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activity and mechanism of action of Nu-3, a protonated modified nucleotide”.《Ann Clin Microbiol Antimicrob》.2011, 第1-9页.

审查员 周陈林

权利要求书2页 说明书545页

(54) 发明名称

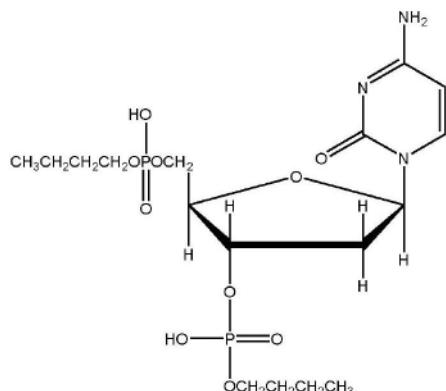
抗微生物化合物、组合物及其用途

(57) 摘要

B 本发明涉及抗微生物化合物、组合物及其用途。公开了式(I)至(III)的抗微生物化合物和组合物以及使用方法。本公开的另一个方面提供一种药物组合物，其包含根据式(I)至(III)的化合物或其药学上可接受的盐，以及一种或多种药学上可接受的载体、赋形剂或稀释剂。本公开的另一个方面提供一种在有需要的患者中治疗细菌感染的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。

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1. 具有下式的化合物或其药学上可接受的盐在制备用于治疗有需要的患者中的细菌感染的药物中的用途：



式(III)

所述治疗通过向患者施用有效量的所述化合物或其药学上可接受的盐。

2. 根据权利要求1所述的用途，其中所述施用选自口服和肠胃外。
3. 根据权利要求1或2所述的用途，其中使用化合物或其药学上可接受的盐在洗剂、糊剂、凝胶、霜剂、软膏、油剂或其他粘性组合物中进行所述施用。
4. 根据权利要求1或2所述的用途，其中使用化合物或其药学上可接受的盐在粉末、溶液或混悬剂中进行所述施用。
5. 根据权利要求1或2所述的用途，其中使用化合物或其药学上可接受的盐在胶囊、片剂、粉末、液体混悬剂、液体溶液、酏剂、糖浆剂或浓缩滴剂中进行所述施用。
6. 根据权利要求1所述的用途，其中向所述患者施用至少一种另外的活性成分。
7. 根据权利要求1所述的用途，其中所述施用作为多剂量方案进行。
8. 根据权利要求1所述的用途，其中所述施用作为长期治疗方案进行。
9. 根据权利要求1所述的用途，其中每天一次或多次进行所述施用。
10. 根据权利要求1所述的用途，其中施用至患者的化合物或其药学上可接受的盐的量为每kg患者体重约0.1至约1000mg化合物或其药学上可接受的盐。
11. 根据权利要求1所述的用途，其中施用至患者的化合物或其药学上可接受的盐的量为每kg患者体重约0.1至约500mg化合物或其药学上可接受的盐。
12. 根据权利要求1所述的用途，其中施用至患者的化合物或其药学上可接受的盐的量为每kg患者体重约0.1至约300mg化合物或其药学上可接受的盐。
13. 根据权利要求1所述的用途，其中施用至患者的化合物或其药学上可接受的盐的量为每kg患者体重约0.1至约200mg化合物或其药学上可接受的盐。
14. 根据权利要求1所述的用途，其中施用至患者的化合物或其药学上可接受的盐的量为每kg患者体重约0.1至约100mg化合物或其药学上可接受的盐。
15. 根据权利要求1所述的用途，其中所述患者为人。
16. 根据权利要求1所述的用途，其中所述药学上可接受的盐为钠盐。
17. 根据权利要求16所述的用途，其中所述钠盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钠。
18. 根据权利要求1所述的用途，其中所述感染选自伤口感染、溃疡感染、膀胱感染、肾

脏感染、肺部感染、外耳道感染、细菌性阴道感染和脓疱病感染，及其组合。

19. 根据权利要求1所述的用途，其中所述感染是糖尿病足溃疡感染或烧伤伤口感染及其组合。

抗微生物化合物、组合物及其用途

[0001] 本申请是申请号为201880030624.4,申请日为2018年3月12日,发明名称为“抗微生物化合物、组合物及其用途”的中国专利申请的分案申请。

[0002] 相关申请的交叉引用

[0003] 本申请要求于2017年3月10日提交的美国临时专利申请系列号62/470,025和62/470,039的优先权,其通过引用整体并入本文。

技术领域

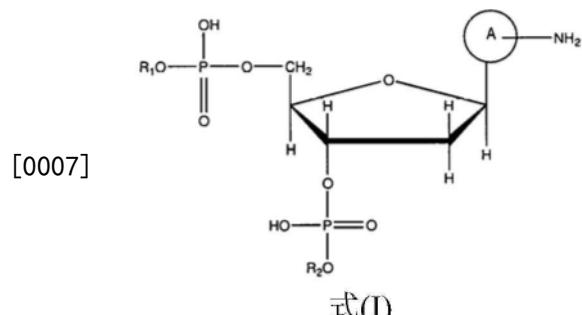
[0004] 本公开提供新颖的抗微生物化合物和组合物及其用途。

背景技术

[0005] Bisphosphocin® 化合物具有抗微生物活性。美国专利号7,868,162公开了 Bisphosphocin® 化合物。

发明内容

[0006] 本公开提供一种具有下式的化合物:



[0008] 或其药学上可接受的盐,

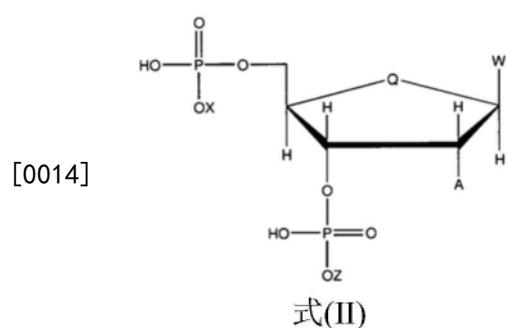
[0009] 其中:

[0010] A为单环、双环或三环碳环或杂环部分,和

[0011] R₁和R₂各自为C₁-C₈烷基部分。

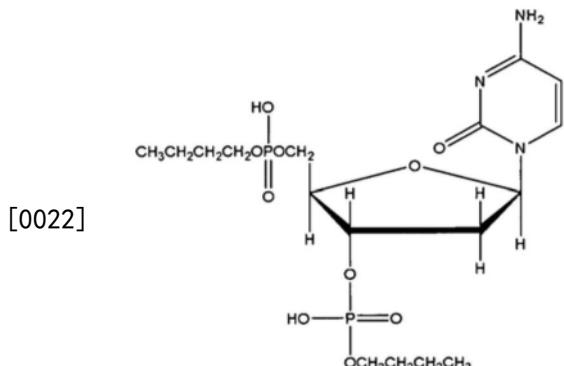
[0012] 在一些实施方案中,R₁和R₂各自为丁基。

[0013] 本公开的另一方面提供一种具有下式的化合物:



[0015] 其中:

- [0016] Q为氧或硫；
 [0017] W为氨基取代的或胍基取代的含氮杂环部分；
 [0018] X和Z为末端封闭基团；和
 [0019] A为H、烷基、卤素、烷氧基、烷基-(0-烷基)、芳基、烯基、烷醇或苯酚。
 [0020] 本公开的另一方面提供一种化合物，其选自具体实施方式部分的表1中所描述的 Cmpd 1至2520中的任一个。
 [0021] 本公开的另一方面提供一种具有下式的化合物：



式(III)

- [0023] 或其药学上可接受的盐。
 [0024] 本公开的另一方面提供一种药物组合物，其包含根据式(I)至(III)的化合物或其药学上可接受的盐，以及一种或多种药学上可接受的载体、赋形剂或稀释剂。
 [0025] 本公开的另一方面提供一种在有需要的患者中治疗糖尿病足溃疡感染的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。
 [0026] 本公开的另一方面提供一种在有需要的患者中治疗复杂泌尿道感染的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。
 [0027] 本公开的另一方面提供一种在有需要的患者中治疗囊性纤维化引起的肺部感染的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。
 [0028] 本公开的另一方面提供一种在有需要的患者中治疗呼吸机获得性肺炎的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。
 [0029] 本公开的另一方面提供一种在有需要的患者中治疗烧伤口的感染的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。
 [0030] 本公开的另一方面提供一种在有需要的患者中治疗外耳炎的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。
 [0031] 本公开的另一方面提供一种在有需要的患者中治疗细菌性阴道病的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。
 [0032] 本公开的另一方面提供一种在有需要的患者中治疗脓疱病的方法，所述方法包括向患者施用有效量的根据式(I)至(III)的化合物或其药学上可接受的盐。
 [0033] 本公开的另一方面提供一种根据式(I)至(III)的化合物或其药学上可接受的盐，其用于治疗的用途。
 [0034] 本公开的另一方面提供根据式(I)至(III)的化合物或其药学上可接受的盐在制

备药物中的用途。

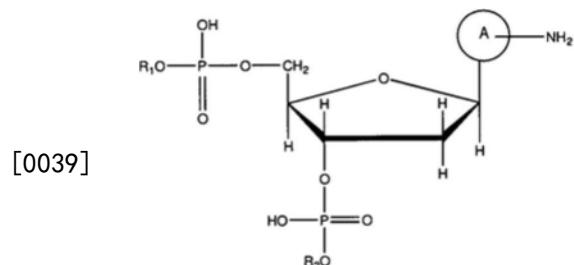
[0035] 在一些实施方案中,式(I)至(III)的化合物或其药学上可接受的盐具有在本公开之前无法预期的某些令人惊讶的特征和优势。根据本公开的一些实施方案,式(I)至(III)的化合物或其药学上可接受的盐的一个优势在于,当此类化合物和/或盐在较高pH水平(较低酸性)下配制时,此类化合物和/或盐具有高水平的生物活性。不受任何理论的束缚,据信根据一些实施方案的式(I)至(III)的化合物或其药学上可接受的盐的游离氨基或胍基在较高pH水平时赋予了期望的生物活性。已经发现根据本公开的一些实施方案的式(I)至(III)的化合物或其药学上可接受的盐在高于约pH 3的pH水平时出乎意料地更有效。因此,据信根据一些实施方案的式(I)至(III)的化合物或其药学上可接受的盐可用于适应症,其中长期暴露于抗微生物剂是有利的,如微生物感染。不同于在低于约pH 3时配制的一些药物在局部、吸入或膀胱内施用途径中引起不可接受的接触刺激,根据一些实施方案的式(I)至(III)的化合物或其药学上可接受的盐与局部、吸入和膀胱内施用途径是相容的。此外,根据一些实施方案的式(I)至(III)的化合物或其药学上可接受的盐对慢速生长细菌有效,因为化合物或其盐在短时间内表现出在较高的pH值时的高水平生物活性(速效抗微生物机制)。

[0036] 根据具体实施方式和权利要求,其他方面和实施方案将是显然的。

具体实施方式

[0037] 以下描述的实施方案并不旨在穷举或将本发明限制为以下详细描述中公开的精确形式。相反,选择并描述了实施方案以使得本领域技术人员可以了解和理解本公开的原理和实施。

[0038] 本公开提供一种具有下式的化合物:



式(I)

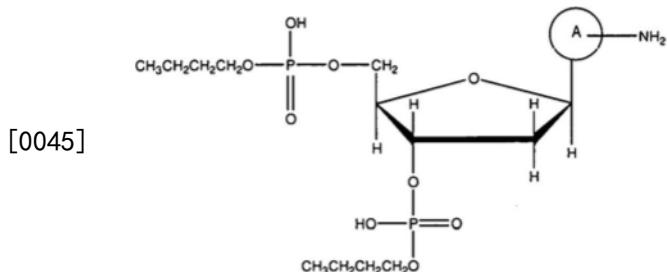
[0040] 或其药学上可接受的盐,

[0041] 其中:

[0042] A为单环、双环或三环碳环或杂环部分,和

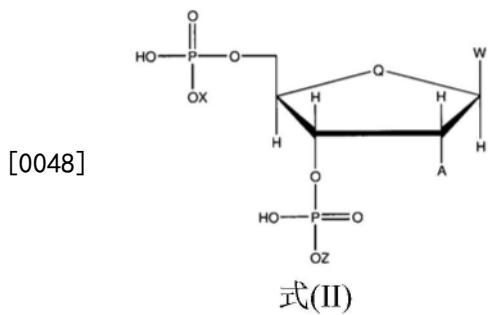
[0043] R₁和R₂各自为C₁-C₈烷基部分。

[0044] 在一些实施方案中,R₁和R₂各自为丁基,如下所示:



[0046] 或其药学上可接受的盐。

[0047] 本公开还提供一种具有下式的化合物：



[0049] 其中：

[0050] Q为氧或硫；

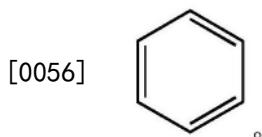
[0051] W为氨基取代的或胍基取代的含氮杂环部分；

[0052] X和Z为末端封闭基团；和

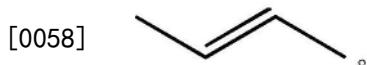
[0053] A为H、烷基、卤素、烷氧基、烷基-(0-烷基)、芳基、烯基、烷醇或苯酚。

[0054] 如本文所使用，术语“末端封闭基团”是指任何化学部分，其防止质子化的化合物的大量核酸酶降解，特别是核酸外切酶降解。末端基团可以是使得式(II)化合物适当质子化的任何化学部分，包括但不限于H、OH、SH、NH2、烷基、烷醇基等。

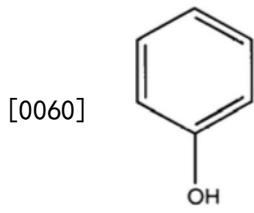
[0055] 在一些实施方案中，A为烷基。在一些实施方案中，烷基为CH₃-或CH₃-CH₂-。在一些实施方案中，A为卤素。在一些实施方案中，卤素为F-、Cl-、Br-或I-。在一些实施方案中，A为烷氧基。在一些实施方案中，烷氧基为CH₃-0-CH₂-或CH₃-CH₂-0-CH₂-。在一些实施方案中，A为烷基-(0-烷基)。在一些实施方案中，烷基-(0-烷基)为CH₃-0-或CH₃-CH₂-0-。在一些实施方案中，A为芳基。在一些实施方案中，芳基为：



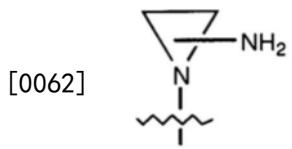
[0057] 在一些实施方案中，A为烯基。在一些实施方案中，烯基为：



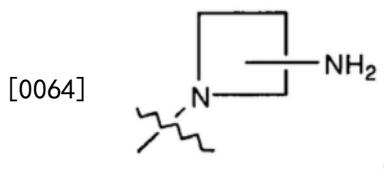
[0059] 在一些实施方案中，A为烷醇。在一些实施方案中，烷醇为-CH₂-OH或-CH₂-CH₂-OH。在一些实施方案中，A为苯酚。在一些实施方案中，苯酚为：



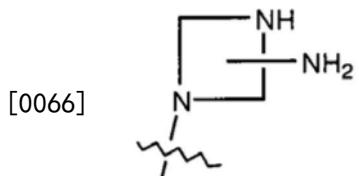
[0061] 在一些实施方案中,W为如下所述的氨基取代的氮杂环丙烷:



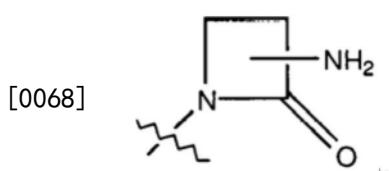
[0063] 在一些实施方案中,W为如下所述的氨基取代的氮杂环丁烷:



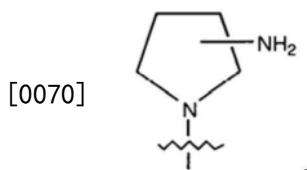
[0065] 在一些实施方案中,W为如下所述的氨基取代的1,3-氮杂环丁烷:



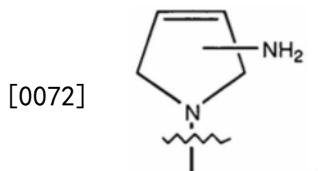
[0067] 在一些实施方案中,W为如下所述的氨基取代的氮杂环丁烷-2-酮(β -内酰胺):



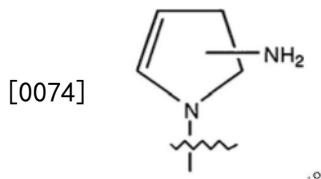
[0069] 在一些实施方案中,W为如下所述的氨基取代的吡咯烷:



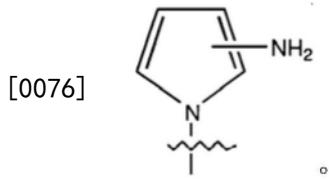
[0071] 在一些实施方案中,W为如下所述的氨基取代的3-吡咯啉:



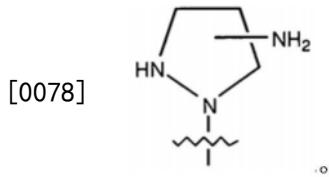
[0073] 在一些实施方案中,W为如下所述的氨基取代的2-吡咯啉:



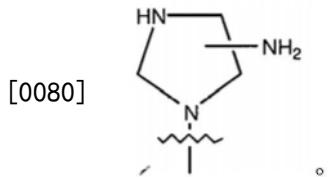
[0075] 在一些实施方案中,W为如下所述的氨基取代的1H-吡咯:



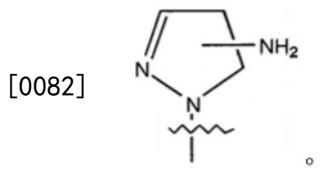
[0077] 在一些实施方案中,W为如下所述的氨基取代的吡唑烷:



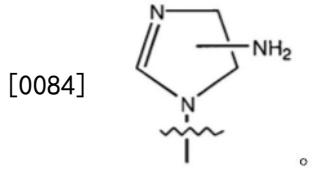
[0079] 在一些实施方案中,W为如下所述的氨基取代的咪唑烷:



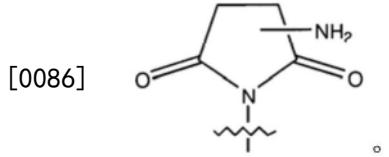
[0081] 在一些实施方案中,W为如下所述的氨基取代的2-吡唑啉:



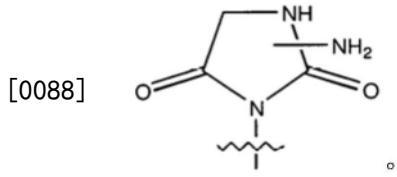
[0083] 在一些实施方案中,W为如下所述的氨基取代的2-咪唑啉:



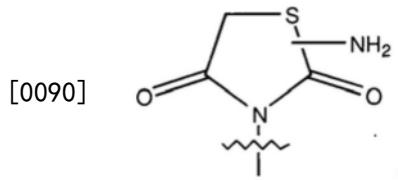
[0085] 在一些实施方案中,W为如下所述的氨基取代的琥珀酰亚胺:



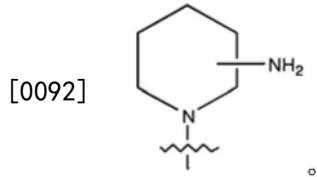
[0087] 在一些实施方案中,W为如下所述的氨基取代的乙内酰脲:



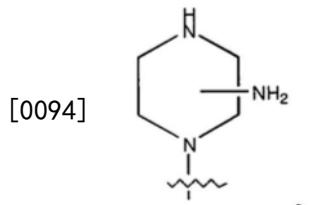
[0089] 在一些实施方案中,W为如下所述的氨基取代的2,4-噻唑烷二酮:



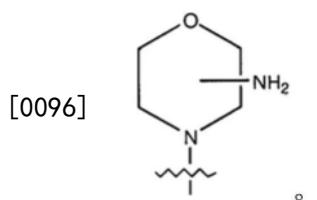
[0091] 在一些实施方案中,W为如下所述的氨基取代的哌啶:



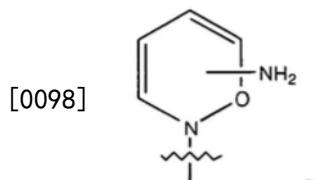
[0093] 在一些实施方案中,W为如下所述的氨基取代的哌嗪:



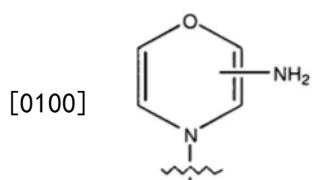
[0095] 在一些实施方案中,W为如下所述的氨基取代的吗啉:



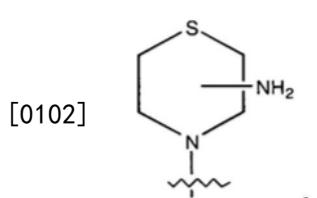
[0097] 在一些实施方案中,W为如下所述的氨基取代的2H-1,2-噁唑烷:



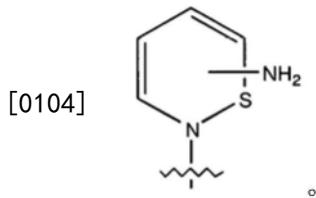
[0099] 在一些实施方案中,W为如下所述的氨基取代的4H-1,4-噁唑烷:



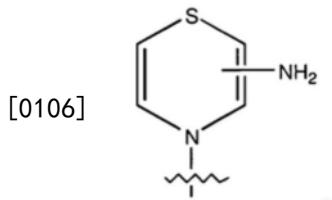
[0101] 在一些实施方案中,W为如下所述的氨基取代的硫代吗啉:



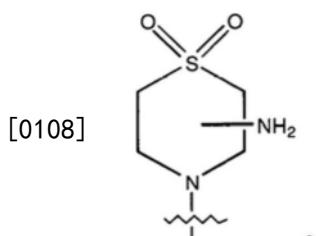
[0103] 在一些实施方案中,W为如下所述的氨基取代的2H-1,2-噻嗪:



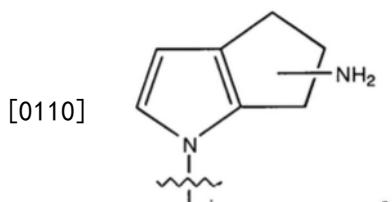
[0105] 在一些实施方案中,W为如下所述的氨基取代的4H-1,4-噻嗪:



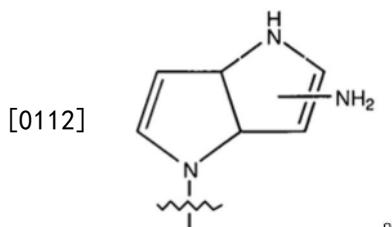
[0107] 在一些实施方案中,W为如下所述的氨基取代的硫代吗啉二氧化物:



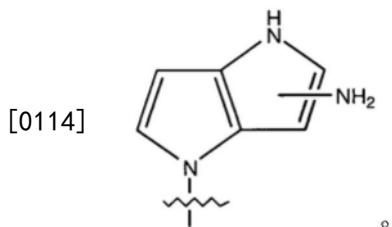
[0109] 在一些实施方案中,W为如下所述的氨基取代的1,4,5,6-四氢环-戊[b]吡咯:



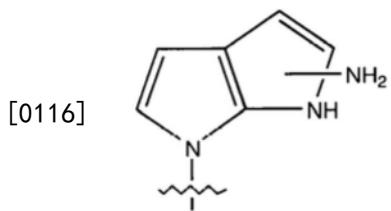
[0111] 在一些实施方案中,W为如下所述的氨基取代的1,3a,4,6a-四氢吡咯并-[3,2-b]吡咯:



[0113] 在一些实施方案中,W为如下所述的氨基取代的1,4-二氢吡咯并-[3,2-b]吡咯:

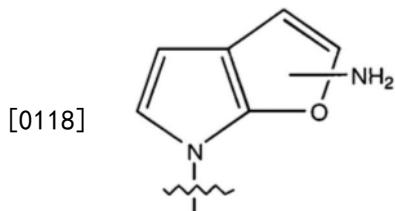


[0115] 在一些实施方案中,W为如下所述的氨基取代的1,6-二氢吡咯并-[2,3-b]吡咯:



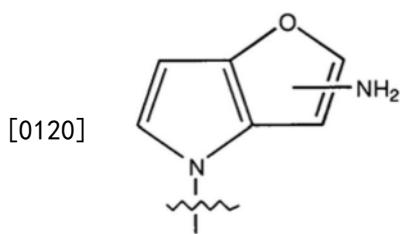
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[0117] 在一些实施方案中,W为如下所述的氨基取代的6H-呋喃并[2,3-b]吡咯:



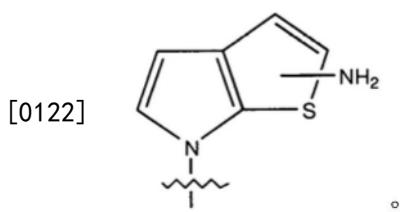
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[0119] 在一些实施方案中,W为如下所述的氨基取代的4H-呋喃并[3,2-b]吡咯:



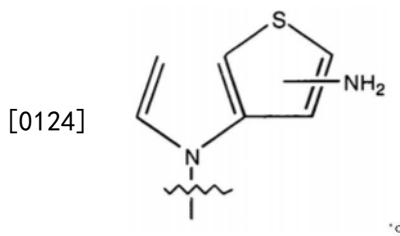
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[0121] 在一些实施方案中,W为如下所述的氨基取代的6H-噻吩并[2,3-b]吡咯:



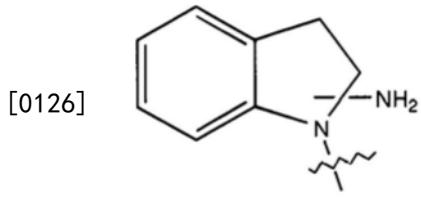
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[0123] 在一些实施方案中,W为如下所述的氨基取代的4H-噻吩并[3,2-b]吡咯:



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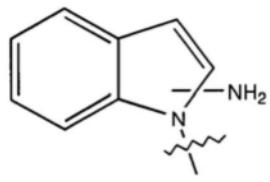
[0125] 在一些实施方案中,W为如下所述的氨基取代的二氢吲哚:



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[0127] 在一些实施方案中,W为如下所述的氨基取代的1H-吲哚:

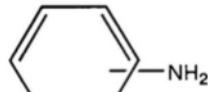
[0128]



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[0129]

在一些实施方案中,W为如下所述的氨基取代的2H-异吲哚:

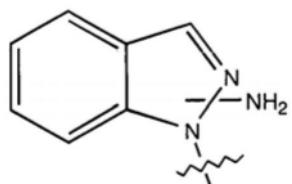


[0130]

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[0131]

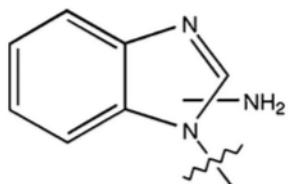
在一些实施方案中,W为如下所述的氨基取代的1H-吲唑:



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[0132]

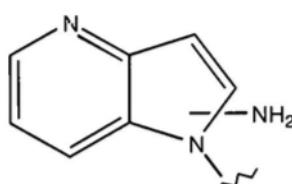
在一些实施方案中,W为如下所述的氨基取代的苯并咪唑:



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[0134]

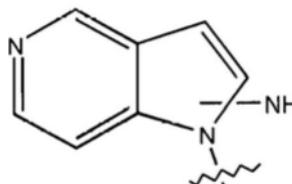
在一些实施方案中,W为如下所述的氨基取代的4-氮杂吲哚:



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[0137]

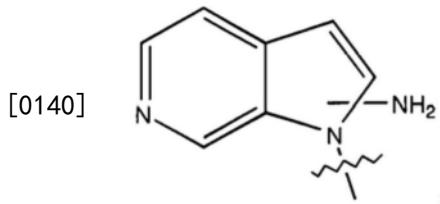
在一些实施方案中,W为如下所述的氨基取代的5-氮杂吲哚:



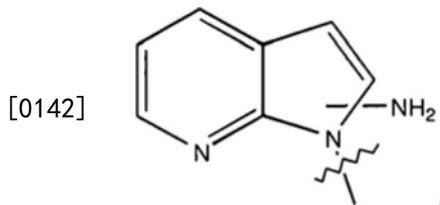
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[0139]

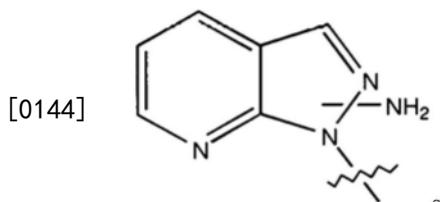
在一些实施方案中,W为如下所述的氨基取代的6-氮杂吲哚:



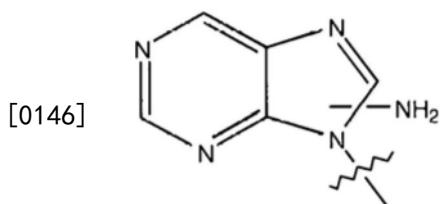
[0141] 在一些实施方案中,W为如下所述的氨基取代的7-氮杂吲哚:



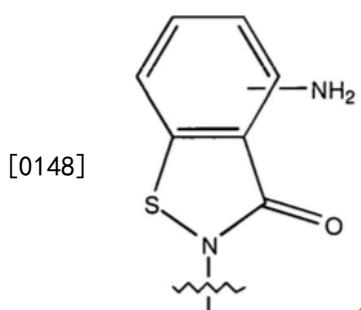
[0143] 在一些实施方案中,W为如下所述的氨基取代的7-氮杂吲唑:



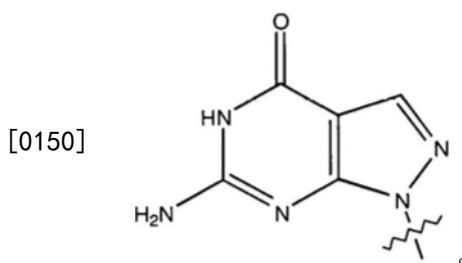
[0145] 在一些实施方案中,W为如下所述的氨基取代的嘌呤:



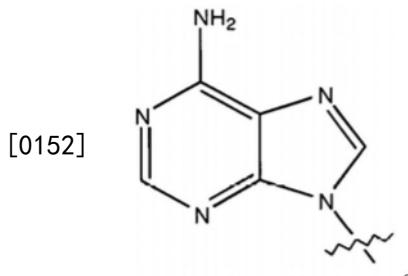
[0147] 在一些实施方案中,W为如下所述的氨基取代的1,2-苯并异噻唑-3(2H)-酮:



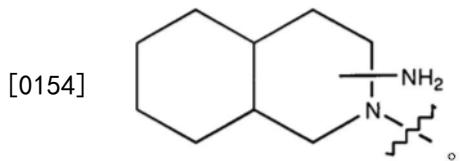
[0149] 在一些实施方案中,W为如下所述的氨基取代的鸟嘌呤:



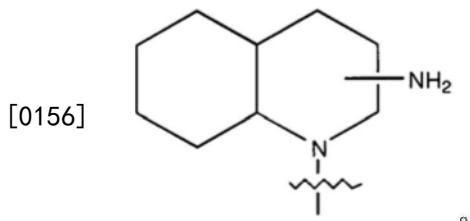
[0151] 在一些实施方案中,W为如下所述的氨基取代的腺嘌呤:



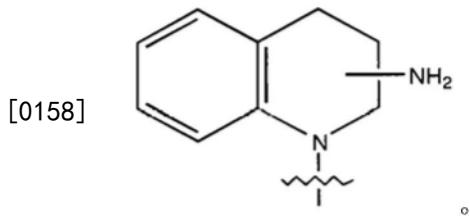
[0153] 在一些实施方案中,W为如下所述的氨基取代的十氢异喹啉:



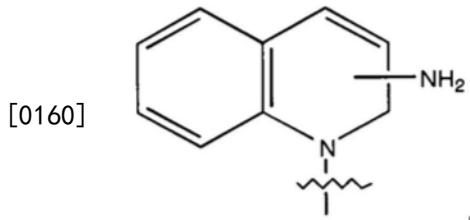
[0155] 在一些实施方案中,W为如下所述的氨基取代的十氢喹啉:



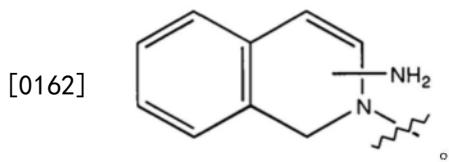
[0157] 在一些实施方案中,W为如下所述的氨基取代的1,2,3,4-四氢喹啉:



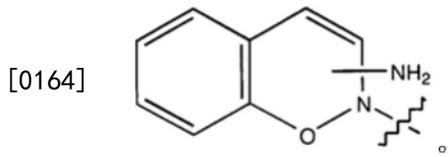
[0159] 在一些实施方案中,W为如下所述的氨基取代的1,2-二氢喹啉:



[0161] 在一些实施方案中,W为如下所述的氨基取代的1,2-二氢异喹啉:

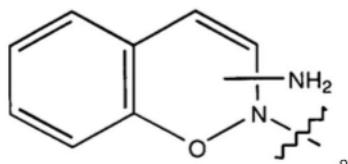


[0163] 在一些实施方案中,W为如下所述的氨基取代的2H-苯并-[e][1,2]𫫇嗪:



[0165] 在一些实施方案中,W为如下所述的氨基取代的喹啉2(1H)-酮:

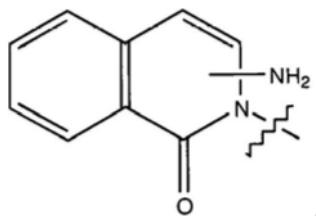
[0166]



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[0167] 在一些实施方案中,W为如下所述的氨基取代的异喹啉1(2H)-酮:

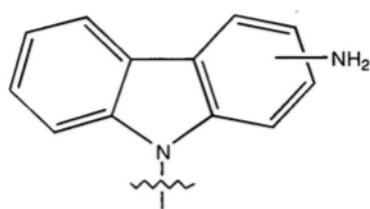
[0168]



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[0169] 在一些实施方案中,W为如下所述的氨基取代的咔唑:

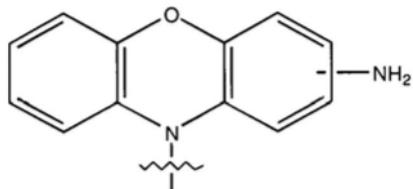
[0170]



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[0171] 在一些实施方案中,W为如下所述的氨基取代的吩噁嗪:

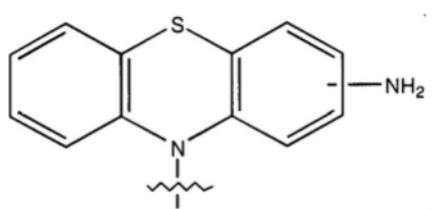
[0172]



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[0173] 在一些实施方案中,W为如下所述的氨基取代的吩噻嗪:

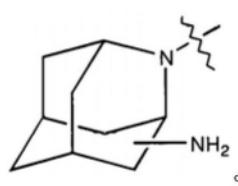
[0174]



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[0175] 在一些实施方案中,W为如下所述的氨基取代的2-氮杂金刚烷:

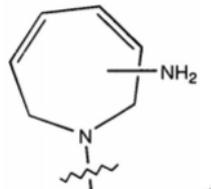
[0176]



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[0177] 在一些实施方案中,W为如下所述的氨基取代的2,3-二氢氮杂卓:

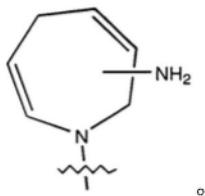
[0178]



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[0179] 在一些实施方案中,W为如下所述的氨基取代的2,5-二氢氮杂卓:

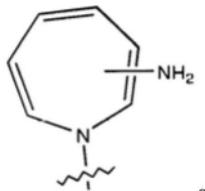
[0180]



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[0181] 在一些实施方案中,W为如下所述的氨基取代的氮杂卓:

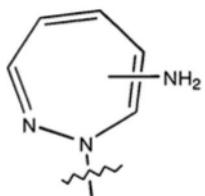
[0182]



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[0183] 在一些实施方案中,W为如下所述的氨基取代的1,2-氮杂卓:

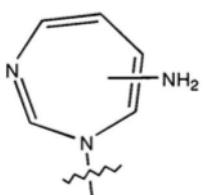
[0184]



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[0185] 在一些实施方案中,W为如下所述的氨基取代的1,3-氮杂卓:

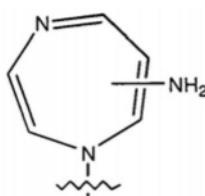
[0186]



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[0187] 在一些实施方案中,W为如下所述的氨基取代的1,4-氮杂卓:

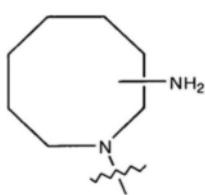
[0188]



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[0189] 在一些实施方案中,W为如下所述的氨基取代的氮杂环辛烷(azocane):

[0190]



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[0191] 在一些实施方案中,W为胍基取代的氮杂环丙烷。在一些实施方案中,W为胍基取代的氮杂环丁烷。在一些实施方案中,W为胍基取代的1,3-氮杂环丁烷。在一些实施方案中,W为胍基取代的氮杂环丁烷-2-酮(β -内酰胺)。在一些实施方案中,W为胍基取代的吡咯烷。在一些实施方案中,W为胍基取代的3-吡咯啉。在一些实施方案中,W为胍基取代的2-吡咯啉。在一些实施方案中,W为胍基取代的1H-吡咯。在一些实施方案中,W为胍基取代的吡唑烷。

[0192] 在一些实施方案中, W为胍基取代的咪唑烷。在一些实施方案中, W为胍基取代的2-吡唑啉。在一些实施方案中, W为胍基取代的2-咪唑啉。在一些实施方案中, W为胍基取代的琥珀酰亚胺。在一些实施方案中, W为胍基取代的乙内酰脲。在一些实施方案中, W为胍基取代的2,4-噻唑烷二酮。

[0193] 在一些实施方案中, W为胍基取代的哌啶。在一些实施方案中, W为胍基取代的哌嗪。在一些实施方案中, W为胍基取代的吗啉。在一些实施方案中, W为胍基取代的2H-1,2-噁唑烷。在一些实施方案中, W为胍基取代的4H-1,4-噁唑烷。在一些实施方案中, W为胍基取代的硫代吗啉。

[0194] 在一些实施方案中, W为胍基取代的2H-1,2-噻嗪。在一些实施方案中, W为胍基取代的4H-1,4-噻嗪。在一些实施方案中, W为胍基取代的硫代吗啉二氧化物。在一些实施方案中, W为胍基取代的1,4,5,6-四氢环-戊[b]吡咯。在一些实施方案中, W为胍基取代的1,3a,4,6a-四氢吡咯并-[3,2-b]吡咯。在一些实施方案中, W为胍基取代的1,4-二氢吡咯并-[3,2-b]吡咯。

[0195] 在一些实施方案中, W为胍基取代的1,6-二氢吡咯并-[2,3-b]吡咯。在一些实施方案中, W为胍基取代的6H-呋喃并[2,3-b]吡咯。在一些实施方案中, W为胍基取代的4H-呋喃并[3,2-b]吡咯。在一些实施方案中, W为胍基取代的6H-噻吩并[2,3-b]吡咯。在一些实施方案中, W为胍基取代的4H-噻吩并[3,2-b]吡咯。在一些实施方案中, W为胍基取代的二氢吲哚。

[0196] 在一些实施方案中, W为胍基取代的1H-吲哚。在一些实施方案中, W为胍基取代的2H-异吲哚。在一些实施方案中, W为胍基取代的1H-吲唑。在一些实施方案中, W为胍基取代的苯并咪唑。在一些实施方案中, W为胍基取代的4-氮杂吲哚。在一些实施方案中, W为胍基取代的5-氮杂吲哚。

[0197] 在一些实施方案中, W为胍基取代的6-氮杂吲哚。在一些实施方案中, W为胍基取代的7-氮杂吲哚。在一些实施方案中, W为胍基取代的7-氮杂吲唑。在一些实施方案中, W为胍基取代的嘌呤。在一些实施方案中, W为胍基取代的1,2-苯并异噻唑-3(2H)-酮。

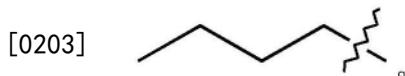
[0198] 在一些实施方案中, W为胍基取代的鸟嘌呤。在一些实施方案中, W为胍基取代的腺嘌呤。在一些实施方案中, W为胍基取代的十氢异喹啉。在一些实施方案中, W为胍基取代的十氢喹啉。在一些实施方案中, W为胍基取代的1,2,3,4-四氢喹啉。在一些实施方案中, W为胍基取代的1,2-二氢喹啉。

[0199] 在一些实施方案中, W为胍基取代的1,2-二氢异喹啉。在一些实施方案中, W为胍基取代的2H-苯并-[e][1,2]噁嗪。在一些实施方案中, W为胍基取代的喹啉2(1H)-酮。在一些实施方案中, W为胍基取代的异喹啉1(2H)-酮。在一些实施方案中, W为胍基取代的咔唑。在一些实施方案中, W为胍基取代的吩噁嗪。

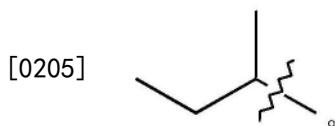
[0200] 在一些实施方案中, W为胍基取代的吩噻嗪。在一些实施方案中, W为胍基取代的2-氮杂金刚烷。在一些实施方案中, W为胍基取代的2,3-二氢氮杂卓。在一些实施方案中, W为胍基取代的2,5-二氢氮杂卓。在一些实施方案中, W为胍基取代的氮杂卓。在一些实施方案中, W为胍基取代的1,2-氮杂卓。

[0201] 在一些实施方案中, W为胍基取代的1,3-氮杂卓。在一些实施方案中, W为胍基取代的1,4-氮杂卓。在一些实施方案中, W为胍基取代的氮杂环辛烷。

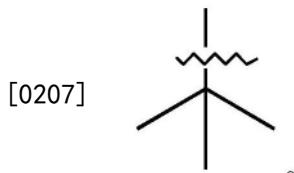
[0202] 在一些实施方案中,X和/或Z为直链烷基链。在一些实施方案中,直链烷基链为:



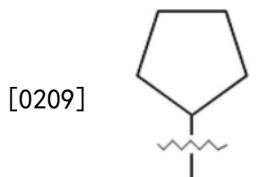
[0204] 在一些实施方案中,X和/或Z为支链烷基链。在一些实施方案中,支链烷基链为:



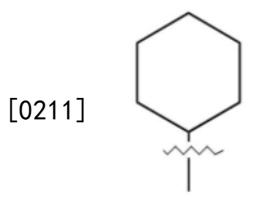
[0206] 在一些实施方案中,X和/或Z为支链烷基链。在一些实施方案中,支链烷基链为:



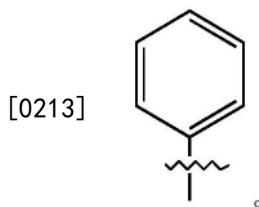
[0208] 在一些实施方案中,X和/或Z为环烷基。在一些实施方案中,环烷基为:



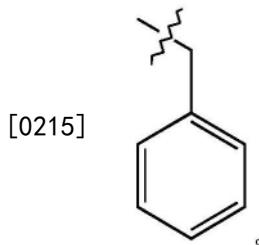
[0210] 在一些实施方案中,X和/或Z为环烷基。在一些实施方案中,环烷基为:



[0212] 在一些实施方案中,X和/或Z为芳基。在一些实施方案中,芳基为:



[0214] 在一些实施方案中,X和/或Z为苄基。在一些实施方案中,苄基为:

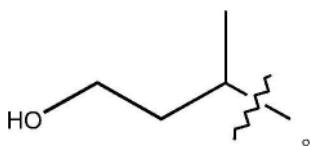


[0216] 在一些实施方案中,X和/或Z为直链烷醇。在一些实施方案中,直链烷醇为:



[0218] 在一些实施方案中,X和/或Z为支链烷醇。在一些实施方案中,支链烷醇为:

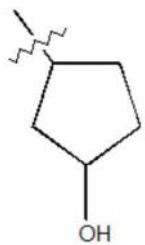
[0219]



[0220]

在一些实施方案中,X和/或Z为环烷醇。在一些实施方案中,环烷醇为:

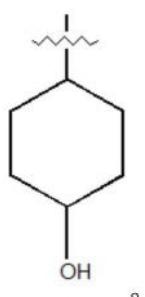
[0221]



[0222]

在一些实施方案中,X和/或Z为环烷醇。在一些实施方案中,环烷醇为:

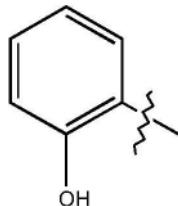
[0223]



[0224]

在一些实施方案中,X和/或Z为酚(phenolic)。在一些实施方案中,酚为:

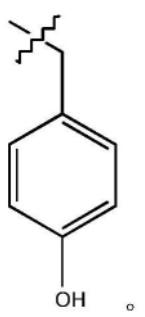
[0225]



[0226]

在一些实施方案中,X和/或Z为4-羟基苄基。在一些实施方案中,4-羟基苄基为:

[0227]



[0228]

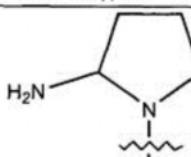
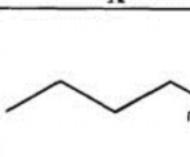
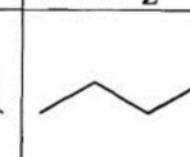
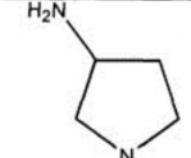
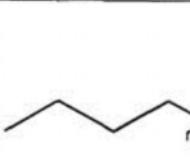
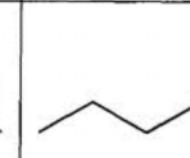
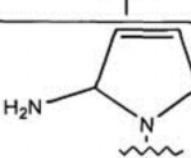
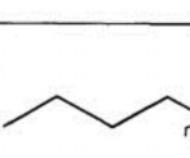
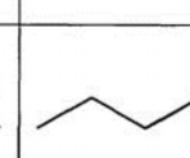
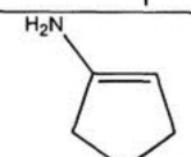
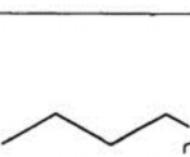
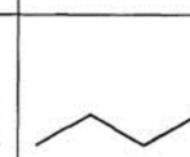
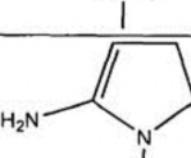
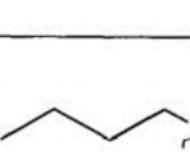
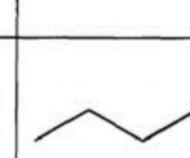
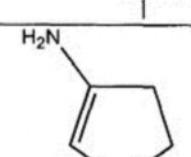
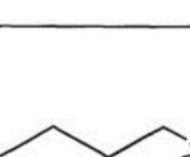
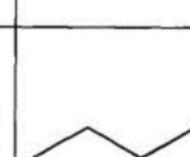
本公开还提供表1中描述的化合物。如本文所使用,术语“Cmpd”是指式(I)化合物或其药学上可接受的盐,其中W、X、Z、A和Q被定义为在表1标记为Cmpd 1至Cmpd 2520的行之一中的W、X、Z、A和Q。例如,在本公开或权利要求书中,“如表1中描述的Cmpd 1”具体是指式(I)化合物或其药学上可接受的盐,其中式(I)化合物或其药学上可接受的盐的W、X、Z、A和Q如下所示:

	W	X	Z	A	Q
[0229]				H	O

[0230] 可以通过参考式(II)化合物、表1和实施例1至3中描述的合成方案来制备Cmpd 1至2520。

[0231] 表1

Cmpd	W	X	Z	A	Q
1				H	O
2				H	O
3				H	O
4				H	O
5				H	O
6				H	O
7				H	O

Cmpd	W	X	Z	A	Q
8				H	O
9				H	O
10				H	O
[0233]				H	O
12				H	O
13				H	O

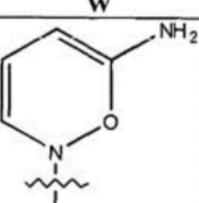
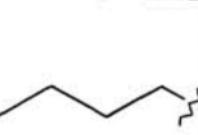
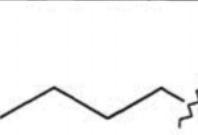
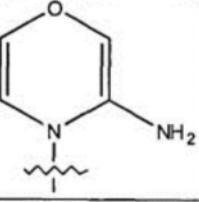
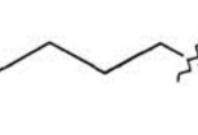
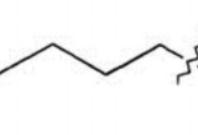
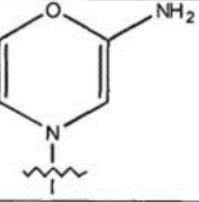
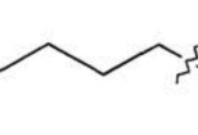
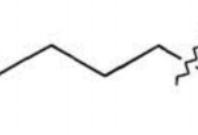
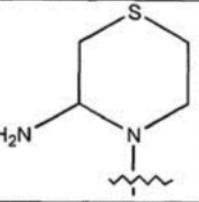
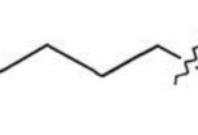
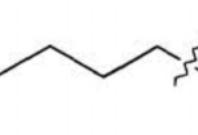
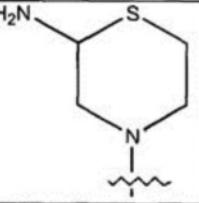
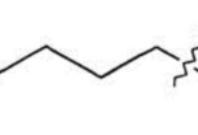
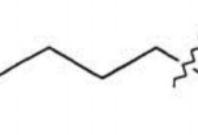
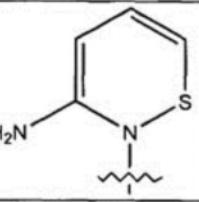
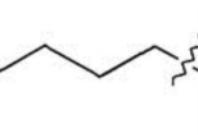
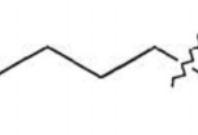
Cmpd	W	X	Z	A	Q
14				H	O
15				H	O
16				H	O
[0234]				H	O
18				H	O
19				H	O

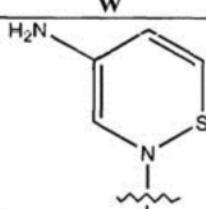
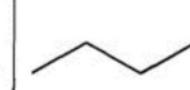
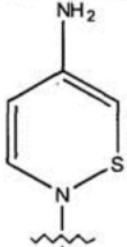
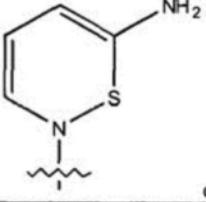
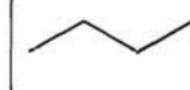
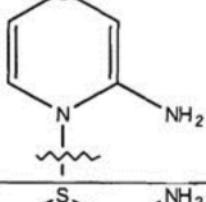
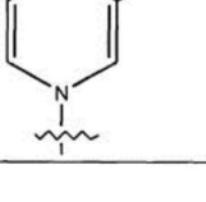
Cmpd	W	X	Z	A	Q
20				H	O
21				H	O
22				H	O
[0235]				H	O
23				H	O
24				H	O
25				H	O

Cmpd	W	X	Z	A	Q
26				H	O
27				H	O
28				H	O
[0236]				H	O
30				H	O
31				H	O

Cmpd	W	X	Z	A	Q
32				H	O
33				H	O
34 [0237]				H	O
35				II	O
36				H	O

Cmpd	W	X	Z	A	Q
37				H	O
38				H	O
39				H	O
[0238]					
40				H	O
41				H	O
42				H	O

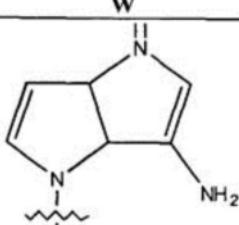
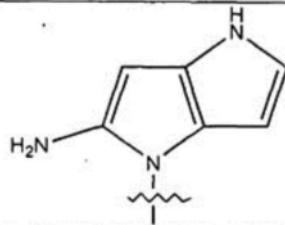
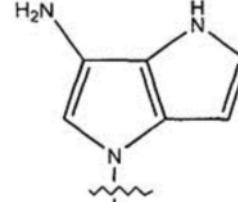
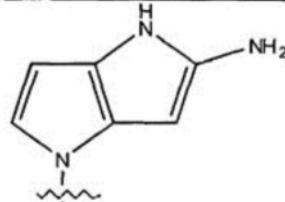
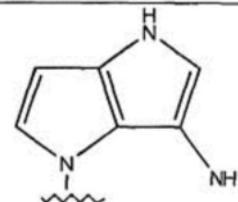
Cmpd	W	X	Z	A	Q
43				H	O
44				H	O
45				H	O
[0239]					
46				H	O
47				H	O
48				H	O

Cmpd	W	X	Z	A	Q
49				H	O
50				H	O
[0240]				H	O
52				H	O
53				H	O

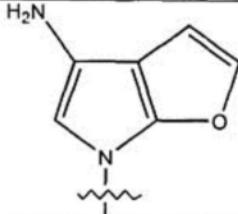
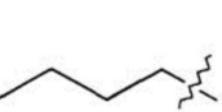
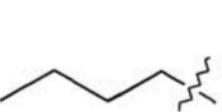
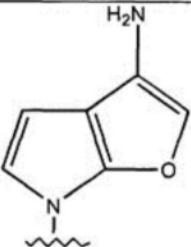
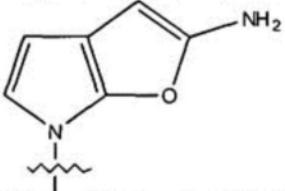
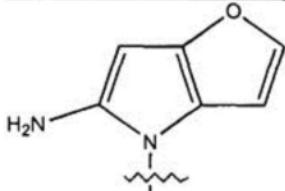
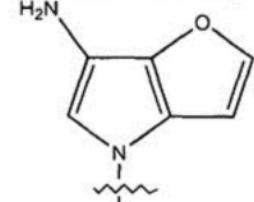
Cmpd	W	X	Z	A	Q
54				H	O
55				H	O
[0241]				H	O
57				H	O
58				H	O

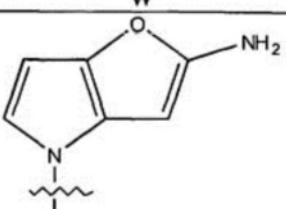
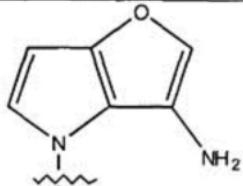
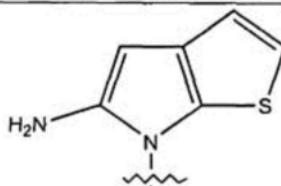
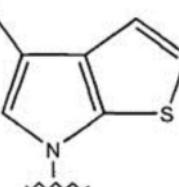
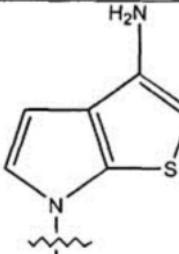
Cmpd	W	X	Z	A	Q
59				H	O
60				H	O
61 [0242]				H	O
62				H	O
63				H	O

[0243]

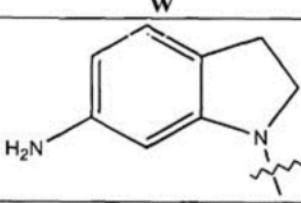
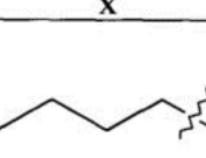
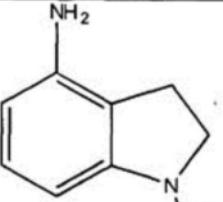
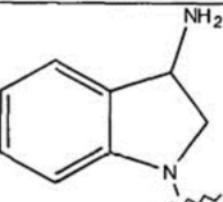
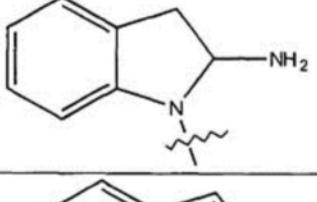
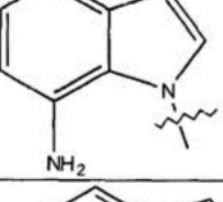
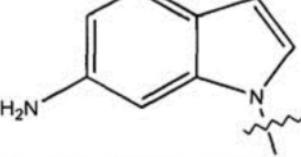
Cmpd	W	X	Z	A	Q
64				H	O
65				H	O
66				H	O
67				H	O
68				H	O

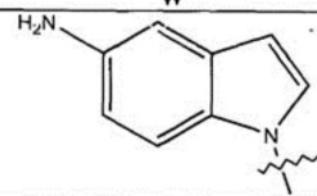
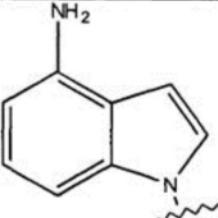
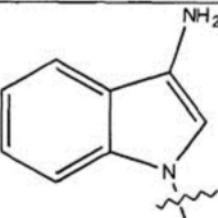
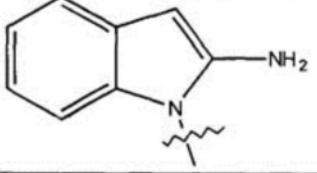
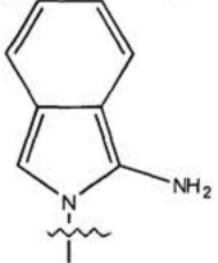
Cmpd	W	X	Z	A	Q
69				H	O
70				H	O
[0244]				H	O
72				H	O
73				H	O

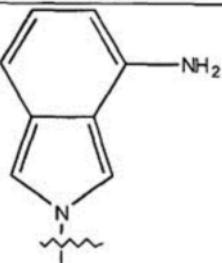
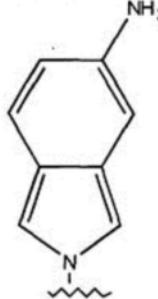
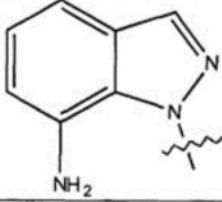
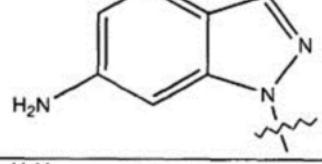
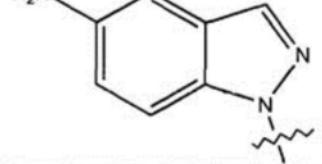
Cmpd	W	X	Z	A	Q
74				H	O
75				H	O
[0245]				H	O
77				H	O
78				H	O

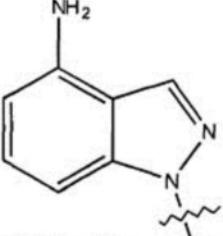
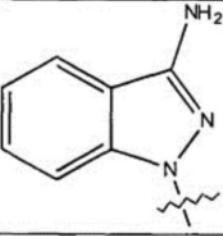
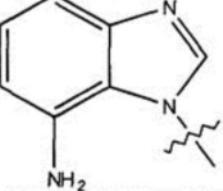
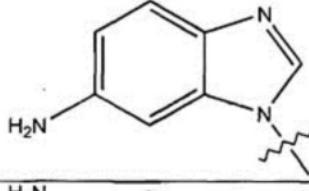
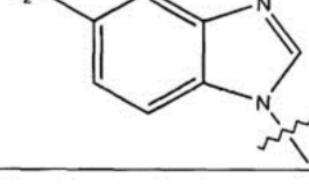
Cmpd	W	X	Z	A	Q
79				H	O
80				H	O
1 [0246]				H	O
82				H	O
83				II	O

Cmpd	W	X	Z	A	Q
84				H	O
85				H	O
86				H	O
[0247]					
87				H	O
88				H	O
89				H	O

Cmpd	W	X	Z	A	Q
90				H	O
91				H	O
92				H	O
[0248]					
93				H	O
94				H	O
95				H	O

Cmpd	W	X	Z	A	Q
96				H	O
97				H	O
98 [0249]				H	O
99				H	O
100				H	O

Cmpd	W	X	Z	A	Q
101				H	O
102				H	O
[0250]					
103				H	O
104				H	O
105				H	O

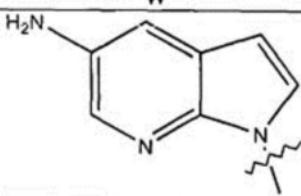
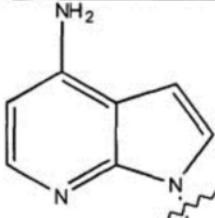
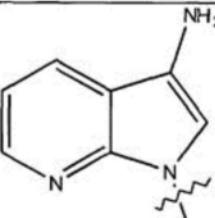
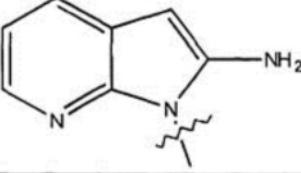
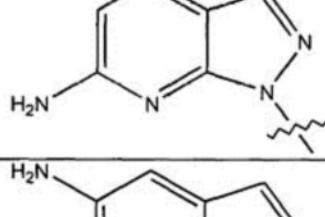
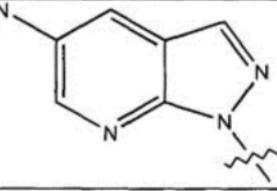
Cmpd	W	X	Z	A	Q
106				H	O
107				H	O
[0251]				H	O
109				H	O
110				H	O

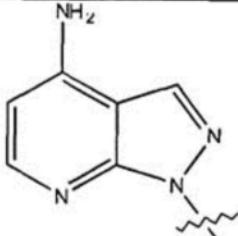
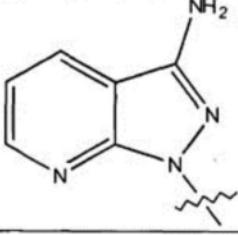
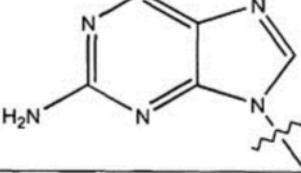
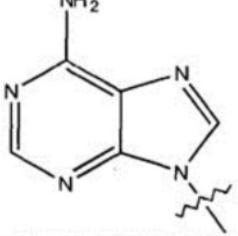
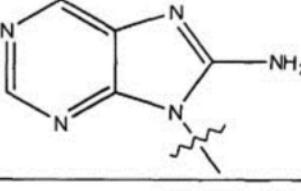
Cmpd	W	X	Z	A	Q
111					O
112				H O	
113				H O	
[0252]					
114				H O	
115				H O	
116				H O	

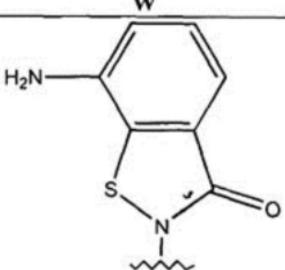
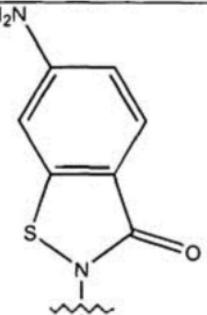
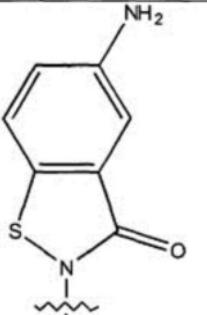
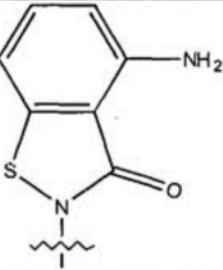
Cmpd	W	X	Z	A	Q
117				H	O
118				H	O
119				H	O
[0253]				H	O
120				H	O
121				H	O
122				H	O

[0254]

Cmpd	W	X	Z	A	Q
123				H	O
124				H	O
125				H	O
126				H	O
127				H	O
128				H	O

Cmpd	W	X	Z	A	Q
129				H	O
130				H	O
131				H	O
[0255]					
132				H	O
133				H	O
134				H	O

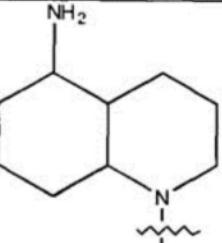
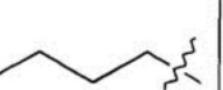
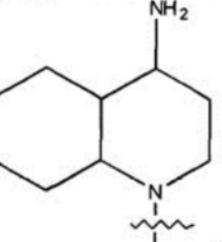
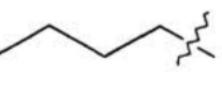
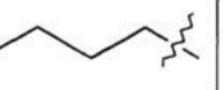
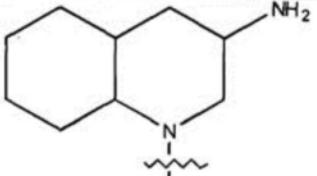
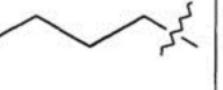
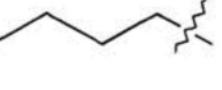
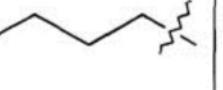
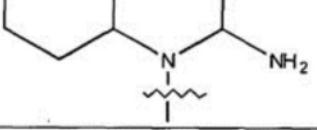
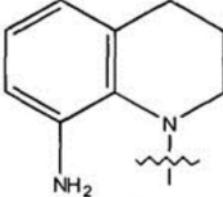
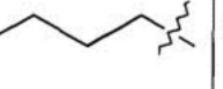
Cmpd	W	X	Z	A	Q
135				H	O
136				H	O
[0256]				H	O
138				H	O
139				H	O

Cmpd	W	X	Z	A	Q
140				H	O
141				H	O
[0257]					
142				H	O
143				H	O

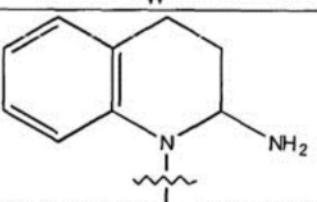
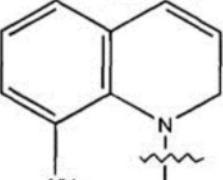
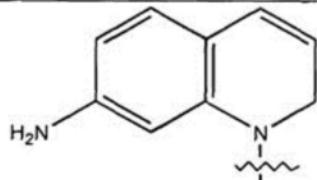
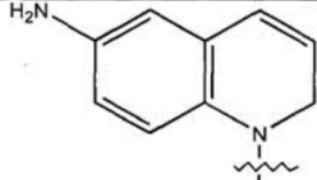
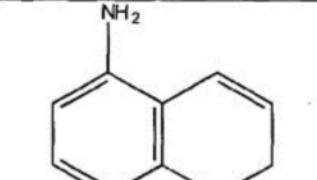
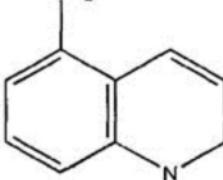
Cmpd	W	X	Z	A	Q
144				H	O
145				H	O
146 [0258]				H	O
147				H	O
148				H	O
149				H	O

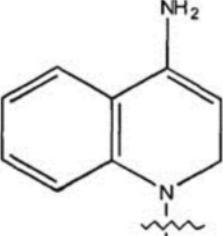
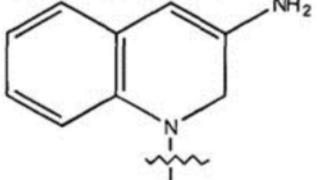
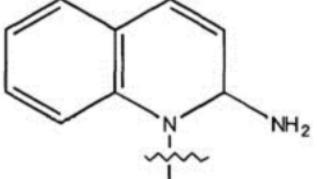
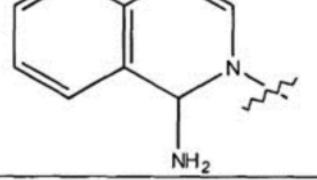
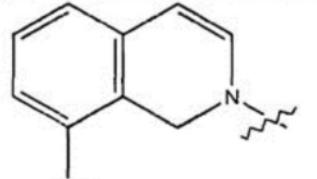
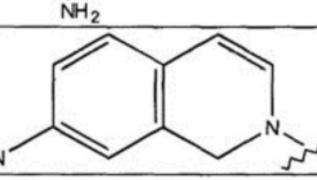
[0259]

Cmpd	W	X	Z	A	Q
150				H	O
151				H	O
152				H	O
153				H	O
154				H	O
155				H	O

Cmpd	W	X	Z	A	Q
156				H	O
157				H	O
[0260]				H	O
158				H	O
159				H	O
160				H	O

Cmpd	W	X	Z	A	Q
161				H	O
162				H	O
[0261]				H	O
163				H	O
164				H	O
165				H	O

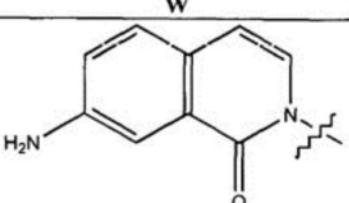
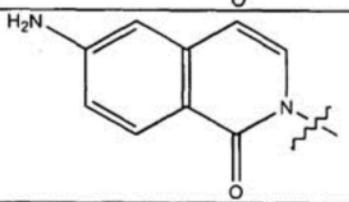
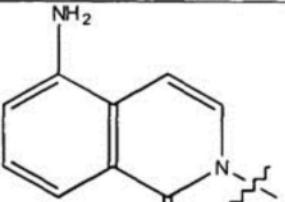
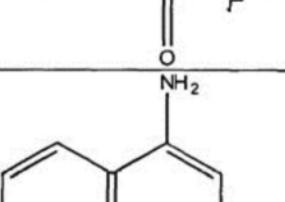
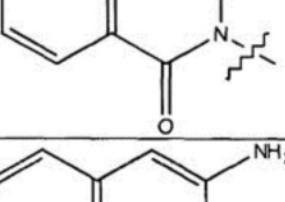
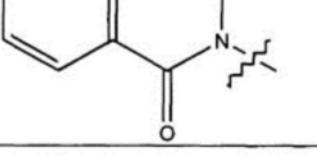
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167				H	O
[0262]				H	O
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169				H	O
170				H	O

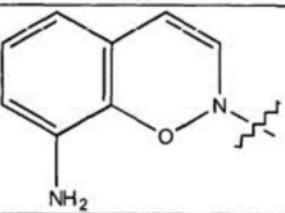
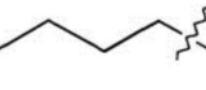
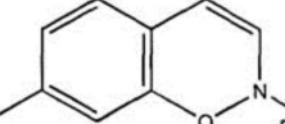
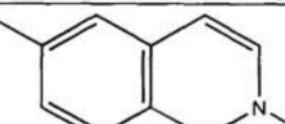
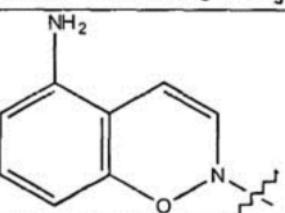
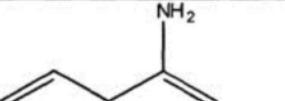
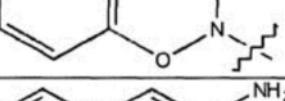
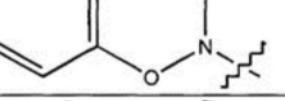
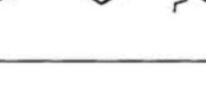
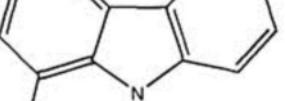
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172				H	O
[0263]				H	O
173				H	O
174				H	O
175				H	O
176				H	O

[0264]

Cmpd	W	X	Z	A	Q
177				H	O
178				H	O
179				H	O
180				H	O
181				H	O
182				H	O

Cmpd	W	X	Z	A	Q
183				H	O
184				H	O
[0265]				H	O
185				H	O
186				H	O
187				H	O

Cmpd	W	X	Z	A	Q
188				H	O
189				H	O
[0266]				H	O
190				H	O
191				H	O
192				H	O

Cmpd	W	X	Z	A	Q
193				H	O
194				H	O
195				H	O
[0267]				H	O
196				H	O
197				H	O
198				H	O
199				H	O

Cmpd	W	X	Z	A	Q
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201				H	O
202				H	O
[0268]					
203				H	O
204				H	O
205				H	O

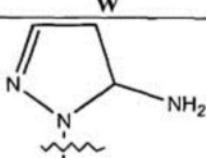
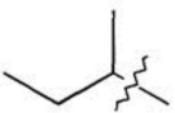
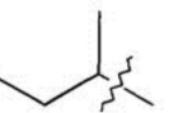
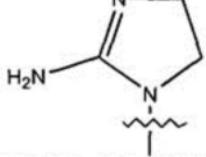
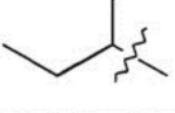
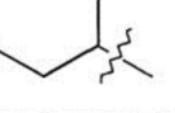
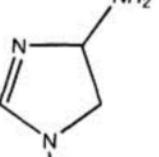
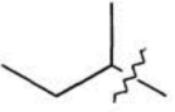
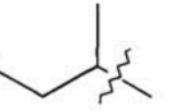
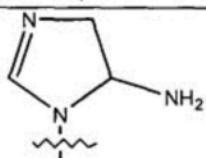
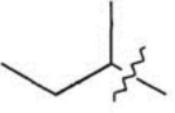
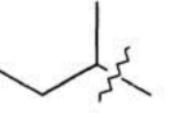
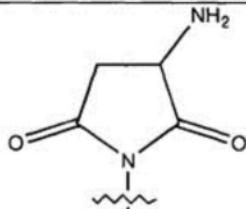
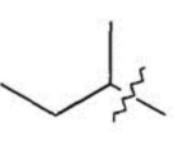
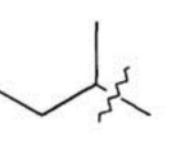
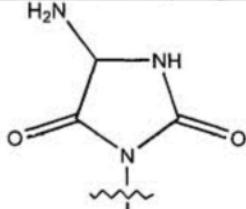
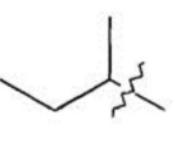
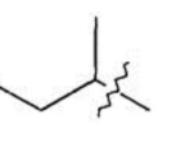
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207				H	O
[0269]				H	O
208				H	O
209				H	O
210				H	O

Cmpd	W	X	Z	A	Q
211				H	O
212				H	O
213				H	O
[0270]					
214				H	O
215				H	O
216				H	O
217				H	O

Cmpd	W	X	Z	A	Q
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219				H	O
220				H	O
[0271]				H	O
221				H	O
222				H	O
223				H	O

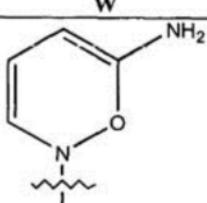
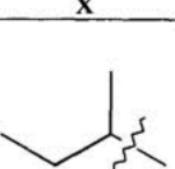
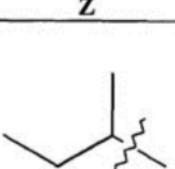
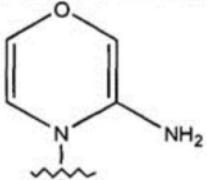
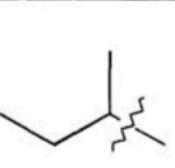
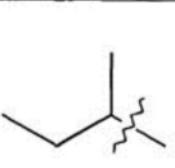
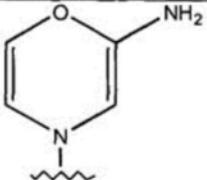
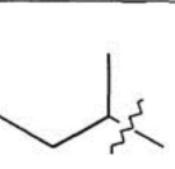
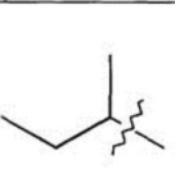
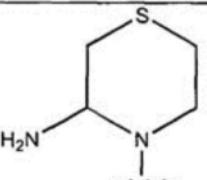
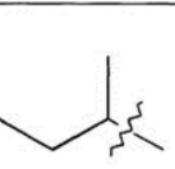
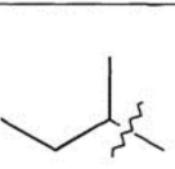
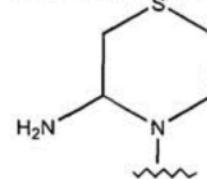
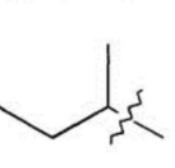
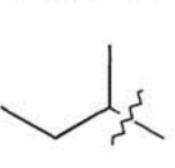
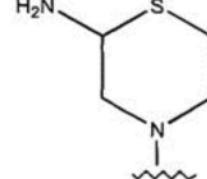
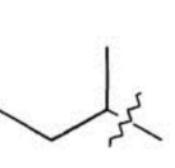
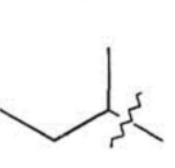
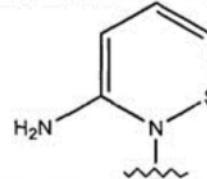
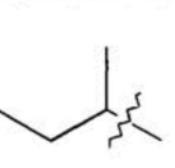
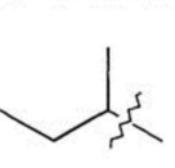
Cmpd	W	X	Z	A	Q
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226				H	O
[0272]				H	O
227				H	O
228				H	O
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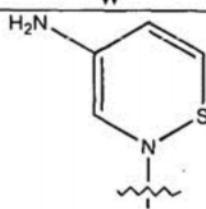
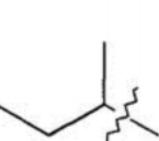
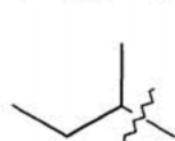
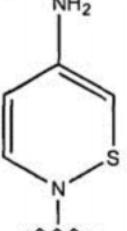
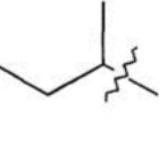
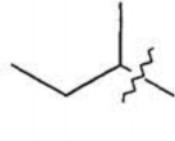
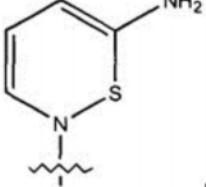
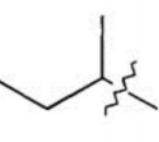
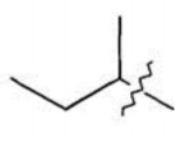
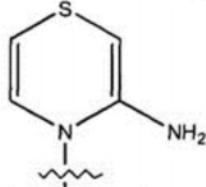
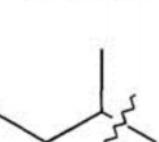
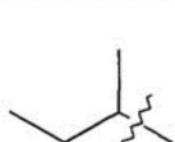
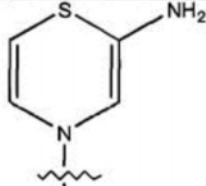
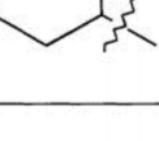
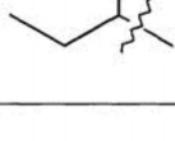
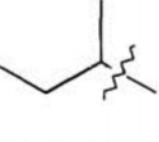
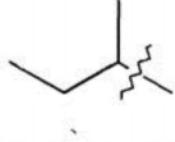
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232				H	O
[0273]					
233				H	O
234				H	O
235				H	O

Cmpd	W	X	Z	A	Q
236				H	O
237				H	O
238				H	O
[0274]					
239				H	O
240				H	O
241				H	O

Cmpd	W	X	Z	A	Q
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243				H	O
[0275]				H	O
244				H	O
245				H	O
246				H	O

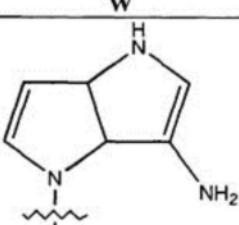
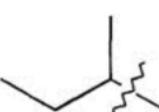
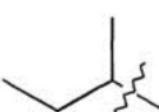
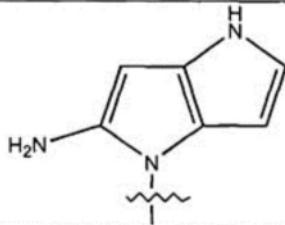
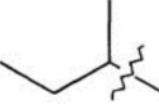
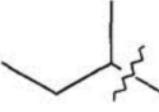
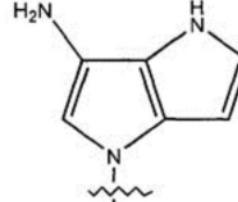
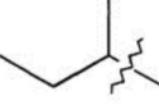
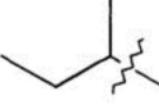
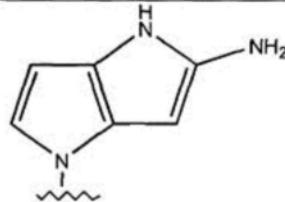
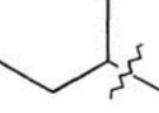
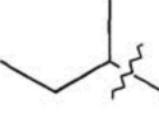
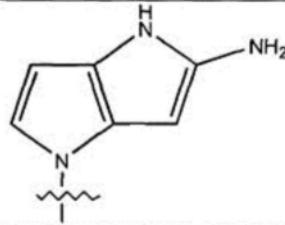
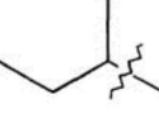
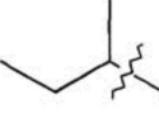
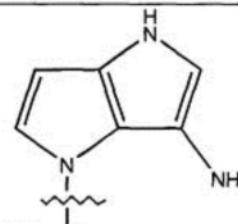
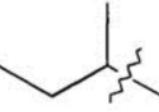
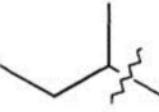
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248				H	O
249				H	O
[0276]					
250				H	O
251				H	O
252				H	O

Cmpd	W	X	Z	A	Q
253				H	O
254				H	O
[0277]				H	O
255				H	O
256				H	O
257				H	O
258				H	O

Cmpd	W	X	Z	A	Q
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260				H	O
[0278]				H	O
261				c	
262				H	O
263					

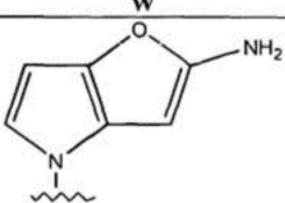
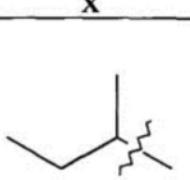
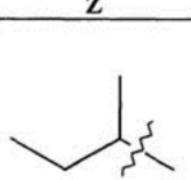
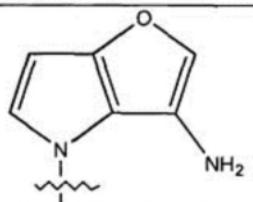
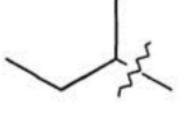
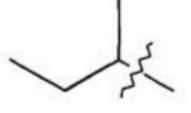
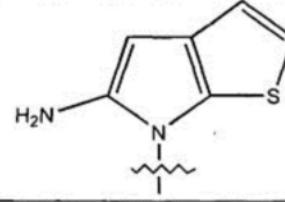
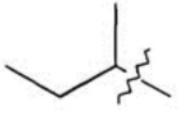
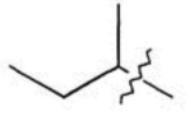
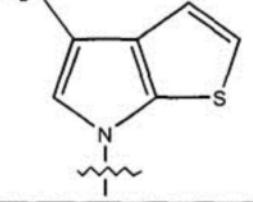
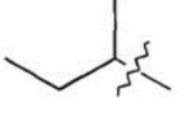
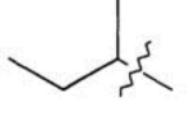
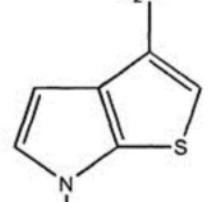
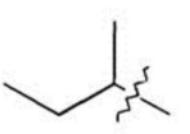
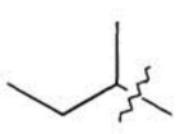
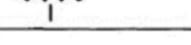
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265				H	O
[0279]					
266				II	O
267				H	O
268				H	O

Cmpd	W	X	Z	A	Q
269				H	O
270				H	O
[0280]				H	O
271				H	O
272				H	O
273				H	O

Cmpd	W	X	Z	A	Q
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275				H	O
[0281]				H	O
276				H	O
277				H	O
278				H	O

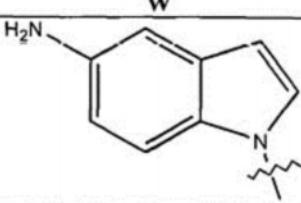
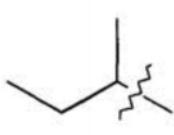
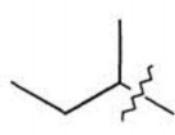
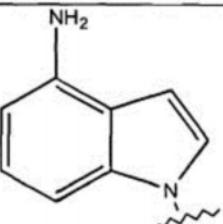
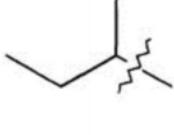
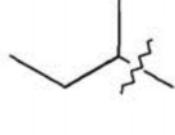
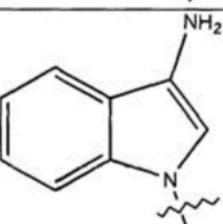
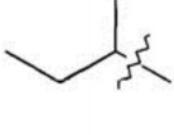
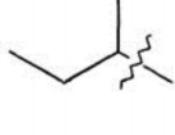
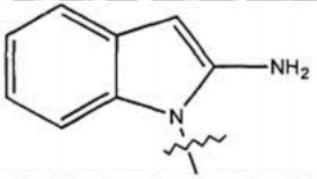
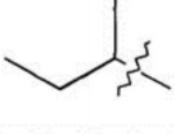
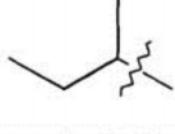
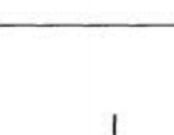
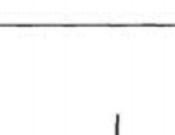
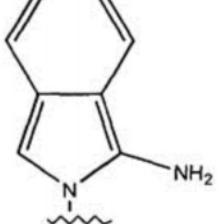
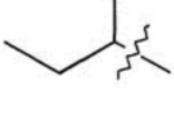
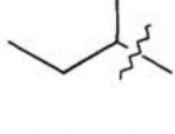
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280				H	O
[0282]				H	O
281				H	O
282				H	O
283				H	O

Cmpd	W	X	Z	A	Q
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285				H	O
[0283]				H	O
286				H	O
287				H	O
288				H	O

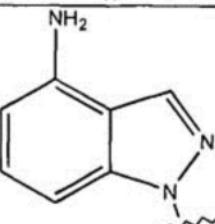
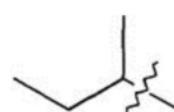
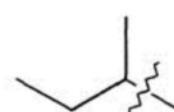
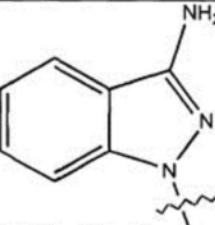
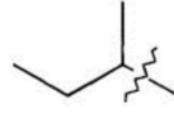
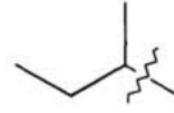
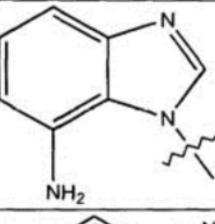
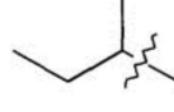
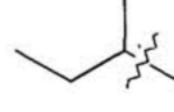
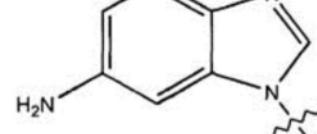
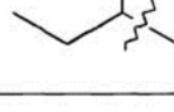
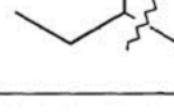
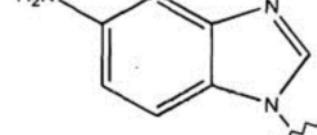
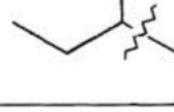
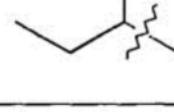
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290				H	O
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291				H	O
292				H	O
293				H	O

Cmpd	W	X	Z	A	Q
294				H	O
295				H	O
[0285]				H	O
296				H	O
297				H	O
298				H	O
299				H	O

Cmpd	W	X	Z	A	Q
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301				H	O
[0286]				H	O
302				H	O
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305				H	O

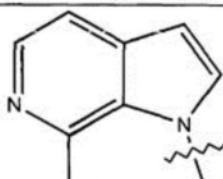
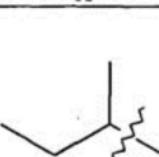
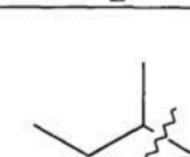
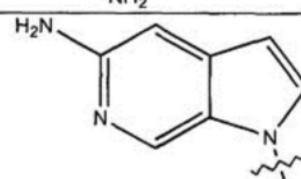
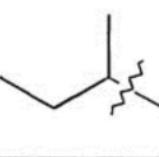
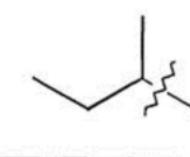
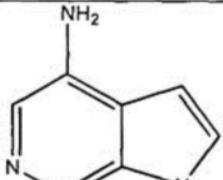
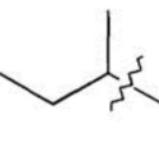
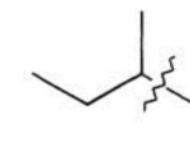
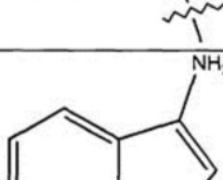
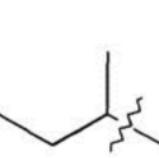
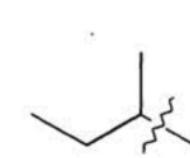
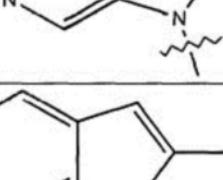
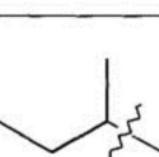
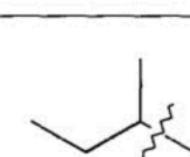
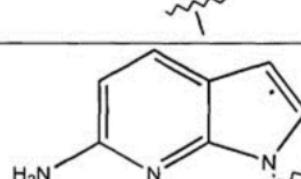
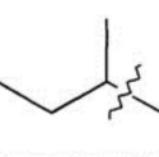
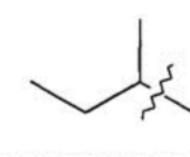
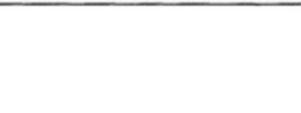
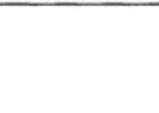
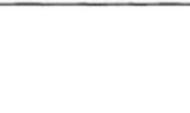
Cmpd	W	X	Z	A	Q
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307				H	O
[0287]				H	O
308				II	O
309				II	O
310				II	O

Cmpd	W	X	Z	A	Q	
311				H	O	
[0288]	312				H	O
	313				H	O
	314				H	O
	315				H	O

Cmpd	W	X	Z	A	Q
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317				H	O
[0289]				H	O
318				H	O
319				H	O
320				H	O

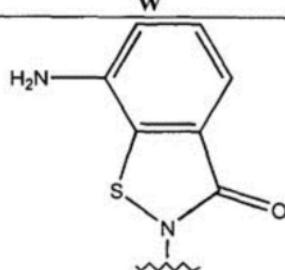
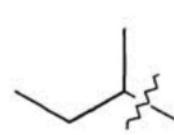
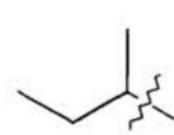
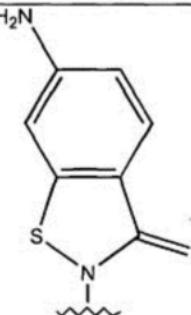
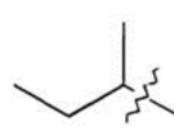
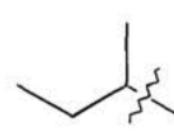
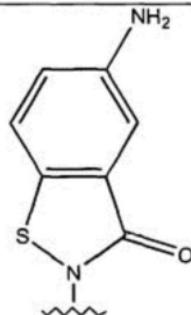
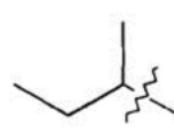
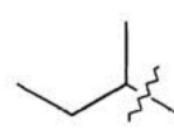
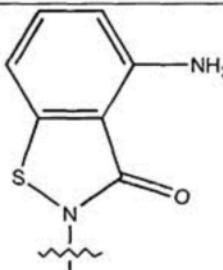
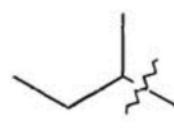
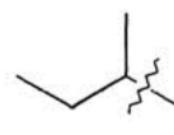
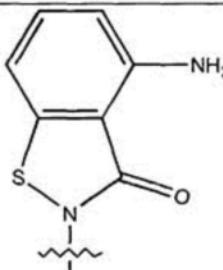
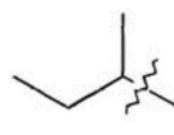
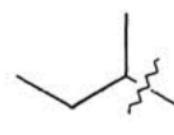
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326				H	O

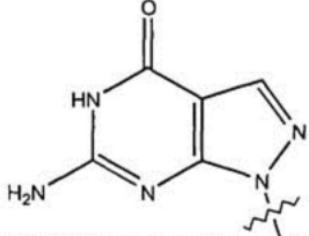
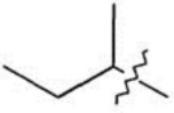
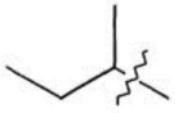
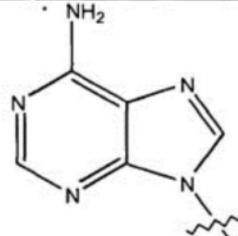
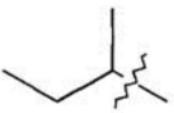
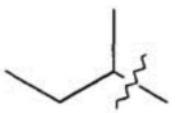
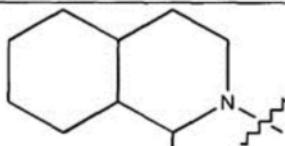
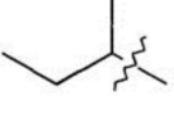
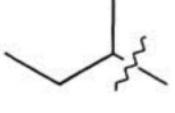
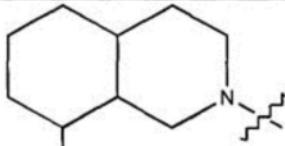
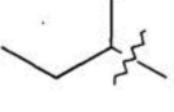
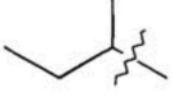
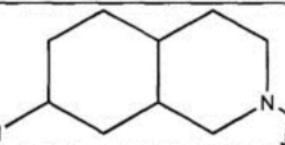
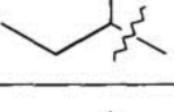
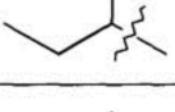
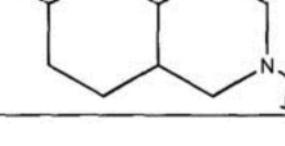
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329				H	O
[0291]				H	O
330				H	O
331				H	O
332				H	O

Cmpd	W	X	Z	A	Q
333				H	O
334				H	O
[0292]				H	O
335				H	O
336				H	O
337				H	O
338				H	O

Cmpd	W	X	Z	A	Q
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[0293]				H	O
341				H	O
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344				H	O

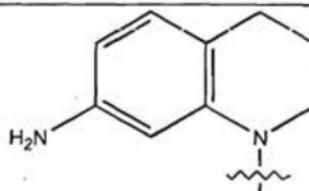
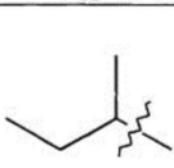
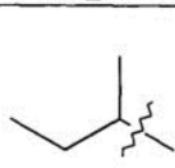
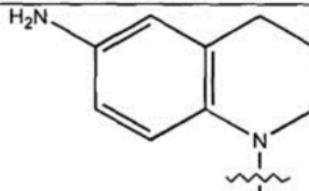
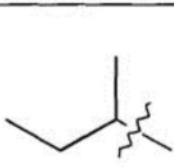
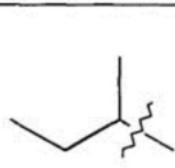
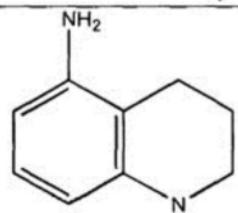
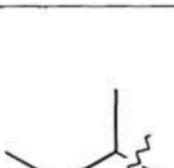
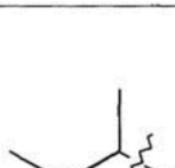
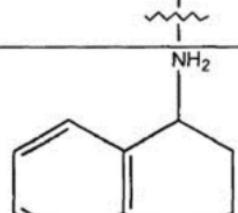
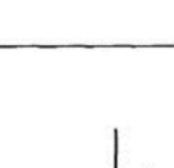
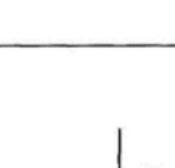
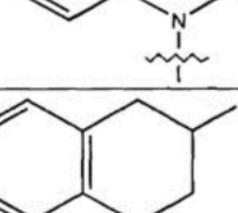
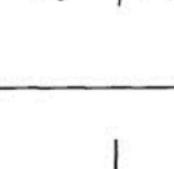
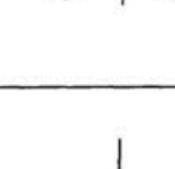
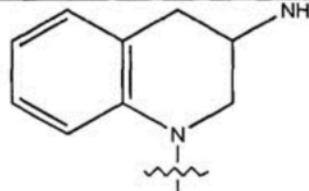
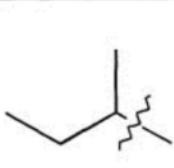
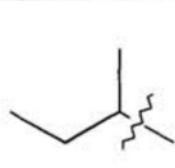
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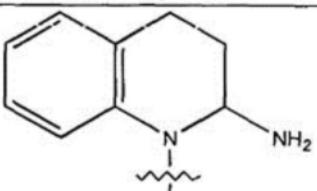
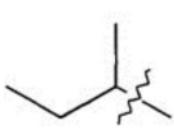
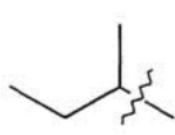
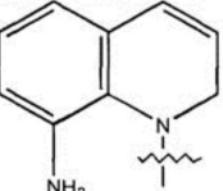
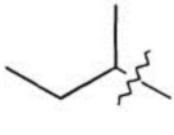
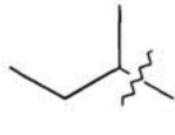
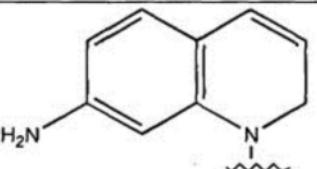
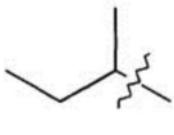
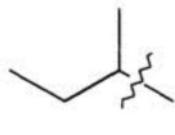
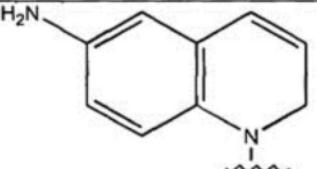
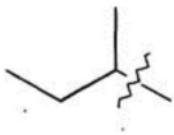
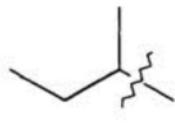
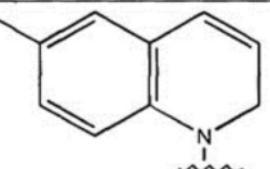
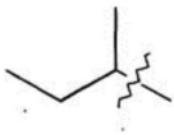
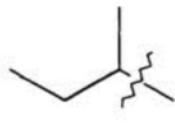
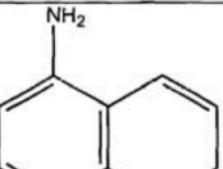
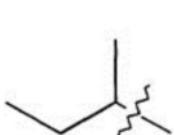
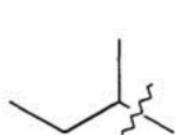
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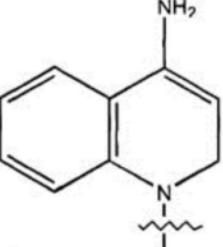
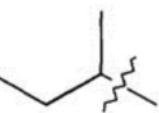
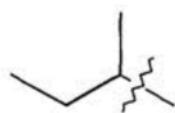
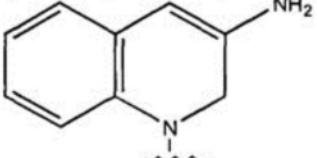
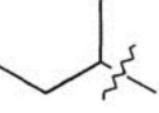
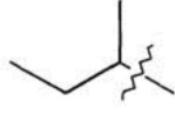
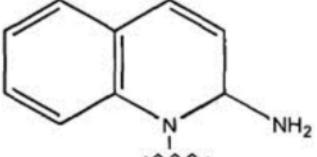
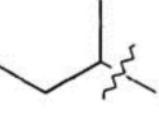
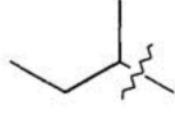
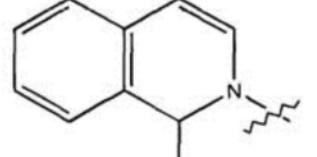
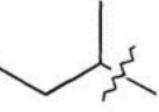
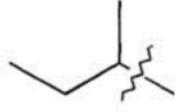
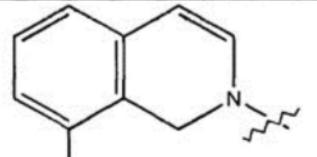
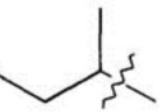
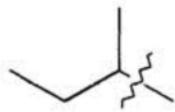
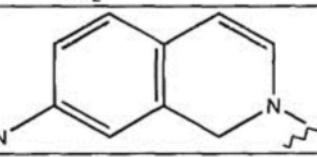
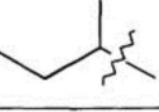
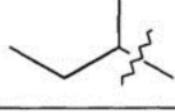
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357				H	O
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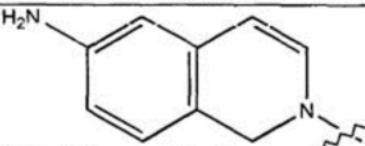
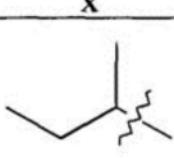
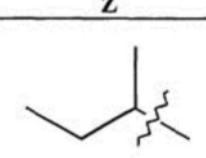
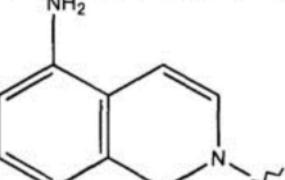
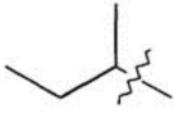
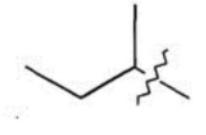
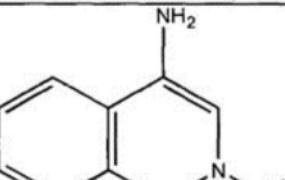
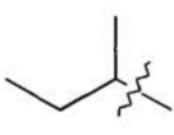
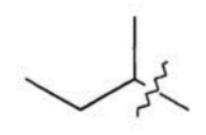
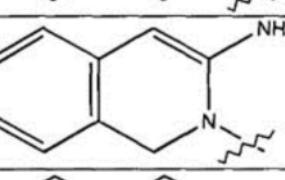
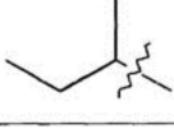
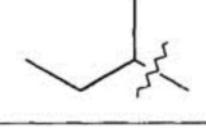
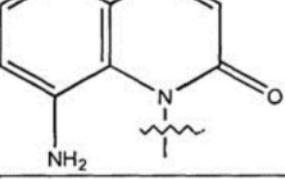
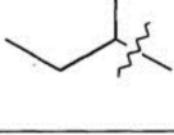
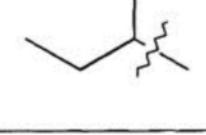
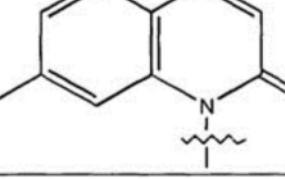
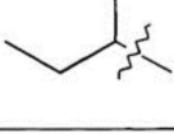
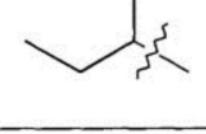
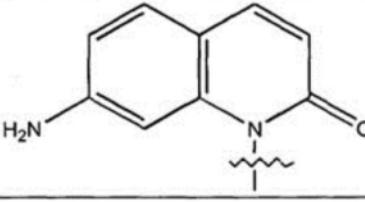
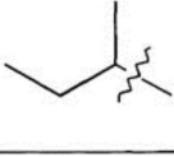
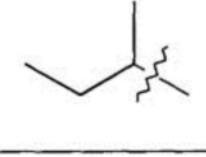
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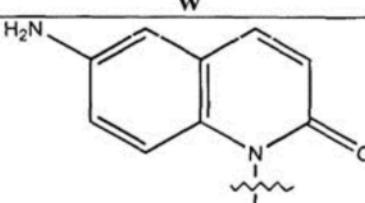
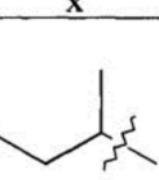
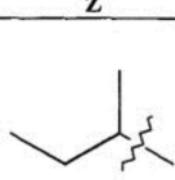
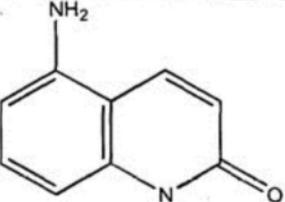
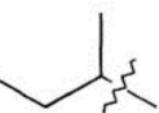
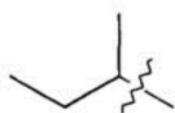
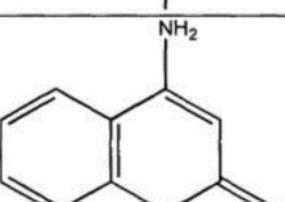
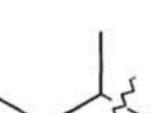
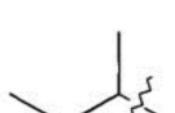
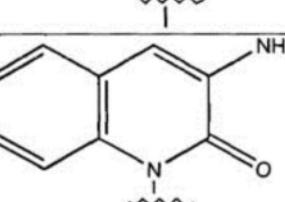
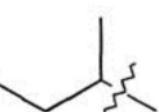
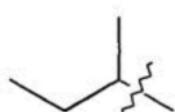
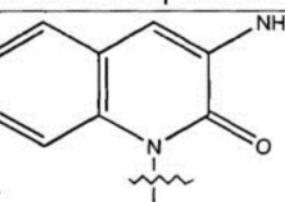
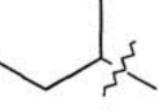
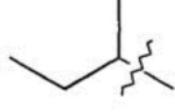
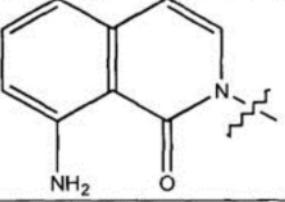
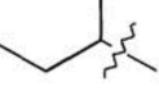
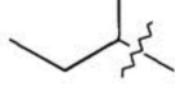
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[0298]				H	O
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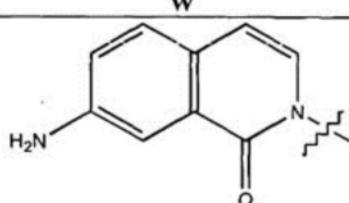
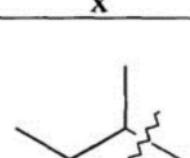
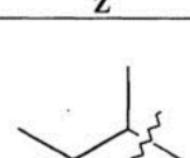
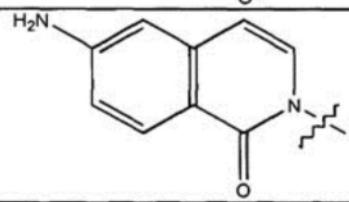
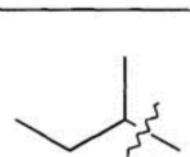
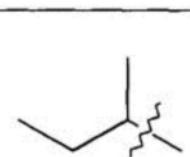
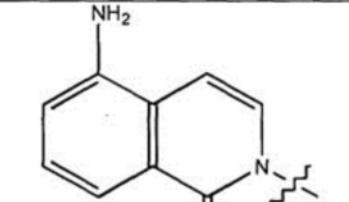
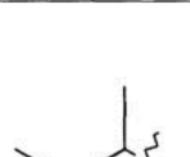
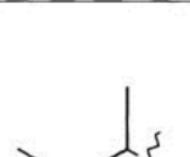
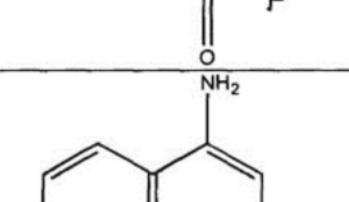
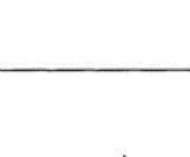
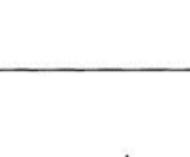
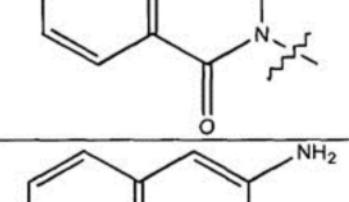
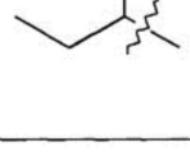
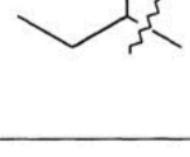
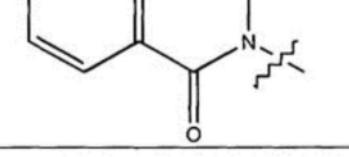
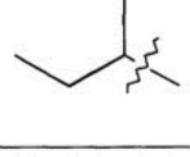
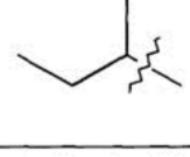
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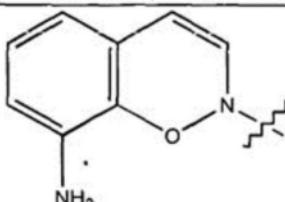
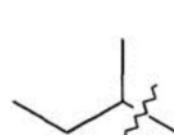
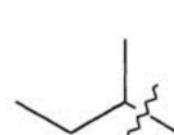
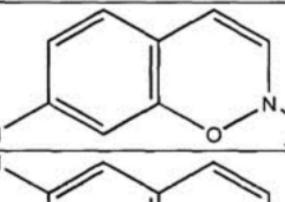
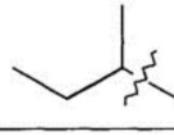
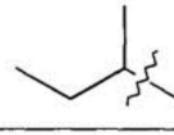
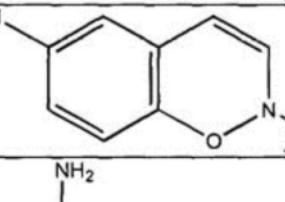
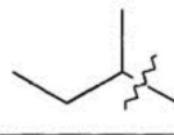
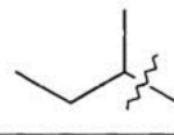
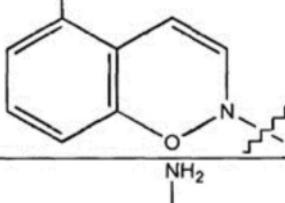
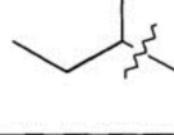
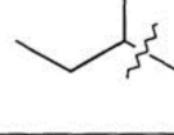
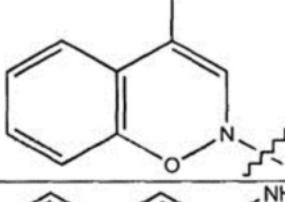
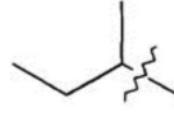
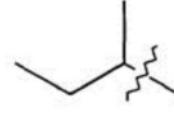
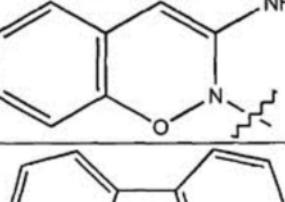
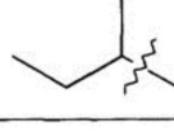
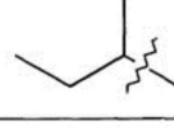
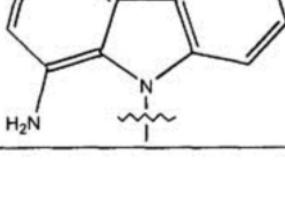
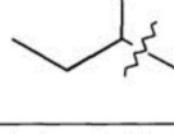
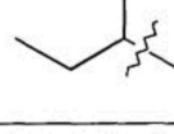
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379				H	O
380				H	O

Cmpd	W	X	Z	A	Q
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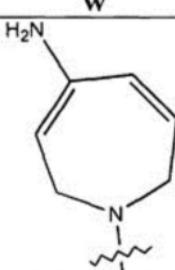
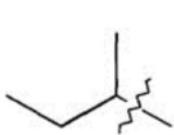
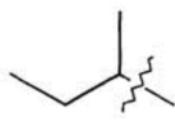
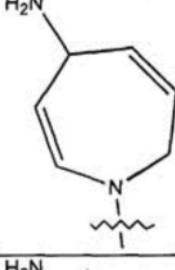
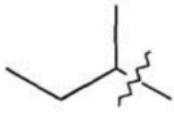
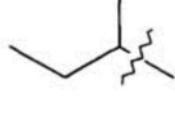
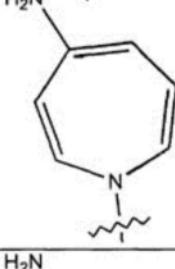
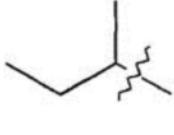
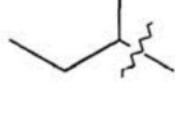
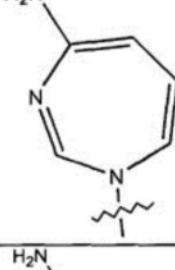
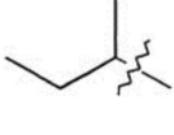
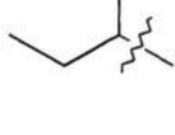
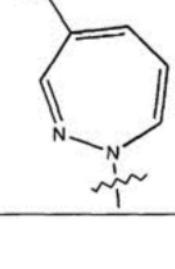
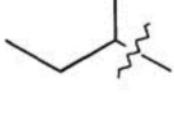
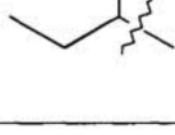
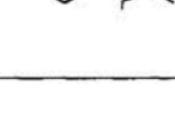
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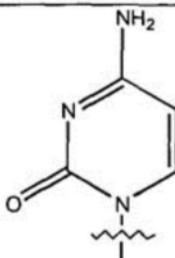
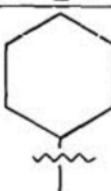
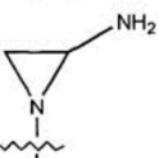
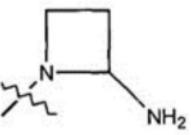
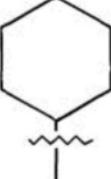
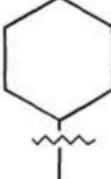
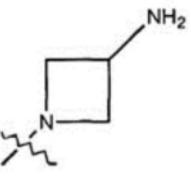
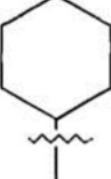
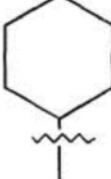
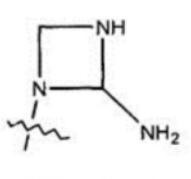
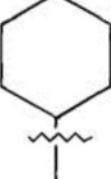
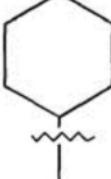
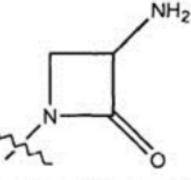
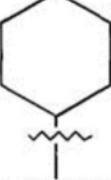
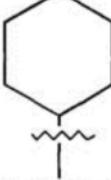
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394				H	O
[0303]				H	O
395				H	O
396				H	O
397				H	O

Cmpd	W	X	Z	A	Q
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399				H	O
[0304]				H	O
400				H	O
401				H	O
402				H	O

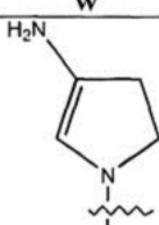
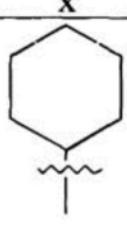
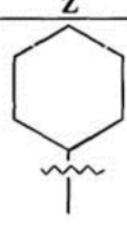
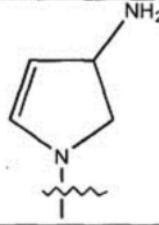
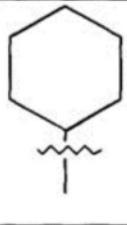
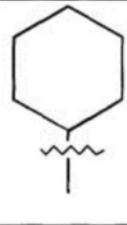
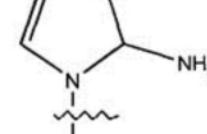
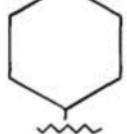
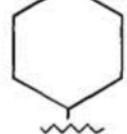
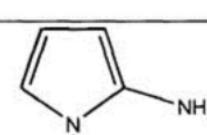
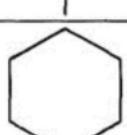
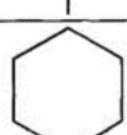
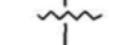
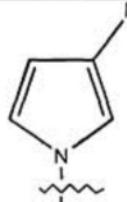
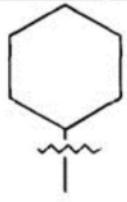
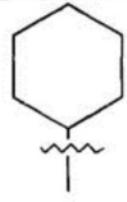
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404				H	O
405				H	O
[0305]				H	O
406				H	O
407				H	O
408				H	O
409				H	O

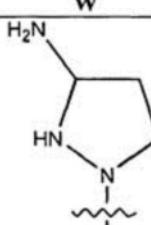
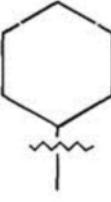
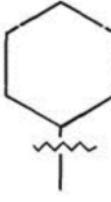
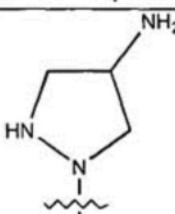
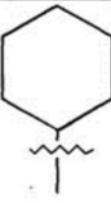
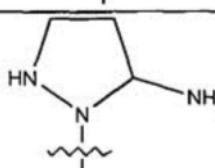
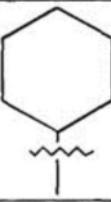
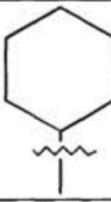
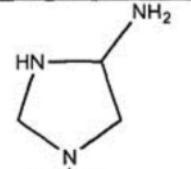
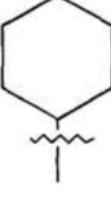
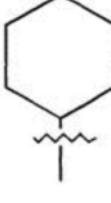
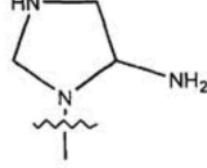
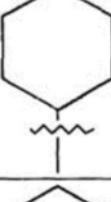
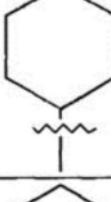
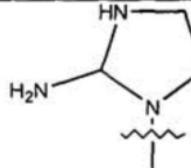
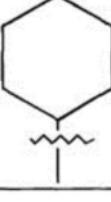
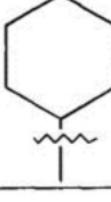
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411				H	O	
[0306]	412				H	O
	413				H	O
	414				H	O
	415				H	O

Cmpd	W	X	Z	A	Q
416				H	O
417				H	O
[0307]				H	O
418				H	O
419				H	O
420				H	O

Cmpd	W	X	Z	A	Q
421				H	O
422				H	O
[0308]				H	O
423				H	O
424				H	O
425				H	O
426				H	O

Cmpd	W	X	Z	A	Q
427				H	O
428				H	O
[0309]				H	O
429				H	O
430				H	O
431				H	O
432				H	O

Cmpd	W	X	Z	A	Q
433				H	O
434				H	O
[0310]				H	O
435				H	O
436				H	O
437				H	O

Cmpd	W	X	Z	A	Q
438				H	O
439				H	O
[0311]				H	O
440				H	O
441				H	O
442				H	O
443				H	O

Cmpd	W	X	Z	A	Q
444				H	O
445				H	O
[0312]				H	O
446				H	O
447				H	O
448				H	O
449				H	O

Cmpd	W	X	Z	A	Q
450				H	O
451				H	O
[0313]				H	O
452				H	O
453				H	O
454				H	O

Cmpd	W	X	Z	A	Q
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456				H	O
[0314]				H	O
457				H	O
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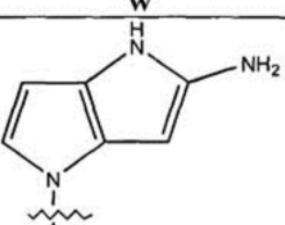
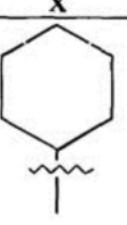
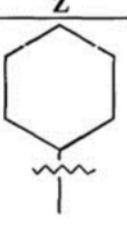
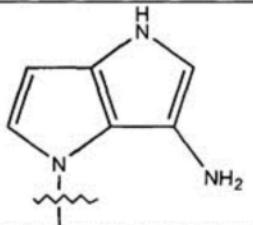
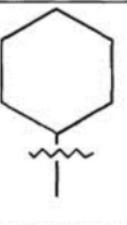
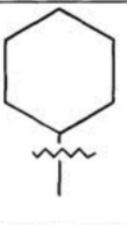
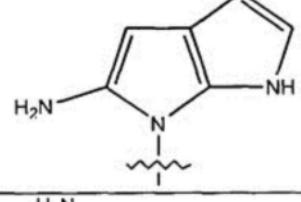
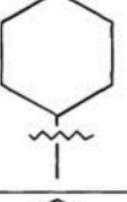
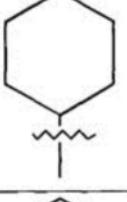
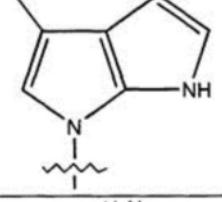
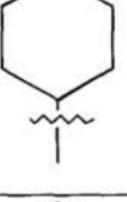
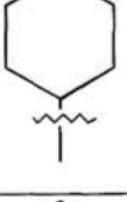
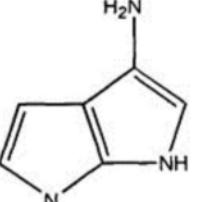
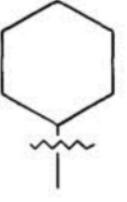
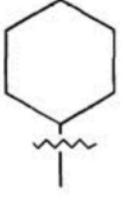
Cmpd	W	X	Z	A	Q
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461				H	O
[0315]				H	O
462				H	O
463				II	O
464				H	O
465				H	O

Cmpd	W	X	Z	A	Q
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467				H	O
468				H	O
[0316]					
469				H	O
470				H	O
471				H	O
	c				

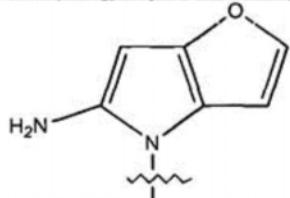
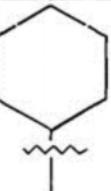
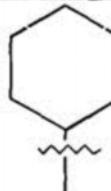
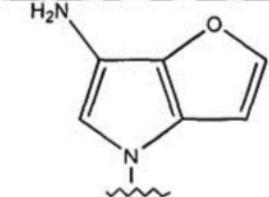
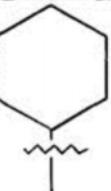
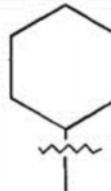
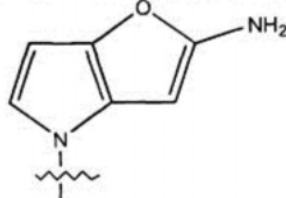
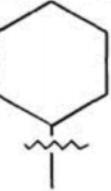
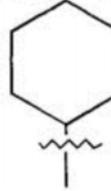
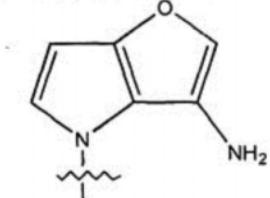
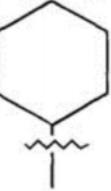
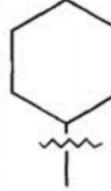
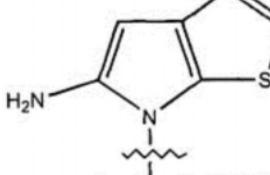
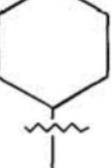
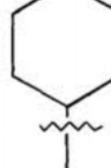
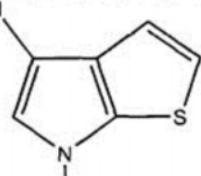
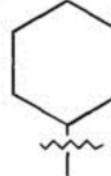
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473				H	O
[0317]				H	O
474				H	O
475				H	O
476				H	O

Cmpd	W	X	Z	A	Q
477				H	O
478				H	O
[0318]					
479				II	O
480				H	O
481				H	O

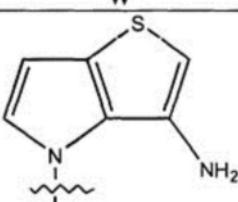
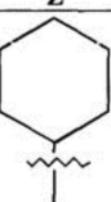
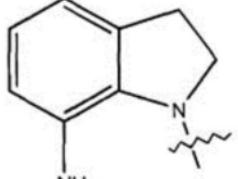
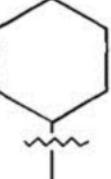
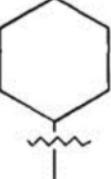
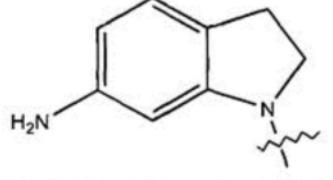
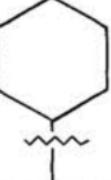
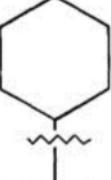
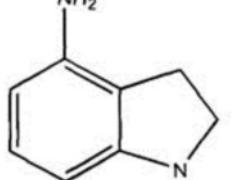
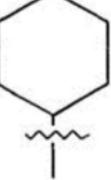
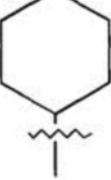
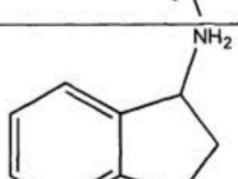
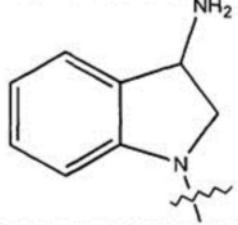
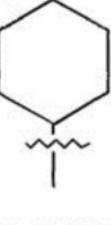
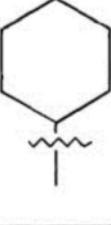
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483				H	O
[0319]				H	O
484				H	O
485				H	O
486				H	O

Cmpd	W	X	Z	A	Q
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488				H	O
[0320]				H	O
489				H	O
490				H	O
491				H	O

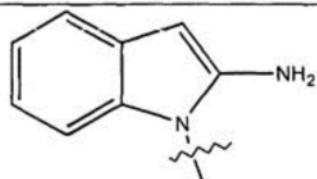
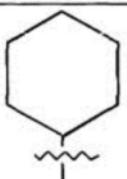
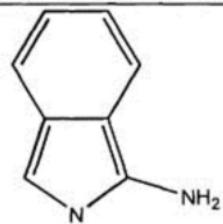
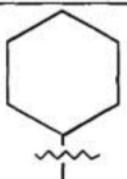
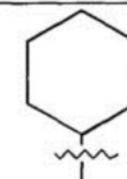
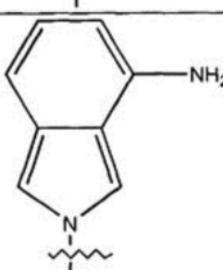
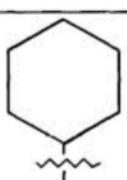
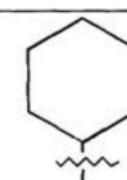
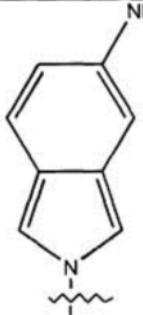
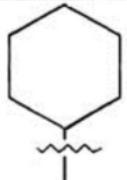
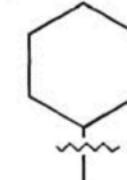
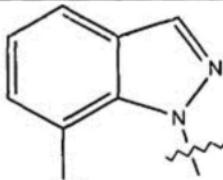
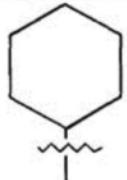
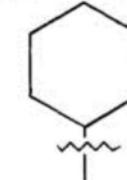
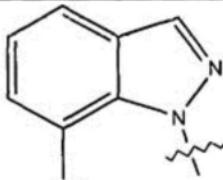
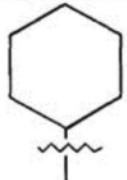
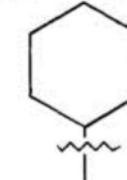
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493				H	O
[0321]				H	O
494				H	O
495				H	O
496				H	O

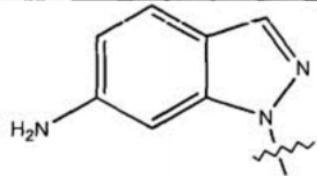
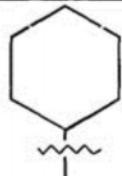
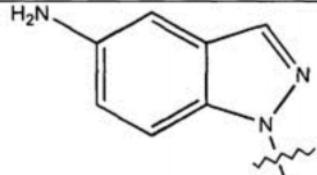
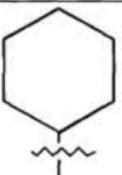
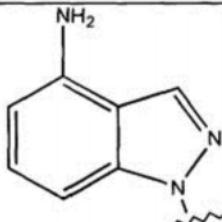
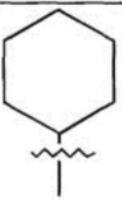
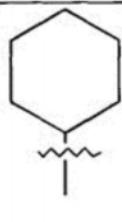
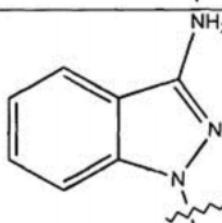
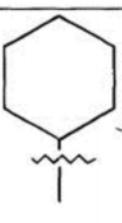
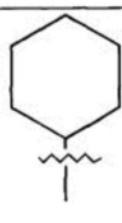
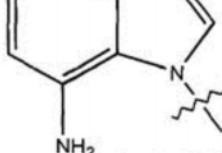
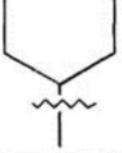
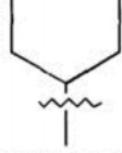
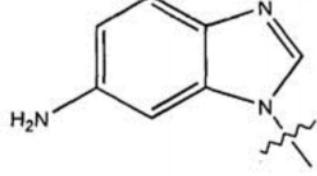
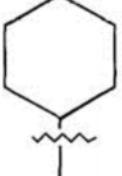
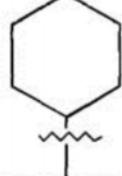
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[0322]				H	O
499				H	O
500				H	O
501				H	O
502				H	O

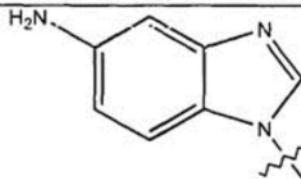
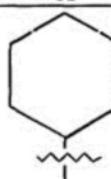
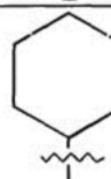
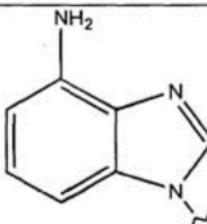
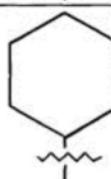
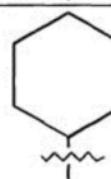
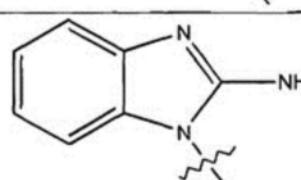
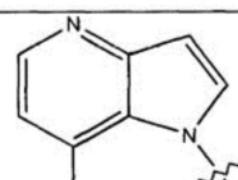
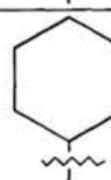
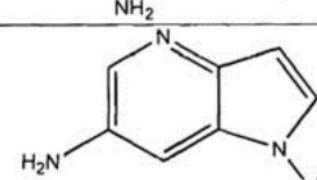
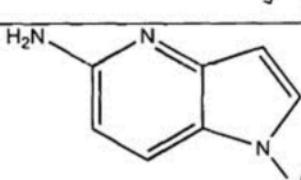
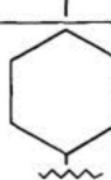
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504				H	O
[0323]				H	O
505				H	O
506				H	O
507				H	O

Cmpd	W	X	Z	A	Q
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509				H	O
[0324]				H	O
510				H	O
511				H	O
512				H	O

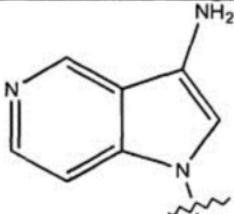
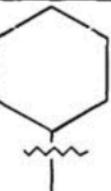
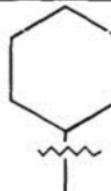
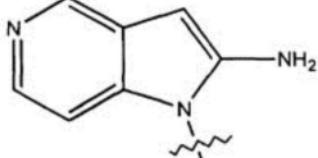
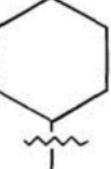
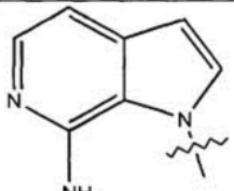
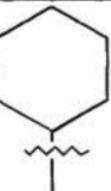
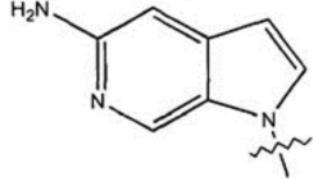
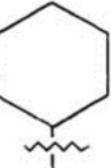
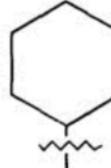
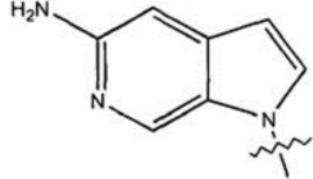
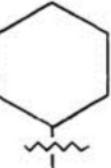
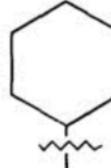
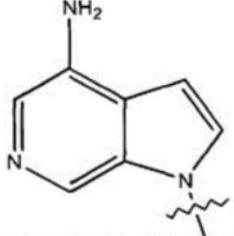
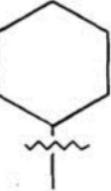
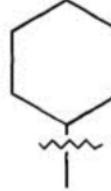
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515				H	O
[0325]					
516				H	O
517				H	O
518				H	O

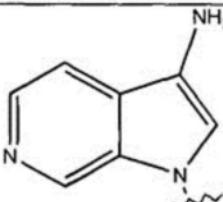
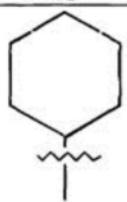
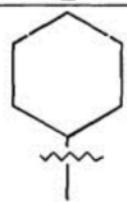
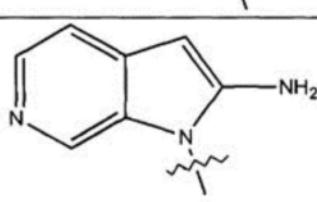
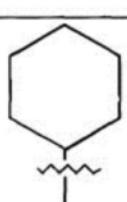
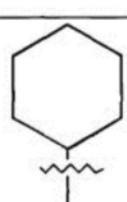
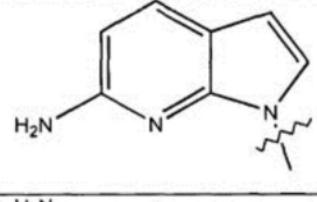
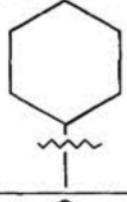
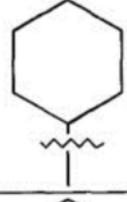
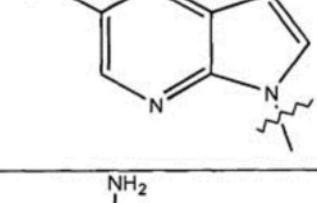
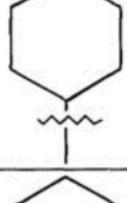
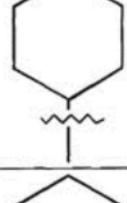
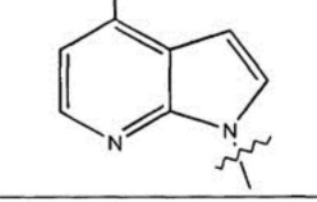
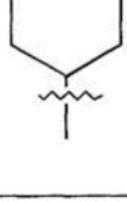
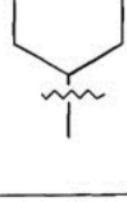
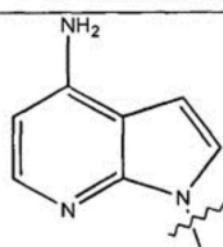
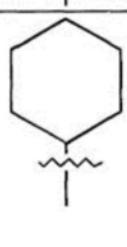
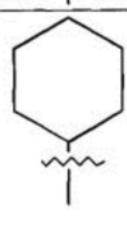
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520				H	O
[0326]				H	O
521				H	O
522				H	O
523				H	O

Cmpd	W	X	Z	A	Q
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525				H	O
[0327]				H	O
526				H	O
527				H	O
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529				H	O

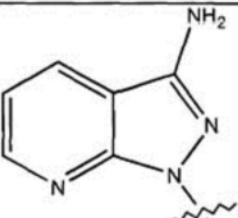
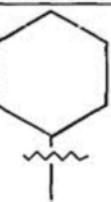
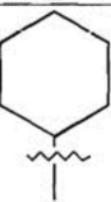
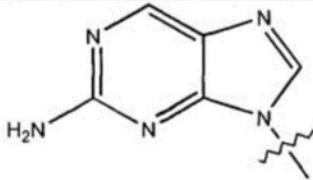
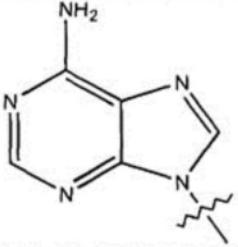
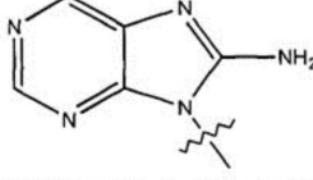
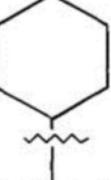
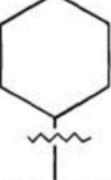
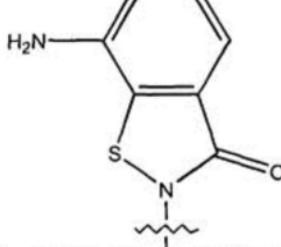
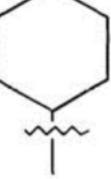
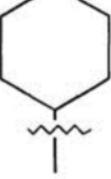
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[0328]				H	O
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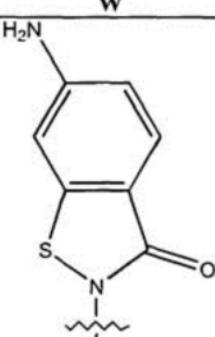
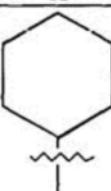
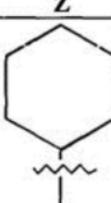
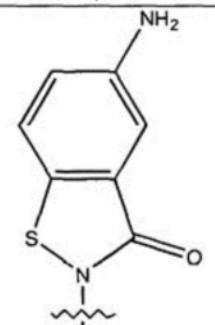
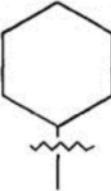
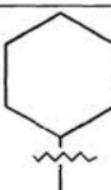
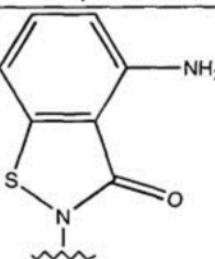
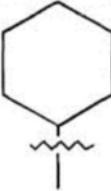
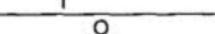
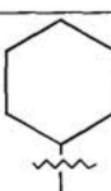
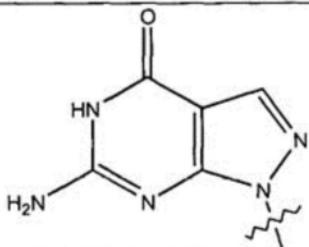
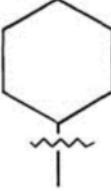
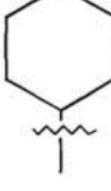
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[0329]				H	O
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Cmpd	W	X	Z	A	Q
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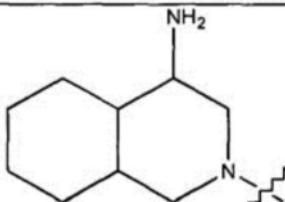
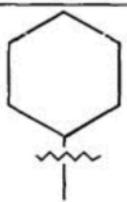
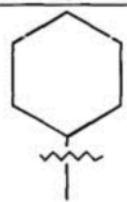
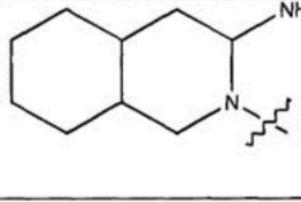
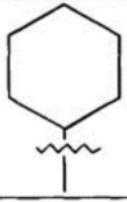
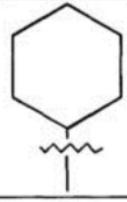
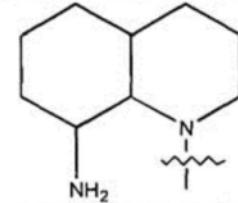
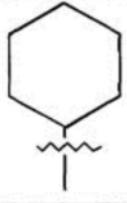
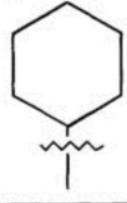
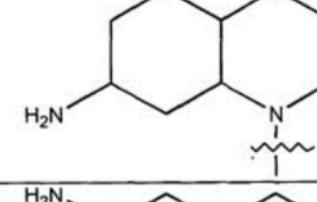
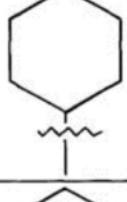
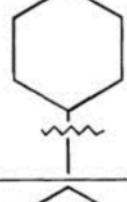
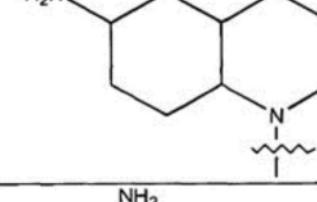
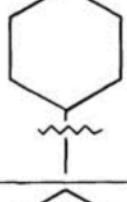
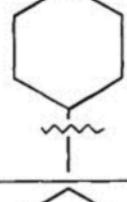
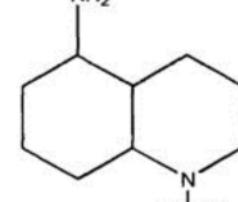
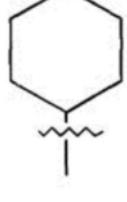
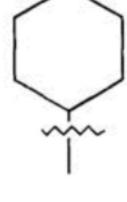
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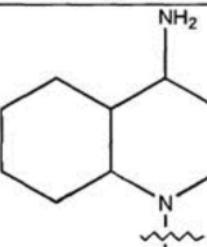
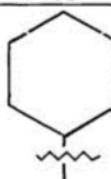
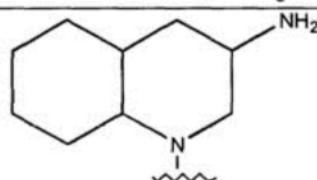
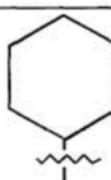
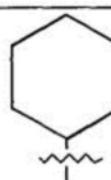
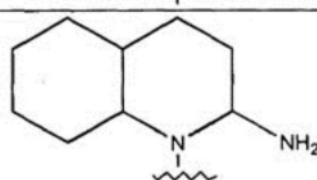
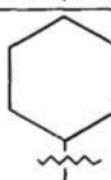
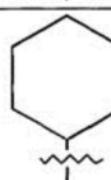
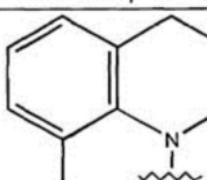
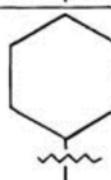
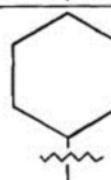
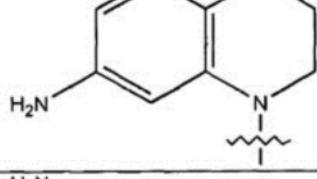
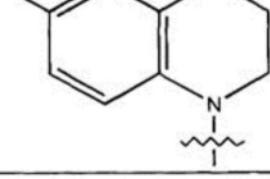
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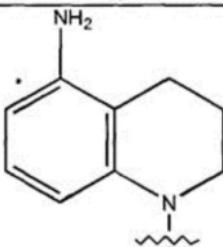
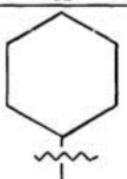
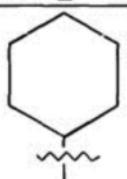
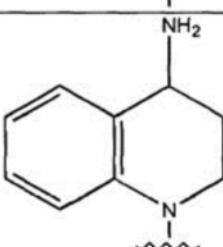
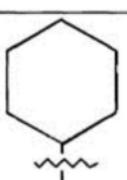
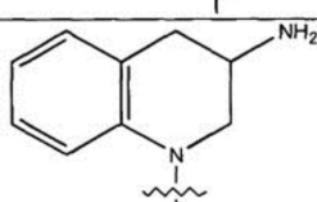
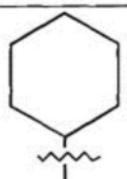
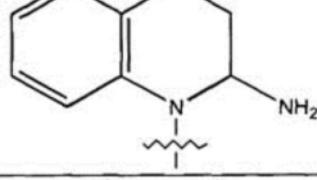
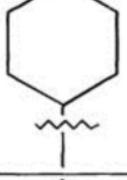
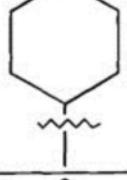
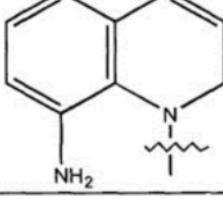
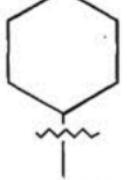
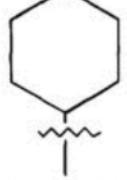
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[0333]				H	O
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559				H	O
560				H	O

Cmpd	W	X	Z	A	Q
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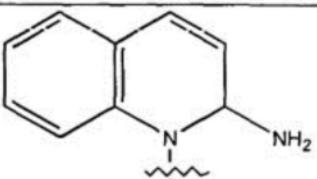
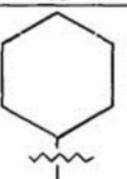
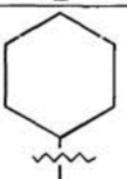
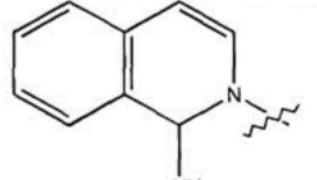
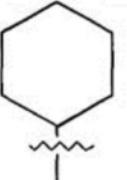
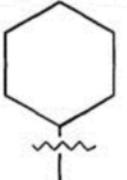
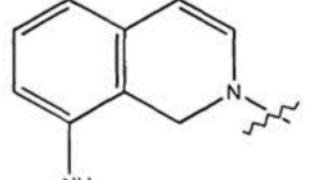
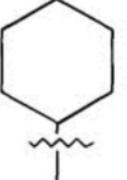
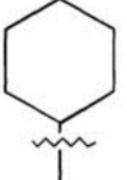
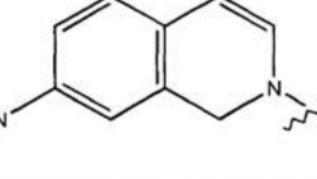
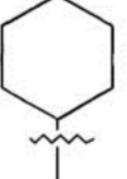
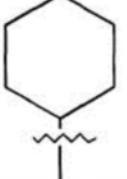
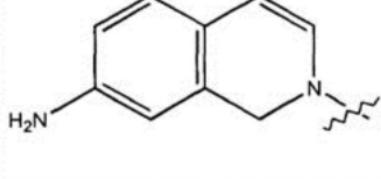
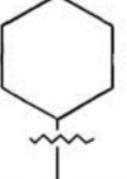
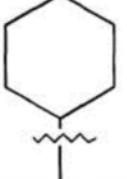
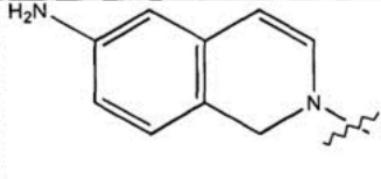
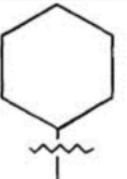
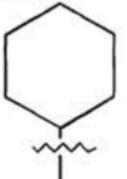
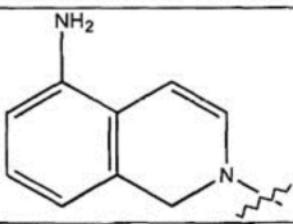
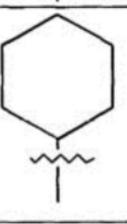
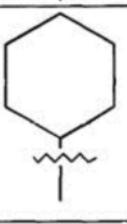
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[0335]					
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568				H	O
569				H	O
570				H	O

Cmpd	W	X	Z	A	Q
571				H	O
572				H	O
573				H	O
[0336]					
574				H	O
575				H	O
576				H	O

Cmpd	W	X	Z	A	Q
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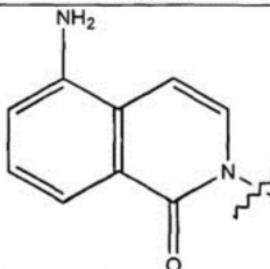
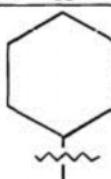
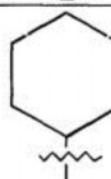
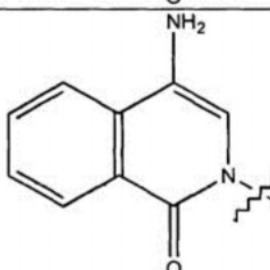
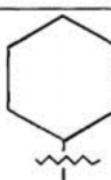
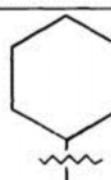
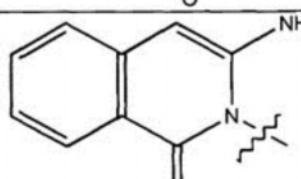
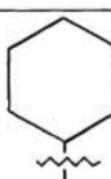
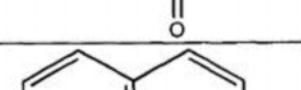
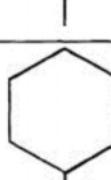
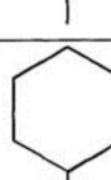
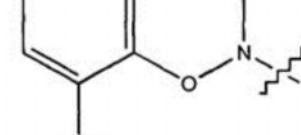
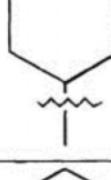
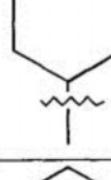
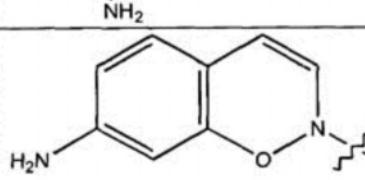
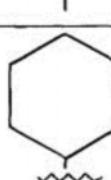
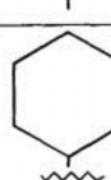
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[0338]				H	O
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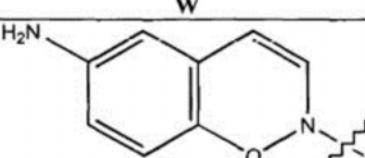
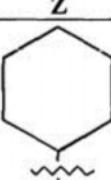
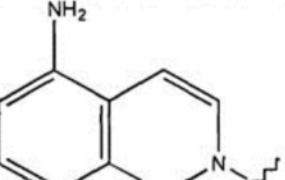
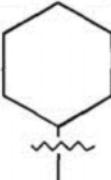
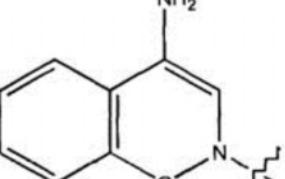
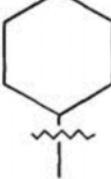
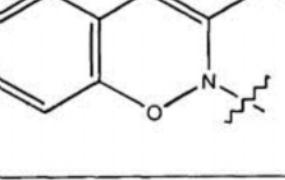
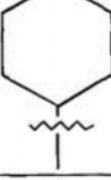
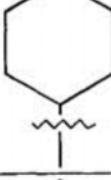
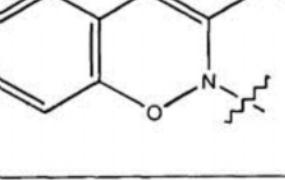
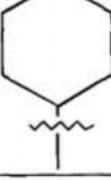
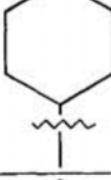
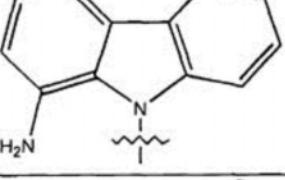
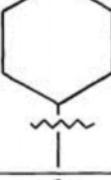
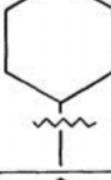
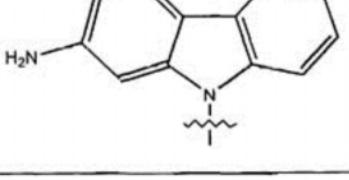
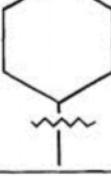
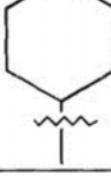
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591				H	O
592				H	O

Cmpd	W	X	Z	A	Q
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594				H	O
[0340]				H	O
595				H	O
596				H	O
597				H	O
598				H	O

Cmpd	W	X	Z	A	Q	
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600				H	O	
[0341]	601				H	O
602				H	O	
603				H	O	
604				H	O	

Cmpd	W	X	Z	A	Q
605				H	O
606				H	O
[0342]				H	O
607				H	O
608				H	O
609				H	O

Cmpd	W	X	Z	A	Q
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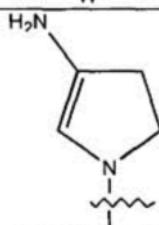
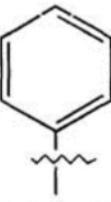
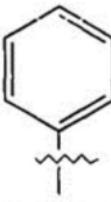
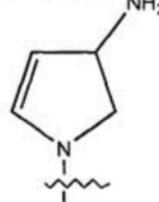
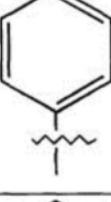
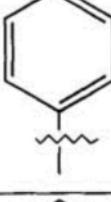
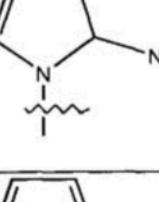
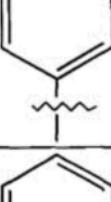
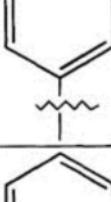
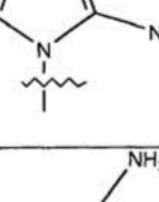
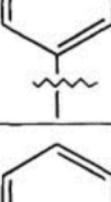
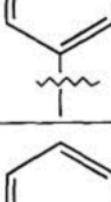
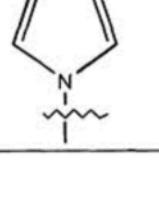
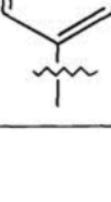
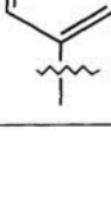
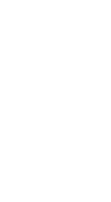
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[0344]				H	O
617				H	O
618				H	O
619				H	O
620				H	O

Cmpd	W	X	Z	A	Q
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622				H	O
[0345]				H	O
623				H	O
624				H	O
625				H	O

Cmpd	W	X	Z	A	Q
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627				H	O
[0346]				H	O
628				H	O
629				H	O
630				H	O

Cmpd	W	X	Z	A	Q
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632				H	O
[0347]				H	O
633				H	O
634				H	O
635				H	O
636				H	O

Cmpd	W	X	Z	A	Q
637				H	O
638				H	O
[0348]				H	O
640				H	O
641				H	O
642				H	O

Cmpd	W	X	Z	A	Q
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644				H	O
[0349]				H	O
645				H	O
646				H	O
647				H	O

Cmpd	W	X	Z	A	Q
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[0350]					
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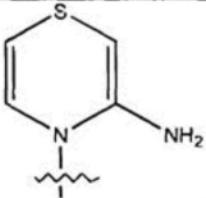
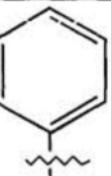
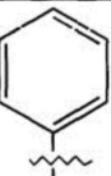
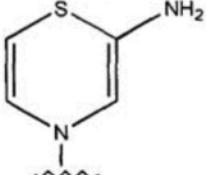
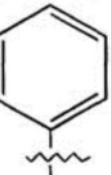
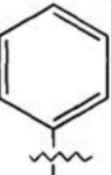
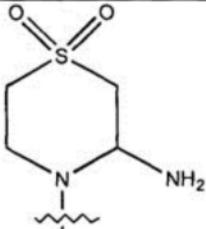
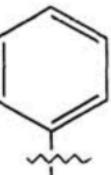
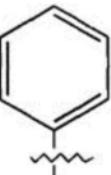
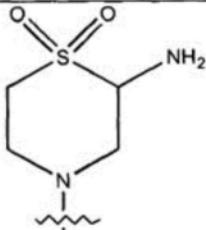
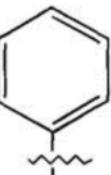
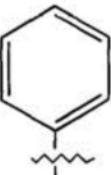
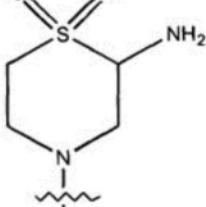
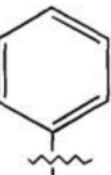
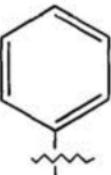
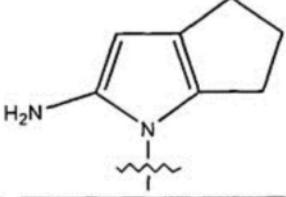
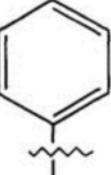
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[0351]				H	O
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657				H	O
658				H	O
659				H	O

Cmpd	W	X	Z	A	Q
660				H	O
661				H	O
[0352]				H	O
663				H	O
664				H	O

Cmpd	W	X	Z	A	Q
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[0353]					
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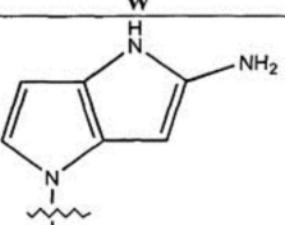
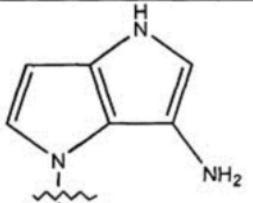
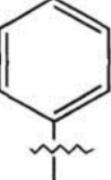
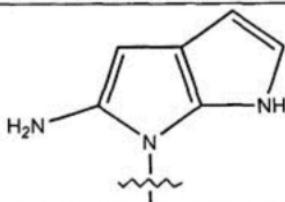
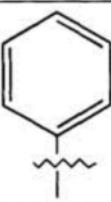
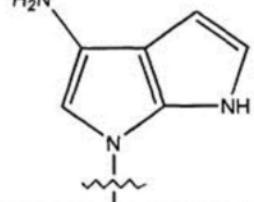
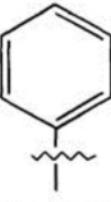
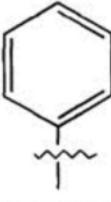
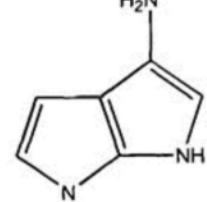
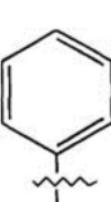
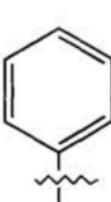
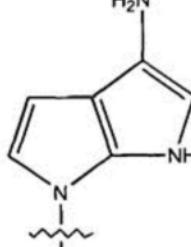
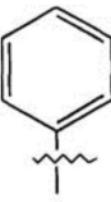
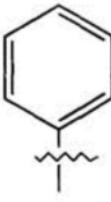
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674				H	O
675				H	O

Cmpd	W	X	Z	A	Q
676				H	O
677				H	O
678				H	O
[0355]					
679				H	O
680				H	O
681				H	O
	c				

Cmpd	W	X	Z	A	Q
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683				H	O
[0356]				H	O
684				H	O
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686				H	O

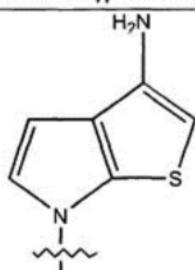
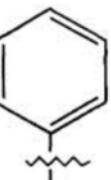
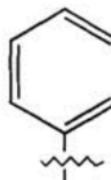
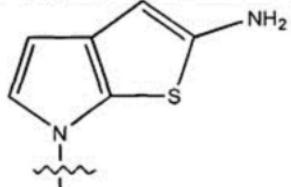
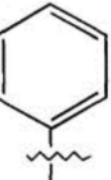
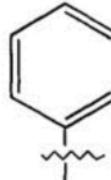
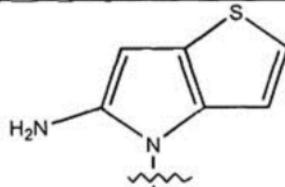
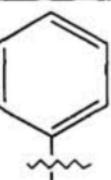
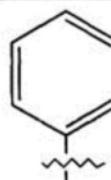
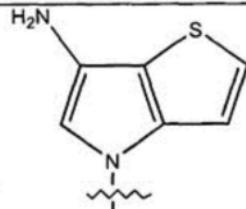
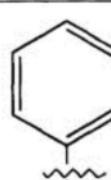
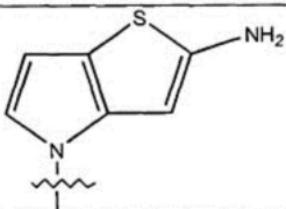
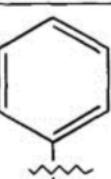
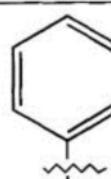
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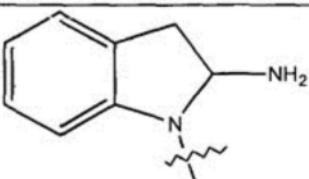
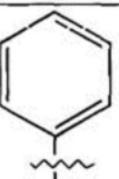
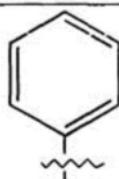
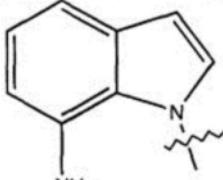
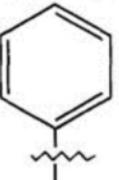
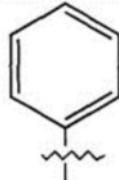
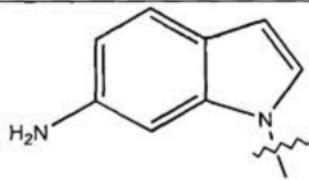
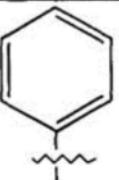
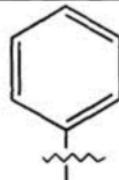
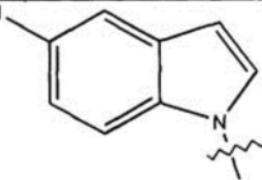
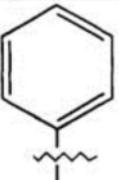
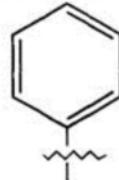
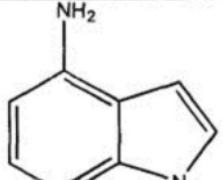
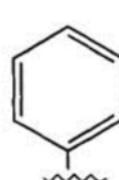
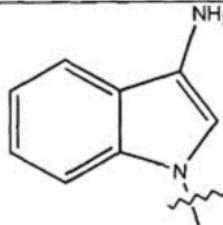
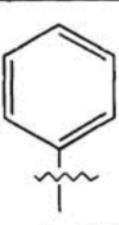
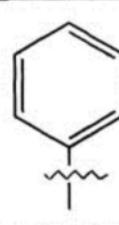
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695				H	O
696				H	O

Cmpd	W	X	Z	A	Q
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698				H	O
[0359]				H	O
699				H	O
700				H	O
701				H	O

Cmpd	W	X	Z	A	Q
702				H	O
703				H	O
[0360]				H	O
705				H	O
706				H	O

Cmpd	W	X	Z	A	Q	
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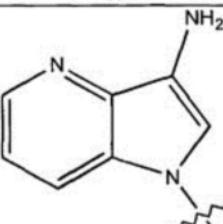
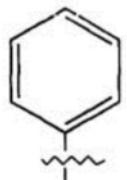
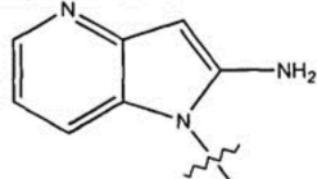
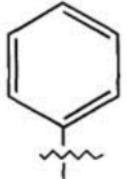
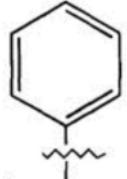
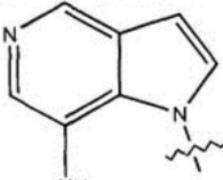
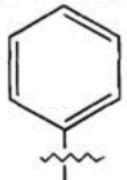
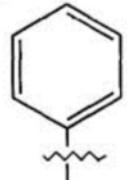
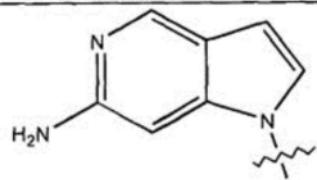
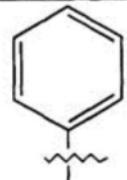
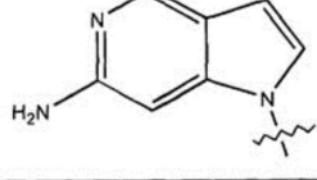
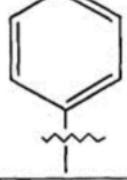
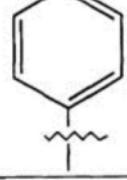
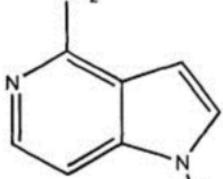
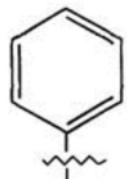
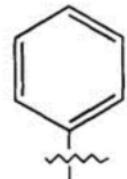
Cmpd	W	X	Z	A	Q
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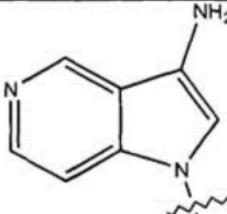
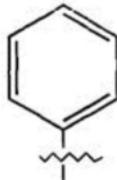
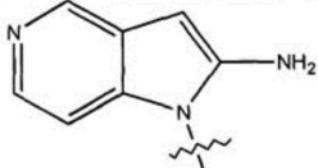
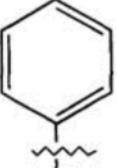
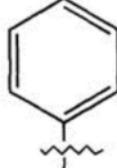
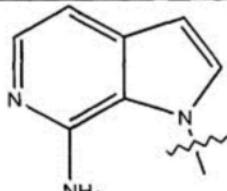
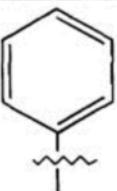
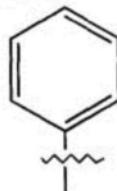
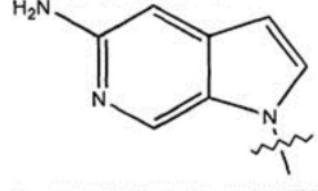
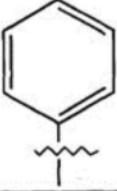
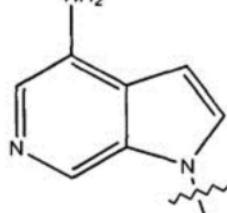
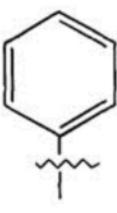
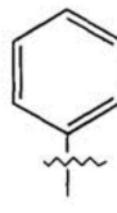
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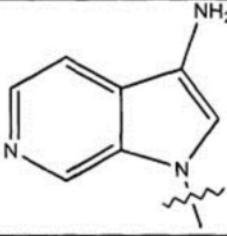
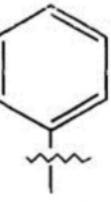
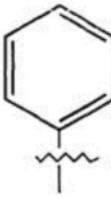
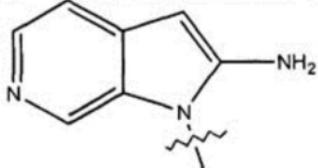
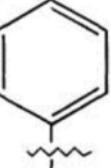
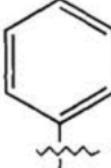
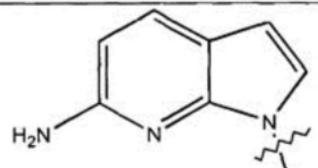
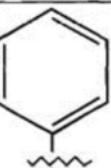
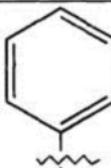
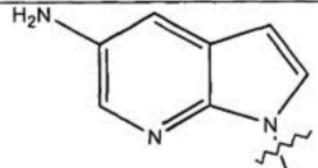
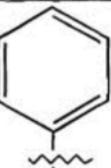
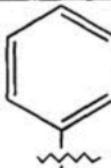
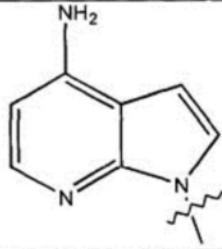
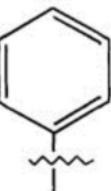
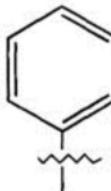
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[0365]				H	O
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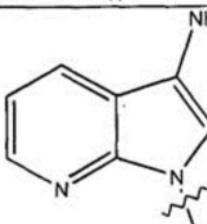
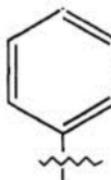
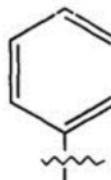
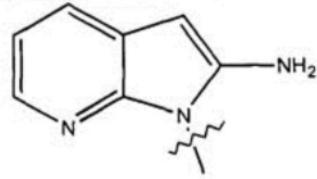
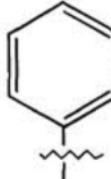
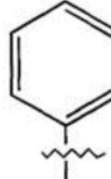
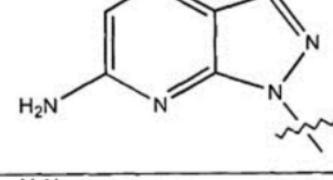
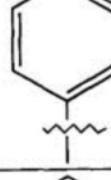
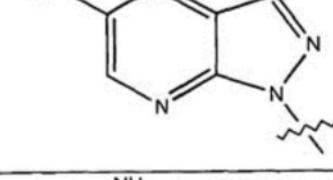
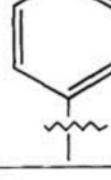
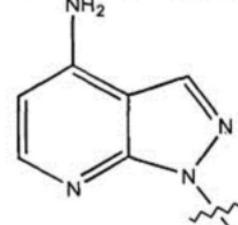
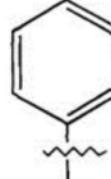
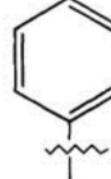
Cmpd	W	X	Z	A	Q
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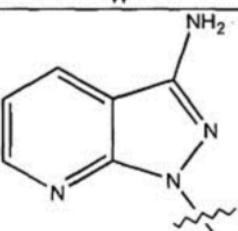
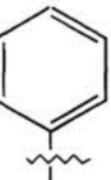
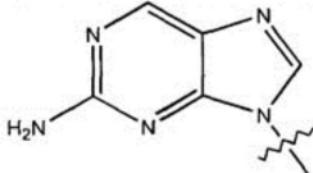
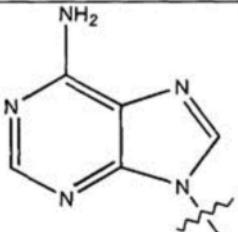
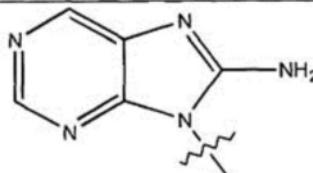
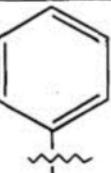
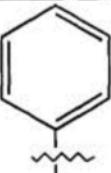
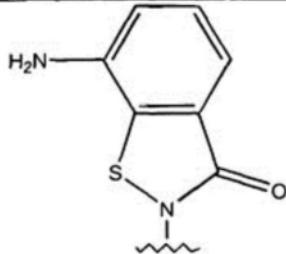
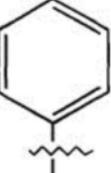
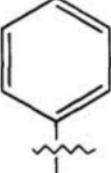
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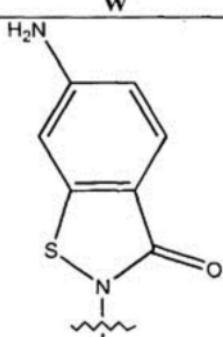
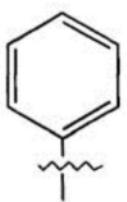
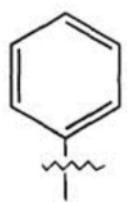
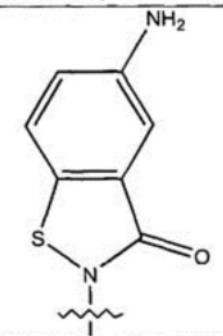
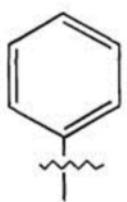
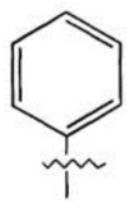
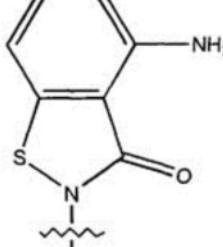
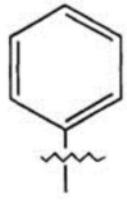
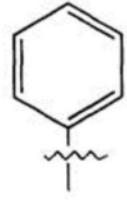
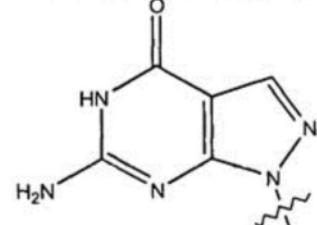
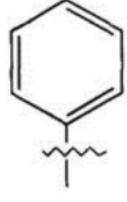
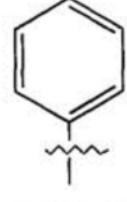
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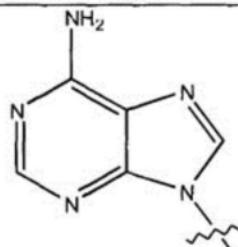
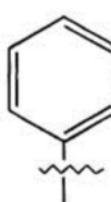
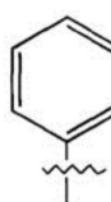
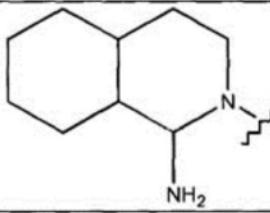
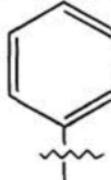
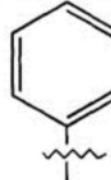
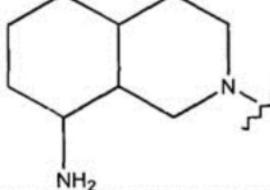
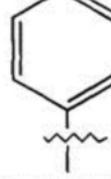
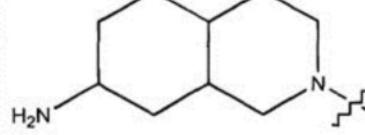
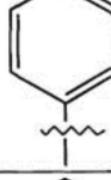
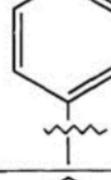
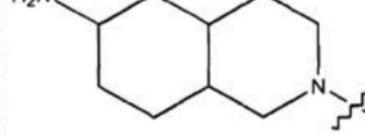
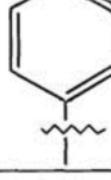
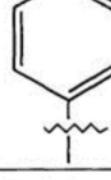
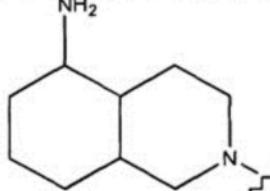
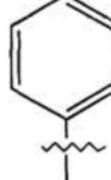
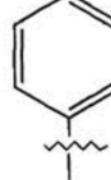
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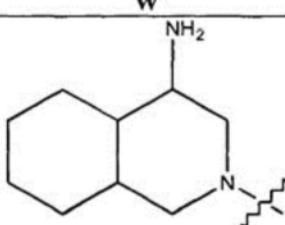
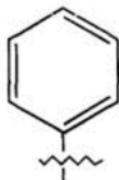
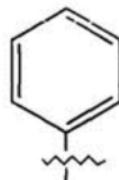
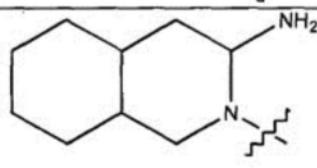
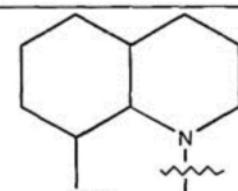
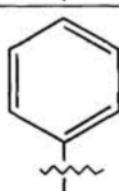
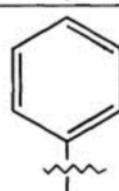
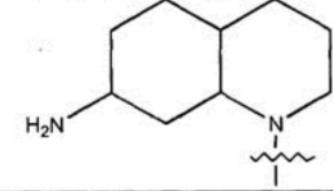
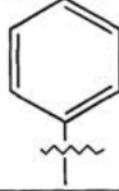
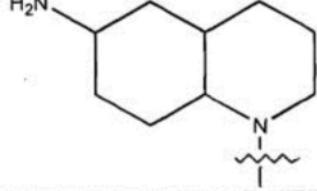
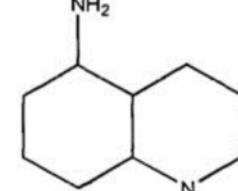
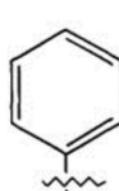
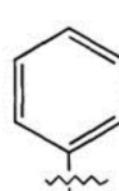
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759				H	O
760				H	O

Cmpd	W	X	Z	A	Q
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762				H	O
[0371]				H	O
764				H	O
765				H	O

Cmpd	W	X	Z	A	Q
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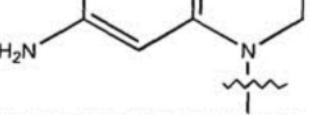
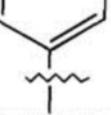
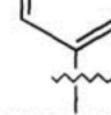
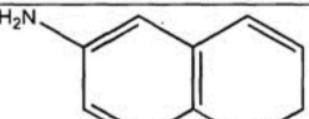
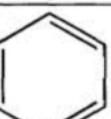
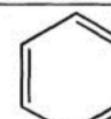
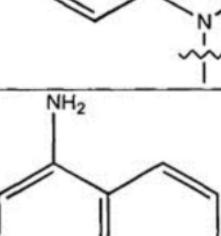
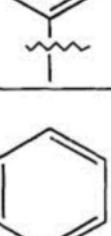
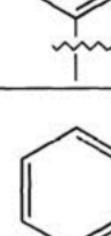
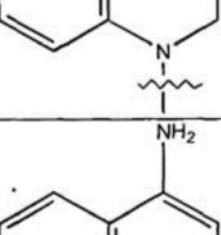
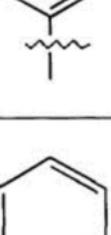
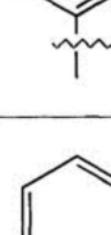
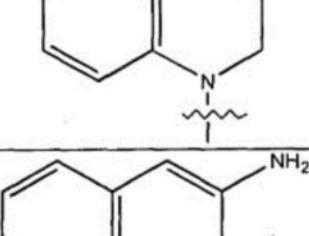
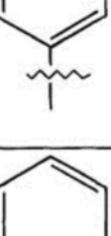
Cmpd	W	X	Z	A	Q
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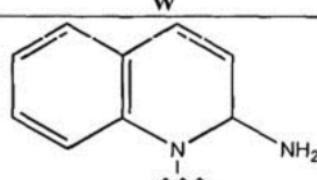
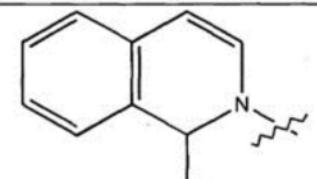
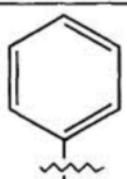
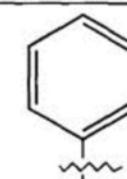
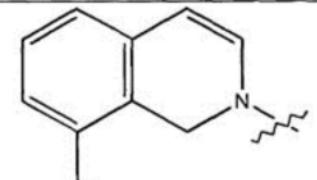
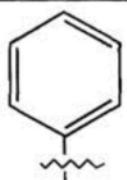
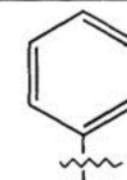
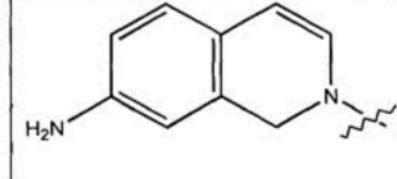
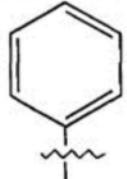
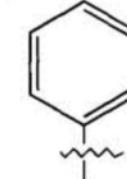
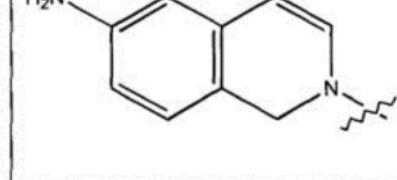
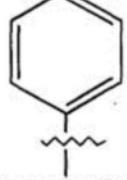
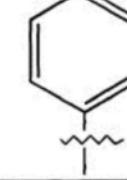
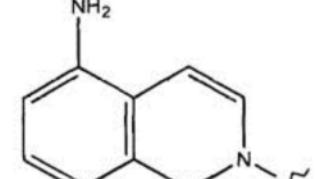
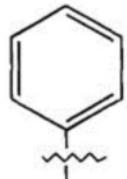
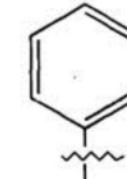
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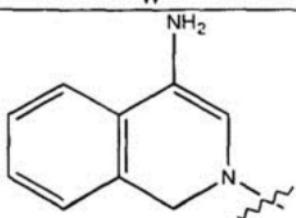
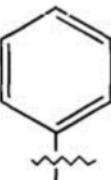
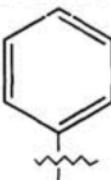
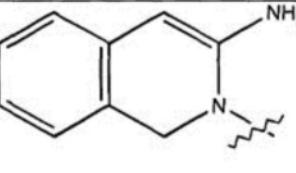
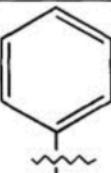
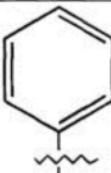
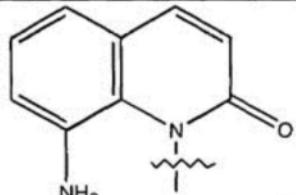
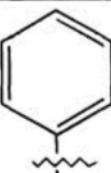
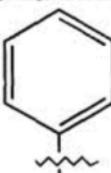
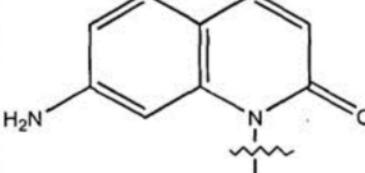
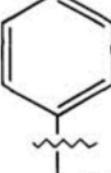
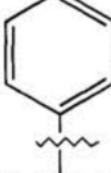
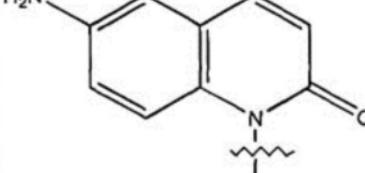
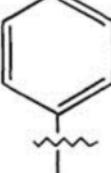
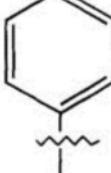
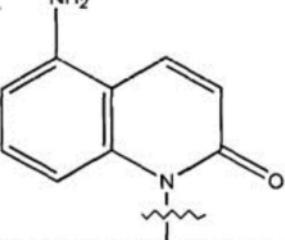
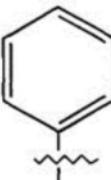
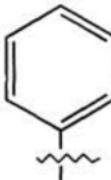
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782				H	O
783				H	O
[0375]					
784				H	O
785				H	O
786				H	O

Cmpd	W	X	Z	A	Q
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788				H	O
[0376]				H	O
789				H	O
790				H	O
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792				H	O

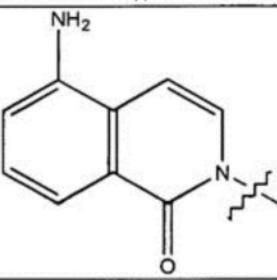
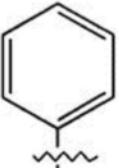
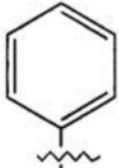
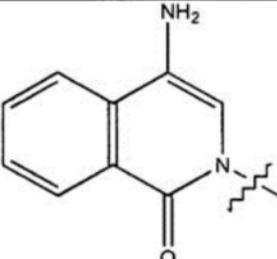
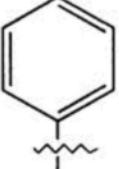
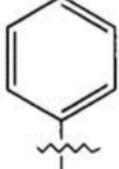
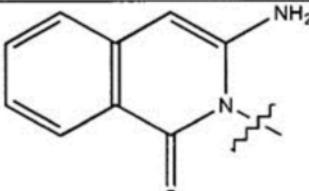
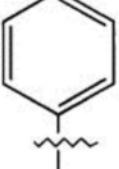
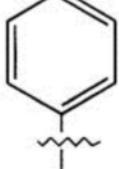
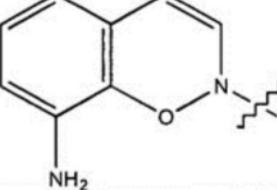
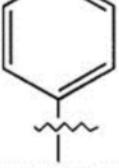
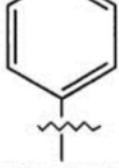
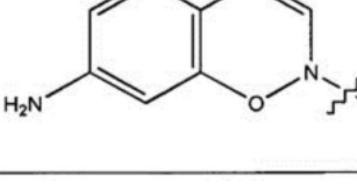
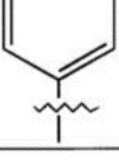
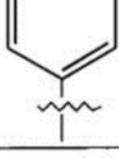
Cmpd	W	X	Z	A	Q
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794				H	O
[0377]				H	O
796				H	O
797				H	O

Cmpd	W	X	Z	A	Q
798				H	O
799				H	O
800				H	O
801				H	O
802				H	O

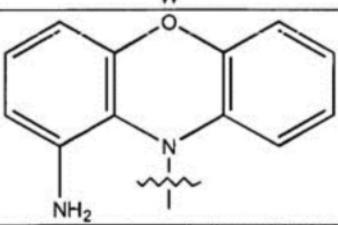
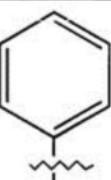
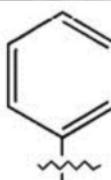
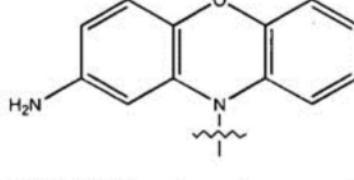
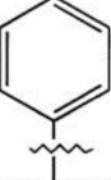
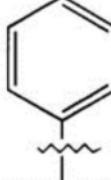
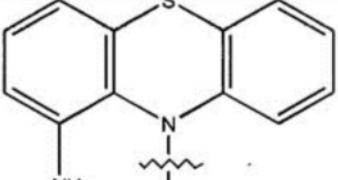
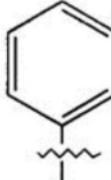
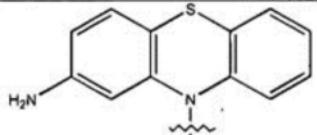
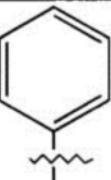
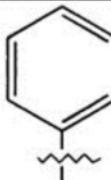
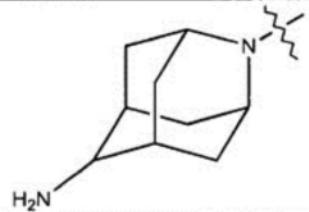
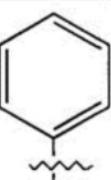
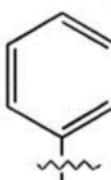
Cmpd	W	X	Z	A	Q
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804				H	O
[0379]				H	O
806				H	O
807				H	O
808				H	O

Cmpd	W	X	Z	A	Q	
809				H	O	
810				H	O	
[0380]	811				H	O
812				H	O	
813				H	O	
814				H	O	

Cmpd	W	X	Z	A	Q
815				H	O
816				H	O
[0381]				H	O
818				H	O
819				H	O

Cmpd	W	X	Z	A	Q
820				H	O
821				H	O
[0382]				H	O
823				H	O
824				H	O

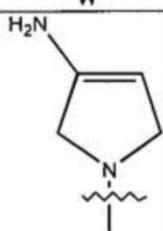
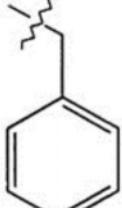
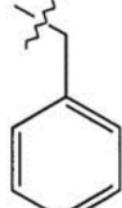
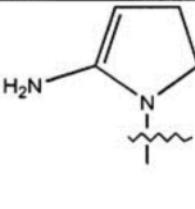
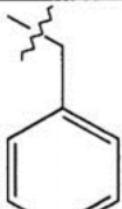
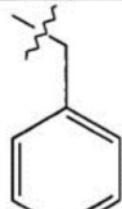
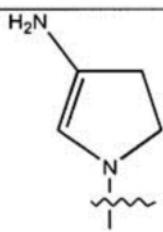
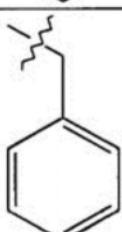
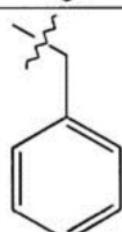
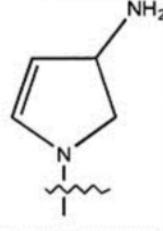
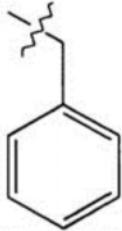
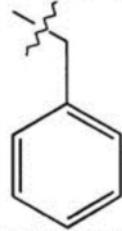
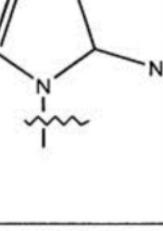
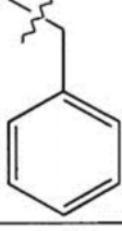
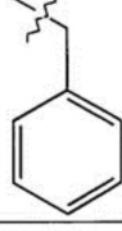
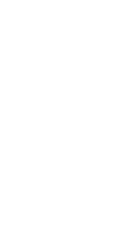
Cmpd	W	X	Z	A	Q
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826				H	O
[0383]				H	O
827				H	O
828				H	O
829				H	O
830				H	O

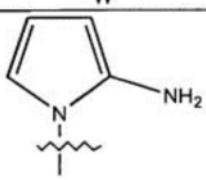
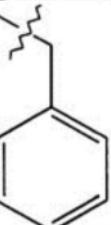
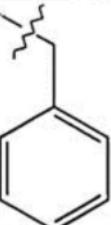
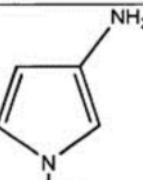
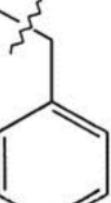
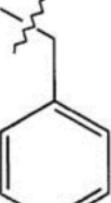
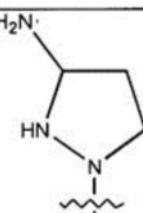
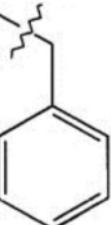
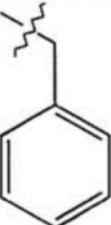
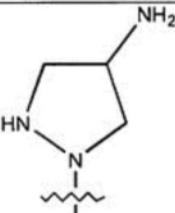
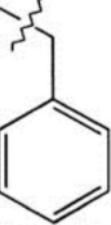
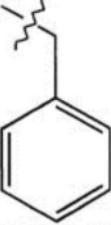
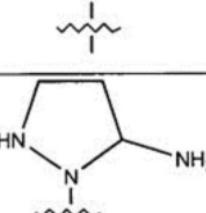
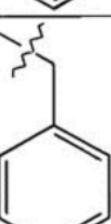
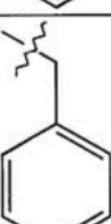
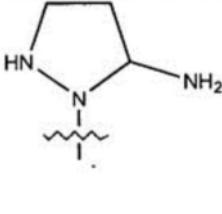
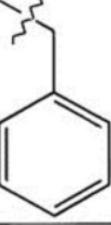
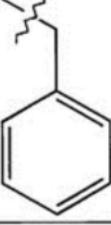
Cmpd	W	X	Z	A	Q
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832				H	O
[0384]				H	O
834				H	O
835				H	O

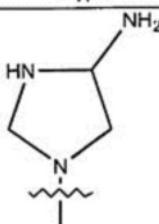
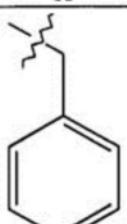
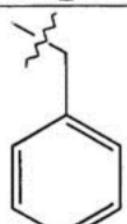
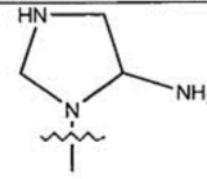
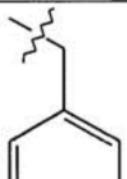
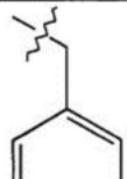
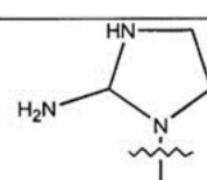
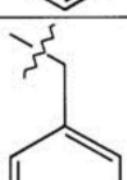
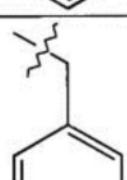
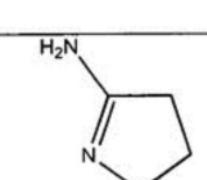
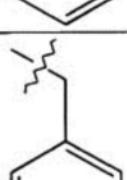
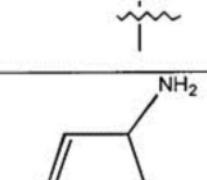
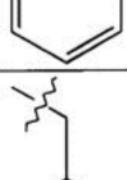
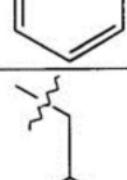
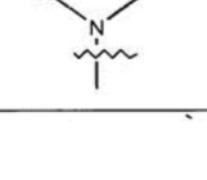
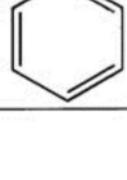
Cmpd	W	X	Z	A	Q
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837				H	O
[0385]				H	O
838				H	O
839				H	O
840				H	O

Cmpd	W	X	Z	A	Q
841				H	O
842				H	O
[0386]				H	O
844				H	O
845				H	O

Cmpd	W	X	Z	A	Q
846				H	O
847				H	O
[0387]				H	O
848				H	O
849				H	O
850				H	O

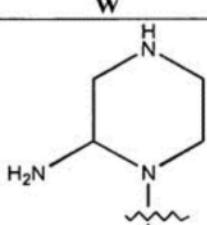
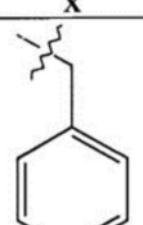
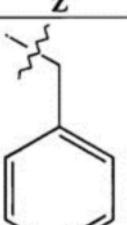
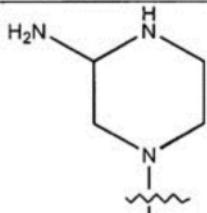
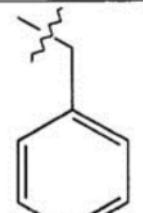
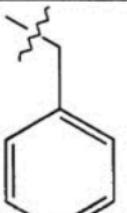
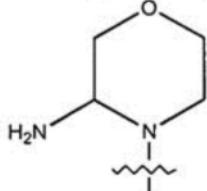
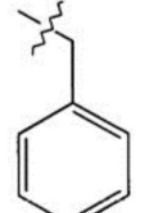
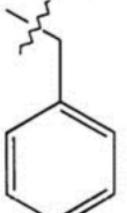
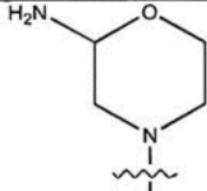
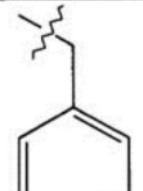
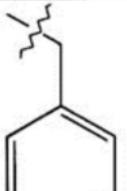
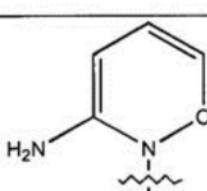
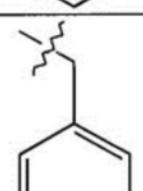
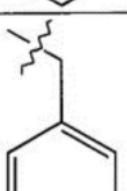
Cmpd	W	X	Z	A	Q
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852				H	O
[0388]				H	O
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854				H	O
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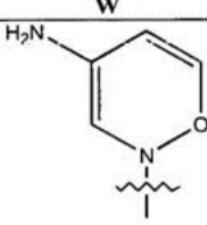
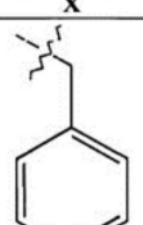
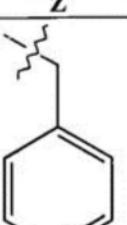
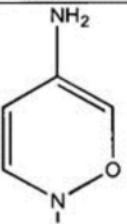
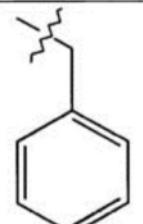
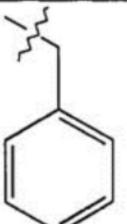
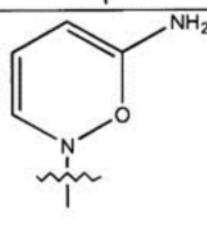
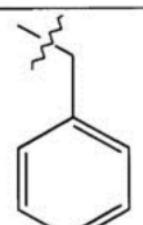
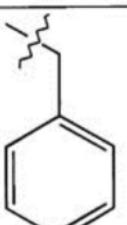
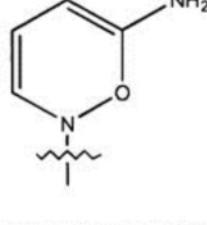
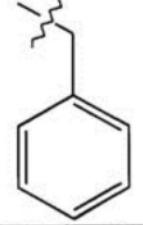
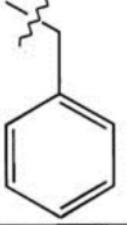
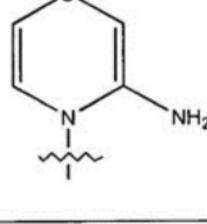
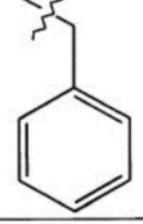
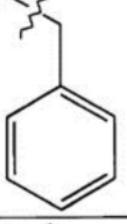
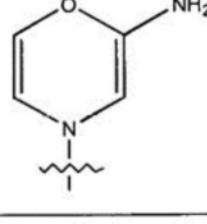
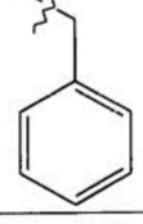
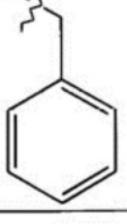
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857				H	O
[0389]				H	O
858				H	O
859				H	O
860				H	O

Cmpd	W	X	Z	A	Q
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862				H	O
[0390]				H	O
863				H	O
864				H	O
865				H	O

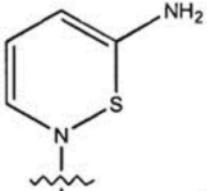
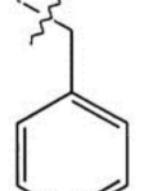
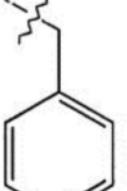
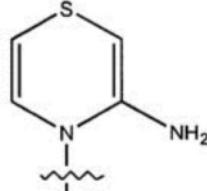
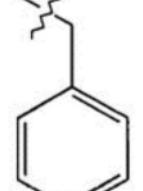
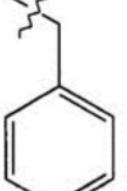
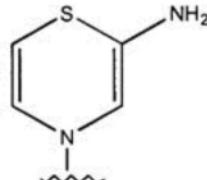
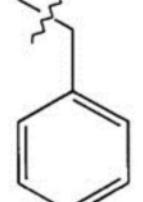
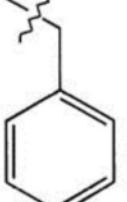
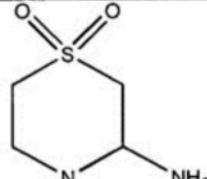
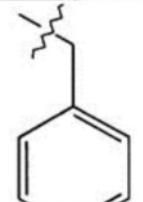
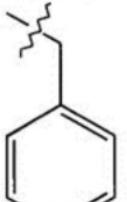
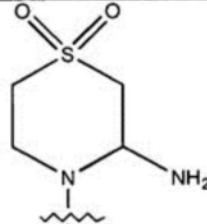
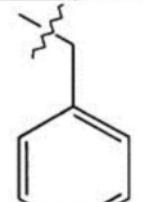
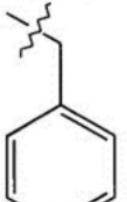
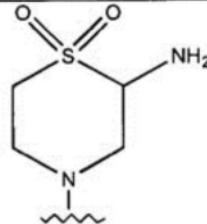
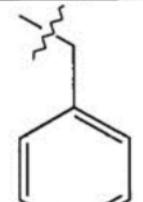
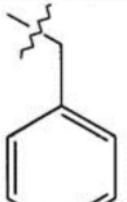
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867				H	O
[0391]				H	O
868				H	O
869				H	O
870				H	O

Cmpd	W	X	Z	A	Q
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872				H	O
[0392]				H	O
873				H	O
874				H	O
875				H	O

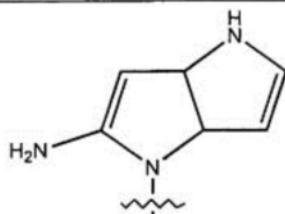
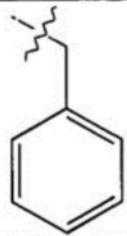
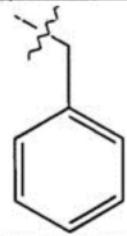
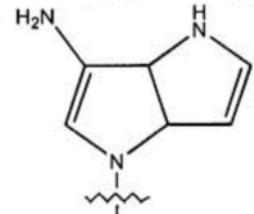
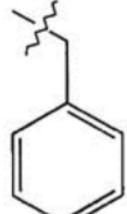
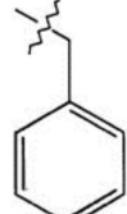
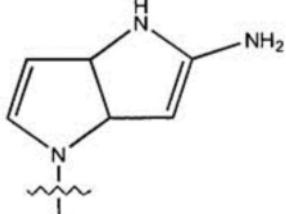
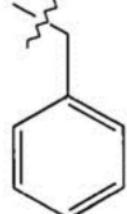
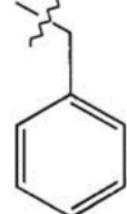
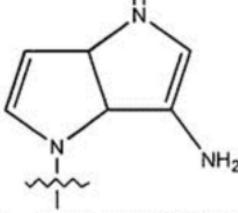
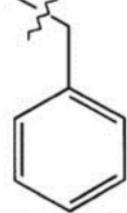
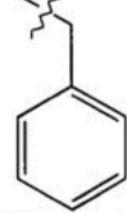
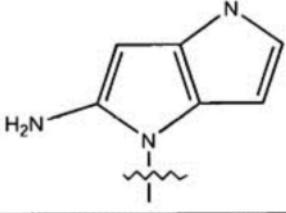
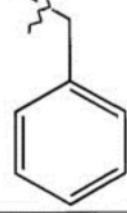
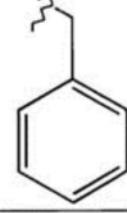
Cmpd	W	X	Z	A	Q
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877				H	O
[0393]				H	O
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879				H	O
880				H	O

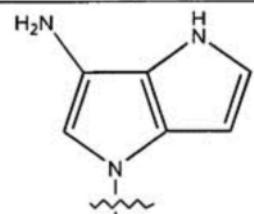
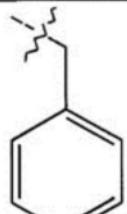
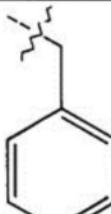
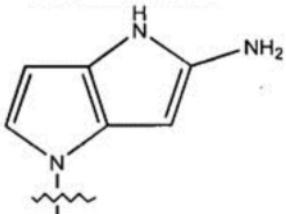
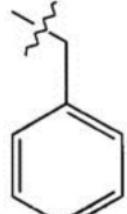
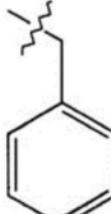
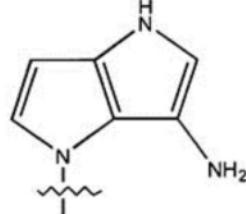
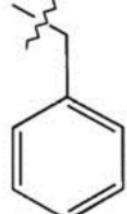
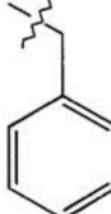
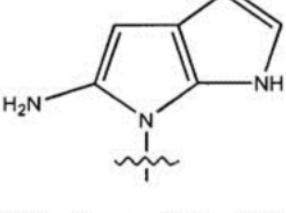
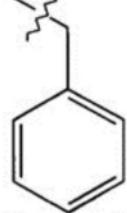
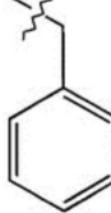
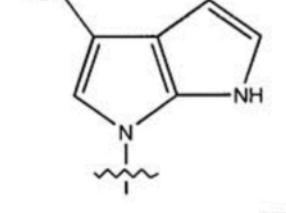
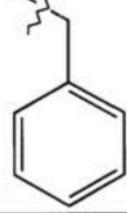
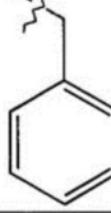
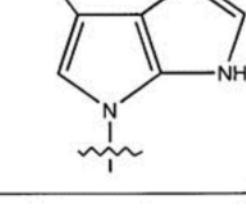
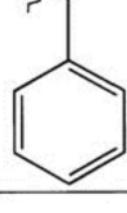
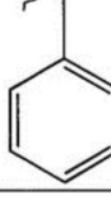
Cmpd	W	X	Z	A	Q
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882				H	O
[0394]				H	O
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884				H	O
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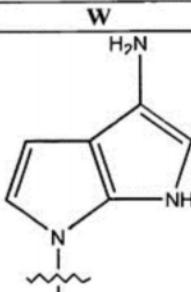
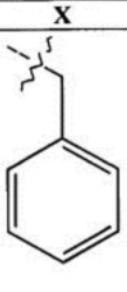
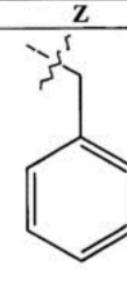
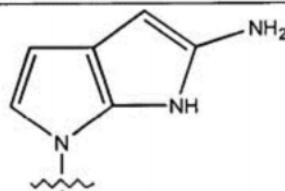
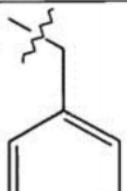
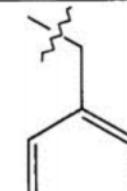
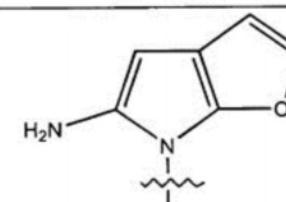
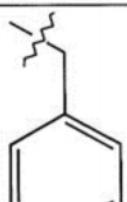
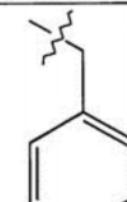
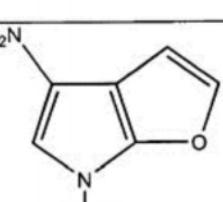
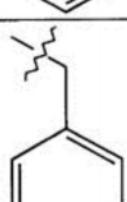
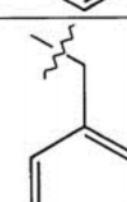
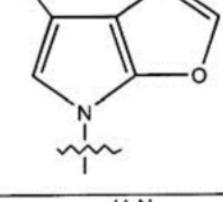
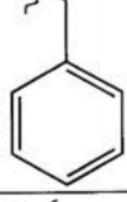
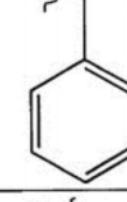
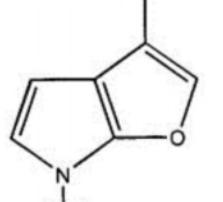
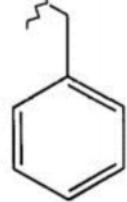
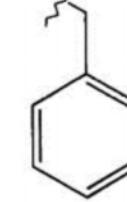
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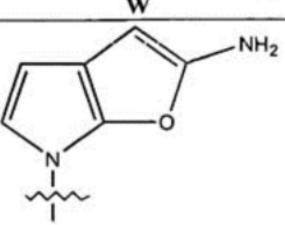
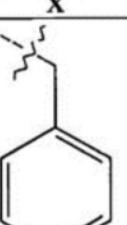
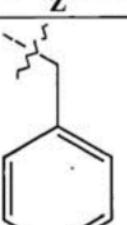
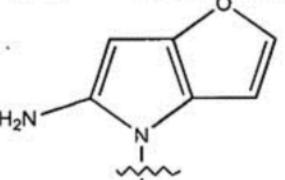
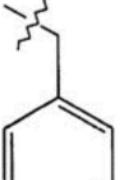
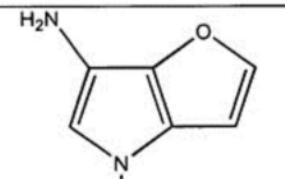
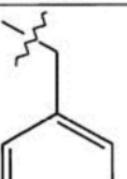
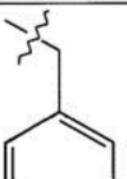
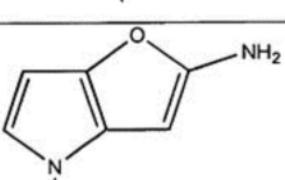
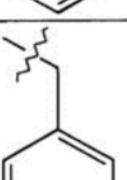
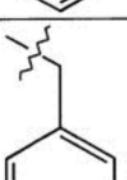
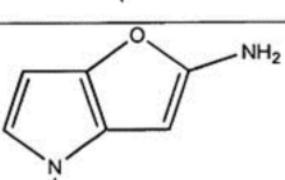
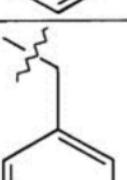
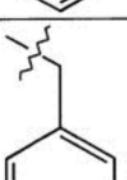
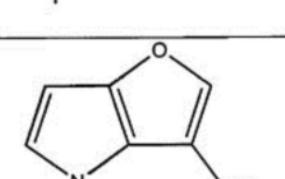
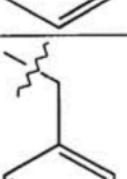
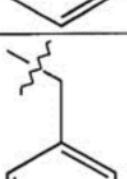
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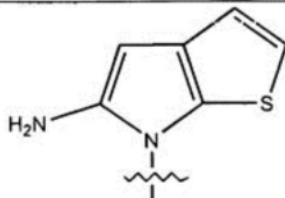
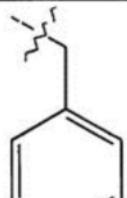
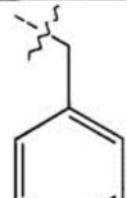
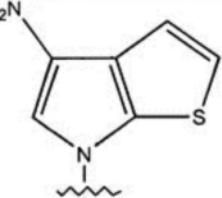
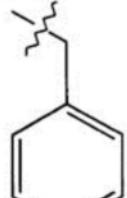
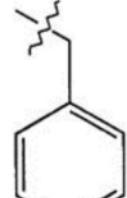
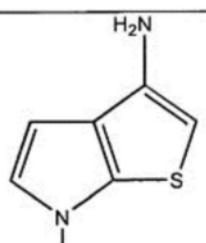
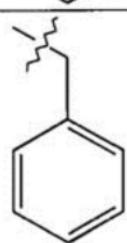
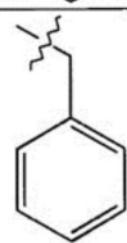
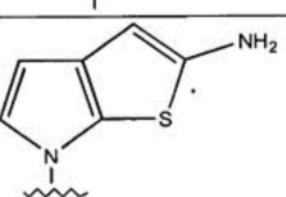
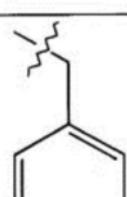
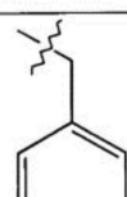
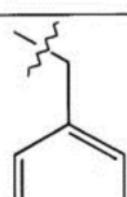
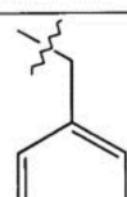
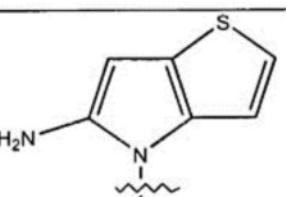
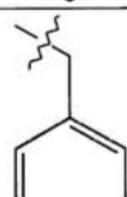
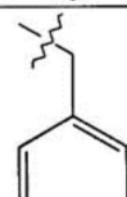
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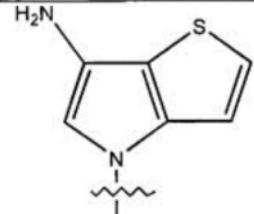
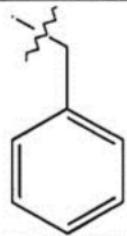
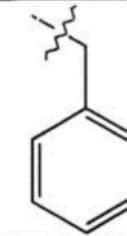
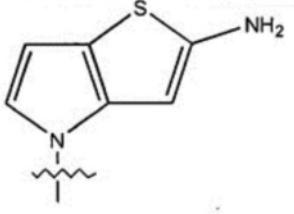
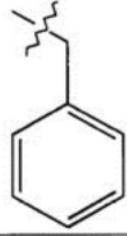
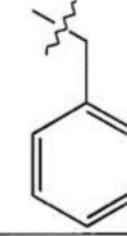
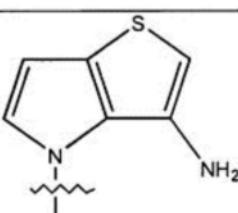
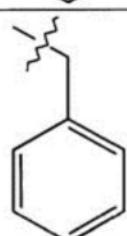
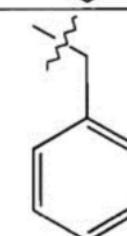
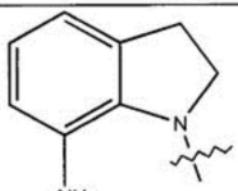
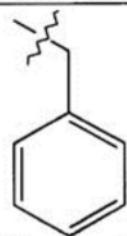
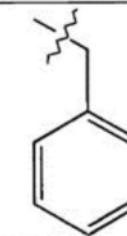
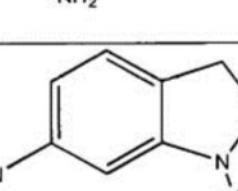
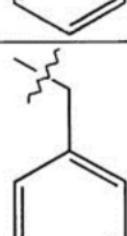
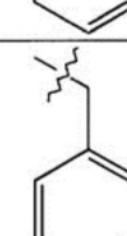
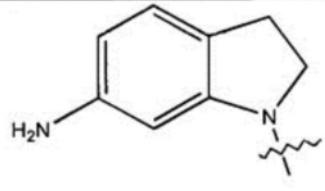
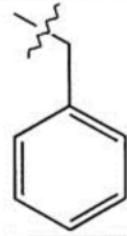
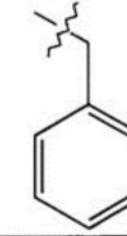
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902				H	O
[0398]				H	O
904				H	O
905				H	O

Cmpd	W	X	Z	A	Q
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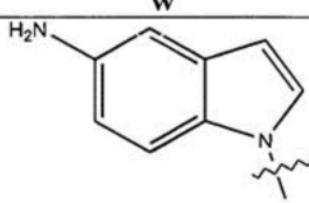
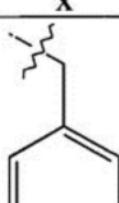
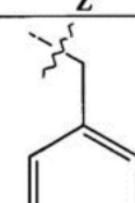
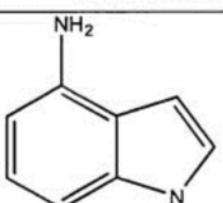
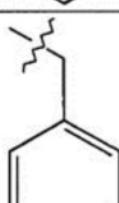
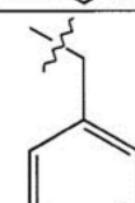
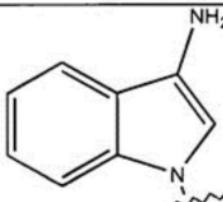
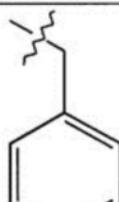
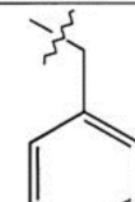
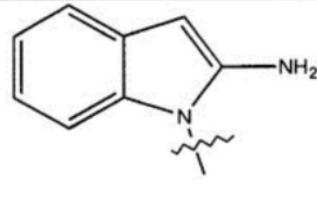
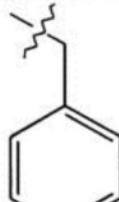
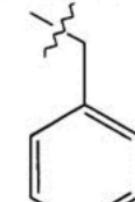
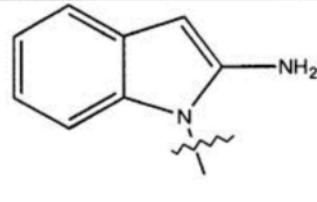
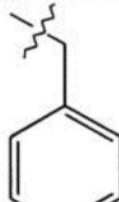
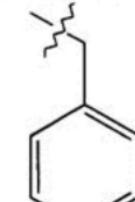
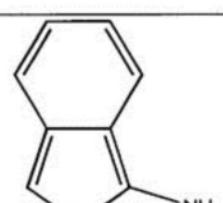
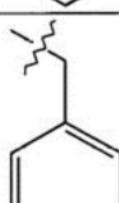
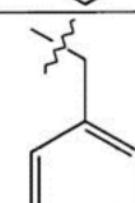
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913				H	O
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Cmpd	W	X	Z	A	Q
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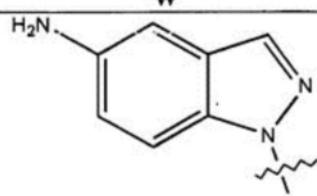
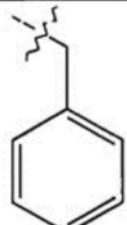
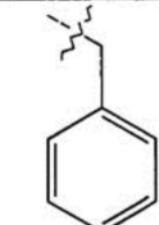
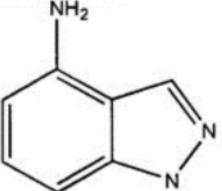
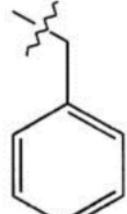
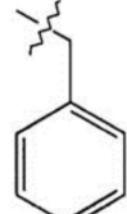
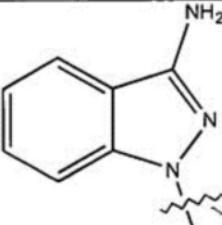
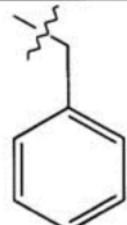
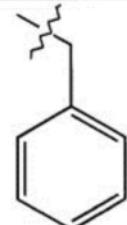
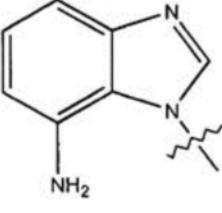
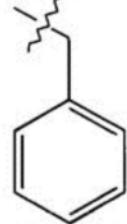
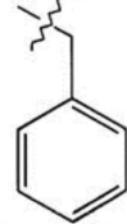
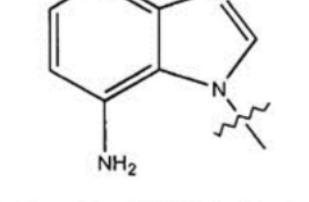
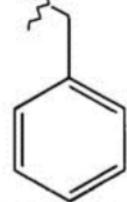
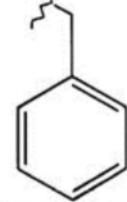
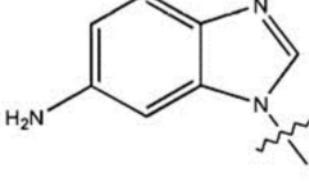
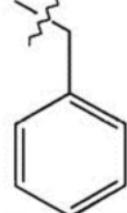
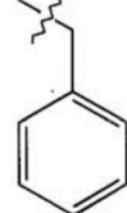
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922				H	O
[0402]				H	O
923				H	O
924				H	O
925				H	O

Cmpd	W	X	Z	A	Q
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927				H	O
[0403]				H	O
928				H	O
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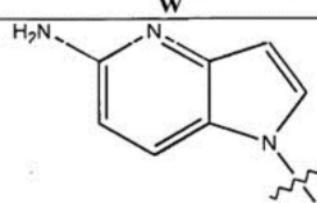
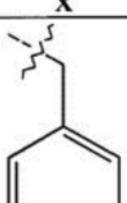
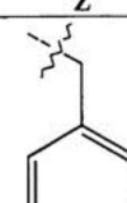
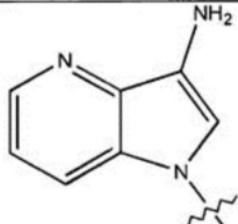
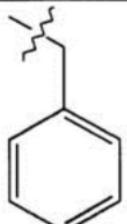
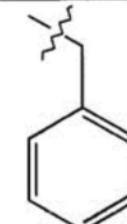
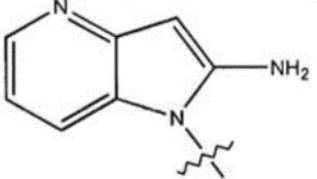
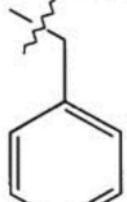
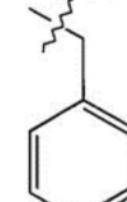
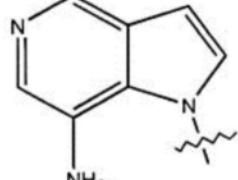
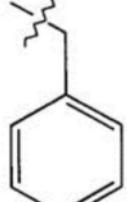
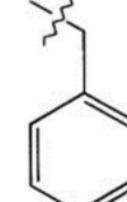
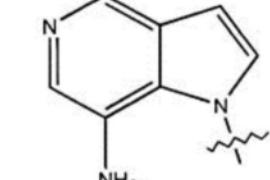
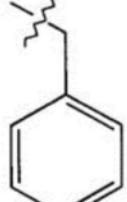
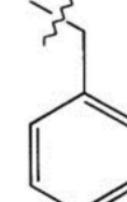
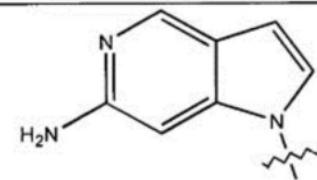
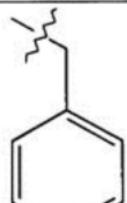
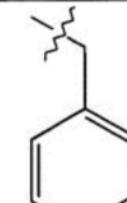
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932				H	O
[0404]				H	O
933				H	O
934				H	O
935				H	O

Cmpd	W	X	Z	A	Q
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937				H	O
[0405]				H	O
938				H	O
939				H	O
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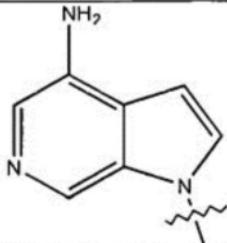
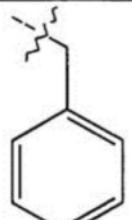
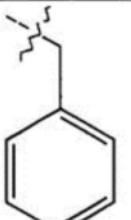
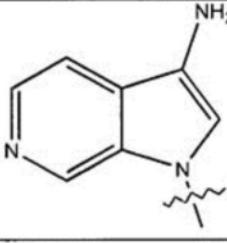
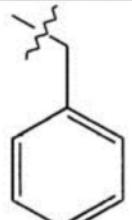
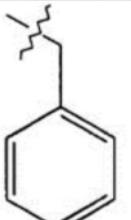
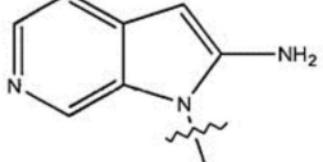
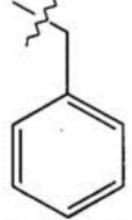
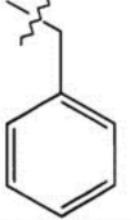
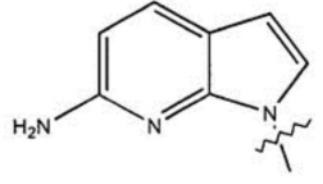
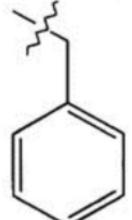
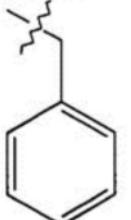
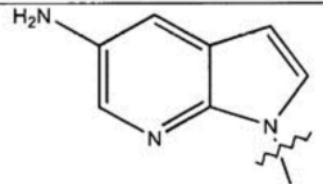
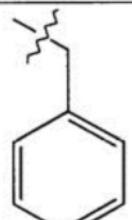
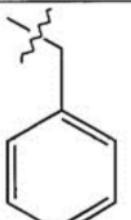
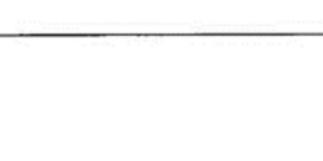
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942				H	O
943				H	O
944				H	O

Cmpd	W	X	Z	A	Q
945				H	O
946				H	O
[0407]				H	O
947				H	O
948				H	O
949				H	O

Cmpd	W	X	Z	A	Q
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[0408]				H	O
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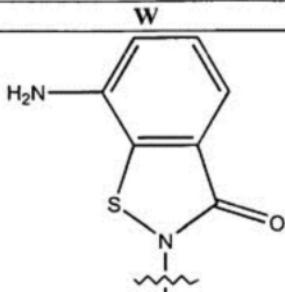
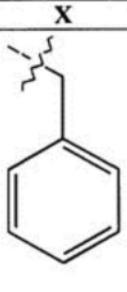
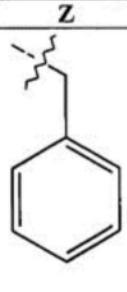
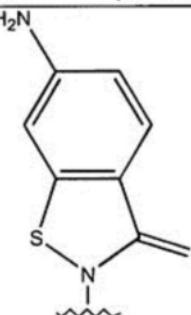
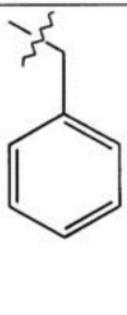
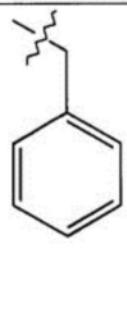
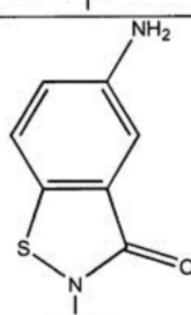
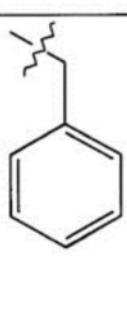
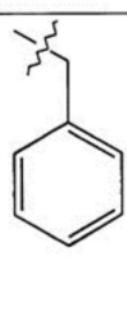
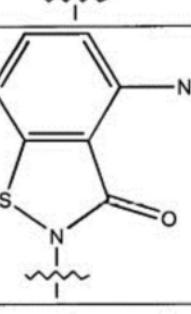
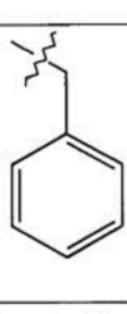
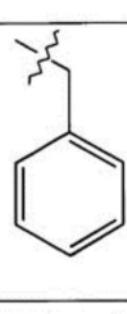
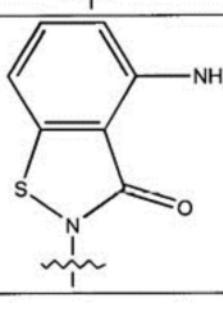
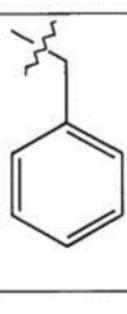
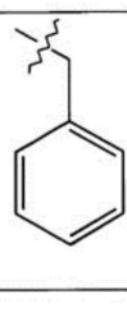
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[0409]				H	O
957				H	O
958				H	O
959				H	O

Cmpd	W	X	Z	A	Q
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961				H	O
[0410]				H	O
962				H	O
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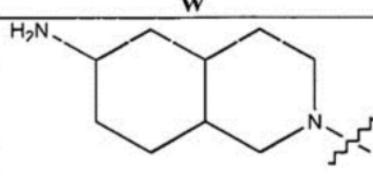
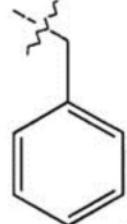
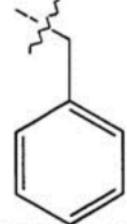
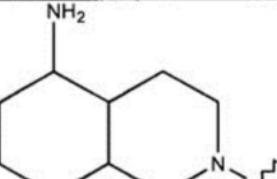
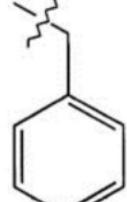
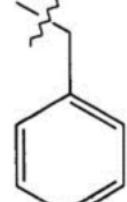
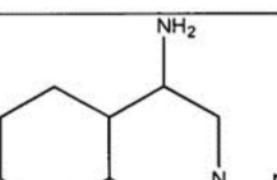
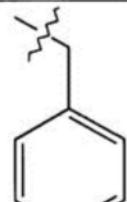
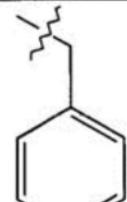
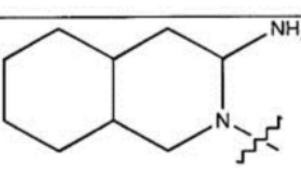
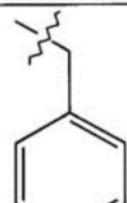
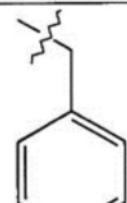
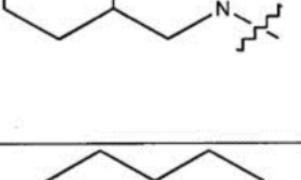
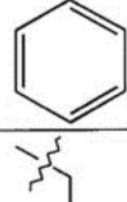
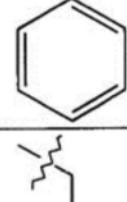
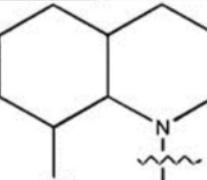
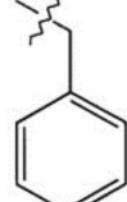
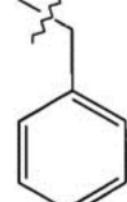
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[0411]				H	O
967				H	O
968				H	O
969				H	O

Cmpd	W	X	Z	A	Q
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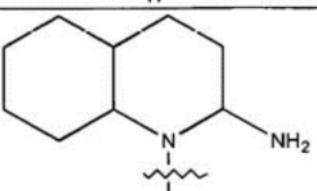
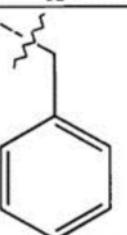
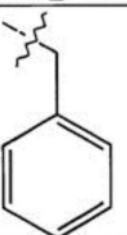
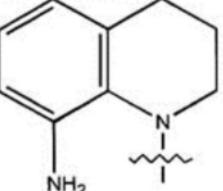
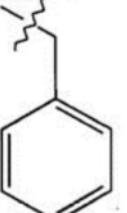
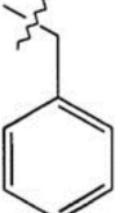
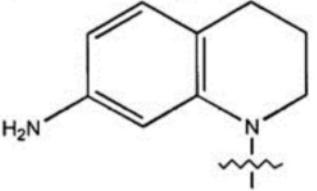
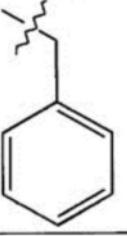
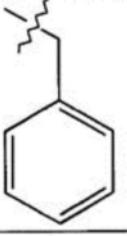
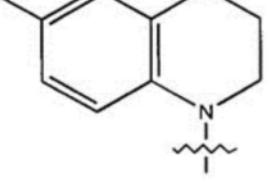
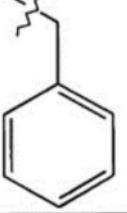
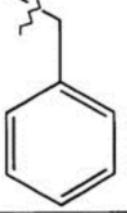
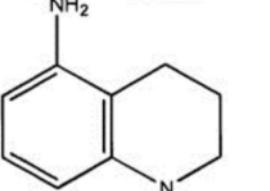
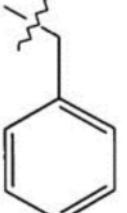
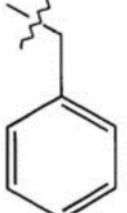
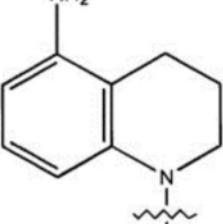
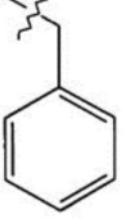
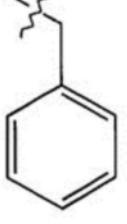
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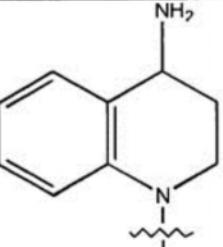
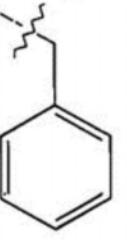
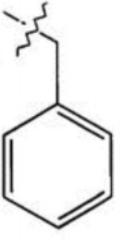
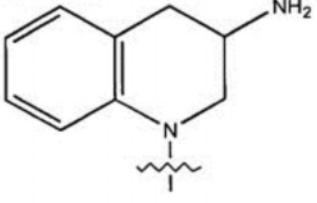
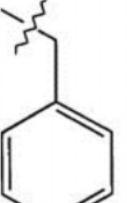
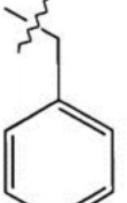
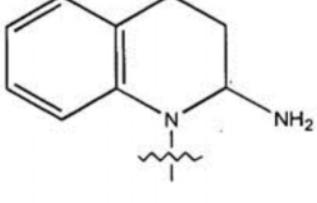
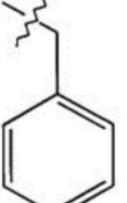
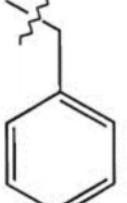
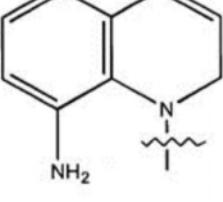
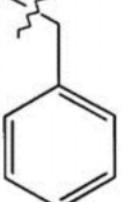
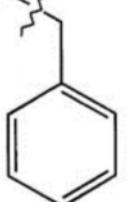
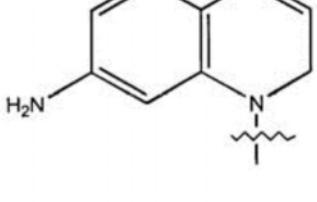
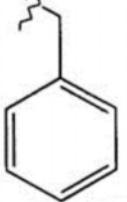
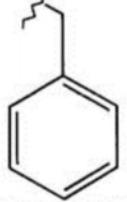
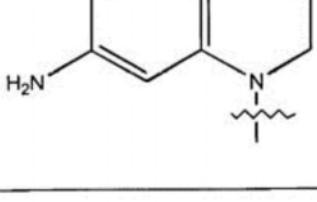
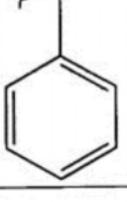
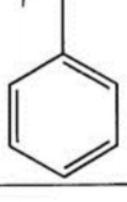
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Cmpd	W	X	Z	A	Q
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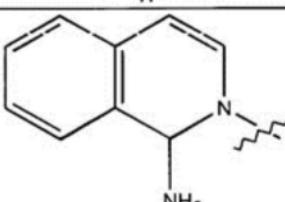
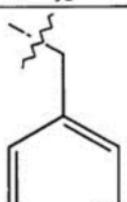
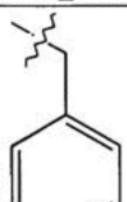
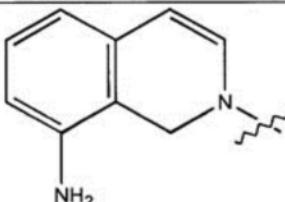
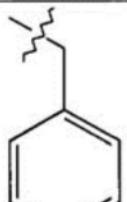
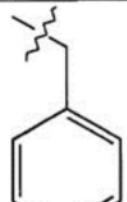
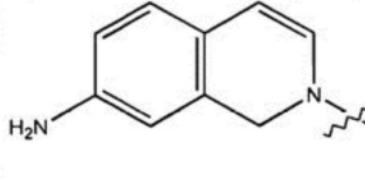
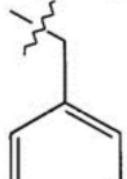
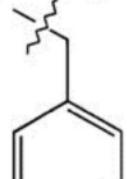
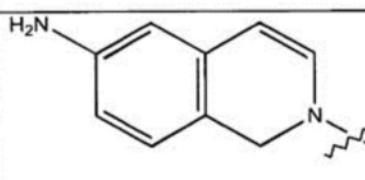
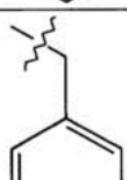
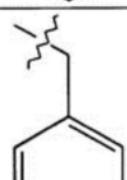
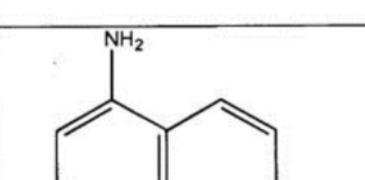
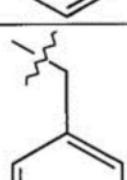
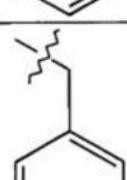
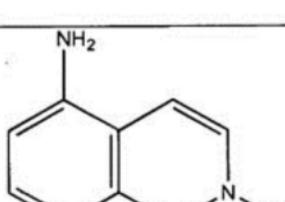
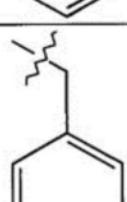
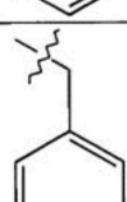
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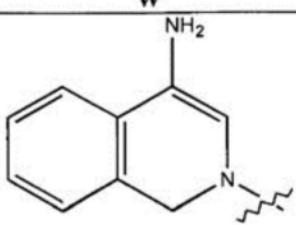
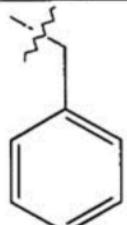
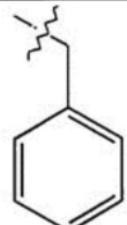
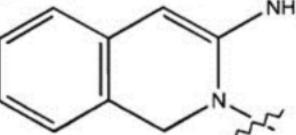
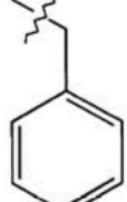
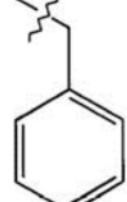
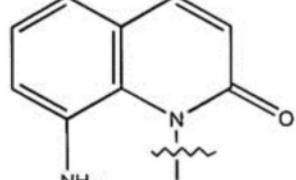
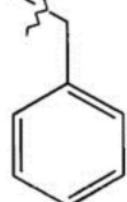
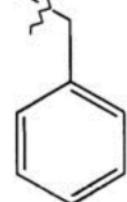
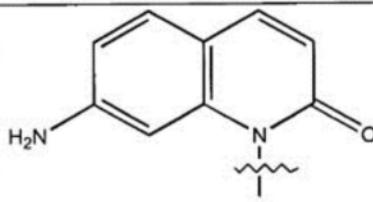
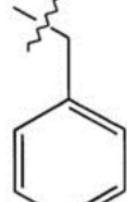
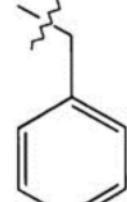
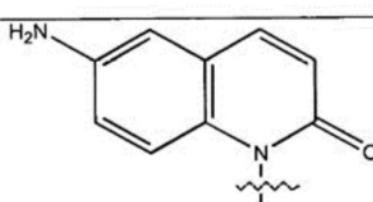
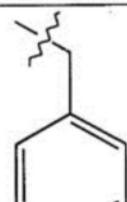
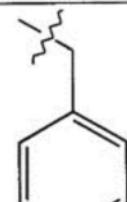
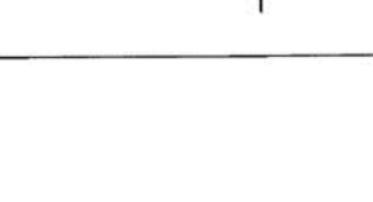
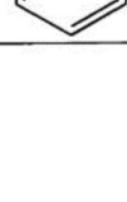
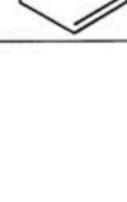
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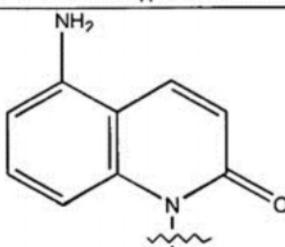
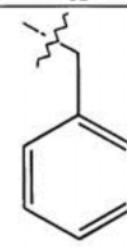
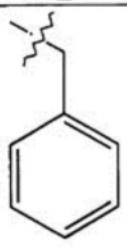
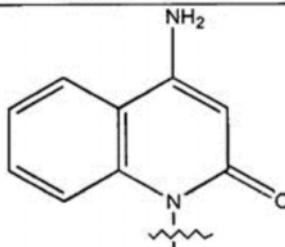
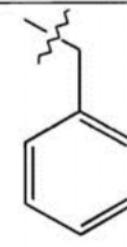
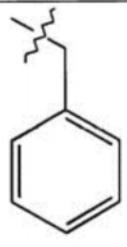
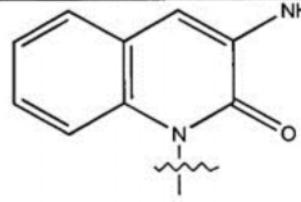
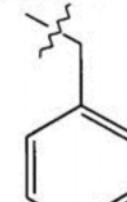
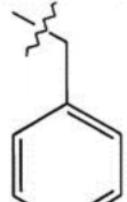
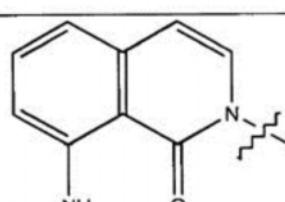
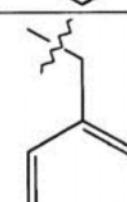
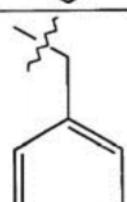
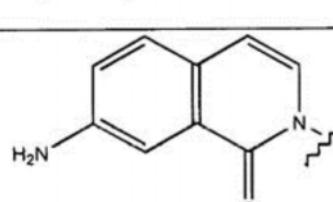
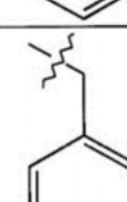
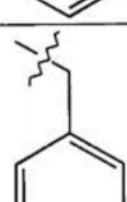
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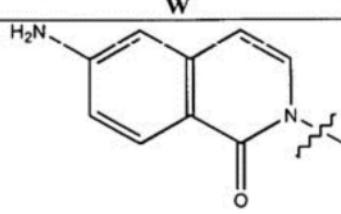
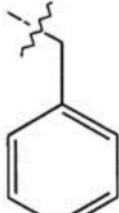
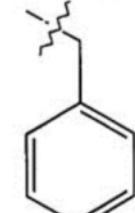
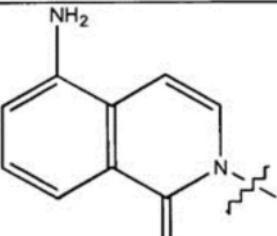
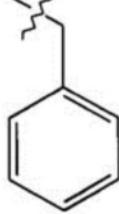
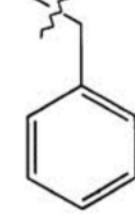
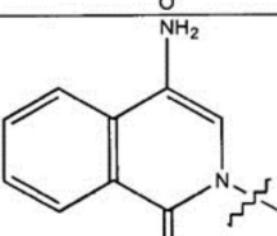
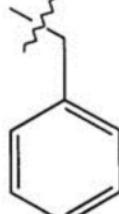
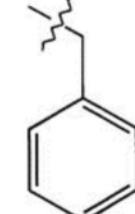
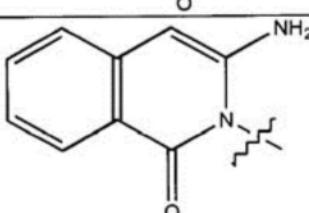
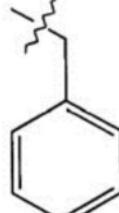
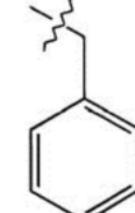
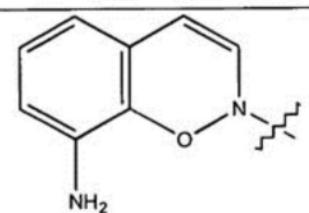
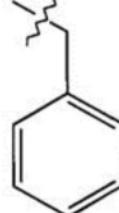
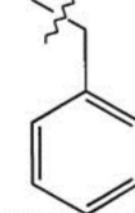
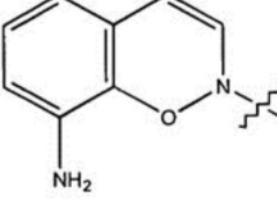
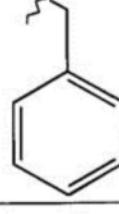
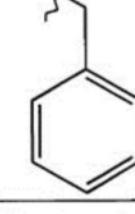
Cmpd	W	X	Z	A	Q
1004				H	O
1005				H	O
[0419]				H	O
1006				H	O
1007				H	O
1008				H	O

Cmpd	W	X	Z	A	Q
1009				H	O
1010				H	O
[0420]				H	O
1011				H	O
1012				H	O
1013				H	O

Cmpd	W	X	Z	A	Q
1014				H	O
1015				H	O
[0421]				II	O
1016				H	O
1017				H	O
1018				H	O

Cmpd	W	X	Z	A	Q
1019				H	O
1020				H	O
[0422]				H	O
1021				H	O
1022				H	O
1023				H	O

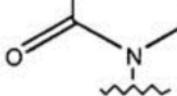
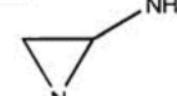
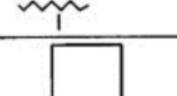
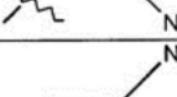
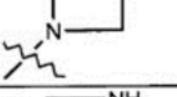
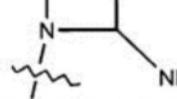
Cmpd	W	X	Z	A	Q
1024				H	O
1025				H	O
[0423]				H	O
1027				H	O
1028				H	O

Cmpd	W	X	Z	A	Q
1029				H	O
1030				H	O
[0424]				H	O
1031				H	O
1032				H	O
1033				H	O

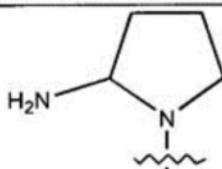
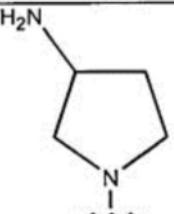
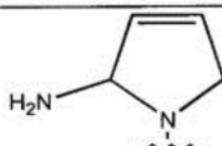
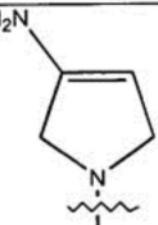
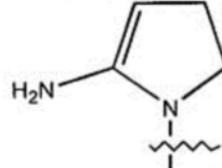
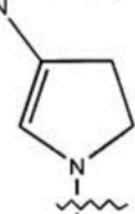
Cmpd	W	X	Z	A	Q
1034				H	O
1035				H	O
[0425]				H	O
1036				H	O
1037				H	O
1038				H	O

Cmpd	W	X	Z	A	Q
1039				H	O
1040				H	O
[0426]				H	O
1041				H	O
1042				H	O
1043				H	O

Cmpd	W	X	Z	A	Q
1044				H	O
1045				H	O
1046				H	O
[0427]				H	O
1047				H	O
1048				H	O
1049				H	O
1050				H	O

Cmpd	W	X	Z	A	Q
1051		HO-----	HO-----	H	O
1052		HO-----	HO-----	H	O
1053		HO-----	HO-----	H	O
1054		HO-----	HO-----	H	O
1055		HO-----	HO-----	H	O
1056		HO-----	HO-----	H	O
1057		HO-----	HO-----	H	O

[0428]

Cmpd	W	X	Z	A	Q
1058				H	O
1059				H	O
1060				H	O
[0429]					
1061				H	O
1062				H	O
1063				H	O

Cmpd	W	X	Z	A	Q
1064		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1065		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1066		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
[0430]		.	.		
1067		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1068		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1069		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O

Cmpd	W	X	Z	A	Q
1070		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1071		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1072		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
[0431]					
1073		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1074		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1075		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O

Cmpd	W	X	Z	A	Q
1076		HO <chem>CCCCC[C@H](O)C</chem>	HO <chem>CCCCC[C@H](O)C</chem>	H	O
1077		HO <chem>CCCCC[C@H](O)C</chem>	HO <chem>CCCCC[C@H](O)C</chem>	H	O
1078		HO <chem>CCCCC[C@H](O)C</chem>	HO <chem>CCCCC[C@H](O)C</chem>	H	O
[0432]					
1079		HO <chem>CCCCC[C@H](O)C</chem>	HO <chem>CCCCC[C@H](O)C</chem>	H	O
1080		HO <chem>CCCCC[C@H](O)C</chem>	HO <chem>CCCCC[C@H](O)C</chem>	H	O
1081		HO <chem>CCCCC[C@H](O)C</chem>	HO <chem>CCCCC[C@H](O)C</chem>	H	O

Cmpd	W	X	Z	A	Q
1082				H	O
1083				H	O
[0433]				H	O
1085				H	O
1086				H	O

Cmpd	W	X	Z	A	Q
1087				H	O
1088				H	O
1089				H	O
[0434]					
1090				H	O
1091				H	O
1092				H	O

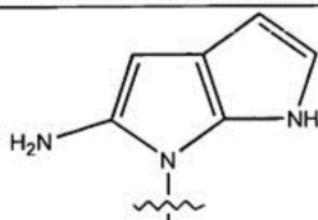
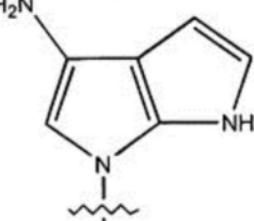
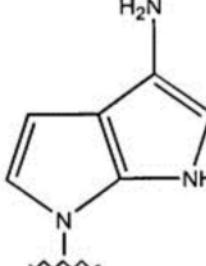
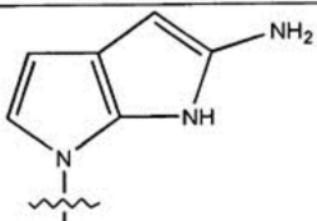
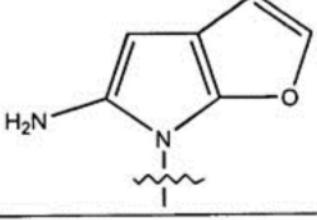
Cmpd	W	X	Z	A	Q
1093		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	H	O
1094		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	H	O
[0435]		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	H	O
1095		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	H	O
1096		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	H	O
1097		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	H	O
1098		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	H	O

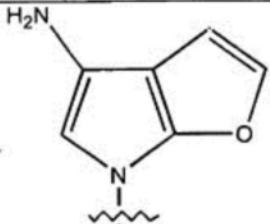
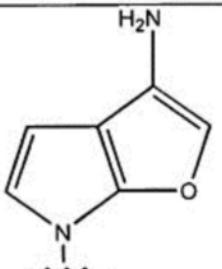
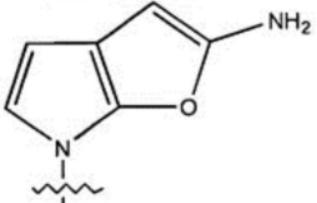
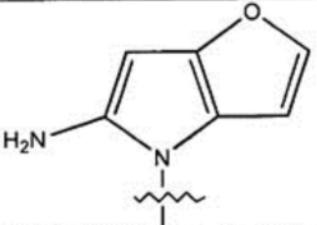
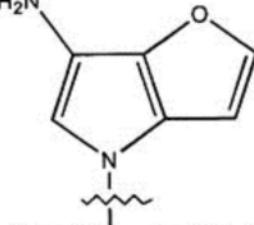
Cmpd	W	X	Z	A	Q
1099				H	O
1100				H	O
[0436]			*		
1101				H	O
1102				H	O
1103				H	O

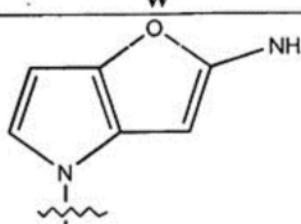
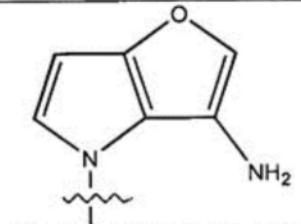
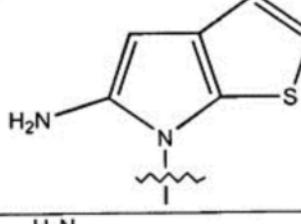
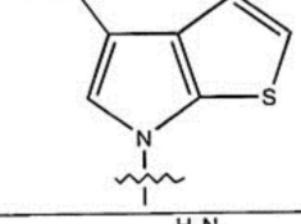
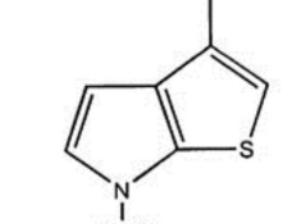
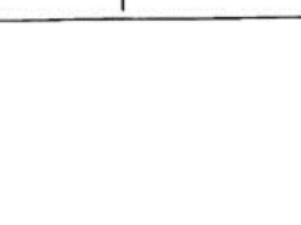
Cmpd	W	X	Z	A	Q
1104		HO	HO	H	O
1105		HO	HO	H	O
[0437]		HO	HO	H	O
1106		HO	HO	H	O
1107		HO	HO	H	O
1108		HO	HO	H	O

Cmpd	W	X	Z	A	Q
1109				H	O
1110				H	O
[0438]				H	O
1111				H	O
1112				H	O
1113				H	O

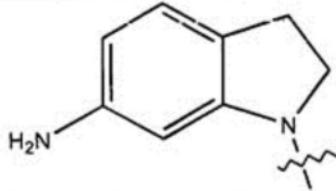
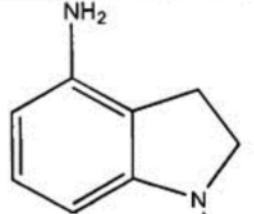
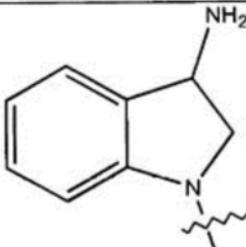
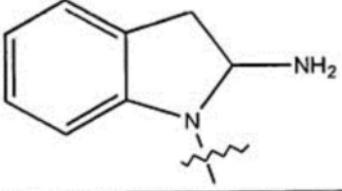
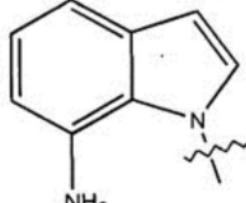
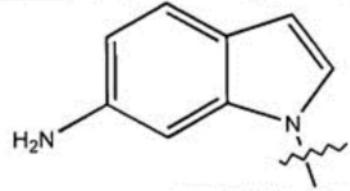
Cmpd	W	X	Z	A	Q
1114		HO	HO	H	O
1115		HO	HO	H	O
[0439]		HO	HO	H	O
1117		HO	HO	H	O
1118		HO	HO	H	O

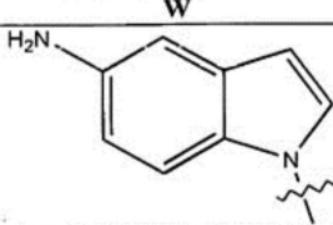
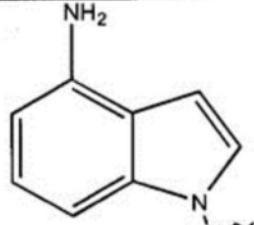
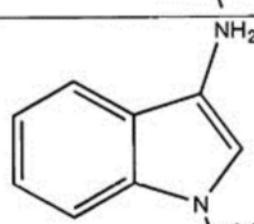
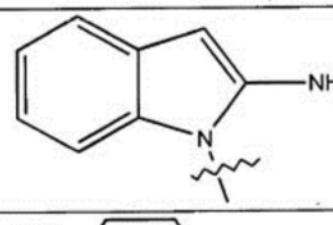
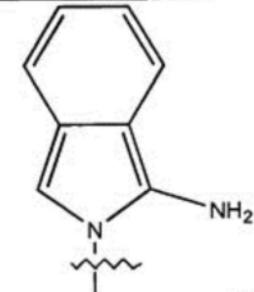
Cmpd	W	X	Z	A	Q
1119		HOCCCCC	HOCCCCC	H	O
1120		HOCCCCC	HOCCCCC	H	O
[0440]		HOCCCCC	HOCCCCC	H	O
1122		HOCCCCC	HOCCCCC	H	O
1123		HOCCCCC	HOCCCCC	H	O

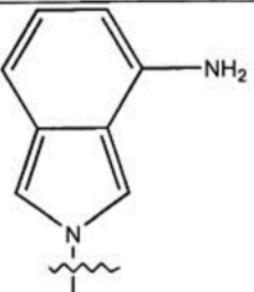
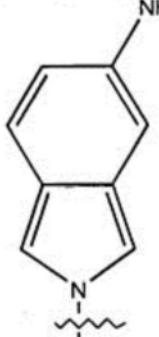
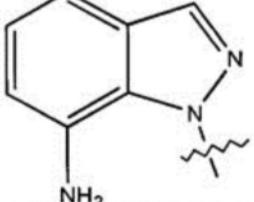
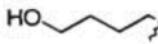
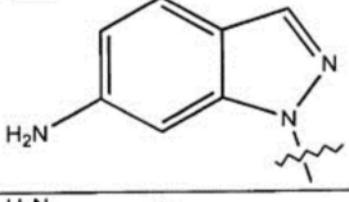
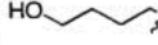
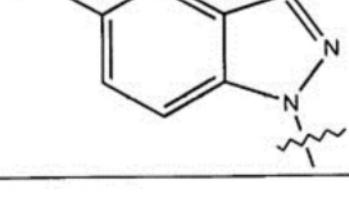
Cmpd	W	X	Z	A	Q
1124		HO 	HO 	H	O
1125		HO 	HO 	H	O
[0441]		HO 	HO 	H	O
1127		HO 	HO 	H	O
1128		HO 	HO 	H	O

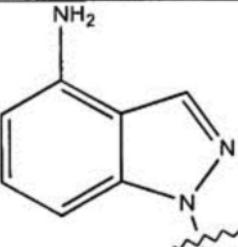
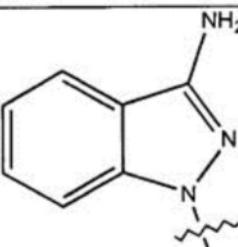
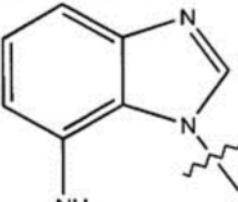
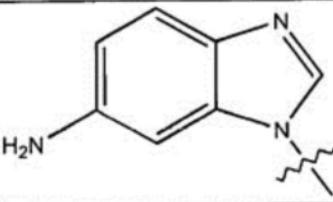
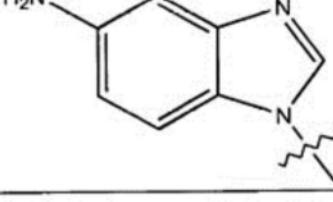
Cmpd	W	X	Z	A	Q
1129		HO <chem>CCCCC/C=C\CCCC</chem>	HO <chem>CCCCC/C=C\CCCC</chem>	H	O
1130		HO <chem>CCCCC/C=C\CCCC</chem>	HO <chem>CCCCC/C=C\CCCC</chem>	H	O
[0442]		HO <chem>CCCCC/C=C\CCCC</chem>	HO <chem>CCCCC/C=C\CCCC</chem>	H	O
1131		HO <chem>CCCCC/C=C\CCCC</chem>	HO <chem>CCCCC/C=C\CCCC</chem>	H	O
1132		HO <chem>CCCCC/C=C\CCCC</chem>	HO <chem>CCCCC/C=C\CCCC</chem>	H	O
1133		HO <chem>CCCCC/C=C\CCCC</chem>	HO <chem>CCCCC/C=C\CCCC</chem>	H	O

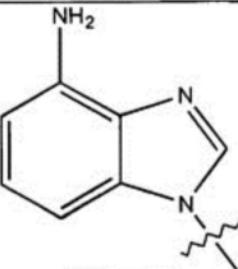
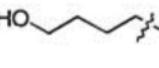
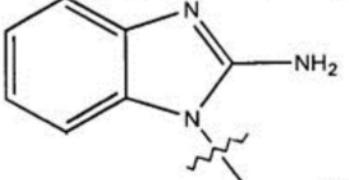
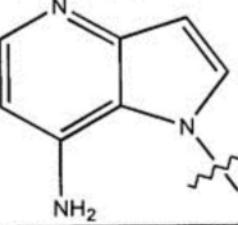
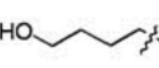
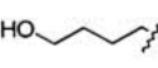
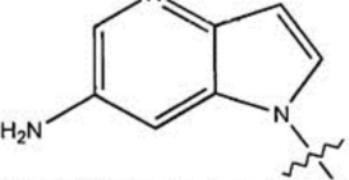
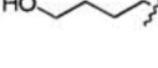
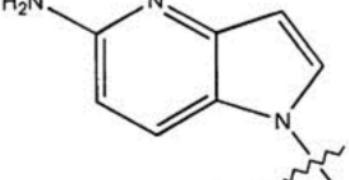
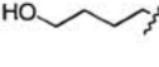
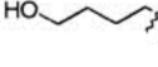
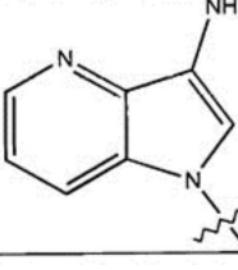
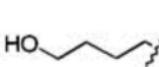
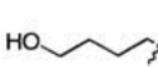
Cmpd	W	X	Z	A	Q
1134				H	O
1135				H	O
[0443]				H	O
1137				H	O
1138				H	O
1139				H	O

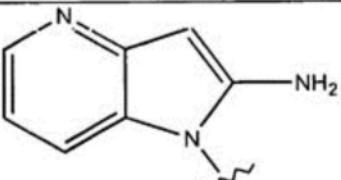
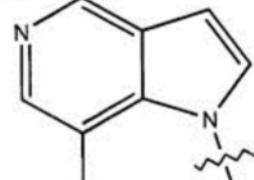
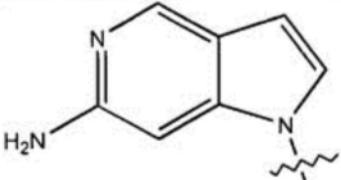
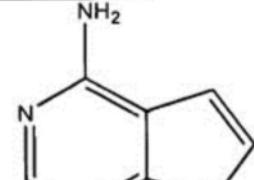
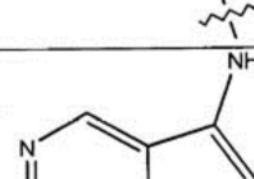
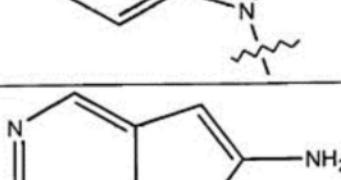
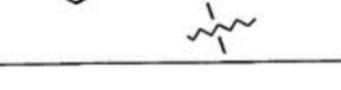
Cmpd	W	X	Z	A	Q
1140		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
1141		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
[0444]		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
1143		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
1144		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
1145		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O

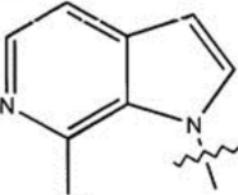
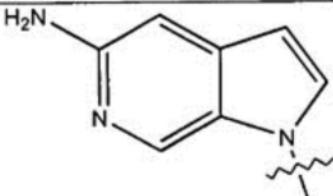
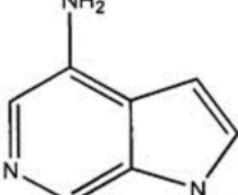
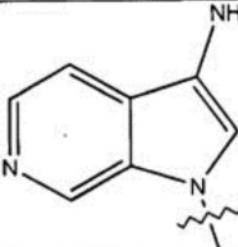
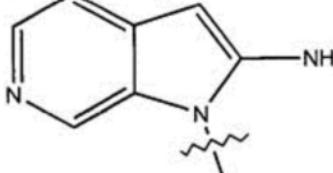
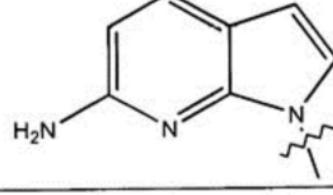
Cmpd	W	X	Z	A	Q
1146		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1147		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
[0445]		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1149		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1150		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O

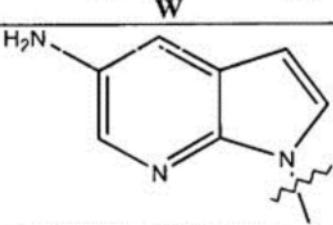
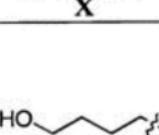
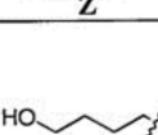
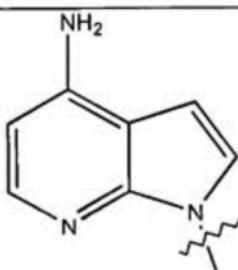
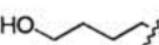
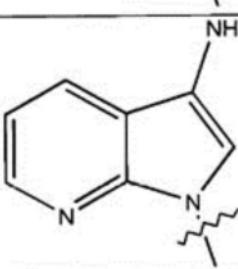
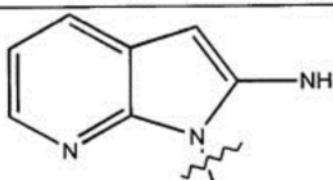
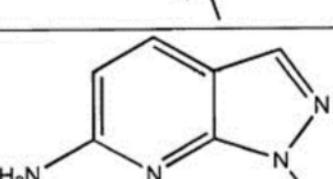
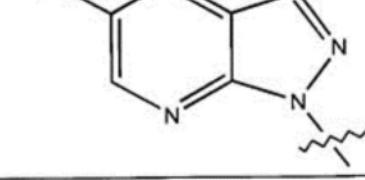
Cmpd	W	X	Z	A	Q
1151		HO 	HO 	H	O
[0446]		HO 	HO 	H	O
1153		HO 	HO 	H	O
1154		HO 	HO 	H	O
1155		HO 	HO 	H	O

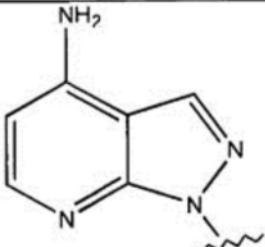
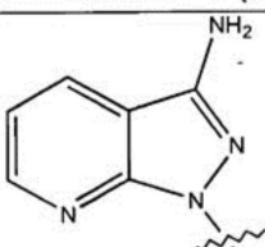
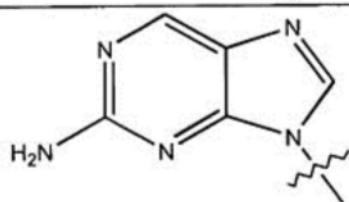
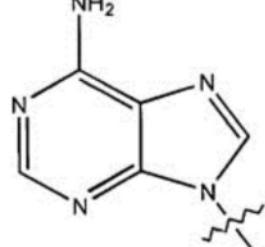
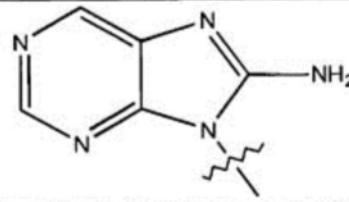
Cmpd	W	X	Z	A	Q
1156		HO 	HO 	H	O
1157		HO 	HO 	H	O
[0447]		HO 	HO 	H	O
1159		HO 	HO 	H	O
1160		HO 	HO 	H	O

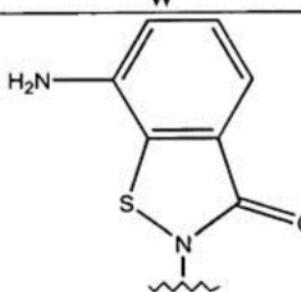
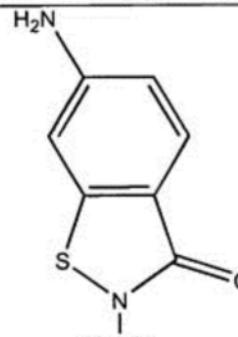
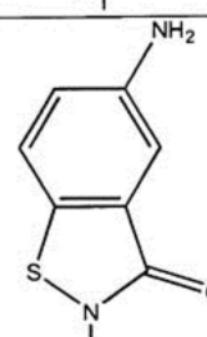
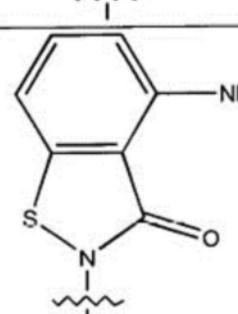
Cmpd	W	X	Z	A	Q
1161		HO 	HO 		O
1162		HO 	HO 	H	O
[0448]		HO 	HO 	H	O
1164		HO 	HO 	H	O
1165		HO 	HO 	H	O
1166		HO 	HO 	H	O

Cmpd	W	X	Z	A	Q
1167		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1168		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1169		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
[0449]		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1170		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1171		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1172		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O

Cmpd	W	X	Z	A	Q
1173		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
1174		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
[0450]		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
1176		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
1177		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O
1178		HO <chem>CCCCC(O)C</chem>	HO <chem>CCCCC(O)C</chem>	H	O

Cmpd	W	X	Z	A	Q
1179				H	O
1180				H	O
[0451]				H	O
1181				H	O
1182				H	O
1183				H	O
1184				H	O

Cmpd	W	X	Z	A	Q
1185		HO <chem>CCCCC/C=C\</chem>	HO <chem>CCCCC/C=C\</chem>	H	O
1186		HO <chem>CCCCC/C=C\</chem>	HO <chem>CCCCC/C=C\</chem>	H	O
[0452]		HO <chem>CCCCC/C=C\</chem>	HO <chem>CCCCC/C=C\</chem>	H	O
1188		HO <chem>CCCCC/C=C\</chem>	HO <chem>CCCCC/C=C\</chem>	H	O
1189		HO <chem>CCCCC/C=C\</chem>	HO <chem>CCCCC/C=C\</chem>	H	O

Cmpd	W	X	Z	A	Q
1190		HO 	HO 	H	O
[0453]		HO 	HO 	H	O
1192		HO 	HO 	H	O
1193		HO 	HO 	H	O

Cmpd	W	X	Z	A	Q
1194		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1195		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
[0454]		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1196		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1197		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1198		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O
1199		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	H	O

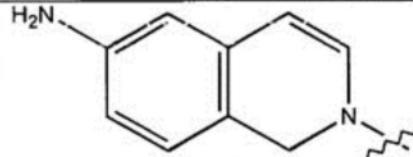
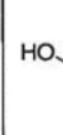
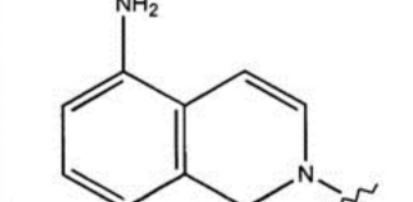
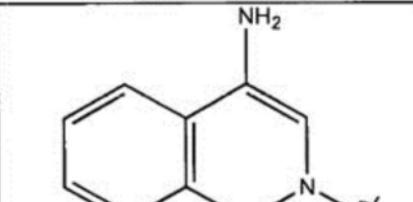
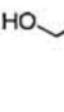
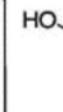
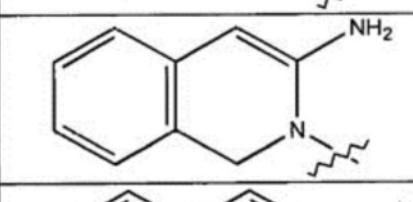
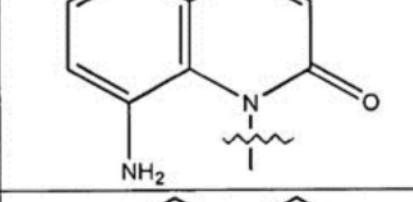
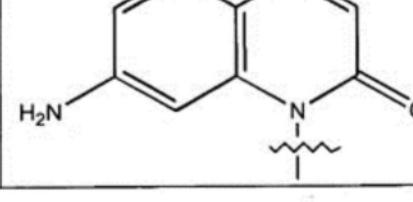
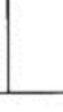
Cmpd	W	X	Z	A	Q
1200		HO	HO	H	O
1201		HO	HO	H	O
1202		HO	HO	H	O
[0455]					
1203		HO	HO	H	O
1204		HO	HO	H	O
1205		HO	HO	H	O

Cmpd	W	X	Z	A	Q
1206		HO	HO	H	O
1207		HO	HO	H	O
[0456]					
1208		HO	HO	H	O
1209		HO	HO	H	O
1210		HO	HO	H	O

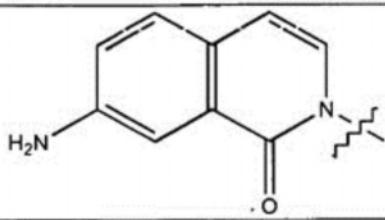
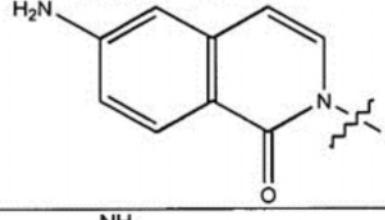
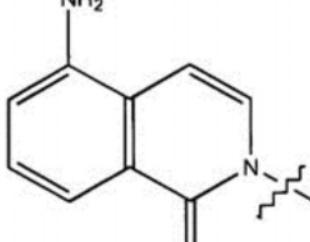
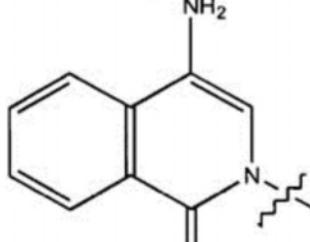
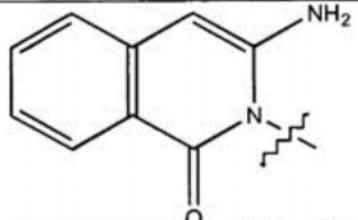
Cmpd	W	X	Z	A	Q
1211		HO	HO	H	O
1212		HO	HO	H	O
[0457]		HO	HO	H	O
1213					
1214		HO	HO	H	O
1215		HO	HO	H	O

Cmpd	W	X	Z	A	Q
1216				H	O
1217				H	O
[0458]				H	O
1218				H	O
1219				H	O
1220				H	O

Cmpd	W	X	Z	A	Q
1221				H	O
1222				H	O
[0459]				H	O
1224				H	O
1225				H	O
1226				H	O

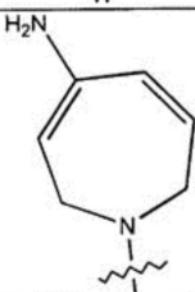
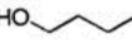
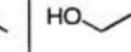
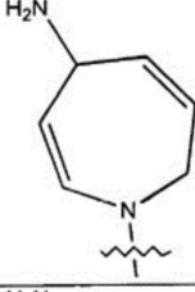
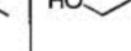
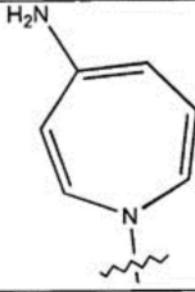
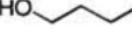
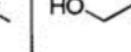
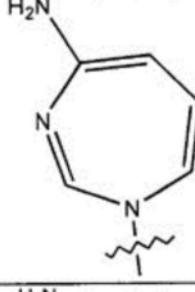
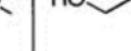
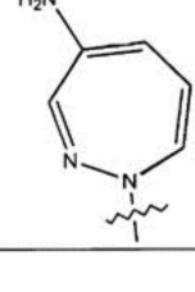
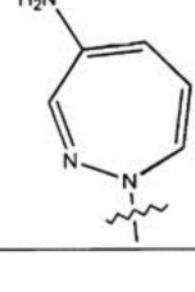
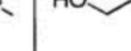
Cmpd	W	X	Z	A	Q
1227		HO 	HO 	H	O
1228		HO 	HO 	H	O
[0460]		HO 	HO 	H	O
1230		HO 	HO 	H	O
1231		HO 	HO 	H	O
1232		HO 	HO 	H	O

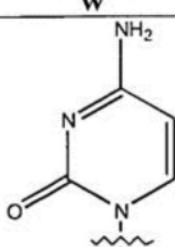
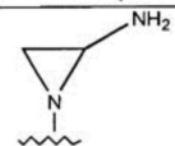
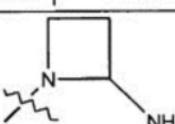
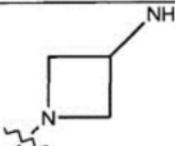
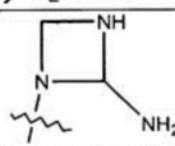
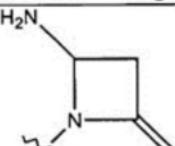
Cmpd	W	X	Z	A	Q
1233				H	O
1234				H	O
[0461]					
1235				H	O
1236				H	O
1237				H	O

Cmpd	W	X	Z	A	Q
1238		HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Cc2ccccc2C1N</chem>	HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Cc2ccccc2C1N</chem>	H	O
1239		HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Cc2ccccc2C1N</chem>	HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Cc2ccccc2C1N</chem>	H	O
[0462]		HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Nc2ccccc2C1</chem>	HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Nc2ccccc2C1</chem>	H	O
1241		HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Cc2ccccc2C1N</chem>	HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Cc2ccccc2C1N</chem>	H	O
1242		HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Cc2ccccc2C1N</chem>	HO <chem>CCCCC[C@H]1CC(=O)N(CCCC)Cc2ccccc2C1N</chem>	H	O

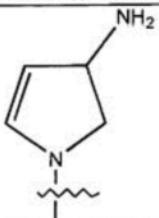
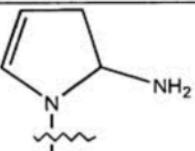
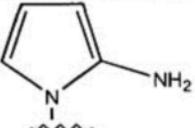
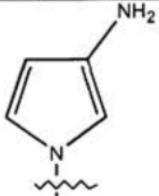
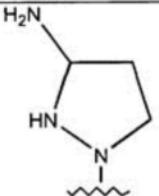
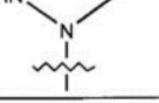
Cmpd	W	X	Z	A	Q
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1244		HO	HO	H	O
1245		HO	HO	H	O
[0463]		HO	HO	H	O
1247		HO	HO	H	O
1248		HO	HO	H	O
1249		HO	HO	H	O

Cmpd	W	X	Z	A	Q	
1250		HO	HO	H	O	
1251		HO	HO	H	O	
[0464]	1252		HO	HO	H	O
1253		HO	HO	H	O	
1254		HO	HO	H	O	
1255		HO	HO	H	O	

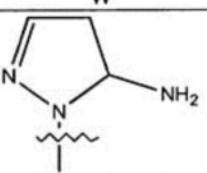
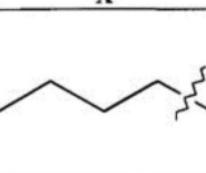
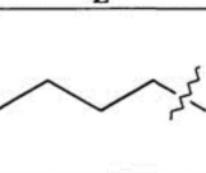
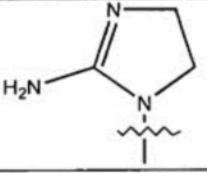
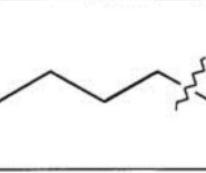
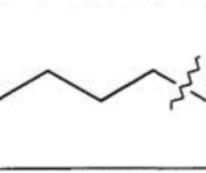
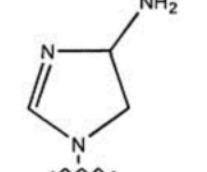
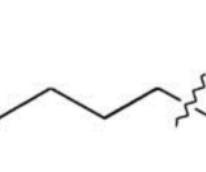
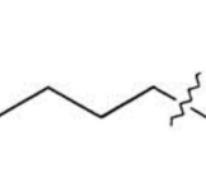
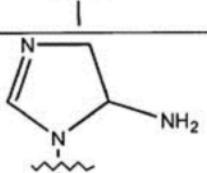
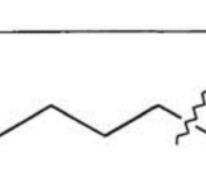
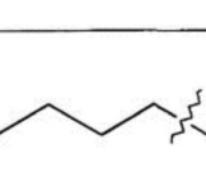
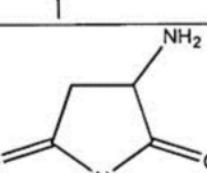
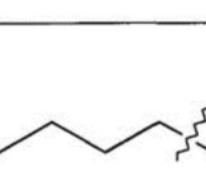
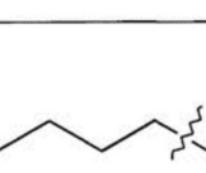
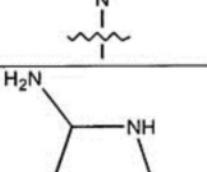
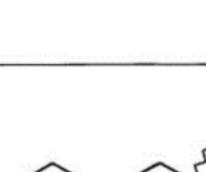
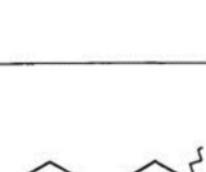
Cmpd	W	X	Z	A	Q
1256		HO 	HO 	H	O
1257		HO 	HO 	H	O
[0465]		HO 	HO 	H	O
1258		HO 	HO 	H	O
1259		HO 	HO 	H	O
1260		HO 	HO 	H	O

Cmpd	W	X	Z	A	Q
1261				OMe	O
1262				OMe	O
1263				OMe	O
[0466]					
1264				OMe	O
1265				OMe	O
1266				OMe	O
1267				OMe	O

Cmpd	W	X	Z	A	Q
1268				OMe	O
1269				OMe	O
1270				OMe	O
[0467]					
1271				OMe	O
1272				OMe	O
1273				OMe	O

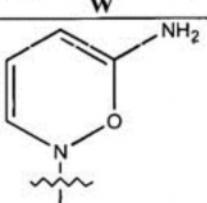
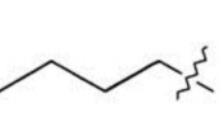
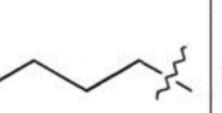
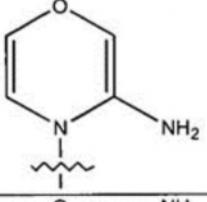
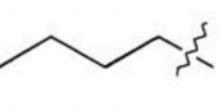
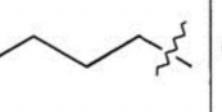
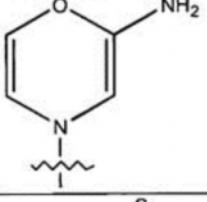
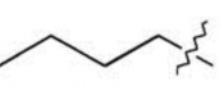
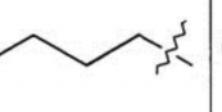
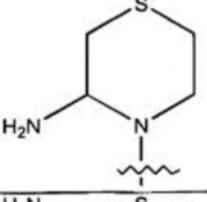
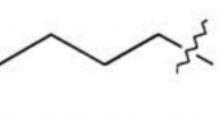
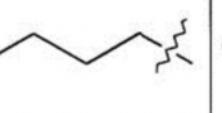
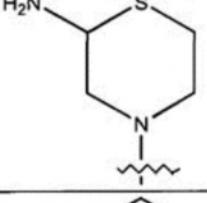
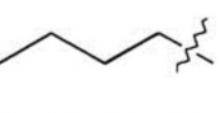
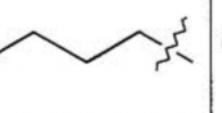
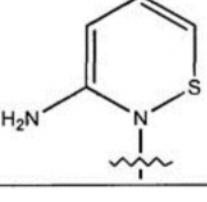
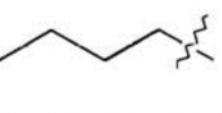
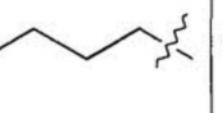
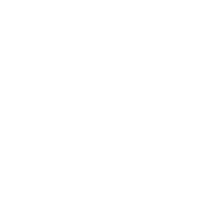
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1275				OMe	O
1276				OMe	O
[0468]				OMe	O
1277				OMe	O
1278				OMe	O
1279				OMe	O

Cmpd	W	X	Z	A	Q
1280				OMe	O
1281				OMe	O
1282				OMe	O
[0469]					
1283				OMe	O
1284				OMe	O
1285				OMe	O

Cmpd	W	X	Z	A	Q
1286				OMe	O
1287				OMe	O
1288				OMe	O
[0470]					
1289				OMe	O
1290				OMe	O
1291				OMe	O

Cmpd	W	X	Z	A	Q
1292				OMe	O
1293				OMe	O
[0471]				OMe	O
1294				OMe	O
1295				OMe	O
1296				OMe	O

Cmpd	W	X	Z	A	Q
1297				OMe	O
1298				OMe	O
1299				OMe	O
[0472]					
1300				OMe	O
1301				OMe	O
1302				OMe	O

Cmpd	W	X	Z	A	Q
1303				OMe	O
1304				OMe	O
[0473]				OMe	O
1305				OMe	O
1306				OMe	O
1307				OMe	O
1308				OMe	O

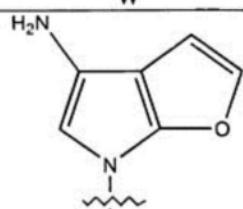
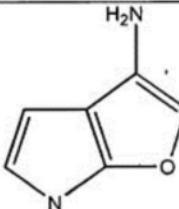
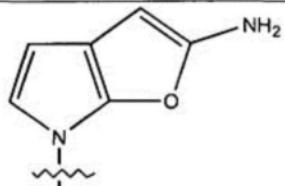
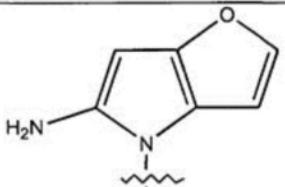
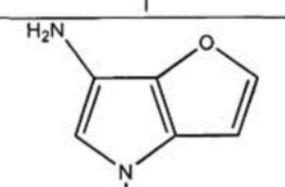
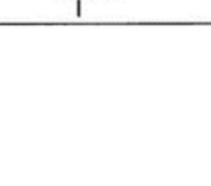
Cmpd	W	X	Z	A	Q
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1310				OMe	O
[0474]				OMe	O
1311				OMe	O
1312				OMe	O
1313				OMe	O

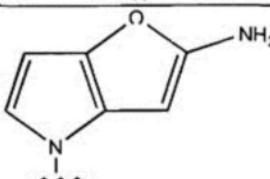
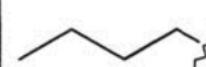
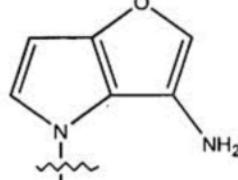
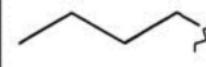
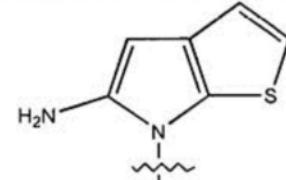
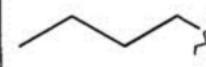
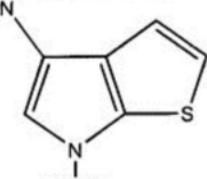
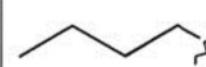
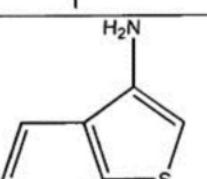
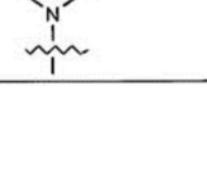
Cmpd	W	X	Z	A	Q
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1315				OMe	O
[0475]				OMe	O
1316				OMe	O
1317				OMe	O
1318				OMe	O

Cmpd	W	X	Z	A	Q
1319				OMe	O
1320				OMe	O
[0476]				OMe	O
1321				OMe	O
1322				OMe	O
1323				OMe	O

Cmpd	W	X	Z	A	Q
1324				OMe	O
1325				OMe	O
[0477]				OMe	O
1326				OMe	O
1327				OMe	O
1328				OMe	O

Cmpd	W	X	Z	A	Q
1329				OMe	O
1330				OMe	O
[0478]				OMe	O
1332				OMe	O
1333				OMe	O

Cmpd	W	X	Z	A	Q
1334				OMe	O
1335				OMe	O
[0479]				OMe	O
1336				OMe	O
1337				OMe	O
1338				OMe	O

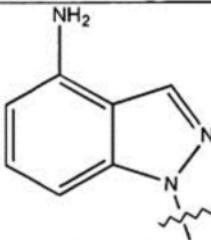
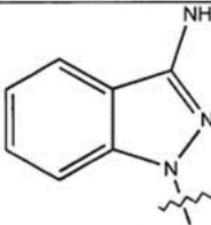
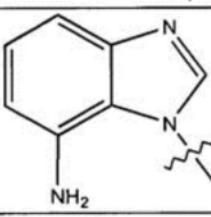
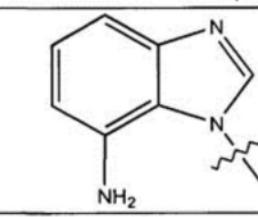
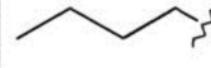
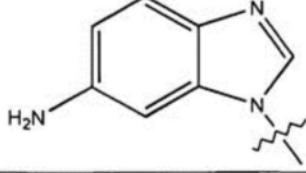
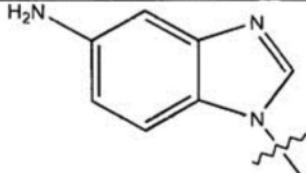
Cmpd	W	X	Z	A	Q
1339				OMe	O
1340				OMe	O
[0480]				OMe	O
1341				OMe	O
1342				OMe	O
1343				OMe	O

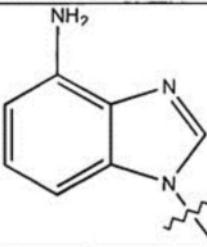
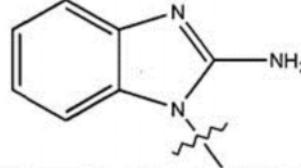
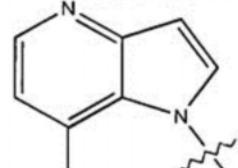
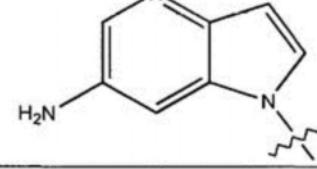
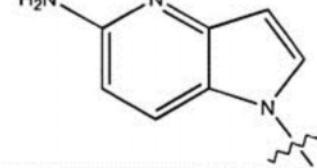
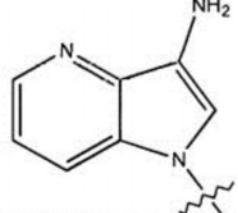
Cmpd	W	X	Z	A	Q
1344				OMe	O
1345				OMe	O
[0481]				OMe	O
1346				OMe	O
1347				OMe	O
1348				OMe	O
1349				OMe	O

Cmpd	W	X	Z	A	Q
1350				OMe	O
1351				OMe	O
[0482]				OMe	O
1352				OMe	O
1353				OMe	O
1354				OMe	O
1355				OMe	O

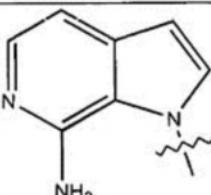
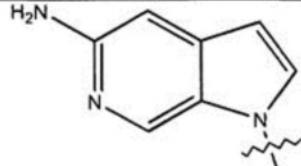
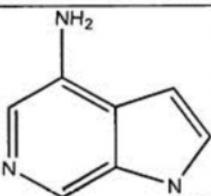
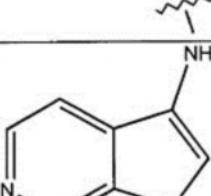
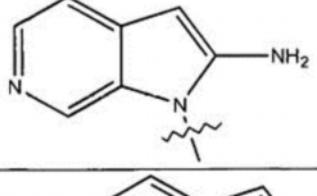
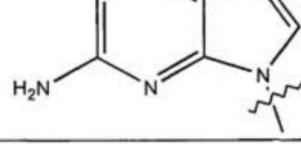
Cmpd	W	X	Z	A	Q
1356				OMe	O
1357				OMe	O
[0483]				OMe	O
1358				OMe	O
1359				OMe	O
1360				OMe	O

Cmpd	W	X	Z	A	Q	
1361				OMe	O	
[0484]	1362				OMe	O
	1363				OMe	O
	1364				OMe	O
	1365				OMe	O

Cmpd	W	X	Z	A	Q
1366				OMe	O
1367				OMe	O
[0485]				OMe	O
1368				OMe	O
1369				OMe	O
1370				OMe	O

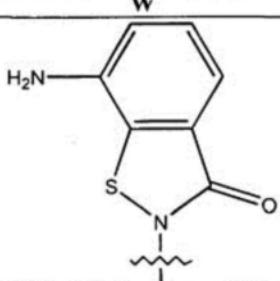
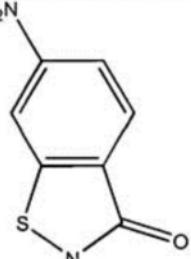
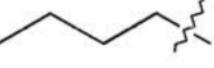
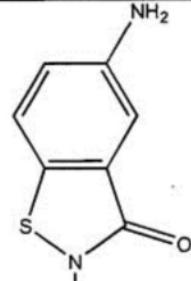
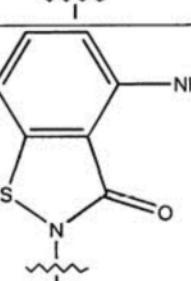
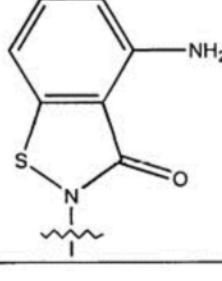
Cmpd	W	X	Z	A	Q	
1371					O	
1372				OMe	O	
[0486]	1373				OMe	O
	1374				OMe	O
	1375				OMe	O
	1376				OMe	O

Cmpd	W	X	Z	A	Q
1377				OMe	O
1378				OMe	O
1379				OMe	O
[0487]				OMe	O
1380				OMe	O
1381				OMe	O
1382				OMe	O

Cmpd	W	X	Z	A	Q
1383				OMe	O
1384				OMe	O
[0488]				OMe	O
1385				OMe	O
1386				OMe	O
1387				OMe	O
1388				OMe	O

Cmpd	W	X	Z	A	Q
1389				OMe	O
1390				OMe	O
[0489]				OMe	O
1391				OMe	O
1392				OMe	O
1393				OMe	O
1394				OMe	O

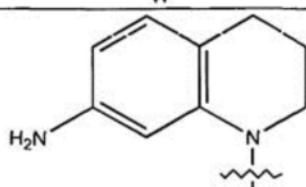
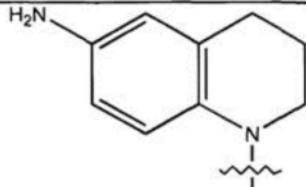
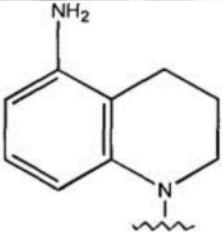
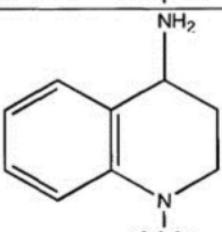
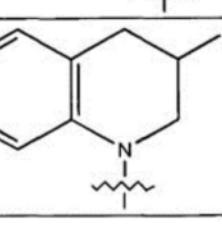
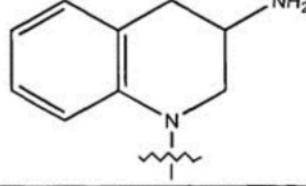
Cmpd	W	X	Z	A	Q
1395				OMe	O
1396				OMe	O
[0490]				OMe	O
1397				OMe	O
1398				OMe	O
1399				OMe	O

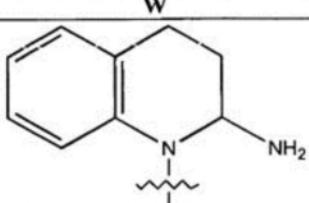
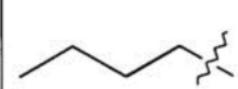
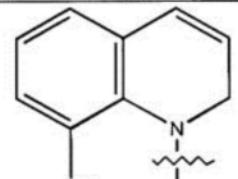
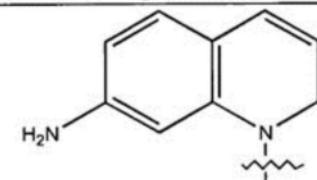
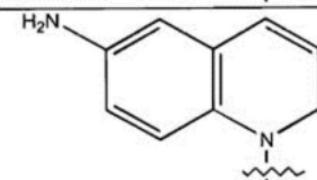
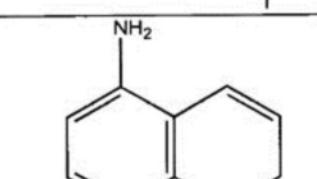
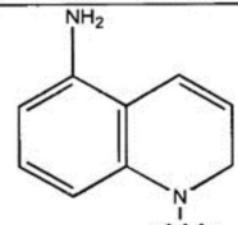
Cmpd	W	X	Z	A	Q
1400				OMe	O
[0491]				OMe	O
1401				OMe	O
1402				OMe	O
1403				OMe	O

Cmpd	W	X	Z	A	Q
1404				OMe	O
1405				OMe	O
[0492]				OMe	O
1406				OMe	O
1407				OMe	O
1408				OMe	O
1409				OMe	O

Cmpd	W	X	Z	A	Q
1410				OMe	O
1411				OMe	O
1412				OMe	O
[0493]					
1413				OMe	O
1414				OMe	O
1415				OMe	O

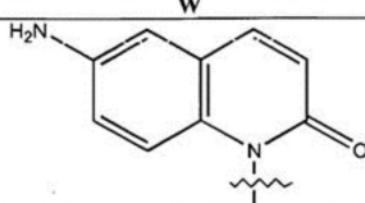
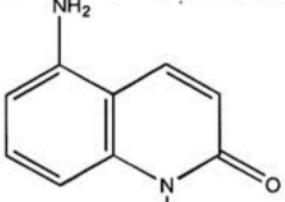
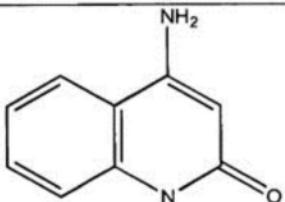
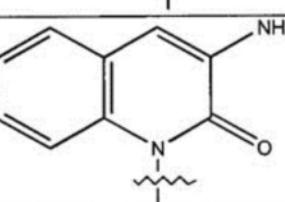
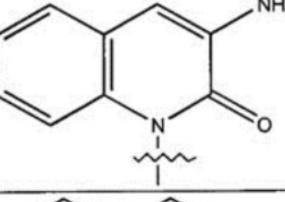
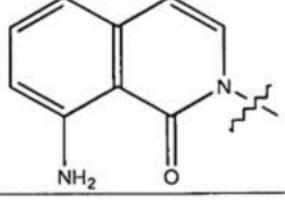
Cmpd	W	X	Z	A	Q
1416				OMe	O
1417				OMe	O
[0494]					
1418				OMe	O
1419				OMe	O
1420				OMe	O

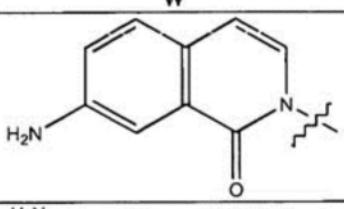
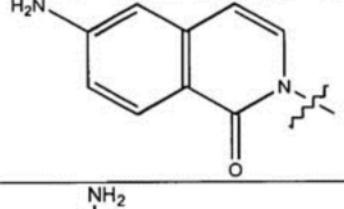
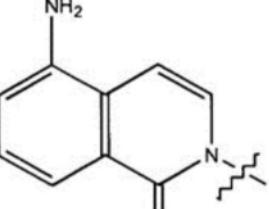
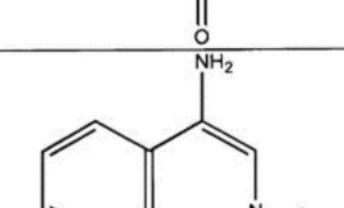
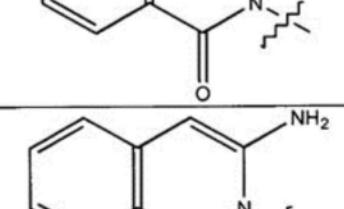
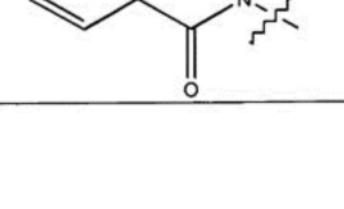
Cmpd	W	X	Z	A	Q
1421				OMe	O
1422				OMe	O
[0495]				OMe	O
1423				OMe	O
1424				OMe	O
1425				OMe	O

Cmpd	W	X	Z	A	Q
1426				OMe	O
1427				OMe	O
[0496]				OMe	O
1428				OMe	O
1429				OMe	O
1430				OMe	O

Cmpd	W	X	Z	A	Q
1431				OMe	O
1432				OMe	O
[0497]				OMe	O
1433				OMe	O
1434				OMe	O
1435				OMe	O
1436				OMe	O

Cmpd	W	X	Z	A	Q
1437				OMe	O
1438				OMe	O
[0498]				OMe	O
1439				OMe	O
1440				OMe	O
1441				OMe	O
1442				OMe	O

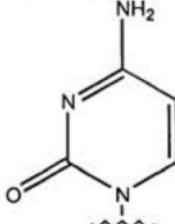
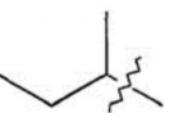
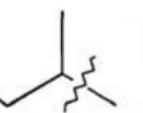
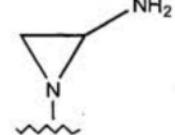
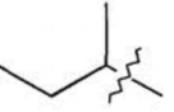
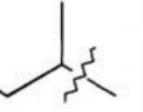
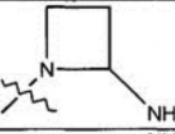
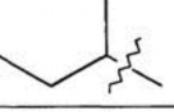
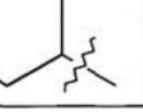
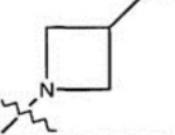
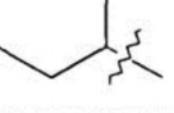
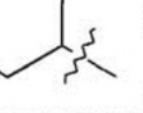
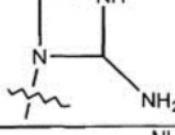
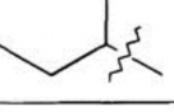
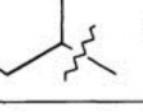
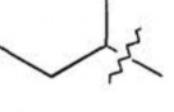
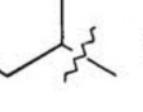
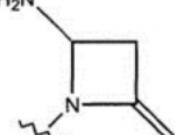
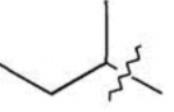
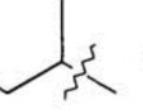
Cmpd	W	X	Z	A	Q
1443				OMe	O
1444				OMe	O
[0499]				OMe	O
1445				OMe	O
1446				OMe	O
1447				OMe	O

Cmpd	W	X	Z	A	Q
1448				OMe	O
1449				OMe	O
[0500]				OMe	O
1450				OMe	O
1451				OMe	O
1452				OMe	O

Cmpd	W	X	Z	A	Q
1453				OMe	O
1454				OMe	O
1455				OMe	O
[0501]				OMe	O
1456				OMe	O
1457				OMe	O
1458				OMe	O
1459				OMe	O

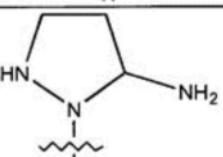
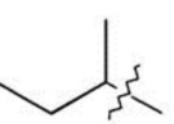
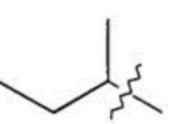
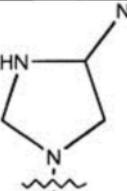
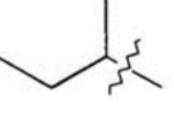
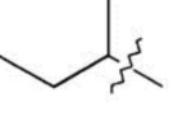
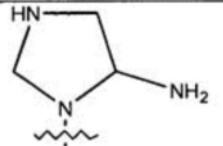
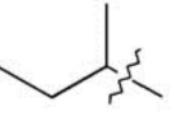
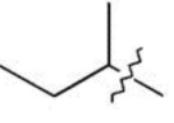
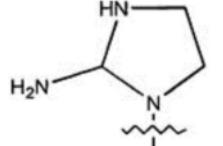
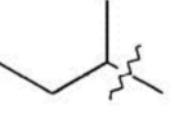
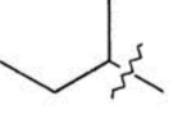
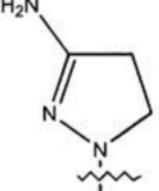
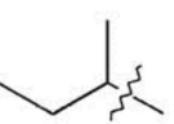
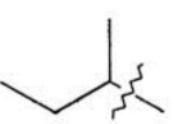
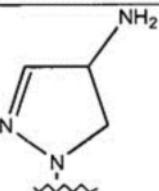
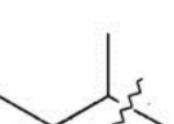
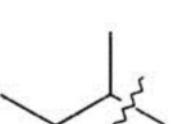
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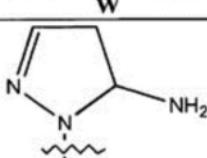
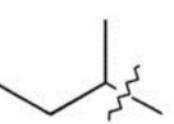
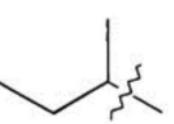
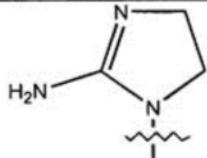
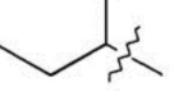
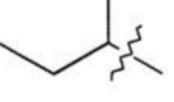
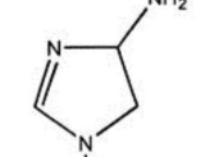
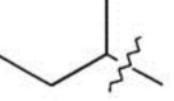
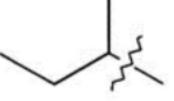
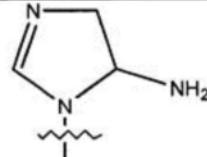
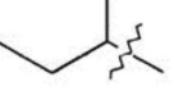
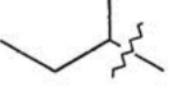
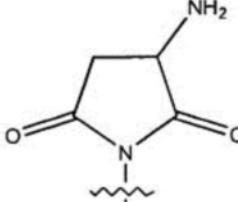
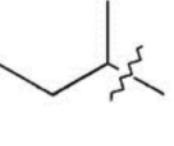
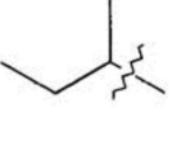
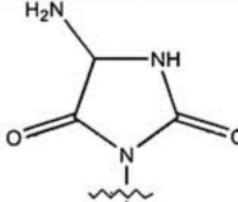
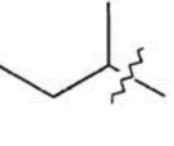
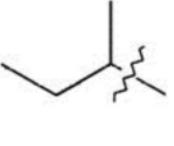
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[0503]				OMe	O
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1469				OMe	O
1470				OMe	O

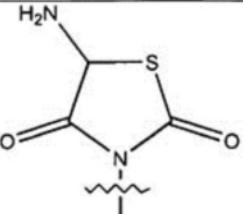
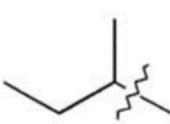
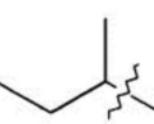
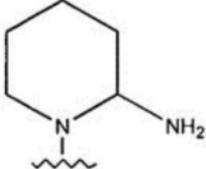
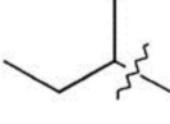
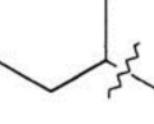
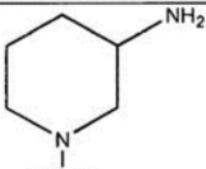
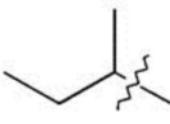
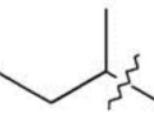
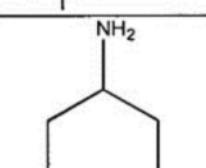
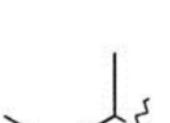
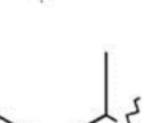
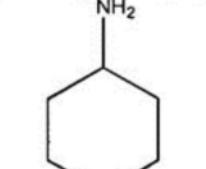
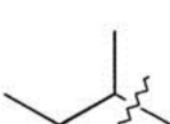
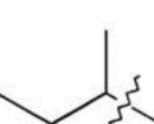
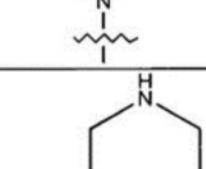
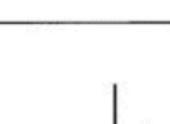
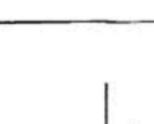
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1473				OMe	O
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1475				OMe	O
1476				OMe	O
1477				OMe	O

Cmpd	W	X	Z	A	Q
1478				OMe	O
1479				OMe	O
1480				OMe	O
[0505]					
1481				OMe	O
1482				OMe	O
1483				OMe	O

Cmpd	W	X	Z	A	Q
1484				OMe	O
1485				OMe	O
1486				OMe	O
[0506]				OMe	O
1487				OMe	O
1488				OMe	O
1489				OMe	O

Cmpd	W	X	Z	A	Q
1490				OMe	O
1491				OMe	O
1492				OMe	O
[0507]					
1493				OMe	O
1494				OMe	O
1495				OMe	O

Cmpd	W	X	Z	A	Q
1496				OMe	O
1497				OMe	O
1498				OMe	O
[0508]					
1499				OMe	O
1500				OMe	O
1501				OMe	O

Cmpd	W	X	Z	A	Q
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[0509]				OMe	O
1504				OMe	O
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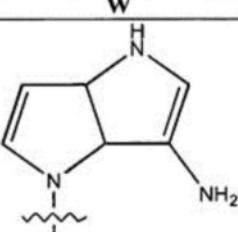
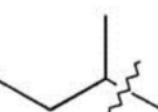
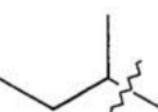
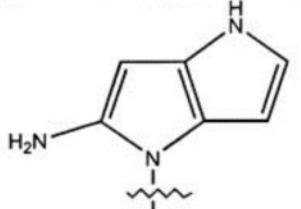
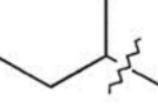
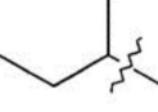
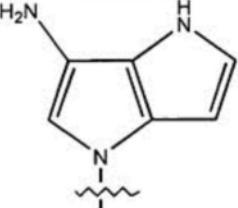
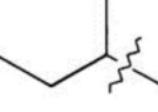
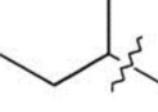
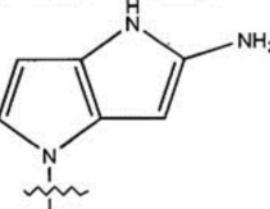
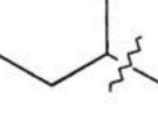
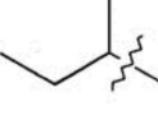
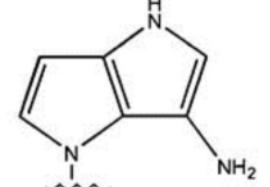
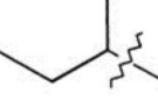
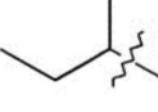
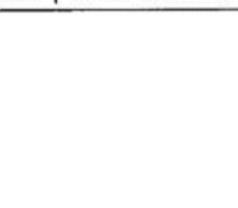
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1508				OMe	O
1509				OMe	O
[0510]					
1510				OMe	O
1511				OMe	O
1512				OMe	O

Cmpd	W	X	Z	A	Q
1513				OMe	O
1514				OMe	O
[0511]				OMe	O
1515				OMe	O
1516				OMe	O
1517				OMe	O
1518				OMe	O

Cmpd	W	X	Z	A	Q
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1520				OMe	O
[0512]					
1521				OMe	O
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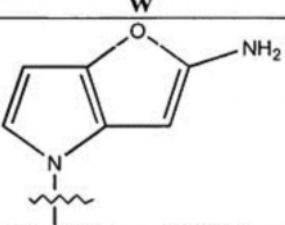
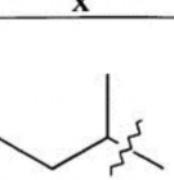
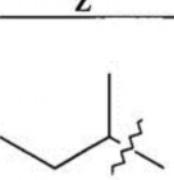
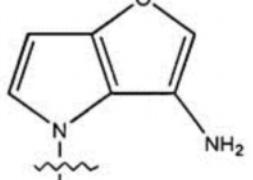
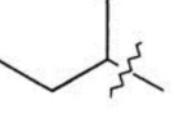
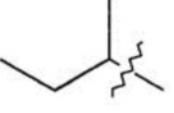
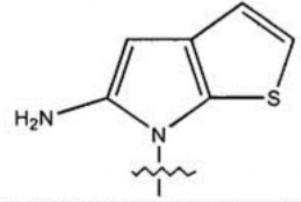
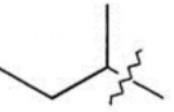
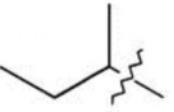
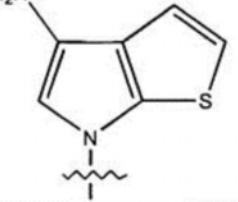
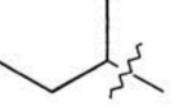
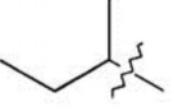
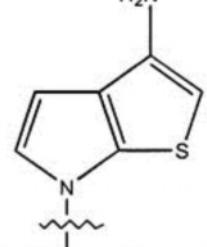
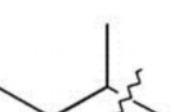
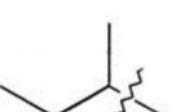
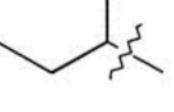
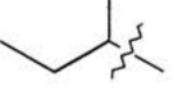
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1525				OMe	O
[0513]				OMe	O
1526				OMe	O
1527				OMe	O
1528				OMe	O

Cmpd	W	X	Z	A	Q
1529				OMe	O
1530				OMe	O
[0514]				OMe	O
1531				OMe	O
1532				OMe	O
1533				OMe	O

Cmpd	W	X	Z	A	Q
1534				OMe	O
1535				OMe	O
[0515]				OMe	O
1536				OMe	O
1537				OMe	O
1538				OMe	O

Cmpd	W	X	Z	A	Q
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[0516]				OMe	O
1541				OMe	O
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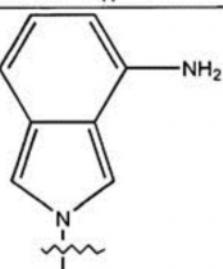
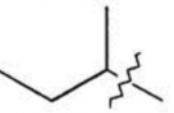
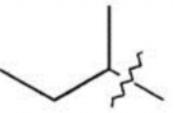
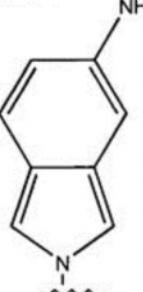
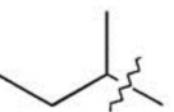
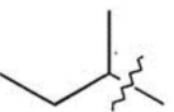
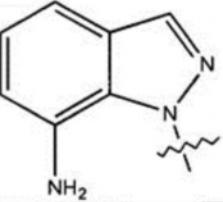
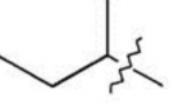
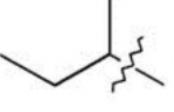
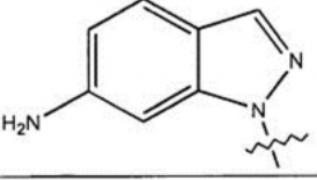
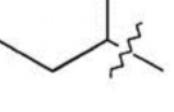
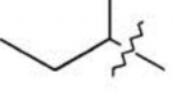
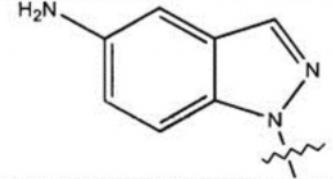
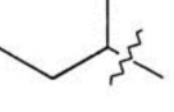
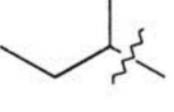
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[0517]				OMe	O
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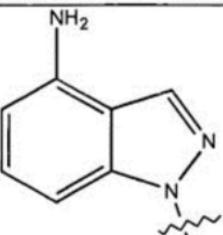
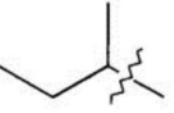
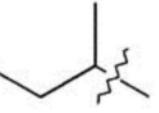
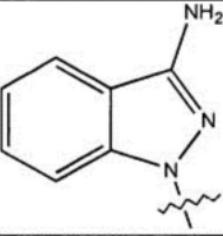
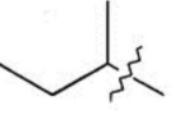
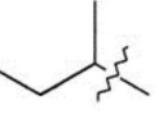
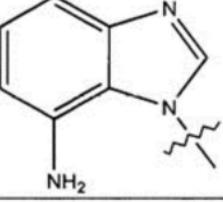
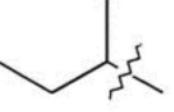
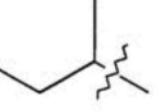
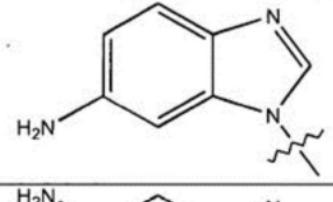
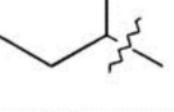
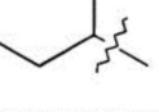
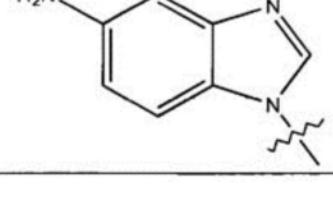
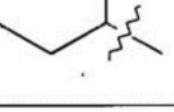
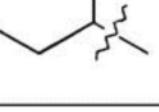
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1550				OMe	O
[0518]				OMe	O
1551				OMe	O
1552				OMe	O
1553				OMe	O

Cmpd	W	X	Z	A	Q	
1554				OMe	O	
1555				OMe	O	
[0519]	1556				OMe	O
	1557				OMe	O
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	1559				OMe	O

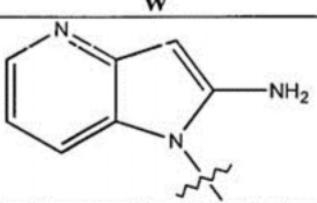
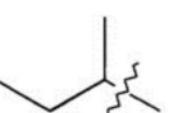
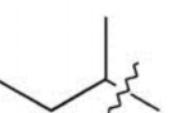
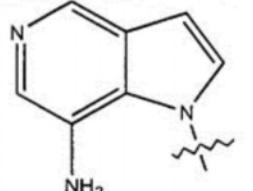
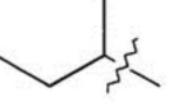
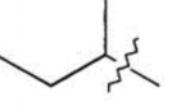
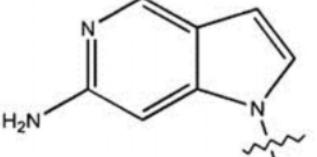
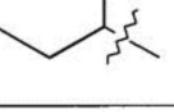
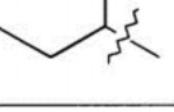
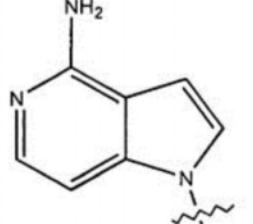
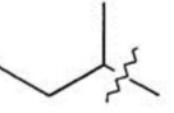
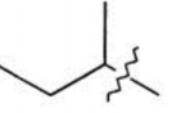
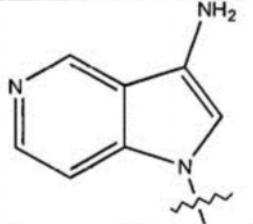
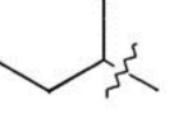
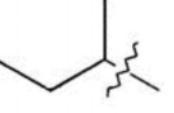
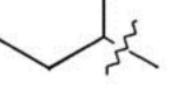
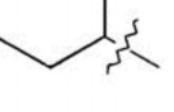
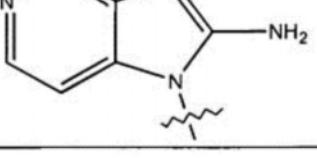
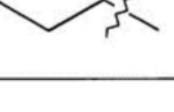
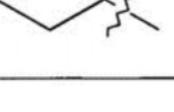
Cmpd	W	X	Z	A	Q
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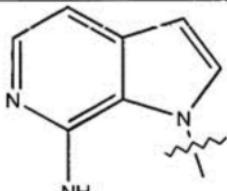
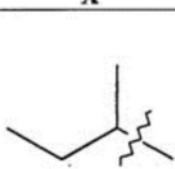
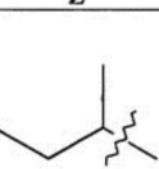
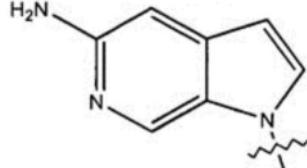
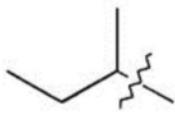
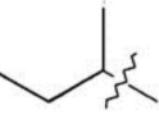
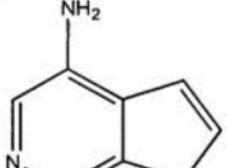
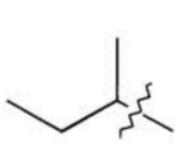
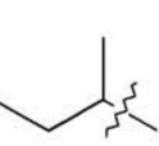
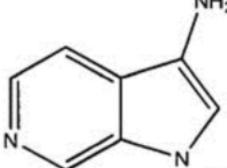
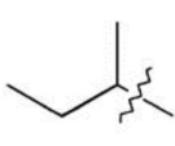
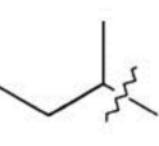
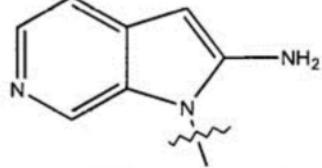
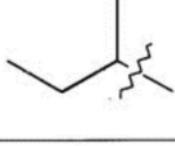
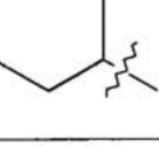
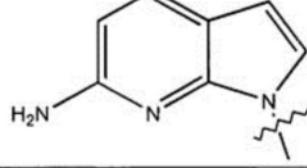
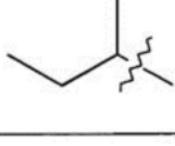
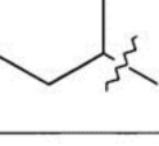
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1567				OMe	O
[0521]				OMe	O
1568				OMe	O
1569				OMe	O
1570				OMe	O

Cmpd	W	X	Z	A	Q	
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[0522]	1572				OMe	O
	1573				OMe	O
	1574				OMe	O
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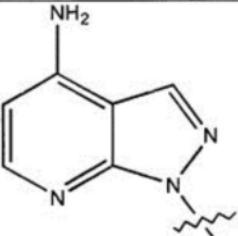
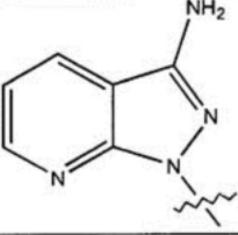
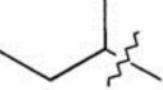
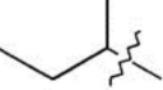
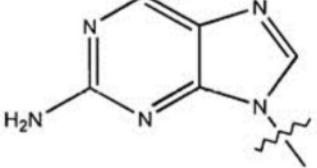
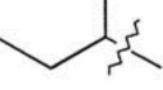
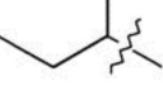
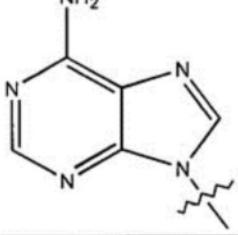
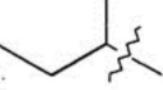
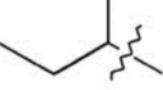
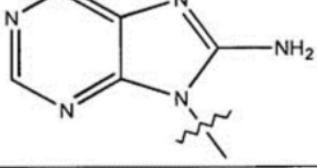
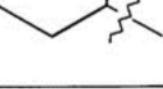
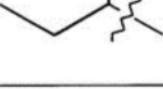
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1577				OMe	O
[0523]					
1578				OMe	O
1579				OMe	O
1580				OMe	O

Cmpd	W	X	Z	A	Q
1581					O
1582				OMe	O
[0524]					
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1584				OMe	O
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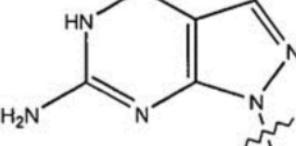
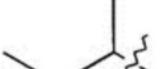
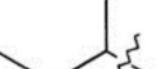
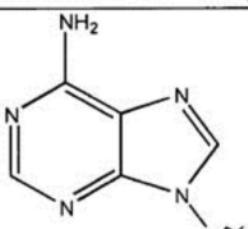
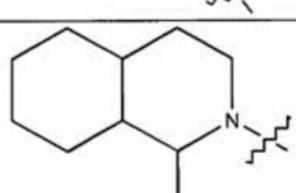
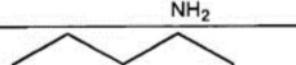
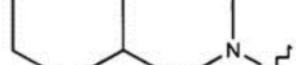
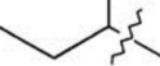
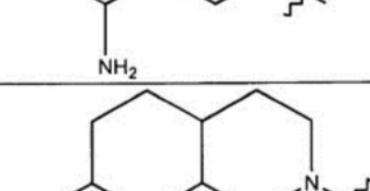
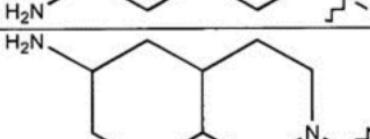
Cmpd	W	X	Z	A	Q
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1588				OMe	O
1589				OMe	O
[0525]				OMe	O
1590				OMe	O
1591				OMe	O
1592				OMe	O

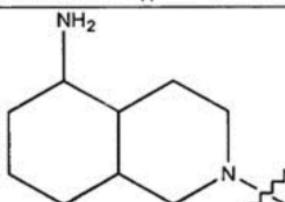
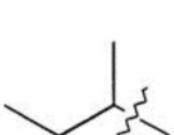
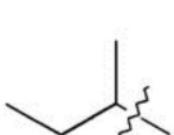
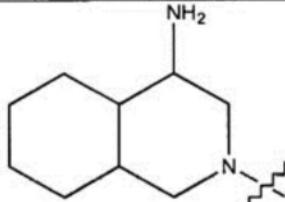
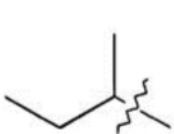
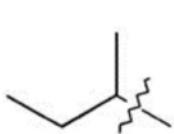
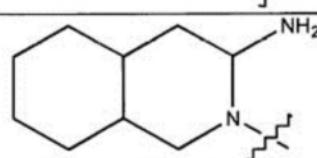
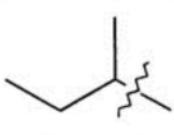
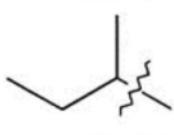
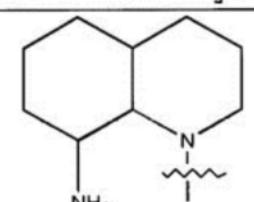
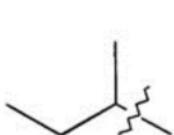
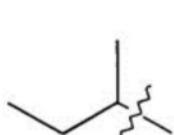
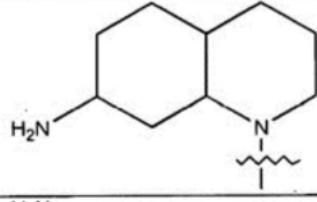
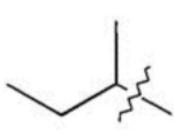
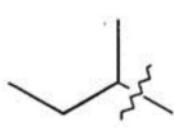
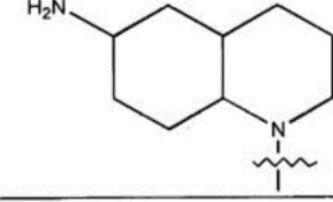
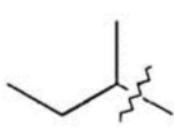
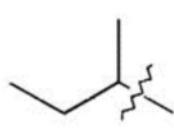
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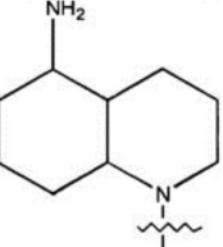
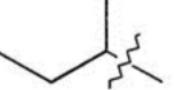
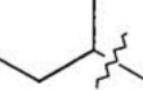
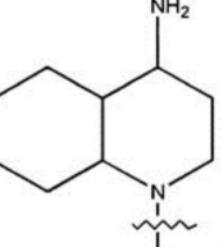
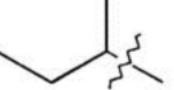
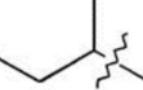
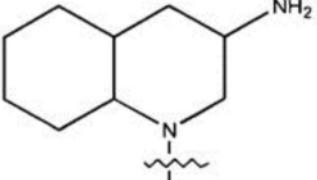
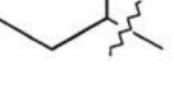
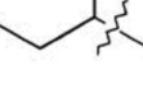
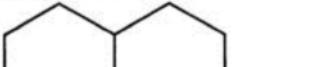
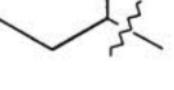
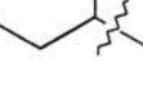
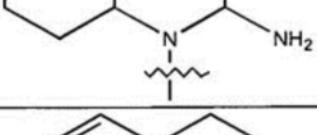
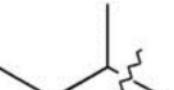
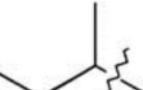
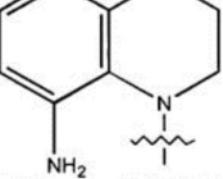
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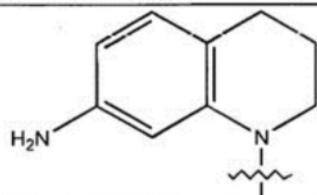
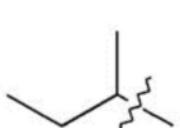
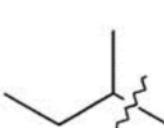
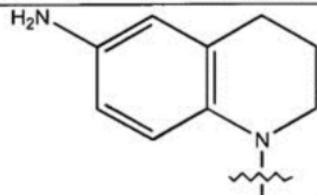
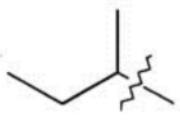
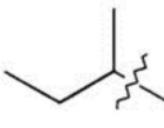
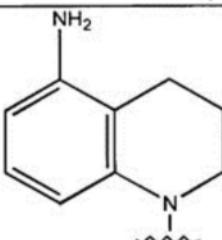
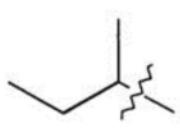
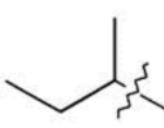
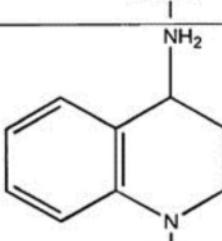
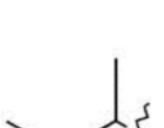
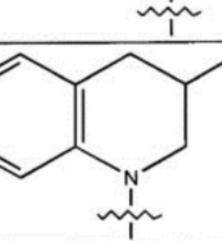
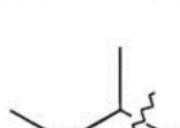
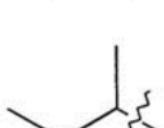
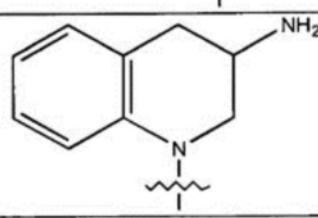
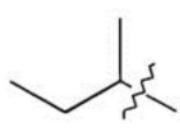
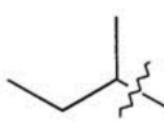
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[0528]				OMe	O
1607				OMe	O
1608				OMe	O
1609				OMe	O

Cmpd	W	X	Z	A	Q
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[0529]				OMe	O
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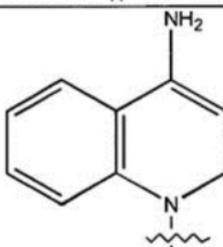
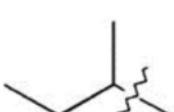
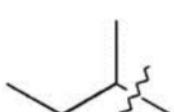
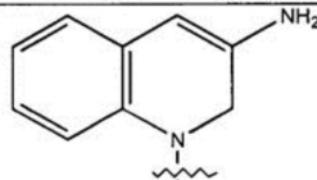
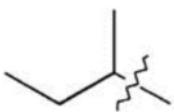
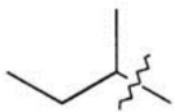
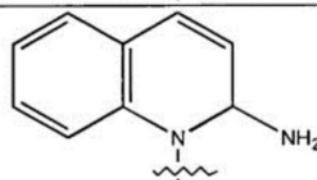
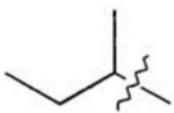
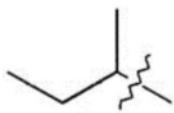
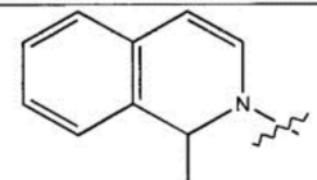
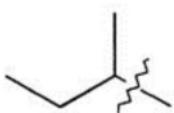
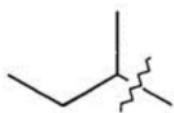
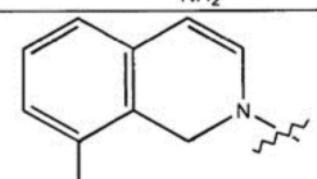
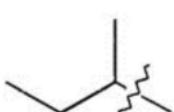
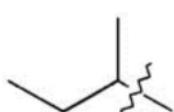
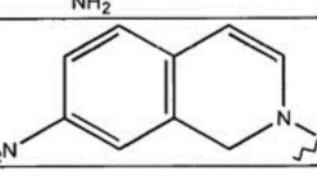
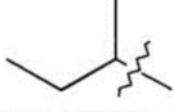
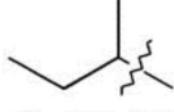
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[0530]				OMe	O
1616				OMe	O
1617				OMe	O
1618				OMe	O
1619				OMe	O

Cmpd	W	X	Z	A	Q
1620				OMe	O
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1622				OMe	O
[0531]					
1623				OMe	O
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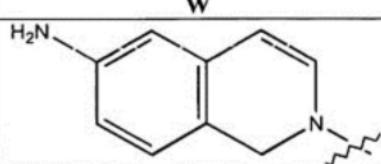
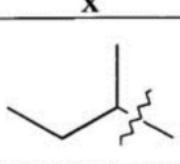
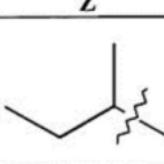
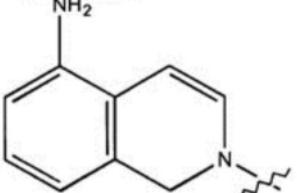
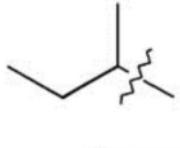
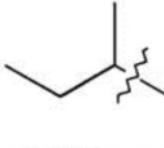
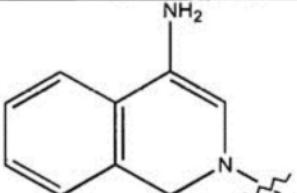
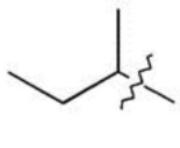
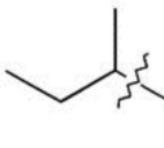
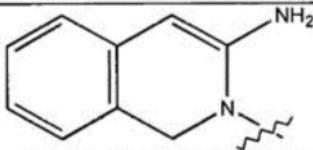
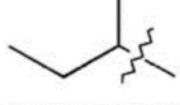
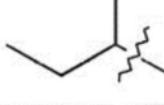
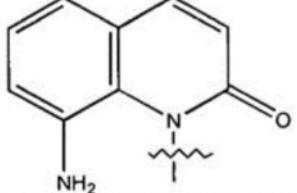
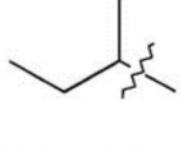
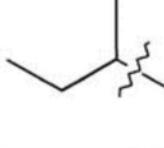
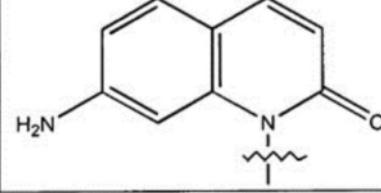
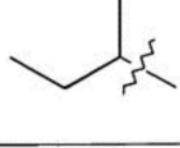
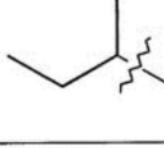
Cmpd	W	X	Z	A	Q
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[0532]				OMe	O
1628				OMe	O
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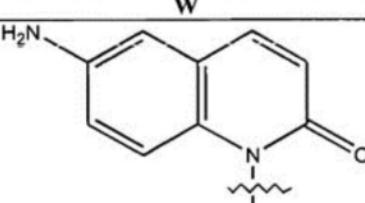
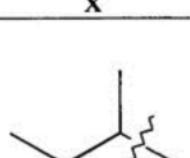
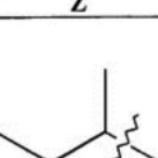
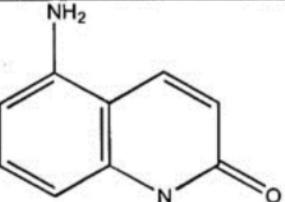
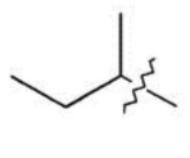
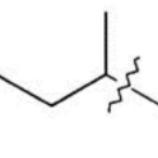
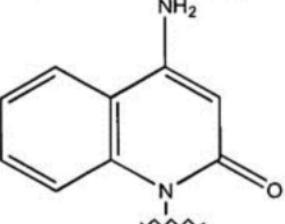
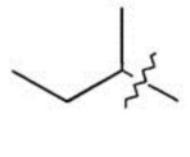
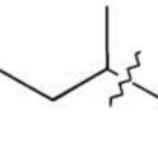
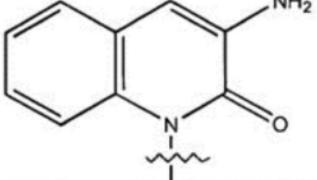
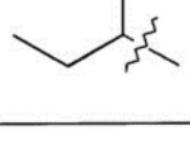
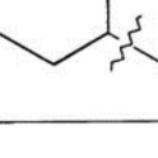
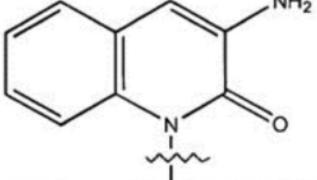
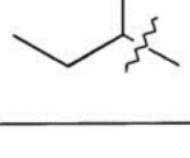
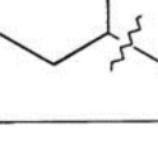
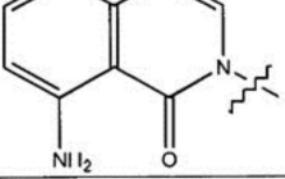
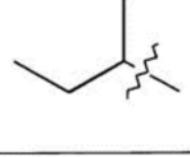
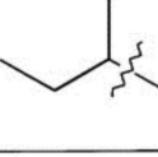
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1632				OMe	O
[0533]				OMe	O
1633				OMe	O
1634				OMe	O
1635				OMe	O

Cmpd	W	X	Z	A	Q
1636				OMe	O
1637				OMe	O
[0534]				OMe	O
1638				OMe	O
1639				OMe	O
1640				OMe	O

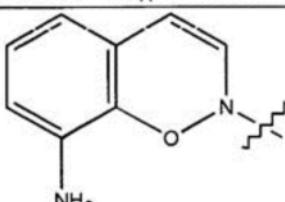
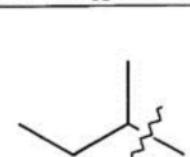
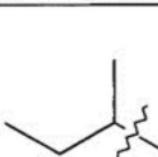
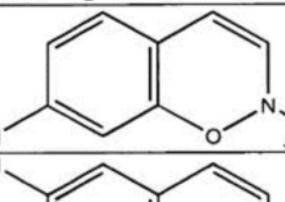
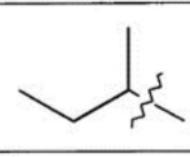
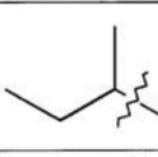
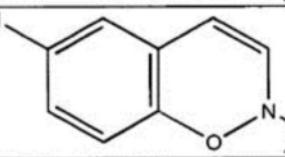
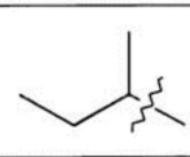
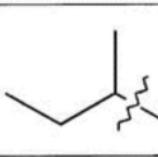
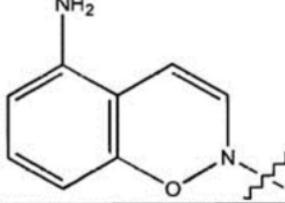
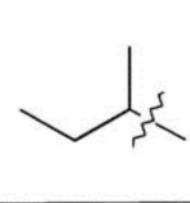
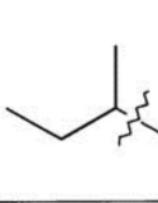
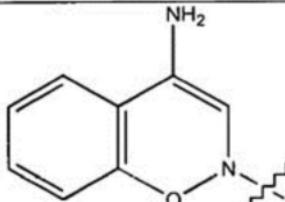
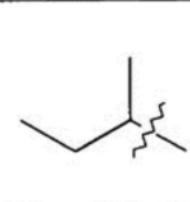
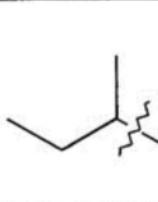
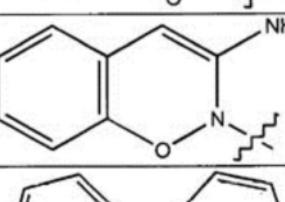
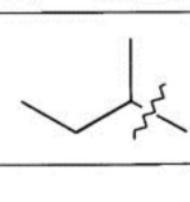
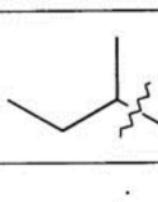
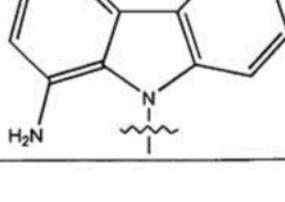
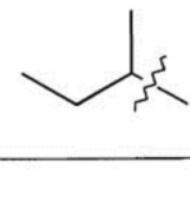
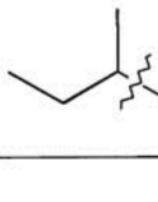
Cmpd	W	X	Z	A	Q
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1644				OMe	O
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1646				OMe	O

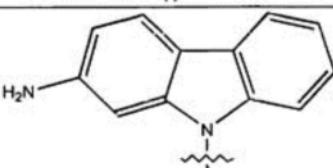
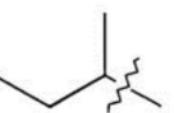
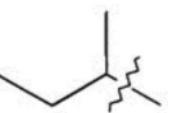
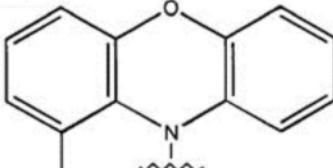
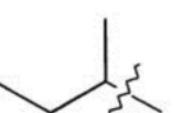
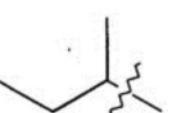
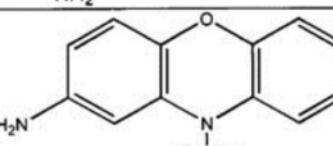
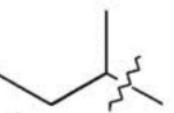
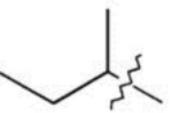
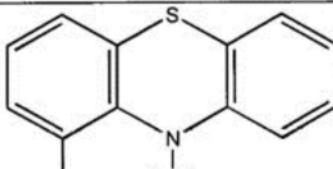
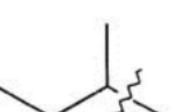
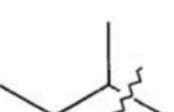
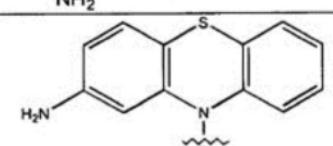
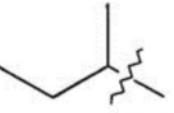
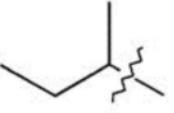
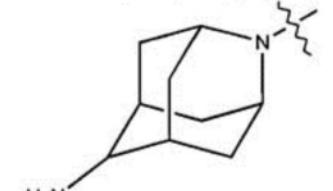
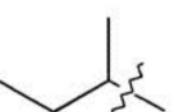
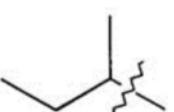
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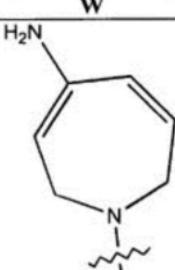
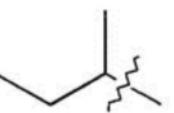
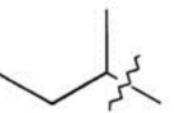
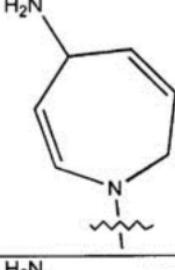
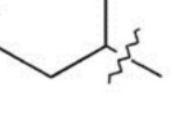
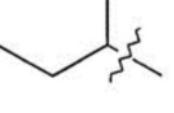
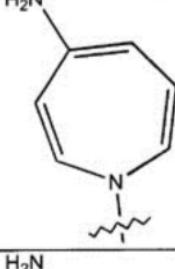
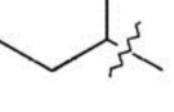
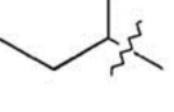
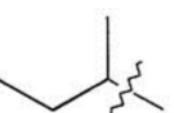
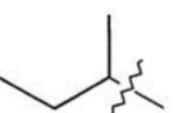
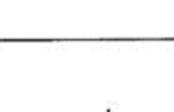
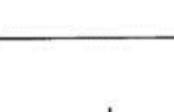
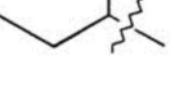
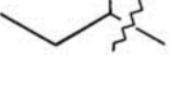
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1648				OMe	O
1649				OMe	O
1650				OMe	O
1651				OMe	O
1652				OMe	O

Cmpd	W	X	Z	A	Q
1653				OMe	O
1654				OMe	O
[0537]				OMe	O
1655				OMe	O
1656				OMe	O
1657				OMe	O

Cmpd	W	X	Z	A	Q
1658				OMe	O
1659				OMe	O
[0538]				OMe	O
1660				OMe	O
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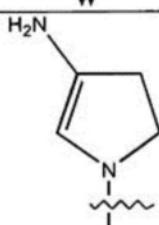
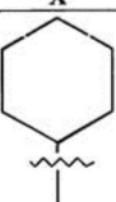
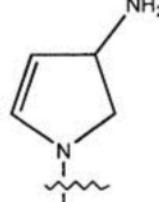
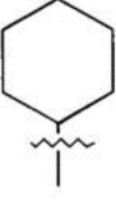
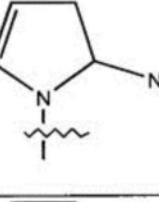
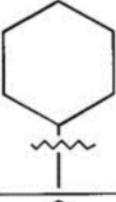
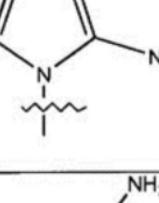
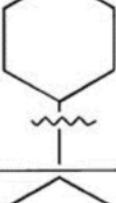
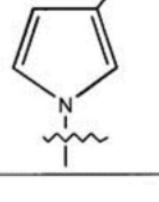
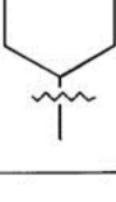
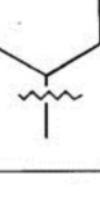
Cmpd	W	X	Z	A	Q
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1664				OMe	O
1665				OMe	O
[0539]				OMe	O
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1667				OMe	O
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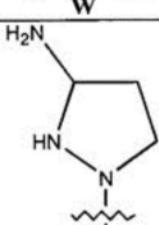
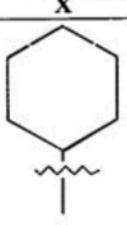
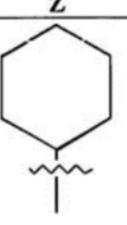
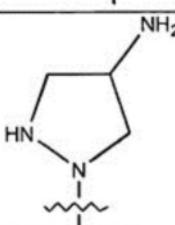
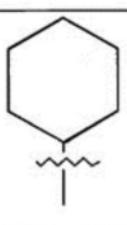
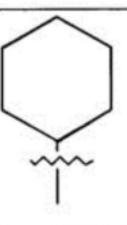
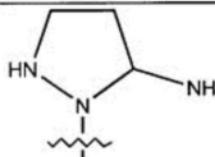
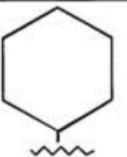
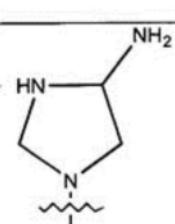
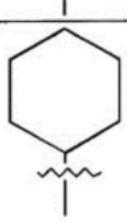
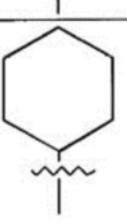
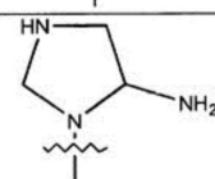
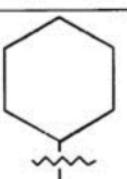
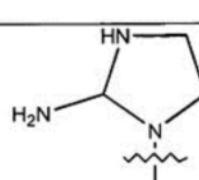
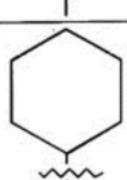
Cmpd	W	X	Z	A	Q	
1670				OMe	O	
1671				OMe	O	
[0540]	1672				OMe	O
	1673				OMe	O
	1674				OMe	O
	1675				OMe	O

Cmpd	W	X	Z	A	Q
1676				OMe	O
1677				OMe	O
[0541]				OMe	O
1678	 [0541]			OMe	O
1679	 1679			OMe	O
1680	 1680			OMe	O

Cmpd	W	X	Z	A	Q
1681				OMe	O
1682				OMe	O
[0542]				OMe	O
1683				OMe	O
1684				OMe	O
1685				OMe	O
1686				OMe	O

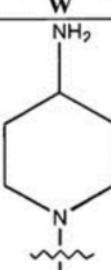
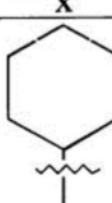
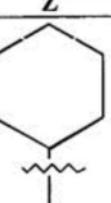
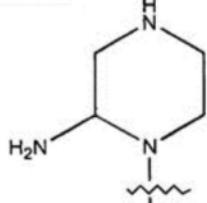
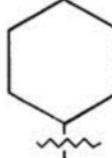
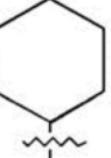
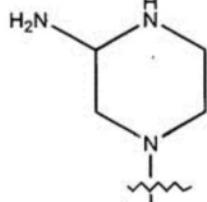
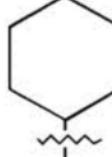
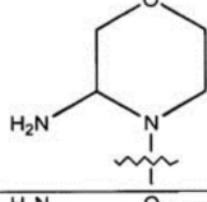
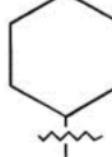
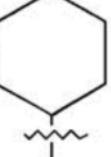
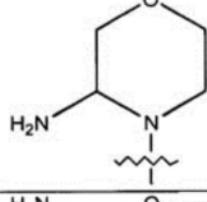
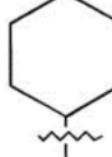
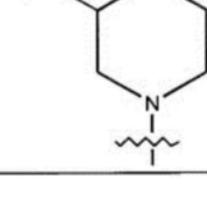
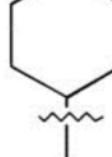
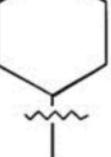
Cmpd	W	X	Z	A	Q
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1688				OMe	O
[0543]				OMe	O
1689				OMe	O
1690				OMe	O
1691				OMe	O
1692				OMe	O

Cmpd	W	X	Z	A	Q
1693				OMe	O
1694				OMe	O
[0544]				OMe	O
1695				OMe	O
1696				OMe	O
1697				OMe	O

Cmpd	W	X	Z	A	Q
1698				OMe	O
1699				OMe	O
[0545]					
1700				OMe	O
1701				OMe	O
1702				OMe	O
1703				OMe	O

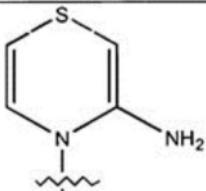
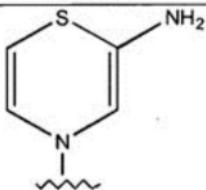
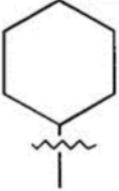
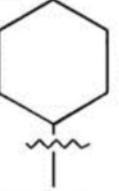
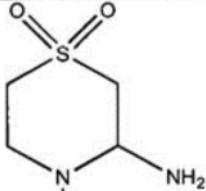
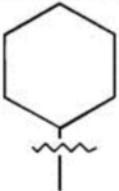
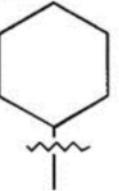
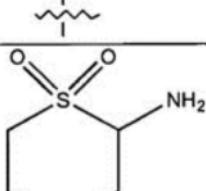
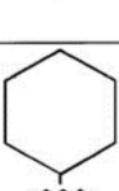
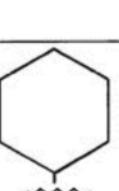
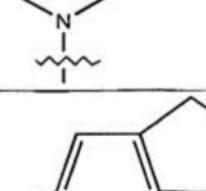
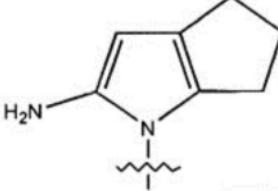
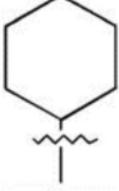
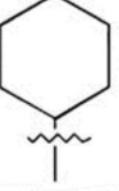
Cmpd	W	X	Z	A	Q
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1705				OMe	O
[0546]				OMe	O
1706				OMe	O
1707				OMe	O
1708				OMe	O
1709				OMe	O

Cmpd	W	X	Z	A	Q
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1711				OMe	O
[0547]				OMe	O
1713				OMe	O
1714				OMe	O

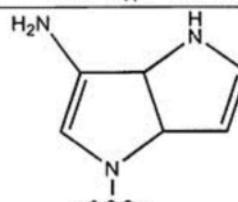
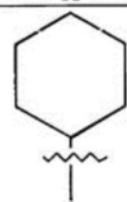
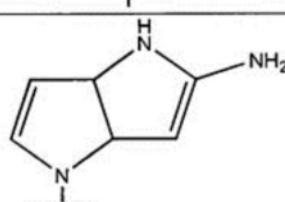
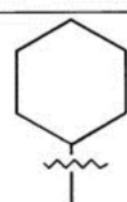
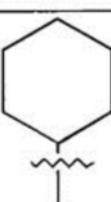
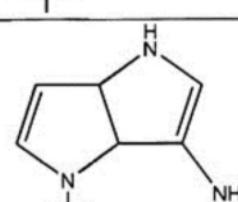
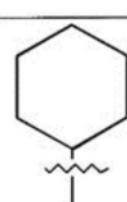
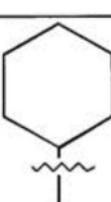
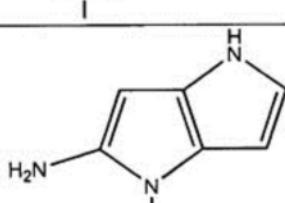
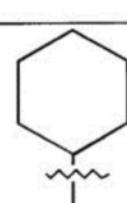
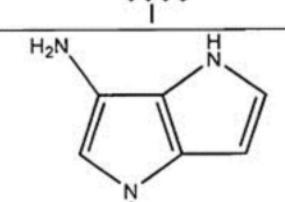
Cmpd	W	X	Z	A	Q
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1716				OMe	O
[0548]				OMe	O
1717				OMe	O
1718				OMe	O
1719				OMe	O

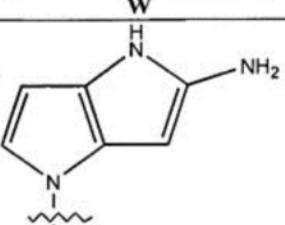
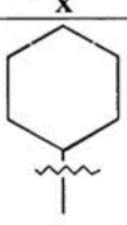
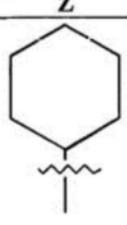
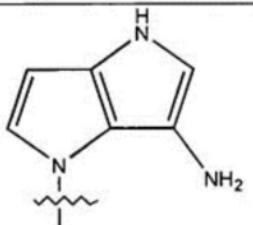
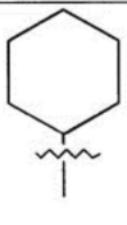
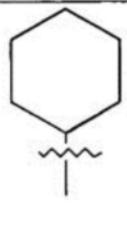
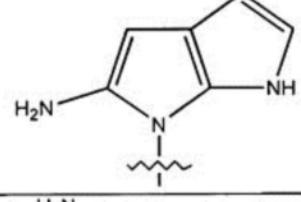
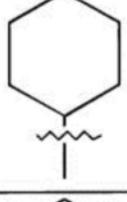
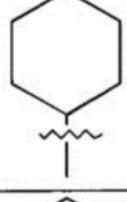
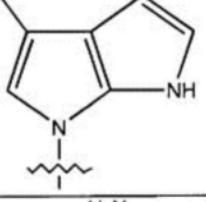
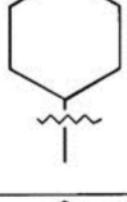
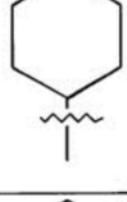
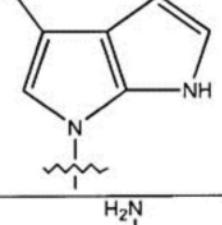
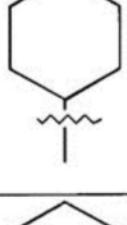
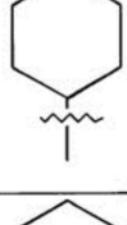
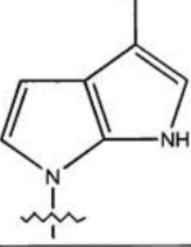
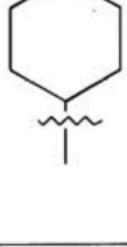
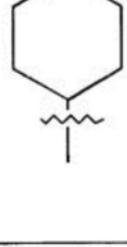
Cmpd	W	X	Z	A	Q
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1721				OMe	O
[0549]				OMe	O
1722				OMe	O
1723				OMe	O
1724				OMe	O
1725				OMe	O

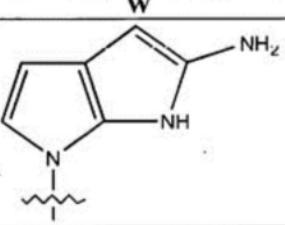
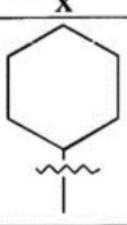
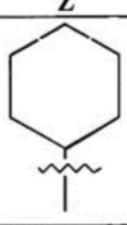
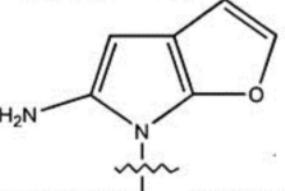
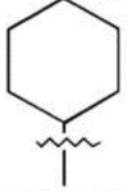
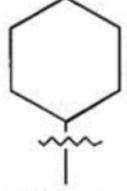
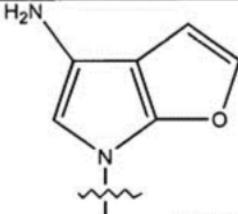
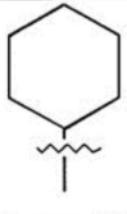
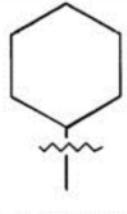
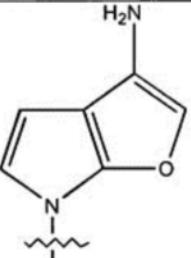
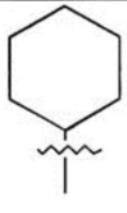
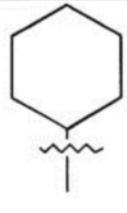
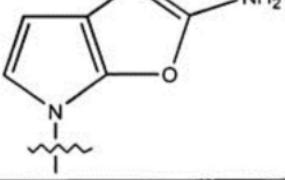
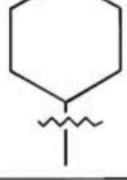
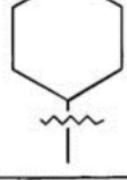
Cmpd	W	X	Z	A	Q
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1727				OMe	O
1728				OMe	O
[0550]					
1729				OMe	O
1730				OMe	O
1731				OMe	O

Cmpd	W	X	Z	A	Q
1732				OMe	O
1733				OMe	O
[0551]				OMe	O
1734				OMe	O
1735				OMe	O
1736				OMe	O

Cmpd	W	X	Z	A	Q
1737				OMe	O
1738				OMe	O
[0552]				OMe	O
1739				OMe	O
1740				OMe	O
1741				OMe	O

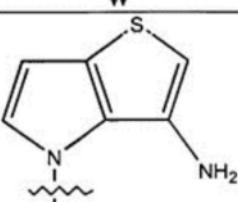
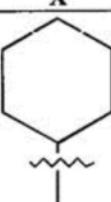
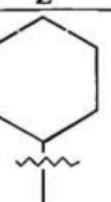
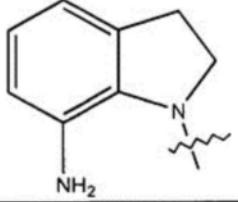
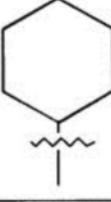
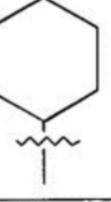
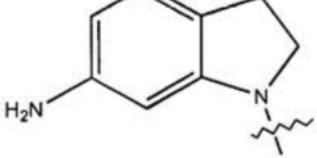
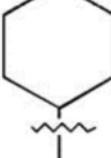
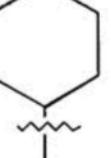
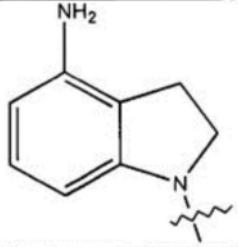
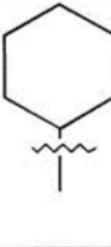
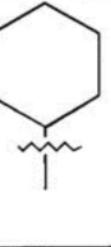
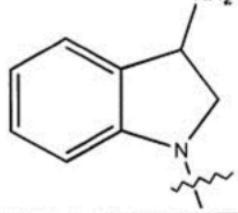
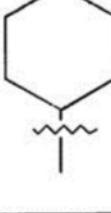
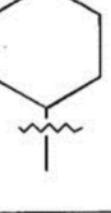
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1743				OMe	O
[0553]				OMe	O
1744				OMe	O
1745				OMe	O
1746				OMe	O

Cmpd	W	X	Z	A	Q
1747				OMe	O
1748				OMe	O
[0554]				OMe	O
1749				OMe	O
1750				OMe	O
1751				OMe	O

Cmpd	W	X	Z	A	Q
1752				OMe	O
1753				OMe	O
[0555]				OMe	O
1754				OMe	O
1755				OMe	O
1756				OMe	O

Cmpd	W	X	Z	A	Q	
1757				OMe	O	
1758				OMe	O	
[0556]	1759				OMe	O
	1760				OMe	O
	1761				OMe	O
	1762				OMe	O

Cmpd	W	X	Z	A	Q
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1764				OMe	O
[0557]				OMe	O
1765				OMe	O
1766				OMe	O
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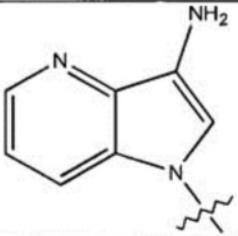
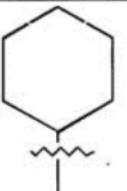
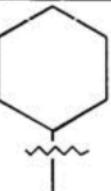
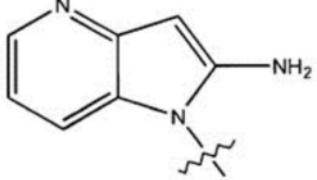
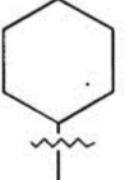
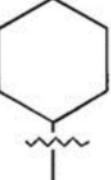
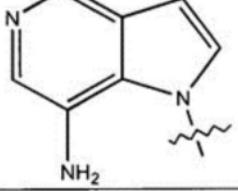
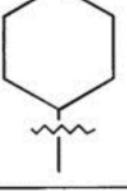
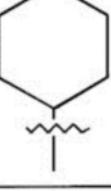
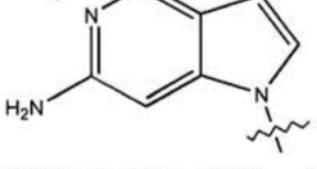
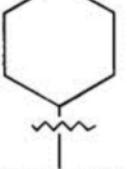
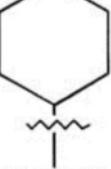
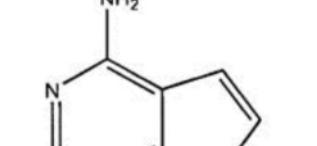
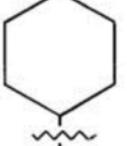
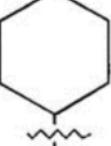
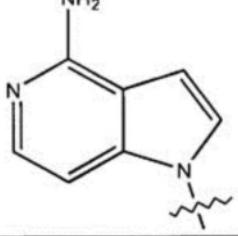
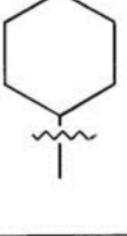
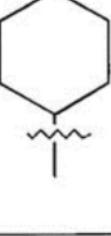
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1769				OMe	O
[0558]				OMe	O
1770				OMe	O
1771				OMe	O
1772				OMe	O

Cmpd	W	X	Z	A	Q
1773				OMe	O
1774				OMe	O
1775				OMe	O
[0559]					
1776				OMe	O
1777				OMe	O
1778				OMe	O

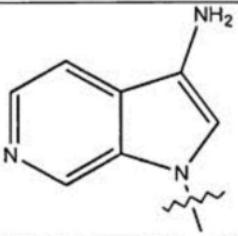
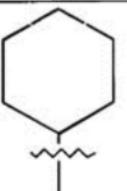
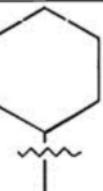
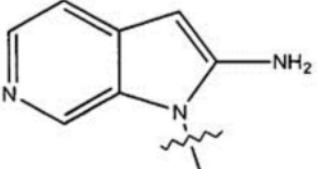
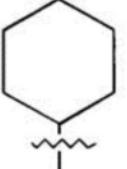
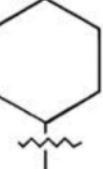
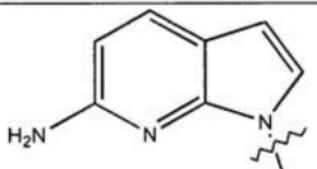
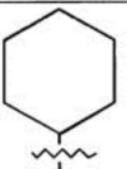
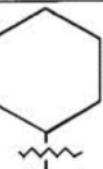
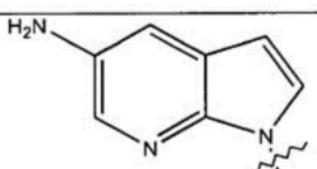
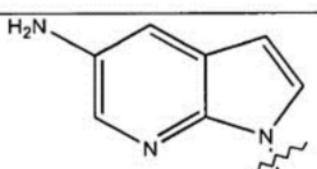
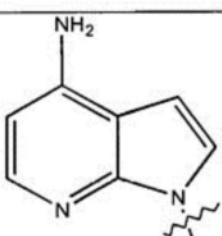
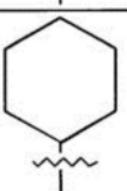
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1780				OMe	O
[0560]				OMe	O
1781				OMe	O
1782				OMe	O
1783				OMe	O

Cmpd	W	X	Z	A	Q
1784				OMe	O
1785				OMe	O
[0561]				OMe	O
1786				OMe	O
1787				OMe	O
1788				OMe	O
1789				OMe	O

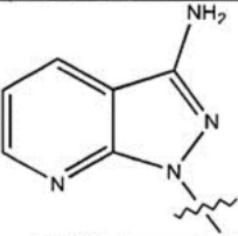
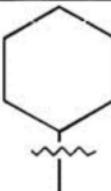
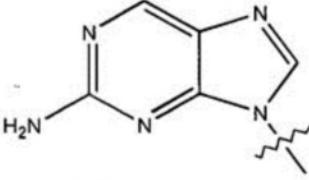
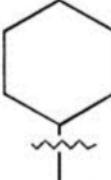
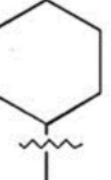
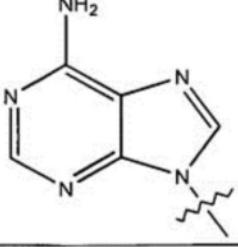
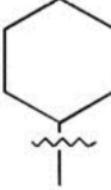
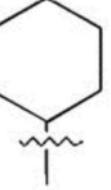
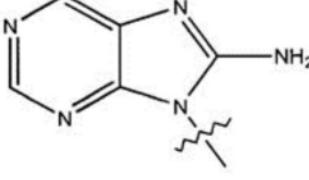
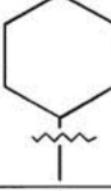
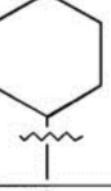
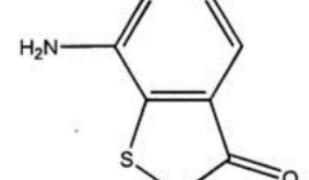
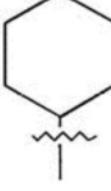
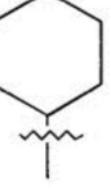
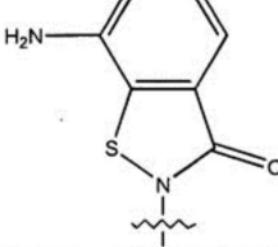
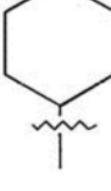
Cmpd	W	X	Z	A	Q
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1791					O
[0562]					
1792				OMe	O
1793				OMe	O
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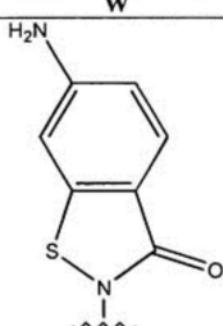
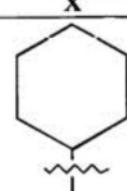
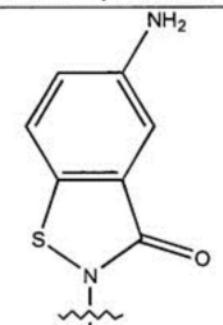
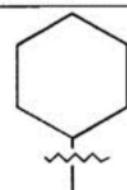
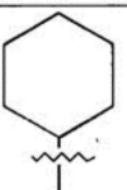
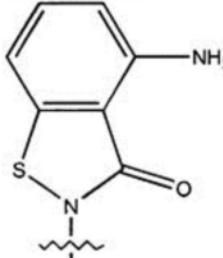
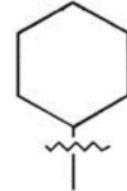
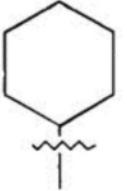
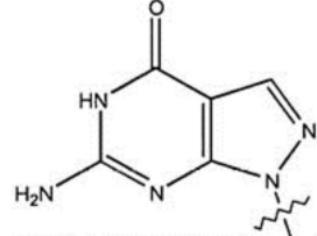
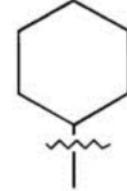
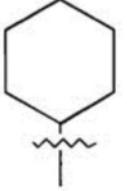
Cmpd	W	X	Z	A	Q
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1797				OMe	O
[0563]				OMe	O
1798				OMe	O
1799				OMe	O
1800				OMe	O

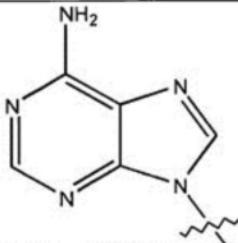
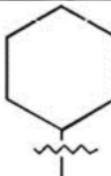
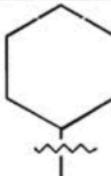
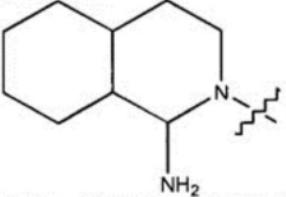
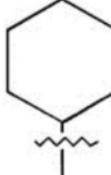
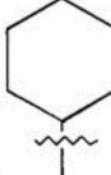
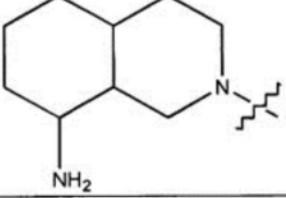
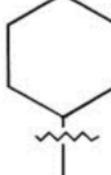
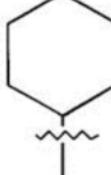
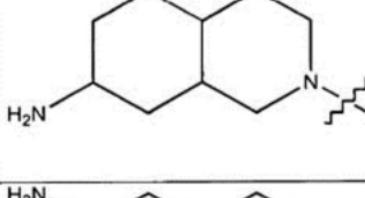
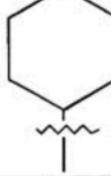
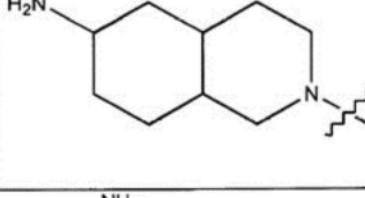
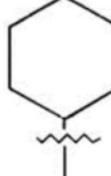
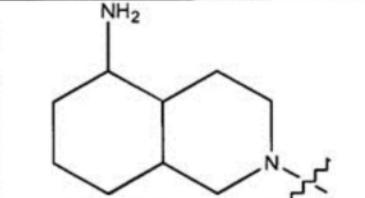
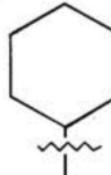
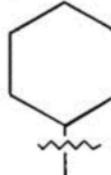
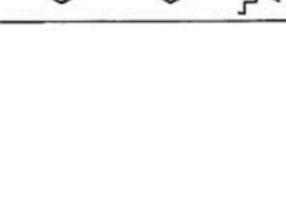
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1802				OMe	O
[0564]				OMe	O
1803				OMe	O
1804				OMe	O
1805				OMe	O

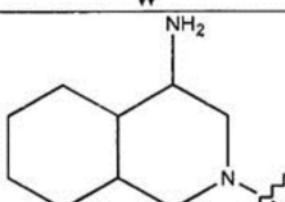
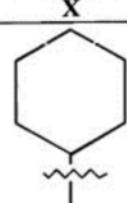
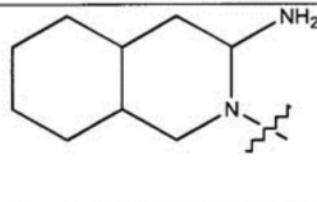
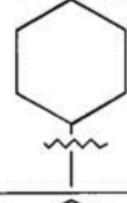
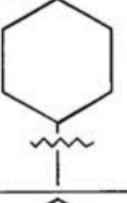
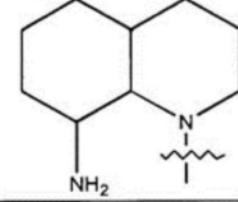
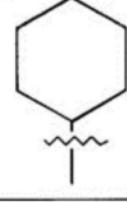
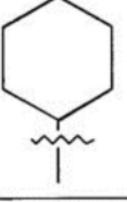
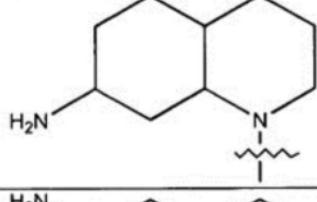
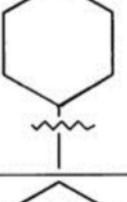
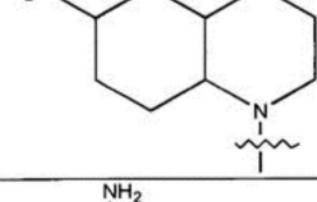
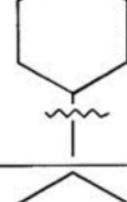
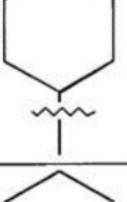
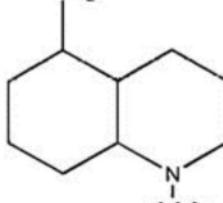
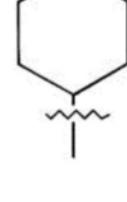
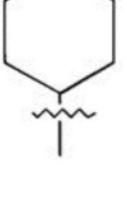
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1807				OMe	O
[0565]				OMe	O
1808				OMe	O
1809				OMe	O
1810				OMe	O

Cmpd	W	X	Z	A	Q
1811				OMe	O
1812				OMe	O
[0566]				OMe	O
1813				OMe	O
1814				OMe	O
1815				OMe	O

Cmpd	W	X	Z	A	Q
1816				OMe	O
1817				OMe	O
[0567]				OMe	O
1818				OMe	O
1819				OMe	O
1820				OMe	O

Cmpd	W	X	Z	A	Q
1821				OMe	O
[0568]				OMe	O
1822				OMe	O
1823				OMe	O
1824				OMe	O

Cmpd	W	X	Z	A	Q
1825				OMe	O
1826				OMe	O
[0569]				OMe	O
1827				OMe	O
1828				OMe	O
1829				OMe	O
1830				OMe	O

Cmpd	W	X	Z	A	Q	
1831				OMe	O	
1832				OMe	O	
[0570]	1833				OMe	O
	1834				OMe	O
	1835				OMe	O
	1836				OMe	O

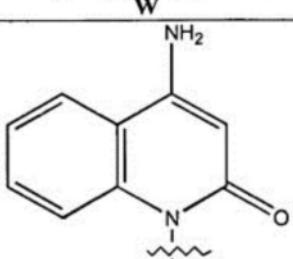
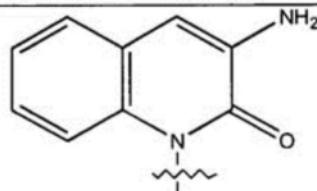
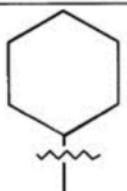
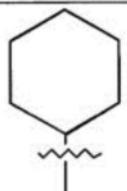
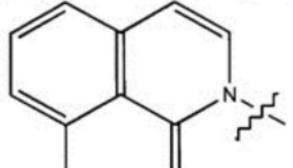
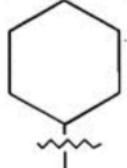
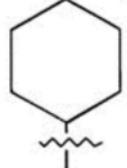
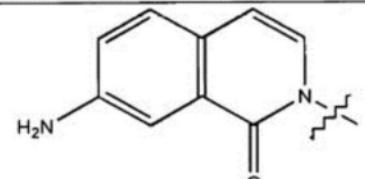
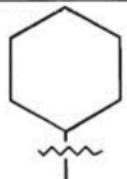
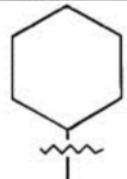
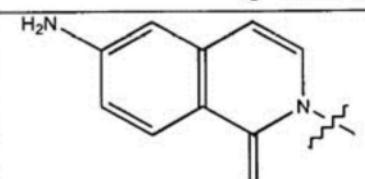
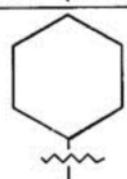
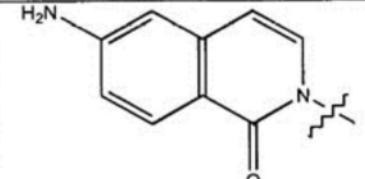
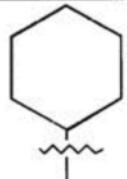
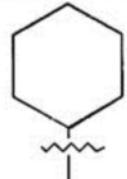
Cmpd	W	X	Z	A	Q
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1838				OMe	O
[0571]				OMe	O
1839				OMe	O
1840				OMe	O
1841				OMe	O
1842				OMe	O

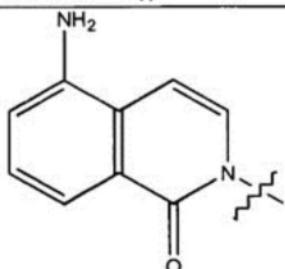
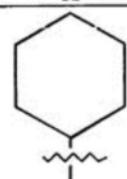
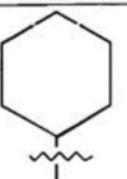
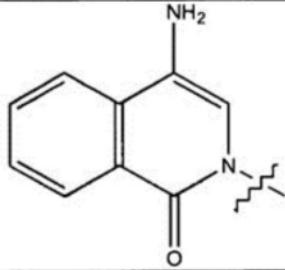
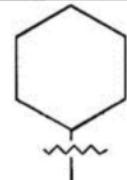
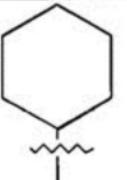
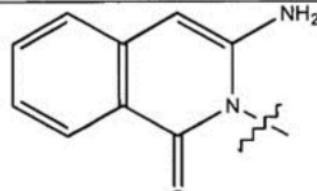
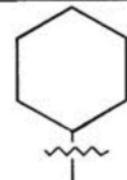
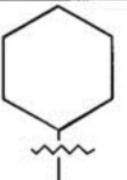
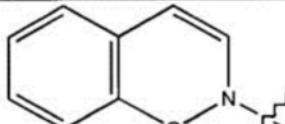
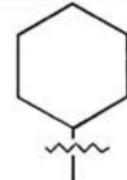
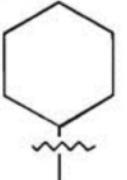
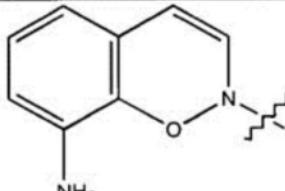
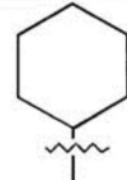
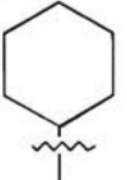
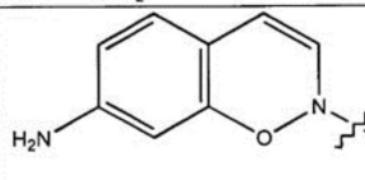
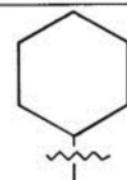
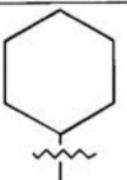
Cmpd	W	X	Z	A	Q
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1844				OMe	O
[0572]				OMe	O
1845				OMe	O
1846				OMe	O
1847				OMe	O

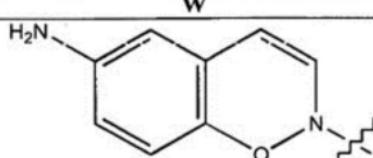
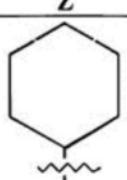
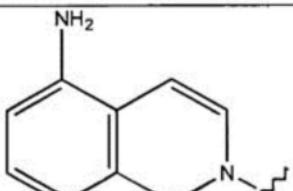
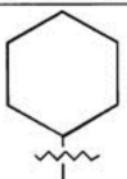
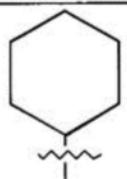
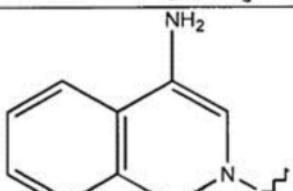
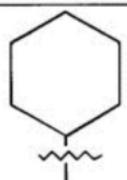
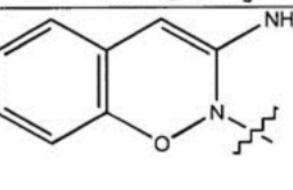
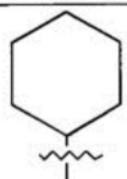
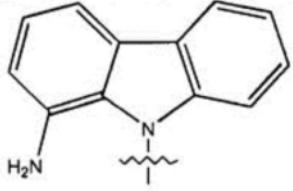
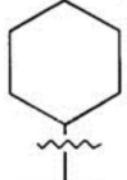
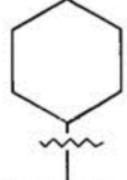
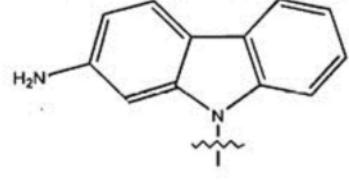
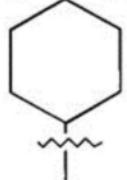
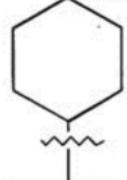
Cmpd	W	X	Z	A	Q
1848				OMe	O
1849				OMe	O
[0573]				OMe	O
1850				OMe	O
1851				OMe	O
1852				OMe	O

Cmpd	W	X	Z	A	Q	
1853				OMe	O	
1854				OMe	O	
[0574]	1855				OMe	O
1856				OMe	O	
1857				OMe	O	
1858				OMe	O	

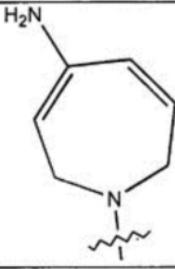
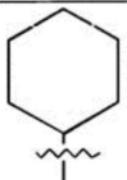
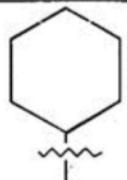
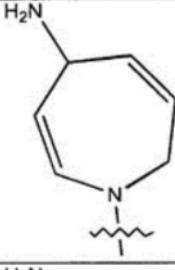
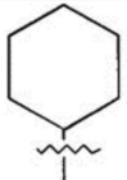
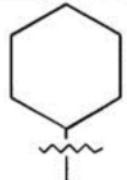
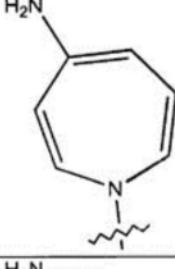
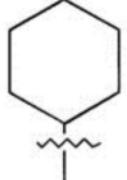
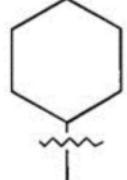
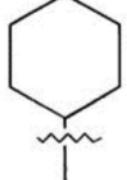
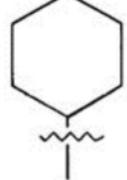
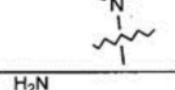
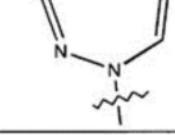
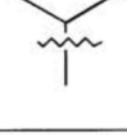
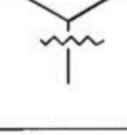
Cmpd	W	X	Z	A	Q	
1859				OMe	O	
1860				OMe	O	
[0575]	1861				OMe	O
	1862				OMe	O
	1863				OMe	O
	1864				OMe	O

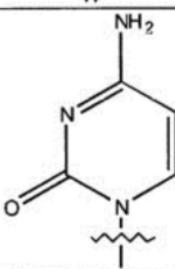
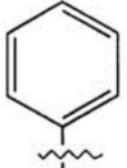
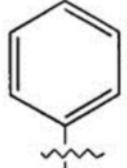
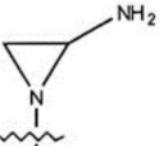
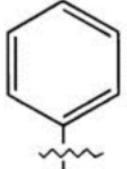
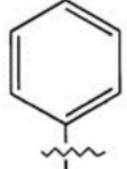
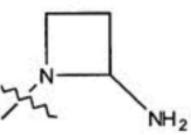
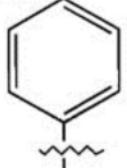
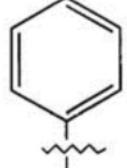
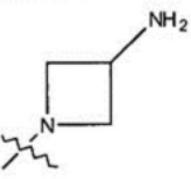
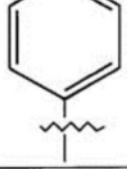
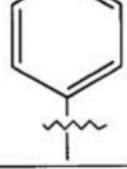
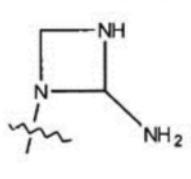
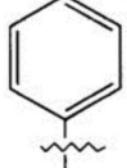
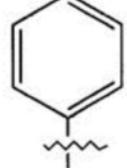
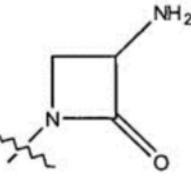
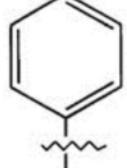
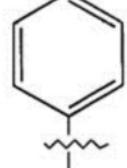
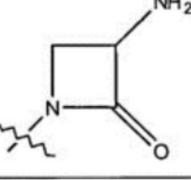
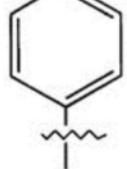
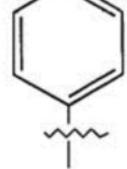
Cmpd	W	X	Z	A	Q
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1866				OMe	O
[0576]				OMe	O
1867				OMe	O
1868				OMe	O
1869				OMe	O

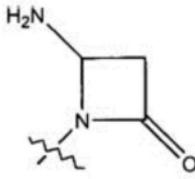
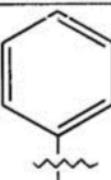
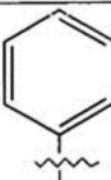
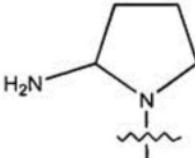
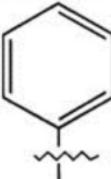
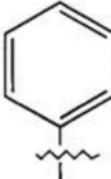
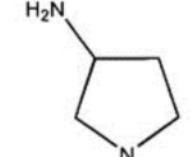
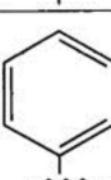
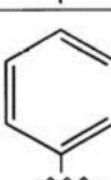
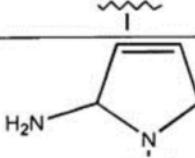
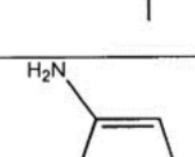
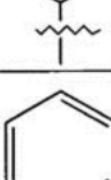
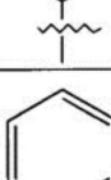
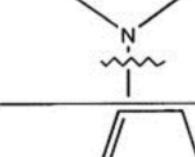
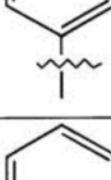
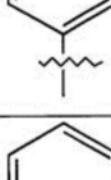
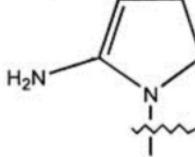
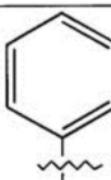
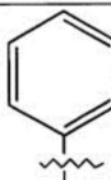
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1871				OMe	O
[0577]				OMe	O
1872				OMe	O
1873				OMe	O
1874				OMe	O

Cmpd	W	X	Z	A	Q	
1875				OMe	O	
1876				OMe	O	
[0578]	1877				OMe	O
	1878				OMe	O
	1879				OMe	O
	1880				OMe	O

Cmpd	W	X	Z	A	Q
1881				OMe	O
1882				OMe	O
[0579]				OMe	O
1883				OMe	O
1884				OMe	O
1885				OMe	O

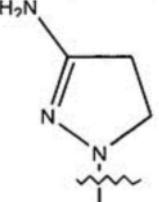
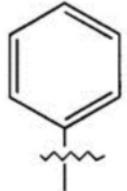
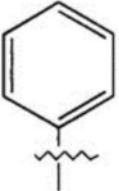
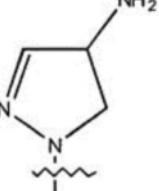
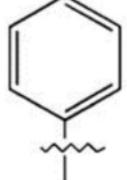
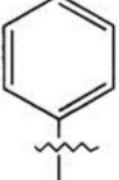
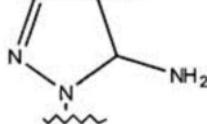
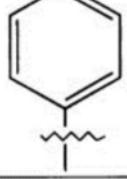
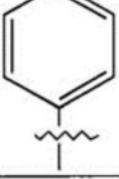
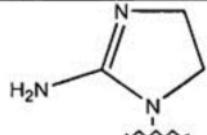
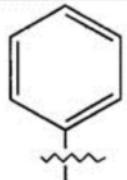
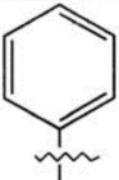
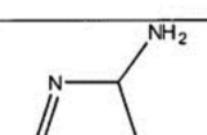
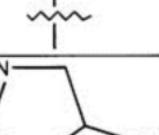
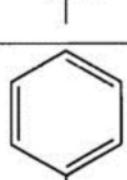
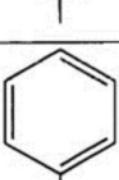
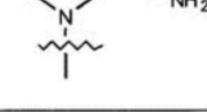
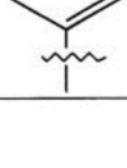
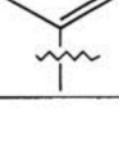
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1887				OMe	O
[0580]				OMe	O
1888				OMe	O
1889				OMe	O
1890				OMe	O

Cmpd	W	X	Z	A	Q
1891				OMe	O
1892				OMe	O
[0581]				OMe	O
1893				OMe	O
1894				OMe	O
1895				OMe	O
1896				OMe	O

Cmpd	W	X	Z	A	Q
1897				OMe	O
1898				OMe	O
[0582]				OMe	O
1899				OMe	O
1900				OMe	O
1901				OMe	O
1902				OMe	O

Cmpd	W	X	Z	A	Q
1903				OMe	O
1904				OMe	O
[0583]				OMe	O
1905				OMe	O
1906				OMe	O
1907				OMe	O

Cmpd	W	X	Z	A	Q
1908				OMe	O
1909				OMe	O
[0584]					
1910				OMe	O
1911				OMe	O
1912				OMe	O
1913				OMe	O

Cmpd	W	X	Z	A	Q
1914				OMe	O
1915				OMe	O
[0585]				OMe	O
1916				OMe	O
1917				OMe	O
1918				OMe	O
1919				OMe	O

Cmpd	W	X	Z	A	Q
1920				OMe	O
1921				OMe	O
[0586]				OMe	O
1922				OMe	O
1923				OMe	O
1924				OMe	O

Cmpd	W	X	Z	A	Q
1925				OMe	O
1926				OMe	O
[0587]				OMe	O
1927				OMe	O
1928				OMe	O
1929				OMe	O

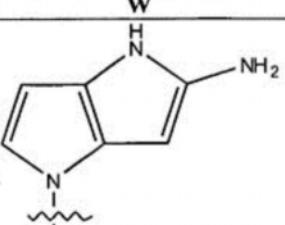
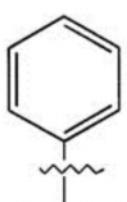
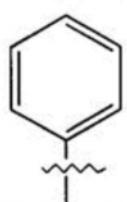
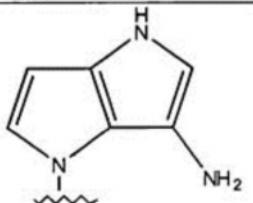
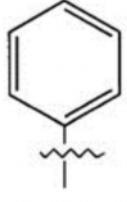
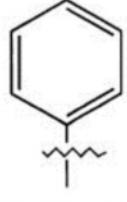
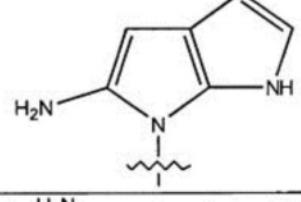
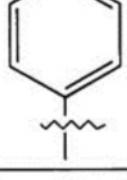
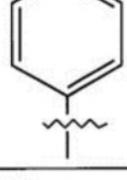
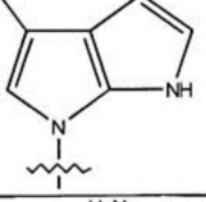
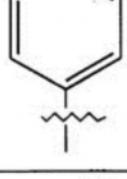
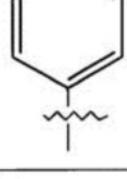
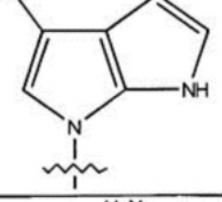
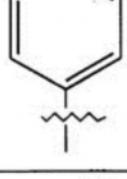
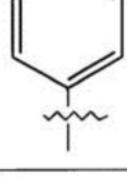
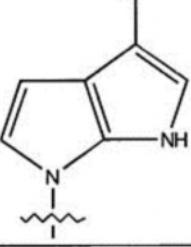
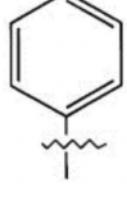
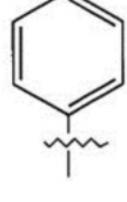
Cmpd	W	X	Z	A	Q
1930				OMe	O
1931				OMe	O
[0588]				OMe	O
1932				OMe	O
1933				OMe	O
1934				OMe	O
1935				OMe	O

Cmpd	W	X	Z	A	Q
1936				OMe	O
1937				OMe	O
1938				OMe	O
[0589]					
1939				OMe	O
1940				OMe	O
1941				OMe	O

Cmpd	W	X	Z	A	Q
1942				OMe	O
1943				OMe	O
[0590]				OMe	O
1944				OMe	O
1945				OMe	O
1946				OMe	O

Cmpd	W	X	Z	A	Q
1947				OMe	O
1948				OMe	O
[0591]				OMe	O
1949				OMe	O
1950				OMe	O
1951				OMe	O

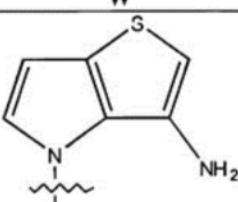
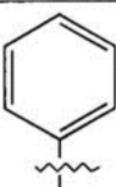
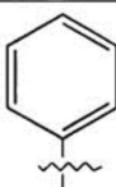
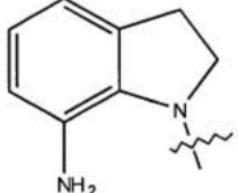
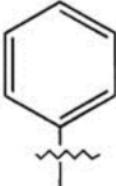
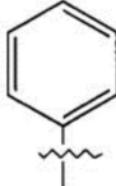
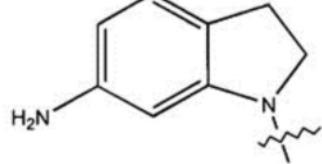
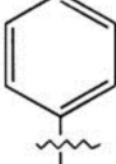
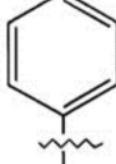
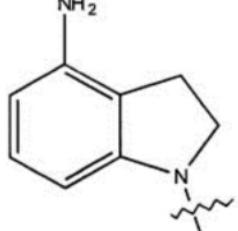
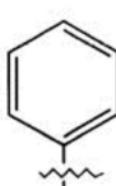
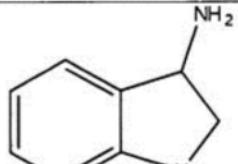
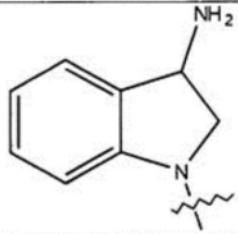
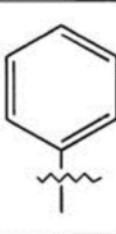
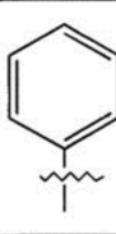
Cmpd	W	X	Z	A	Q
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1953				OMe	O
[0592]				OMe	O
1954				OMe	O
1955				OMe	O
1956				OMe	O

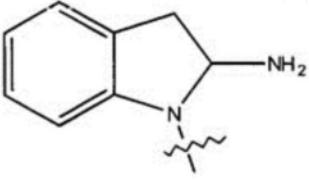
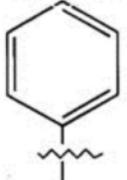
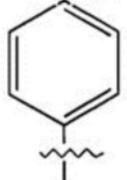
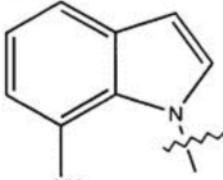
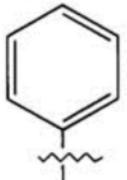
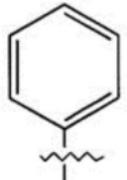
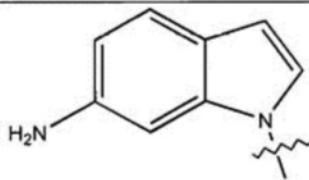
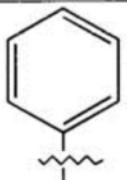
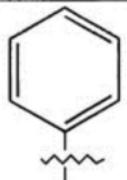
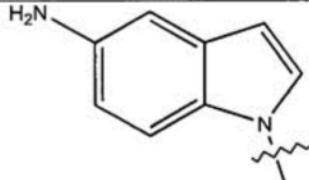
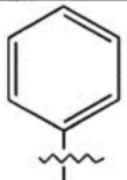
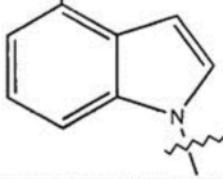
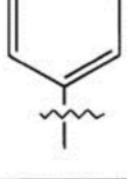
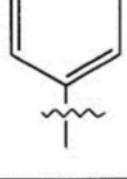
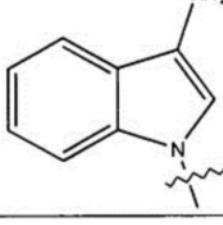
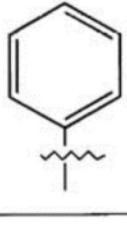
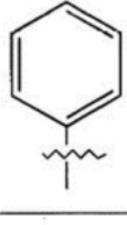
Cmpd	W	X	Z	A	Q
1957				OMe	O
1958				OMe	O
[0593]				OMe	O
1959				OMe	O
1960				OMe	O
1961				OMe	O

Cmpd	W	X	Z	A	Q
1962				OMe	O
1963				OMe	O
[0594]				OMe	O
1964				OMe	O
1965				OMe	O
1966				OMe	O

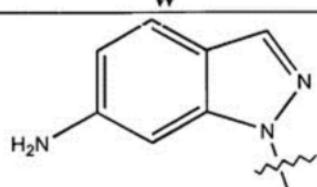
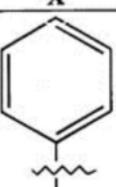
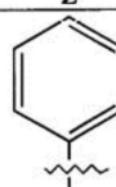
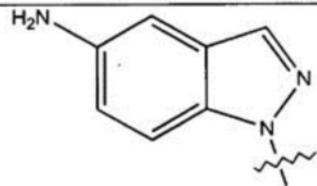
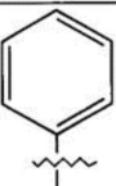
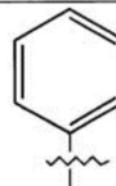
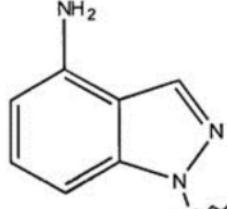
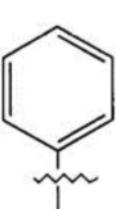
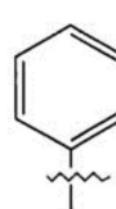
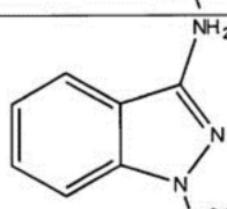
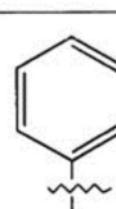
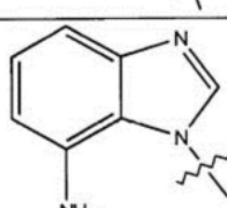
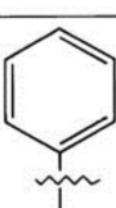
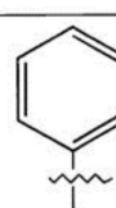
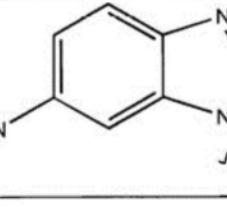
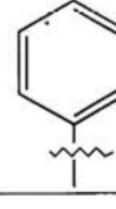
Cmpd	W	X	Z	A	Q
1967				OMe	O
1968				OMe	O
[0595]				OMe	O
1970				OMe	O
1971				OMe	O
1972				OMe	O

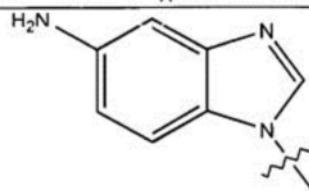
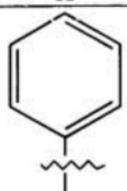
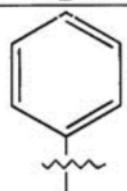
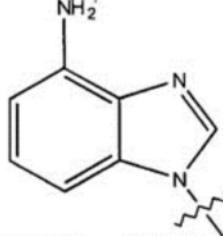
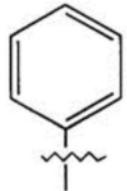
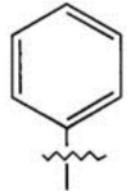
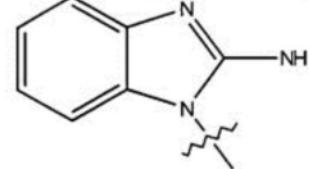
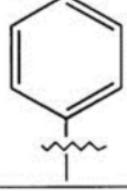
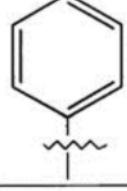
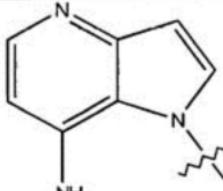
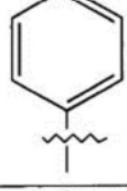
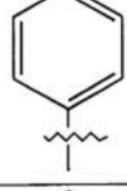
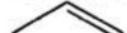
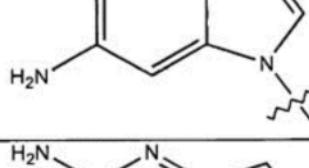
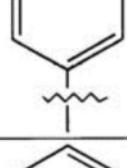
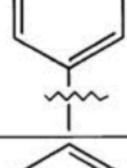
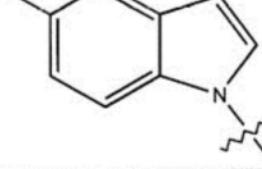
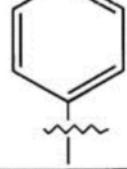
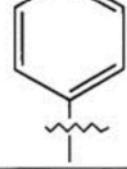
Cmpd	W	X	Z	A	Q
1973				OMe	O
1974				OMe	O
[0596]				OMe	O
1975				OMe	O
1976				OMe	O
1977				OMe	O

Cmpd	W	X	Z	A	Q
1978				OMe	O
1979				OMe	O
[0597]				OMe	O
1980				OMe	O
1981				OMe	O
1982				OMe	O

Cmpd	W	X	Z	A	Q
1983				OMe	O
1984				OMe	O
1985				OMe	O
[0598]				OMe	O
1986				OMe	O
1987				OMe	O
1988				OMe	O

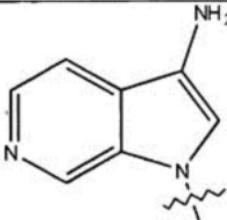
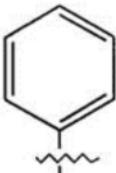
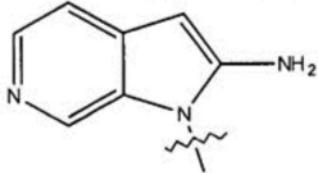
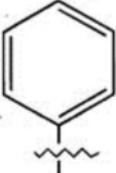
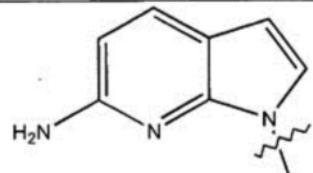
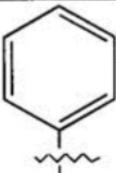
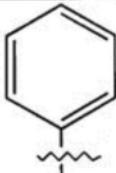
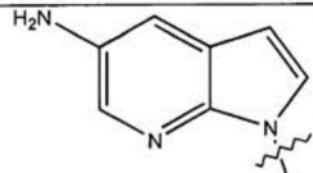
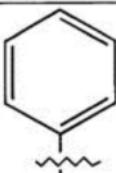
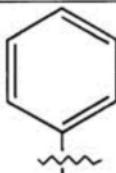
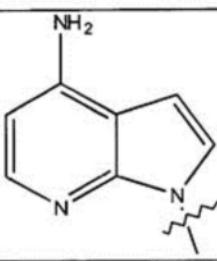
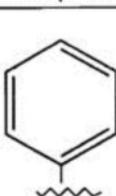
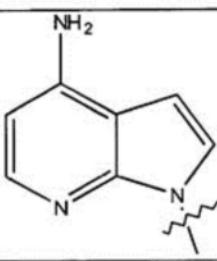
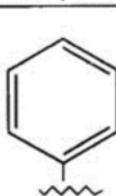
Cmpd	W	X	Z	A	Q
1989				OMe	O
1990				OMe	O
[0599]				OMe	O
1991				OMe	O
1992				OMe	O
1993				OMe	O

Cmpd	W	X	Z	A	Q
1994				OMe	O
1995				OMe	O
[0600]				OMe	O
1996				OMe	O
1997				OMe	O
1998				OMe	O
1999				OMe	O

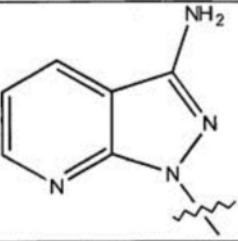
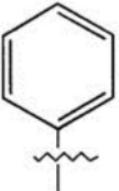
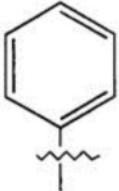
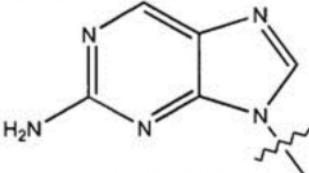
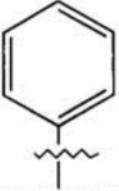
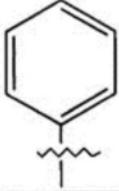
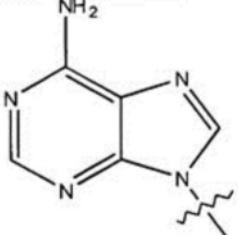
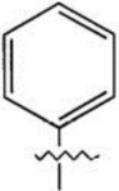
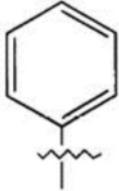
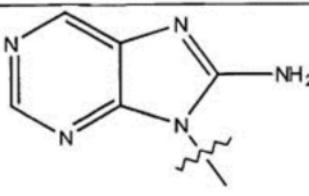
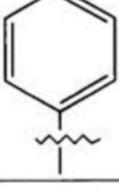
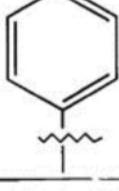
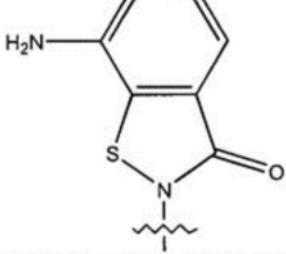
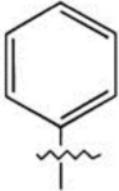
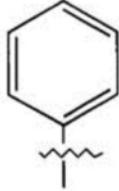
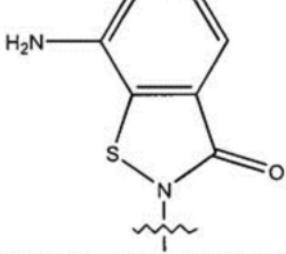
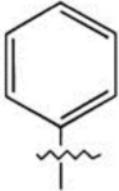
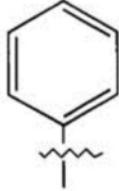
Cmpd	W	X	Z	A	Q
2000				OMe	O
2001					O
[0601]				OMe	O
2002				OMe	O
2003				OMe	O
2004				OMe	O
2005				OMe	O

Cmpd	W	X	Z	A	Q
2006				OMe	O
2007				OMe	O
[0602]				OMe	O
2008				OMe	O
2009				OMe	O
2010				OMe	O

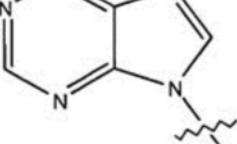
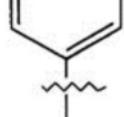
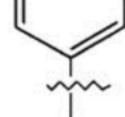
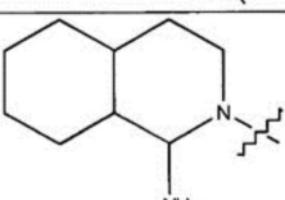
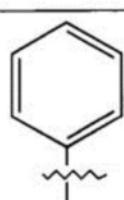
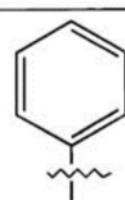
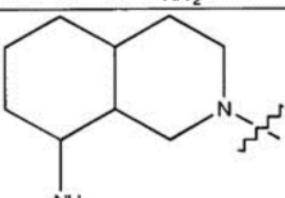
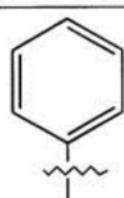
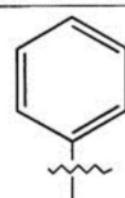
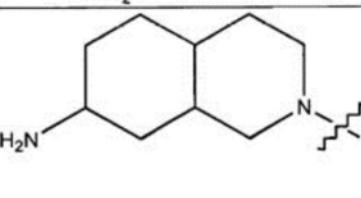
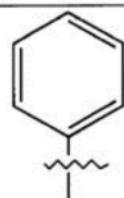
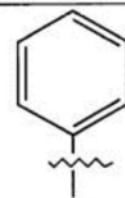
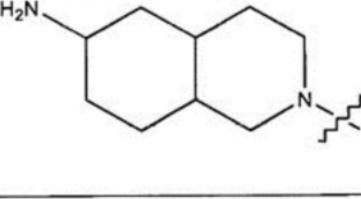
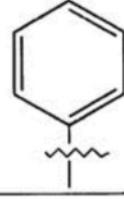
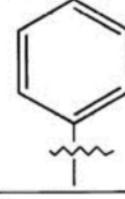
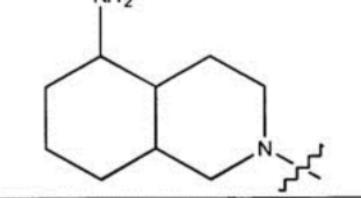
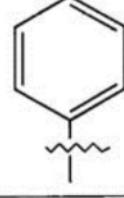
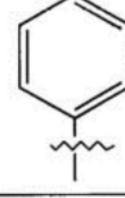
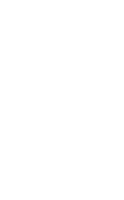
Cmpd	W	X	Z	A	Q
2011				OMe	O
2012				OMe	O
[0603]				OMe	O
2013				OMe	O
2014				OMe	O
2015				OMe	O

Cmpd	W	X	Z	A	Q
2016				OMe	O
2017				OMe	O
[0604]				OMe	O
2018				OMe	O
2019				OMe	O
2020				OMe	O

Cmpd	W	X	Z	A	Q
2021				OMe	O
2022				OMe	O
[0605]				OMe	O
2023				OMe	O
2024				OMe	O
2025				OMe	O

Cmpd	W	X	Z	A	Q
2026				OMe	O
2027				OMe	O
[0606]				OMe	O
2028				OMe	O
2029				OMe	O
2030				OMe	O

Cmpd	W	X	Z	A	Q
2031				OMe	O
[0607]				OMe	O
2032				OMe	O
2033				OMe	O
2034				OMe	O

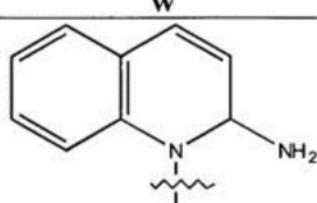
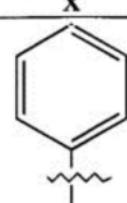
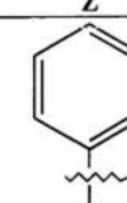
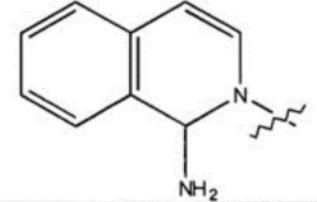
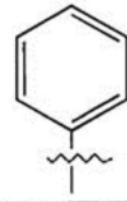
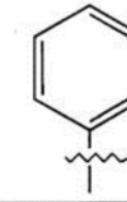
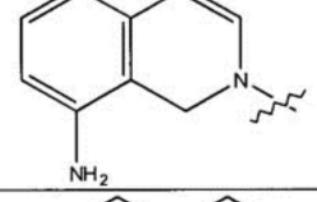
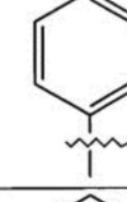
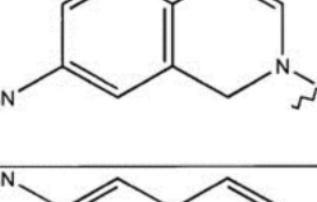
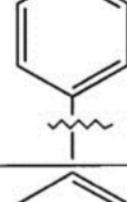
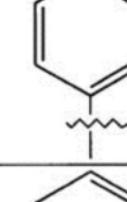
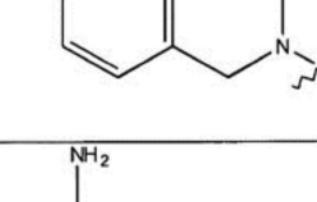
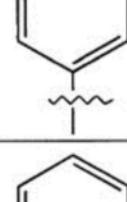
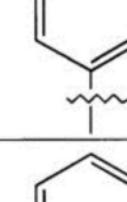
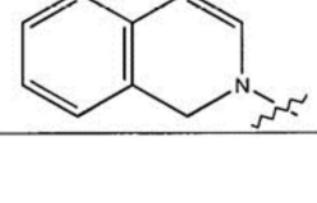
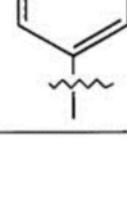
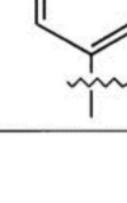
Cmpd	W	X	Z	A	Q
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2036				OMe	O
[0608]				OMe	O
2037				OMe	O
2038				OMe	O
2039				OMe	O
2040				OMe	O

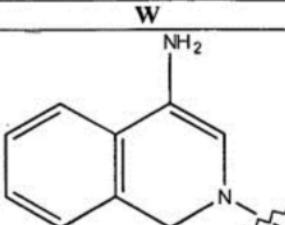
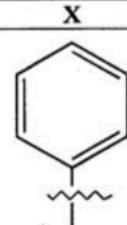
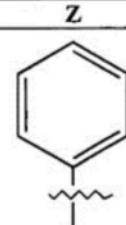
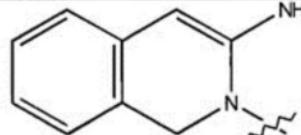
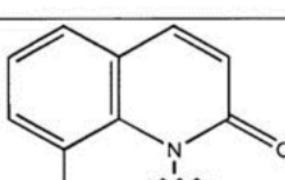
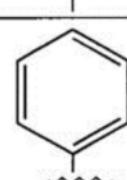
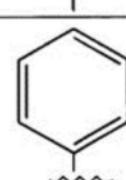
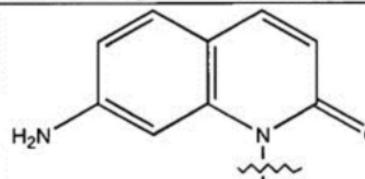
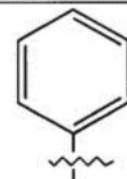
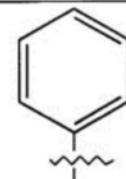
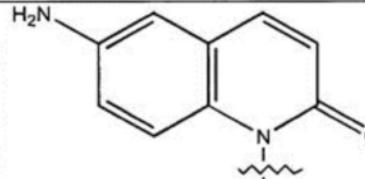
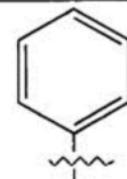
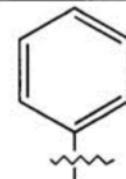
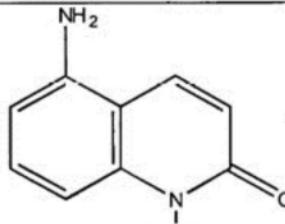
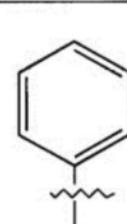
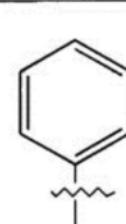
Cmpd	W	X	Z	A	Q	
2041				OMe	O	
2042				OMe	O	
[0609]	2043				OMe	O
	2044				OMe	O
	2045				OMe	O
	2046				OMe	O

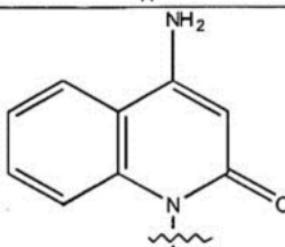
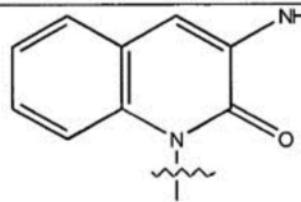
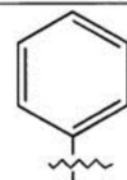
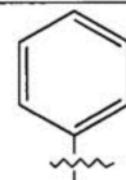
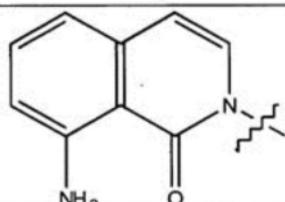
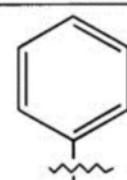
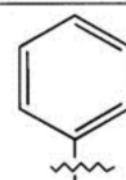
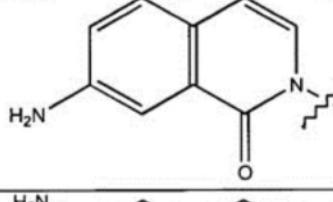
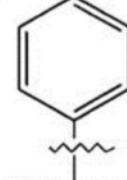
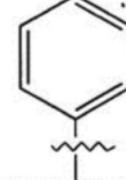
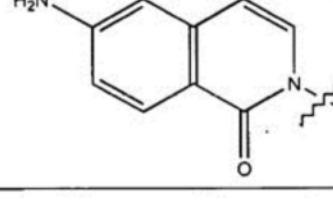
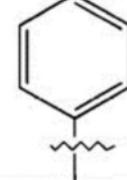
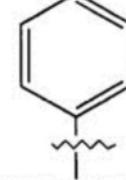
Cmpd	W	X	Z	A	Q
2047				OMe	O
2048				OMe	O
[0610]				OMe	O
2050				OMe	O
2051				OMe	O
2052				OMe	O

Cmpd	W	X	Z	A	Q
2053				OMe	O
2054				OMe	O
[0611]				OMe	O
2055				OMe	O
2056				OMe	O
2057				OMe	O

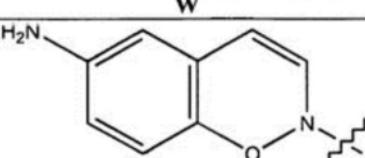
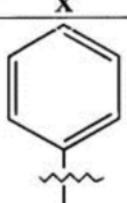
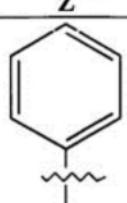
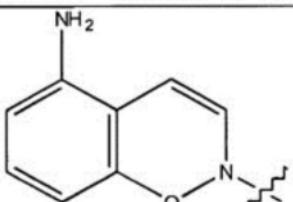
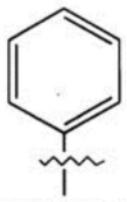
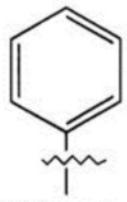
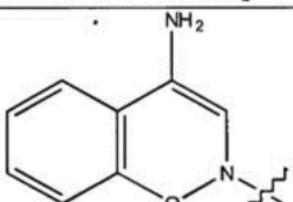
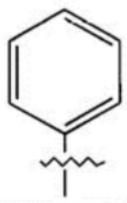
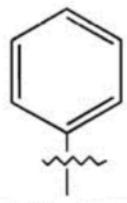
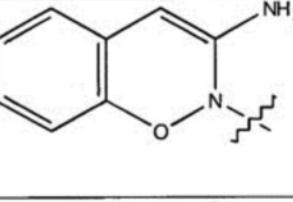
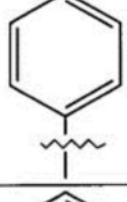
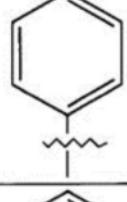
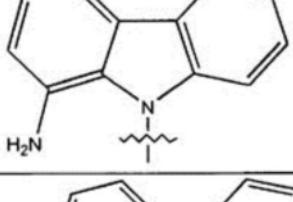
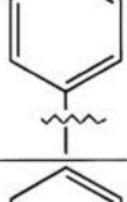
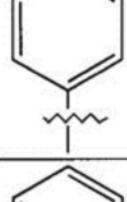
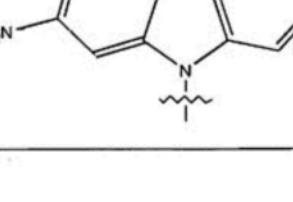
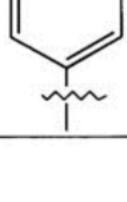
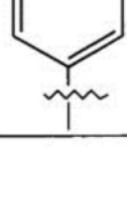
Cmpd	W	X	Z	A	Q
2058				OMe	O
2059				OMe	O
[0612]				OMe	O
2060				OMe	O
2061				OMe	O
2062				OMe	O

Cmpd	W	X	Z	A	Q
2063				OMe	O
2064				OMe	O
[0613]				OMe	O
2065				OMe	O
2066				OMe	O
2067				OMe	O
2068				OMe	O

Cmpd	W	X	Z	A	Q
2069				OMe	O
2070				OMe	O
[0614]				OMe	O
2072				OMe	O
2073				OMe	O
2074				OMe	O

Cmpd	W	X	Z	A	Q
2075				OMe	O
2076				OMe	O
[0615]				OMe	O
2077				OMe	O
2078				OMe	O
2079				OMe	O

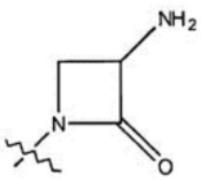
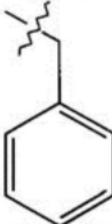
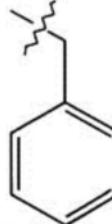
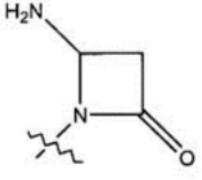
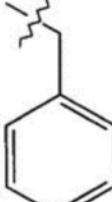
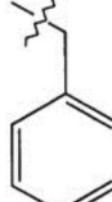
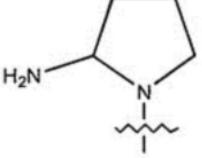
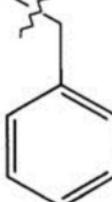
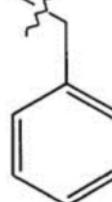
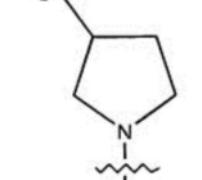
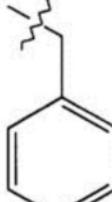
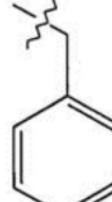
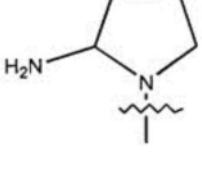
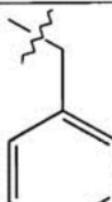
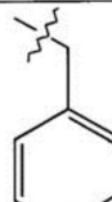
Cmpd	W	X	Z	A	Q
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2081				OMe	O
[0616]					
2082				OMe	O
2083				OMe	O
2084				OMe	O

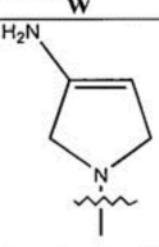
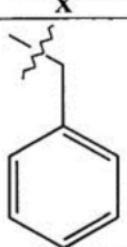
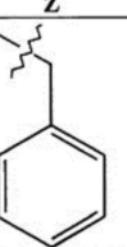
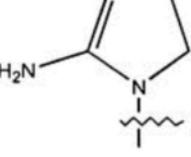
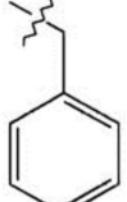
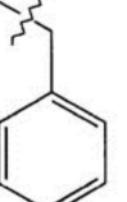
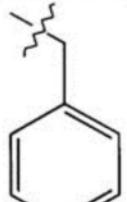
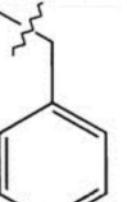
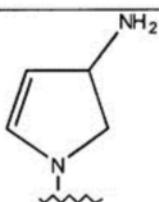
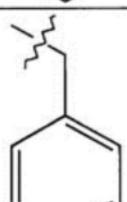
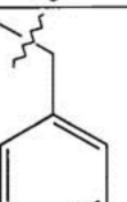
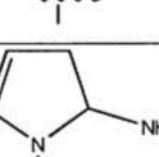
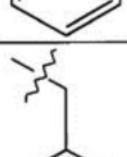
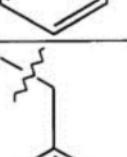
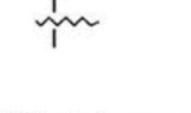
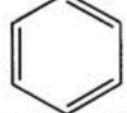
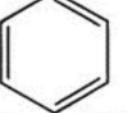
Cmpd	W	X	Z	A	Q
2085				OMe	O
2086				OMe	O
[0617]				OMe	O
2087				OMe	O
2088				OMe	O
2089				OMe	O
2090				OMe	O

Cmpd	W	X	Z	A	Q
2091				OMe	O
2092				OMe	O
[0618]				OMe	O
2093				OMe	O
2094				OMe	O
2095				OMe	O

Cmpd	W	X	Z	A	Q
2096				OMe	O
2097				OMe	O
[0619]				OMe	O
2098				OMe	O
2099				OMe	O
2100				OMe	O

Cmpd	W	X	Z	A	Q
2101				OMe	O
2102				OMe	O
[0620]				OMe	O
2103				OMe	O
2104				OMe	O
2105				OMe	O

Cmpd	W	X	Z	A	Q
2106				OMe	O
2107				OMe	O
[0621]				OMe	O
2109				OMe	O
2110				OMe	O

Cmpd	W	X	Z	A	Q
2111				OMe	O
2112				OMe	O
[0622]				OMe	O
2113				OMe	O
2114				OMe	O
2115				OMe	O

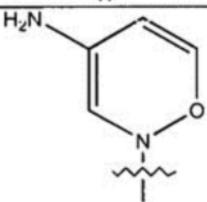
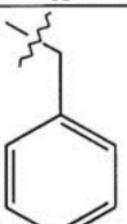
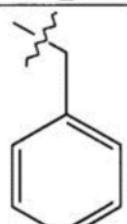
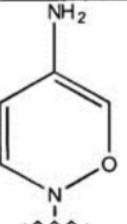
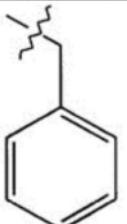
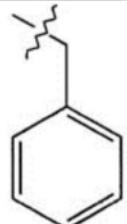
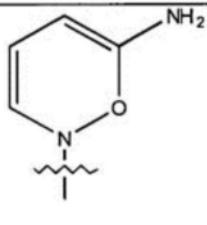
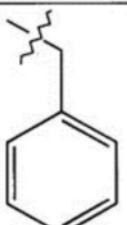
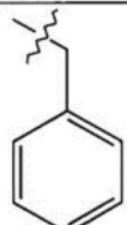
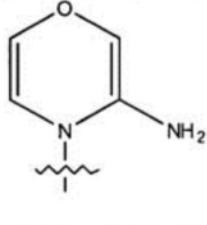
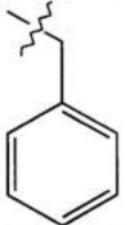
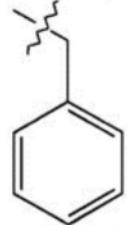
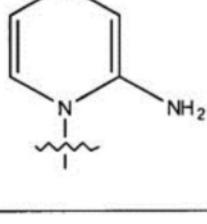
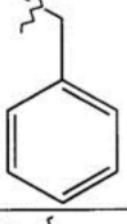
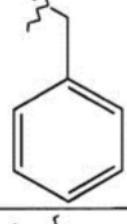
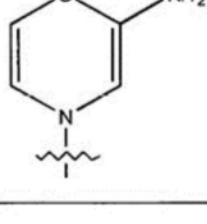
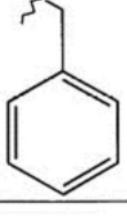
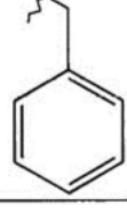
Cmpd	W	X	Z	A	Q
2116				OMe	O
2117				OMe	O
[0623]				OMe	O
2118				OMe	O
2119				OMe	O
2120				OMe	O

Cmpd	W	X	Z	A	Q
2121				OMe	O
2122				OMe	O
[0624]				OMe	O
2123				OMe	O
2124				OMe	O
2125				OMe	O

Cmpd	W	X	Z	A	Q
2126				OMe	O
2127				OMe	O
[0625]				OMe	O
2128				OMe	O
2129				OMe	O
2130				OMe	O

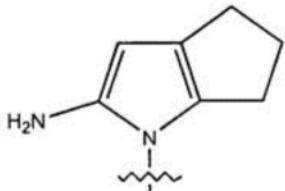
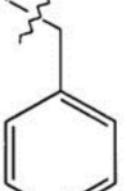
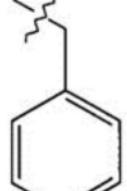
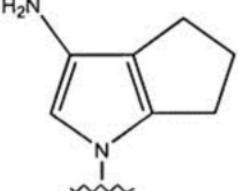
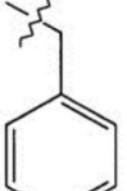
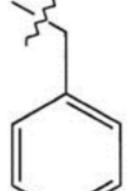
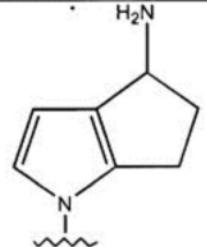
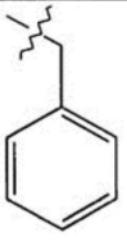
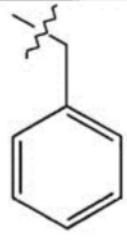
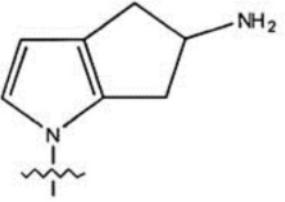
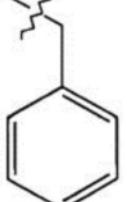
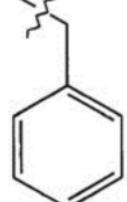
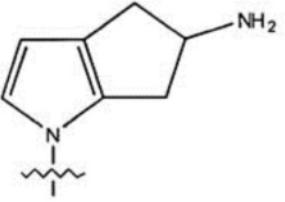
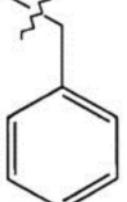
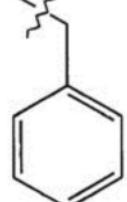
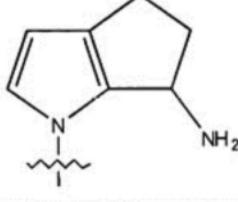
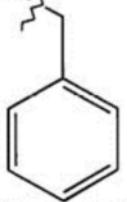
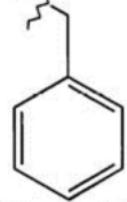
Cmpd	W	X	Z	A	Q
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2132				OMe	O
[0626]				OMe	O
2133				OMe	O
2134				OMe	O
2135				OMe	O

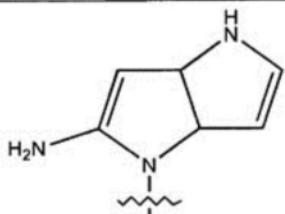
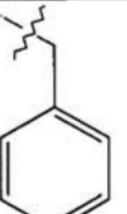
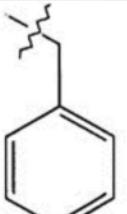
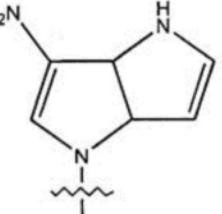
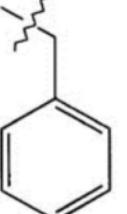
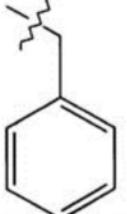
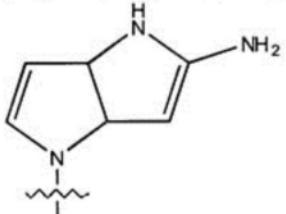
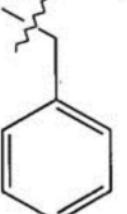
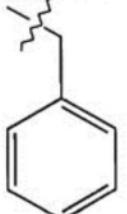
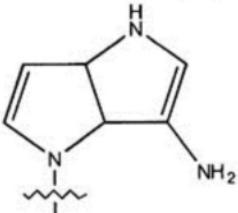
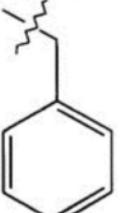
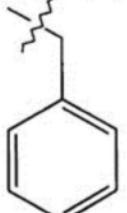
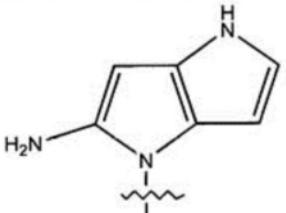
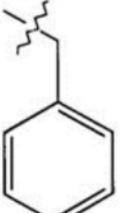
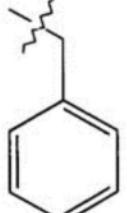
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2137				OMe	O
[0627]				OMe	O
2138				OMe	O
2139				OMe	O
2140				OMe	O

Cmpd	W	X	Z	A	Q
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[0628]				OMe	O
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2144				OMe	O
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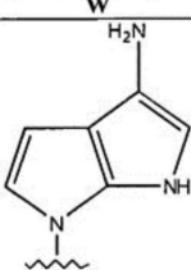
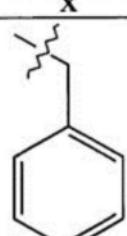
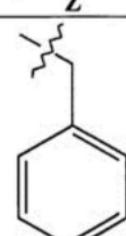
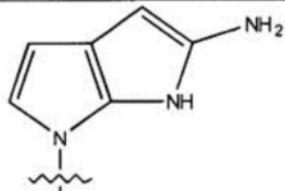
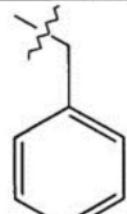
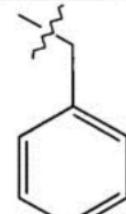
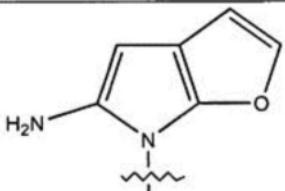
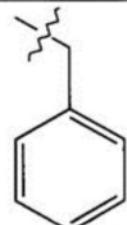
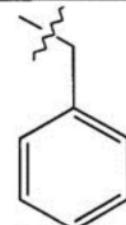
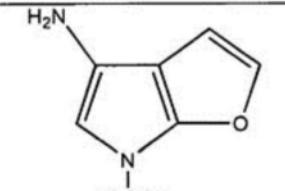
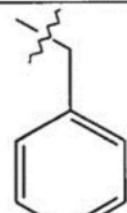
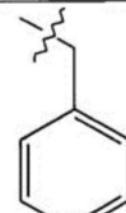
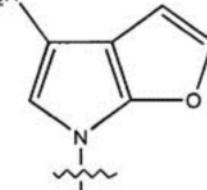
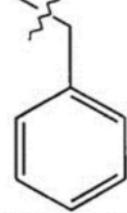
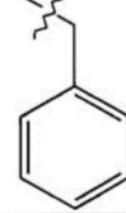
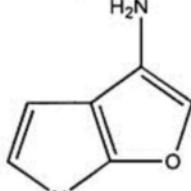
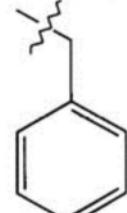
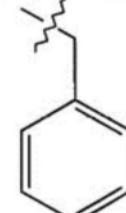
Cmpd	W	X	Z	A	Q
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[0629]				OMe	O
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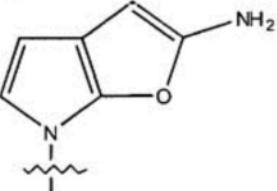
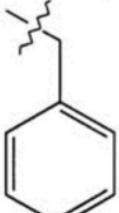
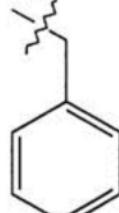
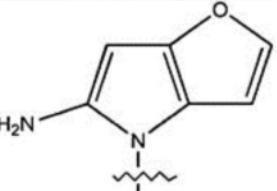
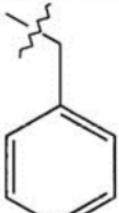
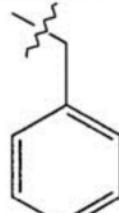
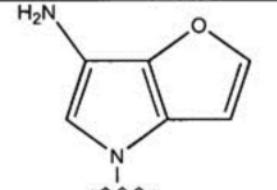
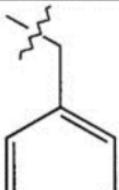
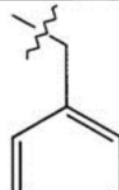
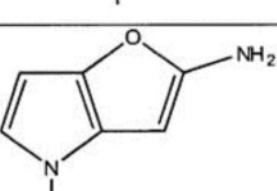
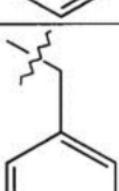
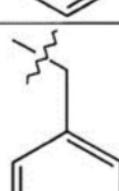
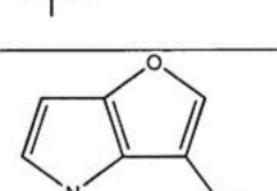
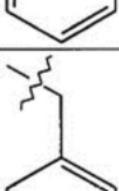
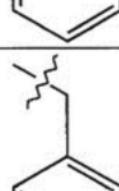
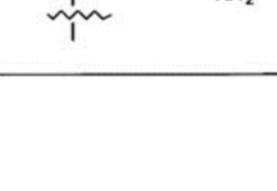
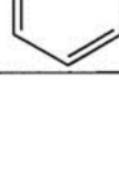
Cmpd	W	X	Z	A	Q
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[0630]				OMe	O
2153				OMe	O
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2155				OMe	O

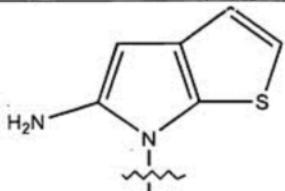
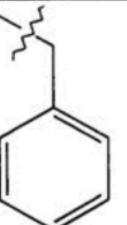
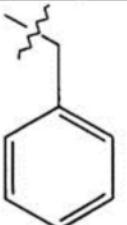
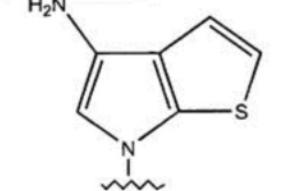
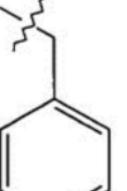
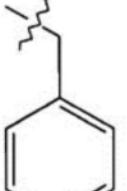
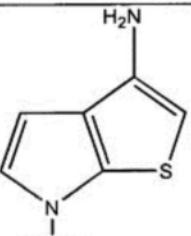
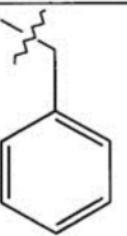
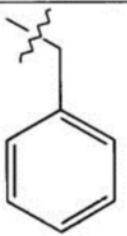
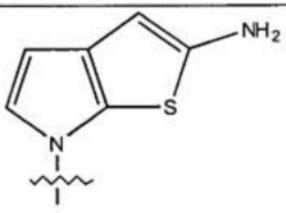
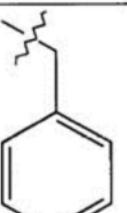
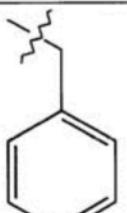
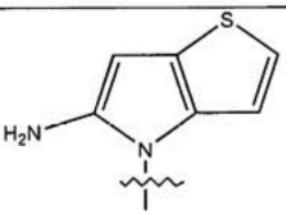
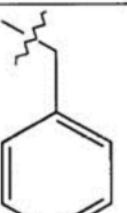
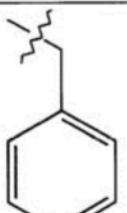
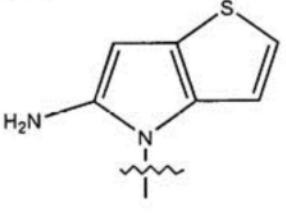
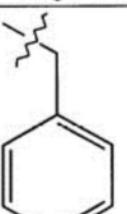
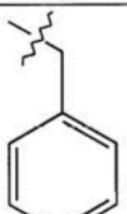
Cmpd	W	X	Z	A	Q
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[0631]				OMe	O
2158				OMe	O
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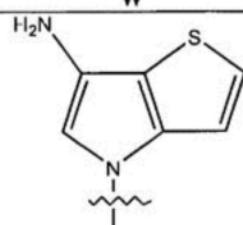
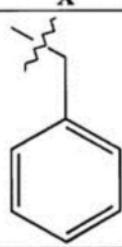
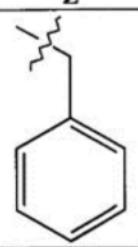
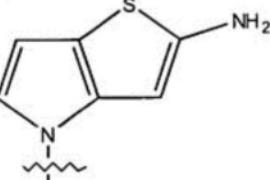
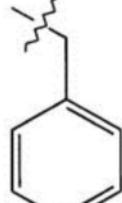
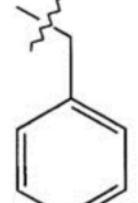
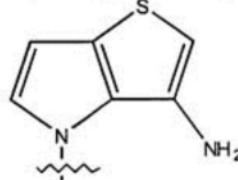
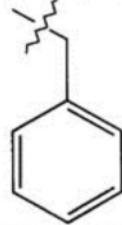
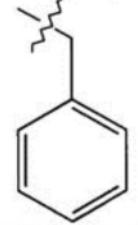
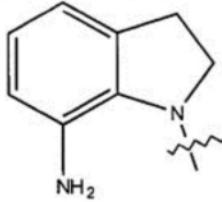
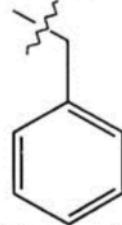
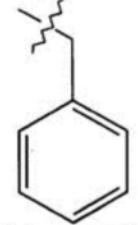
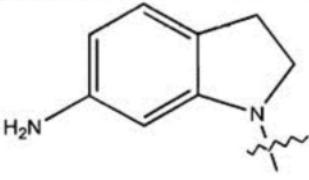
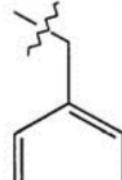
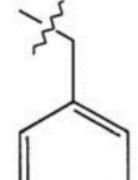
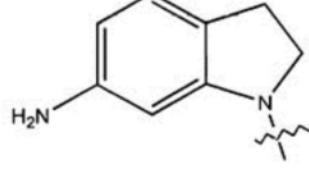
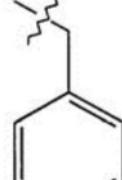
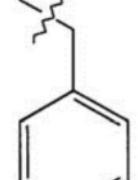
Cmpd	W	X	Z	A	Q
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2162				OMe	O
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2165				OMe	O

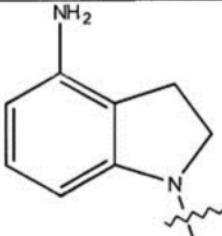
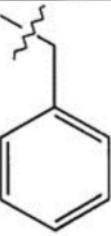
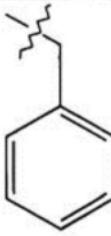
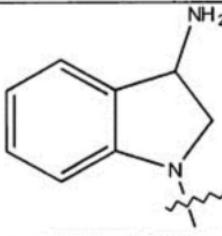
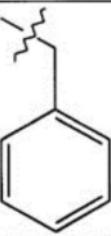
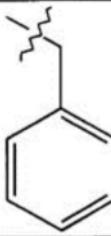
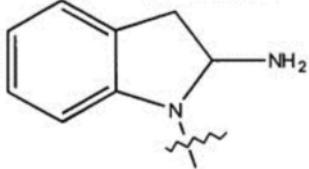
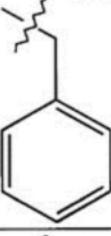
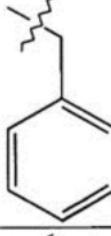
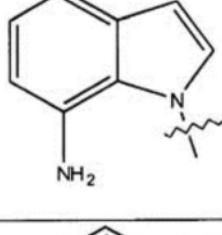
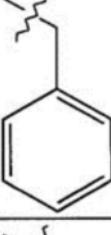
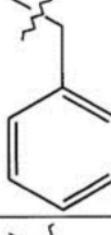
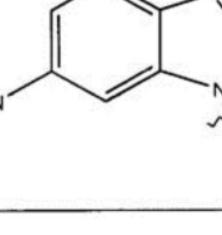
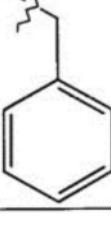
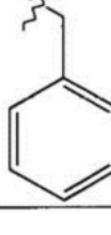
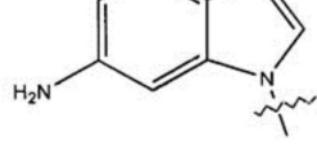
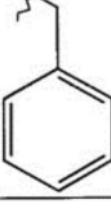
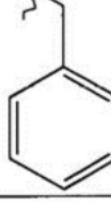
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2167				OMe	O
[0633]				OMe	O
2168				OMe	O
2169				OMe	O
2170				OMe	O

Cmpd	W	X	Z	A	Q
2171				OMe	O
2172				OMe	O
[0634]				OMe	O
2173				OMe	O
2174				OMe	O
2175				OMe	O

Cmpd	W	X	Z	A	Q
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2177				OMe	O
[0635]				OMe	O
2178				OMe	O
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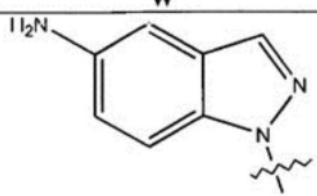
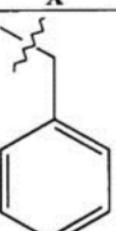
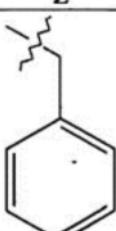
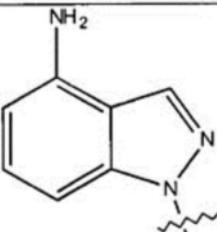
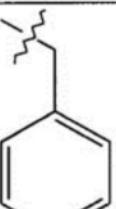
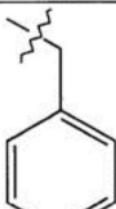
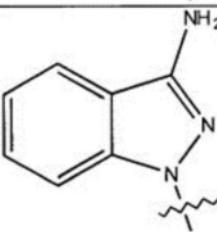
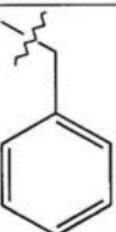
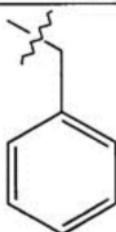
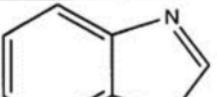
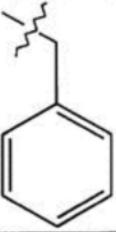
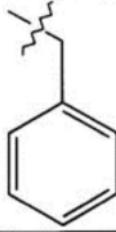
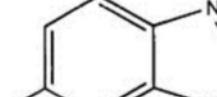
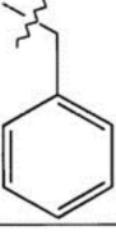
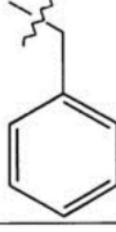
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2183				OMe	O
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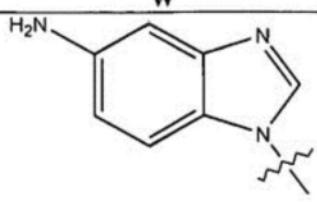
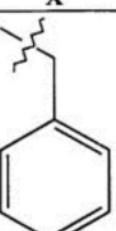
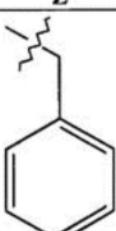
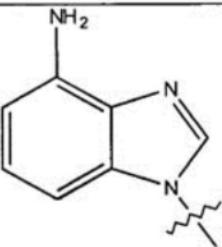
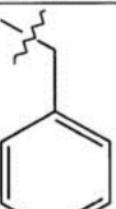
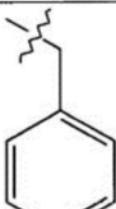
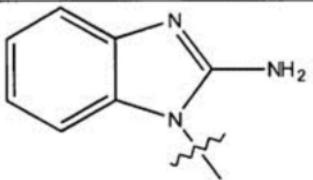
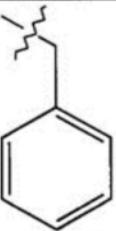
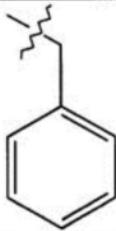
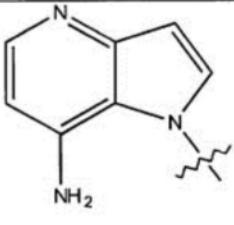
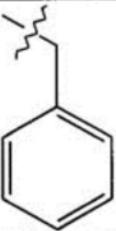
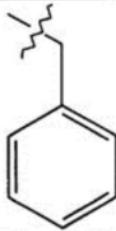
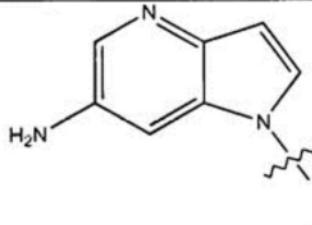
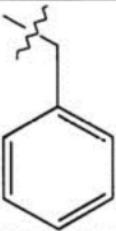
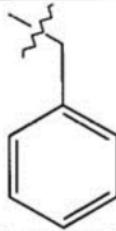
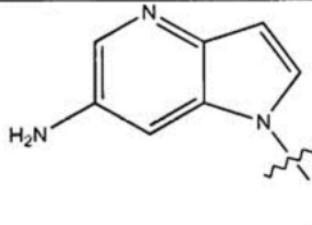
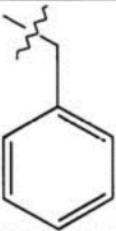
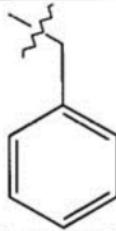
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2187				OMe	O
[0637]				OMe	O
2188				OMe	O
2189				OMe	O
2190				OMe	O

Cmpd	W	X	Z	A	Q
2191				OMe	O
2192				OMe	O
[0638]				OMe	O
2193				OMe	O
2194				OMe	O
2195				OMe	O

Cmpd	W	X	Z	A	Q
2196				OMe	O
2197				OMe	O
[0639]				OMe	O
2198				OMe	O
2199				OMe	O
2200				OMe	O

Cmpd	W	X	Z	A	Q
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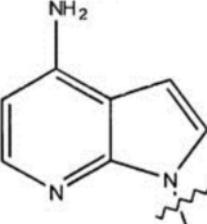
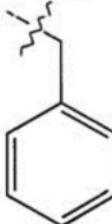
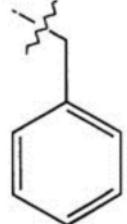
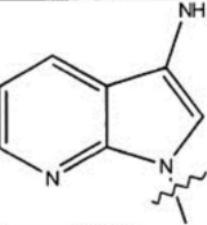
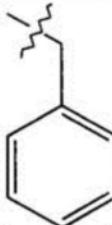
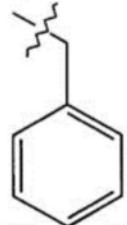
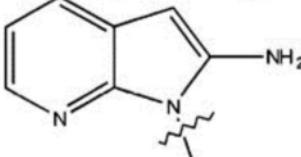
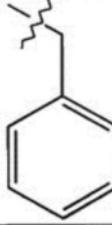
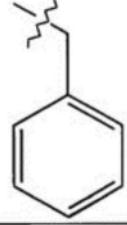
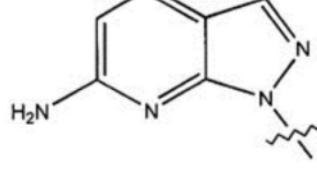
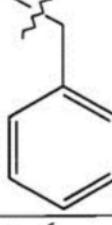
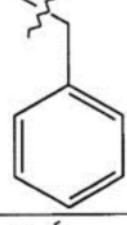
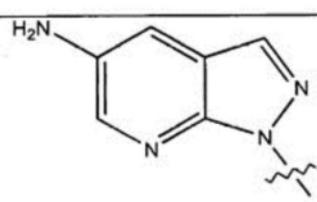
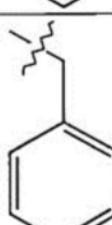
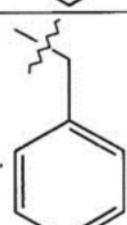
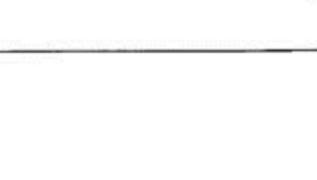
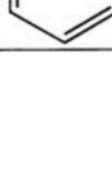
Cmpd	W	X	Z	A	Q
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[0641]				OMe	O
2207				OMe	O
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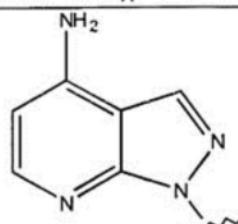
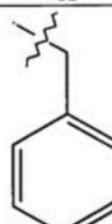
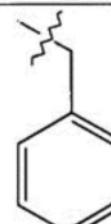
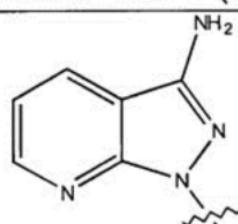
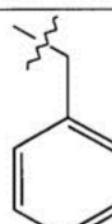
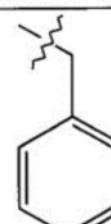
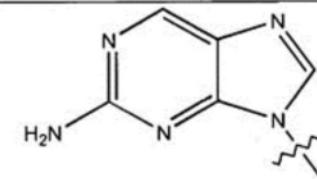
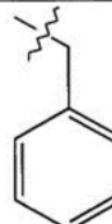
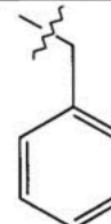
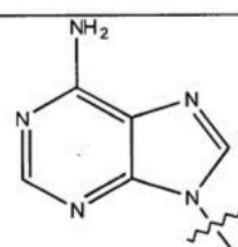
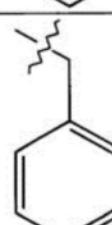
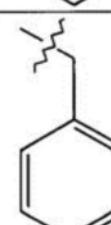
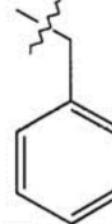
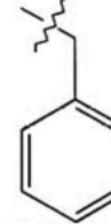
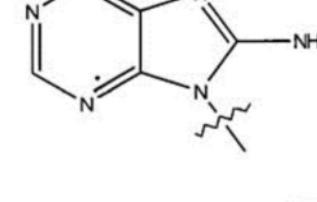
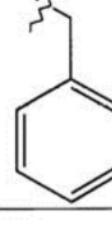
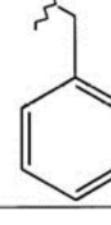
Cmpd	W	X	Z	A	Q
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2211					O
[0642]				OMe	O
2212				OMe	O
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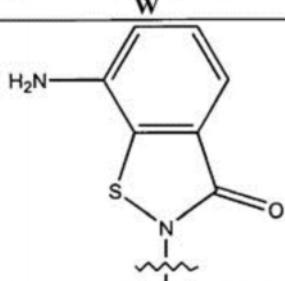
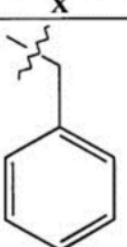
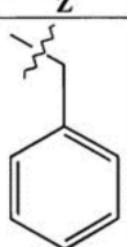
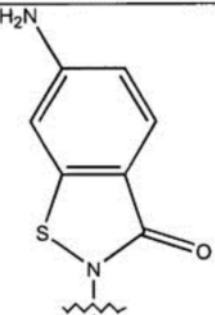
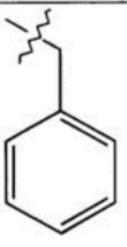
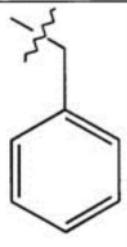
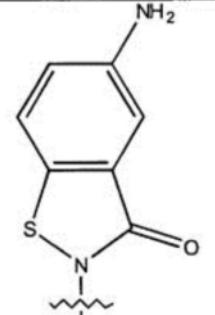
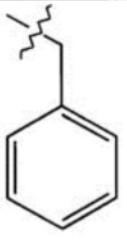
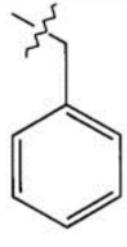
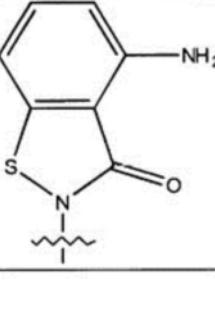
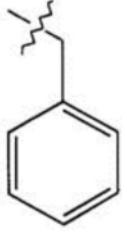
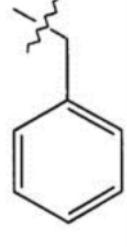
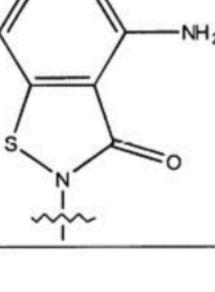
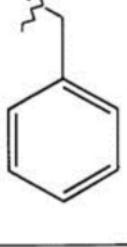
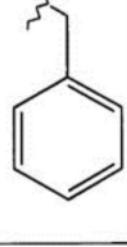
Cmpd	W	X	Z	A	Q
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2216				OMe	O
[0643]				OMe	O
2217				OMe	O
2218				OMe	O
2219				OMe	O

Cmpd	W	X	Z	A	Q
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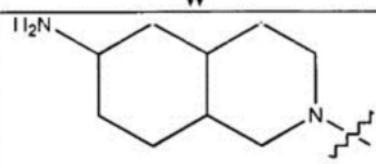
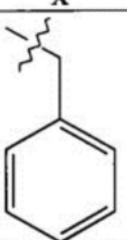
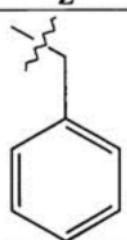
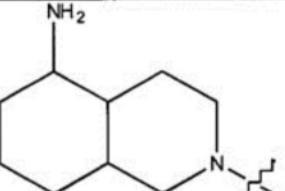
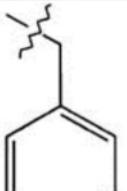
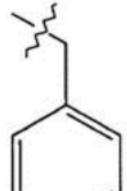
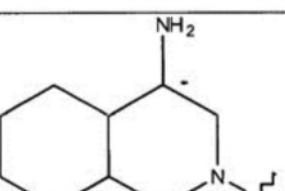
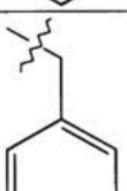
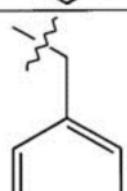
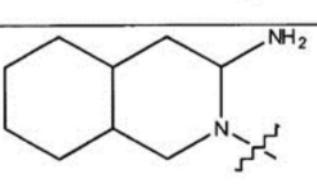
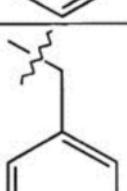
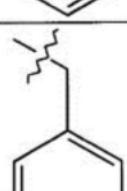
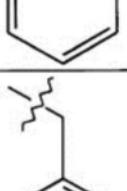
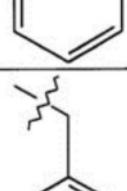
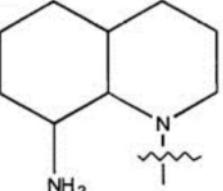
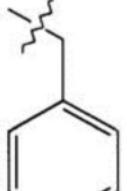
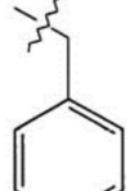
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2226				OMe	O
[0645]				OMe	O
2227				OMe	O
2228				OMe	O
2229				OMe	O

Cmpd	W	X	Z	A	Q
2230				OMe	O
2231				OMe	O
[0646]				OMe	O
2232				OMe	O
2233				OMe	O
2234				OMe	O

Cmpd	W	X	Z	A	Q
2235				OMe	O
2236				OMe	O
[0647]				OMe	O
2237				OMe	O
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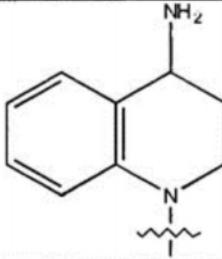
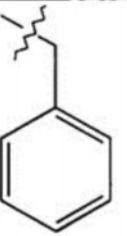
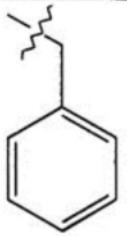
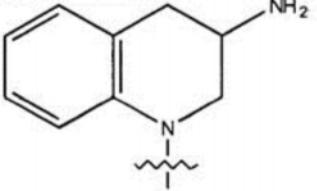
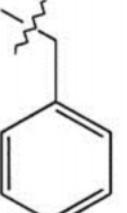
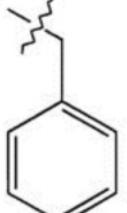
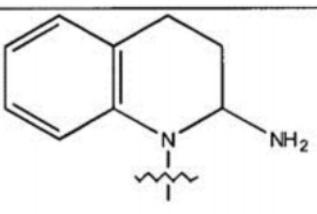
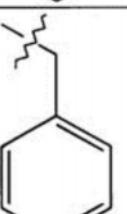
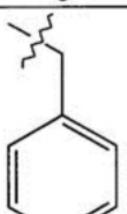
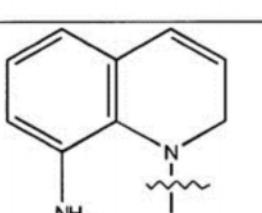
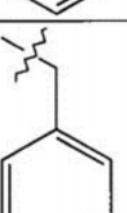
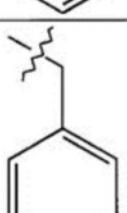
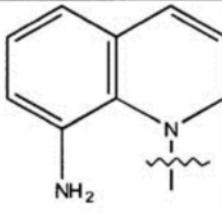
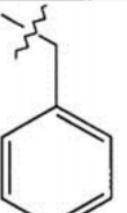
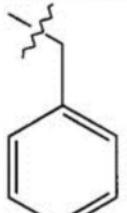
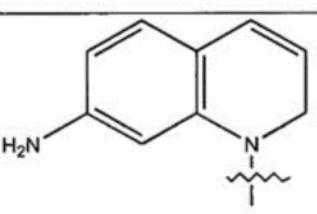
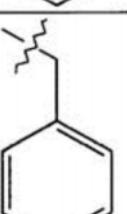
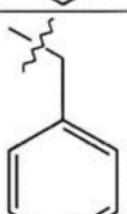
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[0648]				OMe	O
2241				OMe	O
2242				OMe	O
2243				OMe	O

Cmpd	W	X	Z	A	Q
2244				OMe	O
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[0649]				OMe	O
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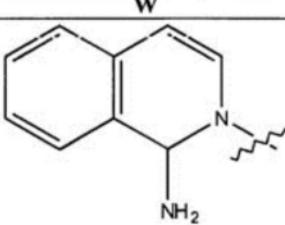
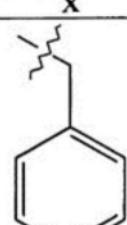
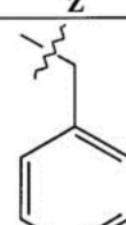
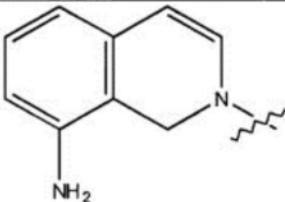
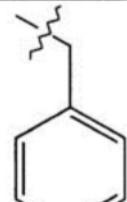
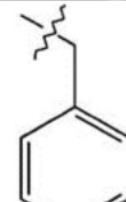
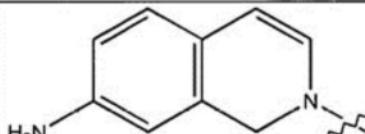
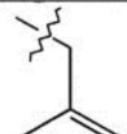
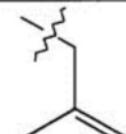
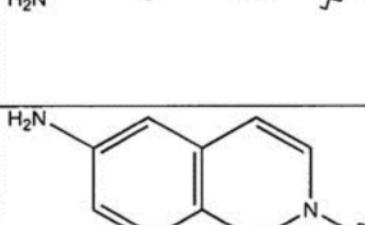
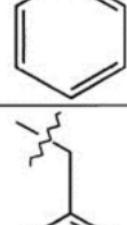
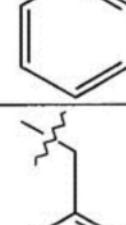
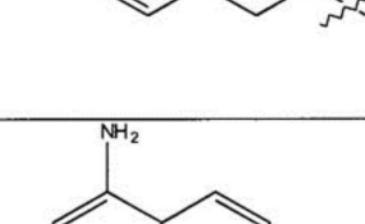
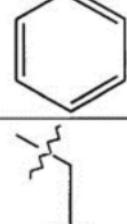
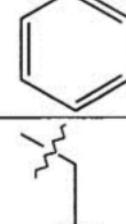
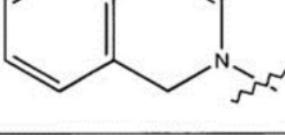
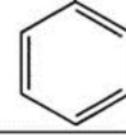
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2250				OMe	O
[0650]				OMe	O
2251				OMe	O
2252				OMe	O
2253				OMe	O

Cmpd	W	X	Z	A	Q
2254				OMe	O
2255				OMe	O
[0651]				OMe	O
2256				OMe	O
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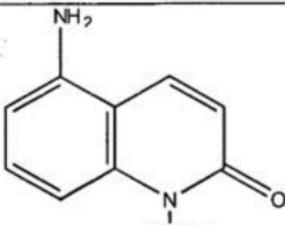
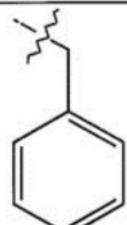
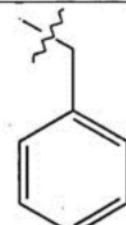
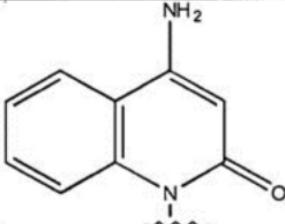
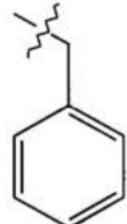
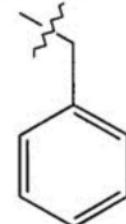
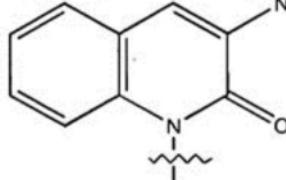
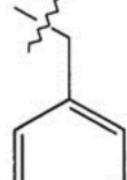
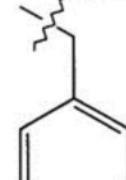
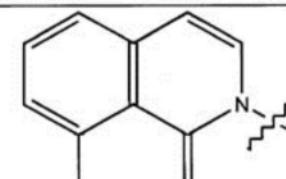
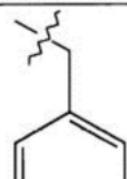
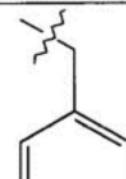
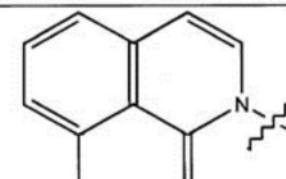
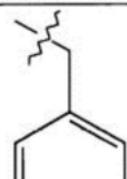
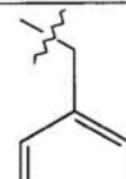
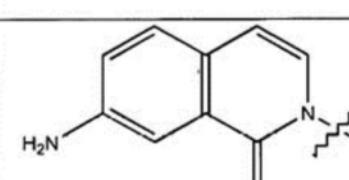
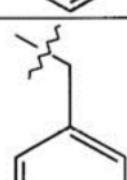
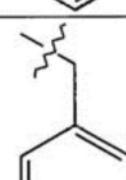
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2260				OMe	O
[0652]				OMe	O
2261				OMe	O
2262				OMe	O
2263				OMe	O

Cmpd	W	X	Z	A	Q
2264				OMe	O
2265				OMe	O
[0653]				OMe	O
2266				OMe	O
2267				OMe	O
2268				OMe	O

Cmpd	W	X	Z	A	Q
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2270				OMe	O
[0654]				OMe	O
2271				OMe	O
2272				OMe	O
2273				OMe	O

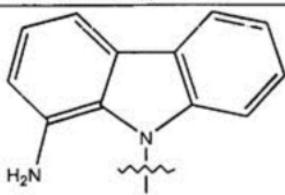
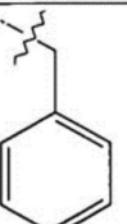
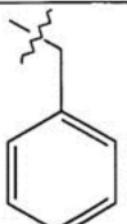
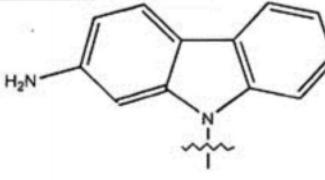
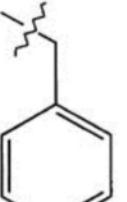
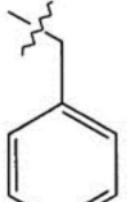
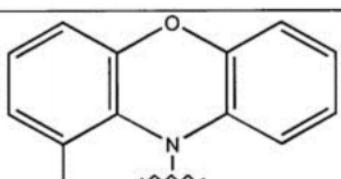
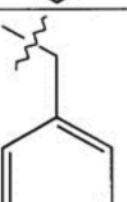
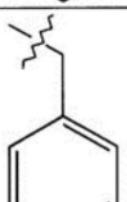
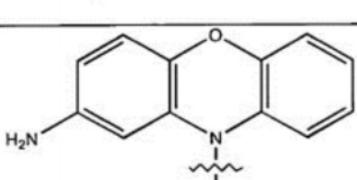
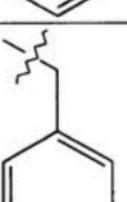
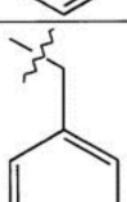
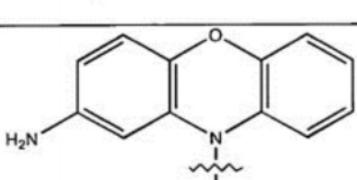
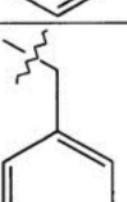
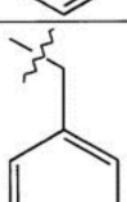
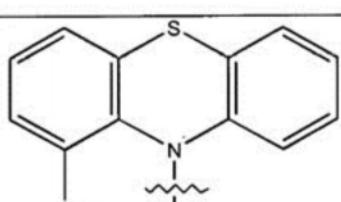
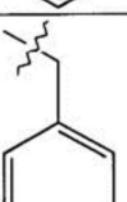
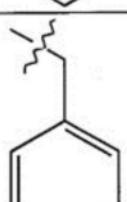
Cmpd	W	X	Z	A	Q
2274				OMe	O
2275				OMe	O
[0655]				OMe	O
2276				OMe	O
2277				OMe	O
2278				OMe	O

Cmpd	W	X	Z	A	Q
2279				OMe	O
2280				OMe	O
[0656]				OMe	O
2281				OMe	O
2282				OMe	O
2283				OMe	O

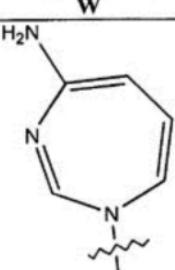
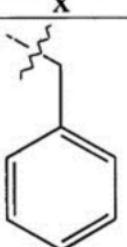
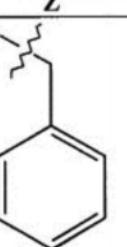
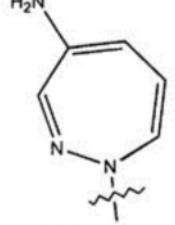
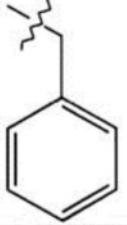
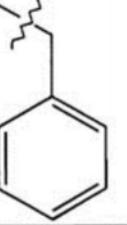
Cmpd	W	X	Z	A	Q
2284				OMe	O
2285				OMe	O
[0657]				OMe	O
2286				OMe	O
2287				OMe	O
2288				OMe	O

Cmpd	W	X	Z	A	Q
2289				OMe	O
2290				OMe	O
[0658]				OMe	O
2291				OMe	O
2292				OMe	O
2293				.	OMe

Cmpd	W	X	Z	A	Q
2294				OMe	O
2295				OMe	O
[0659]				OMe	O
2296				OMe	O
2297				OMe	O
2298				OMe	O

Cmpd	W	X	Z	A	Q
2299				OMe	O
2300				OMe	O
[0660]				OMe	O
2301				OMe	O
2302				OMe	O
2303				OMe	O

Cmpd	W	X	Z	A	Q
2304				OMe	O
2305				OMe	O
[0661]				OMe	O
2306				OMe	O
2307				OMe	O
2308				OMe	O

Cmpd	W	X	Z	A	Q
[0662] 2309				OMe	O
2310				OMe	O

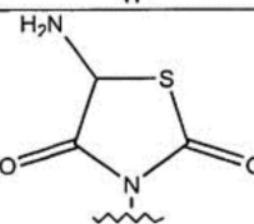
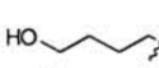
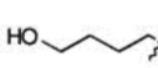
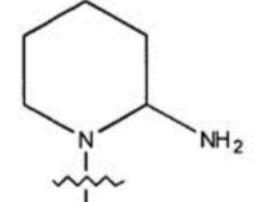
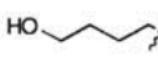
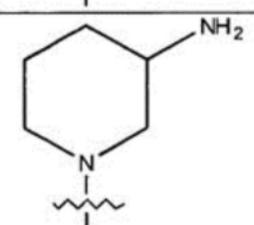
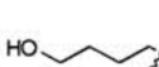
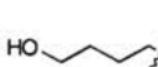
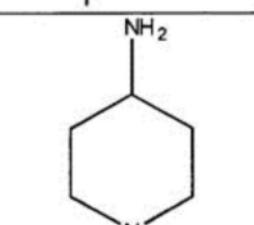
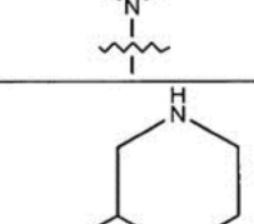
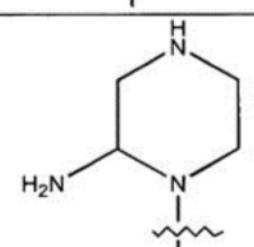
Cmpd	W	X	Z	A	Q
2311		HO~~~~~	HO~~~~~	OMe	O
2312		HO~~~~~	HO~~~~~	OMe	O
2313		HO~~~~~	HO~~~~~	OMe	O
[0663]					
2314		HO~~~~~	HO~~~~~	OMe	O
2315		HO~~~~~	HO~~~~~	OMe	O
2316		HO~~~~~	HO~~~~~	OMe	O
2317		HO~~~~~	HO~~~~~	OMe	O

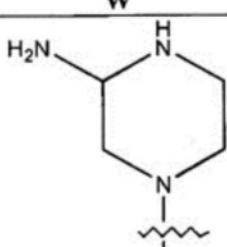
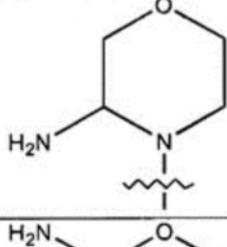
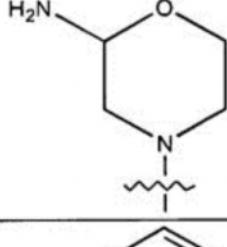
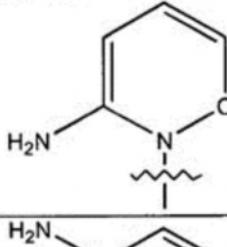
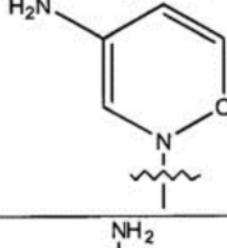
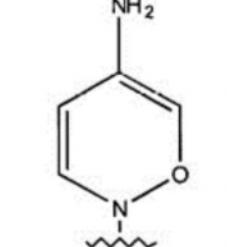
Cmpd	W	X	Z	A	Q
2318				OMe	O
2319				OMe	O
2320				OMe	O
[0664]					
2321				OMe	O
2322				OMe	O
2323				OMe	O

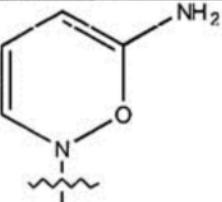
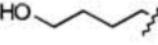
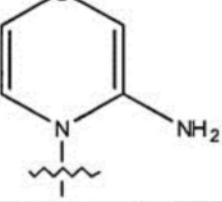
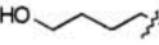
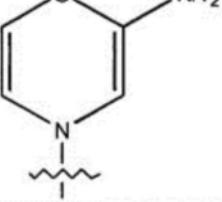
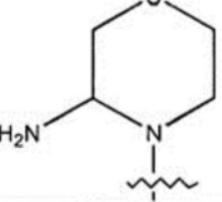
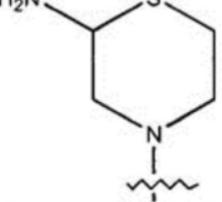
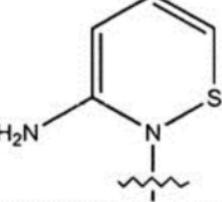
Cmpd	W	X	Z	A	Q
2324				OMe	O
2325				OMe	O
2326				OMe	O
[0665]				OMe	O
2327				OMe	O
2328				OMe	O
2329				OMe	O

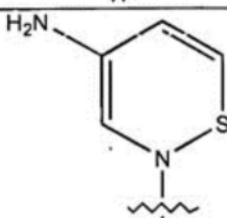
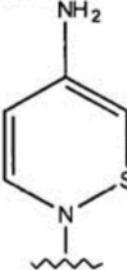
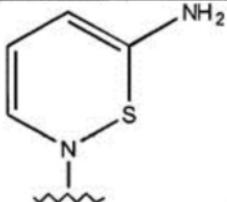
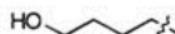
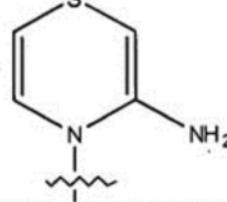
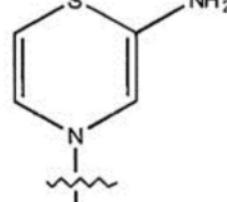
Cmpd	W	X	Z	A	Q
2330		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2331		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2332		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
[0666]					
2333		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2334		.	HO-CH2-CH2-CH2-	OMe	O
2335		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O

Cmpd	W	X	Z	A	Q
2336		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2337		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2338		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
[0667]					
2339		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2340		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2341		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O

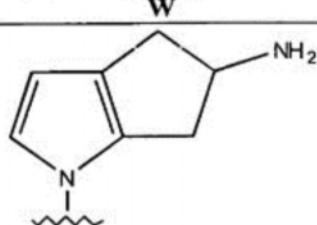
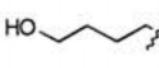
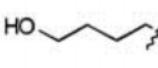
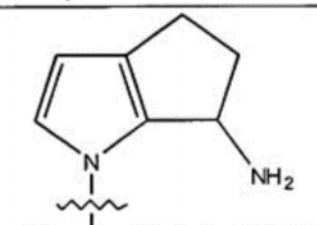
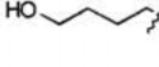
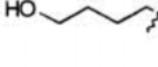
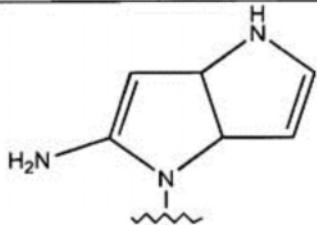
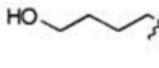
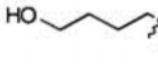
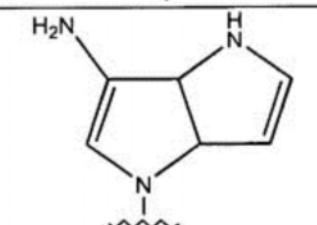
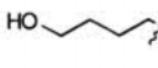
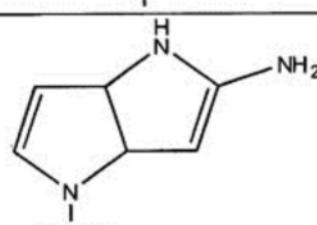
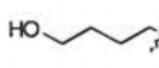
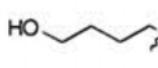
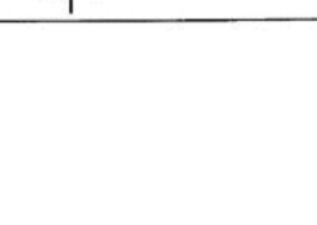
Cmpd	W	X	Z	A	Q
2342				OMe	O
2343				OMe	O
[0668]				OMe	O
2344				OMe	O
2345				OMe	O
2346				OMe	O

Cmpd	W	X	Z	A	Q
2347				OMe	O
2348				OMe	O
2349				OMe	O
[0669]					
2350				OMe	O
2351				OMe	O
2352				OMe	O

Cmpd	W	X	Z	A	Q	
2353				OMe	O	
2354				OMe	O	
[0670]	2355				OMe	O
	2356				OMe	O
	2357				OMe	O
	2358				OMe	O

Cmpd	W	X	Z	A	Q	
2359				OMe	O	
2360				OMe	O	
[0671]				OMe	O	
2361		c			OMe	O
2362				OMe	O	
2363				OMe	O	

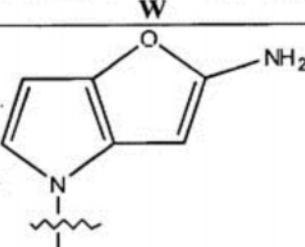
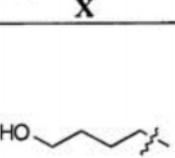
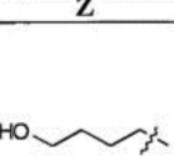
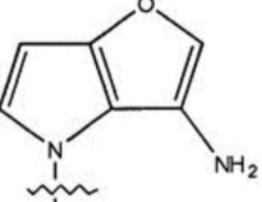
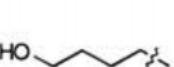
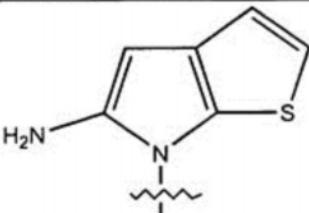
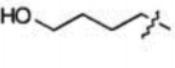
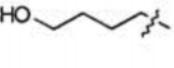
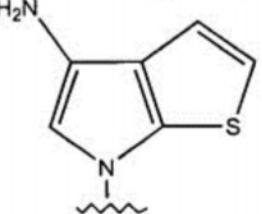
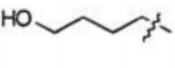
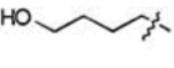
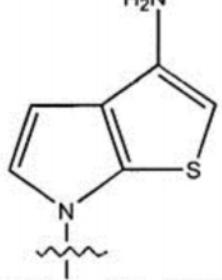
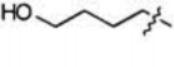
Cmpd	W	X	Z	A	Q
2364		HO	HO	OMe	O
2365		HO	HO	OMe	O
[0672]		HO	HO	OMe	O
2366		HO	HO	OMe	O
2367		HO	HO	OMe	O
2368		HO	HO	OMe	O

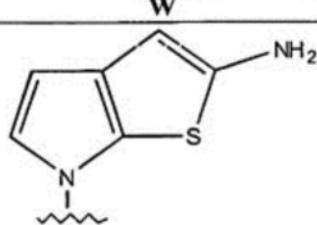
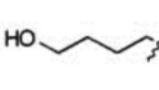
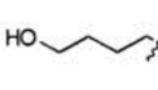
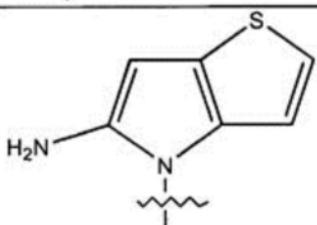
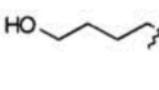
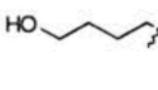
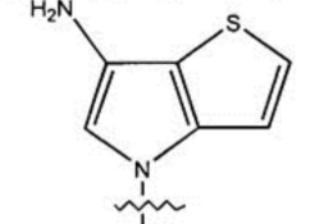
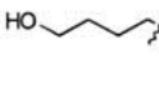
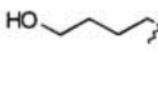
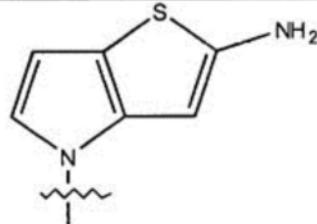
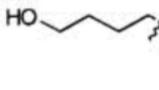
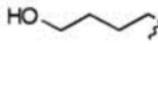
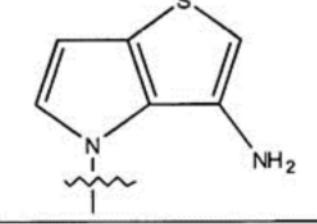
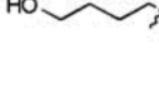
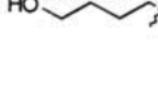
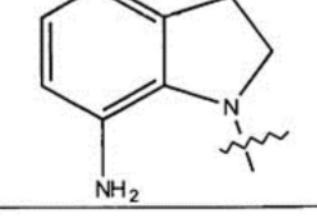
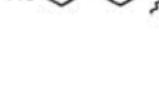
Cmpd	W	X	Z	A	Q
2369		HO 	HO 	OMe	O
2370		HO 	HO 	OMe	O
[0673]		HO 	HO 	OMe	O
2371		HO 	HO 	OMe	O
2372		HO 	HO 	OMe	O
2373		HO 	HO 	OMe	O

Cmpd	W	X	Z	A	Q
2374		HO	HO	OMe	O
2375		HO	HO	OMe	O
[0674]		HO	HO	OMe	O
2376		HO	HO	OMe	O
2377		HO	HO	OMe	O
2378		HO	HO	OMe	O

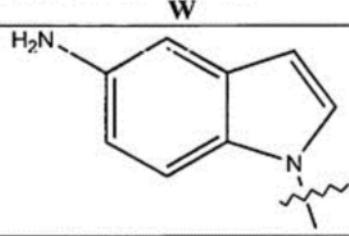
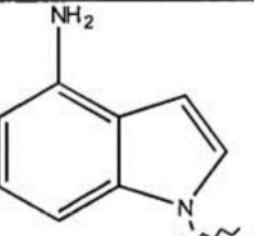
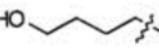
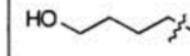
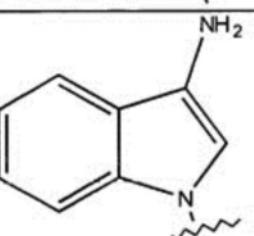
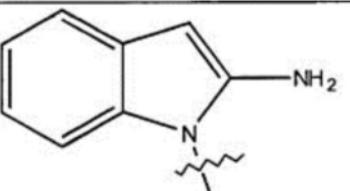
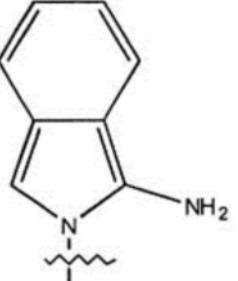
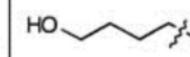
Cmpd	W	X	Z	A	Q
2379		HO	HO	OMe	O
2380		HO	HO	OMe	O
[0675]		HO	HO	OMe	O
2381		HO	HO	OMe	O
2382		HO	HO	OMe	O
2383		HO	HO	OMe	O

Cmpd	W	X	Z	A	Q
2384		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	OMe	O
2385		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	OMe	O
[0676]		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	OMe	O
2386		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	OMe	O
2387		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	OMe	O
2388		HO-CH2-CH2-CH2-CH2-	HO-CH2-CH2-CH2-CH2-	OMe	O

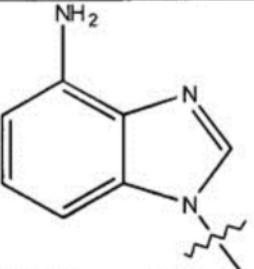
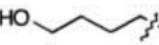
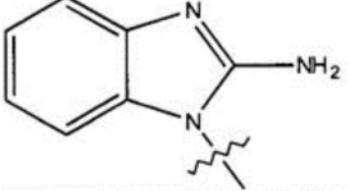
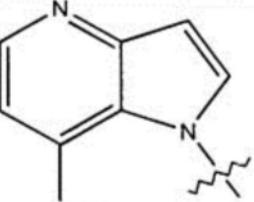
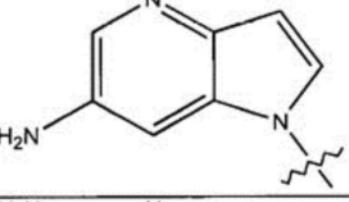
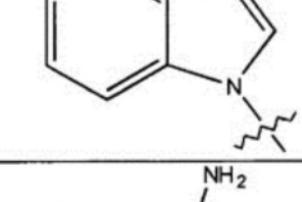
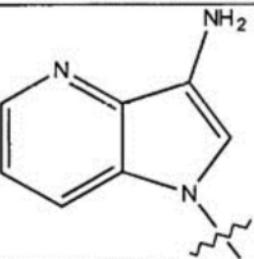
Cmpd	W	X	Z	A	Q
2389				OMe	O
2390				OMe	O
[0677]				OMe	O
2391				OMe	O
2392				OMe	O
2393				OMe	O

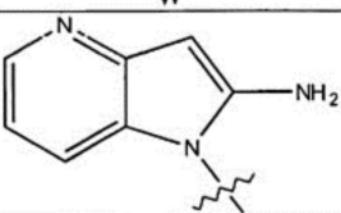
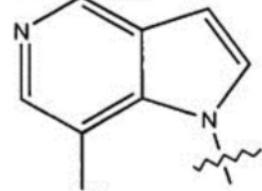
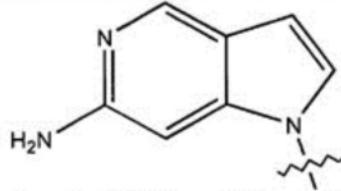
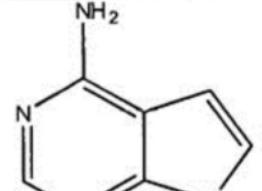
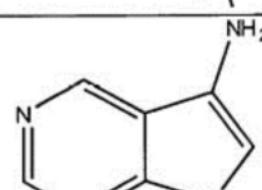
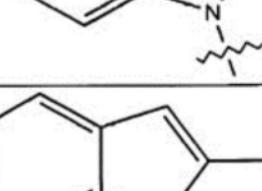
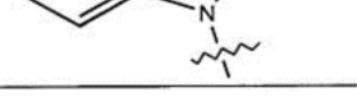
Cmpd	W	X	Z	A	Q	
2394		HO 	HO 	OMe	O	
2395		HO 	HO 	OMe	O	
[0678]	2396		HO 	HO 	OMe	O
	2397		HO 	HO 	OMe	O
	2398		HO 	HO 	OMe	O
	2399		HO 	HO 	OMe	O

Cmpd	W	X	Z	A	Q
2400		HO	HO	OMe	O
2401		HO	HO	OMe	O
[0679]		HO	HO	OMe	O
2402		HO	HO	OMe	O
2403		HO	HO	OMe	O
2404		HO	HO	OMe	O
2405		HO	HO	OMe	O

Cmpd	W	X	Z	A	Q
2406		HO 	HO 	OMe	O
2407		HO 	HO 	OMe	O
[0680]		HO 	HO 	OMe	O
2409		HO 	HO 	OMe	O
2410		HO 	HO 	OMe	O

Cmpd	W	X	Z	A	Q
2411		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
[0681]		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2413		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2414		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2415		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O

Cmpd	W	X	Z	A	Q	
2421		HO 	HO 		O	
2422		HO 	HO 	OMe	O	
[0683]	2423		HO 	HO 	OMe	O
	2424		HO 	HO 	OMe	O
	2425		HO 	HO 	OMe	O
	2426		HO 	HO 	OMe	O

Cmpd	W	X	Z	A	Q
2427		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2428		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2429		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
[0684]		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2430		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2431		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O
2432		HO-CH2-CH2-CH2-	HO-CH2-CH2-CH2-	OMe	O

Cmpd	W	X	Z	A	Q
2433		<chem>OCCCOCCCCC</chem>	<chem>OCCCOCCCCC</chem>	OMe	O
2434		<chem>OCCCOCCCCC</chem>	<chem>OCCCOCCCCC</chem>	OMe	O
[0685]		<chem>OCCCOCCCCC</chem>	<chem>OCCCOCCCCC</chem>	OMe	O
2435		<chem>OCCCOCCCCC</chem>	<chem>OCCCOCCCCC</chem>	OMe	O
2436		<chem>OCCCOCCCCC</chem>	<chem>OCCCOCCCCC</chem>	OMe	O
2437		<chem>OCCCOCCCCC</chem>	<chem>OCCCOCCCCC</chem>	OMe	O
2438		<chem>OCCCOCCCCC</chem>	<chem>OCCCOCCCCC</chem>	OMe	O

Cmpd	W	X	Z	A	Q
2439				OMe	O
2440				OMe	O
[0686]				OMe	O
2441				OMe	O
2442				OMe	O
2443				OMe	O
2444				OMe	O

Cmpd	W	X	Z	A	Q
2445		HO	HO	OMe	O
2446		HO	HO	OMe	O
[0687]		HO	HO	OMe	O
2448		HO	HO	OMe	O
2449		HO	HO	OMe	O

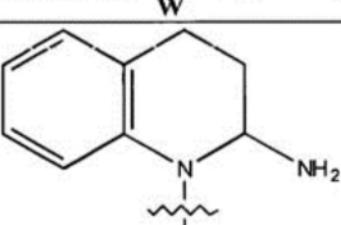
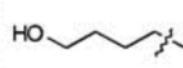
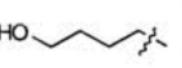
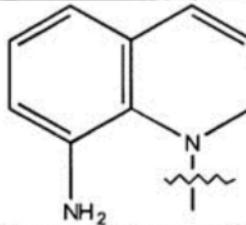
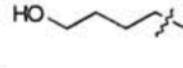
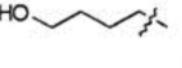
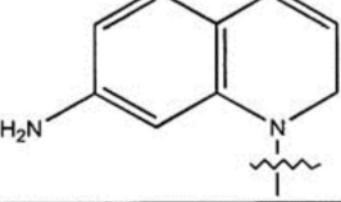
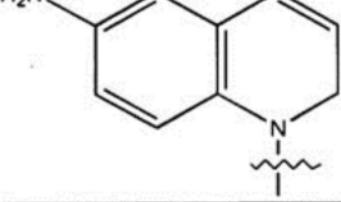
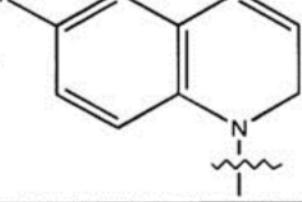
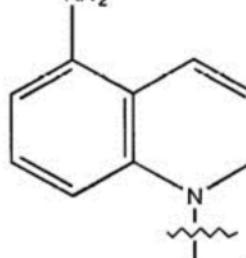
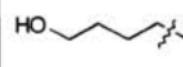
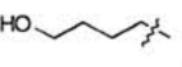
Cmpd	W	X	Z	A	Q
2450		HO	HO	OMe	O
[0688]		HO	HO	OMe	O
2451		HO	HO	OMe	O
2452		HO	HO	OMe	O
2453		HO	HO	OMe	O

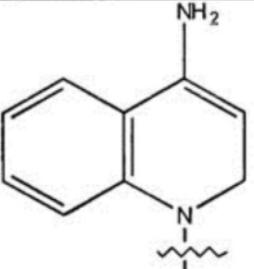
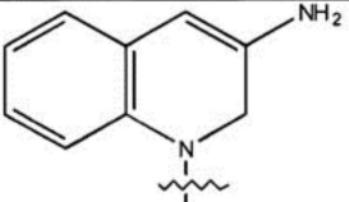
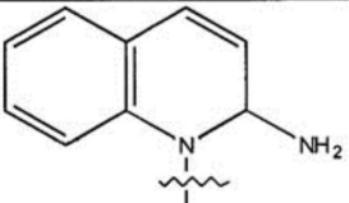
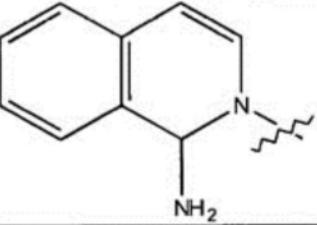
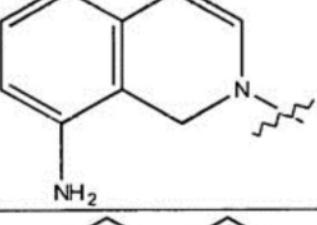
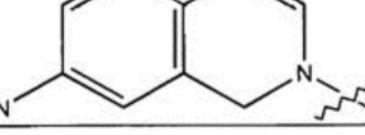
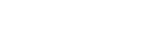
Cmpd	W	X	Z	A	Q
2454		HO	HO	OMe	O
2455		HO	HO	OMe	O
[0689]		HO	HO	OMe	O
2456		HO	HO	OMe	O
2457		HO	HO	OMe	O
2458		HO	HO	OMe	O
2459		HO	HO	OMe	O

Cmpd	W	X	Z	A	Q
2460				OMe	O
2461				OMe	O
[0690]				OMe	O
2463				OMe	O
2464				OMe	O
2465				OMe	O

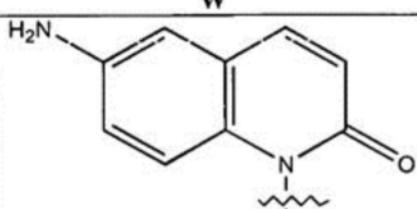
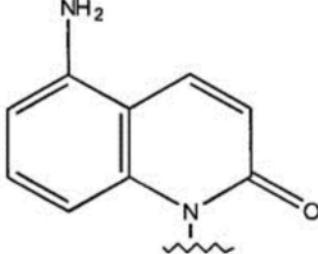
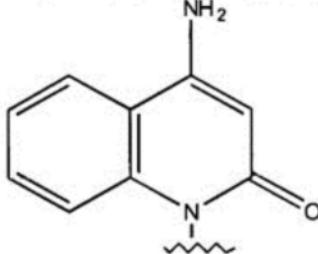
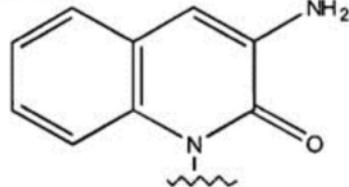
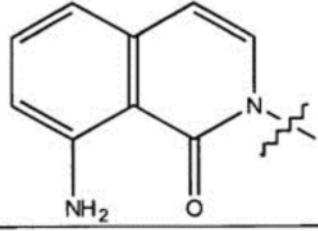
Cmpd	W	X	Z	A	Q
2466				OMe	O
2467				OMe	O
[0691]				OMe	O
2468				OMe	O
2469				OMe	O
2470				OMe	O

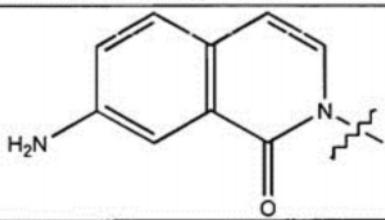
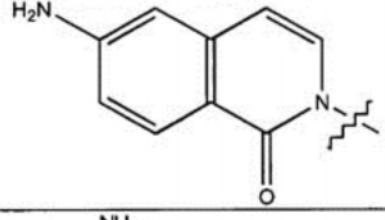
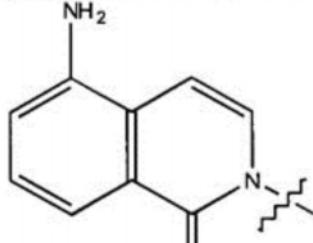
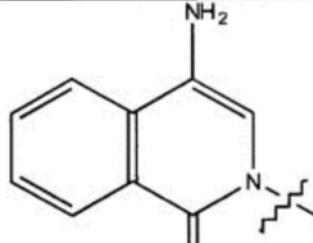
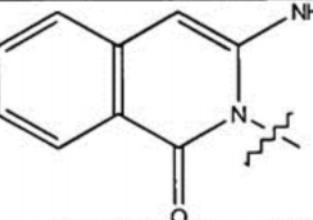
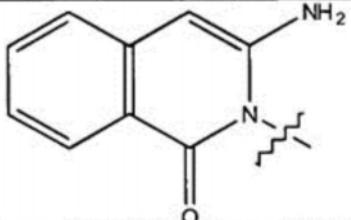
Cmpd	W	X	Z	A	Q
2471				OMe	O
2472				OMe	O
[0692]				OMe	O
2473				OMe	O
2474				OMe	O
2475				OMe	O

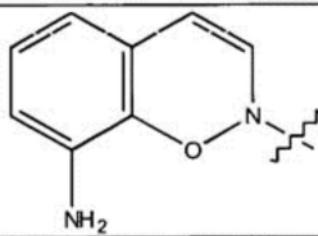
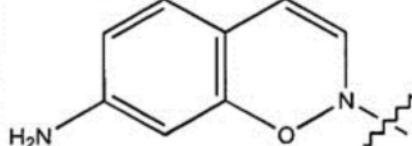
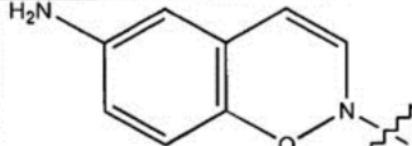
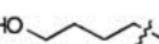
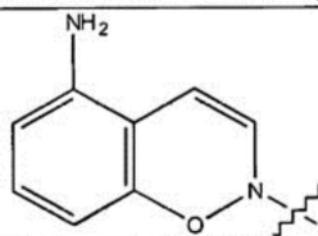
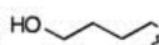
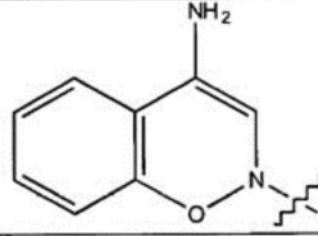
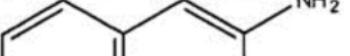
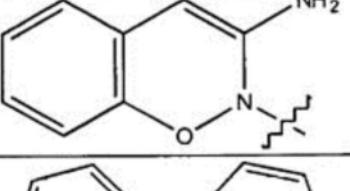
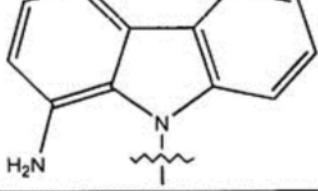
Cmpd	W	X	Z	A	Q
2476				OMe	O
2477				OMe	O
[0693]				OMe	O
2478				OMe	O
2479				OMe	O
2480				OMe	O

Cmpd	W	X	Z	A	Q
2481		HO 	HO 	OMe	O
2482		HO 	HO 	OMe	O
[0694]		HO 	HO 	OMe	O
2484		HO 	HO 	OMe	O
2485		HO 	HO 	OMe	O
2486		HO 	HO 	OMe	O

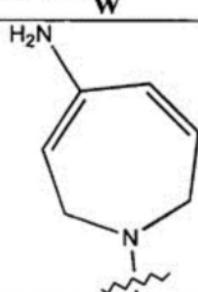
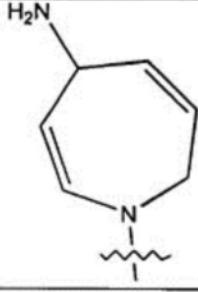
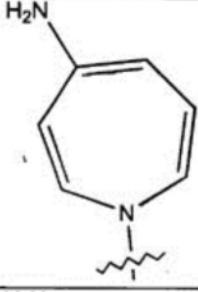
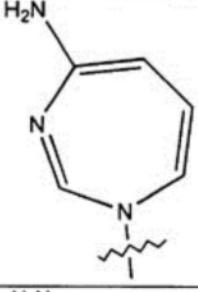
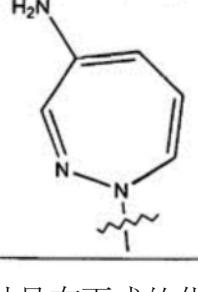
Cmpd	W	X	Z	A	Q	
2487				OMe	O	
2488				OMe	O	
[0695]	2489				OMe	O
	2490				OMe	O
	2491				OMe	O
	2492				OMe	O

Cmpd	W	X	Z	A	Q	
2493				OMe	O	
2494				OMe	O	
[0696]					OMe	O
2495						
2496				OMe	O	
2497				OMe	O	

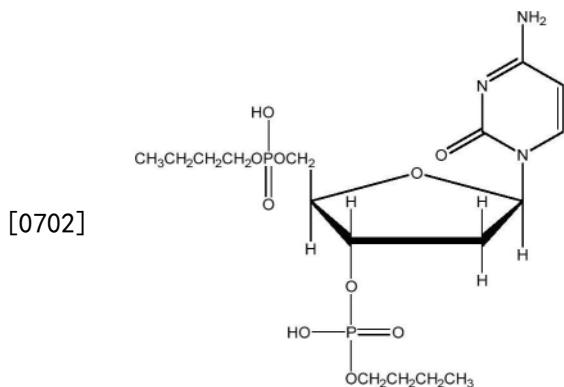
Cmpd	W	X	Z	A	Q
2498				OMe	O
2499				OMe	O
[0697]				OMe	O
2500				OMe	O
2501				OMe	O
2502				OMe	O

Cmpd	W	X	Z	A	Q
2503		HO 	HO 	OMe	O
2504		HO 	HO 	OMe	O
2505		HO 	HO 	OMe	O
[0698]		HO 	HO 	OMe	O
2506		HO 	HO 	OMe	O
2507		HO 	HO 	OMe	O
2508		HO 	HO 	OMe	O
2509		HO 	HO 	OMe	O

Cmpd	W	X	Z	A	Q
2510		HO	HO	OMe	O
2511		HO	HO	OMe	O
[0699]		HO	HO	OMe	O
2513		HO	HO	OMe	O
2514		HO	HO	OMe	O
2515		HO	HO	OMe	O

Cmpd	W	X	Z	A	Q
2516				OMe	O
2517				OMe	O
[0700]				OMe	O
2518				OMe	O
2519				OMe	O
2520				OMe	O

[0701] 本公开还提供一种具有下式的化合物：



式(III)

[0703] 或其药学上可接受的盐。

[0704] 式(III)化合物的化学名称为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钠。式(III)化合物的分子式为C₁₇H₂₉N₃Na₂O₁₀P₂。式(III)化合物的分子量为543.11Da。式(III)化合物在本文中也被称为Nu-8、化合物(III)或Cmpd 1，这些术语在本文中可互换使用。在一些实施方案中，Nu-8包含核糖、两个磷酸酯基团、两个丁基和胞嘧啶。

[0705] 参考本文阐明的具体化合物描述本公开的化合物。此外，本公开的化合物可以以任何数量的不同形式或衍生物存在，全部在本公开的范围内。替代形式或衍生物包括例如药学上可接受的盐、前药和活性代谢产物、互变异构体，和固体形式，包括但不限于不同的晶体形式、多晶型或无定形固体，包括其水合物和溶剂化物，以及其他形式。

[0706] 在本文中除非有相反的说明，本公开的化合物的说明包括该化合物的药学上可接受的盐。因此，本公开的化合物可以为药学上可接受的盐的形式，或可以被配制成药学上可接受的盐。本公开的预期的药学上可接受的盐形式包括但不限于单盐、双盐、三盐、四盐等。本公开的药学上可接受的盐在施用此类药学上可接受的盐的量和浓度时是无毒的。本公开的这种药学上可接受的盐的制剂可以通过改变本公开的化合物的物理特性来促进其药理学用途，而不阻止其发挥其生理作用。

[0707] 如本文所使用，对于盐和制剂组分如载体、赋形剂和稀释剂而言，术语“药学上可接受的”是指对患者无害的，并且与其他成分、活性成分、盐或组分相容的那些盐和组分。药学上可接受的包括“兽医学上可接受的”，因此独立地包括人类和非人类哺乳动物应用。

[0708] 如本文所使用，术语“药学上可接受的盐”是指通常用于形成碱金属盐和形成游离酸或游离碱的加成盐的盐。这些盐包括例如本领域技术人员已知的生理学上可接受的盐，其列于Handbook of Pharmaceutical Salts:Properties, Selection and Use, P.H.Stahl and C.G.Wermuth (Eds.), Wiley-VCH, New York, 2002。盐的形成可以发生在一个或多个具有不稳定质子的位置。本公开化合物的药学上可接受的盐包括酸加成盐和碱加成盐。

[0709] 在一些实施方案中，可以由无机酸或有机酸制备本公开化合物的合适的药学上可接受的酸加成盐。这些无机酸的示例包括但不限于盐酸、氢溴酸、氢碘酸、硝酸、碳酸、硫酸和磷酸。合适的有机酸包括但不限于脂肪族、脂环族、芳香族、芳基脂肪族、杂环、羧酸和磺酸类有机酸，其示例为甲酸、乙酸、丙酸、琥珀酸、乙醇酸、葡萄糖酸、马来酸、双羟萘酸(帕莫酸)、甲磺酸(methanesulfonic acid)、乙磺酸、2-羟基乙磺酸、泛酸、苯磺酸、甲苯磺酸、磺胺酸、甲磺酸(mesylic acid)、环己基氨基磺酸、硬脂酸、海藻酸、β-羟基丁酸、丙二酸、冰醋

酸(galactic acid)和半乳糖醛酸等。药学上可接受的酸式/阴离子盐还包括乙酸盐、苯磺酸盐、苯甲酸盐、碳酸氢盐、酒石酸氢盐、溴化物、乙二胺四乙酸钙、樟脑磺酸盐、碳酸盐、氯化物、柠檬酸盐、二盐酸盐、乙二胺四乙酸盐、乙二磺酸盐、十二烷基硫酸盐(estolate)、乙磺酸盐(esylate)、富马酸盐、葡萄糖酸盐、谷氨酸盐、乙醇酰阿散酸盐(glycolylarsanilate)、己基间苯二酚盐(hexylresorcinate)、氢溴酸盐、盐酸盐、羟萘甲酸盐、碘化物、羟乙磺酸盐、乳酸盐、乳糖醛酸盐(lactobionate)、苹果酸盐、马来酸盐、丙二酸盐、扁桃酸盐、甲磺酸盐、甲基硫酸盐、粘酸盐、萘甲酸盐、硝酸盐、双羟萘酸盐、泛酸盐、磷酸盐/二磷酸盐、聚半乳糖醛酸盐、水杨酸盐、硬脂酸盐、次乙酸盐、琥珀酸盐、硫酸盐、硫酸氢盐、单宁酸盐、酒石酸盐、茶氯酸盐(teoclinate)、甲苯磺酸盐和三乙基碘化物(triethiodide)盐等。

[0710] 在一些实施方案中,本公开化合物的合适的药学上可接受的碱加成盐包括但不限于由铝、钙、锂、镁、钾、钠和锌形成的金属盐,或者由N,N'-二苄基乙二胺、氯普鲁卡因、胆碱、二乙醇胺、乙二胺、N-甲基葡萄糖胺、赖氨酸、精氨酸和普鲁卡因形成的有机盐。可以通过常规手段,通过用合适的酸或碱处理本公开的化合物,从本公开的化合物制备所有这些盐。药学上可接受的碱式/阳离子盐还包括二乙醇胺盐、铵盐、乙醇胺盐、哌嗪盐和三乙醇胺盐等。在一些实施方案中,本公开的药学上可接受的盐包含一价阳离子或二价阳离子。

[0711] 在一些实施方案中,本公开的药学上可接受的盐选自铵盐、钙盐、钠盐、钾盐、镁盐和钴盐。在一些实施方案中,铵盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸铵。在一些实施方案中,钙盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钙。在一些实施方案中,钠盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钠。在一些实施方案中,钾盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钾。在一些实施方案中,镁盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸镁。在一些实施方案中,钴盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钴。

[0712] 可以通过本公开所属领域中已知的标准技术,来制备本公开的药学上可接受的盐。例如,可以将本公开化合物的游离碱形式溶解在合适的溶剂中,如含有合适的酸的水溶液或水-醇溶液,然后通过蒸发溶液来分离。在另一个示例中,可以通过使游离碱和酸在有机溶剂中反应来制备盐。如果特定的化合物为酸,则可以通过任何合适的方法来制备期望的药学上可接受的盐,所述方法包括例如用合适的无机或有机碱处理游离酸。

[0713] 除了本公开的化合物以外,本公开还包括前药(例如,药学上可接受的前药)、活性代谢衍生物(活性代谢物)及其药学上可接受的盐。

[0714] 前药为化合物或其药学上可接受的盐,当所述化合物在生理条件下代谢或通过溶剂分解作用(solvolytic)转化时,将产生期望的活性化合物。通常,前药是无活性的,或者比活性化合物的活性低,但是可以提供一种或多种有利的处理、施用和/或代谢特性。一些前药被酶促活化以产生活性化合物,或者化合物可以进行进一步的化学反应以产生活性化合物。前药可以在一个步骤中从前药形式转变为活性形式,或者可以具有一种或多种中间

形式,所述中间形式具有活性或可以是无活性的。

[0715] 如在The Practice of Medicinal Chemistry, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif, 2001) 中所描述,从概念上讲,前药可以被分为两种非排他性类别,包括生物前体前药和载体前药。通常,生物前体前药是与相应活性药物化合物相比无活性或具有低活性的化合物,其含有一个或多个保护基,并通过代谢或溶剂分解作用转化成活性形式。活性药物形式和任何释放的代谢产物均应具有可接受的低毒性。通常,活性药物化合物的形成涉及以下类型之一的代谢过程或反应:

[0716] 氧化反应: 氧化反应的示例包括但不限于反应如醇、羰基和酸官能团的氧化,脂肪族碳的羟基化,脂环族碳原子的羟基化,芳香族碳原子的氧化,碳-碳双键的氧化,含氮官能团的氧化,硅、磷、砷和硫的氧化,氧化N-脱烷基化,氧化O-和S-脱烷基化,氧化脱氨化以及其他氧化反应。

[0717] 还原反应: 还原反应的示例包括但不限于反应如羰基官能团的还原、醇官能团和碳-碳双键的还原、含氮官能团的还原及其他还原反应。

[0718] 氧化态不变的反应: 氧化态不变的反应的示例包括但不限于反应如酯和醚的水解、碳-氮单键的水解裂解、非芳香族杂环的水解裂解、多个键的水合和脱水、脱水反应引起的新原子连接、水解脱卤化、卤化氢分子的去除及其他此类反应。

[0719] 载体前药为含有转运部分的药物化合物,所述转运部分例如改善摄取和/或对作用部位的定向递送。理想地,对于这种载体前药,药物部分和转运部分间的连接为共价键,前药是无活性的或比药物化合物的活性低,并且前药和任何释放的转运部分是可接受的无毒的。对于其中的转运部分旨在增强摄取的前药,通常转运部分的释放应当是快速的。在其他情况下,期望使用产生缓慢释放的部分,例如某些聚合物或其他部分,如环糊精。这种载体前药通常对于口服施用的药物是有利的。在一些情况下,转运部分提供药物的靶向递送。例如,药物可以与抗体或抗体片段缀合。载体前药可以例如用于改善以下一种或多种性质:增加亲脂性、增加药理作用的持续时间、增加位点特异性、降低毒性和不良反应、和/或改进药物制剂(例如稳定性、水溶性、抑制不良的感官或理化性质)。例如,可以通过羟基与亲脂性羧酸的酯化或羧基与醇(例如脂肪族醇)的酯化,来提高亲脂性。Wermuth, 同上。

[0720] 代谢物(例如活性代谢物)与如上面所描述的前药(例如生物前体前药)重叠。因此,这些代谢物为药理学活性化合物,或进一步代谢为药理学活性化合物的化合物,其为由受试者体内的代谢过程产生的衍生物。其中,活性代谢物为这种药理学活性衍生物化合物。对于前药,前药化合物通常为无活性的,或比代谢产物活性低。对于活性代谢物,母体化合物既可以是活性化合物,也可以是非活性前药。例如,在一些化合物中,一个或多个烷氧基可以被代谢为羟基,同时保持药理活性,和/或羧基可以被酯化,例如葡萄糖酸化(glucuronidation)。在一些情况下,可以有不止一种代谢物,其中一种或多种中间代谢物被进一步代谢以提供活性代谢物。例如,在一些情况下,由代谢葡萄糖酸化产生的衍生物化合物可以是无活性的或低活性的,并且可以被进一步代谢以提供活性代谢物。

[0721] 可以使用本领域已知的常规技术来鉴定本公开的化合物的代谢物,并使用测试(如在Bertolini等人, 1997, J. Med. Chem., 40:2011-2016; Shan等人, 1997, J. Pharm. Sci. 86 (7):756-757; Bagshawe, 1995, Drug Dev. Res., 34:220-230; Wermuth(同上)中描述的那些)确定其活性。

[0722] 本领域技术人员理解,一些化合物可以表现出互变异构现象。在这种情况下,本文提供的化学式仅明确描述了一种可能的互变异构形式。因此,应理解,本公开的化合物旨在代表所描述化合物的任何互变异构形式,而不仅限于化合物结构式所描述的特定互变异构形式。

[0723] 在试剂为固体的情况下,本领域技术人员理解,化合物和盐可以以不同的晶体或多晶型形式存在,或者可以被配制为共晶,或者可以为无定形形式,或者可以是它们的任意组合(例如部分结晶,部分无定形或多晶型物的混合物),所有这些都旨在落入本公开和特定化学式的范围内。盐是通过酸/碱加成而形成的(即,目标化合物的游离碱或游离酸分别与相应的加成碱或加成酸形成酸/碱反应,导致离子电荷相互作用),而共晶是在中性化合物间形成的新化学物种,导致化合物和其他分子物种处于相同的晶体结构中。

[0724] 在一些情况下,本公开的化合物与酸或碱络合,包括但不限于碱加成盐,例如铵、二乙胺、乙醇胺、乙二胺、二乙醇胺、叔丁胺、哌嗪、葡甲胺;酸加成盐,例如乙酸盐、乙酰水杨酸盐、苯磺酸盐、樟脑酸盐、柠檬酸盐、甲酸盐、富马酸盐、戊二酸盐、盐酸盐、马来酸盐、甲磺酸盐、硝酸盐、草酸盐、磷酸盐、琥珀酸盐、硫酸盐、酒石酸盐、硫氰酸盐和甲苯磺酸盐;和氨基酸,例如丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酰胺、谷氨酸、甘氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯丙氨酸、脯氨酸、丝氨酸、苏氨酸、色氨酸、酪氨酸或缬氨酸。

[0725] 此外,本发明的化合物旨在涵盖水合形式或溶剂化形式,以及非水合形式或非溶剂化形式。溶剂化物的其他示例包括但不限于与合适的溶剂(如异丙醇、乙醇、甲醇、DMSO、乙酸乙酯、乙酸或乙醇胺等)组合的本公开的化合物。

[0726] 在一些实施方案中,本公开的化合物为质子化的化合物。如本文所使用,术语“质子化的化合物”是指通过向本公开化合物的质子接受位点加入质子(或带正电荷的氢离子)而被质子化的本公开的化合物。在一些实施方案中,质子接受位点包括本公开化合物的磷酸酯基团,以及本公开化合物的核糖或丁基上的任何其他质子接受位点。

[0727] 随着在本公开化合物中被质子化的质子接受位点数目的增加,当将本公开的化合物溶解于pH为7的水中时获得的pH将降低,因此可以通过在加入本公开的化合物后测量水溶液的pH,来确定本公开化合物的质子化的量。pH表示溶液中氢离子的浓度。具有高浓度氢离子的溶液具有低的pH,因此是酸性的,而具有低浓度氢离子的溶液具有高的pH,因此是碱性的。在一些实施方案中,本公开的化合物被质子化,使得当溶解于水(pH 7)中时,这种化合物形成pH小于约pH 7至约pH 1的水溶液。如本文所使用,术语“约”在与数值一起使用时应理解为包括所指定的量以及该指定量的20%、10%、5%、1%、0.5%和0.1%的变化。在一些实施方案中,本公开的化合物为质子化的化合物,当溶解于水中时具有小于约pH 6至约pH 1的pH。在一些实施方案中,本公开的化合物为质子化的化合物,当溶解于水中时具有约pH 5至约pH 1的pH。在一些实施方案中,本公开的化合物为质子化的化合物,当溶解于水中时具有约pH 4.5至约pH 1的pH。在一些实施方案中,本公开的化合物为质子化的化合物,当溶解于水中时具有约pH 4至约pH 1的pH。在一些实施方案中,本公开的化合物为质子化的化合物,当溶解于水中时具有约pH 3至约pH 1的pH。在一些实施方案中,本公开的化合物为质子化的化合物,当溶解于水中时具有约pH 2至约pH 1的pH。在一些实施方案中,本公开的化合物为质子化的化合物,当溶解于水中时具有约pH 3至约pH 5的pH。在一些实施方案中,

本公开的化合物为质子化的化合物,当溶解于水中时具有约pH 3至约pH 4的pH。

[0728] 在一些实施方案中,可以通过在强酸的存在下温育本公开的化合物来实现质子化。尽管可以通过将质子加入到化合物的反应位点上来使本公开的化合物质子化,但是本公开化合物的其他修饰也是可能的,并且旨在涵盖于如本文所使用的术语质子化的化合物中。在一些实施方案中,可以通过使纯化的、部分纯化的或粗的化合物经受低pH(例如,酸性)环境,来生成本公开化合物的质子化形式。在一些实施方案中,可以用酸使纯化的或粗的化合物质子化,所述酸包括磷酸、硝酸、盐酸和乙酸。

[0729] 本领域技术人员已知的制备本公开的质子化化合物的其他程序同样被理解为也落入本公开的范围内。在一些实施方案中,一旦本公开的化合物被质子化后,可以将这些化合物与任何不期望的组分(例如过量的酸)分离。技术人员知道许多将化合物与不期望的组分分离的方法,包括但不限于使用H⁺阳离子交换剂(例如,H⁺-SCX)。在一些实施方案中,本公开的化合物可以在质子化之后经历色谱法。在一些实施方案中,在质子化后,将本公开的化合物在聚(苯乙烯-二乙烯基苯)基树脂(例如,Hamilton的PRP-1或3,和Polymer Lab的PLRP)上洗脱。

[0730] 在一些实施方案中,本公开的质子化化合物可以直接使用。在一些实施方案中,可以例如经由沉淀、反相色谱法、渗滤或凝胶过滤进一步处理本公开的质子化化合物,以去除任何过量的酸或盐。在一些实施方案中,可以通过冻干、溶剂蒸发等浓缩本公开的质子化化合物。在一些实施方案中,当混悬于水或盐水中时,本公开的化合物通常表现出约pH 3至约pH 5的pH,这取决于质子化/酸化的水平,该水平由在酸化过程中使用多少酸来确定。在一些实施方案中,可以通过使本公开的化合物穿过带有氢离子的阳离子交换柱来使其质子化。

[0731] 在一些实施方案中,在本公开的化合物中利用两个丁基来防止或限制本公开化合物的大量核酸酶降解,包括但不限于核酸外切酶降解。在一些实施方案中,放置丁基以保护本公开化合物的核糖。可以使用分析型HPLC评估功能分子的损失,或通过其他合适的方法来确定酸降解的百分比。酸降解通常是时间的函数。在一些实施方案中,本公开的化合物也具有核酸酶抗性,这使得这些化合物能够在体内环境中维持活性(例如,pH稳定性)。可以通过本领域技术人员已知的方法(例如质谱法),来确定本公开的化合物在含有核酸酶的环境中的降解百分比。核酸酶降解通常是时间的函数。在一些实施方案中,在确定酸或核酸酶降解的程度或速率时使用参比化合物。在一些实施方案中,本公开化合物的稳定性较参比化合物的稳定性高10%、20%、30%、40%、50%、70%、90%、100%、150%、200%、300%、500%或750%。

[0732] 根据一些实施方案,本公开的化合物可以用作抗微生物剂,其具有抗任何微生物的活性。如本文所使用,术语“微生物(microbe)”、“微生物的(microbial)”和类似术语是指细菌、真菌、原生动物、病毒、酵母等。如本文所使用,术语“抗微生物剂”是指本公开的化合物,其具有杀死或抑制微生物生长,或减弱微生物感染的严重性的能力。本公开化合物有效对抗的细菌的非限制性列表包括但不限于革兰氏阳性细菌、革兰氏阴性细菌、缓慢生长细菌和耐酸细菌,以及以下属种中包括的任何物种:气球菌属(Aerococcus)、李斯特菌属(Listeria)、链霉菌属(Streptomyces)、衣原体属(Chlamydia)、乳杆菌属(Lactobacillus)、真杆菌属(Eubacterium)、伯克氏菌属(Burkholderia)、寡养单胞菌属

(*Stentrophomonas*)、无色杆菌属(*Achromobacter*)、*Arachnid*、分枝杆菌属(*Mycobacterium*)、消化链球菌属(*Peptostreptococcus*)、葡萄球菌属(*Staphylococcus*)、棒状杆菌属(*Corynebacterium*)、丹毒丝菌属(*Erysipelothrix*)、嗜皮菌属(*Dermatophilus*)、红球菌属(*Rhodococcus*)、假单胞菌属(*Pseudomonas*)、链球菌属(*Streptococcus*)、芽孢杆菌属(*Bacillus*)、消化球菌属(*Peptococcus*)、肺炎球菌属(*Pneumococcus*)、微球菌属(*Micrococcus*)、奈瑟菌属(*Neisseria*)、克雷伯菌属(*Klebsiella*)、库特氏菌属(*Kurthia*)、诺卡氏菌属(*Nocardia*)、沙雷氏菌属(*Serratia*)、罗思氏菌属(*Rothia*)、埃希氏菌属(*Escherichia*)、丙酸菌属(*Propionibacterium*)、放线菌属(*Actinomyces*)、螺杆菌属(*Helicobacter*)、肠球菌属(*Enterococcus*)、志贺氏菌属(*Shigella*)、弧菌属(*Vibrio*)、梭菌属(*Clostridium*)、沙门氏菌属(*Salmonella*)、耶尔森氏菌属(*Yersinia*)和嗜血杆菌属(*Haemophilus*)。

[0733] 本公开化合物有效对抗的真菌的非限制性列表包括但不限于毛癣菌属(*Trichophyton*)、表皮癣菌属(*Epidermophyton*)、小孢子菌属(*Microsporum*)、白色念珠菌(*Candida albicans*)和其他念珠菌属(*Candida*)物种、圆形糠秕孢子菌(*Pityrosporum orbiculare*)、须毛癣菌(*Trichophyton mentagrophytes*)、红毛癣菌(*Trichophyton rubrum*)、絮状表皮癣菌(*Epidermophyton floccosum*)、和断发毛癣菌(*Trichophyton tonsurans*)。本公开化合物有效对抗的病毒的非限制性列表包括但不限于人免疫缺陷病毒(HIV)、单纯疱疹病毒(HSV)、巨细胞病毒(CMV)、乙型肝炎病毒(HBV)、丙型肝炎病毒(HCV)和流感病毒。

[0734] 在一些实施方案中，本公开的化合物可用于治疗和非治疗医学应用。在包括非治疗医学应用的一些实施方案中，本公开化合物的抗微生物作用允许使用本公开的化合物用于灭菌(例如，患者皮肤的灭菌，或表面或物体(例如，外科器械)的灭菌)或消毒(例如，表面、仪器的清洁，以使表面上没有不期望浓度的致病微生物)。在一些实施方案中，本公开的化合物有效地对抗实验室培养物、消耗品(例如，食品或饮料制剂)、医疗装置、医院设备或工业过程的微生物污染。本文描述了本公开化合物的治疗应用。

[0735] 本公开还提供药物组合物。如本文所使用，术语“药物组合物”是指含有本公开化合物或其药学上可接受的盐的药物制剂，并且其适合于出于治疗目的而施用于患者。如本文所使用，术语“患者”是指用本公开的化合物治疗的活生物体，包括但不限于任何哺乳动物，例如人、其他灵长类动物(例如猴子、黑猩猩等)、伴侣动物(例如狗、猫、马等)、农场动物(例如山羊、绵羊、猪、牛等)、实验动物(例如小鼠、大鼠等)以及野生和动物园动物(例如狼、熊、鹿等)。

[0736] 在一些实施方案中，组合物可以包含至少一种药学上可接受的组分，以提供本公开化合物的改进制剂，包括但不限于一种或多种药学上可接受的载体、赋形剂或稀释剂。载体、赋形剂或稀释剂可以采取多种形式，这取决于施用所期望的制剂形式。

[0737] 如本文所使用，术语“载体”包括但不限于碳酸钙、磷酸钙、各种糖如乳糖、葡萄糖或蔗糖、淀粉类、纤维素衍生物、明胶、脂质、脂质体、纳米颗粒、作为溶剂或用于混悬液的生理上可接受的液体，包括例如注射用水(WFI)的无菌溶液、盐水溶液、葡萄糖溶液、汉克溶液(Hank's solution)、林格氏溶液、植物油、矿物油、动物油、聚乙二醇、液体石蜡等。

[0738] 如本文所使用，术语“赋形剂”通常包括但不限于填充剂、粘合剂、崩解剂、助流剂、

润滑剂、络合剂、增溶剂、稳定剂、防腐剂和表面活性剂,可以选择它们以促进通过特定途径施用化合物。合适的赋形剂还可以包括例如胶体二氧化硅、硅胶、滑石粉、硅酸镁、硅酸钙、硅铝酸钠、三硅酸镁、粉状纤维素、大晶体纤维素、羧甲基纤维素、交联羧甲基纤维素钠、苯甲酸钠、碳酸钙、碳酸镁、硬脂酸、硬脂酸铝、硬脂酸钙、硬脂酸镁、硬脂酸锌、硬脂富马酸钠、syloid、stearowet C、氧化镁、淀粉、羟基乙酸淀粉钠、单硬脂酸甘油酯、二山嵛酸甘油酯、棕榈硬脂酸甘油酯、氢化植物油、氢化棉籽油、蓖麻籽油、矿物油、聚乙二醇(例如PEG4000-8000)、聚氧乙二醇、泊洛沙姆、聚维酮、交聚维酮、交联羧甲基纤维素钠、海藻酸、酪蛋白、甲基丙烯酸二乙烯基苯共聚物、多库酯钠(sodium docusate)、环糊精(例如2-羟丙基- δ -环糊精)、聚山梨酸酯(例如聚山梨酯80)、西曲溴铵(cetrimide)、TPGS(d- α -生育酚聚乙二醇1000琥珀酸酯)、十二烷基硫酸镁、十二烷基硫酸钠、聚乙二醇醚、聚乙二醇的二脂肪酸酯、或聚氧化烯脱水山梨糖醇脂肪酸酯(例如,聚氧乙烯脱水山梨糖醇酯Tween®)、聚氧乙烯脱水山梨糖醇脂肪酸酯、脱水山梨糖醇脂肪酸酯(例如来自脂肪酸如油酸、硬脂酸或棕榈酸的脱水山梨糖醇脂肪酸酯)、甘露醇、木糖醇、山梨糖醇、麦芽糖、乳糖、乳糖一水合物或喷雾干燥的乳糖、蔗糖、果糖、磷酸钙、二碱式磷酸钙(dibasic calcium phosphate)、三碱式磷酸钙(tribasic calcium phosphate)、硫酸钙、葡萄糖结合剂(dextrates)、右旋糖酐、糊精、右旋糖、乙酸纤维素、麦芽糖糊精、二甲基硅油、聚葡萄糖、壳聚糖、明胶、HPMC(羟丙基甲基纤维素)、HPC(羟丙基纤维素)、羟乙基纤维素等。

[0739] 如技术人员所理解的,根据本公开可以使用本领域中已知的任何稀释剂。在本公开的一些实施方案中,稀释剂为水溶性的。在本公开的一些实施方案中,稀释剂为水不溶性的。如本文所使用,术语“稀释剂”包括但不限于水、盐水、磷酸盐缓冲盐水(PBS)、右旋糖、甘油、乙醇、乙酸钠或乙酸铵缓冲溶液等,及其组合。

[0740] 在一些实施方案中,本公开的药物组合物包含至少一种另外的活性成分。如本文所使用,术语“活性成分”是指治疗活性化合物及其任何前药,以及化合物和前药的药学上可接受的盐、水合物和溶剂化物。可以将其他活性成分与本公开的化合物组合,并且可以单独施用或在相同的药物组合物中施用。基于用本公开化合物的治疗,本领域技术人员可以确定要给予的其他活性成分的量。

[0741] 在一些实施方案中,组合物为人药物组合物。如本文所使用,术语“人药物组合物”是指旨在施用于人的药物组合物。

[0742] 本公开的药物组合物适合通过任何合适的手段施用于患者,包括但不限于用于施用常规抗微生物剂的那些手段。本公开的药物组合物可以使用普通技术人员会考虑的任何合适途径来施用,包括但不限于口服、静脉内(“IV”)注射或输注、膀胱内、皮下(“SC”)、肌肉内(“IM”)、腹膜内、皮内、眼内、吸入(和肺内)、鼻内、经皮、表皮下(epicutaneously)、皮下、局部、粘膜、鼻、眼、印于皮肤(impression into skin)、阴道内、子宫内、宫颈管内和直肠。这样的剂型应使得本公开的化合物能够到达靶细胞。其他因素在本领域中是熟知的,并且包括考虑因素如毒性和阻碍化合物或组合物发挥其作用的剂型。技术和制剂通常可见于Remington:The Science and Practice of Pharmacy,第21版,Lippincott,Williams and Wilkins,Philadelphia,Pa.,2005。

[0743] 在一些实施方案中,本公开的药物组合物适合于局部施用。如本文所使用,术语“局部施用”是指将本公开的化合物施用于患者的皮肤表面,以使本公开的化合物穿过皮肤

层。术语局部施用还涵盖经皮施用和经粘膜施用。如本文所使用，术语“经皮”是指本公开的化合物穿过患者的至少一个皮肤层。如本文所使用，“经粘膜”是指本公开的化合物穿过患者的粘膜。除非另有说明或暗示，术语“局部施用”、“经皮施用”和“经粘膜施用”在本文中可互换使用。

[0744] 用于在患者体内将生物活性化合物递送至微生物的多种局部递送系统是本领域熟知的。通过选择本领域合适的载体，这种系统包括但不限于洗剂、霜剂、凝胶、油剂、软膏、溶液、混悬剂、乳剂等。在一些实施方案中，药物组合物以包含多元醇的凝胶的形式施用。

[0745] 合适的载体包括但不限于植物油或矿物油、白矿脂(例如白色软石蜡)、支链脂肪或油、动物脂肪和高分子量醇(例如大于C12)。在一些实施方案中，选择载体，以使得本公开的化合物是可溶的。在一些实施方案中，如果需要，还可以包含乳化剂、稳定剂、保湿剂和抗氧化剂以及赋予颜色或香味的试剂。在一些实施方案中，有机溶剂或共溶剂(如乙醇或丙醇)可以用在本公开的药物组合物中。在一些实施方案中，溶剂的蒸发在处理过的表面上留下残留物，以抑制再感染。

[0746] 在一些实施方案中，使用适合于被渗透的屏障的渗透剂。这种渗透剂通常是本领域公知的，并且包括但不限于胆汁盐和夫西地酸衍生物。在一些实施方案中，可以使用清洁剂以促进渗透。在一些实施方案中，由矿物油、自乳化蜂蜡和水的混合物配制用于局部施用的霜剂，其中将溶解于少量溶剂(例如油)中的本公开化合物混合在混合物中。所使用的特定局部递送系统取决于微生物的位置。

[0747] 在一些实施方案中，还可以将其他材料加入到本公开的局部药物组合物中，其具有附加的保湿作用，并改善药物组合物的稠度。这种化合物的示例包括但不限于鲸蜡基酯蜡、硬脂醇、鲸蜡醇、甘油、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、quaternium-15、保湿剂、挥发性甲基硅氧烷流体和聚二有机硅氧烷-聚氧化烯。参见例如美国专利号5,153,230和4,421,769。在一些实施方案中，如果期望药物组合物具有附加的清洁作用，则可以加入化学物质，如十二烷基硫酸钠或羧酸的金属盐。

[0748] 在一些实施方案中，许多非挥发性润肤剂可用于本公开的药物组合物中。这种非挥发性润肤剂的非限制性示例列于McCutcheon's, Vol. 2 Functional Materials, North American Edition, (1992), pp. 137-168, 和CTFA Cosmetic Ingredient Handbook, 第二版 (1992) (其在第572-575页列出皮肤调理剂(Skin-Conditioning Agents)，且在第580页列出皮肤防护剂(Skin Protectants))中。在一些实施方案中，非挥发性润肤剂包括硅酮、烃、酯及其混合物。在一些实施方案中，酯包括单官能和双官能脂肪酸的酯，所述脂肪酸被醇和多元醇(即，具有两个或多个羟基的醇)酯化。在一些实施方案中，将长链脂肪酸的长链酯(即，用C10-40脂肪醇酯化的C10-40脂肪酸)用于本公开的药物组合物中。可用于本公开药物组合物中的酯的非限制性示例包括但不限于选自己二酸二异丙酯、肉豆蔻酸异丙酯、棕榈酸异丙酯、丙酸肉豆蔻酯、二硬脂酸乙二醇酯、棕榈酸2-乙基己酯、新戊酸异癸酯、C12-15醇苯甲酸酯、二-2-乙基己基马来酸酯、二十六烷基棕榈酸酯(cetyl palmitate)、肉豆蔻酸肉豆蔻酯、硬脂醇硬脂酸酯、十六烷基硬脂酸酯、山嵛醇山嵛酸酯(behenyl behenrate)及其混合物的那些。

[0749] 可用于本公开药物组合物的硅酮润肤剂的示例包括但不限于聚烷基硅氧烷、环聚烷基硅氧烷和聚烷基芳基硅氧烷。合适的市售可得聚烷基硅氧烷包括聚二甲基硅氧烷，也

被称为二甲硅油(dimethicone)，其非限制性示例包括由General Electric Company销售的VicasilTM系列和由Dow Corning Corporation销售的Dow CorningTM 200系列。市售可得的聚烷基硅氧烷包括环甲基硅氧烷(Dow CorningTM 244液体、Dow CorningTM 344液体、Dow CorningTM 245液体和Dow CorningTM 345)等。合适的市售可得的三甲基甲硅烷氧基硅酸盐作为与二甲硅油的混合物，以Dow CorningTM 593液体出售。聚二甲基硅氧醇(dimethiconol)也可用于本公开的药物组合物中，其为羟基封端的二甲基硅氧烷。合适的市售可得聚二甲基硅氧醇通常作为与二甲硅油或环甲基硅油(cyclomethicone)的混合物(例如Dow CorningTM 1401、1402和1403液体)出售。合适的市售可得聚烷基芳基硅氧烷包括SF1075甲基苯基液体(由General Electric Company销售)和556化妆品级苯基三甲硅油液体(由Dow Corning Corporation销售)。

[0750] 适合于在本公开的药物组合物中使用的烃包括但不限于具有约10至约30个碳原子的直链和支链烃。在一些实施方案中，直链和支链烃具有约12至约24个碳原子。在一些实施方案中，直链和支链烃具有约16至约22个碳原子。这种烃材料的非限制性示例包括十二烷、角鲨烷、胆固醇、5氢化聚异丁烯、二十二烷(即，C22烃)、十六烷和异十六烷(由Presperse, South Plainsfield, N.J.以PermethylTM 101A销售的市售可得的烃)等。

[0751] 在一些实施方案中，本公开的局部药物组合物包含丙二醇。在一些实施方案中，丙二醇用作表面活性剂，并帮助本公开化合物的渗透、接触和吸收。在一些实施方案中，丙二醇用作防腐剂。在一些实施方案中，本公开的药物组合物包含非离子表面活性剂如，例如聚山梨酯。通过进一步降低表面张力，这种表面活性剂提供了本公开的药物组合物与粘膜(如阴道粘膜)的更好的表面接触。

[0752] 还可以任选地将本公开的局部药物组合物与亲脂相如，例如乳剂和脂质体分散体一起配制。在一些实施方案中，脂质体制剂可以延长本公开化合物的循环时间，增加本公开化合物的渗透性，并改善本公开的化合物作为抗微生物剂的整体功效。在一些实施方案中，本公开的化合物可以与脂质、阳离子脂质或阴离子脂质组合。在一些实施方案中，所得的乳剂或脂质体混悬剂与本公开化合物的pH稳定性质一起可以有效地提高本公开药物组合物的体内活性半衰期。适合于与本公开的药物组合物一起使用的阴离子脂质的示例包括但不限于心磷脂，二肉豆蔻酰基、二棕榈酰基、二油酰基磷脂酰胆碱，磷脂酰甘油、棕榈酰油酰磷脂酰胆碱、磷脂酰甘油、磷脂酸、溶血磷脂酸、磷脂酰丝氨酸、磷脂酰肌醇、和阴离子形式的胆固醇。

[0753] 在一些实施方案中，将本公开的化合物掺入脂质体中。在一些实施方案中，在这些脂质体中使用中性脂质、胆固醇、和/或聚乙二醇(PEG)。在一些实施方案中，脂质体组合物由部分氢化的大豆磷脂酰胆碱(PHSC)、胆固醇、甲氧基封端的PEG(mPEG)、和/或二硬脂酰磷脂酰乙醇胺(DSPE)组成。可以根据本领域已知的任何合适的方法来制备脂质体。

[0754] 在一些实施方案中，通过鼻内喷雾或栓剂(直肠或阴道)进行局部施用。通过将本公开的化合物与脂质载体(如可可油、可可脂、甘油、明胶、聚乙二醇等)混合来制备栓剂。在一些实施方案中，局部施用包含用本公开的化合物和任选地本领域已知的一种或多种载体、赋形剂或稀释剂浸渍的经皮贴剂或敷料，如绷带。在一些实施方案中，这种敷料包括但不限于半透膜、泡沫、亲水胶体和藻酸钙拭子。在一些实施方案中，在整个剂量方案中，剂量施用将是连续的而不是间歇的。

[0755] 在一些实施方案中,本公开的药物组合物适合于口服施用。如本文所使用,术语“口服施用”是指将本公开的化合物施用至患者的口腔以摄入胃肠道。在一些实施方案中,本公开的药物组合物可以被配制成常规的口服剂型,包括但不限于胶囊、片剂、粉末剂和液体制剂如混悬剂、溶液、酏剂、糖浆、浓缩滴剂等。在一些实施方案中,可以将本公开的化合物与固体赋形剂组合,任选地研磨所得的混合物,以及如果需要,在加入合适的助剂后任选地处理颗粒的混合物,以获得例如片剂、包衣片剂、硬胶囊、软胶囊、溶液(例如水溶液、酒精或油性溶液)等。在一些实施方案中,适合于在本公开的口服药物组合物中使用的赋形剂包括但不限于填充剂如糖,包括乳糖、葡萄糖、蔗糖、甘露醇或山梨糖醇;纤维素制剂,例如玉米淀粉、小麦淀粉、大米淀粉、马铃薯淀粉、明胶、黄蓍胶、甲基纤维素、羟丙基甲基纤维素、羧甲基纤维素(CMC)钠和/或聚乙烯吡咯烷酮(PVP或聚维酮);和油性赋形剂,包括植物油和动物油,如向日葵油、橄榄油或鱼肝油。在一些实施方案中,本公开的口服药物组合物还可以含有崩解剂如,例如交联聚乙烯吡咯烷酮、琼脂或海藻酸或其盐,如海藻酸钠;润滑剂,如滑石粉或硬脂酸镁;增塑剂,如甘油或山梨糖醇;甜味剂,如蔗糖、果糖、乳糖或阿斯巴甜;天然或人工调味剂如,例如薄荷、冬青油或樱桃调味剂;或染料或颜料,其可以用于确定或表征不同的剂量或组合。在一些实施方案中,本公开的口服药物组合物还可以含有具有合适的包衣的糖衣丸芯。在一些实施方案中,可以使用浓缩的糖溶液,其可以任选地含有例如阿拉伯树胶、滑石粉、聚乙烯吡咯烷酮、卡波姆凝胶、聚乙二醇、二氧化钛、漆(lacquer)溶液和合适的有机溶剂或溶剂混合物。

[0756] 在一些实施方案中,可以口服使用的本公开的药物组合物包括但不限于由明胶制成的推入配合(push-fit)胶囊(“gelscaps”),以及由明胶和增塑剂(如甘油或山梨醇)制成的密封软胶囊。在一些实施方案中,推入配合胶囊可以含有本公开的化合物,所述化合物与填充剂如乳糖、粘合剂如淀粉、和/或润滑剂如滑石粉或硬脂酸镁以及任选的稳定剂混合。在包括软胶囊的一些实施方案中,可以将活性化合物溶解或混悬在合适的液体中,如脂肪油、液体石蜡、液体聚乙二醇等。

[0757] 在一些实施方案中,本公开的药物组合物适合于吸入施用。如本文所使用,术语“吸入施用”是指在吸入期间通过患者的鼻子或嘴递送本公开的化合物,并使化合物穿过患者的肺壁。在一些实施方案中,适合吸入施用的本公开的药物组合物可以被配制成干粉末或合适的溶液、混悬剂或气雾剂。在一些实施方案中,可以将粉末和溶液与本领域已知的合适的添加剂一起配制。在一些实施方案中,粉末可以包括合适的粉末基质,如乳糖或淀粉。在一些实施方案中,溶液可以包含丙二醇、无菌水、乙醇、氯化钠、和其他添加剂如,例如酸、碱和缓冲盐。在一些实施方案中,可以经由喷雾器(spray)、泵、雾化器、雾化器(nebulizer)等通过吸入来施用这种溶液或混悬剂。在一些实施方案中,适合于吸入施用的本公开的药物组合物还可以与其他吸入治疗剂组合使用,所述其他吸入治疗剂包括但不限于皮质类固醇如,例如丙酸氟替卡松、倍氯米松二丙酸酯、曲安奈德、布地奈德和糠酸莫米他松;β激动剂如,例如沙丁胺醇、沙美特罗和福莫特罗;抗胆碱能剂,例如异丙托溴铵或噻托溴铵;血管扩张剂如,例如treprostinal和伊洛前列素;酶如,例如DNA酶;治疗性蛋白质;免疫球蛋白抗体;寡核苷酸如,例如单链或双链DNA或RNA、siRNA;抗生素如,例如妥布霉素;毒蕈碱受体拮抗剂;白三烯拮抗剂;细胞因子拮抗剂;蛋白酶抑制剂;色甘酸钠(cromolyn sodium);nedocri1 sodium;和色甘酸钠(sodium cromoglycate)。

[0758] 在一些实施方案中,本公开的药物组合物适合于膀胱内施用。如本文所使用,术语“膀胱内施用”是指将本公开的化合物直接递送至患者的膀胱中。在一些实施方案中,经由导管施用药物组合物。在一些实施方案中,导管为尿道导管。

[0759] 在一些实施方案中,本公开的药物组合物适合于肠胃外施用。如本文所使用,术语“肠胃外施用”是指本公开的化合物被注射或输入患者中,并且包括但不限于静脉内、肌内、动脉内、鞘内、心室内、囊内、眶内、心脏内、真皮内、腹膜内、经气管、皮下、表皮下(subcuticular)、关节内、囊下、蛛网膜下、脊柱内、脑脊髓内和胸骨内注射和输注。在一些实施方案中,适合于肠胃外施用的本公开的药物组合物可以在无菌液体溶液中配制,所述无菌液体溶液包括但不限于生理上相容的缓冲液或溶液如,例如盐水溶液、汉克溶液或林格氏溶液。在一些实施方案中,可以将适合于肠胃外施用的本公开的药物组合物制备成非水性溶液(例如甘油、丙二醇、乙醇、液体聚乙二醇、三醋精、植物油等)中的分散体。在一些实施方案中,溶液还可以含有防腐剂如,例如对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、氯丁醇、苯酚、山梨酸、硫柳汞等。此外,适合于肠胃外施用的本公开的药物组合物可以被配制为固体形式,包括例如冻干形式,并在使用前重新溶解或混悬。在一些实施方案中,经由针头施用药物组合物。

[0760] 在一些实施方案中,本公开提供用本公开的化合物预处理导管的方法和组合物,例如,以防止在将导管插入患者中后的感染。在一些实施方案中,本公开的方法包括在将导管插入患者中之前用本公开的化合物涂布导管。在一些实施方案中,本公开提供一种组合物,其包含用本公开的化合物涂布的导管。在一些实施方案中,这种方法和组合物可以在患者中用作感染的预防性治疗。

[0761] 本公开还提供治疗方法。如本文所使用,术语“治疗(treating)”、“治疗(treatment)”、“疗法(therapy)”和类似术语是指以有效量施用本公开的化合物或药物组合物,以预防、减轻或缓解疾病或病症的一种或多种症状(即,适应症)和/或延长被治疗患者的生存期。在一些实施方案中,“治疗(treating)”、“治疗(treatment)”、“疗法(therapy)”和类似术语还包括但不限于减少或消除患者的感染。

[0762] 在实施本公开的方法时,将有效量的本公开的化合物施用于需要其的患者。如本文所使用,术语“有效量”在施用的情况下是指本公开的化合物或药物组合物的量,当施用至患者时,其足以预防、减轻或缓解疾病或病症(即,适应症)的一种或多种症状和/或延长被治疗患者的生存期。这种量在被治疗的患者中应当不引起不良事件或只引起很少的不良事件。类似地,这种量在被治疗的患者中应当不引起毒性作用或只引起很少的毒性作用。本领域技术人员将理解,本公开的化合物或药物组合物的量根据许多因素变化,包括但不限于本公开的化合物的活性(体外活性,例如本公开的化合物相对于靶标,或动物疗效模型中的体内活性)、动物模型中的药代动力学结果(例如,生物半衰期或生物利用度)、被治疗患者的类型、患者的年龄、大小、体重和一般身体状况、与患者有关的疾病、以及在治疗中采用的给药方案。

[0763] 在本公开的一些实施方案中,递送至有需要的患者的本公开化合物的有效量可以被定量为每千克患者体重微克本公开化合物。在一些实施方案中,施用至患者的本公开化合物的量为每千克(kg)患者体重约0.1至约1000毫克(mg)本公开化合物。在一些实施方案中,施用至患者的本公开化合物的量为每千克患者体重约0.1至约500mg本公开化合物。在

一些实施方案中,施用至患者的本公开化合物的量为每千克患者体重约0.1至约300mg本公开化合物。在一些实施方案中,施用至患者的本公开化合物的量为每千克患者体重约0.1至约200mg本公开化合物。在一些实施方案中,施用至患者的本公开化合物的量为每千克患者体重约0.1至约100mg本公开化合物。如本领域普通技术人员所理解,可以使用多剂量。

[0764] 在本公开的一些实施方案中,以多剂量方案施用本公开的化合物。如本文所使用,术语“多剂量方案”是指超过一天的治疗时间段。在本公开的一些实施方案中,多剂量方案为长达约2天的时间段。在本公开的一些实施方案中,多剂量方案为长达约3天的时间段。在本公开的一些实施方案中,多剂量方案为长达约4天的时间段。在本公开的一些实施方案中,多剂量方案为长达约5天的时间段。

[0765] 在本公开的一些实施方案中,多剂量方案为长达约6天的时间段。在本公开的一些实施方案中,多剂量方案为长达约7天的时间段。在本公开的一些实施方案中,多剂量方案为长达约14天的时间段。在本公开的一些实施方案中,多剂量方案为长达约一个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约两个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约三个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约四个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约五个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约六个月的时间段。在本文中可以使用其他时间段。

[0766] 在本公开的一些实施方案中,将本公开的化合物作为长期治疗方案的一部分施用。如本文所使用,术语“长期治疗方案”是指在患者的一生中在长期的一段时间内用本公开的化合物治疗。在一些实施方案中,长期治疗为终生治疗。

[0767] 在本公开的一些实施方案中,以单剂量施用本公开的化合物。在本公开的一些实施方案中,以单一单位剂量(single unit dose)施用本公开的化合物。如本文所使用,术语“单位剂量”为预定量的本公开的化合物。本公开的化合物的量通常等于施用至患者的本公开化合物的剂量,或这种剂量的方便分数如,例如这种剂量的一半或三分之一。根据本公开的方法,术语“单一剂量”和“单一单位剂量”包括实施方案,其中可以将组合物作为单次应用施用和作为多次应用施用。

[0768] 在一些实施方案中,还可以将本公开的化合物与一种或多种另外的活性成分组合用于治疗相同的疾病或病症。在一些实施方案中,这种组合使用包括在不同时间施用本公开的化合物和一种或多种另外的活性成分,或者共同施用本公开的化合物和一种或多种另外的活性成分。在一些实施方案中,可以通过本领域普通技术人员熟知的方法改变组合使用的本公开的化合物或一种或多种另外的活性成分的剂量,例如,相对于单独使用的本公开的化合物或一种或多种其他活性成分降低给药量。在一些实施方案中,共同施用包括在同一剂型中同时施用本公开的化合物和另外的活性成分,在分开的剂型中同时施用本公开的化合物和另外的活性成分,以及分开放施用本公开的化合物和另外的活性成分。

[0769] 应理解,组合使用包括使用一种或多种另外的活性成分或其他医药学程序,其中一种或多种另外的活性成分或其他医药学程序可以在不同的时间(例如,在短时间内,如在小时(例如1、2、3、4-24小时等)内)施用,或在比本公开的化合物或药物组合物更长的时间(例如1-2天、2-4天、4-7天、1-4周等)内施用,或与本公开的化合物或药物组合物同时施用。组合使用还包括使用一种或多种另外的活性成分或其他医药学程序(其仅施用一次或不频

繁施用,如手术)以及本公开的化合物或药物组合物,所述本公开的化合物或药物组合物在施用一种或多种另外的活性成分或完成其他医药学程序之前或之后在短时间或更长时间内施用。

[0770] 在一些实施方案中,本公开提供本公开的化合物或药物组合物及一种或多种另外的活性成分的递送,所述另外的活性成分通过不同的施用途径或通过相同的施用途径来递送。在一些实施方案中,用于任何施用途径的组合使用包括在任何药物组合物中递送本公开的化合物或药物组合物及通过相同的施用途径一起递送的一种或多种另外的活性成分,所述任何药物组合物包括药物组合物,其中两种化合物在化学上连接,使得这些化合物在施用时保持其治疗活性。在一些实施方案中,可以将一种或多种另外的活性成分与本公开的化合物或药物组合物共同施用。在一些实施方案中,通过共同施用的组合使用包括施用化学结合的化合物的共同制剂(*co-formulation*)或制剂,或者在分开的制剂中在彼此的短时间(例如在1小时、2小时、3小时、长达24小时等)内施用两种或更多种化合物,其通过相同或不同的途径施用。在一些实施方案中,分开的制剂的共同施用包括通过经由一种装置(例如相同的吸入装置、相同的注射器等)的递送的共同施用,或者在彼此的短时间内由分开的装置的施用。在一些实施方案中,通过同一途径递送的本公开的化合物或药物组合物与一种或多种另外的活性成分的共同制剂包括共同制备材料以使得它们可以通过一种装置施用,包括组合在一种制剂中的分开的化合物,或经修饰的化合物以使得化合物在化学上连接,但仍保持其生物学活性。在一些实施方案中,这种在化学上连接的化合物可以具有在体内基本上保持的连接,或者连接可以在体内断裂,从而将两种活性组分分开。

[0771] 本公开还提供一种在有需要的患者中治疗感染的方法。在一些实施方案中,方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用,术语“感染”是指患者身体的任何微生物感染。感染包括微生物入侵患者的身体,并随后在患者的身体内繁殖。

[0772] 本公开还提供一种在有需要的患者中治疗下肢(lower extremity)溃疡的感染的方法。在一些实施方案中,方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用,术语“感染”是指患者身体的任何微生物感染。感染包括微生物入侵患者的身体,并随后在患者的身体内繁殖。如本文所使用,术语“下肢”是指患者身体的下肢(lower limb),包括但不限于臀部、大腿、腿部、脚踝和足部。如本文所使用,术语“溃疡”是指在患者下肢的任何地方发现的开放性伤口。

[0773] 在一些实施方案中,本公开提供一种在有需要的患者中治疗糖尿病足溃疡的感染的方法。在一些实施方案中,方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。在一些实施方案中,患者患有I型糖尿病或II型糖尿病。如本文所使用,术语“糖尿病足溃疡”是指位于患者足部任何地方的开放性伤口。在一些实施方案中,伤口位于患者足部的脚后跟、中足和/或前足。如本文所使用,术语“治疗”在糖尿病足溃疡的情况下还包括但不限于减少或消除患者的感染,在一些实施方案中,这导致限制足溃疡在尺寸、面积和/或深度上的进展;减少足溃疡的尺寸、面积和/或深度;提高治愈率和/或减少治愈时间;使足溃疡愈合(约100%上皮形成,无引流);和/或降低截肢发生率或减缓截肢的时间。

[0774] 在一些实施方案中,患者为人。在一些实施方案中,施用为局部施用。在一些实施方案中,使用化合物或其药学上可接受的盐在洗剂、糊剂、凝胶、霜剂、软膏、油剂或其他粘

性组合物中进行施用。在一些实施方案中，向患者施用至少一种另外的活性成分。在一些实施方案中，施用作为多剂量方案进行。在一些实施方案中，多剂量方案为长达约一个月的时间段。在本公开的一些实施方案中，多剂量方案为长达约两个月的时间段。在本公开的一些实施方案中，多剂量方案为长达约三个月的时间段。在本公开的一些实施方案中，多剂量方案为长达约四个月的时间段。在本文中可以使用其他时间段。

[0775] 在一些实施方案中，每天一次或多次进行施用。在一些实施方案中，每天一次进行施用。在一些实施方案中，每天两次进行施用。在一些实施方案中，每天三次进行施用。在一些实施方案中，每天四次进行施用。

[0776] 本公开还提供一种在有需要的患者中治疗泌尿道感染的方法。在一些实施方案中，方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用，术语“泌尿道”是指产生、储存和排出尿的患者身体器官，其包括但不限于肾脏、输尿管、膀胱和尿道。如本文所使用，术语“泌尿道感染”是指患者的泌尿道的感染，其包括但不限于简单泌尿道感染和复杂泌尿道感染。如本文所使用，术语“简单泌尿道感染”是指微生物感染患者的结构和功能正常的泌尿道。如本文所使用，术语“复杂泌尿道感染”是指微生物感染患者的结构和功能异常的泌尿道。在一些实施方案中，复杂泌尿道感染为导管相关性泌尿道感染。如本文所使用，术语“导管相关性泌尿道感染”是指在具有留置导尿管的患者中发生的复杂泌尿道感染。

[0777] 在一些实施方案中，患者为人。在一些实施方案中，施用为膀胱内施用。在一些实施方案中，使用本公开的化合物或其药学上可接受的盐在液体溶液或混悬剂中进行施用。在一些实施方案中，向患者施用至少一种另外的活性成分。在一些实施方案中，施用作为多剂量方案进行。在本公开的一些实施方案中，多剂量方案为长达约2天的时间段。在本公开的一些实施方案中，多剂量方案为长达约3天的时间段。在本公开的一些实施方案中，多剂量方案为长达约4天的时间段。在本公开的一些实施方案中，多剂量方案为长达约5天的时间段。在本公开的一些实施方案中，多剂量方案为长达约6天的时间段。在本公开的一些实施方案中，多剂量方案为长达约7天的时间段。在本公开的一些实施方案中，多剂量方案为长达约14天的时间段。在本公开的一些实施方案中，施用作为长期治疗方案进行。在本文中可以使用其他时间段。

[0778] 在一些实施方案中，每天一次或多次进行施用。在一些实施方案中，每天一次进行施用。在一些实施方案中，每天两次进行施用。在一些实施方案中，每天三次进行施用。在一些实施方案中，每天四次进行施用。

[0779] 本公开还提供一种在有需要的患者中治疗肺部感染的方法。在一些实施方案中，方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用，术语“肺部感染”是指患者肺部单侧或双侧的感染。在一些实施方案中，肺部感染源自肺部病症。如本文所使用，术语“肺部病症”是指感染和非感染引起的呼吸系统疾病和功能障碍。

[0780] 肺部病症的非限制性示例包括但不限于遗传病症、获得性病症、原发病症、继发病症、哮喘、慢性阻塞性肺病、囊性纤维化、细支气管炎、肺炎、支气管炎、肺气肿、成人呼吸窘迫综合征、过敏、肺癌、小细胞肺癌、原发性肺癌、转移性肺癌、支气管扩张、支气管肺发育不良、慢性支气管炎、慢性下呼吸道疾病、哮吼(croup)、高原肺水肿、肺纤维化、间质性肺疾病、反应性气道疾病、淋巴管肌瘤病(lymphangioleiomyomatosis)、新生儿呼吸窘迫综合

征、副流感、胸膜积液、胸膜炎、气胸、原发性肺动脉高压、鹦鹉热、继发于各种原因的肺水肿、肺栓塞、继发于各种原因的肺动脉高压、继发于各种原因的呼吸衰竭、睡眠呼吸暂停、结节病、吸烟、喘鸣、急性呼吸窘迫综合征、感染性疾病、SARS、肺结核、鹦鹉热感染、Q热、副流感、呼吸道合胞病毒、及其组合,以及以上任何一项或组合所导致的病症。

[0781] 在本公开的一些实施方案中,提供一种在有需要的患者中治疗由囊性纤维化引起的肺部感染的方法。在一些实施方案中,方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用,术语“囊性纤维化”是指一种遗传疾病,其引起异常稠的粘液的产生,导致肺部感染以及对肺、消化系统和患者身体其他器官的损伤。

[0782] 在一些实施方案中,施用为吸入施用。在一些实施方案中,向患者施用至少一种另外的活性成分。在一些实施方案中,患者为人。在一些实施方案中,使用本公开的化合物或其药学上可接受的盐在液体溶液、混悬剂或干粉末中进行施用。在一些实施方案中,施用作为多剂量方案进行。在一些实施方案中,多剂量方案为长达约一个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约两个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约三个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约四个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约五个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约六个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约七个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约八个月的时间段。在本文中可以使用其他时间段。

[0783] 在一些实施方案中,每天一次或多次进行施用。在一些实施方案中,每天一次进行施用。在一些实施方案中,每天两次进行施用。在一些实施方案中,每天三次进行施用。在一些实施方案中,每天四次进行施用。

[0784] 在本公开的一些实施方案中,提供一种在有需要的患者中治疗肺炎的方法。在一些实施方案中,方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用,术语“肺炎”是指微生物感染患者肺部单侧或双侧,导致肺组织的炎症。在一些实施方案中,肺炎为呼吸机获得性肺炎。如本文所使用,术语“呼吸机获得性肺炎”是指由于患者被连接到机械式呼吸机而引起的肺炎。呼吸机获得性肺炎包括在为患者插管并接受机械通气超过约48小时后发生的肺炎。

[0785] 在一些实施方案中,施用为吸入施用。在一些实施方案中,向患者施用至少一种另外的活性成分。在一些实施方案中,患者为人。在一些实施方案中,使用本公开的化合物或其药学上可接受的盐在液体溶液、混悬剂或干粉末中进行施用。在一些实施方案中,施用作为多剂量方案进行。在本公开的一些实施方案中,多剂量方案为长达约7天的时间段。在本公开的一些实施方案中,多剂量方案为长达约14天的时间段。在本公开的一些实施方案中,多剂量方案为长达约21天的时间段。在一些实施方案中,多剂量方案为长达约一个月的时间段。在本公开的一些实施方案中,多剂量方案为长达约两个月的时间段。在本文中可以使用其他时间段。

[0786] 在一些实施方案中,每天一次或多次进行施用。在一些实施方案中,每天一次进行施用。在一些实施方案中,每天两次进行施用。在一些实施方案中,每天三次进行施用。在一些实施方案中,每天四次进行施用。

[0787] 本公开还提供一种在有需要的患者中治疗烧伤伤口的感染的方法。在一些实施方

案中,方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用,术语“烧伤伤口”是指对患者身体的烧伤损伤,其涉及对患者皮肤和可能地患者皮肤下面的组织的伤害。本领域技术人员已知有三种主要的烧伤程度类型,包括但不限于一度、二度和三度烧伤。在一些实施方案中,本公开所设想的治疗烧伤伤口的感染的方法用于治疗一度、二度和/或三度烧伤。

[0788] 在一些实施方案中,患者为人。在一些实施方案中,施用为局部施用。在一些实施方案中,使用本公开的化合物或其药学上可接受的盐在洗剂、凝胶、霜剂、软膏、油剂、溶液、混悬剂、乳剂或其他粘性组合物中进行施用。在一些实施方案中,向患者施用至少一种另外的活性成分。在一些实施方案中,施用作为多剂量方案进行。在本公开的一些实施方案中,多剂量方案为长达约2天的时间段。在本公开的一些实施方案中,多剂量方案为长达约3天的时间段。在本公开的一些实施方案中,多剂量方案为长达约4天的时间段。在本公开的一些实施方案中,多剂量方案为长达约5天的时间段。在本公开的一些实施方案中,多剂量方案为长达约6天的时间段。在本公开的一些实施方案中,多剂量方案为长达约7天的时间段。在本公开的一些实施方案中,多剂量方案为长达约14天的时间段。在本公开的一些实施方案中,多剂量方案为长达约21天的时间段。在一些实施方案中,多剂量方案为长达约一个月的时间段。在一些实施方案中,多剂量方案为长达约两个月的时间段。在本文中可以使用其他时间段。

[0789] 在一些实施方案中,每天一次或多次进行施用。在一些实施方案中,每天一次进行施用。在一些实施方案中,每天两次进行施用。在一些实施方案中,每天三次进行施用。在一些实施方案中,每天四次进行施用。

[0790] 本公开还提供一种在有需要的患者中治疗外耳炎的方法。在一些实施方案中,方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用,术语“外耳炎”是指患者的外耳道的感染。

[0791] 在一些实施方案中,患者为人。在一些实施方案中,施用为直接向患者外耳道的局部施用。在一些实施方案中,使用本公开的化合物或其药学上可接受的盐在液体溶液、混悬剂、洗剂、糊剂、凝胶、霜剂、软膏、油剂或其他粘性组合物中进行施用。在一些实施方案中,向患者施用至少一种另外的活性成分。在一些实施方案中,施用作为多剂量方案进行。在本公开的一些实施方案中,多剂量方案为长达约7天的时间段。在本公开的一些实施方案中,多剂量方案为长达约14天的时间段。在本公开的一些实施方案中,多剂量方案为长达约21天的时间段。在一些实施方案中,多剂量方案为长达约一个月的时间段。在本文中可以使用其他时间段。

[0792] 在一些实施方案中,每天一次或多次进行施用。在一些实施方案中,每天一次进行施用。在一些实施方案中,每天两次进行施用。在一些实施方案中,每天三次进行施用。在一些实施方案中,每天四次进行施用。

[0793] 本公开还提供一种在有需要的患者中治疗细菌性阴道病的方法。在一些实施方案中,方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用,术语“细菌性阴道病”是指患者阴道的感染,其由阴道中天然存在的细菌的过度生长引起。

[0794] 在一些实施方案中,患者为女性。在一些实施方案中,施用为局部施用。在一些实施方案中,使用本公开的化合物或其药学上可接受的盐在洗剂、凝胶、霜剂、软膏、油剂、溶

液、混悬剂、乳剂或其他粘性组合物中进行施用。在一些实施方案中，向患者施用至少一种另外的活性成分。在一些实施方案中，施用作为多剂量方案进行。在本公开的一些实施方案中，多剂量方案为长达约7天的时间段。在本公开的一些实施方案中，多剂量方案为长达约14天的时间段。在本公开的一些实施方案中，多剂量方案为长达约21天的时间段。在一些实施方案中，多剂量方案为长达约一个月的时间段。在本文中可以使用其他时间段。

[0795] 在一些实施方案中，每天一次或多次进行施用。在一些实施方案中，每天一次进行施用。在一些实施方案中，每天两次进行施用。在一些实施方案中，每天三次进行施用。在一些实施方案中，每天四次进行施用。

[0796] 本公开还提供一种在有需要的患者中治疗脓疱病的方法。在一些实施方案中，方法包括向患者施用有效量的本公开的化合物或其药学上可接受的盐。如本文所使用，术语“脓疱病”是指患者皮肤的感染，其导致水疱、脓疱、黄色结皮等。

[0797] 在一些实施方案中，患者为人。在一些实施方案中，施用为局部施用。在一些实施方案中，使用本公开的化合物或其药学上可接受的盐在洗剂、凝胶、霜剂、软膏、油剂、溶液、混悬剂、乳剂或其他粘性组合物中进行施用。在一些实施方案中，向患者施用至少一种另外的活性成分。在一些实施方案中，施用作为多剂量方案进行。在本公开的一些实施方案中，多剂量方案为长达约2天的时间段。在本公开的一些实施方案中，多剂量方案为长达约3天的时间段。在本公开的一些实施方案中，多剂量方案为长达约4天的时间段。在本公开的一些实施方案中，多剂量方案为长达约5天的时间段。在本公开的一些实施方案中，多剂量方案为长达约6天的时间段。在本公开的一些实施方案中，多剂量方案为长达约7天的时间段。在本公开的一些实施方案中，多剂量方案为长达约14天的时间段。在本公开的一些实施方案中，多剂量方案为长达约21天的时间段。在一些实施方案中，多剂量方案为长达约一个月的时间段。在本文中可以使用其他时间段。

[0798] 在一些实施方案中，每天一次或多次进行施用。在一些实施方案中，每天一次进行施用。在一些实施方案中，每天两次进行施用。在一些实施方案中，每天三次进行施用。在一些实施方案中，每天四次进行施用。

[0799] 本公开还提供一种试剂盒。在一些实施方案中，试剂盒包含根据本公开的化合物或其药学上可接受的盐，或根据本公开的药物组合物。如本文所使用，术语“试剂盒”是指任何制品如，例如包装、容器等，其含有根据本公开的化合物或其药学上可接受的盐或根据本公开的药物组合物。在一些实施方案中，将根据本公开的化合物或其药学上可接受的盐或根据本公开的药物组合物包装在小瓶、瓶、管、烧瓶或贴剂中，其可以进一步包装在盒子、包膜、袋子等中。在一些实施方案中，根据本公开的化合物或其药学上可接受的盐或根据本公开的药物组合物经美国食品和药物管理局或美国或美国以外的司法管辖区或地区的类似监管机构批准用于向患者施用。在一些实施方案中，试剂盒包括书面使用说明和/或其他说明，表明根据本公开的化合物或其药学上可接受的盐或根据本公开的药物组合物适合或批准用于向患者施用。在一些实施方案中，将本公开的化合物或组合物以单位剂量或单一单位剂量形式包装如，例如单一单位剂量丸剂、胶囊等。在一些实施方案中，试剂盒包含分配器。

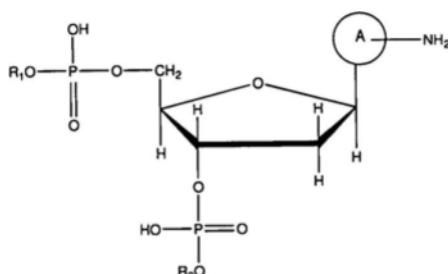
[0800] 本公开还提供本公开的化合物或其药学上可接受的盐在制备药物中的用途。如本文所使用，术语“药物”是指根据本公开的药物组合物。在一些实施方案中，药物组合物包含

在任何制品中,例如包装、容器等。

[0801] 除了在本公开的其他地方描述和提供的方面和实施方案以外,还设想了实施方案的以下非限制性列表。

[0802] 1.一种具有下式的化合物:

[0803]



式(I)

[0804] 或其药学上可接受的盐,

[0805] 其中:

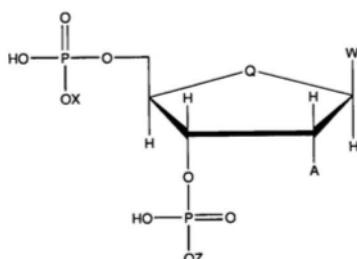
[0806] A为单环、双环或三环碳环或杂环部分,和

[0807] R₁和R₂各自为C₁-C₈烷基部分。

[0808] 2.根据条款1所述的化合物,其中R₁和R₂各自为丁基。

[0809] 3.一种具有下式的化合物:

[0810]



式(II)

[0811] 其中:

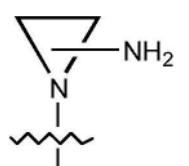
[0812] Q为氧或硫;

[0813] W为氨基取代的或胍基取代的含氮杂环部分;

[0814] X和Z为末端封闭基团;和

[0815] A为H、烷基、卤素、烷氧基、烷基-(0-烷基)、芳基、烯基、烷醇或苯酚。4.根据条款3所述的化合物,其中W为:

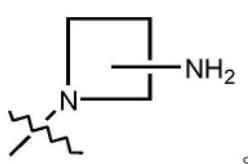
[0816]



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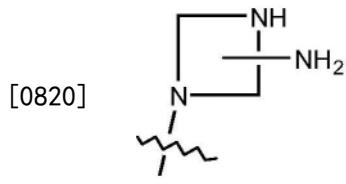
[0817] 5.根据条款3所述的化合物,其中W为:

[0818]



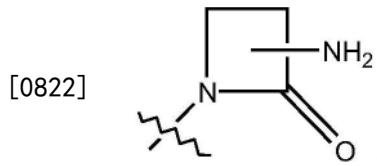
。

[0819] 6. 根据条款3所述的化合物,其中W为:



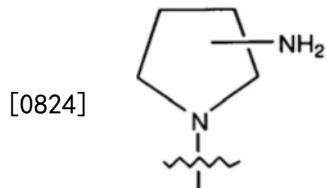
。

[0821] 7. 根据条款3所述的化合物,其中W为:



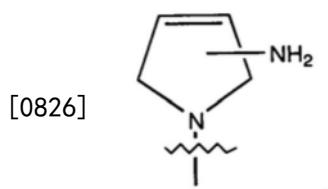
。

[0823] 8. 根据条款3所述的化合物,其中W为:



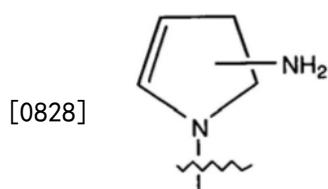
。

[0825] 9. 根据条款3所述的化合物,其中W为:



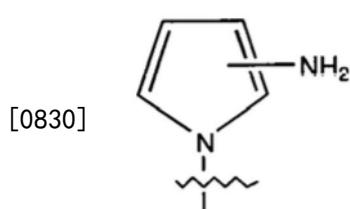
。

[0827] 10. 根据条款3所述的化合物,其中W为:



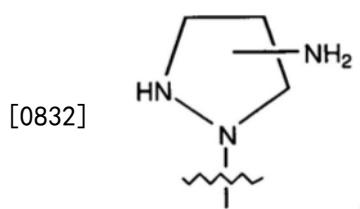
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[0829] 11. 根据条款3所述的化合物,其中W为:



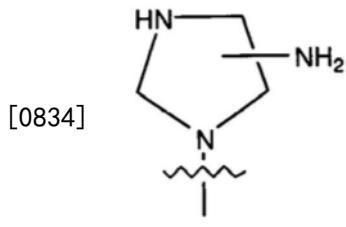
。

[0831] 12. 根据条款3所述的化合物,其中W为:

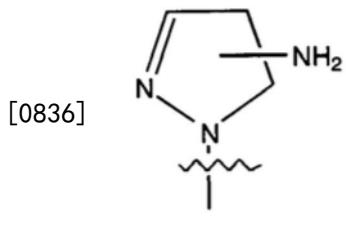


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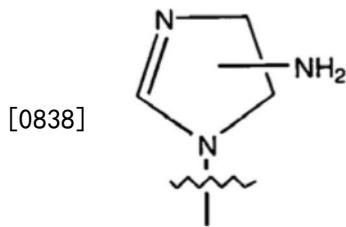
[0833] 13. 根据条款3所述的化合物,其中W为:



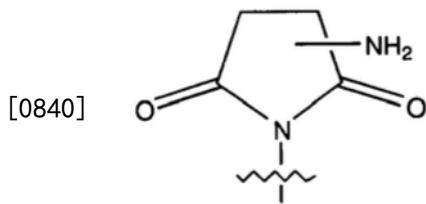
[0835] 14. 根据条款3所述的化合物,其中W为:



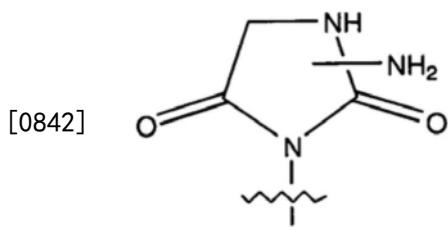
[0837] 15. 根据条款3所述的化合物,其中W为:



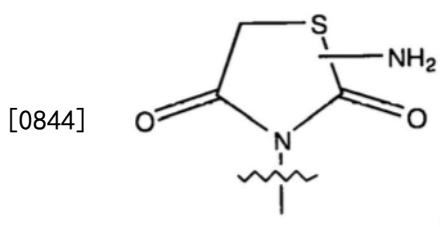
[0839] 16. 根据条款3所述的化合物,其中W为:



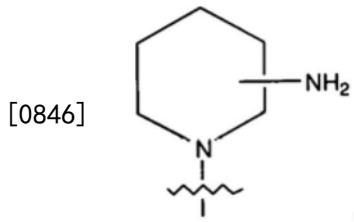
[0841] 17. 根据条款3所述的化合物,其中W为:



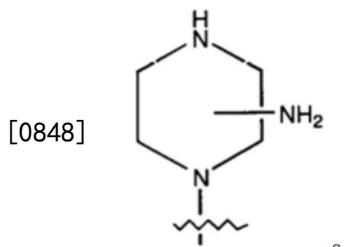
[0843] 18. 根据条款3所述的化合物,其中W为:



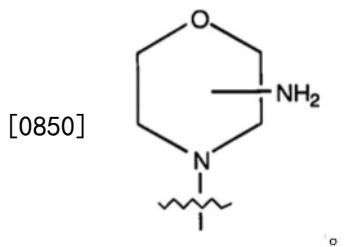
[0845] 19. 根据条款3所述的化合物,其中W为:



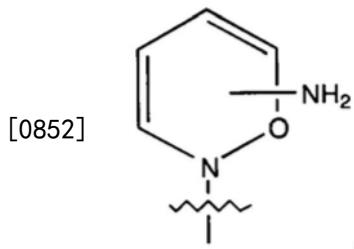
[0847] 20. 根据条款3所述的化合物, 其中W为:



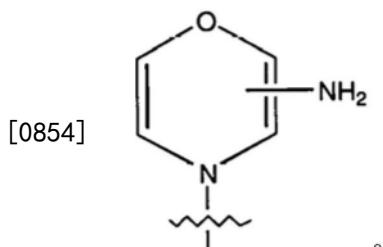
[0849] 21. 根据条款3所述的化合物, 其中W为:



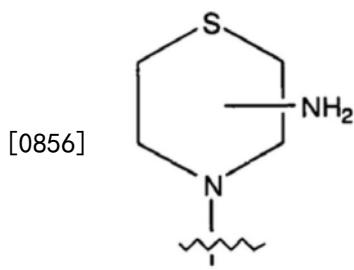
[0851] 22. 根据条款3所述的化合物, 其中W为:



[0853] 23. 根据条款3所述的化合物, 其中W为:

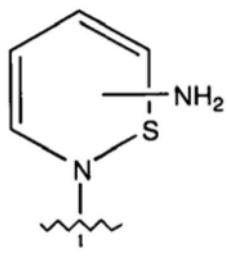


[0855] 24. 根据条款3所述的化合物, 其中W为:



[0857] 25. 根据条款3所述的化合物, 其中W为:

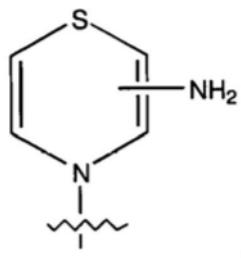
[0858]



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[0859] 26. 根据条款3所述的化合物, 其中W为:

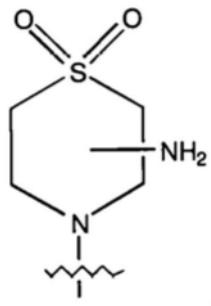
[0860]



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[0861] 27. 根据条款3所述的化合物, 其中W为:

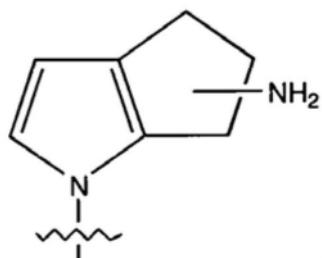
[0862]



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[0863] 28. 根据条款3所述的化合物, 其中W为:

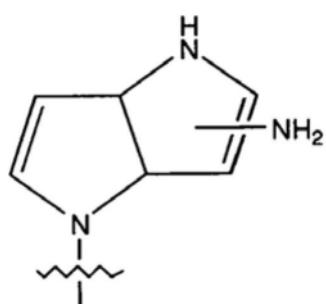
[0864]



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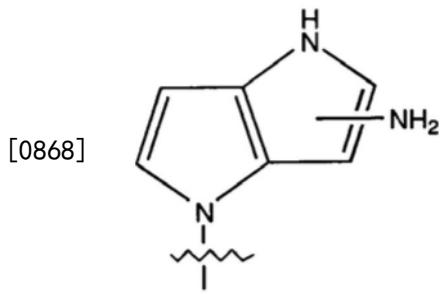
[0865] 29. 根据条款3所述的化合物, 其中W为:

[0866]

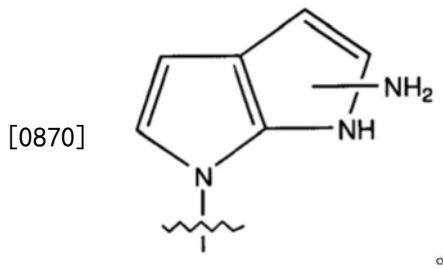


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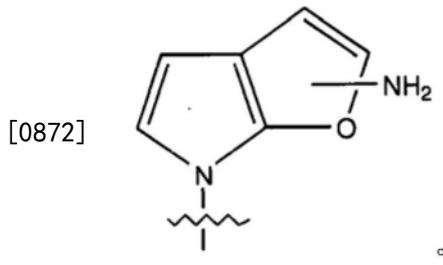
[0867] 30. 根据条款3所述的化合物, 其中W为:



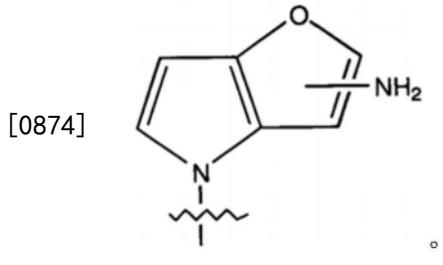
[0869] 31. 根据条款3所述的化合物, 其中W为:



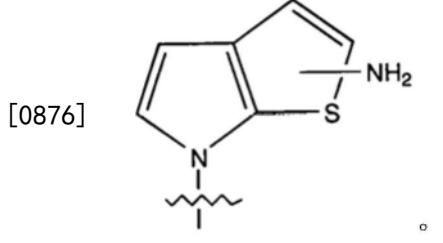
[0871] 32. 根据条款3所述的化合物, 其中W为:



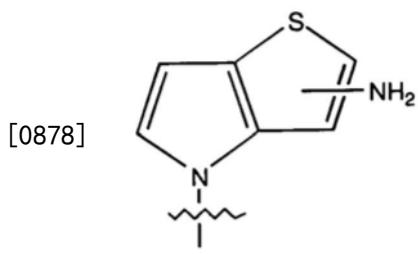
[0873] 33. 根据条款3所述的化合物, 其中W为:



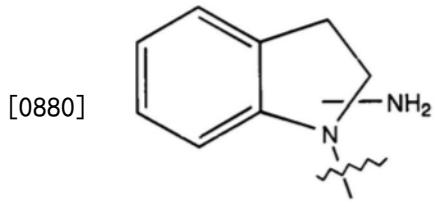
[0875] 34. 根据条款3所述的化合物, 其中W为:



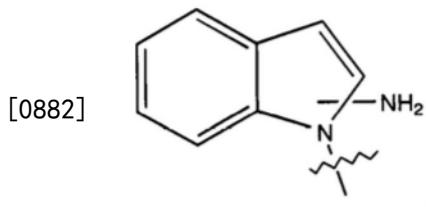
[0877] 35. 根据条款3所述的化合物, 其中W为:



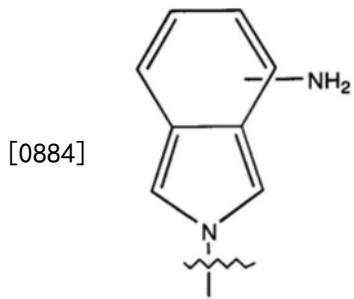
[0879] 36. 根据条款3所述的化合物,其中W为:



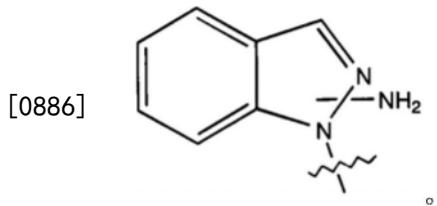
[0881] 37. 根据条款3所述的化合物,其中W为:



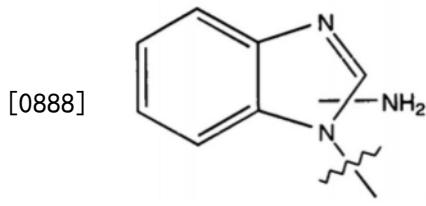
[0883] 38. 根据条款3所述的化合物,其中W为:



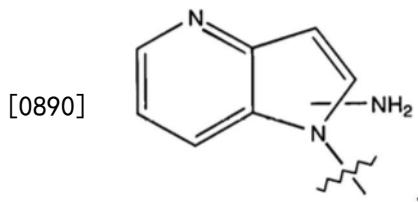
[0885] 39. 根据条款3所述的化合物,其中W为:



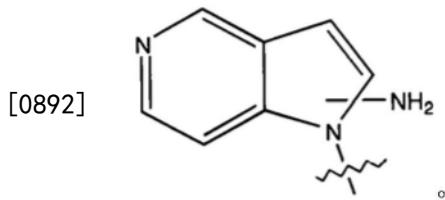
[0887] 40. 根据条款3所述的化合物,其中W为:



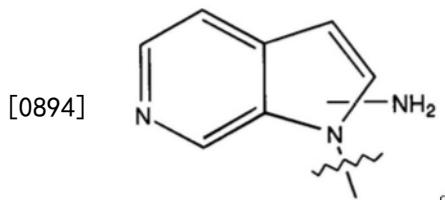
[0889] 41. 根据条款3所述的化合物,其中W为:



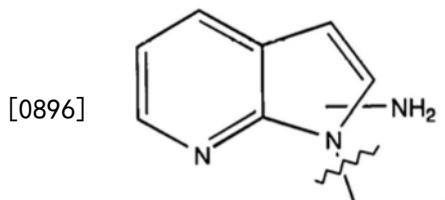
[0891] 42. 根据条款3所述的化合物, 其中W为:



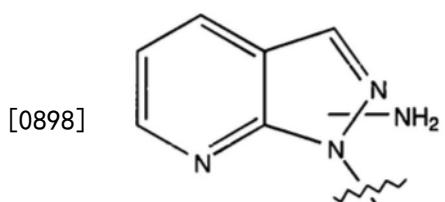
[0893] 43. 根据条款3所述的化合物, 其中W为:



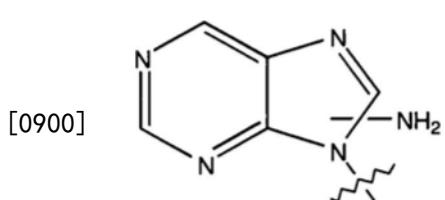
[0895] 44. 根据条款3所述的化合物, 其中W为:



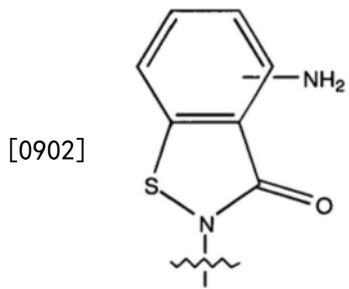
[0897] 45. 根据条款3所述的化合物, 其中W为:



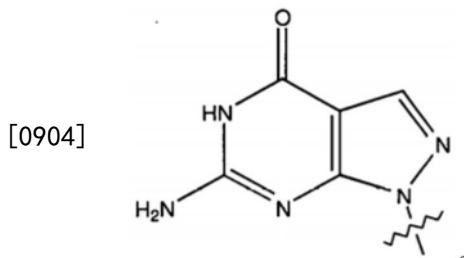
[0899] 46. 根据条款3所述的化合物, 其中W为:



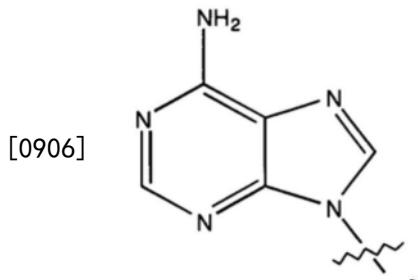
[0901] 47. 根据条款3所述的化合物, 其中W为:



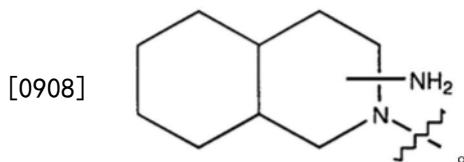
[0903] 48. 根据条款3所述的化合物，其中W为：



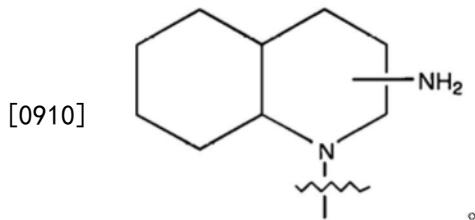
[0905] 49. 根据条款3所述的化合物，其中W为：



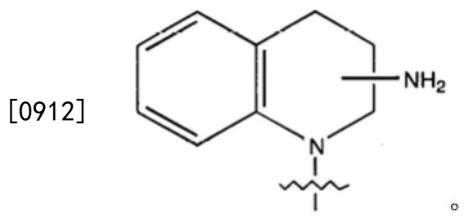
[0907] 50. 根据条款3所述的化合物，其中W为：



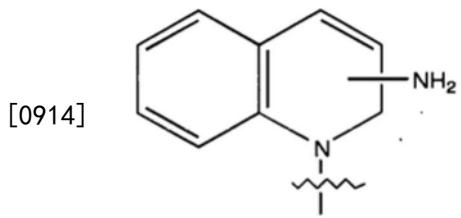
[0909] 51.根据条款3所述的化合物,其中W为:



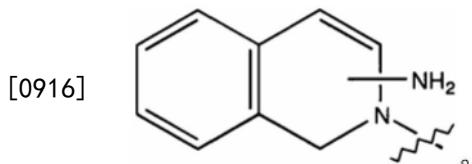
[0911] 52. 根据条款3所述的化合物，其中W为：



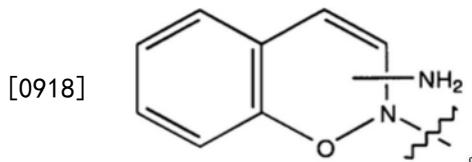
[0913] 53. 根据条款3所述的化合物，其中W为：



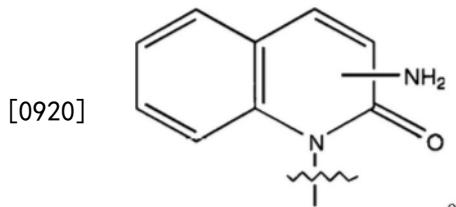
[0915] 54. 根据条款3所述的化合物,其中W为:



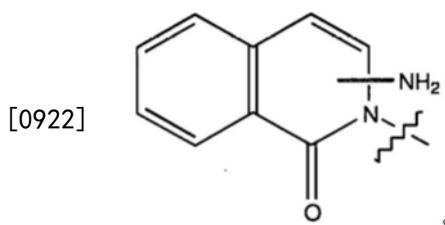
[0917] 55. 根据条款3所述的化合物,其中W为:



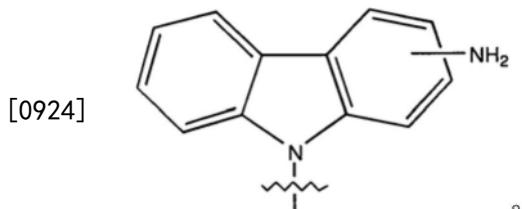
[0919] 56. 根据条款3所述的化合物,其中W为:



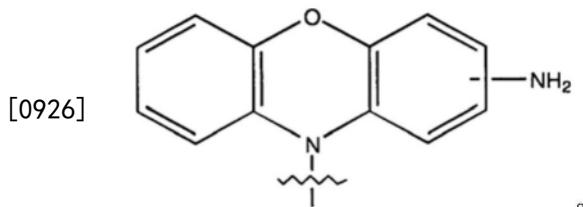
[0921] 57. 根据条款3所述的化合物,其中W为:



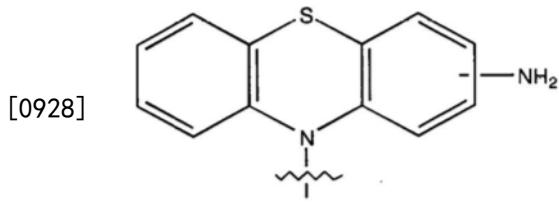
[0923] 58. 根据条款3所述的化合物,其中W为:



[0925] 59. 根据条款3所述的化合物,其中W为:



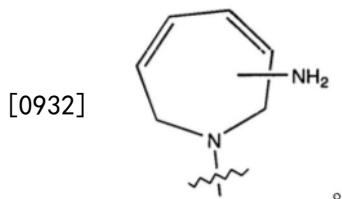
[0927] 60. 根据条款3所述的化合物,其中W为:



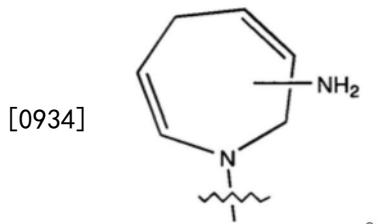
[0929] 61. 根据条款3所述的化合物, 其中W为:



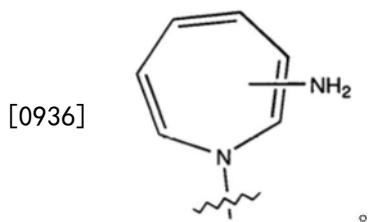
[0931] 62. 根据条款3所述的化合物, 其中W为:



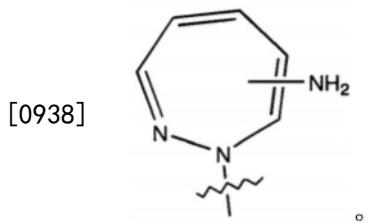
[0933] 63. 根据条款3所述的化合物, 其中W为:



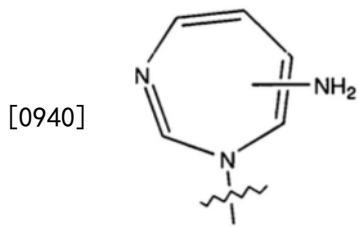
[0935] 64. 根据条款3所述的化合物, 其中W为:



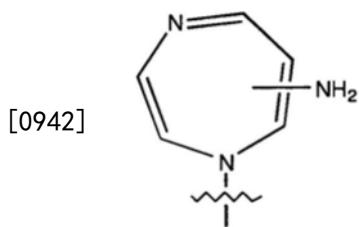
[0937] 65. 根据条款3所述的化合物, 其中W为:



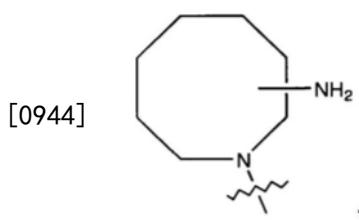
[0939] 66. 根据条款3所述的化合物, 其中W为:



[0941] 67. 根据条款3所述的化合物, 其中W为:



[0943] 68. 根据条款3所述的化合物, 其中W为:



[0945] 69. 根据条款3所述的化合物, 其中W为胍基取代的氮杂环丙烷。

[0946] 70. 根据条款3所述的化合物, 其中W为胍基取代的氮杂环丁烷。

[0947] 71. 根据条款3所述的化合物, 其中W为胍基取代的1,3-氮杂环丁烷。

[0948] 72. 根据条款3所述的化合物, 其中W为胍基取代的氮杂环丁烷-2-酮(β -内酰胺)。

[0949] 73. 根据条款3所述的化合物, 其中W为胍基取代的吡咯烷。

[0950] 74. 根据条款3所述的化合物, 其中W为胍基取代的3-吡咯啉。

[0951] 75. 根据条款3所述的化合物, 其中W为胍基取代的2-吡咯啉。

[0952] 76. 根据条款3所述的化合物, 其中W为胍基取代的1H-吡咯。

[0953] 77. 根据条款3所述的化合物, 其中W为胍基取代的吡唑烷。

[0954] 78. 根据条款3所述的化合物, 其中W为胍基取代的咪唑烷。

[0955] 79. 根据条款3所述的化合物, 其中W为胍基取代的2-吡唑啉。

[0956] 80. 根据条款3所述的化合物, 其中W为胍基取代的2-咪唑啉。

[0957] 81. 根据条款3所述的化合物, 其中W为胍基取代的琥珀酰亚胺。

[0958] 82. 根据条款3所述的化合物, 其中W为胍基取代的乙内酰脲。

[0959] 83. 根据条款3所述的化合物, 其中W为胍基取代的2,4-噻唑烷二酮。

[0960] 84. 根据条款3所述的化合物, 其中W为胍基取代的哌啶。

[0961] 85. 根据条款3所述的化合物, 其中W为胍基取代的哌嗪。

[0962] 86. 根据条款3所述的化合物, 其中W为胍基取代的吗啉。

[0963] 87. 根据条款3所述的化合物, 其中W为胍基取代的2H-1,2-𫫇唑烷。

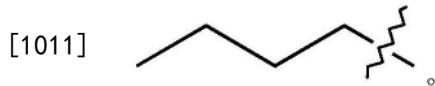
[0964] 88. 根据条款3所述的化合物, 其中W为胍基取代的4H-1,4-𫫇唑烷。

[0965] 89. 根据条款3所述的化合物, 其中W为胍基取代的硫代吗啉。

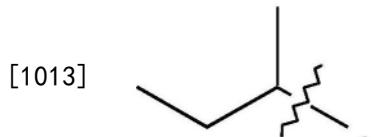
[0966] 90. 根据条款3所述的化合物, 其中W为胍基取代的2H-1,2-噻嗪。

- [0967] 91. 根据条款3所述的化合物, 其中W为胍基取代的4H-1,4-噻嗪。
- [0968] 92. 根据条款3所述的化合物, 其中W为胍基取代的硫代吗啉二氧化物。
- [0969] 93. 根据条款3所述的化合物, 其中W为胍基取代的1,4,5,6-四氢环-戊[b]吡咯。
- [0970] 94. 根据条款3所述的化合物, 其中W为胍基取代的1,3a,4,6a-四氢吡咯并-[3,2-b]吡咯。
- [0971] 95. 根据条款3所述的化合物, 其中W为胍基取代的1,4-二氢吡咯并-[3,2-b]吡咯。
- [0972] 96. 根据条款3所述的化合物, 其中W为胍基取代的1,6-二氢吡咯并-[2,3-b]吡咯。
- [0973] 97. 根据条款3所述的化合物, 其中W为胍基取代的6H-呋喃并[2,3-b]吡咯。
- [0974] 98. 根据条款3所述的化合物, 其中W为胍基取代的4H-呋喃并[3,2-b]吡咯。
- [0975] 99. 根据条款3所述的化合物, 其中W为胍基取代的6H-噻吩并[2,3-b]吡咯。
- [0976] 100. 根据条款3所述的化合物, 其中W为胍基取代的4H-噻吩并[3,2-b]吡咯。
- [0977] 101. 根据条款3所述的化合物, 其中W为胍基取代的二氢吲哚。
- [0978] 102. 根据条款3所述的化合物, 其中W为胍基取代的1H-吲哚。
- [0979] 103. 根据条款3所述的化合物, 其中W为胍基取代的2H-异吲哚。
- [0980] 104. 根据条款3所述的化合物, 其中W为胍基取代的1H-吲唑。
- [0981] 105. 根据条款3所述的化合物, 其中W为胍基取代的苯并咪唑。
- [0982] 106. 根据条款3所述的化合物, 其中W为胍基取代的4-氮杂吲哚。
- [0983] 107. 根据条款3所述的化合物, 其中W为胍基取代的5-氮杂吲哚。
- [0984] 108. 根据条款3所述的化合物, 其中W为胍基取代的6-氮杂吲哚。
- [0985] 109. 根据条款3所述的化合物, 其中W为胍基取代的7-氮杂吲哚。
- [0986] 110. 根据条款3所述的化合物, 其中W为胍基取代的7-氮杂吲唑。
- [0987] 111. 根据条款3所述的化合物, 其中W为胍基取代的嘌呤。
- [0988] 112. 根据条款3所述的化合物, 其中W为胍基取代的1,2-苯并异噻唑-3(2H)-酮。
- [0989] 113. 根据条款3所述的化合物, 其中W为胍基取代的鸟嘌呤。
- [0990] 114. 根据条款3所述的化合物, 其中W为胍基取代的腺嘌呤。
- [0991] 115. 根据条款3所述的化合物, 其中W为胍基取代的十氢异喹啉。
- [0992] 116. 根据条款3所述的化合物, 其中W为胍基取代的十氢喹啉。
- [0993] 117. 根据条款3所述的化合物, 其中W为胍基取代的1,2,3,4-四氢喹啉。
- [0994] 118. 根据条款3所述的化合物, 其中W为胍基取代的1,2-二氢喹啉。
- [0995] 119. 根据条款3所述的化合物, 其中W为胍基取代的1,2-二氢异喹啉。
- [0996] 120. 根据条款3所述的化合物, 其中W为胍基取代的2H-苯并-[e][1,2]噁唑。
- [0997] 121. 根据条款3所述的化合物, 其中W为胍基取代的喹啉2(1H)-酮。
- [0998] 122. 根据条款3所述的化合物, 其中W为胍基取代的异喹啉1(2H)-酮。
- [0999] 123. 根据条款3所述的化合物, 其中W为胍基取代的咔唑。
- [1000] 124. 根据条款3所述的化合物, 其中W为胍基取代的吩噁嗪。
- [1001] 125. 根据条款3所述的化合物, 其中W为胍基取代的吩噻嗪。
- [1002] 126. 根据条款3所述的化合物, 其中W为胍基取代的2-氮杂金刚烷。
- [1003] 127. 根据条款3所述的化合物, 其中W为胍基取代的2,3-二氢氮杂卓。
- [1004] 128. 根据条款3所述的化合物, 其中W为胍基取代的2,5-二氢氮杂卓。

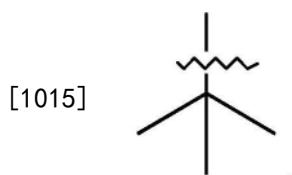
- [1005] 129. 根据条款3所述的化合物, 其中W为胍基取代的氮杂卓。
- [1006] 130. 根据条款3所述的化合物, 其中W为胍基取代的1,2-氮杂卓。
- [1007] 131. 根据条款3所述的化合物, 其中W为胍基取代的1,3-氮杂卓。
- [1008] 132. 根据条款3所述的化合物, 其中W为胍基取代的1,4-氮杂卓。
- [1009] 133. 根据条款3所述的化合物, 其中W为胍基取代的氮杂环辛烷。
- [1010] 134. 根据条款3至133中任一项所述的化合物, 其中X为



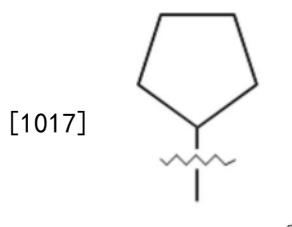
- [1012] 135. 根据条款3至133中任一项所述的化合物, 其中X为



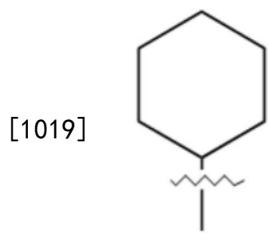
- [1014] 136. 根据条款3至133中任一项所述的化合物, 其中X为



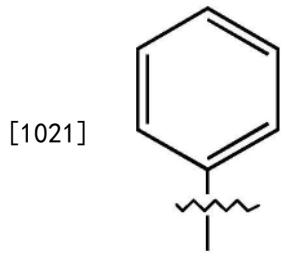
- [1016] 137. 根据条款3至133中任一项所述的化合物, 其中X为



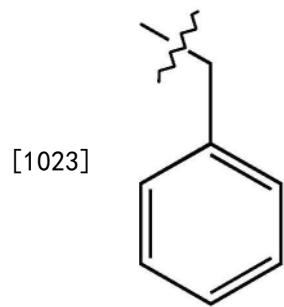
- [1018] 138. 根据条款3至133中任一项所述的化合物, 其中X为



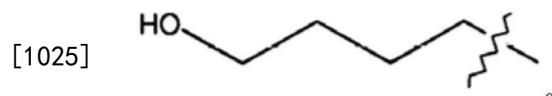
- [1020] 139. 根据条款3至133中任一项所述的化合物, 其中X为



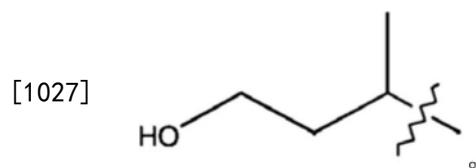
- [1022] 140. 根据条款3至133中任一项所述的化合物, 其中X为



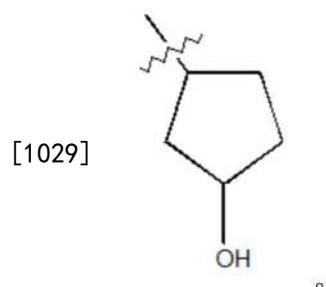
[1024] 141. 根据条款3至133中任一项所述的化合物, 其中X为



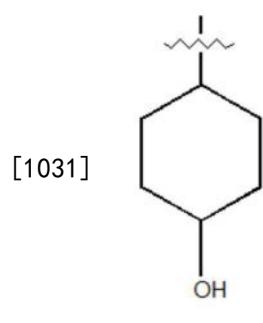
[1026] 142. 根据条款3至133中任一项所述的化合物, 其中X为



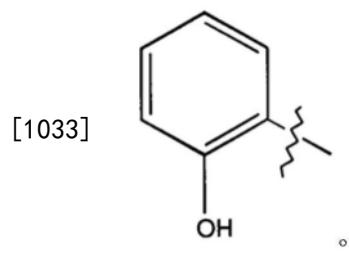
[1028] 143. 根据条款3至133中任一项所述的化合物, 其中X为



[1030] 144. 根据条款3至133中任一项所述的化合物, 其中X为

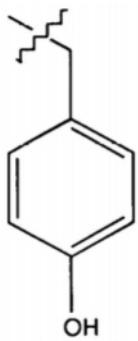


[1032] 145. 根据条款3至133中任一项所述的化合物, 其中X为



[1034] 146. 根据条款3至133中任一项所述的化合物, 其中X为

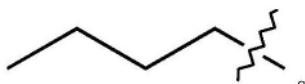
[1035]



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[1036] 147. 根据条款3至146中任一项所述的化合物, 其中Z为

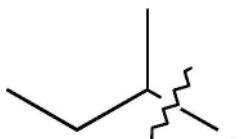
[1037]



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[1038] 148. 根据条款3至146中任一项所述的化合物, 其中Z为

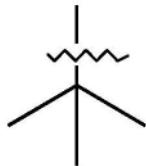
[1039]



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[1040] 149. 根据条款3至146中任一项所述的化合物, 其中Z为

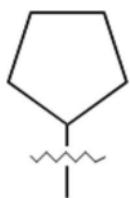
[1041]



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[1042] 150. 根据条款3至146中任一项所述的化合物, 其中Z为

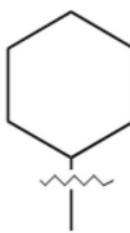
[1043]



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[1044] 151. 根据条款3至146中任一项所述的化合物, 其中Z为

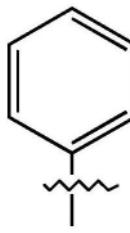
[1045]



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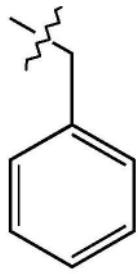
[1046] 152. 根据条款3至146中任一项所述的化合物, 其中Z为

[1047]



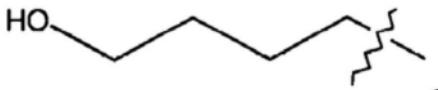
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[1048] 153. 根据条款3至146中任一项所述的化合物, 其中Z为



[1049]

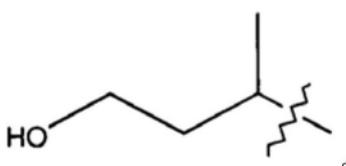
[1050] 154. 根据条款3至146中任一项所述的化合物, 其中Z为



[1051]

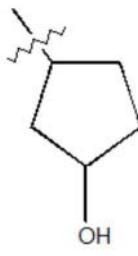
[1052] 155. 根据条款3至146中任一项所述的化合物, 其中Z为

[1053]



[1054]

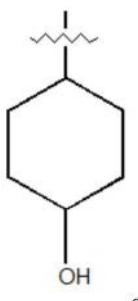
[1055] 156. 根据条款3至146中任一项所述的化合物, 其中Z为



[1055]

[1056] 157. 根据条款3至146中任一项所述的化合物, 其中Z为

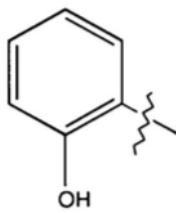
[1057]



[1058]

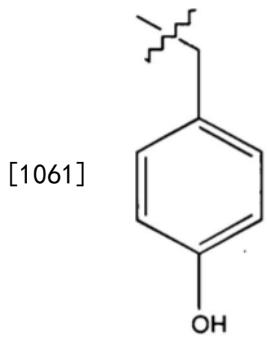
[1059] 158. 根据条款3至146中任一项所述的化合物, 其中Z为

[1059]



[1060]

[1060] 159. 根据条款3至146中任一项所述的化合物, 其中Z为



- [1062] 160. 一种化合物, 其选自如在表1中所描述的Cmpd 1至2520中的任一个。
- [1063] 161. 如在表1中所描述的Cmpd 1。
- [1064] 162. 根据条款160所述的化合物的药学上可接受的盐, 其选自铵盐、钙盐、钠盐、钾盐、镁盐和钴盐。
- [1065] 163. 根据条款162所述的药学上可接受的盐, 其中所述铵盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸铵。
- [1066] 164. 根据条款162所述的药学上可接受的盐, 其中所述钙盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钙。
- [1067] 165. 根据条款162所述的药学上可接受的盐, 其中所述钠盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钠。
- [1068] 166. 根据条款162所述的药学上可接受的盐, 其中所述钾盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钾。
- [1069] 167. 根据条款162所述的药学上可接受的盐, 其中所述镁盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸镁。
- [1070] 168. 根据条款162所述的药学上可接受的盐, 其中所述钴盐为((2R,3S,5R)-5-(4-氨基-2-氧代嘧啶-1(2H)-基)-3-((丁氧基氧化磷-基)氧基)四氢呋喃-2-基)甲基丁基磷酸钴。
- [1071] 169. 根据条款160所述的化合物或其药学上可接受的盐, 其中所述化合物或其药学上可接受的盐为质子化的化合物, 当溶解于水中时其具有约pH 3至约pH 5的pH。
- [1072] 170. 根据条款160所述的化合物或其药学上可接受的盐, 其中所述化合物或其药学上可接受的盐为质子化的化合物, 当溶解于水中时其具有约pH 3至约pH 4的pH。
- [1073] 171. 一种药物组合物, 其包含根据条款160所述的化合物或其药学上可接受的盐, 以及一种或多种药学上可接受的载体、赋形剂或稀释剂。
- [1074] 172. 条款171的药物组合物, 其中所述药物组合物包含至少一种另外的活性成分。
- [1075] 173. 条款171或172的药物组合物, 其中所述药物组合物为人药物组合物。
- [1076] 174. 条款171至173中任一项的药物组合物, 其中所述药物组合物适合于局部施

用。

[1077] 175. 条款171至174中任一项的药物组合物,其中将所述药物组合物以洗剂、凝胶、霜剂、软膏、油剂、溶液、混悬剂、乳剂或其他粘性组合物的形式施用。

[1078] 176. 条款171至175中任一项的药物组合物,其中将所述药物组合物以包含多元醇的凝胶的形式施用。

[1079] 177. 条款171至173中任一项的药物组合物,其中所述药物组合物适合于口服施用。

[1080] 178. 条款177的药物组合物,其中将所述药物组合物以胶囊、片剂、粉末、液体混悬剂、溶液、酏剂、糖浆剂或浓缩滴剂的形式施用。

[1081] 179. 条款171至173中任一项的药物组合物,其中所述药物组合物适合于吸入施用。

[1082] 180. 条款179的药物组合物,其中将所述药物组合物以干粉末、溶液、混悬剂或气雾剂的形式施用。

[1083] 181. 条款171至173中任一项的药物组合物,其中所述药物组合物适合于膀胱内施用。

[1084] 182. 条款181的药物组合物,其中经由导管施用所述药物组合物。

[1085] 183. 条款171至173中任一项的药物组合物,其中所述药物组合物适合于肠胃外施用。

[1086] 184. 条款183的药物组合物,其中经由针头施用所述药物组合物。

[1087] 185. 一种在有需要的患者中治疗糖尿病足溃疡感染的方法,所述方法包括向患者施用有效量的根据条款160所述的化合物或其药学上可接受的盐。

[1088] 186. 条款185的方法,其中所述施用为局部施用。

[1089] 187. 条款185或条款186的方法,其中使用化合物或其药学上可接受的盐在洗剂、糊剂、凝胶、霜剂、软膏、油剂或其他粘性组合物中进行所述施用。

[1090] 188. 条款185至187中任一项的方法,其中使用化合物或其药学上可接受的盐在凝胶中进行所述施用。

[1091] 189. 条款185至188中任一项的方法,其中向所述患者施用至少一种另外的活性成分。

[1092] 190. 条款185至189中任一项的方法,其中所述患者为人。

[1093] 191. 条款185至190中任一项的方法,其中所述施用作为多剂量方案进行。

[1094] 192. 条款191的方法,其中所述多剂量方案为长达约一个月的时间段。

[1095] 193. 条款191的方法,其中所述多剂量方案为长达约两个月的时间段。

[1096] 194. 条款191的方法,其中所述多剂量方案为长达约三个月的时间段。

[1097] 195. 条款191的方法,其中所述多剂量方案为长达约四个月的时间段。

[1098] 196. 条款185至195中任一项的方法,其中每天一次进行施用。

[1099] 197. 一种在有需要的患者中治疗复杂泌尿道感染的方法,所述方法包括向患者施用有效量的根据条款160所述的化合物或其药学上可接受的盐。

[1100] 198. 条款197的方法,其中泌尿道感染为导管相关性泌尿道感染。

[1101] 199. 条款197或198的方法,其中所述施用为膀胱内施用。

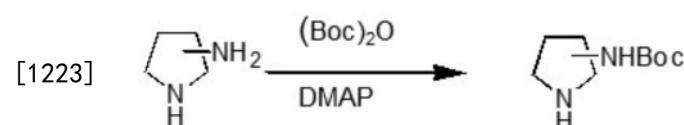
- [1102] 200. 条款197至199中任一项的方法,其中使用化合物或其药学上可接受的盐在液体溶液或混悬剂中进行所述施用。
- [1103] 201. 条款197至200中任一项的方法,其中向所述患者施用至少一种另外的活性成分。
- [1104] 202. 条款197至201中任一项的方法,其中所述患者为人。
- [1105] 203. 条款197至202中任一项的方法,其中所述施用作为多剂量方案进行。
- [1106] 204. 条款203的方法,其中所述多剂量方案为长达约2天的时间段。
- [1107] 205. 条款203的方法,其中所述多剂量方案为长达约3天的时间段。
- [1108] 206. 条款203的方法,其中所述多剂量方案为长达约4天的时间段。
- [1109] 207. 条款203的方法,其中所述多剂量方案为长达约5天的时间段。
- [1110] 208. 条款203的方法,其中所述多剂量方案为长达约6天的时间段。
- [1111] 209. 条款203的方法,其中所述多剂量方案为长达约7天的时间段。
- [1112] 210. 条款203的方法,其中所述多剂量方案为长达约14天的时间段。
- [1113] 211. 条款197至202中任一项的方法,其中所述施用作为长期治疗方案进行。
- [1114] 212. 条款197至211中任一项的方法,其中每天一次进行施用。
- [1115] 213. 一种在有需要的患者中治疗囊性纤维化引起的肺部感染的方法,所述方法包括向患者施用有效量的根据条款160所述的化合物或其药学上可接受的盐。
- [1116] 214. 条款213的方法,其中所述施用为吸入施用。
- [1117] 215. 条款213或214的方法,其中使用化合物或其药学上可接受的盐在干粉末、溶液、混悬剂或气雾剂中进行所述施用。
- [1118] 216. 条款213至215中任一项的方法,其中向所述患者施用至少一种另外的活性成分。
- [1119] 217. 条款213至216中任一项的方法,其中所述患者为人。
- [1120] 218. 条款213至217中任一项的方法,其中所述施用作为多剂量方案进行。
- [1121] 219. 条款213至218的方法,其中所述多剂量方案为长达约一个月的时间段。
- [1122] 220. 条款218的方法,其中所述多剂量方案为长达约两个月的时间段。
- [1123] 221. 条款218的方法,其中所述多剂量方案为长达约三个月的时间段。
- [1124] 222. 条款218的方法,其中所述多剂量方案为长达约四个月的时间段。
- [1125] 223. 条款218的方法,其中所述多剂量方案为长达约五个月的时间段。
- [1126] 224. 条款218的方法,其中所述多剂量方案为长达约六个月的时间段。
- [1127] 225. 条款218的方法,其中所述多剂量方案为长达约七个月的时间段。
- [1128] 226. 条款218的方法,其中所述多剂量方案为长达约八个月的时间段。
- [1129] 227. 条款213至217中任一项的方法,其中每天一次进行施用。
- [1130] 228. 一种在有需要的患者中治疗呼吸机获得性肺炎的方法,所述方法包括向患者施用有效量的根据条款160所述的化合物或其药学上可接受的盐。
- [1131] 229. 条款228的方法,其中所述施用为吸入施用。
- [1132] 230. 条款228或229的方法,其中使用化合物或其药学上可接受的盐在液体溶液、混悬剂或干粉末中进行所述施用。
- [1133] 231. 条款228至230中任一项的方法,其中向所述患者施用至少一种另外的活性成

分。

- [1134] 232. 条款228至231中任一项的方法,其中所述患者为人。
- [1135] 233. 条款228至232中任一项的方法,其中所述施用作为多剂量方案进行。
- [1136] 234. 条款233的方法,其中所述多剂量方案为长达约7天的时间段。
- [1137] 235. 条款233的方法,其中所述多剂量方案为长达约14天的时间段。
- [1138] 236. 条款233的方法,其中所述多剂量方案为长达约21天的时间段。
- [1139] 237. 条款233的方法,其中所述多剂量方案为长达约一个月的时间段。
- [1140] 238. 条款228至237中任一项的方法,其中每天一次进行施用。
- [1141] 239. 一种在有需要的患者中治疗烧伤伤口的感染的方法,所述方法包括向患者施用有效量的根据条款160所述的化合物或其药学上可接受的盐。
- [1142] 240. 条款239的方法,其中所述施用为局部施用。
- [1143] 241. 条款239或240的方法,其中使用化合物在洗剂、凝胶、霜剂、软膏、油剂、溶液、混悬剂、乳剂或其他粘性组合物中进行所述施用。
- [1144] 242. 条款239至241中任一项的方法,其中向所述患者施用至少一种另外的活性成分。
- [1145] 243. 条款239至242中任一项的方法,其中所述患者为人。
- [1146] 244. 条款239至243中任一项的方法,其中所述施用作为多剂量方案进行。
- [1147] 245. 条款244的方法,其中所述多剂量方案为长达约2天的时间段。
- [1148] 246. 条款244的方法,其中所述多剂量方案为长达约3天的时间段。
- [1149] 247. 条款244的方法,其中所述多剂量方案为长达约4天的时间段。
- [1150] 248. 条款244的方法,其中所述多剂量方案为长达约5天的时间段。
- [1151] 249. 条款244的方法,其中所述多剂量方案为长达约6天的时间段。
- [1152] 250. 条款244的方法,其中所述多剂量方案为长达约7天的时间段。
- [1153] 251. 条款244的方法,其中所述多剂量方案为长达约14天的时间段。
- [1154] 252. 条款244的方法,其中所述多剂量方案为长达约21天的时间段。
- [1155] 253. 条款244的方法,其中所述多剂量方案为长达约一个月的时间段。
- [1156] 254. 条款239至253中任一项的方法,其中每天一次或多次进行施用。
- [1157] 255. 条款239至253中任一项的方法,其中每天一次进行施用。
- [1158] 256. 条款239至253中任一项的方法,其中每天两次进行施用。
- [1159] 257. 条款239至253中任一项的方法,其中每天三次进行施用。
- [1160] 258. 条款239至253中任一项的方法,其中每天四次进行施用。
- [1161] 259. 一种在有需要的患者中治疗外耳炎的方法,所述方法包括向患者施用有效量的根据条款160所述的化合物或其药学上可接受的盐。
- [1162] 260. 条款259的方法,其中所述施用为直接向患者外耳道的局部施用。
- [1163] 261. 条款259或260的方法,其中使用化合物在洗剂、凝胶、霜剂、软膏、油剂、溶液、混悬剂、乳剂或其他粘性组合物中进行所述施用。
- [1164] 262. 条款259至261中任一项的方法,其中向所述患者施用至少一种另外的活性成分。
- [1165] 263. 条款259至262中任一项的方法,其中所述患者为人。

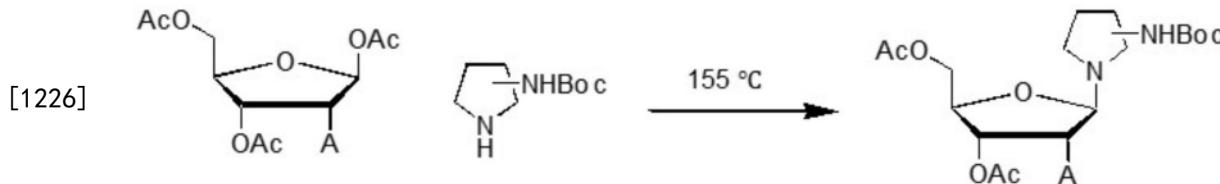
- [1166] 264. 条款259至263中任一项的方法,其中所述施用作为多剂量方案进行。
- [1167] 265. 条款264的方法,其中所述多剂量方案为长达约7天的时间段。
- [1168] 266. 条款264的方法,其中所述多剂量方案为长达约14天的时间段。
- [1169] 267. 条款264的方法,其中所述多剂量方案为长达约21天的时间段。
- [1170] 268. 条款264的方法,其中所述多剂量方案为长达约一个月的时间段。
- [1171] 269. 条款259至268中任一项的方法,其中每天一次或多次进行施用。
- [1172] 270. 条款259至268中任一项的方法,其中每天一次进行施用。
- [1173] 271. 条款259至268中任一项的方法,其中每天两次进行施用。
- [1174] 272. 条款259至268中任一项的方法,其中每天三次进行施用。
- [1175] 273. 一种在有需要的患者中治疗细菌性阴道病的方法,所述方法包括向患者施用有效量的根据条款160所述的化合物或其药学上可接受的盐。
- [1176] 274. 条款273的方法,其中所述施用为局部施用。
- [1177] 275. 条款273或274的方法,其中使用化合物在洗剂、凝胶、霜剂、软膏、油剂、溶液、混悬剂、乳剂或其他粘性组合物中进行所述施用。
- [1178] 276. 条款273至275中任一项的方法,其中使用凝胶进行所述施用。
- [1179] 277. 条款273至276中任一项的方法,其中向所述患者施用至少一种另外的活性成分。
- [1180] 278. 条款273至277中任一项的方法,其中所述患者为女性。
- [1181] 279. 条款273至278中任一项的方法,其中所述施用作为多剂量方案进行。
- [1182] 280. 条款279的方法,其中所述多剂量方案为长达约7天的时间段。
- [1183] 281. 条款279的方法,其中所述多剂量方案为长达约14天的时间段。
- [1184] 282. 条款279的方法,其中所述多剂量方案为长达约21天的时间段。
- [1185] 283. 条款273至282中任一项的方法,其中每天一次或多次进行施用。
- [1186] 284. 条款273至282中任一项的方法,其中每天一次进行施用。
- [1187] 285. 一种在有需要的患者中治疗脓疱病的方法,所述方法包括向患者施用有效量的根据条款160所述的化合物或其药学上可接受的盐。
- [1188] 286. 条款285的方法,其中所述施用为局部施用。
- [1189] 287. 条款285或286的方法,其中使用化合物在洗剂、凝胶、霜剂、软膏、油剂、溶液、混悬剂、乳剂或其他粘性组合物中进行所述施用。
- [1190] 288. 条款285至287中任一项的方法,其中使用凝胶进行所述施用。
- [1191] 289. 条款285至288中任一项的方法,其中向所述患者施用至少一种另外的活性成分。
- [1192] 290. 条款285至289中任一项的方法,其中所述患者为人。
- [1193] 291. 条款285至290中任一项的方法,其中所述施用作为多剂量方案进行。
- [1194] 292. 条款291的方法,其中所述多剂量方案为长达约2天的时间段。
- [1195] 293. 条款291的方法,其中所述多剂量方案为长达约3天的时间段。
- [1196] 294. 条款291的方法,其中所述多剂量方案为长达约4天的时间段。
- [1197] 295. 条款291的方法,其中所述多剂量方案为长达约5天的时间段。
- [1198] 296. 条款291的方法,其中所述多剂量方案为长达约6天的时间段。

- [1199] 297. 条款291的方法,其中所述多剂量方案为长达约7天的时间段。
- [1200] 298. 条款291的方法,其中所述多剂量方案为长达约14天的时间段。
- [1201] 299. 条款291的方法,其中所述多剂量方案为长达约21天的时间段。
- [1202] 300. 条款285至299中任一项的方法,其中每天一次或多次进行施用。
- [1203] 301. 条款285至299中任一项的方法,其中每天一次进行施用。
- [1204] 302. 条款285至299中任一项的方法,其中每天两次进行施用。
- [1205] 303. 一种试剂盒,其包含根据条款160所述的化合物或其药学上可接受的盐或根据条款171至184中任一项所述的药物组合物。
- [1206] 304. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗的用途。
- [1207] 305. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗糖尿病足溃疡感染的用途。
- [1208] 306. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗复杂泌尿道感染的用途。
- [1209] 307. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗囊性纤维化引起的肺部感染的用途。
- [1210] 308. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗呼吸机获得性肺炎的用途。
- [1211] 309. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗烧伤伤口的感染的用途。
- [1212] 310. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗外耳炎的用途。
- [1213] 311. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗细菌性阴道病的用途。
- [1214] 312. 根据条款160所述的化合物或其药学上可接受的盐,其用于治疗脓疱病的用途。
- [1215] 313. 根据条款160所述的化合物或其药学上可接受的盐在制备药物中的用途。
- [1216] 314. 一种用根据条款160所述的化合物或其药学上可接受的盐涂布导管的方法,所述方法包括在将导管插入患者中之前用化合物或其药学上可接受的盐涂布导管。
- [1217] 315. 一种组合物,其包含用根据条款160所述的化合物或其药学上可接受的盐涂布的导管。
- [1218] 实施例
- [1219] 下面描述与本公开有关的实施例。在大多数情况下,可以使用替代技术。实施例旨在阐明而非限制或约束如在权利要求中所阐述的本发明的范围。
- [1220] 实施例1
- [1221] 具有氨基取代的含氮杂环部分的式(II)化合物的一般合成方案
- [1222] 步骤-1. 氨基取代的含氮杂环的保护。



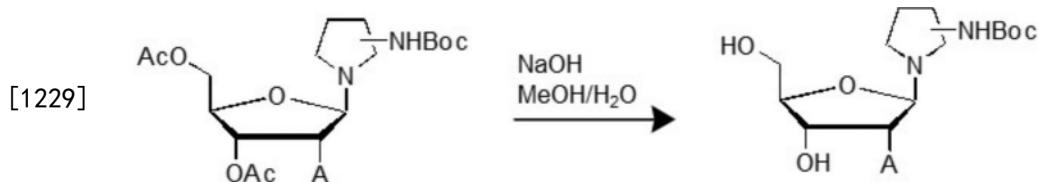
[1224] 在有机溶剂(如甲醇)中,在碱(如4-(二甲基氨基)吡啶(DMAP))的存在下,用二碳酸二叔丁酯($(BOC)_2O$)处理氨基取代的含氮杂环,以使环外胺氮Boc保护。

[1225] 步骤-2.核苷碱基糖基化



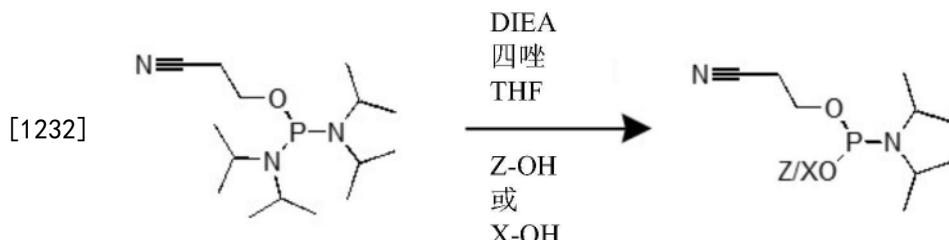
[1227] 在加热条件下,将步骤1中制备的Boc保护的氨基取代的含氮杂环与乙酰基保护的核糖/脱氧核糖衍生物偶联,所述衍生物在异头碳处为亲电的。

[1228] 步骤-3.乙酰基的脱保护



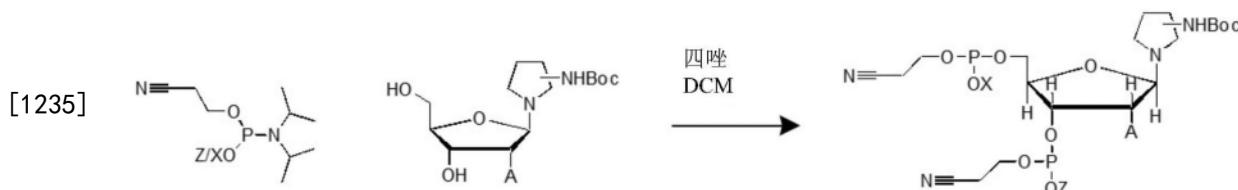
[1230] 将步骤2中制备的糖基化核苷碱基用NaOH、MeOH和H₂O处理,以使乙酰基保护基脱保护,并提供伯羟基和仲羟基。

[1231] 步骤-4.亚磷酰化(phosphitylating)试剂的制备



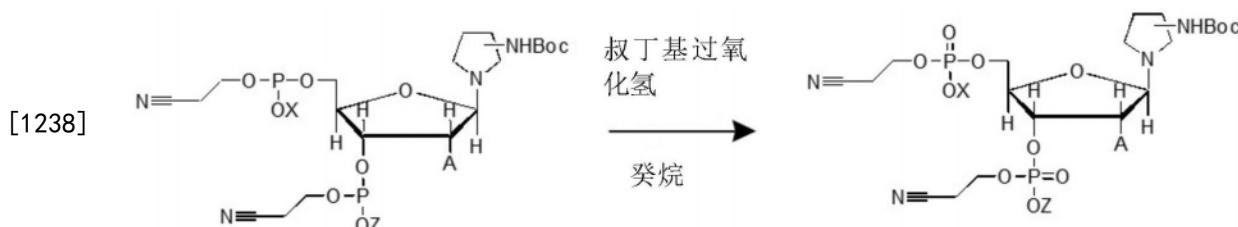
[1233] 步骤4可以作为步骤5的前体发生,并且是独立于步骤1-3的过程。在N,N-二异丙基乙胺(DIEA)的存在下,以四唑为催化剂,使醇与亚磷酰胺(phosphinamide)在THF中反应。

[1234] 步骤-5.亚磷酰化



[1236] 在二氯甲烷(DCM)中,以四唑为催化剂,用步骤4中制备的亚磷酰化试剂将步骤3中制备的Boc保护物种核苷碱基双亚磷酰化(bis-phosphinylate)。

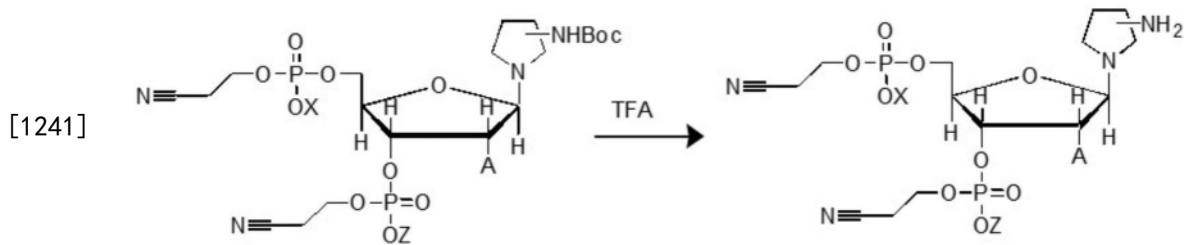
[1237] 步骤-6.氧化



[1239] 在梭烷的存在下,通过用叔丁基过氧化氢(TBTH)氧化步骤5中制备的双亚磷酰化

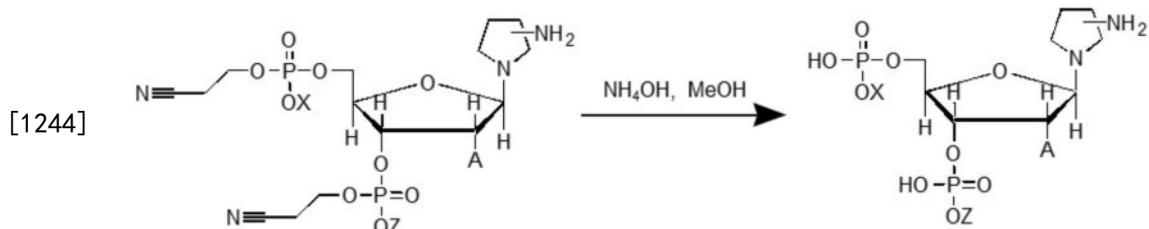
的化合物来生成双磷酸酯 (bis-phosphonate)。

[1240] 步骤-7. 氨基取代的含氮杂环的脱保护。



[1242] 在三氟乙酸 (TFA) 的存在下,在DCM中去除步骤6中制备的氨基取代的含氮杂环的Boc保护基。

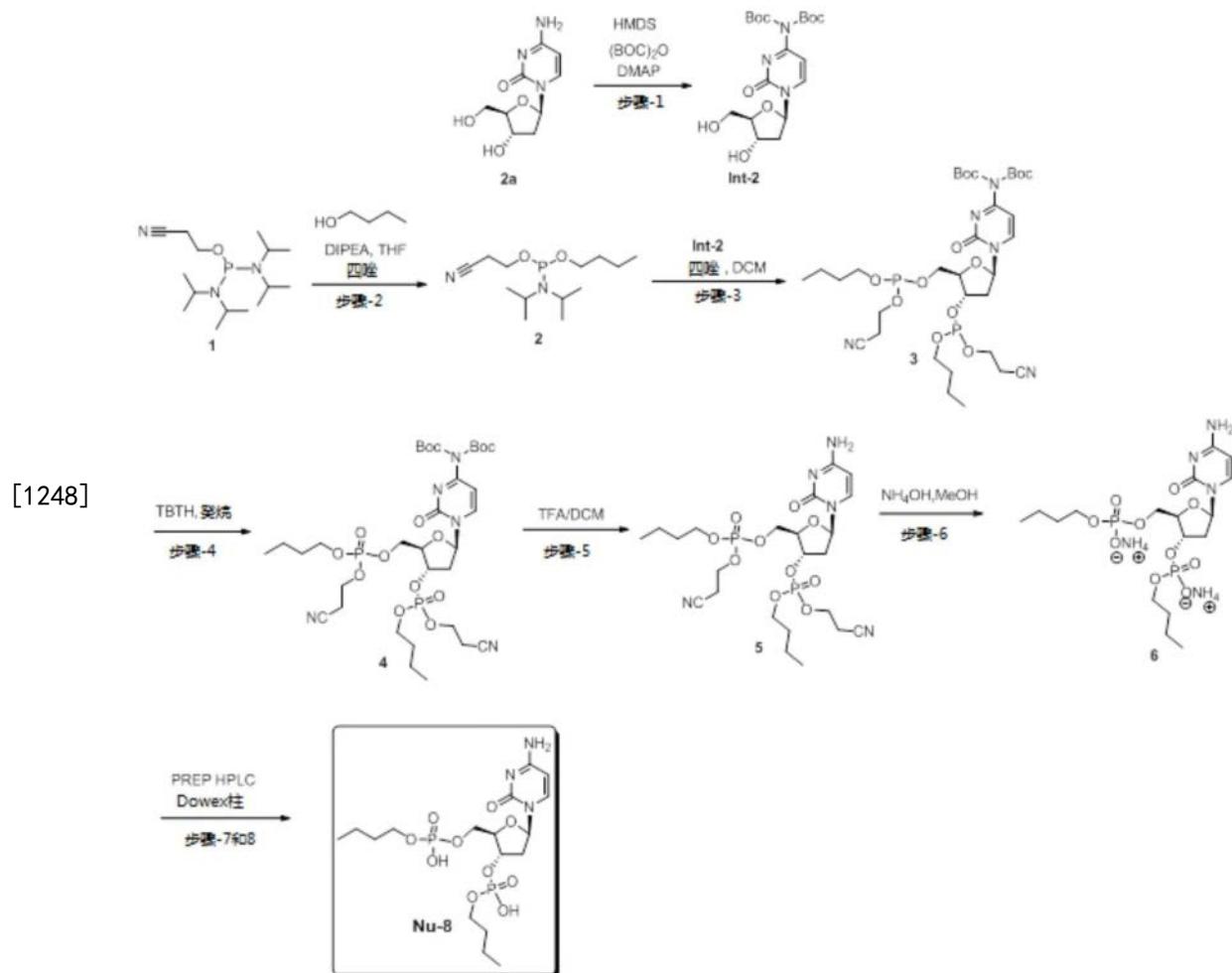
[1243] 步骤-8. 磷酸二酯的脱保护



[1245] 用甲醇氢氧化铵 (NH_4OH , MeOH) 水解步骤7中制备的磷酸二酯的 β -氰乙基保护基, 得到目标化合物。

[1246] 实施例2

[1247] Nu-8的合成



[1249] 步骤-1. 胺的保护(构建块(Building Block)关键中间体)

[1250] 将胞嘧啶2a加入到甲醇中的六甲基二硅氮烷(HMDS)、4-(二甲基氨基)吡啶(DMAP)、三甲基硅烷基三氟甲磺酸酯和二碳酸二叔丁酯((BOC)₂O)中,以通过生成BOC保护的化合物Int-2来保护2a的氮原子。

[1251] 步骤-2. 亚磷酰化试剂的制备(构建块关键中间体)

[1252] 在N,N-二异丙基乙胺(DIEA)的存在下,以四唑为催化剂,使正丁醇与亚磷酰胺1在THF中反应。将粗产物在中性氧化铝上进行色谱法,先后用己烷和己烷中2%的乙酸乙酯洗脱。(通过TLC)合并纯级分,并在真空下蒸发至残余物。

[1253] 步骤-3. 关键中间体的偶联

[1254] 在二氯甲烷(DCM)/二甲基甲酰胺(DMF)溶剂中,以四唑为催化剂,用试剂2将BOC保护的物种Int-2双亚磷酰化以生成3。将反应混合物浓缩至残余物,并将粗产物立即在下一步中氧化。

[1255] 步骤-4和5. 氧化和氨基脱保护

[1256] 在癸烷的存在下,将粗产物3用叔丁基过氧化氢(TBTH)氧化,以生成双磷酸酯物种4。在三氟乙酸(TFA)的存在下,在DCM中去除BOC基团以得到5。将粗产物在硅胶上进行色谱法,用乙酸乙酯洗脱。(通过TLC)合并纯级分,并在真空下蒸发至残余物。

[1257] 步骤-6. 磷酸二酯的脱保护

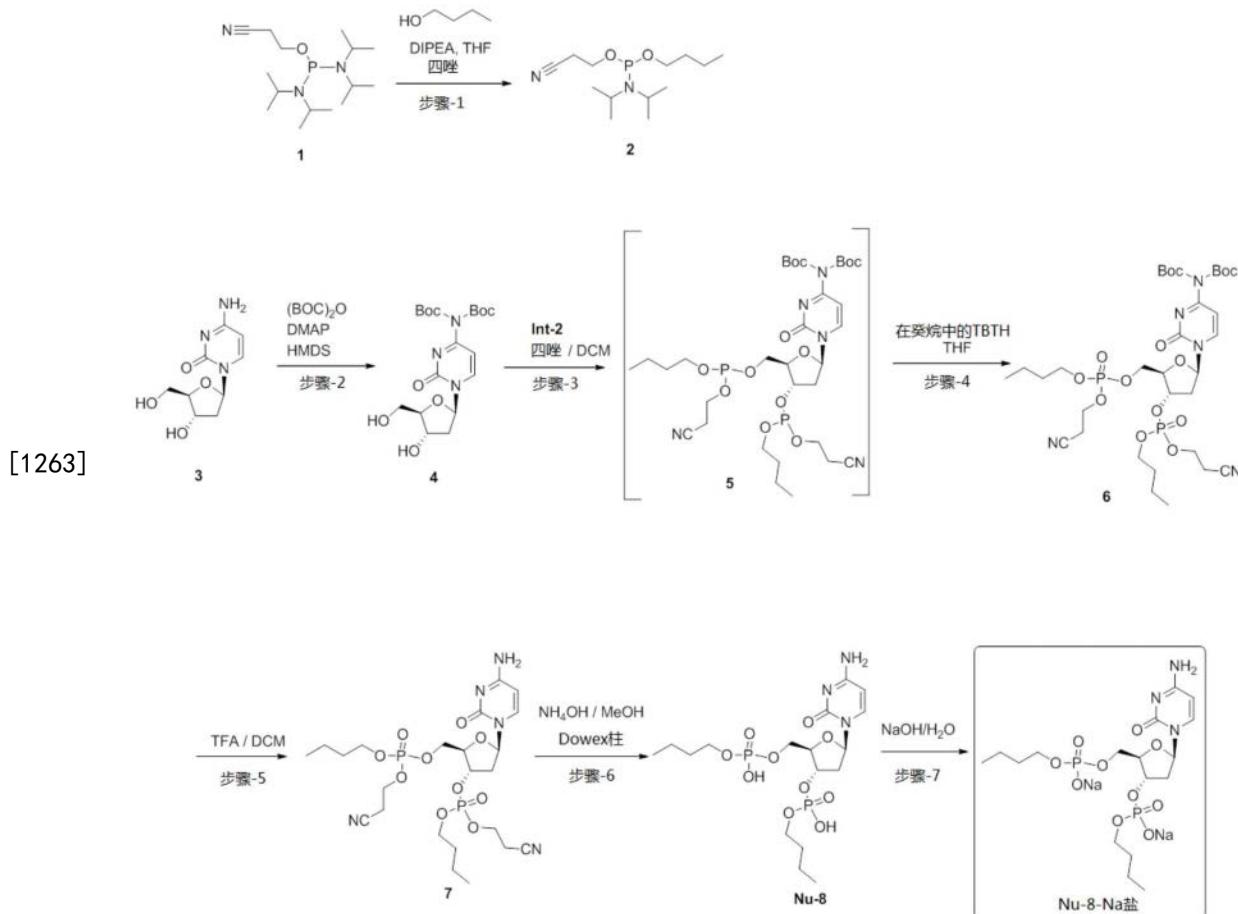
[1258] 用甲醇氢氧化铵(NH₄OH, MeOH)水解5得到粗的(I)铵盐(6)。

[1259] 步骤-7和8.纯化

[1260] 通过制备型HPLC纯化6,并用Dowex 50WX8-200树脂将其转化为游离酸。蒸发水性洗脱液得到(I),将其用纯化水稀释,以提供在其环境pH下的20%溶液。

[1261] 实施例3

[1262] Nu-8钠盐的合成



[1264] 化合物-2的合成

[1265] 向化合物-1(1.0kg,3.3222mol)在THF(6L)中的溶液中加入DIEA(1.370mL,8.3055mol)和四唑(230g,3.3222mol),然后在0℃滴加在THF(6L)中的正丁醇(275mL,2.99mol)持续12h。将反应混合物在室温搅拌24h。通过TLC监测反应进程,并在反应完成后将固体滤出。将滤液在40℃减压蒸发,以得到粗化合物。将粗化合物溶解在乙酸乙酯(5L)中。将有机层用水(3L)和盐水(2L)洗涤。有机层经无水Na₂SO₄干燥,过滤,并减压蒸发溶剂,以获得粗化合物。通过柱色谱法在碱性氧化铝(A1₂O₃)上纯化粗化合物,用在石油醚中的0-2%EtOAc洗脱化合物,得到作为浅黄色液体的化合物-2(700g,76.92%)。H-NMR(400MHz,氯仿-d)δ4.18-4.07(m,1H),4.02(q,J=6.6Hz,1H),3.93-3.74(m,4H),2.65(td,J=6.5,3.6Hz,2H),1.31-1.23(m,4H),1.18(dd,J=6.8,3.8Hz,12H),0.93(td,J=7.4,3.1Hz,3H).LC-MS:275(M+H)。

[1266] 化合物-4的合成

[1267] 向化合物-3(300g,1.321mol)在六甲基二硅氮烷(638g,3.964mol)中的溶液中加入DMAP(16.11g,0.132mol),然后在0℃加入TMSOTf(7.22g,0.039mol),将所得的反应混合

物在室温搅拌1h。在起始原料完成后,在0℃加入Boc-酸酐(1.4L,6.605mol)持续1h,并将反应混合物在室温搅拌16h。向反应物中加入甲醇(3L),然后在0℃加入三乙胺(1.5L)持续1h,并将反应混合物在室温搅拌20h。减压浓缩反应混合物以得到粗化合物。将粗化合物用乙酸乙酯(3L)稀释,并用水(1.0L)和盐水(1.0L)溶液洗涤;有机层经无水Na₂SO₄干燥,过滤,并在减压下蒸发溶剂,以得到粗化合物。通过柱色谱法硅胶(100-200目)纯化粗化合物,用在DCM中的0-3%MeOH洗脱化合物,得到作为灰白色固体的化合物-4(180g,31.89%)。H-NMR(300MHz,DMSO-d₆)δ88.41(d,J=7.5Hz,1H),6.84(d,J=7.5Hz,1H),6.06(t,J=6.2Hz,1H),5.28(d,J=4.3Hz,1H),5.07(q,J=4.6,4.0Hz,1H),4.21(q,J=4.1Hz,1H),3.87(q,J=3.7Hz,1H),3.71-3.49(m,2H),2.32(m,1H),2.03(dt,J=13.0,6.2Hz,1H),1.49(s,18H),LC-MS:275(M+H)。

[1268] 化合物-6的合成

[1269] 在0℃,向搅拌的化合物-4(180g,0.421mol)在THF(1.0L)中的溶液中加入DIEA(348mL,2.105mol)和四唑(176g,2.526mol)。在0℃,向所得的反应混合物中滴加化合物-2(519g,1.896mol)在THF(800mL)中的溶液持续1h。将反应混合物在室温搅拌16h。反应完成后,在0℃滴加在癸烷中的叔丁基过氧化氢(505mL,5M),并将反应混合物在室温搅拌6h。通过TLC监测反应。反应完成后,将反应混合物在40℃浓缩,用乙酸乙酯(3L)稀释,并用水(1L)和盐水(1L)溶液洗涤。有机层经无水Na₂SO₄干燥,过滤,并减压蒸发溶剂,得到粗化合物(350g粗产物)。通过柱色谱法在硅胶(100-200目)柱上纯化粗化合物,用在DCM中的0-5%MeOH洗脱。浓缩所有收集的纯级分,得到作为酒红色液体的纯化合物-6(220g,64.83%)。H-NMR(300MHz,DMSO-d₆)δ88.19(dd,J=7.6,1.3Hz,1H),6.88(d,J=7.5Hz,1H),6.13(t,J=10.5Hz,1H),4.99(s,1H),4.44(s,1H),4.26-3.96(m,10H),3.00-2.84(m,4H),2.57-2.79(m,2H),1.70-1.54(m,4H),1.50(s,18H),1.35(m,4H),0.88(qd,J=7.5,2.5Hz,6H);LC-MS:806(M+H)。

[1270] 化合物-7的合成

[1271] 在0℃,向化合物-6(220g,0.273mol)在DCM(4.4L)中的溶液中滴加TFA(210mL,2.732mol)。将反应混合物在室温搅拌24h。通过TLC监测反应。反应完成后,减压蒸发溶剂,得到粗化合物。通过柱色谱法硅胶(230-400目)纯化粗化合物。用在DCM中的0-10%MeOH洗脱化合物。将所有收集的纯级分浓缩,得到作为浅黄色液体的纯化合物-7(170g,84.67%)。H-NMR(300MHz,DMSO-d₆)δ7.61(d,J=7.5Hz,1H),7.27(d,J=13.9Hz,2H),6.19(t,J=6.9Hz,1H),5.74(d,J=7.4Hz,1H),4.96(s,1H),4.10-3.93(m,11H),2.93(q,J=6.2Hz,4H),2.29(d,J=13.1Hz,2H),1.61(h,J=7.1Hz,4H),1.35(p,J=7.3Hz,4H),0.89(dq,J=7.9,4.2Hz,6H);LC-MS:606(M+H)。

[1272] Nu-8的合成

[1273] 在0℃,向化合物-7(720g,1.1900mol)在MeOH(5.0L)中的搅拌溶液中加入氨水溶液(600mL)。将反应混合物在室温搅拌4h。通过TLC监测反应。反应完成后,减压蒸发MeOH,水层用DCM(1.5L)洗涤。使水层通过Dowex-H⁺树脂。减压去除水,得到作为灰白色固体的Nu-8(260g,43.84%)。H-NMR(300MHz,DMSO-d₆)δ88.94(s,1H),8.49(s,1H),7.97(d,J=7.8Hz,1H),6.08(t,J=6.1Hz,1H),5.95(d,J=7.7Hz,1H),4.76(q,J=5.8Hz,1H),4.15(q,J=4.1Hz,1H),4.08(s,1H),3.83(m,6H),2.43(t,J=5.6Hz,2H),1.67-1.44(m,4H),1.44-1.26

(m, 4H) , 0.95-0.82 (m, 6H) , LC-MS: 500.15 (M+H) 。

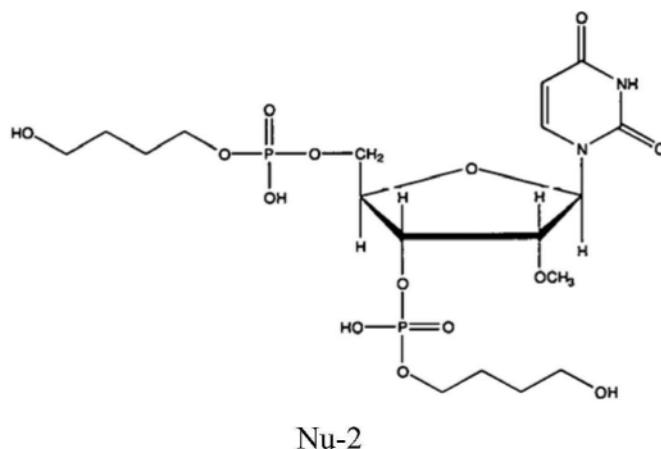
[1274] Nu-8钠盐的合成

[1275] 在0℃, 向化合物-Nu-8(260g, 0.478mol)在水(2.6L)中的搅拌溶液中滴加1N NaOH(950mL)。将反应混合物在室温搅拌2h。通过TLC监测反应。反应完成后, 水层用DCM(1.5L)洗涤。减压蒸发水层, 得到作为灰白色固体的Nu-8钠盐(265g, 93%)。H-NMR (300MHz, DMSO-d₆) δ 7.81 (d, J=7.2Hz, 1H) , 7.2 (bs, 1H) , 7.0 (bs, 1H) , 6.16 (t, J=4Hz, 1H) , 5.71 (d, J=7.6Hz, 1H) , 4.69 (bs, 1H) , 3.75 (m, 1H) , 3.71 (m, 1H) , 3.8 (m, 4H) , 2.2 (q, 1H) , 1.89-1.96-1.44 (m, 1H) , 1.49-1.39 (m, 4H) , 1.34-1.23 (m, 4H) , 0.88-0.84 (m, 6H) 。

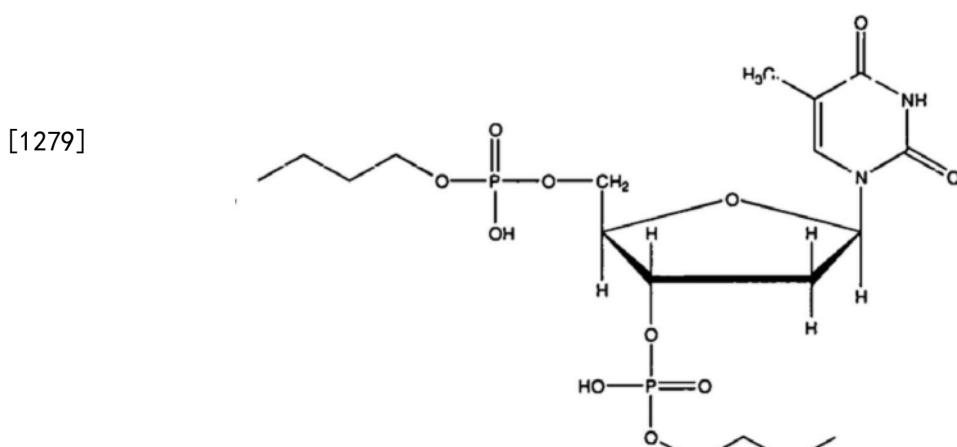
[1276] 实施例4

[1277] Bisphosphocin® 化合物Nu-2、Nu-4和Nu-5及式(I)化合物的比较物理性质研究

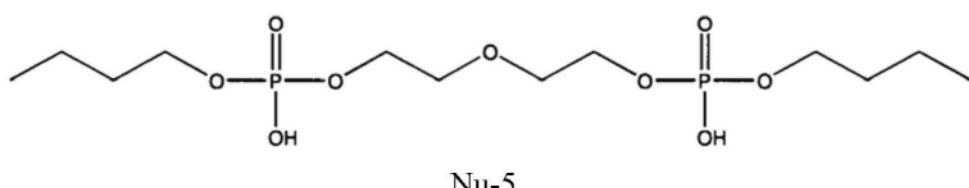
[1278] 已知的Bisphosphocin® 化合物Nu-2、Nu-4和Nu-5的结构如下所示:



Nu-2



Nu-4



Nu-5

[1280] 进行了pH研究, 以显示与 Bisphosphocin® 化合物Nu-2、Nu-4和Nu-5相比Nu-8的pH值。通过用23mL DI水稀释2mL的250mg/mL Nu-2溶液来制备20mg/mL Nu-2溶液。以相同的方式

式制备20mg/mL Nu-4和Nu-5溶液。在5mL容量瓶中称取401.65mg Nu-8，并用DI水稀释至一定体积。通过用15mL DI水稀释5mL的80.3mg/mL Nu-8溶液来制备20mg/mL Nu-8溶液。用经校准的pH计测量20mg/mL的Nu-2、Nu-4、Nu-5和Nu-8的pH值。结果示于表2。表2还显示了式(I)化合物和参比化合物Nu-2、Nu-4和Nu-5的其他物理性质的总结。

[1281] 表2

[1282]

	Nu-2	Nu-4	Nu-5	Nu-8
pH(2%溶液)	0.99	0.94	0.93	1.49
pKa	2.30	2.30	2.28	3.20
溶解度	-	-	-	137
Pow	0.0407	0.0592	0.0480	0.0662

[1283] 与参比化合物Nu-2、Nu-4和Nu-5相比，制备成2%水溶液的Nu-8提供最强碱性(pH最高)的溶液。不希望受任何特定理论的束缚，相信Nu-8结构中存在的游离环外氨基改变了Nu-8溶液的pH，从而导致与Bisphosphocins®Nu-2、Nu-4和Nu-5相比，Nu-8的作用更迅速，在更高的pH水平时更有效。

[1284] 此外，pKa测量显示，与Bisphosphocins®Nu-2、Nu-4和Nu-5相比，Nu-8具有最低的酸解离常数，其为分子解离成氢离子和相应的共轭碱的量度。不希望受任何特定理论的束缚，相信与参比Bisphosphocins®化合物Nu-2、Nu-4和Nu-5中存在的酸性质子的数目相比，Nu-8在其结构中不具有与氢离子一样多的能够解离到溶液中的酸性质子。参比Bisphosphocins®化合物具有酸性质子，如羟基质子和甲酯质子，其可以解离至溶液中。

[1285] 总之，与参比化合物Nu-2、Nu-4和Nu-5相比，制备成2%水溶液的Nu-8提供了最强碱性(pH最高)的溶液，并且在更高的pH水平时作用更迅速，更有效。

[1286] 实施例5

[1287] 在小鼠中用Nu-8治疗幽门螺杆菌(Helicobacter Pylori)

[1288] 动物

[1289] 本研究中使用的小鼠品系为C57/BL6, 5-6周龄，体重为18-22克。根据NIH指南，将小鼠每五只关在一个笼子里，自由进食和饮水。

[1290] 细菌株

[1291] 来自人临床分离株的幽门螺杆菌SS1 (CagA+, VacA+) 细菌株适合于小鼠模型，并已在该感染模型中验证。

[1292] 感染

[1293] 在感染前6天，将冷冻原液划线接种到一至两个哥伦比亚5%绵羊血琼脂板上，并将板在37°C进行微需氧孵育72小时。72小时后，将板生长物传代培养到五个哥伦比亚5%绵羊血琼脂板上，并像以前一样孵育。再孵育72小时后，将板去除，并将板生长物混悬在无菌0.9%盐水中，至530nm处的OD为1.5-2.0。该OD大约等于1.0e+09CFU/mL，其用于在全部3个感染日口服感染小鼠。为了感染小鼠，经由20-22G强饲法针头(gavage needle)向小鼠口服给予0.25mL的1.0e+09CFU/mL。仅在第一次感染前需要使小鼠禁食。

[1294] 处理

[1295] 在感染后1周，用Nu-8处理小鼠。以0.2mL/剂量口服施用多剂量抗生素治疗。每天

施用2次抗生素，并持续7天。对照组仅施用载体。

[1296] 采样

[1297] 在对动物实施安乐死之前18小时，从笼子中取出食物，并且每个笼子上都清楚地标明动物正在实验性禁食。将小鼠安乐死(CO_2 和颈椎脱位)。将小鼠安乐死后，通过将食道从胃的上方切除，并将十二指肠从幽门区域切除来将每个胃取出。将离体的胃放入无菌培养皿中，并用无菌1X PBS冲洗腔内容物。将每个经冲洗的胃放入含有2mL的1X PBS的14mL Falcon管中，并保存在冰上。将每个胃均质化，在1X PBS中10倍连续稀释，点样接种到Columbia琼脂(含有3.5%裂解马血土壤选择性抗生素补充剂)上，并在37°C进行微需氧孵育5天。然后，进行菌落计数。

[1298] 剂量反应

[1299] 以不同剂量(mg/kg)口服施用Nu-8，每天两次，持续7天。在给药前，确定用于处理的制剂、浓度和剂量体积。阳性对照组由三联疗法(奥美拉唑、阿莫西林和克拉霉素)组成。阴性对照使用无药物的给药溶液。给药计划示于表3。接种和处理计划示于表4。

[1300] 表3

组别	化合物	剂量	剂量浓度 体积	方案	#动物 ^a
1	Nu-8	0.2 mg	1 mg/mL, 0.2 mL	PO; bid x 7 天	16
2		1.0 mg	5 mg/mL, 0.2 mL		16
3		2.0 mg	10 mg/mL, 0.2 mL		16
4	PrevPac	31 mg/kg	31 mg/kg	bid x 7 天	16
5	载体	na	na	bid x 7 天	5
6	感染对照	na	na	bid x 7 天	20

[1302] ^a对于治疗和复发终点分别为8只动物

[1303] 表4

天数	程序
-11	感染
-10	
-9	感染
-8	
-7	感染
0	处理和对照采样
1	
2	
3	处理
4	
5	
6	
7	第 7 天采样
14	第 14 天采样

[1304] [1305] 结果

[1306] 在三天用6.16、6.6和6.37_{log10} CFU的接种物感染小鼠。最后一次感染后一周(第0天-开始处理)平均胃滴度为6.74_{log10} CFU。在之后的两周中,计数保持一致,其中未经处理的对照组在第7天和第14天的平均滴度分别为6.86和6.66_{log10} CFU(参见表5,其显示了用Nu-8和Prevpac处理后,小鼠中幽门螺杆菌SS1的平均细菌胃滴度)。对于1、5和10mg/mL的剂量溶液,Nu-8显示出剂量响应,其中在第7天细菌胃滴度分别为5.62、5.21和4.74_{log10} CFU,在第14天分别为6.2、5.67和5.81_{log10} CFU。Prevpac(例如,克拉霉素、奥美拉唑和阿莫西林)在第7天将细菌滴度降低至3.22_{log10} CFU,其在第14天反弹至6.19_{log10} CFU。尽管在第7天,Nu-8的处理不如三联疗法有效,但与Prevpac相比,Nu-8在第14天(最后一次施用剂量后7天)显示出更小的反弹,其中5和10mg/mL剂量组有更低的计数(参见表5)。总之,这些结果支持使用Nu-8作为幽门螺杆菌感染的长期治疗,对于其他革兰氏阴性细菌预期获得这种结果。

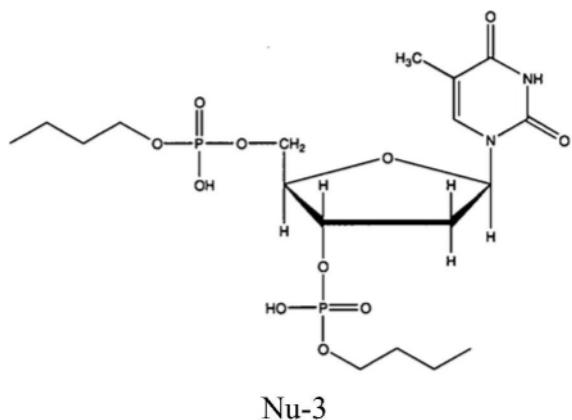
[1307] 表5

组别	测试	剂量	浓度剂量体积	方案	时间点	Log10	SD	
[1308]	Cp,[pim (I)]	1	0.2 mg	1 mg/mL, 0.2 mL	PO, bid 持续 7 天	+7 天	5.62	0.6
						+14 天	6.2	0.86
		2	1.0 mg	5 mg/mL, 0.2 mL	PO, bid 持续 7 天	+7 天	5.21	0.26
						+14 天	5.67	0.23
		3	2 mg	10 mg/mL, 0.2 mL	PO, bid 持续 7 天;	+7 天	4.74	0.68
						+14 天	5.81	0.74
	4	PREVPAC	31 mg/kg	31 mg/kg	PO, bid 持续 7 天	+7 天	3.22	0.52
						+14 天	6.19	0.69
	5	载体 处理的	na	na	PO, bid 持续 7 天	+7 天	6.59	0.12
	6	未处理的对 照	na	na	na	第 0 天	6.74	0.37
					na	+7 天	6.86	0.54
					na	+14 天	6.66	0.76

[1309] 实施例6

[1310] 与 Bisphosphocin® 化合物Nu-3、Nu-4和Nu-5相比,用于评估Nu-8的构效关系的细菌细胞学分析

[1311] 已知的Bisphosphocin® 化合物Nu-3的结构如下所示:



[1312]

[1313] 方法和材料

[1314] 该细菌细胞学分析 (BCP) 研究使用之前在Nonejuie, P., Burkart, M., Poglianoa, K., Pogiano, J. (2013) . Bacterial cytological profiling rapidly identifies the cellular pathways targeted by antibacterial molecules. Proc.Natl.Acad.Sci.U.S.A.110(40):16169-16174.doi:10.1073/pnas.1311066110中描述的方法和材料。

[1315] 将大肠杆菌(E.coli)ATCC 25922或铜绿假单胞菌(P.aeruginosa)K2732的野生型菌株在30°C在富介质(无缓冲2x溶原性液体培养基[LB])中生长至OD₆₀₀ ~ 0.4。然后将这些培养物分开,并在未缓冲或缓冲的LB中用适当浓度的Nu-8处理每个样品(终混合物OD₆₀₀ ~ 0.1)。将无Nu-8暴露的细胞用磷酸缓冲至pH 4。

[1316] 在缓冲至pH 4的LB介质中进行BCP。测量Nu-3、Nu-4、Nu-5和Nu-8对每种细菌株的最小抑制浓度(MIC)。如本领域普通技术人员所理解,最小抑制浓度为在孵育过夜后,抑制微生物的可见生长的抗微生物剂的最低浓度。用三种不同浓度(1、0.5和0.25x MIC)的Nu-3、Nu-4、Nu-5和Nu-8分别处理细胞,并在30min、2h和4h收集样品用于成像。在三个时间

点(治疗开始后5分钟、4h和24h)测定细胞活力。

[1317] 为了对大肠杆菌成像,将经处理的细胞用 $1\mu\text{g}/\text{mL}$ FM4-64、 $2\mu\text{g}/\text{mL}$ DAPI和 $0.5\mu\text{M}$ SYTOXGreen (Molecular Probes/Invitrogen) 染色。将铜绿假单胞菌样品用 $0.5\mu\text{M}$ SYTOX Green、 $28\mu\text{g}/\text{mL}$ DAPI和 $4.5\mu\text{g}/\text{mL}$ FM 4-64染色。如Poglano,J.,Osborne,N.,Sharp,M.D.,Abanes-De Mello,A.,Perez,A.,Sun,Y.-L.和Poglano,K. (1999),A vital stain for studying membrane dynamics in bacteria:a novel mechanism controlling septation during *Bacillus subtilis* sporulation.*Molecular Microbiology*,31: 1149-1159.doi:10.1046/j.1365-2958.1999.01255.x中所描述,将细胞转移到琼脂糖垫(20% LB, 1% 琼脂糖)中用于成像。

[1318] 结果

[1319] BCP结果表明,Nu-3、Nu-4、Nu-5和Nu-8中的每一个都影响大肠杆菌(ATCC25922)和铜绿假单胞菌(K2732)中的细胞包膜。用Nu-3、Nu-4、Nu-5和Nu-8的处理导致大肠杆菌(ATCC 25922)在较高的处理浓度(缓冲的pH 4)时的DNA缩合。Nu-4、Nu-5和Nu-8增加大肠杆菌(ATCC 25922)和铜绿假单胞菌(K2732)的细胞膜通透性(缓冲的pH 4或在未缓冲的LB中),而Nu-3、Nu-4和Nu-5导致大肠杆菌(ATCC 25922)的细胞壁变形(未缓冲的LB)。用Nu-8的处理快速且显著降低细胞活力,并且在作用上优于Nu-3、Nu-4和Nu-5。具体地,Nu-8在几分钟内将细胞活力由初始的 10^9 的CFU/mL降低至 $<10^2$ CFU/mL。在处理数小时内,Nu-3、Nu-4和Nu-5也以较慢的速度将CFU/mL降低至 $<10^{2-3}$ 。

[1320] 总之,这些结果支持使用Nu-8治疗感染(其中速效抗微生物机制是优选的)如,例如泌尿道感染和与糖尿病足溃疡相关的细菌感染等。

[1321] 实施例7

[1322] Bisphosphocin®化合物Nu-3和Nu-5和Nu-8在递增的pH值下对抗大肠杆菌和铜绿假单胞菌的抗微生物功效增加

[1323] 使用临床和实验室标准协会(Clinical and Laboratory Standards Institute, CLSI;3-7)建立的与每种生物体相关的液体培养基(Mueller HintonBroth)微稀释程序进行MIC测试。根据CLSI (3-7) 制备MIC板。为了制备测试板,使用自动液体处理机进行连续稀释和液体转移。在本研究中使用的自动液体处理机包括Multidrop384 (Labsystems, Helsinki,Finland) 和Biomek 2000(Beckman Coulter,Fullerton CA)。使用1M柠檬酸或1M NaOH缓冲液将溶液稀释至期望的pH。按照CLSI方法 (3、5-7) 制备每种测试生物的标准化接种物,使其在适当的介质中等于0.5McFarland标准,然后进行另外的1:20稀释(厌氧菌为1:10)。

[1324] 然后使用Biomek 2000,从低到高的药物浓度将 $10\mu\text{L}$ 稀释的0.5McFarland混悬液接种到平板上,最终浓度约为 5×10^5 CFU/mL每孔。孵育未接种的板,用于评估药物在测试介质中的溶解度。将板堆叠3至4层高,在顶部板上盖上无菌盖,并根据CLSI孵育18至24小时。MIC记录为各个化合物抑制生物体可见生长的最低浓度。

[1325] 如表6所示,在相同pH时,Nu-8对大肠杆菌和铜绿假单胞菌的MIC功效大于Bisphosphocin®化合物Nu-3和Nu-5。具体地,在pH范围(pH 3-4)中,Nu-8抗微生物活性优于Nu-3和Nu-5,所述pH范围被认为对于多种施用途径如,例如局部、吸入和膀胱内施用的临床使用是重要的。

[1326] 表6

	pH 1	pH 3	pH 4 (MIC) mg/mL	pH 5	pH 7
大肠杆菌					
Nu-3	12.5	>100	--	>100	>100
Nu-5	6.25	100	--	100	100
Nu-8	9.8	37.5	75	>75	>75
铜绿假单胞菌					
Nu-3	12.5	>100	--	>100	>100

[1327]	Nu-5	6.25	100	--	100	100
	Nu-8	9.38	18.75	37.5	75	>75

[1329] 实施例8

[1330] 在pH 4、5.5和7时,Nu-3相比于Nu-8对革兰氏阴性和革兰氏阳性细菌的细菌细胞学分析

[1331] 方法和材料

[1332] 该细菌细胞学分析(BCP)研究使用之前在Nonejuie,P., Burkart,M., Poglianoa, K., Pogiano,J. (2013) .Bacterial cytological profiling rapidly identifies the cellular pathways targeted by antibacterial molecules. Proc.Natl.Acad.Sci.U.S.A.110(40):16169-16174.doi:10.1073/pnas.1311066110中描述的方法和材料。

[1333] 对于活细胞计数,使细胞生长至OD₆₀₀≈0.4,并以1:1稀释至含有不同化合物浓度的缓冲或未缓冲介质中。然后收集样品,并在96孔板上连续稀释(1:10)。将来自每个孔的五微升点在LB板上,在30℃孵育,并在第二天计数活细胞。

[1334] 在暴露10、30、120和240min时收集样品,用于活细胞计数和成像。为了进行成像,将大肠杆菌和金黄色葡萄球菌(*S.aureus*)每个时间点的200μL经处理的细胞用0.8μg/mL FM4-64、1.5μg/mL DAPI和0.4μM SYTOXGreen(Molecular Probes/Invitrogen)染色。将铜绿假单胞菌样品用0.4μM SYTOX Green、28μg/mL DAPI和1μg/mL FM 4-64染色。将细胞转移到琼脂糖垫(20%LB,1%琼脂糖)中用于成像。

[1335] 对于Nu-3和Nu-8储备液(在pH 4、5.5和7时),储备液浓度为500mg/mL。对于pH 4,通过将Nu-3溶解在25mM柠檬酸盐缓冲液中并将Nu-8溶解在350mM柠檬酸中来制备储备液。对于pH 5.5,通过将Nu-3溶解于25mM柠檬酸盐-磷酸盐中并将Nu-8溶解于25mM柠檬酸盐中来制备储备液。对于pH 7,通过将Nu-3和Nu-8溶解于25mM Sorensen磷酸盐缓冲液中来制备储备液。用50mM柠檬酸盐缓冲液(对于pH 4)、50mM柠檬酸盐-磷酸盐缓冲液(对于pH 5.5)和50mM Sorensen磷酸盐缓冲液(对于pH 7)来制备2X LB(溶原性液体培养基)溶液。

[1336] 结果

[1337] 在pH 4或更高时进行的BCP程序的实验条件下,Nu-8对野生型大肠杆菌(ATCC 25922)、野生型铜绿假单胞菌(PA01;K2732)和甲氧西林敏感型金黄色葡萄球菌(ATCC 29213)比Nu-3(等摩尔浓度)更有效,其在一定范围的暴露时间、浓度和缓冲介质中迅速改变细胞活力、细胞生长和细胞通透性(Linnaeus Bioscience 10-2-2017Report)。未经处理的在pH 4、5.5和7时培养的大肠杆菌不受影响。相对于在中性pH值时测定的相似参数,大肠

杆菌的细胞生长、细胞活力和细胞通透性在长达24h的研究中保持一致。在pH 4时,在相似的浓度(112.5和225mg/mL)时,Nu-8比Nu-3更有效,其在10min的处理中显著降低细胞活力(细胞活力由 $\log 10^7$ CFU/mL降低至 $<\log 10^3$ CFU/mL),而在240min的处理期间,112.5mg/mL的Nu-3减慢了细胞生长,导致在24h时更低的细胞活力(细胞生长延迟长达240min,10⁷CFU/mL[仅pH 4,细胞生长在240min 10⁸CFU/mL]在24h内降至10^{4.5}CFU/mL),在225mg/mL的Nu-3在240min内降低细胞活力($<10^3$ CFU/mL)。在处理10分钟时,在检测到细胞通透性的明显变化之前出现了细胞活力。在pH 5.5和7时,Nu-8改变大肠杆菌的细胞通透性并降低细胞活力和生长,而Nu-3则无作用。

[1338] 仅在pH 4时,铜绿假单胞菌快速受到影响,其中细胞生长和活力降低,且细胞通透性增加至最大100% (在10至30min的处理内)。单独在pH 5.5和7时,细胞生长、细胞活力及细胞通透性均不受影响(相对于在中性pH时测定的相似参数)。在pH 4时,Nu-3和Nu-8与在pH 4时单独观察到的相比通常在作用上相加,并降低细胞活力。相对于浓度为两倍(112.5mg/mL)的Nu-3(其在120min内降低细胞活力($<10^3$ CFU/mL)),56.5mg/mL的Nu-8更有效地在30min内降低了细胞活力($<10^3$ CFU/mL)。112.5mg/mL的Nu-8在10min内降低细胞活力($<10^3$ CFU/mL),超过了类似的Nu-3处理以及单独的pH 4(在10min内~10⁶CFU/mL)。另外在pH 5.5和7时,相对于112.5mg/mL的Nu-3(其几乎没有改变细胞通透性($<6\%$)且对细胞生长没有作用),112.5mg/mL的Nu-8更有活性,引起细胞通透性增加 $<20\%$,且细胞生长减少。在pH 7时,只有Nu-8(225mg/mL)增加细胞通透性(在10min内~37%),这随后不再持久,并且细胞生长比在pH 7时略低。

[1339] 单独在pH 4时,金黄色葡萄球菌显示细胞生长和细胞活力降低,细胞通透性略有增加($<8\%$)。单独在pH 5.5时,细胞生长抑制长达240min,然后在24h后恢复,并且细胞通透性不受影响。在pH 7时,所有细胞参数均不受影响。在pH 4时,相比于在单独的pH 4时的细胞活力(在240min时~10⁷CFU/mL,且在24h时10⁴CFU/mL),125mg/mL的Nu-8稍微增加了细胞通透性($<4.3\%$),具有增强的杀伤活性(从研究开始时的10^{7.5}CFU/mL到240min时的10³CFU/mL,且在24h时 $<10^3$ CFU/mL)。125mg/mL的Nu-3产生低的细胞通透性($<10\%$),并且细胞生长略有下降,类似于在单独的pH 4时的情况。在250mg/mL时,Nu-8在10min内降低细胞活力(~10⁴CFU/mL)且后续没有恢复($<10^3$ CFU/mL),并增加细胞通透性(~60%)。250mg/mL的Nu-3活性较低,在240min至24h内轻微增加细胞通透性($<10\%$),降低细胞活力($<10^3$ CFU/mL)。在pH 5.5和7时,Nu-3和Nu-8(125mg/mL和250mg/mL)均轻微降低细胞生长长达24h,且对细胞通透性的作用最小($<5\%$)。

[1340] 总之,该研究表明,在计划用于临床使用的3-4的pH范围内,Nu-8的性能将优于Nu-3。

[1341] 实施例9

[1342] Nu-8对通常与细菌有关的菌株的抗微生物活性

[1343] 在该研究中评价的细菌株包括大肠杆菌(*Escherichia coli*)、克雷伯氏菌属物种(*Klebsiella* spp)、粘质沙雷氏菌(*Serratia marcescens*)、奇异变形杆菌(*Proteus mirabilis*)/普通变形杆菌(*Proteus vulgaris*)、柠檬酸杆菌属物种(*Citrobacter* spp)、普罗维登斯菌属物种(*Providencia* spp)、摩氏摩根菌(*Morganella morganii*)、铜绿假单胞菌(*Pseudomonas aeruginosa*)、金黄色葡萄球菌(*Staphylococcus aureus*) (仅MRSA) 和

粪肠球菌(*Enterococcus faecalis*)。用柠檬酸将Nu-8测试溶液调节到pH 3.5，并根据CLSI方法，在相应地补充以促进特定菌株生长的Mueller-Hinton液体培养基中评价MIC。

[1344] 在人类和小鼠的尿液中测量Nu-8在pH 3.5时的MIC，其相当于在相似条件下在Mueller Hinton液体培养基中的Nu-8的MIC。表7显示Nu-8对其中确定的细菌株的MIC。

[1345] 表7

测试生物体 (分离菌数量)	在 pH 3.5 时 Nu-8 MIC (mg/mL) (MIC ₅₀ 和 MIC ₉₀)
革兰氏阴性	
大肠杆菌 (5)	37.5
肺炎克雷伯氏菌 (<i>Klebsiella pneumoniae</i>) (5) (包括	37.5-75
粘质沙雷氏菌 (5)	37.5-75
奇异变形杆菌/普通变形杆菌 (5)	4.69-18.75
柠檬酸杆菌属物种 (5)	18.75-37.5
普罗维登斯菌属物种 (5)	9.38-37.5
摩氏摩根菌 (5)	18.75
流感嗜血杆菌 (<i>Haemophilus influenzae</i>) (5)	4.69-9.38
其他	
铜绿假单胞菌 (20)	9.38-18.75 (18.75 和 18.75)
革兰氏阳性	
金黄色葡萄球菌 (20) (MRSA)	9.38-37.5 (18.75 和 37.5)
粪肠球菌 (5) (VSE 和	4.69-18.75
肺炎链球菌 (<i>Streptococcus pneumoniae</i>) (PRSP)	9.38-18.75

[1347] 还使用溶原性液体培养基(LB)在pH 4作为生长介质来确定MIC。在这些条件下，Nu-8对大肠杆菌和铜绿假单胞菌具有活性，MIC分别为54和27mg/mL。

[1348] 总之，这些结果证明Nu-8对革兰氏阴性菌和革兰氏阳性菌有效，其被认为对于多种施用途径如，例如局部、吸入和膀胱内施用的临床使用是重要的。

[1349] 实施例10

[1350] Nu-8在BALB/c小鼠泌尿道感染模型中对大肠杆菌的初始功效评价

[1351] 使从Envigo订购的雌性BALB/c小鼠(20-22g)适应居住条件，并按照动物使用规约(Animal Use Protocol, AUP)编号TP-08进行处理。用自由获取的辐照的Teklad Global 2918啮齿动物饮食和水喂养动物。小鼠以6只/笼饲养在bioBubble®洁净室中的静止笼(具有辐照的1/8"Teklad corn cobbedding 7902)中，所述洁净室以每小时100次完全换气的方式将H.E.P.A过滤后的空气送入气泡环境。环境被控制在74°±4°F的温度范围和30-70%的湿度范围内。本实验中进行的所有程序均遵守美国国立卫生研究院(National Institutes of Health)的法律、法规和指南，并获得TransPharm临床前解决方案动物护理和使用委员会(TransPharm Preclinical Solutions Animal Care and Use Committee)的批准。

[1352] 大肠杆菌的临床分离株(菌株CFT073, TPPS 1041)购自密歇根大学。

[1353] 使生物体在补充有5%绵羊血细胞的胰酶解酪蛋白(trypticase)大豆琼脂板上，在环境气氛中在37°C生长过夜。无菌擦拭培养物，并将其转移至胰酶解酪蛋白大豆液体培养基管中。在600nm处确定光密度。稀释培养物，以提供30µL体积的约7.5log₁₀ CFU每只小鼠的接种物。细菌挑战的滴注构成研究的0小时时间。在接种前通过光密度估算接种物计数，并在接种后通过稀释和倒计数确认。

[1354] 在细菌挑战前一小时,将水从动物笼中移出。在第0天的0小时,使用异氟烷麻醉小鼠,并通过用拇指向腹部施加适度的压力使尿液从膀胱中排出。经由经泌尿道注射30 μ L的体积使小鼠感染细菌。挑战后,将水立即放回笼中。在BL2外科手术套件中进行挑战。挑战接种物的最终计数显示递送的负荷 (delivered burden) 为7.81log₁₀个生物每只小鼠。

[1355] 每次给药前即刻制备Nu-8(测试物)。将Nu-8溶解在无菌盐水中,并用磷酸调节至pH 3.5。在挑战后23小时,将水从动物笼中移出。一小时后,使用异氟烷麻醉小鼠,并从膀胱中排出残留尿液。根据表8(显示动物挑战和处理计划(Animal Challenge and Treatment Schedule)),以30 μ L的体积经由经泌尿道给药用测试物或对照物处理小鼠。收获时间为处理小鼠器官的时间。所有处理均在BSL2外科手术套件中进行。在处理施用后,立即使用氰基丙烯酸酯薄纸堵住泌尿道开口。

[1356] 表8

Grp	N	挑战		处理			收获时间 ^a
		大肠杆菌	ROA	描述	ROA	剂量 (mg/kg)	
[1357]	6	7.5 log ₁₀	经泌尿道	盐水pH 3.5	经泌尿道	NA	60 min
				庆大霉素		50	60 min
				Nu-8 pH 3.5		1025	20 min
				Nu-8 pH 3.5		1025	60 min

[1358] ^a相对于在0小时的挑战

[1359] 用于评估感染进展的主要终点为每克膀胱组织的平均细菌负荷。在处理施用和泌尿道闭塞后60或20分钟,通过CO₂窒息使小鼠安乐死。无菌取出膀胱,称重,然后使用微珠搅拌器在1mL TSB中均质化。将所得的均质液连续稀释(至10⁻⁷),并在补充有5%绵羊血细胞的胰酶解酪蛋白大豆琼脂板上,在环境气氛中在°C生长过夜。计算菌落形成单位(CFU),并计算每克膀胱组织均质液的总细菌负荷。

[1360] 使用Microsoft Excel计算几何平均CFU以及平均标准误差(SEM),并使用GraphPad Prism v.7.0为数据作条形图。假设方差不相等,使用Student's t检验,通过在Excel中比较不同处理组的几何平均细菌负荷,来进行组间统计比较。双尾P值≤0.05被认为显著的。

[1361] 在处理后60分钟时,组1中载体处理的小鼠显示5.31log₁₀的平均膀胱CFU负荷,而组2中庆大霉素处理的动物显示6.11log₁₀ CFU。在处理后20分钟,与载体处理的对照组相比,用Nu-8处理的小鼠显示显著降低的平均膀胱CFU负荷(2.91log₁₀)。在60分钟时,这些小鼠显示3.71log₁₀ CFU的负荷。

[1362] 总之,Nu-8显示在处理后20分钟动物膀胱中的大肠杆菌在统计学上显著减少,这证明Nu-8在泌尿道感染动物模型中有效对抗大肠杆菌。这些结果是用于人类疗法的预测模型。

[1363] 实施例11

[1364] Nu-8在BALB/c小鼠泌尿道感染模型中对大肠杆菌的确证功效评价

[1365] 使从Envigo订购的雌性BALB/c小鼠(20-22g)适应居住条件,并按照动物使用规约(AUP)编号TP-08进行处理。用自由获取的辐照的Teklad Global 2918啮齿动物饮食和水喂养动物。小鼠以6只/笼饲养在bioBubble®洁净室中的静止笼(具有辐照的1/8"Teklad

corn cobbedding 7902) 中,所述洁净室以每小时100次完全换气的方式将H.E.P.A过滤后的空气送入气泡环境。环境被控制在 $74^{\circ}\pm 4^{\circ}\text{F}$ 的温度范围和30-70%的湿度范围内。本实验中进行的所有程序均遵守美国国立卫生研究院的法律、法规和指南,并获得TransPharm临床前解决方案动物护理和使用委员会的批准。

[1366] 大肠杆菌的临床分离株(菌株CFT073, TPPS 1041)购自密歇根大学。

[1367] 使生物体在补充有5%绵羊血细胞的胰酶解酪蛋白大豆琼脂板上,在环境气氛中在 37°C 生长过夜。无菌擦拭培养物,并将其转移至胰酶解酪蛋白大豆液体培养基管中。在600nm处确定光密度。稀释培养物,以提供 $30\mu\text{L}$ 体积的约 $7.5\log_{10}$ CFU每只小鼠的接种物。细菌挑战的滴注构成研究的0小时时间。在接种前通过光密度估算接种物计数,并在接种后通过稀释和倒计数确认。

[1368] 在细菌刺激前一小时,将水从动物笼中移出。在第0天的0小时,使用异氟烷麻醉小鼠,并通过用拇指向腹部施加适度的压力使尿液从膀胱中排出。经由经泌尿道注射 $30\mu\text{L}$ 的体积使小鼠感染细菌。挑战后,将水立即放回笼中。在BL2外科手术套件中进行刺激。挑战接种物的最终计数显示递送的负荷为 $7.8\log_{10}$ 个生物每只小鼠。

[1369] 每次给药前即刻制备Nu-8(测试物)。将Nu-8溶解在无菌盐水中,并用磷酸调节至pH 3.5。在挑战后23小时,将水从动物笼中移出。一小时后,使用异氟烷麻醉小鼠,并从膀胱中排出残留尿液。根据表9(显示动物刺激和处理计划),以 $30\mu\text{L}$ 的体积经由经泌尿道给药用测试物或对照物处理小鼠。所有处理均在BSL2外科手术套件中进行。

[1370] 在处理施用后,立即使用Locktite凝胶超级胶封闭泌尿道开口。将一滴胶水放在泌尿道开口处,并使用组织钳将开口夹住5-10秒钟,以确保将泌尿道开口封闭且粘合剂干燥。泌尿道闭塞后,动物仍处于麻醉状态。在麻醉下每5分钟旋转一次小鼠(从前面到背面)。

[1371] 表9

Grp	N	刺激		处理			收获时间 ^a
		大肠杆菌	ROA	描述	ROA	剂量(mg/kg)	
[1372]	6	7.5 \log_{10}	经泌尿道	PBS pH 3.5	经泌尿道	NA	20 min
				Nu-8 pH 3.5		205	20 min
				Nu-8 pH 3.5		410	24 hr
				Nu-8 pH 3.5		820	20 min
				Nu-8 pH 3.5		820	10 min
							20 min

[1373] ^a相对于在0小时的刺激

[1374] 用于评估感染进展的主要终点为每克膀胱组织的平均细菌负荷。在处理施用和泌尿道闭塞后10或20分钟,通过CO₂窒息使小鼠安乐死。剖开腹腔以暴露膀胱,并将尿道在膀胱附近夹住以防止尿液泄漏。注意在通过切开灯远端的尿道来取出膀胱时,切勿从膀胱排出尿液。无菌取出膀胱(含尿液),并转移至装有1mL TSB的预先称重的小瓶中。然后切开膀胱以将尿液与组织一起释放到小瓶中。称量组织,并使用微珠搅拌器均质化。将所得的均质液连续稀释(至 10^{-7}),置于 $5\mu\text{L}$ 双份点(duplicate spots)中,并在补充有5%绵羊血细胞的胰酶解酪蛋白大豆琼脂板上,在环境气氛中在 37°C 生长过夜。对于每个样品,未稀释的(纯净的)均质液也置于 $100\mu\text{L}$ 的体积中。计算菌落形成单位(CFU),并计算每克膀胱组织均质液的总细菌负荷。

[1375] 使用Microsoft Excel计算几何平均CFU以及平均标准误差(SEM),并使用

GraphPad Prism v.7.0为数据作条形图。假设方差不相等,使用Student's t检验,通过在Excel中比较不同处理组的几何平均细菌负荷,来进行组间统计比较。双尾P值≤0.05被认为是显著的。

[1376] 在处理后10分钟,用820mg/kg Nu-8处理的动物显示6.31log10的平均膀胱CFU负荷。

[1377] 在处理后20分钟,组1中载体处理的小鼠显示6.81log10 CFU/g组织的平均值。接受205、410和820mg/kg的Nu-8的小鼠分别显示6.5、5.0和5.41log10的细菌负荷。

[1378] 总之,Nu-8显示在处理后20分钟动物膀胱中的大肠杆菌减少,这证明Nu-8在泌尿道感染动物模型中有效对抗大肠杆菌。这些结果是用于人类疗法的预测模型。

[1379] 实施例12

[1380] 用经泌尿道处理通过大肠杆菌诱导的大鼠泌尿道感染(UTI)模型

[1381] 使雌性Sprague-Dawley大鼠(n=6只/组)在泌尿道内感染预定接种量的大肠杆菌。在感染后的指定时间(取决于体内生长曲线),将动物麻醉(氯胺酮/甲苯噻嗪),并经泌尿道施用中性盐水(第1组),经磷酸调节的pH 3.5的盐水(第2组),103和207mg/kg的pH 3.5的测试化合物Nu-8(分别为第3组和第4组)。当调节pH时,监测所添加的磷酸的体积,并随后确定pH调节的剂量溶液的终浓度。目的是使pH调节后的终浓度在期望剂量的10%以内,以便报告pH调节后的终浓度。施用体积为300μL。表10(动物挑战和处理计划)总结了研究组。

[1382] 表10

[1383]	组编号	N	接种量 CFU/300 L/大鼠 (大肠杆菌ATCC25922)		第二次感染后处理4小时 (300 μL 经泌尿道)	终端程序 (直接从膀胱 采集尿液)
			第一次感染	第二次感染		
[1383]	1	10	1x10 ⁸	1x10 ⁸	对照盐水, 中性pH	处理后60分钟
	2	10			对照盐水pH 3.5	
	3	10			Nu-8 pH 3.5; 103 mg/kg	
	4	10			Nu-8 pH 3.5; 207 mg/kg	

[1384] 在每次感染前两个小时,剥夺动物饮水。在氯胺酮和甲苯噻嗪轻度麻醉下,通过经泌尿道施用300μL细菌混悬液使每只动物感染两次,间隔24小时。在感染前,通过指压将尿液排空,将套管经由尿道轻轻插入膀胱,并将300μL细菌混悬液注入膀胱。在感染后,轻轻拔出套管,将动物倒置放置1min,然后放入笼中。

[1385] 处理后60分钟,通过在K2EDTA抗凝剂下放血(在氯胺酮/甲苯噻嗪麻醉下)将所有组的动物处死,并在无菌条件下采集尿液用于CFU测定。

[1386] 在60min,对于盐水的pH 3.5溶液、103mg/kg和207mg/kg的Nu-8剂量,每组膀胱组织(组织加尿液)的每mL平均CFU log10分别为5.67、5.53和4.60Log10CFUs/mL膀胱组织。pH 7的盐水对照的Log 10CFUs/mL膀胱组织为5.51。与盐水pH3.5对照组相比,在用207mg/kg BW的剂量的Nu-8处理的组中,观察到CFU计数的统计学显著降低。用Nu-8处理的组和盐水pH 7对照组之间的CFU计数没有统计学显著的差异。

[1387] 总之,该大鼠研究证实了实施例10和11中所示的小鼠研究,所有这些研究均表明,Nu-8在处理后20分钟显示出动物膀胱中大肠杆菌的统计学显著降低。该研究的结果再次证

实,Nu-8在泌尿道感染动物模型中对大肠杆菌有效。这些结果是用于人类疗法的预测模型。

[1388] 实施例13

[1389] 具有复杂泌尿道感染的人类患者的Nu-8治疗

[1390] 人类患者被确定为具有复杂泌尿道感染。将含有有效量Nu-8的液体溶液形式的药物组合物经由导管膀胱内施用至患者。监测患者直到症状减轻或缓解,并且如果确定这种施用对于治疗是必要的或有帮助的,则可以将药物组合物另外施用一次或多次。

[1391] 实施例14

[1392] 具有囊性纤维化引起的肺部感染的人类患者的Nu-8治疗

[1393] 人类患者被确定为具有囊性纤维化引起的肺部感染。将含有有效量Nu-8的液体溶液形式的药物组合物经由喷雾器吸入施用至患者。监测患者直到症状减轻或缓解,并且如果确定这种施用对于治疗是必要的或有帮助的,则可以将药物组合物另外施用一次或多次。

[1394] 实施例15

[1395] 具有糖尿病足溃疡感染的人类患者的Nu-8治疗

[1396] 人类患者被确定为具有糖尿病足溃疡。将含有有效量Nu-8的凝胶形式的药物组合物局部施用至患者的糖尿病足溃疡处。监测患者直到症状减轻或缓解,并且如果确定这种施用对于治疗是必要的或有帮助的,则可以将药物组合物另外施用一次或多次。

[1397] 实施例16

[1398] 具有呼吸机获得性肺炎的人类患者的Nu-8治疗

[1399] 人类患者被确定为具有呼吸机获得性肺炎。将含有有效量Nu-8的液体溶液形式的药物组合物经由喷雾器吸入施用至患者。监测患者直到症状减轻或缓解,并且如果确定这种施用对于治疗是必要的或有帮助的,则可以将药物组合物另外施用一次或多次。

[1400] 实施例17

[1401] 具有烧伤伤口的感染的人类患者的Nu-8治疗

[1402] 人类患者被确定为具有烧伤伤口的感染。将含有有效量Nu-8的凝胶形式的药物组合物局部施用至患者的烧伤伤口处。监测患者直到症状减轻或缓解,并且如果确定这种施用对于治疗是必要的或有帮助的,则可以将药物组合物另外施用一次或多次。

[1403] 实施例18

[1404] 具有脓疱病的人类患者的Nu-8治疗

[1405] 人类患者被确定为具有脓疱病。将含有有效量Nu-8的凝胶形式的药物组合物局部施用至患者的水疱、脓疱和/或黄色结壳处。监测患者直到症状减轻或缓解,并且如果确定这种施用对于治疗是必要的或有帮助的,则可以将药物组合物另外施用一次或多次。

[1406] 实施例19

[1407] 具有外耳炎的人类患者的Nu-8治疗

[1408] 人类患者被确定为具有外耳炎。将含有有效量Nu-8的液体溶液形式的药物组合物直接局部施用至患者的外耳道中。监测患者直到症状减轻或缓解,并且如果确定这种施用对于治疗是必要的或有帮助的,则可以将药物组合物另外施用一次或多次。

[1409] 实施例20

[1410] 具有细菌性阴道病的女性患者的Nu-8治疗

[1411] 女性患者被确定为具有细菌性阴道病。将含有有效量Nu-8的凝胶形式的药物组合物局部施用至患者的阴道上或阴道内。监测患者直到症状减轻或缓解，并且如果确定这种施用对于治疗是必要的或有帮助的，则可以将药物组合物另外施用一次或多次。

[1412] 尽管以上已经公开了实施方案，但是本发明并不限于所公开的实施方案。相反，本申请旨在涵盖使用其一般原理的本发明的任何变型、使用或改进。此外，本申请旨在涵盖与本公开相背离的，落入本发明所属领域的已知或惯用实践之内，且落入所附权利要求书的范围之内的那些。