

一种用于核酸的 5'端加帽的含卤化合物及其应用

技术领域

本发明涉及生物技术领域和合成化学领域，具体涉及一类核苷类化合物，具体
5 涉及一种用于核酸（RNA）的 5'端加帽的含卤化合物及其应用。

背景技术

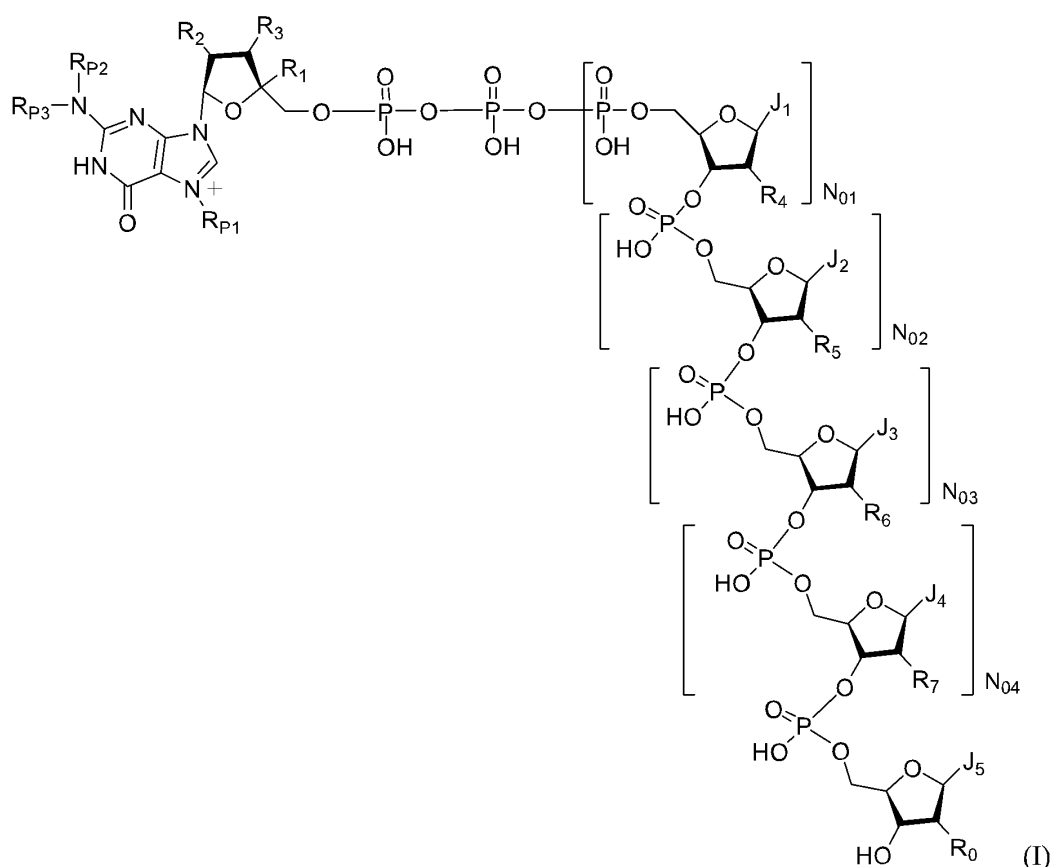
近年来，随着全球新冠疫情形势变化，信使 RNA（mRNA）技术与其疫苗药物
实现了从实验室到临床应用的突破。随着新冠疫苗的空前成功，市场对于 mRNA 技
术的预期大幅高涨。mRNA 技术应用场景不仅仅是在新冠这样的传染病领域，在预
10 防性疫苗、治疗性药物，甚至包括细胞编程和再生疗法等方面发展潜力巨大。

帽结构是细胞中广泛存在的一种 RNA 修饰，其在维持 mRNA 的稳定性和调控
蛋白翻译等活动中发挥关键作用。目前很多研究都致力于对帽结构做进一步的化学
修饰，以进一步增强 mRNA 的翻译效率的同时降低其免疫原性。

发明内容

15 本发明提供了一种用于核酸（RNA）的 5'端加帽的含卤化合物、其药学上可接
受的盐、其溶剂化物和其立体异构体，及其应用。该类化合物在一端的核苷上具有
各种修饰或未修饰的 7-甲基鸟嘌呤碱基，在另一端的核苷 2'位上具有卤素取代基。
使用该类化合物对 mRNA 的 5'端加帽反应具有较高的加帽率，并且具有较好的体外
转录效率，同时，在细胞水平和活体上如小鼠上都有较高的翻译表达效率。

20 本发明提供了一种用于核酸的 5'端加帽的含卤化合物，或其药学上可接受的
盐、或溶剂化物、或其立体异构体，所述化合物具有式(I)的结构：



其中：

R₀选自F、Cl、Br、I中的任意一种；

R₁为选自-H，-OH，C₁₋₄烷基和C₁₋₄烷氧基的基团；

5 R₂为选自-H，-OH，C₁₋₆烷基和C₁₋₆烷氧基中的任意一种；

任选地 R₁与R₂通过化学键连接成环，且-R₁-R₂-为-(CH₂)_q-O-、-O-(CH₂)_q-和-(CH₂)_m-O-(CH₂)_n-中的任意一种，其中q、m、n各自独立地为1、2或3；

R₃为H，-OH，-SH，-N₃，-NH₂，卤素，-CN，C₁₋₆烷氧基，-O(CH₂)_sCN，-SR_{3a}，-O(CH₂)_pR_{3b}，OCOR_{3c}，O(CH₂)_pCOR_{3c}，-O(CH₂)_tSH，-O(CH₂)_pOH，-O(CH₂)_pN₃，-O(CH₂)_pNH₂中的任意一种，其中t、p和s各自独立地为1-6的任意一个整数，R_{3a}为C₁₋₆烷基，R_{3b}为任选被一个或多个R_{3d}取代的C₆₋₁₂芳基或任选被一个或多个R_{3d}取代的C₅₋₁₂杂芳基，R_{3c}为任选被一个或多个R_{3d}取代的C₁₋₁₀烷基，任选被一个或多个R_{3d}取代的C₁₋₁₀烯基，任选被一个或多个R_{3d}取代的C₅₋₁₂环烷基或任选被一个或多个R_{3d}取代的C₅₋₁₂环烯基，其中R₃任选被一个或多个R_{3c}取代，R_{3d}和R_{3c}选自自由

15 烷基、烯基、烷氧基、卤素、氰基、氨基、硝基、-OH、-SH所组成的组；

R₄、R₅、R₆、R₇ 各自独立地选自 -H、-OH、-OCH₃、卤素、-CN、-SH 中的任意一种；

N₀₁、N₀₂、N₀₃、N₀₄ 各自独立地选自 0 或 1；

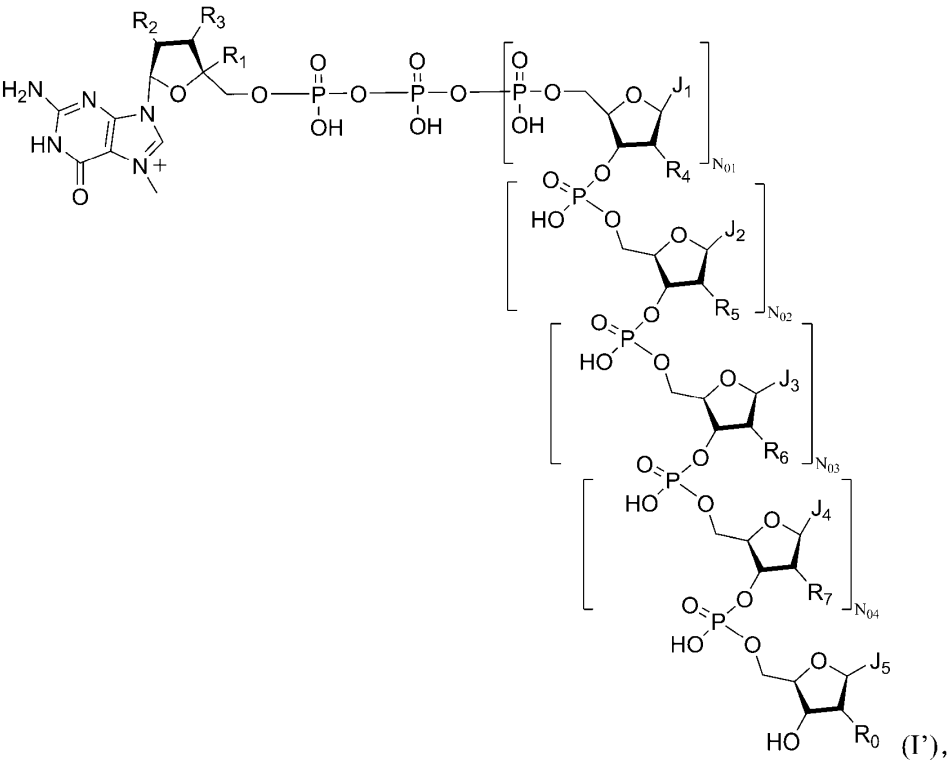
J₁、J₂、J₃、J₄、J₅ 各自独立地选自天然或修饰的嘧啶核苷酸碱基、天然或修饰的嘌呤核苷酸碱基；

R_{P1} 为 C₁-C₆ 烷基，优选 C₁-C₃ 烷基，该烷基上任选被 -SH、-N₃，C₂-C₆ 烯基或 C₂-C₆ 炔基取代；

R_{P2} 和 R_{P3} 各自独立地选自 H、C₁-C₆ 烷基、C₂-C₆ 烯基、C₂-C₆ 炔基、环烷基、环烯基、环炔基、PEG 基、COR_{P4}、SO₂R_{P4}，所述基团任选被 -CN、-N₃、-SH、炔基取代，R_{P4} 选自 H 和 C₁-C₆ 烷基；R_{P2} 和 R_{P3} 任选连接成环；

前提是，当 N₀₁、N₀₂、N₀₃、N₀₄ 均为 0，J₅ 是鸟嘌呤碱基，R₂ 为 -OH 时，R₃ 不为甲氧基。

在优选实施方式中，本发明的化合物具有式(I')的结构：



其中，式(I')中的各基团具有如上关于式(I)所述的相同的含义。

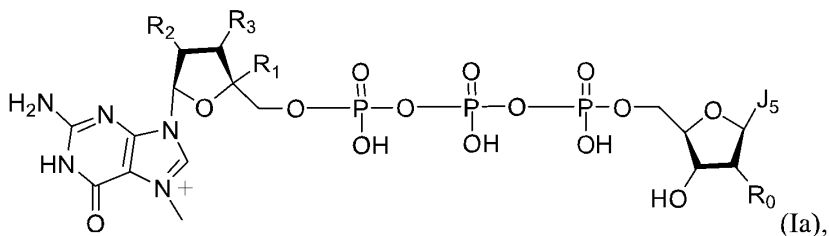
在优选实施方式中, J₁、J₂、J₃、J₄、J₅ 中至少一个是修饰的核苷酸碱基, 优选修饰的嘌呤核苷酸碱基, 更优选甲基修饰的嘌呤核苷酸碱基, 更优选 6-N-甲基腺嘌呤。

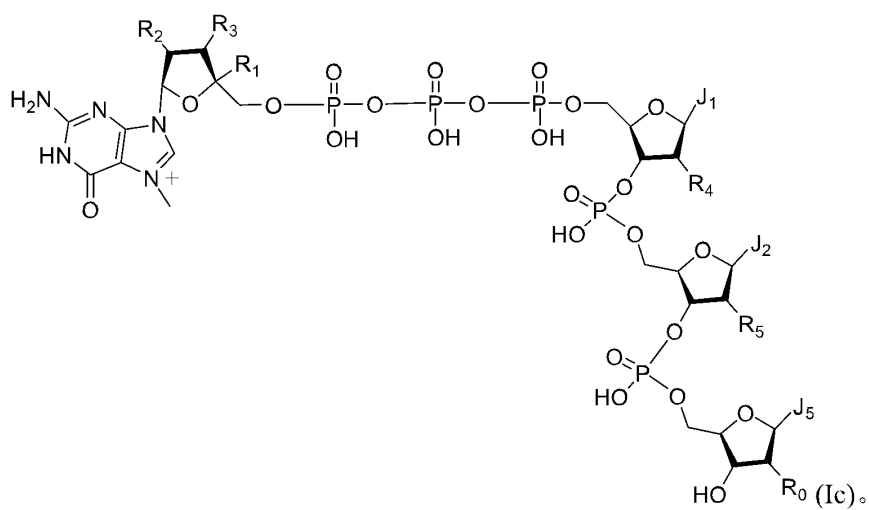
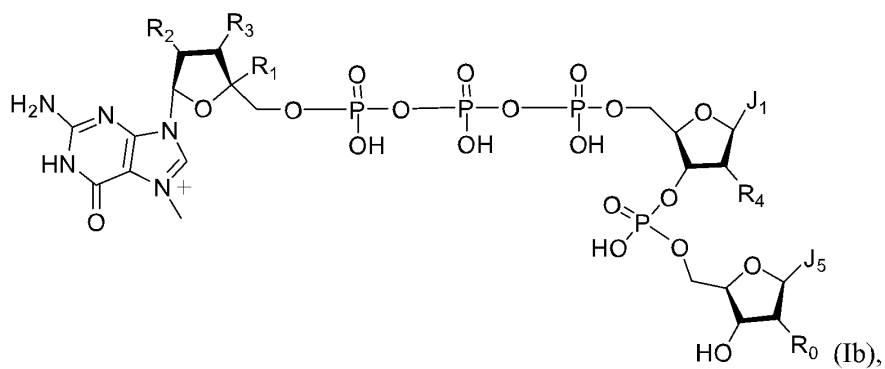
在优选实施方式中, R₃ 为 -H, -OH, -SH, -N₃, -NH₂, 卤素, -CN, C₁₋₆ 烷氧基, -O(CH₂)_pCN, -SR_{3a}, -O(CH₂)_pR_{3b}, OCOR_{3c}, O(CH₂)_pCOR_{3c}, -O(CH₂)_pSH, -O(CH₂)_pOH, -O(CH₂)_pN₃, -O(CH₂)_pNH₂ 中的任意一种, 其中 t、p 和 s 各自独立地为 1-6, 优选为 1-4 的任意一个整数, R_{3a} 为 C₁₋₄ 烷基, R_{3b} 为任选被一个或多个 R_{3d} 取代的 C₆₋₁₀ 芳基或任选被一个或多个 R_{3d} 取代的 C₅₋₁₀ 杂芳基, R_{3c} 为任选被一个或多个 R_{3d} 取代的 C₅₋₁₀ 环烷基或任选被一个或多个 R_{3d} 取代的 C₅₋₁₀ 环烯基, 其中 R₃ 任选被一个或多个 R_{3e} 取代, R_{3d} 和 R_{3e} 选自自由 C₁₋₄ 烷基、C₂₋₄ 烯基、C₁₋₄ 烷氧基、卤素、氰基、氨基、硝基、-OH、-SH 所组成的组。

在另外的优选实施方式中, R, R₃ 为 -H, -OH, -SH, -N₃, -NH₂, 卤素, -CN, C₁₋₃ 烷氧基, -O(CH₂)_pCN, -SR_{3a}, -O(CH₂)_pR_{3b}, OCOR_{3c}, O(CH₂)_pCOR_{3c}, -O(CH₂)_pSH, -O(CH₂)_pOH, -O(CH₂)_pN₃, -O(CH₂)_pNH₂ 中的任意一种, 其中 p 和 s 各自独立地为 1-3 的任意一个整数, t 为 1-4 的任意一个整数, R_{3a} 为甲基或乙基, R_{3b} 为任选被一个或两个 R_{3d} 取代的 C₅₋₁₀ 杂芳基, R_{3c} 为任选被一个或两个 R_{3d} 取代的 C₅₋₁₀ 环烷基或任选被一个或两个 R_{3d} 取代的 C₅₋₁₀ 环烯基, 其中 R₃ 任选被一个或多个 R_{3e} 取代, R_{3d} 和 R_{3e} 选自自由 C₁₋₄ 烷基、C₂₋₄ 烯基、C₁₋₄ 烷氧基、卤素、氰基、氨基、硝基、-OH、-SH 所组成的组。

在另外的优选实施方式中, R_{3b} 为任选被 C₁₋₄ 烷基取代的 C₅ 或 C₆ 杂芳基, 例如任选被 C₁₋₄ 烷基取代的四嗪基, R_{3c} 为任选被 C₁₋₄ 烷基、卤素、氰基、氨基、硝基取代的 C₅₋₁₀ 环烯基, 例如任选被 C₁₋₄ 烷基、卤素、氰基、氨基、硝基取代的降冰片烯基或环辛烯基, 例如未被取代的降冰片烯基或环辛烯基。

在优选的实施方式中, 所述化合物具有式(Ia)、式(Ib)或式(Ic)的结构:



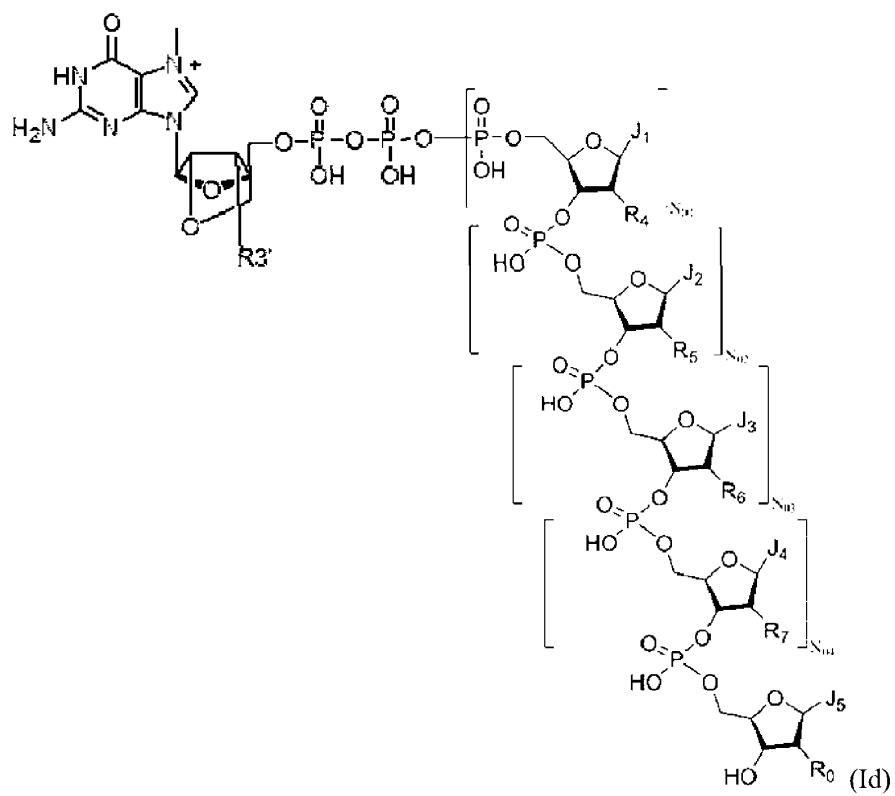


在优选实施方式中， R_0 为 -F 或 -Cl，和/或

R_4 和 R_5 各自独立地选自 H、OH、 OCH_3 、F、Cl、-CN、-SH 中的任意一种，优

5 选 H、OH、 OCH_3 、F 中的任意一种。

在另外的优选实施方式中，所述化合物具有式(Id)的结构：

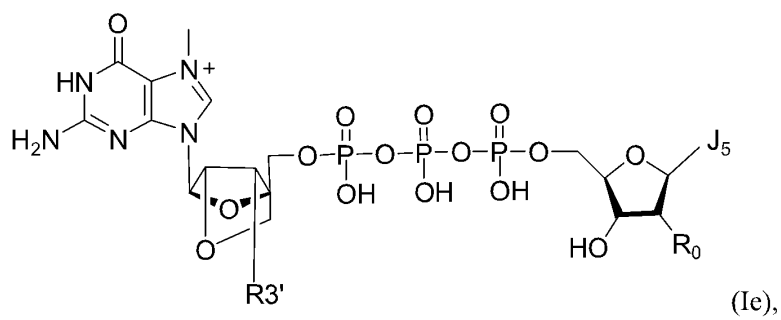


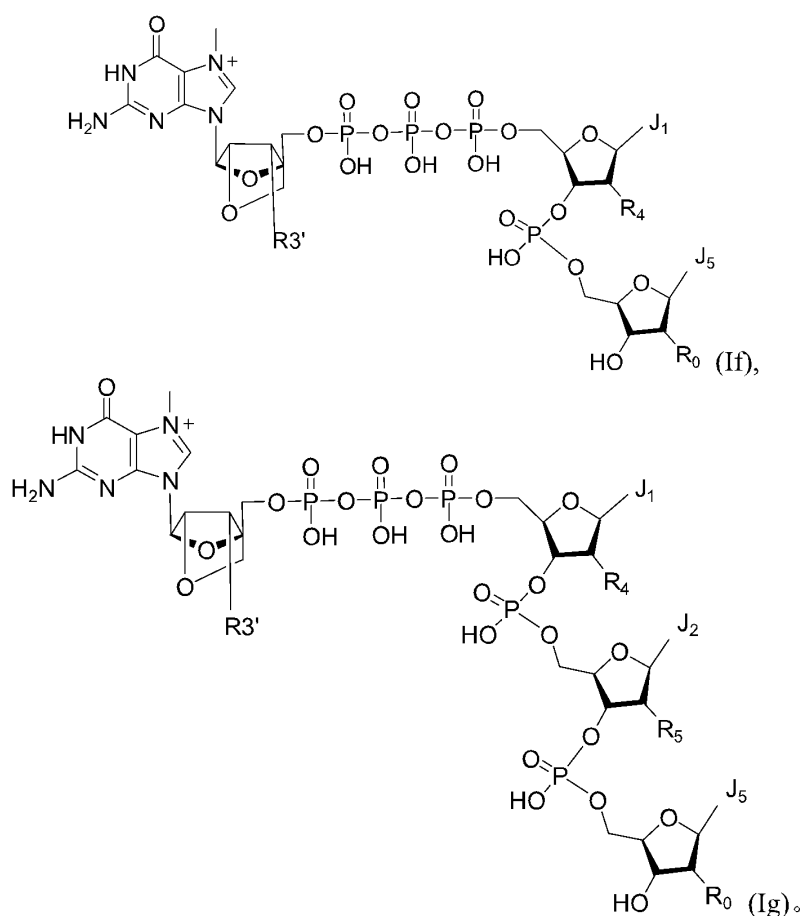
其中,

R_3' 具有如上关于 R_3 限定的含义;

其余基团具有如上所述的含义。

- 5 在优选实施方式中, 所述化合物具有式(Ie)、式(If)或式(Ig)的结构:





在优选实施方式中， R_0 为 -F 或 -Cl，和/或

R_4 和 R_5 各自独立地选自 H、OH、OCH₃、F、Cl、-CN、-SH 中的任意一种，优
5 选 H、OH、OCH₃、F 中的任意一种。

在最优选的实施方式中，所述化合物具有如表 1 中所示的结构之一。

在优选的实施方式中，本发明的化合物以药学上可接受的盐的形式存在，优选
以三乙胺盐，钠盐，钾盐，铵盐或三羟甲基氨基甲烷盐酸盐的形式存在。

本发明的另一方面涉及如上所述的化合物作为体外共转录 RNA 加帽试剂的应
10 用。

本发明的又一方面涉及一种 RNA 分子，其包含如上所述的化合物作为帽结构或
帽结构片段。

本发明的再一方面涉及一种药物组合物，其包含如上所述的 RNA 分子，以及药
学上可接受的载体。

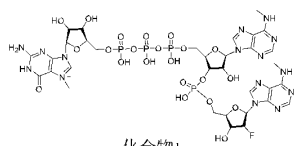
15 本发明还涉及一种合成 RNA 分子的方法，其包括以下步骤：将如上所述的化合

物，与多核苷酸模板共孵育，进行模板转录。

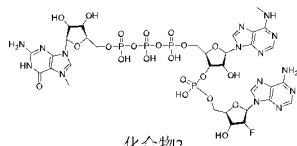
本发明另外涉及一种加帽 RNA 转录反应系统，其包括：多核苷酸模板，如上所述的化合物，NTPs 和 RNA 聚合酶。

根据本发明的一些具体实施方案，所述化合物（或帽类似物）具有以下表 1 中
5 所示的结构之一：

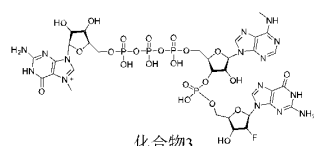
表 1：



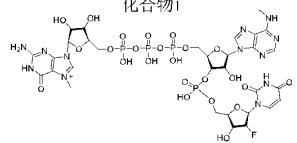
化合物1



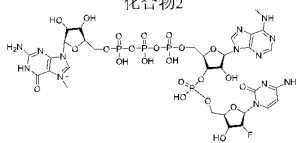
化合物2



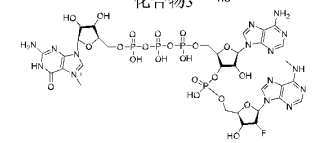
化合物3



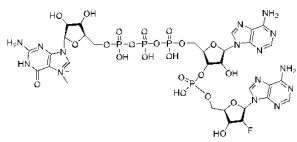
化合物4



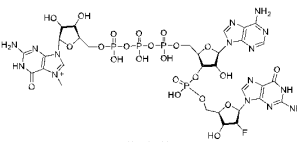
化合物5



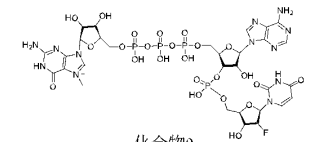
化合物6



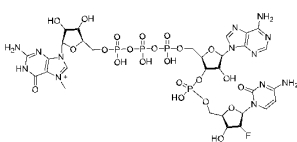
化合物7



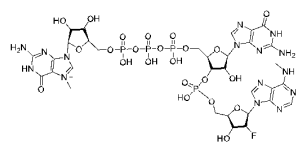
化合物8



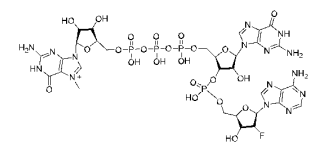
化合物9



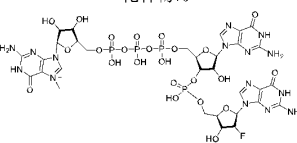
化合物10



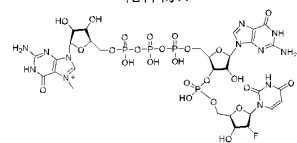
化合物11



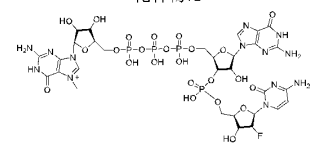
化合物12



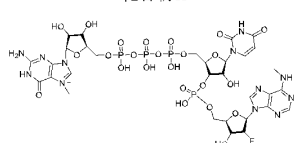
化合物13



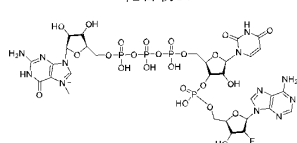
化合物14



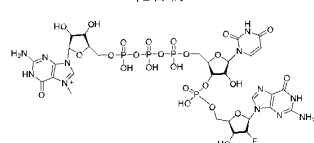
化合物15



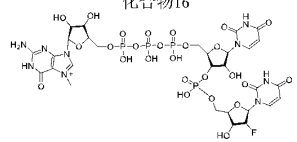
化合物16



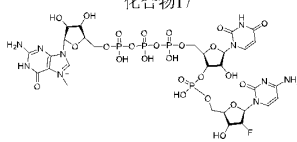
化合物17



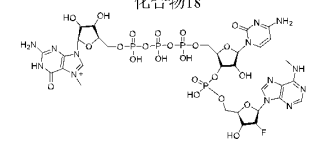
化合物18



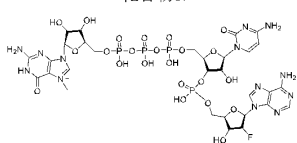
化合物19



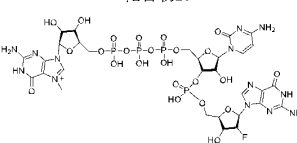
化合物20



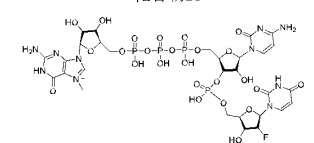
化合物21



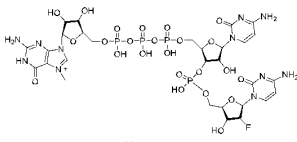
化合物22



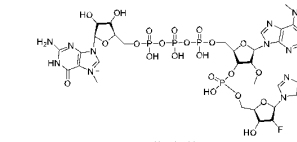
化合物23



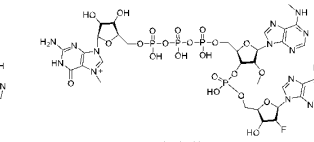
化合物24



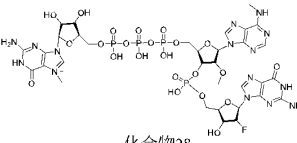
化合物25



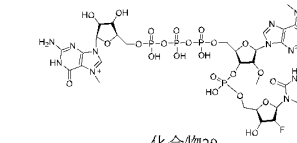
化合物26



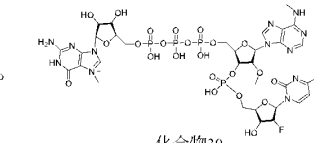
化合物27



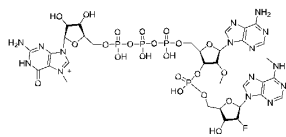
化合物28



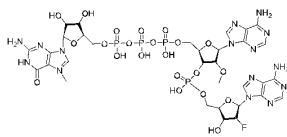
化合物29



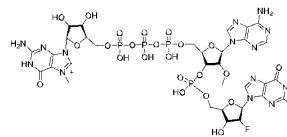
化合物30



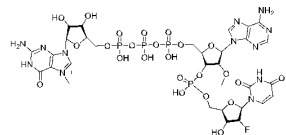
化合物31



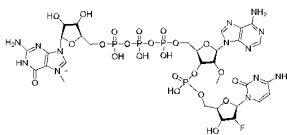
化合物32



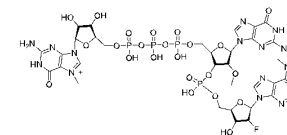
化合物33



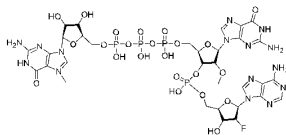
化合物34



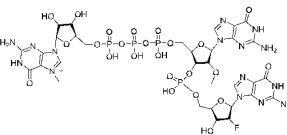
化合物35



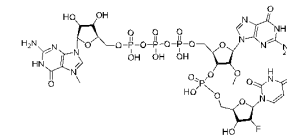
化合物36



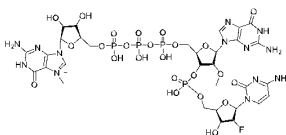
化合物37



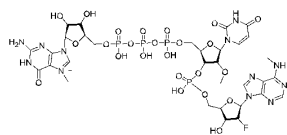
化合物38



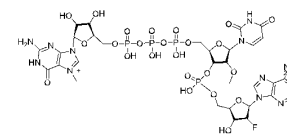
化合物39



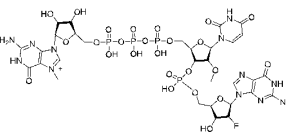
化合物40



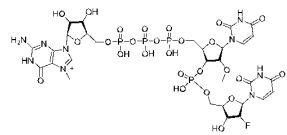
化合物41



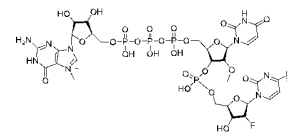
化合物42



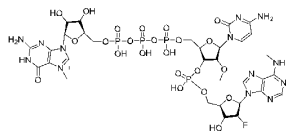
化合物43



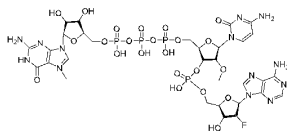
化合物44



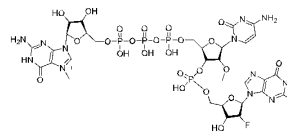
化合物45



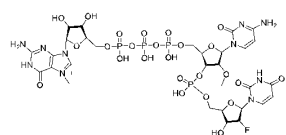
化合物46



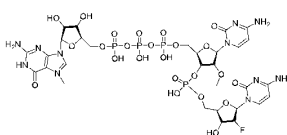
化合物47



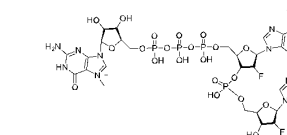
化合物48



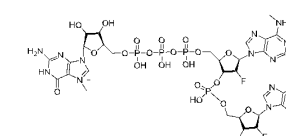
化合物49



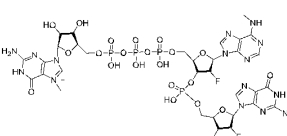
化合物50



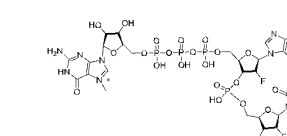
化合物51



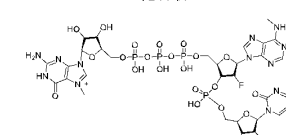
化合物52



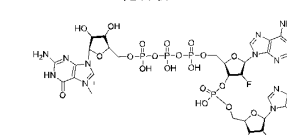
化合物53



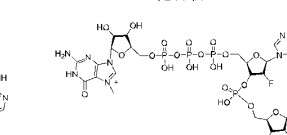
化合物54



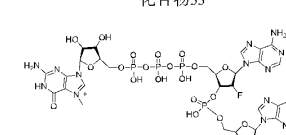
化合物55



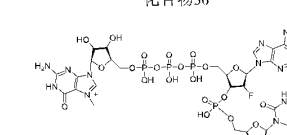
化合物56



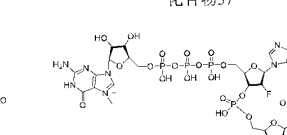
化合物57



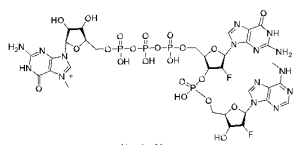
化合物58



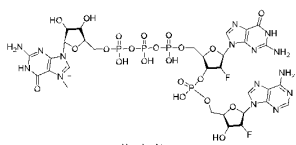
化合物59



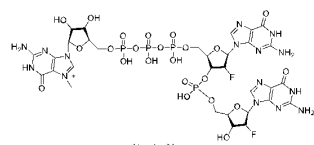
化合物60



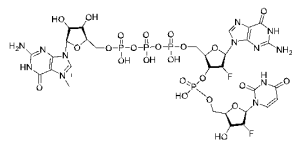
化合物61



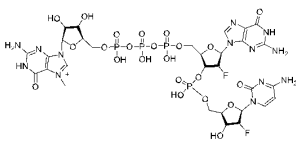
化合物62



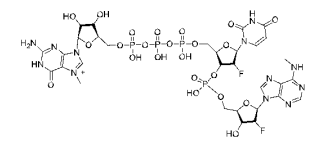
化合物63



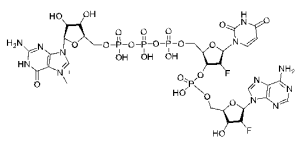
化合物64



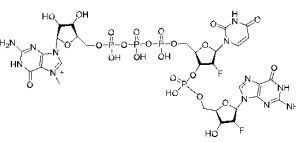
化合物65



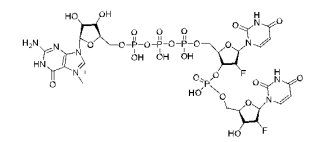
化合物66



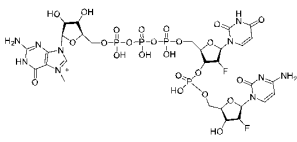
化合物67



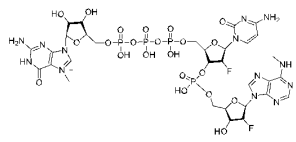
化合物68



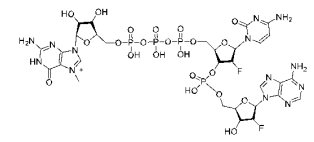
化合物69



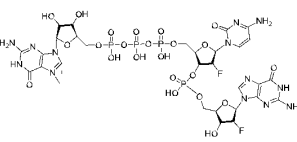
化合物70



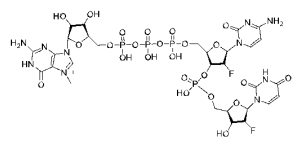
化合物71



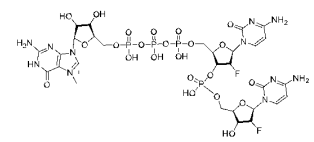
化合物72



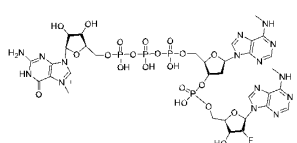
化合物73



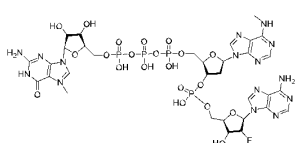
化合物74



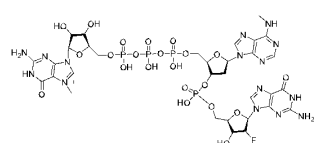
化合物75



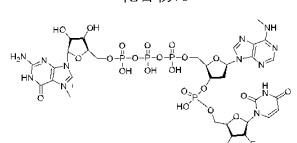
化合物76



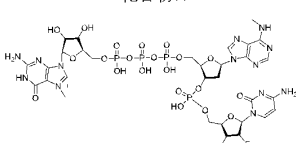
化合物77



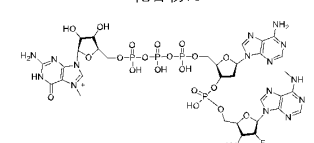
化合物78



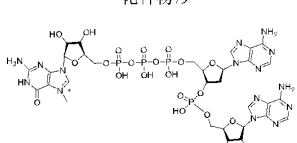
化合物79



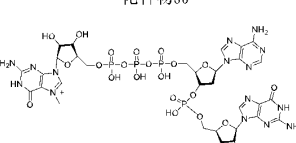
化合物80



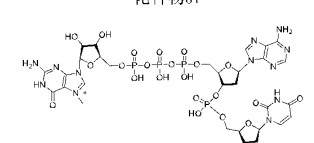
化合物81



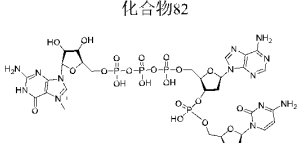
化合物82



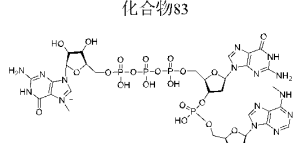
化合物83



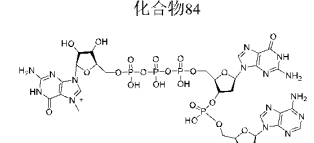
化合物84



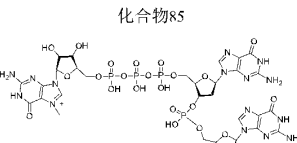
化合物85



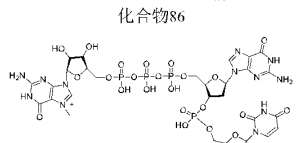
化合物86



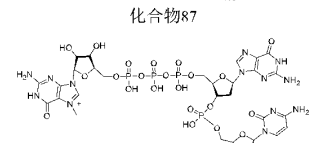
化合物87



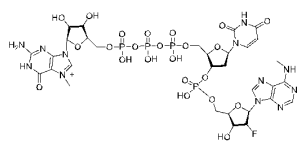
化合物88



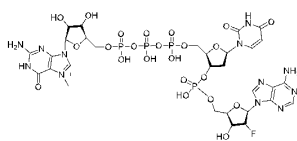
化合物89



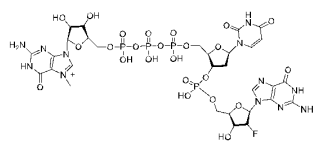
化合物90



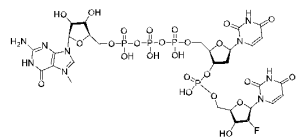
化合物91



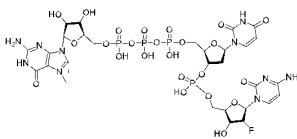
化合物92



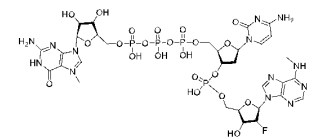
化合物93



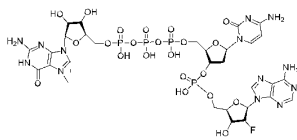
化合物94



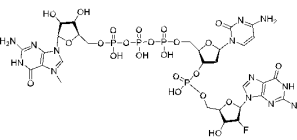
化合物95



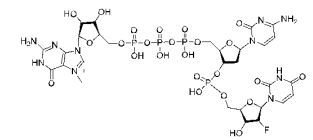
化合物96



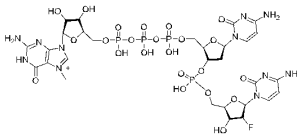
化合物97



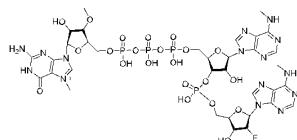
化合物98



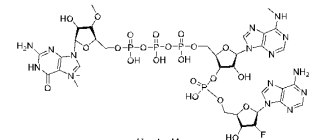
化合物99



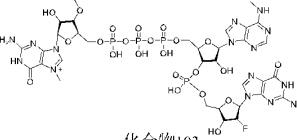
化合物100



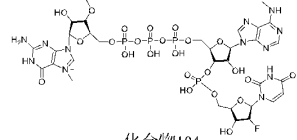
化合物101



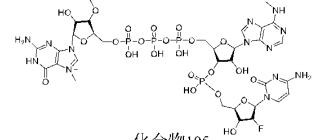
化合物102



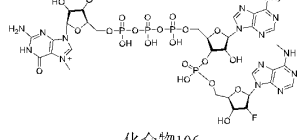
化合物103



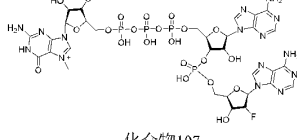
化合物104



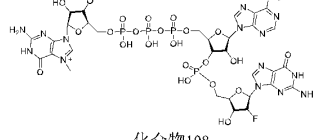
化合物105



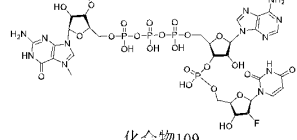
化合物106



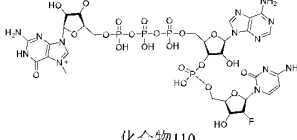
化合物107



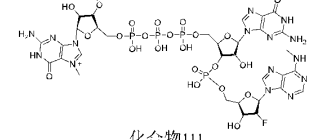
化合物108



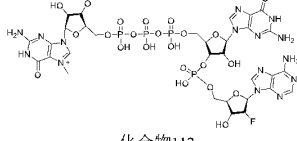
化合物109



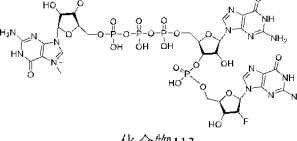
化合物110



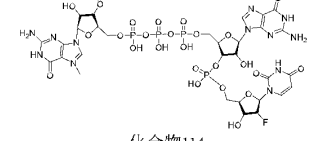
化合物111



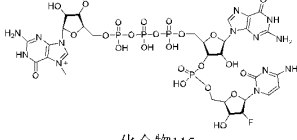
化合物112



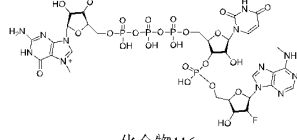
化合物113



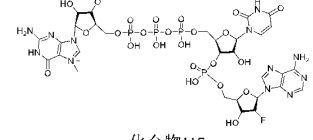
化合物114



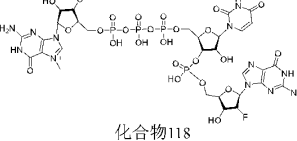
化合物115



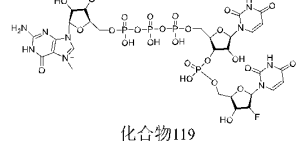
化合物116



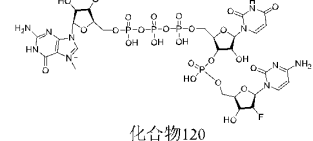
化合物117



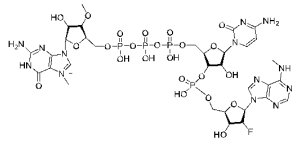
化合物118



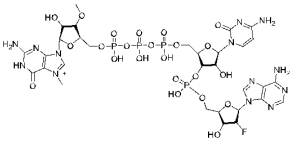
化合物119



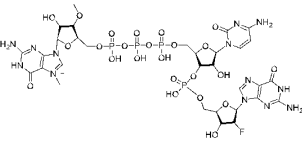
化合物120



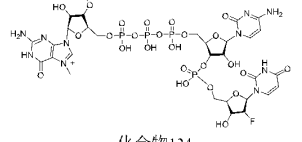
化合物121



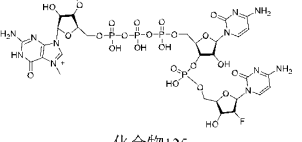
化合物122



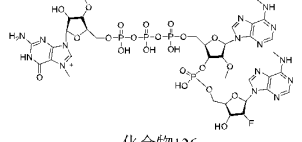
化合物123



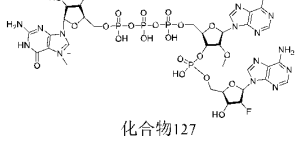
化合物124



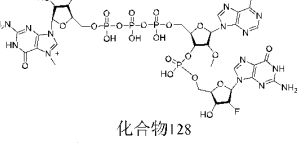
化合物125



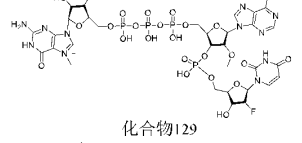
化合物126



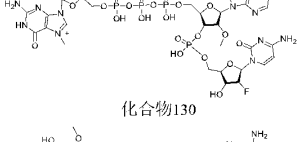
化合物127



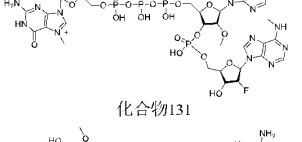
化合物128



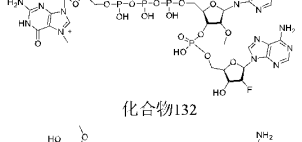
化合物129



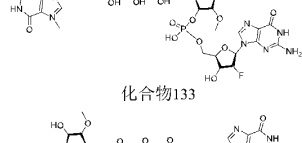
化合物130



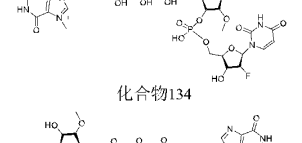
化合物131



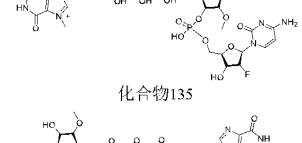
化合物132



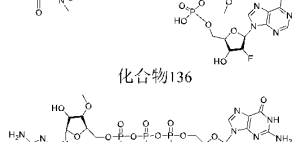
化合物133



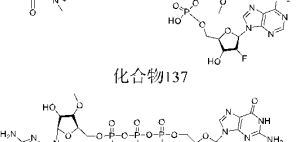
化合物134



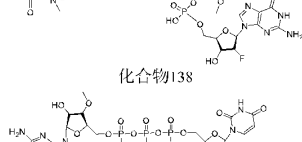
化合物135



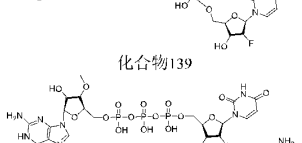
化合物136



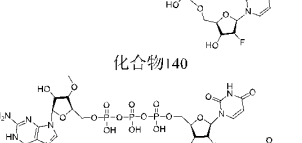
化合物137



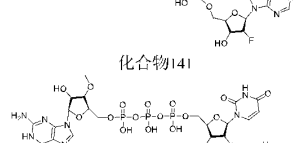
化合物138



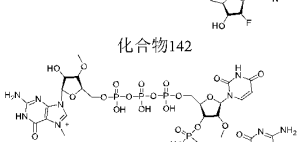
化合物139



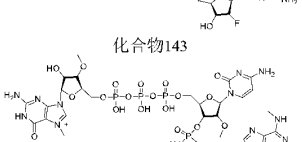
化合物140



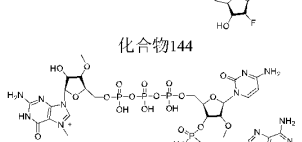
化合物141



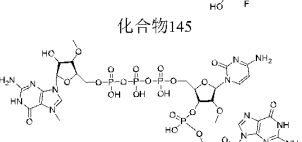
化合物142



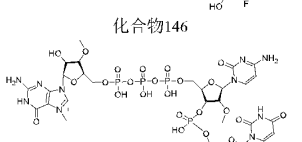
化合物143



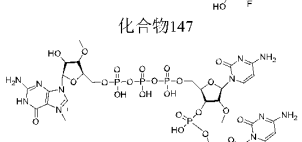
化合物144



化合物145



化合物146



化合物147



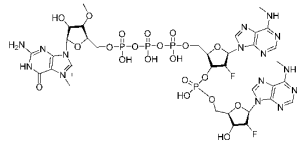
化合物148



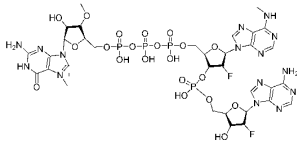
化合物149



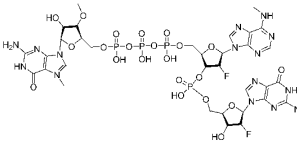
化合物150



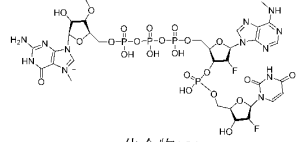
化合物151



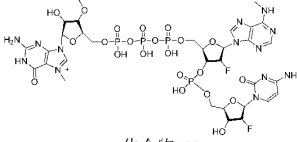
化合物152



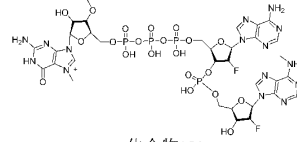
化合物153



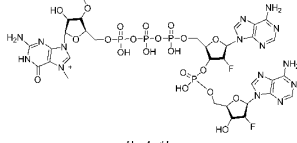
化合物154



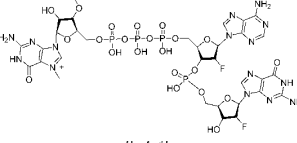
化合物155



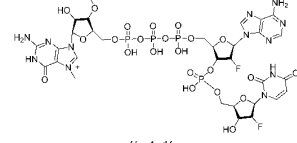
化合物156



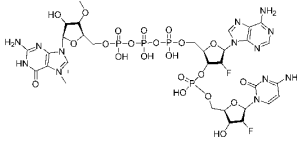
化合物157



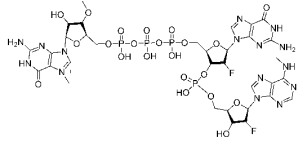
化合物158



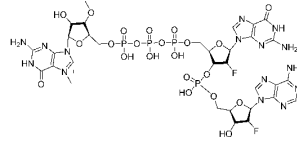
化合物159



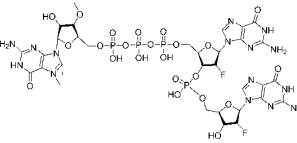
化合物160



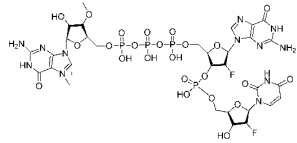
化合物161



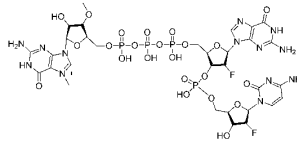
化合物162



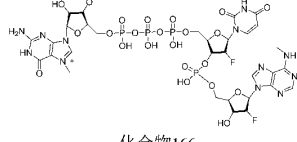
化合物163



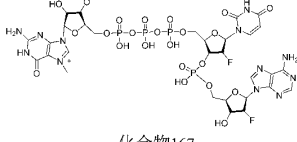
化合物164



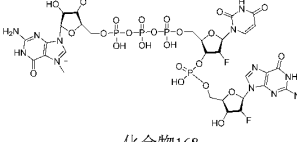
化合物165



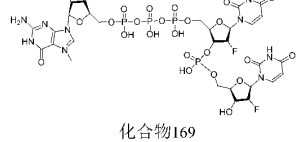
化合物166



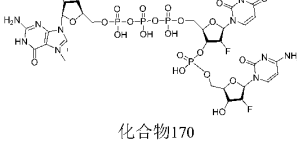
化合物167



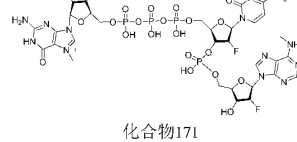
化合物168



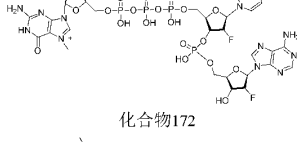
化合物169



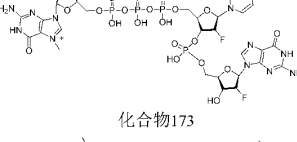
化合物170



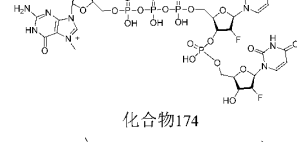
化合物171



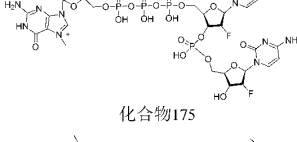
化合物172



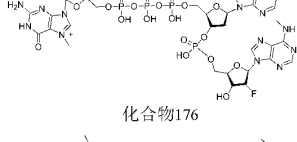
化合物173



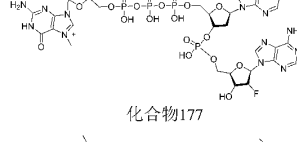
化合物174



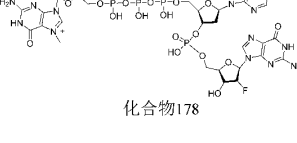
化合物175



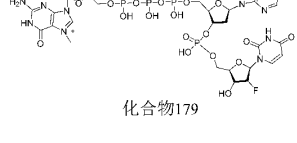
化合物176



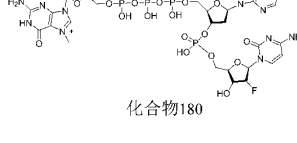
化合物177



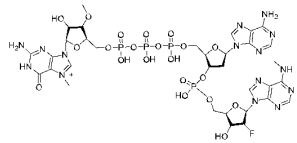
化合物178



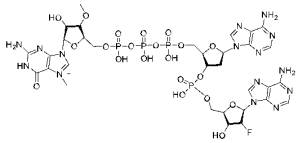
化合物179



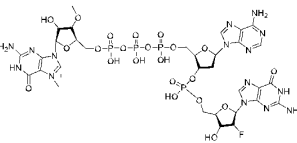
化合物180



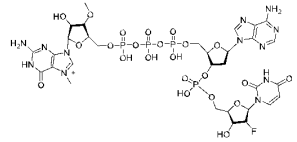
化合物181



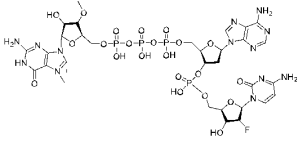
化合物182



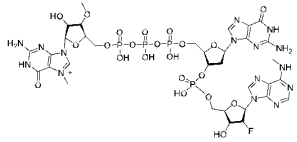
化合物183



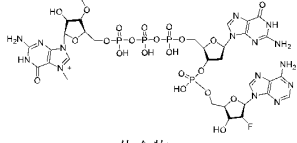
化合物184



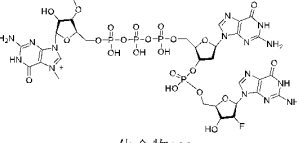
化合物185



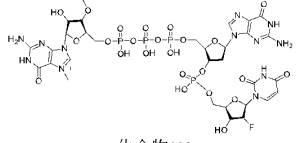
化合物186



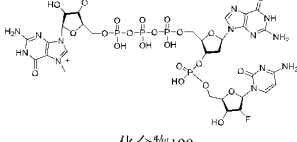
化合物187



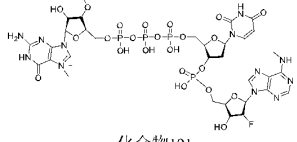
化合物188



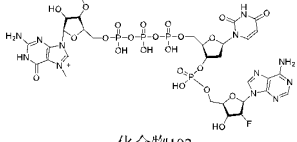
化合物189



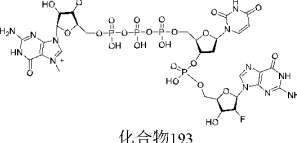
化合物190



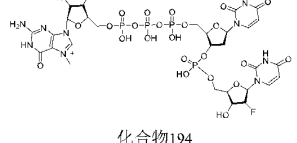
化合物191



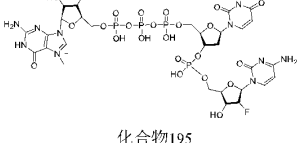
化合物192



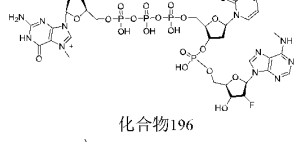
化合物193



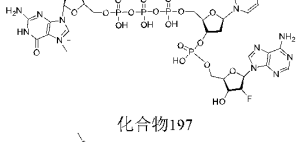
化合物194



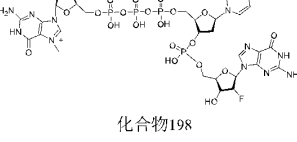
化合物195



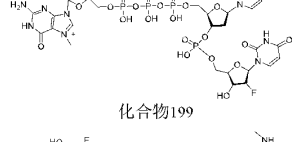
化合物196



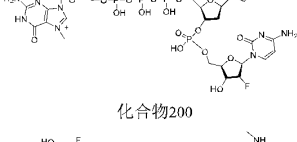
化合物197



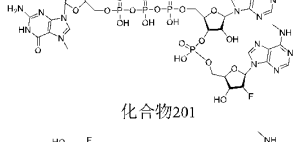
化合物198



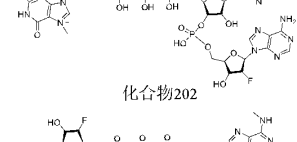
化合物199



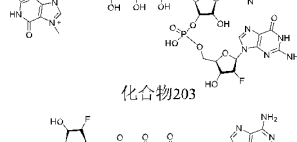
化合物200



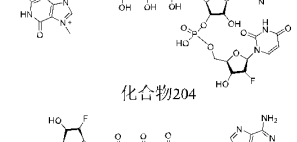
化合物201



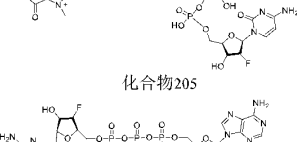
化合物202



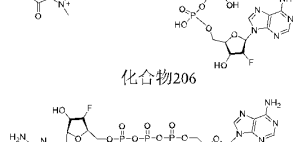
化合物203



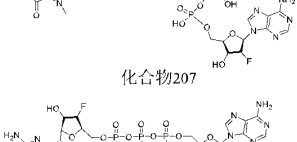
化合物204



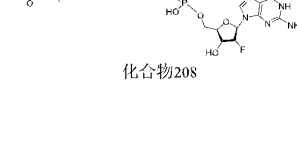
化合物205



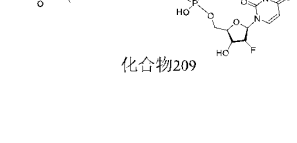
化合物206



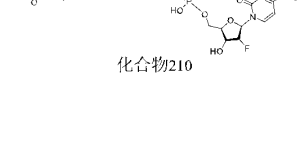
化合物207



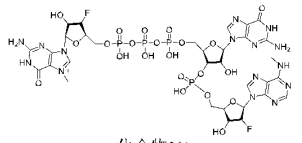
化合物208



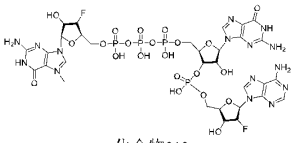
化合物209



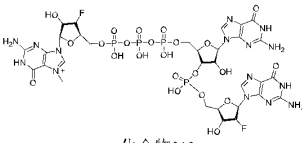
化合物210



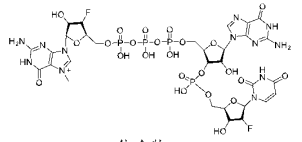
化合物211



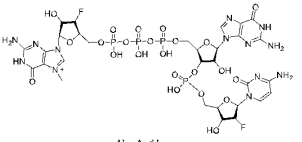
化合物212



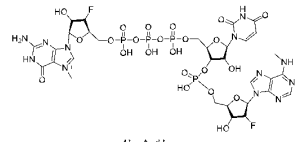
化合物213



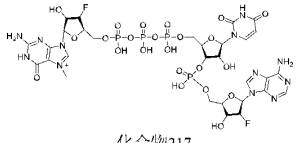
化合物214



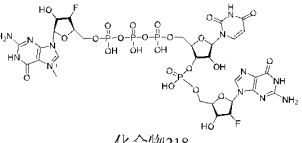
化合物215



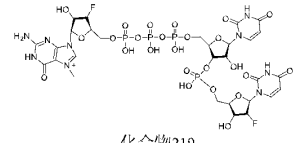
化合物216



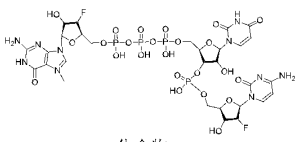
化合物217



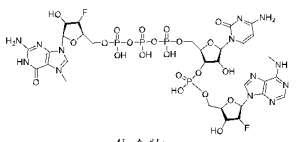
化合物218



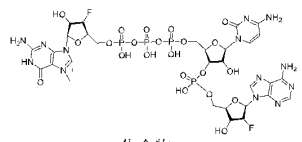
化合物219



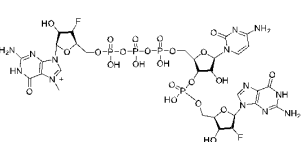
化合物220



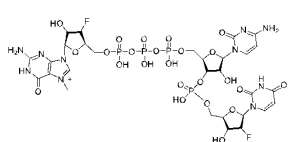
化合物221



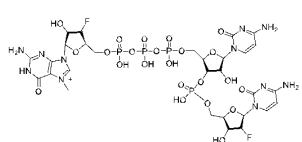
化合物222



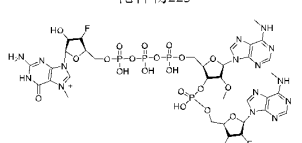
化合物223



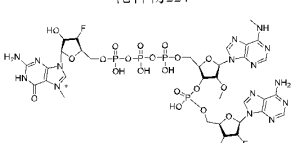
化合物224



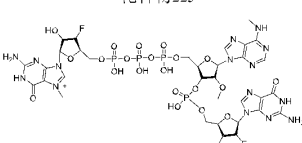
化合物225



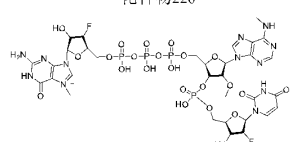
化合物226



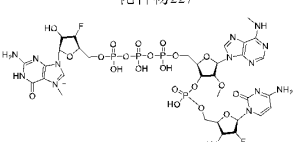
化合物227



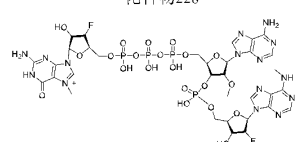
化合物228



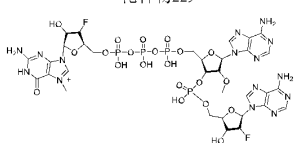
化合物229



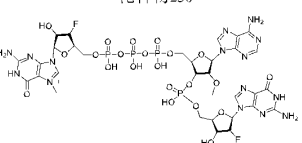
化合物230



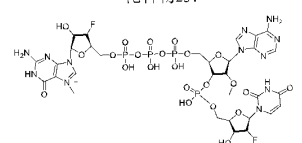
化合物231



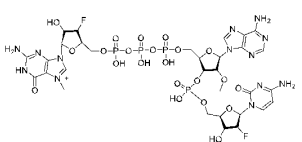
化合物232



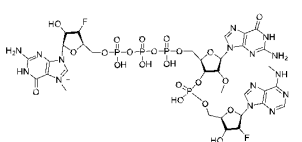
化合物233



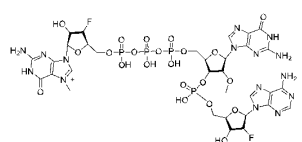
化合物234



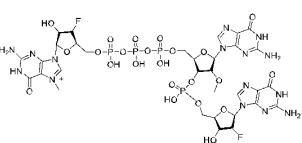
化合物235



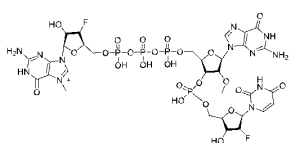
化合物236



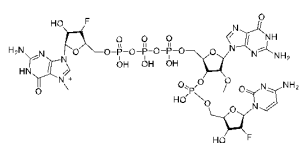
化合物237



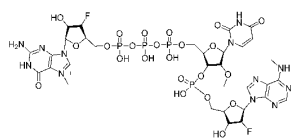
化合物238



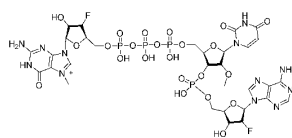
化合物239



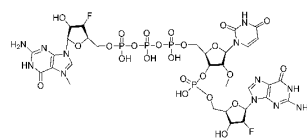
化合物240



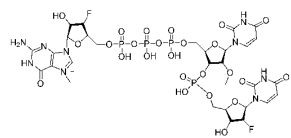
化合物241



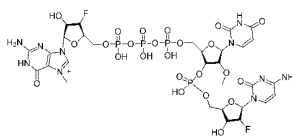
化合物242



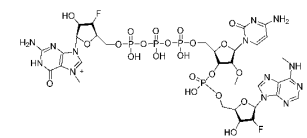
化合物243



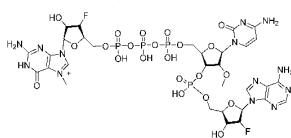
化合物244



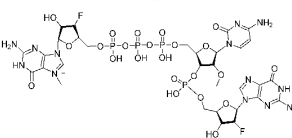
化合物245



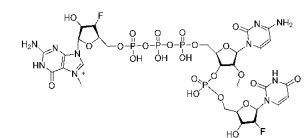
化合物246



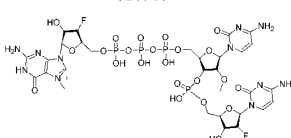
化合物247



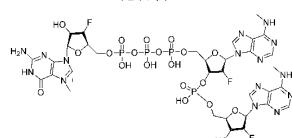
化合物248



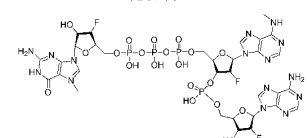
化合物249



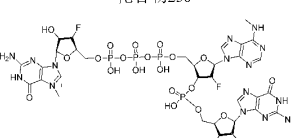
化合物250



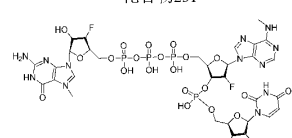
化合物251



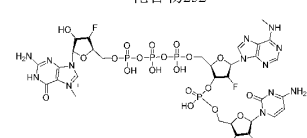
化合物252



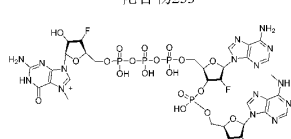
化合物253



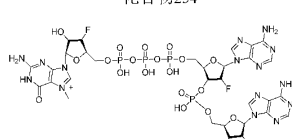
化合物254



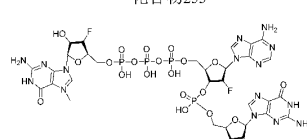
化合物255



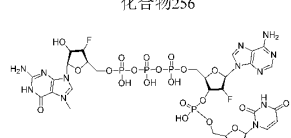
化合物256



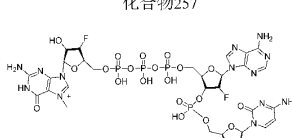
化合物257



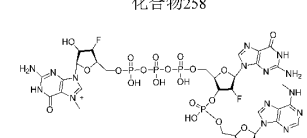
化合物258



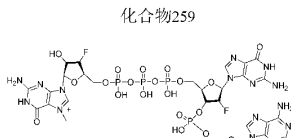
化合物259



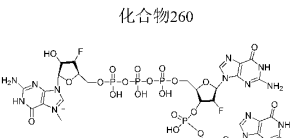
化合物260



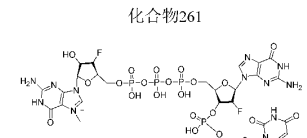
化合物261



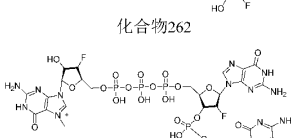
化合物262



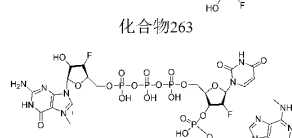
化合物263



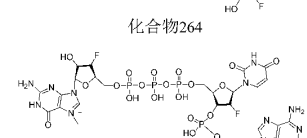
化合物264



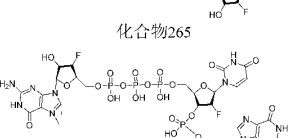
化合物265



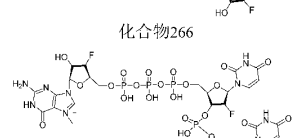
化合物266



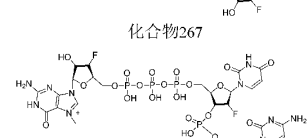
化合物267



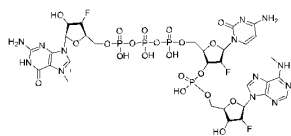
化合物268



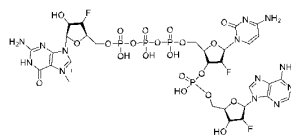
化合物269



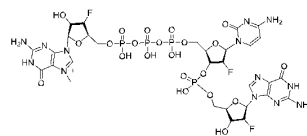
化合物270



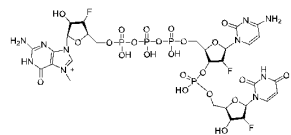
化合物271



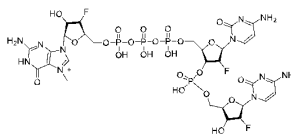
化合物272



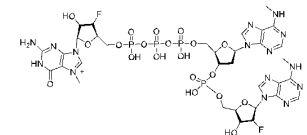
化合物273



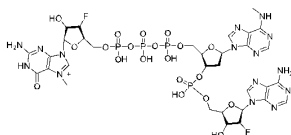
化合物274



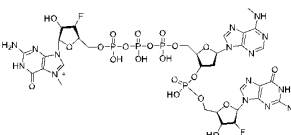
化合物275



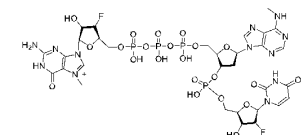
化合物276



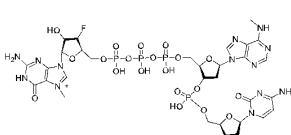
化合物277



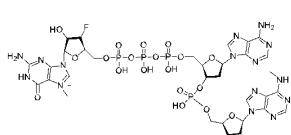
化合物278



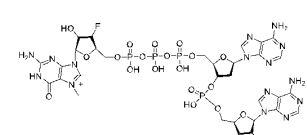
化合物279



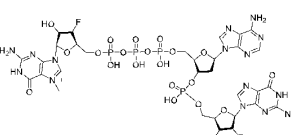
化合物280



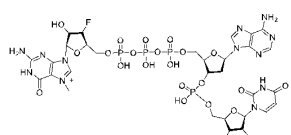
化合物281



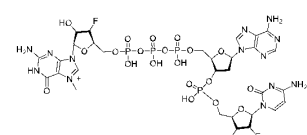
化合物282



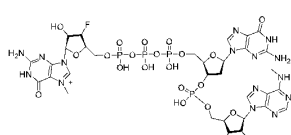
化合物283



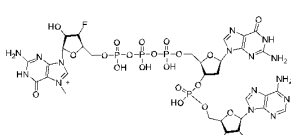
化合物284



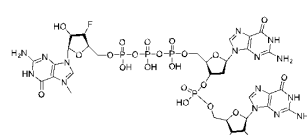
化合物285



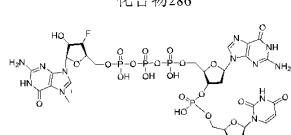
化合物286



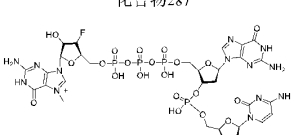
化合物287



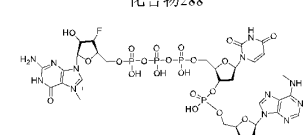
化合物288



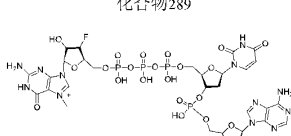
化合物289



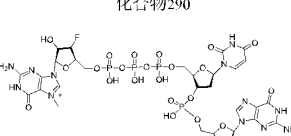
化合物290



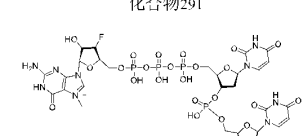
化合物291



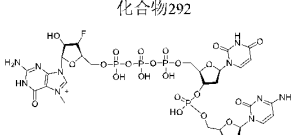
化合物292



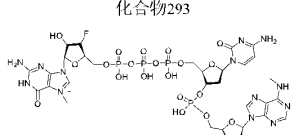
化合物293



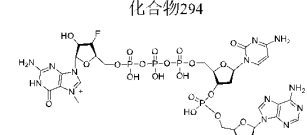
化合物294



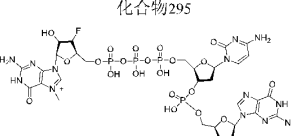
化合物295



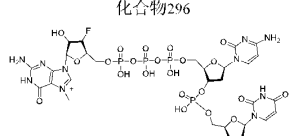
化合物296



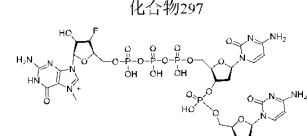
化合物297



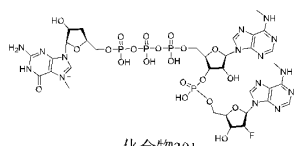
化合物298



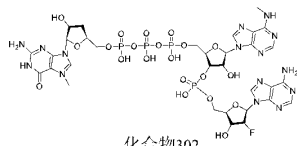
化合物299



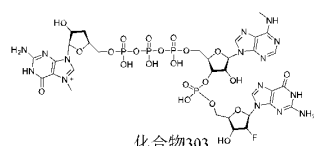
化合物300



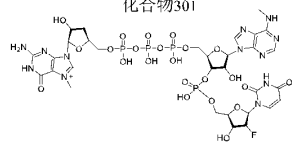
化合物301



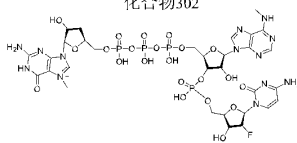
化合物302



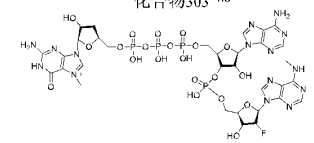
化合物303



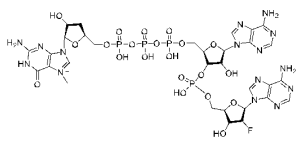
化合物304



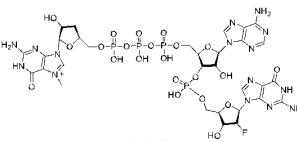
化合物305



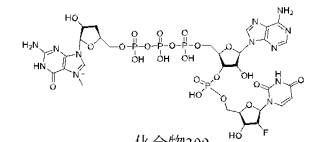
化合物306



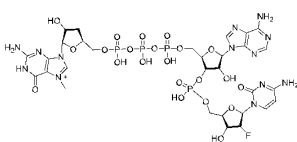
化合物307



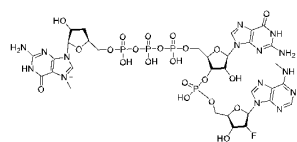
化合物308



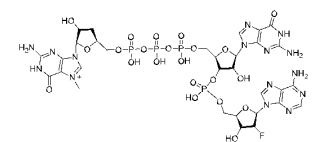
化合物309



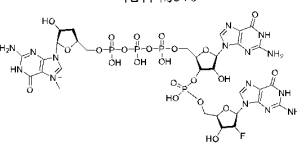
化合物310



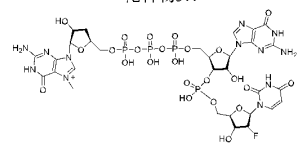
化合物311



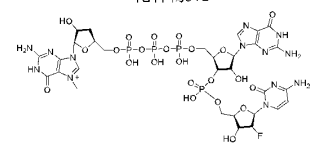
化合物312



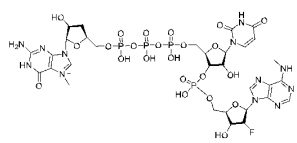
化合物313



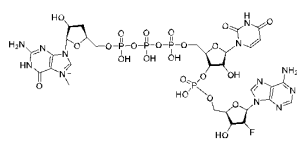
化合物314



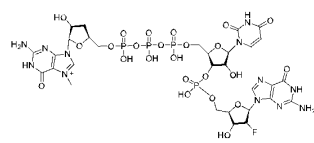
化合物315



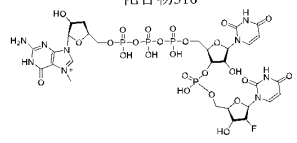
化合物316



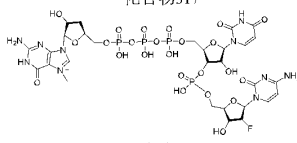
化合物317



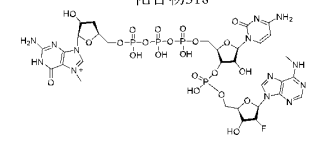
化合物318



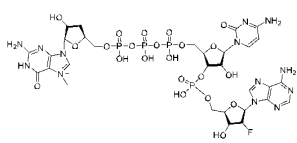
化合物319



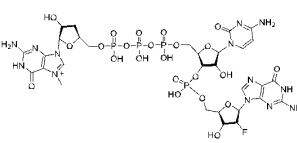
化合物320



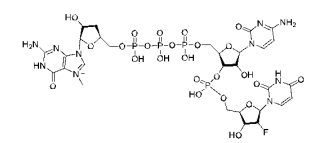
化合物321



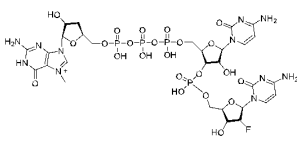
化合物322



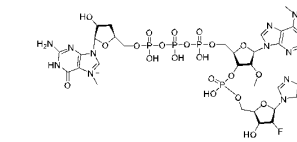
化合物323



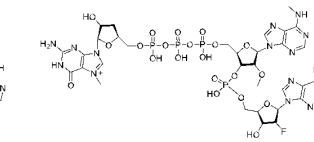
化合物324



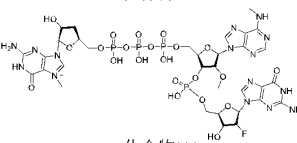
化合物325



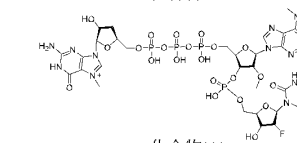
化合物326



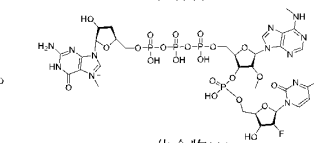
化合物327



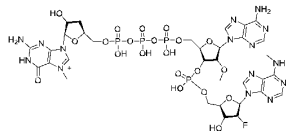
化合物328



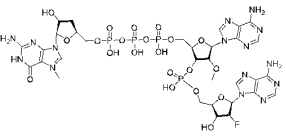
化合物329



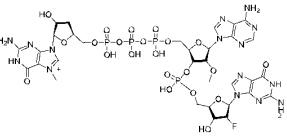
化合物330



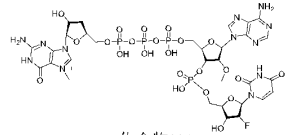
化合物331



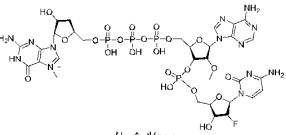
化合物332



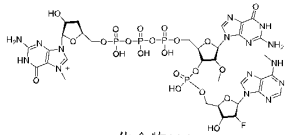
化合物333



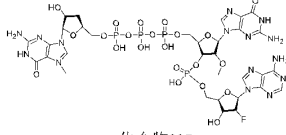
化合物334



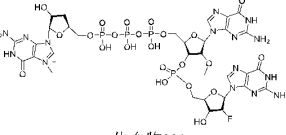
化合物335



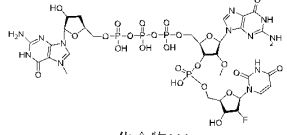
化合物336



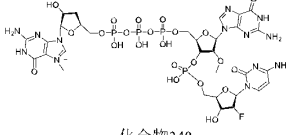
化合物337



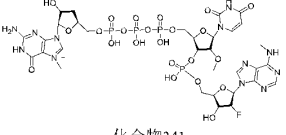
化合物338



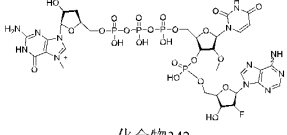
化合物339



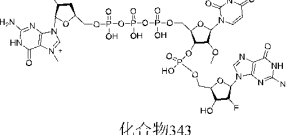
化合物340



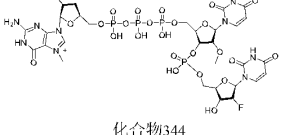
化合物341



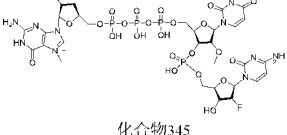
化合物342



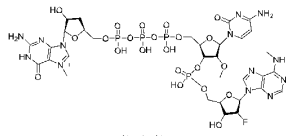
化合物343



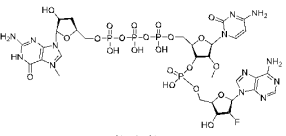
化合物344



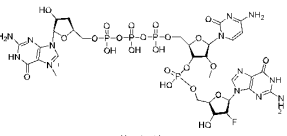
化合物345



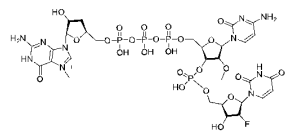
化合物346



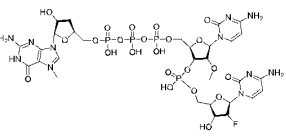
化合物347



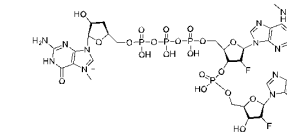
化合物348



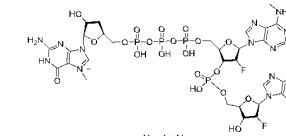
化合物349



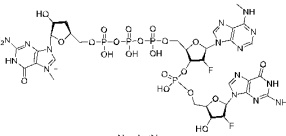
化合物350



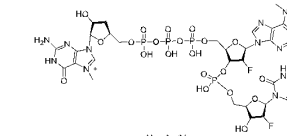
化合物351



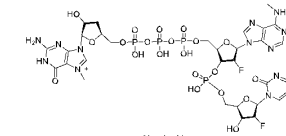
化合物352



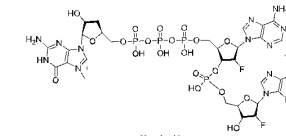
化合物353



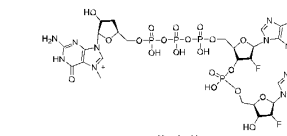
化合物354



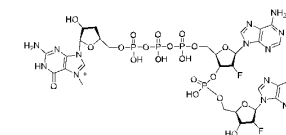
化合物355



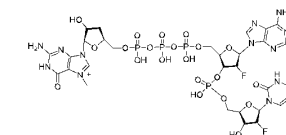
化合物356



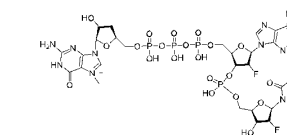
化合物357



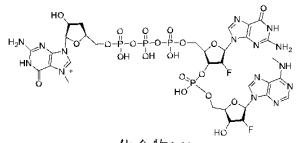
化合物358



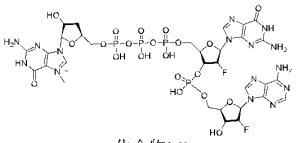
化合物359



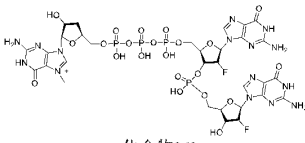
化合物360



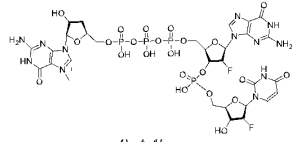
化合物361



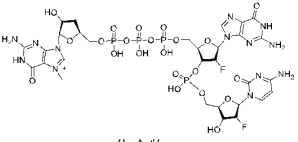
化合物362



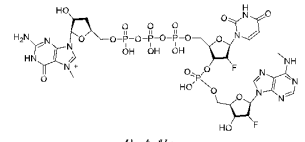
化合物363



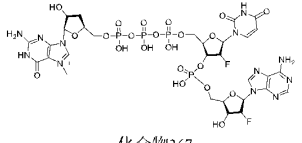
化合物364



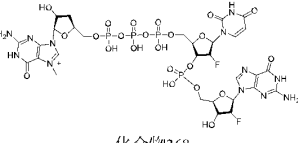
化合物365



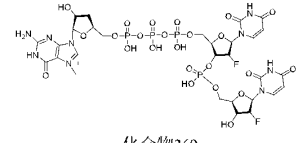
化合物366



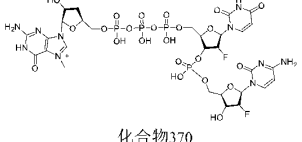
化合物367



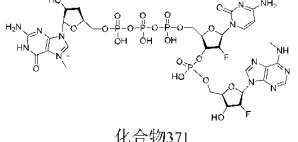
化合物368



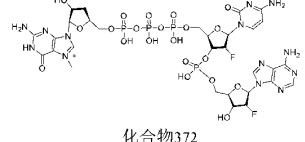
化合物369



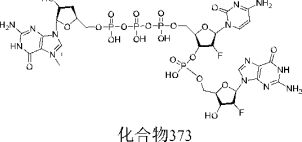
化合物370



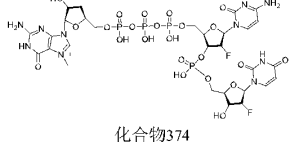
化合物371



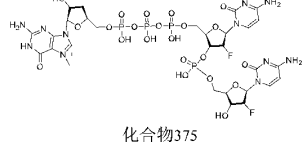
化合物372



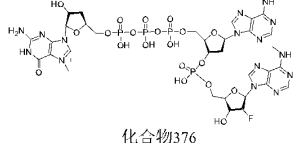
化合物373



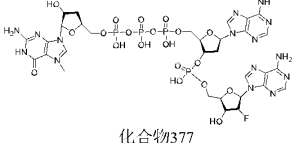
化合物374



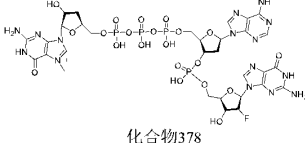
化合物375



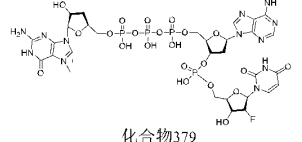
化合物376



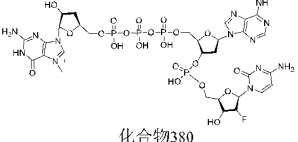
化合物377



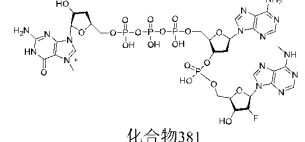
化合物378



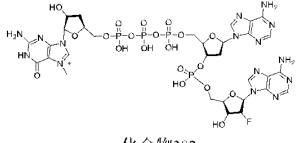
化合物379



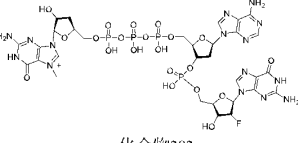
化合物380



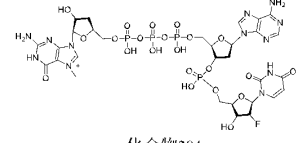
化合物381



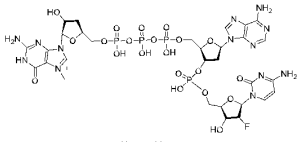
化合物382



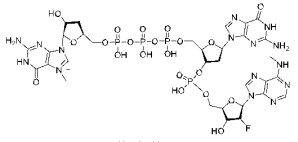
化合物383



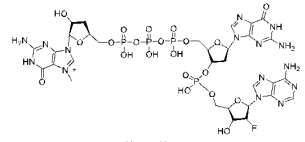
化合物384



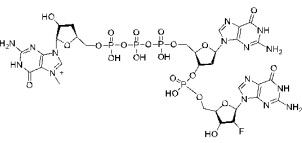
化合物385



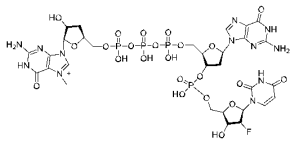
化合物386



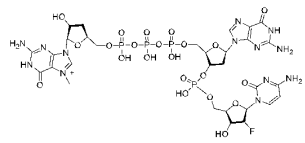
化合物387



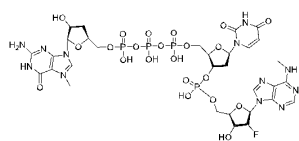
化合物388



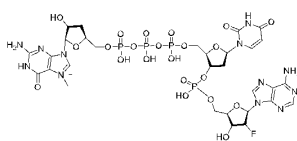
化合物389



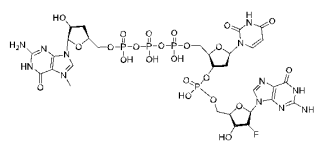
化合物390



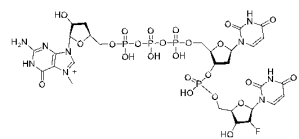
化合物391



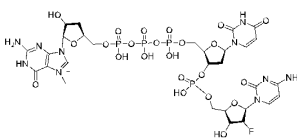
化合物392



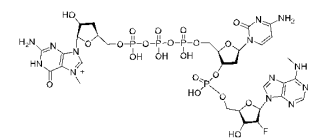
化合物393



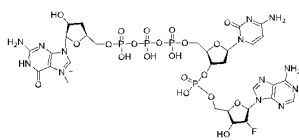
化合物394



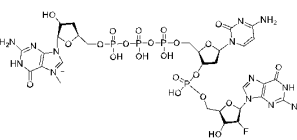
化合物395



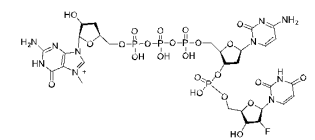
化合物396



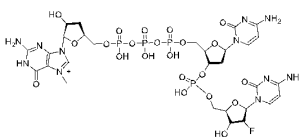
化合物397



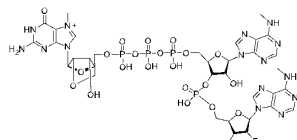
化合物398



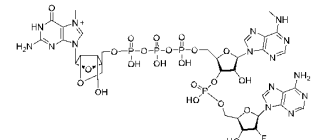
化合物399



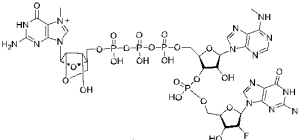
化合物400



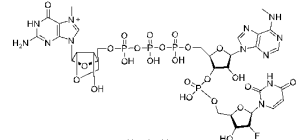
化合物401



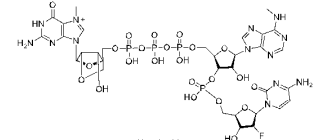
化合物402



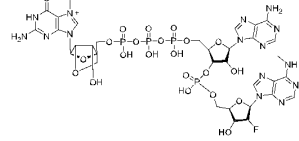
化合物403



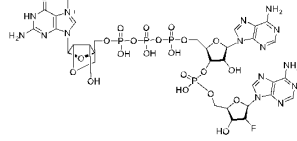
化合物404



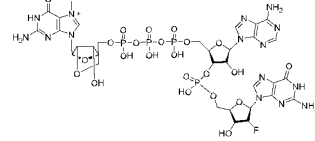
化合物405



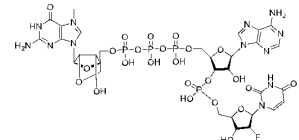
化合物406



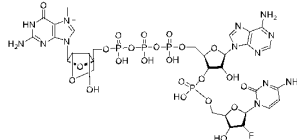
化合物407



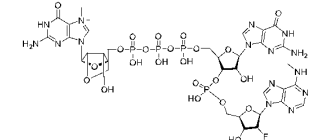
化合物408



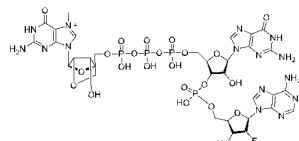
化合物409



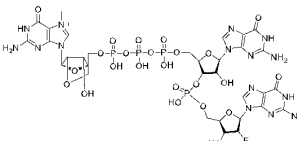
化合物410



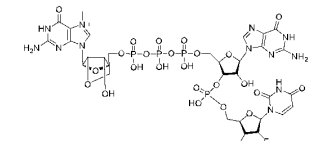
化合物411



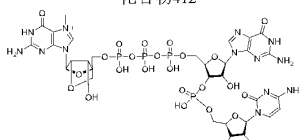
化合物412



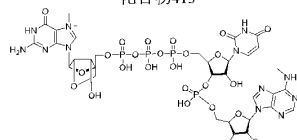
化合物413



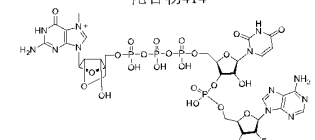
化合物414



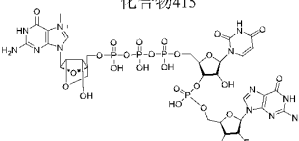
化合物415



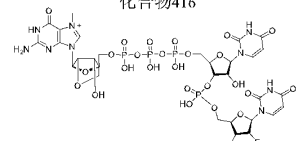
化合物416



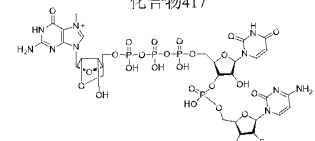
化合物417



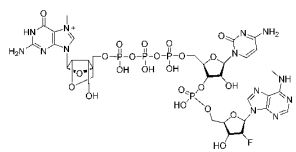
化合物418



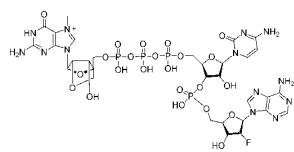
化合物419



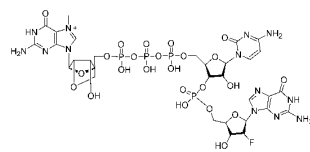
化合物420



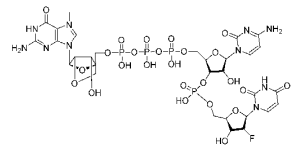
化合物421



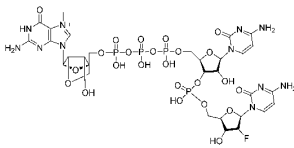
化合物422



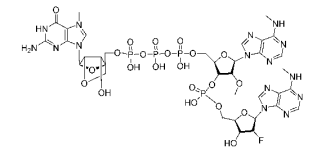
化合物423



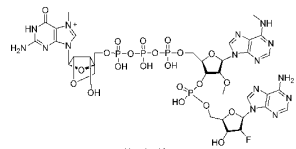
化合物424



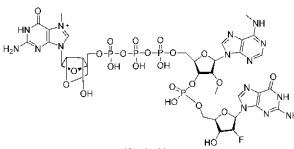
化合物425



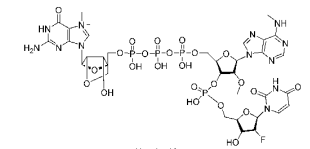
化合物426



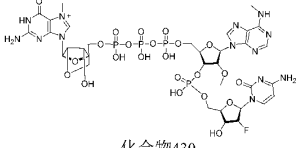
化合物427



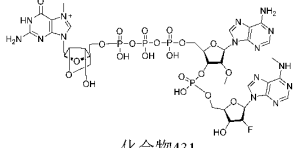
化合物428



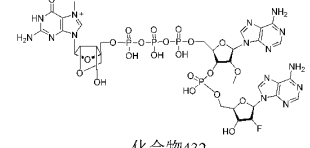
化合物429



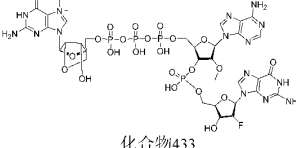
化合物430



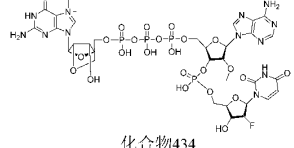
化合物431



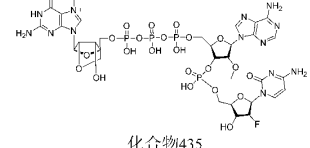
化合物432



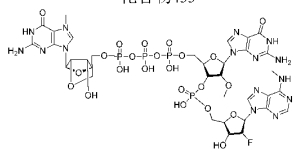
化合物433



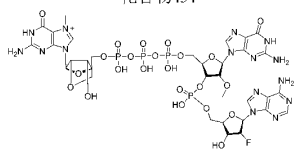
化合物434



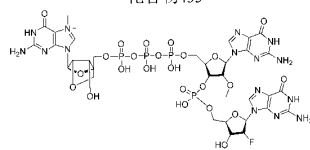
化合物435



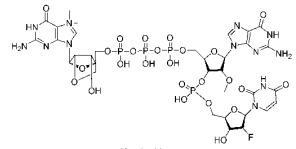
化合物436



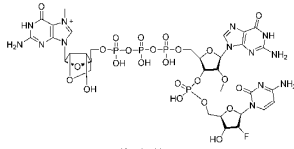
化合物437



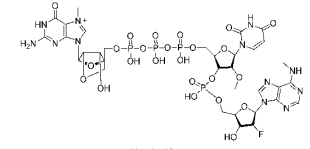
化合物438



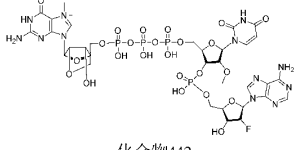
化合物439



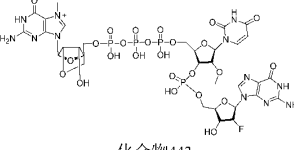
化合物440



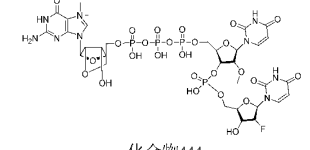
化合物441



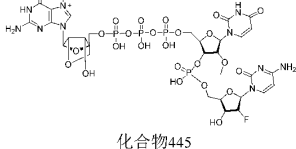
化合物442



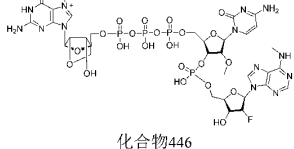
化合物443



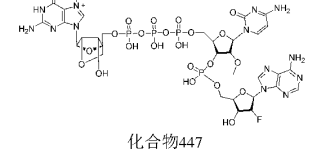
化合物444



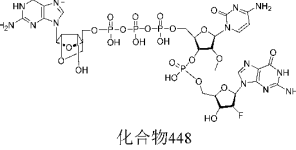
化合物445



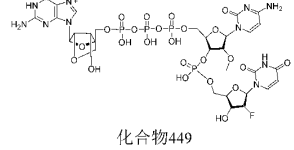
化合物446



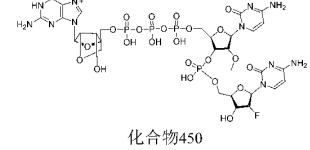
化合物447



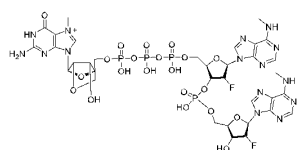
化合物448



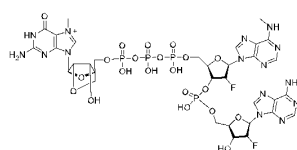
化合物449



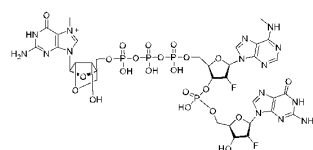
化合物450



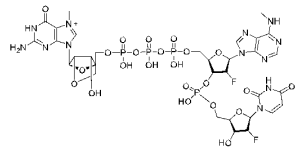
化合物451



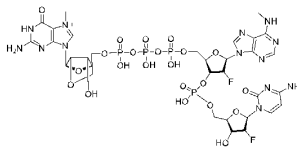
化合物452



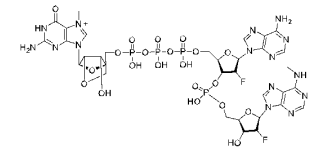
化合物453



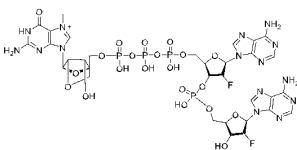
化合物454



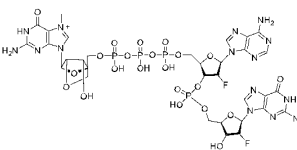
化合物455



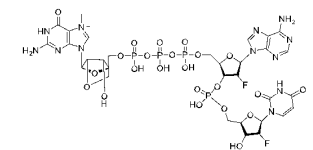
化合物456



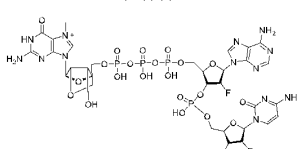
化合物457



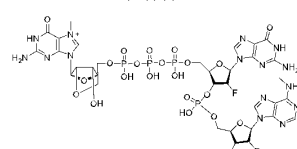
化合物458



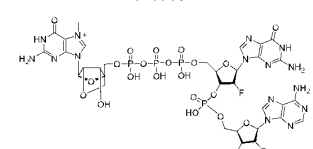
化合物459



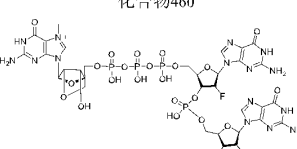
化合物460



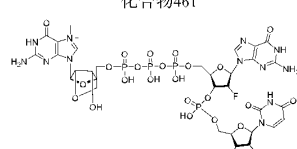
化合物461



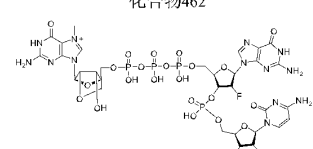
化合物462



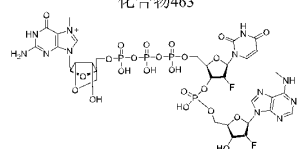
化合物463



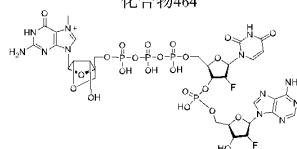
化合物464



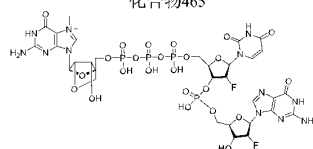
化合物465



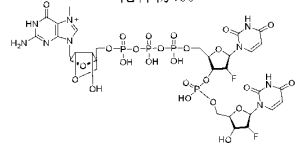
化合物466



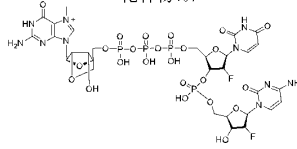
化合物467



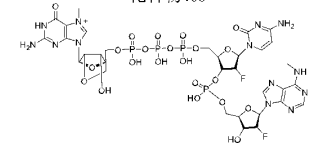
化合物468



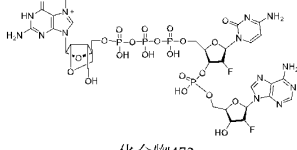
化合物469



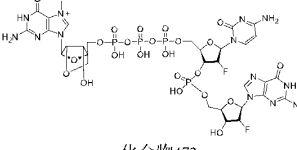
化合物470



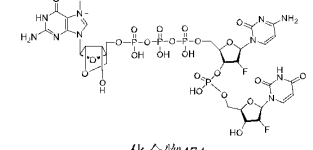
化合物471



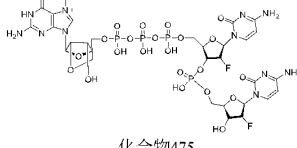
化合物472



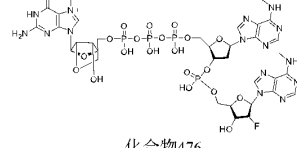
化合物473



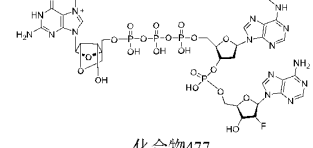
化合物474



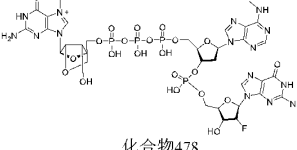
化合物475



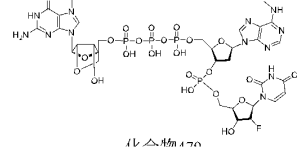
化合物476



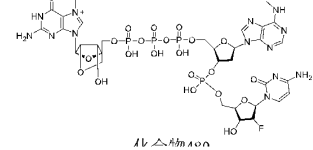
化合物477



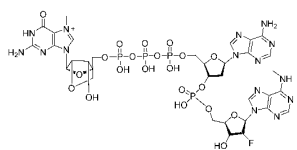
化合物478



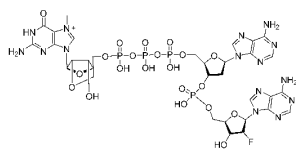
化合物479



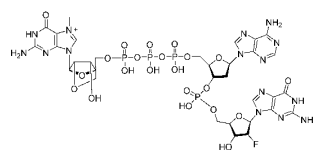
化合物480



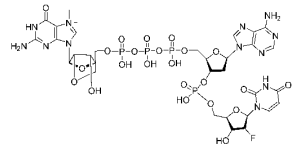
化合物481



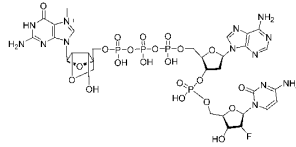
化合物482



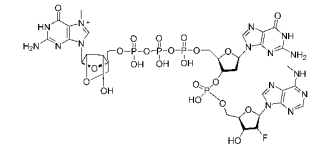
化合物483



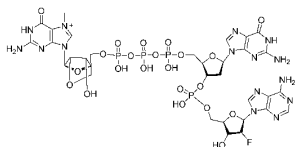
化合物484



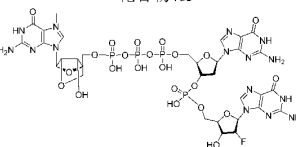
化合物485



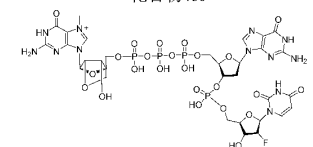
化合物486



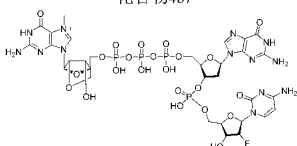
化合物487



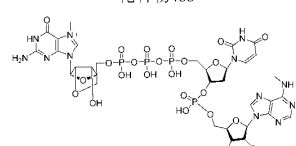
化合物488



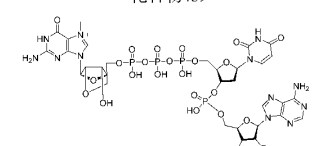
化合物489



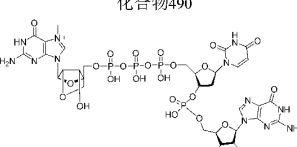
化合物490



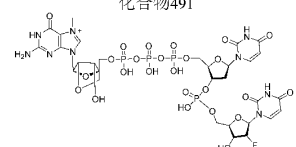
化合物491



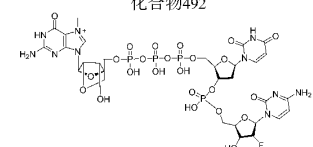
化合物492



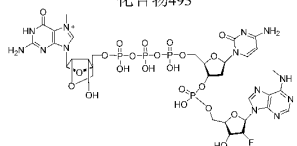
化合物493



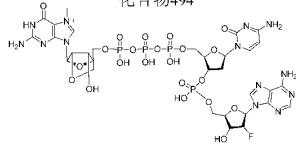
化合物494



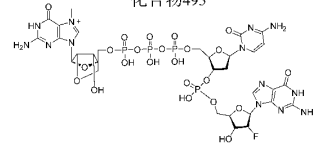
化合物495



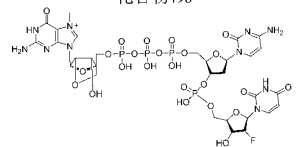
化合物496



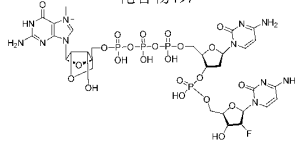
化合物497



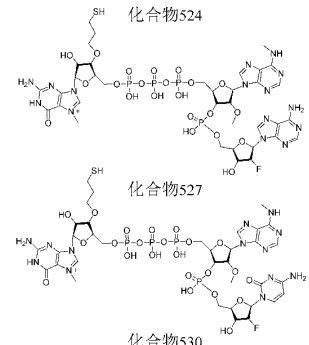
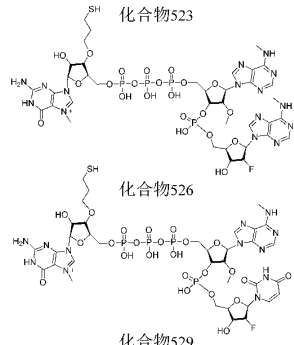
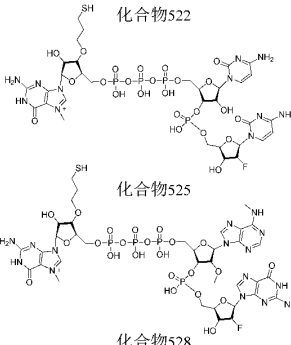
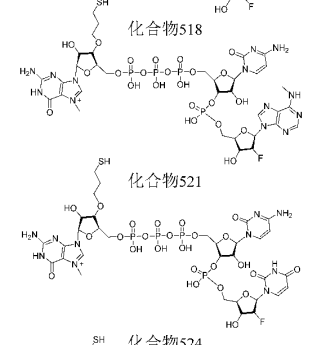
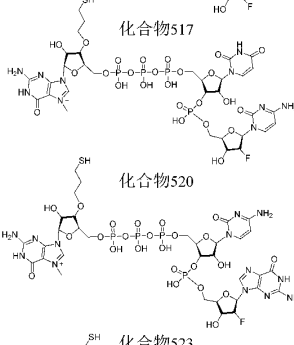
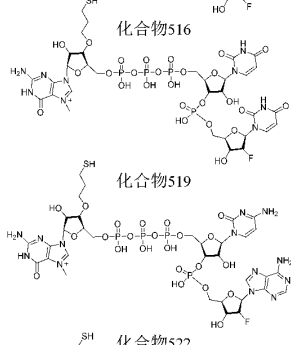
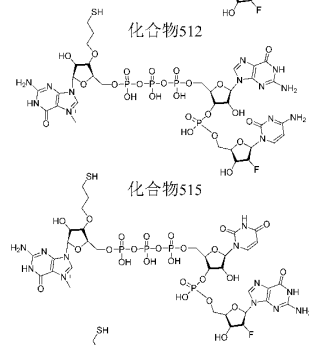
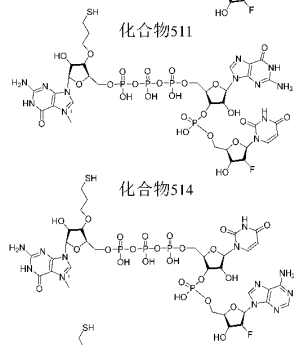
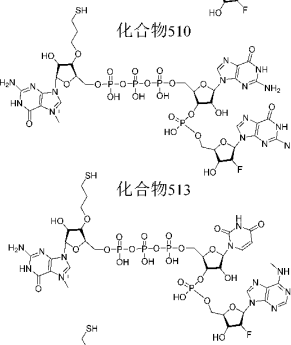
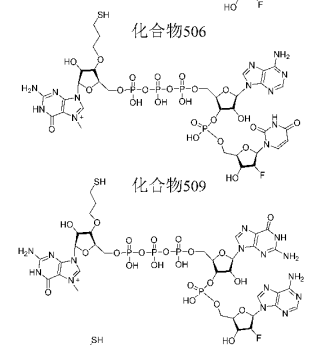
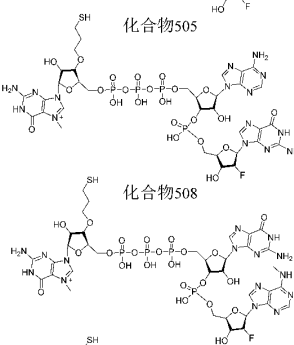
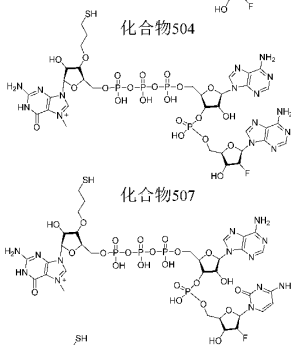
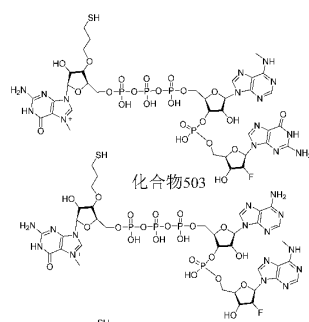
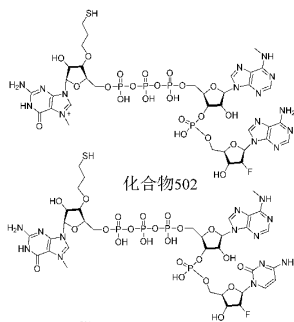
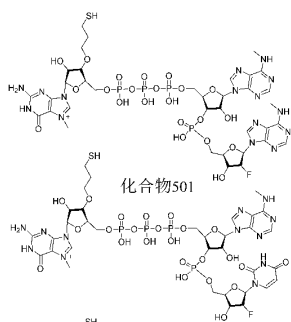
化合物498

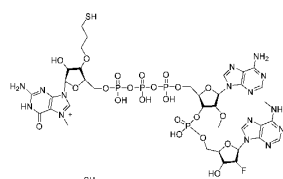


化合物499

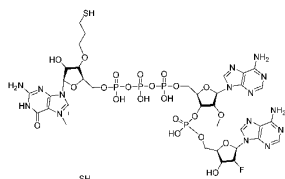


化合物500

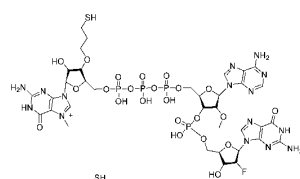




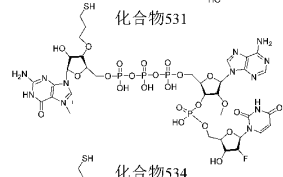
化合物531



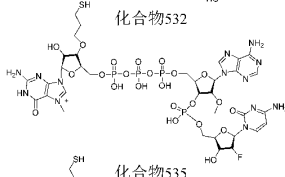
化合物532



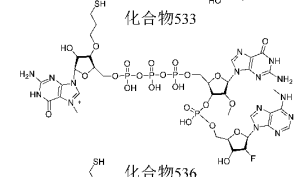
化合物533



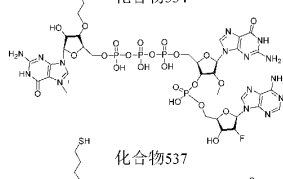
化合物534



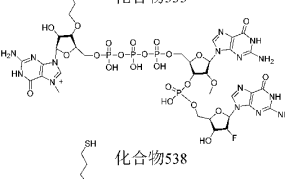
化合物535



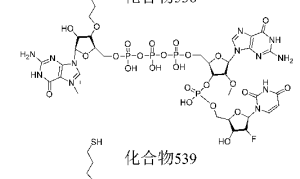
化合物536



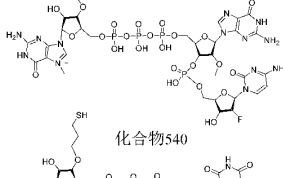
化合物537



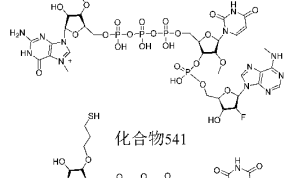
化合物538



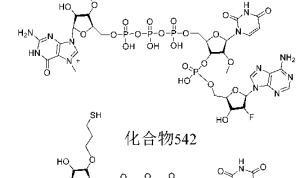
化合物539



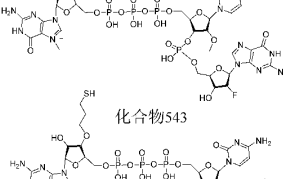
化合物540



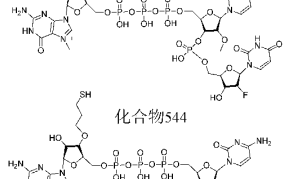
化合物541



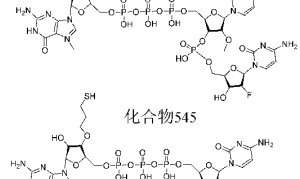
化合物542



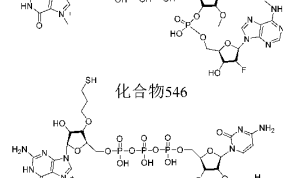
化合物543



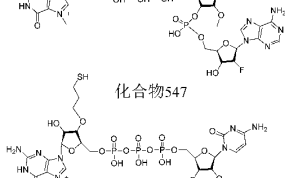
化合物544



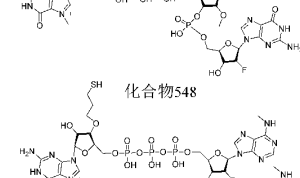
化合物545



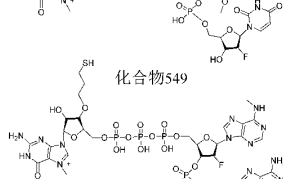
化合物546



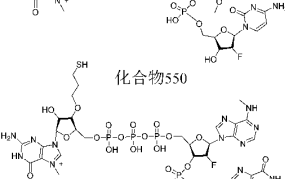
化合物547



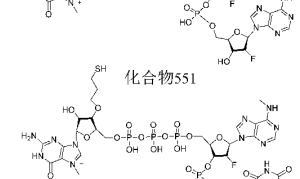
化合物548



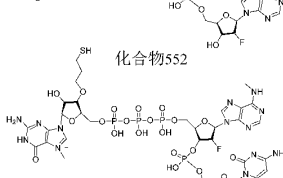
化合物549



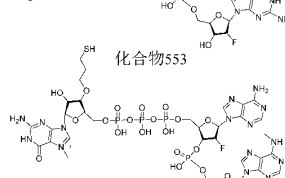
化合物550



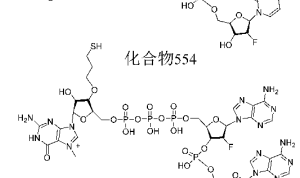
化合物551



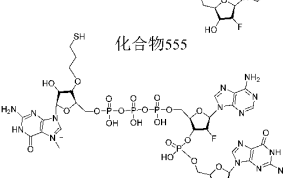
化合物552



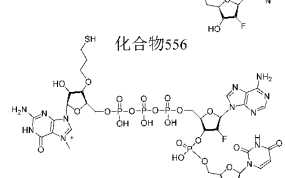
化合物553



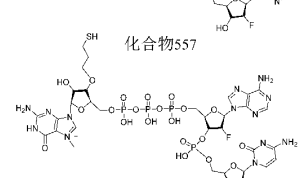
化合物554



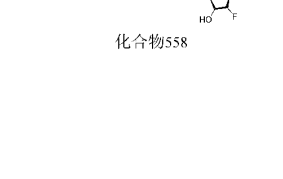
化合物555



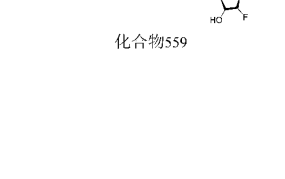
化合物556



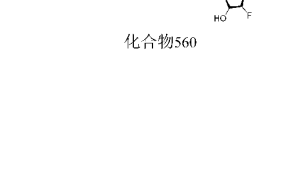
化合物557



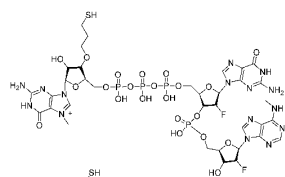
化合物558



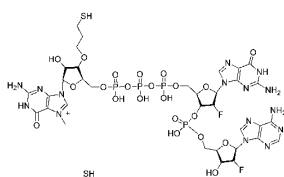
化合物559



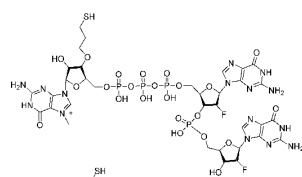
化合物560



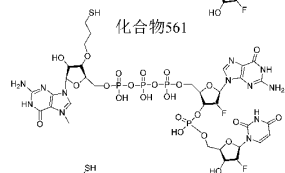
化合物561



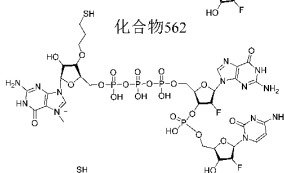
化合物562



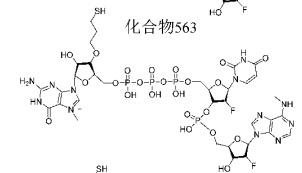
化合物563



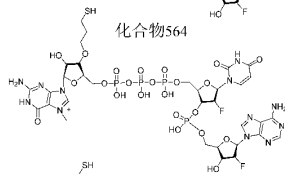
化合物564



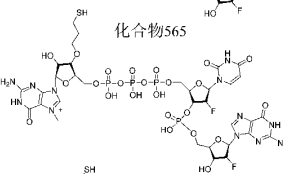
化合物565



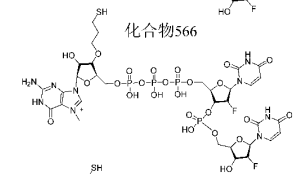
化合物566



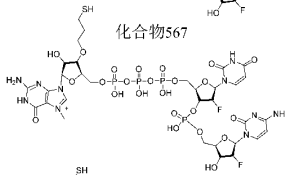
化合物567



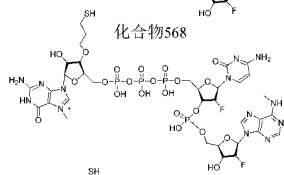
化合物568



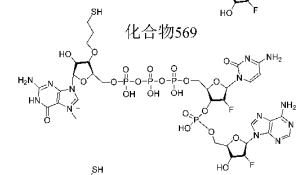
化合物569



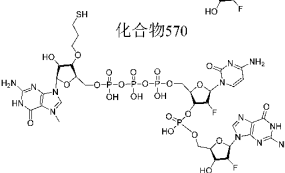
化合物570



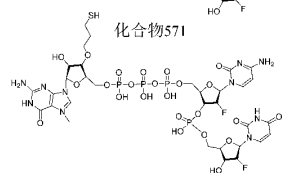
化合物571



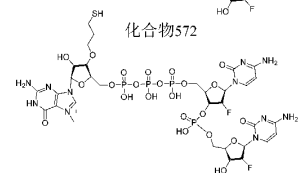
化合物572



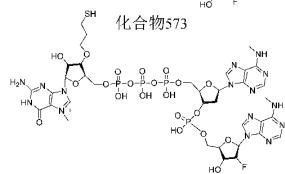
化合物573



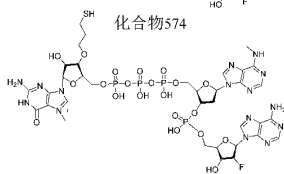
化合物574



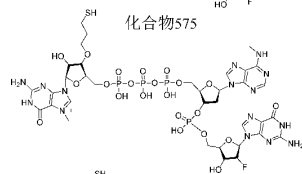
化合物575



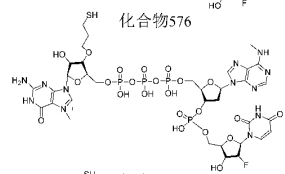
化合物576



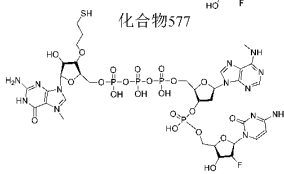
化合物577



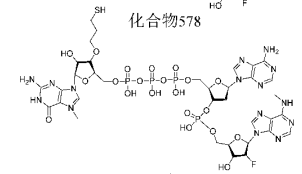
化合物578



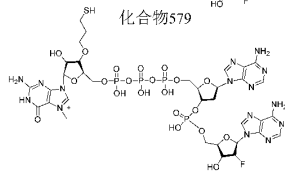
化合物579



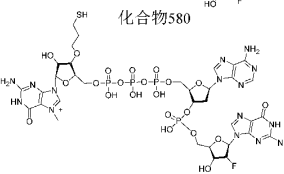
化合物580



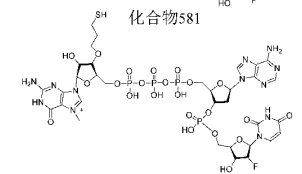
化合物581



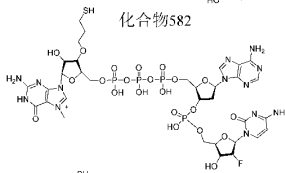
化合物582



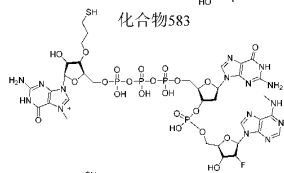
化合物583



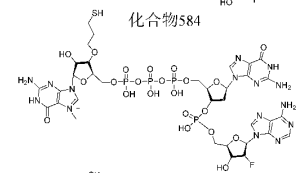
化合物584



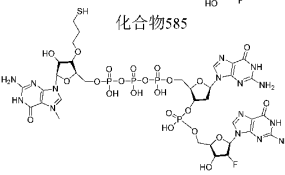
化合物585



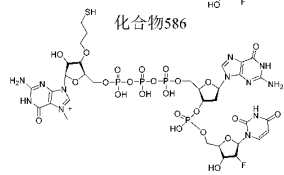
化合物586



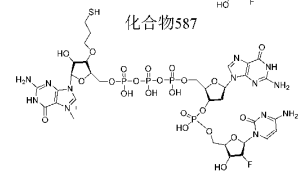
化合物587



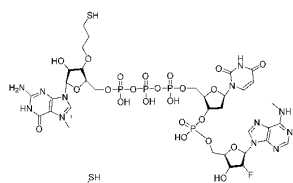
化合物588



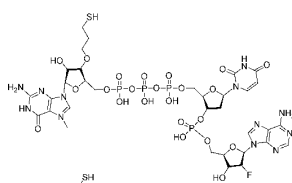
化合物589



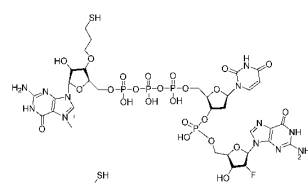
化合物590



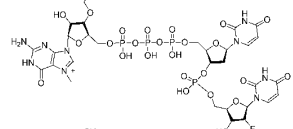
化合物591



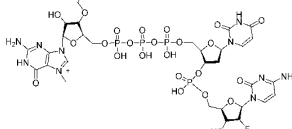
化合物592



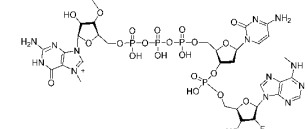
化合物593



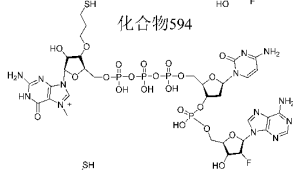
化合物594



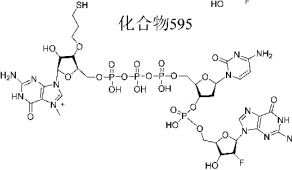
化合物595



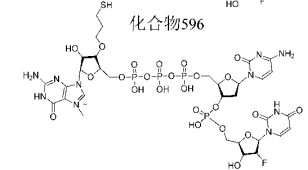
化合物596



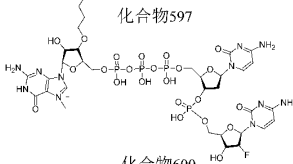
化合物597



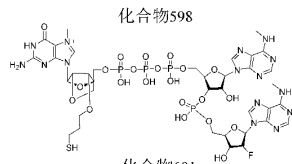
化合物598



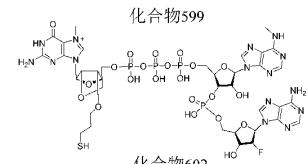
化合物599



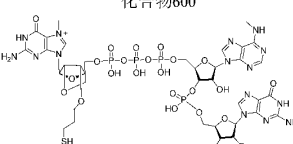
化合物600



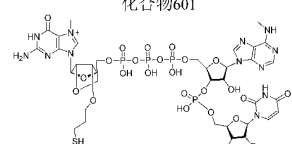
化合物601



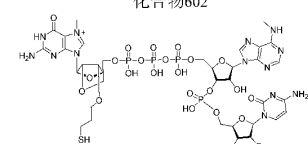
化合物602



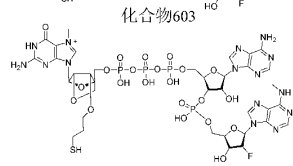
化合物603



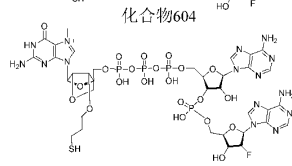
化合物604



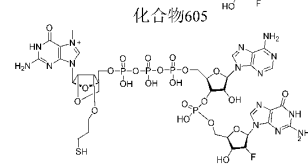
化合物605



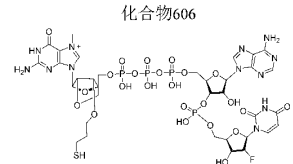
化合物606



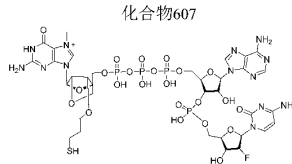
化合物607



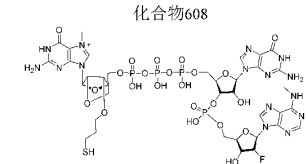
化合物608



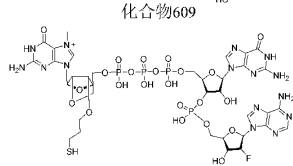
化合物609



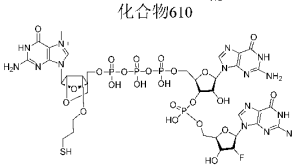
化合物610



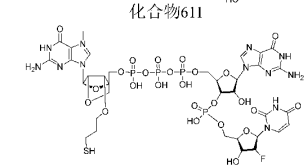
化合物611



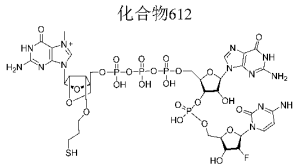
化合物612



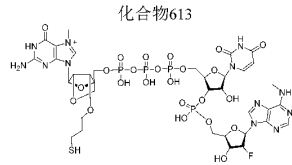
化合物613



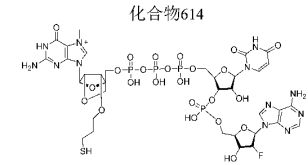
化合物614



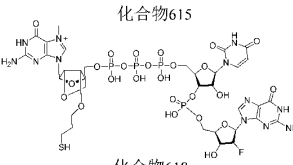
化合物615



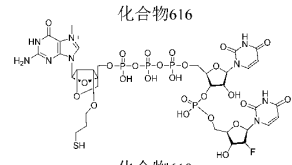
化合物616



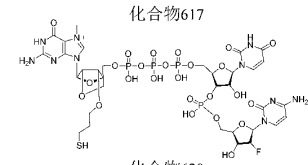
化合物617



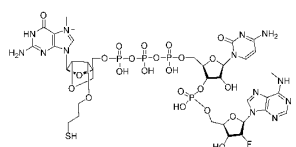
化合物618



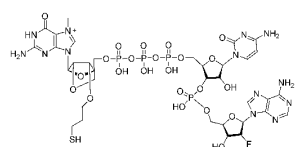
化合物619



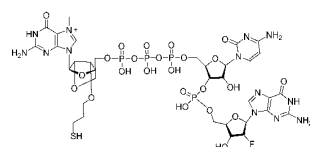
化合物620



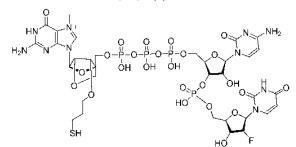
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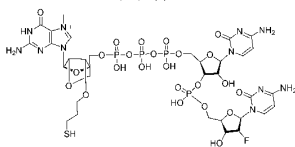
化合物622



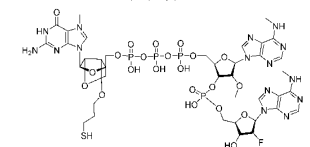
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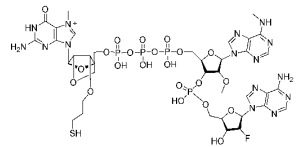
化合物624



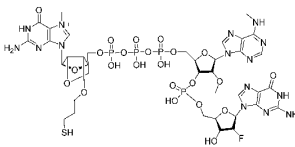
化合物625



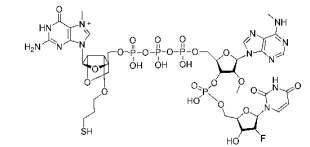
化合物626



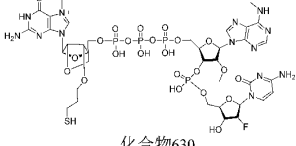
化合物627



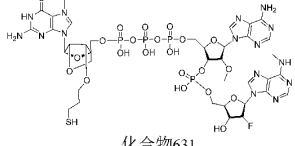
化合物628



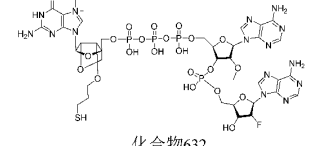
化合物629



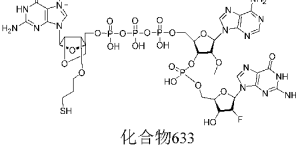
化合物630



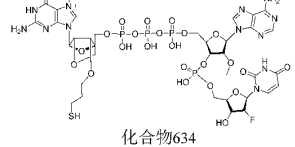
化合物631



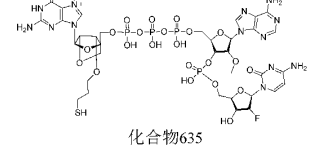
化合物632



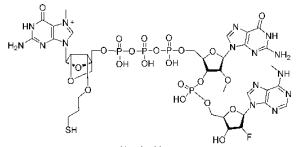
化合物633



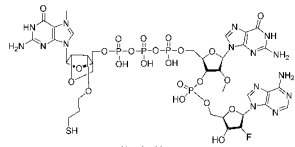
化合物634



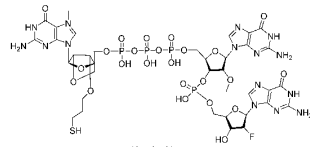
化合物635



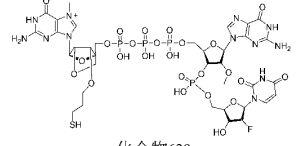
化合物636



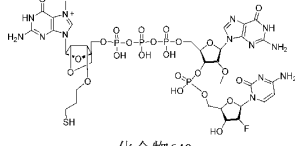
化合物637



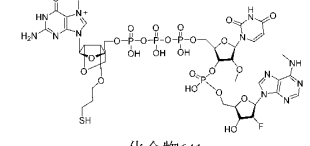
化合物638



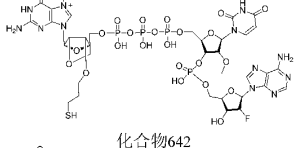
化合物639



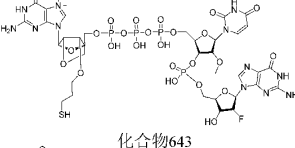
化合物640



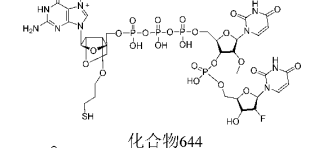
化合物641



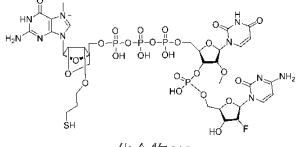
化合物642



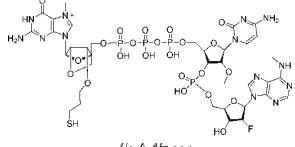
化合物643



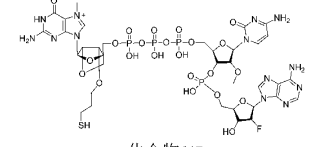
化合物644



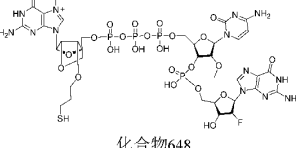
化合物645



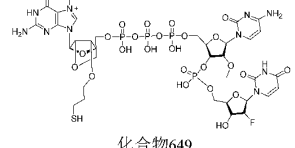
化合物646



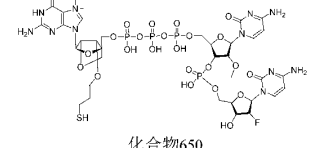
化合物647



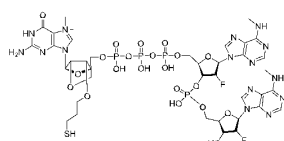
化合物648



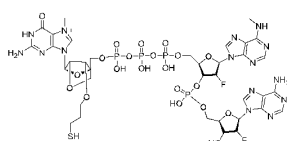
化合物649



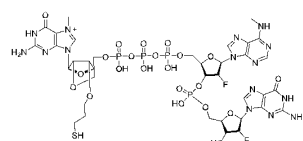
化合物650



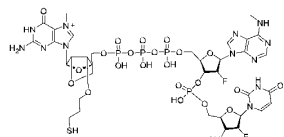
化合物651



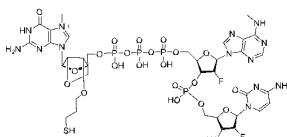
化合物652



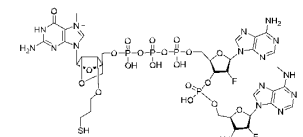
化合物653



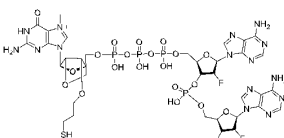
化合物654



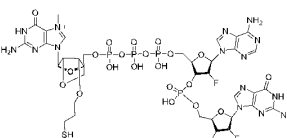
化合物655



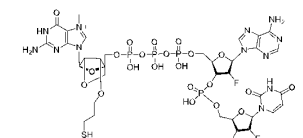
化合物656



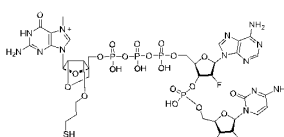
化合物657



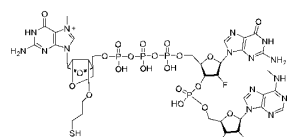
化合物658



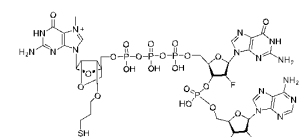
化合物659



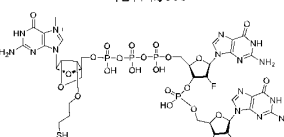
化合物660



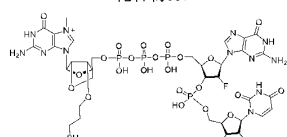
化合物661



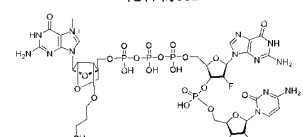
化合物662



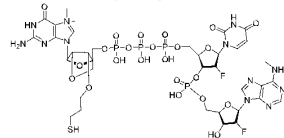
化合物663



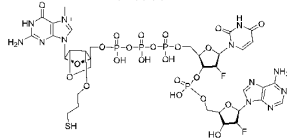
化合物664



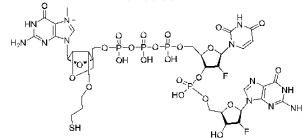
化合物665



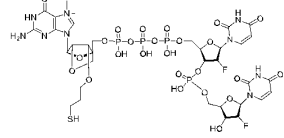
化合物666



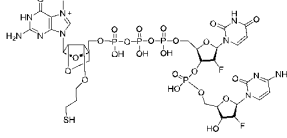
化合物667



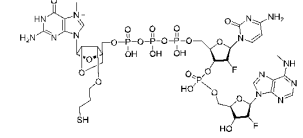
化合物668



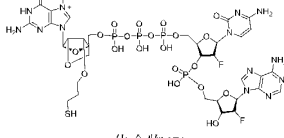
化合物669



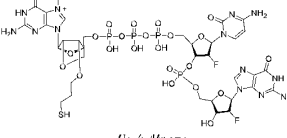
化合物670



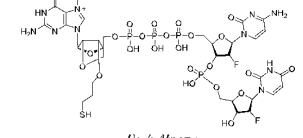
化合物671



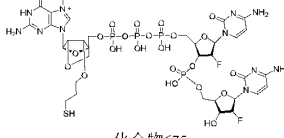
化合物672



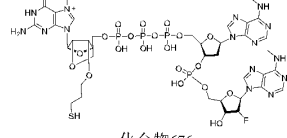
化合物673



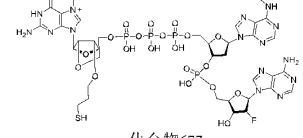
化合物674



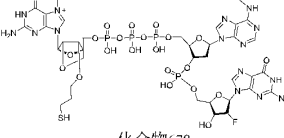
化合物675



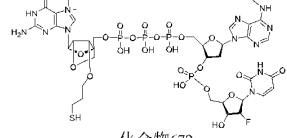
化合物676



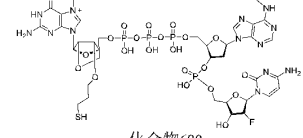
化合物677



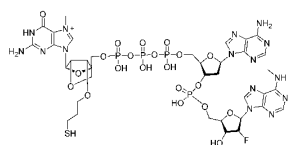
化合物678



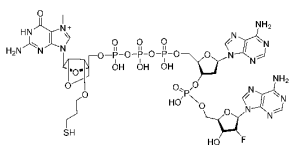
化合物679



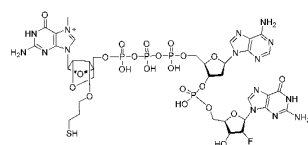
化合物680



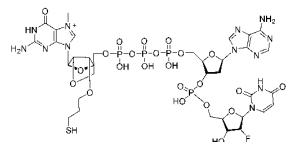
化合物681



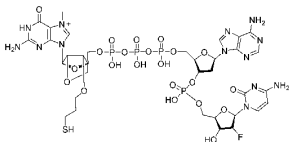
化合物682



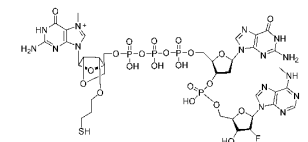
化合物683



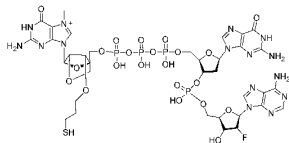
化合物684



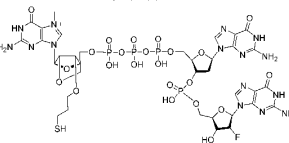
化合物685



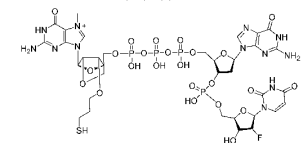
化合物686



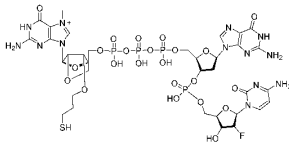
化合物687



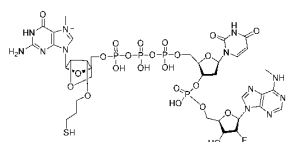
化合物688



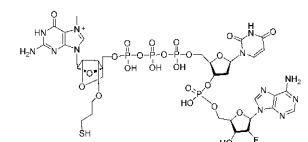
化合物689



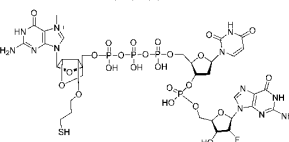
化合物690



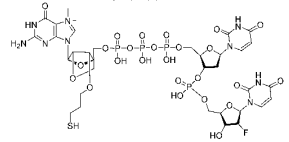
化合物691



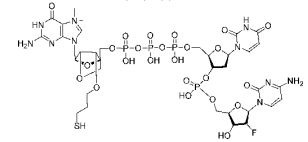
化合物692



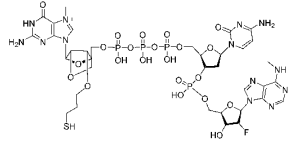
化合物693



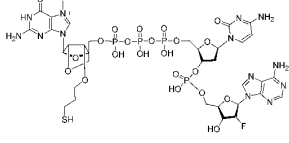
化合物694



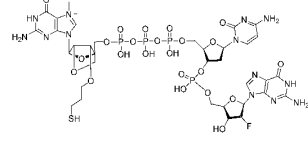
化合物695



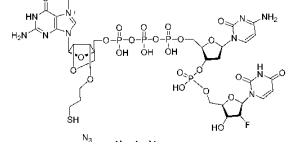
化合物696



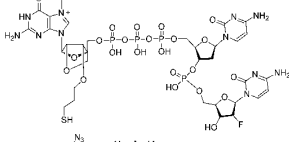
化合物697



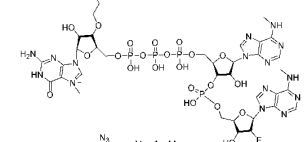
化合物698



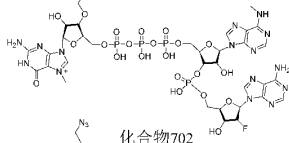
化合物699



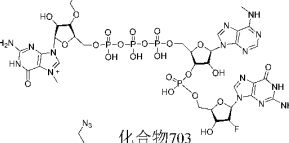
化合物700



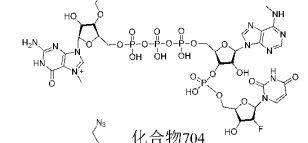
化合物701



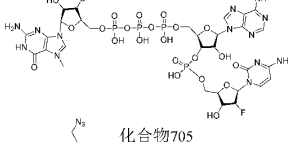
化合物702



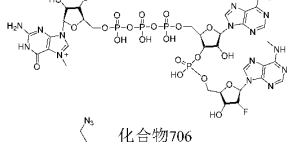
化合物703



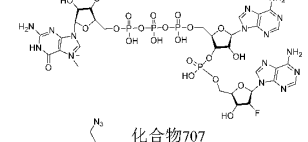
化合物704



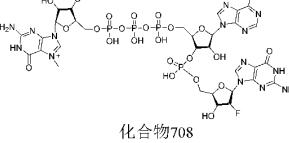
化合物705



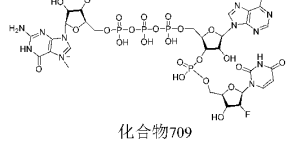
化合物706



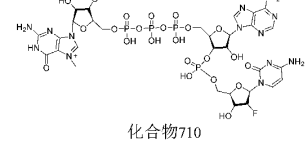
化合物707



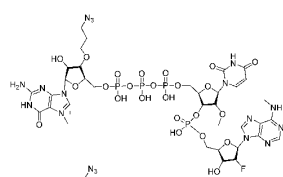
化合物708



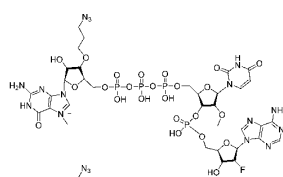
化合物709



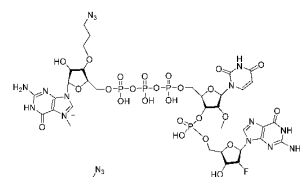
化合物710



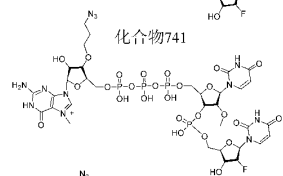
化合物741



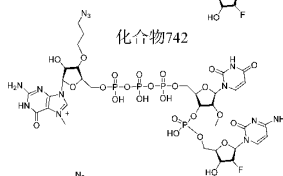
化合物742



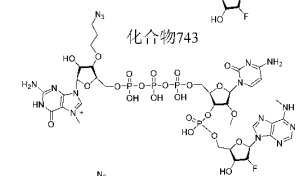
化合物743



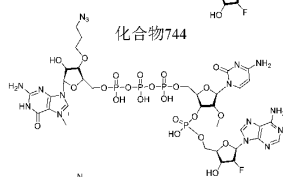
化合物744



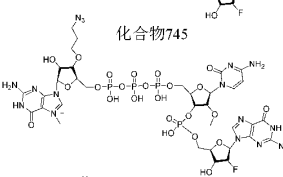
化合物745



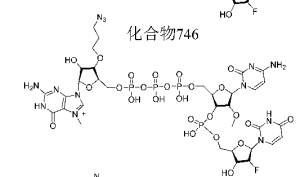
化合物746



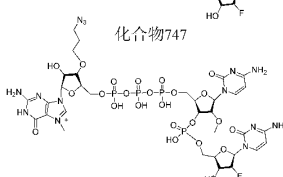
化合物747



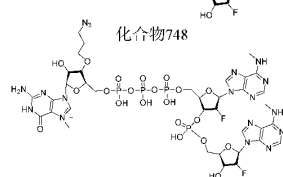
化合物748



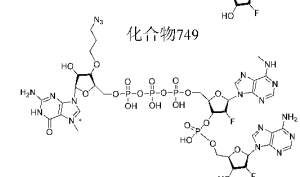
化合物749



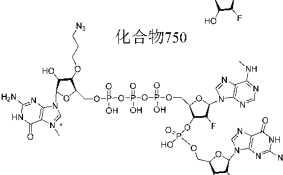
化合物750



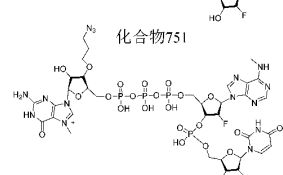
化合物751



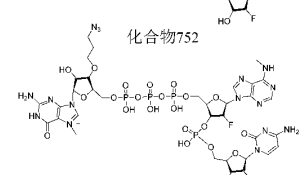
化合物752



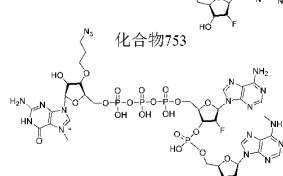
化合物753



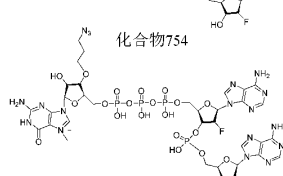
化合物754



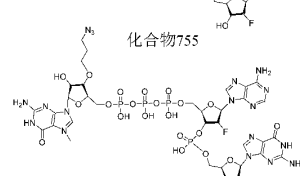
化合物755



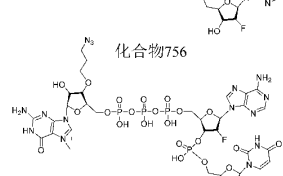
化合物756



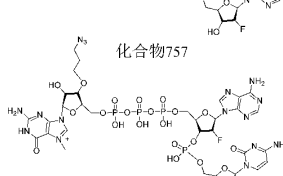
化合物757



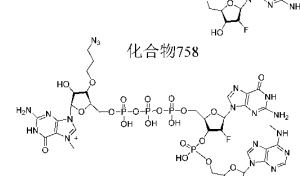
化合物758



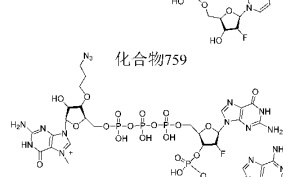
化合物759



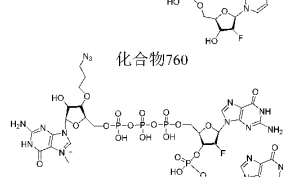
化合物760



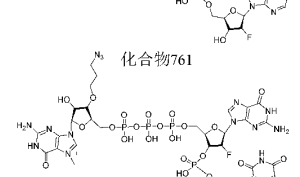
化合物761



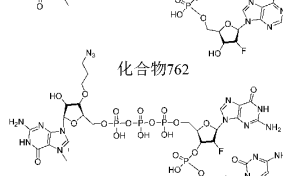
化合物762



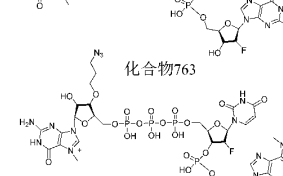
化合物763



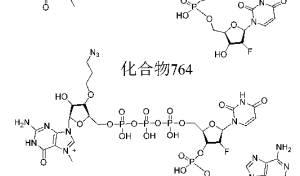
化合物764



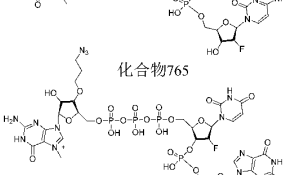
化合物765



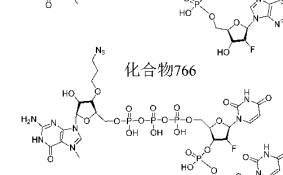
化合物766



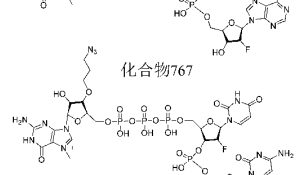
化合物767



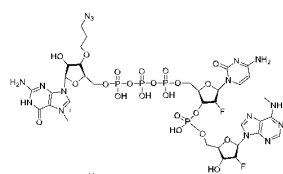
化合物768



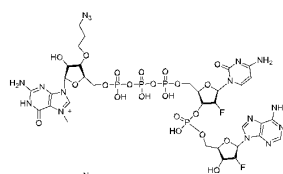
化合物769



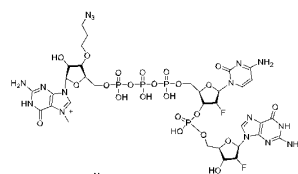
化合物770



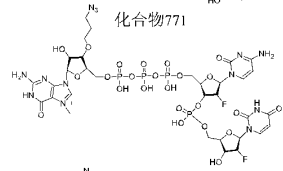
化合物771



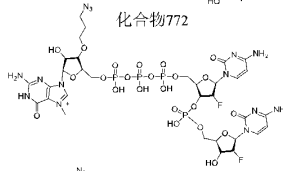
化合物772



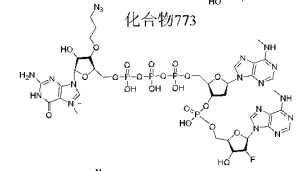
化合物773



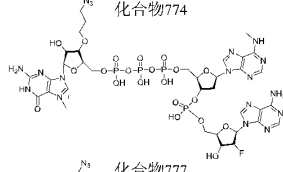
化合物774



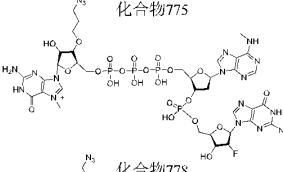
化合物775



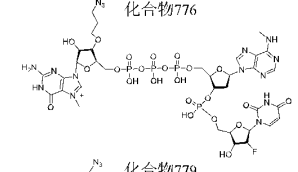
化合物776



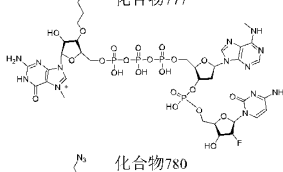
化合物777



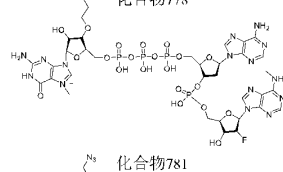
化合物778



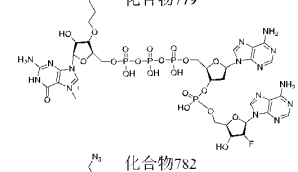
化合物779



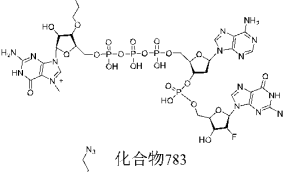
化合物780



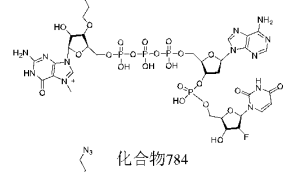
化合物781



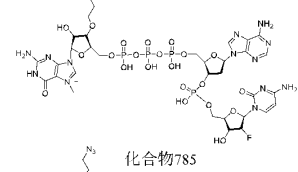
化合物782



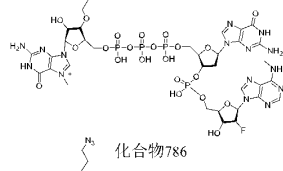
化合物783



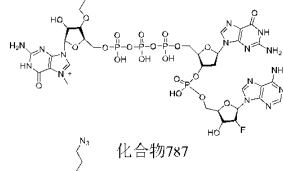
化合物784



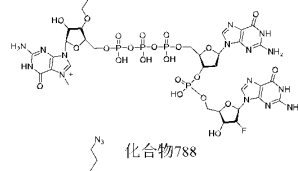
化合物785



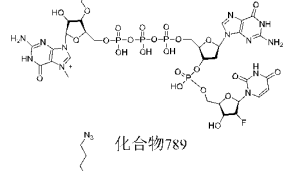
化合物786



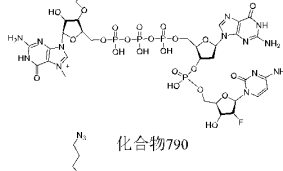
化合物787



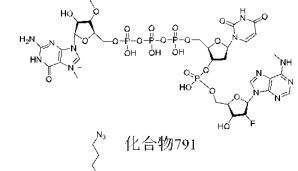
化合物788



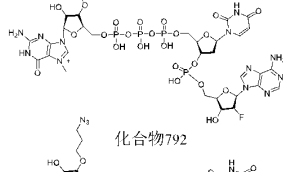
化合物789



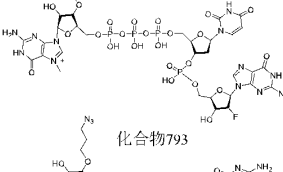
化合物790



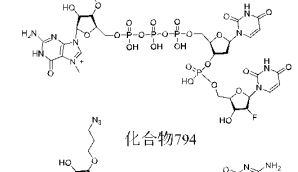
化合物791



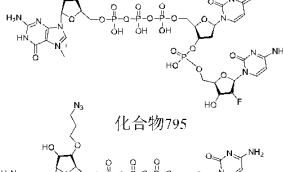
化合物792



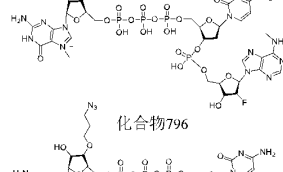
化合物793



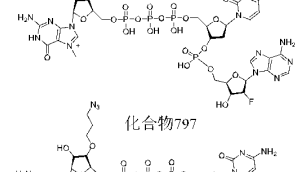
化合物794



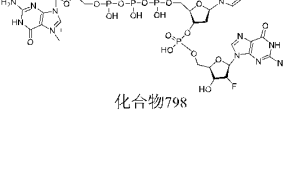
化合物795



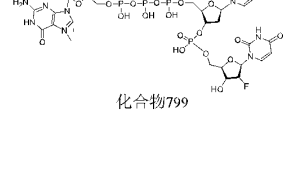
化合物796



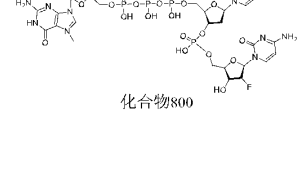
化合物797



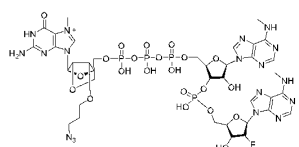
化合物798



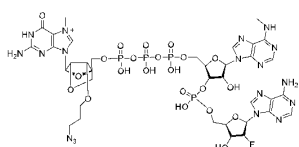
化合物799



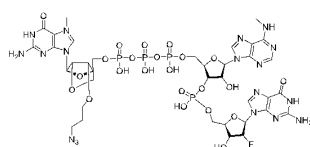
化合物800



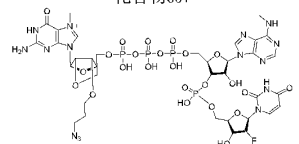
化合物801



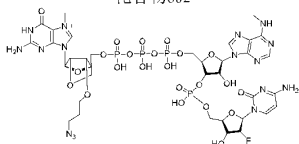
化合物802



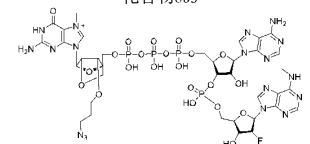
化合物803



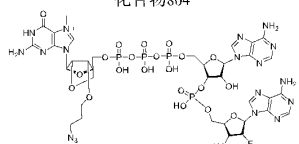
化合物804



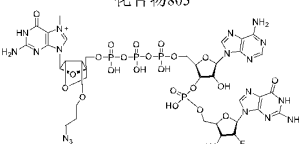
化合物805



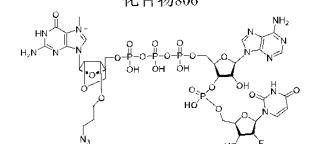
化合物806



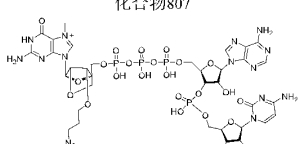
化合物807



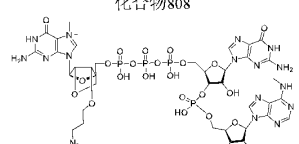
化合物808



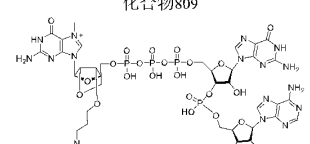
化合物809



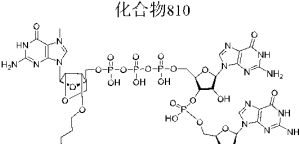
化合物810



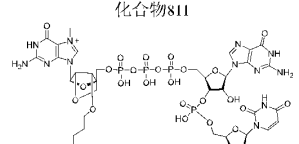
化合物811



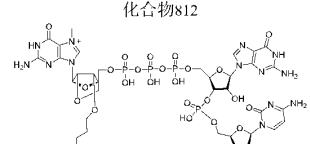
化合物812



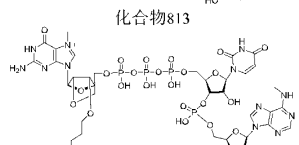
化合物813



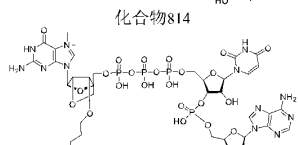
化合物814



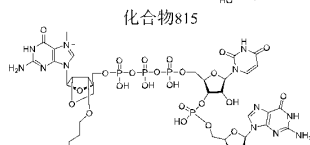
化合物815



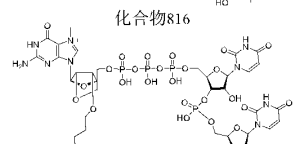
化合物816



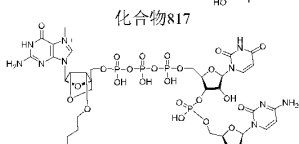
化合物817



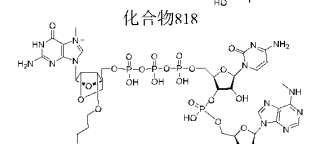
化合物818



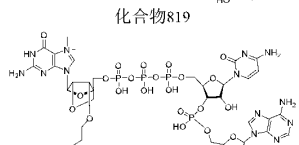
化合物819



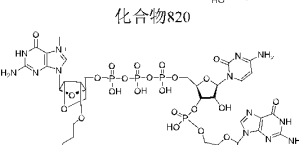
化合物820



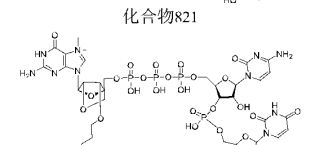
化合物821



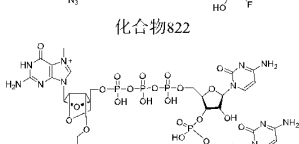
化合物822



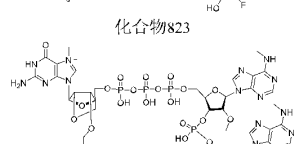
化合物823



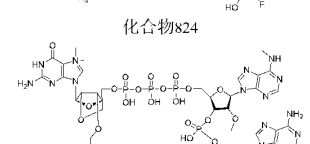
化合物824



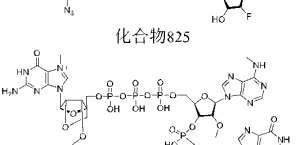
化合物825



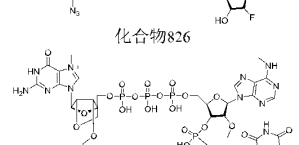
化合物826



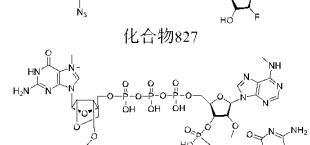
化合物827



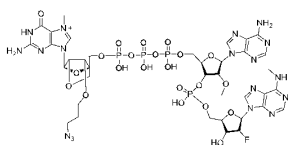
化合物828



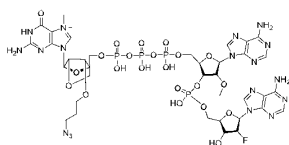
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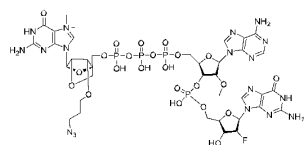
化合物830



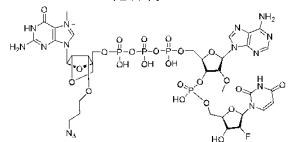
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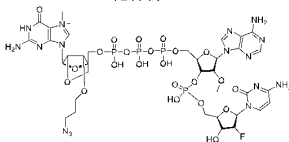
化合物832



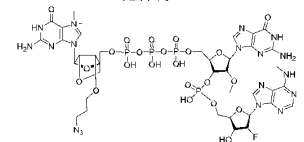
化合物833



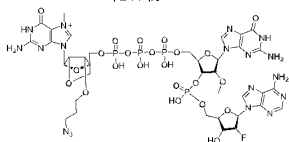
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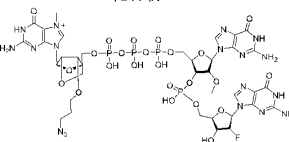
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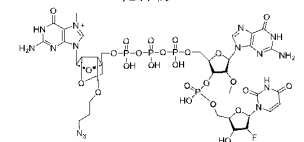
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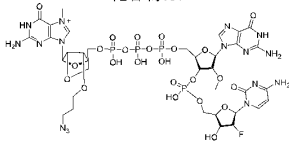
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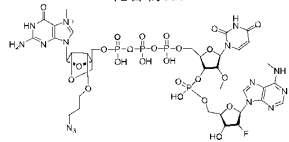
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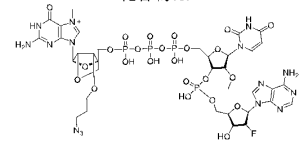
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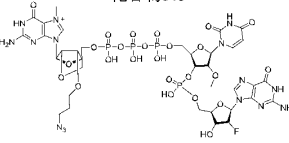
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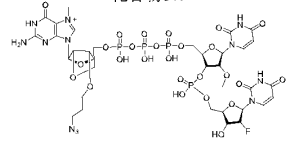
化合物841



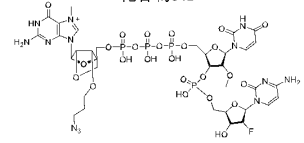
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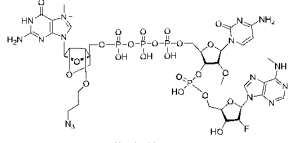
化合物843



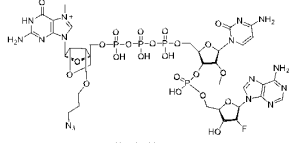
化合物844



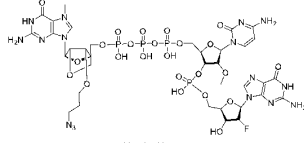
化合物845



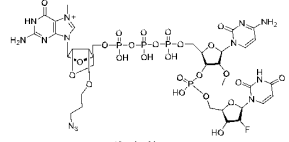
化合物846



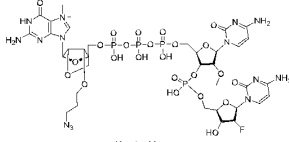
化合物847



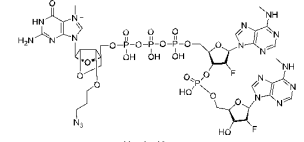
化合物848



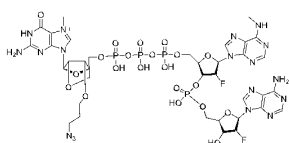
化合物849



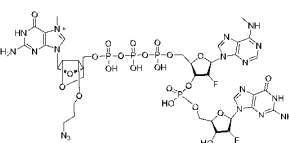
化合物850



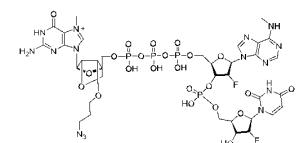
化合物851



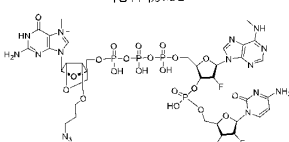
化合物852



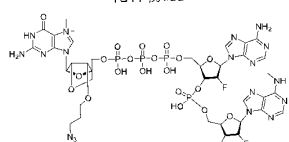
化合物853



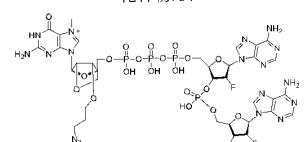
化合物854



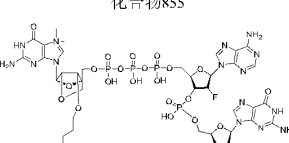
化合物855



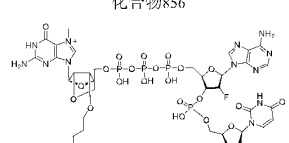
化合物856



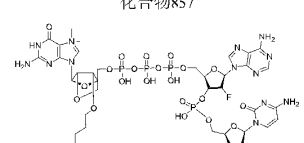
化合物857



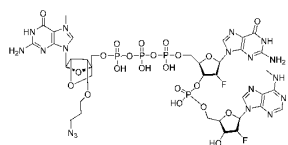
化合物858



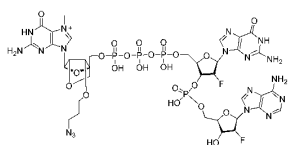
化合物859



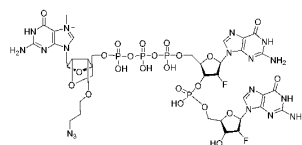
化合物860



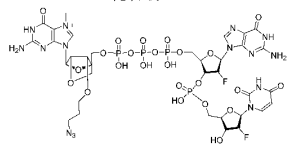
化合物861



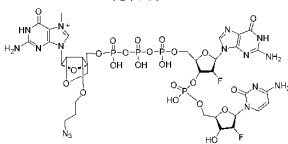
化合物862



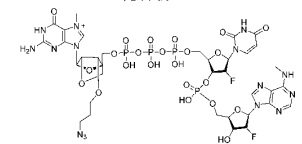
化合物863



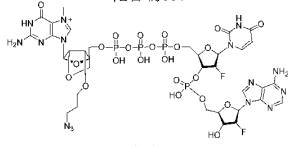
化合物864



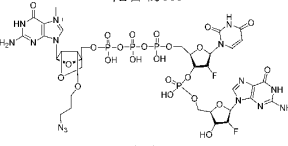
化合物865



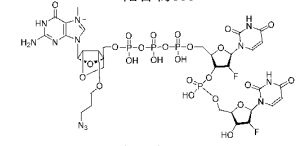
化合物866



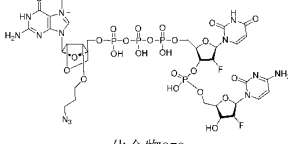
化合物867



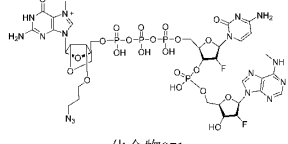
化合物868



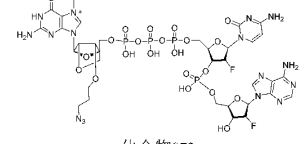
化合物869



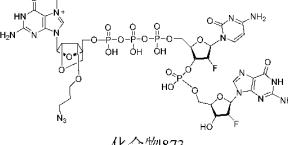
化合物870



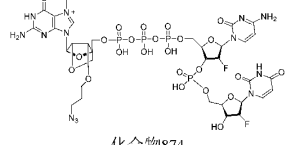
化合物871



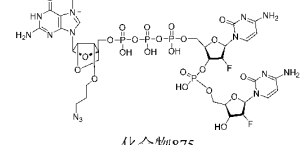
化合物872



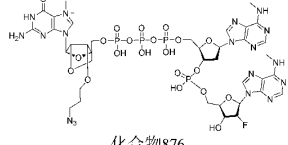
化合物873



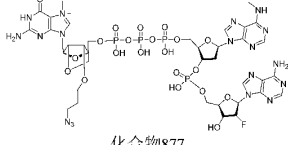
化合物874



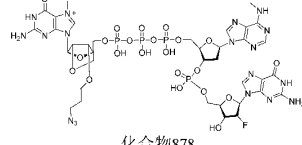
化合物875



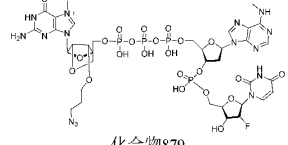
化合物876



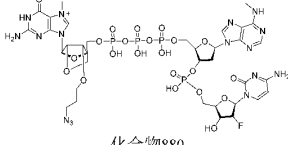
化合物877



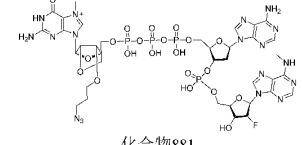
化合物878



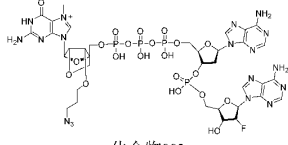
化合物879



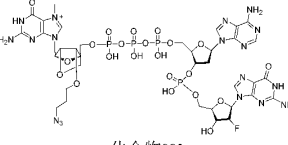
化合物880



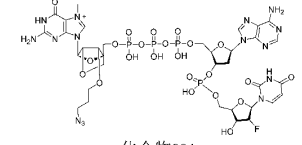
化合物881



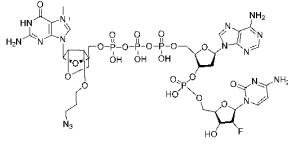
化合物882



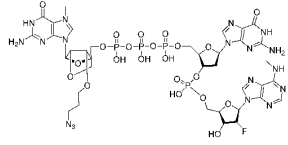
化合物883



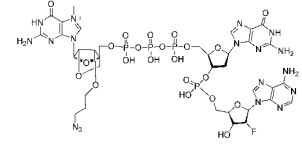
化合物884



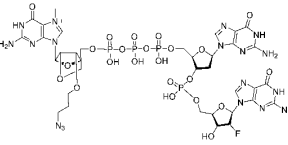
化合物885



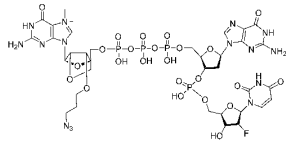
化合物886



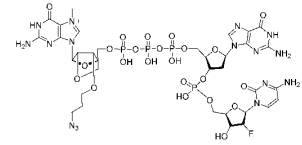
化合物887



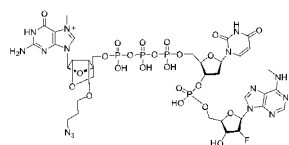
化合物888



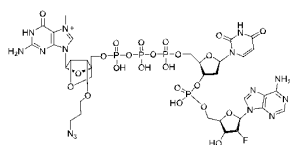
化合物889



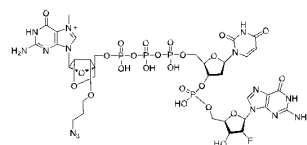
化合物890



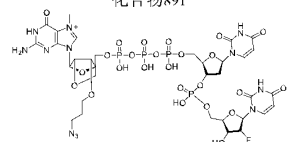
化合物891



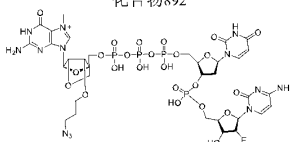
化合物892



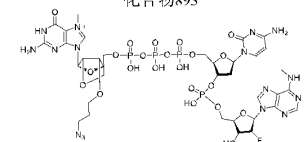
化合物893



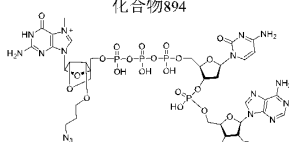
化合物894



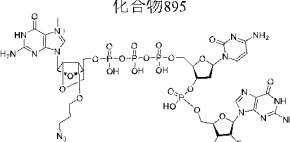
化合物895



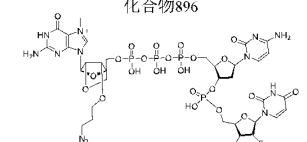
化合物896



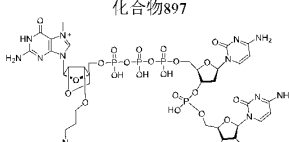
化合物897



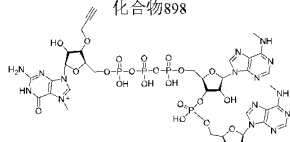
化合物898



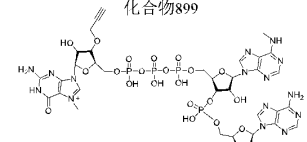
化合物899



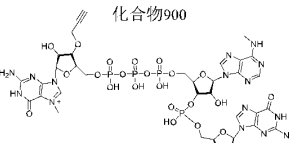
化合物900



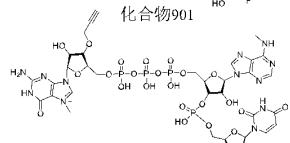
化合物901



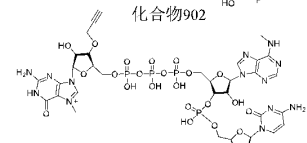
化合物902



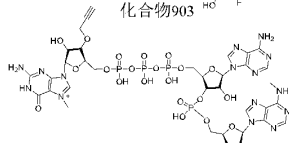
化合物903



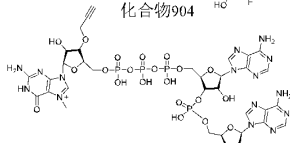
化合物904



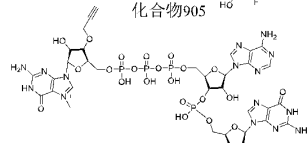
化合物905



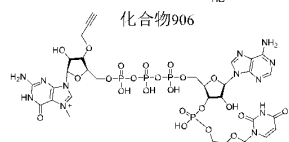
化合物906



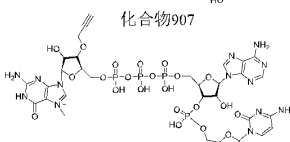
化合物907



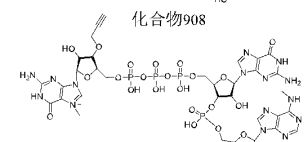
化合物908



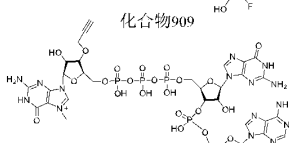
化合物909



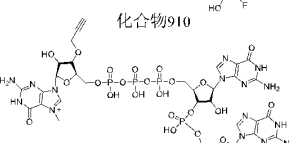
化合物910



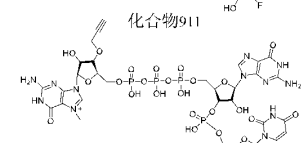
化合物911



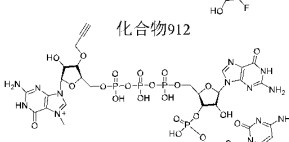
化合物912



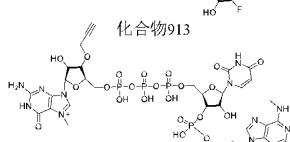
化合物913



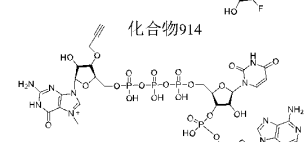
化合物914



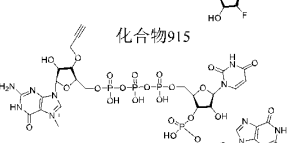
化合物915



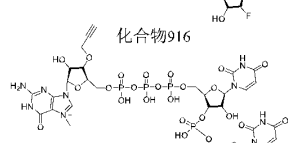
化合物916



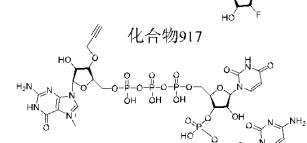
化合物917



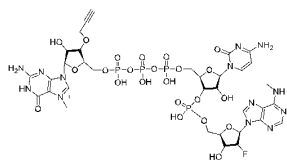
化合物918



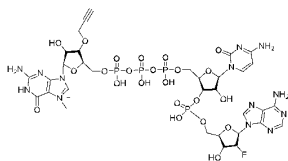
化合物919



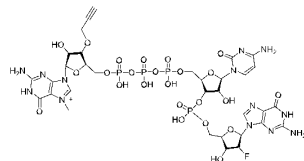
化合物920



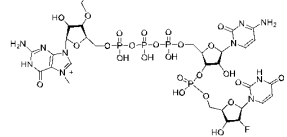
化合物921



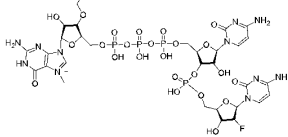
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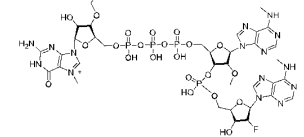
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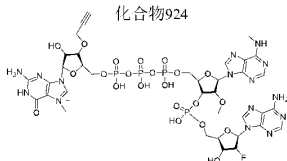
化合物924



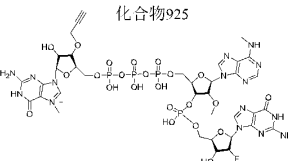
化合物925



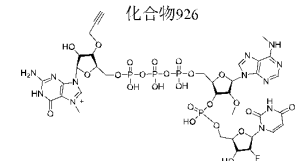
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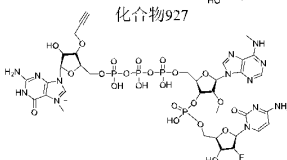
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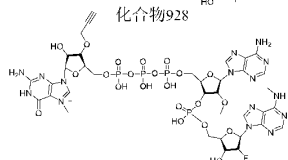
化合物928



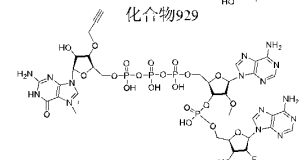
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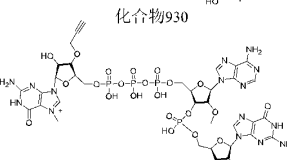
化合物930



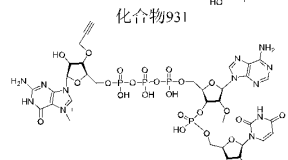
化合物931



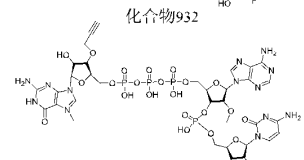
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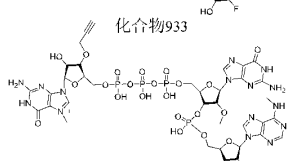
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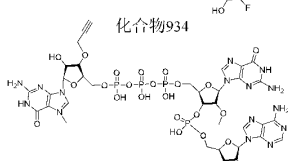
化合物934



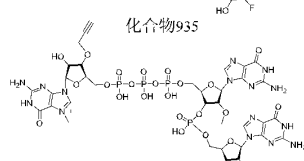
化合物935



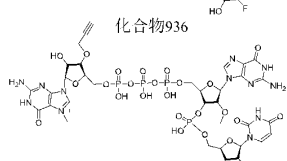
化合物936



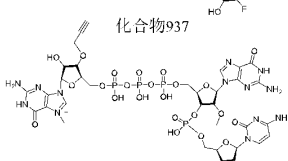
化合物937



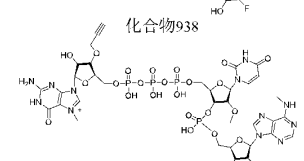
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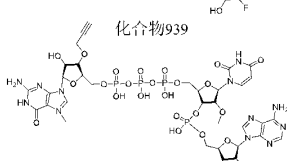
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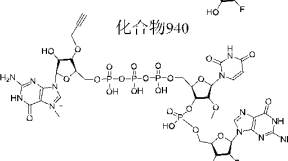
化合物940



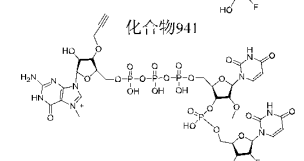
化合物941



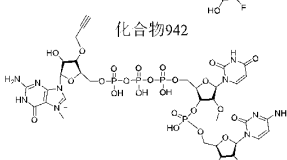
化合物942



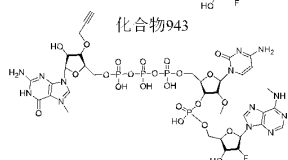
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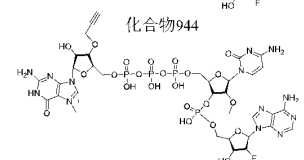
化合物944



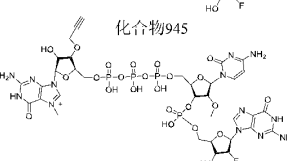
化合物945



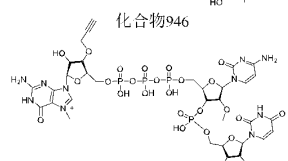
化合物946



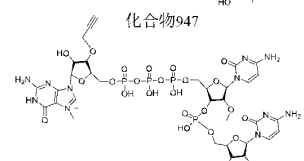
化合物947



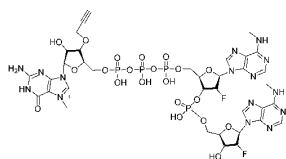
化合物948



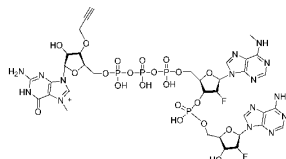
化合物949



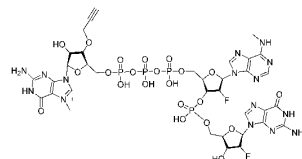
化合物950



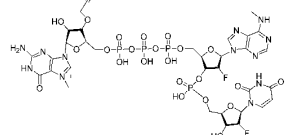
化合物951



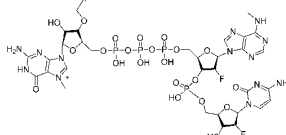
化合物952



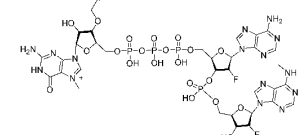
化合物953



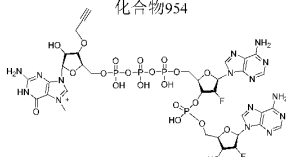
化合物954



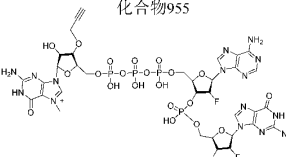
化合物955



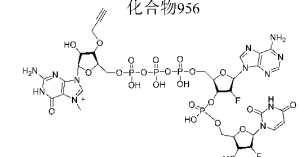
化合物956



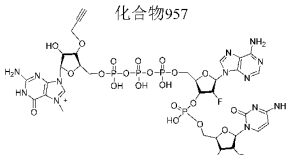
化合物957



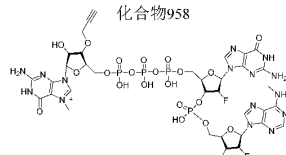
化合物958



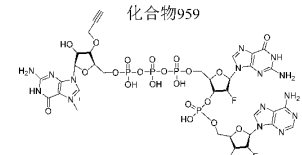
化合物959



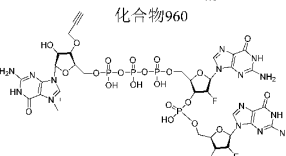
化合物960



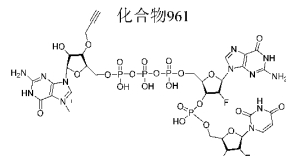
化合物961



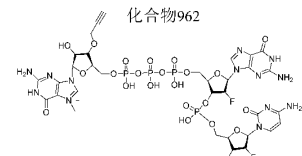
化合物962



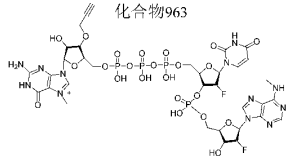
化合物963



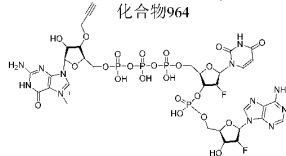
化合物964



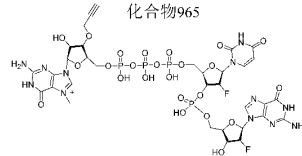
化合物965



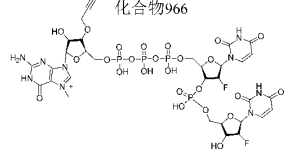
化合物966



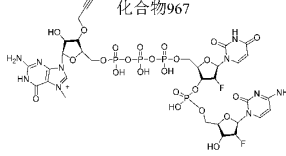
化合物967



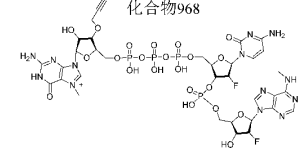
化合物968



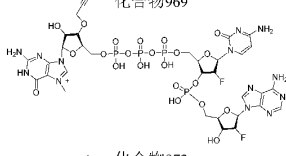
化合物969



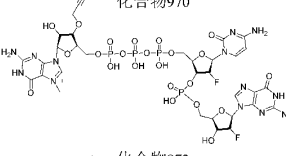
化合物970



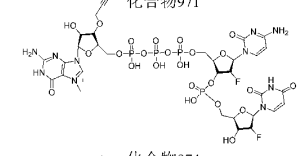
化合物971



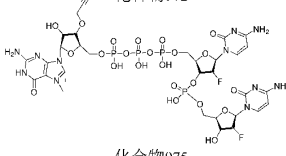
化合物972



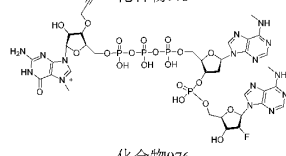
化合物973



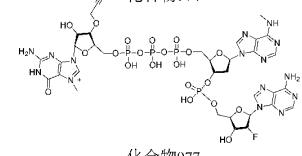
化合物974



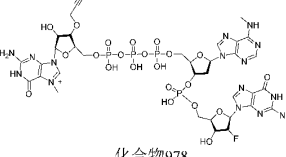
化合物975



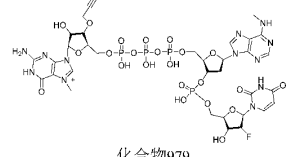
化合物976



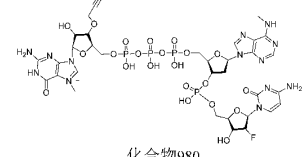
化合物977



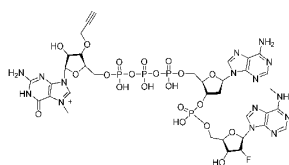
化合物978



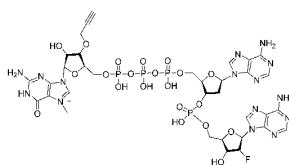
化合物979



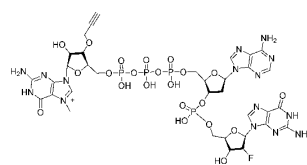
化合物980



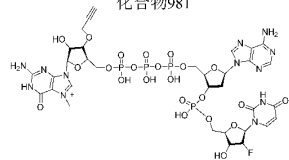
化合物981



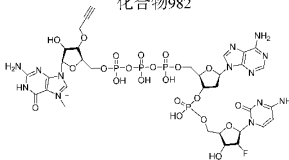
化合物982



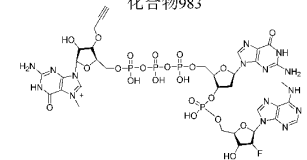
化合物983



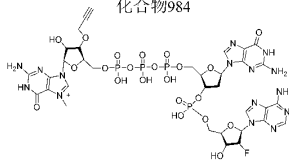
化合物984



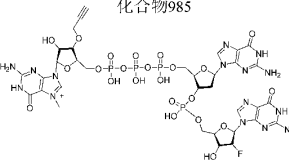
化合物985



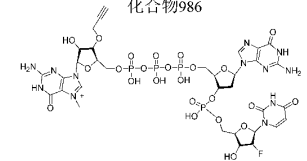
化合物986



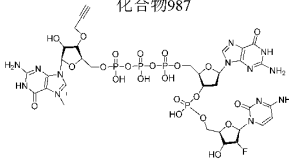
化合物987



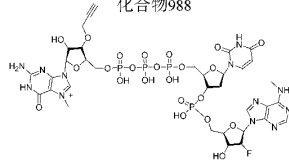
化合物988



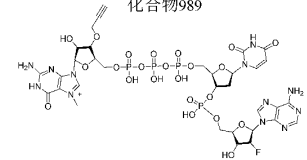
化合物989



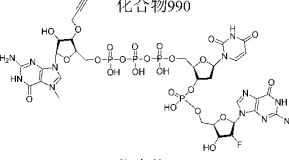
化合物990



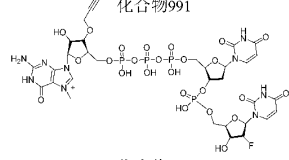
化合物991



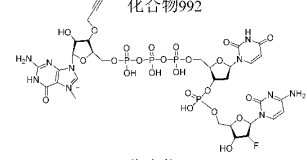
化合物992



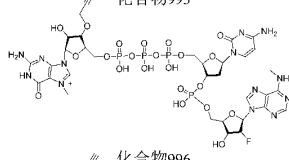
化合物993



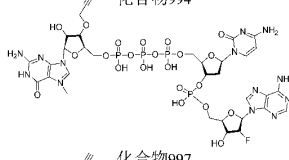
化合物994



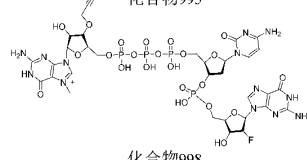
化合物995



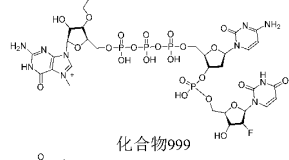
化合物996



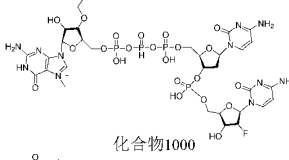
化合物997



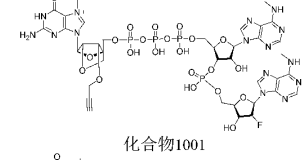
化合物998



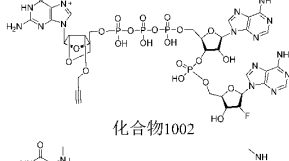
化合物999



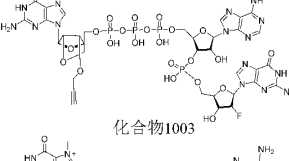
化合物1000



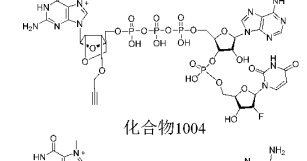
化合物1001



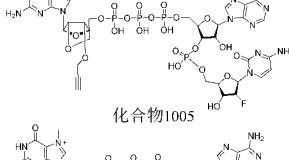
化合物1002



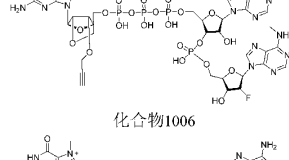
化合物1003



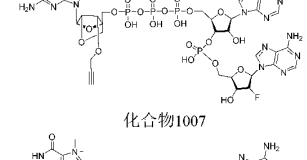
化合物1004



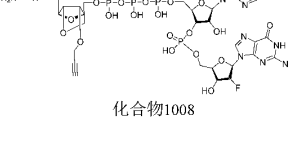
化合物1005



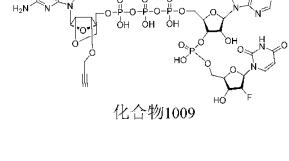
化合物1006



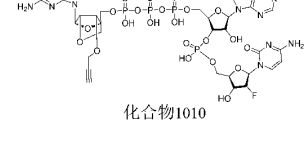
化合物1007



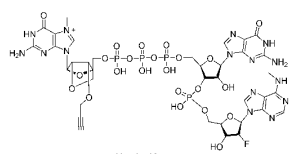
化合物1008



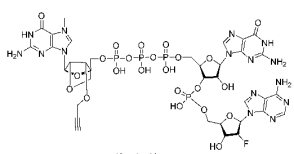
化合物1009



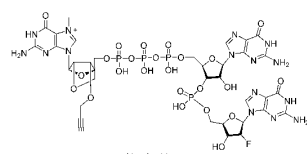
化合物1010



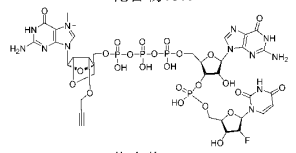
化合物1011



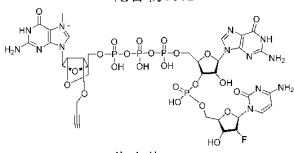
化合物1012



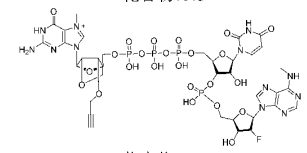
化合物1013



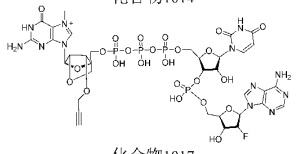
化合物1014



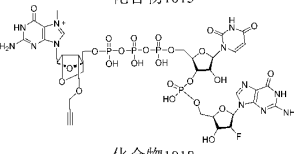
化合物1015



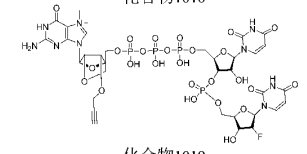
化合物1016



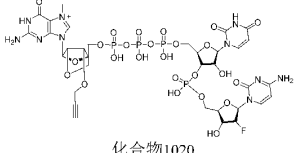
化合物1017



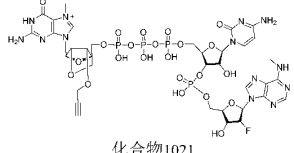
化合物1018



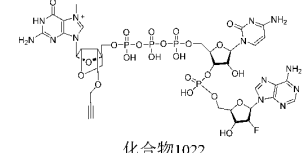
化合物1019



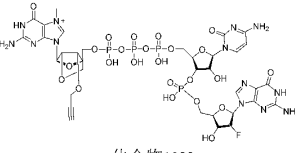
化合物1020



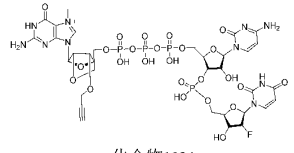
化合物1021



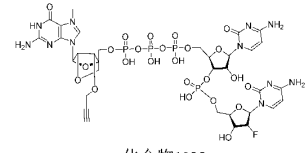
化合物1022



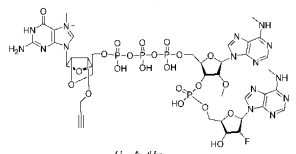
化合物1023



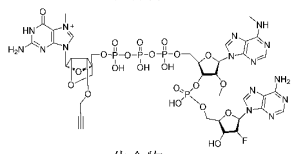
化合物1024



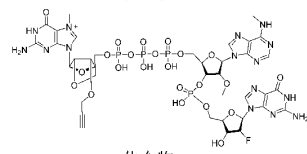
化合物1025



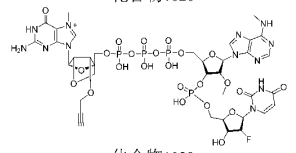
化合物1026



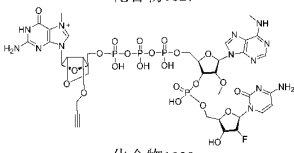
化合物1027



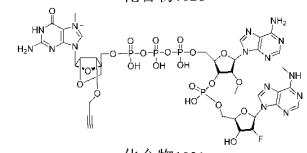
化合物1028



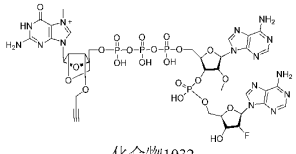
化合物1029



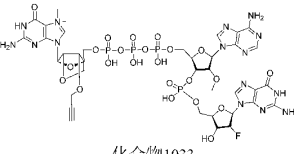
化合物1030



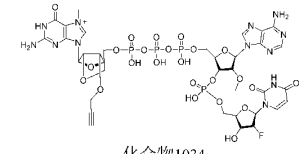
化合物1031



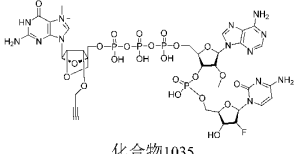
化合物1032



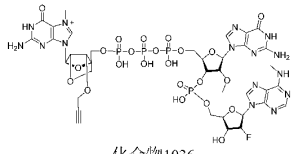
化合物1033



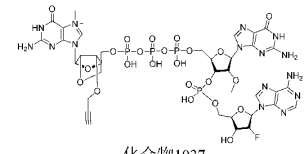
化合物1034



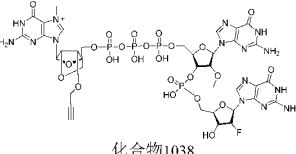
化合物1035



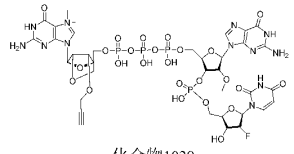
化合物1036



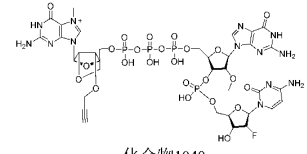
化合物1037



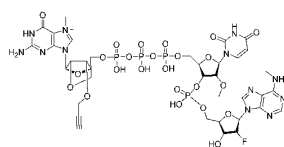
化合物1038



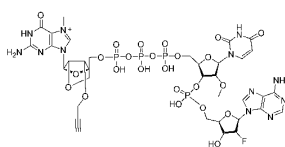
化合物1039



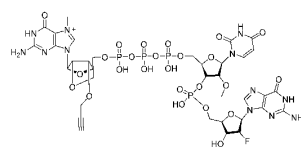
化合物1040



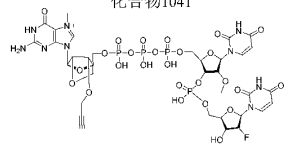
化合物1041



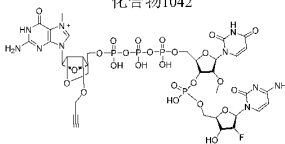
化合物1042



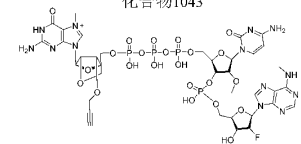
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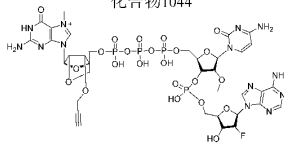
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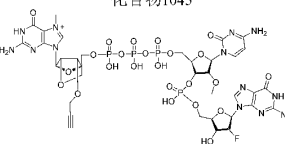
化合物1045



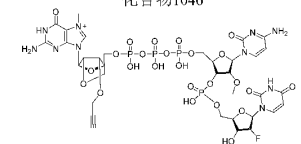
化合物1046



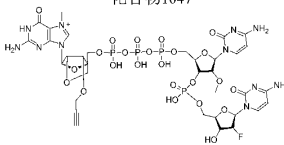
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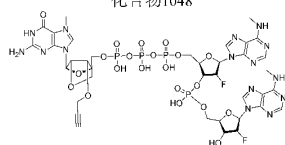
化合物1048



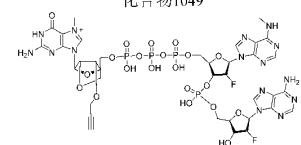
化合物1049



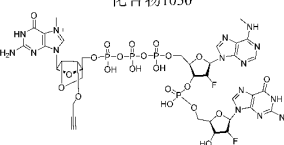
化合物1050



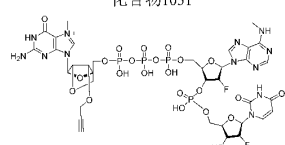
化合物1051



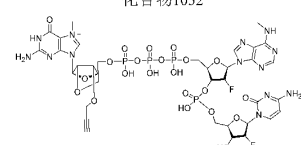
化合物1052



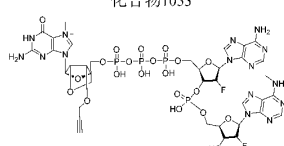
化合物1053



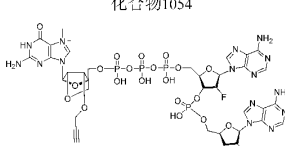
化合物1054



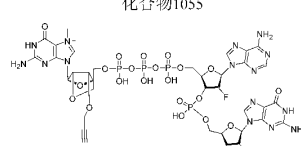
化合物1055



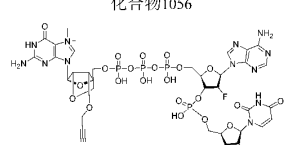
化合物1056



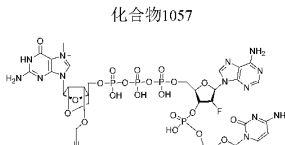
化合物1057



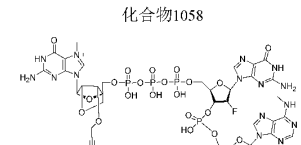
化合物1058



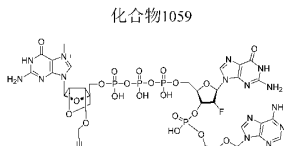
化合物1059



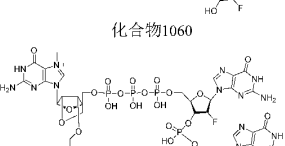
化合物1060



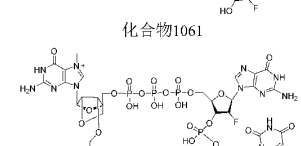
化合物1061



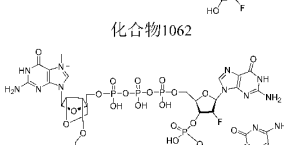
化合物1062



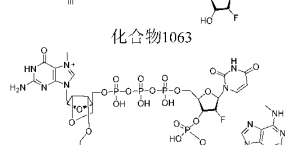
化合物1063



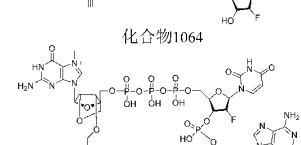
化合物1064



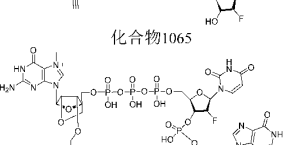
化合物1065



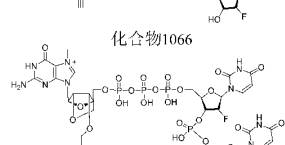
化合物1066



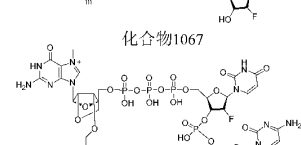
化合物1067



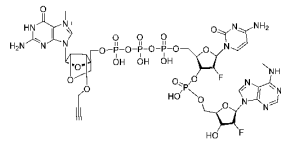
化合物1068



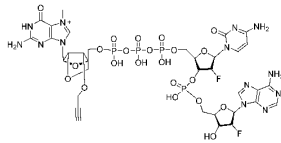
化合物1069



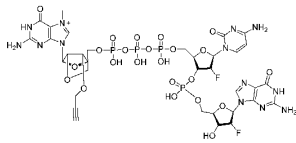
化合物1070



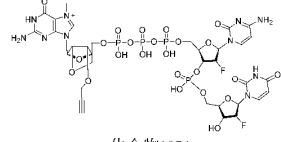
化合物1071



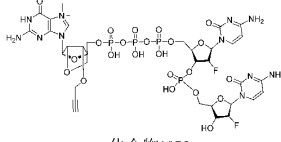
化合物1072



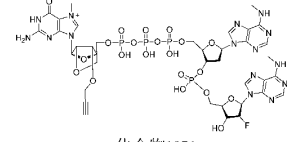
化合物1073



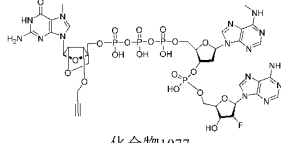
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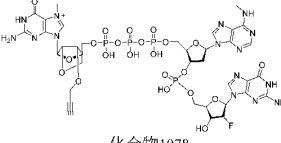
化合物1075



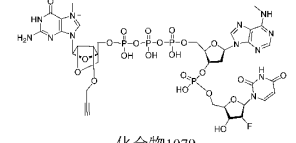
化合物1076



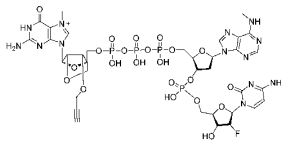
化合物1077



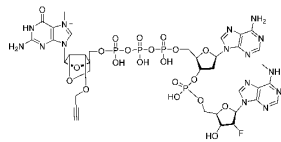
化合物1078



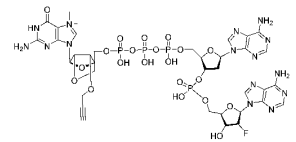
化合物1079



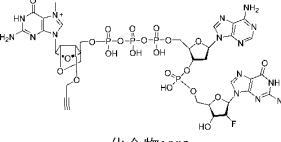
化合物1080



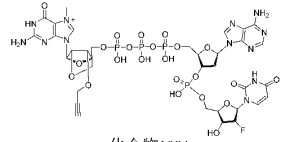
化合物1081



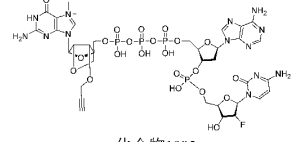
化合物1082



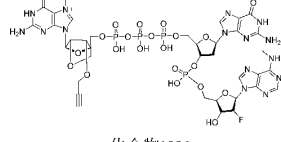
化合物1083



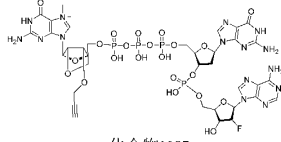
化合物1084



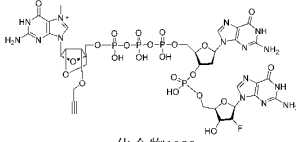
化合物1085



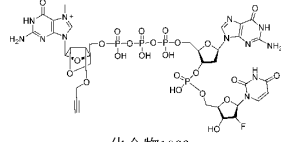
化合物1086



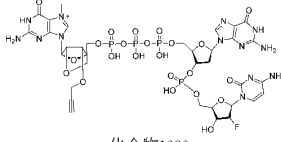
化合物1087



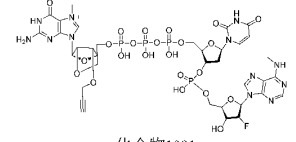
化合物1088



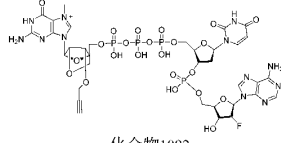
化合物1089



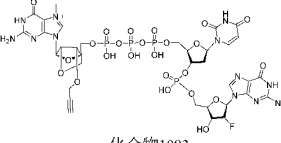
化合物1090



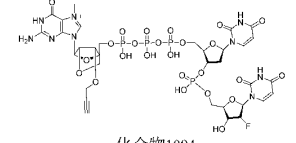
化合物1091



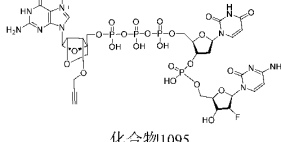
化合物1092



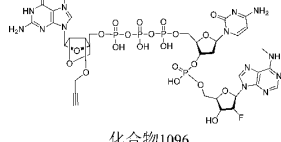
化合物1093



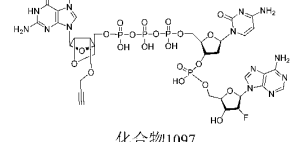
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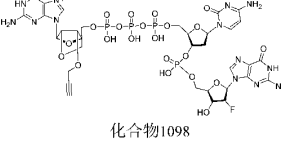
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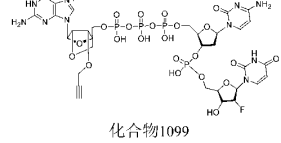
化合物1096



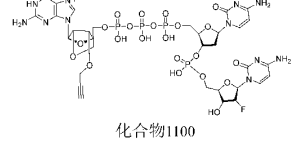
化合物1097



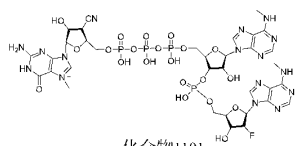
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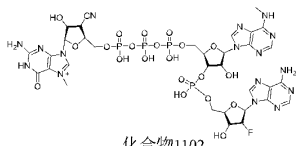
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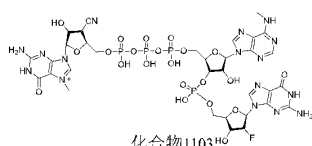
化合物1100



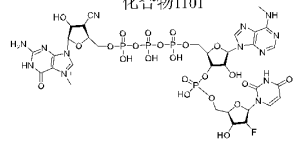
化合物1101



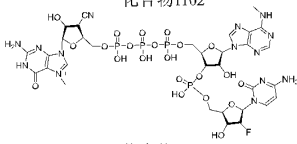
化合物1102



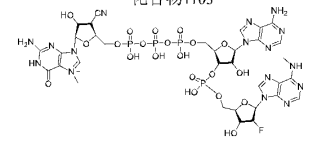
化合物1103



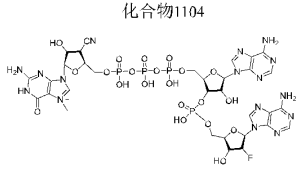
化合物1104



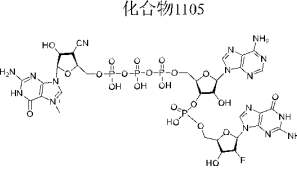
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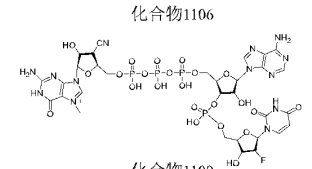
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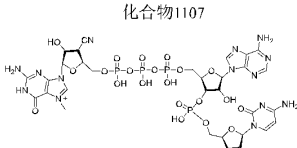
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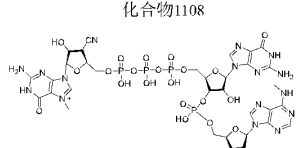
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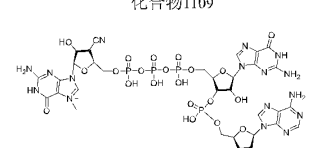
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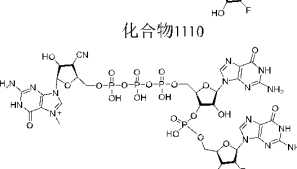
化合物1110



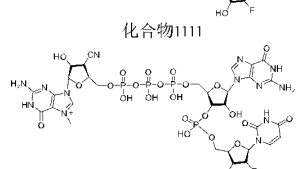
化合物1111



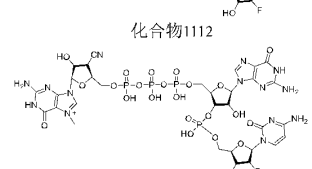
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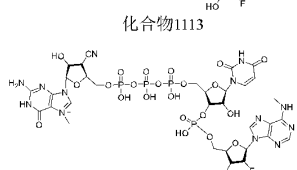
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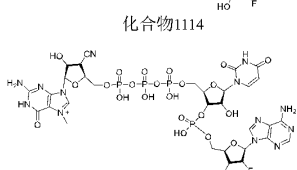
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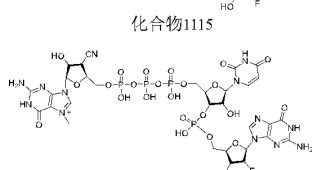
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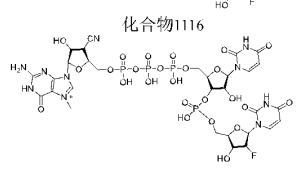
化合物1116



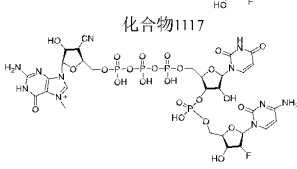
化合物1117



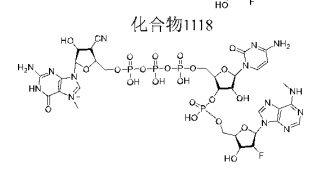
化合物1118



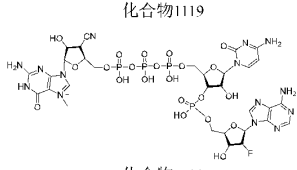
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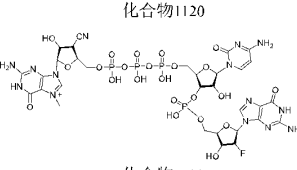
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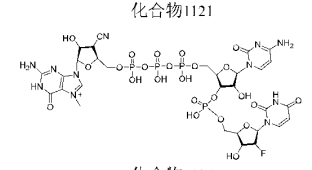
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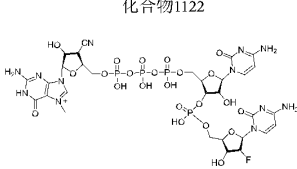
化合物1122



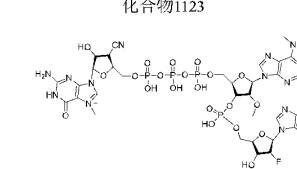
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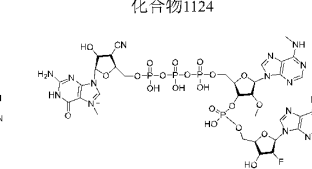
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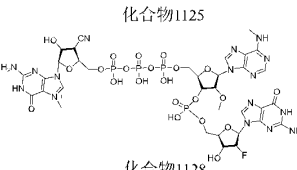
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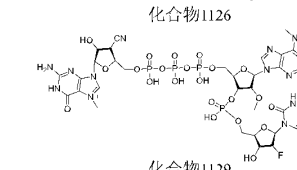
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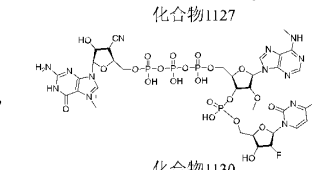
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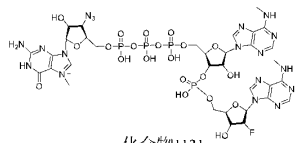
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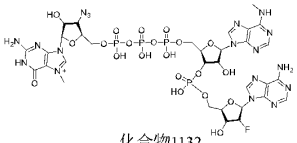
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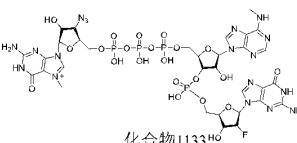
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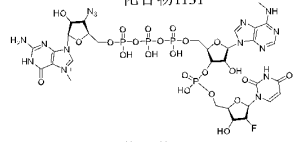
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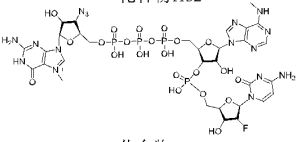
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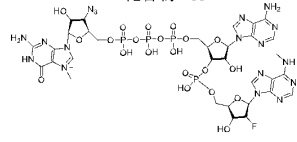
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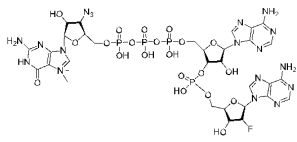
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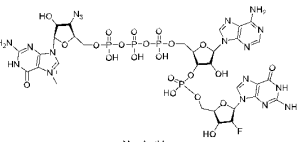
化合物1135



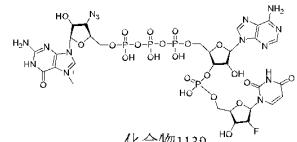
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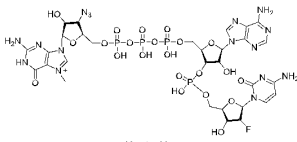
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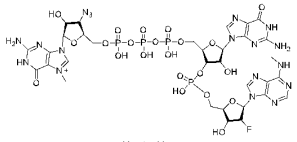
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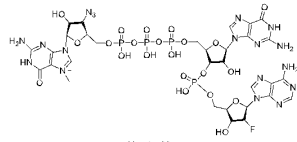
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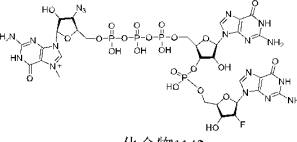
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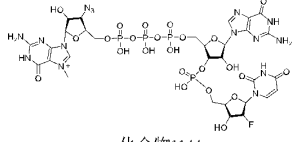
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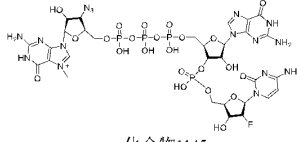
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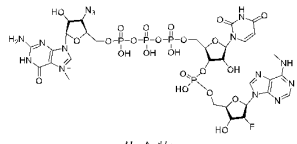
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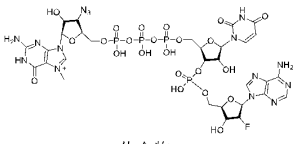
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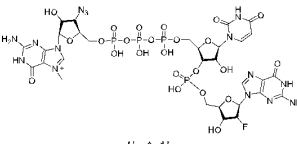
化合物1145



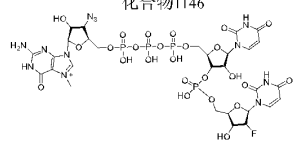
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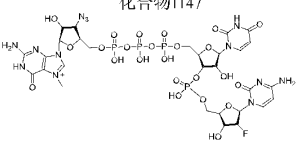
化合物1147



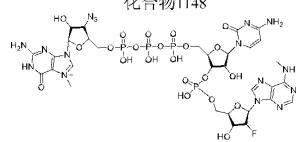
化合物1148



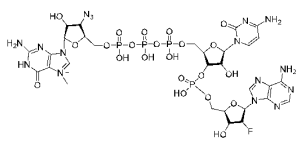
化合物1149



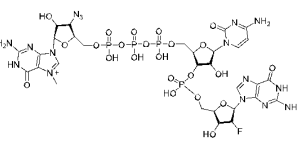
化合物1150



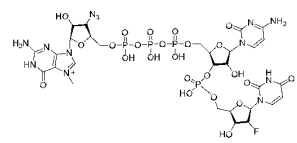
化合物1151



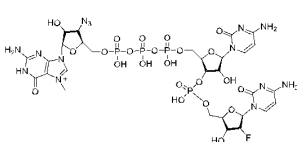
化合物1152



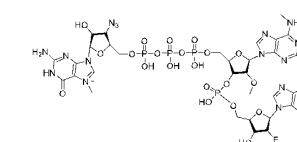
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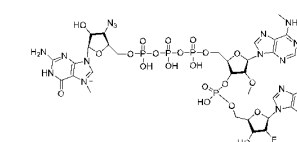
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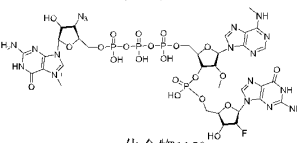
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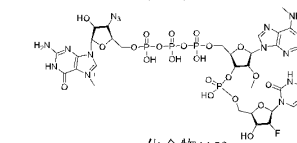
化合物1156



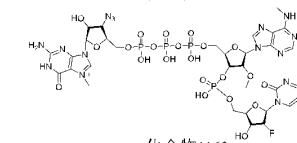
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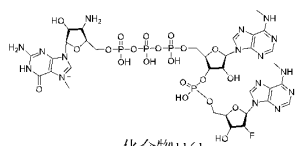
化合物1158



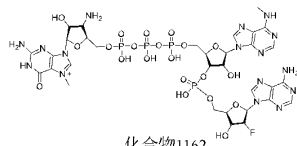
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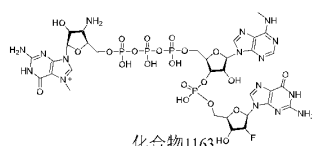
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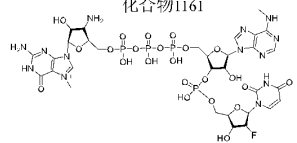
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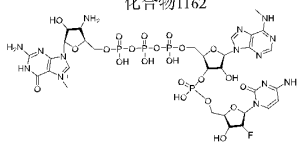
化合物1162



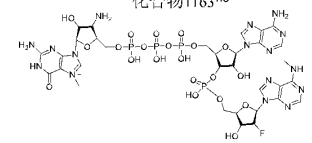
化合物1163



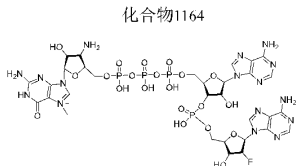
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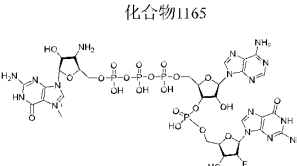
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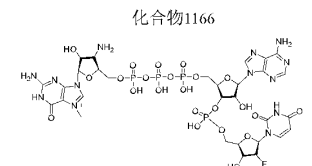
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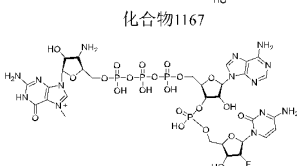
化合物1167



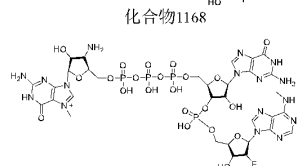
化合物1168



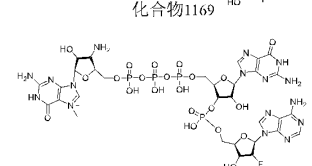
化合物1169



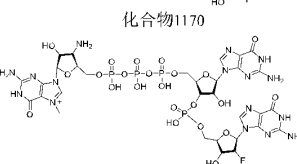
化合物1170



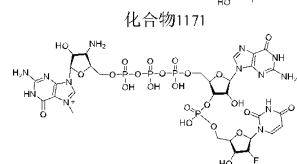
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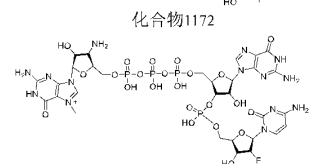
化合物1172



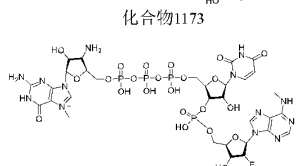
化合物1173



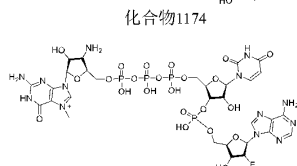
化合物1174



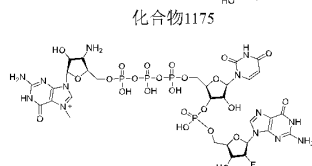
化合物1175



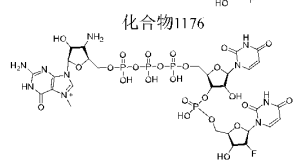
化合物1176



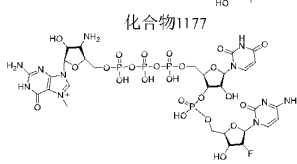
化合物1177



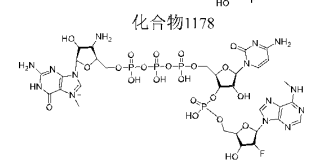
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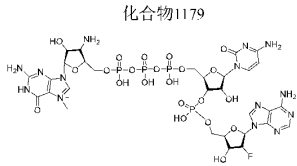
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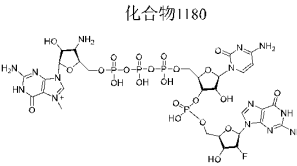
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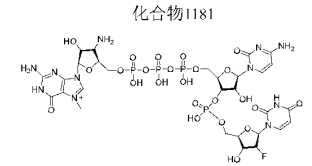
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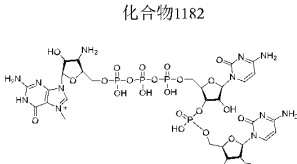
化合物1182



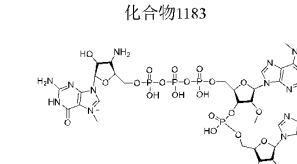
化合物1183



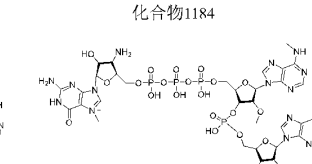
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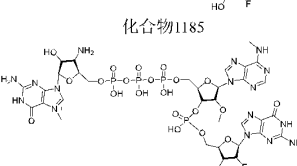
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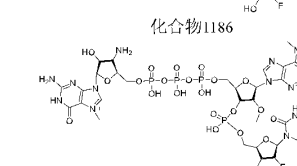
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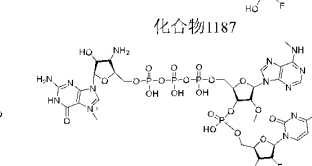
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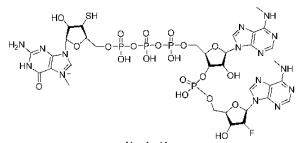
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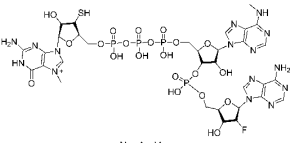
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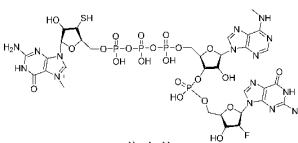
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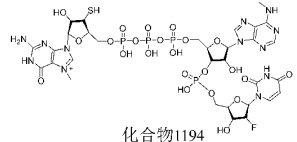
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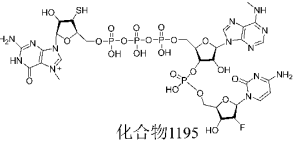
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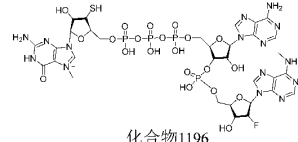
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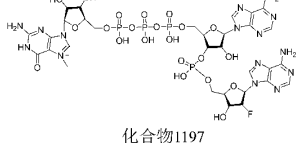
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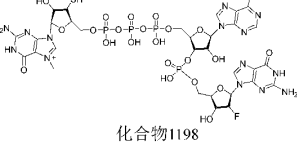
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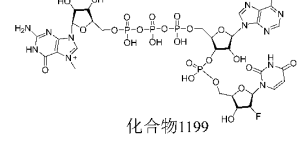
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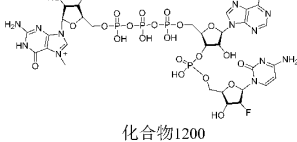
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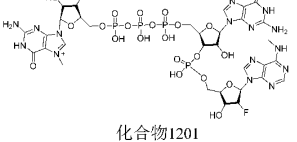
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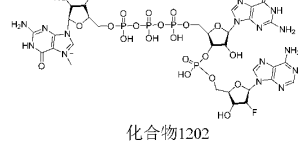
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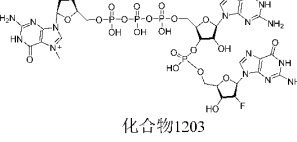
化合物1200



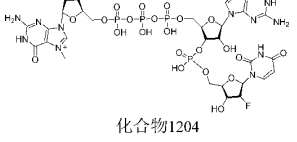
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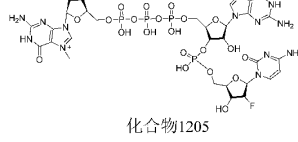
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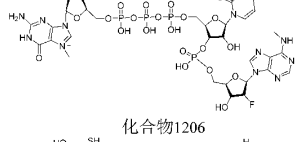
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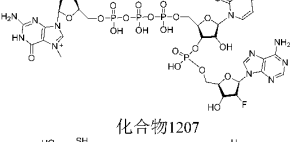
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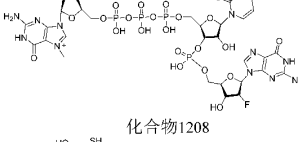
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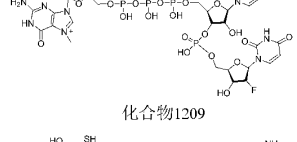
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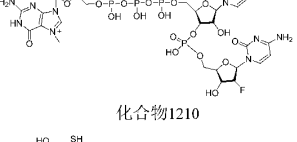
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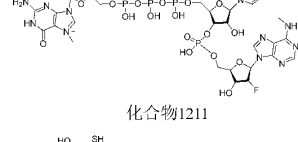
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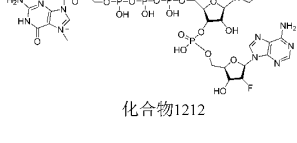
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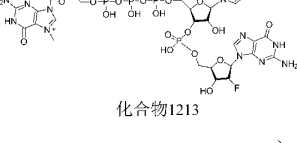
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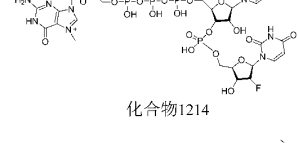
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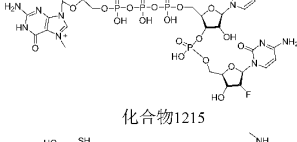
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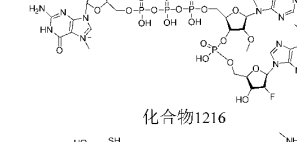
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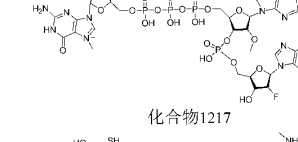
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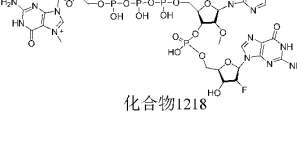
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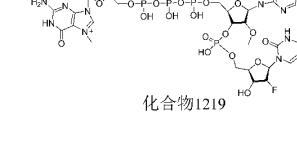
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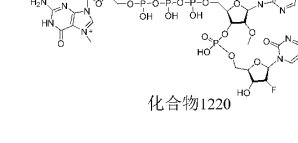
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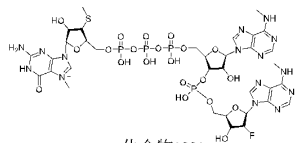
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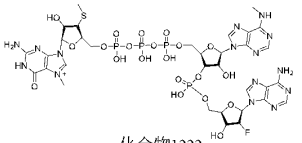
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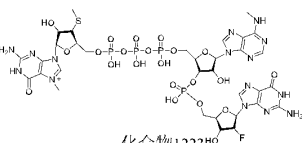
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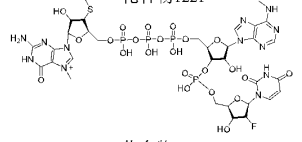
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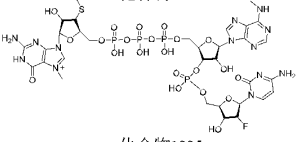
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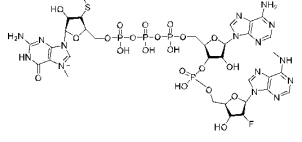
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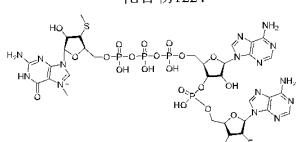
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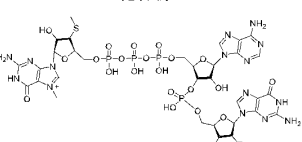
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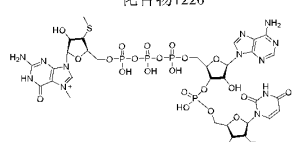
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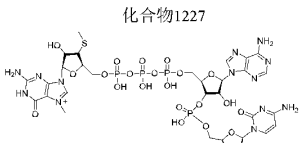
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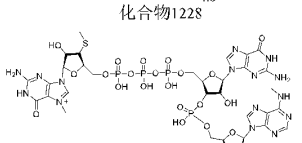
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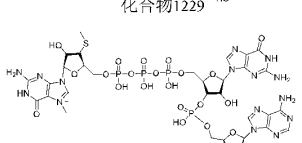
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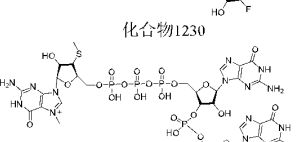
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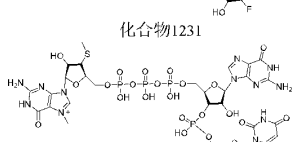
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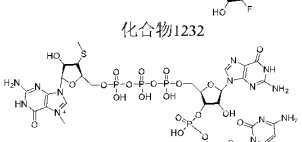
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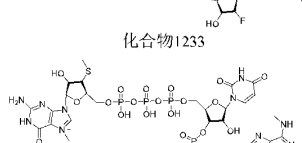
化合物1233



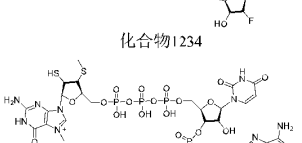
化合物1234



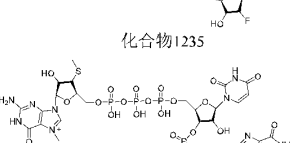
化合物1235



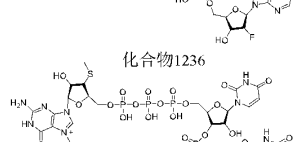
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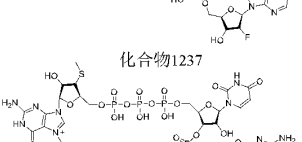
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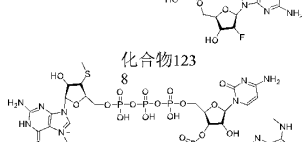
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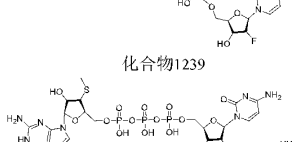
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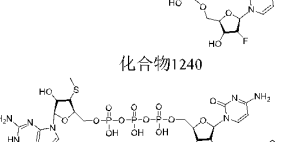
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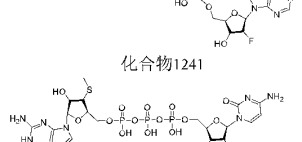
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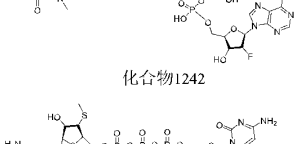
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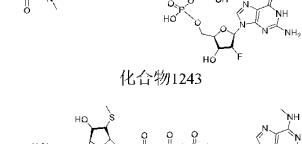
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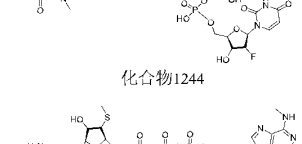
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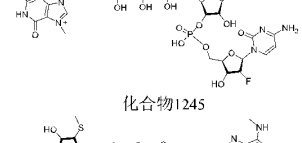
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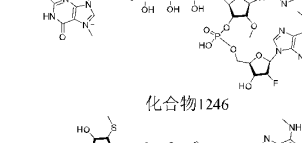
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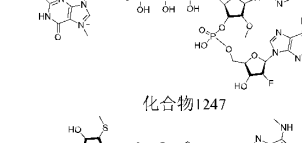
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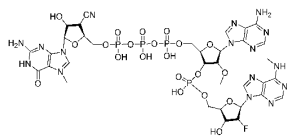
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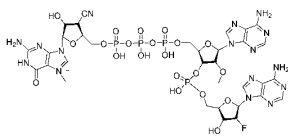
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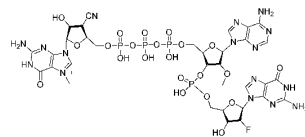
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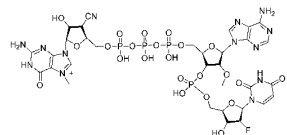
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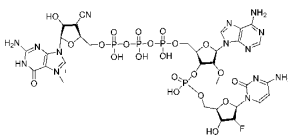
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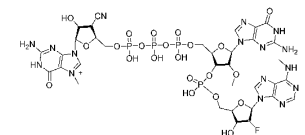
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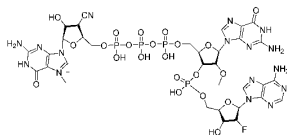
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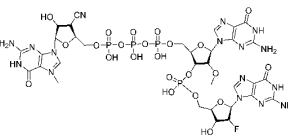
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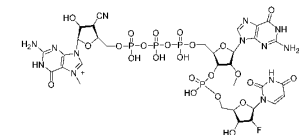
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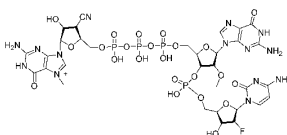
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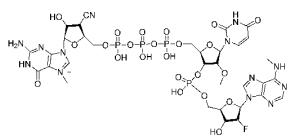
化合物1258



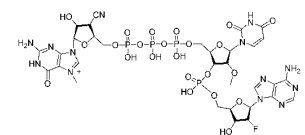
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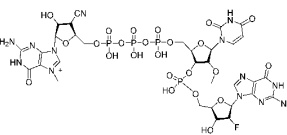
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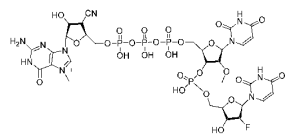
化合物1261



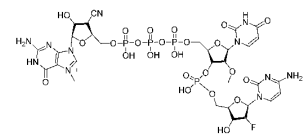
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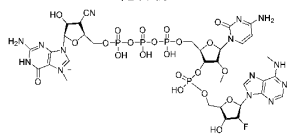
化合物1263



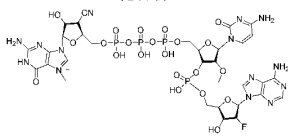
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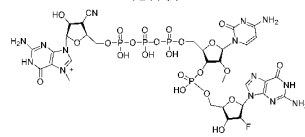
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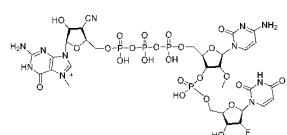
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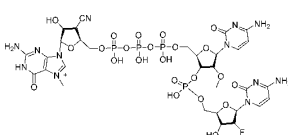
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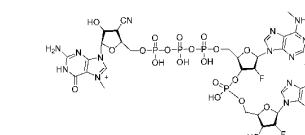
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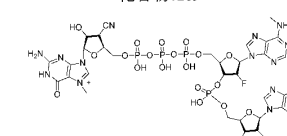
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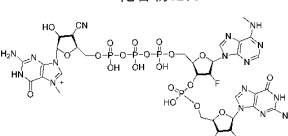
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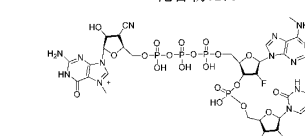
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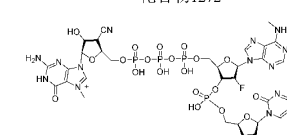
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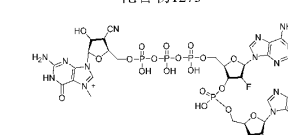
化合物1273



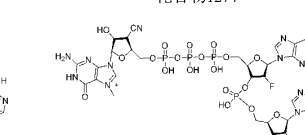
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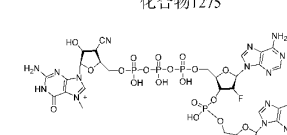
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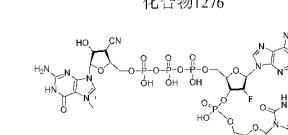
化合物1276



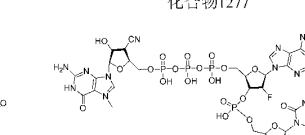
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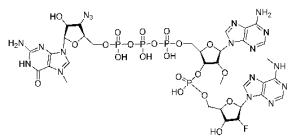
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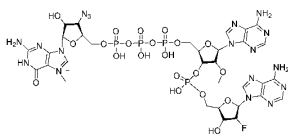
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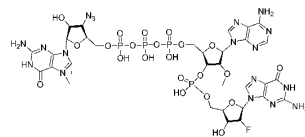
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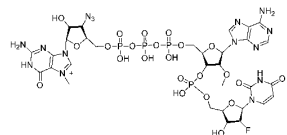
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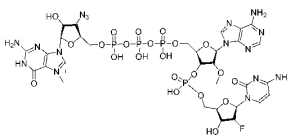
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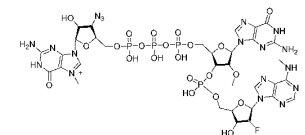
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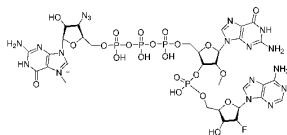
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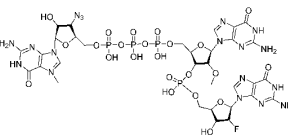
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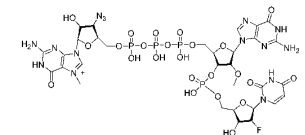
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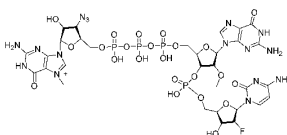
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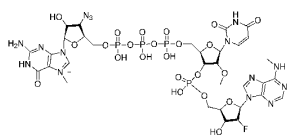
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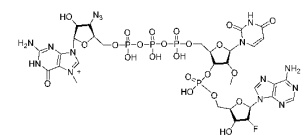
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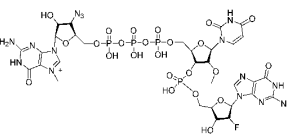
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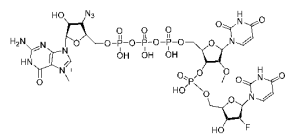
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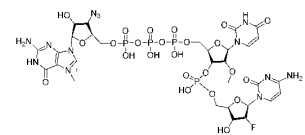
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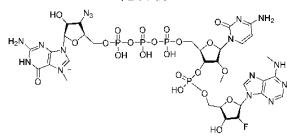
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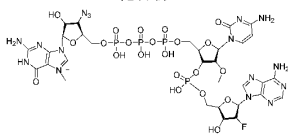
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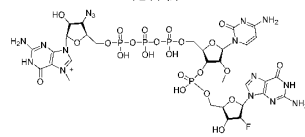
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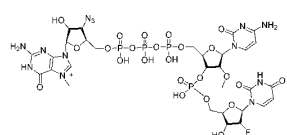
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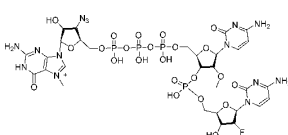
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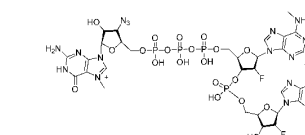
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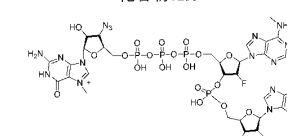
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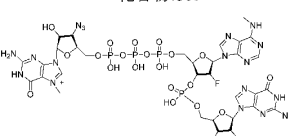
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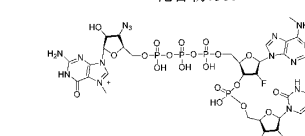
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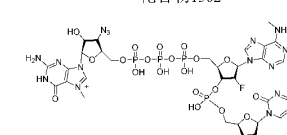
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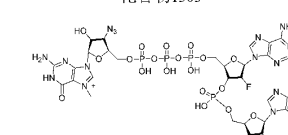
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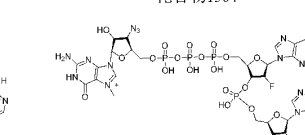
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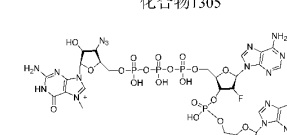
化合物1305



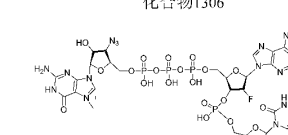
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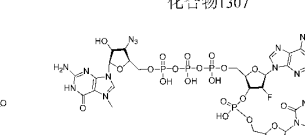
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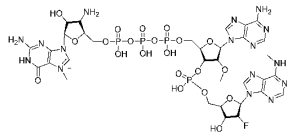
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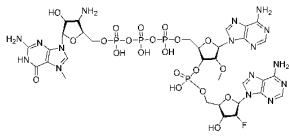
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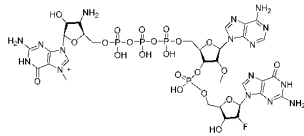
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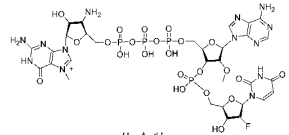
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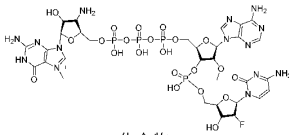
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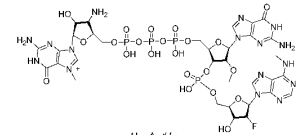
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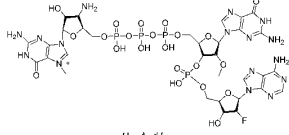
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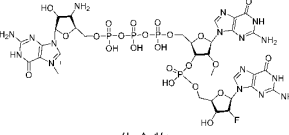
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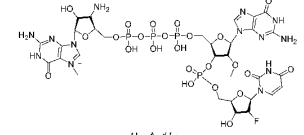
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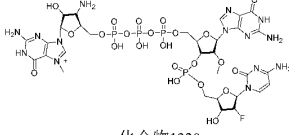
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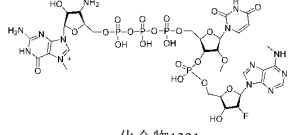
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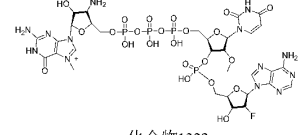
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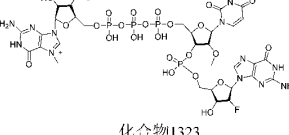
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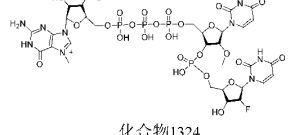
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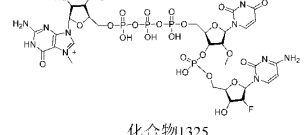
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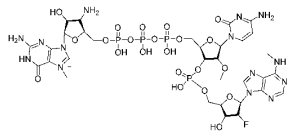
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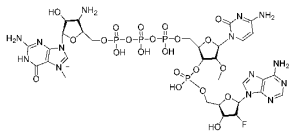
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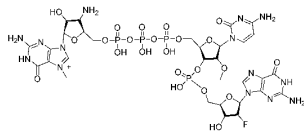
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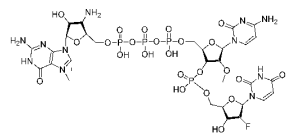
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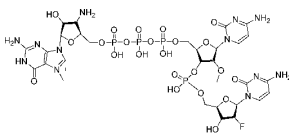
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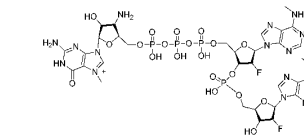
化合物1328



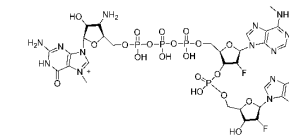
化合物1329



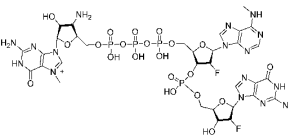
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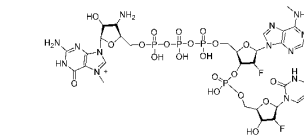
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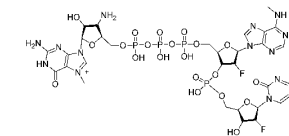
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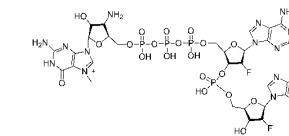
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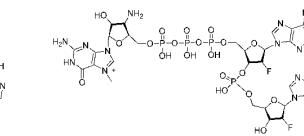
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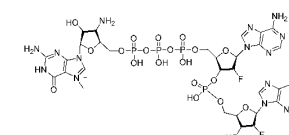
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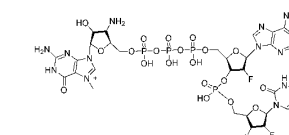
化合物1336



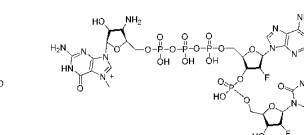
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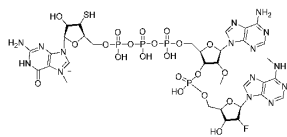
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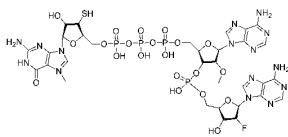
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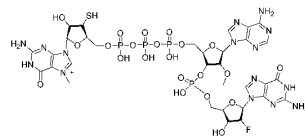
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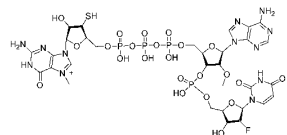
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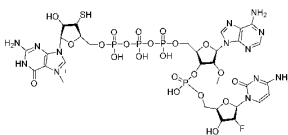
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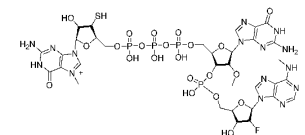
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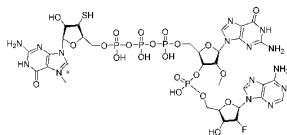
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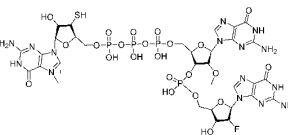
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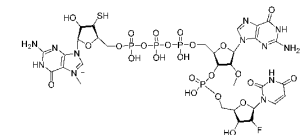
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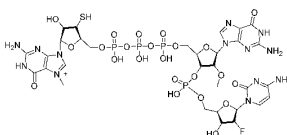
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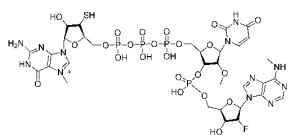
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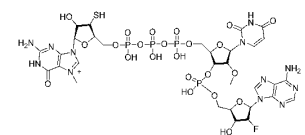
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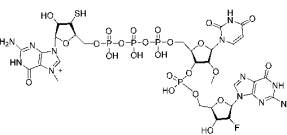
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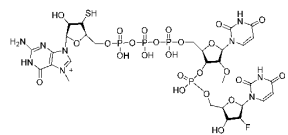
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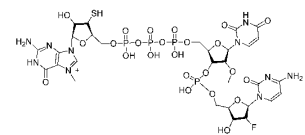
化合物1352



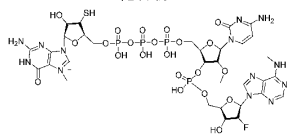
化合物1353



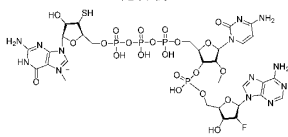
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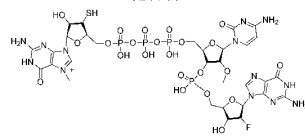
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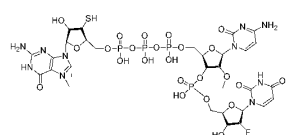
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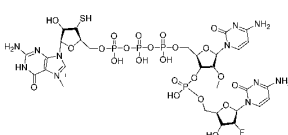
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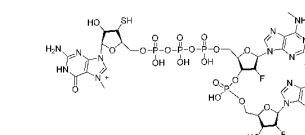
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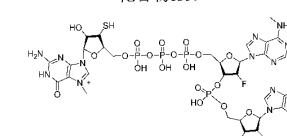
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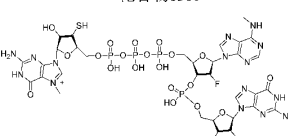
化合物1360



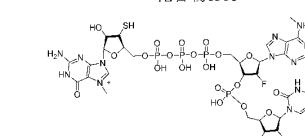
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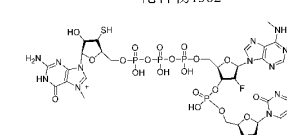
化合物1362



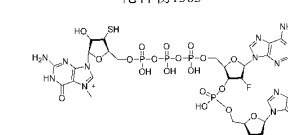
化合物1363



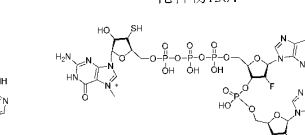
化合物1364



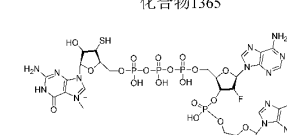
化合物1365



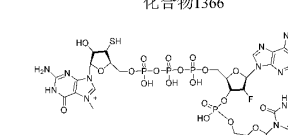
化合物1366



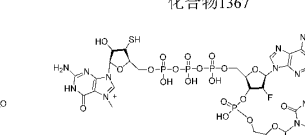
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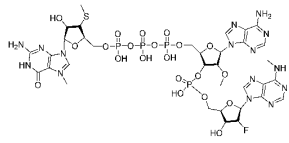
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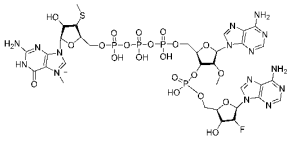
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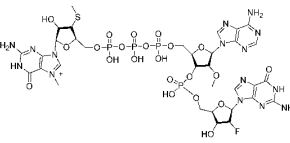
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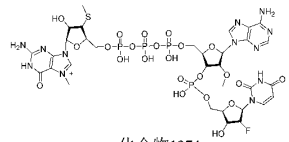
化合物1371



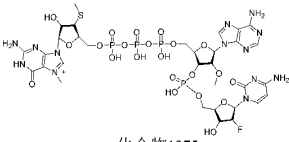
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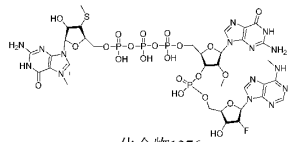
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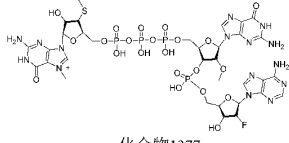
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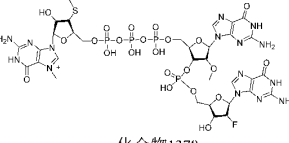
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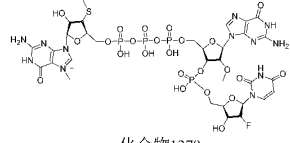
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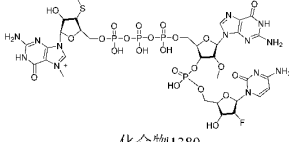
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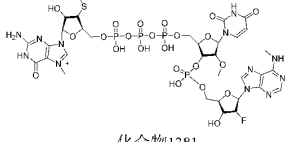
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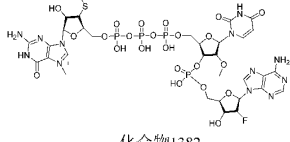
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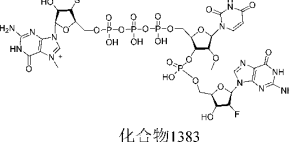
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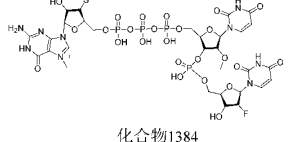
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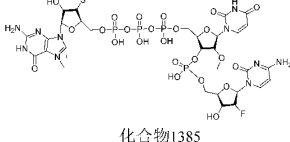
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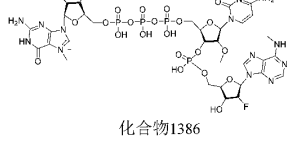
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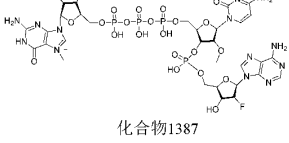
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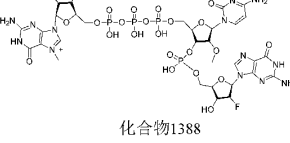
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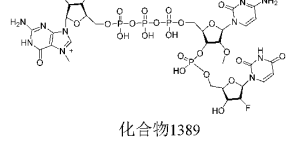
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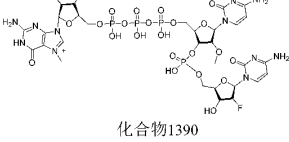
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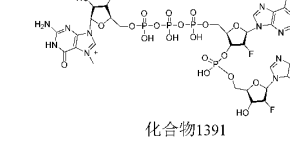
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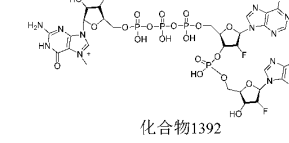
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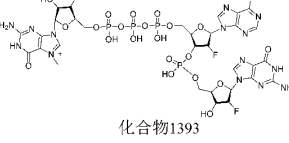
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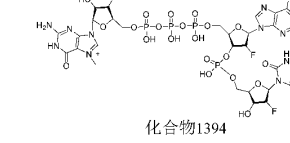
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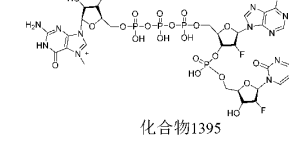
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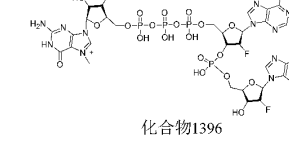
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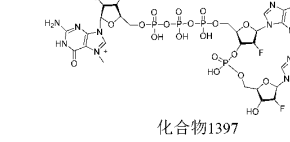
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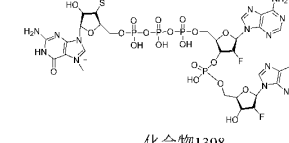
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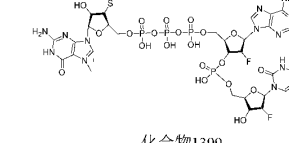
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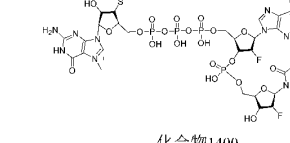
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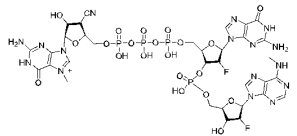
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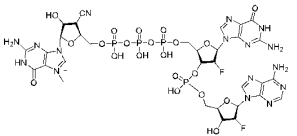
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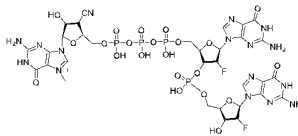
化合物1400



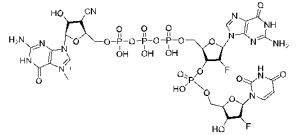
化合物1401



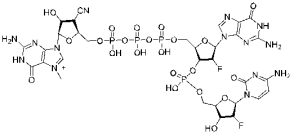
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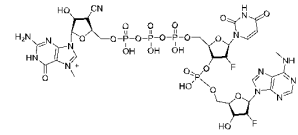
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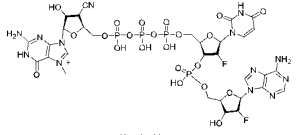
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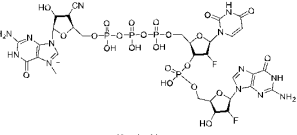
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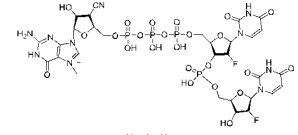
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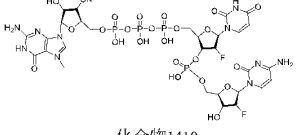
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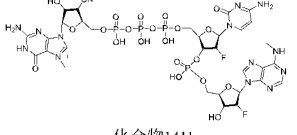
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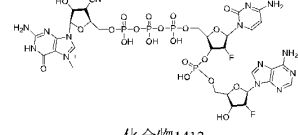
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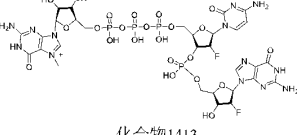
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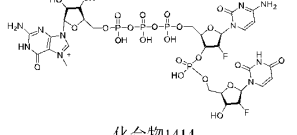
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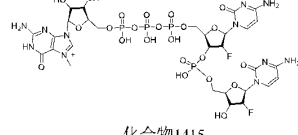
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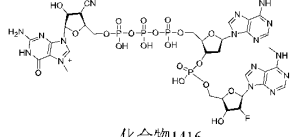
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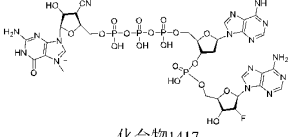
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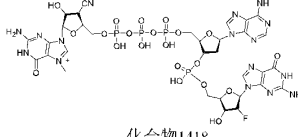
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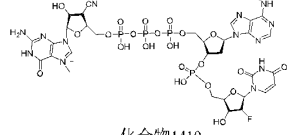
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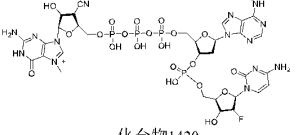
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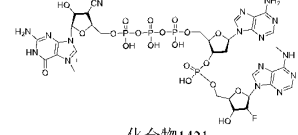
化合物1418



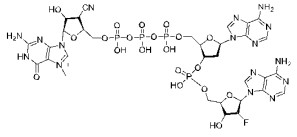
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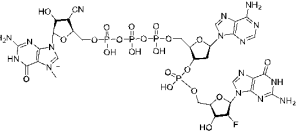
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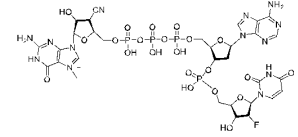
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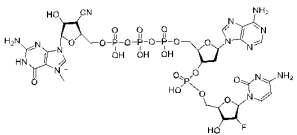
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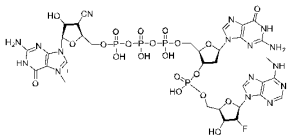
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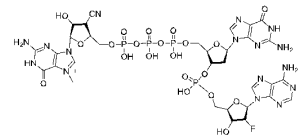
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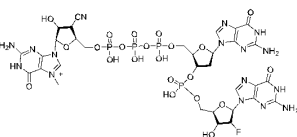
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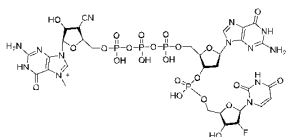
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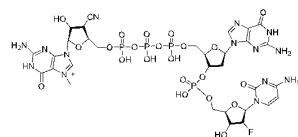
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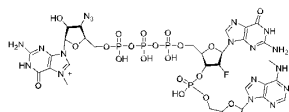
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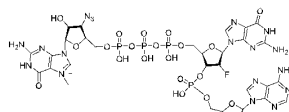
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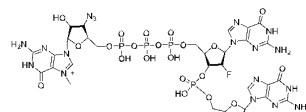
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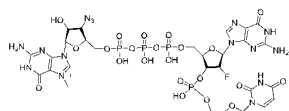
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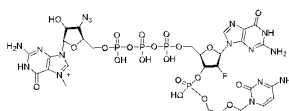
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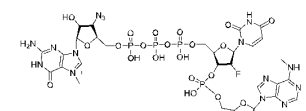
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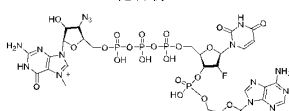
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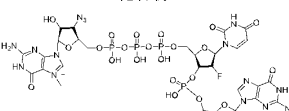
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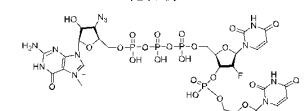
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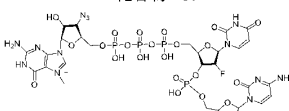
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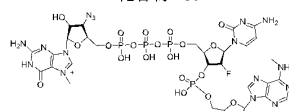
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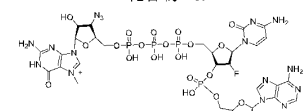
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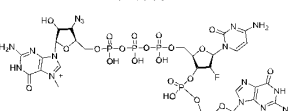
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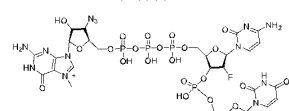
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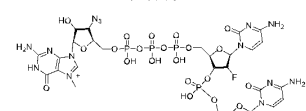
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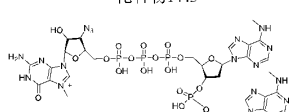
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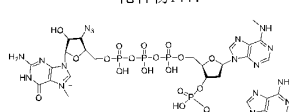
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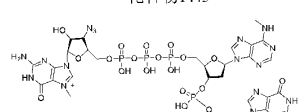
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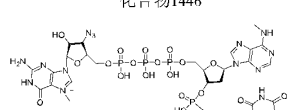
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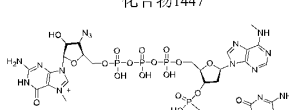
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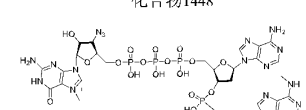
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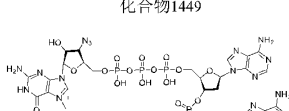
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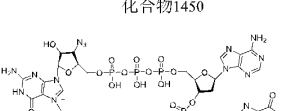
化合物1450



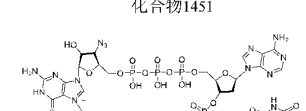
化合物1451



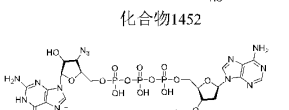
化合物1452



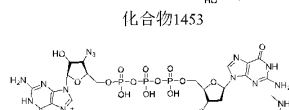
化合物1453



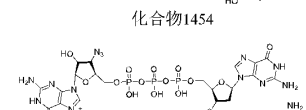
化合物1454



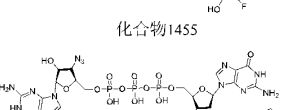
化合物1455



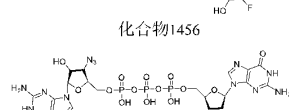
化合物1456



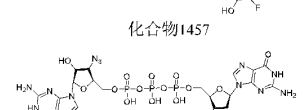
化合物1457



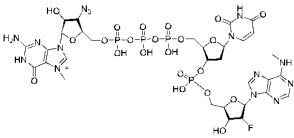
化合物1458



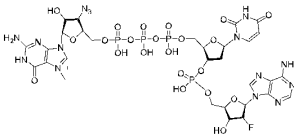
化合物1459



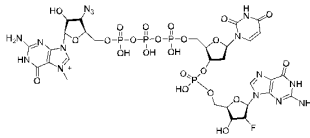
化合物1460



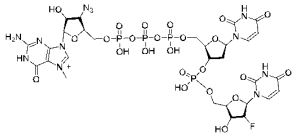
化合物1461



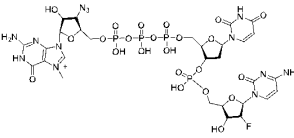
化合物1462



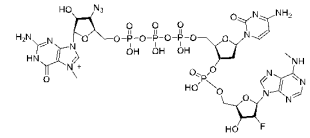
化合物1463



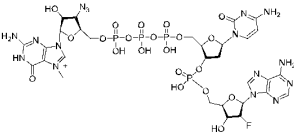
化合物1464



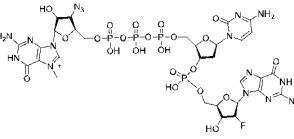
化合物1465



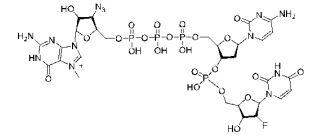
化合物1466



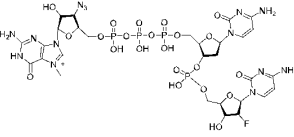
化合物1467



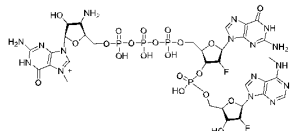
化合物1468



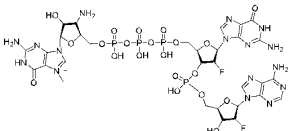
化合物1469



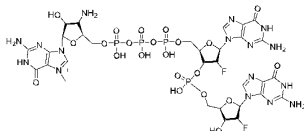
化合物1470



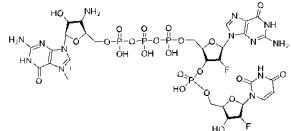
化合物1471



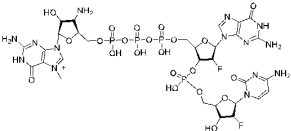
化合物1472



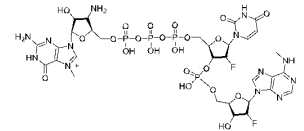
化合物1473



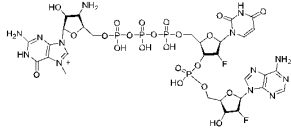
化合物1474



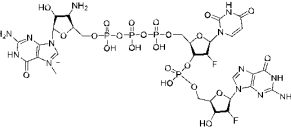
化合物1475



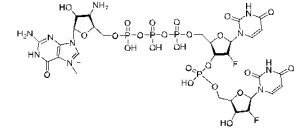
化合物1476



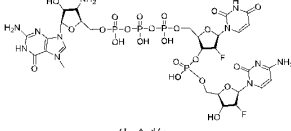
化合物1477



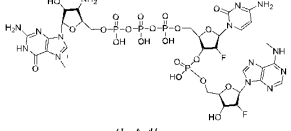
化合物1478



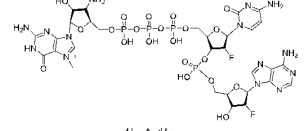
化合物1479



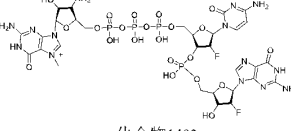
化合物1480



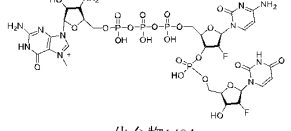
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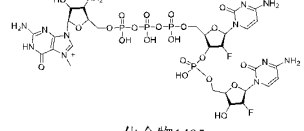
化合物1482



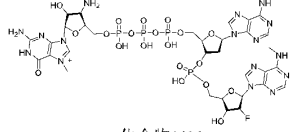
化合物1483



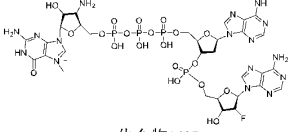
化合物1484



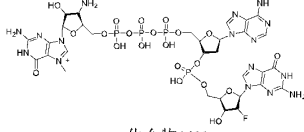
化合物1485



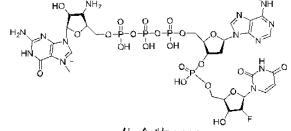
化合物1486



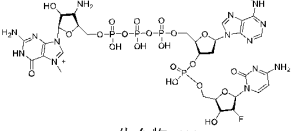
化合物1487



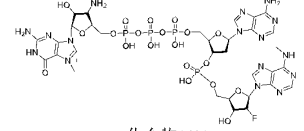
化合物1488



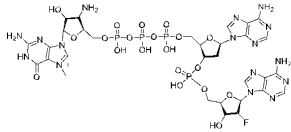
化合物1489



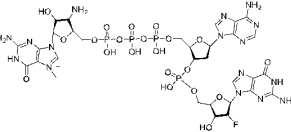
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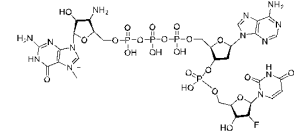
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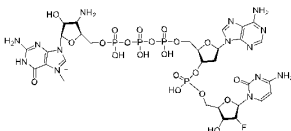
化合物1492



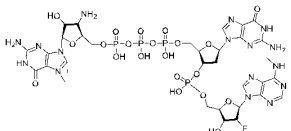
化合物1493



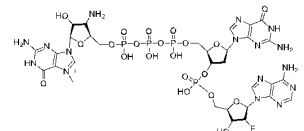
化合物1494



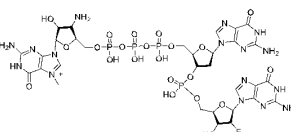
化合物1495



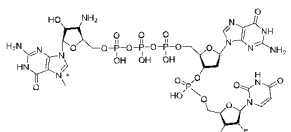
化合物1496



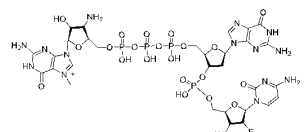
化合物1497



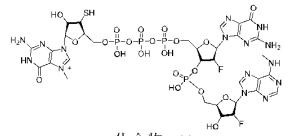
化合物1498



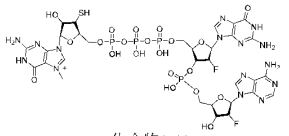
化合物1499



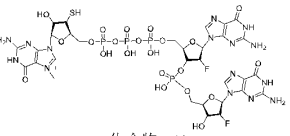
化合物1500



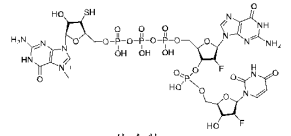
化合物1501



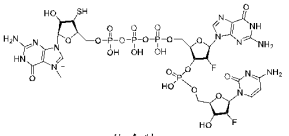
化合物1502



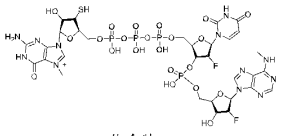
化合物1503



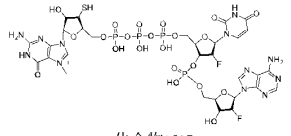
化合物1504



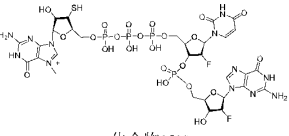
化合物1505



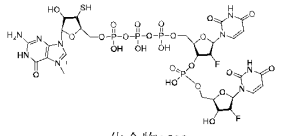
化合物1506



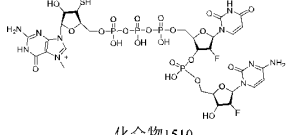
化合物1507



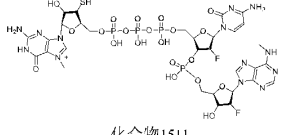
化合物1508



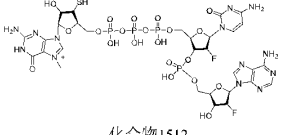
化合物1509



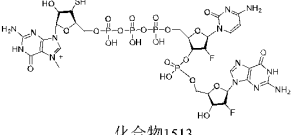
化合物1510



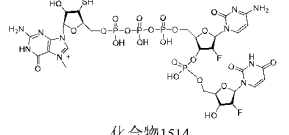
化合物1511



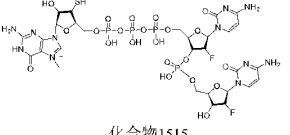
化合物1512



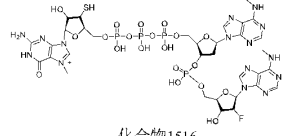
化合物1513



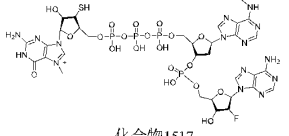
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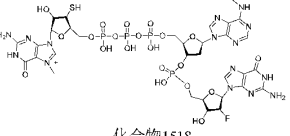
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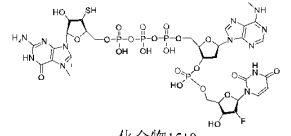
化合物1516



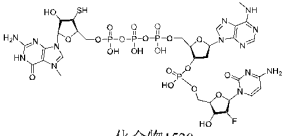
化合物1517



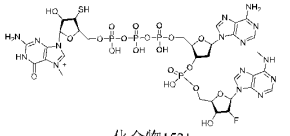
化合物1518



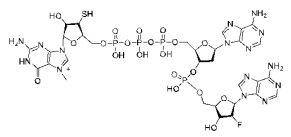
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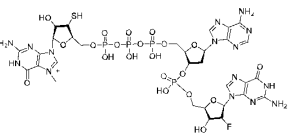
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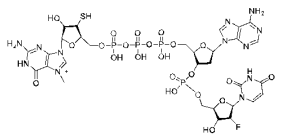
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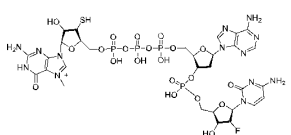
化合物1522



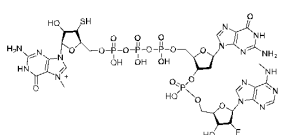
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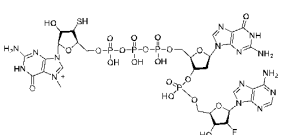
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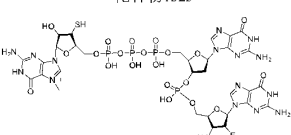
化合物1525



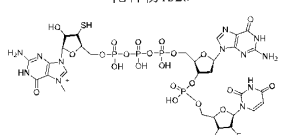
化合物1526



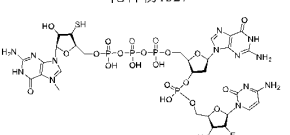
化合物1527



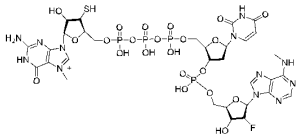
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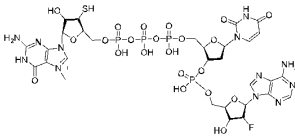
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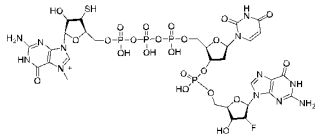
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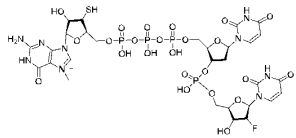
化合物1531



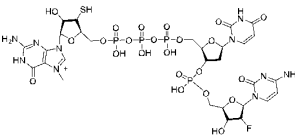
化合物1532



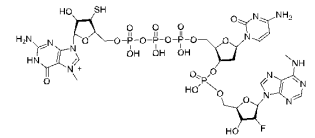
化合物1533



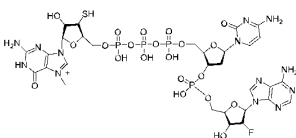
化合物1534



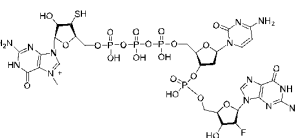
化合物1535



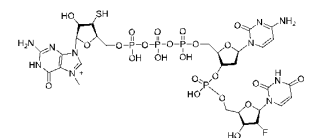
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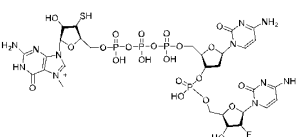
化合物1537



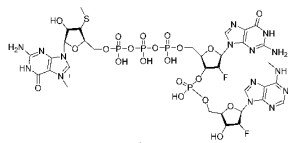
化合物1538



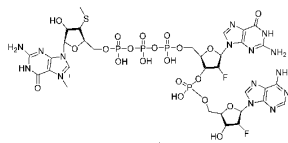
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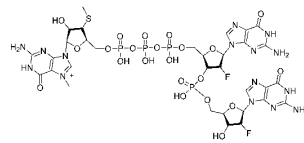
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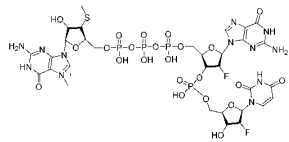
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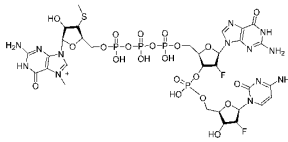
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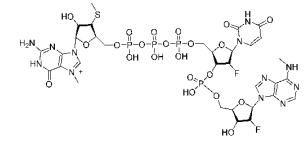
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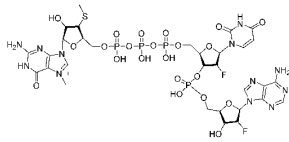
化合物1544



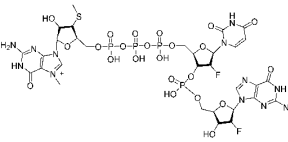
化合物1545



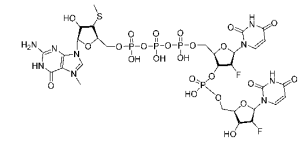
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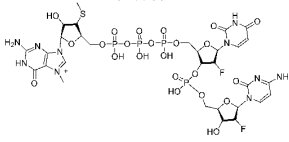
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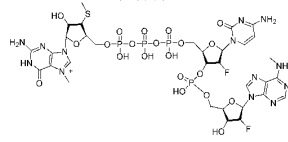
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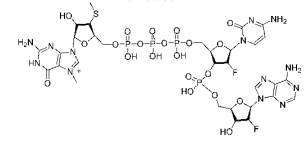
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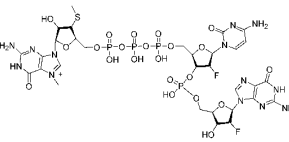
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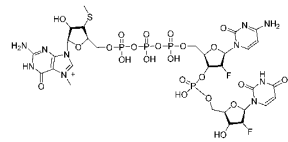
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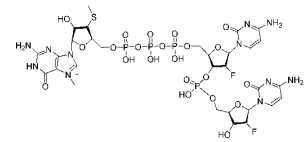
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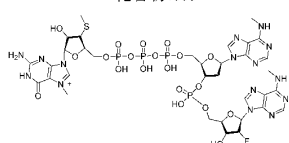
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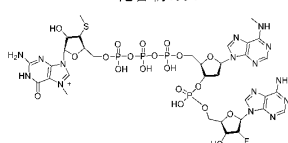
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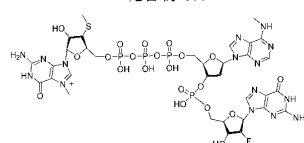
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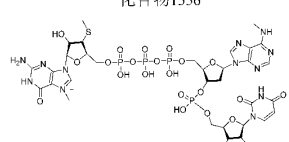
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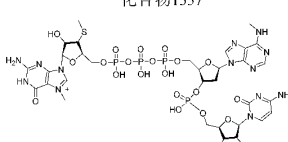
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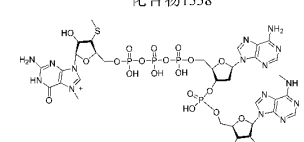
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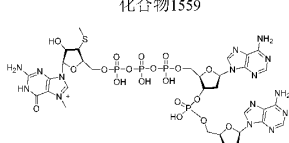
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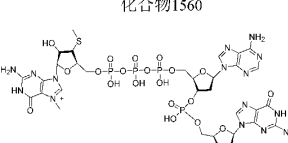
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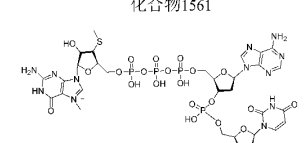
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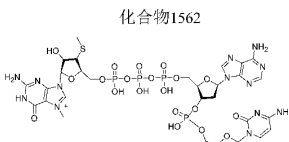
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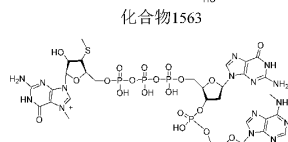
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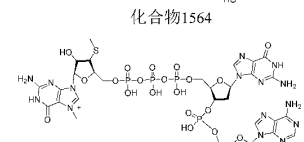
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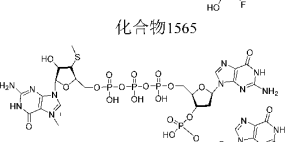
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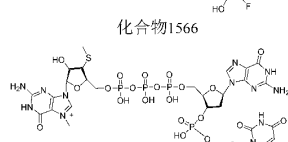
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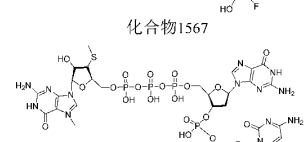
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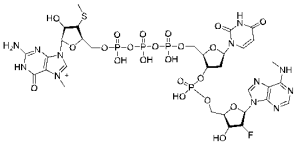
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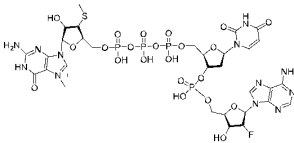
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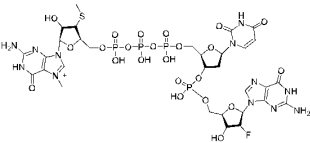
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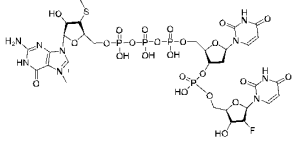
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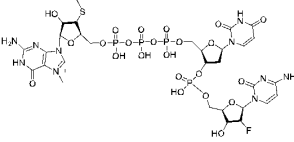
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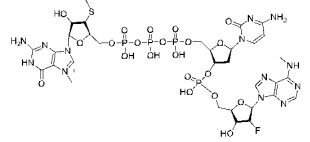
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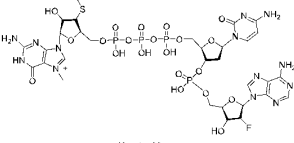
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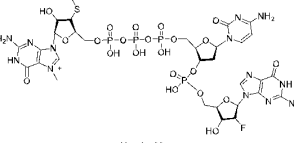
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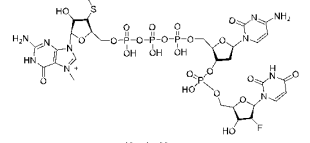
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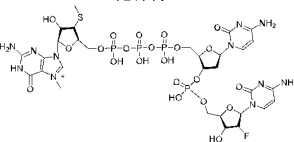
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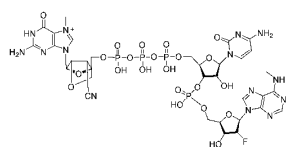
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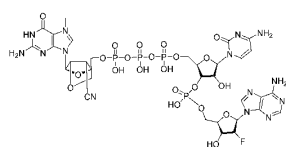
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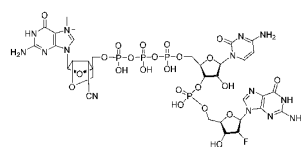
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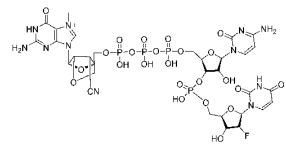
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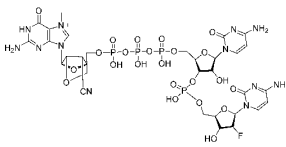
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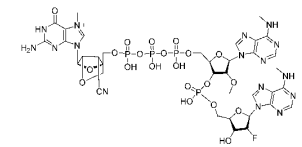
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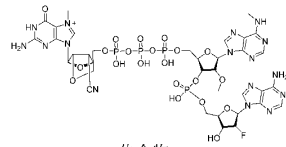
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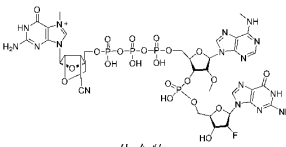
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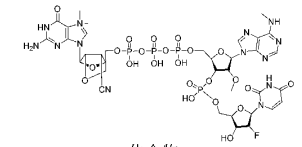
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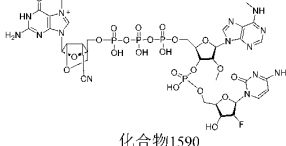
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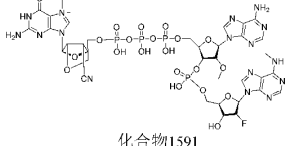
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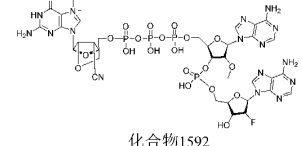
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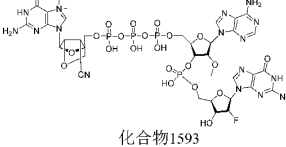
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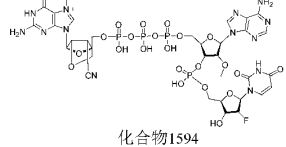
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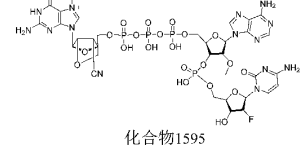
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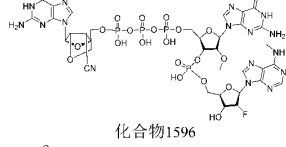
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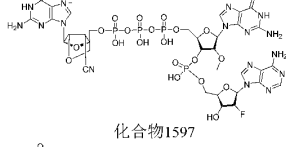
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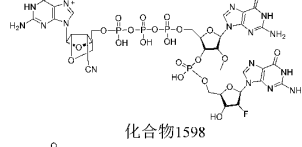
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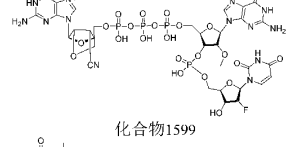
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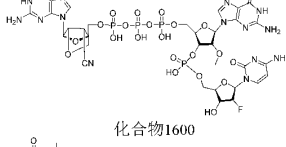
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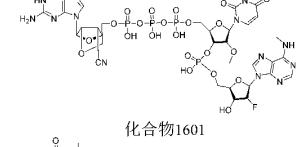
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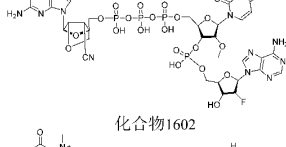
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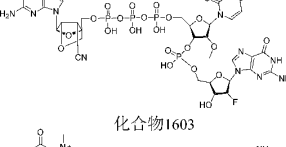
化合物1600



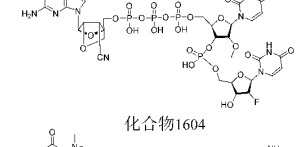
化合物1601



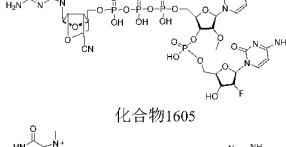
化合物1602



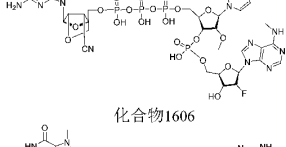
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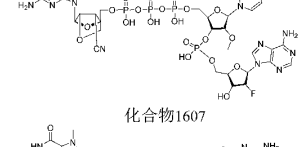
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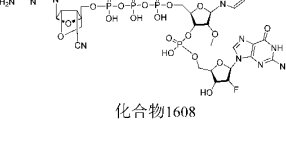
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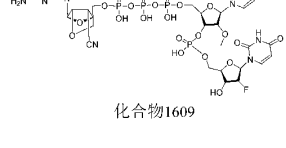
化合物1606



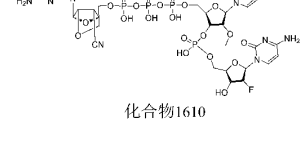
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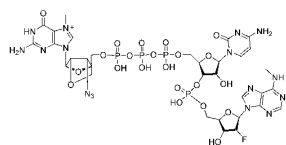
化合物1608



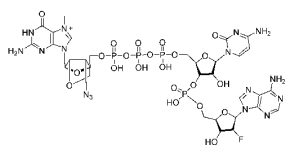
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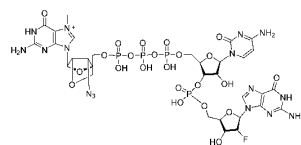
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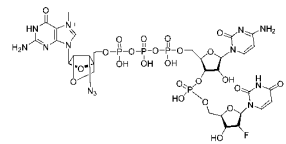
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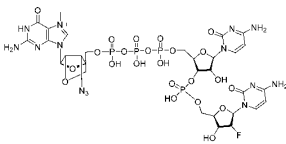
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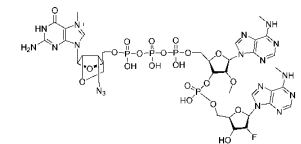
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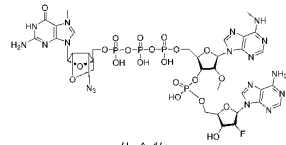
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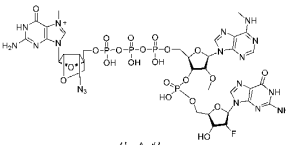
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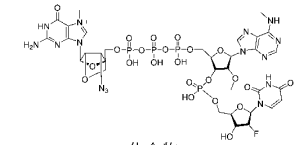
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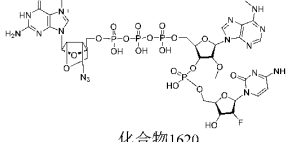
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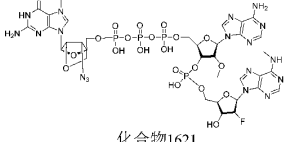
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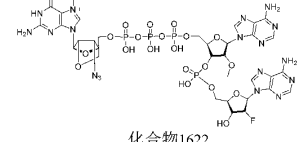
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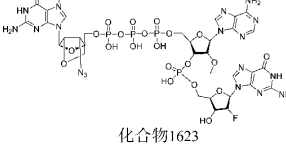
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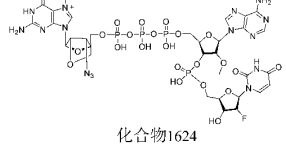
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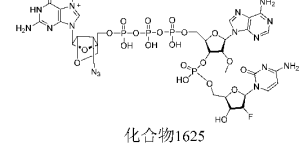
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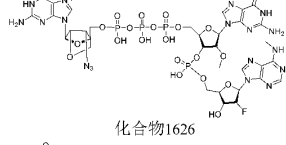
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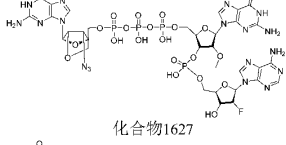
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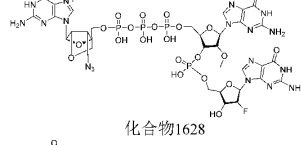
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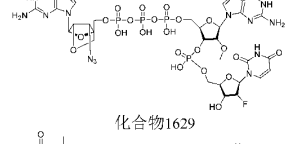
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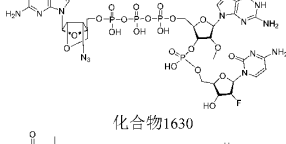
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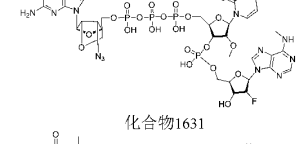
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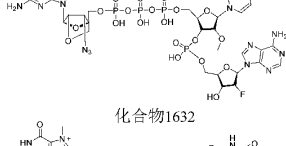
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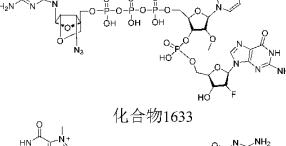
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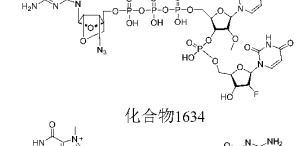
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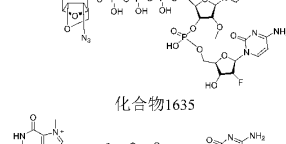
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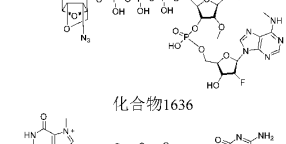
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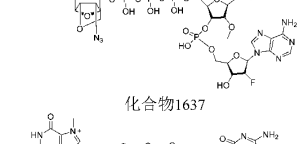
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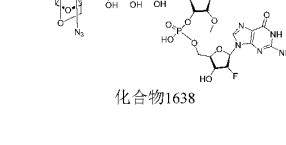
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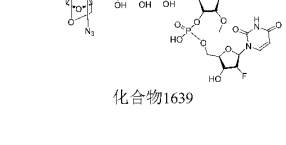
化合物1636



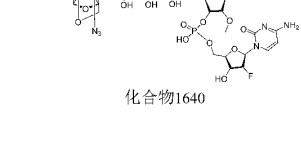
化合物1637



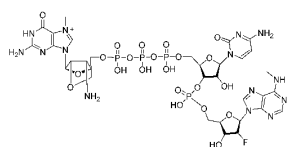
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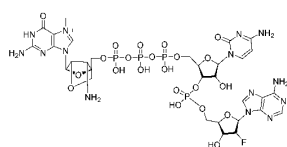
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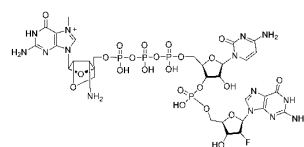
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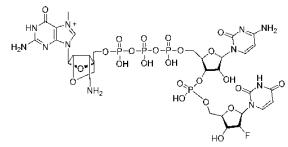
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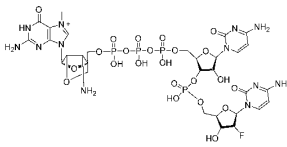
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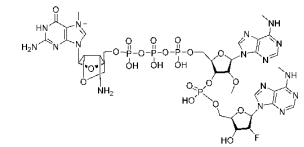
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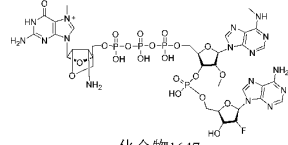
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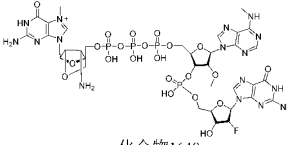
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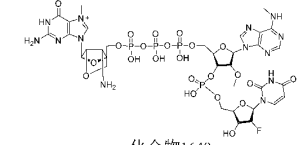
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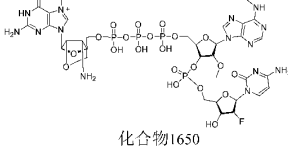
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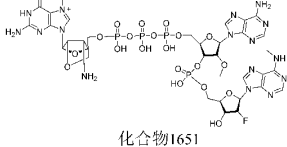
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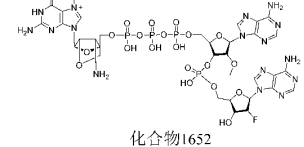
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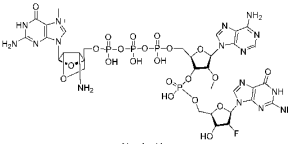
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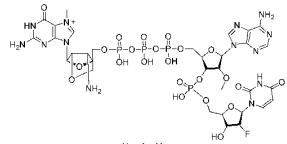
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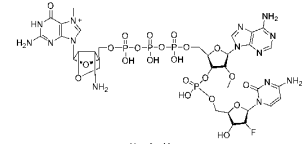
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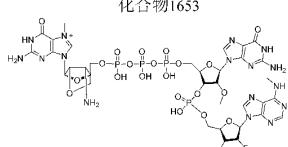
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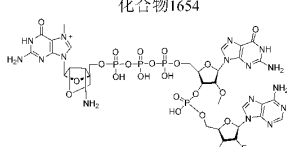
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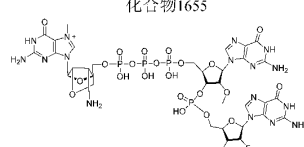
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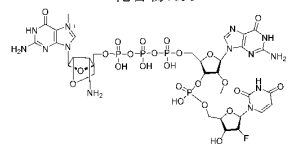
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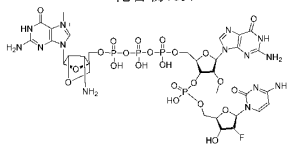
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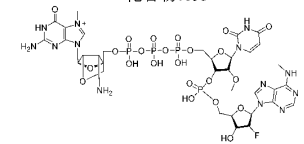
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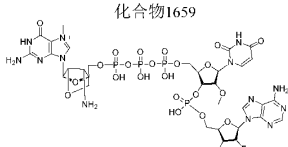
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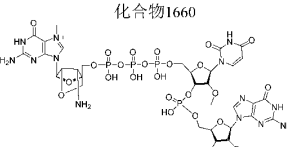
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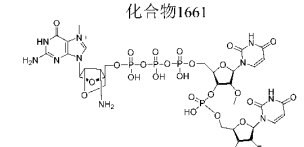
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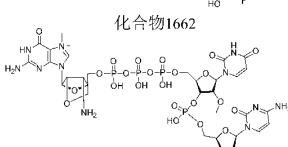
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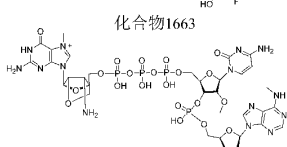
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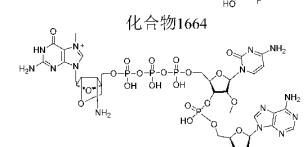
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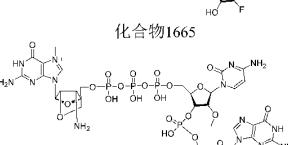
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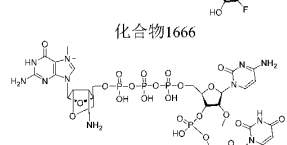
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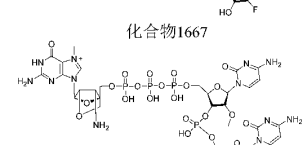
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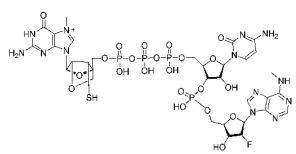
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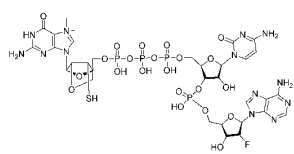
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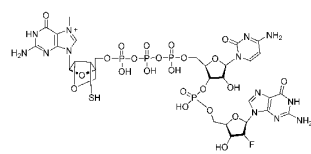
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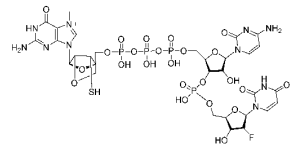
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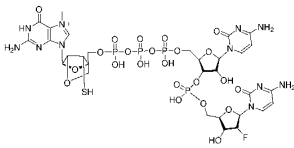
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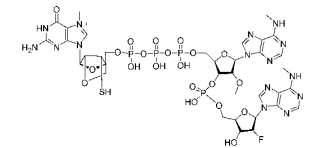
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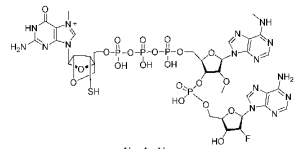
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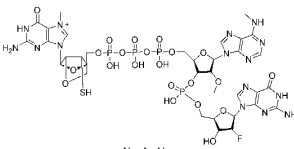
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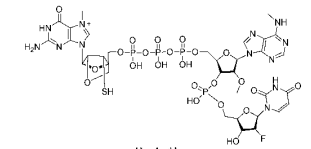
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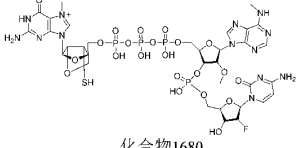
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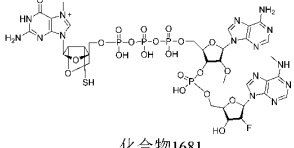
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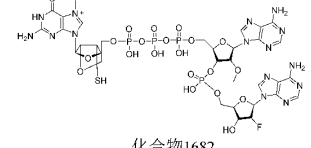
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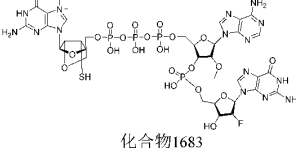
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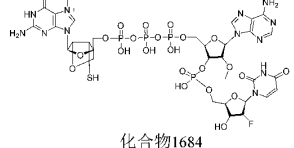
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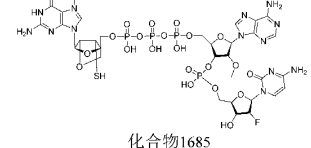
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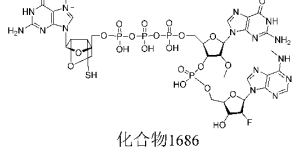
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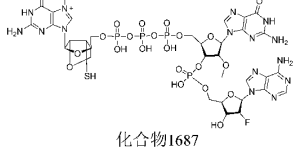
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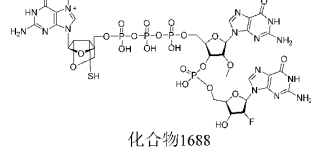
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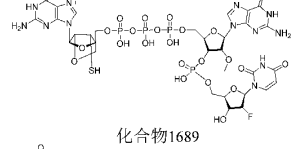
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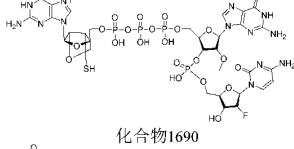
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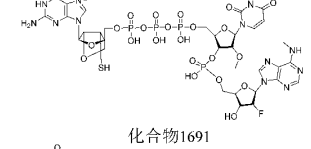
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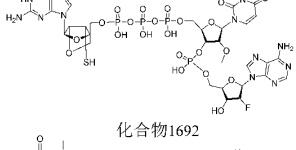
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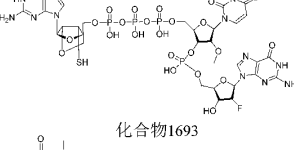
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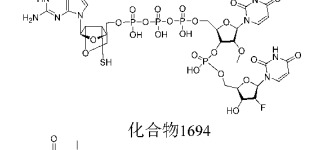
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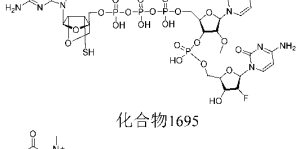
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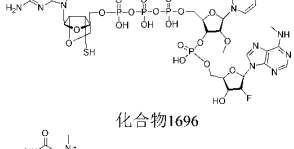
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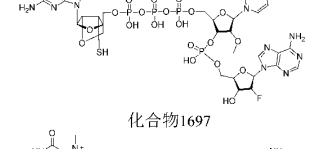
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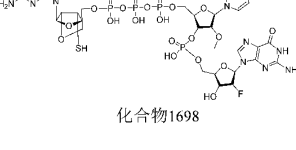
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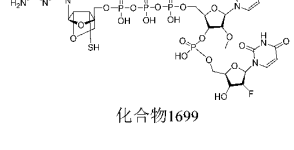
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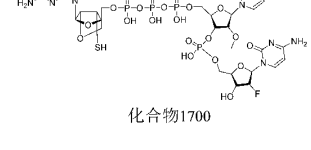
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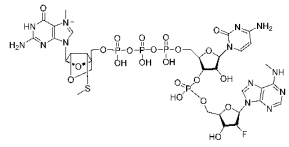
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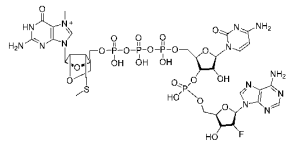
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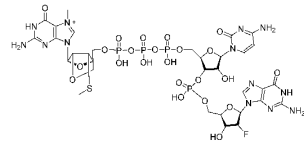
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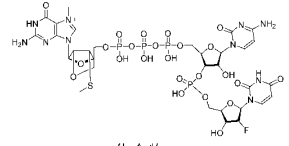
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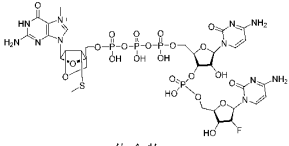
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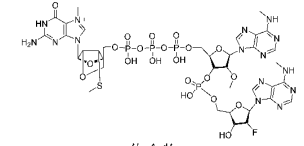
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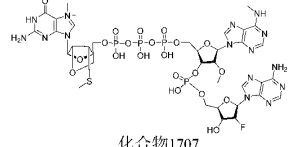
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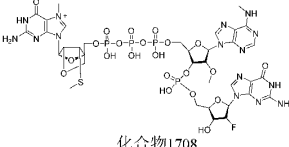
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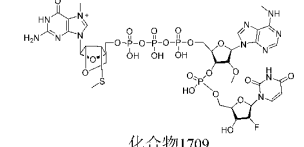
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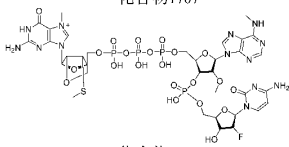
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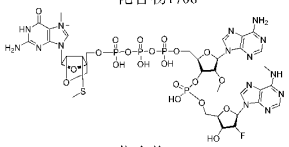
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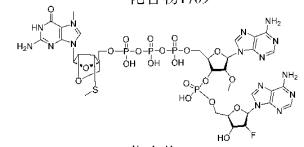
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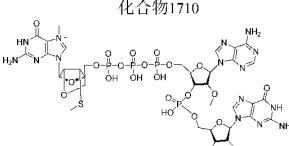
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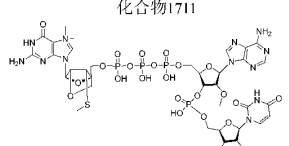
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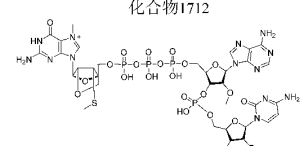
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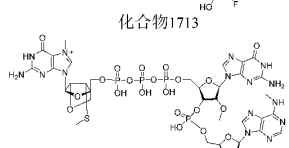
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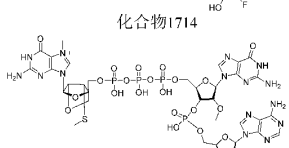
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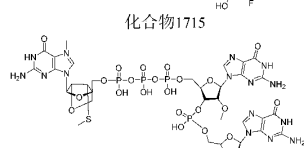
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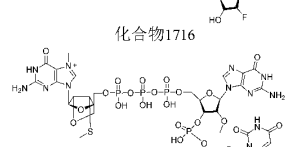
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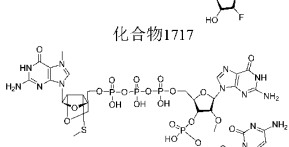
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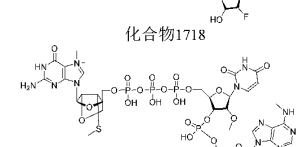
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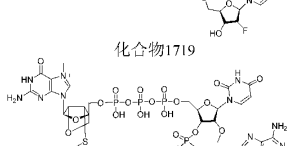
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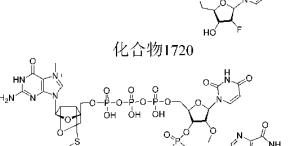
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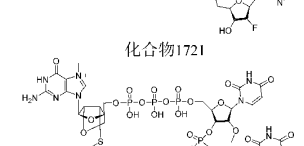
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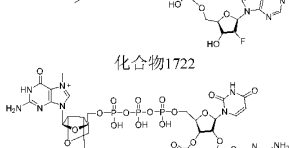
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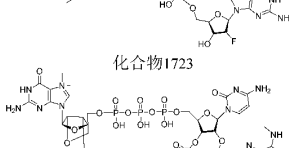
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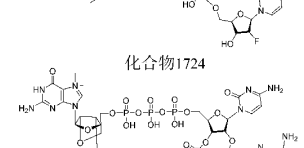
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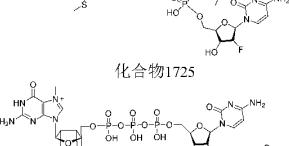
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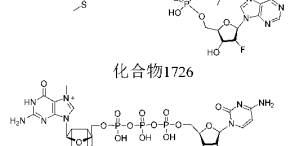
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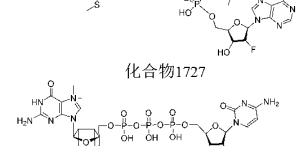
化合物1727



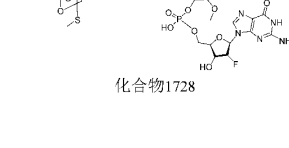
化合物1728



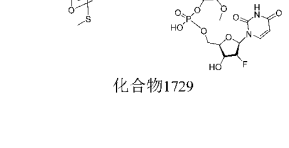
化合物1729



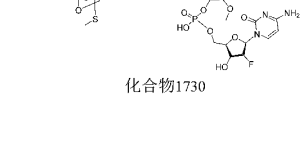
化合物1730



化合物1731



化合物1732



化合物1733



化合物1734



化合物1735



化合物1736



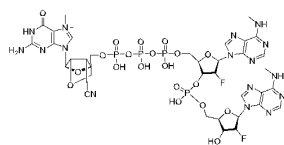
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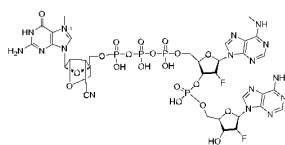
化合物1738



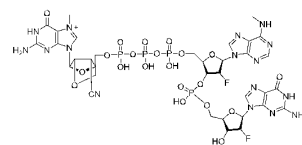
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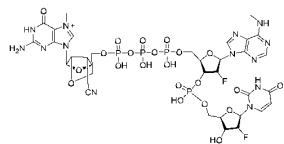
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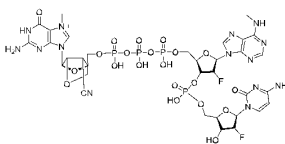
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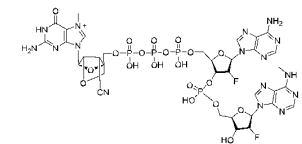
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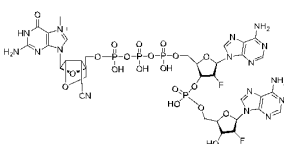
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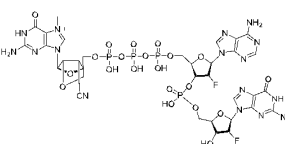
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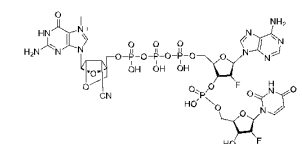
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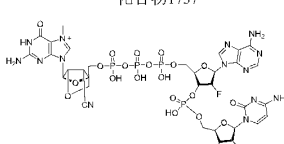
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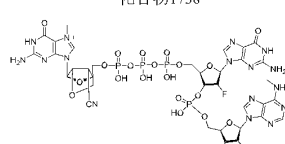
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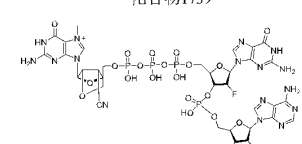
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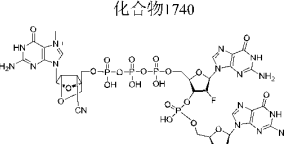
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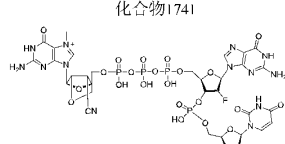
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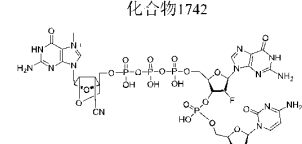
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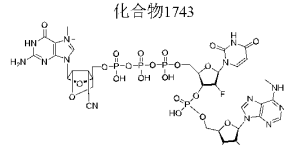
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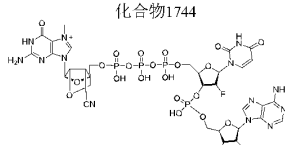
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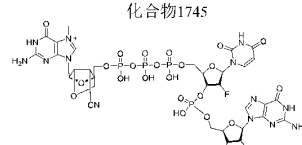
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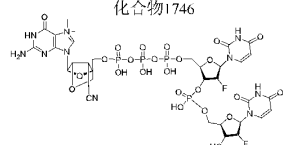
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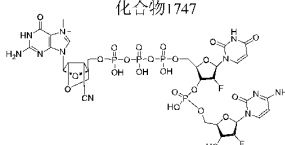
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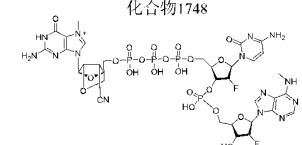
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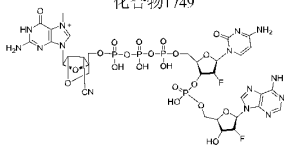
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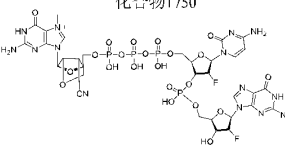
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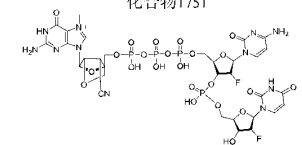
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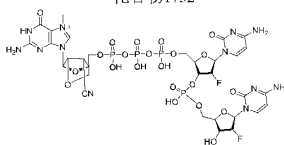
化合物1752



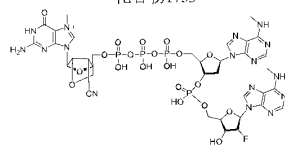
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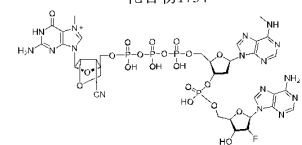
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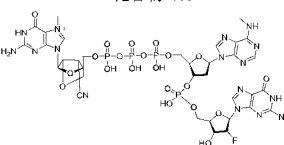
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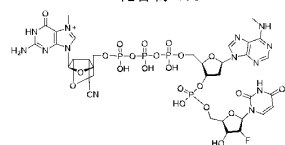
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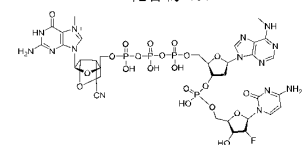
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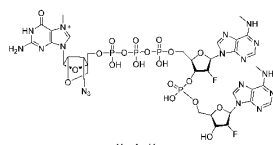
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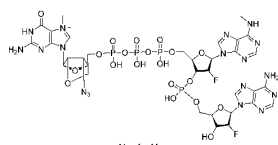
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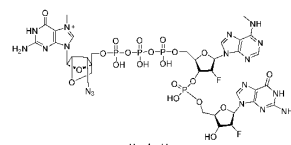
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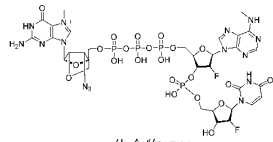
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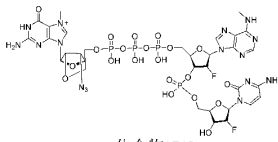
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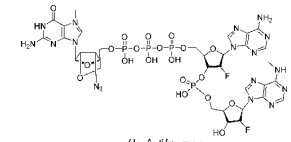
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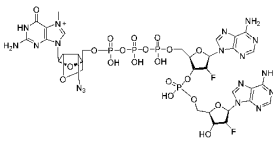
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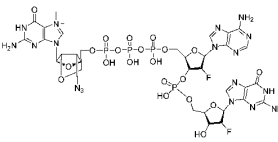
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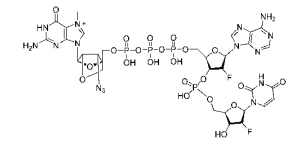
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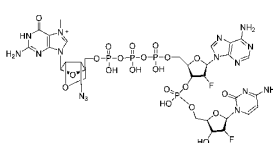
化合物1767



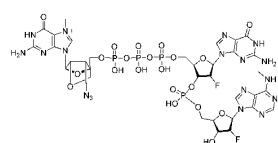
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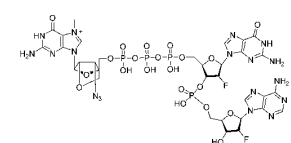
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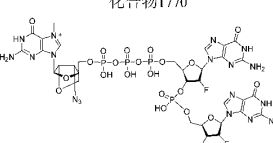
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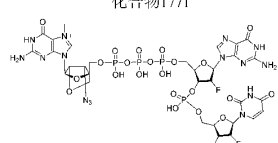
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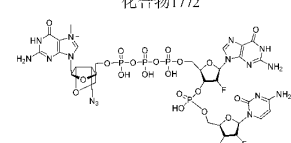
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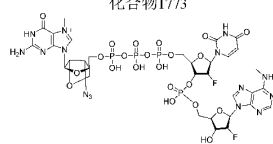
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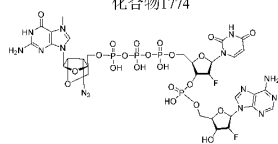
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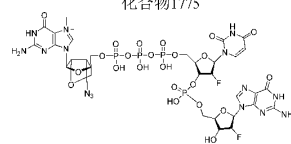
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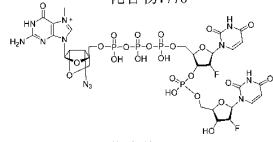
化合物1776



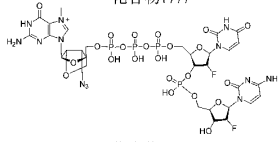
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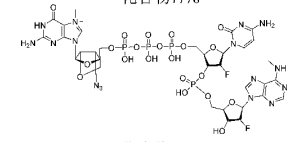
化合物1778



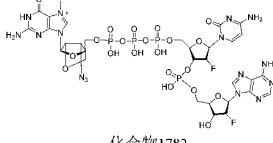
化合物1779



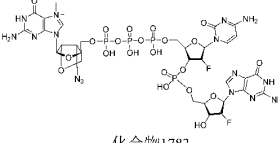
化合物1780



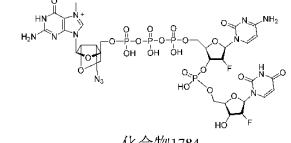
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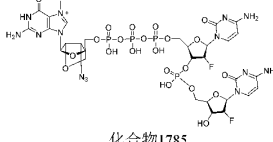
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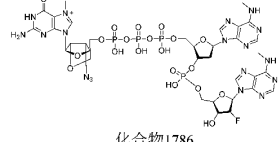
化合物1783



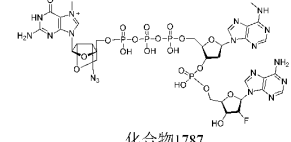
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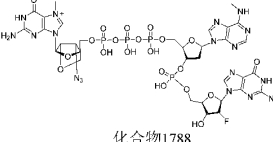
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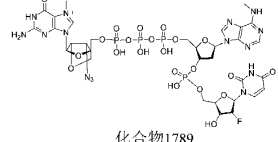
化合物1786



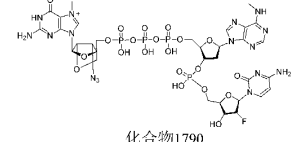
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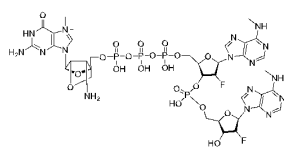
化合物1788



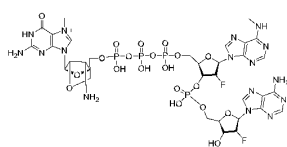
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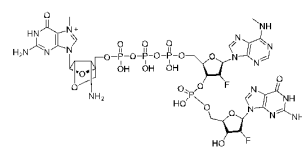
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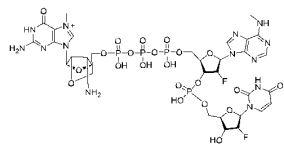
化合物1791



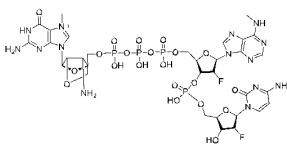
化合物1792



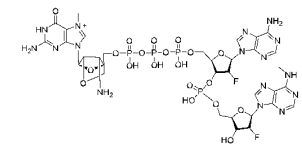
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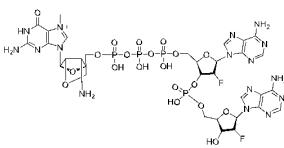
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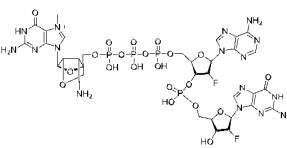
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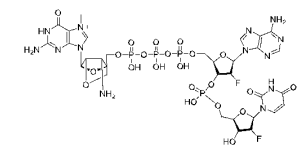
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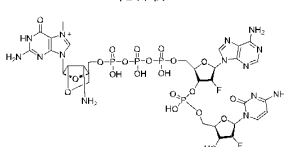
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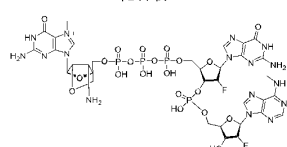
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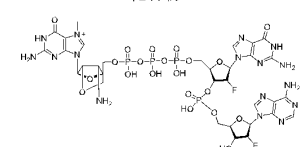
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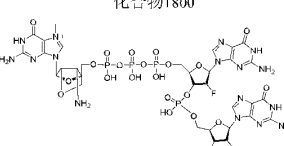
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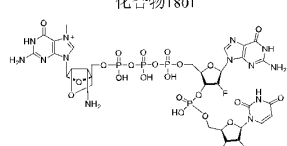
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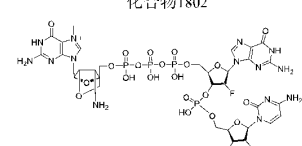
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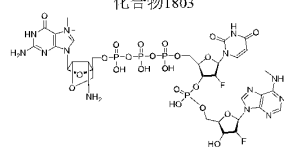
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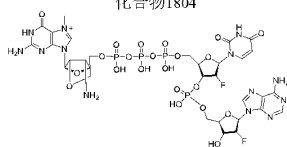
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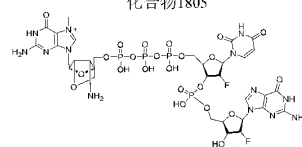
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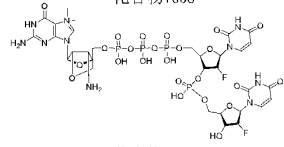
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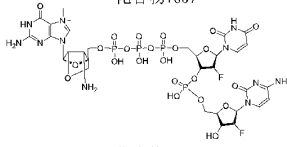
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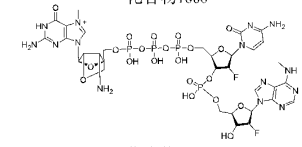
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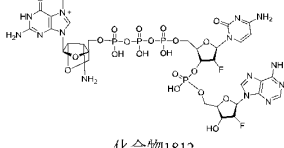
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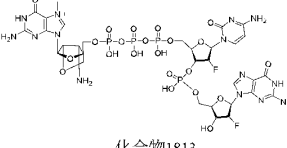
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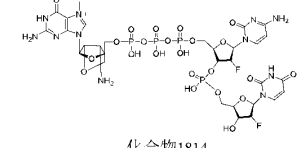
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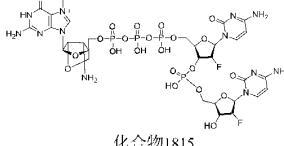
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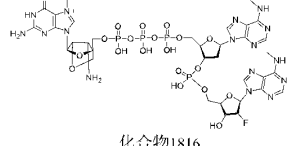
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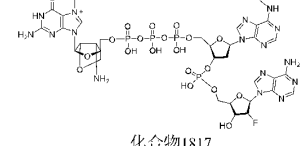
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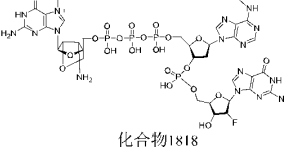
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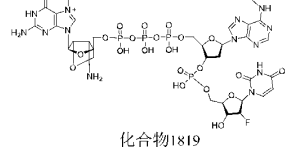
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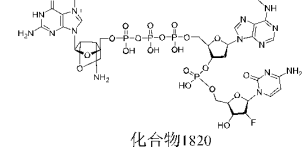
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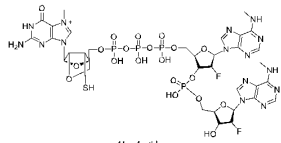
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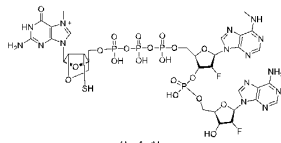
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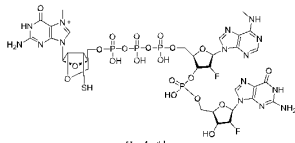
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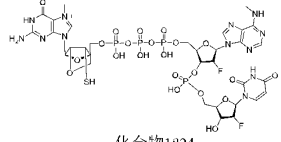
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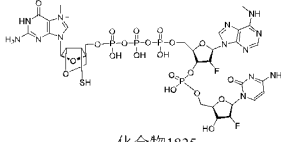
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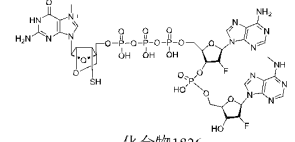
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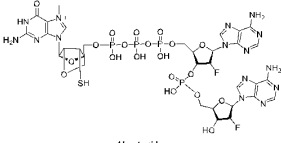
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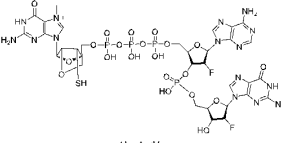
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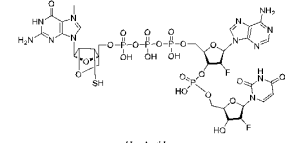
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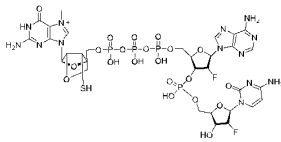
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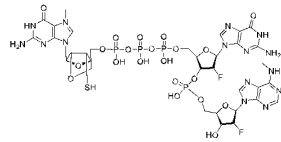
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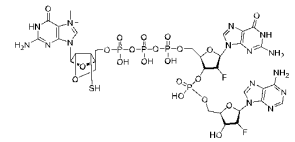
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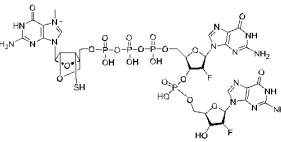
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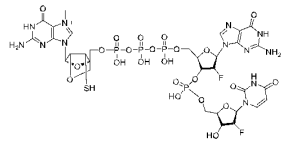
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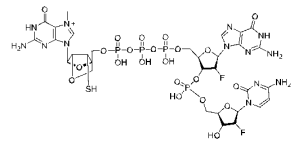
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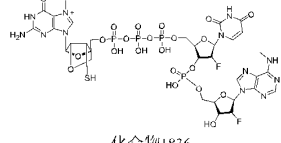
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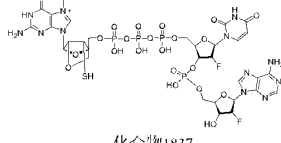
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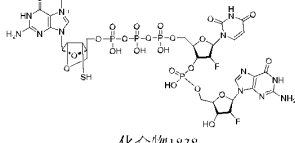
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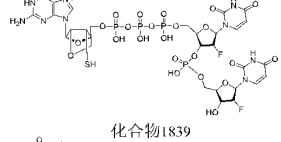
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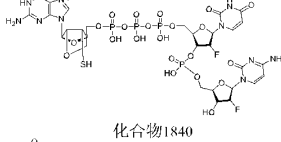
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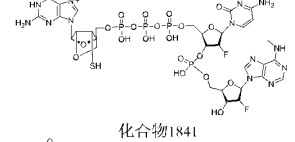
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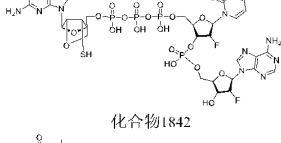
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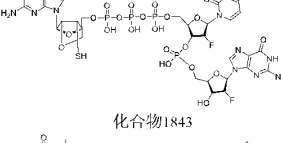
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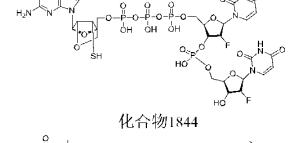
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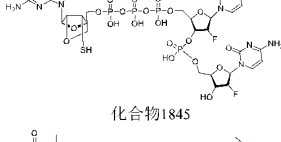
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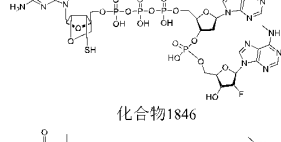
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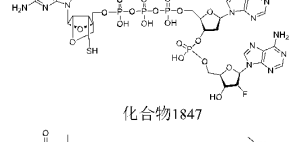
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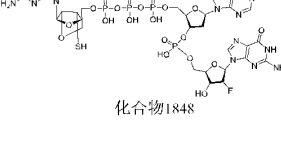
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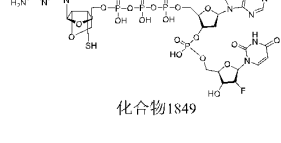
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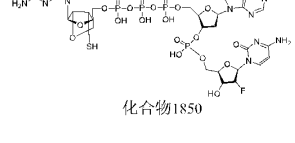
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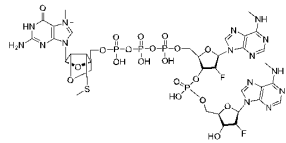
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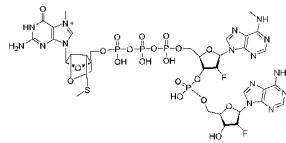
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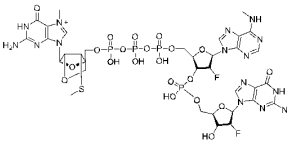
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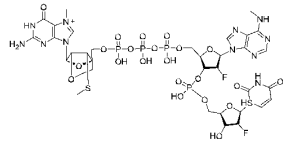
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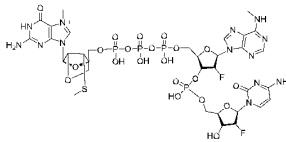
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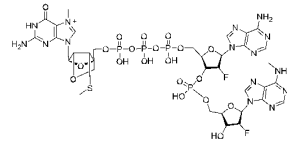
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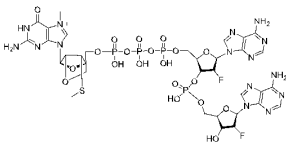
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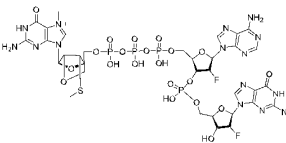
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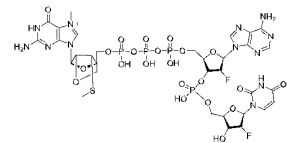
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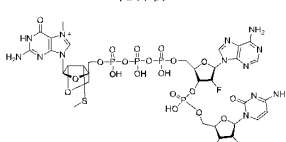
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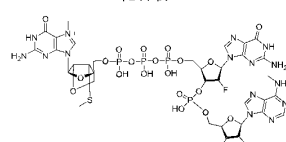
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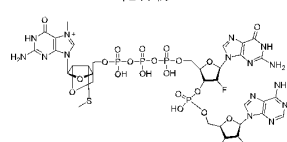
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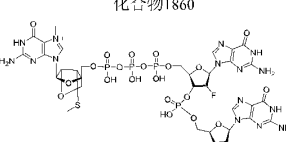
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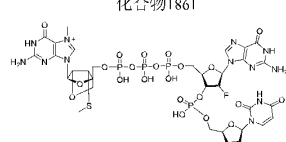
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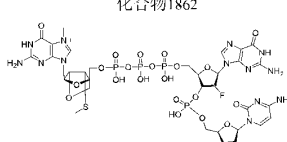
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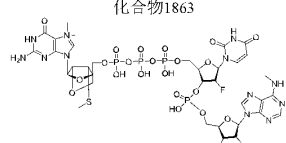
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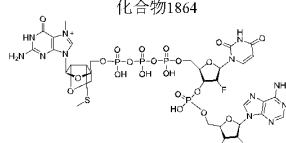
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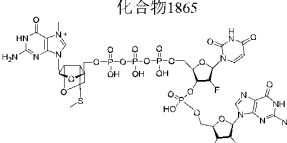
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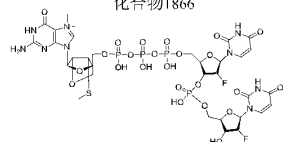
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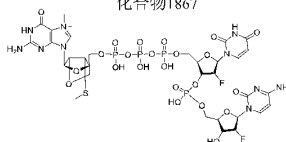
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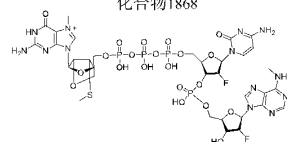
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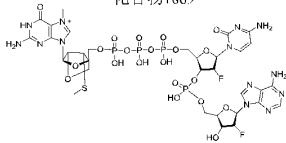
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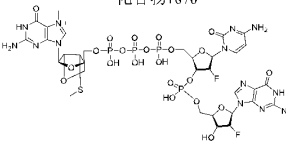
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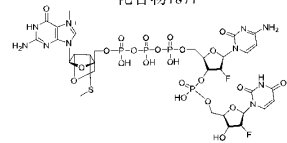
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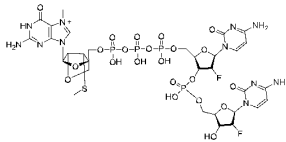
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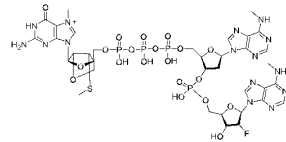
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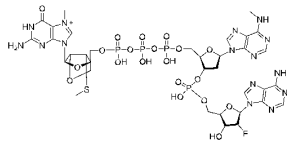
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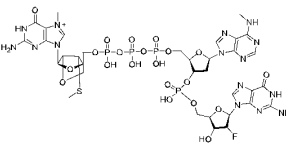
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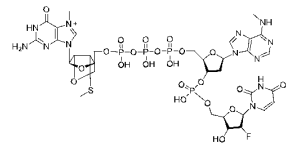
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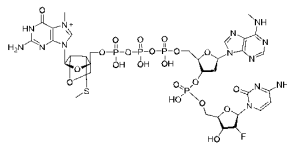
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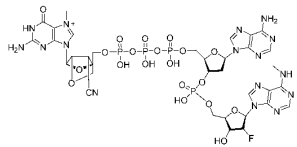
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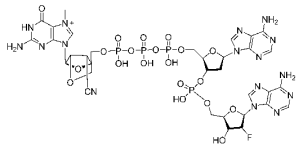
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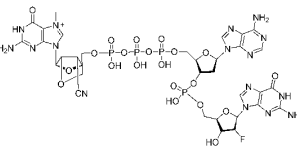
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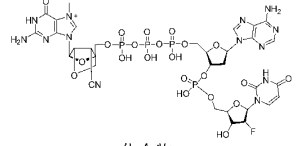
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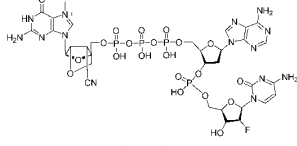
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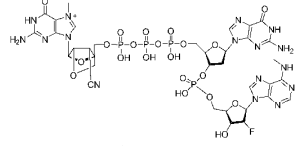
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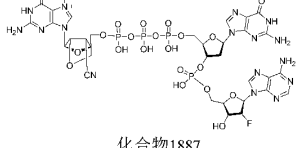
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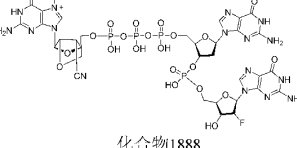
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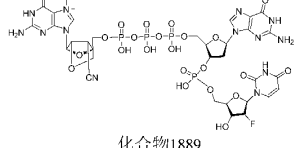
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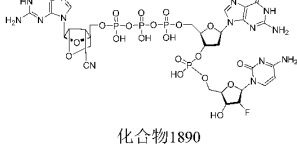
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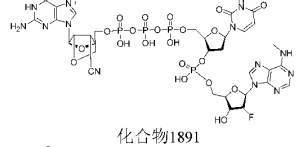
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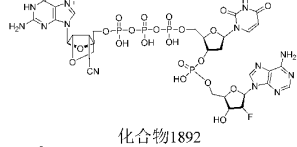
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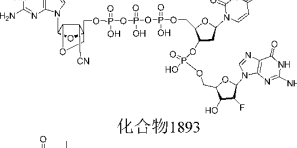
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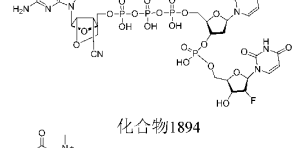
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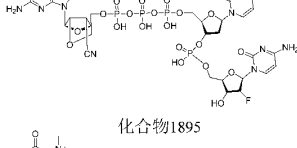
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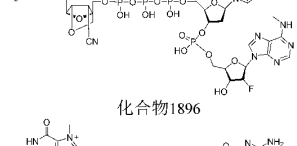
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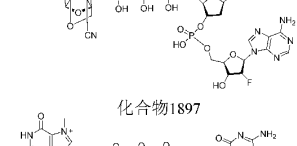
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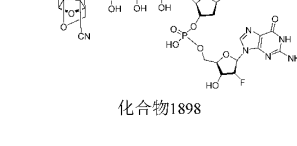
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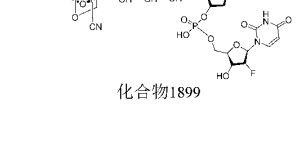
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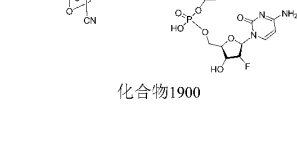
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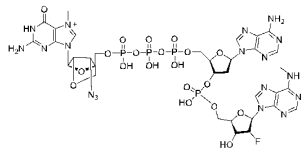
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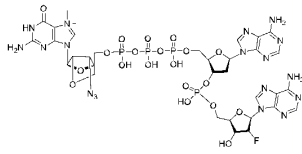
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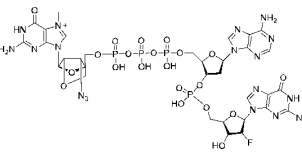
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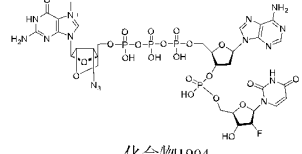
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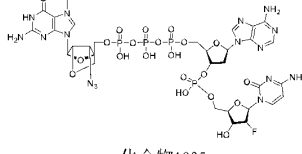
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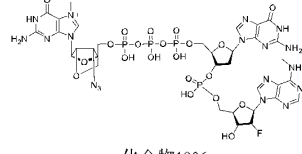
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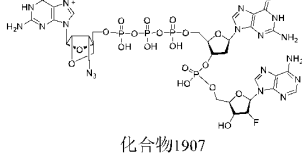
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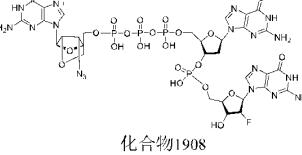
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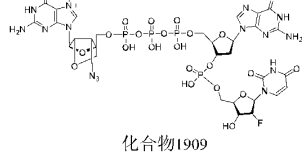
化合物1906



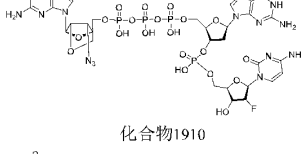
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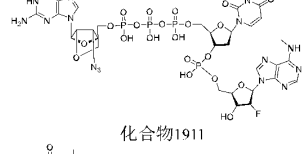
化合物1908



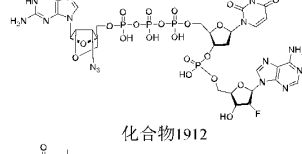
化合物1909



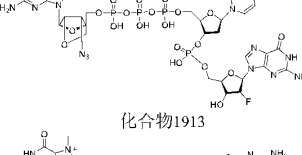
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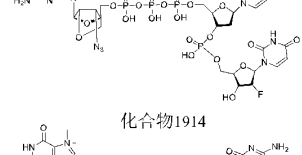
化合物1911



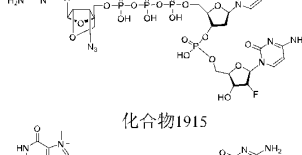
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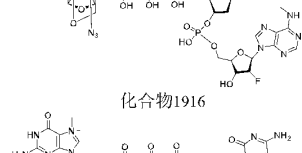
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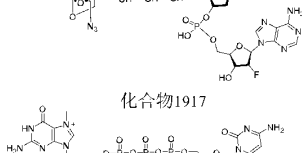
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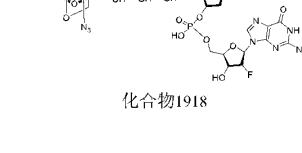
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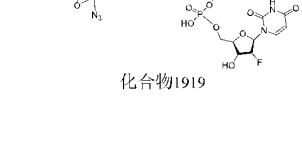
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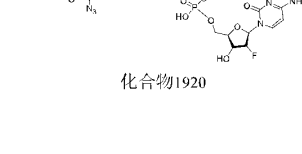
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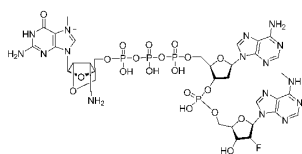
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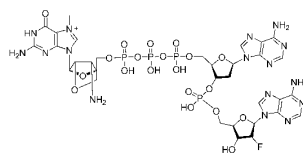
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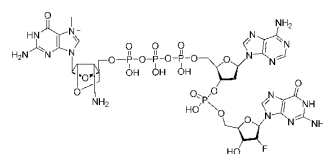
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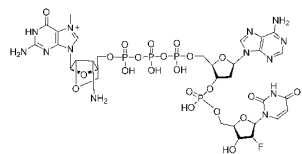
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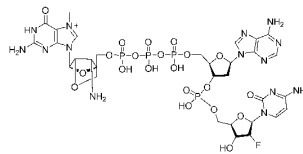
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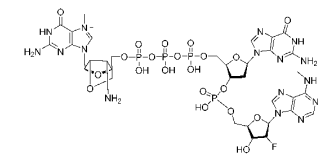
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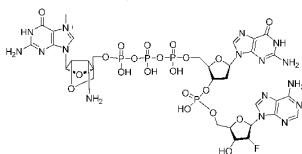
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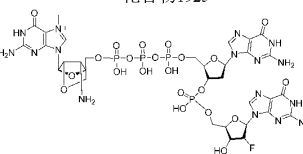
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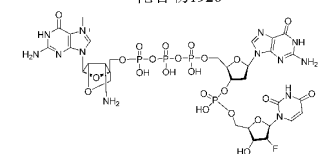
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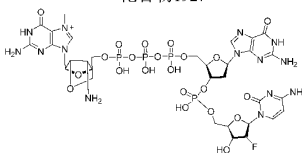
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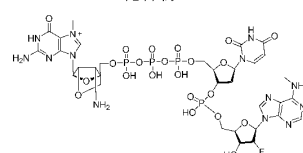
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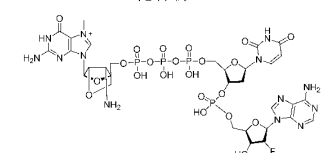
化合物1929



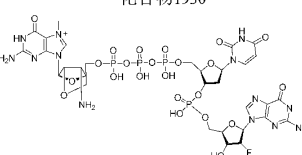
化合物1930



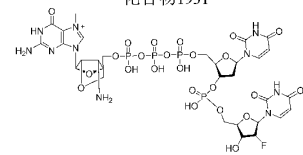
化合物1931



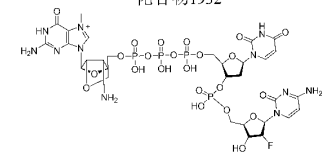
化合物1932



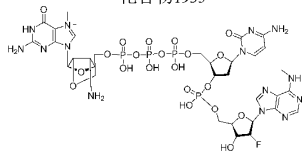
化合物1933



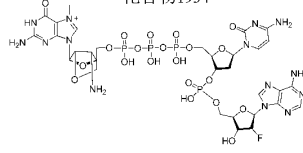
化合物1934



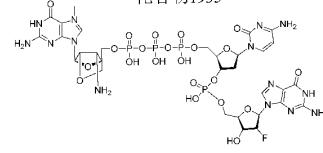
化合物1935



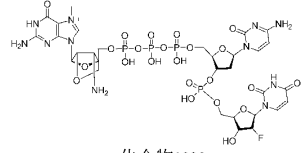
化合物1936



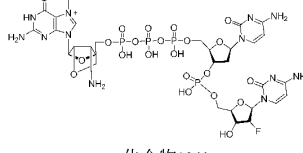
化合物1937



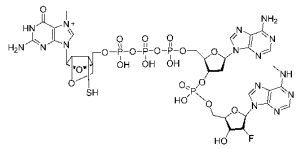
化合物1938



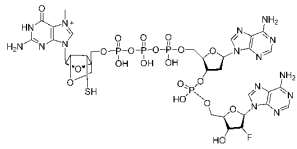
化合物1939



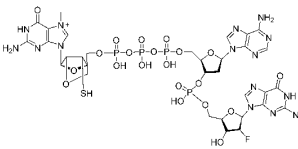
化合物1940



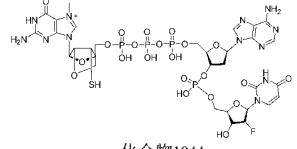
化合物1941



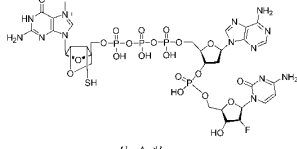
化合物1942



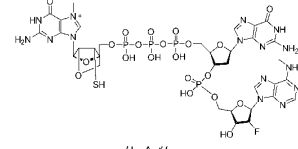
化合物1943



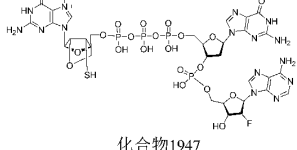
化合物1944



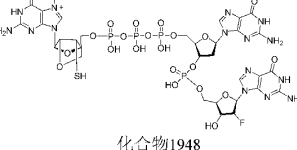
化合物1945



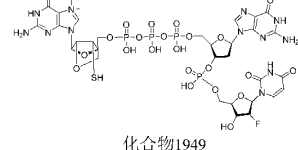
化合物1946



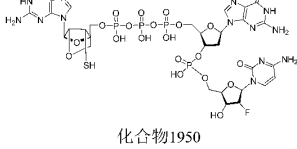
化合物1947



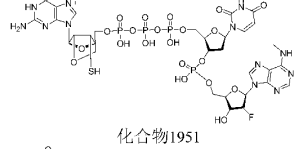
化合物1948



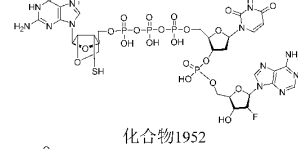
化合物1949



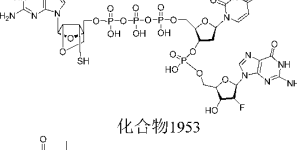
化合物1950



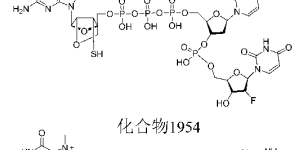
化合物1951



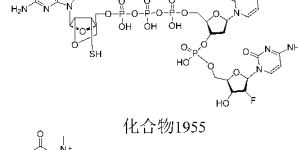
化合物1952



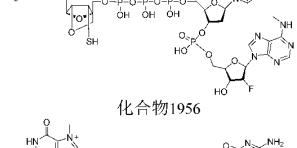
化合物1953



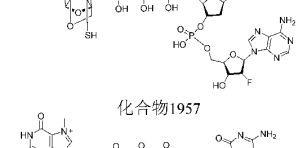
化合物1954



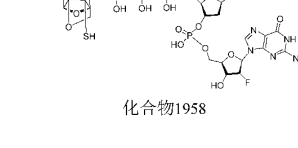
化合物1955



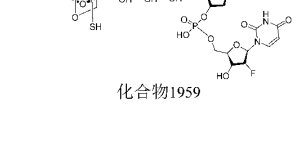
化合物1956



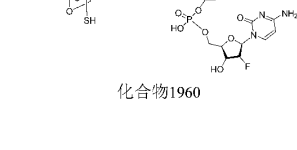
化合物1957



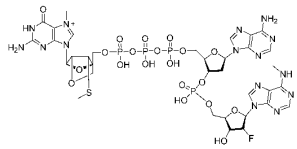
化合物1958



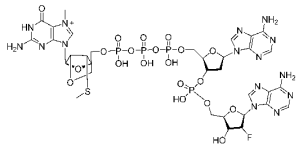
化合物1959



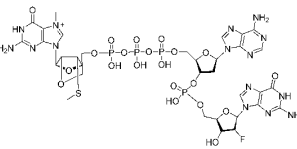
化合物1960



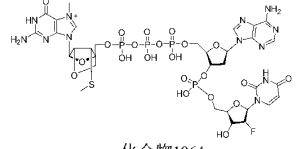
化合物1961



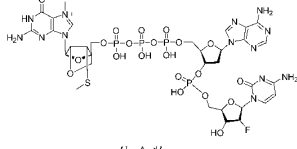
化合物1962



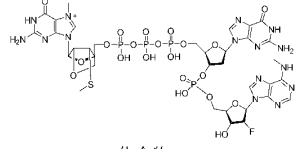
化合物1963



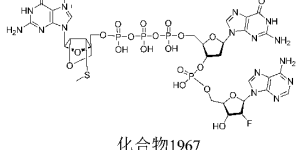
化合物1964



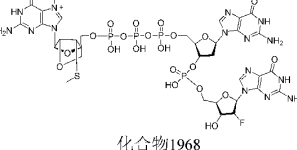
化合物1965



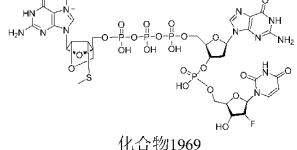
化合物1966



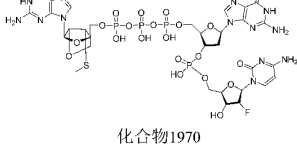
化合物1967



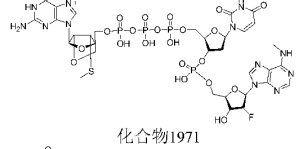
化合物1968



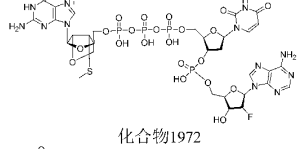
化合物1969



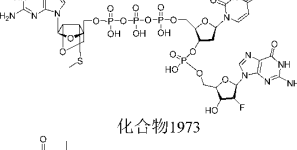
化合物1970



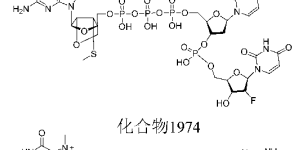
化合物1971



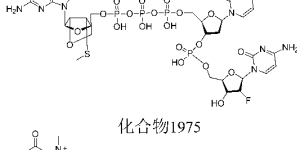
化合物1972



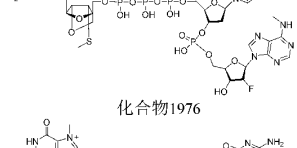
化合物1973



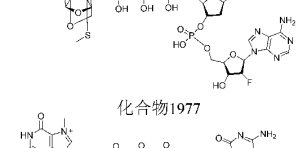
化合物1974



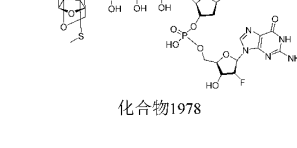
化合物1975



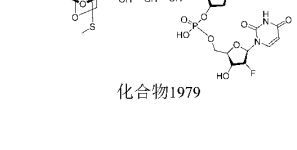
化合物1976



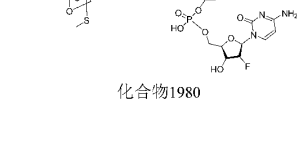
化合物1977



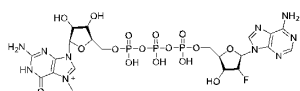
化合物1978



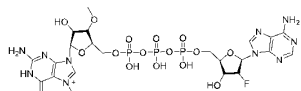
化合物1979



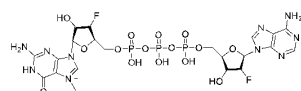
化合物1980



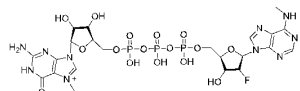
化合物1981



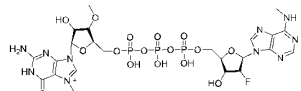
化合物1982



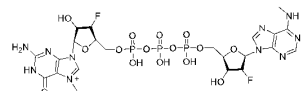
化合物1983



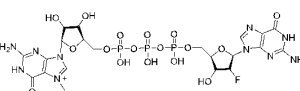
化合物1984



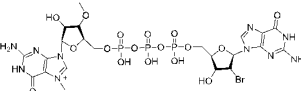
化合物1985



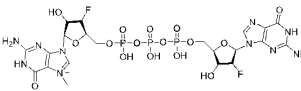
化合物1986



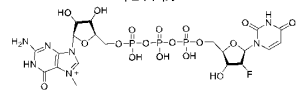
化合物1987



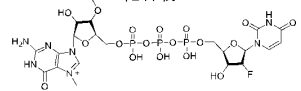
化合物1988



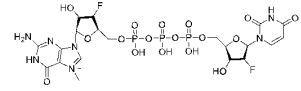
化合物1989



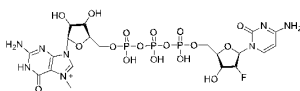
化合物1990



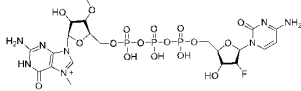
化合物1991



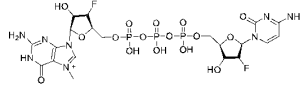
化合物1992



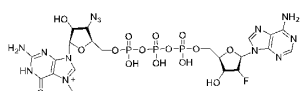
化合物1993



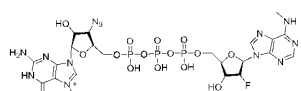
化合物1994



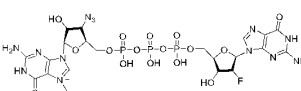
化合物1995



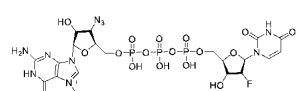
化合物1996



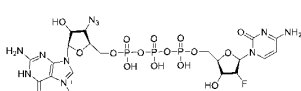
化合物1997



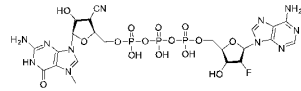
化合物1998



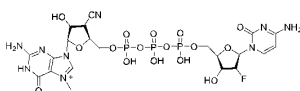
化合物1999



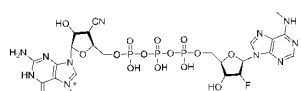
化合物2000



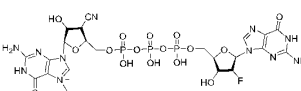
化合物2001



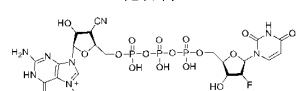
化合物2002



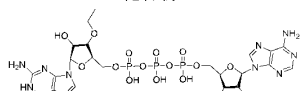
化合物2003



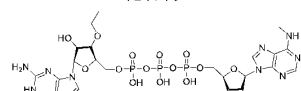
化合物2004



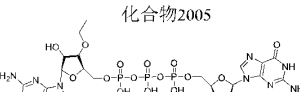
化合物2005



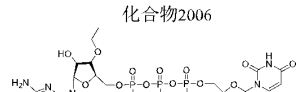
化合物2006



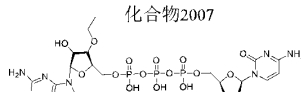
化合物2007



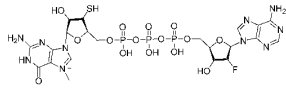
化合物2008



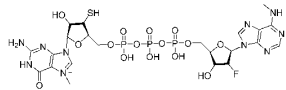
化合物2009



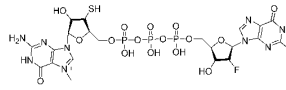
化合物2010



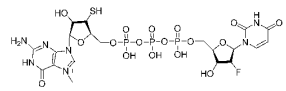
化合物2011



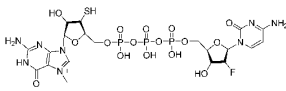
化合物2012



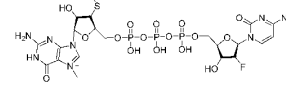
化合物2013



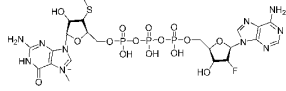
化合物2014



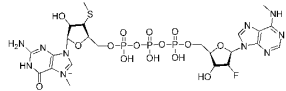
化合物2015



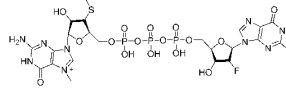
化合物2016



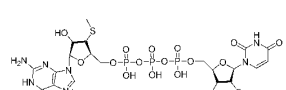
化合物2017



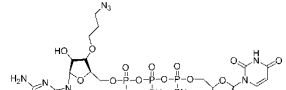
化合物2018



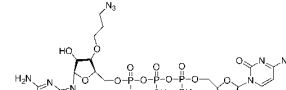
化合物2019



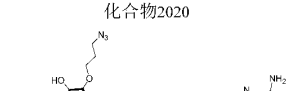
化合物2020



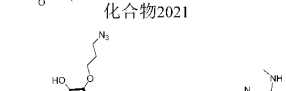
化合物2021



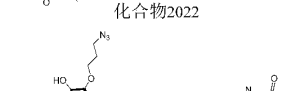
化合物2022



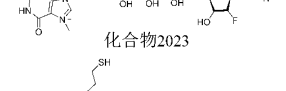
化合物2023



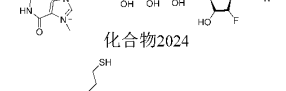
化合物2024



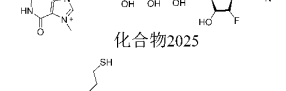
化合物2025



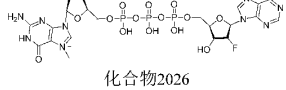
化合物2026



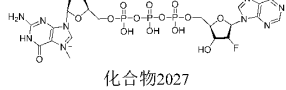
化合物2027



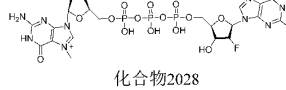
化合物2028



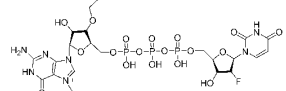
化合物2029



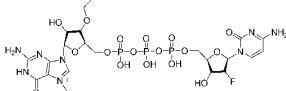
化合物2030



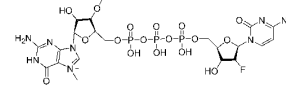
化合物2031



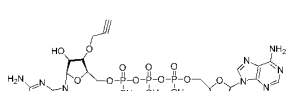
化合物2032



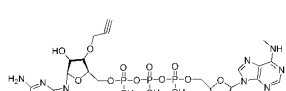
化合物2033



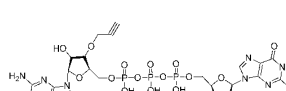
化合物2034



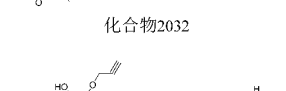
化合物2035



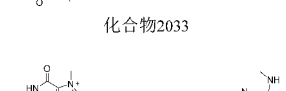
化合物2036



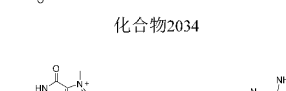
化合物2037



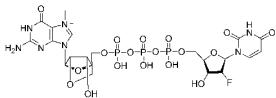
化合物2038



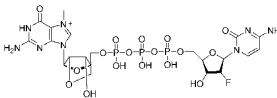
化合物2039



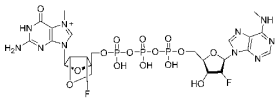
化合物2040



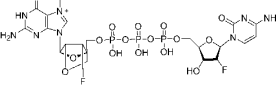
化合物2041



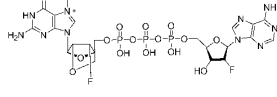
化合物2042



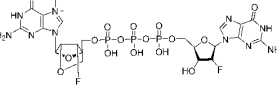
化合物2043



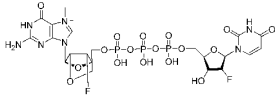
化合物2044



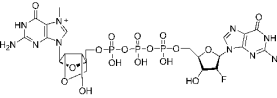
化合物2045



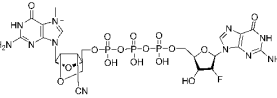
化合物2046



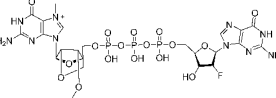
化合物2047



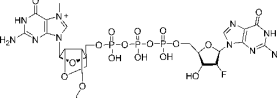
化合物2048



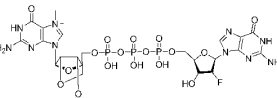
化合物2049



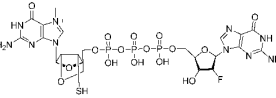
化合物2050



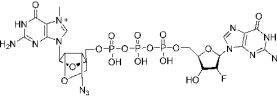
化合物2051



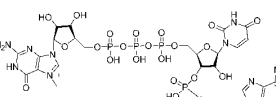
化合物2052



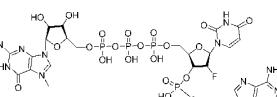
化合物2053



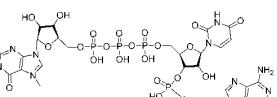
化合物2054



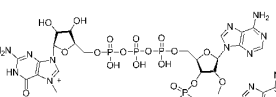
化合物2055



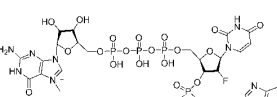
化合物2056



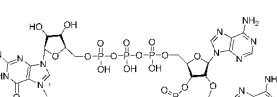
化合物2057



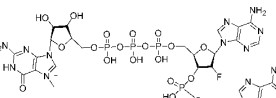
化合物2058



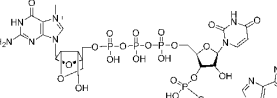
化合物2059



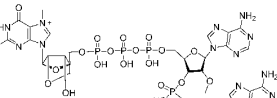
化合物2060



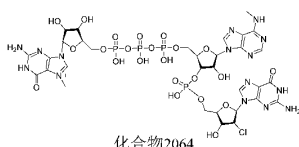
化合物2061



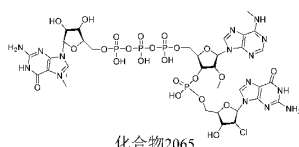
化合物2062



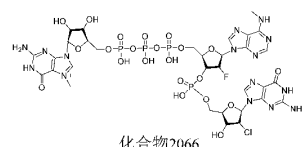
化合物2063



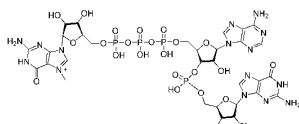
化合物2064



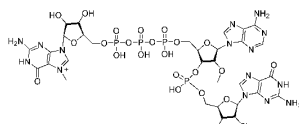
化合物2065



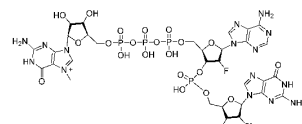
化合物2066



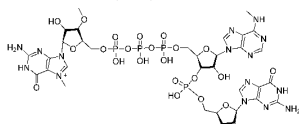
化合物2067



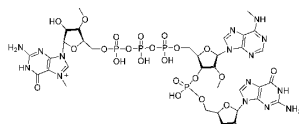
化合物2068



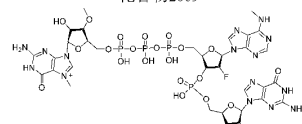
化合物2069



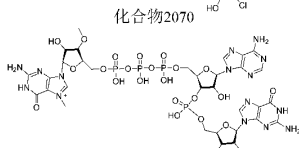
化合物2070



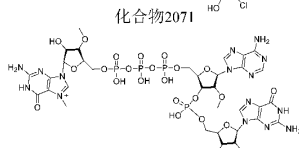
化合物2071



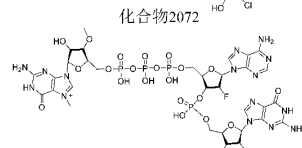
化合物2072



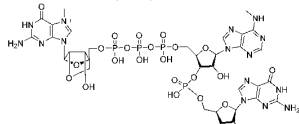
化合物2073



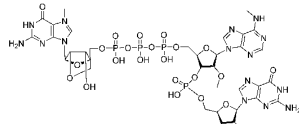
化合物2074



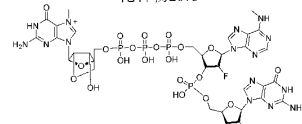
化合物2075



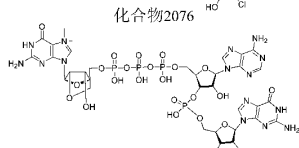
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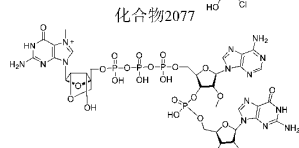
化合物2077



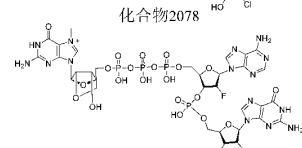
化合物2078



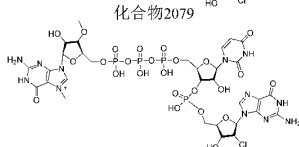
化合物2079



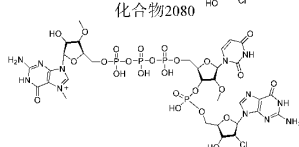
化合物2080



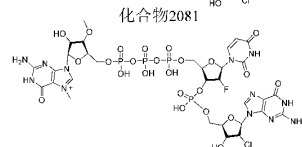
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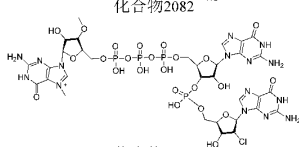
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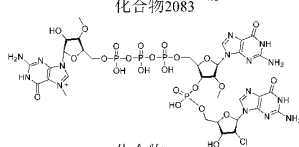
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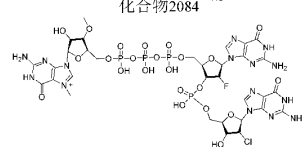
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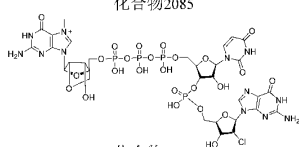
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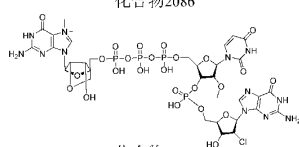
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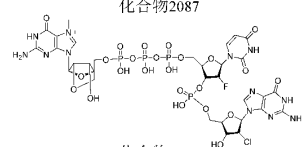
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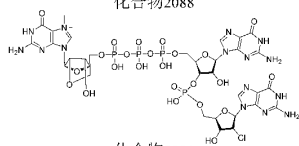
化合物2088



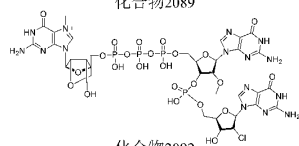
化合物2089



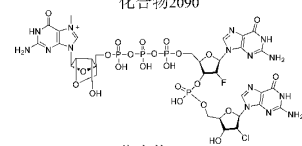
化合物2090



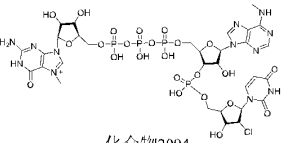
化合物2091



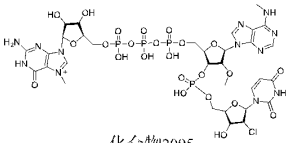
化合物2092



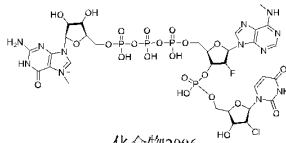
化合物2093



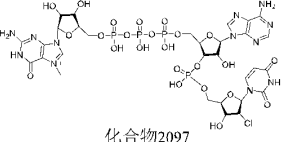
化合物2094



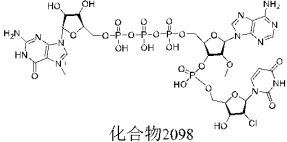
化合物2095



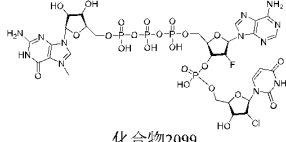
化合物2096



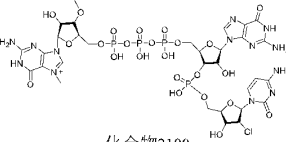
化合物2097



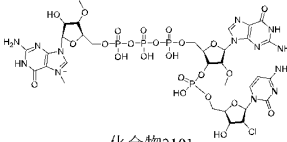
化合物2098



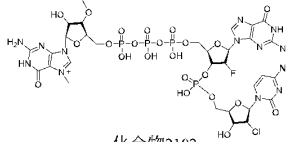
化合物2099



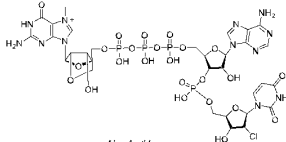
化合物2100



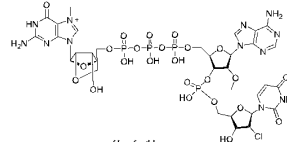
化合物2101



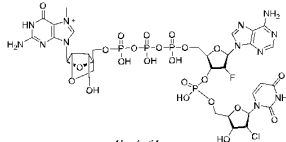
化合物2102



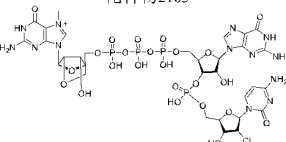
化合物2103



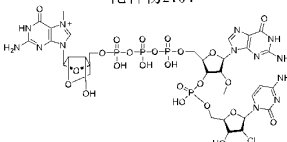
化合物2104



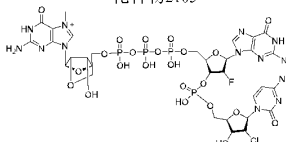
化合物2105



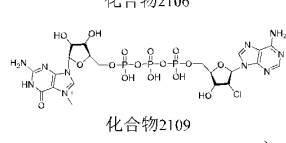
化合物2106



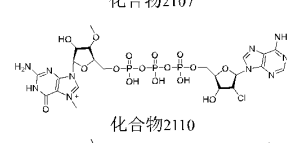
化合物2107



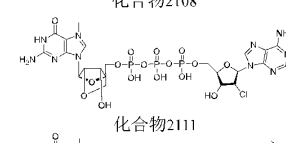
化合物2108



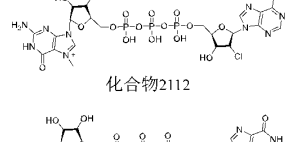
化合物2109



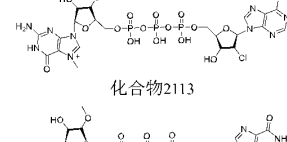
化合物2110



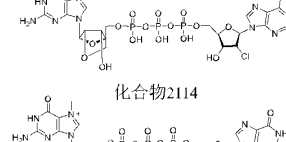
化合物2111



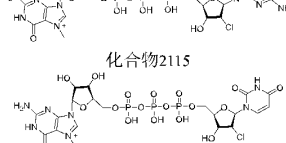
化合物2112



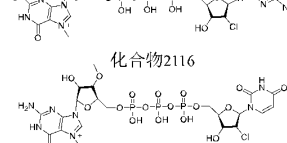
化合物2113



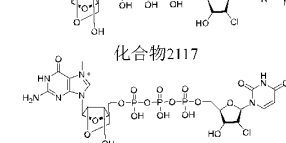
化合物2114



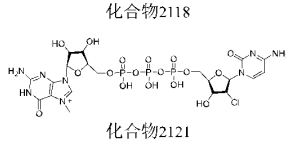
化合物2115



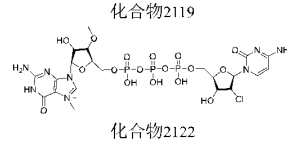
化合物2116



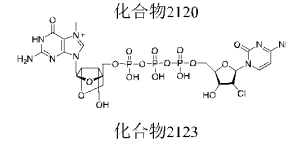
化合物2117



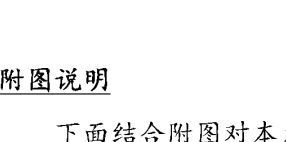
化合物2118



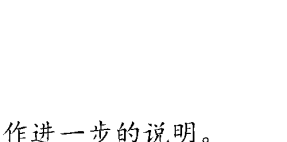
化合物2119



化合物2120



化合物2121



化合物2122



化合物2123

附图说明

下面结合附图对本发明作进一步的说明。

图1示出不同帽类似物的 mRNA 在 HEK293T 细胞中的荧光成像图。

图2示出了不同帽类似物的 mRNA 在 HEK293T 细胞中的荧光强度。

图 3 示出了不同帽类似物的 mRNA 在 HepG2 细胞中的荧光强度。

图 4 示出了不同帽类似物的 mRNA 在不同脏器中的表达效率。

具体实施方式

本发明提供一种用于 RNA 的 5'端加帽的含卤化合物（“帽类似物”或“加帽类似物”）、其药学上可接受的盐、其溶剂化物和其立体异构体及其应用。使用该类似化合物对 mRNA 的 5'端加帽反应具有较高的加帽率，并且具有较好的体外转录效率，同时，在细胞水平有较高的翻译表达效率。

在进一步描述本发明之前，下面的章节中收集了说明书、实施例、和附加的权利要求中使用的某些术语。本文所列定义应被本领域技术人员根据本发明的其余部分来阅读并理解。除非另外定义，否则本文使用的所有技术和科学术语均具有本发明所属领域普通技术人员通常理解相同的含义。

定义

除非另有说明，当公开或要求保护任何类型的范围时，意图单独公开或要求保护该范围可有理由涵盖的各可能的数值，包括涵盖在其中的任何子范围。例如基团个数为 1 至 6 表明该范围内的整数，其中 1-6 应理解包括 1、2、3、4、5、6，也包括 1-5、1-4 和 1-3 的子范围。

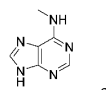
本公开的说明书应该被解释为与化学键的法则和原理一致。在一些情况下，可能为了在给定的位置适应取代基而除去氢原子。

本公开中使用的“包括”、“含有”或者“包含”等类似的词语意指出现该词前面的要素涵盖出现在该词后面列举的要素及其等同，而不排除未记载的要素。本文所用的术语“含有”或“包括(包含)”可以是开放式、半封闭式和封闭式的。换言之，所述术语也包括“基本上由.....组成”、或“由.....组成”。

术语“药学上可接受的”在本申请中是指：化合物或组合物在化学上和/或在毒理学上与构成制剂的其它成分和/或与用其预防或治疗疾病或病症的人类或哺乳动物相容。

天然或修饰的嘧啶类核苷酸碱基包括但不限于：尿嘧啶、胸腺嘧啶、胞嘧啶、5-甲基胞嘧啶，5-氟尿嘧啶、5-氟胞嘧啶等。

天然或修饰的嘌呤类核苷酸碱基包括但不限于：腺嘌呤、鸟嘌呤、6-N-甲基腺嘌呤、6-N, N₂-二甲基腺嘌呤、2-N-甲基鸟嘌呤、2-N, N₂-二甲基鸟嘌呤，7-甲基鸟



嘌呤等，其中 6-N-甲基腺嘌呤的结构为 。

本申请中的核苷酸碱基可以被修饰或替换以提供寡核苷酸。例如，可以用这些碱基或用合成的和天然的核苷酸碱基（例如肌苷，胸腺嘧啶，黄嘌呤，次黄嘌呤，nubularine，异鸟嘌呤或结核菌素）和任选进行修饰。或者，可以使用任何天然或合成的碱基的取代或修饰的类似物。例子包括 2-（卤代）腺嘌呤，2-（烷基）腺嘌呤，2-（丙基）腺嘌呤，2-（氨基）腺嘌呤，2-（氨基烷基）腺嘌呤，2-（氨基丙基）腺嘌呤，2-（甲硫基）-N6-（异戊烯基）腺嘌呤，6-（烷基）腺嘌呤，6-（甲基）腺嘌呤，7-（脱氮杂）腺嘌呤，8-（烯基）腺嘌呤，8-（烷基）腺嘌呤，8-（炔基）腺嘌呤，8-（氨基）腺嘌呤，8-（卤代）腺嘌呤，8-（羟基）腺嘌呤，8-（硫代烷基）腺嘌呤，8-（硫醇）腺嘌呤，N6-（异戊基）腺嘌呤，N6-（甲基）腺嘌呤，N6，n6-（二甲基）腺嘌呤，2-（烷基）鸟嘌呤，2-（丙基）鸟嘌呤，6-（烷基）鸟嘌呤，6-（甲基）鸟嘌呤，7-（烷基）鸟嘌呤，7-（甲基）鸟嘌呤，7-（脱氮杂）鸟嘌呤，8-（烷基）鸟嘌呤，8-（烯基）鸟嘌呤，8-（炔基）鸟嘌呤，8-（氨基）鸟嘌呤，8-（卤代）鸟嘌呤，8-（羟基）鸟嘌呤，8-（硫代烷基）鸟嘌呤，8-（硫醇）鸟嘌呤，N-（甲基）鸟嘌呤，2-（硫代）胞嘧啶，3-（脱氮杂）-5-（氮杂）胞嘧啶，3-（烷基）胞嘧啶，3-（甲基）胞嘧啶，5-（烷基）胞嘧啶，5-（炔基）胞嘧啶，5-（卤代）胞嘧啶，5-（甲基）胞嘧啶，5-（丙炔基）胞嘧啶，5-（丙炔基）胞嘧啶，5-（三氟甲基）胞嘧啶，6-（偶氮）胞嘧啶，N-4-（乙酰）胞嘧啶，3-（3-氨基-3-羧丙基）尿嘧啶，2-（硫代）尿嘧啶，5-（甲基）-2-（硫代）尿嘧啶，5-（甲氨基甲基）-2-（硫代）尿嘧啶，4-（硫代）尿嘧啶，5-（甲基）-4-（硫代）尿嘧啶，5-（甲氨基甲基）-4-（硫代）尿嘧啶，5-（甲基）-2，4-（二硫代）尿嘧啶，5-（甲氨基甲基）-2，4-（二硫代）尿嘧啶，5-（2-氨基丙基）尿嘧啶，5-（烷基）尿嘧啶，5-（炔基）尿嘧啶，5-（烯丙基氨基）尿嘧啶，5-（氨基烯丙基）尿嘧啶，5-（氨基烷基）尿嘧啶，5-（胍基烷基）尿嘧啶，5-（1，3-二唑-1-烷基）尿嘧啶，5-（氰基烷基）尿嘧啶，5-（二烷基氨基烷基）尿嘧啶，5-（二甲基氨基烷基）尿嘧啶，5-（卤代）尿嘧啶，5-（甲氧基）尿嘧啶，尿嘧啶-5-氧代乙酸，5-（甲氧羰基甲基）-2-（硫代）尿嘧啶，5-（甲氧羰基甲基）尿嘧啶，5-（丙炔基）尿嘧啶，5-（丙炔基）尿嘧啶，5-（三氟甲基）尿嘧啶，6-（偶氮）尿嘧啶，二氮尿嘧啶，3-（甲基）尿嘧啶，5-尿嘧啶（即，假尿嘧啶），2-（硫代）伪尿嘧啶

啉, 4-(硫代)伪尿嘧啶, 2, 4-(二硫代)嘌呤嘧啶, 5-(烷基)伪尿嘧啶, 5-(甲基)伪尿嘧啶, 5-(烷基)-2-(硫代)伪尿嘧啶, 5-(甲基)-2-(硫代)伪尿嘧啶, 5-(烷基)-4-(硫代)伪尿嘧啶, 5-(甲基)-4-(硫代)伪尿嘧啶, 5-(烷基)-2, 4-(二硫代)伪尿嘧啶, 5-(甲基)-2, 4-(二硫代)伪尿嘧啶, 1-取代的伪尿嘧啶, 1-取代的2-(硫代)-伪尿嘧啶, 1-取代的4-(硫代)伪尿嘧啶, 1-取代的2, 4-(二硫代)伪尿嘧啶, 1-(氨基羰基乙烯基)-伪尿嘧啶, 1-(氨基羰基乙烯基)-2-(硫代)-伪尿嘧啶, 1-(氨基羰基乙烯基)-4-(硫代)伪尿嘧啶, 1-(氨基羰基乙烯基)-2, 4-(二硫代)伪尿嘧啶, 1-(氨基烷基氨基羰基乙烯基)-伪尿嘧啶, 1-(氨基烷基氨基羰基乙烯基)-2-(硫代)-伪尿嘧啶, 1-(氨基烷基氨基羰基乙烯基)-4-(硫代)伪尿嘧啶, 1-(氨基烷基氨基羰基乙烯基)-2, 4-(二硫代)伪尿嘧啶, 1, 3-(二氮杂)-2-(氧代)-吩噻嗪-1-基, 1-(氮杂)-2-(硫代)-3-(氮杂)-吩噻嗪-1-基, 1, 3-(二氮杂)-2-(氧代)-吩噻嗪-1-基, 1-(氮杂)-2-(硫代)-3-(氮杂)-吩噻嗪-1-基, 7-取代的1, 3-(二氮杂)-2-(氧代)-吩噻嗪-1-基, 7-取代的1-(氮杂)-2-(硫代)-3-(氮杂)-吩噻嗪-1-基, 7-取代的1, 3-(二氮杂)-2-(氧代)-吩噻嗪-1-基, 7-(氨基烷基羟基)-1, 3-(二氮杂)-2-(氧代)-吩噻嗪-1-基, 7-(氨基烷基羟基)-1-(氮杂)-2-(硫代)-3-(氮杂)-吩噻嗪-1-基, 7-(氨基烷基羟基)-1, 3-(二氮杂)-2-(氧代)-吩噻嗪-1-基, 7-(氨基烷基羟基)-1-(氮杂)-2-(硫代)-3-(氮杂)-吩噻嗪-1-基, 7-(胍基烷基羟基)-1, 3-(二氮杂)-2-(氧代)-吩噻嗪-1-基, 7-(胍基烷基羟基)-1-(氮杂)-2-(硫代)-3-(氮杂)-吩噻嗪-1-基, 7-(胍基烷基羟基)-1, 3-(二氮杂)-2-(氧代)-吩噻嗪-1-基, 7-(胍基烷基羟基)-1-(氮杂)-2-(硫代)-3-(氮杂)-吩噻嗪-1-基, 1, 3, 5-(三氮杂)-2, 6-(二氧杂)萘, 肌苷, 黄嘌呤, 次黄嘌呤, 牛布拉林, 结核菌素, 异鸟苷, 肌苷基, 2-氮杂-肌苷基, 7-脱氮杂-肌苷基, 硝基咪唑基, 硝基吡唑基, 硝基苯并咪唑基, 硝基吲唑基, 氨基吲唑基, 吡咯并嘧啶基, 3-(甲基)异碳苯乙烯基, 5-(甲基)异碳苯乙烯基, 3-(甲基)-7-(丙炔基)异碳苯乙烯基, 7-(氮杂)吲唑基, 6-(甲基)-7-(氮杂)吲唑基, 亚氨基吡啶基, 9-(甲基)-亚氨基吡啶基, 吡咯并吡嗪基, 异碳苯乙烯基, 7-(丙炔基)异碳苯乙烯基, 丙炔基-7-(氮杂)吲唑基, 2, 4, 5-(三甲基)苯基, 4-(甲基)吲唑基, 4, 6-(二甲基)吲唑基, 苯基, 萘基, 蒽基, 菲基, 芘基, 芪基, 四苯基, 并五苯

基, 二氟甲基, 4-(氟)-6-(甲基)苯并咪唑, 4-(甲基)苯并咪唑, 6-(偶氮)胸腺嘧啶, 2-吡啶酮, 5-硝基咪唑, 3-硝基吡咯, 6-(氮杂)嘧啶, 2-(氨基)嘌呤, 2, 6-(二氨基)嘌呤, 5-取代嘧啶, 2-取代嘌呤, N6-取代嘌呤, O6-取代的嘌呤, 取代的1, 2, 4-三唑或其任何O-烷基化或N-烷基化衍生物。

- 5 “立体异构体”是指具有相同化学构造, 但原子或基团在空间上排列方式不同的化合物。立体异构体包括对映异构体、非对映异构体、构象异构体(旋转异构体)、几何异构体(顺/反)异构体、阻转异构体, 等等。

“通过化学键连接成环”是指通过碳碳键、碳氧键、碳氮键、碳硫键等将两个基团连接, 构成环状结构, 必要时相应的基团可减少1-2个氢原子。

- 10 表述“任选被取代”是指基团中一个、两个、三个或多于三个氢原子可以被各个取代基彼此独立地取代。所述取代基可选自烷基、烯基、烷氧基、卤素、氰基、氨基、硝基、-OH。

- 术语“烷基”是指饱和的直链或支化碳链。优选地, 该链包含1个至10个碳原子, 即1个、2个、3个、4个、5个、6个、7个、8个、9个或10个碳原子, 优选包含1至6个碳原子, 最优选包含1至3个碳原子。所述烷基例如为甲基、乙基、
15 正丙基、异丙基、丁基、异丁基、叔丁基、戊基、己基、戊基或辛基。所述烷基任选地被取代。

- 术语“烷氧基”包括-O-烷基基团和其中O原子在烷基链内的烷基基团, 例如-CH₂-O-CH₃, 其包含1个至10个碳原子, 优选包含1至6个碳原子, 最优选包含1
20 至3个碳原子。所述烷氧基任选地被取代。

术语“烯基”包括含有至少两个碳原子和至少一个碳-碳双键的直链烷基基团和支链烷基基团两者, 其包含2个至10个碳原子, 优选包含2至6个碳原子, 最优选包含2至3个碳原子。所述烯基任选地被取代。

- 术语“炔基”包括含有至少两个碳原子和至少一个碳-碳三键的直链烷基基团和支链烷基基团两者, 其包含2个至10个碳原子, 优选包含2至6个碳原子, 最优选包含2至3个碳原子。所述炔基任选地被取代。
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- 术语“环烷基”、“环烯基”、“环炔基”本身或与其他术语组合, 分别表示“烷基”、“烯基”和“炔基”的环状形式, 其中优选3个、4个、5个、6个、7个、8个、9个或10个原子成环, 例如环丙基、环丁基、环戊基、环己基、环庚基、环辛基、环丙烯基、环丁烯基、环戊烯基、环己烯基、环庚烯基、环辛烯基、
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环丙炔基、环丁炔基、环己炔基、环戊炔基等，其中环烯基或环炔基与其他基团的连接位置可以在任何适当的位置处。术语“环烷基”、“环烯基”和“环炔基”还意在包括其双环、三环和多环形式，其可为螺环或桥环。“环烷基”、“环烯基”和“环炔基”任选地被取代。环烷基和环烯基的实例包括环丙基、环丁基、环戊基、环己基、1-环己烯基、3-环己烯基、环庚基、螺[3,3]庚基、螺[3,4]辛基、螺[4,3]辛基、螺[3,5]壬基、螺[5,3]壬基、螺[3,6]癸基、螺[6,3]癸基、螺[4,5]癸基、螺[5,4]癸基、双环[2.2.1]庚基、双环[2.2.2]辛基、金刚烷基、降冰片烯基等。

术语“芳基”优选是指含有 6 个碳原子的芳香族单环、含有 10 个碳原子的芳香族双环体系或含有 14 个碳原子的芳香族三环体系。实例是苯基、萘基或蒽基。芳基任选地被取代。

术语“杂芳基”优选是指五元或六元芳香族单环，其中至少一个碳原子被 1 个、2 个、3 个或 4 个(对于五元环)或 1 个、2 个、3 个、4 个或 5 个(对于六元环)相同或不同的杂原子取代，杂原子优选选自 O、N 和 S；芳香族双环体系，其中 8 个、9 个、10 个、11 个或 12 个碳原子中的 1 个、2 个、3 个、4 个、5 个或 6 个碳原子被相同或不同的杂原子取代，杂原子优选选自 O、N 和 S；或芳香族三环体系，其中 13 个、14 个、15 个、16 个碳原子中的 1 个、2 个、3 个、4 个、5 个或 6 个碳原子被相同或不同的杂原子取代，杂原子优选选自 O、N 和 S。实例是噁唑基、异噁唑基、1,2,5-噁二唑基、1,2,3-噁二唑基、吡咯基、咪唑基、吡唑基、1,2,3-三唑基、噻唑基、异噻唑基、1,2,3-噻二唑基、1,2,5-噻二唑基、吡啶基、嘧啶基、吡嗪基、1,2,3-三嗪基、1,2,4-三嗪基、1,3,5-三嗪基、1,2,4,5-四嗪基、1-苯并呋喃基、2-苯并呋喃基、吲哚基、异吲哚基、苯并噻吩基、2-苯并噻吩基、1H-吡啶基、苯并咪唑基、苯并噁唑基、吲哚并噻吩基、2,1-苯并噁唑基、苯并噻唑基、1,2-苯并异噻唑基、2,1-苯并异噻唑基、苯并三唑基、喹啉基、异喹啉基、喹喔啉基、喹唑啉基、喹啉基、1,2,3-苯并三嗪基或 1,2,4-苯并三嗪基。

术语“PEG 基”是指一个或多个-CH₂-CH₂-O-或 CH₃-CH₂-O-单元连接起来的基团，例如 CH₃-CH₂-O-(CH₂-CH₂-O)_x-，其中 x 选自 0 至 6 的整数，优选 0 至 4 的整数。PEG 基可以任选被取代。

术语“药学上可接受的盐”是指本公开化合物的相对无毒的加成盐。例如，参见 S. M. Berge 等人“Pharmaceutical Salts”，J. Pharm. Sci. 1977, 66, 1-19。

本公开化合物的适合的药学上可接受的盐可以是例如在链或环中携带氮原子的

具有足够碱性的本公开化合物的酸加成盐，例如与如下无机酸形成的酸加成盐：例如盐酸、氢溴酸、氢碘酸、硫酸、磷酸或硝酸，或者与如下有机酸形成的酸加成盐：例如甲酸、乙酸、乙酰乙酸、丙酮酸、三氟乙酸、丙酸、丁酸、己酸、庚酸、十一烷酸、月桂酸、苯甲酸、水杨酸、2-(4-羟基苯甲酰基)苯甲酸、樟脑酸、肉桂酸、环戊烷丙酸、3-羟基-2-萘甲酸、烟酸、扑酸、果胶酯酸、过硫酸、3-苯基丙酸、苦味酸、特戊酸、2-羟基乙磺酸、衣康酸、氨基磺酸、三氟甲磺酸、十二烷基硫酸、乙磺酸、苯磺酸、对甲苯磺酸、甲磺酸、2-萘磺酸、萘二磺酸、樟脑磺酸、柠檬酸、酒石酸、硬脂酸、乳酸、草酸、丙二酸、琥珀酸、苹果酸、己二酸、藻酸、马来酸、富马酸、D-葡萄糖酸、扁桃酸、抗坏血酸、葡庚酸、甘油磷酸、天冬氨酸、磺基水杨酸或硫氰酸。

另外，具有足够酸性的本发明化合物的另一种适合的药学上可接受的盐是碱金属盐例如钠盐或钾盐，碱土金属盐例如钙盐或镁盐，铵盐，三乙胺盐，或与提供生理学上可接受的阳离子的有机碱形成的盐，例如与如下物质形成的盐：N-甲基葡糖胺、二甲基葡糖胺、乙基葡糖胺、赖氨酸、二环己基胺、1,6-己二胺、乙醇胺、葡糖胺、肌氨酸、丝氨酸、三羟基甲基氨基甲烷、氨基丙二醇、1-氨基-2,3,4-丁三醇。另外，碱性含氮基团可用如下试剂季铵化：低级烷基卤化物，例如甲基、乙基、丙基和丁基氯化物、溴化物和碘化物；硫酸二烷基酯，例如硫酸二甲酯、硫酸二乙酯、硫酸二丁酯和硫酸二戊酯；长链卤化物例如癸基、月桂基、肉豆蔻基和硬脂基氯化物、溴化物和碘化物；芳烷基卤化物如苄基和苯乙基溴化物等。

本领域技术人员还会认识到，所要求保护的化合物的酸加成盐可通过多种已知方法中的任意一种使所述化合物与适当的无机酸或有机酸反应来制备。或者，本公开的酸性化合物的碱金属盐和碱土金属盐通过各种已知的方法使其与适当的碱反应来制备。

本发明包括本公开化合物的所有可能的盐，其可为单一盐或所述盐的任意比例的任意混合物。

术语“溶剂化物”是通过将本发明化合物与溶剂分子组合、物理结合和/或溶剂化形成的物质，例如二溶剂化物、单溶剂化物或半溶剂化物，其中溶剂分子的比例与本发明化合物的比例分别为约 2:1、约 1:1 或约 1:2。这种物理结合在不同程度上涉及离子化和共价键合（包括氢键合）。在某些情况下（例如，当一种或多种溶剂分子结合到结晶固体的晶格中时），可以分离溶剂化物。因此，溶剂化物包括溶液相

和可分离的溶剂化物。本发明的化合物可以与药学上可接受的溶剂(例如水、甲醇和乙醇)呈溶剂化形式,并且本申请旨在涵盖本发明化合物的溶剂化和非溶剂化形式。一种溶剂化物是水合物。

本申请中使用的术语“药物组合物”是指用于识别、预防或治疗组织状态或疾病的物质和/或物质的组合。药物组合物被配制成为适合于施用给患者以诊断、预防和/或治疗疾病。另外,药物组合物是指活性剂与惰性或活性载体的组合,使该组合物适合于治疗用途。

如本文所用,术语“载体”是指与治疗剂一起施用的稀释剂、佐剂、赋形剂或载剂。这种药物载体可以是无菌液体,例如在水和油中的盐水溶液,包括石油、动物、植物或合成来源的那些,例如花生油、大豆油、矿物油、芝麻油等。当药物组合物静脉内施用时,盐溶液是优选的载体。盐溶液以及葡萄糖水溶液和甘油溶液也可以用作液体载体,特别是用于可注射溶液。合适的药物赋形剂包括淀粉、葡萄糖、乳糖、蔗糖、明胶、麦芽、大米、面粉、白垩、硅胶、硬脂酸钠、单硬脂酸甘油酯、滑石粉、氯化钠、脱脂奶粉、甘油、丙烯、乙二醇、水、乙醇等。如果需要,该组合物还可包含少量的润湿剂或乳化剂或 pH 缓冲剂。合适的药物载体的实例在 E.W.Martin 的“Remington's Pharmaceutical Sciences”中有所描述。

术语“卤素”是指氟、氯、溴和碘。

术语“任选”是指该情形可发生也可不发生。

实施例

所用试剂和模型

实施例的起始材料是市售可得和/或可以以有机合成领域技术人员熟知的多种方法进行制备。有机合成领域的技术人员会在下述合成方法中适当地选择反应条件(包括溶剂、反应气氛、反应温度、实验的持续时间和后处理)。有机合成领域的技术人员会理解,存在于分子各部分上的官能团应当与所提出的试剂和反应相容。

合成的所有试剂、化合物均可在中国通过一般商业渠道购得,供应商包括 Sigma-Aldrich (美国), 上海兆维科技发展有限公司 (Trinlink Cleancap), jetMESSENGER (Polyplus-transfection®), 上海泰坦科技股份有限公司等。

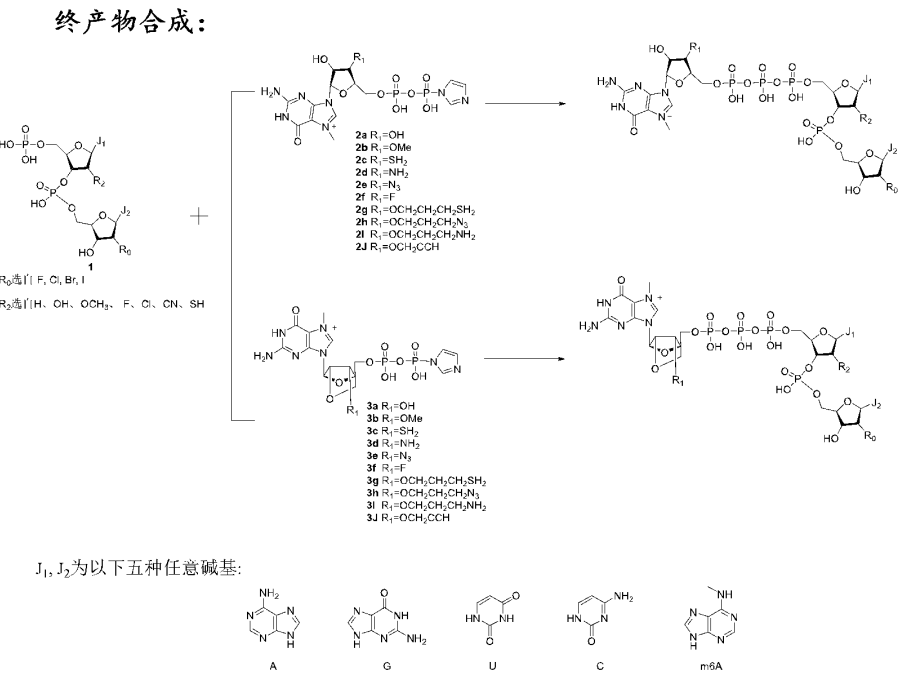
细胞模型: HEK293T 细胞购自上海中科院细胞库, HepG2 细胞购自武汉普诺赛生命科技有限公司。

所用主要仪器：多功能酶标仪（MolecularDevices），流式细胞仪(CytoFLEX S 系列)。

化合物制备与鉴定：核磁共振仪（Bruker 300MHz）、液相色谱-质谱联用仪（Agilent 6150/1290）、高效液相色谱仪（Agilent1260）。

5 细胞实验：倒置荧光显微镜（广州市明美光电技术有限公司）、细胞培养箱（Thermo Fisher Scientific）。

以下通过具体实施例详细说明本发明的实施过程和产生的有益效果，旨在帮助 10 阅读者更好地理解本发明的实质和特点，不作为对本案可实施范围的限定。



终产物合成方法 1

0.4g 化合物 1 溶于 8mL 无水 DMSO 中，氩气保护下加入 2eq 的化合物 2 和 20eq 的无水氯化锌。反应液在氩气保护下，室温 25℃搅拌 24 小时。TLC 监测反应 15 结束后，用 150mL 的 0.25 M EDTA 溶液终止反应，将混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0 M 的碳酸氢铵洗脱液线性梯度洗脱。收集含产物洗脱液冻干得产品。

终产物合成方法 2

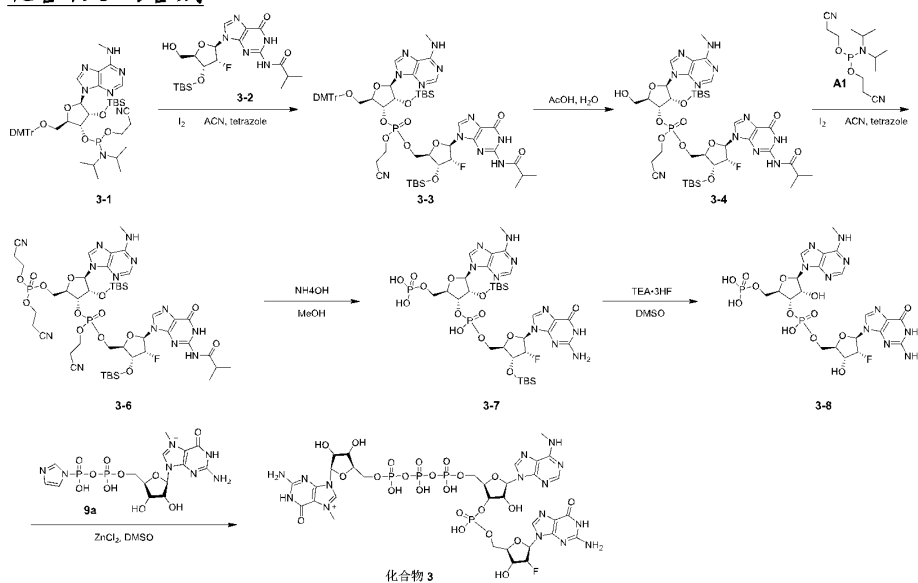
0.2g 化合物 2 溶于 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L

的氯化亚锰水溶液中，然后 0.2g 化合物 **1** 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。TLC 监测反应结束后，用 150mL 的 0.25M EDTA 溶液终止反应，将混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵洗脱液线性梯度洗脱。收集含产物洗脱液冻干得产品。

5 代表性结构化合物的合成

实施例 1

化合物 3 的合成



步骤 1:

- 10 将化合物 **3-2** (2.38 g,) 加入到四氮唑 (1.76 g) 的乙腈溶液中 (63 mL) 加入三口瓶中，置换氦气三次；然后在室温下 25℃，将化合物 **3-1** (5 g) 溶于 10 mL 乙腈加入到上述溶液中，所得溶液在室温下 25℃ 搅拌 1 小时，没有发现明显放热，点板监测显示化合物 **3-1** 消失。然后向溶液中逐滴加入碘的吡啶/四氢呋喃/水的溶液 (0.5 mmol/mL，吡啶：四氢呋喃：水=1：8：1)，直到溶液不再褪色为止，然后反应液继续搅拌 0.5 小时，点板监测氧化完成。向反应液中加饱和亚硫酸钠水溶液 (10 mL) 淬灭后，再加 50 mL 水稀释，用二氯甲烷 (50 mLx 2) 萃取，合并有机相用水 (50 mL) 洗涤一次，浓缩得到淡黄色油状产物 **3-3** (8 g，粗品)。

步骤 2:

- 20 将化合物 **3-3** (8 g, 粗品) 溶于 40 mL 的乙酸和 10 mL 水中，反应在 25℃ 下搅拌 16 小时，点板监测化合物 **3-3** 消失，有极性大的点产生。反应液直接真空浓缩。浓

缩后加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱, EA, 10min, DCM: MeOH, 10-20% 20min, 流速 30ml/min) 浓缩得到白色固体产物 **3-4** (2.8 g, 51% 两步收率)。

步骤 3:

配 28 mL 的四氮唑的乙腈溶液 (0.4 mmol/mL)。化合物 **3-4** (2.8 g) 加入到上述溶
5 液中, 然后将化合物 **4I** (3 g) 在室温下 25°C 加入到该溶液中, 置换氮气三次, 反应
液在室温下 25°C 搅拌 1 小时。点板监测显示反应完全。反应液在冰水浴下冷却到
10°C 以下, 滴加碘的吡啶/四氢呋喃/水的溶液 (0.5 mmol/mL, 吡啶: 四氢呋喃: 水
= 1: 8: 1), 直到反应液不褪色。点板监测显示氧化反应完成。反应液加 10 mL 饱和
亚硫酸钠水溶液淬灭, 再加水稀释。用乙酸乙酯萃取三次, 合并有机相用无水硫酸
10 钠干燥, 过滤。加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱, EA, 10min, DCM:
MeOH, 10-20% 20min, 流速 30ml/min)。浓缩得到白色泡沫状固体化合物 **3-6** (2.6
g, 78.2% 收率)。

步骤 4:

将化合物 **3-6** (2.6 g) 溶于甲醇 (30 mL), 然后加入浓氨水 (30 mL), 所得溶液在室
15 温下 25°C 搅拌 60 小时, 点板监显示化合物 **1-6** 反应完全。反应液真空浓缩, 加甲醇
再次浓缩, 得到淡黄色油状液体化合物 **3-7** (2.4 g, 粗品), 粗品直接投下一步。

步骤 5:

将化合物 **3-7** (2.4 g, 粗品) 溶于 DMSO (3 mL), 然后加入三乙胺三氢氟酸盐 (3.5
mL), 反应液在 50°C 下搅拌 1 小时, 点板显示化合物 **3-7** 反应完全。反应液加水稀释
20 到 50 mL, 用 1N 的 NaOH 水溶液调节 pH=5.5, 将混合物装载到 DEAE Sephadex 柱
上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩
大部分水, 剩余液体经冻干后, 得到目标化合物的胺盐 **3-8** (0.8 g, 33.7% 收率),
产物性状为白色固体。

步骤 6:

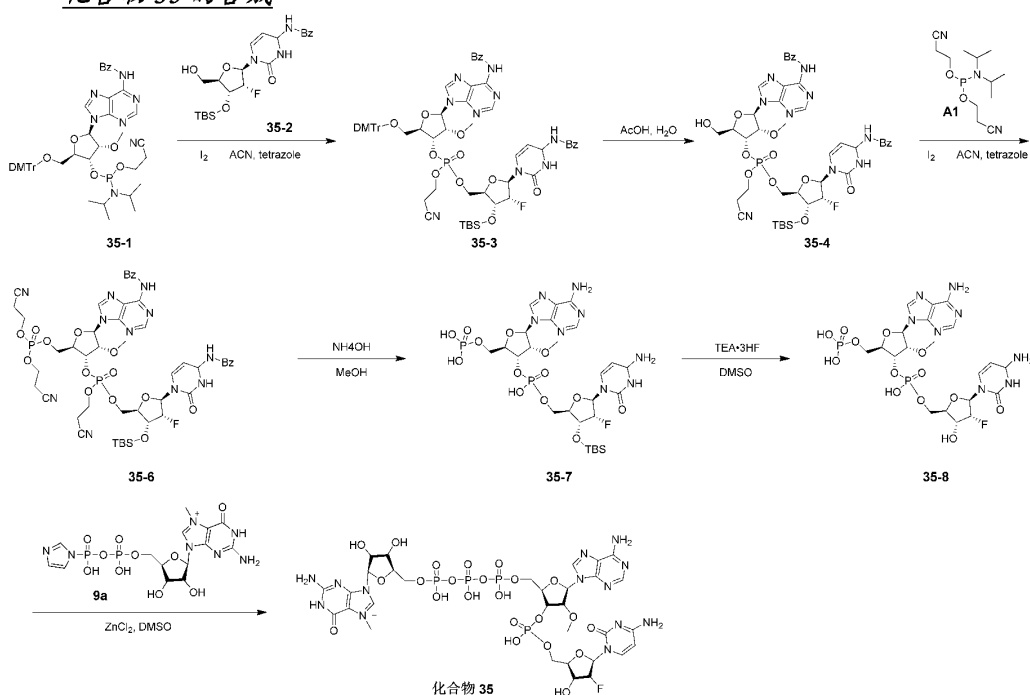
25 将化合物 **9a** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和
0.2mol/L 的氯化亚锰水溶液中, 然后化合物 **3-8** (200 mg) 加入到该溶液中。反应液在
室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应液加入提前冷却 0°C 的 EDTA
二钠盐溶液 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使
用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩
30 余液体经冻干后, 得到白色粉末状产物化合物 **5**, 为铵盐 (65 mg)。

^1H NMR (400 MHz, D_2O) 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)。

^{31}P NMR (162 MHz, D_2O) δ -0.80, -11.55, -23.03。

5 实施例 2

化合物 35 的合成



步骤 1:

将化合物 35-2 (2.07 g) 加入到四氢唑 (1.6 g) 的乙腈溶液中 (56 mL) 加入三口瓶中，
 10 置换氩气三次，然后在室温下 25°C ，化合物 35-1 (5 g) 溶于 10 mL 乙腈加入到上述溶
 液中，所得溶液在室温下 25°C 搅拌 1 小时，没有发现明显放热，点板监测显示化合
 物 2-I 消失。然后向溶液中逐滴加入碘的溶液 (5 g 碘溶于 40 mL 的混合溶液中 THF:
 H_2O : pyridine = 8: 1: 1, 配成 0.5mmol/mL 的溶液)，直到溶液不再褪色为止，然后反
 应液继续搅拌 0.5 小时，点板监测氧化完成。向反应液中加 Na_2SO_3 水溶液 (10 mL)
 15 淬灭后，再加 50 mL 水稀释，用二氯甲烷 (50 mL $\times$ 2) 萃取，合并有机相用水 (50 mL)
 洗涤一次，浓缩得到淡黄色油状产物 35-3 (7.5 g, 粗品)。

步骤 2:

将化合物 35-3 (7.2 g, 粗品) 溶于 40 mL 的乙酸和 10 mL 水中，反应在 25°C 下搅

拌 16 小时, 点板监测化合物 **35-3** 消失, 有极性大的点产生。反应液直接真空浓缩。浓缩后加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱, EA, 10min, DCM: MeOH, 10-20% 20min, 流速 30ml/min) 浓缩得到白色固体产物 **35-4** (2.8 g, 54.8% 两步收率)。

5 步骤 3:

配 28 mL 的四氮唑的乙腈溶液 (0.4 mmol/mL)。化合物 **35-4** (2.8 g) 加入到上述溶液中, 然后化合物 **41** (2.26 g) 在室温下 25°C 加入到该溶液中, 置换氮气三次, 反应液在室温下 25°C 搅拌 1 小时。点板监测显示反应完全。反应液在冰水浴下冷却到 10°C 以下, 滴加碘的吡啶/四氢呋喃/水的溶液 (0.5 mmol/mL, 吡啶: 四氢呋喃: 水 = 1: 8: 1), 直到反应液不褪色。点板监测显示氧化反应完成。反应液加 10 mL 饱和亚硫酸钠水溶液淬灭, 再加水稀释。用乙酸乙酯萃取三次, 合并有机相用无水硫酸钠干燥, 过滤。加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱, EA, 10min, DCM: MeOH, 10-20% 20min, 流速 30ml/min)。浓缩得到白色泡沫状固体 **35-6** (3.1 g, 93.5% 收率)。

15 步骤 4:

将化合物 **35-6** (3.1 g) 溶于甲醇 (30 mL), 然后加入浓氨水 (30 mL), 所得溶液在室温下 25°C 搅拌 60 小时, 点板监显示化合物 **35-6** 反应完全。反应液真空浓缩, 加甲醇再次浓缩, 得到淡黄色油状液体化合物 **35-7** (2.4 g, 粗品)。

步骤 5:

20 将化合物 **35-7** (2.4 g, 粗品) 溶于 DMSO (3 mL), 然后加入三乙胺三氢氟酸盐 (3.5 mL), 反应液在 50°C 下搅拌 1 小时, 点板显示化合物 **35-7** 反应完全。反应液加水稀释到 50 mL, 用 1N 的 NaOH 水溶液调节 pH=5.5, 将混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0 M 的 TEAB 洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到目标化合物的三乙胺盐 **35-8** (1.5 g, 51% 收率), 产物性状为白色固体。

25 步骤 5:

室温 (25 °C) 氩气保护下, 分别加入化合物 **35-8** (500 mg), 化合物 **9a** (500 mg) 和无水氯化锌 (1.2 g), 然后用注射器加入无水的 DMSO (8 mL) 反应 24 小时, 点板显示大部分化合物反应。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液 (1.6 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0 M 的碳酸氢铵水

30

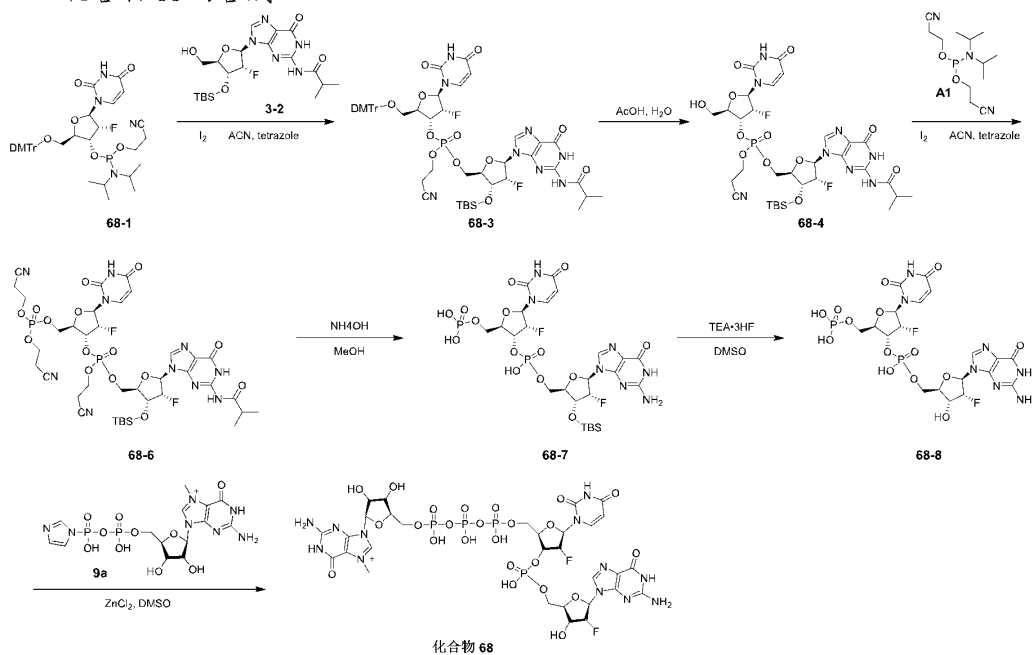
溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **35**, 为铵盐 (120 mg)。

^1H NMR (400 MHz, D_2O) 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)。

5 ^{31}P NMR (162 MHz, D_2O) δ -1.25, -11.58, -22.98。

实施例 3

化合物 **68** 的合成



步骤 1:

10 将化合物 **3-2** (2.07 g) 加入到四氢唑 (1.6 g) 的乙腈溶液中 (56 mL) 加入三口瓶中, 置换氩气三次, 然后在室温下 25°C , 化合物 **68-1** (5 g) 溶于 10 mL 乙腈加入到上述溶液中, 所得溶液在室温下 25°C 搅拌 1 小时, 没有发现明显放热, 点板监测显示化合物 **68-1** 消失。然后向溶液中逐滴加入碘的溶液 (5 g 碘溶于 40 mL 的混合溶液中 THF: H_2O : pyridine = 8: 1: 1, 配成 0.5 mmol/mL 的溶液), 直到溶液不再褪色为止, 然后反

15 应液继续搅拌 0.5 小时, 点板监测氧化完成。向反应液中加 Na_2SO_3 水溶液 (10 mL) 淬灭后, 再加 50 mL 水稀释, 用二氯甲烷 (50 mL $\times 2$) 萃取, 合并有机相用水 (50 mL) 洗涤一次, 浓缩得到淡黄色油状产物 **68-3** (7.5 g, 粗品)。

步骤 2:

将化合物 **68-3** (7.2 g, 粗品) 溶于 40 mL 的乙酸和 10 mL 水中, 反应在 25°C 下搅

拌 16 小时, 点板监测化合物 **68-3** 消失, 有极性大的点产生。反应液直接真空浓缩。浓缩后加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱, EA, 10min, DCM: MeOH, 10-20% 20min, 流速 30ml/min) 浓缩得到白色固体产物 **68-4** (2.8 g, 54.8%两步收率)。

5 步骤 3:

配 28 mL 的四氮唑的乙腈溶液 (0.4 mmol/mL)。化合物 **68-4** (2.8 g) 加入到上述溶液中, 然后化合物 **41** (2.26 g) 在室温下 25°C 加入到该溶液中, 置换氮气三次, 反应液在室温下 25°C 搅拌 1 小时。点板监测显示反应完全。反应液在冰水浴下冷却到 10°C 以下, 滴加碘的吡啶/四氢呋喃/水的溶液 (0.5 mmol/mL, 吡啶: 四氢呋喃: 水 = 1: 8: 1), 直到反应液不褪色。点板监测显示氧化反应完成。反应液加 10 mL 饱和亚硫酸钠水溶液淬灭, 再加水稀释。用乙酸乙酯萃取三次, 合并有机相用无水硫酸钠干燥、过滤。加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱, EA, 10min, DCM: MeOH, 10-20% 20min, 流速 30ml/min)。浓缩得到白色泡沫状固体 **68-6** (3.1 g, 93.5%收率)

15 步骤 4:

将化合物 **68-6** (3.1 g) 溶于甲醇 (30 mL), 然后加入浓氨水 (30 mL), 所得溶液在室温下 25°C 搅拌 60 小时, 点板显示化合物 **68-6** 反应完全。反应液真空浓缩, 加甲醇再次浓缩, 得到淡黄色油状液体化合物 **68-7** (2.4 g, 粗品)

步骤 5:

20 将化合物 **68-7** (2.4 g, 粗品) 溶于 DMSO (3 mL), 然后加入三乙胺三氢氟酸盐 (3.5 mL), 反应液在 50°C 下搅拌 1 小时, 点板显示化合物 **68-7** 反应完全。反应液加水稀释到 50 mL, 用 1N 的 NaOH 水溶液调节 pH=5.5, 将混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0 M 的 TEAB 洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到目标化合物的三乙胺盐 **68-8** (1.5 g, 51%收率),
25 产物性状为白色固体。

步骤 6:

室温 (25 °C) 氩气保护下, 分别加入化合物 **68-8** (500 mg), **9a** (500 mg) 和无水氯化锌 (1.2 g), 然后用注射器加入无水的 DMSO (8 mL) 反应 24 小时, 点板显示大部分原料反应。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.6 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0 M 的碳酸氢铵水溶液洗

脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **68**, 为铵盐 (120 mg)。

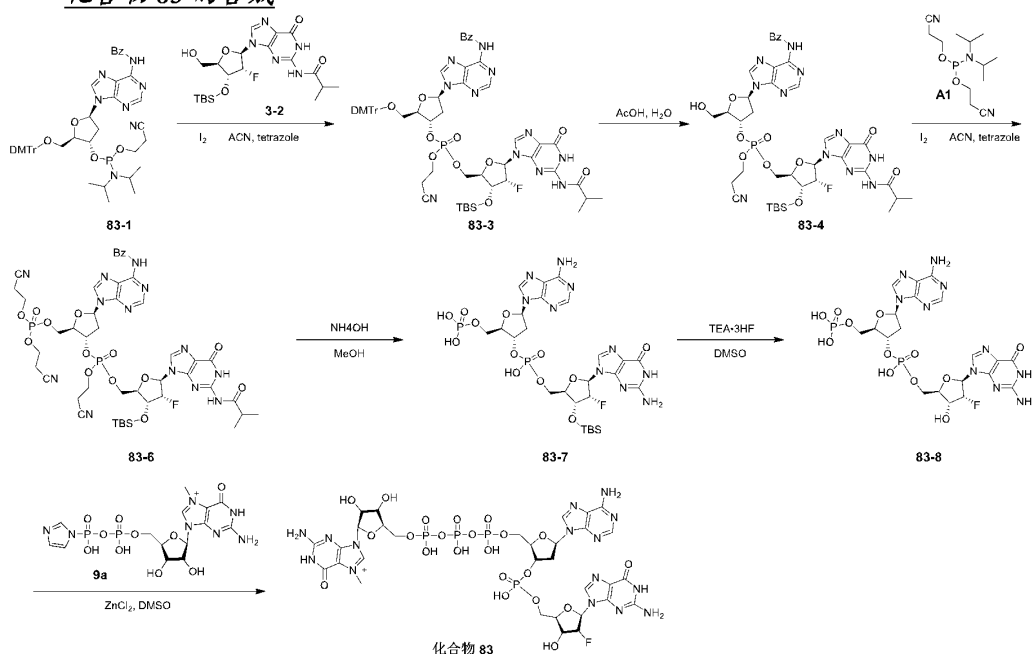
^1H NMR (400 MHz, D_2O) δ 7.75 (s, 1H), 7.61 (d, $J = 8.1$ Hz, 1H), 5.97 (dd, $J = 17.8$, 2.3 Hz, 1H), 5.85 – 5.65 (m, 3H), 5.28 (ddd, $J = 52.2$, 4.7, 2.3 Hz, 1H), 5.01 (dt, $J = 51.5$, 3.4 Hz, 1H), 4.57 – 4.51 (m, 2H), 4.48 (t, $J = 4.2$ Hz, 1H), 4.34 (t, $J = 5.1$ Hz, 1H), 4.24 – 4.07 (m, 7H), 4.02 (t, $J = 4.3$ Hz, 2H), 3.93 (s, 3H)。

^{31}P NMR (162 MHz, D_2O) δ -1.30, -11.57 (dd, $J = 25.8$, 18.4 Hz), -22.98 (t, $J = 18.3$ Hz)。

实施例 4

10

化合物 **83** 的合成



步骤 1:

将化合物 **3-2** (2.1 g) 加入到四氮唑 (1.6 g) 的乙腈溶液 (56 mL) 中加入三口瓶中, 置换氩气三次, 然后在室温下 25°C , 化合物 **83-1** (5 g) 溶于 10 mL 乙腈加入到上述溶液中, 所得溶液在室温下 25°C 搅拌 1 小时, 没有发现明显放热, 点板监测显示化合物 **83-1** 消失。然后向溶液中逐滴加入碘的溶液 (5 g 碘溶于 40 mL 的混合溶液中 THF: H_2O : pyridine = 8: 1: 1, 配成 0.5 mmol/mL 的溶液), 直到溶液不再褪色为止, 然后反应液继续搅拌 0.5 小时, 点板监测氧化完成。向反应液中加 Na_2SO_3 水溶液 (10 mL) 淬灭后, 再加 50 mL 水稀释, 用二氯甲烷 (50 mL x 2) 萃取, 合并有机相用水 (50 mL)

洗涤一次，浓缩得到淡黄色油状产物 **83-3** (7.4 g, 粗品)。

步骤 2:

将化合物 **83-3** (7.4 g, 粗品) 溶于 40 mL 的乙酸和 10 mL 水中，反应在 25°C 下搅拌 16 小时，点板监测化合物 **83-3** 消失，有极性大的点产生。反应液直接真空浓
5 缩。浓缩后加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱，EA，10min，DCM: MeOH，10-20% 20min，流速 30ml/min) 浓缩得到白色固体产物 **83-4** (2.8 g，54.8% 两步收率)。

步骤 3:

配 28 mL 的四氮唑的乙腈溶液 (0.4 mmol/mL)。化合物 **83-4** (2.8 g) 加入到上述
10 溶液中，然后 **AI** (2.26 g) 在室温下 25°C 加入到该溶液中，置换氮气三次，反应液在室温下 25°C 搅拌 1 小时。点板监测显示反应完全。反应液在冰水浴下冷却到 10°C 以下，滴加碘的吡啶/四氢呋喃/水的溶液 (0.5 mmol/mL，吡啶：四氢呋喃：水=1：8：1)，直到反应液不褪色。点板监测显示氧化反应完成。反应液加 10 mL 饱和亚硫酸钠水溶液淬灭，再加水稀释。用乙酸乙酯萃取三次，合并有机相用无水硫酸钠干
15 燥，过滤。加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱，EA，10min，DCM: MeOH，10-20%，20min，流速 30ml/min)。浓缩得到白色泡沫状固体 **83-6** (3.1 g，93.5% 收率)。

步骤 4:

将化合物 **83-6** (3.1 g) 溶于甲醇 (30 mL)，然后加入浓氨水 (30 mL)，所得溶液在室
20 温下 25°C 搅拌 60 小时，点板监显示化合物 **83-6** 反应完全。反应液真空浓缩，加甲醇再次浓缩，得到淡黄色油状液体化合物 **83-7** (2.4 g，粗品)。

步骤 5:

将化合物 **83-7** (2.4 g, 粗品) 溶于 DMSO (3 mL)，然后加入三乙胺三氢氟酸盐 (3.5 mL)，反应液在 50°C 下搅拌 1 小时，点板显示化合物 **83-7** 反应完全。反应液加水稀
25 释到 50 mL，用 1N 的 NaOH 水溶液调节 pH=5.5，将混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0 M 的 TEAB 洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到目标化合物的三乙胺盐 **83-8** (1.5 g，51% 收率)，产物性状为白色固体。

步骤 6:

30 室温 (25 °C) 氩气保护下，分别加入化合物 **83-8** (500 mg)、化合物 **9a** (500 mg)

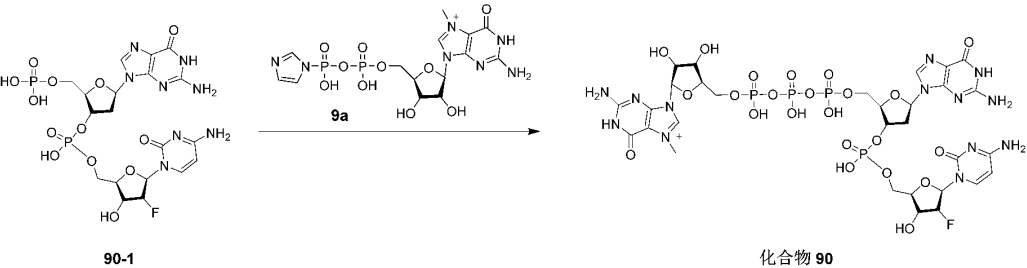
和无水氯化锌(1.2 g), 然后用注射器加入无水的 DMSO (8 mL)反应 24 小时, 点板显示大部分原料反应。将反应加入提前冷却 0℃的 EDTA 二钠盐溶液中(1.6 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **83**, 为铵盐 (120 mg)。

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)。

实施例 5

化合物 90 的合成



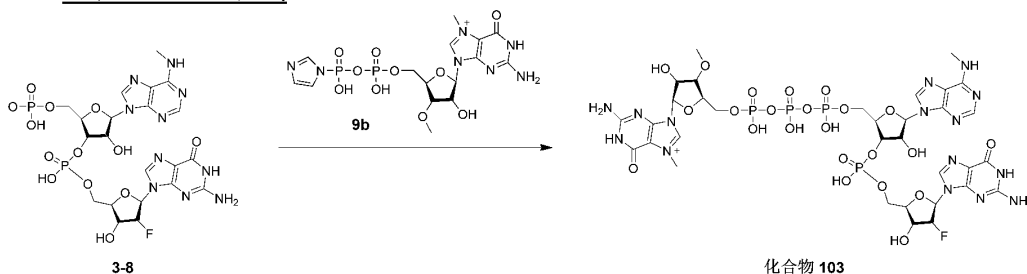
化合物 **9a** (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后化合物 **90-1** (200 mg)加入到该溶液中。反应液在室温下 25℃搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **90**, 为铵盐 (50 mg)。

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。

实施例 6

化合物 103 的合成



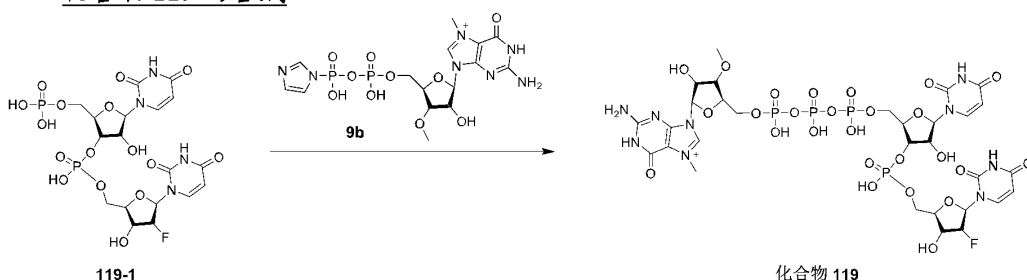
化合物 **9b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和
 5 0.2mol/L 的氯化亚锰水溶液中, 然后化合物 **3-8** (200 mg) 加入到该溶液中。反应液在
 室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA
 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用
 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩
 余液体经冻干后, 得到白色粉末状产物化合物 **103**, 为铵盐 (60 mg)。

10 ^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 (ttt, $J = 2.9, 1.5, 0.7$ Hz, 1H), 3.98
 (d, $J = 0.7$ Hz, 3H), 3.44 (d, $J = 1.4$ Hz, 3H), 3.08 (s, 3H)。

15 ^{31}P NMR (162 MHz, D_2O) δ 0.60, -10.29, -21.23。

实施例 7

化合物 119 的合成



化合物 **9b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和
 20 0.2mol/L 的氯化亚锰水溶液中, 然后化合物 **119-1** (200 mg) 加入到该溶液中。反应液在
 室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的
 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将

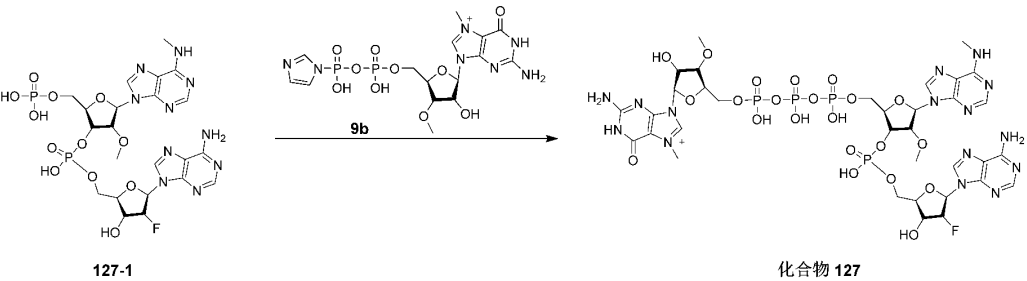
产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **119**, 为铵盐 (65 mg)。

^1H NMR (400 MHz, D_2O) δ 7.81 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.76 (dd, $J = 7.8, 1.8$ Hz, 1H), 6.17 (dt, $J = 2.5, 0.7$ Hz, 1H), 5.90 (d, $J = 7.8$ Hz, 1H), 5.85 – 5.73 (m, 2H), 5.53 (dddd, $J = 25.2, 3.9, 1.7, 0.9$ 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。

实施例 8

化合物 127 合成



化合物 **9b** (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后化合物 **127-1** (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **127**, 为铵盐 (82 mg)。

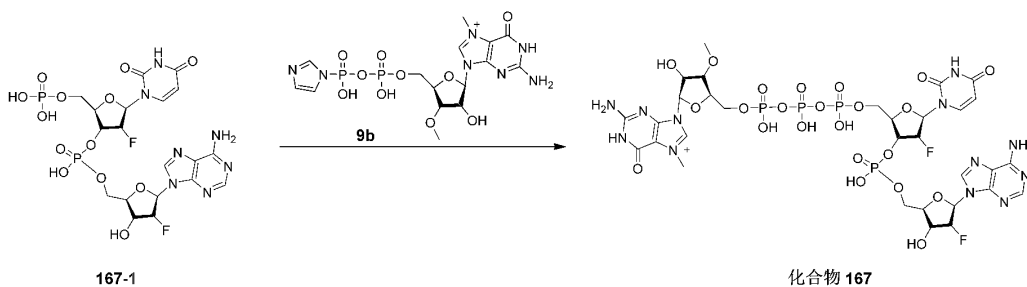
^1H NMR (400 MHz, D_2O) δ 8.29 (s, 1H), 8.24 (d, $J = 0.7$ Hz, 1H), 8.21 – 8.18 (m, 2H), 6.54 – 6.00 (m, 3H), 5.27 (dddd, $J = 46.5, 7.0, 4.0, 0.6$ Hz, 1H), 4.97 (dddd, $J = 8.0, 4.4, 2.9, 0.7$ Hz, 1H), 4.77 (tqd, $J = 4.4, 1.5, 0.7$ Hz, 1H), 4.71 (ddd, $J = 3.9, 2.6, 0.7$ Hz, 1H), 4.45 (dddd, $J = 25.2,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

实施例 9

化合物 167 的合成

25



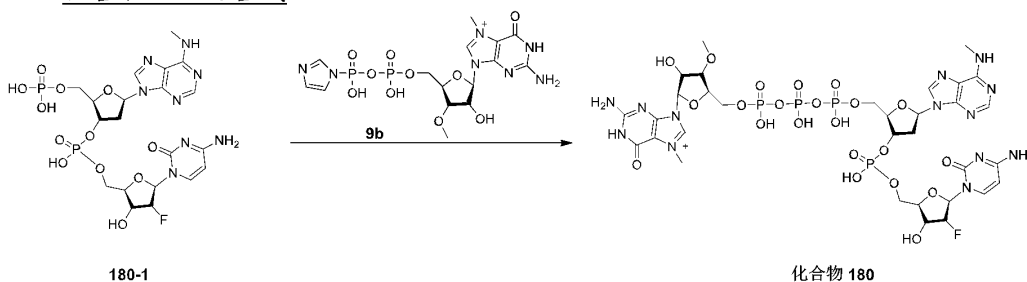
化合物 **9b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后化合物 **24-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **167**, 为铵盐 (62 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。

实施例 10

化合物 180 的合成



化合物 **9b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后 180-1 (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余

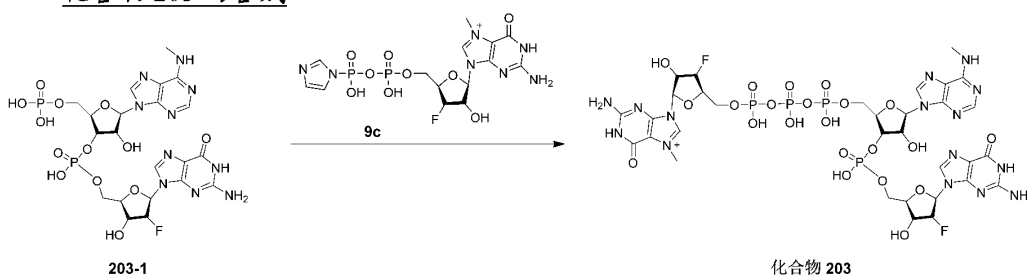
液体经冻干后, 得到白色粉末状产物化合物 **180**, 为铵盐 (95 mg)。

^1H NMR (400 MHz, D_2O) 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)。

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

实施例 11

化合物 203 的合成



10 化合物 **9c** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后化合物 **203-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

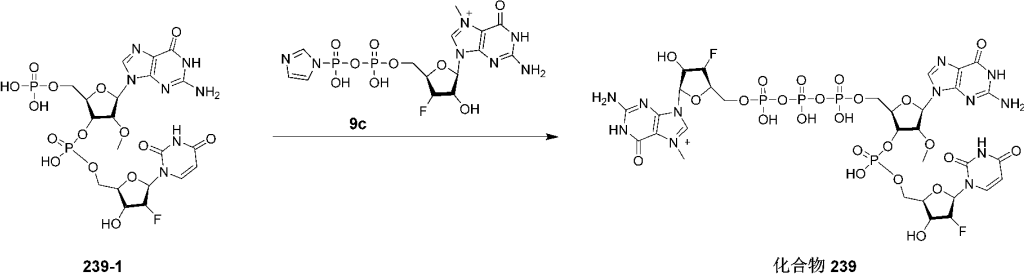
15 水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **203**, 为铵盐 (95 mg)。

^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)。

20 ^{31}P NMR (162 MHz, D_2O) δ 0.60, -10.29, -21.22。

实施例 12

化合物 239 的合成



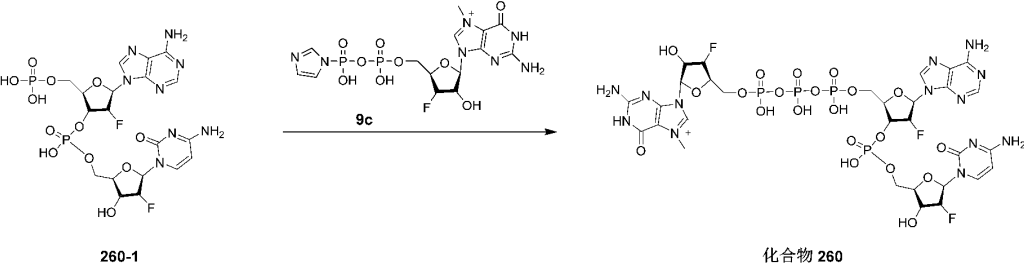
化合物 **9c** (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后化合物 **239-1** (200 mg)加入到该溶液中。反应液在室温下 25℃搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **239**，为铵盐 (95 mg)。

^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。

实施例 13

化合物 260 的合成



化合物 **9c** (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后化合物 **260-1** (200 mg)加入到该溶液中。反应液在室温下 25℃搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **260**，为铵盐 (75 mg)。

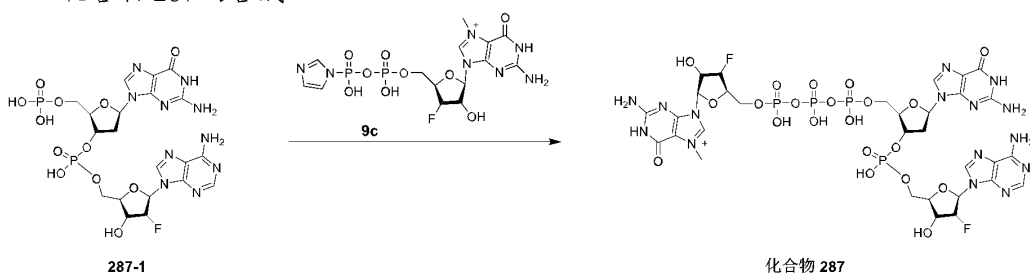
^1H NMR (400 MHz, D_2O) δ 8.24 (d, $J = 0.7$ Hz, 1H), 8.20 (s, 1H), 7.70 (dd, $J = 7.4$,

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。

5 实施例 14

化合物 287 的合成



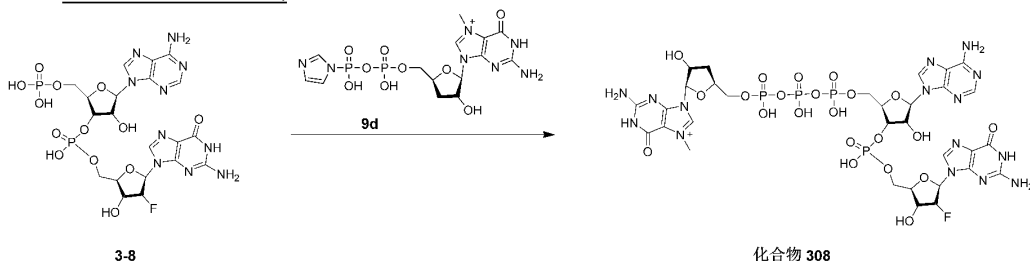
9c (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **287-1** (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **287**，为铵盐 (75 mg)。

^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。

实施例 15

20 化合物 126 的合成



9d (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L

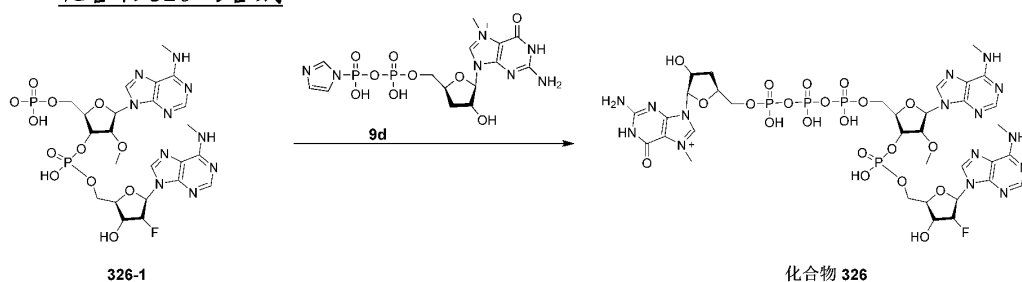
的氯化亚锰水溶液中, 然后 **3-8** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **308**, 为铵盐 (60 mg)。

^1H NMR (400 MHz, D_2O) 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)。

^{31}P NMR (162 MHz, D_2O) δ -0.9, -10.29, -21.27。

实施例 16

化合物 **326** 的合成



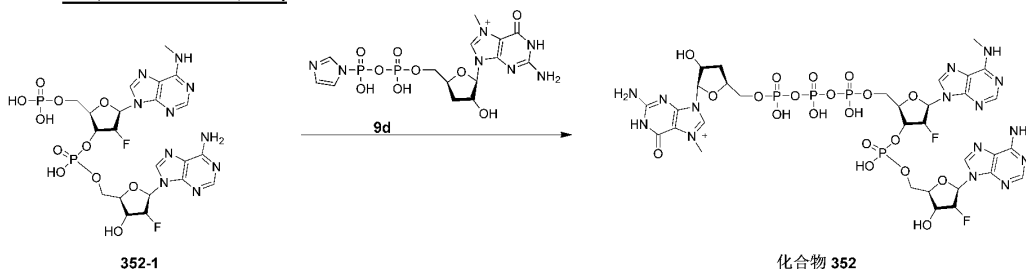
化合物 **9d** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **326-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **326**, 为铵盐 (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。

实施例 17

化合物 352 的合成



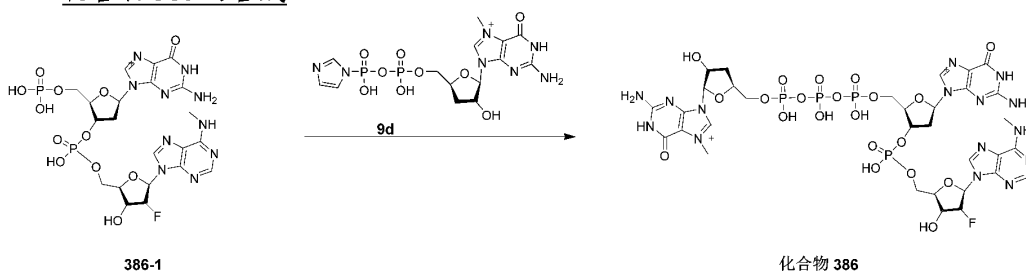
将化合物 **9d** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **352-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **352**, 为铵盐 (74 mg)。

¹H NMR (400 MHz, D₂O) 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)。

³¹P NMR (162 MHz, D₂O) -0.55, -10.32, -21.28。

实施例 18

化合物 386 的合成



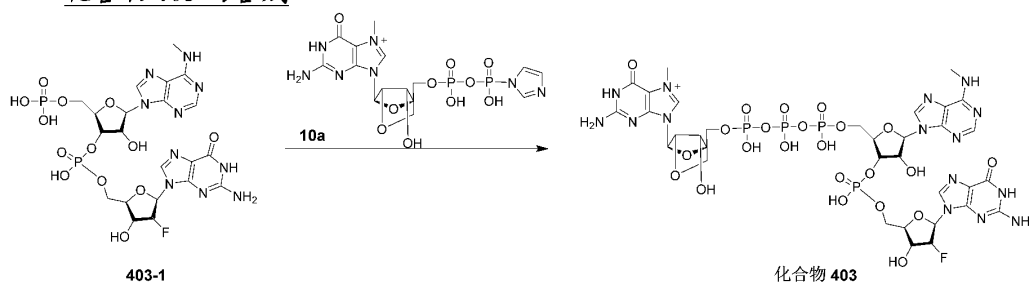
将化合物 **9d** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后 386-1 (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **386**, 为铵盐 (60 mg)。

^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)。

5 ^{31}P NMR (162 MHz, D_2O) δ -0.85, -10.09, -21.23。

实施例 19

化合物 403 的合成



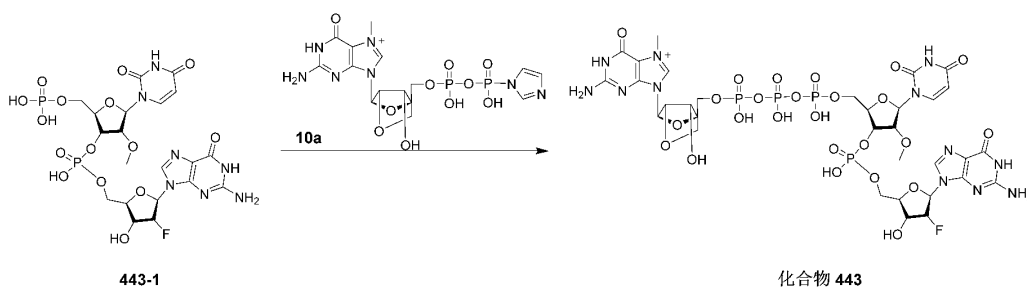
将化合物 **10a** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和
 10 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **403-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **403**，为铵盐 (55 mg)。

15 ^1H NMR (400 MHz, D_2O) 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)。

20 ^{31}P NMR (162 MHz, D_2O) δ -0.90, -11.41, -22.93。

实施例 20

化合物 443 的合成



将化合物 **10a** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **443-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的

5 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **443**, 为铵盐 (70 mg)。

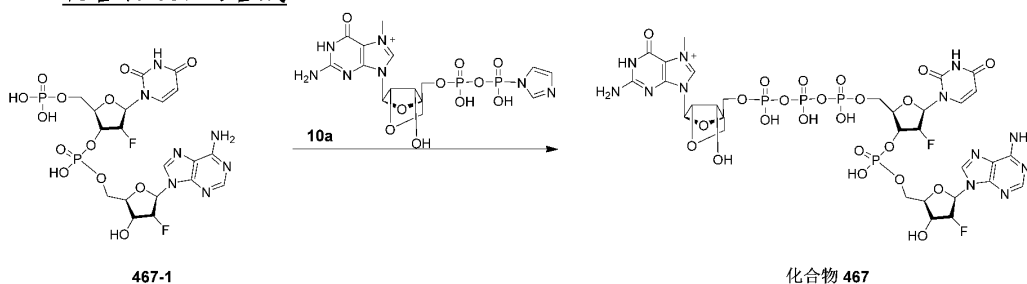
^1H NMR (400 MHz, D_2O) δ 8.02 (d, $J = 0.7$ Hz, 1H), 7.75 (dd, $J = 7.8, 1.8$ Hz, 1H), 6.45 (ddq, $J = 25.2, 1.6, 0.9$ Hz, 1H), 6.33 (dd, $J = 2.7, 0.6$ Hz, 1H), 5.93 – 5.65 (m, 2H),

10 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。

实施例 21

15 化合物 467 的合成



将化合物 **10a** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **467-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的

20 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

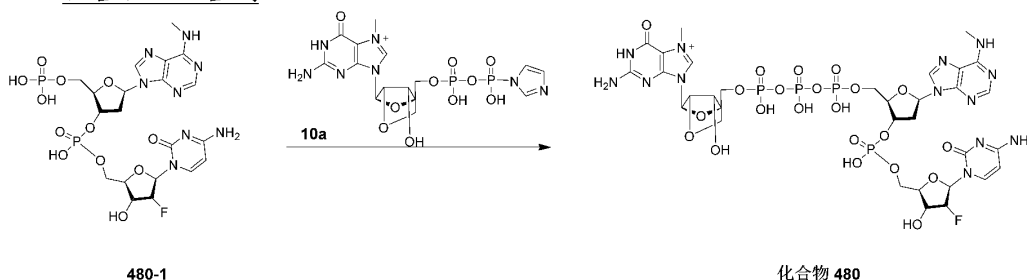
水，剩余液体经冻干后，得到白色粉末状产物化合物 **467**，为铵盐（75 mg）。

^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)。

5 ^{31}P NMR (162 MHz, D_2O) δ -0.99, -11.40, -23.06。

实施例 22

化合物 480 合成



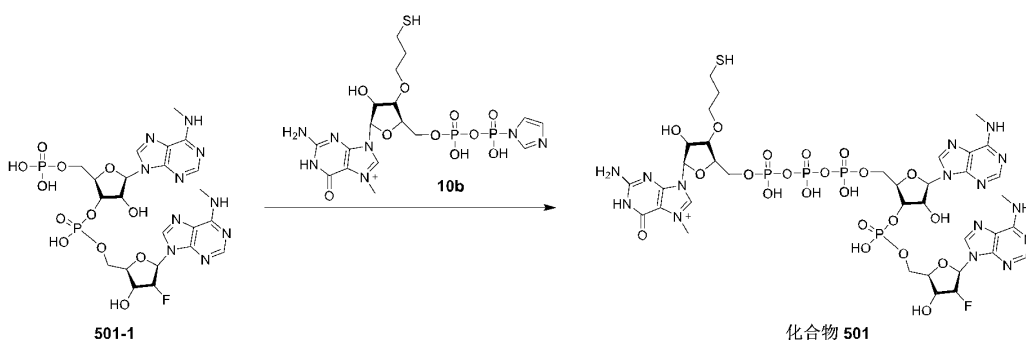
10 10a (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **480-1** (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **480**，为铵盐（85 mg）。

^1H NMR (400 MHz, D_2O) 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)。

20 ^{31}P NMR (162 MHz, D_2O) δ 0.60, -9.01, -10.23, -21.17。

实施例 23

化合物 501 合成



将化合物 **10b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **501-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的

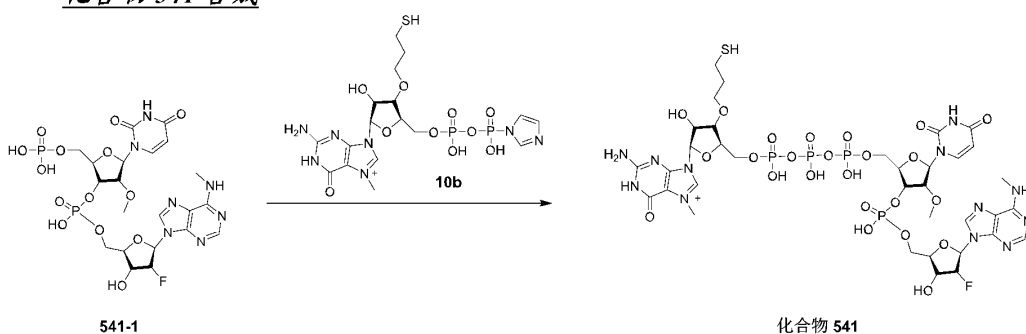
5 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **501**, 为铵盐 (92 mg)。

¹H NMR (400 MHz, D₂O) 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)。

10 ³¹P NMR (162 MHz, D₂O) δ 0.60, -9.10, -10.31, -21.17。

实施例 24

化合物 541 合成



15

将化合物 **10b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **541-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将

20 产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

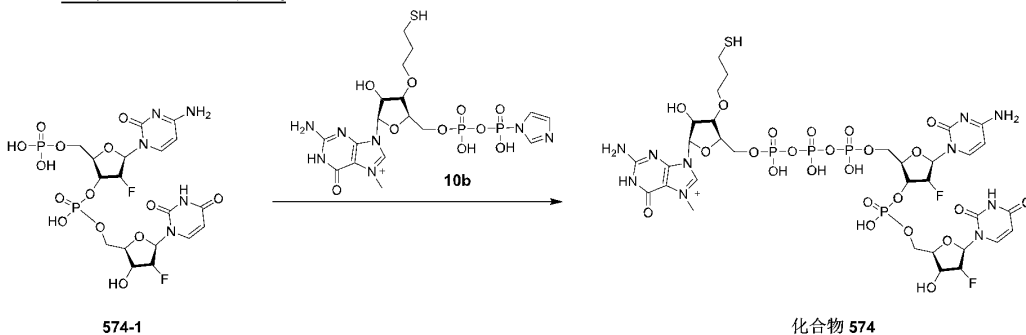
水，剩余液体经冻干后，得到白色粉末状产物化合物 **541**，为铵盐（85 mg）。

¹H NMR (400 MHz, D₂O) 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.

实施例 25

化合物 574 的合成



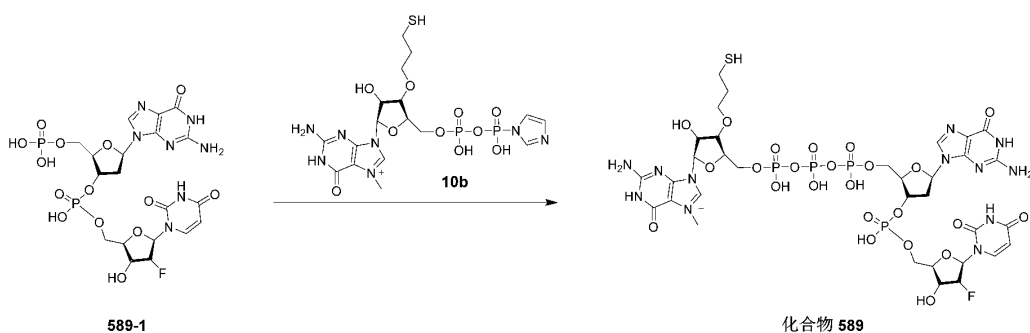
将化合物 **10b** (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **574-1** (200 mg)加入到该溶液中。反应液在室温下 25℃搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **574**，为铵盐 (80 mg)。

¹H NMR (400 MHz, D₂O) 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, 20 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.

实施例 26

化合物 589 的合成



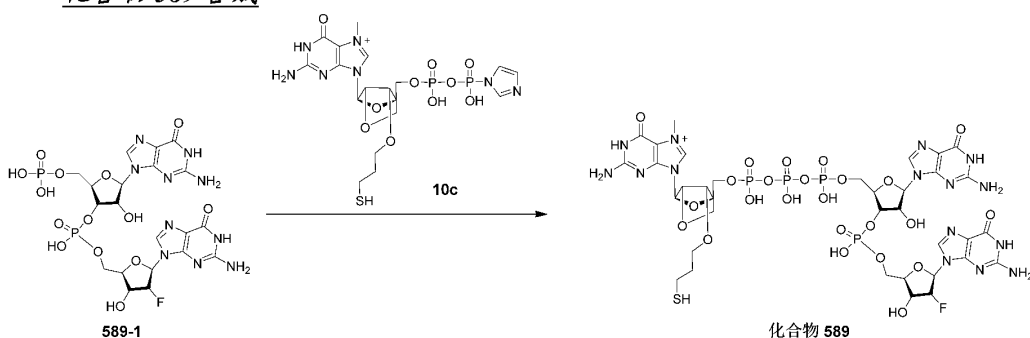
将化合物 **10b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **589-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **589**，为铵盐 (58mg)。

^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。

实施例 27

化合物 589 合成



15

将化合物 **10c** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **589-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分

20

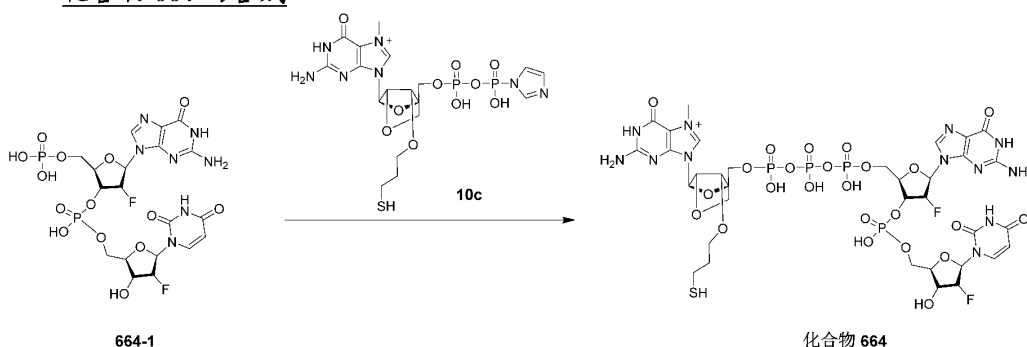
水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **589**, 为铵盐 (88 mg)。

^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。

实施例 28

化合物 664 的合成



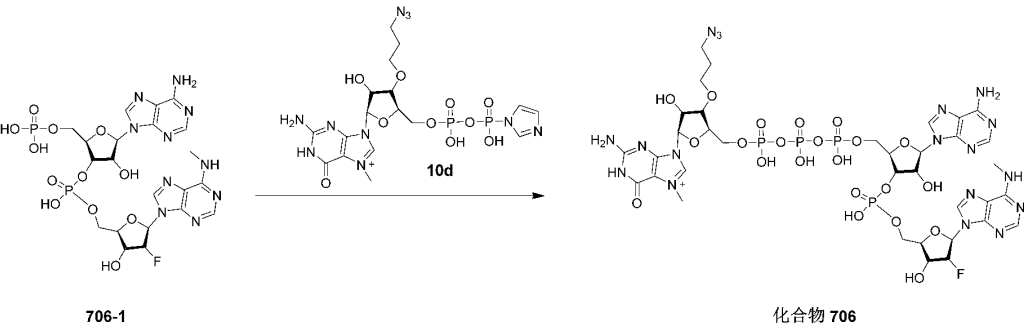
10 将化合物 **10c** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **664-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **664**, 为铵盐 (60 mg)。

^1H NMR (400 MHz, D_2O) 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)。

20 ^{31}P NMR (162 MHz, D_2O) δ -0.85, -10.09, -21.23。

实施例 29

化合物 706 的合成



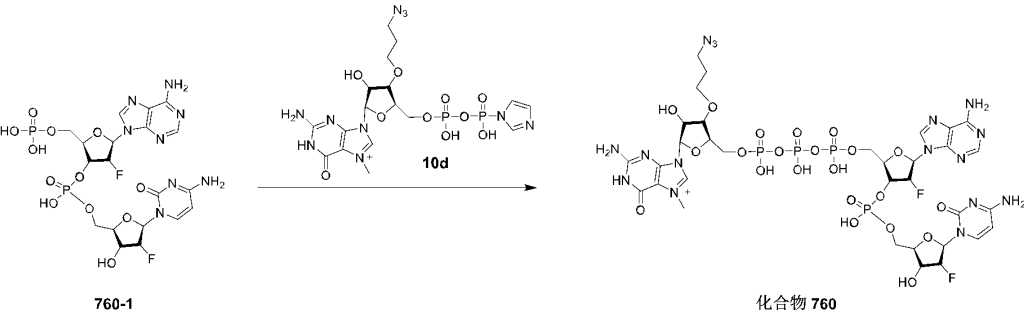
将化合物 **10d** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **706-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **706**，为铵盐 (55 mg)。

¹H NMR (400 MHz, D₂O) 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)。

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

实施例 30

化合物 760 的合成



将化合物 **10d** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **760-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分

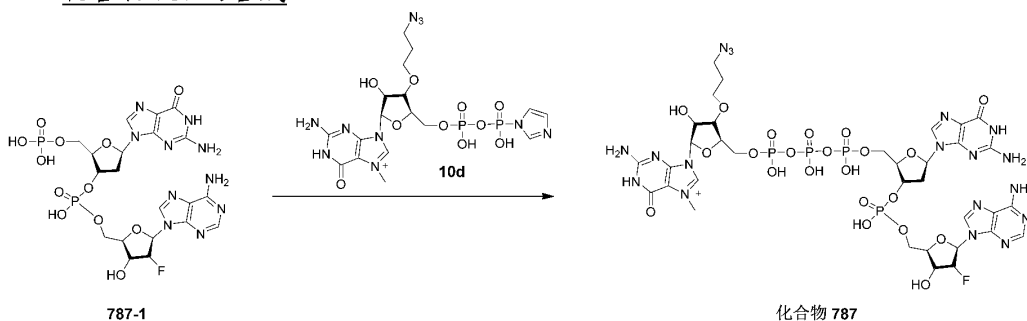
水，剩余液体经冻干后，得到白色粉末状产物化合物 **760**，为铵盐（70 mg）。

^1H NMR (400 MHz, D_2O) 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)。

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

实施例 31

化合物 **787** 的合成



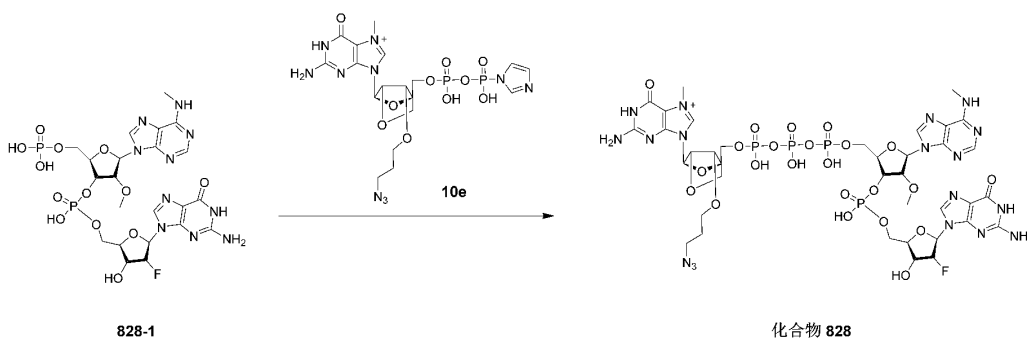
将化合物 **10d** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **787-7** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **787**，为铵盐（75 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。

实施例 32

化合物 **828** 合成



将化合物 **10e** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **828-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

5 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **828**, 为铵盐 (85 mg)。

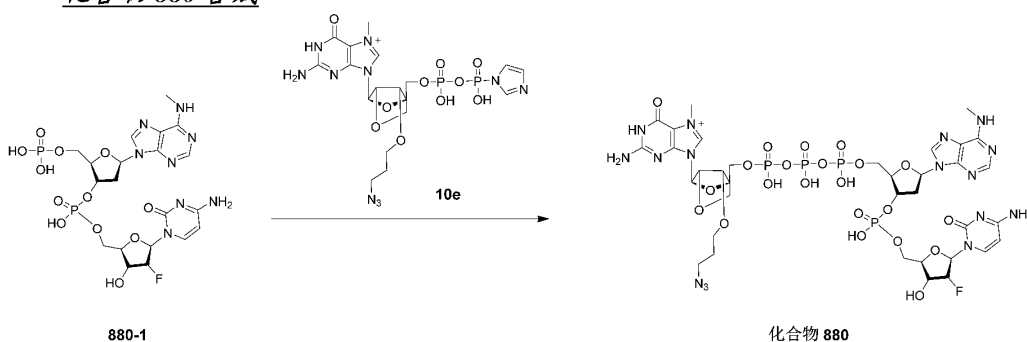
^1H NMR (400 MHz, D_2O) δ 8.27 (s, 1H), 8.19 (d, $J = 0.6$ Hz, 1H), 7.95 (d, $J = 0.7$ Hz, 1H), 6.63 – 6.29 (m, 3H), 5.28 (dddd, $J = 46.4, 6.9, 1.6, 0.7$ Hz, 1H), 4.62 (ddqd, $J = 4.5,$

10 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。

实施例 33

15 化合物 880 合成



将化合物 **10e** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **880-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

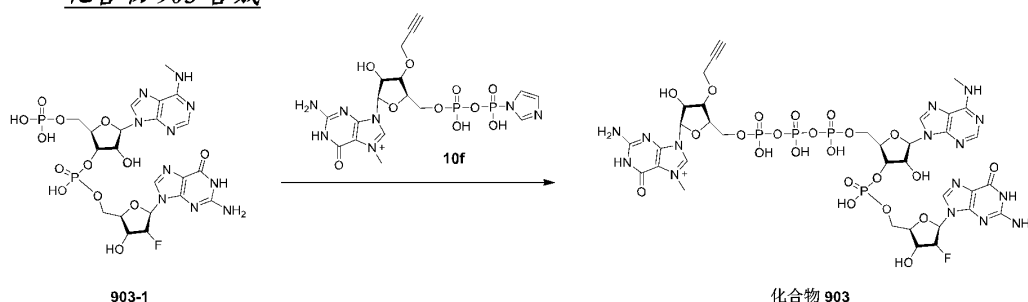
EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **880**, 为铵盐 (92 mg)。

^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。

实施例 34

10 化合物 903 合成



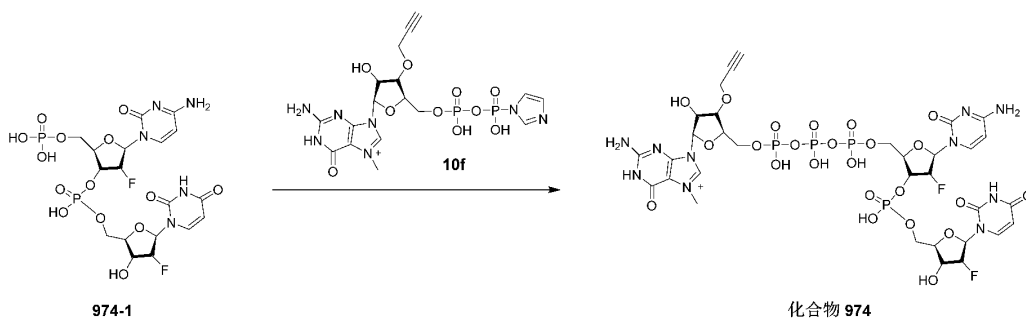
将化合物 **10f** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **903-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **903**, 为铵盐 (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。

实施例 35

化合物 974 的合成



将化合物 **10f** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **974-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的

5 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **974**, 为铵盐 (80 mg)。

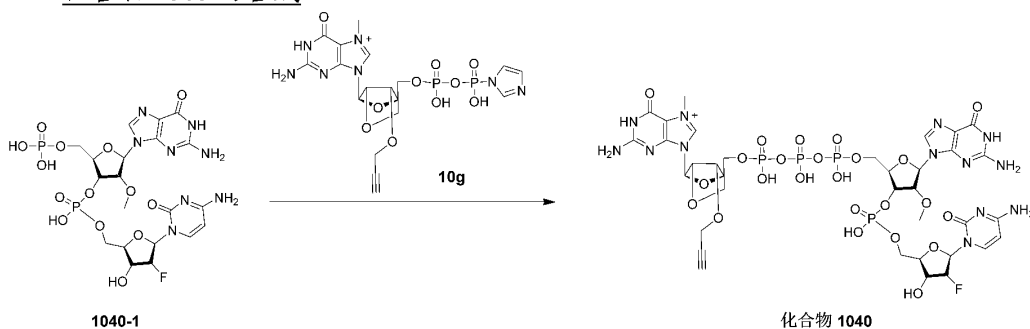
^1H NMR (400 MHz, D_2O) δ 7.76 (ddd, $J = 44.0, 7.5, 1.8$ Hz, 2H), 6.20 (dq, $J = 2.3, 0.8$ Hz, 1H), 5.97 (dd, $J = 56.9, 7.5$ Hz, 2H), 5.64 – 5.41 (m, 2H), 5.34 – 4.98 (m, 2H), 4.89

10 – 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。

实施例 36

化合物 1040 的合成



15

将化合物 **10g** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1040-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的

20 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

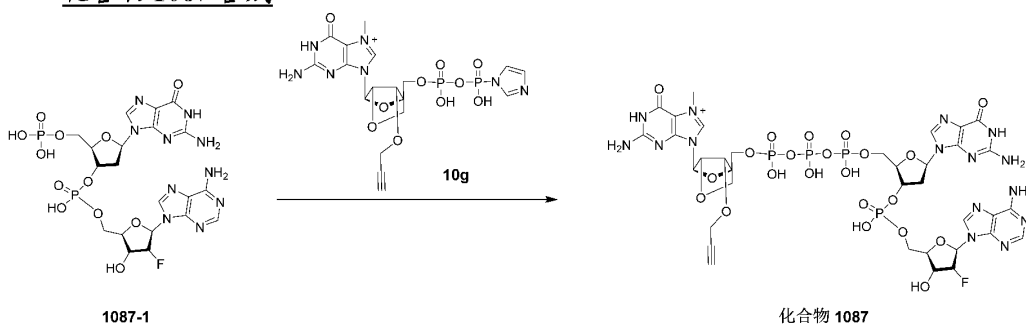
水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1040**, 为铵盐 (58mg)。

^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。

实施例 37

化合物 1087 合成



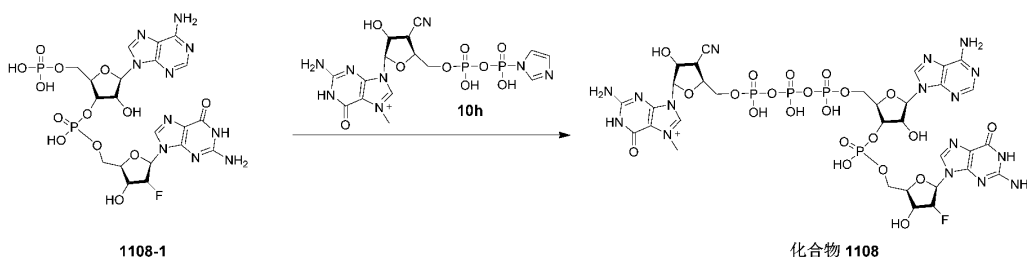
将化合物 **10g** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1087-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1087**, 为铵盐 (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。

实施例 38

化合物 1108 合成



将化合物 **10h** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1108-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

5 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1108**, 为铵盐 (88 mg)。

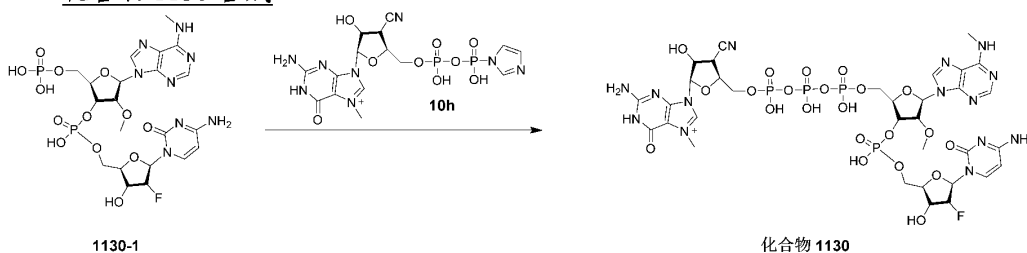
¹H NMR (400 MHz, D₂O) δ 8.33 – 8.15 (m, 2H), 8.02 (d, J = 0.7 Hz, 1H), 6.45 (ddq, J = 25.2, 1.5, 0.8 Hz, 1H), 6.32 – 5.94 (m, 2H), 5.22 (dddd, J = 46.4, 7.0, 1.7, 0.7 Hz, 1H),

10 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)。

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

实施例 39

化合物 1130 合成



15 将化合物 **10h** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1130-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将

20 产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1130**, 为铵盐 (88 mg)。

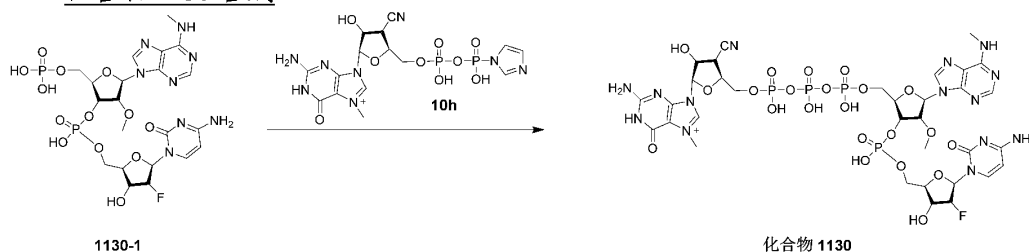
¹H NMR (400 MHz, D₂O) δ 8.51 – 8.01 (m, 2H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 6.31 – 6.15 (m, 2H), 6.04 (d, J = 7.3 Hz, 1H), 5.56 – 5.22 (m, 1H), 4.97 (dddd, J = 8.0, 4.4, 2.9,

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)。

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

实施例 40

5 化合物 1130 合成



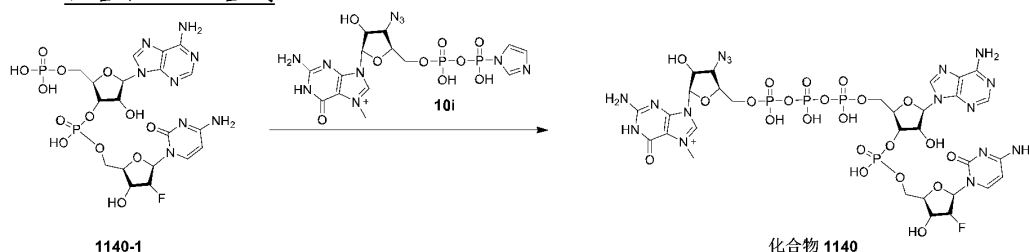
将化合物 **10h** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **1130-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **1130**，为铵盐 (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。

实施例 41

20 化合物 1140 合成



将化合物 **10i** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **1140-1** (200 mg) 加入到该溶液中。反

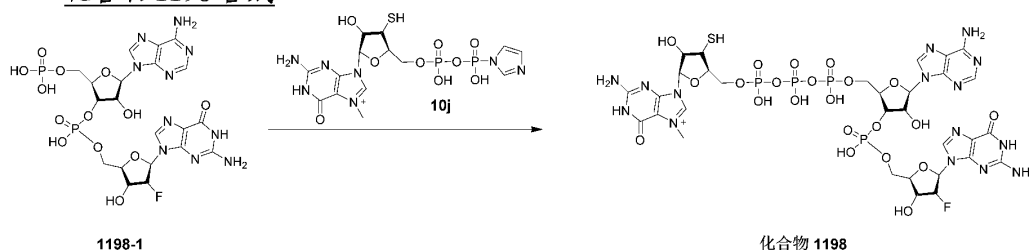
应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1140**, 为铵盐 (88 mg)。

- 5 ^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。

实施例 42

10 化合物 1198 合成



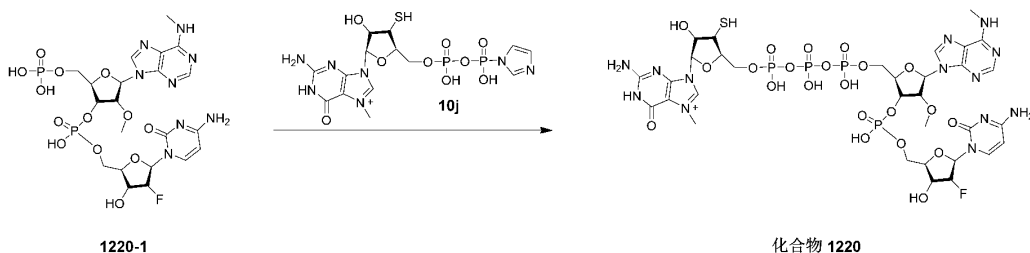
将化合物 **10j** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1198-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1198**, 为铵盐 (88 mg)。

- 15 ^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。

实施例 43

20 化合物 1220 合成



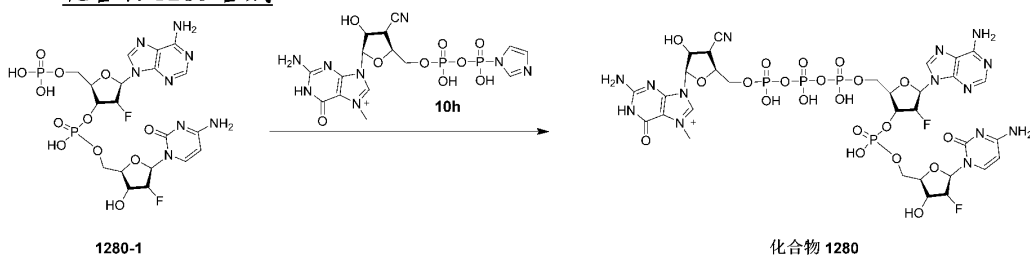
将化合物 **10j** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1220-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1220**, 为铵盐 (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。

实施例 44

化合物 1280 合成



将化合物 **10h** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1280-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1280**, 为铵盐 (88 mg)。

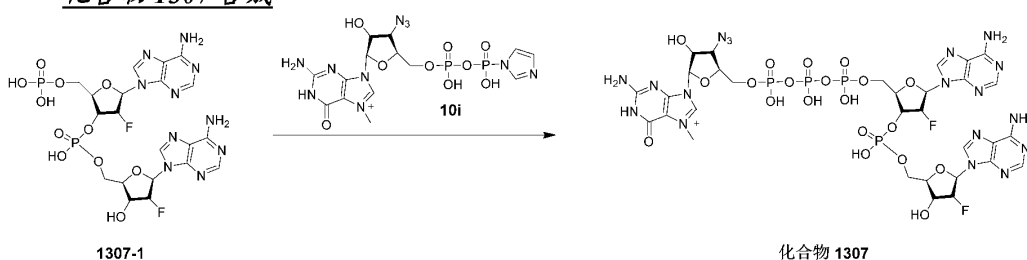
^1H NMR (400 MHz, D_2O) δ 8.24 (d, $J = 0.7$ Hz, 1H), 8.20 (s, 1H), 7.70 (dd, $J = 7.4$, 1.8 Hz, 1H), 6.43 (ddq, $J = 25.2$, 1.5, 0.8 Hz, 1H), 6.24 (p, $J = 0.8$ Hz, 1H), 6.04 (d, $J = 7.3$

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。

5 实施例 45

化合物 1307 合成



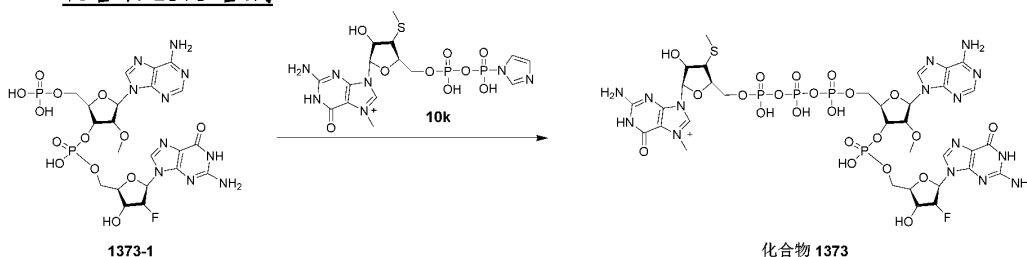
将化合物 **10i** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **1307-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **1307**，为铵盐 (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。

实施例 46

化合物 1373 合成



20

将化合物 **10k** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **1373-1** (200 mg) 加入到该溶液中。反

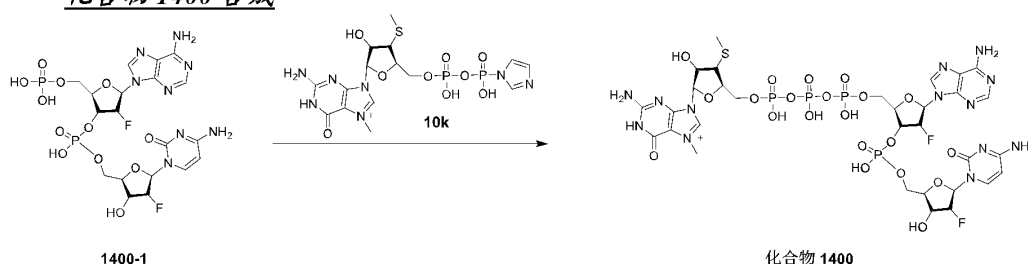
应在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1373**, 为铵盐 (88 mg)。

- 5 ^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),
10 2.09 (s, 3H)。

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

实施例 47

化合物 1400 合成



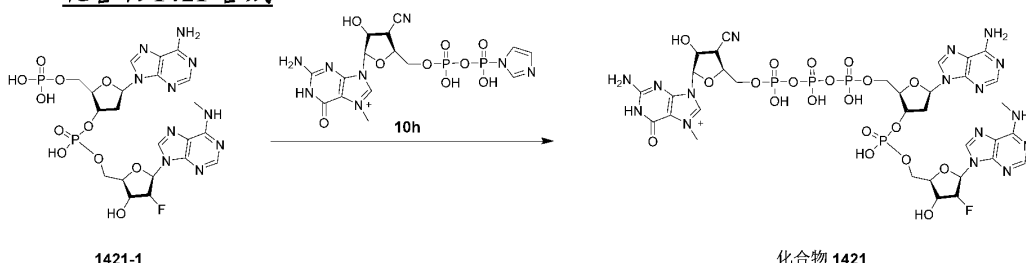
- 15 将化合物 **10k** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1400-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分
20 水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1400**, 为铵盐 (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)。
25

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

实施例 48

化合物 1421 合成



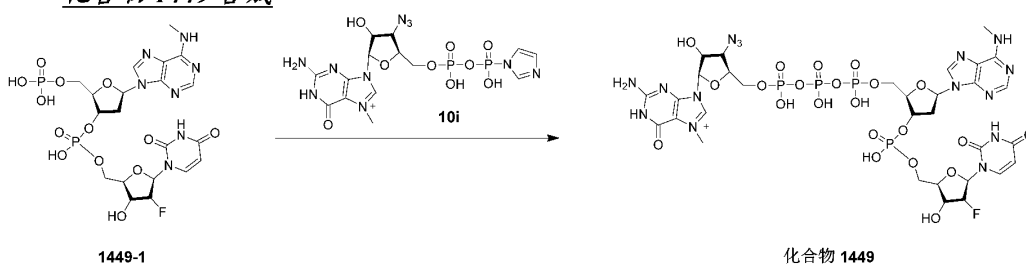
将化合物 **10h** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1421-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1421**, 为铵盐 (88 mg)。

¹H NMR (400 MHz, D₂O) 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)。

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

实施例 49

化合物 1449 合成



将化合物 **10i** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1449-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

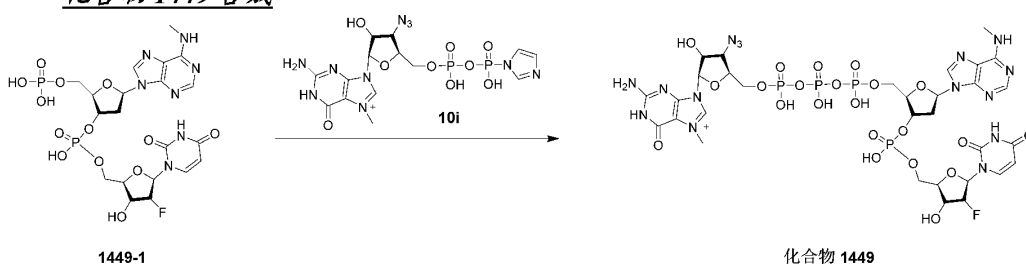
水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1449**, 为铵盐 (88 mg)。

^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。

实施例 50

化合物 1449 合成



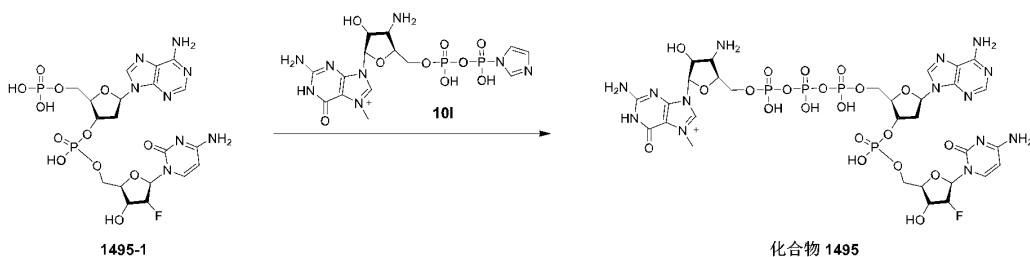
将化合物 **10i** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1449-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1449**, 为铵盐 (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。

实施例 51

化合物 1495 合成



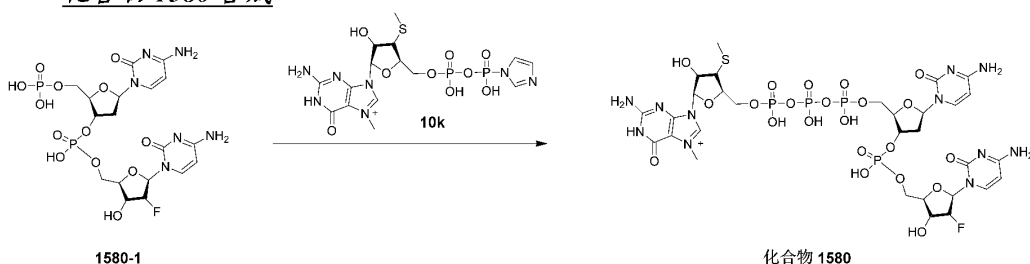
将化合物 **101** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1495-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1495**, 为铵盐 (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。

实施例 52

化合物 1580 合成



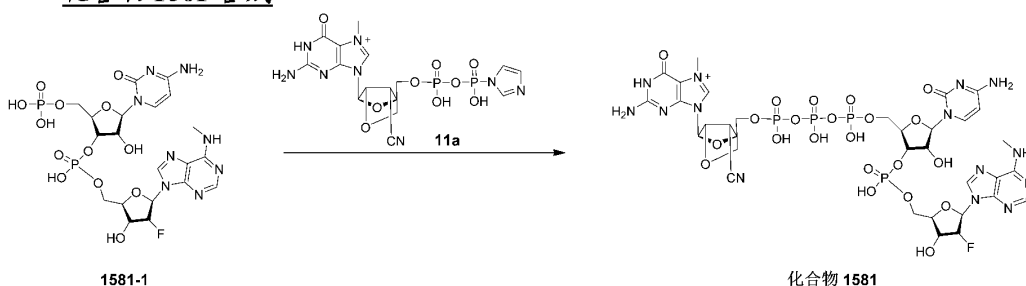
将化合物 **10k** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1580-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1580**, 为铵盐 (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。

实施例 53

化合物 1581 合成



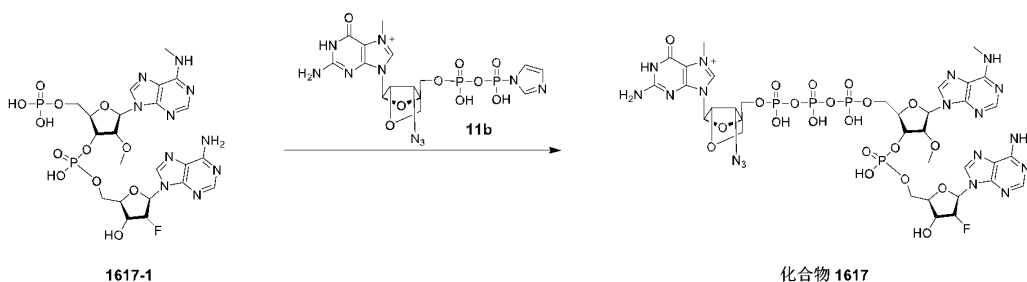
10 将化合物 **11a** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **1581-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **1581**，为铵盐 (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)。

20 ^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26。

实施例 54

化合物 1617 合成



将化合物 **11b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1617-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

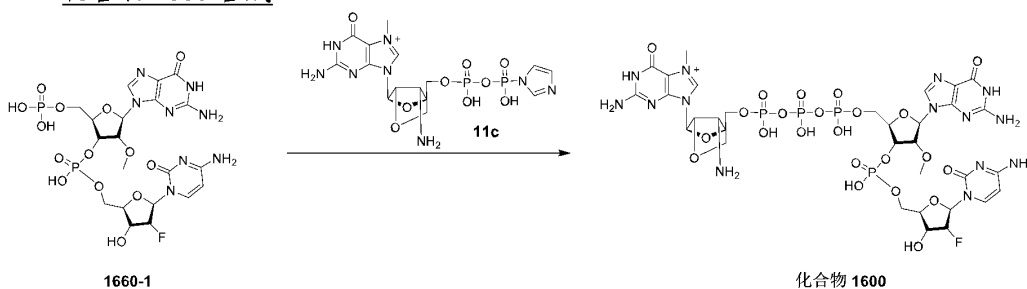
5 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1617**, 为铵盐 (88 mg)。

^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)。

10 ^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26。

实施例 55

15 化合物 1660 合成



将化合物 **11c** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1660-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

20 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

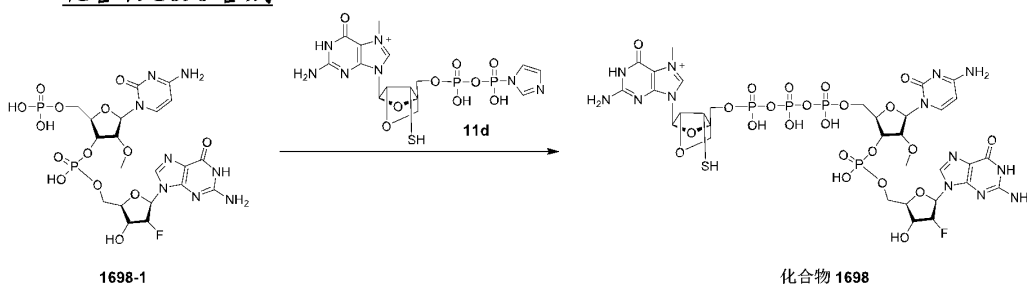
水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1600**, 为铵盐 (88 mg)。

^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)。

5 ^{31}P NMR (162 MHz, D_2O) δ 0.85, -10.24, -21.26。

实施例 56

化合物 1698 合成



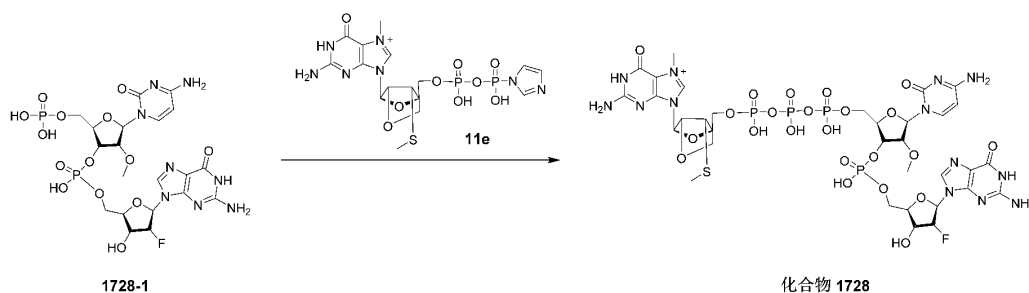
将化合物 **11d** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和
10 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1698-1** (200 mg) 加入到该溶液中。反
反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的
EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将
产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分
水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1698**, 为铵盐 (88 mg)。

15 ^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。

20 实施例 57

化合物 1728 合成



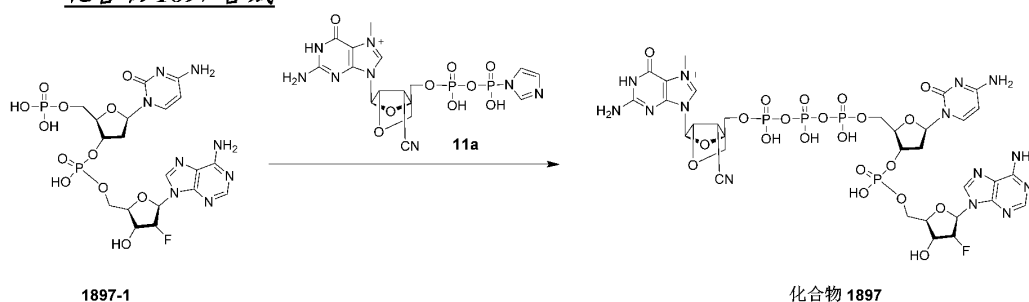
将化合物 **11e** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1728-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1728**, 为铵盐 (88 mg)。

¹H NMR (400 MHz, D₂O) 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)。

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

实施例 58

化合物 1897 合成



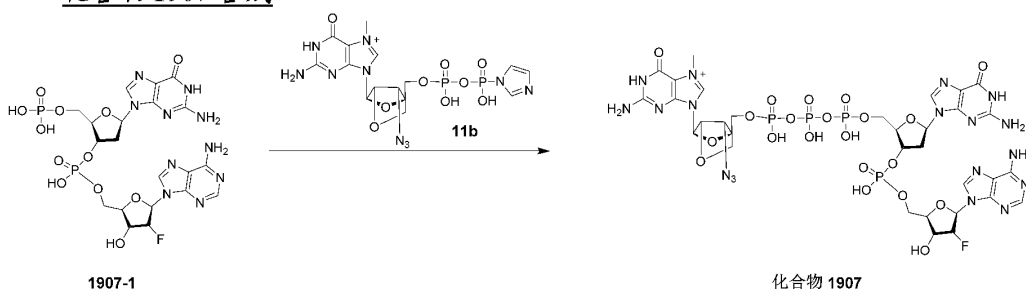
将化合物 **11a** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1897-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1897**, 为铵盐 (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。

实施例 59

化合物 1907 合成



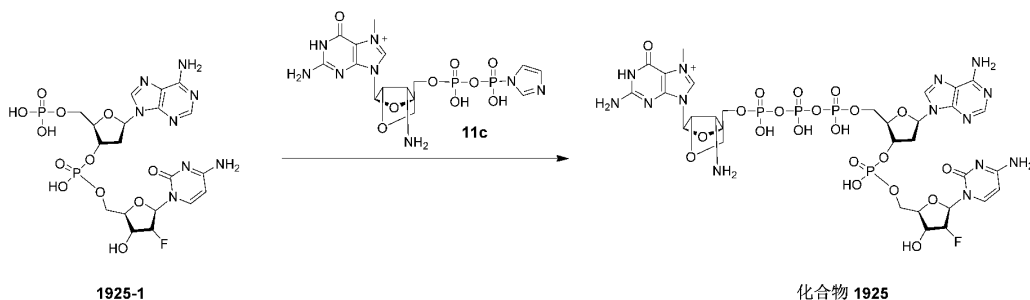
将化合物 **11b** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **1907-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应液加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **1907**，为铵盐 (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。

实施例 60

化合物 1925 合成



将化合物 **11c** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1925-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

5 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1925**, 为铵盐 (88 mg)。

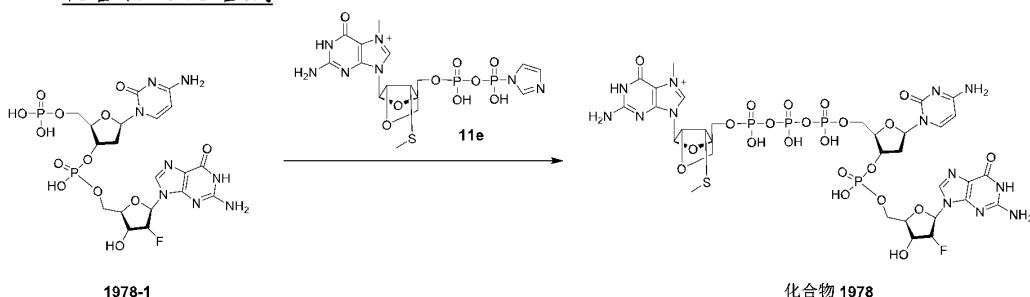
^1H NMR (400 MHz, D_2O) δ 8.30 (d, $J = 0.5$ Hz, 1H), 8.20 (s, 1H), 7.70 (dd, $J = 7.4$, 1.8 Hz, 1H), 6.42 – 6.36 (m, 1H), 6.31 (dd, $J = 2.0$, 0.6 Hz, 1H), 6.04 (d, $J = 7.3$ Hz, 1H),

10 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。

实施例 61

化合物 1978 合成



15

将化合物 **11e** (200 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1978-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

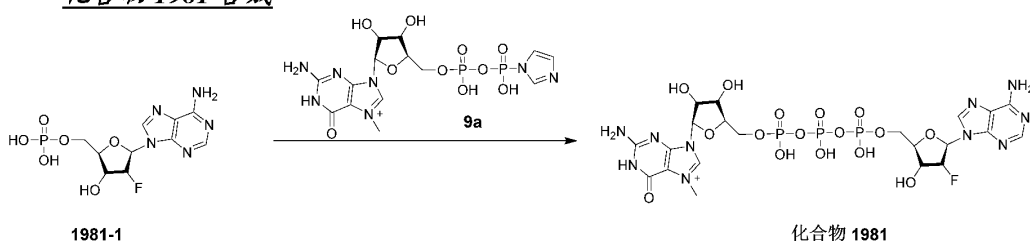
20 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1978**, 为铵盐 (88 mg)。

^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。

实施例 62

化合物 1981 合成



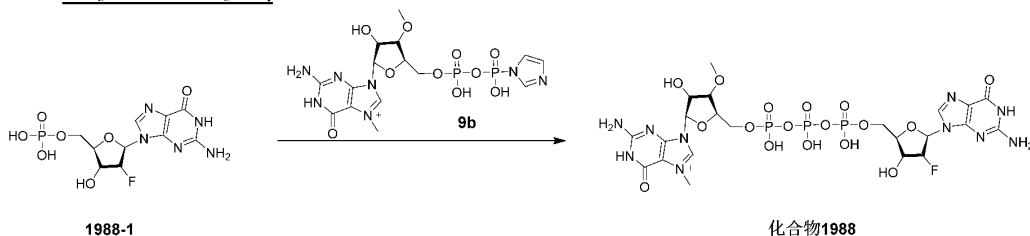
将化合物 **9a** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后将化合物 **1981-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **1981**，为铵盐 (88 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。

实施例 63

化合物 1988 合成



将化合物 **9b** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和

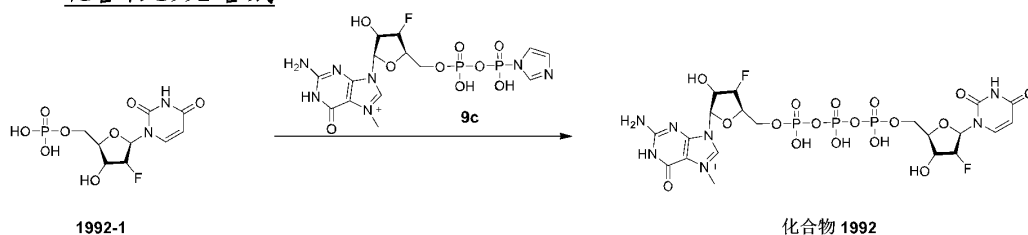
0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1988-1** (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1988**, 为铵盐 (88 mg)。

^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 (dtt, $J = 4.2, 2.1, 1.1$ Hz, 1H), 3.98 (s, 3H), 3.44 (s, 3H)。

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

实施例 64

化合物 1992 合成



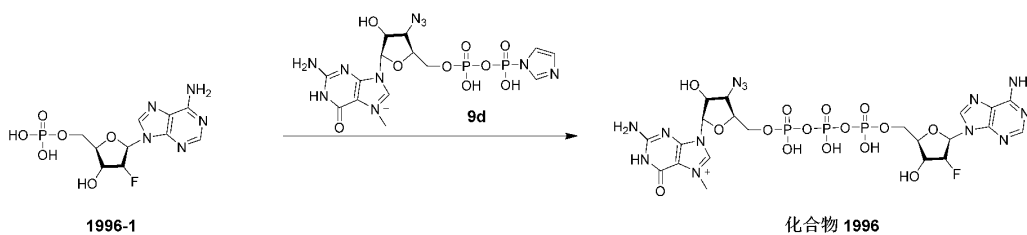
将化合物 **9c** (250 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1992-1** (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1992**, 为铵盐 (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。

实施例 65

化合物 1996 合成



将化合物 **9d** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **1996-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

5 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **1996**, 为铵盐 (88 mg)。

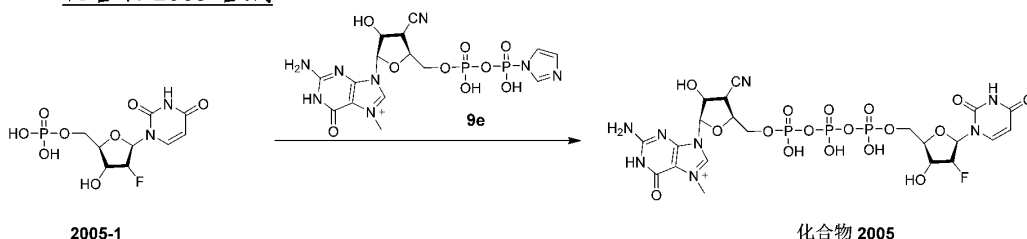
^1H NMR (400 MHz, D_2O) δ 8.18 (s, 1H), 8.14 (d, $J = 0.6$ Hz, 1H), 6.41 (ddq, $J = 25.2$, 4.0, 0.8 Hz, 1H), 6.31 – 6.22 (m, 1H), 5.45 – 4.99 (m, 1H), 4.79 – 4.50 (m, 2H), 4.46 –

10 4.05 (m, 7H), 3.92 (s, 3H)。

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

实施例 66

化合物 2005 合成



15 将化合物 **9e** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2005-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

20 水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2005**, 为铵盐 (88 mg)。

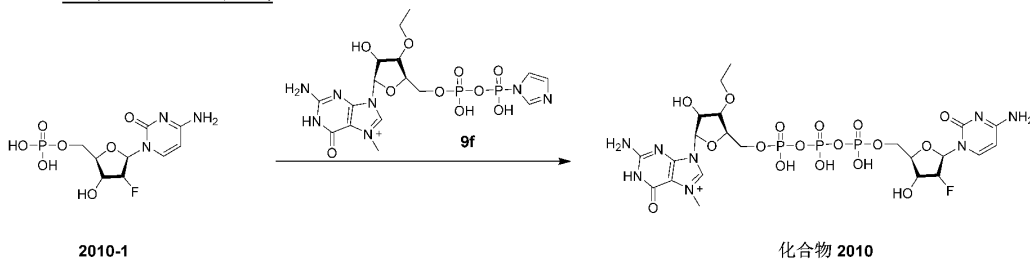
^1H NMR (400 MHz, D_2O) δ 7.81 (dd, $J = 7.8$, 1.8 Hz, 1H), 6.24 (p, $J = 0.8$ Hz, 1H), 5.90 (d, $J = 7.8$ Hz, 1H), 5.74 – 5.30 (m, 1H), 4.89 – 4.64 (m, 1H), 4.60 – 4.43 (m, 2H), 4.43 – 4.37 (m, 1H), 4.36 – 4.11 (m, 5H), 3.98 (s, 3H), 3.65 (ddd, $J = 3.6$, 2.6, 0.6 Hz,

1H).

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

实施例 67

化合物 2010 合成



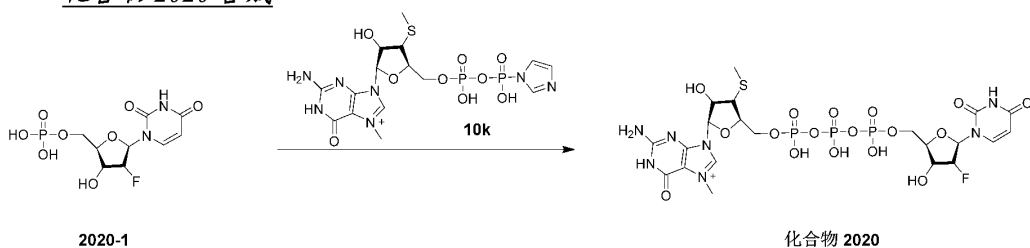
将化合物 **9f** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后 **2010-1** (200 mg) 加入到该溶液中。反应液在室温下 25℃ 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃ 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 **2010**，为铵盐 (88 mg)。

¹H NMR (400 MHz, D₂O) 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)。

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

实施例 68

化合物 2020 合成



20 将化合物 **10k** (250 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2020-1** (200 mg)加入到该溶液中。反应液在室温下 25℃搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0℃的

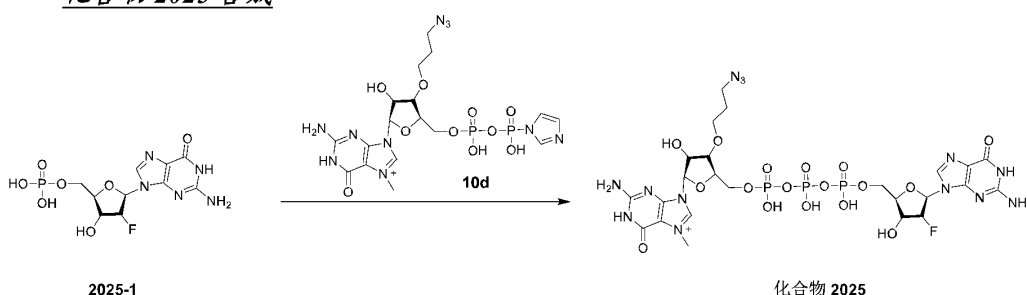
EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2020**, 为铵盐 (88 mg)。

^1H NMR (400 MHz, D_2O) 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)。

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

实施例 69

10 化合物 2025 合成

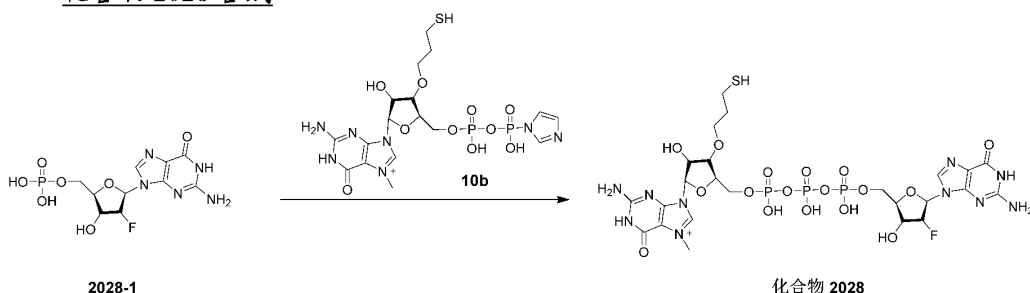


将化合物 **10d** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2025-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2025**, 为铵盐 (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。

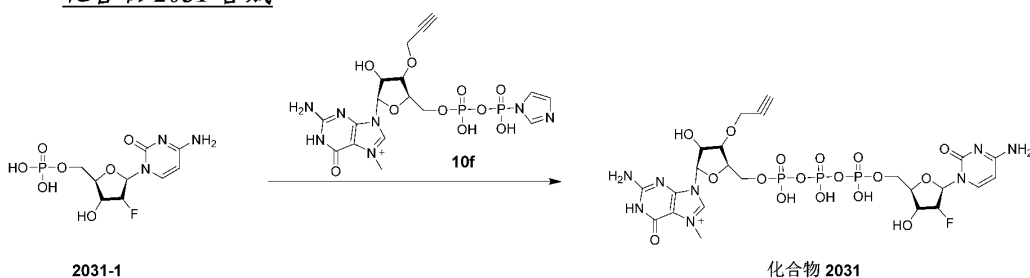
25 实施例 70

化合物 2028 合成

将化合物 **10b** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2028-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2028**, 为铵盐 (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。

实施例 71化合物 2031 合成

将化合物 **10f** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2031-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

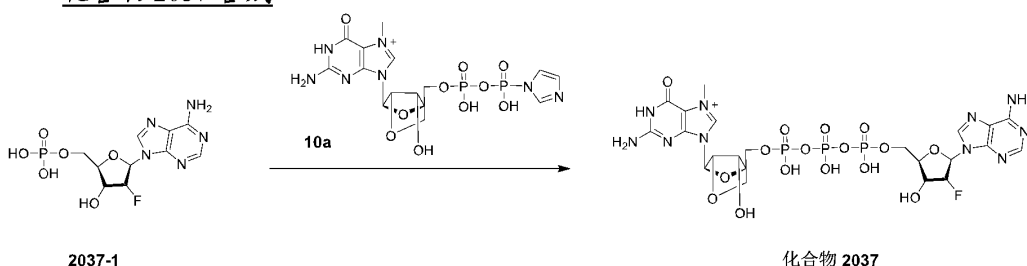
水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2031**, 为铵盐 (88 mg)。

^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。

实施例 72

化合物 2037 合成



10 将化合物 **10a** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2037-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

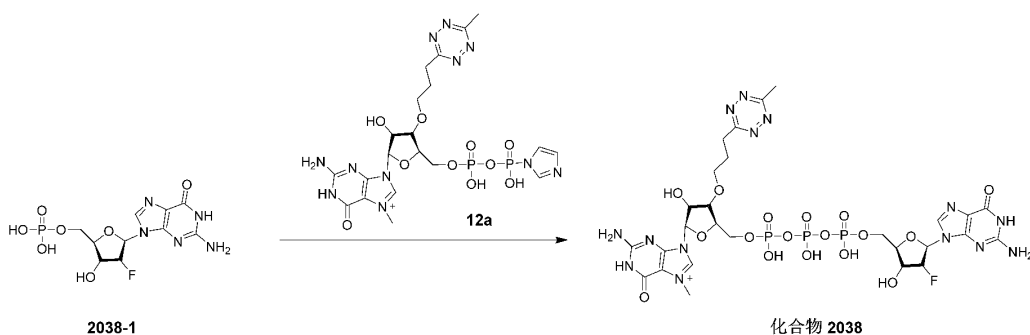
15 水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2037**, 为铵盐 (88 mg)。

^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。

20 实施例 73

化合物 2038 合成



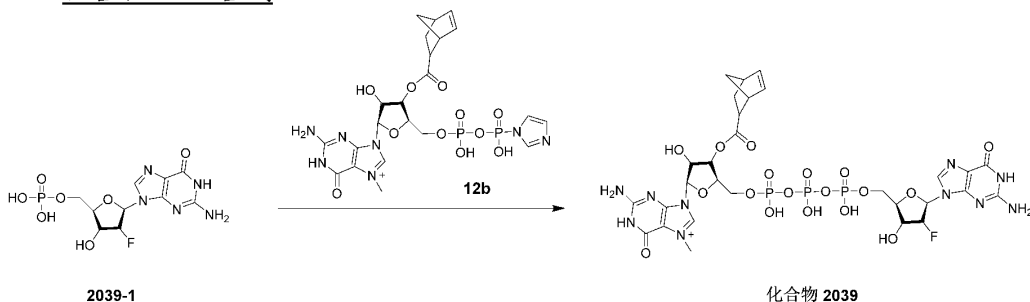
将化合物 **12a** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2038-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2038**, 为铵盐 (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。

实施例 74

化合物 2039 合成



将化合物 **12b** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2039-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

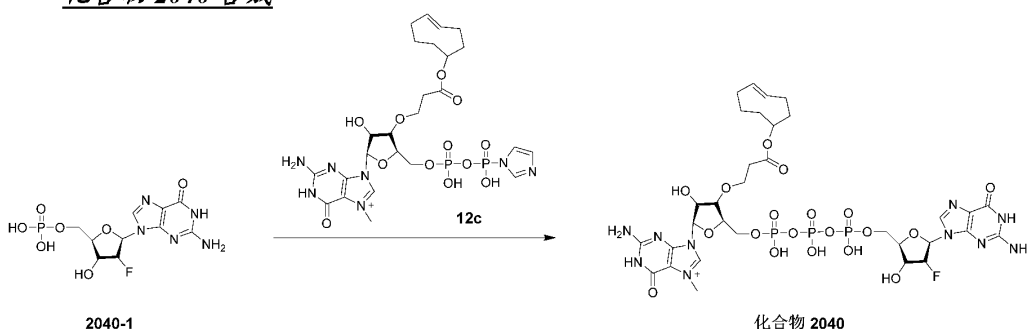
水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2039**, 为铵盐 (88 mg)。

^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。

实施例 75

化合物 2040 合成



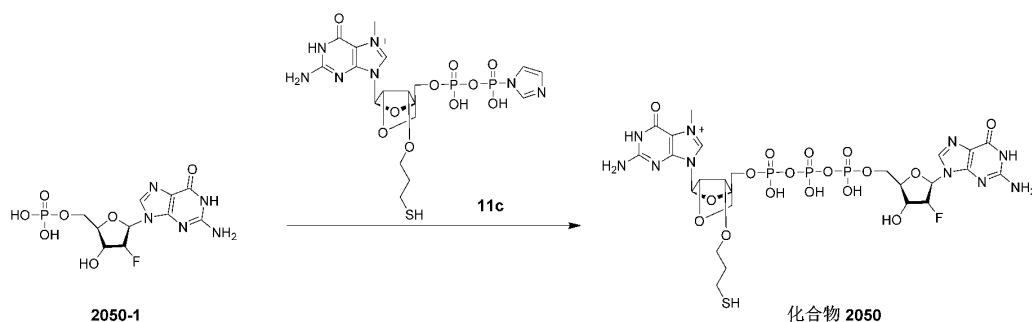
将化合物 **12c** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2040-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2040**, 为铵盐 (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), 6.26 – 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)。

^{31}P NMR (162 MHz, D_2O) δ -10.25, -21.23。

实施例 76

化合物 2050 合成



将化合物 *11c* (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 *2050-1* (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

5 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 *2050*, 为铵盐 (88 mg)。

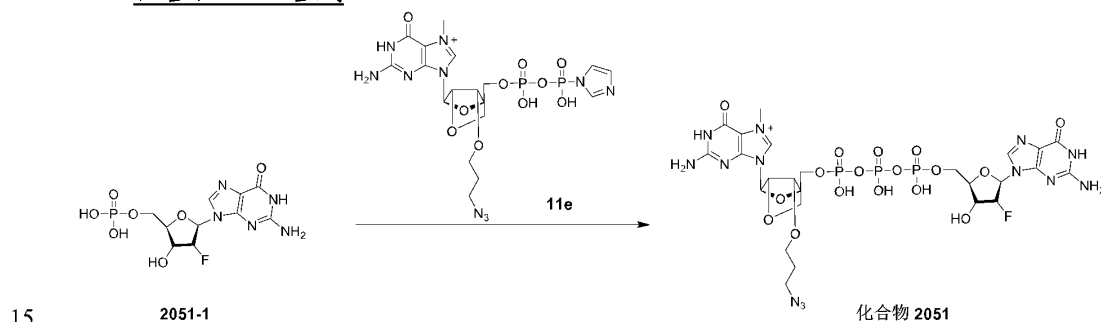
¹H NMR (400 MHz, D₂O) δ 8.02 (d, J = 0.7 Hz, 1H), 6.65 – 6.28 (m, 2H), 5.39 – 5.11 (m, 1H), 4.87 (t, J = 3.1 Hz, 1H), 4.65 – 4.47 (m, 1H), 4.39 – 4.21 (m, 5H), 4.15 (d, J = 3.1

10 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)。

³¹P NMR (162 MHz, D₂O) δ -10.21, -21.25。

实施例 77

化合物 2051 合成



将化合物 *11e* (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 *2051-1* (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的

15 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分

20

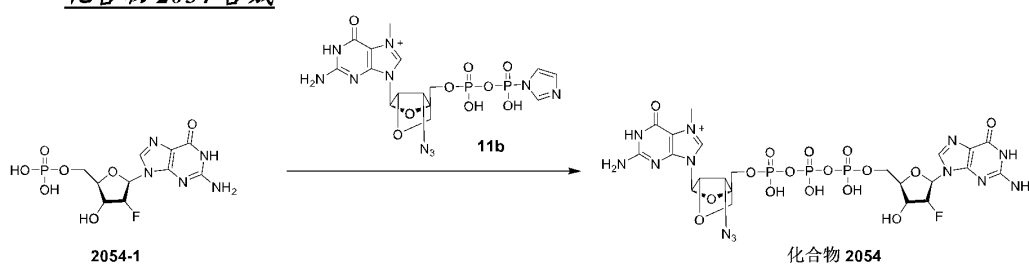
水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2051**, 为铵盐 (88 mg)。

^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。

实施例 78

化合物 2054 合成



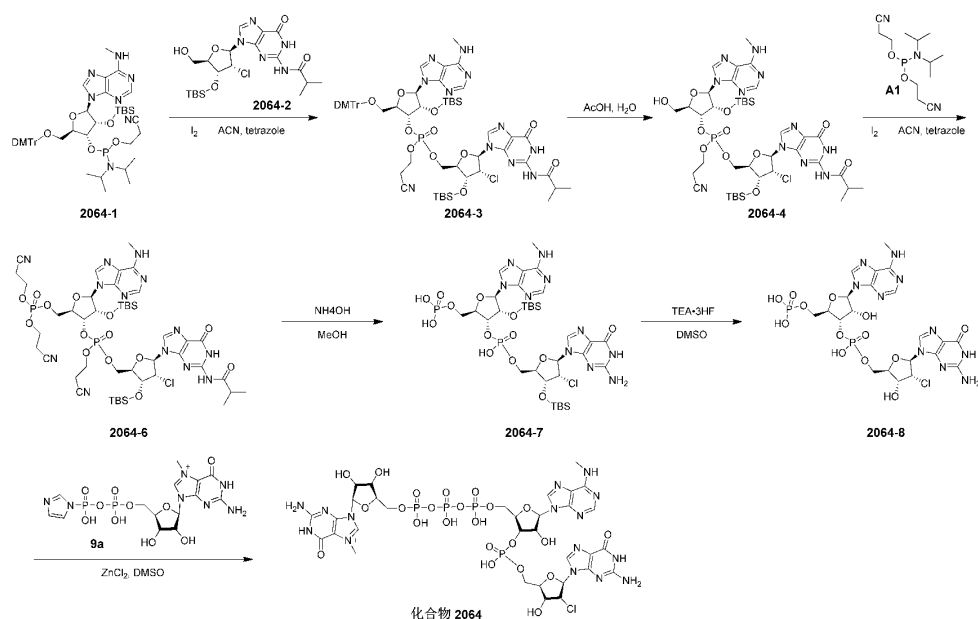
将化合物 **11b** (250 mg) 加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后将化合物 **2054-1** (200 mg) 加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中 (1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 **2054**, 为铵盐 (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。

实施例 79

化合物 2064 的合成



将 2064-2 (2.38 g) 加入到四氮唑 (1.76 g) 的乙腈溶液 (63 mL) 加入三口瓶中，置换氮气三次，然后在室温下 25℃，2064-1 (5 g) 溶于 10 mL 乙腈加入到上述溶液中，所得溶液在室温下 25℃ 搅拌 1 小时，没有发现明显放热，点板监测显示原料 2064-1 消失。然后向溶液中逐滴加入碘的吡啶/四氢呋喃/水的溶液 (0.5 mmol/mL，吡啶：四氢呋喃：水=1：8：1)，直到溶液不再褪色为止，然后反应液继续搅拌 0.5 小时，点板监测氧化完成。向反应液中加饱和亚硫酸钠水溶液 (10 mL) 淬灭后，再加 50 mL 水稀释，用二氯甲烷 (50 mL×2) 萃取，合并有机相用水 (50 mL) 洗涤一次，浓缩得到淡黄色油状产物 2064-3 (8 g，粗品)。

10 将化合物 2064-3 (8 g，粗品) 溶于 40 mL 的乙酸和 10 mL 水中，反应在 25℃ 下搅拌 16 小时，点板监测 3-3 消失，有极性大的点产生。反应液直接真空浓缩。浓缩后加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱，EA，10min，DCM：MeOH，10-20% 20min，流速 30ml/min) 浓缩得到白色固体产物 2064-4 (2.8 g，51% 两步收率)。

配 28 mL 的四氮唑的乙腈溶液 (0.4 mmol/mL)。2064-4 (2.8 g) 加入到上述溶液中，然后 A1 (3 g) 在室温下 25℃ 加入到该溶液中，置换氮气三次，反应液在室温下 25℃ 搅拌 1 小时。点板监测显示反应完全。反应液在冰水浴下冷却到 10℃ 以下，滴加碘的吡啶/四氢呋喃/水的溶液 (0.5 mmol/mL，吡啶：四氢呋喃：水=1：8：1)，直到反应液不褪色。点板监测显示氧化反应完成。反应液加 10 mL 饱和亚硫酸钠水溶液淬灭，再加水稀释。用乙酸乙酯萃取三次，合并有机相用无水硫酸钠干燥，过滤。加适量硅胶和 DCM 拌样、纯化 (40 g 正相柱，EA，10min，DCM：MeOH，10-20

20% 20min, 流速 30ml/min)。浓缩得到白色泡沫状固体 2064-6 (2.6 g, 78.2%收率)。

将化合物 2064-6 (2.6 g)溶于甲醇 (30 mL), 然后加入浓氨水(30 mL), 所得溶液在室温下 25°C搅拌 60 小时, 点板监显示原料 2064-6 反应完全。反应液真空浓缩, 加
5 甲醇再次浓缩, 得到淡黄色油状液体化合物 2064-7 (2.4 g, 粗品), 粗品直接投下一步。

将化合物 2064-7 (2.4 g, 粗品)溶于 DMSO (3 mL), 然后加入三乙胺三氢氟酸盐 (3.5 mL), 反应液在 50°C下搅拌 1 小时, 点板显示原料 3-7 反应完全。反应液加水稀释到 50 mL, 用 1N 的 NaOH 水溶液调节 pH=5.5, 将混合物装载到 DEAE Sephadex
10 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到目标化合物的胺盐 2064-8 (0.8 g, 33.7%收率), 产物性状为白色固体。

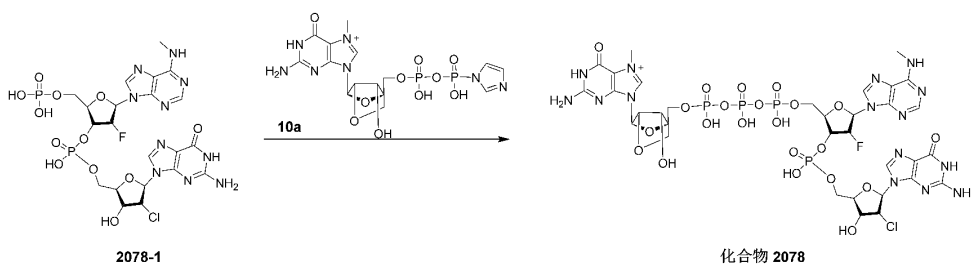
9a (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后 2064-8 (200 mg)加入到该溶液中。反应液在室温下 25°C
15 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 2064, 为铵盐 (65 mg)。

^1H NMR (400 MHz, D_2O) 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).

^{31}P NMR (162 MHz, D_2O) δ -0.80, -11.55, -23.03。

25 实施例 80

化合物 2078 的合成



10a (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后 2078-1 (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液

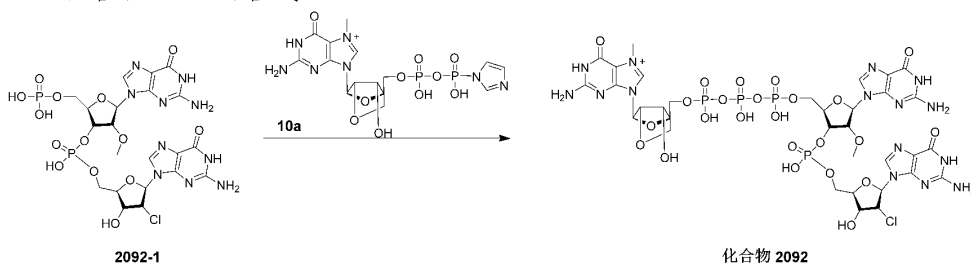
5 中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 2078, 为铵盐 (55 mg)。

^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)。

10 ^{31}P NMR (162 MHz, D_2O) δ -0.90, -11.50, -22.95。

实施例 81

化合物 2092 的合成



15

10a (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后 2092-1 (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液

20 中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 2092, 为铵盐 (65 mg)。

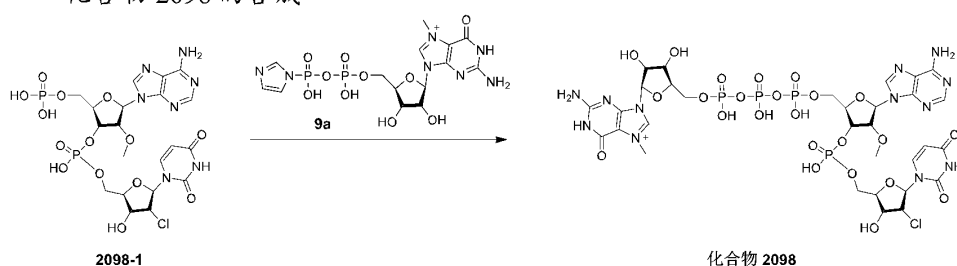
^1H NMR (400 MHz, D_2O) δ 8.19 (s, 1H), 8.08 (s, 1H), 6.37 – 6.19 (m, 2H), 6.09 (dd,

$J = 2.8, 0.8 \text{ Hz}$, 1H), 4.97 (ddd, $J = 4.4, 2.9, 0.7 \text{ Hz}$, 1H), 4.76 – 4.70 (m, 1H), 4.64 (t, $J = 2.8 \text{ Hz}$, 1H), 4.55 – 4.45 (m, 3H), 4.44 – 4.35 (m, 2H), 4.33 (d, $J = 2.8 \text{ Hz}$, 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。

5 实施例 82

化合物 2098 的合成



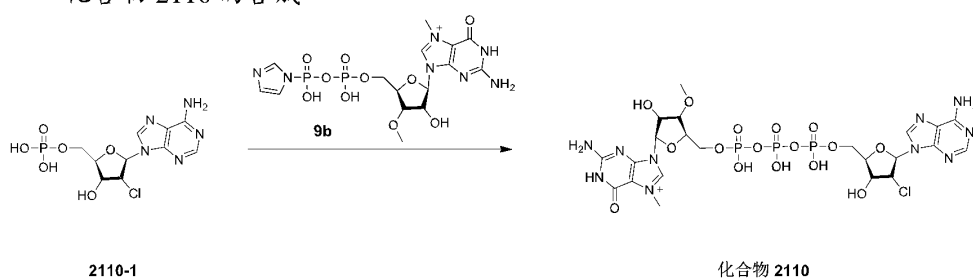
9a (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中，然后 2098-1 (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水)，混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱，所得组分真空浓缩大部分水，剩余液体经冻干后，得到白色粉末状产物化合物 2098，为铵盐 (70 mg)。

^1H NMR (400 MHz, D_2O) δ 8.42 (s, 1H), 8.18 (s, 1H), 7.93 (d, $J = 7.9 \text{ Hz}$, 1H), 6.15 (dq, $J = 4.1, 0.7 \text{ Hz}$, 1H), 6.10 (dd, $J = 2.9, 0.7 \text{ Hz}$, 1H), 6.01 (ddd, $J = 2.7, 1.7, 0.8 \text{ Hz}$, 1H), 5.91 (d, $J = 7.8 \text{ Hz}$, 1H), 5.02 – 4.88 (m, 1H), 4.77 (dddd, $J = 5.9, 4.3, 1.5, 0.7 \text{ Hz}$, 1H), 4.55 (ddd, $J = 5.3, 2.9, 0.6 \text{ Hz}$, 1H), 4.48 (qt, $J = 3.3, 0.8 \text{ Hz}$, 1H), 4.36 (ddd, $J = 7.3, 2.8, 0.6 \text{ Hz}$, 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。

20 实施例 83

化合物 2110 的合成



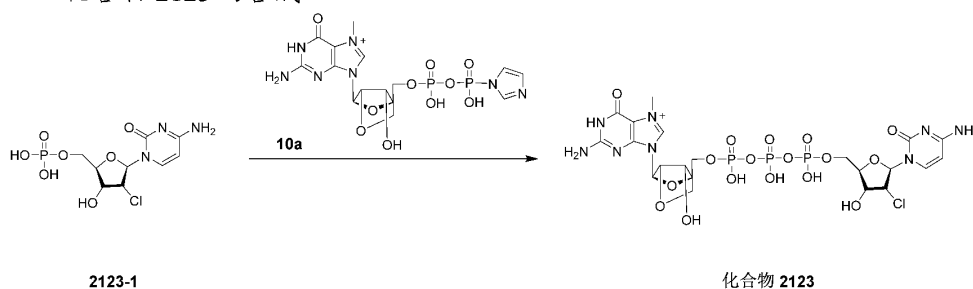
9b (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后 2110-1 (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 2110, 为铵盐 (70 mg)。

^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。

实施例 84

化合物 2123 的合成



10a (200 mg)加入到 16 mL 的 pH 7.0 的含 0.2mol/L 的 N-甲基吗啡啉和 0.2mol/L 的氯化亚锰水溶液中, 然后 2123-1 (200 mg)加入到该溶液中。反应液在室温下 25°C 搅拌 16 小时。点板显示有产物生成。将反应加入提前冷却 0°C 的 EDTA 二钠盐溶液中(1.4 g, 加 80 mL 的水), 混合物装载到 DEAE Sephadex 柱上。将产物使用 0-1.0M 的碳酸氢铵水溶液洗脱液线性梯度洗脱, 所得组分真空浓缩大部分水, 剩余液体经冻干后, 得到白色粉末状产物化合物 2123, 为铵盐 (50 mg)。

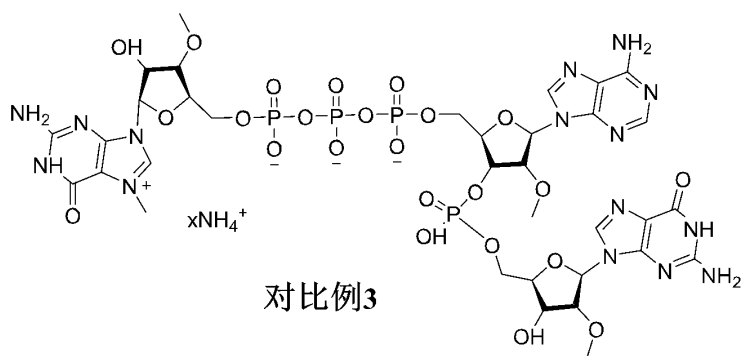
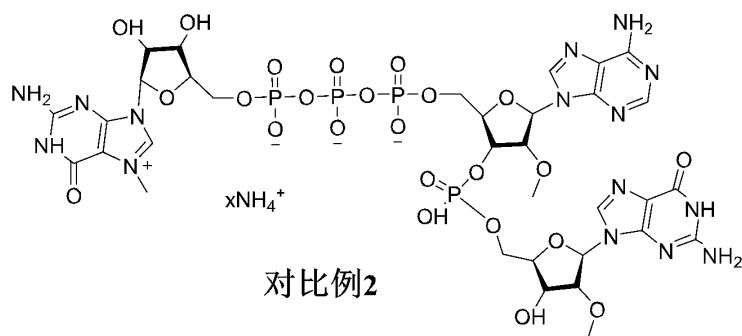
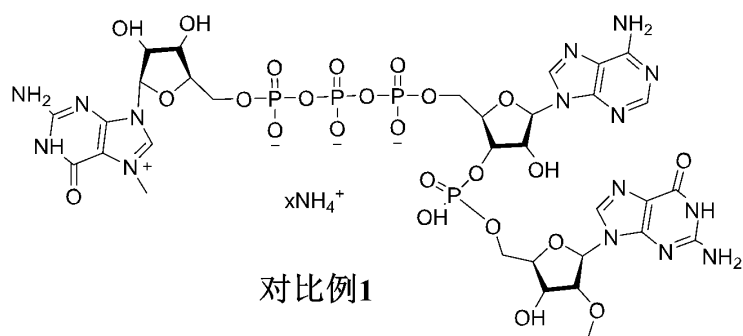
^1H NMR (400 MHz, D_2O) δ 7.62 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.24 (dd, $J = 2.7, 0.6$ Hz, 1H), 6.12 (ddt, $J = 2.6, 1.6, 0.7$ Hz, 1H), 5.96 (d, $J = 7.3$ Hz, 1H), 4.64 (t, $J = 2.8$ Hz, 1H), 4.49 (d, $J = 11.6$ Hz, 1H), 4.42 (ddd, $J = 5.3, 2.4, 0.7$ Hz, 1H), 4.39 (d, $J = 11.6$ Hz, 1H), 4.33 (d, $J = 2.8$ Hz, 1H), 4.27 (td, $J = 5.1, 0.7$ Hz, 1H), 4.21 – 4.05 (m, 4H), 4.04 – 3.96 (m, 4H).

^{31}P NMR (162 MHz, D_2O) δ -10.70, -20.75。

实施例 85

加帽 mRNA 合成效率检测

- a) 线性化质粒, 并对 DNA 模板进行纯化。
- b) 体外转录合成 mRNA, 分别使用本发明中的加帽类似物以及对比例 1 Trilink CleanCap, 对比例 2 和对比例 3 帽类似物。其中对比例 1 商购获得, 对比例 2 和对比例 3 根据 WO2022/036858 中公开的方法获得。



10 本发明中所用 mRNA 制备最小反应体系如表 1。

表 1. 体外转录体系

组分	用量
T7 RNA 聚合酶	4 μL (200 U)
RNase inhibitor	0.5 μL (20 U)
无机焦磷酸酶	1μL (0.5 U)
100mM ATP	1.5 μL
100mM CTP	1.5 μL
100mM GTP	1.5 μL
100mM ψTP	1.5 μL
100mM 帽类似物	1.5 μL
10×buffer	2 μL
DNA 模版	1μL
水	4 μL
合计	20 μL

c) 在实验过程中，充分混匀以上试剂后，于 37 °C下孵育。4 小时后加入脱氧核糖核酸酶 (DNase) 继续孵育 30 分钟去除 DNA 模板，消化完成后加入 LiCl 溶液，

5 预冷，16000rpm 离心 15min，去上清。加入 70%乙醇离心后去再去上清，之后加入一定量无酶水保存。之后利用 Nanodrop One 对纯化后的 mRNA 样品进行定量检测，如下表 2 所示。实验结果表明本发明中的卤代帽类似物在 mRNA 合成中的产物收率与对比例相比有所提升。

表 2 每 1mL mRNA 合成反应体系所得的终产物质量 (mg)

化合物编号	8	68	168	173	433	458	468	33	对比例 2
产物质量	4.7	5.8	5.6	5.2	4.9	4.8	5.3	5.3	4.2
化合物编号	58	76	101	158	408	1982	2017	2037	2058
产物质量	5.5	5.4	5.3	4.9	5.7	5.8	5.8	5.5	4.6

10 d) 采用酶切方式处理上述纯化后的 mRNA ，随后通过液相质谱联用 (LC-MS) 分离鉴定不同大小的寡核苷酸片段，提供酶切片段的精确分子量信息，再结合理论酶切分子量，可以归属并得到样品的加帽效率。

本发明中的帽类似物所合成的 mRNA 加帽率均在 90%-98%之间。从经纯化后的加帽 mRNA 看来，本发明化合物均表现出很好的加帽效率。

在不同细胞中评估不同加帽类似物绿色荧光蛋白 mRNA 的表达效率。

本发明分别实验了不同加帽绿色荧光蛋白 mRNA 在 HEK293T、HepG2 细胞中的表达效率。以绿色荧光蛋白 GFP 编码序列作为 DNA 模版，利用本发明所述的帽类似物作为其中的原料进行 mRNA 的体外转录，随后将不同的 mRNA 产物进行细胞

- 5 a) 将上述不同的细胞以 2×10^5 个细胞进行铺板 (96 孔板)。
- b) 将 300 μ L mRNA buffer 与 6 μ g RNA 混匀，再加入 6 μ L 转染试剂(JetMESSENGER)混匀，静置 10 min 后将混合物加入到每孔细胞中，补足转染培养基(Opti-MEM)至 2 mL/孔，37 $^{\circ}$ C，5% CO₂ 的条件下培育 6 h。
- 10 c) 更换为新鲜的完全培养基同条件继续培养 24 h 后，荧光显微镜观察 GFP 荧光强度。结果如图 1 所示，图中可以明显看出本发明中的 mRNA 表达效率要高于对比例。

d) 所转染细胞培养 24 h 后，经处理后利用流式细胞仪(CytoFLEX S 系列)对其进行检测，所检测荧光强度与目的蛋白翻译效率成正比，分析所得结果如图 2 和 3 所示。

其中图 2 是编码绿色荧光蛋白的不同帽类似物的 mRNA 在 HEK293T 细胞中的荧光强度分析图。横坐标是帽类似物的化合物数字编号，纵坐标是流式细胞仪所检测的荧光强度值。相比于对比例 1 和对比例 2，本发明中的帽类似物在 HEK293T 细胞中的荧光强度值较为突出。例如化合物 468 的平均荧光强度值为对比例 2 的 1.5 倍，对比例 1 的 1.6 倍，化合物 158 的平均荧光强度值为对比例 2 的 1.3 倍，对比例 1 的 1.4 倍。

图 3 是不同帽类似物的 mRNA 在 Hep G2 细胞中的荧光强度统计图。相比较而言，含有本发明中的帽类似物在 Hep G2 细胞中 mRNA 翻译表达蛋白的效率要高于对比例。其中氟代的核苷二聚体帽类似物如化合物 1982，以及氟代的核苷四聚体帽类似物如 2057 的蛋白表达量也有较为明显的提升。

实施例 87

不同帽类似物合成的 mRNA 在小鼠体内的表达效率测试

- a) 利用本发明的帽类似物制备编码荧光素酶 luciferase 的 mRNA，将所得 mRNA 稀释至 pH 4.0 的柠檬酸缓冲液中；将阳离子脂质 DLin-MC3-DMA：DSPC：

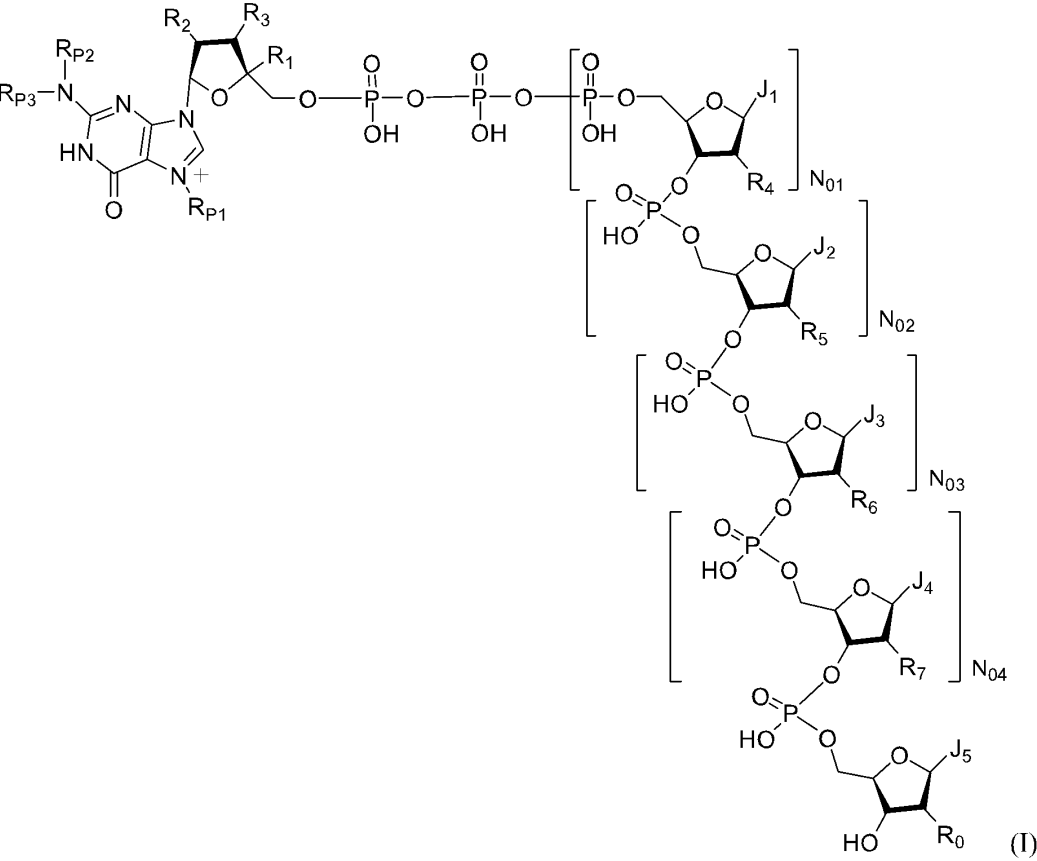
胆固醇：PEG 脂质（DMG-PEG2000）按照摩尔比 50：10：38.5：1.5 溶于乙醇。

5 b) 将 3 mL mRNA 缓冲液和 1 mL 脂质溶液分别装入两个 5 mL 注射器，安装于微流控注射泵上，设定注射泵流速，将收集到的产品放入透析袋中，随后超滤浓缩至理想浓度，再将脂质纳米颗粒经 0.22 μm 无菌过滤器过滤，保存待用。

c) 将含有 5 μg mRNA 的 Luciferase mRNA-脂质纳米颗粒于 6-8 周龄的雌性 Balb/c 小鼠通过尾静脉注射，每种 Luciferase mRNA-脂质纳米颗粒注射 5 只小鼠进行平行实验，24 小时注射荧光素酶底物，使用 PerkinElmer 小动物成像系统进行检测。发光强度与有效目的蛋白翻译效率成正比。mRNA 在小鼠不同器官中的相对
10 荧光强度如图 4 所示。本发明中不同卤代帽类似的 mRNA 在不同脏器中的表达效率明显高于对比例。

权利要求书

1. 一种用于核酸 5'端加帽的化合物，或其药学上可接受的盐、或溶剂化物、或其立体异构体，所述化合物具有式(I)的结构：



其特征在于：

- 5 R_0 选自 F、Cl、Br、I 中的任意一种；
 R_1 为选自 -H、-OH、 C_{1-4} 烷基和 C_{1-4} 烷氧基的基团；
 R_2 为选自 -H、-OH、 C_{1-6} 烷基和 C_{1-6} 烷氧基中的任意一种；
 任选地 R_1 与 R_2 通过化学键连接成环，且 - R_1 - R_2 - 为 $-(CH_2)_q-O-$ 、 $-O-(CH_2)_q-$ 和 $-(CH_2)_m-O-(CH_2)_n-$ 中的任意一种，其中 q 、 m 、 n 各自独立地为 1、2 或 3；
- 10 R_3 为 H、-OH、-SH、-N₃、-NH₂、卤素、-CN、 C_{1-6} 烷氧基、 $-O(CH_2)_sCN$ 、-SR_{3a}、-O(CH₂)_pR_{3b}、OCOR_{3c}、O(CH₂)_pCOR_{3c}、 $-O(CH_2)_tSH$ 、 $-O(CH_2)_pOH$ 、 $-O(CH_2)_pN_3$ 、 $-O(CH_2)_pNH_2$ 中的任意一种，其中 t 、 p 和 s 各自独立地为 1-6 的任意一个整数， R_{3a} 为 C_{1-6} 烷基， R_{3b} 为任选被一个或多个 R_{3d} 取代的 C_{6-12} 芳基或任选被一个或多个 R_{3d} 取

代的 C₅₋₁₂ 杂芳基, R_{3c} 为任选被一个或多个 R_{3d} 取代的 C₁₋₁₀ 烷基, 任选被一个或多个 R_{3d} 取代的 C₁₋₁₀ 烯基, 任选被一个或多个 R_{3d} 取代的 C₅₋₁₂ 环烷基或任选被一个或多个 R_{3d} 取代的 C₅₋₁₂ 环烯基, 其中 R₃ 任选被一个或多个 R_{3c} 取代, R_{3d} 和 R_{3e} 选自由烷基、烯基、烷氧基、卤素、氰基、氨基、硝基、-OH、-SH 所组成的组;

- 5 R₄、R₅、R₆、R₇ 各自独立地选自 -H、-OH、-OCH₃、卤素、-CN、-SH 中的任意一种;

N₀₁、N₀₂、N₀₃、N₀₄ 各自独立地选自 0 或 1;

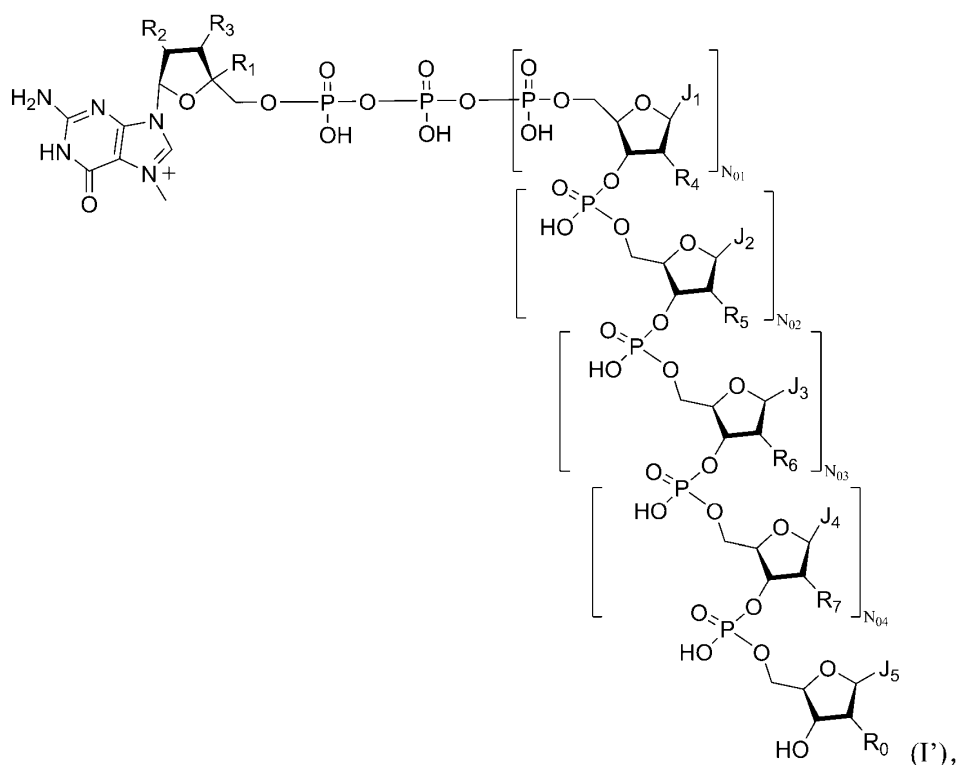
J₁、J₂、J₃、J₄、J₅ 各自独立地选自天然或修饰的嘧啶核苷酸碱基、天然或修饰的嘌呤核苷酸碱基;

- 10 R_{P1} 为 C₁-C₆ 烷基, 优选 C₁-C₃ 烷基, 该烷基上任选被 -SH, -N₃, C₂-C₆ 烯基或 C₂-C₆ 炔基取代;

R_{P2} 和 R_{P3} 各自独立地选自 H、C₁-C₆ 烷基、C₂-C₆ 烯基、C₂-C₆ 炔基、环烷基、环烯基、环炔基、PEG 基、COR_{P4}、SO₂R_{P4}, 所述基团任选被 -CN、-N₃、-SH、炔基取代, R_{P4} 选自 H 和 C₁-C₆ 烷基; R_{P2} 和 R_{P3} 任选连接成环;

- 15 前提是, 当 N₀₁、N₀₂、N₀₃、N₀₄ 均为 0, J₅ 是鸟嘌呤碱基, R₂ 为 -OH 时, R₃ 不为甲氧基。

2. 如权利要求 1 所述的化合物, 其药学上可接受的盐、或溶剂化物、或其立体异构体, 其特征在于, 所述化合物具有式(I')的结构:



其中，式(I')中的各基团具有如权利要求1中所述的含义。

3. 如权利要求1或2所述的化合物，或其药学上可接受的盐、或溶剂化物、或其立体异构体，其特征在于，J₁、J₂、J₃、J₄、J₅中至少一个是修饰的核苷酸碱基，
 5 优选修饰的嘌呤核苷酸碱基，更优选甲基修饰的嘌呤核苷酸碱基，更优选 6-N-甲基腺嘌呤。

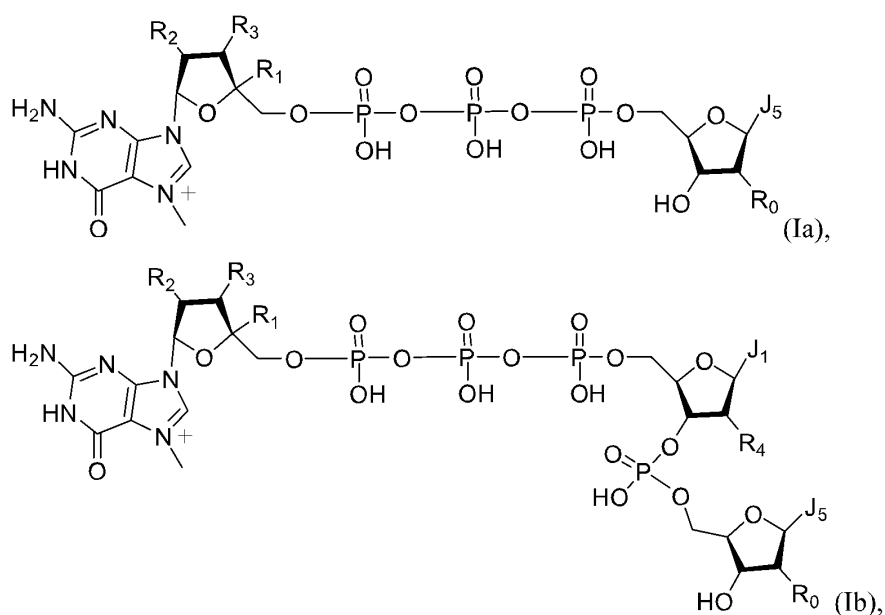
4. 如权利要求1至3中任一项所述的化合物，或其药学上可接受的盐、或溶剂化物、或其立体异构体，其中，

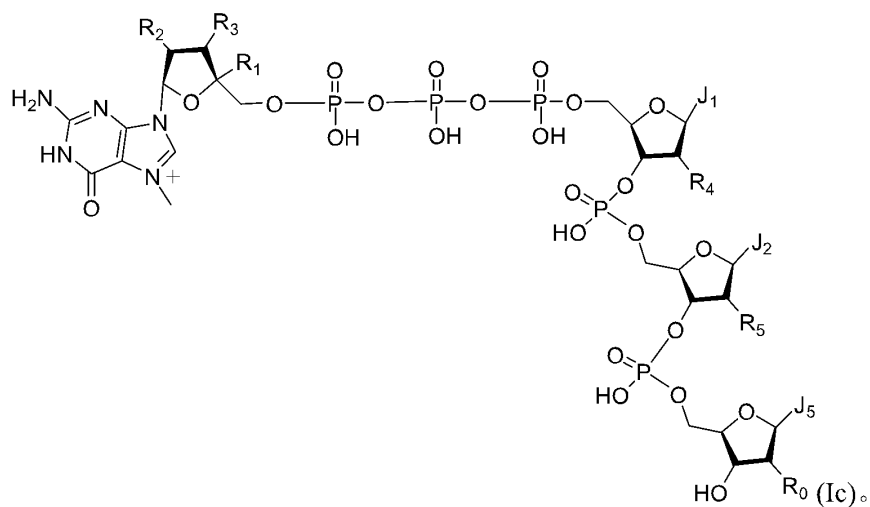
- R₃为-H, -OH, -SH, -N₃, -NH₂, 卤素, -CN, C₁₋₆烷氧基, -O(CH₂)_pCN, -SR_{3a}, -
 10 O(CH₂)_pR_{3b}, OCOR_{3c}, O(CH₂)_pCOR_{3c}, -O(CH₂)_pSH, -O(CH₂)_pOH, -O(CH₂)_pN₃, -
 O(CH₂)_pNH₂中的任意一种, 其中 t、p 和 s 各自独立地为 1-6, 优选为 1-4 的任意一个
 整数, R_{3a}为 C₁₋₄烷基, R_{3b}为任选被一个或多个 R_{3d}取代的 C₆₋₁₀芳基或任选被一个
 或多个 R_{3d}取代的 C₅₋₁₀杂芳基, R_{3c}为任选被一个或多个 R_{3d}取代的 C₅₋₁₀环烷基或任
 选被一个或多个 R_{3d}取代的 C₅₋₁₀环烯基, 其中 R₃任选被一个或多个 R_{3e}取代, R_{3d}和
 15 R_{3e}选自由 C₁₋₄烷基、C₂₋₄烯基、C₁₋₄烷氧基、卤素、氰基、氨基、硝基、-OH、-SH
 所组成的组,

优选地, R_3 为 -H, -OH, -SH, -N₃, -NH₂, 卤素, -CN, C₁₋₃ 烷氧基, -O(CH₂)_pCN, -SR_{3a}, -O(CH₂)_pR_{3b}, OCOR_{3c}, O(CH₂)_pCOR_{3c}, -O(CH₂)_pSH, -O(CH₂)_pOH, -O(CH₂)_pN₃, -O(CH₂)_pNH₂ 中的任意一种, 其中 p 和 s 各自独立地为 1-3 的任意一个整数, t 为 1-4 的任意一个整数, R_{3a} 为甲基或乙基, R_{3b} 为任选被一个或两个 R_{3d} 取代的 C₅₋₁₀ 杂芳基, R_{3c} 为任选被一个或两个 R_{3d} 取代的 C₅₋₁₀ 环烷基或任选被一个或两个 R_{3d} 取代的 C₅₋₁₀ 环烯基, 其中 R_3 任选被一个或多个 R_{3c} 取代, R_{3d} 和 R_{3e} 选自由 C₁₋₄ 烷基、C₂₋₄ 烯基、C₁₋₄ 烷氧基、卤素、氰基、氨基、硝基、-OH、-SH 所组成的组,

更优选地, R_{3b} 为任选被 C₁₋₄ 烷基取代的 C₅ 或 C₆ 杂芳基, 例如任选被 C₁₋₄ 烷基取代的四嗪基, R_{3c} 为任选被 C₁₋₄ 烷基、卤素、氰基、氨基、硝基取代的 C₅₋₁₀ 环烯基, 例如任选被 C₁₋₄ 烷基、卤素、氰基、氨基、硝基取代的降冰片烯基或环辛烯基, 例如未被取代的降冰片烯基或环辛烯基。

5. 如权利要求 1 至 4 中任一项所述的化合物, 或其药学上可接受的盐、或溶剂化物、或其立体异构体, 其中所述化合物具有式(Ia)、式(Ib)或式(Ic)的结构:



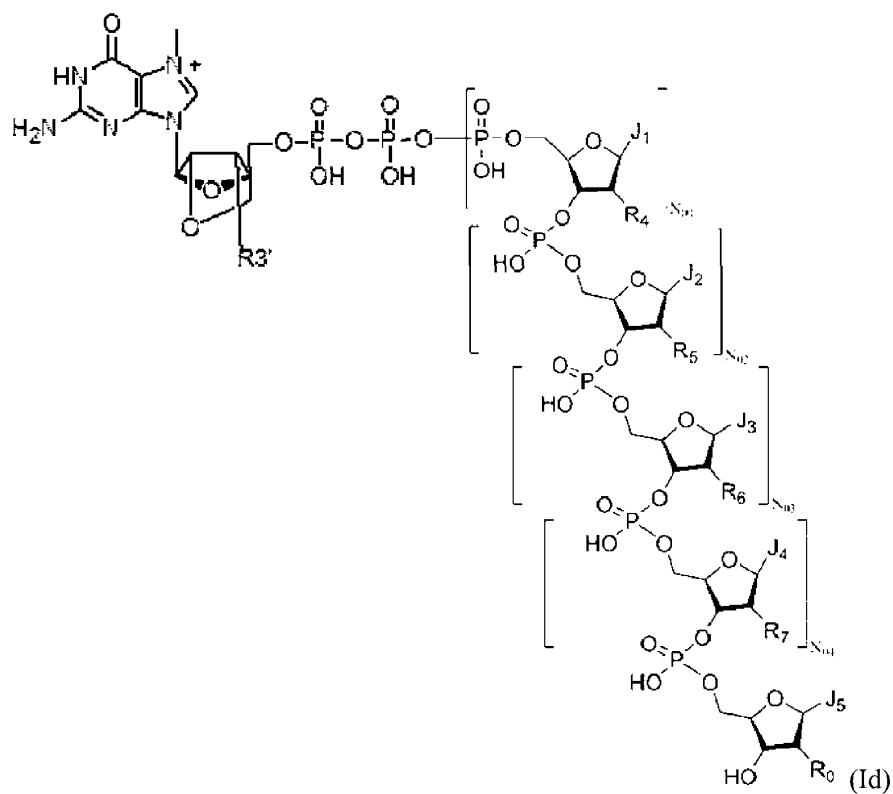


6. 如权利要求 5 所述的化合物，或其药学上可接受的盐、或溶剂化物、或其立体异构体，其中，

R₀ 为 -F 或 -Cl，和/或

- 5 R₄ 和 R₅ 各自独立地选自 H、OH、OCH₃、F、Cl、-CN、-SH 中的任意一种，优选 H、OH、OCH₃、F 中的任意一种。

7. 如权利要求 1 至 4 中任一项所述的化合物，或其药学上可接受的盐、或溶剂化物、或其立体异构体，其中所述化合物具有式(Id)的结构：

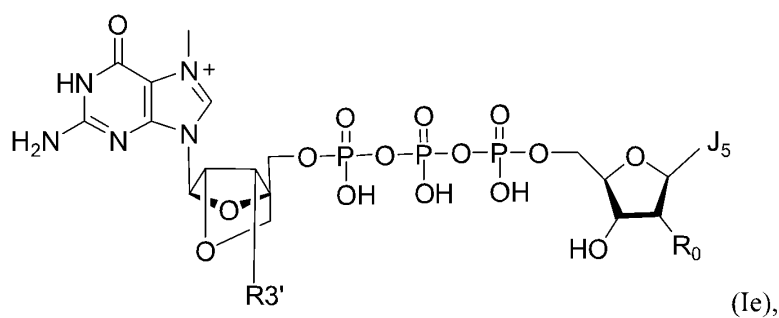


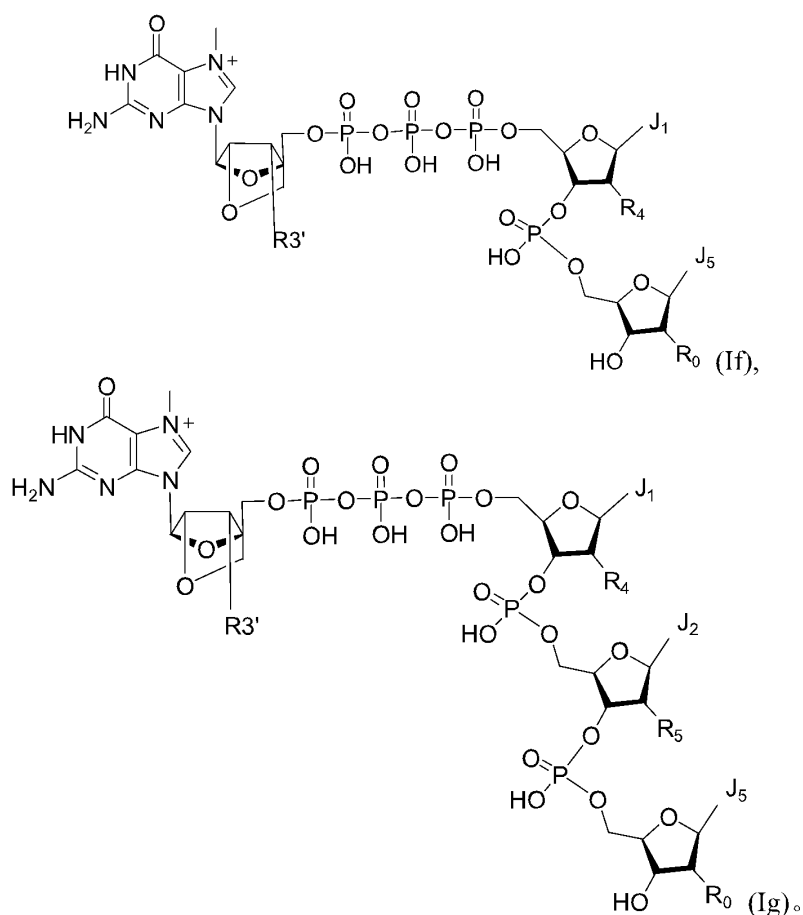
其中,

R3'具有如权利要求1或4中关于R3限定的含义;

其余基团具有如权利要求1至4中所述的含义。

- 5 8. 如权利要求7所述的化合物, 或其药学上可接受的盐、或溶剂化物、或其立体异构体, 其中所述化合物具有式(Ie)、式(If)或式(Ig)的结构:





9. 如权利要求 8 所述的化合物, 或其药学上可接受的盐、或溶剂化物、或其立体异构体, 其中,

5 R₀ 为 -F 或 -Cl, 和/或

R₄ 和 R₅ 各自独立地选自 H、OH、OCH₃、F、Cl、-CN、-SH 中的任意一种, 优选 H、OH、OCH₃、F 中的任意一种。

10. 如权利要求 1 所述的化合物, 或其药学上可接受的盐、或溶剂化物、或其立体异构体, 其中所述化合物具有如说明书表 1 中所示的结构之一。

10 11. 如权利要求 1 至 10 中任一项所述的化合物, 或溶剂化物、或其立体异构体, 其中所述化合物以药学上可接受的盐的形式存在, 优选以三乙胺盐, 钠盐, 钾盐, 铵盐或三羟甲基氨基甲烷盐酸盐的形式存在。

12. 如权利要求 1-11 中任一项所述的化合物作为体外共转录 RNA 加帽试剂的应用。

13. 一种 RNA 分子，其特征在于，包含权利要求 1-11 中任一项所述的化合物作为帽结构或帽结构片段。

14. 一种药物组合物，其特征在于，包含权利要求 13 所述的 RNA 分子，以及药学上可接受的载体。

5 15. 一种合成 RNA 分子的方法，其特征在于，包括以下步骤：将权利要求 1-11 任一项所述的化合物，与多核苷酸模板共孵育，进行模板转录。

16. 一种加帽 RNA 转录反应系统，其特征在于，包括：多核苷酸模板，权利要求 1-11 任一项所述的化合物，NTPs 和 RNA 聚合酶。