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A61K31/4427 (2006.01) *A61P3/10 (2006.01)*
A61P25/00 (2006.01)

(30)優先權：2009/06/25 美國 61/220,480
2010/01/07 美國 61/293,087
2010/01/07 美國 61/293,133

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申請專利範圍項數：31 項 圖式數：10 共 260 頁

(54)名稱

ＮＨ－酸性化合物之前驅藥

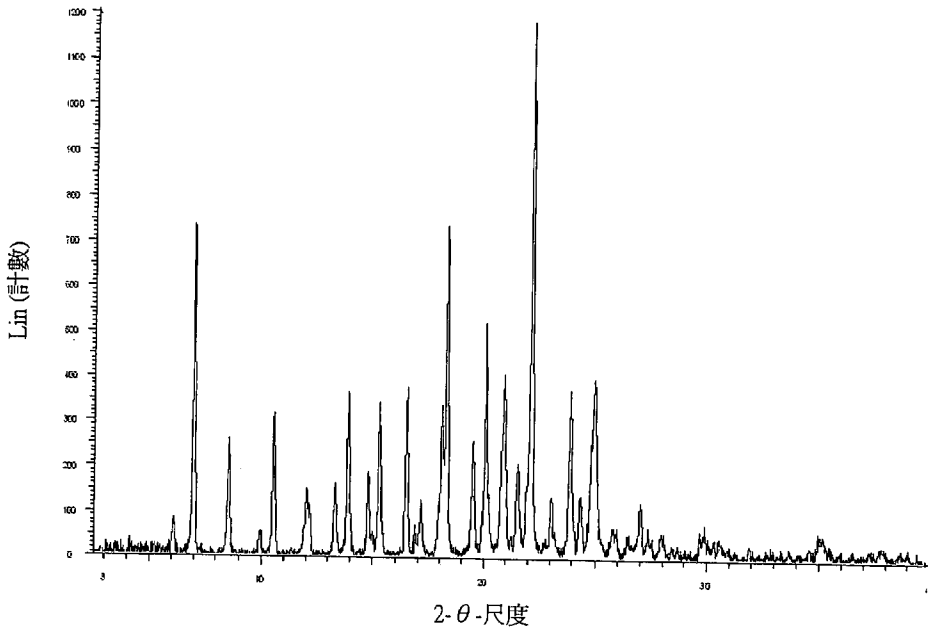
PRODRUGS OF NH-ACIDIC COMPOUNDS

(57)摘要

本發明提供一種藉由投藥給一病患一有效量的本發明的一前驅藥化合物來持續輸送一含有內醯胺、醯亞胺、醯胺、磺醯胺、胺甲酸酯或尿素的母體藥之方法，其中在投藥給該病患上，來自該前驅藥的該母體藥的釋放是持續的釋放。適合於使用在本發明的方法中的前驅藥化合物是經由羰基連結的前驅藥部分所衍生的母體藥的不穩定綴合物。本發明的前驅藥化合物可被用於治療該含有內醯胺、醯亞胺、醯胺、磺醯胺、胺甲酸酯或尿素的母體藥作為一治療是有用的任何病況。

The invention provides a method of sustained delivery of a lactam, imide, amide, sulfonamide, carbamate or urea containing parent drug by administering to a patient an effective amount of a prodrug compound of the invention wherein upon administration to the patient, release of the parent drug from the prodrug is sustained release. Prodrug compounds suitable for use in the methods of the invention are labile conjugates of parent drugs that are derivatized through carbonyl linked prodrug moieties. The prodrug

compounds of the invention can be used to treat any condition for which the lactam, imide, amide, sulfonamide, carbamate or urea containing parent drug is useful as a treatment.



第 1 圖

I483935

公告本

發明專利說明書

（本說明書格式、順序，請勿任意更動，※記號部分請勿填寫）

※申請案號：99120800

※申請日：99.6.25　　※IPC 分類：

C07D 401/12 (2006.01)
C07D 401/14 (2006.01)
C07D 471/04 (2006.01)
C07D 417/12 (2006.01)
A61K 31/496 (2006.01)
A61K 31/506 (2006.01)
A61K 31/4427 (2006.01)
A61P 3/10 (2006.01)
A61P 25/00 (2006.01)

一、發明名稱：（中文/英文）

NH-酸性化合物之前驅藥
PRODRUGS OF NH-ACIDIC COMPOUNDS

二、中文發明摘要：

本發明提供一種藉由投藥給一病患一有效量的本發明的一前驅藥化合物來持續輸送一含有內醯胺、醯亞胺、醯胺、磺醯胺、胺甲酸酯或尿素的母體藥之方法，其中在投藥給該病患上，來自該前驅藥的該母體藥的釋放是持續的釋放。適合於使用在本發明的方法中的前驅藥化合物是經由羰基連結的前驅藥部分所衍生的母體藥的不穩定綴合物。本發明的前驅藥化合物可被用於治療該含有內醯胺、醯亞胺、醯胺、磺醯胺、胺甲酸酯或尿素的母體藥作為一治療是有用的任何病況。

三、英文發明摘要：

The invention provides a method of sustained delivery of a lactam, imide, amide, sulfonamide, carbamate or urea containing parent drug by administering to a patient an effective amount of a prodrug compound of the invention wherein upon administration to the patient, release of the parent drug from the prodrug is sustained release. Prodrug compounds suitable for use in the methods of the invention are labile conjugates of parent drugs that are derivatized through carbonyl linked prodrug moieties. The prodrug compounds of the invention can be used to treat any condition for which the lactam, imide, amide, sulfonamide, carbamate or urea containing parent drug is useful as a treatment.

四、指定代表圖：

(一)本案指定代表圖為：第（ 1 ）圖。

(二)本代表圖之元件符號簡單說明：(無)

五、本案若有化學式時，請揭示最能顯示發明特徵的化學式：

六、發明說明：

【發明所屬之技術領域】

相關申請案

本件申請案主張於2009年6月25日提申的美國臨時申請案第61/220,480號；2010年1月7日提申的美國臨時申請案第61/293,087號；以及2010年1月7日提申的美國臨時申請案第61/293,133號的優先權之優勢。上面申請案(們)的全部教示在此被併入本案以作為參考資料。

發明領域

本發明是有關於含有內醯胺(lactam)、醯胺(amide)、醯亞胺(imide)、磺醯胺(sulfonamide)、胺甲酸酯(carbamate)、尿素(urea)、苯甲醯胺(benzamide)以及醯基苯胺(acylaniline)的藥效團(pharmacophores)的前驅藥(prodrugs)。

【先前技術】

發明背景

藥物輸送系統(drug delivery systems)對於一生物活性劑(biologically active agent)的安全以及有效的投藥時常是緊要的。或許當病患順從性(patient compliance)以及一致性的給藥被納入考量時，這些系統的重要性最被瞭解。例如，減少關於一藥物的給藥需求由1天4次至每天單一劑量(dose)就確保病患順從性以及最佳化治療而言會具有顯著的價值。

最佳化一藥物的生物可利用性(bioavailability)具有許多潛在的益處。關於病患便利性以及被增強的順從性，一

般而言被認可的是：較少頻率的給藥是所欲的。藉由延長藥物被釋放經過的期間，每劑量作用的一較長的持續期間被預期。這將接而導致給藥參數(dosing parameter)的一全面的改善，諸如一天服藥物一次(其中先前已需要每天4個劑量)或者一週給藥一次或甚至更低的頻率(當每天給藥是先前所需要的)。許多藥物目前被給藥每天一次，但不是所有這些藥物具有適合於精確地24小時的給藥間隔(dosing intervals)的藥物動力學性質(pharmacokinetic properties)。延長這些藥物被釋放經過的期間亦將是有益的。

在藥物治療的基本考量之一者涉及在血液位準(blood levels)與治療活性之間的相關性。關於大部分的藥物，首要重要的是：血清位準維持在一最小有效濃度(minimally effective concentration)與一可能毒性位準(potentially toxic level)之間。就藥物動力學而言，一藥物的血液位準的波峰(peaks)以及波谷(troughs)正好理想地符合在血清濃度的治療窗期(therapeutic window)內。關於特定的治療試劑，這個窗期是非常狹以至於劑量配方(dosage formulation)變得緊要。

爲了滿足關於經改善的生物可利用性的需求，數種藥物釋放調節技術已被發展。例如，難溶解的5,5-二苯基咪唑啶-2,4-二酮(5,5-diphenylimidazolidine-2,4-diones)已被衍生成磷酸酯(phosphate ester)前驅藥以改善溶解度(Stella等人，美國專利第4,260,769號，1981)。腸衣包覆(enteric coatings)已被使用作為一在胃中的藥品(pharmaceuticals)的

保護劑(protector)，並且使用蛋白質性微球體(proteinaceous microspheres)、脂質體(liposomes)或多醣(polysaccharides)微囊封(microencapsulating)活性劑在減少活性劑的酵素性降解(enzymatic degration)已經是有效的。抑制酵素的佐劑(enzyme inhibiting adjuvants)亦已被使用於預防酵素性降解。

一廣泛範圍的藥學配方經由微囊封活性劑於二羧酸(dicarboxylic acid)、經修飾的胺基酸(modified amino acid)或熱縮合的胺基酸(thermally condensed amino acid)的醯胺中而提供持續的釋放。提供緩慢釋放的添加劑亦可被混合以一大量系列的活試劑在錠劑(tablets)配方中。

雖然微囊封以及腸衣包覆技術將被增強的穩定性以及時間-釋放性質給予活性劑物質，這些技術蒙受許多缺點。活性劑的併入時常視擴散入微囊封的基質(matrix)而定，該擴散可能是沒有定量的並且可能使劑量再現性(dosage reproducibility)複雜化。此外，囊封的藥物依賴基質的擴散出去或基質的降解或者這兩者，基質的擴散出去或基質的降解高度地視該活性劑的化學性質以及水溶解度而定。相反地，水-溶性的微球體以一無限的程度膨脹，並且不幸地，可以在充滿可用於持續釋放的有限的活性試劑中釋放該活性劑。再者，在一些技術中，關於活性劑釋放所需要的降解程序的控制是不可信賴的。例如，因為一腸衣包覆的活性劑視pH而定以釋放該活性試劑，並且pH以及滯留時間(residence time)會變化，釋放速率是難以控制。

數種可植入的(implantable)藥物輸送系統已利用多肽(polypeptide)接附至藥物。此外，併入藥物至它們的基質內的其他大的聚合物載劑(polymeric carriers)被使用作為用於藥物的逐漸釋放的植入物(implants)。又另一技術結合共價藥物(covalent drug)接附以脂質體形成(liposome formation)的優點，其中活性成分(active ingredient)被接附至高度排序的脂薄膜(lipid films)。

然而，關於一能夠輸送迄今沒有已被配方或難以配方於一用於釋放超過一時間的持續期間的持續釋放配方之特定活性劑並且便利於病患給藥的活性劑輸送系統仍有一需要。

關於減少每天給藥的需求、並且容許於母體藥(parent drug)的控制與持續的釋放以及亦避免不規則的釋放之藥物的持續輸送系統以及與典型溶解所控制的持續釋放方法衝突的繁複配方有一普遍認可的需要。

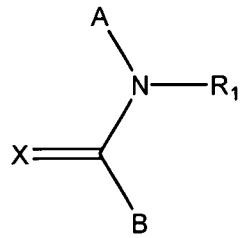
【發明內容】

發明概要

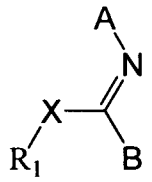
本發明藉由延長在一含有內醯胺、醯胺、醯亞胺、磺醯胺、胺甲酸酯、尿素、苯甲醯胺、醯基苯胺以及環醯胺(cyclic amide)的母體藥投藥給病患後被釋放以及被吸收的期間，以及提供一要比該母體藥本身更長的每劑量的作用期間而完成這個。在一個具體例中，適合於使用在本發明的方法中的化合物是含有內醯胺、醯胺、醯亞胺、磺醯胺、胺甲酸酯、尿素、苯甲醯胺、醯基苯胺以及環醯胺的母體

藥的衍生物(derivatives)，該等母體藥在醯胺的氮或氧原子上被取代以一不穩定的醛-連結的前驅藥部分(aldehyde-linked prodrug moietics)。較佳地，該前驅藥部份在生理情況(physiological conditions)下是疏水性的(hydrophobic)並且降低母體藥的極性(polarity)以及溶解度(solubility)。

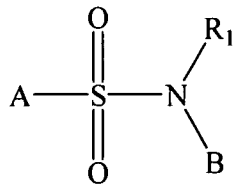
在一個具體例中，本發明提供一具有下列化學式I、II或III的前驅藥化合物：



化學式I



化學式II



化學式III

以及它的幾何異構物(geometric isomers)、鏡像異構物(enantiomers)、非鏡像異構物(diastereomers)、消旋物(racemates)、藥學上可接受的鹽類(pharmaceutically acceptable salts)以及溶劑合物(solvates)；

其中A和B與它們所接附的-N(C=X)-或-N=C-X-或-$S(O)_2$-N-基團一起形成一母體藥；

X是-S-或-O-；

R_1是選自於：$-C(R_A)(R_B)-OR_{20}$、$-C(R_A)(R_B)-OC(O)OR_{20}$、$-C(R_A)(R_B)-OC(O)R_{20}$、$-C(R_A)(R_B)-OC(O)NR_{20}R_{21}$、$-(C(R_A)(R_B))-OPO_3MY$、$-(C(R_A)(R_B))-OP(O)(OR_{20})(OR_{21})$、$-[C(R_A)(R_B)O]_z-R_{20}$、$-[C(R_A)(R_B)O]_z-C(O)OR_{20}$、

$-[C(R_A)(R_B)O]_z-C(O)R_{20}$ 、 $-[C(R_A)(R_B)O]_z-C(O)NR_{20}R_{21}$ 、 $-[C(R_A)(R_B)O]_z-OPO_3MY$ 、 $-[C(R_A)(R_B)O]_z-P(O)_2(OR_{20})M$ 以及 $-[C(R_A)(R_B)O]_z-P(O)(OR_{20})(OR_{21})$；

其中z是2或3；

其中各個R_A以及R_B是獨立地選自於：氫、鹵素(halogen)、脂族(aliphatic)、經取代的脂族、芳基(aryl)或經取代的芳基；

各個R_{20}以及R_{21}是獨立地選自於：氫、脂族、經取代的脂族、芳基或經取代的芳基；

Y以及M是相同或不同的，並且各個是一單價陽離子(monovalent cation)；或者M與Y一起是一為二價陽離子(divalent cation)，以及

其中當該母體藥含有一具有化學式I的5,5-二苯基咪唑啶-2,4-二酮部分，R_1不是$-CH(R_A)OPO_3MY$、$-CH(R_A)OP(O)(OH)_2$或$-CH(R_A)OC(O)R_{20}$。

本發明進一步提供一種用於藉由投藥一具有一不穩定的部分之母體藥的綴合物(conjugate)來持續輸送一母體藥的方法，其中該綴合物是由化學式I、II或III來表示。

圖式簡單說明

本發明的前述以及其他目的、特徵與優點由下列本發明的較佳具體例的更特別的說明[如在隨文檢附的圖式(其中像參考特性意指遍及不同觀點的相同部分)中所例示說明的]將變得明顯。在例示說明本發明的原理時，該等圖式不需要衡量、強調而被放置。

第1圖：化合物-7的PXRD光譜(spectrum)。

第2圖：化合物-7的IR光譜。

第3圖：化合物-7的拉曼光譜(Raman spectrum)。

第4圖：化合物-7的TGA溫度記錄圖(thermogram)。

第5圖：化合物-7的DSC溫度記錄圖。

第6圖：在AMPH誘發的移動運動模型(locomotion model)中化合物-4的藥力學(Pharmacodynamic, PD)研究。

第7圖：在經AMPH誘發的移動運動模型中化合物-7的藥力學(PD)研究。

第8圖：在靜脈內投藥(intravenous administration)化合物7 (0.5 mg/Kg)給大鼠之後，阿立哌唑(aripiprazole)的血漿濃度。

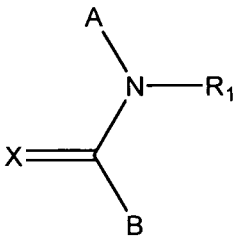
第9圖：在肌肉內投藥(intramuscular administration) 30 mg/Kg的化合物7給狗之後，阿立哌唑、去氫阿立哌唑(dehydroaripiprazole)以及化合物7的血漿濃度。

第10圖：在靜脈內投藥[20 mg皮利酮(pioglitazone)等量的(equivalent)]給大鼠之後，皮利酮、化合物-1002以及化合物-1008的藥物動力學圖譜(pharmacokinetic profile)。

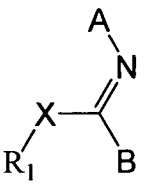
【實施方式】

較佳實施例之詳細說明

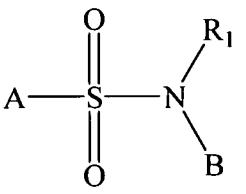
本發明的一個方面提供一具有下列通式I、II或III的化合物：



化學式I



化學式II



化學式III

或它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、它的藥學上可接受的鹽類以及溶劑合物；

其中A和B與它們所接附的-N(C=X)-或-N=C-X-或-$S(O)_2$-N-一起形成一母體藥；

X是-S-或-O-；

R_1是選自於：-$C(R_A)(R_B)$-OR_{20}、-$C(R_A)(R_B)$-$OC(O)OR_{20}$、-$C(R_A)(R_B)$-$OC(O)R_{20}$、-$C(R_A)(R_B)$-$OC(O)NR_{20}R_{21}$、-$(C(R_A)(R_B))$-OPO_3MY、-$(C(R_A)(R_B))$-$OP(O)(OR_{20})(OR_{21})$、-$[C(R_A)(R_B)O]_z$-R_{20}、-$[C(R_A)(R_B)O]_z$-$C(O)OR_{20}$、-$[C(R_A)(R_B)O]_z$-$C(O)R_{20}$、-$[C(R_A)(R_B)O]_z$-$C(O)NR_{20}R_{21}$、-$[C(R_A)(R_B)O]_z$-OPO_3MY、-$[C(R_A)(R_B)O]_z$-$P(O)_2(OR_{20})M$以及-$[C(R_A)(R_B)O]_z$-$P(O)(OR_{20})(OR_{21})$；

其中各個R_A以及R_B是獨立地選自於：氫、鹵素、脂族、經取代的脂族、芳基或經取代的芳基；

各個R_{20}以及R_{21}是獨立地選自於：氫、脂族、經取代的脂族、芳基或經取代的芳基；

Y以及M是相同或不同的，並且各個是一單價陽離子；或者M與Y一起是一為二價陽離子，以及

其中當該母體藥含有一具有化學式I的5,5-二苯基咪唑

啶-2,4-二酮部分，R_1不是$-CH(R_A)OPO_3MY$、$-CH(R_A)OP(O)(OH)_2$或$-CH(R_A)OC(O)R_{20}$。

在一個具體例中，具有化學式I、II以及III的本發明的化合物是較少溶解的，並且當相較於它們被衍生出自的母體藥時較佳地是至少一嚴重較少溶解的等級。在一個具體例中，當溶解度在室溫、在一磷酸鹽緩衝液(pH7.4)中被測量時，該等具有化學式I、II以及III的前驅藥具有一小於大約0.5 mg/ml、較佳地小於大約0.1 mg/ml、較佳地小於大約0.01 mg/ml、較佳地小於大約0.001 mg/ml、較佳地小於大約0.0001 mg/ml以及甚至更佳地小於大約0.00001 mg/ml的水性溶解度(aqueous solubility)。

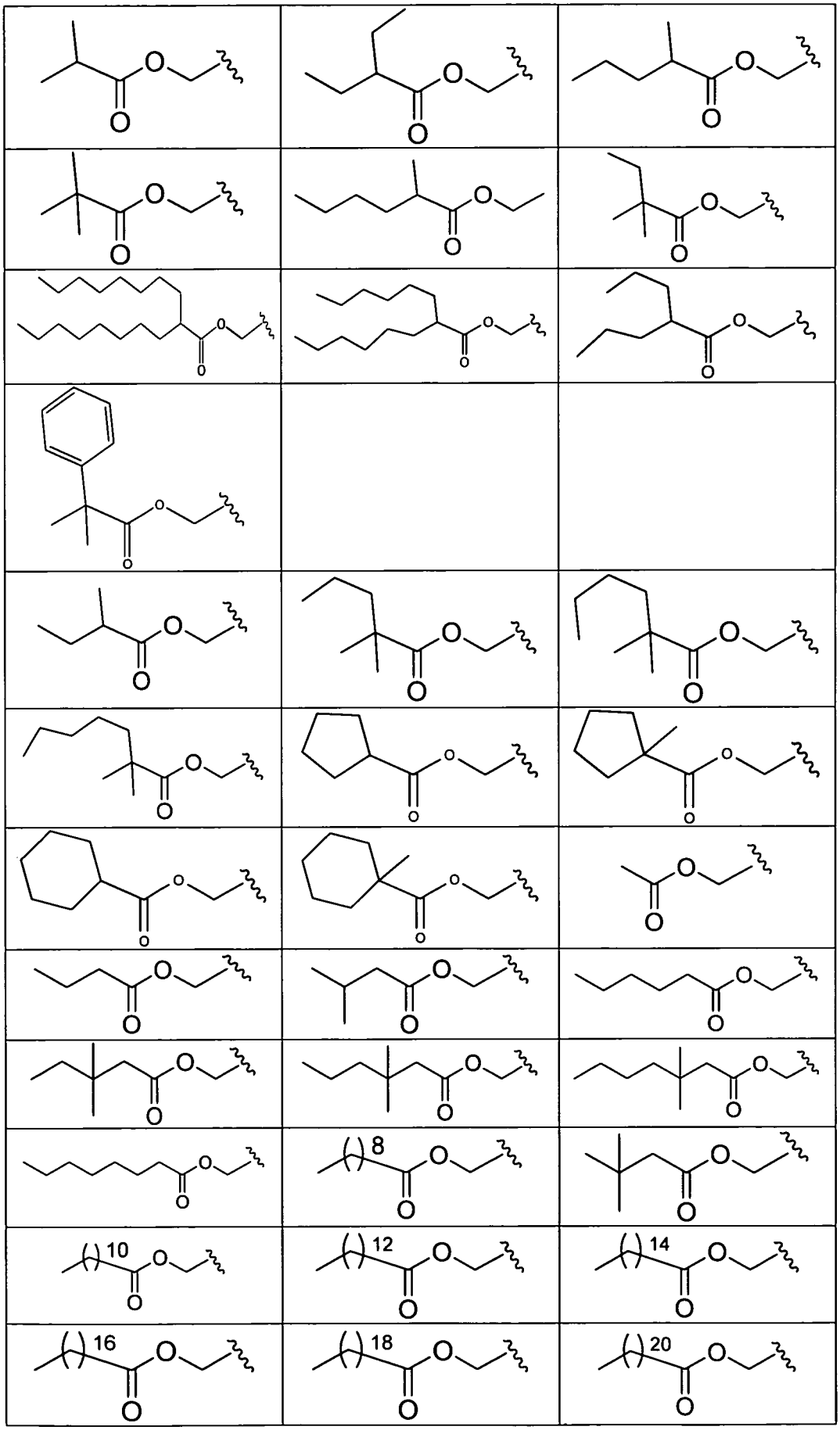
在一個較佳的具體例中，一本發明的化合物當被投藥[例如，口服地(orally)或非經腸道地(parenterally)]給一個體時提供母體藥持續輸送超過小時、天、週或月。例如，該等化合物可提供該母體藥的持續輸送歷時至少8、12、24、36或48小時或者至少4、7、15、30、60、75或90天或者更長。在沒有被一理論束縛下，被相信的是：本發明的化合物在非經腸道的投藥[例如皮下的(subcutaneous)、肌肉內的或腹膜內的注射(intraperitoneal injection)]時形成一不可溶的蓄積 (depot)。在一個具體例中，一本發明的前驅藥可進一步包含有一用於提供該前驅藥不受酵素性或化學性降解的額外保護之持續釋放輸送系統。

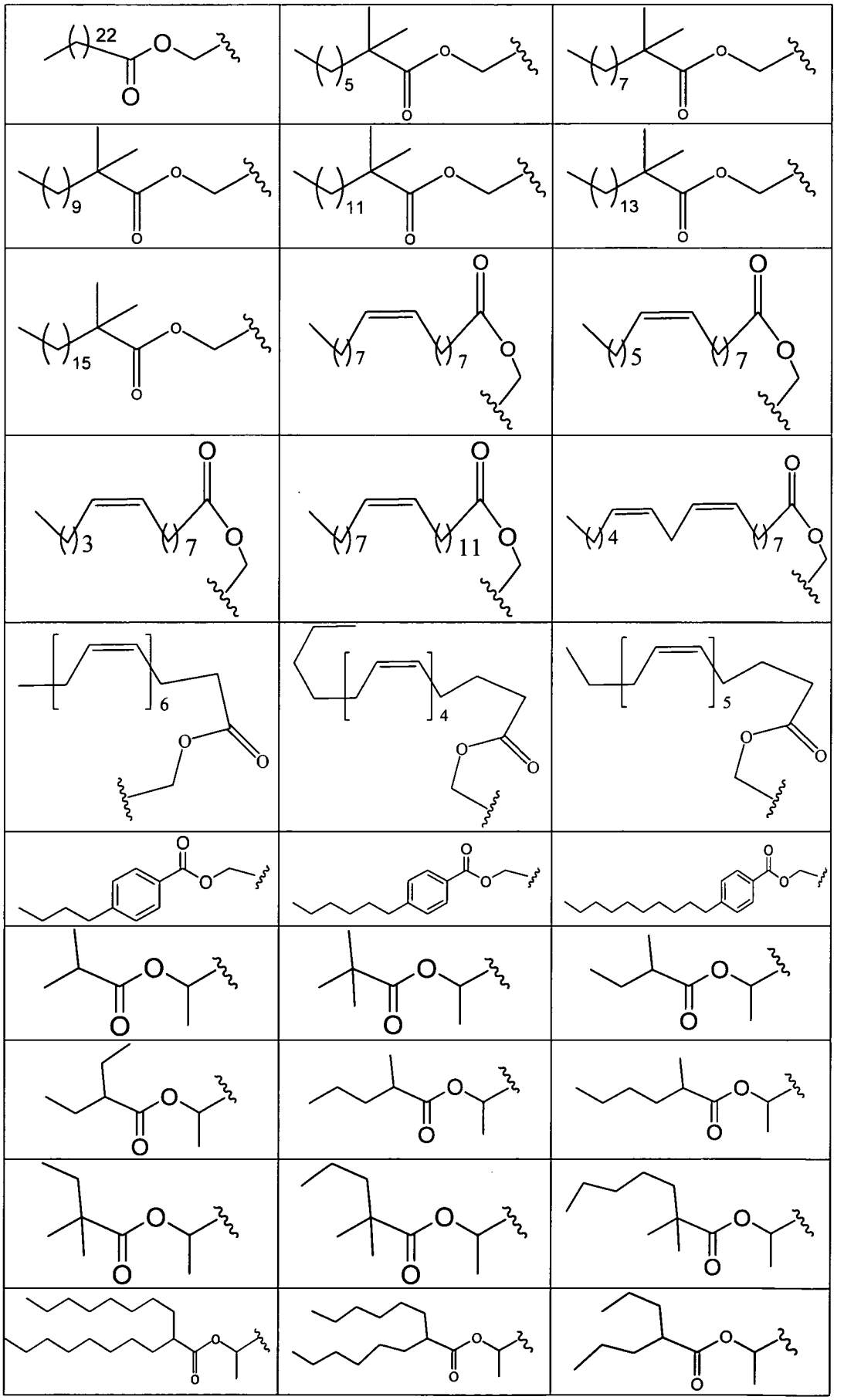
在另一個具體例中，本發明提供一種用於持續輸送一含有母體內醯胺、醯胺、醯亞胺、磺醯胺、胺甲酸酯、尿

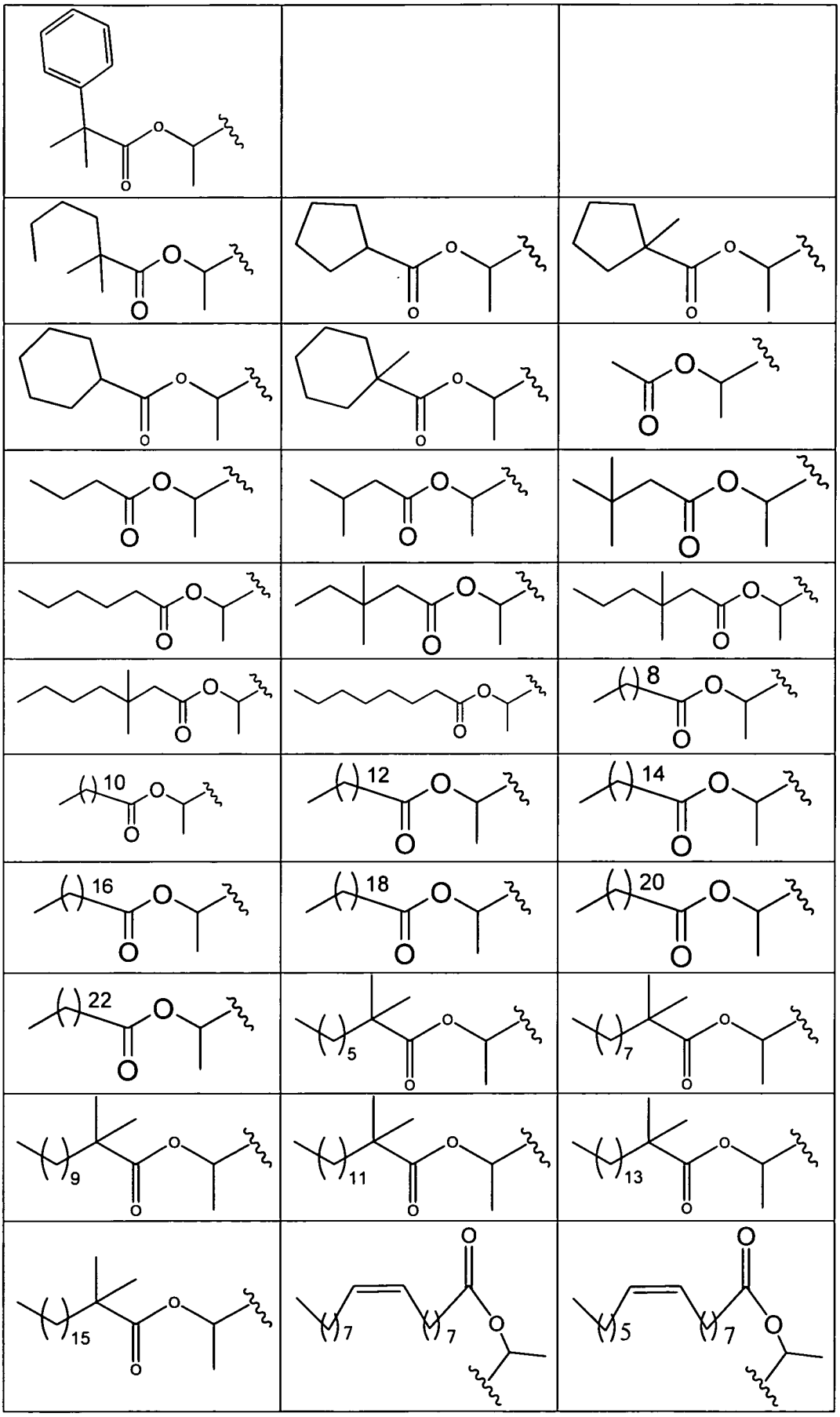
素、苯甲醯胺或醯基苯胺的藥物給一需要它的個體的方法。各個這些基團包含有一醯胺的N-H基團。該方法包含有投藥給一個體一有效量的一藉由在NH基團上取代一不穩定的、疏水性醛-連結的前驅藥部分所形成的前驅藥，其中該前驅藥相較於該母體藥在生理情況下已降低溶解度，並且在投藥之後提供要比在投藥該母體藥之後所觀察到的位準更長的該母體藥的持續治療位準。在一個較佳的具體例中，該醯胺的N-H基團具有一為大約5至大約22、較佳地大約5至大約21以及較佳地大約5至大約20的pKa。

在一個較佳的具體例中，R_1是選自於表-1。

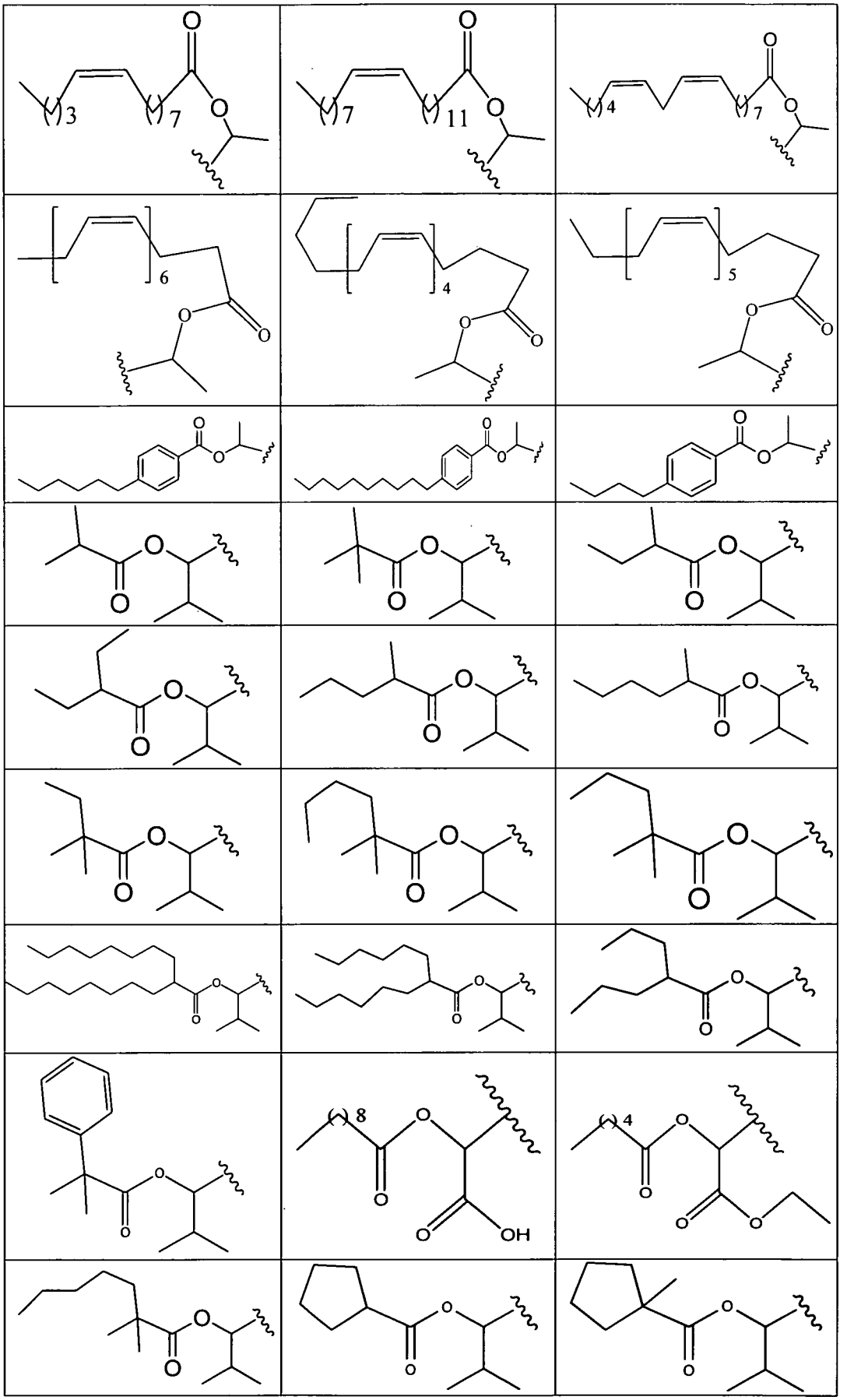
表1

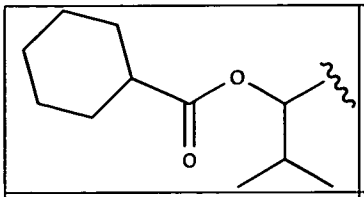
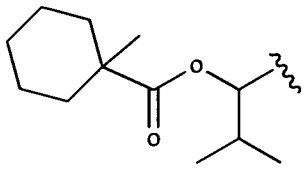
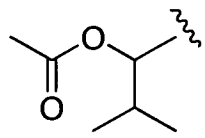
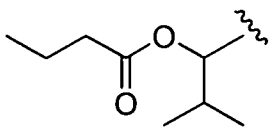
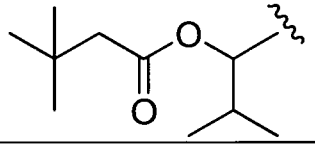
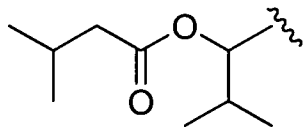
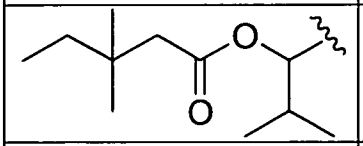
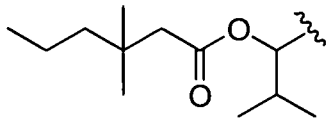
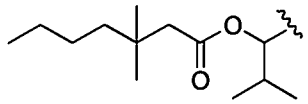
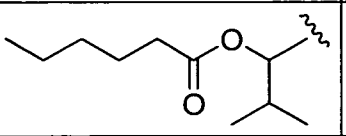
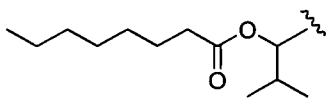
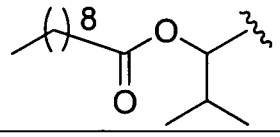
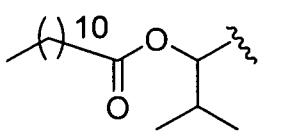
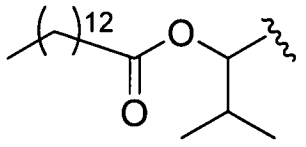
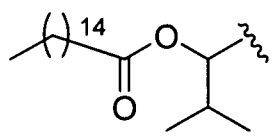
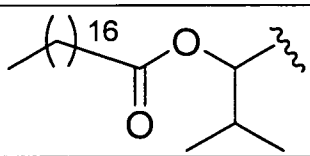
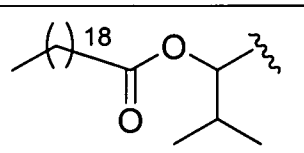
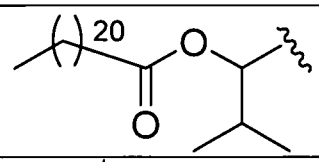
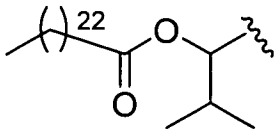
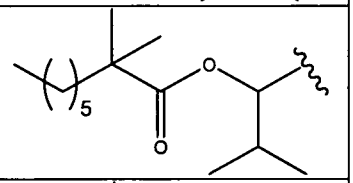
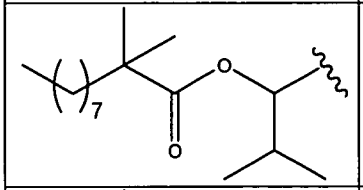
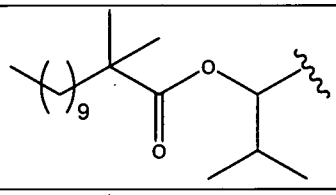
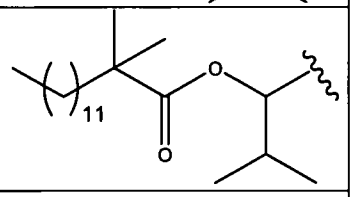
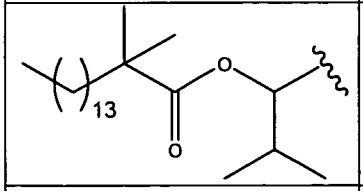
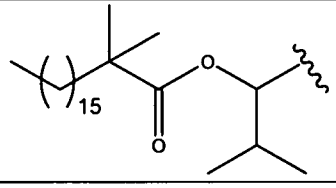
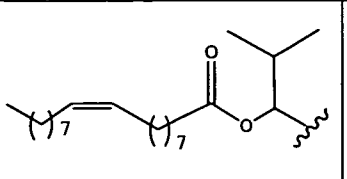
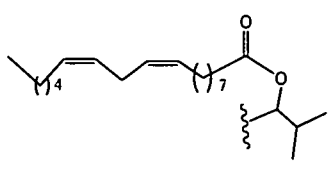
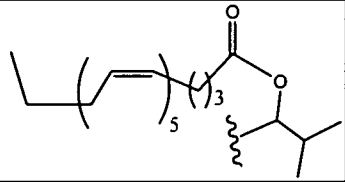
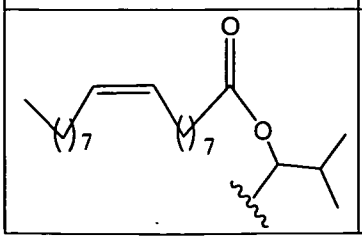
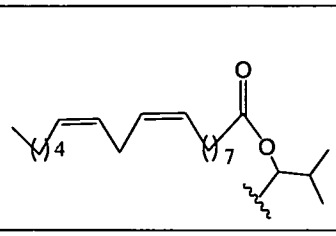
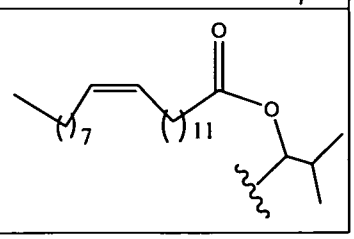


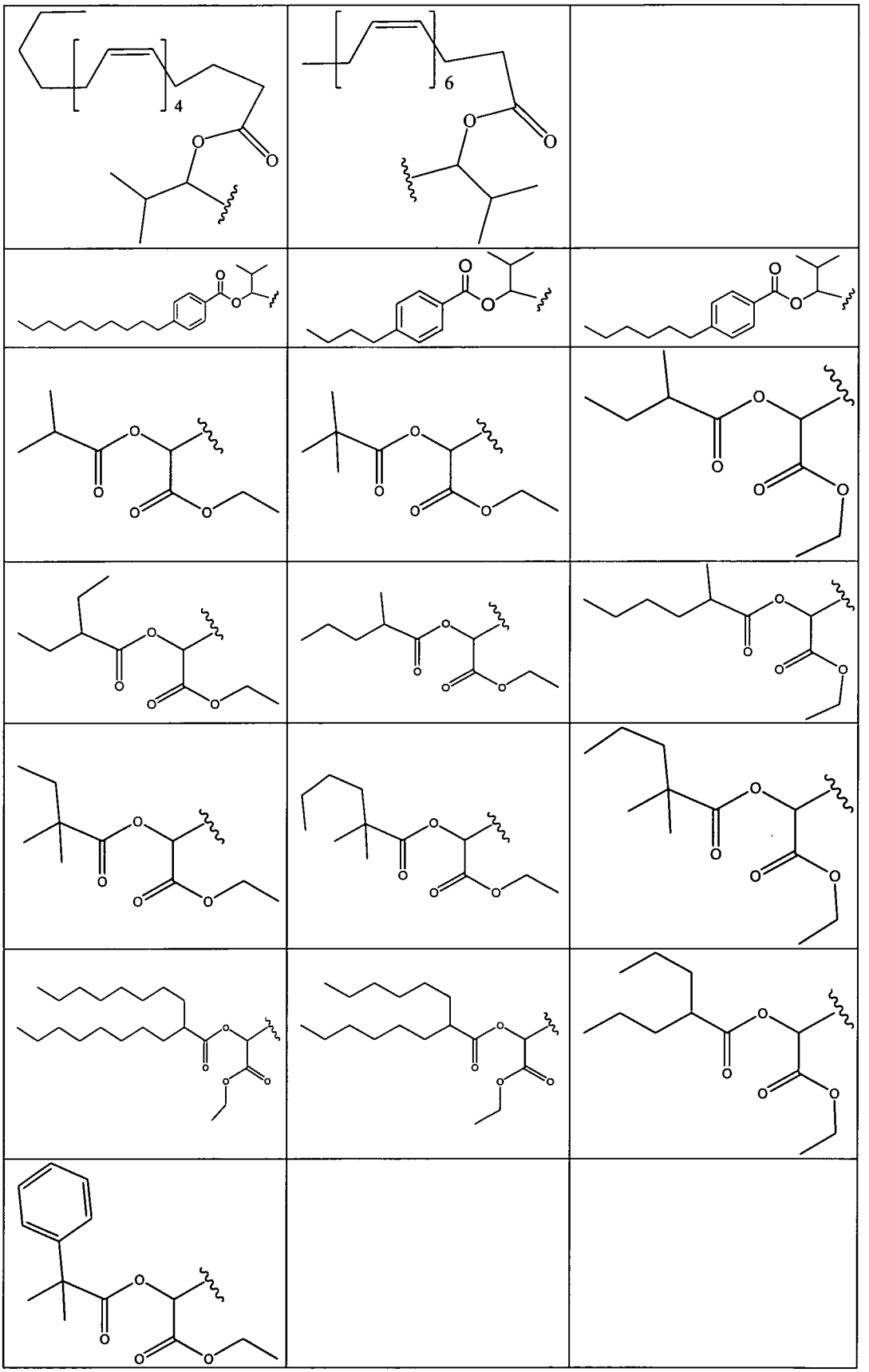


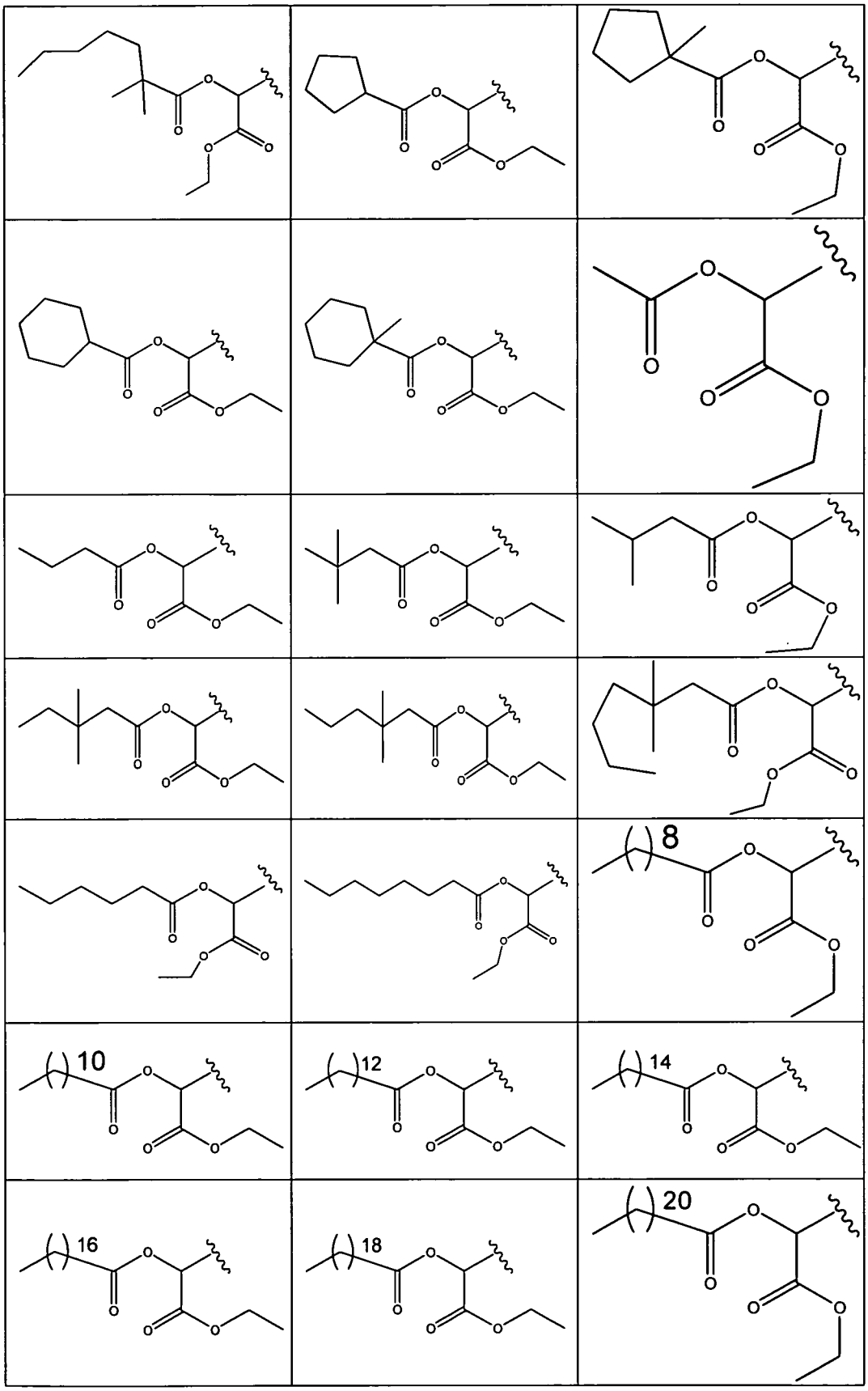


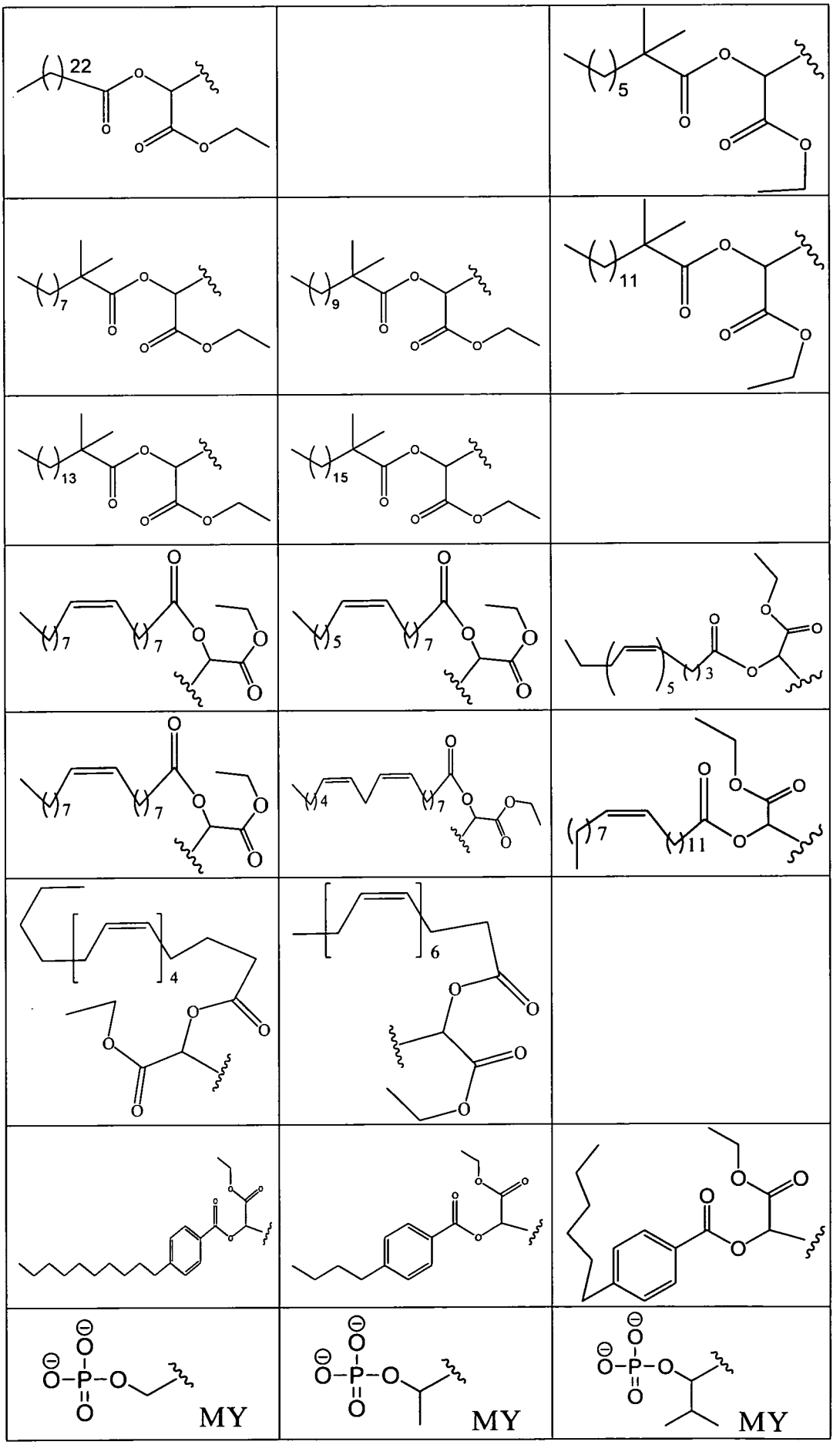
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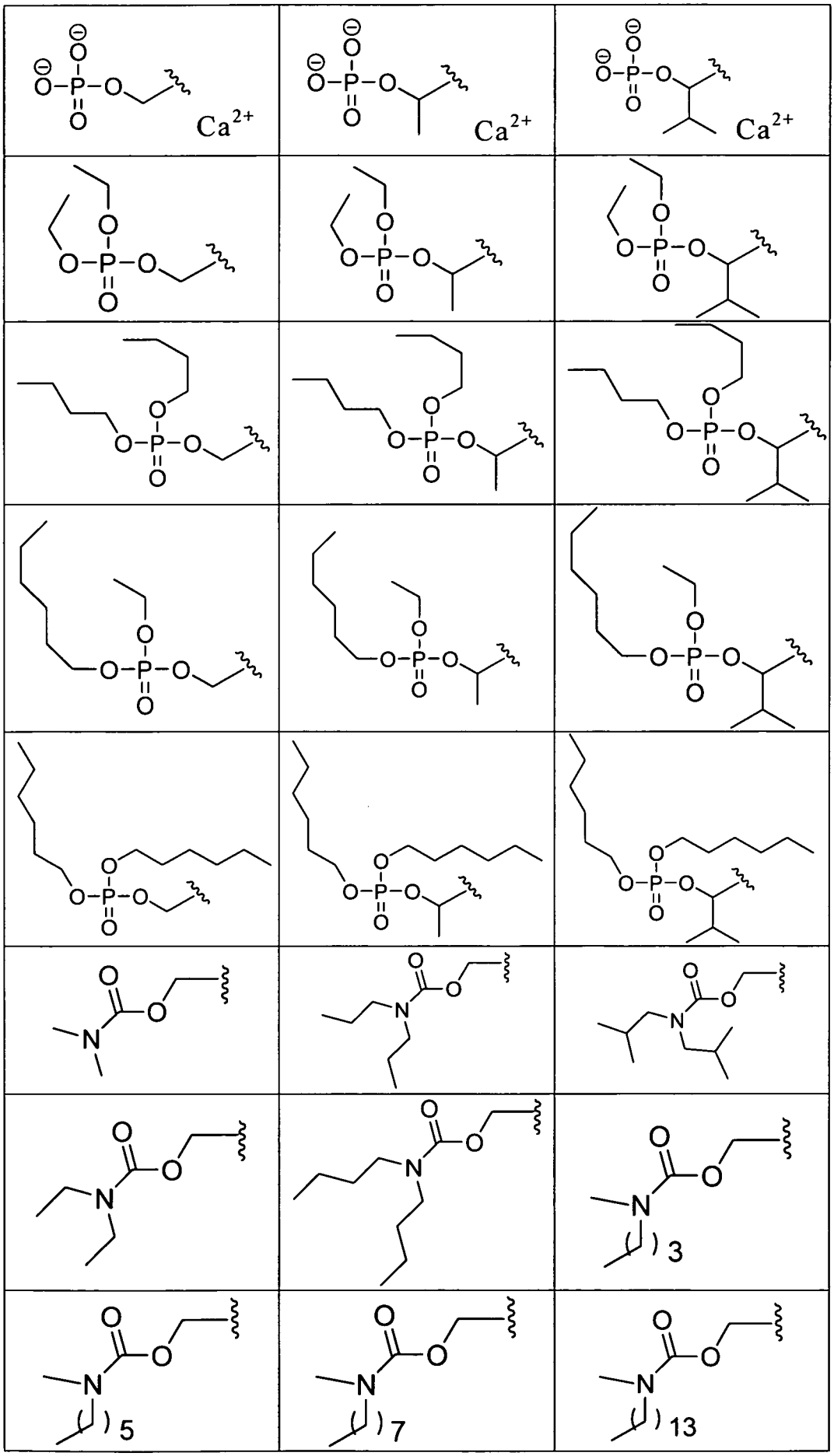


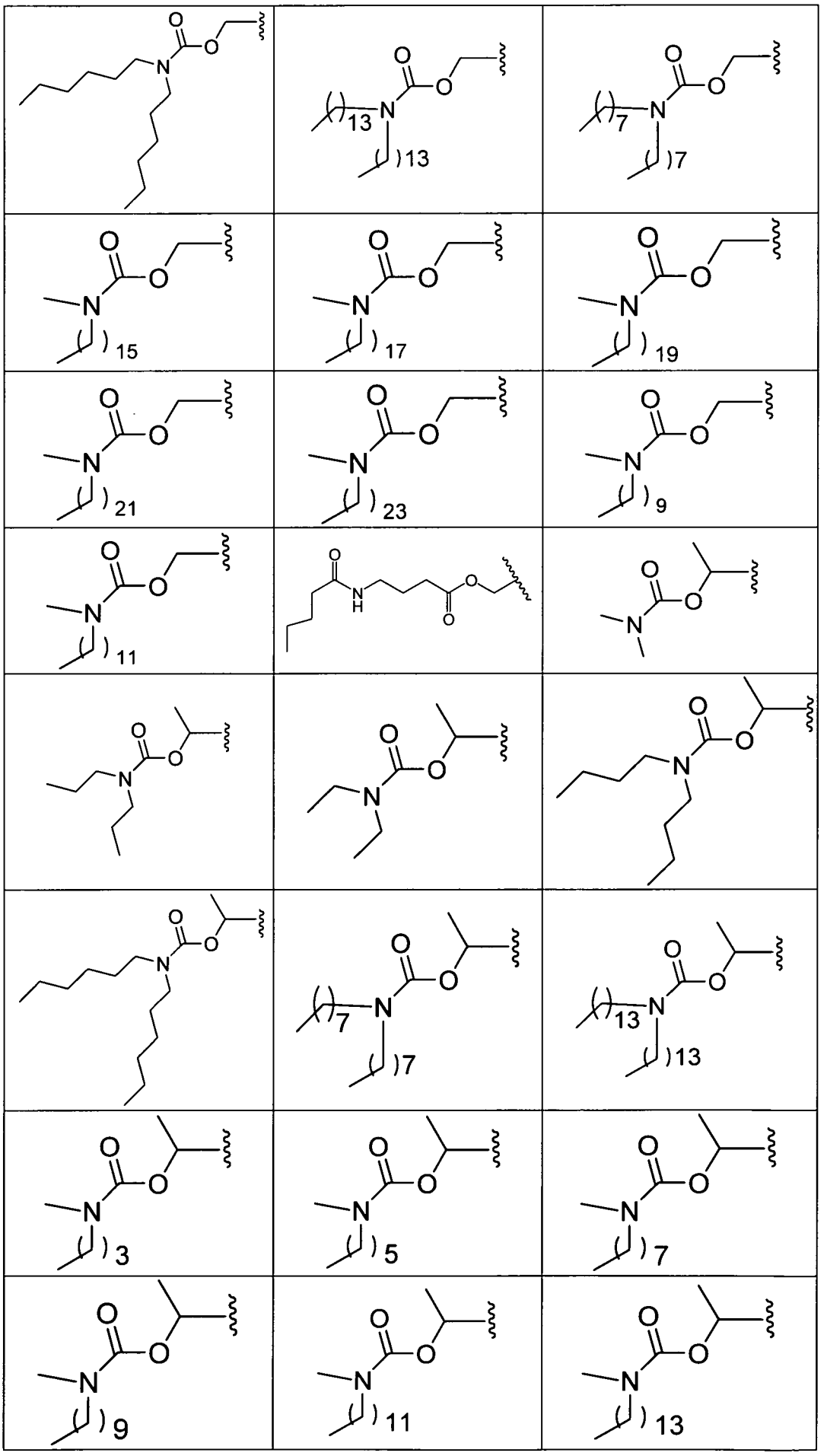
		
		
		
		
		
		
		
		
		
		
		

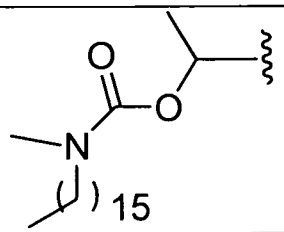
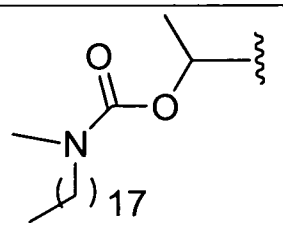
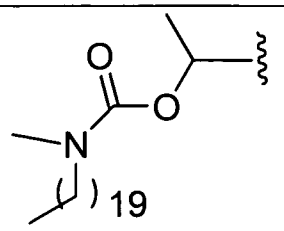
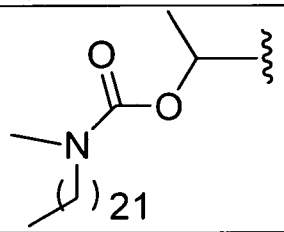
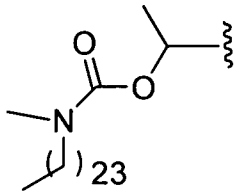
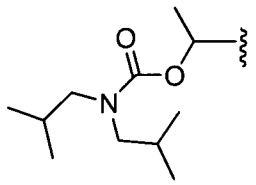
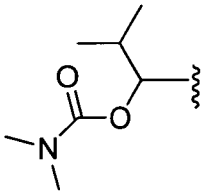
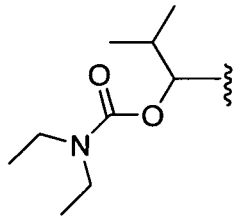
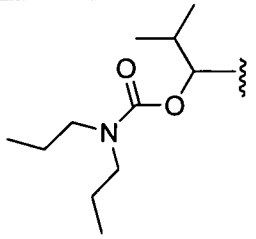
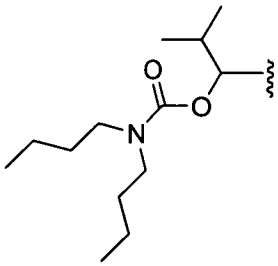
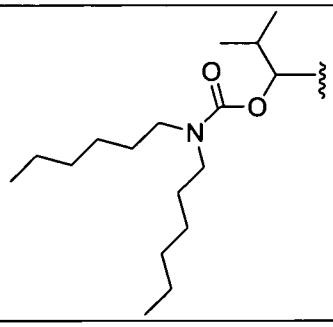
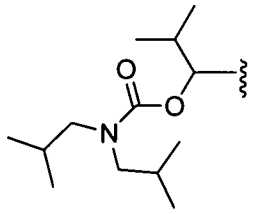
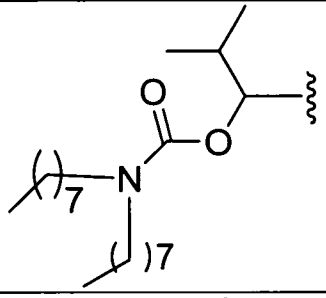
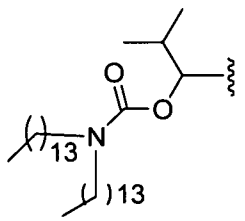
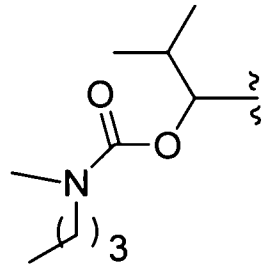
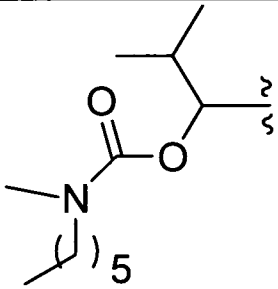
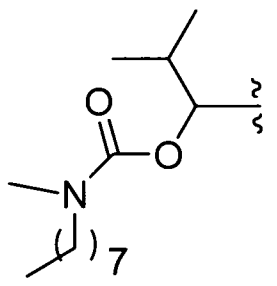
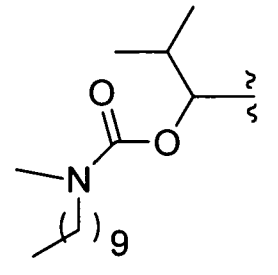


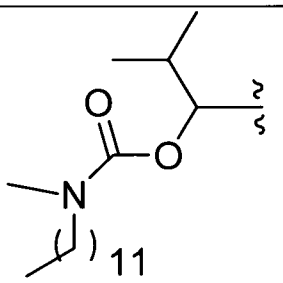
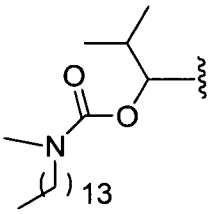
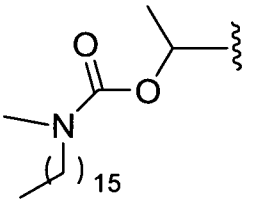
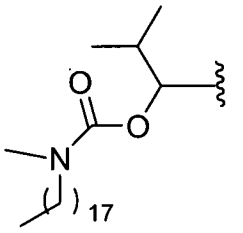
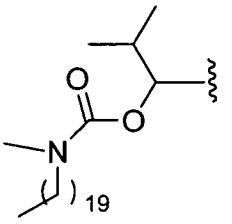
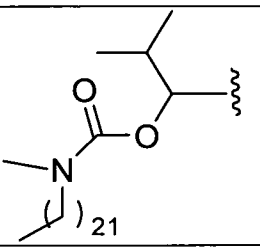
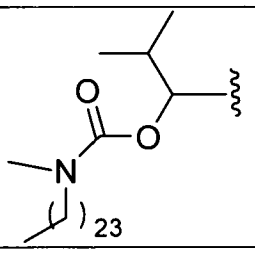
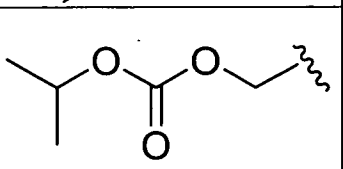
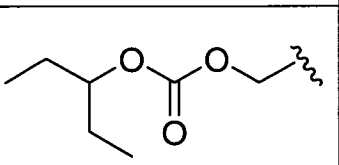
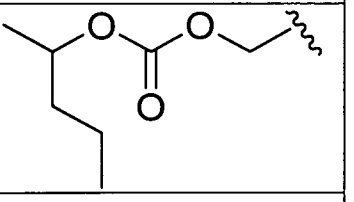
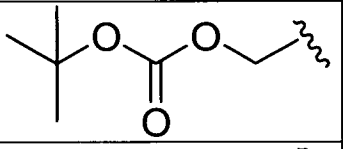
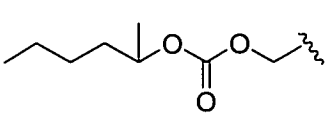
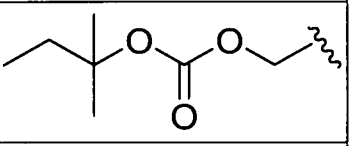
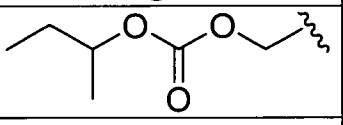
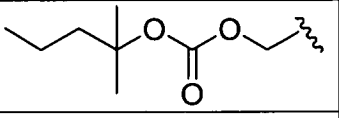
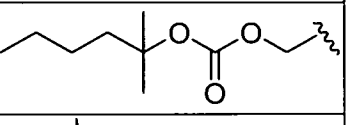
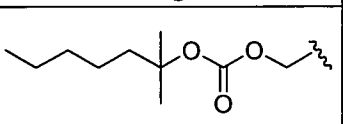
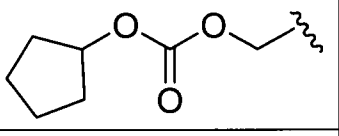
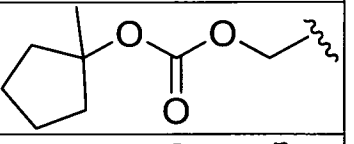
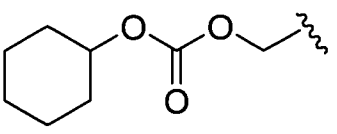
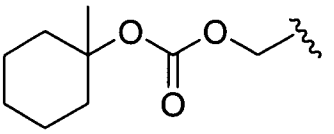
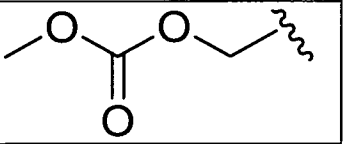
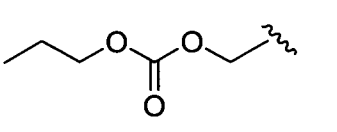
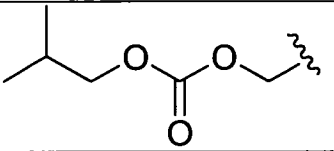
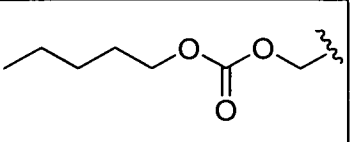
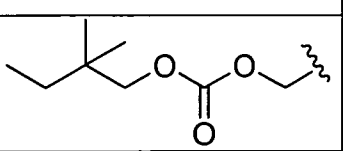
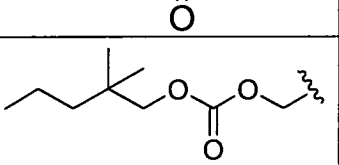
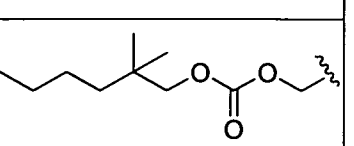
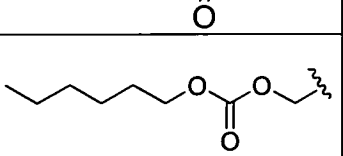
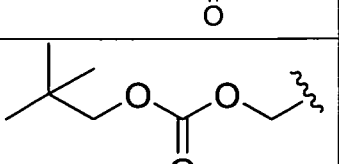
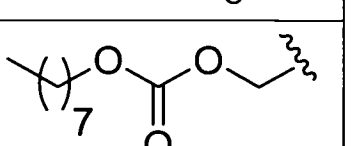
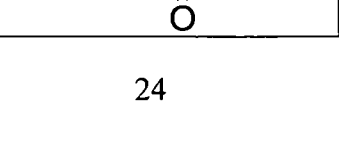
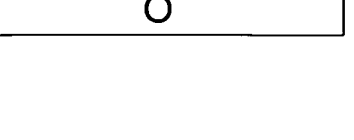

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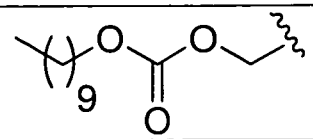
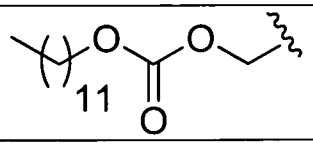
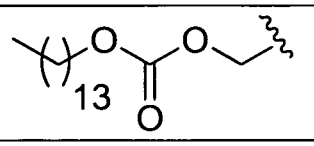
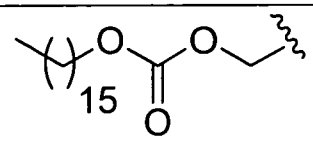
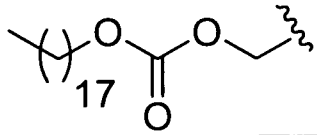
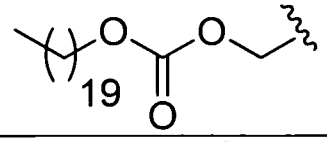
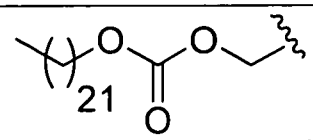
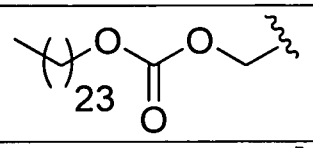
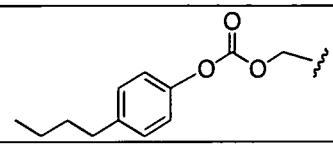
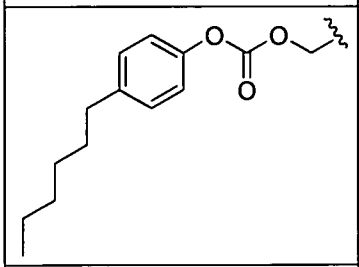
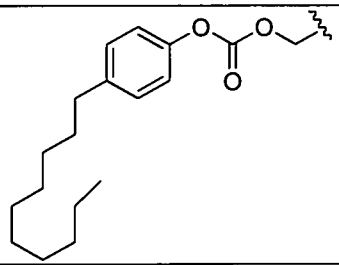
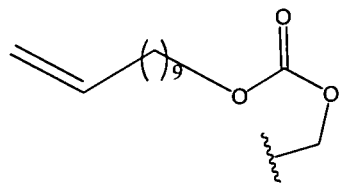
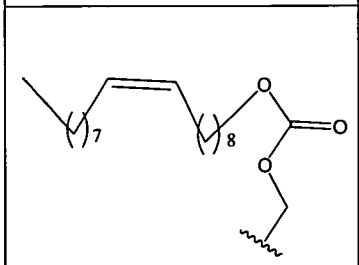
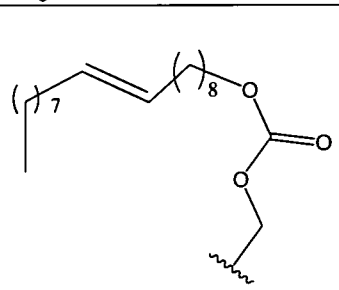
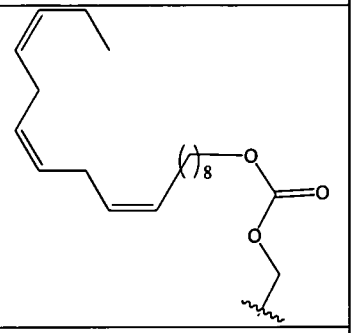
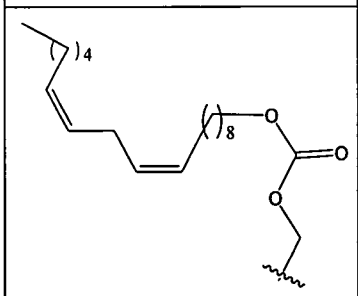
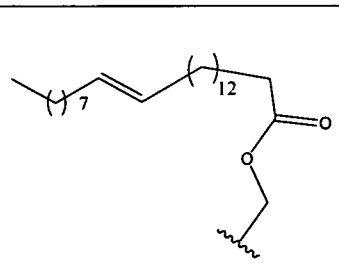
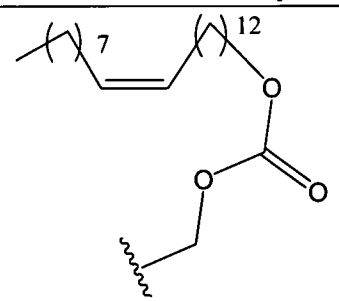
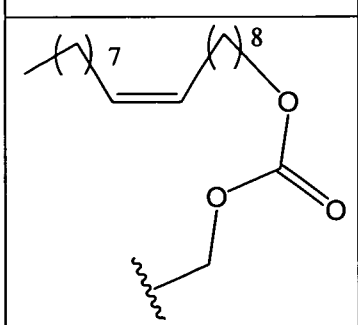
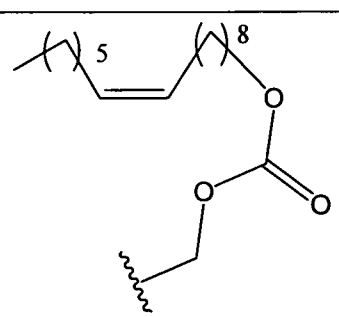
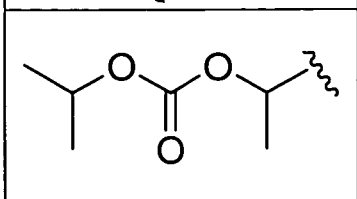
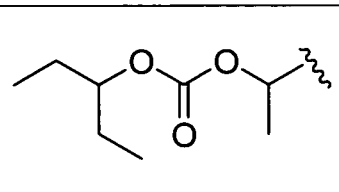
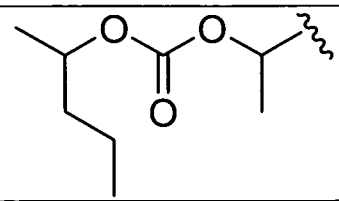

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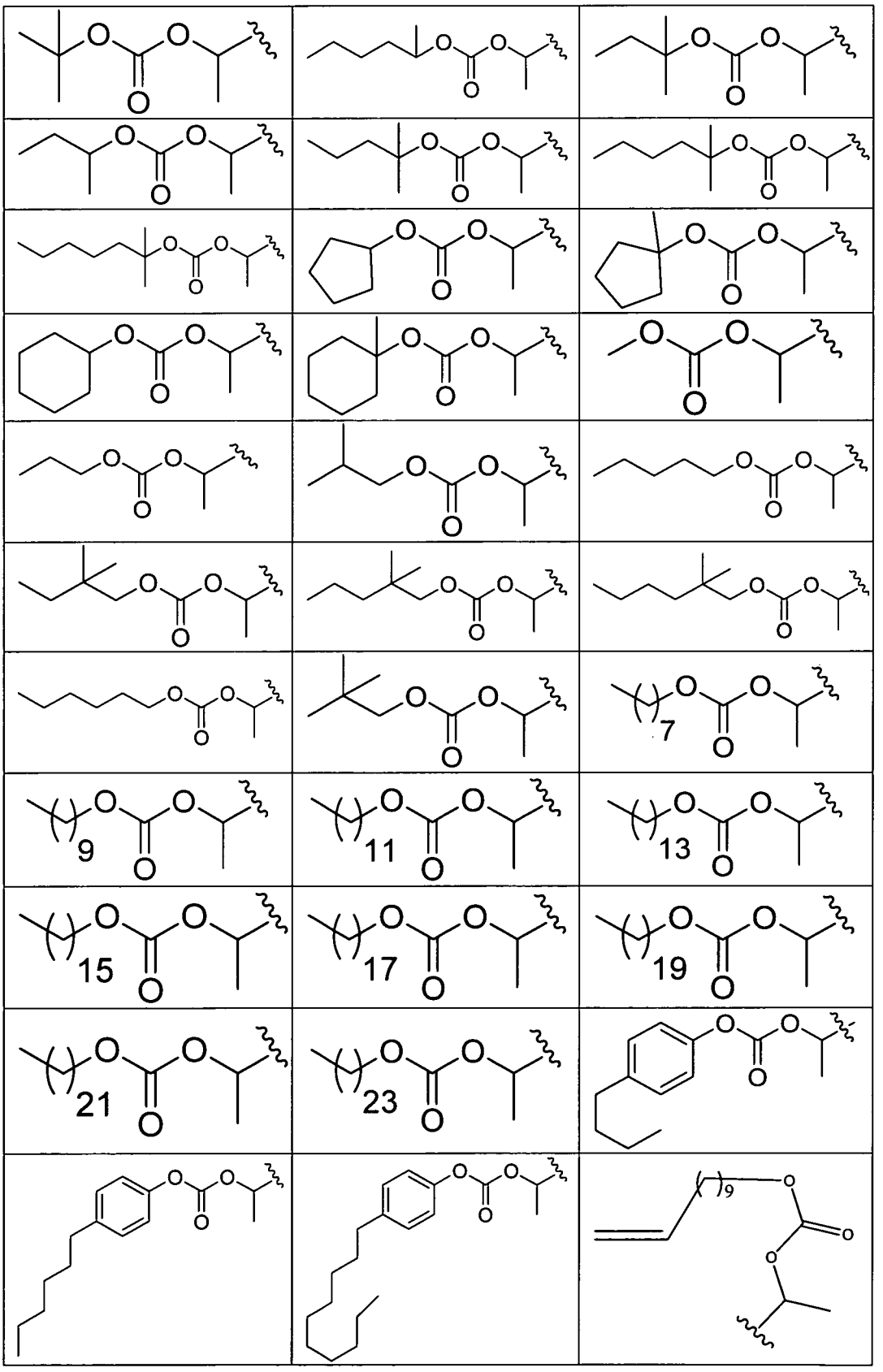


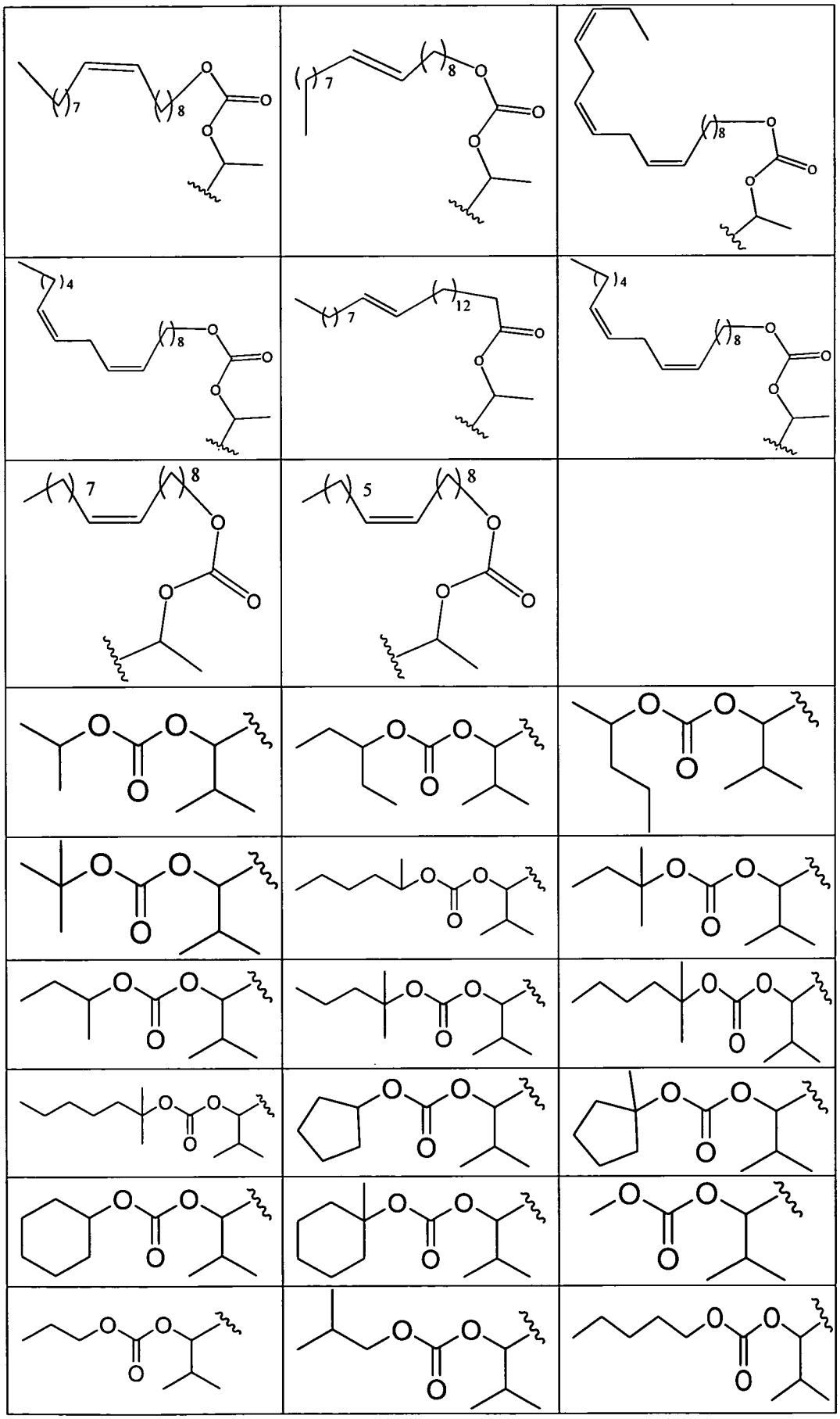


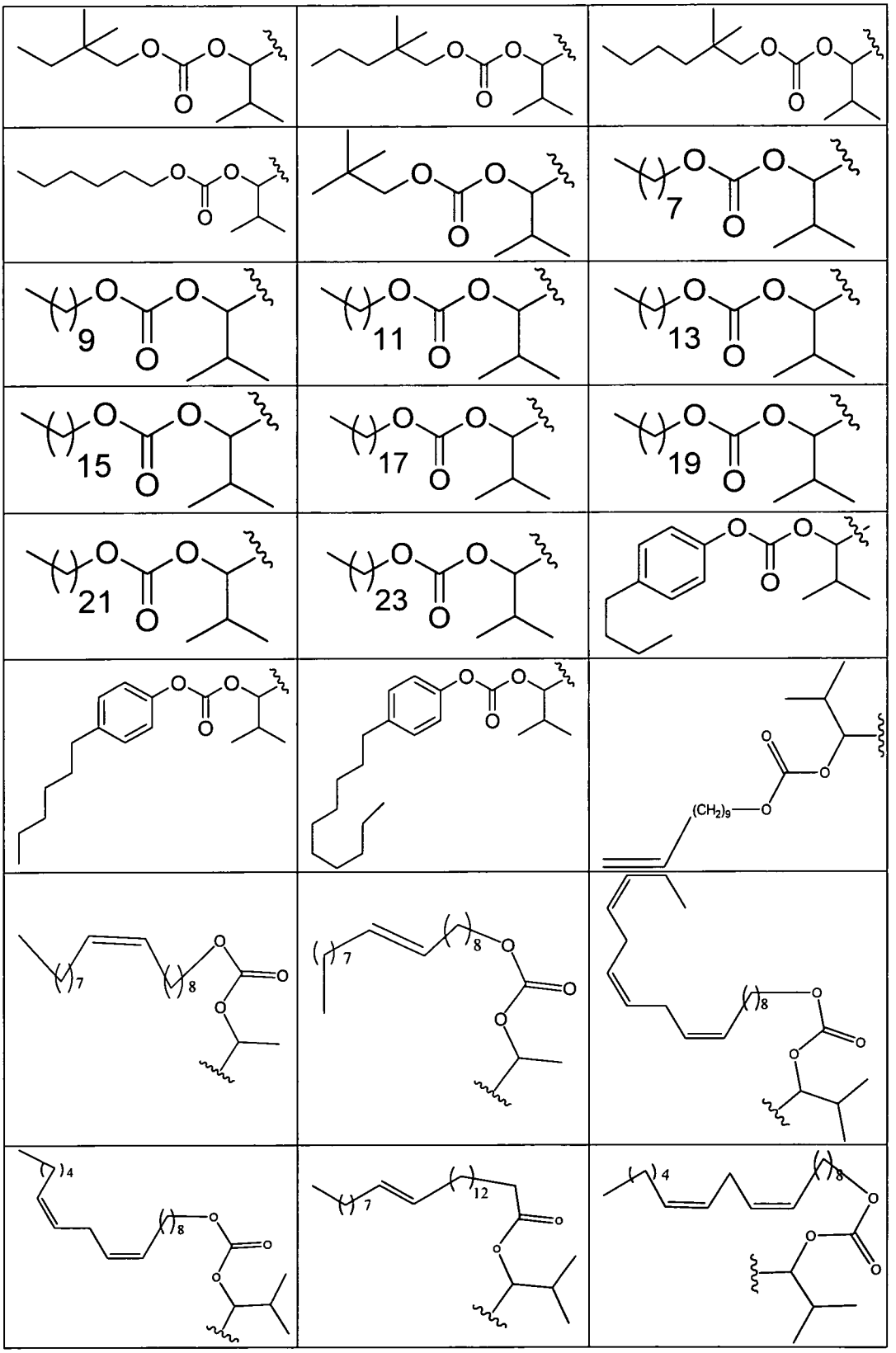
		
		
		
		
		
		

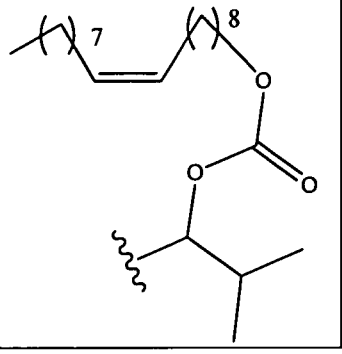
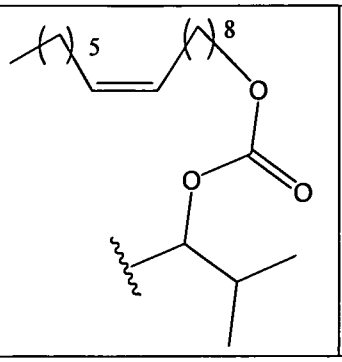
		
		
		
		
		
		
		
		
		
		
		
		



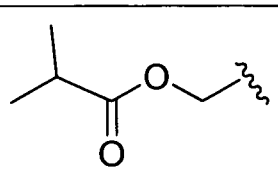
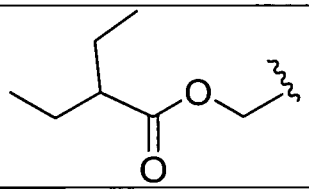
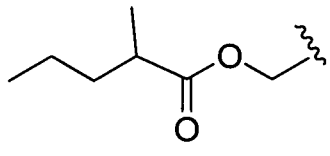
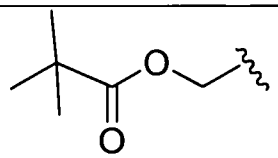
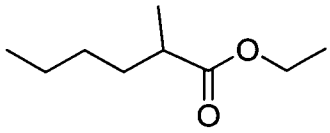
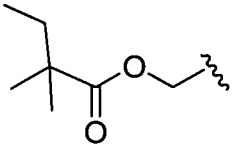
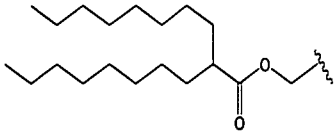
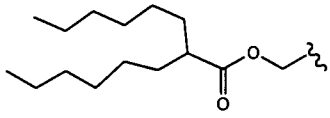
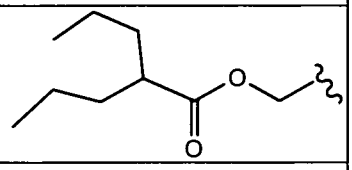
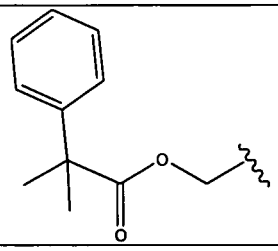
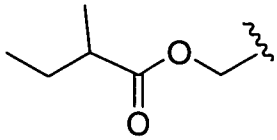
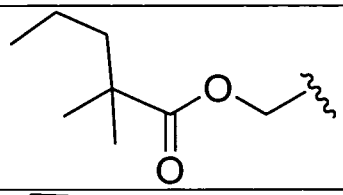
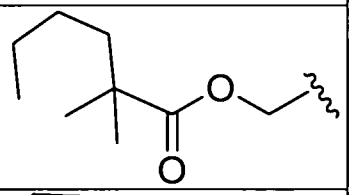
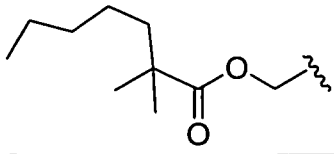
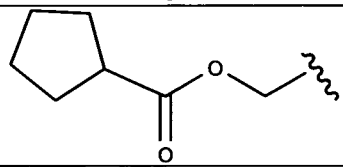
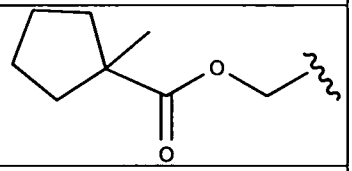
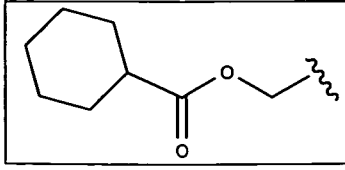
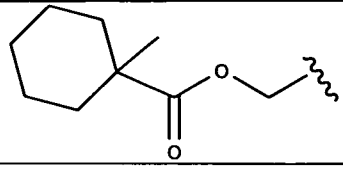
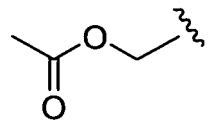


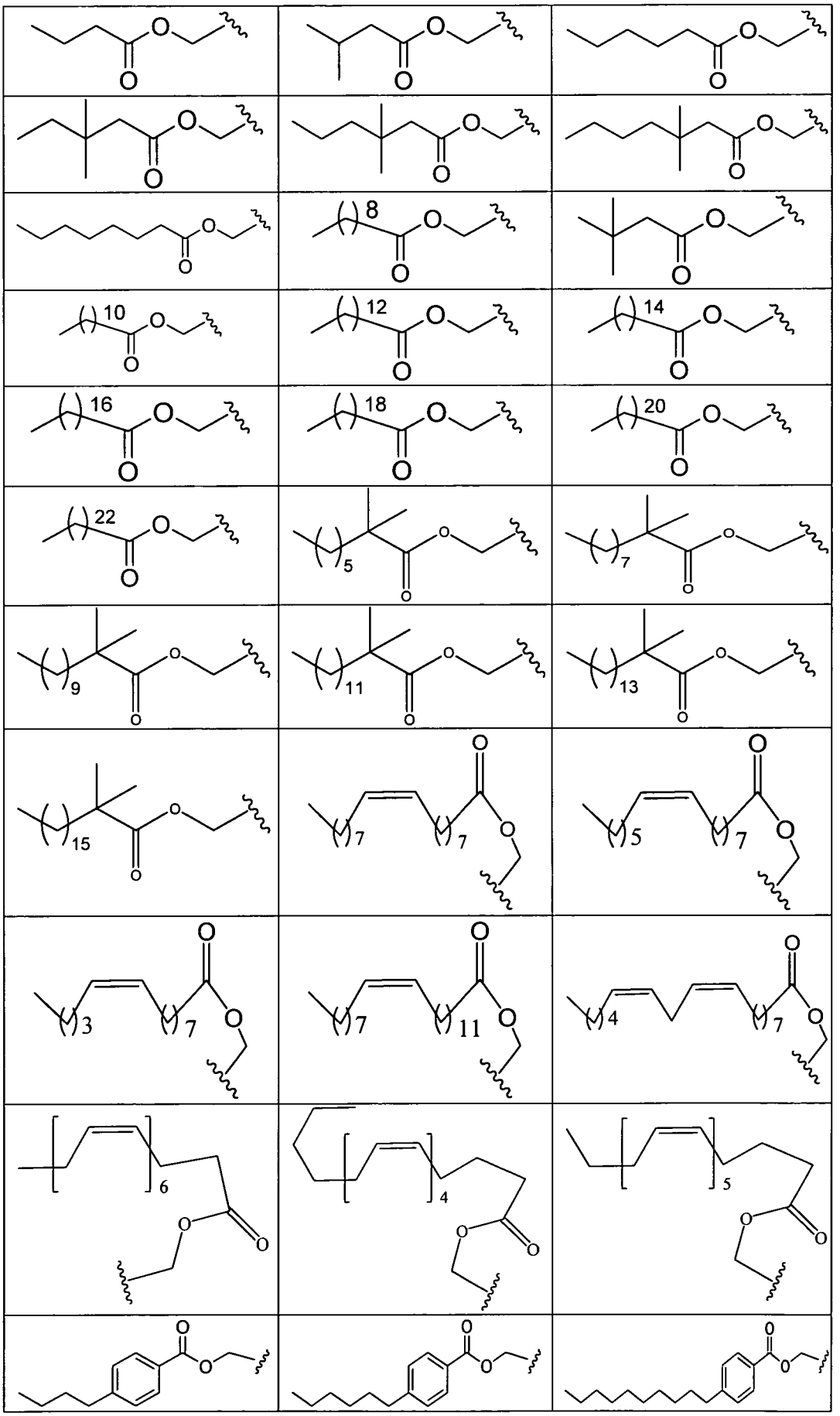


在一個更佳的具體例中，R_1是選自於表2。

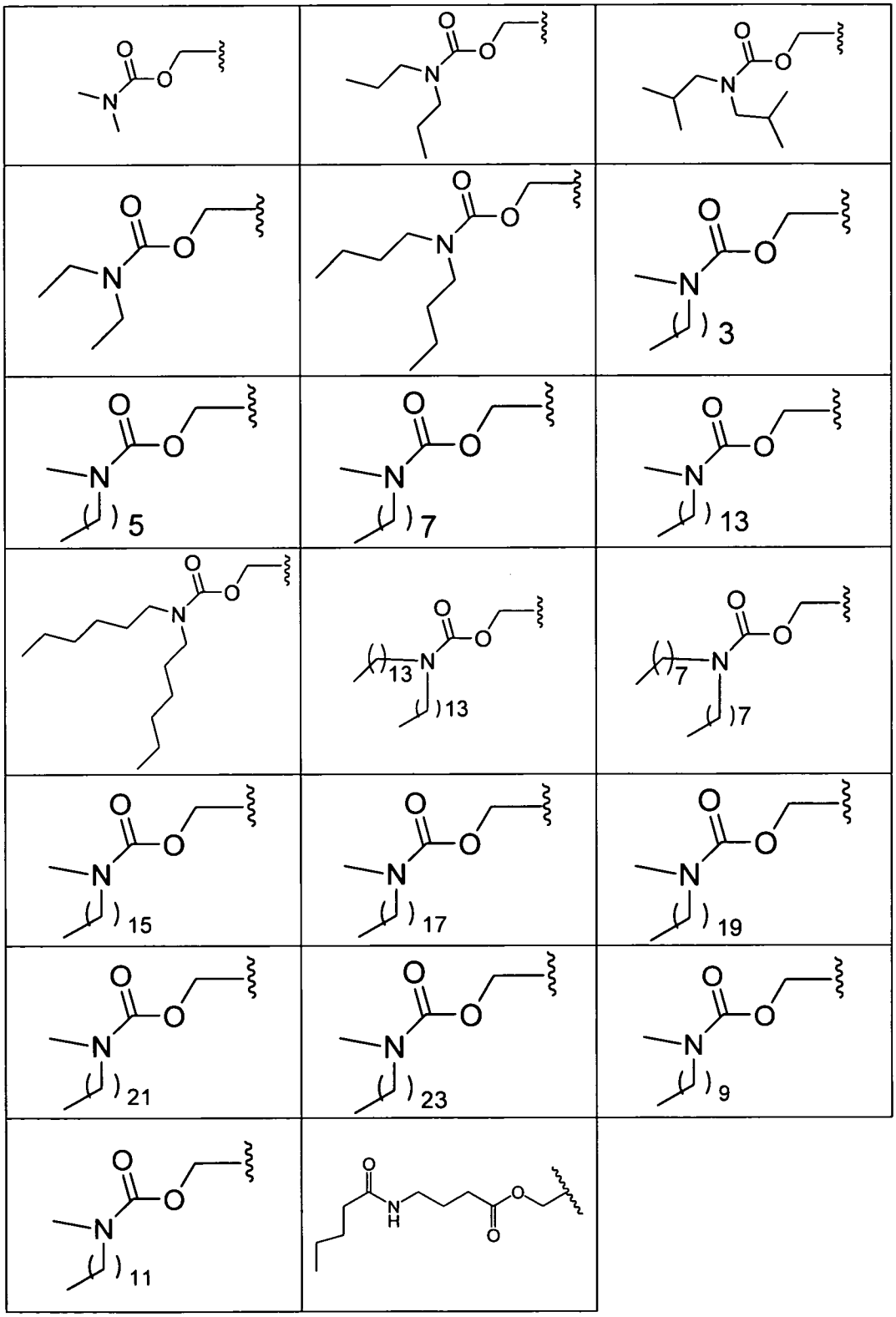
表2



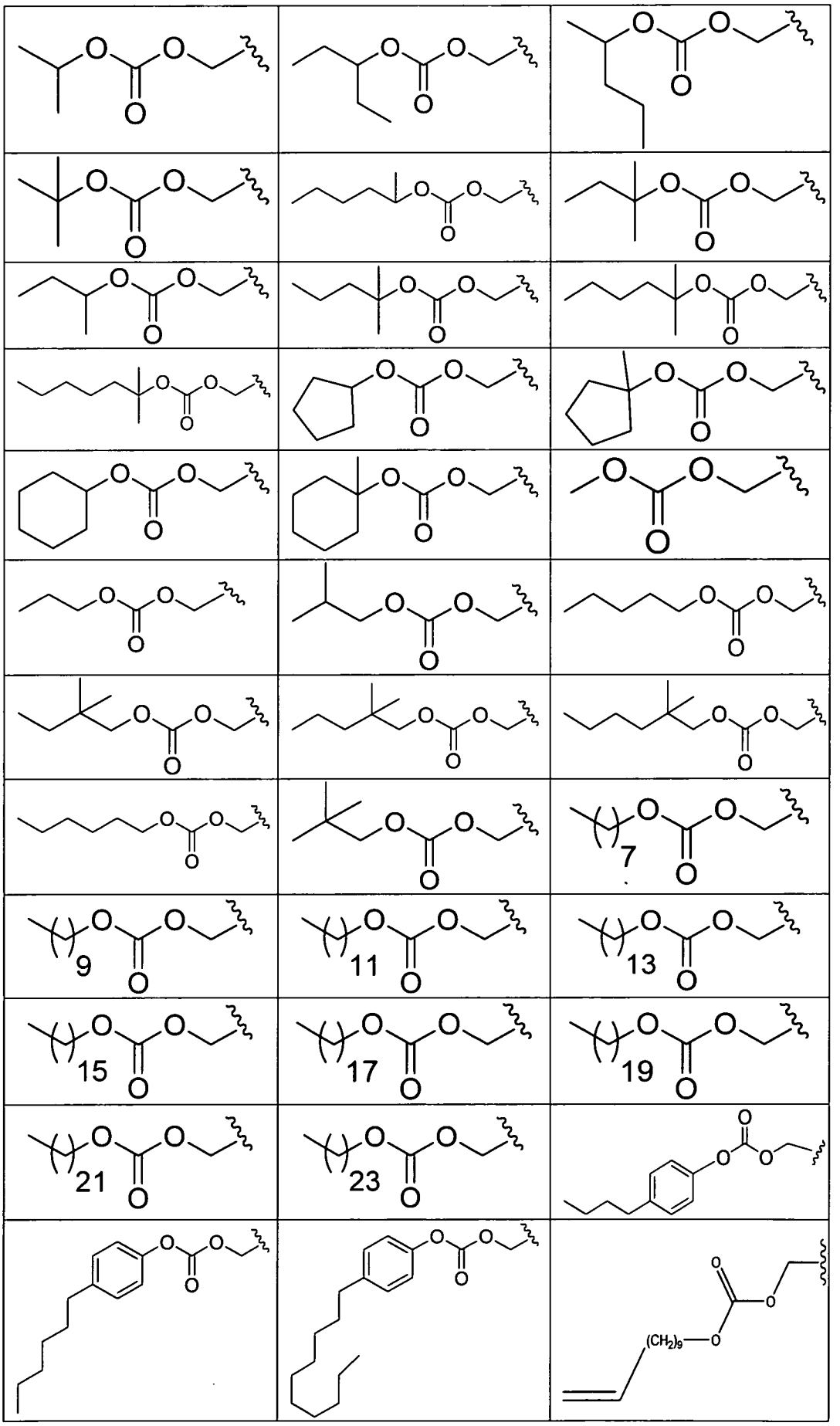
在一個更佳的具體例中，R_1是選自於表3。

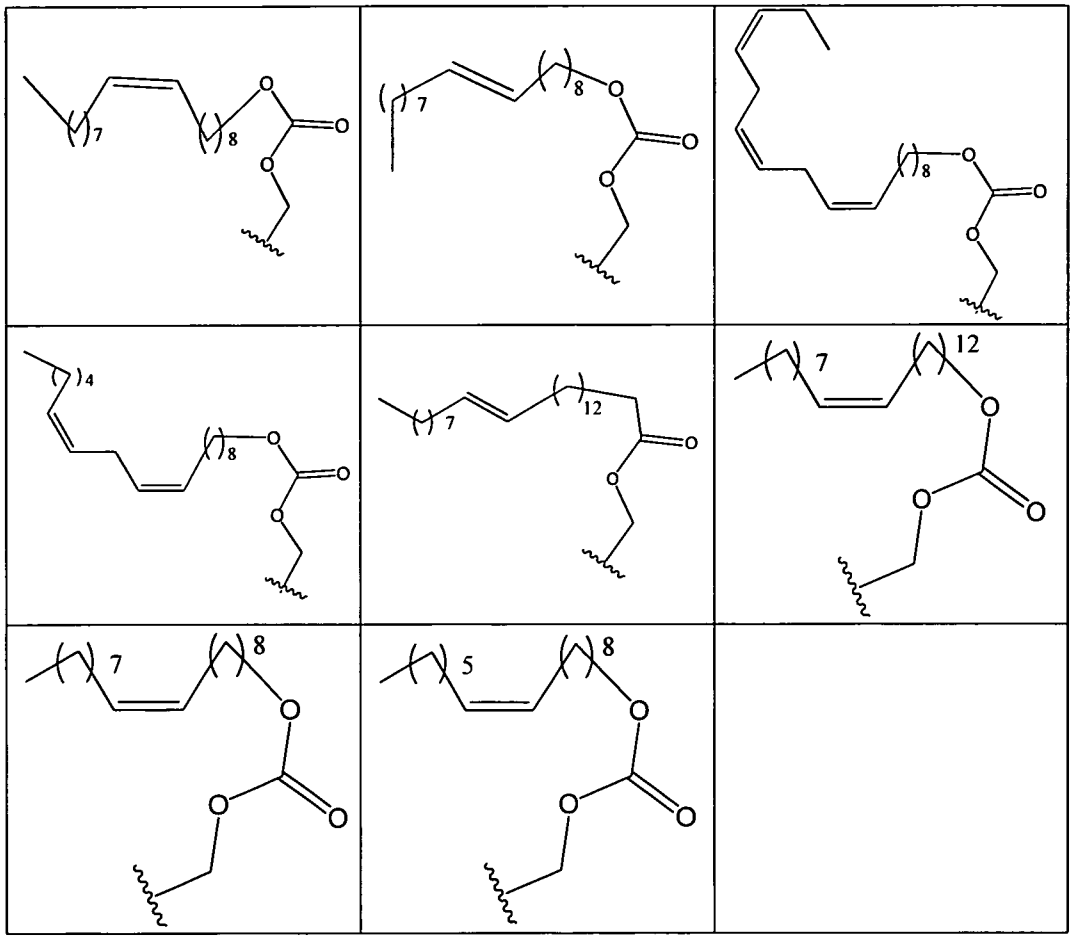
表3



在一個更佳的具體例中，R_1是選自於表4。

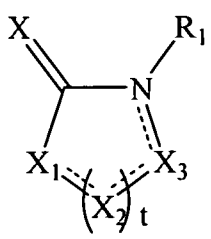
表4



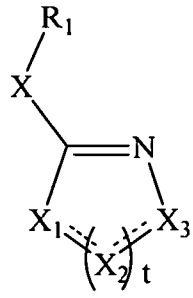


含有內醯胺、環尿素(cyclic urea)、醯亞胺、胺甲酸酯的藥效團的前驅藥

在一個具體例中，本發明的化合物是以如下面所例示說明的化學式IV或V來表示，或它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、它的藥學上可接受的鹽類共-晶體(co-crystal)以及溶劑合物：



化學式IV



化學式V

其中 ┈┈ 代表一單或雙鍵；

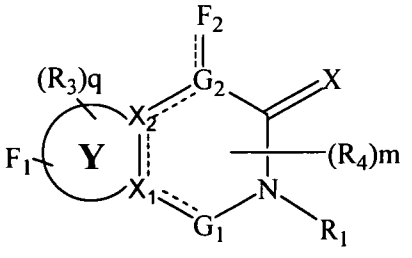
X以及R_1是如上面所定義的；

各個X_1、X_2以及X_3是獨立地選自於：不存在、-S-、-O-、-S(O)-、-S(O)$_2$-、-N(R_{10})-、-C(O)-、-C(OR_{10})(R_{11})-、-[C(R_{10})(R_{11})]$_v$-、-C(R_{10})=C(R_{10})-；其中v是0、1、2、3、4、5、6、7、8、9或10。

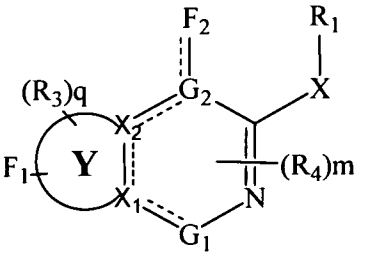
其中各個R_{10}以及R_{11}是獨立地選自於：不存在、氫、鹵素、脂族、經取代的脂族、芳基或經取代的芳基；另擇地，2個R_{10}和R_{11}與它們所接附的原子一起可形成一額外選擇性地經取代的3、4、5、6或7員環；以及

t是0、1、2或3。

在一個具體例中，本發明的化合物是以如下面所例示說明的化學式VI或VII來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式VI



化學式VII

其中 ┈┈ 代表一單或雙鍵；

X、X_1、X_2以及R_1是如上面所定義的；

環Y是一含有1、2或3環的選擇性地經取代的環烷基、環烯基、雜環基或芳基；

各個F_1以及F_2是獨立地選自於：不存在以及R_5-A-Cy_1-B-D-；

其中A是選自於：不存在、選擇性地經取代的烷基、選擇性地經取代的烯基、選擇性地經取代的炔基、-S-、-O-、-S(O)-、$-S(O)_2-$、$-S[C(R_{30})(R_{31})]_u-$、$-S(O)[C(R_{30})(R_{31})]_u-$、$-S(O)_2[C(R_{30})(R_{31})]_u-$、$-O[C(R_{30})(R_{31})]_u-$、$-N(R_{30})-$、$-N(R_{30})[C(R_{31})(R_{32})]_u-$、$-[C(R_{30})(R_{31})]_u$、$-C(O)[C(R_{30})(R_{31})]_u-$；

其中各個u獨立地是1、2、3、4、5、6或7；

Cy_1是不存在或一選擇性地經取代的環烷基、選擇性地經取代的環烯基、選擇性地經取代的雜環基、選擇性地經取代的芳基或選擇性地經取代的雜芳基；

B是不存在或一連接子(linker)；

D是選自於：不存在、-O-、$-NR_{33}$、$-C(R_{34})(R_{35})-$、-S-、-S(O)-、$-S(O)_2-$以及-C(O)-；

各個G_1以及G_2是獨立地選自於：不存在、-S-、-O-、-S(O)-、$-S(O)_2-$、$-SC(R_{40})(R_{41})-$、$-S(O)C(R_{40})(R_{41})-$、$-S(O)_2C(R_{40})(R_{41})-$、$-C(O)-$、$-C(OR_{40})(R_{41})-$、$-OC(R_{40})(R_{41})-$、$-N(R_{40})-$、$-C(R_{40})=C(R_{41})-$、$-N(R_{40})-C(R_{41})(R_{42})-$以及$-[C(R_{40})(R_{41})]_u-$；

各個R_3、R_4、R_5、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{40}、R_{41}以及R_{42}是獨立地選自於：不存在、氫、鹵素、$-OR_{10}$、$-SR_{10}$、$-NR_{10}R_{11}$、$-C(O)R_{10}$、選擇性地經取代的脂族、選擇性地經取代的芳基或選擇性地經取代的雜環基；

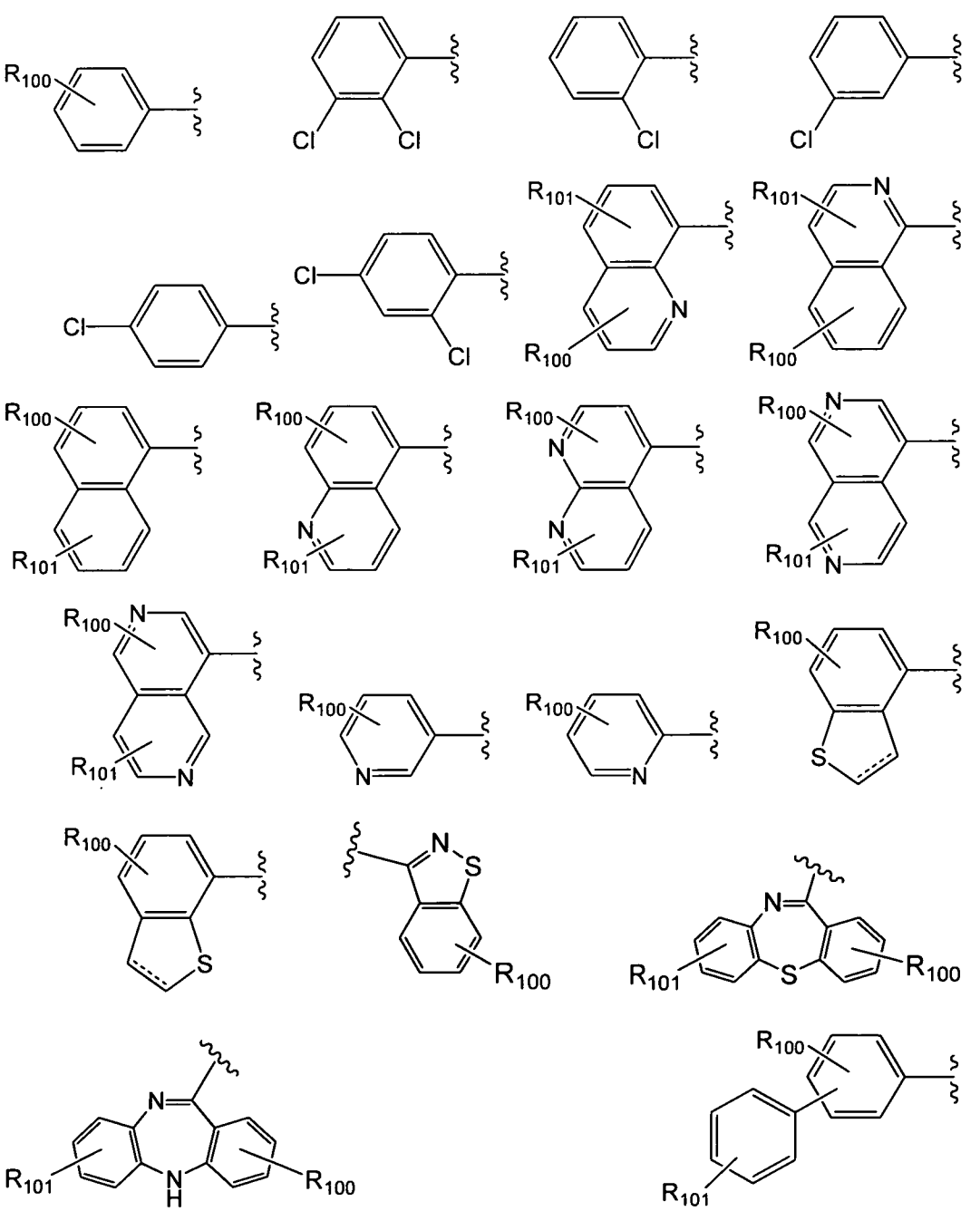
另擇地，2個R_3基團或2個R_4基團或1個R_3基團和1個R_4

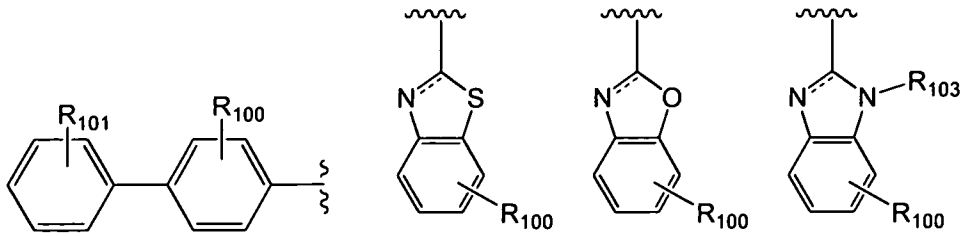
基團與它們所接附的原子和任何居間的原子(intervening atoms)一起形成一選擇性地經取代的環；

m以及q是獨立地選自於0、1以及2。

在一個較佳的具體例中，G_2是選自於：-N-或-C(R_{10})-。

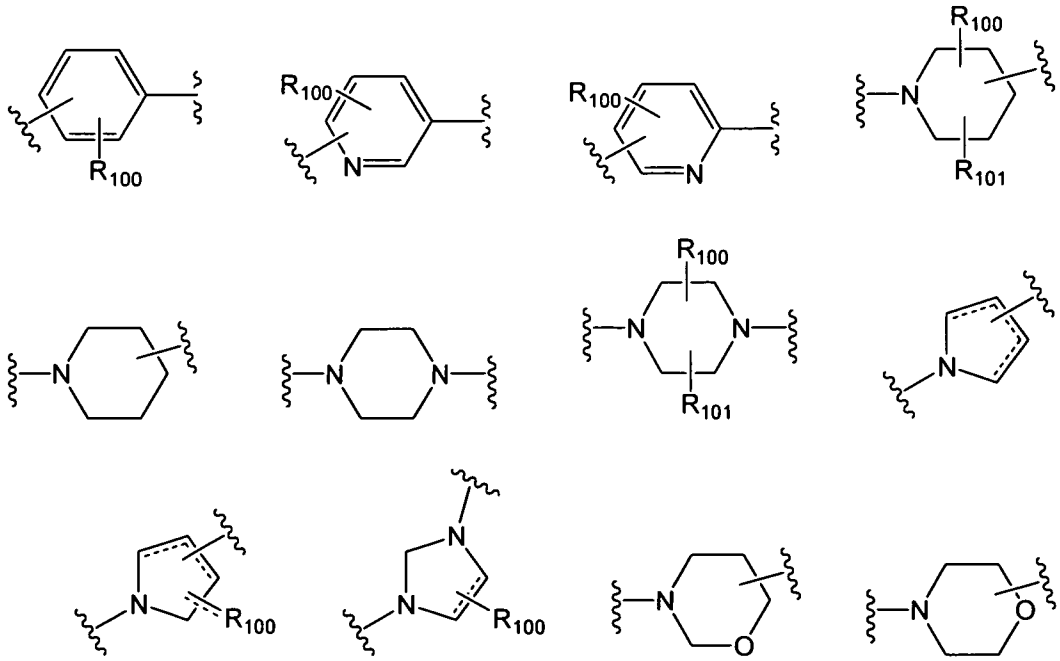
在一個較佳的具體例中，該R_5部分是一選自於下列的芳基或雜芳基基團：

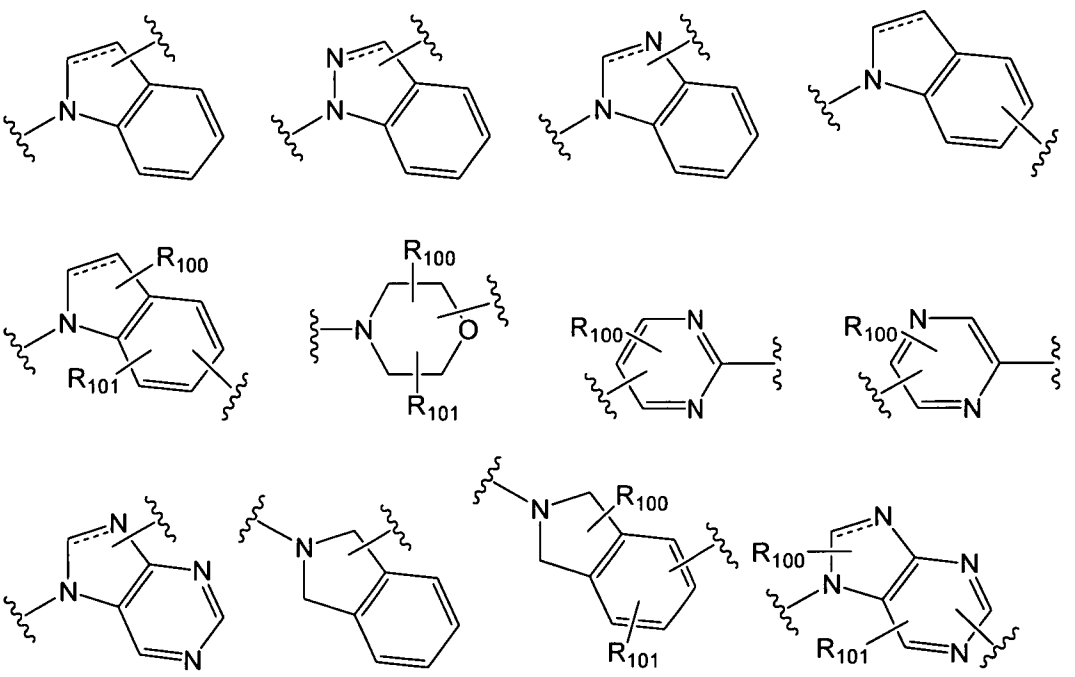




其中R_{100}以及R_{101}各個代表1至4個獨立地選自於下列的取代基：氫、鹵素、選擇性地經取代的C_1-C_8烷基、選擇性地經取代的C_2-C_8烯基、選擇性地經取代的C_2-C_8炔基、選擇性地經取代的C_3-C_8環烷基、選擇性地經取代的C_1-C_8烷氧基、選擇性地經取代的C_1-C_8烷基胺基以及選擇性地經取代的C_1-C_8芳基；以及R_{103}是選自於：氫、鹵素、選擇性地經取代的C_1-C_8烷基、選擇性地經取代的C_2-C_8烯基、選擇性地經取代的C_2-C_8炔基、選擇性地經取代的C_3-C_8環烷基、選擇性地經取代的C_1-C_8烷氧基、選擇性地經取代的C_1-C_8烷基胺基以及選擇性地經取代的C_1-C_8芳基。

在一個較佳的具體例中，Cy_1是選自於：

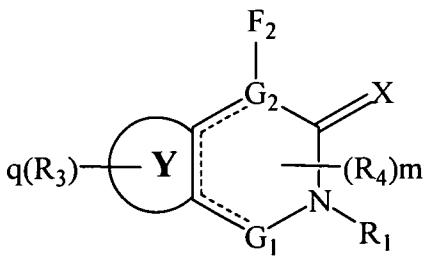




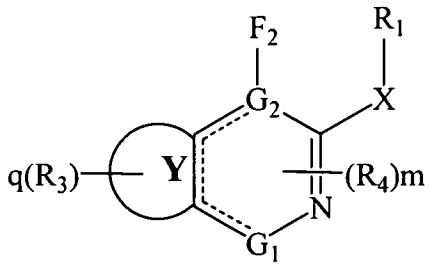
在一個較佳的具體例中，二價的B是一直接的鍵、一直鏈(straight chain)的C_1-C_{10}烷基、C_1-C_{10}烯基、C_1-C_{10}炔基、C_1-C_{10}烷氧基、烷氧基C_1-C_{10}烷氧基、C_1-C_{10}烷基胺基、烷氧基C_1-C_{10}烷基胺基、C_1-C_{10}烷基羰基胺基、C_1-C_{10}烷基胺基羰基、芳氧基C_1-C_{10}烷氧基、芳氧基C_1-C_{10}烷基胺基、芳氧基C_1-C_{10}烷基胺基羰基、C_1-C_{10}烷基胺基烷基胺基羰基、C_1-C_{10}烷基(N-烷基)胺基烷基-胺基羰基、烷基胺基烷基胺基、烷基羰基胺基烷基胺基、烷基(N-烷基)胺基烷基胺基、(N-烷基)烷基羰基胺基烷基胺基、烷基胺基烷基、烷基胺基烷基胺基烷基、烷基哌咔並烷基、哌咔並烷基、烷基哌咔並、烯基芳氧基C_1-C_{10}烷氧基、烯基芳基胺基C_1-C_{10}烷氧基、烯基芳基烷基胺基C_1-C_{10}烷氧基、烯基芳氧基C_1-C_{10}烷基胺基、烯基芳氧基C_1-C_{10}烷基胺基羰基、哌咔並烷基芳基、雜芳基C_1-C_{10}烷基、雜芳基C_2-C_{10}烯基、雜芳基C_2-C_{10}炔基、雜芳基C_1-C_{10}烷基胺基、雜芳基C_1-C_{10}烷氧基、雜芳

氧基C_1-C_{10}烷基、雜芳氧基C_2-C_{10}烯基、雜芳氧基C_2-C_{10}炔基、雜芳氧基C_1-C_{10}烷基胺基或雜芳氧基C_1-C_{10}烷氧基。

在一個具體例中，本發明的化合物是以如下面所例示說明的化學式VIII或VIIIA來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



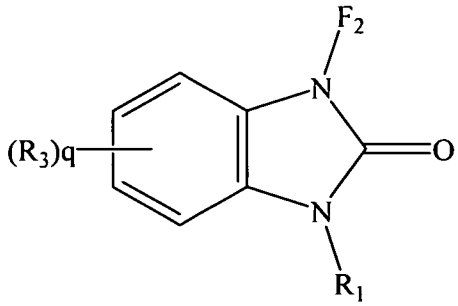
化學式VIII



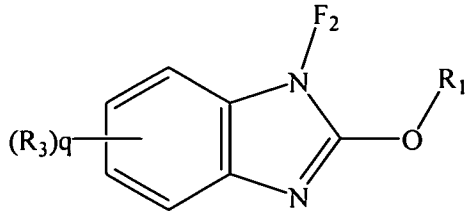
化學式 VIIIA

其中環Y、R_1、R_3、R_4、G_1、G_2、X、F_2、m以及q是如上面所定義的。

在一個更佳的具體例中，本發明的化合物是以如下面所例示說明的化學式IX或X來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式IX



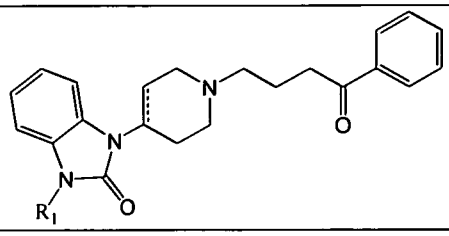
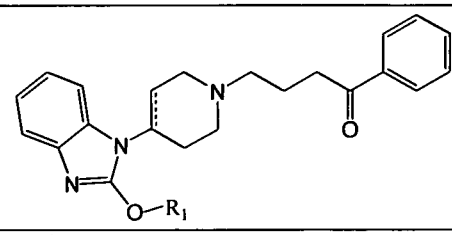
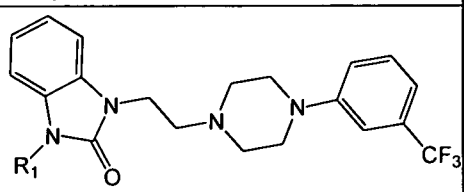
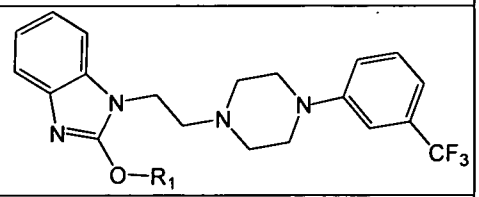
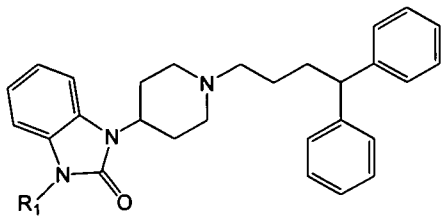
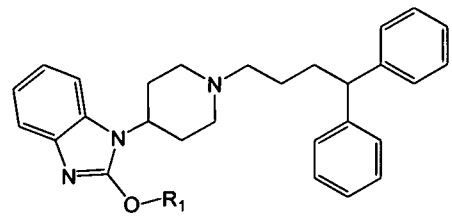
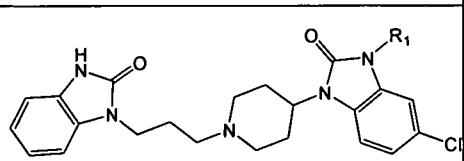
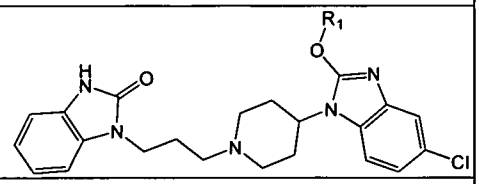
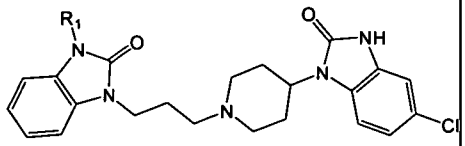
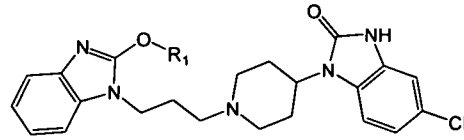
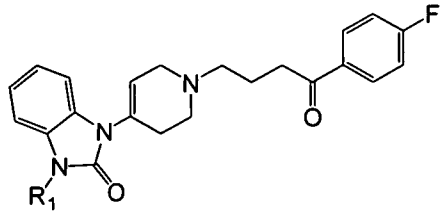
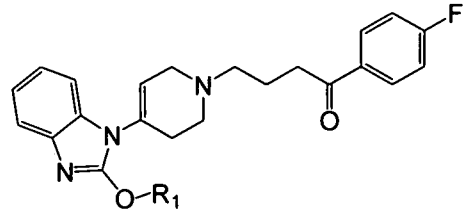
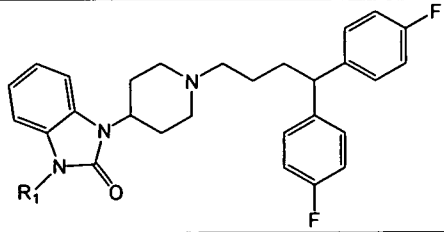
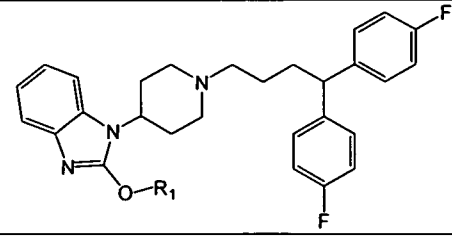
化學式X

其中R_1、R_3、F_2以及q是如上面所定義的。

在一個較佳的具體例中，一化合物是選自於表IX-X。

一更佳的具體例是一來自表IX-X的化合物，其中R_1是選自於表1-4。

表IX-X

編號	結構	編號	結構
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

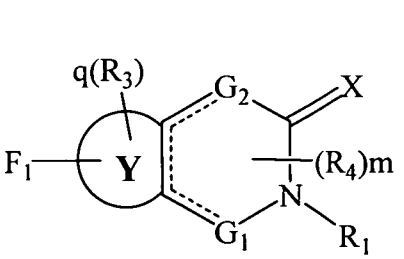
在一個更佳的具體例中，多潘立酮(domperidone)的前驅藥被揭示。(來自表IX-X的化學式4以及11)。一更佳的具

體例是一來自表IX-X的具有化學式4的化合物，其中R_1是選自於表1。在一個更佳的具體例中，一來自表IX-X的具有化學式4的化合物(其中R_1是選自於表2-4)被揭示。

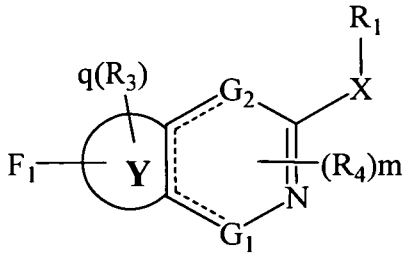
在一個更佳的具體例中，氟哌利多(droperidol)的前驅藥被揭示。(來自表IX-X的化學式6以及13)。在一個更佳的具體例中，一來自表IX-X的具有化學式6的化合物(其中R_1是選自於表1)被揭示。一更佳的具體例是一來自表IX-X的具有化學式6的化合物，其中R_1是選自於表2-4。

在一個更佳的具體例中，匹莫齊特(pimozide)的前驅藥被揭示。(來自表IX-X的化學式7以及14)。在一個更佳的具體例中，一來自表IX-X的具有化學式7的化合物(其中R_1是選自於表1)被揭示。在一個更佳的具體例中，一來自表IX-X的具有化學式7的化合物(其中R_1是選自於表2-4)被揭示。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XI或XII來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



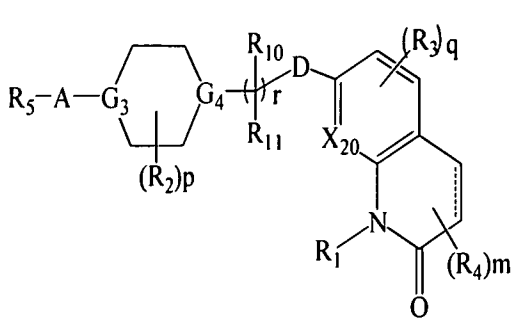
化學式XI



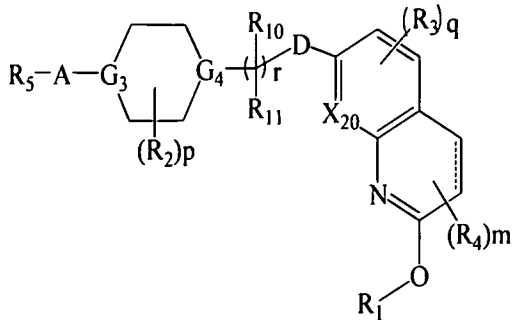
化學式XII

其中環Y、R_1、R_3、R_4、X、F_1、G_1、G_2、m以及q是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIA或XIIA來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XIA



化學式XIIA

其中R_1、R_3、R_4、R_5、R_{10}、R_{11}、A、D、m以及q是如上面所定義的；

R_2是選自於：不存在、氫、鹵素、$-OR_{10}$、$-SR_{10}$、$-NR_{10}R_{11}-$、選擇性地經取代的脂族、選擇性地經取代的芳基或芳基或選擇性地經取代的雜環基；

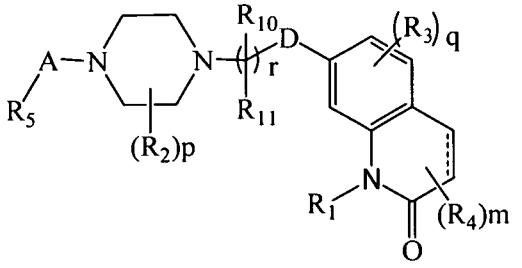
r是0、1、2、3、4、5、6、7、8、9、10或11；

各個G_3以及G_4是獨立地選自於：-N-以及$-C(R_{10})-[C(R_{10})(R_{11})]_a-$，其中a是0、1或2；

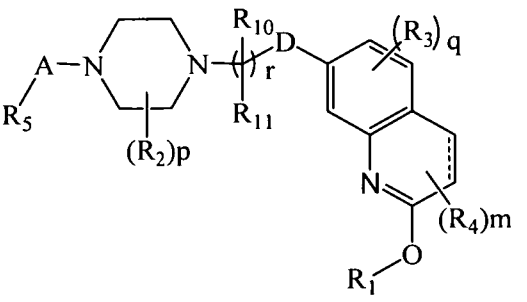
X_{20}是$-C(R_{10})-$或-N-；以及

p是0、1、2或3。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIB或XIIB來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



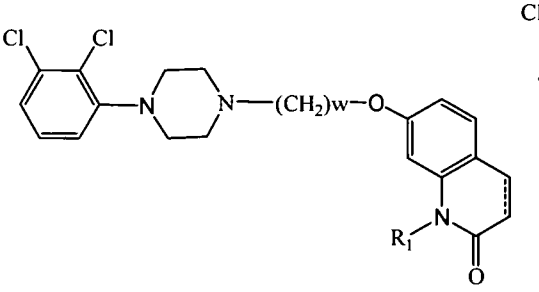
化學式XIB



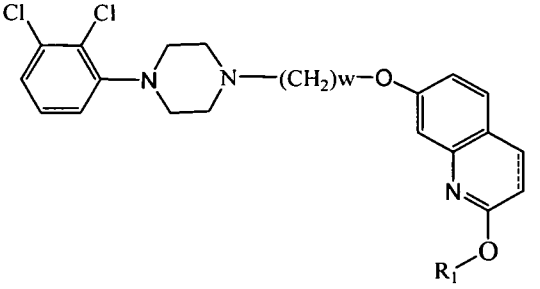
化學式XIIB

其中R_1、R_2、R_3、R_4、R_5、R_{10}、R_{11}、A、D、m、p以及q是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIC或XIIC來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XIC

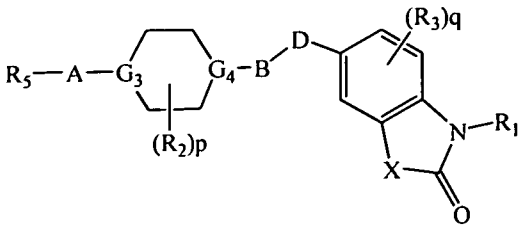


化學式XIIC

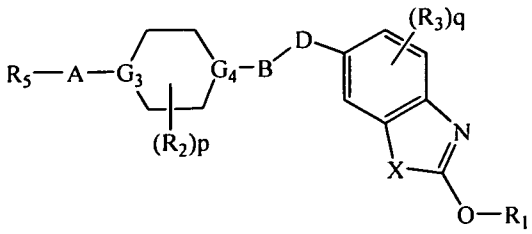
其中R_1是如上面所定義的；以及

w是1、2、3、4、5、6、7、8、9、10或11。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XID或XIID來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



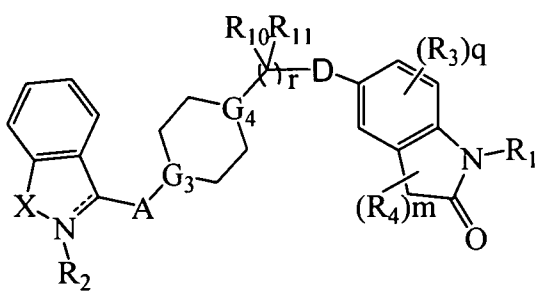
化學式XID



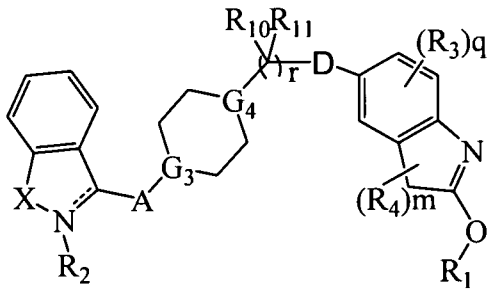
化學式XIID

其中，X_1、R_1、R_2、R_3、R_5、A、B、D、G_3、G_4、p、q、R_{10}以及R_{11}是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIE或XIIE來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



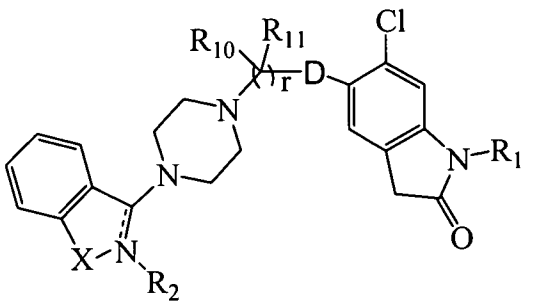
化學式XIE



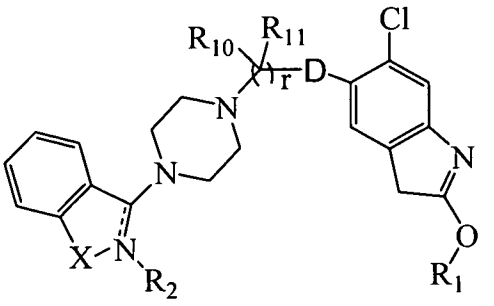
化學式XIIE

其中X、R_1、R_2、R_3、R_4、A、D、G_3、G_4、m、q、r、R_{10}以及R_{11}是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIF或XIIF來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



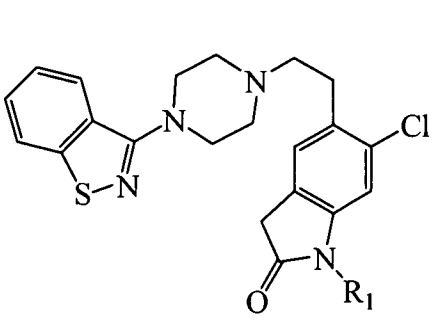
化學式XIF



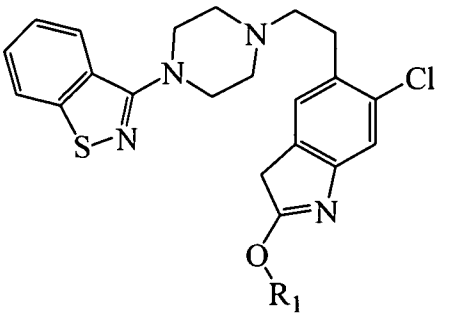
化學式XIIF

其中，X、R_1、R_2、D、r、R_{10}以及R_{11}是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIG或XIIG來表示，或它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



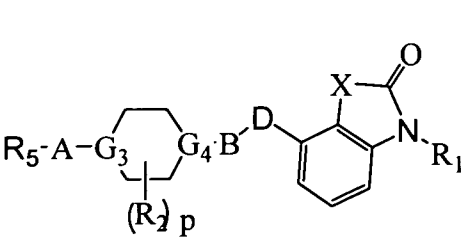
化學式XIG

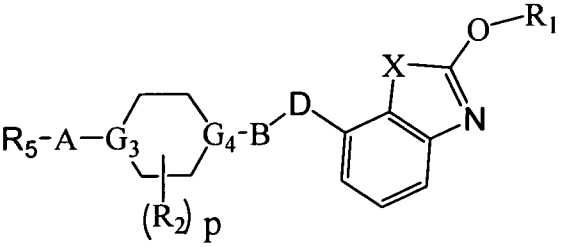


化學式XIIG

其中R_1是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIH或XIIH來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：

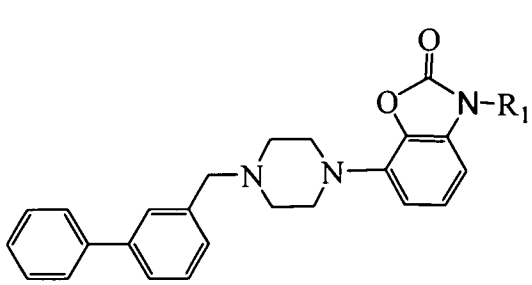


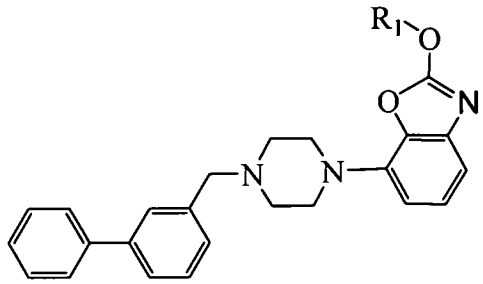


化學式XIH　　化學式XIIH

其中，X、R_1、R_2、R_5、A、D、G_3、G_4以及p是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XI-I或XII-I來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：

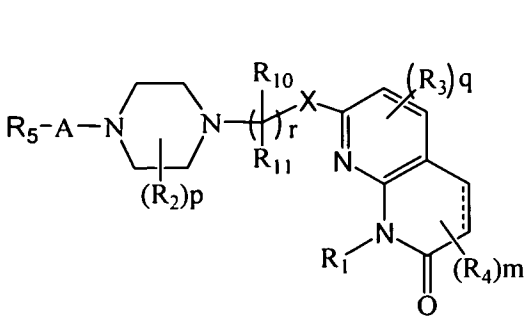


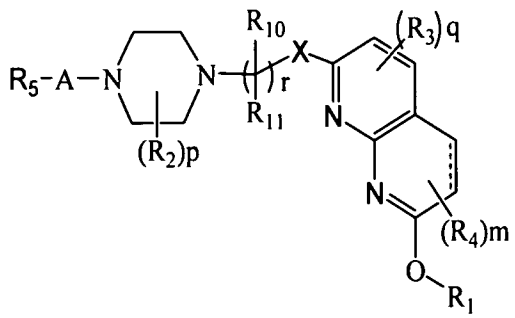


化學式XI-I　　化學式XII-I

其中R_1是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIJ或XIIJ來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



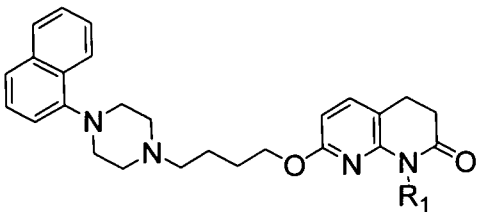


化學式XIJ　　化學式XIIJ

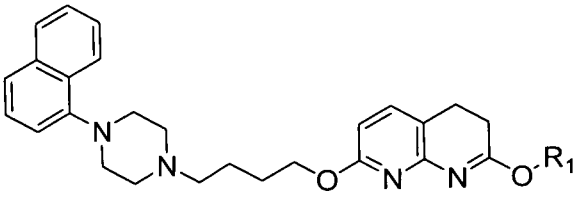
其中X、R_1、R_2、R_3、R_4、R_5、A、D、G_3、G_4、p、R_{10}以

及R_{11}是如上面所定義的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIK或XIIK來表示，或它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XIK

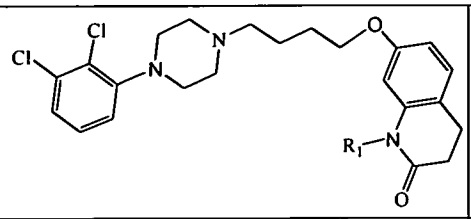
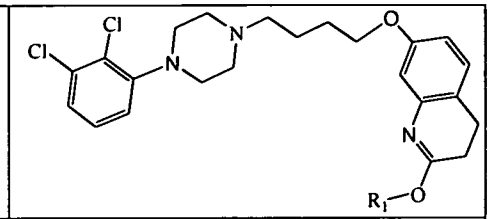
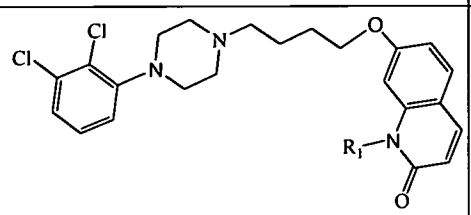
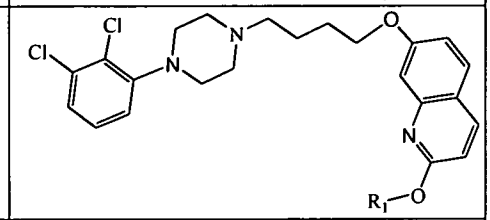
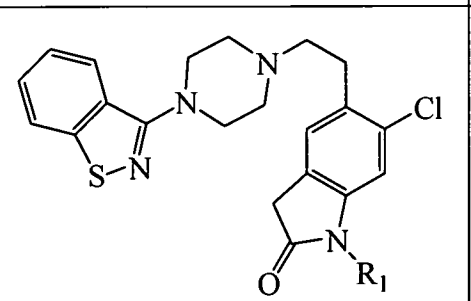
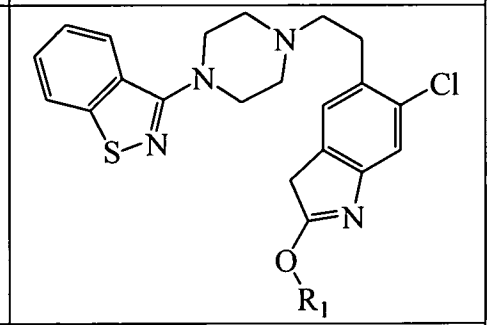
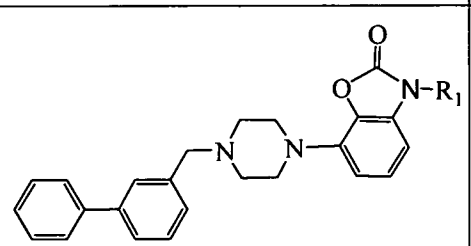
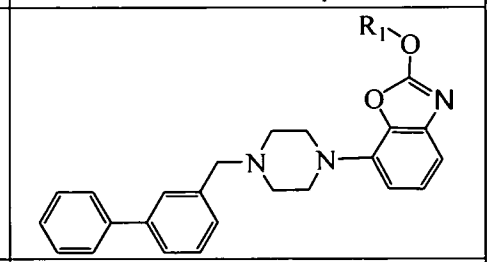
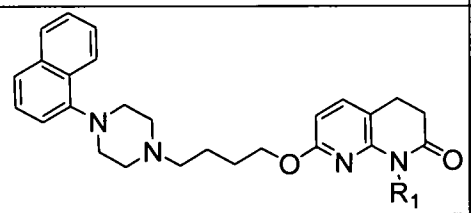
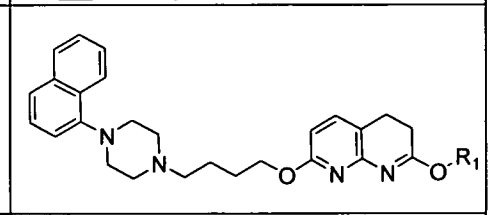
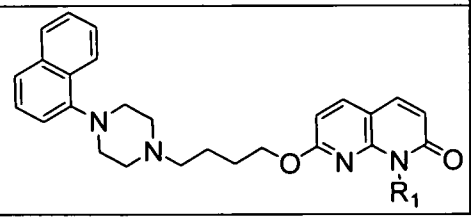
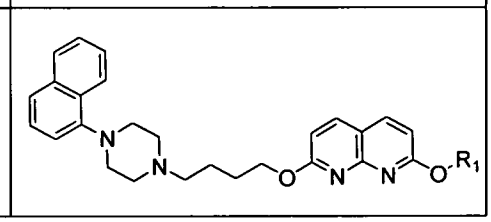


化學式XIIK

其中R_1是如上面所定義的。

在一個較佳的具體例中，一化合物是選自於表XI-XII。一更佳的具體例是一來自表XI-XII的化合物，其中R_1是選自於表1-4。

表XI-XII

1		7	
2		8	
3		9	
4		10	
5		11	
6		12	

在一個更佳的具體例中，阿立哌唑(aripiprazole)的前驅藥被揭示(來自表XI-XII的化學式1以及7)。在一個更佳的具體例中，一具有化學式1的化合物(其中R_1是選自於表1)被揭示。在一個更佳的具體例中，一具有化學式1的化合物(其

中R_1是選自於表2-4)被揭示。

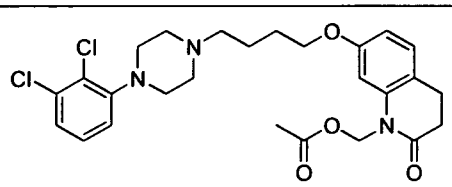
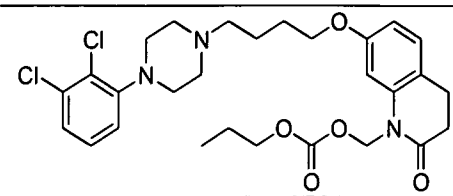
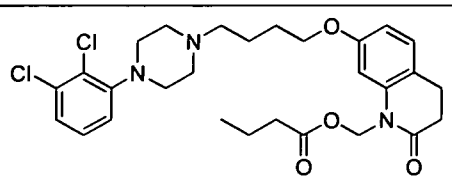
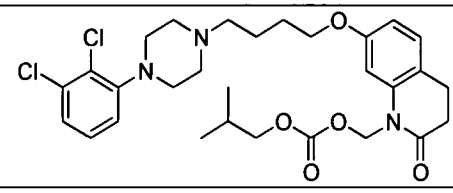
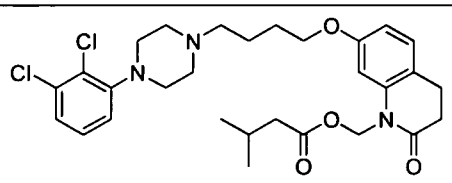
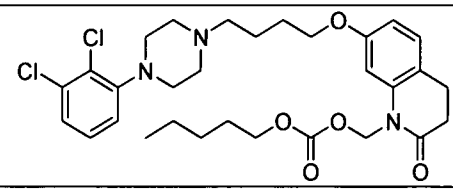
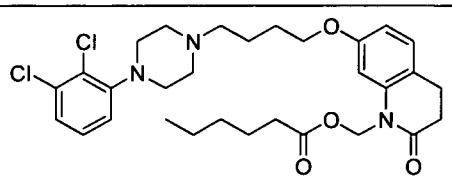
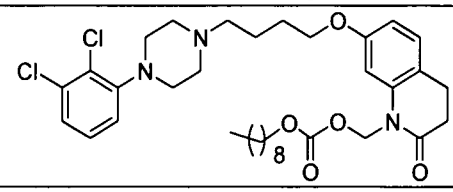
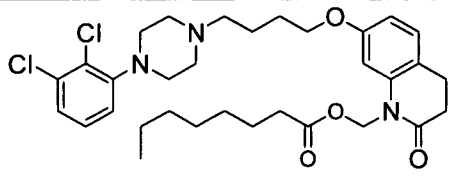
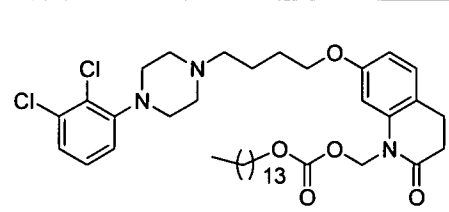
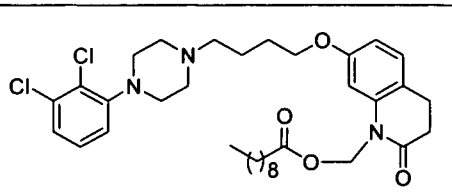
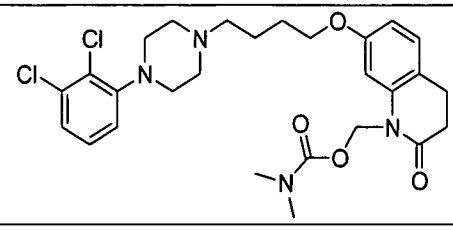
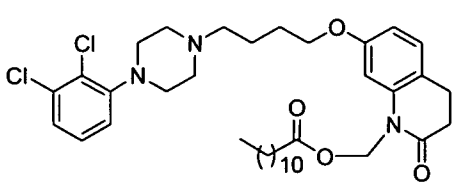
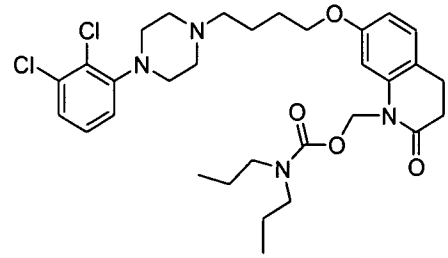
在一個更佳的具體例中，去氫阿立哌唑(dehydroaripiprazole)的前驅藥被揭示(來自表XI-XII的化學式2以及8)。在一個更佳的具體例中，一具有化學式2的化合物(其中R_1是選自於表1)被揭示。在一個更佳的具體例中，一具有化學式2的化合物(其中R_1是選自於表2-4)被揭示。

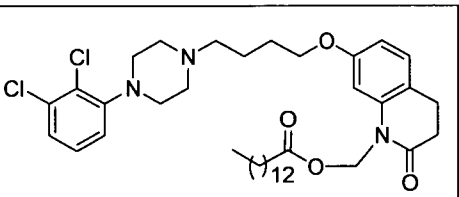
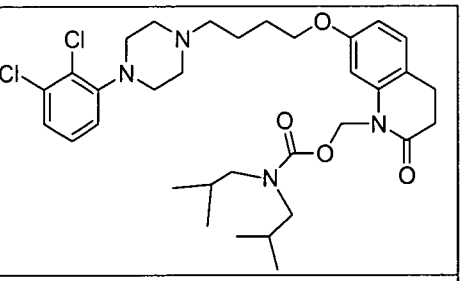
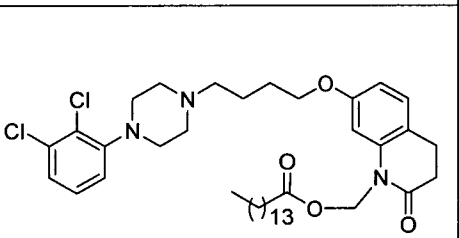
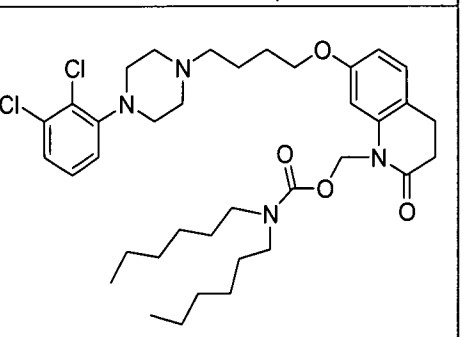
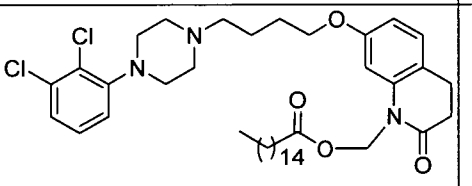
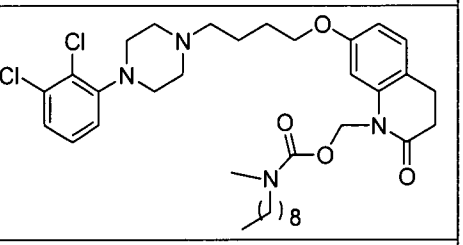
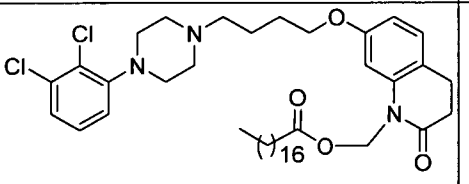
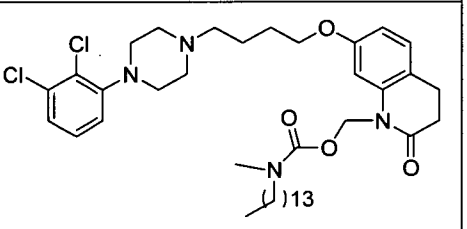
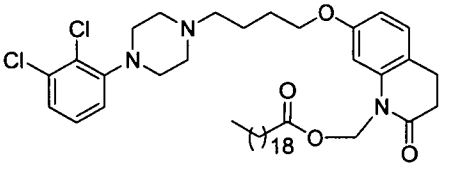
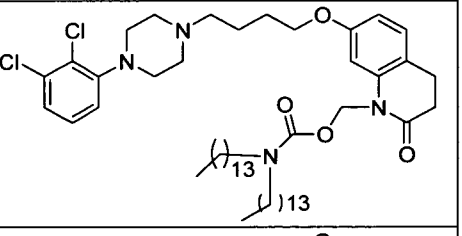
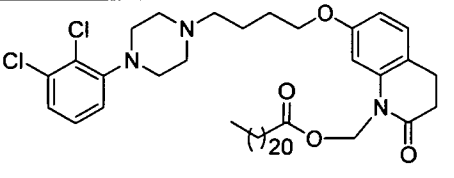
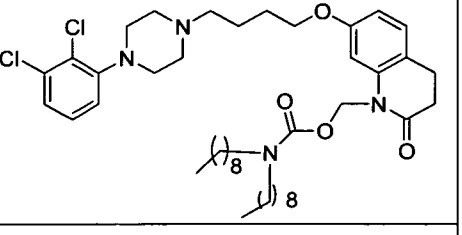
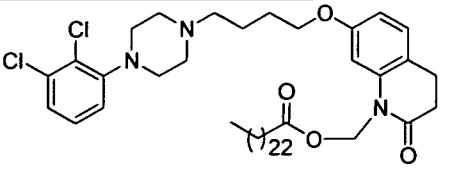
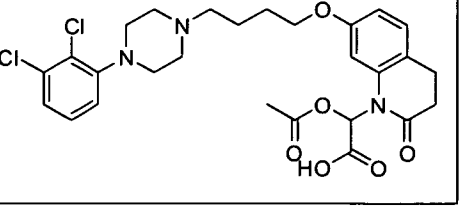
在一個更佳的具體例中，齊拉西酮(ziprasidone)的前驅藥被揭示(來自表XI-XII的化學式3以及9)。在一個更佳的具體例中，一具有化學式3的化合物(其中R_1是選自於表1)被揭示。在一個更佳的具體例中，一具有化學式3的化合物(其中R_1是選自於表2-4)被揭示。

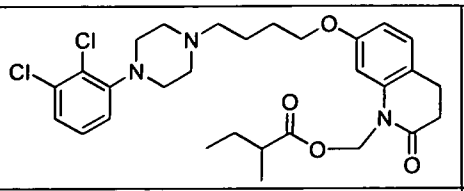
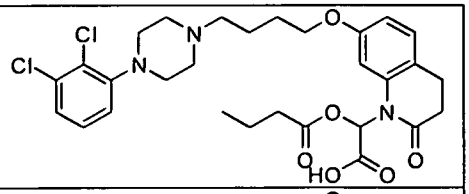
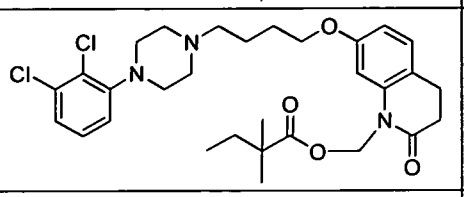
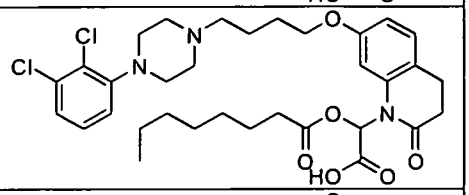
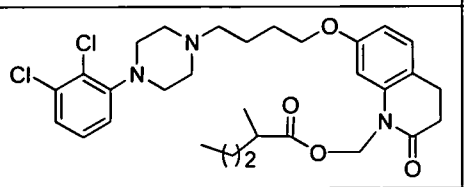
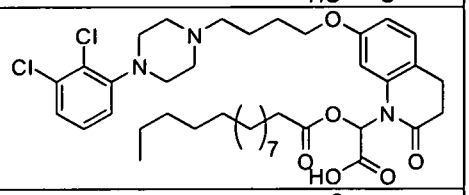
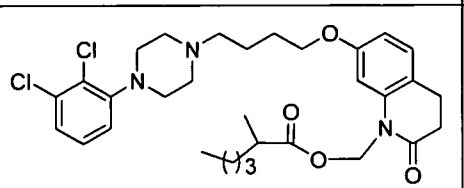
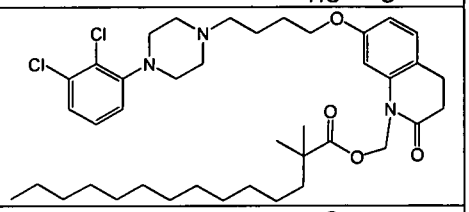
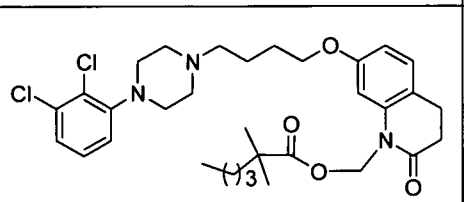
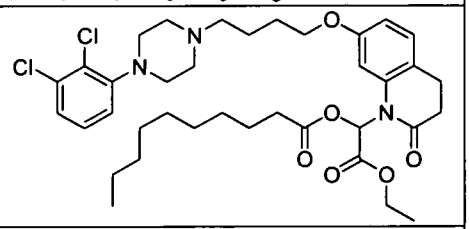
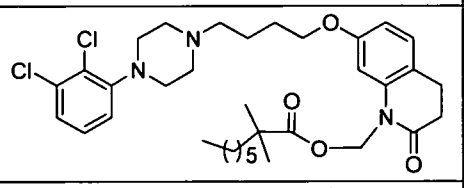
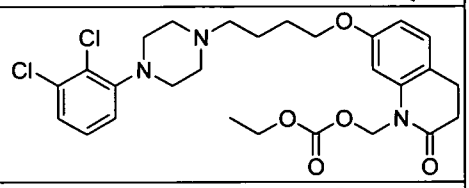
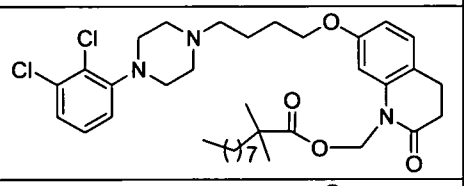
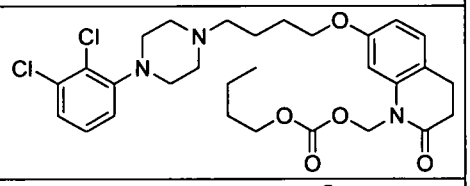
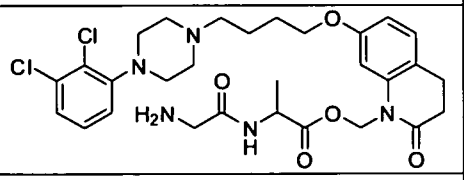
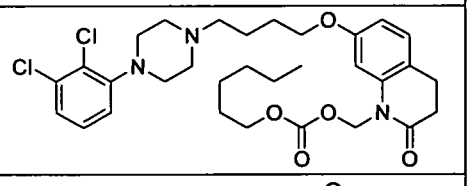
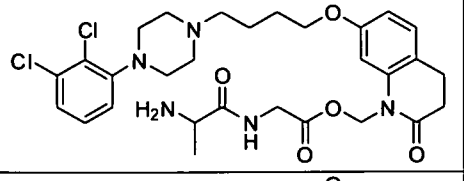
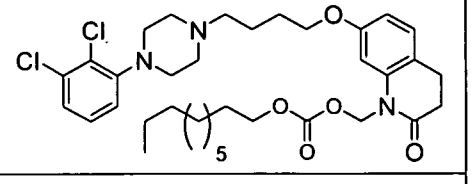
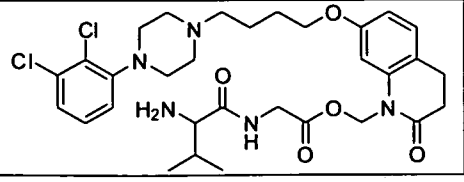
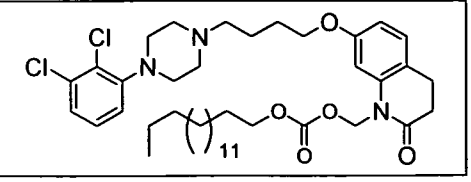
在一個更佳的具體例中，百芬普那(bifeprunox)的前驅藥被揭示(來自表XI-XII的化學式4以及11)。在一個更佳的具體例中，一具有化學式4的化合物(其中R_1是選自於表1)被揭示。在一個更佳的具體例中，一具有化學式4的化合物(其中R_1是選自於表2-4)被揭示。

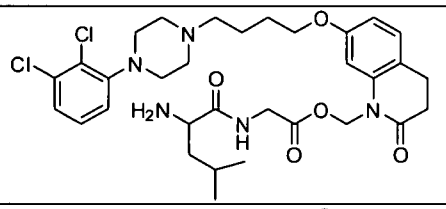
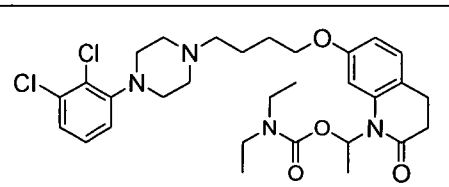
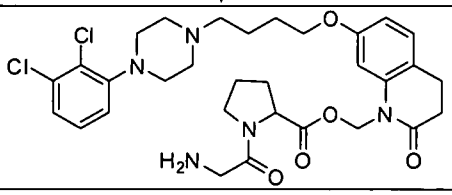
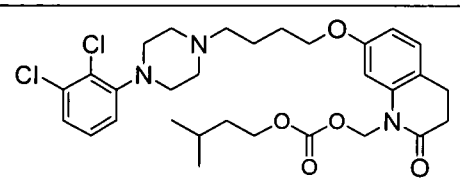
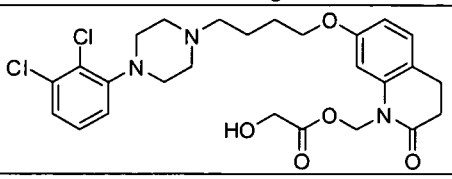
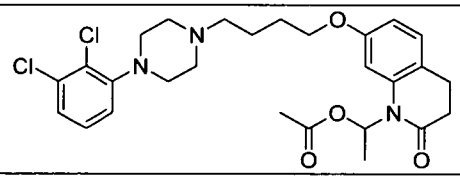
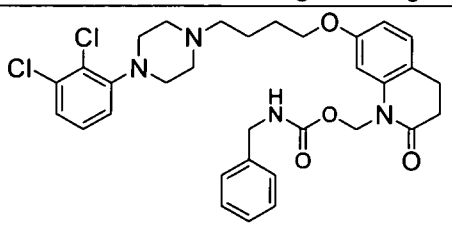
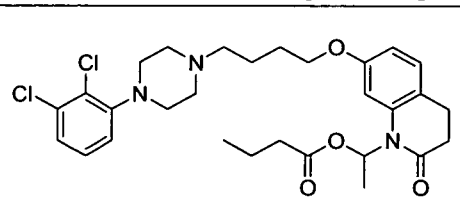
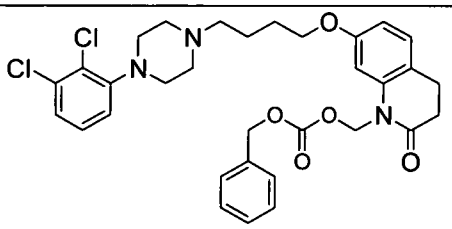
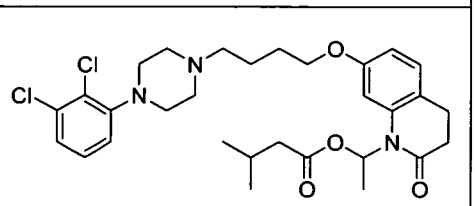
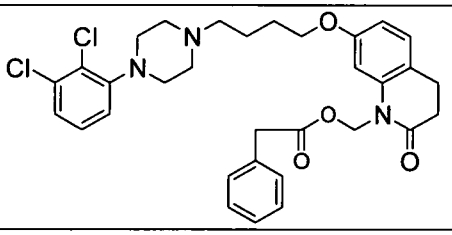
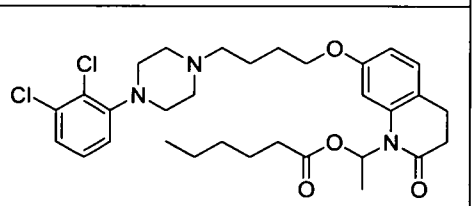
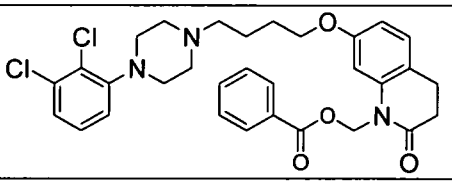
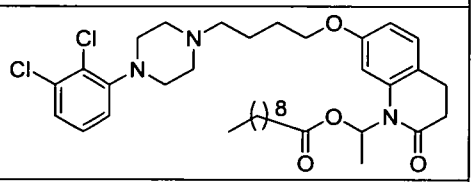
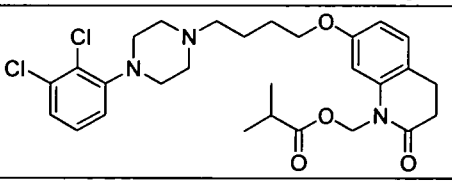
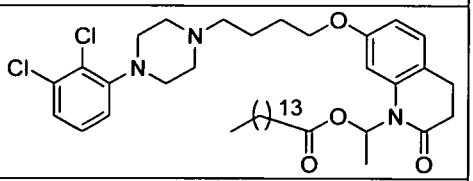
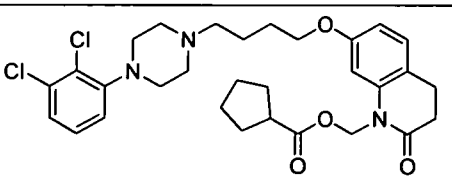
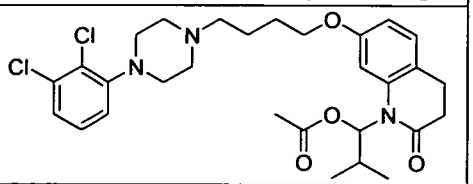
依據本發明的代表性化合物是那些選自於下面表A－I者以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：

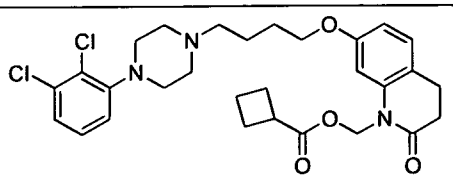
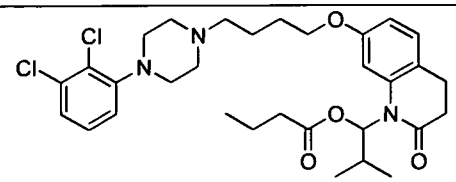
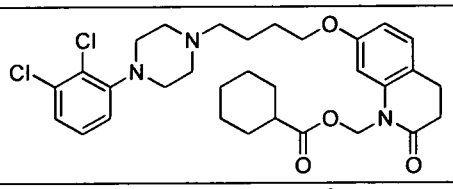
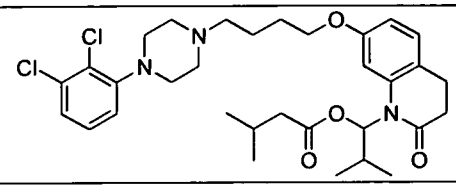
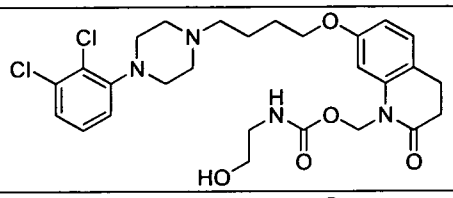
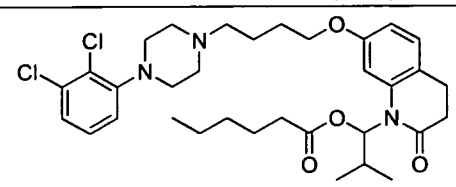
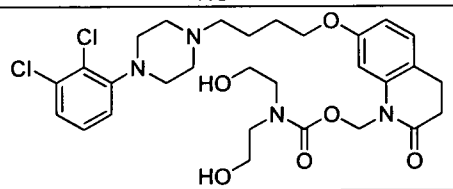
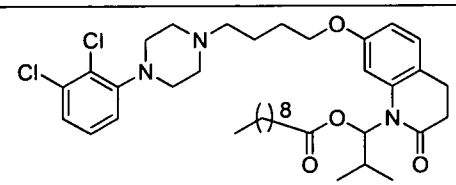
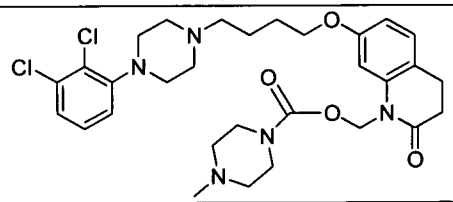
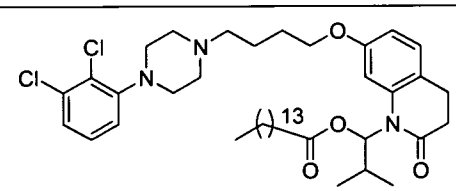
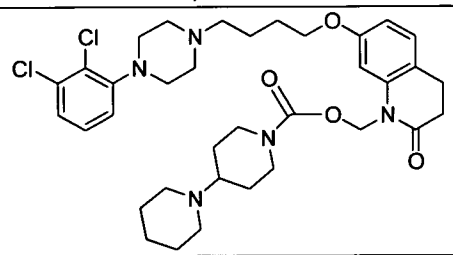
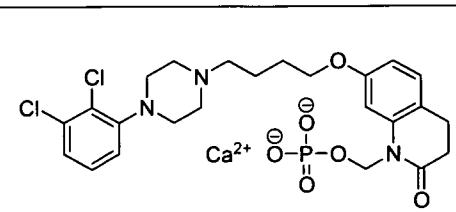
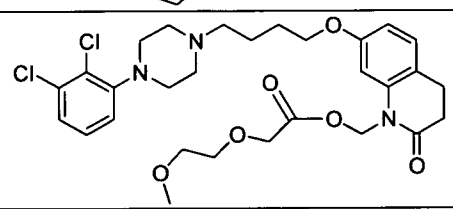
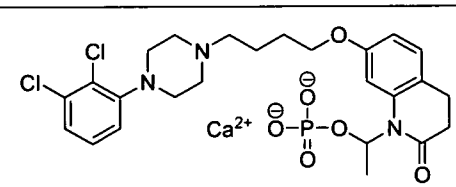
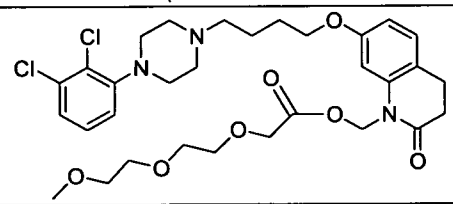
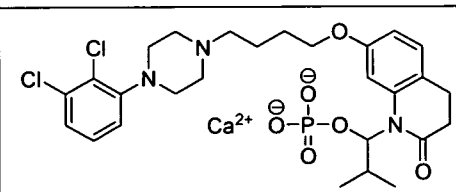
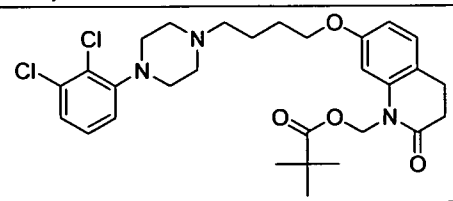
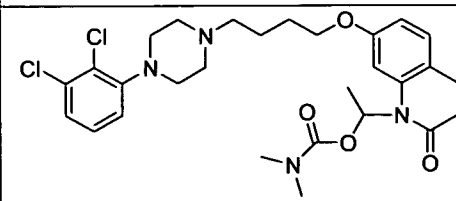
表A

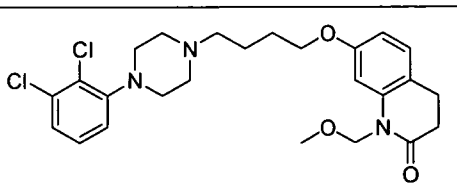
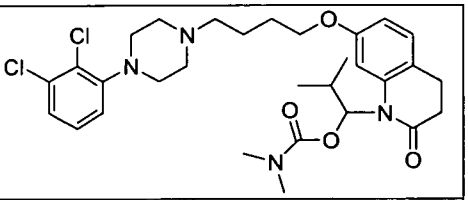
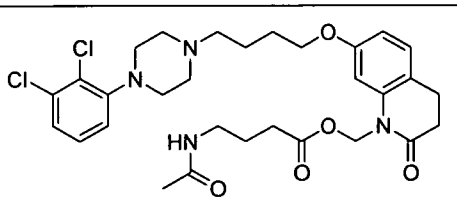
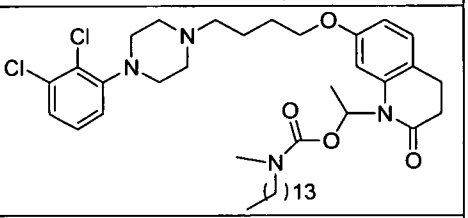
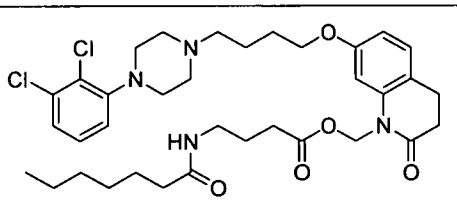
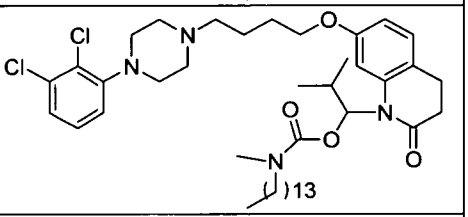
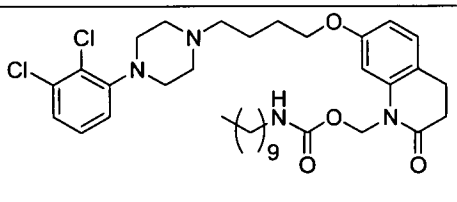
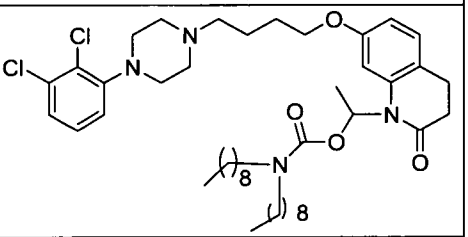
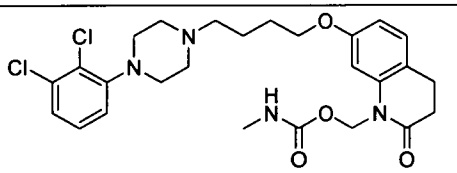
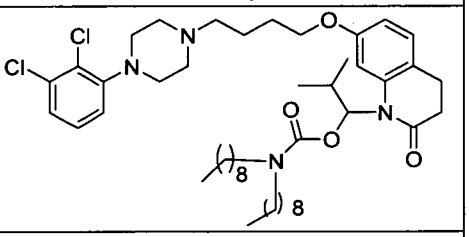
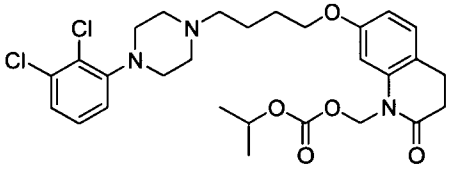
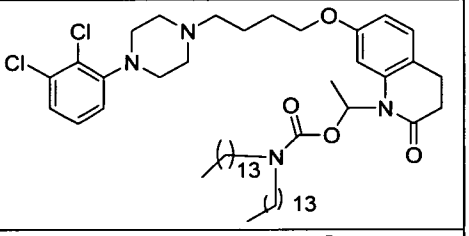
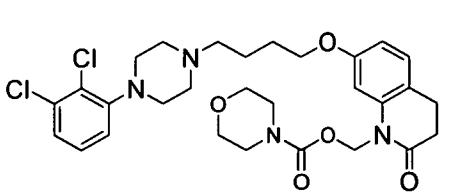
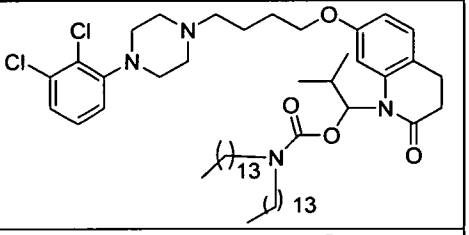
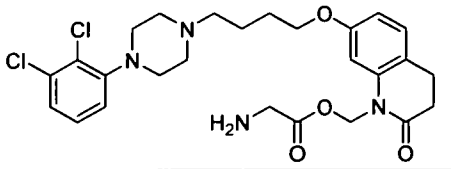
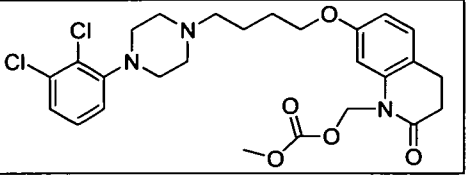
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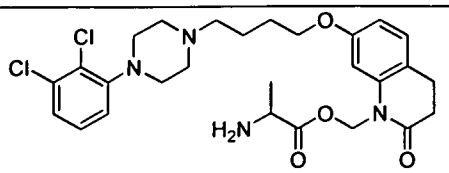
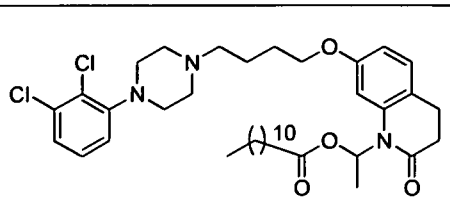
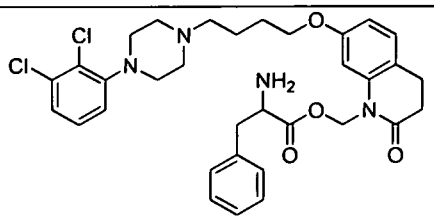
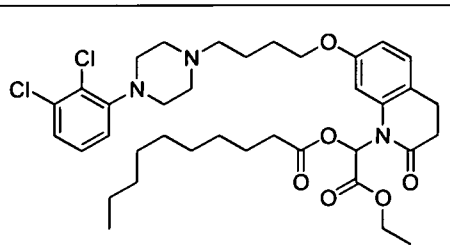
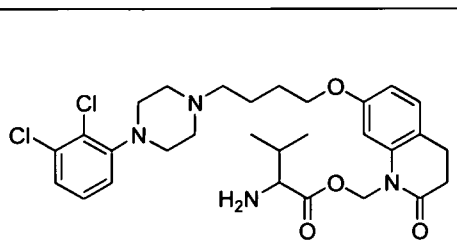
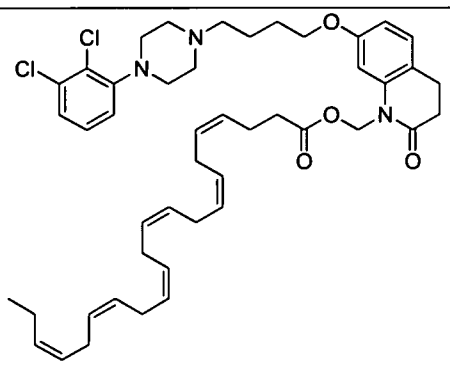
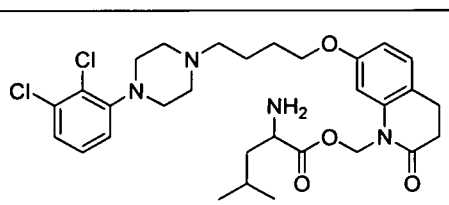
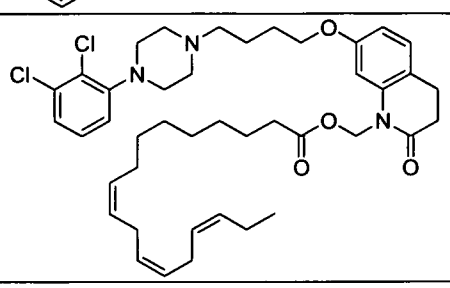
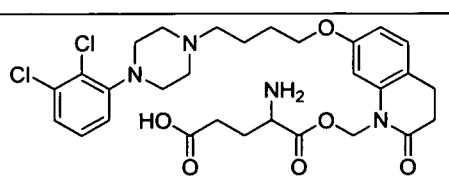
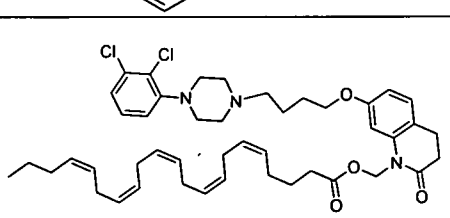
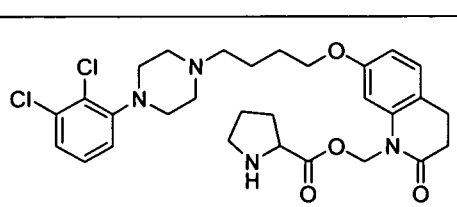
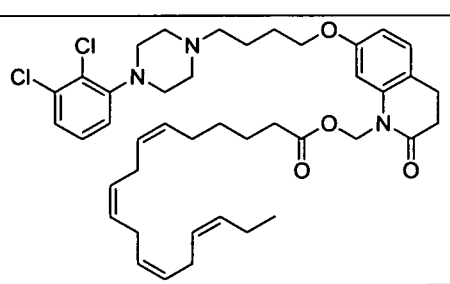
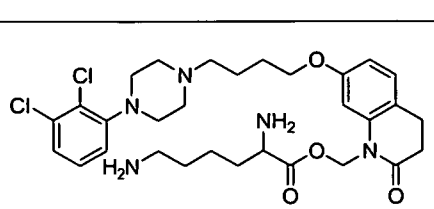
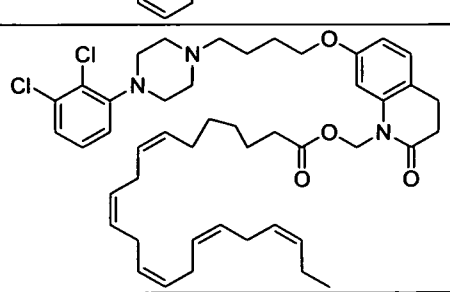
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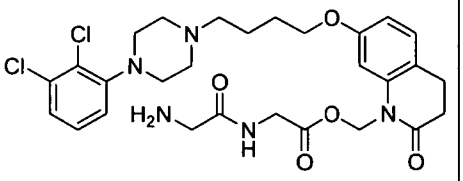
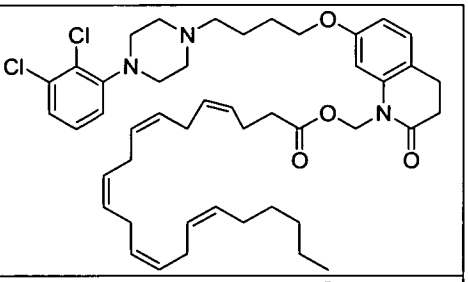
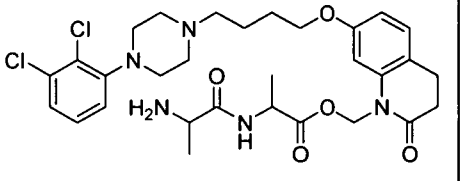
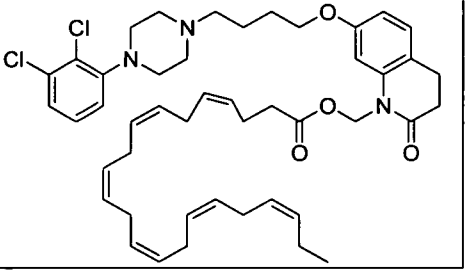
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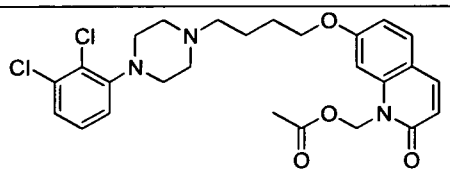
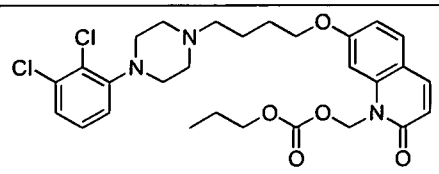
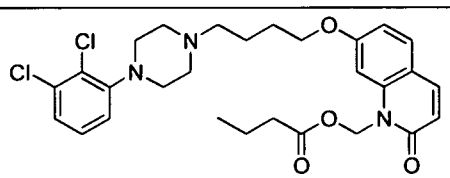
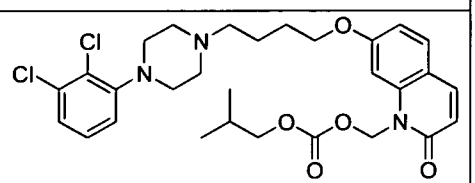
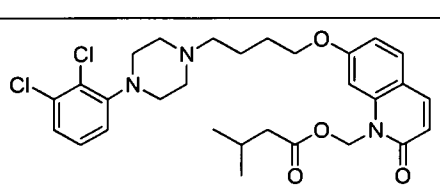
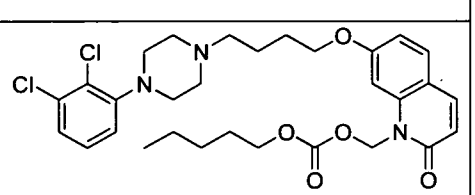
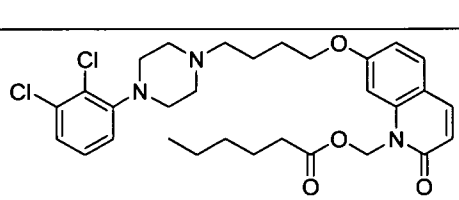
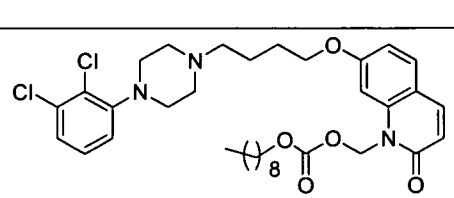
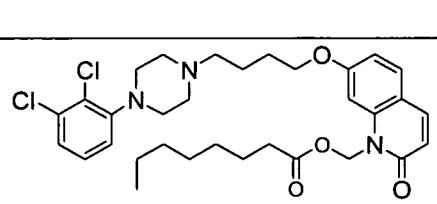
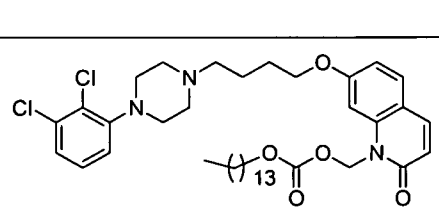
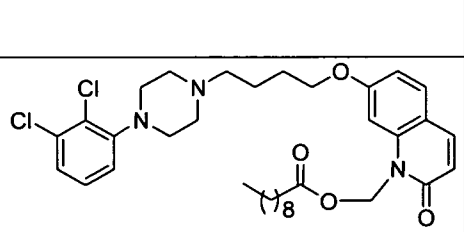
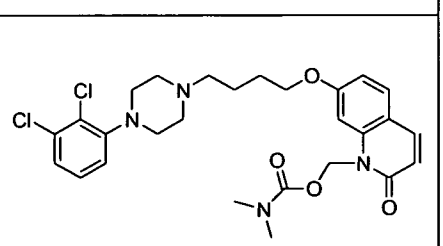
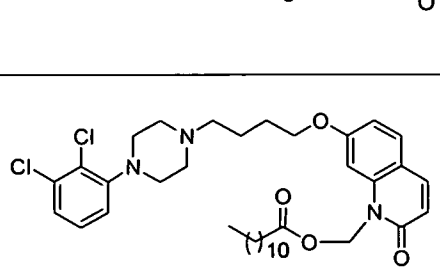
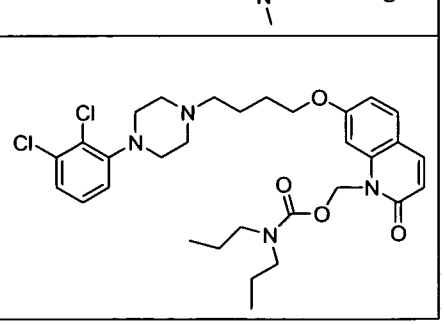
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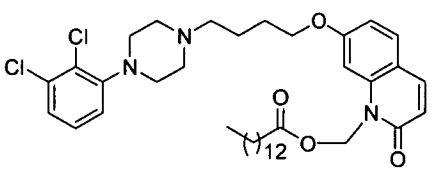
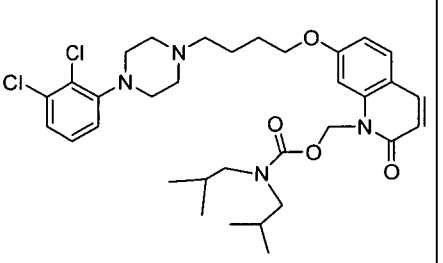
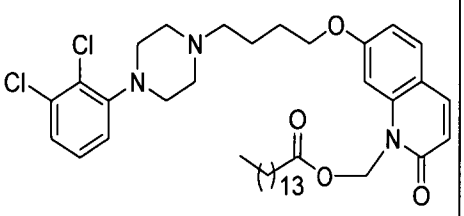
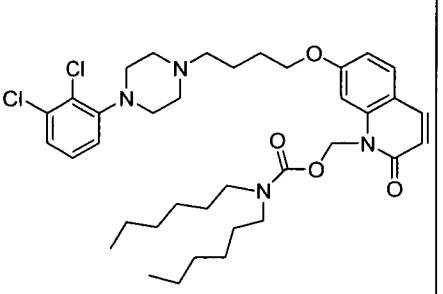
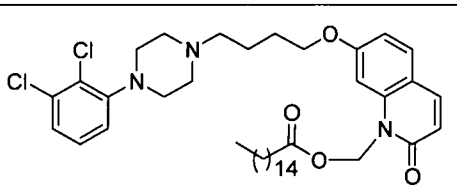
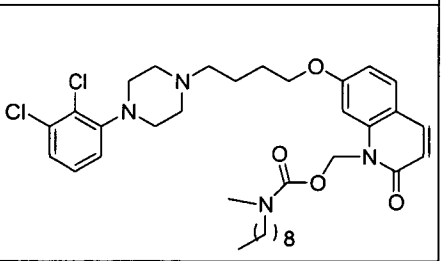
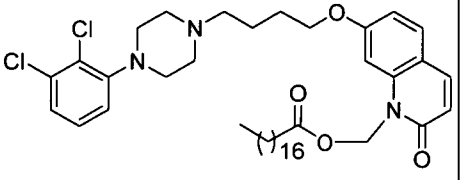
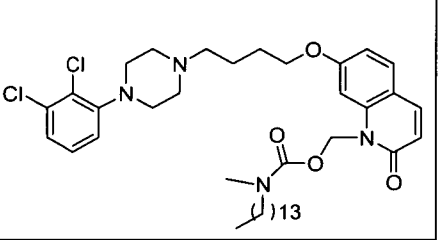
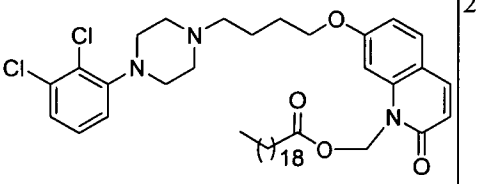
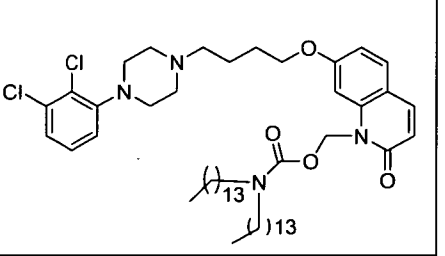
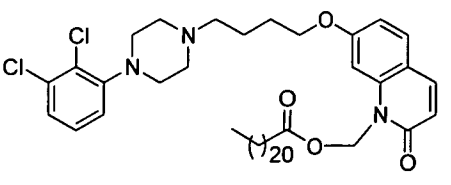
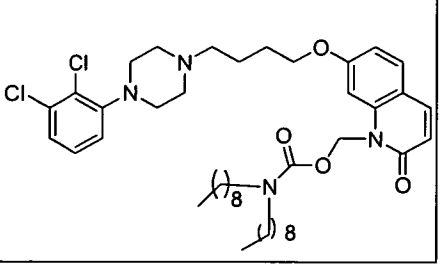
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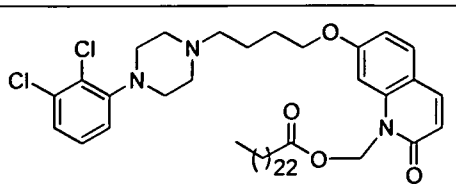
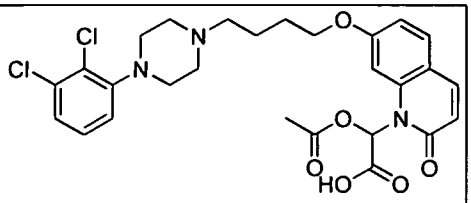
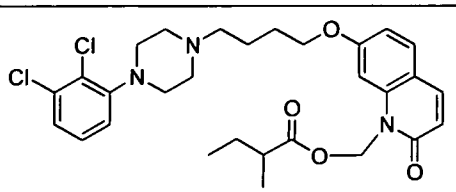
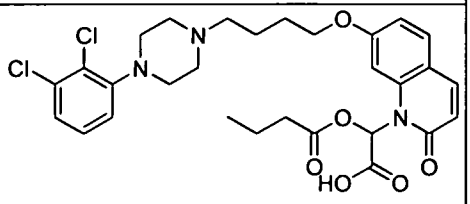
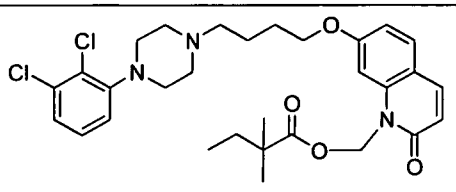
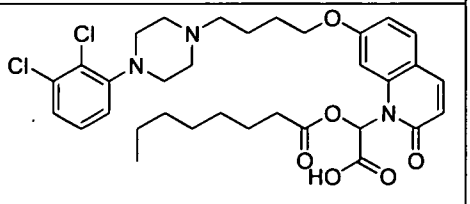
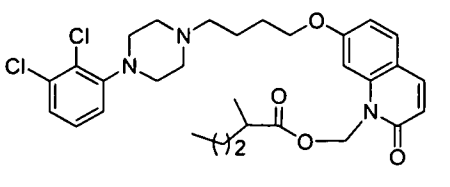
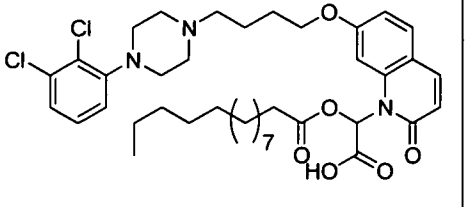
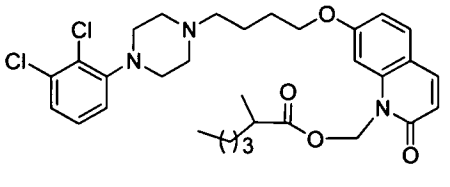
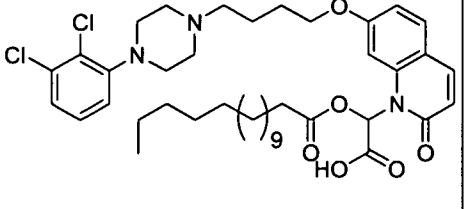
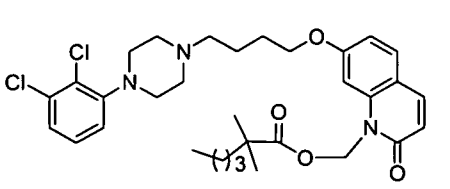
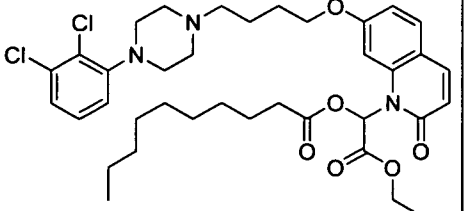
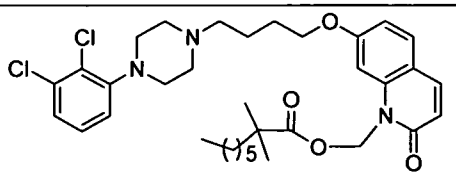
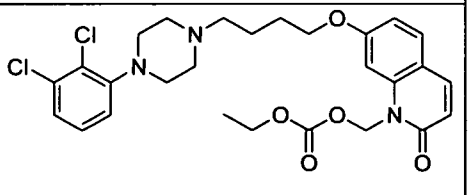
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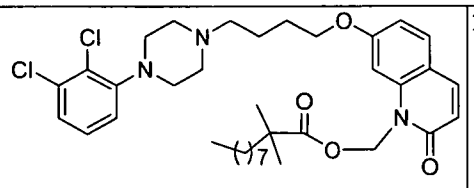
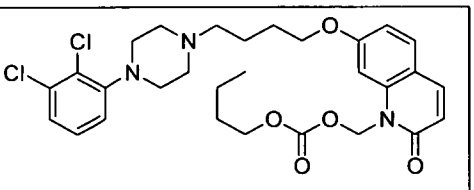
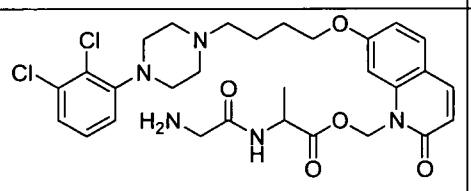
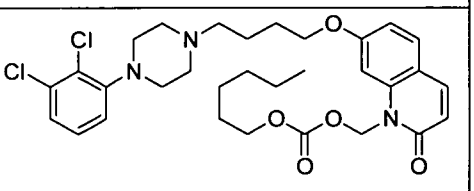
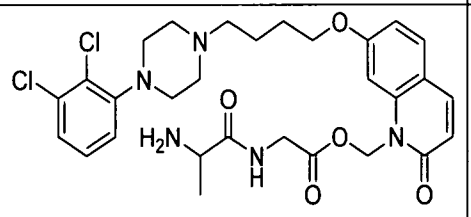
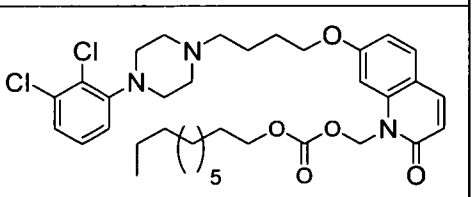
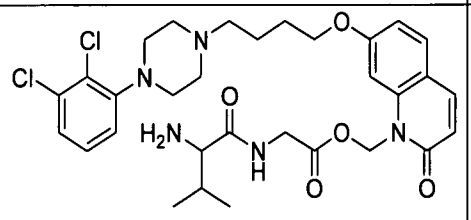
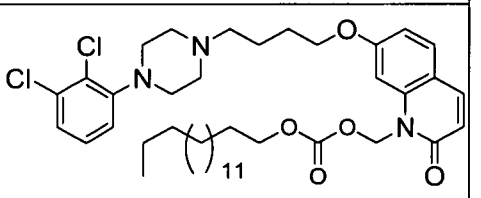
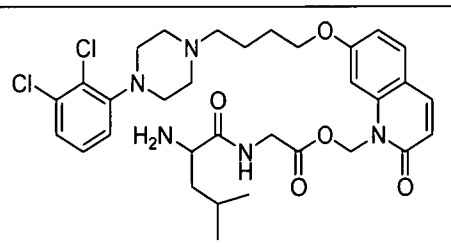
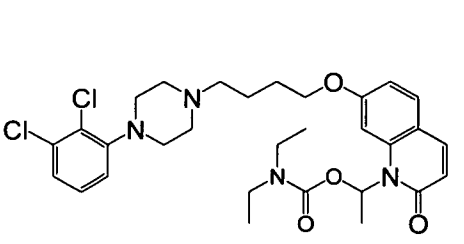
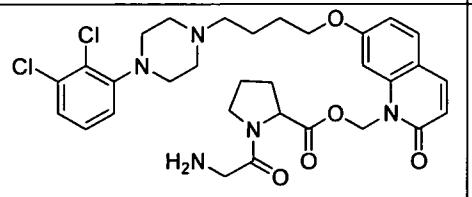
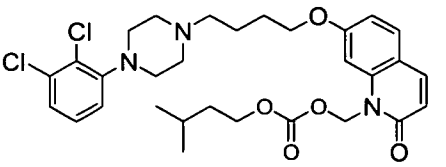
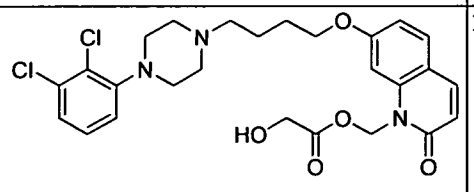
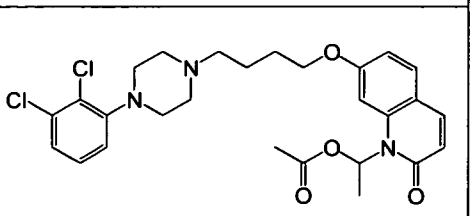
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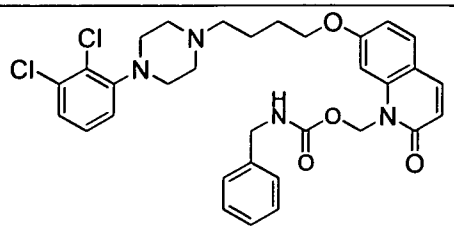
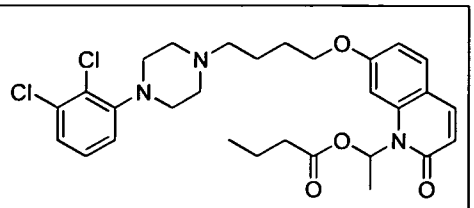
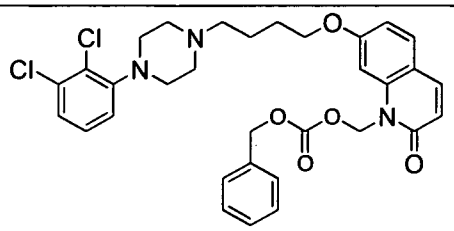
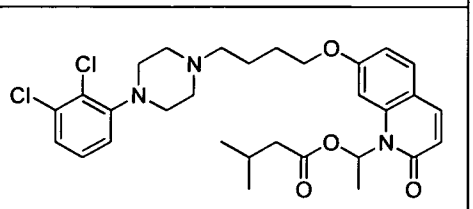
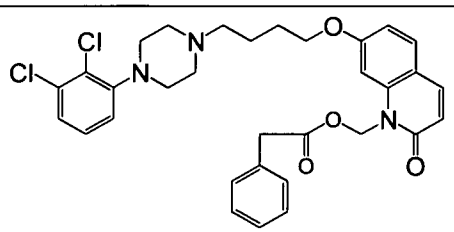
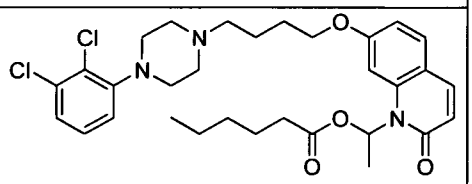
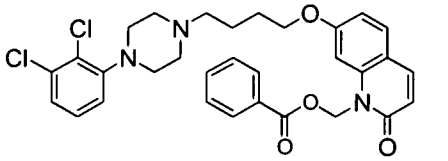
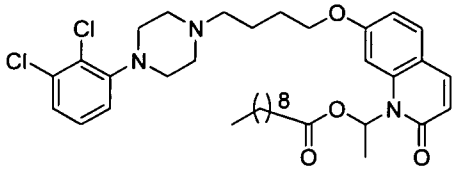
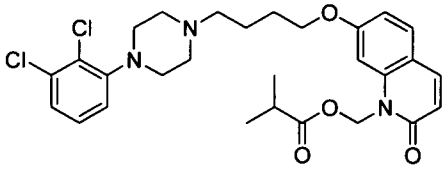
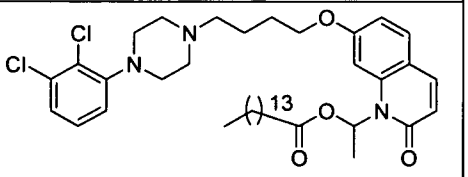
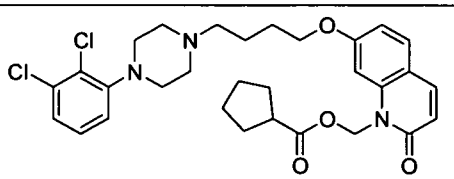
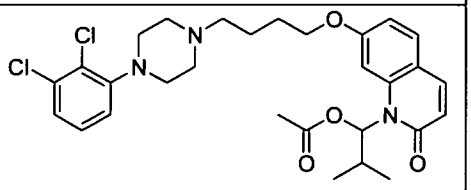
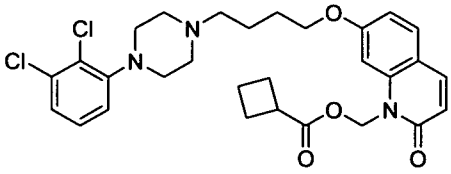
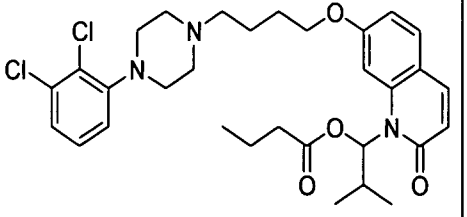
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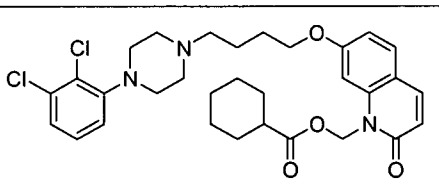
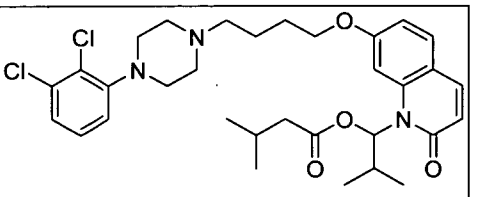
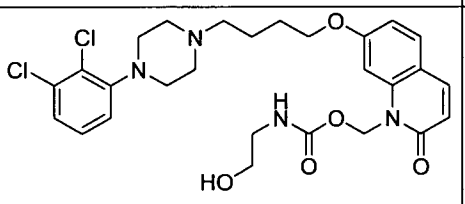
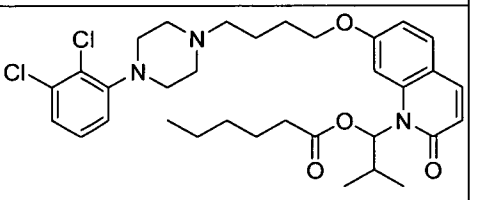
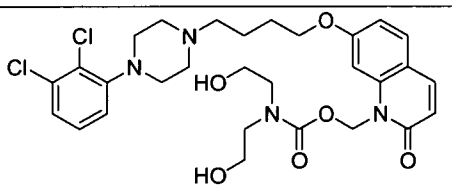
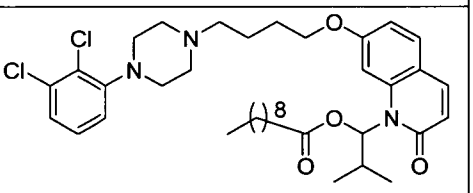
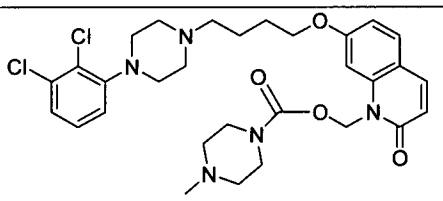
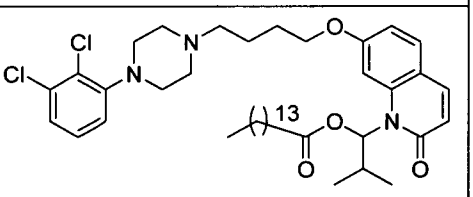
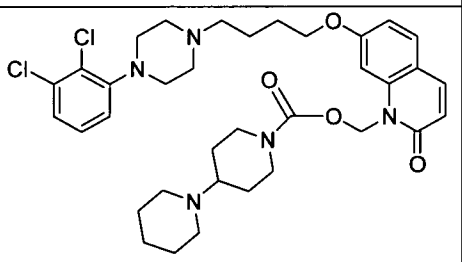
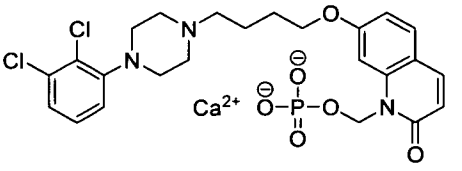
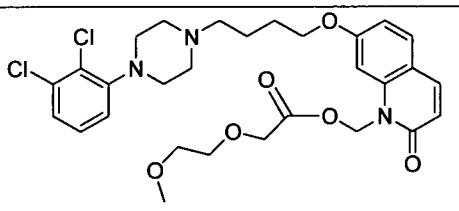
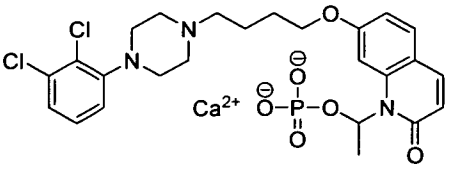
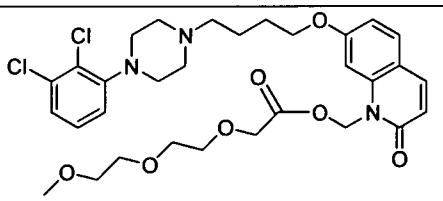
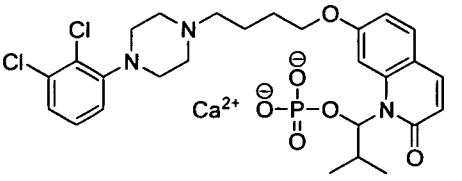
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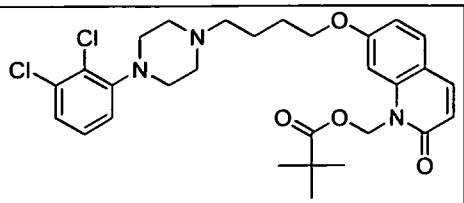
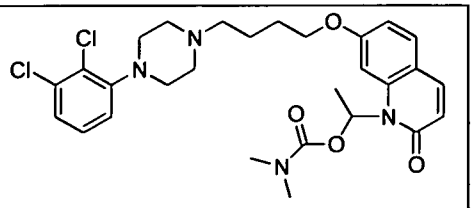
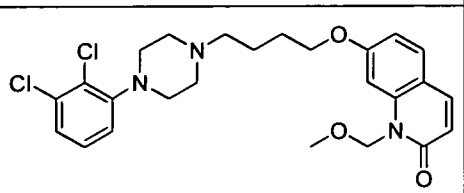
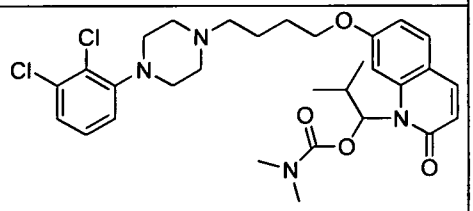
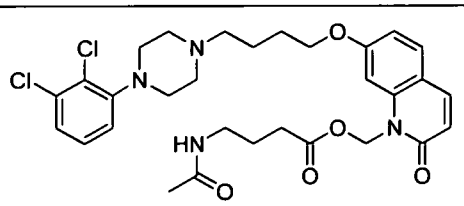
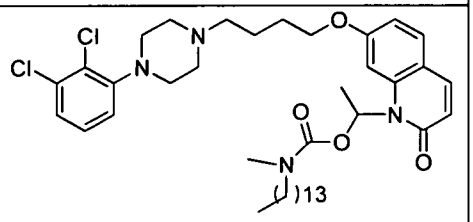
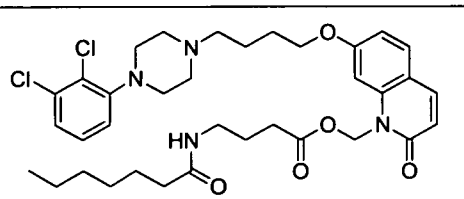
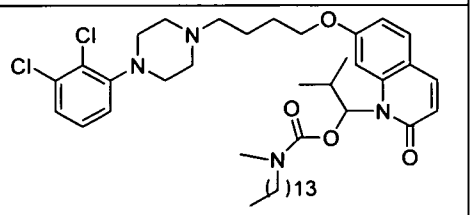
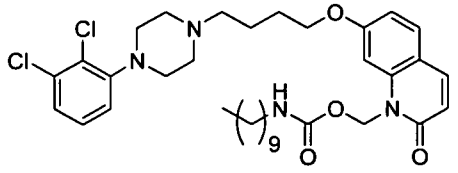
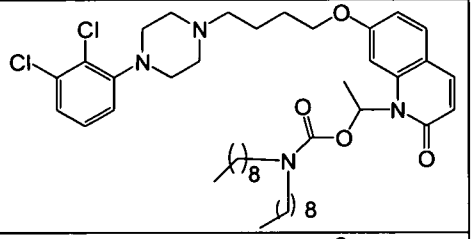
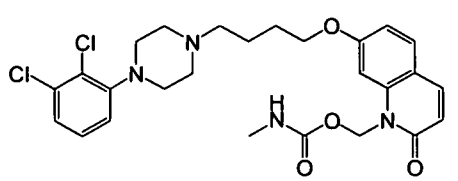
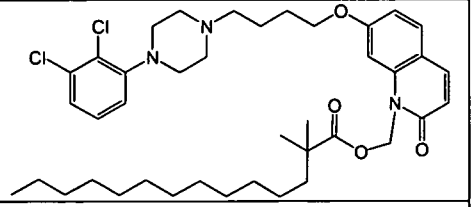
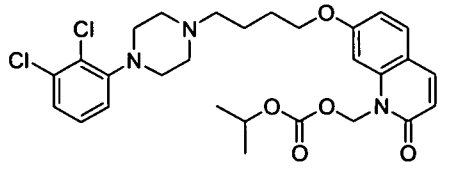
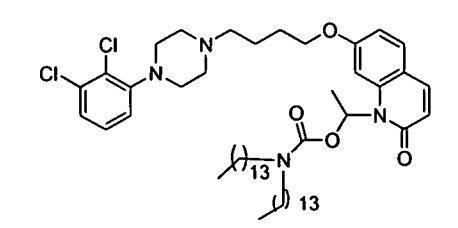
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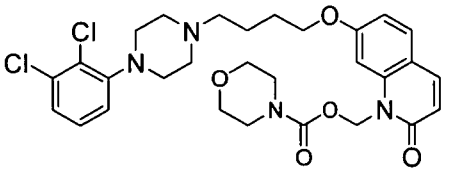
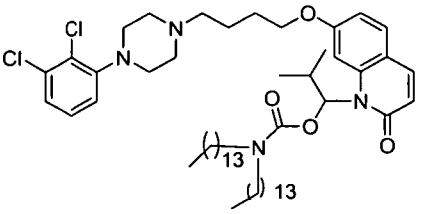
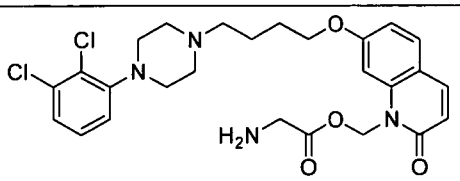
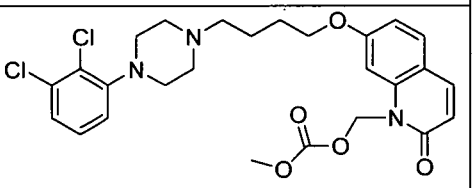
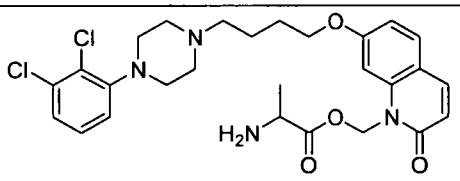
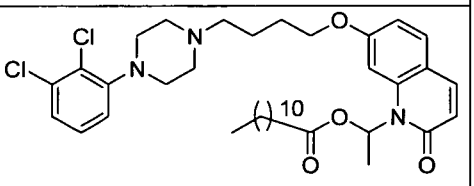
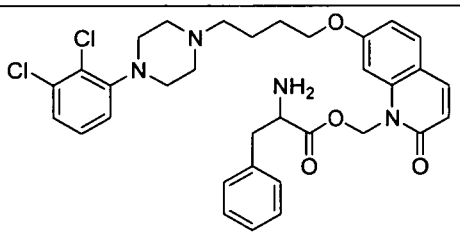
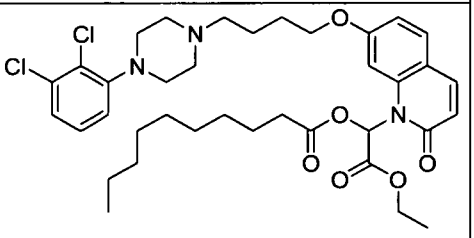
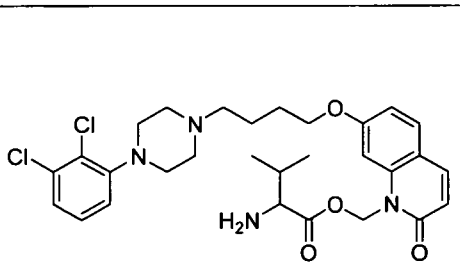
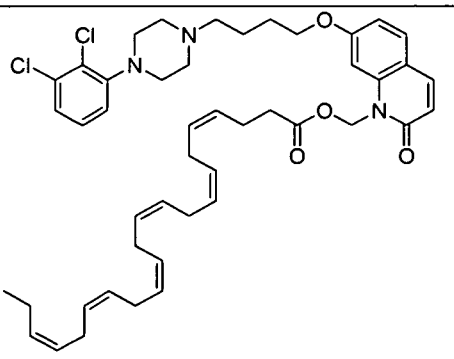
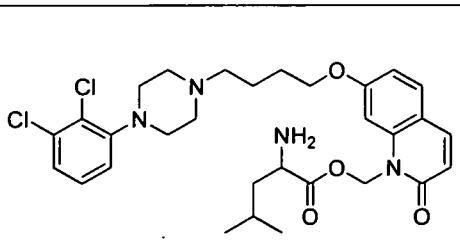
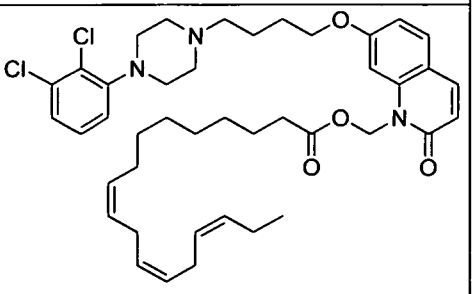
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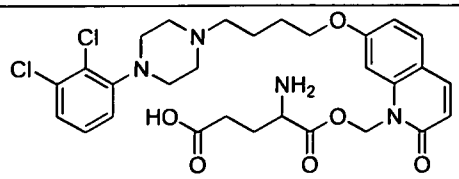
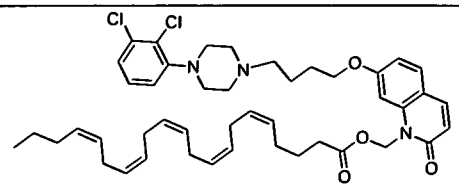
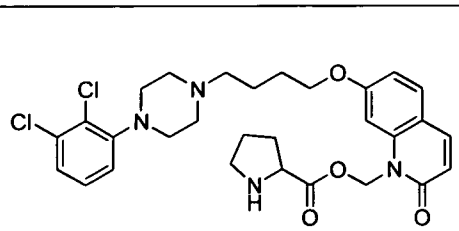
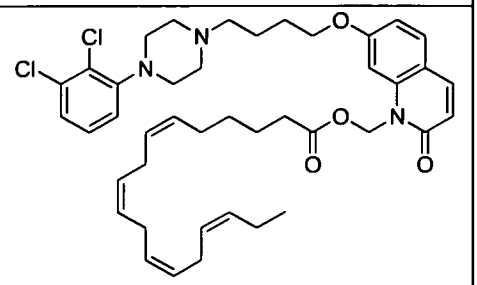
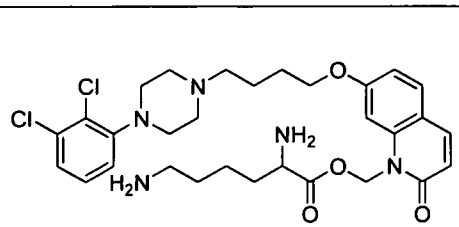
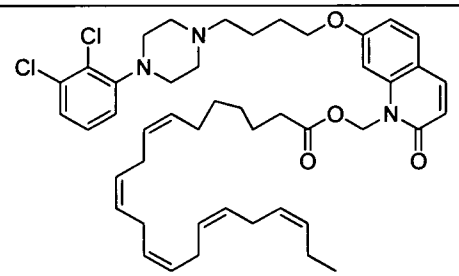
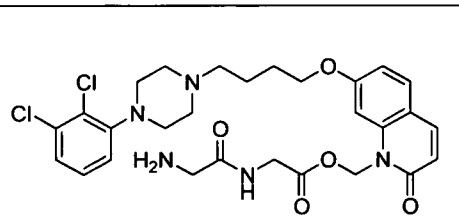
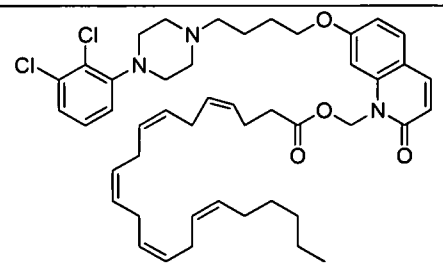
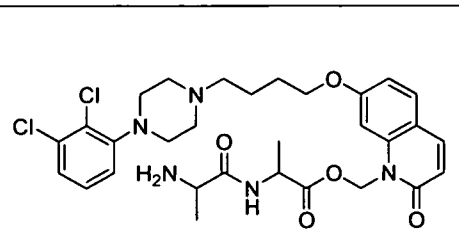
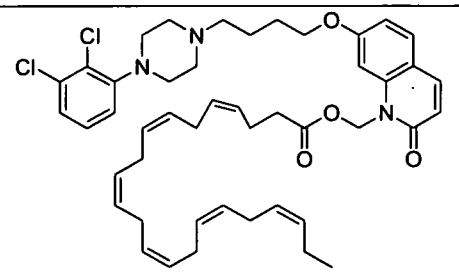
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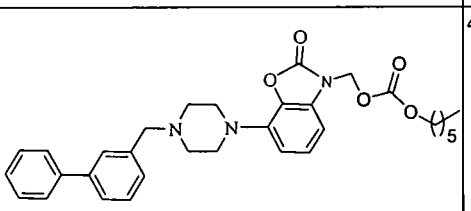
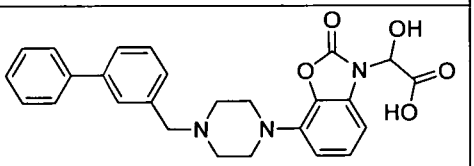
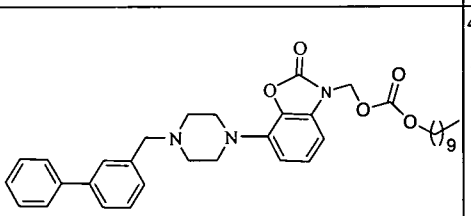
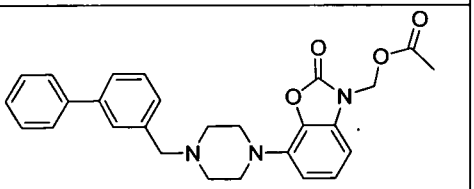
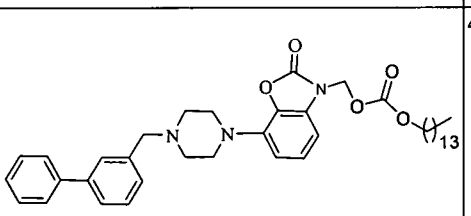
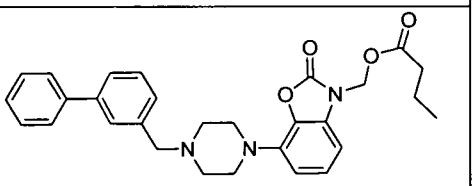
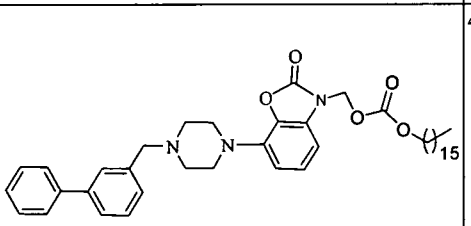
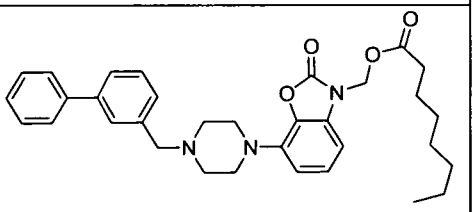
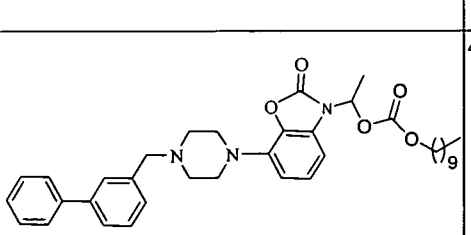
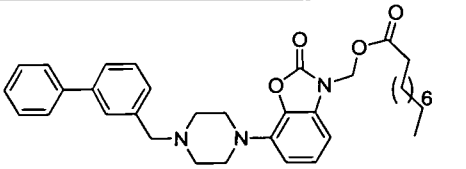
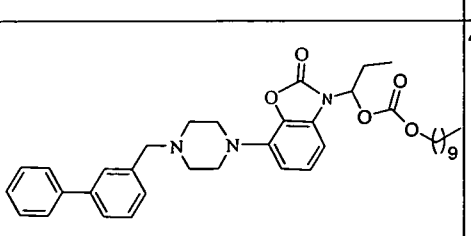
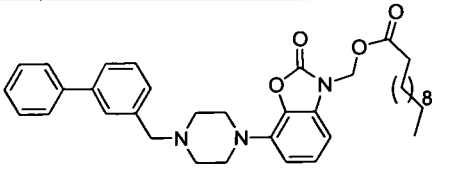
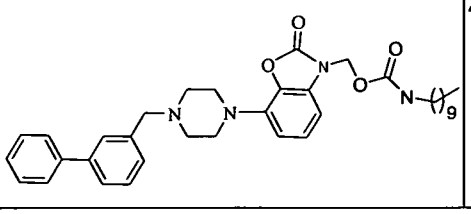
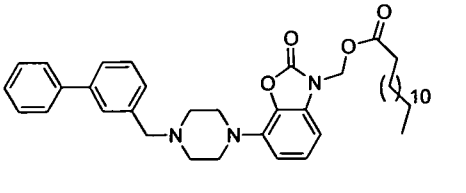
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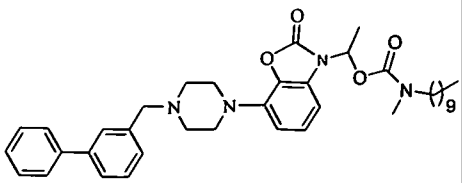
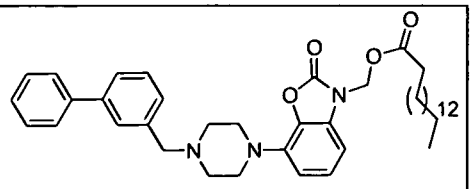
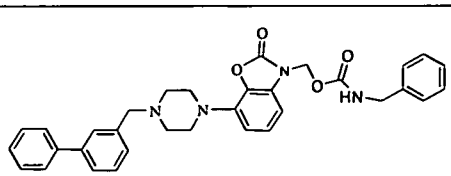
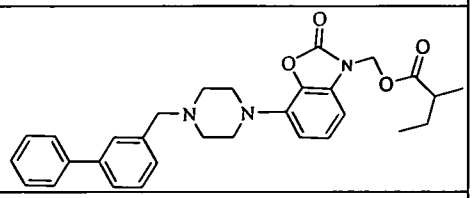
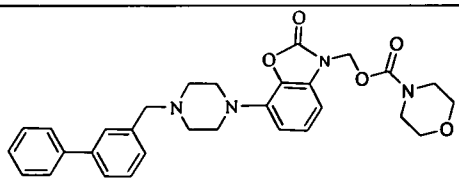
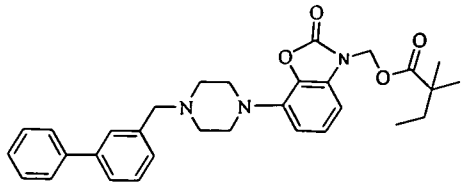
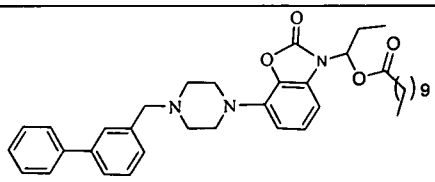
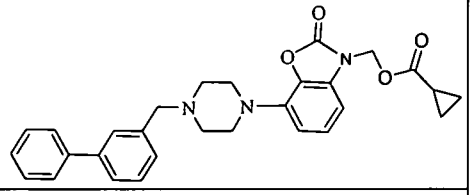
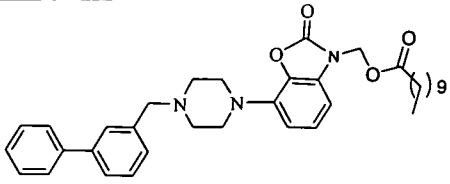
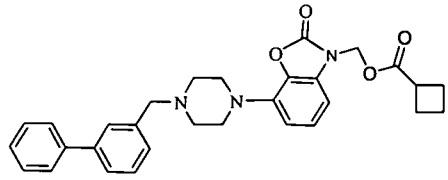
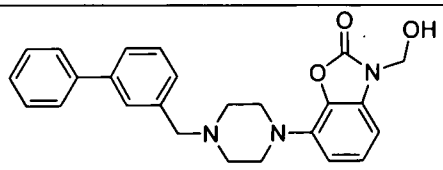
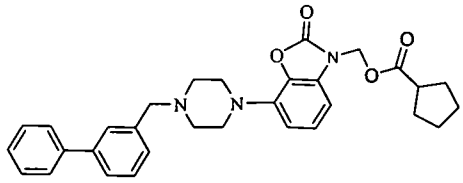
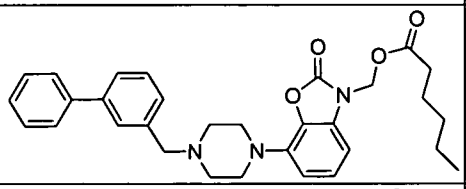
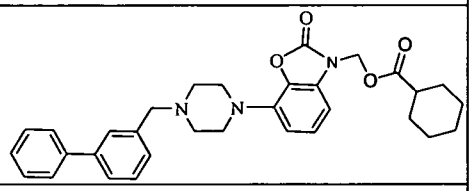
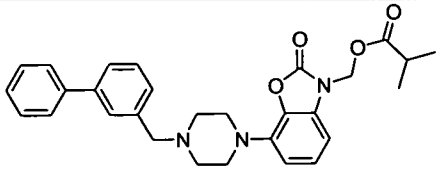
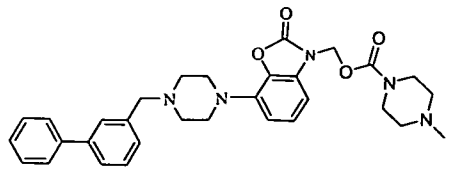
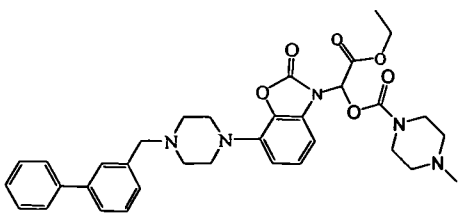
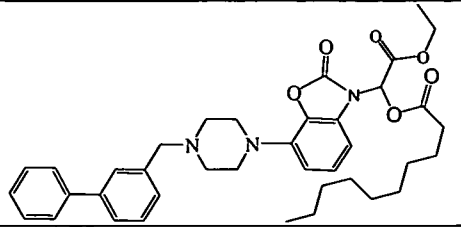
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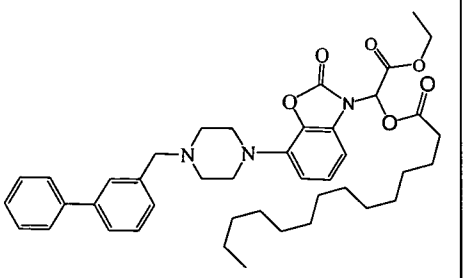
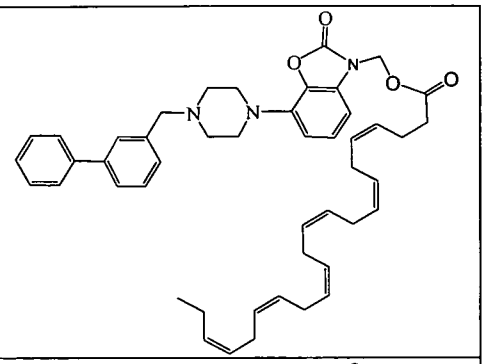
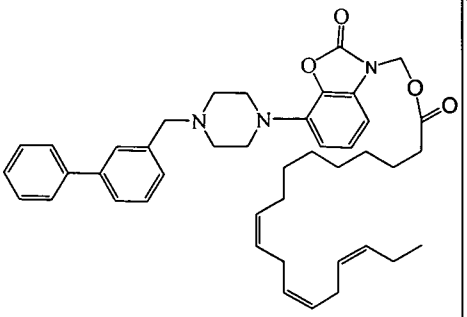
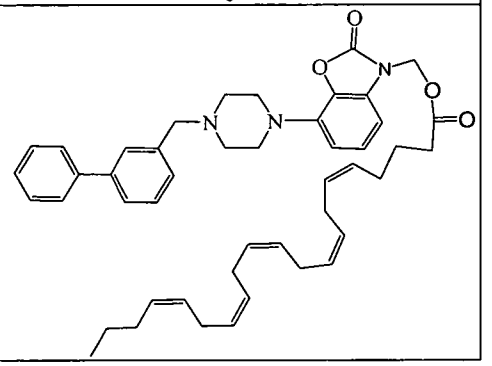
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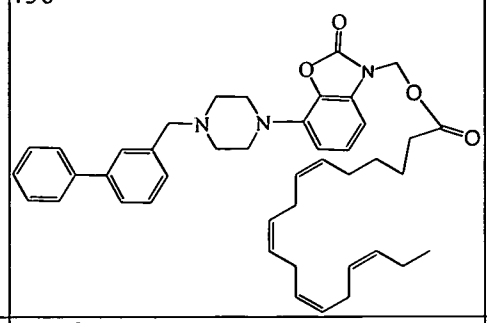
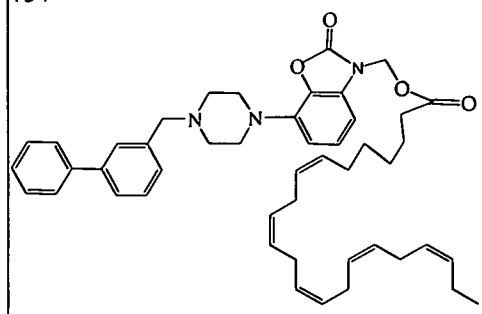
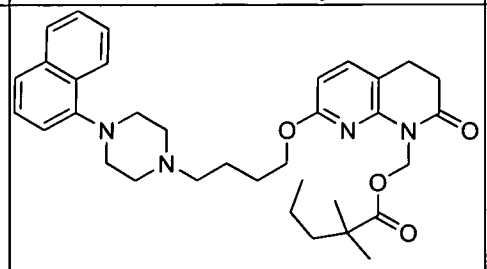
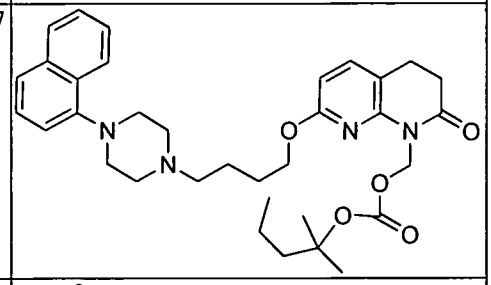
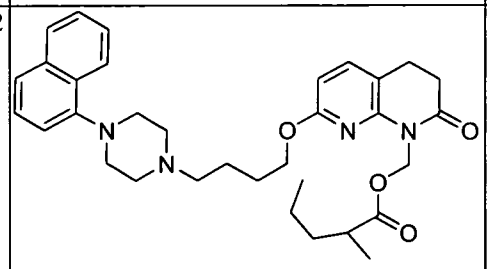
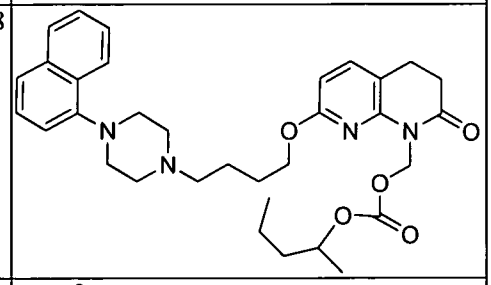
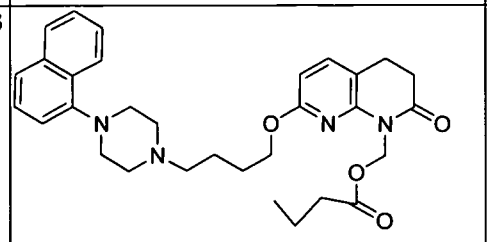
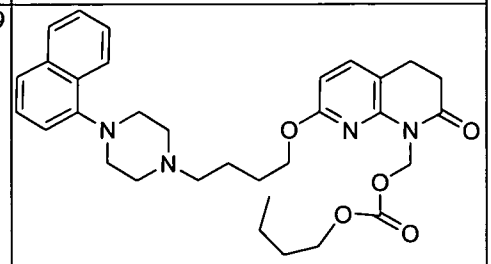
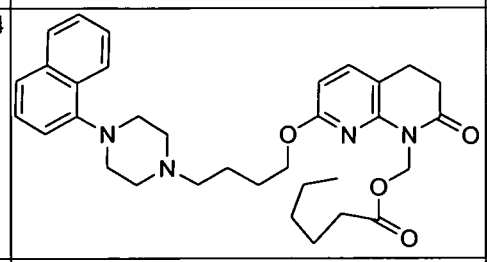
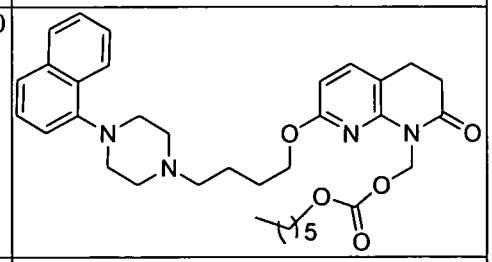
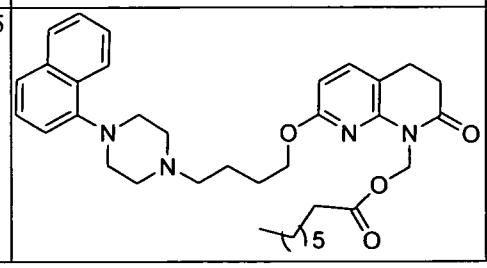
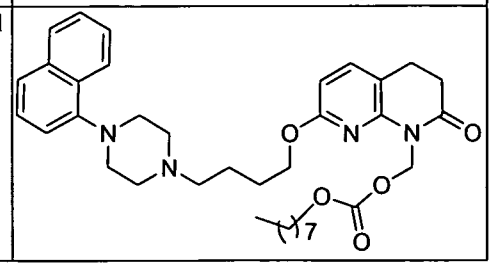
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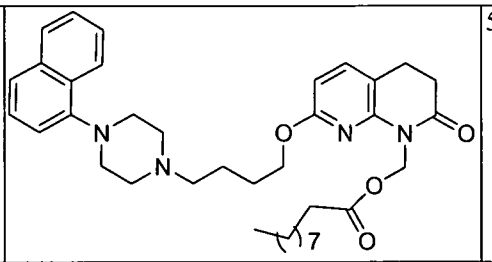
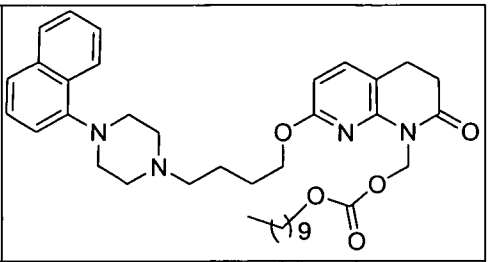
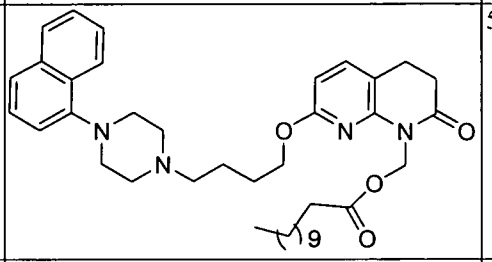
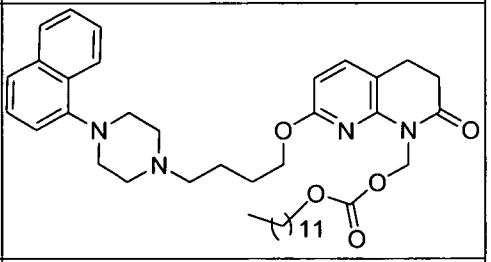
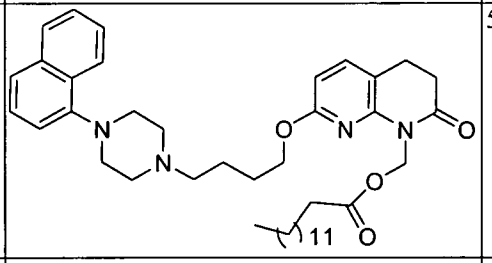
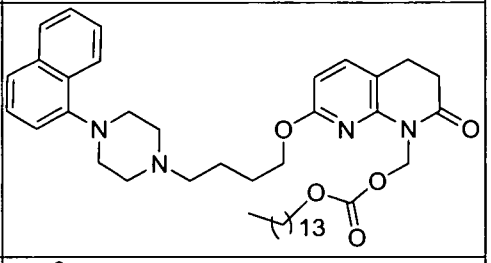
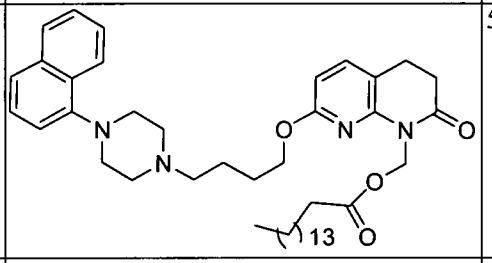
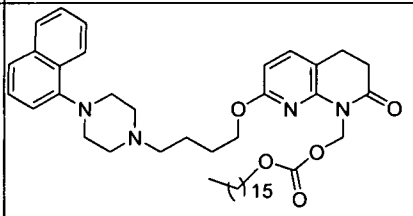
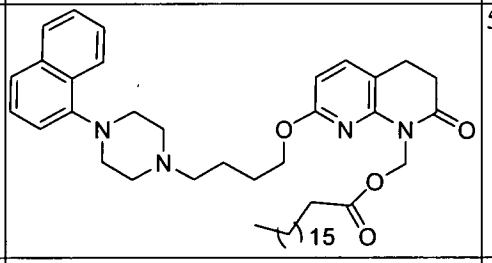
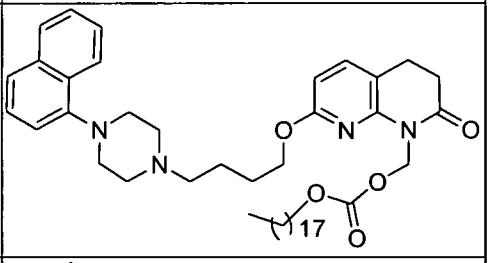
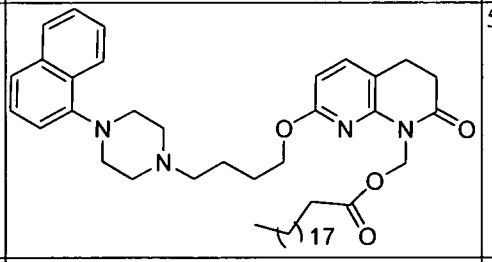
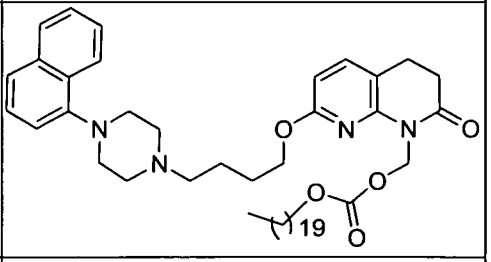
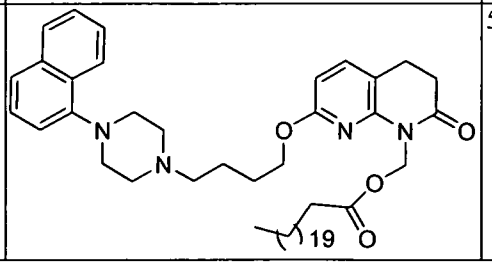
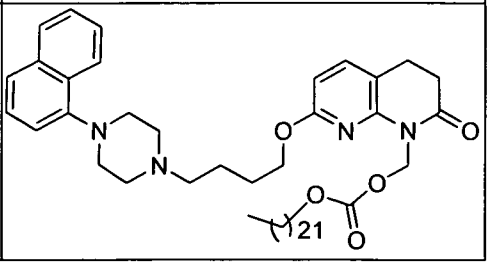
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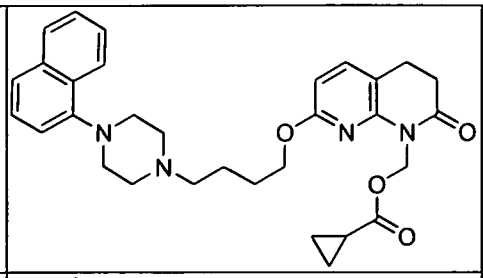
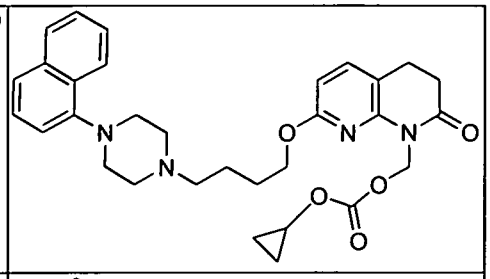
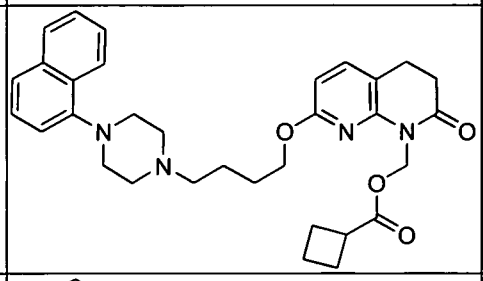
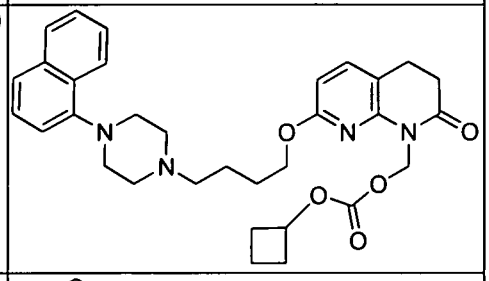
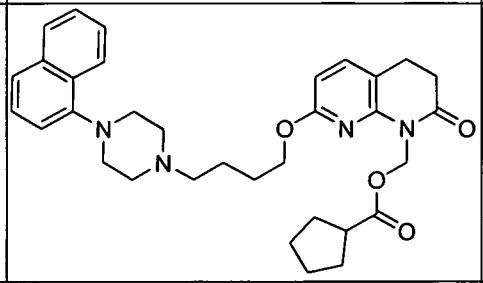
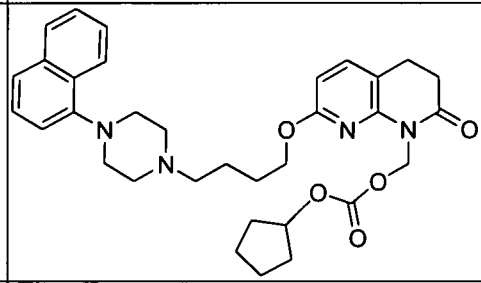
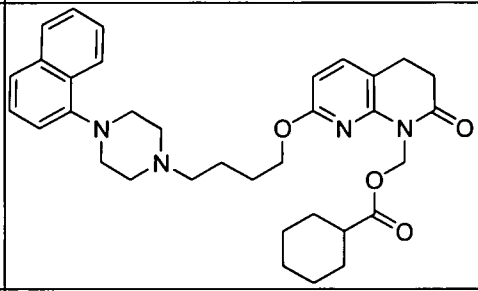
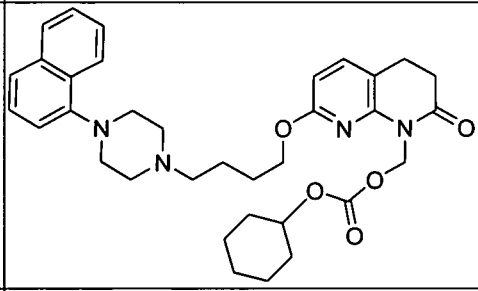
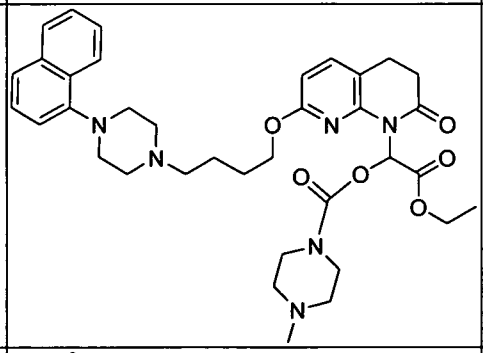
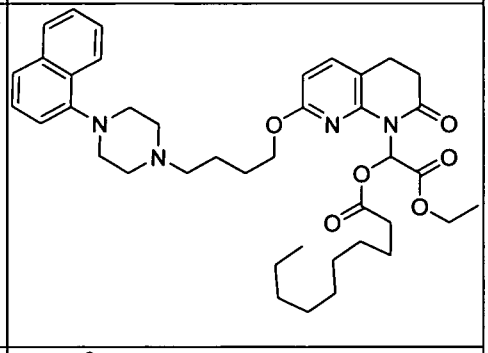
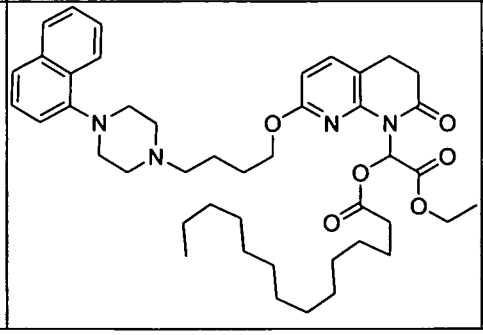
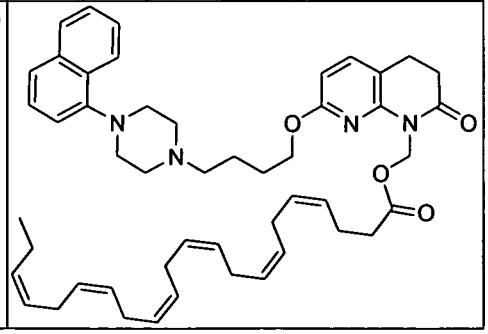
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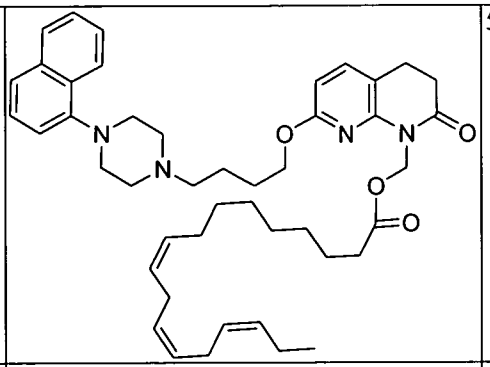
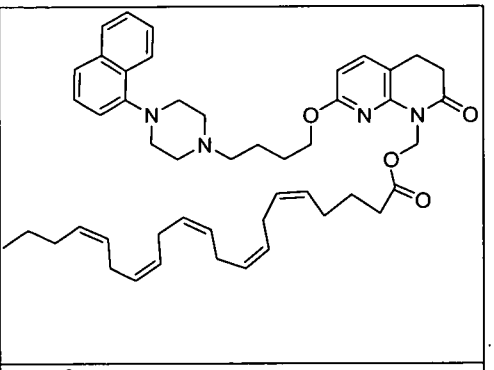
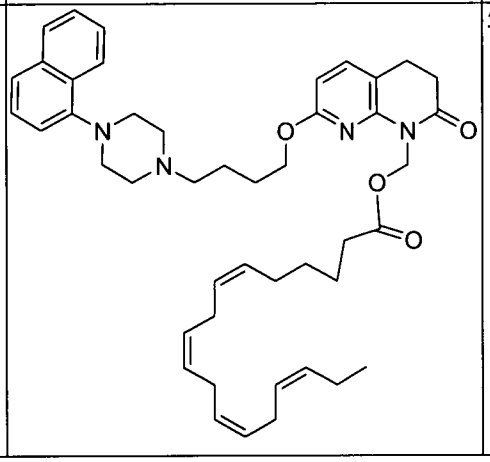
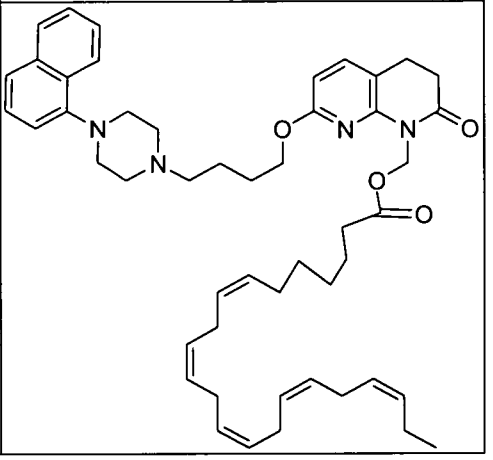
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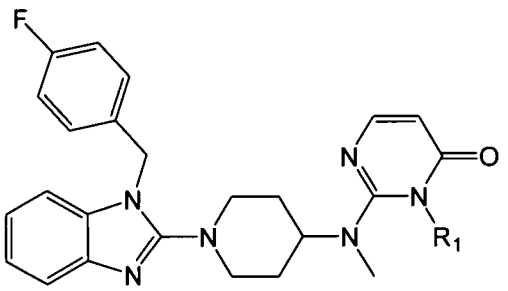
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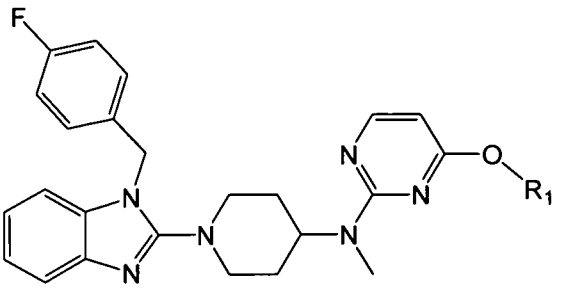
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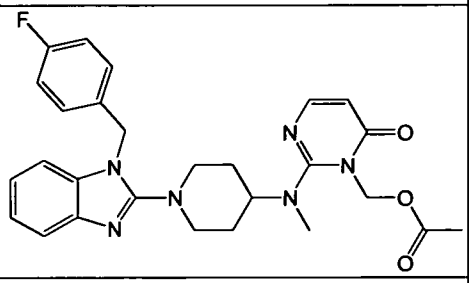
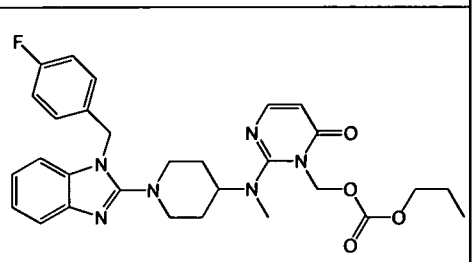
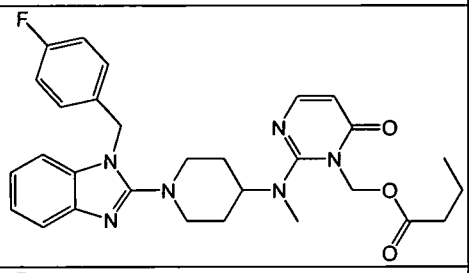
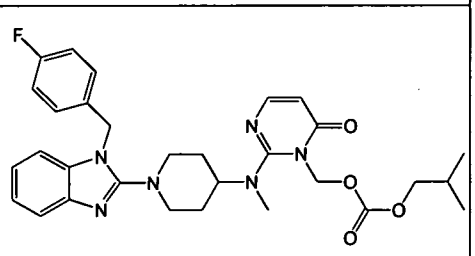
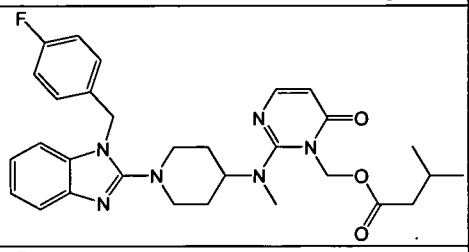
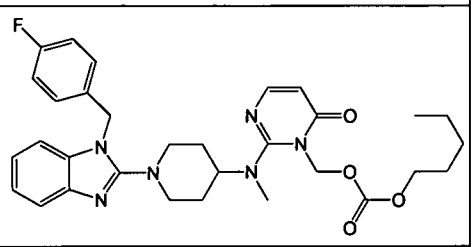
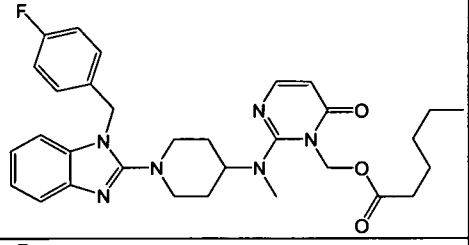
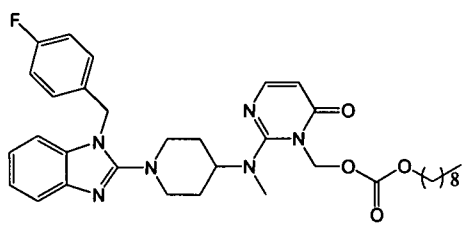
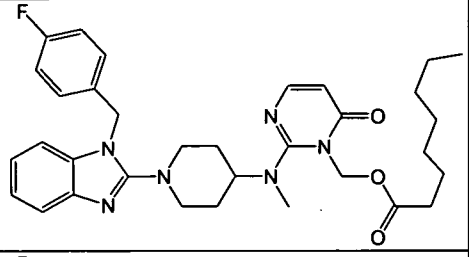
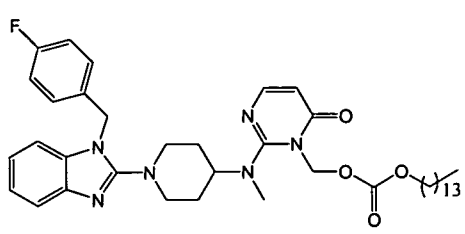
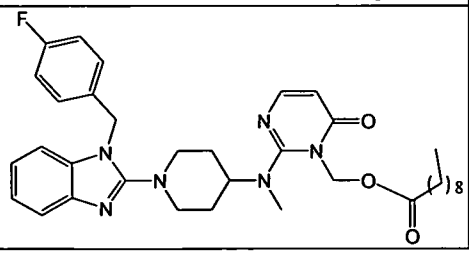
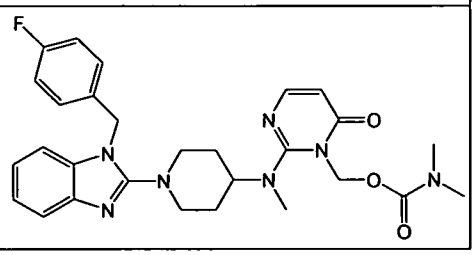
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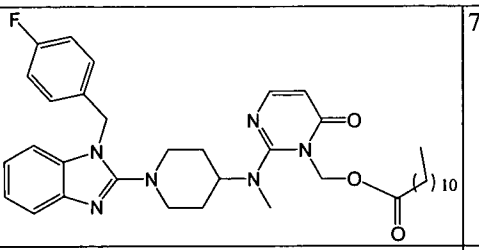
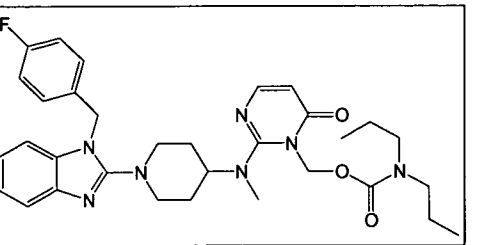
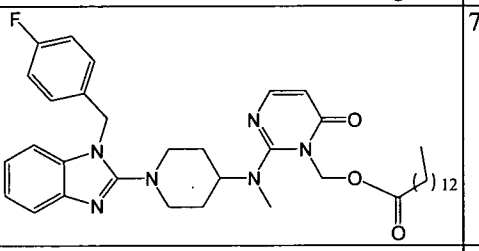
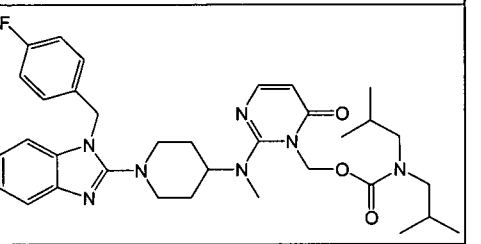
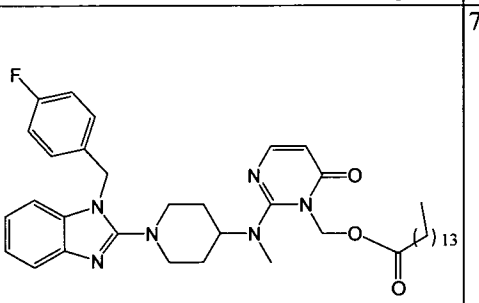
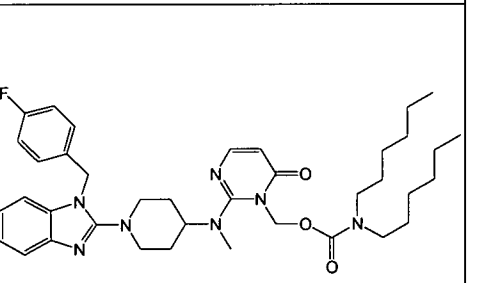
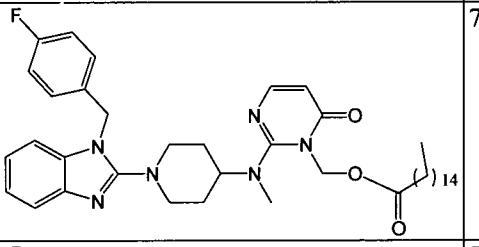
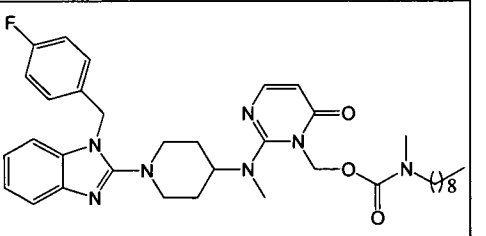
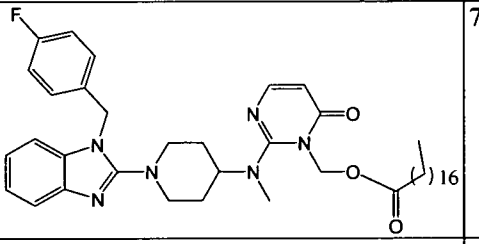
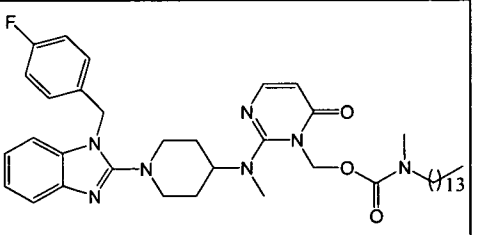
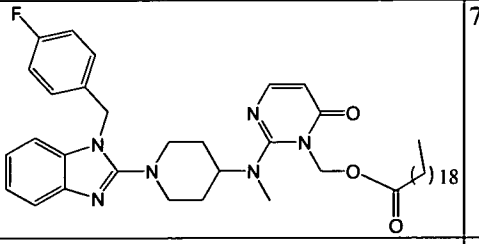
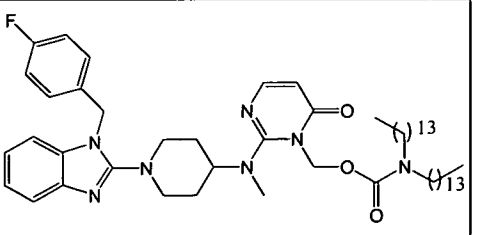
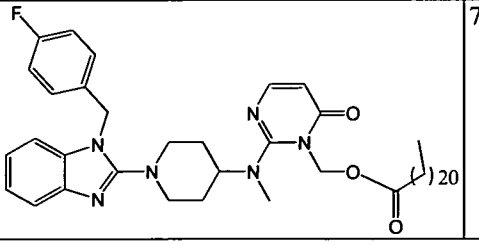
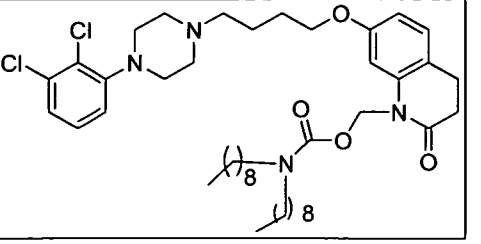


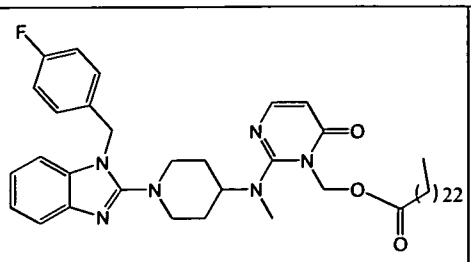
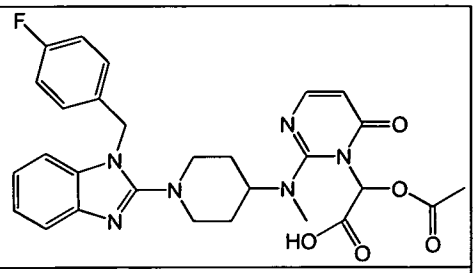
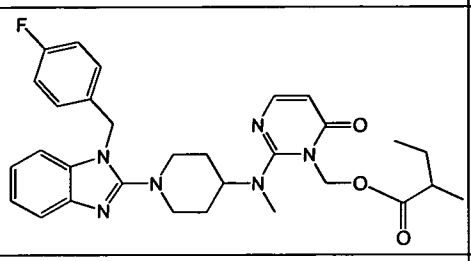
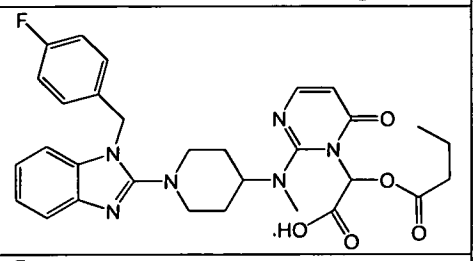
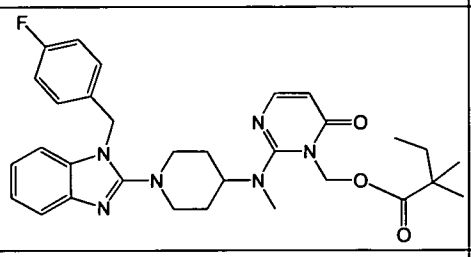
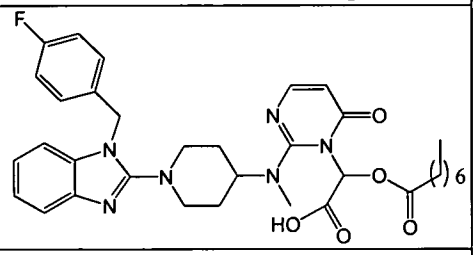
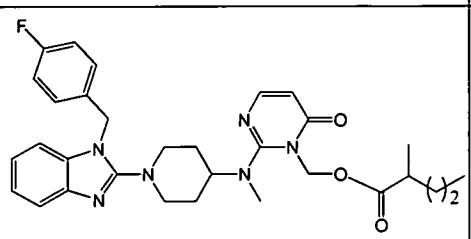
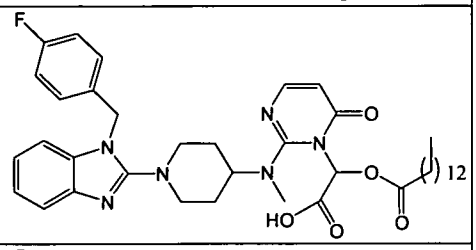
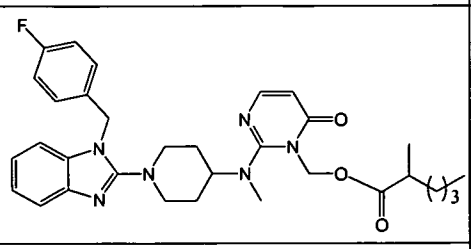
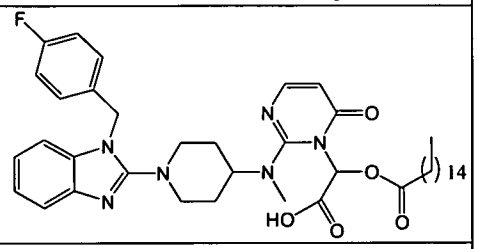
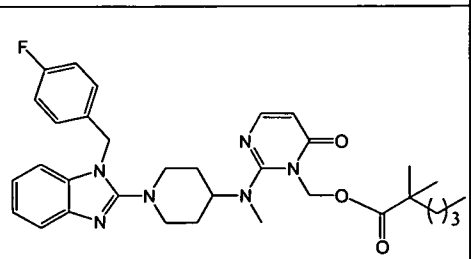
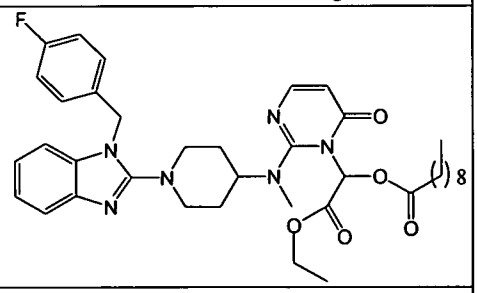
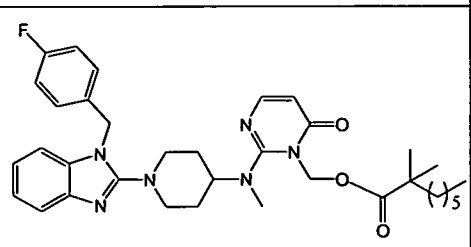
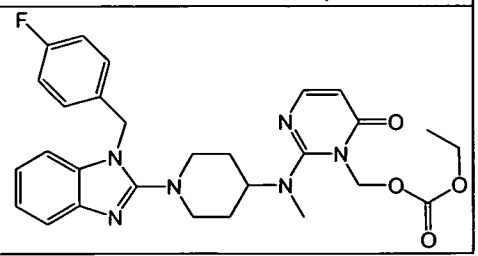
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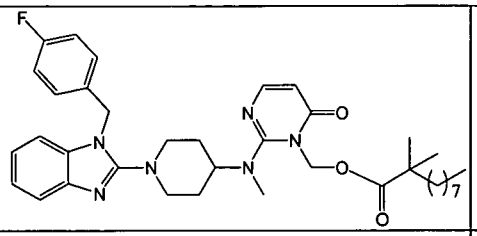
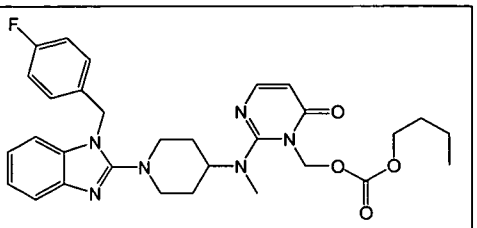
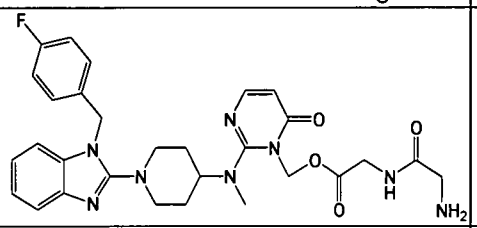
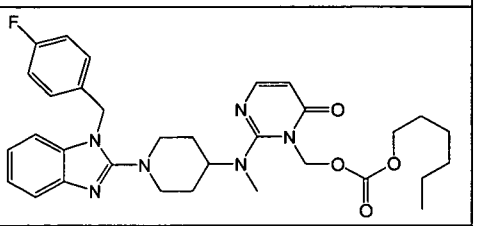
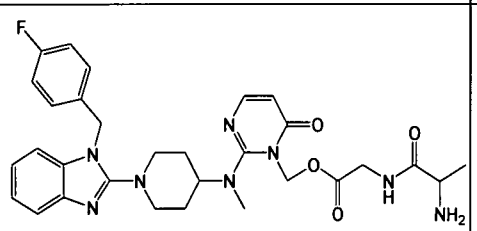
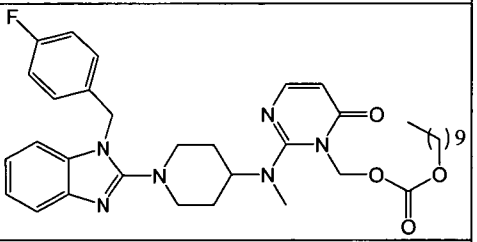
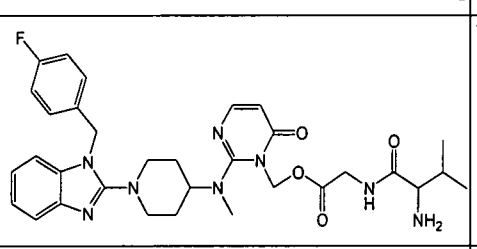
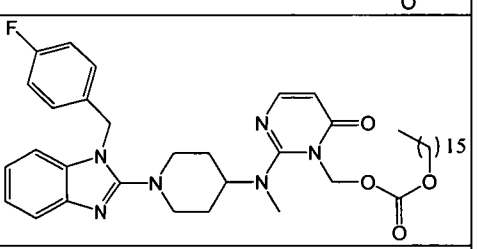
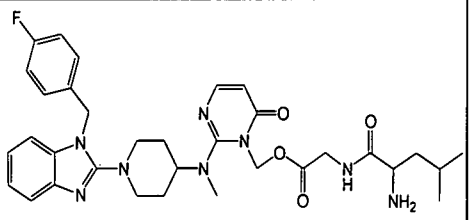
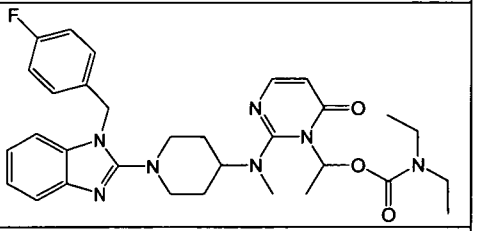
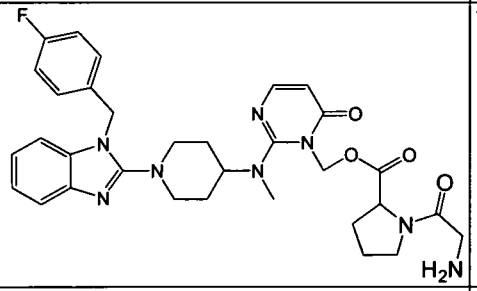
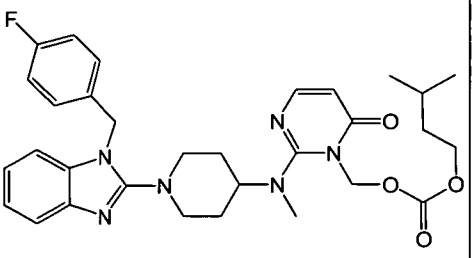
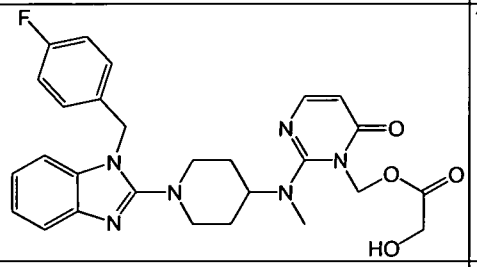
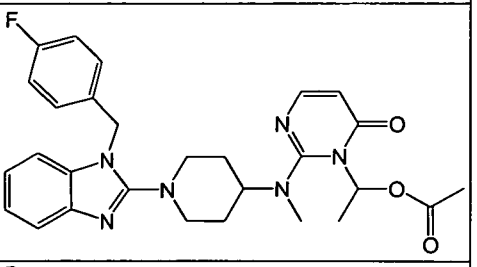
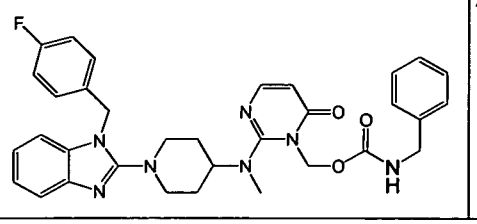
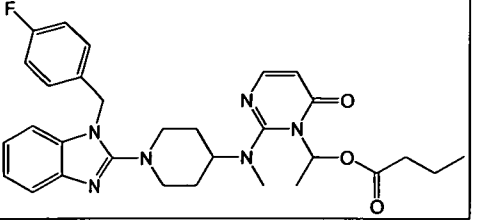
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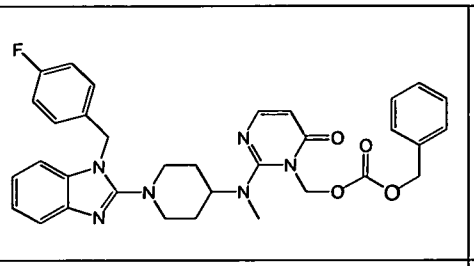
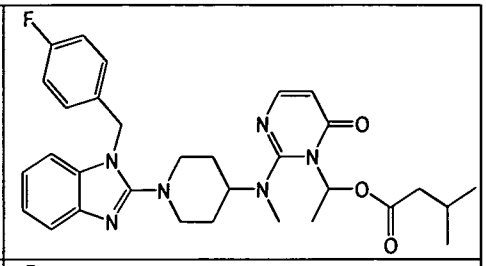
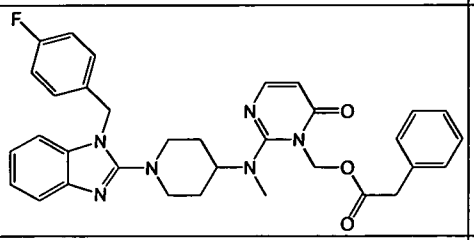
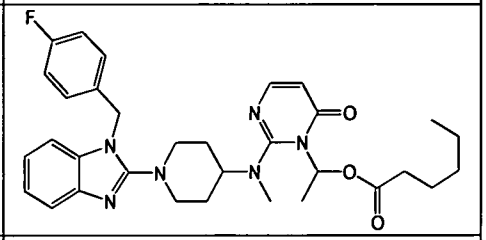
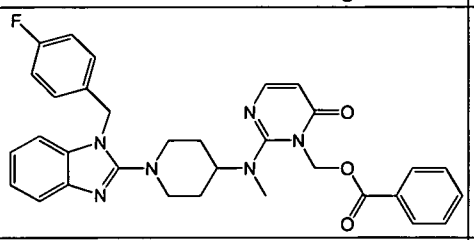
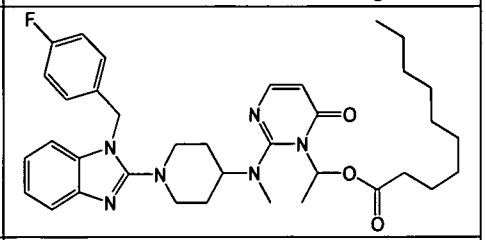
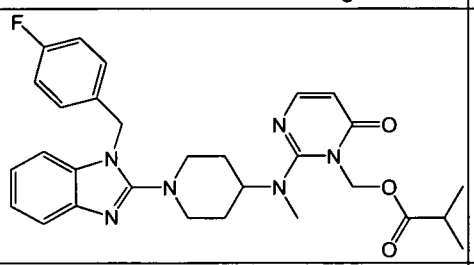
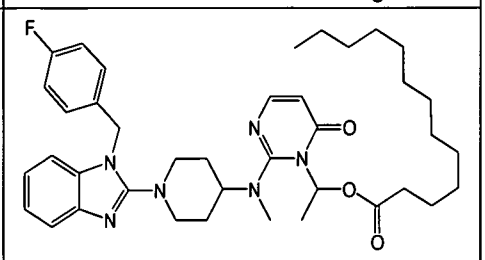
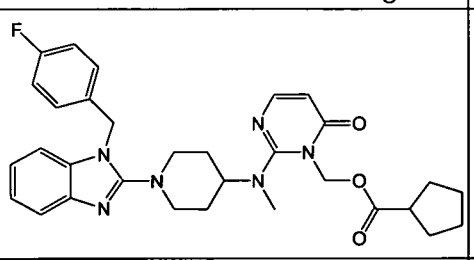
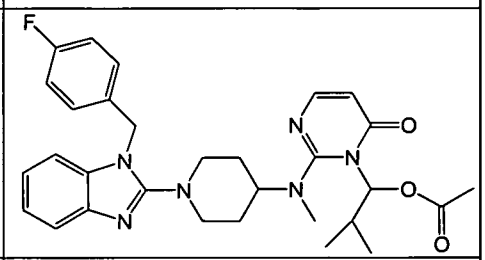
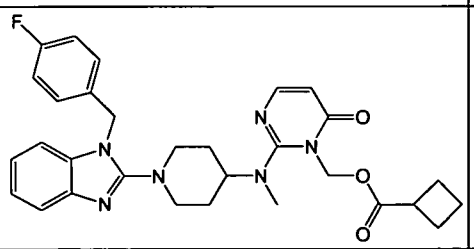
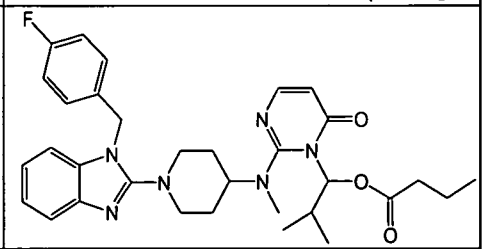
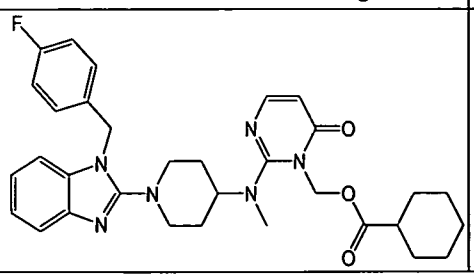
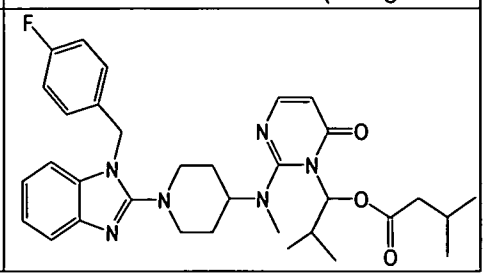
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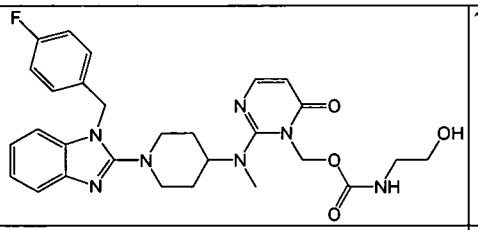
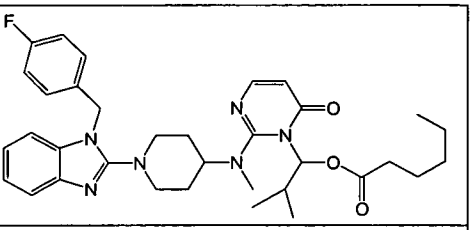
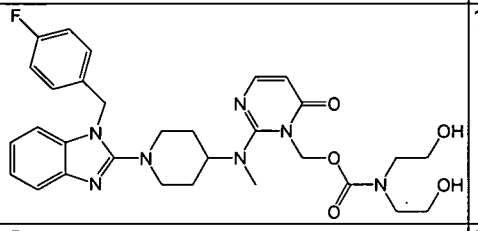
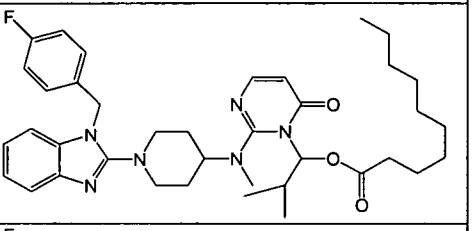
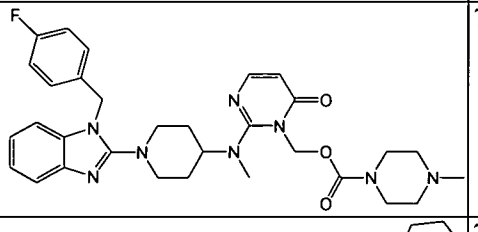
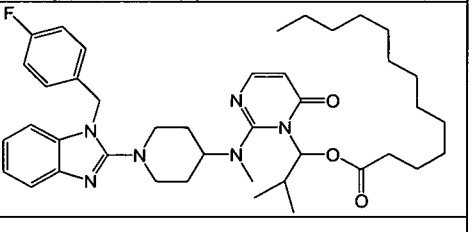
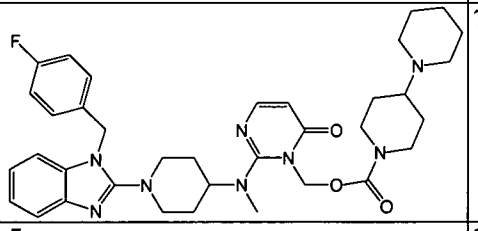
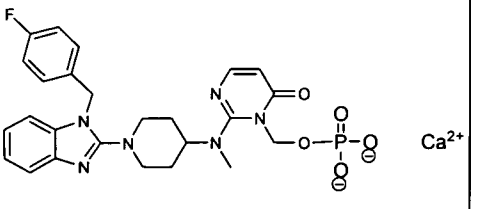
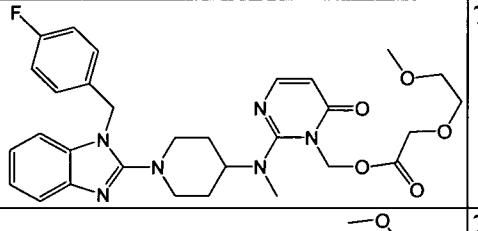
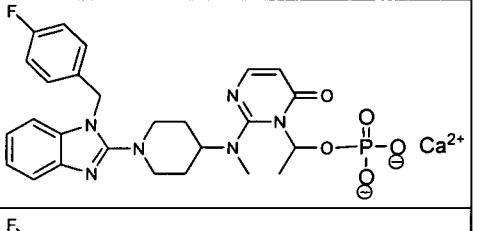
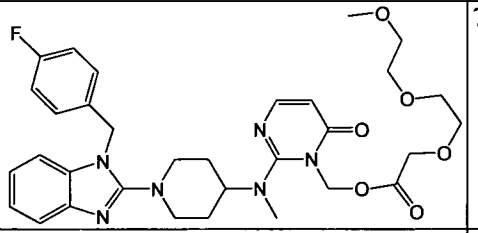
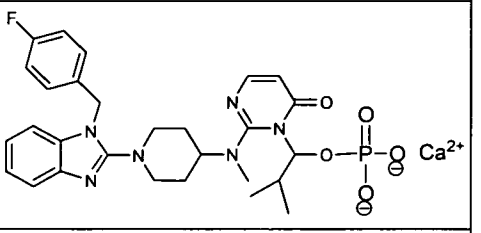
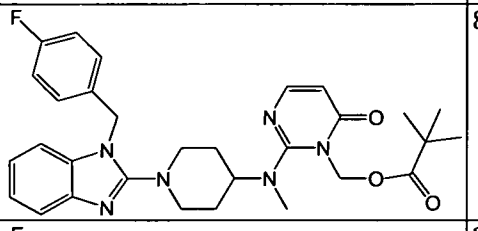
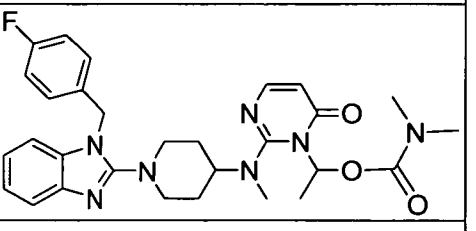
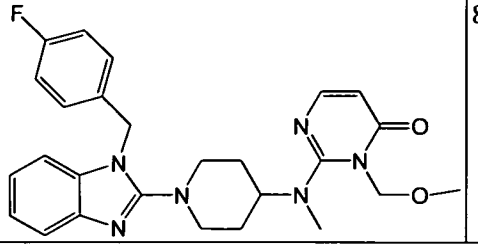
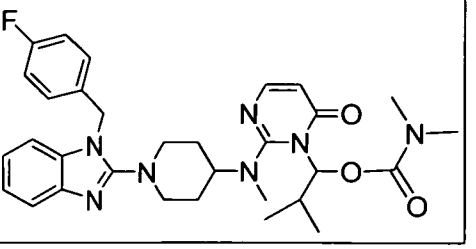
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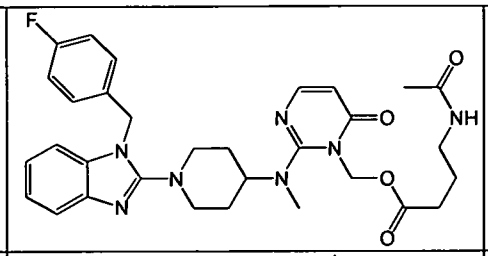
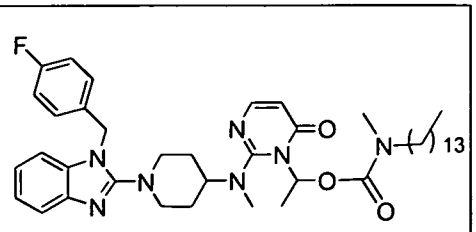
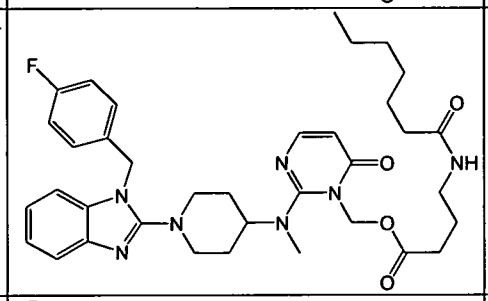
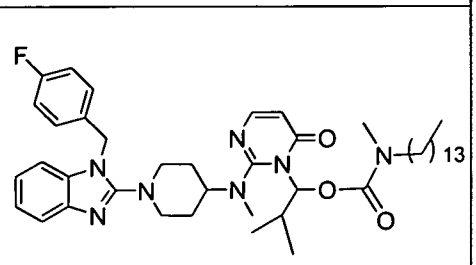
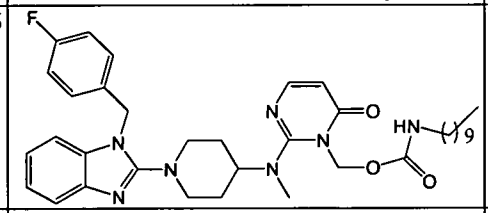
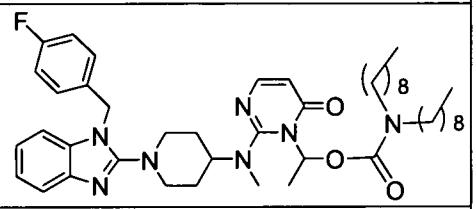
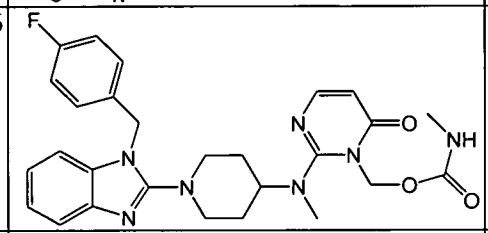
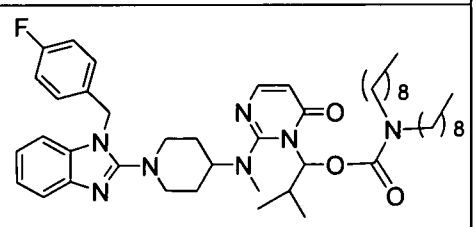
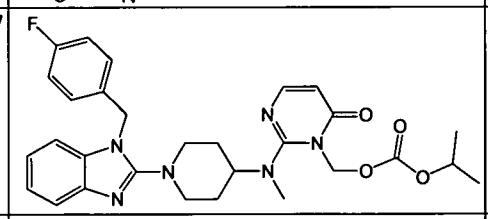
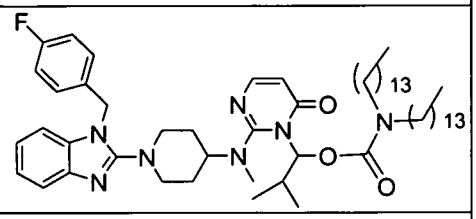
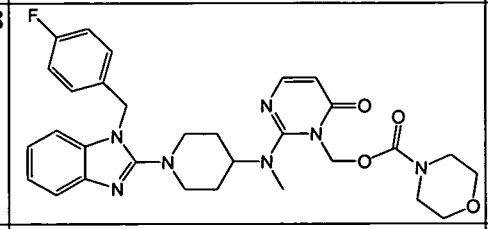
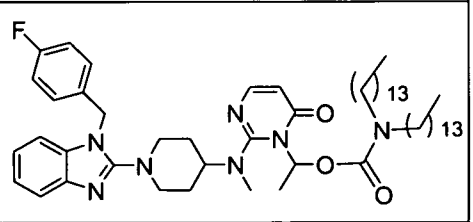
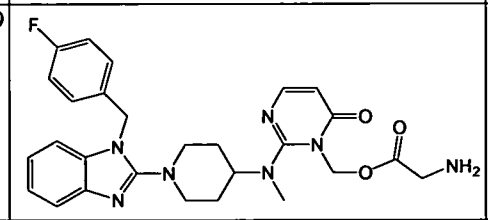
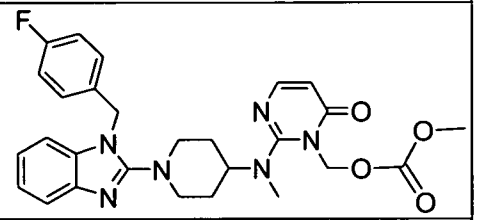
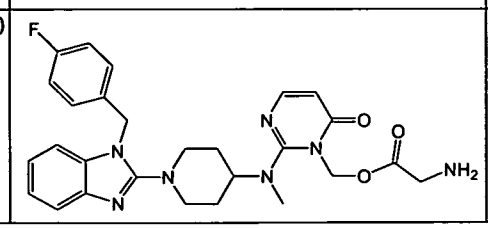
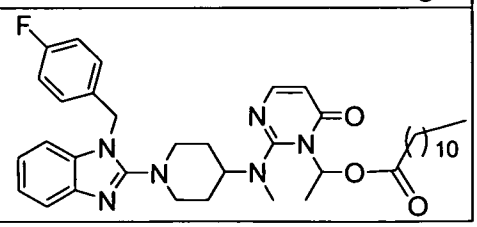
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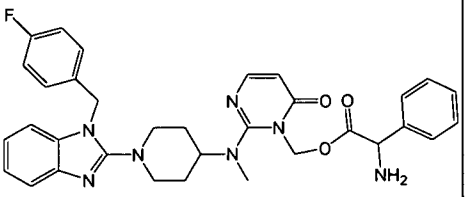
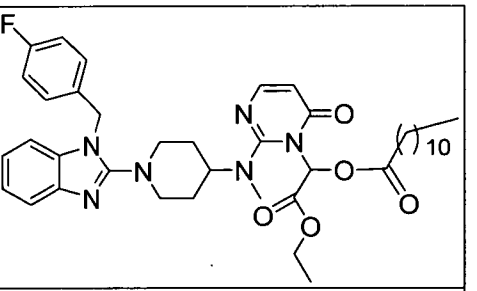
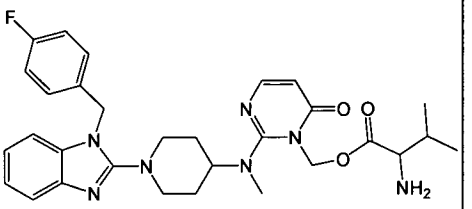
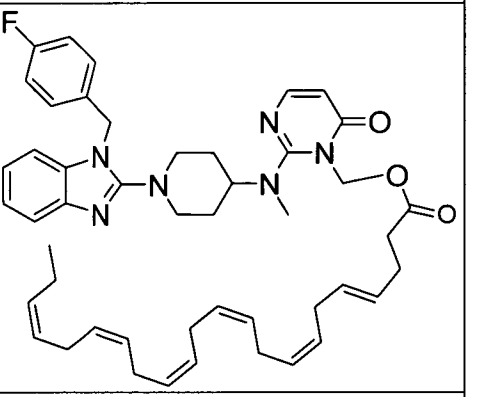
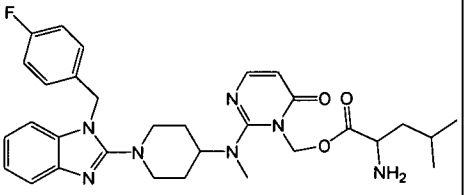
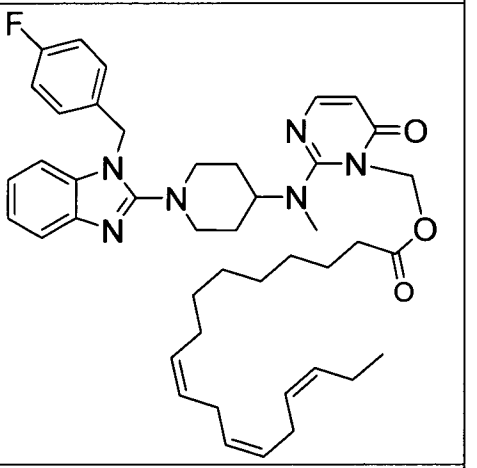
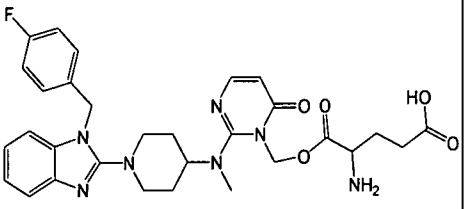
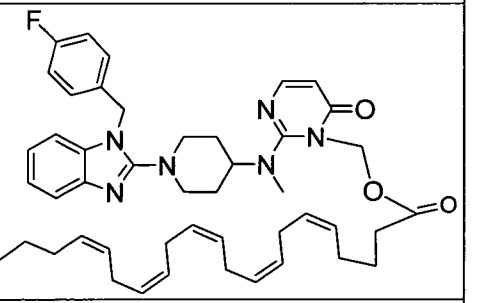
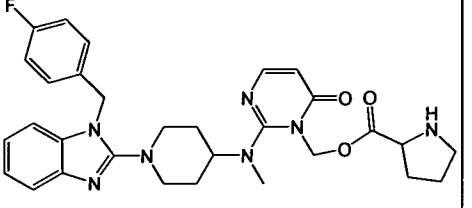
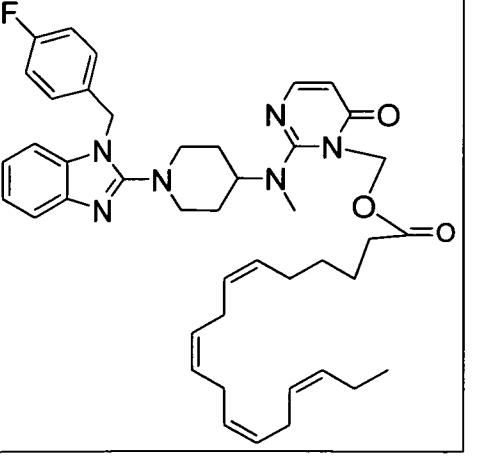
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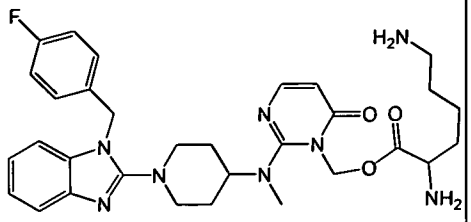
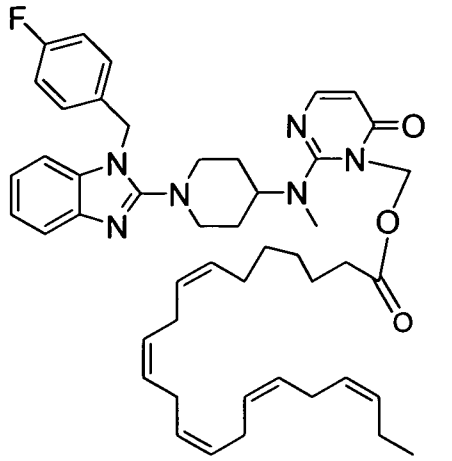
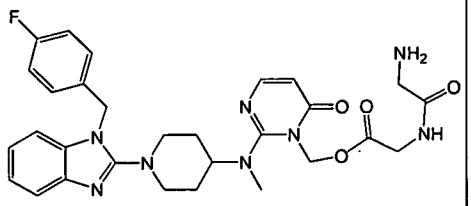
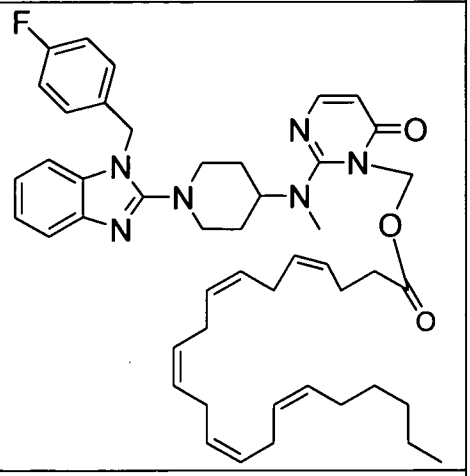
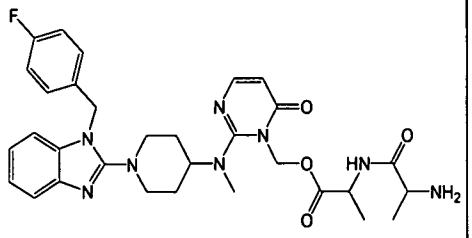
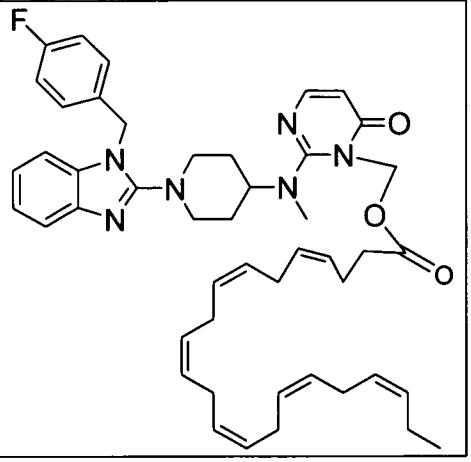
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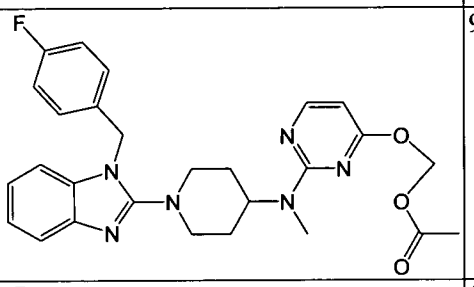
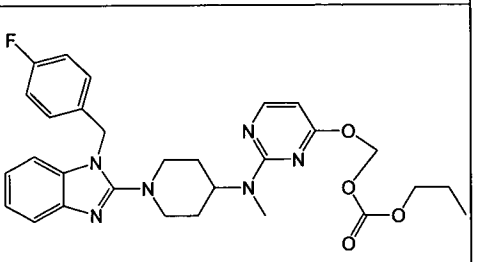
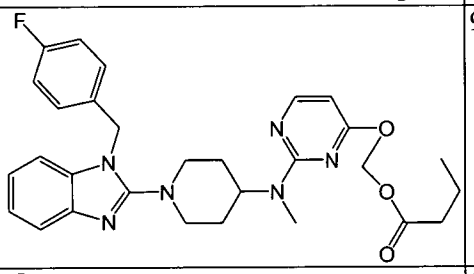
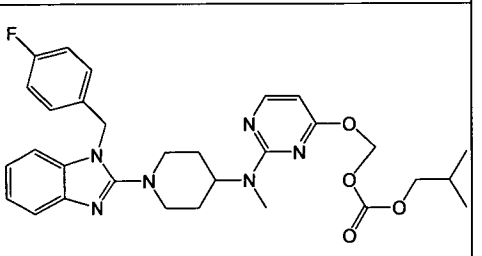
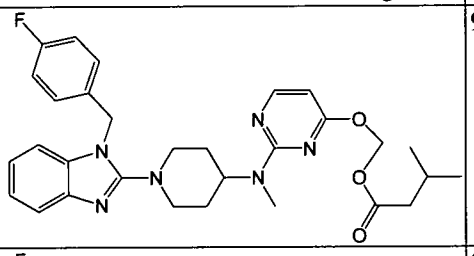
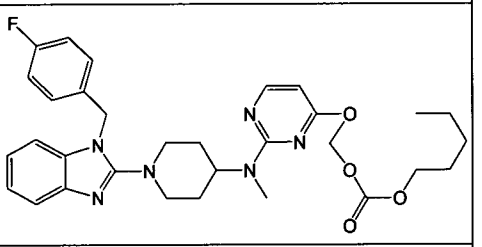
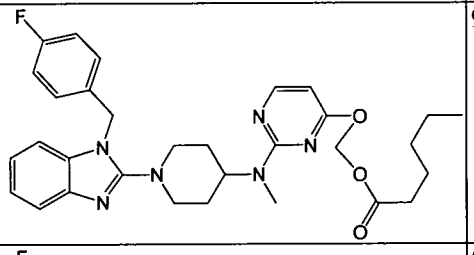
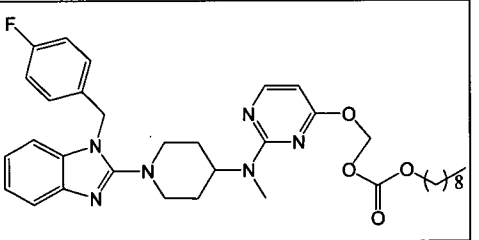
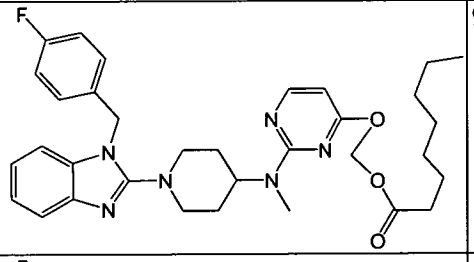
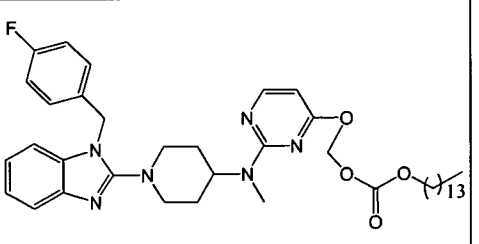
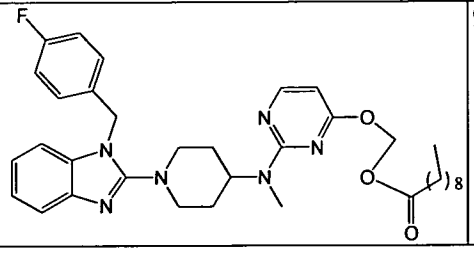
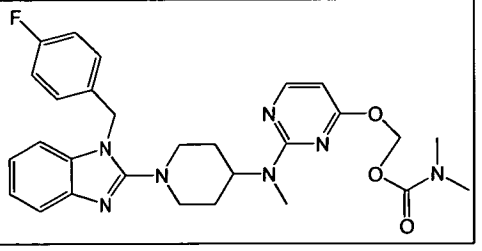
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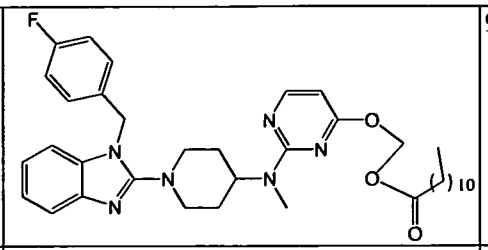
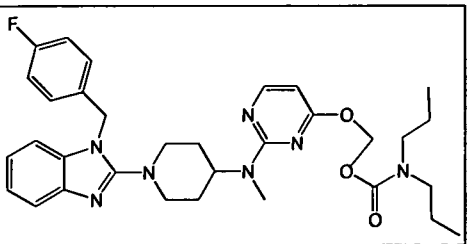
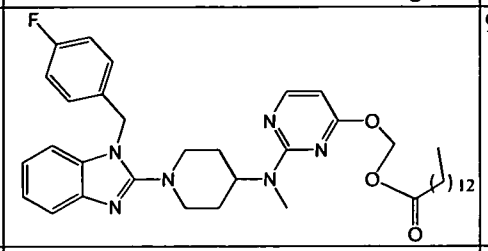
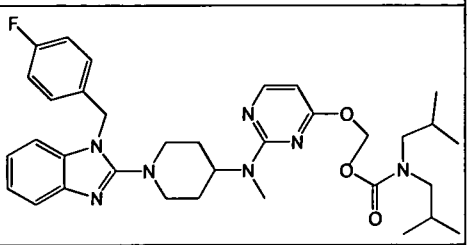
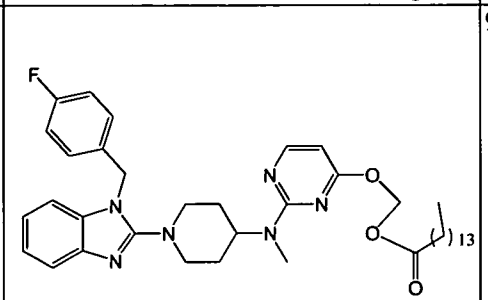
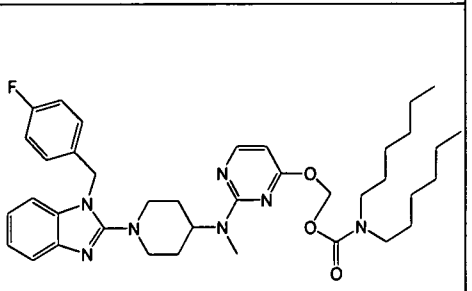
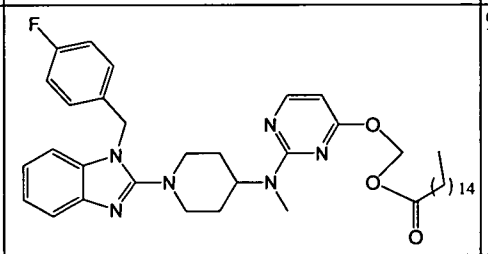
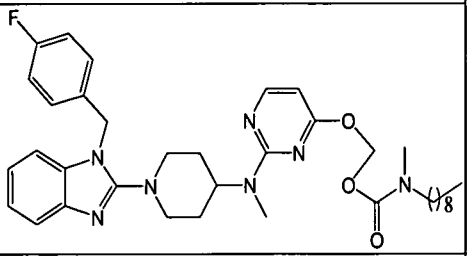
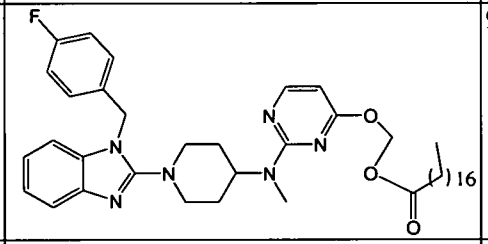
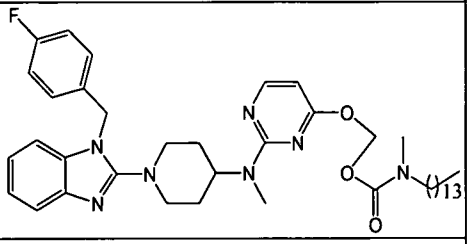
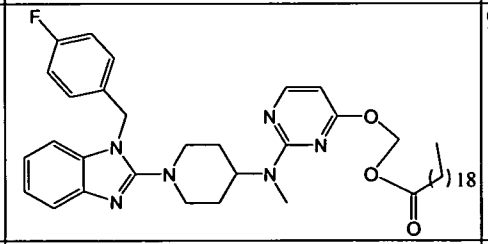
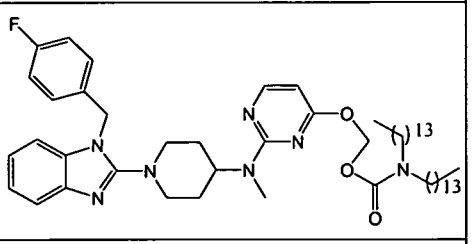
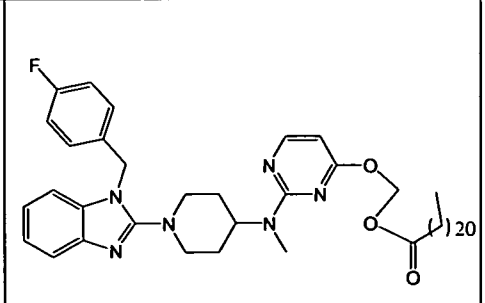
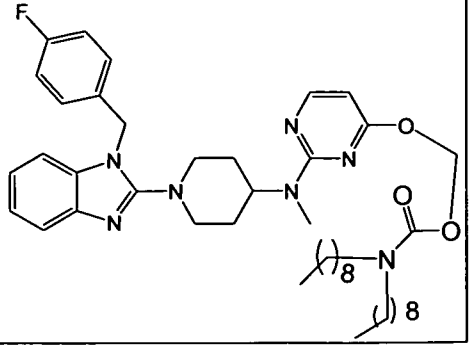
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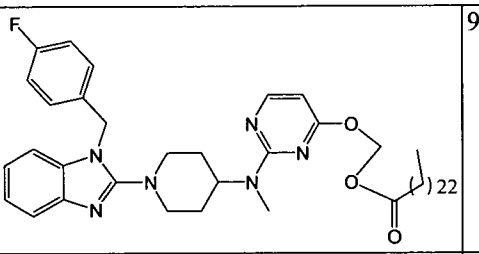
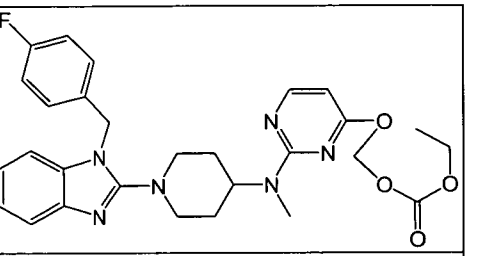
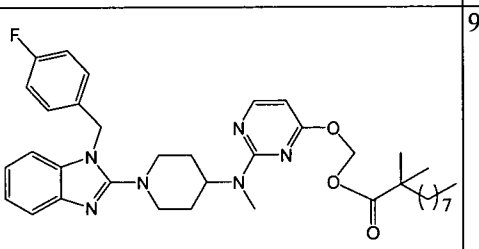
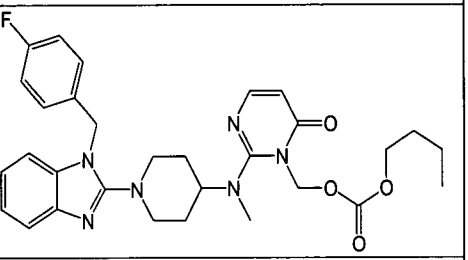
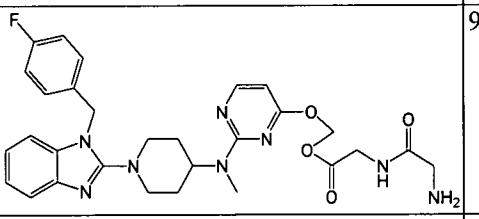
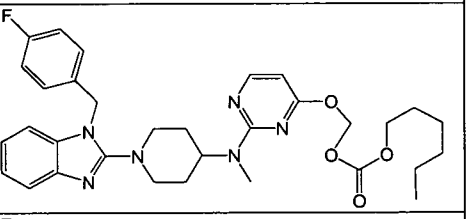
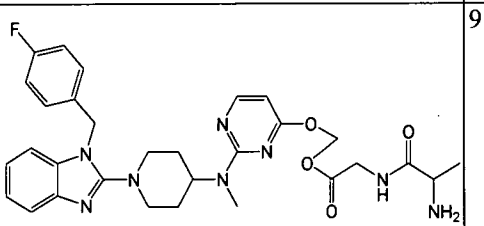
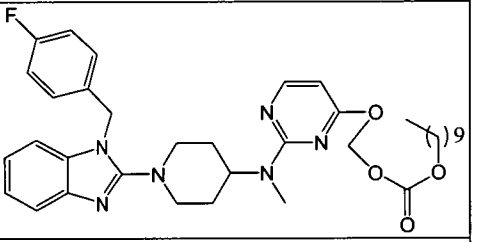
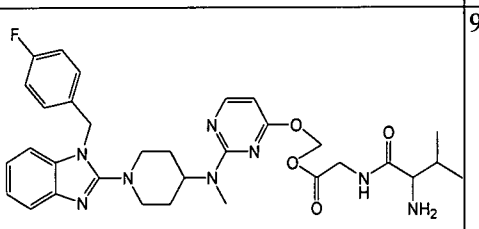
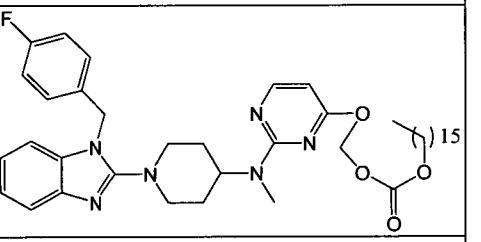
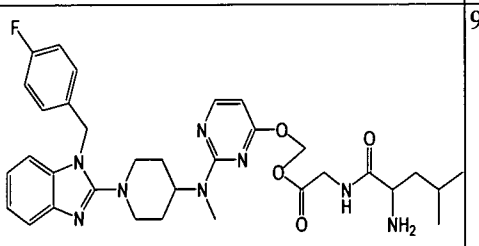
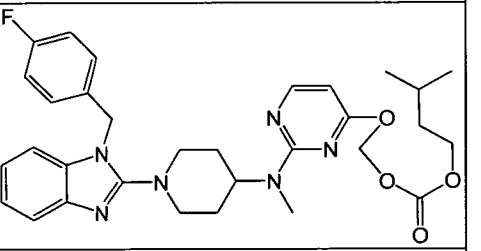
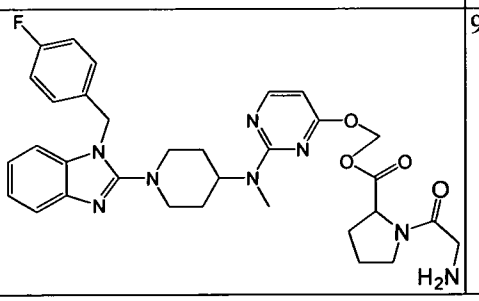
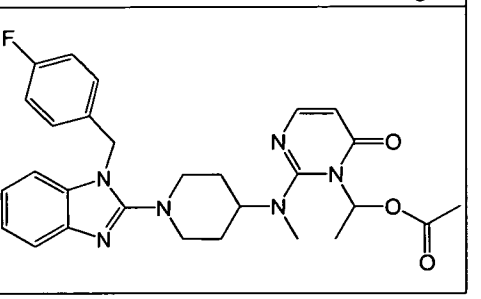
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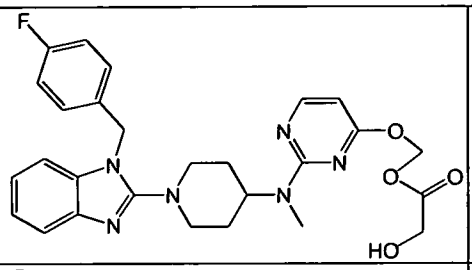
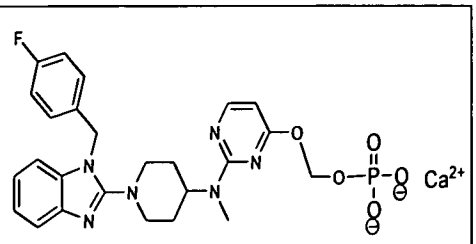
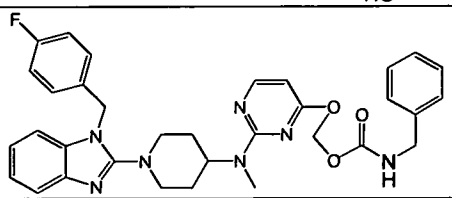
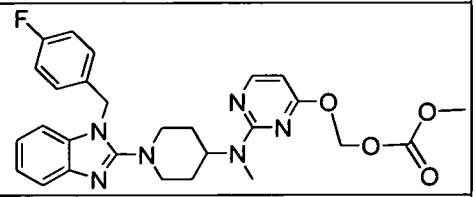
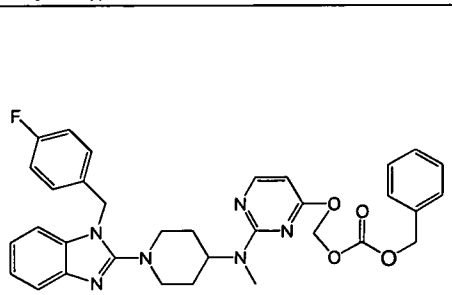
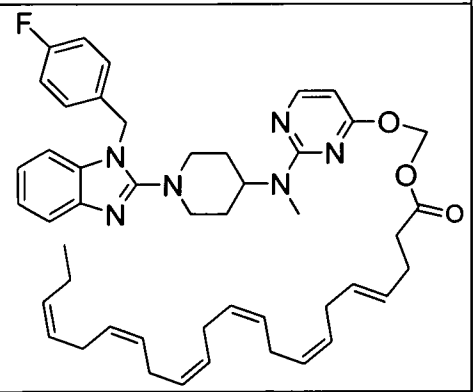
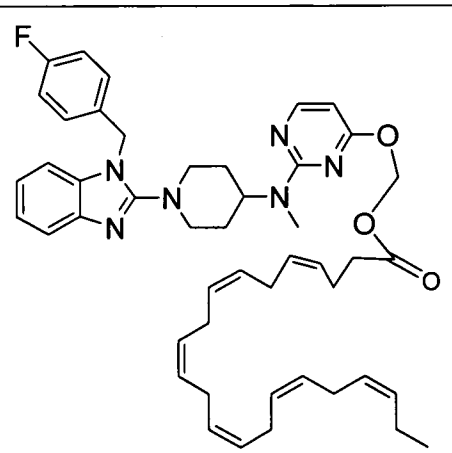
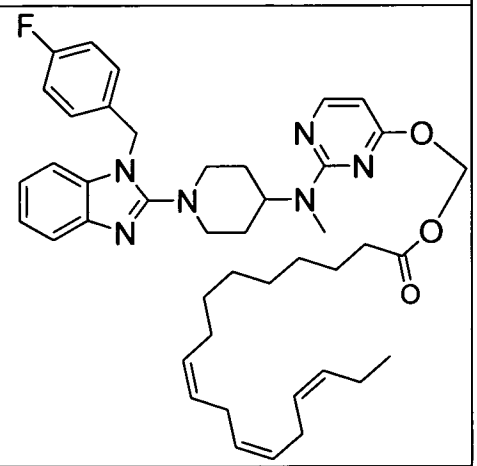
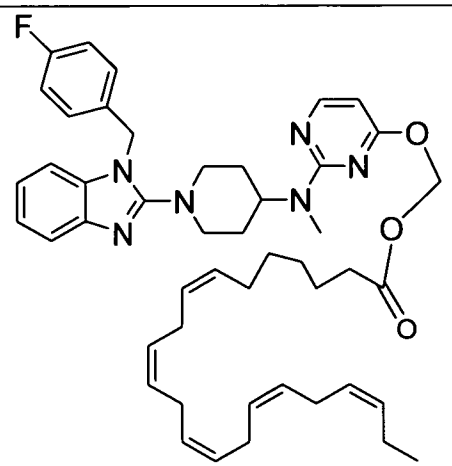
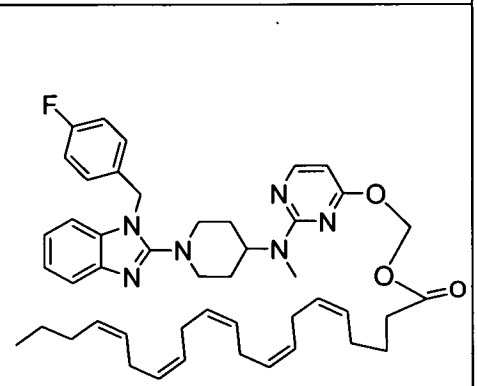
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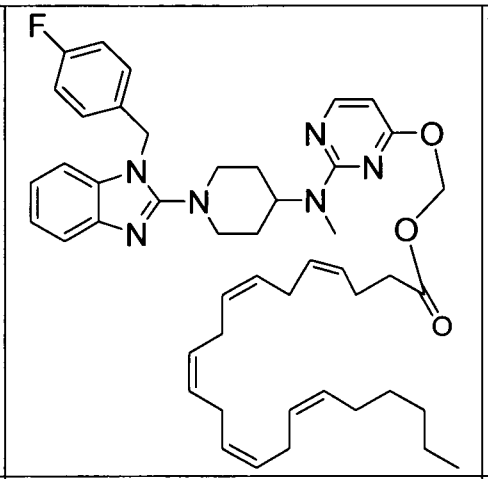
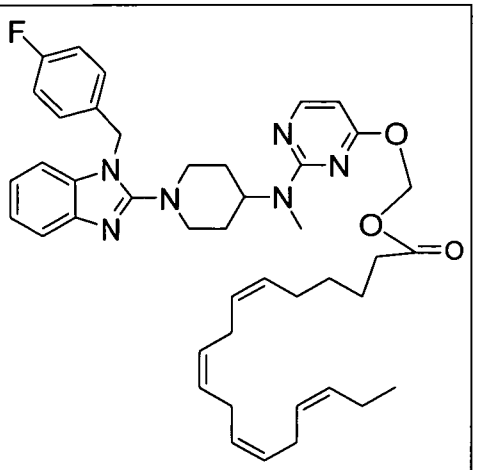
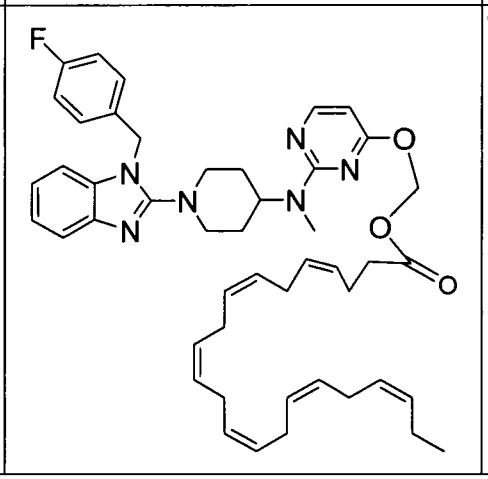
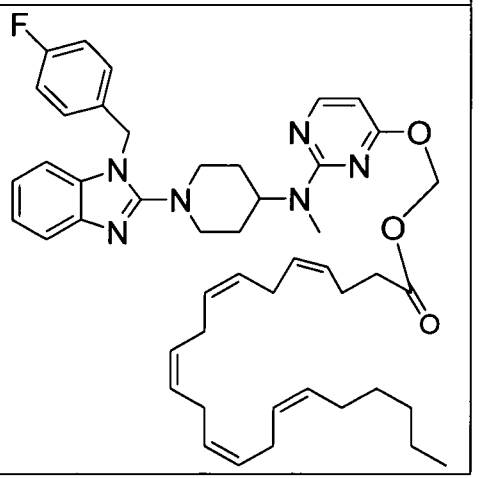
表F

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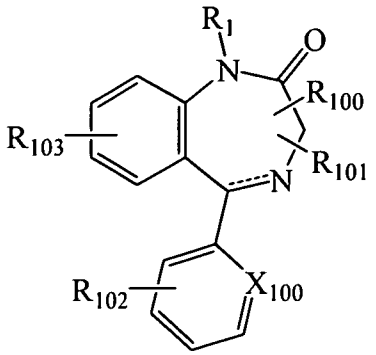
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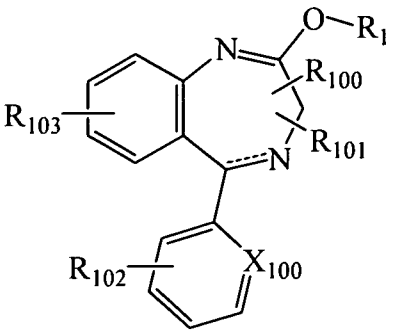
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926 	953 

具有化學式IX、X、XI、XII的化合物並且特別地表A-D的化合物對於治療神經(neurological)以及精神疾患(psychiatric disorder)[包括精神分裂症(schizophrenia)、躁症(mania)、焦慮(anxiety)以及雙極性情感疾病(bipolar disease)]是有用的。這些化合物藉由切割不穩定的部分(R_1)而提供母體藥效團的持續釋放。就其本身而論，該等具有化學式IX、X、XI、XII的化合物並且特別地表A-D的化合物對於藉由提供母體藥的持續釋放來治療神經疾患是有用的。

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XIII或XIV來表示，或它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XIII



化學式XIV

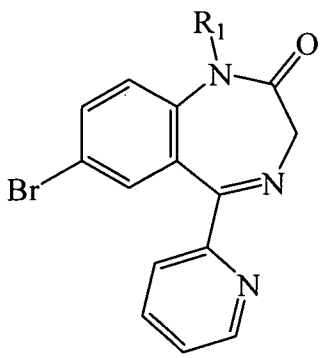
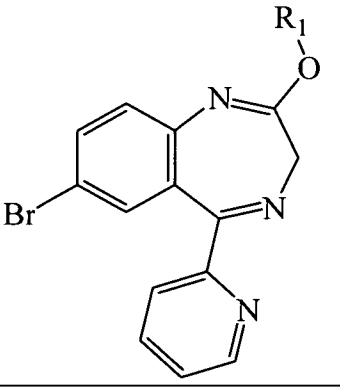
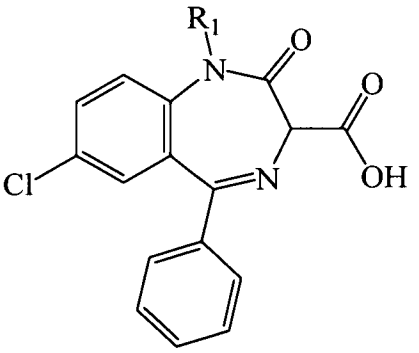
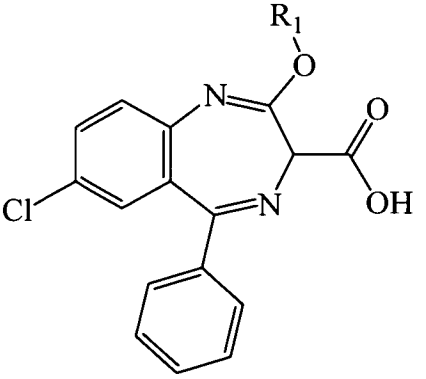
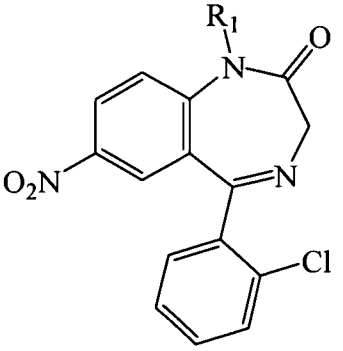
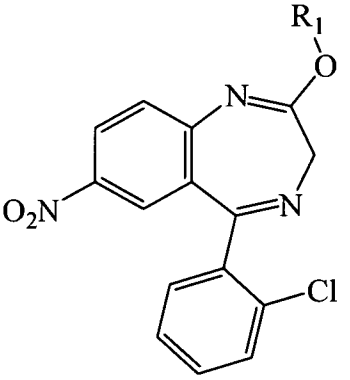
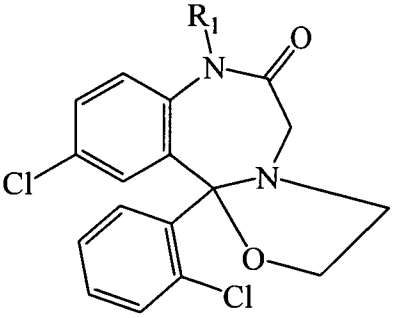
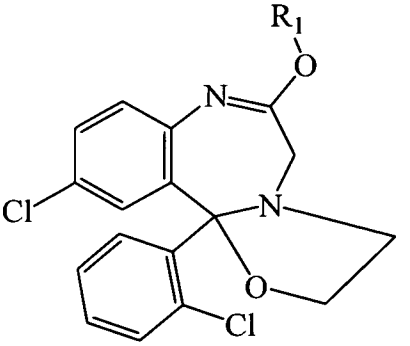
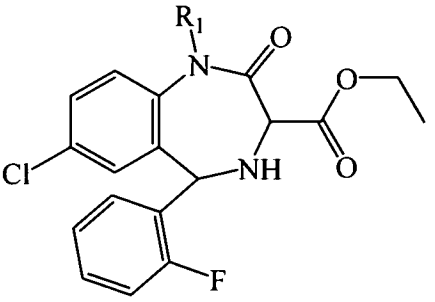
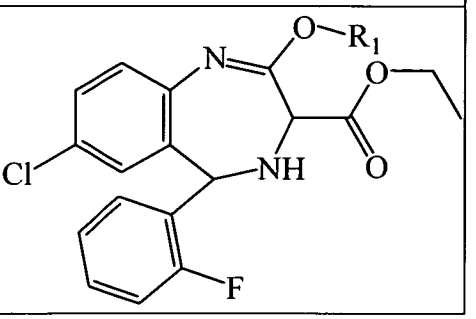
其中R_{100}、R_{101}、R_{102}以及R_{103}是獨立地選自於：不存在、氫、鹵素、$-OR_{10}$、$-SR_{10}$、$-NR_{10}R_{11}$-、選擇性地經取代的脂族、選擇性地經取代的芳基或芳基或選擇性地經取代的雜環基；

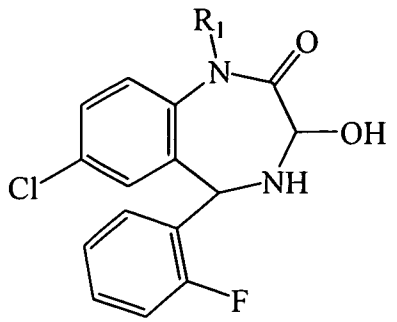
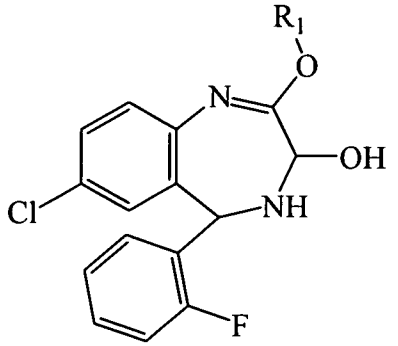
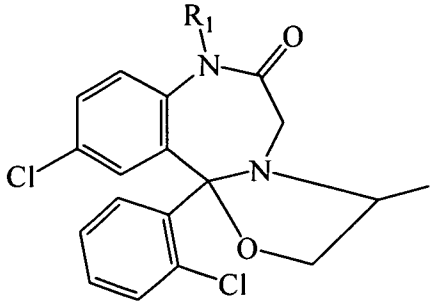
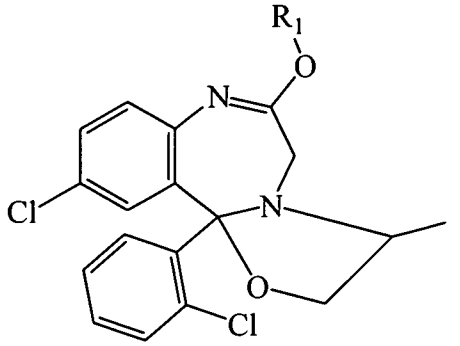
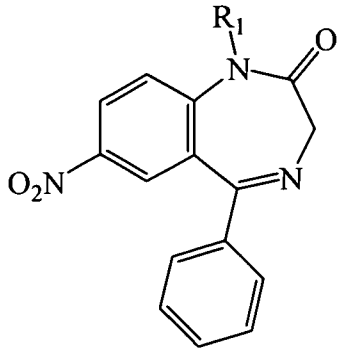
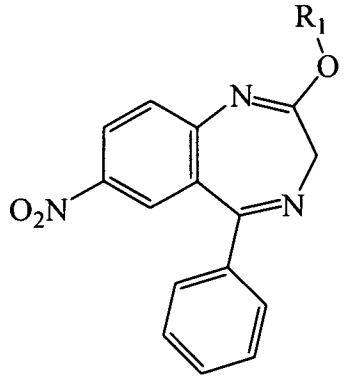
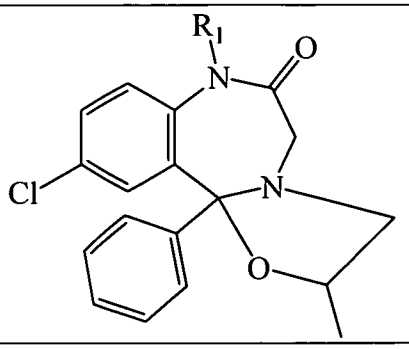
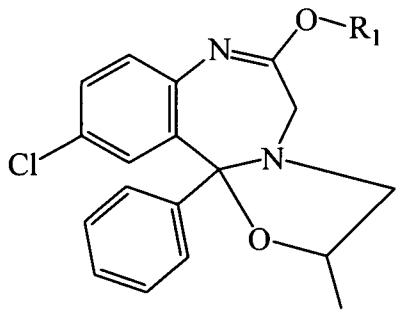
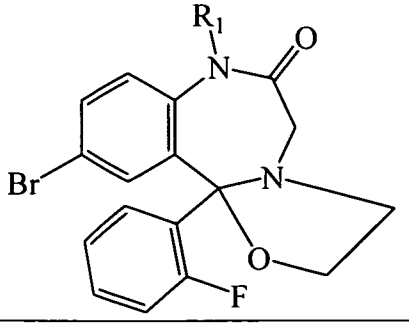
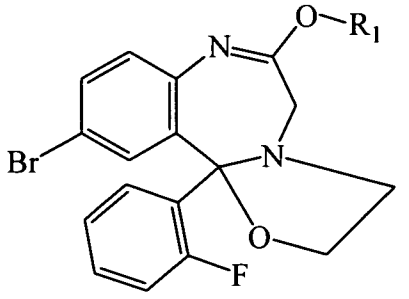
另擇地，2個R_{100}和R_{101}與它們所接附的原子和任何居間的原子一起形成一選擇性地經取代的環；以及

R_{100}是-CH或-N-。

一較佳的具體例是一選自於表XIII-XIV的化合物。一更佳的具體例是一來自表XIII-XIV的化合物，其中R_1是選自於表1-4。

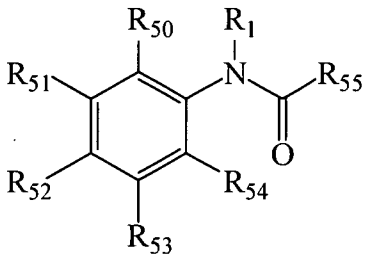
表 XIII-XIV

1		11	
2		12	
3		13	
4		14	
5		15	

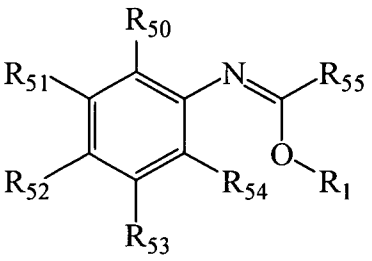
6		16	
7		17	
8		18	
9		19	
10		20	

醯基苯胺的前驅藥

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XV或XVI來表示，或它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XV



化學式XVI

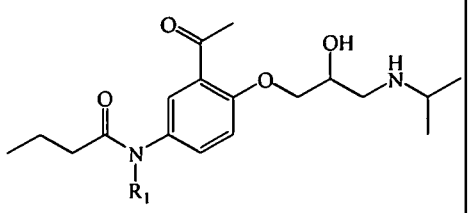
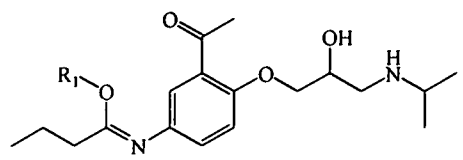
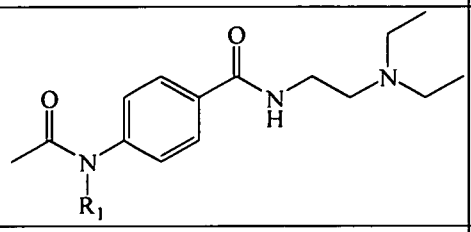
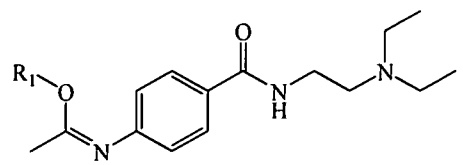
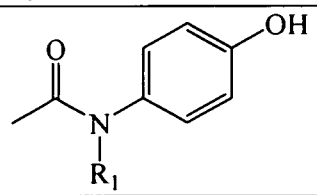
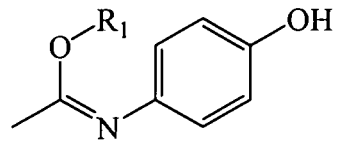
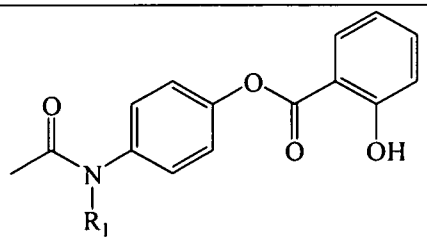
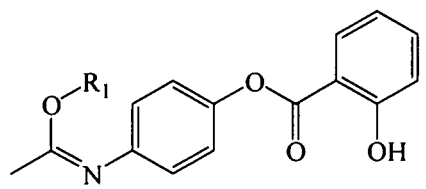
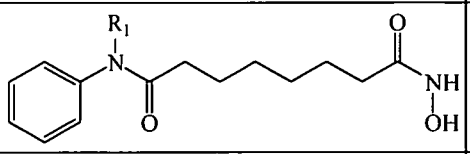
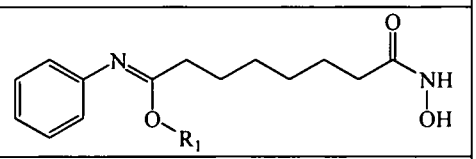
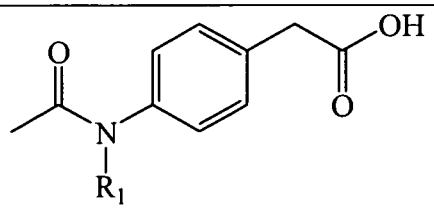
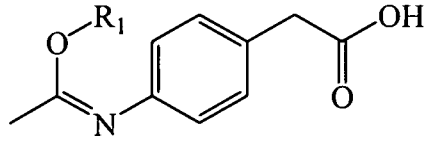
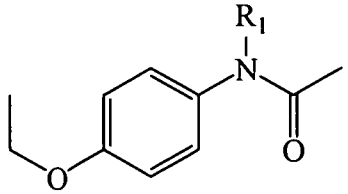
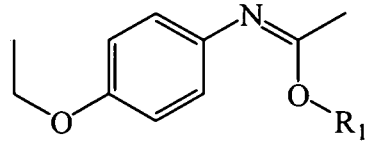
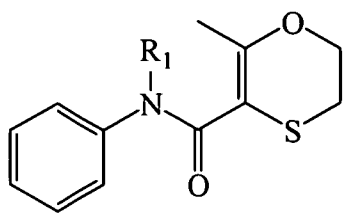
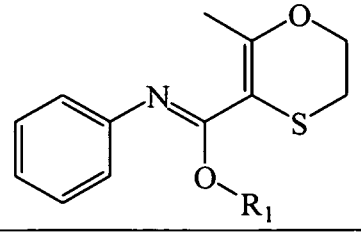
其中R_1是如上面所定義的；

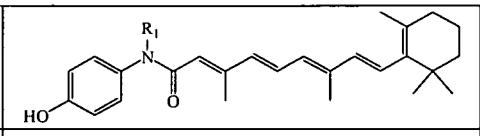
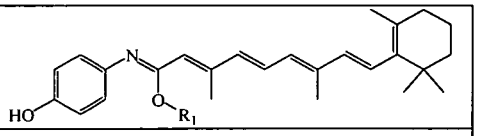
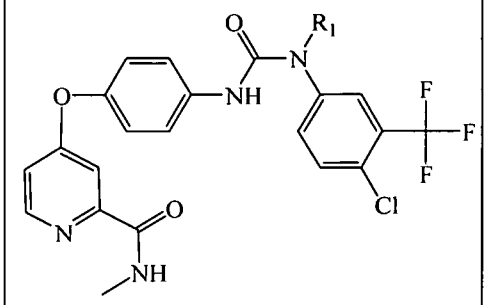
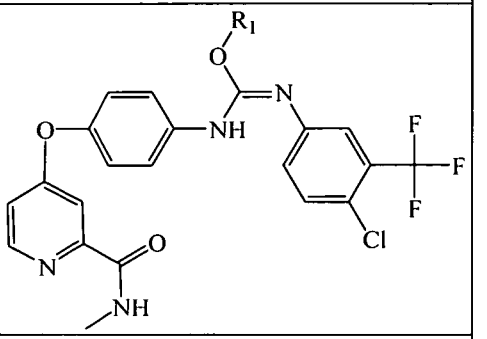
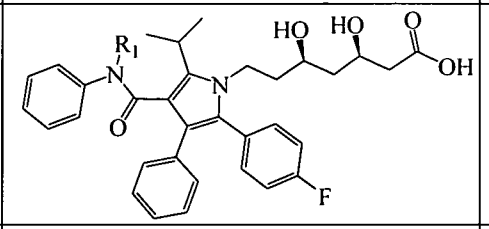
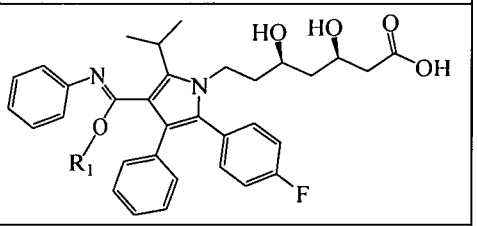
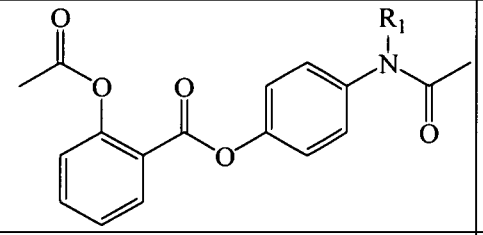
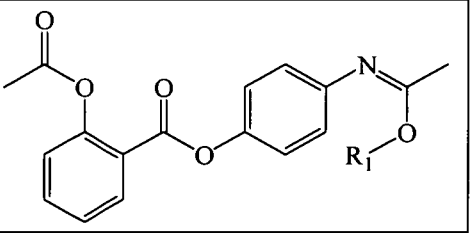
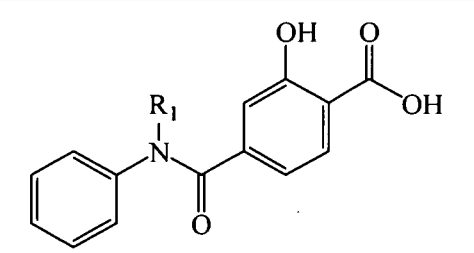
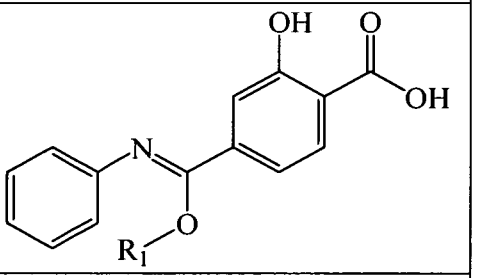
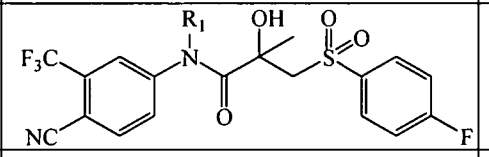
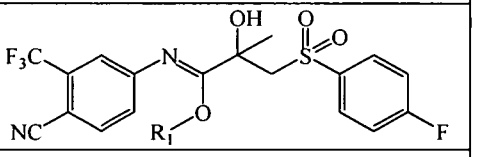
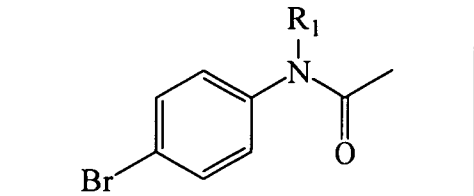
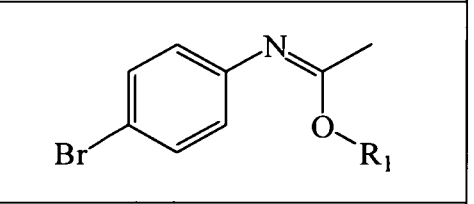
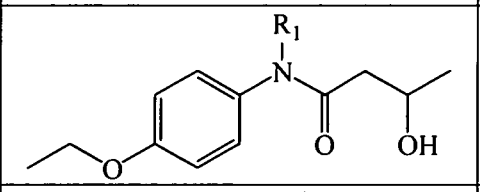
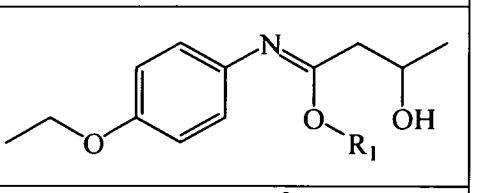
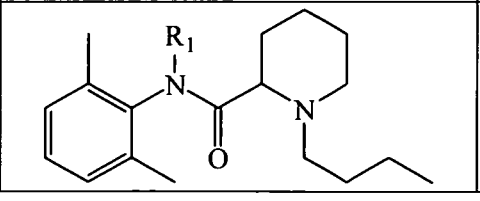
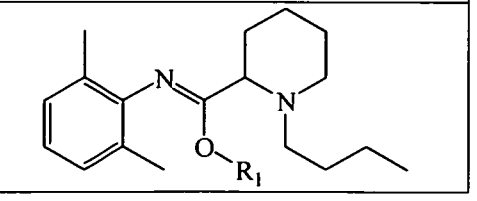
各個R_{50}、R_{51}、R_{52}、R_{53}、R_{54}以及R_{55}是獨立地選自於：氫、鹵素、$-OR_{10}$、$-SR_{10}$、$-NR_{10}R_{11}-$、選擇性地經取代的脂族、選擇性地經取代的芳基或芳基或選擇性地經取代的雜環基；

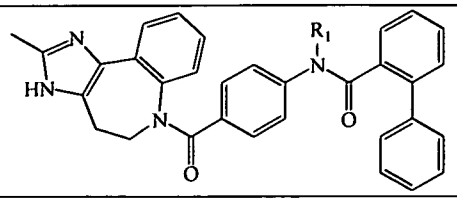
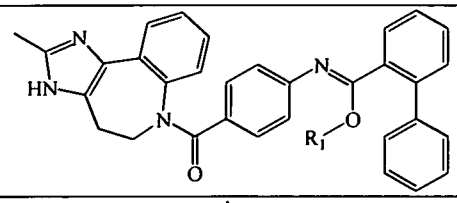
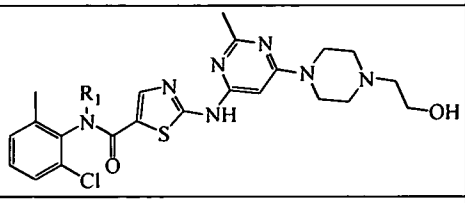
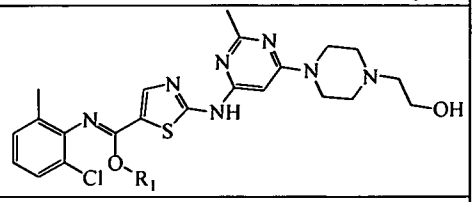
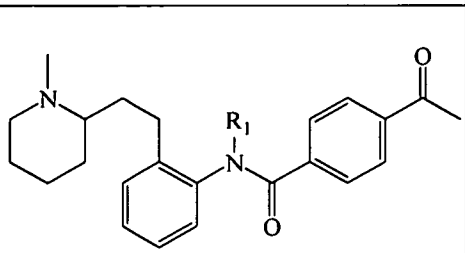
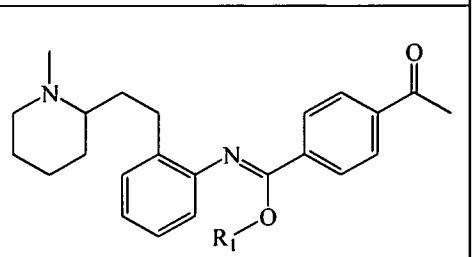
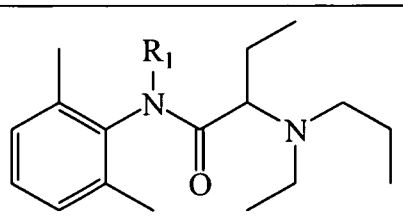
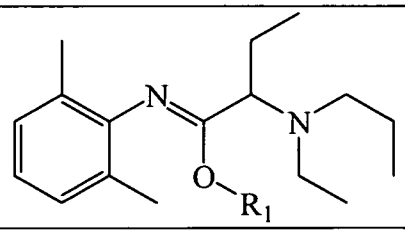
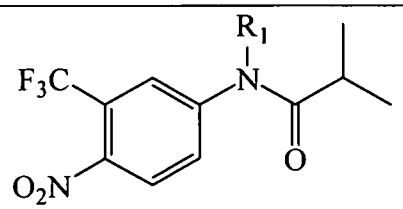
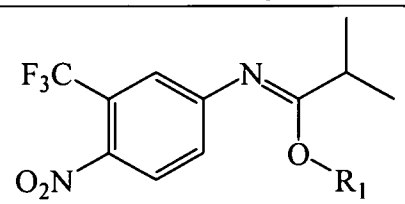
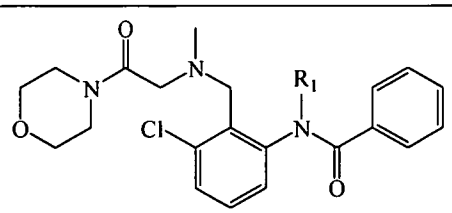
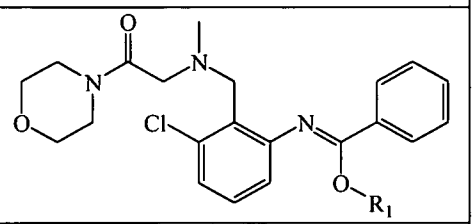
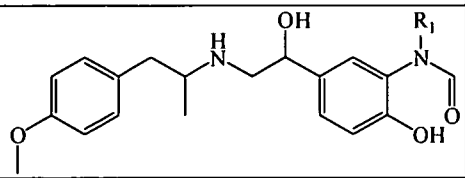
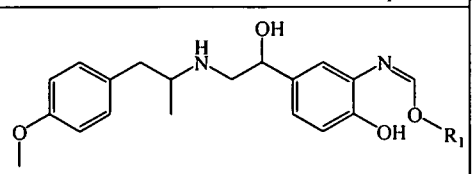
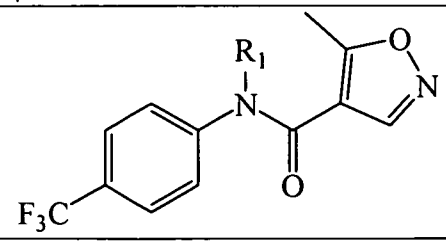
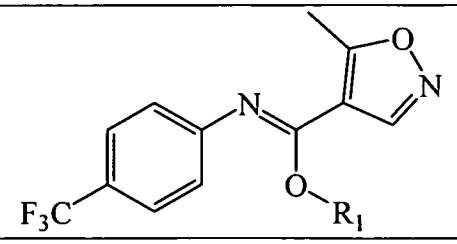
另擇地，二或多個R_{50}、R_{51}、R_{52}、R_{53}、R_{54}和R_{55}與它們所接附的原子一起形成一選擇性地經取代的環。

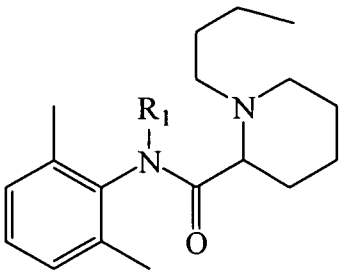
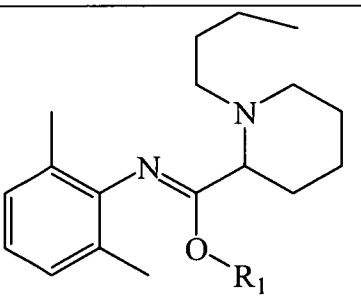
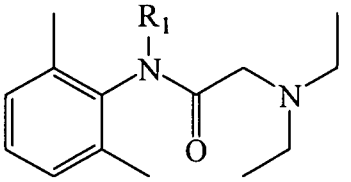
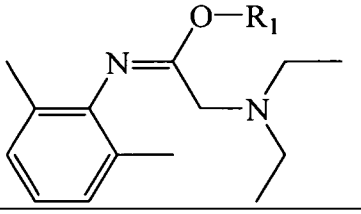
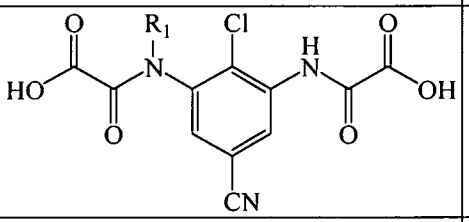
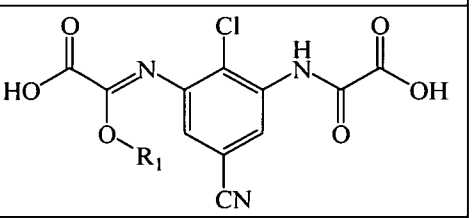
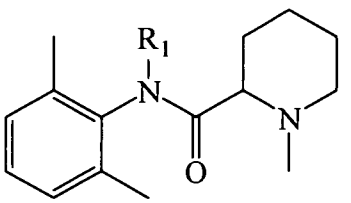
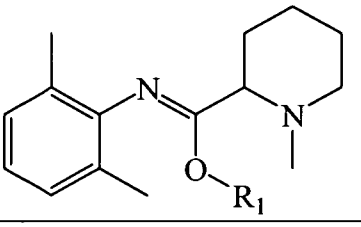
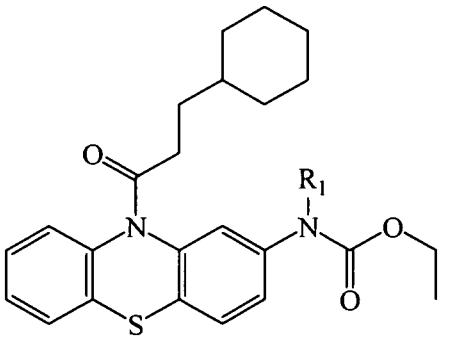
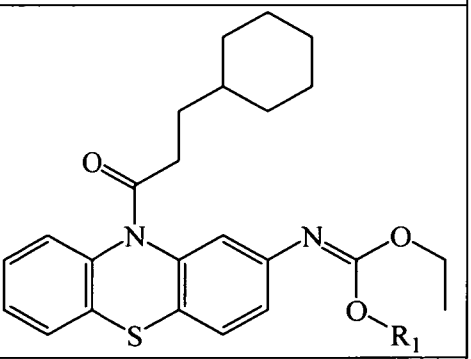
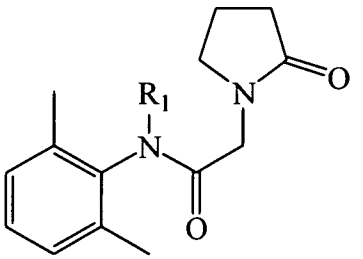
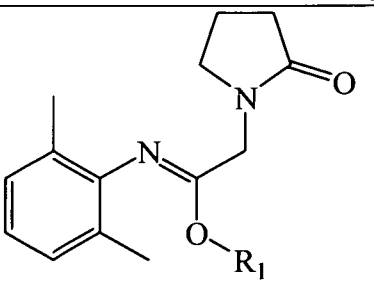
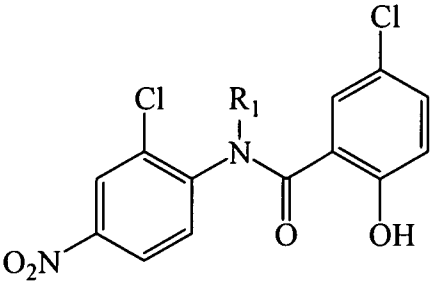
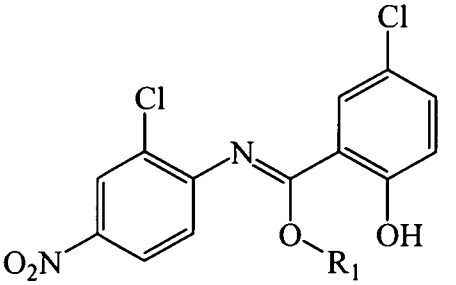
一較佳的具體例是一選自於表XV-XVI的化合物。一更佳的具體例是一來自表XV-XVI的化合物，其中R_1是選自於表1-4。

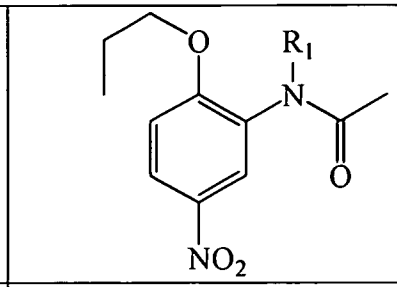
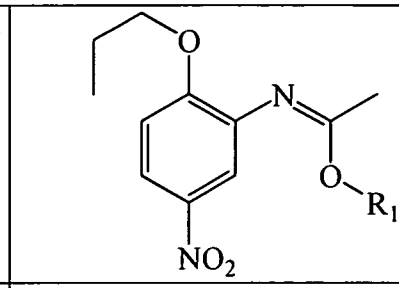
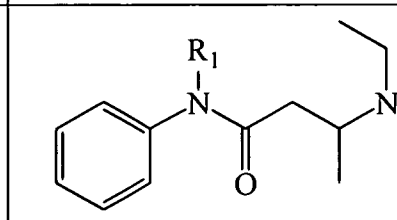
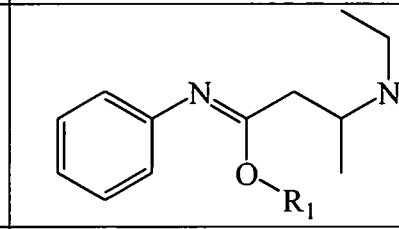
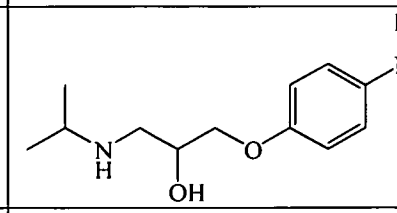
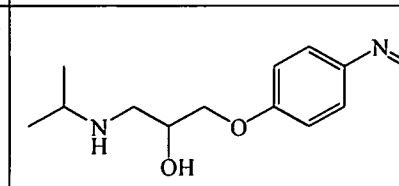
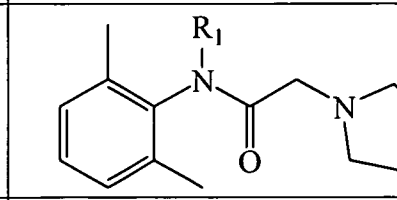
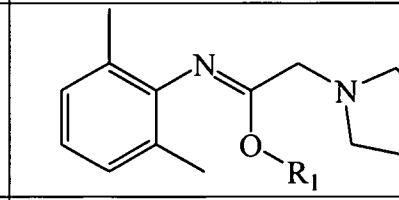
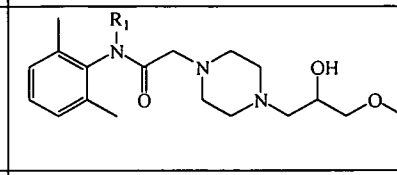
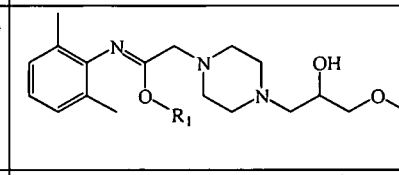
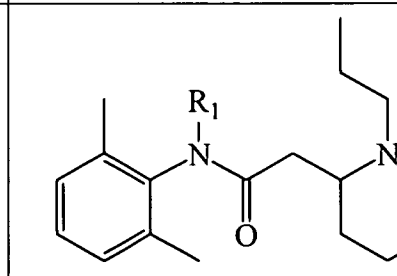
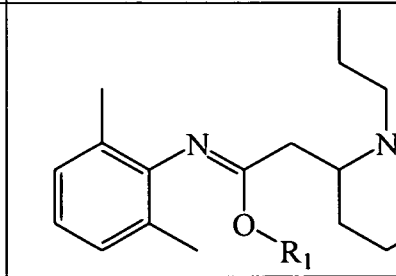
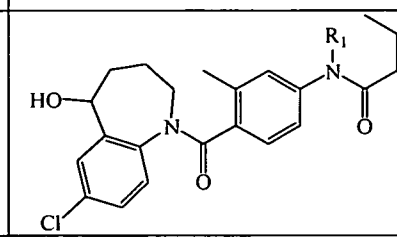
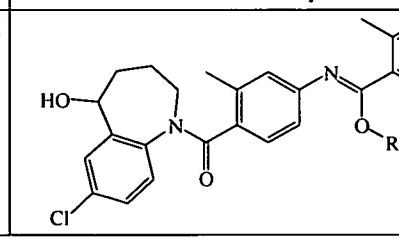
表XV-XVI

1		40	
2		41	
3		42	
4		43	
5		44	
6		45	
7		46	
8		47	

9		48	
10		49	
11		50	
12		51	
13		52	
14		53	
15		54	
16		55	
17		56	

18		57	
19		58	
20		59	
21		60	
22		61	
23		62	
24		63	
25		64	

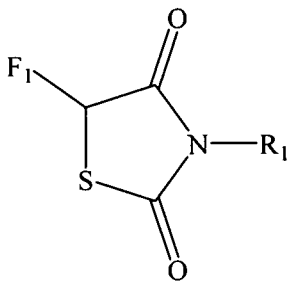
26		65	
27		66	
28		67	
29		68	
30		69	
31		70	
32		71	

33		72	
34		73	
35		74	
36		75	
37		76	
38		77	
39		78	

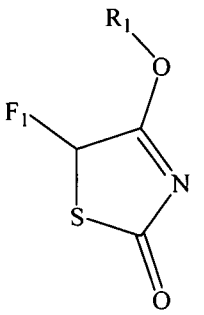
噻唑烷酮(Thiazolidinones)

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XVII、XVIII或XIX來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上

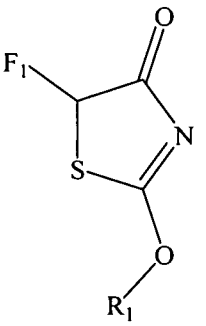
可接受的鹽類以及溶劑合物：



化學式XVII



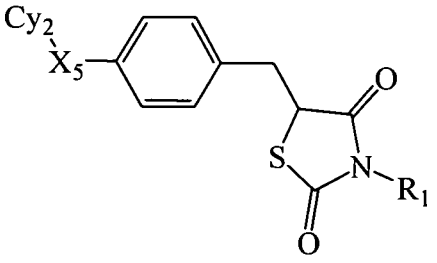
化學式XVIII



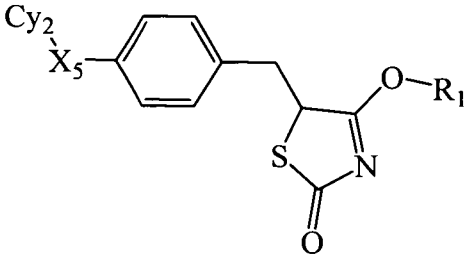
化學式XIX

其中F_1以及R_1是如上面所定義的。

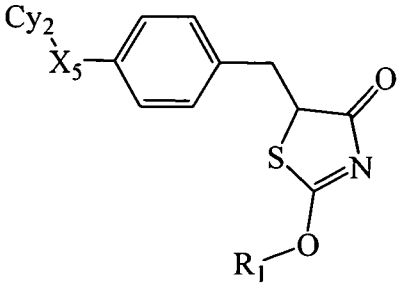
一較佳的具體例是一具有如下面所例示說明的化學式XX、XXI或XXII的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XX



化學式XXI



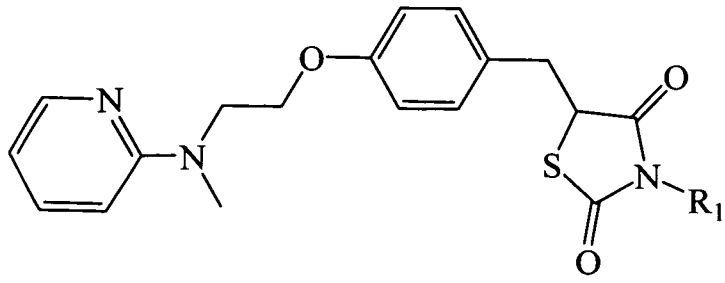
化學式XXII

其中R_1是如上面所定義的；

Cy_2是一選擇性地經取代的雜環基環；以及

X_5是選自於：不存在、-S-、-O-、-S(O)-、-$S(O)_2$-、-$N(R_{10})$-、-C(O)-、-$C(OR_{10})(R_{11})$-、-$[C(R_{10})(R_{11})]_v$-、-$O[C(R_{10})(R_{11})]_v$-、-$O[C(R_{10})(R_{11})]_vO$-、-$S[C(R_{10})(R_{11})]_vO$-、-$NR_{12}[C(R_{10})(R_{11})]_vO$-、-$NR_{12}[C(R_{10})(R_{11})]_vS$-、-$S[C(R_{10})(R_{11})]_v$-、-$C(O)[C(R_{10})(R_{11})]_v$-以及-$C(R_{10})=C(R_{10})$-；其中v是0、1、2、3、4、5、6、7、8、9或10。

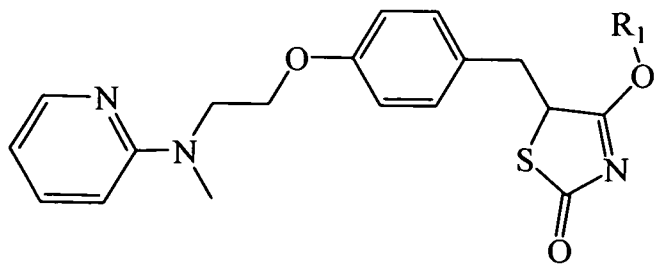
一較佳的具體例是一具有如下面所例示說明的化學式XXIV的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XXIV

在化學式XXIV的一個更佳具體例中，R_1是選自於表1-4。

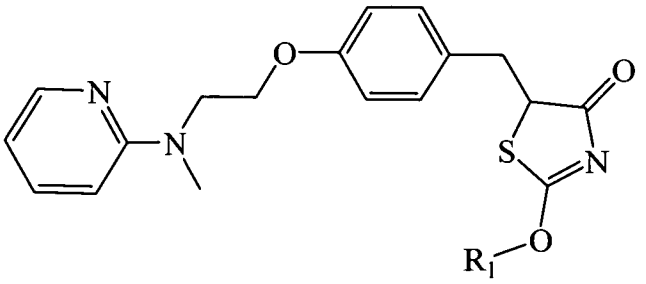
一較佳的具體例是一具有如下面所例示說明的化學式XXIV的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XXV

在化學式XXV的一個更佳具體例中，R_1是選自於表1-4。

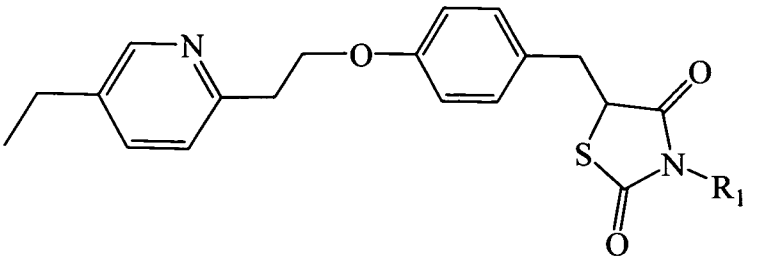
一較佳的具體例是一具有如下面所例示說明的化學式XXVI的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XXVI

在化學式XXVI的一個更佳具體例中，R_1是選自於表1-4。

一較佳的具體例是一具有如下面所例示說明的化學式XXVII的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：

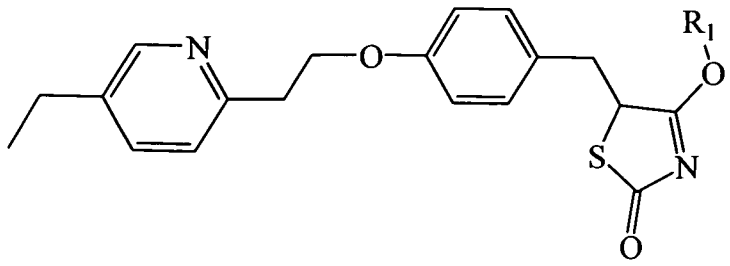


化學式XXVII

在化學式XXVII的一個更佳具體例中，R_1是選自於表1-4。

一較佳的具體例是一具有如下面所例示說明的化學式

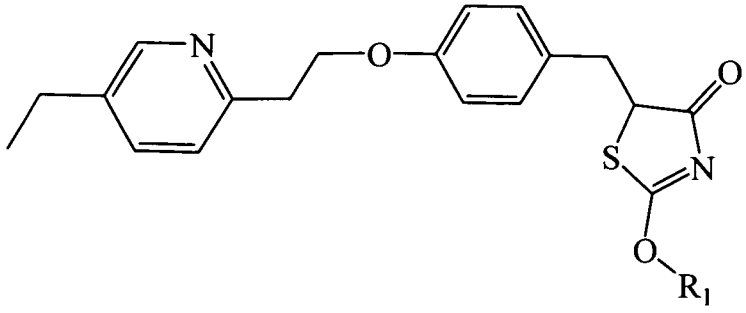
XXVIII的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XXVIII

在化學式XXVIII的一個更佳具體例中，R_1是選自於表1-4。

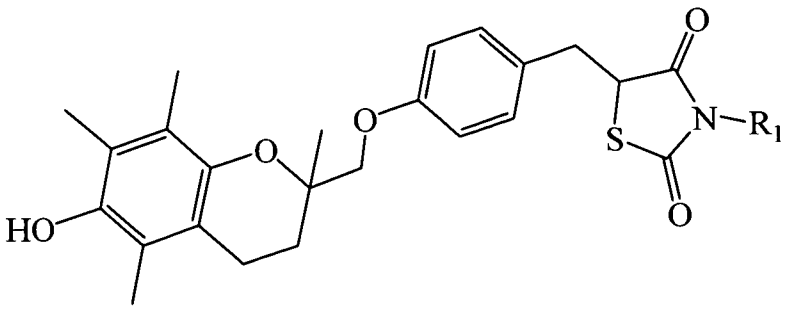
一較佳的具體例是一具有如下面所例示說明的化學式XXIV的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XXIX

在化學式XXIX的一個更佳具體例中，R_1是選自於表1-4。

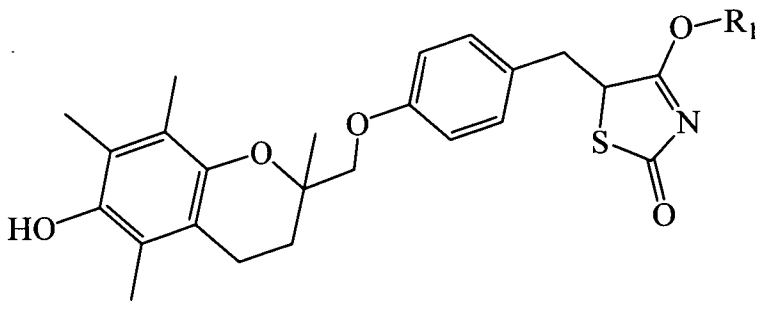
一較佳的具體例是一具有如下面所例示說明的化學式XXIV的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XXX

在化學式XXX的一個更佳具體例中，R_1是選自於表1。

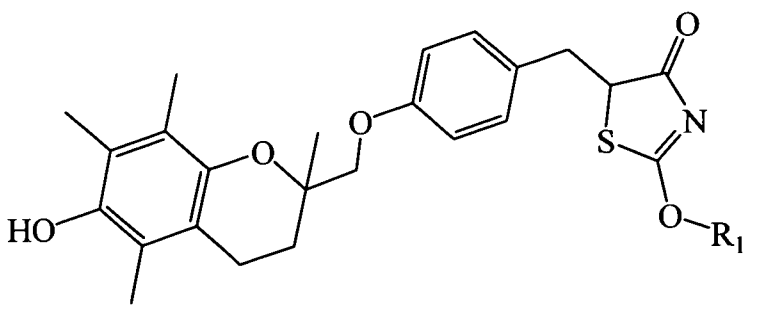
一較佳的具體例是一具有如下面所例示說明的化學式XXXI的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XXXI

在化學式XXXI的一個更佳具體例中，R_1是選自於表1。

一較佳的具體例是一具有如下面所例示說明的化學式XXXII的化合物，以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：

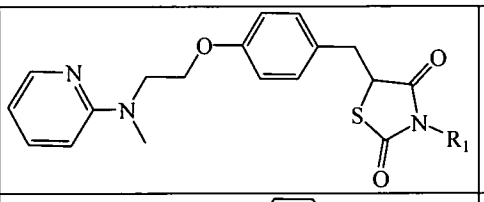
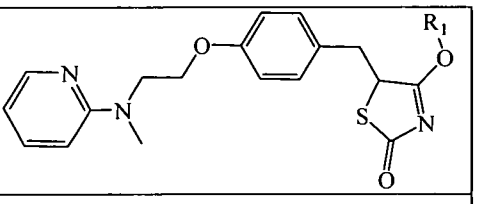
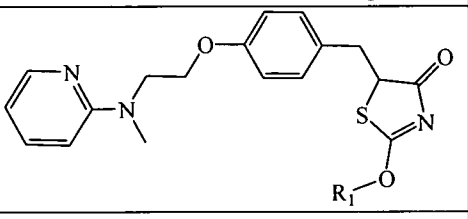
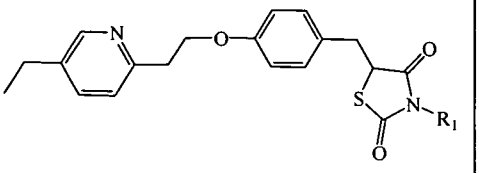
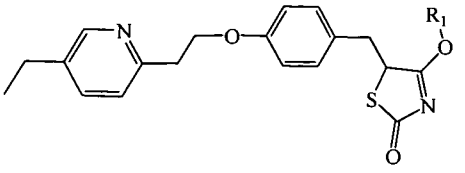
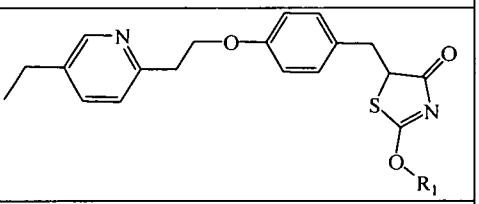
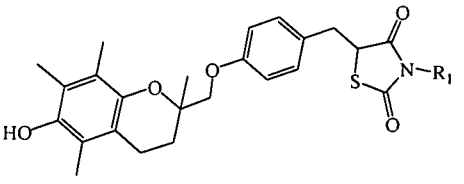
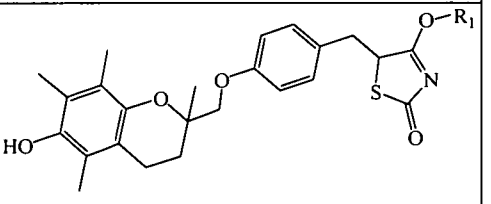
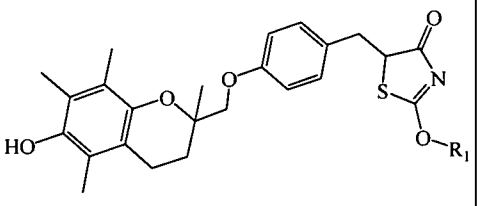
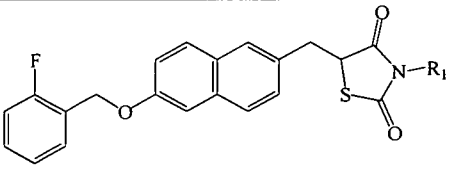
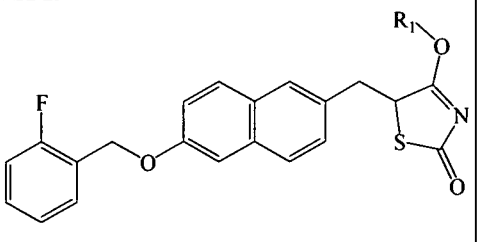
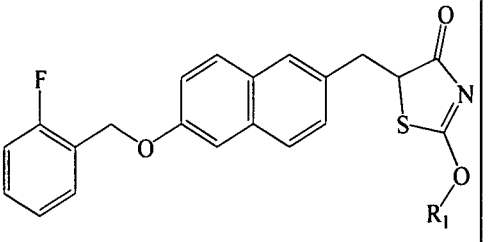
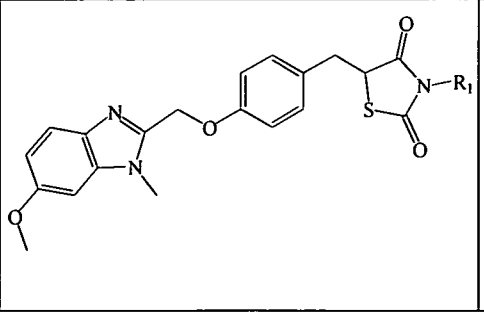
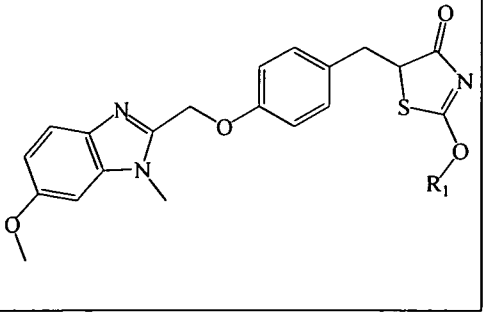


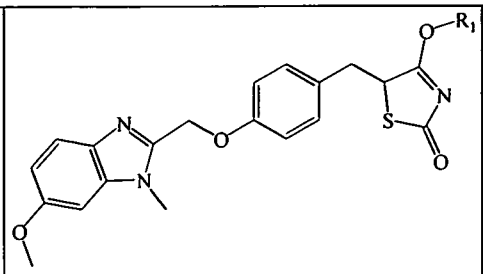
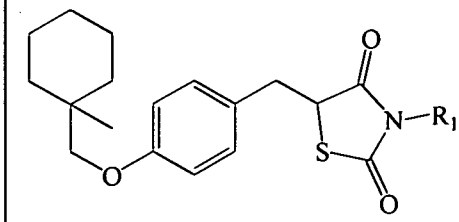
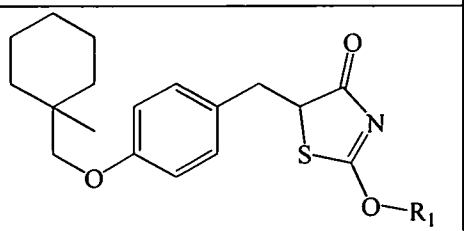
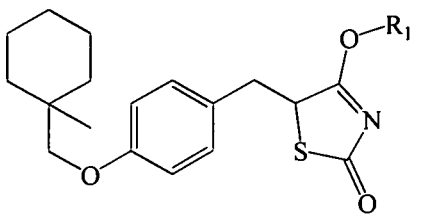
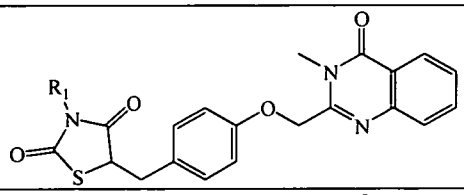
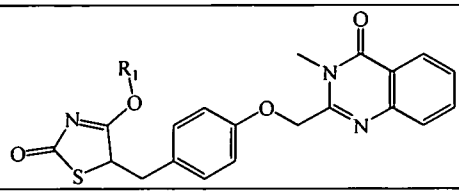
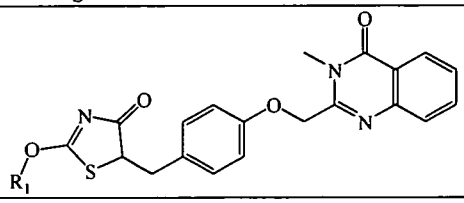
化學式XXXII

在一個更佳的具有化學式XXXII的具體例中，R_1是選自於表1。

在一個較佳的具體例中，一具有化學式XX-XXII的化合物是選自於下面的表XX-XXII。一更佳的具體例是一具有表XX-XXII的化合物，其中R_1是選自於表1-4。

表 XX-XXII

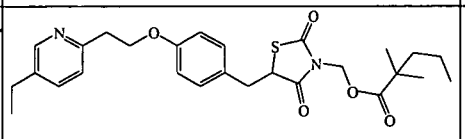
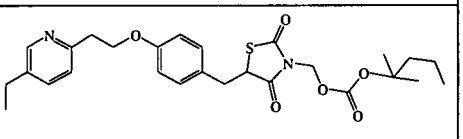
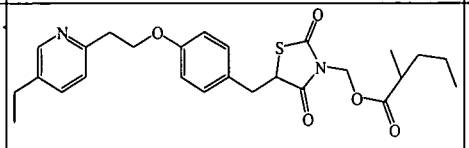
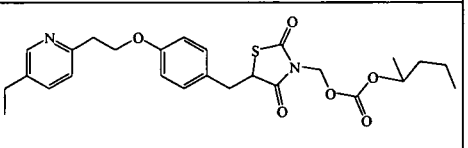
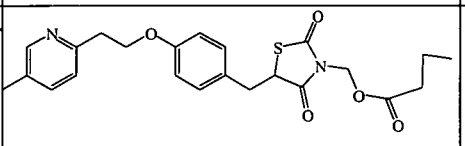
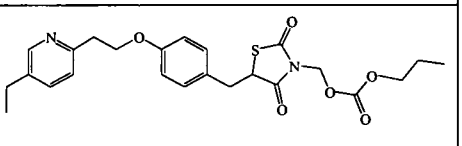
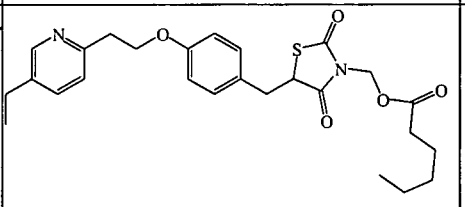
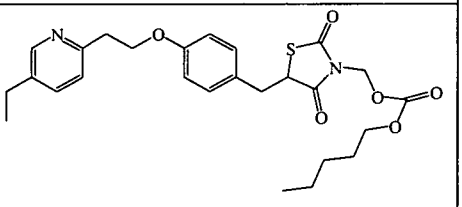
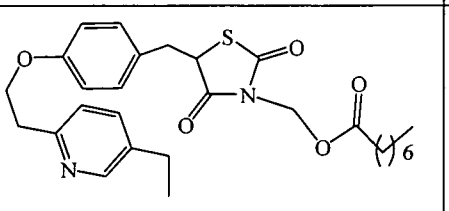
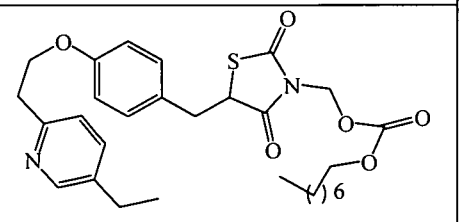
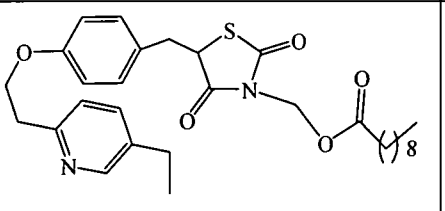
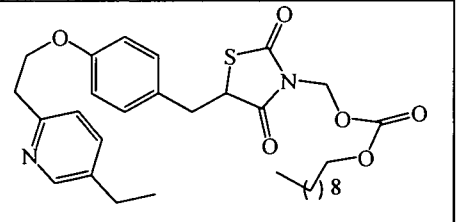
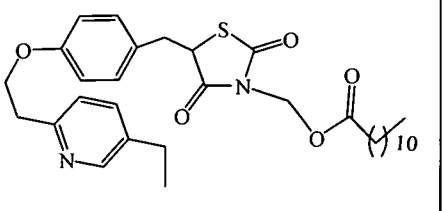
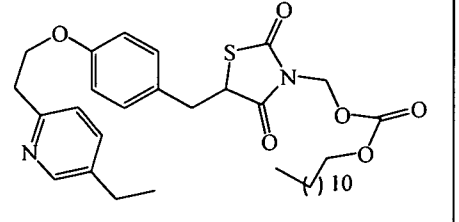
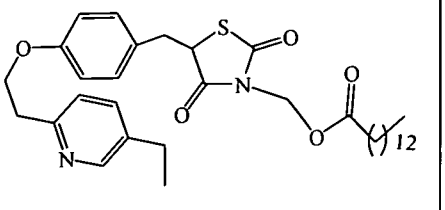
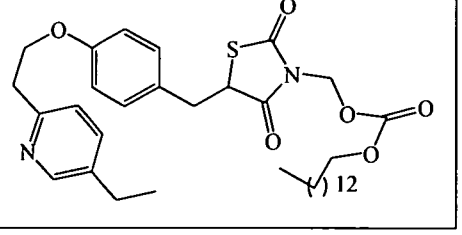
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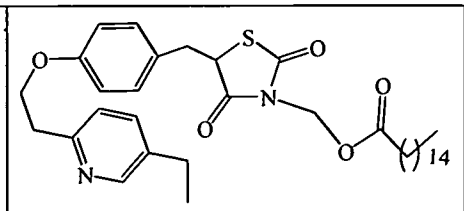
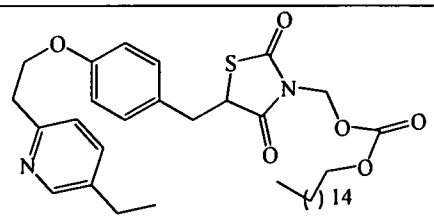
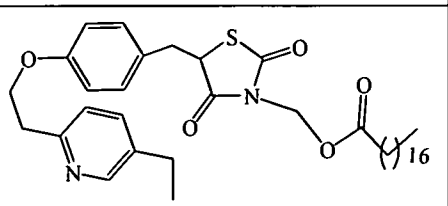
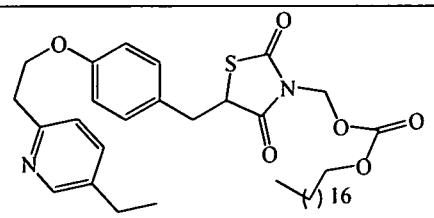
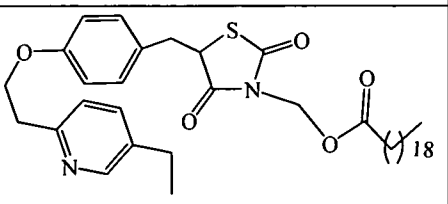
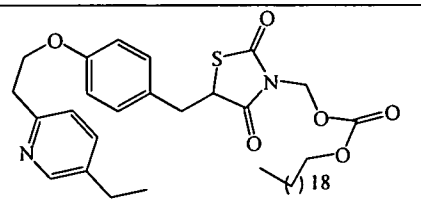
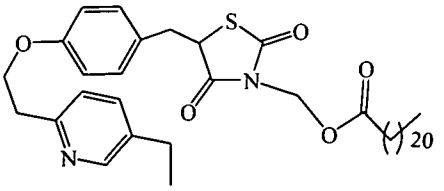
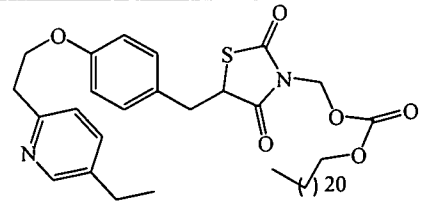
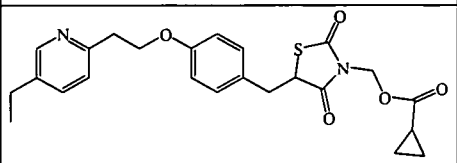
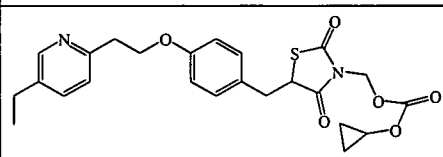
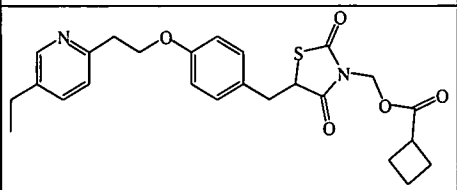
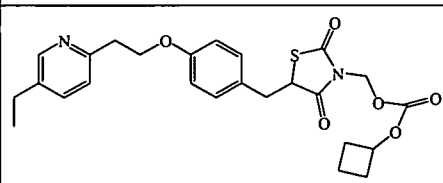
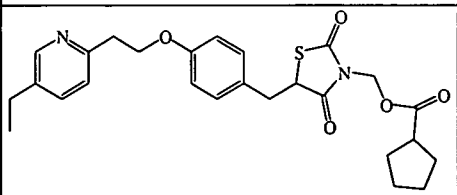
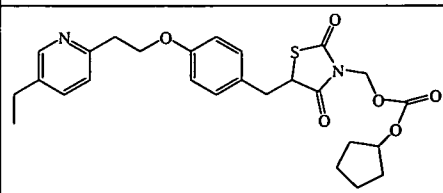
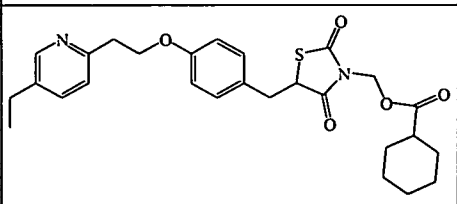
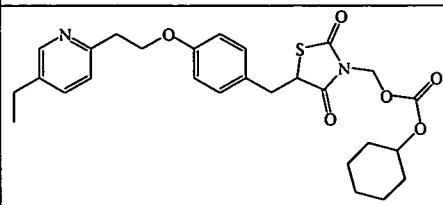
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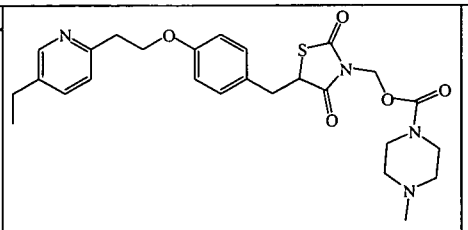
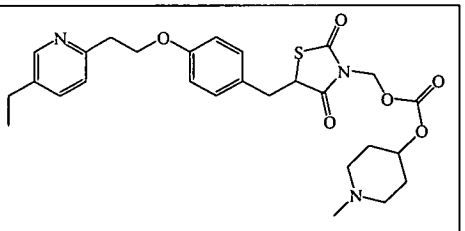
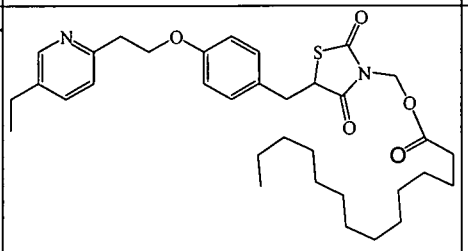
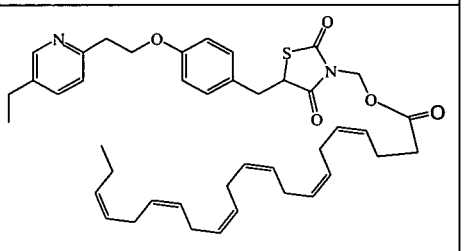
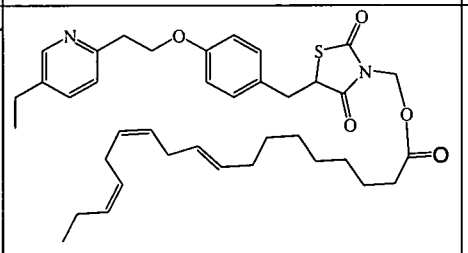
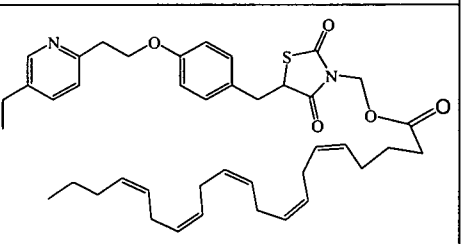
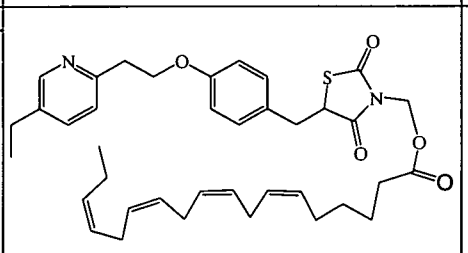
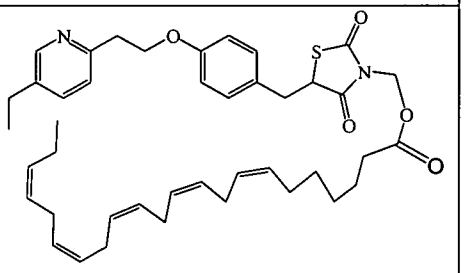
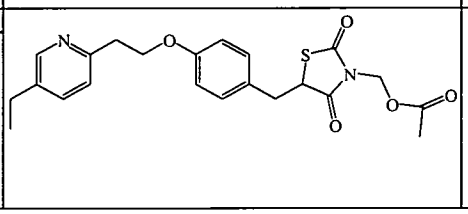
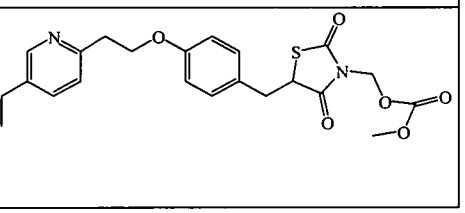
具有化學式XVII至XXII的噻唑烷酮前驅藥對於治療第2型糖尿病(type 2 diabetes mellitus)是有用的。此處所提供的是一種藉由投藥一具有化學式XVII至XXXII的前驅藥(特別是上面表XX-XXII的一化合物)來治療第2型糖尿病的方法，其中該前驅藥提供持續釋放的該母體藥。該母體藥由切割不穩定的R_1部分所產生。

在一些具體例中，一具有化學式XXVII的化合物是選自於表G：

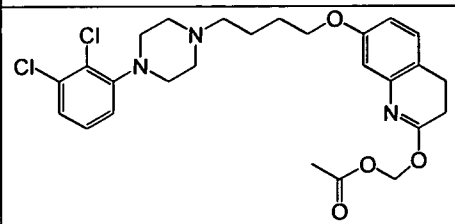
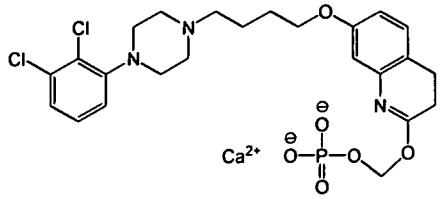
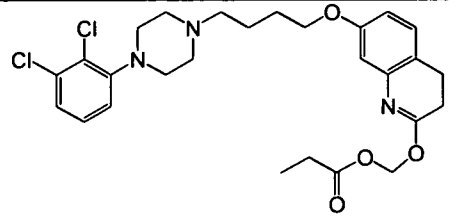
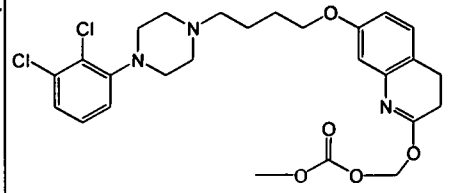
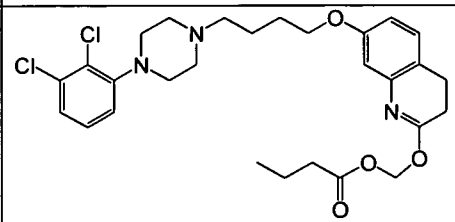
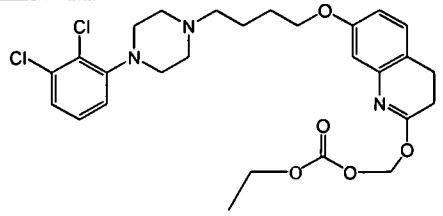
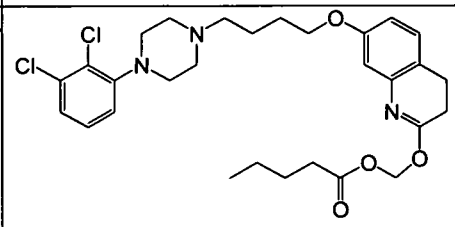
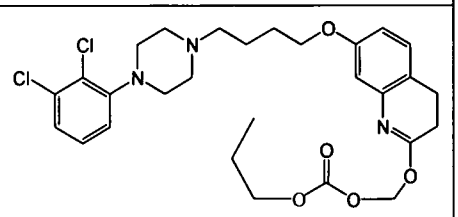
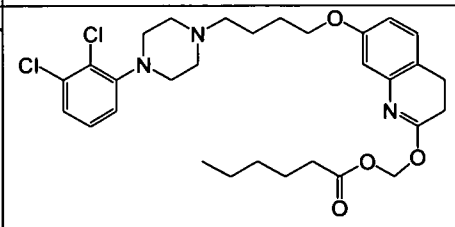
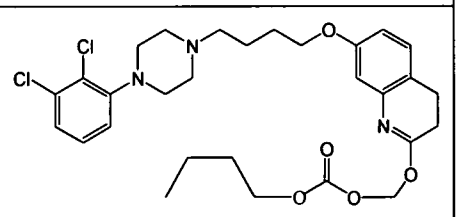
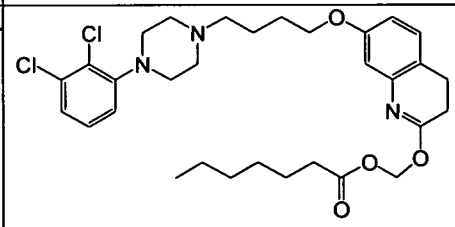
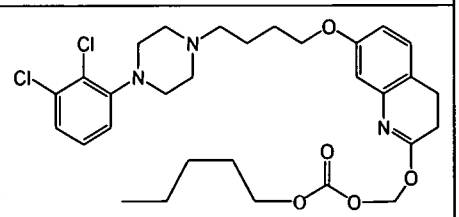
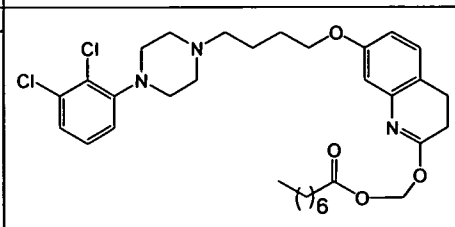
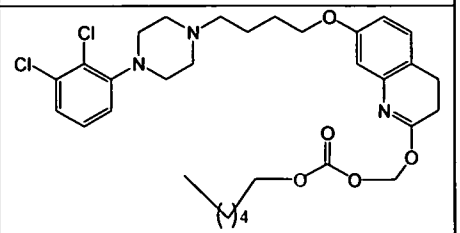
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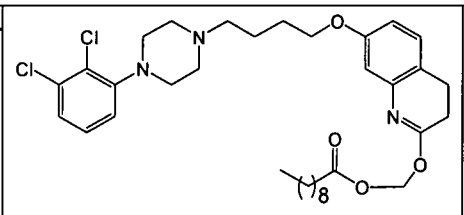
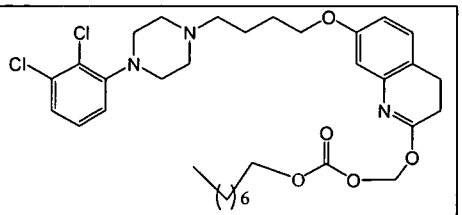
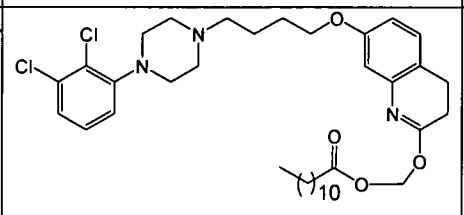
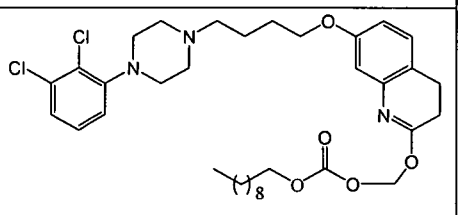
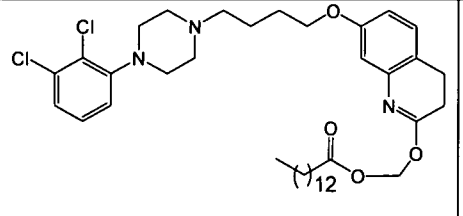
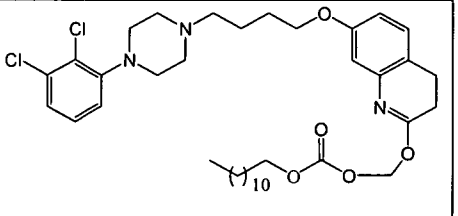
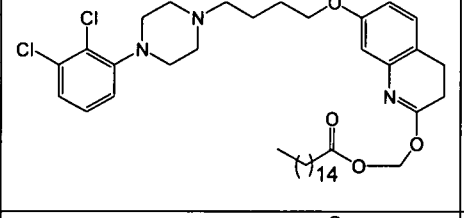
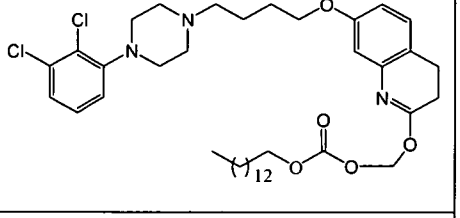
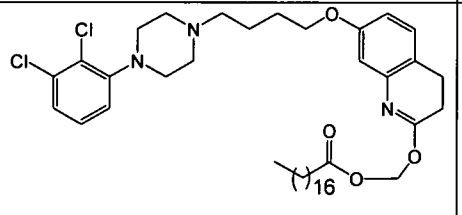
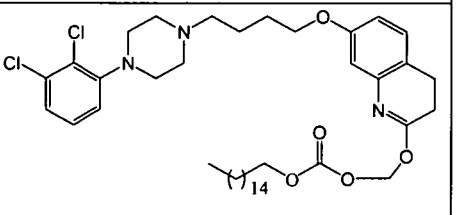
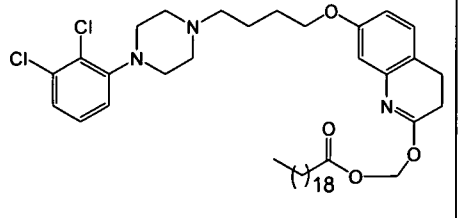
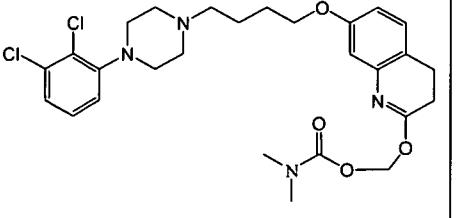
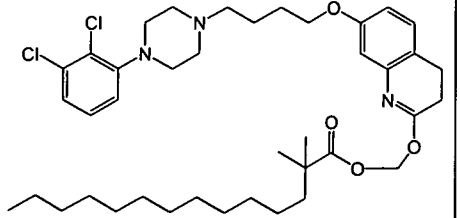
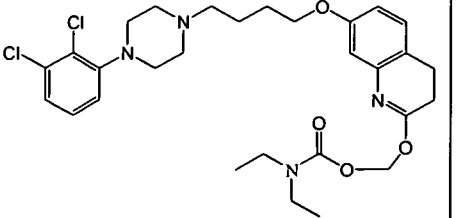
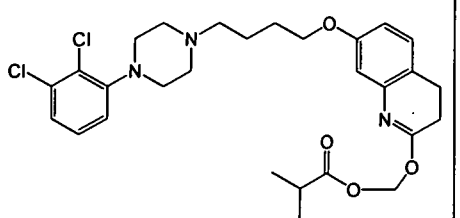
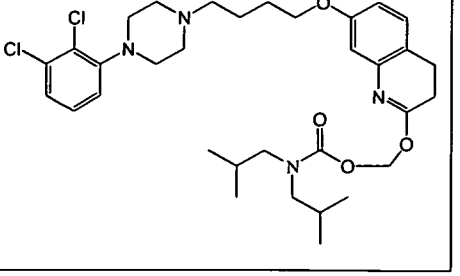
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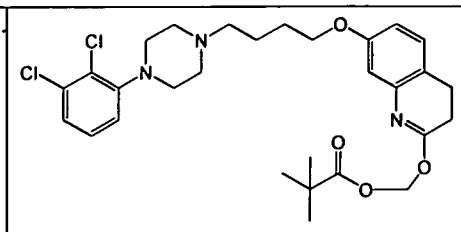
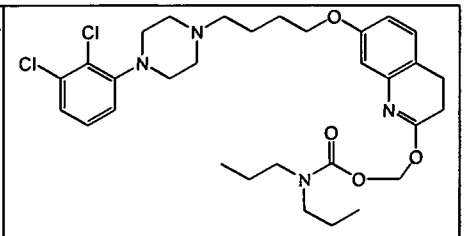
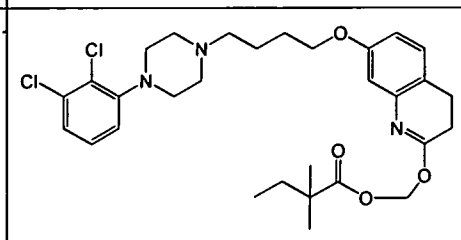
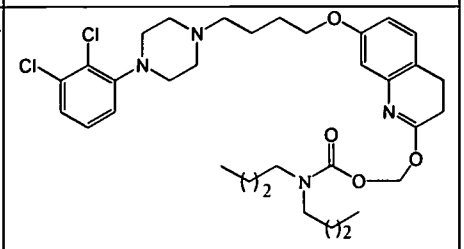
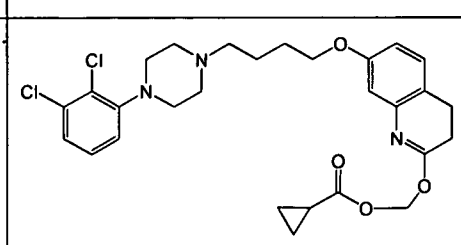
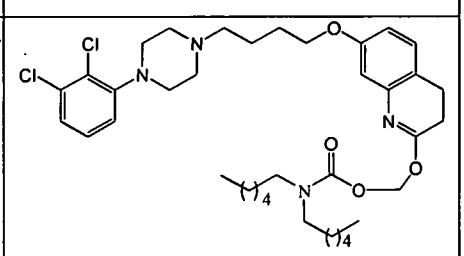
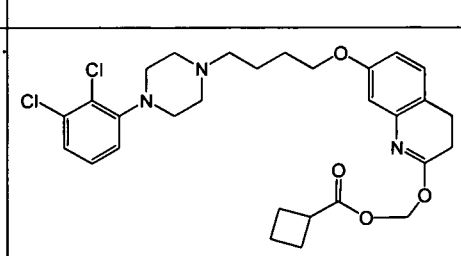
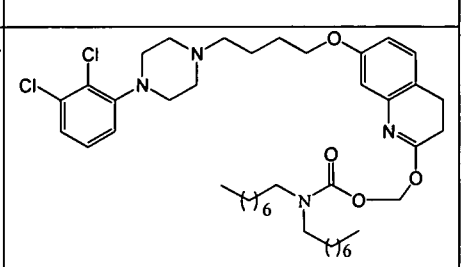
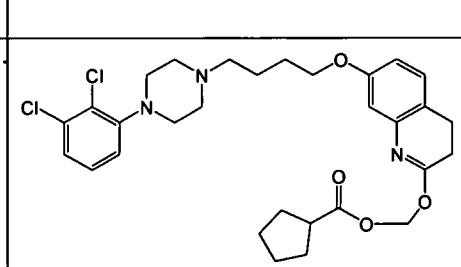
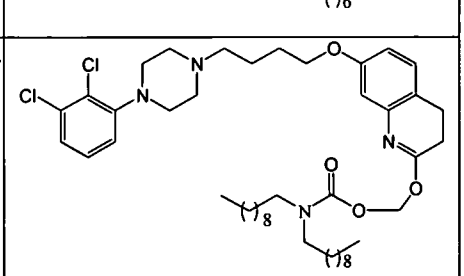
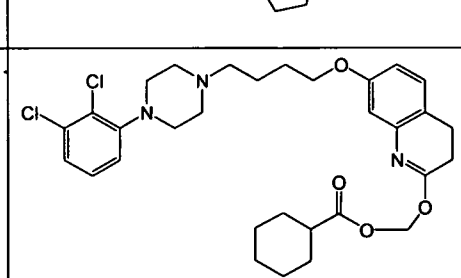
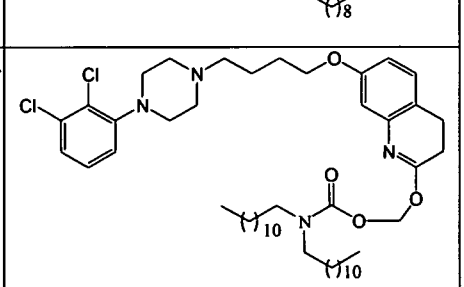
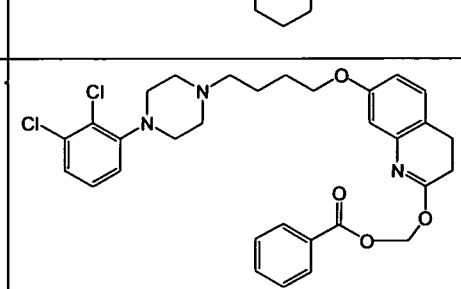
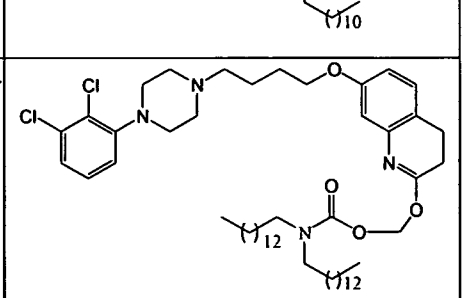
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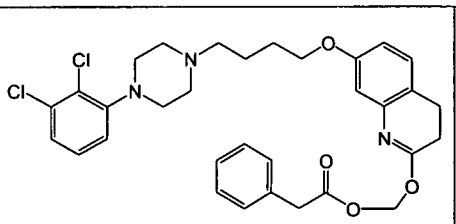
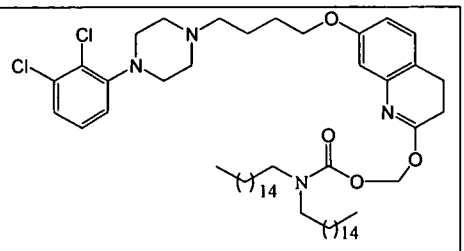
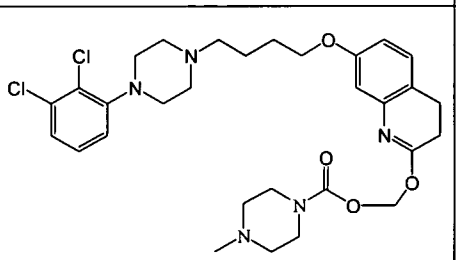
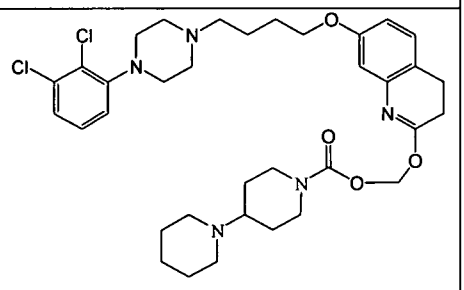
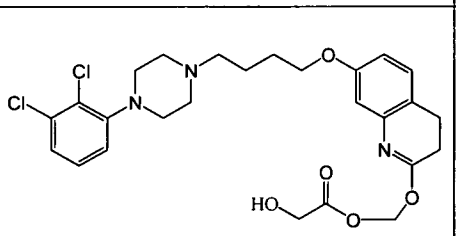
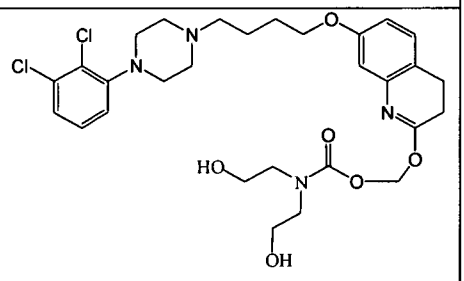
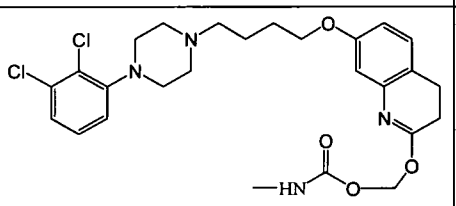
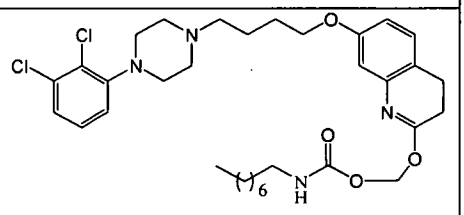
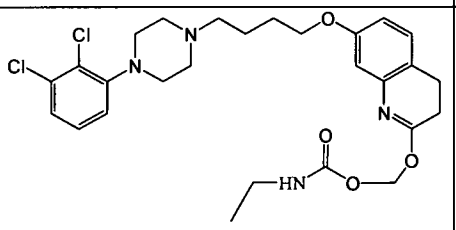
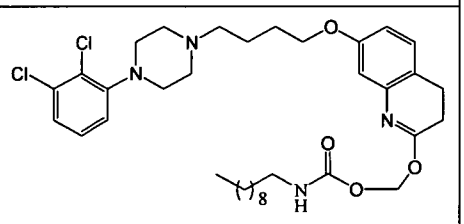
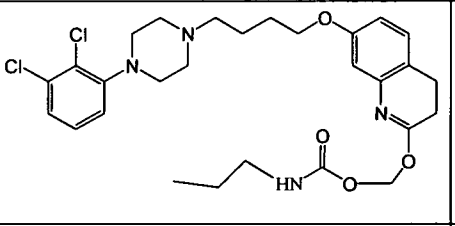
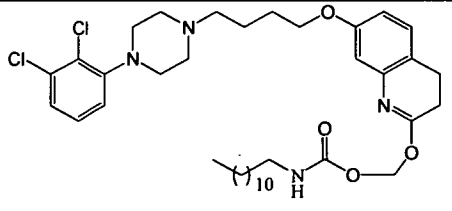
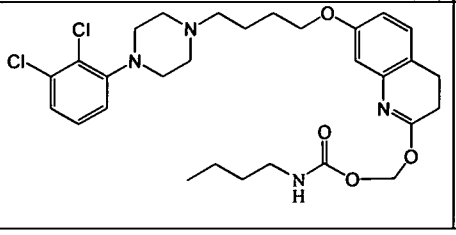
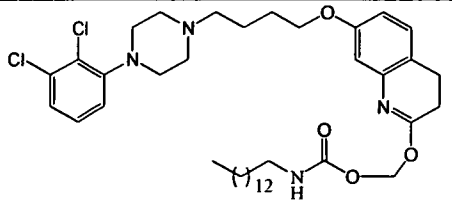
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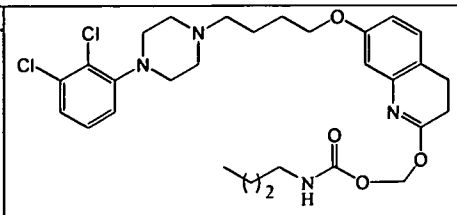
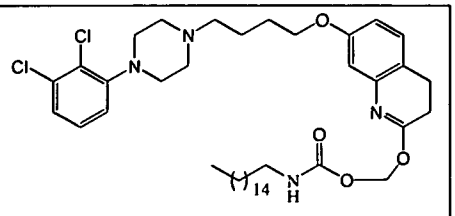
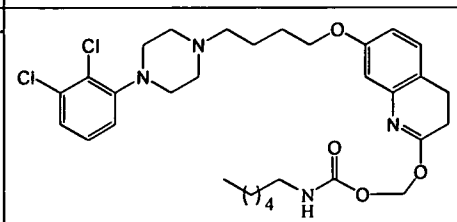
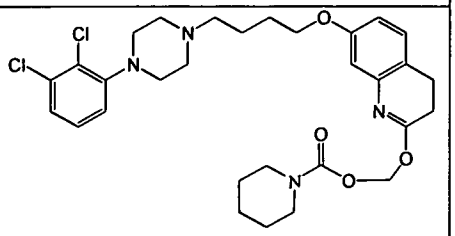
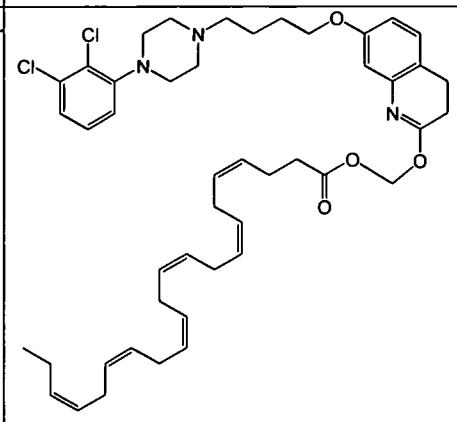
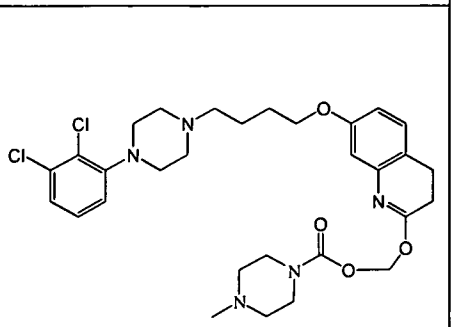
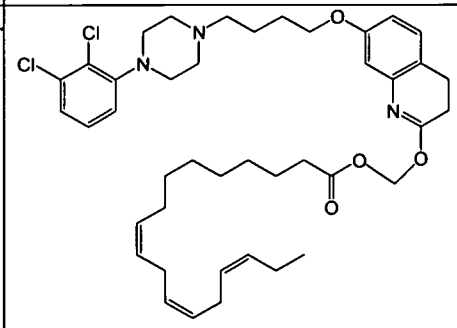
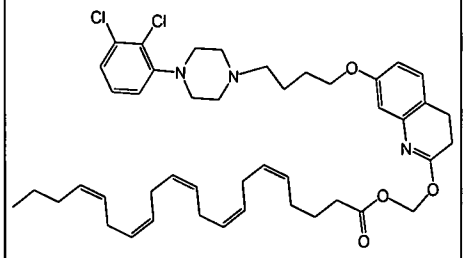
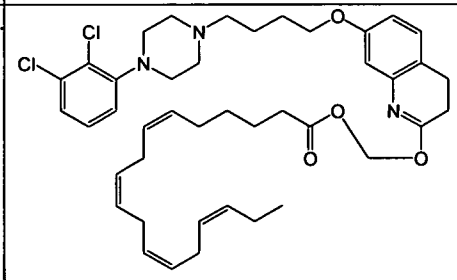
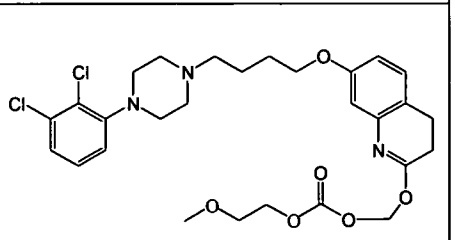
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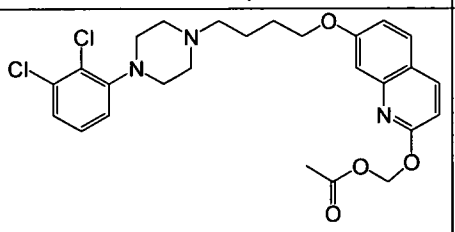
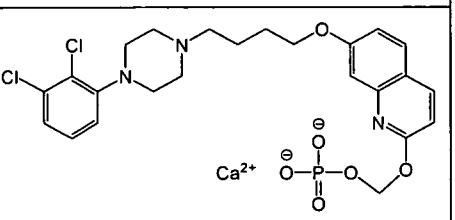
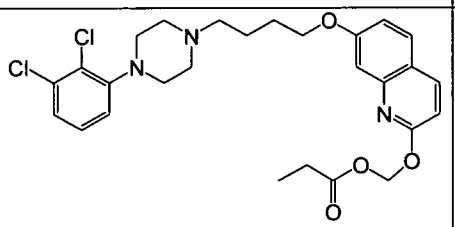
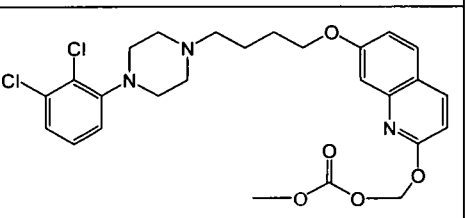
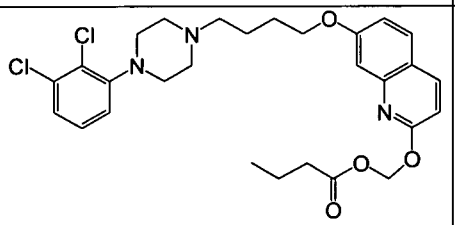
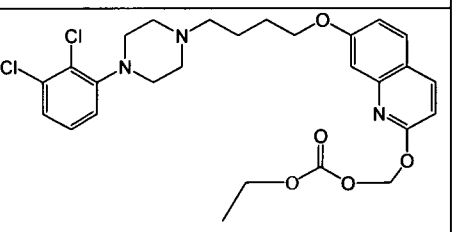
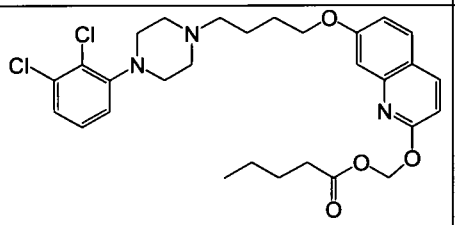
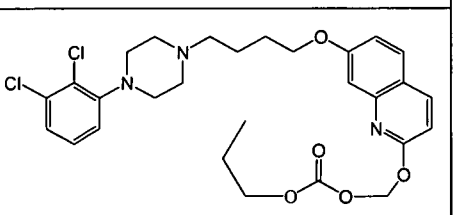
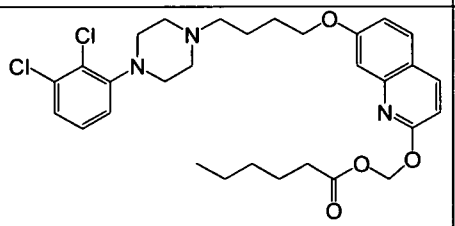
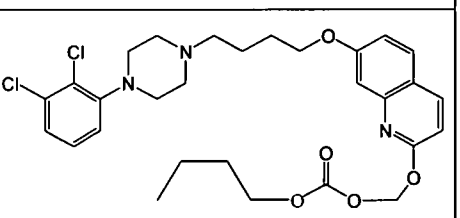
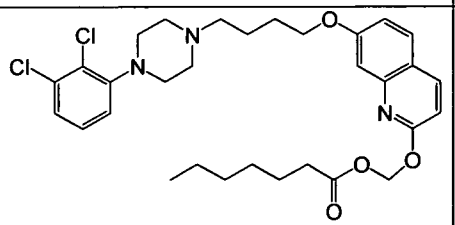
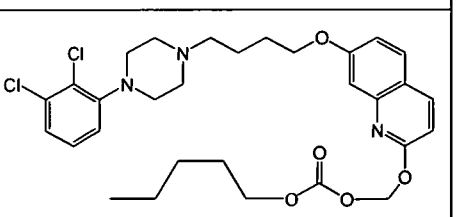
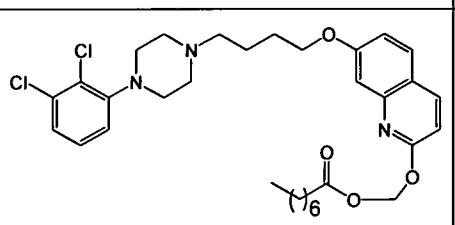
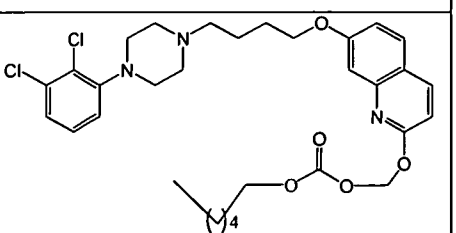
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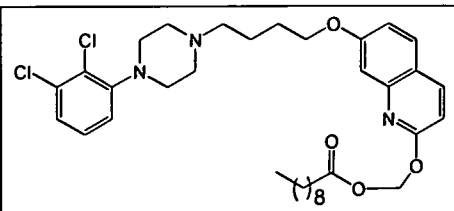
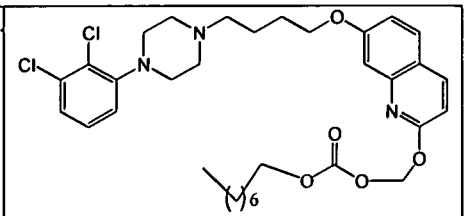
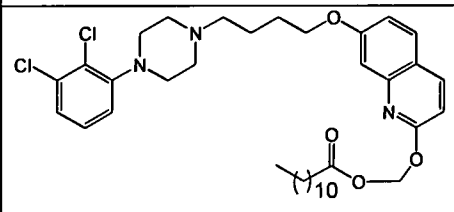
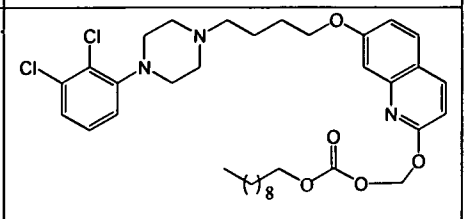
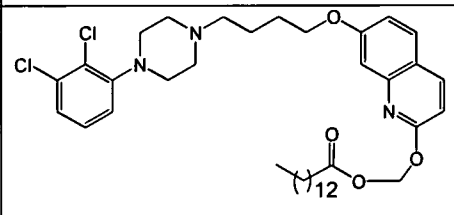
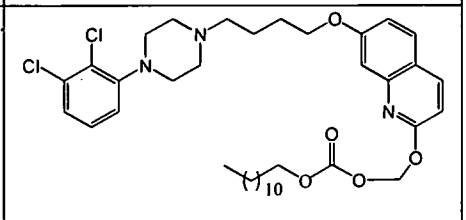
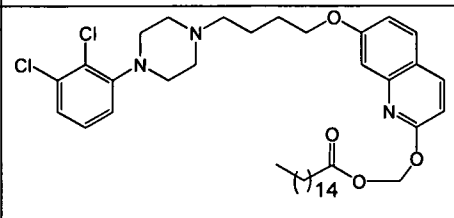
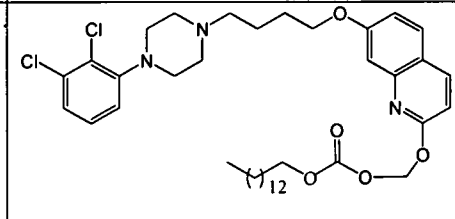
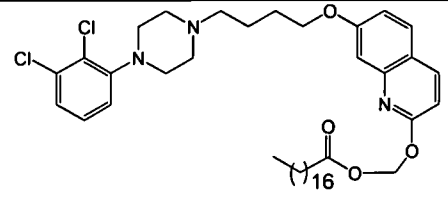
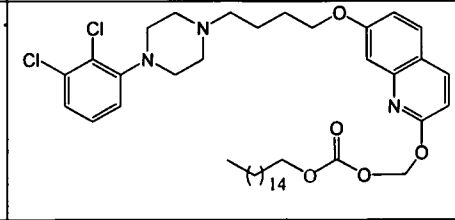
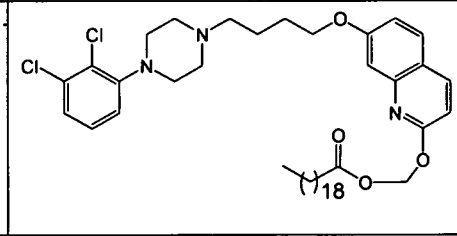
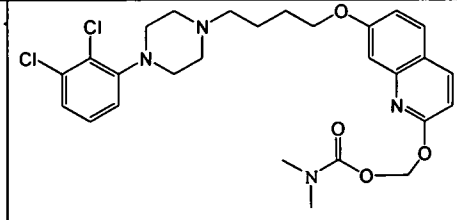
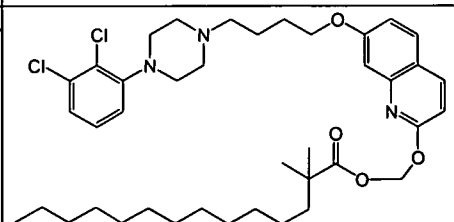
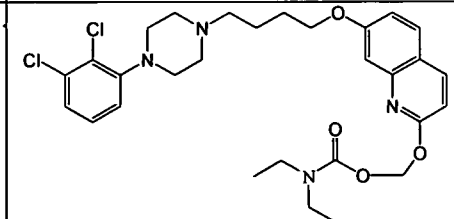
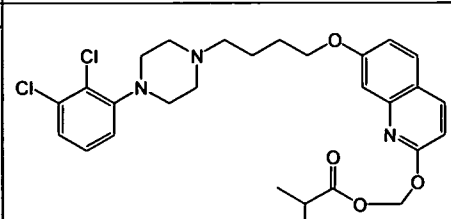
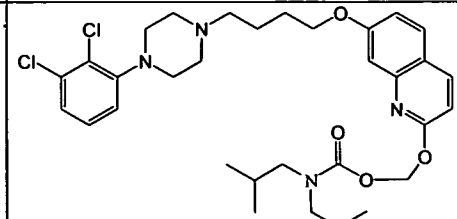
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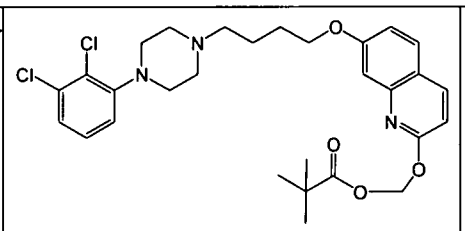
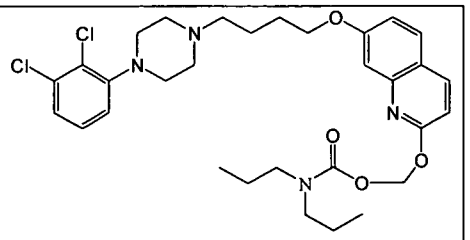
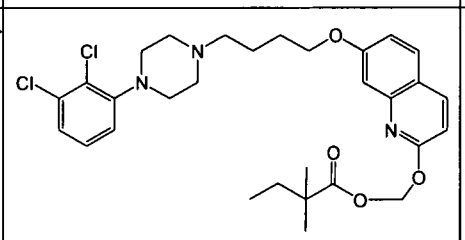
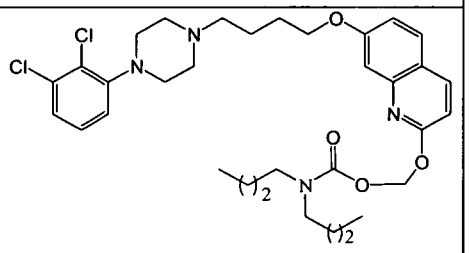
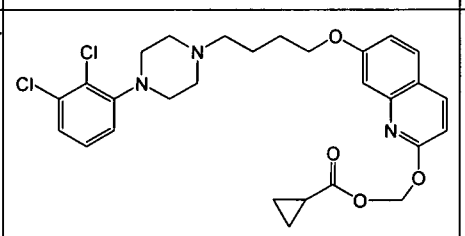
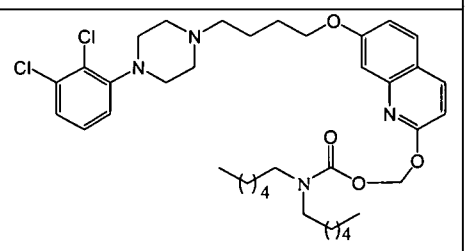
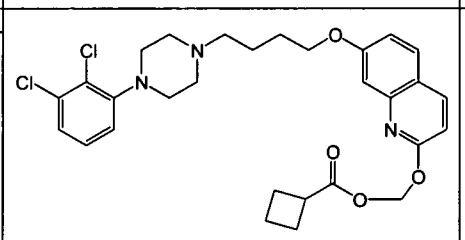
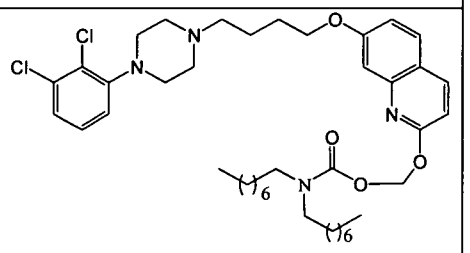
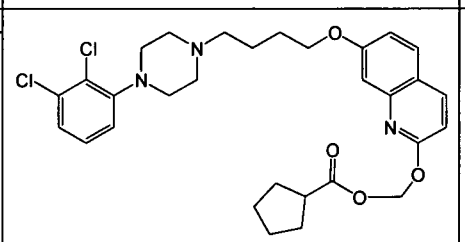
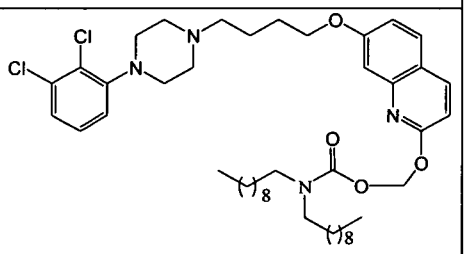
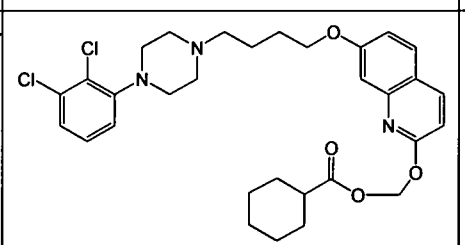
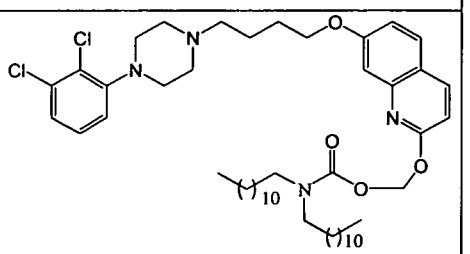
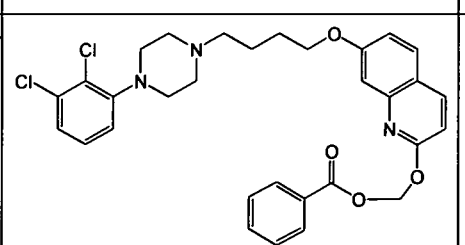
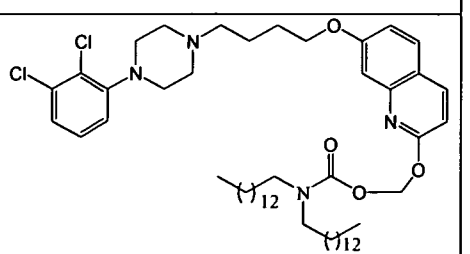
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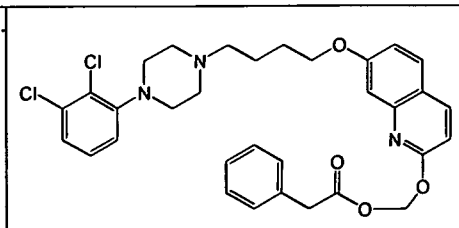
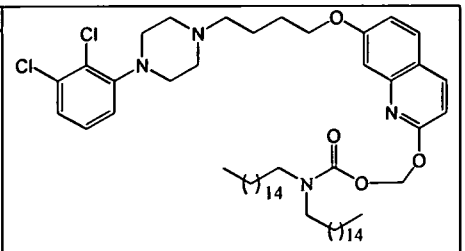
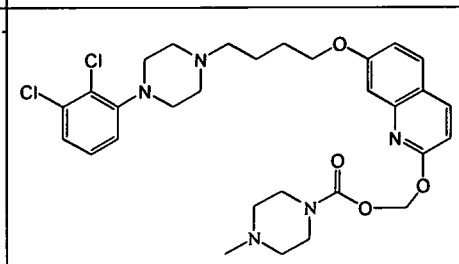
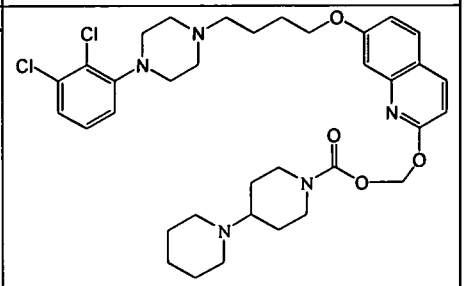
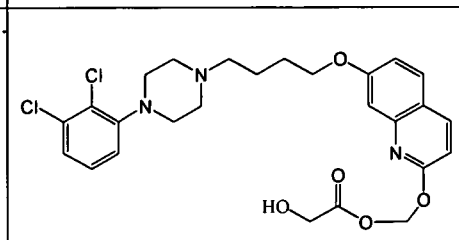
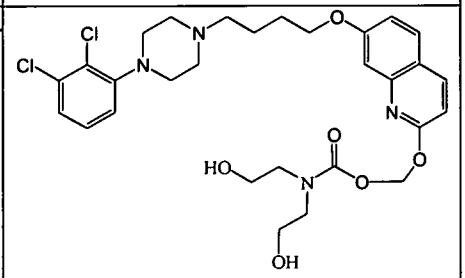
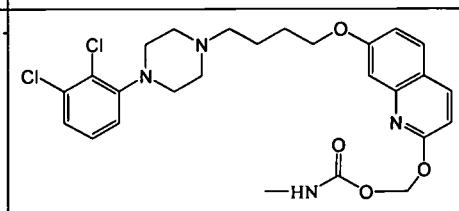
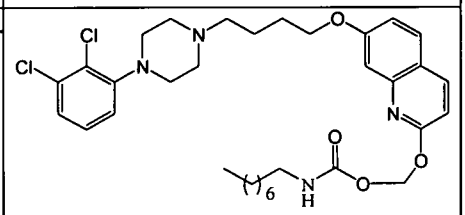
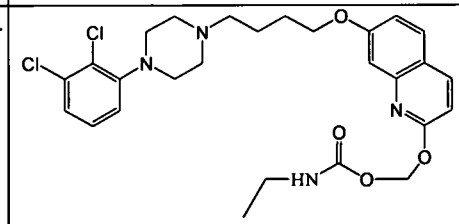
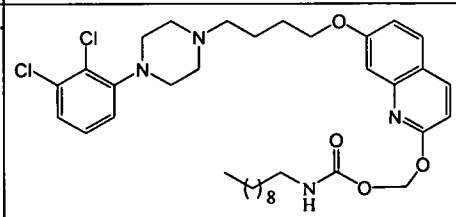
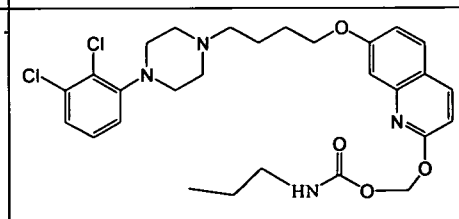
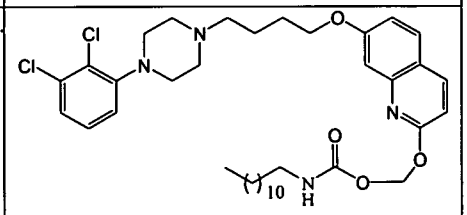
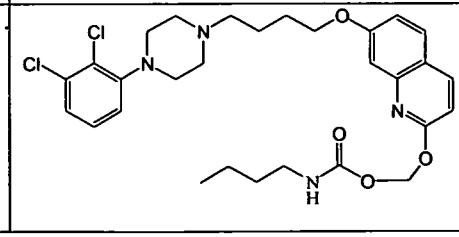
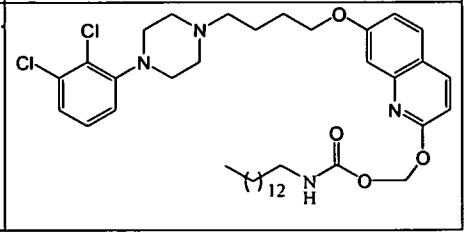
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1130.		1164.	
1131.		1165.	
1132.		1166.	
1133.		1167.	

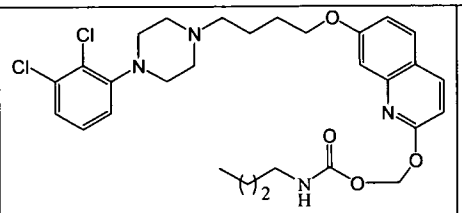
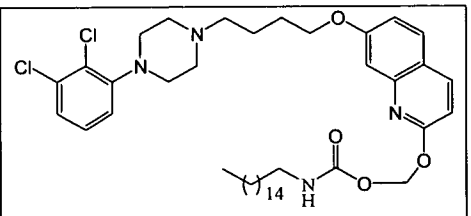
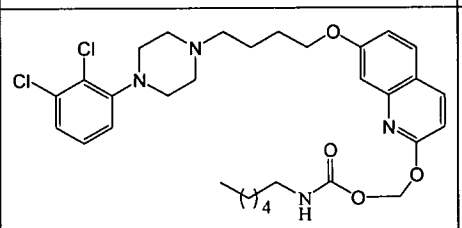
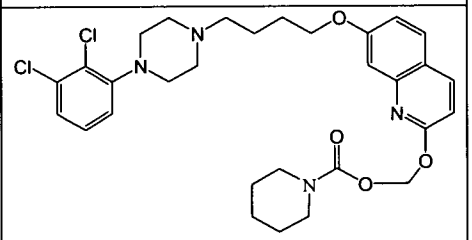
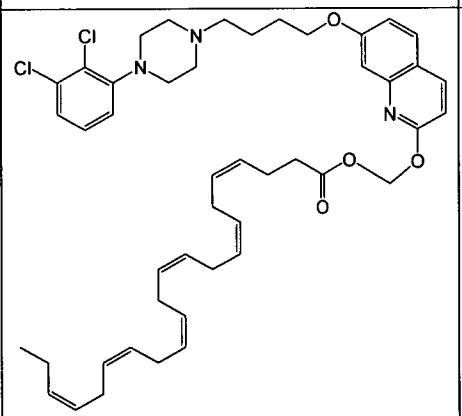
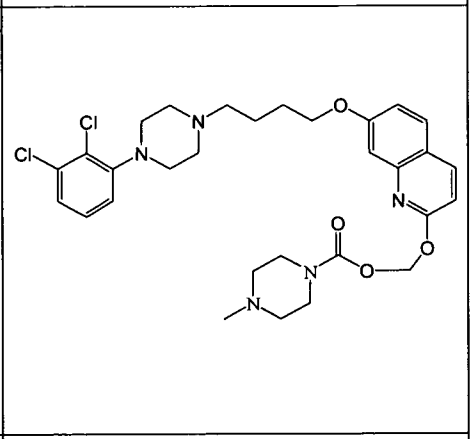
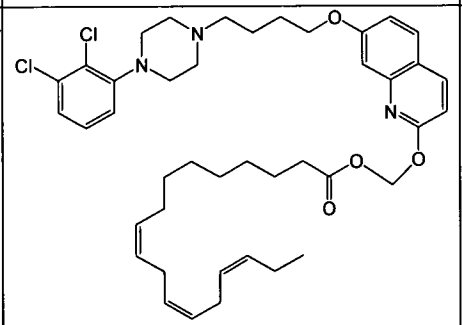
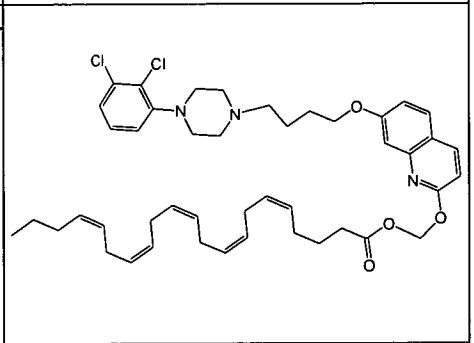
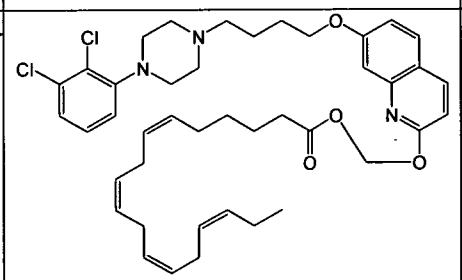
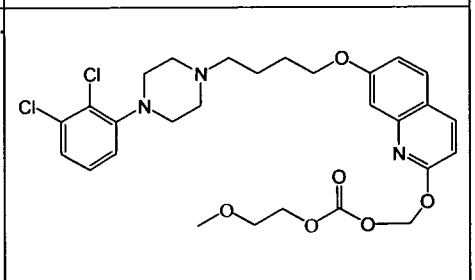
表I

編號	結構	編號	結構
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1201.		1235.	
1202.		1236.	
1203.		1237.	
1204.		1238.	
1205.		1239.	
1206.		1240.	

1207		1241	
1208		1242	
1209		1243	
1210		1244	
1211		1245	
1212		1246	
1213		1247	
1214		1248	

1215.		1249.	
1216.		1250.	
1217.		1251.	
1218.		1252.	
1219.		1253.	
1220.		1254.	
1221.		1255.	

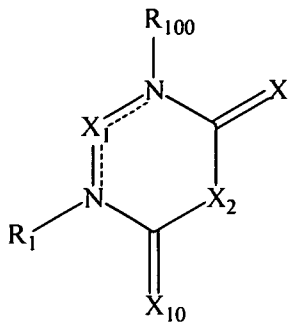
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1224.		1258.	
1225.		1259.	
1226.		1260.	
1227.		1261.	
1228.		1262.	

1229.		1263.	
1230.		1264.	
1231.		1265.	
1232.		1266.	
1233.		1267.	

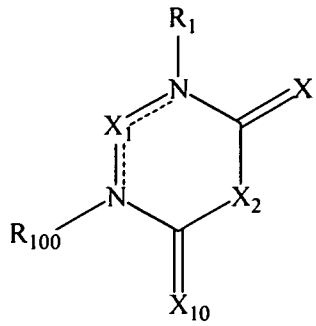
巴比妥酸鹽(barbiturates)

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XXXIII-XXXVII來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可

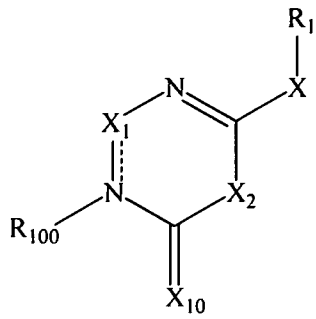
接受的鹽類以及溶劑合物：



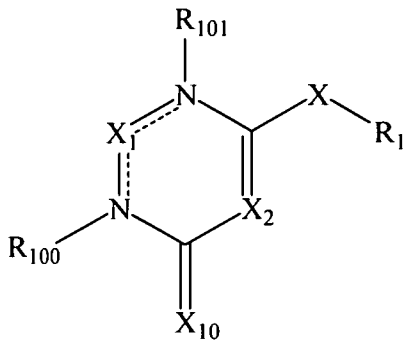
化學式XXXIII



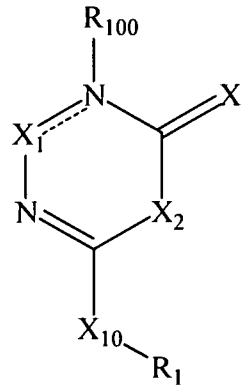
化學式XXXIV



化學式XXXV



化學式XXXVI

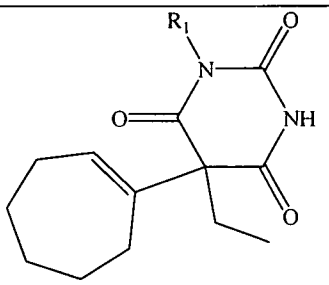
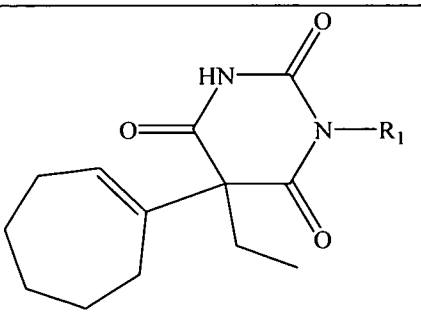
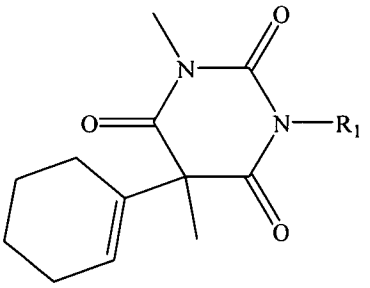
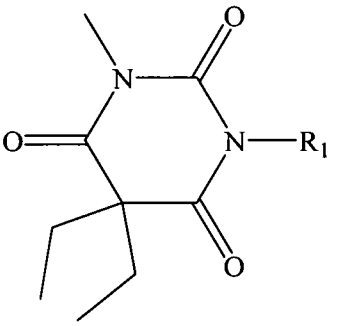
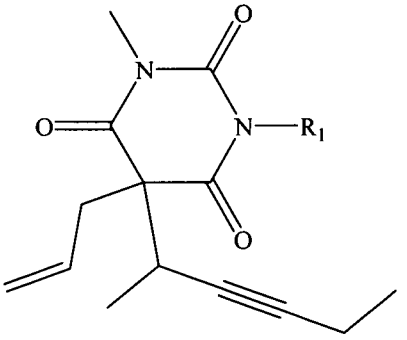
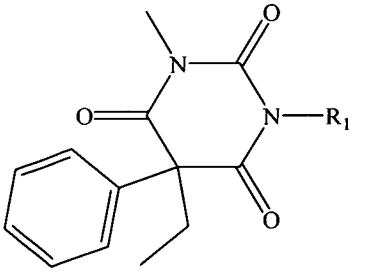
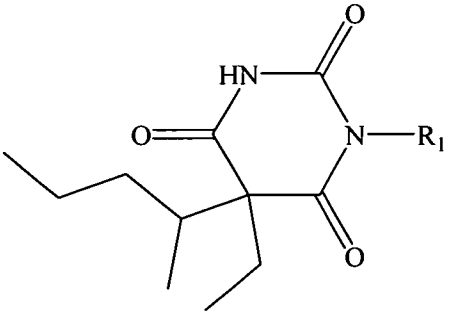
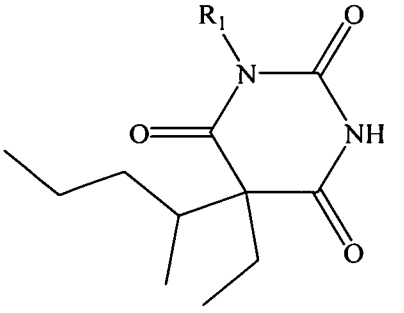
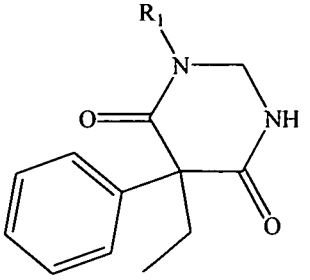
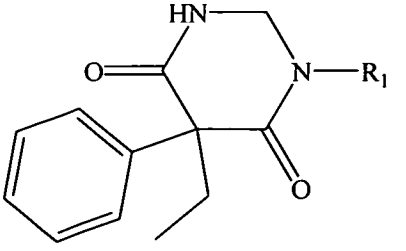


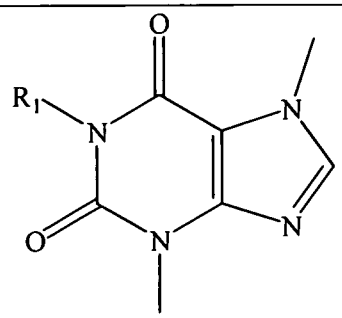
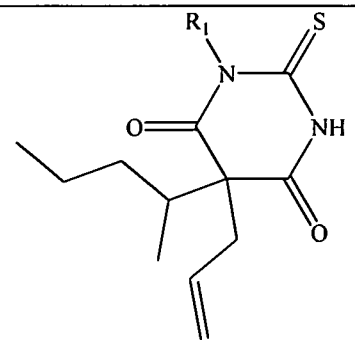
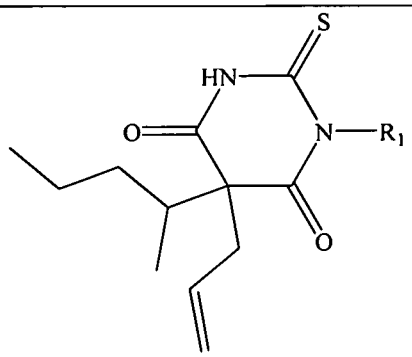
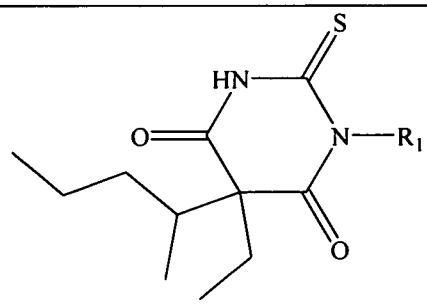
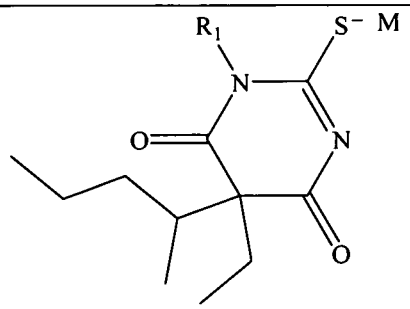
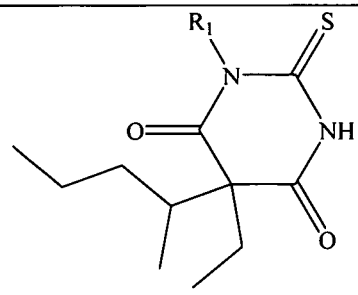
化學式XXXVII

其中，X、X_1、X_2、R_{100}、R_{101}以及R_1是如上面所描述的；X_{10}是-S或-O。

在一個較佳的具體例中，一來自表XXXIII-XXXVII的化合物被提供。一更佳的具體例是表XXXIII-XXXVII中的一化合物，其中R_1是選自於表1-4。

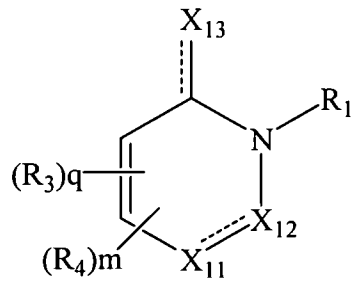
表 XXXIII-XXXIV

1		9	
2		10	
3		11	
4		12	
5		13	

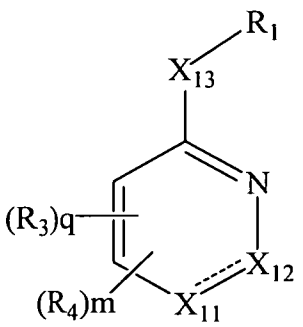
6		14	
7		15	
8		16	

吡啶酮(Pyridone)嘧啶酮(pyrimidone)以及嘧啶酮(pyrimidione)前驅藥

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XXXVIII或XXXIX來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XXXVIII



化學式XXXIX

其中X、R_1、R_3、R_4、m以及q是如上面所定義的；

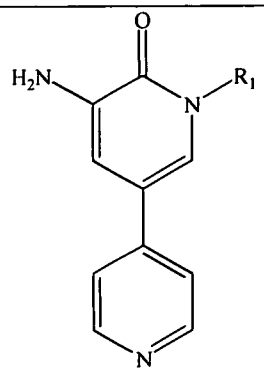
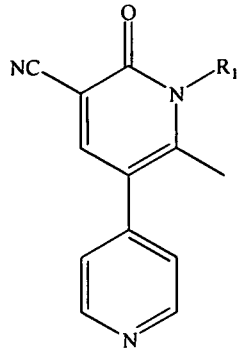
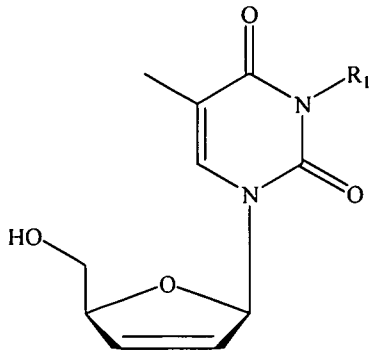
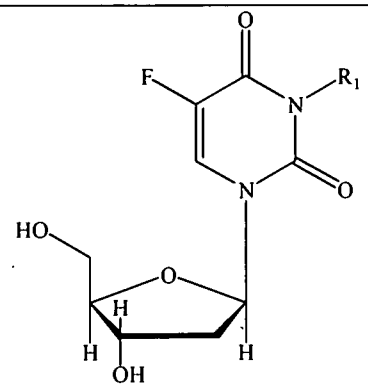
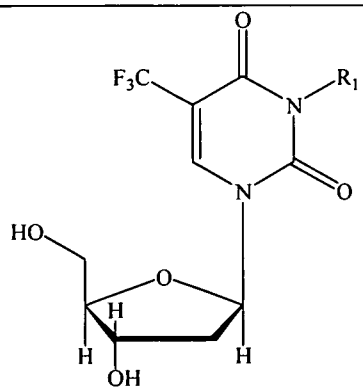
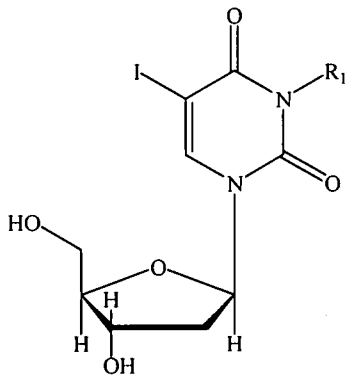
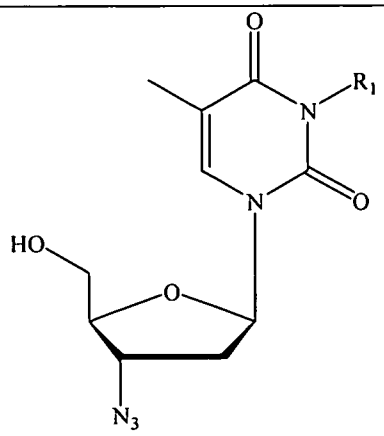
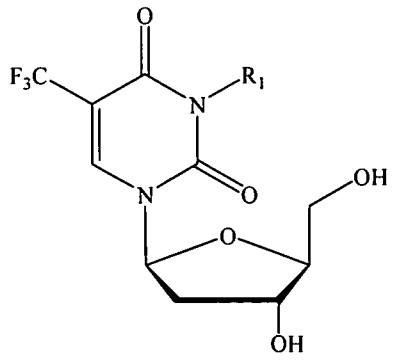
X_{11}是-N-或-C(R_{10})-；

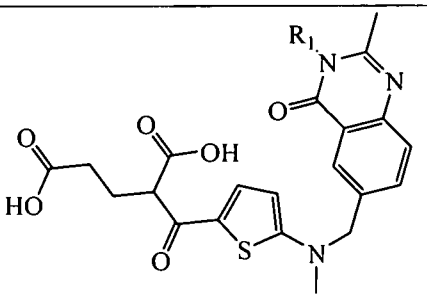
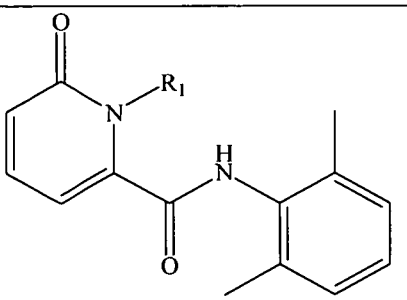
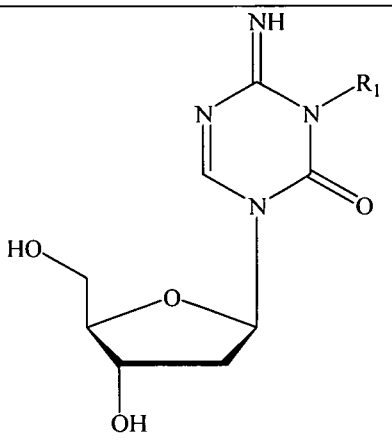
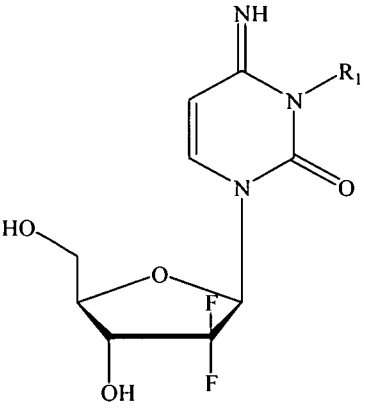
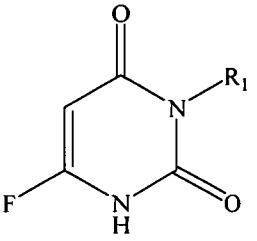
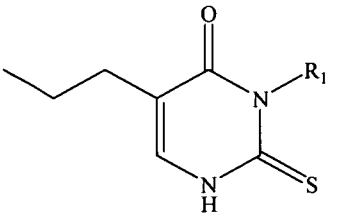
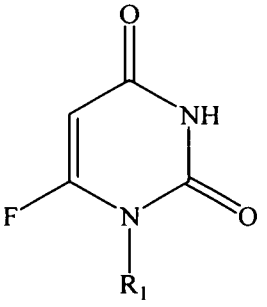
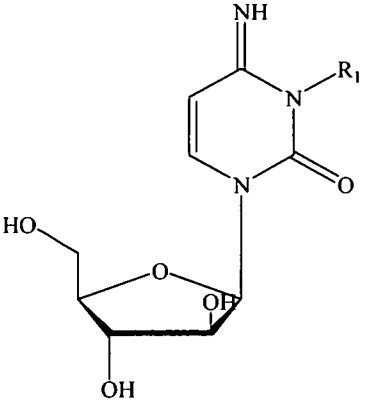
X_{12}是-C(O)-、-C(S)-、-C(R_{10})(R_{11})-或-C(R_{10})(OR_{11})-；以及

X_{13}是-O、-S、-N(R_{10})(R_{11})、-OR_{10}-。

一較佳的具體例是一選自於表XXXVIII-XXXIX的化合物。一更佳的具體例是一來自表XXXVIII-XXXVIX的化合物，其中R_1是選自於表1-4。

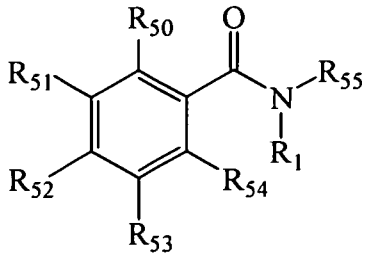
表XXXVIII

1		9	
2		10	
3		11	
4		12	

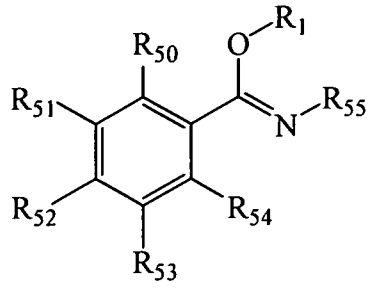
5		13	
6		14	
7		15	
8		16	

苯甲醯胺藥效團的前驅藥

在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XL或XLI來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



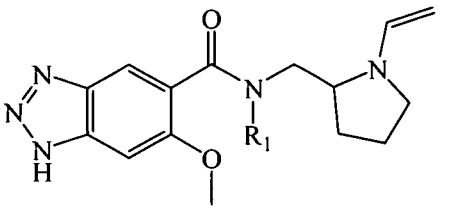
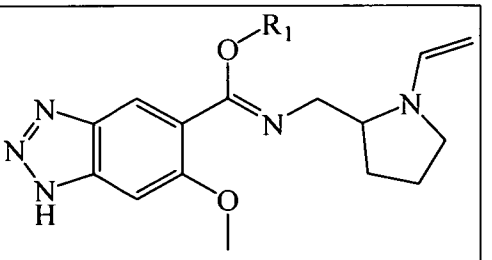
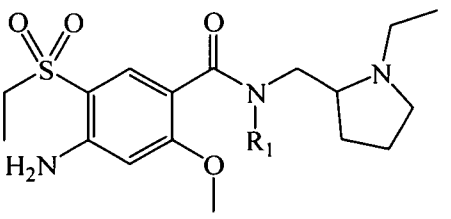
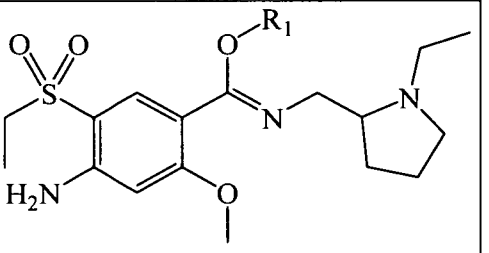
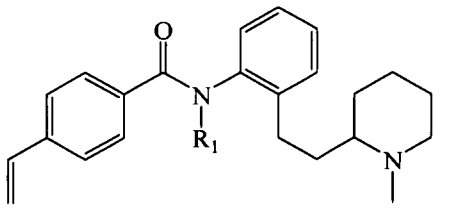
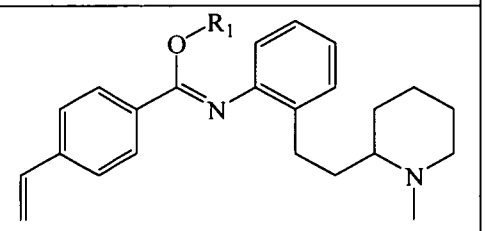
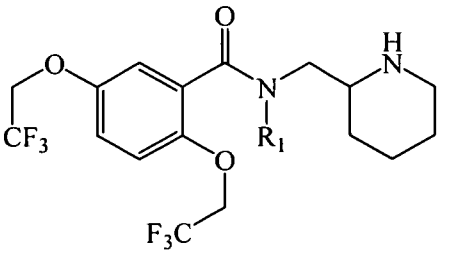
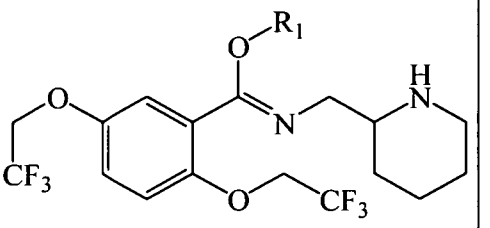
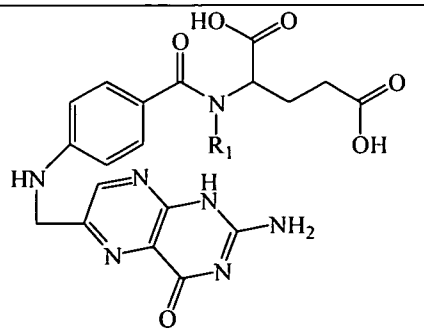
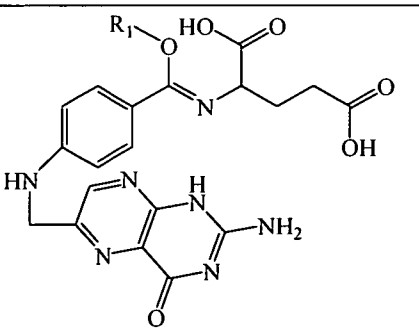
化學式XL

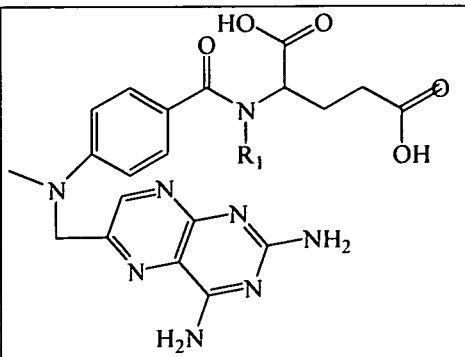
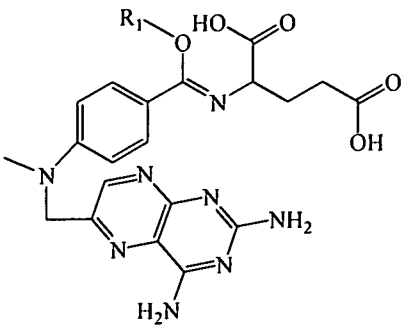
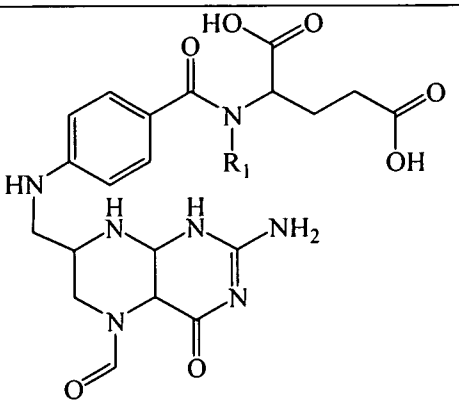
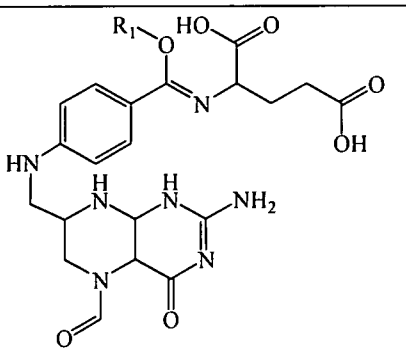
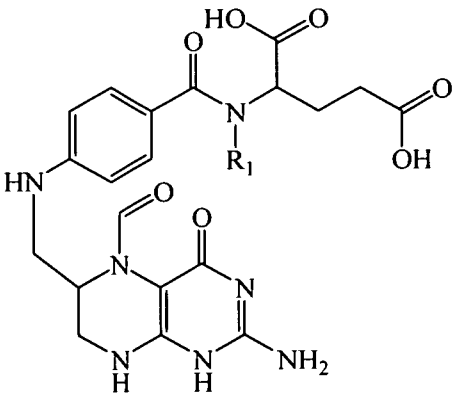
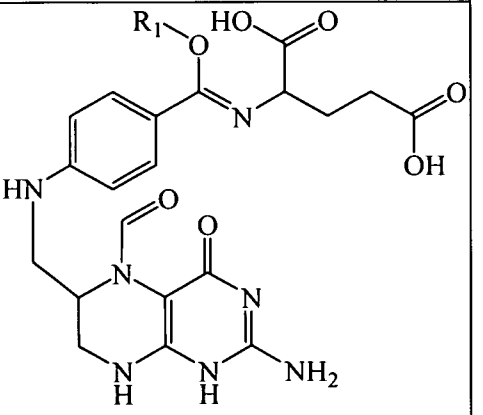
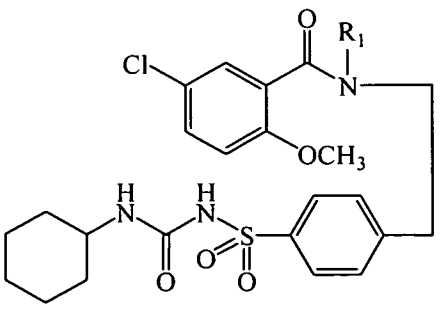
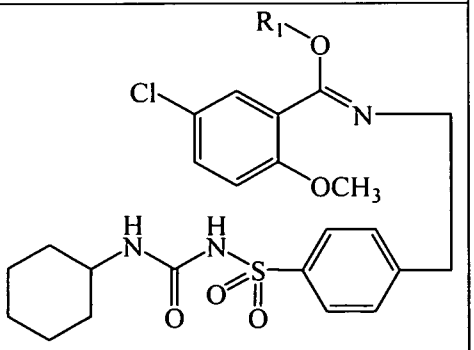


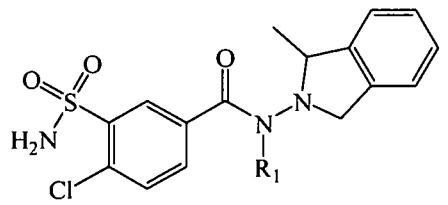
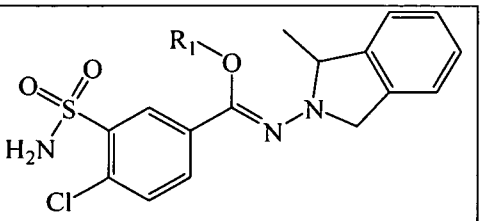
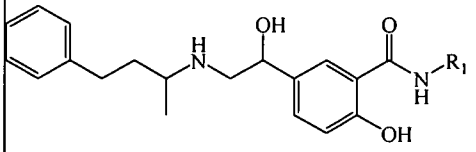
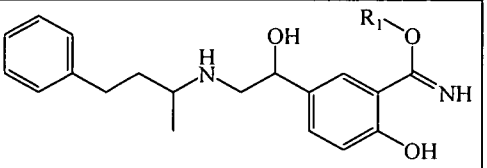
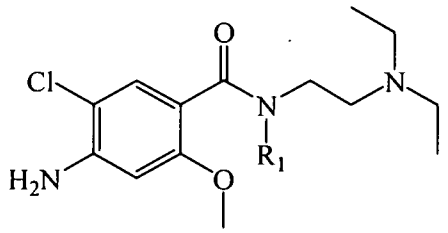
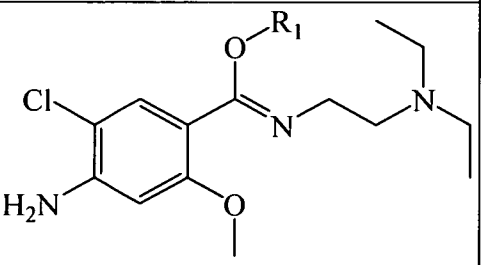
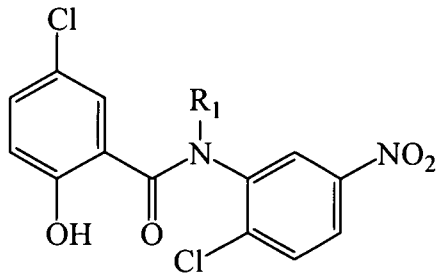
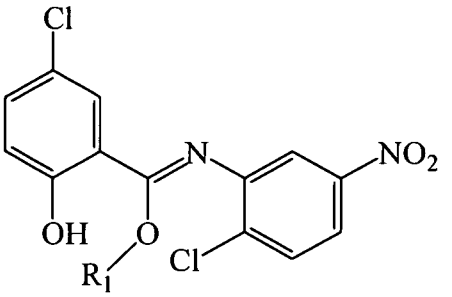
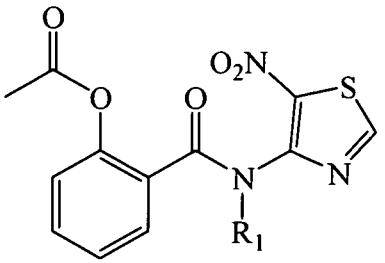
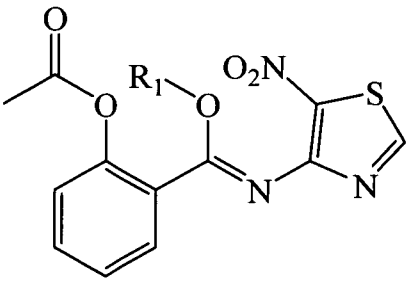
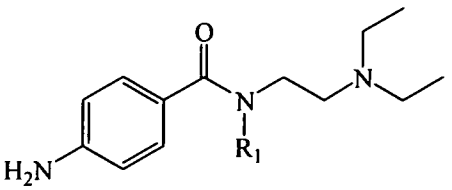
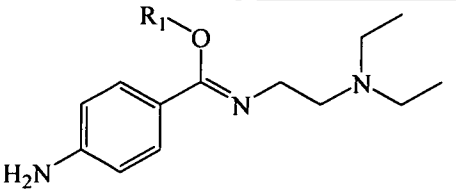
化學式XLI

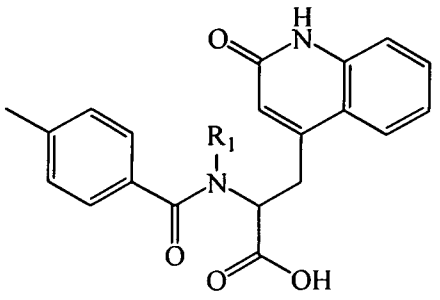
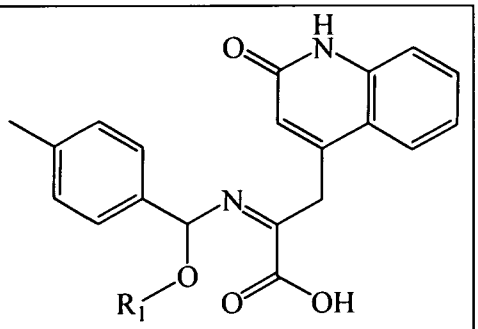
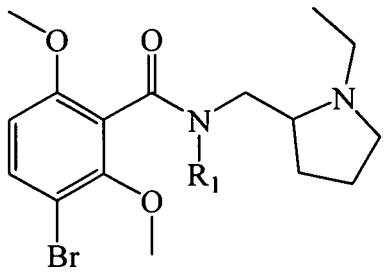
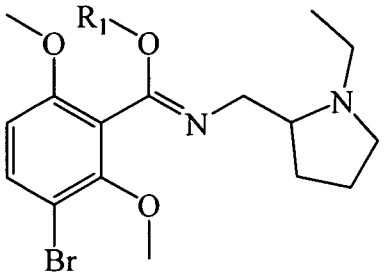
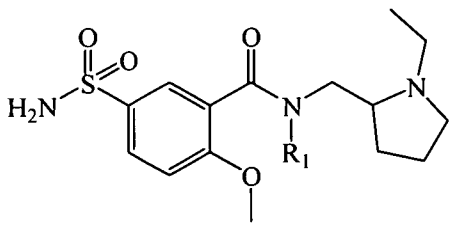
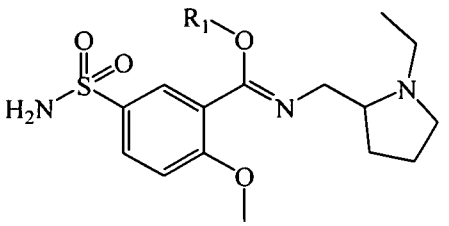
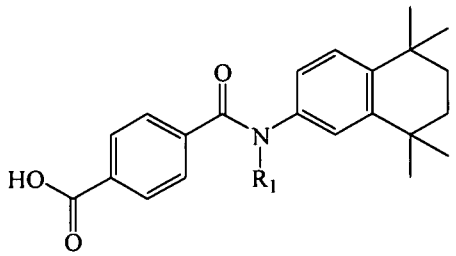
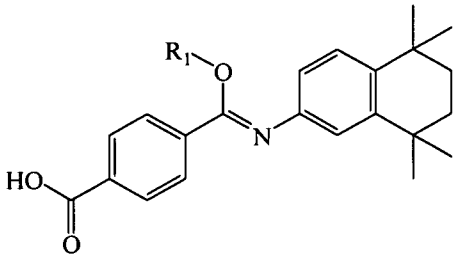
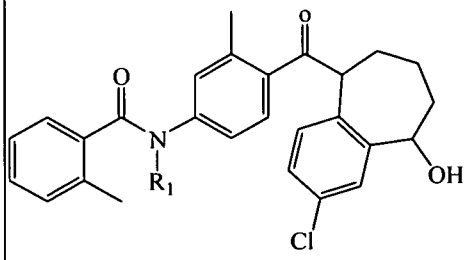
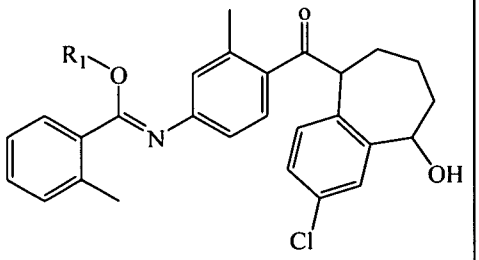
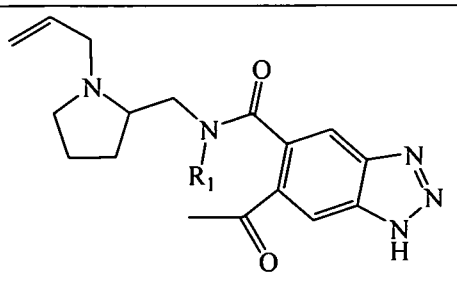
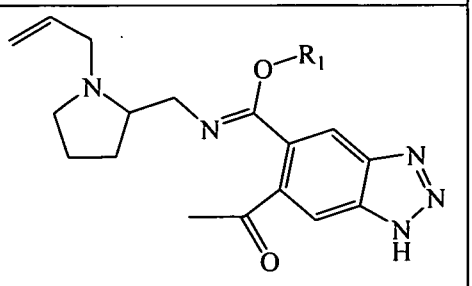
其中R_1、R_{50}、R_{51}、R_{52}、R_{53}、R_{54}以及R_{55}是如上面所定義的。

表 XL-XLI

1		22	
2		23	
3		24	
4		25	
5		26	

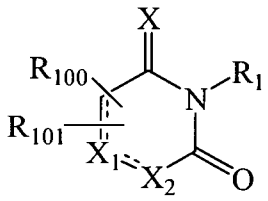
6		27	
7		28	
8		29	
9		30	

10		31	
11		32	
12		33	
13		34	
14		35	
15		36	

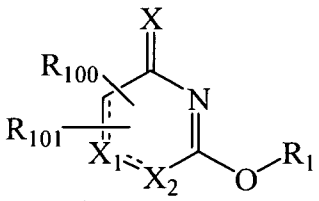
16		37	
17		38	
18		39	
19		40	
20		41	
21		42	

醯亞胺藥效團的前驅藥

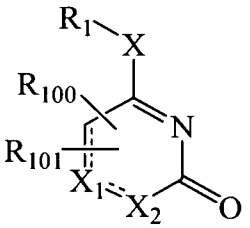
在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式XLII、XLIII或XLIV來表示，以及它們的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：



化學式XLII



化學式XLIII

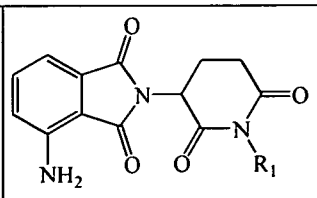
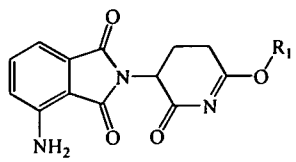
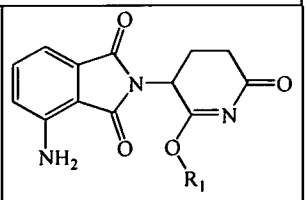
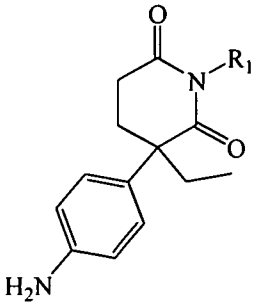
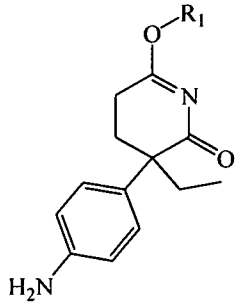
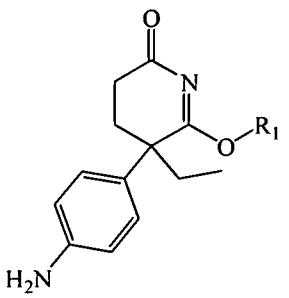
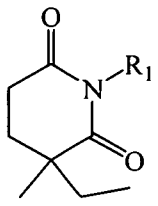
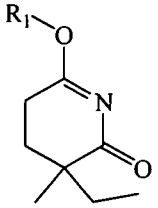
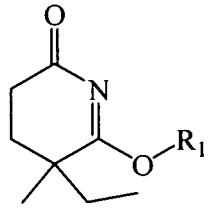
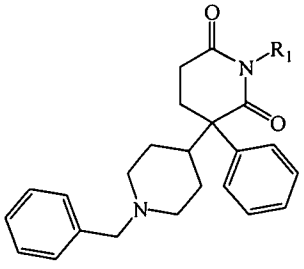
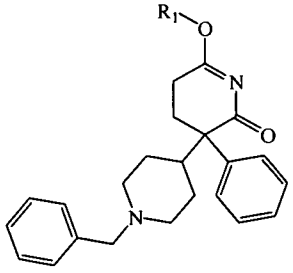
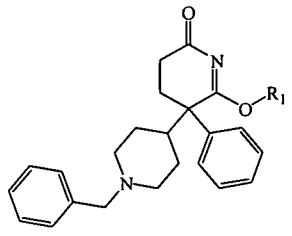
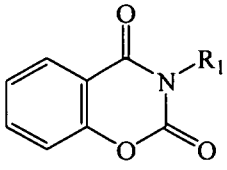
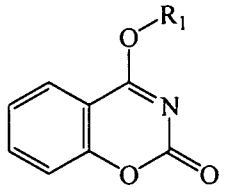
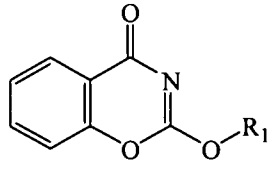
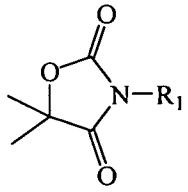
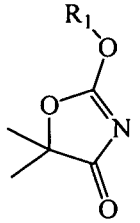
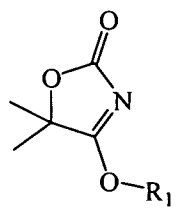
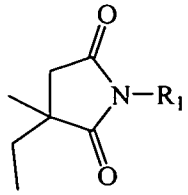
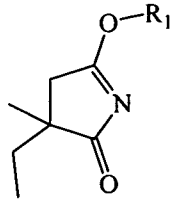
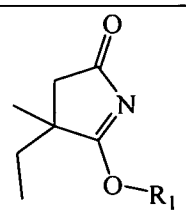


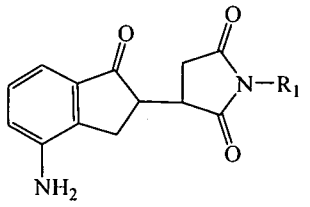
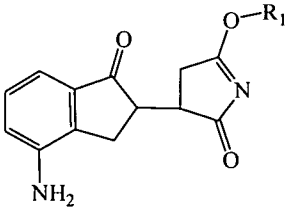
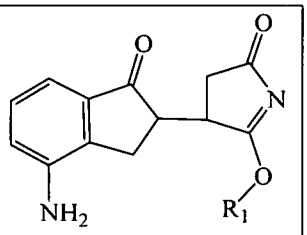
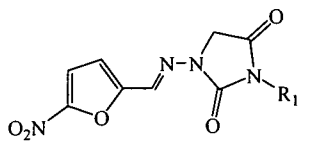
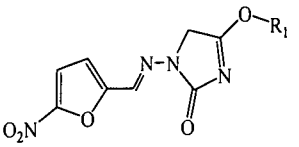
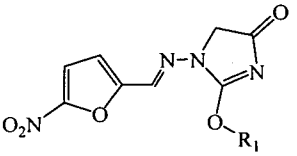
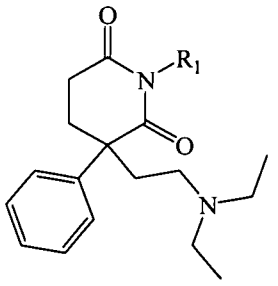
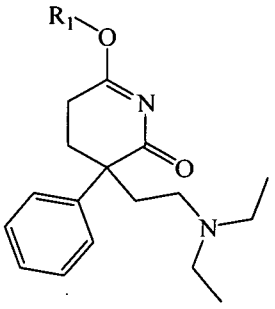
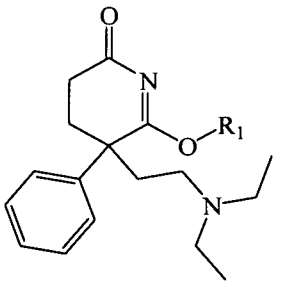
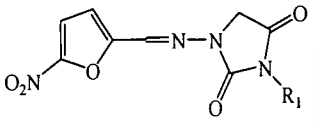
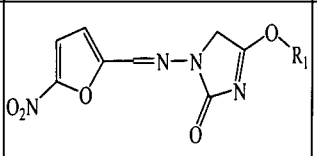
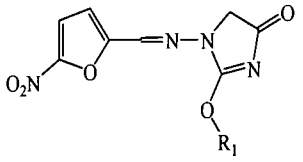
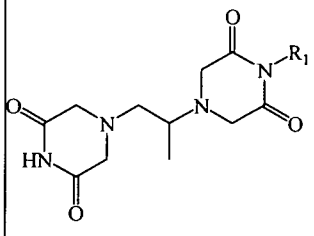
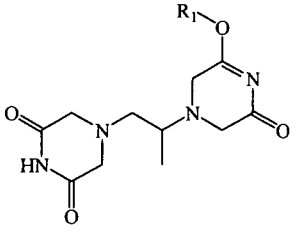
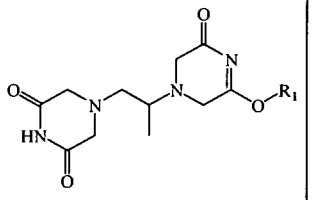
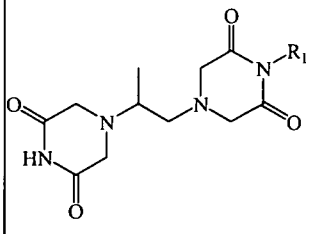
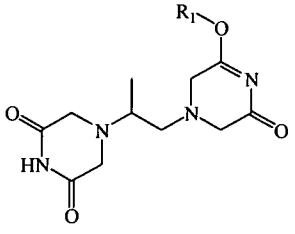
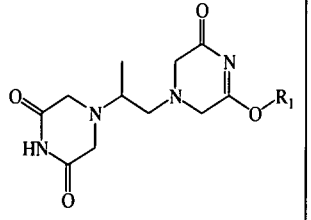
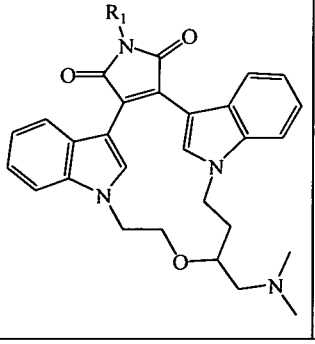
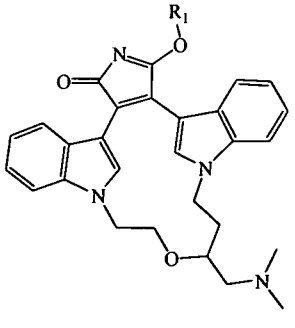
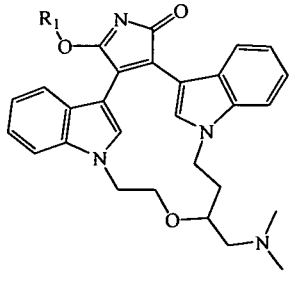
化學式XLIV

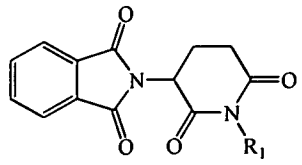
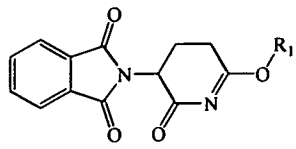
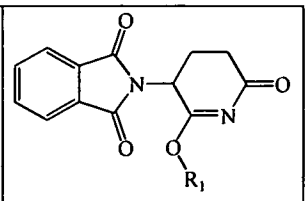
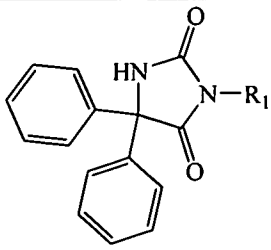
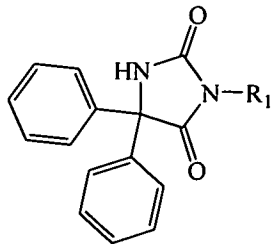
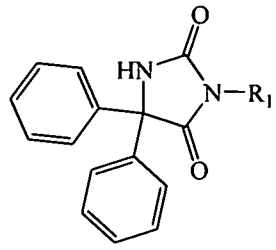
其中R_1、R_{100}、R_{101}、X、X_1以及X_2是如上面所定義的；另擇地，R_{100}和R_{101}與它們所接附的原子一起形成一選擇性地經取代的3、4、5、6或7員環。

一較佳的具體例是一選自於表XLII-XLIV的化合物。一更佳的具體例是一來自表XLII-XLIV的化合物，其中R_1是選自於表1-4。

表XLII-XLIV

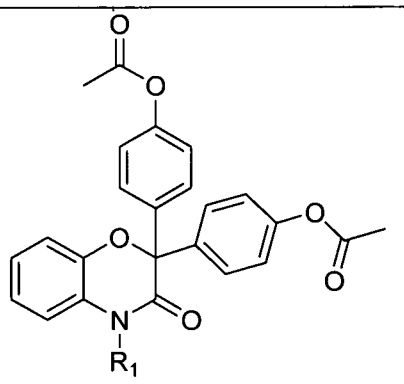
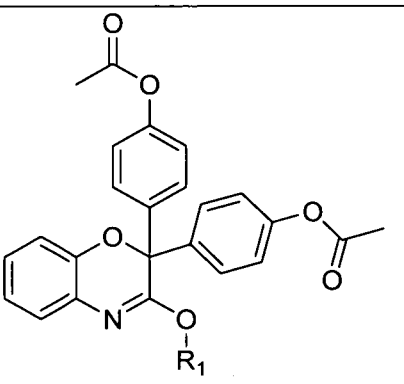
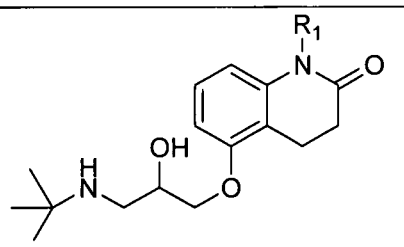
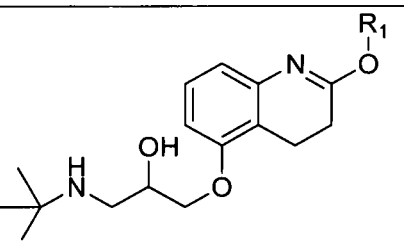
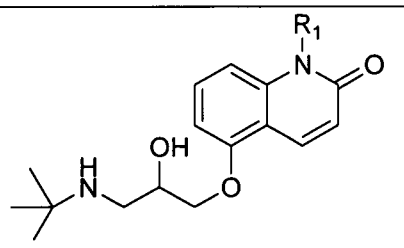
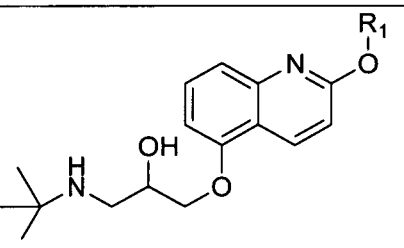
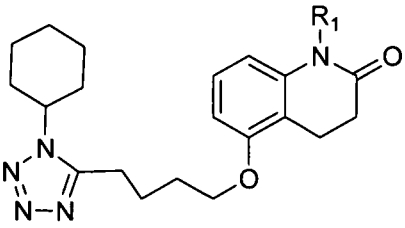
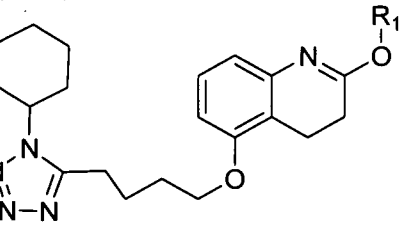
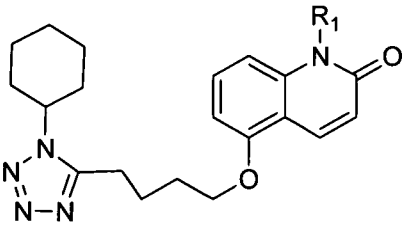
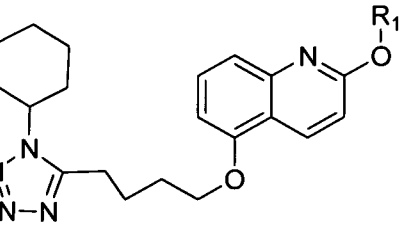
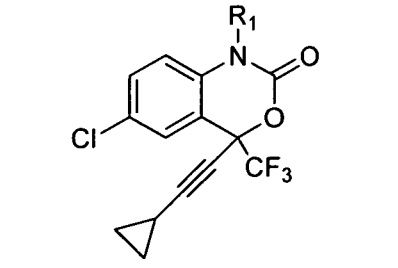
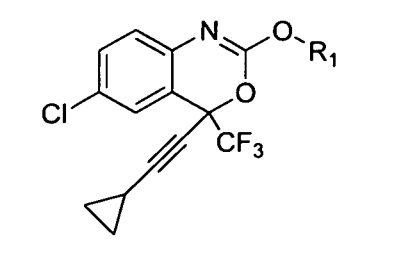
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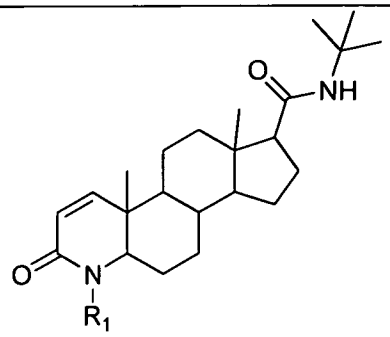
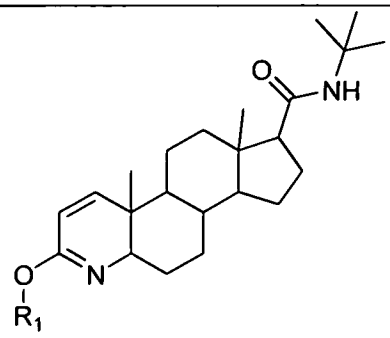
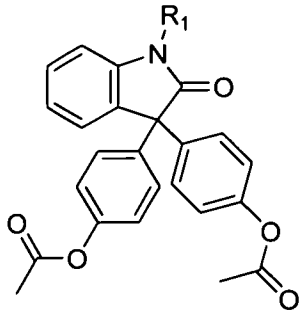
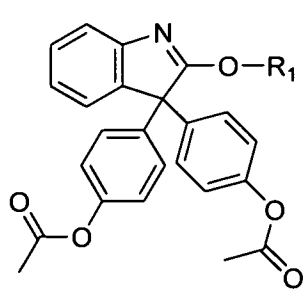
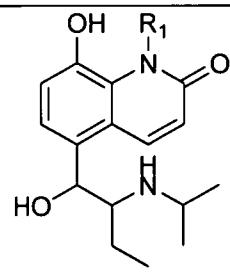
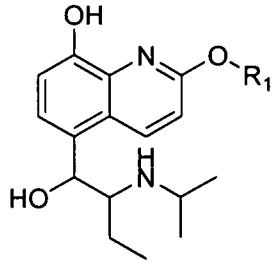
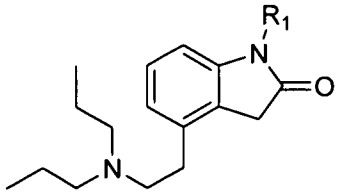
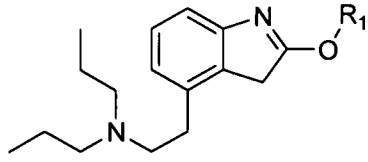
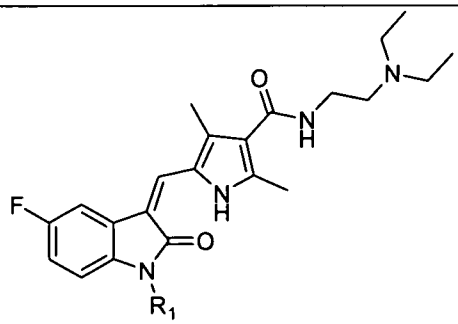
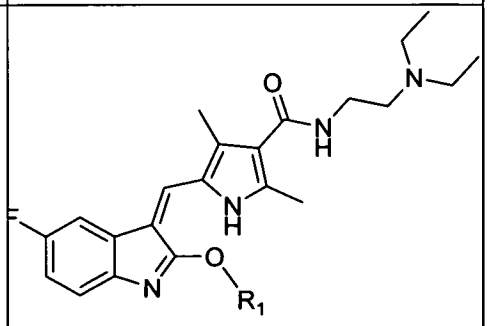
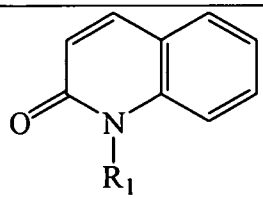
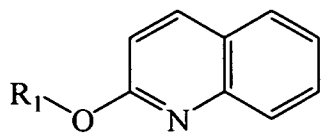
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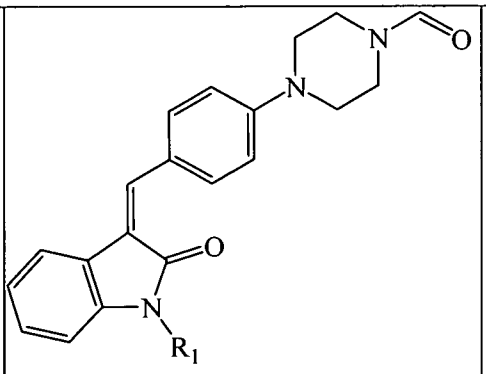
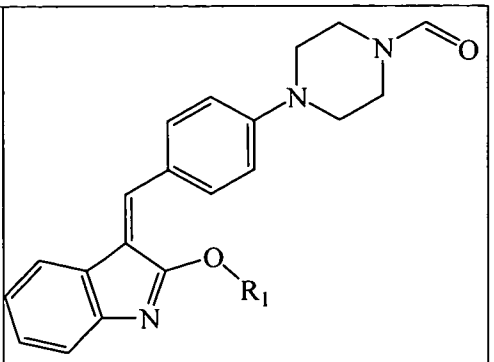
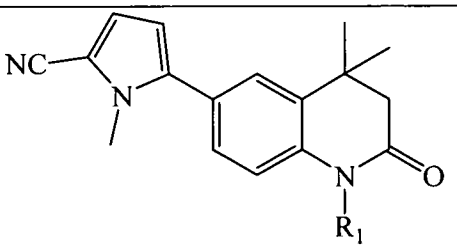
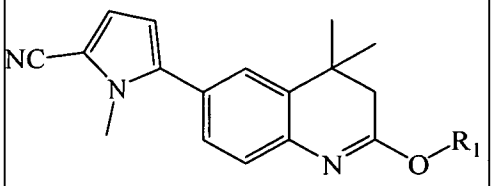
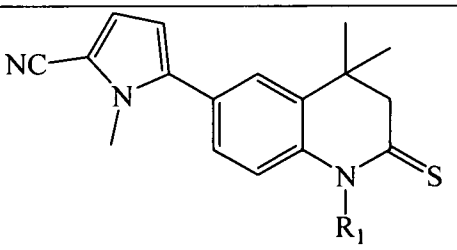
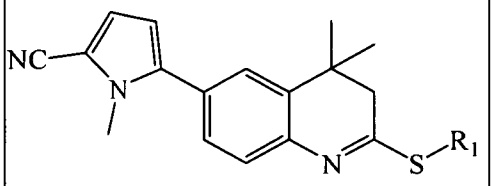
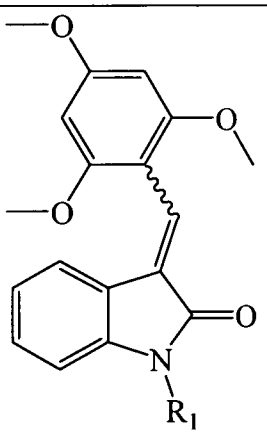
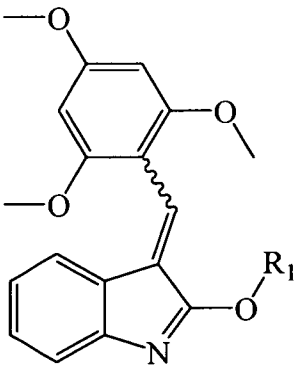
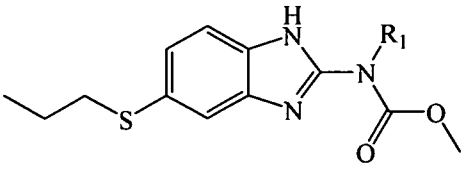
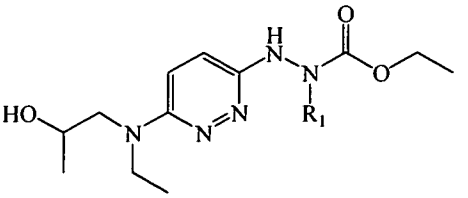
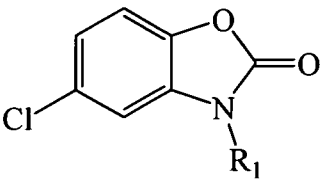
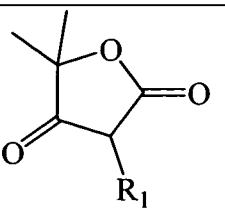
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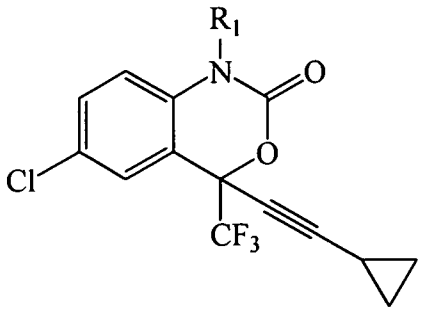
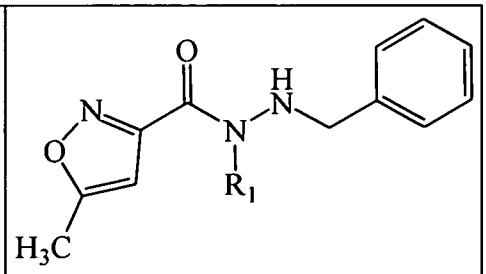
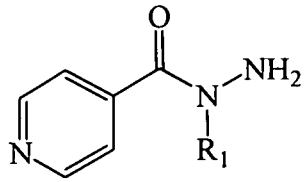
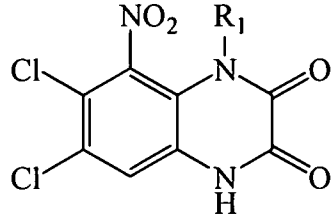
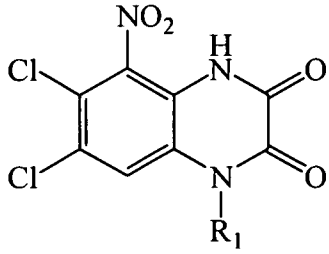
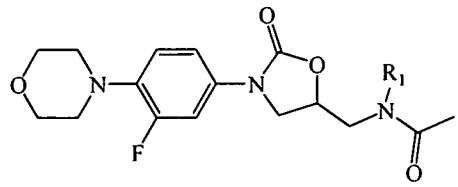
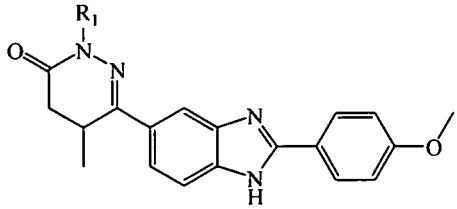
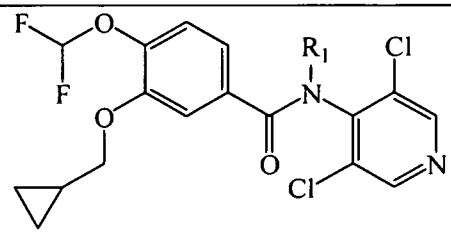
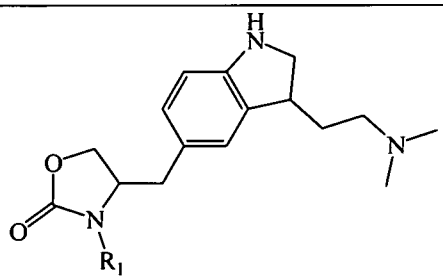
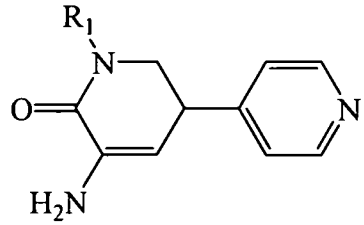
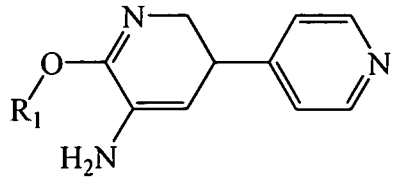
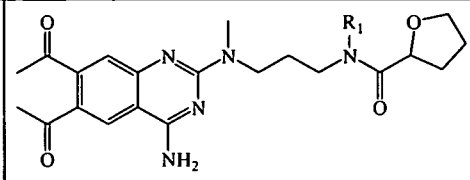
在另一個具體例中，具有化學式IV-VII的本發明的化合物是選自於表IV-VII。

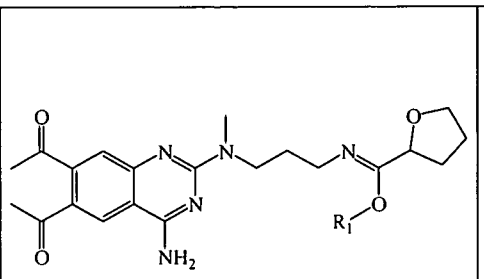
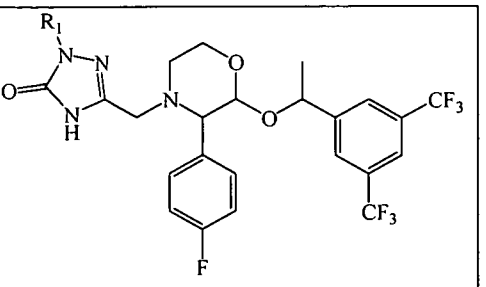
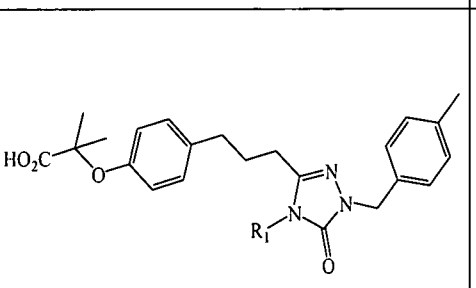
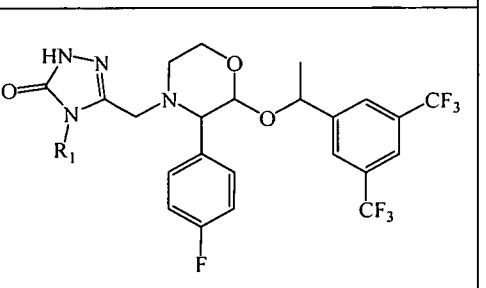
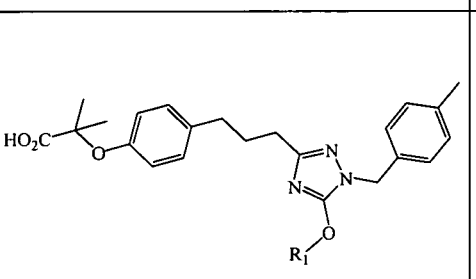
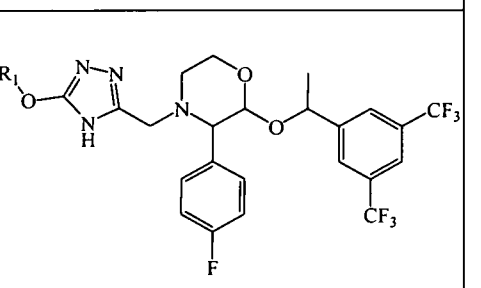
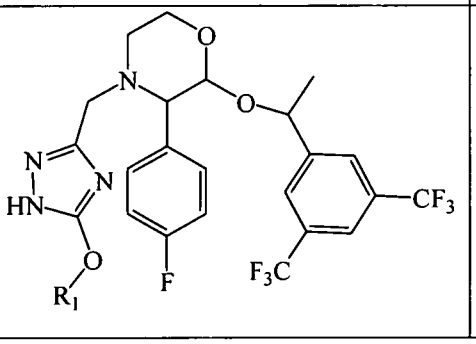
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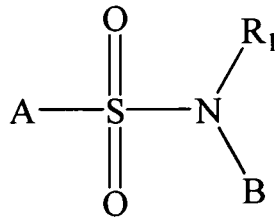
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磺醯胺藥效團的前驅藥

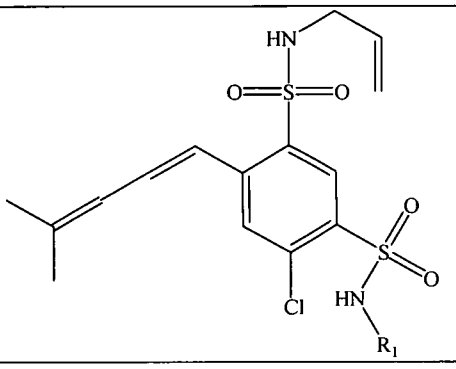
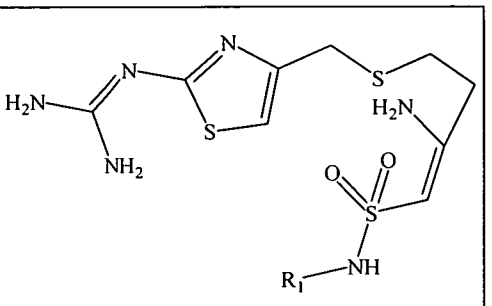
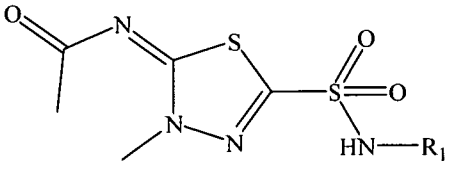
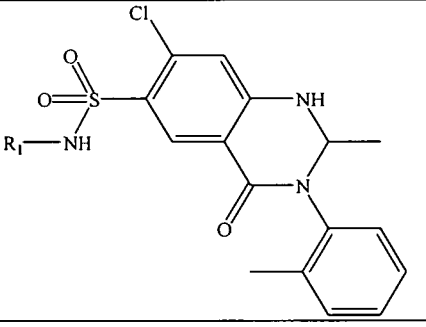
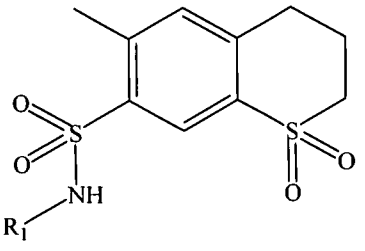
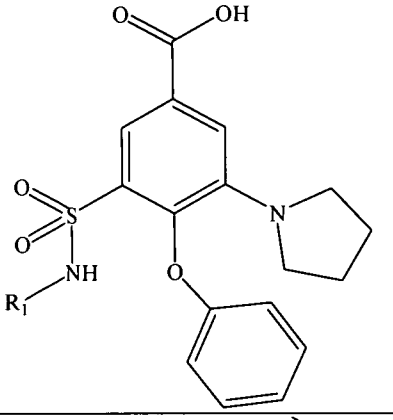
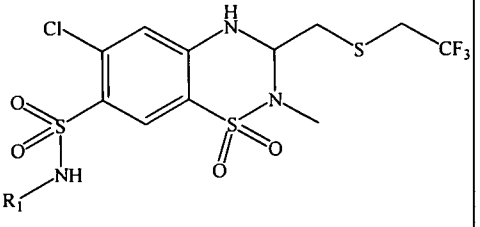
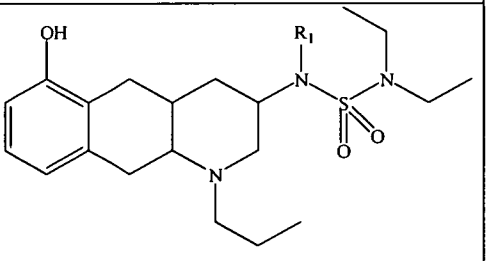
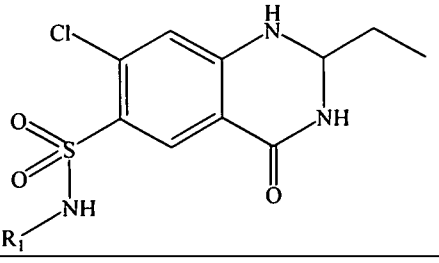
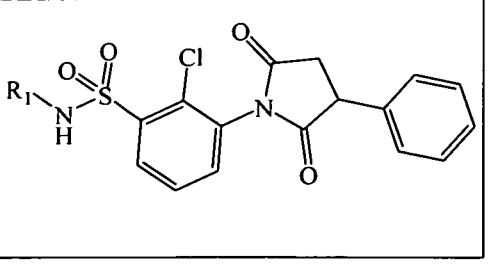
在另一個具體例中，本發明的化合物是以如下面所例示說明的化學式III來表示，或它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物：

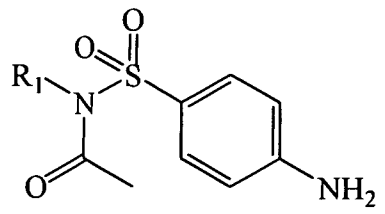
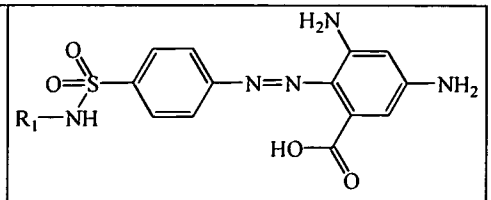
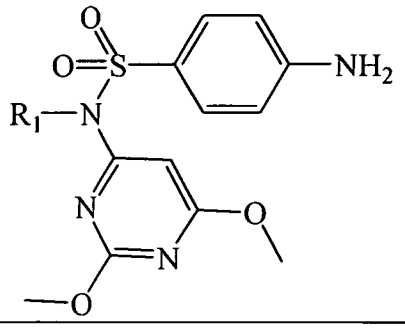
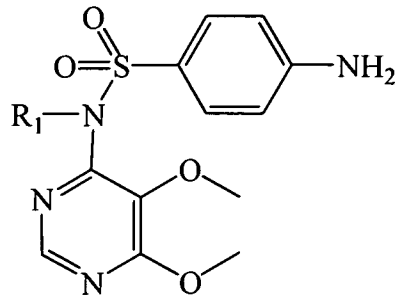
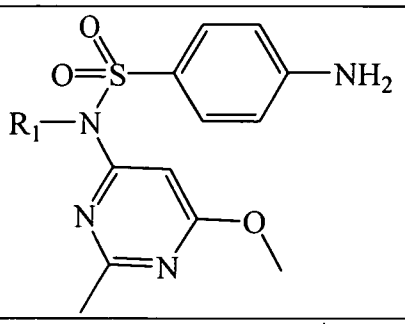
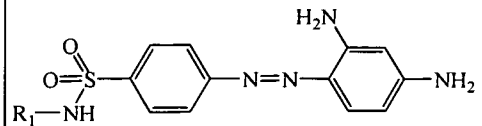
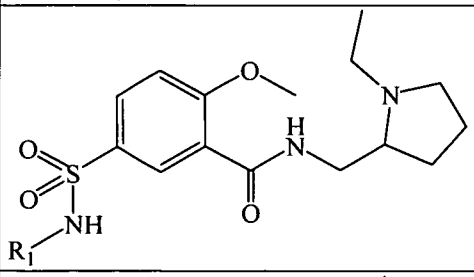
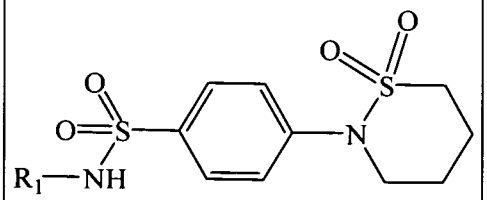
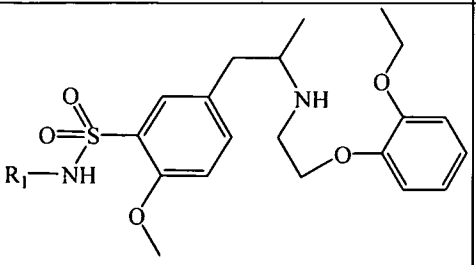
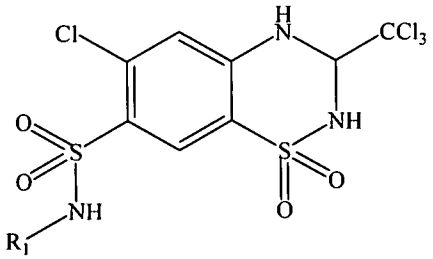


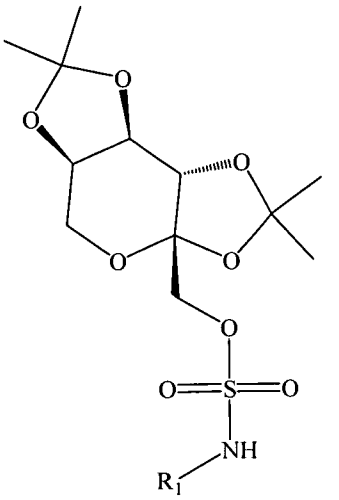
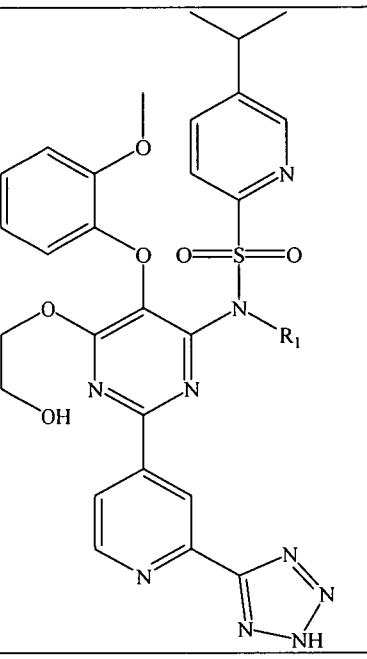
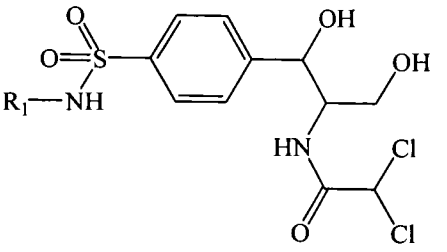
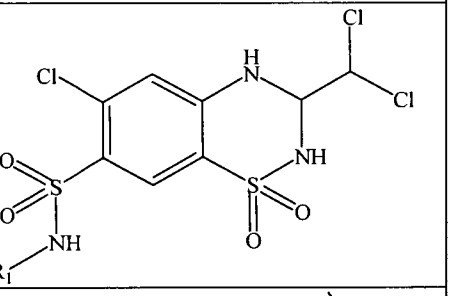
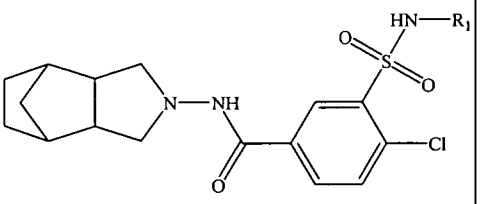
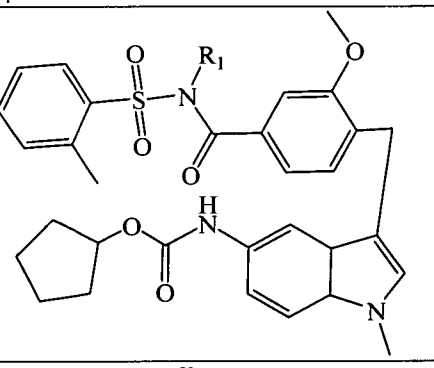
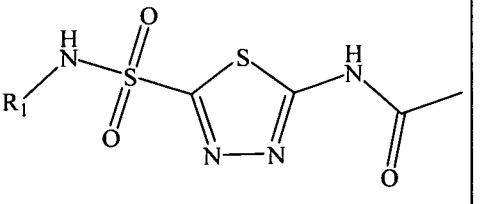
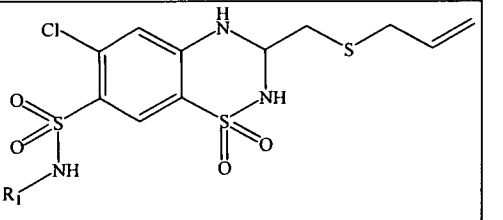
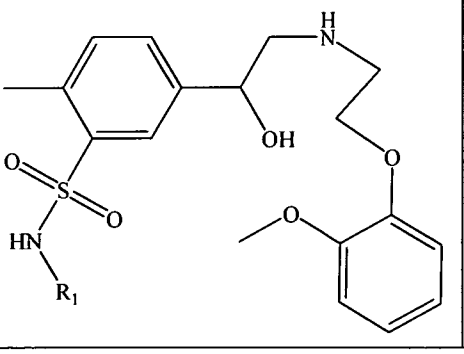
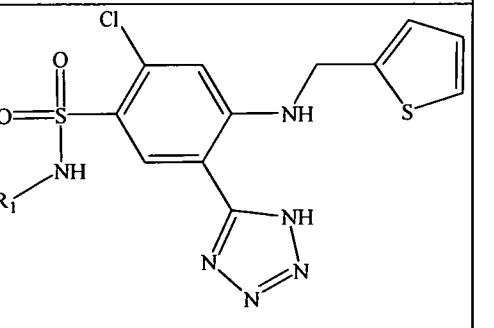
化學式III

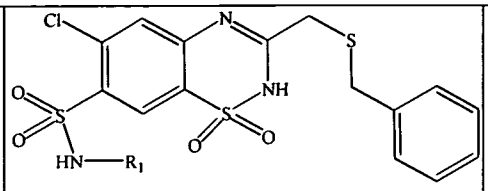
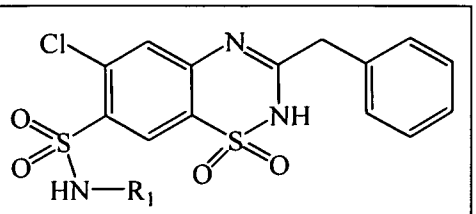
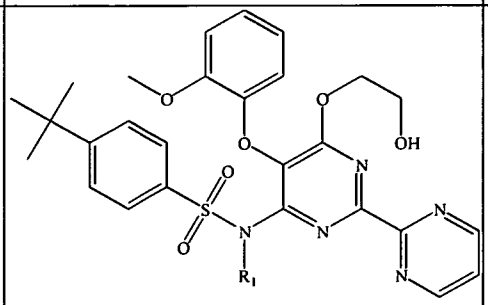
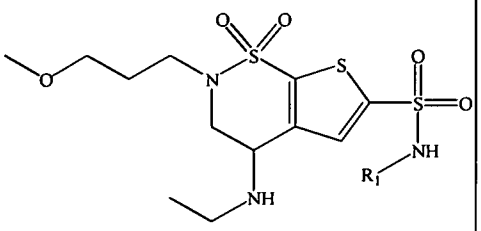
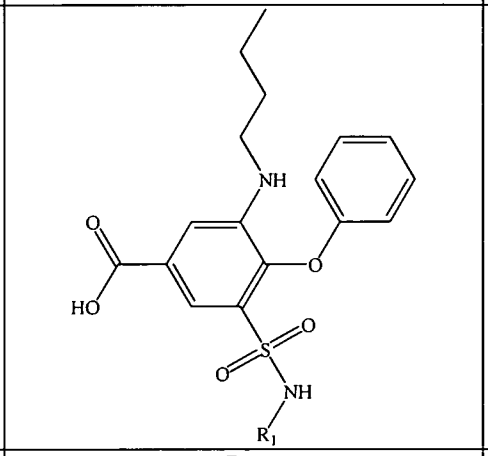
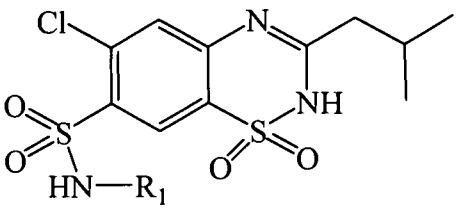
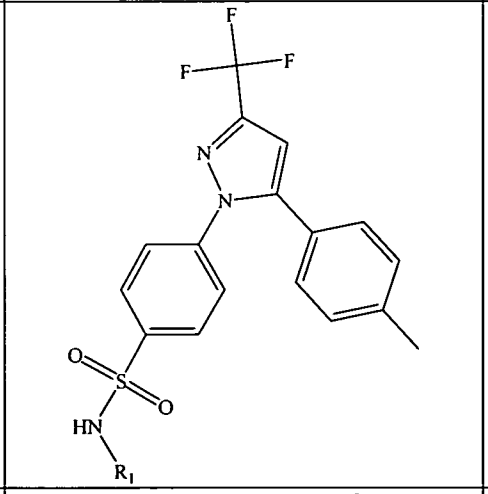
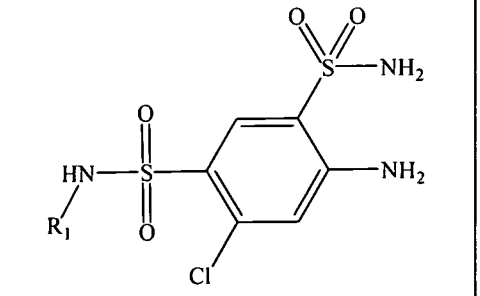
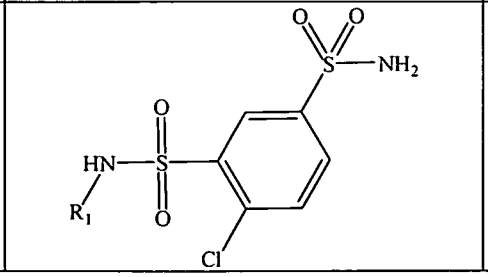
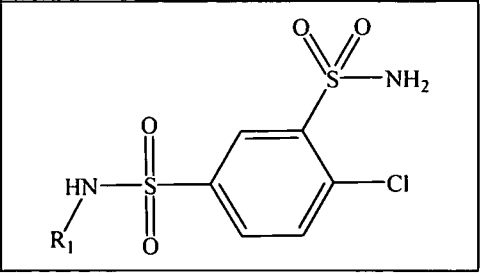
一較佳的具體例是一選自於表III的化合物。一更佳的具體例是一來自表III的化合物，其中R_1是選自於表1-4。

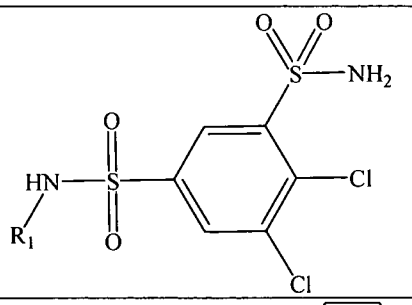
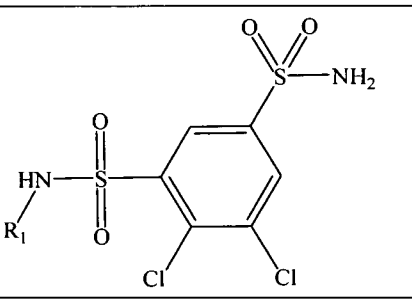
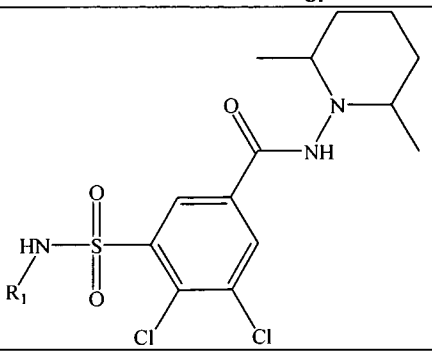
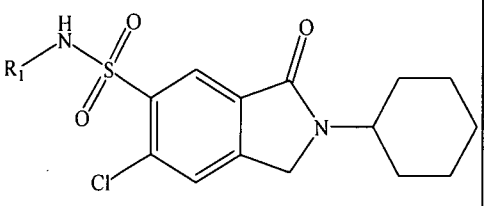
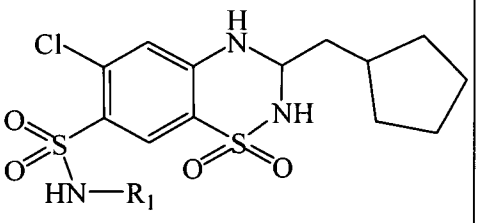
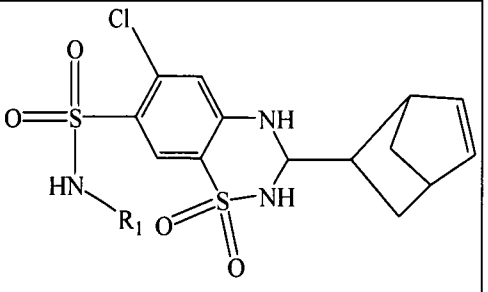
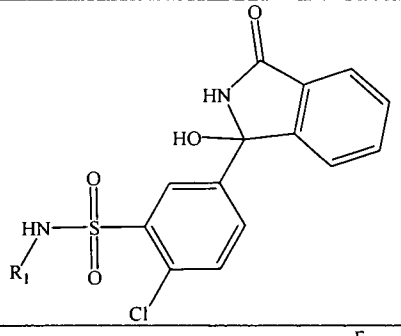
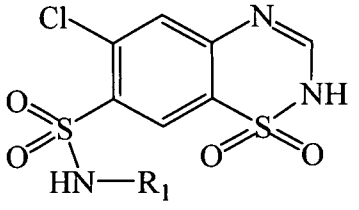
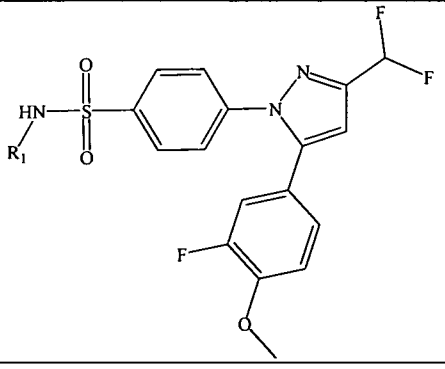
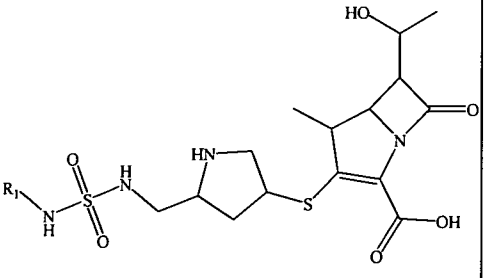
表 III

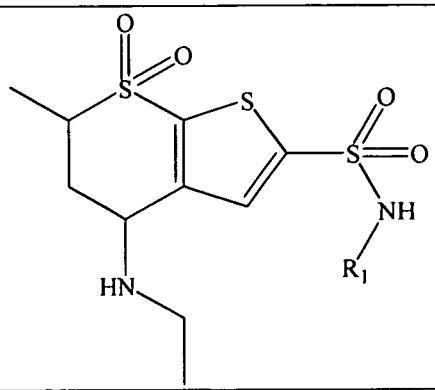
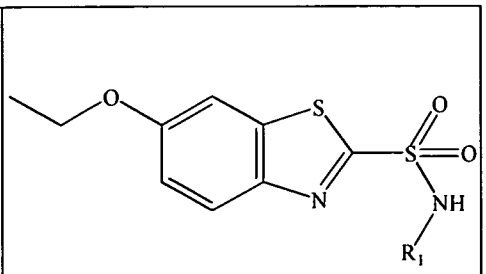
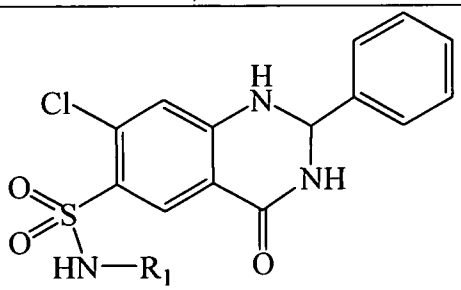
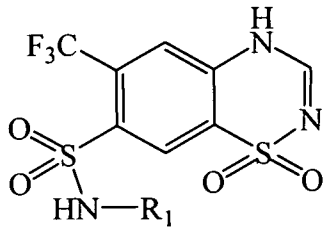
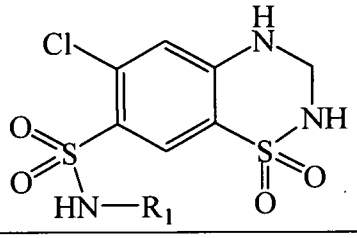
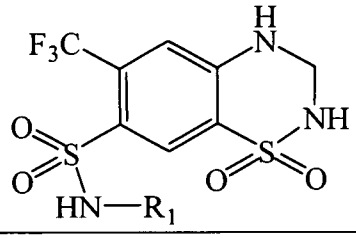
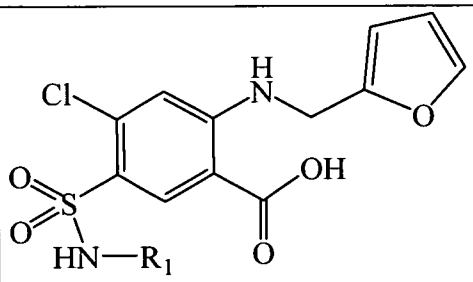
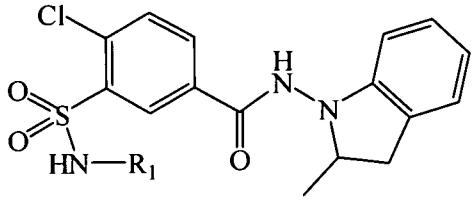
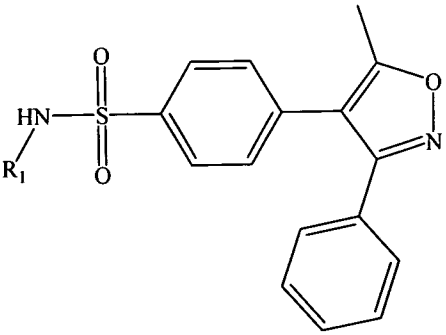
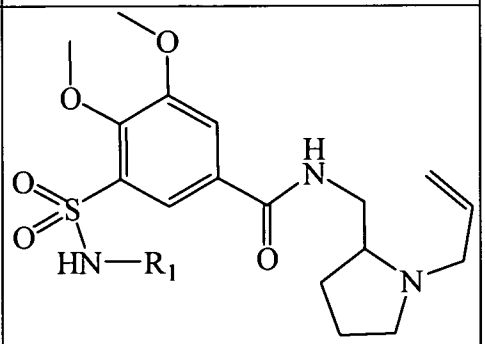
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5		41	

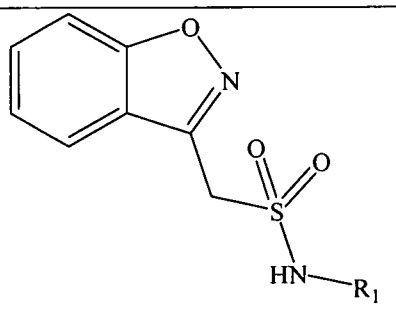
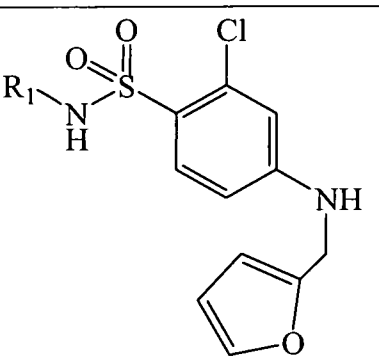
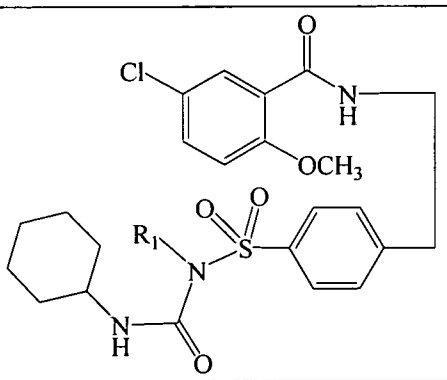
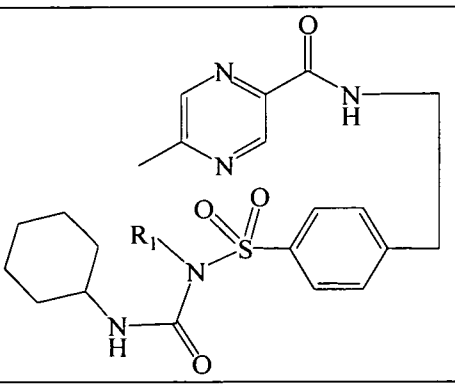
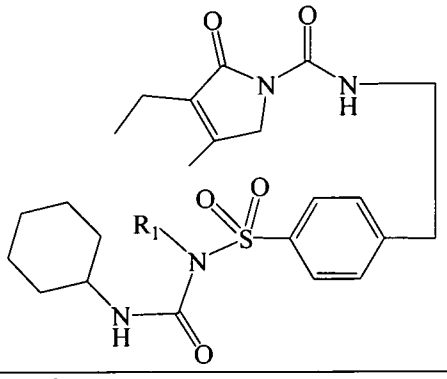
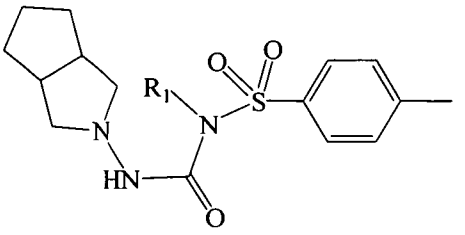
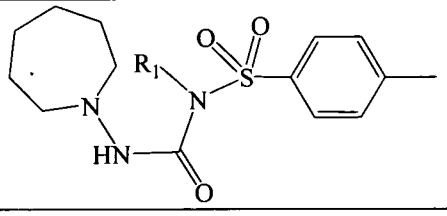
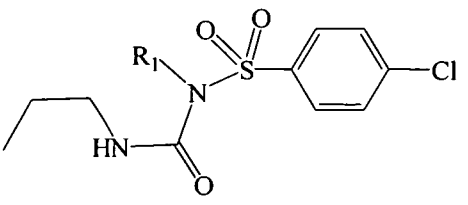
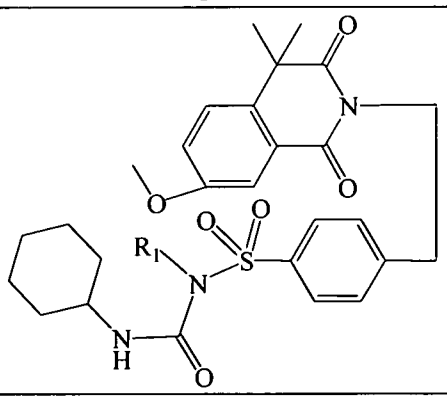
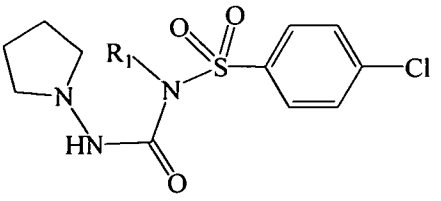
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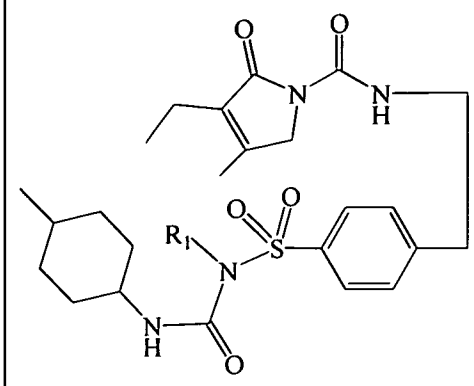
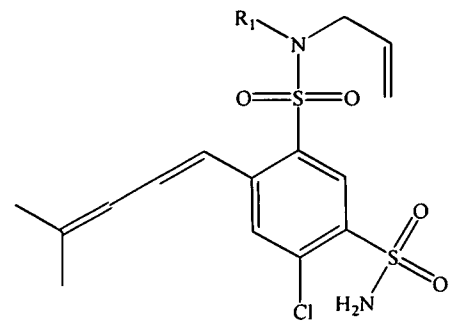
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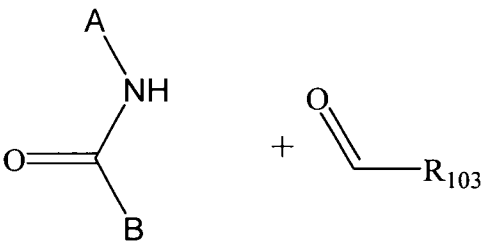
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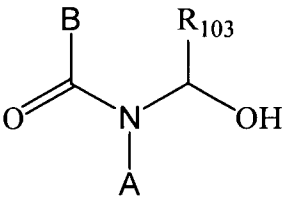
具有化學式III的並且特別地表III的氯苯噻嗪噻嗪(chlorothiazide)以及氫氯苯噻嗪噻嗪(hydrochlorothiazide)化合物對於治療高血壓(hypertension)、鬱血性心臟衰竭(congestive heart failure)、骨質疏鬆症(osteoporosis)、症狀性水腫(symptomatic edema)、周邊水腫(peripheral edema)、腎結石(kidney stones)、糖尿病、腎性尿崩症(nephrogenic diabetes insipidus)、血鈣過高(hypercalcaemia)、登特氏症(Dent's disease)以及梅尼爾氏症(Meniere's disease)是有效的。化學式III以及表III的化合物藉由切割不穩定的R_1部分提供母體藥的持續釋放。具有化學式III的化合物(例如III-63至III-71)作為用於治療糖尿病的前驅藥是有用的。

在本發明的另一個方面，一種將具有化學式XLV的化合物與二級醯胺(secondary amides)轉化成經取代的三級醯胺(tertiary amides)的一般方法被提供(途徑1)。

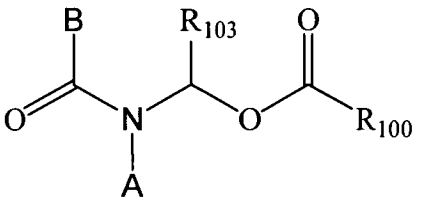
途徑1



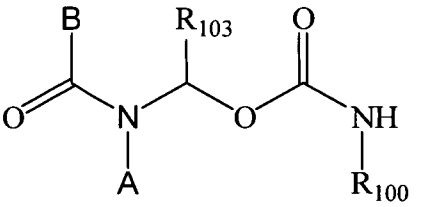
化學式XLV



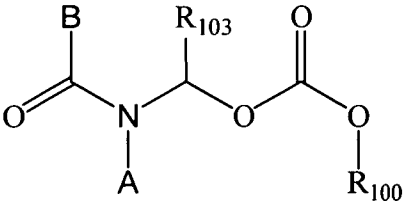
化學式XLVI



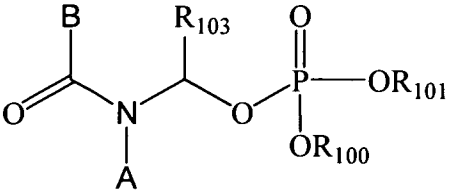
化學式XLVII



化學式XLVIII



化學式XLIX



化學式L

除了醛或酮與具有化學式XLV的化合物的反應外，其

他用於轉化二級內醯胺基團的方法可被使用。例如，在惰性溶劑(iner solvent)中烷基化(alkylation)繼而添加鈉，或者添加氫氧化鉀(potassium hydroxide)或氫氧化鈉(sodium hydroxide)繼而烷基鹵化物(alkyl halide) 添加可被使用。微波(microwave)為基礎的合成操作程序亦可被使用於將二級內醯胺轉化成本申請案的經取代的三級內醯胺化合物。(關於一般性回顧，參見March J. *Advanced Organic Chemistry*, Wiley, 1992；Inoue et al., *Bull. Chem. Soc. Jpn.*, **58**, 2721-2722, 1985；Mijin et. al., *J .Serb. Chem. Soc.*, 73(10) 945-950, 2008；Bogdal et al., *Molecules*, 1999, 4, 333-337；美國專利第5,041,659號)。

本發明進一步地是有關於藉由投藥一具有化學式I-III的化合物來持續輸送一具有化學式XLV的化合物。在投藥一具有化學式I-III的化合物時，該不穩定的R_1部份可被酵素地、化學地切除或經由第一相代謝(first phase metabolism)而得到一具有化學式XLV的化合物。在沒有被任何理論束縛下，被假設的是：關於一些具有化學式I-III的化合物，在切割該R_1部份時，一具有化學式XLV的化合物的釋放導致一治療活性劑。例如該活性成分可以是阿立哌唑、齊拉西酮或百芬普那。在一個具體例中，持續釋放包含有在投藥一具有化學式I-III的化合物之後一治療有效量(therapeutically effective amount)的一具有化學式XLV的化合物在病患的血流(blood stream)中歷時一為至少大約8、較佳地至少大約12、更佳地至少大約24以及甚至更佳地至少

大約36小時的期間。在一個具體例中，該具有化學式XLV的化合物存在在病患的血流中歷時一選自於下列的期間：至少48小時、至少4天、至少1週以及至少1個月。在一個具體例中，一具有化學式I-III的化合物藉由注射而被投藥。

具有化學式IX、X、XI、XII、XIII、XIV、XXXIII、XXXIV、XXXV、XXXVI以及XXXVIII的化合物對於治療神經以及心理疾患(psychological disorders)是有用的。神經以及精神疾患包括，但不限於：疾患諸如在心臟繞道手術(cardiac bypass surgery)以及移植(grafting)之後的大腦缺陷(cerebral deficit)、中風(stroke)、大腦缺血(cerebral ischemia)、脊髓創傷(spinal cord trauma)、頭部創傷、周產期缺氧(perinatal hypoxia)、心跳停止(cardiac arrest)、低血糖神經元損傷(hypoglycemic neuronal damage)、痴呆(dementia)(包括AIDS-誘發的痴呆)、阿滋海默症(Alzheimer's disease)、杭丁頓氏舞蹈症(Huntington's Chorea)、縮性脊髓側索硬化症(amyotrophic lateral sclerosis)、眼損傷(ocular damage)、視網膜病(retinopathy)、認知疾患(cognitive disorders)、自發性與藥物-誘發的帕金森氏症(idiopathic and drug-induced Parkinson's disease)、肌肉痙攣(muscular spasms)以及與肌肉痙攣狀態(muscular spasticity)有關的疾患[包括震顫(tremors)、癲癇(epilepsy)、抽搐(convulsions)、延遲性癲癇持續狀態(prolonged status epilepticus)繼發的大腦缺陷]、偏頭痛(migraine)[包括偏頭痛頭痛(migraine headache)]、尿失禁(urinary

incontinence)、物質耐受性(substance tolerance)、物質戒斷(substance withdrawal)[包括：物質諸如鴉片劑(opiates)、尼古丁(nicotine)、菸草產物(tobacco products)、酒精、苯二氮平類藥物(benzodiazepines)、古柯鹼(cocaine)、鎮靜劑(sedatives)、安眠藥(hypnotics)等等]、精神病(psychosis)、精神分裂症、焦慮[包括廣泛式焦慮疾患(generalized anxiety disorder)、恐慌疾患(panic disorder)、社交懼怕症(social phobia)、強迫疾患(obsessive compulsive disorder)、以及創傷後壓力疾患(post-traumatic stress disorder, PTSD)]、情感疾患(mood disorders)[包括憂鬱症(depression)、躁症、雙極性情感疾患]、晝夜節律疾患(circadian rhythm disorders)[包括時差(jet lag)以及輪班工作(shift work)]、三叉神經痛(trigeminal neuralgia)、失聽(hearing loss)、耳鳴(tinnitus)、眼睛的黃斑退化(macular degeneration)、嘔吐(emesis)、腦水腫(brain edema)、疼痛[包括急性以及慢性的疼痛狀態(acute and chronic pain states)、劇痛(severe pain)、頑固疼痛(intractable pain)、神經病性疼痛(neuropathic pain)、炎性疼痛(inflammatory pain)、以及創傷後疼痛(post-traumatic pain)]、遲發性不自主運動(tardive dyskinesia)、睡眠疾患(sleep disorders)[包括嗜睡症(narcolepsy)]、注意力缺失/過動疾患(attention deficit/hyperactivity disorder)、飲食疾患(eating disorders)以及品行疾患(conduct disorder)。

定義

下面所列舉的是用於描述本發明的各種不同的術語的

定義。這些定義適用於該等被使用遍及本說明書以及申請專利範圍的術語，除非另外在特定的實例中個別地或有如一較大族群的部分被限制。

術語“脂族基團”或“脂族”意指一可以是飽和的(saturated)(例如單鍵)或者含有一或多個不飽和(unsaturation)(例如，雙鍵和/或三鍵)的單元的非-芳族(non-aromatic)部分。一脂族基團可以是直鏈的、分支的(branched)或環的，含有碳、氫或者選擇性地一或多個雜原子(heteroatoms)並且可以是經取代的或未經取代的。除了脂族烴(aliphatic hydrocarbon)基團外，脂族基團包括，例如，聚烷氧基烷基(polyalkoxyalkyls)[諸如聚烷撐二醇(polyalkylene glycols)]、多胺(polyamines)以及例如聚亞胺(polyimine)。該等脂族基團可進一步被取代。要被瞭解的是：脂族基團可以包括如此處所描述的烷基、經取代的烷基、烯基、經取代的烯基、炔基、經取代的炔基以及經取代的或未經取代的環烷基基團。

術語“醯基”意指一被取代以氫、烷基、部分飽和的或完全飽和的環烷基、部分飽和的或完全飽和的雜環、芳基或雜芳基的羰基。例如，醯基包括基團諸如(C_1-C_6)烷醯基(alkanoyl)[例如，甲醯基(formyl)、乙醯基(acetyl)、丙醯基、丁醯基、戊醯基(valeryl)、己醯基(caproyl)、t-丁基乙醯基等等]、(C_3-C_6)環烷基羰基(例如，環丙基羰基、環丁基碳基、環戊基羰基、環己基羰基等等)、雜環羰基[例如，吡咯啶基羰基(pyrrolidinylcarbonyl)、吡咯啶-2-酮-5-羰基、哌啶基羰

基(piperidinylcarbonyl)、哌啡基羰基(piperazinylcarbonyl)、四氫呋喃基羰基(tetrahydrofuranylcarbonyl)等等]、芳醯基(aroyl)(例如，苯甲醯基)以及雜芳醯基[例如，噻吩基-2-羰基(thiophenyl-2-carbonyl)、噻吩基-3-羰基、呋喃基-2-羰基(furanyl-2-carbonyl)、呋喃基-3-羰醯基、1H-吡咯甲醯-2-羰基(1H-pyrroyl-2-carbonyl)、1H-吡咯甲醯-3-羰基、苯并[b]噻吩基-2-羰基等等(benzo[b]thiophenyl-2-carbonyl)]。此外，醯基基團的烷基、環烷基、雜環、芳基以及雜芳基部分可以是在個別的定義中所描述的基團的任一者。當被表示為"選擇性地經取代的"時，醯基基團可以是未經取代的或選擇性地被取代以一或多個獨立地選自於在下面關於"經取代的"的定義中所列舉的取代基的群組之取代基(典型地，1至3個取代基)，或者醯基基團的烷基、環烷基、雜環、芳基以及雜芳基部分可分別如在上面的較佳以及更佳的取代基的列表中所描述的而被取代。

術語"烷基"被意欲包括具有特定數目的碳之分支的以及直鏈、經取代或未經取代的飽和脂族煙基(aliphatic hydrocarbon radicals)/基團(groups)這兩者。較佳的烷基基團包含有大約1至大約24個碳原子("C_1-C_{24}")、較佳地大約7至大約24個碳原子("C_7-C_{24}")、較佳地大約8至大約24個碳原子("C_8-C_{24}")、較佳地大約9至大約24個碳原子("C_9-C_{24}")。其他較佳的烷基基團包含有大約1至大約8個碳原子("C_1-C_8")，諸如大約1至大約6個碳原子("C_1-C_6")或諸如大約1至大約3個碳原子("C_1-C_3")。C_1-C_6烷基(alkyl radicals)

的實例包括，但不限於：甲基、乙基、丙基、異丙基、*n*-丁基、特-丁基(*tert*-butyl)、n-戊基、新戊基(neopentyl)以及n-己基基團。

術語“烯基”意指具有至少1個碳-碳雙鍵的線性或分支的基(radicals)。該等基較佳地含有自大約2至大約24個碳原子(“C_2-C_{24}”)、較佳地大約7至大約24個碳原子(“C_7-C_{24}”)、較佳地大約8至大約24個碳原子(“C_8-C_{24}”)以及較佳地大約9至大約24個碳原子(“C_9-C_{24}”)。其他較佳的烯基(alkenyl radicals)是具有2至大約10個碳原子的“低級烯基(lower alkenyl)”，諸如乙烯基(ethenyl)、烯丙基(allyl)、丙烯基(propenyl)、丁烯基(butenyl)以及4-甲基丁烯基。較佳的低級烯基包括2至大約6個碳原子(“C_2-C_6”)。術語“烯基”以及“低級烯基”涵括具有“順式(cis)”以及“反式(trans)”位向(orientation)，或者另擇地“E”以及“Z”位向的基。

術語“炔基”意指具有至少1個碳-碳三鍵的線性或分支的基。該等基較佳地含有自大約2至大約24個碳原子(“C_2-C_{24}”)、較佳地大約7至大約24個碳原子(“C_7-C_{24}”)、較佳地大約8至大約24個碳原子(“C_8-C_{24}”)以及較佳地大約9至大約24個碳原子(“C_9-C_{24}”)。其他較佳的炔基是具有2至大約10個碳原子的“低級炔基”，諸如炔丙基(propargyl)、1-丙炔基(1-propynyl)、2-丙炔基、1-丁炔基(1-butyne)、2-丁炔基以及1-戊炔基(1-pentynyl)。較佳的低級炔基包括2至大約6個碳原子(“C_2-C_6”)。

術語“環烷基”意指具有3至大約12個碳原子(“C_3-C_{12}”)

的飽和碳環基(carbocyclic radicals)。術語“環烷基”涵括具有3至大約12個碳原子的飽和碳環基。該等基的實例包括環丙基、環丁基、環戊基以及環己基。

術語“環烯基”意指具有3至大約12個碳原子的部分不飽和碳環基。含有2個雙鍵(可以或可以不被綴合)的部分不飽和碳環基的環烯基可被稱為“環烷基二烯基(cycloalkyldienyl)”。更佳的環烯基是具有4至大約8個碳原子的“低級環烯基”基。該等基的實例包括環丁烯基、環戊烯基以及環己烯基。

如此處所用的，術語“烷撐(alkylene)”意指一具有特定數量的碳原子之衍生自一直鏈或分支的飽和烴鏈之雙價基團。烷撐基團的實例包括，但不限於：乙撐(ethylene)、丙撐(propylene)、丁撐(butylene)、3-甲基-戊撐(3-methy-pentylene)、以及5-乙基-己撐(5-ethyl-hexylene)。

如此處所用的，術語“烯撐(alkenylene)”表示一含有特定數量的碳原子、具有至少一碳-碳雙鍵的衍生自一直鏈或分支的烴部分之雙價基團。烯撐基團包括，但不限於：例如，乙烯撐(ethenylene)、2-丙烯撐(2-propenylene)、2-丁烯撐(2-butenylene)、1-甲基-2-丁烯-1-撐(1-methyl-2-buten-1-ylene)以及類似之物。

如此處所用的，術語“炔撐(alkynylene)”表示一含有特定數量的碳原子、具有至少一碳-碳三鍵的衍生自一直鏈或分支的烴部分之雙價基團。代表性炔撐基團包括，但不限於：例如，丙炔撐(propynylene)、1-丁炔撐(1-butylnylene)、

2-甲基-3-己炔撐(2-methyl-3-hexylene)以及類似之物。

術語“烷氧基”意指各個具有1至大約24個碳原子或較佳地1至大約12個碳原子的烷基部份之線性或分支的含有氧基的基(oxy-containing radicals)，。更佳的烷氧基是具有1至大約10個碳原子以及更佳地具有1至大約8個碳原子的“低級烷氧基”。該等基的實例包括甲氧基、乙氧基、丙氧基、丁氧基以及特-丁氧基。

術語“烷氧基烷基”意指具有一或多個被接附至烷基的烷氧基之烷基，那就是形成單烷氧基烷基以及二烷氧基烷基。

術語“芳基”，單獨或組合的，意指一含有1、2或3環的碳環芳族系統，其中該等環可以一懸垂(pendent)的方式被接附一起或可以被融合 (fused)。術語“芳基”涵括芳族基，諸如苯基(phenyl)、萘基(naphthyl)、四氫萘基(tetrahydronaphthyl)、氫茚(indane)以及聯苯(biphenyl)。

術語“雜環基(heterocyclyl)”、“雜環(heterocycle)”、雜環的(heterocyclic)”或“雜環(heterocyclo)”意指飽和的、部分不飽和的以及不飽和的含有雜原子的環形基(heteroatom-containing ring shaped radicals)，該含有雜原子的環形基亦可被對應地稱為“雜環基”、“雜環烯基(heterocyclylalkenyl)”以及“雜芳基”，其中該等雜原子可選自於氮、硫以及氧。飽和雜環基的實例包括含有1至4個氮原子之飽和的3至6-員雜單環基團(heteromonocyclic group)[例如吡咯啶基(pyrrolidiny)、咪唑啶基

(imidazolidinyl)、N-六氫吡啶(piperidino)、哌啡基(piperaziny)等等]；含有1至2個氧原子以及1至3個氮原子之飽和的3至6-員雜單環基團[例如嗎福啉基(morpholinyl)等等]；含有1至2個硫原子以及1至3個氮原子之飽和的3至6-員雜單環基團[例如四氫噻唑基(thiazolidinyl)等等]。部份不飽和的雜環基的實例包括二氫噻吩(dihydrothiophene)、二氫哌喃(dihydropyran)、二氫呋喃(dihydrofuran)、以及二氫噻唑(dihydrothiazole)。雜環基可包括一為五價的(pentavalent)氮原子，諸如四唑鎓(tetrazolium)以及吡啶陽離子(pyridinium)基。術語"雜環"亦涵括其中雜環基被融合以芳基或環烷基的基。該等被融合的雙環基的實例包括苯并呋喃(benzofuran)、苯并噻吩(benzothiophene)以及類似之物。

術語"雜芳基"意指不飽和的芳族環雜環基。雜芳基的實例包括含有1至4個氮原子之不飽和的3至6員雜單環基團[例如，吡咯基(pyrrolyl)、吡咯啉基(pyrrolinyl)、咪唑基(imidazolyl)、吡唑基(pyrazolyl)、吡啶基(pyridyl)、嘧啶(pyrimidyl)、吡啡基(pyrazinyl)、嗒啡基(pyridazinyl)、三唑基(triazolyl)(例如，4H-1,2,4-三唑基、1H-1,2,3-三唑基、2H-1,2,3-三唑基等等)、四唑基(tetrazolyl)(例如1H-四唑基、2H-四唑基等等)等等]；含有1至5個氮原子之不飽和的縮合雜環基(condensed heterocyclyl)基團[例如，吲哚基(indolyl)、異吲哚基(isoindolyl)、吲啡基(indolizinyl)、苯并咪唑基(benzimidazolyl)、喹啉基(quinolyl)、異喹啉基(isoquinolyl)、吲唑基(indazolyl)、苯并三唑基

(benzotriazolyl)、四唑并嗒咔基(tetrazolopyridazinyl)(例如，四唑并[1,5-b]嗒咔基等等)等等]；含有一氧原子之不飽和的3至6-員雜單環基團[例如，哌喃基(pyranyl)、呋喃基(furyl)等等]；含有一硫原子之不飽和的3至6-員雜單環基團[例如，噻吩基(thienyl)等等]；含有1至2個氧原子以及1至3個氮原子之不飽和的3至6-員雜單環基團[例如，噁唑基(oxazolyl)、異噁唑基(isoxazolyl)、噁二唑基(oxadiazolyl)(例如，1,2,4-噁二唑基、1,3,4-噁二唑基、1,2,5-噁二唑基等等)等等]；含有1至2個氧原子以及1至3個氮原子之不飽和的縮合雜環基基團[例如苯并噁唑基(benzoxazolyl)、苯并噁二唑基(benzoxadiazolyl)等等]；含有1至2個硫原子以及1至3個氮原子之不飽和的3至6-員雜單環基團[例如，噻唑基(thiazolyl)、噻二唑基(thiadiazolyl)(例如，1,2,4-噻二唑基、1,3,4-噻二唑基、1,2,5-噻二唑基等等)等等]；含有1至2個硫原子以及1至3個氮原子之不飽和的縮合雜環基基團[例如苯并噻唑基(benzothiazolyl)、苯并噻二唑基(benzothiadiazolyl)等等]以及類似之物。

術語“雜環烷基”意指經雜環取代的烷基(alkyl radicals)。更佳的雜環烷基是在雜環基團中具有1至6個碳原子的“低級雜環烷基”基。

術語“烷硫基(alkylthio)”意指含有一具有1至大約10個被接附至一雙價硫原子的碳原子之線性或分支的烷基的基。較佳的烷硫基具有1至大約24個碳原子、較佳地1至大約12個碳原子的烷基。更佳的烷硫基具有烷基，該烷基是

具有1至大約10個碳原子的“低級烷硫基”。最佳的是具有1至大約8個碳原子的低級烷基的烷硫基。該等低級烷硫基的實例包括甲硫基(methylthio)、乙硫基(ethylthio)、丙硫基(propylthio)、丁硫基(butylthio)以及戊硫基(hexylthio)。

術語“芳烷基(aralkyl)”或“芳基烷基(arylalkyl)”意指經芳基取代的烷基，諸如苄基(benzyl)、二苯基甲基、三苯基甲基、苯基乙基以及二苯基乙基。

術語“芳氧基”意指經由一氧原子而被接附至其他基的芳基。

術語“芳烷氧基(aralkoxyl)”或“芳基烷氧基(arylakoxyl)”意指經由一氧原子而被接附至其他基的芳烷基。

術語“胺基烷基”意指被取代以胺基的烷基基團。較佳的胺基烷基具有大約1至大約24個碳原子或者較佳地1至大約12個碳原子的烷基。更佳的胺基烷基是具有1至大約10個碳原子的烷基的“低級胺基烷基”。最佳的是具有1至8個碳原子的低級烷基的胺基烷基。該等基的實例包括胺基甲基、胺基乙基以及類似之物。

術語“烷基胺基” 表示被取代以1或2個烷基的胺基基團。較佳的烷基胺基具有大約1至大約20個碳原子或較佳地1至大約12個碳原子的烷基基團。更佳的烷基胺基是具有1至大約10個碳原子的烷基的“低級烷基胺基”。最佳的是具有1至大約8個碳原子的低級烷基的烷基胺基。適合的低級烷基胺基可以是經單取代的N-烷基胺基或經二取代的N,N-

烷基胺基，諸如N-甲基胺基、N-乙基胺基、N,N-二甲基胺基、N,N-二乙基胺基或類似之物。

術語“經取代的”意指將在一被給予的結構中的一或多個氫基置換以一特定取代基的基，該取代基包括，但不限於：鹵基(halo)、烷基、烯基、炔基、芳基、雜環基、硫醇(thiol)、烷基硫基、芳基硫基(arylthio)、烷基硫基烷基、芳基硫基烷基、烷基磺醯基(alkylsulfonyl)、烷基磺醯基烷基、芳基磺醯基烷基、烷氧基、芳氧基、芳烷氧基(aralkoxy)、胺基羰基、烷基胺基羰基、芳基胺基羰基、烷氧基羰基、芳氧基羰基、鹵基烷基、胺基、三氟甲基(trifluromethyl)、氰基(cyano)、硝基(nitro)、烷基胺基、芳基胺基、烷基胺基烷基、芳基胺基烷基、胺基烷基胺基、羥基(hydroxyl)、烷氧基烷基、羰基烷基、烷氧基羰基烷基、胺基羰基烷基、醯基、芳烷氧基羰基、羧酸(carboxylic acid)、磺酸(sulfonic acid)、磺醯基、膦酸(phosphonic acid)、芳基、雜芳基、雜環以及脂族。要被瞭解的是：該取代基可進一步被取代。

簡單地說，從頭至尾被定義以及被意指的化學部份在對於那些熟習此技藝者而言清楚的適當結構情況之下可以是單價(univalent)化學部份(例如烷基、芳基等等)或多價部份。例如，一“烷基”部份可以被意指一單價基(例如CH_3-CH_2-)，或者在其他例子中，一為二價連結部份可以是“烷基”，在該例子中熟習此技藝者會了解該烷基是一等同於術語“烷撐”的二價基團(例如-CH_2-CH_2-)。相似地，在二價部份被需要以及被陳述為“烷氧基”、“烷胺基”、“芳基氧

基”、“烷基硫基”、“芳基”、“雜芳基”、“雜環”、“烷基”、“烯基”、“炔基”、“脂族”或“環烷基”的情況下，那些熟習此技藝者會瞭解術語“烷氧基”、“烷基胺基”、“芳基氧基”、“烷基硫基”、“芳基”、“雜芳基”、“雜環”、“烷基”、“烯基”、“炔基”、“脂族”或“環烷基”意指對應的二價部份。

如此處所用的術語“鹵素”或“鹵基”意指一選自於氟、氯、溴以及碘的原子。

如此處所用的術語“化合物”、“藥物”以及“前驅藥”全部包括具有如此處所描述的化學式的化合物、藥物以及前驅藥之藥學上可接受的鹽類、共-晶體、溶劑合物、水合物(hydrate)、多晶型物(polymorphs)、鏡像異構物、非鏡像異構物、消旋物以及類似之物。

被指示為經由可變化的接附點而被接附的取代基可被接附至環結構上的任何可用的位置。

如此處所用的，關於治療的標的方法之術語“有效量的該標的化合物”意指一當被輸送有如部分所欲的劑量攝生法(regimes)時，帶來關於處理疾病或疾患至臨床上可接受的標準的該標的化合物的數量。

“治療(treatment)”或“治療(treating)”意指一種用於在一病患中獲得有益的或所欲的臨床結果的方法。關於本發明的目的，有益的或所欲的臨床結果包括，但不限於下列的一或多個：症狀的減輕(alleviation)、一疾病程度的縮減、一疾病狀況的穩定(亦即不惡化)、預防疾病的擴散[亦即轉移(metastasis)]、預防疾病的發生或復發、疾病進展的延遲

或減慢、疾病狀況的改善(amelioration)以及緩解(remission)(無論部分或整體的)。

如此處所用的術語"不穩定"意指本發明的前驅藥對於經歷在活體內的(*in vivo*)酵素性和/或化學性切割因而形成該母體藥的能力(capacity)。如此處所用的術語"前驅藥"意指一如此處所揭示的化合物，該化合物是一含有雜芳族NH的母體藥之一不穩定的衍生化合物，當該不穩定的衍生化合物在活體內被投藥給一病患時，藉由化學和/或酵素的水解(hydrolysis)而變成被切割的，因而形成該母體藥，藉此一足夠量的被意欲要被輸送至該病患的該化合物可以一持續釋放的方式用於它意欲的治療用途。

藥學組成物(pharmaceutical compositions)

本發明的藥學組成物包含有一治療有效量的一與一或多種藥學上可接受的載劑或賦形劑(excipient)一起被配方的本發明的化合物。

如此處所用的，術語"藥學上可接受的載劑或賦形劑"意指一非-毒性、惰性固體、半-固體、凝膠(gel)或液體填充劑(liquid filler)、稀釋劑(diluents)、囊封材料或任何類型的配方助劑(auxiliary)。可作為藥學上可接受的載劑的材料的一些實例是糖[諸如乳糖(lactose)、葡萄糖(glucose)以及蔗糖(sucrose)]；環糊精(cyclodextrin)[諸如α-(alpha-)(α)、β-(beta-)(β)以及γ-(gamma) (γ)環糊精]；澱粉(starches)[諸如玉米澱粉以及馬鈴薯澱粉]；纖維素(cellulose)以及它的衍生物[諸如羧基甲基纖維素鈉(sodium carboxymethyl

cellulose)、乙基纖維素以及乙酸纖維素(cellulose acetate)]；粉末狀黃著(powdered tragacanth)；麥芽(malt)；明膠(gelatin)；滑石(talc)；賦形劑[諸如可可脂(cocoa butter)以及栓劑蠟(suppository waxes)；油[諸如花生油(peanut oil)、棉籽油(cottonseed oil)、紅花油(safflower oil)、芝麻油(sesame oil)、橄欖油(olive oil)、玉米油(corn oil)以及大豆油(soybean oil)；甘醇(glycols)[諸如丙二醇(propylene glycol)]；酯(esters)[諸如油酸乙酯(ethyl oleate)以及月桂酸乙酯(ethyl laurate)]；瓊脂(agar)；緩衝劑(buffering agents)[氫氧化鎂(magnesium hydroxide)以及氫氧化鋁(aluminum hydroxide)]；藻酸(alginic acid)；無發熱性水(pyrogen-free water)；等張鹽水(isotonic saline)；林格氏液(Ringer's solution)；乙醇與磷酸緩衝溶液，以及其他無-毒性相容的潤滑劑(lubricants)[諸如月桂基硫酸鈉(sodium lauryl sulfate)以及硬脂酸鎂(magnesium stearate)]，以及染色劑(coloring agents)、釋放劑(releasing agents)、包衣劑(coating agents)、甜味、調味與香料劑(sweetening, flavoring and perfuming agents)、防腐劑(preservatives)以及抗氧化劑(antioxidants)亦可依據配方者的判斷而存在於組成物中。

本發明的藥學組成物可口服地、非經腸道地、藉由吸入噴霧(inhalation spray)、局部地(topically)、直腸地(rectally)、經鼻地(nasally)、頰內地(buccally)、陰道地(vaginally)或經由一經植入的儲庫(reservoir)而被投藥。在一個較佳的具體例中，投藥是藉由注射的非經腸道的投藥。

本發明的藥學組成物可含有任何習知的非-毒性的藥學上可接受的載劑、佐劑或載劑(vehicles)。在一些例子中，該配方的pH可以藥學上可接受的酸、鹼或緩衝液而被調整俾以增強該經配方的化合物或它的輸送形式的穩定性。如此處所用的術語非經腸道的包括皮下的(subcutaneous)、皮內的(intracutaneous)、靜脈內的、肌肉內的、關節內的(intraarticular)、動脈內的(intraarterial)、滑液內的(intrasynovial)、胸骨內的(intrasternal)、椎管內的(intrathecal)、病灶內的(intralesional)以及顱內的(intracranial)注射或注入(infusion)技術。

用於口服投藥的液體劑型(dosage form)包括藥學上可接受的乳劑(emulsions)、微乳劑(microemulsions)、溶液、懸浮液(suspensions)、糖漿(syrups)以及酏劑(elixirs)。除了活性化合物之外，該液體劑型可含有常被使用在本技藝中的惰性稀釋劑諸如，例如，水或其他溶劑、助溶劑(solubilizing agents)以及乳化劑(emulsifiers){諸如乙醇、異丙醇(isopropyl alcohol)、碳酸乙酯(ethyl carbonate)、乙酸乙酯(ethyl acetate)、苯甲醇(benzyl alcohol)、苯甲酸苄酯(benzyl benzoate)、丙二醇、1,3-丁二醇(1,3-butylene glycol)、二甲基甲醯胺(dimethylformamide)、油[特別地棉籽、花生(groundnut)、玉米、胚芽(germ)、橄欖、蓖麻(castor)以及芝麻油]、甘油(glycerol)、四氫呋喃甲醇(tetrahydrofurfuryl alcohol)、聚乙二醇(polyethylene glycols)與去水山梨醇(sorbitan)的脂肪酸酯以及它們的混合物}。除

了惰性稀釋劑，該口服的組成物亦可包括佐劑，諸如潤濕劑(wetting agents)、乳化以及懸浮劑(emulsifying and suspending agents)、甜味、調味與香料劑。

可注射的製劑(injectable preparations)[例如，無菌(sterile)可注射的水性(aqueous)或油性的(oleaginous)懸浮液]可依據知曉的技藝使用適合的分散(dispersing)或潤濕劑以及懸浮劑而被配方。無菌可注射的製劑亦可以是無菌可注射的懸浮液或乳劑(諸如INTRALIPID®、LIPOSYN®或OMEGAVEN®或溶液)，呈一非-毒性非經腸道地可接受的稀釋劑或溶劑[例如，如一配於1,3-丁二醇(1,3-butanediol)中的溶液]。INTRALIPID®是一含有10-30%大豆油、1-10%蛋黃磷脂(egg yolk phospholipids)、1-10%甘油(glycerin)以及水的靜脈內脂肪乳劑。LIPOSYN®亦是一含有2-15%紅花油、2-15%大豆油、0.5-5%卵磷脂(egg phosphatides)、1-10%甘油(glycerin)以及水的靜脈內脂肪乳劑。OMEGAVEN®是一含有大約5-25%魚油(fish oil)、0.5-10%卵磷脂、1-10%甘油(glycerin)以及水的用於注入的乳劑。在該等可被採用的可接受的載劑以及溶劑中是水、林格氏液、USP以及等張氯化鈉溶液(isotonic sodium chloride solution)。此外，無菌、不揮發油(fixed oils)是習知被採用作為一溶劑或懸浮介質(medium)。爲了這個目的，任何調和的不揮發油可被採用，包括合成的單-或二-甘油酯(mono- or diglycerides)。此外，脂肪酸[諸如油酸(oleic acid)]可被使用在可注射的製劑。

該等可注射的配方可被滅菌，例如，藉由經由一細菌-滯留的濾紙(bacterial-retaining filter)的過濾，或藉由併入呈無菌固體組成物(在使用前可被溶解或分散在無菌水或者其他無菌可注射的介質)的形式的滅菌劑。

依據本發明的額外的持續釋放可藉由使用一具有較差水溶解度的結晶體(crystalline)或非晶質材料(amorphous material)的液體懸浮液而被完成。該藥物的吸收速率繼而視它的溶解速率而定，該溶解速率依次可視晶體大小以及結晶體形式而定。另擇地，一非經腸道地投藥的藥物形式的延遲吸收是藉由溶解或懸浮該藥物於一油載劑中而被完成。可注射的蓄積形式是藉由形成該藥物的微囊封基質在生物可降解的(biodegradable)聚合物[諸如聚乳酸交酯-聚乙交酯(polylactide-polyglycolide)]中而被製造。視藥物對聚合物的比例以及所採用的特定聚合物的性質而定，藥物釋放的速率可被控制。其他生物可降解的聚合物的實例包括聚(原酯)[poly(orthoester)]以及聚(酐)[poly(anhydrides)]。蓄積可注射配方亦可藉由裹入該藥物於與身體組織相容的脂質體或微乳劑(其可)中而被製備。

在一個較佳具體例中，該配方提供一能夠將該前驅藥暴露於水減到最小的持續釋放輸送系統。這個可藉由配方該前驅藥與一持續釋放輸送系統而被完成，該系統是一能夠最小化水至基質內的擴散的聚合物基質。包含有該基質的適合的聚合物包括聚乳酸交酯(PLA)聚合物以及乳酸交酯/乙交酯(PLGA)共聚物(co-polymers)。

另擇地，該持續釋放輸送系統可包含有適合用於注射或口服輸送的聚陰離子(poly-anionic)分子或樹脂(resins)。適合的聚陰離子分子包括被配方以形成一難溶塊體(mass)的環糊精以及聚磺酸鹽，該難溶塊體將該前驅藥暴露於水減到最小並且該前驅藥自該難溶塊體緩慢地離開。

用於直腸的(rectal)或陰道的投藥的組成物較佳地是可藉由混合本發明的化合物與適合的非-刺激性的(non-irritating)賦形劑或載劑(諸如可可脂、聚乙二醇或一栓劑蠟)而被製備的栓劑(suppository)，該等栓劑在環境溫度(ambient temperature)下是固體但是在體溫下是液體並且因此在直腸或陰道腔中融化並且釋放該活性化合物。

用於口服投藥的固體劑型包括膠囊(capsules)、錠劑、丸劑(pills)、粉末(powders)以及細顆粒(granules)。在該等固體劑型中，該活性化合物被混合以至少一惰性的、藥學上可接受的賦形劑或載劑[諸如檸檬酸鈉(citrate sodium)或磷酸二鈣(dicalcium phosphate)]和/或：a)填充劑或增量劑(extenders)[諸如澱粉、乳糖、蔗糖、葡萄糖、甘露糖醇(mannitol)以及矽酸(silicic acid)]；b)黏合劑(binder)[諸如，例如，羧基甲基纖維素、藻酸鹽(alginates)、明膠、聚乙烯基吡咯啶酮(polyvinylpyrrolidinone)、蔗糖以及阿拉伯樹膠(acacia)]；c)保濕劑(humectant)(諸如，甘油)；d)崩解劑(disintegrating agents)[諸如瓊脂-瓊脂、碳酸鈣、馬鈴薯或樹薯澱粉(tapioca starch)、藻酸、特定的矽酸鹽(silicates)以及碳酸鈉]；e)溶液阻滯劑(solution retarding agents)[諸如石

蠟(paraffin)] ；f)吸收促進劑(absorption accelerators)[諸如四級銨化合物(quaternary ammonium compounds)]；g)潤濕劑[諸如，例如，鯨蠟醇(cetyl alcohol)以及單硬脂酸甘油酯(glycerol monostearate)]；h)吸收劑(absorbents)[諸如高嶺土(kaolin)以及膨土(bentonite clay)]；以及i)潤滑劑(諸如滑石、硬脂酸鈣、硬脂酸鎂、固體聚乙二醇、月桂基硫酸鈉)以及它們的混合物。在膠囊、錠劑以及丸劑的例子中，該劑型亦可包含有緩衝劑。

一相似類型的固體組成物亦可使用該等賦形劑[如乳糖或奶糖(milk sugar)以及高分子量聚乙二醇以及類似之物]而被採用作為在軟與硬-填充的明膠膠囊中的填充劑。

錠劑、糖衣錠(dragees)、膠囊、丸劑以及細顆粒的固體劑型可與包衣(coating)以及殼[諸如腸衣以及其他在藥學配方技藝中被熟知的包衣]而被製備。它們可選擇性地含有失透劑(opacifyimg agents)並且亦可以具有一組成物，它們只釋放活性成分(等)，或者較佳地在腸道(intestinal tract)的一特定部分選擇性地以一延遲的方式。可被使用的嵌埋的組成物(embedding compositions)的實例包括聚合的物質以及蠟。

用於一本發明的化合物的局部或穿皮的(transdermal)投藥的劑型包括軟膏(ointments)、糊(pastes)、乳膏(creams)、洗劑(lotions)、凝膠、粉末、溶液、噴霧、吸入劑(inhalants)或貼片(patches)。該活性組份在無菌條件下被混合以一藥學上可接受的載劑以及任何所需的防腐劑或如

可被需要的緩衝液。眼的配方(ophthalmic formulation)、耳朵藥水(ear drops)、眼睛軟膏(eye ointments)、粉末以及溶液亦可被預期在本發明的範疇內。

除了一本發明的活性化合物之外，該等軟膏、糊、乳膏以及凝膠可含有賦形劑，諸如動物以及植物脂肪、油、蠟、石蠟、澱粉、黃著、纖維素衍生物、聚乙二醇、聚矽氧(silicones)、膨土(bentonites)、矽酸、滑石以及氧化鋅(zinc oxide)或它們的混合物。

除了本發明的活性化合物之外，粉末以及噴霧可含有賦形劑，諸如乳糖、滑石、矽酸、氫氧化鋁、矽酸鈣(calcium silicates)以及聚醯胺粉末(polyamide powder)或這些物質的混合物。噴霧可另外含有慣常的推進劑(propellant)，諸如氯氟烴(chlorofluorohydrocarbon)。

穿皮的貼片具有提供經控制的輸送一化合物至身體的額外優點。該等劑型可藉由溶解或分散該化合物在該適當的介質中而被製造。吸收增強劑(absorption enhancers)亦可被使用以增加該化合物穿過皮膚的通量(flux)。該速率可藉由提供一速率控制膜或藉由分散該化合物於一聚合物基質或凝膠中而被控制。

關於肺的輸送(pulmonary delivery)，一本發明的治療組成物呈固體或液體微粒(particulate)的形式藉由直接投藥(例如吸入)至呼吸系統(respiratory system)而被配方以及投藥給病患。被製備用於實施本發明的該活性化合物的固體或液體微粒形式包括能呼吸的大小的顆粒(particles)：那

是，一小到足以在吸入時通過口以及喉(larynx)並且至肺的支氣管(bronchi)以及肺泡(alveoli)內的大小的顆粒。氣溶膠化的(aerosolized)治療劑(therapeutics)[特別地氣溶膠化的抗生素(antibiotics)]的輸送是本技藝中所知曉的(參見，例如授予VanDevanter等人的美國專利第5,767,068號、授予Smith等人的美國專利第5,508,269號以及Montgomery的WO 98/43650，它們全部在此被併入本案以作為參考資料)。一抗生素的肺輸送的討論亦在美國專利第6,014,969號(在此被併入本案以作為參考資料)中被發現。

一"治療有效量"的一本發明的前驅藥化合物意指一在一可應用於任何醫學治療的合理的益處/風險比例中提供一治療的效用在該被治療的個體上的化合物的數量。該治療效用可以是客觀的(亦即，藉由一些測試或指標而可測量的)或主觀的(亦即，個體給予一效用的指示或感受)。

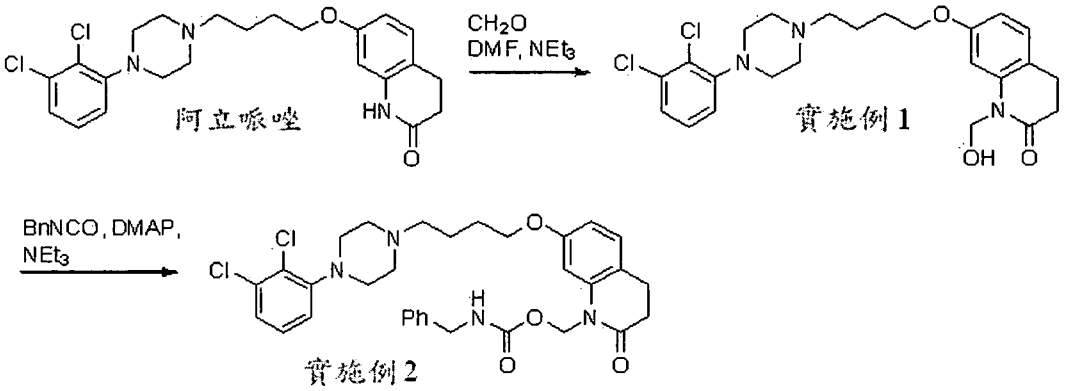
依據本發明，一本發明的前驅藥的治療有效量典型地根據該母體藥的標的治療量。關於給藥以及給藥的頻率的資訊可容易地用於本發明的前驅藥所衍生出自的許多母體藥，並且關於本發明的各個前驅藥的標的治療量可被計算。依據本發明，相同劑量的一本發明的前驅藥相較於該母體藥提供一更長的持續時間的治療效用。因此，若一單一劑量的該母體藥提供12小時的治療有效性(effectiveness)，提供比12小時更長的治療有效性的一依據本發明的相同母體藥的前驅藥將被認為達成一"持續釋放"。

一本發明的前驅藥的精確劑量視數種因子而定，該等因子包括該母體藥的性質與劑量以及被連結至該母體藥的該前驅藥部份的化學特性。最終地，一本發明的前驅藥的有效劑量以及給藥頻率會由主治醫生在聽診醫學判斷(sound medical judgment)的範疇內而被決定。用於任何特定病患的特定治療有效的劑量位準以及劑量頻率會視各種不同的因子而定，該等因子包括正被治療的疾患以及該疾患的嚴重性；所採用的特定化合物的活性；所採用的特定組成物；該病患的年齡、體重、一般健康、性別以及飲食；投藥的時間、投藥的途徑以及該所採用的特定化合物的排出的速率；治療的持續時間；被使用在與所採用的該特定的結合或同時地的藥物；以及在醫學技藝中被熟知的類似因子。

實施例

本發明的化合物以及方法參照下列的實施例將被更加瞭解，該等實施例僅被意欲作為一例示說明而不限制本發明的範疇。關於揭示的具體例的各種不同的改變以及修飾對於那些熟習此技藝者將是明顯的，並且該等改變以及修飾[包括(沒有限制)那些有關於本發明的化學結構、取代基、衍生物、配方和/或方法者]可被製造而沒有背離本發明的精神以及隨文檢附的申請專利範圍的範疇。用於內醯胺化合物的製備的一般方法可在下列的刊物中被發現：美國專利第7,160,888號；美國專利第5,462,934號；美國專利第4,914,094號；美國專利第4,234,584號；美國專利第4,514,401

號；美國專利第5,462,934號；美國專利第4,468,402號；WO 2006/090273 A2；WO 2008/150848 A1；WO 2006/112464 A1；WO 2008/132600 A1。



7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-1-(羥基甲基)-3,4-二氫喹啉-2(1H)-酮[7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-1-(hydroxymethyl)-3,4-dihydroquinolin-2(1H)-one]的製備(實施例1：化合物A1)

阿立哌唑(20g, 45 mmol)、三乙基胺(1mL, 7.1 mmol)、甲醛(37%水性溶液，70 mL)以及二甲基甲醯胺(200 mL)的一混合物被加熱至80℃歷時20小時。該反應混合物被冷卻、以乙酸乙酯(400 mL)予以稀釋以及以水/鹽水(1:1，3 × 500 mL)予以清洗。有機相於$MgSO_4$上予以乾燥、予以過濾並且在真空下予以蒸發至乾燥俾以得到有如一白色固體的半縮醛胺(hemi-aminal) **A1** (18.6 g，含有25%阿立哌唑，65%產率根據**A1**)。

^{1}H NMR ($CDCl_3$, 300MHz)複雜混合的訊號起因於具有阿立哌唑的污染，主要信號δ 5.34 (s, 2H, $OHCH_2N$); m/z

(M^+H) 478以及480。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基苄基胺甲酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl benzylcarbamate](實施例2：化合物28)

加入異氰酸苄酯(benzylisocyanate)(1.03 mL, 8.3 mmol)至一配於二氯甲烷(30 mL)中的來自實施例1的半縮醛胺**A1**(4 g, 8.4 mmol)、4-二甲基胺基吡啶(0.15g, 1.3 mmol)以及三乙基胺(1.1 mL, 7.5 mmol)的溶液，並且該反應混合物被攪拌歷時24小時。該反應混合物繼而在35℃下被加熱歷時20小時，予以冷卻並且以水/鹽水(1:1，50 mL)予以清洗。有機相於$MgSO_4$上予以乾燥、予以過濾並且在真空下予以蒸發至乾燥。殘餘物藉由在矽石(silica)上以乙酸乙酯/二氯甲烷/甲醇(1：1：0.1)洗提的層析法(chromatography)而被進一步純化俾以得到有如一灰白色泡沫的所欲產物(530 mg，14%產率)。^1H NMR ($CDCl_3$, 300 MHz) δ 1.58-1.88 (m, 4H), 2.48 (t, 2H), 2.60-2.72 (m, 6H), 2.85 (m, 2H), 300-3.12 (m, 4H), 3.96 (t, 2H), 4.40 (d, 2H), 5.13 (NH), 5.96 (s, 2H), 6.58 (dd, 1H), 6.79 (d, 1H), 6.92-6.98 (m, 1H), 7.04 (d, 1H), 7.12-7.16 (m, 1H), 7.23-7.35 (m, 6H)；m/z (M^+H) 611.12以及613.10。

下列的化合物以一類似於實施例2的方式而被製備。

7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫

喹啉-1(2H)-基)甲基乙基碳酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl ethyl carbonate](實施例3：化合物79)

該所欲的產物被分離出有如一黃色的油(830 mg，24%產率)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 1.78 (t, 3H), 1.52-1.61 (m, 2H), 1.63-1.76 (m, 2H), 2.31-2.40 (m, 2H), 2.40-2.60 (m, 6H), 2.73-2.80 (m, 2H), 2.91-2.99 (m, 4H), 3.96 (t, 3H), 4.11 (q, 2H), 5.87(s, 2H), 6.60-6.70 (m, 2H), 7.07-7.12 (m, 2H), 7.24-7.30 (m, 2H)；m/z (M^+H) 550.48以及552.40。

丁基(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基碳酸酯[butyl (7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl carbonate](實施例4：化合物80)

該所欲的產物被分離出有如一黃色的油(750 mg，21%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H), 1.33-1.45 (m, 2H), 1.59-1.80 (m, 4H), 1.80-1.92 (m, 2H), 2.49 (t, 2H), 2.58-2.75 (m, 6H), 2.85 (t, 2H), 3.00-3.13 (m, 4H), 3.98 (t, 2H), 4.18 (t, 2H), 5.92 (s, 2H), 6.58 (dd, 1H), 6.67 (d, 1H), 6.92-6.99 (m, 1H), 7.03 (dd, 1H), 7.10-7.20 (m, 2H)；m/z (M^+H) 578.10以及580.08。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫

喹啉-1(2H)-基)甲基己基碳酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl hexyl carbonate](實施例5：化合物81)

該所欲的產物被分離出有如一黃色的油(1.77 g，62%產率)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.80 (t, 3H), 1.15-1.30 (m, 6H), 1.50-1.60 (m, 4H), 1.65-1.73 (m, 2H), 2.35 (t, 2H), 2.41-2.60 (m, 6H), 2.78 (t, 2H), 2.88-3.00 (m, 4H), 3.95 (t, 2H), 4.06 (t, 2H), 5.86 (s, 2H), 6.60-6.70 (m, 2H), 7.05-7.15 (m, 2H), 7.22-7.28 (m 2H)；m/z (M^+H) 606.15以及608.15。

癸基(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基碳酸酯[decyl (7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl carbonate](實施例6：化合物82)

該所欲的產物被分離出有如一黃色的油(1.42 g，46%產率)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.79 (m, 3H), 1.13-1.30 (m, 14H), 1.48-1.60 (m, 4H), 1.65-1.75 (m, 2H), 2.33 (t, 2H), 2.41-2.60 (m, 6H), 2.72-2.80 (m, 2H), 2.89-2.98 (m, 4H), 3.95 (t, 2H), 4.05 (t, 2H), 5.86 (s, 2H), 6.60-6.70 (m, 2H), 7.05-7.13 (m, 2H), 7.22-7.28 (m, 2H)；m/z (M^+H) 662.56以及664.54。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫

喹啉-1(2H)-基)甲基十六基碳酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl hexadecyl carbonate](實施例7：化合物83)

該所欲的產物被分離出有如一黃色的油(1.55 g，44%產率)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.80 (t, 3H), 1.10-1.29 (m, 26H), 1.49-1.60 (m, 4H), 1.65-1.75 (m, 2H), 2.33 (t, 2H), 2.43-2.55 (m, 6H), 2.78 (t, 2H), 2.90-2.95 (m, 4H), 3.95 (t, 2H), 4.05 (t, 2H), 5.84 (s, 2H), 6.60-6.68 (m, 2H), 7.05-7.12 (m, 2H), 7.24-7.29 (m, 2H)；m/z $(M-C_{10}H_{20})^+$ 606.52以及608.54。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基嗎福啉-4-羧酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl morpholine-4-carboxylate](實施例8：化合物49)

該所欲的產物被分離出有如一黃色的油(1.52 g，55%產率)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 1.50-1.75 (m, 4H), 2.35 (t, 2H), 2.42-2.61 (m, 6H), 2.70-2.82 (m, 2H), 2.88-3.00 (m, 4H), 3.26-3.40 (m, 4H), 3.40-3.60 (m, 4H), 3.94 (t, 2H), 5.81 (s, 2H), 6.61 (dd, 1H), 6.68 (d, 1H), 7.05-7.13 (m, 2H), 7.20-7.30 (m, 2H)；m/z (M^+H) 591.11以及593.15。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基二乙基胺甲酸酯

[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl diethylcarbamate](實施例9：化合物84)

該所欲的產物被分離出有如一黃色的油(0.83 g，31%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00-1.20 (m, 6H), 1.65-1.88 (m, 4H), 2.45-2.52 (m, 2H), 2.58-2.83 (m, 6H), 2.82-2.90 (m, 2H), 3.00-3.12 (m, 4H), 3.18-3.38 (m, 4H), 3.97 (t, 2H), 5.91 (s, 2H), 6.58 (dd, 1H), 6.77 (d, 1H), 6.94-6.98 (m, 1H), 7.06 (d, 1H), 7.15-7.20 (m, 2H)；m/z (M^+H) 577.48以及579.46。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基異戊基碳酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl isopentyl carbonate](實施例10：化合物85)

加入一配於四氫呋喃(50 mL)中的3-甲基-1-丁醇的溶液(1.7 mL, 15.7 mmol)至一配於四氫呋喃(100 mL)中的光氣(phosgene)(20%配於甲苯中，54 mL，110 mmol)的溶液超過1小時。在4小時之後，揮發物在真空下被移除並且殘餘物被加入至一配於二氯甲烷(30 mL)中的半縮醛胺**A1**(3 g, 4.7 mmol)、4-二甲基胺基吡啶(0.3g, 1.9 mmol)、吡啶(10 mL)以及三乙基胺(1.3 mL, 9.4 mmol)的溶液。在予以攪拌歷時72小時之後，反應混合物以乙酸乙酯(100 mL)予以稀釋並且以5%水性$NaHCO_3$/鹽水(1:1, 100 mL)予以清洗。有機相

於$MgSO_4$上予以乾燥、予以過濾並且在真空下予以蒸發。殘餘物藉由在矽石上以乙酸乙酯/二氯甲烷/甲醇(1：1：0.1)洗提的層析法而被進一步純化俾以得到有如一黃色油的所欲產物(1.54 g，55%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90-1.95 (m, 6H), 1.50-1.60 (m, 4H), 1.65-1.79 (m, 2H), 1.79-1.89 (m, 2H), 2.50 (t, 2H), 2.60-2.72 (m, 6H), 2.82-2.90 (m, 2H), 3.02-3.11 (m, 4H), 3.98 (t, 2H), 4.21 (t, 2H), 5.92 (s, 2H), 6.56 (dd, 1H), 6.67 (d, 1H), 6.95-7.00 (m, 1H), 7.05 (d, 1H), 7.13-7.19 (m, 2H)；m/z (M^+H) 592.48以及594.46。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基乙酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl acetate](實施例11：化合物1)



一配於無水四氫呋喃(THF, 80 mL)中的來自實施例1的化合物-A1(50.63 g, 0.150mol)的溶液被處理以乙酸酐(15.3 mL, 0.16 mol)並且在60°C下(油浴)予以加熱歷時2.0小時。加入三甲基胺(2.0 mL, 0.014 mol)至上面的溶液，並且在60°C下予以攪拌歷時16小時。溶劑使用一旋轉式蒸發器(rotator evaporator)而被移除。加入乙酸乙酯(150 mL)以及庚烷(50 mL)至所形成的粗混合物。該溶液以$NaHCO_3$(5%水

性溶液, 250 mL)予以清洗。在分開兩層之後，水性層的pH值被調整至超過7。該水性層使用有機混合物被進一步萃取。有機層被分開並且以5% $NaHCO_3$溶液、繼而去離子水以及鹽水予以清洗。該溶液使用無水$MgSO_4$予以乾燥、予以過濾並且在真空下予以蒸發。所形成的產物使用矽膠管柱層析法[使用乙醇：乙酸乙酯(5：95)作為洗提液]而被純化。含有所欲的產物的分離部分(fraction)被合併並且加入d-酒石酸(d-tartaric acid)[12.5 g 被溶解於乙醇：水(60：5)中]，導致該所欲的化合物(48.78 g，89%產率)的沉澱。^1H NMR ($CDCl_3$, 300 MHz) δ 1.73 (m, 2H), 1.84 (m, 2H), 2.12 (s, 3H), 2.50 (t, 2H), 2.68 (m, 6H), 2.87 (dd, 2H), 3.08 (m, 4H), 3.98 (t, 2H), 5.91 (s, 2H), 6.59 (m, 2H), 6.96 (dd, 1H), 7.08 (dd, 1H), 7.15 (m, 2H)。

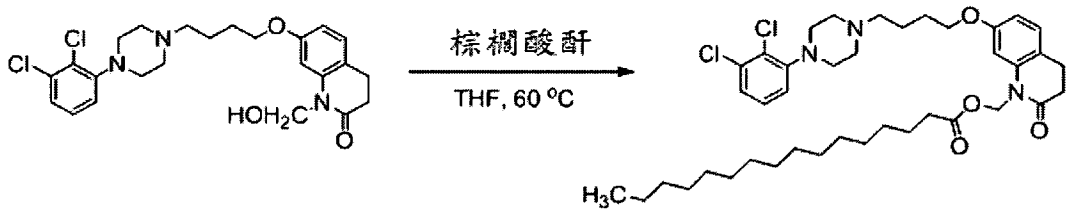
下列的化合物以一類似於實施例11的方式而被製備。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基十二酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl dodecanoate](實施例12：化合物7)

該所欲的產物被分離出有如一結晶固體(0.3 g，21%產率)。分子量由質譜儀分析所確認。第2至6圖顯示該所欲的產物的PXRD、IR、拉曼、TGA光譜。^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H), 1.24 (m, 16H), 1.62 (m, 2H), 1.83 (m, 2H), 1.86 (m, 2H), 2.36 (t, 2H), 2.49 (t, 2H), 2.68 (m, 6H),

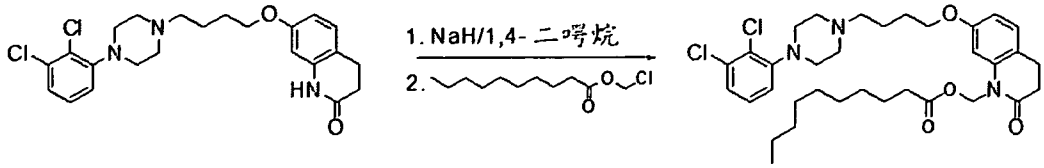
2.86 (dd, 2H), 3.08 (m, 4H), 3.97 (t, 2H), 5.91 (s, 2H), 6.59 (m, 2H), 6.96 (dd, 1H), 7.07 (dd, 1H), 7.14 (m, 2H)。關於化合物7的進一步特性(PXRD、IR、拉曼、TGA以及DSC光譜)請參見第1至5圖。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基棕櫚酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl palmitate](實施例13：化合物10)



該所欲的產物被分離出有如一結晶固體(4.2 g，70%產率)。分子量(716.6)由質譜儀分析所確認。^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H),1.25 (m, 24 H), 1.64 (m, 2H), 1.72 (m, 2H), 1.84 (m, 2H), 2.36 (t, 2H), 2.49 (t, 2H), 2.68 (m, 6H), 2.86 (dd, 2H), 3.08 (m, 4H), 3.97 (t, 2H), 5.92 (br s, 2H), 6.59 (dd, 1H), 6.60 (s, 1H), 6.96 (dd, 1H), 7.07 (d, 1H), 7.14 (m, 2H)。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基癸酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl decanoate](實施例14：化合物6)



上面的氯甲基酯於4 Å分子篩上予以乾燥。一配於1,4-二㗁烷(800 mL)中的阿立哌唑(45公克，0.1 mol)的溶液被超音波處理(sonicate)俾以完全地溶解阿立哌唑，並且接而以NaH [38 g，0.95 mol，60%分散液(dispersion)]予以處理一部份。在室溫下攪拌這個反應混合物歷時15分鐘之後，該反應混合物被逐滴地處理以氯甲基酯(0.3 mol.)以及一催化量(catalytic amount)的碘化鈉(0.05 mol.)。所形成的混濁混合物被加熱至90℃歷時2小時，予以冷卻至環境溫度並且被倒入至水中。該產物以乙酸乙酯予以萃取，並且合併的乙酸乙酯層以鹽水予以清洗、於硫酸鈉上予以乾燥、予以過濾以及在減壓下予以濃縮。在矽膠上的管柱層析法提供該所欲的產物(12.5公克，70%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H), 1.20 (m, 12H), 1.63 (m, 2H), 1.70 (m, 2H), 1.83 (m, 2H), 2.35 (t, 2H), 2.50 (t, 2H), 2.68 (m, 6H), 2.86 (t, 2H), 3.08 (m, 4H), 3.97 (t, 2H), 5.92 (s, 2H), 6.58 (dd, 1H), 6.61 (d, 1H), 6.94 (dd, 1H), 7.06 (d, 1H), 7.14-7.17 (m, 2H)；m/z (M^+H) 632.88。

下列的化合物(實施例15-29)是以一類似於實施例2的方式而被製備：

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基苯甲酸酯

[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl benzoate](實施例15：化合物31)

該所欲的產物被分離出有如一黃色的油。^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60-1.85 (m, 4H), 2.45 (t, 2H), 2.55-2.70 (m, 4H), 2.70-2.78 (m, 2H), 2.85-2.92 (m, 2H), 3.00-3.10 (m, 4H), 3.94 (t, 2H), 6.16 (s, 2H), 6.60 (d, 1H), 6.72 (dd, 1H), 6.90-6.95 (m, 1H), 7.05-7.18 (m, 2H), 7.35-7.42 (m, 2H), 7.52-7.60 (m, 1H), 8.00-8.08 (m, 2H)。m/z (M^+H) 582.3。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基丁酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl butyrate](實施例16：化合物2)

該所欲的產物藉由在矽石上以乙酸乙酯/二氯甲烷/甲醇(1：1：0.1)洗提的層析法而被分離俾以得到一黃色的油(2.0 g，87%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H), 1.60-1.90 (m, 6H), 2.34 (t, 2H), 2.51 (t, 2H), 2.61-2.73 (m, 6H), 2.82-2.90 (m, 2H), 3.02-3.12 (m, 4H), 3.96 (t, 2H), 5.91 (s, 1H), 6.55-6.61 (m, 2H), 6.93-6.98 (m, 1H), 7.05 (d, 1H), 7.11-7.18 (m, 2H)。m/z (M^+H) 548.2以及550.2。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基己酸酯

[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl hexanoate](實施例17：化合物4)

該所欲的產物被分離有如一黃色的油(3.69 g，87%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H), 1.11-1.28 (m, 4H), 1.40-1.78 (m, 6H), 2.20-2.40 (m, 4H), 2.40-2.60 (m, 6H), 2.73-2.81 (m, 2H), 2.85-3.00 (m, 4H), 3.88-4.00 (m, 2H), 5.75-5.83 (m, 2H), 6.55-6.62 (m, 2H), 7.03-7.12 (m, 2H), 7.20-7.26 (m, 2H)。m/z (M^+H) 576.4以及578.4。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基十四酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl tetradecanoate](實施例18：化合物8)

該所欲的產物被分離出有如一淡黃色的油(5.3 g，74%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H), 1.07-1.37 (m, 22H), 1.55-1.70 (m, 2H), 1.70-1.90 (m, 4H), 2.34 (t, 2H), 2.53 (t, 2H), 2.65-2.78 (m, 6H), 2.82-2.90 (m, 2H), 3.02-3.12 (m, 4H), 3.96 (t, 2H), 5.91 (s, 2H), 6.55-6.62 (m, 2H), 6.92-6.98 (m, 1H), 7.05 (d, 1H), 7.11-7.18 (m, 2H)。m/z (M^+H) 688.4以及690.4。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基辛酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo

-3,4-dihydroquinolin-1(2H)-yl)methyl octanoate](實施例19：化合物5)

該所欲的產物被分離出有如一黃色的油(2.2 g，87%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, 3H), 1.15-1.35 (m, 10H, 1.55-1.87 (m, 6H), 2.34 (t, 2H), 2.53 (t, 2H), 2.65-2.73 (m, 4H), 2.85 (dd, 2H), 3.01-3.11 (m, 4H), 3.95 (t, 2H), 5.85-5.92 (m, 2H), 2.53-2.60 (m, 2H), 6.91-6.97 (m, 1H), 7.05 (d, 1H), 7.10-7.16 (m, 2H)。m/z (M^+H) 604.3以及606.3。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基異丙基碳酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl isopropyl carbonate](實施例20：化合物48)

該所欲的產物被分離出有如一橘色的油(2.4 g，68%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (d, 6H), 1.62-1.77 (m, 2H), 1.77-1.89 (m, 2H), 2.48 (t, 2H), 2.60-2.71 (m, 6H), 2.81-2.90 (m, 2H), 3.01-3.11 (m, 4H), 3.98 (t, 2H), 4.89-4.97 (m, 1H), 5.92 (s, 2H), 6.57 (d, 1H), 6.68 (d, 1H), 6.91-7.00 (m, 1H), 7.05 (dd, 1H), 7.11-7.18 (m, 2H)。m/z (M^+H) 564.3以及566.3。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基甲基胺甲酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl methylcarbamate]

(實施例21：化合物47)

該所欲的產物被分離出有如一黃色的油(1.3 g，52%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68-1.88 (m, 4H), 2.49 (dd, 2H), 2.60-2.73 (m, 6H), 2.80-2.90 (m, 5H), 3.02-3.12 (m, 4H), 3.95-4.02 (m, 2H), 5.90 (s, 2H), 6.57 (d, 1H), 6.77 (d, 1H), 6.93-6.70 (m, 1H), 7.05 (d, 1H), 7.10-7.19 (m, 2H)。m/z (M^+H) 535.5以及537.5。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基癸基胺甲酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl decylcarbamate](實施例22：化合物46)

該所欲的產物被分離出有如一黃色的油(0.50 g，14%產率)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H), 1.18-1.35 (m, 16H), 1.42-1.53 (m, 2H), 1.67-1.79 (m, 2H), 1.79-1.87 (m, 2H), 2.48 (t, 2H), 2.58-2.72 (m, 4H), 2.80-2.90 (m, 2H), 3.01-3.12 (m, 4H), 3.15-3.22 (m, 2H), 3.98 (t, 2H), 4.78 (NH), 5.90 (s, 2H), 6.58 (d, 1H), 6.78 (d, 1H), 6.93-7.00 (m, 1H), 7.04 (d, 1H), 7.10-7.16 (m, 2H)。m/z (M^+H) 661.6以及663.6。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基異丁酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl isobutyrate](實施例

23：化合物32)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, 6H), 1.68-1.88 (m, 4H), 2.45-2.73 (m, 9H), 2.87 (dd, 2H), 3.03-3.12 (m, 2H), 3.95 (t, 2H), 5.91 (s, 2H), 6.55-6.60 (m, 2H), 6.93-6.97 (m, 1H), 7.04-7.09 (m, 1H), 7.12-7.19 (m, 2H)。m/z (M^+H) 548.15。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基環戊烷羧酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl cyclopentanecarboxylate](實施例24：化合物33)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47-1.93 (m, 13H), 2.50-2.60 (m, 2H), 2.60-2.90 (m, 8H), 3.02-3.15 (m, 4H), 3.95 (t, 2H), 5.89 (s, 2H), 6.50-6.60 (m, 2H), 6.90-6.95 (m, 1H), 7.02-7.07 (m, 1H), 7.10-7.19 (m, 2H)。m/z (M^+H) 574.15。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基環丁烷羧酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl cyclobutanecarboxylate](實施例25：化合物34)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82-1.91 (m, 3H), 1.22-1.30 (m, 2H), 1.75-2.05 (m, 6H), 2.05-2.40 (m, 6H), 2.68-2.73 (m, 2H), 2.84-2.90 (m, 2H), 3.06-3.22 (m, 4H), 3.96 (t, 2H), 5.91 (s, 2H), 6.55-6.59 (m, 2H), 6.97 (dd, 1H), 7.07 (d, 1H),

7.12-7.18 (m, 2H)。m/z (M^+H) 560.19。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基環己烷羧酸酯

[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl cyclohexanecarboxylate](實施例26：化合物35)

^1H NMR ($CDCl_3$, 300 MHz) δ 1.15-1.35 (m, 3H), 1.35-1.55 (m, 2H), 1.55-1.95 (m, 10H), 2.21-2.40 (m, 1H), 2.52-2.60 (m, 1H), 2.62-3.00 (m, 8H), 3.02-3.12 (m, 4H), 3.95 (t, 2H), 5.89 (s, 2H), 6.50-6.60 (m, 2H), 6.93-6.97 (m, 1H), 7.02-7.06 (m, 1H), 7.10-7.15 (m, 2H)。m/z (M^+H) 588.24。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基2-(2-甲氧基乙氧基)乙酸酯

[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl 2-(2-methoxyethoxy)acetate](實施例27：化合物40)

^1H NMR ($CDCl_3$, 300 MHz) δ 1.56-1.90 (m, 6H), 2.43-2.55 (m, 2H), 2.55-2.80 (m, 4H), 2.81-2.90 (m, 2H), 3.37 (s, 3H), 3.55-3.61 (m, 2H), 3.72-3.79 (m, 2H), 4.20 (s, 2H), 5.97 (s, 2H), 6.55-6.59 (m, 2H), 6.91-6.98 (m, 1H), 7.09 (d, 1H), 7.11-7.15 (m, 2H)。m/z (M^+H) 594.17。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基2-(2-(2-甲氧基乙氧基)乙氧基)乙酸酯

[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo

-3,4-dihydroquinolin-1(2H)-yl)methyl 2-(2-(2-methoxyethoxy)ethoxy)acetate](實施例28：化合物41)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65-1.93 (m, 6H), 2.49-2.60 (m, 2H), 2.61-2.77 (m, 4H), 2.81-2.90 (m, 2H), 3.02-3.20 (m, 4H), 3.36 (s, 3H), 3.51-3.57 (m, 2H), 3.60-3.70 (m, 4H), 3.72-3.78 (m, 2H), 3.92-3.99 (m, 2H), 4.20 (s, 2H), 5.97 (s, 2H), 6.55-6.59 (m, 2H), 6.95-6.99 (m, 1H), 7.05-7.09 (m, 1H), 7.11-7.18 (m, 2H)。m/z (M^+H) 638.30。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基三甲基乙酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl pivalate](實施例29：化合物42)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 9H), 1.65-1.88 (m, 4H), 2.45-2.55 (m, 2H), 2.60-2.73 (m, 6H), 2.82-2.91 (m, 2H), 3.02-3.13 (m, 4H), 3.95 (t, 2H), 5.89 (s, 2H), 6.54-6.60 (m, 2H), 6.92-6.99 (m, 1H), 7.06 (d, 1H), 7.13-7.17 (m, 2H)；m/z (M^+H) 562.39。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基2-羥基乙基胺甲酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl 2-hydroxyethylcarbamate](實施例30：化合物36)

2-(((7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲氧基)羰基胺基)乙基甲基丙烯酸酯(2.0 g)以一類似於實施例2的方法而被合成。這個在室溫下與16% NH_3/MeOH反應歷時18小時並且接而在40℃下被濃縮。殘餘物藉由以1：1：0.1至1：1：0.2的DCM/EtOAc/MeOH洗提的矽石層析法而被純化。所形成的黃色的油從EtOAc/庚烷中被再結晶俾以得到有如一白色固體的標題化合物(1.2 g，67%)。

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60-1.88 (m, 4H), 2.40-2.50 (m, 2H), 2.50-2.75 (m, 6H), 2.75-2.89 (m, 2H), 2.95-3.15 (m, 4H), 3.20-3.40 (m, 2H), 2.58-3.78 (m, 2H), 3.89-4.05 (m, 2H), 5.30-5.45 (m, NH), 5.91 (s, 2H), 6.55 (dd, 1H), 6.73 (d, 1H), 6.91-6.96 (m, 1H), 6.98-7.03 (m, 1H), 7.04-7.18 (m, 2H)。m/z (M^+H) 565.16。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基雙(2-羥基乙基)胺甲酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl bis(2-hydroxyethyl)carbamate](實施例31：化合物37)

在室溫下加入吡啶(0.68 mL)、繼而*p*-硝基苯基氯甲酸酯(1.27 g, 0.0063 mol)至一配於二氯甲烷(30 mL)中的半縮醛胺A1(2g, 0.0042 mol)的溶液。在90分鐘之後，二乙醇胺(3.5 g, 0.0334 mol)以及三乙基胺(1.2 mL, 0.084 mol)被加入。在3小時之後，反應物以二氯甲烷予以稀釋並且以飽合

的$NaHCO_3$予以清洗、於$MgSO_4$上予以乾燥以及予以蒸發。殘餘物在矽石上以1：1：0.1至1：1：0.2的DCM/EtOAc/MeOH洗提而被純化俾以得到有如一無色膠的標題化合物(0.83 g，33%)。

^1H NMR ($CDCl_3$, 300 MHz) δ 1.70-1.82 (m, 4H), 2.42-2.52 (m, 2H), 2.59-2.79 (m, 6H), 2.80-2.90 (m, 2H), 3.00-3.12 (m, 4H), 3.40-3.48 (m, 2H), 3.50-3.58 (m, 2H), 3.61-3.70 (m, 2H), 3.85-3.90 (m, 2H), 3.99-4.06 (m, 2H), 5.90 (m, 2H), 6.57 (d, 1H), 6.70 (dd, 1H), 6.92-6.98 (m, 1H), 7.07 (d, 1H), 7.10-7.20 (m, 2H)。m/z (M^+H) 609.21。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基4-甲基哌啡-1-羧酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl 4-methylpiperazine-1-carboxylate](實施例32：化合物38)

化合物141是以一類似於實施例28的方法而被合成。

^1H NMR ($CDCl_3$, 300 MHz) δ 1.68-1.88 (m, 4H), 2.25-2.42 (m, 7H), 2.45-2.55 (m, 2H), 2.61-2.76 (m, 6H), 2.85 (dd, 2H), 3.02-3.16 (m, 4H), 3.40-3.60 (m, 4H), 3.97 (t, 2H), 5,92 (s, 2H), 6.59 (d, 1H), 6.74 (d, 1H), 6.92-6.98 (m, 1H), 7.02-7.07 (m, 1H), 7.10-7.16 (m, 2H)。m/z (M^+H) 604.24。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基1,4'-二哌啶-1'-羧酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo

-3,4-dihydroquinolin-1(2H)-yl)methyl 1,4'-bipiperidine-1'-carboxylate](實施例33：化合物39)

化合物142是以一類似於實施例28的方法而被合成。^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26-2.06 (m, 14H), 2.31-2.91 (m, 17H), 2.95-3.18 (m, 4H), 3.97 (t, 2H), 4.0-4.37 (m, 2H), 5.91 (s, 2H), 6.58 (dd, 1H), 6.74 (d, 1H), 6.90-6.99 (m, 1H), 7.05 (d, 1H), 7.11-7.18 (m, 2H)；m/z (M^+H) 672.25。

7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-1-(甲氧基甲基)-3,4-二氫喹啉-2(1H)-酮[7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-1-(methoxymethyl)-3,4-dihydroquinolin-2(1H)-one](實施例34，化合物100)

加入亞硫醯氯(thionyl chloride)(1.5 mL, 12.6 mmol)至一配於二氯甲烷(20 mL)中的半縮醛胺A1的混合物(2.0 g, 4.2 mmol)，並且在室溫下予以攪拌歷時2小時。加入甲醇(10 mL)至反應混合物並且予以攪拌一另外的2小時。該反應物被倒入至$NaHCO_3$(aq)內並且以二氯甲烷予以萃取。有機相於$MgSO_4$上予以乾燥、予以蒸發並且殘餘物在矽石上以1：1：0.1的二氯甲烷/乙酸乙酯/甲醇洗提而被純化俾以得到有如一乳膏固體(cream solid)的標題化合物(1.3 g, 63%)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65-1.83 (m, 4H), 2.47 (t, 2H), 2.58-2.70 (m, 6H), 2.82 (dd, 2H), 2.99-3.01 (m, 4H), 3.38 (s, 3H), 3.96 (t, 2H), 5.27 (s, 2H), 6.55 (dd, 1H), 6.88 (dd, 1H), 6.91-6.96 (m, 1H), 7.03 (d, 1H), 7.08-7.15 (m, 2H)。m/z

(M^+H) 492.05。

1-(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)-2-乙氧基-2側氧乙基癸酸酯[1-(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)-2-ethoxy-2-oxoethyl decanoate](實施例35：化合物111)

阿立哌唑(2.0 g, 4.5 mmol)、乙醛酸乙酯(ethyl glyoxylate)(50%溶液配於甲苯中，2.7 mL)、K_2CO_3 (0.49 g, 3.6 mmol)、溴化四丁基銨(tetrabutylammonium bromide)(0.57 g, 1.8 mmol)以及二氯甲烷(20 mL)的一混合物在迴流(reflux)下被加熱歷時4小時。該反應混合物被冷卻並且迅速地以水予以清洗，於$MgSO_4$上予以乾燥並且予以過濾。所形成的溶液被處理以吡啶(1.8 mL, 22.2 mmol)以及繼而癸醯氯(decanoylchloride)(4.6 mL, 22.2 mmol)。在被攪拌歷時3小時之後，甲醇(1 mL)被加入並且被攪拌一另外的10分鐘。該反應混合物以飽和的$NaHCO_3$ (aq)予以清洗、於$MgSO_4$上予以乾燥、予以過濾並且予以蒸發。殘餘物在矽石上以1：1：0.1的二氯甲烷/乙酸乙酯/甲醇洗提而被純化俾以得到有如一黃色的油的標題化合物(1.2 g, 38%)。

^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H), 1.11 (t, 3H), 1.05-1.40 (m, 12H), 1.59-1.75 (m, 2H), 1.75-1.98 (m, 4H), 2.40-2.54 (m, 2H), 2.60-3.07 (m, 10H), 3.15-3.32 (m, 4H), 3.89-3.99 (m, 2H), 4.09-4.21 (m, 2H), 6.57 (dd, 1H), 6.67 (d, 1H), 6.95-7.00 (m, 1H), 7.08 (dd, 1H), 7.12-7.20 (m, 2H),

7.27-7.32 (m, 1H)。m/z (M^+H) 704.38。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基4-乙醯胺基丁酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl 4-acetamidobutanoate](實施例36：化合物44)

加入三乙基胺(2.3 mL, 16.4 mmol)至一配於二氯甲烷(30 mL)中的半縮醛胺A1 (2.6 g, 5.5 mmol)的 懸浮液，繼而加入甲磺醯氯(0.47 g, 6.0 mmol)超過3分鐘。該反應混合物被攪拌歷時25分鐘並且接而N-乙醯基-4-胺基丁酸(N-acetyl-4-aminobutyric acid)(1.6g, 10.1 mmol)被加入。該反應混合物接而在迴流下被加熱歷時18小時，予以冷卻並且以飽和的$NaHCO_3$ (aq)予以清洗。有機相於$MgSO_4$上予以乾燥、予以過濾並且予以蒸發。殘餘物進一步在矽石上以1：1：0.1至1：1：0.2的二氯甲烷/乙酸乙酯/甲醇洗提而被純化俾以得到有如一灰白色固體的標題化合物(1.1 g, 34%)。

^1H NMR ($CDCl_3$, 300 MHz) δ 1.70-1.80 (m, 2H), 1.80-1.90 (m, 4H), 1.97 (s, 3H), 2.41 (t, 2H), 2.50-2.57 (m, 2H), 2.60-2.75 (m, 6H), 2.83-2.88 (m, 2H), 3.03-3.12 (m, 4H), 3.24-3.32 (m, 2H), 3.95-4.00 (m, 2H), 5.85-5.92 (m, 3H), 6.58 (d, 2H), 6.92-6.96 (m, 1H), 7.05 (d, 1H), 7.12-7.16 (m, 2H).)。m/z (M^+H) 605.08。

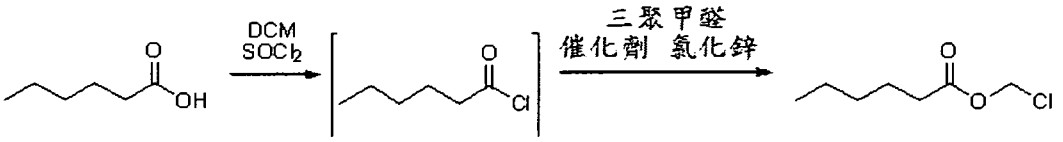
(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫

喹啉-1(2H)-基)甲基4-辛醯胺基丁酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl 4-octanamidobutanoate](實施例37：化合物45)

化合物149 (1.4 g)是以一類似於化合物148的方法而被純化。

^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.79 (t, 3H), 1.10-1.28 (m, 8H), 1.38-1.48 (m, 2H), 1.50-1.77 (m, 6H), 1.93-2.00 (m, 2H), 2.25-2.40 (m, 4H), 2.40-2.60 (m, 6H), 2.72-2.81 (m, 2H), 2.87-3.02 (m, 6H), 3.90-4.00 (m, 2H), 5.82 (s, 2H), 6.58-6.63 (m, 2H), 7.04-7.02 (m, 2H), 7.20-7.30 (m, 2H)。m/z (M^+H) 689.47。

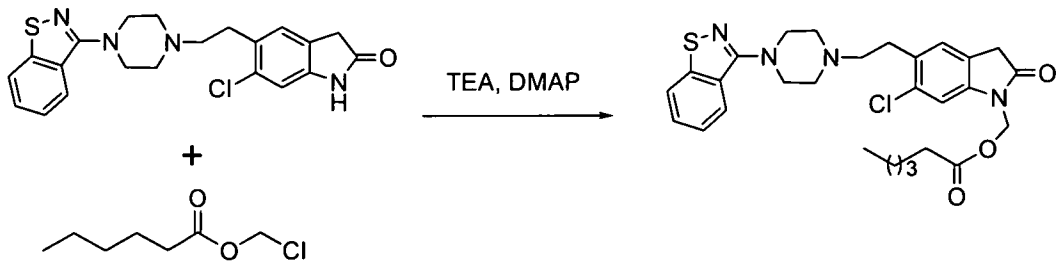
(5-(2-(4-(苯并[d]異噻唑-3-基)哌啡-1-基)乙基)-6-氯-2-側氧吲哚啉-1-基)甲基己酸酯[(5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloro-2-oxoindolin-1-yl)methyl hexanoate](實施例38：化合物322)



步驟1：亞硫醯氯(12.31 g, 103 mmol)繼而催化量的N,N-二甲基甲醯胺(DMF, 0.1 mL)在25-30°C下被加入至一配於二氯甲烷(DCM, 100 mL)中的己酸(hexanoic acid)(10 g, 86 mmol)的溶液。在藉由TLC分析起始材料結束時，反應溶液

在氮氣氛圍(nitrogen atmosphere)下在相同的溫度被攪拌歷時2小時。揮發物在低於40°C、減壓下被蒸發而提供一黏性液體材料己醯氯(大約10.5 g)。

步驟2：在惰性氛圍(inert atmosphere)下在25至30°C加入三聚甲醛(3.8 g, 128 mmol)以及無水$ZnCl_2$ (0.232 g, 17 mmol)至上面的己醯氯，並且接而被加熱至90°C。厚的團塊在90-95℃下被攪拌歷時5小時，該團塊在冷卻之後提供粗產物己酸氯甲酯，己酸氯甲酯藉由矽膠管柱層析法而被純化。**^{1}H-NMR ($CDCl_3$, 500 MHz):** δ 5.70 (s, 2H), 2.39-2.33 (m, 2H), 1.69-1.61(m, 2H), 1.33-1.28 (m, 4H), 0.90-0.88 (t, J=7, 3H)。



步驟3：配於氯化甲烷(6 mL)中的己酸氯甲酯(3.18 g, 19.0 mmol)在25-30℃下被添加至一配於二氯甲烷(240 mL)中的齊拉西酮自由鹼(ziprasidone free base)(4.0 g, 9.6 mmol)、三乙基胺(4.0 mL, 27 mmol)以及4-二甲基吡啶(DMAP, 0.708 g, 5 mmol)的懸浮液。反應溶液在相同溫度下被攪拌歷時24小時。粗混合物以水(100 mL)繼而鹽水溶液(100 mL)予以清洗，在低於40°C、真空下溶劑蒸發之後提供粗標題產物化合物322，化合物322進一步藉由矽膠管柱層析法而被純化。(1.4 g，27%產率)。

^{1}H-NMR($CDCl_3$, 500 MHz)：δ 7.92-7.90 (d, J=7.5,1H), 7.82-7.80 (d, J = 7.5,1H),7.48-7.45 (t, J = 7.5,1H), 7.37-7.34 (t, J = 7.5,1H), 7.17 (s,1H), 7.05 (s, 1H), 5.72 (s, 2H), 3.60-3.55 (m,6H), 2.98-2.95 (t, J = 7.5,2H), 2.79-2.78 (m, 4H), 2.68-2.65 (t, J = 8.5, 2H), 2.35-2.32 (t, J = 7.5,2H), 1.64-1.61 (t, J = 7.5, 2H), 1.29-1.25 (m, 4H), 0.88-0.85 (t, J = 7, 3H)。

質量(mass)(m/z) = 541 [M^+ + 1]。

(5-(2-(4-(苯并[d]異噻唑-3-基)哌啡-1-基)乙基)-6-氯-2-側氧吲哚啉-1-基)甲基十二酸酯 {(5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloro-2-oxoindolin-1-yl)methyl dodecanoate}(實施例39：化合物324)

化合物324是以一類似於化合物322 (實施例38)的方法而被合成。

^{1}H-NMR($CDCl_3$, 500 MHz)：δ 7.92-7.90 (d, J = 7.5, 1H), 7.82-7.80 (d, J = 7.5,1H) ,7.48-7.45 (t, J = 7.5, 1H), 7.37-7.34 (t, J = 7.5, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 5.72 (s, 2H), 3.60-3.55 (m, 6H), 2.98-2.95 (t, J = 8, 2H), 2.79-2.77 (m, 4H), 2.68-2.65 (t, J = 8, 2H), 2.34-2.31 (t, J = 7,2H), 1.63-1.60 (m, ,2H), 1.24 (s, 16H), 0.89-0.86 (t, J = 7, 3H)。

質量(m/z) = 625.5 [M^+ + 1]。

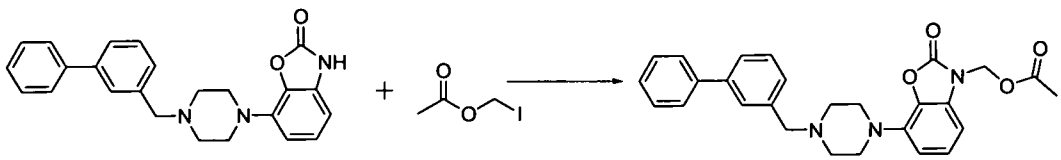
(5-(2-(4-(苯并[d]異噻唑-3-基)哌啡-1-基)乙基)-6-氯-2-側氧吲哚啉-1-基)甲基棕櫚酸酸酯

{(5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloro-2-oxoindolin-1-yl)methyl palmitate}(實施例40：化合物326)

^{1}H-NMR ($CDCl_3$, 500 MHz)：δ 7.92-7.90 (d, *J* = 7.5, 1H), 7.82-7.80 (d, *J* = 7.5, 1H), 7.48-7.45 (t, *J* = 7.5, 1H), 7.37-7.34 (t, *J* = 7.5, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 5.72 (s, 2H), 3.60-3.55 (m, 6H), 2.98-2.95 (t, *J* = 8, 2H), 2.79-2.77 (m, 4H), 2.68-2.65 (t, *J* = 8, 2H), 2.34-2.31 (t, *J* = 8, 2H), 1.63-1.56 (m, 2H), 1.25-1.23 (m, 24H), 0.88-0.86 (t, *J* = 7, 2H)。

質量(m/z) = 681.5 [M^+ + 1]。

(7-[(4-聯苯-3-基甲基)哌啡-1-基]-2-側氧苯并[d]噁唑-3(2H)-基)甲基乙酸酯{(7-[(4-biphenyl-3-ylmethyl)piperazin-1-yl]-2-oxobenzo[d]oxazol-3(2H)-yl)methyl acetate}(實施例41，化合物416)



步驟1、乙酸氯甲酯的合成：乙醯氯(5 g, 0.06 mol)在在氬氣(Argon)、0°C下被逐滴地加入至三聚甲醛(8.5 g, 0.06 mol)以及無水氯化鋅(0.175 g, 0.02 mol)的一混合物。該反應混合物被加溫至室溫並且被攪拌歷時1小時，接而被加熱至90°C歷時18小時。固體被過濾掉、以二氯甲烷予以清洗，並且濾液在37°C、真空下被濃縮俾以提供所欲的產物(6.6

g，94%產率)。該產物直接地(沒有純化)被用於下一個步驟並且以經活化的分子篩(4 Å)予以儲存。

步驟2、乙酸碘甲酯(iodomethyl acetate)的合成：碘化鈉(27.6 g, 0.18 mol)被加入至一配於乙腈(66 mL)中的乙酸氯甲酯的溶液(6.6 g, 0.06 mol)。反應燒瓶被覆蓋在鋁箔(aluminum foil)中以避光並且在環境溫度下被攪拌歷時15小時。反應混合物被分配在二氯甲烷以及水之間，並且水性層以二氯甲烷予以萃取。合併的有機物(organics)以水性飽和的$NaHCO_3$、10%水性亞硫酸鈉溶液以及鹽水予以清洗，繼而以硫酸鈉予以乾燥並且被濃縮俾以得到有如一黃色的油的產物(1.13 g，12%產率)。

步驟3：n-丁基鋰(n-butyl lithium)(1.6 M配於己烷中；3.8 mL，0.007 mol)在-78°C下從一注射器中被逐滴地加入至一被攪拌的配於四氫呋喃中的百芬普那(1.46 g, 0.003 mol)的溶液。在1小時之後，一乙酸碘甲酯(1.13 g, 0.005 mol)的溶液在-70°C下被逐滴地加入。該反應混合物被攪拌歷時15小時。該反應混合物被倒在一氯化銨的飽和水性溶液中並且以乙酸乙酯予以萃取。合併的有機層以1 N NaOH溶液以及鹽水予以清洗，接而以硫酸鈉予以乾燥並且在真空下予以濃縮。藉由快速層析法(flash chromatography)的純化提供化合物416。(0.25 g，14%產率)。^{1}H NMR (DMSO, 400 MHz) δ 2.034 (s, 3H), 2.565 (s, 4H), 3.183 (s, 4H), 3.597 (s, 2H), 5.765 (s, 2H), 6.696-6.717 (d, 1H), 6.882-6.901 (d, 1H), 7.091-7.182 (t, 1H), 7.315-7.370 (q, 2H), 7.404-7.473 (m,

3H), 7.515-7.555 (d, 1H), 7.59 (d, 1H), 7.639-7.657 (d, 2H)。m/z (M+H) 457。

(7-[(4-聯苯-3-基甲基)哌啡-1-基]-2-側氧苯并[d]噁唑-3(2H)-基)甲基丁酸酯{(7-[(4-biphenyl-3-ylmethyl)piperazin-1-yl]-2-oxobenzo[d]oxazol-3(2H)-yl)methyl butyrate}(實施例42，化合物417)

化合物417以一類似於實施例41的方法使用丁醯氯而被製備。藉由快速層析法的純化提供所欲的產物(1.25 g，45%產率)。^{1}H NMR (DMSO, 400 MHz) δ 1.065 (t, 3H),1.448-1.54 (m, 2H), 2.284-2.320 (t , 2H) , 2.564 (s, 4H), 3.184 (s, 4H), 3.597 (s, 2H), 5.787(s, 2H), 6.694-6.713 (d, 1H), 6.878-6.896 (d, 1H), 7.092-7.133 (t, 1H), 7.315-7.370 (q, 2H), 7.422-7.533 (m, 3H), 7.535-7.555 (d, 1H), 7.639 (d, 1H), 7.657-7.660 (d, 2H)。m/z (M+H) 485。

(7-[(4-聯苯-3-基甲基)哌啡-1-基]-2-側氧苯并[d]噁唑-3(2H)-基)甲基己酸酯{(7-[(4-biphenyl-3-ylmethyl)piperazin-1-yl]-2-oxobenzo[d]oxazol-3(2H)-yl)methyl hexanoate}(實施例43，化合物413)

化合物413以一類於實施例41的方法使用己醯氯而被製備。藉由快速層析法的純化提供所欲的產物(0.6 g，60%產率)。^{1}H NMR (DMSO, 400 MHz) δ 0.774 (t, 3H), 1.114-1.187 (m, 4H), 1.433-1.506 (m , 2H), 2.291-2.328 (t, 2H), 2.564 (s, 4H), 3.182 (s, 4H), 3.597 (s, 2H), 5.783 (s, 2H), 6.693-6.713 (d, 1H), 6.870-6.890 (d, 1H), 7.090-7.130 (t,

1H), 7.314-7.351 (q, 2H), 7.422-7.472 (m, 3H), 7.535-7.554 (d, 1H), 7.589 (d, 1H), 7.638-7.656 (d, 2H)。m/z (M+H) 513。

(7-[(4-聯苯-3-基甲基)哌啡-1-基]-2-側氧苯并[d]噁唑-3(2H)-基)甲基棕櫚酸酯{7-[(4-biphenyl-3-ylmethyl)piperazin-1-yl]-2-oxobenzo[d]oxazol-3(2H)-yl}methyl palmitate}(實施例44，化合物422)

化合物422以一類於實施例41的方法使用棕櫚醯氯(palmitoyl chloride)而被製備。藉由快速層析法的純化提供所欲的產物(0.5 g，47%產率)。^{1}H NMR (DMSO, 400 MHz) δ 0.819 (t, 3H), 1.127-1.302 (m, 22H), 1.437-1.454 (t, 2H), 2.287-2.305 (t, 2H), 2.564 (s, 4H), 3.182 (s, 4H), 3.596 (s, 2H), 5.784(s, 2H), 6.688-6.708 (d, 1H), 6.863-6.882 (d, 1H), 7.083-7.124 (t, 1H), 7.331-7.368 (q, 2H), 7.400-7.470 (m, 3H), 7.534-7.553 (d, 1H), 7.587 (d, 1H), 7.635-7.653 (d, 2H)。m/z (M+H) 653。

(7-[(4-聯苯-3-基甲基)哌啡-1-基]-2-側氧苯并[d]噁唑-3(2H)-基)甲基葵酸酯{(7-[(4-biphenyl-3-ylmethyl)piperazin-1-yl]-2-oxobenzo[d]oxazol-3(2H)-yl)methyl decanoate}(實施例45，化合物419)

化合物419以一類於實施例41的方法使用葵醯氯(decanoyl chloride)而被製備。藉由快速層析法的純化提供所欲的產物(0.8 g，77%產率)。^{1}H NMR (DMSO, 400 MHz) δ 0.795-0.829 (t, 3H), 1.140-1.211 (m, 12H), 1.438-1.471 (t, 2H), 2.288-2.324 (t, 2H), 2.562 (s, 4H), 3.181 (s, 4H), 3.595

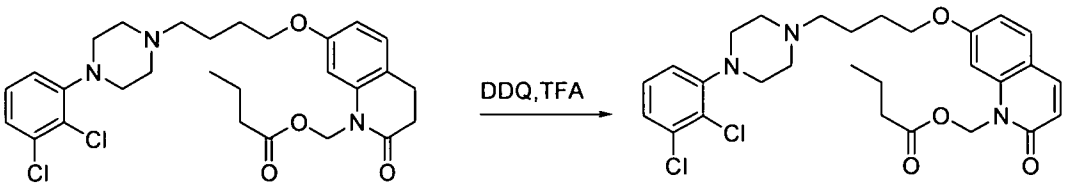
(s, 2H), 5.783(s, 2H), 6.689-6.709 (d, 1H), 6.856-6.884 (d, 1H), 7.083-7.124 (t, 1H), 7.311-7.367 (q, 2H), 7.400-7.470 (m, 3H), 7.533-7.552 (d, 1H), 7.587 (d, 1H), 7.635-7.653 (d, 2H)。m/z (M+H) 569。

(7-[(4-聯苯-3-基甲基)哌啡-1-基]-2-側氧苯并[d]噁唑-3(2H)-基)甲基異丁酸酯{(7-[(4-biphenyl-3-ylmethyl)piperazin-1-yl]-2-oxobenzo[d]oxazol-3(2H)-yl)methyl isobutyrate}(實施例46，化合物414)

化合物414以一類於實施例41的方法使用異丁醯氯(isobutyryl chloride)而被製備。藉由快速層析法的純化提供所欲的產物(0.3 g，15%產率)。^{1}H NMR (DMSO, 400 MHz) δ 1.027-1.044 (d, 6H), 2.478-2.553 (m, 1H), 2.562 (s, 4H), 3.185 (s, 4H), 3.597 (s, 2H), 5.785 (s, 2H), 6.692-6.713 (d, 1H), 6.873-6.892 (d, 1H), 7.093-7.134 (t, 1H), 7.315-7.369 (q, 2H), 7.403-7.472 (m, 3H), 7.533-7.555 (d, 1H), 7.590 (d, 1H), 7.657-7.660 (d, 2H)。m/z (M+H) 485。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧喹啉-1(2H)-基)甲基丁酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxoquinolin-1(2H)-yl)methyl butyrate](實施例47，化合物151)

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基丁酸酯(化合物2)如在上面實施例16中所描述的而被製備。



化合物2　　化合物151

加入TFA (2.74 mL, 35.63 mmol)繼而配於THF (40 mL)中的2,3-二氯-5,6-二氰苯醌(2,3-dichloro-5,6-dicyanobenzoquinone, DDQ; 7.01 g, 30.88 mmol)至一配於THF (100 mL)中的(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧-3,4-二氫喹啉-1(2H)-基)甲基丁酸酯(3.26 g, 5.94 mmol)的攪拌溶液。該反應物在室溫下被攪拌歷時超過週末。該反應物以水(100 mL)予以淬火(quenched)並且接而被倒入至水(600 mL)以及二氯甲烷(100 mL)中。固體$NaHCO_3$ (100 g)被加入並且該混合物被攪拌歷時大約30分鐘。二氯甲烷(200 mL)被加入並且該混合物被過濾。所收集的濾液被轉移至一分液漏斗(separating funnel)中並且層被分開。水性層以二氯甲烷(2 × 100 mL)予以萃取，以及合併的有機物以水(3 × 100 mL)、鹽水(100 mL)予以清洗並且於$MgSO_4$上予以乾燥。在過濾之後，揮發物被移除。粗物質藉由以0至4%甲醇/(1:1的乙酸乙酯/二氯甲烷)洗提的矽石層析法而被純化。油從甲醇中被再結晶俾以得到化合物151 (2.03 g，3.72 mmol，63%產率)。

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, d), 7.45 (1H, d), 7.19-7.06 (2H, m), 6.99-6.90 (1H, m), 6.88-6.78 (2H, m), 6.52 (1H, d), 6.33 (2H, s), 4.06 (2H, t), 3.17-2.99 (4H, bs),

2.74-2.43 (6H, m), 2.35 (2H, t), 1.94-1.54 (6H, m), 0.93 (3H, t)。

下列的化合物是以一類似於實施例47的方法從它們對應的3,4二氫前驅物而被合成：

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧喹啉-1(2H)-基)甲基棕櫚酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxoquinolin-1(2H)-yl)methyl palmitate](實施例48，化合物159)

化合物159以一類似於實施例47的方法從化合物10而被合成。

2.04 g。^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, d), 7.44 (1H, d), 7.18-7.10 (2H, m), 6.98-6.91 (1H, m), 6.87-6.80 (2H, m), 6.52 (1H, d), 6.32 (2H, s), 4.05 (2H, t), 3.15-2.99 (4H, bs), 2.74-2.44 (6H, m), 2.35 (2H, t), 1.92-1.83 (2H, m), 1.80-1.68 (2H, m) 1.66-1.55 (2H, m), 1.32-1.14 (24H, m), 0.87 (3H, t)。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧喹啉-1(2H)-基)甲基月桂酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxoquinolin-1(2H)-yl)methyl laurate](實施例49，化合物156)

化合物156以一類似於實施例47的方法從化合物7而被合成。

1.37 g。^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, d), 7.43 (1H, d), 7.17-7.10 (2H, m), 6.96-6.92 (1H, m), 6.87-6.80 (2H, m),

6.51 (1H, d), 6.33 (2H, s), 4.06 (2H, t), 3.12-3.01 (4H, bs), 2.71-2.59 (4H, bs), 2.50 (2H, t), 2.35 (2H, t), 1.92-1.83 (2H, m), 1.78-1.69 (2H, m) 1.66-1.55 (2H, m), 1.32-1.16 (16H, m), 0.86 (3H, t)。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧喹啉-1(2H)-基)甲基硬脂酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxoquinolin-1(2H)-yl)methyl stearate](實施例50，化合物160)

化合物160以一類似於實施例47的方法從化合物11而被合成。

1.38 g。^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, d), 7.44 (1H, d), 7.17-7.11 (2H, m), 6.97-6.92 (1H, m), 6.87-6.79 (2H, m), 6.51 (1H, d), 6.32 (2H, s), 4.05 (2H, t), 3.13-3.00 (4H, bs), 2.73-2.58 (4H, bs), 2.50 (2H, t), 2.35 (2H, t), 1.92-1.83 (2H, m), 1.79-1.69 (2H, m) 1.66-1.55 (2H, m), 1.32-1.14 (28H, m), 0.87 (3H, t)。

(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧喹啉-1(2H)-基)甲基乙酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxoquinolin-1(2H)-yl)methyl acetate](實施例51，化合物150)

化合物150以一類似於實施例47的方法從化合物1而被合成。

1.61 g。^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, d), 7.45 (1H, d), 7.18-7.11 (2H, m), 6.98-6.92 (1H, m), 6.90-6.80 (2H, m),

6.52 (1H, d), 6.32 (2H, s), 4.07 (2H, t), 3.14-3.01 (4H, bs), 2.73-2.59 (4H, bs), 2.51 (2H, t), 2.12 (3H, s), 1.95-1.82 (2H, m), 1.82-1.68 (2H, m)。

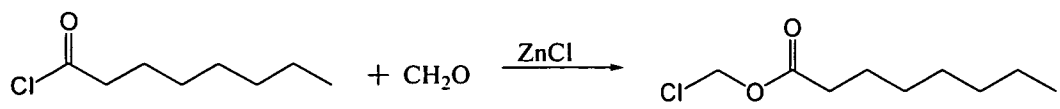
(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧喹啉-1(2H)-基)甲基2,2-二甲基丁酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxoquinolin-1(2H)-yl)methyl 2,2-dimethylbutanoate](實施例52，化合物165)

化合物165是以一類似於實施例47的方法從化合物16而被合成。

1.02 g。^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, d), 7.43 (1H, d), 7.17-7.10 (2H, m), 6.97-6.92 (1H, m), 6.83-6.79 (2H, m), 6.51 (1H, d), 6.31 (2H, s), 4.05 (2H, t), 3.12-3.02 (4H, bs), 2.71-2.60 (4H, bs), 2.50 (2H, t), 1.92-1.83 (2H, m), 1.78-1.68 (2H, m) 1.55 (2H, q), 1.15 (6H, s), 0.81 (3H, t)。

(2-(N-(1-(1-(4-氟苄基)-1H-苯并[d]咪唑-2-基)哌啡-4-基)-N-甲基胺基)-6-側氧嘧啶-1(6H)-基)甲基辛酸酯[(2-(N-(1-(1-(4-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-N-methylamino)-6-oxopyrimidin-1(6H)-yl)methyl octanoate](實施例53，化合物704)

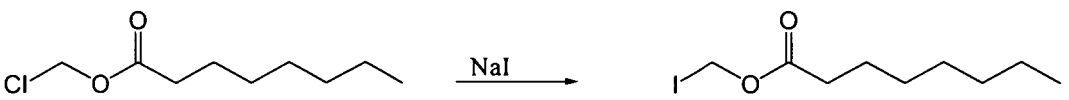
步驟1：



辛醯氯(octanoyl chloride)(10 g, 0.06 mol)在氬氣、0°C

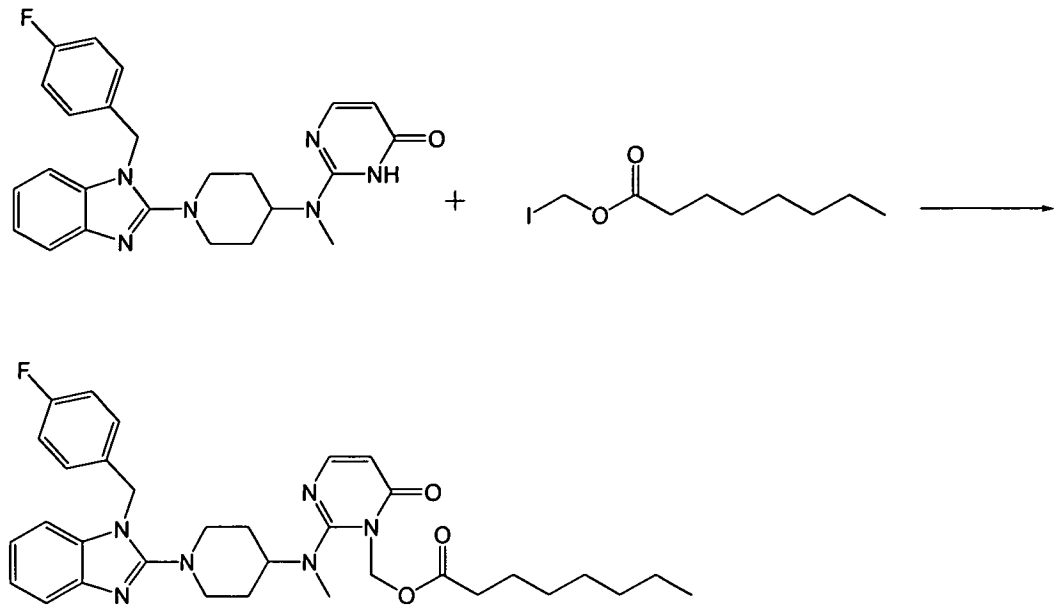
下被逐滴地添加至三聚甲醛(8.07 g, 0.06 mol)以及無水氯化鋅(0.163 g, 0.0012 mol)的一混合物中。在添加完成之後，該反應混合物在25°C下被攪拌歷時1小時，並且接而被加熱至90°C歷時16小時。固體被過濾掉並且以二氯甲烷予以清洗。濾液在37°C、真空下被濃縮俾以提供所欲的辛酸氯甲酯(chloromethyl octanoate)(9.5 g，84%產率)，辛酸氯甲酯被直接地(沒有純化)用於下一個步驟中。這個產物被儲存於經活化的分子篩(4 Å)上以維持它乾燥。

步驟2：



碘化鈉(21.7 g, 0.1449 mol)被加入至一配於乙腈(100 ml)中的辛酸氯甲酯(chloromethyl octanoate)(9.5 g, 0.0483 mol)的溶液。燒瓶被覆蓋在鋁箔中以避光並且在25°C下被攪拌歷時16小時。反應混合物被分配在二氯甲烷以及水之間，水性層進一步以二氯甲烷予以萃取。合併的有機萃取物以水性飽和的$NaHCO_3$、10%水性亞硫酸鈉溶液以及鹽水予以清洗，並且最終地以硫酸鈉予以乾燥並且在真空下被濃縮俾以提供有如一黃色的油的產物(8.4 g，71%產率)。這個產物被拿去下一個步驟而沒有進一步的純化。

步驟3：



n-丁基鋰(1.5 M配於己烷中；14.6 mL，0.0042 mol)在-78°C下被逐滴地加入至一配於四氫呋喃(50 ml)中的2-(N-(1-(1-(4-氟苯基)-1H-苯并[d]咪唑-2-基)哌啶-4-基)-N-甲基胺基)嘧啶-4(3H)-酮[咪唑斯汀(Mizolastine)，14.3 g, 0.00696 mol]的攪拌溶液。在1小時之後，反應混合物在-70°C下被逐滴地處理以一辛酸碘甲酯(2.5 g, 0.0231 mol)。該反應混合物在25°C下被攪拌歷時16小時。該反應混合物被倒入至氯化銨溶液並且以乙酸乙酯予以萃取。合併的有機物以水性氫氧化鈉(1 N)以及鹽水予以清洗，並且接而以硫酸鈉予以乾燥並且在真空下予以濃縮。快速層析法提供所欲的產物(0.45 g，17%產率)。

^{1}H NMR (DMSO, 400 MHz) δ 0.815 (t, 3H),1.117-1.235 (m, 10H), 1.474-1.491 (t, 2H), 1.638-1.665 (d, 2H), 1.992-2.010 (m, 2H), 2.292-2.230 (t, 2H), 2.992 (s, 3H), 3.027-3.088 (t, 2H), 3.55-3.62 (t, 2H), 4.625 (s, 1H) 5.311 (s, 2H), 6.040 (s, 2H), 6.110-6.124 (d, 1H), 7.014-7.076 (m, 2H), 7.148-7.253

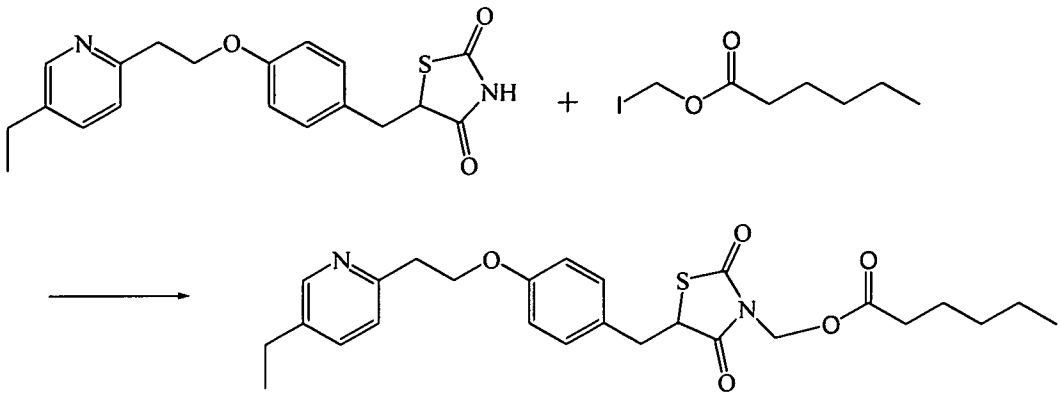
(m, 5H), 7.442-7.460 (d, 1H), 8.187-8.201 (d, 1H)。m/z (M^+H) 589。

(2-(N-(1-(1-(4-氟苄基)-1H-苯并[d]咪唑-2-基)哌啶-4-基)-N-甲基胺基)-6-側氧嘧啶-1(6H)-基)甲基月桂酸酯[(2-(N-(1-(1-(4-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-N-methylamino)-6-oxopyrimidin-1(6H)-yl)methyl laurate](實施例54，化合物706)

化合物706使用一如實施例53的類似操作程序使用月桂醯氯(lauroyl chloride)而被合成。

^1H NMR (DMSO, 400M Hz) δ 0.791-0.826 (t, 3H), 1.134-1.210 (m, 16H), 1.446 (t , 2H) , 1.642-1.925 (d, 2H), 1.956-2.008 (m, 2H), 2.266-2.301 (t, 2H), 2.968 (s, 3H), 3.003-3.063 (t, 2H), 3.31-3.62 (t, 2H), 4.625 (s, 1H) 5.286 (s, 2H), 6.015 (s, 2H), 6.085-6.099 (d, 1H), 7.015-7.072 (m, 2H), 7.122-7.215 (m, 5H), 7.418-7.436 (d, 1H), 8.159-8.172 (d, 1H)。m/z (M^+H) 645.5。

(5-(4-(2-(5-乙基吡啶-2-基)乙氧基)苄基)-2,4-二側氧四氫噻唑-3-基)甲基己酸酯[(5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2,4-dioxothiazolidin-3-yl)methyl hexanoate](實施例55，化合物1003)



步驟1：己酸氯甲酯以一如在上面實施例53的步驟1所描述的類似方法從己醯氯(hexanoyl chloride)而被合成。

步驟2：己酸碘甲酯是來自己酸氯甲酯以一如在上面實施例53的步驟2所描述的類似方法而被合成。

步驟3：一配於二甲基甲醯胺中的皮利酮(Pioglitazone)(3.0 g, 0.0084 mol)的溶液在25°C下被處理以乾燥的K_2CO_3 (3.48 g, 0.0252)。在40分鐘之後，一己酸碘甲酯(4.29 g, 0.0168 mol)的溶液被逐滴地加入。反應混合物被攪拌歷時15小時，接而被倒在水中並且以乙酸乙酯予以萃取。被合併的有機層以硫酸鈉予以乾燥並且在真空下被濃縮。產物藉由快速層析法而被純化俾以獲得所欲的產物(1.9 g，44%產率)。

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86-0.90 (t, 3H), 1.22-1.29 (m, 8H), 1.58-1.62 (t, 2H), 2.27-2.31 (t, 2H), 2.62-2.64 (d, 2H), 3.04-3.099 (q, 1H), 3.21-3.25 (t, 2H), 3.452-3.497 (q, 1H), 4.30-4.34 (t, 2H), 4.46-4.48 (d, 1H), 5.513-5.51(d, 2H), 6.81-6.85 (t, 2H), 7.09-7.11 (d, 2H), 7.18-7.20 (d, 1H), 7.46-7.48 (q, 1H), 8.38-8.39 (d, 1H) m/z (M^+H) 485。

(5-(4-(2-(5-乙基吡啶-2-基)乙氧基)苄基)-2,4-二側氧四氫噻

唑-3-基)甲基月桂酸酯[(5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2,4-dioxothiazolidin-3-yl)methyl laurate](實施例56，化合物1006)

化合物1006使用一如實施例55的類似操作程序使用月桂醯氯而被合成。

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.802-0.836 (t, 3H), 1.133-1.171 (t, 4H), 1.197-1.235 (d, 15H), 1.308 (s, 1H), 1.419-1.452 (t, 2H), 2.172.254 (q, 2H), 2.533-2.590 (q, 2H), 3.044-3.118 (m, 3H), 4.251-4.284 (t, 2H), 4.97-5.005 (q, 1H), 5.345-5.413 (q, 2H), 6.82-6.841 (d, 2H), 7.09-7.11 (d, 2H), 7.23-7.25 (d, 1H), 7.53-7.55 (q, 1H), 8.33-8.34 (d, 1H) m/z (M^+H) 569。

(5-(4-(2-(5-乙基吡啶-2-基)乙氧基)苄基)-2,4-二側氧四氫噻唑-3-基)甲基棕櫚酸酯[(5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2,4-dioxothiazolidin-3-yl)methyl palmitoate](實施例57，化合物1008)

化合物1008使用一如實施例55的類似操作程序使用棕櫚醯氯而被合成。

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.870 (s, 3H), 1.23-1.26 (t, 27H), 1.57-1.61 (t, 2H), 2.27-2.31 (t, 2H), 2.61.265 (t, 2H), 3.06-310 (t, 1H), 3.22-3.25 (t, 2H), 3.45-3.46 (d, 1H), 4.31-4.34 (t, 2H), 4.45-4.49 (q, 1H), 5.487-5.541 (q, 2H), 6.83-6.85 (d, 2H), 7.09-7.11 (d, 2H), 7.19-7.26 (t, 1H), 7.47-7.49 (q, 1H), 8.393-8.397 (d, 1H) m/z (M^+H) 625。

(5-(4-(2-(5-乙基吡啶-2-基)乙氧基)苄基)-2,4-二側氧四氫噻唑-3-基)甲基硬脂酸酯[(5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2,4-dioxothiazolidin-3-yl)methyl stearoate](實施例58，化合物1009)

化合物1009使用一如實施例55的類似操作程序使用硬脂醯氯(stearoyl chloride)而被合成。

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.874-0.894 (t, 3H), 1.222-1.260 (t, 30H), 1.570-1.603 (d, 1H), 2.27-2.31 (t, 2H), 2.609-2.266 (q, 2H) , 3.04-3.10 (q, 1H), 3.20-3.24 (t, 2H), 3.46-3.50 (q, 1H), 4.302-4.335 (t, 2H), 4.453-4.487 (q, 1H), 5.488-5.552 (q, 2H), 6.83-6.86 (d, 2H), 7.09-7.11 (d, 2H), 7.17-7.19 (d, 1H), 7.44-7.47 (d, 1H), 8.386-8.391 (d, 1H) m/z (M^+H) 653。

(5-(4-(2-(5-乙基吡啶-2-基)乙氧基)苄基)-2,4-二側氧四氫噻唑-3-基)甲基肉荳蔻酸酯[(5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2,4-dioxothiazolidin-3-yl)methyl myristoate](實施例59，化合物1007)

化合物1007使用一如實施例55的類似操作程序使用肉荳蔻醯氯(myristoyl chloride)而被合成。

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.854-0.887 (t, 3H), 1.226-1.262 (t, 24H), 1.57-1.604 (t, 2H), 2.27-2.308 (t, 2H), 2.609-2.265 (t, 2H), 3.035-3.094 (q, 1H), 3.223-3.256 (t, 2H), 3.456-3.500 (q, 1H), 4.307-4.340 (t, 2H), 4.463-4.487 (t, 1H), 5.487-5.540 (q, 2H), 6.832-6.852 (d, 2H), 7.092-7.114 (d,

2H), 7.198-7.217 (d, 1H), 7.475-7.491 (d, 1H), 8.393-8.397 (d, 1H) m/z (M^+H) 596。

(5-(4-(2-(5-乙基吡啶-2-基)乙氧基)苄基)-2,4-二側氧四氫噻唑-3-基)甲基丁酸酯[(5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2,4-dioxothiazolidin-3-yl)methyl butyrate](實施例60，化合物1002)

化合物1002使用一如實施例55的類似操作程序使用丁醯氯而被合成。

^1H NMR ($CDCl_3$, 400 MHz) δ 0.798-0.835 (t, 3H), 1.133-1.212 (q, 4H), 1.417-1.509 (m, 2H), 2.210-2.246 (t, 2H), 2.482-2.2591(q, 2H), 3.047-3.118 (q, 3H), 4.253-4.286 (t, 2H), 4.983-5.016 (q, 1H), 5.353-5.415 (q, 2H), 6.824-6.845 (d, 2H), 7.097-7.118 (d, 2H) ,7.239-7.258 (d, 1H), 7.538-7.563 (d, 1H), 8.340-8.365 (d, 1H) m/z (M^+H) 458。

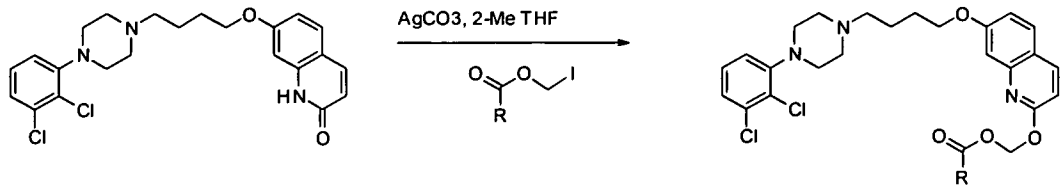
(5-(4-(2-(5-乙基吡啶-2-基)乙氧基)苄基)-2,4-二側氧四氫噻唑-3-基)甲基環己烷羧酸酯[(5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-2,4-dioxothiazolidin-3-yl)methyl cyclohexanecarboxylate](實施例60，化合物1015)

化合物1015是使用一如實施例55的類似操作程序使用環己甲醯氯(cyclohexanecarbonyl chloride)而被合成。

^1H NMR ($CDCl_3$, 400 MHz) δ 1.181-1.293 (m, 7H), 1.359-1.449 (m, 2H), 2.624 (s, 1H), 1.714-1.738 (t, 2H),

1.843-1.874 (q, 2H), 2.244-2.319 (m, 1H), 2.607-2.664 (q, 2H), 3.049-3.107 (q, 1H), 3.22.-3.253 (t, 2H), 3.340-3.485 (q, 1H), 5.481-5.534 (q, 2H), 6.831-6.853 (d, 2H), 7.091-7.113 (d, 2H), 7.193-7.213 (d, 1H), 7.465-7.590 (q, 1H), 8.392-8.396 (d, 1H) m/z (M^+H) 497。

用於合成的一般途徑



((7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)喹啉-2-基)氧基)甲基己基碳酸酯[((7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2-yl)oxy)methyl hexyl carbonate](實施例61，化合物1240)

在室溫下加入配於2-甲基四氫呋喃(4 mL)中的碳酸銀(1.853 g, 6.72 mmol)以及己基碘甲基碳酸酯(hexyl iodomethyl carbonate)(2.021 g, 7.05 mmol)至一配於2-甲基四氫呋喃(30 mL)中的去氫-阿立哌唑(1.5 g, 3.36 mmol)(dehydro-aripiprazole)的溶液。反應物被攪拌歷時4.5天。該反應物以水(30 mL)予以淬火並且經由矽藻土(celite)予以過濾。該反應物以乙酸乙酯(3 × 20 mL)予以萃取、以鹽水(20 mL)予以清洗、於$MgSO_4$上予以乾燥並且予以濃縮。產物藉由在矽石上以1：1的乙酸乙酯比二氯甲烷至配於1：1的乙酸乙酯比二氯甲烷中的2% MeOH洗提的管柱層

析法而被純化俾以提供有如一黃色的油的化合物-1240 (1.08 g)。

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d), 7.60 (1H, d), 7.21 (1H, m), 7.14 (2H, m), 7.03 (1H, dd), 6.94 (1H, m), 6.81 (1H, d), 6.26 (2H, s), 4.18 (2H, m), 4.12 (2H, t), 3.09 (4H, m), 2.68 (4H, m), 2.53 (2H, m), 1.91 (2H, m), 1.78 (2H, m), 1.63 (2H, m), 1.28 (6H, m), 0.86 (3H, t)。$[M+H]^+$ = 604.2。

((7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)喹啉-2-基)氧基)甲基辛酸酯

[((7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2-yl)oxy)methyl octanoate](實施例62，化合物1206)

在室溫下加入碳酸銀(0.864 g, 3.13 mmol)以及辛酸碘甲酯(0.764 g, 2.68 mmol)至一配於2-甲基四氫呋喃(25 mL)中的去氫-阿立哌唑(1.0 g, 2.24 mmol)的溶液。反應物被攪拌歷時5天。該反應物以H_2O(30 mL)予以淬火並且經由矽藻土予以過濾。該反應物以乙酸乙酯(3 × 20 mL)予以萃取，以5% w/v亞硫酸納(15 mL)、鹽水(20 mL)予以清洗，於$MgSO_4$上予以乾燥並且予以濃縮。產物藉由在矽石上以0至70%配於庚烷中的乙酸乙酯洗提的管柱層析法而被純化俾以提供有如一淡橘色的油的化合物1206 (0.602 g)。

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, d), 7.60 (1H, d), 7.21 (1H, m), 7.14 (2H, m), 7.07 (1H, dd), 6.95 (1H, m), 6.79 (1H, d), 6.24 (2H, s), 4.12 (2H, m), 3.09 (4H, m), 2.68 (4H, m), 2.54 (2H, m), 2.36 (2H, t), 1.90 (2H, m), 1.77 (2H, m),

1.61 (4H, m), 1.23 (6H, m), 0.83 (3H, t)。$[M+H]^+$ = 602.2。

((7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)喹啉-2-基)氧基)甲基十二酸酯

[((7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2-yl)oxy)methyl dodecanoate](實施例63，化合物1208)

實驗操作程序以如在實施例62中用於化合物-1206的相同方法而被進行，俾以得到有如一黃色的油的1208 (0.738 g)。

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, d), 7.60 (1H, d), 7.20 (1H, d), 7.14 (2H, m), 7.05 (1H, dd), 6.95 (1H, m), 6.80 (1H, d), 6.24 (2H, s), 4.13 (2H, m), 3.09 (4H, m), 2.68 (4H, m), 2.54 (2H, m), 2.36 (2H, t), 1.93 (2H, m), 1.80 (2H, m), 1.60 (4H, m), 1.23 (14H, m), 0.86 (3H, t)。$[M+H]^+$ = 658.4。

((7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)喹啉-2-基)氧基)甲基丁酸酯

[((7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2-yl)oxy)methyl butyrate](實施例64，化合物1202)

實驗操作程序以如在實施例62中用於化合物-1206的相同方法而被進行，俾以得到有如一黃色的油的1202 (0.695 g)。

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, d), 7.61 (1H, d), 7.20 (1H, d), 7.14 (2H, m), 7.04 (1H, dd), 6.96 (1H, m), 6.79 (1H, d), 6.25 (2H, s), 4.13 (2H, m), 3.09 (4H, m), 2.69 (4H, m), 2.54 (2H, m), 2.35 (2H, t), 1.91 (2H, m), 1.78 (2H, m),

1.66 (2H, m), 0.94 (3H, t)。$[M+H]^+$ = 546.1。

實施例65：((7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)喹啉-2-基)氧基)甲基 2,2-二甲基十四酸酯[((7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2-yl)oxy)methyl 2,2-dimethyltetradecanoate](化合物1213)以及(7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)-2-側氧喹啉-1(2H)-基)甲基 2,2-二甲基十四酸酯[(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxoquinolin-1(2H)-yl)methyl 2,2-dimethyltetradecanoate](化合物255)

實驗操作程序以如在實施例62中用於化合物-1206的相同方法而被進行俾以得到化合物-255以及化合物-1212這兩者。化合物-1213被分離出(0.586 g)有如一黃色的油，以及化合物-255被分離出(0.156 g)有如一黃色的油。

化合物-1213：^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (1H, d), 7.59 (1H, d), 7.16 (3H, m), 7.03 (1H, dd), 6.97 (1H, m), 6.78 (1H, d), 6.22 (2H, s), 4.12 (2H, m), 3.10 (4H, m), 2.73 (4H, m), 2.57 (2H, t), 1.91 (2H, m), 1.80 (2H, m), 1.46 (2H, d), 1.01 – 1.33 (26H, m), 0.87 (3H, t)。$[M+H]^+$ = 714.3。

化合物-255：^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, d), 7.42 (1H, d), 7.15 (2H, m), 6.96 (1H, m), 6.82 (2H, m), 6.51 (1H, d), 6.32 (2H, s), 4.04 (2H, t), 3.07 (4H, m), 2.66 (4H, m), 2.49 (2H, m), 1.87 (2H, m), 1.76 (2H, m), 1.45 (2H, m), 1.01 – 1.36 (26H, m), 0.87 (3H, t)。$[M+H]^+$ = 714.3。

((7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)喹啉-2-基)氧基)甲基二乙基胺甲酸酯[((7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2-yl)oxy)methyl diethylcarbamate](實施例66，化合物1247)

實驗操作程序以如在實施例-62中用於化合物-1206的相同方法而被進行。反應物在室溫下、在5天後是不完全的(incomplete)。該反應物先被加熱至60℃歷時2天，隨後如在實施例-62中的發展(work-up)以及純化操作程序俾以得到有如一黃色的油的化合物-1247 (0.053 g)。

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (1H, d), 7.60 (1H, d), 7.20 (1H, m), 7.15 (2H, m), 7.04 (1H, dd), 6.95 (1H, m), 6.81 (1H, d), 6.24 (2H, s), 4.11 (2H, m), 3.28 (4H, m), 3.09 (4H, m), 2.70 (4H, m), 2.54 (2H, m), 1.90 (2H, m), 1.78 (2H, m), 1.13 (3H, q), 1.03 (3H, q)。$[M+H]^+$ = 575.2。

((7-(4-(4-(2,3-二氯苯基)哌啡-1-基)丁氧基)喹啉-2-基)氧基)甲基三甲基乙酸酯[((7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)quinolin-2-yl)oxy)methyl pivalate](實施例67，化合物1215)

實驗操作程序以如在實施例實施例-62中用於化合物-1206的相同方法而被進行，俾以得到有如一黃色的油的化合物1215 (0.555 g)。

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, d), 7.60 (1H, d), 7.15 (3H, m), 7.05 (1H, dd), 6.97 (1H, m), 6.79 (1H, d), 6.22

(2H, s), 4.12 (2H, m), 3.10 (4H, m), 2.68 (4H, m), 2.54 (2H, m), 1.91 (2H, m), 1.78 (2H, m), 1.19 (9H, s)。$[M+H]^+$ = 560.1。

實施例68：在大鼠中的藥物動力學評估(Pharmacokinetic Evaluation in Rats)

在肌肉內注射後在大鼠中的前驅藥的藥物動力學評估

動物：雄性Sprague-Dawley大鼠(Charles River Laboratories, Wilmington, MA)被獲得。大約24隻大鼠在各個研究中被使用。大鼠在到達的時間是大約350-375 g。大鼠每籠[具有任意採食地(*ad libitum*)的食物(chow)以及水]被飼養2隻。在飼養房中的環境條件：64-67°F、30%至70%相對濕度以及12：12小時的光:暗週期。所有的實驗是由機構動物管理與使用委員會(institutional animal care and use committee)所認可。

藥物動力學研究：大鼠是以一25規格(gauge)、5/8吋針(needle)與1 cc注射器而被IM給藥抽取自含有測試化合物(參見表E)的小玻璃瓶(vial)的0.3 mL懸浮液。在以異氟烷(isoflourane)麻醉(anesthesia)之後，小鼠(mouse)被注射在後肢(hind limb)的肌肉中。在以異氟烷短暫麻醉之後，血液樣品經由一側面的尾巴靜脈(lateral tail vein)而被收集。一27½G針以及1 cc注射器[沒有一抗凝劑(anticoagulant)]被用於血液收集。在投藥之後的6小時、24小時以及2、5、7、9、12、14、21、28、35天的各個取樣時間點，大約350μL的全血被收集。一但被收集，全血被立即地轉移至含有K2 EDTA

的管子(tube)中，予以翻轉10-15次並且立即地予以放置在冰上。該管子在室溫下以＞14,000 g's [11500 RPMs，使用Eppendorf Centrifuge 5417C、F45-30-11轉子(rotor)]被離心歷時2分鐘俾以分離血漿。血漿樣品被轉移至經標示的採血管(plain tube)(Microtainer®)並且被冷凍儲存在＜-70℃。

數據分析：在血漿藥品中的藥物濃度藉由液相層析法(liquid chromatography)-質譜儀(mass spectroscopy)使用針對各個化合物的適當參數而被分析。半衰期(half-life)、分布的體積(volume of distribution)、清除(clearance)、最高濃度以及AUC是藉由使用WinNonlin Version 5.2軟體(Pharsight, St. Louis, MO)而被計算出。

結果與討論：結果被顯示在表J中。如在表J中所顯示的，各個被測試的化合物提供一相較於當被單獨投藥的母體藥是擴大的血漿濃度。

表J

所使用的API形式(化合物編號)	賦形劑	劑量**(mg/kg)	AUC_{0-14} (ng*天/mL)	AUC_{0-T} (ng*天/mL)
82	配於油酸乙酯(ethyl oleate)中的溶液	57	204	NC
2	配於1% HPMC(配於PBS+0.2% Tween 20)中的再結晶的結晶體懸浮液	67	1016.9	1139.8
81	配於油酸乙酯中的溶液	56	584	NC
48	配於1% HPMC(配於PBS+0.2% Tween 20)中的經研磨的結晶體懸浮液。被測量並且被稀釋至正確的濃度*	70.00	2238	2264.6
5	配於具有DPPC、甘油以及NCOH的水中的油酸乙酯乳劑	67	1728.6	1742
6	配於油酸乙酯中的溶液	67	67	327
6	配於具有DPPC與甘油的水中的油乳劑	67	1490.3	1678.1
47	配於1% HPMC中的經研磨的結晶體懸浮液	100.0	113	176
85	配於1% HPMC(配於PBS+0.2% Tween 20)中的經研磨的結晶體懸浮液。。被測量並且被稀釋至正確的濃度*。	67	1233.9	1348
1	懸浮在1% HPMC中的結晶體材料	56.7	1673	1938
7	配於1% HPMC(配於PBS+0.2% Tween 20)中的再結晶的結晶體懸浮液	67	512.0	1169.5
32	配於1% HPMC(配於PBS+0.2% Tween 20)中的經研磨的結晶體懸浮液。。被測量並且被稀釋至正確的濃度*。	67	1334.4	1486
8	配於1% HPMC(配於PBS+0.2% Tween 20)中的經研磨的結晶體懸浮液	24	580.3	666.1

49	配於1% HPMC中的經研磨的結晶體懸浮液	73.3	152	199.7
34	配於1% HPMC(配於PBS＋0.2% Tween 20)中的經研磨的結晶體懸浮液。被測量並且被稀釋至正確的濃度*	43.33	2050	2095.8
79	配於油酸乙酯中的前驅藥溶液	67	954	NC
79	配於1% HPMC(配於PBS＋0.2% Tween 20)中的再結晶的結晶體懸浮液	67	907.4	940
31	配於1% HPMC(配於PBS＋0.2% Tween 20)中的再結晶的結晶體懸浮液	67	819.0	997
10	配於1% HPMC(配於PBS＋0.2% Tween 20)中的再結晶的結晶體懸浮液	67	302	786.6
4	配於1% HPMC(配於PBS＋0.2% Tween 20)中的再結晶的結晶體懸浮液	67	1455.4	1678
1002	配於2% CMC、0.2% Tween 20、PBS緩衝液(302 mOsm/Kg、pH 6.7)中的結晶體材料	67	5350	5972
1008	配於2% CMC、0.2% Tween 20、PBS緩衝液(302 mOsm/Kg、pH 6.7)中的結晶體材料	67	5000	6763

實施例69：關於皮利酮、化合物1002以及1008的藥物動力學研究

化合物1002以及1008的PK圖譜(profile)是使用一如上面所描述的類似模型而與皮利酮相比較。20 mg的皮利酮或20 mg等量的皮利酮前驅藥被肌肉內地投藥。結果被列表顯示在如上述的表J中。第10圖顯示PK圖譜以及與皮利酮的比較。

實施例70：使用一安非他命(amphetamine)-誘發的移動運

動模型的藥力學(pharmacodynamic)研究

前言：在治療精神分裂症以及雙極性情感疾患有用的本發明的前驅藥在高移動運動(hyperlocomotion)的嚙齒動物模型中顯示可預測的效度(validity)。D-安非他命-誘發的移動運動被假設成模擬形成關於神經分裂症的"多巴胺假說(dopamine hypothesis)"的基礎之多巴胺的高活性(dopaminergic hyperactivity)。該AMPH-誘發的高活性模型提供抗精神病化合物(antipsychotic compound)效力(efficacy)的一簡單、初始的篩選。參見，Fell et al., *Journal of Pharmacology and Experimental Therapeutics* (2008) 326:209-217。安非他命誘發的高活性被用於篩選各種不同劑量的經口服地投藥(PO)的阿立哌唑的前驅藥配方俾以測量在一急性高移動運動範例中藥力學效力。該研究的假說是導致~100-200 ng/ml的血漿濃度的阿立哌唑前驅藥配方的PO投藥會產生AMPH-誘發的移動運動的一顯著衰減(attenuation)。

為了評估一藥物的心理動作刺激性質(psychomotor stimulant properties)、促焦慮(anxiogenic)/抗焦慮(anxiolytic)或鎮靜(sedative)性質，一般的行為以及活性可在實驗動物(典型地大鼠以及小鼠)中被測量。就其本身而論，開放-空間(open-field)研究可提供對於測試化合物的行為效用的瞭解。本發明的特定前驅藥在治療精神分裂症以及雙極性情感疾患是有用的。阿立哌唑是一些本發明的前驅藥所衍生出自的一母體含有內醯胺的藥，它在治療精神分裂症以及

雙極性情感疾患是有用的。該等本發明的阿立哌唑前驅藥在高移動運動的嚙齒動物模型中顯示可預期的效度。D-安非他命-誘發的移動運動被假設成模擬形成關於神經分裂症的"多巴胺假說"的基礎之多巴胺的高活性。同樣地，麩胺酸NMDA受體拮抗劑(glutamate NMDA receptor antagonist)(MK-801、PCP等等)誘發的移動運動被假設成模擬精神分裂症的NMDA低活性(hypoactivity)假說(Fell等人，如上述)。這些藥物-誘發的高活性的測試提供抗精神病化合物效力的簡單、初始的篩選。安非他命誘發的高活性會被使用於篩選各種不同的阿立哌唑的前驅藥(在油溶液中被PO投藥)以測量藥力學效力。在這個研究所做的D-AMPH誘發的移動運動的結果會與在D-AMPH中皮下的(S.C.)阿立哌唑投藥的歷史結果相比較。該研究的假說是在移動運動測試中導致100-200 ng/ml的阿立哌唑濃度之阿立哌唑前驅藥的PO曝露在抗精神病效力的活體內(*in-vivo*)測量中會展現效力。

材料：實驗動物：12隻Sprague Dawley大鼠被購自於Charles River Laboratory。該等大鼠在收取自供應商時大約90天大，並且重量落在350-275公克的範圍內。一大鼠被放置在一籠子中並且被容許適應歷時大約1週。該等大鼠被提供任意採食地的食物以及水。

給藥D-安非他命(D-AMPH)的溶液：D-AMPH被購自於Sigma Aldrich。D-安非他命HCl被製備於0.9%鹽水中至一為1.5 mg/ml的濃度。D-安非他命以每體重一為1 ml/kg (=

1.5mg/kg)的劑量而被I.P.給予。依據歷史文獻，鹽形式的校正不被使用。在各個測試期間前30分鐘，D-安非他命從固體形式而被新鮮地製備。

給藥阿立哌唑的前驅藥衍生物的溶液：表K：

研究組	配方(途徑)	劑量 mg/大鼠	給藥體積 mL	N
A	化合物-7口服油溶液(PO)	7.5	1.5	4
B	化合物-4口服油溶液(PO)	20	1.5	4
C	化合物-4口服油溶液(PO)	10	1.5	4
D	化合物-7口服油溶液(PO)	10	1.5	4
E	化合物-4口服油溶液(PO)	0.66	1.5	4
F	化合物-7口服油溶液(PO)	20	1.5	4
G	鹽水(PO)	0	1.5	4

行為箱：行為箱(behavior chamber)被購自於Med Associates, Inc. of St. Albans, VT, Model ENV-515。用於測量動物移動的軟體與行為箱是由供應商所提供。

方法：在習慣於動物房1週之後，活性評估被開始。動物在牠們被移出箱子之前開始適應於行為箱歷時大約15分鐘，並且被PO注射以1.5 ml的一本發明的阿立哌唑前驅藥化合物(在投藥之後大約1小時呈產生100-200 ng/ml的PK位準的濃度)。在一額外的15分鐘之後，動物被放回該行為箱中歷時一額外30分鐘的藥物-基線測試期間(drug-baseline test session)。小鼠接而藉由IP注射而被投藥D-AMPH(1.5mg/kg)，繼而一為60分鐘的實驗行為的測量期間。被測量的參數是a)被測量的總距離[主要測量(primary measure)]；b)行動移動(ambulatory moves)的總數目(次要測量)；c)垂直移動的總數目(次要測量)以及d)不動花費的時間(次要測量)。

血液取樣：尾巴靜脈血液在實驗日移動運動活性測量(前驅藥投藥後2小時)之後以及再次在第二天一對應於前驅

藥投藥後22小時的時間點而被立即地取得。在以異氟烷麻醉之後，血液樣品經由一側面的尾巴靜脈(lateral tail vein)而被收集。一為27½G注射器(沒有一抗凝劑)被使用於血液收集，並且全血被轉移至含有K2 EDTA的預冷凍[濕冰(wet ice)]管子中。每隻動物0.5 ml的血液在每個時間點被收集。該等管子被翻轉15-20次並且立即地被放回濕冰上直到被離心(≥14,000 g)歷時2分鐘俾以分離血漿。在這個方法中被製備的血漿樣品被轉移至經標示的採血管 (Microtainer®)中並且被冷凍儲存在＜-70℃。

行為數據取得：行為數據藉由與行為箱有關的套裝軟體(software package)而被電子地獲得。數據經由GraphPad Prism® 5軟體(GraphPad Software, Inc., La Jolla, CA)而被轉換以及分析。數據使用2-因子重覆測量ANOVA而被分析。

結果與討論：結果被顯示在第6與7圖。結果表示：相較於僅被投藥鹽水的小鼠，口服投藥D-AMPH在由老鼠所行走的總距離上引起一顯著的增加。結果亦表示：本發明的阿立哌唑前驅藥化合物4顯著地抑制在由D-AMPH所引起的行走距離上的增加。由化合物4所引起的行走距離的抑制沒有出現劑量依賴。同樣地，阿立哌唑前驅藥化合物7以及47在20 mg的較高劑量下出現顯著地抑制在由D-AMPH所引起的行走距離上的增加。這個數據指示：依據本發明，該前驅藥化合物在活體內被切割以釋放該母體藥(在這個實施例是阿立哌唑)俾以在該動物上提供預期的藥理學效用。

在此所參照的專利以及科學文獻建立對於那些熟習此技藝者而言是可用的知識。在此所引述的所有美國專利案以及公開或未公開的美國專利申請案被併入本案以作為參考資料。在此所引述的所有公開的外國專利案以及專利申請案藉此被併入本案以作為參考資料。在此所引述的所有其他公開的參考資料、文件、手稿以及科學文獻藉此被併入本案以作為參考資料。

雖然本發明連同它的較佳具體例已被特別地顯示以及描述，那些熟習此技藝者會瞭解的是：在形式以及細節上的各種不同的改變在此可被做出而沒有背離由隨文檢附的申請專利範圍所涵括的本發明的範疇。

【圖式簡單說明】

第1圖：化合物-7的PXRD光譜。

第2圖：化合物-7的IR光譜。

第3圖：化合物-7的拉曼光譜。

第4圖：化合物-7的TGA溫度記錄圖。

第5圖：化合物-7的DSC溫度記錄圖。

第6圖：在AMPH誘發的移動運動模型中化合物-4的藥力學(PD)研究。

第7圖：在經AMPH誘發的移動運動模型中化合物-7的藥力學(PD)研究。

第8圖：在靜脈內投藥化合物7 (0.5 mg/Kg)給大鼠之後，阿立哌唑的血漿濃度。

第9圖：在肌肉內投藥30 mg/Kg的化合物7給狗之後，

阿立哌唑、去氫阿立哌唑以及化合物7的血漿濃度。

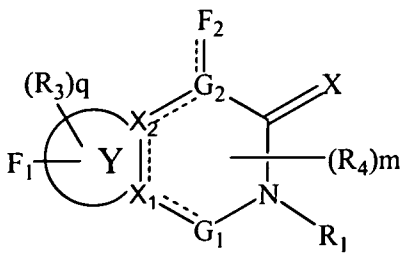
第10圖：在靜脈內投藥(20 mg皮利酮等效的)給大鼠之後，皮利酮、化合物-1002以及化合物-1008的藥物動力學圖譜。

【主要元件符號說明】

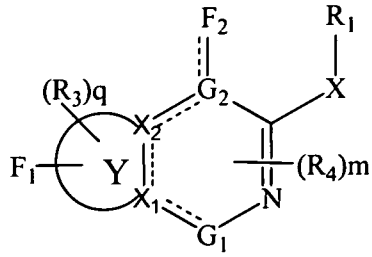
(無)

七、申請專利範圍：

1. 一種具有下列化學式VI或VII的化合物：



化學式VI



化學式VII

以及它的幾何異構物、鏡像異構物、非鏡像異構物、消旋物、藥學上可接受的鹽類以及溶劑合物；

其中┈┈代表一單或雙鍵；

X是-S-或-O-；

R_1是選自於$-C(R_A)(R_B)-OC(O)OR_{20}$、$-C(R_A)(R_B)-OC(O)R_{20}$及$-C(R_A)(R_B)-OC(O)NR_{20}R_{21}$；

其中各個R_A以及R_B是氫；

各個R_{20}以及R_{21}獨立地選自於：氫、脂族、經取代的脂族、芳基或經取代的芳基；

各個X_1、X_2以及X_3是獨立地選自於：不存在、-S-、-O-、$-S(O)-$、$-S(O)_2-$、$-N(R_{10})-$、-C(O)-、$-C(OR_{10})(R_{11})-$、$-[C(R_{10})(R_{11})]_v-$、$-C(R_{10})(R_{11})=C(R_{10})(R_{11})-$；其中v是0、1、2、3、4、5、6、7、8、9或10；

各個R_{10}以及R_{11}獨立地是：不存在、氫、鹵素、脂族、經取代的脂族、芳基或經取代的芳基；另擇地，2個R_{10}和R_{11}與它們所接附的原子和任何居間的原子一起可形成一額外選擇性地經取代的3、4、5、6或7員環；

環Y代表一含有1、2或3環的選擇性地經取代的環烷基、環烯基、雜環基或芳基；

各個F_1以及F_2是獨立地選自於：不存在以及R_5-A-Cy_1-B-D-；

其中A是選自於：不存在、選擇性地經取代的烷基、選擇性地經取代的烯基、選擇性地經取代的炔基、-S-、-O-、-S(O)-、-$S(O)_2$-、-$S[C(R_{30})(R_{31})]_u$-、-$S(O)[C(R_{30})(R_{31})]_u$-、-$S(O)_2[C(R_{30})(R_{31})]_u$-、-$O[C(R_{30})(R_{31})]_u$-、-$N(R_{30})$-、-$N(R_{30})[C(R_{31})(R_{32})]_u$-、-$[C(R_{30})(R_{31})]_u$-、-$C(O)[C(R_{30})(R_{31})]_u$-；

其中各個u獨立地是1、2、3、4、5、6或7；

Cy_1是不存在或一選擇性地經取代的環烷基、選擇性地經取代的環烯基、選擇性地經取代的雜環基、選擇性地經取代的芳基或選擇性地經取代的雜芳基；

B是不存在或一連接子；

D是選自於：不存在、-O-、-NR_{33}、-$C(R_{34})(R_{35})$-、-S-、-S(O)-、-$S(O)_2$-、-C(O)-；

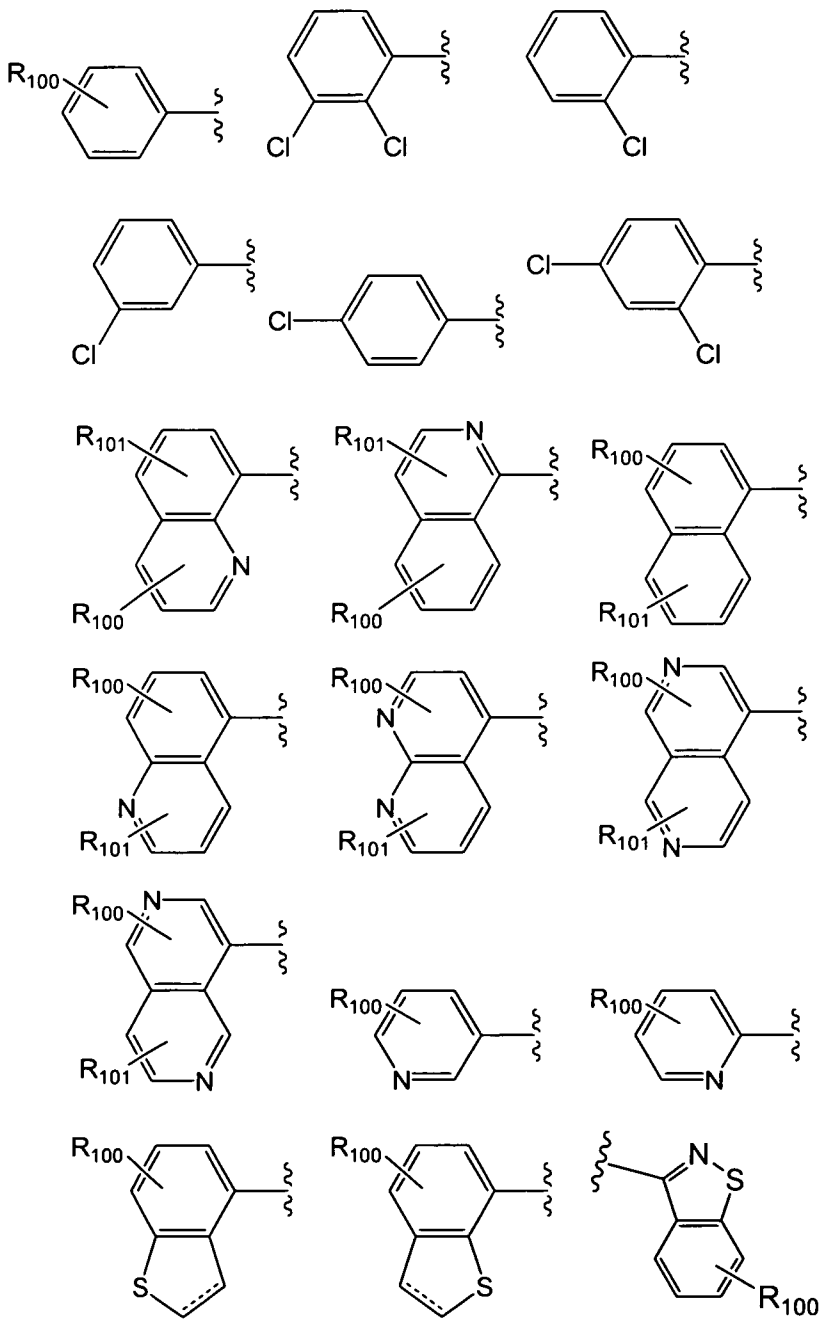
各個G_1以及G_2是獨立地選自於：不存在、-S-、-O-、-S(O)-、-$S(O)_2$-、-$SC(R_{40})(R_{41})$-、-$S(O)C(R_{40})(R_{41})$-、-$S(O)_2C(R_{40})(R_{41})$-、-C(O)-、-$C(OR_{40})(R_{41})$-、-$OC(R_{40})(R_{41})$-、-$N(R_{40})$-、-$C(R_{40})=C(R_{41})$-、-$N(R_{40})$-$C(R_{41})(R_{42})$-、-$[C(R_{40})(R_{41})]_u$-；

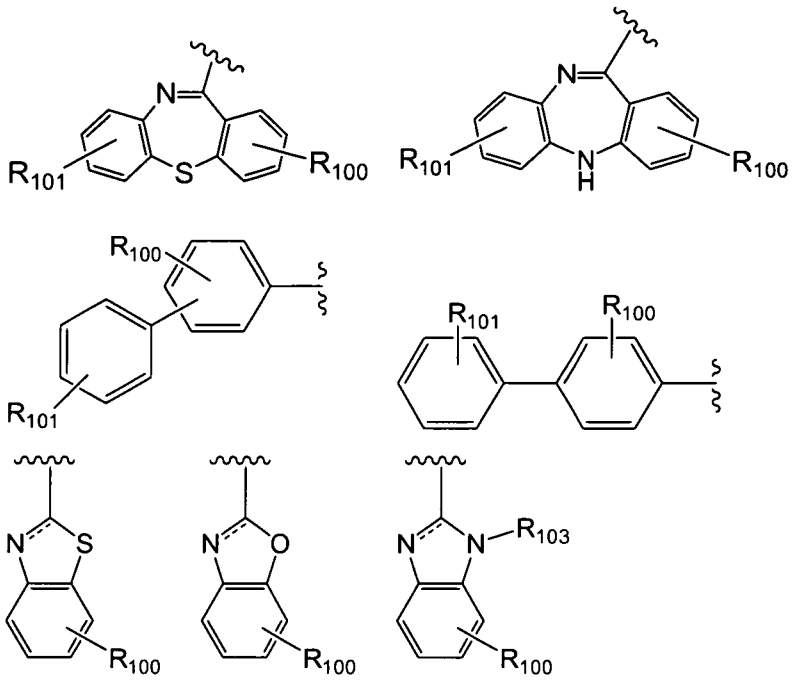
各個R_3、R_4、R_5、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{40}、R_{41}以及R_{42}是獨立地選自於：不存在、氫、鹵素、-OR_{10}、

$-SR_{10}$、$-NR_{10}R_{11}$、$-C(O)R_{10}$、選擇性地經取代的脂族、選擇性地經取代的芳基或選擇性地經取代的雜環基；另擇地，2個R_3基團一起或2個R_4基團一起或1個R_3基團與1個R_4基團一起形成一選擇性地經取代的環；

m以及q是獨立地選自於：0、1以及2。

2. 如申請專利範圍第1項的化合物，其中R_5是選自於：

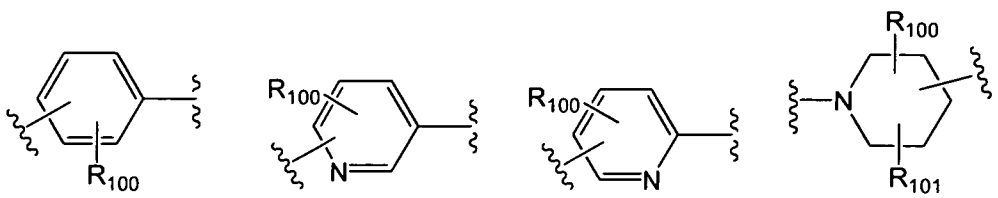


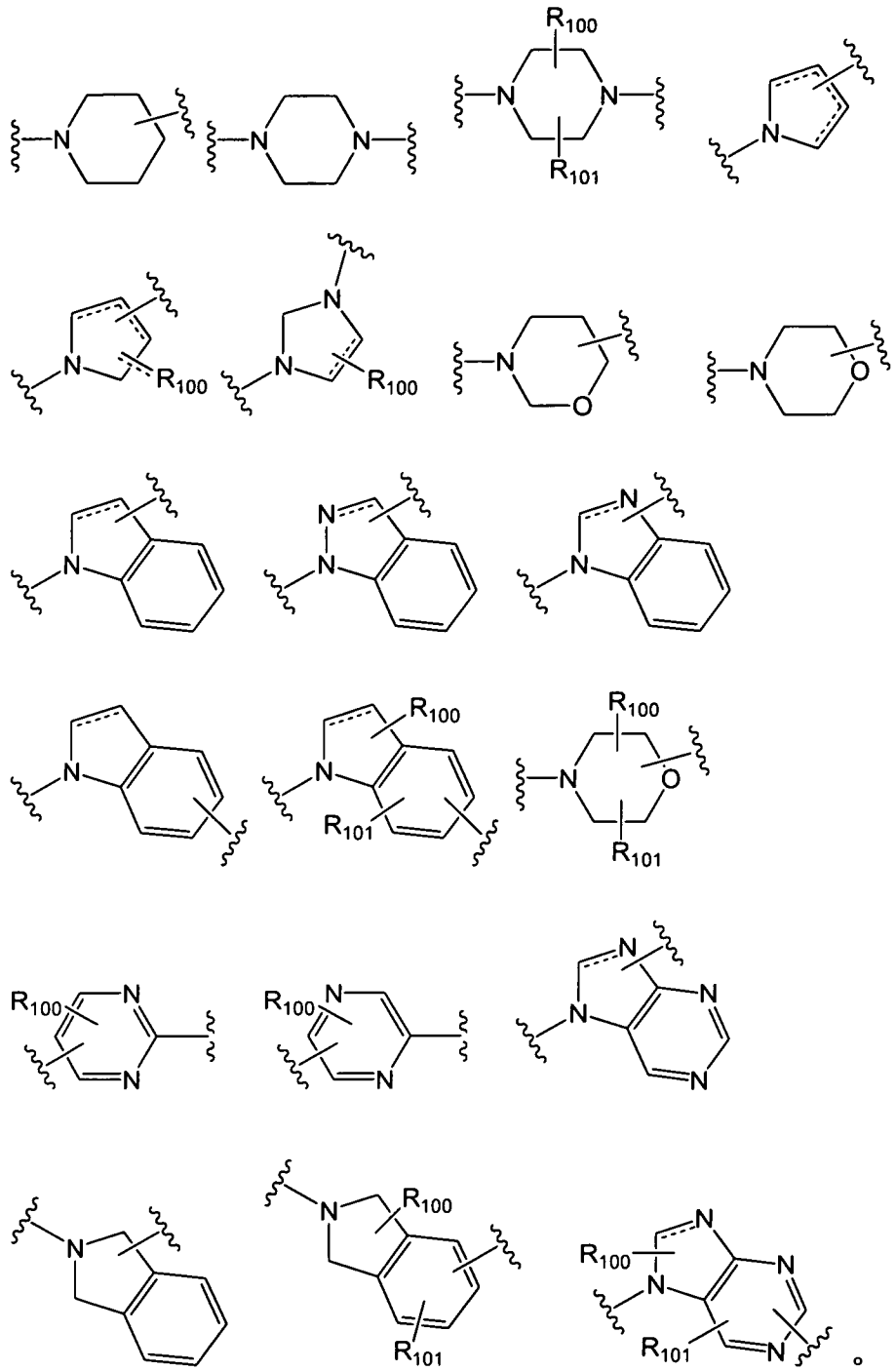


其中R_{100}以及R_{101}各個代表1至4個獨立地選自於下列的取代基：氫、鹵素、選擇性地經取代的C_1-C_8烷基、選擇性地經取代的C_2-C_8烯基、選擇性地經取代的C_2-C_8炔基、選擇性地經取代的C_3-C_8環烷基、選擇性地經取代的C_1-C_8烷氧基、選擇性地經取代的C_1-C_8烷基胺基以及選擇性地經取代的C_1-C_8芳基；以及

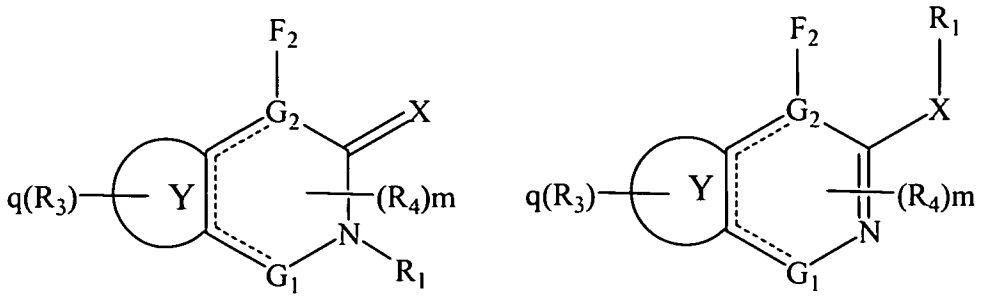
R_{103}是選自於：氫、鹵素、選擇性地經取代的C_1-C_8烷基、選擇性地經取代的C_2-C_8烯基、選擇性地經取代的C_2-C_8炔基、選擇性地經取代的C_3-C_8環烷基、選擇性地經取代的C_1-C_8烷氧基、選擇性地經取代的C_1-C_8烷基胺基以及選擇性地經取代的C_1-C_8芳基。

3. 如申請專利範圍第1項的化合物，其中Cy_1是選自於：





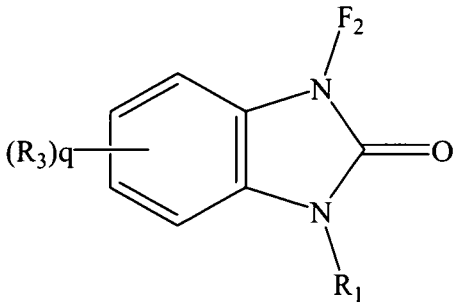
4. 如申請專利範圍第1項的化合物，其具有下列化學式：

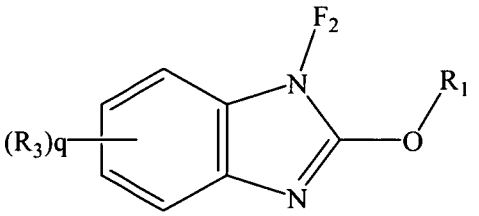


化學式VIII　　化學式VIIIA

其中環Y、R_1、R_3、R_4、G_1、G_2、X、F_2、m以及q是如申請專利範圍第1項中所定義的。

5. 如申請專利範圍第4項的化合物，其具有下列化學式：

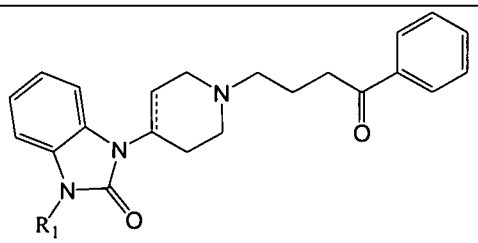
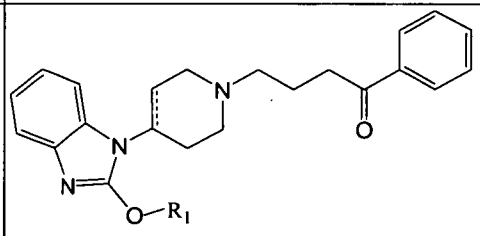
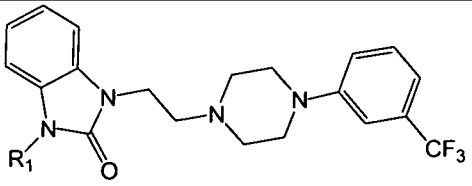
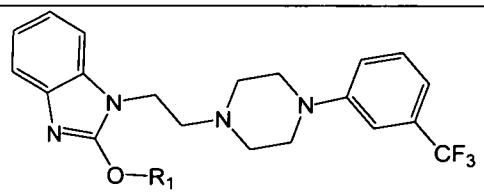
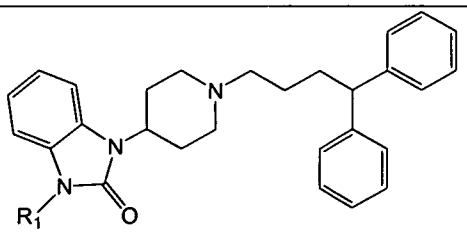
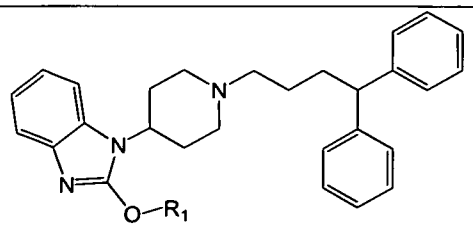
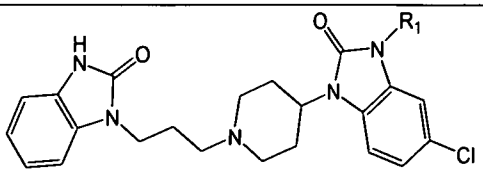
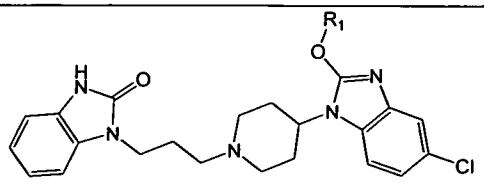


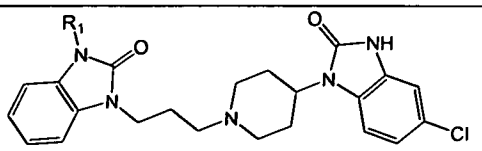
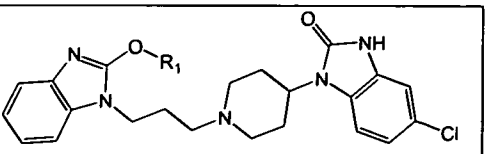
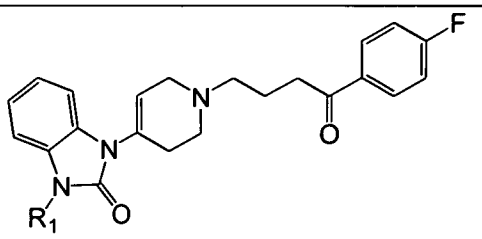
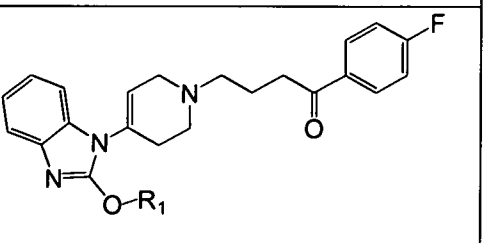
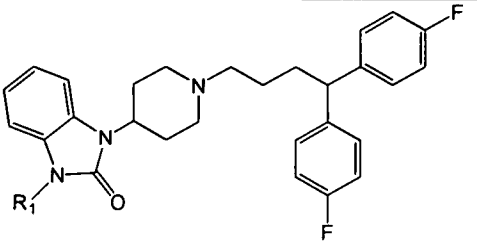
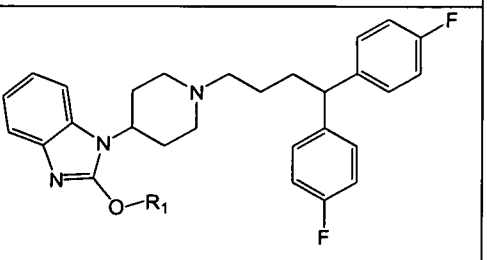


化學式IX　　化學式X

其中R_1、R_3、F_2以及q是如申請專利範圍第1項中所定義的。

6. 如申請專利範圍第5項的化合物，其選自於下面表IX-X：

編號	結構	編號	結構
1		8	
2		9	
3		10	
4		11	

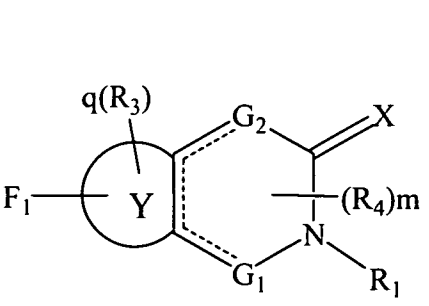
5		12	
6		13	
7		14	

其中R_1是選自於$-C(R_A)(R_B)-OC(O)OR_{20}$、$-C(R_A)(R_B)-OC(O)R_{20}$及$-C(R_A)(R_B)-OC(O)NR_{20}R_{21}$；

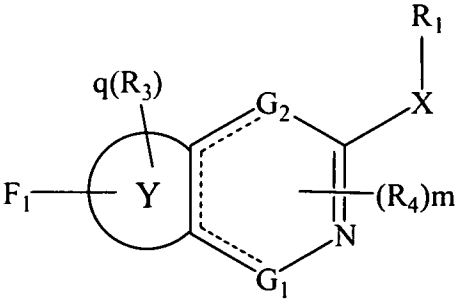
其中各個R_A以及R_B是氫；

各個R_{20}以及R_{21}獨立地選自於：氫、脂族、經取代的脂族、芳基或經取代的芳基。

7. 如申請專利範圍第1項的化合物，其具有下列化學式：



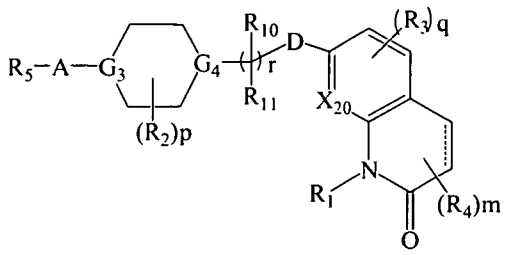
化學式XI



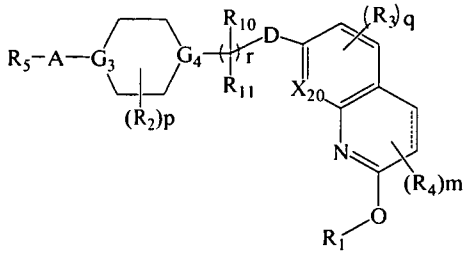
化學式XII

其中環Y、R_1、R_3、R_4、X、F_1、G_1、G_2、m以及q是如申請專利範圍第1項中所定義的。

8. 如申請專利範圍第7項的化合物，其具有下列化學式：



化學式XIA



化學式XIIA

其中R_1、R_3、R_4、R_5、R_{10}、R_{11}、A、D、m以及q是如申請專利範圍第1項中所定義的；

R_2是選自於：不存在、氫、鹵素、-OR_{10}、-SR_{10}、-$NR_{10}R_{11}$-、選擇性地經取代的脂族、選擇性地經取代的芳基或芳基或選擇性地經取代的雜環基；

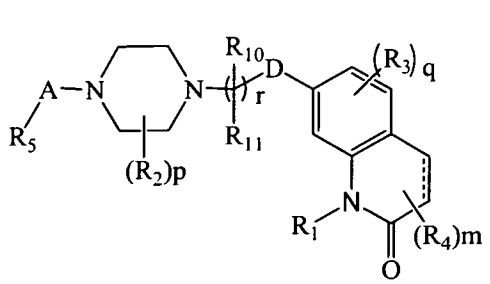
r是0、1、2、3、4、5、6、7、8、9、10或11；

各個G_3以及G_4是獨立地選自於：-N-、-$C(R_{10})$-$[C(R_{10})(R_{11})]_a$-，其中a是0、1或2；

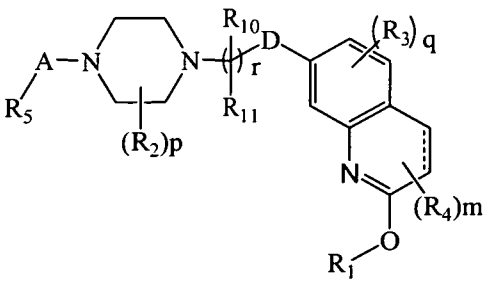
X_{20}是-$C(R_{10})$-或-N-；以及

p是選自0、1、2或3。

9. 如申請專利範圍第8項的化合物，其具有下列化學式：



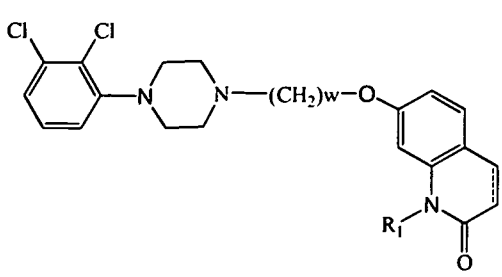
化學式XIB



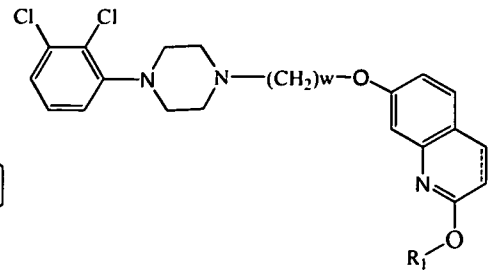
化學式XIIB

其中R_1、R_2、R_3、R_4、R_5、R_{10}、R_{11}、A、D、m以及q是如申請專利範圍第1項中所定義的，而p是如申請專利範圍第8項中所定義的。

10. 一種具有下列化學式XIC或XIIC之化合物：



化學式XIC



化學式XIIC

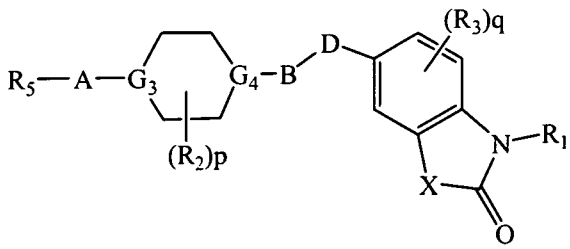
其中R_1是選自於$-C(R_A)(R_B)-OC(O)OR_{20}$、$-C(R_A)(R_B)-OC(O)R_{20}$及$-C(R_A)(R_B)-OC(O)NR_{20}R_{21}$；

其中各個R_A以及R_B是氫；

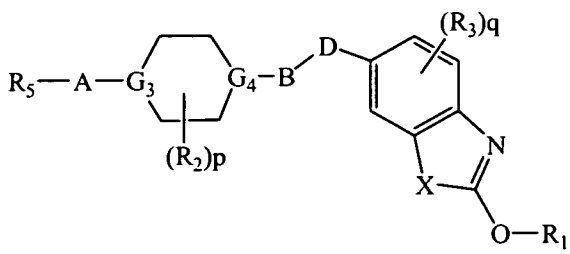
各個R_{20}以及R_{21}獨立地選自於：氫、脂族、經取代的脂族、芳基或經取代的芳基；以及

w是1、2、3、4、5、6、7、8、9、10或11。

11. 如申請專利範圍第7項的化合物，其具有下列化學式：



化學式XID

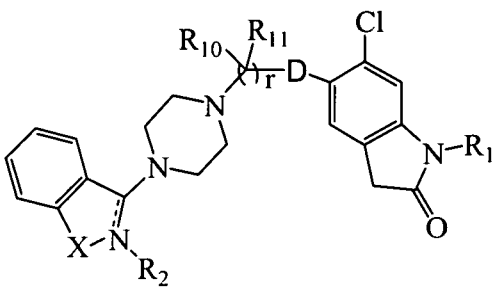


化學式XIID

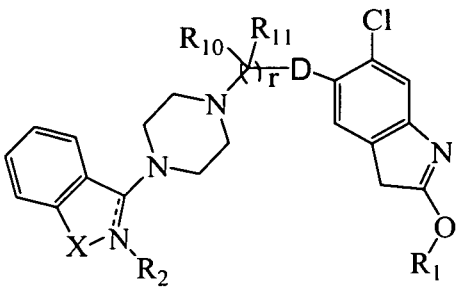
其中，X_1、R_1、R_2、R_3、R_5、A、B、D、q、R_{10}以及R_{11}

是如申請專利範圍第1項中所定義的，而G_3、G_4、p是如申請專利範圍第8項中所定義的。

12. 如申請專利範圍第11項的化合物，其具有下列化學式：



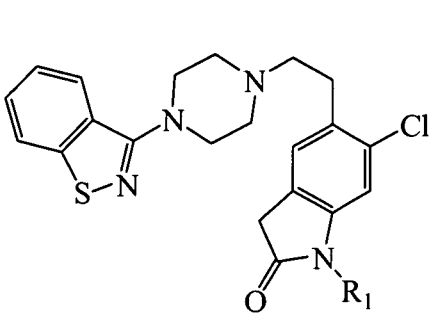
化學式XIF



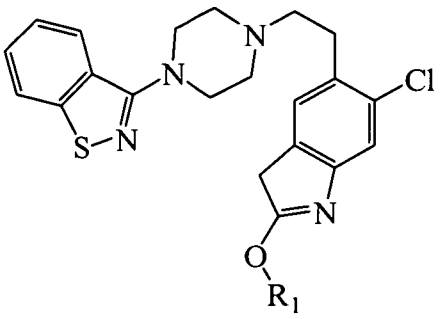
化學式XIIF

其中，X、R_1、R_2、D、r、R_{10}以及R_{11}是如申請專利範圍第1項中所定義的。

13. 如申請專利範圍第12項的化合物，其具有下列化學式：



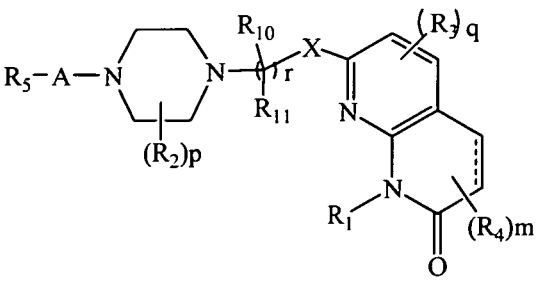
化學式XIG



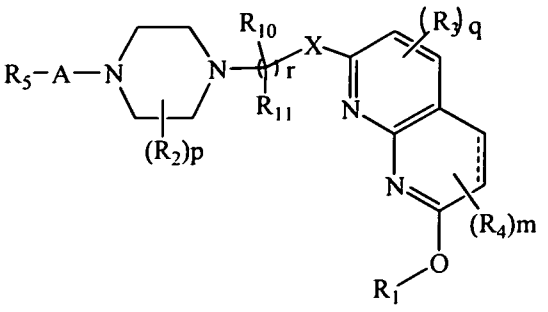
化學式XIIG

其中R_1是如申請專利範圍第1項中所定義的。

14. 如申請專利範圍第8項的化合物，其具有下列化學式：



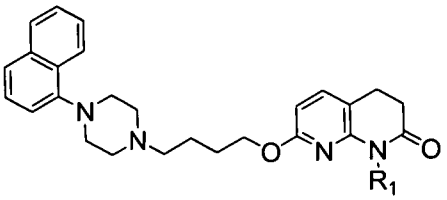
化學式XIJ



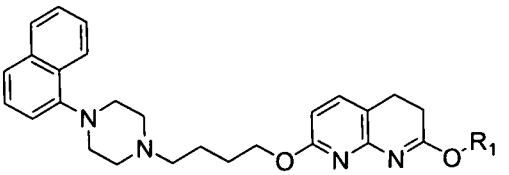
化學式XIIJ

其中，X、R_1、R_2、R_3、R_4、R_5、A、D、R_{10}以及R_{11}是如申請專利範圍第1項中所定義的，而G_3、G_4、p是如申請專利範圍第8項中所定義的。

15. 如申請專利範圍第13項的化合物，其具有下列化學式XIK以及XIIK：



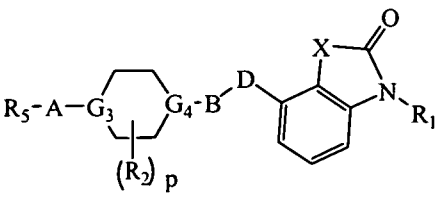
化學式XIK



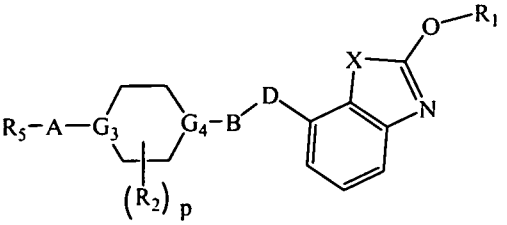
化學式XIIK

其中R_1是如申請專利範圍第1項中所定義的。

16. 如申請專利範圍第1項的化合物，其具有下列化學式：



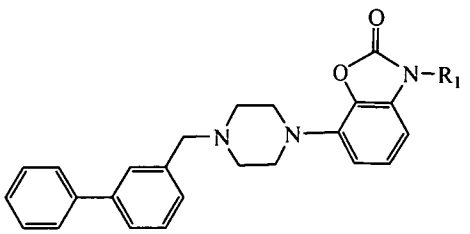
化學式XIH



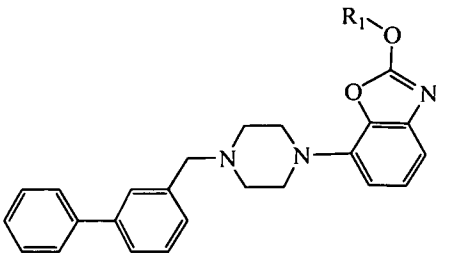
化學式XIIH

其中，X、R_1、R_2、R_5、A、D是如申請專利範圍第1項中所定義的，而G_3、G_4以及p是如申請專利範圍第8項中所定義的。

17. 如申請專利範圍第16項的化合物，其具有下列化學式：



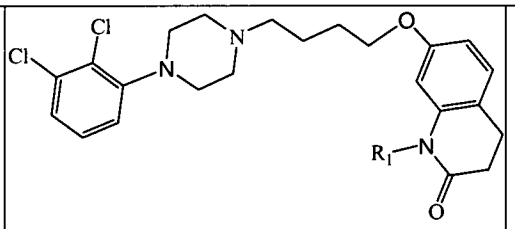
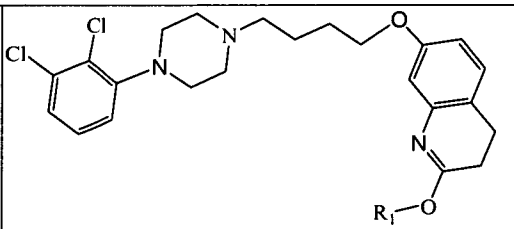
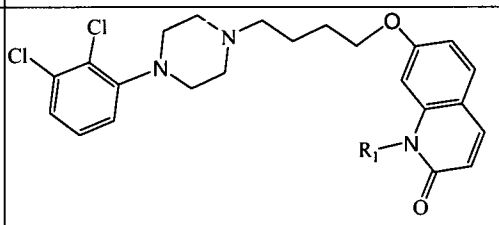
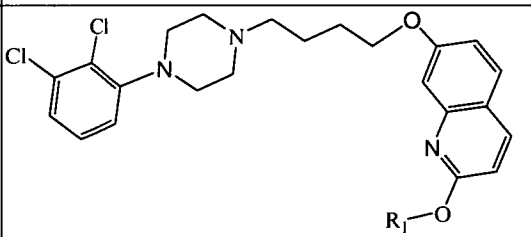
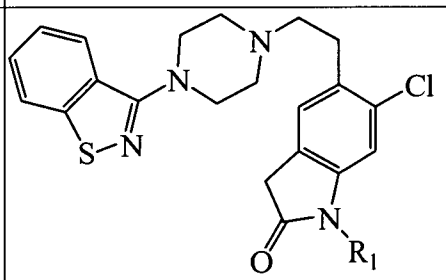
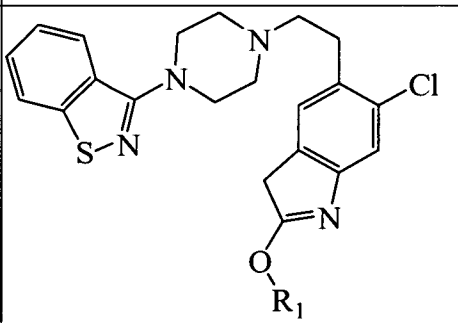
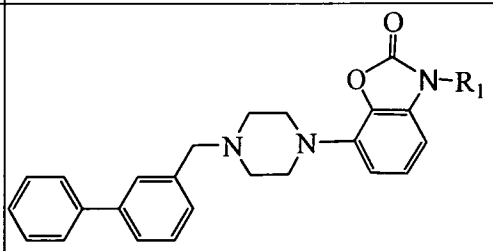
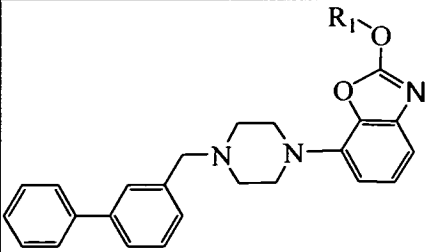
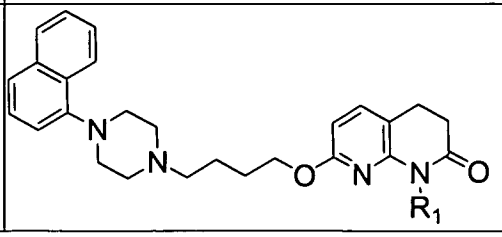
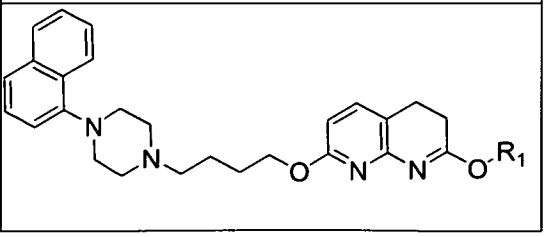
化學式XI-I

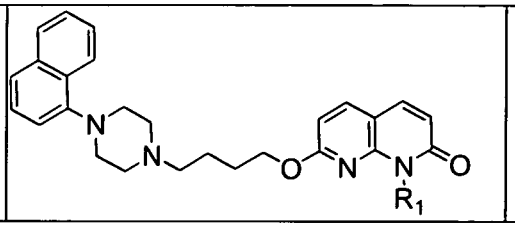
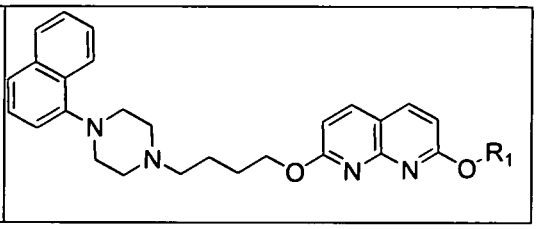


化學式XII-I

其中R_1是如申請專利範圍第1項中所定義的。

18. 一種化合物，其選自於下面表XI-XII：

1		7	
2		8	
3		9	
4		10	
5		11	

6		12	

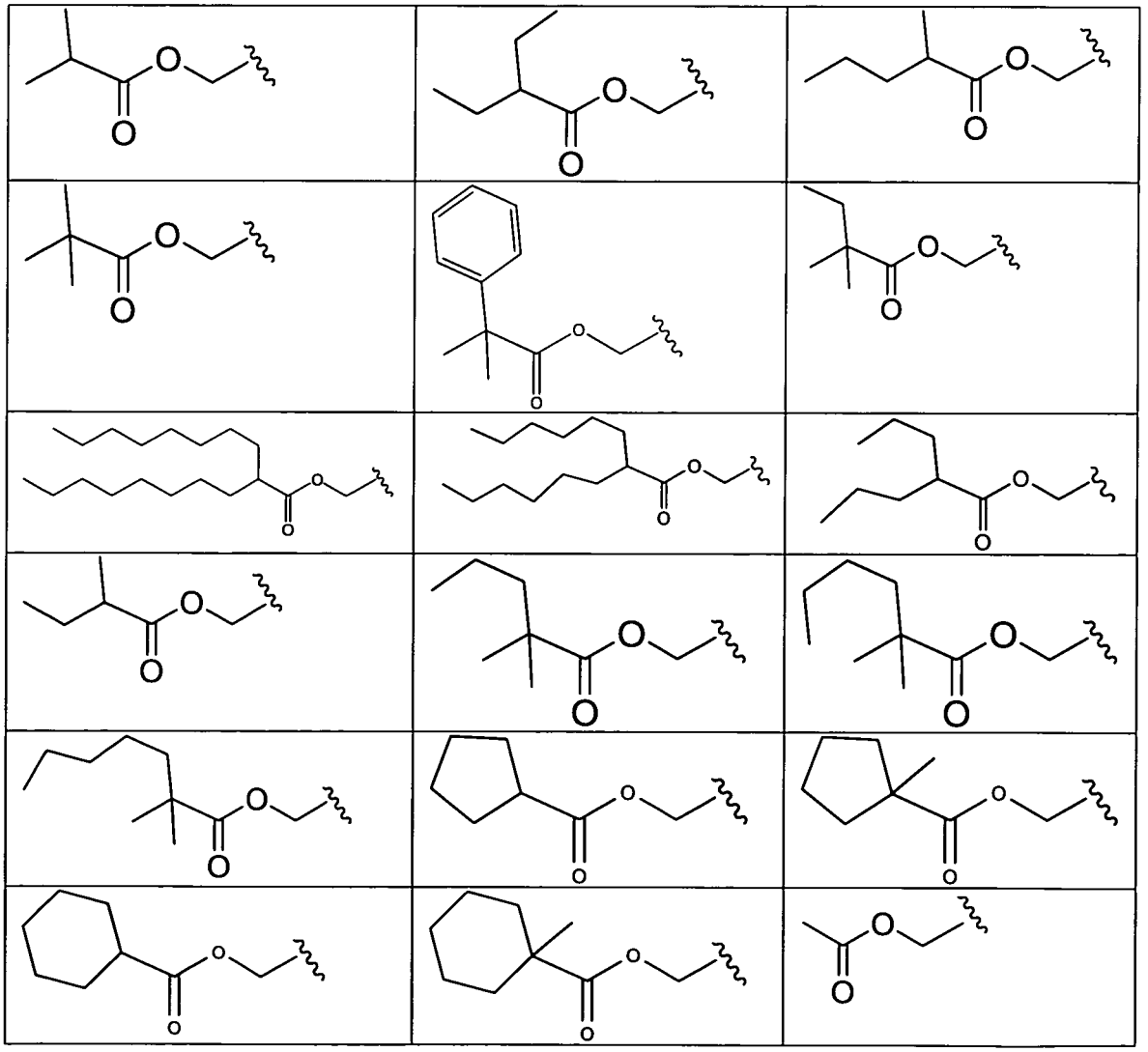
其中 R_1 是選自於 $-C(R_A)(R_B)-OC(O)OR_{20}$ 、$-C(R_A)(R_B)-OC(O)R_{20}$及$-C(R_A)(R_B)-OC(O)NR_{20}R_{21}$；

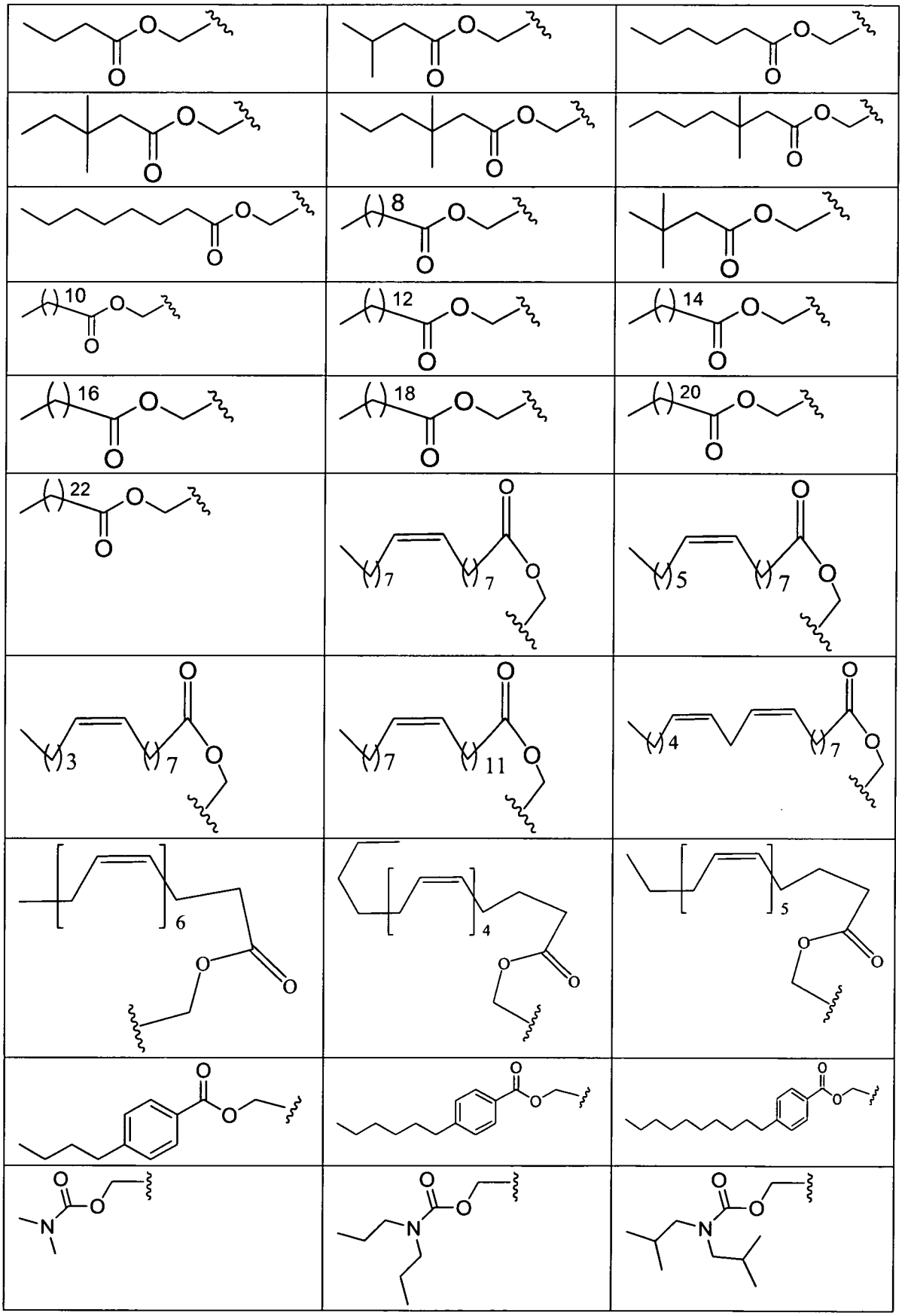
其中各個R_A以及R_B是氫；

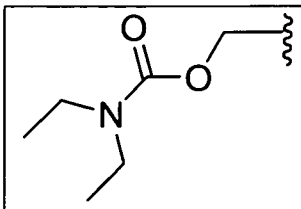
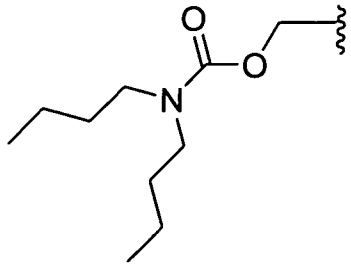
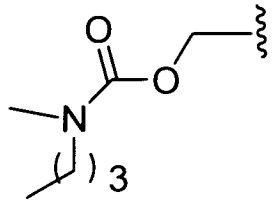
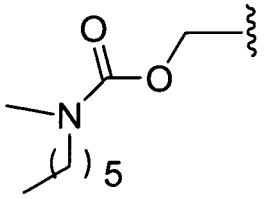
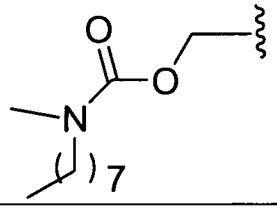
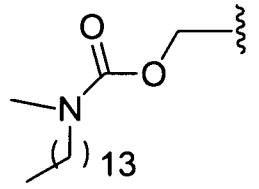
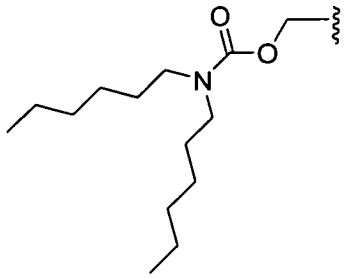
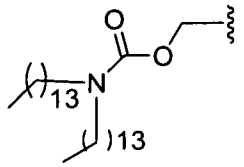
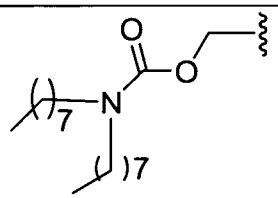
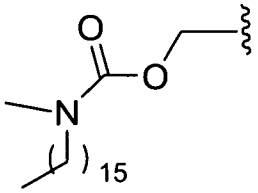
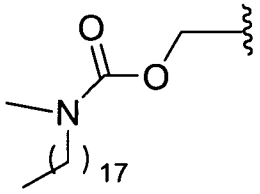
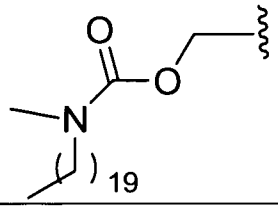
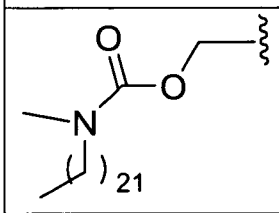
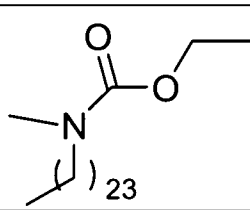
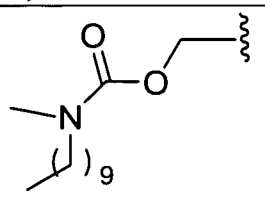
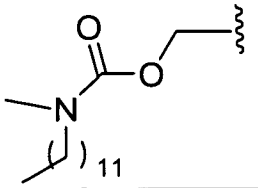
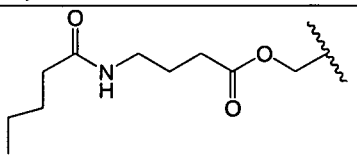
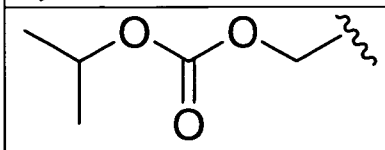
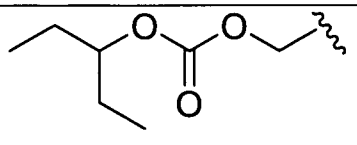
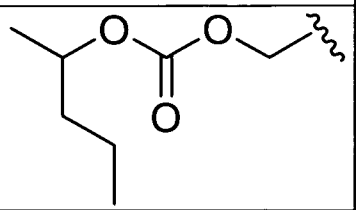
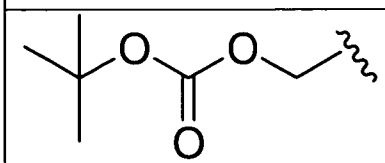
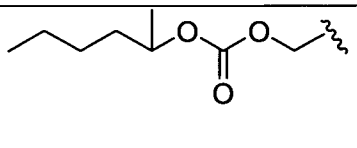
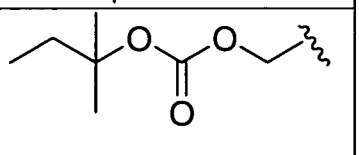
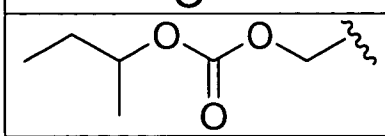
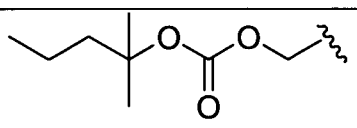
各個R_{20}以及R_{21}獨立地選自於：氫、脂族、經取代的脂族、芳基或經取代的芳基。

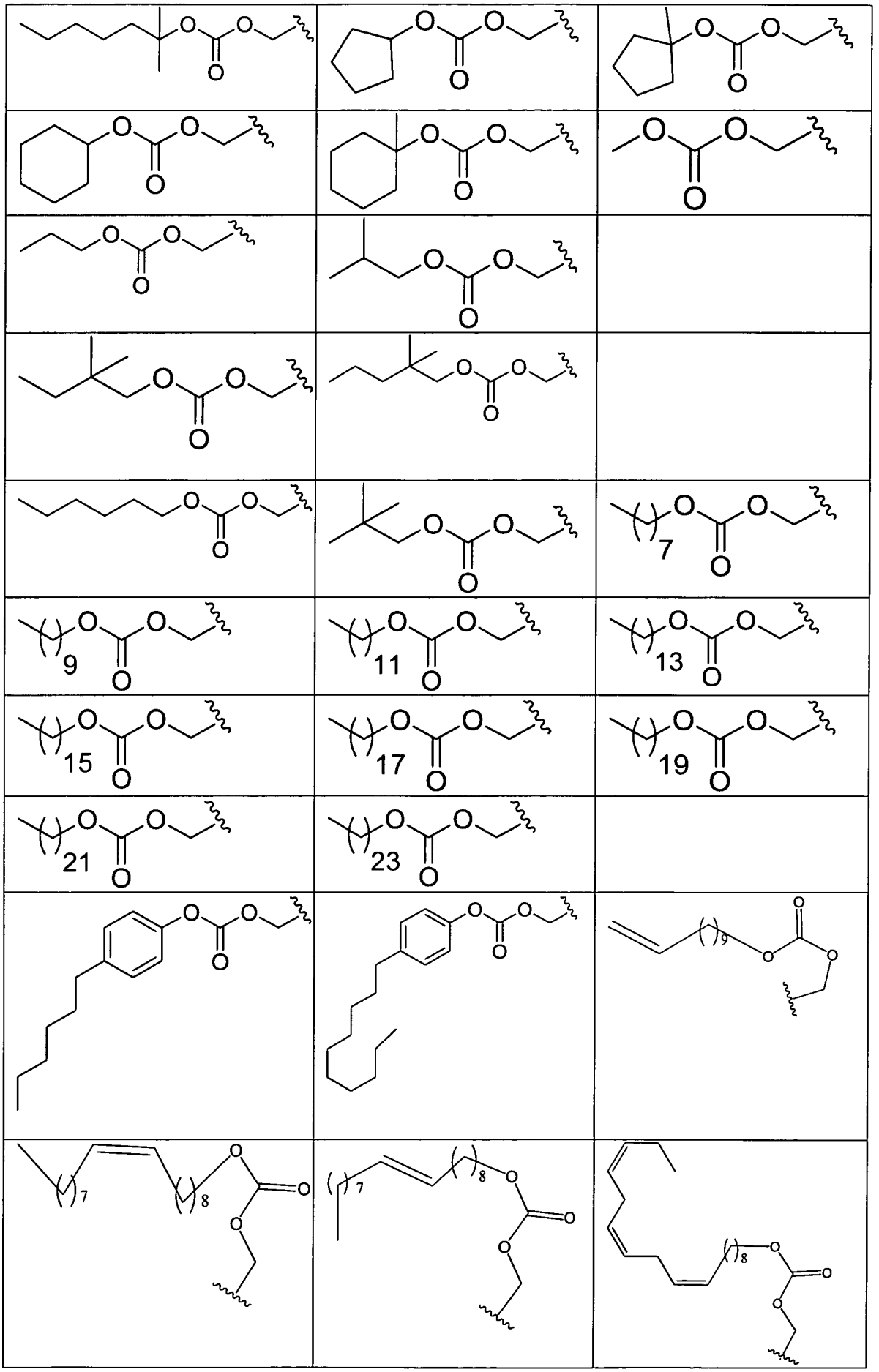
19. 如申請專利範圍第18項的化合物，其中R_1是選自於下面表1：

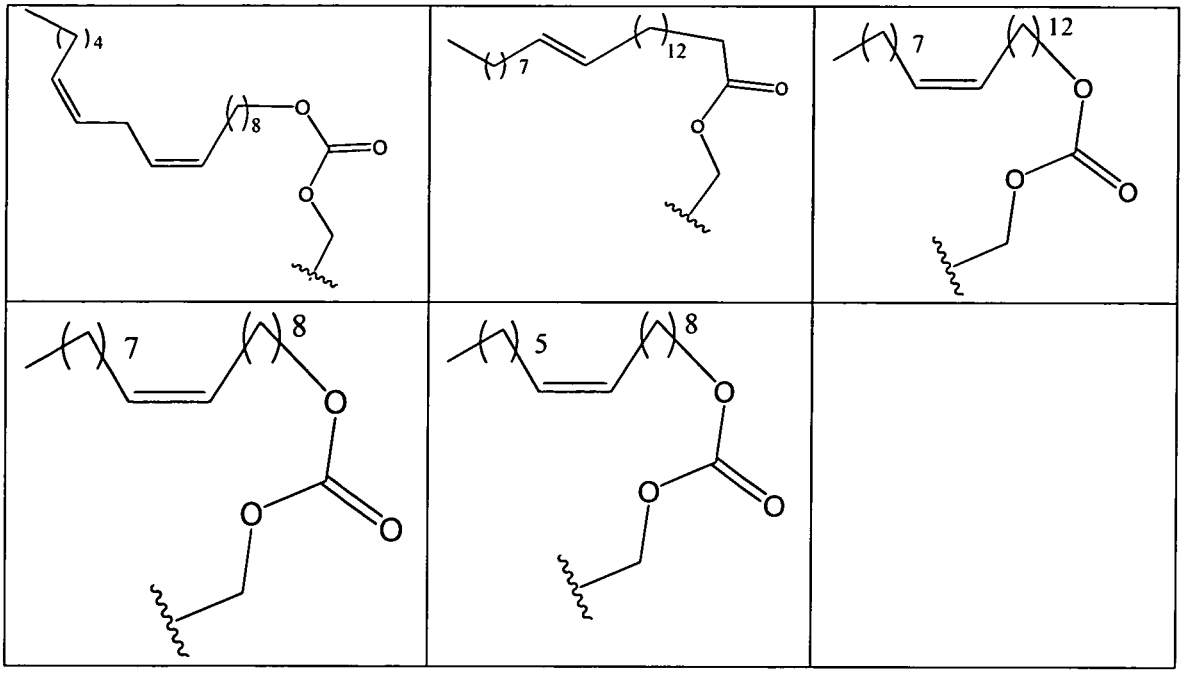
表1





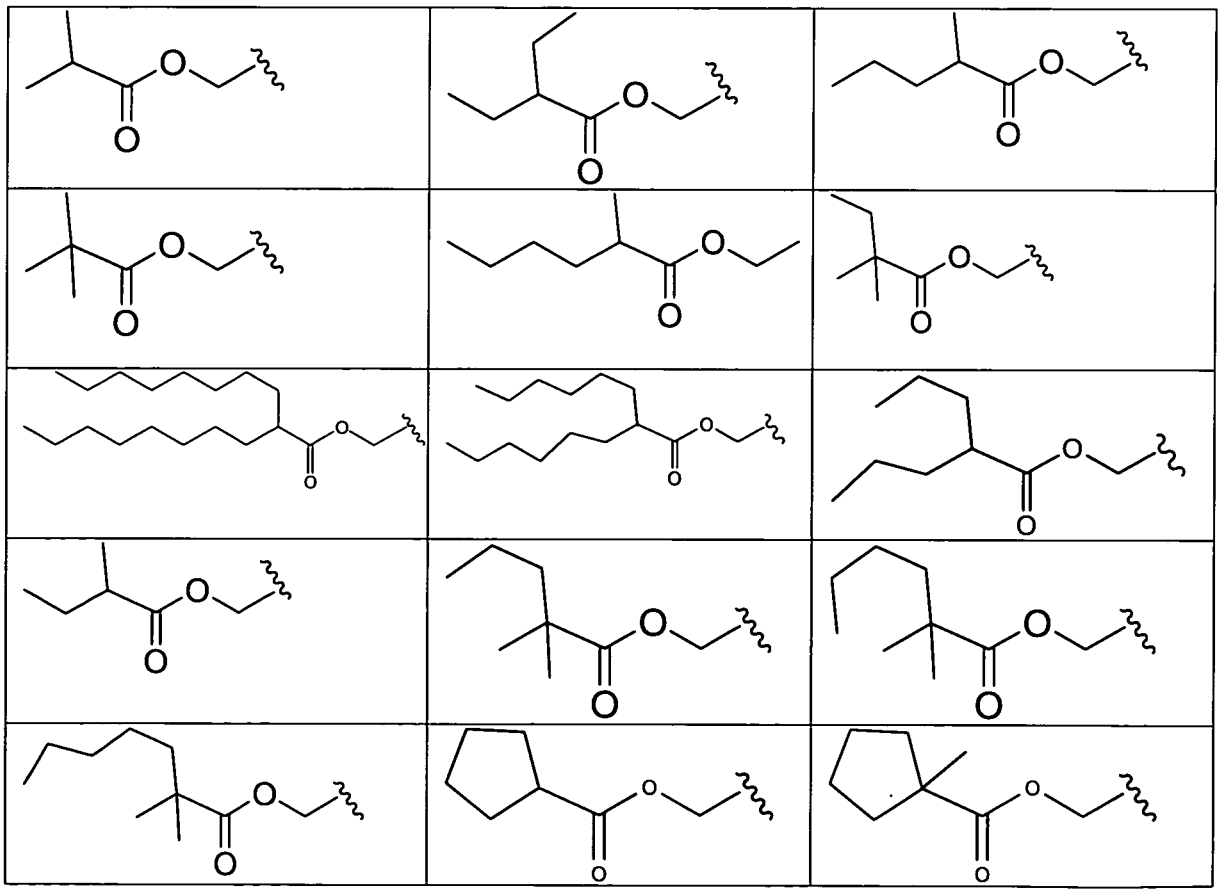


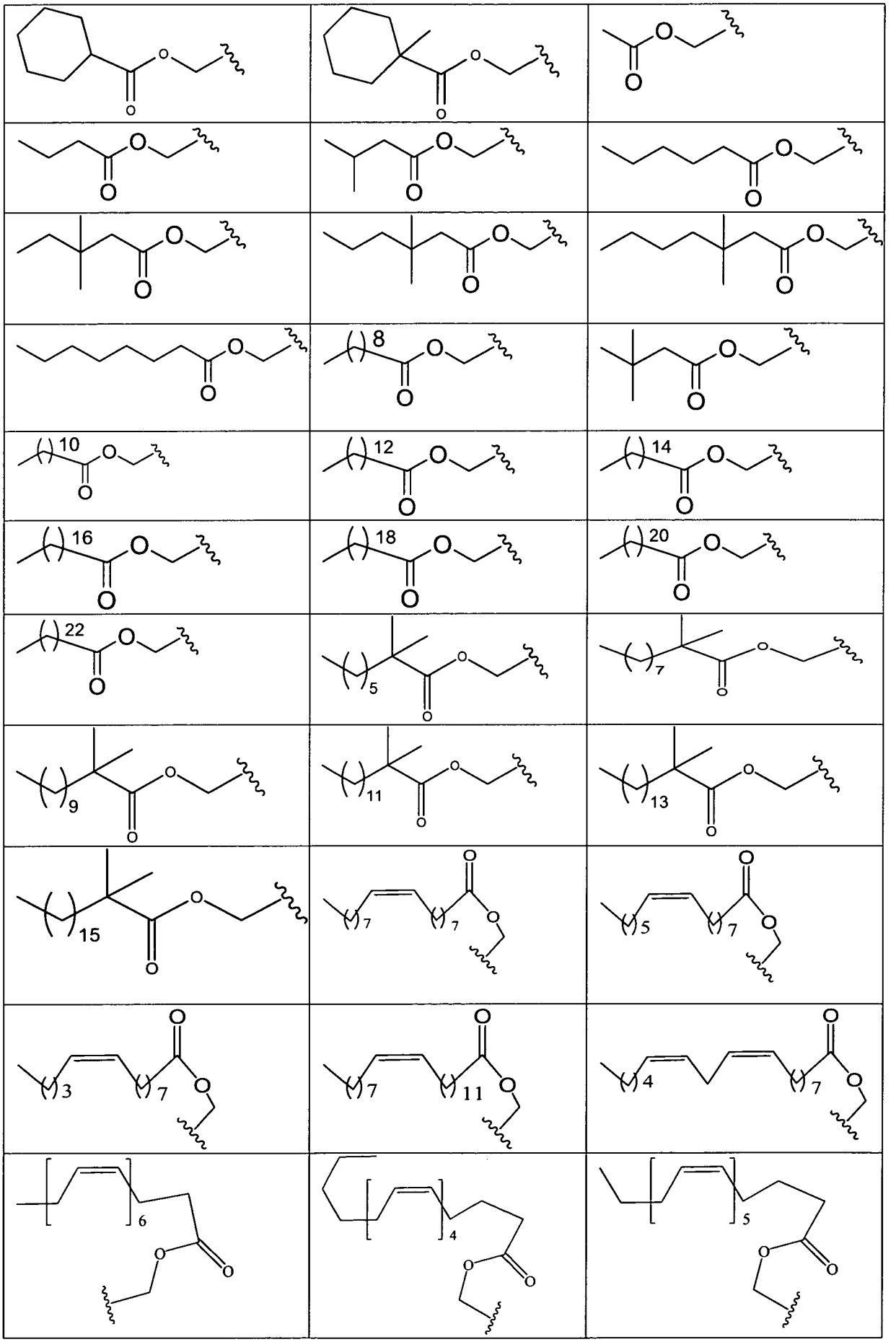


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20. 如申請專利範圍第18項的化合物，其中R_1是選自於下面表2：

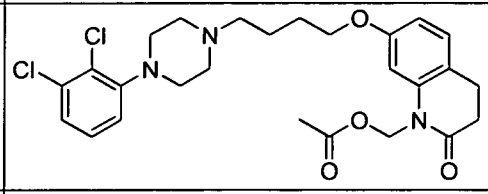
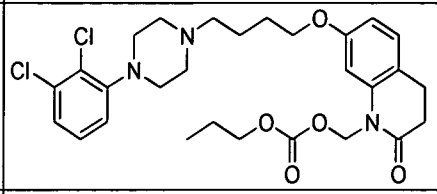
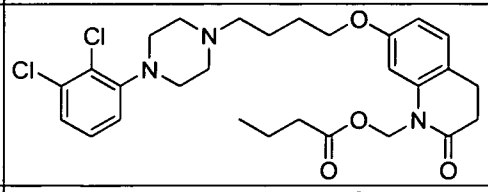
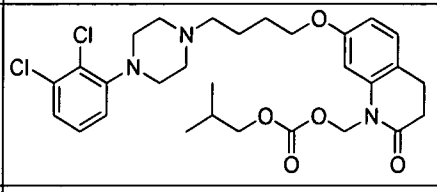
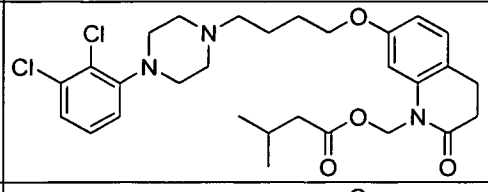
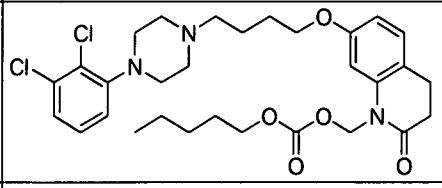
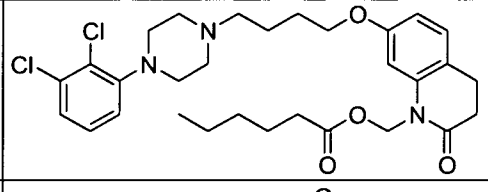
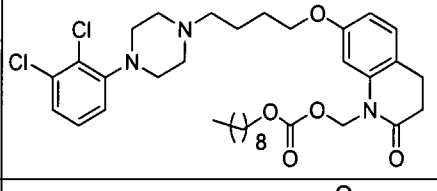
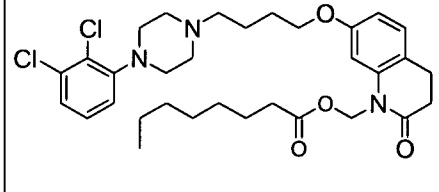
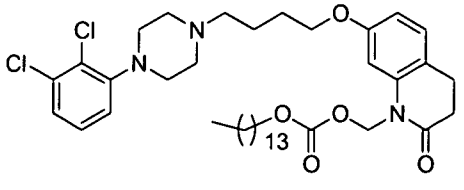
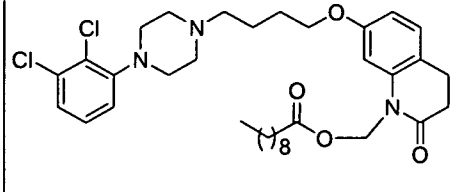
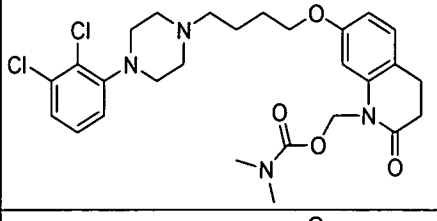
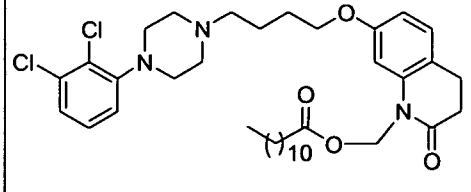
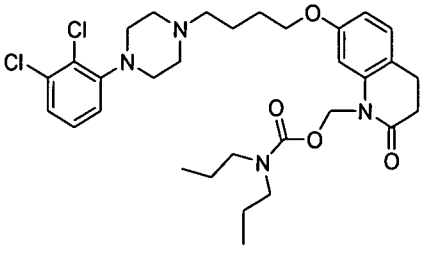
表2

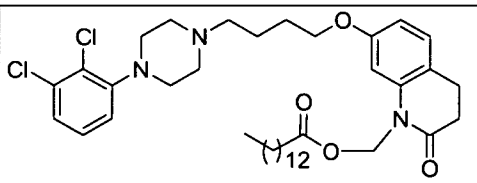
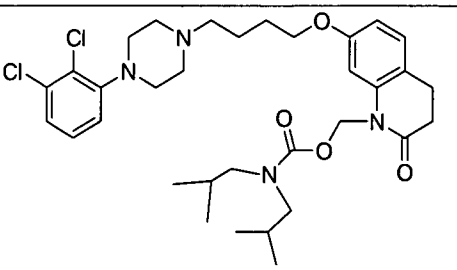
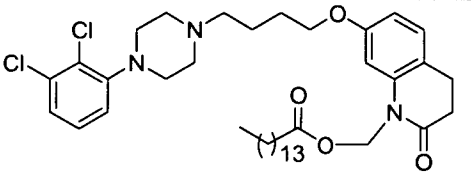
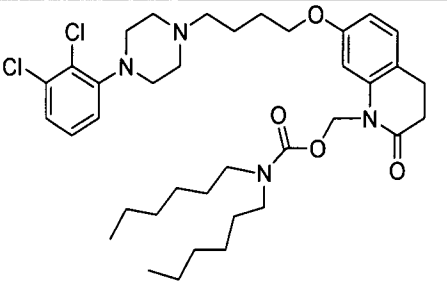
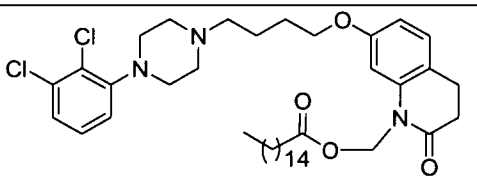
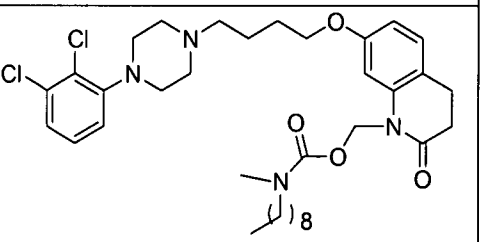
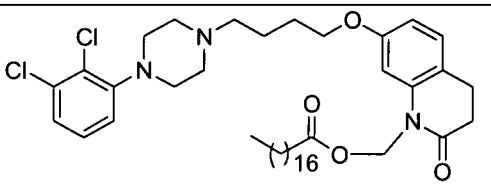
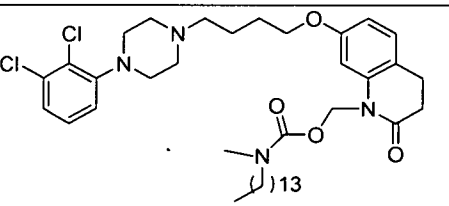
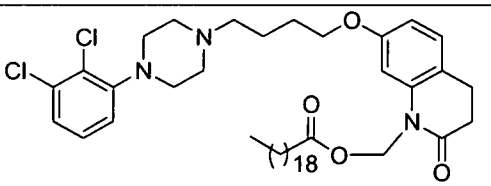
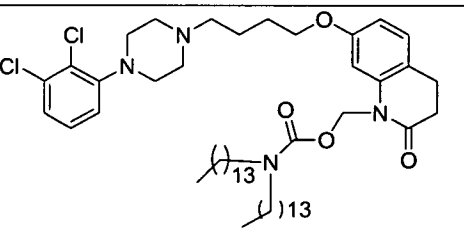
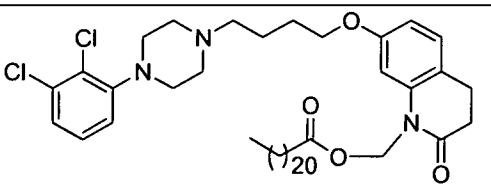
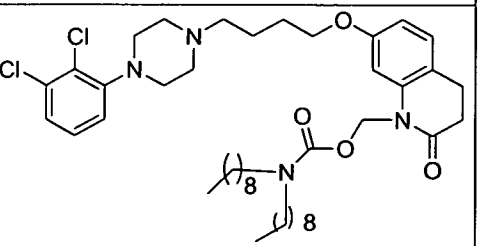


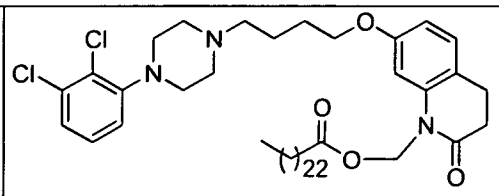
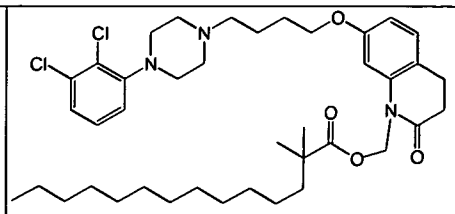
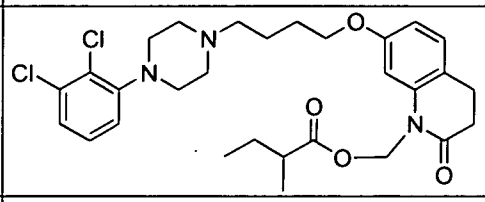
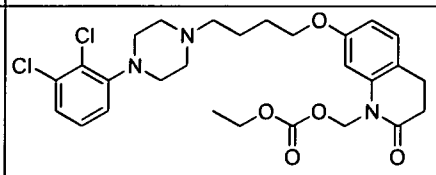
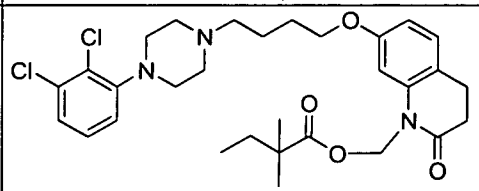
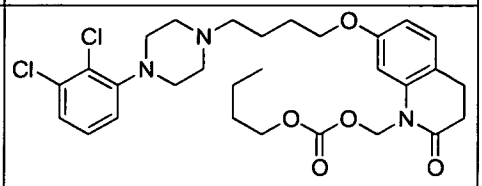
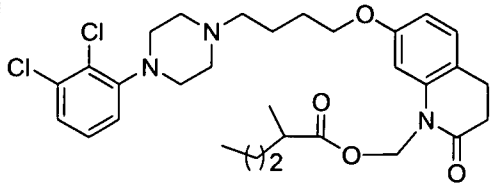
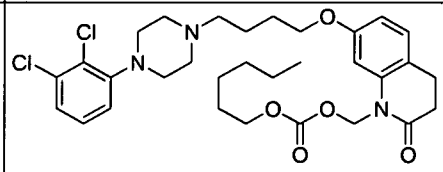
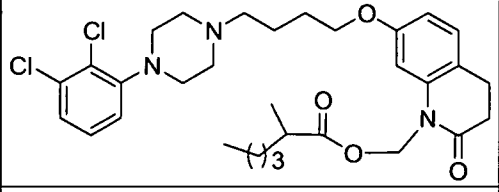
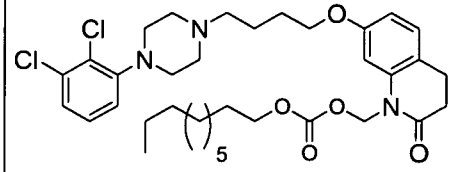
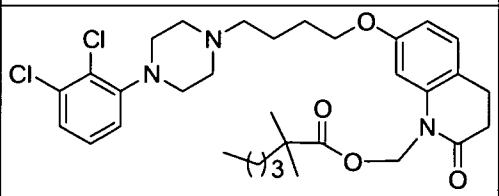
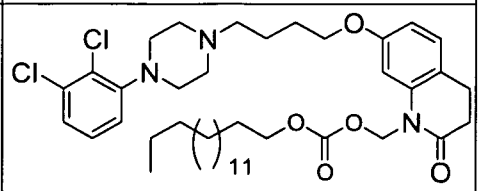
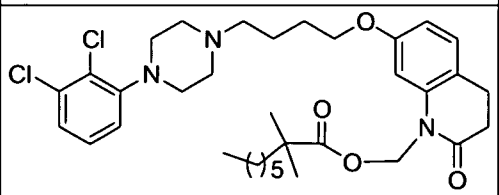
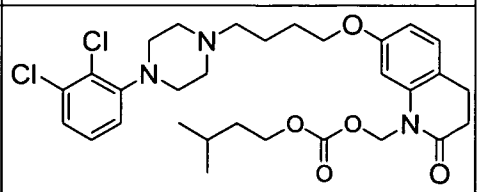
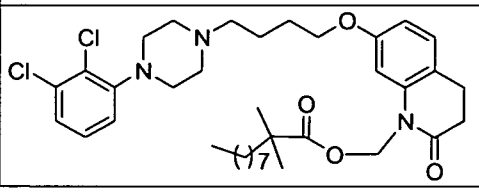
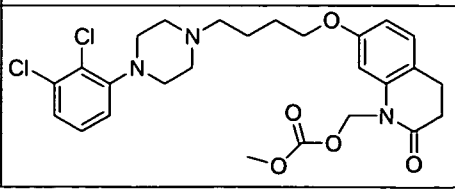


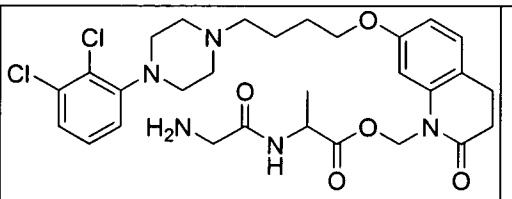
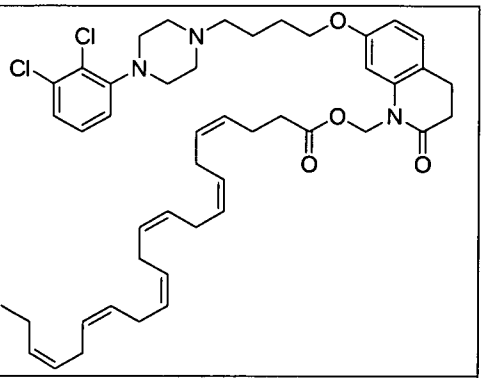
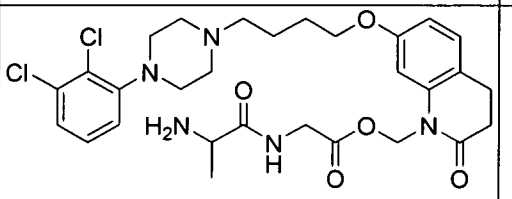
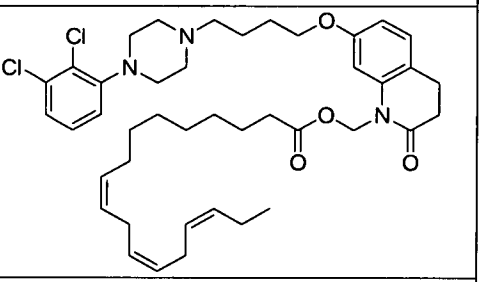
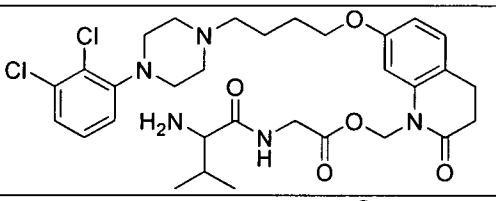
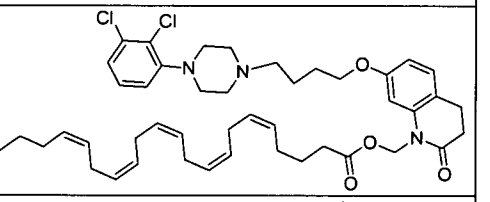
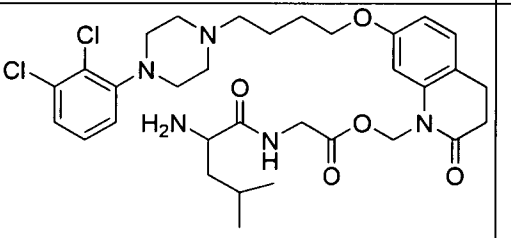
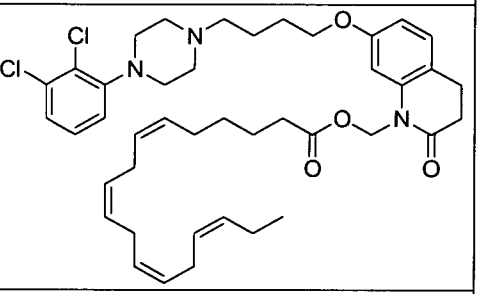
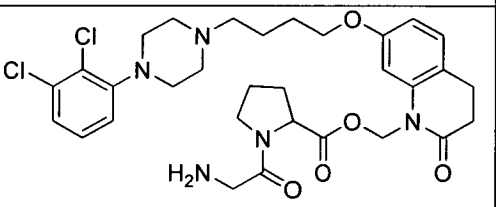
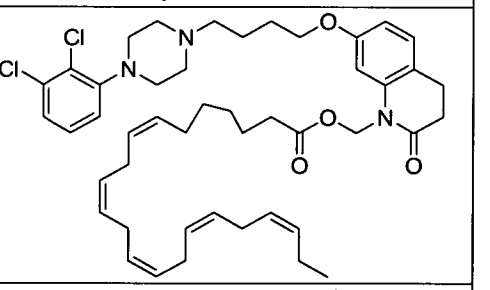
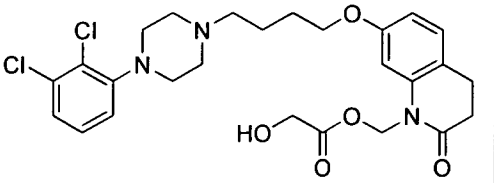
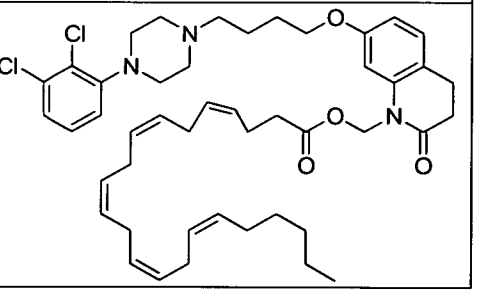
21. 如申請專利範圍第18項的化合物，其選自於下面表A、或表B：

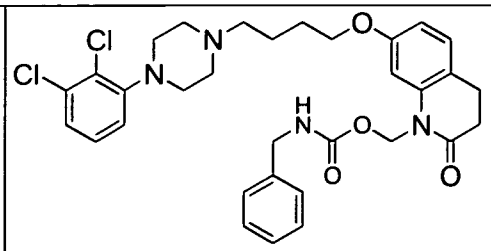
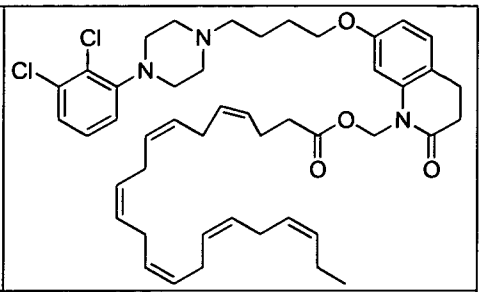
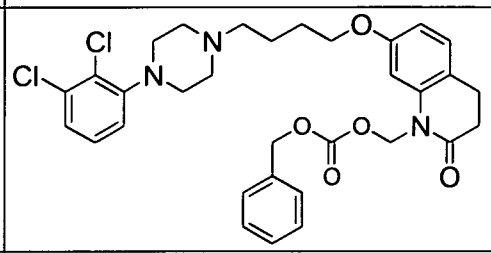
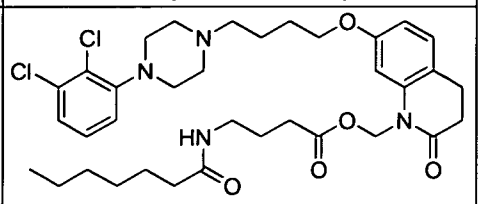
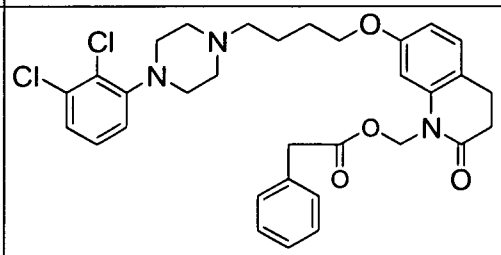
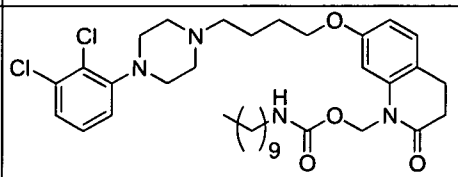
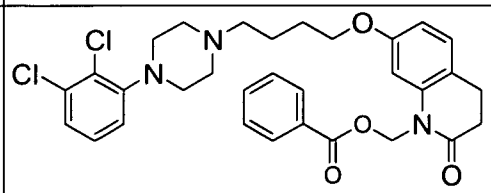
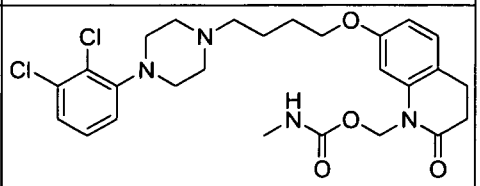
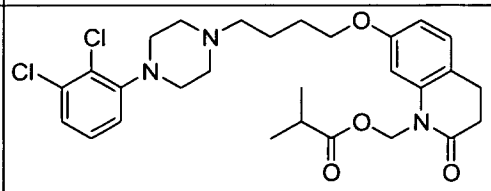
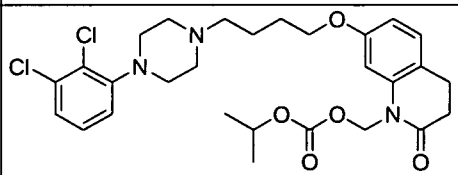
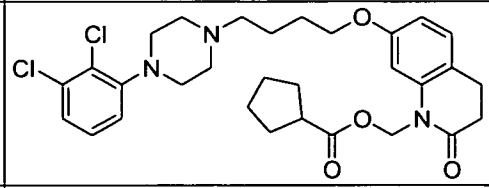
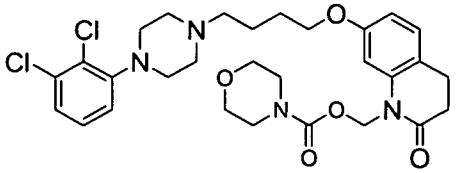
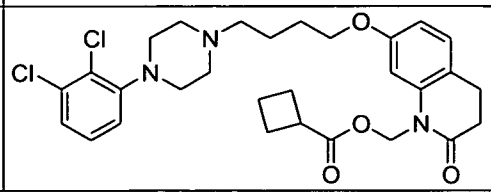
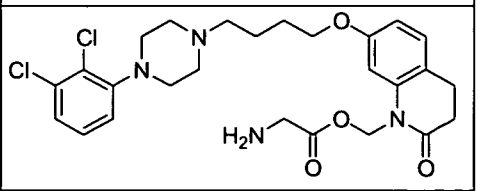
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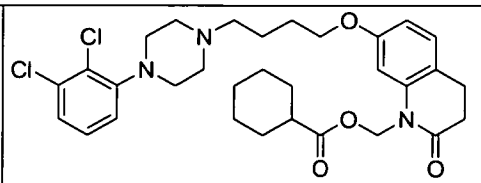
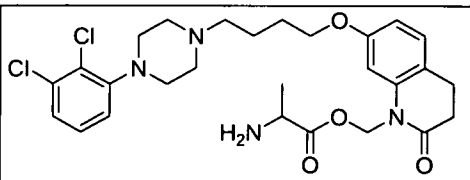
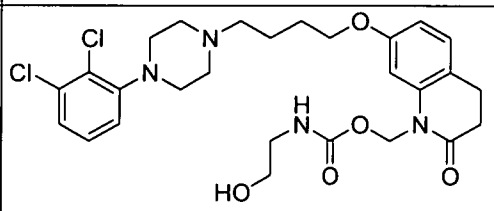
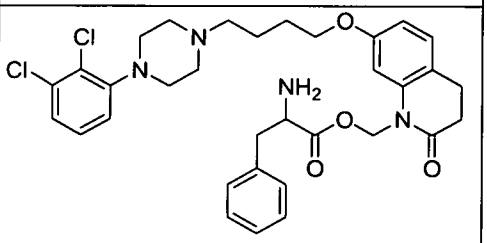
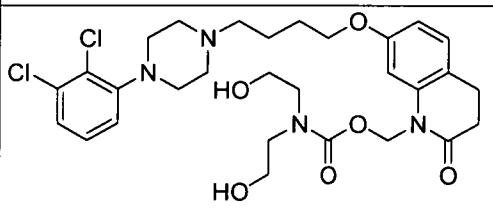
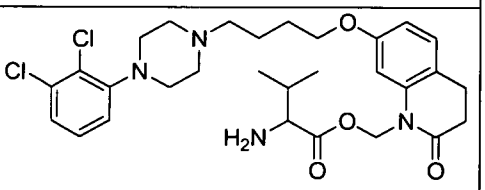
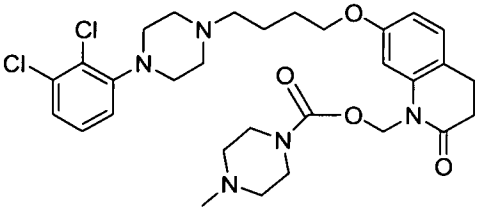
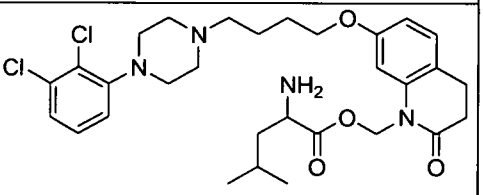
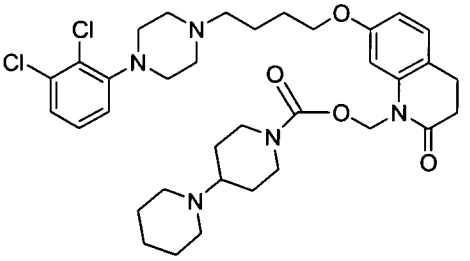
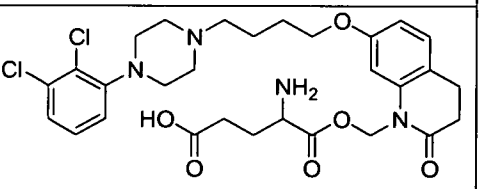
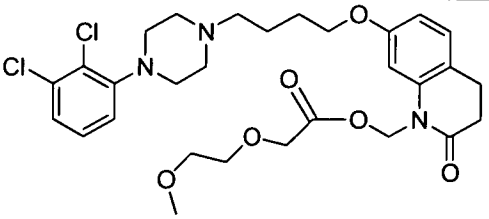
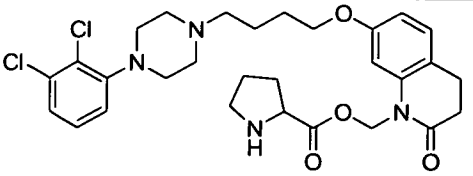
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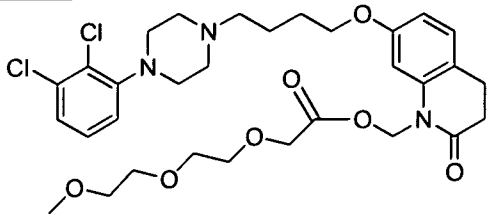
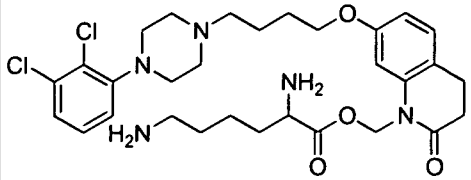
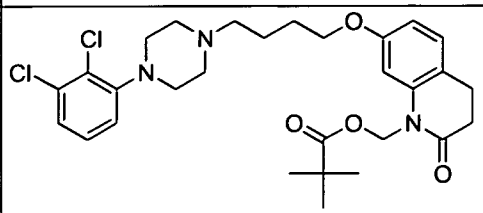
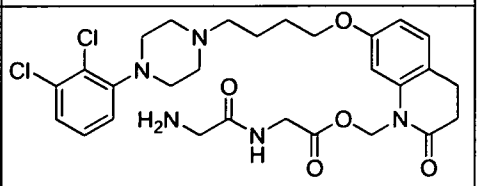
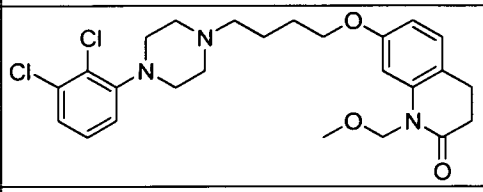
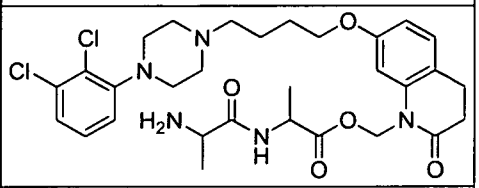
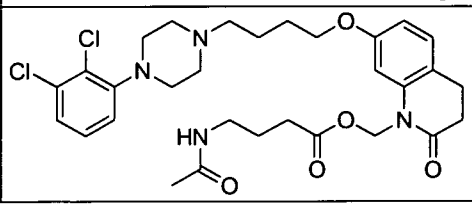
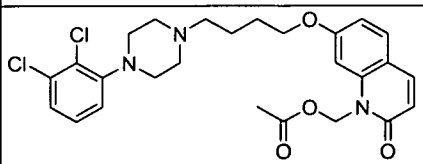
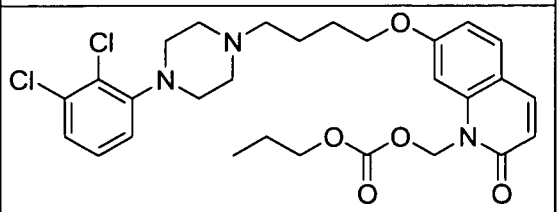
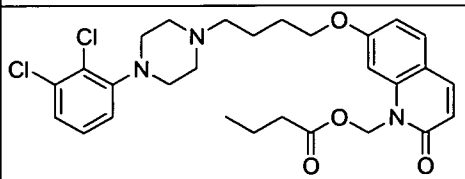
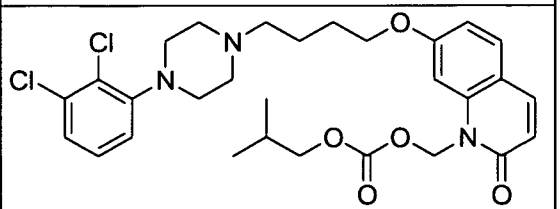
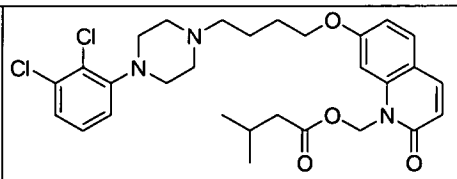
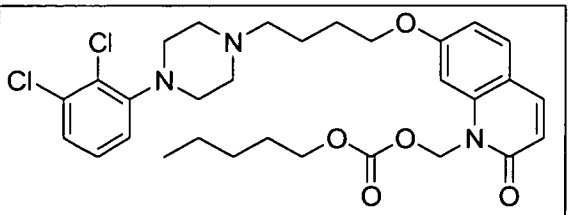
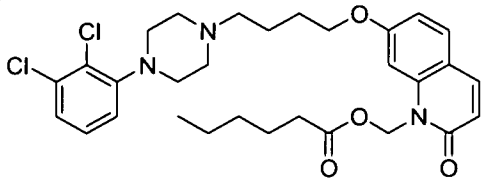
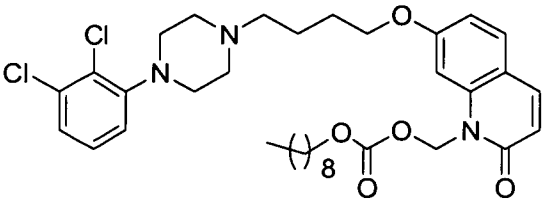
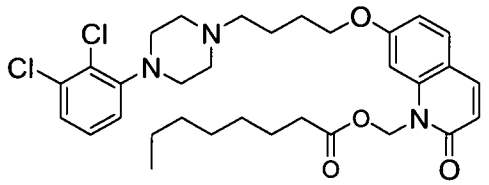
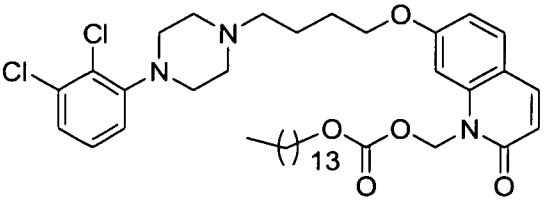
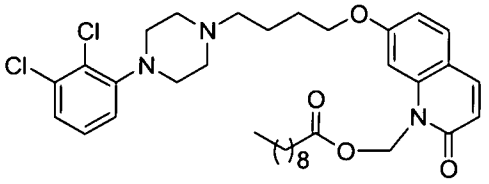
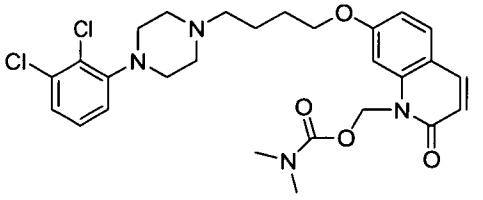
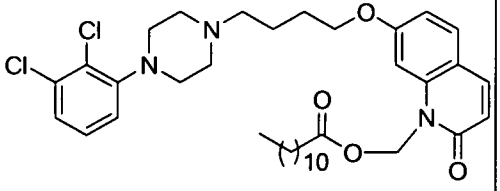
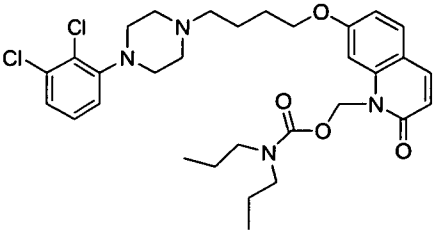
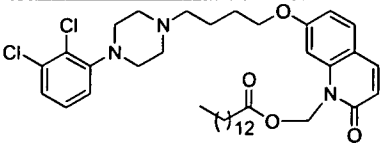
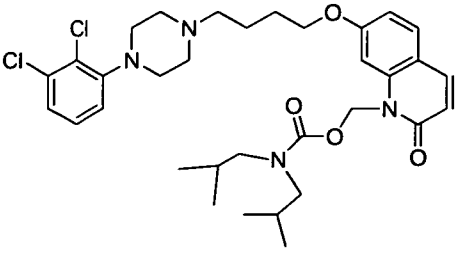
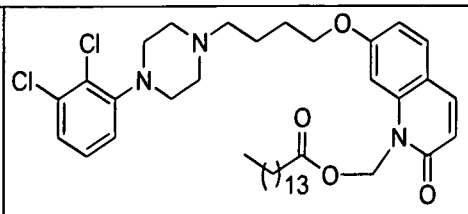
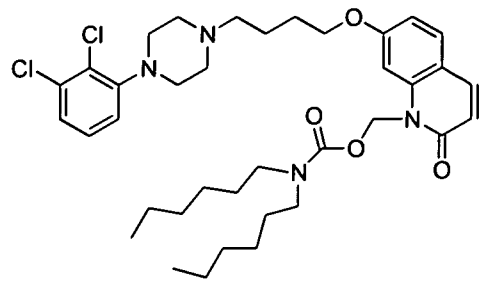
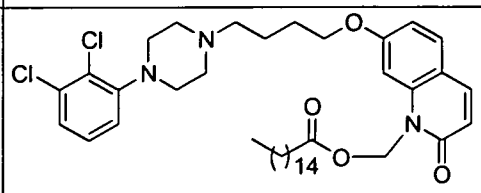
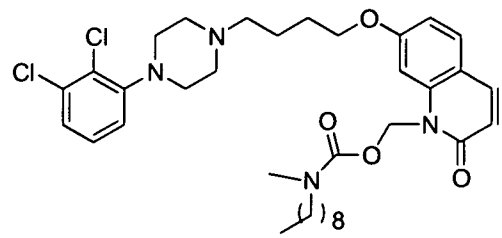
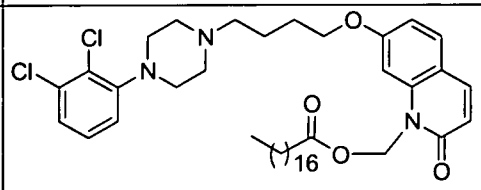
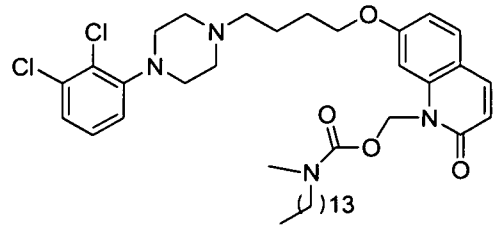
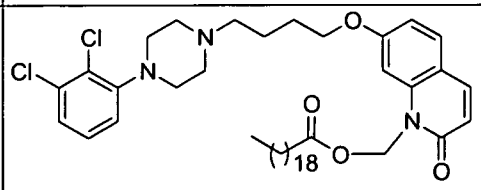
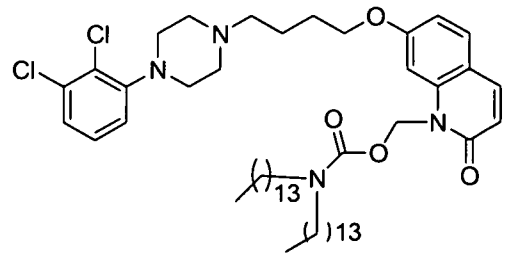
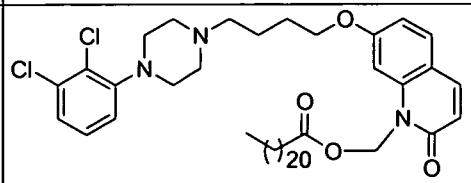
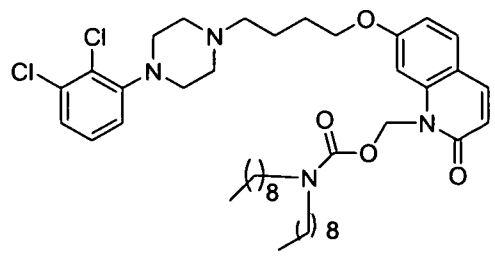
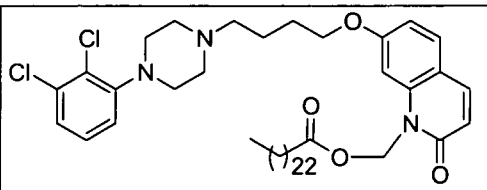
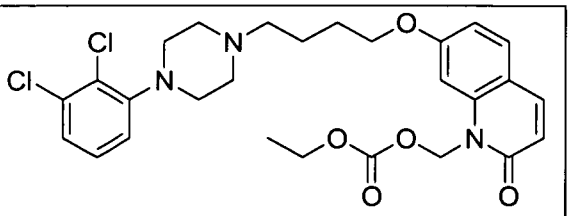
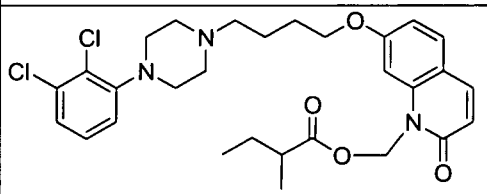
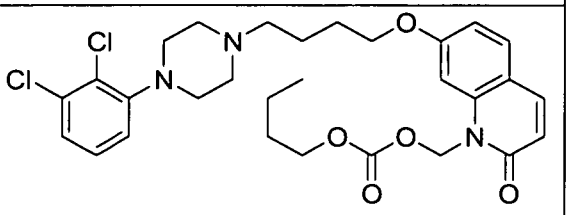
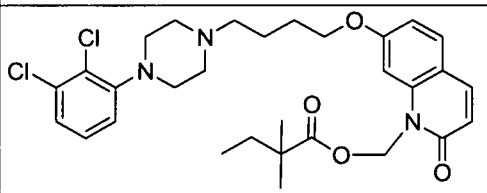
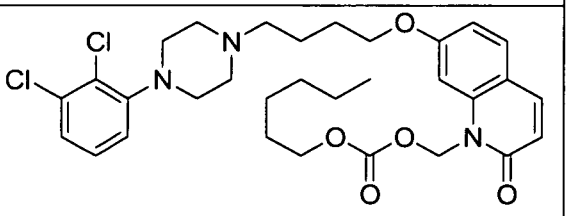
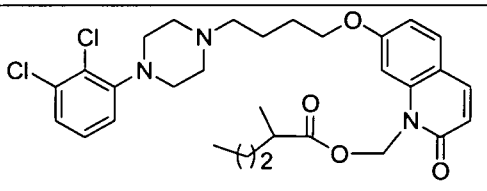
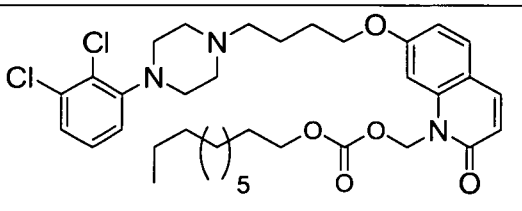
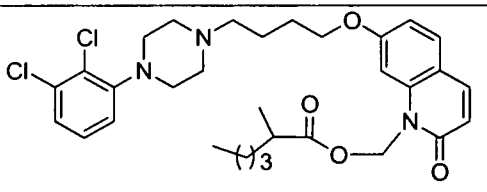
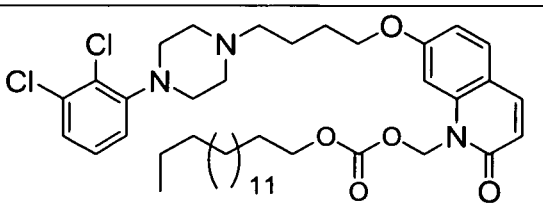
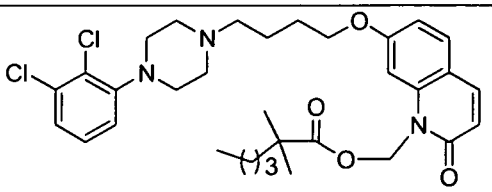
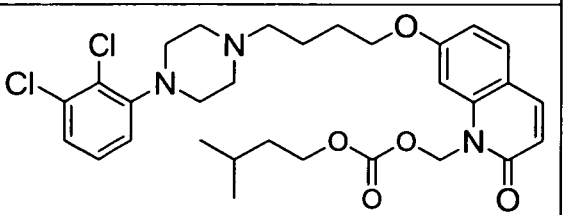
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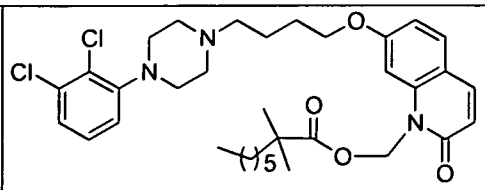
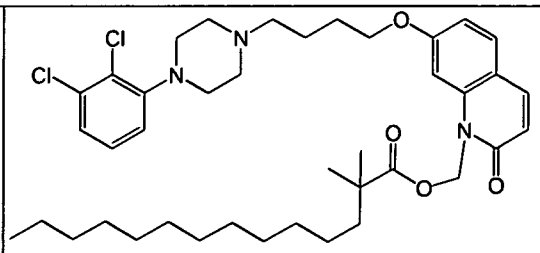
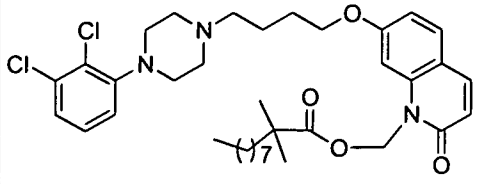
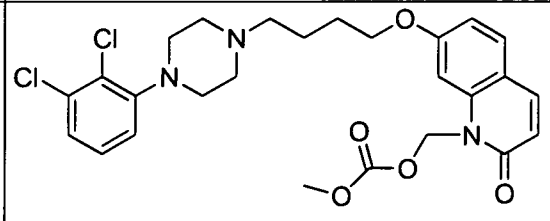
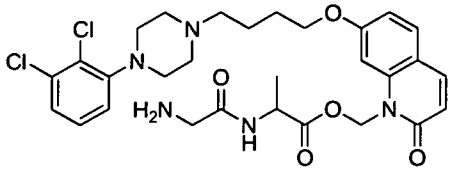
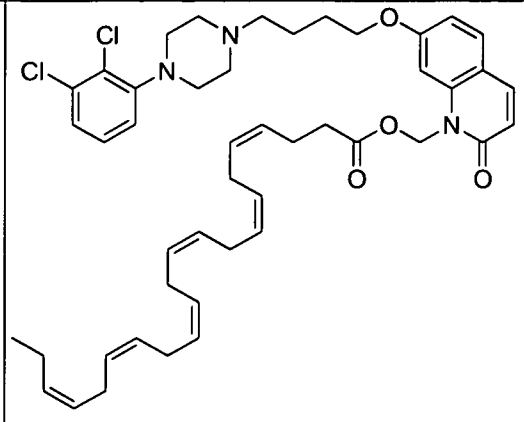
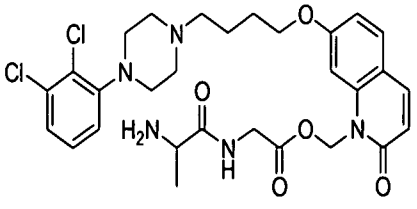
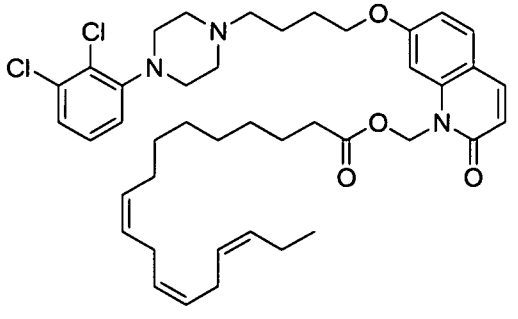
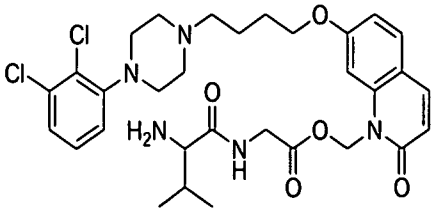
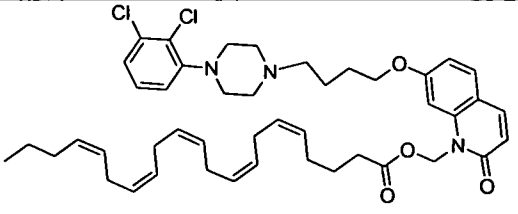
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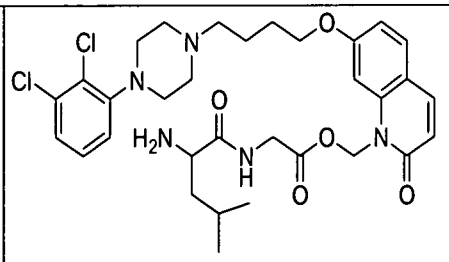
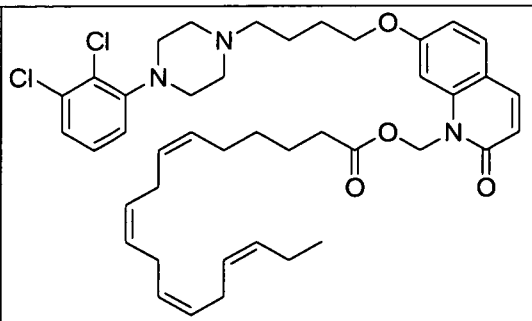
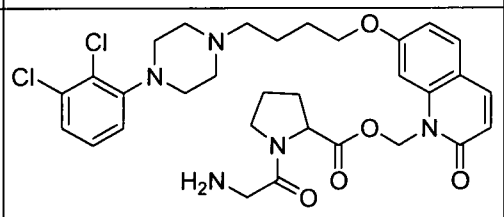
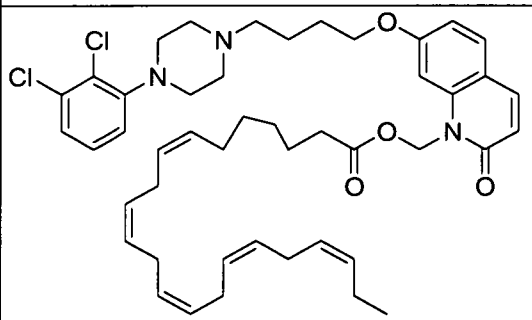
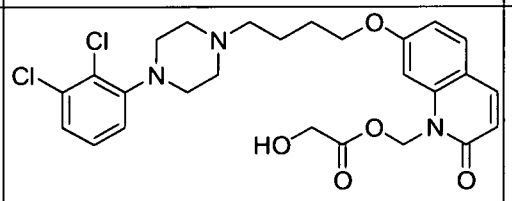
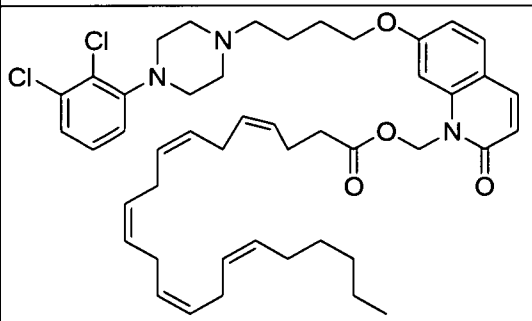
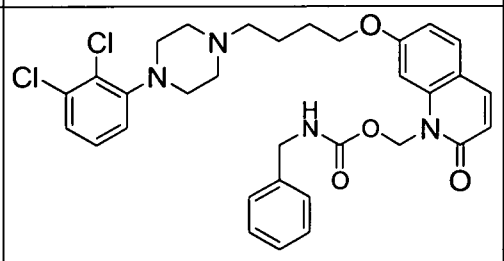
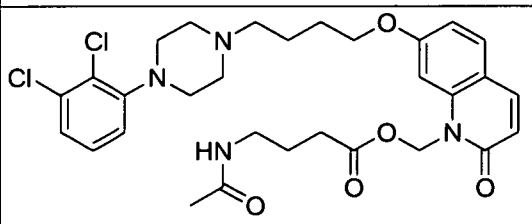
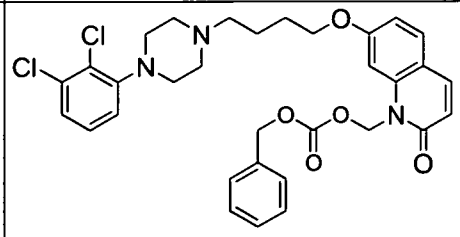
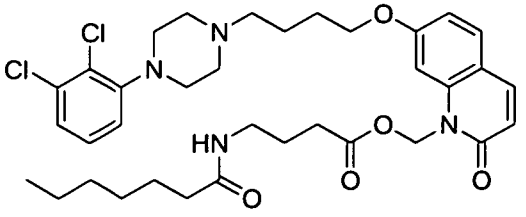
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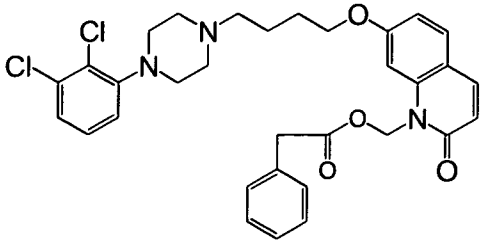
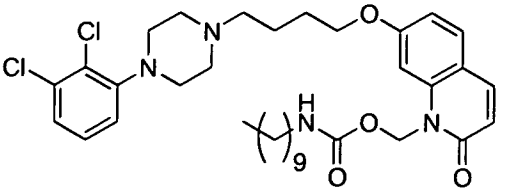
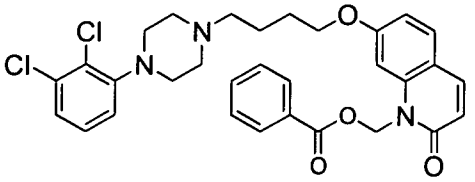
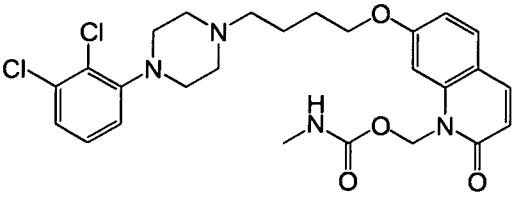
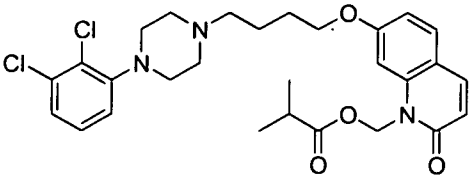
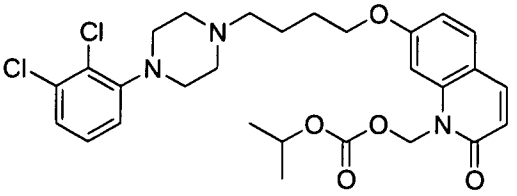
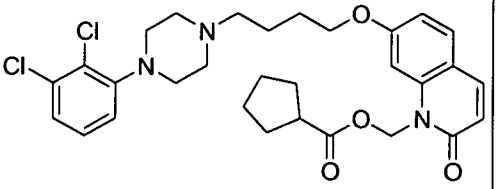
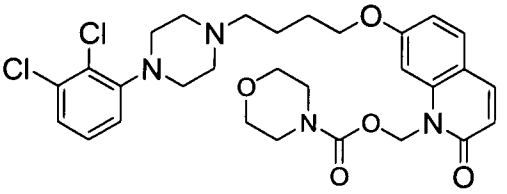
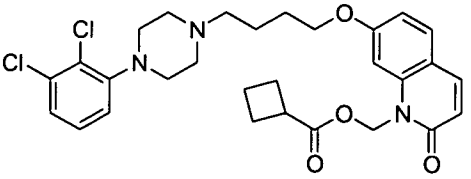
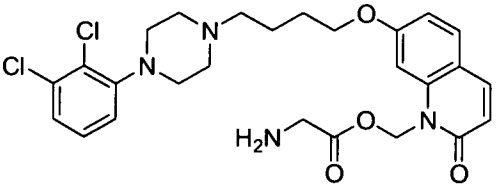
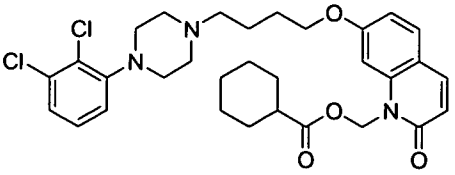
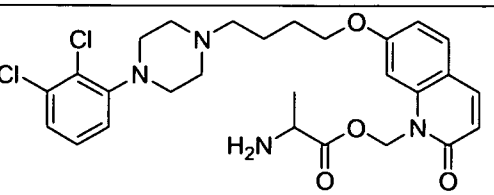
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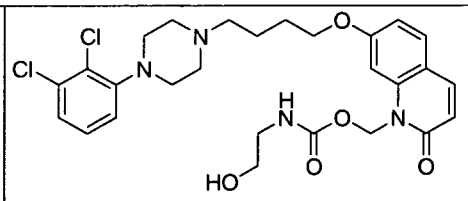
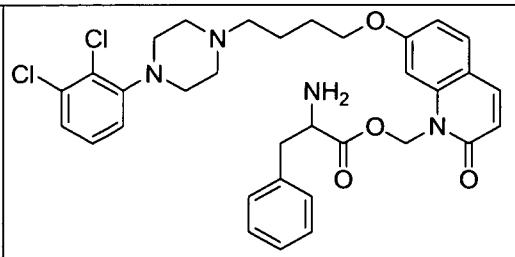
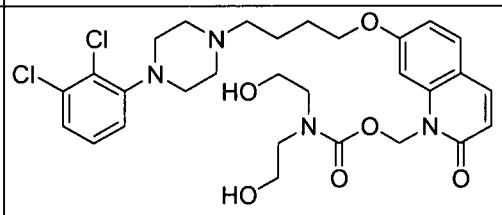
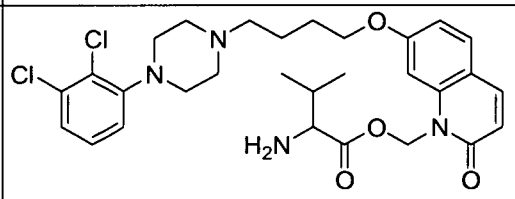
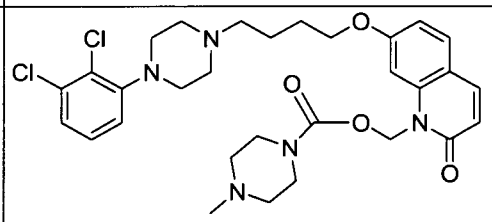
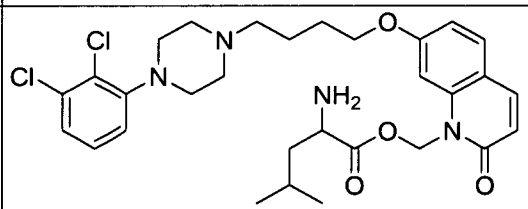
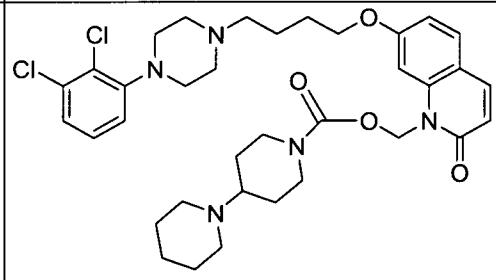
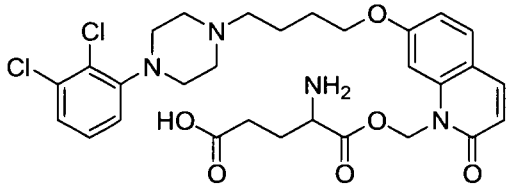
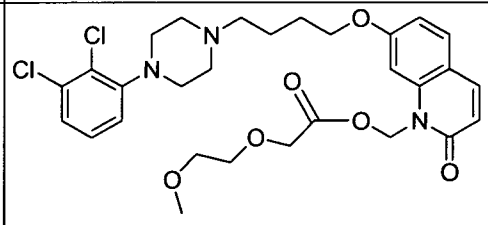
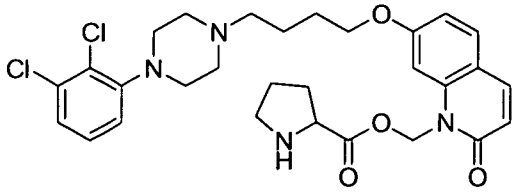
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162		221	

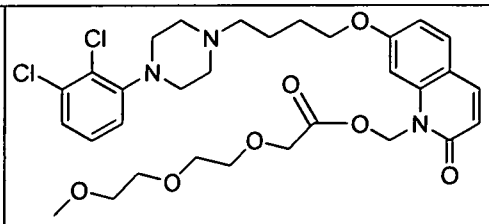
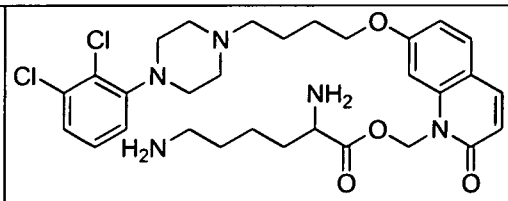
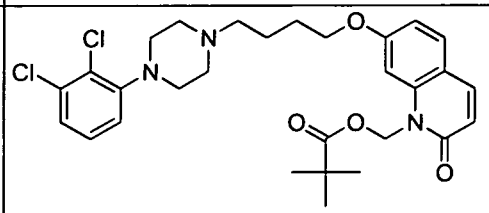
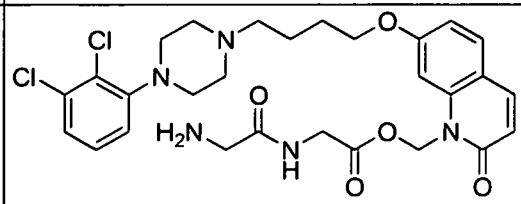
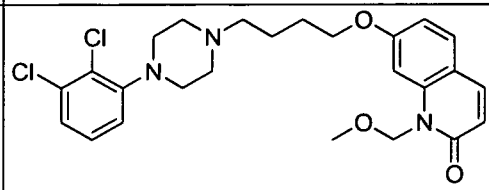
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167		232	
168		234	

169		255	
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177		193	
178		194	

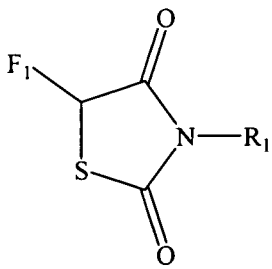
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189		205	

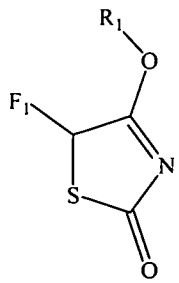
190		206	
191		207	
192			

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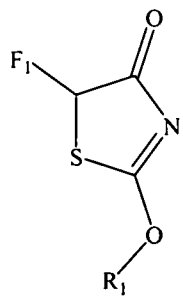
22. 一種具有下列化學式之化合物：



化學式XVII



化學式XVIII



化學式XIX

其中

R_1 是選自於 $-C(R_A)(R_B)-OC(O)OR_{20}$ 、$-C(R_A)(R_B)-OC(O)R_{20}$及$-C(R_A)(R_B)-OC(O)NR_{20}R_{21}$；

其中各個R_A以及R_B是氫；

各個R_{20}以及R_{21}獨立地選自於：氫、脂族、經取代的脂族、芳基或經取代的芳基；

F_1是R_5-A-Cy_1-B-D-；

其中A是選自於：不存在、選擇性地經取代的烷基、選擇性地經取代的烯基、選擇性地經取代的炔基、-S-、-O-、-S(O)-、-$S(O)_2$-、-$S[C(R_{30})(R_{31})]_u$-、-$S(O)[C(R_{30})(R_{31})]_u$-、-$S(O)_2[C(R_{30})(R_{31})]_u$-、-$O[C(R_{30})(R_{31})]_u$-、-$N(R_{30})$-、-$N(R_{30})[C(R_{31})(R_{32})]_u$-、-$[C(R_{30})(R_{31})]_u$-、-$C(O)[C(R_{30})(R_{31})]_u$-；

其中各個u獨立地是1、2、3、4、5、6或7；

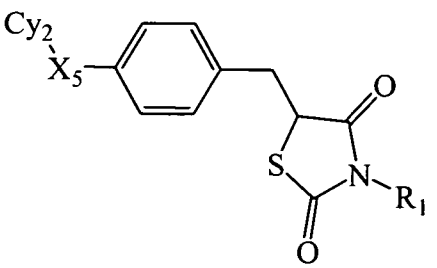
Cy_1是不存在或一選擇性地經取代的環烷基、選擇性地經取代的環烯基、選擇性地經取代的雜環基、選擇性地經取代的芳基或選擇性地經取代的雜芳基；

B是不存在或一連接子；

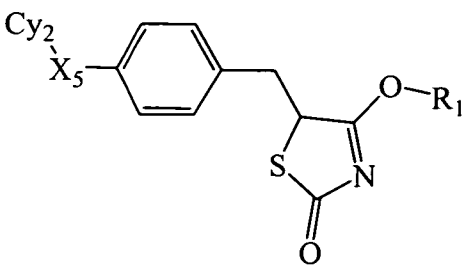
D是選自於：不存在、-O-、-NR_{33}、-$C(R_{34})(R_{35})$-、-S-、-S(O)-、-$S(O)_2$-、-C(O)-；

各個R_5、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}以及R_{35}是獨立地選自於：不存在、氫、鹵素、-OR_{10}、-SR_{10}、-$NR_{10}R_{11}$、-$C(O)R_{10}$、選擇性地經取代的脂族、選擇性地經取代的芳基或選擇性地經取代的雜環基。

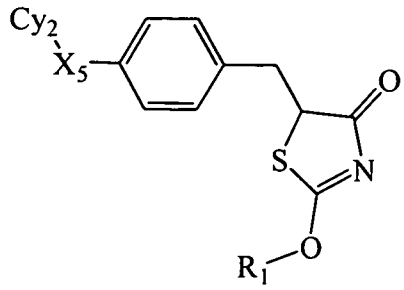
23. 如申請專利範圍第22項的化合物，其具有下列化學式：



化學式XX



化學式XXI



化學式XXII

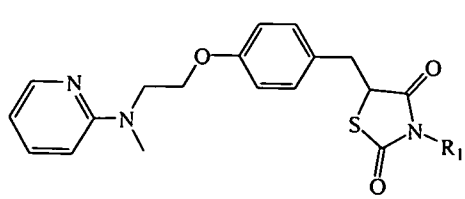
其中R_1是選自於$-C(R_A)(R_B)-OC(O)OR_{20}$、$-C(R_A)(R_B)-OC(O)R_{20}$及$-C(R_A)(R_B)-OC(O)NR_{20}R_{21}$；

其中各個R_A以及R_B是氫；

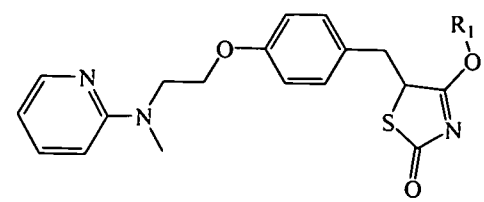
各個R_{20}以及R_{21}獨立地選自於：氫、脂族、經取代的脂族、芳基或經取代的芳基；Cy_2是一選擇性地經取代的雜環的環；以及

X_5是選自於：不存在、-S-、-O-、$-S(O)-$、$-S(O)_2-$、$-N(R_{10})-$、$-C(O)-$、$-C(OR_{10})(R_{11})-$、$-[C(R_{10})(R_{11})]_v-$、$-O[C(R_{10})(R_{11})]_v-$、$-O[C(R_{10})(R_{11})]_vO-$、$-S[C(R_{10})(R_{11})]_vO-$、$-NR_{12}[C(R_{10})(R_{11})]_vO-$、$-NR_{12}[C(R_{10})(R_{11})]_vS-$、$-S[C(R_{10})(R_{11})]_v-$、$-C(O)[C(R_{10})(R_{11})]_v-$、以及$-C(R_{10})(R_{11})=C(R_{10})(R_{11})-$；其中v是0、1、2、3、4、5、6、7、8、9或10。

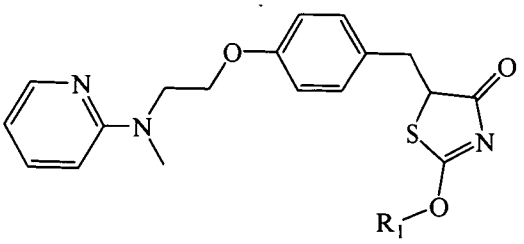
24. 如申請專利範圍第22項的化合物，其具有下列化學式：



化學式XXIV



化學式XXV

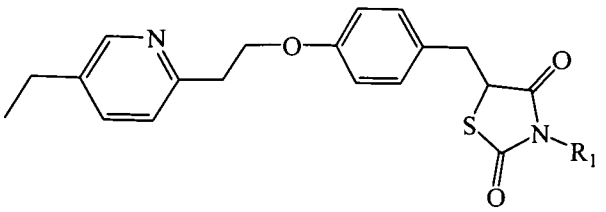


化學式XXVI

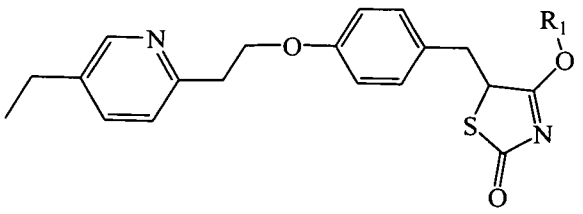
其中R_1是如申請專利範圍第1項中所定義的。

25. 如申請專利範圍第24項的化合物，其中R_1是選自於如申請專利範圍第19項中所界定的表1。

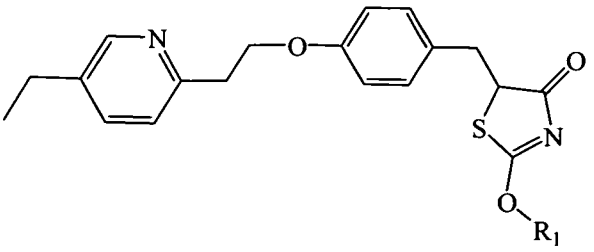
26. 如申請專利範圍第22項的化合物，其具有下列化學式：



化學式XXVII



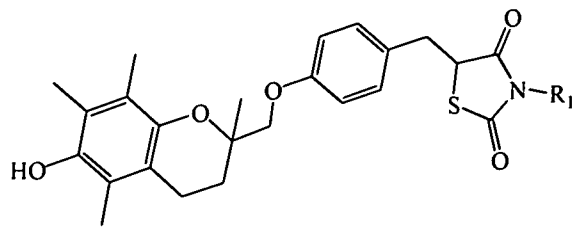
化學式XXVIII



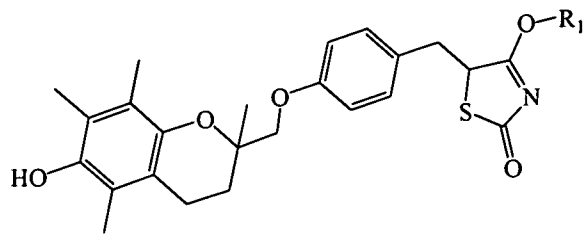
化學式XXVIX

其中R_1是如申請專利範圍第1項中所定義的。

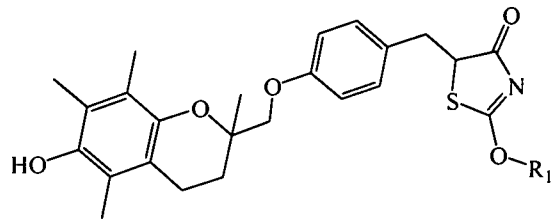
27. 如申請專利範圍第22項的化合物，其具有下列化學式：



化學式XXX



化學式XXXI

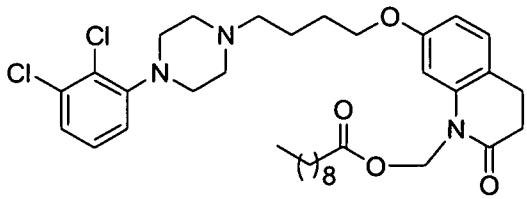


化學式XXXII

其中R_1是如申請專利範圍第1項中所定義的。

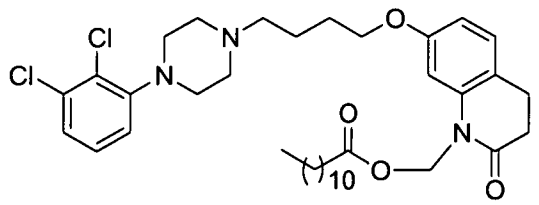
28. 如申請專利範圍第27項的化合物，其中R_1是選自於如申請專利範圍第19項中所界定的表1。

29. 一種具有下列通式之化合物，



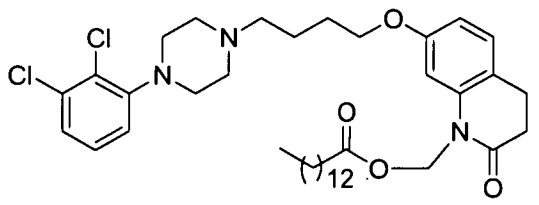
，或其藥學上可接受的鹽類。

30. 一種具有下列通式之化合物，



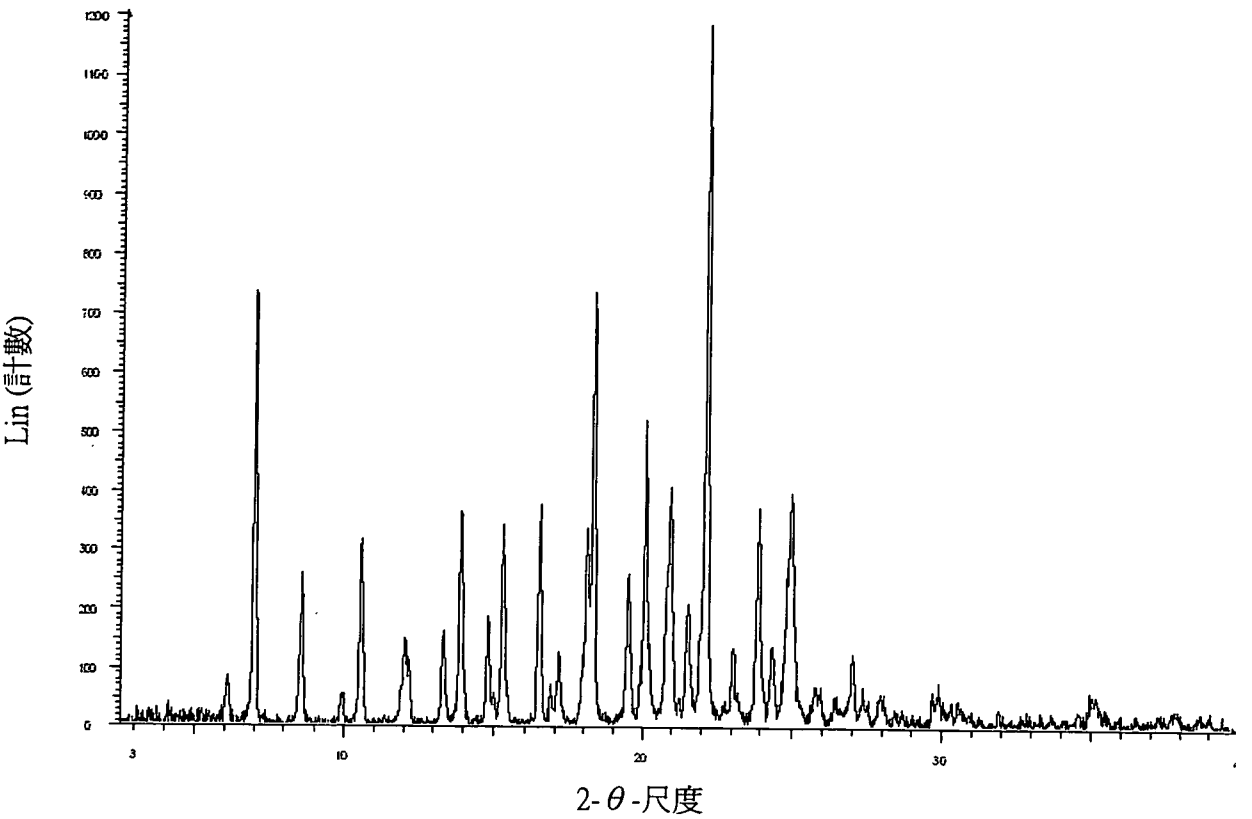
，或其藥學上可接受的鹽類。

31. 一種具有下列通式之化合物，



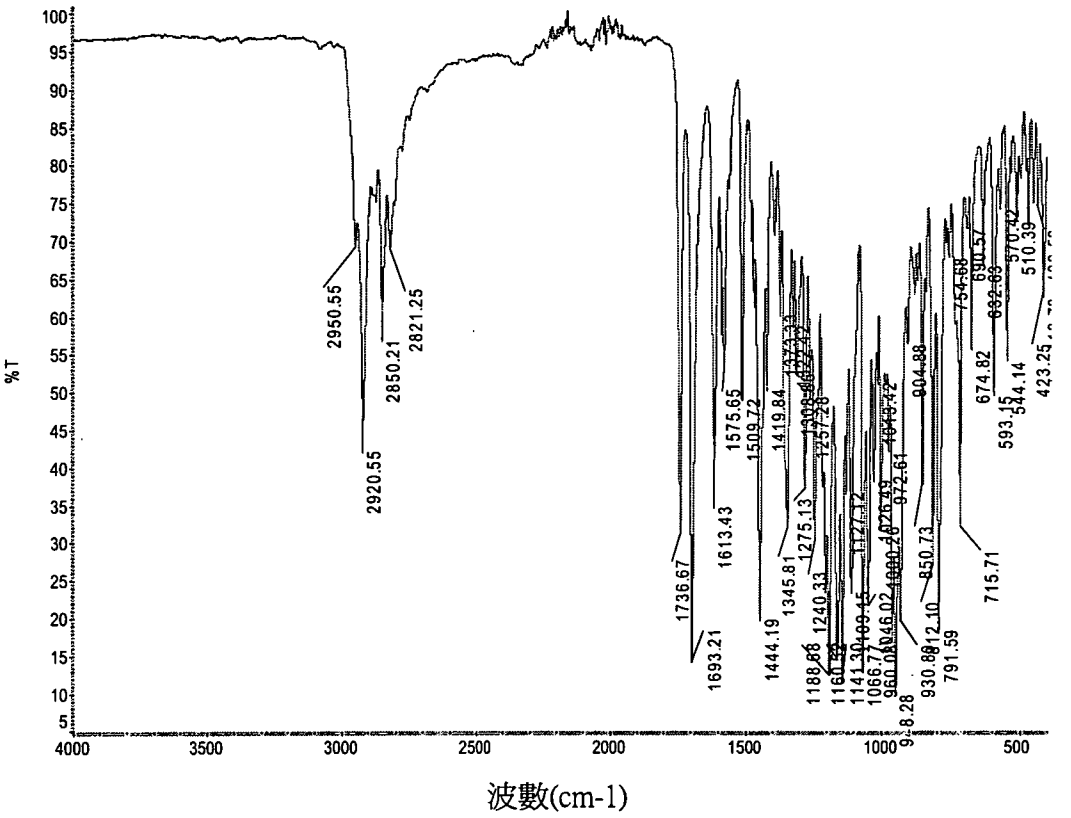
，或其藥學上可接受的鹽類。

4000.3033



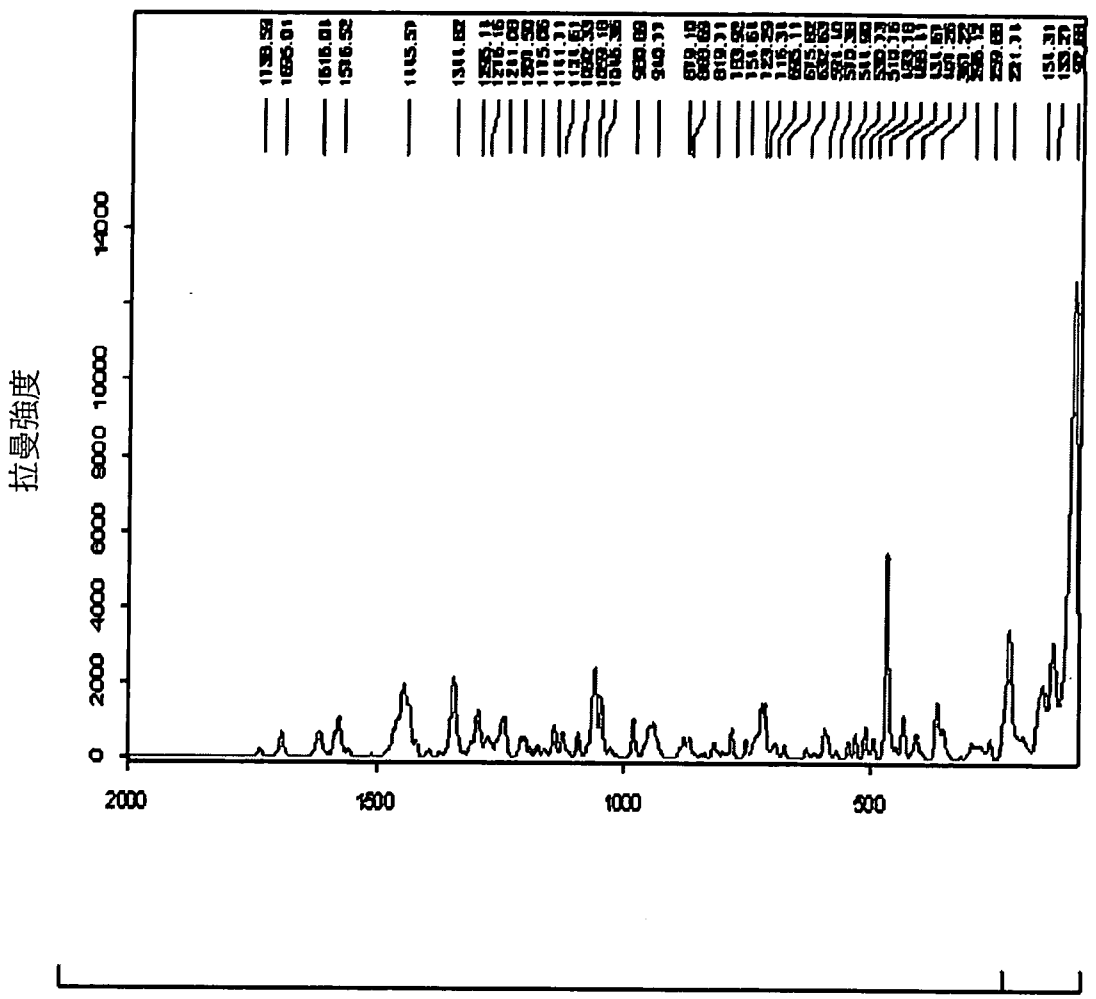
第 1 圖

4000.3033



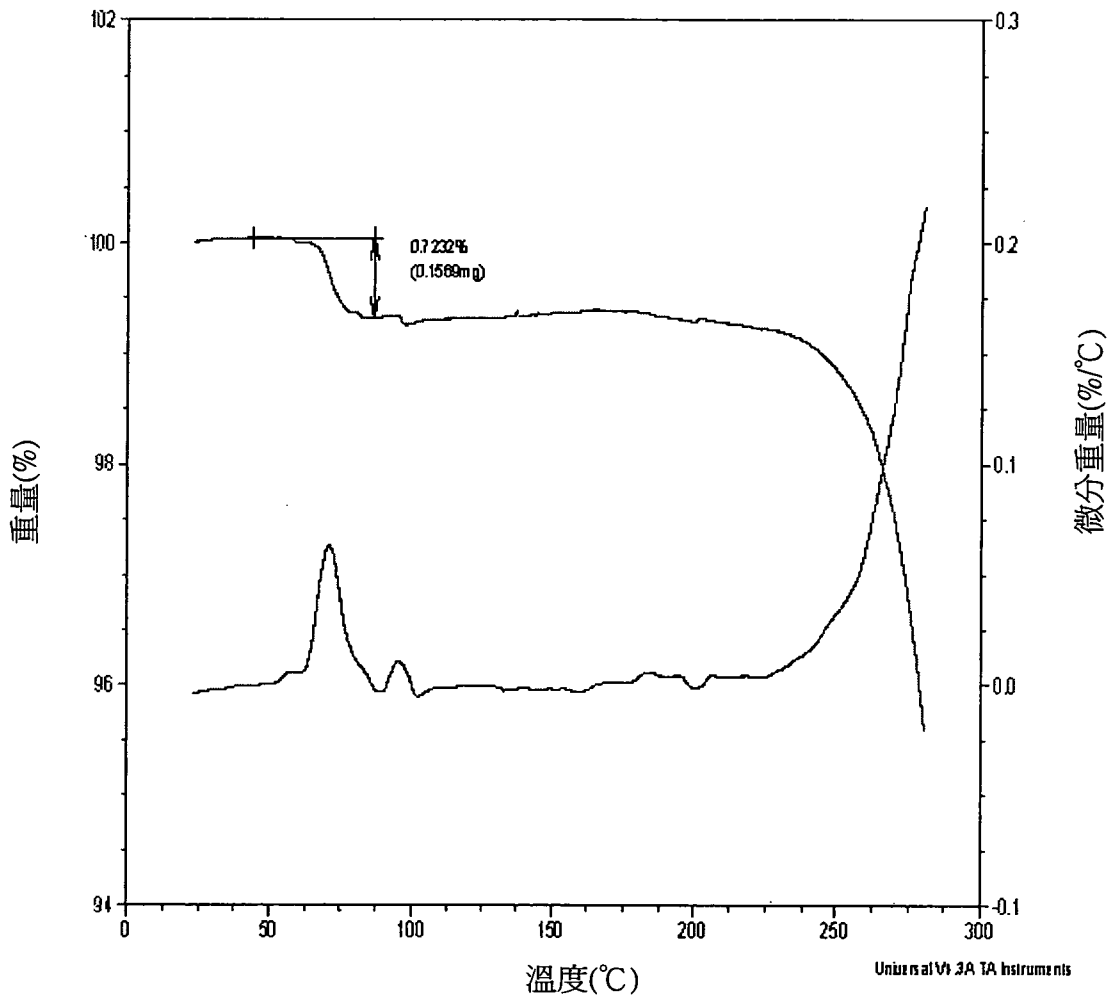
第 2 圖

4000.3033



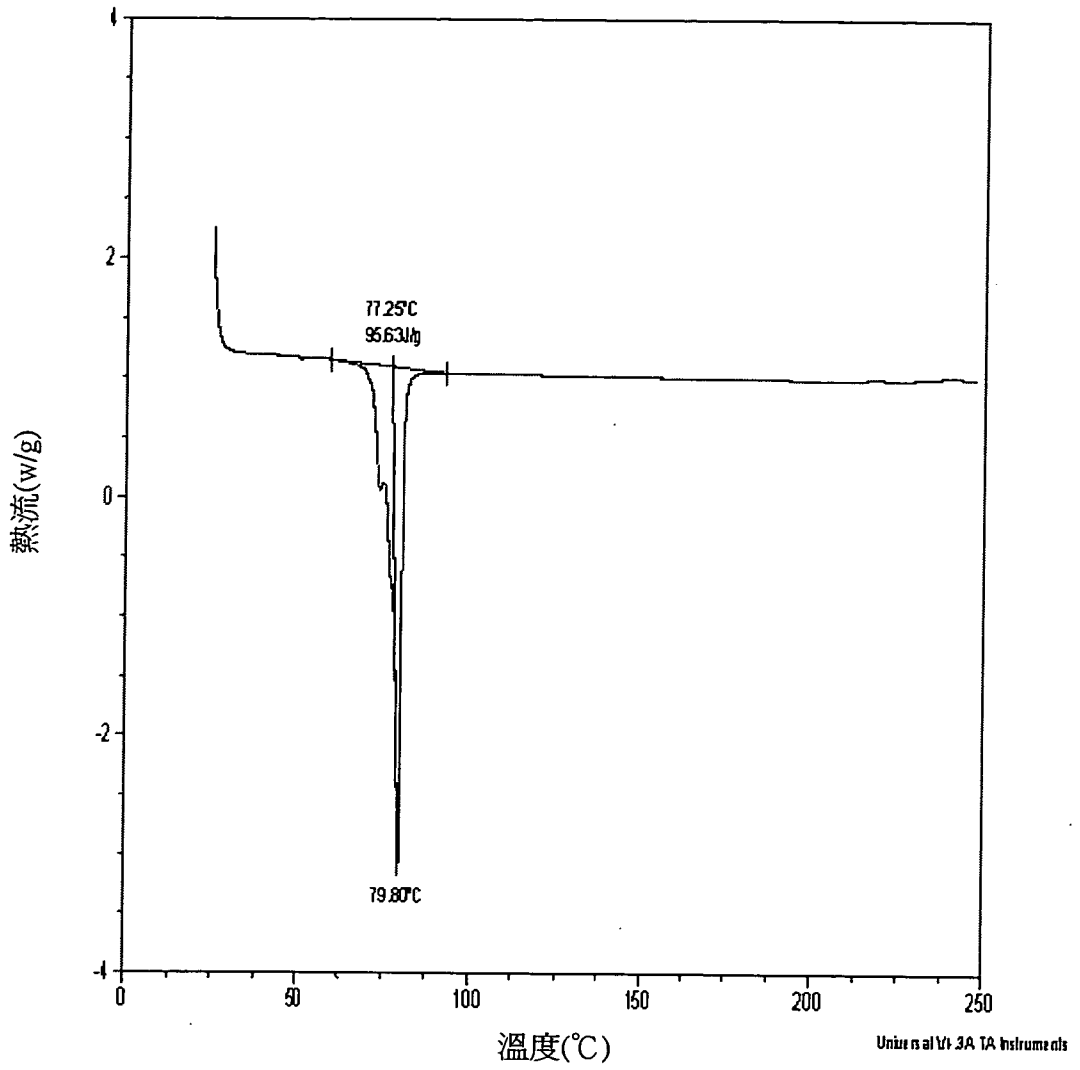
第 3 圖

4000.3033



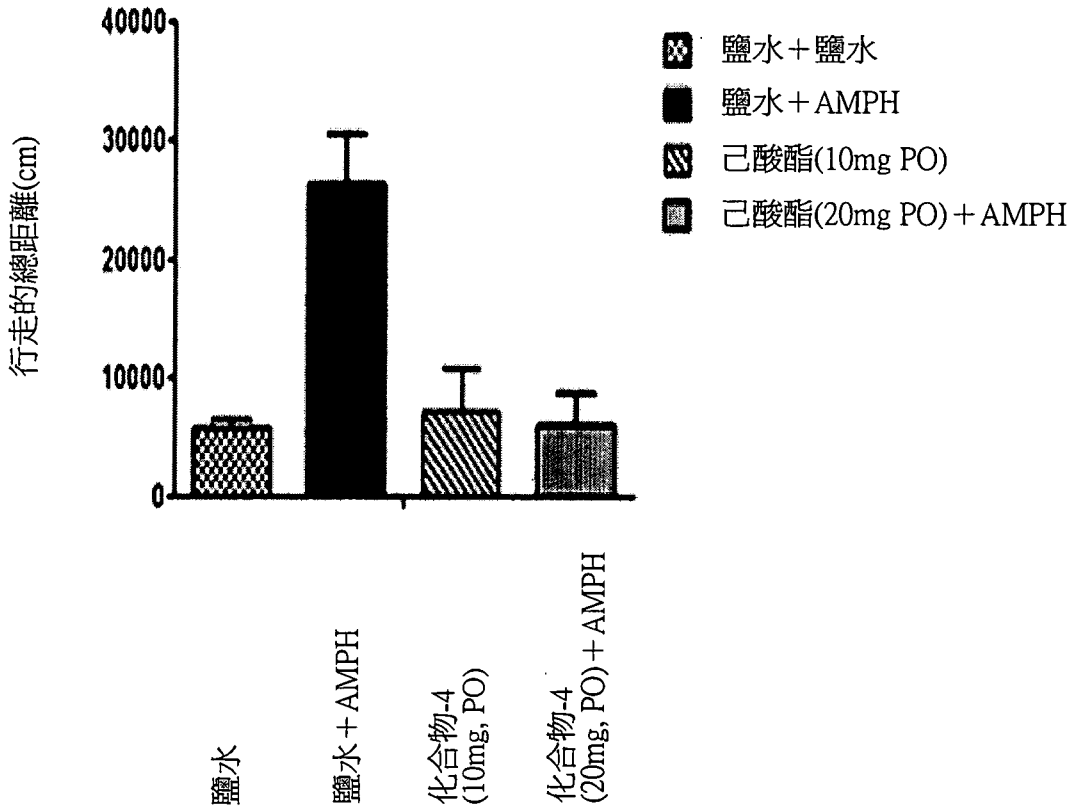
第 4 圖

4000.3033



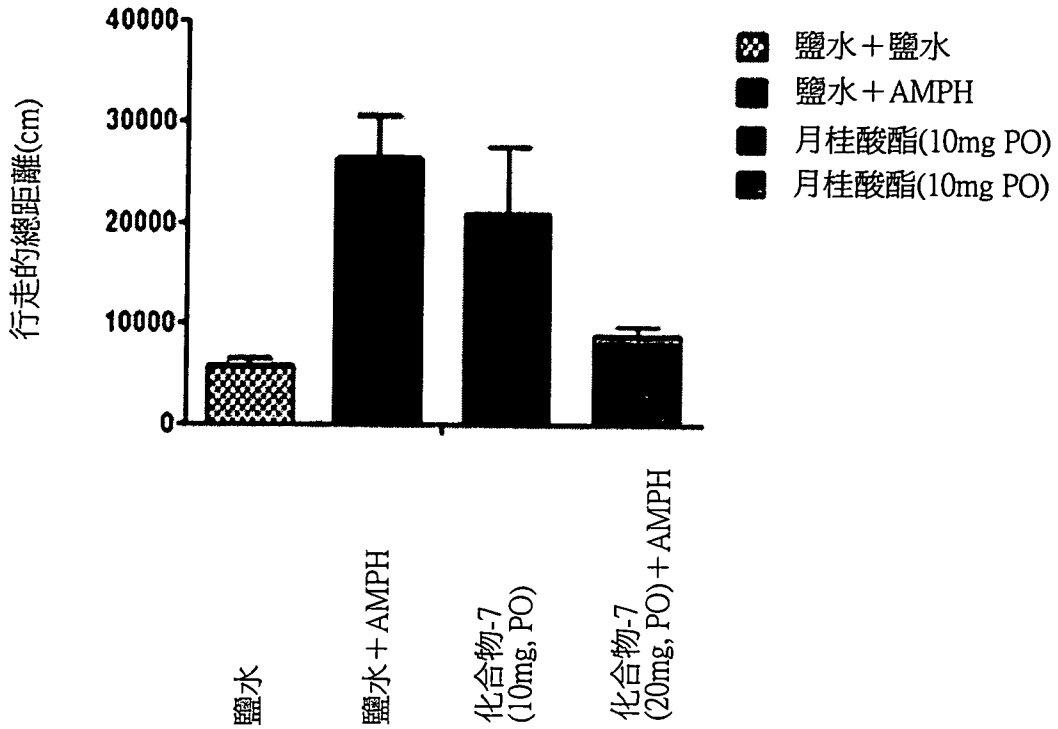
第 5 圖

4000.3033



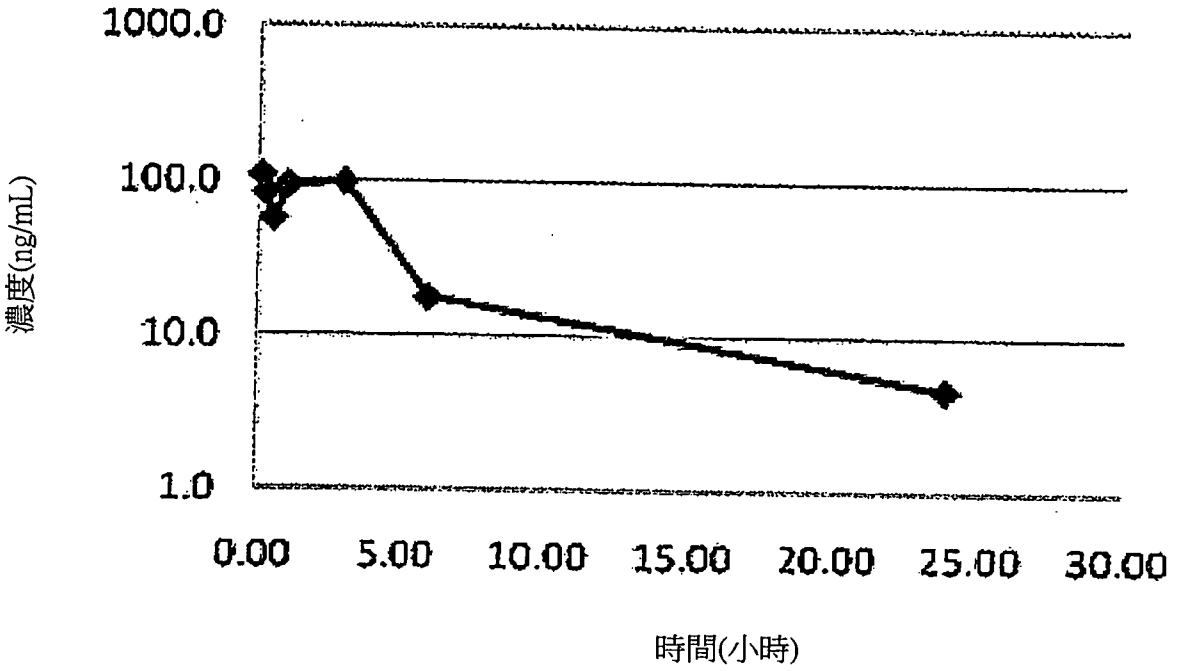
第 6 圖

4000.3033



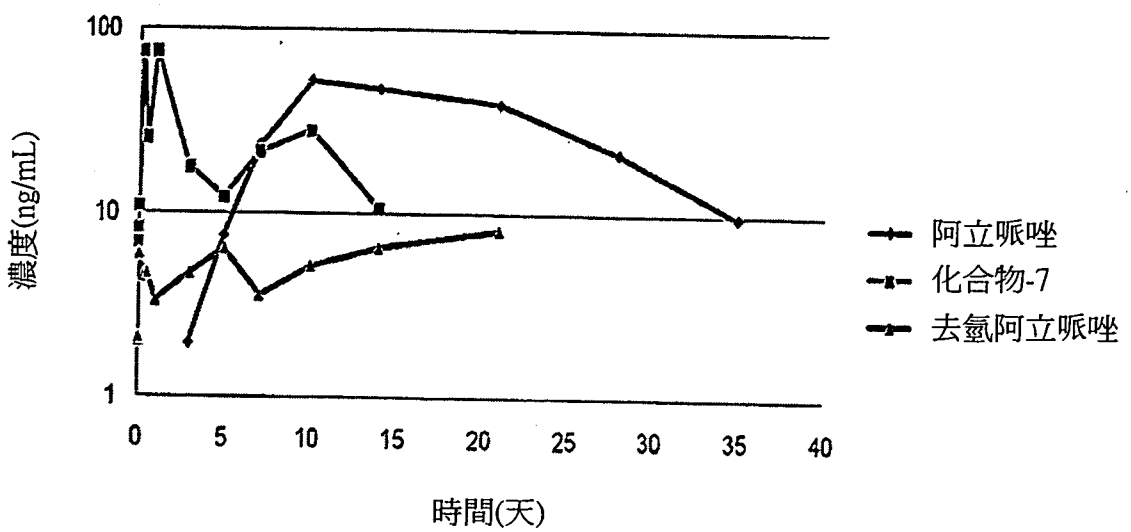
第 7 圖

4000.3033



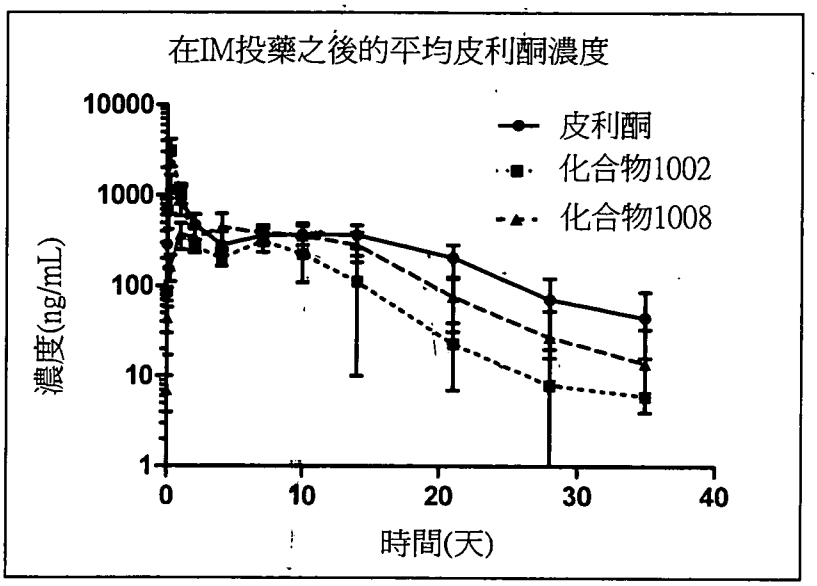
第 8 圖

4000.3033



第 9 圖

4000.3033



第 10 圖