NOVEL MULTI-DRUG RESISTANCE MODIFIER

TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel compounds which maintain, increase, or restore sensitivity of cells to therapeutic or prophylactic agents. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well-suited for treatment of multi-drug resistant cells, for prevention of the development of multi-drug resistance and for use in multi-drug resistant cancer therapy.

BACKGROUND OF THE INVENTION

A major problem affecting the efficacy of chemotherapy is the evolution of cells which, upon exposure to a chemotherapeutic drug, become resistant to a multitude of structurally unrelated drugs and therapeutic agents. The appearance of such multi-drug resistance often occurs in the presence of overexpression of the 170-kDA membrane P-glycoprotein (gp-170). The gp-170 protein is present in the plasma membranes of some healthy tissues, in addition to cancer cell lines, and is homologous to bacterial transport proteins (Hait et al., Cancer Communications, Vol. 1(1), 35 (1989); West, TIBS, Vol. 15, 42 (1990)).

The protein acts as an export pump, conferring drug resistance through active extrusion of toxic chemicals. Although the mechanism for the pump is unknown, it is speculated that the gp-170 protein functions by expelling substances that share certain chemical or physical characteristics, such as hydrophobicity, the presence of carbonyl groups, or the existence of a glutathione conjugate (see West).

Various chemical agents have been administered to repress multi-drug resistance and restore drug sensitivity. While some drugs have improved the responsiveness of MDR cells to chemotherapeutic agents, they often have been accompanied by undesirable clinical side effects (see Hait et al.). For example, although cyclosporin A ("CsA"), a widely accepted immunosuppressant, can sensitize certain carcinoma cells to chemotherapeutic agents (Slater et al., Br. J. Cancer, Vol. 54, 235 (1986)), the concentrations needed to achieve that effect produce significant immunosuppression in patients whose immune systems are already compromised by chemotherapy (see Hait et al.). Similarly, calcium transport blockers and calmodulin inhibitors both sensitize multi-drug resistant ("MDR") cells, but each produces undesirable physiological effects (see Hait et al.; Twentyman et al., Br. J. Cancer, Vol. 56, 55 (1987)).

Recent developments have led to agents said to be of potentially greater clinical value in the sensitization of MDR cells. These agents include analogs of CsA which do not exert an immunosuppressive effect, such as 11-methyl-leucine cyclosporin (11-met-leu CsA) (see Hait et al.; Twentyman et al.), or agents that may be effective at low doses, such as the immunosuppressant FK-506 (Epand and Epand, Anti-Cancer Drug Design 6, 189 (1991)). Despite these

developments, the need remains for effective agents which may be used to resensitize MDR cells to therapeutic or prophylactic agents or to prevent the development of multi-drug resistance.

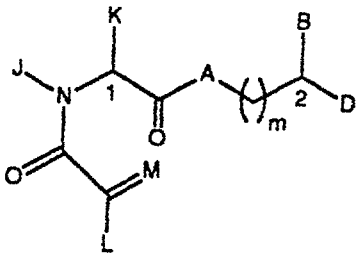
SUMMARY OF THE INVENTION

The present invention provides novel compounds that are useful to maintain, increase or restore drug sensitivity in multi-drug resistant ("MDR") cells, compositions containing those compounds and methods for using them. The compounds of this invention may be used alone or in combination with other therapeutic or prophylactic agents to maintain, increase or restore the therapeutic or prophylactic effects of drugs in cells, especially MDR cells, or to prevent the development of MDR cells. According to one embodiment of this invention, these novel compounds, compositions and methods are advantageously used to aid or enhance chemotherapy regimens for the treatment or prophylaxis of cancer and other diseases.

The present invention also provides methods for preparing the compounds of this invention and intermediates useful in those methods.

DETAILED DESCRIPTION OF THE INVENTION

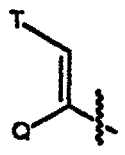
This invention relates to a novel class of compounds characterized by the ability to prevent multi-drug resistance or to maintain, increase or restore drug sensitivity in multi-drug resistant ("MDR") cells. More particularly, these compounds are represented by the formula (I):



(I)

wherein A is CH_2, oxygen, NH or N-(C1-C4 alkyl);
wherein B and D are independently:

(i) hydrogen, Ar, (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2, N, and NR, wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said heteroatom-containing chain to form a ring, and wherein said ring is optionally fused to an Ar group; or

(ii) 

wherein Q is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl or alkynyl;

wherein T is Ar or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl, and O-(C2-C4)-alkenyl;

wherein Ar is a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, and mono and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 which may contain in either or both rings a total of 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur -- such ring systems include heterocyclic aromatic groups selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyraxolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolylo, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbzaolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl;

wherein Ar may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl,

O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-(C1-C5-straight or branched alkyl or alkenyl) carboxamides, N,N-di-(C1-C5-straight or branched alkyl or C2-C5-straight or branched alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, and q is 0-2;

wherein L is either hydrogen or U; M is either oxygen or CH-U, provided that if L is hydrogen, then M is CH-U or if M is oxygen then L is U;

wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C2-C4)straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrolidinyl, 1,3-dioxolyl, 2-imidazolinyl, imidazolidinyl, 2H-pyranyl, 4H-pyranyl, piperidyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl, and heterocyclic aromatic groups as defined above;

where Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro,

trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

wherein J is hydrogen, (C1-C2) alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from the group consisting of O, S, SO and SO_2; and

wherein m is 0-3.

The stereochemistry at positions 1 and 2 (formula I) may be independently R or S.

Preferably, at least one of B or D is independently a straight chain terminated by an aryl group, i.e., a group represented by the formula $-(CH_2)_r-(X)-(CH_2)_s-Ar$, wherein

r is 0-4;

s is 0-1;

Ar is as defined above; and

each X is independently selected from the group consisting of CH_2, O, S, SO, SO_2, N, and NR, wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen atom and the Ar group.

According to one embodiment of this invention, the heterocyclic aromatic groups are selected from the group consisting of furan, thiophene, pyrrole, pyridine, indolizine, indole, isoindole, benzo[b]furan, benzo[b]thiophene, 4H-quinolizine, quinoline, isoquinoline, 1,2,3,4-tetrahydroquinoline, isoxazole, and 1,2,3,4-tetrahydroisoquinoline.

According to another embodiment of this invention, at least one of B or D is selected from the group consisting of (C2-C10)-straight or branched alkynyl, (C5-C7)-cycloalkyl substituted (C2-C6)-straight or branched alkynyl, (C5-C7)-cycloalkenyl substituted (C2-C6)-straight or branched alkynyl, and Ar substituted (C2-C6)-straight or branched alkynyl.

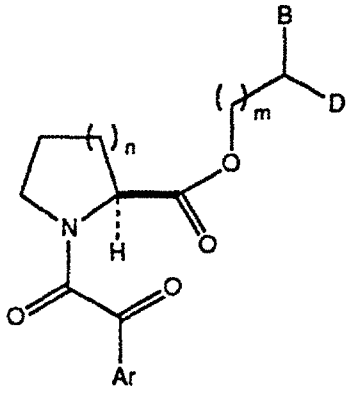
Also within the scope of this invention are compounds of formula (I), wherein at least one of B or D is selected from the group consisting of Ar', Ar'-substituted (C1-C6)-straight or branched alkyl, and Ar'-substituted (C2-C6)-straight or branched alkenyl or alkynyl; wherein Ar' is an Ar group substituted with one to three substituents which are independently selected from the group consisting of N-(straight or branched C1-C5 alkyl or C2-C5 alkenyl) carboxamides, N,N-di-(straight or branched C1-C5 alkyl or C2-C5 alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, wherein q is 0-2.

Examples of some preferred compounds of formula (I), wherein J and K are taken together to form a 5-7 membered heterocyclic ring, are shown in Table 1 and are further illustrated in the examples herein.*

---

* It should be understood that with respect to the aspects of this invention relating to the use of compounds described herein in compositions or methods for treating or preventing multi-drug resistance, those compounds are represented by formula (I), as defined above. With respect to the aspect of this invention relating to the novel compounds described herein, those compounds are represented by formula (I), as defined above, except that B and D can not be hydrogen.

Table 1



Cpd.	n	m	B	D	Ar
2	1	0	3-(Pyridin-2-yl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
3	2	0	3-Phenylpropyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
4	2	0	3-Phenoxyphenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
5	2	0	Phenyl	2-Phenoxyphenyl	3,4,5-Trimethoxyphenyl
6	2	0	Phenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
7	2	0	2-(Pyridin-2-yl)ethyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
8	2	0	*E*-3-[*trans*-(4-Hydroxycyclohexyl)]-2-methyl-eth-2-enyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
9	2	0	3-(Pyridin-3-yl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
10	2	0	Benzyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
11	2	0	Benzyl	3-(3-indolyl)propyl	3,4,5-Trimethoxyphenyl
12	2	0	2-Phenylethyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
13	2	0	2-(4-Methoxyphenyl)ethyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
14	2	0	2-(4-Methoxyphenyl)ethyl	3-Phenylpropyl	Phenyl
15	2	0	3-(N-benzimidazolyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
16	2	1	Benzyl	2-Phenylethyl	3,4,5-Trimethoxyphenyl
17	2	0	3-(4-Methoxyphenyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
18	2	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	Phenyl

No.	n	m	B	D	Ar
19	2	0	3-(Pyridin-2-yl)-propyl	3-Phenylpropyl	Phenyl
20	2	0	3-(Pyridin-2-yl)-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
21	2	0	3-(Pyridin-2-yl)-propyl	3-Phenylpropyl	*tert*-Butyl
22	2	0	3-(Pyridin-2-yl)-propyl N-oxide	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
23	2	0	3-[N-(7-azaindolyl)-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
24	2	0	3-(Pyridin-3-yl)-propyl	3-(4-Methoxyphenyl)propyl	3,4,5-Trimethoxyphenyl
25	2	0	3-(N-Purinyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
26	2	0	3-(4-Hydroxymethyl-phenyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
27	2	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	3-Benzyloxyphenyl
28	2	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	3-Allyloxyphenyl
29	2	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	3-Isopropoxyphenyl
30	2	0	3-(Thiophen-2-yl)-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
31	2	0	3-(4-Carboxyphen-yl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
32	2	0	3-Phenylbutyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
33	2	0	2-Hydroxymethyl-phenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
34	2	0	2-Allyloxyphenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
35	2	0	3-(3-Hydroxymeth-ylphenyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
36	2	0	3-(3-Carboxyphen-yl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
37	2	0	3-Hydroxymethyl-phenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
38	2	0	2-Hydroxyphenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
39	2	0	Pyridin-3-yl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
40	2	0	3-(Thiopen-2-yl)-propyl	4-Phenylbutyl	3,4,5-Trimethoxyphenyl
41	2	0	5-Phenylpentyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl

No.	n	m	B	D	Ar
42	2	0	3-Allyloxypropyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
43	2	0	3-[4-(N,N-Dimethyl-aminecarbonyl)-phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
44	2	0	3-[4-(Morpholine-4-carbonyl)phenyl)-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
45	2	0	4-Allyoxybutyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
46	2	0	3-Allyloxyprop-1-ynyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
47	2	0	3-[4-(Piperidine-1-carbonyl)phenyl)-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
48	2	0	5-Allyloxynonyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
49	2	0	Methyl	3,5-Bis(benzyl-oxy)phenyl	3,4,5-Trimethoxyphenyl
50	2	0	2-Allyloxyethyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
51	2	0	3-Allyloxy-(*E*)-prop-1-enyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
52	2	0	3-[3-(Morpholine-4-carbonyl)phenyl]-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
53	2	0	Dec-9-enyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
54	2	0	3-[4-(N-Benzyl-aminecarbonyl)-phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
55	2	0	3-[4-(Thiomorpho-line-4-carbonyl)-phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
56	2	0	3-(Morpholine-4-carbonyl)phenyl-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
57	2	0	3-[4-(1-Methyl piperazine-4-carbon-yl)phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
58	2	0	3-[4-(1-Benzylpip-erazine-4-carbon-yl)phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
59	2	0	3-[3-(N-Benzyl-aminecarbonyl)-phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl

No.	n	m	B	D	Ar
60	2	0	3-[4-(N-Pyridin-2-ylaminecarbonyl)-phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
61	2	0	Pryidin-3-yl	3-(Pyridin-3-yl)-propyl	3,4,5-Trimethoxyphenyl
62	2	0	Prop-2-enyl	3,4-Bis-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
63	2	0	Pyridin-3-yl	3-(Pyridin-4-yl-methoxy)phenyl	3,4,5-Trimethoxyphenyl
64	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-methoxy)phenyl	3,4,5-Trimethoxyphenyl
65	2	0	3-Phenylpropyl	3,4-Bis-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
66	2	0	Methyl	3,4-Bis-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
67	2	0	3-Phenylpropyl	2,3,4-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
68	2	0	3-Phenylpropyl	3-(Morpholine-4-carbonyl)-4-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
69	2	0	Methyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
70	2	0	3-Phenylpropyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
71	2	0	Methyl	3,5-Bis-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
72	2	0	3,5-Bis-(Pyridin-4-ylmethoxy)phenyll	Methyl	3,4,5-Trimethoxyphenyl
73	2	0	Methyl	3,5-Bis-(Pyridin-4-ylmethoxy)-4-methyl-phenyl	3,4,5-Trimethoxyphenyl
74	2	0	Ethyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
75	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Ethyl	3,4,5-Trimethoxyphenyl
76	2	0	Methyl	3,4,5-Tris-(Pyrazin-2-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
77	2	0	Methyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4-Dimethoxyphenyl
78	2	0	Ethenyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl

No.	n	m	B	D	Ar
79	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Ethenyl	3,4,5-Trimethoxyphenyl
80	2	0	Propyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
81	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Propyl	3,4,5-Trimethoxyphenyl
82	2	0	Methyl	3,4,5-Tris-(Thiophen-3-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
83	2	0	3,4,5-Tris-(Thiophen-3-ylmethoxy)phenyl	Methyl	3,4,5-Trimethoxyphenyl
84	2	0	Methyl	2-Isopropoxy-3,4-Bis-(Pyridin-4-ylmethoxy)-phenyl	3,4,5-Trimethoxyphenyl
85	2	0	2-Isopropoxy-3,4-Bis-(Pyridin-4-ylmethoxy)-phenyl	Methyl	3,4,5-Trimethoxyphenyl
86	1	0	Methyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
87	1	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Methyl	3,4,5-Trimethoxyphenyl
88	2	0	Methyl	3,4,5-Tris-(*Pyridin-4*-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
89	2	0	Benzyloxymethyl	Benzyloxyphenyl	3,4,5-Trimethoxyphenyl
90	2	0	Methyl	3,4,5-Tris-(Benzyl-oxy)phenyl	3,4,5-Trimethoxyphenyl
91	2	0	3-Phenylpropyl	3-(Pyridin-3-yl-carbonyl)phenyl	3,4,5-Trimethoxyphenyl
92	2	0	3-(Pyridin-3-yl-carbonyl)phenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
93	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-methoxy)phenyl	3,4-Dimethoxyphenyl
94	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	4-Benzyloxy-3,5-di-methoxyphenyl
95	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	4-Allylyoxy-3,5-di-methoxyphenyl
96	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3-Benzyloxy-4-methoxyphenyl
97	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3-Allyloxy-4-methoxyphenyl

No.	n	m	B	D	Ar
98	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3-[3-Phenyl-(*E*)-prop-2-enyl]-4-methoxyphenyl
99	2	0	3-Phenylpropyl	4-(Pyridin-4-yl-carbonyl)phenyl	4-Benzyloxy-3,5-di-methoxyphenyl
100	2	0	3-Phenylpropyl	4-(Pyridin-4-yl-carbonyl)phenyl	3-Benzyloxy-4-methoxyphenyl
101	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3,4,5-Trimethoxyphenyl
102	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3,4-Dimethoxyphenyl
103	2	0	3-Phenylpropyl	Phenyl	3-Benzyloxy-4-methoxyphenyl
104	2	0	3-Phenylpropyl	Phenyl	4-Benzyloxy-3,5-di-methoxyphenyl
105	1	0	3-(Pyridin -3-yl)-propyl	3-Phenylpropyl	*tert*-Butyl
106	2	0	3-(Pyridin -3-yl)-propyl	3-(Pyridin-3-yl)-propyl	3,4,5-Trimethoxyphenyl
107	1	0	Benzyloxymethyl	Benzyloxyphenyl	3,4,5-Trimethoxyphenyl
108	1	0	3-(Pyridin -3-yl)-propyl	3-(Pyridin-3-yl)-propyl	3,4,5-Trimethoxyphenyl
109	2	0	3-(Pyridin -3-yl)-propyl	3-(Pyridin-3-yl)-propyl	Isopropyl
110	2	0	3-(Pyridin -3-yl)-propyl	3-(Pyridin-3-yl)-propyl	Thiophen-2-yl
111	2	0	3-(Pyridin -3-yl)-propyl	3-(Pyridin-3-yl)-propyl	3,4-Methylenedioxy-phenyl
112	2	0	3-(Pyridin -3-yl)-prop-2-ynyl	3-(Pyridin-3-yl)-prop-2-ynyl	3,4-Methylenedioxy-phenyl
113	2	0	3-(Pyridin -3-yl)-prop-2-ynyl	3-(Pyridin-3-yl)-prop-2-ynyl	3,4,5-Trimethoxyphenyl
114	2	0	3-(Pyridin -2-yl)-propyl	3-(Pyridin-2-yl)-propyl	3,4,5-Trimethoxyphenyl
115	2	0	Isopropyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
116	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Isopropyl	3,4,5-Trimethoxyphenyl
117	2	0	Prop-2-enyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl
118	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Prop-2-enyl	3,4,5-Trimethoxyphenyl

The most preferred compounds of this invention are (S)-1-(2-oxo-2-(3,4,5-trimethoxyphenyl) acetyl)piperidine-2-carboxylic acid-4-pyridin-3-yl-1-(3-pyridin-3-yl)propyl)butyl ester, and (R)-1-(2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl) piperidine-2-carboxylic acid-4-pyridin-3-yl-1-(3-pyridin-3-yl) propyl)butyl ester, pharmaceutically acceptable derivatives thereof and mixtures thereof.

As use herein, the compounds of this invention, including the compounds of formula (I), are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to maintain, increase or restore sensitivity of MDR cells to therapeutic or prophylactic agents or to prevent development of multi-drug resistance.

Compounds of this invention represented by formula (I) may be obtained using any conventional technique. Preferably, these compounds are chemically synthesized from readily available starting materials, such as alpha-amino acids. Modular and convergent methods for the synthesis of these compounds are also preferred. In a convergent approach, for example, large sections of the final product are brought together in the final stages of the synthesis, rather than by incremental addition of small pieces to a growing molecular chain.

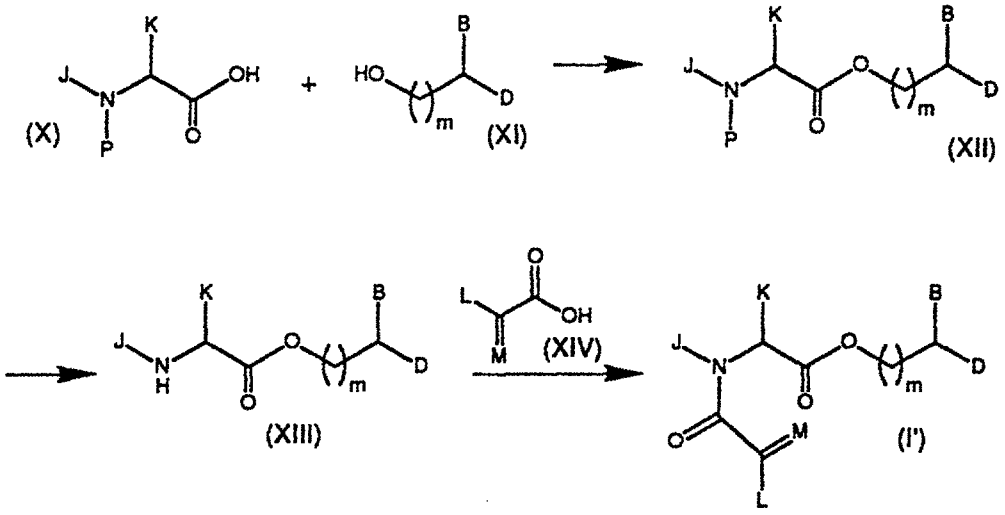
Scheme 1 illustrates a representative example of a convergent process for the synthesis of compounds

of formula (I'), a preferred subset of compounds of formula (I), wherein A is oxygen. The process comprises esterification of a protected alpha-amino acid of formula (X), wherein P is a protecting group, with an alcohol of formula (XI). Protected alpha-amino acids are well known in the art and many are commercially available. For example, common protecting groups and convenient methods for the protection of amino acids are described in T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Chemistry, 2nd Ed., John Wiley and Sons, New York (1991). Alkoxycarbonyl groups are preferred for protection of the nitrogen atom in compounds of formula (X), with t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), allyloxycarbonyl (Alloc), and trimethylsilylethoxycarbonyl (Teoc) being more preferred.

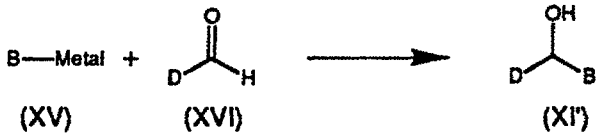
After esterification, compounds of formula (XII) are deprotected under suitable deprotection conditions (see Greene, supra), and the free amino group of (XIII) is then acylated with a compound of formula (XIV), or an activated derivative thereof, to yield a compound of formula (I'). Methods for activation of carboxyl functionalities in carboxylic acids such as compounds of formula (XIV) are well known and many activating agents are commercially available.

Alcohols of formula (XI) wherein m is 0 (XI') can also be conveniently prepared, for example, as illustrated in Schemes 2 and 3. Reaction of an organometallic reagent of formula (XV) and an aldehyde of formula (XVI) provides alcohols of formula (XI') (Scheme 2).

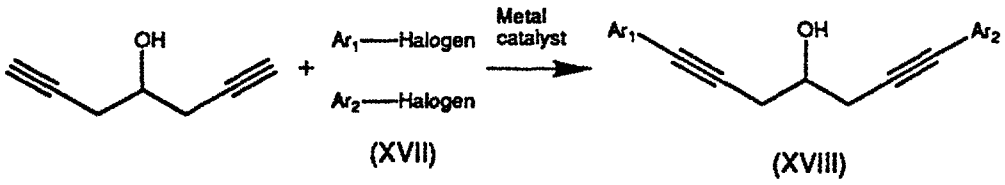
Scheme 1



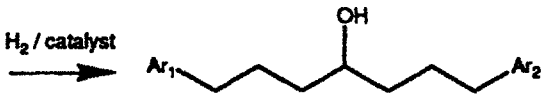
Scheme 2



Scheme 3



Ar_1 and Ar_2 are independently Ar groups as defined in the text.



Alternatively (Scheme 3), 1,6-heptadiyn-4-ol can be coupled via a metal-catalyzed reaction to aromatic halides of formula (XVII) to give an alcohol of formula (XVIII). Subsequent hydrogenation provides an alcohol of formula (XI''), a preferred subset of alcohols of formula (XI).

Thus, this invention also provides a method for preparing compounds of formula (I') comprising the steps of:

(a) esterifying a protected amino acid of formula (X) with an alcohol of formula (XI) to give an intermediate of formula (XII);

(b) deprotecting the amino protecting group in the intermediate of formula (XII) to give an amino ester of formula (XIII); and

(c) acylating the free amino group in the compound of formula (XIII) with a compound of formula (XIV) or an activated derivative thereof.

It should be appreciated by those of ordinary skill in the art that a large variety of compounds of formula (I) may be readily prepared, according to the processes illustrated in synthetic Schemes 1, 2 and 3. The same processes may be used for the synthesis of many different end-products, by altering the variables in the starting materials.

For example, compounds of formula (I'') (not shown) wherein A is NH or N-(C1-C4 alkyl) can be synthesized by a peptide coupling reaction between a carboxylic acid of formula (X) and an amine of formula (XI''') (not shown) to give an amide of formula (XII'). This step is analogous to the first esterification reaction of Scheme 1. The steps leading from (XII') to (I'') are also analogous to those from (XII) to (I') shown in Scheme 1.

Optically active compounds of formula (I) may also be prepared using optically active starting materials, thus obviating the need for resolution of enantiomers or separation of diastereomers at a late stage in the synthesis.

It will also be appreciated by those of ordinary skill in the art that the above synthetic schemes are not intended to comprise a comprehensive list of all means by which the compounds or the intermediates of this invention may be synthesized. Further methods or modifications of the above general schemes will be evident to those of ordinary skill in the art.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds of this invention are characterized by the ability to increase, restore or maintain the sensitivity of MDR cells to cytotoxic compounds, such as, for example, those typically used in chemotherapy. Based on that ability, the compounds of this invention are advantageously used as chemosensitizing agents, to increase the effectiveness of chemotherapy in individuals who are afflicted with drug-resistant cancers, tumors, metastases or disease. In addition, the compounds of this invention are capable of maintaining sensitivity to therapeutic or prophylactic agents in non-resistant cells. Therefore,

the compounds of this invention are useful in treating or preventing multi-drug resistance in a patient. The term "patient" as used herein refers to mammals, including humans. And the term "cell" refers to mammalian cells, including human cells.

As used herein, the terms "sensitizing agent", "sensitizer", "chemosensitizing agent", "chemosensitizer" and "MDR modifier" denote a compound having the ability to increase or restore the sensitivity of an MDR cell, or to maintain the sensitivity of a non-resistant cell, to one or more therapeutic or prophylactic agents. The term "MDR sensitization" and "sensitization" and "resensitization" refer to the action of such a compound in maintaining, increasing, or restoring drug sensitivity.

According to one embodiment of this invention, compounds of this invention that are useful in increasing, restoring or maintaining drug sensitivity are also capable of binding to the protein FKBP-12 or other related FK-506 binding proteins such as FKBP-13, FKBP-26 and FKBP-52. In vitro tests (data not shown) of these compounds demonstrate that the agents bind to FKBP-12. Thus, this invention also comprises a class of chemosensitizing agents other than FK-506, characterized by the ability to bind to the FK binding protein-12 or related FK binding proteins, pharmaceutical compositions including such agents and a physiologically acceptable adjuvant, carrier or vehicle, and methods of using those compositions for treating or preventing multi-drug resistance in a patient.

Preferred compounds suitable for use in preventing or modulating multi-drug resistance are those which are not significantly immunosuppressive at clinically useful or prophylactically or

therapeutically active levels -- i.e., the effect, if any, of immunosuppression does not outweigh the value of sensitization activity of the compound to the patient. Such immunosuppressive capabilities can be ascertained by the in vitro assays set forth in United States patent application Serial Nos. 07/547,814 (now United States patent 5,192,773), 07/704,734, 07/697,785 and 07/881,152, the disclosures of which are incorporated herewith.

The compounds of the present invention may be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long

chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions of this invention comprise any of the compounds of the present invention, or pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates,

waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

According to this invention, the pharmaceutical compositions may be in the form of a sterile injectable preparation, for example a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as do natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried

corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical

compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It should be understood, however, that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the

severity of the particular disease being treated. The amount of active ingredient may also depend upon the therapeutic or prophylactic agent, if any, with which the ingredient is co-administered. As used herein, the term "pharmaceutically effective amount" refers to an amount effective to prevent multi-drug resistance or maintain, increase or restore drug sensitivity in MDR cells.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 50 mg/kg body weight per day of the active ingredient compound are useful. A typical preparation will contain between about 5% and about 95% active compound (w/w). Preferably, such preparations contain between about 20% and about 80% active compound.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may comprise a combination of a compound of this invention and another therapeutic or prophylactic agent.

For example, the compounds may be administered either alone or in combination with one or more therapeutic agents, such as chemotherapeutic agents, (e.g., actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, tenipaside, taxol and colchicine) and/or a chemosensitizing agent (e.g., cyclosporin A and analogs, phenothiazines and thioxantheres), in order to increase the susceptibility of the MDR cells within the patient to the agent or agents.

In order that this invention may be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Examples

General Methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 500 MHz on a Bruker AMX 500. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.0). Analytical high performance liquid chromatography was performed on either a Waters 600E or a Hewlett Packard 1050 liquid chromatograph.

Example 1

Synthesis of (S)-1,7-Diphenyl-4-heptanyl N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (3)

4-Phenyl-1-butyraldehyde (119). To a solution of 3.2 mL (20.8 mmol) of 4-phenyl-1-butanol (Aldrich Chemical Co.) in 20 mL of CH_2Cl_2 at 0 °C was added 3.2 g of powdered 3 Å molecular sieves and then 5.37 g (24.9 mmol) of pyridinum chlorochromate (PCC). The resulting suspension was stirred at 0 °C for 1 h at which time an additional 2.16 g (10.0 mmol) of PCC was added and the reaction mixture was warmed to room temperature. After stirring at ambient temperature for 0.5 h, the reaction mixture was diluted with ether and filtered through celite to give 2.5 g of the crude product. Flash chromatography (elution with 5% ethyl acetate in hexane) yielded 700 mg of the aldehyde 119. ^{1}H NMR was consistent with the structure.

3-Phenyl-1-propylmagnesium bromide (120). To a suspension of 736 mg (30.3 mmol) of magnesium turnings in 50 mL of THF at room temperature was added 50 μL of 1,2-dibromoethane followed by the dropwise addition of 5.5 g (25.1 mmol) of 1-bromo-3-phenylpropane (Aldrich Chemical Co.). After stirring at room temperature for 0.5 h, the supernatant was

transfered via cannula to a 100 mL storage vessel and subsequently used as a 0.5 M THF solution of the Grignard reagent 120.

1,7-Diphenyl-4-heptanol (121). To a solution of 700 mg (4.7 mmol) of 4-phenyl-1-butanal (119) in 5.0 mL of THF at 0 °C was added 10.0 mL (5.0mmol) of 3-phenyl-1-propylmagnesium bromide (120) and the resulting mixture was stirred at 0 °C for 0.5 h. The mixture was then quenched by the dropwise addition of saturated NH_4Cl and diluted with ether. The phases were separated and the organic layer was washed with water and brine and then dried over $MgSO_4$. Concentration gave 1.12 g of the alcohol 121 as an oil. ^1H NMR spectrum was consistent with the structure.

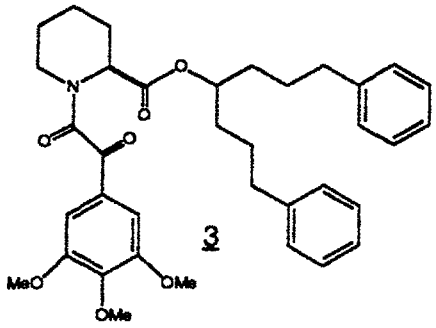
(S)-Boc-1-Pipecolyl-1,7-dipenyl-4-heptanyl ester (122). To a solution of 164 mg (0.72 mmol) of Boc-L-Pipecolic acid in 5.0 mL of CH_2Cl_2 at room temperature was added 174 mg (0.65 mmol) of alcohol 121, 140 mg (0.72 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and a catalytic amount of N,N-dimethylaminopyridine (DMAP). The reaction mixture was stirred at ambient temperature for 0.5 h and then applied directly to a silica gel column. Elution with 10% ethyl acetate in hexane afforded 76.2 mg of the ester 122 as an oil. ^1H NMR spectrum was consistent with the structure.

(S)-1,7-Diphenyl-4-heptanylpipecolate (123). To a solution of 47 mg (0.10 mmol) of the ester 122 in 1.0 mL of CH_2Cl_2 at ambient temperature was added 1.0 mL of trifluoroacetic acid. After stirring at room temperature for 0.5 h, the resulting solution was neutralized by the dropwise addition of saturated

K_2CO_3. The layers were separated and the organic phase was washed with water, dried over $MgSO_4$ and concentrated to yield 23 mg of the amine 123 as an oil. ^1H NMR consistent with structure.

3,4,5-Trimethoxybenzoylformic acid (124). To a solution of 9.2 g (43.4 mmol) of 3,4,5-trimethoxyacetophenone (Aldrich Chemical Co.) in 35 mL of pyridine was added 6.3 g (56.7 mmol) of selenium dioxide and the resulting solution was heated at reflux overnight. The reaction mixture was cooled to room temperature, filtered through celite and concentrated to yield a dark brown oil which was dissolved into ethyl acetate and washed with 1.0 N HCl and then with saturated $NaHCO_3$. The basic aqueous layer was diluted with ether and acidified with concentrated HCl. The layers were separated and the organic phase was washed with brine and then dried over Na_2SO_4 to give 8.4 g of the acid 124 as a pale yellow solid. ^1H NMR consistent with structure.

(*S*)-1,7-Diphenyl-4-heptanyl N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (3). To a solution of 23 mg (0.06 mmol) of the amine 123 in 1.0 mL of CH_2Cl_2 at room temperature was added 21.8 mg (0.09 mmol) of the acid 124 and then 17.9 mg(0.09 mmol) of EDC and the resulting solution was stirred at room temperature for 0.5 h and applied directly to a silica gel column. Elution with 15% ethyl acetate in hexane gave 8.4 mg of the amide 3 as a mixture of rotamers. ^1H NMR (500MHz $CDCl_3$ δ 7.35-7.06(m), 5.32 (br s), 5.00 (br s), 4.88 (br s), 4.58 (d), 4.31 (br s), 3.95 (s), 3.89 (s), 3.44 (d), 3.21 (t), 3.04 (t), 2.54 (br s), 2.51 (br s), 2.42 (br s), 2.30 (d), 2.15 (d), 1.83-1.21 (m).



3

Example 2

Synthesis of (*R* and *S*)-1-(3-Phenoxy)phenyl-4-phenyl-1-butyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (4).

3-Phenoxybenzaldehyde (125). To a solution of 1.8 mL (10.3 mmol) of 3-phenoxybenzyl alcohol (Aldrich Chemical Co.) in 20 mL of CH_2Cl_2 at room temperature was added 1.5 g of powdered 4 Å molecular sieves and 2.5 g of activated MnO_2. The resulting suspension was stirred at room temperature for 0.5 h, at which time an additional 2.5 g of MnO_2 was added. After stirring at room temperature for 0.5 h the reaction mixture was filtered through celite to give 1.84 g of the aldehyde 125 as an oil. ^1H NMR consistent with structure.

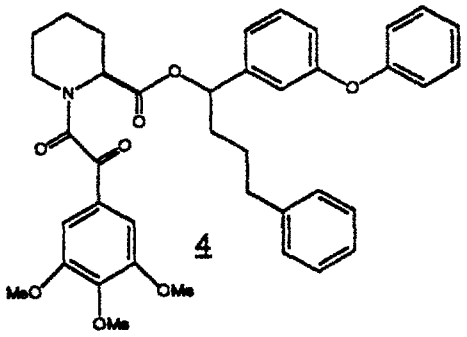
(*R* and *S*)-1-(3-Phenoxy)phenyl-4-phenyl-1-butanol (126). The alcohol 126 was prepared from 190 mg (0.96 mmol) of aldehyde 125 and 2.0 mL (1.0 mmol) of the Grignard reagent 120 in 2.0 mL of THF as described above for the synthesis of the alcohol 121 in Example 1. Flash chromatography (elution with 10% ethyl acetate in hexane) afforded 108 mg of the racemic alcohol 126. ^1H NMR consistent with structure.

(*S*)-N-3,4,5-(Trimethoxyphenyl)glyoxyl pipecolic acid (127). To a slurry of 953.3 mg (3.4 mmol) of the tartrate salt of (*S*)-pipecolic acid

(Egbertson, M. and Danishefsky, S. J. J. Org. Chem. 1989, 54, 11) in 7.0 mL of CH_2Cl_2 at 0 °C was added 3.9 mL (22.39 mmol) of diisopropylethylamine and 2.4 mL (18.9 mmol) of chlorotrimethylsilane and the resulting solution was allowed to stir at 0 °C for 0.5 h. In a separate reaction flask 450 μL (5.2 mmol) of oxalyl chloride and three drops of DMF were added to a solution of 820 mg (3.4 mmol) of acid 124 in 7.0 mL of CH_2Cl_2. After the evolution of gas ceased, the entire contents of the second flask were added to the first reaction vessel and the resulting mixture was allowed to stir at room temperature for 1 h. The reaction mixture was concentrated, dissolved into ether and washed with 0.5 N HCl and then saturated $NaHCO_3$. The basic aqueous phase was acidified with concentrated HCl and extracted with ether. The ethereal extracts were washed with water, brine, dried over $MgSO_4$ and concentrated to give 490 mg of the acid 127. ^1H NMR consistent with structure.

(*R* and *S*)-1-(3-Phenoxy)phenyl-4-phenyl-1-butyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (4). To a solution of 29.4 mg (0.08 mmol) of acid 127 in 2.0 mL of CH_2Cl_2 at room temperature was added 11 μL (0.13 mmol) of oxalyl chloride and three drops of DMF and the reaction mixture was allowed to stir at room temperature for 0.5 h and was then concentrated and suspended in 1.0 mL of benzene. To this suspension was added 32.0 mg (0.1 mmol) of alcohol 126 and 13.4 mg (0.1 mmol) of silver cyanide. The resulting mixture was heated at reflux overnight, cooled to room temperature and concentrated. Flash chromatography (elution with 10% ethyl acetate in hexane) gave 8.8 mg of the ester 4 as a mixture of diastereomers. ^1H NMR (500MHz $CDCl_3$) δ7.34-7.19 (m), 7.18-7.03 (m) 7.02-6.84

(m), 6.83-6.72 (m), 5.73 (q), 5.69-5.55 (m), 5.38 (t), 4.55 (br d), 4.35 (dd), 3.94 (s), 3.92 (s), 3.89 (s), 3.83 (s), 3.73 (s), 3.63 (s), 3.48-3.35 (m), 3.20 (t), 23.10 (t), 2.60 (q), 2.40 (dd), 1.95-1.91 (m), 1.90-1.45 (m).



4

Example 3

Synthesis of (*R* and *S*)-6-Phenyl-1-(3-pyridyl)-3-hexyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)-pipecolate (7).

3-(3-Pyridyl)-1-propylaldehyde (128). To a solution of 2.3 g (5.46 mmol) of the Dess-Martin periodinane (Dess, D.B.; Martin, J.C. *J. Org. Chem.* 1983, *48*, 4155) in 10 mL of CH_2Cl_2 at 0 °C was added 470 μL (3.65 mmol) of 3-(3-pyridyl)-1-propanol and the resulting mixture was allowed to warm from 0 °C to ambient temperature over a 1.5 h period. To this solution was added 6.0 g (38.22 mmol) of $Na_2S_2O_3$ in saturated $NaHCO_3$ and the reaction mixture was allowed to stir at room temperature for 15 min. The reaction was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 3:1 hexane;acetone) yielded the product aldehyde 128 as an oil. ^1H NMR consistent with structure.

(*R* and *S*)-6-Phenyl-1-(3-pyridyl)-3-hexanol (129). The alcohol 129 was prepared from 125 mg (0.92 mmol) of aldehyde 128 and 2.0 mL (1.0 mmol) of 120 in

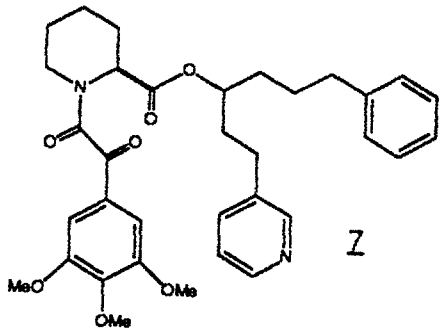
2.0 mL of THF as described above for the synthesis of alcohol 121 in Example 1 to give 221 mg of the crude alcohol 129. ^{1}H NMR consistent with structure.

(S)-Boc-Pipecolyl-*(R and S)*-6-Phenyl-1-(3-pyridyl)-3-hexyl ester (130). The ester 130 was prepared from 125 mg (0.49 mmol) of alcohol 129, 93 mg (0.41 mmol) of Boc-pipecolic acid, 94 mg (0.49 mmol) of EDC and a catalytic amount of DMAP in 1.0 mL of CH_2Cl_2 and 1.0 mL of DMF as described above for the synthesis of 122 in Example 1. Flash chromatography (elution with 2:1 hexane: ethyl acetate) gave 105 mg of the diastereomeric ester 130 as an oil. ^{1}H NMR consistent with structure.

(R and S)-6-Phenyl-1-(3-pyridyl)-3-hexyl *(S)*-pipecolate (131). The amine 131 was synthesized by treating 95 mg (0.20 mmol) of the ester 130 with 1.0 mL of trifluoroacetic acid in 3.0 mL of CH_2Cl_2 as described above for the preparation of amine 123 in Example 1, giving 58 mg of the diastereomeric amine 131 as an oil. ^{1}H NMR consistent with structure.

(R and S)-6-Phenyl-1-(3-pyridyl)-3-hexyl *(S)*-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (7). The ester 7 was prepared from 54 mg (0.15 mmol) of the amines 131, 50 mg (0.22 mmol) of the acid 124 and 42 mg (0.22 mmol) of EDC in 3.0 mL of CH_2Cl_2 as described above in the synthesis of ester 3 in Example 1. Flash chromatography (elution with 1:1 ethyl acetate:hexane) gave 73 mg of the diasteromeric ester 7 as a mixture of rotamers. ^{1}H NMR (500MHz $CDCl_3$) δ 8.48-8.42 (m), 7.50-7.41 (m), 7.32 (d), 7.27-7.03 (m), 5.38 (d), 5.31 (d), 5.06-5.01 (m), 4.97-4.93 (m), 4.60 (br d), 3.92 (s), 3.88 (s), 3.86 (s), 3.84 (s), 3.82 (s), 3.79 (s), 3.46

(br d), 3.27 (br t), 2.73-2.68 (m), 2.38-2.29 (m), 1.98-1.76 (m), 1.75-1.60 (m), 1.56-1.51 (m), 1.38-1.20 (m).



I

Example 4

Synthesis of (*R* and *S*)-(*E*)-1-[*trans*-(4-Hydroxycyclohexyl)]-2-methyl-6-phenyl-3-hex-1-enyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (8).

cis-and *trans*-4-(*tert*-Butyldimethylsilyloxy)-cyclohexan-1-ol (132) and (133). To a solution of 3.43 g (21.7 mmol) of *cis*- and *trans*-methyl 4-hydroxycyclohexane carboxylate (Noyce, D.S.; Denney, D.B. J. Am. Chem. Soc. Vol. 74, 5912 (1952)) in 45 mL of methylene chloride at 0 °C was added 3.0 mL (26.0 mmol) of 2,6-lutidine followed by 5.5 mL (23.0 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. The ice bath was removed and the reaction mixture was allowed to stir at 25 °C for 2 h, at which time the solution was poured into saturated sodium bicarbonate. The layers were partitioned and the organic layer was washed with saturated copper sulfate and water and then dried over $MgSO_4$ to give 5.9 g of the crude methyl esters. A solution of 5.72 g (21.0 mmol) of this mixture in 45 mL of anhydrous THF was treated with 400 mg (10.5 mmol) of lithium aluminum hydride. The reaction mixture was stirred at 25 °C for 0.5 h and was then quenched by the slow addition of a saturated solution of Rochelle's salt. The mixture was diluted

with ether, the layers were partitioned and the aqueous layer was washed twice with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 4.9 g of the diastereomeric alcohols. Flash chromatography (elution with 1:5 ethyl acetate-hexane) gave 650 mg of 132, 1.10 g of 133 and 2.40 g of a mixture of the two. Data for 132: ^1H NMR (300 MHz, $CDCl_3$) δ 3.99-3.92(m), 3.46(d), 1.72-1.58 (m), 1.57-1.36(m), 0.86(s), 0.08(s). Data for 133: ^1H NMR (300 MHz, $CDCl_3$) δ 3.47(dddd), 3.38(d), 1.86-1.67(m), 1.47-1.16(m), 1.05-0.77(m), 0.72(s), 0.02(s).

(E)-Ethyl 3-[*trans*-(4-*tert*-Butyldimethylsilyloxycyclohexyl)]-2-methylprop-2-enoate (134). To a -78 °C solution of oxalyl chloride (785 μL, 9.0 mmol) in 10 mL of methylene chloride was added dimethylsulfoxide (1.3 mL, 18.0 mmol). The resulting solution was stirred for 5 min and then 1.1 g (4.5 mmol) of the alcohol 133 was added in 10 mL of methylene chloride. The reaction mixture was stirred at -78 °C for 45 min at which time 3.8 mL (27.0 mmol) of triethylamine was added and the solution was allowed to warm to ambient temperature. The reaction was quenched with 1.0 N HCl and the aqueous layer was extracted with three portions of methylene chloride. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness to give 1.0 g of the intermediate aldehyde. A solution of this aldehyde (450 mg, 1.86 mmol) was treated directly with 710 mg (1.95 mmol) of (carbethoxyethylidene)triphenylphosphorane in 5.0 mL of methylene chloride. The resulting reaction mixture was stirred at ambient temperature overnight and was then poured into water. The layers were partitioned and the aqueous layer was extracted twice with methylene chloride. The combined organic layers were

dried over $MgSO_4$ and concentrated to yield the enoate 134 containing a minor amount of the Z isomer. ^1H NMR consistent with structure.

(*E*)-3-[*trans*-(4-*tert*-Butyldimethylsilyloxycyclohexyl)]-2-methylprop-2-en-1-ol (135). To a solution of 860 mg (2.6 mmol) of enoate 134 in 5.0 mL of anhydrous tetrahydrofuran at 25 °C was added 50 mg (1.3 mmol) of lithium aluminum hydride and the resulting mixture was allowed to stir for 30 min. The reaction was quenched by the slow addition of saturated Rochelle's salt and diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic extracts were washed with both water and brine and then dried over $MgSO_4$. Evaporation and flash chromatography (elution with 15% ethyl acetate in hexane) gave 370 mg of the allylic alcohol 135. ^1H NMR consistent with structure.

(*E*)-3-[*trans*-(4-*tert*-Butyldimethylsilyloxycyclohexyl)]-2-methylprop-2-en-1-al (136). To a -78 °C solution of oxalyl chloride (105 μL, 1.2 mmol) in 1.0 mL of methylene chloride was added dimethylsulfoxide (170 μL, 2.4 mmol). The resulting solution was stirred for 5 min and then 170 mg (0.6 mmol) of the alcohol 135 was added in 1.0 mL of methylene chloride. The reaction mixture was stirred at -78 °C for 45 min at which time 500 μL (3.6 mmol) of triethylamine was added and the solution was allowed to warm to ambient temperature. The reaction was quenched with 1.0 N HCl and the aqueous layer was extracted with three portions of methylene chloride. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness to give

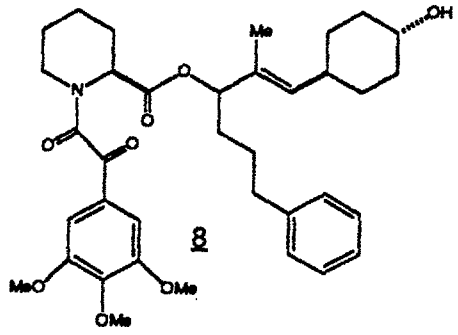
the crude aldehyde 136 which was used directly in the next reaction. ^{1}H NMR consistent with structure.

(R and S)-(E)-1-[trans-(4-tert-Butyldimethylsilyloxycyclohexyl)]-2-methyl-6-phenylhex-1-en-3-ol (137). The alcohol 137 was prepared from the crude aldehyde 136 and 1.5 mL (0.75 mmol) of 120 in 2.0 mL of THF as described above for the synthesis of alcohol 121 in Example 1 to give 220 mg of the crude diastereomeric alcohol 137. Flash chromatography (elution with 20% ethyl acetate in hexane) afforded 146 mg of the alcohol 137 as an oil. ^{1}H NMR consistent with structure.

(R and S)-(E)-1-[trans-(4-tert-Butyldimethylsilyloxycyclohexyl)]-2-methyl-6-phenyl-3-hex-1-enyl (S)-N-(3,4,6-trimethoxyphenylglyoxyl)pipecolate (138). To a solution of 75.7 mg (0.22 mmol) of acid 127 in 2.5 mL of CH_2Cl_2 at room temperature was added 30 μL (0.34 mmol) of oxalyl chloride and three drops of DMF and the reaction mixture was allowed to stir at room temperature for 0.5 h and was then concentrated and suspended in 1.0 mL of benzene. To this suspension was added 43.4 mg (0.11 mmol) of alcohol 137 and 28.8 mg (0.22 mmol) of silver cyanide. The resulting mixture was heated at reflux overnight, cooled to room temperature and concentrated. Flash chromatography (elution with 4% acetone in hexane) gave 17.5 mg of the ester 138 as a mixture of diastereomers. ^{1}H NMR consistent with structure.

(R and S)-(E)-1-[trans-(4-Hydroxycyclohexyl)]-2-methyl-6-phenyl-3-hex-1-enyl (S)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (8). To a solution

of 17.5 mg (0.02 mmol) of the ester 138 in 1.0 mL of CH_3CN at room temperature was added 10 drops of a 95:5 solution of CH_3CN:5% HF and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was neutralized with saturated K_2CO_3 and extracted into ether. The ether layers were washed with water, dried over $MgSO_4$ and concentrated to yield 7.2 mg of crude material. Flash chromatography (elution with 15% acetone in hexane) gave 4.9 mg of the diastereomeric alcohol 8 as a mixture of rotamers. ^1H NMR (500MHZ, $CDCl_3$) δ 7.38-7.02(m), 5.35-5.01(m), 4.62-4.53(m), 4.28(t), 3.95(s), 3.89(s), 3.87(s), 3.86(s), 3.85(s), 3.81(s), 3.55(m), 3.45(m), 3.20(m), 3.10-2.90(m), 2.60-2.45(m), 2.32(t), 2.10(t), 1.95(d), 1.85-1.40(m), 1.39-1.02(m).



8

Example 5

Synthesis of (*R* and *S*)-5-(3-indolyl)-1-phenyl-2-pentyl (*S*)-N-(3,4,5-tri-methoxyphenylglyoxyl)pipecolate (11).

N-Methyl-N-Methoxy-4-(3-indolyl)butyramide (139). To a slurry of 1.75 g (8.61 mmol) of 3-indolebutyric acid (Aldrich Chemical Co.) in acetonitrile at room temperature was added 7.0 mL (40.2 mmol) of N,N-diisopropylethylamine, 3.8 g (21.5 mmol) of N,N-dimethylhydroxylamine hydrochloride and 4.19 g (9.5 mmol) of benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent) and the resulting mixture was allowed to stir at room

temperature overnight and was than concentrated to dryness. The residue was dissolved into ethyl acetate and washed with water, 0.5 N HCl, saturated $NaHCO_3$ and brine and then dried over $MgSO_4$ and concentrated. Flash chromatography (elution with a gradient of 2-10% ether in methylene chloride) provided 2.0 g of the amide 139. ^1H NMR consistent with structure.

Benzyl-3-(3-indolyl)propyl ketone (140). To a solution of 147 mg (0.60 mmol) of amide 139 in 4.0 mL of THF at -78 °C was added 1.31 mL (1.31 mmol) of benzylmagnesium chloride (1.0 M in Et_2O) and the reaction mixture was allowed to warm to room temperature and stir for 3 h. The reaction was quenched with 5% $KHSO_4$ and extracted into ether. The combined ethereal layers were washed with brine and dried over $MgSO_4$. Flash chromatography (elution with 25% ether in hexane) gave 108 mg of the ketone 140. ^1H NMR consistent with structure.

(*R* and *S*)-5-(3-indolyl)-1-phenyl-2-pentanol (141). To a slurry of 105 mg (0.38 mmol) of ketone 140 in 3.0 mL of MeOH at 0 °C was added 30 mg (0.79 mmol) of solid $NaBH_4$ and the resulting suspension was allowed to stir for 3 h. The reaction mixture was quenched with 5% $KHSO_4$ and extracted into ethyl acetate. The combined organic extracts were washed with brine and dried over $MgSO_4$. Flash chromatography (elution with 4% ether in methylene chloride) gave 81 mg of the alcohol 141 as a white solid. ^1H NMR consistent with structure.

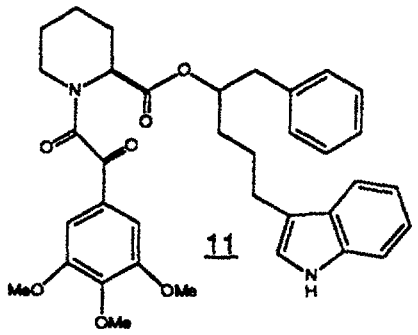
(*S*)-Boc-Pipecolyl-(*R* and *S*)-5-(3-indolyl)-1-phenyl-2-pentyl ester (142). The ester 142 was prepared from 80 mg (0.29 mmol) of alcohol 141, 82 mg

(0.36 mmol) of (S)-Boc-pipecolic acid, 66 mg (0.34 mmol) of EDC and a catalytic amount of 4-pyrrolidinopyridine in 2.0 mL of CH_2Cl_2 (mixture was allowed to stir overnight at room temperature) as described above for the synthesis of ester 122 in Example 1. Flash chromatography (elution with 4:10:26 ether: methylene chloride: hexane) gave 108 mg of the diastereomeric ester 142 as a white foam. ^{1}H NMR consistent with structure.

(R and S)-5-(3-indolyl)-1-phenyl-2-pentyl *(S)*-pipecolate hydrochloride salt (143). Anhydrous HCl was bubbled into a solution of 103 mg (0.21 mmol) of the ester 142 in 10 mL of EtOAc at -20 °C for 10 min and then the reaction mixture was purged with N_2. Concentration gave 108 mg of the crude amine 143 as the hydrochloride salt. ^{1}H NMR consistent with structure.

(R and S)-5-(3-indolyl)-1-phenyl-2-pentyl *(S)*-N-(3,4,5-trimethoxyphenylglyoxyl)pipocolate (11). To a slurry of 108 mg of the crude amino hydrochloride 143 in CH_3CN at room temperature was added 91 μL (0.52 mmol) of N,N-diisopropylethylamine, 76 mg (0.31 mmol) of acid 124, and 111 mg (0.25 mmol) of the BOP reagent and the resulting mixture was stirred at room temperature for two days and then was concentrated to dryness. The residue was reconstituted into 75 mL of ethyl acetate and then sequentially washed with water, 5% $KHSO_4$, saturated $NaHCO_3$ and brine and then dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 4% ether in methylene chloride) gave 56.7 mg of the diastereomeric amide 11 as a rotameric mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98(d), 7.56(t), 7.38,-6.73(m), 5.38-5.14(m), 3.90(m), 3.38(brt), 3.10

(brt), 2.97-2.60(m), 2.31(d), 2.10(d), 1.98-1.17(m), 0.8(m). R_f 0.51 (10% ether in methylene chloride).



11

Example 6

Synthesis of (R and S)-2-Benzyl-4-phenyl-1-butyl (S)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (16).

(*R* and *S*)-2-Benzyl-4-phenyl-1-butyric acid (144). To a solution of 1.06 g (6.43 mmol) of 4-phenylbutyric acid in 20 mL of THF at 0 °C was added 193 mg (6.43 mmol) of solid NaH (80% in mineral oil). After stirring at 0 °C for 0.5 h, 3.2 mL (6.43 mmol) of lithium diisopropyl amide-THF complex (2.0 M) was added and the resulting red solution was stirred at 0 °C for 45 min. To this mixture was added 765 μL (6.43 mmol) of benzyl bromide and the solution was then allowed to stir overnight at room temperature. The reaction mixture was quenched by the slow addition of saturated $NaHCO_3$ and then washed with ether. The basic extracts were acidified with solid $KHSO_4$ and partitioned with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to

give 484 mg of the acid 144. ^{1}H NMR consistent with structure.

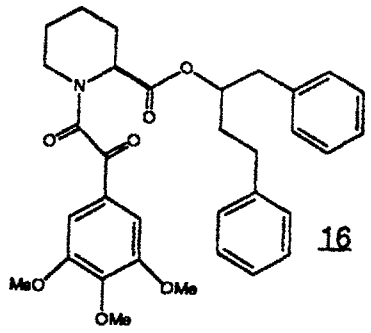
(*R* and *S*)-2-Benzyl-4-phenyl-1-butanol (145). To a solution of 469 mg (1.84 mmol) of acid 144 in 3.0 mL of THF at -78° 0 was added 2.03 mL (2.03 mmol) of lithium aluminum hydride (1.0 M in THF) and the resulting solution was allowed to warm to room temperature and stir overnight. The reaction mixture was quenched by the slow addition of Rochelle's salt and partitioned with ether. The combined ether extracts were washed with water and brine and dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 2% ether in methylene chloride) afforded 264 mg of the alcohol 145. ^{1}H NMR consistent with structure.

(*S*)-Boc-Pipecolyl-(*R* and *S*)-2-Benzyl-4-phenyl-1-butyl ester (146). The ester 146 was prepared from 264 mg (1.10 mmol) of alcohol 145, 302 mg (1.32 mmol) of (S)-Boc-L-pipecolic acid, 253 mg (1.32 mmol) of EDC and a catalytic amount of 4-pyrrolidinopyridine in 2.0 mL of CH_2Cl_2 (mixture was allowed to stir at room temperature for 3 days) as described above for the synthesis of ester 122 in Example 1. Flash chromatography (elution with 1:5:14 ether: methylene chloride: hexane) gave 375 mg of the diastereomeric ester 146. ^{1}H NMR consistent with structure.

(*R* and *S*)-2-Benzyl-4-phenyl-1-butyl (*S*)-pipecolate hydrochloride salt (147). Anhydrous HCl was bubbled into a solution of 375 mg (0.83 mmol) of the ester 146 in 10 mL of EtOAc at -20 °C for 10 min and then the reaction mixture was purged with N_2.

Concentration gave 352 mg of the crude amine 147 as the hydrochloride salt. ^{1}H NMR consistent with structure.

(*R* and *S*)-2-Benzyl-4-phenyl-1-butyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (16). To a slurry of 54 mg (0.14 mmol) of the crude amine hydrochloride 147 in 2.0 mL of CH_3CN at room temperature was added 60 μL (0.35 mmol) of N,N-diisopropylethylamine, 50 mg (0.21 mmol) of acid 124, and 73 mg (0.16 mmol) of the BOP reagent and the resulting mixture was stirred for 3 days at room temperature and was then concentrated to dryness. The residue was reconstituted into 75 mL of ethyl acetate and then sequentially washed with water, 5% $KHSO_4$, saturated $NaHCO_4$ and brine and then dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 2% ether in methylene chloride) gave 52.7 mg of the diastereomeric amide 16 as a rotameric mixture. ^{1}H NMR (500 MHZ, $CDCl_3$ δ 7.21-7.01 (m), 5,41 (brs), 4.21 (dd), 4.08 (dd), 4.12 (d), 3.88 (d), 3.95 (s), 3.91 (s), 3.49 (d), 3.39 (dt), 2.80-2.62 (m), 2.38 (brt), 2.09 (br s), 1.8701.20 (m). R_f 0.9 (1:3:26 Methanol: ether:methylene chloride).



16

Example 7

Synthesis of (*R* and *S*)-1-Phenyl-7-(2-pyridyl)-4-heptyl (*S*)-N-(*tert*-butylglyoxyl)pipecolate (21).

(*E* and *Z*)-3-(1,3-Dioxan-2-yl)-1-(2-pyridyl)-1-propene (148 and 149). To a suspension of 4.6 g (10.2 mmol) of [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide (Aldrich Chemical Co.) in 50 mL of THF at 0 °C was added 6.4 mL (10.2 mmol) of n-butyl lithium (1.6 M in hexanes) and the resulting red solution was allowed to stir at 0 °C for 0.5 h. To this solution was added 880 μL (9.3 mmol) of 2-pyridinecarboxaldehyde (Aldrich Chemical Co.). The reaction mixture was allowed to stir at room temperature for 1 h and was then poured into water and partitioned with ether. The combined either extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 3:1 hexane:ethyl acetate) gave 0.43 g of *E*-3-(1,3-dioxan-2-yl)-1-(2-pyridyl)-1-propene (148) and 1.12 g of *Z*-3-(1,3-dioxan-2-yl)-1-(2-pyridyl)-1-propene (149). ^1H NMRs consistent with structures.

1-(1,3-Dioxan-2-yl)-3-(2-pyridyl)propane (150). Through a suspension of 800 mg (4.2 mmol) of olefin 149 and 100 mg of 10% palladium on carbon was bubbled a steady stream of hydrogen gas for a period of 10 min. The reaction mixture was then filtered through celite and concentrated to give 805 mg of the acetal 150 as a colorless oil. ^1H NMR consistent with structure.

4-(2-Pyridyl)-1-butyraldehyde (151). A solution of 420 mg (2.2 mmol) of acetal 150 in 4.0 mL of THF and 3.0 mL of 4N HCl was stirred at room temperature for 1.5 h and was then neutralized by the slow addition of solid $NaHCO_3$. The reaction mixture

was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to yield 288 mg of the aldehyde 151. ^1H NMR consistent with structure.

(*R* and *S*)-1-Phenyl-7-(2-pyridyl)-4-heptanol (152). The alcohol 152 was prepared from 288 mg (1.93 mmol) of aldehyde 151 and 2.3 mL (2.3 mmol) of 120 in 3.0 mL of THF as described above for the synthesis of alcohol 121 in Example 1 to give 520 mg of the crude alcohol 152. ^1H NMR consistent with structure.

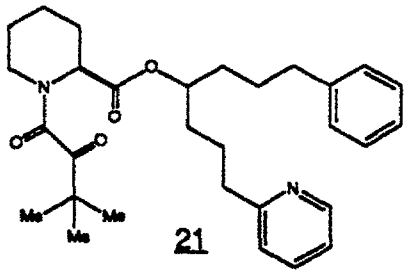
(*S*)-Boc-Pipecolyl-(*R* and *S*)-1-Phenyl-7-(2-pyridyl)-4-heptyl ester (153). The ester 153 was prepared from 520 mg (1.93 mmol) of alcohol 152, 442 mg (1.93 mmol) of (*S*)-Boc-L-pipecolic acid, 370 mg (1.93 mmol) of EDC and a catalytic amount of DMAP in 4.0 mL of CH_2Cl_2 and 4.0 mL of DMF as described above for the synthesis of 122 in Example 1. Flash chromatography (elution with 3:1 hexane: ethyl acetate) gave 740 mg of the diastereomeric ester 153 as an oil. ^1H NMR consistent with structure.

(*R* and *S*)-1-Phenyl-7-(2-pyridyl)-4-heptyl (*S*)-pipecolate (154). The amine 154 was synthesized by treating 740 mg (1.54 mmol) of the ester 153 with 2.0 mL of trifluoroacetic acid in 5.0 mL of CH_2Cl_2 as described above for the preparation of 123 in Example 1 giving 580 mg of the diastereomeric amine 154 as an oil. ^1H NMR consistent with structure.

(*R* and *S*)-1-Phenyl-7-(2-pyridyl)-4-heptanol (*S*)-N-methyloxalylpipecolate (155). To a solution of 48 mg (0.13 mol) of the amine 154 in 1.0 mL of CH_2Cl_2 at 0 °C was added 33 μL (0.19 mmol) of N,N-diisopropylethylamine and 14 μL (0.15 mmol) of

methyloxalyl chloride and the resulting solution was warmed to room temperature and allowed to stir overnight. The reaction mixture was diluted with ethyl acetate, washed with saturated NH_4Cl and brine, dried over $MgSO_4$ and then concentrated. Flash chromatography (elution with 25-30% ethyl acetate in hexane) gave 49 mg of the diastereomeric amide 155 as a mixture of rotamers. ^1H NMR consistent with structure.

(*R* and *S*)-1-Phenyl-7-(2-pyridyl)-4-heptanol (*S*)-N-(*tert*-butylglyoxyl)-pipecolate (21). To a solution of the amide 155 in 1.2 mL of THF at -78 °C was added *tert*-butyl lithium dropwise until TLC showed the consumption of the starting material. The reaction mixture was quenched with saturated NH_4Cl and partitioned with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 30% ethyl acetate in hexane) gave the diasteromeric amide 21 as a mixture of rotamers. ^1H NMR (500 Mhz, $CDCl_3$) δ 8.50 (5), 7.57 (5), 7.20-7.05 (m), 5.23 (d), 5.18 (d), 4.56 (d), 4.44 (br d), 4.13 (d), 3.69 (br d), 3.37-3.28 (m), 3.13-3.00(m), 2.85-2.70 (m), 2.65-2.54 (m), 2.38-2.15 (m), 1.82-1.65(m), 1.56-1.44(m), 1.55-1.30(m), 1.27(s), 1.21 (s).



21

Example 8

Synthesis of (*S*)-1-[2-Oxo-2-(3,4,5-trimethoxyphenyl)acetyl]piperidine-2-carboxylic acid (R and S)-1-(3-phenylpropyl)-4-pyridin-3-yl-butyl ester (9).

(*E* and *Z*)-3-(1,3-Dioxan-2-yl)-1-(3-pyridyl)-1-propene (156). To a suspension of 9.9 g (22.4 mmol) of [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide (Aldrich Chemical Co.) in 50 mL of THF at 0 °C was added 14.0 mL (22.4 mmol) of butyl lithium (1.6 M in hexanes) and the resulting red solution was allowed to stir at 0 °C for 0.5 h. To this solution was added 1.8 mL (18.7 mmol) of 3-pyridinecarboxaldehyde (Aldrich Chemical Co.) and the reaction mixture was allowed to stir at room temperature for 1.5 h and was then poured into water and partitioned with ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 2:1 hexane:ethyl acetate) gave 3.3 g of the alkene 156 as a mixture of olefin isomers. ^1H NMR consistent with structure.

1-(1,3-Dioxan-2-yl)-3-(3-pyridyl)propane (157). Through a solution of 3.2 g (16.7 mmol) of olefin 156 and 300 mg of 10% palladium on carbon was bubbled a steady stream of hydrogen gas for a period of 10 min. The reaction mixture was then filtered through celite and concentrated to give 2.8 g of the acetal 157 as a colorless oil. ^1H NMR consistent with structure.

4-(3-Pyridyl)-1-butyraldehyde (158). A solution of 1.5 g (7.8 mmol) of acetal 157 in 10.0 mL of THF and 10.0 mL of 4N HCl was stirred overnight at room temperature and was then neutralized by the slow addition of solid $NaHCO_3$. The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$ and

concentrated to yield 1.1 g of the aldehyde 158. ^1H NMR consistent with structure.

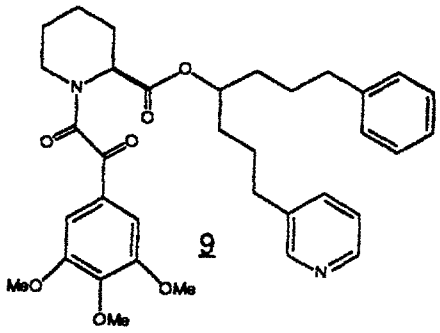
(*R* and *S*)-1-Phenyl-7-(3-pyridyl)-4-heptanol (159). The alcohol 159 was prepared from 1.1 g (7.4 mmol) of aldehyde 158 and 8.1 mL (8.1 mmol) of 120 in 30.0 mL of THF as described above for the synthesis of 121 in Example 1 to give 1.9 g of the crude alcohol 159. ^1H NMR consistent with structure.

(*S*)-Boc-Pipecolyl-(*R* and *S*)-1-Phenyl-7-(3-pyridyl)-4-heptyl ester (160). The ester 160 was prepared from 1.65 g (6.12 mmol) of alcohol 159, 1.54 g (6.73 mmol) of (*S*)-Boc-pipecolic acid, 1.29 g (6.73 mmol) of EDC and a catalytic amount of DMAP in 8.0 mL of CH_2Cl_2 and 8.0 mL of DMF as described above for the synthesis of 122 in Example 1. Flash chromatography (elution with 2:1 hexane:ethyl acetate) gave 1.42 g of the diastereomeric ester 160 as an oil. ^1H NMR consistent with structure.

(*R* and *S*)-1-Phenyl-7-(3-pyridyl)-4-heptyl (*S*)-pipecolate (161). The amine 161 was synthesized by treating 1.42 g (2.95 mmol) of the ester 160 with 2.0 mL of trifluoroacetic acid in 8.0 mL of CH_2Cl_2 as described above for the preparation of 123 in Example 1 giving 1.02 g of the diastereomeric amine 161 as an oil. ^1H NMR consistent with structure.

(*R* and *S*)-1-Phenyl-7-(3-pyridyl)-4-heptyl (*S*)-N-(3,4,5-trimethoxy-phenylglyoxyl)pipecolate (9). The ester 9 was prepared from 995 mg (2.61 mmol) of the amine 161, 645 mg (2.87 mmol) of the acid 124 and 551 mg (2.87 mmol) of EDC in 6.0 mL of CH_2Cl_2 as described above in the synthesis of ester 3 in Example 1. Flash

chromatography (elution with 3:1 acetone:hexane) gave 976 mg of the diasteromeric amide 9 as a mixture of rotamers. ^{1}H NMR consistent with structure.

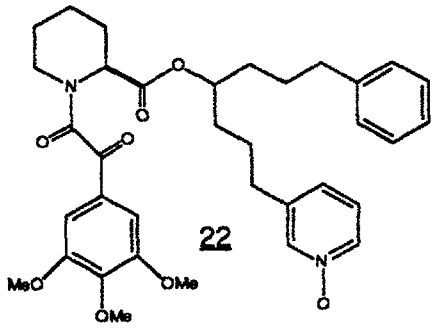


9

Example 9

Synthesis of (*R* and *S*)-1-Phenyl-7-(3-pyridyl)-4-heptyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate N-oxide (22).

(*R* and *S*)-1-Phenyl-7-(3-pyridyl)-4-heptyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate N-oxide (22). To a solution of 15 mg (0.02 mmol) of the amide 9 in 2.0 mL of CH_2Cl_2 at room temperature was added 9.3 μL (0.03 mmol) of 55% 3-chloroperoxybenzoic acid and the resulting solution was allowed to stir overnight at room temperature. Flash chromatography (elution with 100% acetone) gave 12.6 mg of the N-oxide 22 as a mixture of rotamers. ^{1}H NMR (500MHz $CDCl_3$) δ 8.10 (m), 7.46-7.02 (m), 5.88 (d), 5.80 (d), 5.06-5.00 (m), 4.95-4.89 (m), 4.61 (m), 4.31 (dd), 3.87 (s), 3.84 (s), 3.83 (s), 3.81 (s), 3.78 (s), 3.50 (br d), 3.27 (ddd), 3.12 (ddd), 3.00 (ddd), 2.67-2.49 (m), 2.32 (br d), 1.86-1.78 (m), 1.5501.50 (m), 1.39-1.22 (m).



22

Example 10

Synthesis of (*R* and *S*)-1-Phenyl-7-purinyl-4-heptyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (25).

4-Chlorobutyraldehyde (162). To a solution of 19.1 g (0.16 mol) of 4-chloro-1-butanol (Aldrich Chemical Co.) in 50 mL of CH_2Cl_2 at 0 °C was added 1.0 g of powdered 4 Å molecular sieves and 38.7 g (0.18 mol) of pyridinium dichromate and the resulting suspension was stirred at 0 °C for 45 min. The reaction mixture was diluted with ether, filtered through celite and concentrated. The residue was vacuum distilled (bp 45-55 °C) to yield 5.0 g of the aldehyde 162 as an oil. ^1H NMR consistent with structure.

(*R* and *S*)-1-Chloro-7-phenyl-4-heptanol (163). The alcohol 163 was prepared from 182 mg (1.7 mmol) of aldehyde 162 and 1.9 mL (1.9 mmol) of 120 in 20.0 mL of THF as described above for the synthesis of 121 in Example 1 to give 128 mg of the alcohol 163 (flash chromatography in 100% methylene chloride). ^1H NMR consistent with structure.

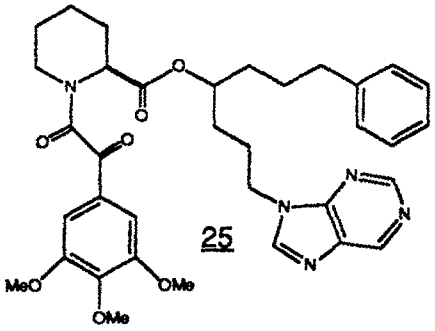
(*S*)-Boc-Pipecolyl-(*R* and *S*)-1-Chloro-7-phenyl-4-heptyl ester (164). The ester 164 was prepared from 128 mg (0.56 mmol) of alcohol 163, 156 mg (0.68 mmol) of (*S*)-Boc-pipecolic acid, 1380 mg (0.68 mmol) of EDC and a catalytic amount of 4-pyrrolidinopyridine in 2.0 mL of CH_2Cl_2 as described above for the synthesis of 122 in Example 1. Flash chromatography (elution with 1:5:14 ether: methylene chloride: hexane) gave 159 mg of the diastereomeric ester 164. ^1H NMR consistent with structure.

(*S*)-Boc-Pipecolyl-(*R* and *S*)-1-Phenyl-7-purinyl-4-heptyl ester (165). To a solution of 34 mg (0.28 mmol) of purine in 3.0 mL of DMF at room temperature was added 8.4 mg (0.28 mmol) of solid NaH (80% in mineral oil) and the resulting solution was allowed to stir at room temperature for 10 min. To this reaction mixture was added 62 mg (0.14 mmol) of the ester 164 and 10 mg of NaCl and this mixture was stirred overnight at room temperature and then concentrated to dryness. The residue was dissolved into ethyl acetate, washed sequentially with water, saturated $NaHCO_3$, and brine and then dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 15% 5:10:85 NH_4OH:MeOH:CH_2Cl_2 in CH_2Cl_2) gave 56 mg of the substituted purine 165 as an oil. ^1H NMR consistent with structure.

(*R* and *S*)-1-Phenyl-7-purinyl-4-heptyl (*S*)-pipecolate hydrochloride salt (166). Anhydrous HCl was bubbled into a solution of 53.7 mg (0.10 mmol) of the ester 165 in 10 ml of EtOAc at -20 °C for 10 min and then the reaction mixture was purged with N_2. Concentration gave the crude amine 166 as the hydrochloride salt. ^1H NMR consistent with structure.

(*R* and *S*)-1-Phenyl-7-purinyl-4-heptyl (*S*)-N-(3,4,5-trimethoxyphenylglyoxyl)pipecolate (25). To a slurry of the crude amine hydrochloride 166 in CH_3CN at room temperature was added 45 μL (0.26 mmol) of N,N-diisopropylethylamine, 37 mg (0.15 mmol) of acid 124, and 54 mg (0.12 mmol) of the BOP reagent and the resulting mixture was stirred at room temperature for two days and then was concentrated to dryness. The residue was reconstituted into 75 mL of ethyl acetate

and then sequentially washed with water, 5% $KHSO_4$, saturated $NaHCO_4$ and brine and then dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 1:4:36 MeOH:Et_2O:CH_2Cl_2) gave 26.5 mg of the diastereomeric amide 25 as a rotameric mixture. ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (s), 8.95 (m), 8.09 (m), 7.36-7.05 (m), 5.31 (m), 4.28 (m), 3.90 (m), 3.46 (br t), 3.20 (m), 2.58 (m), 2.28 (br d), 2.17-1.18 (m), R_f 0.1 (30% ether in methylene chloride).



25

Example 11

Synthesis of (S)-1-[2-Oxo-2-(3,4,5-trimethoxyphenyl)-acetyl]piperidine-2-carboxylic acid (*R* and *S*)-4-[4-(morpholine-4-carbonyl)phenyl]-1-(3-phenylpropyl)butyl ester (44).

4-Formylbenzoic acid methyl ester (167). To a suspension of 9.6 g (63.6 mmol) of 4-carboxybenzaldehyde (Aldrich Chemical Co.) in 100 mL of CH_2Cl_2 at 0 °C was added excess trimethylsilyldiazomethane and the resulting mixture was allowed to stir at 0 °C for 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to give 4.3 g of the ester 167 as an oil. ^1H NMR consistent with the product.

(*E* and *Z*)-4-[3-[1,3]-Dioxolan-2-yl-propenyl)-benzoic acid methyl ester (168). The olefin was

prepared from 4.3 g (26.2 mmol) of the aldehyde 167, 13.94 g of [1-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide and 12.6 mL (32.0 mmol) of *n*-BuLi in 75 mL of THF as described for the synthesis of 156 in Example 8. Flash chromatography (elution with 10% ethyl acetate in hexane) gave 3.27 g of the olefin 168. ^{1}H NMR consistent with the product.

4-[3-[1,3]-Dioxolan-2-yl-propyl)benzoic acid methyl ester (169). The olefin 169 (3.21 g, 12.9 mmol) was hydrogenated over 328 mg of 10% Pd/C in 50 mL of EtOH as described for compound 157 in Example 8. Filtration and evaporation gave 2.85 g of 169 as an oil. ^{1}H NMR consistent with the product.

[4-(3-[1,3]-Dioxan-2-yl-propyl)phenyl]-methanol (170). To a solution of 2.85 g (11.4 mmol) of ester 169 in 25 mL of THF at 0 °C was added 4.4 mL (24.7 mmol) of diisobutylaluminum hydride and the resulting mixture was allowed to stir at 0 °C for 15 min. The reaction was quenched with saturated potassium sodium tartrate and extracted three times with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to yield 2.58 g of the crude alcohol 170 as an oil. ^{1}H NMR consistent with the product.

2-[3-(4-*tert*-Butyldiphenylsilyloxymethyl-phenyl)propyl]-[1,3]-dioxolane (171). To a solution of 2.58 g (11.6 mmol) of alcohol 170 and 1.19 g (17.5 mmol) of imidazole in 50 mL of CH_2Cl_2 was added 3.4 mL (13.1 mmol) of *tert*-butylchlorodiphenyl silane and the resulting mixture was allowed to stir at room temperature for 1 h. The mixture was then diluted with ethyl acetate and washed with 0.5 N HCl. The organic

layer was dried over $MgSO_4$, filtered and concentrated. Flash chromatography (elution with 5% ethyl acetate in hexane) afforded 5.5 g of 171. ^1H NMR consistent with the product.

4-(4-tert-Butyldiphenylsilyloxymethylphenyl) butyraldehyde (172). To a solution of 5.5 g (11.9 mmol) of the dioxolane 171 in 40 mL of THF at room temperature was added 40 mL of 4.0N HCl and the resulting solution was allowed to stir for 1 h. The mixture was neutralized with solid K_2CO_3, extraced with ethyl acetate and concentrated. The crude mixture was dissolved into 25 mL of CH_2Cl_2 to which was added 600 mg (8.8 mmol) of imidazole and 1.9 mL (7.3 mmol) of *tert*-butylchlorodiphenyl silane. The resulting mixture was allowed to stir overnight at room temperature and was then poured into 0.5 N HCl and extracted with ethyl acetate. The organics were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (elution with 8% ethyl acetate in hexane) gave 2.12 g of the aldehyde 172 as an oil. ^1H NMR consistent with the product.

1-(4-*tert*-Butyldiphenylsilyloxymethylphenyl)-7-phenyl-heptan-4-ol (173). The alcohol 173 was prepared from 2.12 g (5.0 mmol) of 172 and 9.0 mL (9 mmol) of 120 in 50 mL of THF as described for the synthesis of 121 in Example 1. Flash chromatography (elution with 10% ethyl acetate in hexane) gave 3.3 g of the alcohol 173. ^1H NMR consistent with the product.

(*S*)-Piperidine-1,2-dicarboxylic acid (*R* and *S*)-2-[4-(4-*tert*-butyldiphenylsilyloxymethylphenyl)-1-(3-phenylpropyl)butyl] ester 1-tert-butyl ester (174). The ester 174 was prepared from 3.3 g (6.15 mmol) of

alcohol 173, 1.7 g (7.4 mmol) of (S)-Boc-pipecolic acid, 1.4 g (7.3 mmol) of EDC and a catalytic amount of DMAP in 35 mL of CH_2Cl_2 as described above for the synthesis of 122 in example 1. Flash chromatography (elution with 5% ethyl acetate in hexame) provided 2.4 g of the ester 174. ^1H NMR consistent with the product.

(S)-Piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (*R* and *S*)-2-[4-(4-hydroxymethylphenyl)-1-(3-phenylpropyl)butyl] ester (175). To a solution of 750 mg (1.0 mmol) of the ester 174 in 10 mL of THF was added 1.1 mL (1.1 mmol) of a solution of tetrabutylammonium fluoride (1.0 M in THF) and the resulting mixture was allowed to stir at room temperature for 15 min. The mixture was diluted with ethyl acetate, washed with 5% $KHSO_4$, dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 20% ethyl acetate in hexane) gave 308 mg of the alcohol 175. ^1H NMR consistent with the product.

(S)-Piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (*R* and *S*)-2-[4-(4-carboxyphenyl)-1-(3-phenylpropyl) butyl] ester (176). To a solution of 326 mg (0.64 mmol) of the alcohol 175 in 3.0 mL of acetone was added 0.5 mL (1.27 mmol) of the Jones reagent and the resulting mixture was allowed to stir at room temperature for 1 h, and was then filtered through a pad of celite and concentrated. Flash chromatography (elution with 2% MeOH in CH_2Cl_2) gave 155 mg of the acid 176. ^1H NMR consistent with the product.

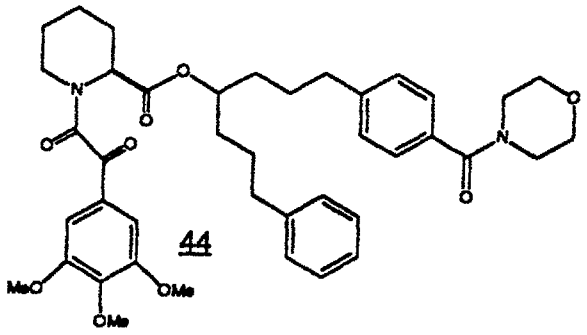
(S)-Piperidine-2-carboxylic acid (*R* and *S*)-4-(4-carboxyphenyl)-1-(3-phenylpropyl)butyl ester Trifluoroacetate salt (177). To a solution of 155 mg

(0.3 mmol) of the acid 176 in 3.0 mL of CH_2Cl_2 was added 500 μL of trifluoroacetic acid and the resulting solution was allowed to stir at room temperature for 3 h at which time the volatiles were removed *in vacuo*. The crude residue was suspended in 5.0 mL of dry benzene and the volatiles were removed to yield an anhydrous sample of the salt 177.

(*S*)-1-[2-Oxo-2-(3,4,5-trimethoxyphenyl)-acetyl]piperidine-2-carboxylic acid (*R* and *S*)-4-(4-carboxyphenyl)-1-(3-phenylpropyl)butyl ester (178). To a suspension of 159 mg (0.3 mmol) of the salt 177 in 2.5 mL of CH_2Cl_2 at 0 °C was added 110 μL (0.63 mmol) of N,N-diisopropylethylamine and then 40 μL (0.31 mmol) of chlorotrimethylsilane and the resulting mixture was allowed to stir at 0 °C for 30 min. To this solution was added 85 mg (0.44 mmol) EDC and 106 mg (0.44 mmol) of the acid 124 and the reaction mixture was allowed to stir at room temperature overnight. The mixture was diluted with ethyl acetate and washed with 0.5N HCl, water, brine, dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 30% MeOH in CH_2Cl_2) gave 97 mg of the product 178 as a mixture of rotamers. ^1H NMR consistent with the product.

(*S*)-1-[2-Oxo-2-(3,4,5-trimethoxyphenyl)-acetyl]piperidine-2-carboxylic acid (*R* and *S*)-4-[4-(morpholine-4-carbonyl)phenyl]-1-(3-phenylpropyl)butyl ester (44). To a solution of 11.2 mg (17 μmol) of the acid 178 in 1.0 mL of CH_2Cl_2 was added 4.1 mg (21.4 μmol) of EDC and 1.8 mg (20.7 μmol) of morpholine and the resulting solution was allowed to stir overnight at room temperature. Flash chromatography (elution with 20% MeOH in CH_2Cl_2) gave 7.6 mg of the amide 44 as a mixture of rotamers. ^1H NMR (500MHz $CDCl_3$) δ 7.32 (d),

7.30 (d), 7.26 (s), 7.21-7.08 (m), 5.33 (m), 5.01 (m), 4.92 (m), 3.92 (s), 3.89 (s), 3.88 (s), 3.87 (s), 3.86 (s), 3.85 (s), 3.81-3.53 (m), 3.42 (brd), 3.29-3.21 (m), 3.05 (m), 2.61 (m), 2.42 (dd), 2.31 (d), 2.12 (m), Y1.83 (m), 1.73-1.42 (m), 1.42-1.20 (m).



44

Example 12 -- NMR DATA

We have prepared other compounds of formula (I) by methods substantially similar to those described in the above Examples 1-11 and those illustrated in Schemes 1-3. The NMR spectral data for these compounds are summarized below. Compounds are numbered according to the numbering scheme of Table 1.

Compound 2: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.42-8.33(m), 7.51(d), 7.42(d), 7.38(s), 7.31(d), 7.29-7.05(m), 5.01(s,br), 4.8(m), 4.71(m), 4.62(m), 3.92-3.83(m), 3.81(d), 3.60-3.51(m), 3.50-3.45(m), 2.65-2.51(m), 2.50-2.39(m), 2.38-2.22(m), 2.05(m), 1.95(m), 1.81-1.68(m), 1.67-1.49(m), 1.48-1.31(m), 1.22(s).

Compound 5: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.39-6.80(m), 6.75(d), 5.47(m), 4.55(m), 4.45(m), 3.95-3.78(m), 3.49-3.40(m), 3.22-3.11(m), 2.49-2.38(m), 1.88-1.67(m), 1.61-1.42(m), 1.37-1.14(m).

Compound 6: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.36-7.19(m), 7.18-7.02(m), 5.77(t), 5.65(m), 5.39(m), 4.60-4.52(m), 4.35(m), 3.93-3.82(m), 3.71-3.63(m), 3.48-3.42(m), 3.41-3.34(m), 3.28-3.19(m), 3.12-3.07(m), 2.65-2.58(m), 2.57-2.48(m), 2.42-2.31(m), 2.02-1.94(m), 1.91-1.21(m), 1.11-1.02(m).

Compound 10: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.35-6.98(m), 5.35(d), 5.3-5.14(m), 4.52(bd), 4.24(bs), 3.97-3.87(m), 3.49(t), 3.12(q), 3.00-2.56(m), 2.46(t), 2.32(d), 2.18(d), 2.11(d), 1.93(d), 1.83-1.56(m), 1.55-1.38(m), 1.32-1.18(m), 0.94-0.72(m).

Compound 12: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.37(s), 7.31-7.06(m), 6.98(d), 5.39(dd), 5.09-5.00(m), 4.99-4.93(m),

4.73(d), 4.38(m), 3.98-3.86(m), 3.91(s), 3.50(d), 3.34-3.24(m), 3.09(t), 2.73-2.16(m), 2.02-1.24(m).

Compound 13: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.38(s), 7.29-7.21(m), 7.20-7.03(m), 6.99(d), 6.88(d), 6.82-6.73(m), 5.40-5.32(m), 5.04-4.98(m), 4.97-4.91(m), 4.61(d), 4.37(d), 3.93-3.83(m), 3.81-3.74(m), 3.53-3.47(d,br), 3.32-3.22(m), 3.11-3.04(m), 2.65-2.12(m), 1.97-1.21(m).

Compound 14: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.04(d), 7.97(t), 7.59-7.48(m), 7.47-7.41(m), 7.31-7.22(m), 7.21-7.02(m), 6.98-6.91(m), 6.82-6.76(m), 5.43-5.38(m), 5.12-5.03(m), 4.93(m), 4.65-4.60(m), 4.38(m), 3.79(m), 3.53-3.48(m), 3.23(q), 3.11-2.99(m), 2.68-2.29(m), 2.19(t), 1.98-1.31(m).

Compound 15: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.05-7.92(m), 7.78(d), 7.47-7.03(m), 6.42(bs), 5.33(d), 5.01(m), 4.94(m), 4.59(bd), 4.32-4.14(m), 4.08-4.00(m), 3.97-3.84(m), 3.77-3.68(m), 3.45(bd), 3.17-3.08(m), 2.97(t), 2.60(t), 2.48(t), 2.35-2.21(m), 2.11(d), 2.05-1.10(m), 0.91-0.79(m).

Compound 17: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.38-6.92(m), 6.82-6.71(m), 5.38-5.29(m), 5.06-4.85(m), 4.60(d), 4.31(d), 3.94-3.81(m), 3.79-3.70(m), 3.51-3.41(m), 3.23(t,br), 3.06(t), 2.62-2.22(m), 2.15(d), 1.82-1.29(m).

Compound 18: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.55-8.38(m), 8.08-8.00(m), 7.98(d), 7.68(t), 7.59(t), 7.50-7.45(m), 7.45-7.41(m), 7.29-7.25(m), 7.25-7.08(m), 5.40(m), 5.11(m), 4.93(m), 4.61(brd), 4.38(m), 3.61(m), 3.51-3.46(m), 3.26-3.15(m), 3.08-2.96(m), 2.70-2.61(m),

2.58-2.49(m), 2.38(brd), 2.19(brd), 1.83-1.78(m), 1.78-1.59(m), 1.56-1.43(m), 1.41-1.24(m).

Compound 19: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.52-8.49(m), 8.04(d), 7.96(d), 7.64(t), 7.61-7.57(m), 7.52(t), 7.46-7.41(m), 7.26-7.22(m), 7.17(t), 7.12-7.08(m), 5.41(d), 5.12(m), 4.93(m), 4.61(brd), 4.38(d), 3.89-3.83(m), 3.67-3.61(m), 3.53-3.48(m), 3.28-3.19(m), 3.06-3.00(m), 2.83(brt), 2.72(brt), 2.65(brt), 2.52(brt), 2.48(brd), 2.21(brd), 1.89-1.73(m), 1.73-1.70(m), 1.70-1.48(m), 1.48-1.33(m).

Compound 20: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.50(d), 7.61(dd), 7.28-7.25(m), 7.21-7.16(m), 7.12(dd), 5.38(brd), 5.09-5.02(m), 4.93-4.90(m), 4.62(brd), 4.34(m), 3.94(s), 3.92(s), 3.91(s), 3.90(s), 3.89(s), 3.49(brddd), 3.28(ddd), 3.09(dd), 2.83(t), 2.74(m), 2.63(brd), 2.49(dd), 2.36(brd), 2.19(brd), 1.86-1.70(m), 1.70-1.62(m), 1.59-1.52(m), 1.48-1.23(m).

Compound 23: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.30(d), 8.28(d), 7.79(d), 7.34(s), 7.31-7.00(m), 6.43(s), 5.33(d), 5.06(d), 4.94(m), 4.59(d), 4.42-4.10(m), 4.04(s), 3.96(s), 3.94(s), 3.91(s), 3.81(s), 3.77(s), 3.48(d), 3.27(dt), 3.05(dt), 2.67-2.47(m), 2.32(d), 2.14(d), 2.03-1.22(m), 0.94-0.81(m).

Compound 26: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.32(d), 7.27-6.99(m), 5.34-5.28(m), 5.00(s,br), 4.61(d), 4.30(d), 3.92-3.81(m), 3.02(t), 2.54-2.48(m), 2.47-2.39(m), 2.34-2.22(m), 2.14(d), 1.82-1.14(m).

Compound 27: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.46-8.38(m), 7.68-7.50(m), 7.49-7.30(m), 7.29-7.08(m), 5.48(m), 5.16-5.02(m), 4.98-4.90(m), 4.60(d), 4.32(d), 3.51-

3.42(m), 3.26-3.12(m), 3.11-2.98(m), 2.65-2.42(m), 2.32(d,br), 2.14(d,br), 1.83-1.22(m).

Compound 28: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.45-8.32(m), 7.62-7.53(m), 7.52-7.43(m), 7.42-7.05(m), 6.09-5.98(m), 5.44-5.25(m), 5.09(s,br), 4.92(s,br), 4.64-4.51(m), 4.31(d), 3.50-3.41(m), 3.24-3.12(m), 3.07-2.94(m), 2.68-2.45(m), 2.32(d,br), 2.14(d,br), 1.83-1.26(m).

Compound 29: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.44-8.37(m), 7.58-7.51(m), 7.50-7.08(m), 5.35(t,br), 5.10(s,br), 4.93(s,br), 4.68-4.54(m), 4.32(d), 3.51-3.42(m), 3.25-3.12(m), 3.00(q), 2.69-2.45(m), 2.38-2.29(m), 2.14(d,br), 1.82-1.20(m).

Compound 30: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.35(s), 7.29-7.20(m), 7.19-7.02(m), 6.89(m), 6.77(m), 5.34(d), 5.03(m), 4.91(m), 4.61(d), 4.33(d), 3.95-3.88(m), 3.48(d), 3.31-3.21(m), 3.05(t,br), 2.87-2.43(m), 2.32(d,br), 2.18(d,br), 1.87-1.21(m).

Compound 31: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.00(s,br), 7.34(s,br), 7.31-7.02(m), 5.34(s,br), 5.31(s,br), 5.03(s,br), 4.92(d,br), 4.61(d,br), 4.33(s,br), 3.96-3.84(m), 3.48(d,br), 3.24(s,br), 2.76-2.42(m), 2.32(d,br), 2.15(m), 1.87-1.20(m).

Compound 32: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.38(d), 7.30-7.08(m), 7.07-7.03(d), 5.35-5.31(m), 4.98(m), 4.88(m), 4.59(m), 4.31(m), 3.97-3.86(m), 3.46(d,br), 3.29-3.18(m), 3.04(m), 2.65-2.42(m), 2.35-2.22(m), 1.83-1.14(m), 1.10(m).

Compound 33: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.38(d), 7.32-7.24(m), 7.24(d), 7.21(d), 7.01(s), 7.00(s), 6.02-

5.99(m), 5.92-5.88(m), 5.38(d), 5.36(d), 4.70(ABq), 4.69(ABq), 4.64(ABq), 4.32(brd), 3.91(s), 3.89(s), 3.88(s), 3.74(s), 3.73(s), 3.48(brddd), 3.36(brd), 3.20(ddd), 3.06-2.97(m), 2.62(t), 2.58(t), 2.38(brd), 2.21(brd), 2.08-2.04(m), 1.90-1.74(m), 1.73-1.46(m), 1.38-1.33(m), 1.24(t).

Compound 34: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.33(s), 7.30(d), 7.29(s), 7.28-7.20(m), 7.18-7.11(m), 6.95-6.90(m), 6.83(d), 6.82(d), 6.31-6.28(m), 6.02-5.91(m), 5.43-5.40(m), 5.21(dd), 4.53(d), 3.91(s), 3.89(s), 3.86(s), 3.85(s), 3.84(s), 3.76(s), 3.71(s), 3.45(brddd), 3.40(brddd), 3.28(ddd), 3.15(ddd), 3.02(ddd), 2.62(dd), 2.40(brd), 1.94-1.89(m), 1.87-1.67(m), 1.65-1.50(m).

Compound 35: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.34-7.29(m), 7.28-7.11(m), 7.10-6.93(m), 5.35-5.28(m), 5.09-4.98(m), 4.90(m), 4.64-4.44(m), 4.30(m), 3.95-3.81(m), 3.46(t,br), 3.31-3.19(m), 3.03(m), 2.66-2.38(m), 2.34-2.25(m), 2.16(m), 1.85-1.19(m).

Compound 36: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.93-7.81(m), 7.78(s), 7.41-7.01(m), 5.32(s,br), 5.02(s,br), 4.90(m), 4.58(d), 4.31(s,br), 3.95-3.80(m), 3.45(d), 3.22(t), 3.05(m), 2.72-2.48(m), 2.47(d), 1.83-1.43(m), 1.42-1.18(m).

Compound 37: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.38(s), 7.30(s), 7.30-7.02(m), 7.01(s), 5.80-5.83(m), 5.68(dd), 5.62(dd), 5.38(d), 5.36(d), 4.66(s), 4.65(ABq), 4.54(s), 4.32(brd), 4.28(brd), 3.90(s), 3.88(s), 3.86(s), 3.85(s), 3.84(s), 3.78(s), 3.76(s), 3.43(brddd), 3.39(brddd), 3.24(ddd), 3.12(ddd), 3.06(ddd), 2.97(ddd), 2.62(t), 2.57(t), 2.48(brd),

2.24(brd), 2.01-1.94(m), 1.89-1.73(m), 1.72-1.65(m), 1.65-1.58(m), 1.52-1.49(m), 1.40-1.33(m), 1.12-1.08(m).

Compound 40: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.36(s), 7.29-7.19(m), 7.18-7.06(m), 6.89(m), 6.75(s), 5.32(s,br), 4.94(t), 3.95-3.84(m), 3.46(d,br), 3.22(m), 2.82(t), 2.61(t), 2.30(m), 1.82-1.19(m).

Compound 41: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.37(d), 7.29-7.08(m), 7.04(d), 5.34(m), 4.97(m), 4.61(d), 4.33(m), 3.96-3.88(t), 3.86(d), 3.48(d), 3.25(m), 3.09(m), 2.65-2.52(m), 2.48(m), 2.32(d), 2.18(d), 1.86-1.49(m), 1.48-1.15(m).

Compound 42: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.34(d), 7.2(m), 7.13(m), 7.0-7.1(m), 5.87(m), 5.32(m), 5.22(dd), 5.12(dd), 5.0(m), 4.89(bm), 4.57(bd), 4.30(bm), 3.80-3.95(m), 3.45(bd), 3.40(m), 3.32(m), 3.22(dt), 3.05(bm), 2.60(m), 2.52(bm), 2.44(m), 2.30(m), 2.15(bm), 1.75(m), 1.60(m), 1.54(m), 1.20-1.45(bm).

Compound 43: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.36-7.30(m), 7.29-7.20(m), 7.19-7.04(m), 5.34(m), 5.01(s,br), 4.91(m), 4.59(d), 4.31(s,br), 3.95-3.86(m), 3.47(d,br), 3.25(t,br), 3.14-2.90(m), 2.68-2.52(m), 2.45(t), 2.32(d), 2.18(d), 1.85-1.46(m), 1.45-1.18(m).

Compound 45: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.35(d), 7.25(m), 7.15(m), 7.10(d), 7.05(d), 5.87(m), 5.38(bd), 5.34(m), 5.22(dd), 5.14(dd), 4.95(bm), 4.88(bm), 4.58(bd), 4.32(m), 3.82-3.95(m), 3.45(bd), 3.40(t), 3.25(m), 3.05(bm), 2.60(bm), 2.44(m), 2.34(bd), 2.18(bd), 1.78(m), 1.48-1.70(m), 1.20-1.45(m).

Compound 46: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.32(s), 7.25(m), 7.16(m), 7.10(t), 5.85(m), 5.50(dt), 5.38(dd), 5.25(dd), 5.18(d), 4.58(bm), 4.35(bm), 4.15(s), 4.06(d), 4.02(d), 3.85-3.95(m), 3.46(bd), 3.25(m), 3.08(bt), 2.98(bt), 2.65(t), 2.58(t), 2.53(t), 2.35(bt), 2.20(bd), 1.70-1.88(m), 1.50-1.70(m), 1.20-1.42(m).

Compound 47: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.44(d), 7.42-7.06(m), 5.45-5.30(m), 5.12-4.91(m), 4.03-3.83(m), 3.82-3.19(m), 2.72-2.26(m), 1.91-1.22(m)

Compound 48: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.34(d), 7.25(m), 7.20(d), 7.15(m), 7.10(d), 7.05(d), 5.88(m), 5.32(bt), 5.24(dd), 5.14(dd), 4.96(m), 4.86(m), 4.58(bd), 4.30(bm), 3.85-3.95(m), 3.45(bd), 3.38(t), 3.32(t), 3.25(m), 3.05(m), 2.60(m), 2.32(bd), 2.16(bd), 1.78(m), 1.48-1.72(m), 1.20-1.45(m).

Compound 49: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.28-7.42, 6.57-6.61(m), 6.45-6.51(m), 5.80-5.87(dd), 5.70-5.77(dd), 5.37-5.41(brd), 5.34-5.37(brd), 4.94-5.07(dd), 4.53-4.60(brd), 4.35-4.38(m), 3.80-3.95(m), 3.74(s), 3.38-3.50(brdd), 3.22-3.31(ddd), 3.15-3.22(ddd), 2.96-3.08(m), 2.32-2.44(brdd), 1.73-1.85(m), 1.48-1.75(m), 1.54-1.56(d), 1.15-1.48(m).

Compound 50: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.34(d), 7.24(m), 7.15(m), 7.10(d), 7.04(d), 5.85(m), 5.32(m), 5.22(dd), 5.15(m), 5.00(m), 4.58(bd), 4.30(bs), 3.74-3.95(m), 3.44(m), 3.25(bt), 3.04(bm), 2.62(m), 2.45(t), 2.30(bd), 2.18(bd), 1.88(m), 1.78(m), 1.46-1.72(m), 1.22-1.45(m).

Compound 51: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.34(s), 7.25(m), 7.20(d), 7.14(m), 7.10(d), 7.06(d), 5.87(m), 5.78(dt), 5.68(m), 5.45-5.60(m), 5.35(d), 5.24(m), 5.15(d), 4.58(bd), 3.85-3.96(m), 3.45(m), 3.24(m), 3.04(m), 2.62(m), 2.56(t), 2.49(dt), 2.34(dt), 2.18(bm), 1.48-1.82(m), 1.24-1.40(m).

Compound 52: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.40-7.03(m), 5.38-5.28(m), 5.02(s,br), 4.90(m), 4.60(d), 4.32(s,br), 3.99-3.87(m), 3.86-3.31(m), 3.30-3.21(t,br), 3.11-3.02(q,br), 2.69-2.50(m), 2.47(m), 2.32(d), 2.14(d), 1.89-1.48(m), 1.47-1.21(m).

Compound 53: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.40(d), 7.35(d), 7.30(d), 7.28(s), 6.60(d), 6.55(d), 6.52(t), 6.49(t), 5.86(q), 5.78(q), 5.42(d), 5.08(s), 4.64(bd), 4.35(m), 3.88-3.98(m), 3.46(bd), 3.21(dt), 3.05(dt), 2.36(bd), 2.18(bd), 1.80(m), 1.74(bd), 1.64(s), 1.56(d), 1.48-1.55(m), 1.40(d), 1.15-1.30(m).

Compound 54: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.52(m), 7.82-7.71(m), 7.70-7.62(m), 7.55-7.42(m), 7.38-7.01(m), 5.36-5.29(m), 5.01(m), 4.90(m), 4.79-4.67(m), 4.59(d), 4.39-4.11(m), 3.96-3.73(m), 3.44(d), 3.22(t), 3.09-3.00(q,br), 2.72-2.41(m), 2.30(d), 2.14(d), 1.86-1.43(m), 1.42-1.02(m), 0.98-0.73(m).

Compound 55: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.38(d), 7.33(d), 7.29-7.02(m), 5.32(m), 5.01(m), 4.90(m), 4.59(m), 4.30(m), 4.08-3.51(m), 3.46(d), 329-3.18(m), 3.11-2.98(q,br), 2.81-2.32(m), 2.30(d), 2.14(d), 1.84-1.19(m).

Compound 56: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 7.39-7.30(m),

7.27-7.20(brs), 7.20-7.15(brt), 7.14-7.06(brd), 5.81-5.78(brt), 5.77-5.72(brt), 5.34-5.30(brd), 5.28(s), 4.60-4.55(brd), 5.33(brs), 3.91(s), 3.88(s), 3.80(brs), 3.79-3.48(m), 3.47-3.30(brd), 3.28-3.20(brt), 3.01-2.94(brt), 2.66-2.60(t), 2.59-2.54(t), 2.42-2.35(brd), 2.25-2.19(brd), 2.04-1.93(m), 1.89-1.73(m), 1.72-1.65(m), 1.64-1.57(m), 1.54(brs), 1.39-1.25(m), 1.20(brs).

Compound 57: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.32(d), 7.31-7.01(m), 5.31(m), 5.00(m), 4.90(m), 4.59(m), 4.30(m), 3.93-3.83(m), 3.82-3.63(m), 3.49-3.38(m), 3.22(t), 3.10-2.98(t), 2.68-2.21(m), 2.12(m), 1.82-1.21(m).

Compound 58: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.33-7.01(m), 5.31(m), 4.99(m), 4.89(m), 4.59(d), 4.29(m), 3.92-3.84(m), 3.83-3.64(m), 3.55-3.28(m), 3.22(t), 3.04(m), 2.63-2.22(m), 2.14(d), 1.81-1.21(m).

Compound 59: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.71-7.52(m), 7.42(m), 7.39-7.04(m), 6.72-6.59(m), 5.32(m), 5.22(m), 5.11(m), 5.01(m), 4.99-4.90(m), 4.69-4.52(m), 4.39-4.26(m), 3.99-3.79(m), 3.46(t), 3.22(t), 3.11-2.94(m), 2.72-2.40(m), 2.29(t), 2.20-2.11(m), 1.88-1.19(m), 0.89(m).

Compound 60: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.53(m), 7.80(m), 7.72-7.53(m), 7.39-7.03(m), 5.36-5.28(dd), 5.12-4.98(m), 4.92(m), 4.79-4.52(m), 4.31(m), 3.98-3.81(m), 3.45(m), 3.31-3.19(q,br), 3.11-3.00(m), 2.72-2.43(m), 2.31(d), 2.20-2.11(m), 1.88-1.22(m).

Compound 61: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.45(s,br), 7.60-7.49(m), 7.38-7.21(m), 5.38-5.31(m), 5.03-4.98(m),

3.99-3.88(m), 3.50(d,br), 3.29(q), 2.65(m), 2.38-2.31(m), 1.88-1.13(m), 0.92-0.74(m).

Compound 62: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.55-8.65(m), 7.32-7.40(m), 6.80-7.00(m), 5.74-5.78(m), 5.62-5.71(m), 5.85-5.89(brd), 5.80-5.84(brd), 5.13-5.21(m), 5.03-5.10(m), 4.77-4.81(dd), 3.87-3.94(m), 3.80(s), 3.79(s), 3.72(s), 3.38-3.46(brdd), 3.14-3.28(m), 2.66-2.83(m), 2.48-2.58(m), 2.28-2.48(m), 1.32-1.18(m).

Compound 63: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.62(d), 8.61-8.58(m), 7.64(dd), 7.59(dd), 7.32-7.24(m), 7.12(d), 6.92(dd), 6.89-6.83(m), 6.82(d), 6.79(d), 6.74(d), 5.48(d), 5.07(d), 4.60(m), 4.44(brdd), 3.91(s), 3.90(s), 3.86(s), 3.84(s), 3.83(s), 3.78(s), 3.44(brd), 3.18(ddd), 2.92(ddd), 2.40(brt), 2.32(brt), 1.89-1.70(m), 1.62-1.48(m).

Compound 64: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.59(d), 8.58(d), 7.32-7.04(m), 6.99-6.80(m), 5.62(dd), 5.61(dd), 5.38(dd), 5.06(s), 5.02(d), 4.99(d), 4.53(m), 4.36(m), 3.91(s), 3.90(s), 3.89(s), 3.88(s), 3.84(s), 3.69(s), 3.61(s), 3.46(brd), 3.41(brd), 3.24(dd), 3.12(dd), 2.62(t), 2.58(t), 2.34(brt), 1.99-1.92(m), 1.86-1.42(m).

Compound 66: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.56-8.51(m), 7.35-7.28(m), 7.27-7.22(m), 7.14(s), 7.07(s), 6.93-6.88(m), 6.87-6.80(m), 6.79-6.71(m), 6.65-6.62(m), 5.81(q), 5.71(q), 5.32-5.27(m), 5.20-4.98(m), 4.57-4.47(m), 4.28-4.23(m), 3.92-3.70(m), 3.40(brd), 3.20(brd), 3.11(ddd), 3.00-2.89(m), 2.33(d), 2.26(d), 2.20(d), 2.07(d), 1.80-1.57(m), 1.56-1.25(m), 1.24-1.17(m), 1.13-1.00(m).

Compound 67: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.63-8.54(m), 8.53-8.44(m), 7.38-7.11(m), 7.10-6.99(m), 6.78(d), 6.72(dd), 6.63(dd), 6.53(d), 6.44(d), 6.14(dd), 6.08(dd), 6.00(dd), 5.88(dd), 5.39(d), 5.31(d), 5.23-4.95(m), 4.61-4.50(m), 4.32-4.29(m), 3.91(s), 3.90(s), 3.88-3.74(m), 3.71(s), 3.64-3.58(m), 3.47-3.38(m), 3.37-3.32(m), 3.24(ddd), 3.13(ddd), 3.07(ddd), 2.94(ddd), 2.62-2.45(m), 2.38-2.29(m), 2.20-2.11(m), 2.00-1.88(m), 1.87-1.40(m), 1.39-1.08(m).

Compound 68: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.61(d), 7.38(d), 7.31(s), 7.28-7.22(m), 7.14(dd), 7.10(d), 7.04(d), 6.83(d), 5.23(dd), 5.14(dd), 5.36(d), 5.11(brs), 4.58(m), 4.31(m), 3.91(s), 3.90(s), 3.89(s), 3.88(s), 3.82-3.79(m), 3.78-3.64(m), 3.51-3.44(m), 3.40(brd), 3.26-3.10(m), 2.63(dd), 2.32(brd), 2.00-1.92(m), 1.88-1.40(m), 1.08-1.00(m).

Compound 69: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.60-8.57(m), 8.56-8.53(m), 7.38-7.35(m), 7.32-7.17(m), 6.53(s), 6.52(s), 5.83(q), 5.76(q), 5.38-5.32(m), 5.17-5.05(m), 4.67-4.60(m), 4.30-4.28(m), 4.13-4.08(m), 3.96-3.82(m), 3.80(s), 3.45(brd), 3.28(ddd), 2.97(ddd), 2.77-2.72(m), 2.53-2.43(m), 2.36-2.22(m), 2.15-1.92(m), 1.86-0.79(m).

Compound 70: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.59-8.43(m), 7.38-6.98(m), 6.65(s), 6.57(s), 6.53(m), 6.43(m), 5.88-5.84(m), 5.68-5.64(m), 5.63-5.59(m), 5.58-5.54(m), 5.35-5.28(m), 5.15-5.00(m), 4.99(d), 4.92(d), 4.58(d), 4.51(d), 4.33(d), 4.26(d), 3.89(s), 3.87(s), 3.83(s), 3.79(s), 3.72(s), 3.65(s), 3.45-3.37(m), 3.21(ddd), 3.10(ddd), 2.95-2.83(m), 2.62-2.42(m), 2.28(d), 2.21(d), 1.92-1.26(m), 1.17-1.12(m), 1.11-1.01(m).

Compound 71: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.64(d), 7.35(d), 7.28(s), 6.60(d), 6.55(d), 6.52(t), 6.49(t), 5.86(q), 5.78(q), 5.42(d), 5.08(s), 4.64(bd), 4.35(m), 3.88-3.98(m), 3.46(bd), 3.21(dt), 3.05(dt), 2.36(bd), 2.18(bd), 1.80(m), 1.74(bd), 1.64(s), 1.56(d), 1.48-1.55(m), 1.40(d), 1.15-1.30(m).

Compound 72: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.62(d), 7.35(d), 7.28(s), 6.60(d), 6.50(d), 6.45(t), 6.42(t), 5.85(q), 5.73(q), 5.40(d), 5.10(d), 5.04(d), 4.58(bd), 4.38(m), 3.92(s), 3.88(s), 3.82(s), 3.72(s), 3.50(bd), 3.30(dt), 3.01(dt), 2.40(bd), 2.30(bd), 1.85(m), 1.64(bs), 1.56(d), 1.48(d), 1.35-1.45(m).

Compound 73: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.55-8.65(brd), 7.32-7.42(brdd), 7.28(s), 7.20(s), 6.50-6.55(m), 5.72-5.87(m), 5.32-5.39(m), 5.05-5.17(m), 4.58-4.64(brd), 4.53-4.58(brd), 4.34-4.36(brd), 4.25-4.29(brd), 3.71-3.96(ms), 3.40-3.48(m), 3.23-3.30(ddd), 3.13-3.22(ddd), 2.17-2.37(m), 1.10-1.86(m), 1.48-1.52(d).

Compound 74: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.62-8.58(d), 8.57-8.51(d), 7.38-7.35(d), 7.33-7.28(m), 7.27(s), 7.18(s), 6.61(s), 6.59(s), 5.65-5.60(t), 5.55-5.50(t), 5.40-5.36(d), 5.18-5.05(m), 4.67-4.63(brd), 4.33-4.30(d), 3.96(s), 3.93(s), 3.92(s), 3.87(s), 3.50-3.43(brd), 3.25-3.16(dt), 3.05-2.97(dt), 2.32-2.28(brd), 2.14-2.08(brd), 1.95-1.85(m), 1.84-1.64(m), 1.63-1.56(brd), 1.55-1.42(m), 1.35-1.23(m), 1.22-1.12(m), 0.92-0.83(t), 0.73-0.68(t).

Compound 75: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.62-8.58(m), 8.57-8.53(d), 7.41-7.39(d), 7.38-7.35(d), 7.27(s),

7.23(s), 7.13(s), 6.61(s), 6.51(s), 5.60-5.55(t), 5.54-5.50(t), 5.39-5.35(d), 5.15(s), 5.14-5.10(m), 5.09(s), 5.07(s), 5.01(s), 5.00(s), 4.60-4.55(brd), 4.51-4.49(t), 4.40-4.38(brd), 3.90(s), 3.85(s), 3.80(s), 3.73(s), 3.48-3.43(brd), 3.30-3.22(dt), 2.95-2.88(dt), 2.38-2.32(brd), 2.27-2.22(brd), 1.90-1.70(m), 1.69-1.62(brd), 1.59-1.50(m), 1.46-1.35(m), 1.26(s), 0.90-0.85(t), 0.82-0.78(t).

Compound 76: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.95(s), 8.80(d), 8.55(m), 8.50(m), 7.34(s), 7.30(s), 7.28(s), 6.76(s), 6.73(s), 5.85(q), 5.77(q), 5.40(m), 5.20-5.35(m), 4.60(m), 4.35(m), 3.85-3.98(m), 3.80(s), 3.48(bt), 3.18-3.30(m), 3.00(m), 2.40(bd), 2.32(bd), 2.26(bd), 1.65-1.90(m), 1.60(s), 1.55(dd), 1.48(d), 1.40(m), 1.12(m).

Compound 77: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.43-8.53(m), 7.20-7.56(m), 7.04(s), 7.01(s), 6.75-6.92(m), 6.62(brs), 5.78-5.85(m), 5.68-5.77(m), 5.80-5.84(brd), 5.02-5.12(m), 3.76-4.00(m), 3.64-3.76(m), 3.49-3.60(m), 3.38-3.49(m), 3.32-3.34(d), 3.21-3.27(m), 3.02-3.18(m), 2.73-2.82(m), 2.37-2.53(m), 2.24-2.32(m), 2.20(s), 2.15(s), 1.27-1.72(m), 1.07-1.22(m), 0.92-0.97(dd), 0.82-0.86(dd).

Compound 78: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.65-8.56(d), 8.55-8.51(d), 7.40-7.35(d), 7.34-7.20(m), 7.16(s), 6.70-6.60(m), 6.21-6.18(d), 6.15-6.11(d), 5.97-5.88(m), 5.83-5.75(m), 5.45-5.40(d), 5.32(s), 5.28(s), 5.27(s), 5.21-5.18(m), 5.13(s), 5.11(s), 4.67-4.61(brd), 4.51-4.49(d), 4.35-4.33(d), 4.05-4.00(m), 3.95(s), 3.94(s), 3.90(s), 3.84-3.82(d), 3.81(s), 3.66-3.60(q), 3.50-3.45(brd), 3.40(s), 3.30(s), 3.23-3.17(dt), 3.03-2.97(brt), 3.86-3.80(brt), 2.60-2.55(brt), 2.50-

2.40(m), 2.30-2.25(brd), 2.20(s), 2.15-2.10(brd), 1.90-1.65(m), 1.64-1.60(brd), 1.56-1.43(m), 1.36-1.27(m), 1.26-1.11(m).

Compound 79: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.65-8.59(d), 8.58-8.52(d), 7.40-7.35(d), 7.32-7.28(d), 7.25-7.24(d), 7.13(s), 6.65(s), 6.60(s), 6.20-6.18(d), 6.12-6.10(d), 5.97-5.90(m), 5.89-5.75(m), 5.43-5.38(d), 5.33-5.20(m), 5.16(s), 5.15(s), 5.10(s), 4.60-4.58(brd), 4.51-4.49(d), 4.40-4.38(d), 4.05-4.00(m), 3.93-3.85(m), 3.83(s), 3.82(s), 3.79(s), 3.65-3.60(q), 3.50-3.45(brd), 3.39(s), 3.30-3.18(m), 2.95-2.80(m), 2.61-2.55(m), 2.39-2.32(brd), 2.20(s), 1.90-1.75(m), 1.74-1.66(m), 1.65-1.60(m), 1.59-1.48(m), 1.47-1.31(m), 1.27-1.22(m), 1.20-1.18(d).

Compound 80: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.62-8.58(d), 8.56-8.52(d), 7.40-7.35(d), 7.30(brs), 7.26(s), 7.18(s), 6.62(s), 6.60(s), 5.72-5.68(t), 5.62-5.58(t), 5.40-5.36(d), 5.30(s), 5.18(s), 5.17-5.13(d), 5.10(s), 4.66-4.61(br d), 4.60-4.58(m), 4.31-4.29(br d), 3.96(s), 3.95(s), 3.92(s), 3.87(s), 3.49-3.43(br d), 3.24-3.16(dt), 3.04-2.96(brt), 2.32-2.28(br d), 2.17(s), 2.13-2.06(m), 2.91-2.85(m), 2.81-1.64(m), 1.63-1.55(m), 1.54-1.40(m), 1.36-1.00(m), 0.93-0.87(t), 0.83-0.77(t).

Compound 81: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.62-8.58(d), 8.56-8.52(d), 7.41-7.39(d), 7.38-7.35(d), 7.33-7.28(d), 7.27(s), 7.23(s), 7.11(s), 6.60(s), 6.50(s), 5.65-5.61(t), 5.60-5.97(t), 5.38-5.35(d), 5.30(s), 5.15(s), 5.13-5.10(d), 5.08(s), 5.06(s), 5.01(s), 4.59-4.54(brd), 4.40-4.38(brd), 3.91(s), 3.85(s), 3.80(s), 3.74(s), 3.48-3.42(brd), 3.30-3.23(dt), 2.95-2.90(brt),

2.38-2.32(brd), 2.18(s), 1.90-1.75(m), 1.74-1.46(m), 1.44-1.10(m), 0.94-0.88(t), 0.87-0.82(t).

Compound 82: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 7.28-7.35(m), 7.26(s), 7.24(m), 7.14(d), 7.10(d), 6.65(s), 6.57(s), 5.85(q), 5.78(q), 5.40(d), 5.13(s), 5.07(q), 5.04(s), 4.60(bd), 4.38(d), 3.92(s), 3.88(s), 3.80(s), 3.48(bd), 3.26(dt), 2.95(dt), 2.40(bd), 2.25(bd), 1.82(m), 1.64(bd), 1.56(s), 1.54(d), 1.46(d), 1.38(m).

Compound 83: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 7.36(s), 7.34(m), 7.27(m), 7.22(d), 7.13(dd), 7.08(dd), 6.65(s), 5.85(q), 5.75(q), 5.40(d), 5.10(d), 5.04(s), 4.63(bd), 4.34(d), 3.95(s), 3.92(s), 3.88(s), 3.46(bd), 3.22(dt), 3.04(dt), 2.33(bd), 2.15(bd), 1.80(m), 1.70(dt), 1.55(d), 1.46-1.58(m), 1.36(d), 1.14(m).

Compound 84: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.53(d), 8.52(d), 7.42(d), 7.31(s), 7.27(d), 7.17(s), 6.52(ABq), 5.81(q), 5.74(q), 5.10(d), 5.04(s), 5.03(s), 4.58-4.50(m), 4.31(m), 3.91(s), 3.88(s), 3.87(s), 3.85(s), 3.41(brd), 3.18(ddd), 3.00(ddd), 2.29(brd), 2.12(brd), 1.78-1.72(m), 1.68(brd), 1.52(d), 1.36(d), 1.32(d), 1.31(d), 1.11(m).

Compound 85: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.51(d), 7.42(d), 7.31(s), 7.28(d), 7.25(s), 7.13(s), 6.58(s), 5.80(q), 5.76(q), 5.33(d), 5.10(s), 5.02(s), 4.56-4.50(m), 4.31(brd), 3.90(s), 3.88(s), 3.81(s), 3.79(s), 3.46(brd), 3.24(ddd), 2.90(ddd), 2.33(brd), 2.21(brd), 1.85-1.74(m), 1.62(m), 1.51(d), 1.47(d), 1.31(d), 1.29(d).

Compound 86: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.61-8.45(m), 7.38-7.28(m), 6.68(s), 6.49(s), 5.79(q), 5.61(q), 5.19-

5.01(m), 4.72-4.63(m), 3.89-3.67(m), 3.65-3.45(m), 2.85(t), 2.58(t), 2.39-2.23(m), 2.11-1.92(m), 1.72-1.45(m), 1.39-1.16(m), 0.89(m).

Compound 87: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.60-8.46(m), 7.38-7.15(m), 6.74-6.63(m), 6.62(s), 6.52-6.47(m), 5.75(q), 5.61(m), 5.32-5.25(m), 5.15-5.01(m), 4.72-4.59(m), 3.93-3.80(m), 3.75(m), 3.62-3.43(m), 2.39-1.55(m), 1.50(dd), 1.36-1.21(m).

Compound 88: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 9.16(d), 8.74(d), 8.70(d) 7.85(d), 7.50(t), 7.27(d), 6.68(s), 5.80(m), 5.70(m), 5.38(bd), 5.31(bd), 5.24(s), 5.20(d), 4.60(m), 4.34(dd), 3.88-3.95(m), 3.84(s), 3.75(s), 3.45(bd), 3.24(dt), 3.19(dt), 2.98(bt), 2.34(bd), 2.30(bd), 2.22(bd), 1.10-1.90(m), 1.52(d), 1.45(d).

Compound 89: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 7.36-7.22(m), 5.43(d), 5.36(quintet), 5.25(quintet), 4.60-4.35(m), 3.95(s), 3.91(s), 3.88(s), 3.03(d), 3.67(d), 3.47-3.40(brd), 3.24(dt), 3.07(dt), 2.38(br d), 2.22(br d), 1.85-1.60(m), 1.58-1.25(m).

Compound 91: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 9.01-8.93(m), 8.78(m), 8.06(m), 7.75(s), 7.68(t), 7.61(m), 7.57(d), 7.51-7.41(m), 7.28-7.19(m), 7.15(t), 7.12-7.05(m), 7.03(s), 5.82(q), 5.73(t), 5.33(d), 4.55(d), 4.33(d), 3.93-3.78(m), 3.73(s), 3.43(d,br), 3.21(dt), 3.01(t), 2.63(t), 2.58(t), 2.39(d,br), 2.22(d), 2.09-1.94(m), 1.92-1.43(m), 1.41-1.14(m).

Compound 92: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.94(d), 8.81(m), 8.08(m), 7.75(s), 7.69(t), 7.55(d), 7.48(t), 7.42(m), 7.31(s), 7.29-7.07(m), 7.02(d), 5.81(t), 5.71(t), 5.40(d), 4.56(d), 4.34(d), 3.92-3.79(m), 3.40(d,br),

3.11(dt), 2.96(t), 2.61(t), 2.50(m), 2.22-1.91(m), 1.90-1.35(m), 1.20(s), 1.02(m), 0.83(t).

Compound 93: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.62-8.55(m), 7.66-7.58(m), 7.57-7.56(m), 7.52-7.46(m), 7.40-7.30(m), 7.29-7.20(m), 7.19-7.04(m), 6.96-6.79(m), 6.77-6.69(m), 5.85-5.77(m), 5.70-5.62(m), 5.43-5.38(m), 5.10-4.98(m), 4.64-4.52(m), 4.39-4.35(m), 4.08-4.06(m), 4.02-3.99(m), 3.98-3.90(m), 3.89-3.84(m), 3.83-3.68(m), 3.48-3.40(m), 3.18(ddd), 3.14(ddd), 2.96(ddd), 2.92(ddd), 2.68-2.58(m), 2.57-2.51(m), 2.37(dd), 2.24-2.11(m), 2.05-1.94(m), 1.89-1.41(m), 1.40-1.23(m), 1.22-1.10(m).

Compound 94: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.61-8.55(m), 7.47-7.40(m), 7.38-7.02(m), 6.92-6.88(m), 6.87-6.82(m), 6.81-6.71(m), 6.68-6.64(m), 5.77-5.72(m), 5.65-5.59(m), 5.40-5.36(m), 5.11-5.04(m), 5.02(s), 4.97(s), 4.58-4.52(m), 4.36-4.33(m), 3.87(s), 3.83(s), 3.77(s), 3.70(s), 3.57-3.52(m), 3.48-3.36(m), 3.24(ddd), 3.12(ddd), 2.99(ddd), 2.81(ddd), 2.66-2.53(m), 2.41-2.31(m), 2.28-2.22(m), 2.02-1.92(m), 1.88-1.45(m), 1.44-1.21(m).

Compound 95: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.91-8.75(m), 7.38-7.29(m), 7.28-7.02(m), 6.92-6.80(m), 6.79-6.76(m), 6.74-6.71(m), 6.69-6.64(m), 6.09-5.98(m), 5.78-5.70(m), 5.65-5.60(m), 5.40-5.34(m), 5.32-5.26(m), 5.19-5.13(m), 5.09-5.00(m), 4.63-4.52(m), 4.36-4.32(m), 3.95-3.63(m), 3.46(brd), 3.41(brd), 3.24(ddd), 3.12(ddd), 3.02-2.92(m), 2.67-2.45(m), 2.41-2.30(m), 2.27-2.21(m), 2.20-2.12(m), 2.01-1.90(m), 1.89-1.04(m).

Compound 96: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.59-8.54(m), 7.67-7.57(m), 7.55-7.49(m), 7.47-7.38(m), 7.37-7.05(m), 6.95-6.71(m), 5.83(t), 5.78(t), 5.68(t), 5.65(t), 5.42-

5.37(m), 5.28(s), 5.23-4.95(m), 4.62-4.52(m), 4.38-4.32(m), 3.93(s), 3.92(s), 3.88(s), 3.87(s), 3.47-3.38(m), 3.18-3.07(m), 2.98-2.87(m), 2.67-2.58(m), 2.57-2.50(m), 2.41-2.30(m), 2.22-2.17(m), 2.16-2.11(m), 2.03-1.92(m), 1.89-1.21(m), 1.20-1.09(m).

Compound 97: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.62-8.52(m), 7.64-7.54(m), 7.52-7.46(m), 7.42-7.04(m), 6.97-6.78(m), 6.77-6.70(m), 6.12-5.97(m), 5.85-5.76(m), 5.69-5.61(m), 5.46-5.35(m), 5.33-5.24(m), 5.10-5.01(m), 4.70-4.52(m), 4.39-4.33(m), 3.92(s), 3.91(s), 3.88(s), 3.87(s), 3.48-3.41(m), 3.18-3.10(m), 2.97-.2.90(m), 2.67-2.57(m), 2.56-2.50(m), 2.42-2.31(m), 2.23-2.10(m), 2.04-1.93(m), 1.89-1.10(m).

Compound 98: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.59-8.53(m), 7.67-7.44(m), 7.39-7.03(m), 6.94-6.78(m), 6.77-6.66(m), 6.46-6.33(m), 6.03-5.93(m), 5.83(t), 5.78(t), 5.68(t), 5.64(t), 5.42-5.37(m), 5.08-4.97(m), 4.92-4.66(m), 4.64-4.52(m), 4.40-4.33(m), 3.94(s), 3.92(s), 3.90(s), 3.88(s), 3.87-3.84(m), 3.48-3.40(m), 3.20-3.08(m), 2.98-2.88(m), 2.64-2.57(m), 2.56-2.50(m), 2.41-2.31(m), 2.23-2.17(m), 2.16-2.10(m), 2.03-1.92(m), 1.88-1.08(m).

Compound 99: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.67-8.58(m), 8.54-8.48(m), 7.49-7.03(m), 6.95-6.87(m), 6.86-6.82(m), 6.72-6.68(m), 5.78-5.68(m), 5.63-5.57(m), 5.40-5.31(m), 5.14-4.93(m), 4.59-4.51(m), 4.35-4.30(m), 3.90-3.78(m), 3.73(s), 3.71(s), 3.45(brd), 3.38(brd), 3.22(ddd), 3.11(ddd), 2.99-2.91(m), 2.67-2.48(m), 2.42-2.39(m), 2.26-2.18(m), 2.17-2.11(m), 2.05-1.92(m), 1.89-1.18(m), 1.09-0.98(m).

Compound 100: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.63-8.56(m), 7.68-7.59(m), 7.57-7.40(m), 7.39-7.20(m), 7.19-7.04(m),

7.03-6.98(m), 6.97-6.81(m), 6.78-6.71(m), 5.80(s), 5.77(s), 5.67(t), 5.62(t), 5.40-5.34(m), 5.27-4.94(m), 4.62-4.52(m), 4.38-4.32(m), 3.94(s), 3.92(s), 3.91(s), 3.88(s), 3.87(s), 3.82(s), 3.81(s), 3.47-3.37(m), 3.18-3.05(m), 3.00-2.90(m), 2.68-2.50(m), 2.43-2.29(m), 2.22-2.09(m), 2.07-1.95(m), 1.90-1.63(m), 1.62-1.20(m), 1.14-1.02(m).

Compound 101: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.64-8.58(m), 7.43-7.30(m), 7.29-7.19(m), 7.18-7.02(m), 6.98-6.94(m), 6.93-6.87(m), 6.86-6.83(m), 6.77-6.73(m), 5.73(t), 5.71(t), 5.62(t), 5.60(t), 5.41-5.32(m), 5.10-5.05(m), 4.58-4.52(m), 4.35-4.30(m), 3.94(s), 3.93(s), 3.91(s), 3.90(s), 3.88(s), 3.84(s), 3.83(s), 3.78(s), 3.76(s), 3.45(brd), 3.38(brd), 3.22(ddd), 3.10(ddd), 3.06-2.92(m), 2.67-2.53(m), 2.52-2.48(m), 2.42-2.29(m), 2.28-2.11(m), 2.04-1.94(m), 1.88-1.20(m), 1.08-0.98(m).

Compound 102: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.63-8.57(m), 7.66-7.60(m), 7.58-7.54(m), 7.53-7.47(m), 7.41-7.31(m), 7.27-7.20(m), 7.19-7.03(m), 6.92-6.70(m), 5.80(t), 5.77(t), 5.67(t), 5.61(t), 5.40-5.36(m), 5.09-5.02(m), 4.70-4.52(m), 4.37-4.33(m), 3.92(s), 3.91(s), 3.89(s), 3.88(s), 3.87(s), 3.86(s), 3.85(s), 3.82-3.77(m), 3.48-3.40(m), 3.18-3.09(m), 2.98-2.88(m), 2.66-2.42(m), 2.40-2.10(m), 2.04-1.94(m), 1.89-1.62(m), 1.61-1.18(m), 1.14-1.13(m).

Compound 103: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.76-7.59(m), 7.50-7.40(m), 7.38-7.18(m), 7.17-7.05(m), 6.93-6.87(m), 6.77-6.73(m), 6.18-6.15(m), 5.85(t), 5.79(t), 5.20(t), 5.16(t), 5.41-5.38(m), 5.21-5.08(m), 4.60-4.52(m), 4.37-4.32(m), 3.92(s), 3.91(s), 3.88(s), 3.87(s), 3.47-3.37(m), 3.17-3.03(m), 2.97-2.91(m), 2.64-2.58(m),

2.57-2.50(m), 2.42-2.33(m), 2.05-1.95(m), 1.90-1.80(m), 1.79-1.62(m), 1.61-1.31(m), 1.13-1.08(m).

Compound 104: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 7.47-7.41(m), 7.37-7.02(m), 5.78-5.72(m), 5.18(t), 5.12(t), 5.40-5.37(m), 5.10(s), 5.08(s), 5.07(s), 5.05(s), 4.59-4.51(m), 4.37-4.31(m), 3.87(s), 3.85(s), 3.77(s), 3.73(s), 3.45(brd), 3.37(brd), 3.24(ddd), 3.10(ddd), 3.02-2.94(m), 2.65-2.59(m), 2.58-2.53(m), 2.52-2.46(m), 2.43-2.35(m), 2.27-2.22(m), 2.21-2.15(m), 2.05-1.94(m), 1.89-1.30(m), 1.10-1.01(m).

Compound 105: ^{1}H NMR(500MHz $CDCl_3$), (mixture of diastereomers, mixture of rotomers) δ 8.39(d), 7.64(q), 7.52(q), 7.43(m), 7.29-7.03(m), 5.02-4.88(m), 4.60(q), 4.46(q), 3.62(m), 3.52-3.38(m), 2.68-2.49(m), 2.31-2.13(m), 2.09-1.75(m), 1.74-1.44(m), 1.29-1.16(m).

Compound 106: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.43-8.34(m), 7.46(ddt), 7.39(ddt), 7.32(s), 7.19-7.15(m), 5.32(br d), 5.28(s), 5.04-4.98(m), 4.92-4.88(m), 4.85(br d), 3.92(s), 3.90(s), 3.88(s), 3.87(s), 3.45(br d), 3.23(dt), 3.05(dt), 2.64-2.02(m), 2.29(br d), 2.13(br d), 1.82-1.48(m).

Compound 107: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 7.34-7.23(m), 5.31(quintet), 5.12(quintet), 4.74(dd), 4.69(dd), 4.52(dq), 4.41(dq), 3.93(s), 3.90(s), 3.82(s), 3.70(m), 3.56-3.43(m), 2.34-1.88(m).

Compound 108: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.50-8.31(m), 7.62(d), 7.57(d), 7.46(d), 7.44-7.31(m), 7.30(s), 7.19(q), 7.10(q), 5.00(m), 4.80(m), 4.69(m), 4.56(m), 3.97-3.71(m), 3.61-3.43(m), 2.68-2.41(m), 2.34-2.12(m), 2.08-1.84(m), 1.83-1.72(m), 1.71-1.42(m), 1.29-1.13(m).

Compound 109: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.48-8.32(m), 7.53(dd), 7.47(m), 7.25-7.14(m), 5.02-4.89(m), 4.79(m), 4.49(m), 3.73-3.55(m), 3.48(quintet), 3.30(quintet), 2.69-2.44(m), 2.32-1.41(m), 1.32-1.04(m), 1.01(m).

Compound 110: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.63-8.51(m), 8.50-8.31(m), 8.06(m), 7.93-7.85(m), 7.84-7.76(m), 7.69(d), 7.51-7.40(m), 7.23-7.11(m), 7.09(t), 5.32(d), 5.20(m), 5.08(m), 4.95(m), 4.61-4.52(m), 3.80(m), 3.61(m), 3.39(t), 3.21(dt), 2.94(dt), 2.74-2.44(m), 2.40(d), 2.31(m), 2.22-2.14(m), 2.13-1.91(m), 1.90-1.13(m).

Compound 110: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.46-8.36(m), 7.61(dd), 7.52(dd), 7.50-7.40(m), 7.22-7.15(m), 6.87(dd), 6.83(dd), 6.07(s), 6.04(dd), 5.35(d), 5.10-5.06(m), 4.98-4.92(m), 4.6(br d), 4.34(d), 3.4(br d), 3.15(dt), 2.98(dt), 2.68-2.50(m), 2.24(br d), 1.8-1.46(m), 1.37-1.24(m).

Compound 112: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.7(d), 8.6(d), 7.7.-7.6(dd), 7.45(s), 7.3-7.2(m), 6.9(d), 6.1(d), 5.3(m), 4.6(d), 4.4(d), 3.45(dd), 3.4-3.3(m), 3.1-2.9(m), 2.85-2.8(m), 2.4(dd), 1.97-1.7(m), 1.6-1.35(m).

Compound 113: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.7(d), 8.6(d), 8.5(m), 7.7-7.6(dd), 7.3(s), 7.2(m), 5.4(d), 5.3(m), 4.6(brd), 4.4(brd), 3.95(s), 3.90(s), 3.85(s), 3.45(dd), 3.3-3.2(dd), 3.1-2.9(m), 2.4(dd), 1.95(s), 1.9-1.7(m), 1.6-1.35(m).

Compound 114: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.49(d), 7.52(q), 7.31(s), 7.18(s), 7.12-6.99(m), 5.31(d), 4.99(m), 4.54(d), 3.92-3.79(m), 3.42(d,br), 3.22(dt), 3.02(dt),

2.81-2.62(m), 2.60(t), 2.30(d,br), 2.13(d), 1.82-1.19(m).

Compound 115: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.63-8.53(m), 7.43-7.37(d), 7.35-7.23(m), 7.17(s), 6.56(s), 6.54(s), 5.48-5.42(d), 5.41-5.38(d), 5.32-5.29(d), 5.20-5.10(m), 4.68-4.62(brd), 4.32-4.30(d), 4.00-3.90(m), 3.86(s), 3.53-3.47(brd), 3.25-3.20(dt), 3.05-3.00(dt), 2.37-2.21(brd), 2.10-2.00(m), 1.92-1.87(m), 1.80-1.70(m), 1.69-1.59(m), 1.57-1.43(m), 1.34-1.15(m), 0.97-0.92(d), 0.85-0.78(d), 0.77-0.75(d), 0.66-0.64(d).

Compound 116: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.65-8.55(m), 7.42-7.40(d), 7.39-7.37(d), 7.33-7.30(d), 7.26(s), 7.22(s), 7.10(s), 6.60(s), 6.42(s), 5.42-5.40(d), 5.39-5.37(d), 5.34-5.32(d), 5.16(s), 5.15-5.11(m), 5.10(s), 5.07-4.94(q), 4.60-4.55(brd), 4.41-4.39(brd), 3.93(s), 3.84(s), 3.80(s), 3.70(s), 3.48-3.43(brd), 3.30-3.22(dt), 2.96-2.90(dt), 2.39-2.35(brd), 2.29-2.25(brd), 2.05-2.00(m), 1.90-1.75(m), 1.65-1.60(m), 1.59-1.48(m), 1.47-1.33(m), 0.95-0.87(d), 0.86-0.83(d), 0.82-0.78(d), 0.73-0.69(d).

Compound 117: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.65-8.60(d), 8.59-8.52(d), 7.45-7.39(d), 7.38-7.23(m), 7.21(s), 6.67(s), 6.66(s), 5.83-5.79(t), 5.78-5.75(t), 5.74-5.63(m), 5.53-5.48(m), 5.45-5.41(brd), 5.20-5.05(m), 5.04(s), 5.01(s), 4.99(s), 4.72-4.68(brd), 4.35-4.32(brd), 3.98(s), 3.97(s), 3.93(s), 3.90(s), 3.85(s), 3.55-3.48(brd), 3.32-3.24(dt), 3.10-3.03(dt), 2.70-2.62(m), 2.61-2.56(m), 2.55-2.45(m), 2.39-2.32(brd), 2.20-2.15(brd), 1.97-1.70(m), 1.69-1.60(m), 1.59-1.47(m), 1.40-1.20(m), 0.93-0.90(m).

Compound 118: ^{1}H NMR(500MHz $CDCl_3$), (single diastereomer, mixture of rotomers) δ 8.66-8.62(d),

8.61-8.59(d), 7.46-7.44(d), 7.43-7.40(d), 7.39-7.33(d), 7.31(s), 7.28(s), 7.16(s), 6.68(s), 6.57(s), 5.80-5.75(t), 5.74-5.67(m), 5.43-5.40(d), 5.20-5.05(m), 4.64-4.60(brd), 4.43-4.41(brd), 3.96(s), 3.90(s), 3.85(s), 3.78(s), 3.53-3.49(brd), 3.35-3.28(dt), 3.02-2.96(brt), 2.70-2.50(m), 2.42-2.36(brd), 2.32-2.29(brd), 1.91-1.78(m), 1.73-1.68(brd), 1.63-1.55(m), 1.50-1.40(m).

Example 13 -- MDR SENSITIZATION ASSAYS

To assay the ability of the compounds according to this invention to increase the antiproliferative activity of a drug, cell lines which are known to be resistant to a particular drug may be used. These cell lines include, but are not limited to, the L1210, P388D, CHO and MCF7 cell lines. Alternatively, resistant cell lines may be developed. The cell line is exposed to the drug to which it is resistant, or to the test compound; cell viability is then measured and compared to the viability of cells which are exposed to the drug in the presence of the test compound.

We have carried out assays using L1210 mouse leukemia cells transformed with the pHaMDR1/A retrovirus carrying a MDR1 cDNA, as described by Pastan et al., Proc. Natl. Acad. Sci., Vol. 85, 4486-4490. (1988). The resistant line, labelled L1210VMDRC.06, was obtained from Dr. M. M. Gottesman of the National Cancer Institute. These drug-resistant transfectants had been selected by culturing cells in 0.06 mg/ml colchicine.

Multi-drug resistance assays were conducted by plating cells (2×10^3, 1×10^4, or 5×10^4 cells/well) in 96 well microtiter plates and exposing them to a concentration range of doxorubicin (50 nM-10

μM) in the presence or absence of multi-drug resistance modifier compounds ("MDR inhibitors") of this invention (1, 2.5 or 10 μM) as described in Ford et al., Cancer Res., Vol. 50, 1748-1756. (1990). After culture for 3 days, the viability of cells was quantitated using MTT (Mossman) or XTT dyes to assess mitochondrial function. All determinations were made in replicates of 4 or 8. Also see, Mossman T., J. Immunol. Methods, Vol. 65, 55-63 (1983).

Results were determined by comparison of the IC_{50} for doxorubicin alone to the IC_{50} for doxorubicin + MDR inhibitor. An MDR ratio was calculated (IC_{50} Dox/ IC_{50} Dox + Inhibitor) and the integer value used for comparison of compound potencies.

In all assays, compounds according to this invention were tested for intrinsic antiproliferative or cytotoxic activity. The results are summarized in Table 2 below. As demonstrated in Table 2, the compounds generally caused <10% cytotoxicity at concentrations of 10 μM or greater.

Compounds of formula (I) have also been assayed for MDR sensitization activity with other MDR cell lines including several human cell lines (e.g., myeloma cells (8226/DOX6, 8226/DOX40, MDR10V, MR 20), melanoma cells (VCR 4.5, VBL 3.0, COL-1), GM3639 T cells, MCF-7 breast carcinoma, A549 bronchogenic adenocarcinoma, LOX melanoma, P388/ADR, and P388 VMDRC.04), and different chemotherapeutic drugs (e.g., doxorubicin, vincristine, vinblastine, taxol, colchicine, and etoposide). Results similar to those shown in Table 2 were obtained in these assays (data not shown), further demonstrating the effectiveness of the compounds of this invention in multi-drug resistance sensitization.

Table 2: Evaluation of Compounds for Reversal of Multidrug Resistance

Cmpd	IC_{50}Dox Alone	IC_{50} + 1 μM	IC_{50}Dox + 2.5 μM	IC_{50}Dox + 10 μM	MDR Ratio 1 μM	MDR Ratio 2.5 μM	MDR Ratio 10 μM
2	900nM	400		<60	2.25		>15
4	800	400		<60	2		2.7
6	900	300		<60	3		>15
8	800	500		100	1.6		8
10	6500		625			10.4	
11	700	200		<60	3.5		>12
12	6500		350			18.6	
15	800	400		<60	2		>13
21	1000	700		90	1.4		11.1
27	1200	900		200	1.3		6
31	1300	900		500	1.4		2.6
43	6500		600			10.8	
44	400	200		<60	2		>6
47	900	800		100	1.1		9
48	1400	800		100	1.75		14
49	5000		700			7.1	
52	900	500		<60	1.8		>15
53	1600	700		200	2.3		8
54	6500		510			12.7	
55	900	400		<60	2.25		>15
56	400	300		<60	1.3		>7
64	1500	700		400	2.1		3.75
66	1600	1300		400	1.3		4
69	800	400		<60	2		>13
84	6000		350			17.1	
98	6000		2000			3	
105	9000	2800		500	3.2		18
CsA	1800	80			22.5		
FK506	400	400		100	1		4

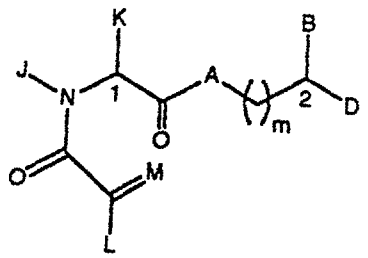
While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products, processes and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

* C L M S *

CLAIMS

We claim:

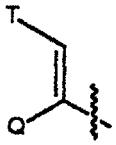
1. A compound of formula (I):



(I)

wherein A is CH_2, oxygen, NH or N-(C1-C4 alkyl);
wherein B and D are independently

(i) Ar, (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2, N, and NR, wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said heteroatom-containing chain to form a ring, and wherein said ring is optionally fused to an Ar group; or

(ii) 

wherein Q is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl or alkynyl;

wherein T is Ar or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl or O-(C2-C4)-alkenyl;

provided that at least one of B or D is independently selected from the group consisting of (C2-C10)-straight or branched alkynyl, (C5-C7)-cycloalkyl substituted (C2-C6)-straight or branched alkynyl, (C5-C7)-cycloalkenyl substituted (C2-C6)-straight or branched alkynyl, and Ar substituted (C2-C6)-straight or branched alkynyl;

wherein Ar is a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl; or a

heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl,

benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl;

wherein Ar may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-(C1-C5-straight or branched alkyl or alkenyl) carboxamides, N,N-di-(C1-C5-straight or branched alkyl or C2-C5-straight or branched alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, and q is 0-2;

wherein L is either hydrogen or U; M is either oxygen or CH-U, provided that if L is hydrogen, then M is CH-U or if M is oxygen, then L is U;

wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C2-C4)straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

* C L M S *

wherein Y is a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl; or a

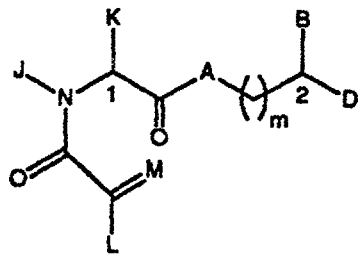
heterocyclic aromatic groups as defined above;

wherein Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

wherein J is hydrogen, (C1-C2) alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from the group consisting of O, S, SO and SO_2; and

wherein m is 0-3.

2. A compound of formula (I):



(I)

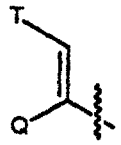
wherein A is CH_2, oxygen, NH or N-(C1-C4 alkyl);

wherein B and D are independently:

(i) Ar, (C1-C10)-straight or branched alkyl, alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, alkenyl or alkynyl,

* C L M S *

(C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, alkenyl or alkynyl, or Ar substituted (C1-C6)-straight or branched alkyl, alkenyl, or alkynyl; wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO and SO_2; or

(ii) 

wherein Q is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl;

wherein T is Ar or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl, and O-(C2-C4)-alkenyl;

provided that at least one of B or D is independently selected from the group consisting of (C2-C10)-straight or branched alkynyl, (C5-C7)-cycloalkyl substituted (C2-C6)-straight or branched alkynyl, (C5-C7)-cycloalkenyl substituted (C2-C6)-straight or branched alkynyl, and Ar substituted (C2-C6)-straight or branched alkynyl;

wherein Ar is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and mono and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 which may contain in either or both rings a total of 1-4 heteroatoms independently selected from oxygen, nitrogen and sulfur;

wherein Ar may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-(C1-C5-straight or branched alkyl or alkenyl) carboxamides, N,N-di-(C1-C5-straight or branched alkyl or alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, and q is 0-2;

wherein L is either hydrogen or U and M is either oxygen or CH-U, provided that if L is hydrogen, then M is CH-U or if M is oxygen then L is U;

wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C1-C4)straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C1-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and mono and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 which may contain in



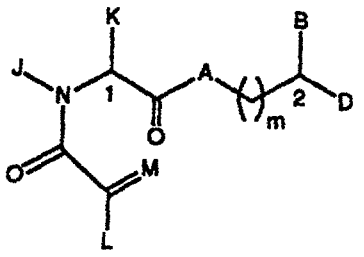
either or both rings a total of 1-4 heteroatoms independently selected from oxygen, nitrogen and sulfur;

wherein Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

wherein J is hydrogen (C1-C2) alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain an O, S, SO or SO_2 substituent therein; and

wherein m is 0-3.

3. A compound of formula (I):



(I)

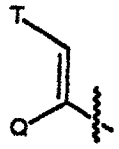
wherein A is CH_2, oxygen, NH or N-(C1-C4 alkyl);

wherein B and D are independently

(i) Ar, (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or

* C L M S *

branched alkenyl or alkynyl, or Ar substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2, N, and NR, wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said heteroatom-containing chain to form a ring, and wherein said ring is optionally fused to an Ar group; or

(ii) 

wherein Q is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl or alkynyl;

wherein T is Ar or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl and O-(C2-C4)-alkenyl;

provided that at least one of B or D is independently selected from the group consisting of Ar', Ar'-substituted (C1-C6)-straight or branched alkyl, and Ar'-substituted (C2-C6)-straight or branched alkenyl or alkynyl;

wherein Ar' is an Ar group substituted with one to three substituents which are independently selected from the group consisting of N-(straight or branched

C1-C5 alkyl or C2-C5 alkenyl) carboxamides, N,N-di-(straight or branched C1-C5 alkyl or C2-C5 alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, wherein q is 0-2;

wherein Ar is a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl; or a

heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl;

wherein Ar may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl,

O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-(C1-C5-straight or branched alkyl or alkenyl) carboxamides, N,N-di-(C1-C5-straight or branched alkyl or C2-C5-straight or branched alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, and q is 0-2;

wherein L is either hydrogen or U and M is either oxygen or CH-U, provided that if L is hydrogen, then M is CH-U or if M is oxygen then L is U;

wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C2-C4)straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, and heterocyclic aromatic groups as defined above;

where Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl,

O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

wherein J is hydrogen, (C1-C2) alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from the group consisting of O, S, SO and SO_2; and

wherein m is 0-3.

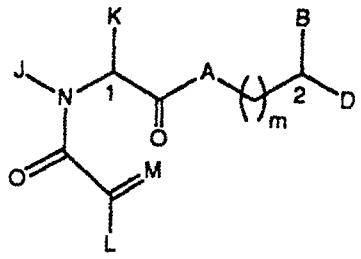
4. A pharmaceutical composition for treatment or prevention of multi-drug resistance comprising a pharmaceutically effective amount of a compound according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier, adjuvant or vehicle.

5. The pharmaceutical composition according to claim 4, further comprising a chemotherapeutic agent.

6. The pharmaceutical composition according to claim 4 or 5, further comprising a chemosensitizer, other than the compound according to any one of claims 1 to 3.

7. A method for treating or preventing multi-drug resistance in a patient comprising the step of administering to said patient a pharmaceutical composition comprising a pharmaceutically effective amount of a compound and a pharmaceutically acceptable carrier, adjuvant or vehicle, said compound being a compound of formula (I):





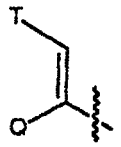
(I)

wherein A is CH_2, oxygen, NH or N-(C1-C4 alkyl);

wherein B and D are independently:

(i) hydrogen, Ar, (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2, N, and NR, wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said heteroatom-containing chain to form a ring, and wherein said ring is optionally fused to an Ar group; or

* C L M S *

(ii) 

wherein Q is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl or alkynyl;

wherein T is Ar or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl, and O-(C2-C4)-alkenyl;

wherein Ar is a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl; or

a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl;

wherein Ar may contain one to three substituents which are independently selected from the group

* C L M S *

consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-(C1-C5-straight or branched alkyl or alkenyl) carboxamides, N,N-di-(C1-C5-straight or branched alkyl or C2-C5-straight or branched alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, and q is 0-2;

wherein L is either hydrogen or U; M is either oxygen or CH-U, provided that if L is hydrogen, then M is CH-U or if M is oxygen, then L is U;

wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C2-C4)straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrolidinyl, 1,3-dioxolyl, 2-imidazolinyl, imidazolidinyl, 2H-pyranyl, 4H-pyranyl, piperidyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl,

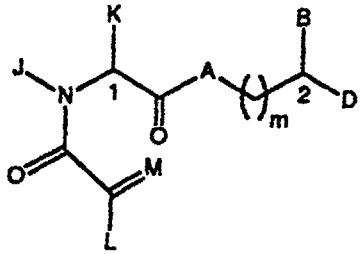
piperazinyl, quinuclidinyl, and heterocyclic aromatic groups as defined above;

where Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

wherein J is hydrogen, (C1-C2) alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from the group consisting of O, S, SO and SO_2; and

wherein m is 0-3.

8. A method for treating or preventing multi-drug resistance in a patient comprising the step of administering to said patient a pharmaceutical composition comprising a pharmaceutically effective amount of a compound and a pharmaceutically acceptable carrier, adjuvant or vehicle, said compound being a compound of formula (I):



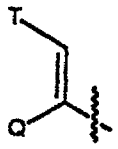
(I)

wherein A is CH_2, oxygen, NH or N-(C1-C4 alkyl);

wherein B and D are independently:

* C L M S *

(i) Ar, (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, alkenyl or alkynyl, or Ar substituted (C1-C6)-straight or branched alkyl, alkenyl, or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2; or

(ii) 

wherein Q is hydrogen, (C1-C6)-straight or branched alkyl or (C1-C6)-straight or branched alkenyl;

wherein T is Ar or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl, or O-(C1-C4)-alkenyl;

wherein Ar is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and mono and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 which may contain in either or both rings a total of 1-4 heteroatoms independently selected from oxygen, nitrogen and sulfur;

wherein Ar may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro,

* C L M S *

trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-(C1-C5-straight or branched alkyl or alkenyl) carboxamides, N,N-di-(C1-C5-straight or branched alkyl or alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, and q is 0-2;

wherein L is either hydrogen or U and M is either oxygen or CH-U, provided that if L is hydrogen, then M is CH-U or if M is oxygen then L is U;

wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C1-C4)straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C1-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and mono and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 which may contain in either or both rings a total of 1-4 heteroatoms independently selected from oxygen, nitrogen and sulfur;

* C L M S *

wherein Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

wherein J is hydrogen (C1-C2) alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from the group consisting of O, S, SO and SO_2; and

wherein m is 0-3.

9. The method according to claim 7 or claim 8, wherein, in formula (I), at least one of B or D is independently selected from the group consisting of (C2-C10)-straight or branched alkynyl; (C5-C7)-cycloalkyl substituted (C2-C6)-straight or branched alkynyl; (C5-C7)-cycloalkenyl substituted (C2-C6)-straight or branched alkynyl; and Ar substituted (C2-C6)-straight or branched alkynyl.

10. The method according to claim 7 or claim 8, wherein, in formula (I), at least one of B or D is independently selected from the group consisting of Ar', Ar'-substituted (C1-C6)-straight or branched alkyl, and Ar'-substituted (C2-C6)-straight or branched alkenyl or alkynyl;

wherein Ar' is an Ar group substituted with one to three substituents which are independently selected from the group consisting of N-(straight or branched

C1-C5 alkyl or C2-C5 alkenyl) carboxamides, N,N-di-(straight or branched C1-C5 alkyl or C2-C5 alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl, wherein q is 0-2.

11. The method according to any one of claims 7 to 10, wherein, in formula (I), J and K are taken together to form a 5-7 membered ring.

12. The method according to any one of claims 7 to 11, wherein, in formula (I), at least one of B or D is independently represented by the formula -$(CH_2)_r$-(X)-$(CH_2)_s$-Ar, wherein:

r is 0-4;

s is 0-1;

Ar is as defined in claim 1; and

each X is independently selected from the group consisting of CH_2, O, S, SO, SO_2, N, and NR, wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen atom and the Ar group.

13. The method according to claim 7, wherein said compound of formula (I) is selected from the group consisting of:

* C L M S *

(S)-1-(2-oxo-2-(3,4,5-trimethoxyphenyl) acetyl)piperidine-2-carboxylic acid-4-pyridin-3-yl-1-(3-pyridin-3-yl)propyl)butyl ester;

(R)-1-(2-oxo-2-(3,4,5-trimethoxyphenyl) acetyl)piperidine-2-carboxylic acid-4-pyridin-3-yl-1-(3-pyridin-3-yl)propyl)butyl ester;

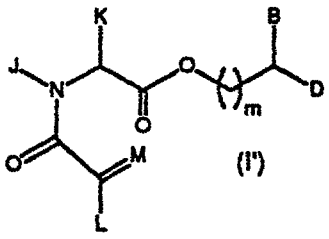
pharmaceutically acceptable derivatives thereof, and mixtures thereof.

14. The method according to any one of claims 7 to 13, wherein the compound is administered orally.

15. The method according to any one of claims 7 to 14, wherein the compound is not substantially immunosuppressive at the dosage level required to cause chemosensitization.

16. The use of a compound according to any one of claims 1 to 3 for treating or preventing multi-drug resistance in a patient.

17. A process for the synthesis of a compound of formula (I'):



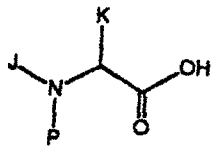
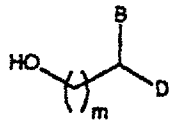
(I')

(I")

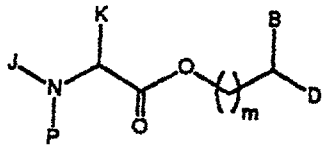
comprising the steps of:

(a) esterifying a protected amino acid of formula (X) with an alcohol of formula (XI):

* C L M S *

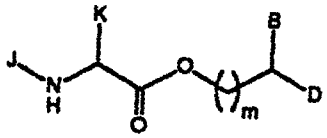
(X)   (XI)

to give an intermediate of formula (XII):



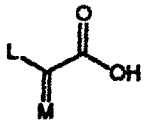
(XII);

(b) deprotecting the amino protecting group in the intermediate of formula (XII) to give an amino ester of formula (XIII):

 (XIII);

and

(c) acylating the free amino group in the compound of formula (XIII) with a compound of formula (XIV):

 (XIV)

or an activated derivative thereof;

wherein P is a protecting group and A, B, D, J, K, L, and M are defined as in claim 1.

* C L M S *

18. The process according to claim 17, wherein said protecting group is an alkoxycarbonyl group.



THIS SHEET HAS BEEN REPLACED

ABSTRACT

The present invention relates to novel compounds which maintain, increase, or restore sensitivity of cells to therapeutic or prophylactic agents. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well-suited for treatment of multi-drug resistant cells, for prevention of the development of multi-drug resistance and for use in multi-drug resistant cancer therapy.

This Sheet Has Been Replaced

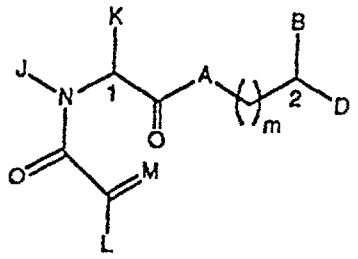
THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEET
29 JUL 1996

ABSTRACT

NOVEL MULTI-DRUG RESISTANCE MODIFIER

The present invention relates to novel compounds of formula (I) which maintain, increase, or restore sensitivity of cells to therapeutic or prophylactic agents. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well-suited for treatment of multi-drug resistant cells, for prevention of the development of multi-drug resistance and for use in multi-drug resistant cancer therapy.

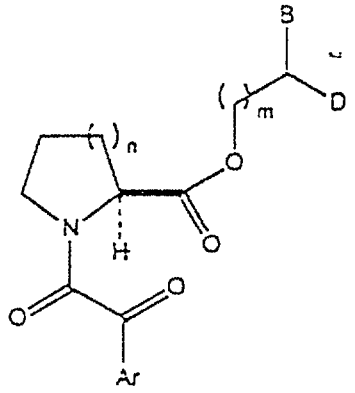


(I)

This Sheet Has Been Replaced

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention relates to novel compounds of formula (I) which maintain, increase, or restore sensitivity of cells to therapeutic or prophylactic agents. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well-suited for treatment of multi-drug resistant cells, for prevention of the development of multi-drug resistance and for use in multi-drug resistant cancer therapy.



(I)

REPLACEMENT SHEET
09 DEC 1996