



(86) Date de dépôt PCT/PCT Filing Date: 2002/06/21
(87) Date publication PCT/PCT Publication Date: 2003/01/03
(85) Entrée phase nationale/National Entry: 2003/12/17
(86) N° demande PCT/PCT Application No.: US 2002/019767
(87) N° publication PCT/PCT Publication No.: 2003/000676
(30) Priorité/Priority: 2001/06/21 (09/886,666) US

(51) Cl.Int.⁷/Int.Cl.⁷ C07D 323/02, A61P 33/06,
C07D 521/00, C07D 405/14, C07D 493/10,
C07D 419/08, C07D 405/08

(71) Demandeur/Applicant:
MEDICINES FOR MALARIA VENTURE, CH

(72) Inventeurs/Inventors:
VENNERSTROM, JONATHAN L., US;
CHOLLET, JACQUES, CH;
DONG, YUXIANG, US;
MATILE, HUGUES, CH;
PADMANILAYAM, MANIYAN, US;
TANG, YUANQING, US;
CHARMAN, WILLIAM N., AU

(74) Agent: TORYS LLP

(54) Titre : ANTIPALUDIQUES A BASE DE 1,2,4-TRIOXOLANE
(54) Title: 1,2,4-TRIOXOLANE ANTIMALARIALS

(57) **Abrégé/Abstract:**

A means and method for treating malaria, schistosomiasis, and cancer using a spiro or dispiro 1,2,4-trioxolane is described. The preferred 1,2,4-trioxolanes include a spiroadamantane group on one side of the trioxolane group, and a spirocyclohexyl on the other side of the trioxolane group, whereby the spirocyclohexyl ring is preferably substituted at the 4-position. In comparison to artemisinin semisynthetic derivatives, the compounds of this invention are structurally simple, easy to synthesize, non-toxic, and potent against malarial parasites.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/000676 A1

(51) International Patent Classification⁷: **C07D 323/02**,
493/10, 405/14, 405/08, 419/08, 521/00, A61P 33/06

(21) International Application Number: PCT/US02/19767

(22) International Filing Date: 21 June 2002 (21.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/886,666 21 June 2001 (21.06.2001) US

(71) Applicant (*for all designated States except US*):
MEDICINES FOR MALARIA VENTURE [CH/CH];
International Centre Cointrin, Entrance G, 3rd Floor, Route
de Pré-Bois 20, Post Box 1826, CH-1215 Geneva 15 (CH).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **VENNERSTROM, Jonathan, L.** [US/US]; University of Nebraska Medical Center, College of Pharmacy, 986025 Nebraska Medical Center, Omaha, NE 68198-6025 (US). **CHOLLET, Jacques** [CH/CH]; Pharma Research Department, Infectious Diseases, F. Hoffman - La Roche Ltd., CH-4002 Basel (CH). **DONG, Yuxiang** [CN/US]; University of Nebraska Medical Center, College of Pharmacy, 986025 Nebraska Medical Center, Omaha, NE 68198-6025 (US). **MATILE, Hugues** [CH/CH]; Pharma Research Department, Infectious Diseases, F. Hoffman - La Roche Ltd., CH-4002 Basel (CH). **PADMANILAYAM, Maniyan** [IN/US]; University of Nebraska Medical Center, College of Pharmacy, 986025 Nebraska Medical Center, Omaha,

NE 68198-6025 (US). **TANG, Yuanqing** [CN/US]; University of Nebraska Medical Center, College of Pharmacy, 986025 Nebraska Medical Center, Omaha, NE 68198-6025 (US). **CHARMAN, William, N.** [AU/AU]; Victorian College of Pharmacy, Monash University, Parkville, VIC 3052 (AU).

(74) Agent: **MARSH, Wendy, K.**; McKee, Voorhees & Sease, P.L.C., 801 Grand Avenue, Suite 3200, Des Moines, IA 50309-2721 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 1,2,4-TRIOXOLANE ANTIMALARIALS

(57) Abstract: A means and method for treating malaria, schistosomiasis, and cancer using a spiro or dispiro 1,2,4-trioxolane is described. The preferred 1,2,4-trioxolanes include a spiroadamantane group on one side of the trioxolane group, and a spirocyclohexyl on the other side of the trioxolane group, whereby the spirocyclohexyl ring is preferably substituted at the 4-position. In comparison to artemisinin semisynthetic derivatives, the compounds of this invention are structurally simple, easy to synthesize, non-toxic, and potent against malarial parasites.



WO 03/000676 A1

TITLE: **SPIRO AND DISPIRO 1,2,4-TRIOXOLANE ANTIMALARIALS**

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating malaria.

5 Specifically, this invention relates to pharmaceutical compositions including spiro and dispiro trioxolanes, and methods of their use and manufacture.

BACKGROUND OF THE INVENTION

Malaria is an acute and often chronic infectious disease resulting from the presence of protozoan parasites within red blood cells. Caused by single-celled parasites of the
10 genus *Plasmodium*, malaria is transmitted from person to person by the bite of female mosquitos.

Although once prevalent in North America and other temperate regions of the world, today malaria occurs mostly in tropical and subtropic countries. Each year, between 400 million and 600 million people contract the disease, and 1.5 million to 2.7 million die
15 of the disease.

Four species of *Plasmodium* protozoan parasites are generally responsible for malaria, including *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*, and *Plasmodium ovale*. Of the four, *Plasmodium falciparum* is the most dangerous, accounting for half of all clinical cases of malaria and 90% of deaths from the disease.

20 The transmission of malaria begins when a female mosquito bites a human already infected with the malaria parasite. When the infected mosquito bites another human, sporozoites in the mosquito's saliva are transferred into the blood, which then travel to the liver. In the liver, the sporozoites divide rapidly, then enter the bloodstream where they invade red blood cells. Inside these blood cells, the merozoites multiply rapidly until they
25 cause the red blood cells to burst, releasing into the blood stream a new generation of merozoites that then infect other red blood cells.

The symptoms associated with malaria are generally associated with the bursting of the red blood cells. The destruction of the red blood cells spills wastes, toxin, and other debris into the blood. This in turn causes an intense fever that can leave the infected
30 individual exhausted and bedridden. More severe symptoms associated with repeat infections and/or infection by *Plasmodium falciparum* include anemia, severe headaches, convulsions, delirium and, in some instances, death.

The treatment of malaria has been especially difficult due to the ability of malaria parasites to develop resistance to drugs. Quinine, an antimalarial compound that is extracted from the bark of the South American cinchona tree, is one of the oldest and most effective pharmaceuticals in existence. The downside to quinine is that it is short-acting, and fails to prevent disease relapses. Further, quinine is associated with side effects ranging from dizziness to deafness.

Chloroquine is a synthetic chemical similar to quinine. It became the drug of choice for malaria when it was developed in the 1940s due to its effectiveness, ease of manufacture, and general lack of side effects. However, in the last few decades, malaria parasites in many areas of the world have become resistant to chloroquine.

Mefloquine is another synthetic analog of quinine that has been used in the treatment of malaria. Malaria parasites have also developed resistance to mefloquine, however. Mefloquine is also associated with undesirable central nervous side effects in some patients, including hallucinations and vivid nightmares.

Antifolate drugs are effective against malaria parasites by inhibiting their reproduction. Although the parasites have also developed a resistance to antifolate drugs, the drugs can still be used effectively in combination with other types of antimalarials. The use of combination therapies in treating malaria has the drawbacks of being inconvenient and expensive, however.

More recent developments in the treatment of malaria have involved the use of the peroxide functional group, as exemplified by the drug artemisinin, which contains a unique 1,2,4-trioxane heterocyclic pharmacophore. The antimalarial action of artemisinin is due to its reaction with the iron in free heme molecules in the malaria parasite with the generation of free radicals leading to cellular destruction.

The discovery of artemisinin (qinghaosu), a naturally occurring endoperoxide sesquiterpene lactone (Meshnick et al., 1996; Vroman et al. 1999; Dhingra et al., 2000) initiated a substantial effort to elucidate its molecular mechanism of action (Jefford, 1997; Cumming et al., 1997) and to identify novel antimalarial peroxides (Dong and Vennerstrom, 2001). Many synthetic 1,2,4-trioxanes, 1,2,4,5-tetraoxanes, and other endoperoxides have been prepared.

Although the clinically useful semisynthetic artemisinin derivatives are rapid acting and potent antimalarial drugs, they have several disadvantages including recrudescence, neurotoxicity, (Wesche et al., 1994) and metabolic instability. (White, 1994). A fair number of these compounds are quite active *in vitro*, but most suffer from low oral activity. (White, 1994; van Agtmael et al., 1999). Although many synthetic antimalarial 1,2,4-trioxanes have since been prepared (Cumming et al., 1996; Jefford, 1997), there exists a need in the art to identify new peroxide antimalarial agents, especially those which are easily synthesized, are devoid of neurotoxicity, and which possess improved pharmacokinetic properties, e.g. improved stability, oral absorption, etc.

Various trioxolanes have been synthesized by various methods. See e.g. Keul, H., Chemische Berichte, vol. 108, no. 4, 1975, pp. 1207-1217; Tabuchi, T. et al., J. Org. Chem., vol. 56, 1991, pp. 6591-6595; Dussault, P.H., Perkin Trans., vol. 1, 2000, pp. 3006-3013; Griesbaum K. et al., Tetrahedron, vol. 53, no. 15, 1997, pp. 5463-5470. However, until now it has not been known in the art that certain types of trioxolanes are especially useful in the prophylaxis and treatment of malaria.

Accordingly, it is a primary objective of the present invention to provide compositions and methods for prophylaxis and treatment of malaria using spiro and dispiro 1,2,4-trioxolanes.

It is a further objective of the present invention to provide a composition and method for prophylaxis and treatment of malaria using spiro and dispiro 1,2,4-trioxolanes that is nontoxic.

It is a further objective of the present invention to provide a composition and method for prophylaxis and treatment of malaria using spiro and dispiro 1,2,4-trioxolanes that is metabolically stable and orally active.

It is yet a further objective of the present invention to provide a composition and method for prophylaxis and cost-effective treatment of malaria using spiro and dispiro 1,2,4-trioxolanes.

It is a further objective of the present invention to provide compositions and methods for prophylaxis and treatment of malaria using spiro and dispiro 1,2,4-trioxolanes that can be used either as stand-alone medicaments or in combination with other agents.

It is still a further objective of the present invention to provide novel intermediates for synthesizing compositions for prophylaxis and treatment of malaria.

The method and means of accomplishing each of the above objectives as well as others will become apparent from the detailed description of the invention which follows
5 hereafter.

SUMMARY OF THE INVENTION

The invention describes a method and composition for treating malaria with spiro and dispiro 1,2,4-trioxolanes, their prodrugs and analogues. The trioxolanes of this invention are sterically hindered on one side of the trioxolane heterocycle in order to provide chemical and metabolic stability to the trioxolane ring for better *in vivo* activity.

5 The spiro and dispiro trioxolanes are preferably sterically hindered with an unsubstituted, mono-, di-, or poly-substituted C₅-C₁₂ spiro cycloalkyl group, which is most preferably spiroadamantane. The spiro and dispiro trioxolanes also preferably include a spirocyclohexyl that is preferably functionalized or substituted at the 4-position or a spiropiperidyl ring that is functionalized or substituted at the nitrogen atom. The invention
10 embraces achiral, achiral diastereomers, racemic mixtures, as well as enantiomeric forms of the compounds.

The trioxolanes of this invention possess excellent potency and efficacy against *Plasmodium* parasites, and a low degree of neurotoxicity. In addition, several of the trioxolanes are suitable for both oral and non-oral administration. Moreover, in
15 comparison to artemisinin semisynthetic derivatives, the compounds of this invention are structurally simple, easy and inexpensive to synthesize, and can be used effectively alone or in conjunction with other antimalarials.

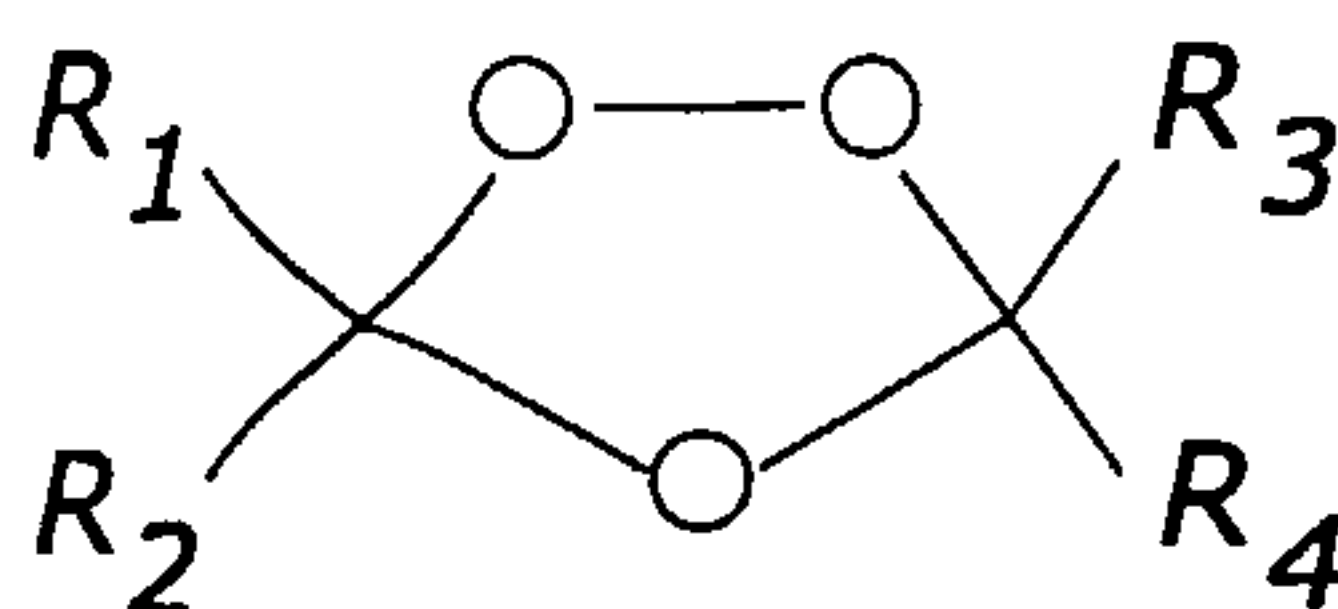
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention relates to the development of spiro and dispiro 1,2,4-
20 trioxolanes for use in the prophylaxis and treatment of malaria. The present invention is predicated upon the unexpected discovery that trioxolanes that are relatively sterically hindered on at least one side of the trioxolane heterocycle provide metabolic and chemical stability to the trioxolane ring, thereby providing better *in vivo* activity, especially with respect to oral administration.

25 As used herein the term "prophylaxis-effective amount" refers to a concentration of compound of this invention that is effective in inhibiting or preventing infection and subsequent disease by malarial parasites. Likewise, the term "treatment-effective amount" refers to a concentration of compound that is effective in treating malaria in terms of preventing an increase in the concentration of malarial parasites, decreasing the
30 concentration of malarial parasites, and/or "curing" a malaria infection, i.e. survival for 30 days post-infection.

Tetrasubstituted trioxolanes are relatively stable peroxidic compounds based on literature precedent (Griesbaum et al., 1997a; 1997b). This may be due, in part, to the lack of α -hydrogen atoms. The present inventors have synthesized new compounds in the trioxolane class having both superior antimalarial potency and oral efficacy. Furthermore, the compounds of this invention have low toxicity, and half-lives conducive to treatment of malaria which are believed will permit short-term treatment regimens comparing favorably to other artemisinin-like drugs. These compounds may also be used in malaria prophylaxis.

The tetrasubstituted trioxolanes of this invention have the following general structural formula:



wherein R_1 , R_2 , R_3 , and R_4 represent combinations of ring systems, acyclic systems, and functional groups that provide sufficient steric hindrance about the trioxolane ring in order to give the ring chemical and metabolic stability. R_1 , R_2 , R_3 and R_4 may be the same or different, and may be a linear or branched alkyl, aryl, or alkaryl group which is optionally substituted. In the alternative, R_1 and R_2 taken together and/or R_3 and R_4 taken together may form an alicyclic group which is optionally interrupted by one or more oxygen, sulfur or nitrogen atoms and which group is optionally substituted. In no event may any of R_1 , R_2 , R_3 or R_4 be hydrogen.

Preferably, R_1 and R_2 taken together and/or R_3 and R_4 taken together is a mono- or di-substituted C_5 - C_{12} spirocycloalkyl group which is optionally interrupted by one or more oxygen, sulfur, or nitrogen atoms, and which group is optionally substituted.

Most preferably, R_1 and R_2 taken together or R_3 and R_4 is spiroadamantane. It is hypothesized that the sterically demanding adamantane protects the trioxolane ring from premature chemical or metabolic decomposition in situ.

The inventors have further found that in the most preferred compounds of this invention, R_1 and R_2 taken together is adamantane, and R_3 and R_4 taken together is a

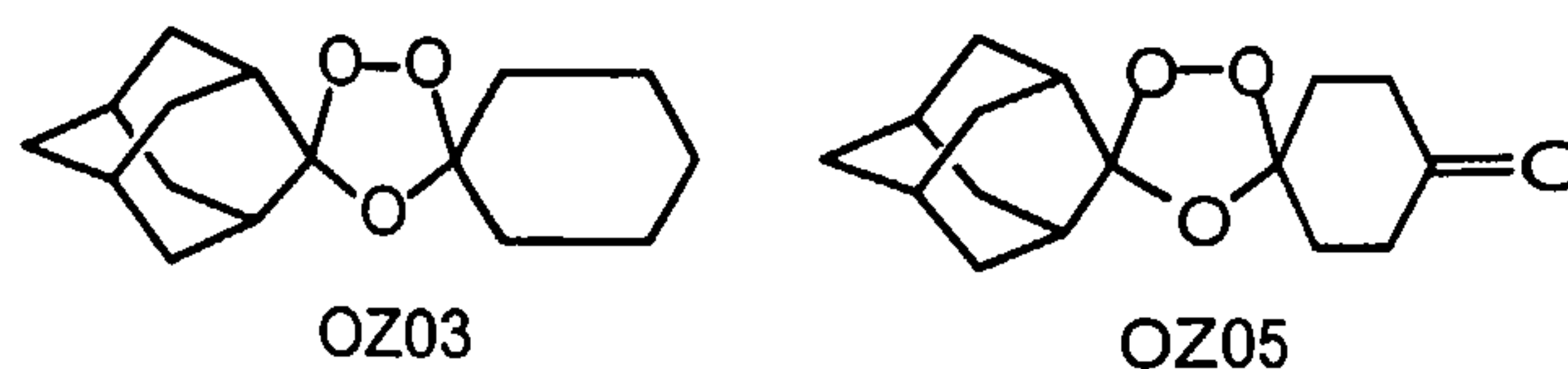
spirocyclohexyl ring that is functionalized or substituted at the 4-position. The spirocyclohexyl ring may be optionally interrupted by one or more oxygen, sulfur or nitrogen atoms. The functional group may be a linear or branched alkyl, ketone, acid, alcohol, amine, amide, sulfonamide, guanidine, ether, ester, oxime, urea, oxime ether, sulfone, lactone, carbamate, semicarbazone, phenyl, heterocycle, or alicyclic group which is optionally substituted. The functional group is preferably an amide. It has now been unexpectedly found that amide-containing substituents at the 4-position provide antimalarial compounds with good oral absorption, good antimalarial activity, and good pharmacokinetics, i.e. rates of absorption, metabolism, and elimination that are most suitable and advantageous for the prophylaxis and treatment of malaria.

It has also been found that a heteroatom in the spirocyclohexyl ring generally causes the compound to more rapidly metabolize. Thus, for purposes of the pharmaceutical compositions of this invention, such compounds are not preferred.

Other substituents at the 4-position of the spirocyclohexyl ring are also possible that fall within the scope of this invention. The spirocyclohexyl ring may also be substituted at other positions besides the 4-position. For instance, the inventors have synthesized several compounds substituted at the 2-position of the spirocyclohexyl ring that provide excellent antimalarial potency.

Preferred compounds of this invention include an alkyl group connecting the substituent at the 4-position to the spirocyclohexyl ring. The alkyl group is preferably methyl or ethyl, with methyl being most preferred. The alkyl "bridge" group also improves the metabolic stability (i.e. oral activity and pharmacokinetics) of the antimalarial compounds of this invention.

The present inventors have identified two orally active lead dispiro-1,2,4-trioxolanes, OZ03 and OZ05:



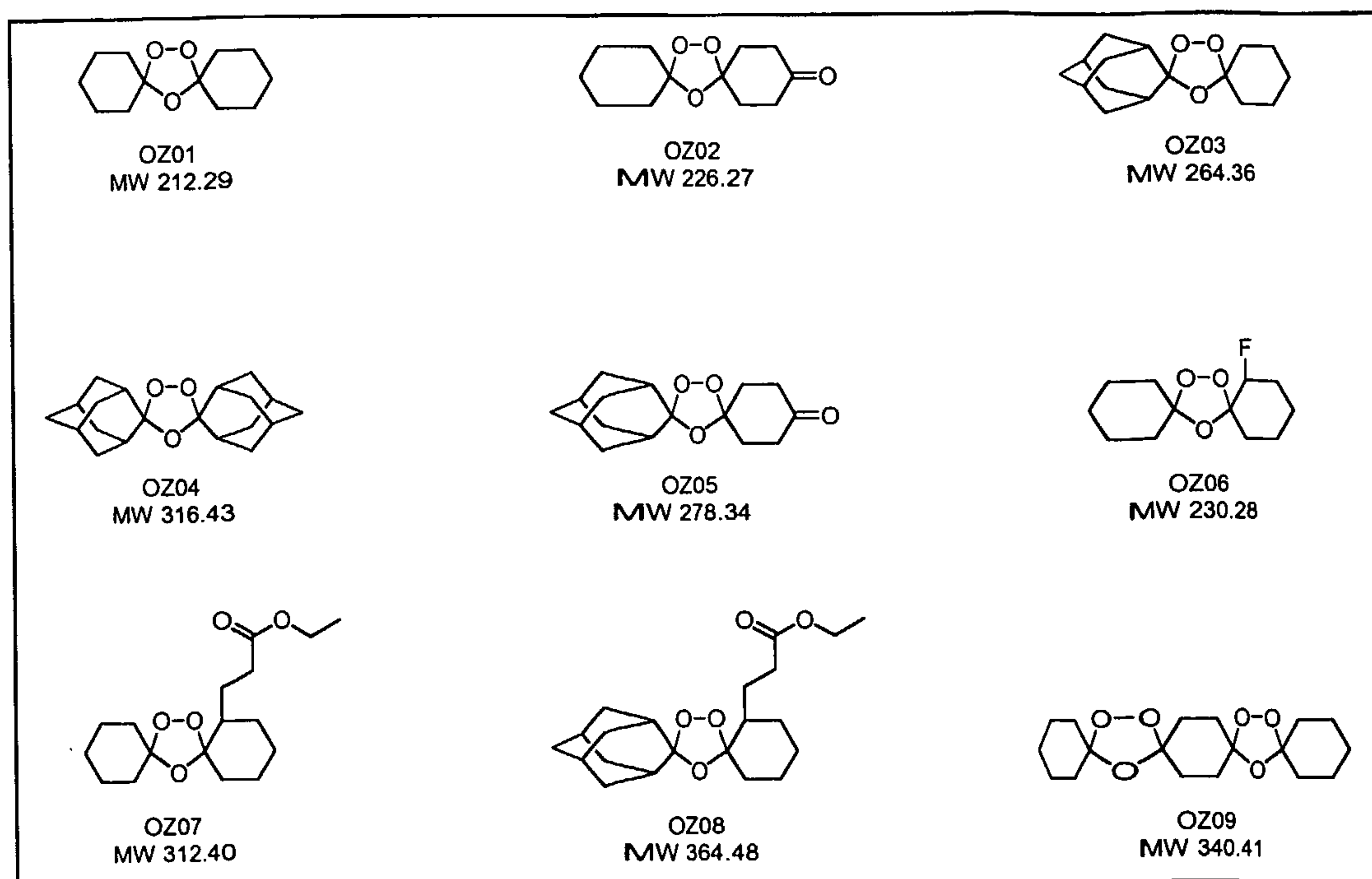
These trioxolanes have IC_{50} s between 1 and 5 ng/ml against *P. falciparum* *in vitro*, and presumably possess good therapeutic indices as no toxicity is evidence for either compound

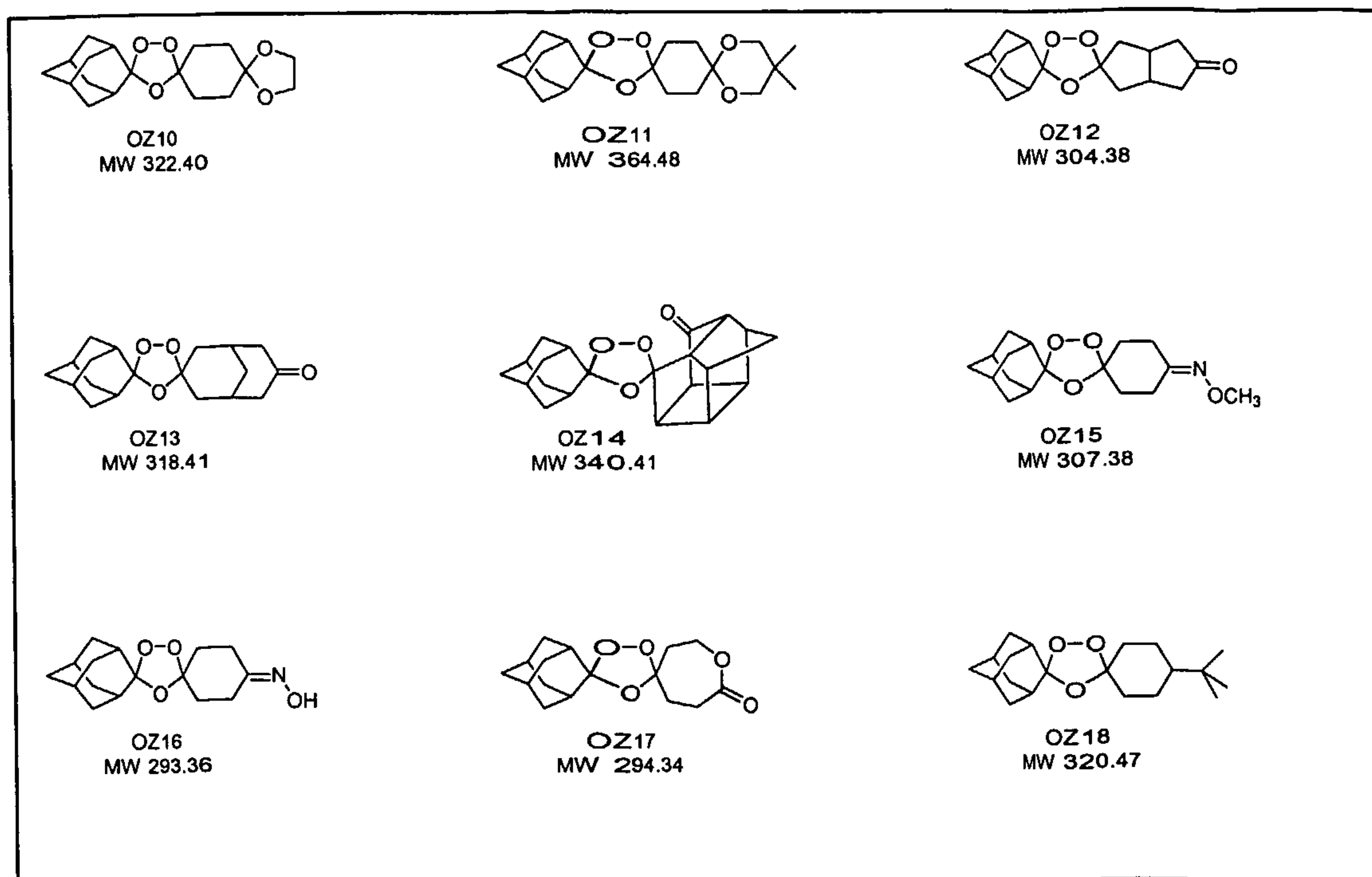
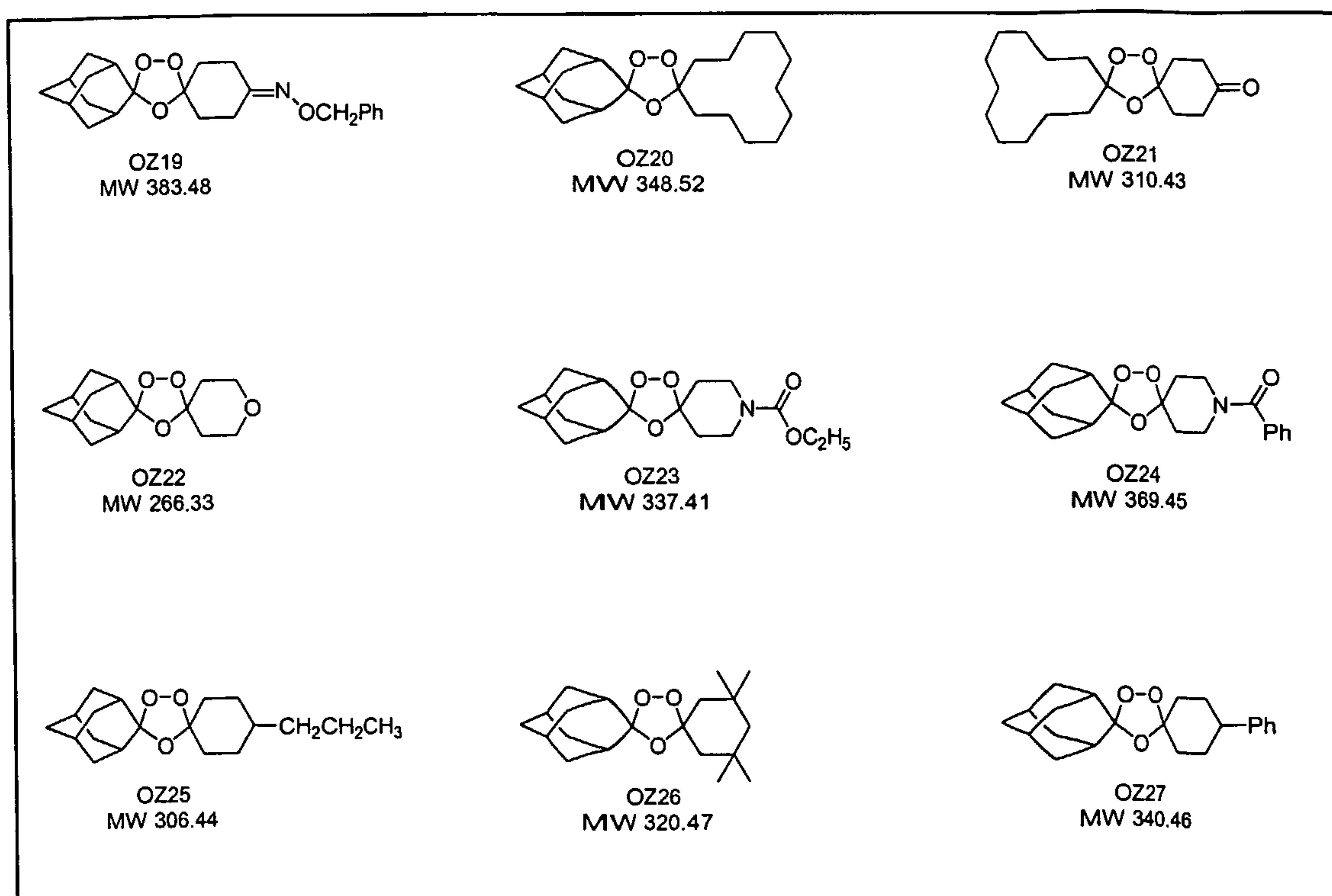
in a neuroblastoma cell line or at single 640 mg/kg doses in mice in the Rane test. These results contrast with published data (de Almeida Barbosa et al., 1992; 1996) disclosing the weak in vitro antimalarial potency of several tricyclic trioxolanes, the best of which has an IC_{50} of 2000 ng/ml against *P. falciparum* *in vitro*.

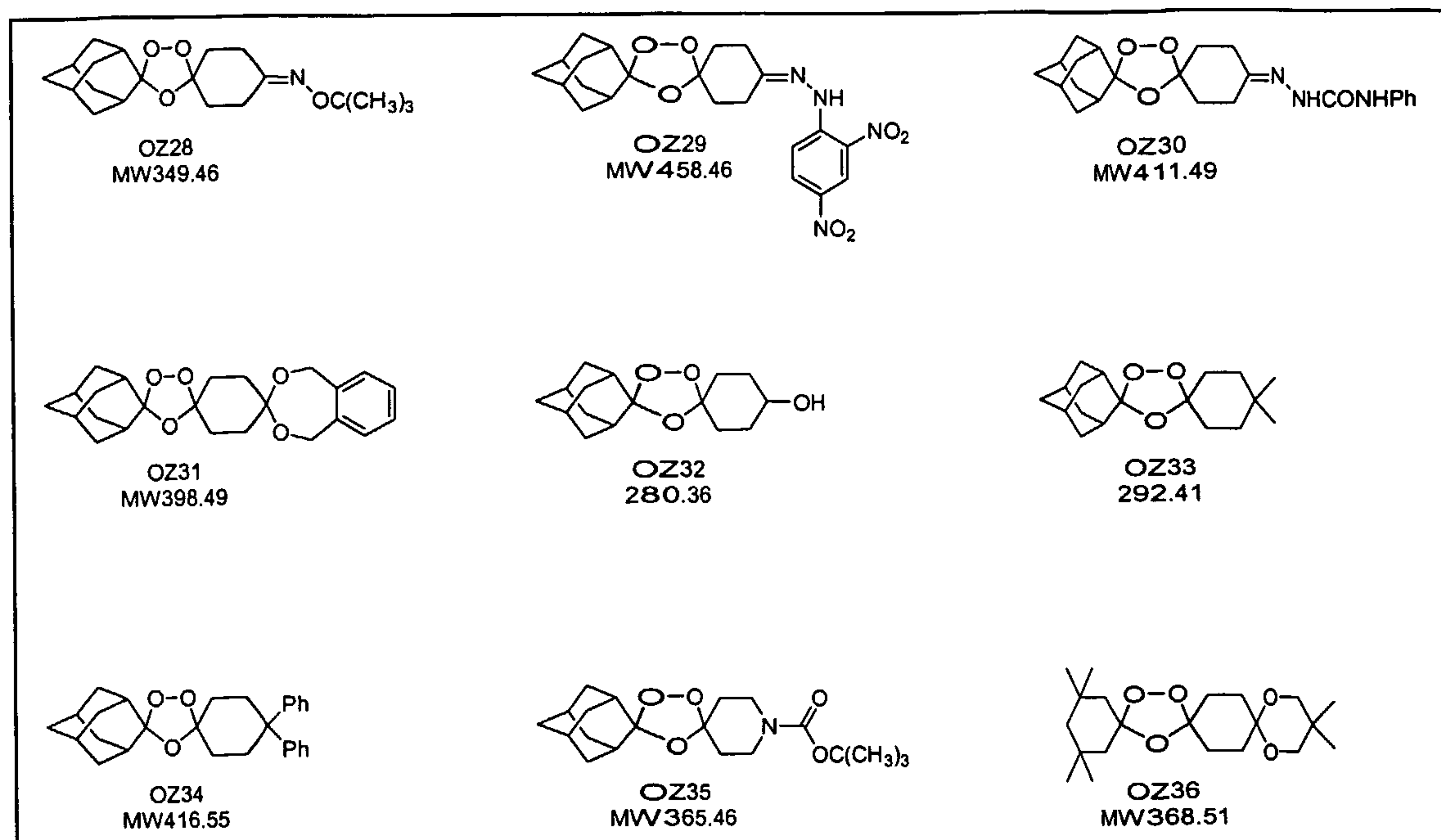
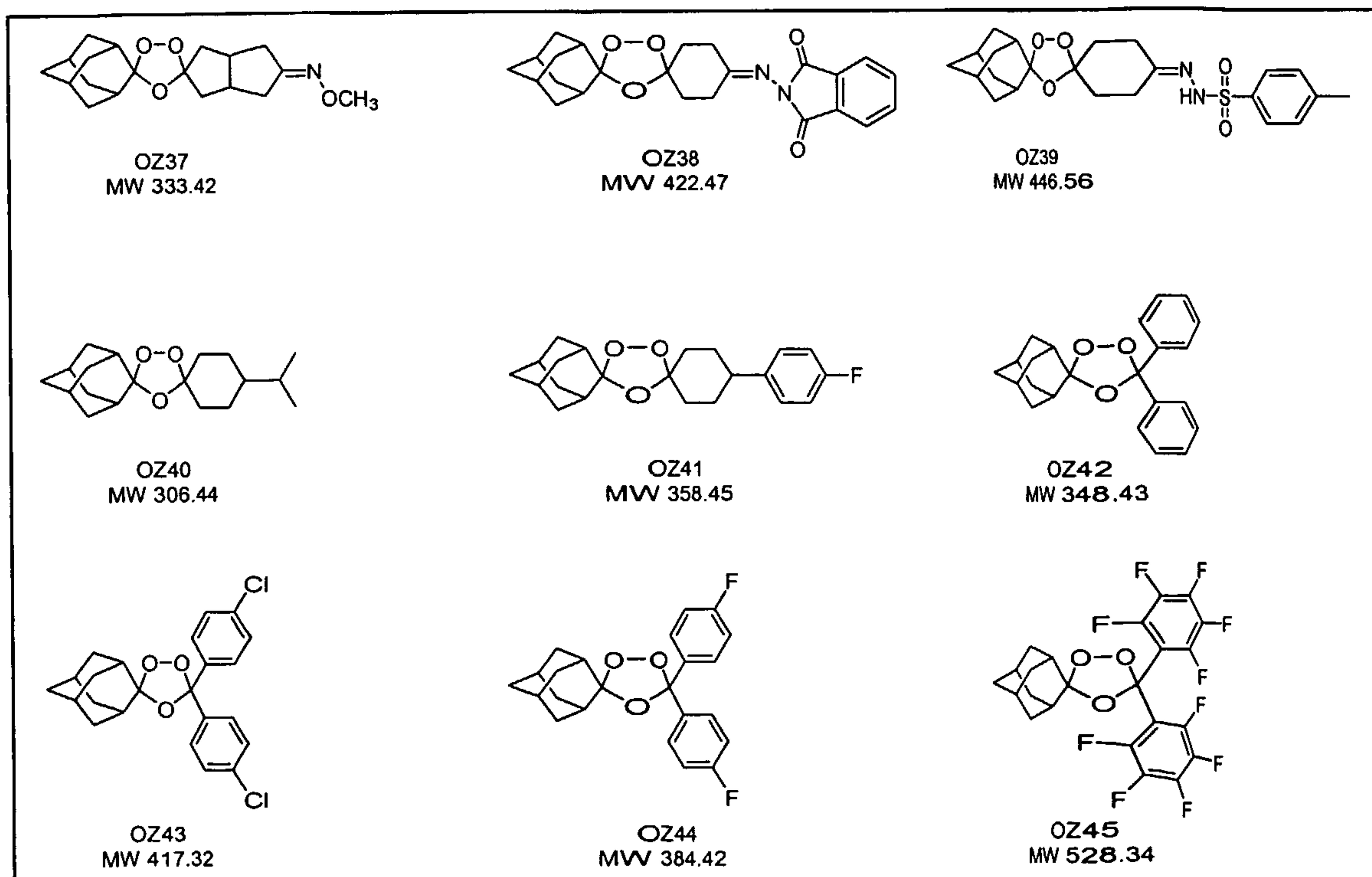
5 A notable feature of these trioxolanes in comparison to the artemisinin semisynthetic derivatives is their structural simplicity. A potential advantage of trioxolanes over both trioxanes (Jefford, 1997; Cumming et al., 1997) and tetraoxanes (Vennerstrom et al., 2000) is a more convenient access to structurally diverse, non-symmetrical, and in many cases, achiral compounds.

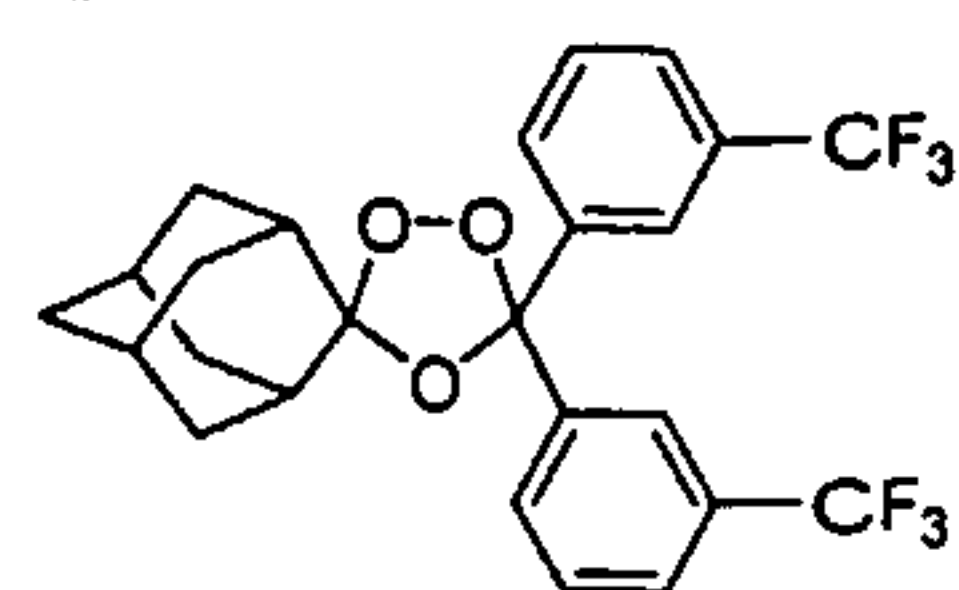
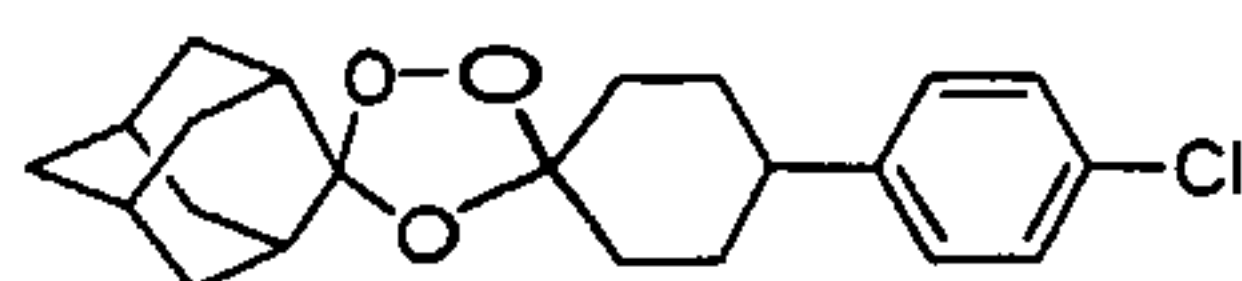
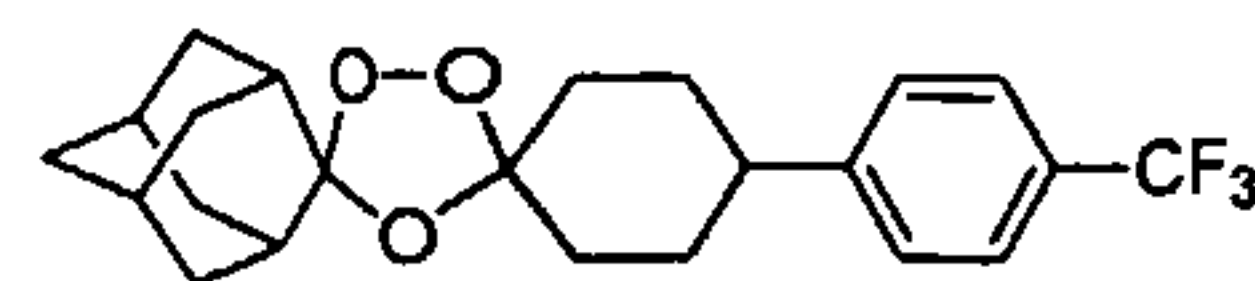
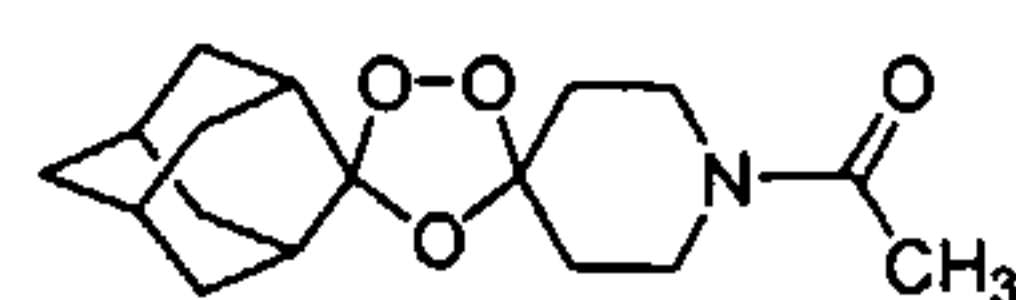
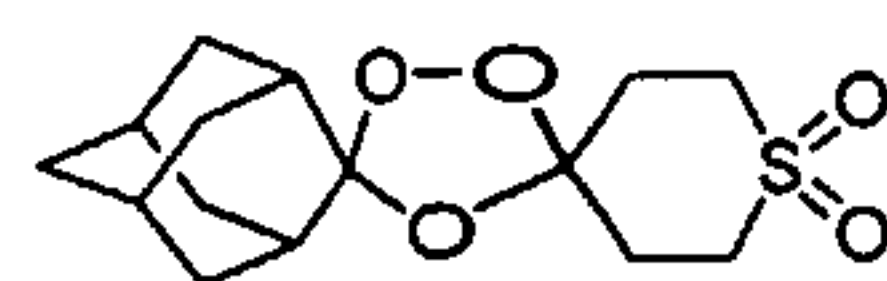
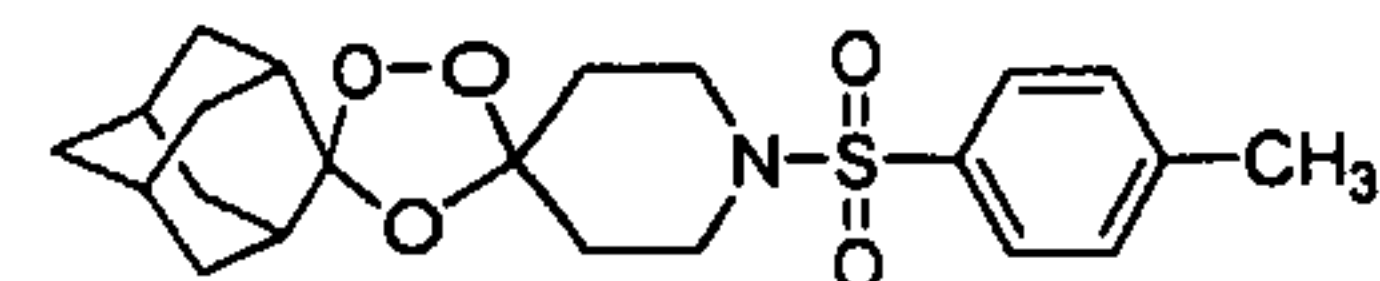
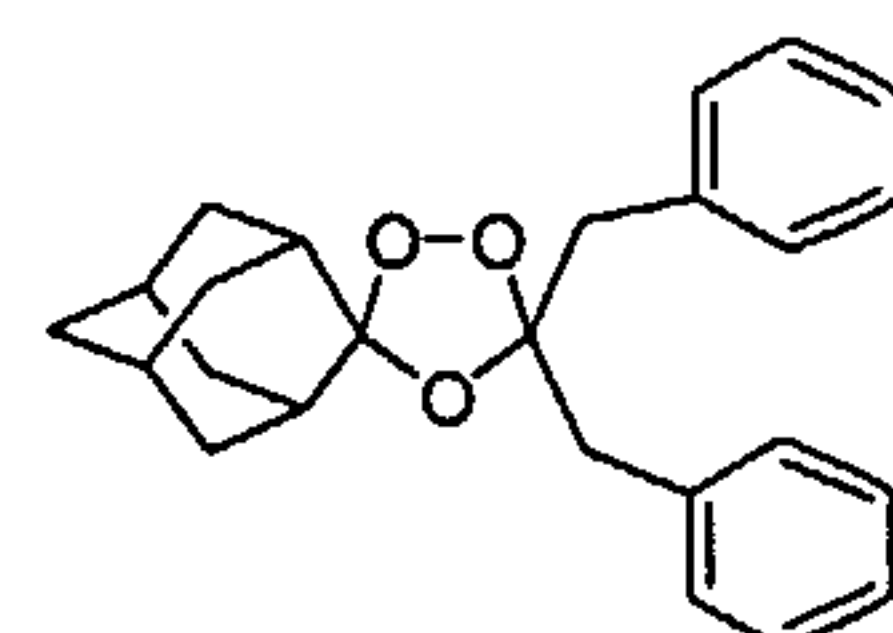
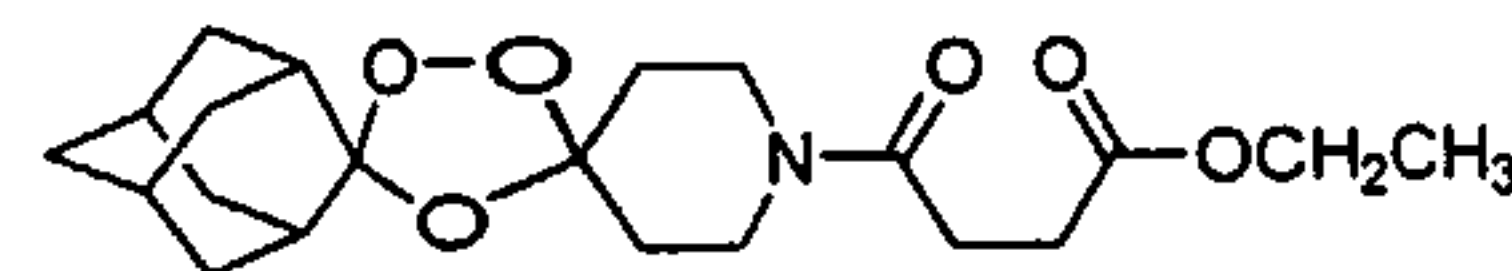
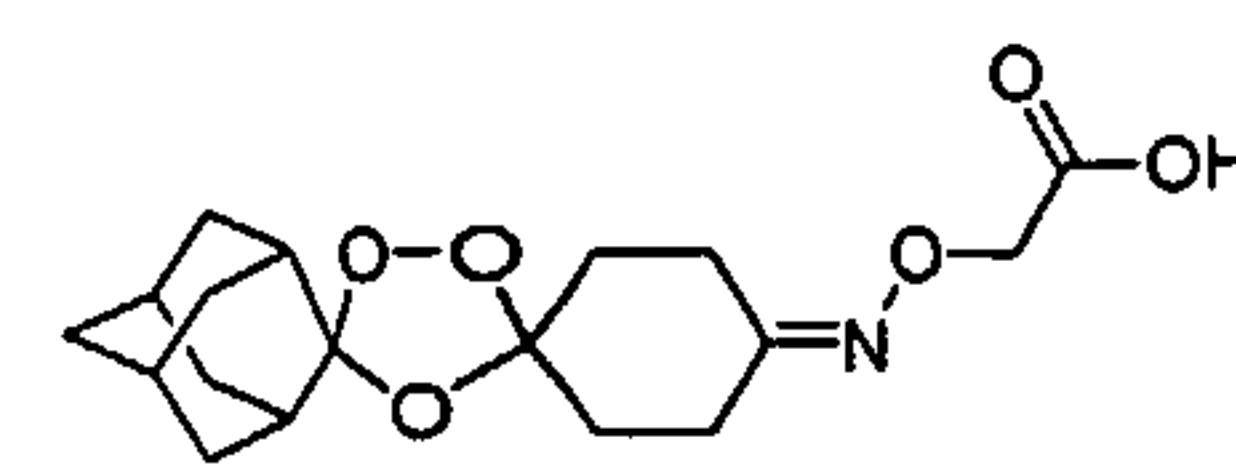
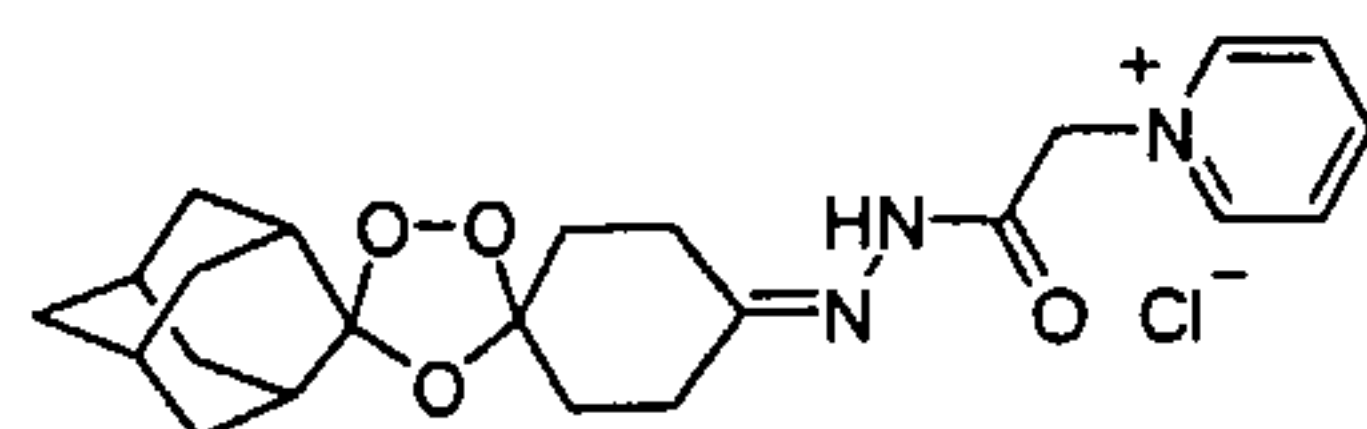
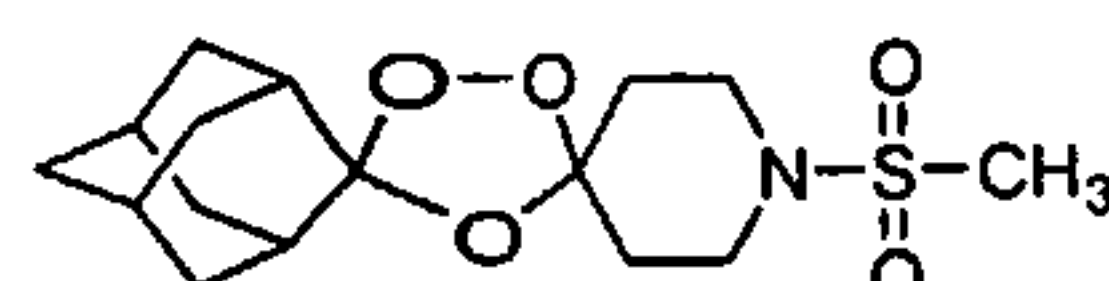
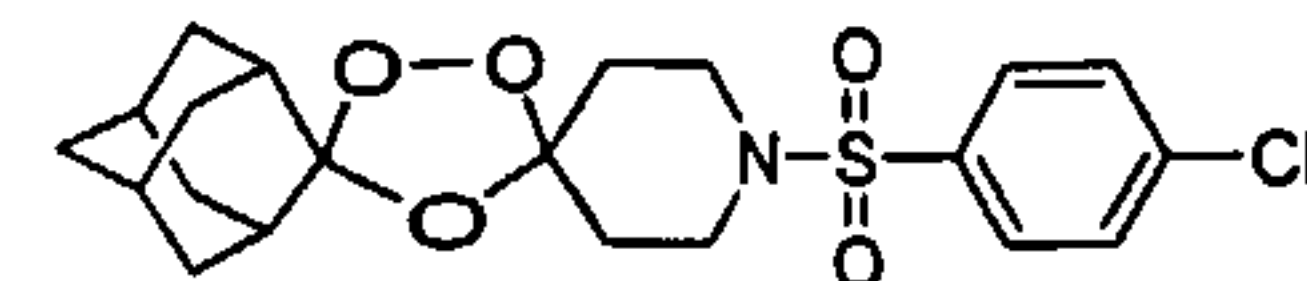
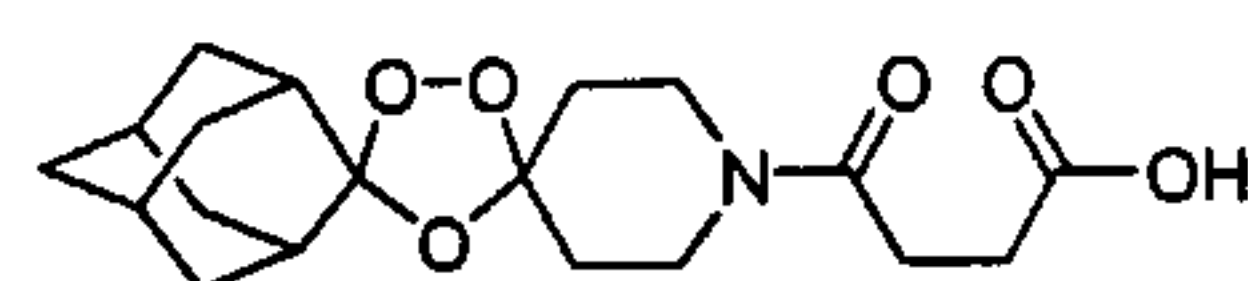
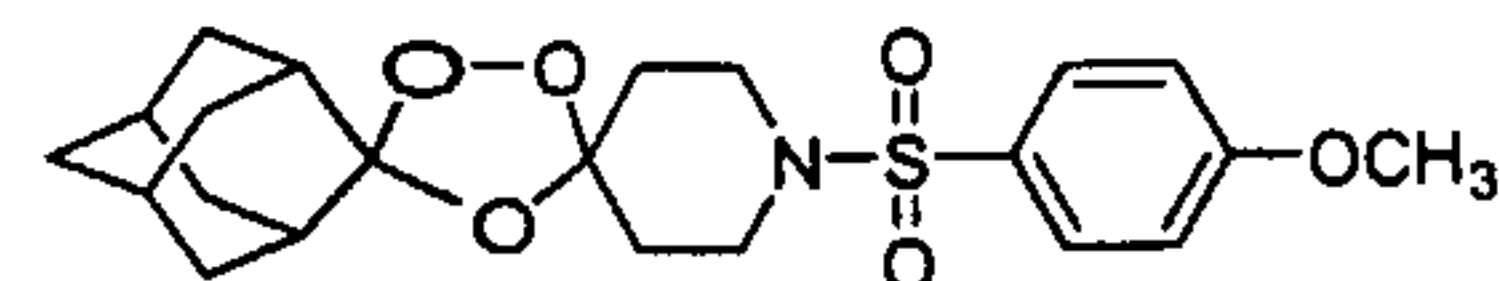
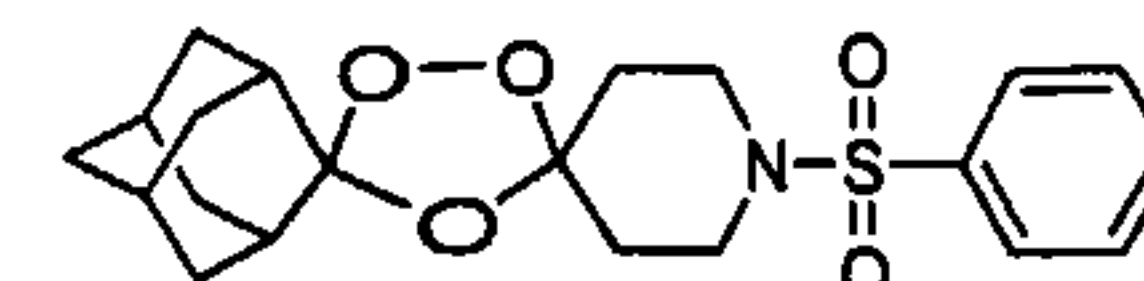
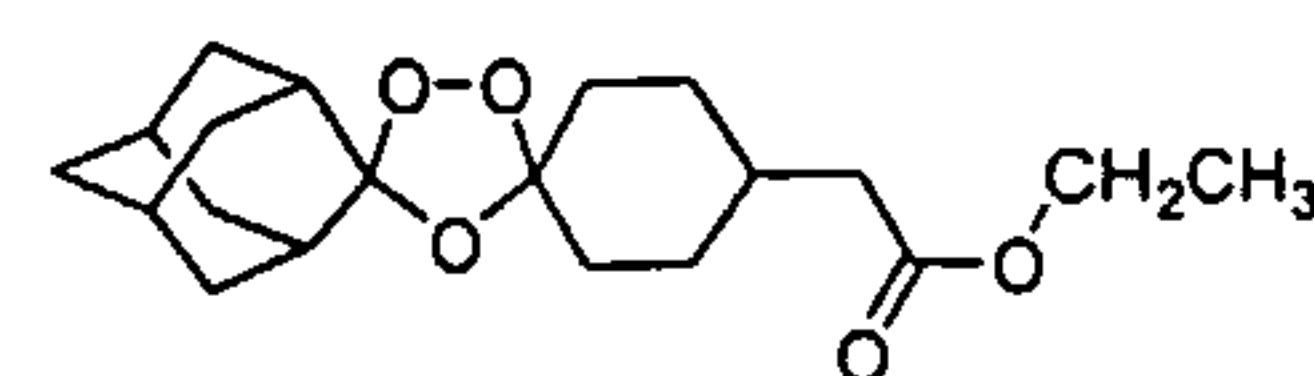
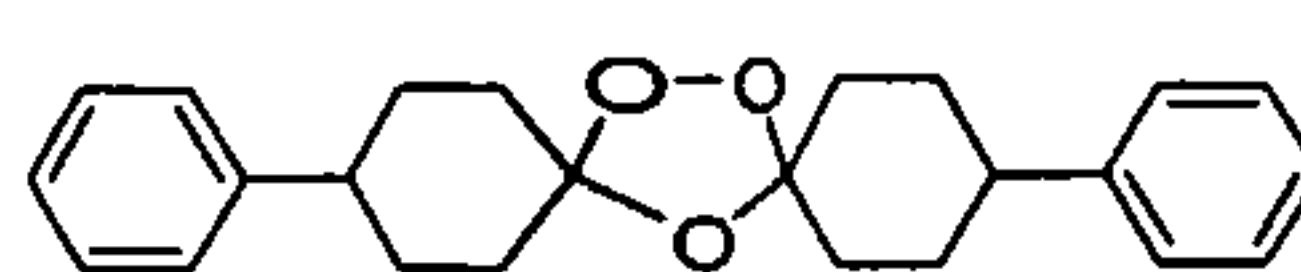
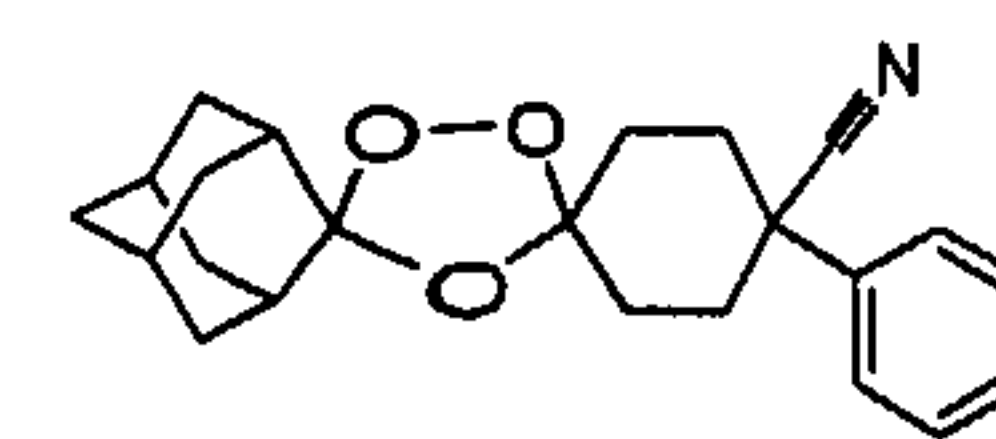
10 Below are several dispiro 1,2,4-trioxolanes synthesized in accordance with the teachings of this invention. "OZ" is an internal designation for these compounds that will be used throughout the remainder of the application for convenience:

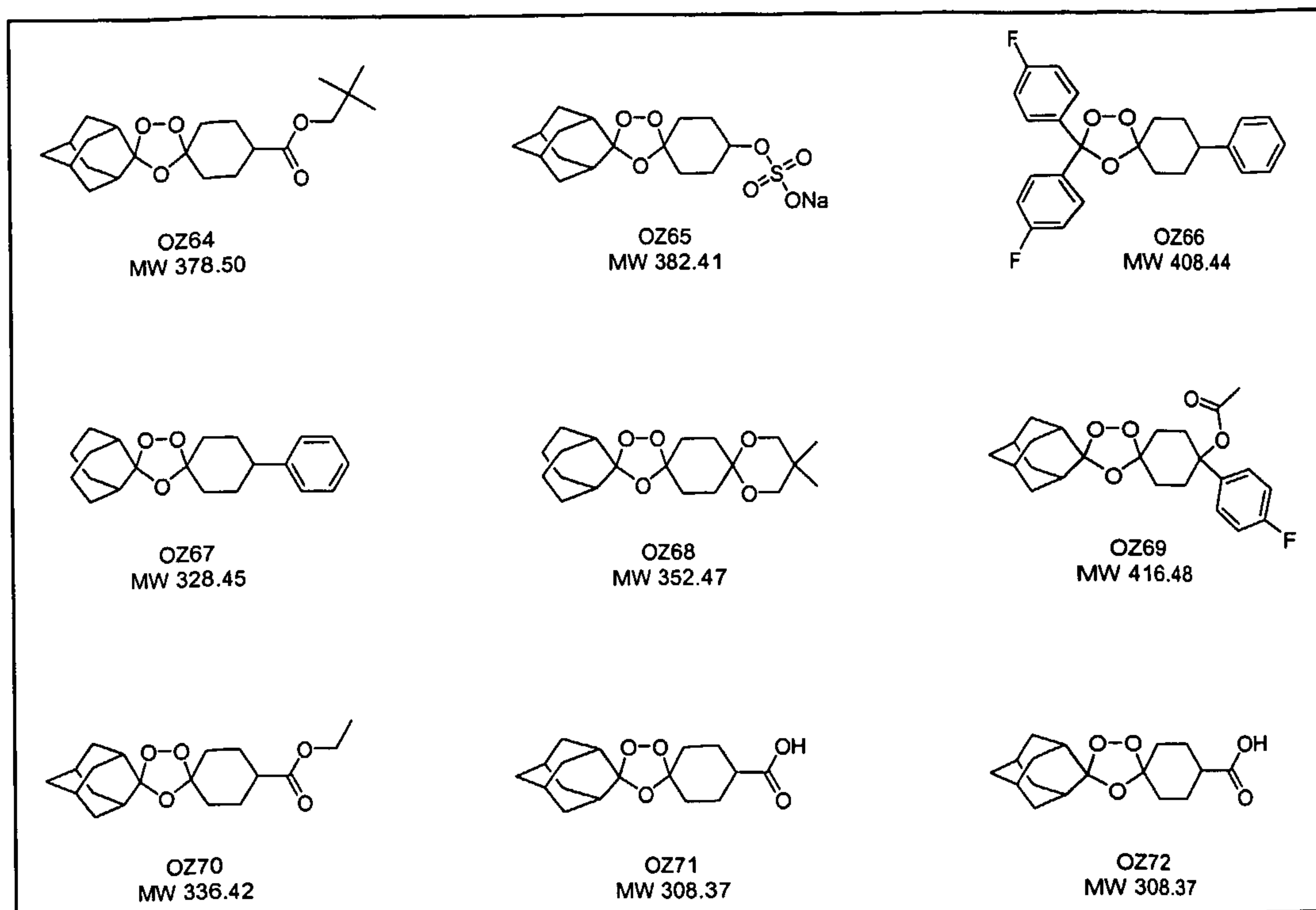
OZ Series 1 (OZ01–OZ09)



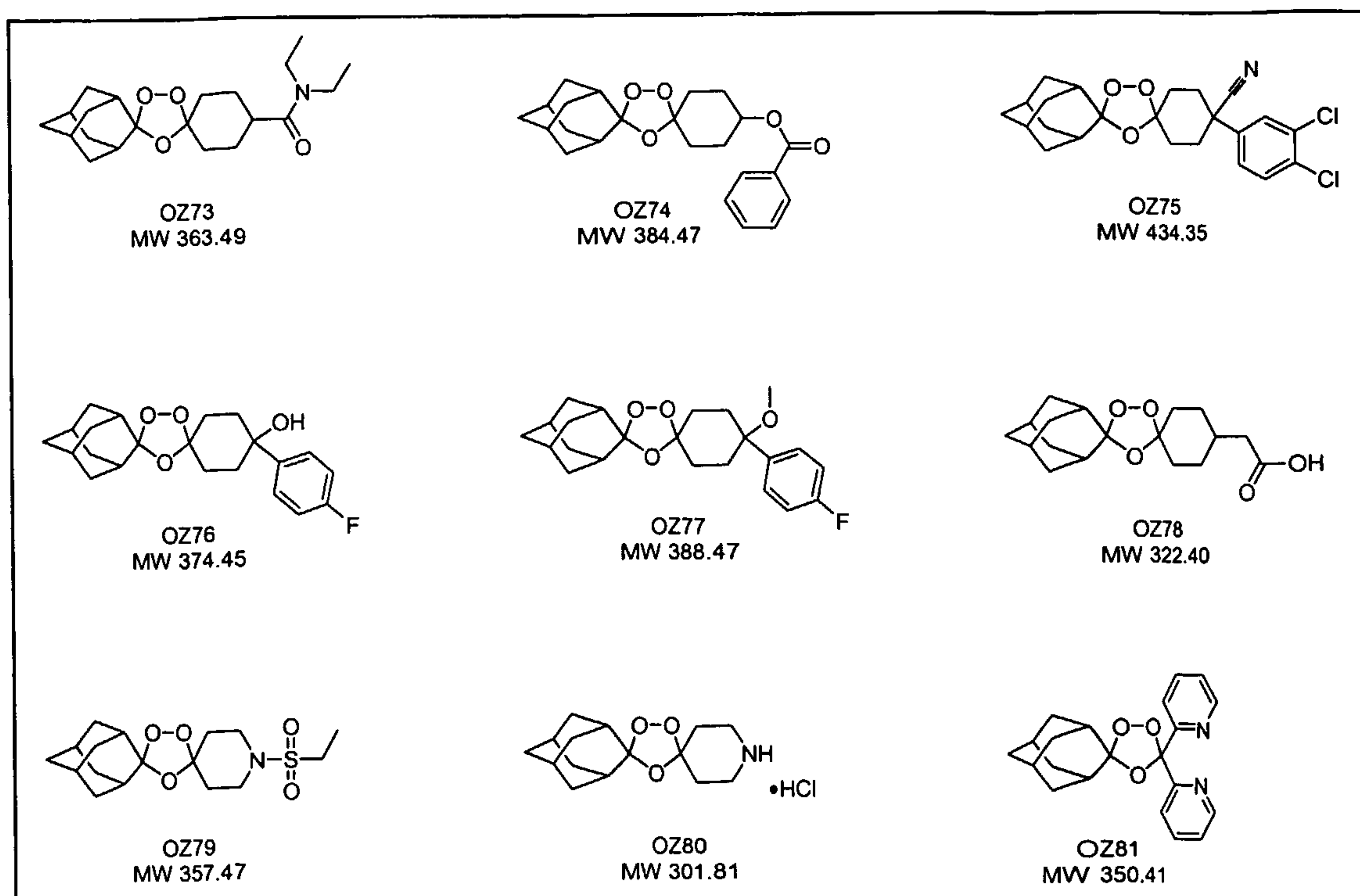
OZ Series 2 (OZ10–OZ18)**OZ Series 3 (OZ19–OZ27)**

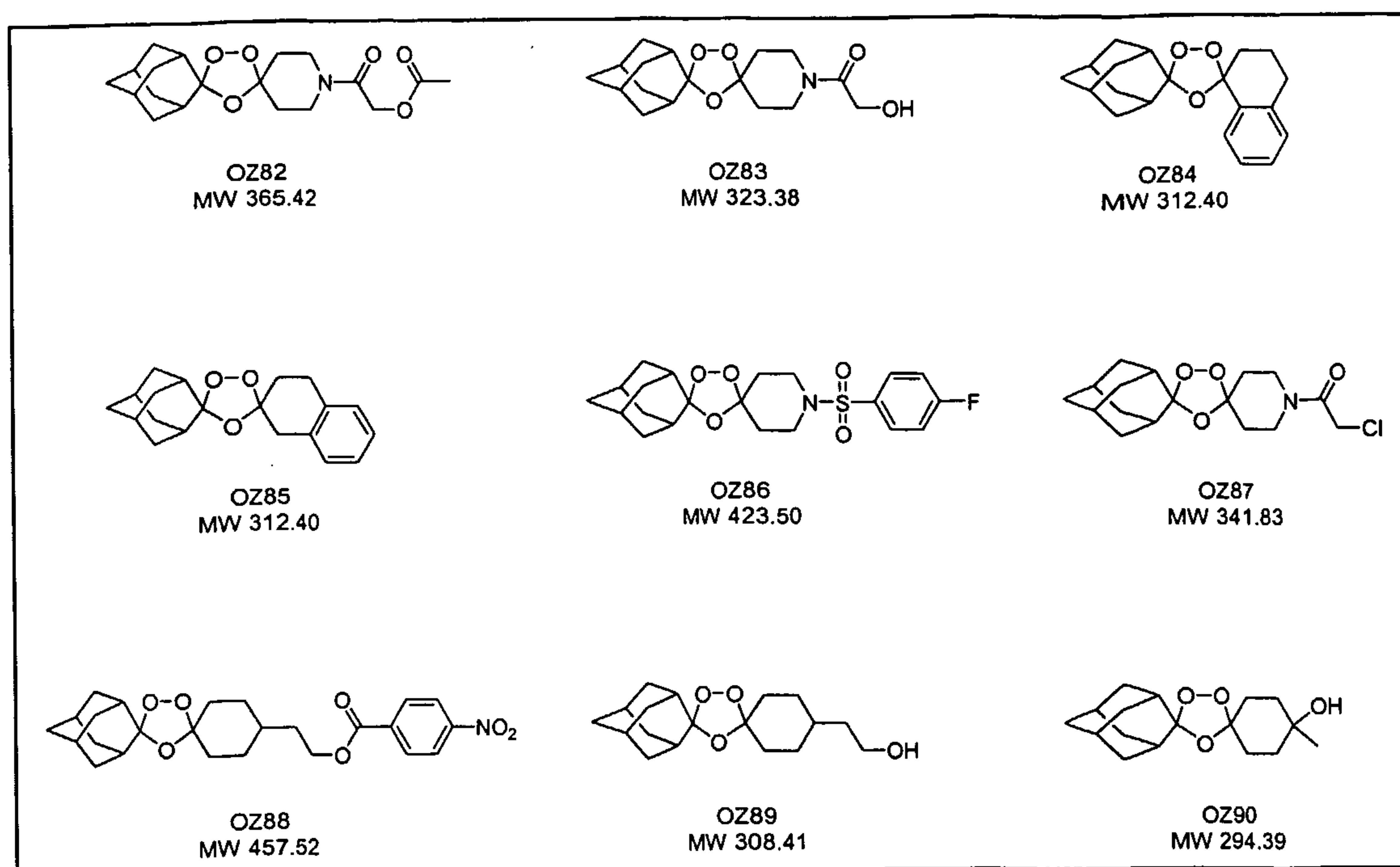
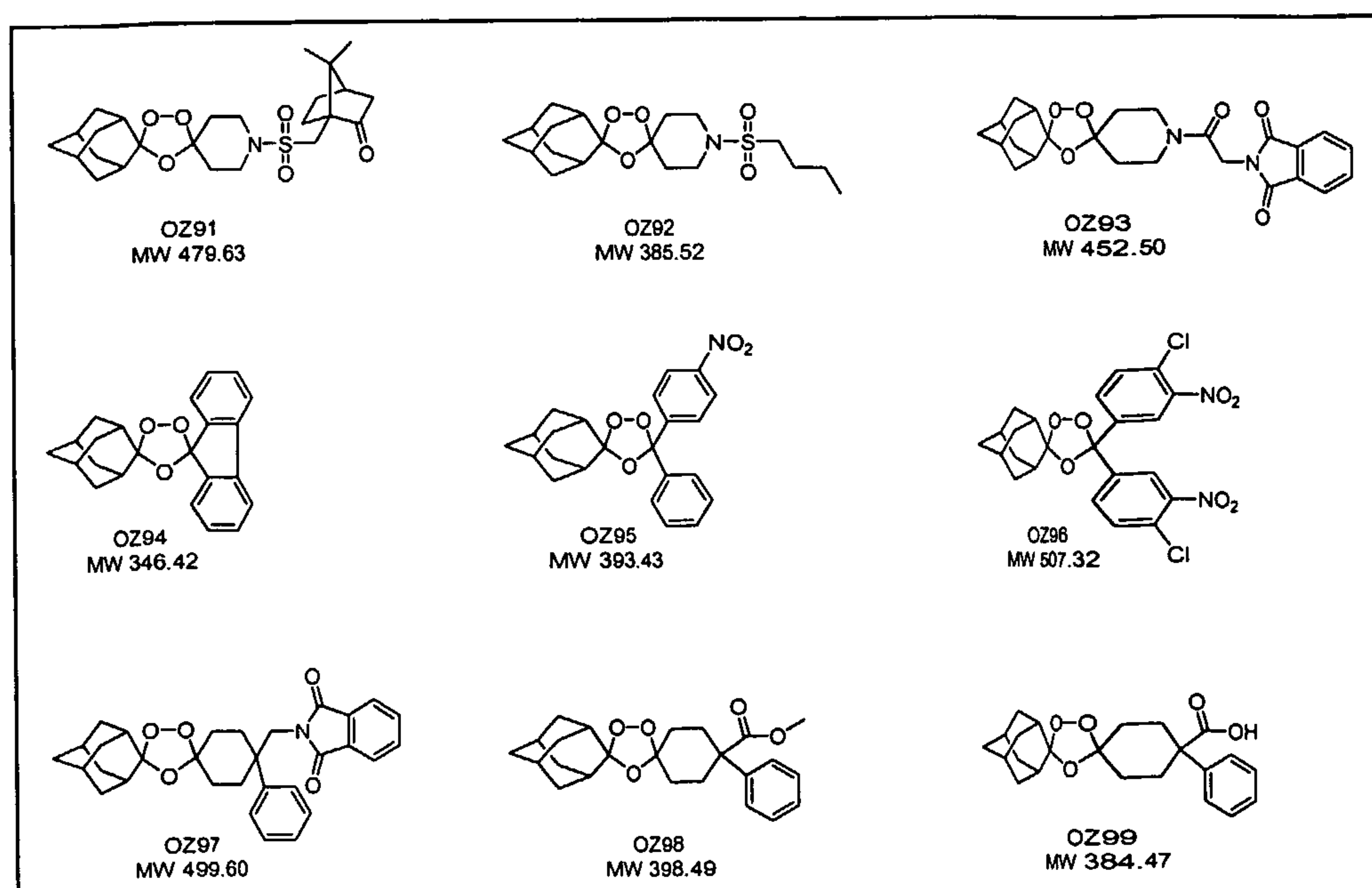
OZ Series 4 (OZ28–OZ36)**OZ Series 5 (OZ37–OZ45)**

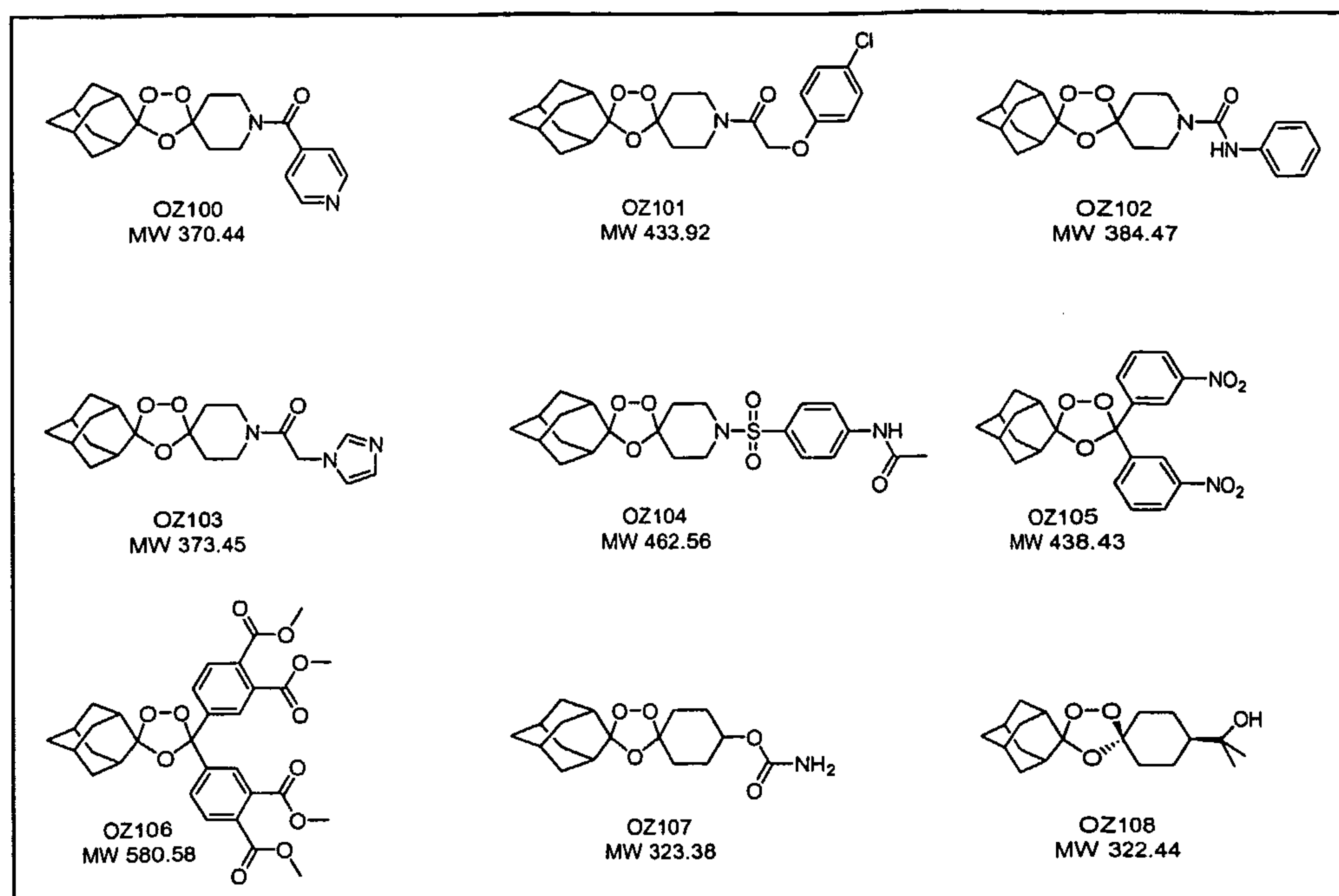
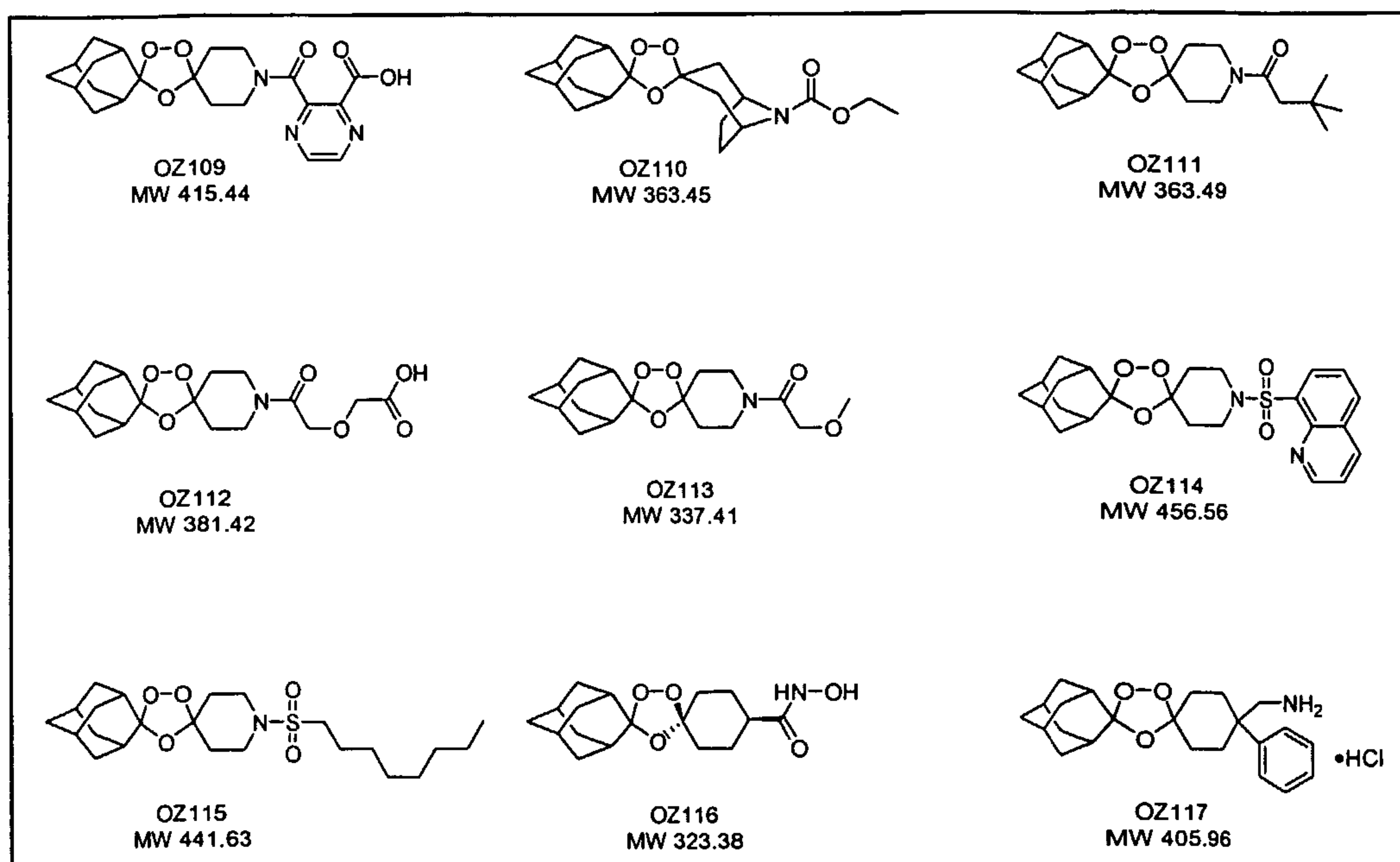
OZ Series 6 (OZ46–OZ54)OZ46
MW 484.43OZ47
MW 374.90OZ48
MW 408.45OZ49
MW 307.38OZ50
MW 314.40OZ51
MW 419.54OZ52
MW 376.49OZ53
MW 393.47OZ54
MW 351.39**OZ Series 7 (OZ55–OZ63)**OZ55
MW 447.95OZ56
MW 343.44OZ57
MW 439.95OZ58
MW 365.42OZ59
MW 435.53OZ60
MW 405.51OZ61
MW 350.45OZ62
MW 364.48OZ63
MW 365.47

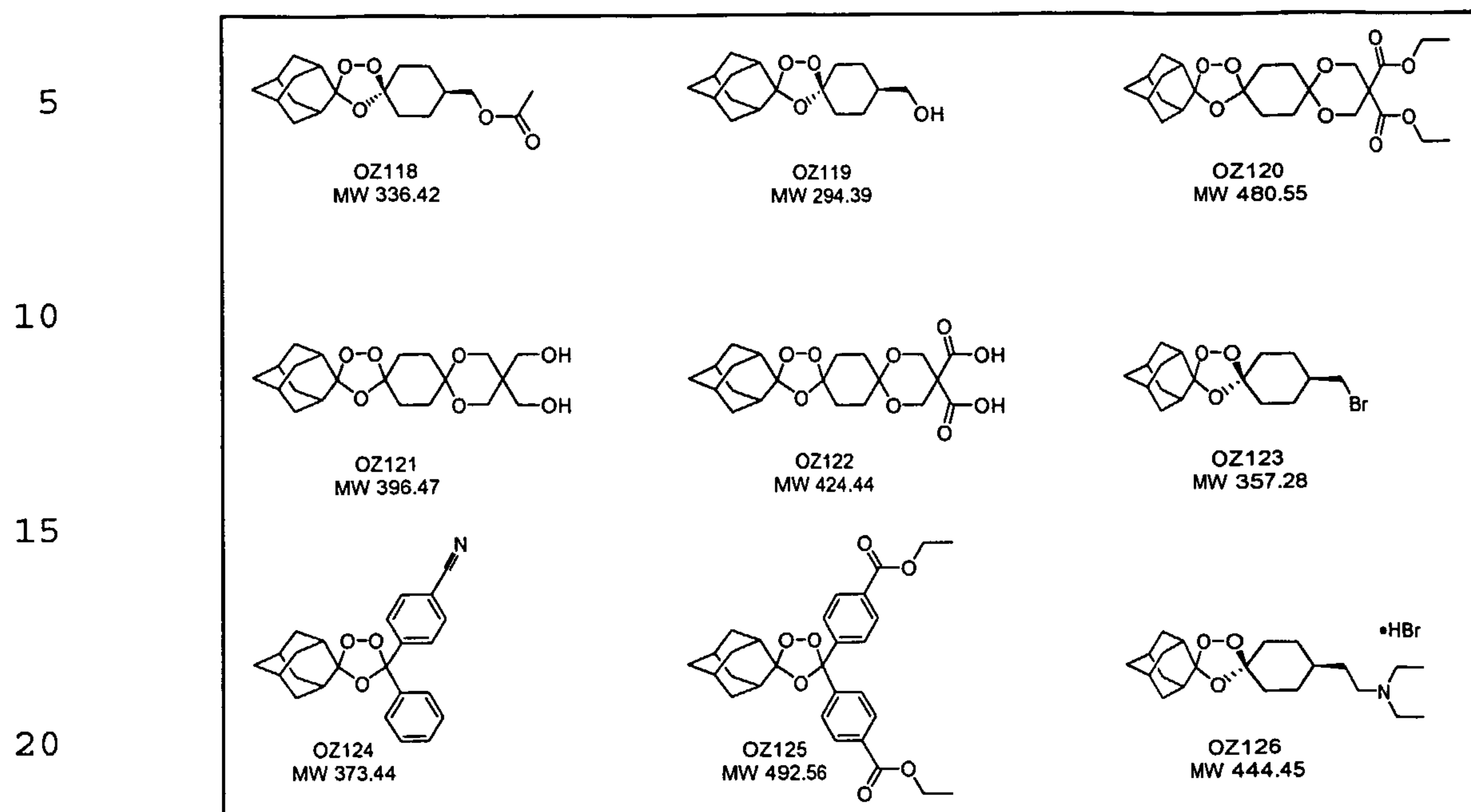
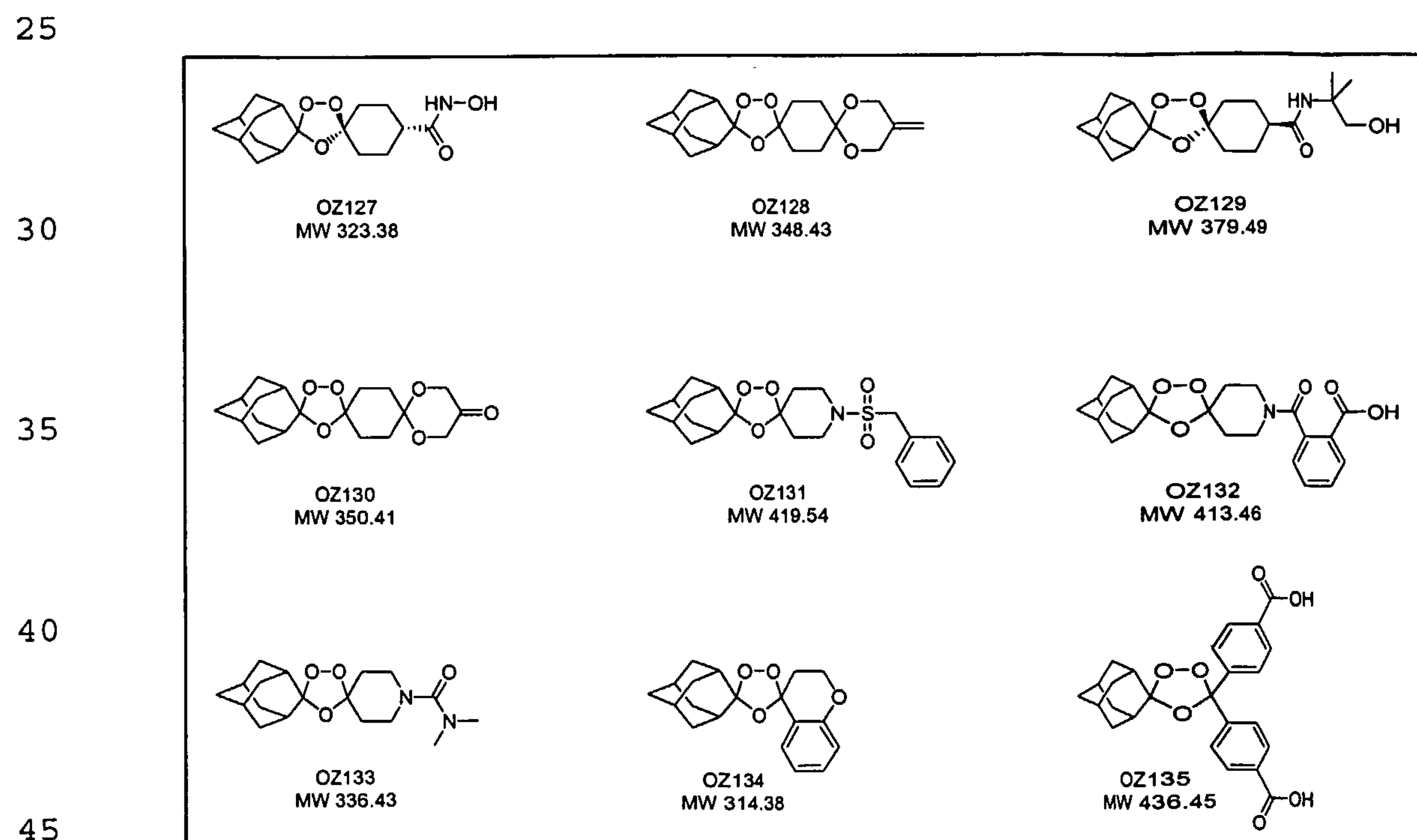
OZ Series 8 (OZ64-OZ72)

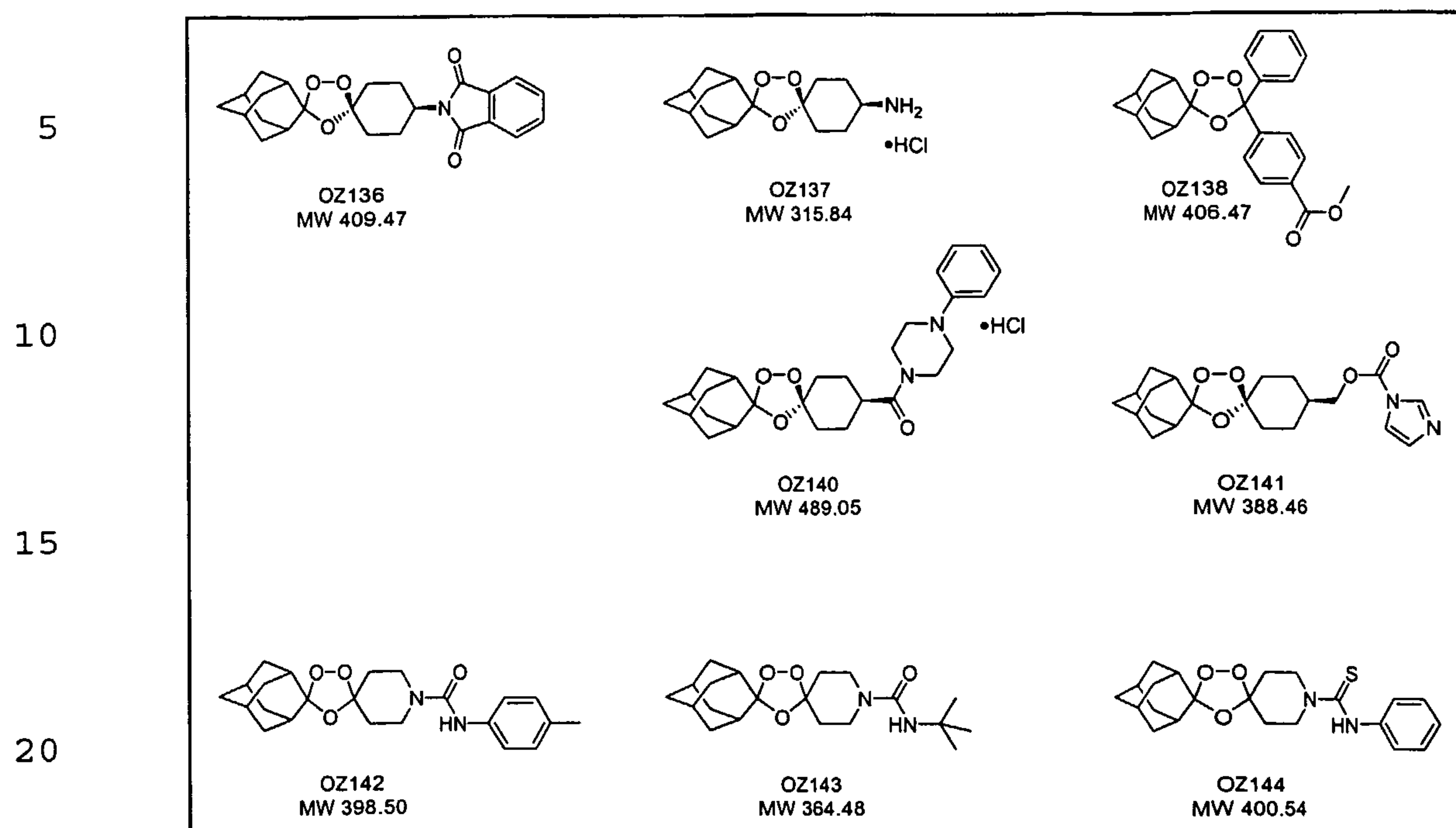
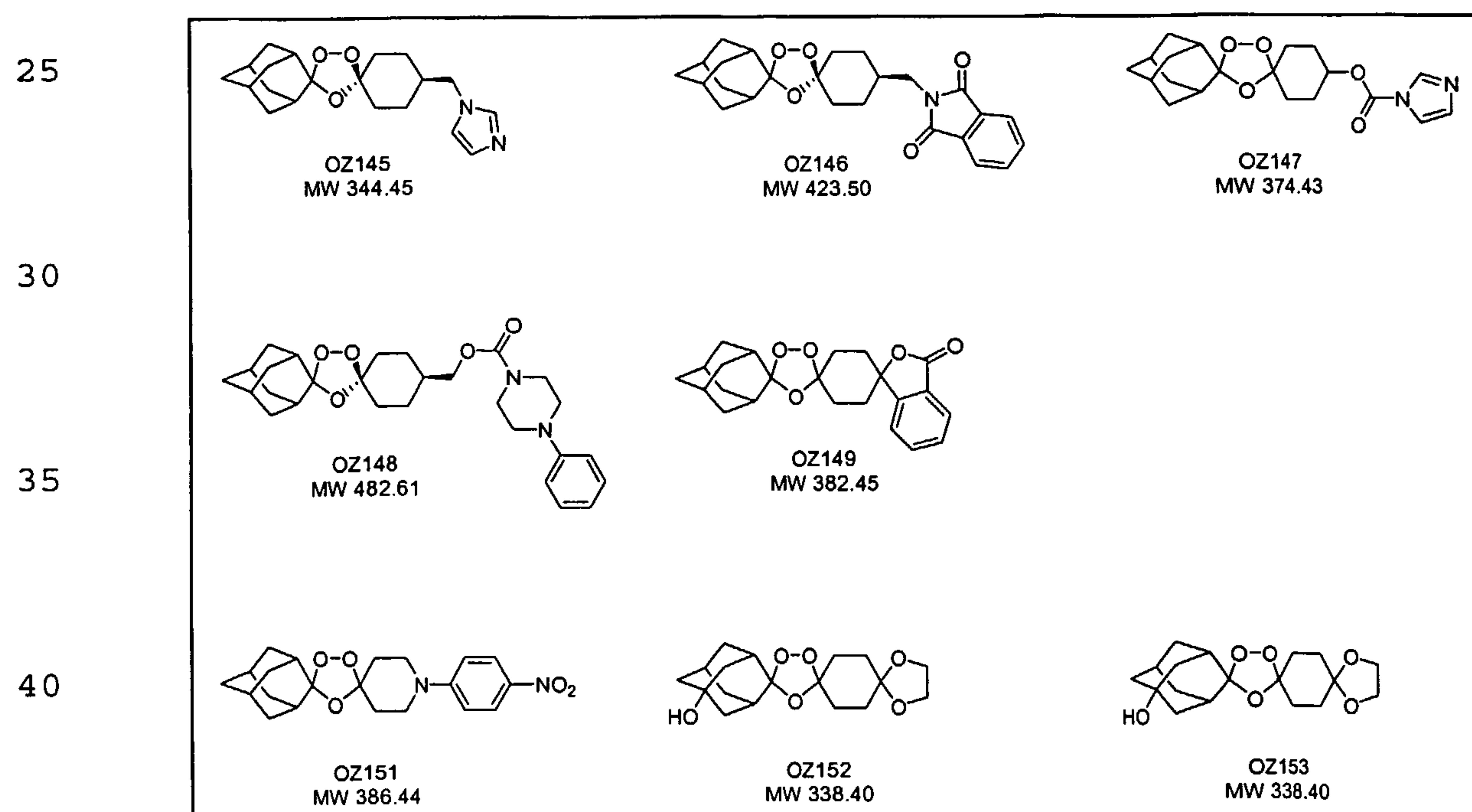
10

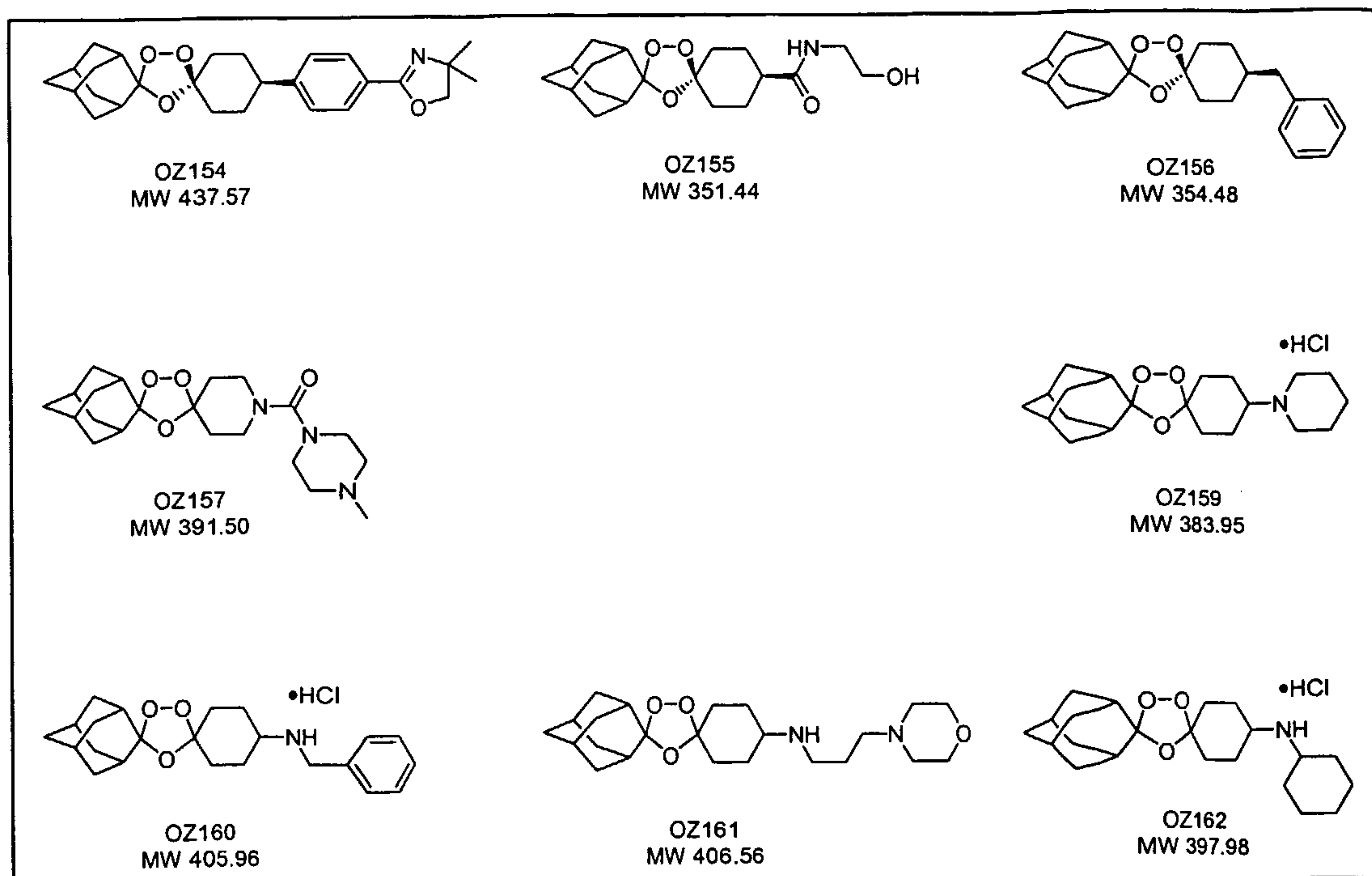
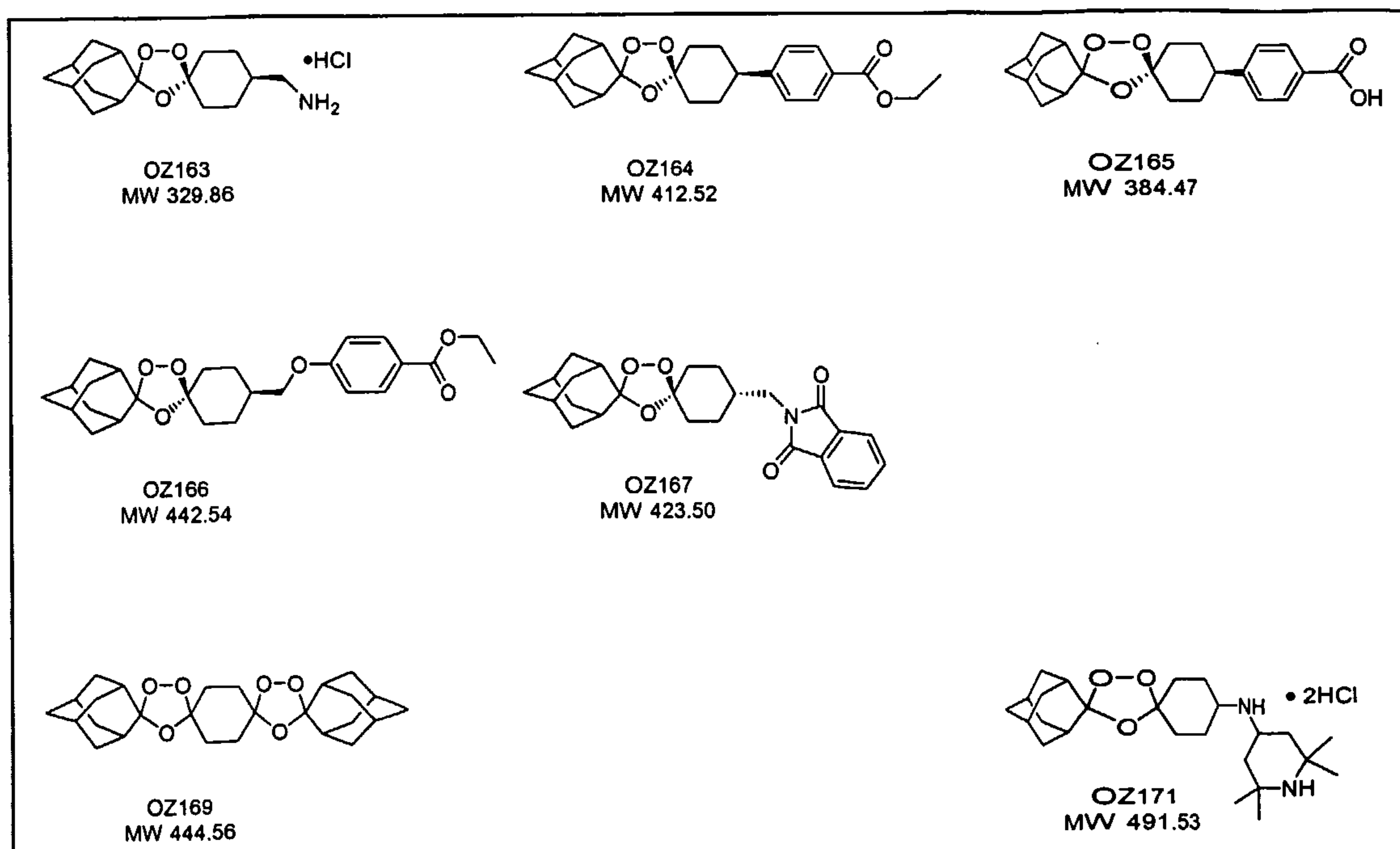
OZ Series 9 (OZ73-OZ81)

OZ Series 10 (OZ82–OZ90)**OZ Series 11 (OZ91–OZ99)**

OZ Series 12 (OZ100–OZ108)**OZ Series 13 (OZ109–OZ117)**

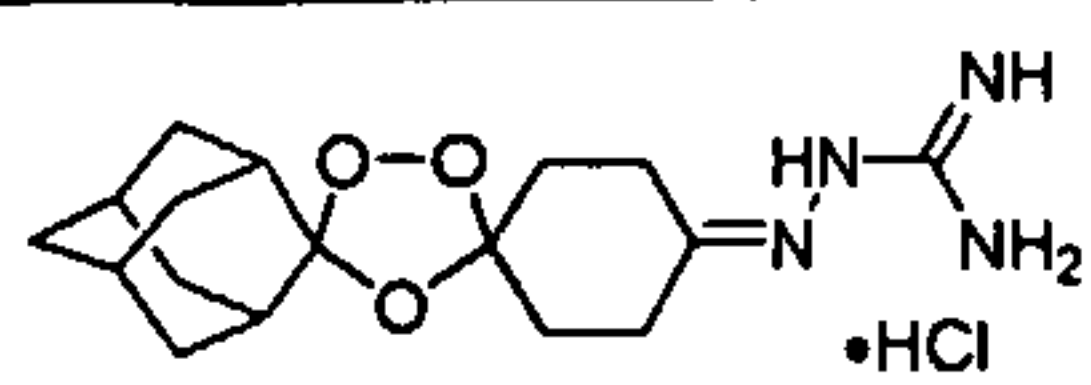
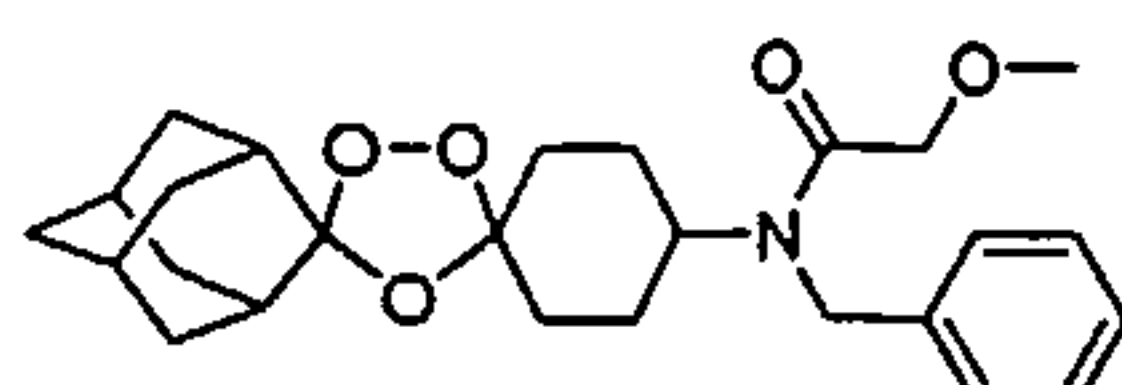
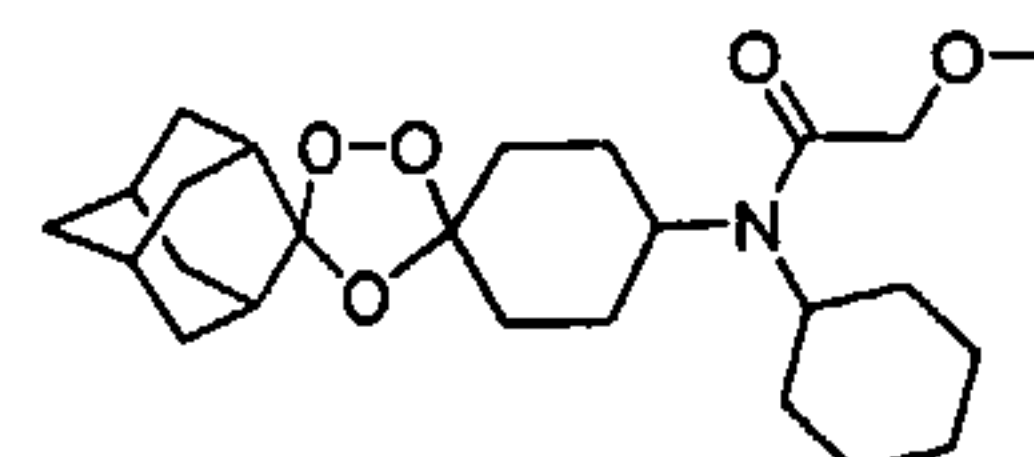
OZ Series 14 (OZ118–OZ126)**OZ Series 15 (OZ127–OZ135)**

OZ Series 16 (OZ136–OZ144)**OZ Series 17 (OZ145–OZ153)**

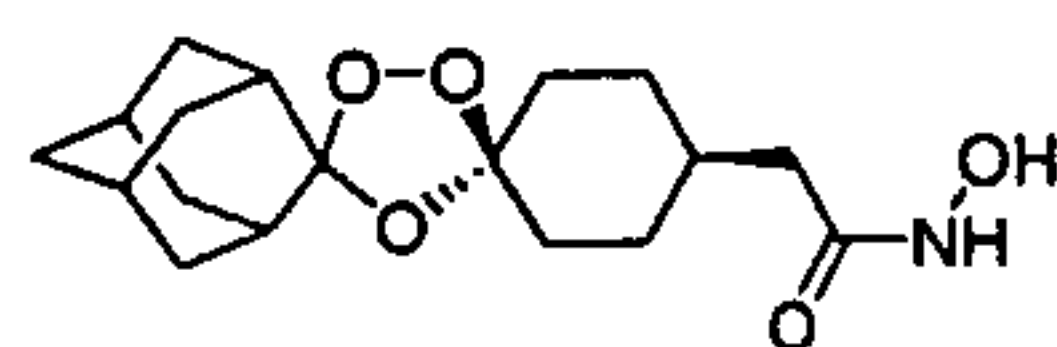
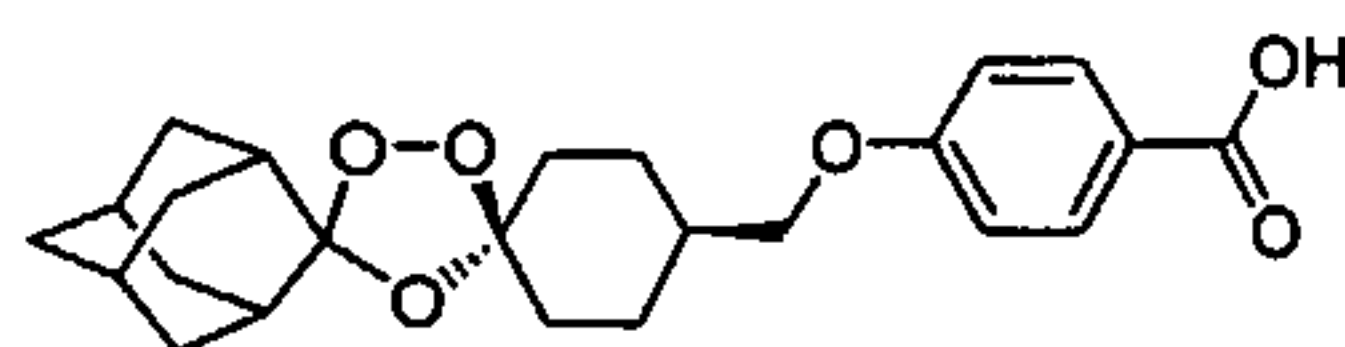
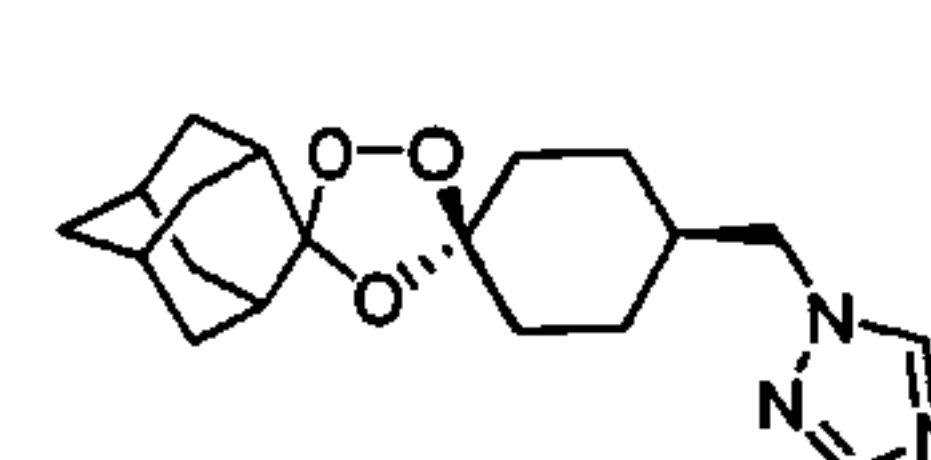
OZ Series 18 (OZ154–OZ162)**OZ Series 19 (OZ163–OZ171)**

OZ Series 20 (OZ172–OZ180)

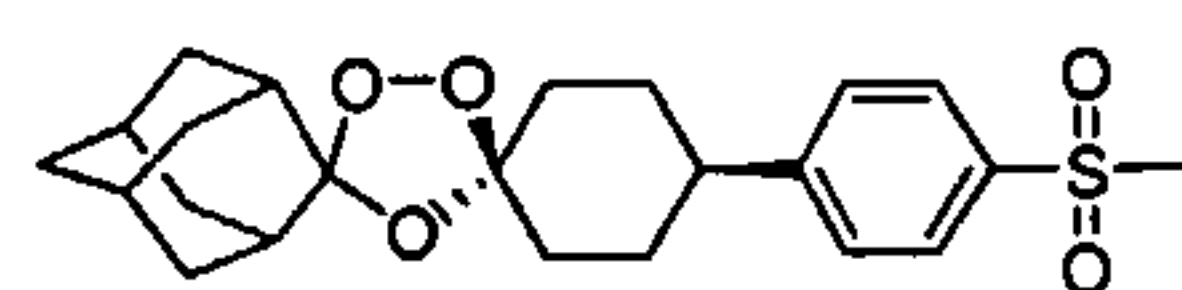
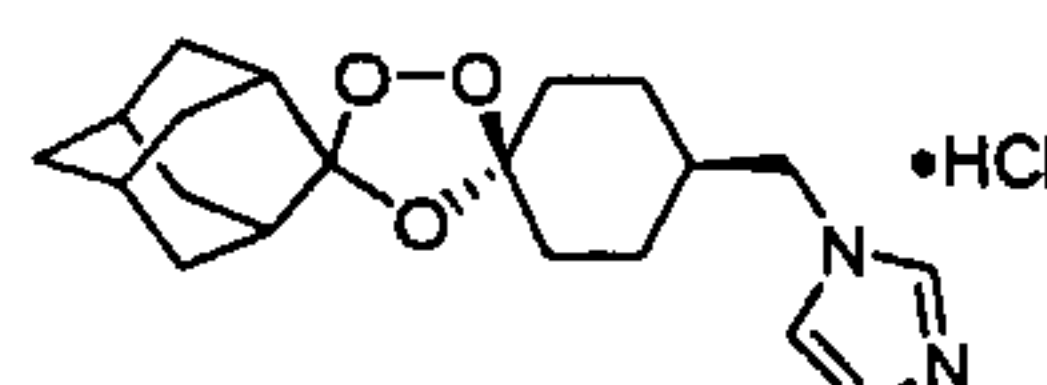
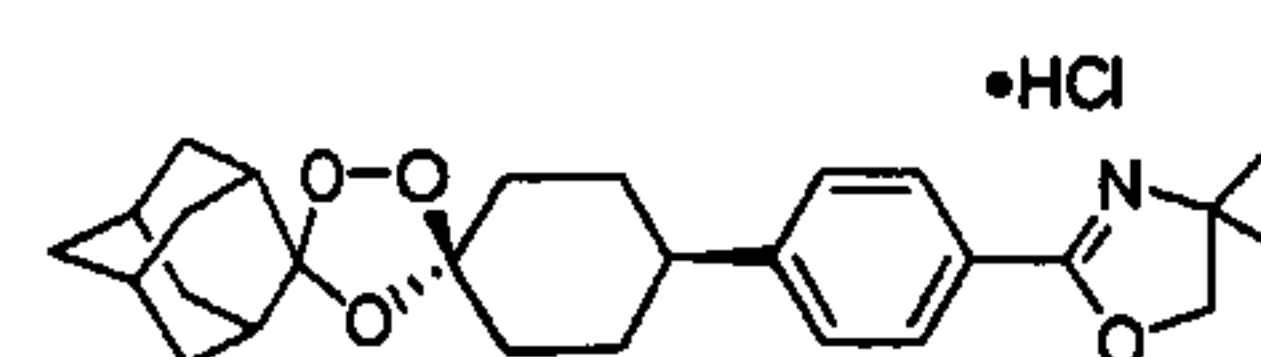
5

OZ172
MW 370.87OZ173
MW 441.56OZ174
MW 433.58

10

OZ175
MW 337.41OZ176
MW 414.49OZ177
MW 345.44

15

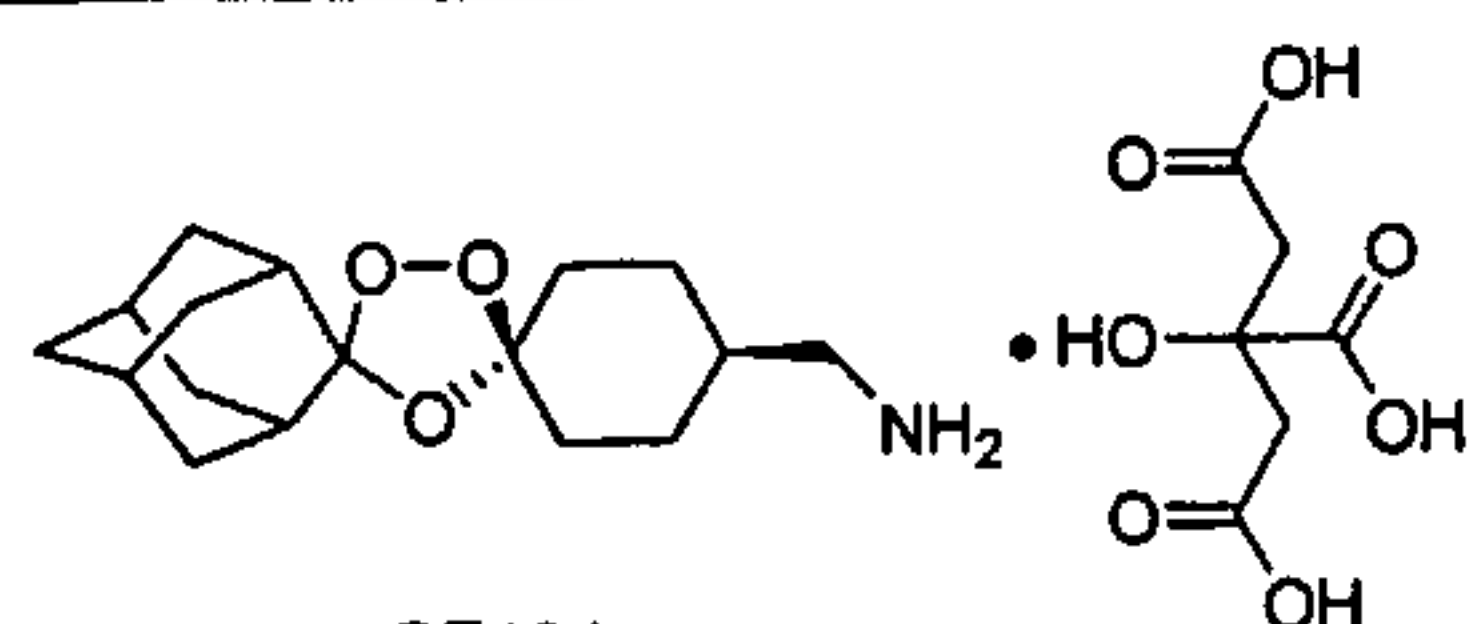
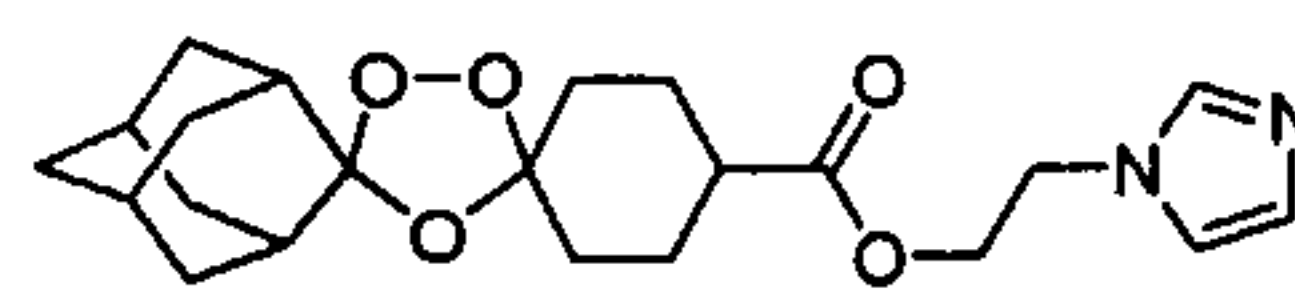
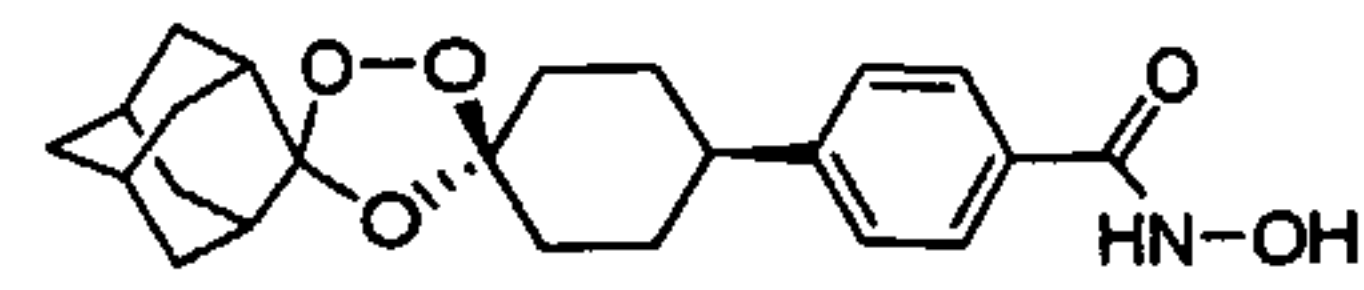
OZ178
MW 418.55OZ179
MW 380.91OZ180
MW 474.03

20

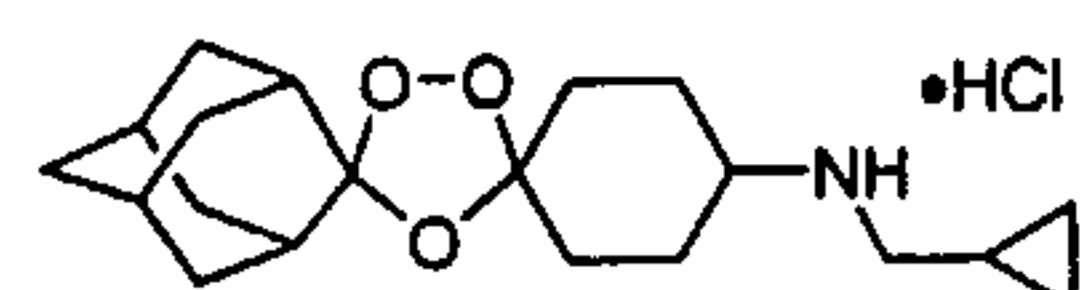
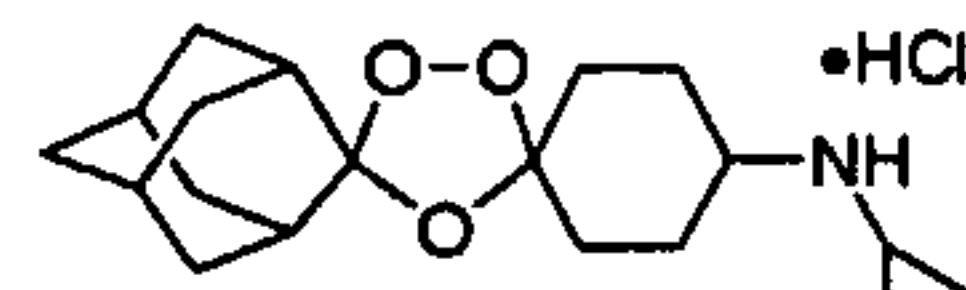
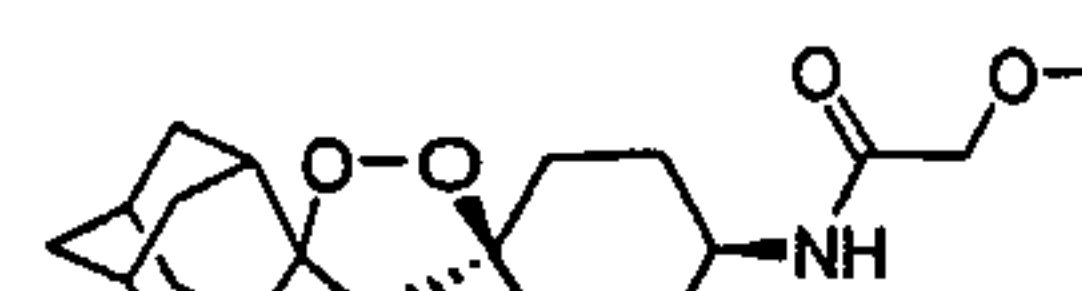
25

OZ Series 21 (OZ181–OZ189)

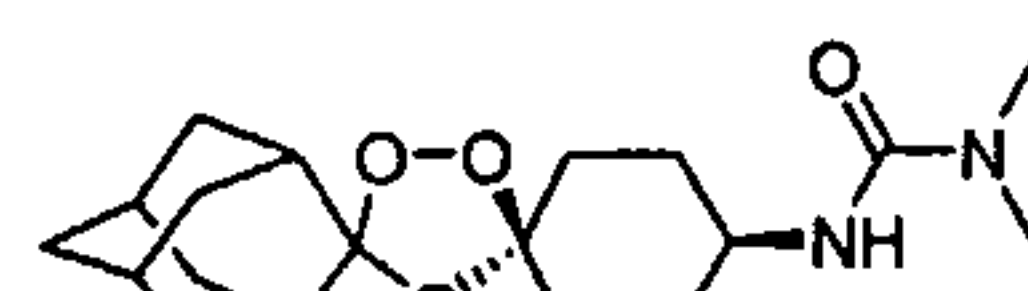
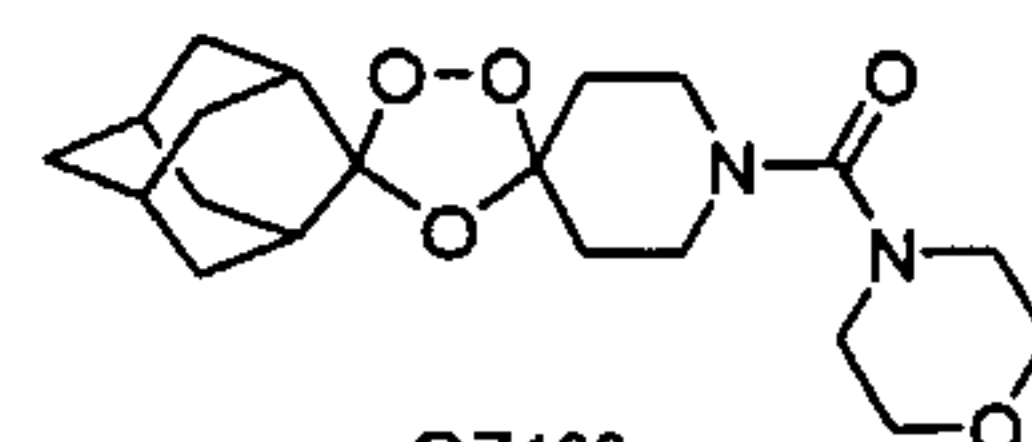
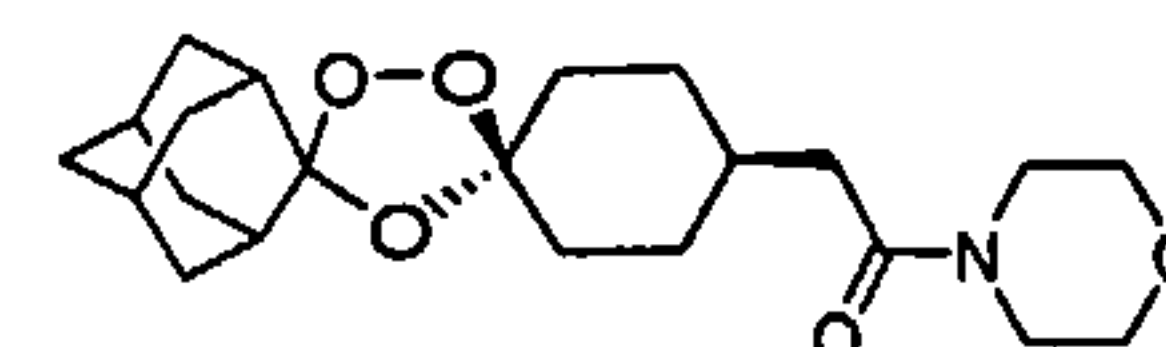
30

OZ181
MW 485.52OZ182
MW 402.48OZ183
MW 399.48

35

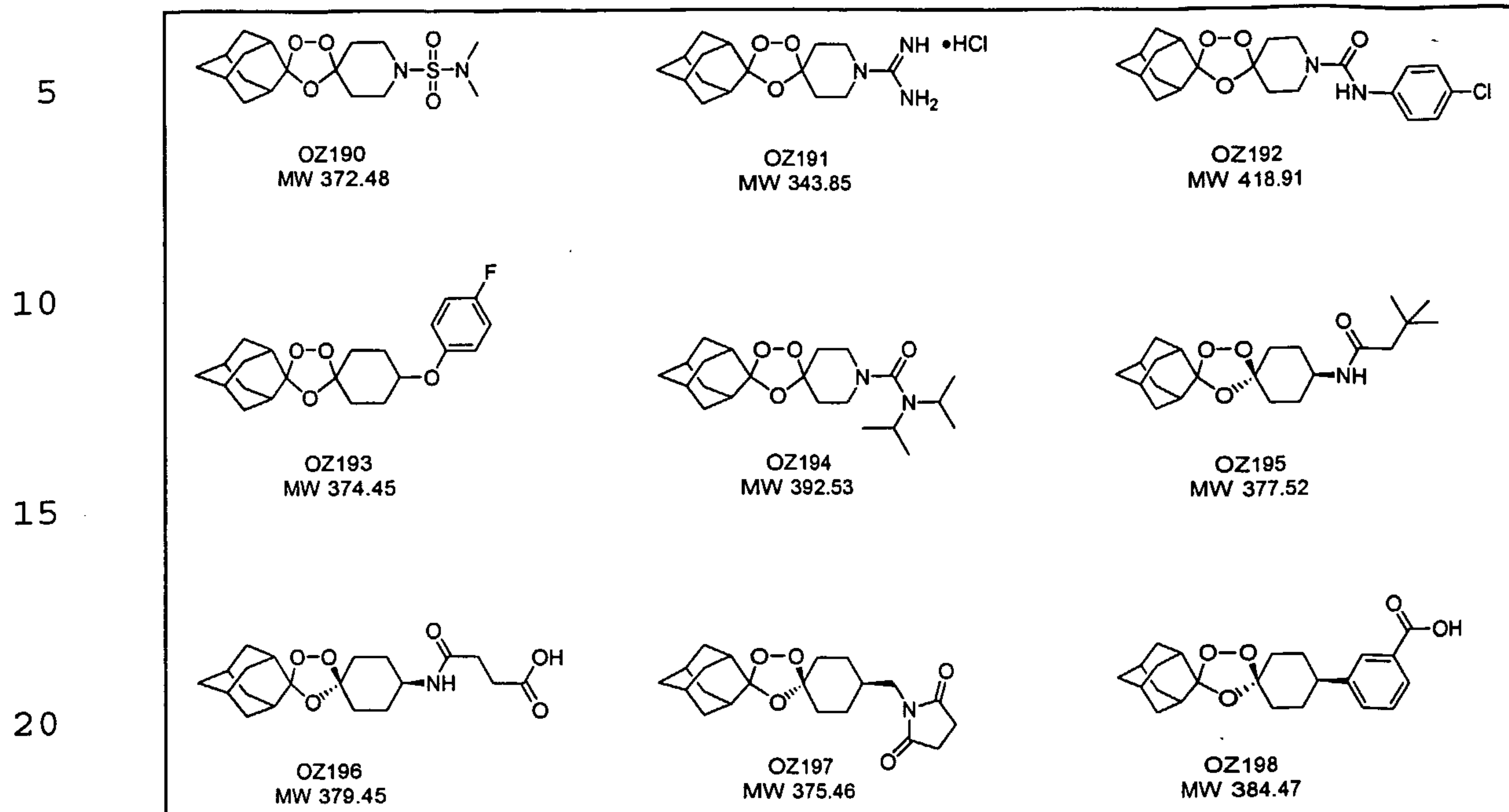
OZ184
MW 389.93OZ185
MW 355.90OZ186
MW 351.44

40

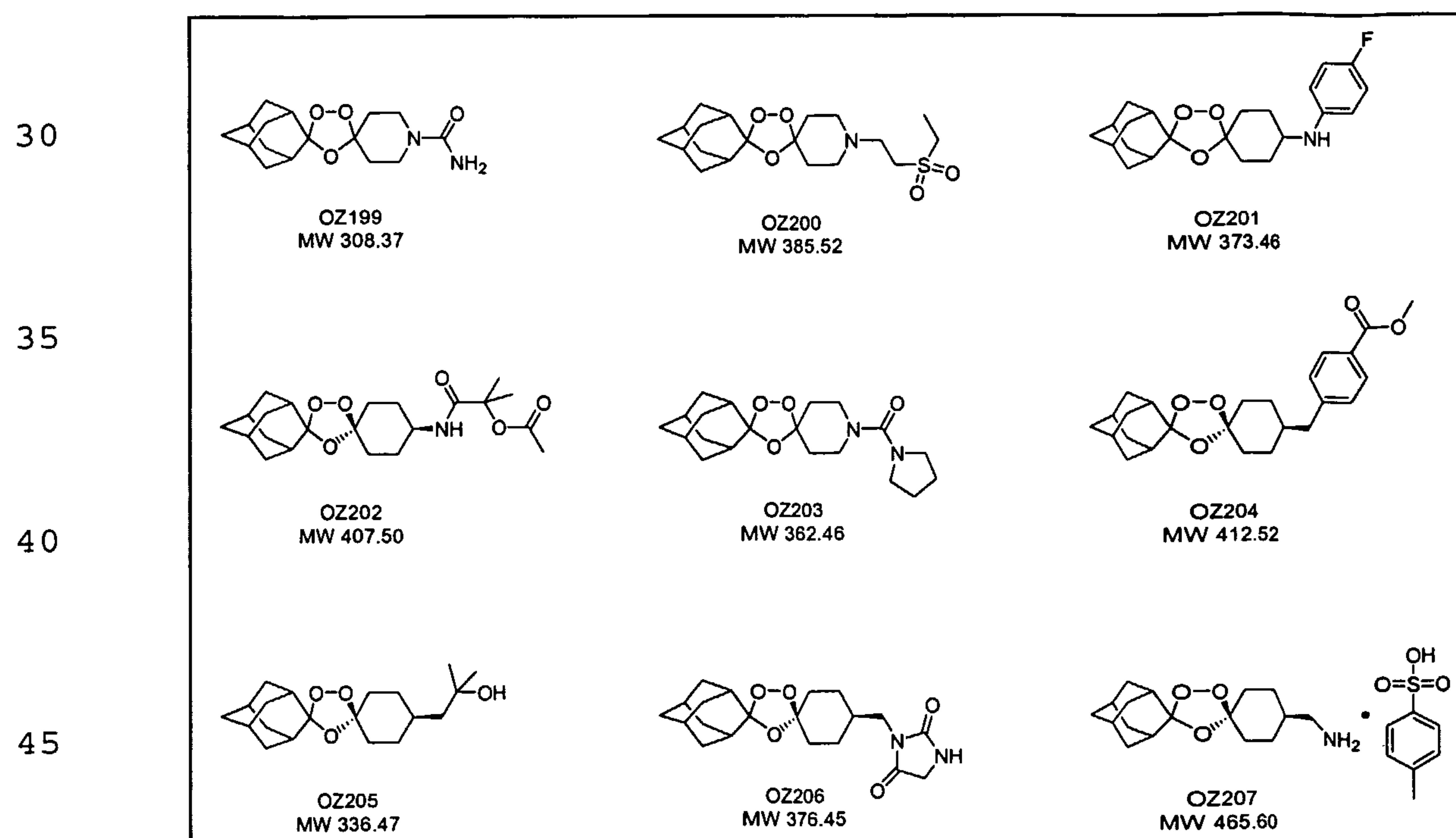
OZ187
MW 350.45OZ188
MW 378.46OZ189
MW 391.50

45

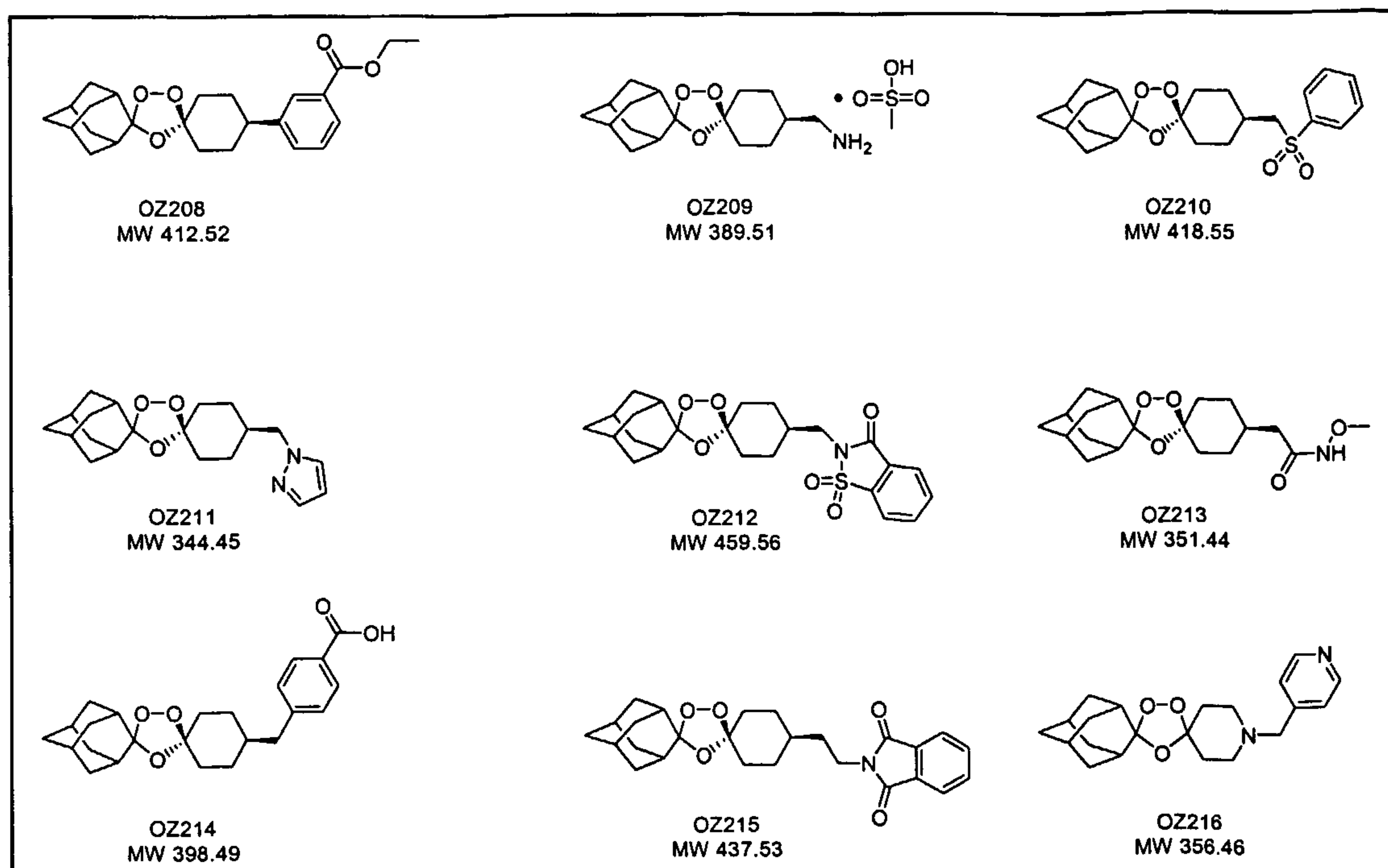
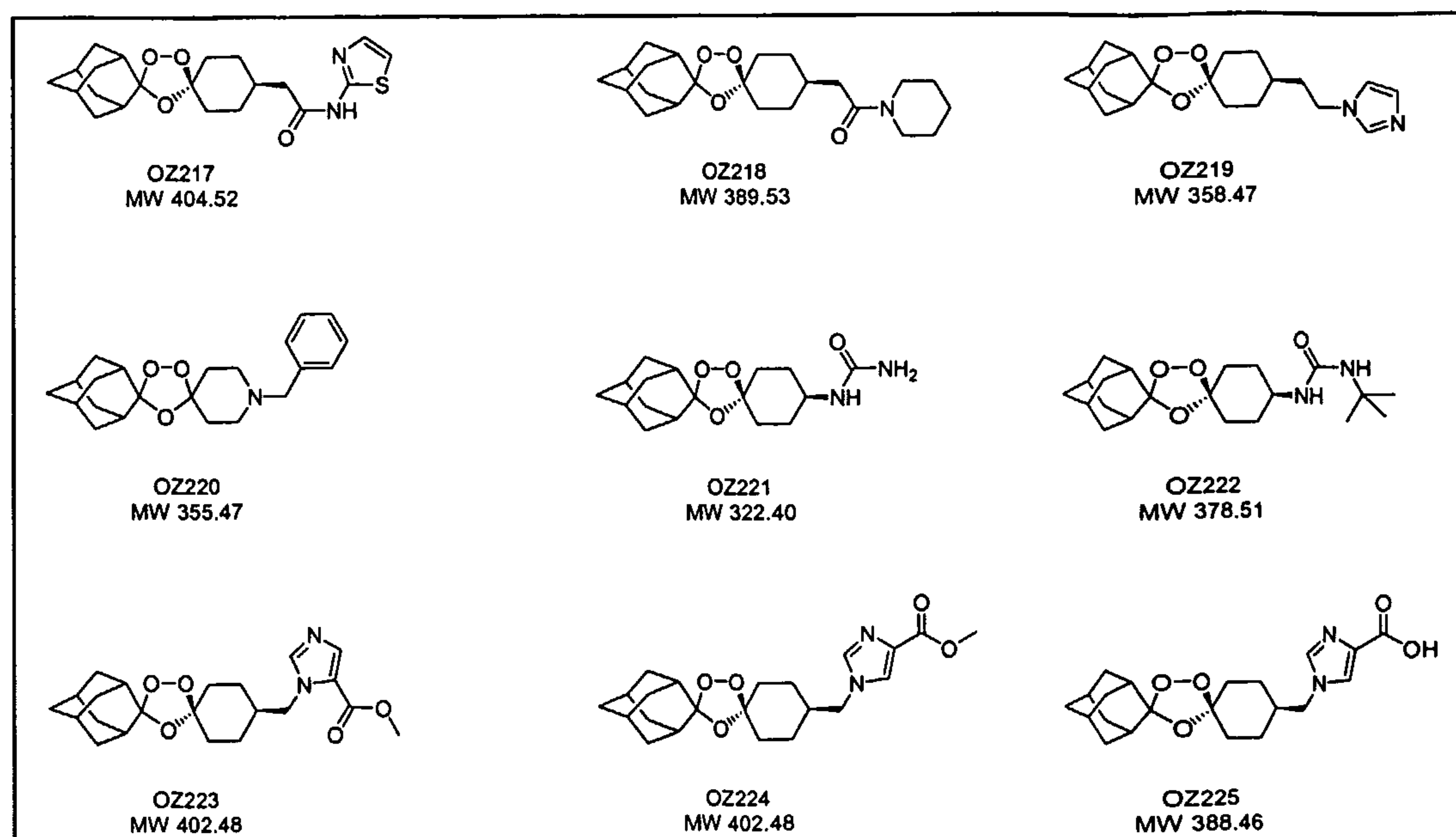
50

OZ Series 22 (OZ190–OZ198)

25

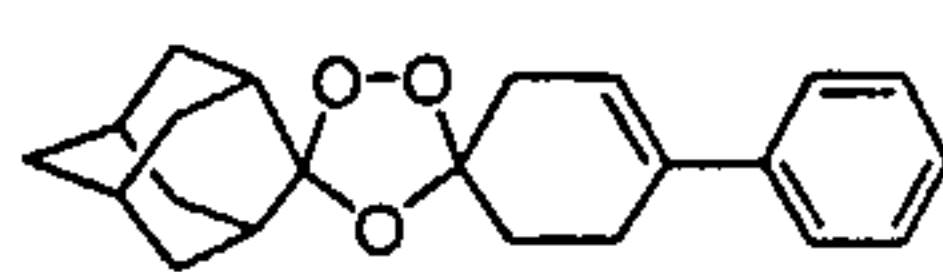
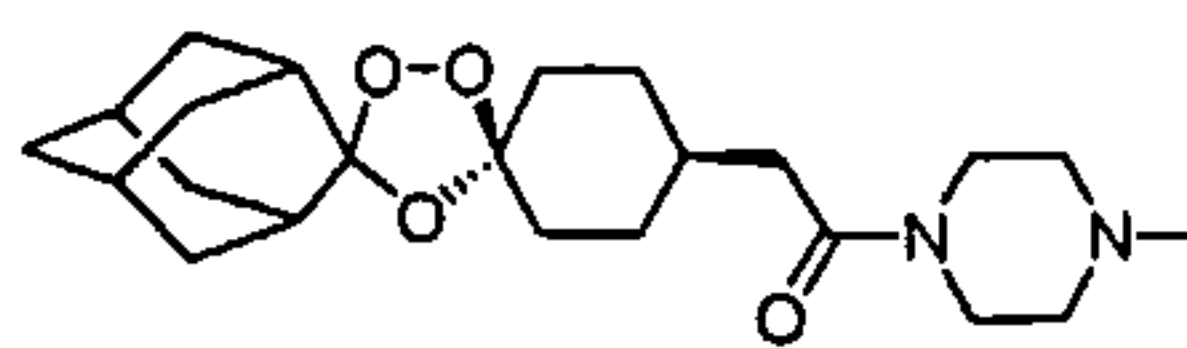
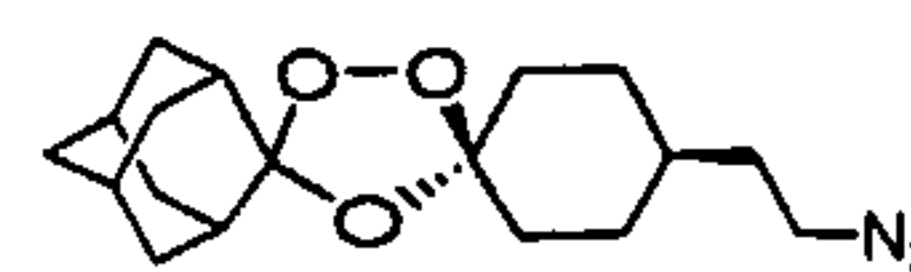
OZ Series 23 (OZ199–OZ207)

50

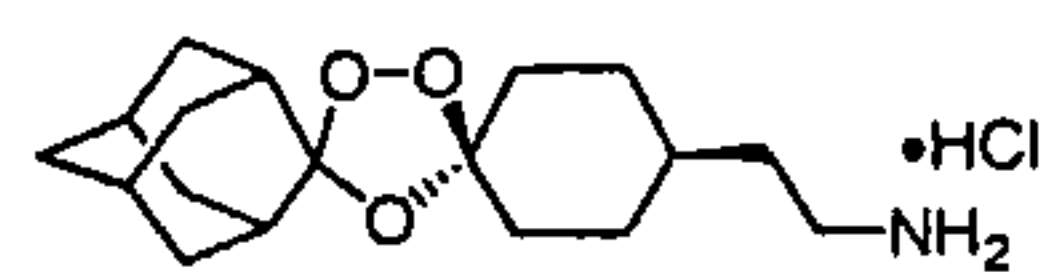
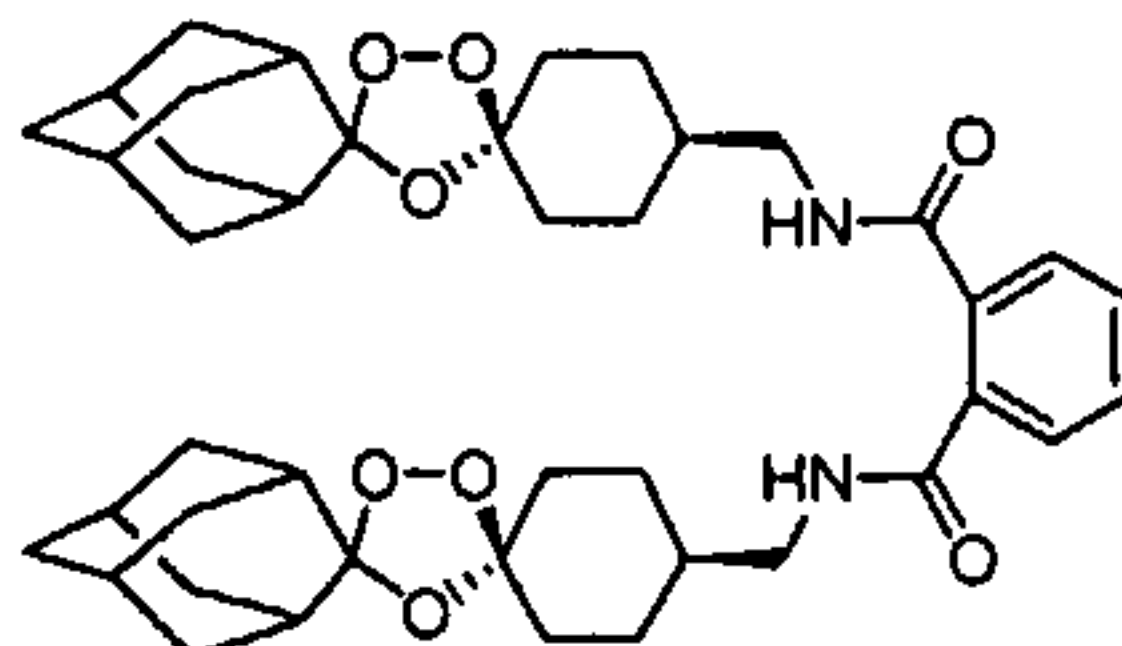
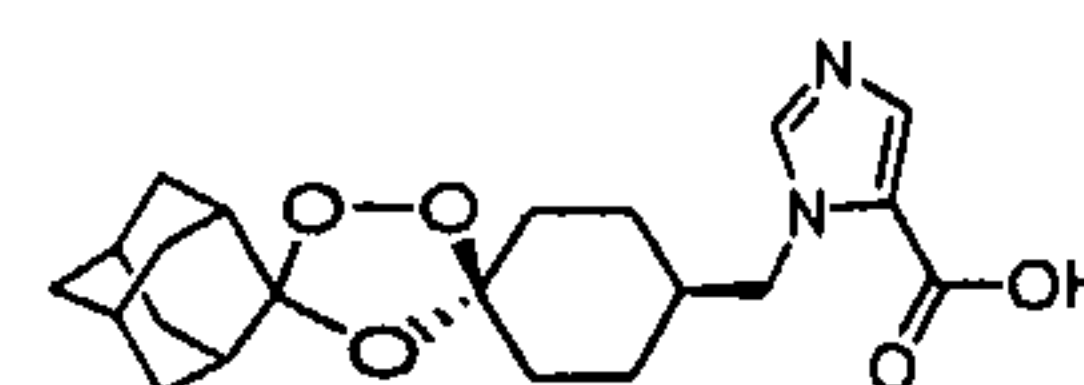
OZ Series 24 (OZ208–OZ216)**OZ Series 25 (OZ217–OZ225)**

OZ Series 26 (OZ226–OZ234)

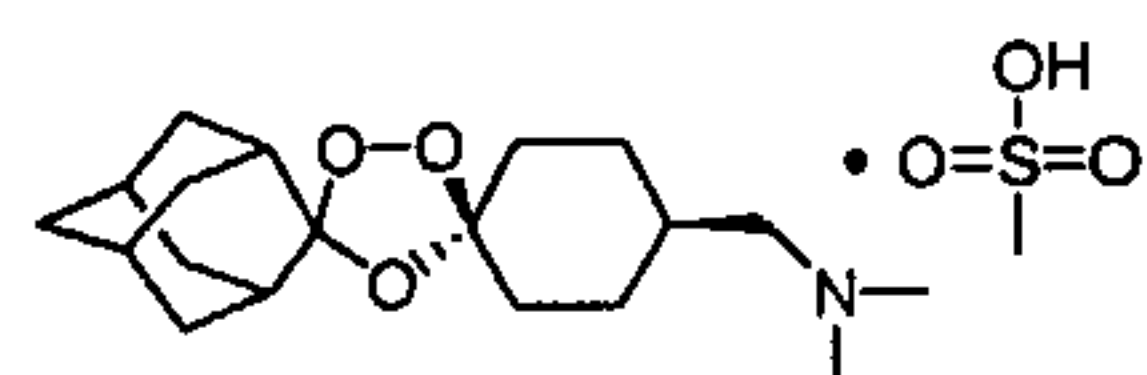
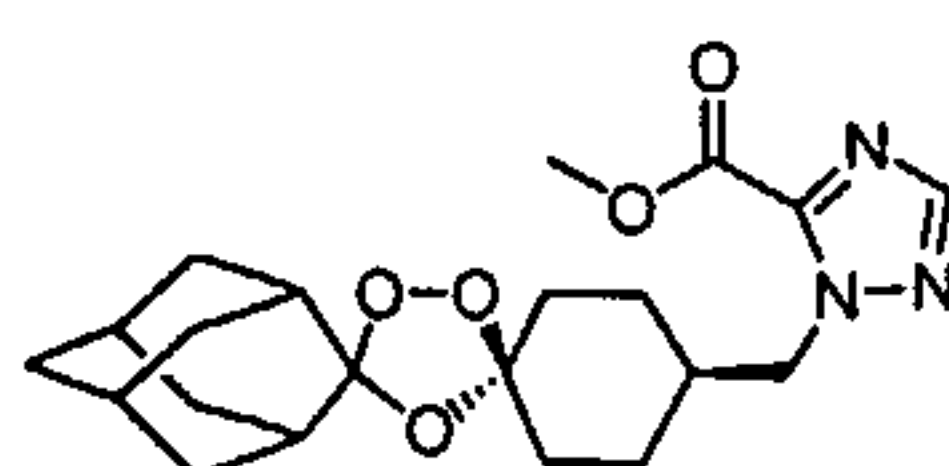
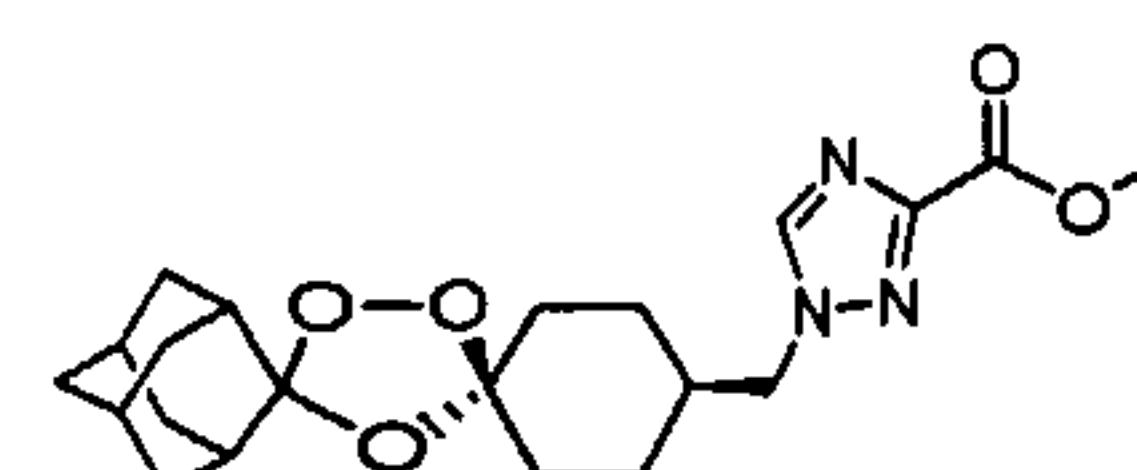
5

OZ226
MW 338.44OZ227
MW 404.54OZ228
MW 333.43

10

OZ229
MW 343.89OZ230
MW 716.90OZ231
MW 388.46

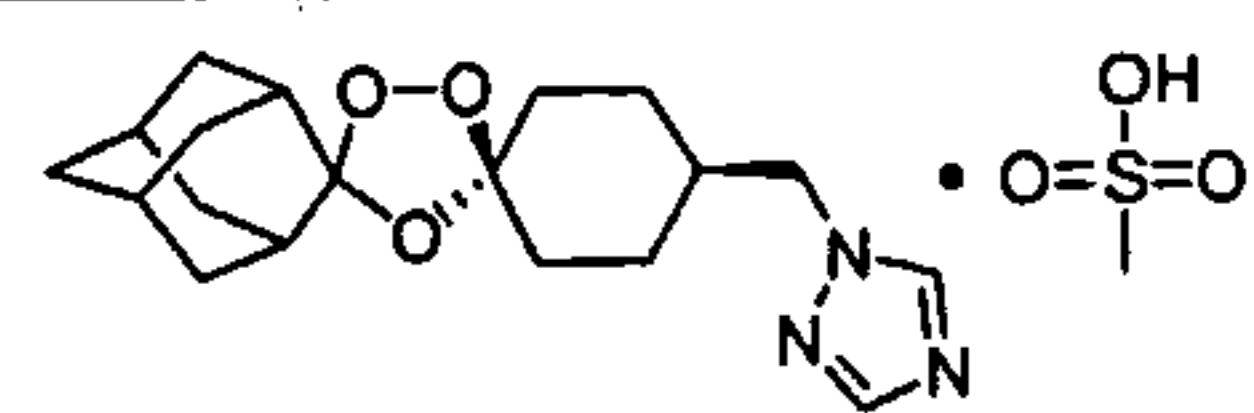
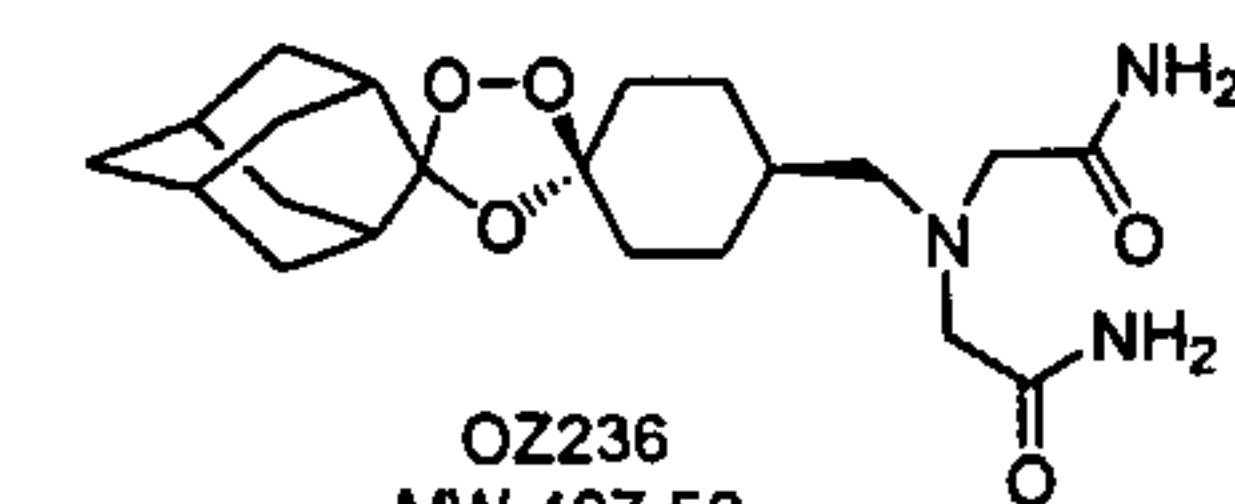
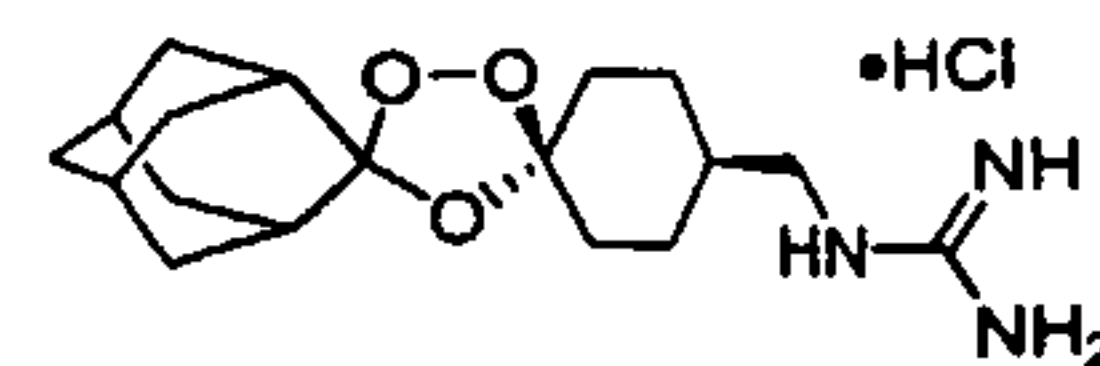
15

OZ232
MW 417.56OZ233
MW 403.47OZ234
MW 403.47

20

OZ Series 27 (OZ235–OZ243)

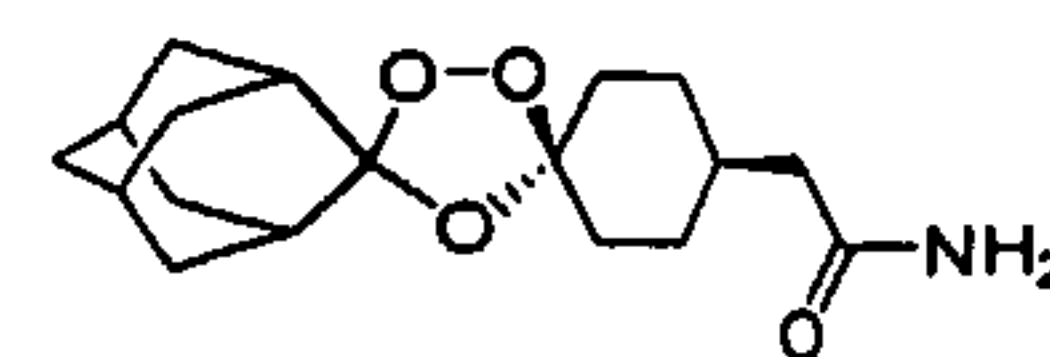
25

OZ235 (OZ177b)
MW 441.54OZ236
MW 407.50OZ237
MW 371.90

30

35

40

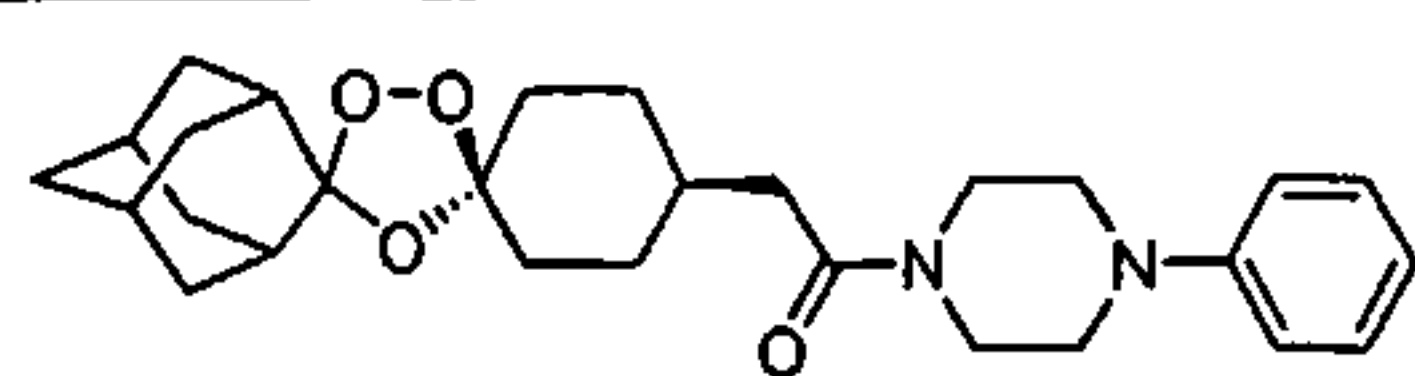
OZ243
MW 321.41

45

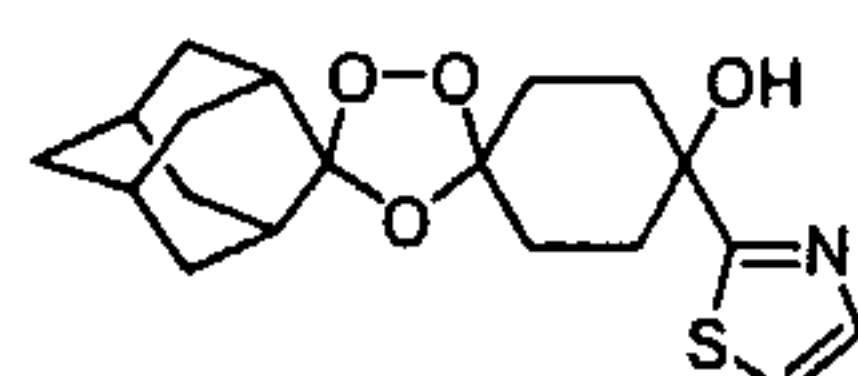
50

OZ Series 28 (OZ244–OZ252)

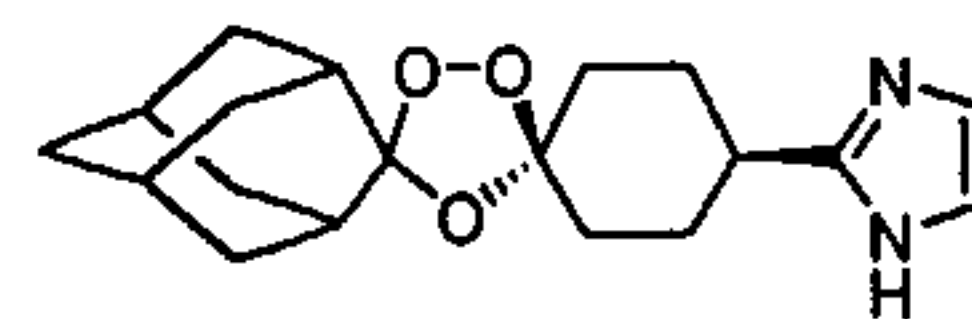
5

OZ244
MW 466.61

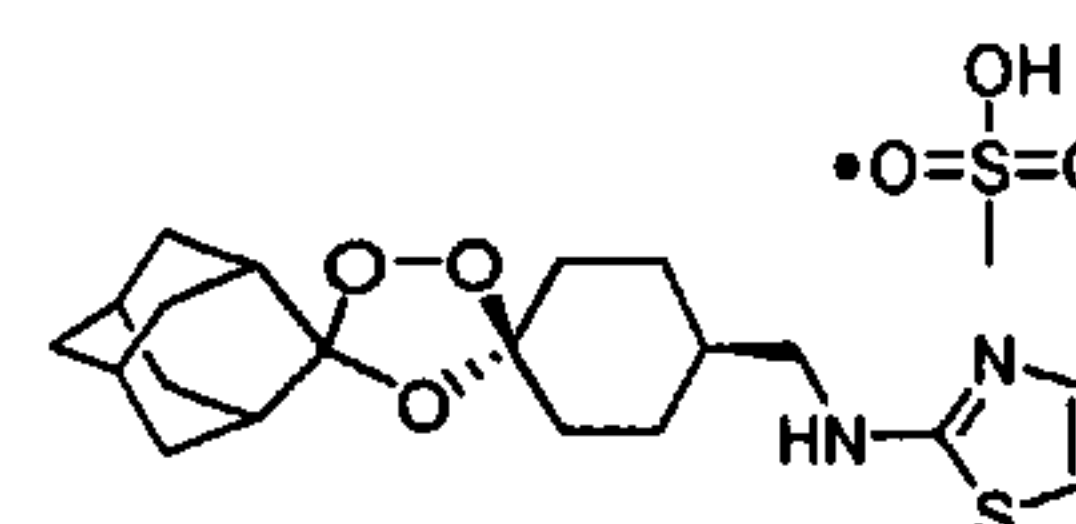
10

OZ247
MW 363.47

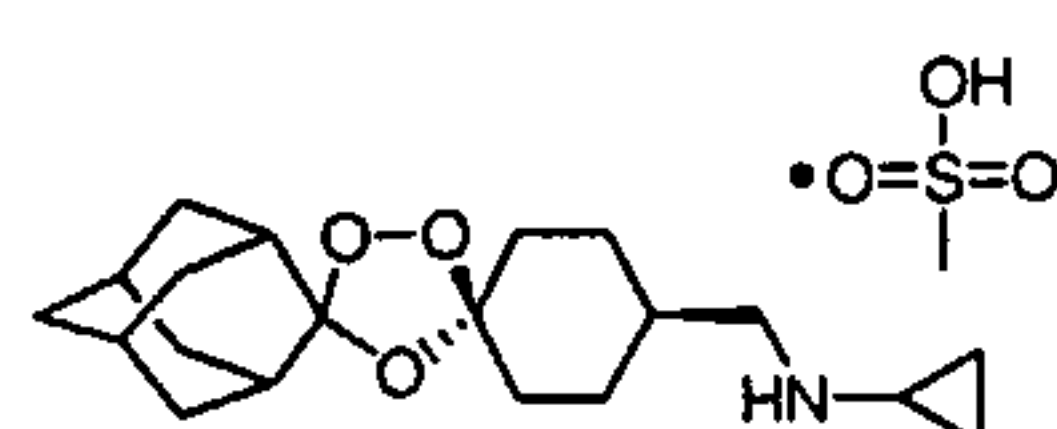
15

OZ251
MW 330.42

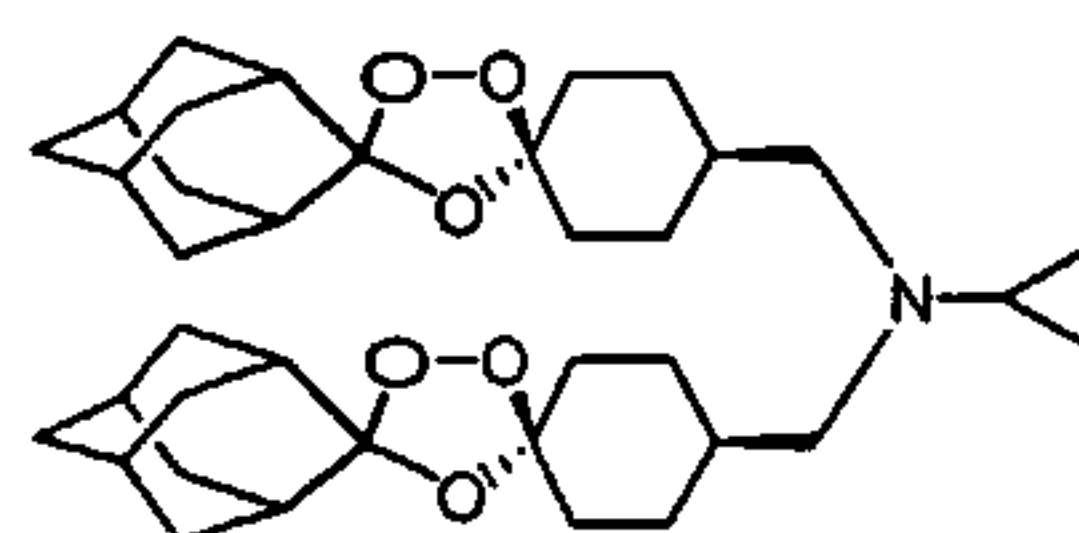
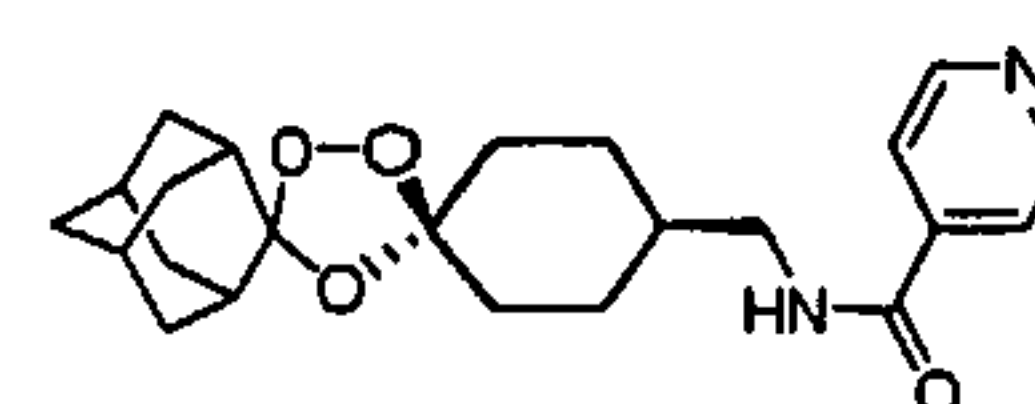
20

OZ252
MW 472.62**OZ Series 29 (OZ253–OZ261)**

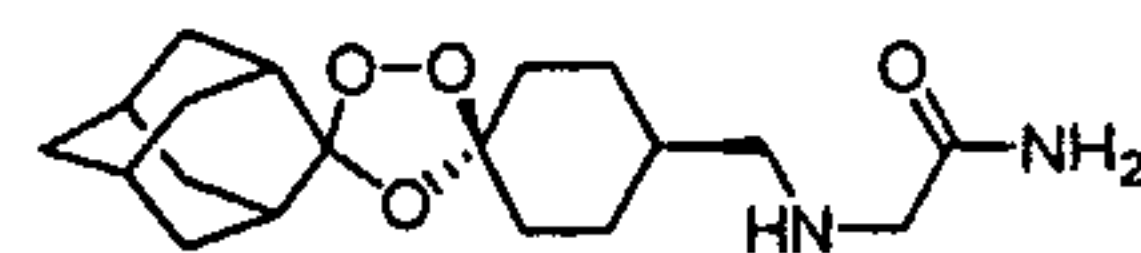
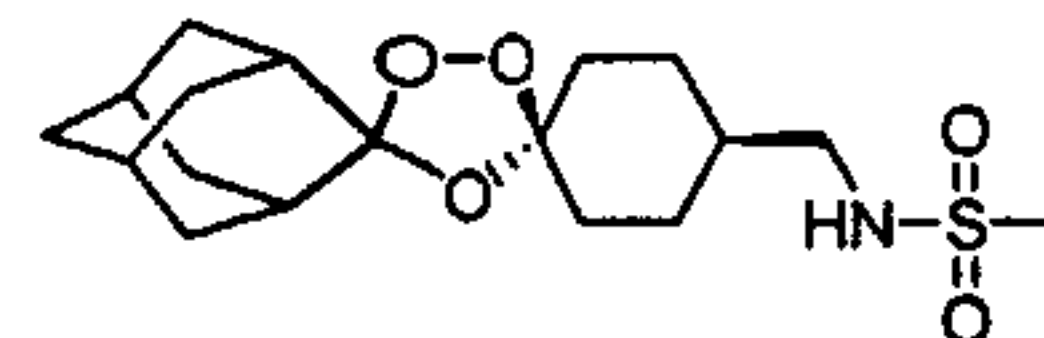
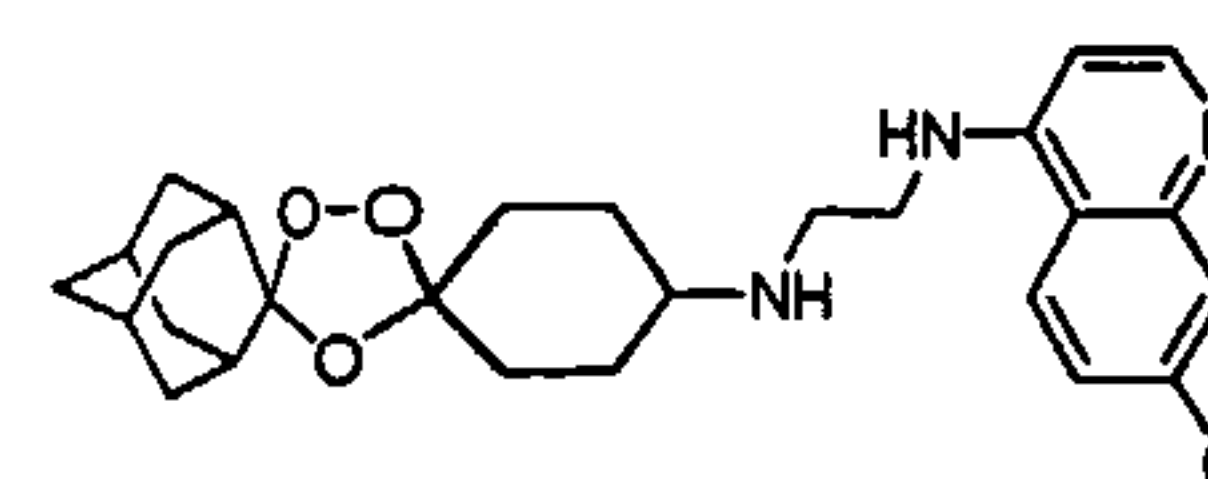
25

OZ253
MW 429.57

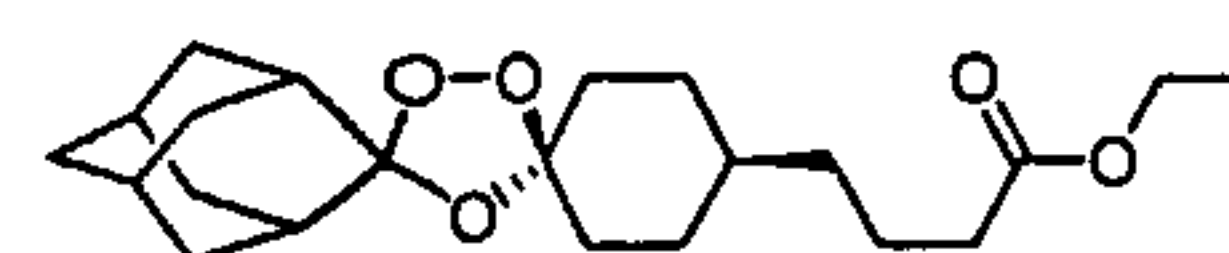
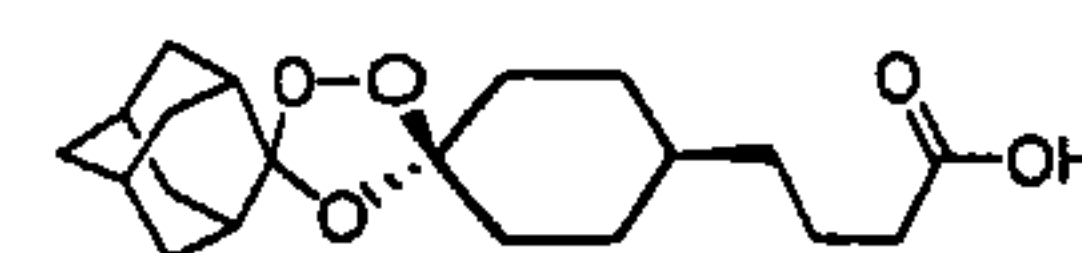
30

OZ254
MW 609.84OZ255
MW 398.50

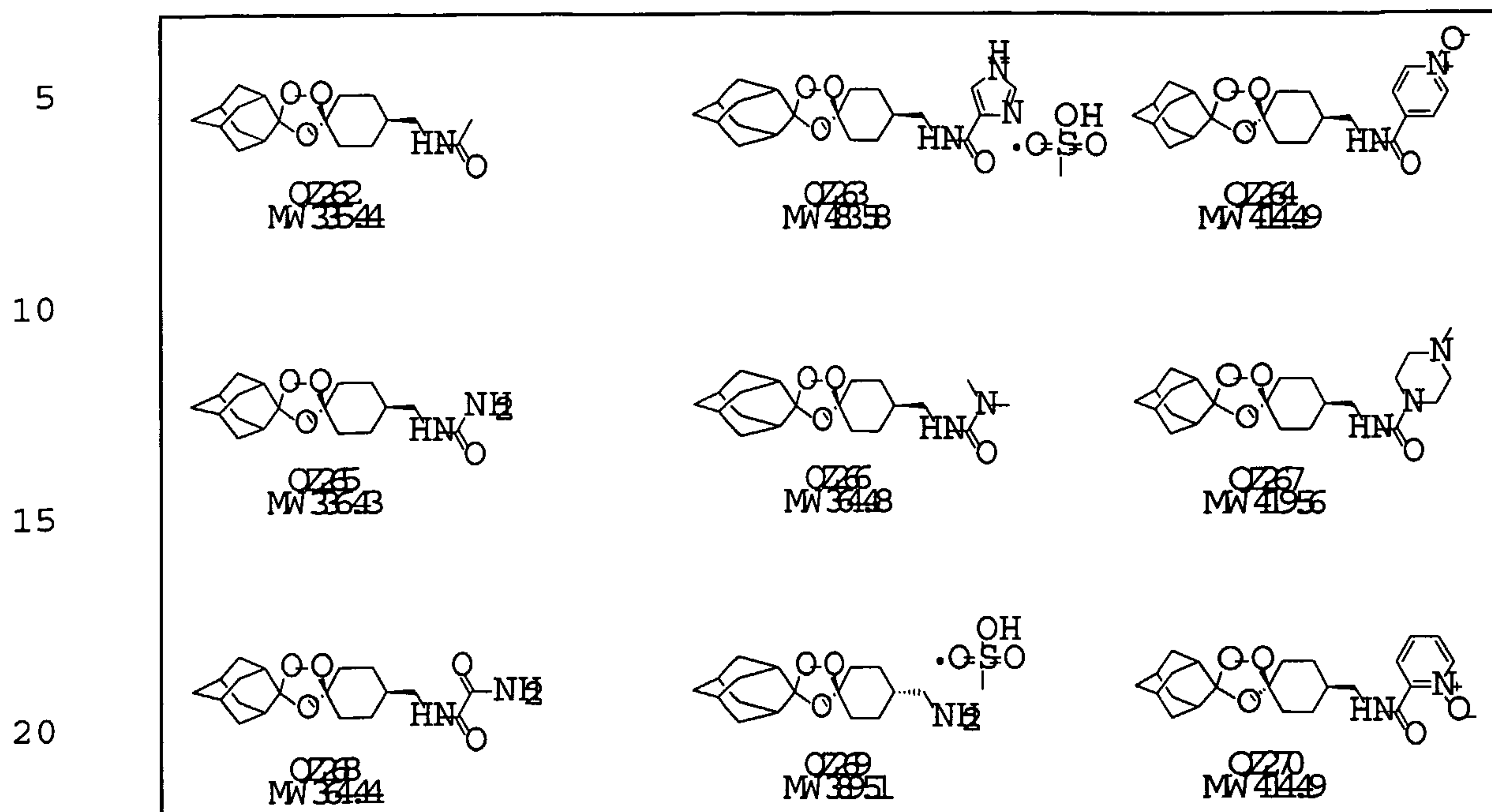
35

OZ256
MW 350.45OZ257
MW 371.49OZ258
MW 484.03

40

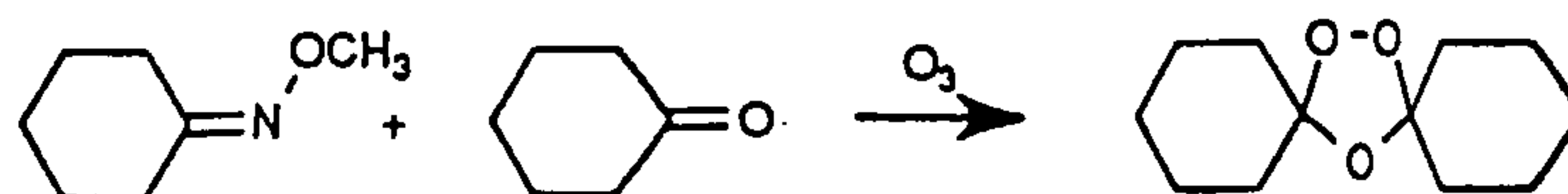
OZ260
MW 378.50OZ261
MW 350.45

45

OZ Series 30 (OZ262–OZ270)

The prototype trioxolanes of this invention are OZ03 and OZ05. Preferred compounds identified thus far include OZ03, OZ05, OZ11, OZ25, OZ27, OZ61, OZ71, OZ78, OZ127, OZ145, OZ156, OZ163, OZ175, OZ177, OZ179, OZ181, OZ189, OZ205, OZ207, OZ209, OZ210, OZ219, OZ227, OZ229, OZ235, OZ255, OZ256, OZ257, OZ263, OZ264, OZ265, OZ266, OZ267, OZ268, OZ269, and OZ270. The most preferred compounds are OZ78, OZ163, OZ181, OZ207, OZ209, OZ255, OZ256, OZ257, OZ263, OZ264, and OZ267. In general, the highest *in vitro* potency against malarial parasites is obtained for trioxolanes functionalized or substituted at the 4-position of the spirocyclohexyl ring. As a general rule, non-symmetrical, achiral trioxolanes are also preferred.

Notable features of these spiro and dispiro 1,2,4-trioxolanes in comparison to the artemisinin semisynthetic derivatives are their structural simplicity and ease of synthesis. For example, dispiro trioxolanes may be easily synthesized by the coozonolysis of the *O*-methyl oximes of cycloalkanones in the presence of the requisite cycloalkanone derivatives according to the method of Griesbaum et al. (1997a; 1997b) as illustrated below for the symmetrical dispiro cyclohexyl trioxolane:

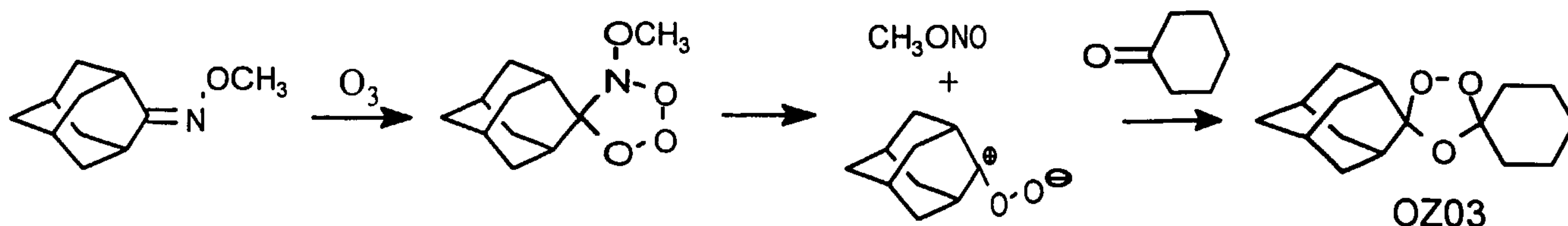


5

If yields are low in this cozonolysis reaction, yields can improve dramatically when the *O*-methyloxime and ketone are "reversed." This novel procedure provides a uniquely convenient method to synthesize spiro and dispiro trioxolanes. The trioxolanes may be purified by crystallization or by flash column chromatography. Their structures and purity may be confirmed by analytical HPLC, ^1H and ^{13}C NMR, IR, melting point and elemental analysis.

Recently, Griesbaum et al. (1997b) discovered that tetrasubstituted 1,2,4-trioxolanes are conveniently obtained by ozonolysis of *O*-alkyl ketone oximes in the presence of carbonyl compounds. Advantages of the oxime ether route over the alkene approach include convenient synthesis of starting materials (oxime ethers vs. tetrasubstituted alkenes), higher yield and selectivity of formation of desired trioxolanes by the judicious selection of paired reaction substrates.

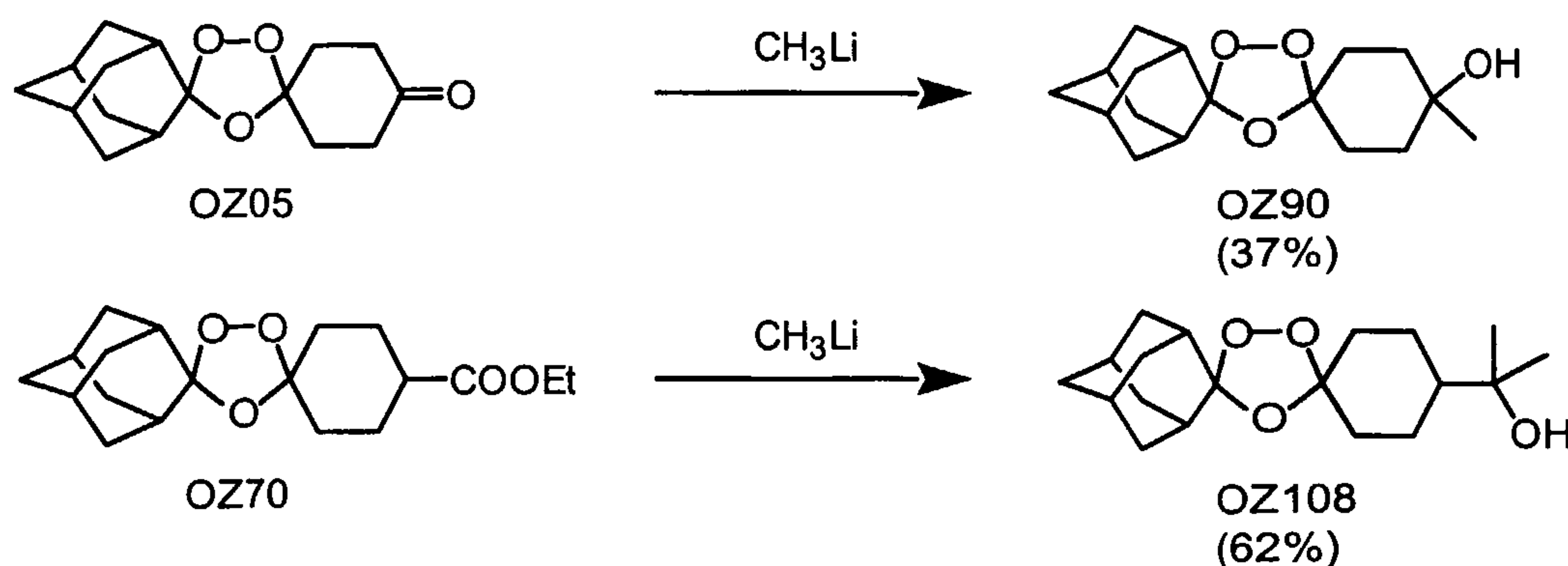
Formation of a trioxolane from an oxime ether and a ketone is presumed to be a three-step process. The sequence begins by the electrophilic addition of ozone to the oxime double bond to form a primary ozonide. Second, the very unstable primary adduct fragments to a reactive carbonyl oxide driven in part by the concomitant expulsion of the relatively stable methyl nitrite. Third, the carbonyl oxide undergoes a [3 + 2] cycloaddition with a ketone to give the secondary ozonide or 1,2,4-trioxolane. It remains to be



determined whether this is a stepwise or a concerted recombination process.

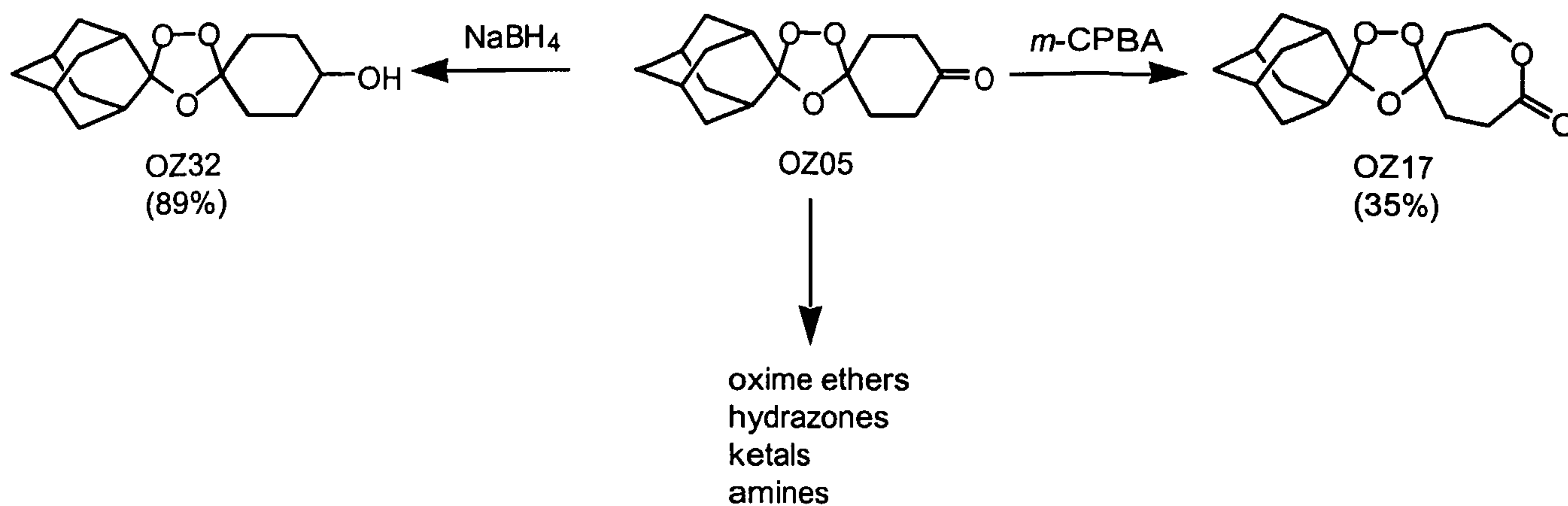
As illustrated above by the synthesis of OZ03, all of the target dispiro trioxolanes contain a spiroadamantane and can be synthesized by the coozonolysis of adamantanone *O*-methyl oxime in the presence of the requisite cycloalkanone derivative. The preferred reaction solvents for the coozonolysis reactions are hydrocarbon solvents such as pentane or cyclohexane; more polar solvents tend to decrease the yield of the reaction. When ketones are not readily soluble in pentane or cyclohexane, a mixed solvent (pentane/methylene chloride) or methylene chloride alone may be used. Several factors govern the ratio of oxime ether to ketone. In some reactions, in order to avoid diperoxide (1,2,4,5-tetraoxane) formation, to preclude diozonide formation from diketones, and to promote the reaction with readily pentane soluble ketones, excess ketone (2:1) is used. Most commonly in the discovery synthesis stage, and especially in cases where ketones are not readily soluble in pentane, expensive, or difficult to remove in the reaction workup, a 1:1 ratio of ketone to oxime ether may be used. In large scale trioxolane syntheses, a 1.5-fold excess of oxime ether can be used to achieve higher conversions of ketones into the desired product trioxolanes without causing purification problems.

There are several examples of where post-ozonolysis transformations were used to obtain trioxolane target compounds difficult, or in some cases, impossible to obtain directly (Kashima et al., 1987) by the coozonolysis method. Trioxolane tertiary alcohols OZ90 and

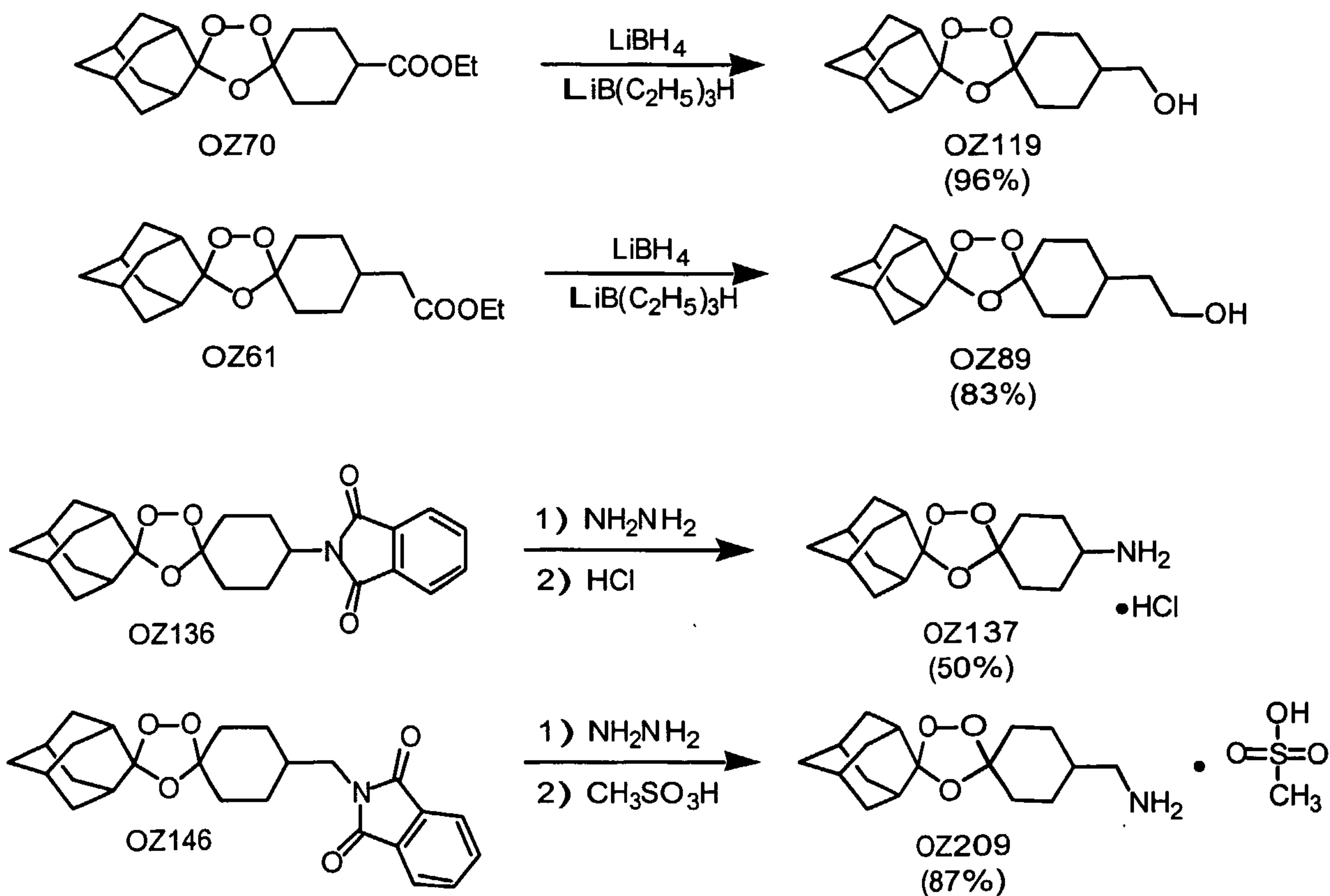


OZ108 can be obtained by methyllithium treatment of trioxolane ketone OZ05 and trioxolane ester OZ70, respectively. In other reactions, trioxolane lactone OZ17 and trioxolane alcohol OZ32 were obtained by treatment of OZ05 with *m*-CPBA and sodium borohydride, respectively. In addition, various oxime ethers, hydrazones, ketals, and amines (reductive amination with sodium triacetoxyborohydride) were also obtained from trioxolane ketone OZ05 in good to excellent yields. In the examples noted above, it is

evident that troxolane ketone OZ05 is a key intermediate as its ketone functional group provides a convenient means for functional group transformation.

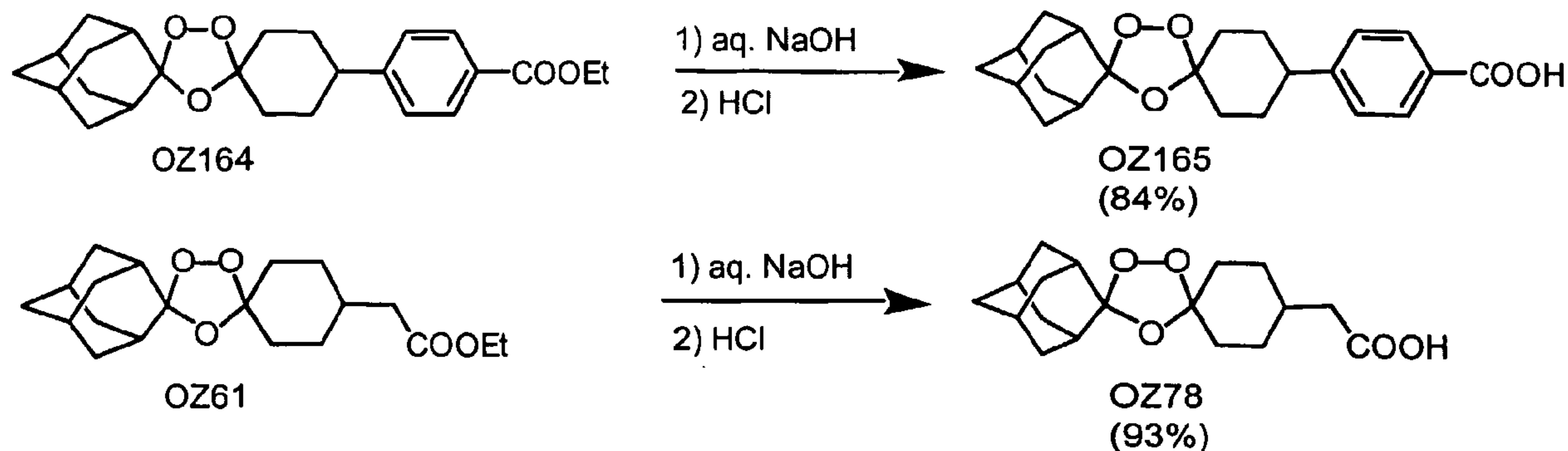


Further evidence of the stability of these trioxolanes to reducing agents is shown by the reduction of trioxolane esters OZ70 and OZ61 into their corresponding trioxolane alcohols OZ119 and OZ89 with a mixture of lithium borohydride and lithium triethylborohydride, and the hydrazinolysis of the trioxolane phthalimides OZ136 and

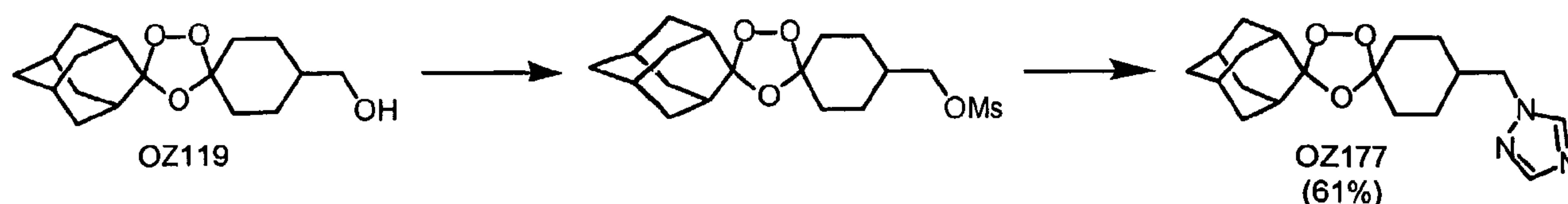


OZ146 into their corresponding trioxolane amines OZ137 and OZ209.

As shown in the examples below, trioxolane esters can be conveniently converted into their corresponding trioxolane acids.



In addition to trioxolane ketone OZ05, trioxolane amine OZ209, trioxolane ester OZ61 and trioxolane acid OZ78, trioxolane alcohols OZ119 and OZ89 and their corresponding mesylates (no assigned OZ #s) have and will continue to be key intermediates for post-ozonolysis synthetic transformations. A recent example is the



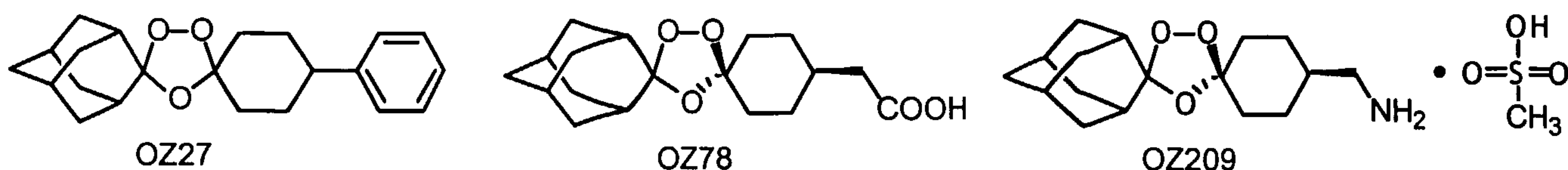
synthesis of trioxolane triazole OZ177 in a reaction between the mesylate derivative of OZ119 and the sodium salt of 1,2,4-triazole.

It has been found that the coozonolysis method using oxime methyl ethers offers a rapid, flexible, and predictable access to structurally diverse trioxolanes. In fact, several key trioxolanes that have served as important building blocks have been prepared in large scale including OZ05 (100 mmol), OZ61 (100 mmol), and OZ146 (60 mmol), with no decrease in reaction yields over the usual 5-10 mmol scale. Furthermore, both OZ61 and OZ146 can be conveniently isolated as white solids by addition of ethanol to the crude reaction mixtures.

Differential scanning calorimetry (DSC) experiments (Cammenga, and Epple, 1995) reveal that these compounds have good thermal stability, comparable to artemisinin. The average T_m , dec was $160 \pm 15^\circ\text{C}$ compared to a T_m , dec of 181°C for artemisinin. It

is presumed that thermal decomposition of these trioxolanes was initiated by formation of a 1,5 diradical produced by homolytic cleavage of the peroxide bond of the trioxolane ring.

Since most of the target trioxolanes contain the symmetrical spiroadamantane structural framework, their stereochemistry is largely a function of the starting material ketone structure or reagents used in post-ozonolysis reactions. For OZ27 and other similarly 1,4-substituted trioxolanes, two achiral diastereomers are possible. However, as exemplified by OZ27, the majority of these trioxolanes were isolated as single achiral diastereomers rather than as mixtures of two achiral diastereomers. For example, in OZ27, no chirality is present since the trioxolane ring and phenyl substituent are in a 1,4 relationship in a six membered ring. Such compounds possess a plane of symmetry.



As determined by X-ray crystallography, the assignment of stereochemistry for OZ78, OZ209 and their derivatives was determined to be *cis* where the peroxide oxygens are in an axial position.

The following cycloalkanone and cycloalkanedione starting materials can be obtained from Aldrich Chemical Co. or from TCI American Organic Chemicals: cyclohexanone, cyclododecanone, 1,4-cyclohexanedione, 2-adamantanone, bicyclo[3.3.1]nonan-9-one, tetrahydro-4*H*-pyran-4-one, 1-carboethoxy-4-piperidone, 1-benzoyl-4-piperidone, α -tetralone, β -tetralone, bicyclo[3.3.1]nonan-3,7-dione, 1,4-cyclohexanedione-*mono*-2,2-dimethyltrimethylene ketal, *cis*-bicyclo[3.3.0]octane-3,7-dione, and 4-carboethoxycyclohexanone.

The cycloalkanone starting materials may also be synthesized. For instance, the inventors have synthesized 4,4-dimethylcyclohexanone and 4,4-diphenylcyclohexanone by catalytic hydrogenation (Augustine, 1958) of the commercially available enones. Also, 2-carboethoxyethylcyclohexanone was synthesized by treatment of the pyrrolidine enamine of cyclohexanone with ethyl acrylate (Stork et al., 1963). Persons skilled in the art can readily ascertain other appropriate means of synthesizing the starting materials and compounds in accordance with this invention.

The spiro and dispiro trioxolane compositions of the present invention may be generally used for the prophylaxis and treatment of malaria. The trioxolane compositions of the present invention are administered along with a pharmaceutically acceptable carrier. Any pharmaceutically acceptable carrier may be generally used for this purpose, provided
5 that the carrier does not significantly interfere with the stability or bioavailability of the trioxolane compounds of this invention.

The trioxolanes of this invention can be administered in any effectively pharmaceutically acceptable form to warm blooded animals, including human and other animal subjects, e.g. in topical, lavage, oral, suppository, parenteral, or infusible dosage
10 forms, as a topical, buccal, sublingual, or nasal spray or in any other manner effective to deliver the agents. The route of administration will preferably be designed to optimize delivery and/or localization of the agents to target cells.

In addition to the active compounds i.e. the trioxolanes, the pharmaceutical compositions of this invention may contain suitable excipients and auxiliaries which
15 facilitate processing of the active compounds into preparations which can be used pharmaceutically. Oral dosage forms encompass tablets, capsules, and granules. Preparations which can be administered rectally include suppositories. Other dosage forms include suitable solutions for administration parenterally or orally, and compositions which can be administered buccally or sublingually.

20 The pharmaceutical preparations of the present invention are manufactured in a manner which is itself well known in the art. For example the pharmaceutical preparations may be made by means of conventional mixing, granulating, dragee-making, dissolving, lyophilizing processes. The processes to be used will depend ultimately on the physical properties of the active ingredient used.

25 Suitable excipients are, in particular, fillers such as sugars for example, lactose or sucrose mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch, paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium
30 carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added, such as the above-mentioned starches as well as carboxymethyl starch,

cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are flow-regulating agents and lubricants, for example, such as silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate and/or polyethylene glycol. Oral dosage forms may be provided with suitable coatings which, if
5 desired, may be resistant to gastric juices.

For this purpose concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such
10 as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, dyestuffs and pigments may be added to the tablet coatings, for example, for identification or in order to characterize different combination of compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer
15 such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition stabilizers may
20 be added. Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of the active compounds with the suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols, or higher alkanols. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active
25 compounds with a base. Possible base material include for example liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of active compounds in water-soluble or water-dispersible form. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered.
30 Suitable lipophilic solvents or vehicles include fatty oils for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection

suspensions may contain substances which increase the viscosity of the suspension, including for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Such compositions may also comprise adjuvants such as preserving, wetting, emulsifying, and dispensing agents. They may also be sterilized, for example, by filtration through a
5 bacteria-retaining filter, or by incorporating sterilizing agents into the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved or suspended in sterile water, saline, or other injectable medium prior to administration.

In addition to administration with conventional carriers, active ingredients may be administered by a variety of specialized delivery drug techniques which are known to those
10 of skill in the art, such as portable infusion pumps.

The trioxolane compositions of the present invention are administered along with a pharmaceutically acceptable carrier in an amount sufficient to prevent malarial infection and/or treat an active infection. The trioxolane compounds of this invention have extremely low toxicity and a low degree of side effects even at high doses. The dosing
15 range of the trioxolane compositions will vary depending on a number of factors, such as whether it is used for prophylaxis or treatment of an active infection, route of administration, dosing schedule, etc. In general, the therapeutic dose of trioxolane may range between about 0.1-1000 mg/kg/day, with between about 1-100 mg/kg/day being preferred. The foregoing doses may be administered as a single dose or may be divided
20 into multiple doses for administration. The trioxolane compositions may be administered once to several times daily. For malaria prevention, a typical dosing schedule could be, for example, 2.0-1000 mg/kg weekly beginning 1-2 weeks prior to malaria exposure taken up until 1-2 weeks post-exposure.

The spiro and dispiro trioxolanes of this invention have been found to be effective
25 in the treatment of schistosomiasis. Schistosomiasis ranks second behind malaria in terms of socioeconomic and public health importance in tropical and subtropical areas. The disease is endemic in 74 developing countries, infecting more than 200 million people in rural agricultural and peri-urban areas. An estimated 500-600 million people worldwide are at risk from the disease.

30 The major forms of human schistosomiasis are caused by five species of water-borne flatworm, or blood flukes, called schistosomes. One of these species is *Schistosoma*

mansoni, which has been reported in 53 countries in Africa, the Eastern Mediterranean, the Caribbean, and South America. The parasites enter the body through contact with infested surface water, primarily among people engaged in agriculture and fishing. The parasites normally infect the host during the cercaria, or larval stage. Once inside the host, the cercaria develop into adults or schistosomes.

Current treatments for schistosomiasis have focused primarily on prophylaxis, i.e. prevention of host infection by cercaria. Currently, praziquantel is the most widely used drug for treatment of schistosomiasis. While artemether has demonstrated activity in the prophylaxis of schistosomiasis, it has not shown any activity against adult *S. mansoni*.

It has now been unexpectedly discovered that the spiro and dispiro trioxolanes of this invention are active against both cercaria and adult *S. mansoni*, *S. japonicum* when administered in the dosages and manner outlined above with respect to treatment of malarial parasites. It is also believed the trioxolanes of this invention will be active against *S. haematobium*. Preferred compounds identified for use in the treatment of schistosomiasis include OZ03, OZ05, OZ11, OZ16, OZ23, OZ25, OZ27, OZ32, OZ71, OZ78, OZ89, OZ90, OZ119, OZ145, OZ163, OZ205, OZ207, OZ209, OZ210, OZ219, OZ227, OZ229, OZ235, OZ255, OZ256, OZ257, OZ263, OZ264, OZ265, OZ266, OZ267, OZ268, OZ269, and OZ270. Most preferred compounds are OZ05, OZ23, OZ25, OZ71, OZ78, OZ89, OZ119, OZ163, OZ205, OZ207, and OZ209. Preferred dosing levels of the spiro and dispiro trioxolanes are about 100-200 mg/kg/day orally. The prototype trioxolanes of this invention are OZ03 and OZ05.

The spiro and dispiro trioxolanes of this invention may also have effectiveness in the treatment of cancer. Compounds having an endoperoxide moiety that is reactive with heme and iron have shown an ability to kill cancer cells. (See e.g. U.S. Pat. No. 5,578,637, the disclosure of which is hereby incorporated by reference). As noted with respect to artemisinin, trioxolanes' mechanism of action against malarial parasites is based on the ability of trioxolane compounds to react with the iron in free heme molecules in malaria parasites, with the generation of free radicals leading to cellular destruction. Similarly, trioxolanes are selective against cancer cells due to the higher concentration of transferrin receptors on cancer cell membranes that pick up iron at a higher rate than normal cells. In the presence of the trioxolanes of this invention, the cancer cells will accumulate high

concentrations of free radicals, leading to cell death. For cancer treatment, the trioxolanes of this invention may be administered in the doses and manner outlined above.

Other drugs besides trioxolanes which are compatible with the carrier ingredients may also be incorporated into the carrier. Such drugs may be readily ascertained by those of ordinary skill in the art and may include, for instance, antibiotics, other antimalarials, antiinflammatory agents, etc.

It is understood that the present invention contemplates the use of not only the above-stated trioxolane compounds themselves, but their prodrugs which metabolize to the compound and the analogues and biologically active salt forms thereof, as well as optical isomers which provide the same pharmaceutical results.

The following examples are offered to illustrate but not limit the invention. Thus, they are presented with the understanding that various formulation modifications as well as method of delivery modifications may be made and still be within the spirit of the invention.

15

EXAMPLE 1

General Procedure for the Preparation of 1,2,4-Trioxolanes

Synthesis of *O*-methyl 2-adamantanone oxime (representative procedure). To a solution of 2-adamantanone (4.51 g, 30 mmol) in methanol (30 ml) were added pyridine (4.5 ml) and methoxylamine hydrochloride (3.76 g, 45.0 mmol). The reaction mixture was stirred at room temperature for 48 h, concentrated in vacuo, and diluted with CH₂Cl₂ (50 ml) and water (50 ml). The organic layer was separated, and the aqueous layer extracted with CH₂Cl₂ (30 ml). The combined organic extracts were washed with 1 M HCl (30 ml x 2) and saturated aqueous NaCl (30 ml), and dried over MgSO₄. Evaporation in vacuo afforded *O*-methyl 2-adamantanone oxime (4.77 g, 89%) as a colorless solid. mp 70–71 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.60–2.10 (m, 12H), 2.54 (s, 1H), 3.47 (s, 1H), 3.82 (s, 3H).

Ref: Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. A New Synthetic Route to Prostaglandins. *Tetrahedron Lett.* **1986**, 27, 2199–2202.

***O*-Methyl cyclohexanone oxime.** Yield, 76%; colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 1.40–1.80 (m, 6H), 2.20 (t, J = 6.0 Hz, 2H), 2.45 (t, J = 6.1 Hz, 2H), 3.81 (s, 3H).

O-Methyl cyclododecanone oxime. Yield, 98%; colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 1.20–1.49 (m, 14H), 1.50–1.60 (m, 2H), 1.61–1.70 (m, 2H), 2.22 (t, $J = 6.8$ Hz, 2H), 2.35 (t, $J = 6.6$ Hz, 2H), 3.81 (s, 3H).

O-Methyl 3,3,5,5-tetramethylcyclohexanone oxime. Yield, 91%; colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 0.96 (s, 6H), 0.97 (s, 6H), 1.33 (s, 2H), 1.95 (s, 2H), 2.20 (s, 2H), 3.80 (s, 3H).

O-Methyl 4-phenylcyclohexanone oxime. Yield, 92%; colorless solid; mp 45–47°C; ^1H NMR (500 MHz, CDCl_3) δ 1.57–1.76 (m, 2H), 1.82–1.92 (m, 1H), 1.99–2.13 (m, 2H), 2.19–2.30 (m, 1H), 2.47–2.56 (m, 1H), 2.72–2.81 (m, 1H), 3.32–3.42 (m, 1H), 3.85 (s, 3H), 7.17–7.34 (m, 5H).

O-Methyl bicyclo[3.3.1]nonan-9-one oxime. Yield, 96%; colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 1.46–1.62 (m, 2H), 1.72–2.11 (m, 10H), 2.47 (br s, 1H), 3.40 (br s, 1H), 3.82 (s, 3H).

1-(*p*-Toluenesulfonyl)-4-piperidone. To a solution of 4-piperidone monohydrate hydrochloride (7.68 g, 50 mmol) in methylene chloride (50 ml) were added sequentially *p*-toluenesulfonyl chloride (10.50 g, 55.07 mmol) and triethylamine (21 ml). The mixture was stirred at room temperature for 16 h before being quenched with water (100 ml). The organic layer was washed with 1 M HCl (100 ml) and brine (100 ml), and dried over sodium sulfate. Evaporation of the solvent gave the desired ketone (8.60 g, 68%) as a colorless solid. mp 130–132 °C; ^1H NMR (500 MHz, CDCl_3) δ 2.40 (s, 3H), 2.58 (t, $J = 6.4$ Hz, 4H), 3.38 (t, $J = 6.4$ Hz, 4H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.68 (d, $J = 8.3$ Hz, 2H).

1-[3-(Ethoxycarbonyl)propionyl]-4-piperidone. To a solution of 4-piperidone monohydrate hydrochloride (7.68 g, 50 mmol) and triethylamine (21 ml) in methylene chloride (100 ml) was added 3-(ethoxycarbonyl)propionyl chloride (9.87 g, 60 mmol) at 0 °C over a period of 10 min. The mixture was stirred at room temperature for 16 h before being quenched with water (100 ml). The organic layer was separated and the aqueous layer was extracted with methylene chloride (100 ml). The combined organic layers were washed with 1M HCl (100 ml), saturated aqueous sodium bicarbonate (100 ml), and brine (100 ml), dried over sodium sulfate, and concentrated. Purification by flash chromatography (silica gel, 30% ether in hexanes) gave the desired ketone (3.80 g, 33%) as a light yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 1.27 (t, $J = 7.3$ Hz, 3H), 2.48 (t, $J =$

6.4Hz, 2H), 2.53 (t, J = 6.4 Hz, 2H), 2.68 (s, 4H), 3.82 (t, J = 6.3 Hz, 2H), 3.82 (t, J = 6.3 Hz, 2H), 4.16 (q, J = 7.3 Hz, 2H).

1,1-Dioxotetrahydrothiopyran-4-one. To a solution of tetrahydrothiopyran-4-one (400 mg, 3.45 mmol) in acetonitrile (5 ml) was added aqueous Na₂EDTA (3 ml, 0.0004 M). A mixture of oxone (6.30 g, 10.30 mmol) and sodium bicarbonate (2.70, 32 mmol) was added in small portions to the above solution over a period of 20 min. The slurry was stirred for another 1 h before being quenched with methylene chloride. The organic solvent was decanted and the solid residue was triturated with ethyl acetate (3 x 25 ml). The combined organic layers were dried over sodium sulfate and concentrated to give the desired ketone (0.37 g, 73%) as a colorless solid. mp 170–172 °C (lit. 168–170 °C); ¹H NMR (500 MHz, CDCl₃) 2.99 (t, J = 6.8 Hz, 4H), 3.39 (t, J = 6.8 Hz, 4H). Ref: Yang, D.; Yip, Y.-C.; Jiao, G.-S.; Wong, M.-K. Design of Efficient Ketone Catalysts for Epoxidation by Using the Field Effect. *J. Org. Chem.*, 1998, 63, 8952-8956.

Synthesis of 1-benzenesulfonyl-4-piperidone (representative procedure). To a solution of 4-piperidone monohydrate hydrochloride (4.59 g, 30 mmol), triethylamine (12.5 ml, 90 mmol) in CH₂Cl₂ (50 ml) was added benzenesulfonyl chloride (5.30 g, 30 mmol). The mixture was stirred at 25 °C for 16 h. After evaporation of solvents, the residue was triturated with water (100 ml), filtered, and further purified by recrystallization from hexanes/CH₂Cl₂ (3:1) to afford the desired ketone (5.97 g, 83%) as a colorless solid. mp 116–118 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.54 (t, J = 6.4Hz, 4H), 3.41 (t, J = 6.4Hz, 4H), 7.58 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.0 Hz, 1H), 7.81 (d, J = 7.8 Hz, 2H).

1-(4-Methoxybenzenesulfonyl)-4-piperidone. Yield, 77%; colorless solid; mp 130–132 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.56 (t, J = 6.4 Hz, 4H), 3.38 (t, J = 6.3 Hz, 4H), 3.95 (s, 3H), 7.00 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H).

1-(4-Chlorobenzenesulfonyl)-4-piperidone. Yield, 73%; colorless solid; mp 166–168 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.55 (t, J = 6.4 Hz, 4H), 3.41 (t, J = 6.4 Hz, 4H), 7.54 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H).

1-Methanesulfonyl-4-piperidone. To a suspension of 4-piperidone monohydrate hydrochloride (2.0 g, 13 mmol) and K₂CO₃ (9.0 g, 65.2 mmol) in acetone (40 ml) was added methanesulfonyl chloride (5.96 g, 52.1 mmol) at 0–5 °C. The mixture was stirred at 25 °C for 24 h. The solid material was removed by filtration, and the filtrate was

concentrated to dryness. The residue was purified by flash chromatography (silica gel, 80% ether in hexanes) to afford the desired ketone (1.20 g, 52%) as a colorless solid. mp 102–104 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.58 (t, J = 6.4 Hz, 4H), 2.90 (s, 3H), 3.60 (t, J = 6.4 Hz, 4H).

5 **Ethoxycarbonylmethylene triphenylphosphorane.** To a solution of triphenylphosphine (26.20 g, 100 mmol) in benzene (150 ml) was added ethyl bromoacetate (16.70 g, 100 mmol) at 0–5 °C. The mixture was kept at room temperature for 16 h. The resulting phosphonium salt was filtered, washed with benzene (100 ml), and dried. To a solution of the solid in water (200 ml) was added benzene (200 ml), followed
10 by 10% NaOH solution (100 ml). The organic layer was separated, and the aqueous layer was extracted with benzene (200 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), concentrated to 50 ml in vacuo, and poured onto hexane (200 ml). The precipitate was filtered and dried to afford the desired phosphorane (28.00 g, 80%) as a colorless solid. mp 128–130°C.

15 **4-Oxocyclohexylideneacetic acid ethyl ester.** To a solution of 1,4-cyclohexanedione (5.00 g, 44.64 mmol) in benzene (100 ml) was added the ylide (15.55 g, 44.68 mole). The mixture was heated under reflux for 12 h. After removal of the solvent by evaporation, the residue was purified by flash chromatography (silica gel, 5% ethyl acetate in hexanes) to afford the ketone ester (5.80 g, 71%) as a colorless oil. ¹H NMR (500 MHz,
20 CDCl₃) δ 1.26 (t, J = 6.4 Hz, 3H), 2.42–2.50 (m, 4H), 2.60–2.66 (m, 2H), 3.12–3.20 (m, 2H), 4.16 (q, J = 6.4 Hz, 2H), 5.86 (s, 1H).

4-Oxocyclohexaneacetic acid ethyl ester. To a solution of the unsaturated ester (2.50g, 13.74 mmol) in ethanol (25 ml) was added Raney nickel (1.0 g). The mixture was stirred at room temperature under H₂ (balloon) for 24 h. After the catalyst was removed by
25 filtration, the filtrate was concentrated to give the alcohol ester, which was used for the Jones' oxidation without further purification. To a solution of the above residue in acetone (20 ml) at 0 °C was added Jones' reagent (6 ml), prepared by dissolving CrO₃ (27.20 g) in concentrated sulfuric acid (25 ml) and further diluting the solution to 100 ml with water. The reaction was stirred at 0 °C for 2 h before being quenched with isopropanol (3 ml). The
30 organic solvent was removed in vacuo and the residue was diluted with ether (100 ml) and washed with water (50 ml) and brine (50 ml). The organic layer was dried over MgSO₄ and

concentrated to afford the ketone ester (1.80 g, 71%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 1.26 (t, J = 6.4 Hz, 3H), 1.44–1.48 (m, 3H), 2.08–2.10 (m, 2H), 2.29–2.31 (d, J = 8.3 Hz, 2H), 2.39–2.40 (m, 4H), 4.18 (q, J = 6.4 Hz, 2H).

4-Oxocyclohexanecarboxylic acid. A mixture of ethyl 4-oxocyclohexanecarboxylate (1.74 g, 10 mmol), methanol (25 ml), and 17% aq. KOH (5 ml) was heated at 50 °C for 1.5 h. After being cooled to room temperature, the reaction mixture was acidified to pH 3 with conc. HCl, concentrated to 10 ml under reduced pressure, and extracted with chloroform (3 x 15 ml). The combined organic layers were dried over MgSO₄, filtered, and concentrated to afford the desired ketone acid (1.30 g, 91%) as a colorless solid. mp 62–64 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.05–2.10 (m, 2H), 2.23–2.27 (m, 2H), 2.35–2.41 (m, 2H), 2.49–2.54 (m, 2H), 2.80–2.84 (m, 1H).

Neopentyl 4-oxocyclohexanecarboxylate. To a solution of 4-oxocyclohexanecarboxylic acid (852 mg, 6 mmol), triphenylphosphine (1.59 g, 6 mmol), and neopentyl alcohol (635 mg, 7.2 mmol) in dry THF (18 ml) at 0 °C was added dropwise a solution of diethyl azodicarboxylate (0.96 ml, 6 mmol) in dry THF (7.5 ml). The reaction was stirred at rt overnight before being quenched by addition of saturated aqueous NaHCO₃ (50 ml). The aqueous phase was separated and extracted with CH₂Cl₂ (2 x 30 ml). The organic extracts were combined, dried over MgSO₄, and concentrated in vacuo. The residue was diluted with ether (10 ml) and petroleum ether (20 ml) and filtered to remove triphenylphosphine oxide. The solvent was removed in vacuo and the residue was purified by chromatography (20% ether in petroleum ether) to afford the desired ketone ester (820 mg, 65%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 0.96 (s, 9H), 2.04–2.07 (m, 2H), 2.22–2.25 (m, 2H), 2.34–2.40 (m, 2H), 2.46–2.50 (m, 2H), 2.80 (m, 1H), 3.82 (s, 2H).

4-Hydroxy-4-(4-fluorophenyl)cyclohexanone ethylene ketal. To a 500 ml round-bottom flask equipped with a mechanical stirrer, condenser and addition funnel were added magnesium turnings (3.50 g, 140 mmol) and enough THF to cover the Mg. A solution of 1-bromo-4-fluorobenzene (12.45 g, 70.43 mmol) in THF (90 ml) was added dropwise at such a rate that the reaction maintained a gentle reflux following reaction- initiation (the initiation may be accomplished by warming the flask). After the mixture was refluxed for an additional 2.5 h, a solution of 1,4-cyclohexanedione monoethylene ketal (10.00 g, 64.03 mmol) in THF (75 ml) was added dropwise. The mixture was kept at refluxing for an

additional 2 h before being quenched with saturated ammonium chloride solution (7 ml). After removal of the magnesium salts by filtration, the filtrate was concentrated to dryness. The residue was dissolved in CHCl_3 and washed with water and brine. The organic layer was separated, dried over MgSO_4 , and concentrated. The residue was purified by flash chromatography (30% ether in petroleum ether) to afford the desired alcohol (13.50 g, 87%) as a colorless solid. mp 133–134 °C. ^1H NMR (500 MHz, CDCl_3) δ 1.69 (d, J = 11.7 Hz, 2H), 1.79 (d, J = 12.2 Hz, 2H), 2.05–2.18 (m, 4H), 3.98 (m, 4H), 7.02 (t, J = 8.3, 2H), 7.47–7.50 (m, 2H).

4-Hydroxy-4-(4-fluorophenyl)cyclohexanone. A mixture of 4-hydroxy-4-(4-fluorophenyl)cyclohexanone ethylene ketal (7.20 g, 28.6 mmol), THF (125 ml) and 5% aq. HCl (65 ml) was refluxed for 14 h. The reaction mixture was cooled to rt, concentrated to 60 ml, and extracted with CH_2Cl_2 (3 x 60 ml). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. The residue was purified by crystallization from hexanes to afford the desired alcohol ketone (5.30 g, 89%) as a colorless solid. mp 111–114 °C (lit. 115–117 °C). ^1H NMR (500 MHz, CDCl_3) δ 2.17–2.20 (m, 2H), 2.23–2.29 (m, 2H), 2.32–2.37 (m, 2H), 2.87–2.94 (m, 2H), 7.04–7.07 (m, 2H), 7.48–7.51 (m, 2H).

4-Acetoxy-4-(4-fluorophenyl)cyclohexanone. To a solution of 4-hydroxy-4-(4-fluorophenyl)cyclohexanone (520 mg, 2.5 mmol), pyridine (2 ml) and 4-dimethylaminopyridine (46 mg) in CH_2Cl_2 (25 ml) at 0 °C was added dropwise a solution of acetic anhydride (1 ml) in CH_2Cl_2 (5 ml). The mixture was warmed to room temperature and stirred for 28 h before being quenched with water (30 ml). The organic phase was washed with 1 M HCl (2 x 30 ml) and brine (30 ml), dried over MgSO_4 , and concentrated in vacuo. The residue was purified by flash chromatography (25% ether in petroleum ether) to afford the desired ketone (510 mg, 82%) as a colorless solid. mp 113–115 °C. ^1H NMR (500 MHz, CDCl_3) δ 2.11 (s, 3H), 2.20 (m, 2H), 2.43 (m, 2H), 2.68 (m, 2H), 2.86 (m, 2H), 7.05 (t, J = 8.3, 2H), 7.35–7.38 (m, 2H).

General procedure for the preparation of 1,2,4-trioxolanes. Ozone was produced with an OREC ozone generator (0.6 L/min O_2 , 60 V), passed through an empty gas washing bottle that was cooled to –78 °C, and bubbled through a solution of an *O*-methyl ketone oxime and a ketone in pentane/ CH_2Cl_2 at 0 °C. *O*-methyl oximes of cyclohexanone, 2-adamantanone, and 3,3,5,5-tetramethylcyclohexanone (1 mmol) were

consumed within 3 min while *O*-methyl cyclododecanone oxime (1 mmol) required 6 min to disappear. After completion, the solution was flushed with oxygen for 5 min before being concentrated in vacuo at room temperature to give a residue that was purified by flash chromatography.

5

7,14,15-Trioxadispiro[5.1.5.2]pentadecane (OZ01). A solution of *O*-methyl cyclohexanone oxime (1.27 g, 10 mmol) and cyclohexanone (1.96 g, 20 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ01** (1.23 g, 58%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 1.20–2.00 (m, 20H); ^{13}C NMR (75 MHz, CDCl_3) δ 23.80, 24.91, 34.65, 108.84.

3-Oxo-7,14,15-trioxadispiro[5.1.5.2]pentadecane (OZ02). A solution of *O*-methyl cyclohexanone oxime (1.27 g, 10 mmol) and 1,4-cyclohexanedione (2.24 g, 20 mmol) in pentane (60 ml) and CH_2Cl_2 (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in petroleum ether) to afford trioxolane **OZ02** (0.88 g, 39%) as a colorless solid. mp 52–54 °C (lit. 53 °C); ^1H NMR (300 MHz, CDCl_3) δ 1.30–1.90 (m, 10H), 2.16 (t, J = 7.0 Hz, 4H), 2.53 (t, J = 7.0 Hz, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 23.77, 24.81, 32.97, 34.41, 37.78, 106.89, 110.03, 203.07. Ref: Griesbaum, K.; Liu, X.; Kassiaris, A.; Scherer, M. Ozonolyses of *O*-Alkylated Ketoximes in the Presence of Carbonyl Groups: A Facile Access to Ozonides. *Libigs Ann./Recueil* 1997, 1381–1390.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane (OZ03). A solution of *O*-methyl cyclohexanone oxime (1.27 g, 10 mmol) and 2-adamantanone (3.00 g, 20 mmol) in pentane (200 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ03** (1.55 g, 46%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 1.30–2.10 (m, 24H); ^{13}C NMR (75 MHz, CDCl_3) δ 23.84, 24.97, 26.48, 26.89, 34.73, 34.77, 34.81, 36.40, 36.79, 108.85, 111.15. Ref: Keul, H. Über Konstitution und Entstehung der Ozonide von Bis-adamantylen und von Bis-bicyclo[3.3.1]non-9-yliden. *Chem. Ber.* 1975, 108, 1207–1217.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-2''-adamantane (OZ04). A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and 2-adamantanone (3.00 g, 20 mmol) in pentane (200 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ04** (1.38 g, 40%) as a colorless solid. mp 150 °C dec (lit. 140–144 °C dec); ¹H NMR (300 MHz, CDCl₃) δ 1.50–2.20 (m, 28H); ¹³C NMR (75 MHz, CDCl₃) δ 26.52, 26.97, 34.70, 34.95, 36.58, 36.81, 111.19. Ref: Keul, H. Über Konstitution und Entstehung der Ozonide von Bis-adamantyliden und von Bis-bicyclo[3.3.1]non-9-yliden. *Chem. Ber.* **1975**, *108*, 1207–1217.

Adamantane-2-spiro-3'-8'-oxo-1',2',4'-trioxaspiro[4.5]decane (OZ05). A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and 1,4-cyclohexanedione (2.24 g, 20 mmol) in pentane (60 ml) and CH₂Cl₂ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in petroleum ether) to afford trioxolane **OZ05** (1.23 g, 44%) as a colorless solid. mp 126–128 °C (ethanol/H₂O 1:1); ¹H NMR (300 MHz, CDCl₃) δ 1.70–2.05 (m, 14H), 2.16 (t, J = 7.2 Hz, 4H), 2.53 (t, J = 7.2 Hz, 4H); ¹³C NMR: (75 MHz, CDCl₃) δ 26.38, 26.79, 33.08, 34.74, 34.84, 36.26, 36.67, 37.84, 106.94, 112.43, 209.36. Anal. Calcd for C₁₆H₂₂O₄: C, 69.04; H, 7.97. Found: C, 68.53; H, 7.97.

1-Fluoro-7,14,15-trioxadispiro[5.1.5.2]pentadecane (OZ06). A solution of *O*-methyl cyclohexanone oxime (0.64 g, 5 mmol) and 2-fluorocyclohexanone (0.58 g, 5 mmol) in pentane (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ06** (0.68 g, 59%, 2.4:1 mixture of two diastereomers) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.30–2.20 (m, 18H), 4.54 (ddd, J = 48.9, 5.6, 2.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 19.48 (d, J = 3.9 Hz), 22.67, 23.55, 23.82, 24.78, 29.36 (d, J = 20.4 Hz), 30.97, 33.76, 34.75, 89.86 (d, J = 179.8 Hz), 106.38 (d, J = 20.3 Hz), 110.24 assigned to the major isomer; 19.12 (d, J = 3.3 Hz), 22.73, 23.44, 23.93, 24.80, 28.31 (d, J = 20.2 Hz), 29.13, 33.47, 34.91, 88.06 (d, J = 180.0 Hz), 106.45 (d, J = 23.0 Hz), 109.68 assigned to the minor isomer; ¹⁹F NMR (282 MHz, CDCl₃) δ –19.2 (bs, 2.4F) assigned to the major isomer; –13.2 (t, J = 43.5 Hz, 1F) assigned to the minor isomer. Anal. Calcd for C₁₂H₁₉FO₃: C, 62.59; H, 8.32. Found: C, 62.59; H, 8.21.

1-[2-(Ethoxycarbonyl)ethyl]-7,14,15-trioxadispiro[5.1.5.2]pentadecane (OZ07).

A solution of *O*-methyl cyclohexanone oxime (1.27 g, 10 mmol) and 2-[2-(ethoxycarbonyl)ethyl]cyclohexanone (3.96 g, 20 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 6% ether in petroleum ether) to afford trioxolane **OZ07** (1.77 g, 57%, 1:1 mixture of two diastereomers) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.27 (t, J = 7.2 Hz, 3H), 1.20–1.89 (m, 19H), 1.90–2.20 (m, 2H), 2.21–2.50 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 14.16, 22.74, 23.35, 23.48, 23.56, 23.63, 23.92, 23.95, 24.80, 24.84, 28.52, 28.81, 32.59, 32.65, 33.85, 34.14, 34.62, 34.68, 34.74, 41.14, 42.00, 60.14, 108.84, 108.95, 110.38, 110.53, 173.63, 173.67. Anal. Calcd for C₁₇H₂₈O₅: C, 65.36; H, 9.03. Found: C, 65.60; H, 8.94.

Adamantane-2-spiro-3'-6'-[2'-(ethoxycarbonyl)ethyl]-1',2',4'-

trioxaspiro[4.5]decane (OZ08). A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and 2-[2-(ethoxycarbonyl)ethyl]cyclohexanone (3.96 g, 20 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 6% ether in petroleum ether) to afford trioxolane **OZ08** (2.10 g, 58%, 4:3 mixture of two diastereomers) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.26 (t, J = 7.2 Hz, 3H), 1.20–2.19 (m, 25H), 2.21–2.49 (m, 2H), 4.13 (q, J = 7.2 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 14.08, 22.93, 23.37, 23.46, 23.48, 23.65, 23.89, 26.29, 26.34, 26.71, 28.42, 28.89, 32.46, 32.52, 34.06, 34.20, 34.31, 34.60, 34.67, 35.18, 35.25, 35.74, 35.99, 36.63, 36.80, 41.15, 42.00, 60.01, 110.34, 110.47, 111.07, 111.13, 173.49, 173.56. Anal. Calcd for C₂₁H₃₂O₅: C, 69.20; H, 8.85. Found: C, 68.34; H, 8.39.

7,12,19,20,23,24-Hexaoxatetrspiros[5.1.2.1.5.2.2.2]tetracosane (OZ09).

A solution of *O*-methyl cyclohexanone oxime (1.27 g, 10 mmol) and 1,4-cyclohexanedione (0.37 g, 3.3 mmol) in pentane (40 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ09** (0.56 g, 50%, 1:1 mixture of two diastereomers) as a colorless solid. mp 83–84 °C (lit. 83.5 °C); ¹H NMR (300 MHz, CDCl₃) δ 1.25–1.83 (m, 20H), 1.92 (s, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 23.75, 24.83, 24.86, 31.38, 34.46, 107.50, 107.57, 109.34. Ref: Griesbaum, K.;

Liu, X.; Dong, Y. Diozonides from Cozonolyses of Suitable *O*-Methyl Oximes and Ketoses. *Tetrahedron* **1997**, *53*, 5463–5470.

Adamantane-2-spiro-3'-1',2',4',9',12'-pentaoxadispiro[4.2.4.2]tetradecane (OZ10). A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and 1,4-dioxaspiro[4.5]decan-8-one (1.56 g, 10 mmol) in pentane (90 ml) and CH₂Cl₂ (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ10** (1.06 g, 33%) as a colorless solid. mp 84–85 °C (ethanol); ¹H NMR (300 MHz, CDCl₃) δ 1.64–2.13 (m, 22H), 3.97 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 26.39, 26.80, 31.66, 32.01, 34.68, 34.77, 36.26, 36.70, 64.30, 107.78, 107.97, 111.49. Anal. Calcd for C₁₈H₂₆O₅: C, 67.06; H, 8.13. Found: C, 67.28; H, 8.35.

Adamantane-2-spiro-3'-11',11'-dimethyl-1',2',4',9',13'-pentaoxadispiro[4.2.5.2]pentadecane (OZ11). A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and 3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one (1.98 g, 10 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ11** (1.43 g, 39%) as a colorless solid. mp 123–125 °C (ethanol); ¹H NMR (300 MHz, CDCl₃) δ 0.99 (s, 6H), 1.61–2.14 (m, 22H), 3.51 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 22.66, 26.43, 26.84, 29.41, 30.16, 30.46, 34.73, 34.82, 36.30, 36.75, 70.24, 70.19, 96.67, 108.47, 111.51. Anal. Calcd for C₂₁H₃₂O₅: C, 69.20; H, 8.85. Found: C, 69.17; H, 8.97.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-3''-7''-oxo-cis-bicyclo[3.3.0]octane (OZ12). A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and *cis*-bicyclo[3.3.0]octane-3,7-dione (2.76 g, 20 mmol) in pentane (60 ml) and CH₂Cl₂ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 15% ether in petroleum ether) to afford trioxolane **OZ12** (0.51 g, 17%) as a colorless solid. mp 122–124 °C (ethanol/H₂O 4:1); ¹H NMR (300 MHz, CDCl₃) δ 1.60–2.05 (m, 16H), 2.13–2.41 (m, 4H), 2.43–2.62 (m, 2H), 2.70–2.93 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 26.43, 26.79, 34.71, 34.84, 35.96, 36.72, 36.97, 41.42, 44.15, 111.82, 117.66, 219.55. Anal. Calcd for C₁₈H₂₄O₄: C, 71.03; H, 7.95. Found: C, 71.18; H, 7.80.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-3''-7''-

oxobicyclo[3.3.1]nonane (OZ13). A solution of *O*-methyl 2-adamantanone oxime (0.64 g, 3.55 mmol) and bicyclo[3.3.1]nonane-3,7-dione (1.08 g, 7.10 mmol) in pentane (45 ml) and CH₂Cl₂ (45 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to afford trioxolane **OZ13** (0.10 g, 9%) as a colorless solid. mp 153–155 °C (ethanol/H₂O 1:1); ¹H NMR (300 MHz, CDCl₃) δ 1.55–2.10 (m, 20H), 2.32–2.70 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 26.45, 26.66, 28.87, 31.30, 34.32, 34.80, 36.15, 36.79, 39.94, 45.89, 107.15, 113.66, 208.12. Anal. Calcd for C₁₉H₂₆O₄: C, 71.67; H, 8.23. Found: C, 71.68; H, 8.19.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-8''-11''-

oxopentacyclo[5.4.0.0^{2'',6''}.0^{3'',10''}.0^{5'',9''}]undecane (OZ14). A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (3.48 g, 20 mmol) in CH₂Cl₂ (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 20% ether in petroleum ether) to afford trioxolane **OZ14** (0.77 g, 23%) as a colorless solid. mp 106 °C dec (ethanol); ¹H NMR (300 MHz, CDCl₃) δ 1.45–2.15 (m, 16H), 2.45–3.05 (m, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 26.36, 26.63, 34.53, 34.56, 35.10, 36.05, 36.33, 36.54, 38.94, 41.07, 41.16, 41.98, 42.52, 45.14, 50.81, 51.80, 112.91, 113.01, 213.36. Anal. Calcd for C₂₁H₂₄O₄: C, 74.09; H, 7.11. Found: C, 74.00; H, 7.29.

Adamantane-2-spiro-3'-8'-methoxyimino-1',2',4'-trioxaspiro[4.5]decane

(OZ15). To a solution of **OZ05** (0.557 g, 2.0 mmol) in CH₂Cl₂ (5 ml) and methanol (5 ml) were added pyridine (0.30 ml) and methoxylamine hydrochloride (0.250 g, 3.0 mmol), and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by recrystallizations from ethanol/H₂O (20 ml, 1:1) and from ethanol/H₂O (15 ml, 2:1) to give trioxolane **OZ15** (0.51 g, 83%) as a colorless solid. mp 97–99 °C (ethanol/H₂O 2:1); ¹H NMR (300 MHz, CDCl₃) δ 1.60–2.10 (m, 18H), 2.30–2.81 (m, 4H), 3.84 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 21.54, 26.40, 26.81, 28.74, 32.59, 33.85, 34.72, 34.77, 34.84, 36.28, 36.70, 61.15, 107.92, 112.00, 156.93. Anal. Calcd for C₁₇H₂₅NO₄: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.58; H, 8.29; N, 4.41.

Adamantane-2-spiro-3'-8'-hydroxyimino-1',2',4'-trioxaspiro[4.5]decane

(**OZ16**). To a solution of **OZ05** (0.557 g, 2.0 mmol) in CH₂Cl₂ (5 ml) and methanol (5 ml) were added pyridine (0.30 ml) and hydroxylamine hydrochloride (0.210 g, 3.0 mmol), and the reaction was stirred at room temperature for 24 h. The reaction mixture was

concentrated in vacuo to provide a crude residue that was purified by recrystallization from ethanol/H₂O (20 ml, 1:1) to give trioxolane **OZ16** (0.43 g, 73%) as a colorless solid. mp 137–139 °C (ethanol/H₂O 1:1); ¹H NMR (300 MHz, CDCl₃) δ 1.62–2.10 (m, 18H), 2.32–2.88 (m, 4H), 8.60–8.95 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 20.97, 26.41, 26.81, 28.72, 32.48, 33.74, 34.74, 34.80, 34.84, 36.29, 36.70, 107.91, 112.06, 157.94. Anal. Calcd for C₁₆H₂₃NO₄: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.65; H, 7.96; N, 4.75.

Adamantane-2-spiro-3'-9'-oxo-1',2',4',8'-tetraoxaspiro[4.6]undecane (OZ17).

To a solution of **OZ05** (0.84 g, 3.0 mmol) in CH₂Cl₂ (70 ml) were added NaHCO₃ (0.51 g, 6.0 mmol) and 3-chloroperoxybenzoic acid (1.20 g). The reaction was stirred at room temperature for 46 h before being quenched with H₂O (60 ml). The aqueous layer was extracted with CH₂Cl₂ (10 ml x 2), and the combined extracts were washed with H₂O, dried over MgSO₄, and concentrated to give a crude residue that was purified by flash chromatography (silica gel, 40% ether in petroleum ether) to afford trioxolane **OZ17** (0.31 g, 35%) as a colorless solid. mp 116–118 °C (ethanol); ¹H NMR (300 MHz, CDCl₃) δ 1.62–2.10 (m, 18H), 2.32–2.88 (m, 4H), 8.60–8.95 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 26.25, 26.65, 28.54, 31.87, 34.62, 34.64, 34.67, 34.71, 36.19, 36.50, 38.35, 63.86, 107.60, 112.89, 174.63. Anal. Calcd for C₁₆H₂₂O₅: C, 65.29; H, 7.53. Found: C, 65.48; H, 7.80.

cis-Adamantane-2-spiro-3'-8'-*t*-butyl-1',2',4'-trioxaspiro[4.5]decane (OZ18).

A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and 4-*tert*-butylcyclohexanone (3.09 g, 20 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ18** (1.68 g, 52%) as a colorless solid. mp 123–124 °C (ethanol); ¹H NMR (300 MHz, CDCl₃) δ 0.84 (s, 9H), 0.89–1.10 (m, 1H), 1.14–1.35 (m, 2H), 1.55–1.85 (m, 12H), 1.86–2.10 (m, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 24.71, 26.49, 26.89, 27.57, 32.27, 34.79, 36.38, 36.82, 46.66, 108.95, 111.12. Anal. Calcd for C₂₀H₃₂O₃: C, 74.96; H, 10.06. Found: C, 75.25; H, 10.06.

Adamantane-2-spiro-3'-8'-benzyloxyimino-1',2',4'-trioxaspiro[4.5]decane (OZ19). To a solution of **OZ05** (0.56 g, 2.0 mmol) in CH₂Cl₂ (5 ml) and methanol (5 ml) were added pyridine (0.30 ml) and *O*-benzylhydroxylamine hydrochloride (0.48 g, 3.0 mmol), and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by recrystallizations from ethanol/H₂O (20 ml, 1:1) and from ethanol/H₂O (15 ml, 2:1) to give trioxolane **OZ19** (0.66 g, 86%) as a colorless solid. mp 62–64 °C (ethanol/H₂O 2:1); ¹H NMR (300 MHz, CDCl₃) δ 1.60–2.10 (m, 18H), 2.32–2.50 (m, 2H), 2.53–2.67 (m, 1H), 2.72–2.86 (m, 1H), 5.08 (s, 2H), 7.25–7.42 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 21.87, 26.41, 26.81, 28.76, 32.61, 33.87, 34.72, 34.74, 34.79, 34.85, 36.29, 36.70, 75.36, 107.94, 111.99, 127.67, 127.90, 128.31, 137.99, 157.57. Anal. Calcd for C₂₃H₂₉NO₄: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.30; H, 7.49; N, 3.77.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.11]hexadecane (OZ20). A solution of *O*-methyl cyclododecanone oxime (2.11 g, 10 mmol) and 2-adamantanone (3.0 g, 20 mmol) in pentane (90 ml) and CH₂Cl₂ (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ20** (1.88 g, 54%) as a colorless solid. mp 73–75 °C (ethanol/H₂O 3:1); ¹H NMR (300 MHz, CDCl₃) δ 1.18–1.60 (m, 18H), 1.62–2.10 (m, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 20.07, 22.05, 22.37, 25.81, 26.07, 26.49, 26.88, 31.37, 34.76, 34.86, 36.38, 36.79, 111.33, 112.59. Anal. Calcd for C₂₂H₃₆O₃: C, 75.82; H, 10.41. Found: C, 75.65; H, 10.69.

3-Oxo-7,20,21-trioxadispiro[5.1.11.2]heneicosane (OZ21). A solution of *O*-methyl cyclododecanone oxime (2.11 g, 10 mmol) and 1,4-cyclohexanedione (2.24 g, 20 mmol) in pentane (60 ml) and CH₂Cl₂ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in petroleum ether) to afford trioxolane **OZ21** (1.29 g, 42%) as a colorless solid. mp 78–80 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.10–1.65 (m, 18H), 1.70–1.90 (m, 4H), 2.15 (t, J = 7.0 Hz, 4H), 2.52 (t, J = 7.1 Hz, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 20.03, 22.04, 22.39, 25.76, 26.03, 31.12, 32.92, 37.80, 107.00, 113.73, 209.29. Anal. Calcd for C₁₈H₃₀O₄: C, 69.64; H, 9.74. Found: C, 69.49; H, 9.81.

Adamantane-2-spiro-3'-1',2',4',8'-tetraoxaspiro[4.5]decane (OZ22). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and tetrahydro-4*H*-pyran-4-one (1.00 g, 10 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2 to 10% ether in petroleum ether) to afford trioxolane **OZ22** (0.87 g, 65%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.20–2.30 (m, 18H), 3.50–4.10 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 26.33, 26.73, 34.60, 34.68, 35.43, 36.30, 36.60, 65.67, 105.91, 111.76. Anal. Calcd for C₁₅H₂₂O₄: C, 67.64; H, 8.33. Found: C, 67.83; H, 8.21.

Adamantane-2-spiro-3'-8'-ethoxycarbonyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ23). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1-ethoxycarbonyl-4-piperidone (1.71 g, 10 mmol) in pentane (80 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10 to 20% ether in petroleum ether) to afford trioxolane **OZ23** (0.43 g, 26%) as a colorless solid. mp 44–46 °C (ethanol/H₂O 5:2); ¹H NMR (300 MHz, CDCl₃) δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.60–2.10 (m, 18H), 3.40–3.75 (m, 4H), 4.14 (q, *J* = 7.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 14.66, 26.40, 26.79, 34.35, 34.71, 34.79, 36.35, 36.68, 41.69, 61.42, 106.88, 112.06, 155.33. Anal. Calcd for C₁₈H₂₇NO₅: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.96; H, 7.73; N, 4.15.

Adamantane-2-spiro-3'-8'-benzoyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ24). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1-benzoyl-4-piperidone (2.03 g, 10 mmol) in pentane (60 ml) and CH₂Cl₂ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 30 to 50% ether in petroleum ether) to afford trioxolane **OZ24** (0.61 g, 33%) as a colorless solid. mp 130–132 °C (ethanol/H₂O 1:1); ¹H NMR (300 MHz, CDCl₃) δ 1.60–2.15 (m, 18H), 3.51 (br s, 2H), 3.77 (br s, 1H), 3.96 (br s, 1H), 7.30–7.50 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 26.35, 26.75, 34.20 (br), 34.69, 34.77, 35.03 (br), 36.30, 36.62, 40.01 (br), 45.41 (br), 106.75, 112.25, 126.77, 128.49, 129.71, 135.74, 170.39. Anal. Calcd for C₂₂H₂₇NO₄: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.63; H, 7.24; N, 3.95.

cis-Adamantane-2-spiro-3'-8'-propyl-1',2',4'-trioxaspiro[4.5]decane (OZ25). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4-propylcyclohexanone

(1.40 g, 10 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ25** (0.89 g, 58%) as a colorless solid. mp 49–51 °C (ethanol/H₂O 2:1); ¹H NMR (300 MHz, CDCl₃) δ 0.88 (t, J = 7.2 Hz, 3H), 1.05–1.45 (m, 7H), 1.50–2.10 (m, 20H); ¹³C NMR (75 MHz, CDCl₃) δ 14.31, 20.18, 26.49, 26.89, 30.12, 34.29, 34.78, 35.83, 36.39, 36.82, 38.52, 109.15, 111.07. Anal. Calcd for C₁₉H₃₀O₃: C, 74.47; H, 9.87. Found: C, 74.44; H, 10.02.

Adamantane-2-spiro-3'-7',9'-tetramethyl-1',2',4'-trioxaspiro[4.5]decane (OZ26). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 3,3,5,5-tetramethylcyclohexanone (1.54 g, 10 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ26** (0.77 g, 48%) as a colorless solid. mp 71–72 °C (ethanol/H₂O 1:1); ¹H NMR (300 MHz, CDCl₃) δ 1.03 (s, 6H), 1.07 (s, 6H), 1.24 (s, 1H), 1.25 (s, 1H), 1.59 (s, 4H), 1.61–2.10 (m, 14H); ¹³C NMR (75 MHz, CDCl₃) δ 26.50, 26.91, 31.47, 31.69, 32.36, 34.77, 34.92, 36.38, 36.83, 45.70, 51.46, 110.26, 110.96. Anal. Calcd for C₂₀H₃₂O₃: C, 74.96; H, 10.06. Found: C, 75.06; H, 9.96.

cis-Adamantane-2-spiro-3'-8'-phenyl-1',2',4'-trioxaspiro[4.5]decane (OZ27). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4-phenylcyclohexanone (1.74 g, 10 mmol) in pentane (80 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) to afford trioxolane **OZ27** (0.83 g, 49%) as a colorless solid. mp 103–105 °C (ethanol/H₂O 2:1); ¹H NMR (300 MHz, CDCl₃) δ 1.55–2.20 (m, 22H), 2.45–2.65 (m, 1H), 7.10–7.40 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 26.47, 26.87, 31.42, 34.58, 34.72, 34.79, 36.39, 36.79, 42.93, 108.39, 111.37, 126.14, 126.75, 128.37, 146.14. Anal. Calcd for C₂₂H₂₈O₃: C, 77.61; H, 8.29. Found: C, 77.81; H, 8.17.

Adamantane-2-spiro-3'-8'-*t*-butyloxyimino-1',2',4'-trioxaspiro[4.5]decane (OZ28). To a solution of **OZ05** (0.557 g, 2.0 mmol) in CH₂Cl₂ (5 ml) and methanol (5 ml) were added pyridine (0.30 ml) and *O*-(*tert*-butyl)hydroxylamine hydrochloride (0.356 g, 3.0 mmol), and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by recrystallizations

from ethanol/H₂O (20 ml, 1:1) and from ethanol/H₂O (14 ml, 2.5:1) to give trioxolane **OZ28** (0.63 g, 90%) as a colorless solid. mp 68–70 °C (ethanol/H₂O 2.5:1); ¹H NMR (500 MHz, CDCl₃) δ 1.26 (s, 9H), 1.60–2.10 (m, 18H), 2.32–2.45 (m, 2H), 2.50–2.60 (m, 1H), 2.65–2.76 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 21.54, 26.50, 26.91, 27.54, 28.97, 32.77, 34.13, 34.78, 34.80, 34.86, 34.91, 36.39, 36.80, 77.38, 108.31, 111.87, 155.29.

Anal. Calcd for C₂₀H₃₁NO₄: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.75; H, 8.74; N, 4.00.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decan-8'-one 2,4-dinitrophenylhydrazone (OZ29). A solution of **OZ05** (0.28 g, 1.0 mmol) in ethanol (5 ml) and CH₂Cl₂ (1.5 ml) was added to a solution of 2,4-dinitrophenylhydrazine (0.30 g, 1.5 mmol), sulfuric acid (1.5 ml) and H₂O (2.3 ml) in ethanol (7.5 ml), and the reaction was stirred at room temperature for 10 min before being quenched with ethanol (20 ml). The resulting precipitate was immediately filtered, washed with ethanol, and recrystallized from ethanol (20 ml) to afford trioxolane **OZ29** (0.39 g, 85%) as a yellow solid. mp 142–144 °C dec (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.20 (m, 18H), 2.45–2.85 (m, 4H), 7.94 (d, J = 9.8 Hz, 1H), 8.27 (dd, J = 9.8, 2.0 Hz, 1H), 9.09 (d, 2.9 Hz, 1H), 11.12 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 23.54, 26.44, 26.85, 31.89, 32.40, 33.59, 34.73, 34.80, 35.01, 36.34, 36.37, 36.70, 107.41, 112.50, 116.27, 123.45, 129.18, 129.98, 137.91, 145.22, 157.65. Anal. Calcd for C₂₂H₂₆N₄O₇: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.74; H, 5.65; N, 12.02.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decan-8'-one 4-phenylsemicarbazone (OZ30). To a solution of **OZ05** (0.28 g, 1.0 mmol) in ethanol (5 ml) and CH₂Cl₂ (1.5 ml) was added a solution of 4-phenylsemicarbazide (0.17 g, 1.1 mmol) in ethanol (5 ml) and CH₂Cl₂ (2 ml), and the reaction was stirred at room temperature for 1 h before being heated to 50 °C for 30 min. The solution was cooled to room temperature and the resulting precipitate was filtered, washed with ethanol, and dried to afford trioxolane **OZ30** (0.37 g, 90%) as a colorless solid. mp 161–163 °C dec (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.10 (m, 18H), 2.48–2.61 (m, 3H), 2.62–2.69 (m, 1H), 7.02–7.09 (m, 1H), 7.23–7.35 (m, 2H), 7.48–7.54 (m, 2H), 8.24 (s, 1H), 9.11 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 23.17, 26.46, 26.87, 31.88, 32.57, 33.92, 34.75, 34.79, 34.93, 36.35, 36.37, 36.75, 107.75, 112.17, 119.33, 123.10, 128.84, 138.26, 150.83, 154.31. Anal. Calcd for C₂₃H₂₉N₃O₄: C, 67.13; H, 7.10; N, 10.21. Found: C, 66.86; H, 6.92; N, 10.04.

Adamantane-2-spiro-3'-11',12'-benzo-1',2',4',9',14'-

pentaoxidispiro[4.2.6.2]hexadecane (OZ31). To a solution of **OZ05** (0.28 g, 1.0 mmol) in 1,2-dimethoxyethane (10 ml) were added 1,5-dihydro-3-methoxy-2,4-benzodioxepin (0.20 g, 1.1 mmol) and *p*-toluenesulfonic acid monohydrate (38 mg), and the reaction was stirred at room temperature for 30 min before being quenched by addition of saturated NaHCO₃ solution (1.0 ml). The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by recrystallizations from ethanol/H₂O (15 ml, 2:1) and from ethanol (10 ml) to give trioxolane **OZ31** (0.22 g, 56%) as a colorless solid. mp 149–151 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.20 (m, 22H), 4.80–4.94 (m, 4H), 7.02–7.09 (m, 2H), 7.13–7.22 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.53, 26.94, 29.46, 31.12, 34.81, 34.91, 36.42, 36.84, 64.65, 101.38, 108.42, 111.65, 126.09, 126.15, 126.75, 138.01, 138.09. Anal. Calcd for C₂₄H₃₀O₅: C, 72.34; H, 7.59. Found: C, 72.51; H, 7.70.

Adamantane-2-spiro-3'-8'-hydroxy-1',2',4'-trioxaspiro[4.5]decane (OZ32).

A solution of NaBH₄ (42 mg, 1.1 mmol) in ethanol (10 ml) containing 3 drops of 1.0 M aq NaOH was added to a solution of **OZ05** (0.277g, 1.0 mmol) in THF (5 ml) at 0 °C over a period of 5 min. The reaction was stirred at room temperature for 1 h before being quenched with EtOAc (10 ml). The solvent was removed using rotary evaporation and the crude product dissolved in EtOAc (50 ml) and washed with saturated aqueous bicarbonate (10 ml), water (10 ml), and brine (10 ml). The organic layer was dried over MgSO₄, filtered, and concentrated to give trioxolane **OZ32** (0.25 g, 89%, 1:1 mixture of two diastereomers) as a colorless solid. mp 100–106 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.45–2.20 (m, 22H), 3.70–3.80 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.52, 26.94, 30.76, 31.26, 31.59, 32.07, 34.80, 34.88, 34.92, 36.38, 36.46, 36.83, 67.46, 68.06, 108.09, 108.19, 111.50, 111.68. Anal. Calcd for C₁₆H₂₄O₄: C, 68.54; H, 8.63. Found: C, 68.36; H, 8.44.

Adamantane-2-spiro-3'-8',8'-dimethyl-1',2',4'-trioxaspiro[4.5]decane (OZ33).

A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4,4-dimethylcyclohexanone (1.26 g, 10 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ33** (0.72 g, 49%) as a colorless solid. mp 125–127 °C (ethanol/H₂O 3:1); ¹H NMR (500 MHz, CDCl₃)

δ 0.92 (s, 3H), 0.95 (s, 3H), 1.42 (t, $J = 6.4$ Hz, 4H), 1.62–2.10 (m, 18H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.46, 26.72 (br), 26.87, 28.87 (br), 29.41, 30.80, 34.75, 34.83, 36.37, 36.52, 36.79, 109.07, 111.19. Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_3$: C, 73.93; H, 9.65. Found: C, 74.16; H, 9.55.

5 **Adamantane-2-spiro-3'-8',8'-diphenyl-1',2',4'-trioxaspiro[4.5]decane (OZ34).**

A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4,4-diphenylcyclohexanone (1.25 g, 5 mmol) in pentane (60 ml) and CH_2Cl_2 (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) to afford trioxolane **OZ34**

10 (0.48 g, 23%) as a colorless solid. mp 155–157 °C (ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.40–2.20 (m, 18H), 2.32–2.65 (m, 4H), 7.00–7.42 (m, 10H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.52, 26.91, 31.51, 34.05, 34.79, 34.87, 36.45, 36.83, 45.47, 108.66, 111.46, 125.79, 125.88, 126.72, 127.17, 128.30, 128.46, 145.94, 147.63. Anal. Calcd for $\text{C}_{28}\text{H}_{32}\text{O}_3$: C, 80.73; H, 7.74. Found: C, 80.95; H, 7.61.

15 **Adamantane-2-spiro-3'-8'-*t*-butoxycarbonyl-1',2',4'-trioxa-8'-**

azaspiro[4.5]decane (OZ35). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1-*tert*-butoxycarbonyl-4-piperidone (1.99 g, 10 mmol) in pentane (80 ml) and CH_2Cl_2 (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 15% ether in petroleum ether) to afford trioxolane **OZ35** (0.73 g, 40%) as a colorless solid. mp 82–84 °C (ethanol/ H_2O 2:1); ^1H NMR (500 MHz, CDCl_3) δ 1.46 (s, 9H), 1.62–2.10 (m, 18H), 3.40–3.70 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.48, 26.88, 28.41, 34.45, 34.76, 34.85, 36.43, 36.76, 41.60 (br), 79.73, 107.07, 112.01, 154.60. Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.52; H, 8.39; N, 3.80.

25 **2,2,4,4,14,14-Hexamethyl-7,12,16,19,20-pentaoxatrispiro[5.1.2.5.2.2]icosane**

(OZ36). A solution of *O*-methyl 3,3,5,5-tetramethylcyclohexanone oxime (0.92 g, 5 mmol) and 3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one (1.98 g, 10 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ36** (0.70 g, 38%) as a colorless solid. mp 95–97 °C (ethanol); ^1H NMR (500 MHz, CDCl_3) δ 0.97 (s, 6H), 1.03 (s, 6H), 1.04 (s, 6H), 1.20–1.29 (m, 2H), 1.55 (d, $J = 3.2$ Hz,

2H), 1.63 (d, $J = 3.7$ Hz, 2H), 1.83 (t, $J = 6.4$ Hz, 4H), 1.86–2.04 (m, 4H), 3.50 (s, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 22.68, 29.47, 30.20, 30.40, 30.91, 32.21, 32.30, 45.59, 51.43, 70.29, 96.70, 107.94, 110.58. Anal. Calcd for $\text{C}_{21}\text{H}_{36}\text{O}_5$: C, 68.44; H, 9.85. Found: C, 68.24; H, 9.70.

5 **Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-3''-7''-methoxyimino-*cis*-bicyclo[3.3.0]octane (OZ37).** To a solution of **OZ12** (0.304 g, 1.0 mmol) in CH_2Cl_2 (5 ml) and ethanol (5 ml) were added pyridine (0.15 ml) and methoxylamine hydrochloride (0.125 g, 1.5 mmol), and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by
10 recrystallization from ethanol/ H_2O (15 ml, 2:1) to give trioxolane **OZ37** (0.32 g, 96%) as a colorless solid. mp 118–120 °C (ethanol/ H_2O 2:1); ^1H NMR (500 MHz, CDCl_3) δ 1.62–2.05 (m, 16H), 2.14–2.25 (m, 2H), 2.33–2.42 (m, 2H), 2.55–2.74 (m, 4H), 3.84 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.49, 26.88, 33.23, 34.73, 34.85, 34.89, 35.99, 36.17, 36.79, 39.21, 39.33, 40.62, 41.42, 61.40, 111.54, 118.11, 165.40. Anal. Calcd for
15 $\text{C}_{19}\text{H}_{27}\text{NO}_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.54; H, 7.96; N, 4.29.

Adamantane-2-spiro-3'-8'-(*N*-phthalimido)imino-1',2',4'-trioxaspiro[4.5]decane (OZ38). To a solution of **OZ05** (0.454 g, 1.63 mmol) and *N*-aminophthalimide (0.290 g, 1.79 mmol) in CH_2Cl_2 (5 ml) and ethanol (5 ml) was added acetic acid (0.5 ml), and the reaction was heated to 50 °C for 2 h. The reaction mixture was
20 cooled to room temperature, filtered through Celite, washed with CH_2Cl_2 , and the solvent was removed in vacuo. The residue was purified by recrystallization from ethanol (10 ml) to give trioxolane **OZ38** (0.45 g, 65%) as a colorless solid. mp 146–148 °C (ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.65–2.07 (m, 16H), 2.10–2.19 (m, 2H), 2.43–2.58 (m, 2H), 2.78–2.90 (m, 2H), 7.70–7.79 (m, 2H), 7.84–7.90 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3)
25 δ 26.43, 26.82, 28.12, 32.41, 33.15, 33.81, 34.72, 34.76, 34.79, 34.88, 36.30, 36.32, 36.70, 107.20, 112.28, 123.54, 131.08, 134.20, 164.32, 180.89. Anal. Calcd for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.12; H, 6.03; N, 6.57.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decan-8'-one tosylhydrazone (OZ39). To a solution of **OZ05** (0.28 g, 1.0 mmol) and *p*-toluenesulfonylhydrazide (0.21 g, 1.1 mmol) in CH_2Cl_2 (5 ml) and ethanol (5 ml) was added acetic acid (0.5 ml), and the
30 reaction was heated to 50 °C for 2 h. The reaction mixture was cooled to room temperature

and concentrated in vacuo. The residue was purified by recrystallization from ethanol/H₂O (15 ml, 2:1) to give trioxolane **OZ39** (0.26 g, 58%) as a colorless solid. mp 137 °C dec (ethanol/H₂O 2:1); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.52–2.10 (m, 18H), 2.15–2.65 (m, 4H), 2.38 (s, 3H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 2H), 10.23 (s, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 20.92, 23.84, 25.72, 26.12, 31.05, 31.80, 33.09, 34.17, 34.29, 35.58, 35.97, 107.55, 111.19, 127.44, 129.31, 136.28, 143.01, 158.63. Anal. Calcd for C₂₃H₃₀N₂O₅S: C, 61.86; H, 6.77; N, 6.27. Found: C, 61.71; H, 6.81; N, 6.53.

***cis*-Adamantane-2-spiro-3'-8'-isopropyl-1',2',4'-trioxaspiro[4.5]decane (OZ40).**

A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4-

isopropylcyclohexanone (1.40 g, 10 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ40** (0.47 g, 31%) as a colorless solid. mp 67–69 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 0.85 (d, *J* = 6.8 Hz, 6H), 1.02–1.13 (m, 1H), 1.17–1.32 (m, 2H), 1.40–1.52 (m, 1H), 1.60–2.10 (m, 20H); ¹³C NMR (125.7 MHz, CDCl₃) δ 19.82, 26.54, 26.85, 26.94, 32.12, 34.54, 34.81, 34.83, 36.44, 36.87, 42.57, 109.11, 111.10. Anal. Calcd for C₁₉H₃₀O₃: C, 74.47; H, 9.87. Found: C, 74.21; H, 9.86.

***cis*-Adamantane-2-spiro-3'-8'-(4'-fluorophenyl)-1',2',4'-trioxaspiro[4.5]decane (OZ41).**

A solution of *O*-methyl 2-adamantanone oxime (0.36 g, 2 mmol) and 4-(4-

fluorophenyl)cyclohexanone (0.38 g, 2 mmol) in pentane (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ41** (0.36 g, 50%) as a colorless solid. mp 103–106 °C (ethanol/H₂O 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.58–2.25 (m, 22H), 2.43–2.70 (m, 1H), 6.90–7.02 (m, 2H), 7.11–7.22 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.43, 26.84, 31.57, 34.63, 34.76, 36.36, 36.75, 42.15, 108.24, 111.41, 115.06 (d, *J* = 21.4 Hz), 128.03 (d, *J* = 7.4 Hz), 141.75 (d, *J* = 3.0 Hz), 161.26 (d, *J* = 244.1 Hz). Anal. Calcd for C₂₂H₂₇FO₃: C, 73.72; H, 7.59. Found: C, 73.65; H, 7.66.

Adamantane-2-spiro-3'-5',5'-diphenyl-1',2',4'-trioxolane (OZ42). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and benzophenone (0.91 g, 5 mmol) in pentane (90 ml) and CH₂Cl₂ (10 ml) was treated with ozone according to the general

procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ42** (0.55 g, 32%) as a colorless solid. mp 105–107 °C (ethanol/H₂O 2:1); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.10 (m, 12H), 2.16–2.30 (m, 2H), 7.25–7.42 (m, 6H), 7.45–7.60 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.56, 26.98, 34.86, 35.07, 36.21, 36.88, 109.68, 113.92, 126.97, 128.05, 128.56, 140.06. Anal. Calcd for C₂₃H₂₄O₃: C, 79.28; H, 6.94. Found: C, 79.32; H, 6.96.

Adamantane-2-spiro-3'-5',5'-bis(4'-chlorophenyl)-1',2',4'-trioxolane (OZ43).

A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4,4'-dichlorobenzophenone (1.26 g, 5 mmol) in pentane (80 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 1% ether in petroleum ether) to afford trioxolane **OZ43** (0.55 g, 26%) as a colorless solid. mp 128–130 °C (ethanol/H₂O 5:2); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.05 (m, 12H), 2.10–2.30 (m, 2H), 7.20–7.60 (m, 8H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.46, 26.88, 34.80, 35.00, 36.17, 36.74, 108.78, 114.42, 128.33, 128.43, 134.93, 138.20. Anal. Calcd for C₂₃H₂₂Cl₂O₃: C, 66.19; H, 5.31. Found: C, 66.37; H, 5.12.

Adamantane-2-spiro-3'-5',5'-bis(4'-fluorophenyl)-1',2',4'-trioxolane (OZ44).

A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4,4'-difluorobenzophenone (1.09 g, 5 mmol) in pentane (90 ml) and CH₂Cl₂ (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford trioxolane **OZ44** (0.87 g, 45%) as a colorless solid. mp 86–89 °C (ethanol/H₂O 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.05 (m, 12H), 2.06–2.40 (m, 2H), 6.90–7.20 (m, 4H), 7.35–7.65 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.41, 26.84, 34.77, 34.96, 36.17, 36.71, 108.95, 114.21, 115.06 (d, J = 21.3 Hz), 128.96 (d, J = 8.4 Hz), 135.56, 162.95 (d, J = 248.0 Hz). Anal. Calcd for C₂₃H₂₂F₂O₃: C, 71.86; H, 5.77. Found: C, 71.78; H, 5.87.

Adamantane-2-spiro-3'-5',5'-bis(2',3',4',5',6'-pentafluorophenyl)-1',2',4'-trioxolane (OZ45). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and decafluorobenzophenone (1.81 g, 5 mmol) in pentane (90 ml) and CH₂Cl₂ (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 1% ether in petroleum ether) to afford trioxolane **OZ45** (0.60 g, 23%) as a colorless solid. mp 92–95 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ

1.62–2.03 (m, 12H), 2.06–2.20 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.37, 26.70, 34.78, 34.83, 35.91, 36.50, 103.85 (m), 113.07 (m), 115.63, 136.83 (m), 138.84 (m), 140.95 (m), 143.00 (m), 143.54 (m), 145.54 (m). Anal. Calcd for $\text{C}_{23}\text{H}_{14}\text{F}_{10}\text{O}_3$: C, 52.29; H, 2.67. Found: C, 52.31; H, 2.77.

5 **Adamantane-2-spiro-3'-5',5'-bis[3'-(trifluoromethyl)phenyl]-1',2',4'-trioxolane**

(OZ46). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 3,3'-bis(trifluoromethyl)benzophenone (1.59 g, 5 mmol) in pentane (80 ml) and CH_2Cl_2 (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 1% ether in petroleum ether) to afford trioxolane

10 **OZ46** (0.62 g, 26%) as a colorless solid. mp 60–62 °C (ethanol/ H_2O 1:1); ^1H NMR (500 MHz, CDCl_3) δ 1.60–2.05 (m, 12H), 2.10–2.30 (m, 2H), 7.40–7.57 (m, 2H), 7.59–7.75 (m, 4H), 7.82 (s, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.46, 26.85, 34.82, 34.94, 36.13, 36.71, 108.36, 114.99, 123.53 (q, $J = 3.8$ Hz), 123.93 (q, $J = 272.4$ Hz), 125.84 (q, $J = 3.8$ Hz), 128.93, 130.17, 130.98 (q, $J = 32.8$ Hz), 140.60. Anal. Calcd for $\text{C}_{25}\text{H}_{22}\text{F}_6\text{O}_3$: C, 61.98; H, 4.58. Found: C, 61.70; H, 4.71.

cis-Adamantane-2-spiro-3'-8'-(4'-chlorophenyl)-1',2',4'-trioxaspiro[4.5]decane

(OZ47). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4-(4-chlorophenyl)cyclohexanone (1.05 g, 5 mmol) in pentane (80 ml) and CH_2Cl_2 (20 ml) was treated with ozone according to the general procedure. The crude product was purified by

20 flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ47** (0.68 g, 36%) as a colorless solid. mp 122–124 °C (ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.60–2.18 (m, 22H), 2.40–2.60 (m, 1H), 7.05–7.30 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.59, 26.99, 31.43, 34.68, 34.86, 36.53, 36.89, 42.40, 108.22, 111.48, 128.12, 128.52, 131.84, 144.63. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{ClO}_3$: C, 70.48; H, 7.26. Found: C, 70.50; H, 7.38.

cis-Adamantane-2-spiro-3'-8'-[4'-(trifluoromethyl)phenyl]-1',2',4'-

trioxaspiro[4.5]decane (OZ48). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 4-[4-(trifluoromethyl)phenyl]cyclohexanone (1.21 g, 5 mmol) in pentane (90 ml) and CH_2Cl_2 (10 ml) was treated with ozone according to the general procedure. The

30 crude product was purified by flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ48** (0.96 g, 47%) as a colorless solid. mp 115–117 °C

(ethanol/H₂O 2:1); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.20 (m, 22H), 2.50–2.70 (m, 1H), 7.26–7.65 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.60, 27.01, 31.26, 34.64, 34.88, 36.56, 36.90, 42.91, 108.13, 111.57, 124.33 (q, J = 269.3 Hz), 125.38 (q, J = 3.8 Hz), 127.14, 128.67 (q, J = 32.8 Hz), 150.21. Anal. Calcd for C₂₃H₂₇F₃O₃: C, 67.63; H, 6.66.

5 Found: C, 67.41; H, 6.48.

Adamantane-2-spiro-3'-8'-acetyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ49).

A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1-acetyl-4-piperidone (0.71 g, 5 mmol) in pentane (60 ml) and CH₂Cl₂ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica

10 gel, ether) to afford trioxolane **OZ49** (0.22 g, 14%) as a colorless solid. mp 77–79 °C (ethanol/H₂O 1:2); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.05 (m, 18H), 2.11 (s, 3H), 3.45–3.70 (m, 3H), 3.72–3.86 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 21.22, 26.51, 26.91, 34.14, 34.74, 34.83, 35.00, 35.16, 36.44, 36.51, 36.76, 39.42, 44.15, 106.75, 112.26, 168.77. Anal. Calcd for C₁₇H₂₅NO₄: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.18; H, 7.96;

15 N, 4.47.

Adamantane-2-spiro-3'-1',2',4'-trioxa-8'-thiaspiro[4.5]decane 8',8'-dioxide

(**OZ50**). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1,1-dioxotetrahydrothiopyran-4-one (0.74 g, 5 mmol) in pentane (25 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified

20 by flash chromatography (silica gel, 50% ether in hexanes) to afford trioxolane **OZ50** (0.23 g, 15%) as a colorless solid. mp 128–129 °C (ethanol/H₂O 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.05 (m, 14H), 2.38 (t, J = 6.3 Hz, 4H), 3.10–3.30 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.36, 26.76, 32.31, 34.74, 34.84, 36.31, 36.59, 48.81, 104.97, 113.33. Anal. Calcd for C₁₅H₂₂O₅S: C, 57.30; H, 7.05. Found: C, 57.44; H, 6.97.

Adamantane-2-spiro-3'-8'-(*p*-toluenesulfonyl)-1',2',4'-trioxa-8'-

azaspiro[4.5]decane (OZ51). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1-(*p*-toluenesulfonyl)-4-piperidone (1.30 g, 5 mmol) in pentane (45 ml) and CH₂Cl₂ (25 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 25% ether in hexanes) to afford

30 trioxolane **OZ51** (0.33 g, 16%) as a colorless solid. mp 124–125 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.05 (m, 18H), 2.44 (s, 3H), 2.85–3.02 (m, 2H), 3.27–3.42 (m,

2H), 7.32 (d, $J = 8.3$ Hz, 2H), 7.64 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 21.47, 26.48, 26.87, 34.06, 34.76, 34.79, 36.42, 36.73, 44.26, 106.00, 112.34, 127.62, 129.71, 133.94, 143.60. Anal. Calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_5\text{S}$: C, 62.98; H, 6.97; N, 3.34. Found: C, 62.99; H, 6.88; N, 3.12.

5 **Adamantane-2-spiro-3'-5',5'-dibenzyl-1',2',4'-trioxolane (OZ52).** A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1,3-diphenylacetone (1.10 g, 5 mmol) in pentane (60 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 1% ether in hexanes) to afford trioxolane **OZ52** (1.10 g, 58%) as a colorless solid. mp 86–88 °C (ethanol/ H_2O 1:1);
 10 ^1H NMR (500 MHz, CDCl_3) δ 1.40–2.10 (m, 14H), 2.93 (d, $J = 4.2$ Hz, 2H), 3.04 (d, $J = 4.2$ Hz, 2H), 7.10–7.40 (m, 10H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.49, 26.93, 34.81, 34.90, 36.13, 36.80, 41.92, 110.37, 112.48, 126.58, 127.89, 130.89, 135.70. Anal. Calcd for $\text{C}_{25}\text{H}_{28}\text{O}_3$: C, 79.75; H, 7.50. Found: C, 79.57; H, 7.39.

Adamantane-2-spiro-3'-8'-[3'-(ethoxycarbonyl)propionyl]-1',2',4'-trioxa-8'-
 15 **azaspiro[4.5]decane (OZ53).** A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1-[3-(ethoxycarbonyl)propionyl]-4-piperidone (1.20 g, 5 mmol) in pentane (45 ml) and CH_2Cl_2 (15 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 25% ether in hexanes) to afford trioxolane **OZ53** (0.60 g, 30%) as a colorless solid. mp 116–117 °C (ethanol/ H_2O
 20 1:1); ^1H NMR (500 MHz, CDCl_3) δ 1.26 (t, $J = 7.1$ Hz, 3H), 1.60–2.10 (m, 18H), 2.55–2.75 (m, 4H), 3.45–3.70 (m, 3H), 3.72–3.87 (m, 1H), 4.15 (q, $J = 7.2$ Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 14.17, 26.50, 26.90, 27.84, 29.45, 34.17, 34.74, 34.98, 35.06, 36.48, 36.76, 39.81, 43.10, 60.51, 106.80, 112.26, 169.60, 173.02. Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.96; H, 7.81; N, 3.40.

25 **Adamantane-2-spiro-3'-8'-carboxymethoxyimino-1',2',4'-**
trioxaspiro[4.5]decane (OZ54). To a solution of **OZ05** (0.278 g, 1.0 mmol) in methanol (5 ml) were added pyridine (0.16 g, 2.0 mmol) and carboxymethoxylamine hemihydrochloride (0.262 g, 1.2 mmol). The reaction was stirred at room temperature for 4 h. After the solvent was removed in vacuo, the crude residue was acidified with 2 M HCl
 30 (25 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The combined extracts were dried over Na_2SO_4 and concentrated to give a residue that was triturated in hexanes to afford

trioxolane **OZ54** (0.30 g, 85%) as a colorless solid. mp 126–128 °C (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.10 (m, 18H), 2.33–2.50 (m, 2H), 2.59–2.70 (m, 1H), 2.72–2.90 (m, 1H), 4.62 (s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 22.08, 26.52, 26.92, 28.55, 32.54, 33.76, 34.80, 34.87, 34.92, 36.41, 36.79, 69.71, 107.77, 112.15, 160.04, 174.84.

5 Anal. Calcd for C₁₈H₂₅NO₆: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.48; H, 7.16; N, 3.84.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decan-8'-one

pyridinioacetylhydrazone chloride (OZ55). To a solution of **OZ05** (278 mg, 1 mmol) in ethanol (10 ml) and acetic acid (1 ml) was added Girard's reagent P (190 mg, 1 mmol). The mixture was stirred at 25 °C for 24 h. The solvent was removed in vacuo, and the residue

10 was purified by recrystallization from ether/methanol (95:5) to afford trioxolane **OZ55** (140 mg, 31%, 2:1 mixture of two tautomers) as a yellowish solid. mp 88–90 °C (ether/methanol 9:1); ¹H NMR (500 MHz, CD₃OD) δ 1.58–2.39 (m, 18H), 2.43–2.92 (m, 4H), 5.72 (s, minor isomer), 5.94 (s, major isomer), 8.10–8.28 (m, 2H), 8.61–8.78 (m, 1H), 8.90–9.14 (m, 2H); ¹³C NMR (125.7 MHz, CD₃OD) δ 21.36, 24.51, 25.72, 27.88, 28.29, 29.00, 29.08, 31.93, 32.59, 32.80, 32.87, 33.58, 33.68, 33.89, 34.83, 35.73, 35.77, 35.92, 36.63, 37.22, 37.72, 38.78, 39.02, 40.18, 40.25, 41.08, 61.72 (m), 62.77 (m), 108.80, 108.92, 113.21, 128.86, 129.00, 129.20, 147.46, 147.66, 157.71, 163.30, 167.86, 175.75. Anal. Calcd for C₂₃H₃₀ClN₃O₄•H₂O: C, 59.28; H, 6.92; N, 9.02. Found: C, 58.88; H, 7.24; N, 8.83.

20 **Adamantane-2-spiro-3'-8'-methanesulfonyl-1',2',4'-trioxa-8'-**

azaspiro[4.5]decane (OZ56). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1-methanesulfonyl-4-piperidone (0.90 g, 5.1 mmol) in pentane (50 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 20% ether in hexanes) to afford trioxolane **OZ56** (0.33 g, 19%) as a colorless solid. mp 146–148 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.08 (m, 18H), 2.81 (s, 3H), 3.26–3.34 (m, 2H), 3.38–3.47 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.50, 26.90, 34.28, 34.79, 34.87, 35.56, 36.47, 36.75, 44.07, 106.02, 112.48. Anal. Calcd for C₁₆H₂₅NO₅S: C, 55.95; H, 7.34; N, 4.08. Found: C, 56.06; H, 7.33; N, 3.91.

30 **Adamantane-2-spiro-3'-8'-(4'-chlorobenzenesulfonyl)-1',2',4'-trioxa-8'-**

azaspiro[4.5]decane (OZ57). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5

mmol) and 1-(4-chlorobenzenesulfonyl)-4-piperidone (1.37 g, 5 mmol) in pentane (25 ml) and CH₂Cl₂ (75 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 25% ether in hexanes) to afford trioxolane **OZ57** (0.19 g, 9%) as a colorless solid. mp 142–144 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.09 (m, 18H), 2.96–3.05 (m, 2H), 3.27–3.36 (m, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.45, 26.83, 34.05, 34.74, 34.78, 36.40, 36.70, 44.26, 105.79, 112.46, 128.93, 129.46, 135.55, 139.45. Anal. Calcd for C₂₁H₂₆ClNO₅S: C, 57.33; H, 5.96; N, 3.18. Found: C, 57.59; H, 6.00; N, 3.08.

Adamantane-2-spiro-3'-8'-(3'-carboxypropionyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ58). To a suspension of **OZ53** (500 mg, 1.27 mmol) in ethanol (5 ml) was added KOH (225 mg, 4 mmol) dissolved in water (5 ml). The mixture was heated at 50 °C for 4 h. Ethanol was removed in vacuo and the residue was washed with CH₂Cl₂ (2 x 10 ml). The aqueous layer was acidified to pH 2 with 3 M aq. HCl and extracted with CH₂Cl₂ (2 x 10 ml). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The residue was purified by recrystallization from ethanol to afford trioxolane **OZ58** (200 mg, 43%) as a colorless solid. mp 124–126 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.10 (m, 18H), 2.60–2.80 (m, 4H), 3.50–3.70 (m, 3H), 3.72–3.89 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.51, 26.90, 27.95, 29.57, 34.13, 34.75, 34.83, 35.00, 36.45, 36.50, 36.76, 40.04, 43.27, 106.62, 112.37, 170.20, 176.15. Anal. Calcd for C₁₉H₂₇NO₆: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.60; H, 7.53; N, 3.70.

Adamantane-2-spiro-3'-8'-(4'-methoxybenzenesulfonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ59). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5 mmol) and 1-(4-methoxybenzenesulfonyl)-4-piperidone (1.35 g, 5 mmol) in pentane (50 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 20% ether in hexanes) to afford trioxolane **OZ59** (0.40 g, 18%) as a colorless solid. mp 116–118 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.05 (m, 18H), 2.89–3.01 (m, 2H), 3.28–3.41 (m, 2H), 3.88 (s, 3H), 6.99 (d, J = 9.3 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.46, 26.85, 34.02, 34.74, 34.78, 36.40, 36.71, 44.27, 55.60, 105.99, 112.32, 114.32, 128.45,

129.68, 163.13. Anal. Calcd for $C_{22}H_{29}NO_6S$: C, 60.67; H, 6.71; N, 3.22. Found: C, 60.81; H, 6.79; N, 3.10.

Adamantane-2-spiro-3'-8'-benzenesulfonyl-1',2',4'-trioxa-8'-

azaspiro[4.5]decane (OZ60). A solution of *O*-methyl 2-adamantanone oxime (0.90 g, 5

5 mmol) and 1-benzenesulfonyl-4-piperidone (1.20 g, 5 mmol) in pentane (40 ml) and

CH_2Cl_2 (60 ml) was treated with ozone according to the general procedure. The crude

product was purified by flash chromatography (silica gel, 20% ether in hexanes) to afford

trioxolane **OZ60** (0.20 g, 10%) as a colorless solid. mp 130–132 °C (95% ethanol); ^1H

NMR (500 MHz, $CDCl_3$) δ 1.60–2.09 (m, 18H), 2.92–3.05 (m, 2H), 3.29–3.42 (m, 2H),

10 7.50–7.57 (m, 2H), 7.58–7.64 (m, 1H), 7.73–7.81 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$)

δ 26.46, 26.85, 34.07, 34.75, 34.79, 36.41, 36.72, 44.28, 105.95, 112.38, 127.55, 129.10,

132.79, 136.96. Anal. Calcd for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45. Found: C, 62.38;

H, 6.88; N, 3.44.

cis-Adamantane-2-spiro-3'-8'-ethoxycarbonylmethyl-1',2',4'-

15 **trioxaspiro[4.5]decane (OZ61).** A solution of *O*-methyl 2-adamantanone oxime (0.90 g,

5 mmol) and 4-(ethoxycarbonylmethyl)cyclohexanone (1.00 g, 5.4 mmol) in pentane (80

ml) and CH_2Cl_2 (20 ml) was treated with ozone according to the general procedure. The

crude product was purified by flash chromatography (silica gel, 2% ether in hexanes) to

afford trioxolane **OZ61** (0.35 g, 20%) as a colorless solid. mp 62–64 °C (95% ethanol); ^1H

20 NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 1.20–1.32 (m, 2H), 1.60–2.10 (m,

21H), 2.20 (d, J = 6.8 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ

14.23, 26.59, 26.99, 29.94, 33.24, 33.99, 34.84, 34.86, 36.50, 36.90, 40.92, 60.16, 108.48,

111.31, 172.67. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.62.

3,11-Diphenyl-7,14,15-trioxadispiro[5.1.5.2]pentadecane (OZ62). A solution of

25 *O*-methyl 4-phenylcyclohexanone oxime (1.02 g, 5 mmol) and 4-phenylcyclohexanone

(0.87 g, 5 mmol) in pentane (90 ml) and CH_2Cl_2 (10 ml) was treated with ozone according

to the general procedure. The crude product was purified by flash chromatography (silica

gel, 2% ether in hexanes) to afford trioxolane **OZ62** (0.45 g, 25%, 1:1 mixture of two

diastereomers) as a colorless solid. mp 136–138 °C (95% ethanol); ^1H NMR (500 MHz,

30 $CDCl_3$) δ 1.65–2.20 (m, 16H), 2.52–2.62 (m, 2H), 7.16–7.35 (m, 10H); ^{13}C NMR (125.7

MHz, $CDCl_3$) δ 31.14, 31.46, 34.53, 34.64, 42.99, 43.27, 108.43, 108.86, 126.19, 126.79,

126.86, 128.39, 128.41, 146.08, 146.11. Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74.

Found: C, 79.22; H, 7.68.

Adamantane-2-spiro-3'-8'-cyano-8'-phenyl-1',2',4'-trioxaspiro[4.5]decane

(OZ63). A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 4-cyano-4-phenylcyclohexanone (2.00 g, 10 mmol) in pentane (60 ml) and CH_2Cl_2 (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ63** (1.85 g, 51%) as a colorless solid. mp 137–138 °C (ethanol/ H_2O 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–2.38 (m, 22H), 7.25–7.55 (m, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.55, 26.92, 31.92, 34.84, 34.89, 36.53, 36.81, 43.21, 106.90, 112.14, 121.71, 125.53, 128.13, 129.02, 139.88. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.46; H, 7.39; N, 3.86.

***cis*-Adamantane-2-spiro-3'-8'-neopentyloxycarbonyl-1',2',4'-trioxaspiro[4.5]decane**

(OZ64). A solution of *O*-methyl 2-adamantanone oxime (0.54 g, 3 mmol) and 4-(neopentyloxycarbonyl)cyclohexanone (0.64 g, 3 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 4% ether in petroleum ether) to afford trioxolane **OZ64** (0.70 g, 62%, 4:1 mixture of two diastereomers). Recrystallization from 95% ethanol gave the analytically pure *cis*-isomer (0.20 g, 18%) as a colorless solid. mp 84–86 °C (95% ethanol); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.60–2.10 (m, 22H), 2.32–2.44 (m, 1H), 3.76 (s, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.32, 26.45, 26.57, 26.98, 31.41, 33.42, 34.83, 34.88, 36.50, 36.87, 41.69, 73.70, 107.98, 111.54, 174.76. Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.00; H, 8.98.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane-8'-yl sodium sulfate

(OZ65). A mixture of **OZ32** (0.42 g, 1.5 mmol), sulfur trioxide pyridine complex (0.60 g, 3.8 mmol), pyridine (0.75 ml), and acetic anhydride (0.75 ml) was heated at 50 °C with stirring for 30 min. The reaction mixture was cooled to room temperature, diluted with petroleum ether (30 ml), and kept at –20 °C overnight. The precipitate was collected by filtration, washed with petroleum ether/benzene (5:1), and dried in a vacuum oven. The dried solid residue was dissolved in chloroform (12 ml), cooled in an ice bath, and filtered to remove the insoluble sulfur trioxide pyridine complex. The filtrate was concentrated to

afford the pyridinium sulfate of **OZ32** (0.65 g, 100%). To a suspension of the above pyridinium salt (0.50 g) in water (6 ml) was added 10 % aqueous sodium carbonate (6 ml) while shaking. The mixture was kept at $-20\text{ }^{\circ}\text{C}$ for 4 h. The precipitate was filtered, washed with cold water (2 ml), and dried in a vacuum oven to give trioxolane **OZ65** (0.35 g, 61%,
 5 2:1 mixture of two diastereomers) as a colorless solid. mp $154\text{ }^{\circ}\text{C}$ dec (water); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 1.50–2.02 (m, 22H), 4.12–4.22 (m, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 25.88, 26.28, 28.84, 29.24, 30.26, 30.68, 34.30, 34.36, 35.78, 35.89, 36.17, 70.66, 71.08, 108.05, 108.09, 110.68, 110.72. Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{NaO}_7\text{S}\cdot\text{H}_2\text{O}$: C, 47.99; H, 6.29. Found: C, 47.67; H, 6.59.

10 **3,3-Bis(4-fluorophenyl)-8-phenyl-1,2,4-trioxaspiro[4.5]decane (OZ66).** A solution of *O*-methyl 4-phenylcyclohexanone oxime (1.02 g, 5 mmol) and 4,4'-difluorobenzophenone (1.09 g, 5 mmol) in pentane (90 ml) and CH_2Cl_2 (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 3% ether in petroleum ether) to afford trioxolane **OZ66** (0.56 g,
 15 27%, 3:1 mixture of two diastereomers) as a colorless solid. mp $87\text{--}90\text{ }^{\circ}\text{C}$ (ethanol/ H_2O 2.5:1); ^1H NMR (500 MHz, CDCl_3) δ 1.60–2.15 (m, 8H), 2.51–2.70 (m, 1H), 6.99–7.09 (m, 4H), 7.16–7.36 (m, 5H), 7.44–7.53 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 31.23, 31.34, 34.20, 34.48, 42.85, 43.01, 108.84, 109.29, 111.20, 111.29, 115.15 (d, $J = 21.4\text{ Hz}$), 115.18 (d, $J = 21.4\text{ Hz}$), 126.29, 126.33, 126.74, 126.83, 128.47, 128.95 (d, $J = 8.4\text{ Hz}$),
 20 129.01 (d, $J = 6.1\text{ Hz}$), 135.33, 135.36, 145.74, 145.79, 163.05 (d, $J = 248.0\text{ Hz}$). Anal. Calcd for $\text{C}_{25}\text{H}_{22}\text{F}_2\text{O}_3$: C, 73.52; H, 5.43. Found: C, 73.53; H, 5.51.

cis-Bicyclo[3.3.1]nonane-9-spiro-3'-8'-phenyl-1',2',4'-trioxaspiro[4.5]decane (OZ67). A solution of *O*-methyl bicyclo[3.3.1]nonan-9-one oxime (0.84 g, 5 mmol) and 4-phenylcyclohexanone (0.87 g, 5 mmol) in pentane (80 ml) and CH_2Cl_2 (20 ml) was treated
 25 with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 3% ether in petroleum ether) to afford trioxolane **OZ67** (0.54 g, 33%) as a colorless solid. mp $120\text{--}122\text{ }^{\circ}\text{C}$ (ethanol/ H_2O 4:1); ^1H NMR (500 MHz, CDCl_3) δ 1.41–1.60 (m, 2H), 1.61–2.20 (m, 20H), 2.49–2.60 (m, 1H), 7.14–7.35 (m, 5H); ^{13}C
 NMR (125.7 MHz, CDCl_3) δ 20.51, 20.93, 29.47, 29.68, 31.49, 34.88, 36.44, 43.05,
 30 108.32, 111.35, 126.16, 126.78, 128.40, 146.22. Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_3$: C, 76.79; H, 8.59. Found: C, 76.90; H, 8.39.

Bicyclo[3.3.1]nonane-9-spiro-3'-11',11'-dimethyl-1',2',4',9',13'-pentaoxadispiro[4.2.5.2]pentadecane (OZ68). A solution of *O*-methyl bicyclo[3.3.1]nonan-9-one oxime (0.84 g, 5 mmol) and 3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one (0.99 g, 5 mmol) in pentane (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) to afford trioxolane **OZ68** (0.72 g, 41%) as a colorless solid. mp 122–124 °C (ethanol/H₂O 5:1); ¹H NMR (500 MHz, CDCl₃) δ 0.97 (s, 6H), 1.40–1.56 (m, 2H), 1.62–2.16 (m, 20H), 3.49 (s, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 20.48, 20.91, 22.71, 29.40, 29.54, 29.73, 30.21, 30.64, 36.34, 70.30, 70.33, 96.76, 108.46, 111.50. Anal. Calcd for C₂₀H₃₂O₅: C, 68.15; H, 9.15. Found: C, 68.25; H, 9.06.

Adamantane-2-spiro-3'-8'-acetoxy-8'-(4'-fluorophenyl)-1',2',4'-trioxaspiro[4.5]decane (OZ69). A solution of *O*-methyl 2-adamantanone oxime (0.36 g, 2 mmol) and 4-acetoxy-4-(4-fluorophenyl)cyclohexanone (0.50 g, 2 mmol) in pentane (100 ml) and CH₂Cl₂ (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) to afford trioxolane **OZ69** (0.44 g, 53%) as a colorless solid. mp 147–149 °C (ethanol/H₂O 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.19 (m, 20H), 2.07 (s, 3H), 2.53 (apparent d, J = 12.2 Hz, 2H), 6.96–7.04 (m, 2H), 7.27–7.33 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 21.93, 26.57, 26.98, 30.31, 33.71, 34.86, 34.88, 36.51, 36.87, 80.67, 107.76, 111.82, 115.20 (d, J = 21.4 Hz), 128.30 (d, J = 8.4 Hz), 139.92 (d, J = 3.1 Hz), 161.95 (d, J = 245.7 Hz), 169.43. Anal. Calcd for C₂₄H₂₉FO₅: C, 69.21; H, 7.02. Found: C, 68.98; H, 7.09.

Adamantane-2-spiro-3'-8'-ethoxycarbonyl-1',2',4'-trioxaspiro[4.5]decane (OZ70). A solution of *O*-methyl 2-adamantanone oxime (3.58 g, 20 mmol) and 4-(ethoxycarbonyl)cyclohexanone (3.40 g, 20 mmol) in pentane (160 ml) and CH₂Cl₂ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) to afford trioxolane **OZ70** (3.10 g, 46%, 2.5:1 mixture of two diastereomers) as a colorless oil. Two analytically pure diastereomers were obtained by subsequent flash chromatography (silica gel, 3% ether in petroleum ether). For the *trans*-isomer (minor): yield, 9%; colorless oil; ¹H

NMR (500 MHz, CDCl₃) δ 1.26 (t, J = 7.1 Hz, 3H), 1.58–2.10 (m, 22H), 2.34 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 14.15, 25.99, 26.50, 26.90, 33.10, 34.72, 34.84, 36.41, 36.79, 41.15, 60.20, 107.93, 111.66, 174.74. For the *cis*-isomer (major): yield, 14%; colorless solid; mp 38–39 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.25 (t, J = 7.1 Hz, 3H), 1.58–2.10 (m, 22H), 2.32 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 14.13, 26.18, 26.51, 26.92, 33.31, 34.76, 34.81, 36.42, 36.81, 41.38, 60.22, 107.90, 111.40, 174.70. Anal. Calcd for C₁₉H₂₈O₅: C, 67.83; H, 8.39. Found: C, 68.06; H, 8.50.

***trans*-Adamantane-2-spiro-3'-8'-carboxy-1',2',4'-trioxaspiro[4.5]decane**

10 **(OZ71)**. A mixture of *trans*-OZ70 (0.34 g, 1 mmol), methanol (10 ml), and KOH (0.2 g) dissolved in water (1.2 ml) was heated at 50 °C for 1.5 h and then cooled to rt. The reaction mixture was acidified with conc. HCl (0.5 ml) and cooled to –20 °C. The precipitate was filtered and washed with cold ethanol/H₂O (1:1). The filtrate was diluted with water and extracted with chloroform (2 x 10 ml). The combined organic layers were dried over
15 MgSO₄, filtered, and concentrated in vacuo. Recrystallization of the combined solids from ethanol/H₂O (1:1) afforded trioxolane OZ71 (0.25 g, 81%) as a colorless solid. mp 158–159 °C (ethanol/H₂O 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.58–2.12 (m, 22H), 2.42 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 25.84, 26.54, 26.94, 33.02, 34.79, 34.92, 36.46, 36.84, 40.78, 107.86, 111.85, 180.61. Anal. Calcd for C₁₇H₂₄O₅: C, 66.21; H, 7.84. Found:
20 C, 66.12; H, 7.60.

***cis*-Adamantane-2-spiro-3'-8'-carboxy-1',2',4'-trioxaspiro[4.5]decane (OZ72).**

A mixture of *cis*-OZ70 (0.40 g, 1.2 mmol), methanol (12 ml), and KOH (0.2 g) dissolved in water (1.2 ml) was heated at 50 °C for 1.5 h and then cooled to rt. The reaction mixture was acidified with conc. HCl (0.6 ml) and cooled at –20 °C. The precipitate was filtered
25 and washed with cold ethanol/H₂O (1:1). The filtrate was diluted with water and extracted with chloroform (2 x 10 ml). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. Recrystallization of the combined solids from ethanol/H₂O (1:1) afforded trioxolane OZ72 (0.33 g, 89%) as a colorless solid. mp 148–150 °C (ethanol/H₂O 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.59–2.10 (m, 22H), 2.38 (m,
30 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.00, 26.55, 26.96, 33.25, 34.82, 34.87, 36.47,

36.85, 40.99, 107.80, 111.58, 180.51. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.13; H, 7.68.

***cis*-Adamantane-2-spiro-3'-8'-diethylaminocarbonyl-1',2',4'-**

trioxaspiro[4.5]decane (OZ73). A solution of *O*-methyl 2-adamantanone oxime (1.43 g, 8 mmol) and *N,N*-diethyl-4-oxo-cyclohexanecarboxamide (1.61 g, 8 mmol) in pentane (100 ml) and CH_2Cl_2 (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10 to 35% ether in hexanes) to afford trioxolane **OZ73** (1.00 g, 34%). Recrystallization from hexanes/ CH_2Cl_2 (9:1) gave the analytically pure *cis*-isomer (0.60 g, 21%) as a colorless solid. mp 115–117 °C (hexanes/ CH_2Cl_2 9:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, J = 7.3 Hz, 3H), 1.19 (t, J = 7.3 Hz, 3H), 1.60–2.14 (m, 22H), 2.36–2.46 (m, 1H), 3.32 (q, J = 7.3 Hz, 2H), 3.36 (q, J = 7.3 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.09, 14.95, 26.53, 26.96, 27.08, 33.81, 34.78, 34.85, 36.45, 36.85, 39.16, 40.08, 41.74 107.92, 111.21, 174.14. Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.17; H, 9.03; N, 3.80.

Adamantane-2-spiro-3'-8'-benzoyloxy-1',2',4'-trioxaspiro[4.5]decane (OZ74).

A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and 4-benzoyloxycyclohexanone (2.18 g, 10 mmol) in pentane (120 ml) and CH_2Cl_2 (30 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 6% ether in petroleum ether) to afford trioxolane **OZ74** (2.00 g, 52%, 2:1 mixture of two diastereomers) as a colorless solid. mp 103–106 °C (95% ethanol); ^1H NMR (500 MHz, $CDCl_3$) δ 1.59–2.18 (m, 22H), 5.12–5.21 (m, 1H), 7.40–7.48 (m, 2H), 7.52–7.61 (m, 1H), 8.01–8.09 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.57, 26.99, 28.23, 28.50, 30.62, 31.01, 34.84, 34.92, 34.94, 36.45, 36.53, 36.87, 69.91, 70.45, 107.88, 107.98, 111.74, 111.80, 128.33, 129.57, 130.75, 130.80, 132.83, 165.84, 165.91. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.65; H, 7.45.

Adamantane-2-spiro-3'-8'-cyano-8'-(3',4'-dichlorophenyl)-1',2',4'-

trioxaspiro[4.5]decane (OZ75). A solution of *O*-methyl 2-adamantanone oxime (0.85 g, 4.7 mmol) and 4-cyano-4-(3,4-dichlorophenyl)cyclohexanone (1.30 g, 4.7 mmol) in pentane (50 ml) and CH_2Cl_2 (70 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 8% ether in hexanes) to afford trioxolane **OZ75** (0.62 g, 30%) as a colorless solid. mp 143–145 °C

(ethanol/H₂O 4:1); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.33 (m, 22H), 7.33 (dd, J = 8.3, 2.4 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.52, 26.90, 31.78, 34.84, 34.87, 36.52, 36.78, 42.75, 106.54, 112.38, 120.85, 125.00, 127.87, 130.99, 132.63, 133.42, 140.09. Anal. Calcd for C₂₃H₂₅Cl₂NO₃: C, 63.60; H, 5.80; N, 3.22. Found: C, 63.70; H, 5.80; N, 3.22.

Adamantane-2-spiro-3'-8'-(4'-fluorophenyl)-8'-hydroxy-1',2',4'-trioxaspiro[4.5]decane (OZ76). A mixture of **OZ69** (2.40 g, 5.76 mmol), methanol (56 ml), and 17 % aq. KOH (5.6 ml) was heated at 50 °C for 2 h. The reaction mixture was cooled to rt, concentrated to 10 ml, diluted with water (40 ml), and extracted with
 10 chloroform (40 ml × 3). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo. The residue was purified by crystallization from ethanol/H₂O (1:1) to give **OZ76** (1.87 g, 87%) as a colorless solid. mp 122–124 °C (ethanol/H₂O 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.18 (m, 20H), 2.25 (td, J = 13.7, 4.4 Hz, 2H), 6.98–7.14 (m, 2H), 7.38–7.56 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.54, 26.94, 30.25, 34.84,
 15 36.49, 36.53, 36.84, 71.85, 108.22, 111.62, 115.02 (d, J = 21.1 Hz), 126.17 (d, J = 7.8 Hz), 144.03 (d, J = 3.2 Hz), 161.87 (d, J = 245.4 Hz). Anal. Calcd for C₂₂H₂₇FO₄: C, 70.57; H, 7.27. Found: C, 70.37; H, 7.27.

Adamantane-2-spiro-3'-8'-(4'-fluorophenyl)-8'-methoxy-1',2',4'-trioxaspiro[4.5]decane (OZ77). A solution of *O*-methyl 2-adamantanone oxime (0.63 g, 3.5 mmol) and 4-(4-fluorophenyl)-4-methoxycyclohexanone (0.78 g, 3.5 mmol) in pentane
 20 (100 ml) and CH₂Cl₂ (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ77** (0.34 g, 25%) as a colorless solid. mp 121–123 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.27 (m, 22H), 2.97 (s, 3H), 6.97–7.14 (m,
 25 2H), 7.30–7.45 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.58, 26.98, 30.04, 32.80, 34.86, 34.88, 36.52, 36.88, 49.89, 75.82, 108.38, 111.51, 115.08 (d, J = 21.1 Hz), 127.66 (d, J = 7.8 Hz), 140.33, 161.98 (d, J = 245.5 Hz). Anal. Calcd for C₂₃H₂₉FO₄: C, 71.11; H, 7.52. Found: C, 70.90; H, 7.50.

cis-Adamantane-2-spiro-3'-8'-carboxymethyl-1',2',4'-trioxaspiro[4.5]decane (OZ78). To a solution of **OZ61** (998 mg, 2.85 mmol) in 95% ethanol (10 ml) was added
 30 15% aq. NaOH (10 ml). The mixture was heated at 60–65 °C for 2 h, cooled to rt, and

acidified with 6 M HCl (10 ml). The suspension was kept at 0–5 °C for 1 h and filtered.

Recrystallization of the solid from 95% ethanol afforded trioxolane **OZ78** (700 mg, 76%)

as a colorless solid. mp 146–148 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.19–

1.41 (m, 2H), 1.60–2.05 (m, 21H), 2.27 (d, J = 6.8 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃)

5 δ 26.58, 26.97, 29.91, 33.00, 33.95, 34.86, 36.49, 36.89, 40.39, 108.38, 111.40, 177.75.

Anal. Calcd for C₁₈H₂₆O₅: C, 67.06; H, 8.13. Found: C, 67.20; H, 8.13.

Adamantane-2-spiro-3'-8'-ethanesulfonyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ79). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5.0 mmol) and 1-

ethanesulfonyl-4-piperidone (955 mg, 5.0 mmol) in pentane (50 ml) and CH₂Cl₂ (50 ml)

10 was treated with ozone according to the general procedure. The crude product was purified

by flash chromatography (silica gel, 20% ether in hexanes) to afford trioxolane **OZ79** (700

mg, 39%) as a colorless solid. mp 110–112 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ

1.37 (t, J = 7.3 Hz, 3H), 1.62–2.08 (m, 18H), 2.97 (q, J = 7.5 Hz, 2H), 3.28–3.41 (m, 2H),

3.43–3.56 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 7.91, 26.48, 26.88, 34.70, 34.78,

15 34.86, 36.46, 36.74, 44.00, 44.85, 106.20, 112.40. Anal. Calcd for C₁₇H₂₇NO₅S: C, 57.12;

H, 7.61; N, 3.92. Found: C, 56.94; H, 7.52; N, 3.89.

Adamantane-2-spiro-3'-1',2',4'-trioxa-8'-azaspiro[4.5]decane hydrochloride (OZ80). To a solution of **OZ35** (1.41 g, 3.86 mmol) in ether (10 ml) was added 1 M

ethereal HCl (40 ml). The mixture was stirred at rt for 16 h, and the resulting precipitate

20 was filtered and washed with ether (2 x 5 ml) to afford trioxolane **OZ80** (400 mg, 34%) as

a colorless solid. mp 138–140 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.61–2.05 (m,

14H), 2.19 (br s, 4H), 2.34 (br s, 4H), 9.72 (br s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ

26.37, 26.74, 31.35, 34.70, 34.79, 36.32, 36.60, 42.31, 104.12, 113.08. Anal. Calcd for

C₁₅H₂₄ClNO₃: C, 59.69; H, 8.02; N, 4.64. Found: C, 59.78; H, 7.89; N, 4.70.

25 **Adamantane-2-spiro-3'-5',5'-bis(2'-pyridyl)-1',2',4'-trioxolane (OZ81).** A

solution of *O*-methyl 2-adamantanone oxime (716 g, 4.0 mmol) and di-2-pyridyl ketone

(777 mg, 4.2 mmol) in pentane (70 ml) and CH₂Cl₂ (30 ml) was treated with ozone

according to the general procedure. The crude product was purified by flash

chromatography (silica gel, 4% ethanol in ether) to afford trioxolane **OZ81** (620 mg, 44%)

30 as a colorless solid. mp 135–136 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.10 (m,

12H), 2.27 (d, J = 12 Hz, 2H), 7.21 (ddd, J = 8.5, 5.0, 1.0 Hz, 2H), 7.76 (ddd, J = 8.0, 8.0,

2.0 Hz, 2H), 7.95 (d, $J = 8.0$ Hz, 2H), 8.55 (dd, $J = 4.5, 1.0$ Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.50, 26.86, 34.81, 34.88, 35.93, 36.74, 107.92, 114.58, 121.16, 123.16, 136.38, 149.12, 158.20. Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.94; H, 6.30; N, 7.91. The reaction using 2 equiv of the ketone under the same conditions
 5 gave after purification the **OZ81** (680 mg, 49%).

Adamantane-2-spiro-3'-8'-acetoxyacetyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ82). A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 1-acetoxyacetyl-4-piperidone (3.82 g, 20 mmol) in pentane (50 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by
 10 flash chromatography (silica gel, 80% ether in heaxanes) to afford trioxolane **OZ82** (1.82 g, 50%) as a colorless solid. mp 112–114 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.62–2.06 (m, 18H), 2.19 (s, 3H), 3.39–3.55 (m, 2H), 3.60–3.69 (m, 1H), 3.73–3.87 (m, 1H), 4.73 (AB system, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 20.54, 26.46, 26.85, 34.00, 34.76, 34.96, 36.43, 36.71, 40.06, 42.41, 61.27, 106.49, 112.41, 164.85, 170.43. Anal. Calcd for
 15 $\text{C}_{19}\text{H}_{27}\text{NO}_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.20; H, 7.48; N, 3.84.

Adamantane-2-spiro-3'-8'-hydroxyacetyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ83). To a solution of **OZ82** (600 mg, 1.64 mmol) in THF (5 ml) were added water (3 ml) and 15% aq. NaOH (3 ml). The mixture was stirred at rt for 16 h and extracted with CH_2Cl_2 (3 x 10 ml). The combined extracts were dried over MgSO_4 and concentrated.
 20 Crystallization of the residue from methanol to afford trioxolane **OZ83** (360 mg, 68%) as a colorless solid. mp 152–154 °C (methanol); ^1H NMR (500 MHz, CDCl_3) δ 1.61–2.07 (m, 18H), 3.28–3.43 (m, 2H), 3.64–3.79 (m, 1H), 3.80–3.91 (m, 1H), 4.18 (d, $J = 4.4$ Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.43, 26.83, 33.99, 34.71, 34.79, 34.95, 36.38, 36.43, 36.68, 40.39, 41.22, 59.69, 106.37, 112.49, 170.03. Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_5$: C, 63.14;
 25 H, 7.79; N, 4.33. Found: C, 63.20; H, 7.85; N, 4.26.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-1''-3'',4''-dihydro-2''H-naphthalene (OZ84). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and α -tetralone (710 mg, 5 mmol) in pentane (90 ml) and CH_2Cl_2 (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash
 30 chromatography (silica gel, 1% ether in hexanes) to afford trioxolane **OZ84** (360 mg, 23%) as a colorless solid. mp 90–92 °C (methanol/ether 9:1); ^1H NMR (500 MHz, CDCl_3) δ

1.64–2.22 (m, 16H), 2.37–3.53 (m, 2H), 2.72–3.89 (m, 2H), 7.12 (d, $J = 7.3$ Hz, 1H), 7.19–7.35 (m, 2H), 7.65 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 20.63, 26.65, 27.09, 29.24, 34.09, 34.14, 34.99, 35.00, 35.78, 36.43, 37.00, 37.22, 107.73, 112.40, 126.23, 127.97, 128.69, 129.36, 131.93, 140.70. Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3$: C, 76.89; H, 7.74. Found: C, 76.77; H, 8.00.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-2''-3'',4''-dihydro-1''H-naphthalene (OZ85). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and β -tetralone (710 mg, 5 mmol) in pentane (90 ml) and CH_2Cl_2 (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in hexanes) to afford trioxolane **OZ85** (400 mg, 26%) as a colorless solid. mp 64–66 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.62–2.18 (m, 16H), 2.96 (t, $J = 6.6$ Hz, 2H), 3.12 (AB system, 2H), 7.02–7.21 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.59, 26.97, 27.72, 31.78, 34.78, 34.83, 34.86, 34.99, 36.53, 36.55, 36.88, 38.19, 108.44, 112.02, 125.95, 126.10, 128.32, 129.08, 133.89, 135.51. Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3$: C, 76.89; H, 7.74. Found: C, 76.77; H, 7.61.

Adamantane-2-spiro-3'-8'-(4'-fluorobenzenesulfonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ86). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 1-(4-fluorobenzenesulfonyl)-4-piperidone (1.22 g, 5 mmol) in pentane (50 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 25% ether in hexanes) to afford trioxolane **OZ86** (450 mg, 21%) as a colorless solid. mp 122–124 °C (95% ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.60–2.05 (m, 18H), 2.92–3.06 (m, 2H), 3.25–3.38 (m, 2H), 7.16–7.28 (m, 2H), 7.74–7.84 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.46, 26.85, 34.05, 34.76, 34.80, 36.42, 36.71, 44.29, 105.83, 112.46, 116.39 (d, $J = 22.9$ Hz), 130.23 (d, $J = 9.2$ Hz), 133.03, 165.30 (d, $J = 254.8$ Hz). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{FNO}_5\text{S}$: C, 59.56; H, 6.19; N, 3.31. Found: C, 59.75; H, 6.40; N, 3.27.

Adamantane-2-spiro-3'-8'-chloroacetyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ87). A solution of *O*-methyl 2-adamantanone oxime (2.01 g, 11.17 mmol) and 1-chloroacetyl-4-piperidone (3.02 g, 17.09 mmol) in pentane (50 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 25% ether in heaxanes) to afford trioxolane **OZ87** (1.60

g, 42%) as a colorless solid. mp 112–114 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.10 (m, 18H), 3.51–3.72 (m, 3H), 3.74–3.88 (m, 1H), 4.07 (AB system, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.43, 26.82, 33.96, 34.72, 34.92, 36.41, 36.68, 40.24, 40.83, 40.88, 40.94, 44.15, 50.73, 106.43, 112.38, 164.98. Anal. Calcd for C₁₇H₂₄ClNO₄: C, 59.73; H, 7.08; N, 4.10. Found: C, 59.60; H, 7.23; N, 4.06.

***cis*-Adamantane-2-spiro-3'-8'-[2'-(4'-nitrobenzoyloxy)ethyl]-1',2',4'-trioxaspiro[4.5]decane (OZ88).** A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 4-[2-(4-nitrophenoxy)ethyl]cyclohexanone (1.45 g, 5 mmol) in pentane (80 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in petroleum ether) to afford trioxolane **OZ88** (1.10 g, 48%) as a colorless solid. mp 124–126 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.22–1.39 (m, 2H), 1.41–1.58 (m, 2H), 1.62–2.11 (m, 21H), 4.41 (t, J = 6.6 Hz, 2H), 8.19 (d, J = 8.3 Hz, 2H), 8.28 (d, J = 8.8 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.58, 26.98, 30.05, 33.42, 34.12, 34.85, 36.52, 36.89, 64.26, 108.61, 111.40, 123.55, 130.67, 135.84, 150.67, 164.71. Anal. Calcd for C₂₅H₃₁NO₇: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.76; H, 6.90; N, 3.18.

***cis*-Adamantane-2-spiro-3'-8'-(2'-hydroxyethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ89).** To a solution of **OZ88** (610 mg, 1.33 mmol) in THF (10 ml) at rt was added NaOH solution (400 mg, 10 mmol) in water (5 ml). The mixture was stirred at rt for 6 h, concentrated, and extracted with CH₂Cl₂ (2 x 20 ml). The organic layers were combined, washed with water (10 ml) and brine (10 ml), dried over MgSO₄, and evaporated. The residue was recrystallized from ethanol/water (2:1) to give trioxolane **OZ89** (220 mg, 54%) as a colorless solid. mp 88–90 °C (ethanol/water 2:1); ¹H NMR (500 MHz, CDCl₃) δ 1.09–2.15 (m, 25H), 3.61–3.79 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.58, 26.97, 30.15, 32.72, 34.20, 34.84, 34.86, 36.49, 36.89, 39.12, 60.85, 108.89, 111.25. Anal. Calcd for C₁₈H₂₈O₄: C, 70.10; H, 9.15. Found: C, 70.24; H, 9.24.

Adamantane-2-spiro-3'-8'-hydroxy-8'-methyl-1',2',4'-trioxaspiro[4.5]decane (OZ90). To a solution of methyllithium (1.85 ml, 1.4 M in ether, 2.4 mmol) and lithium perchlorate (0.26 g, 2.4 mmol) in THF (2 ml) at –78 °C was added a solution of **OZ05** (556 mg, 2 mmol) in THF (20 ml). The reaction was stirred at –78 °C for 2 h before being quenched with methanol (2 ml). The mixture was allowed to warm up to rt and

concentrated in vacuo. The residue was dissolved in CH₂Cl₂ and washed with 1 M HCl (20 ml), water (20 ml), and brine (20 ml). The organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 25% ether in petroleum ether) to afford trioxolane **OZ90** (215 mg, 37%, 1.4:1 mixture of two diastereomers) as a colorless solid. mp 91–94 °C (hexanes/CH₂Cl₂ 9:1); ¹H NMR (500 MHz, CDCl₃) δ 1.29 (s, 3H), 1.60–2.12 (m, 22H) assigned to the major isomer; 1.25 (s, 3H), 1.60–2.12 (m, 22H) assigned to the minor isomer; ¹³C NMR (125.7 MHz, CDCl₃) δ 26.54, 26.56, 26.95, 26.97, 29.37, 30.05, 30.31, 30.54, 34.79, 34.83, 34.87, 34.96, 36.44, 36.46, 36.49, 36.73, 36.86, 68.57, 68.96, 108.52, 108.57, 111.42, 111.51. Anal. Calcd for C₁₇H₂₆O₄: C, 69.36; H, 8.90. Found: C, 69.19; H, 8.82.

Adamantane-2-spiro-3'-8'-[(1'S)-10'-camphorsulfonyl]-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ91). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 1-[(1*S*)-10-camphorsulfonyl]-4-piperidone (1.56 g, 4.98 mmol) in pentane (50 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 30% ether in hexanes) to afford trioxolane **OZ91** (860 mg, 36%) as a colorless solid. mp 72–74 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 0.88 (s, 3H), 1.13 (s, 3H), 1.38–1.51 (m, 1H), 1.55–2.21 (m, 22H), 2.32–2.46 (m, 1H), 2.47–2.61 (m, 1H), 2.76 (d, *J* = 14.6 Hz, 1H), 3.35 (d, *J* = 14.6 Hz, 1H), 3.34–3.59 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 19.72, 19.94, 25.12, 26.46, 26.84, 26.89, 34.49, 34.72, 34.80, 36.40, 36.71, 42.54, 42.91, 43.84, 43.86, 45.84, 47.82, 58.25, 106.16, 112.26, 214.78. Anal. Calcd for C₂₅H₃₇NO₆S: C, 62.60; H, 7.78; N, 2.92. Found: C, 62.80; H, 7.60; N, 2.92.

Adamantane-2-spiro-3'-8'-(1'-butanesulfonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ92). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 1-(1-butanesulfonyl)-4-piperidone (1.12 g, 5.11 mmol) in pentane (50 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 30% ether in hexanes) to afford trioxolane **OZ92** (700 mg, 36%) as a colorless solid. mp 62–64 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 0.95 (t, *J* = 7.6 Hz, 3H), 1.32–1.57 (m, 2H), 1.59–2.21 (m, 20H), 2.81–3.02 (m, 2H), 3.22–3.59 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 13.48, 21.68,

25.24, 26.50, 26.90, 34.67, 34.78, 34.87, 36.48, 36.75, 43.94, 50.09, 106.20, 112.38. Anal. Calcd for $C_{19}H_{31}NO_5S$: C, 59.19; H, 8.10; N, 3.63. Found: C, 59.38; H, 7.99; N, 3.45.

Adamantane-2-spiro-3'-8'-(phthalimidoacetyl)-1',2',4'-trioxa-8'-

azaspiro[4.5]decane (OZ93). To a solution of **OZ87** (342 mg, 1 mmol) in acetonitrile (10 ml) was added potassium phthalimide (200 mg, 1.08 mmol). The reaction solution was heated at 60–65 °C for 36 h and cooled to rt. The solvent was removed by evaporation, and the residue was triturated with water (20 ml) and filtered. Recrystallization of the solid from methanol gave trioxolane **OZ93** (379 mg, 84%) as a colorless solid. mp 152–154 °C (methanol); ^1H NMR (500 MHz, $CDCl_3$) δ 1.59–2.11 (m, 18H), 3.45–3.71 (m, 3H), 3.72–3.89 (m, 1H), 4.51 (s, 2H), 7.65–7.79 (m, 2H), 7.82–7.97 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.47, 26.86, 33.94, 34.75, 36.44, 36.72, 38.96, 40.38, 42.62, 106.49, 112.36, 123.43, 132.38, 133.93, 163.88, 167.87. Anal. Calcd for $C_{25}H_{28}N_2O_6$: C, 66.36; H, 6.24; N, 6.19. Found: C, 66.19; H, 6.07; N, 6.19.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-9''-fluorene (OZ94). A

solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 9-fluorenone (1.80 g, 10 mmol) in pentane (80 ml) and CH_2Cl_2 (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 1% ether in hexanes) to afford trioxolane **OZ94** (650 mg, 38%) as a colorless solid. mp 150–152 °C (methanol/ether 9:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.62–2.25 (m, 12H), 2.47 (s, 2H), 7.27 (dd, $J = 7.6, 7.6$ Hz, 2H), 7.38 (dd, $J = 7.6, 7.6$ Hz, 2H), 7.53 (d, $J = 7.3$ Hz, 2H), 7.57 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.61, 26.99, 34.89, 35.10, 36.51, 36.87, 111.76, 112.99, 120.02, 125.22, 128.42, 130.81, 140.29, 140.99. Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.56; H, 6.23.

Adamantane-2-spiro-3'-5'-(4'-nitrophenyl)-5'-phenyl-1',2',4'-trioxolane

(OZ95). A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 4-nitrobenzophenone (2.27 g, 10 mmol) in pentane (70 ml) and CH_2Cl_2 (80 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ95** (1.60 g, 41%) as a colorless solid. mp 114–116 °C (ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–2.26 (m, 14H), 7.32–7.41 (m, 3H), 7.42–7.49 (m, 2H), 7.75 (d, $J = 8.8$ Hz, 2H), 8.22 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.46, 26.88, 34.61, 34.78, 34.81, 35.42, 36.04,

36.24, 36.71, 108.77, 114.65, 123.37, 126.86, 127.62, 128.43, 129.39, 137.62, 148.00, 148.26. Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.12; H, 5.66; N, 3.58.

Adamantane-2-spiro-3'-5',5'-bis(4'-chloro-3'-nitrophenyl)-1',2',4'-trioxolane

5 **(OZ96)**. A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 4,4'-dichloro-3,3'-dinitrobenzophenone (2.09 g, 10 mmol) in pentane (80 ml) and CH_2Cl_2 (75 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ96** (2.03 g, 40%) as a pale yellow solid. mp 113–115 °C (ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–2.25 (m, 14H), 7.50–7.71 (m, 4H), 8.04 (d, J = 2.0 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.30, 26.68, 34.75, 34.92, 36.06, 36.49, 106.72, 116.10, 123.73, 128.27, 131.00, 132.31, 139.19, 148.02. Anal. Calcd for $C_{23}H_{20}Cl_2N_2O_7$: C, 54.45; H, 3.97; N, 5.52. Found: C, 54.46; H, 4.09; N, 5.53.

Adamantane-2-spiro-3'-8'-phenyl-8'-phthalimidomethyl-1',2',4'-

15 **trioxaspiro[4.5]decane (OZ97)**. A solution of *O*-methyl 2-adamantanone oxime (0.75 g, 4.2 mmol) and 4-phenyl-4-phthalimidomethylcyclohexanone (1.40 g, 4.2 mmol) in pentane (100 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 12% ethyl acetate in hexanes) to afford trioxolane **OZ97** (0.62 g, 30%) as a colorless solid. mp 150–152 °C (ethanol); ^1H NMR (500 MHz, $CDCl_3$) δ 1.50–1.99 (m, 20H), 2.40 (app d, J = 14.2 Hz, 2H), 3.63 (s, 2H), 7.18–7.30 (m, 1H), 7.31–7.40 (m, 2H), 7.41–7.50 (m, 2H), 7.65–7.72 (m, 2H), 7.73–7.85 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.52, 26.88, 30.80, 30.88, 34.79, 36.43, 36.82, 43.90, 108.57, 111.33, 123.22, 126.67, 127.10, 128.78, 132.02, 133.84, 141.13, 168.44. Anal. Calcd for $C_{31}H_{33}NO_5$: C, 74.53; H, 6.66; N, 2.80. Found: C, 74.54; H, 6.71; N, 2.80.

Adamantane-2-spiro-3'-8'-methoxycarbonyl-8'-phenyl-1',2',4'-

trioxaspiro[4.5]decane (OZ98). A solution of *O*-methyl 2-adamantanone oxime (2.15 g, 12 mmol) and 4-methoxycarbonyl-4-phenylcyclohexanone (2.79 g, 12 mmol) in pentane (100 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. 30 The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ98** (1.07 g, 22%) as a colorless solid. mp 127–129 °C

(ethanol/CH₂Cl₂ 9:1); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.15 (m, 20H), 2.53 (app d, J = 13.2 Hz, 2H), 3.67 (s, 3H), 7.20–7.44 (m, 5H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.54, 26.94, 31.93, 31.98, 34.82, 34.87, 36.48, 36.85, 50.06, 52.22, 108.03, 111.58, 125.78, 127.06, 128.59, 142.39, 174.86. Anal. Calcd for C₂₄H₃₀O₅: C, 72.34; H, 7.59. Found: C, 72.12; H, 7.48.

Adamantane-2-spiro-3'-8'-carboxy-8'-phenyl-1',2',4'-trioxaspiro[4.5]decane (OZ99). A mixture of **OZ98** (0.42 g, 1.05 mmol), KOH (1.00 g, 17.85 mmol), ethanol (30 ml), THF (25 ml), and water (10 ml) was heated at 50 °C for 5 h. The reaction mixture was cooled to rt, concentrated to 10 ml, diluted with water (20 ml), acidified with conc. HCl (2.0 ml), and extracted with CHCl₃ (3 x 25 ml). The combined extracts were dried over MgSO₄, filtered, and concentrated. Recrystallization of the residue from hexanes/CH₂Cl₂ (7:3) afforded trioxolane **OZ99** (0.31 g, 77%) as a colorless solid. mp 153–156 °C (hexanes/CH₂Cl₂ 7:3); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.19 (m, 20H), 2.54 (app d, J = 11.7 Hz, 2H), 7.20–7.53 (m, 5H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.58, 26.98, 31.54, 31.83, 34.84, 34.90, 36.51, 36.88, 49.62, 107.96, 111.67, 126.04, 127.34, 128.68, 141.44, 180.55. Anal. Calcd for C₂₃H₂₈O₅: C, 71.85; H, 7.34. Found: C, 71.66; H, 7.32.

Adamantane-2-spiro-3'-8'-(4'-pyridinylcarbonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ100). To a solution of **OZ80** (225 mg, 0.85 mmol) in CH₂Cl₂ (10 ml) was added triethylamine (258 mg, 2.55 mmol). The solution was then cooled to 0–5 °C, and isonicotinoyl chloride hydrochloride (180 mg, 1.01 mmol) was added. The resulting mixture was stirred at rt for 16 h before evaporation to dryness. The residue was triturated with water and filtered. Recrystallization of the solid from methanol at –20 °C gave trioxolane **OZ100** (190 mg, 69%) as a colorless solid. mp 140–142 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.58–2.16 (m, 18H), 3.31–3.58 (m, 2H), 3.68–3.85 (m, 1H), 3.86–4.06 (m, 1H), 7.19–7.37 (m, 2H), 8.60–8.80 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.47, 26.87, 34.13, 34.76, 34.87, 35.18, 36.45, 36.71, 40.03, 45.20, 106.47, 112.49, 120.96, 143.47, 150.37, 167.77. Anal. Calcd for C₂₁H₂₆N₂O₄: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.22; H, 7.06; N, 7.68.

Adamantane-2-spiro-3'-8'-(4'-chlorophenoxyacetyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ101). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 1-(4-chlorophenoxyacetyl)-4-piperidone (1.34 g, 5 mmol) in pentane (50 ml)

and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 30% ether in hexanes) to afford trioxolane **OZ101** (300 mg, 14%) as a colorless solid. mp 148–150 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.59–2.19 (m, 18H), 3.48–3.71 (m, 3H), 3.72–3.87 (m, 1H), 4.67 (AB system, 2H), 6.80–6.95 (m, 2H), 7.15–7.35 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.47, 26.86, 34.15, 34.75, 34.93, 35.19, 36.43, 36.71, 40.21, 43.13, 68.16, 106.54, 112.38, 115.99, 126.80, 129.55, 156.57, 166.03. Anal. Calcd for C₂₃H₂₈ClNO₅: C, 63.66; H, 6.50; N, 3.23. Found: C, 63.82; H, 6.46; N, 3.30.

Adamantane-2-spiro-3'-8'-(phenylaminocarbonyl)-1',2',4'-trioxa-8'-

azaspiro[4.5]decane (OZ102). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in CH₂Cl₂ (10 ml) at 0–5 °C was added phenyl isocyanate (140 mg, 1.2 mmol). The reaction mixture was stirred at rt for 3 h, diluted with CH₂Cl₂ (10 ml), and washed with water (10 ml), 10% aq. NaHCO₃ (10 ml), 2 M HCl (10 ml), water (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and concentrated. The residue was triturated with hexanes (20 ml), filtered, and dried to afford trioxolane **OZ102** (370 mg, 96%) as a colorless solid. mp 146–148 °C (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.11 (m, 18H), 3.42–3.76 (m, 4H), 6.46 (s, 1H), 7.04 (dd, J = 7.3, 7.3 Hz, 1H), 7.15–7.44 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.52, 26.91, 34.42, 34.80, 34.89, 36.49, 36.77, 42.44, 106.80, 112.28, 120.13, 123.29, 128.91, 139.00, 154.88. Anal. Calcd for C₂₂H₂₈N₂O₄: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.78; H, 7.14; N, 7.50.

Adamantane-2-spiro-3'-8'-(1'H-imidazol-1'-ylacetyl)-1',2',4'-trioxa-8'-

azaspiro[4.5]decane (OZ103). To a solution of **OZ87** (342 mg, 1 mmol) in acetonitrile (10 ml) was added imidazole (201 mg, 3 mmol). The mixture was heated at 60–65 °C for 36 h before evaporation to dryness. The crude product was purified by flash chromatography (silica gel, 5% methanol in dichloromethane) and by subsequent recrystallization from hexanes/ether (9:1) to give trioxolane **OZ103** (132 mg, 35%) as a colorless solid. mp 138–140 °C (hexanes/ether 9:1); ¹H NMR (500 MHz, CDCl₃) δ 1.59–2.21 (m, 18H), 3.43–3.60 (m, 2H), 3.61–3.72 (m, 1H), 3.73–3.91 (m, 1H), 4.79 (s, 2H), 6.97 (br s, 1H), 7.12 (br s, 1H), 7.52 (br s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.46, 26.86, 33.98, 34.76, 34.95, 36.44, 36.70, 40.41, 43.02, 48.09, 106.22, 112.54, 120.04 (br s),

129.67, 138.10 (br s), 164.47. Anal. Calcd for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.29; N, 11.25. Found: C, 64.12; H, 7.02; N, 11.09.

Adamantane-2-spiro-3'-8'-[[4-(acetylamino)phenyl]sulfonyl]-1',2',4'-trioxa-8'-

azaspiro[4.5]decane (OZ104). To a solution of **OZ80** (300 mg, 1 mmol) in CH_2Cl_2 (10

5 ml) was added triethylamine (303 mg, 3 mmol). The solution was then cooled to 0–5 °C, and 4-acetamidobenzenesulfonyl chloride (280 mg, 1.2 mmol) was added. The resulting mixture was stirred at rt for 16 h before evaporation to dryness. The residue was triturated with water (15 ml) and filtered. Recrystallization of the solid from methanol/ CH_2Cl_2 (9:1) at –20 °C gave trioxolane **OZ104** (300 mg, 65%) as a colorless solid. mp 122–124 °C

10 (methanol/ CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.50–2.12 (m, 18H), 2.19 (s, 3H), 2.90–3.08 (m, 2H), 3.15–3.37 (m, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.93–8.16 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 24.51, 26.46, 26.83, 34.05, 34.74, 34.76, 36.39, 36.70, 44.26, 105.86, 112.41, 119.44, 128.73, 131.51, 142.35, 168.72. Anal. Calcd for $C_{23}H_{30}N_2O_6S$: C, 59.72; H, 6.54; N, 6.06. Found: C, 59.58; H, 6.60; N, 5.81.

15 **Adamantane-2-spiro-3'-5',5'-bis(3'-nitrophenyl)-1',2',4'-trioxolane (OZ105).** A

solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 3,3'-dinitrobenzophenone (2.72 g, 10 mmol) in pentane (60 ml) and CH_2Cl_2 (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 90% ether in hexanes) to afford trioxolane **OZ105** (0.90 g, 20 21%) as a colorless solid. mp 131–134 °C (ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–2.45 (m, 14H), 7.59 (dd, J = 7.8, 7.8 Hz, 2H), 7.81–7.88 (m, 2H), 8.22–8.28 (m, 2H), 8.41 (dd, J = 2.0, 2.0 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.37, 26.76, 34.77, 34.95, 36.09, 36.58, 107.55, 115.64, 121.71, 124.10, 129.67, 132.47, 141.33, 148.46. Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 63.26; H, 5.00; N, 6.47.

25 **Adamantane-2-spiro-3'-5',5'-bis[3',4'-di(methoxycarbonyl)phenyl]-1',2',4'-**

trioxolane (OZ106). A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 3,3',4,4'-tetra(methoxycarbonyl)benzophenone (4.14 g, 10 mmol) in pentane (70 ml) and CH_2Cl_2 (80 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 80% ether in hexanes) to afford trioxolane **OZ106** (2.03 g, 35%) as a colorless solid. mp 52–54 °C (ether); ^1H NMR (500 30 MHz, $CDCl_3$) δ 1.60–2.35 (m, 14H), 3.907 (s, 6H), 3.909 (s, 6H), 7.66 (dd, J = 8.0, 1.5 Hz,

2H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.87 (d, $J = 1.5$ Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.38, 26.77, 34.75, 34.91, 35.99, 36.62, 52.64, 52.66, 107.85, 115.18, 127.10, 129.03, 129.29, 132.05, 132.71, 142.41, 167.29, 167.55. Anal. Calcd for $\text{C}_{31}\text{H}_{32}\text{O}_{11}$: C, 64.13; H, 5.56. Found: C, 64.28; H, 5.46.

5 **Adamantane-2-spiro-3'-8'-[(aminocarbonyl)oxy]-1',2',4'-**

trioxaspiro[4.5]decane (OZ107). A solution of trichloroacetyl isocyanate (0.44 g, 2.25 mmol) and **OZ32** (0.42 g, 1.50 mmol) in CH_2Cl_2 (5 ml) was stirred at 0°C for 4 h. The reaction mixture was warmed up to rt, concentrated, dissolved in methanol (20 ml), and cooled to 0°C . To this cooled solution was added 5% aq. Na_2CO_3 solution (20 ml). The

10 resulting mixture was stirred at 0°C for 1 h, warmed up to rt, and stirred at rt overnight.

The reaction solution was diluted with water (50 ml) and extracted with CHCl_3 (3 x 40 ml). The combined organic layers were washed with water (30 ml) and brine (30 ml), dried over MgSO_4 , and concentrated. Recrystallization of the residue from hexanes/chloroform (3:1) gave trioxolane **OZ107** (250 mg, 52%, 10:1 mixture of two diastereomers) as a colorless

15 solid. mp $160\text{--}162^\circ\text{C}$ (hexanes/chloroform 3:1); ^1H NMR (500 MHz, CDCl_3) δ 1.50–2.25 (m, 22H), 4.72–4.98 (m, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.52, 26.93, 28.60, 31.01, 34.80, 34.88, 36.39, 36.82, 70.81, 107.85, 111.69, 156.34. Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.91; H, 7.56; N, 4.31.

***cis*-Adamantane-2-spiro-3'-8'-(1'-hydroxy-1'-methylethyl)-1',2',4'-**

20 **trioxaspiro[4.5]decane (OZ108).** To a solution of methyllithium (3.80 ml, 1.4 M in ether, 5.4 mmol) in ether (5 ml) at -78°C was added a solution of **OZ70** (0.70 g, 2.1 mmol) in ether (20 ml). The reaction was stirred at -78°C for 3 h before being quenched with saturated aq. ammonium chloride (20 ml). The mixture was extracted with ether (3 x 30 ml), and the organic layers were washed with water (30 ml) and brine (30 ml), dried over

25 MgSO_4 , filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 20% ether in hexanes) to afford trioxolane **OZ108** (0.42 g, 62%) as a colorless solid. mp $126\text{--}128^\circ\text{C}$ (ethanol/ H_2O 4:1); ^1H NMR (500 MHz, CDCl_3) δ 1.17 (s, 6H), 1.06–1.55 (m, 3H), 1.58–2.30 (m, 20H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 24.85, 26.59, 26.99, 27.02, 34.50, 34.85, 36.50, 36.90, 47.76, 72.51, 108.70, 111.28. Anal.

30 Calcd for $\text{C}_{19}\text{H}_{30}\text{O}_4$: C, 70.77; H, 9.38. Found: C, 70.64; H, 9.15.

Adamantane-2-spiro-3'-8'-[(3'-carboxypyrazinyl)carbonyl]-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ109). To a solution of **OZ80** (301 mg, 1 mmol) in CH₂Cl₂ (5 ml) at 0–5 °C were added triethylamine (101 mg, 1 mmol) and 2,3-pyrazinedicarboxylic anhydride (156 mg, 1 mmol). The resulting mixture was stirred at rt for 16 h before
5 evaporation to dryness. The residue was triturated with water (10 ml) and filtered. Recrystallization of the solid from methanol gave trioxolane **OZ109** (300 mg, 72%) as a colorless solid. mp 128–130°C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.52–2.21 (m, 18H), 3.21–3.43 (m, 2H), 3.79–3.96 (m, 1H), 3.97–4.14 (m, 1H), 8.71 (s, 1H), 8.79 (s, 1H);
¹³C NMR (125.7 MHz, CDCl₃) δ 26.54, 26.92, 33.73, 34.32, 34.78, 34.83, 34.84, 34.96,
10 36.48, 36.52, 36.79, 39.94, 44.80, 106.79, 112.42, 140.16, 143.16, 146.96, 151.73, 163.03, 165.23. Anal. Calcd for C₂₁H₂₅N₃O₆: C, 60.71; H, 6.07; N, 10.11. Found: C, 60.46; H, 5.93; N, 9.96.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-3''-8''-ethoxycarbonyl-8''-azabicyclo[3.2.1]octane (OZ110). A solution of *O*-methyl 2-adamantanone oxime (895
15 mg, 5.0 mmol) and *N*-carboethoxytropinone (1.01 g, 5.2 mmol) in pentane (80 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 15% ether in hexanes) to afford trioxolane **OZ110** (300 mg, 17%, 2:1 mixture of two diastereomers) as a colorless solid.
mp 98–100 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.27 (t, J = 7.1 Hz, 3H), 1.58–2.39 (m, 22H), 4.15 (q, J = 6.8 Hz, 2H), 4.18–4.45 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 14.67,
20 26.45, 26.50, 26.86, 26.89, 27.16, 27.60 (br s), 33.22, 34.68, 34.82, 35.06, 36.37, 36.41, 36.74, 36.77, 37.05, 40.42 (br s), 52.44, 52.75, 52.78, 60.88, 60.93, 60.96, 106.98, 107.71, 110.39, 112.46, 153.70. Anal. Calcd for C₂₀H₂₉NO₅: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.12; H, 7.90; N, 3.82.

Adamantane-2-spiro-3'-8'-(3',3'-dimethylbutanoyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ111). To a solution of **OZ80** (302 mg, 1 mmol) in CH₂Cl₂ (10
25 ml) at 0–5 °C were added triethylamine (303 mg, 3 mmol) and trimethylacetyl chloride (185 mg, 1.5 mmol). The resulting mixture was stirred at rt for 16 h, then diluted with CH₂Cl₂ (10 ml), and washed with water (10 ml) and brine (10 ml). The organic phase was
30 separated, dried over MgSO₄, and concentrated. Crystallization of the residue from methanol gave trioxolane **OZ111** (140 mg, 39%) as a colorless solid. mp 98–100°C

(methanol); ^1H NMR (500 MHz, CDCl_3) δ 1.05 (s, 9H), 1.58–2.11 (m, 18H), 2.27 (AB system, 2H), 3.46–3.69 (m, 3H), 3.75–3.90 (m, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.60, 26.99, 30.06, 31.39, 34.37 (br s), 34.85, 35.34 (br s), 36.57, 36.85, 39.44 (br s), 44.40 (br s), 44.75, 106.92, 112.25, 170.30. Anal. Calcd for $\text{C}_{21}\text{H}_{33}\text{NO}_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.52; H, 8.89; N, 3.72.

Adamantane-2-spiro-3'-8'-[(carboxymethoxy)acetyl]-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ112). To a solution of **OZ80** (302 mg, 1 mmol) in CH_2Cl_2 (10 ml) was added triethylamine (101 mg, 1 mmol). The solution was then cooled to 0–5 °C, and diglycolic anhydride (116 mg, 1 mmol) was added. The resulting mixture was stirred at rt for 16 h before evaporation to dryness. The residue was triturated with water (10 ml) and filtered. Recrystallization of the solid from methanol gave trioxolane **OZ112** (250 mg, 66%) as a colorless solid. mp 126–128 °C (methanol); ^1H NMR (500 MHz, CDCl_3) δ 1.59–2.18 (m, 18H), 3.29–3.49 (m, 2H), 3.63–3.77 (m, 1H), 3.79–3.91 (m, 1H), 4.22 (s, 2H), 4.42 (s, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.44, 26.84, 33.91, 34.72, 34.80, 34.97, 36.45, 36.68, 40.56, 42.21, 70.94, 72.00, 106.08, 112.64, 169.20, 171.40. Anal. Calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_7$: C, 59.83; H, 7.14; N, 3.67. Found: C, 59.67; H, 7.16; N, 3.56.

Adamantane-2-spiro-3'-8'-methoxyacetyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ113). To a solution of **OZ80** (301 mg, 1 mmol) in CH_2Cl_2 (10 ml) was added triethylamine (303 mg, 3 mmol). The solution was then cooled to 0–5 °C, and methoxyacetyl chloride (163 mg, 1.5 mmol) was added. The resulting mixture was stirred at rt for 16 h and washed with water (5 ml) and brine (5 ml). The organic phase was separated, dried over MgSO_4 , and concentrated to give trioxolane **OZ113** (325 mg, 96%) as a colorless solid. mp 76–78 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.59–2.17 (m, 18H), 3.42 (s, 3H), 3.43–3.73 (m, 3H), 3.75–3.89 (m, 1H), 4.11 (AB system, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.57, 26.97, 34.32 (br s), 34.83, 34.92, 35.25 (br s), 36.55, 36.82, 39.98 (br s), 42.87 (br s), 58.96, 72.21, 106.78, 112.30, 167.54. Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.94; H, 8.03; N, 4.30.

Adamantane-2-spiro-3'-8'-(8'-quinolinesulfonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ114). To a solution of **OZ80** (151 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) was added triethylamine (150 mg, 1.49 mmol). The solution was then cooled to 0–5 °C, and 8-quinolinesulfonyl chloride (115 mg, 0.5 mmol) was added. The resulting mixture

was stirred at rt for 12 h before evaporation to dryness. The residue was triturated with water (5 ml) and filtered. Recrystallization of the solid from methanol gave trioxolane **OZ114** (215 mg, 94%) as a colorless solid. mp 142–144 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.55–2.21 (m, 18H), 3.40–3.61 (m, 2H), 3.62–3.85 (m, 2H), 7.51 (dd, J = 8.2, 3.9 Hz, 1H), 7.61 (dd, J = 8.2, 8.2 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 8.23 (dd, J = 8.3, 1.5 Hz, 1H), 8.47 (dd, J = 7.3, 1.5 Hz, 1H), 9.05 (dd, J = 3.9, 1.5 Hz, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.58, 26.97, 34.82, 34.88, 34.90, 36.54, 36.83, 44.37, 106.74, 112.16, 121.98, 125.47, 129.12, 132.68, 133.24, 136.30, 137.86, 144.33, 151.10. Anal. Calcd for C₂₄H₂₈N₂O₅S: C, 63.14; H, 6.18; N, 6.14. Found: C, 62.94; H, 6.16; N, 6.00.

Adamantane-2-spiro-3'-8'-(1'-octanesulfonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ115). To a solution of **OZ80** (200 mg, 0.66 mmol) and triethylamine (200 mg, 1.98 mmol) in CH₂Cl₂ (5 ml) at 0–5 °C was added 1-octanesulfonyl chloride (170 mg, 0.8 mmol). The resulting mixture was stirred at rt for 12 h before evaporation to dryness. The residue was triturated with water (10 ml) and filtered. Recrystallization of the solid from methanol gave trioxolane **OZ115** (160 mg, 55%) as a colorless solid. mp 54–56 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 0.88 (t, J = 6.8 Hz, 3H), 1.17–1.49 (m, 10H), 1.61–2.21 (m, 20H), 2.90 (t, J = 8.1 Hz, 2H), 3.24–3.39 (m, 2H), 3.41–3.57 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 13.95, 22.56, 23.26, 26.55, 26.95, 28.49, 28.93, 29.04, 31.71, 34.71, 34.82, 34.91, 36.53, 36.79, 43.97, 50.46, 106.24, 112.41. Anal. Calcd for C₂₃H₃₉NO₅S: C, 62.55; H, 8.90; N, 3.17. Found: C, 62.38; H, 8.76; N, 3.25.

cis-Adamantane-2-spiro-3'-8'-[(hydroxyamino)carbonyl]-1',2',4'-trioxaspiro[4.5]decane (OZ116). A solution of ethyl chloroformate (0.26 g, 2.4 mmol), **OZ72** (0.62 g, 2.0 mmol), and triethylamine (0.27 g, 2.6 mmol) in ether (6 ml) was stirred at 0 °C for 10 min. The solid was removed by filtration, and the filtrate was added to a freshly prepared solution of hydroxylamine. [To a suspension of KOH (168 mg, 3.0 mmol) in methanol (1 ml) at 0 °C was added a solution of hydroxylamine hydrochloride (0.20 g, 3 mmol) in methanol (3 ml). The reaction mixture was stirred at 0 °C for 15 min and filtered to remove solid by-products. The filtrate was used as such.] The resulting mixture was stirred at rt for 1 h and concentrated. The crude product was purified by flash chromatography (silica gel, 8% methanol in chloroform) to afford trioxolane **OZ116** (0.23

g, 36%) as a colorless solid. mp 130–132 °C (ethanol/water 1:2); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.40–2.19 (m, 23H), 8.60 (s, 1H), 10.35 (s, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.87, 26.27, 26.50, 33.03, 34.28, 34.30, 35.84, 36.15, 39.04, 107.85, 110.64, 171.30. Anal. Calcd for C₁₇H₂₅NO₅: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.97; H, 7.57; N, 4.26.

Adamantane-2-spiro-3'-8'-(aminomethyl)-8'-phenyl-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ117). A solution of **OZ97** (1.60 g, 3.2 mmol) and hydrazine monohydrate (325 mg, 6.5 mmol) in chloroform (27 ml) and methanol (3 ml) was heated at 50 °C for 36 h. The reaction mixture was cooled to rt and filtered to remove solid by-products. The filtrate was washed with water (20 ml) and brine (20 ml), dried over MgSO₄, filtered, and concentrated. The solid was dissolved in ether (30 ml), treated with 1 M ethereal HCl (6 ml), and filtered. Recrystallization from hexanes/chloroform (2:1) gave trioxolane **OZ117** (0.22 g, 17%) as a colorless solid. mp 156 °C dec (hexanes/chloroform 2:1); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.42–2.05 (m, 20H), 2.32 (apparent d, J = 13.7 Hz, 2H), 2.89 (s, 2H), 7.26–7.39 (m, 1H), 7.41–7.62 (m, 4H), 7.80 (br s, 3H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.82, 26.19, 30.08, 34.24, 35.76, 36.09, 49.37, 107.89, 110.70, 126.97, 127.14, 128.98, 139.82. Anal. Calcd for C₂₃H₃₂ClNO₃: C, 68.05; H, 7.95; N, 3.45. Found: C, 67.92; H, 7.69; N, 3.72.

cis-Adamantane-2-spiro-3'-8'-acetoxymethyl-1',2',4'-trioxaspiro[4.5]decane (OZ118). A solution of *O*-methyl 2-adamantanone oxime (1.34 g, 7.5 mmol) and 4-acetoxymethylcyclohexanone (1.28 g, 7.5 mmol) in pentane (100 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ118** (1.15 g, 46%) as a colorless solid. mp 39–41 °C (ethanol/H₂O 7:3); ¹H NMR (500 MHz, CDCl₃) δ 1.18–1.31 (m, 2H), 1.59–2.19 (m, 21H), 2.05 (s, 3H), 3.90 (d, J = 6.3 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 20.77, 26.62, 26.77, 27.02, 33.71, 34.86, 34.88, 35.67, 36.54, 36.91, 68.49, 108.57, 111.40, 170.90. Anal. Calcd for C₁₉H₂₈O₅: C, 67.83; H, 8.39. Found: C, 67.70; H, 8.32.

cis-Adamantane-2-spiro-3'-8'-hydroxymethyl-1',2',4'-trioxaspiro[4.5]decane (OZ119). A solution of **OZ70** (0.81 g, 2.4 mmol), lithium borohydride (1.2 ml, 2.4 mmol, 2 M in THF), and lithium triethylborohydride (0.24 ml, 0.24 mmol, 1 M in THF) in ether

(2.5 ml) was stirred at rt for 3 h. The reaction mixture was diluted with ether (5 ml), washed with 3 M aq. NaOH (2 x 5 ml), water (2 x 5 ml) and brine (5 ml), dried over MgSO₄, filtered, and concentrated in vacuo to afford trioxolane **OZ119** (0.68 g, 96%) as a colorless solid. mp 97–99 °C (ethanol/H₂O 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.09–1.27 (m, 2H), 1.42–2.19 (m, 21H), 3.47 (d, J = 6.5 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.63, 26.66, 27.03, 33.86, 34.87, 34.90, 36.56, 36.93, 38.97, 67.63, 108.91, 111.32. Anal. Calcd for C₁₇H₂₆O₄: C, 69.36; H, 8.90. Found: C, 69.58; H, 8.63.

Adamantane-2-spiro-3'-11',11'-bis(ethoxycarbonyl)-1',2',4',9',13'-pentaoadispiro[4.2.5.2]pentadecane (OZ120). A solution of *O*-methyl 2-adamantanone oxime (2.69 g, 15 mmol) and 3,3-bis(ethoxycarbonyl)-1,5-dioxaspiro[5.5]undecan-9-one (4.71 g, 15 mmol) in pentane (100 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in petroleum ether) to afford trioxolane **OZ120** (3.60 g, 50%) as a colorless solid. mp 74–77 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.27 (t, J = 7.1 Hz, 6H), 1.61–2.18 (m, 22H), 4.24 (q, J = 7.2 Hz, 4H), 4.28 (s, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 13.91, 26.55, 26.95, 29.35, 30.45, 34.77, 34.87, 36.43, 36.83, 39.26, 53.95, 61.77, 62.10, 97.54, 108.22, 111.56, 167.84. Anal. Calcd for C₂₅H₃₆O₉: C, 62.48; H, 7.55. Found: C, 62.62; H, 7.32.

Adamantane-2-spiro-3'-11',11'-bis(hydroxymethyl)-1',2',4',9',13'-pentaoadispiro[4.2.5.2]pentadecane (OZ121). A solution of **OZ120** (1.00 g, 2.18 mmol), lithium borohydride (2.10 ml, 4.20 mmol, 2 M in THF), and lithium triethylborohydride (0.42 ml, 0.42 mmol, 1 M in THF) in ether (5 ml) was stirred at rt for 3 h. The reaction mixture was diluted with ether (10 ml) and washed with 3 M aq. NaOH (2 x 10 ml), water (2 x 10 ml), and brine (10 ml). The combined aqueous layers were extracted with CHCl₃ (3 x 50 ml), and the chloroform extract was washed with water (2 x 50 ml) and brine (50 ml). The ether extract and chloroform extract were combined, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 5% methanol in chloroform) to afford trioxolane **OZ121** (0.40 g, 46%) as a colorless solid. mp 146–148 °C (ethanol/H₂O 3:2); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.60–2.15 (m, 22H), 3.36 (d, J = 4.9 Hz, 4H), 3.61 (s, 2H), 3.62 (s, 2H), 4.49 (t, J = 5.4 Hz, 2H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.86, 26.26, 29.34, 30.21, 34.27, 34.36, 35.77,

36.13, 39.07, 60.69, 61.44, 61.48, 96.00, 108.15, 110.84. Anal. Calcd for $C_{21}H_{32}O_7 \cdot 0.077CHCl_3$: C, 62.40; H, 7.97. Found: C, 62.76; H, 7.77.

Adamantane-2-spiro-3'-11',11'-dicarboxy-1',2',4',9',13'-pentaoadispiro[4.2.5.2]pentadecane (OZ122). A solution of **OZ120** (0.73 g, 1.5 mmol),
 5 15% aq. KOH (4.2 ml) in methanol (30 ml) was heated at 50 °C for 2 h. After being cooled to rt, the reaction mixture was concentrated to 5 ml, acidified with conc. HCl, and extracted with $CHCl_3$ (5 x 50 ml). The combined organic layers were washed with water (2 x 50 ml) and brine (50 ml), dried over $MgSO_4$, filtered, and concentrated to afford trioxolane **OZ122** (0.38 g, 58%) as a colorless solid. mp 151–153 °C (water); ^1H NMR (500 MHz, $DMSO-d_6$) δ
 10 δ 1.51–2.14 (m, 22H), 4.13 (s, 2H), 4.15 (s, 2H); ^{13}C NMR (125.7 MHz, $DMSO-d_6$) δ 25.86, 26.26, 29.16, 30.16, 34.27, 34.37, 35.77, 36.13, 52.89, 61.65, 96.49, 107.99, 110.92, 169.11. Anal. Calcd for $C_{21}H_{28}O_9$: C, 59.43; H, 6.65. Found: C, 59.42; H, 6.66.

cis-Adamantane-2-spiro-3'-8'-bromomethyl-1',2',4'-trioxaspiro[4.5]decane (OZ123). A solution of *O*-methyl 2-adamantanone oxime (2.15 g, 12 mmol) and 4-
 15 bromomethylcyclohexanone (2.30 g, 12 mmol) in pentane (100 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 3% ether in hexanes) to afford trioxolane **OZ123** (1.62 g, 38%) as a colorless solid. mp 138–140 °C (ethanol); ^1H NMR (500 MHz, $CDCl_3$) δ 1.21–1.41 (m, 2H), 1.51–2.21 (m, 21H), 3.28 (d, $J = 6.3$ Hz, 2H); ^{13}C NMR (125.7 MHz,
 20 $CDCl_3$) δ 26.64, 27.04, 28.83, 33.73, 34.88, 34.90, 36.55, 36.93, 38.63, 38.76, 108.41, 111.47. Anal. Calcd for $C_{17}H_{25}BrO_3$: C, 57.15; H, 7.05. Found: C, 57.20; H, 6.99.

Adamantane-2-spiro-3'-5'-(4'-cyanophenyl)-5'-phenyl)-1',2',4'-trioxolane (OZ124). A solution of *O*-methyl 2-adamantanone oxime (0.86 g, 4.80 mmol) and 4-cyanobenzophenone (1.00 g, 4.80 mmol) in pentane (50 ml) and CH_2Cl_2 (60 ml) was
 25 treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ124** (0.30 g, 17%) as a colorless solid. mp 136–137 °C (ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–2.35 (m, 14H), 7.31–7.39 (m, 3H), 7.40–7.48 (m, 2H), 7.62–7.73 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.50, 26.92, 34.70, 34.80, 34.84, 35.39, 36.08, 36.25, 36.76, 108.84,
 30 112.50, 114.57, 118.43, 126.85, 127.42, 128.38, 129.27, 131.97, 137.97, 146.30. Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.58; H, 6.32; N, 3.76.

Adamantane-2-spiro-3'-5',5'-bis[4'-(ethoxycarbonyl)phenyl]-1',2',4'-trioxolane (OZ125). A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 4,4'-bis(ethoxycarbonyl)benzophenone (3.26 g, 10 mmol) in pentane (60 ml) and CH₂Cl₂ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ125** (1.77 g, 36%) as a colorless solid. mp 143–145 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.38 (t, J = 7.1 Hz, 6H), 1.60–2.07 (m, 12H), 2.20 (app d, J = 12.2 Hz, 2H), 4.37 (q, J = 7.2 Hz, 4H), 7.58 (d, J = 8.3 Hz, 4H), 8.03 (d, J = 8.3 Hz, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 14.28, 26.52, 26.94, 34.84, 35.06, 36.17, 36.78, 61.01, 108.84, 114.60, 126.69, 129.52, 131.10, 144.22, 166.06. Anal. Calcd for C₂₉H₃₂O₇: C, 70.71; H, 6.55. Found: C, 70.52; H, 6.32.

cis-Adamantane-2-spiro-3'-8'-[2'-(diethylamino)ethyl]-1',2',4'-trioxaspiro[4.5]decane hydrobromide (OZ126). **Step 1.** A solution of *O*-methyl 2-adamantanone oxime (716 mg, 4 mmol) and 4-(2-bromoethyl)cyclohexanone (820 mg, 4 mmol) in pentane (72 ml) and CH₂Cl₂ (8 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 1% ether in hexanes) to afford **cis-Adamantane-2-spiro-3'-8'-(2'-bromoethyl)-1',2',4'-trioxaspiro[4.5]decane** (800 mg, 54%) as a colorless solid. mp 62–64 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.18–1.22 (m, 2H), 1.72–2.10 (m, 23H), 3.42 (t, 2H, J = 6.8 Hz). **Step 2.** To a solution of the above bromide (371 mg, 1 mmol) in acetonitrile (5 ml) were added diethylamine (140 mg, 2 mmol) and triethylamine (101 mg, 1 mmol). The mixture was heated at 60–65 °C for 60 h before removal of solvents. The residue was triturated with water (5 ml) and filtered. Recrystallization of the solid from ethanol gave trioxolane **OZ126** (170 mg, 43%) as a colorless solid. mp 152–154 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.20–1.34 (m, 2H), 1.41 (t, J = 7.3 Hz, 6H), 1.60–2.25 (m, 23H), 2.95–3.04 (m, 2H), 3.05–3.19 (m, 4H), 12.17 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 8.69, 26.61, 27.00, 29.13, 29.84, 33.90, 34.34, 34.86, 34.88, 36.54, 36.90, 46.55, 49.51, 108.27, 111.54. Anal. Calcd for C₂₂H₃₇NO₃•0.5HBr: C, 65.41; H, 9.36; N, 3.47. Found: C, 65.24; H, 9.54; N, 3.46.

trans-Adamantane-2-spiro-3'-8'-[(hydroxyamino)carbonyl]-1',2',4'-trioxaspiro[4.5]decane (OZ127). A solution of ethyl chloroformate (0.13 g, 1.2 mmol),

OZ71 (0.31 g, 1.0 mmol), and triethylamine (0.13 g, 1.3 mmol) in ether (5 ml) was stirred at 0 °C for 10 min. The solid was removed by filtration, and the filtrate was added to a freshly prepared solution of hydroxylamine. [To a suspension of KOH (84 mg, 1.5 mmol) in methanol (1 ml) at 0 °C was added a solution of hydroxylamine hydrochloride (0.10 g, 1.5 mmol) in methanol (2 ml). The reaction mixture was stirred at 0 °C for 15 min and filtered to remove solid by-products. The filtrate was used as such.] The resulting mixture was stirred at rt for 1 h and concentrated. The crude product was purified by crystallization from hexanes/chloroform (5:1) to afford trioxolane **OZ127** (0.15 g, 47%) as a colorless solid. mp 136–138 °C (hexanes/chloroform 5:1); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.42–2.23 (m, 23H), 8.60 (s, 1H), 10.36 (s, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.87, 26.26, 26.40, 32.95, 34.26, 34.42, 35.81, 36.13, 39.26, 107.88, 110.95, 171.35. Anal. Calcd for C₁₇H₂₅NO₅: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.89; H, 7.59; N, 4.40.

Adamantane-2-spiro-3'-11'-methylene-1',2',4',9',13'-

pentaoxidispiro[4.2.5.2]pentadecane (OZ128). Step 1. A mixture of **OZ05** (1.12 g, 4 mmol), TFA (0.70 ml), CH₂Cl₂ (10 ml), and methanol (70 ml) was stirred at rt for 16 h. The reaction was quenched with NaHCO₃ (2.0 g) and stirred for additional 1 h before evaporation to dryness. The residue was dissolved in CH₂Cl₂ (20 ml), washed with water and brine, dried over MgSO₄, filtered, and concentrated to afford dimethyl ketal of **OZ05** (1.31 g, 100%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 1.66–2.02 (m, 22H), 3.18 (s, 3H), 3.19 (s, 3H). **Step 2.** A mixture of the above ketal (1.30 g, 4 mmol), 2-methylene-1,3-propanediol (0.70 g, 8 mmol), and *p*-TsOH (0.5 g) in CH₂Cl₂ (70 ml) and THF (10 ml) was stirred at rt for 16 h. The reaction was quenched with NaHCO₃ (1.0 g), stirred for additional 1 h, and diluted with water (70 ml). After separation of the organic layer, the aqueous layer was extracted with CH₂Cl₂ (2 x 50 ml). The combined organic layers were washed with water and brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 8% ether in hexanes) to afford trioxolane **128** (0.87 g, 63%) as a colorless solid. mp 58–59 °C (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 1.59–2.21 (m, 22H), 4.31 (s, 4H), 4.86 (s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.60, 27.02, 29.97, 30.69, 34.84, 34.94, 36.49, 36.90, 63.63, 97.60, 107.92, 108.38, 111.59, 141.15. Anal. Calcd for C₂₀H₂₈O₅: C, 68.94; H, 8.10. Found: C, 68.77; H, 7.93.

***cis*-Adamantane-2-spiro-3'-8'-[(2'-hydroxy-1',1'-dimethylethylamino)carbonyl]-1',2',4'-trioxaspiro[4.5]decane (OZ129).** A solution of **OZ72** (0.77 g, 2.50 mmol), DCC (0.78 g, 3.75 mmol), HOBT (0.51 g, 3.75 mmol), and 2-amino-2-methyl-1-propanol (0.33 g, 3.75 mmol) in DMF (20 ml) was heated at 50–60 °C for 6 h. After being cooled to rt, the reaction mixture was acidified with 1 M aq. HCl (100 ml) and extracted with ethyl acetate (4 x 60 ml). The combined extracts were washed with water and brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 50% ethyl acetate in hexanes) to afford trioxolane **129** (0.44 g, 46%) as a colorless solid. mp 163–164 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.27 (s, 6H), 1.60–2.24 (m, 23H), 3.56 (s, 2H), 4.80 (s, 1H), 5.47 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 24.77, 26.62, 27.03, 27.21, 33.64, 34.86, 34.90, 36.55, 36.91, 44.24, 55.95, 70.66, 107.78, 111.60, 175.63. Anal. Calcd for C₂₁H₃₃NO₅: C, 66.46; H, 8.76; N, 3.69. Found: C, 66.41; H, 8.56; N, 3.76.

Adamantane-2-spiro-3'-11'-oxo-1',2',4',9',13'-pentaoadispiro[4.2.5.2]pentadecane (OZ130). A solution of **OZ128** (0.65 g, 1.9 mmol) in CH₂Cl₂ (80 ml) at –78 °C was treated with ozone for 10 min, flashed with oxygen for 5 min before addition of triphenylphosphine (0.49 g, 1.9 mmol). The reaction mixture was warmed up to rt and stirred at rt for 1 h before evaporation to dryness. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ130** (0.37 g, 57%) as a colorless solid. mp 76–79 °C (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 1.61–2.21 (m, 22H), 4.17 (s, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.61, 27.03, 29.80, 30.81, 34.85, 34.96, 36.52, 36.89, 66.92, 66.94, 99.14, 107.96, 111.82, 207.00. Anal. Calcd for C₁₉H₂₆O₆: C, 65.13; H, 7.48. Found: C, 65.38; H, 7.58.

Adamantane-2-spiro-3'-8'-phenylmethanesulfonyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ131). To a solution of **OZ80** (301 mg, 1.0 mmol) and toluenesulfonyl chloride (192 mg, 1.0 mmol) in CH₂Cl₂ (10 ml) at 0–5 °C was added triethylamine (303 mg, 3.0 mmol). The resulting mixture was stirred at rt for 16 h before evaporation to dryness. The residue was triturated with water, filtered, and crystallized from ethanol to give trioxolane **OZ131** (320 mg, 76%) as a colorless solid. mp 148–150 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.59–2.21 (m, 18H), 3.06–3.24 (m, 2H), 3.25–3.41 (m, 2H), 4.22 (s, 2H), 7.27–7.60 (m, 5H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.53,

26.94, 34.77, 34.79, 34.89, 36.50, 36.78, 44.20, 57.79, 106.20, 112.28, 128.79, 129.12, 130.67. Anal. Calcd for C₂₂H₂₉NO₅S: C, 62.98; H, 6.97; N, 3.34. Found: C, 63.16; H, 6.79; N, 3.46.

Adamantane-2-spiro-3'-8'-(2'-carboxybenzoyl)-1',2',4'-trioxa-8'-

5 **azaspiro[4.5]decane (OZ132).** To a solution of **OZ80** (301 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) in CH₂Cl₂ (10 ml) at 0–5 °C was added phthalic anhydride (148 mg, 1.0 mmol). The resulting mixture was stirred at rt for 24 h before evaporation to dryness. The residue was triturated, filtered, and crystallized from ethanol to give trioxolane **OZ132** (285 mg, 69%) as a colorless solid. mp 162–164 °C (ethanol); ¹H
10 NMR (500 MHz, DMSO-*d*₆) δ 1.57–2.21 (m, 18H), 3.01–3.32 (m, 2H), 3.35–4.04 (m, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.52 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.64 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 13.14 (br s, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.84, 26.23, 33.29, 33.54, 34.25, 34.34, 35.74, 35.79, 36.07, 38.82, 44.26, 107.05, 111.35, 126.62, 128.43, 128.63, 130.03, 132.42, 138.38, 166.90, 168.45. Anal. Calcd for C₂₃H₂₇NO₆: C,
15 66.81; H, 6.58; N, 3.39. Found: C, 67.02; H, 6.65; N, 3.40.

Adamantane-2-spiro-3'-8'-[(dimethylamino)carbonyl]-1',2',4'-trioxa-8'-

azaspiro[4.5]decane (OZ133). To a solution of **OZ80** (301 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) in CH₂Cl₂ (10 ml) at 0–5 °C was added dimethylcarbamoyl chloride (115 mg, 1.07 mmol). The resulting mixture was stirred at rt
20 for 16 h before evaporation to dryness. The residue was triturated, and filtered, and crystallized from methanol to give trioxolane **OZ133** (260 mg, 77%) as a colorless solid. mp 106–108 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.11 (m, 18H), 2.82 (s, 6H), 3.21–3.47 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.61, 27.01, 34.52, 34.84, 34.94, 36.59, 36.87, 38.53, 44.69, 107.28, 111.95, 164.66. Anal. Calcd for C₁₈H₂₈N₂O₄: C,
25 64.26; H, 8.39; N, 8.33. Found: C, 64.49; H, 8.36; N, 8.42.

Adamantane-2-spiro-3'-1',2',4'-trioxolane-5'-spiro-4''-2'',3''-dihydro-4''H-1''-

benzopyran (OZ134). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 4-chromanone (740 mg, 5 mmol) in cyclohexane (80 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by
30 flash chromatography (silica gel, 2% ether in hexanes) to afford trioxolane **OZ134** (590 mg, 38%) as a colorless solid. mp 136–138 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ

1.61–2.38 (m, 14H), 2.39–2.61 (m, 2H), 4.23–4.51 (m, 2H), 6.83 (d, $J = 8.3$ Hz, 1H), 6.96 (dd, $J = 8.3, 8.3$ Hz, 1H), 7.27 (ddd, $J = 8.6, 8.6, 1.6$ Hz, 1H), 7.53 (dd, $J = 7.8, 1.6$ Hz, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.61, 27.03, 33.46, 33.97, 34.89, 34.94, 35.78, 36.43, 36.91, 37.08, 64.65, 103.93, 112.95, 117.04, 120.68, 128.26, 131.42, 157.71. Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_4$: C, 72.59; H, 7.05. Found: C, 72.48; H, 6.87.

Adamantane-2-spiro-3'-5',5'-bis(4'-carboxyphenyl)-1',2',4'-trioxolane (OZ135). A mixture of **OZ125** (0.44 g, 0.89 mmol), THF (7 ml), and 40% aq. KOH (4.5 ml) was heated at 50 °C for 5 days. The reaction mixture was cooled to rt and extracted with ether (5 x 20 ml). The aqueous layer was acidified to pH = 3 with conc. HCl. The resulting precipitate was filtered and recrystallized from ethanol/water (2:1) to afford trioxolane **OZ135** (0.35 g, 90%) as a colorless solid. mp 170 °C (EtOAc) dec; ^1H NMR (500 MHz, CDCl_3) δ 1.60–2.05 (m, 12H), 2.13 (app d, $J = 11.7$ Hz, 2H), 7.60 (d, $J = 8.8$ Hz, 4H), 7.98 (d, $J = 8.8$ Hz, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 25.79, 26.19, 34.25, 34.42, 35.56, 35.99, 108.40, 113.95, 126.42, 129.46, 131.47, 143.44, 166.69. Anal. Calcd for $\text{C}_{25}\text{H}_{24}\text{O}_7$: C, 68.80; H, 5.54. Found: C, 68.64; H, 5.34.

cis-Adamantane-2-spiro-3'-8'-phthalimido-1',2',4'-trioxaspiro[4.5]decane (OZ136). A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 4-phthalimidocyclohexanone (2.43 g, 10 mmol) in pentane (60 ml) and CH_2Cl_2 (80 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 80% ether in hexanes) to afford trioxolane **OZ136** (1.20 g, 29%) as a colorless solid. mp 156–158 °C (ether); ^1H NMR (500 MHz, CDCl_3) δ 1.60–2.19 (m, 20H), 2.45–2.63 (m, 2H), 4.18 (tt, $J = 12.4, 3.9$ Hz, 1H), 7.64–7.76 (m, 2H), 7.77–7.89 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.60, 26.89, 27.00, 33.81, 34.85, 36.45, 36.89, 49.35, 107.43, 111.50, 123.06, 132.13, 133.75, 168.01. Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.16; H, 6.43; N, 3.43.

cis-Adamantane-2-spiro-3'-8'-amino-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ137). A solution of **OZ136** (0.81 g, 1.98 mmol) and hydrazine monohydrate (198 mg, 3.96 mmol) in chloroform (16 ml) and methanol (2 ml) was heated under nitrogen at 50 °C for 24 h. The reaction mixture was cooled to rt, filtered to remove solid by-products, and concentrated. The solid residue was dissolved in CHCl_3 , washed with water and brine, dried over MgSO_4 , filtered, and concentrated. The oily amine was

dissolved in ether (2 ml), treated with 1 M ethereal HCl (7 ml), and filtered to give trioxolane **OZ137** (0.31 g, 50%) as a colorless solid. mp 132 °C dec (ether); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.41–1.59 (m, 2H), 1.60–2.15 (m, 20H), 3.10 (br s, 1H), 8.12 (br s, 3H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.83, 26.23, 27.46, 31.33, 34.27, 34.30, 35.73, 36.10, 47.31, 107.24, 110.96. Anal. Calcd for C₁₆H₂₆ClNO₃: C, 60.85; H, 8.30; N, 4.43. Found: C, 60.64; H, 8.16; N, 4.70.

Adamantane-2-spiro-3'-5'-[4'-(methoxycarbonyl)phenyl]-5'-phenyl-1',2',4'-trioxolane (OZ138). A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 4-(methoxycarbonyl)benzophenone (2.40 g, 10 mmol) in pentane (40 ml) and CH₂Cl₂ (90 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ138** (1.00 g, 25%) as a colorless solid. mp 144–146 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.29 (m, 14H), 3.91 (s, 3H), 7.31–7.39 (m, 3H), 7.43–7.52 (m, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.58, 26.99, 33.32, 34.86, 34.88, 35.31, 36.13, 36.31, 36.86, 51.99, 109.28, 114.26, 126.76, 126.96, 128.22, 128.97, 129.42, 130.37, 138.83, 145.73, 166.69. Anal. Calcd for C₂₅H₂₆O₅: C, 73.87; H, 6.45. Found: C, 74.07; H, 6.55.

cis-Adamantane-2-spiro-3'-8'-[(4'-phenyl-1'-piperazinyl)carbonyl]-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ140). A solution of **OZ72** (0.31 g, 1.0 mmol), DCC (0.27 g, 1.3 mmol), and HOBT (0.16 g, 1.3 mmol) in CHCl₃ (15 ml) was stirred at 0 °C for 15 min before 1-phenylpiperazine (0.21 g, 1.3 mmol) was added. The mixture was then warmed to rt, stirred overnight, and concentrated. The residue was purified by flash chromatography (silica gel, 1% methanol in chloroform) to afford a solid, which was dissolved in chloroform (20 ml) and filtered. The filtrate was concentrated, redissolved in chloroform (15 ml) and ether (30 ml), and filtered. The filtrate was treated with 1 M ethereal HCl (1.5 ml) to afford trioxolane **OZ140** (0.36 g, 74%) as a colorless solid. mp. 155–158 °C (chloroform/ether, 1:2); ¹H NMR (500 MHz, CDCl₃) δ 1.42–2.23 (m, 22H), 2.44–2.62 (m, 1H), 3.51 (br s, 4H), 4.28 (br s, 4H), 7.42–7.60 (m, 3H), 7.79–7.95 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.59, 26.80, 27.01, 33.54, 34.84, 34.89, 36.54, 36.87, 38.53, 39.32, 55.25, 107.61, 111.61, 121.22, 130.05, 130.57, 142.36, 173.49. Anal. Calcd for C₂₇H₃₇ClN₂O₄: C, 66.31; H, 7.63; N, 5.73. Found: C, 66.26; H, 7.45; N, 5.83.

***cis*-Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane-8'-methyl imidazole-1-carboxylate (OZ141).** To a solution of **OZ119** (0.29 g, 1 mmol) in CH₃CN(10 ml) and THF (3 ml) was added 1,1'-carbonyldiimidazole (0.21 g, 1.3 mmol). The mixture was stirred at rt for 2 h before being quenched with cold water (50 ml). The resulting precipitate
 5 was collected by filtration, washed with water, and dried to afford trioxolane **OZ141** (0.34 g, 91%) as a colorless solid. mp 110–112°C (water); ¹H NMR (500 MHz, CDCl₃) δ 1.25–1.50 (m, 2H), 1.51–2.21 (m, 21H), 4.25 (d, J = 6.3 Hz, 2H), 7.07 (s, 1H), 7.42 (s, 1H), 8.13 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.61, 27.02, 33.54, 34.86, 34.88, 35.66, 36.57, 36.90, 72.07, 108.17, 111.59, 117.03, 130.76, 137.07, 148.71. Anal. Calcd for C₂₁H₂₈N₂O₅:
 10 C, 64.93; H, 7.27; N, 7.21. Found: C, 65.12; H, 7.12; N, 7.25.

Adamantane-2-spiro-3'-8'-(*p*-tolylaminocarbonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ142). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in CH₂Cl₂ (10 ml) at 0 °C was added *p*-tolyl isocyanate (133 mg, 1 mmol). The mixture was stirred at rt for 3 h before removal of solvents. The residue was
 15 triturated with water (10 ml) and filtered. Recrystallization of the solid from 95% ethanol gave trioxolane **OZ142** (280 mg, 70%) as a colorless solid. mp 150–152 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.61–2.19 (m, 18H), 2.29 (s, 3H), 3.43–3.71 (m, 4H), 6.44 (s, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 20.65, 26.60, 26.99, 34.46, 34.84, 34.94, 36.58, 36.84, 42.46, 106.90, 112.25, 120.44,
 20 129.40, 132.85, 136.53, 155.13. Anal. Calcd for C₂₃H₃₀N₂O₄: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.10; H, 7.50; N, 7.08.

Adamantane-2-spiro-3'-8'-(*t*-butylaminocarbonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ143). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in CH₂Cl₂ (10 ml) at 0 °C was added *tert*-butyl isocyanate (100 mg, 1
 25 mmol). The mixture was stirred at rt for 6 h before removal of solvents. The residue was triturated with water (10 ml) and filtered. Recrystallization of the solid from 95% ethanol gave trioxolane **OZ143** (185 mg, 51%) as a colorless solid. mp 142–144 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.35 (s, 9H), 1.62–2.09 (m, 18H), 3.35–3.59 (m, 4H), 4.34 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.60, 27.00, 29.51, 34.38, 34.84, 34.93, 36.57,
 30 36.86, 42.22, 50.82, 107.13, 112.08, 156.72. Anal. Calcd for C₂₀H₃₂N₂O₄: C, 65.91; H, 8.85; N, 7.69. Found: C, 66.19; H, 8.50; N, 7.62.

Adamantane-2-spiro-3'-8'-(phenylaminothiocarbonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ144). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in CH₂Cl₂ (10 ml) at 0 °C was added phenyl isothiocyanate (135 mg, 1 mmol). The mixture was stirred at rt for 6 h before removal of solvents. The residue was
 5 triturated with water (10 ml) and filtered. Recrystallization of the solid from 95% ethanol gave trioxolane **OZ144** (224 mg, 56%) as a colorless solid. mp 136–138 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.19 (m, 18H), 3.78–4.05 (m, 4H), 7.07–7.18 (m, 3H), 7.32 (s, 1H), 7.28–7.37 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.56, 26.96, 34.09, 34.82, 34.92, 36.52, 36.81, 47.59, 106.54, 112.45, 122.59, 125.13, 129.27, 140.42, 184.18.
 10 Anal. Calcd for C₂₂H₂₈N₂O₃S: C, 65.97; H, 7.05; N, 6.99. Found: C, 65.93; H, 7.15; N, 7.13.

cis-Adamantane-2-spiro-3'-8'-(1'H-imidazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ145). **Step 1.** To a solution of **OZ119** (0.29 g, 1 mmol) and triethylamine (0.15 g, 1.5 mmol) in CH₂Cl₂ (5 ml) at 0 °C was added dropwise a solution
 15 of methanesulfonyl chloride (0.14 g, 1.2 mmol) in CH₂Cl₂ (1 ml). The mixture was stirred at rt for 1 h before being quenched with water (5 ml). After separation of the aqueous layer, the organic layer was washed with water (5 ml) and brine (5 ml), dried over MgSO₄, filtered, and concentrated to afford the methanesulfonate (0.34 g, 92%) as a colorless solid. mp 82–84 °C (75% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.25–1.34 (m, 2H), 1.66–2.02
 20 (m, 21H), 3.00 (s, 3H), 4.04 (d, J = 6.3 Hz, 2H). **Step 2.** To a suspension of 60% NaH (0.08 g, 2 mmol) in DMF (4 ml) under nitrogen at 0 °C was added a solution of imidazole (0.14 g, 2 mmol) in DMF (4 ml). The mixture was stirred for 30 min before a solution of the above methanesulfonate (0.34 g, 0.9 mmol) in DMF (4 ml) was added dropwise. The mixture was heated at 50 °C for 2 h before being quenched with water (40 ml) and then extracted with
 25 ethyl acetate (3 x 30 ml). The combined extracts were washed with brine (3 x 30 ml), dried over MgSO₄, filtered, and concentrated. Crystallization of the residue from hexanes/CH₂Cl₂ (4:1) gave trioxolane **OZ145** (0.17 g, 55%) as a colorless solid. mp 125–128 °C (hexanes/CH₂Cl₂, 4:1); ¹H NMR (500 MHz, CDCl₃) δ 1.17–1.39 (m, 2H), 1.55–2.18 (m, 21H), 3.77 (d, J = 7.3 Hz, 2H), 6.86 (s, 1H), 7.05 (s, 1H), 7.42 (s, 1H); ¹³C
 30 NMR (125.7 MHz, CDCl₃) δ 26.59, 26.99, 27.70, 33.58, 34.85, 34.87, 36.53, 36.88, 37.97,

52.49, 108.25, 111.60, 119.16, 129.55, 137.43. Anal. Calcd for $C_{20}H_{28}N_2O_3 \cdot 0.2H_2O$: C, 69.02; H, 8.22; N, 8.05. Found: C, 68.81; H, 8.11; N, 7.96.

***cis*-Adamantane-2-spiro-3'-8'-phthalimidomethyl-1',2',4'-**

trioxaspiro[4.5]decane (OZ146). A solution of *O*-methyl 2-adamantanone oxime (2.23 g, 12.4 mmol) and 4-phthalimidomethylcyclohexanone (3.20 g, 12.4 mmol) in pentane (100 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 25% ether in hexanes) to afford trioxolane **OZ146** (1.66 g, 32%) as a colorless solid. mp 147–150 °C (ethanol); ^1H NMR (500 MHz, $CDCl_3$) δ 1.23–1.44 (m, 2H), 1.45–2.08 (m, 21H), 3.56 (d, J = 7.0 Hz, 2H), 7.69–7.74 (m, 2H), 7.81–7.89 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.61, 27.01, 27.88, 33.66, 34.85, 34.87, 35.70, 36.51, 36.92, 43.12, 108.52, 111.35, 123.22, 132.20, 133.86, 168.47. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 71.16; H, 6.75; N, 3.21.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane-8'-yl imidazole-1-

carboxylate (OZ147). To a solution of **OZ32** (0.28 g, 1 mmol) in CH_3CN (10 ml) and THF (3 ml) was added 1,1'-carbonyldiimidazole (0.21 g, 1.3 mmol). The mixture was stirred at 60–70 °C for 2 h before being cooled to rt and diluted with cold water (50 ml). The resulting precipitate was collected by filtration, washed with water, and dried to afford trioxolane **OZ147** (0.32 g, 90%, 1:1 mixture of two diastereomers) as a colorless solid. mp 116–118 °C (water); ^1H NMR (500 MHz, $CDCl_3$) δ 1.62–2.21 (m, 22H), 5.05–5.22 (m, 1H), 7.07 (s, 0.5H), 7.08 (s, 0.5H), 7.41 (s, 0.5H), 7.43 (s, 0.5H), 8.13 (s, 0.5H), 8.15 (s, 0.5H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.58, 27.00, 28.05, 28.32, 30.53, 30.88, 34.83, 34.94, 36.48, 36.56, 36.85, 74.61, 75.01, 107.24, 107.30, 112.01, 112.11, 117.01, 117.04, 130.74, 137.08, 148.09, 148.14. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 64.22; H, 7.00; N, 7.30.

***cis*-Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane-8'-methyl 4-phenylpiperazine-1-carboxylate (OZ148).** To a solution of **OZ141** (310 mg, 0.86 mmol) in THF (10 ml) at 0 °C was added methyl triflate (142 mg, 0.86 mmol). The mixture was stirred at 0 °C for 30 min before 1-phenylpiperazine (140 mg, 0.86 mmol) was added. The reaction was stirred at rt for 18 h before removal of solvents. Crystallization of the residue from ethanol/water (3:1) gave trioxolane **OZ148** (323 mg, 83%) as a colorless solid. mp

145–146 °C (ethanol/water, 3:1); ^1H NMR (500 MHz, CDCl_3) δ 1.21–1.42 (m, 2H), 1.58–2.10 (m, 21H), 3.15 (br s, 4H), 3.63 (br s, 4H), 3.96 (d, J = 6.2 Hz, 2H), 6.90 (dd, J = 7.5, 7.5 Hz, 1H), 6.93 (d, J = 7.8 Hz, 2H), 7.28 (dd, J = 8.6, 7.4 Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.61, 26.79, 27.01, 33.77, 34.87, 34.88, 36.03, 36.55, 36.91, 43.81, 49.46, 69.57, 108.61, 111.39, 116.71, 120.40, 129.20, 151.27, 155.45. Anal. Calcd for $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_5$: C, 69.68; H, 7.94; N, 5.80. Found: C, 69.83; H, 7.98; N, 5.86.

Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane-8'-spiro-1''-3''-oxo-3''*H*-isobenzofuran (OZ149). A solution of *O*-methyl 2-adamantanone oxime (0.54 g, 3 mmol) and spiro[cyclohexane-1,1'(3'*H*)-isobenzofuran]-3',4-dione (0.65 g, 3 mmol) in pentane (50 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 25% ether in hexanes) to afford trioxolane **OZ149** (0.50 g, 44%) as a colorless solid. mp 160–162 °C (ethanol/water, 3:1); ^1H NMR (500 MHz, CDCl_3) δ 1.65–2.12 (m, 18H), 2.21 (ddd, J = 13.8, 13.8, 3.9 Hz, 2H), 2.31 (ddd, J = 13.7, 13.7, 4.0 Hz, 2H), 7.38 (d, J = 7.5 Hz, 1H), 7.52 (dd, J = 7.5, 7.5 Hz, 1H), 7.67 (dd, J = 7.5, 7.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.61, 26.97, 30.73, 34.27, 34.85, 34.88, 36.60, 36.86, 84.97, 107.56, 112.05, 120.85, 124.64, 125.96, 129.25, 134.08, 153.70, 169.43. Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{O}_5$: C, 72.23; H, 6.85. Found: C, 72.12; H, 6.65.

Adamantane-2-spiro-3'-8'-(4'-nitrophenyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ151). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in CH_3CN (10 ml) was added 4-nitrophenyl triflate (271 mg, 1 mmol). The mixture was stirred at 65 °C for 64 h before removal of solvents. The crude product was purified by flash chromatography (silica gel, 5% ether in hexanes) and by subsequent crystallization from methanol to afford trioxolane **OZ151** (120 mg, 31%) as a yellowish solid. mp 140–142 °C (methanol); ^1H NMR (500 MHz, CDCl_3) δ 1.61–2.19 (m, 18H), 3.48–3.75 (m, 4H), 6.83 (d, J = 9.3 Hz, 2H), 8.11 (d, J = 9.3 Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.54, 26.94, 33.84, 34.82, 34.92, 36.55, 36.79, 45.57, 106.63, 112.40, 112.93, 126.05, 138.63, 154.14. Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.40; H, 6.66; N, 7.29.

5-Hydroxyadamantane-2-spiro-3'-1',2',4',9',12'-pentaoxidispiro[4.2.4.2]tetradecane (OZ152). Step 1. A solution of *O*-methyl 5-acetoxy-

2-adamantanone oxime (1.18 g, 5.0 mmol) and 1,4-dioxaspiro[4.5]decane-8-one (790 mg, 5.0 mmol) in pentane (20 ml) and CH₂Cl₂ (100 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to afford **5-acetoxyspiro[4.2.4.2]tetradecane** (0.61 g, 32%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 1.78–2.28 (m, 24H), 3.95 (s, 4H). **Step 2.** A mixture of the above acetate trioxolane (1.30 g, 3.42 mmol), EtOH (7 ml), and 30% aq. KOH (6 ml) was heated at 50 °C for 2 h. After removal of the solvent, the residue was diluted with water and extracted with ether. The organic layer was washed with water and brine, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 80% ether in hexanes) to afford trioxolane **OZ152** (100 mg, 9%, minor isomer, eluted first) as a colorless solid and trioxolane **OZ153** (414 mg, 36%, major isomer, eluted second) as a colorless solid. For **OZ152**: mp 132–134 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.56–2.19 (m, 21H), 3.95 (s, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 29.27, 31.65, 32.11, 33.52, 38.10, 42.13, 44.59, 64.39, 67.01, 107.84, 108.47, 110.40. Anal. Calcd for C₁₈H₂₆O₆: C, 63.89; H, 7.74. Found: C, 64.02; H, 7.81.

5-Hydroxyspiro[4.2.4.2]tetradecane (OZ153). For preparation, see **OZ152**. mp 112–114 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.54–2.22 (m, 21H), 3.98 (s, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 28.85, 31.72, 32.09, 33.40, 38.31, 42.11, 44.54, 64.36, 67.37, 107.80, 108.50, 110.36. Anal. Calcd for C₁₈H₂₆O₆: C, 63.89; H, 7.74. Found: C, 64.03; H, 7.66.

cis-Adamantane-2-spiro-3'-8'-[4'-(4',5'-dihydro-4',4'-dimethyl-2'-oxazolyl)phenyl]-1',2',4'-trioxaspiro[4.5]decane (OZ154). A solution of *O*-methyl 2-adamantanone oxime (1.32 g, 7.4 mmol) and 4-[4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl]cyclohexanone (2.00 g, 7.4 mmol) in pentane (100 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10 to 30% ether in hexanes) to afford trioxolane **OZ154** (0.80 g, 25%) as a colorless solid. mp 138–140 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.37 (s, 6H), 1.59–2.16 (m, 22H), 2.51–2.68 (m, 1H), 4.08 (s, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.63,

27.03, 28.38, 31.29, 34.70, 34.88, 34.90, 36.56, 36.93, 42.98, 67.52, 79.15, 108.26, 111.46, 126.22, 126.70, 128.44, 149.58, 162.01. Anal. Calcd for C₂₇H₃₅NO₄: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.35; H, 8.08; N, 3.18.

***cis*-Adamantane-2-spiro-3'-8'-[[2'-hydroxyethyl]amino]carbonyl]-1',2',4'-**

5 **trioxaspiro[4.5]decane (OZ155).** A solution of **OZ72** (0.31 g, 1.0 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.29 g, 1.5 mmol), HOBT (0.20 g, 1.5 mmol), and 2-aminoethanol (0.09 g, 1.5 mmol) in DMF (10 ml) was stirred at rt for 18h before being quenched with 2 M aq. HCl (30 ml). The mixture was extracted with ethyl acetate (4 x 30 ml), and the combined extracts were washed with water (2 x 30
10 ml) and brine (30 ml), dried over MgSO₄, and concentrated. The residue was purified by flash chromatography (silica gel, 5% methanol in CH₂Cl₂) to afford trioxolane **OZ155** (0.16 g, 46%) as a colorless solid. mp 114–116 °C (ether/CH₂Cl₂ 2:1); ¹H NMR (500 MHz, CDCl₃) δ 1.59–2.08 (m, 22H), 2.17 (br s, 1H), 3.38–3.45 (m, 2H), 3.71 (t, J = 4.8 Hz, 2H), 6.13 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.44, 26.84, 26.99, 33.58, 34.75, 34.78,
15 36.35, 36.75, 42.27, 43.58, 62.31, 107.77, 111.53, 176.04. Anal. Calcd for C₁₉H₂₉NO₅: C, 64.93; H, 8.32; N, 3.99. Found: C, 64.68; H, 8.11; N, 3.93.

***cis*-Adamantane-2-spiro-3'-8'-benzyl-1',2',4'-trioxaspiro[4.5]decane (OZ156).**

A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 4-benzylcyclohexanone (940 mg, 5 mmol) in cyclohexane (80 ml) and CH₂Cl₂ (20 ml) was
20 treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in hexanes) and by subsequent recrystallization from ethanol/CH₂Cl₂ (19:1) to afford trioxolane **OZ156** (825 mg, 47%) as a colorless solid. mp 87–89 °C (ethanol/CH₂Cl₂, 19:1); ¹H NMR (500 MHz, CDCl₃) δ 1.18–1.37 (m, 2H), 1.49–2.20 (m, 21H), 2.50 (d, J = 7.2 Hz, 2H), 7.09–7.40 (m, 5H); ¹³C NMR (125.7 MHz,
25 CDCl₃) δ 26.49, 26.88, 29.93, 34.15, 34.78, 34.79, 36.39, 36.81, 38.16, 42.89, 108.94, 111.19, 125.78, 128.16, 129.07, 140.86. Anal. Calcd for C₂₃H₃₀O₅: C, 77.93; H, 8.53. Found: C, 78.17; H, 8.45.

**Adamantane-2-spiro-3'-8'-[(4'-methyl-1'-piperazinyl)carbonyl]-1',2',4'-trioxo-
8'-azaspiro[4.5]decane (OZ157).** To a solution of **OZ80** (301 mg, 1 mmol) and
30 triethylamine (404 mg, 4 mmol) in CH₂Cl₂ (7 ml) at 0 °C was added 4-methyl-1-piperazinecarbonyl chloride hydrochloride (220 mg, 1.1 mmol). The mixture was stirred at

rt for 16 h, diluted with CH₂Cl₂ (10 ml), washed with water (2 x 10 ml) and brine (10 ml), dried over MgSO₄, and concentrated. Crystallization of the residue from ethanol gave trioxolane **OZ157** (105 mg, 27%) as a colorless solid. mp 146–148 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.61–2.09 (m, 18H), 2.30 (s, 3H), 2.31–2.48 (m, 4H), 3.21–3.47 (m, 8H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.61, 27.01, 34.52, 34.85, 34.95, 36.59, 36.87, 44.77, 46.14, 46.87, 54.91, 107.24, 112.04, 163.68. Anal. Calcd for C₂₁H₃₃N₃O₄: C, 64.42; H, 8.50; N, 10.73. Found: C, 64.34; H, 8.37; N, 10.61.

Adamantane-2-spiro-3'-8'-(1'-piperidiny)-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ159). To a solution of **OZ05** (555 mg, 2 mmol) in 1,2-dichloroethane (10 ml) were added piperidine (187 mg, 2.2 mmol) and acetic acid (10 drops). The reaction mixture was stirred at rt for 15 min before sodium triacetoxyborohydride (677 mg, 3.2 mmol) was added. The mixture was stirred for 5 h before being quenched with 1 M aq. NaOH (2 ml). The resulting mixture was extracted with CH₂Cl₂ (40 ml), washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO₄, and concentrated. The residue was dissolved in ether (2 ml), treated with excess 2 M ethereal HCl, and filtered to give trioxolane **OZ159** (460 mg, 60%, 1:1 mixture of two diastereomers) as a colorless solid. mp 128 °C dec (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.39 (br s, 1H), 1.58–2.20 (m, 23H), 2.21–2.60 (m, 4H), 2.78 (br s, 2H), 3.11 (br s, 1H), 3.28–3.59 (m, 2H), 11.94 (br s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 22.53, 22.69, 22.73, 23.33, 23.43, 26.37, 26.40, 26.78, 32.65, 32.81, 34.66, 34.69, 34.72, 34.91, 36.28, 36.64, 49.77, 49.98, 63.81, 64.20, 106.50, 106.56, 112.20, 112.37. Anal. Calcd for C₂₁H₃₄ClNO₃•0.25H₂O: C, 64.93; H, 8.95; N, 3.61. Found: C, 64.48; H, 8.59; N, 3.63.

Adamantane-2-spiro-3'-8'-(benzylamino)-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ160). To a solution of **OZ05** (555 mg, 2 mmol) in 1,2-dichloroethane (10 ml) were added benzylamine (236 mg, 2.2 mmol) and acetic acid (10 drops). The reaction mixture was stirred at rt for 15 min before sodium triacetoxyborohydride (677 mg, 3.2 mmol) was added. The mixture was stirred for 5 h before being quenched with 1 M aq. NaOH (2 ml). The resulting mixture was extracted with CH₂Cl₂ (40 ml), washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO₄, and concentrated. The residue was dissolved in ether (2 ml), treated with excess 2 M ethereal HCl, and filtered to give trioxolane **OZ160** (567 mg, 70%, 2:1 mixture of two diastereomers) as a colorless solid.

mp 160 °C dec (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.42–2.31 (m, 22H), 2.78–2.89 (m, 1H), 3.91–4.19 (m, 2H), 7.31–7.46 (m, 3H), 7.59–7.71 (m, 2H), 10.00 (br s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 25.95, 26.53, 26.89, 32.21, 34.78, 34.92, 36.38, 36.45, 36.81, 47.82, 53.65, 106.71, 106.79, 111.72, 112.33, 129.07, 129.12, 129.30, 129.35, 130.25, 130.51, 130.57. Anal. Calcd for C₂₃H₃₂ClNO₃: C, 68.05; H, 7.95; N, 3.45. Found: C, 67.89; H, 7.71; N, 3.35.

Adamantane-2-spiro-3'-8'-[[3'-(4'-morpholinyl)propyl]amino]-1',2',4'-trioxaspiro[4.5]decane (OZ161). To a solution of **OZ05** (555 mg, 2 mmol) in 1,2-dichloroethane (10 ml) were added 4-(3-aminopropyl)morpholine (317 mg, 2.2 mmol) and acetic acid (10 drops). The reaction mixture was stirred at rt for 15 min before sodium triacetoxymethylborohydride (677 mg, 3.2 mmol) was added. The mixture was stirred for 5 h before being quenched with 1 M aq. NaOH (2 ml). The resulting mixture was extracted with CH₂Cl₂ (40 ml), washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO₄, and concentrated. The residue was dissolved in ether (2 ml), treated with excess 2 M ethereal HCl, and filtered to give trioxolane **OZ161** (552 mg, 68%, 1:1 mixture of two diastereomers) as a colorless solid. mp 70–72 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.31–2.20 (m, 24H), 2.32–2.60 (m, 7H), 2.61–2.78 (m, 2H), 3.62–3.83 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.29, 26.70, 26.77, 26.81, 29.61, 30.02, 31.97, 32.42, 34.55, 34.59, 34.63, 34.70, 36.16, 36.20, 36.61, 43.27, 45.76, 46.00, 53.62, 53.64, 54.62, 54.86, 57.31, 57.42, 66.80, 108.35, 108.39, 111.05, 111.34. Anal. Calcd for C₂₃H₃₈N₂O₄: C, 67.95; H, 9.42; N, 6.89. Found: C, 67.84; H, 9.30; N, 6.68.

Adamantane-2-spiro-3'-8'-(cyclohexylamino)-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ162). To a solution of **OZ05** (555 mg, 2 mmol) in 1,2-dichloroethane (10 ml) were added cyclohexylamine (218 mg, 2.2 mmol) and acetic acid (10 drops). The reaction mixture was stirred at rt for 15 min before sodium triacetoxymethylborohydride (677 mg, 3.2 mmol) was added. The mixture was stirred for 5 h before being quenched with 1 M aq. NaOH (2 ml). The resulting mixture was extracted with CH₂Cl₂ (40 ml), washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO₄, and concentrated. The residue was dissolved in ether (2 ml), treated with excess 2 M ethereal HCl, and filtered to give **OZ162** (516 mg, 65%, 1:1 mixture of two diastereomers) as a colorless solid. mp 240 °C dec (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.26 (br s, 2H), 1.55–2.42 (m, 30H), 2.97–3.21

(m, 2H), 9.33 (br s, 1H), 9.37 (br s, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 24.83, 24.87, 26.56, 26.90, 26.97, 29.45, 32.58, 34.80, 34.82, 34.94, 36.39, 36.51, 36.85, 52.70, 54.89, 55.12, 106.82, 106.91, 111.67, 112.32. Anal. Calcd for $\text{C}_{22}\text{H}_{36}\text{ClNO}_3$: C, 66.39; H, 9.12; N, 3.52. Found: C, 66.28; H, 8.97; N, 3.54.

5 ***cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ163)**. A solution of **OZ146** (423 mg, 1 mmol) and hydrazine monohydrate (150 mg, 3 mmol) in chloroform (9 ml) and methanol (1 ml) was heated at 55 °C for 48 h. The reaction mixture was cooled to rt and filtered to remove solid by-products. The filtrate was washed with water (10 ml) and brine (10 ml), dried over MgSO_4 , filtered,
10 and concentrated. The solid was dissolved in ether (10 ml), treated with 1 M ethereal HCl (1.2 ml), and filtered. Recrystallization from ether gave trioxolane **OZ163** (80 mg, 24%) as a yellowish solid. mp 146 °C dec (ether); ^1H NMR (500 MHz, CDCl_3) δ 1.23–1.42 (m, 2H), 1.59–2.20 (m, 21H), 2.86 (br s, 2H), 8.35 (br s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.45, 26.86, 27.61, 33.27, 34.45, 34.76, 36.37, 36.77, 39.25, 44.88, 107.92, 111.52. Anal.
15 Calcd for $\text{C}_{17}\text{H}_{28}\text{ClNO}_3$: C, 61.90; H, 8.56; N, 4.25. Found: C, 59.83; H, 8.21; N, 5.07.

***cis*-Adamantane-2-spiro-3'-8'-[4'-(ethoxycarbonyl)phenyl]-1',2',4'-trioxaspiro[4.5]decane (OZ164)**. A solution of *O*-methyl 2-adamantanone oxime (1.10 g, 6.2 mmol) and 4-[4-(ethoxycarbonyl)phenyl]cyclohexanone (1.70 g, 6.2 mmol) in pentane (100 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure.
20 The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ164** (1.60 g, 63%) as a colorless solid. mp 129–132 °C (hexanes/ether 9:1); ^1H NMR (500 MHz, CDCl_3) δ 1.38 (t, J = 7.2 Hz, 3H), 1.63–2.22 (m, 22H), 2.56–2.71 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 7.96 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 14.34, 26.49, 26.89, 31.18, 34.59, 34.80, 36.42,
25 36.80, 42.99, 60.76, 108.18, 111.51, 126.77, 128.54, 129.74, 151.39, 166.57. Anal. Calcd for $\text{C}_{25}\text{H}_{32}\text{O}_5$: C, 72.79; H, 7.82. Found: C, 72.83; H, 7.90.

***cis*-Adamantane-2-spiro-3'-8'-(4'-carboxyphenyl)-1',2',4'-trioxaspiro[4.5]decane (OZ165)**. A mixture of **OZ164** (1.38 g, 3.35 mmol), KOH (1.13 g), THF (30 ml), methanol (30 ml), and water (6 ml) was heated at 50 °C for 2 h. The
30 mixture was concentrated to 10 ml, diluted with water (50 ml), and extracted with ethyl acetate. The aqueous layer was acidified with 1 M aq. HCl to pH = 2, and the resulting

solid was collected by filtration to give trioxolane **OZ165** (1.08 g, 84%) as a colorless solid. mp 157 °C dec; ¹H NMR (500 MHz, CDCl₃) δ 1.63–2.22 (m, 22H), 2.57–2.72 (m, 1H), 7.31 (d, J = 8.3 Hz, 2H), 8.03 (d, J = 8.1 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.49, 26.90, 31.14, 34.58, 34.81, 36.43, 36.80, 43.10, 108.14, 111.54, 126.99, 127.23, 130.46, 152.54, 171.45. Anal. Calcd for C₂₃H₂₈O₅: C, 71.85; H, 7.34. Found: C, 71.68; H, 7.33.

cis-Adamantane-2-spiro-3'-8'-[[4'-(ethoxycarbonyl)phenoxy]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ166). To a solution of **OZ119** (0.59 g, 2.0 mmol), triphenylphosphine (0.63 g, 2.4 mmol), and ethyl 4-hydroxybenzoate (0.50 g, 3.0 mmol) in THF (12 ml) at 0 °C was added dropwise a solution of diisopropyl azodicarboxylate (0.65 g, 3.2 mmol) in THF (0.5 ml). The mixture was then warmed to rt and stirred at rt for 2 h before removal of solvents. The crude product was purified by flash chromatography (silica gel, 20% ether in hexanes) to afford trioxolane **OZ166** (0.65 g, 73%) as a colorless solid. mp 142–143 °C (hexanes/ether 9:1); ¹H NMR (500 MHz, CDCl₃) δ 1.38 (t, J = 7.2 Hz, 3H), 1.30–1.58 (m, 2H), 1.60–2.21 (m, 21H), 3.82 (d, J = 5.9 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 14.35, 26.48, 26.85, 26.87, 33.72, 34.78, 34.80, 36.14, 36.40, 36.79, 60.58, 72.43, 108.64, 111.41, 113.97, 122.84, 131.50, 162.75, 166.38. Anal. Calcd for C₂₆H₃₄O₆: C, 70.56; H, 7.74. Found: C, 70.72; H, 7.76.

trans-Adamantane-2-spiro-3'-8'-phthalimidomethyl-1',2',4'-trioxaspiro[4.5]decane (OZ167). For the major isomer (*cis*), see **OZ146**. A solution of *O*-methyl 2-adamantanone oxime (2.23 g, 12.4 mmol) and 4-phthalimidomethylcyclohexanone (3.20 g, 12.4 mmol) in pentane (100 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 25% ether in hexanes and 40% CH₂Cl₂ in hexanes) to afford trioxolane **OZ167** (0.16 g, 3%) as a colorless solid. mp 140–142 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.40–2.17 (m, 23H), 3.60 (d, J = 7.5 Hz, 2H), 7.68–7.75 (m, 2H), 7.82–7.88 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.63, 27.03, 27.69, 33.46, 34.83, 34.99, 35.71, 36.51, 36.93, 42.98, 108.58, 111.74, 123.25, 132.19, 133.91, 168.52. Anal. Calcd for C₂₅H₂₉NO₅: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.75; H, 7.03; N, 3.25.

Adamantane-2-spiro-3'-1',2',4',9',10',12'-hexaoxadispiro[4.2.4.2]tetradecane-11'-spiro-2''-adamantane (OZ169). A solution of *O*-methyl 2-adamantanone oxime (1.80 g, 10 mmol) and 1,4-cyclohexanedione (2.24 g, 20 mmol) in pentane (60 ml) and CH₂Cl₂ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ169** (346 mg, 16%, 2:1 mixture of two diastereomers) as a colorless solid. mp 156–158 °C (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 1.92 (s, 8H), 1.60–2.25 (m, 28H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.45, 26.83, 26.86, 31.57, 34.72, 34.75, 34.80, 34.84, 36.29, 36.31, 36.74, 107.65, 107.71, 111.72. Anal. Calcd for C₂₆H₃₆O₆: C, 70.24; H, 8.16. Found: C, 70.18; H, 8.28.

Adamantane-2-spiro-3'-8'-[(2',2',6',6'-tetramethyl-4'-piperidinyl)amino]-1',2',4'-trioxaspiro[4.5]decane dihydrochloride (OZ171). To a solution of **OZ05** (555 mg, 2 mmol) in 1,2-dichloroethane (10 ml) were added 4-amino-2,2,6,6-tetramethylpiperidine (344 mg, 2.2 mmol) and acetic acid (10 drops). The reaction mixture was stirred at rt for 15 min before sodium triacetoxyborohydride (677 mg, 3.2 mmol) was added. The mixture was stirred for 5 h before being quenched with 1 M aq. NaOH (2 ml). The resulting mixture was extracted with CH₂Cl₂ (40 ml), washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO₄, and concentrated. The residue was dissolved in ether (2 ml), treated with excess 2 M ethereal HCl, and filtered to give trioxolane **OZ171** (650 mg, 66%, 1:1 mixture of two diastereomers) as a colorless solid. mp 165 °C dec (ether); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.43 (s, 6H), 1.45 (s, 6H), 1.46–2.37 (m, 26H), 3.14–3.40 (m, 1H), 3.55–3.79 (m, 1H), 8.28–8.45 (m, 1H), 9.25–9.47 (m, 2H), 9.55–9.72 (m, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 24.03, 24.07, 25.96, 26.38, 29.78, 31.70, 34.38, 34.43, 34.55, 35.81, 35.88, 36.22, 37.00, 45.66, 45.71, 50.74, 50.93, 56.22, 56.26, 107.42, 107.46, 111.13, 111.41. Anal. Calcd for C₂₅H₄₄Cl₂N₂O₃•1.5 H₂O: C, 57.90; H, 9.14; N, 5.40. Found: C, 57.65; H, 8.74; N, 5.36.

Adamantane-2-spiro-3'-8'-oxo-1',2',4'-trioxaspiro[4.5]decane amidinohydrazone hydrochloride (OZ172). To a solution of **OZ05** (555 mg, 2 mmol) in THF (11 ml), water (3 ml), and ethanol (3.5 ml) were added 2 M aq. HCl (1.5 ml) and aminoguanidine bicarbonate (299 mg, 2.2 mmol). The mixture was stirred at rt for 30 h before removal of solvents. The residue was triturated with ethanol (10 ml) and the

resulting precipitate was collected by filtration and washed with THF to give trioxolane **OZ172** (476 mg, 64%) as a colorless solid. mp 150 °C dec (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.46–2.27 (m, 18H), 2.42–2.61 (m, 2H), 2.62–2.83 (m, 2H), 6.34 (s, 1H), 7.63 (br s, 2H), 7.91 (s, 1H), 10.95 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 24.83, 26.37, 26.77, 31.72, 32.49, 33.62, 34.70, 34.74, 34.84, 36.23, 36.26, 36.65, 107.26, 112.27, 156.57, 157.93. Anal. Calcd for C₁₇H₂₇ClN₄O₃: C, 55.05; H, 7.34; N, 15.11. Found: C, 55.14; H, 7.51; N, 15.30.

Adamantane-2-spiro-3'-8'-[(methoxyacetyl)benzylamino]-1',2',4'-trioxaspiro[4.5]decane (OZ173). To a solution of **OZ160** (342 mg, 0.84 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (255 mg, 2.53 mmol) and methoxyacetyl chloride (137 mg, 1.26 mmol). The resulting mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), and washed with water (10 ml) and brine (10 ml). The organic layer was separated, dried over MgSO₄, and concentrated. The residue was triturated with ether to give trioxolane **OZ173** (110 mg, 30%, 3:2 mixture of two diastereomers) as a colorless solid. mp 132–134 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.47–2.20 (m, 22H), 3.38 (s, 1.8H), 3.48 (s, 1.2H), 3.99 (s, 1.2H), 4.23 (s, 0.8H), 4.46 (s, 1.2H), 4.55 (s, 0.8H), 4.42–4.58 (m, 1H), 7.09–7.46 (m, 5H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.41, 26.80, 26.87, 27.11, 28.74, 33.31, 33.54, 34.67, 34.74, 34.93, 36.29, 36.72, 44.76, 45.52, 51.71, 55.36, 59.20, 71.54, 72.30, 107.56, 111.65, 125.61, 126.74, 127.10, 127.30, 128.33, 128.78, 137.93, 139.04, 169.30, 169.82. Anal. Calcd for C₂₆H₃₅NO₅: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.76; H, 8.02; N, 3.08.

Adamantane-2-spiro-3'-8'-[(methoxyacetyl)cyclohexylamino]-1',2',4'-trioxaspiro[4.5]decane (OZ174). To a solution of **OZ162** (330 mg, 0.83 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (251 mg, 2.49 mmol) and methoxyacetyl chloride (135 mg, 1.24 mmol). The resulting mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), and washed with water (10 ml) and brine (10 ml). The organic layer was separated, dried over MgSO₄, and concentrated. The residue was triturated with ether to give trioxolane **OZ174** (109 mg, 30%, 4:1 mixture of two diastereomers) as a colorless solid. mp 140–142 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.02–2.20 (m, 30H), 2.32–2.72 (m, 2H), 2.81–3.05 (m, 1H), 3.40 (s, 2.4H), 3.42 (s, 0.6H), 3.48–3.69 (m, 1H), 4.02 (s, 1.6H), 4.03 (m, 0.4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 25.25, 26.00, 26.44, 26.84, 27.89, 29.77,

33.50, 34.21, 34.77, 36.32, 36.73, 55.51, 56.10, 58.84, 73.12, 73.71, 107.39, 107.52, 111.83, 168.17. Anal. Calcd for C₂₅H₃₉NO₅: C, 69.25; H, 9.07; N, 3.23. Found: C, 69.12; H, 9.06; N, 3.23.

***cis*-Adamantane-2-spiro-3'-8'-(2'-hydroxyamino-2'-oxoethyl)-1',2',4'-**

5 **trioxaspiro[4.5]decane (OZ175).** To a solution of **OZ78** (322 mg, 1.0 mmol) in ether (10 ml) at 0 °C were added triethylamine (202 mg, 2 mmol) and ethyl chloroformate (217 mg, 2 mmol). The mixture was stirred at 0 °C for 15 min before a freshly prepared solution of hydroxylamine was added. [A suspension of hydroxylamine hydrochloride (170 mg, 2.48 mmol) and sodium bicarbonate (203 mg, 2.48 mmol) in methanol (5 ml) was stirred at rt
10 for 15 min. The supernatant was used as such.] The resulting mixture was stirred at rt for 12 h, diluted with ether (10 ml), washed with water (10 ml), dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 5% methanol in CH₂Cl₂) and by subsequent recrystallization from ethanol to afford trioxolane **OZ175** (95 mg, 28%) as a colorless solid. mp 138–140 °C (ethanol); ¹H NMR (500 MHz, DMSO-*d*₆) δ 0.81–1.27 (m, 3H), 1.40–2.19 (m, 22H), 8.65 (s, 1H), 10.33 (s, 1H); ¹³C NMR
15 (125.7 MHz, DMSO-*d*₆) δ 25.84, 26.25, 29.40, 32.60, 33.35, 34.26, 35.81, 36.13, 38.68, 108.33, 110.44, 167.91. Anal. Calcd for C₁₈H₂₇NO₅: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.11; H, 8.10; N, 3.97.

***cis*-Adamantane-2-spiro-3'-8'-[(4'-carboxyphenoxy)methyl]-1',2',4'-**

20 **trioxaspiro[4.5]decane (OZ176).** A mixture of **OZ166** (0.30 g, 0.68 mmol), KOH (0.38 g), THF (10 ml), methanol (10 ml), and water (2 ml) was heated at 50 °C for 3 h. The mixture was concentrated to 5 ml, diluted with water (15 ml), and acidified with 1 M aq. HCl (1 ml). The resulting solid was collected by filtration to give trioxolane **OZ176** (0.21 g, 75%) as a colorless solid. mp 165–168 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.15–1.27
25 (m, 2H), 1.50–2.17 (m, 21H), 3.88 (d, J = 6.2 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.99, 26.40, 26.53, 33.27, 34.45, 35.35, 35.95, 36.26, 72.09, 108.70, 110.71, 114.41, 123.04, 131.50, 162.47, 167.15. Anal. Calcd for C₂₄H₃₀O₆: C, 69.54; H, 7.30. Found: C, 69.67; H, 7.21.

***cis*-Adamantane-2-spiro-3'-8'-(1'*H*-1',2',4'-triazol-1'-ylmethyl)-1',2',4'-**

30 **trioxaspiro[4.5]decane (OZ177).** To a suspension of 60% NaH (0.08 g, 2 mmol) in DMF (4 ml) under nitrogen at 0°C was added a solution of 1,2,4-triazole (0.14 g, 2 mmol) in

DMF (4 ml). The mixture was stirred for 30 min before a solution of the methanesulfonate of **OZ119** (0.37 g, 1.0 mmol) in DMF (4 ml) was added dropwise. The mixture was heated at 50 °C for 2 h before being quenched with water (40 ml) and then extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with brine (3 x 30 ml), dried over
 5 MgSO₄, filtered, and concentrated. Crystallization of the residue from hexanes/ether (4:1) gave trioxolane **OZ177** (0.21 g, 61%) as a colorless solid. mp 123–124 °C (hexanes/ether 4:1); ¹H NMR (500 MHz, CDCl₃) δ 1.17–1.42 (m, 2H), 1.50–2.19 (m, 21H), 4.02 (d, J = 7.0 Hz, 2H), 7.95 (s, 1H), 8.02 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.43, 26.82, 27.48, 33.43, 34.75, 36.35, 36.47, 36.73, 54.84, 108.19, 111.57, 143.35, 152.10. Anal.
 10 Calcd for C₁₉H₂₇N₃O₃: C, 66.06; H, 7.88; N, 12.16. Found: C, 65.86; H, 8.06; N, 11.89.

cis-Adamantane-2-spiro-3'-8'-[(4'-methylsulfonyl)phenyl]-1',2',4'-trioxaspiro[4.5]decane (OZ178). A solution of *O*-methyl 2-adamantanone oxime (0.54 g, 3 mmol) and 4-[4-(methylsulfonyl)phenyl]cyclohexanone (0.75 g, 3 mmol) in pentane (50 ml) and CH₂Cl₂ (50 ml) was treated with ozone according to the general procedure. The
 15 crude product was purified by flash chromatography (silica gel, 30% ethyl acetate in hexanes) to afford trioxolane **OZ178** (0.22 g, 18%) as a colorless solid. mp 132–135 °C (hexanes/CH₂Cl₂ 4:1); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.19 (m, 22H), 2.60–2.74 (m, 1H), 3.04 (s, 3H), 7.40 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.48, 26.88, 31.14, 34.48, 34.80, 36.43, 36.78, 42.94, 44.53, 107.95, 111.64,
 20 127.59, 127.80, 138.45, 152.59. Anal. Calcd for C₂₃H₃₀O₅S: C, 66.00; H, 7.22. Found: C, 66.08; H, 7.16.

cis-Adamantane-2-spiro-3'-8'-(1'*H*-imidazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ179). To a solution of **OZ145** (1.08 g, 3.1 mmol) in ether (80 ml) was added 1 M ethereal HCl (3.5 ml). The resulting precipitate was
 25 collected by filtration to afford trioxolane **OZ179** (1.14 g, 97%) as a colorless solid. mp 153–156 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.19–1.46 (m, 2H), 1.50–2.19 (m, 21H), 4.24 (br s, 2H), 7.15 (s, 1H), 7.42 (s, 1H), 9.70 (s, 1H), 15.94 (br s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.38, 26.77, 27.26, 33.20, 34.71, 36.29, 36.68, 37.17, 54.75, 107.85, 111.62, 119.72, 121.22, 135.82. Anal. Calcd for C₂₀H₂₉ClN₂O₃: C, 63.06; H, 7.67; N, 7.35. Found:
 30 C, 63.21; H, 7.63; N, 7.30.

***cis*-Adamantane-2-spiro-3'-8'-[4'-(4',5'-dihydro-4',4'-dimethyl-2'-oxazolyl)phenyl]-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ180).** To a solution of **OZ154** (0.21 g, 0.48 mmol) in ether (9 ml) and CH₂Cl₂ (1 ml) was added 1 M ethereal HCl (0.5 ml). The resulting precipitate was collected by filtration to afford trioxolane **OZ180** (0.20 g, 88%) as a colorless solid. mp 143–145 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.58–2.25 (m, 28H), 2.58–2.80 (m, 1H), 4.69 (br s, 2H), 7.44 (br s, 2H), 8.40 (br s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.44, 26.84, 27.19, 30.87, 34.37, 34.76, 36.39, 36.74, 43.21, 63.92, 83.36, 107.83, 111.59, 117.60, 128.16, 131.38, 156.27, 168.98. Anal. Calcd for C₂₇H₃₆ClNO₄: C, 68.41; H, 7.65; N, 2.95. Found: C, 68.26; H, 7.80; N, 2.90.

***cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane citrate (OZ181).** **Step 1.** A solution of **OZ146** (1.00 g, 2.36 mmol) and hydrazine monohydrate (0.50 g, 10 mmol) in chloroform (22.5 ml) and methanol (2.5 ml) was heated under nitrogen at 55 °C for 25 h. The reaction mixture was cooled to rt and filtered to remove solid by-products. The filtrate was washed with water (10 ml) and brine (10 ml), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, CHCl₃/MeOH/Et₃N, 90:10:1) to afford ***cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane** (0.63 g, 91%) as a colorless solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.14–1.22 (m, 2H), 1.30–1.40 (m, 2H), 1.60–2.10 (m, 21H), 2.55 (d, J = 6.6 Hz, 2H). **Step 2.** To a solution of the above amine (0.40 g, 1.36 mmol) in acetone (10 ml) was added a solution of citric acid (0.25 g, 1.30 mmol) in acetone (10 ml). The mixture was stirred at rt for 30 min and filtered. The filtrate was concentrated and treated with ether (25 ml). The resulting precipitate was collected by filtration, re-dissolved in methanol (5 ml), and concentrated to afford trioxolane **OZ181** (0.30 g, 45%) as a colorless solid. mp 76–77 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.04–1.21 (m, 2H), 1.56–2.04 (m, 21H), 2.53 (AB system, 4H), 2.69 (d, J = 7.3 Hz, 2H), 7.78 (br s, 3H), 11.50 (br s, 2H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.95, 26.37, 27.10, 33.01, 33.88, 34.40, 34.42, 35.90, 36.23, 43.61, 44.43, 71.35, 108.29, 110.81, 171.39. Anal. Calcd for C₂₃H₃₅NO₁₀•0.4H₂O: C, 55.52; H, 7.36; N, 2.82. Found: C, 55.25; H, 7.25; N, 2.66.

Adamantane-2-spiro-3'-8'-[[2'-(1'*H*-imidazol-1'-yl)ethoxy]carbonyl]-1',2',4'-trioxaspiro[4.5]decane (OZ182). To a solution of **OZ72** (0.31 g, 1.0 mmol), triphenylphosphine (0.26 g, 1.0 mmol), and 1-(2-hydroxyethyl)imidazole (0.11 g, 1.0

mmol) in THF (10 ml) at 0 °C was added dropwise a solution of diisopropyl azodicarboxylate (0.20 g, 1.0 mmol) in THF (2 ml). The mixture was then warmed to rt and stirred at rt for 16 h before removal of solvents. The crude product was purified by flash chromatography (silica gel, 1% methanol in methylene chloride) to afford trioxolane

5 **OZ182** (0.21 g, 52%, 3:1 mixture of two diastereomers) as a colorless solid. mp 75–76 °C (ether/hexanes 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.18 (m, 22H), 2.25–2.48 (m, 1H), 4.20 (t, J = 5.3 Hz, 2H), 4.33 (t, J = 5.1 Hz, 2H), 6.94 (s, 1H), 7.09 (s, 1H), 7.57 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.11, 26.27, 26.44, 26.47, 26.84, 26.87, 33.21, 33.40, 34.75, 34.76, 34.78, 34.81, 36.35, 36.37, 36.75, 36.78, 41.15, 45.87, 63.06, 107.65, 108.11, 111.38, 111.61, 119.02, 129.31, 137.33, 174.34. Anal. Calcd for C₂₂H₃₀N₂O₅: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.86; H, 7.58; N, 6.78.

cis-Adamantane-2-spiro-3'-8'-[4'-[(hydroxyamino)carbonyl]phenyl]-1',2',4'-trioxaspiro[4.5]decane (**OZ183**). A mixture of ethyl chloroformate (0.13 g, 1.2 mmol), **OZ165** (0.41 g, 1.0 mmol), and triethylamine (0.13 g, 1.3 mmol), ether (5 ml), THF (5 ml), 15 and DMF (5 ml) was stirred at 0 °C for 1 h. The solid was removed by filtration, and the filtrate was added to a freshly prepared solution of hydroxylamine. [To a suspension of KOH (84 mg, 1.5 mmol) in methanol (1 ml) at 0 °C was added a solution of hydroxylamine hydrochloride (0.10 g, 1.5 mmol) in methanol (2 ml). The reaction mixture was stirred at 0 °C for 15 min and filtered to remove solid by-products. The filtrate was used as such.] The 20 resulting mixture was stirred at rt for 1 h and concentrated. The crude product was triturated with chloroform (6 ml) at 45 °C for 10 min and cooled to rt. The precipitate was collected by filtration and recrystallized from chloroform/methanol (2:1) to afford trioxolane **OZ183** (0.13 g, 33%) as a colorless solid. mp 167–168 °C (chloroform/methanol 2:1); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.40–2.17 (m, 22H), 2.57–2.80 (m, 1H), 7.29 (d, J = 7.8 Hz, 2H), 7.67 (d, J = 7.8 Hz, 2H), 8.95 (s, 1H), 11.14 (s, 1H); 25 ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 26.03, 26.44, 31.06, 34.21, 34.48, 36.01, 36.30, 41.61, 108.26, 110.83, 126.82, 127.25, 130.92, 149.41, 164.47. Anal. Calcd for C₂₃H₂₉NO₅: C, 69.15; H, 7.32; N, 3.51. Found: C, 68.89; H, 7.30; N, 3.70.

Adamantane-2-spiro-3'-8'-[(cyclopropylmethyl)amino]-1',2',4'-trioxaspiro[4.5]decane hydrochloride (**OZ184**). To a solution of **OZ05** (555 mg, 2 30 mmol) in 1,2-dichloroethane (10 ml) were added cyclopropanemethylamine (156 mg, 2.2

mmol) and acetic acid (10 drops). The reaction mixture was stirred at rt for 15 min before sodium triacetoxyborohydride (677 mg, 3.2 mmol) was added. The mixture was stirred for 5 h before being quenched with 1 M aq. NaOH (2 ml). The resulting mixture was extracted with CH₂Cl₂ (40 ml), washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over
 5 MgSO₄, and concentrated. The residue was dissolved in ether (2 ml), treated with excess 2 M ethereal HCl, and filtered to give trioxolane **OZ184** (401 mg, 54%, 1:1 mixture of two diastereomers) as a colorless solid. mp 110 °C dec (ether); ¹H NMR (500 MHz, CDCl₃) δ 0.39–0.60 (m, 2H), 0.61–0.85 (m, 2H), 1.22–1.43 (m, 1H), 1.59–2.45 (m, 22H), 2.76–3.02 (m, 2H), 3.08–3.35 (m, 1H), 9.65 (br s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 4.83, 4.87,
 10 7.06, 7.13, 25.87, 25.94, 26.37, 26.73, 26.77, 32.29, 34.67, 34.70, 34.79, 36.20, 36.28, 36.66, 48.93, 49.25, 54.42, 54.60, 106.74, 106.75, 111.77, 112.28. Anal. Calcd for C₂₀H₃₂ClNO₃: C, 64.94; H, 8.72; N, 3.79. Found: C, 65.18; H, 8.56; N, 3.83.

Adamantane-2-spiro-3'-8'-(cyclopropylamino)-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ185). To a solution of **OZ05** (555 mg, 2 mmol) in 1,2-dichloroethane
 15 (10 ml) were added cyclopropylamine (125 mg, 2.2 mmol) and acetic acid (10 drops). The reaction mixture was stirred at rt for 15 min before sodium triacetoxyborohydride (677 mg, 3.2 mmol) was added. The mixture was stirred for 5 h before being quenched with 1 M aq. NaOH (2 ml). The resulting mixture was extracted with CH₂Cl₂ (40 ml), washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO₄, and concentrated. The residue
 20 was dissolved in ether (2 ml), treated with excess 2 M ethereal HCl, and filtered to give trioxolane **OZ185** (348 mg, 49%, 1:1 mixture of two diastereomers) as a colorless solid. mp 102–103 °C dec (ether); ¹H NMR (500 MHz, CDCl₃) δ 0.69–1.05 (m, 2H), 1.20–1.45 (m, 2H), 1.59–2.21 (m, 20H), 2.22–2.45 (m, 2H), 2.46–2.69 (m, 1H), 3.01–3.39 (m, 1H), 9.62 (br s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 3.85, 26.21, 26.24, 26.40, 26.76, 26.80,
 25 27.49, 27.94, 32.35, 34.70, 34.73, 34.86, 36.24, 36.32, 36.70, 56.85, 57.19, 106.76, 106.78, 111.84, 112.34. Anal. Calcd for C₁₉H₃₀ClNO₃: C, 64.12; H, 8.50; N, 3.94. Found: C, 64.00; H, 8.38; N, 3.84.

cis-Adamantane-2-spiro-3'-8'-[(methoxyacetyl)amino]-1',2',4'-trioxaspiro[4.5]decane (OZ186). To a solution of **OZ137** (550 mg, 1.74 mmol) in CH₂Cl₂
 30 (10 ml) at 0 °C were added triethylamine (350 mg, 3.48 mmol) and methoxyacetyl chloride (198 mg, 1.82 mmol). The resulting mixture was stirred at rt for 16 h, diluted with CH₂Cl₂

(10 ml), and washed with water (10 ml) and brine (10 ml). The organic layer was separated, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 85% ether in hexanes) to give trioxolane **OZ186** (379 mg, 62%) as a colorless solid. mp 105–106 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.40–1.61 (m, 2H), 1.62–2.21 (m, 20H), 3.41 (s, 3H), 3.86 (s, 2H), 3.80–3.96 (m, 1H), 6.35–6.49 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.34, 26.72, 29.67, 32.56, 34.64, 36.20, 36.63, 45.84, 58.94, 71.83, 107.53, 111.47, 168.65. Anal. Calcd for C₁₉H₂₉NO₅: C, 64.93; H, 8.32; N, 3.99. Found: C, 64.81; H, 8.31; N, 3.91.

cis-Adamantane-2-spiro-3'-8'-[[(dimethylamino)carbonyl]amino]-1',2',4'-trioxaspiro[4.5]decane (OZ187). To a solution of **OZ137** (550 mg, 1.74 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (352 mg, 3.48 mmol) and dimethylcarbonyl chloride (197 mg, 1.82 mmol). The resulting mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), and washed with water (10 ml) and brine (10 ml). The organic layer was separated, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 90% ether in hexanes) to give trioxolane **OZ187** (346 mg, 57%) as a colorless solid. mp 142–144 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.32–1.55 (m, 2H), 1.62–2.21 (m, 20H), 2.88 (s, 6H), 3.62–3.85 (m, 1H), 4.15–4.29 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.42, 26.79, 30.67, 32.86, 34.72, 36.07, 36.28, 36.72, 47.91, 107.94, 111.45, 157.69. Anal. Calcd for C₁₉H₃₀N₂O₄: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.30; H, 8.68; N, 8.06.

Adamantane-2-spiro-3'-8'-(4'-morpholinylcarbonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ188). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (202 mg, 2 mmol) in CH₂Cl₂ (7 ml) at 0 °C was added 4-morpholinecarbonyl chloride (170 mg, 1.1 mmol). The mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), washed with water (2 x 10 ml) and brine (10 ml), dried over MgSO₄, and concentrated. Crystallization of the residue from ethanol gave trioxolane **OZ188** (310 mg, 82%) as a colorless solid. mp 132–134 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.60–2.21 (m, 18H), 3.18–3.28 (m, 4H), 3.29–3.58 (m, 4H), 3.60–3.82 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.42, 26.82, 34.37, 34.73, 34.82, 36.39, 36.70, 44.59, 47.41, 66.62, 107.03, 112.04, 163.66. Anal. Calcd for C₂₀H₃₀N₂O₅: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.24; H, 7.84; N, 7.44.

***cis*-Adamantane-2-spiro-3'-8'-[2'-(4'-morpholinyl)-2'-oxoethyl]-1',2',4'-trioxaspiro[4.5]decane (OZ189).** To a solution of **OZ78** (322 mg, 1.0 mmol) in ether (10 ml) at 0 °C were added triethylamine (202 mg, 2 mmol) and ethyl chloroformate (217 mg, 2 mmol). The mixture was stirred at 0 °C for 15 min before morpholine (175 mg, 2 mmol) was added. The resulting mixture was stirred at rt for 12 h, diluted with ether (10 ml), washed with water (10 ml), dried over MgSO₄, and concentrated. The crude product was purified by crystallization from ethanol to afford trioxolane **OZ189** (290 mg, 74%) as a colorless solid. mp 118–120 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.16–1.35 (m, 2H), 1.60–2.16 (m, 21H), 2.21 (d, J = 6.9 Hz, 2H), 3.38–3.54 (m, 2H), 3.55–3.82 (m, 6H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.48, 26.86, 30.28, 33.26, 34.05, 34.79, 36.39, 36.79, 39.01, 41.93, 46.18, 66.66, 66.97, 108.58, 111.35, 170.67. Anal. Calcd for C₂₂H₃₃NO₅: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.46; H, 8.39; N, 3.34.

Adamantane-2-spiro-3'-8'-(dimethylaminosulfonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ190). To a stirred solution of **OZ80** (301 mg, 1 mmol) in CH₂Cl₂ (10 ml) at rt were added triethylamine (0.4 ml, 3 mmol) and dimethylaminosulfonyl chloride (0.13 ml, 1.2 mmol). The mixture was stirred at rt for 3 h before removal of the solvent. The residue was diluted with ether (15 ml), washed with water (2 x 10 ml), dried over MgSO₄, and concentrated. Crystallization of the residue from ether/hexanes (1:1) gave trioxolane **OZ190** (301 mg, 81%) as a colorless solid. mp 104–106 °C (ether/hexanes 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.17 (m, 18H), 2.82 (s, 6H), 3.29–3.53 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.40, 26.79, 34.24, 34.71, 34.80, 36.36, 36.67, 38.18, 44.51, 106.23, 112.25. Anal. Calcd for C₁₇H₂₈N₂O₅S: C, 54.82; H, 7.58; N, 7.52. Found: C, 54.70; H, 7.38; N, 7.50.

Adamantane-2-spiro-3'-8'-amidino-1',2',4'-trioxa-8'-azaspiro[4.5]decane hydrochloride (OZ191). To a stirred solution of **OZ80** (301 mg, 1 mmol) and triethylamine (202 mg, 2 mmol) in DMF (2 ml) and CH₂Cl₂ (2 ml) at rt was added *N,N*-diisopropylethylamine (130 mg, 2 mmol). After 1*H*-pyrazole-1-carboxamidino hydrochloride (147 mg, 1 mmol) was added, the reaction mixture became a cloudy suspension. The stirring was continued for 3 h during which period the reaction mixture turned into a clear solution. Addition of dry ether (15 ml) to the above solution produced a colorless precipitate, which was then filtered and washed with ether (3 x 5 ml). The

collected solid was recrystallized from ether/CH₂Cl₂ (3:1) to give trioxolane **OZ191** (302 mg, 88%) as a colorless solid. mp 144–148 °C (ether/CH₂Cl₂, 3:1); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.57–2.17 (m, 18H), 3.41–3.69 (m, 4H), 7.72 (s, 4H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.93, 26.31, 33.61, 34.38, 34.43, 35.76, 36.15, 43.39, 106.29, 111.74, 156.36. Anal. Calcd for C₁₆H₂₆ClN₃O₃: C, 55.89; H, 7.62; N, 12.22. Found: C, 55.73; H, 7.54; N, 12.23.

Adamantane-2-spiro-3'-8'-[(4'-chlorophenylamino)carbonyl]-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ192). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (202 mg, 2 mmol) in CH₂Cl₂ (7 ml) at 0–5 °C was added 4-chlorophenyl isocyanate (154 mg, 1 mmol). The reaction mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), and washed with water (2 x 10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and concentrated. The residue was purified by crystallization from methanol to afford trioxolane **OZ192** (346 mg, 83%) as a colorless solid. mp 132–134 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.61–2.17 (m, 18H), 3.42–3.77 (m, 4H), 6.43 (s, 1H), 7.17–7.37 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.41, 26.81, 34.34, 34.73, 34.82, 36.38, 36.67, 42.34, 106.65, 112.32, 121.19, 128.20, 128.86, 137.53, 154.46. Anal. Calcd for C₂₂H₂₇ClN₂O₄: C, 63.08; H, 6.50; N, 6.69. Found: C, 62.95; H, 6.36; N, 6.65.

Adamantane-2-spiro-3'-8'-(4'-fluorophenoxy)-1',2',4'-trioxaspiro[4.5]decane (OZ193). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 4-(4-fluorophenoxy)cyclohexanone (950 mg, 5.1 mmol) in cyclohexane (80 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in hexanes) and by subsequent recrystallization from ethanol/CH₂Cl₂ (19:1) to afford trioxolane **OZ193** (250 mg, 13%) as a colorless solid. mp 102–104 °C (ethanol/CH₂Cl₂ 19:1); ¹H NMR (500 MHz, CDCl₃) δ 1.57–2.21 (m, 22H), 4.29–4.41 (m, 1H), 6.79–6.89 (m, 2H), 6.91–7.05 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.48, 26.88, 27.82, 30.06, 34.79, 34.85, 36.43, 36.79, 72.54, 108.22, 111.71, 115.87 (d, *J* = 23.3 Hz), 117.44 (d, *J* = 8.2 Hz), 153.44, 157.34 (d, *J* = 239.0 Hz). Anal. Calcd for C₂₂H₂₇FO₄: C, 70.57; H, 7.27. Found: C, 70.71; H, 7.33.

Adamantane-2-spiro-3'-8'-[(diisopropylamino)carbonyl]-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ194). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (303 mg, 3 mmol) in CH₂Cl₂ (10 ml) at 0–5 °C was added diisopropylcarbonyl chloride

(164 mg, 1 mmol). The resulting mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), and washed with water (2 x 10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and concentrated. The residue was purified by crystallization from methanol to afford trioxolane **OZ194** (290 mg, 74%) as a colorless solid. mp 114–116 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.27 (d, J = 6.8 Hz, 12H), 1.60–2.21 (m, 18H), 3.11–3.39 (m, 4H), 3.60 (sep, J = 6.6 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 21.57, 26.44, 26.84, 34.39, 34.72, 34.81, 36.40, 36.73, 45.26, 47.52, 107.29, 111.79, 163.59. Anal. Calcd for C₂₂H₃₆N₂O₄: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.14; H, 9.13; N, 7.11.

***cis*-Adamantane-2-spiro-3'-8'-[(*tert*-butylacetyl)amino]-1',2',4'-**

trioxaspiro[4.5]decane (OZ195). To a solution of **OZ137** (550 mg, 1.74 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (529 mg, 5.22 mmol) and *tert*-butylacetyl chloride (304 mg, 2.26 mmol). The resulting mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), and washed with water (10 ml) and brine (10 ml). The organic layer was separated, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 75% ether in hexanes) to give trioxolane **OZ195** (335 mg, 51%) as a colorless solid. mp 142–144 °C (ether); ¹H NMR (500 MHz, CDCl₃) δ 1.02 (s, 9H), 1.30–1.51 (m, 2H), 1.52–1.99 (m, 20H), 1.96 (s, 2H), 3.79–3.95 (m, 1H), 5.23–5.28 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.44, 26.82, 29.77, 30.00, 30.79, 32.76, 34.76, 36.31, 36.74, 46.45, 50.69, 107.76, 111.63, 170.97. Anal. Calcd for C₂₂H₃₅NO₄: C, 69.99; H, 9.34; N, 3.71. Found: C, 70.15; H, 9.38; N, 3.65.

***cis*-Adamantane-2-spiro-3'-8'-[(3'-carboxy-1'-oxopropyl)amino]-1',2',4'-**

trioxaspiro[4.5]decane (OZ196). To a solution of **OZ137** (550 mg, 1.74 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (350 mg, 3.48 mmol) and succinic anhydride (176 mg, 1.74 mmol). The resulting mixture was stirred at rt for 24 h, concentrated, and triturated with water (3 x 10 ml), hexanes (2 x 10 ml), and THF (5 ml) to give trioxolane **OZ196** (350 mg, 53%) as a colorless solid. mp 122–124 °C (THF); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.33–1.57 (m, 2H), 1.62–2.19 (m, 20H), 2.31–2.41 (m, 2H), 2.42–2.57 (m, 2H), 3.65–3.82 (m, 1H), 7.83–7.87 (m, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 26.00, 26.39, 29.34, 29.43, 32.20, 34.43, 35.88, 36.26, 45.65, 108.07, 110.81, 170.41, 173.99. Anal. Calcd for C₂₀H₂₉NO₆: C, 63.31; H, 7.70; N, 3.69. Found: C, 63.46; H, 7.68; N, 3.84.

***cis*-Adamantane-2-spiro-3'-8'-[(2',5'-dioxo-1'-pyrrolidinyl)methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ197).** To a solution of **OZ119** (0.29 g, 1 mmol), triphenylphosphine (0.42 g, 1.6 mmol), and succinimide (0.11 g, 1.1 mmol) in THF (6 ml) at 0 °C was added a solution of DIPAD (0.32 g, 1.6 mmol) in THF (1 ml). The mixture was warmed to rt and stirred overnight. After removal of the solvent, the crude product was purified by flash chromatography (silica gel, 25% ether in hexanes) and by subsequent recrystallization from hexanes/CH₂Cl₂ (3:1) to give trioxolane **OZ197** (0.30 g, 80%) as a colorless solid. mp 147–148 °C (hexanes/CH₂Cl₂ 3:1); ¹H NMR (500 MHz, CDCl₃) δ 1.37–1.59 (m, 2H), 1.61–2.35 (m, 21H), 2.92 (s, 4H), 3.59 (d, J = 7.1 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.39, 26.79, 27.70, 28.02, 33.46, 34.69, 34.71, 34.74, 36.28, 36.71, 43.75, 108.32, 111.25, 177.26. Anal. Calcd for C₂₁H₂₉NO₅: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.12; H, 7.81; N, 3.63.

***cis*-Adamantane-2-spiro-3'-8'-(3'-carboxyphenyl)-1',2',4'-trioxaspiro[4.5]decane (OZ198).** A mixture of **OZ208** (0.38 g, 0.92 mmol), KOH (0.36 g), THF (10 ml), methanol (10 ml), and water (2 ml) was heated at 50 °C for 2 h. The mixture was concentrated, diluted with water (10 ml), and acidified with 1 M aq. HCl to pH = 2. The resulting solid was collected by filtration and washed with hexanes/ether (10 ml, 2:1) to give trioxolane **OZ198** (0.28 g, 79%) as a colorless solid. mp 150–152 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.63–2.22 (m, 22H), 2.58–2.73 (m, 1H), 7.40 (dd, J = 7.7, 7.7 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.97 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.51, 26.91, 31.31, 34.63, 34.82, 36.43, 36.82, 42.72, 108.21, 111.49, 128.13, 128.60, 128.75, 129.46, 132.06, 146.59, 171.58. Anal. Calcd for C₂₃H₂₈O₅: C, 71.85; H, 7.34. Found: C, 71.74; H, 7.30.

Adamantane-2-spiro-3'-8'-carbamoyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ199). To a solution of **OZ80** (450 mg, 1.49 mmol) in CH₂Cl₂ (12 ml) at rt were added pyridine (1.2 ml, 14.9 mmol), HOAc (0.82 ml, 14.9 mmol), triethylamine (0.4 ml, 2.98 mmol), and potassium cyanate (243 mg, 2.98 mmol). After being stirred for 35 h the reaction mixture was poured into a mixture of ether (50 ml) and water (50 ml). The organic layer was separated, washed with brine (15 ml), dried over MgSO₄, and concentrated. Crystallization of the residue from ether/CH₂Cl₂ (3:1) afforded trioxolane **OZ199** (449 mg, 98%) as a colorless solid. mp 140–142 °C (ether/CH₂Cl₂ 3:1); ¹H NMR (500 MHz, CDCl₃)

δ 1.57–2.21 (m, 18H), 3.31–3.69 (m, 4H), 4.55 (s, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.41, 26.81, 34.27, 34.73, 34.81, 36.37, 36.69, 42.25, 106.72, 112.21, 157.65. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4 \cdot 0.4\text{H}_2\text{O}$: C, 60.89; H, 7.92; N, 8.88. Found: C, 60.86; H, 7.60; N, 8.84.

Adamantane-2-spiro-3'-8'-[2'-(ethylsulfonyl)ethyl]-1',2',4'-trioxa-8'-

5 **azaspiro[4.5]decane (OZ200)**. To a stirred solution of **OZ80** (450 mg, 1.49 mmol) in CH_2Cl_2 (10 ml) and methanol (10 ml) at rt was added triethylamine (0.4 ml, 2.98 mmol) followed by ethyl vinyl sulfone (0.15 ml, 1.49 mmol). The resulting mixture was stirred at rt for 3 h before removal of the solvents. The residue was diluted with ether (15 ml), washed with water (2 x 10 ml), dried (MgSO_4), and concentrated. Crystallization of the
10 crude product from ether/hexanes (1:1) afforded trioxolane **OZ200** (415 mg, 72%) as a colorless solid. mp 105–107 °C (ether/hexanes 1:1); ^1H NMR (500 MHz, CDCl_3) δ 1.39 (t, J = 7.6 Hz, 3H), 1.57–2.21 (m, 18H), 2.41–2.59 (m, 2H), 2.60–2.78 (m, 2H), 2.89 (t, J = 6.5 Hz, 2H), 3.09 (t, J = 6.5 Hz, 2H), 3.14 (q, J = 7.4 Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 6.59, 26.40, 26.80, 34.33, 34.71, 34.79, 36.34, 36.69, 48.56, 49.74, 50.94, 51.10,
15 106.54, 111.85. Anal. Calcd for $\text{C}_{19}\text{H}_{31}\text{NO}_5\text{S}$: C, 59.19; H, 8.10; N, 3.63. Found: C, 58.98; H, 7.95; N, 3.65.

cis-Adamantane-2-spiro-3'-8'-[(4'-fluorophenyl)amino]-1',2',4'-

trioxaspiro[4.5]decane (OZ201). To a solution of **OZ05** (555 mg, 2 mmol) in 1,2-dichloroethane (10 ml) were added 4-fluoroaniline (236 mg, 2.12 mmol) and acetic acid
20 (10 drops). The reaction mixture was stirred at rt for 15 min before sodium triacetoxyborohydride (677 mg, 3.2 mmol) was added. The mixture was stirred for 5 h before being quenched with 1 M aq. NaOH (2 ml). The resulting mixture was extracted with CH_2Cl_2 (40 ml), washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO_4 , and concentrated to give an oil (517 mg, 69%, 2:1 mixture of two diastereomers).
25 Trituration with ether and hexanes gave trioxolane **OZ201** (280 mg, 37%) as a colorless solid. mp 118–120 °C (hexanes); ^1H NMR (500 MHz, CDCl_3) δ 1.37–1.52 (m, 2H), 1.53–2.21 (m, 20H), 3.19–3.27 (m, 1H), 3.28–3.49 (m, 1H), 6.41–6.63 (m, 2H), 6.77–6.99 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.46, 26.87, 30.10, 32.75, 34.77, 34.81, 36.34, 36.76, 50.92, 108.08, 111.58, 114.14 (d, J = 7.3 Hz), 115.71 (d, J = 22.4 Hz), 143.44,
30 155.70 (d, J = 234.9 Hz). Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{FNO}_3$: C, 70.75; H, 7.56; N, 3.75. Found: C, 70.85; H, 7.42; N, 3.76.

***cis*-Adamantane-2-spiro-3'-8'-[(2'-acetoxy-2'-methylpropionyl)amino]-1',2',4'-trioxaspiro[4.5]decane (OZ202).** To a solution of **OZ137** (550 mg, 1.74 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (529 mg, 5.22 mmol) and 2-acetoxy-2-methylpropionyl chloride (430 mg, 2.61 mmol). The resulting mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), and washed with water (10 ml) and brine (10 ml). The organic layer was separated, dried over MgSO₄, and concentrated. The crude product was purified by trituration with hexanes to give trioxolane **OZ202** (350 mg, 49%) as a colorless solid. mp 130–132 °C (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 1.35–1.52 (m, 2H), 1.61 (s, 6H), 1.62–2.06 (m, 20H), 2.07 (s, 3H), 3.75–3.95 (m, 1H), 5.77–5.93 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 21.87, 24.29, 26.43, 26.81, 29.73, 32.68, 34.75, 36.30, 36.73, 46.51, 81.35, 107.66, 111.65, 169.15, 172.35. Anal. Calcd for C₂₂H₃₃NO₆: C, 64.84; H, 8.16; N, 3.44. Found: C, 64.80; H, 7.93; N, 3.52.

Adamantane-2-spiro-3'-8'-(1'-pyrrolidinylcarbonyl)-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ203). To a solution of **OZ80** (301 mg, 1 mmol) and triethylamine (303 mg, 3 mmol) in CH₂Cl₂ (10 ml) at 0 °C was added 1-pyrrolidinecarbonyl chloride (118 mg, 1 mmol). The mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (10 ml), and washed with water (2 x 10 ml) and brine (10 ml). The organic layer was separated, dried over MgSO₄, and concentrated. Crystallization of the residue from methanol gave trioxolane **OZ203** (152 mg, 42%) as a colorless solid. mp 130–132 °C (methanol); ¹H NMR (500 MHz, CDCl₃) δ 1.61–2.15 (m, 22H), 3.23–3.57 (m, 8H); ¹³C NMR (125.7 MHz, CDCl₃) δ 25.53, 26.44, 26.83, 34.51, 34.73, 34.82, 36.40, 36.72, 43.94, 48.38, 107.26, 111.90, 162.56. Anal. Calcd for C₂₀H₃₀N₂O₄: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.33; H, 8.30; N, 7.60.

***cis*-Adamantane-2-spiro-3'-8'-[(4'-methoxycarbonylphenyl)methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ204).** A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 4-[(4-methoxycarbonylphenyl)methyl]cyclohexanone (1.27 g, 5 mmol) in cyclohexane (80 ml) and CH₂Cl₂ (20 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in hexanes) and subsequent recrystallization from ethanol/CH₂Cl₂ (19:1) to afford trioxolane **OZ204** (950 mg, 46%) as a colorless solid. mp 104–106 °C (ethanol/CH₂Cl₂ 19:1); ¹H NMR (500 MHz, CDCl₃) δ 1.19–1.37 (m, 2H), 1.49–2.07 (m, 21H), 2.56 (d, J = 6.9 Hz,

2H), 3.90 (s, 3H), 7.20 (d, J = 7.9 Hz, 2H), 7.95 (d, J = 7.9 Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.48, 26.87, 29.90, 34.08, 34.78, 36.38, 36.80, 38.00, 42.86, 51.95, 108.76, 111.28, 127.91, 129.08, 129.57, 146.42, 167.12. Anal. Calcd for $\text{C}_{25}\text{H}_{32}\text{O}_5$: C, 72.79; H, 7.82. Found: C, 72.72; H, 7.85.

5 ***cis*-Adamantane-2-spiro-3'-8'-(2'-hydroxy-2'-methylpropyl)-1',2',4'-trioxaspiro[4.5]decane (OZ205)**. To a solution of **OZ61** (350 mg, 1 mmol) in CH_2Cl_2 at -78°C was added methyllithium (3 ml, 1.6 M in ether, 4.8 mmol). The reaction was stirred at -78°C for 2 h before being quenched with water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic layers
10 were washed with water (10 ml) and brine (10 ml), dried over MgSO_4 , filtered, and concentrated. The crude product was purified by crystallization from ethanol to afford trioxolane **OZ205** (262 mg, 78%) as a colorless solid. mp $96-98^\circ\text{C}$ (ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.23 (s, 6H), 1.21–1.37 (m, 2H), 1.40 (d, J = 5.5 Hz, 2H), 1.43–1.61 (m, 1H), 1.62–2.09 (m, 20H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.49, 26.89, 30.03, 31.99,
15 32.47, 34.31, 34.78, 34.80, 36.40, 36.82, 49.76, 71.39, 108.62, 111.17. Anal. Calcd for $\text{C}_{20}\text{H}_{32}\text{O}_4$: C, 71.39; H, 9.59. Found: C, 71.44; H, 9.39.

***cis*-Adamantane-2-spiro-3'-8'-[(2',4'-dioxo-3'-imidazolidinyl)methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ206)**. To a solution of **OZ119** (0.29 g, 1 mmol), triphenylphosphine (0.42 g, 1.6 mmol), and hydantoin (0.11 g, 1.1 mmol) in DMF (6 ml)
20 and THF (6 ml) at 0°C was added a solution of DIPAD (0.32 g, 1.6 mmol) in THF (1 ml). The mixture was warmed to rt and stirred overnight. After removal of the solvents, the crude product was purified by flash chromatography (silica gel, 25% acetone in hexanes) and subsequent recrystallization from hexanes/ CH_2Cl_2 (5:1) to give trioxolane **OZ206**
(0.21 g, 56%) as a colorless solid. mp $158-160^\circ\text{C}$ (hexanes/ CH_2Cl_2 5:1); ^1H NMR (500
25 MHz, CDCl_3) δ 1.21–1.41 (m, 2H), 1.58–2.19 (m, 21H), 3.40 (d, J = 6.9 Hz, 2H), 3.99 (s, 2H), 5.81 (s, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.47, 26.87, 27.69, 33.54, 34.77, 34.79, 35.10, 36.36, 36.79, 43.76, 46.27, 108.43, 111.36, 158.35, 171.31. Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.68; H, 7.31; N, 7.39.

***cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane *p*-tosylate (OZ207)**. To a solution of *cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-
30 **1',2',4'-trioxaspiro[4.5]decane** (1.465 g, 5 mmol) in ether (60 ml) and CH_2Cl_2 (20 ml)

was added a solution of *p*-TsOH (0.96 g, 5 mmol) in ether (80 ml). The resulting mixture was placed at -20°C overnight. The solid was collected by filtration to afford trioxolane **OZ207** (2.24 g, 96%) as a colorless solid. mp $162-164^{\circ}\text{C}$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 1.01–1.23 (m, 2H), 1.51–2.07 (m, 21H), 2.29 (s, 3H), 2.68 (app t, $J = 5.7$ Hz, 2H), 7.12 (d, $J = 7.8$ Hz, 2H), 7.48 (d, $J = 8.3$ Hz, 2H), 7.68 (br s, 3H); ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$) δ 20.93, 25.95, 26.36, 27.08, 32.99, 33.86, 34.40, 34.41, 35.89, 36.22, 43.63, 108.28, 110.80, 125.65, 128.21, 137.77, 145.87. Anal. Calcd for $\text{C}_{24}\text{H}_{35}\text{NO}_6\text{S}$: C, 61.91; H, 7.58; N, 3.01. Found: C, 61.78; H, 7.38; N, 2.97.

***cis*-Adamantane-2-spiro-3'-8'-[(3'-ethoxycarbonyl)phenyl]-1',2',4'-**

trioxaspiro[4.5]decane (OZ208). A solution of *O*-methyl 2-adamantanone oxime (0.65 g, 2.6 mmol) and 4-[3-(ethoxycarbonyl)phenyl]cyclohexanone (0.47 g, 2.6 mmol) in pentane (50 ml) and CH_2Cl_2 (25 ml) was treated with ozone according to the general procedure.

The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford trioxolane **OZ208** (0.50 g, 47%) as a colorless solid. mp $72-73^{\circ}\text{C}$ (95% ethanol);

^1H NMR (500 MHz, CDCl_3) δ 1.39 (t, $J = 7.1$ Hz, 3H), 1.61–2.21 (m, 22H), 2.55–2.69 (m, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 7.35 (dd, $J = 7.6, 7.6$ Hz, 1H), 7.39 (d, $J = 7.7$ Hz, 1H), 7.88 (d, $J = 7.7$ Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 14.35, 26.50, 26.90, 31.33, 34.64, 34.81, 36.43, 36.81, 42.78, 60.90, 108.24, 111.47, 127.48, 127.98, 128.41, 130.62, 131.21, 146.38, 166.70. Anal. Calcd for $\text{C}_{25}\text{H}_{32}\text{O}_5$: C, 72.79; H, 7.82. Found: C,

72.61; H, 7.60.

***cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane mesylate (OZ209).** To a solution of *cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-

1',2',4'-trioxaspiro[4.5]decane (0.30 g, 1.02 mmol) in ether (10 ml) and CH_2Cl_2 (5 ml) was added a solution of methanesulfonic acid (0.10 g, 1.04 mmol) in ether (30 ml). The

resulting mixture was concentrated to 10 ml and placed at -20°C overnight. The solid was collected by filtration to afford trioxolane **OZ209** (0.34 g, 86%) as a colorless solid. mp

$146-148^{\circ}\text{C}$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 1.01–1.23 (m, 2H), 1.51–2.07 (m, 21H), 2.34 (s, 3H), 2.69 (app t, $J = 6.0$ Hz, 2H), 7.70 (br s, 3H); ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$) δ 25.95, 26.36, 27.09, 33.01, 33.85, 34.39, 34.41, 35.89, 36.22, 43.61, 108.28, 110.79.

Anal. Calcd for $\text{C}_{18}\text{H}_{31}\text{NO}_6\text{S}$: C, 55.50; H, 8.02; N, 3.60. Found: C, 55.41; H, 7.94; N, 3.58.

***cis*-Adamantane-2-spiro-3'-8'-[(phenylsulfonyl)methyl]-1',2',4'-trioxa-8'-azaspiro[4.5]decane (OZ210).** A solution of *O*-methyl 2-adamantanone oxime (1.79 g, 10 mmol) and 4-[(phenylsulfonyl)methyl]cyclohexanone (1.20 g, 4.76 mmol) in pentane (50 ml) and CH₂Cl₂ (25 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 33% ether in hexanes) to afford trioxolane **OZ210** (0.78 g, 39%) as a colorless solid. mp 120–122 °C (ether/hexanes 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.25–1.46 (m, 2H), 1.60–2.21 (m, 21H), 2.99 (d, J = 6.3 Hz, 2H), 7.54–7.62 (m, 2H), 7.63–7.70 (m, 1H), 7.88–7.96 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.44, 26.83, 30.11, 31.19, 33.69, 34.75, 34.76, 36.35, 36.75, 61.79, 107.77, 111.53, 127.73, 129.32, 133.63, 140.21. Anal. Calcd for C₂₃H₃₀O₅S: C, 66.00; H, 7.22. Found: C, 66.15; H, 7.10.

***cis*-Adamantane-2-spiro-3'-8'-(1'*H*-pyrazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ211).** To a suspension of 60% NaH (0.08 g, 2 mmol) in DMF (4 ml) under nitrogen at 0 °C was added a solution of pyrazole (0.14 g, 2 mmol) in DMF (4 ml). The mixture was stirred for 30 min before a solution of the methanesulfonate of **OZ119** (0.37 g, 1.0 mmol) in DMF (4 ml) was added dropwise. The reaction mixture was heated at 50 °C for 2 h, quenched with water (40 ml), and then extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with brine (3 x 30 ml), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 33% ether in hexanes) to afford trioxolane **OZ211** (0.28 g, 81%) as a colorless solid. mp 103–106 °C (hexanes/CH₂Cl₂, 4:1); ¹H NMR (500 MHz, CDCl₃) δ 1.19–1.37 (m, 2H), 1.53–2.18 (m, 21H), 3.77 (d, J = 7.1 Hz, 2H), 6.22 (s, 1H), 7.33 (s, 1H), 7.51 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.47, 26.85, 27.63, 33.60, 34.77, 36.37, 36.78, 37.16, 57.46, 105.02, 108.52, 111.43, 129.63, 139.41. Anal. Calcd for C₂₀H₂₈N₂O₃: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.88; H, 8.18; N, 8.17.

***cis*-Adamantane-2-spiro-3'-8'-[(1',1'-dioxido-3'-oxo-1',2'-benzisothiazol-2'(3'*H*)-yl)methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ212).** To a solution of **OZ119** (0.29 g, 1 mmol), triphenylphosphine (0.42 g, 1.6 mmol), and saccharin (0.20 g, 1.1 mmol) in THF (10 ml) at 0 °C was added a solution of DIPAD (0.32 g, 1.6 mmol) in THF (1 ml). The mixture was warmed to rt and stirred overnight. After removal of the solvent, the crude product was purified by flash chromatography (silica gel, 25% ether in hexanes) and by

subsequent recrystallization from hexanes/CH₂Cl₂ (4:1) to give trioxolane **OZ212** (0.17 g, 37%) as a colorless solid. mp 152–155 °C (hexanes/CH₂Cl₂, 4:1); ¹H NMR (500 MHz, CDCl₃) δ 1.23–1.45 (m, 2H), 1.59–2.18 (m, 21H), 3.63 (d, J = 7.4 Hz, 2H), 7.80–7.90 (m, 2H), 7.93 (d, J = 7.1 Hz, 1H), 8.06 (d, J = 7.4 Hz, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.49, 26.88, 27.79, 33.50, 34.79, 34.80, 35.14, 36.39, 36.81, 44.49, 108.43, 111.39, 120.93, 125.22, 127.33, 134.31, 134.73, 137.64, 159.26. Anal. Calcd for C₂₄H₂₉NO₆S: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.74; H, 6.18; N, 3.02.

cis-Adamantane-2-spiro-3'-8'-[[methoxyamino]carbonyl]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ213). To a solution of **OZ78** (322 mg, 1 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (202 mg, 2 mmol) and ethyl chloroformate (217 mg, 2 mmol). After the mixture was stirred at 0 °C for 15 min, methoxylamine was added. [To a suspension of methoxylamine hydrochloride (167 mg, 2 mmol) in methanol (5 ml) was added NaHCO₃ (164 mg, 2 mmol). The mixture was stirred at rt for 15 min]. The resulting mixture was stirred at rt for 12 h, diluted with CH₂Cl₂ (10 ml), washed with water (10 ml), dried over MgSO₄, and concentrated. The crude product was purified by crystallization from methanol to afford trioxolane **OZ213** (0.17 g, 48%) as a colorless solid. mp 72–74 °C (methanol); ¹H NMR (500 MHz, DMSO-*d*₆) δ 0.99–1.21 (m, 2H), 1.45–2.11 (m, 23H), 3.56 (s, 3H), 10.93 (s, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.96, 26.37, 29.54, 32.64, 33.50, 34.40, 35.91, 36.25, 38.86, 63.34, 108.49, 110.64, 168.09. Anal. Calcd for C₁₉H₂₉NO₅: C, 64.93; H, 8.32; N, 3.99. Found: C, 64.79; H, 8.13; N, 3.76.

cis-Adamantane-2-spiro-3'-8'-[(4'-carboxyphenyl)methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ214). A mixture of **OZ204** (412 mg, 1 mmol), NaOH (120 mg, 3 mmol), methanol (10 ml), and water (10 ml) was stirred at rt for 16 h. After removal of the solvents, the residue was acidified with 6 M aq. HCl (4 ml) to pH = 2, and the resulting precipitate was collected by filtration and further crystallized from 95% ethanol to give trioxolane **OZ214** (182 mg, 46%) as a colorless solid. mp 160–162 °C (95% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.09–1.39 (m, 2H), 1.43–2.22 (m, 21H), 2.59 (d, J = 7.1 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 8.04 (d, J = 7.9 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.49, 26.88, 29.92, 34.08, 34.79, 36.39, 36.80, 38.00, 42.95, 108.74, 111.31, 126.98, 129.23, 130.24, 147.48, 171.61. Anal. Calcd for C₂₄H₃₀O₅: C, 72.34; H, 7.59. Found: C, 72.16; H, 7.37.

***cis*-Adamantane-2-spiro-3'-8'-phthalimidoethyl-1',2',4'-trioxaspiro[4.5]decane**

(OZ215). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 4-phthalimidoethylcyclohexanone (1.35 g, 5 mmol) in cyclohexane (85 ml) and CH₂Cl₂ (15 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 15% ether in hexanes) and by subsequent crystallization from ethanol to afford trioxolane **OZ215** (1.33 g, 61%) as a colorless solid. mp 136–138 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.15–1.43 (m, 3H), 1.49–2.21 (m, 22H), 3.70 (d, *J* = 7.5 Hz, 2H), 7.62–7.78 (m, 2H), 7.79–7.97 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.48, 26.87, 29.81, 33.78, 34.04, 34.76, 34.79, 36.05, 36.38, 36.80, 108.73, 111.18, 123.14, 132.16, 133.84, 168.33. Anal. Calcd for C₂₆H₃₁NO₅: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.50; H, 6.93; N, 3.16.

Adamantane-2-spiro-3'-8'-(4'-pyridinylmethyl)-1',2',4'-trioxa-8'-

azaspiro[4.5]decane (OZ216). To a stirred solution of **OZ80** (200 mg, 0.66 mmol) in 1,2-dichloroethane (5 ml) at rt was added triethylamine (0.2 ml, 1.2 mmol) followed by 4-pyridinecarboxaldehyde (71 mg, 0.66 mmol) and sodium triacetoxyborohydride (197 mg, 0.924 mmol). The resulting mixture was stirred at rt for 2 h, quenched with saturated aqueous NaHCO₃ (5 ml), and extracted with EtOAc (3 x 10 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. Crystallization of the crude product from ether/methanol (3:1) gave trioxolane **OZ216** (167 mg, 71%) as a colorless solid. mp 124–126 °C (ether/methanol 3:1); ¹H NMR (500 MHz, CDCl₃) δ 1.59–2.19 (m, 18H), 2.37–2.51 (m, 4H), 3.52 (s, 2H), 7.27 (d, *J* = 4.9 Hz, 2H), 8.54 (d, *J* = 5.0 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.45, 26.87, 34.45, 34.74, 34.83, 36.40, 36.75, 51.24, 61.20, 106.94, 111.70, 123.63, 148.00, 149.81. Anal. Calcd for C₂₁H₂₈N₂O₃: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.80; H, 7.77; N, 7.65.

***cis*-Adamantane-2-spiro-3'-8'-[[[(2'-thiazolyl)amino]carbonyl]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ217).** To a solution of **OZ78** (322 mg, 1 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (303 mg, 3 mmol) and ethyl chloroformate (217 mg, 2 mmol). The mixture was stirred at 0 °C for 15 min before 2-aminothiazole (100 mg, 1 mmol) was added. The resulting mixture was stirred at rt for 12 h, concentrated, and triturated with water. The crude product was purified by crystallization from ethanol to afford trioxolane **OZ217** (0.29 g, 72%) as a colorless solid. mp 160–162 °C (ethanol); ¹H

NMR (500 MHz, CDCl₃) δ 1.19–1.47 (m, 2H), 1.51–2.18 (m, 21H), 2.46 (d, J = 6.9 Hz, 2H), 7.02 (d, J = 3.6 Hz, 1H), 7.42 (d, J = 3.6 Hz, 1H), 12.51 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.46, 26.84, 30.10, 33.23, 33.91, 34.77, 36.37, 36.77, 42.81, 108.35, 111.45, 113.68, 136.10, 159.96, 170.18. Anal. Calcd for C₂₁H₂₈N₂O₄S: C, 62.35; H, 6.98; N, 6.93. Found: C, 62.28; H, 6.92; N, 6.87.

***cis*-Adamantane-2-spiro-3'-8'-[(1'-piperidinylcarbonyl)methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ218).** To a solution of **OZ78** (322 mg, 1.0 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triethylamine (202 mg, 2 mmol) and ethyl chloroformate (217 mg, 2 mmol). The mixture was stirred at 0°C for 15 min before piperidine (100 mg, 1.2 mmol) was added. The resulting mixture was stirred at rt for 12 h, concentrated, and triturated with water. The crude product was purified by crystallization from ethanol to afford trioxolane **OZ218** (0.24 g, 62%) as a colorless solid. mp 98–100 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.15–1.39 (m, 2H), 1.43–2.17 (m, 27H), 2.21 (d, J = 6.8 Hz, 2H), 3.30–3.49 (m, 2H), 3.50–3.65 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 24.57, 25.66, 26.49, 26.60, 26.87, 30.31, 33.43, 34.11, 34.79, 36.39, 36.81, 39.26, 42.69, 46.87, 108.72, 111.29, 170.28. Anal. Calcd for C₂₃H₃₅NO₄: C, 70.92; H, 9.06; N, 3.60. Found: C, 70.83; H, 8.99; N, 3.60.

***cis*-Adamantane-2-spiro-3'-8'-(1'*H*-imidazol-1'-ylethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ219).** **Step 1.** To a solution of **OZ89** (924 mg, 3 mmol) and triethylamine (606 mg, 6 mmol) in CH₂Cl₂ (30 ml) at 0°C was added methanesulfonyl chloride (516 mg, 4.5 mmol). The mixture was stirred at rt for 1 h, diluted with CH₂Cl₂ (20 ml), and washed with water (2 x 10 ml) and brine (10 ml). The organic layer was dried over MgSO₄, filtered, and concentrated to afford the methanesulfonate (1.16 g, 100%) as a colorless solid. **Step 2.** To a solution of imidazole (100 mg, 1.5 mmol) in DMF (5 ml) was added 60% NaH (75 mg, 1.9 mmol). The mixture was stirred for 15 min before a solution of the above methanesulfonate (0.40 g, 1 mmol) in DMF (2 ml) was added dropwise. The mixture was heated at 50 °C for 3 h, quenched with water (15 ml), and then extracted with ether (3 x 20 ml). The combined extracts were dried over MgSO₄, filtered, and concentrated. Crystallization of the residue from hexanes/ether (19:1) gave trioxolane **OZ219** (0.22 g, 61%) as a colorless solid. mp 116–118 °C (hexanes/ether, 19:1); ¹H NMR (500 MHz, CDCl₃) δ 1.11–1.39 (m, 3H), 1.51–2.18 (m, 22H), 3.95 (t, J = 8.0 Hz, 2H), 6.89

(s, 1H), 7.06 (s, 1H), 7.46 (s, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.46, 26.85, 29.80, 33.26, 33.93, 34.77, 36.38, 36.77, 37.35, 44.81, 108.48, 111.40, 118.65, 129.52, 136.95. Anal. Calcd for $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.14; H, 8.27; N, 7.81.

Adamantane-2-spiro-3'-8'-benzyl-1',2',4'-trioxa-8'-azaspiro[4.5]decane

5 **(OZ220)**. To a stirred solution of **OZ80** (200 mg, 0.66 mmol) in 1,2-dichloroethane (5 ml) at rt was added triethylamine (0.2 ml, 1.2 mmol) followed by benzaldehyde (70 mg, 0.66 mmol) and sodium triacetoxyborohydride (197 mg, 0.924 mmol). The resulting mixture was stirred at rt for 2 h, quenched with saturated aqueous NaHCO_3 (5 ml), and extracted with EtOAc (3 x 10 ml). The combined organic extracts were dried over MgSO_4 , filtered,
10 and concentrated. Crystallization of the crude product from ether/methanol (3:1) gave trioxolane **OZ220** (177 mg, 75%) as a colorless solid. mp 108–110 °C (ether/methanol 3:1); ^1H NMR (500 MHz, CDCl_3) δ 1.58–2.21 (m, 18H), 2.38–2.52 (m, 2H), 2.53–2.69 (m, 2H), 3.51 (s, 2H), 7.18–7.45 (m, 5H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.47, 26.88, 34.46, 34.75, 34.83, 36.40, 36.78, 51.09, 62.50, 107.26, 111.56, 126.99, 128.21, 128.96,
15 138.63. Anal. Calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.52; H, 8.17; N, 4.03.

cis-Adamantane-2-spiro-3'-8'-[(aminocarbonyl)amino]-1',2',4'-

trioxaspiro[4.5]decane (OZ221). To a solution of **OZ137** (550 mg, 1.74 mmol) in CH_2Cl_2 (10 ml) at rt were added pyridine (1.38 g, 17.4 mmol), acetic acid (1.01 g, 16.8 mmol),
20 triethylamine (349 mg, 3.45 mmol), and KOCN (278 mg, 3.45 mmol). The resulting mixture was stirred at rt for 48 h, diluted with ether (100 ml), and washed with water (100 ml) and brine (25 ml). The organic layer was separated, dried over MgSO_4 , and concentrated to give trioxolane **OZ221** (166 mg, 30%) as a colorless solid. mp 140–142 °C (ether); ^1H NMR (500 MHz, CDCl_3) δ 1.35–1.52 (m, 2H), 1.62–2.21 (m, 20H), 3.51–3.54
25 (m, 1H), 4.70 (s, 2H), 4.58–5.03 (m, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.43, 26.80, 30.34, 32.61, 34.76, 36.30, 36.73, 47.41, 107.88, 111.66, 158.32. Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.06; H, 8.29; N, 8.49.

cis-Adamantane-2-spiro-3'-8'-[[(tert-butylamino)carbonyl]amino]-1',2',4'-

trioxaspiro[4.5]decane (OZ222). To a solution of **OZ137** (315 mg, 1 mmol) in CH_2Cl_2
30 (10 ml) at 0 °C were added triethylamine (350 mg, 3.48 mmol) and *tert*-butyl isocyanate (100 mg, 1 mmol). The resulting mixture was stirred at rt for 7 h before removal of

solvents. The residue was triturated with water (10 ml) and further purified by crystallization from 95% ethanol to give trioxolane **OZ222** (300 mg, 79%) as a colorless solid. mp 130 °C dec (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.32 (s, 9H), 1.22–2.21 (m, 22H), 3.64 (s, 1H), 4.28 (s, 1H), 4.37 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.44, 26.81, 29.54, 30.64, 32.83, 34.75, 36.30, 36.74, 47.05, 50.29, 108.01, 111.53. Anal. Calcd for C₂₁H₃₄N₂O₄: C, 66.64; H, 9.05; N, 7.40. Found: C, 66.65; H, 9.01; N, 7.22.

cis-Adamantane-2-spiro-3'-8'-(5'-methoxycarbonyl-1'H-imidazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ223). To a suspension of 60% NaH (0.24 g, 6 mmol) in DMF (5 ml) under nitrogen at 0°C was added a solution of methyl 4-

imidazolecarboxylate (0.76 g, 6 mmol) in DMF (18 ml). The mixture was stirred for 30 min before a solution of the methanesulfonate of **OZ119** (0.96 g, 2.6 mmol) in DMF (6 ml) was added dropwise. The reaction mixture was heated at 55 °C overnight, quenched with water (100 ml), and then extracted with CH₂Cl₂ (3 x 50 ml). The combined extracts were washed with water and brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 40% ethyl acetate in hexanes, then 5% methanol in CH₂Cl₂) to afford trioxolane **OZ223** (0.21 g, 20%, eluted first) as a colorless solid and trioxolane **OZ224** (0.36 g, 47%, eluted second) as a colorless solid. For **OZ223**: mp 148–150 °C (hexanes/CH₂Cl₂, 4:1); ¹H NMR (500 MHz, CDCl₃) δ 1.17–1.41 (m, 2H), 1.55–2.18 (m, 21H), 3.85 (s, 3H), 4.13 (d, J = 7.0 Hz, 2H), 7.52 (s, 1H), 7.75 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.43, 26.83, 27.43, 33.45, 34.74, 36.34, 36.74, 36.96, 51.43, 52.08, 108.33, 111.48, 122.20, 138.15, 142.54, 160.70. Anal. Calcd for C₂₂H₃₀N₂O₅: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.78; H, 7.41; N, 6.97.

cis-Adamantane-2-spiro-3'-8'-(4'-methoxycarbonyl-1'H-imidazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ224). For the preparation of **OZ224**, see **OZ223**. mp 150–152 °C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.15–1.39 (m, 2H), 1.49–2.15 (m, 21H), 3.81 (d, J = 7.4 Hz, 2H), 3.89 (s, 3H), 7.44 (s, 1H), 7.57 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.42, 26.81, 27.53, 33.39, 34.75, 36.34, 36.72, 37.73, 51.66, 52.95, 108.01, 111.68, 125.29, 133.99, 138.15, 163.25. Anal. Calcd for C₂₂H₃₀N₂O₅: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.79; H, 7.34; N, 6.85.

cis-Adamantane-2-spiro-3'-8'-(4'-carboxy-1'H-imidazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ225). A mixture of **OZ224** (0.16 g, 0.4 mmol), 15% KOH (1.5

ml), and methanol (15 ml) was heated at 55 °C for 4 h. After being cooled to rt, the mixture was concentrated to 3 ml, diluted with water (15 ml), and acidified with acetic acid to pH = 5. The solid was collected by filtration to afford trioxolane **OZ225** (0.10 g, 64%) as a colorless solid. mp 162 °C dec; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.01–1.23 (m, 2H), 1.40–2.05 (m, 21H), 3.87 (d, *J* = 7.3 Hz, 2H), 7.64 (s, 1H), 7.71 (s, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.96, 26.37, 27.05, 33.03, 34.42, 35.90, 36.25, 36.66, 51.32, 108.54, 110.75, 125.80, 134.59, 138.63, 164.23. Anal. Calcd for C₂₁H₂₈N₂O₅•H₂O: C, 62.05; H, 7.44; N, 6.89. Found: C, 62.36; H, 7.16; N, 6.50.

Adamantane-2-spiro-3'-8'-phenyl-1',2',4'-trioxaspiro[4.5]dec-7'-ene (OZ226).

Step 1. Addition of phenyllithium to OZ05. To a stirred solution of **OZ05** (1.10 g, 4.0 mmol) in ether (50 ml) at –78 °C was added phenyllithium (2.6 ml, 1.8 M, 4.40 mmol). The reaction mixture was allowed to reach rt during 3 h and quenched with saturated aq. NH₄Cl solution (30 ml). After the ether layer was separated, the aqueous layer was extracted with ether (3 x 40 ml). The combined organic extracts were washed with brine (50 ml), dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to afford the trioxolane carbinol intermediate (923 mg, 65 %, 1:1 mixture of two diastereomers) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 1.58–2.39 (m, 22H), 7.19–7.28 (m, 1H), 7.29–7.40 (m, 2H), 7.42–7.55 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.64, 26.66, 27.06, 27.08, 30.36, 30.46, 34.84, 34.90, 34.91, 35.10, 36.45, 36.51, 36.57, 36.63, 36.92, 36.95, 72.08, 72.38, 108.39, 108.41, 111.52, 111.64, 124.41, 124.57, 126.98, 127.07, 128.32, 128.35, 148.11, 148.30.

Step 2. Dehydration of the carbinol intermediate. To a stirred solution of the above carbinol (550 mg, 1.54 mmol) in CH₂Cl₂ (10 ml) at –10 °C was added triethylamine (1.0 ml, 7.75 mmol) followed by a solution of methanesulfonyl chloride (0.25 ml, 3.10 mmol) in CH₂Cl₂ (5 ml). The resulting mixture was stirred at 0 °C for 8 h and poured into water (10 ml). After separation of the organic layer, the aqueous layer was extracted with CH₂Cl₂ (3 x 15 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% ether in hexanes) and by subsequent recrystallization from ether/hexanes (1:1) to afford trioxolane **OZ226** (435 mg, 83 %) as a colorless solid. mp 62–64 °C (ether/hexanes, 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.42–2.21 (m, 16H), 2.40–2.73 (m, 4H), 5.73–5.99 (m, 1H),

7.02–7.45 (m, 5H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.54, 26.71, 27.10, 31.36, 34.81, 34.88, 34.95, 35.12, 35.23, 36.64, 36.70, 36.98, 107.80, 111.81, 120.95, 125.27, 126.96, 128.25, 136.69, 141.52. Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{O}_3$: C, 78.07; H, 7.74. Found: C, 78.28; H, 7.81.

5 ***cis*-Adamantane-2-spiro-3'-8'-[[*(4'*-methyl-1'-piperazinyl)carbonyl]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ227)**. To a solution of **OZ78** (322 mg, 1 mmol) in CH_2Cl_2 (10 ml) at 0°C were added triethylamine (303 mg, 3 mmol) and ethyl chloroformate (217 mg, 2 mmol). The mixture was stirred at 0 °C for 15 min before 1-methylpiperazine (110 mg, 1.1 mmol) was added. The resulting mixture was stirred at rt for
10 12 h, diluted with CH_2Cl_2 (10 ml), washed with water (10 ml), dried over MgSO_4 , and concentrated. The crude product was purified by crystallization from ethanol to afford trioxolane **OZ227** (0.19 g, 47%) as a colorless solid. mp 96–98 °C (ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.15–1.37 (m, 2H), 1.59–2.18 (m, 21H), 2.21 (d, $J = 6.9$ Hz, 2H), 2.29 (s, 3H), 2.30–2.58 (m, 4H), 3.40–3.57 (m, 2H), 3.58–3.78 (m, 2H); ^{13}C NMR (125.7 MHz,
15 CDCl_3) δ 26.64, 27.02, 30.34, 33.41, 34.13, 34.87, 36.56, 36.93, 39.18, 41.62, 45.75, 45.94, 54.89, 55.31, 108.66, 111.32, 170.46. Anal. Calcd for $\text{C}_{23}\text{H}_{36}\text{N}_2\text{O}_4$: C, 68.29; H, 8.97; N, 6.92. Found: C, 68.07; H, 8.69; N, 6.81.

***cis*-Adamantane-2-spiro-3'-8'-(azidoethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ228)**. For the preparation of the mesylate of **OZ89**, see **OZ219**. To a solution of NaN_3
20 (375 mg, 5 mmol) in DMF (5 ml) was added the mesylate (760 mg, 2 mmol) in DMF (2 ml). The mixture was stirred at 50–55 °C for 16 h before being quenched with water (15 ml). After separation of the organic layer, the aqueous layer was extracted with ether (3 x 20 ml). The combined organic layers were dried over MgSO_4 , filtered, and concentrated. The residue was purified by crystallization from ethanol to give trioxolane **OZ228** (618
25 mg, 93%) as a colorless solid. mp 58–60 °C (ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.11–1.37 (m, 2H), 1.38–1.48 (m, 1H), 1.49–1.61 (m, 2H), 1.62–2.18 (m, 20H), 3.29 (t, $J = 7.0$ Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.69, 27.10, 29.91, 33.63, 34.13, 34.92, 34.94, 35.02, 36.62, 36.99, 49.44, 108.69, 111.37. Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{N}_3\text{O}_3$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.68; H, 7.94; N, 12.47.

30 ***cis*-Adamantane-2-spiro-3'-8'-(aminoethyl)-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ229)**. To a solution of **OZ228** (333 mg, 1 mmol) in THF (7 ml) were

added triphenylphosphine (262 mg, 1 mol) and water (1 ml). The mixture was stirred at rt for 16 h and diluted with 2 M aq. HCl (5 ml). The precipitate was filtered, and washed with CH₂Cl₂ (10 ml), and dried to give trioxolane **OZ229** (194 mg, 56%) as a colorless solid. mp 150–152 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.00–1.19 (m, 2H), 1.25–2.08 (m, 23H), 2.67–2.89 (m, 2H), 8.04 (s, 3H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.83, 26.23, 29.33, 32.40, 33.02, 33.37, 34.24, 34.26, 35.81, 36.11, 36.81, 108.36, 110.45. Anal. Calcd for C₁₈H₃₀ClNO₃: C, 62.87; H, 8.79; N, 4.07. Found: C, 63.00; H, 8.58; N, 4.34.

***N,N'*-Bis[*cis*-[adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]dec-8'-yl)methyl]-1,2-benzenedicarboxamide (OZ230)**. A solution of **OZ146** (10.40 g, 24.60 mmol) and hydrazine monohydrate (5.00 g, 50 mmol) in chloroform (180 ml) and methanol (20 ml) was heated under nitrogen at 55°C for 24 h. The reaction mixture was cooled to rt and filtered to remove solid by-products. The filtrate was washed with water (100 ml) and brine (100 ml), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, CHCl₃/MeOH/Et₃N, 90:10:1) to afford trioxolane **OZ230** (1.60 g, 20%, eluted first) and ***cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane** (5.10 g, 71%, eluted second). **OZ230** was obtained as a colorless solid. mp 164–166 °C (CHCl₃/ethanol 9:1); ¹H NMR (500 MHz, CDCl₃) δ 1.19–1.39 (m, 4H), 1.59–2.11 (m, 42H), 3.19–3.35 (m, 4H), 6.75–6.88 (m, 2H), 7.41–7.52 (m, 2H), 7.53–7.65 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.48, 26.88, 27.81, 33.77, 34.79, 36.29, 36.39, 36.80, 45.39, 108.54, 111.38, 128.51, 130.27, 134.51, 169.27. Anal. Calcd for C₄₂H₅₆N₂O₈: C, 70.37; H, 7.87; N, 3.91. Found: C, 70.50; H, 7.81; N, 3.99.

***cis*-Adamantane-2-spiro-3'-8'-(5'-carboxy-1'*H*-imidazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ231)**. A mixture of **OZ223** (0.10 g, 0.25 mmol), 15% KOH (1.0 ml), methanol (10 ml), and THF (2 ml) was heated at 55 °C for 4 h. After being cooled to room temperature, the mixture was concentrated to 3 ml, diluted with water (15 ml), and acidified with acetic acid to pH = 5. The solid was collected by filtration to afford trioxolane **OZ231** (77 mg, 79%) as a colorless solid. mp 164–166 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.03–1.37 (m, 2H), 1.38–2.18 (m, 21H), 4.16 (d, *J* = 6.7 Hz, 2H), 7.58 (s, 1H), 7.89 (s, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.86, 26.26, 26.88, 32.92, 34.29, 35.81, 36.14, 36.44, 50.38, 108.39, 110.62, 122.87 (br s), 137.04 (br s), 143.25 (br s),

161.10. Anal. Calcd for $C_{21}H_{28}N_2O_5 \cdot 0.5H_2O$: C, 63.46; H, 7.35; N, 7.05. Found: C, 63.41; H, 7.11; N, 6.71.

***cis*-Adamantane-2-spiro-3'-8'-[(dimethylamino)methyl]-1',2',4'-trioxaspiro[4.5]decane mesylate (OZ232).** A solution of ***cis*-Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane** (293 mg, 1 mmol), formaldehyde (162 mg, 37% aq. solution, 2 mmol), sodium triacetoxyborohydride (612 mg, 2.8 mmol) in 1,2-dichloroethane (15 ml) was stirred at rt for 4 h before being quenched with saturated aq. $NaHCO_3$ (10 ml). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated. The resulting crude product was dissolved in CH_2Cl_2 /ether (1:5, 10 ml) and treated with a solution of methanesulfonic acid (96 mg, 1 mmol) in ether (2 ml). The precipitate was collected by filtration to afford trioxolane **OZ232** (230 mg, 55%) as a colorless solid. mp 130 °C dec; ^1H NMR (500 MHz, $DMSO-d_6$) δ 1.25–1.45 (m, 2H), 1.59–2.16 (m, 21H), 2.82 (s, 3H), 2.87 (app t, $J = 6.2$ Hz, 2H), 2.91 (app d, $J = 4.6$ Hz, 6H), 10.61 (s, 1H); ^{13}C NMR (125.7 MHz, $DMSO-d_6$) δ 26.57, 26.96, 28.20, 32.46, 33.37, 34.84, 36.50, 36.85, 39.25, 44.35, 64.04, 107.55, 111.77. Anal. Calcd for $C_{20}H_{35}NO_6S \cdot 0.6H_2O$: C, 55.92; H, 8.53; N, 3.26. Found: C, 55.71; H, 8.08; N, 3.12.

***cis*-Adamantane-2-spiro-3'-8'-(5'-methoxycarbonyl-1'*H*-1',2',4'-triazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ233).** To a suspension of 60% NaH (0.20 g, 5 mmol) in DMF (5 ml) under nitrogen at 0 °C was added a solution of methyl 1*H*-1,2,4-triazole-3-carboxylate (0.64 g, 5 mmol) in DMF (5 ml). The mixture was stirred for 1 h before a solution of the methanesulfonate of **OZ119** (0.93 g, 2.5 mmol) in DMF (5 ml) was added dropwise. The reaction mixture was heated at 55 °C overnight, quenched with water (60 ml), and then extracted with CH_2Cl_2 (3 x 40 ml). The combined extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 33% to 66% ethyl acetate in hexanes) to afford trioxolane **OZ233** (0.27 g, 27%, eluted first) as a colorless solid and trioxolane **OZ234** (0.21 g, 21%, eluted second) as a colorless solid. For **OZ233**: mp 120–122 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29–1.49 (m, 2H), 1.52–2.16 (m, 21H), 3.99 (s, 3H), 4.50 (d, $J = 7.1$ Hz, 2H), 7.96 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.64, 27.04, 27.46, 33.59,

34.89, 36.57, 36.94, 37.15, 52.90, 55.75, 108.32, 111.53, 150.78, 158.49, 181.90. Anal. Calcd for C₂₁H₂₉N₃O₅: C, 62.51; H, 7.24; N, 10.41. Found: C, 62.40; H, 7.11; N, 10.51.

***cis*-Adamantane-2-spiro-3'-8'-(3'-methoxycarbonyl-1'*H*-1',2',4'-triazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ234).** For the preparation of OZ234, see

5 **OZ233.** mp 144–146 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.23–1.41 (m, 2H), 1.52–2.16 (m, 21H), 3.99 (s, 3H), 4.07 (d, J = 7.2 Hz, 2H), 8.08 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.61, 27.00, 27.55, 33.45, 34.87, 36.50, 36.55, 36.89, 52.55, 55.73, 108.07, 111.70, 144.75, 155.30, 160.13. Anal. Calcd for C₂₁H₂₉N₃O₅: C, 62.51; H, 7.24; N, 10.41. Found: C, 62.62; H, 7.17; N, 10.52.

10 ***cis*-Adamantane-2-spiro-3'-8'-(1'*H*-1',2',4'-triazol-1'-ylmethyl)-1',2',4'-trioxaspiro[4.5]decane mesylate (OZ235).** To a solution of OZ177 (1.20 g, 3.5 mmol) in ether (10 ml) was added a solution of methanesulfonic acid (0.40 g, 4.2 mmol) in ether (10 ml). The resulting mixture was placed at –20 °C overnight. The solid was collected by filtration and dried in vacuo to afford trioxolane OZ235 (1.48 g, 96%) as a colorless solid.
15 mp 139–142 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.26–1.44 (m, 2H), 1.58–2.19 (m, 21H), 2.86 (s, 3H), 4.33 (d, J = 7.1 Hz, 2H), 8.54 (s, 1H), 10.04 (s, 1H), 12.85 (br s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.58, 26.97, 27.29, 33.34, 34.85, 36.21, 36.51, 36.86, 39.65, 56.71, 107.92, 111.69, 142.30, 144.05. Anal. Calcd for C₂₀H₃₁N₃O₆S: C, 54.40; H, 7.08; N, 9.52. Found: C, 54.28; H, 6.92; N, 9.33.

20 ***cis*-Adamantane-2-spiro-3'-8'-[[bis(2'-amino-2'-oxoethyl)amino]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ236).** A mixture of *cis*-adamantane-2-spiro-3'-8'-aminomethyl-1',2',4'-trioxaspiro[4.5]decane (293 mg, 1 mmol), 2-bromoacetamide (138 mg, 1 mmol), and potassium carbonate (276 mg, 2 mmol) in acetonitrile (18 ml) was heated at 50 °C for 16 h before being diluted with water (25 ml). The resulting mixture was
25 extracted with chloroform (3 x 18 ml). The combined extracts were washed with water and brine, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 18% methanol in CH₂Cl₂) and by recrystallization from CHCl₃ to afford trioxolane OZ236 (180 mg, 44%) as a colorless solid. mp 157–159°C (CHCl₃); ¹H NMR (500 MHz, DMSO-*d*₆) δ 0.89–1.16 (m, 2H), 1.38–2.09 (m, 21H), 2.25 (d, J = 7.1
30 Hz, 2H), 2.97 (s, 4H), 7.13 (s, 2H), 7.50 (s, 2H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.96, 26.36, 28.13, 33.51, 33.54, 34.40, 34.42, 35.92, 36.25, 59.21, 61.26, 108.90, 110.57,

172.79. Anal. Calcd for $C_{21}H_{33}N_3O_5$: C, 61.90; H, 8.16; N, 10.31. Found: C, 62.04; H, 7.91; N, 10.12.

***cis*-Adamantane-2-spiro-3'-8'-[[*(*aminoiminomethyl)*amino*]methyl]-1',2',4'-trioxaspiro[4.5]decane hydrochloride (OZ237).** A mixture of ***cis*-adamantane-2-spiro-3'-8'-aminomethyl-1',2',4'-trioxaspiro[4.5]decane** (293 mg, 1 mmol), 1*H*-pyrazole-1-carboxamide hydrochloride (147 mg, 1 mmol), *N,N*-diisopropylethylamine (129 mg, 1 mmol) in DMF (5 ml) was stirred at rt for 16 h before being diluted with ether (50 ml). The solid was collected by filtration and recrystallized from 30% aq. ethanol to afford trioxolane **OZ237** (210 mg, 56%) as a colorless solid. mp 146–149°C (30% aq. ethanol); ¹H NMR (500 MHz, DMSO-*d*₆) δ 0.99–1.21 (m, 2H), 1.39–2.05 (m, 21H), 2.98 (app t, J = 6.0 Hz, 2H), 6.50–7.89 (m, 5H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.86, 26.27, 27.00, 33.05, 34.31, 35.28, 35.83, 36.14, 45.59, 108.41, 110.61, 157.17. Anal. Calcd for $C_{18}H_{30}ClN_3O_3$: C, 58.13; H, 8.13; N, 11.30. Found: C, 58.31; H, 8.27; N, 10.96.

***cis*-Adamantane-2-spiro-3'-8'-(2'-amino-2'-oxoethyl)-1',2',4'-trioxaspiro[4.5]decane (OZ243).** To a solution of **OZ78** (322 mg, 1 mmol) in CH_2Cl_2 (10 ml) at 0°C was added TEA (202 mg, 2 mmol) followed by ethyl chloroformate (217 mg, 2 mmol). After 15 min, ammonia (7 N in methanol, 3 ml) was added, and the stirring was continued for 12 h. The precipitate was filtered and dried to afford trioxolane **OZ243** (210 mg, 65%) as a colorless solid. mp 140–142°C; ¹H NMR (500 MHz, $CDCl_3$) δ 1.09–1.43 (m, 3H), 1.45–2.15 (m, 20H), 2.11 (d, J = 7.1 Hz, 2H), 5.48 (s, 1H), 5.66 (s, 1H); ¹³C NMR (125.7 MHz, $CDCl_3$) δ 26.47, 26.85, 29.97, 33.32, 33.95, 34.77, 36.38, 36.78, 42.55, 108.50, 111.35, 174.39. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.40; H, 8.47; N, 4.39.

***cis*-Adamantane-2-spiro-3'-8'-[[*(*4'-phenyl-1'-piperazinyl)*carbonyl*]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ244).** To a solution of **OZ78** (322 mg, 1 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added TEA (202mg, 2mmol) followed by ethyl chloroformate (217 mg, 2 mmol). After 15 min, 1-phenylpiperazine (162 mg, 1 mmol) was added, and the stirring was continued for 12 h. The reaction mixture was concentrated, diluted with water, and filtered. The crude product was purified by recrystallization from ethanol to give trioxolane **OZ244** (280 mg, 60%) as a colorless solid. mp 140–142°C (ethanol); ¹H NMR (500 MHz, $CDCl_3$) δ 1.18–1.38 (m, 2H), 1.55–2.18 (m, 21H), 2.26 (d, J = 6.9 Hz, 2H),

3.02–3.29 (m, 4H), 3.55–3.70 (m, 2H), 3.71–3.89 (m, 2H), 6.81–7.02 (m, 3H), 7.20–7.38 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.48, 26.86, 30.30, 33.34, 34.06, 34.78, 36.39, 36.79, 39.18, 41.51, 45.69, 49.47, 49.77, 108.59, 111.33, 116.58, 120.51, 129.22, 150.91, 170.50. Anal. Calcd for $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_4$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.22; H, 8.16; N, 5.99.

Adamantane-2-spiro-3'-8'-hydroxy-8'-(2'-thiazolyl)-1',2',4'-trioxaspiro[4.5]decane (OZ247). To a stirred solution of 2-bromothiazole (246 mg, 1.5 mmol) in dry THF (4 ml) under N_2 at -78°C was added *n*-BuLi (1.6 M in hexanes, 1 ml, 1.5 mmol). The resulting bright yellow solution was stirred for 1 h at the same temperature, and then a solution of **OZ05** (415 mg, 1.5 mmol) in dry THF (10 ml) was added. The mixture was allowed to reach 0°C , poured into ice-water mixture (15 ml), and extracted with ether (3 x 25 ml). The combined organic extracts were washed with brine (25 ml), dried over MgSO_4 , and concentrated. The crude product was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) followed by recrystallization from hexanes/ether (9:1) to afford trioxolane **OZ247** (202 mg, 37%, 1:1 mixture of 2 diastereomers) as a colorless solid. mp $64\text{--}66^\circ\text{C}$ (hexanes/ether 9:1); ^1H NMR (500 MHz, CDCl_3) δ 1.60–2.42 (m, 22H), 3.18 (s, 0.5H), 3.40 (s, 0.5H), 7.28 (d, $J = 3.0$ Hz, 0.5H), 7.30 (d, $J = 3.0$ Hz, 0.5H), 7.69 (d, $J = 3.3$ Hz, 0.5H), 7.72 (d, $J = 3.0$ Hz, 0.5H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.45, 26.46, 26.85, 29.98, 30.09, 34.73, 34.77, 34.79, 34.86, 36.34, 36.40, 36.48, 36.75, 36.77, 72.44, 73.00, 107.91, 107.97, 111.61, 111.84, 119.02, 141.95, 142.16, 177.99, 178.23. Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_4\text{S}$: C, 62.78; H, 6.93; N, 3.85. Found: C, 62.94; H, 7.01; N, 3.89.

cis-Adamantane-2-spiro-3'-8'-(1'*H*-imidazol-2'-yl)-1',2',4'-trioxaspiro[4.5]decane (OZ251). **Step 1.** To a solution of oxalyl chloride (0.99 g, 7.8 mmol) in CH_2Cl_2 (50 ml) at -78°C was added methyl sulfoxide (1.41 g, 18 mmol) dropwise. The mixture was stirred at -78°C for 30 min before **OZ119** (1.76 g, 6 mmol) in CH_2Cl_2 (5 ml) was added. After the resulting mixture was stirred for 45 min, triethylamine (3.03 g, 30 mmol) was added. The mixture was warmed to rt for 2 h and quenched with water (50 ml). The organic layer was washed with water (2 x 30 ml) and brine, dried over MgSO_4 , and concentrated. The crude product (1.80 g) was crystallized from 50% ethanol to afford the desired aldehyde, **cis-Adamantane-2-spiro-3'-8'-formyl-1',2',4'**

trioxaspiro[4.5]decane, (0.82 g, 47%) as a colorless solid. mp 74–76 °C (50% ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.64–2.02 (m, 22 H), 2.20–2.30 (m, 1 H), 9.63 (d, J = 1.1 Hz, 1H). **Step 2.** To a solution of the above aldehyde (292 mg, 1mmol) and 40 % glyoxal (145 mg, 1 mmol) in methanol (12 ml) at 0°C was added ammonia (0.45 ml, 7 N in methanol). The resulting mixture was stirred at rt overnight and concentrated. The crude product was crystallized from hexanes/CH₂Cl₂ (3:2) to afford trioxolane **OZ251** (240 mg, 73%) as a colorless solid. mp 138–140°C (hexanes/CH₂Cl₂, 3:2); ¹H NMR (500 MHz, CDCl₃) δ 1.58–2.23 (m, 22H), 2.75–2.98 (m, 1H), 6.96 (s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.54, 26.94, 29.11, 33.92, 34.82, 34.86, 36.23, 36.47, 36.84, 108.00, 111.54, 121.10 (br s), 151.00. Anal. Calcd for C₁₉H₂₆N₂O₃: C, 69.06; H, 7.93; N, 8.48. Found: C, 69.04; H, 7.93; N, 8.60.

cis-Adamantane-2-spiro-3'-8'-[(2'-thiazolylamino)methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ252). A mixture of **cis-Adamantane-2-spiro-3'-8'-formyl-1',2',4'-trioxaspiro[4.5]decane** (292 mg, 1.0 mmol), 2-aminothiazole (150 mg, 1.5 mmol), and acetic acid (240 mg, 4.0 mmol) in CH₂Cl₂ (10 ml) and ClCH₂CH₂Cl (10 ml) was stirred at rt for 2.5 h before sodium triacetoxymethylborohydride (422 mg, 2.0 mmol) was added. The resulting mixture was stirred at rt overnight and then quenched with saturated aq. NaHCO₃ (50 ml). The organic layer was separated and washed with water and brine, dried over MgSO₄, and concentrated. The crude prude was purified by flash chromatography (silica gel, 2% CH₃OH in CH₂Cl₂). The enriched product was dissolved in ether/CH₂Cl₂ (4:1, 20 ml), treated with methanesulfonic acid (40 mg, 0.4 mmol), and placed at –20°C overnight. After the solvent was decanted, the residue was washed with ether and dried in vacuo to afford trioxolane **OZ252** (110 mg, 23%) as a colorless solid. mp 136–138°C; ¹H NMR (500 MHz, CDCl₃) δ 1.20–1.41 (m, 2H), 1.50–2.21 (m, 21H), 2.88 (s, 3H), 3.11 (app t, J = 6.1 Hz, 2H), 6.54 (d, J = 4.1 Hz, 1H), 7.05 (d, J = 4.1 Hz, 1H), 10.51 (s, 1H), 14.17 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.46, 26.84, 27.88, 33.44, 34.77, 35.66, 36.38, 36.76, 39.45, 54.26, 104.97, 108.18, 111.57, 127.14, 170.79. Anal. Calcd for C₂₁H₃₂N₂O₆S₂: C, 53.37; H, 6.82; N, 5.93. Found: C, 53.16; H, 6.76; N, 5.91.

cis-Adamantane-2-spiro-3'-8'-[(cyclopropylamino)methyl]-1',2',4'-trioxaspiro[4.5]decane mesylate (OZ253). To a solution **cis-adamantane-2-spiro-3'-8'-formyl-1',2',4'-trioxaspiro[4.5]decane** (292 mg, 1.0 mmol), cyclopropylamine (57 mg,

1.0 mmol), and acetic acid (90 mg, 1.5 mmol) in 1,2-dichloroethane (10 ml) was added sodium triacetoxymethylborohydride (295 mg, 1.4 mmol). The mixture was stirred for 2 h and then quenched with saturated aq. NaHCO₃ (20 ml). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 ml). The combined organic extracts were washed with water and brine, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 20% ether in hexanes, 400 ml; then 10% methanol in CH₂Cl₂, 300 ml) to give two fractions. The first fraction (130 mg) was crystallized from CH₃OH/CH₂Cl₂ (6:1) to afford trioxolane **OZ254** (96 mg, 31%) as a colorless solid. The second fraction (160 mg) was dissolved in ether (3 ml) and treated with a solution of methanesulfonic acid (46 mg) in ether (3 ml). The precipitate was collected by filtration and dried in vacuo to afford trioxolane **OZ253** (160 mg, 37%) as a colorless solid. For **OZ253**: mp 144–147°C (ether); ¹H NMR (500 MHz, CDCl₃) δ 0.77–0.95 (m, 2H), 1.10–1.22 (m, 2H), 1.23–1.41 (m, 2H), 1.50–2.19 (m, 21H), 2.50–2.69 (m, 1H), 2.73 (s, 3H), 2.82–3.02 (m, 2H), 8.63 (s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 3.70, 26.46, 26.86, 27.89, 31.23, 33.10, 33.43, 34.77, 36.38, 36.77, 39.51, 54.07, 107.97, 111.50. Anal. Calcd for C₂₁H₃₅NO₆S: C, 58.72; H, 8.21; N, 3.26. Found: C, 58.65; H, 8.15; N, 3.35.

***N,N*-Bis(*cis*-adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane-8'-methyl)cyclopropylamine (OZ254).** For the preparation of trioxolane **OZ254**, see **OZ253**. mp 138–140°C (CH₃OH/CH₂Cl₂ 6:1); ¹H NMR (500 MHz, CDCl₃) δ 0.22–0.35 (m, 2H), 0.36–0.48 (m, 2H), 0.97–1.15 (m, 4H), 1.45–2.15 (m, 43H), 2.28 (d, J = 7.1 Hz, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 6.80, 26.52, 26.92, 28.68, 34.09, 34.43, 34.80, 34.82, 36.42, 36.85, 38.74, 63.12, 109.31, 111.15. Anal. Calcd for C₃₇H₅₅NO₆: C, 72.87; H, 9.09; N, 2.30. Found: C, 72.83; H, 8.95; N, 2.33.

***cis*-Adamantane-2-spiro-3'-8'-[[4'-pyridinylcarbonyl)amino]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ255).** To a solution of **OZ209** (389 mg, 1.0 mmol) and triethylamine (0.6 g, 6 mmol) in CH₂Cl₂ (10 ml) at 0 °C was added a solution of isonicotinoyl chloride hydrochloride (267 mg, 1.5 mmol) in CH₂Cl₂ (10 ml). The resulting mixture was stirred at rt overnight before being quenched with water (20 ml). After separation of the organic phase, the aqueous layer was extracted with CH₂Cl₂ (20 ml). The combined organic extracts were washed with water and brine, dried over MgSO₄, and concentrated. The crude product was crystallized from 40% aq. ethanol to afford trioxolane

OZ255 (410 mg, 103%) as a colorless solid. mp 145–146°C (40% aq. ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.19–1.41 (m, 2H), 1.55–2.19 (m, 21H), 3.34 (app t, J = 6.3 Hz, 2H), 6.36 (br s, 1H), 7.61 (d, J = 4.4 Hz, 2H), 8.75 (br s, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.46, 26.85, 27.82, 33.71, 34.78, 36.21, 36.38, 36.76, 45.41, 108.46, 111.49, 120.87, 141.70, 150.57, 165.63. Anal. Calcd for C₂₃H₃₀N₂O₄: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.18; H, 7.43; N, 7.04.

cis-Adamantane-2-spiro-3'-8'-[(2'-amino-2'-oxoethyl)amino]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ256). A mixture of **OZ209** (389 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in acetonitrile (40 ml) was stirred for 15 min before 2-bromoacetamide (138 mg, 1 mmol) and potassium carbonate (276 mg, 2 mmol) were added. The mixture was heated at 50°C for 16 h, then diluted with water (25 ml), and extracted with CH₂Cl₂ (3 x 20 ml). The combined organic extracts were washed with water and brine, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 6% CH₃OH in CH₂Cl₂) to afford trioxolane **OZ256** (90 mg, 26%) as a colorless solid. mp 136–138°C; ¹H NMR (500 MHz, CDCl₃) δ 1.05–1.31 (m, 2H), 1.37–2.19 (m, 22H), 2.49 (d, J = 6.4 Hz, 2H), 3.25 (s, 2H), 5.95 (s, 1H), 7.04 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.43, 26.83, 28.07, 33.86, 34.74, 34.76, 36.35, 36.52, 36.75, 52.52, 55.72, 108.73, 111.31, 174.84. Anal. Calcd for C₁₉H₃₀N₂O₄•0.25H₂O: C, 63.80; H, 8.68; N, 7.83. Found: C, 63.68; H, 8.25; N, 7.82.

cis-Adamantane-2-spiro-3'-8'-[(methanesulfonyl)amino]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ257). To a solution of **OZ209** (389 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in CH₂Cl₂ (10 ml) at 0°C was added a solution of methanesulfonyl chloride (171 mg, 1.5 mmol) in CH₂Cl₂ (1.5 ml). The mixture was stirred at rt for 16 h, washed with water and brine, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 5% CH₃OH in CH₂Cl₂) to afford trioxolane **OZ257** (290 mg, 78%) as a colorless solid. mp 124–126 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.15–1.33 (m, 2H), 1.45–2.17 (m, 21H), 2.95 (s, 3H), 2.99 (app t, J = 6.7 Hz, 2H), 4.31 (br s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.47, 26.86, 27.55, 33.60, 34.78, 34.79, 36.38, 36.77, 40.36, 48.54, 108.40, 111.50. Anal. Calcd for C₁₈H₂₉NO₅S: C, 58.20; H, 7.87; N, 3.77. Found: C, 58.32; H, 7.74; N, 3.83.

Adamantane-2-spiro-3'-8'-[[2'-[(7'-chloro-4'-quinolinyl)amino]ethyl]amino]-1',2',4'-trioxaspiro[4.5]decane (OZ258). To a stirred solution of **OZ05** (75 mg, 0.27 mmol) in CH₂Cl₂ (5 ml) at rt under N₂ was added *N*²-(7-chloro-4-quinolinyl)-1,2-diaminoethane (176 mg, 0.34 mmol) followed by sodium triacetoxyborohydride (72 mg, 0.34 mmol). The resulting mixture was stirred at rt for 24 h before being poured into water (10 ml). The organic layer was separated, dried, and concentrated. Recrystallization of the crude product from ethanol afforded trioxolane **OZ258** (86 mg, 66%) as a colorless solid. mp 146–148°C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.42–2.21 (m, 23H), 2.55–2.77 (m, 1H), 3.05 (t, J = 5.6 Hz, 2H), 3.34 (br s, 2H), 5.90 (br s, 1H), 6.39 (d, J = 5.2 Hz, 1H), 7.37 (dd, J = 8.8, 1.9 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 1.9 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.65, 27.08, 30.17, 32.23, 34.86, 35.06, 36.60, 36.94, 42.89, 45.17, 54.43, 99.36, 108.36, 111.80, 121.09, 125.40, 125.46, 128.93, 134.98, 149.20, 150.00, 152.06. Anal. Calcd for C₂₇H₃₄ClN₃O₃: C, 67.00; H, 7.08; N, 8.68. Found: C, 67.18; H, 7.12; N, 8.49.

Adamantane-2-spiro-3'-8'-(3'-pyridinylamino)-1',2',4'-trioxaspiro[4.5]decane (OZ259). To afford trioxolane **OZ259** (? mg, 83 %, 1:1 mixture of 2 diastereomers) as a colorless solid. mp 132–134 °C (?); ¹H NMR (500 MHz, CDCl₃) δ 1.42–2.23 (m, 22H), 3.25–3.49 (m, 1H), 3.59–3.83 (m, 1H), 6.82–6.90 (m, 1H), 7.02–7.12 (m, 1H), 7.90–7.96 (m, 1H), 7.98–8.04 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.40, 26.81, 26.83, 29.40, 29.86, 32.16, 32.60, 34.69, 34.72, 34.76, 34.87, 36.29, 36.32, 36.71, 49.54, 49.87, 107.86, 111.60, 111.81, 118.78, 118.85, 123.67, 136.22, 136.45, 138.57, 138.61, 143.06. Anal. Calcd for C₂₁H₂₈N₂O₃: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.88; H, 7.91; N, 7.84.

cis-Adamantane-2-spiro-3'-8'-[3'-(ethoxycarbonyl)propyl]-1',2',4'-trioxaspiro[4.5]decane (OZ260). A solution of *O*-methyl 2-adamantanone oxime (895 mg, 5 mmol) and 4-[3-(ethoxycarbonyl)propyl]cyclohexanone (710 mg, 3.35 mmol) in cyclohexane (85 ml) and CH₂Cl₂ (15 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) and by subsequent crystallization from ethanol to afford trioxolane **OZ260** (660 mg, 52%) as a colorless solid. mp 52–54°C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.01–1.37 (m, 5H), 1.25 (t, J = 7.1 Hz, 3H), 1.47–2.21 (m, 22H), 2.27 (t, J = 7.6 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 14.24, 22.63, 26.51, .

26.90, 30.01, 34.19, 34.55, 34.79, 34.81, 35.66, 35.90, 36.41, 36.83, 60.18, 108.99, 111.17, 173.68. Anal. Calcd for C₂₂H₃₄O₅: C, 69.81; H, 9.05. Found: C, 69.82; H, 8.96.

***cis*-Adamantane-2-spiro-3'-8'-(3'-carboxypropyl)-1',2',4'-**

trioxaspiro[4.5]decane (OZ261). To a solution of **OZ260** (250 mg, 0.66 mmol) in 95% ethanol (5 ml) was added 15% NaOH solution (1 ml). The mixture was stirred at 25 °C for 24 h before being concentrated and acidified with 6 M aq. HCl (3 ml). The precipitate was filtered, washed with water, and crystallized from ethanol to give trioxolane **OZ261** (186 mg, 81%) as a colorless solid. mp 156–158°C (ethanol); ¹H NMR (500 MHz, CDCl₃) δ 1.03–1.39 (m, 5H), 1.45–2.20 (m, 22H), 2.27 (t, J = 7.4 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 22.33, 26.50, 26.90, 29.98, 34.06, 34.17, 34.81, 35.55, 35.87, 36.40, 36.83, 108.96, 111.19, 179.14. Anal. Calcd for C₂₀H₃₀O₅: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.49.

***cis*-Adamantane-2-spiro-3'-8'-[(acetylamino)methyl]-1',2',4'-**

trioxaspiro[4.5]decane (OZ262). To a solution of **OZ209** (389 mg, 1 mmol) and triethylamine (505 mg, 5 mmol) in CH₂Cl₂ (10 ml) at 0°C was added dropwise a solution of acetyl chloride (140 mg, 1.9 mmol) in CH₂Cl₂ (5 ml). The mixture was stirred at rt for 16 h, washed with water and brine, dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (silica gel, 5% CH₃OH in CH₂Cl₂) and by crystallization from hexanes/CH₂Cl₂ (3:1) to afford trioxolane **OZ262** (150 mg, 45%) as a colorless solid. mp 102°C dec (hexanes/CH₂Cl₂, 3:1); ¹H NMR (500 MHz, CDCl₃) δ 1.15–1.37 (m, 2H), 1.41–2.09 (m, 21H), 1.98 (s, 3H), 3.11 (app t, J = 6.3 Hz, 2H), 5.52 (br s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 23.34, 26.46, 26.85, 27.72, 33.73, 34.76, 34.77, 36.16, 36.37, 36.77, 44.87, 108.60, 111.38, 170.03. Anal. Calcd for C₁₉H₂₉NO₄: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.26; H, 8.70; N, 4.18.

***cis*-Adamantane-2-spiro-3'-8'-[[[(1'*H*-imidazol-4'-yl)carbonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane mesylate (OZ263).** To a solution of 4-imidazolecarboxylic acid (134 mg, 1.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (290 mg, 1.5 mmol), and 1-hydroxybenzotriazole (200 mg, 1.5 mmol) in DMF (40 ml) under N₂ was added a solution of **OZ209** (389 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) in DMF (5 ml). The resulting mixture was stirred at r.t. for 48 h before being quenched with water (120 ml). The mixture was extracted with CH₂Cl₂ (3 x 40 ml). The

combined organic extracts were washed with water and brine, dried over MgSO_4 , and concentrated. The crude product was dissolved in CH_2Cl_2 (10 ml) and treated with methanesulfonic acid (90 mg). The solid was collected by filtration and recrystallized from ether/ CH_2Cl_2 / CH_3OH (3:1:1) to afford trioxolane **OZ 263** (72 mg, 15%) as a colorless solid. mp 161–162°C (ether/ CH_2Cl_2 / CH_3OH 3:1:1); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 1.02–1.23 (m, 2H), 1.45–2.09 (m, 21H), 2.32 (s, 3H), 3.13 (app t, $J = 6.3$ Hz, 2H), 8.12 (s, 1H), 8.73 (br s, 1H), 9.03 (s, 1H), 14.47 (br s, 2H); ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$) δ 25.96, 26.36, 27.64, 33.34, 34.41, 35.77, 35.90, 36.23, 44.06, 108.68, 110.66, 119.91, 120.22, 128.13, 128.22, 135.92, 136.09, 157.40. Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_7\text{S}$: C, 54.64; H, 6.88; N, 8.69. Found: C, 54.72; H, 6.76; N, 8.90.

***cis*-Adamantane-2-spiro-3'-8'-[[[(1'-oxido-4'-pyridinyl)carbonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ264)**. To a solution of isonicotinic acid *N*-oxide (167 mg, 1.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (290 mg, 1.5 mmol), and 1-hydroxybenzotriazole (200 mg, 1.5 mmol) in DMF (10 ml) under N_2 was added a solution of **OZ209** (389 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) in DMF (5 ml). The resulting mixture was stirred at rt for 16 h before being quenched with water (50 ml). The precipitate was collected by filtration to afford trioxolane **OZ264** (340 mg, 82 %) as a colorless solid. mp 152–154°C; ^1H NMR (500 MHz, CDCl_3) δ 1.21–1.43 (m, 2H), 1.49–2.11 (m, 21H), 3.33 (app t, $J = 6.2$ Hz, 2H), 6.54 (br s, 1H), 7.69 (d, $J = 6.3$ Hz, 2H), 8.20 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.44, 26.84, 27.82, 33.69, 34.77, 36.18, 36.37, 36.75, 45.56, 108.43, 111.52, 124.32, 131.08, 139.29, 163.52. Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_5$: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.81; H, 7.18; N, 6.55.

***cis*-Adamantane-2-spiro-3'-8'-[[[(aminocarbonyl)amino]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ265)**. A mixture of **OZ209** (389 mg, 1 mmol), pyridine (790 mg, 10 mmol), acetic acid (600 mg, 10 mmol), triethylamine (303 mg, 3 mmol), and potassium cyanate (164 mg, 2 mmol) in CH_2Cl_2 (10 ml) was stirred at r.t. for 38 h. The mixture was then washed with water and brine, dried over MgSO_4 , and concentrated. The crude product was recrystallized from 40% aq. ethanol to afford trioxolane **OZ265** (250 mg, 74%) as a colorless solid. mp 138–140 °C (40% aq. ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.11–1.33 (m, 2H), 1.41–2.18 (m, 21H), 3.02 (app t, $J = 5.5$ Hz, 2H), 4.64 (br s, 2H), 5.09

(br s, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.45, 26.84, 27.66, 33.75, 34.76, 36.36, 36.65, 36.76, 45.85 (br s), 108.69, 111.35, 158.96. Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.40; H, 8.15; N, 8.46.

***cis*-Adamantane-2-spiro-3'-8'-[[[(dimethylamino)carbonyl]amino]methyl]-**

5 **1',2',4'-trioxaspiro[4.5]decane (OZ266).** To a solution of **OZ209** (389 mg, 1.0 mmol) and triethylamine (202 mg, 2.0 mmol) in CH_2Cl_2 (10 ml) at 0°C was added dimethylcarbonyl chloride (120 mg, 1.1 mmol). The mixture was stirred at rt for 16 h before being washed with water and brine, dried over MgSO_4 , and concentrated. The crude product was crystallized from 50% aq. ethanol to afford trioxolane **OZ266** (270 mg, 74%) as a colorless
10 solid. mp $153\text{--}155^\circ\text{C}$ (50% aq. ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.14–1.33 (m, 2H), 1.44–2.17 (m, 21H), 2.91 (s, 6H), 3.09 (app t, $J = 6.2$ Hz, 2H), 4.46 (br s, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.49, 26.88, 27.77, 33.84, 34.79, 36.19, 36.39, 36.61, 36.80, 46.25, 108.85, 111.30, 158.43. Anal. Calcd for $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_4$: C, 65.91; H, 8.85; N, 7.69. Found: C, 66.16; H, 8.80; N, 7.90.

15 ***cis*-Adamantane-2-spiro-3'-8'-[[[(4'-methyl-1'-piperazinyl)carbonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ267).** To a solution of **OZ209** (389 mg, 1.0 mmol) and triethylamine (404 mg, 4.0 mmol) in CH_2Cl_2 (10 ml) at 0°C was added 4-methyl-1-piperazinecarbonyl chloride hydrochloride (240 mg, 1.2 mmol). The mixture was stirred at rt for 16 h before being washed with water and
20 brine, dried over MgSO_4 , and concentrated. The crude product was crystallized from 60% aq. ethanol to afford trioxolane **OZ267** (280 mg, 67%) as a colorless solid. mp 82°C dec (60% aq. ethanol); ^1H NMR (500 MHz, CDCl_3) δ 1.11–1.30 (m, 2H), 1.43–2.15 (m, 21H), 2.31 (s, 3H), 2.39 (t, $J = 5.1$ Hz, 4H), 3.09 (app t, $J = 6.2$ Hz, 2H), 3.38 (t, $J = 5.1$ Hz, 4H), 4.59 (app t, $J = 5.5$ Hz, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 26.45, 26.84, 27.77, 33.78, 34.76, 36.35, 36.48, 36.76, 43.71, 46.08, 46.18, 54.64, 108.77, 111.29, 157.69. Anal. Calcd for $\text{C}_{23}\text{H}_{37}\text{N}_3\text{O}_4$: C, 65.84; H, 8.89; N, 10.02. Found: C, 65.91; H, 8.64; N, 10.07.

***N*-(*cis*-Adamantane-2-spiro-3'-1',2',4'-trioxaspiro[4.5]decane-8'-**

methyl)oxamide (OZ268). To a solution of oxamic acid (107 mg, 1.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (290 mg, 1.5 mmol), and 1-
30 hydroxybenzotriazole (200 mg, 1.5 mmol) in DMF (15 ml) under N_2 was added a solution of **OZ209** (389 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) in DMF (5 ml). The

resulting mixture was stirred at rt for 16 h before being quenched with water (80 ml). The precipitate was collected by filtration to afford trioxolane **OZ268** (320 mg, 88%) as a colorless solid. mp 152–155 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 0.95–1.23 (m, 2H), 1.39–2.13 (m, 21H), 2.97 (app t, J = 6.5 Hz, 2H), 7.74 (s, 1H), 7.80 (s, 1H), 8.67 (app t, J = 6.2 Hz, 1H); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 25.97, 26.38, 27.55, 33.30, 34.41, 35.47, 35.91, 36.25, 44.03, 108.70, 110.62, 160.50, 162.38. Anal. Calcd for C₁₉H₂₈N₂O₅: C, 62.62; H, 7.74; N, 7.69. Found: C, 62.80; H, 7.55; N, 7.89.

***trans*-Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane mesylate (OZ269).** A mixture of **OZ167** (2.54 g, 6.0 mmol) and hydrazine monohydrate (1.80 g, 36.0 mmol) in chloroform/ethanol (7:3, 60 ml) was heated at 55–65°C for 24 h. After being cooled to rt, the solid byproduct was filtered off and the filtrate was washed with water (2 x 40 ml) and brine (20 ml). The combined aqueous layers were extracted with CH₂Cl₂ (3 x 30 ml). The CH₂Cl₂ extracts were washed with water (50 ml) and brine (50 ml). The combined organic solutions were dried over MgSO₄ and concentrated. The residue was dissolved in CH₂Cl₂ (10 ml) and treated with a solution of methanesulfonic acid (0.6 g) in CH₂Cl₂ (2 ml). The product was precipitated by addition of ether (40 ml) and collected by filtration to afford trioxolane **OZ269** (1.80 g, 77%) as a colorless solid. mp 140–141 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.32–1.52 (m, 2H), 1.54–2.15 (m, 21H), 2.76 (s, 3H), 2.87 (app t, J = 6.3 Hz, 2H), 7.60 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.44, 26.86, 27.24, 33.23, 34.56, 34.71, 34.90, 36.33, 36.74, 39.29, 44.63, 108.06, 111.81. Anal. Calcd for C₁₈H₃₁NO₆S•0.4H₂O: C, 53.84; H, 8.12; N, 3.49. Found: C, 53.51; H, 7.64; N, 3.66.

***cis*-Adamantane-2-spiro-3'-8'-[[[(1'-oxido-2'-pyridinyl)carbonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane (OZ270).** To a solution of picolinic acid *N*-oxide (167 mg, 1.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (290 mg, 1.5 mmol), and 1-hydroxybenzotriazole (200 mg, 1.5 mmol) in DMF (10 ml) under N₂ was added a solution of **OZ209** (389 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) in DMF (5 ml). The resulting mixture was stirred at r.t. for 16 h before being quenched with water (80 ml). The precipitate was collected by filtration to afford trioxolane **OZ270** (338 mg, 82%) as a colorless solid. mp 140–143°C; ¹H NMR (500 MHz, CDCl₃) δ 1.22–1.45 (m, 2H), 1.46–2.15 (m, 21H), 3.36

(app t, J = 6.4 Hz, 2H), 7.35–7.43 (m, 1H), 7.44–7.50 (m, 1H), 8.26 (d, J = 6.3 Hz, 1H), 8.44 (dd, J = 8.2, 1.9 Hz, 1H), 11.35 (s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 26.45, 26.84, 27.96, 33.75, 34.75, 34.76, 36.18, 36.34, 36.77, 44.97, 108.64, 111.30, 127.15, 127.26, 128.89, 140.50, 140.69, 159.64. Anal. Calcd for C₂₃H₃₀N₂O₅: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.47; H, 7.12; N, 6.75.

EXAMPLE 2

Antimalarial Activity of OZ01-OZ270

Each trioxolane was screened against the chloroquine-resistant K1 and chloroquine-sensitive NF54 strains of *P. falciparum* *in vitro*. In the single dose STI *in vivo* screen, Moro SPF or NMRI mice infected with the ANKA strain of *P. berghei* (groups of three mice) were treated on day one post-infection with trioxolanes dissolved or suspended in 3% ethanol and 7% Tween 80. Trioxolanes were administered as single 10 mg/kg doses sc and po. Trioxolanes were also administered as single 10 mg/kg doses in standard suspending vehicle (SSV). SSV consists of 0.5% w/v CMC, 0.5% v/v benzyl alcohol, 0.4% v/v Tween 80, and 0.9% w/v sodium chloride in water. Antimalarial activity was measured by percent reduction in parasitemia on day three post-infection and survival times compared to an untreated control group. Survival to day 30 post-infection is considered to be a cure. For comparative analysis, in Table 1 below data is presented for trioxolanes OZ01-OZ270 along with the controls, fenozan, artemisinin, arteether, artemether, and artesunate:

Table 1

Compd	IC ₅₀ (ng/ml) K1/NF54	Activity (%) po/SSVpo/sc	Survival (days) po/SSVpo/sc
NONE	---	0	5.6 ± 0.3
OZ01	>100/>100	0/NA/0 ¹	5.3/NA/5.3 ¹
OZ02	>100/94	0/NA/0 ¹	5.0/NA/5.0 ¹
OZ03	1.2/1.6	94/NA/100	7.2/NA/11.9
OZ04	>100/>100	0/NA/0 ¹	5.3/NA/5.3 ¹

OZ05	0.19/0.36	94/74/99.7	7.1/6.2/8.6
OZ06	18/22	T/NA/T ¹	1.0/NA/1.0 ¹
OZ07	66/49	0/NA/0 ¹	6.0/NA/5.7 ¹
OZ08	2.4/2.8	99.7/NA/99.9 ¹	8.0/NA/9.7 ¹
OZ09	32/39	0/NA/81 ¹	5.0/NA/6.3 ¹
OZ10	0.40/0.67	99.6/NA/99.98	8.9/NA/10.5
OZ11	1.5/2.7	99.99/98/100	11.4/7.4/18
OZ12	0.60/0.77	75/NA/99.8	7.0/NA/9.3
OZ13	0.40/0.50	56/NA/99.7	6.7/NA/9.7
OZ14	91/>100	23/NA/96	6.0/NA/7.7
OZ15	0.60/1.0	99.8/88/99.9	7.4/6.8/8.2
OZ16	0.45/0.67	79/83/99.2	6.7/6.7/7.3
OZ17	85/>100	0/NA/18	5.3/NA/6.3
OZ18	63/84	0/NA/0	5.0/NA/5.3
OZ19	1.3/2.7	98.3/56/99.98	7.5/6.0/13.4
OZ20	15/20	97/14/90	7.4/6.0/7.0
OZ21	14/25	0/NA/0	5.0/NA/6.0
OZ22	0.32/0.56	35/NA/99.6	6.0/NA/7.7
OZ23	0.29/0.57	99.5/99.34/99.9	7.7/7.0/8.9
OZ24	0.35/0.58	93/66/99.9	7.0/6.8/8.7
OZ25	1.1/2.1	99.9/96/99.97	8.4/7.2/16.5
OZ26	3.1/5.0	88/NA/99.9	7.0/NA/9.7
OZ27	2.2/4.8	99.97/96/99.92	12.6/8.0/17.1

OZ28	2.1/2.5	93/NA/99.97	7.3/NA/12.3
OZ29	9.7/13	0/NA/0	5.0/NA/5.0
OZ30	0.65/1.3	0/NA/86	5.3/NA/9.0
OZ31	3.0/3.0	99.95/90/99.95	9.0/7.3/17.7
OZ32	0.25/0.51	79/93/91	6.7/7.0/8.7
OZ33	2.3/3.5	80/NA/99.97	6.7/NA/11.7
OZ34	42/60	0/NA/0	5.3/NA/5.7
OZ35	1.7/2.1	74/NA/99.98	6.3/NA/9.3
OZ36	24/62	0/NA/0	5.7/NA/5.7
OZ37	1.1/1.6	83/NA/99.98	6.7/NA/13
OZ38	0.86/1.3	83/15/99.98	6.7/5.0/25.3
OZ39	1.4/1.8	61/NA/99.3	6.3/NA/7.7
OZ40	1.4/2.0	99/NA/99.8	7.3/NA/9.0
OZ41	3.5/4.6	99.98/81/99.5	12.1/6.8/10.7
OZ42	2.3/2.6	68/NA/92	6.0/NA/7.0
OZ43	11/7.5	99.97/18/97	8.9/5.4/7.3
OZ44	2.5/2.3	99.3/NA/99.9	7.0/NA/8.3
OZ45	17/27	15/NA/16	6.0/NA/5.0
OZ46	22/19	99/NA/62	7.7/NA/6.0
OZ47	7.5/7.4	99.98/NA/99	12.7/NA/8.0
OZ48	11/13	99.8/NA/42	8.7/NA/6.3
OZ49	0.82/0.93	81/NA/85	6.7/NA/7.3
OZ50	1.1/1.2	77/57/97	7.0/5.7/7.3
OZ51	2.5/2.5	89/NA/100	7.0/NA/14

OZ52	3.1/3.0	88/NA/99.7	6.7/NA/8.0
OZ53	1.4/1.7	9/NA/58	6.0/NA/6.3
OZ54	32/35	85/NA/97	7.0/NA/7.0
OZ55	0.49/0.60	45/NA/97	6.0/NA/7.3
OZ56	0.59/0.64	93/63/99.97	6.7/5.7/10.3
OZ57	3.1/2.8	32/NA/98.4	6.0/NA/7.7
OZ58	7.1/7.2	39/NA/52	6.0/NA/6.3
OZ59	1.4/1.3	51/NA/99.95	6.0/NA/10.0
OZ60	1.1/1.2	71/NA/100	6.0/NA/10.3
OZ61	0.52/0.53	91/NA/96	7.0/NA/7.3
OZ62	33/28	0/NA/0	6.0/NA/5.0
OZ63	1.6/1.6	99.62/65/99.91	7.3/6.0/9.3
OZ64	1.5/1.3	95/NA/98	7.3/NA/8.0
OZ65	57/65	0/NA/1	5.0/NA/5.0
OZ66	44/36	0/NA/0	5.3/NA/5.7
OZ67	>100/>100	0/NA/0	5.0/NA/5.0
OZ68	41/49	1/NA/6	5.0/NA/5.3
OZ69	1.6/1.4	56/NA/40	6.3/NA/6.3
OZ70	1.2/1.1	98/NA/94	7.7/NA/7.7
OZ71	4.5/3.7	98/98/97	7.3/6.7/8.3
OZ72	15/13	97/NA/95	7.7/NA/6.7
OZ73	6.5/8.2	27/NA/36	6.0/NA/6.7
OZ74	2.3/3.5	63/NA/99.97	6.3/NA/10.0

OZ75	2.4/4.3	77/NA/5	7.3/NA/5.0
OZ76	1.7/3.0	49/NA/94	6.3/NA/8.0
OZ77	1.4/2.2	99.9/74/98	9.0/6.0/8.3
OZ78	24/42	94/97/79	8.7/7.0/6.7
OZ79	0.38/0.81	85/99.94	7.0/NA/9.3
OZ80	0.15/0.34	59/NA/84	6.3NA//7.7
OZ81	>100/>100	0/NA/0	5.3/NA/5.0
OZ82	0.48/1.2	91/NA/79	7.3/NA/7.0
OZ83	0.30/0.60	92/78/99.8	7.0/6.3/8.0
OZ84	1.4/2.1	92/NA/99.99	7.7/NA/14.7
OZ85	0.86/1.8	34/NA/99.7	6.0/NA/8.3
OZ86	0.80/2.0	77/NA//99.9	6.7/NA/11.3
OZ87	3.6/4.4	22/NA/53	5.7/NA/6.0
OZ88	5.7/4.2	62/NA/99.1	6.0/NA/11.7
OZ89	0.30/0.75	94/89/99.8	7.3/6.7/8.7
OZ90	0.44/0.84	89/95/99	7.0/7.0/8.0
OZ91	1.4/0.42	20/0/85	5.7/6.0/7.3
OZ92	1.6/0.40	81/35/99.98	6.7/6.3/10.0
OZ93	3.3/0.92	57/3/100	6.7/6.0/13.3
OZ94	57/28	21/0/11	6.0/5.7/5.3
OZ95	2.8/1.3	31/0/49	6.0/6.0/6.0
OZ96	8.4/>10	12/14/19	5.7/5.7/5.3
OZ97	2.2/1.8	59/2/66	6.7/5.3/7.0
OZ98	2.3/0.9	72/11/77	6.3/5.3/7.3

OZ99	77/27	30/40/36	6.3/5.7/6.3
OZ100	1.4/0.34	61/36/80	6.7/6.3/7.0
OZ101	3.0/1.6	44/0/99.97	6.3/5.3/13
OZ102	1.6/0.45	92/73/99.97	7.0/6.7/19.7
OZ103	0.64/0.17	86/63/87	7.3/6.7/7.3
OZ104	1.4/0.50	56/0/99.98	6.3/5.7/12.0
OZ105	5.4/5.0	16/0/28	5.7/5.7/6.3
OZ106	2.2/1.7	0/0/0	5.3/5.0/5.3
OZ107	1.0/0.30	70/32/99.74	6.3/6.3/8.0
OZ108	68/29	0/0/0	5.0/5.0/5.7
OZ109	21/24	2/0/24	5.7/5.7/6.3
OZ110	5.3/2.1	50/0/97.97	6.7/5.3/7.7
OZ111	0.92/0.35	98/79/99.94	7.7/6.3/8.3
OZ112	>10/>10	6/0/36	5.7/5.7/6.3
OZ113	0.95/0.20	92/96/89	7.3/8.0/7.3
OZ114	3.7/2.2	0/0/99.64	5.7/6.0/8.7
OZ115	11/6.9	33/0/97	6.3/5.7/7.3
OZ116	4.2/3.3	97/96/96	7.7/8.3/8.0
OZ117	2.1/1.2	95/96/99.94	7.0/7.7/8.7
OZ118	1.0/0.24	99.0/98/99.57	7.0/8.0/8.3
OZ119	0.83/0.20	99.29/99.15/99.66	7.7/8.0/8.3
OZ120	1.2/0.59	33/8/96	6.0/5.7/8.0
OZ121	0.96/0.41	91/98/99.61	7.3/8.0/7.3

OZ122	>100/>100	10/3/0	5.7/5.3/5.0
OZ123	1.6/1.9	99.66/94/99.96	8.0/7.0/16
OZ124	2.1/1.7	72/17/86	6.3/5.3/7.0
OZ125	68/>100	8/0/0	5.3/5.7/6.0
OZ126	0.20/0.50	55/72/99.44	7.0/6.7/8.5
OZ127	0.61/1.3	95/98/97	7.0/7.7/7.7
OZ128	0.59/1.1	99.93/99.95/99.98	8.3/8.7/11.7
OZ129	10/>10	0/4/0	5.3/5.7/5.7
OZ130	0.62/0.94	98.8/98.9/98.6	9.0/8.0/7.3
OZ131	1.7/4.1	21/41/90	5.7/6.0/8.0
OZ132	9.8/>10	38/0/40	6.3/5.7/6.3
OZ133	0.70/1.1	94/97/72	7.0/7.3/7.0
OZ134	0.88/1.1	72/27/99.95	6.3/6.0/15.3
OZ135	>100/>100	1/0/0	5.3/5.3/5.3
OZ136	23/21	0/0/0	6.0/6.0/6.0
OZ137	11/18	0/6/61	5.7/6.3/7.0
OZ138	10/19	0/5/7	5.7/6.3/6.3
OZ140	5.9/8.2	0/8/60	6.0/6.3/7.0
OZ141	1.7/1.9	98/97/99.89	8.0/8.0/8.7
OZ142	2.3/2.3	0/2/99.98	6.0/6.3/14.3
OZ143	0.98/1.8	48/44/99.85	6.7/6.7/9.7
OZ144	1.4/2.1	99.45/92/99.94	7.3/7.3/16.7
OZ145	0.50/0.76	99.82/99.21/99.87	8.3/10.7/10.7
OZ146	2.2/2.7	62/40/91	7.0/6.3/9.0

OZ147	1.1/1.8	85/71/99.89	8.0/8.0/19.7
OZ148	17/16	38/58/21	7.3/7.7/6.3
OZ149	8.0/8.8	64/3/87	7.7/6.0/14.3
OZ151	3.8/4.0	71/71/99.63	7.3/7.3/11.0
OZ152	3.2/7.2	0/12/22	6.3/6.7/6.7
OZ153	7.7/19	15/23/20	6.3/7.0/6.3
OZ154	5.0/6.1	99.74/81/59	14.7/8.7/7.7
OZ155	12/>10	53/53/73	6.3/7.0/8.3
OZ156	2.1/2.1	99.98/98.8/99.98	17.0/10.3/19.7
OZ157	0.20/0.22	90/80/97	7.3/8.3/8.3
OZ159	0.70/0.94	34/31/98	6.7/6.7/9.0
OZ160	0.70/0.87	45/43/99.94	6.3/6.7/12.0
OZ161	0.40/0.50	59/46/99.96	7.0/6.7/12.7
OZ162	0.50/0.71	41/22/99.55	6.3/6.3/9.3
OZ163	0.2/0.2	99.90/99.94/100	8.0/9.0/9.7
OZ164	59/>10	11/0/7	5.7/5.7/6.3
OZ165	39/>10	18/3/9	6.3/6.0/5.7
OZ166	28/>10	11/0/4	6.7/6.3/5.7
OZ167	6.7/>10	0/6/97	6.0/6.0/7.3
OZ169	15/>10	98/22/99.76	7.7/6.7/9.0
OZ171	1.3/1.4	98/85/99.94	9.0/7.0/9.7
OZ172	3.5/5.0	68/82/100	8.0/10.3/10.3
OZ173	58/32	15/0/80	7.0/6.7/9.7

OZ174	27/34	0/15/90	6.7/7.3/10.3
OZ175	1.4/2.0	99.1/97/92	10.0/12.3/8.7
OZ176	25/35	11/18/24	7.0/7.7/7.0
OZ177	0.9/1.7	99.91/99.88/99.91	12.3/12.7/17.7
OZ178	21/27	32/23/31	7.3/7.3/10.0
OZ179	1.3/1.1	99.91/99.78/99.91	11.3/10.3/11.3
OZ180	3.7/2.8	99.91/97/65	13.7/12.7/10.3
OZ181	0.58/0.35	99.98/99.91/100	9.0/10.0/11.0
OZ182	4.5/5.5	91/96/95	8.0/7.3/7.7
OZ183	0.80/2.1	65/19/81	6.0/6.0/8.3
OZ184	1.0/1.4	54/59/97	6.7/7.0/8.7
OZ185	1.1/1.4	86/56/99.96	7.7/6.7/10.7
OZ186	>10/>10	87/96/67	8.0/9.0/8.0
OZ187	4.0/6.8	77/94/77	7.7/10.0/7.0
OZ188	1.5/3.0	93/98/99.87	8.7/10.0/9.0
OZ189	1.7/3.0	95/99.79/98	9.3/9.0/10.7
OZ190	0.16/1.0	98/78/2	8.7/7.7/5.7
OZ191	6.0/>10	7/5/17	5.7/5.7/6.0
OZ192	2.5/4.4	38/45/99.98	6.0/7.0/13.7
OZ193	5.5/8.3	99.75/93/99.92	9.3/8.0/11.0
OZ194	2.0/6.6	87/73/99.95	8.3/8.0/20.3
OZ195	2.2/3.7	98/99.02/99.75	9.3/10.7/9.0
OZ196	>10/>10	10/0/17	6.0/5.3/5.7
OZ197	1.0/2.0	87/90/99.54	7.7/8.7/10.3

OZ198	>10/>10	4/6/6	5.7/6.0/5.7
OZ199	0.69/1.1	99.48/76/99.44	8.3/7.7/8.7
OZ200	1.0/2.9	81/78/92	7.0/7.3/8.0
OZ201	2.0/3.1	100/100/100	13/10.3/25
OZ202	6.0/7.9	79/51/74	7.0/7.3/7.3
OZ203	3.9/6.7	87/99.42/99.72	7.3/8.7/9.7
OZ204	>10/>10	0/0/0	6.0/6.3/6.0
OZ205	1.5/2.0	99.96/99.94/99.96	10.0/8.7/9.7
OZ206	1.0/2.7	93/92/91	8.0/8.7/9.7
OZ207	0.33/0.57	99.96/99.98/99.98	9.3/12.0/11.3
OZ208	6.0/6.5	0/29/10	6.3/6.7/5.7
OZ209	0.21/0.32	99.94/99.96/99.97	9.5/10.0/12.5
OZ210	1.4/1.6	99.23/77/99.94	9.3/8.0/10.3
OZ211	1.0/1.2	82/78/99.90	8.0/7.3/8.7
OZ212	2.7/2.9	66/25/59	6.7/6.7/8.0
OZ213	2.3/2.8	83/74/85	8.0/8.0/8.0
OZ214	>10/>10	44/54/65	6.3/7.3/7.7
OZ215	6.4/7.3	96/25/39	9.76.3/7.0
OZ216	0.40/0.67	62/69/99.02	6.3/7.7/11.0
OZ217	2.0/2.0	67/8/98	7.0/6.0/8.0
OZ218	2.0/3.0	98/99.30/99.68	10.0/14.3/9.0
OZ219	0.85/1.6	99.89/99.82/99.91	8.7/8.0/9.3
OZ220	6.9/4.9	40/0/99.95	6.0/5.3/10.0

OZ221	>10/>10	80/87/97	6.3/7.0/8.0
OZ222	3.9/6.3	87/75/99.76	7.7/7.0/10.0
OZ223	4.0/>10	89/79/99.57	7.3/6.3/12.0
OZ224	2.0/3.0	0/5/20	6.0/5.7/5.7
OZ225	7.3/>10	0/0/17	5.7/5.7/6.3
OZ226	4.0/4.0	0/0/99.92	5.0/5.3/11.0
OZ227	0.20/0.20	99.68/99.90/99.84	8.3/9.3/10.7
OZ228	2.0/2.1	99.94/28/99.94	10.3/6.0/14.0
OZ229	0.24/0.23	99.96/99.08/99.98	10.0/8.3/12.7
OZ230	3.9/3.6	0/0/0	5.3/5.7/5.7
OZ231	>10/>10	0/0/0	5.3/5.7/6.0
OZ232	0.30/0.50	76/74/99.94	8.0/7.3/8.7
OZ233	1.7/1.9	69/76/99.66	7.0/7.7/8.3
OZ234	3.0/3.6	12/0/0	6.0/6.0/6.3
OZ235	1.0/2.0	99.92/99.97/97	8.7/9.0/8.0
OZ236	2.0/2.0	89/86/98.61	6.3/7.7/7.7
OZ237	5.7/7.1	5/9/52	6.0/6.0/6.7
OZ243	0.91/1.1	87/97/70	7.3/8.7/6.3
OZ244	4.0/4.2	6/0/18	5.7/5.3/6.3
OZ247	1.8/2.3	57/27/99.85	6.3/6.0/9.0
OZ251	0.60/0.35	29/6/99.87	6.7/6.0/9.0
OZ252	2.3/2.2	98.91/99.49/99.82	8.3/9.0/9.3
OZ253	0.56/0.45	75/59/99.82	7.0/6.7/9.3
OZ254	>100/57	27/11/2	6.0/5.7/5.7

OZ255	2.2/1.1	99.61/99.54/99.92	9.0/8.7/10.0
OZ256	0.3/0.2	99.70/99.67/99.95	8.7/8.7/9.7
OZ257	42/21	99.00/99.49/99.84	8.3/7.7/9.7
OZ258	5.8/5.2	75/70/99.95	6.0/6.0/10.7
OZ260	5.6/4.3	72/51/81	6.7/7.0/7.7
OZ261	39/18	61/47/92	7.0/7.0/8.0
OZ262	0.63/0.84	96/98/99.39	11.7/12.3/10.0
OZ263	0.84/1.1	99.53/99.45/99.92	13.0/13.3/11.0
OZ264	1.2/1.5	99.61/99.92/99.97	11.0/10.3/13.7
OZ265	0.56/1.6	99/98/99.67	13.0/9.7/11.7
OZ266	1.1/1.5	99/99.39/99.75	13.7/11.7/11.7
OZ267	0.20/0.34	99.92/99.89/99.97	8.3/8.7/9.3
OZ268	0.44/0.71	99.86/99.47/99.92	9.3/13.3/9.7
OZ269	0.32/0.61	98/86/99.92	10.7/11.3/9.0
OZ270	0.85/1.3	99.17/99.47/99.81	13.7/12.3/11.3
Fenozan	3.2/3.0	99.95/NA/100	8.6/NA/13.4
Artemisinin	1.2/1.9	62/NA/69	6.5/NA/6.8
Arteether	0.41/0.54	98/NA/99.99	7.8/NA/9.5
Artemether	0.45/0.36	98/99.2/99.78	7.9/7.4/9.1
Artesunate	1.4/1.5	65/74/65	6.8/6.4/6.8

¹data at a single 100 mg/kg dose

As shown above, antimalarial activity falls off both when the trioxolane peroxide
5 bond is too exposed or is sterically inaccessible to iron(II) species. Other factors
influencing antimalarial activity include the stability of carbon radicals formed by β -

scission subsequent to the initial electron transfer to the peroxide bond and the influence of steric effects remote from the peroxide bond on the interactions between carbon radicals and potential drug targets. The data also demonstrates that trioxolane carboxylic acids are usually less active than their hydrocarbon, ester, and hydroxamic acid counterparts.

5

EXAMPLE 3

Activity of Trioxolanes Against *P. berghei*

As shown in Table 2 below, the trioxolane compounds possess impressive antimalarial activity against *P. berghei in vivo* as determined in the 4-day Peters test.

10 Based on po ED₅₀/ED₉₀ values, OZ23 was the most orally active compound of all of the trioxolanes and control compounds.

Table 2

Compd	<i>P. berghei</i>		<i>P. yoelii</i>
	ED ₅₀ /ED ₉₀ (mg/kg)		ED ₅₀ /ED ₉₀ (mg/kg)
	po	sc	sc
OZ03	1.0/2.7	0.6/1.1	1.6/3.1
OZ05	1.5/6.1	0.6/1.0	1.4/2.5
OZ10	1.3/3.0	0.5/0.9	1/2.2
OZ11	1.8/3.1	0.5/0.9	1.0/2.1
OZ12	6.8/10.5	0.8/1.4	1.1/2.3
OZ15	2.9/6.3	0.7/1.1	1.4/3.6
OZ23	0.9/2.0	0.5/0.9	0.7
OZ25	1.2/3.7	2.2/3.7	2.7/4.3
OZ27	1.3/2.6	0.2/0.9	4.4/10.2
OZ32	2.6/5.1	0.6/1.3	1.2/3.5
Fenozan	1.9/2.7	1.1/2.3	1.8/4.4
Artesunate	2.4/13	1.5/6.3	5.3/63
Chloroquine	1.7/3.1	1.5/3.0	1.6/28.0

EXAMPLE 4

Neurotoxicity of Trioxolanes

Even though reported clinical neurotoxicity for the semisynthetic artemisinins is very rare (Park et al., 1998), neurotoxicity is a potential drawback for antimalarial peroxides of any structural class. Against the NB2a cell line (Fishwick et al., 1995) trioxolanes OZ03, OZ04, OZ05, OZ07, and OZ08 had relatively high IC₅₀s of 13, 44, 31, 27, and 42 μ M, respectively. In this same screen, dihydroartemisinin, the presumed metabolite of all the semisynthetic artemisinins (Titulaer et al., 1991; White, 1994), was quite neurotoxic with an IC₅₀ of 0.22 μ M. There was no apparent relationship between trioxolane structure and neurotoxicity and these five trioxolanes.

EXAMPLE 5

Onset of Action and Recrudescence of OZ11, OZ27, OZ78, OZ156, OZ175, OZ177, OZ207, and OZ209

Onset of Action and Recrudescence Experiments

The onset of drug action was determined after a single fixed dose of 100 mg/kg (SSV vehicle) po to groups of five animals on day +3 post-infection (day 0). Parasitemias at this point are usually between 25-40%. The infected controls do not survive beyond day +6 post-infection. The reduction of parasitemia is monitored 12, 24, and 48 h after treatment, and the time of recrudescence (> 5% parasitemia) is assessed by daily blood smears for 14 days, followed by intermittent assessment for up to 60 days.

The onset part of this experiment reveals how rapidly a compound reduces parasite load; the recrudescence part of the experiment provides information about the efficacy of the compound against the parasite. A long delay in recrudescence can be due to a very good antiparasitic effect of the compound or to a compound with a long half-life.

Both the trioxolanes and the artemisinins produced a rapid decline in parasitemia, confirming that they are rapidly acting antimalarial agents. In contrast to both chloroquine and these peroxidic antimalarials, mefloquine has a slow onset of action. Recrudescence (> 5% parasitemia) occurs quite rapidly for artemisinin and artesunate. The time of recrudescence increased for the more lipophilic artemisinin derivatives artemether and arteether.

In contrast to artemether, recrudescence occurred much more slowly for the lipophilic trioxolanes OZ11 and OZ27; the recrudescence time for OZ27 was especially marked, superior to that of mefloquine. However, recrudescence times for the relatively polar trioxolanes OZ78 and OZ175 were very similar to that of artemether. The more lipophilic trioxolane (OZ156) of the OZ156/OZ177 pair produced the longest delay in recrudescence, longer than chloroquine, but less than mefloquine. The recrudescence time for OZ177 was roughly equivalent to that of chloroquine.

Strikingly, there was no recrudescence observed for OZ207 and OZ209, two different salt forms (OZ207 – tosylate, OZ209 – mesylate) of aminomethyl trioxolane OZ163 (hydrochloride). The recrudescence data for these two trioxolanes suggests that they are either more powerful antimalarial agents or have longer half-lives than any of the semisynthetic artemisinins.

Table 3

Compd	Time of Recrudescence (days)
OZ11	22.2
OZ27	22.0 (3/5), > 60 (2/5)
OZ78	11.2
OZ156	19.0 (4/5), > 60 (1/5)
OZ175	13.0
OZ177	18.5
OZ207	> 60
OZ209	> 60
Artemisinin	8.4
Artesunate	8.6
Artemether	12.0
Arteether	11.4
Chloroquine	17.8
Mefloquine	28.0

EXAMPLE 6 **Treatment of Schistosomiasis**

Mice (MORO SPF female 18-20g) were infected with 90 (± 10) cecaria of *Schistosoma mansoni* subcutaneously. Following infection, three of the animals were treated with OZ05 p.o., 100 mg/kg on days 7, 14, 21, 28, 35, and 42.

Compared to control mice, two of the treated mice had a reduction in parasitaemia of 100%, and the third mice a reduction in parasitaemia of 53%. In the same assay, mice treated with artemether showed similar activities, but at doses four times higher than that of the OZ05. Further, in the same assay, arteflene (6x600 mg/kg p.o.) and fenozan (6x100 mg/kg p.o.) were inactive.

In addition, the trioxolanes OZ05 200 mg/kg p.o. and OZ11 100 mg/kg p.o. treated once at day 49 of infection showed activity against adult *S. mansoni*. In contrast, artemether shows no activity against adult *S. mansoni*.

EXAMPLE 7

Effect of Trioxolanes on *Schistosoma* Species

Effect of Trioxolane OZ207 on *Schistosoma japonicum*

Table 4

Comparative effect of OZ207 and artemether in mice infected with *Schistosoma japonicum*

Drug	Age of worm	Dose (mg/kg × 1)	Mice without worm	MTWB/ x± SD	WRR/ %	MFWB/ x± SD	FWR R/ %
Control	-	-	0/8	26.6 ± 4.2	-	11.6 ± 2.4	-
OZ207	35 days	200	4/7	9.1 ± 3.9	66	0.6 ± 0.7	95
OZ207	35 days	400	4/6	4.3 ± 1.2	84	0.7 ± 1.2	94
Artemether	35 days	400	0/7	10.1 ± 4.4	62	3.4 ± 1.6	71
OZ207	7days	200	0/8	5.4 ± 2.4	81	2.1 ± 1.0	82

MTWB, mean total worm burden; WRR, worm reduction rate MFWB, mean female worm burden; FWRR, female worm reduction rate.

Table 4 illustrates that the mean total worm burden and mean female worm burden in OZ207 400 mg/kg group was significantly lower than those in artemether 400 mg/kg group ($P<0.01$). The mean female worm burden in OZ207 200 mg/kg group was also significantly lower than that in artemether group ($P<0.01$).

Effect of Trioxolanes on 21-day-old schistosomules

Mice were infected with 100 *Schistosoma mansoni* cercariae on day 21 post-treatment. Each group was treated per os with trioxolanes at a single dose of 200 mg/kg.

Untreated mice served as the control. All groups were killed 4 weeks after treatment and the liver and intestine were removed and separated. The liver and intestine were compressed and alive male and female worms could be seen and counted. The effect of the compounds was evaluated by mean total and female worm burden. The results are shown in Table 5.

Effect of Trioxolanes on adult schistosomes (49-day-old)

Mice were infected with 100 *Schistosoma mansoni* cercariae on day 49 post-treatment. Each group was treated per os with OZ compounds at a single dose of 400 mg/kg. Untreated mice served as the control. All groups were killed 4 weeks after treatment and the liver and intestine were removed and separated. The liver and intestine were compressed and alive male and female worms could be seen and counted. The effect of the compounds was evaluated by mean total and female worm burden, and the results are set forth in Table 5.

Table 5
In Vivo* Activity Against *Schistosoma Mansoni

Compd	% reduction of schistosomule growth at day 21	% reduction of adult worm growth at day 49
OZ 03	74	
OZ 05	90	19, 70 ¹
OZ 10	66	
OZ 11	85	
OZ 12	78	
OZ 15	63	
OZ 16	78	
OZ 19	77	
OZ 22	75	
OZ 23	90	
OZ 24	65	
OZ 25	86	
OZ 27	63	20
OZ 32	73	27
OZ 56	69	
OZ 71	91	
OZ 78	82	
OZ 89	86	
OZ 90	81	

OZ 111	71	
OZ 119	88	
OZ 145	80	
OZ 157	65	
OZ 163	84	
OZ 205	84	
OZ 207	93	
Artemether	82	

¹ 1 x 600 mg per os

EXAMPLE 8

Activity of Trioxolanes Against *P. berghei*

5 In the single dose ED₅₀/ED₉₀/ED₉₉ determinations, Moro SPF or NMRI mice (group of three) infected with the ANKA strain of *Plasmodium berghei* were treated on day one post-infection. Trioxolanes were dissolved or suspended in the standard suspending vehicle (SSV)* and administered as single 10, 6, 3, 1, 0.3, and 0.1 mg/kg doses po and sc. The SSV consists of 0.5% w/v CMC, 0.5% v/v benzyl alcohol, 0.4% v/v Tween 80, and
10 0.9% w/v sodium chloride in water. Antimalarial activity was measured by percent reduction in parasitemia on day three post-infection. The ED₅₀/ED₉₀ values were calculated by nonlinear fitting.

15 *Earlier ED₅₀/ED₉₀ data (Example 3, Table 2) was obtained using 0.5% carboxymethylcellulose or 0.2% Tween 80 vehicle.

Table 6

Compd	ED ₅₀ (mg/kg)	ED ₉₀ (mg/kg)	ED ₉₉ (mg/kg)
OZ05	8.7	12	15
OZ11	4.4	6.2	8.2
OZ27	2.9	5.7	9.9
OZ78	4.2	9.1	17
OZ113	3.6	9.0	19
OZ127	2.5	7.6	19
OZ156	1.3	2.6	4.7
OZ175	3.5	6.2	9.9
OZ177	2.1	3.7	5.8
OZ179	1.4	3.3	6.6
OZ181	0.63	1.8	4.0
OZ205	1.6	3.3	6.0
OZ207	0.37	1.2	3.0

OZ209	0.55	1.4	3.0
OZ219	1.6	3.0	5.2
OZ227	2.3	4.0	6.2
OZ235	4.0	7.1	11
Artesunate	4.7	19	60
Artelinate	4.8	10	18
Artemether	2.2	4.2	7.1
Chloroquine	1.8	3.5	5.9
Mefloquine	4.0	5.4	6.8

Table 6 shows ED50/ED90/ED99 data obtained by po administration of trioxolanes in the SSV formulation. The relatively lipophilic artemether is substantially more active than the more polar artesunate and artelinate. A parallel trend is also evident in the trioxolane data. For example, the highly lipophilic OZ156 is more active than its more polar triazole (OZ177, OZ235) and imidazole (OZ179) analogs, although in this case the potency difference is rather small. With one significant exception (OZ181, OZ207, OZ209), the relatively polar trioxolanes OZ78, OZ113, and OZ127 were less active. In summary, trioxolanes OZ177 and OZ179 were as active and OZ156 and OZ181 were more active than chloroquine, the most active control drug.

EXAMPLE 9

***In Vivo* Toxicity Study of OZ23, OZ32, and OZ78**

The toxic potential of three lead trioxolanes (OZ23 – trioxolane carbamate, OZ32 – trioxolane alcohol and OZ78 – trioxolane acid) was investigated against artesunate in an exploratory tolerance study in male Wistar rats. The doses administered were 100 or 300 mg/kg/day for OZ23 and OZ32, and 30 or 100 mg/kg/day for OZ78 and artesunate. All compounds were suspended in SSV and administered at a constant volume of 5 mL/kg/day. Control animals received the vehicle (SSV) at a volume of 5 mL/kg/day. Six animals per group were treated for 5 consecutive days and 6 animals per group were kept for an additional 1-week recovery period. Examinations included clinical observations, body weight development, clinical laboratory investigations (hematology, clinical chemistry and urine analysis) at the end of the treatment and recovery periods, respectively. At the end of the scheduled study period the rats were sacrificed and necropsied and selected organs were examined histopathologically. Plasma levels of the trioxolanes and artesunate sodium were

analyzed employing validated HPLC/MS assays, and the data examined for evidence of drug accumulation over the course of the study. Results were compared, where possible, to data from previously conducted exploratory pharmacokinetic studies in rats.

All animals survived to the end of the scheduled study period. Clinical
5 observations related to treatment were limited to occasional occurrence of pale feces in animals given the high dose of OZ23, OZ78 or artesunate. Body weight development was reduced during the treatment period for animals receiving the high dose of OZ23 or artesunate, but was mostly compensated during the recovery period. Clinical laboratory investigations revealed minimal and essentially reversible changes mostly in high dose
10 group animals. Liver weights tended to be minimally or slightly increased in animals receiving the trioxolanes or artesunate. Histopathological examinations indicated slight gastric irritation in animals receiving the higher dose of OZ23 or artesunate.

Plasma concentrations of OZ32 and OZ78 observed in the toxicity study in rats were broadly consistent with those noted in exploratory pharmacokinetic studies. Levels of
15 OZ23 were disproportionately higher in the toxicity study than the levels measured in the exploratory pharmacokinetic studies, although insufficient data are available at this stage to confirm the observed non-linearity of OZ23 pharmacokinetics. Importantly, the toxicokinetic analysis revealed no evidence of accumulation of any of the OZ compounds, artesunate sodium or the major metabolite of artesunate sodium, dihydroartemisinin.

20 In conclusion, the toxicological profile of the trioxolanes was found to be comparable to that of artesunate.

It should be appreciated that the spiro and dispiro 1,2,4-trioxolane compositions of this invention may contain trioxolanes within the scope of the formulas described above, or
25 prodrugs or analogues of these compounds or a racemic mixture of either the D or the L form. Also, minor dosage and formulation modifications of the composition and the ranges expressed herein may be made and still come within the scope and spirit of the present invention.

Having described the invention with reference to particular compositions, theories
30 of effectiveness, and the like, it will be apparent to those of skill in the art that it is not intended that the invention be limited by such illustrative embodiments or mechanisms, and

that modifications can be made without departing from the scope or spirit of the invention, as defined by the appended claims. It is intended that all such obvious modifications and variations be included within the scope of the present invention as defined in the appended claims. The claims are meant to cover the claimed components and steps in any sequence
 5 which is effective to meet the objectives there intended, unless the context specifically indicates to the contrary.

All articles cited herein and in the following list are hereby expressly incorporated in their entirety by reference.

CITATIONS

- 10 de Almeida Barbosa, L.-C. et al., The Design, Synthesis and Biological Evaluation of Some Stable Ozonides With Anti-malarial Activity. *J. Chem. Soc. Perkin Trans. I*, 1996, 1101-1105.
- 15 de Almeida Barbosa, L.-C. et al., Synthesis of Some Stable Oozonides With Anti-malarial Activity. *J. Chem. Soc. Perkin Trans. I*, 1992, 3251-3252.
- Augustine, R.L. Stereochemistry of the catalytic hydrogenation of some bicyclic α,β -unsaturated ketones. *J. Org. Chem.*, 1958, 23, 1853-1856.
- 20 Cammenga, H.K. et al., Basic principles of thermoanalytical techniques and their applications in preparative chemistry. *Angew. Chem. Int. Ed. Engl.* 1995, 34, 1171-1187.
- Cumming, J.N. et al., Antimalarial activity of artemisinin (qinghaosu) and related trioxanes: mechanism(s) of action. *Adv. Pharmacol.* 1997. 37, 254-297.
- 25 Dhingra, V.K. et al., Current Status of Artemisinin and Its Derivatives As Antimalarial Drugs. *Life Sci.* 2000, 66, 279-300.
- 30 Dong, Y.; Vennerstrom, J.L Peroxidic Antimalarials. *Expert Opin. Ther. Patents* 2001, 11, 1753-1760.
- Fishwick, J., et al., The Toxicity of Artemisinin and Related Compounds on Neuronal and Glial Cells in Culture. *Chem.-Biol. Interact.* 1995, 96, 263-271.
- 35 Griesbaum, K. et al., Diozonides from cozonolyses of suitable O-methyl oximes and ketones. *Tetrahedron* 1997a, 53, 5463-5470.
- Griesbaum, K. et al., Ozonolyses of O-alkylated ketoximes in the presence of carbonyl groups: a facile access to ozonides. *Liebigs Ann./Recueil.* 1997b, 138 1-1390.
- 40 Jefford, C. Peroxidic Antimalarials. *Adv. Drug Res.* 1997, 29, 271-325.

Kashima, C. et al., Ozonolysis of Five-Membered Heterocycles. *J. Het. Chem.* **1987**, *24*, 637-639.

5 Meshnick, S.R. et al., Artemisinin and the antimalarial endoperoxides: from herbal remedy to targeted chemotherapy. *Microbiol. Rev.* 1996, *60*, 301-315.

Park, B.K. et al., Safety Assessment of Peroxide Antimalarials: Clinical and Chemical Perspectives. *Br. J. Clin. Pharmacol.* 1998, *46*, 521-529.

10 Stork, G. et al., The enamine alkylation and acylation of carbonyl compounds. *J. Amer. Chem. Soc.* 1963, *85*, 207-222.

Titulaer, H.A.C., Zuidema, J., and Lugt, C.B. Formulation and pharmacokinetics of artemisinin and its derivatives. *Int. J. Pharmaceut.* 1991, *69*, 83-92.

15 van Agtmael, M.A. et al., Artemisinin Drugs In the Treatment of Malaria: From Medicinal Herb to Registered Medication. *Trends Pharmacol. Sci.* **1999**, *20*, 199-205.

Vennerstrom, J.L. et al., Synthesis and Antimalarial Activity of Sixteen Dispiro-1,2,4,5-tetraoxane Analogs of WR 148999: Alkyl Substituted 7,8,15,16-
20 Tetraoxadispiro[5.2.5.2]hexadecanes. *J. Med. Chem.* **2000**, *43*, 2753-2758.

Vroman, J.A. et al., Current Progress in the Chemistry, Medicinal Chemistry and Drug Design of Artemisinin Based Antimalarials. *Curr. Pharm. Design* **1999**, *5*, 101-138.

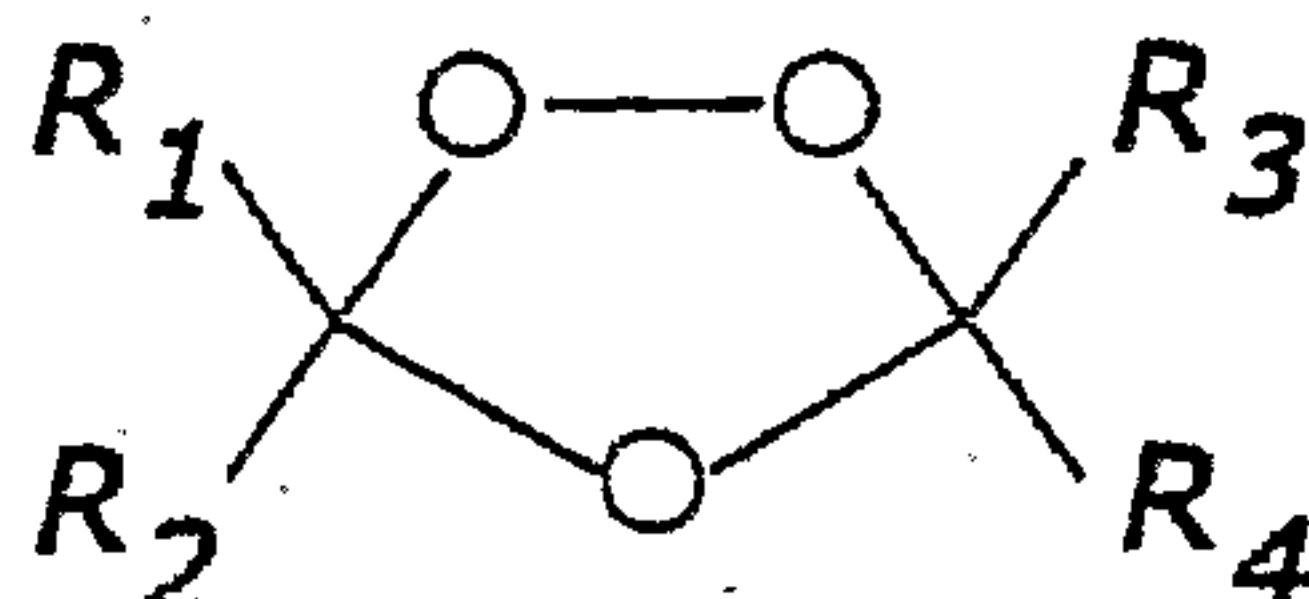
25 Wesche, D.L. et al., Neurotoxicity of artemisinin analogs in vitro. *Antimicrob. Agents. Chemother.* 1994, *38*, 1813-1819.

White, N.J. Clinical pharmacokinetics and pharmacodynamics of artemisinin and derivatives. *Trans. R. Soc. Trop. Med. Hyg.* 1994, *88*, 41-43.

What is claimed is:

1. A spiro or dispiro 1,2,4 trioxolane that is sterically hindered on at least one side of the trioxolane heterocycle.

2. A spiro or dispiro 1,2,4-trioxolane having the following structure:



wherein R₁, R₂, R₃, and R₄ are the same or different, and are selected from the group consisting of substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and substituted or unsubstituted alicyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, and substituted or unsubstituted aromatic or heterocyclic groups, whereby none of R₁, R₂, R₃, or R₄ may be hydrogen; and further providing that R₁ and R₂ taken together and/or R₃ and R₄ taken together may form a substituted or unsubstituted alicyclic group which is optionally interrupted by one or more oxygen, sulfur or nitrogen atoms.

3. A spiro or dispiro 1,2,4-trioxolane according to claim 2 wherein R₁ and R₂ taken together is spiroadamantane and R₃ and R₄ taken together is a spirocyclohexyl ring that is functionalized or substituted at the 4-position.

4. A spiro or dispiro 1,2,4-trioxolane according to claim 3 wherein the spirocyclohexyl ring is interrupted by one or more oxygen, sulfur, or nitrogen atoms.

5. A spiro or dispiro 1,2,4-trioxolane according to claim 3 wherein the spirocyclohexyl ring is functionalized with a substituted or unsubstituted substituent selected from the group consisting of a linear or branched alkyl, ketone, acid, alcohol,

amine, amide, sulfonamide, guanidine, ether, ester, oxime, urea, oxime ether, sulfone, lactone, carbamate, semicarbazone, phenyl, heterocycle, and alicyclic group.

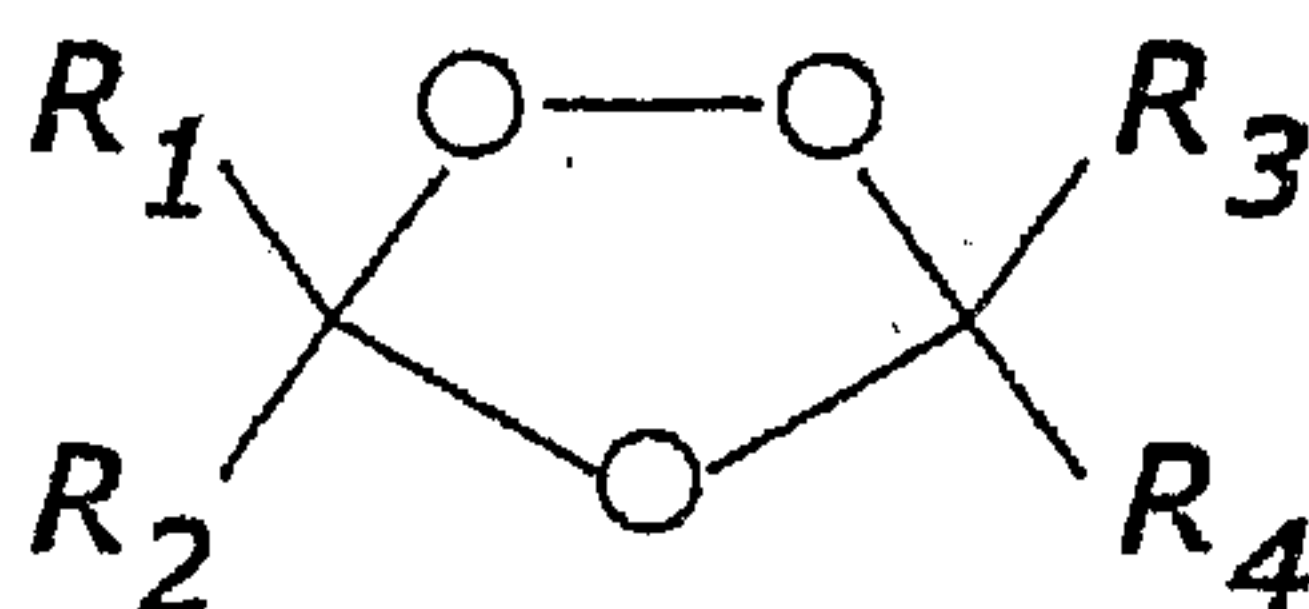
6. A spiro or dispiro 1,2,4-trioxolane according to claim 3 wherein R_1 and R_2 taken together is spiroadamantane and R_3 and R_4 are substituted or unsubstituted phenyl or heterocyclic rings.

7. A spiro or dispiro 1,2,4-trioxolane according to claim 1 wherein the 1,2,4-trioxolane is selected from the group consisting of: OZ05, OZ11, OZ25, OZ27, OZ61, OZ71, OZ78, OZ127, OZ145, OZ156, OZ163, OZ175, OZ177, OZ179, OZ181, OZ189, OZ205, OZ207, OZ209, OZ210, OZ219, OZ227, OZ229, OZ235, OZ255, OZ256, OZ257, OZ263, OZ264, OZ265, OZ266, OZ267, OZ268, OZ269, and OZ270.

8. A spiro or dispiro 1,2,4-trioxolane according to claim 7 wherein the 1,2,4-trioxolane is selected from the group consisting of OZ78, OZ163, OZ181, OZ207, OZ209, OZ255, OZ256, OZ257, OZ263, OZ264, and OZ267.

9. A pharmaceutical composition for prophylaxis and treatment of malaria comprising: a malaria prophylaxis or malaria treatment-effective amount of a spiro or dispiro 1,2,4-trioxolane, its prodrugs and optical isomers thereof, and a pharmaceutically acceptable carrier, said trioxolane being sterically hindered on at least one side of the trioxolane heterocycle.

10. A composition according to claim 9, wherein the spiro or dispiro 1,2,4-trioxolane has the following structure:



wherein R_1 , R_2 , R_3 , and R_4 are the same or different, and are selected from the group consisting of substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups, substituted or unsubstituted alicyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, and substituted or unsubstituted aromatic or heterocyclic groups, whereby none of R_1 , R_2 , R_3 , or R_4 may be hydrogen; and further providing that R_1 and R_2 taken together and/or R_3 and R_4 taken together may form a substituted or unsubstituted alicyclic group which is optionally interrupted by one or more oxygen, sulfur or nitrogen atoms.

11. A composition according to claim 10, wherein R_1 and R_2 taken together and/or R_3 and R_4 taken together is a mono- or di-substituted C_5 - C_{12} spirocyclo group which is optionally interrupted by one or more oxygen, sulfur, or nitrogen atoms, said sulfur or nitrogen atoms being optionally substituted.

12. A composition according to claim 11 wherein R_1 and R_2 taken together and/or R_3 and R_4 taken together is spiroadamantane.

13. A composition according to claim 12 wherein R_1 and R_2 taken together is spiroadamantane and R_3 and R_4 taken together is a spirocyclohexyl ring that is substituted or functionalized at the 4-position.

14. A composition according to claim 12 wherein R_1 and R_2 taken together is spiroadamantane and R_3 and R_4 are substituted or unsubstituted phenyl or heterocyclic rings.

15. A composition according to claim 13 wherein the spirocyclohexyl ring is interrupted by one or more oxygen, sulfur, or nitrogen atoms.

16. A composition according to claim 15 wherein the spirocyclohexyl ring has been replaced with an N-substituted piperidyl.

17. A composition according to claim 9 wherein the spirocyclohexyl ring is functionalized with a substituent selected from the group consisting of a substituted or unsubstituted substituent selected from the group consisting of a linear or branched alkyl, ketone, acid, alcohol, amine, amide, sulfonamide, guanidine, ether, ester, oxime, urea, oxime ether, sulfone, lactone, carbamate, semicarbazone, phenyl, heterocycle, and alicyclic group.

18. A composition according to claim 9 wherein the 1,2,4-trioxolane is selected from the group consisting of: OZ03, OZ05, OZ11, OZ25, OZ27, OZ61, OZ71, OZ78, OZ127, OZ145, OZ156, OZ163, OZ175, OZ177, OZ179, OZ181, OZ189, OZ205, OZ207, OZ209, OZ210, OZ219, OZ227, OZ229, OZ235, OZ255, OZ256, OZ257, OZ263, OZ264, OZ265, OZ266, OZ267, OZ268, OZ269, and OZ270.

19. A composition according to claim 9 wherein the 1,2,4-trioxolane is selected from the group consisting of: OZ78, OZ163, OZ181, OZ207, OZ209, OZ255, OZ256, OZ257, OZ263, OZ264, and OZ267.

20. A composition according to claim 9 that is suitable for administration by a method selected from the group consisting of oral, subcutaneous, intravenous, intranasal, rectal, sublingual, and buccal.

21. Adamantane-2-spiro-3'-8'-carboxymethyl-1',2',4'-trioxaspiro[4.5]decane.

22. Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane hydrochloride.

23. Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane citrate.

24. Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane *p*-tosylate.

25. Adamantane-2-spiro-3'-8'-(aminomethyl)-1',2',4'-trioxaspiro[4.5]decane mesylate.

26. Adamantane-2-spiro-3'-8'-[[[4'-pyridinylcarbonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane.

27. Adamantane-2-spiro-3'-8'-[[[2'-amino-2'-oxoethyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane.

28. Adamantane-2-spiro-3'-8'-[[[methanesulfonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane.

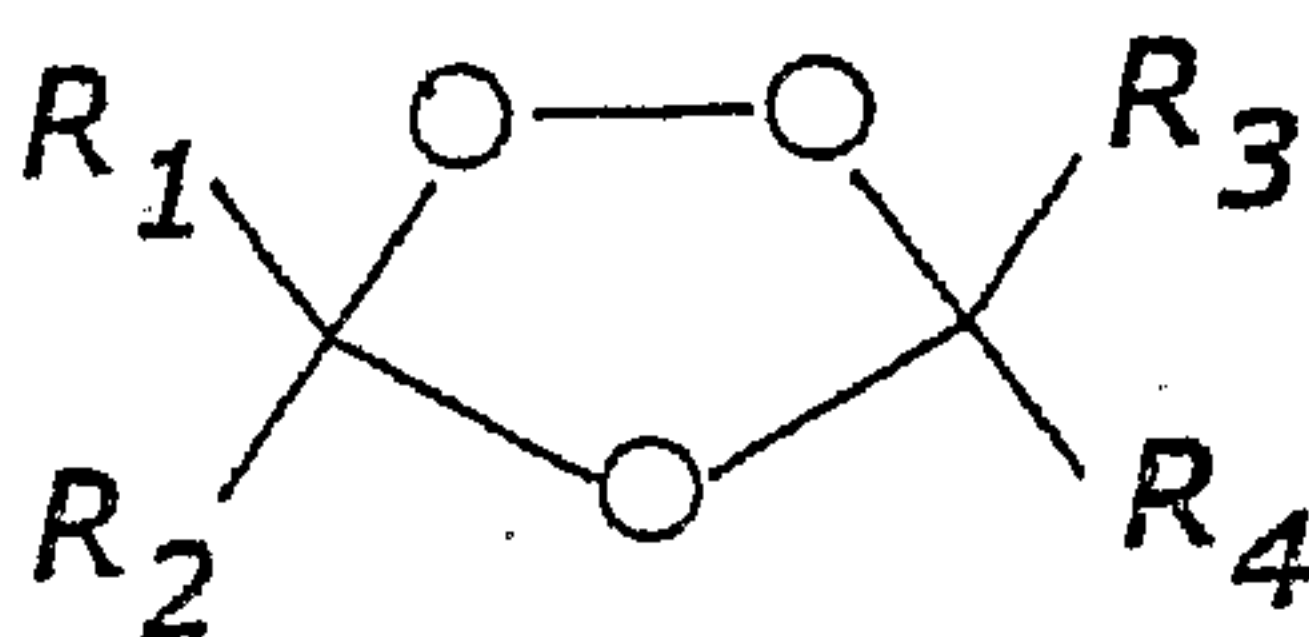
29. Adamantane-2-spiro-3'-8'-[[[(1*H*-imidazol-4'-yl)carbonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane mesylate.

30. Adamantane-2-spiro-3'-8'-[[[(1'-oxido-4'-pyridinyl)carbonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane.

31. Adamantane-2-spiro-3'-8'-[[[(4'-methyl-1'-piperazinyl)carbonyl]amino]methyl]-1',2',4'-trioxaspiro[4.5]decane.

32. A method of preventing or treating malaria comprising:
administering a malaria prevention or malaria treatment effective amount of a spiro or dispiro 1,2,4-trioxolane in a pharmaceutically acceptable carrier, said trioxolane being sterically hindered on at least one side of the trioxolane heterocycle.

33. A method according to claim 32, wherein the spiro or dispiro 1,2,4-trioxolane has the following structure:



wherein R_1 , R_2 , R_3 , and R_4 are the same or different, and are selected from the group consisting of substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups, substituted or unsubstituted alicyclic groups that may be interrupted by one or more
5 oxygen, sulfur or nitrogen atoms, and substituted or unsubstituted aromatic or heterocyclic groups, whereby none of R_1 , R_2 , R_3 , or R_4 may be hydrogen; and further providing that R_1 and R_2 taken together and/or R_3 and R_4 taken together may form a substituted or unsubstituted alicyclic group which is optionally interrupted by one or more oxygen, sulfur or nitrogen atoms.

10

34. A method according to claim 32 wherein the trioxolane is administered in a dose of between about 0.1-1000 mg/kg/day.

15

35. A method according to claim 34 wherein the trioxolane is administered in a dose of between about 1-100 mg/kg/day.

36. A method according to claim 32 wherein the trioxolane is administered in a single dose.

20

37. A method according to claim 32 wherein the trioxolane is administered in divided doses.

25

38. A method according to claim 32 wherein the trioxolane is administered in a malaria-preventive dose beginning 1-2 weeks prior to malaria exposure and ending 1-2 weeks post exposure.

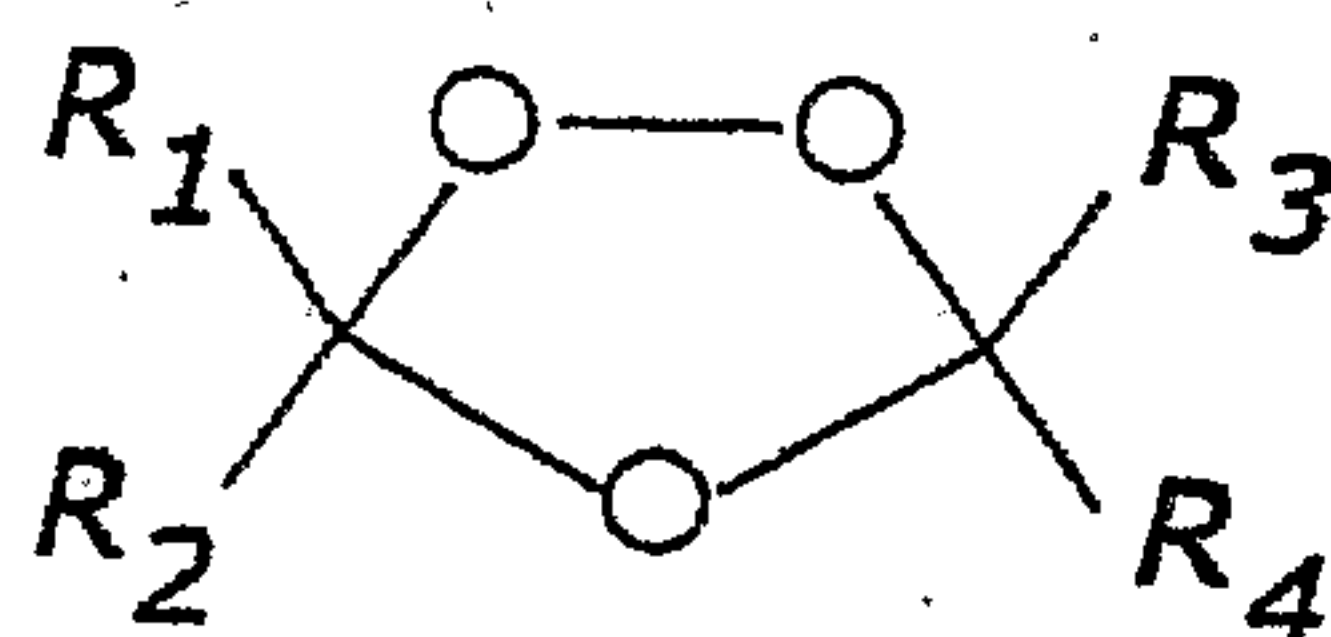
39. A method according to claim 32 wherein the trioxolane is administered in a malaria-curative dose over 1-10 days.

30

40. A method of manufacturing a composition for prophylaxis and treatment of malaria comprising: mixing a malaria prophylaxis or malaria treatment-effective amount of a spiro

or dispiro 1,2,4-trioxolane, its prodrugs and optical isomers thereof, with a pharmaceutically acceptable carrier, said trioxolane being sterically hindered on at least one side of the trioxolane heterocycle.

41. A method according to claim 40, wherein the spiro or dispiro 1,2,4-trioxolane has the following structure:



wherein R_1 , R_2 , R_3 , and R_4 are the same or different, and are selected from the group consisting of substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups, substituted or unsubstituted alicyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, and substituted or unsubstituted aromatic or heterocyclic groups, whereby none of R_1 , R_2 , R_3 , or R_4 may be hydrogen; and further providing that R_1 and R_2 taken together and/or R_3 and R_4 taken together may form a substituted or unsubstituted alicyclic group which is optionally interrupted by one or more oxygen, sulfur or nitrogen atoms

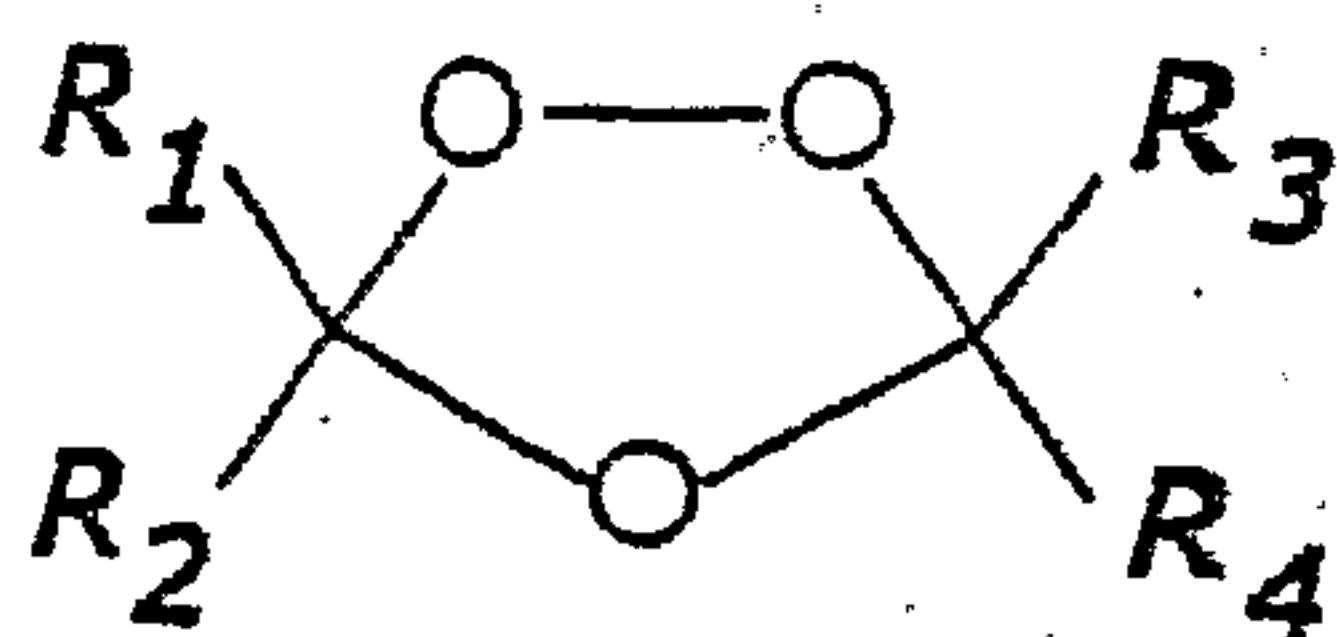
42. A method of treating cancer comprising:

administering a cancer treatment effective amount of a spiro or dispiro 1,2,4-trioxolane in a pharmaceutically acceptable carrier, said trioxolane being sterically hindered on at least one side of the trioxolane heterocycle.

43. A method of prophylaxis or treatment of schistosomiasis comprising:

administering a schistosomiasis prophylaxis or treatment effective amount of a spiro or dispiro 1,2,4-trioxolane in a pharmaceutically acceptable carrier, said trioxolane being sterically hindered on at least one side of the trioxolane heterocycle.

44. A spiro or dispiro 1,2,4-trioxolane having the following structure:



5

wherein R₁ and R₂ taken together is spiroadamantane and R₃ and R₄ taken together is a spirocyclohexyl ring that is functionalized or substituted at the 4-position with an alkyl bridge, whereby said spirocyclohexyl ring may be interrupted by one or more oxygen, sulfur, or nitrogen atoms.

10

45. The spiro or dispiro 1,2,4-trioxolane of claim 44 wherein the alkyl bridge is methyl or ethyl.

15

46. The spiro or dispiro 1,2,4-trioxolane of claim 44 wherein the alkyl bridge is functionalized with a substituent selected from the group consisting of a linear or branched alkyl, ketone, acid, alcohol, amine, amide, sulfonamide, guanidine, ether, ester, oxime, urea, oxime ether, sulfone, lactone, carbamate, semicarbazone, phenyl, heterocycle, and alicyclic group.

20

47. The spiro or dispiro 1,2,4-trioxolane of claim 44 wherein the alkyl bridge is functionalized with a substituent that is a weak base.

48. The spiro or dispiro 1,2,4-trioxolane of claim 47 wherein the weak base comprises an amide.

25

49. The spiro or dispiro 1,2,4-trioxolane of claim 44 wherein the alkyl bridge is methyl.

30

50. A method of synthesizing a dispiro 1,2,4-trioxolane comprising: treating a trioxolane having a functional group selected from the group consisting of a ketone, an aldehyde, an ester, and a phthalimide with a reagent to form a compound selected from the group consisting of lactone, alcohol, oxime ether, hydrazone, ketal, acetal, amine, and acid.

51. The method of claim 50 wherein the trioxolane has a ketone or an aldehyde functional group, and is treated with an oxidizing agent to form a lactone or an acid.

5 52. The method of claim 50 wherein the trioxolane has a ketone or an aldehyde functional group, and is treated with a reducing agent to form an amine or an alcohol.

53. The method of claim 50 wherein the trioxolane has a ketone or an aldehyde functional group, and is treated with a hydroxylamine or a hydrazine to form an oxime
10 ether or a hydrazone, respectively.

54. The method of claim 50 wherein the trioxolane has a ketone or an aldehyde functional group, and is treated with one or more diols and/or alcohols to form a ketal or acetal.

15

55. The method of claim 51 whereby the trioxolane is OZ05.

56. The method of claim 55 whereby OZ05 is treated with a heteroaryllithium, aryllithium, or alkylolithium reagent to form the corresponding tertiary alcohol.

20

57. The method of claim 50 wherein the trioxolane has an ester functional group, and is treated with a reducing agent to form an alcohol.

58. The method of claim 57 whereby the trioxolane is selected from the group
25 consisting of OZ70 and OZ61.

59. The method of claim 58 whereby OZ70 is treated with a reducing agent to form OZ119.

30 60. The method of claim 58 whereby OZ61 is treated with a reducing agent to form OZ89.

61. The method of claim 50 wherein the trioxolane has an ester functional group, and is treated with a hydrolyzing agent to form an acid.

5 62. The method of claim 61 wherein the hydrolyzing agent is aqueous potassium hydroxide.

63. The method of claim 64 wherein OZ61 is treated with a hydrolyzing agent to form OZ78.

10

64. The method of claim 50 wherein the trioxolane has an phthalimide functional group, and is treated with a deprotecting reagent to form an amine.

15 65. The method of claim 64 whereby the phthalimide is selected from the group consisting of OZ136, OZ146, and OZ167.

66. The method of claim 65 whereby OZ136 is treated with a deprotecting reagent to form OZ137.

20 67. The method of claim 65 whereby OZ146 is treated with a deprotecting reagent to form OZ181.

68. The method of claim 68 whereby OZ167 is treated with a deprotecting reagent to form OZ269.

25

69. The method of claim 68 wherein the deprotecting reagent is hydrazine.