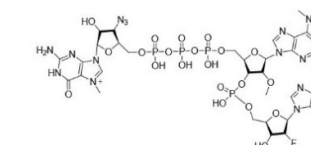
Compound 1153



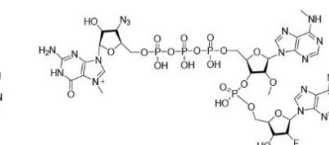
Compound 1154



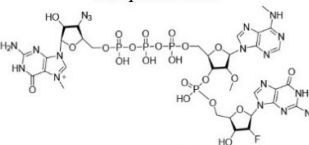
Compound 1155



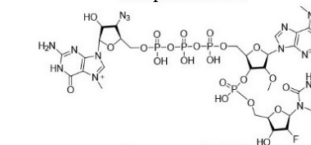
Compound 1156



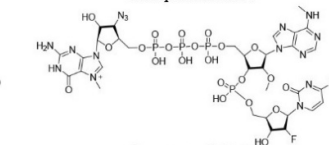
Compound 1157



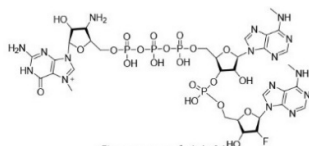
Compound 1158



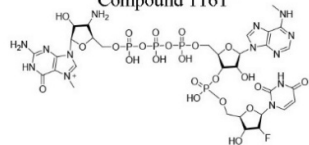
Compound 1159



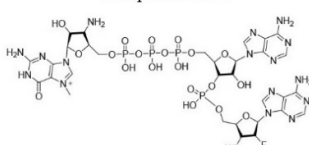
Compound 1160



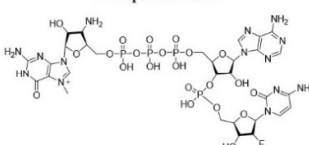
Compound 1161



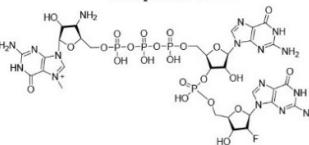
Compound 1164



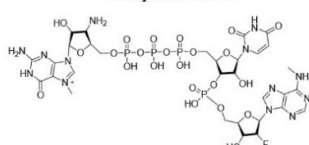
Compound 1167



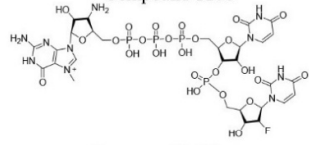
Compound 1170



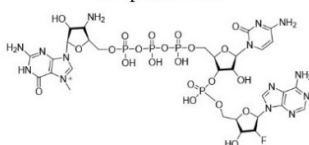
Compound 1173



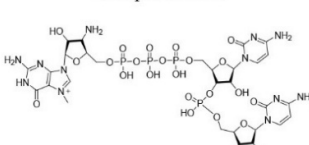
Compound 1176



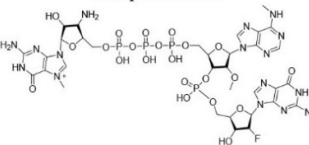
Compound 1179



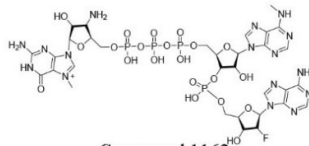
Compound 1182



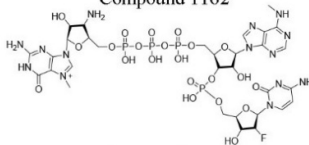
Compound 1185



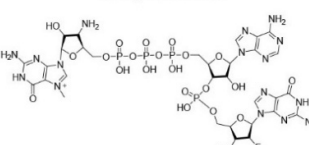
Compound 1188



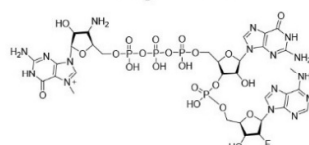
Compound 1162



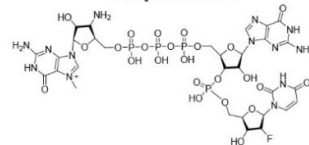
Compound 1165



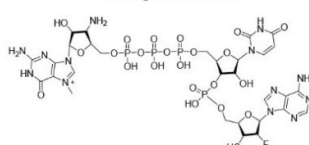
Compound 1168



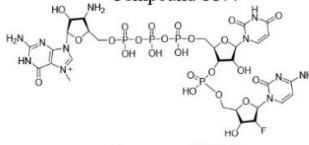
Compound 1171



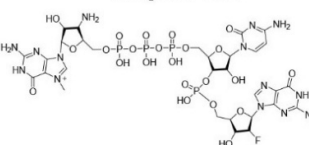
Compound 1174



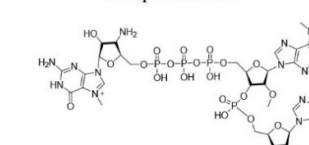
Compound 1177



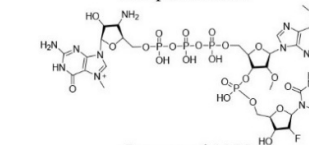
Compound 1180



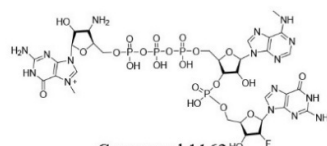
Compound 1183



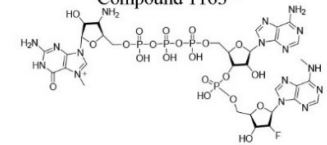
Compound 1186



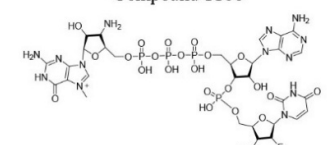
Compound 1189



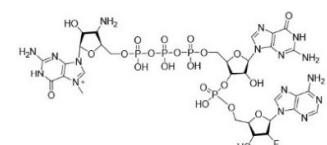
Compound 1163



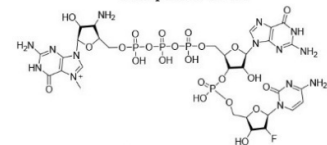
Compound 1166



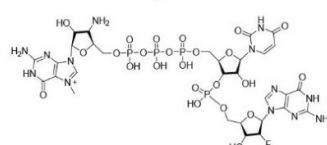
Compound 1169



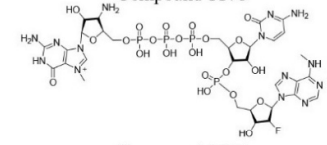
Compound 1172



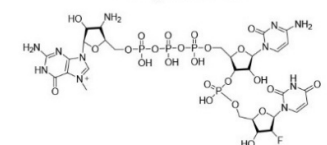
Compound 1175



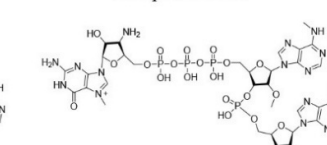
Compound 1178



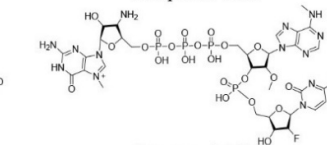
Compound 1181



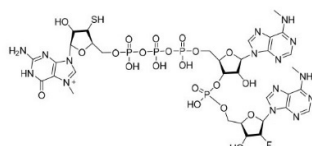
Compound 1184



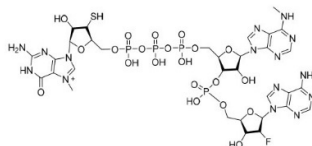
Compound 1187



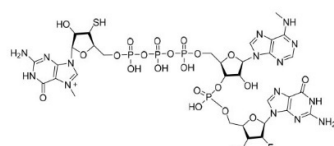
Compound 1190



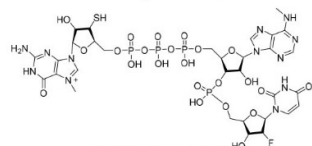
Compound 1191



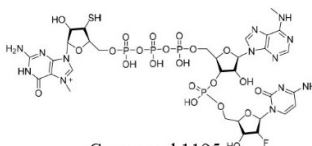
Compound 1192



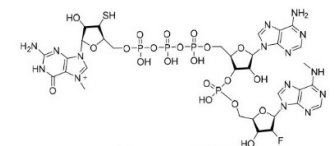
Compound 1193



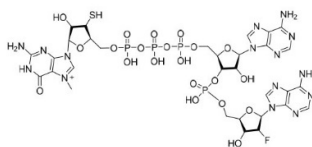
Compound 1194



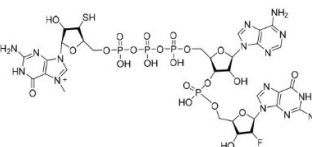
Compound 1195



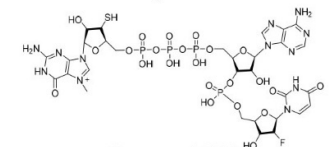
Compound 1196



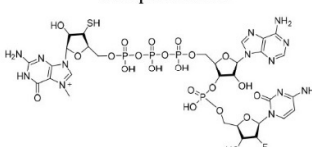
Compound 1197



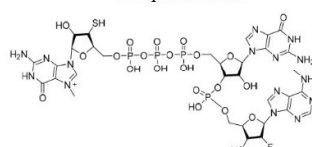
Compound 1198



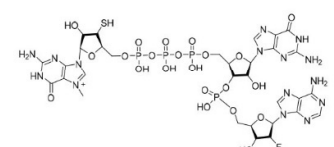
Compound 1199



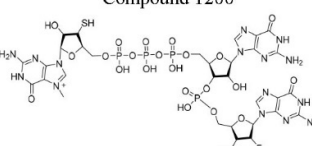
Compound 1200



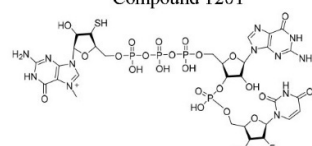
Compound 1201



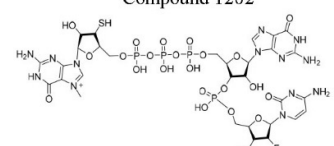
Compound 1202



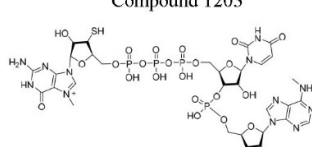
Compound 1203



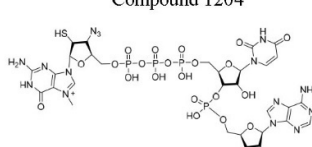
Compound 1204



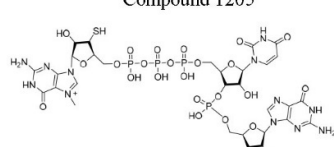
Compound 1205



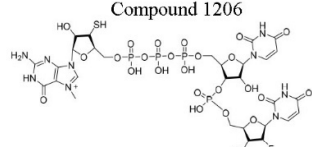
Compound 1206



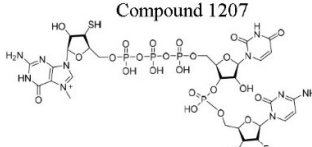
Compound 1207



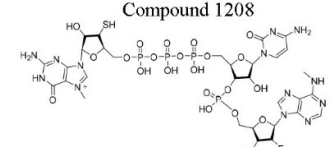
Compound 1208



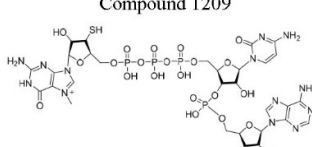
Compound 1209



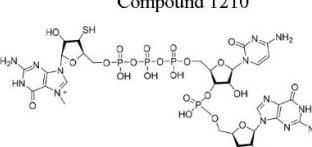
Compound 1210



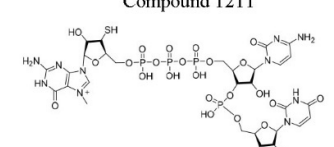
Compound 1211



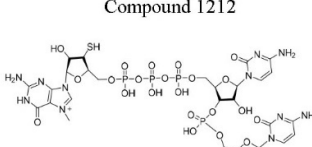
Compound 1212



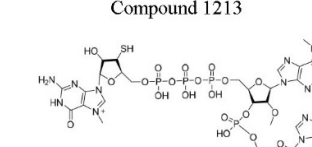
Compound 1213



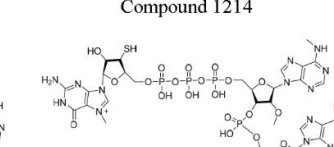
Compound 1214



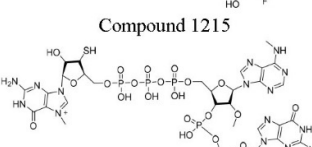
Compound 1215



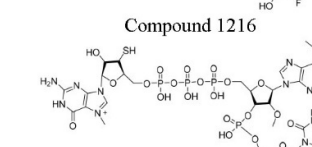
Compound 1216



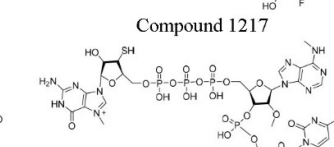
Compound 1217



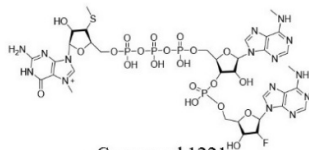
Compound 1218



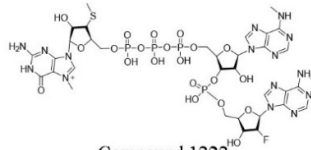
Compound 1219



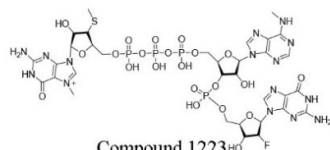
Compound 1220



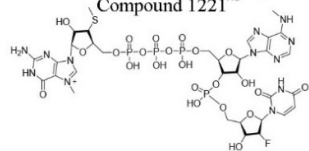
Compound 1221



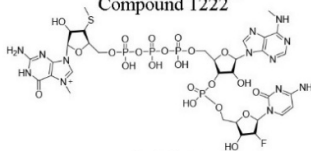
Compound 1222



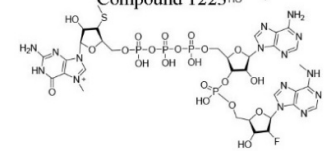
Compound 1223



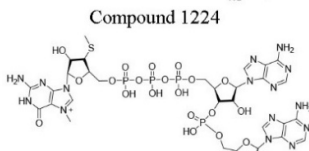
Compound 1224



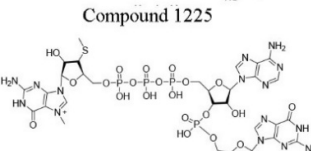
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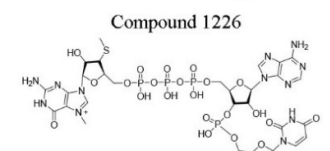
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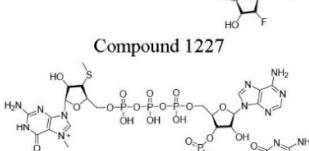
Compound 1227



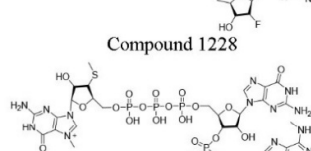
Compound 1228



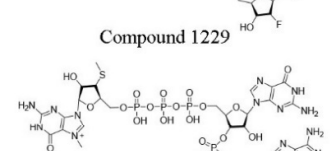
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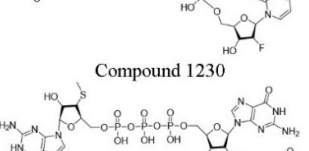
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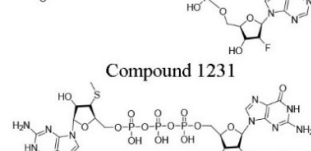
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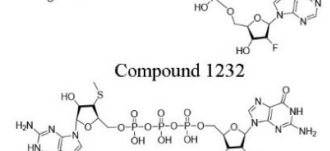
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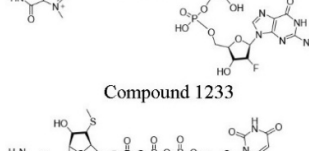
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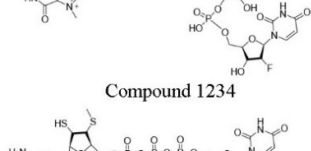
Compound 1234



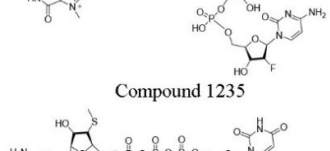
Compound 1235



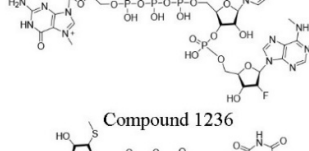
Compound 1236



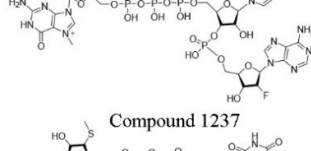
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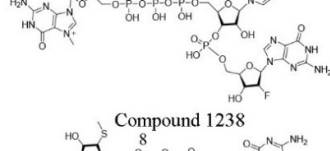
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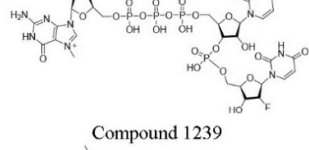
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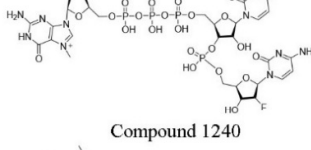
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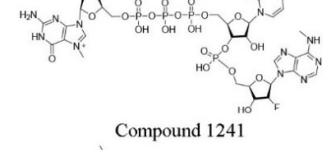
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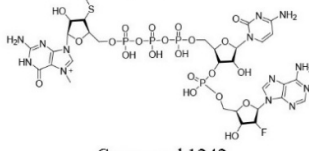
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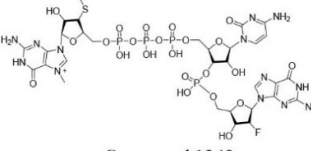
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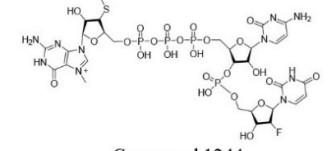
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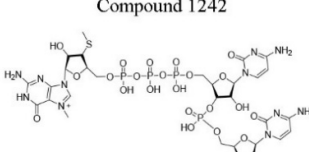
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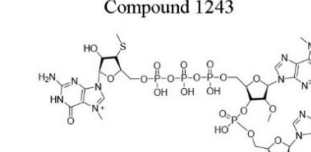
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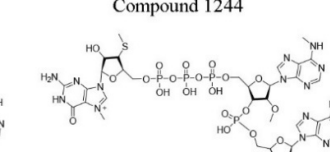
Compound 1247



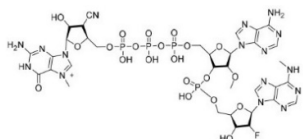
Compound 1248



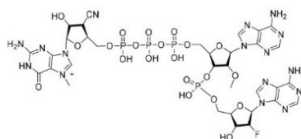
Compound 1249



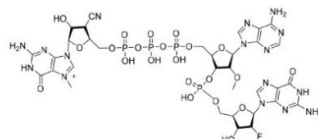
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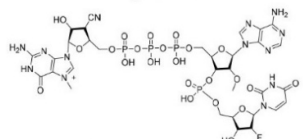
Compound 1251



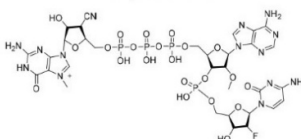
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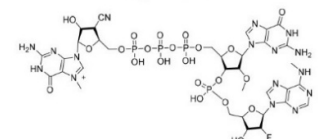
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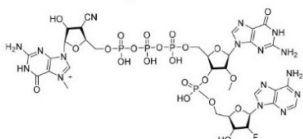
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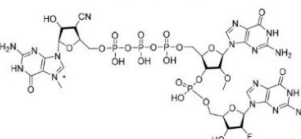
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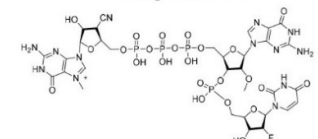
Compound 1256



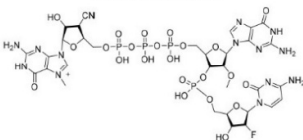
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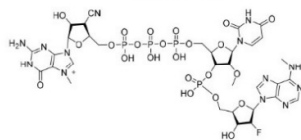
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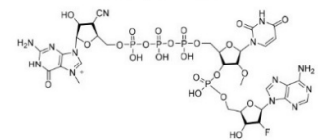
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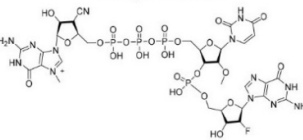
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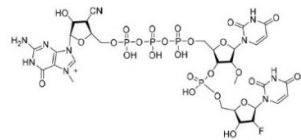
Compound 1261



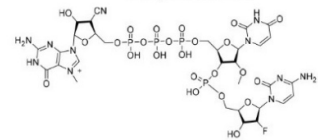
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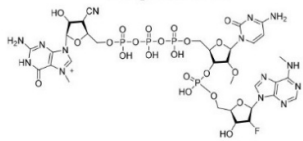
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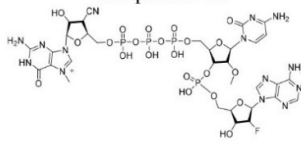
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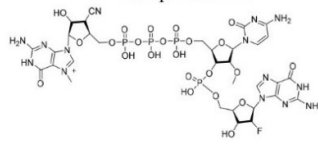
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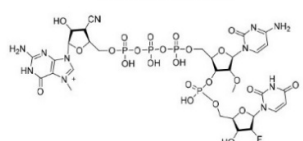
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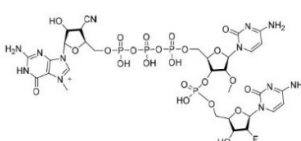
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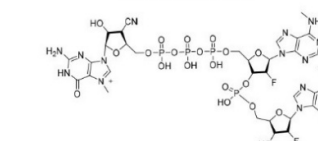
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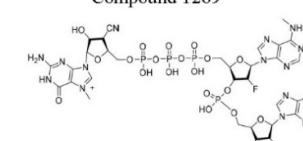
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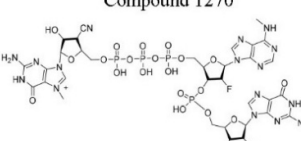
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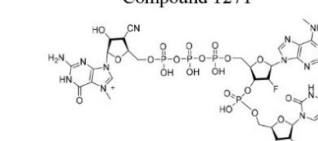
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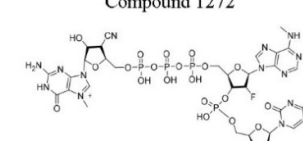
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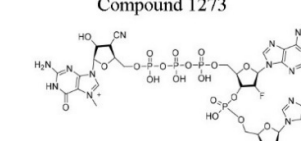
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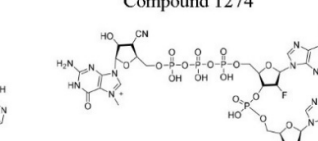
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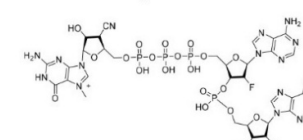
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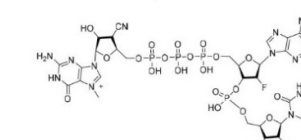
Compound 1276



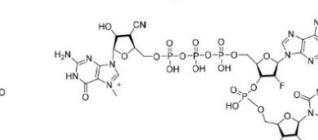
Compound 1277



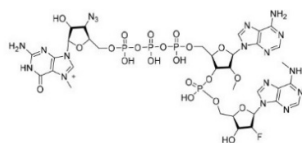
Compound 1278



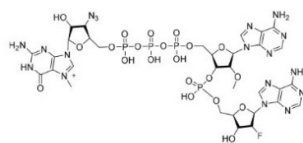
Compound 1279



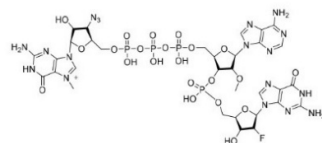
Compound 1280



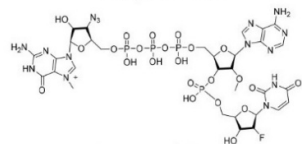
Compound 1281



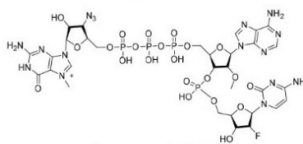
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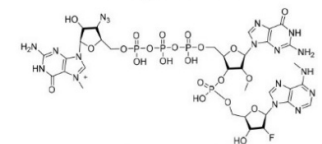
Compound 1283



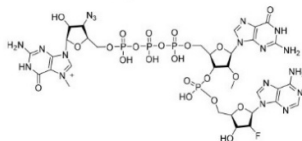
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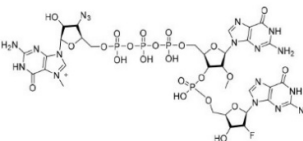
Compound 1285



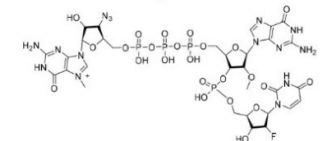
Compound 1286



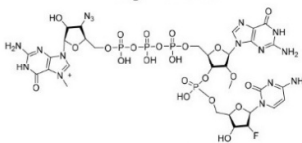
Compound 1287



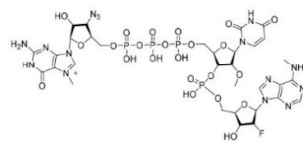
Compound 1288



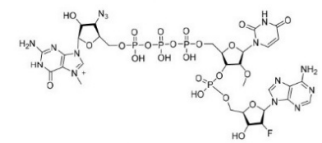
Compound 1289



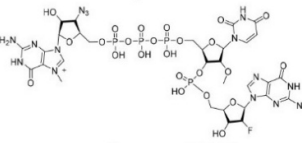
Compound 1290



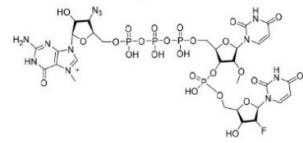
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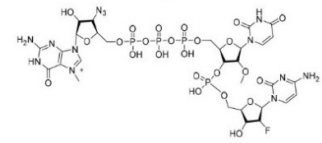
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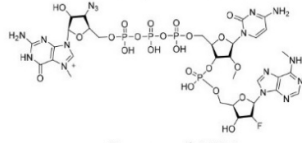
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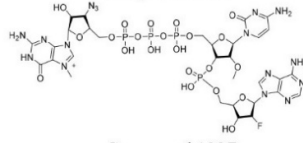
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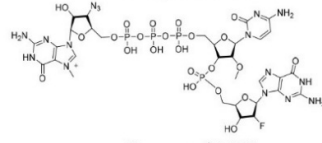
Compound 1295



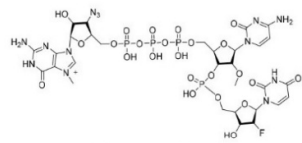
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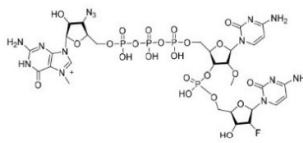
Compound 1297



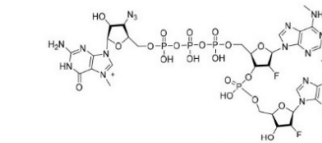
Compound 1298



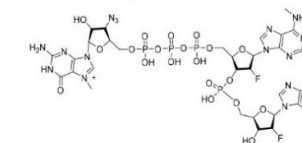
Compound 1299



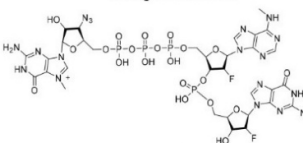
Compound 1300



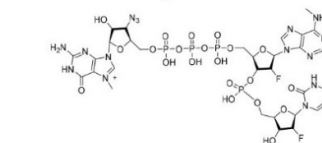
Compound 1301



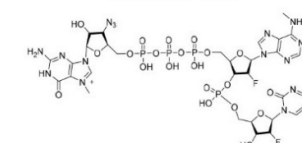
Compound 1302



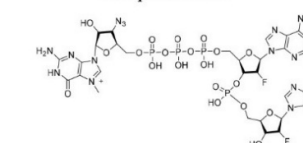
Compound 1303



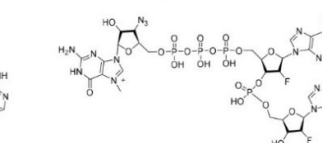
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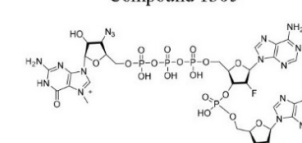
Compound 1305



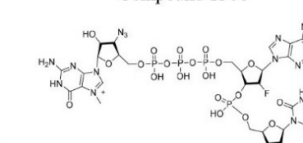
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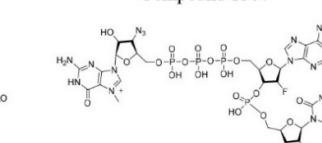
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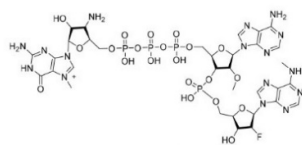
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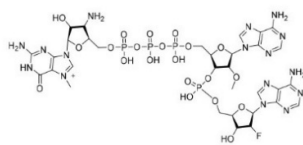
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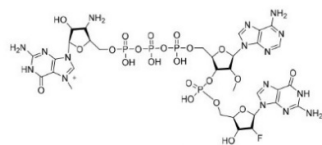
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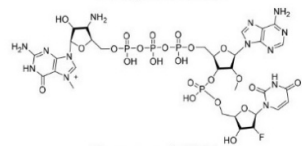
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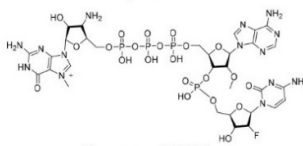
Compound 1312



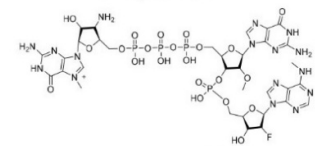
Compound 1313



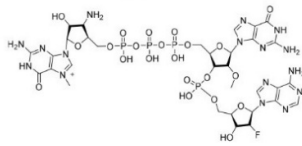
Compound 1314



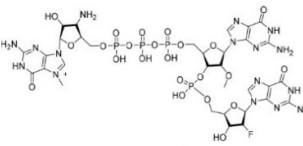
Compound 1315



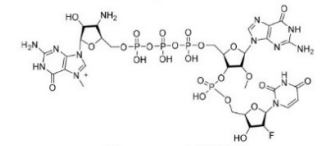
Compound 1316



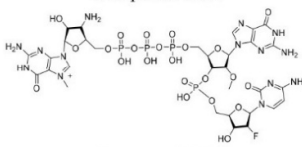
Compound 1317



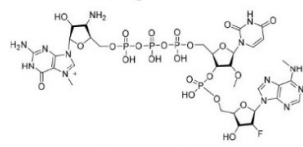
Compound 1318



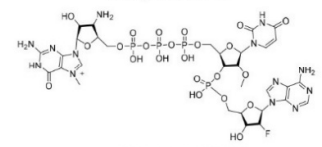
Compound 1319



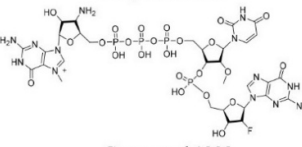
Compound 1320



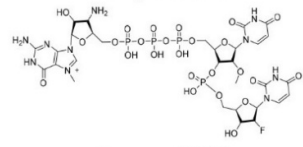
Compound 1321



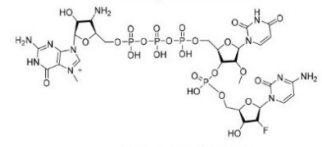
Compound 1322



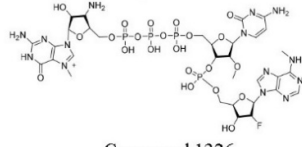
Compound 1323



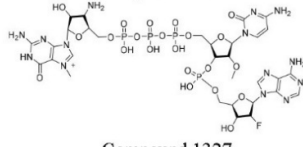
Compound 1324



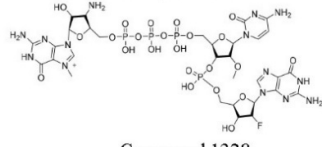
Compound 1325



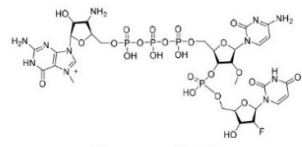
Compound 1326



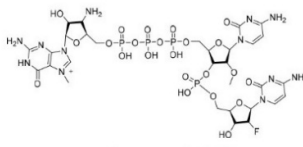
Compound 1327



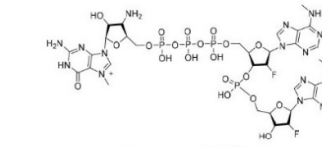
Compound 1328



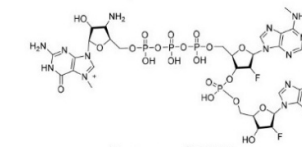
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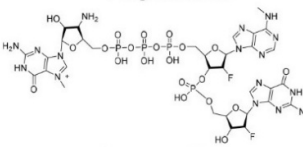
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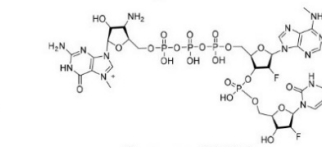
Compound 1331



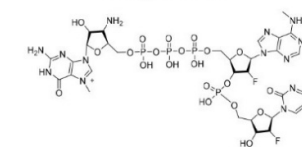
Compound 1332



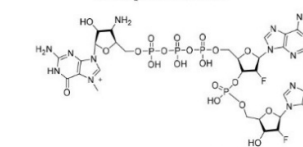
Compound 1333



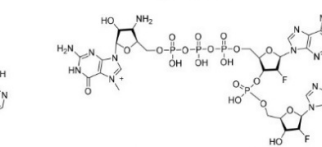
Compound 1334



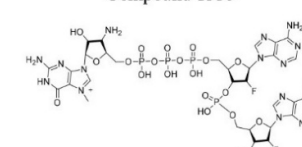
Compound 1335



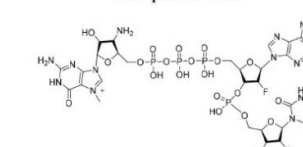
Compound 1336



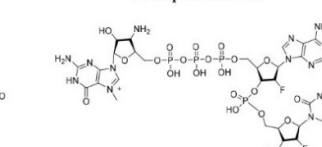
Compound 1337



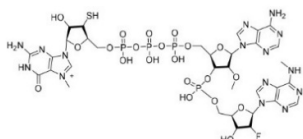
Compound 1338



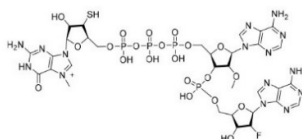
Compound 1339



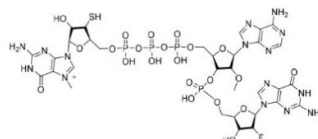
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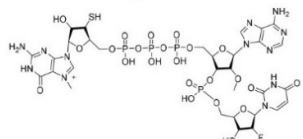
Compound 1341



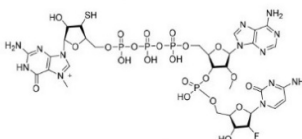
Compound 1342



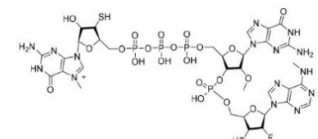
Compound 1343



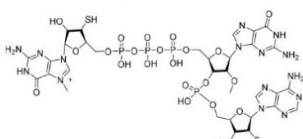
Compound 1344



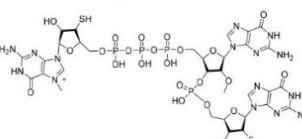
Compound 1345



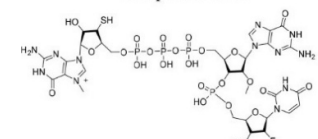
Compound 1346



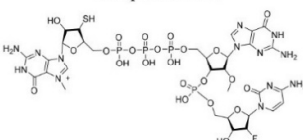
Compound 1347



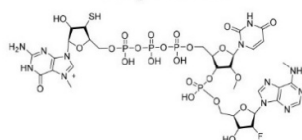
Compound 1348



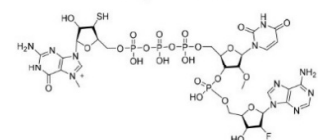
Compound 1349



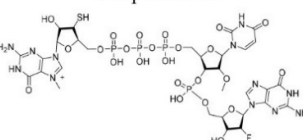
Compound 1350



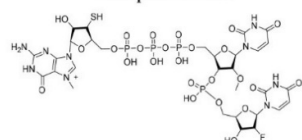
Compound 1351



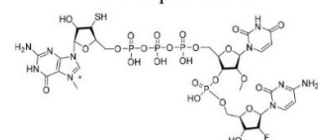
Compound 1352



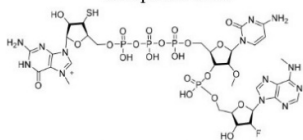
Compound 1353



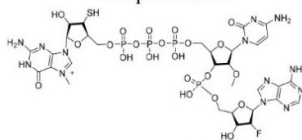
Compound 1354



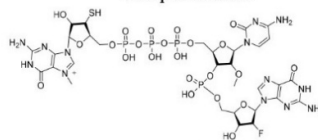
Compound 1355



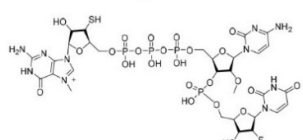
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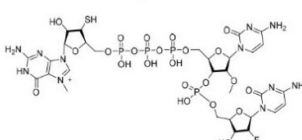
Compound 1357



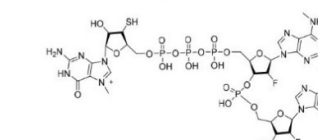
Compound 1358



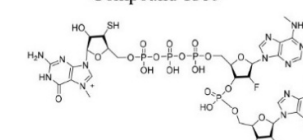
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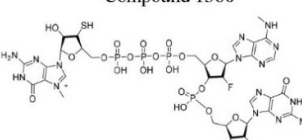
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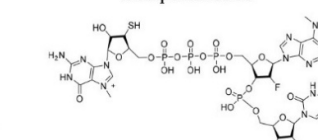
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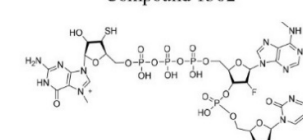
Compound 1362



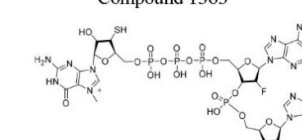
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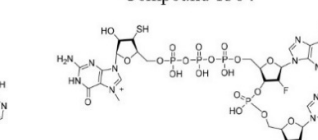
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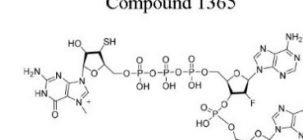
Compound 1365



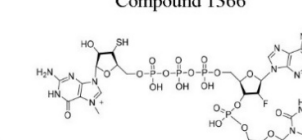
Compound 1366



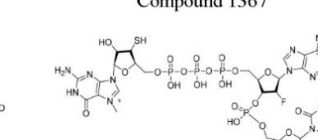
Compound 1367



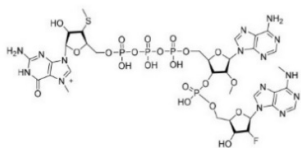
Compound 1368



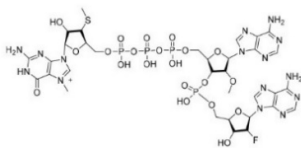
Compound 1369



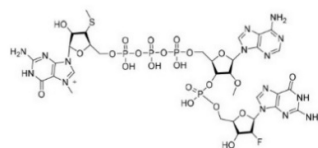
Compound 1370



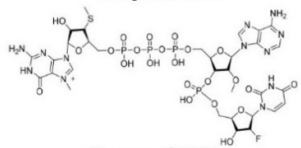
Compound 1371



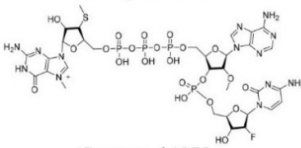
Compound 1372



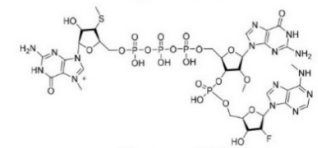
Compound 1373



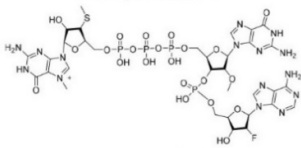
Compound 1374



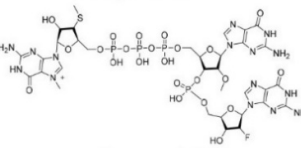
Compound 1375



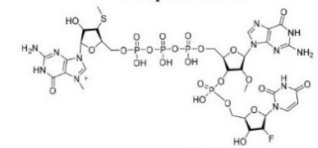
Compound 1376



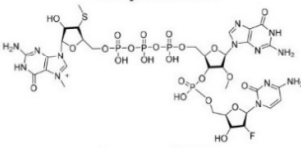
Compound 1377



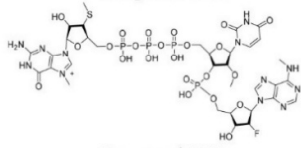
Compound 1378



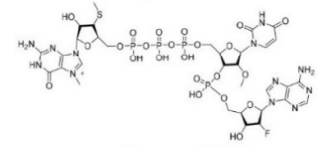
Compound 1379



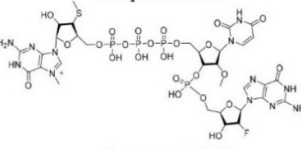
Compound 1380



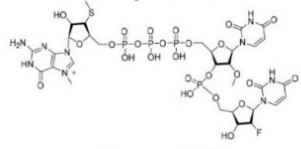
Compound 1381



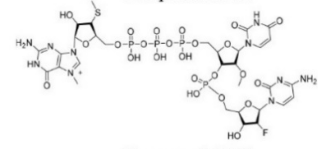
Compound 1382



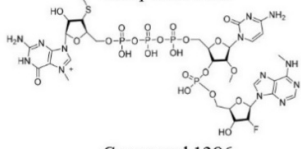
Compound 1383



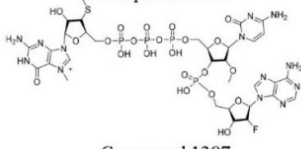
Compound 1384



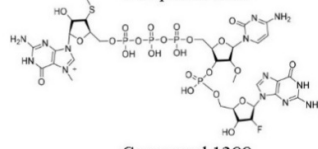
Compound 1385



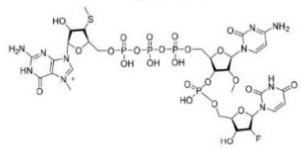
Compound 1386



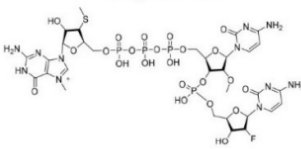
Compound 1387



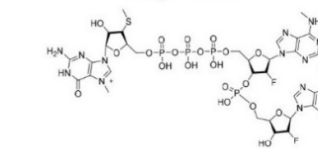
Compound 1388



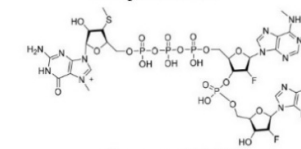
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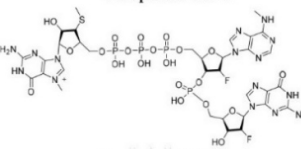
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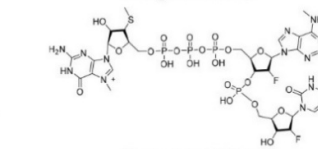
Compound 1391



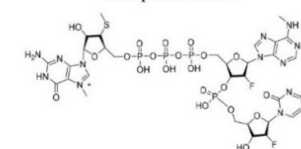
Compound 1392



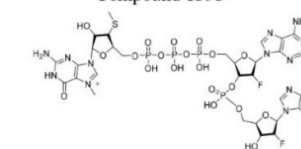
Compound 1393



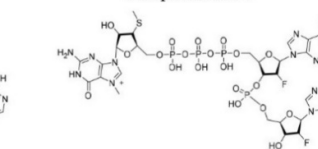
Compound 1394



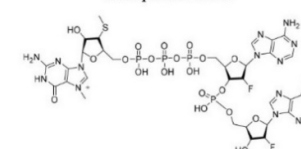
Compound 1395



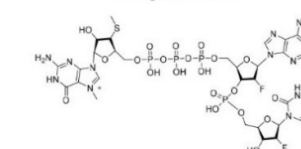
Compound 1396



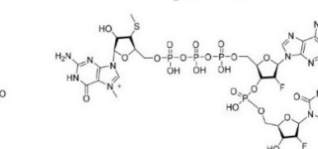
Compound 1397



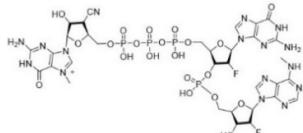
Compound 1398



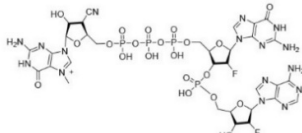
Compound 1399



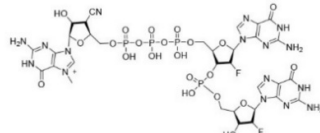
Compound 1400



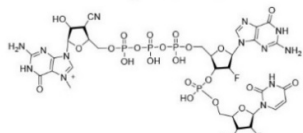
Compound 1401



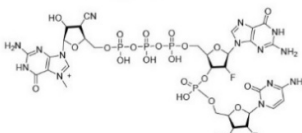
Compound 1402



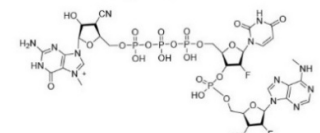
Compound 1403



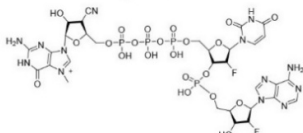
Compound 1404



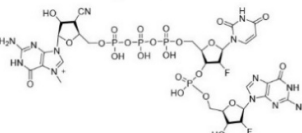
Compound 1405



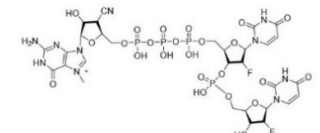
Compound 1406



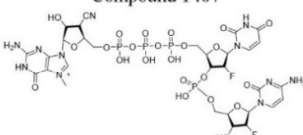
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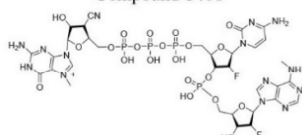
Compound 1408



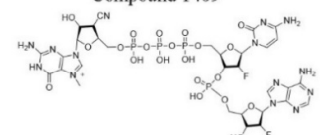
Compound 1409



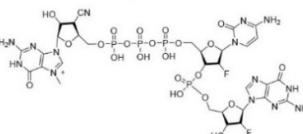
Compound 1410



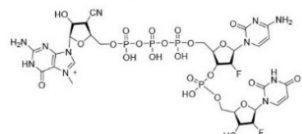
Compound 1411



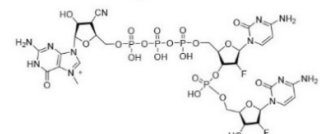
Compound 1412



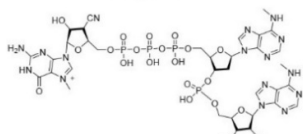
Compound 1413



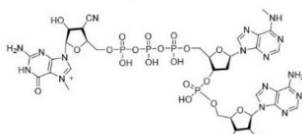
Compound 1414



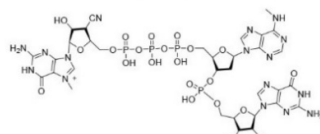
Compound 1415



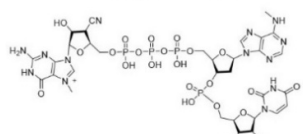
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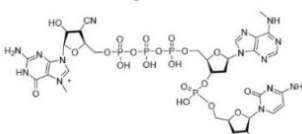
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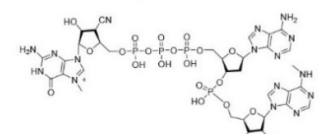
Compound 1418



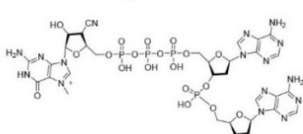
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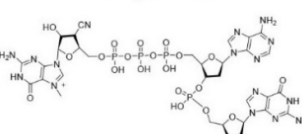
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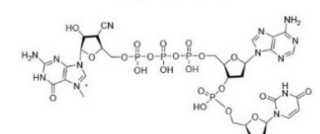
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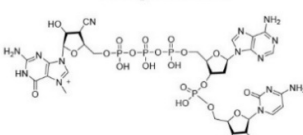
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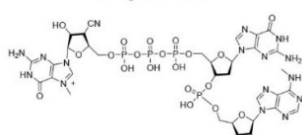
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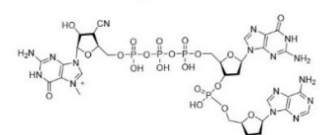
Compound 1424



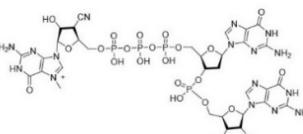
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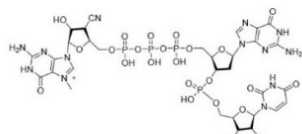
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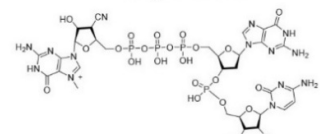
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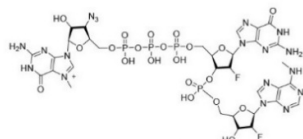
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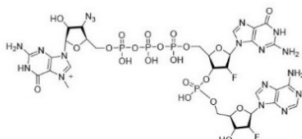
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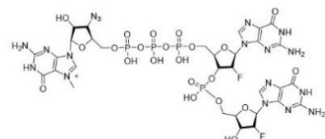
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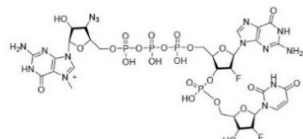
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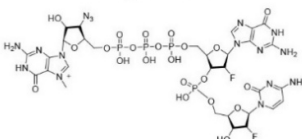
Compound 1432



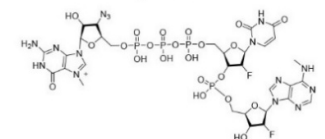
Compound 1433



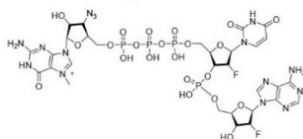
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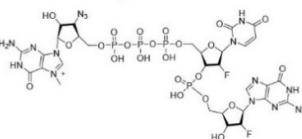
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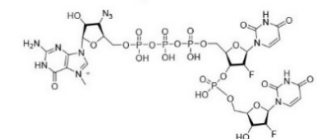
Compound 1436



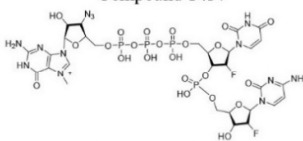
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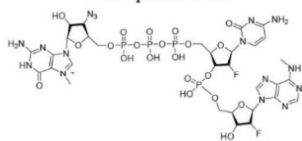
Compound 1438



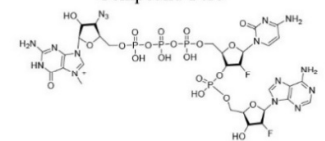
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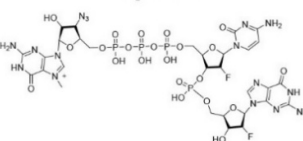
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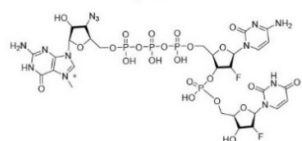
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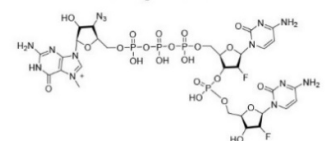
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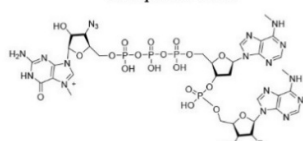
Compound 1443



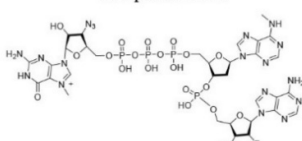
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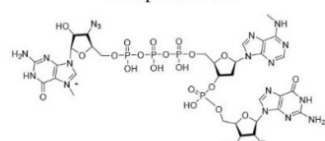
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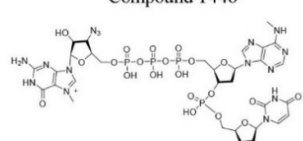
Compound 1446



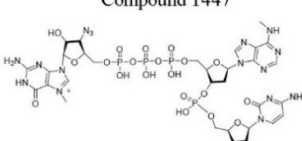
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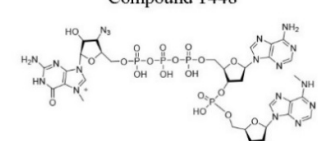
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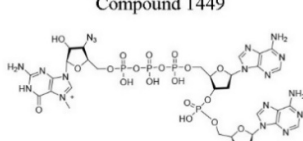
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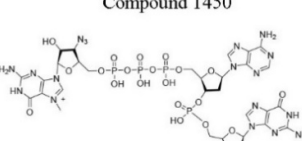
Compound 1450



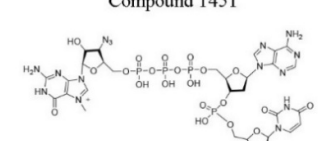
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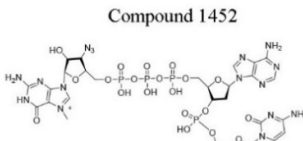
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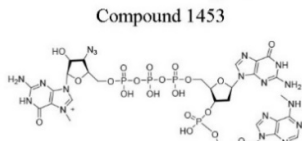
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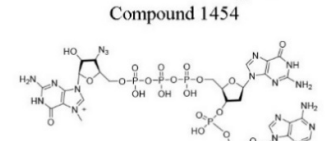
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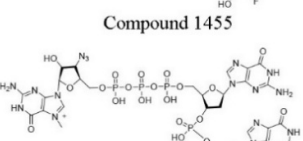
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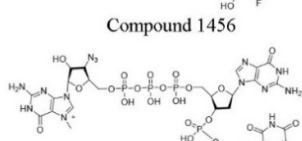
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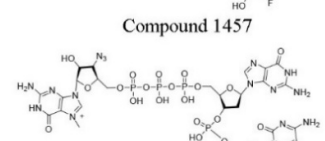
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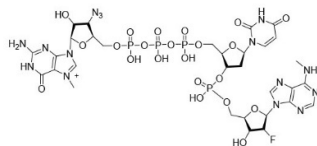
Compound 1458



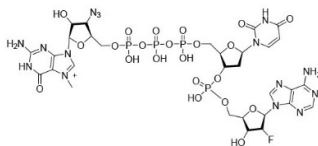
Compound 1459



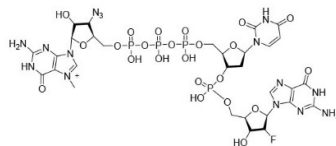
Compound 1460



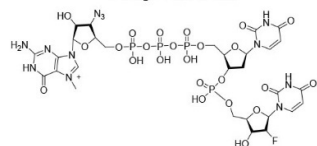
Compound 1461



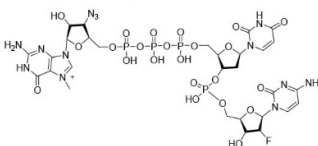
Compound 1462



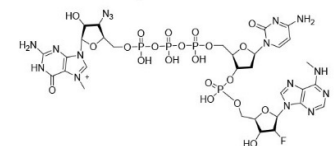
Compound 1463



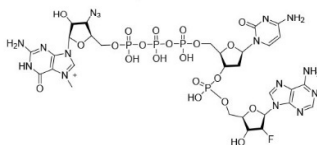
Compound 1464



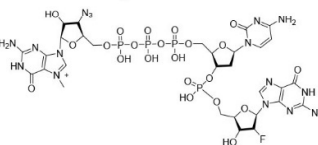
Compound 1465



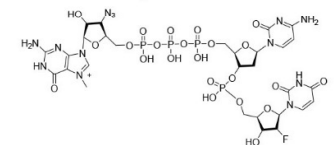
Compound 1466



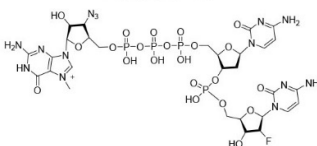
Compound 1467



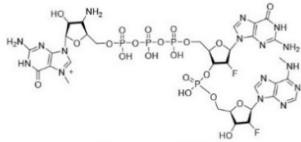
Compound 1468



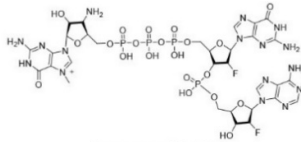
Compound 1469



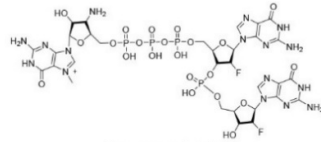
Compound 1470



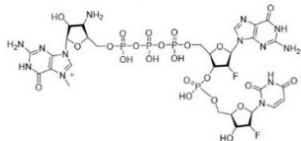
Compound 1471



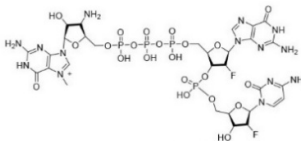
Compound 1472



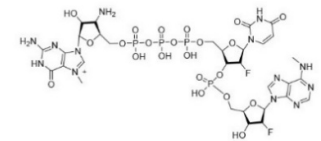
Compound 1473



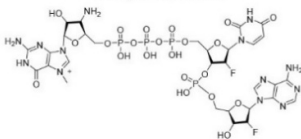
Compound 1474



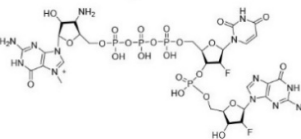
Compound 1475



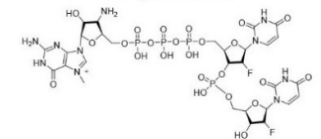
Compound 1476



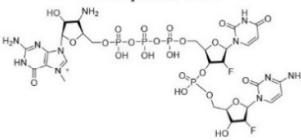
Compound 1477



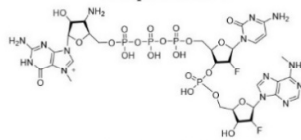
Compound 1478



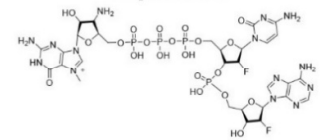
Compound 1479



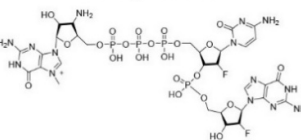
Compound 1480



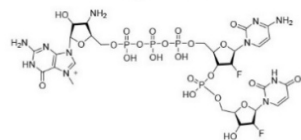
Compound 1481



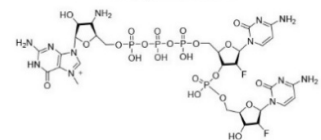
Compound 1482



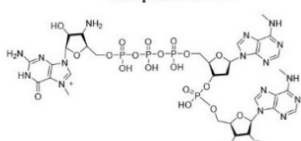
Compound 1483



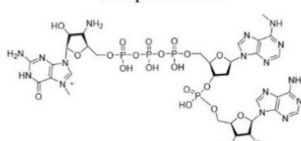
Compound 1484



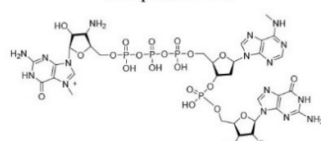
Compound 1485



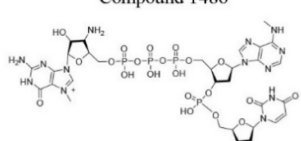
Compound 1486



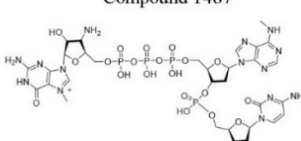
Compound 1487



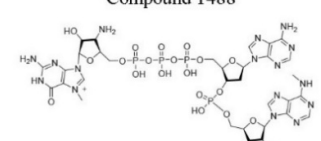
Compound 1488



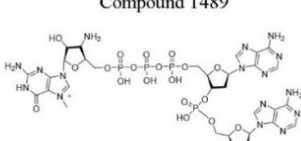
Compound 1489



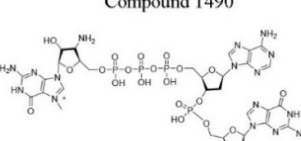
Compound 1490



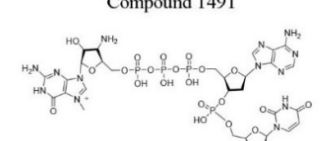
Compound 1491



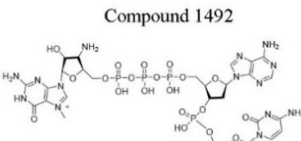
Compound 1492



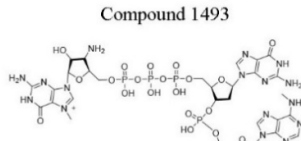
Compound 1493



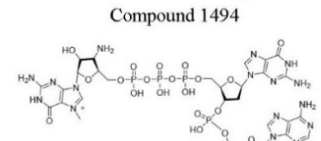
Compound 1494



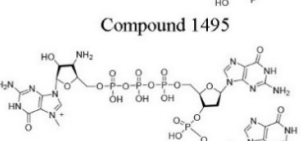
Compound 1495



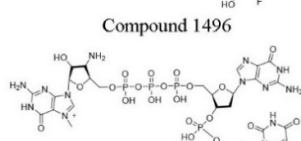
Compound 1496



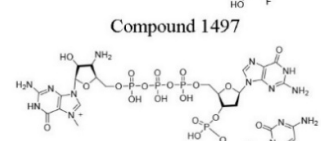
Compound 1497



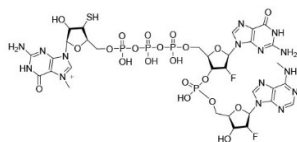
Compound 1498



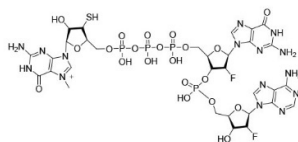
Compound 1499



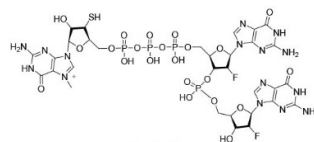
Compound 1500



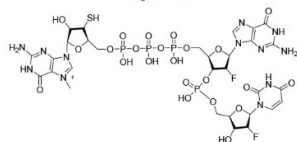
Compound 1501



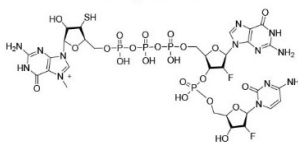
Compound 1502



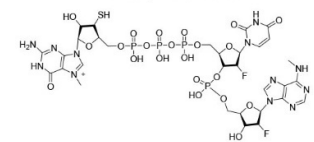
Compound 1503



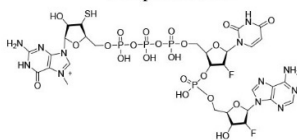
Compound 1504



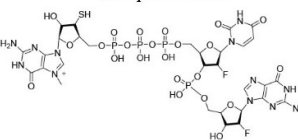
Compound 1505



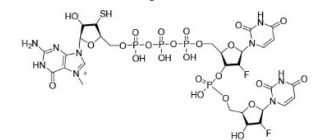
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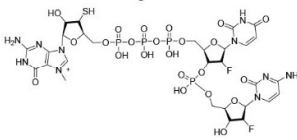
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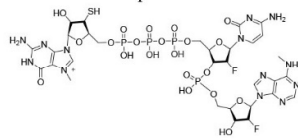
Compound 1508



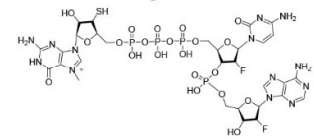
Compound 1509



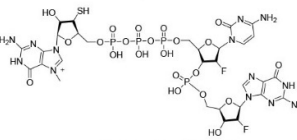
Compound 1510



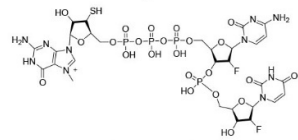
Compound 1511



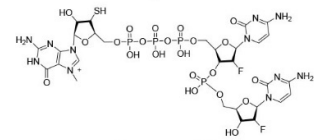
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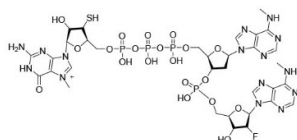
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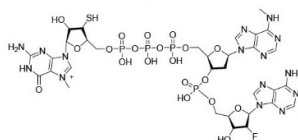
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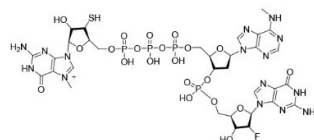
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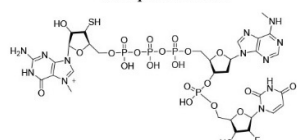
Compound 1516



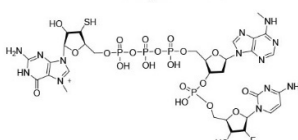
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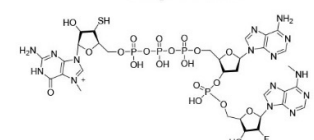
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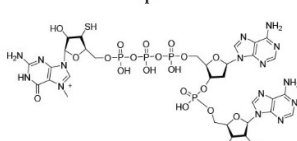
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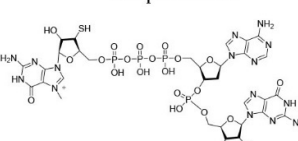
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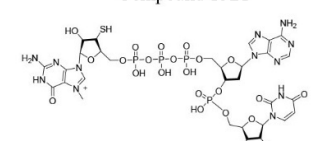
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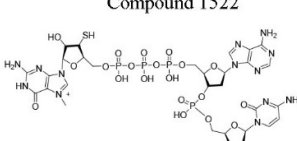
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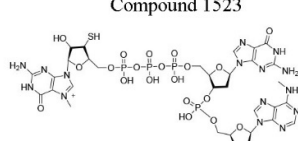
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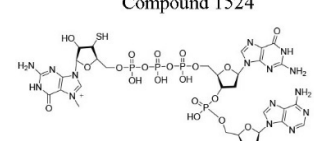
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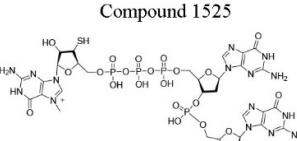
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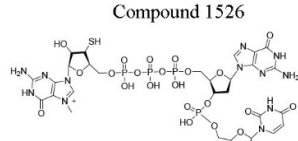
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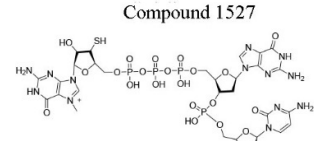
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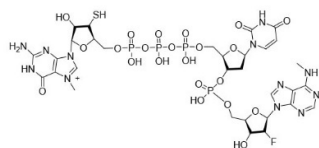
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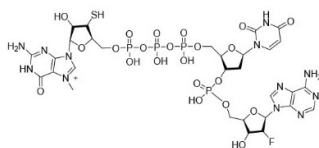
Compound 1529



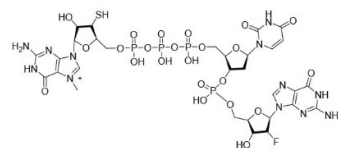
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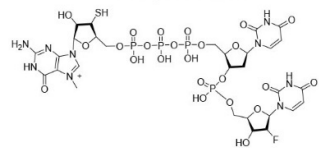
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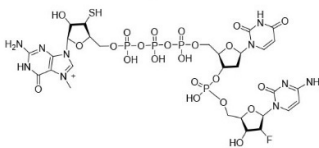
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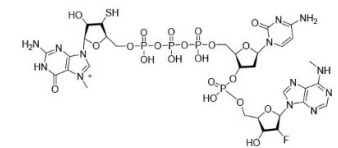
Compound 1533



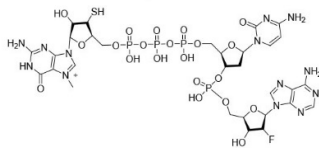
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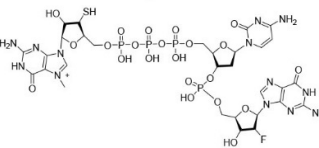
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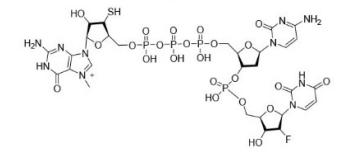
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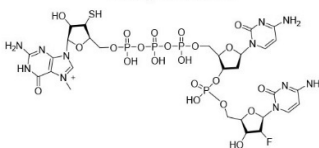
Compound 1537



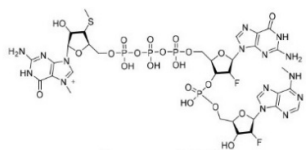
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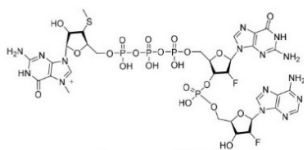
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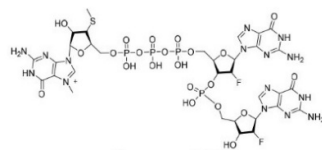
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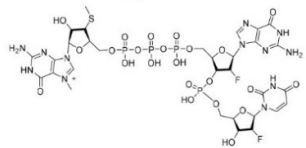
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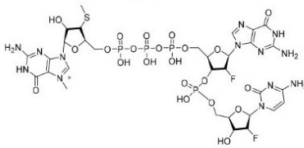
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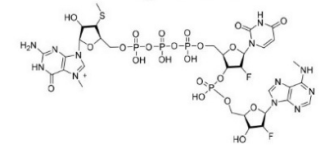
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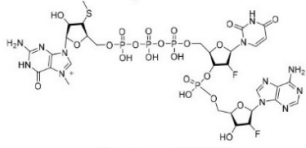
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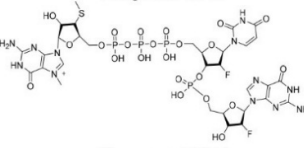
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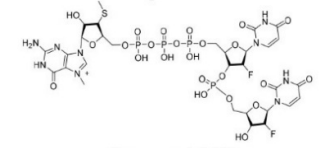
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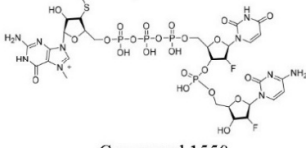
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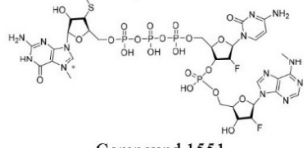
Compound 1548



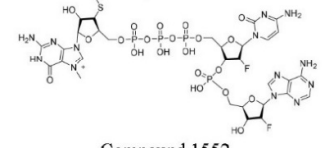
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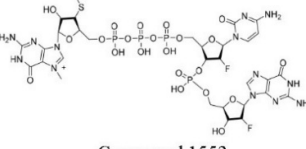
Compound 1550



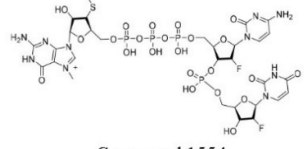
Compound 1551



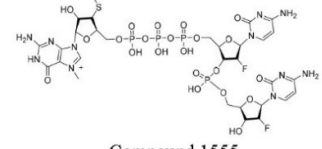
Compound 1552



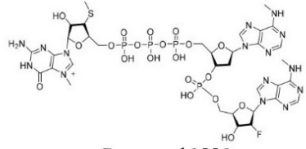
Compound 1553



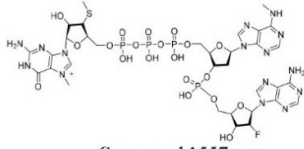
Compound 1554



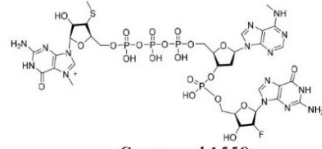
Compound 1555



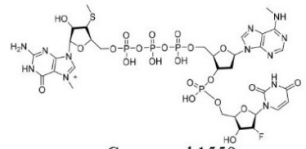
Compound 1556



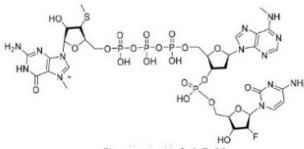
Compound 1557



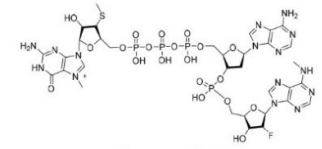
Compound 1558



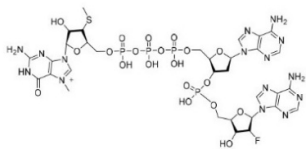
Compound 1559



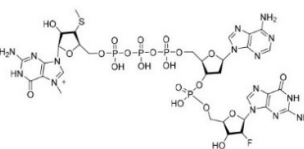
Compound 1560



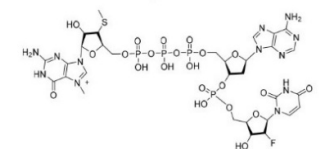
Compound 1561



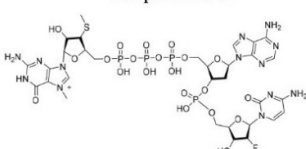
Compound 1562



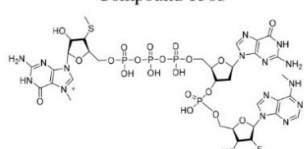
Compound 1563



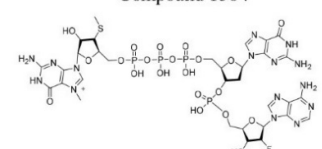
Compound 1564



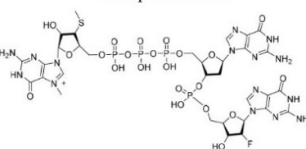
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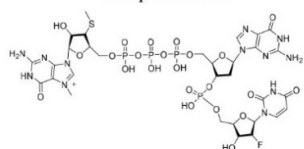
Compound 1566



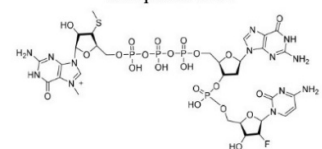
Compound 1567



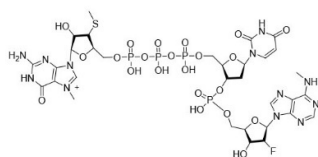
Compound 1568



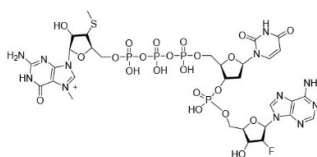
Compound 1569



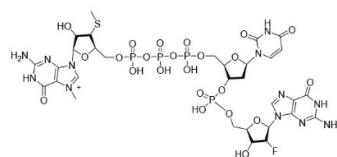
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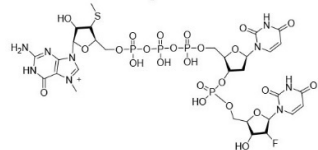
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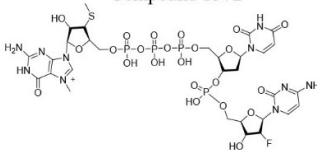
Compound 1572



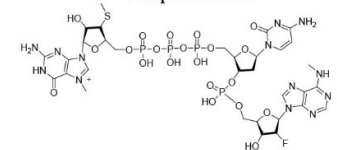
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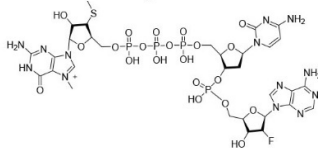
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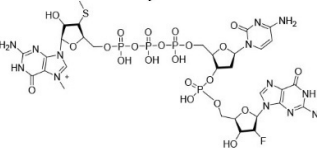
Compound 1575



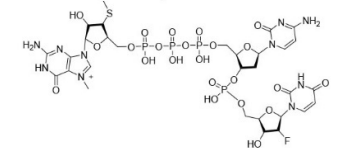
Compound 1576



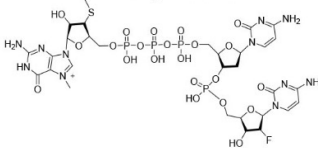
Compound 1577



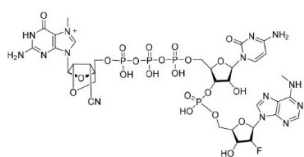
Compound 1578



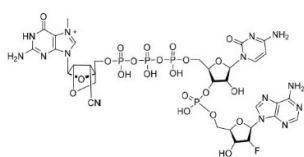
Compound 1579



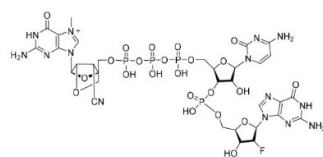
Compound 1580



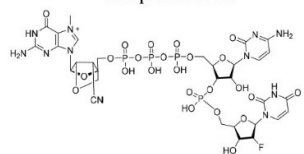
Compound 1581



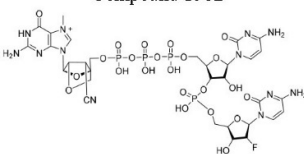
Compound 1582



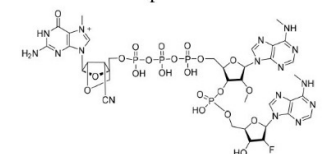
Compound 1583



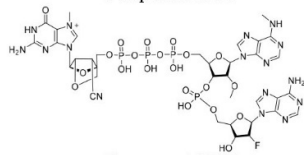
Compound 1584



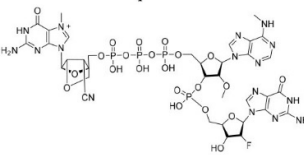
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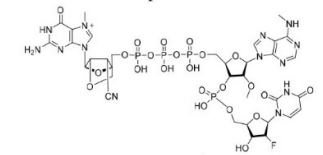
Compound 1586



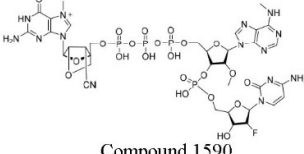
Compound 1587



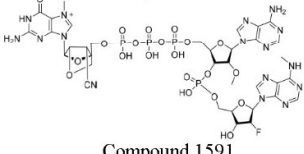
Compound 1588



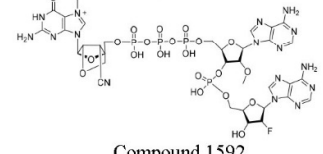
Compound 1589



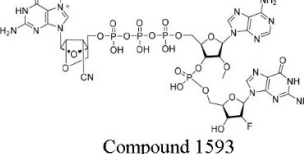
Compound 1590



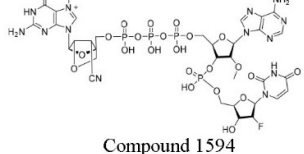
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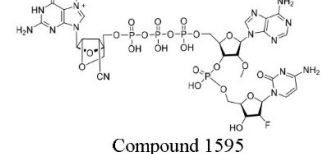
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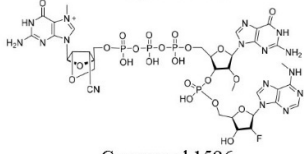
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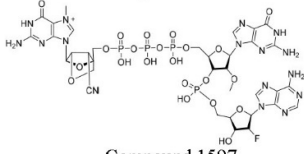
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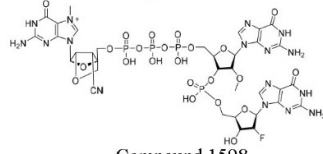
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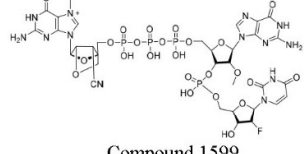
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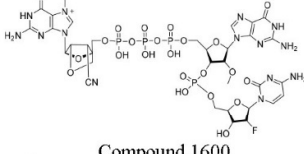
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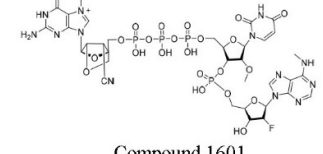
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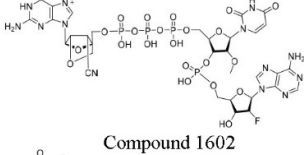
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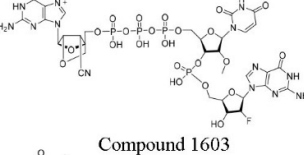
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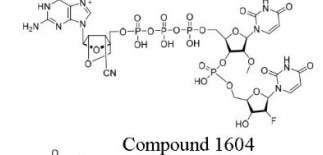
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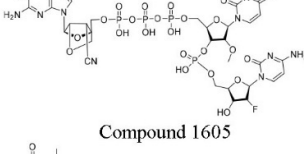
Compound 1602



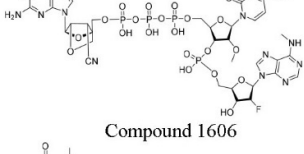
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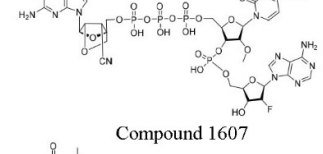
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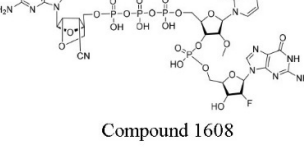
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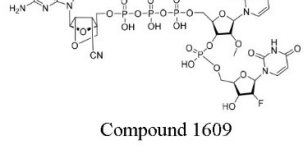
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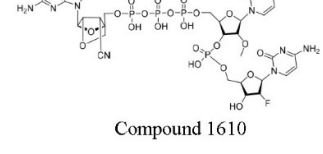
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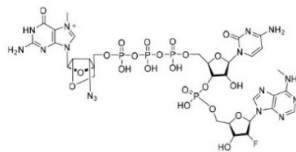
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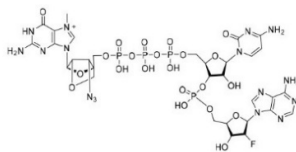
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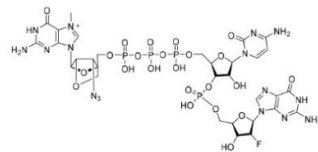
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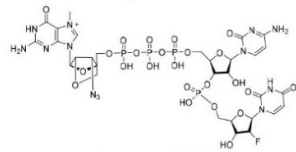
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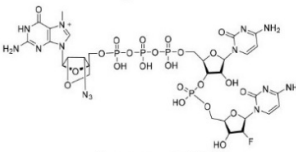
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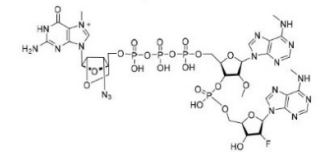
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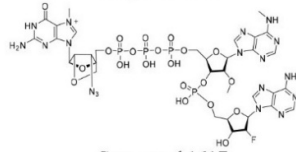
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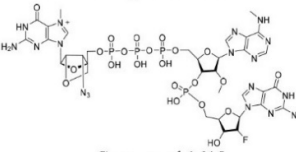
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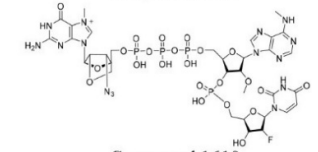
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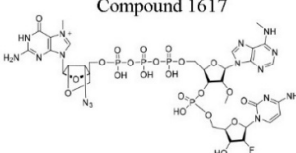
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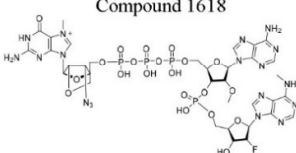
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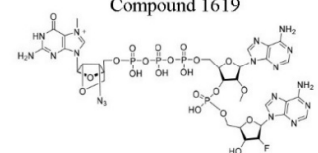
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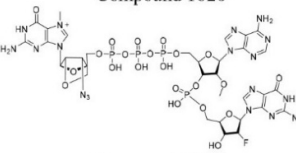
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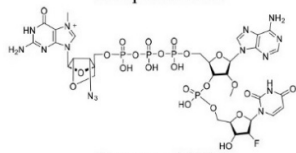
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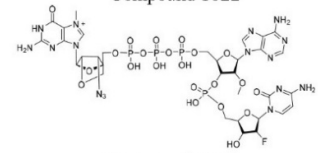
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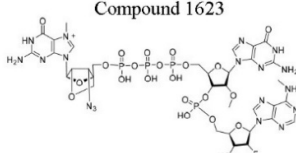
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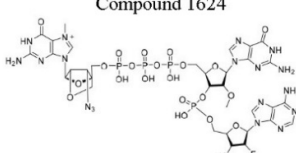
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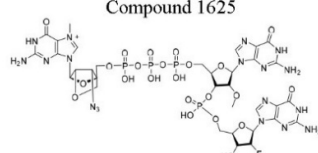
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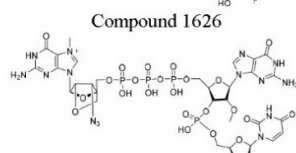
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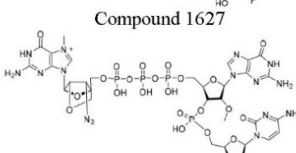
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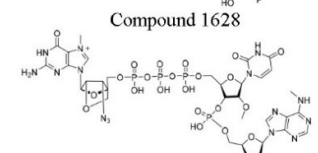
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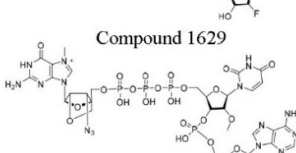
Compound 1629



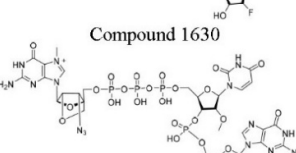
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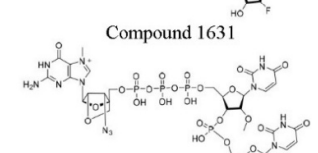
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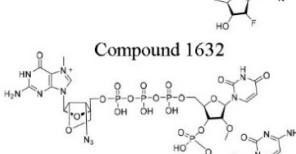
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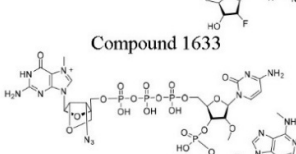
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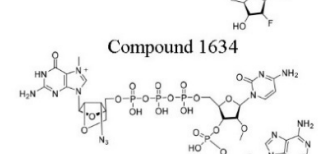
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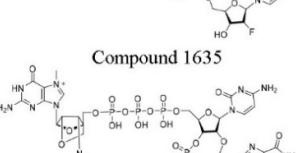
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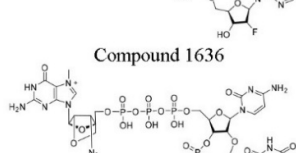
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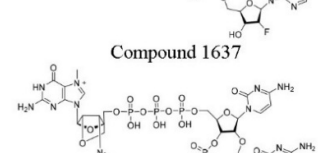
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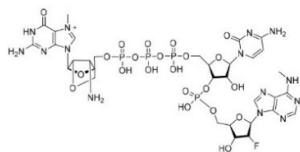
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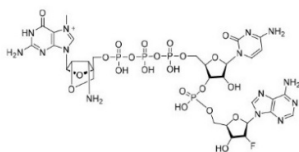
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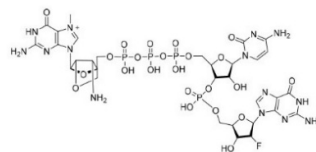
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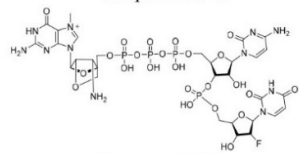
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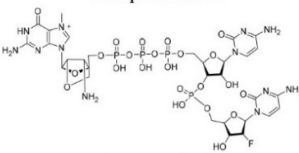
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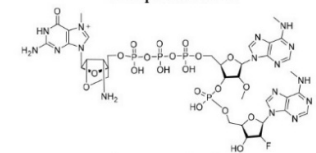
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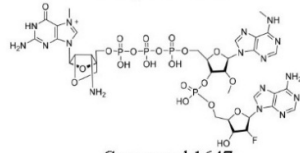
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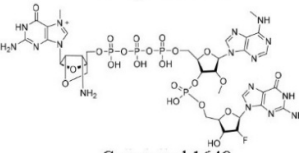
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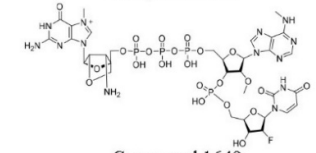
Compound 1646



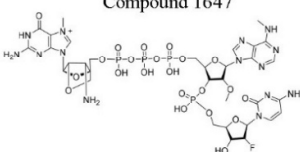
Compound 1647



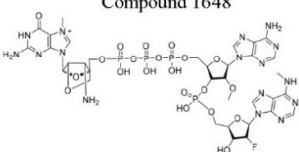
Compound 1648



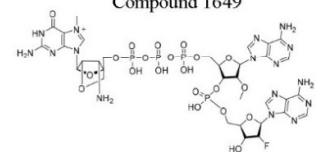
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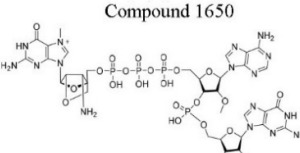
Compound 1650



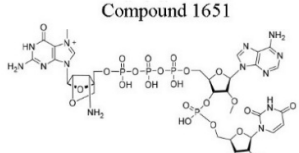
Compound 1651



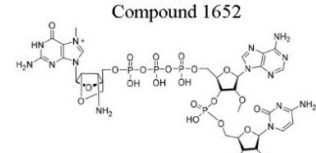
Compound 1652



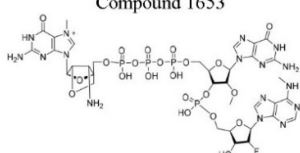
Compound 1653



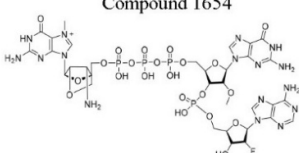
Compound 1654



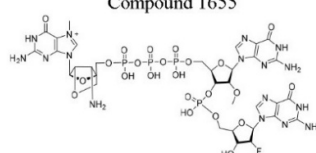
Compound 1655



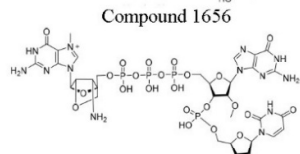
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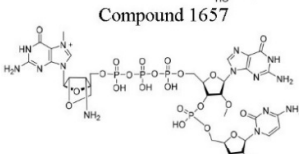
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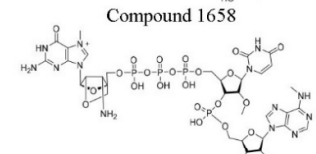
Compound 1658



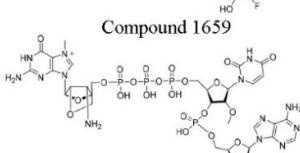
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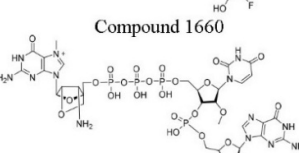
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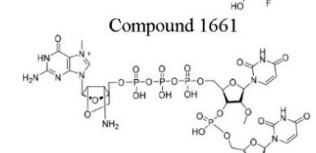
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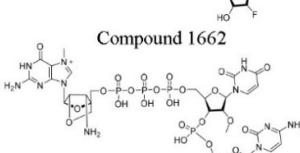
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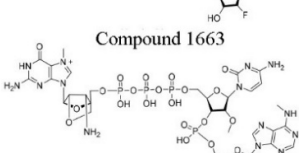
Compound 1663



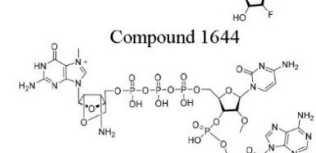
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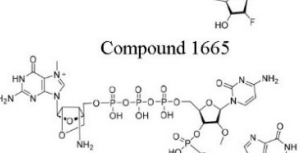
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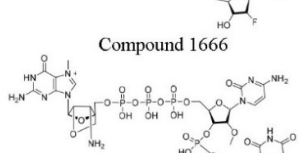
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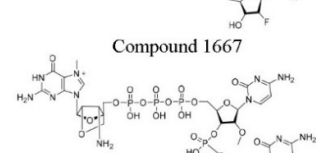
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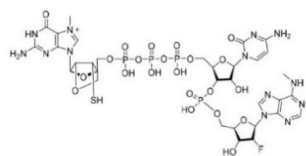
Compound 1668



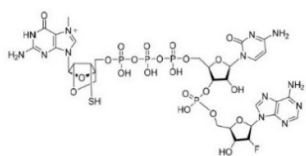
Compound 1669



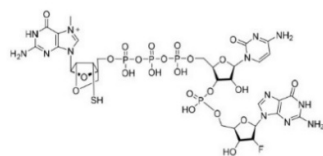
Compound 1670



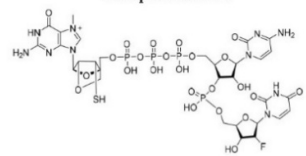
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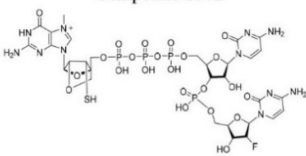
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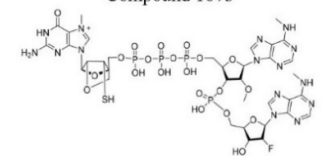
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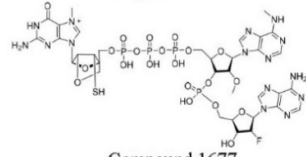
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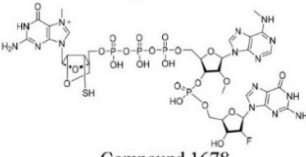
Compound 1675



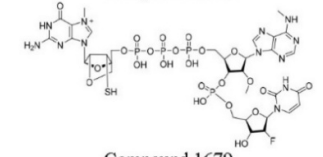
Compound 1676



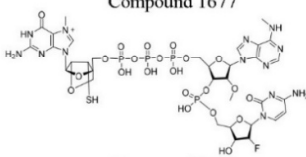
Compound 1677



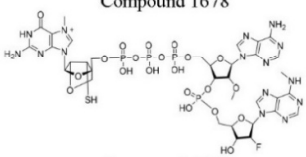
Compound 1678



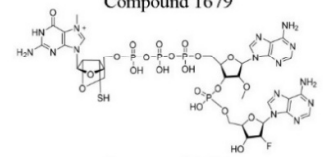
Compound 1679



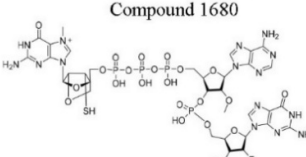
Compound 1680



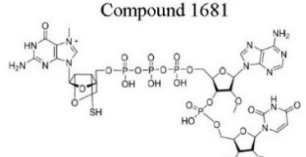
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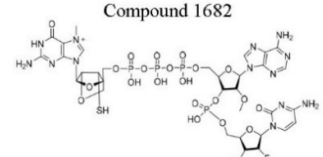
Compound 1682



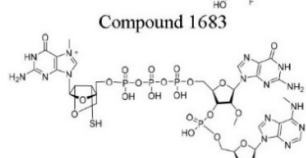
Compound 1683



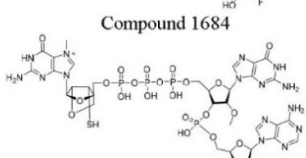
Compound 1684



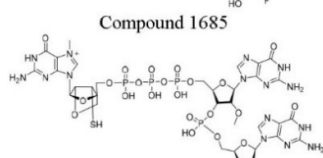
Compound 1685



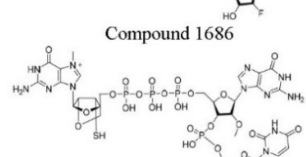
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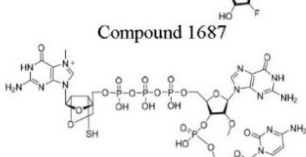
Compound 1687



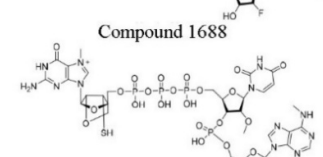
Compound 1688



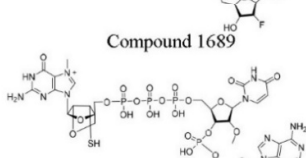
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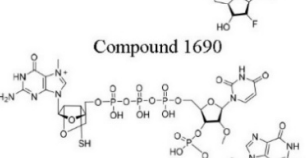
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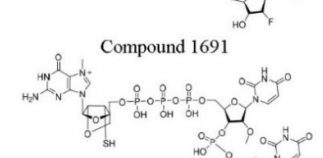
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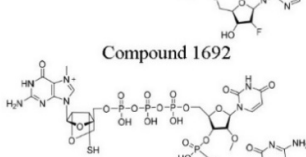
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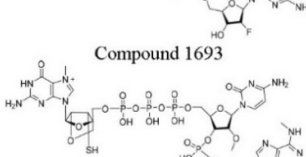
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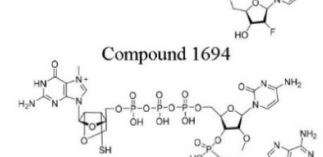
Compound 1694



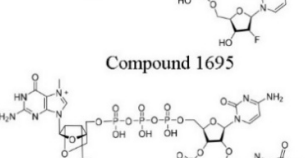
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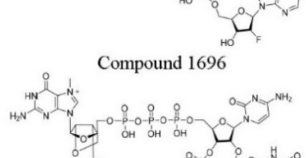
Compound 1696



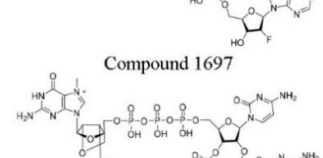
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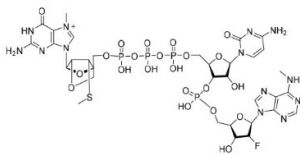
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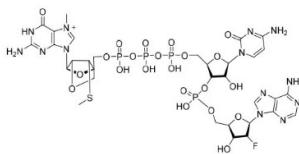
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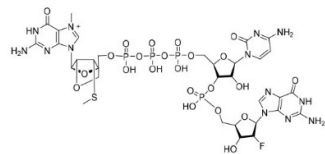
Compound 1700



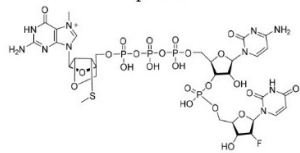
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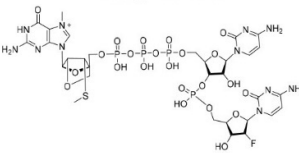
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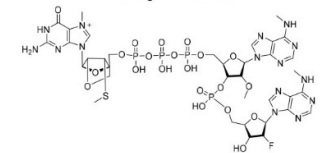
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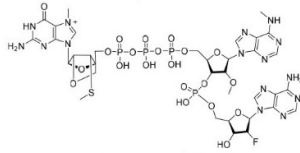
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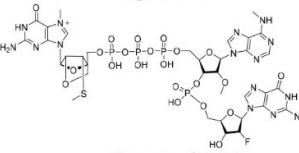
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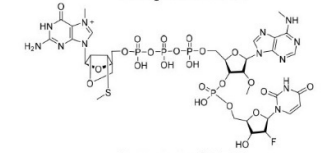
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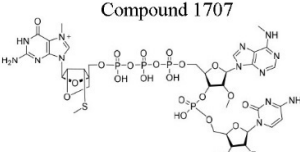
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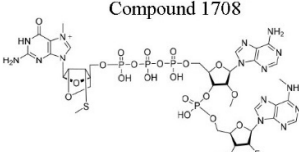
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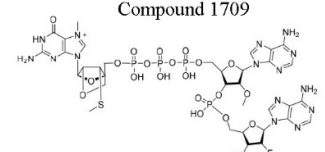
Compound 1709



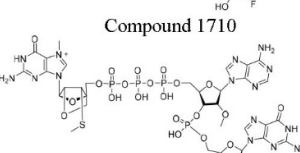
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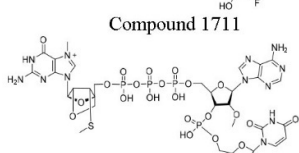
Compound 1711



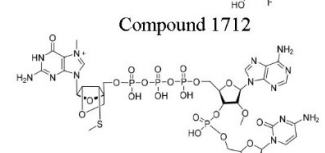
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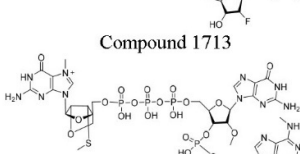
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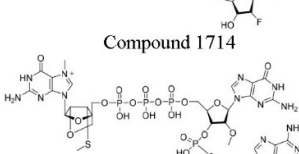
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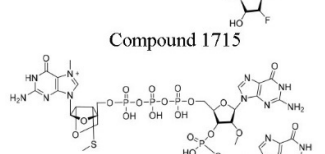
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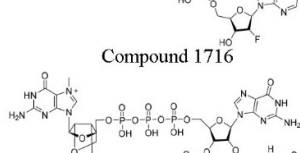
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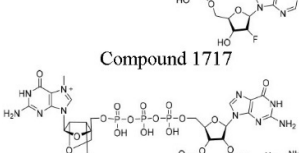
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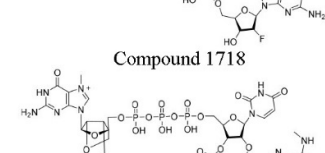
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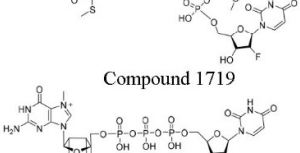
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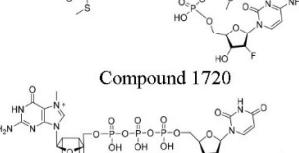
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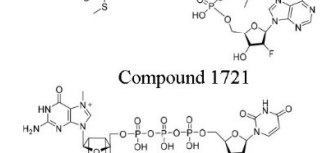
Compound 1721



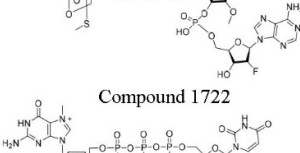
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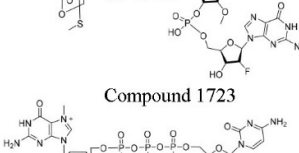
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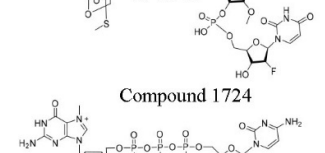
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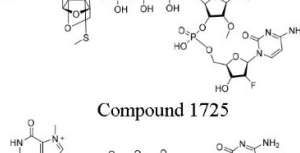
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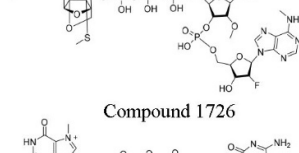
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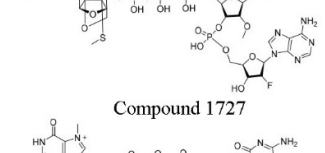
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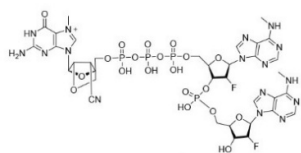
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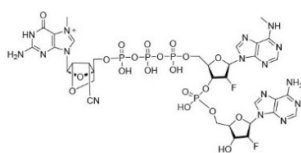
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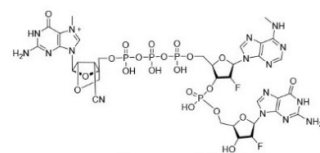
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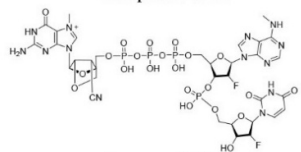
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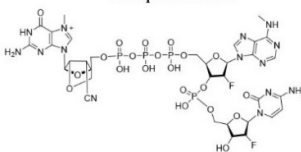
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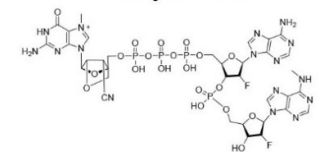
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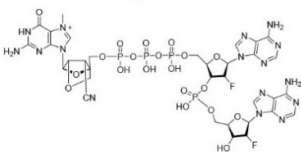
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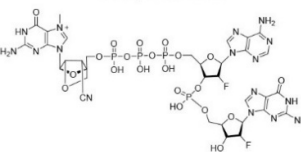
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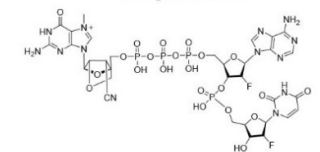
Compound 1736



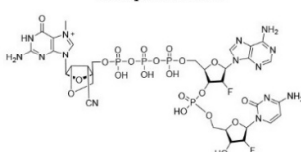
Compound 1737



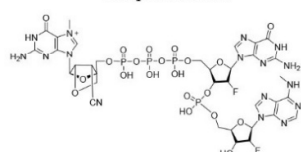
Compound 1738



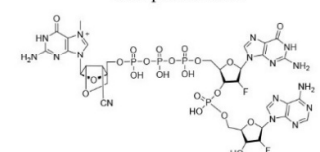
Compound 1739



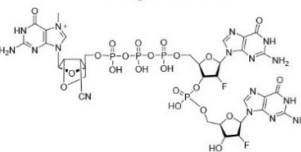
Compound 1740



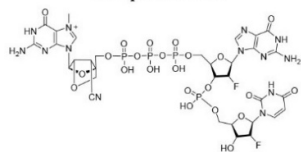
Compound 1741



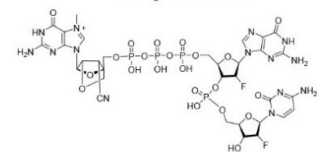
Compound 1742



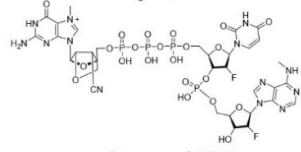
Compound 1743



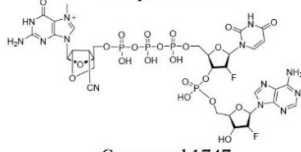
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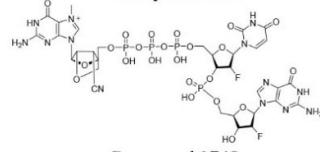
Compound 1745



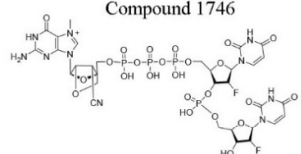
Compound 1746



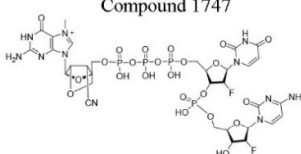
Compound 1747



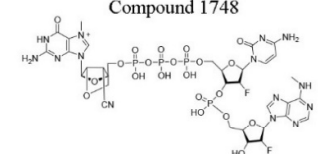
Compound 1748



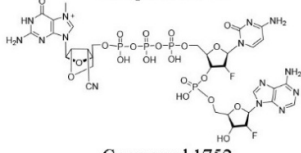
Compound 1749



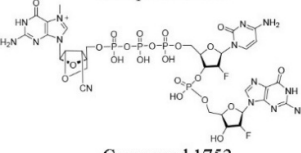
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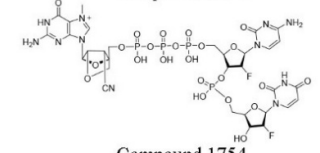
Compound 1751



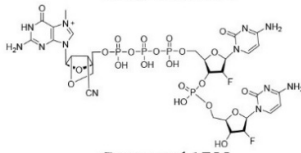
Compound 1752



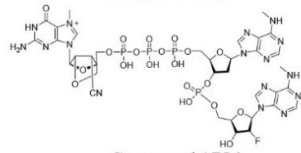
Compound 1753



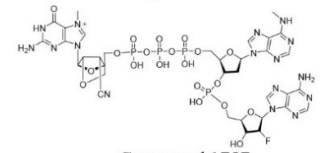
Compound 1754



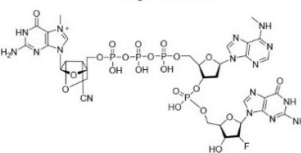
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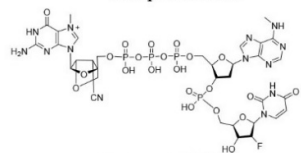
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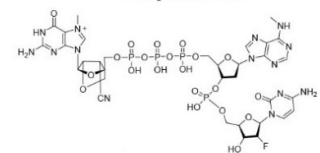
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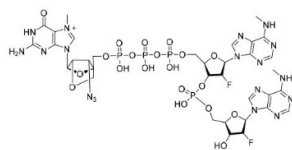
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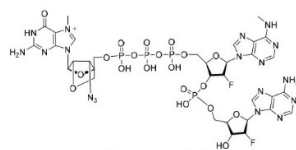
Compound 1759



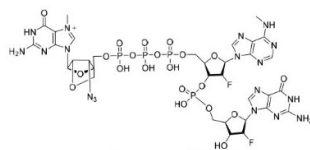
Compound 1760



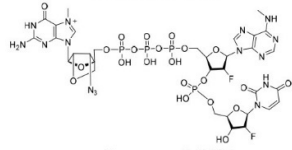
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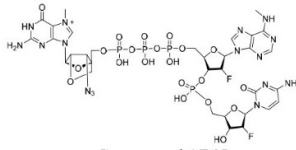
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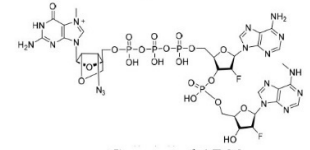
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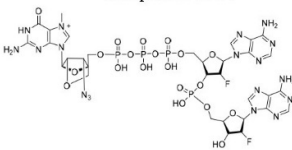
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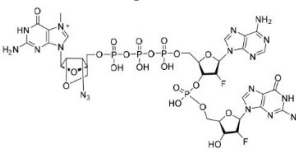
Compound 1765



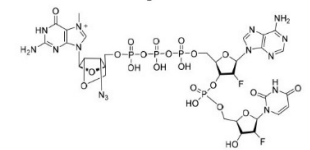
Compound 1766



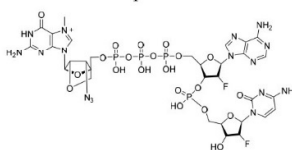
Compound 1767



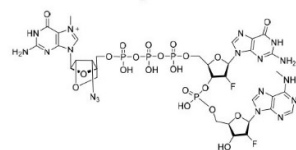
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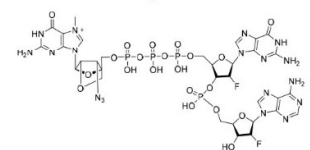
Compound 1769



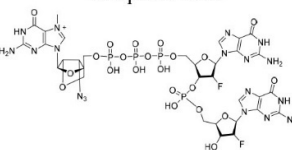
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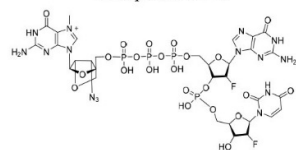
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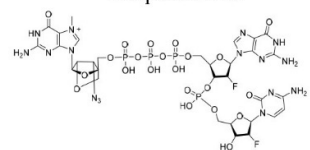
Compound 1772



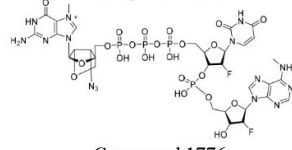
Compound 1773



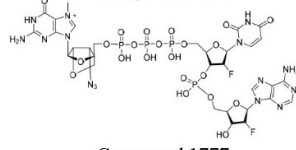
Compound 1774



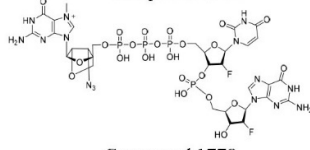
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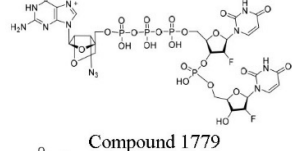
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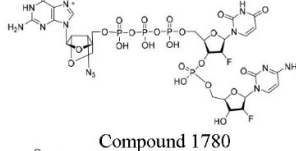
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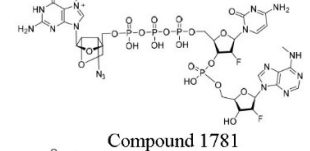
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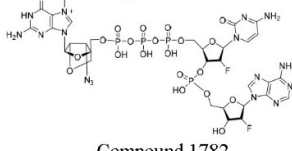
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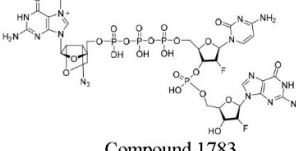
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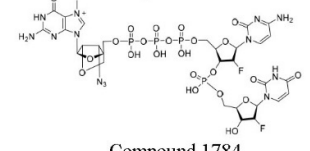
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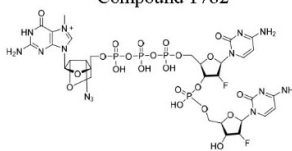
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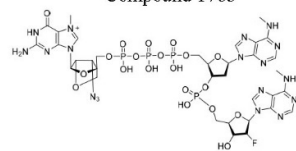
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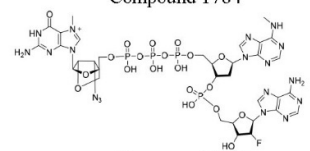
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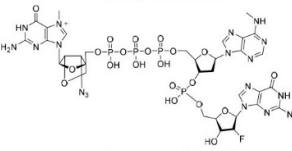
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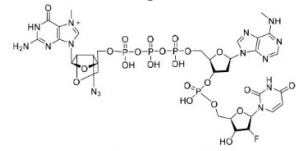
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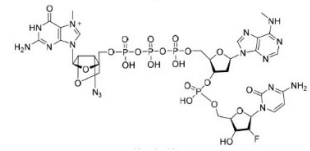
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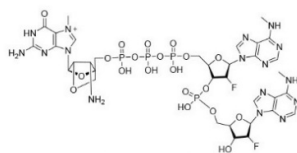
Compound 1788



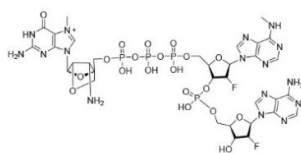
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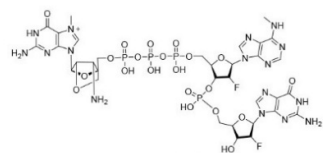
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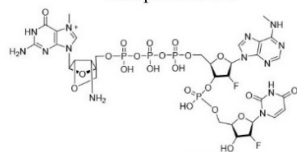
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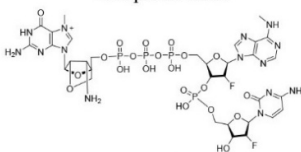
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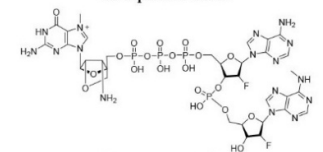
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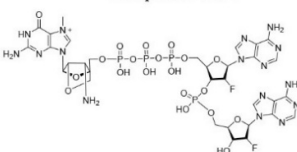
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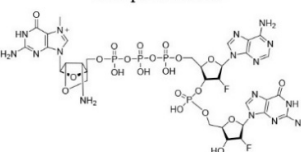
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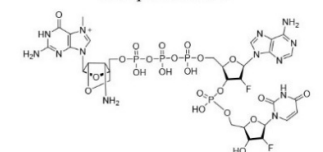
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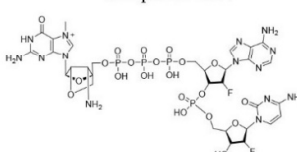
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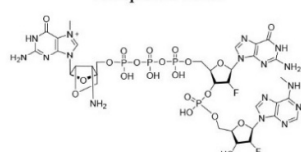
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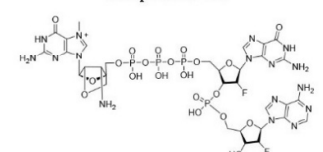
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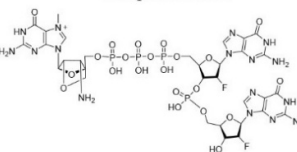
Compound 1800



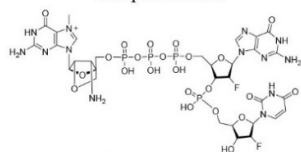
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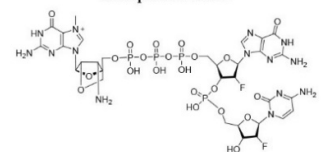
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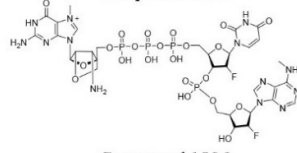
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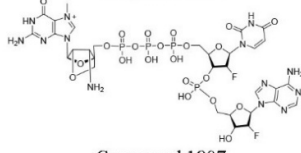
Compound 1804



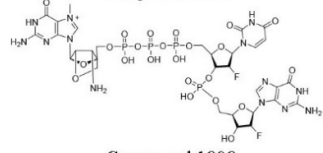
Compound 1805



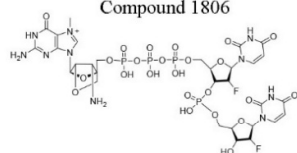
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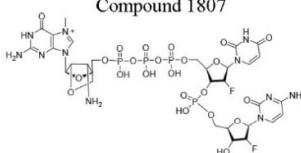
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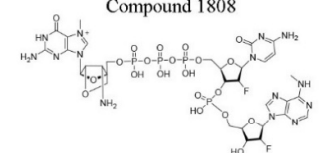
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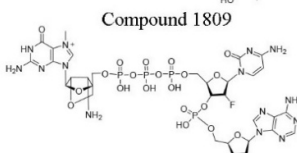
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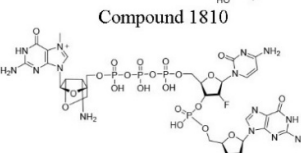
Compound 1810



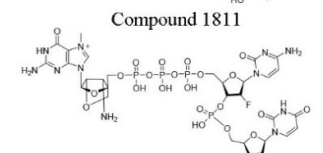
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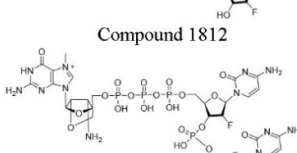
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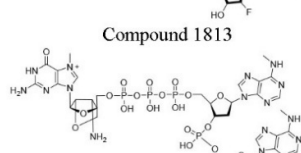
Compound 1813



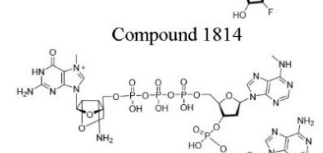
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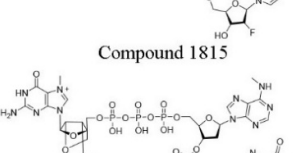
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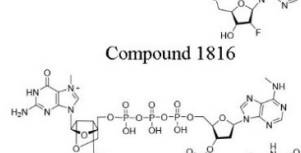
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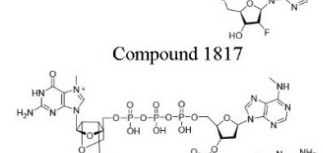
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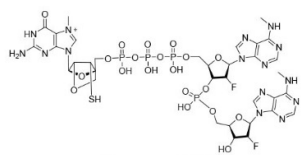
Compound 1818



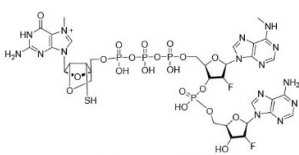
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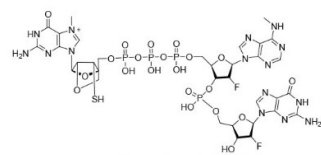
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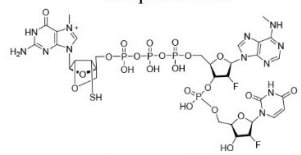
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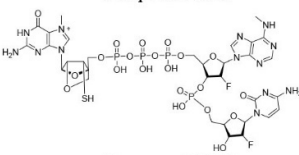
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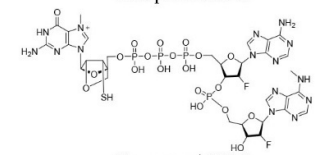
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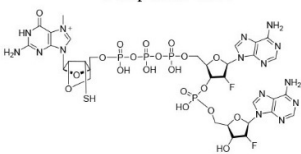
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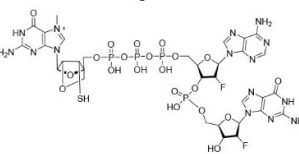
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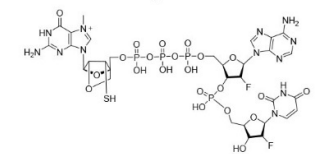
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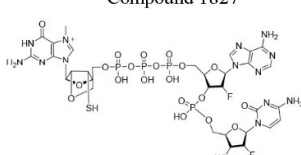
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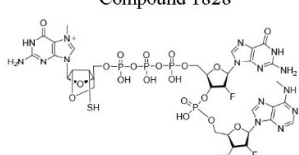
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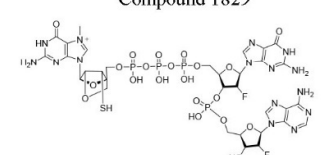
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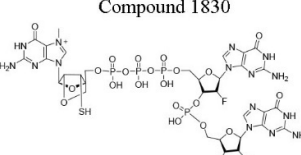
Compound 1830



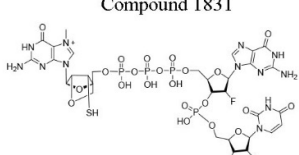
Compound 1831



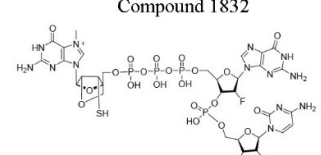
Compound 1832



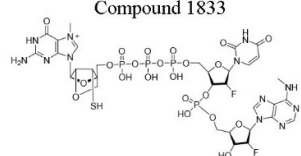
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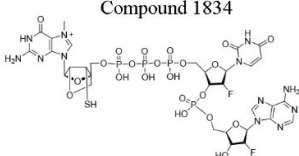
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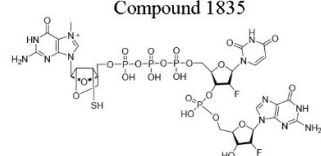
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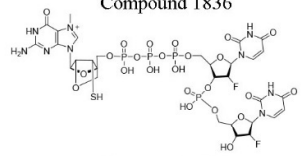
Compound 1836



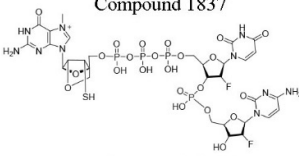
Compound 1837



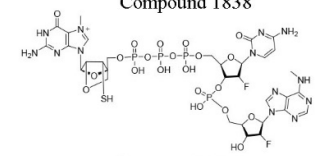
Compound 1838



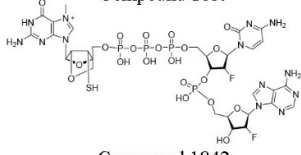
Compound 1839



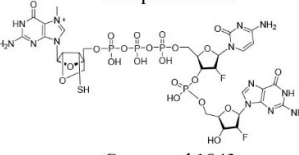
Compound 1840



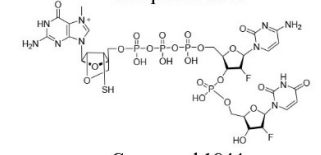
Compound 1841



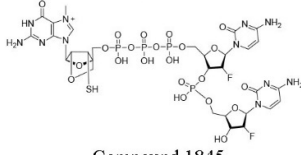
Compound 1842



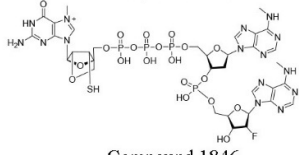
Compound 1843



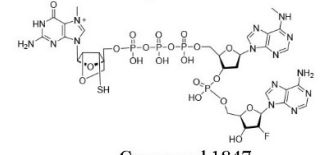
Compound 1844



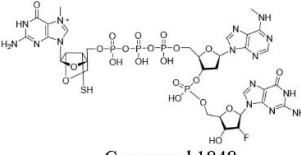
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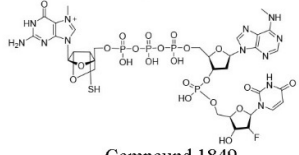
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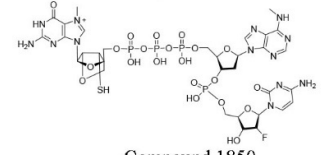
Compound 1847



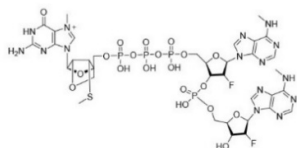
Compound 1848



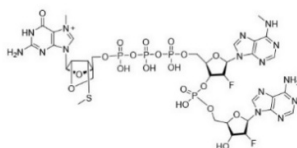
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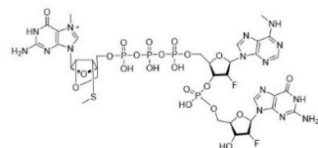
Compound 1850



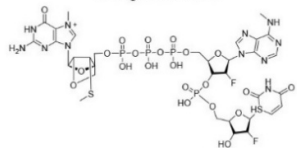
Compound 1851



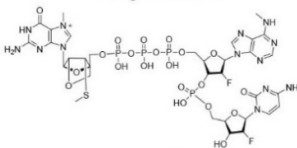
Compound 1852



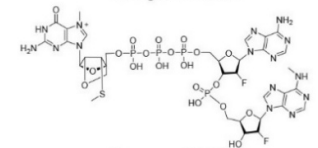
Compound 1853



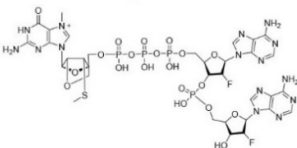
Compound 1854



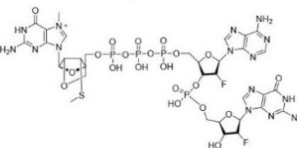
Compound 1855



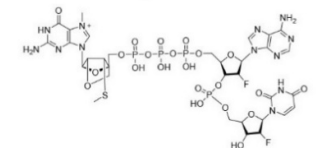
Compound 1856



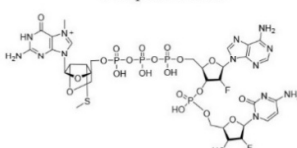
Compound 1857



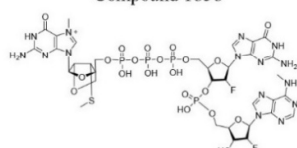
Compound 1858



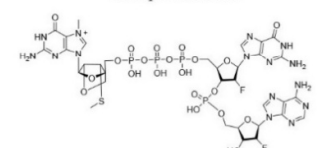
Compound 1859



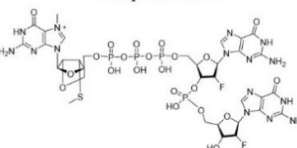
Compound 1860



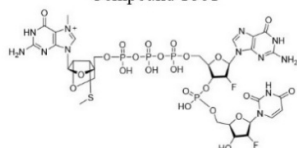
Compound 1861



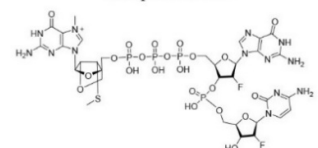
Compound 1862



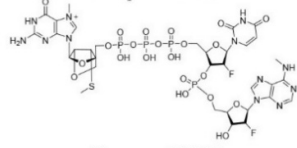
Compound 1863



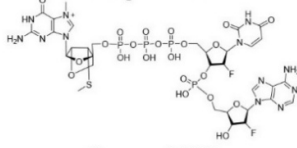
Compound 1864



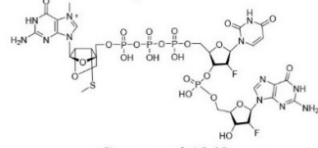
Compound 1865



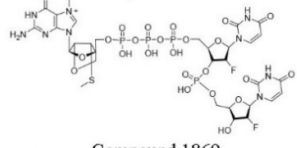
Compound 1866



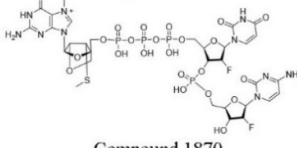
Compound 1867



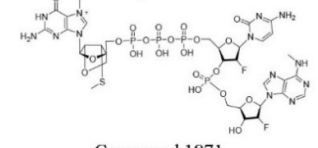
Compound 1868



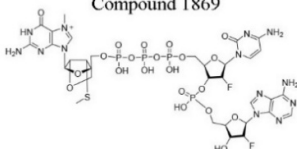
Compound 1869



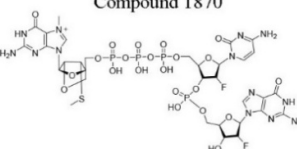
Compound 1870



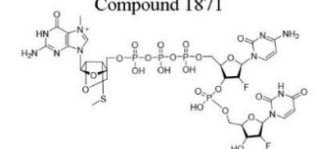
Compound 1871



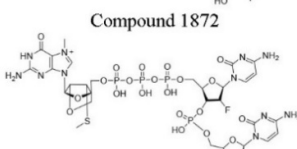
Compound 1872



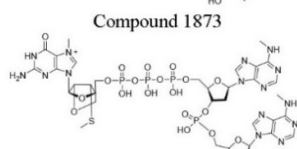
Compound 1873



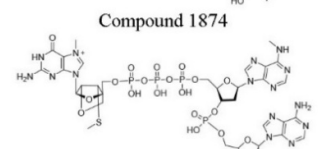
Compound 1874



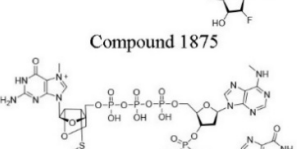
Compound 1875



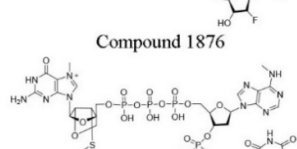
Compound 1876



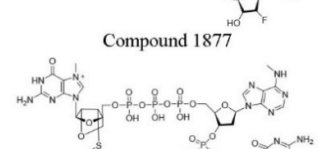
Compound 1877



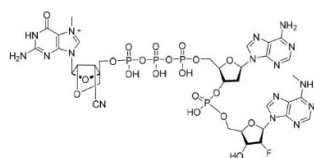
Compound 1878



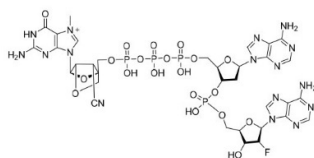
Compound 1879



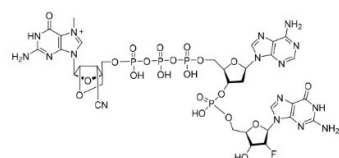
Compound 1880



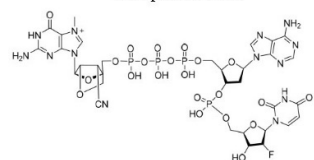
Compound 1881



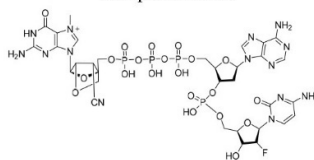
Compound 1882



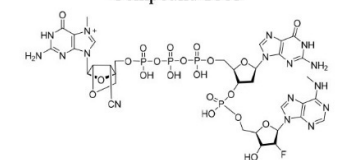
Compound 1883



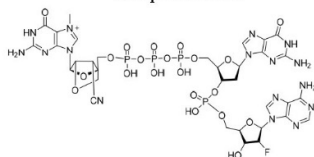
Compound 1884



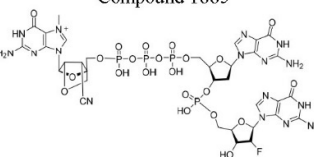
Compound 1885



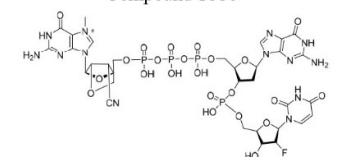
Compound 1886



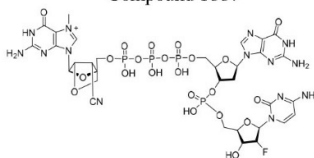
Compound 1887



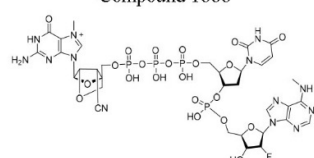
Compound 1888



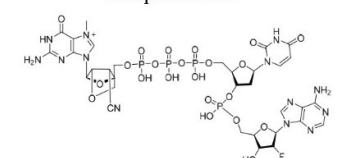
Compound 1889



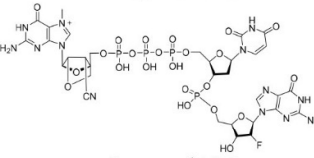
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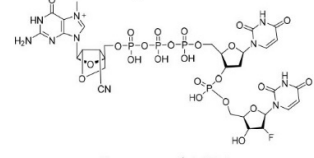
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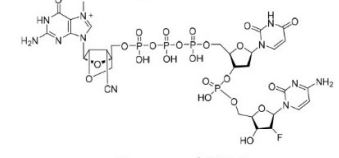
Compound 1892



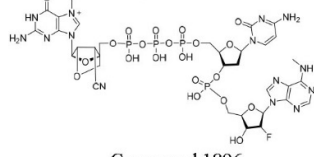
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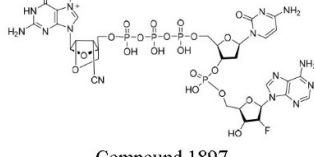
Compound 1894



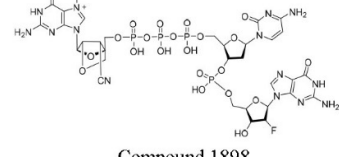
Compound 1895



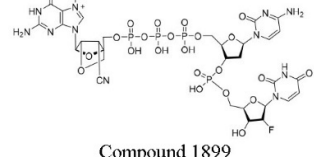
Compound 1896



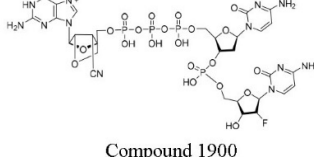
Compound 1897



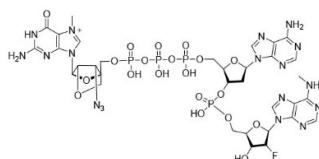
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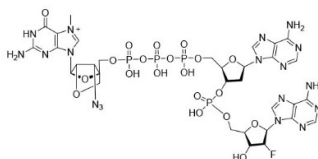
Compound 1899



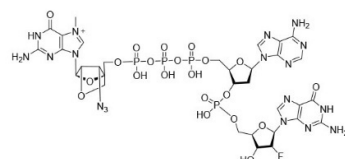
Compound 1900



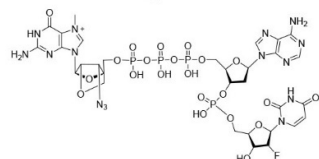
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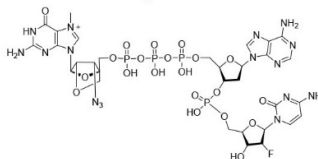
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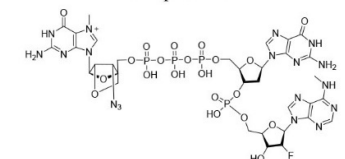
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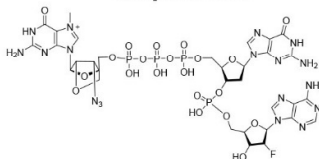
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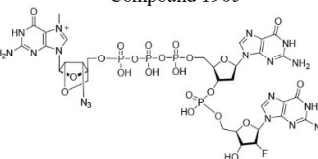
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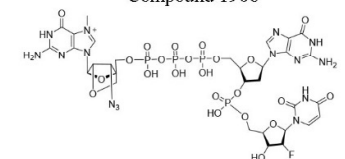
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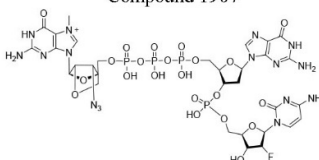
Compound 1907



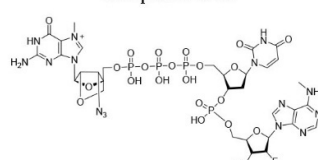
Compound 1908



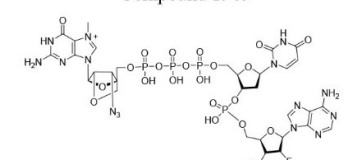
Compound 1909



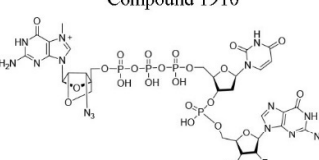
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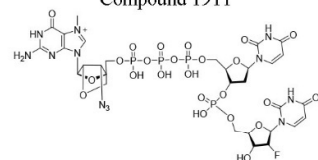
Compound 1911



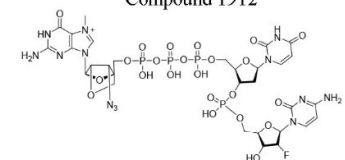
Compound 1912



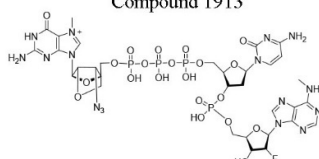
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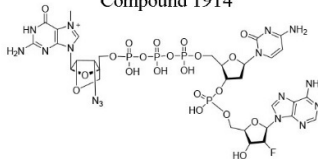
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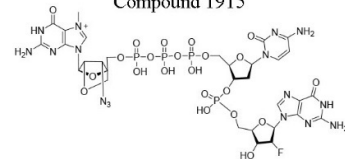
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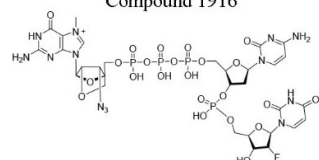
Compound 1916



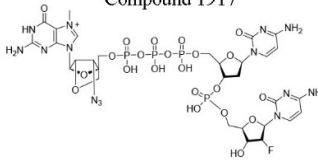
Compound 1917



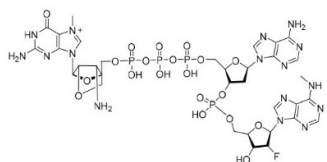
Compound 1918



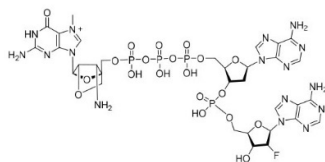
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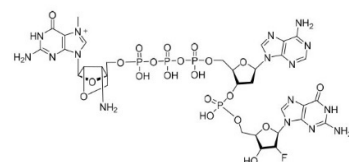
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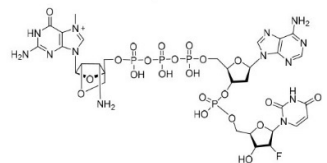
Compound 1921



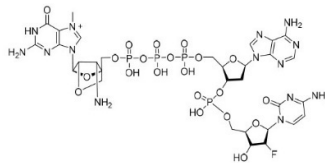
Compound 1922



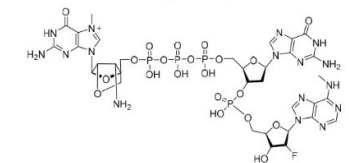
Compound 1923



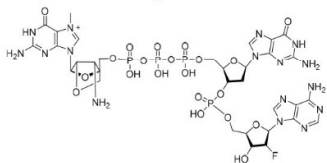
Compound 1924



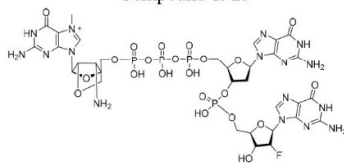
Compound 1925



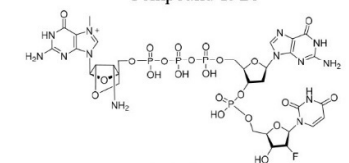
Compound 1926



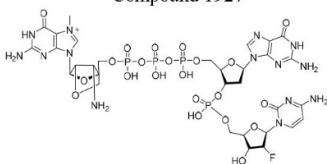
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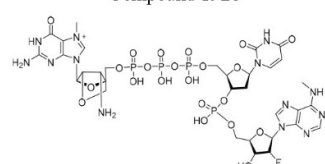
Compound 1928



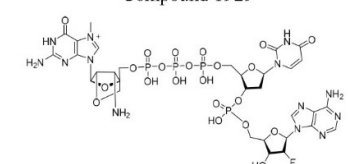
Compound 1929



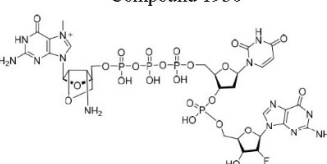
Compound 1930



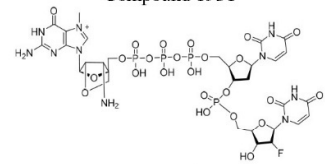
Compound 1931



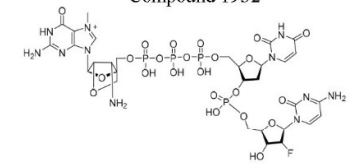
Compound 1932



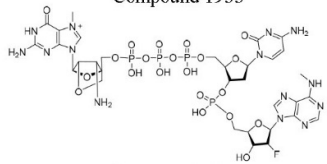
Compound 1933



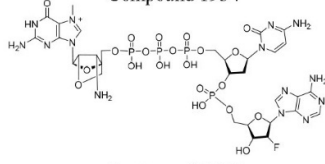
Compound 1934



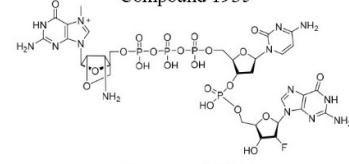
Compound 1935



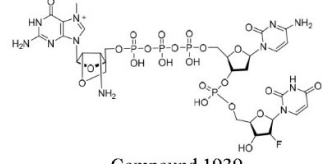
Compound 1936



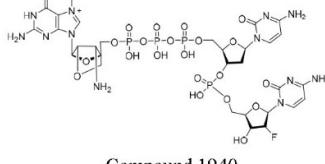
Compound 1937



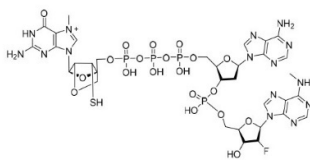
Compound 1938



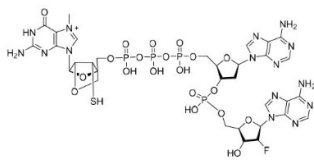
Compound 1939



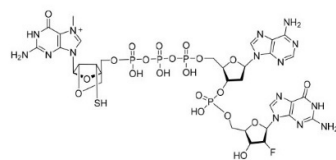
Compound 1940



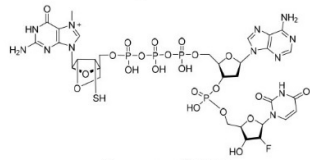
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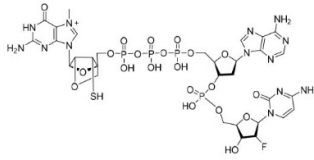
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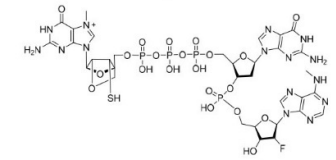
Compound 1943



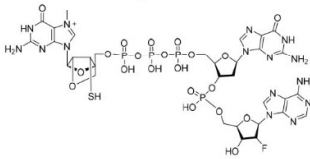
Compound 1944



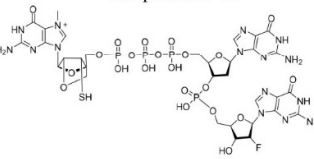
Compound 1945



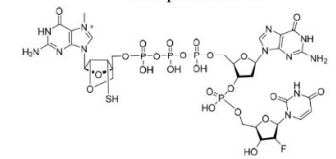
Compound 1946



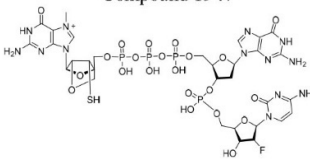
Compound 1947



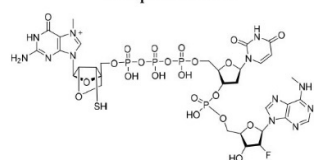
Compound 1948



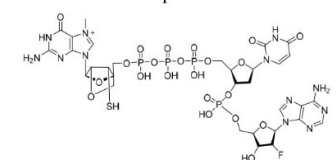
Compound 1949



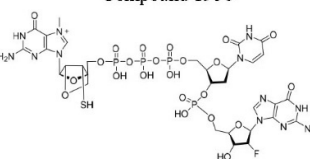
Compound 1950



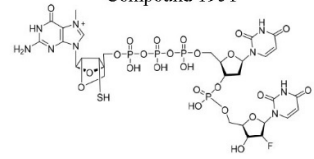
Compound 1951



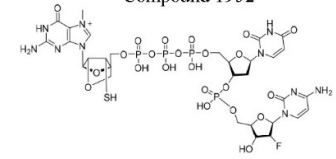
Compound 1952



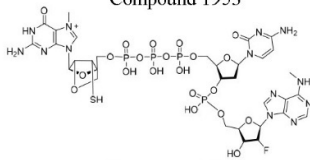
Compound 1953



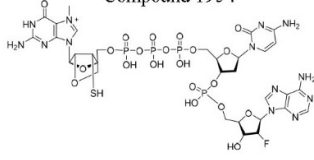
Compound 1954



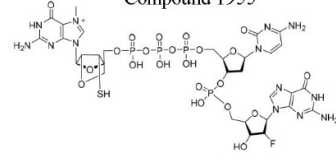
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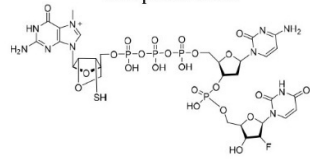
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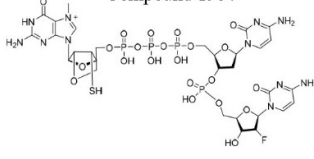
Compound 1957



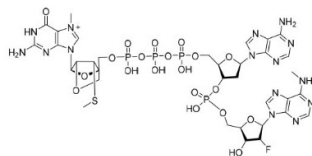
Compound 1958



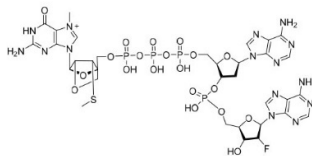
Compound 1959



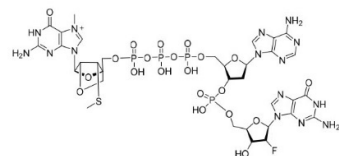
Compound 1960



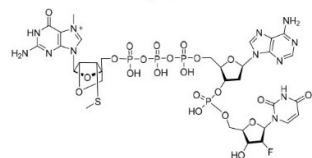
Compound 1961



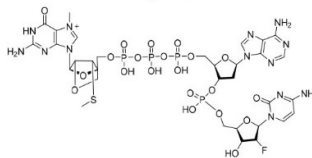
Compound 1962



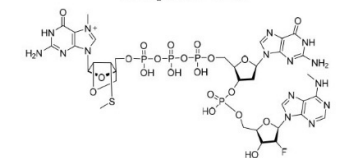
Compound 1963



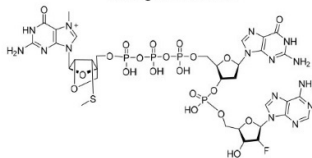
Compound 1964



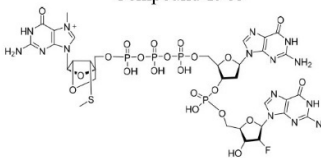
Compound 1965



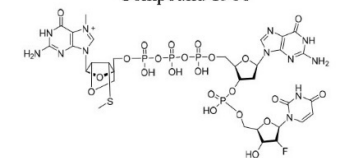
Compound 1966



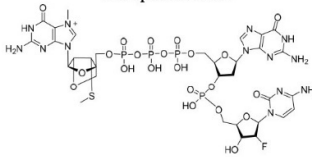
Compound 1967



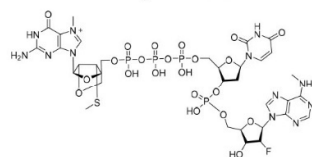
Compound 1968



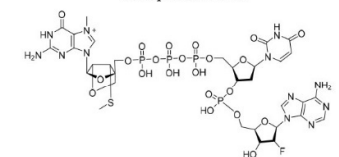
Compound 1969



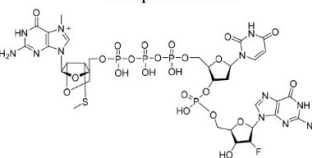
Compound 1970



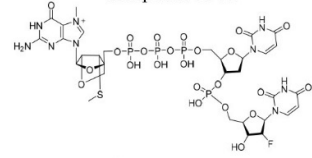
Compound 1971



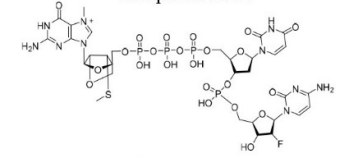
Compound 1972



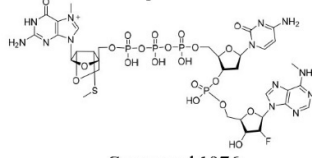
Compound 1973



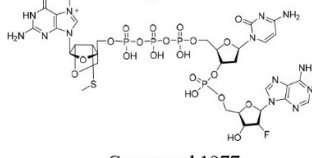
Compound 1974



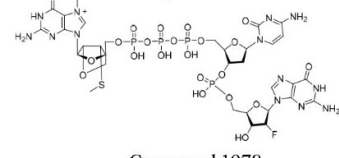
Compound 1975



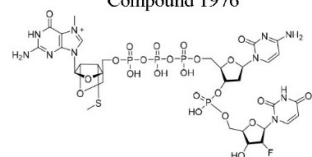
Compound 1976



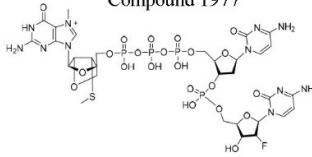
Compound 1977



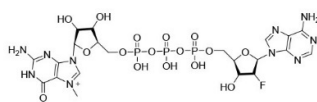
Compound 1978



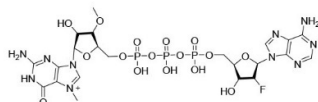
Compound 1979



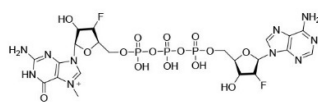
Compound 1980



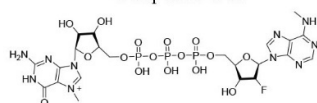
Compound 1981



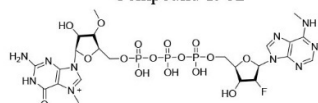
Compound 1982



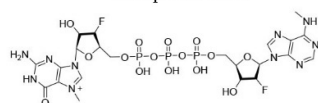
Compound 1983



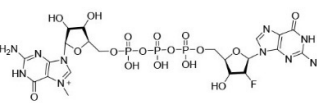
Compound 1984



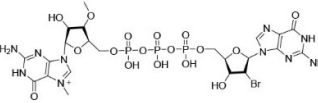
Compound 1985



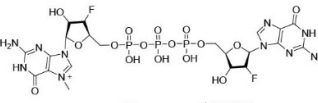
Compound 1986



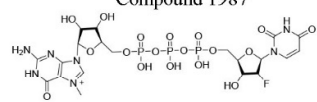
Compound 1987



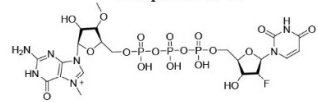
Compound 1988



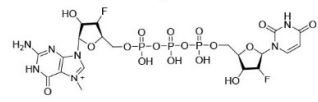
Compound 1989



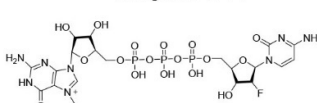
Compound 1990



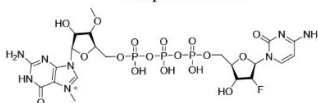
Compound 1991



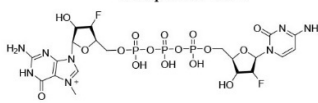
Compound 1992



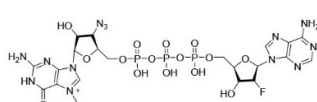
Compound 1993



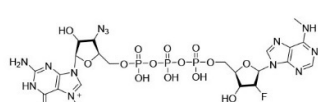
Compound 1994



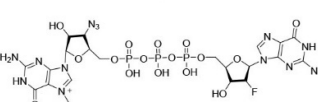
Compound 1995



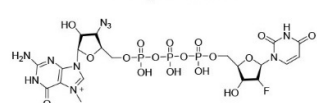
Compound 1996



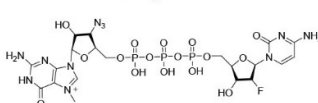
Compound 1997



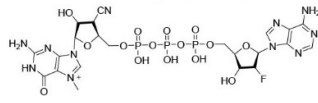
Compound 1998



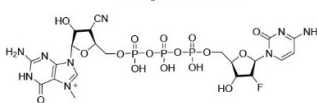
Compound 1999



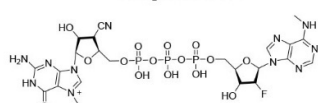
Compound 2000



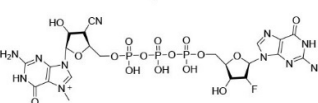
Compound 2001



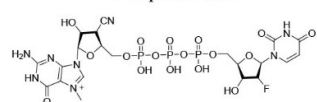
Compound 2002



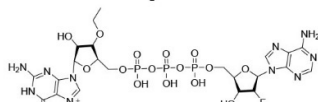
Compound 2003



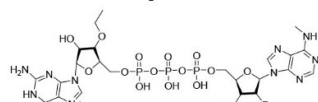
Compound 2004



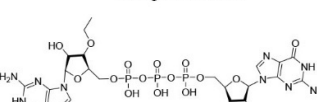
Compound 2005



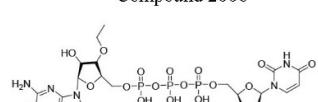
Compound 2006



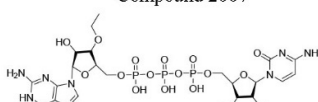
Compound 2007



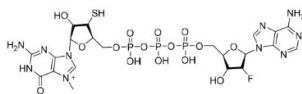
Compound 2008



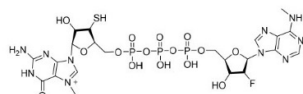
Compound 2009



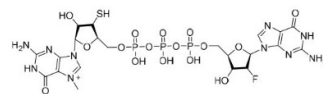
Compound 2010



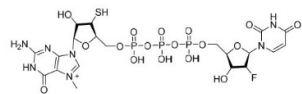
Compound 2011



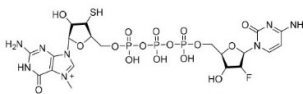
Compound 2012



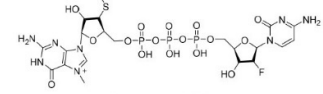
Compound 2013



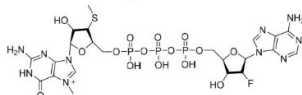
Compound 2014



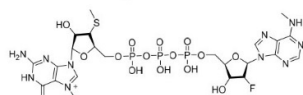
Compound 2015



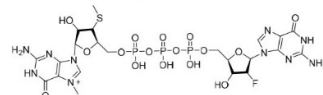
Compound 2016



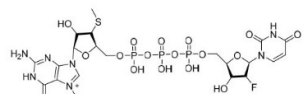
Compound 2017



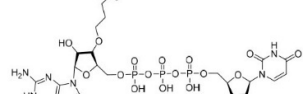
Compound 2018



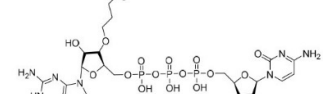
Compound 2019



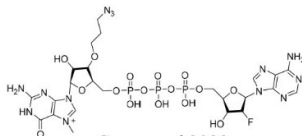
Compound 2020



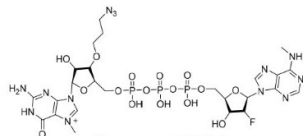
Compound 2021



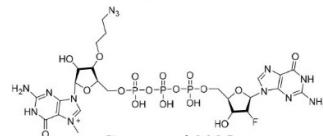
Compound 2022



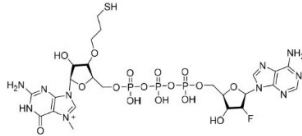
Compound 2023



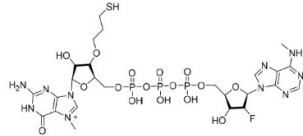
Compound 2024



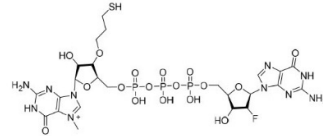
Compound 2025



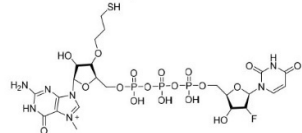
Compound 2026



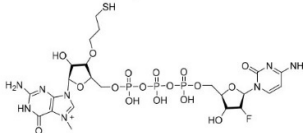
Compound 2027



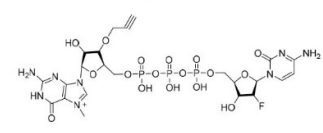
Compound 2028



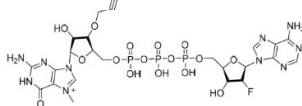
Compound 2029



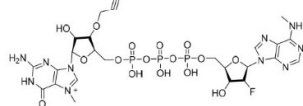
Compound 2030



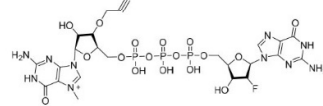
Compound 2031



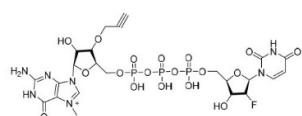
Compound 2032



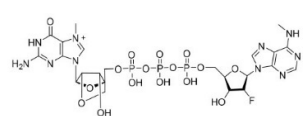
Compound 2033



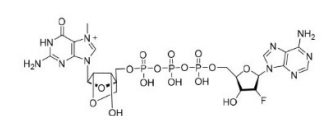
Compound 2034



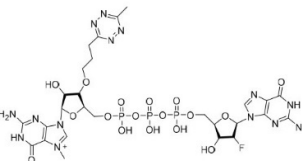
Compound 2035



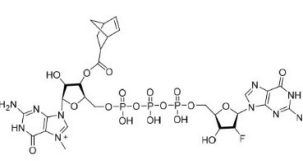
Compound 2036



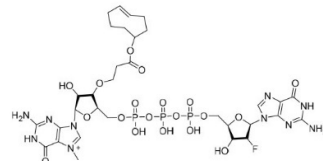
Compound 2037



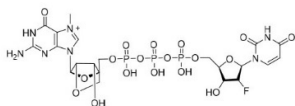
Compound 2038



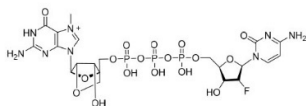
Compound 2039



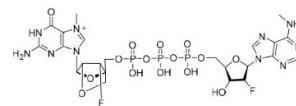
Compound 2040



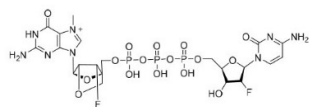
Compound 2041



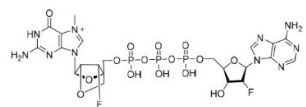
Compound 2042



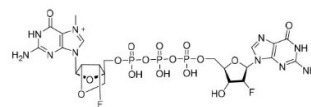
Compound 2043



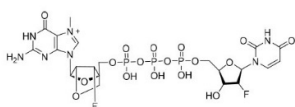
Compound 2044



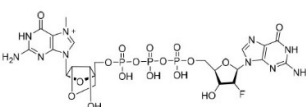
Compound 2045



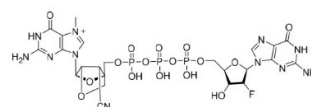
Compound 2046



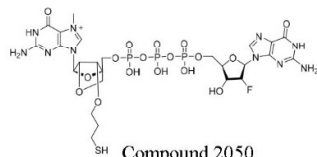
Compound 2047



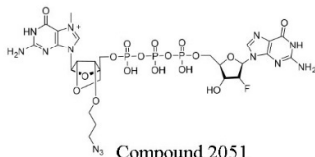
Compound 2048



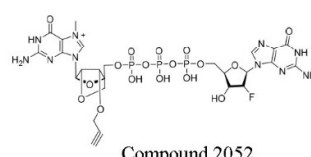
Compound 2049



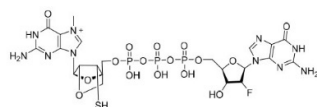
Compound 2050



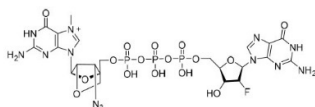
Compound 2051



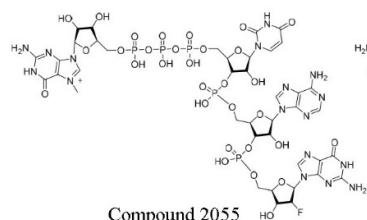
Compound 2052



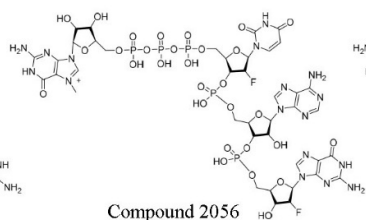
Compound 2053



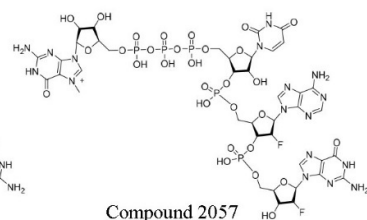
Compound 2054



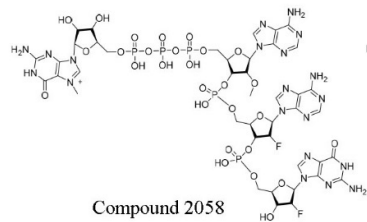
Compound 2055



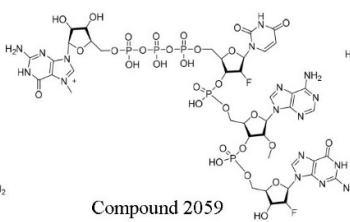
Compound 2056



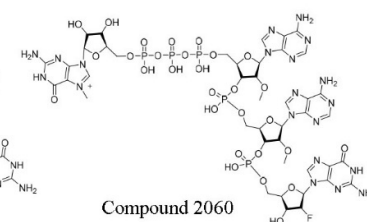
Compound 2057



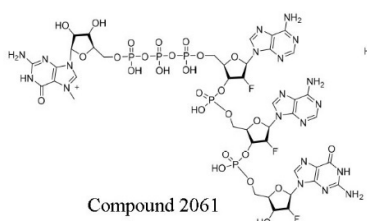
Compound 2058



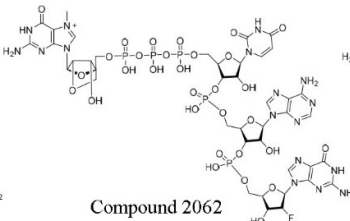
Compound 2059



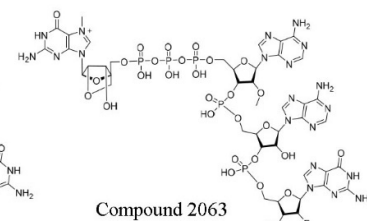
Compound 2060



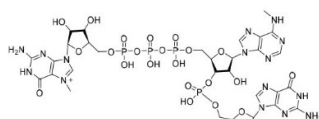
Compound 2061



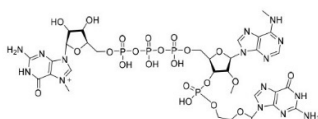
Compound 2062



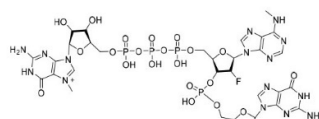
Compound 2063



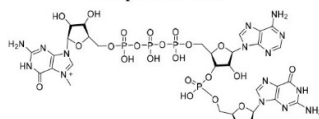
Compound 2064



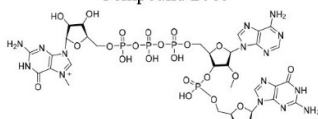
Compound 2065



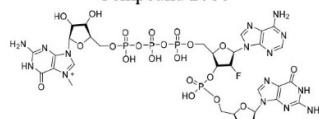
Compound 2066



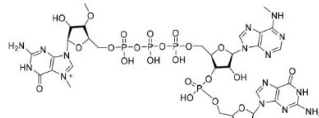
Compound 2067



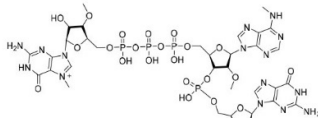
Compound 2068



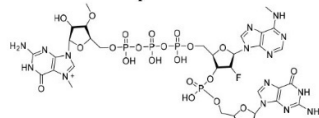
Compound 2069



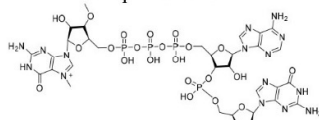
Compound 2070



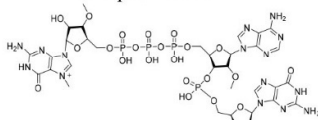
Compound 2071



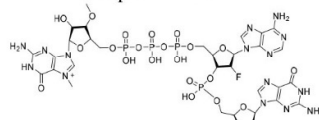
Compound 2072



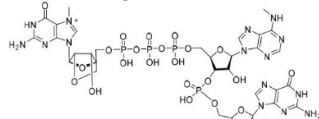
Compound 2073



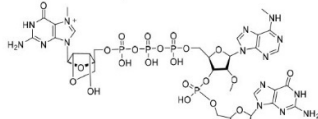
Compound 2074



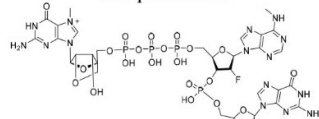
Compound 2075



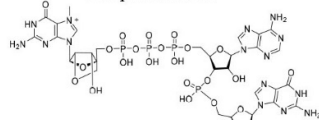
Compound 2076



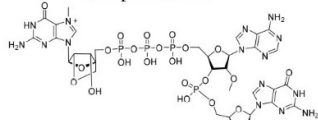
Compound 2077



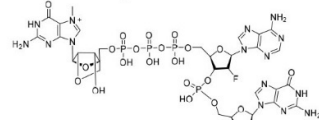
Compound 2078



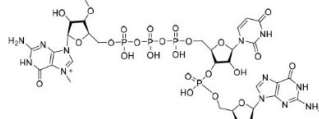
Compound 2079



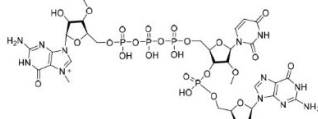
Compound 2080



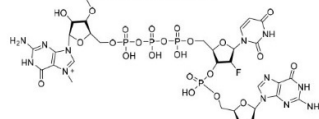
Compound 2081



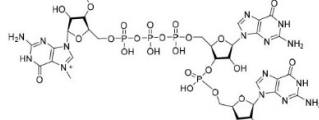
Compound 2082



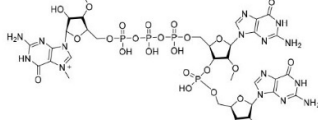
Compound 2083



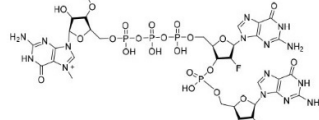
Compound 2084



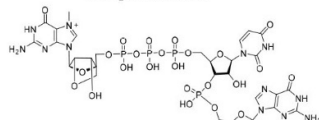
Compound 2085



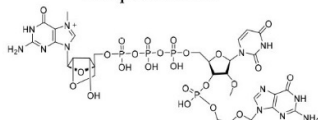
Compound 2086



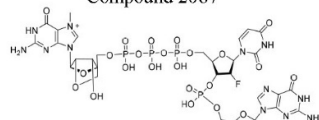
Compound 2087



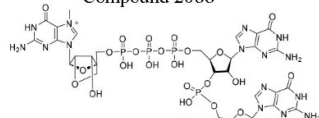
Compound 2088



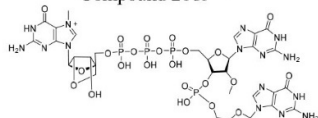
Compound 2089



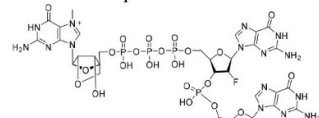
Compound 2090



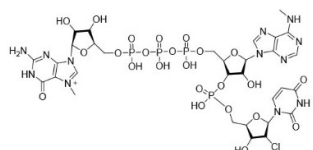
Compound 2091



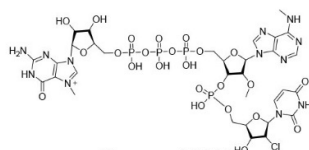
Compound 2092



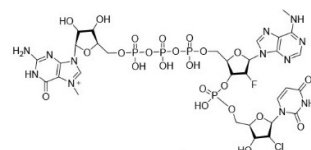
Compound 2093



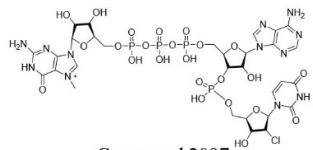
Compound 2094



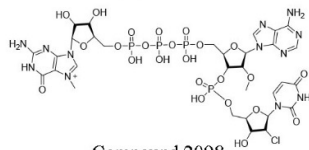
Compound 2095



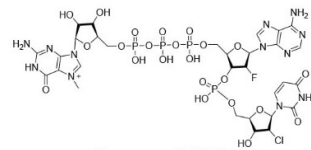
Compound 2096



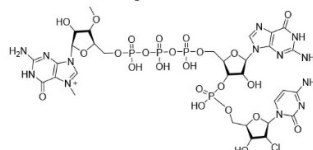
Compound 2097



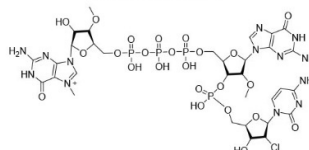
Compound 2098



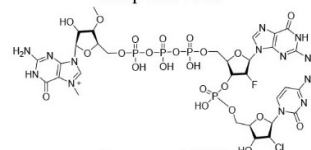
Compound 2099



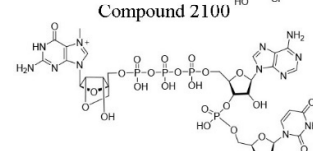
Compound 2100



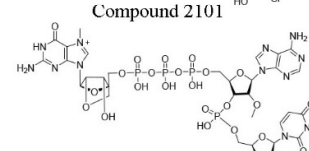
Compound 2101



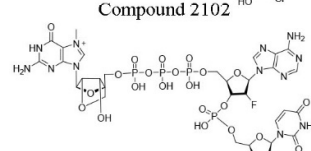
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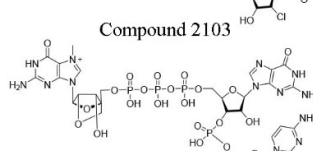
Compound 2103



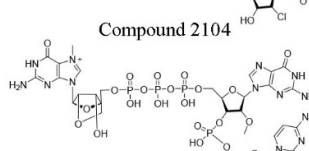
Compound 2104



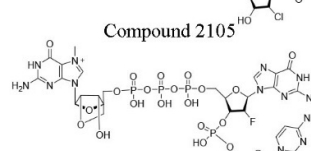
Compound 2105



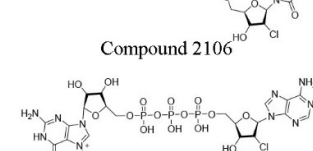
Compound 2106



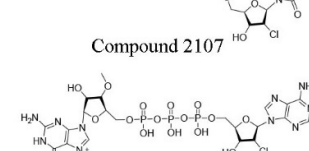
Compound 2107



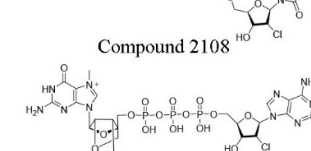
Compound 2108



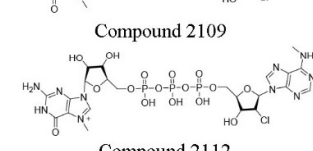
Compound 2109



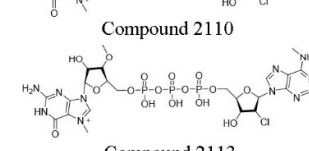
Compound 2110



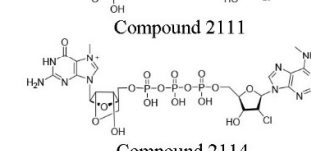
Compound 2111



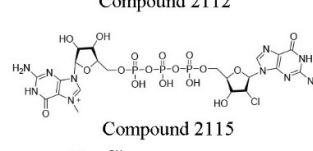
Compound 2112



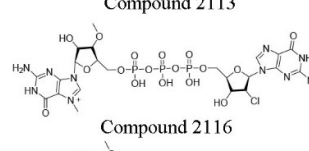
Compound 2113



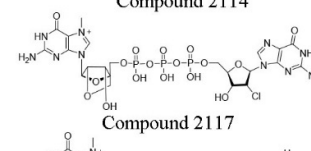
Compound 2114



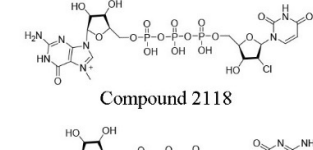
Compound 2115



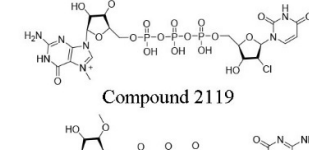
Compound 2116



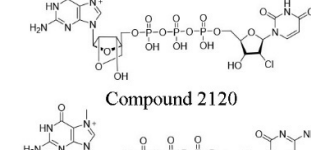
Compound 2117



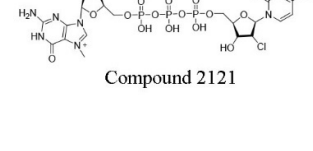
Compound 2118



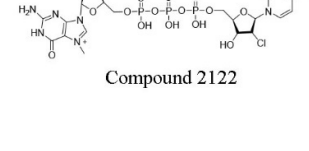
Compound 2119



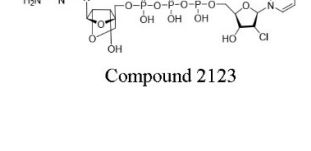
Compound 2120



Compound 2121



Compound 2122



Compound 2123

Brief Description of Drawings

The present invention will be further described below with reference to the accompanying drawings.

FIG. 1 illustrates the fluorescence imaging of mRNA with different cap analogs in HEK293T cells.

FIG. 2 illustrates the fluorescence intensity of mRNA with different cap analogs in HEK293T cells.

FIG. 3 illustrates the fluorescence intensity of mRNA with different cap analogs in HepG2 cells.

FIG. 4 illustrates the expression efficiency of mRNA with different cap analogs in different organs.

Detailed Description

The present invention provides a halogen-containing compound ("cap analog" or "capping analog") for capping 5' end of RNA, a pharmaceutically acceptable salt, solvate, and stereoisomer thereof, and a use of the halogen-containing compound. The use of this compound to cap 5' end of mRNA has a high capping rate and good *in vitro* transcription efficiency. At the same time, it has a high translation expression efficiency at the cellular level.

Before further describing the present invention, several terms used in the specification, examples, and appended claims are collected in the following sections. The definitions listed herein should be read and understood by those skilled in the art in light of the rest of the present invention. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by those skilled in the art to which the present invention belongs.

Definition

Unless otherwise stated, when disclosing or claiming any type of range, it is intended to disclose or claim individually each possible value that the range may reasonably cover, including any sub-ranges contained therein. For example, if the number of groups is 1 to 6, it indicates an integer within the range, and 1 to 6 is understood to include 1, 2, 3, 4, 5, and 6, and should also be understood to include sub-ranges of 1 to 5, 1 to 4, and 1 to 3.

The specification of the present disclosure should be interpreted in consistent with the laws and principles of chemical bonding. In some cases, a hydrogen atom may be removed to accommodate a substituent at a given position.

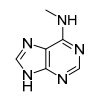
The words "include", "contain", "comprise", or the like used in the present disclosure means that the elements preceding the word include the elements listed after the word and equivalents thereof, without excluding elements that are not described. The terms "contain" or "include (comprise)" used herein may be open, semi-closed or closed. In other words, the terms also include "essentially consisting of" or "consisting of".

The term "pharmaceutically acceptable" as used herein means that a compound or composition is chemically and/or toxicologically compatible with the other ingredients constituting a formulation and/or with humans or mammals for the prevention or treatment of a disease or condition for which the compound or composition is used.

Natural or modified pyrimidine nucleotide bases include, but are not limited to, uracil, thymine, cytosine, 5-methylcytosine, 5-fluorouracil, 5-fluorocytosine, and the like.

Natural or modified purine nucleotide bases include, but are not limited to, adenine, guanine, 6-N-methyladenine, 6-N,N-dimethylaminopurine, 2-N-methylguanine, 2-N,N-dimethylguanine, 7-

methylguanine, and the like. The structure of 6-N-methyladenine is



Nucleotide bases as used herein can be modified or substituted to provide oligonucleotides. For example, modification can be performed by these bases or synthetic and natural nucleotide bases (for example, inoside, thymine, xanthine, hypoxanthine, nubularine, isoguanine or tuberculin) and optionally. Alternatively, substituted or modified analogs of any natural or synthetic base may be used. Examples include 2-(halogenated)adenine, 2-(alkyl)adenine, 2-(propyl)adenine, 2-(amino)adenine, 2-(aminoalkyl)adenine, 2-(aminopropyl)adenine, 2-(methylthio)-N6-(isopentenyl)adenine, 6-(alkyl)adenine, 6-(methyl)adenine, 7-(deaza)adenine, 8-(alkenyl)adenine, 8-(alkyl)adenine, 8-(alkynyl)adenine, 8-(amino)adenine, 8-(halogenated)adenine, 8-(hydroxy)adenine, 8-(thioalkyl)adenine, 8-(thiol)adenine, N6-(isopentyl)adenine, N6-(methyl)adenine, N6,N6-(dimethyl)adenine, 2-(alkyl)guanine, 2-(propyl)guanine, 6-(alkyl)guanine, 6-(methyl)guanine, 7-(alkyl)guanine, 7-(methyl)guanine, 7-(deaza)guanine, 8-(alkyl)guanine, 8-(alkenyl)guanine, 8-(alkynyl)guanine, 8-(amino)guanine, 8-(halogenated)guanine, 8-(hydroxy)guanine, 8-(thioalkyl)guanine, 8-(thiol)guanine, N-(methyl)guanine, 2-(thio)cytosine, 3-(deaza)-5-(aza)cytosine,

3-(alkyl)cytosine, 3-(methyl)cytosine, 5-(alkyl)cytosine, 5-(alkynyl)cytosine, 5-(halogenated)cytosine, 5-(methyl)cytosine, 5-(propynyl)cytosine, 5-(propynyl)cytosine, 5-(trifluoromethyl)cytosine, 6-(azo)cytosine, N-4-(acetyl)cytosine, 3-(3-amino-3-carboxypropyl)uracil, 2-(thio)uracil, 5-(methyl)-2-(thio)uracil, 5-(methylaminomethyl)-2-(thio)uracil, 4-(thio)uracil, 5-(methyl)-4-(thio)uracil, 5-(methylaminomethyl)-4-(thio)uracil, 5-(methyl)-2,4-(dithio)uracil, 5-(methylaminomethyl)-2,4-(dithio)uracil, 5-(2-aminopropyl)uracil, 5-(alkyl)uracil, 5-(alkynyl)uracil, 5-(allylamino)uracil, 5-(aminoallyl)uracil, 5-(aminoalkyl)uracil, 5-(guanidinyl)uracil, 5-(1,3-diazole-1-alkyl)uracil, 5-(cyanoalkyl)uracil, 5-(dialkylaminoalkyl)uracil, 5-(dimethylaminoalkyl)uracil, 5-(halogenated)uracil, 5-(methoxy)uracil, uracil-5-oxoacetic acid, 5-(methoxycarbonylmethyl)-2-(thio)uracil, 5-(methoxycarbonylmethyl)uracil, 5-(propynyl)uracil, 5-(propynyl)uracil, 5-(trifluoromethyl)uracil, 6-(azo)uracil, dihydrouracil, 3-(methyl)uracil, 5-uracil (that is, pseudouracil), 2-(thio)pseudouracil, 4-(thio)pseudouracil, 2,4-(dithio)purine pyrimidine, 5-(alkyl)pseudouracil, 5-(methyl)pseudouracil, 5-(alkyl)-2-(thio)pseudouracil, 5-(methyl)-2-(thio)pseudouracil, 5-(alkyl)-4-(thio)pseudouracil, 5-(methyl)-4-(thio)pseudouracil, 5-(alkyl)-2,4-(dithio)pseudouracil, 5-(methyl)-2,4-(dithio)pseudouracil, 1-substituted pseudouracil, 1-substituted 2-(thio)-pseudouracil, 1-substituted 4-(thio)pseudouracil, 1-substituted 2,4-(dithio)pseudouracil, 1-(aminocarbonylvinyl)-pseudouracil, 1-(aminocarbonylvinyl)-2-(thio)-pseudouracil, 1-(aminocarbonylvinyl)-4-(thio)pseudouracil, 1-(aminocarbonylvinyl)-2,4-(dithio)pseudouracil, 1-(aminoalkylaminocarbonylvinyl)-pseudouracil, 1-(aminoalkylamino-carbonylvinyl)-2-(thio)-pseudouracil, 1-(aminoalkylaminocarbonylvinyl)-4-(thio)pseudouracil, 1-(aminoalkylaminocarbonylvinyl)-2,4-(dithio)pseudouracil, 1,3-(diaz)-2-(oxo)-phenoxazine-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenoxazine-1-yl, 1,3-(diaz)-2-(oxo)-phenothiazine-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenothiazine-1-yl, 7-substituted 1,3-(diaz)-2-(oxo)-phenoxazine-1-yl, 7-substituted 1-(aza)-2-(thioxo)-3-(aza)-phenoxazine-1-yl, 7-substituted 1,3-(diaz)-2-(oxo)-phenothiazine-1-yl, 7-substituted 1-(aza)-2-(thioxo)-3-(aza)-phenothiazine-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazine-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thioxo)-3-(aza)-phenoxazine-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenothiazine-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenothiazine-1-yl, 7-(guanidinoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazine-1-yl, 7-(guanidinoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazine-

1-yl, 7-(guanidinium alkylhydroxy)-1,3-(diaz)-2-(oxo)-phenothiazine-1-yl, 7-(guanidinoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenothiazine-1-yl, 1,3,5-(triaz)-2,6-(diox)-naphthalene, inosine, xanthine, hypoxanthine, Zebularine, tuberculin, isoguanosine, inosinyl, 2-aza-inosinyl, 7-deaza-inosinyl, nitroimidazolyl, nitropyrazolyl, nitrobenzimidazolyl, nitroindazolyl, aminoindolyl, pyrrolopyrimidinyl, 3-(methyl)isocarbostyryl, 5-(methyl)isocarbostyryl, 3-(methyl)-7-(propynyl)isocarbostyryl, 7-(aza)indolyl, 6-(methyl)-7-(aza)indolyl, iminopyridinyl, 9-(methyl)-iminopyridinyl, pyrrolopyrazinyl, isocarbenyryl, 7-(propynyl)isocarbenyryl, propynyl-7-(aza)indolyl, 2,4,5-(trimethyl)phenyl, 4-(methyl)indolyl, 4,6-(dimethyl)indolyl, phenyl, naphthyl, anthracenyl, phenanthrenyl, pyrenyl, stilbenyl, tetraphenyl, pentaphenyl, difluorotolyl, 4-(fluoro)-6-(methyl)benzimidazole, 4-(methyl)benzimidazole, 6-(azo)thymine, 2-pyridone, 5-nitroindole, 3-nitropyrrole, 6-(aza)pyrimidine, 2-(amino)purine, 2,6-(diamino)purine, 5-substituted pyrimidine, 2-substituted purine, N6-substituted purine, O6-substituted purine, substituted 1,2,4-triazole or any O-alkylated or N-alkylated derivative thereof.

"Stereoisomers" refer to compounds that have the same chemical constitution but differ in the arrangement of the atoms or groups in space. Stereoisomers include enantiomers, diastereomers, conformational isomers (rotamers), geometric isomers (cis/trans isomers), atropisomers, and the like.

The expression "connected to form a ring by a chemical bond" means connecting two groups by a carbon-carbon bond, a carbon-oxygen bond, a carbon-nitrogen bond, a carbon-sulfur bond, or the like to form a ring structure. If necessary, hydrogen atoms can be reduced by 1 or 2 from corresponding group.

The expression "optionally substituted" means that one, two, three or more than three hydrogen atoms in a group may be replaced independently by respective substituents. The substituents may be selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, cyano, amino, nitro, and -OH.

The term "alkyl" refers to a saturated straight or branched carbon chain. Preferably, the chain contains 1 to 10 carbon atoms, that is, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, preferably 1 to 6 carbon atoms, most preferably 1 to 3 carbon atoms. The alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, pentyl or octyl. The alkyl is optionally substituted.

The term "alkoxy" includes -O- alkyl groups and alkyl groups in which the O atom is in the alkyl

chain, such as $\text{-CH}_2\text{-O-CH}_3$. The alkoxy contains 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, and most preferably 1 to 3 carbon atoms. The alkoxy is optionally substituted.

The term "alkenyl" includes both straight and branched alkyl groups containing at least two carbon atoms and at least one carbon-carbon double bond. The alkenyl contains 2 to 10 carbon atoms, preferably 2 to 6 carbon atoms, and most preferably 2 to 3 carbon atoms. The alkenyl is optionally substituted.

The term "alkynyl" includes both straight and branched alkyl groups containing at least two carbon atoms and at least one carbon-carbon triple bond. The alkynyl contains 2 to 10 carbon atoms, preferably 2 to 6 carbon atoms, and most preferably 2 to 3 carbon atoms. The alkynyl group is optionally substituted.

The terms "cycloalkyl", "cycloalkenyl" and "cycloalkynyl" are used by themselves or in combination with other terms to represent cyclic forms of "alkyl", "alkenyl" and "alkynyl", respectively. Preferably, the cyclic forms are formed by 3, 4, 5, 6, 7, 8, 9 or 10 atoms in the ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopropynyl, cyclobutynyl, cyclohexynyl, cyclopentynyl, and the like. The connection position of the cycloalkenyl or cycloalkynyl to the other group can be at any suitable position. The terms "cycloalkyl", "cycloalkenyl" and "cycloalkynyl" are also intended to include bicyclic, tricyclic and polycyclic forms thereof, which may be spirocyclic or bridged rings. The "cycloalkyl", "cycloalkenyl" and "cycloalkynyl" are optionally substituted. Examples of cycloalkyl and cycloalkenyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, spiro [3,3] heptyl, spiro [3,4] octyl, spiro [4,3] octyl, spiro [3,5] nonyl, spiro [5,3] nonyl, spiro [3,6] decyl, spiro [6,3] decyl, spiro [4,5] decyl, spiro [5,4] decyl, bicyclo [2.2.1] heptyl, bicyclo [2.2.2] octyl, adamantyl, norbornenyl, and the like.

The term "aryl" preferably refers to an aromatic monocyclic ring containing 6 carbon atoms, an aromatic bicyclic ring system containing 10 carbon atoms or an aromatic tricyclic ring system containing 14 carbon atoms. Examples include phenyl, naphthyl, or anthracenyl. The aryl is optionally substituted.

The term "heteroaryl" preferably refers to: a five-membered aromatic monocyclic ring or a six-membered aromatic monocyclic ring in which at least one carbon atom is replaced by 1, 2, 3 or 4 (for a five-membered ring) or 1, 2, 3, 4 or 5 (for a six-membered ring) identical or different heteroatoms, the heteroatoms being preferably selected from the group consisting of O, N and S; an aromatic bicyclic ring system in which 1, 2, 3, 4, 5 or 6 carbon atoms of 8, 9, 10, 11 or 12 carbon atoms are replaced by identical or different heteroatoms, the heteroatoms being preferably selected from the group consisting of O, N and S; or an aromatic tricyclic ring system in which 1, 2, 3, 4, 5 or 6 carbon atoms of 13, 14, 15, 16 carbon atoms are replaced by identical or different heteroatoms, the heteroatoms being preferably selected from the group consisting of O, N and S. Examples include oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,4,5-tetrazinyl, 1-benzofuranyl, 2-benzofuranyl, indolyl, isoindolyl, benzothienyl, 2-benzothienyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, indoloxazinyl, 2,1-benzoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, quinolyl, 1,2,3-benzotriazinyl or 1,2,4-benzotriazinyl.

The term "PEG group" refers to a group in which one or more $\text{-CH}_2\text{-CH}_2\text{-O-}$ or $\text{CH}_3\text{-CH}_2\text{-O-}$ units are connected, for example, $\text{CH}_3\text{-CH}_2\text{-O-(CH}_2\text{-CH}_2\text{-O)}_x\text{-}$, wherein x is selected from an integer from 0 to 6, preferably an integer from 0 to 4. The PEG group may be optionally substituted.

The term "pharmaceutically acceptable salt" refers to relatively non-toxic addition salts of the compound of the present disclosure. See, for example, S. M. Berge et al. "Pharmaceutical Salts", J. Pharm. Sci. 1977, 66, 1-19.

Suitable pharmaceutically acceptable salts of the compound of the present disclosure may be acid addition salts of the compound of the present disclosure having a nitrogen atom in a chain or ring and having sufficient basicity, such as acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid or nitric acid, or acid addition salts formed with organic acids such as formic acid, acetic acid, acetoacetic acid, pyruvic acid, trifluoroacetic acid, propionic acid, butyric acid, caproic acid, heptanoic acid, undecanoic acid, lauric

acid, benzoic acid, salicylic acid, 2-(4-hydroxybenzoyl)benzoic acid, camphoric acid, cinnamic acid, cyclopentanepropionic acid, 3-hydroxy-2-naphthoic acid, nicotinic acid, pamoic acid, pectinic acid, persulfuric acid, 3-phenylpropionic acid, picric acid, pivalic acid, 2-hydroxyethanesulfonic acid, itaconic acid, sulfamic acid, trifluoromethanesulfonic acid, dodecyl sulfuric acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, naphthalene disulfonic acid, camphorsulfonic acid, citric acid, tartaric acid, stearic acid, lactic acid, oxalic acid, malonic acid, succinic acid, malic acid, adipic acid, alginic acid, maleic acid, fumaric acid, D-gluconic acid, mandelic acid, ascorbic acid, glucoheptonic acid, glycerophosphoric acid, aspartic acid, sulfosalicylic acid or thiocyanic acid.

In addition, another suitable pharmaceutically acceptable salt of the compound of the present invention having sufficient acidity is an alkali metal salt such as a sodium salt or a potassium salt, an alkaline earth metal salt such as a calcium salt or a magnesium salt, an ammonium salt, a triethylamine salt, or a salt formed with an organic base providing a physiologically acceptable cation, such as a salt formed with the following substances: N-methylglucamine, dimethylglucamine, ethylglucosamine, lysine, dicyclohexylamine, 1,6-hexanediamine, ethanolamine, glucosamine, sarcosine, serinol, trihydroxymethylaminomethane, aminopropanediol, 1-amino-2,3,4-butanetriol. In addition, basic nitrogen-containing groups can be quaternized using the following reagents: lower alkyl halides such as methyl, ethyl, propyl and butyl chlorides, bromides, and iodides; dialkyl sulfates such as dimethyl sulfate, diethyl sulfate, dibutyl sulfate, and dipentyl sulfate; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides, and iodides; aralkyl halides such as benzyl bromides and phenethyl bromides, and the like.

Those skilled in the art could also recognize that the acid addition salts of the claimed compound can be prepared by reacting the compound with a suitable inorganic or organic acid by any of a number of known methods. Alternatively, alkali metal salts and alkaline earth metal salts of the acidic compound of the present disclosure can be prepared by reacting the compound with a suitable base by various known methods.

The present invention includes all possible salts of the compound of the present disclosure, which may be a single salt or any mixture of any proportion of the salts.

The term "solvate" is a substance formed by combining, physically binding and/or solvating the compound of the present invention with a solvent molecule, such as a disolvate, a monosolvate or a hemisolvate, in which the ratio of the solvent molecule to the compound of the present invention is about 2:1, about 1:1 or about 1:2, respectively. This physical binding involves ionization and covalent bonding (including hydrogen bonding) to varying degrees. In some cases (for example, when one or more solvent molecules are incorporated into the lattice of a crystalline solid), the solvate can be separated. Therefore, the solvate includes solution phases and separable solvates. The compound of the present invention, together with a pharmaceutically acceptable solvent (such as water, methanol and ethanol), can be present in solvated form, and the present application is intended to cover solvated and non-solvated forms of the compound of the present invention. One of the solvates is a hydrate.

The term "pharmaceutical composition" as used in the present application refers to a substance and/or a combination of substances used to identify, prevent or treat a tissue condition or disease. The pharmaceutical composition is formulated to be suitable for administration to a patient to diagnose, prevent and/or treat a disease. In addition, the pharmaceutical composition refers to a combination of an active agent and an inert or active carrier that makes the composition suitable for therapeutic use.

As used herein, the term "carrier" refers to a diluent, adjuvant, excipient or vehicle used together with a therapeutic agent. This pharmaceutical carrier can be a sterile liquid, such as a saline solution in water and oil, including those of petroleum, animal, plant or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, and the like. When the pharmaceutical composition is administered intravenously, a saline solution is a preferred carrier. A saline solution, an aqueous glucose solution and a glycerol solution can also be used as liquid carriers, particularly as injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glyceryl monostearate, talc, sodium chloride, skim milk powder, glycerol, propylene, ethylene glycol, water, ethanol, and the like. If necessary, the composition may also contain a small amount of a wetting agent, emulsifier, or pH buffer. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

The term "halogen" refers to fluorine, chlorine, bromine and iodine.

The term "optionally" means that this may occur, or may not occur.

Examples

Reagents and Models Used

The starting materials in the examples are commercially available and/or can be prepared by a number of methods well known to those skilled in the art of organic synthesis. Those skilled in the art of organic synthesis will appropriately select reaction conditions (including solvent, reaction atmosphere, reaction temperature, duration of experiment and post-treatment) in the following synthetic methods. Those skilled in the art of organic synthesis will understand that functional groups present on each part of a molecule should be compatible with reagents and reactions provided.

All reagents and compounds synthesized can be purchased through general commercial channels in China. The suppliers include Sigma-Aldrich (USA), Shanghai Hongene Biotech Corporation. (Trinlink Cleancap), jetMESSENGER (Polyplus-transfection®), Shanghai Titan Technology Co., Ltd., and the like.

Cell model: HEK293T cells were purchased from the Shanghai Cell Bank of the Chinese Academy of Sciences, and HepG2 cells were purchased from Wuhan Pricella Biotechnology Co., Ltd.

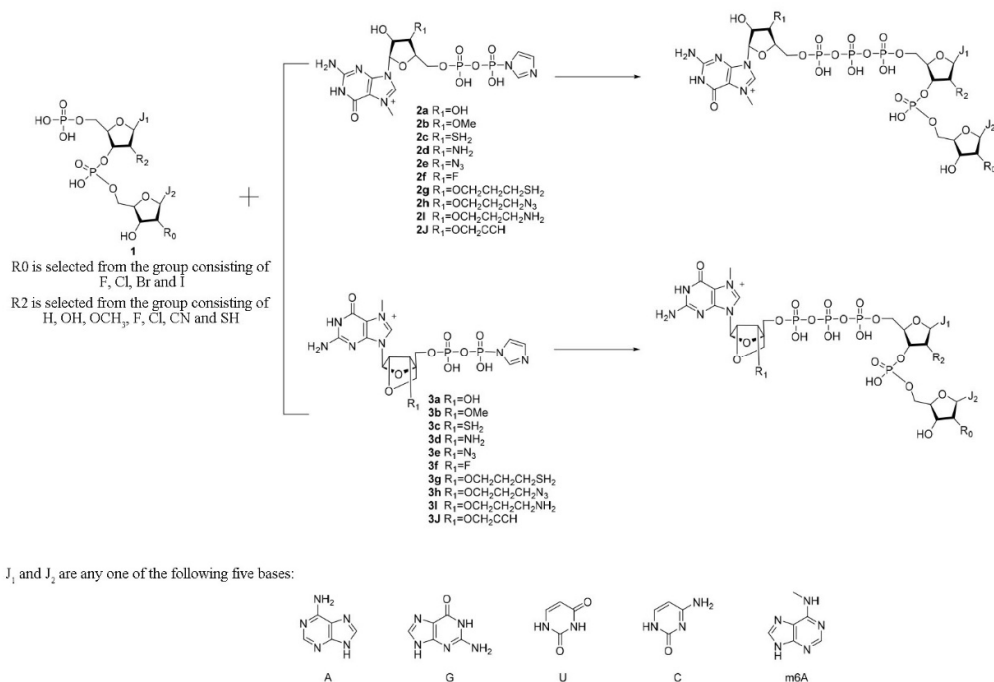
Main instruments used: Multi-mode microplate reader (Molecular Devices), and flow cytometer (CytoFLEX S series).

Compound preparation and identification: Nuclear magnetic resonance spectrometer (Bruker 300MHz), liquid chromatography-mass spectrometry (Agilent 6150/1290), and high-performance liquid chromatography (Agilent 1260).

Cell experiment: Inverted fluorescence microscope (Guangzhou Mingmei Optoelectronic Technology Co., Ltd), and cell culture incubator (Thermo Fisher Scientific).

The implementation process and beneficial effects of the present invention will be described in detail below through specific examples, which are intended to help readers better understand the essence and characteristics of the present invention, and are not intended to limit the implementable scope of the present invention.

Final Product Synthesis:



Final Product Synthesis Method 1

To 8 mL of anhydrous DMSO, 0.4 g of a compound **1** was dissolved, and 2 eq of a compound **2** and 20 eq of anhydrous zinc chloride were added under the protection of argon. The reaction solution was stirred at room temperature 25°C for 24 hours under the protection of argon. After the reaction was completed by TLC monitoring, 150 mL of 0.25 M EDTA solution was used to terminate the reaction, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an ammonium bicarbonate eluent of 0 M to 1.0 M. The product-containing eluent was collected and freeze-dried to obtain a product.

Final Product Synthesis Method 2

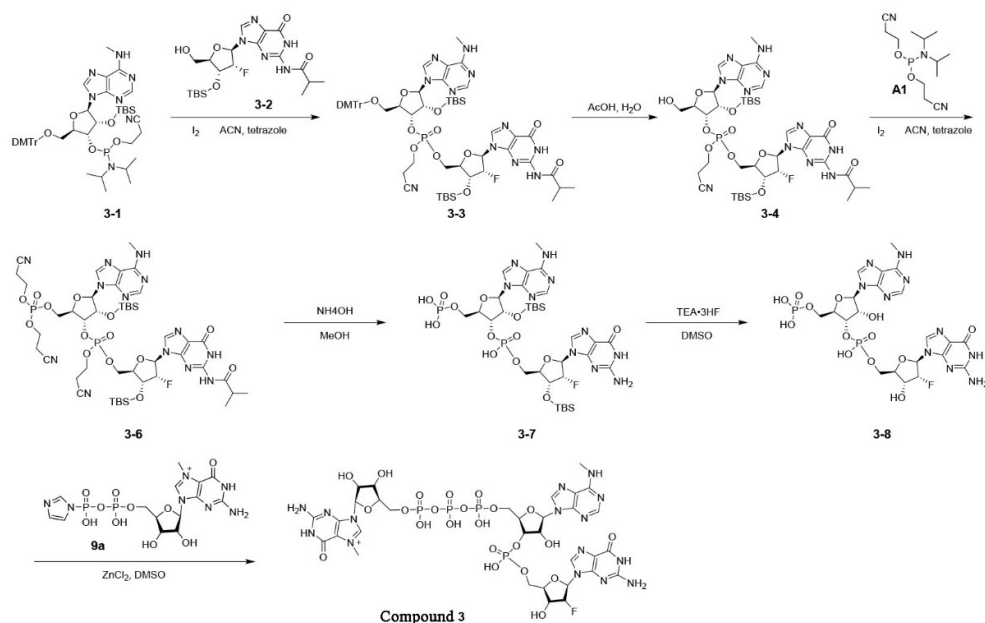
To 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, 0.2 g of the compound **2** was dissolved, and then 0.2 g of the compound **1** was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. After the reaction was completed by TLC monitoring, 150 mL of 0.25 M EDTA solution was used to terminate the reaction, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an ammonium bicarbonate eluent of 0 M to 1.0

M. The product-containing eluent was collected and freeze-dried to obtain a product.

Synthesis of Representative Structural Compounds

Example 1

Synthesis of Compound 3



Step 1:

A compound **3-2** (2.38 g) was added to a solution of tetrazole (1.76 g) in acetonitrile (63 mL) in a three-necked flask, and the atmosphere was replaced with argon three times. Next, at room temperature of 25°C, a compound **3-1** (5 g) was dissolved in 10 mL of acetonitrile and added to the above solution. The resulting solution was stirred at room temperature of 25°C for 1 hour. No obvious heat release was found, and TLC monitoring showed that the compound **3-1** disappeared. Then, into the solution, a solution of iodine in pyridine/tetrahydrofuran/water (0.5 mmol/mL, pyridine: tetrahydrofuran: water = 1:8:1) was added dropwise until the solution no longer faded. After that, the reaction solution was stirred for another 0.5 hours, and TLC monitoring showed that the oxidation was completed. After adding an aqueous saturated solution (10 mL) of sodium sulfite to the reaction solution for quenching, 50 mL of water was further added for dilution, and the mixture was extracted with dichloromethane (50 mL x 2). The organic phases were combined and washed once with water (50 mL), and concentrated to obtain a light yellow oily product **3-3** (8 g, crude product).

Step 2:

The compound **3-3** (8 g, crude product) was dissolved in 40 mL of acetic acid and 10 mL of water, and the reaction solution was stirred at 25°C for 16 hours. TLC monitoring showed that the compound **3-3** disappeared and a spot with large polarity was generated. The reaction solution was directly concentrated in vacuo. After concentration, appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white solid product **3-4** (2.8 g, 51% overall yield over two-step) was obtained.

Step 3:

28 mL of a tetrazole solution in acetonitrile (0.4 mmol/mL) was prepared. The compound **3-4** (2.8 g) was added to the above solution, and then a compound **A1** (3 g) was added to the solution at room temperature of 25°C. The atmosphere was replaced with nitrogen three times, and the reaction solution was stirred at room temperature of 25°C for 1 hour. TLC monitoring showed that the reaction was completed. The reaction solution was cooled to below 10°C in an ice-water bath, and a solution of iodine in pyridine/tetrahydrofuran/water (0.5 mmol/mL, pyridine:tetrahydrofuran:water = 1:8:1) was added dropwise until the reaction solution no longer faded. TLC monitoring showed that the oxidation reaction was completed. The reaction solution was quenched by adding 10 mL of an aqueous saturated solution of sodium sulfite, diluted with water, and extracted three times with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate and filtered. Appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white foamy solid compound **3-6** (2.6 g, 78.2% yield) was obtained.

Step 4:

The compound **3-6** (2.6 g) was dissolved in methanol (30 mL) and concentrated aqueous ammonia (30 mL) was added. The resulting solution was stirred at room temperature of 25°C for 60 hours. TLC monitoring showed that the compound **3-6** was completely reacted. The reaction solution was concentrated in vacuo and concentrated again with methanol to obtain a light yellow oily liquid

compound **3-7** (2.4 g, crude product), which was directly used for the next step.

Step 5:

The compound **3-7** (2.4 g, crude product) was dissolved in DMSO (3 mL) and triethylamine trihydrofluoride (3.5 mL) was added. The reaction solution was stirred at 50°C for 1 hour. TLC monitoring showed that the compound **3-7** was completely reacted. The reaction solution was diluted to 50 mL with water, and the pH was adjusted to 5.5 with 1 N NaOH aqueous solution. The mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent of 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a target compound, amine salt **3-8** (0.8 g, 33.7% yield), which was a white solid.

Step 6:

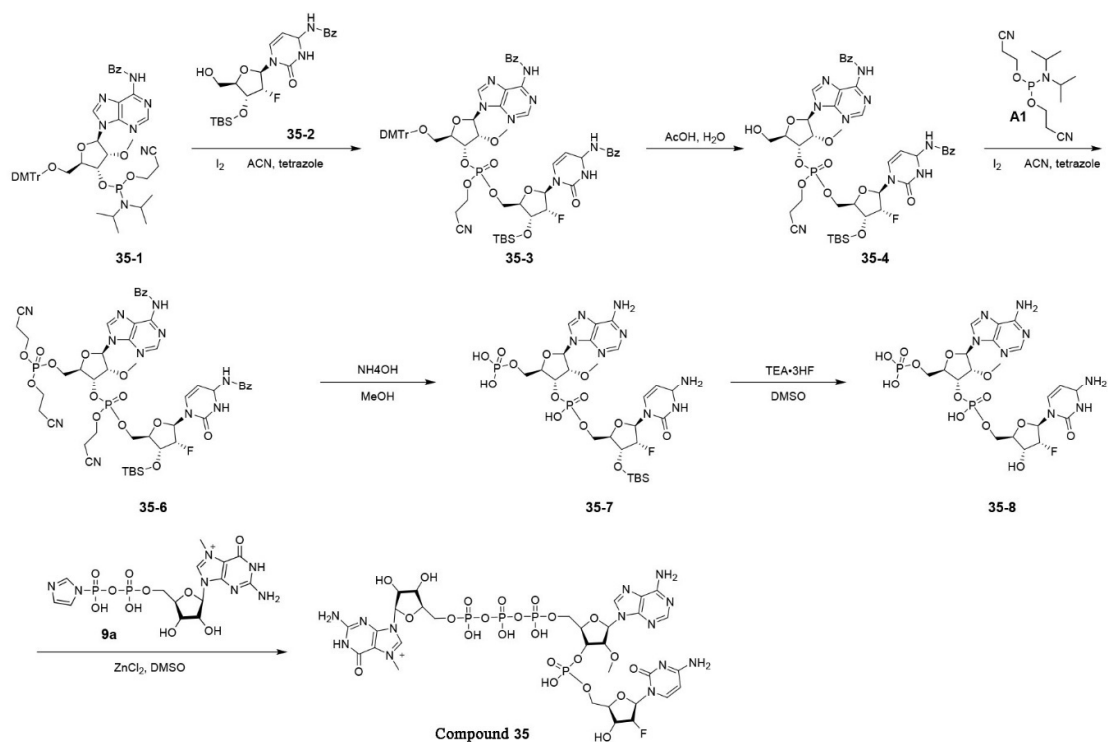
A compound **9a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and the compound **3-8** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **5**, which was an ammonium salt in the form of white powder (65 mg).

¹H NMR (400 MHz, D₂O) δ 8.08 (s, 1H), 7.89 (s, 1H), 7.65 (s, 1H), 5.93 (d, J = 17.9 Hz, 1H), 5.70 (d, J = 6.4 Hz, 2H), 5.28 - 5.02 (m, 1H), 4.58 - 3.99 (m, 14H), 3.84 (s, 3H), 3.00 - 2.70 (m, 3H).

³¹P NMR (162 MHz, D₂O) δ -0.80, -11.55, -23.03.

Example 2

Synthesis of Compound 35



Step 1:

A compound **35-2** (2.07 g) was added to a solution of tetrazole (1.6 g) in acetonitrile (56 mL) in a three-necked flask, and the atmosphere was replaced with argon three times. Next, at room temperature of 25°C, a compound **35-1** (5 g) was dissolved in 10 mL of acetonitrile and added to the above solution. The resulting solution was stirred at room temperature of 25°C for 1 hour. No obvious heat release was found, and TLC monitoring showed that the compound **2-1** disappeared. Then, into the solution, iodine solution (a 0.5 mmol/mL solution was prepared by dissolving 5 g iodine in 40 mL of the mixed solution: THF: H_2O :pyridine = 8:1:1) was added dropwise until the solution no longer faded. After that, the reaction solution was stirred for another 0.5 hours, and TLC monitoring showed that the oxidation was completed. After adding Na_2SO_3 aqueous solution (10 mL) to the reaction solution for quenching, 50 mL of water was further added for dilution, and the mixture was extracted with dichloromethane (50 mL x 2). The organic phases were combined and washed once with water (50 mL), and concentrated to obtain a light yellow oily product **35-3** (7.5 g, crude product).

Step 2:

The compound **35-3** (7.2 g, crude product) was dissolved in 40 mL of acetic acid and 10 mL of water, and the reaction solution was stirred at 25°C for 16 hours. The TLC monitoring showed that

the compound **35-3** disappeared and a spot with large polarity was generated. The reaction solution was directly concentrated in vacuo. After concentration, appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white solid product **35-4** (2.8 g, 54.8% overall yield over two-step) was obtained.

Step 3:

28 mL of a tetrazole solution in acetonitrile (0.4 mmol/mL) was prepared. The compound **35-4** (2.8 g) was added to the above solution, and then a compound **AI** (2.26 g) was added to the solution at room temperature of 25°C. The atmosphere was replaced with nitrogen three times, and the reaction solution was stirred at room temperature of 25°C for 1 hour. TLC monitoring showed that the reaction was completed. The reaction solution was cooled to below 10°C in an ice-water bath, and a solution of iodine in pyridine/tetrahydrofuran/water (0.5 mmol/mL, pyridine:tetrahydrofuran:water = 1:8:1) was added dropwise until the reaction solution no longer faded. TLC monitoring showed that the oxidation reaction was completed. The reaction solution was quenched by adding 10 mL of an aqueous saturated solution of sodium sulfite, diluted with water, and extracted three times with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate and filtered. Appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white foamy solid compound **35-6** (3.1 g, 93.5% yield) was obtained.

Step 4:

The compound **35-6** (3.1 g) was dissolved in methanol (30 mL) and concentrated aqueous ammonia (30 mL) was added. The resulting solution was stirred at room temperature of 25°C for 60 hours. TLC monitoring showed that the compound **35-6** was completely reacted. The reaction solution was concentrated in vacuo and concentrated again with methanol to obtain a light yellow oily liquid compound **35-7** (2.4 g, crude product).

Step 5:

The compound **35-7** (2.4 g, crude product) was dissolved in DMSO (3 mL) and triethylamine

trihydrofluoride (3.5 mL) was added. The reaction solution was stirred at 50°C for 1 hour. TLC monitoring showed that the compound **35-7** was completely reacted. The reaction solution was diluted to 50 mL with water, and the pH was adjusted to 5.5 with 1 N NaOH aqueous solution. The mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using 0 M to 1.0 M TEAB eluent. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a target compound triethylamine salt **35-8** (1.5 g, 51% yield), which was a white solid.

Step 6:

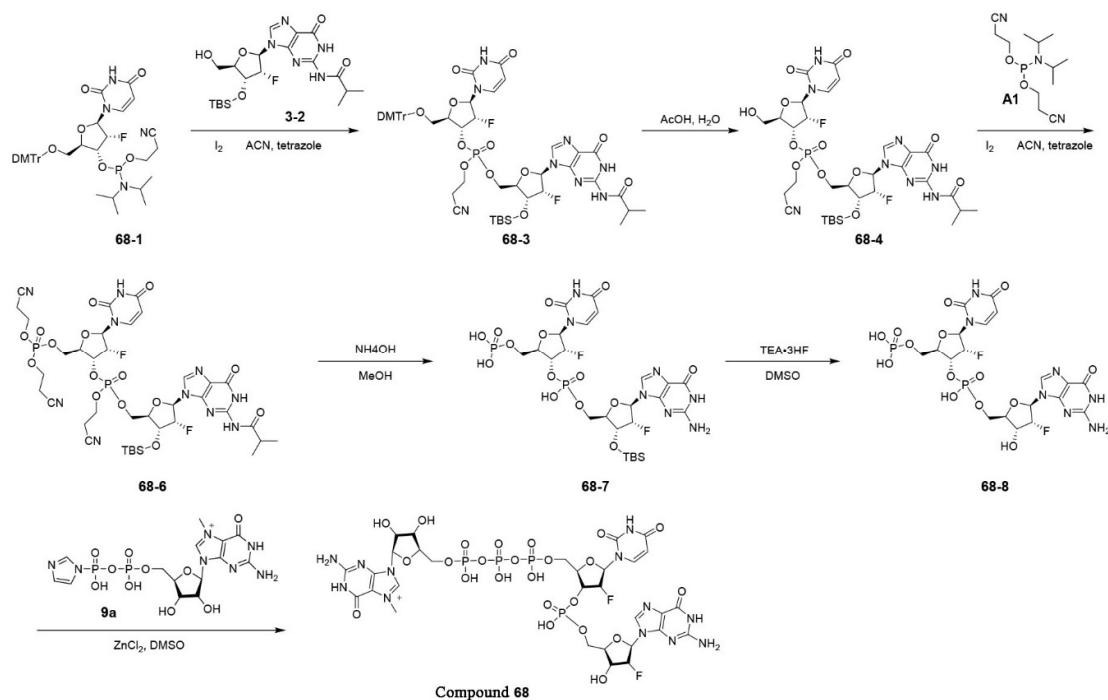
At room temperature (25°C), under the protection of argon, the compound **35-8** (500 mg), the compound **9a** (500 mg) and anhydrous zinc chloride (1.2 g) were added, and anhydrous DMSO (8 mL) was added with a syringe to react for 24 hours. TLC monitoring showed that most of the compounds were reacted. The reaction solution was added to a disodium EDTA solution (1.6 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **35**, which was an ammonium salt in the form of white powder (120 mg).

¹H NMR (400 MHz, D₂O) δ 8.25 (s, 1H), 7.98 (s, 1H), 7.59 (d, J = 7.3 Hz, 1H), 5.99 - 5.53 (m, 4H), 4.96 - 4.80 (m, 1H), 4.46 - 3.99 (m, 14H), 3.90 (s, 3H), 3.41 (s, 3H).

³¹P NMR (162 MHz, D₂O) δ -1.25, -11.58, -22.98.

Example 3

Synthesis of Compound 68



Step 1:

The compound **3-2** (2.07 g) was added to a solution of tetrazole (1.6 g) in acetonitrile (56 mL) in a three-necked flask, and the atmosphere was replaced with argon three times. Next, at room temperature of 25°C, a compound **68-1** (5 g) was dissolved in 10 mL of acetonitrile and added to the above solution. The resulting solution was stirred at room temperature of 25°C for 1 hour. No obvious heat release was found, and TLC monitoring showed that the compound **68-1** disappeared. Then, into the solution, iodine solution (a 0.5 mmol/mL solution was prepared by dissolving 5 g iodine in 40 mL of the mixed solution: THF:H₂O:pyridine = 8:1:1) was added dropwise until the solution no longer faded. After that, the reaction solution was stirred for another 0.5 hours, and TLC monitoring showed that the oxidation was completed. After adding Na₂SO₃ aqueous solution (10 mL) to the reaction solution for quenching, 50 mL of water was further added for dilution, and the mixture was extracted with dichloromethane (50 mL x 2). The organic phases were combined and washed once with water (50 mL), and concentrated to obtain a light yellow oily product **68-3** (7.5 g, crude product).

Step 2:

The compound **68-3** (7.2 g, crude product) was dissolved in 40 mL of acetic acid and 10 mL of water, and the reaction solution was stirred at 25°C for 16 hours. TLC monitoring showed that the

compound **68-3** disappeared and a spot with large polarity was generated. The reaction solution was directly concentrated in vacuo. After concentration, appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white solid product **68-4** (2.8 g, 54.8% overall yield over two-step) was obtained.

Step 3:

28 mL of a tetrazole solution in acetonitrile (0.4 mmol/mL) was prepared. The compound **68-4** (2.8 g) was added to the above solution, and then a compound **A1** (2.26 g) was added to the solution at room temperature of 25°C. The atmosphere was replaced with nitrogen three times, and the reaction solution was stirred at room temperature of 25°C for 1 hour. TLC monitoring showed that the reaction was completed. The reaction solution was cooled to below 10°C in an ice-water bath, and a solution of iodine in pyridine/tetrahydrofuran/water (0.5 mmol/mL, pyridine:tetrahydrofuran:water = 1:8:1) was added dropwise until the reaction solution no longer faded. TLC monitoring showed that the oxidation reaction was completed. The reaction solution was quenched by adding 10 mL of an aqueous saturated solution of sodium sulfite, diluted with water, and extracted three times with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate and filtered. Appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white foamy solid compound **68-6** (3.1 g, 93.5% yield) was obtained.

Step 4:

The compound **68-6** (3.1 g) was dissolved in methanol (30 mL) and concentrated aqueous ammonia (30 mL) was added. The resulting solution was stirred at room temperature of 25°C for 60 hours. TLC monitoring showed that the compound **68-6** was completely reacted. The reaction solution was concentrated in vacuo and concentrated again with methanol to obtain a light yellow oily liquid compound **68-7** (2.4 g, crude product).

Step 5:

The compound **68-7** (2.4 g, crude product) was dissolved in DMSO (3 mL) and triethylamine

trihydrofluoride (3.5 mL) was added. The reaction solution was stirred at 50°C for 1 hour. TLC monitoring showed that the compound **68-7** was completely reacted. The reaction solution was diluted to 50 mL with water, and the pH was adjusted to 5.5 with 1 N NaOH aqueous solution. The mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using 0 M to 1.0 M TEAB eluent. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a target compound triethylamine salt **68-8** (1.5 g, 51% yield), which was a white solid.

Step 6:

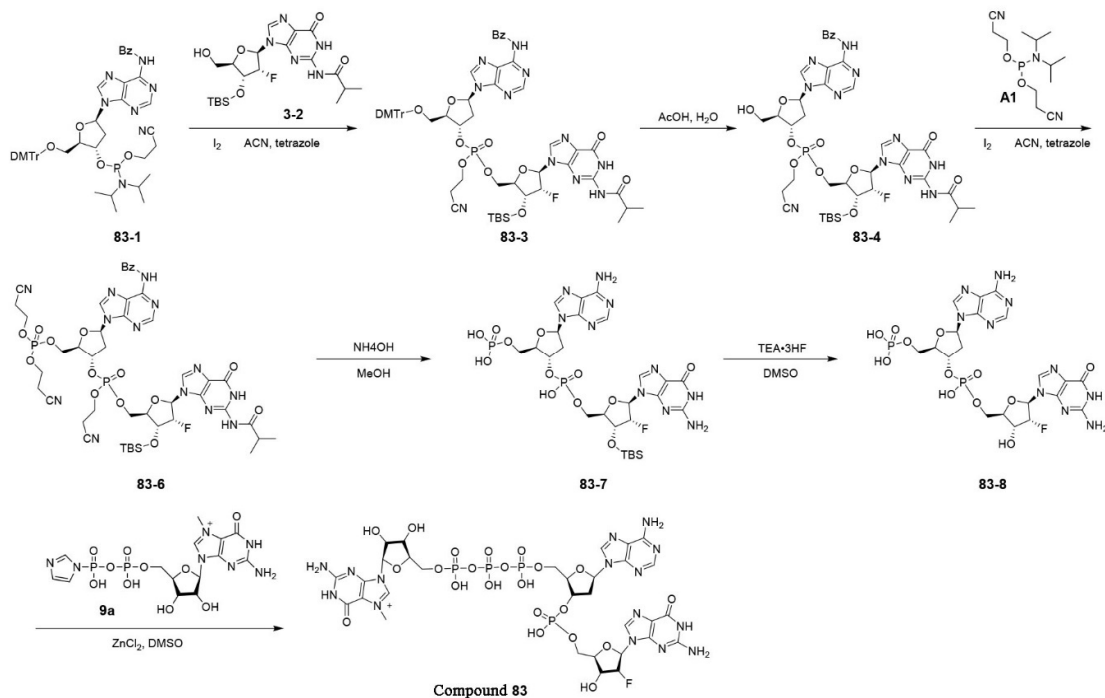
At room temperature (25°C), under the protection of argon, the compound **68-8** (500 mg), the compound **9a** (500 mg) and anhydrous zinc chloride (1.2 g) were added, and anhydrous DMSO (8 mL) was added with a syringe to react for 24 hours. TLC monitoring showed that most of the materials were reacted. The reaction solution was added to a disodium EDTA solution (1.6 g, 80 mL of water was added) cooled to 0°C in advance, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **68**, which was an ammonium salt in the form of white powder (120 mg).

¹H NMR (400 MHz, D₂O) δ 7.75 (s, 1H), 7.61 (d, J = 8.1 Hz, 1H), 5.97 (dd, J = 17.8, 2.3 Hz, 1H), 5.85 - 5.65 (m, 3H), 5.28 (ddd, J = 52.2, 4.7, 2.3 Hz, 1H), 5.01 (dt, J = 51.5, 3.4 Hz, 1H), 4.57 - 4.51 (m, 2H), 4.48 (t, J = 4.2 Hz, 1H), 4.34 (t, J = 5.1 Hz, 1H), 4.24 - 4.07 (m, 7H), 4.02 (t, J = 4.3 Hz, 2H), 3.93 (s, 3H).

³¹P NMR (162 MHz, D₂O) δ -1.30, -11.57 (dd, J = 25.8, 18.4 Hz), -22.98 (t, J = 18.3 Hz).

Example 4

Synthesis of Compound 83



Step 1:

The compound **3-2** (2.1 g) was added to a solution of tetrazole (1.6 g) in acetonitrile (56 mL) in a three-necked flask, and the atmosphere was replaced with argon three times. Next, at room temperature of 25°C, a compound **83-1** (5 g) was dissolved in 10 mL of acetonitrile and added to the above solution. The resulting solution was stirred at room temperature of 25°C for 1 hour. No obvious heat release was found, and TLC monitoring showed that the compound **83-1** disappeared. Then, into the solution, iodine solution (a 0.5 mmol/mL solution was prepared by dissolving 5 g iodine in 40 mL of the mixed solution: THF:H₂O:pyridine = 8:1:1) was added dropwise until the solution no longer faded. After that, the reaction solution was stirred for another 0.5 hours, and TLC monitoring showed that the oxidation was completed. After adding Na₂SO₃ aqueous solution (10 mL) to the reaction solution for quenching, 50 mL of water was further added for dilution, and the mixture was extracted with dichloromethane (50 mL x 2). The organic phases were combined and washed once with water (50 mL), and concentrated to obtain a light yellow oily product **83-3** (7.4 g, crude product).

Step 2:

The compound **83-3** (7.4 g, crude product) was dissolved in 40 mL of acetic acid and 10 mL of water, and the reaction solution was stirred at 25°C for 16 hours. TLC monitoring showed that the

compound **83-3** disappeared and a spot with large polarity was generated. The reaction solution was directly concentrated in vacuo. After concentration, appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white solid product **83-4** (2.8 g, 54.8% overall yield over two-step) was obtained.

Step 3:

28 mL of a tetrazole solution in acetonitrile (0.4 mmol/mL) was prepared. The compound **83-4** (2.8 g) was added to the above solution, and then a compound **A1** (2.26 g) was added to the solution at room temperature of 25°C. The atmosphere was replaced with nitrogen three times, and the reaction solution was stirred at room temperature of 25°C for 1 hour. TLC monitoring showed that the reaction was completed. The reaction solution was cooled to below 10°C in an ice-water bath, and a solution of iodine in pyridine/tetrahydrofuran/water (0.5 mmol/mL, pyridine:tetrahydrofuran:water = 1:8:1) was added dropwise until the reaction solution no longer faded. TLC monitoring showed that the oxidation reaction was completed. The reaction solution was quenched by adding 10 mL of an aqueous saturated solution of sodium sulfite, diluted with water, and extracted three times with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate and filtered. Appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white foamy solid compound **83-6** (3.1 g, 93.5% yield) was obtained.

Step 4:

The compound **83-6** (3.1 g) was dissolved in methanol (30 mL) and concentrated aqueous ammonia (30 mL) was added. The resulting solution was stirred at room temperature of 25°C for 60 hours. TLC monitoring showed that the compound **83-6** was completely reacted. The reaction solution was concentrated in vacuo and concentrated again with methanol to obtain a light yellow oily liquid compound **83-7** (2.4 g, crude product).

Step 5:

The compound **83-7** (2.4 g, crude product) was dissolved in DMSO (3 mL) and triethylamine

trihydrofluoride (3.5 mL) was added. The reaction solution was stirred at 50°C for 1 hour. TLC monitoring showed that the compound **83-7** was completely reacted. The reaction solution was diluted to 50 mL with water, and the pH was adjusted to 5.5 with 1 N NaOH aqueous solution. The mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using 0 M to 1.0 M TEAB eluent. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a target compound triethylamine salt **83-8** (1.5 g, 51% yield), which was a white solid.

Step 6:

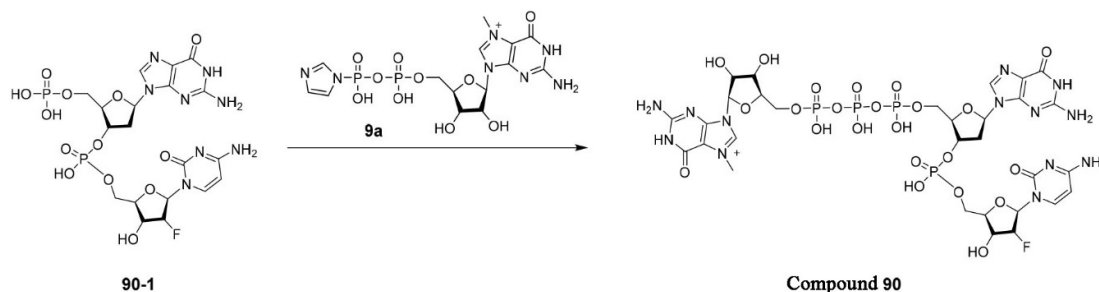
At room temperature (25°C), under the protection of argon, the compound **83-8** (500 mg), the compound **9a** (500 mg) and anhydrous zinc chloride (1.2 g) were added, and anhydrous DMSO (8 mL) was added with a syringe to react for 24 hours. TLC monitoring showed that most of the materials were reacted. The reaction solution was added to a disodium EDTA solution (1.6 g, 80 mL of water was added) cooled to 0°C in advance, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **83**, which was an ammonium salt in the form of white powder (120 mg).

¹H NMR (400 MHz, D₂O) δ 8.30 (d, J = 0.6 Hz, 1H), 8.20 (s, 1H), 8.02 (d, J = 0.7 Hz, 1H), 6.59 - 6.30 (m, 2H), 6.23 - 6.08 (m, 1H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 5.08 - 4.90 (m, 1H), 4.68 - 4.03 (m, 12H), 3.98 (d, J = 0.7 Hz, 3H), 2.76 - 2.48 (m, 2H).

³¹P NMR (162 MHz, D₂O) δ -1.30, -11.57 (dd, J = 25.8, 18.4 Hz), -22.98 (t, J = 18.3 Hz).

Example 5

Synthesis of Compound 90



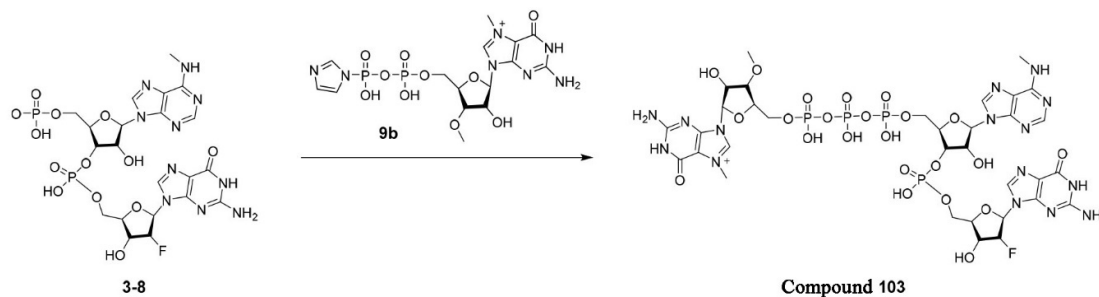
The compound **9a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **90-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **90**, which was an ammonium salt in the form of white powder (50 mg).

¹H NMR (400 MHz, D₂O) δ 7.83 (d, J = 0.6 Hz, 1H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 6.28 (ddq, J = 3.1, 1.5, 0.7 Hz, 1H), 6.20 - 6.13 (m, 1H), 6.04 (d, J = 7.3 Hz, 1H), 5.40 (dddd, J = 25.2, 3.5, 1.8, 0.9 Hz, 1H), 5.09 - 4.93 (m, 1H), 4.81 (dddd, J = 46.4, 7.1, 3.7, 0.7 Hz, 1H), 4.61 (ddd, J = 5.2, 2.8, 0.7 Hz, 1H), 4.41 - 4.05 (m, 11H), 3.98 (d, J = 0.7 Hz, 3H), 2.81 - 2.38 (m, 2H).

³¹P NMR (162 MHz, D₂O) δ -1.17, -11.50, -22.81.

Example 6

Synthesis of Compound 103



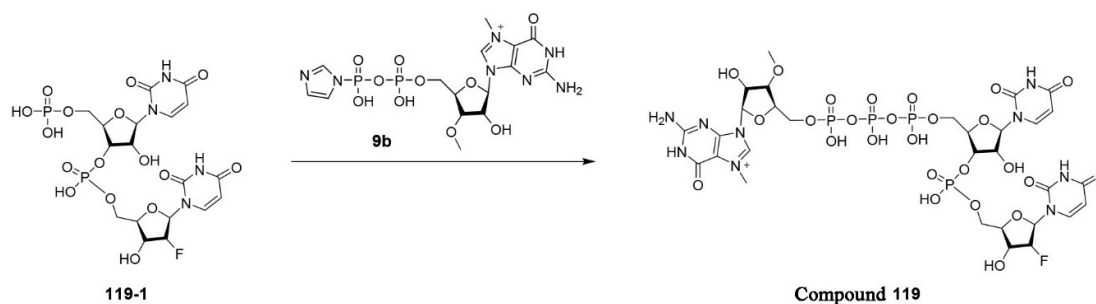
i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **103**, which was an ammonium salt in the form of white powder (60 mg).

^1H NMR (400 MHz, D_2O) δ 8.33 (d, J = 0.5 Hz, 1H), 8.29 (s, 1H), 8.02 (d, J = 0.7 Hz, 1H), 6.45 (ddq, J = 25.2, 1.4, 0.7 Hz, 1H), 6.17 (dq, J = 2.3, 0.8 Hz, 1H), 6.11 (dq, J = 3.1, 0.8 Hz, 1H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 4.88 - 4.62 (m, 3H), 4.45 (dddd, J = 25.2, 6.8, 5.0, 0.7 Hz, 1H), 4.33 - 4.09 (m, 9H), 4.05 (ttd, J = 2.9, 1.5, 0.7 Hz, 1H), 3.98 (d, J = 0.7 Hz, 3H), 3.44 (d, J = 1.4 Hz, 3H), 3.08 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -10.29, -21.23.

Example 7

Synthesis of Compound 119

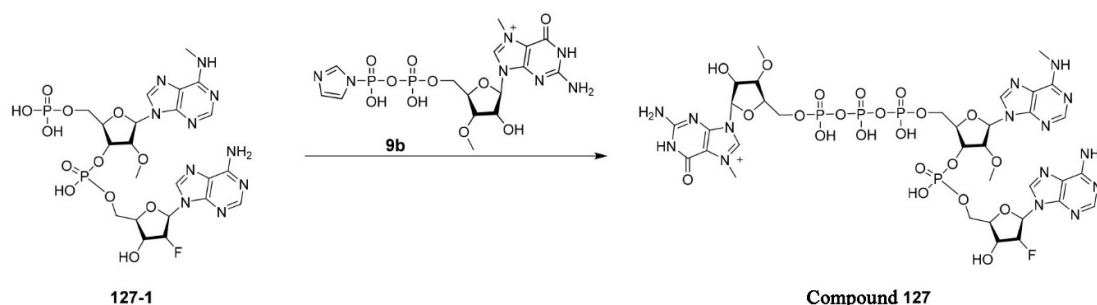


0.9 Hz, 1H), 4.89 - 4.60 (m, 3H), 4.46 - 4.02 (m, 12H), 3.98 (d, J = 0.7 Hz, 3H), 3.44 (d, J = 1.4 Hz, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.62, -10.29, -21.22.

Example 8

Synthesis of Compound 127



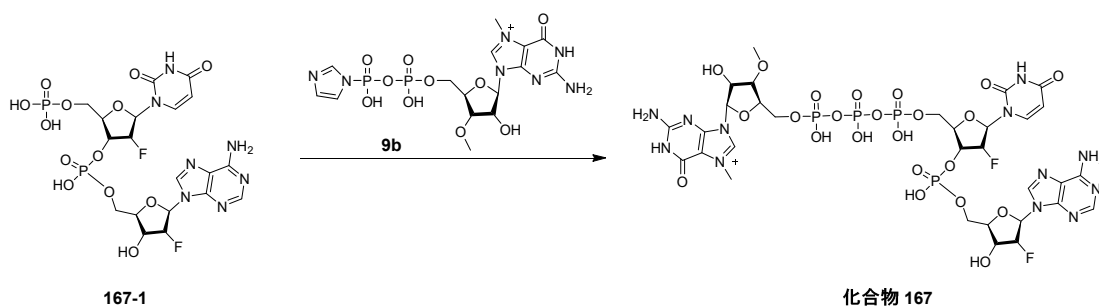
The compound **9b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **127-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **127**, which was an ammonium salt in the form of white powder (82 mg).

^1H NMR (400 MHz, D_2O) δ 8.29 (s, 1H), 8.24 (d, J = 0.7 Hz, 1H), 8.21 - 8.18 (m, 2H), 6.54 - 6.00 (m, 3H), 5.27 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 4.97 (dddd, J = 8.0, 4.4, 2.9, 0.7 Hz, 1H), 4.77 (tqd, J = 4.4, 1.5, 0.7 Hz, 1H), 4.71 (ddd, J = 3.9, 2.6, 0.7 Hz, 1H), 4.45 (dddd, J = 25.2, 6.8, 5.1, 0.7 Hz, 1H), 4.35 (qt, J = 3.0, 0.7 Hz, 1H), 4.29 - 4.08 (m, 8H), 4.05 (ttd, J = 2.9, 1.5, 0.7 Hz, 1H), 3.98 (d, J = 0.7 Hz, 3H), 3.42 (dd, J = 18.0, 1.5 Hz, 6H), 3.08 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -10.29, -21.22.

Example 9

Synthesis of Compound 167



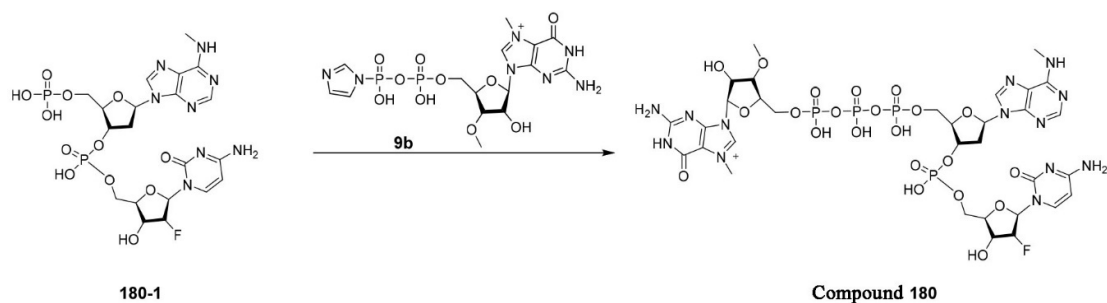
The compound **9b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **24-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **167**, which was an ammonium salt in the form of white powder (62 mg).

^1H NMR (400 MHz, D_2O) δ 8.24 (d, $J = 0.7$ Hz, 1H), 8.20 (s, 1H), 7.81 (dd, $J = 7.9, 1.8$ Hz, 1H), 6.39 (ddt, $J = 25.2, 4.0, 0.7$ Hz, 1H), 6.17 (dq, $J = 2.3, 0.7$ Hz, 1H), 5.90 (d, $J = 7.8$ Hz, 1H), 5.56 (dddt, $J = 25.3, 3.4, 1.8, 0.9$ Hz, 1H), 5.43 - 4.99 (m, 3H), 4.79 - 4.65 (m, 1H), 4.56 - 4.38 (m, 2H), 4.35 - 4.06 (m, 8H), 4.05 (ddq, $J = 4.6, 2.2, 1.1$ Hz, 1H), 3.98 (d, $J = 0.7$ Hz, 3H), 3.44 (d, $J = 1.4$ Hz, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -10.29, -21.22.

Example 10

Synthesis of Compound 180



The compound **9b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0,

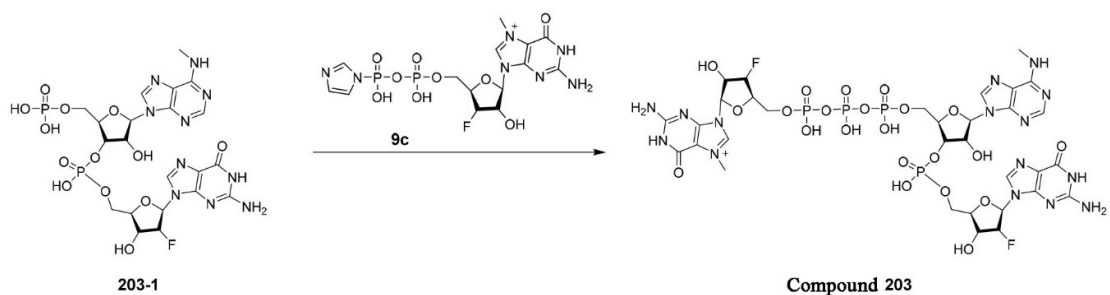
containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **180-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **180**, which was an ammonium salt in the form of white powder (95 mg).

¹H NMR (400 MHz, D₂O) δ 8.35 (d, J = 0.6 Hz, 1H), 8.29 (s, 1H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 6.47 - 6.32 (m, 1H), 6.17 (dq, J = 2.3, 0.8 Hz, 1H), 6.04 (d, J = 7.3 Hz, 1H), 5.54 - 5.33 (m, 1H), 5.10 - 4.94 (m, 1H), 4.91 - 4.64 (m, 2H), 4.48 - 4.03 (m, 11H), 3.98 (d, J = 0.7 Hz, 3H), 3.44 (d, J = 1.4 Hz, 3H), 3.08 (s, 3H), 2.83 - 2.35 (m, 2H).

³¹P NMR (162 MHz, D₂O) δ 0.60, -10.29, -21.22.

Example 11

Synthesis of Compound 203



A compound **9c** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **203-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction

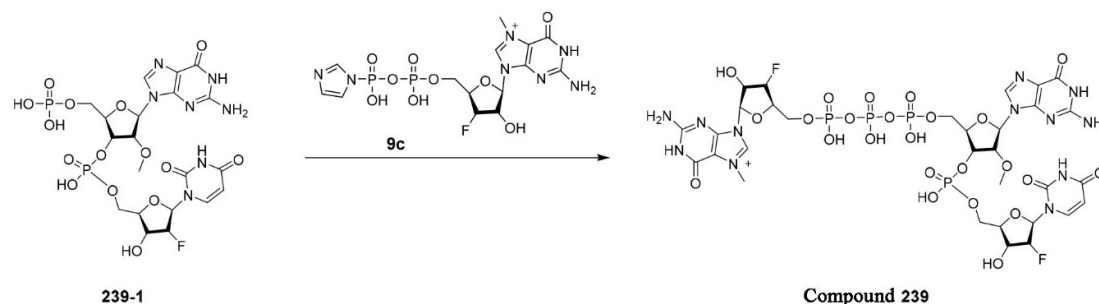
was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **203**, which was an ammonium salt in the form of white powder (95 mg).

^1H NMR (400 MHz, D_2O) δ 8.33 (d, J = 0.6 Hz, 1H), 8.29 (s, 1H), 8.02 (d, J = 0.7 Hz, 1H), 6.45 (ddq, J = 25.2, 1.4, 0.7 Hz, 1H), 6.23 (dt, J = 2.3, 0.8 Hz, 1H), 6.11 (dq, J = 3.1, 0.8 Hz, 1H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 5.00 - 4.68 (m, 4H), 4.65 - 4.39 (m, 2H), 4.38 - 4.05 (m, 8H), 3.98 (d, J = 0.7 Hz, 3H), 3.08 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -10.29, -21.22.

Example 12

Synthesis of Compound 239



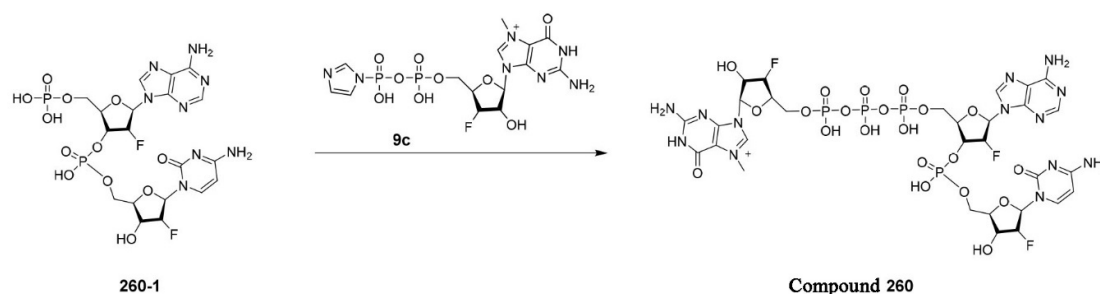
The compound **9c** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **239-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **239**, which was an ammonium salt in the form of white powder (95 mg).

^1H NMR (400 MHz, D_2O) δ 7.88 (d, J = 0.7 Hz, 1H), 7.81 (dd, J = 7.8, 1.8 Hz, 1H), 6.33 - 6.06 (m, 2H), 5.90 (d, J = 7.8 Hz, 1H), 5.53 (dddd, J = 25.2, 3.9, 1.7, 0.9 Hz, 1H), 5.03 - 4.50 (m, 6H), 4.43 - 4.07 (m, 9H), 3.98 (d, J = 0.7 Hz, 3H), 3.40 (d, J = 1.6 Hz, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -10.29, -21.22.

Example 13

Synthesis of Compound 260



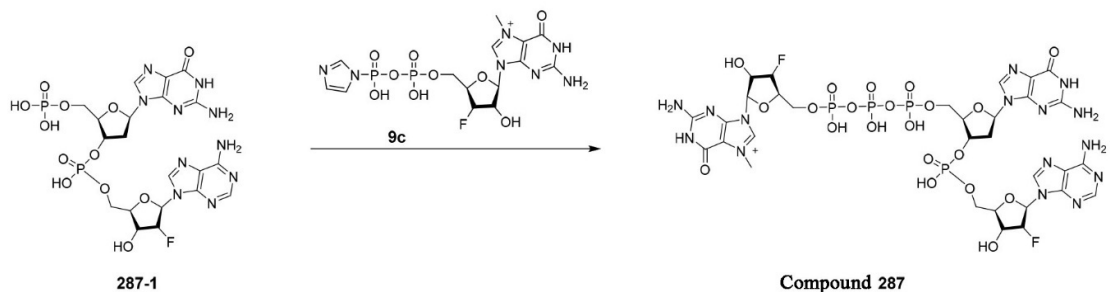
The compound **9c** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **260-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **260**, which was an ammonium salt in the form of white powder (75 mg).

^1H NMR (400 MHz, D_2O) δ 8.24 (d, $J = 0.7$ Hz, 1H), 8.20 (s, 1H), 7.70 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.43 (ddq, $J = 25.2, 1.6, 0.8$ Hz, 1H), 6.27 - 6.20 (m, 1H), 6.04 (d, $J = 7.3$ Hz, 1H), 5.51 - 5.12 (m, 3H), 5.05 - 4.70 (m, 3H), 4.66 - 4.10 (m, 10H), 3.98 (d, $J = 0.7$ Hz, 3H).

^{31}P NMR (162 MHz, D_2O) δ -0.90, -10.29, -21.22.

Example 14

Synthesis of Compound 287



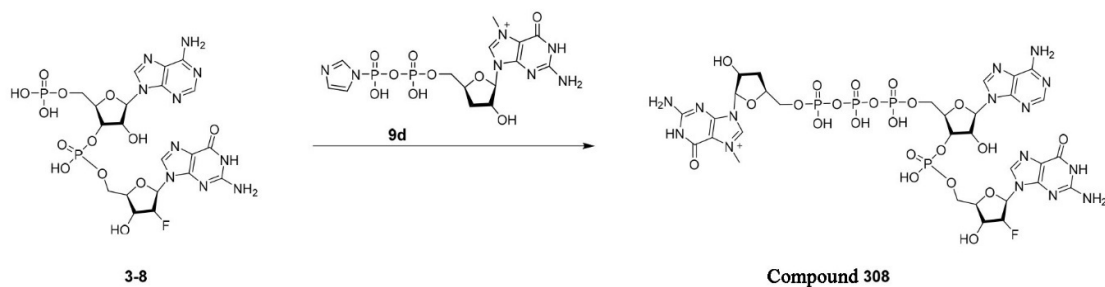
The compound **9c** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **287-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **287**, which was an ammonium salt in the form of white powder (75 mg).

^1H NMR (400 MHz, D_2O) δ 8.24 (d, $J = 0.7$ Hz, 1H), 8.20 (s, 1H), 7.83 (d, $J = 0.6$ Hz, 1H), 6.39 (ddt, $J = 25.2, 4.0, 0.7$ Hz, 1H), 6.28 (ddt, $J = 3.1, 1.5, 0.7$ Hz, 1H), 6.26 - 6.15 (m, 1H), 5.27 (dddd, $J = 46.5, 7.0, 4.0, 0.6$ Hz, 1H), 5.11 - 4.79 (m, 3H), 4.65 - 4.03 (m, 10H), 3.98 (d, $J = 0.7$ Hz, 3H), 2.88 - 2.51 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ -1.11, -10.31, -21.25.

Example 15

Synthesis of Compound 126



A compound **9d** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing

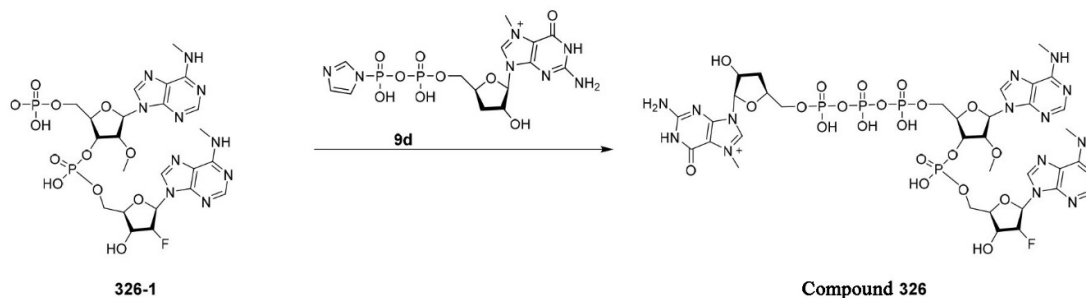
0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and the compound **3-8** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **308**, which was an ammonium salt in the form of white powder (60 mg).

¹H NMR (400 MHz, D₂O) δ 8.28 (d, J = 0.6 Hz, 1H), 8.20 (s, 1H), 8.02 (d, J = 0.7 Hz, 1H), 6.45 (ddq, J = 25.3, 1.6, 0.9 Hz, 1H), 6.21 - 6.07 (m, 2H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 4.98 - 4.68 (m, 2H), 4.57 - 4.03 (m, 11H), 3.98 (d, J = 0.7 Hz, 3H), 2.45 - 1.75 (m, 2H).

³¹P NMR (162 MHz, D₂O) δ -0.9, -10.29, -21.27.

Example 16

Synthesis of Compound 326



The compound **9d** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **326-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a

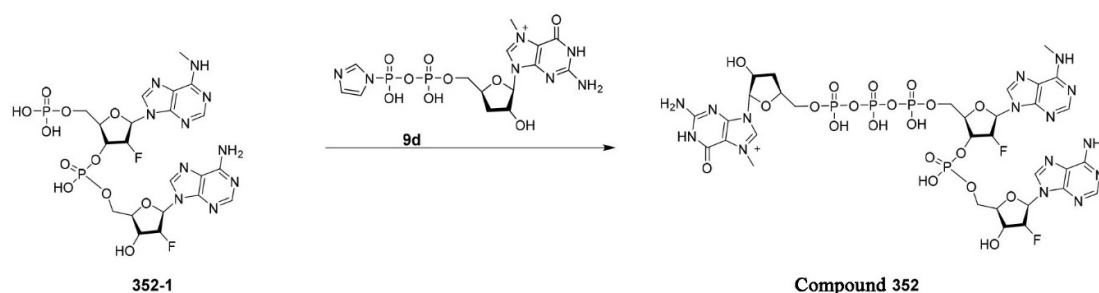
product, compound **326**, which was an ammonium salt in the form of white powder (60 mg).

^1H NMR (400 MHz, D_2O) δ 8.29 (d, J = 1.7 Hz, 3H), 8.20 (d, J = 0.7 Hz, 1H), 6.39 (ddt, J = 25.1, 3.9, 0.7 Hz, 1H), 6.29 - 6.04 (m, 2H), 5.27 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 4.97 (dddd, J = 8.0, 4.4, 2.9, 0.7 Hz, 1H), 4.77 (tqd, J = 4.4, 1.5, 0.7 Hz, 1H), 4.61 - 4.06 (m, 11H), 3.98 (d, J = 0.7 Hz, 3H), 3.40 (d, J = 1.6 Hz, 3H), 3.08 (s, 6H), 2.56 - 1.44 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ -0.78, -10.29, -21.22.

Example 17

Synthesis of Compound 352



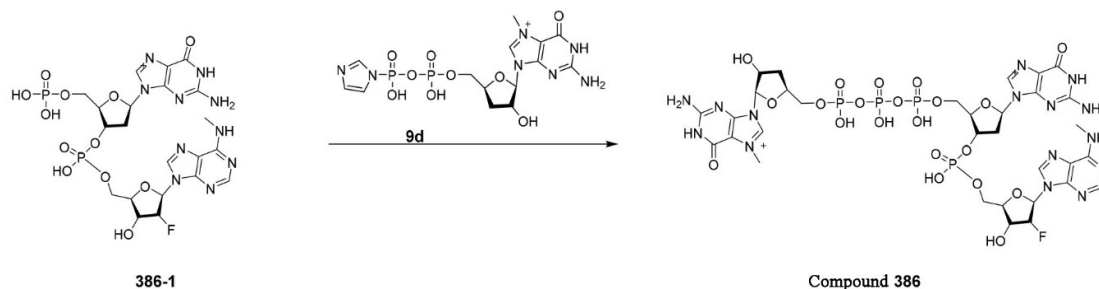
The compound **9d** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **352-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **352**, which was an ammonium salt in the form of white powder (74 mg).

^1H NMR (400 MHz, D_2O) δ 8.33 - 8.27 (m, 2H), 8.24 (d, J = 0.6 Hz, 1H), 8.20 (s, 1H), 6.63 - 6.28 (m, 2H), 6.17 (dt, J = 1.3, 0.7 Hz, 1H), 5.57 - 5.04 (m, 3H), 4.63 - 4.03 (m, 11H), 3.98 (d, J = 0.7 Hz, 3H), 3.08 (s, 3H), 2.63 - 1.60 (m, 2H).

^{31}P NMR (162 MHz, D_2O) -0.55, -10.32, -21.28.

Example 18

Synthesis of Compound 386



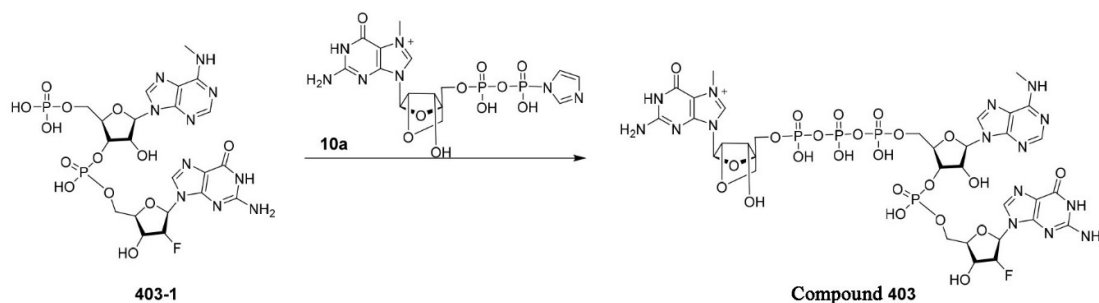
The compound **9d** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **386-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **386**, which was an ammonium salt in the form of white powder (60 mg).

^1H NMR (400 MHz, D_2O) δ 8.38 - 8.22 (m, 2H), 8.18 (d, J = 0.6 Hz, 1H), 6.58 - 6.30 (m, 2H), 6.17 (t, J = 1.0 Hz, 1H), 5.27 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 5.10 - 4.83 (m, 1H), 4.60 - 4.07 (m, 11H), 3.98 (d, J = 0.7 Hz, 3H), 3.08 (s, 3H), 2.69 - 2.46 (m, 2H), 2.34 - 1.69 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ -0.85, -10.09, -21.23.

Example 19

Synthesis of Compound 403



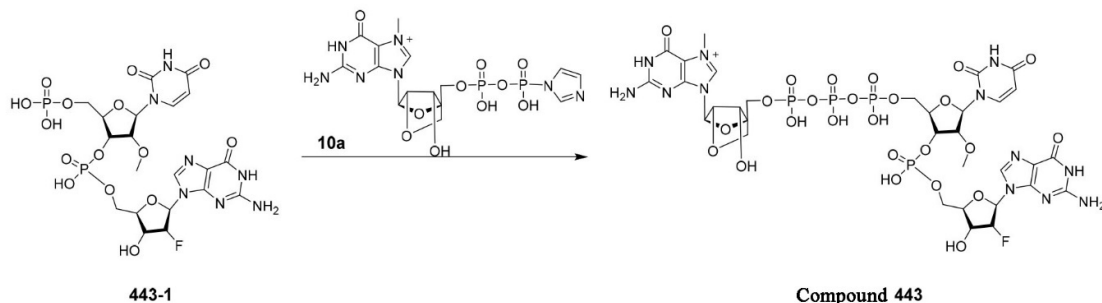
A compound **10a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **403-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **403**, which was an ammonium salt in the form of white powder (55 mg).

¹H NMR (400 MHz, D₂O) δ 8.40 - 8.19 (m, 2H), 8.02 (d, J = 0.7 Hz, 1H), 6.45 (ddq, J = 25.2, 1.4, 0.7 Hz, 1H), 6.33 (dd, J = 2.7, 0.6 Hz, 1H), 6.11 (dq, J = 3.0, 0.7 Hz, 1H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 4.80 (ddd, J = 3.9, 3.1, 0.7 Hz, 1H), 4.74 (dddd, J = 7.9, 3.9, 2.9, 0.7 Hz, 1H), 4.64 (t, J = 2.8 Hz, 1H), 4.51 - 4.08 (m, 10H), 4.02 (d, J = 0.7 Hz, 2H), 3.98 (s, 3H), 3.08 (s, 3H).

³¹P NMR (162 MHz, D₂O) δ -0.90, -11.41, -22.93.

Example 20

Synthesis of Compound 443



The compound **10a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **443-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the

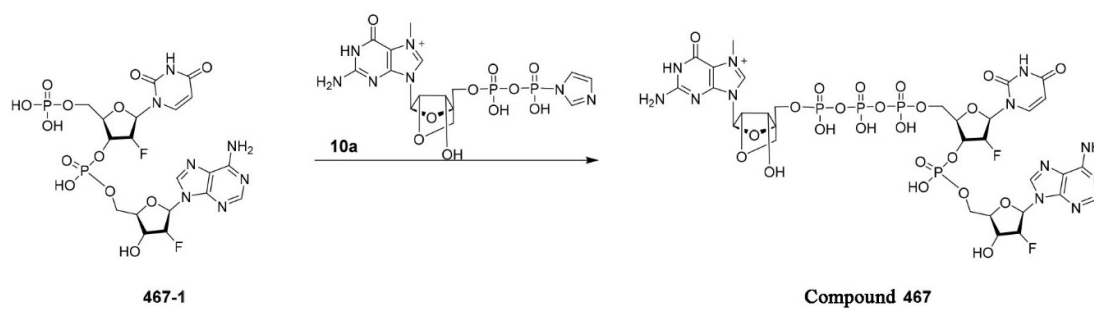
obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **443**, which was an ammonium salt in the form of white powder (70 mg).

^1H NMR (400 MHz, D_2O) δ 8.02 (d, J = 0.7 Hz, 1H), 7.75 (dd, J = 7.8, 1.8 Hz, 1H), 6.45 (ddq, J = 25.2, 1.6, 0.9 Hz, 1H), 6.33 (dd, J = 2.7, 0.6 Hz, 1H), 5.93 - 5.65 (m, 2H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 4.89 (dddd, J = 8.0, 5.4, 4.6, 0.6 Hz, 1H), 4.64 (t, J = 2.8 Hz, 1H), 4.51 - 4.07 (m, 11H), 4.02 (d, J = 0.7 Hz, 2H), 3.98 (s, 3H), 3.47 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.50, -9.18, -10.26, -21.22.

Example 21

Synthesis of Compound 467



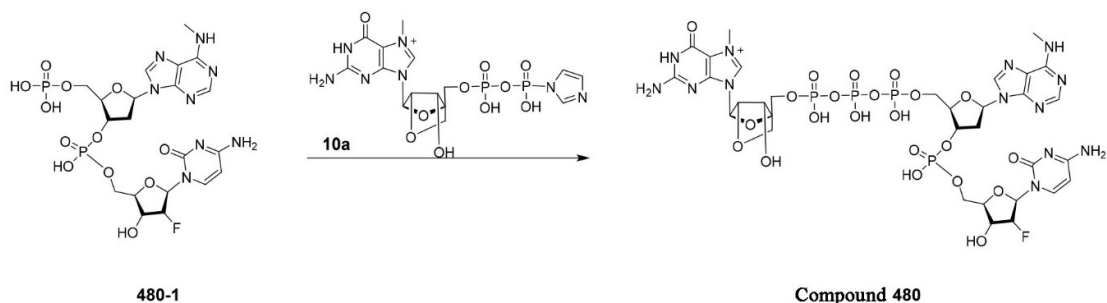
The compound **10a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **467-7** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **467**, which was an ammonium salt in the form of white powder (75 mg).

^1H NMR (400 MHz, D_2O) δ 8.32 - 8.10 (m, 2H), 7.81 (dd, J = 7.9, 1.8 Hz, 1H), 6.54 - 6.21 (m, 2H), 5.90 (d, J = 7.8 Hz, 1H), 5.71 - 4.98 (m, 4H), 4.73 - 4.09 (m, 11H), 4.02 (d, J = 0.7 Hz, 2H), 3.98 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ -0.99, -11.40, -23.06.

Example 22

Synthesis of Compound 480



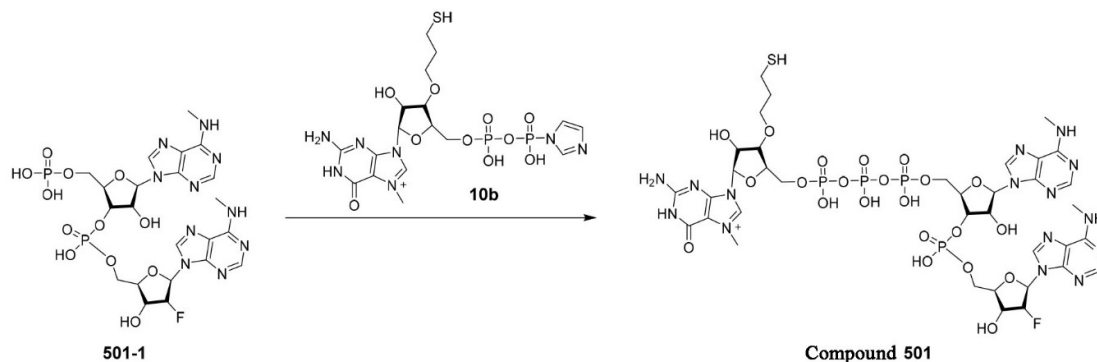
The compound **10a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **480-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **480**, which was an ammonium salt in the form of white powder (85 mg).

¹H NMR (400 MHz, D₂O) δ 8.41 - 8.23 (m, 2H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 6.43 - 6.28 (m, 2H), 6.04 (d, J = 7.3 Hz, 1H), 5.56 - 5.21 (m, 1H), 5.09 - 4.93 (m, 1H), 4.81 (dddd, J = 46.5, 7.1, 3.7, 0.7 Hz, 1H), 4.64 (t, J = 2.8 Hz, 1H), 4.48 - 4.03 (m, 10H), 4.02 (d, J = 0.7 Hz, 2H), 3.98 (d, J = 0.7 Hz, 3H), 3.08 (s, 3H), 2.79 - 2.46 (m, 2H).

³¹P NMR (162 MHz, D₂O) δ 0.60, -9.01, -10.23, -21.17.

Example 23

Synthesis of Compound 501



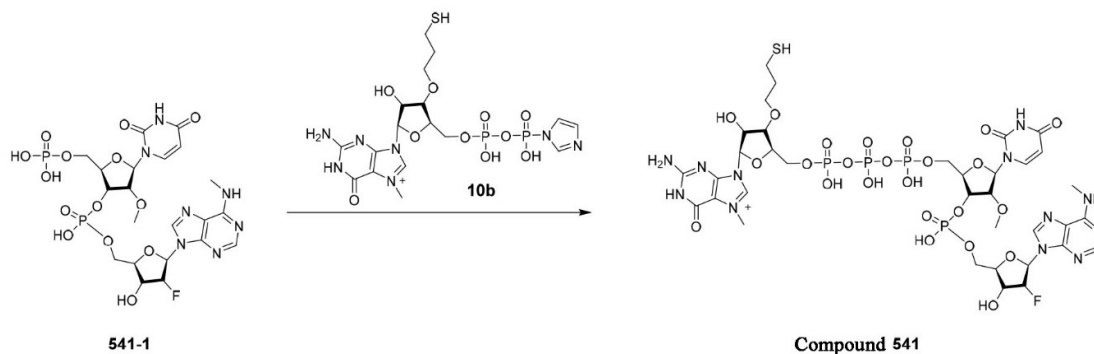
A compound **10b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **501-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **501**, which was an ammonium salt in the form of white powder (92 mg).

^1H NMR (400 MHz, D_2O) δ 8.41 – 8.14 (m, 4H), 6.39 (ddt, $J = 25.3, 4.1, 0.8$ Hz, 1H), 6.25 – 5.98 (m, 2H), 5.27 (dddd, $J = 46.5, 7.0, 4.0, 0.6$ Hz, 1H), 4.83 – 4.61 (m, 3H), 4.45 (dddd, $J = 25.2, 6.8, 5.0, 0.7$ Hz, 1H), 4.36 – 4.07 (m, 10H), 3.98 (d, $J = 0.7$ Hz, 3H), 3.69 – 3.48 (m, 2H), 3.08 (s, 6H), 2.90 – 2.61 (m, 2H), 1.84 (p, $J = 6.5$ Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -9.10, -10.31, -21.17.

Example 24

Synthesis of Compound 541



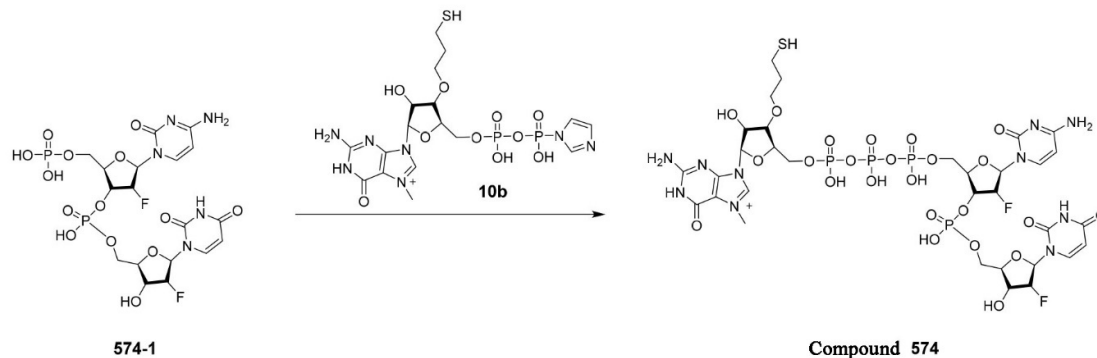
The compound **10b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **541-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **541**, which was an ammonium salt in the form of white powder (85 mg).

^1H NMR (400 MHz, D_2O) δ 8.38 - 8.21 (m, 2H), 7.75 (dd, J = 7.8, 1.8 Hz, 1H), 6.50 - 6.30 (m, 1H), 6.27 - 6.10 (m, 1H), 5.95 - 5.71 (m, 2H), 5.27 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 4.89 (dddd, J = 8.0, 5.4, 4.7, 0.6 Hz, 1H), 4.71 (ddd, J = 3.3, 2.5, 0.7 Hz, 1H), 4.52 - 4.04 (m, 12H), 3.98 (d, J = 0.7 Hz, 3H), 3.75 - 3.54 (m, 2H), 3.47 (d, J = 1.6 Hz, 3H), 3.08 (s, 3H), 2.90 - 2.51 (m, 2H), 1.84 (p, J = 6.5 Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -9.10, -10.22, -21.17.

Example 25

Synthesis of Compound 574



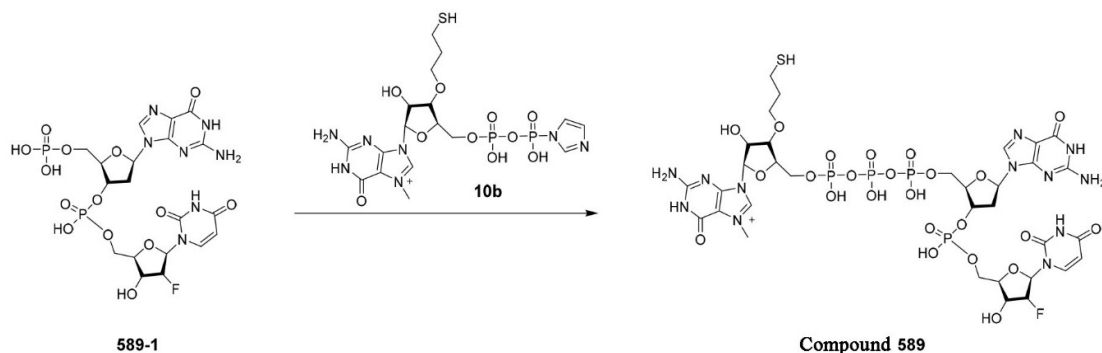
The compound **10b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **574-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **574**, which was an ammonium salt in the form of white powder (80 mg).

^1H NMR (400 MHz, D_2O) δ 7.81 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.70 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.29 - 6.11 (m, 1H), 6.04 (d, $J = 7.3$ Hz, 1H), 5.90 (d, $J = 7.8$ Hz, 1H), 5.63 - 5.42 (m, 2H), 5.33 - 5.00 (m, 2H), 4.89 - 4.64 (m, 2H), 4.55 - 4.05 (m, 11H), 3.98 (d, $J = 0.7$ Hz, 3H), 3.75 - 3.50 (m, 2H), 2.89 - 2.50 (m, 2H), 1.84 (p, $J = 6.5$ Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ -0.22, -9.07, -10.25, -21.27.

Example 26

Synthesis of Compound 589



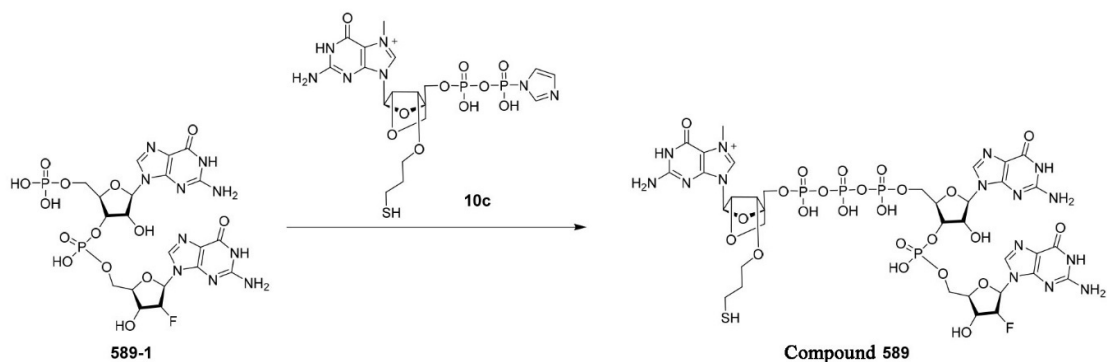
The compound **10b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **589-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **589**, which was an ammonium salt in the form of white powder (58 mg).

^1H NMR (400 MHz, D_2O) δ 7.93 - 7.46 (m, 2H), 6.31 - 6.11 (m, 2H), 5.90 (d, J = 7.8 Hz, 1H), 5.53 (dddd, J = 25.2, 3.9, 1.7, 0.9 Hz, 1H), 5.13 - 4.93 (m, 1H), 4.88 - 4.61 (m, 2H), 4.43 - 4.04 (m, 11H), 3.98 (d, J = 0.7 Hz, 3H), 3.70 - 3.28 (m, 2H), 2.79 - 2.71 (m, 2H), 2.70 - 2.46 (m, 2H), 1.84 (p, J = 6.5 Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.66, -9.13, -10.26, -21.25.

Example 27

Synthesis of Compound 589



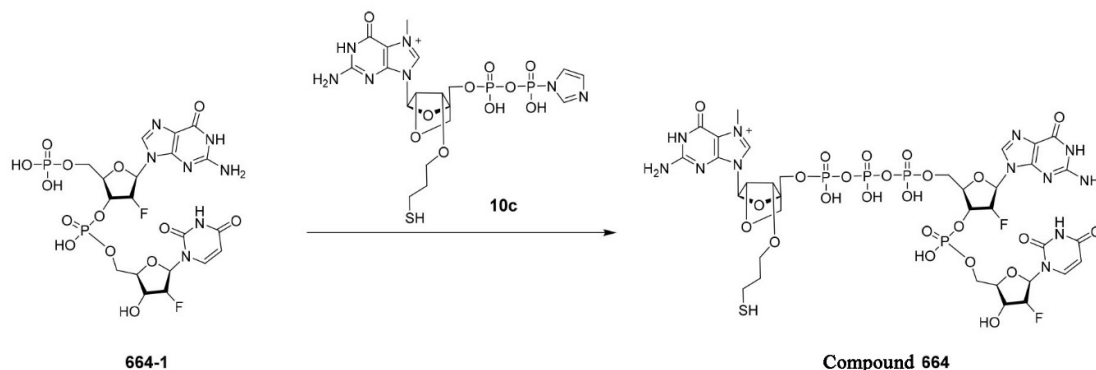
A compound **10c** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and the compound **589-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **589**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.97 (dd, $J = 37.6, 0.6$ Hz, 2H), 6.71 - 6.22 (m, 2H), 6.10 (dq, $J = 1.7, 0.7$ Hz, 1H), 5.22 (dddd, $J = 46.4, 7.0, 1.7, 0.7$ Hz, 1H), 4.87 (t, $J = 3.1$ Hz, 1H), 4.74 (qt, $J = 4.1, 2.2$ Hz, 2H), 4.55 - 4.10 (m, 10H), 4.02 (s, 2H), 3.98 (s, 3H), 3.66 (td, $J = 5.3, 2.9$ Hz, 2H), 3.00 - 2.60 (m, 2H), 1.85 (tt, $J = 6.4, 5.3$ Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 28

Synthesis of Compound 664



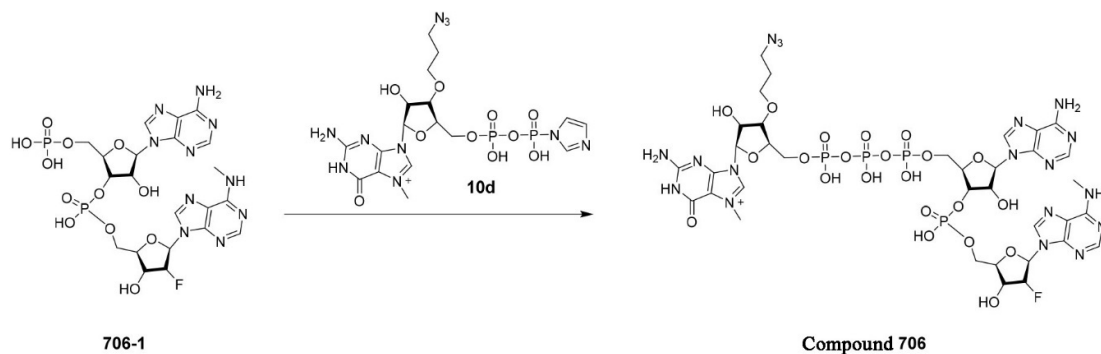
The compound **10c** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **664-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **664**, which was an ammonium salt in the form of white powder (60 mg).

¹H NMR (400 MHz, D₂O) δ 8.02 (d, J = 0.7 Hz, 1H), 7.81 (dd, J = 7.8, 1.8 Hz, 1H), 6.57 - 6.23 (m, 2H), 5.90 (d, J = 7.8 Hz, 1H), 5.71 - 5.42 (m, 1H), 5.39 - 5.16 (m, 2H), 4.94 - 4.67 (m, 2H), 4.56 - 4.08 (m, 10H), 4.02 (s, 2H), 3.98 (s, 3H), 3.66 (td, J = 5.3, 2.9 Hz, 2H), 2.98 - 2.65 (m, 2H), 1.85 (tt, J = 6.4, 5.3 Hz, 2H).

³¹P NMR (162 MHz, D₂O) δ -0.85, -10.09, -21.23.

Example 29

Synthesis of Compound 706



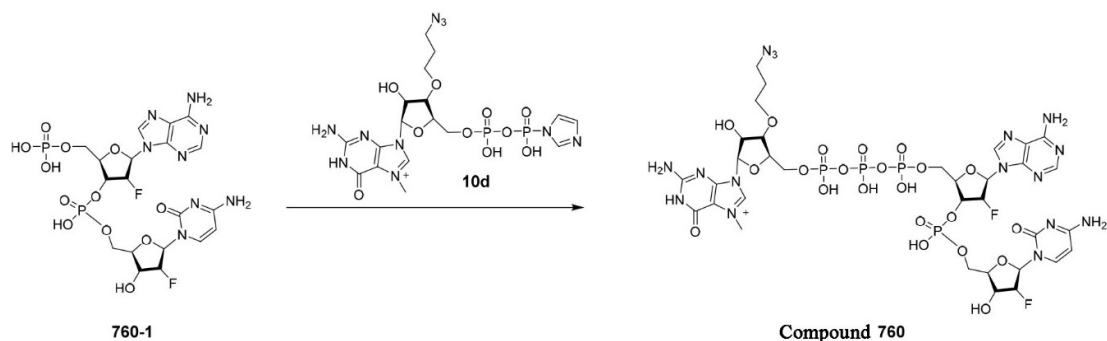
A compound **10d** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **706-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **706**, which was an ammonium salt in the form of white powder (55 mg).

^1H NMR (400 MHz, D_2O) δ 8.40 - 7.81 (m, 4H), 6.84 - 5.90 (m, 3H), 5.31 (dddd, $J = 46.5, 7.0, 4.0, 0.6$ Hz, 1H), 4.76 (dddd, $J = 46.0, 3.3, 2.8, 0.7$ Hz, 2H), 4.54 - 4.18 (m, 9H), 4.09 - 3.95 (m, 3H), 3.92 (d, $J = 0.6$ Hz, 3H), 3.56 (td, $J = 6.4, 1.5$ Hz, 2H), 3.23 (td, $J = 6.3, 0.8$ Hz, 2H), 3.10 (s, 3H), 1.94 (pd, $J = 6.3, 1.0$ Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ -0.90, -11.41, -22.93.

Example 30

Synthesis of Compound 760



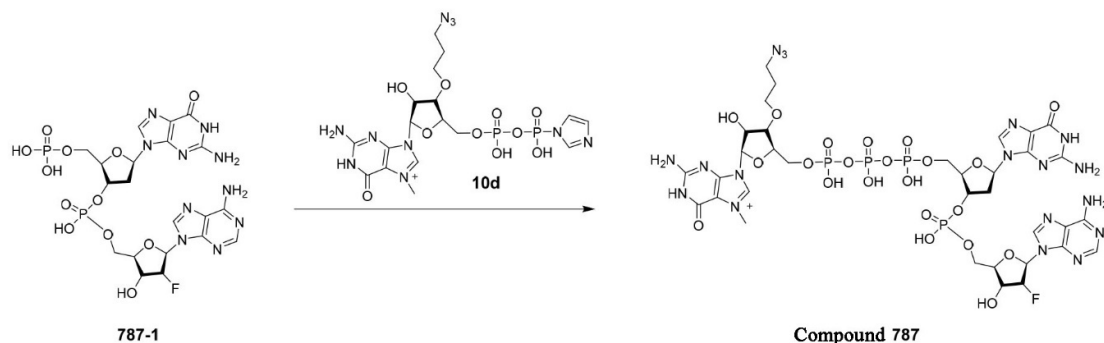
The compound **10d** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **760-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **760**, which was an ammonium salt in the form of white powder (70 mg).

¹H NMR (400 MHz, D₂O) δ 8.28 - 8.06 (m, 2H), 7.69 (dd, J = 7.4, 1.8 Hz, 1H), 6.47 (ddt, J = 25.2, 1.5, 0.8 Hz, 1H), 6.28 (dq, J = 2.3, 0.8 Hz, 1H), 6.15 (d, J = 7.3 Hz, 1H), 5.60 (dddt, J = 25.3, 3.6, 1.8, 0.8 Hz, 1H), 5.42 (dddd, J = 46.5, 2.8, 1.9, 0.7 Hz, 1H), 4.70 (ddd, J = 3.3, 2.5, 0.7 Hz, 1H), 4.50 - 3.96 (m, 13H), 3.92 (d, J = 0.6 Hz, 3H), 3.56 (td, J = 6.5, 1.5 Hz, 2H), 3.36 (t, J = 6.2 Hz, 2H), 1.94 (pd, J = 6.3, 1.0 Hz, 2H).

³¹P NMR (162 MHz, D₂O) δ 0.50, -9.18, -10.26, -21.22.

Example 31

Synthesis of Compound 787



The compound **10d** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **787-7** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture

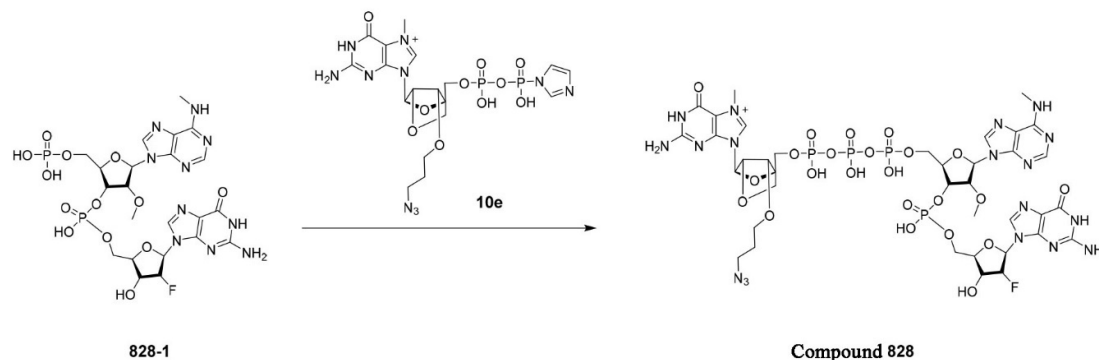
was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **787**, which was an ammonium salt in the form of white powder (75 mg).

^1H NMR (400 MHz, D_2O) δ 8.49 - 7.98 (m, 2H), 7.75 (d, J = 0.5 Hz, 1H), 6.50 - 6.32 (m, 1H), 6.28 (dtd, J = 3.2, 1.6, 0.8 Hz, 2H), 5.31 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 4.70 (ddd, J = 3.3, 2.5, 0.7 Hz, 1H), 4.52 - 4.19 (m, 9H), 4.14 - 3.95 (m, 2H), 3.94 - 3.84 (m, 4H), 3.56 (td, J = 6.4, 1.5 Hz, 2H), 3.23 (td, J = 6.3, 0.8 Hz, 2H), 2.83 - 2.48 (m, 2H), 1.94 (pd, J = 6.3, 1.0 Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ -0.99, -11.40, -23.06.

Example 32

Synthesis of Compound 828



A compound **10e** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **828-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **828**, which was an ammonium salt in the form of white powder (85 mg).

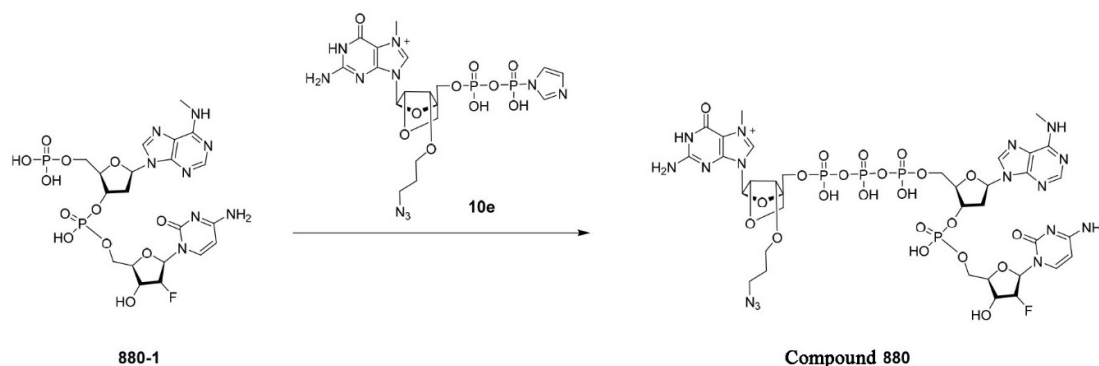
^1H NMR (400 MHz, D_2O) δ 8.27 (s, 1H), 8.19 (d, J = 0.6 Hz, 1H), 7.95 (d, J = 0.7 Hz, 1H), 6.63

- 6.29 (m, 3H), 5.28 (dddd, J = 46.4, 6.9, 1.6, 0.7 Hz, 1H), 4.62 (ddqd, J = 4.5, 3.7, 1.5, 0.6 Hz, 1H), 4.57 - 4.40 (m, 2H), 4.36 - 4.20 (m, 5H), 4.16 - 3.95 (m, 5H), 3.93 - 3.81 (m, 4H), 3.73 - 3.51 (m, 3H), 3.37 (d, J = 1.6 Hz, 3H), 3.23 (td, J = 6.3, 0.8 Hz, 2H), 3.10 (s, 3H), 1.95 (tt, J = 6.3, 5.3 Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -9.01, -10.23, -21.17.

Example 33

Synthesis of Compound 880



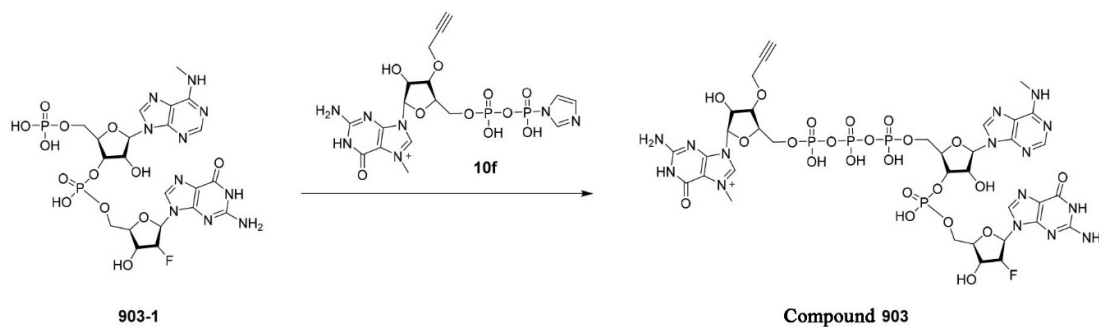
The compound **10e** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **880-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **880**, which was an ammonium salt in the form of white powder (92 mg).

^1H NMR (400 MHz, D_2O) δ 8.35 (d, J = 0.6 Hz, 1H), 8.27 (s, 1H), 7.69 (dd, J = 7.4, 1.8 Hz, 1H), 6.60 - 6.29 (m, 2H), 6.15 (d, J = 7.3 Hz, 1H), 5.89 - 5.26 (m, 1H), 4.52 (dd, J = 11.6, 8.5 Hz, 1H), 4.44 - 3.84 (m, 16H), 3.75 - 3.48 (m, 3H), 3.23 (td, J = 6.3, 0.8 Hz, 2H), 3.10 (s, 3H), 2.87 - 2.56 (m, 2H), 1.95 (tt, J = 6.3, 5.3 Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -9.10, -10.31, -21.17.

Example 34

Synthesis of Compound 903



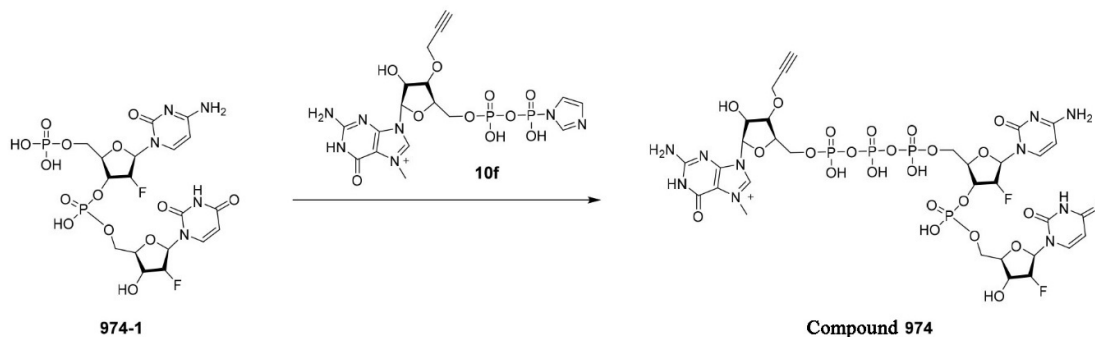
A compound **10f** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **903-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **903**, which was an ammonium salt in the form of white powder (85 mg).

^1H NMR (400 MHz, D_2O) δ 8.48 - 8.18 (m, 2H), 8.02 (d, $J = 0.7$ Hz, 1H), 6.45 (ddq, $J = 25.2, 1.6, 0.8$ Hz, 1H), 6.25 - 6.00 (m, 2H), 5.22 (dddd, $J = 46.4, 7.0, 1.7, 0.7$ Hz, 1H), 4.89 - 4.62 (m, 3H), 4.59 - 4.09 (m, 13H), 3.98 (d, $J = 0.7$ Hz, 3H), 3.08 (s, 3H), 2.42 (t, $J = 3.0$ Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ 0.60, -9.10, -10.22, -21.17.

Example 35

Synthesis of Compound 974



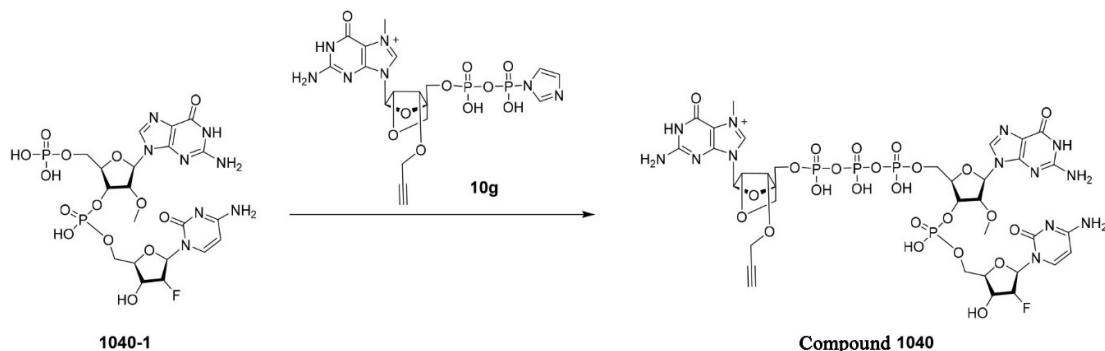
The compound **10f** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **974-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **974**, which was an ammonium salt in the form of white powder (80 mg).

^1H NMR (400 MHz, D_2O) δ 7.76 (ddd, $J = 44.0, 7.5, 1.8$ Hz, 2H), 6.20 (dq, $J = 2.3, 0.8$ Hz, 1H), 5.97 (dd, $J = 56.9, 7.5$ Hz, 2H), 5.64 - 5.41 (m, 2H), 5.34 - 4.98 (m, 2H), 4.89 - 4.63 (m, 2H), 4.55 - 4.08 (m, 13H), 3.98 (d, $J = 0.7$ Hz, 3H), 2.42 (t, $J = 3.0$ Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ -0.22, -9.07, -10.25, -21.27.

Example 36

Synthesis of Compound 1040



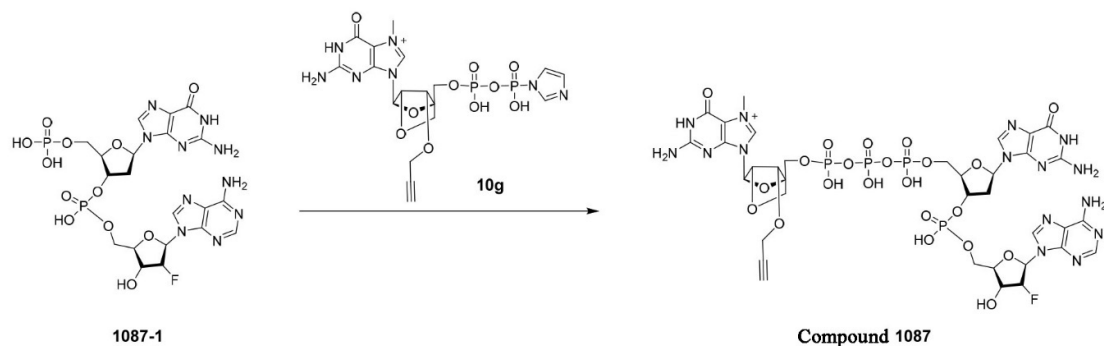
A compound **10g** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1040-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1040**, which was an ammonium salt in the form of white powder (58 mg).

^1H NMR (400 MHz, D_2O) δ 7.88 (d, J = 0.7 Hz, 1H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 6.47 - 6.14 (m, 2H), 6.04 (d, J = 7.3 Hz, 1H), 5.40 (dddd, J = 25.2, 3.5, 1.8, 0.9 Hz, 1H), 5.10 - 4.64 (m, 4H), 4.43 - 4.08 (m, 12H), 4.02 (s, 2H), 3.98 (s, 3H), 3.40 (s, 3H), 2.42 (t, J = 3.0 Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ 0.66, -9.13, -10.26, -21.25.

Example 37

Synthesis of Compound 1087



The compound **10g** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1087-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the

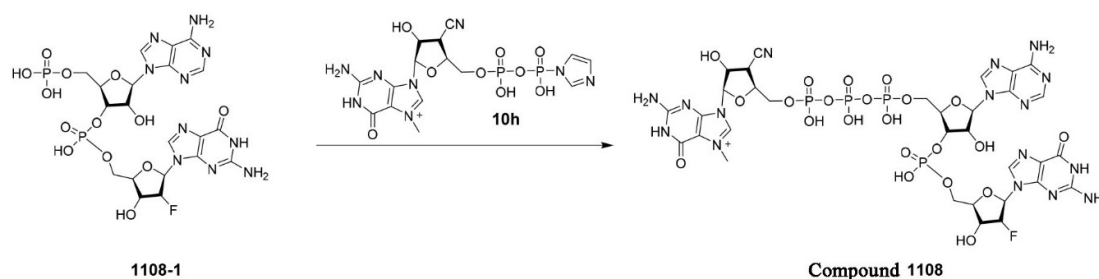
obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1087**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.31 - 8.11 (m, 2H), 7.83 (d, J = 0.6 Hz, 1H), 6.88 - 6.07 (m, 3H), 5.27 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 5.05 - 4.88 (m, 2H), 4.54 - 4.04 (m, 12H), 4.02 (s, 2H), 3.98 (s, 3H), 2.77 - 2.52 (m, 2H), 2.42 (t, J = 3.0 Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 38

Synthesis of Compound 1108



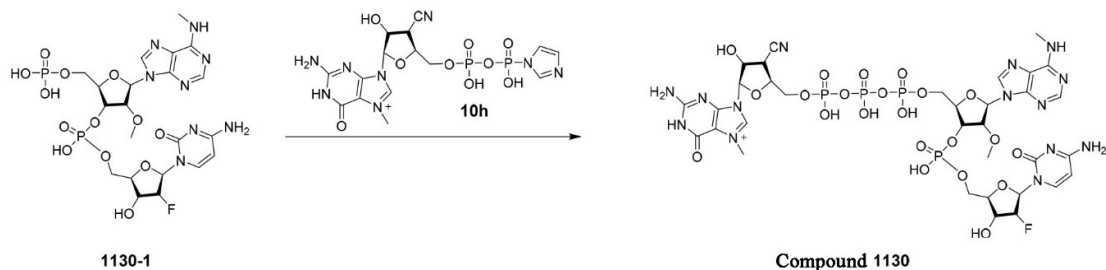
A compound **10h** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1108-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1108**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.33 - 8.15 (m, 2H), 8.02 (d, J = 0.7 Hz, 1H), 6.45 (ddq, J = 25.2, 1.5, 0.8 Hz, 1H), 6.32 - 5.94 (m, 2H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 4.83 - 4.69 (m, 2H), 4.56 (dt, J = 3.8, 0.9 Hz, 1H), 4.51 - 4.06 (m, 10H), 3.98 (d, J = 0.7 Hz, 3H), 3.65 (ddd, J = 3.6, 2.6, 0.6 Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 39

Synthesis of Compound 1130



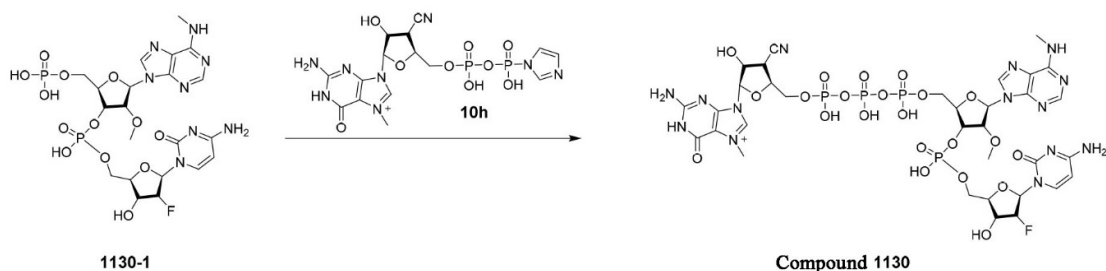
The compound **10h** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1130-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1130**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.51 - 8.01 (m, 2H), 7.70 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.31 - 6.15 (m, 2H), 6.04 (d, $J = 7.3$ Hz, 1H), 5.56 - 5.22 (m, 1H), 4.97 (dddd, $J = 8.0, 4.4, 2.9, 0.7$ Hz, 1H), 4.90 - 4.69 (m, 2H), 4.56 (dt, $J = 3.8, 0.9$ Hz, 1H), 4.48 - 4.10 (m, 10H), 3.98 (s, 3H), 3.65 (ddd, $J = 3.6, 2.6, 0.6$ Hz, 1H), 3.40 (s, 3H), 3.08 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 40

Synthesis of Compound 1130



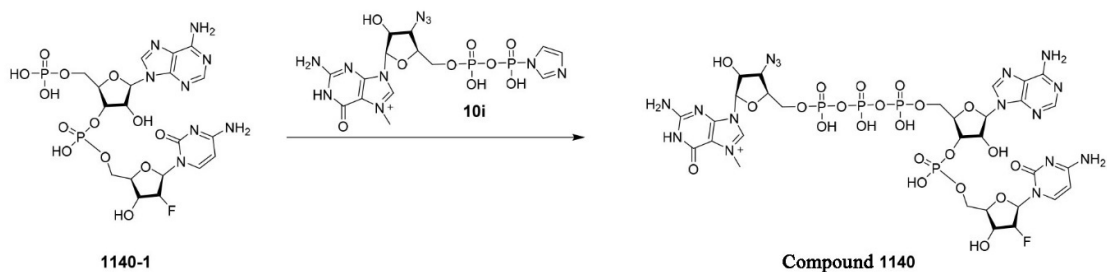
The compound **10h** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1130-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1130**, which was an ammonium salt in the form of white powder (88 mg).

¹H NMR (400 MHz, D₂O) δ 8.51 - 8.01 (m, 2H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 6.31 - 6.15 (m, 2H), 6.04 (d, J = 7.3 Hz, 1H), 5.56 - 5.22 (m, 1H), 4.97 (dddd, J = 8.0, 4.4, 2.9, 0.7 Hz, 1H), 4.90 - 4.69 (m, 2H), 4.56 (dt, J = 3.8, 0.9 Hz, 1H), 4.48 - 4.10 (m, 10H), 3.98 (s, 3H), 3.65 (ddd, J = 3.6, 2.6, 0.6 Hz, 1H), 3.40 (s, 3H), 3.08 (s, 3H).

³¹P NMR (162 MHz, D₂O) δ 0.85, -9.12, -10.24, -21.26.

Example 41

Synthesis of Compound 1140



A compound **10i** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1140-I** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the

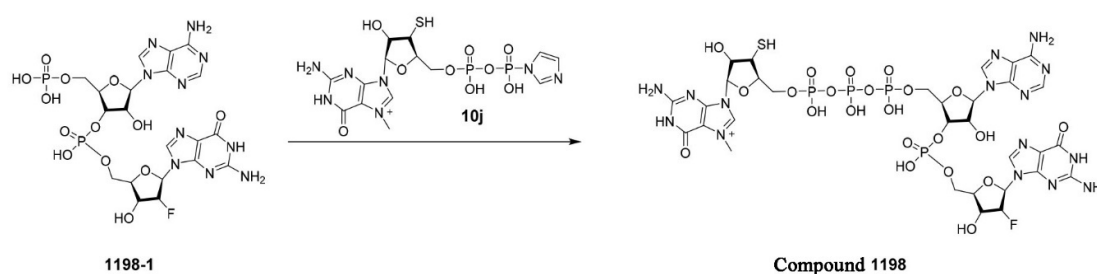
obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1140**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.18 (d, J = 1.3 Hz, 2H), 7.69 (dd, J = 7.4, 1.8 Hz, 1H), 6.36 - 6.26 (m, 1H), 6.20 - 6.09 (m, 2H), 5.80 - 5.38 (m, 1H), 4.82 (ddd, J = 3.9, 3.1, 0.7 Hz, 1H), 4.62 (ddd, J = 5.5, 2.8, 0.7 Hz, 1H), 4.42 - 3.95 (m, 13H), 3.92 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 42

Synthesis of Compound 1198



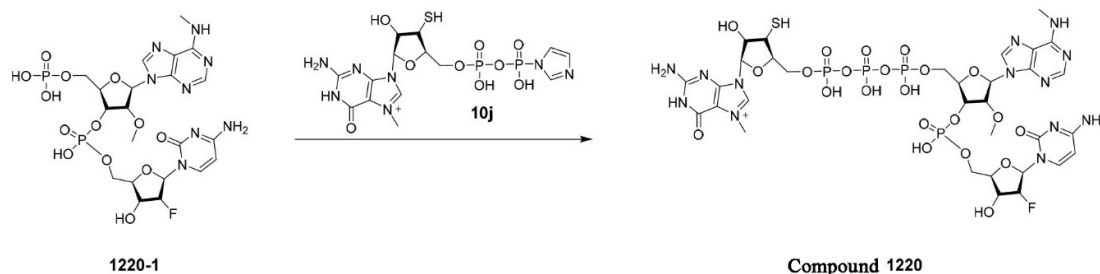
A compound **10j** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1198-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1198**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.28 (d, J = 0.5 Hz, 1H), 8.20 (s, 1H), 8.02 (d, J = 0.7 Hz, 1H), 6.45 (ddq, J = 25.2, 1.5, 0.8 Hz, 1H), 6.22 (dd, J = 3.1, 0.7 Hz, 1H), 6.11 (dd, J = 3.1, 0.7 Hz, 1H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 4.86 - 4.66 (m, 2H), 4.59 - 4.39 (m, 2H), 4.36 - 4.06 (m, 9H), 3.98 (s, 3H), 2.80 (ddd, J = 5.1, 4.0, 0.7 Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 43

Synthesis of Compound 1220



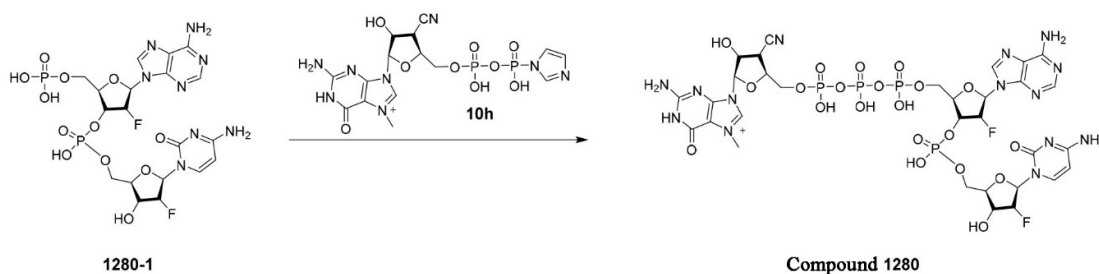
The compound **10j** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1220-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1220**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.29 (s, 1H), 8.20 (d, $J = 0.7$ Hz, 1H), 7.70 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.32 - 6.16 (m, 2H), 6.04 (d, $J = 7.3$ Hz, 1H), 5.61 - 5.20 (m, 1H), 5.07 - 4.65 (m, 3H), 4.50 - 4.06 (m, 11H), 3.98 (s, 3H), 3.40 (s, 3H), 3.08 (s, 3H), 2.86 (ddd, $J = 3.9, 3.3, 0.7$ Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 44

Synthesis of Compound 1280



A compound **10h** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0,

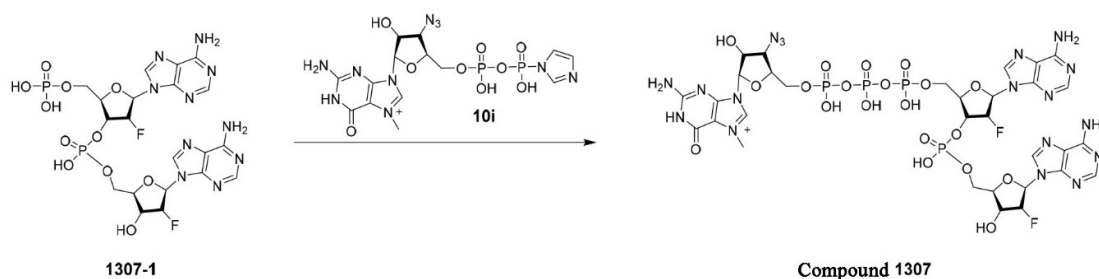
containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1280-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1280**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.24 (d, J = 0.7 Hz, 1H), 8.20 (s, 1H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 6.43 (ddq, J = 25.2, 1.5, 0.8 Hz, 1H), 6.24 (p, J = 0.8 Hz, 1H), 6.04 (d, J = 7.3 Hz, 1H), 5.50 - 5.10 (m, 3H), 4.81 (dddd, J = 46.5, 7.1, 3.7, 0.7 Hz, 1H), 4.56 (dt, J = 3.8, 0.9 Hz, 1H), 4.48 (tdd, J = 3.5, 2.4, 0.8 Hz, 1H), 4.44 - 4.09 (m, 9H), 3.98 (s, 3H), 3.65 (ddd, J = 3.6, 2.6, 0.6 Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 45

Synthesis of Compound 1307



A compound **10i** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1307-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a

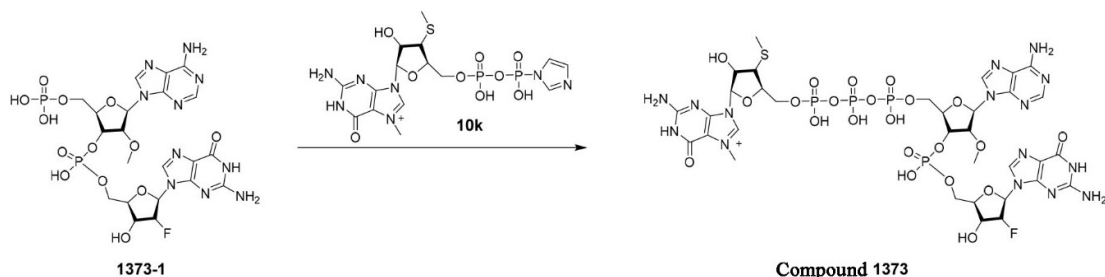
product, compound **1307**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.22 - 8.03 (m, 4H), 6.60 - 6.35 (m, 2H), 6.31 - 6.22 (m, 1H), 5.54 - 5.15 (m, 2H), 4.62 (ddd, J = 5.5, 2.8, 0.7 Hz, 1H), 4.51 - 4.01 (m, 12H), 3.92 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 46

Synthesis of Compound 1373



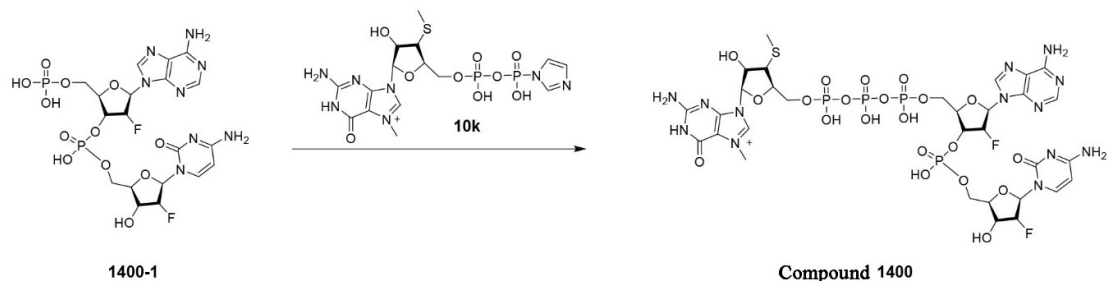
A compound **10k** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1373-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1373**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.40 (d, J = 0.5 Hz, 1H), 8.20 (s, 1H), 8.02 (d, J = 0.7 Hz, 1H), 6.45 (ddq, J = 25.2, 1.6, 0.8 Hz, 1H), 6.35 - 5.85 (m, 2H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 4.97 (dddd, J = 8.0, 4.4, 2.9, 0.7 Hz, 1H), 4.84 - 4.69 (m, 1H), 4.58 (ddd, J = 3.8, 1.6, 0.7 Hz, 1H), 4.45 (dddd, J = 25.2, 6.8, 5.0, 0.7 Hz, 1H), 4.36 - 4.30 (m, 2H), 4.30 - 4.05 (m, 7H), 3.98 (s, 3H), 3.61 (dddd, J = 3.8, 2.6, 1.8, 1.1 Hz, 1H), 3.40 (s, 3H), 2.09 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 47

Synthesis of Compound 1400



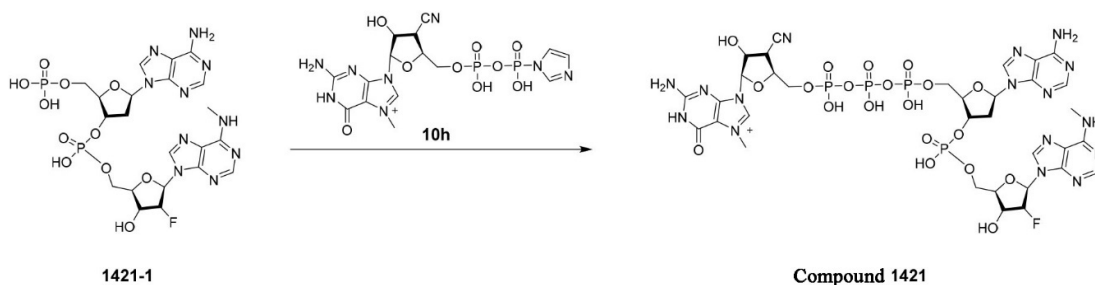
The compound **10k** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1400-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1400**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.43 - 8.11 (m, 2H), 7.70 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.43 (ddq, $J = 25.2, 1.6, 0.8$ Hz, 1H), 6.20 (dt, $J = 1.6, 0.8$ Hz, 1H), 6.04 (d, $J = 7.3$ Hz, 1H), 5.49 - 5.13 (m, 3H), 4.81 (dddd, $J = 46.5, 7.1, 3.7, 0.7$ Hz, 1H), 4.58 (ddd, $J = 3.8, 1.6, 0.7$ Hz, 1H), 4.48 (tdd, $J = 3.5, 2.4, 0.8$ Hz, 1H), 4.42 - 4.03 (m, 9H), 3.98 (s, 3H), 3.61 (dddd, $J = 3.8, 2.5, 1.8, 1.1$ Hz, 1H), 2.09 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 48

Synthesis of Compound 1421



The compound **10h** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0,

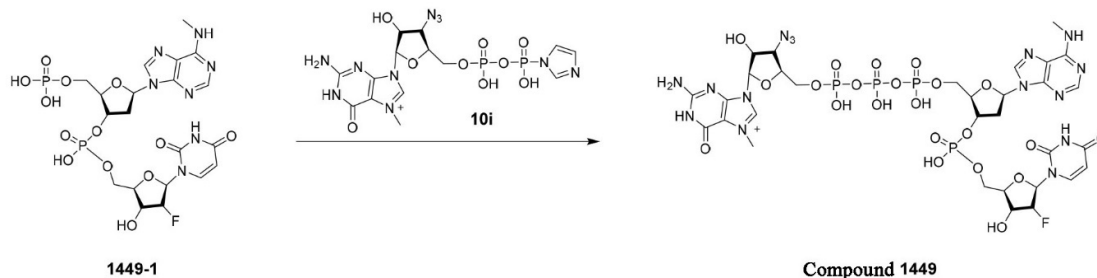
containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1421-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1421**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.51 - 7.89 (m, 4H), 6.46 - 6.31 (m, 2H), 6.24 (p, J = 0.8 Hz, 1H), 5.27 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 5.08 - 4.88 (m, 1H), 4.56 (dt, J = 3.8, 0.9 Hz, 1H), 4.52 - 4.38 (m, 2H), 4.36 - 4.04 (m, 8H), 3.98 (s, 3H), 3.65 (ddd, J = 3.6, 2.6, 0.6 Hz, 1H), 3.08 (s, 3H), 2.80 - 2.52 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 49

Synthesis of Compound 1449



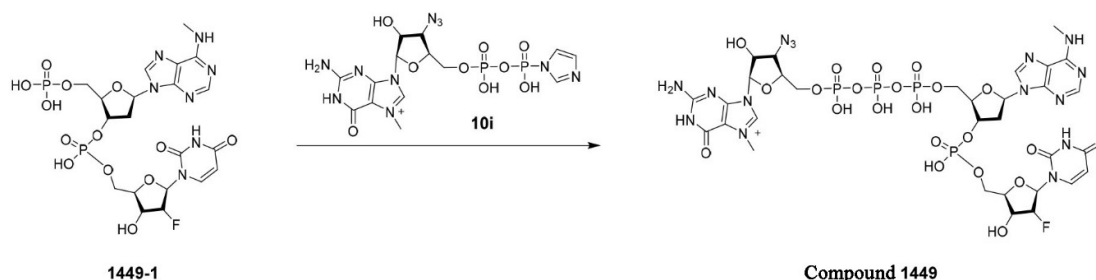
The compound **10i** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1449-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1449**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.40 - 8.08 (m, 2H), 7.59 - 7.18 (m, 2H), 6.48 - 6.34 (m, 1H), 6.24 (dq, J = 4.7, 0.8 Hz, 1H), 5.98 (dddt, J = 25.2, 4.0, 1.7, 0.8 Hz, 1H), 4.72 (ddd, J = 7.4, 4.7, 0.7 Hz, 1H), 4.49 - 3.97 (m, 12H), 3.95 - 3.80 (m, 4H), 3.10 (s, 3H), 2.93 - 2.53 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 50

Synthesis of Compound 1449



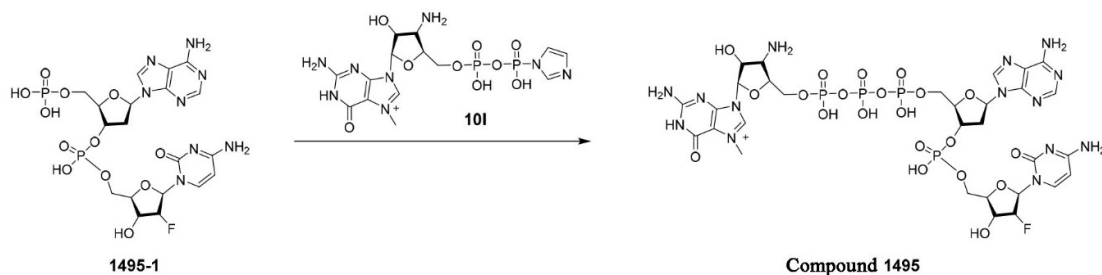
The compound **10i** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1449-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1449**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.40 - 8.08 (m, 2H), 7.59 - 7.18 (m, 2H), 6.48 - 6.34 (m, 1H), 6.24 (dq, J = 4.7, 0.8 Hz, 1H), 5.98 (dddt, J = 25.2, 4.0, 1.7, 0.8 Hz, 1H), 4.72 (ddd, J = 7.4, 4.7, 0.7 Hz, 1H), 4.49 - 3.97 (m, 12H), 3.95 - 3.80 (m, 4H), 3.10 (s, 3H), 2.93 - 2.53 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -9.12, -10.24, -21.26.

Example 51

Synthesis of Compound 1495



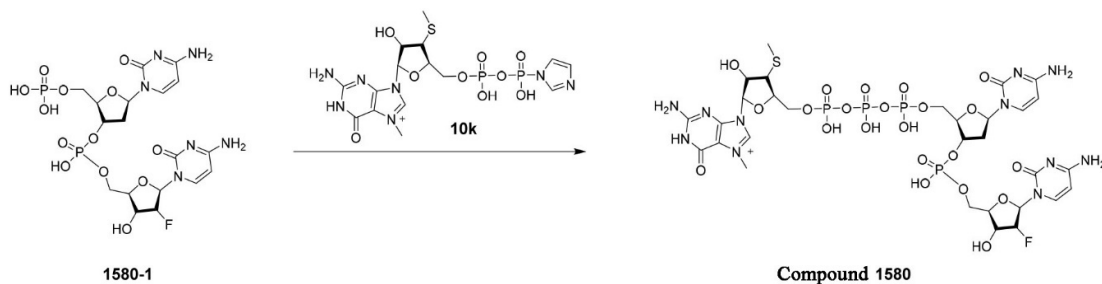
A compound **101** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1495-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1495**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.30 (d, $J = 0.6$ Hz, 1H), 8.20 (s, 1H), 7.70 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.55 - 6.34 (m, 1H), 6.16 (dq, $J = 2.2, 0.8$ Hz, 1H), 6.04 (d, $J = 7.3$ Hz, 1H), 5.40 (dddd, $J = 25.2, 3.4, 1.8, 0.9$ Hz, 1H), 5.12 - 4.93 (m, 1H), 4.81 (dddd, $J = 46.5, 7.1, 3.7, 0.7$ Hz, 1H), 4.41 - 4.04 (m, 11H), 3.98 (s, 3H), 3.63 (ddd, $J = 4.6, 3.1, 0.7$ Hz, 1H), 2.81 - 2.48 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.30, -21.26.

Example 52

Synthesis of Compound 1580



The compound **10k** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound

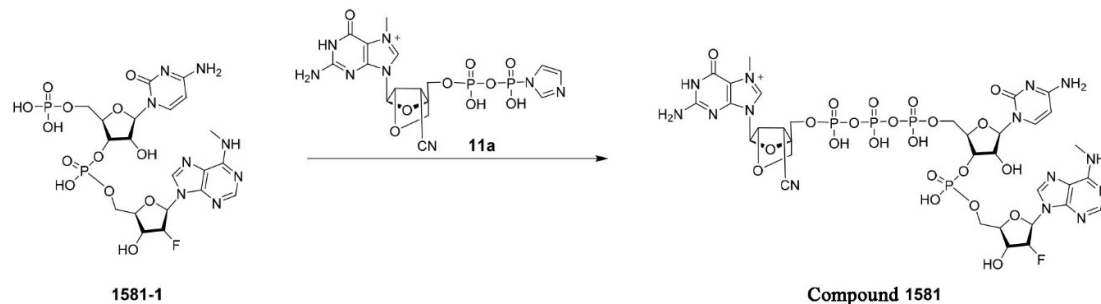
1580-1 (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1580**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.73 (ddd, $J = 24.9, 7.2, 1.8$ Hz, 2H), 6.35 - 6.15 (m, 2H), 6.03 (dd, $J = 12.2, 7.2$ Hz, 2H), 5.40 (dddd, $J = 25.2, 3.5, 1.8, 0.9$ Hz, 1H), 5.10 (dddd, $J = 8.3, 6.4, 4.5, 3.7, 0.7$ Hz, 1H), 4.81 (dddd, $J = 46.5, 7.1, 3.7, 0.7$ Hz, 1H), 4.58 (ddd, $J = 3.8, 1.6, 0.7$ Hz, 1H), 4.39 - 4.00 (m, 10H), 3.98 (s, 3H), 3.74 - 3.47 (m, 1H), 2.61 - 2.28 (m, 2H), 2.09 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 53

Synthesis of Compound 1581



A compound **11a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1581-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a

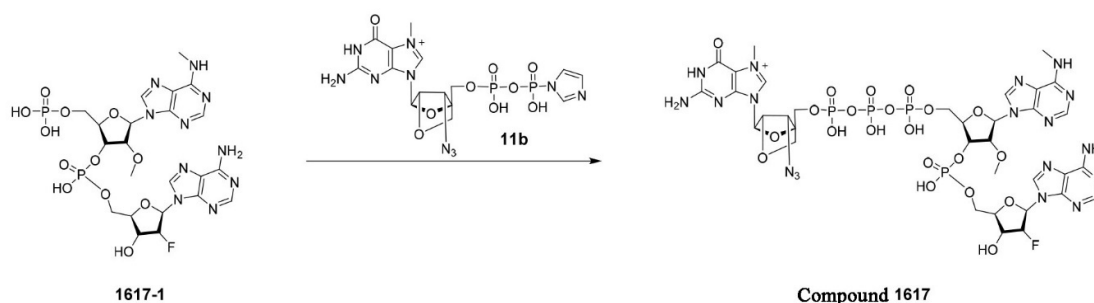
product, compound **1581**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.33 - 7.87 (m, 2H), 7.60 (dd, J = 7.4, 1.8 Hz, 1H), 6.49 - 6.23 (m, 2H), 6.15 - 5.73 (m, 2H), 5.27 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 5.00 (dd, J = 3.2, 2.5 Hz, 1H), 4.80 - 4.62 (m, 1H), 4.53 - 4.32 (m, 4H), 4.31 - 4.10 (m, 6H), 4.09 (s, 2H), 3.98 (s, 3H), 3.96 (d, J = 3.2 Hz, 1H), 3.08 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 54

Synthesis of Compound 1617



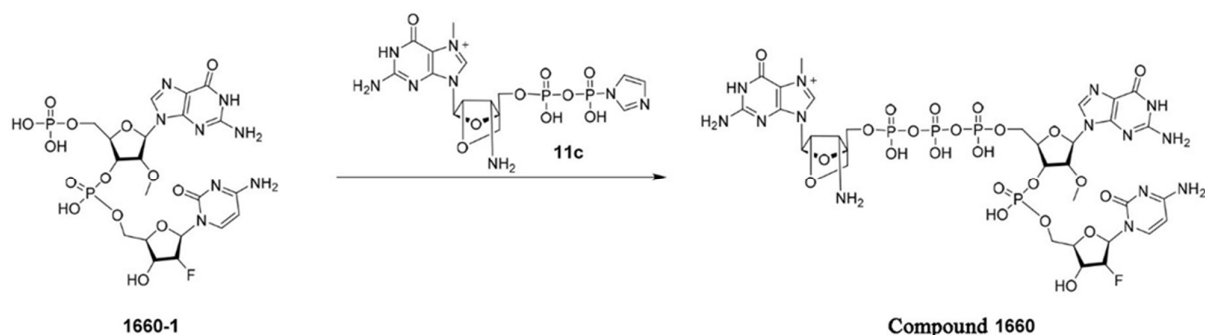
A compound **11b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganese chloride, and a compound **1617-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1617**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.27 (s, 1H), 8.22 - 8.17 (m, 2H), 8.14 (d, J = 0.6 Hz, 1H), 6.60 - 6.31 (m, 3H), 5.31 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 4.81 (dd, J = 4.8, 2.0 Hz, 1H), 4.66 - 4.54 (m, 2H), 4.46 (dddd, J = 25.2, 6.8, 5.0, 0.7 Hz, 1H), 4.36 - 4.21 (m, 6H), 4.19 - 3.99 (m, 4H), 3.92 (d, J = 0.6 Hz, 3H), 3.83 (dd, J = 11.3, 8.5 Hz, 1H), 3.37 (s, 3H), 3.10 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 55

Synthesis of Compound 1660



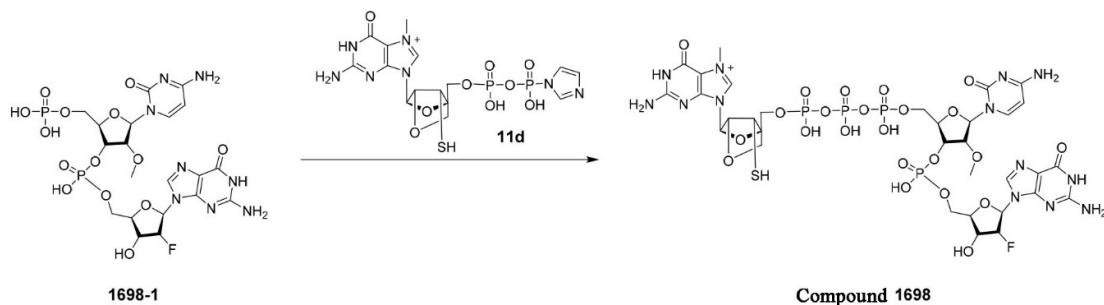
A compound **11c** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1660-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1660**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.88 (d, J = 0.7 Hz, 1H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 6.51 - 6.18 (m, 2H), 6.04 (d, J = 7.3 Hz, 1H), 5.40 (dddd, J = 25.2, 3.5, 1.8, 0.9 Hz, 1H), 5.05 - 4.59 (m, 4H), 4.48 - 4.09 (m, 9H), 4.04 - 3.82 (m, 6H), 3.40 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 56

Synthesis of Compound 1698



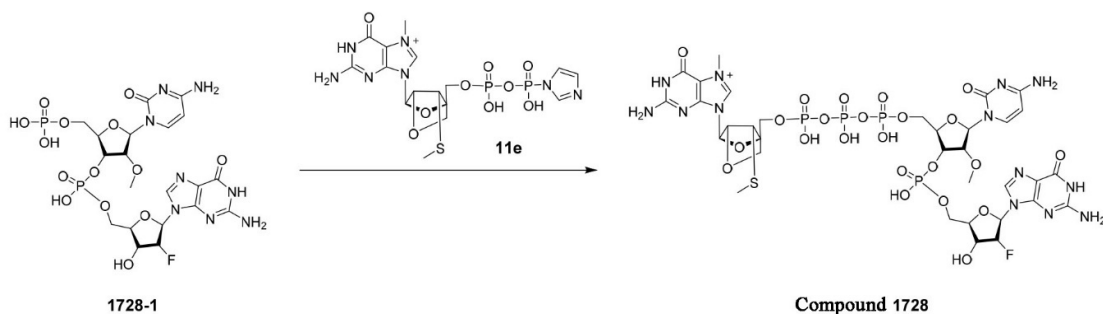
A compound **11d** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1698-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1698**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.02 (d, $J = 0.7$ Hz, 1H), 7.81 (dd, $J = 7.3, 1.8$ Hz, 1H), 6.63 - 6.39 (m, 2H), 6.18 - 5.82 (m, 2H), 5.22 (dddd, $J = 46.4, 7.0, 1.7, 0.7$ Hz, 1H), 4.89 (dddd, $J = 8.0, 5.4, 4.6, 0.6$ Hz, 1H), 4.59 - 4.28 (m, 6H), 4.25 - 4.03 (m, 7H), 3.98 (s, 3H), 3.46 (s, 3H), 3.11 (d, $J = 3.1$ Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 57

Synthesis of Compound 1728



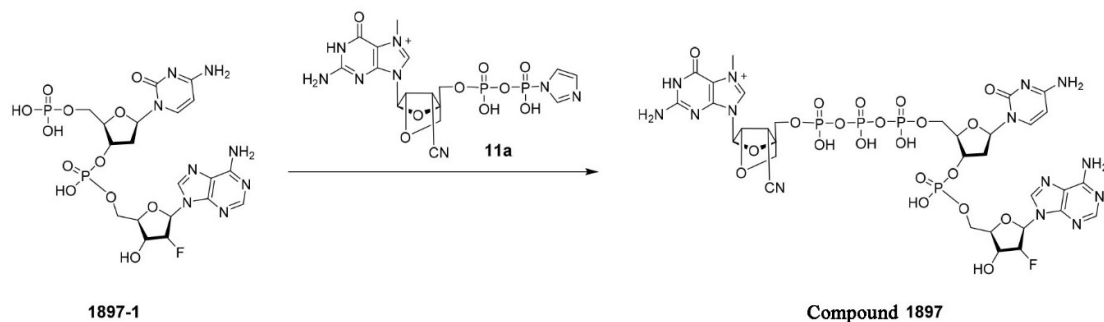
A compound **IIe** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1728-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1728**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.02 (d, J = 0.7 Hz, 1H), 7.81 (dd, J = 7.3, 1.8 Hz, 1H), 6.73 - 6.18 (m, 2H), 6.18 - 5.82 (m, 2H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H), 5.02 - 4.79 (m, 2H), 4.58 - 4.28 (m, 5H), 4.27 - 4.01 (m, 7H), 3.98 (s, 3H), 3.93 (dq, J = 2.9, 1.5 Hz, 1H), 3.46 (s, 3H), 2.10 (d, J = 1.4 Hz, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 58

Synthesis of Compound 1897



The compound **IIa** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1897-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution

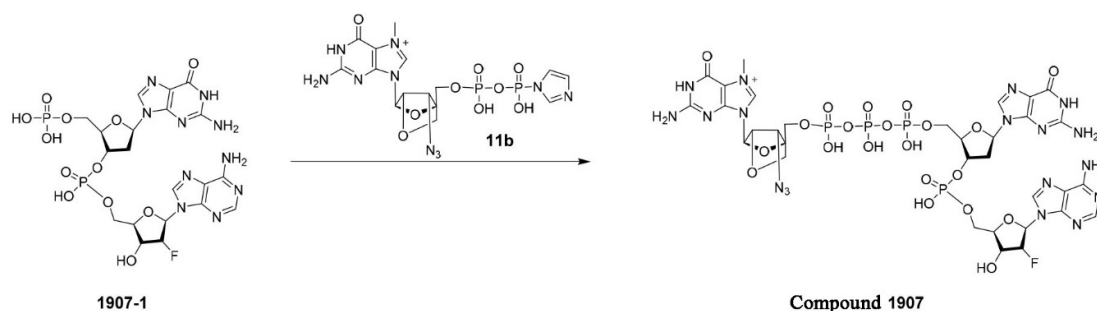
using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1897**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.32 - 8.11 (m, 2H), 7.76 (dd, J = 7.0, 1.8 Hz, 1H), 6.46 - 6.31 (m, 2H), 6.25 (dddd, J = 5.2, 3.3, 1.7, 0.8 Hz, 1H), 6.01 (d, J = 7.2 Hz, 1H), 5.27 (dddd, J = 46.5, 7.0, 4.0, 0.6 Hz, 1H), 5.10 (dddd, J = 8.3, 6.4, 4.5, 3.7, 0.7 Hz, 1H), 5.00 (dd, J = 3.2, 2.5 Hz, 1H), 4.54 - 4.30 (m, 3H), 4.26 - 4.17 (m, 4H), 4.13 - 4.01 (m, 4H), 3.98 (d, J = 0.7 Hz, 3H), 3.96 (d, J = 3.2 Hz, 1H), 2.60 - 2.26 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 59

Synthesis of Compound 1907



The compound **11b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1907-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1907**, which was an ammonium salt in the form of white powder (88 mg).

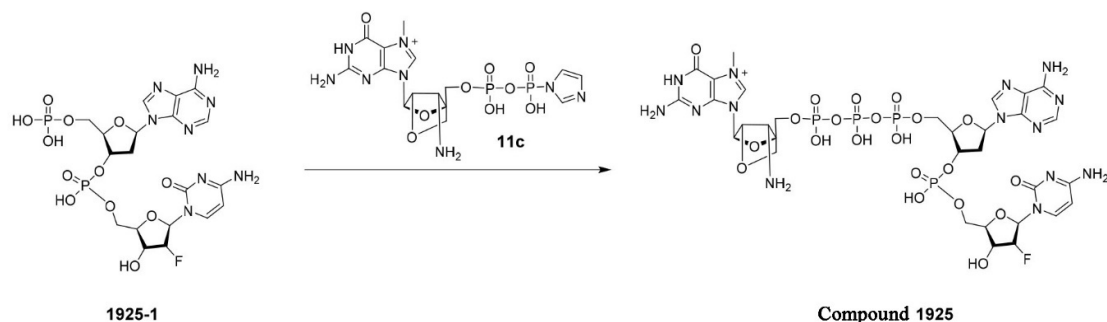
^1H NMR (400 MHz, D_2O) δ 8.18 (s, 1H), 8.14 (d, J = 0.6 Hz, 1H), 7.75 (d, J = 0.5 Hz, 1H), 6.49 (dd, J = 2.0, 0.7 Hz, 1H), 6.47 - 6.35 (m, 1H), 6.28 (ddq, J = 3.0, 1.4, 0.7 Hz, 1H), 5.31 (dddd, J =

46.5, 7.0, 4.0, 0.6 Hz, 1H), 4.81 (dd, $J = 4.8, 2.0$ Hz, 1H), 4.58 (dd, $J = 11.3, 8.5$ Hz, 1H), 4.50 - 4.39 (m, 1H), 4.37 - 4.19 (m, 6H), 4.14 - 3.98 (m, 3H), 3.96 - 3.76 (m, 5H), 2.92 - 2.35 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 60

Synthesis of Compound 1925



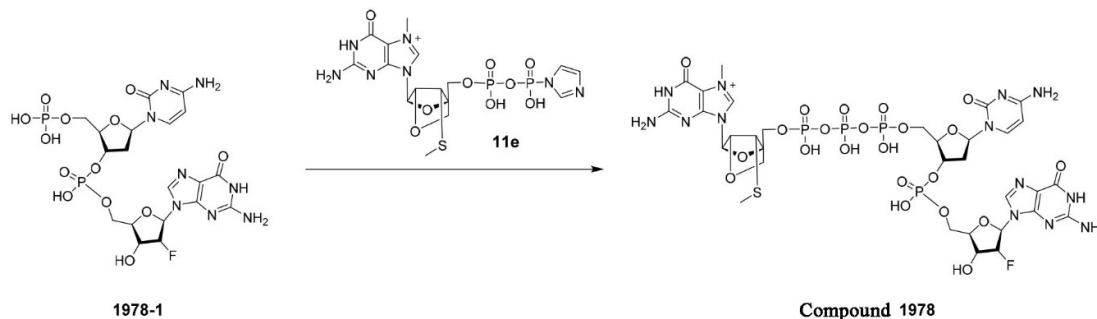
The compound **11c** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1925-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1925**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.30 (d, $J = 0.5$ Hz, 1H), 8.20 (s, 1H), 7.70 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.42 - 6.36 (m, 1H), 6.31 (dd, $J = 2.0, 0.6$ Hz, 1H), 6.04 (d, $J = 7.3$ Hz, 1H), 5.48 - 5.29 (m, 1H), 5.18 - 4.94 (m, 1H), 4.81 (dddd, $J = 46.5, 7.1, 3.7, 0.7$ Hz, 1H), 4.66 (t, $J = 2.2$ Hz, 1H), 4.46 - 4.05 (m, 9H), 4.02 - 3.90 (m, 6H), 2.92 - 2.35 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 61

Synthesis of Compound 1978



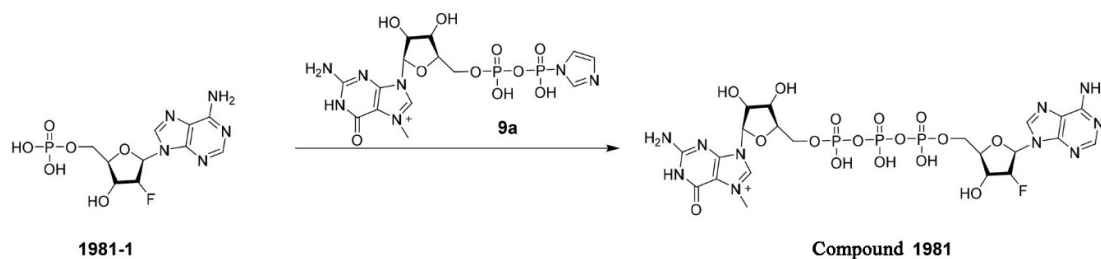
The compound **11e** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1978-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1978**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.02 (d, $J = 0.7$ Hz, 1H), 7.76 (dd, $J = 7.0, 1.8$ Hz, 1H), 6.54 - 6.35 (m, 2H), 6.25 (dddd, $J = 5.2, 3.3, 1.7, 0.8$ Hz, 1H), 6.01 (d, $J = 7.2$ Hz, 1H), 5.37 - 5.03 (m, 2H), 4.88 (dd, $J = 3.1, 2.0$ Hz, 1H), 4.57 - 4.29 (m, 3H), 4.26 - 4.01 (m, 8H), 3.98 (d, $J = 0.7$ Hz, 3H), 3.93 (dq, $J = 3.0, 1.5$ Hz, 1H), 2.71 - 2.26 (m, 2H), 2.10 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26.

Example 62

Synthesis of Compound 1981



The compound **9a** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0,

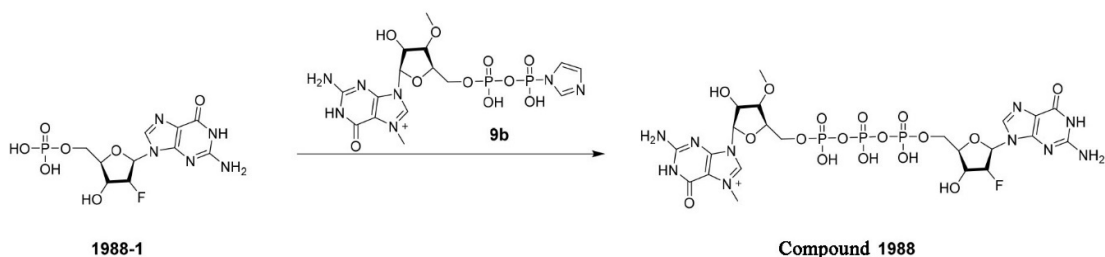
containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1981-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1981**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.30 - 8.00 (m, 2H), 6.39 (ddd, $J = 25.2, 4.0, 0.7$ Hz, 1H), 6.25 - 5.90 (m, 1H), 5.28 (dddd, $J = 46.5, 4.9, 4.1, 0.6$ Hz, 1H), 4.69 - 4.49 (m, 2H), 4.35 (ddd, $J = 5.3, 3.7, 0.7$ Hz, 1H), 4.30 - 4.07 (m, 6H), 3.98 (d, $J = 0.7$ Hz, 3H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 63

Synthesis of Compound 1988



The compound **9b** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1988-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1988**, which was an ammonium salt in the form of white powder (88 mg).

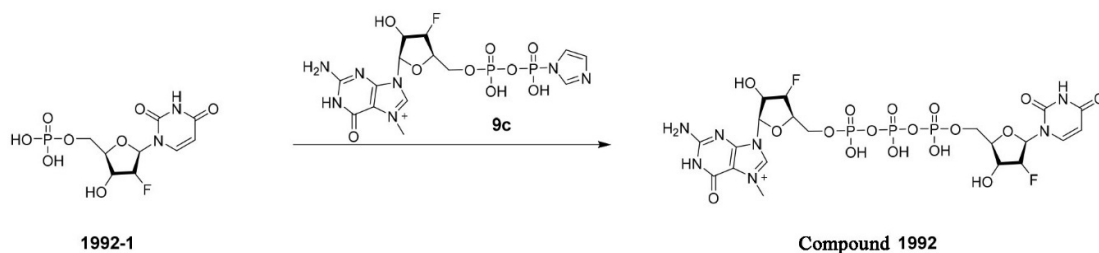
^1H NMR (400 MHz, D_2O) δ 8.02 (d, $J = 0.7$ Hz, 1H), 6.43 (ddd, $J = 25.2, 1.5, 0.8$ Hz, 1H), 6.17

(dt, $J = 2.5, 0.7$ Hz, 1H), 5.61 - 5.11 (m, 1H), 4.96 - 4.44 (m, 2H), 4.30 - 4.22 (m, 4H), 4.21 - 4.10 (m, 2H), 4.06 (dt, $J = 4.2, 2.1, 1.1$ Hz, 1H), 3.98 (s, 3H), 3.44 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 64

Synthesis of Compound 1992



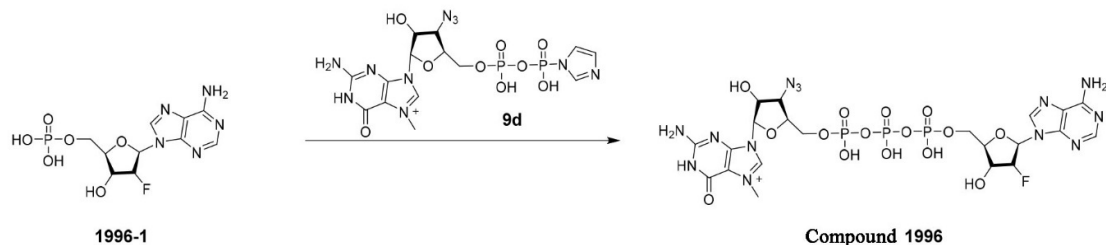
The compound **9c** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1992-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1992**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.81 (dd, $J = 7.8, 1.8$ Hz, 1H), 6.44 - 6.09 (m, 1H), 5.90 (d, $J = 7.8$ Hz, 1H), 5.53 (dddd, $J = 24.4, 3.9, 1.8, 0.9$ Hz, 1H), 5.00 - 4.94 (m, 1H), 4.88 - 4.80 (m, 1H), 4.78 - 4.69 (m, 1H), 4.60 (dtd, $J = 3.8, 2.7, 0.8$ Hz, 1H), 4.57 - 4.51 (m, 1H), 4.33 (ddd, $J = 8.5, 3.7, 1.6$ Hz, 2H), 4.25 - 4.12 (m, 3H), 3.98 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 65

Synthesis of Compound 1996



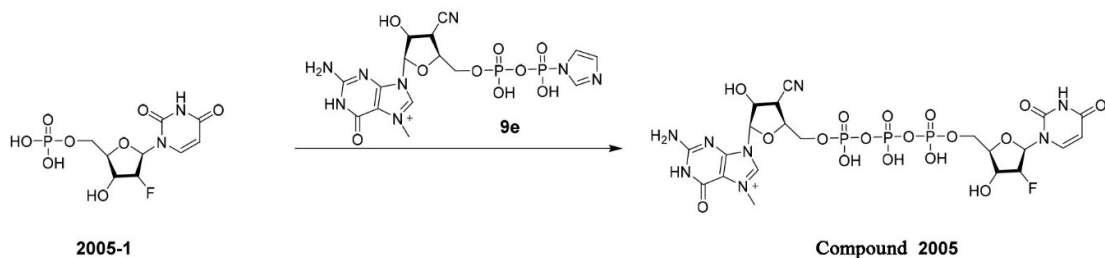
The compound **9d** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **1996-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **1996**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.18 (s, 1H), 8.14 (d, $J = 0.6$ Hz, 1H), 6.41 (ddq, $J = 25.2, 4.0, 0.8$ Hz, 1H), 6.31 - 6.22 (m, 1H), 5.45 - 4.99 (m, 1H), 4.79 - 4.50 (m, 2H), 4.46 - 4.05 (m, 7H), 3.92 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 66

Synthesis of Compound 2005



A compound **9e** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2005-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours.

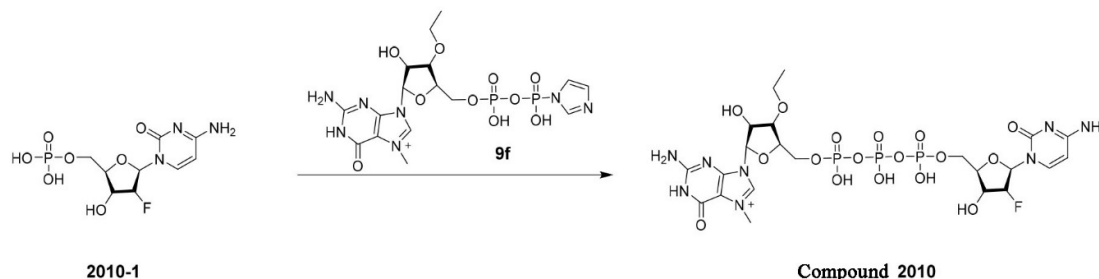
TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2005**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.81 (dd, J = 7.8, 1.8 Hz, 1H), 6.24 (p, J = 0.8 Hz, 1H), 5.90 (d, J = 7.8 Hz, 1H), 5.74 - 5.30 (m, 1H), 4.89 - 4.64 (m, 1H), 4.60 - 4.43 (m, 2H), 4.43 - 4.37 (m, 1H), 4.36 - 4.11 (m, 5H), 3.98 (s, 3H), 3.65 (ddd, J = 3.6, 2.6, 0.6 Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 67

Synthesis of Compound 2010



A compound **9f** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2010-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2010**, which was an ammonium salt in the form of white powder (88 mg).

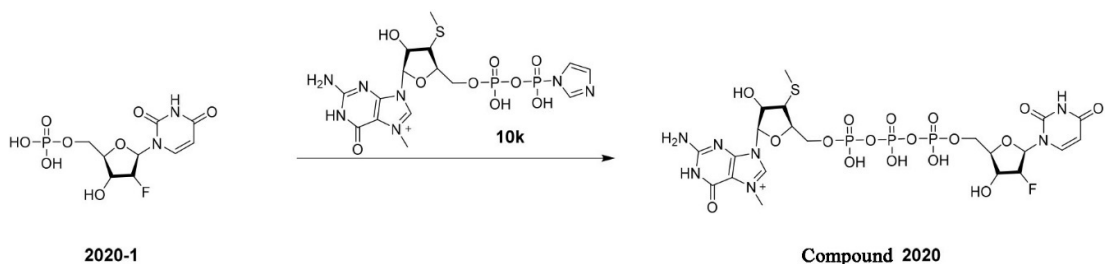
^1H NMR (400 MHz, D_2O) δ 7.70 (dd, J = 7.3, 1.8 Hz, 1H), 6.18 (dq, J = 2.5, 0.8 Hz, 1H), 6.04 (d, J = 7.3 Hz, 1H), 5.40 (dddt, J = 25.1, 3.4, 1.6, 0.8 Hz, 1H), 4.83 (dddd, J = 46.3, 5.2, 3.7, 0.6 Hz,

1H), 4.68 (ddd, J = 3.2, 2.4, 0.7 Hz, 1H), 4.59 - 4.42 (m, 1H), 4.30 - 4.07 (m, 7H), 3.98 (d, J = 0.7 Hz, 3H), 3.59 (p, J = 5.9 Hz, 2H), 1.24 (t, J = 6.0 Hz, 3H).

³¹P NMR (162 MHz, D₂O) δ -10.24, -21.26.

Example 68

Synthesis of Compound 2020



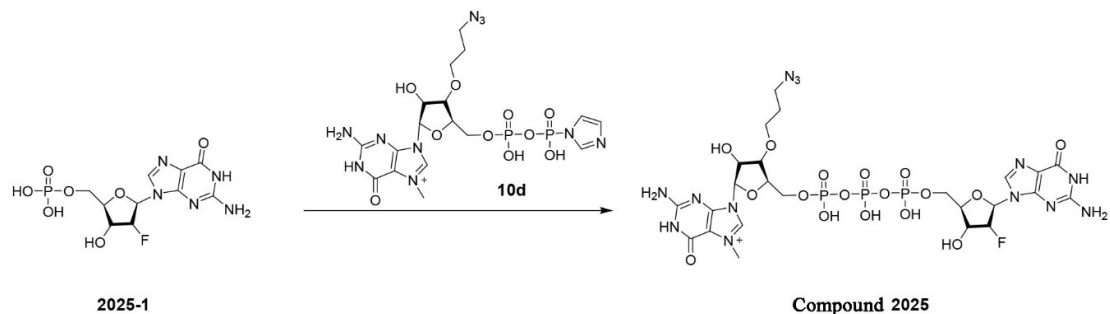
The compound **10k** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2020-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2020**, which was an ammonium salt in the form of white powder (88 mg).

¹H NMR (400 MHz, D₂O) δ 7.81 (dd, J = 7.8, 1.8 Hz, 1H), 6.21 (dq, J = 1.5, 0.8 Hz, 1H), 5.90 (d, J = 7.8 Hz, 1H), 5.62 - 5.35 (m, 1H), 5.00 - 4.69 (m, 1H), 4.62 - 4.41 (m, 2H), 4.36 - 4.11 (m, 6H), 3.98 (d, J = 0.7 Hz, 3H), 3.69 - 3.47 (m, 1H), 2.09 (d, J = 1.4 Hz, 3H).

³¹P NMR (162 MHz, D₂O) δ -10.24, -21.26.

Example 69

Synthesis of Compound 2025



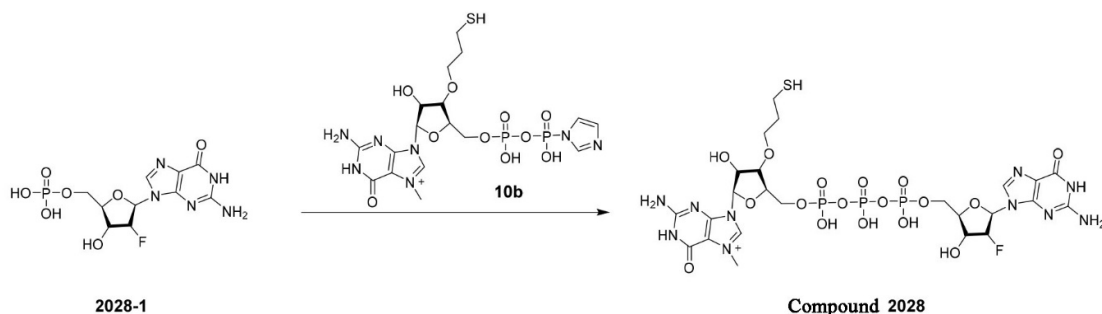
The compound **10d** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2025-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2025**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.95 (d, J = 0.7 Hz, 1H), 6.49 (ddt, J = 25.2, 1.5, 0.8 Hz, 1H), 6.28 (dq, J = 2.3, 0.8 Hz, 1H), 5.31 (dddd, J = 46.3, 5.0, 1.6, 0.7 Hz, 1H), 4.70 (ddd, J = 3.3, 2.5, 0.7 Hz, 1H), 4.58 (dddd, J = 25.2, 4.9, 3.1, 0.6 Hz, 1H), 4.44 - 4.21 (m, 5H), 4.13 (qt, J = 3.1, 0.8 Hz, 1H), 3.98 (ddd, J = 3.1, 2.3, 0.6 Hz, 1H), 3.92 (d, J = 0.6 Hz, 3H), 3.56 (td, J = 6.4, 1.5 Hz, 2H), 3.23 (td, J = 6.3, 0.8 Hz, 2H), 1.94 (pd, J = 6.3, 1.0 Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 70

Synthesis of Compound 2028



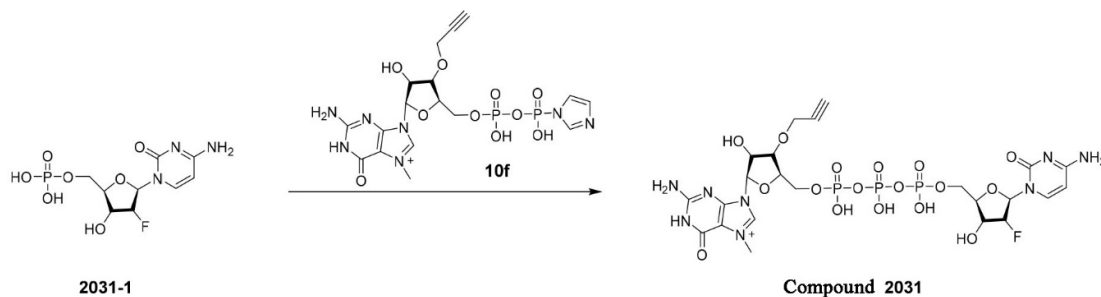
The compound **10b** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2028-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2028**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.02 (d, $J = 0.7$ Hz, 1H), 6.43 (ddd, $J = 25.2, 1.5, 0.8$ Hz, 1H), 6.27 - 6.03 (m, 1H), 5.54 - 5.05 (m, 1H), 4.71 (ddd, $J = 3.3, 2.5, 0.7$ Hz, 1H), 4.59 - 4.45 (m, 1H), 4.37 - 4.06 (m, 7H), 3.98 (d, $J = 0.7$ Hz, 3H), 3.76 - 3.46 (m, 2H), 3.06 - 2.68 (m, 2H), 1.84 (p, $J = 6.5$ Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 71

Synthesis of Compound 2031



The compound **10f** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0,

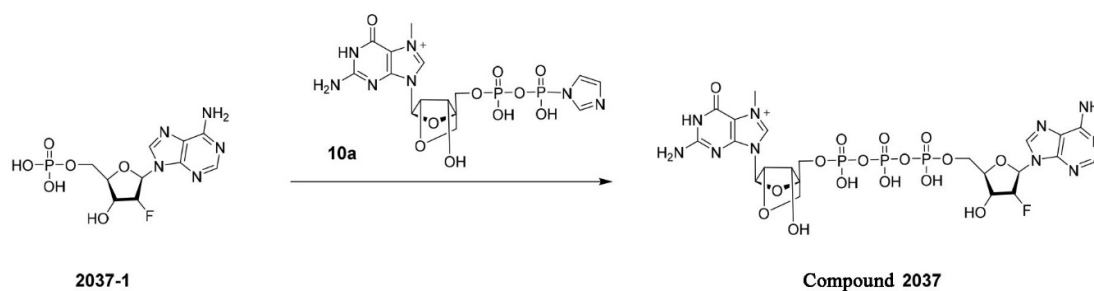
containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2031-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2031**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.70 (dd, $J = 7.3, 1.8$ Hz, 1H), 6.20 (dt, $J = 2.3, 0.7$ Hz, 1H), 6.04 (d, $J = 7.3$ Hz, 1H), 5.40 (dddd, $J = 25.2, 3.5, 1.7, 0.8$ Hz, 1H), 4.97 - 4.69 (m, 2H), 4.59 - 4.41 (m, 1H), 4.35 - 4.09 (m, 9H), 3.98 (d, $J = 0.7$ Hz, 3H), 2.42 (t, $J = 3.0$ Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 72

Synthesis of Compound 2037



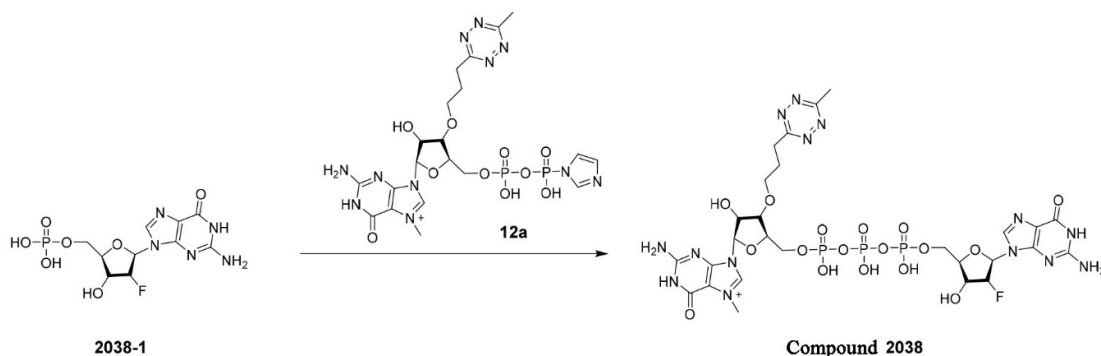
The compound **10a** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2037-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2037**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.42 - 8.05 (m, 2H), 6.55 - 6.15 (m, 2H), 5.28 (dddd, J = 46.4, 7.0, 3.0, 0.7 Hz, 1H), 4.64 (t, J = 2.8 Hz, 1H), 4.55 - 4.19 (m, 7H), 4.00 (dd, J = 12.9, 0.7 Hz, 5H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 73

Synthesis of Compound 2038



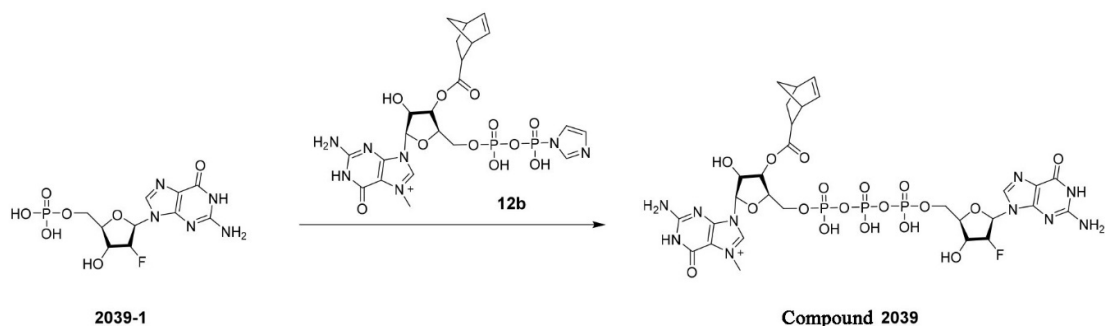
A compound **12a** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2038-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2038**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.02 (d, J = 0.7 Hz, 1H), 6.43 (ddt, J = 25.2, 1.6, 0.8 Hz, 1H), 6.27 - 5.99 (m, 1H), 5.24 (dddd, J = 46.5, 5.1, 1.7, 0.6 Hz, 1H), 4.86 - 4.45 (m, 2H), 4.36 - 4.07 (m, 7H), 3.98 (d, J = 0.7 Hz, 3H), 3.83 - 3.48 (m, 2H), 3.09 - 2.90 (m, 2H), 2.79 (s, 3H), 2.55 - 2.18 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 74

Synthesis of Compound 2039



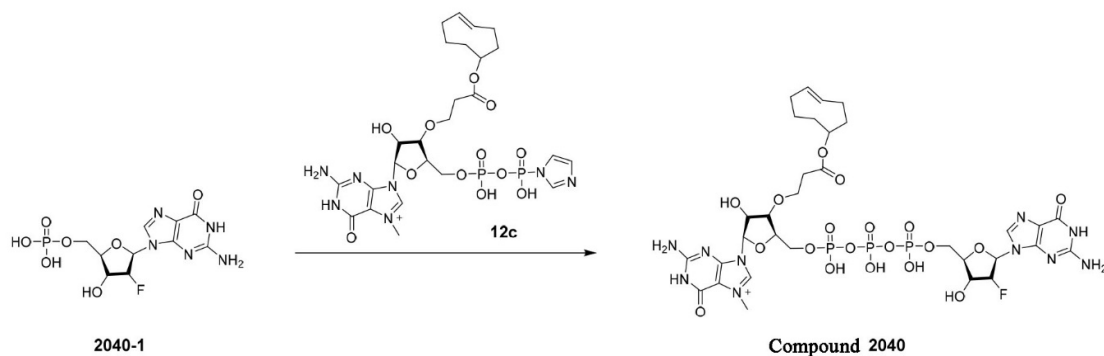
A compound **12b** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2039-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2039**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.02 (d, $J = 0.7$ Hz, 1H), 6.43 (ddd, $J = 25.2, 1.6, 0.8$ Hz, 1H), 6.27 - 5.70 (m, 3H), 5.42 - 5.07 (m, 1H), 5.00 - 4.81 (m, 2H), 4.65 - 4.43 (m, 2H), 4.37 - 4.10 (m, 5H), 3.98 (d, $J = 0.7$ Hz, 3H), 3.38 (ttdd, $J = 5.3, 4.2, 1.8, 1.0$ Hz, 1H), 3.11 - 2.53 (m, 2H), 2.14 - 1.79 (m, 2H), 1.62 - 1.17 (m, 2H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 75

Synthesis of Compound 2040



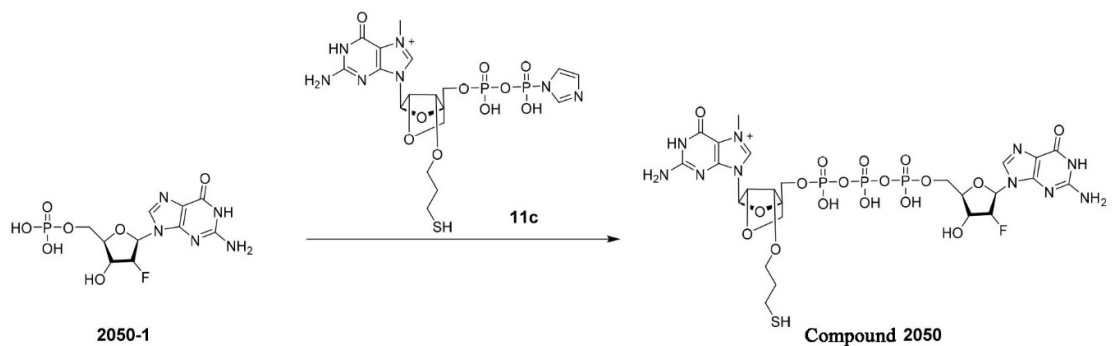
A compound **12c** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2040-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2040**, which was an ammonium salt in the form of white powder (88 mg).

¹H NMR (400 MHz, D₂O) δ 8.02 (d, J = 0.7 Hz, 1H), 6.43 (ddd, J = 25.2, 1.5, 0.8 Hz, 1H), 6.26 - 6.03 (m, 1H), 5.69 - 5.39 (m, 2H), 5.31 - 5.07 (m, 1H), 4.84 - 4.67 (m, 2H), 4.63 - 4.46 (m, 1H), 4.28 - 4.06 (m, 7H), 3.98 (d, J = 0.7 Hz, 3H), 3.89 - 3.69 (m, 2H), 2.58 (td, J = 7.2, 2.9 Hz, 2H), 2.26 - 1.11 (m, 10H).

³¹P NMR (162 MHz, D₂O) δ -10.25, -21.23.

Example 76

Synthesis of Compound 2050



The compound **11c** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2050-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution

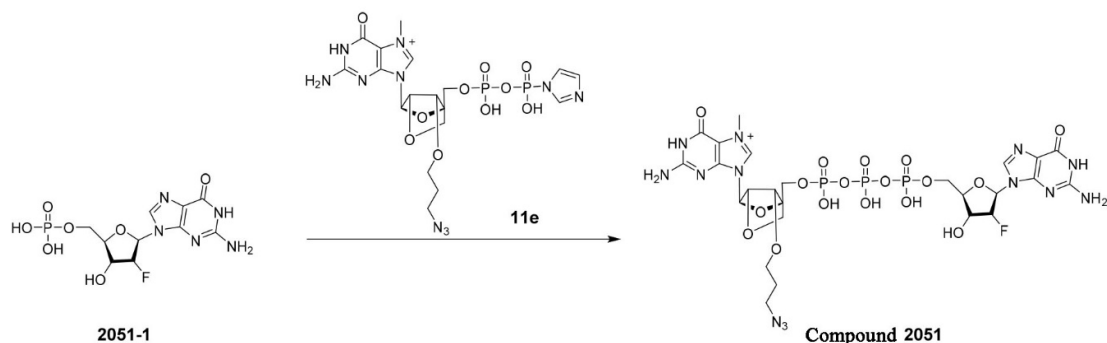
using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2050**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 8.02 (d, $J = 0.7$ Hz, 1H), 6.65 - 6.28 (m, 2H), 5.39 - 5.11 (m, 1H), 4.87 (t, $J = 3.1$ Hz, 1H), 4.65 - 4.47 (m, 1H), 4.39 - 4.21 (m, 5H), 4.15 (d, $J = 3.1$ Hz, 1H), 4.02 (s, 2H), 3.98 (d, $J = 0.7$ Hz, 3H), 3.66 (td, $J = 5.3, 2.9$ Hz, 2H), 2.96 - 2.52 (m, 2H), 1.85 (tt, $J = 6.4, 5.3$ Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ -10.21, -21.25.

Example 77

Synthesis of Compound 2051



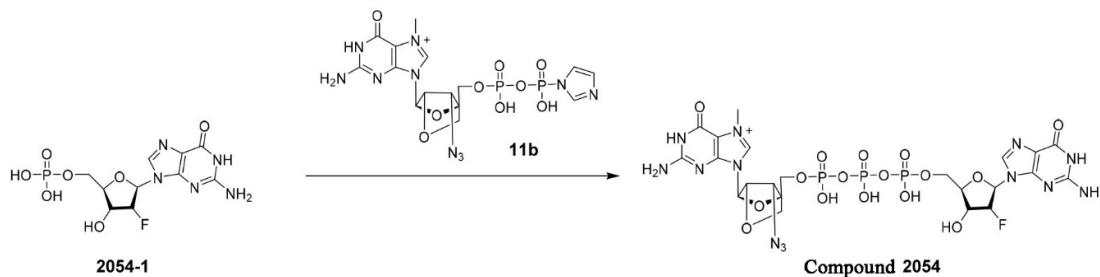
The compound **11e** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2051-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2051**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.95 (d, $J = 0.7$ Hz, 1H), 6.71 - 6.22 (m, 2H), 5.31 (dddd, $J = 46.3, 5.0, 1.6, 0.7$ Hz, 1H), 4.67 - 4.45 (m, 2H), 4.42 - 4.21 (m, 2H), 4.13 (qt, $J = 3.1, 0.8$ Hz, 1H), 4.06 - 3.85 (m, 7H), 3.76 - 3.53 (m, 3H), 3.36 (t, $J = 6.2$ Hz, 2H), 1.95 (tt, $J = 6.3, 5.3$ Hz, 2H).

^{31}P NMR (162 MHz, D_2O) δ -10.34, -21.36.

Example 78

Synthesis of Compound 2054



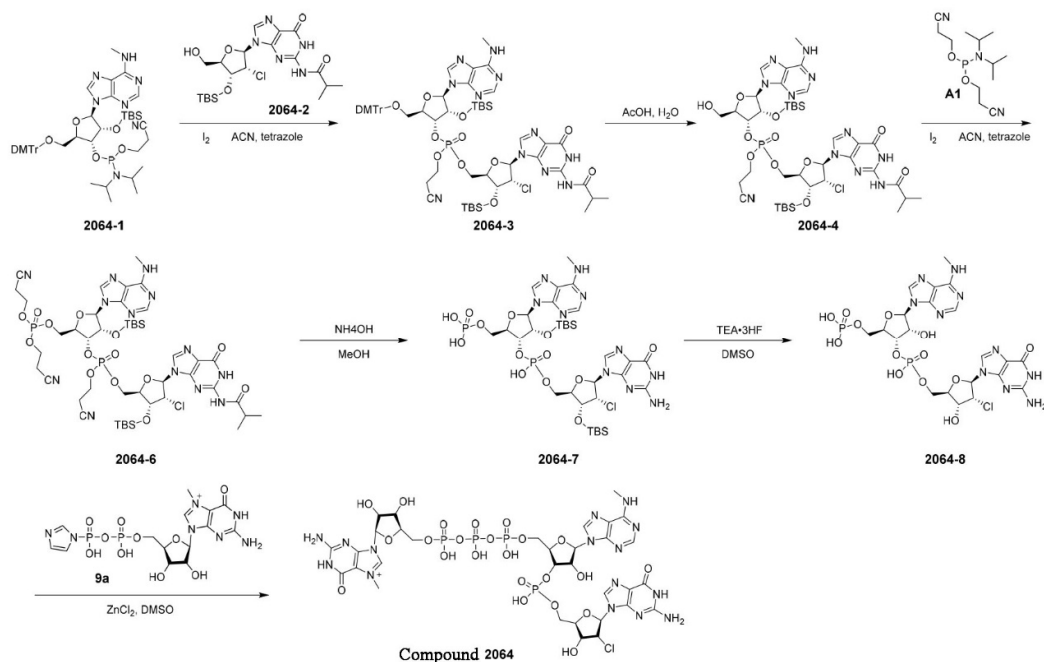
The compound **11b** (250 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and a compound **2054-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2054**, which was an ammonium salt in the form of white powder (88 mg).

^1H NMR (400 MHz, D_2O) δ 7.95 (d, J = 0.7 Hz, 1H), 6.49 (dd, J = 2.0, 0.7 Hz, 1H), 6.44 - 6.19 (m, 1H), 5.31 (dddd, J = 46.4, 6.9, 3.5, 0.8 Hz, 1H), 4.81 (dd, J = 4.8, 2.0 Hz, 1H), 4.58 (dd, J = 11.3, 8.5 Hz, 1H), 4.42 (dddd, J = 25.2, 7.1, 3.2, 0.7 Hz, 1H), 4.36 - 4.23 (m, 3H), 4.14 - 3.99 (m, 3H), 3.92 (d, J = 0.6 Hz, 3H), 3.83 (dd, J = 11.3, 8.5 Hz, 1H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.16.

Example 79

Synthesis of Compound 2064



A compound **2064-2** (2.38 g) was added to a solution of tetrazole (1.76 g) in acetonitrile (63 mL) in a three-necked flask, and the atmosphere was replaced with argon three times. Next, at room temperature of 25°C, a material **2064-1** (5 g) was dissolved in 10 mL of acetonitrile and added to the above solution. The resulting solution was stirred at room temperature of 25°C for 1 hour. No obvious heat release was found, and TLC monitoring showed that the material **2064-1** disappeared. Then, into the solution, a solution of iodine in pyridine/tetrahydrofuran/water (0.5 mmol/mL, pyridine:tetrahydrofuran:water = 1:8:1) was added dropwise until the solution no longer faded. After that, the reaction solution was stirred for another 0.5 hours, and TLC monitoring showed that the oxidation was completed. After adding an aqueous solution (10 mL) of saturated sodium sulfite to the reaction solution for quenching, 50 mL of water was further added for dilution, and the mixture was extracted with dichloromethane (50 mL x 2). The organic phases were combined and washed once with water (50 mL), and concentrated to obtain a light yellow oily product **2064-3** (8 g, crude product).

The compound **2064-3** (8 g, crude product) was dissolved in 40 mL of acetic acid and 10 mL of water, and the reaction solution was stirred at 25°C for 16 hours. TLC monitoring showed that the compound **2064-3** disappeared and a spot with large polarity was generated. The reaction solution was directly concentrated in vacuo. After concentration, appropriate amounts of silica gel and DCM

were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white solid product **2064-4** (2.8 g, 51% overall yield over two-step) was obtained.

28 mL of a tetrazole solution in acetonitrile (0.4 mmol/mL) was prepared. The compound **2064-4** (2.8 g) was added to the above solution, and then the compound **AI** (3 g) was added to the solution at room temperature of 25°C. The atmosphere was replaced with nitrogen three times, and the reaction solution was stirred at room temperature of 25°C for 1 hour. TLC monitoring showed that the reaction was completed. The reaction solution was cooled to below 10°C in an ice-water bath, and a solution of iodine in pyridine/tetrahydrofuran/water (0.5 mmol/mL, pyridine:tetrahydrofuran:water = 1:8:1) was added dropwise until the reaction solution no longer faded. TLC monitoring showed that the oxidation reaction was completed. The reaction solution was quenched by adding 10 mL of an aqueous saturated solution of sodium sulfite, diluted with water, and extracted three times with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate and filtered. Appropriate amounts of silica gel and DCM were added and mixed with the sample, followed by purification (40 g normal phase column, EA, 10 min, DCM: MeOH, 10% to 20%, for 20 min, flow rate: 30 mL/min). After concentration, a white foamy solid compound **2064-6** (2.6 g, 78.2% yield) was obtained.

The compound **2064-6** (2.6 g) was dissolved in methanol (30 mL) and concentrated aqueous ammonia (30 mL) was added. The resulting solution was stirred at room temperature of 25°C for 60 hours. TLC monitoring showed that the raw material **2064-6** was completely reacted. The reaction solution was concentrated in vacuo and concentrated again with methanol to obtain a light yellow oily liquid compound **2064-7** (2.4 g, crude product), which was directly used for the next step.

The compound **2064-7** (2.4 g, crude product) was dissolved in DMSO (3 mL) and triethylamine trihydrofluoride (3.5 mL) was added. The reaction solution was stirred at 50°C for 1 hour. TLC monitoring showed that the raw material **2064-7** was completely reacted. The reaction solution was diluted to 50 mL with water, and the pH was adjusted to 5.5 with 1 N NaOH aqueous solution. The mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the

obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a target compound, amine salt **2064-8** (0.8 g, 33.7% yield), which was a white solid.

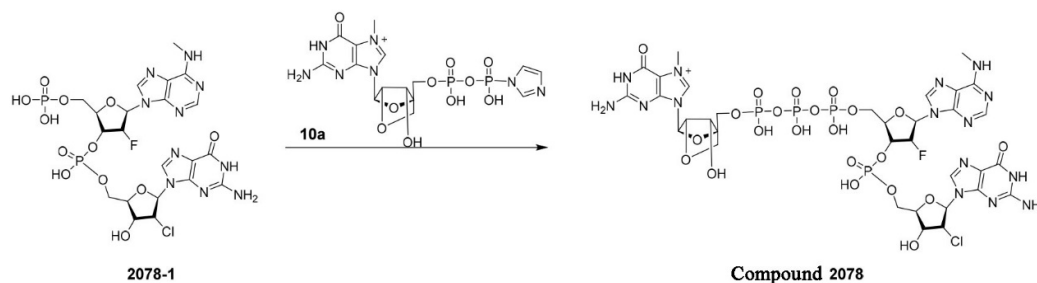
The compound **9a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and **2064-8** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2064**, which was an ammonium salt in the form of white powder (65 mg).

¹H NMR (400 MHz, D₂O) δ 8.33 (s, 1H), 8.29 (s, 1H), 8.04 (s, 1H), 6.25 (t, J = 0.7 Hz, 1H), 6.16 (dt, J = 3.0, 0.7 Hz, 1H), 6.11 (dq, J = 3.0, 0.7 Hz, 1H), 4.80 (ddd, J = 3.8, 2.9, 0.7 Hz, 1H), 4.74 (dddd, J = 7.9, 3.9, 2.9, 0.7 Hz, 1H), 4.61 (ddd, J = 5.2, 2.8, 0.7 Hz, 1H), 4.55 - 4.43 (m, 1H), 4.41 - 4.32 (m, 2H), 4.30 - 4.09 (m, 9H), 3.98 (d, J = 0.7 Hz, 3H), 3.08 (s, 3H).

³¹P NMR (162 MHz, D₂O) δ -0.80, -11.55, -23.03.

Example 80

Synthesis of Compound 2078



The compound **10a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and **2078-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded

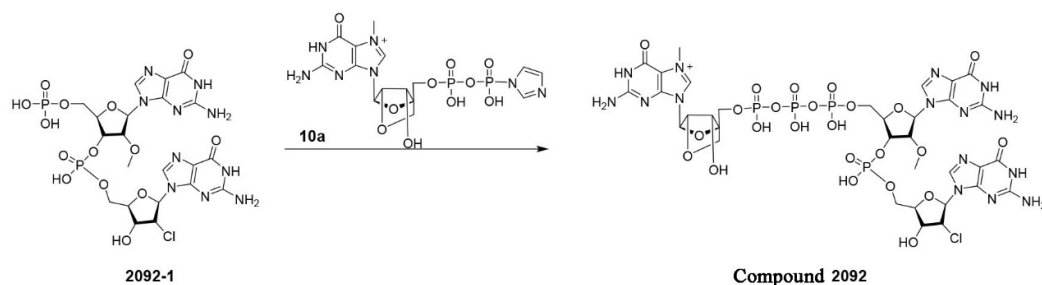
onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2078**, which was an ammonium salt in the form of white powder (55 mg).

^1H NMR (400 MHz, D_2O) δ 8.39 (s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 6.49 (dq, $J = 1.5, 0.7$ Hz, 1H), 6.32 - 6.09 (m, 2H), 5.30 (ddd, $J = 2.6, 1.8, 0.7$ Hz, 1H), 5.25 (ddd, $J = 3.6, 2.9, 0.7$ Hz, 1H), 4.72 - 4.60 (m, 2H), 4.56 - 4.46 (m, 2H), 4.44 - 4.36 (m, 2H), 4.33 (d, $J = 2.8$ Hz, 1H), 4.27 - 4.07 (m, 6H), 4.05 - 3.96 (m, 4H), 3.11 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ -0.90, -11.50, -22.95.

Example 81

Synthesis of Compound 2092



The compound **10a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and **2092-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2092**, which was an ammonium salt in the form of white powder (65 mg).

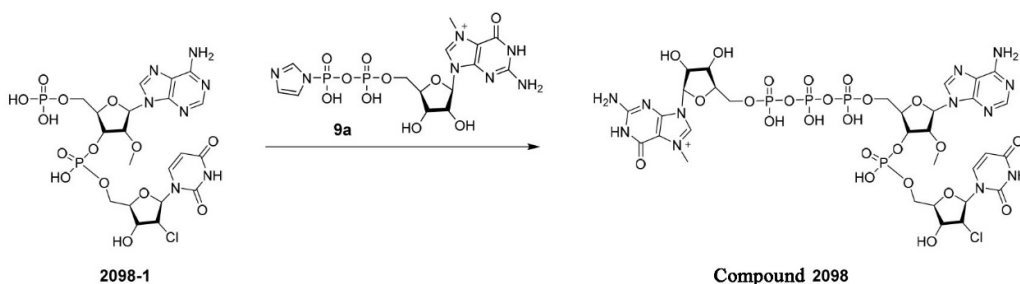
^1H NMR (400 MHz, D_2O) δ 8.19 (s, 1H), 8.08 (s, 1H), 6.37 - 6.19 (m, 2H), 6.09 (dd, $J = 2.8, 0.8$ Hz, 1H), 4.97 (ddd, $J = 4.4, 2.9, 0.7$ Hz, 1H), 4.76 - 4.70 (m, 1H), 4.64 (t, $J = 2.8$ Hz, 1H), 4.55 - 4.45

(m, 3H), 4.44 - 4.35 (m, 2H), 4.33 (d, J = 2.8 Hz, 1H), 4.26 - 4.06 (m, 6H), 4.05 - 3.97 (m, 4H), 3.39 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ -0.95, -11.70, -22.75.

Example 82

Synthesis of Compound 2098



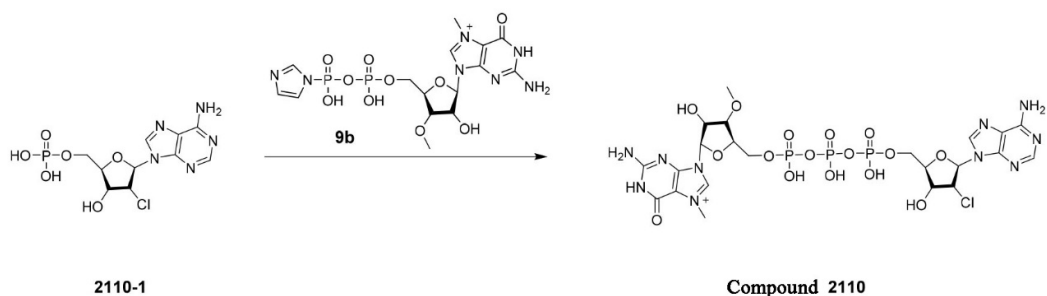
The compound **9a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and **2098-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2098**, which was an ammonium salt in the form of white powder (70 mg).

^1H NMR (400 MHz, D_2O) δ 8.42 (s, 1H), 8.18 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 6.15 (dq, J = 4.1, 0.7 Hz, 1H), 6.10 (dd, J = 2.9, 0.7 Hz, 1H), 6.01 (ddd, J = 2.7, 1.7, 0.8 Hz, 1H), 5.91 (d, J = 7.8 Hz, 1H), 5.02 - 4.88 (m, 1H), 4.77 (dddd, J = 5.9, 4.3, 1.5, 0.7 Hz, 1H), 4.55 (ddd, J = 5.3, 2.9, 0.6 Hz, 1H), 4.48 (qt, J = 3.3, 0.8 Hz, 1H), 4.36 (ddd, J = 7.3, 2.8, 0.6 Hz, 1H), 4.30 - 4.04 (m, 10H), 4.02 (s, 3H), 3.39 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ -0.95, -11.70, -22.75.

Example 83

Synthesis of Compound 2110



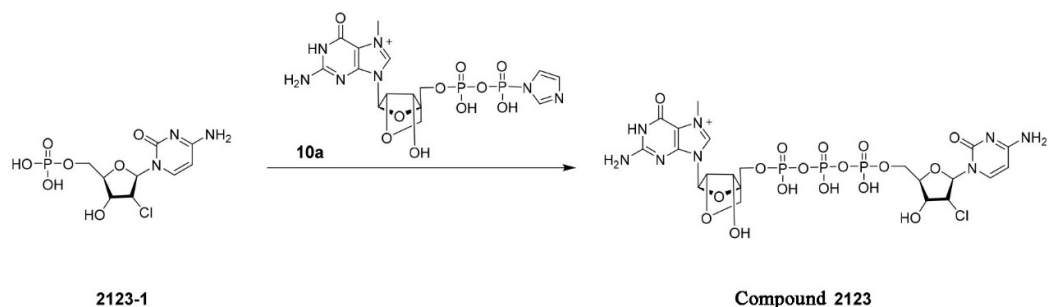
The compound **9b** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and **2110-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours. TLC monitoring showed that a product was generated. The reaction solution was added to a disodium EDTA solution (1.4 g, 80 mL of water was added) pre-cooled to 0°C, and the mixture was loaded onto a DEAE Sephadex column. The product was eluted by linear gradient elution using an eluent, i.e., 0 M to 1.0 M ammonium bicarbonate aqueous solution. Most of the water in the obtained fraction was concentrated in vacuo, and the remaining liquid was freeze-dried to obtain a product, compound **2110**, which was an ammonium salt in the form of white powder (70 mg).

^1H NMR (400 MHz, D_2O) δ 8.41 (s, 1H), 8.18 (s, 1H), 6.31 (dd, $J = 1.4, 0.8$ Hz, 1H), 6.13 (dd, $J = 2.5, 0.8$ Hz, 1H), 4.72 - 4.53 (m, 2H), 4.35 - 4.06 (m, 8H), 4.02 (s, 3H), 3.38 (s, 3H).

^{31}P NMR (162 MHz, D_2O) δ -10.24, -21.26.

Example 84

Synthesis of Compound 2123



The compound **10a** (200 mg) was added to 16 mL of an aqueous solution with a pH of 7.0, containing 0.2 mol/L N-methylmorpholine and 0.2 mol/L manganous chloride, and **2123-1** (200 mg) was added to the solution. The reaction solution was stirred at room temperature of 25°C for 16 hours.

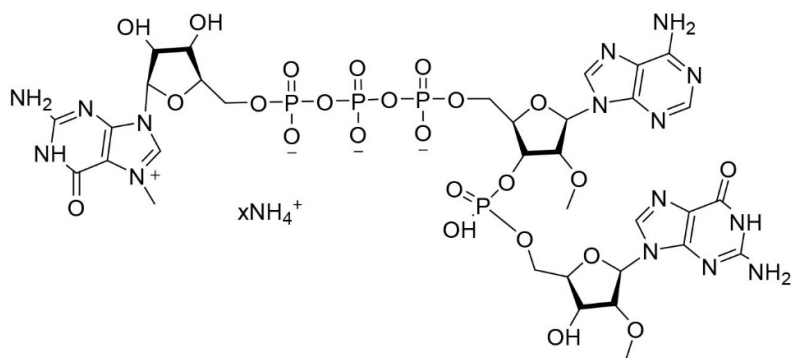
¹H NMR (400 MHz, D₂O) δ 7.62 (dd, J = 7.4, 1.8 Hz, 1H), 6.24 (dd, J = 2.7, 0.6 Hz, 1H), 6.12 (ddt, J = 2.6, 1.6, 0.7 Hz, 1H), 5.96 (d, J = 7.3 Hz, 1H), 4.64 (t, J = 2.8 Hz, 1H), 4.49 (d, J = 11.6 Hz, 1H), 4.42 (ddd, J = 5.3, 2.4, 0.7 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 4.33 (d, J = 2.8 Hz, 1H), 4.27 (td, J = 5.1, 0.7 Hz, 1H), 4.21 - 4.05 (m, 4H), 4.04 - 3.96 (m, 4H).

Example 85

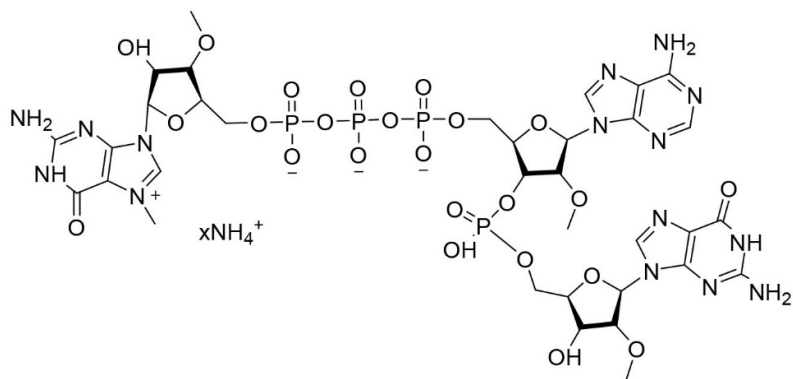
a) A plasmid was linearized and a DNA template was purified.

CN1C=NC2=C1C(=O)N(C)C2.[NH4+].[NH4+].[NH4+].[NH4+].[NH4+].Nc1ncnc2nc(N)nc12.Oc1oc(O)c(COP(=O)([O-])OP(=O)([O-])OP(=O)([O-])OC2OC3C(=O)N4C=NC(=O)N=C4N3O2)c1O

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Comparative Example 2



Comparative Example 3

The minimum reaction system for preparing mRNA used in the present invention is shown in *Table 1*.

Table 1 *In vitro* transcription system

Components	Dosage
T7 RNA polymerase	4 μ L (200 U)
RNase inhibitor	0.5 μ L (20 U)
Inorganic pyrophosphatase	1 μ L (0.5 U)
100mM ATP	1.5 μ L
100mM CTP	1.5 μ L
100mM GTP	1.5 μ L

100mM ψ TP	1.5 μ L
100mM Cap analog	1.5 μ L
10 $\times$ buffer	2 μ L
DNA Template	1 μ L
Water	4 μ L
Total	20 μ L

c) During the experiment, the above reagents were fully mixed and incubated at 37°C. After 4 hours, deoxyribonuclease (DNase) was added and incubated for 30 minutes to remove the DNA template. After digestion, LiCl solution was added, precooled and centrifuged at 1,6000 rpm for 15 minutes to remove the supernatant. 70% ethanol was added and centrifuged to remove the supernatant again, and then a certain amount of enzyme-free water was added for storage. The purified mRNA sample was then quantitatively detected using Nanodrop One, as shown in Table 2 below. The experimental results show that the product yield in mRNA synthesis by the halogenated cap analogs in the present invention is improved compared with the comparative examples.

Table 2 amount (mg) of final product obtained per 1 mL of mRNA synthesis reaction system

Compound number	8	68	168	173	433	458	468	33	Comparative Example 2
Product amount	4.7	5.8	5.6	5.2	4.9	4.8	5.3	5.3	4.2
Compound number	58	76	101	158	408	1982	2017	2037	2058
Product amount	5.5	5.4	5.3	4.9	5.7	5.8	5.8	5.5	4.6

d) After the purified mRNA was treated with enzyme cleavage, oligonucleotide fragments of different sizes were separated and identified by liquid chromatography-mass spectrometry (LC-MS), providing accurate molecular weight information of the enzyme-cleaved fragments. Combined with

the theoretical enzyme-cleaved molecular weight, and attribution, the capping efficiency of the sample can be obtained.

The capping efficiency of mRNA synthesized by the cap analogs of the present invention was between 90% and 98%. From the purified capped mRNA, the compounds of the present invention all showed good capping efficiency.

Example 86

Evaluation of Expression Efficiency of Green Fluorescent Protein mRNA with Different Capping Analogs in Different Cells

The present invention tested the expression efficiency of different capped green fluorescent protein mRNA in HEK293T and HepG2 cells. A green fluorescent protein GFP coding sequence was used as a DNA template, and the cap analogs of the present invention were used as materials for *in vitro* transcription of mRNA. Then, different mRNA products were transfected into cells, and finally fluorescent proteins in the cells were detected by flow cytometry.

- a) The different cells described above were plated at 2×10^5 cells (96-well plate).
- b) 300 μ L of mRNA buffer was mixed evenly with 6 μ g of RNA, and then 6 μ L of a transfection reagent (JetMESENG-ER) was added and mixed evenly. After standing for 10 min, the mixture was added to cells in each well, and a transfection medium (Opti-MEM) was supplemented to reach 2 mL/well. The cells were cultured at 37°C and 5% CO₂ for 6 h.
- c) After the transfection medium was replaced with a fresh complete medium and cultured for 24 h under the same conditions, the GFP fluorescence intensity was observed using a fluorescence microscope. The results are shown in FIG. 1, from which it can be clearly seen that the mRNA expression efficiency in the present invention is higher than that of the comparative examples.
- d) After the transfected cells were cultured for 24 h, the cells were treated and then detected by flow cytometry (CytoFLEX S series). The detected fluorescence intensity was proportional to the translation efficiency of the target protein. The results of the analysis are shown in FIGS. 2 and 3.

FIG. 2 is a fluorescence intensity analysis chart of mRNA coding green fluorescent protein and with different cap analogs in HEK293T cells, the horizontal axis is compound digital number of the cap analogs, and the vertical axis is a fluorescence intensity value detected by flow cytometer.

Compared with Comparative Examples 1 and 2, the fluorescence intensity values of the cap analogs in the present invention in HEK293T cells were more prominent. For example, an average fluorescence intensity value of a compound 468 was 1.5 times that of Comparative Example 2 and 1.6 times that of Comparative Example 1, and an average fluorescence intensity value of a compound 158 was 1.3 times that of Comparative Example 2 and 1.4 times that of Comparative Example 1.

FIG. 3 is a statistical graph of the fluorescence intensity of mRNA with different cap analogs in Hep G2 cells. In comparison, the efficiency of mRNA translation and protein expression of the cap analogs of the present invention in Hep G2 cells is higher than that of the comparative examples. The protein expression levels of fluorinated nucleoside dimer cap analogs such as a compound 1982 and fluorinated nucleoside tetramer cap analogs such as 2057 were also significantly improved.

Example 87

Test of Expression Efficiency of mRNA Synthesized by Different Cap Analogs in Mice

a) The cap analogs of the present invention were used to prepare mRNA of encoding luciferase, and the obtained mRNA was diluted into a citric acid buffer at pH 4.0. Cationic lipids DLin-MC3-DMA, DSPC, cholesterol, and PEG lipids (DMG-PEG2000) were dissolved in ethanol at a molar ratio of 50:10:38.5:1.5.

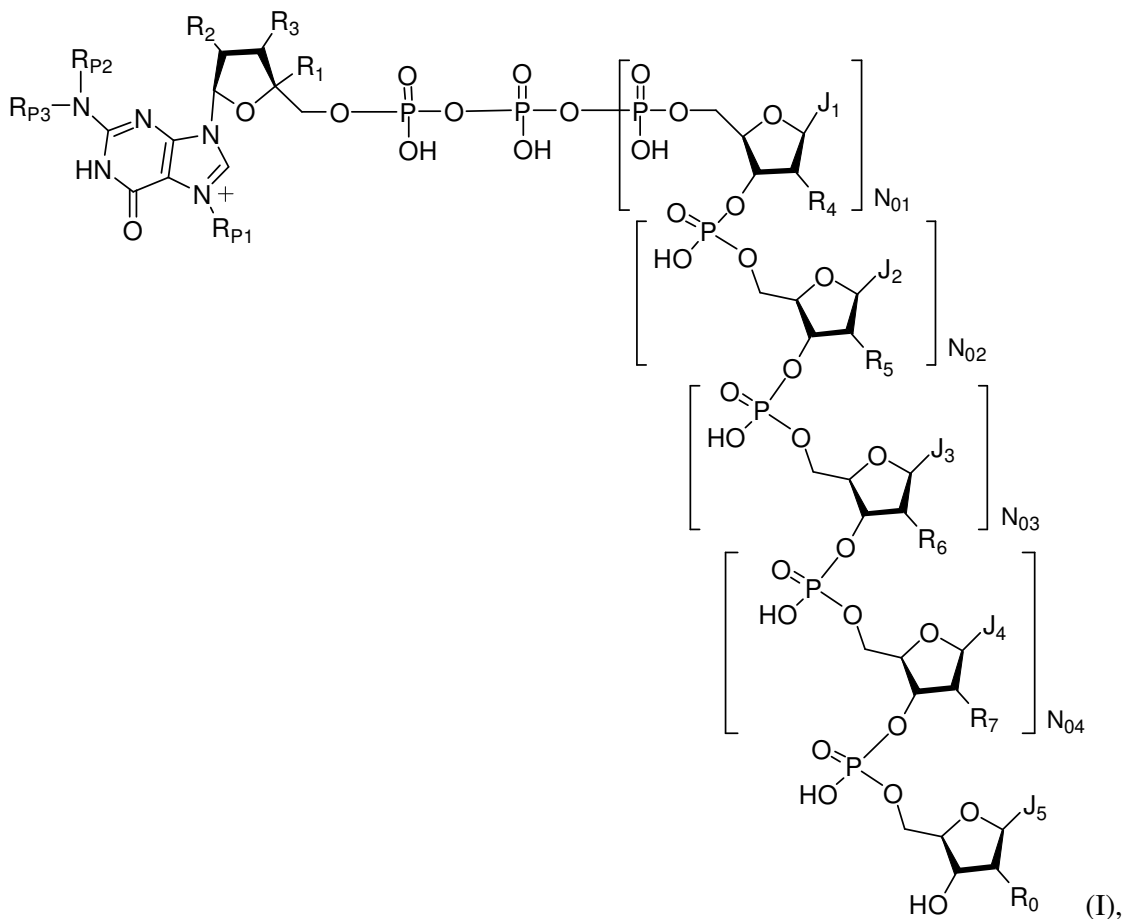
b) Two 5 mL syringes were filled with 3 mL mRNA buffer and 1 mL lipid solution, respectively and then loaded on a microfluidic injection pump, and the flow rate of the injection pump was set. The collected product was placed in a dialysis bag and ultrafiltered and concentrated to an ideal concentration. Then, lipid nanoparticles were filtered through a 0.22 μ m sterile filter and stored for use.

c) Luciferase mRNA-lipid nanoparticles containing 5 μ g of mRNA were injected into female Balb/c mice aged 6 to 8 weeks via tail vein injection. Each kind of Luciferase mRNA-lipid nanoparticle was injected into 5 mice for parallel experiments. A luciferase substrate was injected 24 hours later and detected using a PerkinElmer small animal imaging system. The luminescence intensity was proportional to the translation efficiency of the effective target protein. The relative fluorescence intensity of mRNA in different organs of mice was shown in FIG. 4. The expression efficiency of mRNA with different halogenated caps analog of the present invention in different

organs was significantly higher than that of the comparative examples.

CLAIMS

1. A compound for capping the 5' end of a nucleic acid, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound has a structure of Formula (I):



wherein

R_0 is any one selected from the group consisting of F, Cl, Br and I,

R_1 is a group selected from the group consisting of -H, -OH, C_{1-4} alkyl and C_{1-4} alkoxy,

R_2 is any one selected from the group consisting of -H, -OH, C_{1-6} alkyl and C_{1-6} alkoxy,

optionally, R_1 and R_2 are connected to form a ring by a chemical bond, and $-R_1-R_2-$ is any one of $-(CH_2)_q-O-$, $-O-(CH_2)_q-$ and $-(CH_2)_m-O-(CH_2)_n-$, wherein q , m , and n are each independently 1, 2 or 3,

R_3 is any one of H, -OH, -SH, $-N_3$, $-NH_2$, halogen, -CN, C_{1-6} alkoxy, $-O(CH_2)_sCN$, $-SR_{3a}$, $-O(CH_2)_pR_{3b}$, $OCOR_{3c}$, $O(CH_2)_pCOR_{3c}$, $-O(CH_2)_tSH$, $-O(CH_2)_pOH$, $-O(CH_2)_pN_3$, and -

O(CH₂)_pNH₂, wherein t, p, and s are each independently any integer from 1 to 6; R_{3a} is C₁₋₆ alkyl; R_{3b} is C₆₋₁₂ aryl optionally substituted with one or more R_{3d}, or C₅₋₁₂ heteroaryl optionally substituted with one or more R_{3d}; R_{3c} is C₁₋₁₀ alkyl optionally substituted with one or more R_{3d}, C₁₋₁₀ alkenyl optionally substituted with one or more R_{3d}, C₅₋₁₂ cycloalkyl optionally substituted with one or more R_{3d}, or C₅₋₁₂ cycloalkenyl optionally substituted with one or more R_{3d}; wherein R₃ is optionally substituted with one or more R_{3e}; and R_{3d} and R_{3e} are selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, cyano, amino, nitro, -OH, and -SH,

R₄, R₅, R₆, and R₇ are each independently any one selected from the group consisting of -H, -OH, -OCH₃, halogen, -CN, and -SH,

N₀₁, N₀₂, N₀₃, and N₀₄ are each independently selected from 0 or 1,

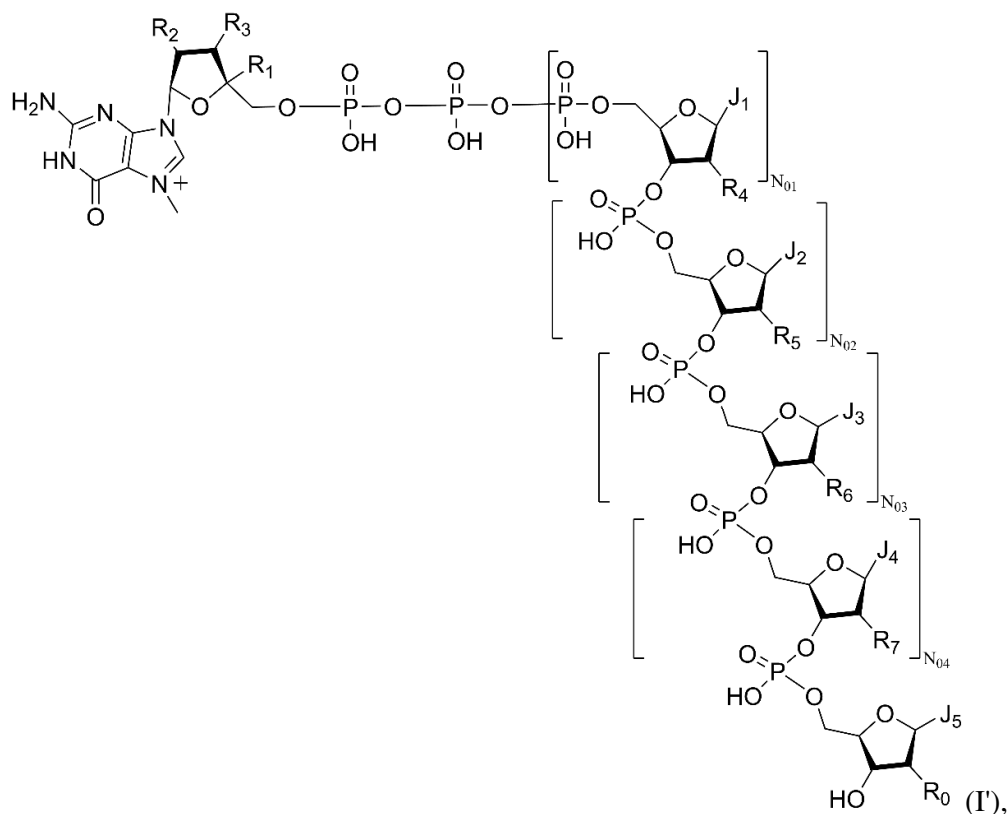
J₁, J₂, J₃, J₄, and J₅ are each independently selected from natural or modified pyrimidine nucleotide bases, or natural or modified purine nucleotide bases,

R_{P1} is C₁ to C₆ alkyl, preferably C₁ to C₃ alkyl, which is optionally substituted with -SH, -N₃, C₂ to C₆ alkenyl or C₂ to C₆ alkynyl,

R_{P2} and R_{P3} are each independently selected from the group consisting of H, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, a PEG group, COR_{P4}, and SO₂R_{P4}, wherein these groups are each optionally substituted with -CN, -N₃, -SH, or alkynyl, R_{P4} is selected from the group consisting of H and C₁ to C₆ alkyl, and R_{P2} and R_{P3} are optionally connected to form a ring,

with the proviso that when N₀₁, N₀₂, N₀₃, and N₀₄ are all 0, J₅ is a guanine base, and when R₂ is -OH, R₃ is not a methoxy group.

2. The compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof according to claim 1, the compound having a structure of Formula (I):



wherein, each group in Formula (I') has a meaning the same as that described in claim 1.

3. The compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof according to claim 1 or 2, wherein

at least one of J₁, J₂, J₃, J₄, and J₅ is a modified nucleotide base, preferably a modified purine nucleotide base, more preferably a methyl-modified purine nucleotide base, and still more preferably 6-N-methyladenine.

4. The compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof according to any one of claims 1 to 3, wherein

R₃ is any one of -H, -OH, -SH, -N₃, -NH₂, halogen, -CN, C₁₋₆ alkoxy, -O(CH₂)_pCN, -SR_{3a}, -O(CH₂)_pR_{3b}, OCOR_{3c}, O(CH₂)_pCOR_{3c}, -O(CH₂)_pSH, -O(CH₂)_pOH, -O(CH₂)_pN₃, and -O(CH₂)_pNH₂, wherein t, p, and s are each independently any integer from 1 to 6, preferably 1 to 4; R_{3a} is C₁₋₄ alkyl; R_{3b} is C₆₋₁₀ aryl optionally substituted with one or more R_{3d}, or C₅₋₁₀ heteroaryl

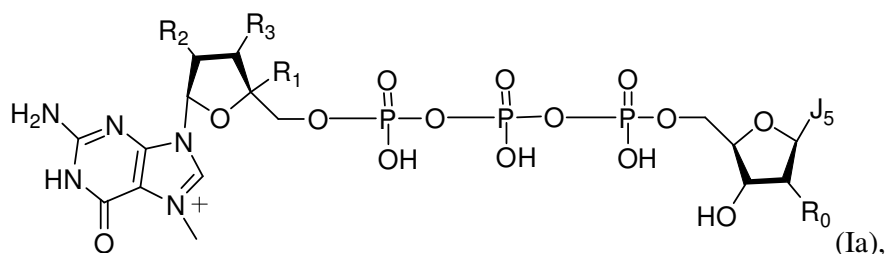
optionally substituted with one or more R_{3d} ; R_{3c} is C_{5-10} cycloalkyl optionally substituted with one or more R_{3d} , or C_{5-10} cycloalkenyl optionally substituted with one or more R_{3d} , wherein R_3 is optionally substituted with one or more R_{3e} ; and R_{3d} and R_{3e} are selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, halogen, cyano, amino, nitro, -OH, and -SH,

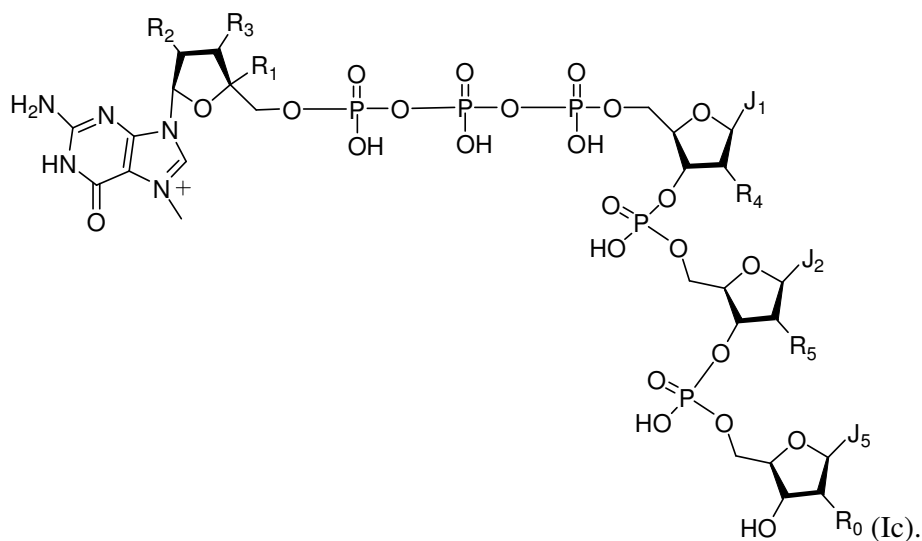
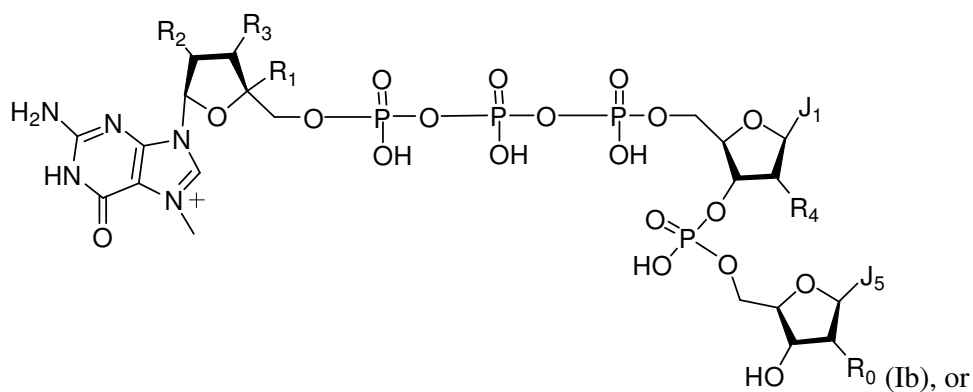
preferably, R_3 is any one of -H, -OH, -SH, -N₃, -NH₂, halogen, -CN, C_{1-3} alkoxy, -O(CH₂)_pCN, -SR_{3a}, -O(CH₂)_pR_{3b}, OCOR_{3c}, O(CH₂)_pCOR_{3c}, -O(CH₂)_pSH, -O(CH₂)_pOH, -O(CH₂)_pN₃, and -O(CH₂)_pNH₂, wherein p and s are each independently any integer from 1 to 3, t is any integer from 1 to 4, R_{3a} is methyl or ethyl, R_{3b} is C_{5-10} heteroaryl optionally substituted with one or two R_{3d} , R_{3c} is C_{5-10} cycloalkyl optionally substituted with one or two R_{3d} , or C_{5-10} cycloalkenyl optionally substituted with one or two R_{3d} , wherein R_3 is optionally substituted with one or more R_{3e} , and R_{3d} and R_{3e} are selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, halogen, cyano, amino, nitro, -OH, and -SH,

more preferably, R_{3b} is C_5 or C_6 heteroaryl optionally substituted with C_{1-4} alkyl, for example, tetrazinyl optionally substituted with C_{1-4} alkyl, and R_{3c} is C_{5-10} cycloalkenyl optionally substituted with C_{1-4} alkyl, halogen, cyano, amino, or nitro, for example, norbornenyl or cyclooctenyl optionally substituted with C_{1-4} alkyl, halogen, cyano, amino, or nitro, and for example, unsubstituted norbornenyl or cyclooctenyl.

5. The compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof according to any one of claims 1 to 4, wherein

the compound has a structure of Formula (Ia), Formula (Ib), or Formula (Ic):



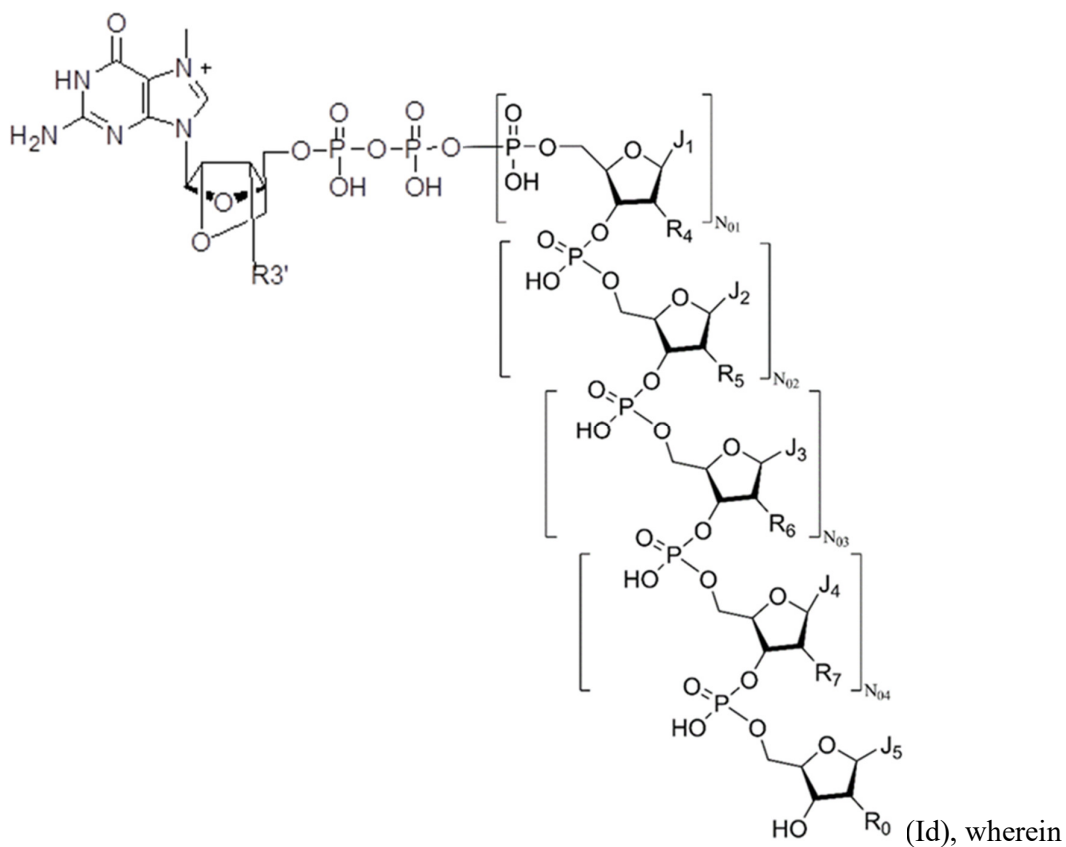


6. The compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof according to claim 5, wherein

R_0 is -F or -Cl, and/or

R_4 and R_5 are each independently any one selected from the group consisting of H, OH, OCH_3 , F, Cl, -CN, and -SH, and preferably any one selected from the group consisting of H, OH, OCH_3 , and F.

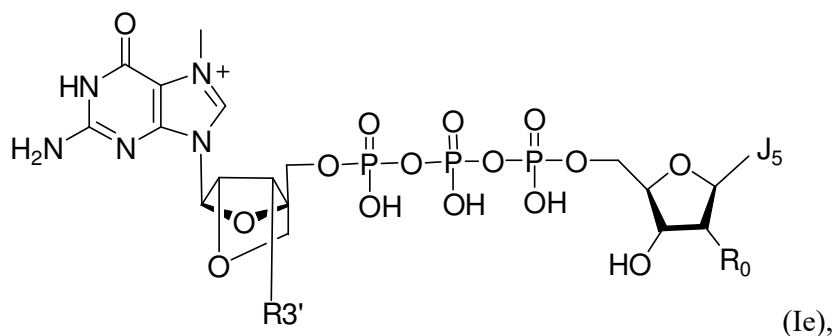
7. The compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof according to any one of claims 1 to 4, wherein the compound having a structure of Formula (Id):

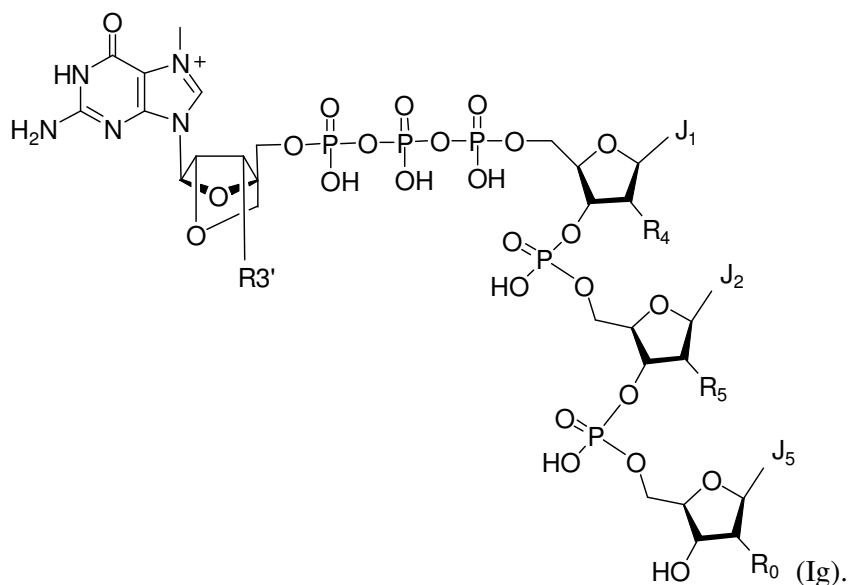


R_3' has a meaning the same as that of R_3 defined in claim 1 or 4, and
the remaining groups have the meanings the same as those described in claims 1 to 4.

8. The compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof according to claim 7, wherein

the compound has a structure of Formula (Ie), Formula (If), or Formula (Ig):





R₄ and R₅ are each independently any one selected from the group consisting of H, OH, OCH₃, F, Cl, -CN, and -SH, and preferably any one selected from the group consisting of H, OH, OCH₃, and F.

the compound has one of the structures shown in Table 1 of the description.

11. The compound or a solvate or stereoisomer thereof according to any one of claims 1 to 10 wherein

the compound is present in the form of a pharmaceutically acceptable salt, and preferably in the form of a triethylamine salt, a sodium salt, a potassium salt, an ammonium salt, or tris(hydroxymethyl)aminomethane hydrochloride.

12. Use of the compound according to any one of claims 1 to 11 as an *in vitro* co-transcriptional RNA-capping reagent.

13. An RNA molecule, comprising:

the compound according to any one of claims 1 to 11 as a cap structure or a cap structure fragment.

14. A pharmaceutical composition, comprising:

the RNA molecule according to claim 13; and
a pharmaceutically acceptable carrier.

15. A method for synthesizing an RNA molecule, the method comprising:

incubating the compound according to any one of claims 1 to 11 with a polynucleotide template in order to perform a template-based transcription.

16. A transcriptional RNA-capping reaction system, comprising:

a polynucleotide template;
the compound according to any one of claims 1 to 11;
NTPs; and
an RNA polymerase.